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Preface

Want to know what scientists and philosophers really think? You will not find that in the typical journal paper or even conference talk. If you are lucky enough to be able to sit down with them at a pub, they may open up to you. But most of us are not so lucky. The 5 Question series offers an alternative to the typical academic publications by providing a format for scholars to freely express their personal opinions and tell their story. In this volume, I have asked a large selection of systems biologists and philosophers to address five questions designed to probe their approaches, aspirations, and frustrations in an informal manner. My hope is that the book will offer you an opening to better understand the people engaged in systems biology or its philosophy, and the implications of this approach for philosophy as well as for science and society. Of course, if you want to pursue the dialogue beyond these initial statements, it is up to you to engage them in discussions about questions that you care the most about. I hope that this volume can serve as a stimulating starting point for further discussions about the philosophical implications of the exciting approach of systems biology.

The emergence of and research within systems biology reveals the depth of the fascinating and overwhelming challenge of understanding biological complexity. While the problem of biological complexity unites systems biology research, the strategies pursued to deal with this challenge are diverse. The wish to compile a selection of viewpoints on philosophy of systems biology in this volume is in part inspired by my own fascination (and frustration) with the difficulty of coming to grips with what systems biology is as I was pursuing my PhD project on the philosophy of systems biology. As I worked my way through much of the literature in and about systems biology, and asked practitioners in the field what systems biology is all about, I realized that there are many different views on what systems biology is or should be. I have come to see these differences, whether revealed through heated scientific disagreements or through subtle methodological diversities, as a rich source for philosophical insights to the characteristics of epistemic cultures and scientific worldviews of practicing scientists. This volume is therefore motivated by an interest in getting insight into the aspects of systems biology which prominent scholars take to be its most salient features, and to give them the chance to freely express their views on what concerns them the most.

To this day, there are interesting differences in how philosophers and practitioners of systems biology characterize what is significant for the approach, what are the most promising future directions for the field, and what they take to be the philosophical foundations of systems biology. There are also different opinions about when the approach emerged. Systems biology is a relatively new field of scientific inquiry, at least in the institutional sense, but it has important precursors in early systems theoretical approaches. The rapid development of systems biology in the 21st Century is in great part due to the availability of new biological data and the need for mathematical and computational strategies to organize and make sense of such data through modeling. The systems biology approach to this task is typically a combination of research strategies from as different disciplines as molecular biology, physics, mathematics, computer science, engineering etc. We are only now beginning to discuss, let alone understand, what the embedding of such research strategies and theoretical frameworks implies for the way living systems are perceived and studied, and for the prospects of solving the great puzzle provided by biological complexity. These are exciting times for philosophy of biology!

In my view, systems biology has great potential to feed back into the philosophy of science. Systems biology has proven mature enough to generate novel and important results which have led to the reinterpretation of central philosophical as well as scientific topics. Among these are the role of mathematical modeling in the life sciences, the nature of biological causation, (anti)reductionism, process ontology, research heuristics etc. The development of systems biology is therefore of interest to philosophers and scientists alike. Moreover, the grand visions of some systems biology to impact or even revolutionize biological and biomedical research makes this approach a topic relevant to readers more broadly interested in understanding the implications of scientific developments for science and society. The contributions of this volume are not intended as review articles but as personal perspectives on the philosophical implications of systems biology, including the scope, aim and future directions of the approach. The questions addressed are as follows:

1. How and why were you initially drawn to systems biology?

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

4. What have been the most significant advances in systems biology?

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

To serve the intended purpose for this volume, I found it important to address practicing scientists as well as philosophers. I am grateful that so many prominent scholars accepted our invitation to provide their perspectives on the abovementioned five questions, and I would like to thank them all for their insightful and thought provoking answers.

Copenhagen, June 2015
Sara Green
Editor

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Copenhagen, June 2015
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1

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Systems Biology: Negotiating Between Holism and Reductionism

1. How and why were you initially drawn to systems biology?

The historical conflict between holists (vitalists) and mechanists has long fascinated me. Often holists pointed out real limitations of mechanistic explanations of their day. The problem, however, is that the holists generally did not have a productive research strategy—a way to advance and defend accounts of how systems as wholes functioned. So the history has largely been one in which mechanists developed more sophisticated accounts of mechanisms that addressed some of the shortcomings of previous mechanistic accounts. In an early, but illuminating example, Bernard responded to the vitalist objections posed by Bichat regarding the indeterminacy of physiological responses and the apparent drive of living organisms to resist death by positing that living systems are organized to maintain the constancy of their internal environment. Subsequently, this provided part of the grounding for Cannon's conception of homeostasis. With the articulation of negative feedback processes as tools for control, mechanisms could be envisaged that would exhibit phenomena that Bichat thought were beyond the capacity of mechanisms.

The growing interest in systems by the Cyberneticists and the proponents of General Systems Theory in the mid 20th Century began to provide conceptual tools that could address whole systems, but these remained, for the most part, small steps that often lost contact with actual biology. The emergence of systems biology in the 21st Century reflects the further development of research tools that can give holists a research agenda that can truly complement the mechanist's highly successful enterprise of identifying component parts and characterizing

their operations. To my mind, there are two distinct types of research methodologies that systems biology has brought forward. The first is the ability to collect and analyze very large corpora of data so that one can gain information about, for example, the pattern of expression of large numbers of genes or activities of large numbers of molecules in cells. The second, and the one that has attracted my interest, is the development of mathematical tools that enable researchers to represent the organization and behavior of systems of large numbers of components that interact non-linearly and are organized non-sequentially. These include the tools of graph theory, computational modeling, and dynamical systems theory.

In many ways, the rhetoric associated with systems biology has exceeded the results that have been secured to date. This has aroused skepticism among critics. In many ways, this early history of systems biology resembles that of artificial intelligence. With new tools (production systems and list programming) proponents of early AI often presented themselves as on the road to accomplishments that proved ultimately to be far more difficult than initially envisaged. But while AI systems that match human cognitive performance overall are still far in the future, AI has made very substantial progress, and in fact many of its tools are being put to use in systems biology. I expect much the same path for systems biology. It is not offering instant solutions. But what is exciting is that it has provided new research tools whose potential will require time to realize.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

As a philosopher of biology, I am most interested in how systems biology can inform philosophy of science by, for example, revealing scientific practices that have not been adequately characterized in philosophical accounts. I do hold out the hope that philosophy of science may make contributions to actual science, but given the sordid track record of applying philosophical analyses within science, I think philosophers should proceed with great humility. One problem that afflicts any cross disciplinary endeavor is that people in one discipline adopt what is put forward in another discipline as decisive when in fact it is one of many views and often represents a stage in the development of that discipline. The remedy is not to rely on textbooks or even review articles, but to engage with the original literature and even the researchers themselves. This may be easier for philosophers than for scientists since we do not have laboratories to run, and investigating the scientific results and processes is the object of our research. But we can also do more to make our work relevant to scientists by presenting our philosophical analyses

in the context relevant to the scientists' research.

I turn, though, to my particular interest as a naturalistically oriented philosopher of science (i.e., a philosopher who takes as his mission to characterize science as it is actually done) in systems biology. Much of my work has focused on explanation and what systems biology provides are examples of different strategies for explaining phenomena than those I have examined previously. This may lead to a replay of what happened when philosophers seriously engaged with cell and molecular biology, which resulted in rejecting the traditional empiricist framework in which the explanatory strategy was to discover laws from which descriptions of phenomena could be derived. Biologists seldom appeal to laws except for those they borrow from physics and chemistry, but instead appeal to mechanisms. Beginning in the late 20th century several philosophers of biology, myself included, began to try to understand what biologists took mechanisms to be, how they represented them and reasoned about them, and especially the strategies they invoked in discovering them. Systems biologists often differentiate their endeavors from those of mechanistic inquiry and even if ultimately their results can be reconciled with mechanistic accounts, what this makes clear is that systems biologists are approaching biological phenomena with a different theoretical perspective and set of research tools. This provides philosophers a rich resource both to examine the challenges systems biologists face in deploying these tools and the types of explanatory accounts they develop using them.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

The most neglected topic, in large part because of the epistemic challenges in understanding it, is the role of organization of systems in giving rise to their dynamic behavior. In the last years of the 20th Century philosophers of biology began to catch up with domains of biology that had been pursuing mechanistic explanations by decomposing mechanisms into their component parts and operations. In fields such as cell and molecular biology, researchers in the 20th Century developed powerful techniques for identifying component structures of biological systems and determining the operations they perform. Although all accounts of mechanistic explanation included reference to the organization of parts and operations as crucial to the ability of mechanisms to generate the phenomenon investigators are trying to explain, there was little discussion of modes of organization and the consequences different modes of organization might have for the dynamic functioning of the mechanism. The epistemic challenge is to identify patterns of organization and determine their effects.

Largely as a consequence of the fact that humans develop new thoughts sequentially, when we approach the interactions of multiple components we think of them carrying out their operations sequentially. When biologists represent a biological mechanism, they often rely on box and arrow diagrams. Inferring the behavior of the mechanism involves following a path through the diagram and mentally simulating the effects of each operation. This strategy works reasonably well when the organization is sequential and the interactions are linear. It can even be extended to slightly less sequential cases such as those in which an operation feeds back on an operation envisioned as occurring earlier. Bernard, Cannon, and the cyberneticists were able to recognize how negative feedback could maintain a system in a stable configuration. By the early 20th Century engineers recognized that negative feedback could also give rise to oscillations, but it is far more challenging to determine through mental rehearsal whether a negative feedback system will generate sustained oscillations, as this depends on the non-linearities in the interactions. Doing so requires mathematical modeling, which depends on not just an appropriate mathematical description of the system but appropriate tools for performing the computations required. Inspired by the feedback mechanism in the operon described by Jacob and Monod, Goodwin developed a mathematical representation, but using an analog computer, he seriously underestimated the value needed for a critical parameter to sustain oscillations. When circadian researchers identified a negative feedback loop as a candidate mechanism for circadian rhythms, Goldbeter revived Goodwin's model, but incorporated delays to enable sustained oscillations with a more realistic parameter value than Goodwin's model required.

Negative and even positive feedback were invoked in the analysis of biological systems in the later years of the 20th Century, but discovering other modes of organization lagged behind. It appeared that there might not be any general principles that could characterize complex biological mechanisms—each might have to be analyzed using its own computational model. If so, the understanding of organization would at best be derivative of mechanistic research directed at identifying parts and operations—after these were identified, mathematical models could be used to determine if the mechanism could generate the phenomenon in question. One could not hope to anticipate the organization, however, from the type of behavior exhibited by the phenomena.

4. What have been the most significant advances in systems biology?

To my mind, the most significant advance brought by systems biology is new tools for analyzing patterns of organization of biological systems that enable biologists to begin to reverse engineer biological

systems. These tools involve applying and developing resources from graph theory, computational modeling, and dynamical systems theory to understand biological systems. I focus first on graph theory. Graph theorists in the mid-20th Century analyzed the most mathematically tractable graphs—random networks and regular lattices. Both of these had important applications to biology in accounting for synchronization of components or repeating sequences of behavior. But at the end of the century Watts and Strogatz focused attention on an intermediate mode of organization in which nodes that are highly connected to their neighbors also have a few connections to more distant nodes. They identified these as small-world networks and, besides noting their widespread occurrence in naturally occurring systems, pointed to their power in processing information. Soon after Barabási and his colleagues recognized that many real-world networks violate another simplifying assumption made in 20th century graph theory—that the number of edges originating in nodes is distributed normally. Instead, the distribution often approximates a power law, with highly connected nodes constituting hubs linking other nodes into modules or providing connections between modules.

Although recognizing that many biological networks, including gene regulatory networks and protein interaction networks, exhibit small-world organization with approximately power-law distribution of connections has proven useful in accounting for properties such as the robustness of biological systems, such analyses of global network structure are still in early stages of development. My hope is that as research progresses, sub-categories within the small-world region might be identified and their dynamical properties analyzed. Just such progress has occurred with respect to local configurations within network structures. By identifying frequently occurring patterns of connections between small numbers of units, commonly referred to as *motifs*, and then developing models to determine the types of behaviors to which such sub-graphs would give rise, Alon, his colleagues, and other researchers have provided potent resources for understanding how systems will behave. An instructive example, analyzed by Tyson and Novak, involves two units each feeding back negatively on the other. Without outside inputs, such a motif will settle into a state in which whatever unit had the highest activation becomes more active. With inputs to one or the other unit, the motif can switch between these two states, and with appropriate parameter values, it realizes a bistable switch in which a much greater increase or decrease in input is required to cause the switch to reverse than was required to drive it into a state to begin with. Given its functionality, it is not surprising that Tyson and Novak found several instances of bistable switches in the eukaryotic cell cycle at points

regulating advances from one stage to another at which it is important for the system not to revert to an earlier stage.

Motif analysis has most frequently been applied at the level of local circuits, but an alternative and potentially extremely valuable application is its use to understand the underlying principles that explain behavior in a complex mechanism. I will exhibit this strategy in Ueda's research on the circadian clock mechanism in animals. Following the discovery of the first clock gene, *per*, in *Drosophila*, and the determination that concentrations of both *per* mRNA and the protein Per oscillate in cells, with the protein lagging several hours behind the mRNA, Hardin et al. proposed a negative feedback mechanism. In their proposal, when Per is in high concentration, it inhibits the transcription of its own gene, thereby reducing transcription until it degrades; only once it is degraded are transcription and translation able to resume. After the initial transcription-translation feedback model was developed, circadian researchers discovered a host of additional genes and proteins involved and identified multiple feedback loops through which they affect each other. Figure 1 provides a representative view of the mechanism. Starting with Goldbeter's 1995 model, the mechanism has been the focus of numerous computational models, many advanced with the goal of trying to identify what are the critical components that enable the mechanism to generate circadian oscillations. Ueda pursued a different approach, which involved finding a way to abstract from the particular genes and proteins to develop a framework that revealed what he proposes is the core organizational principle.

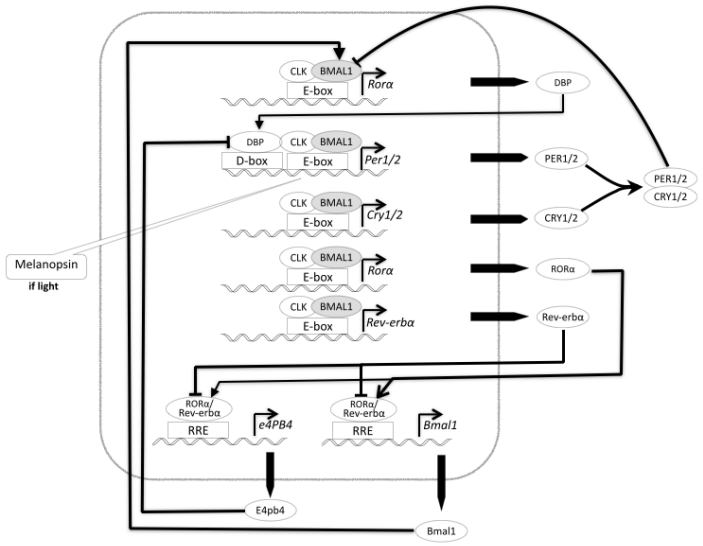


Figure 1. *Diagrammatic representation of the mammalian circadian clock mechanism showing feedback loops through which proteins expressed from clock genes feed back to bind or affecting the binding at promoters on these clock genes.*

Ueda focused on the fact that expression of clock genes is regulated by transcription factors that bind to sequences of DNA in the promoter region known as E-boxes, D-boxes, and Ror-elements (RREs). These are commonly portrayed in representations of the circadian clock, such as Figure 1, but what distinguishes Ueda's approach is that he makes them central. Since one or more are found not only in the promoter regions of all genes viewed as part of the clock mechanism but also many genes that are regulated by the clock, Ueda calls them clock-controlled elements (CCEs). By inserting destabilized luciferase genes into the region regulated by the promoters in a cell culture system and recording the timing of maximum bioluminescence, Ueda was able to determine the time when each CCE was most active. Although the precise time varies by tissue, in the suprachiasmatic nucleus, thought to be the locus of the central clock, E-boxes are most active in the morning, D-boxes about five hours later (evening) and RREs about eight hours later (night). As a result of this investigation, Ueda has introduced an alternative representation of the circadian mechanism (Figure 2a) in which the three CCEs are central and the genes/proteins that are activators or inhibitors of the

CCEs are shown as green or purple ovals with arrows or flat-ended lines connecting them to CCEs to which they bind. Having downplayed the genes and proteins to simply being the vehicles by which the promoter boxes regulate each other, he collapsed multiple linkages that achieve the same effect into single arrows, arriving at Figure 2b. He then recognized that this network is composed of the two motifs shown in Figure 2c (a repressilator and a negative feedback loop), both of which are known to be capable of generating sustained interactions.

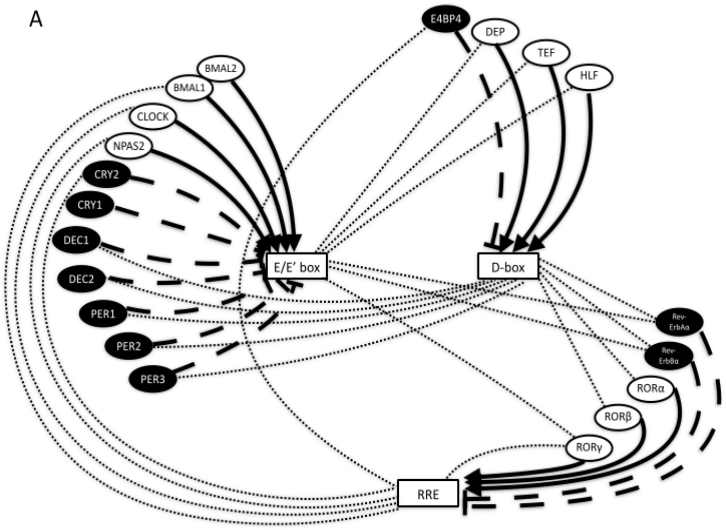
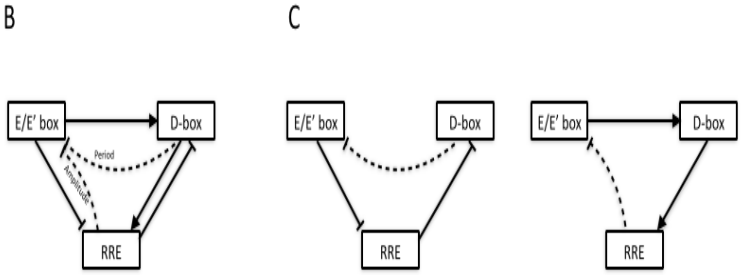


Figure 2A. *The format Ueda developed for representing the mammalian circadian clock mechanism that makes the promoter boxes central. Genes and the proteins into which they are transcribed are not differentiated. Light dotted lines indicated genes/proteins regulated by a given box, dark arrows indicate that the protein activates the promoter and dark dashed end-edged lines indicate that the protein inhibits the promoter. Adapted from Ukai-Tadenuma, M., Kasukawa, T., & Ueda, H. R. (2008). Proof-by-synthesis of the transcriptional logic of mammalian circadian clocks. Nat Cell Biol, 10, 1154-1163.* **2B-2C.** *Ueda's strategy for reducing the multiple connections between promoter boxes to single arrows. C decomposes B into two motifs, a repressilator and a negative feedback loop. B and C are adapted from Ukai-Tadenuma, M., Yamada, R. G., Xu, H., Ripperger, J. A., Liu, A. C., & Ueda, H. R. (2011). Delay in feedback repression by cryptochrome 1 is required for circadian clock function. Cell, 144, 268-281.*



The reason that graph structures such as small-worlds and motifs are of interest in systems biology is that they can provide a foundation for understanding the dynamical behavior of biological systems. To understand the behavior of motifs under different conditions (represented in different parameter values), Alon and Tyson relied on computational modeling. But if researchers want not just to know the results of a computational model, but also to understand how it generates the behavior, they need a means to represent the operation of the model. Dynamical systems theory has provided a number of graphical tools for both mathematically characterizing and graphically representing how a complex system changes its state over time. Graphically, one can represent the state of a system at any time as a point in state space defined by the different variables used to describe the system. Change over time will then involve a trajectory through state space. As a result of the organization of the system, the set of trajectories in state space will be limited, and one can characterize the geometry of the space. Points or regions of the space in which trajectories terminate constitute attractors (these regions might be points (representing a system that settles), continuous cycles (systems that sustain oscillations), or regions in which the system never visits the same exact location twice (systems that are in a chaotic regime). By using one dimension to represent the probability of the system ending up in the location defined by the other dimensions, one can present a landscape in which valleys represent attractors, mountain tops repellers (unstable configurations that can evolve in multiple directs), and ridges separatrices differentiating valleys. The challenge with landscape diagrams is that we can only actually construct such diagrams using two dimensions to represent variables and one for the probability of the defined state. This works well for motifs in which there are only two states whose values are represented as variables. Although we cannot visualize higher-dimensional spaces, the same procedures for constructing a landscape can be applied, allowing researchers to characterize attractors (which may themselves be complex multidimensional structures), repellers, etc., and invoke these to describe the evolution in time of a complex network.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

New tools such as graph theory, mathematical modeling, and dynamical systems theory provide holists with a research program that they previously lacked. Beyond merely criticizing extant mechanistic accounts for failing to take into account the context of the system in which mechanisms operate, they can represent and analyze the behavior of complex systems. The new challenge, though, is to integrate systems-level theorizing with accounts of the underlying mechanism. The need for this stems from the fact that for systems theorists to go beyond describing possible systems by demonstrating that the system structure they identify is actually realized in the biological system in question. The ability of a dynamical model to characterize nuances of the phenomena that are detected empirically provides some evidence that the proffered dynamical account actually characterizes the system. But by far the strongest evidence that a graph represents the actual mechanism is that the nodes can be related to identified parts and edges to operations detected in the mechanism. Likewise, the strongest evidence that a given dynamical account characterizes an actual mechanism is that the variables correspond to properties of parts of the system that can be measured and the equations describe operations that can be empirically investigated.

Relating dynamical and mechanistic accounts is a huge challenge. The tools and reasoning of mechanistic researchers and dynamical systems theorists are very different. In their attempts to decompose mechanisms into parts and operations, mechanistic biologists set up experimental contexts in which many variables are controlled, creating what Cartwright refers to as a nomological machine. If these are well designed, researchers can characterize the structure of the parts and measure precisely the operations in which they engage. But these are often very different from those found naturally in which the components are enmeshed in large-scale systems in which a variety of other components can affect the behavior of any given component. Systems theorists interested in the complex dynamics, on the other hand, turn to mathematical models which may include variables and relations that cannot be experimentally verified but which are needed to generate the desired phenomena. Especially troubling for many mechanists is that dynamical models not only abstract from the detail of actual mechanisms but often idealize by introducing components not believed to occur in the actual system. As Nersessian has observed, when mechanistic investigators and dynamical modelers try to engage each other, they

often talk past each other. The modelers ask for data that cannot be procured with current research tools and experimentalists expect answers that modelers cannot provide.

I finish with what I take to be one promising strategy for bridging the localist approach of mechanists and the global approach of holists that invokes graph theory representations of systems and the analysis of motifs. In pursuing their work on motifs, both Alon and Tyson have applied the analysis of the motifs to well-studied biological mechanisms in which the motifs arise. Here it is possible to relate the values of variables in the mathematical models to those of specific molecules and the relations between variables to reactions that can be demonstrated in experimental conditions. The challenge, however, is that the components characterized in the motif do not occur in isolation, but are embedded in networks. Activity elsewhere in the network can alter the states of components represented as variables in the models or even the parameters used in characterizing relations between variables. This might seem to simply undermine the approach of analyzing motifs, but the hope is that one can add in additional components in a step-by-step manner, preserving key ideas from the motif analysis while incorporating additional features of the systemic context. One reason to hope that such an approach might be successful, at least in many domains, is the recognition that many biological systems have been shown to exhibit small-world organization with the number of edges per node distributed according to a power law. This tends to result in modules with highly interconnected components but with some connections to components of other modules. When motifs occur within modules, then they may show their typical effects being only moderately affected by activity elsewhere in the system.

In discussions of systems biology there is often reference to top-down versus bottom-up causation. In previous work I have argued for making sense of the phenomena for which these terms are used while restricting causation to intra-level contexts (accommodating the downward and upward relations in terms of the constitution relation between parts and wholes). But graph theory provides a potentially more informative way to visualize what have been thought of as intra- and inter-level causal processes while jettisoning the not well-articulated sense of levels. What is needed is a means of detecting within a network cases when a set of nodes constitutes a module that exhibits endogenous dynamical activity (e.g., sustained endogenous oscillation) while still open to influences from elsewhere. Such a module is what might have been characterized as a higher-level entity, but in the graph it is simply an organization of nodes. If one wants, one could draw a circle around the module to indicate that it exhibits an endogenous dynamic in which

each component is responding to other nodes in the module and the response to any input from outside will be modulated by the dynamics within the module. Using a circle for the components in the module as well is appropriate since in fact the entities corresponding to most nodes within a network can themselves be decomposed into a set of organized components. Whether one does so will depend on whether the details of the internal processes in the entities corresponding to the nodes are taken to be important for the explanation sought. Although a causal process will typically impinge on some components of a module more than others, which will then affect other components of the module over time, it may suffice for one's explanatory purposes to simply view the process as affecting the module. Within this network perspective, bottom-up causation arises when local causal processes propagate within a module to generate a system whose responses depend on those local processes. These very causal processes, though, are also what mediate top-down effects as they result in the components of the network behaving differently depending on the state of the network as a whole. This account applies iteratively as one moves (a) in to more local parts of the network and identifies modules with their own systemic patterns of organization wherein the behavior of parts is largely determined by the behavior of other parts or (b) out to more global modules that are formed by realizing such organization between local modules that the activity within local modules is modulated by activity in other modules of the larger structure.

2

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A System Approach to Cancer. From Things to Relations

How and why were you initially drawn to systems biology?

Some contingent facts in my academic life brought me closer to the scientific and philosophical reflection on Systems Biology (henceforth SB). I will briefly introduce them in this section as they frame my thesis about the core issue at stake in (philosophy) of SB: *what is actually fundamental in explanatory terms is not a mere logical endeavour but it is a human enterprise mediated by technology (although not informed by it*) (Bertolaso, 2013b, 2015). This point becomes particularly interesting when focusing on biological explanations. There is an on-going process, in biomedical sciences in particular, that is forcing us to revise epistemological assumptions along the very progress of scientific understanding.

The thing-processes dichotomy

At the beginning of my first thesis in molecular biology, when I started working on the explanatory models of cancer and on their epistemological presuppositions, the increasing evidences that cancer was a process - not a thing - attracted my attention. A claim like this sounded to me, on the one hand, like a claim against received causal explanations that were identifying cancer's causes (and thus defining cancer) in specific 'things' (either molecules, genes or cells). On the other hand, it was implying a peculiar recognition of the causal complexity of this phenomenon which still seems far beyond our explanatory possibilities. In particular cancer's multilevel phenomenology is asking for a clarification of the peculiar causal nature of the hierarchical regulation that is compromised in cancer and that accounts for its pathological

characterization. *Context-dependent, inter-level regulatory dynamics* became the core issue in cancer biology and their explanation the main focus of my research agenda. These kinds of dynamics are, in fact, what I consider the minimal definition of any biological question.

From technology-driven to paradox-driven cancer research

Within the thing-process discussion in the scientific literature, a methodological shift also emerged. Molecular biology, which had been the dominant methodological approach in cancer biology till the 1980s at least, gave way to SB that became the privileged tool in cancer biology analysis. Since we moved away from the paradigm of genetic reductionism (everything is written in our genes), dynamics and interactions became the focus of biological investigation. Genomic patterns of expression, microarrays, metabolomics and proteomics entered the filed of cancer research that was no longer seen as a mere genetic disease. The interest for SB was, therefore, also linked to the awareness of the intrinsic explanatory limits of research programs that decompose complex biological systems into their constituent parts. This process is paradigmatically synthetized in what is called the central dogma of molecular biology that grounds the explanation of how biological information flows from genotype to phenotype: *the linear causal relationship between a gene and the protein in accounting for a phenotype*. Given the complexity of the biological system involved in the neoplastic process, this explanatory approach soon showed its pitfalls.

Some cancer research programs started moving, therefore, from a technology-driven to a paradox-driven approach (Baker, 2013). Some experimental data were contrasting the original assumptions of the Somatic Mutation Theory in explaining cancer (i.e. the theory of cancer that causally and explanatory relates cancer to genetic mutations that are somatically transmitted). I just mention a few paradoxes that I consider paradigmatic among others (Baker and Kramer, 2007): presence of spatially distinct precancerous lesions at the onset of promotion of cancer, spontaneous regression of the neoplastic phenotype, cancer developing after normal tissue is transplanted to other parts of the body or next to stroma previously exposed to carcinogens, the lack of tumours when epithelial cells exposed to a carcinogen were transplanted next to normal stroma, and the development of cancers when Millipore filters were inserted under the skin of rats. All these empirical evidences mainly deal with the *context-dependency of biological function* and with the intrinsic *asymmetric feature of functional explanations* that is lost in some reductionist genetic accounts of cancer (Bertolaso, 2013b) when dealing with the reversibility of the neoplastic cellular phenotype. Such reversibility was apparently incompatible with the irreversibility of the

overall neoplastic process under the same theory.

These facts encouraged me to explore the nature of functional attribution and the disentangling some dimensions of biological explanation. Two epistemological questions emerged that, to some extent, met the main concerns raised by Maureen O'Malley and John Duprè in their paper published in 2005 on SB and on integration of different levels of explanation (O'Malley and Duprè, 2005): a) how complex biological systems should be investigated and b) how their constituent parts are identified. A mere explanatory de-compositional approach, although it allows for a progressive understanding of the molecular mechanisms beyond the functional and developmental aspects of complex systems, does not consider that re-composition of the complex system changes the concrete mechanisms previously independently studied. Or as some philosophers put it: "Something important about complex wholes is lost if they are conceived solely in terms of their least parts, even though it is those parts of which they are in fact composed" (Grene and Depew, 2004, p. 311). To put it in a different way, reductionist pitfalls were related to the reduction of biological explanations through a principle of *causal identity* that the received dogma of molecular biology seems to entail: the same kind of 'information' is contained in a gene and in its product. That is, given a phenotype, either the gene's or its protein's functionality is a necessary and sufficient condition to account for a given phenotype.

Searching for meaning

Finally, SB was born (somehow in cancer research too) by the convergence of different available technologies to analyse in a more comprehensive way a huge quantity of data. Such *simultaneous analysis* offers a more adequate view of the reality of a biological process. However, the question about explanatory relevance of the chosen systems and the search for a meaning (often in terms of correlation) among elements has been posing an unavoidable issue related to our capability to deal with that amount of data and the relevance of the human factor in their interpretation. Such interpretation, in fact, is based on a well-posed scientific question that, as scientists know, usually already entails part of the answer[1]. Any global statistics on a data set (especially multidimensional analyses based on correlation structures of the data) is heavily dependent on the nature of the collective examined. This implies a sensible consideration of the particular meaning different descriptors acquire in the considered set. Any bottom-up approach (from a spec-

[1] This point could open the debate on 'Hypothesis-driven' science. However, this discussion is far beyond the aim of this contribution.

trographic measurement to a principal component analysis for marketing purposes) does not imply a 'normative value' attached to the single variables: the single variables are considered as 'probes' with which researchers sample the system under analysis, and the emerging structures (clusters, components, networks) are 'generated' by the data set. This implies that a different data set can give rise to a different structure of the same variables, exactly like two different molecules give rise to two different spectra when analysed by the same spectrophotometer, that is, by the same set of frequencies (variables)[2]. This fact asks for a very careful selection of the data set in order to avoid biases and thus totally useless results.

Looking for patterns of regularities in order to account for the destiny of blood cells toward specific functions, for example, researchers showed that focusing on genes (presence or absence) or on their expression was not useful (Tsuchiyaa et al. 2009). It is necessary to move up to the level of micro-RNA expression to find such regular patterns. Interestingly micro-RNAs are regulatory molecules and not informational ones. Also in this case, there is no way to explain a phenotype through a principle of causal identity. Paradoxes in explaining biological processes can be better understood by disentangling the principle of *causal identity* into the *mesoscopic principles* of *causality* and of *identity* that work in a synergic way in defining what biological units are relevant from an explanatory point of view (cf. Bertolaso 2013a).

Optimistic people

Evidences that various experimental results were paradoxical under specific theories encouraged some researchers to explore different perspectives, to revise their own views on a specific phenomenon, reacting like Niels Bohr when stated: "How wonderful that we have met with a paradox. Now we have some hope of making progress" (Bohr, 1966, p. 196). What do these people have in common? What was originally just an intuition has now become a conviction: they are optimistic people. Such scientists look for pragmatic truths, i.e. causal relationships that, although always explanatorily partial, are relevant to some pragmatic question and work. Awareness of intrinsic limits of scientific practice just contributes to that humble attitude that usually goes hand in hand with optimism in scientific practice. As a consequence, optimistic scientists usually are convinced that *something is still to be discovered*, a premise that I have found in the introduction of the first volume on the philosophical foundations of SB: "The premise of Systems Biology is that there is something to be discovered, i.e. living systems do have

[2] A. Giuliani, personal communication.

functional properties that cannot be discovered and understood by molecular biology alone; functional properties that are not in the molecules themselves" (Boogered et al. 2007, p. 4). However, as I believe more in convergences than in divergences, let me say something on the apparent contraposition between molecular biology and SB.

I have, in fact, found some optimistic people in cancer research that would define themselves as 'reductionists' (as they usually prefer working in molecular biology) and some that would have defined their work as 'anti-reductionist' (as they usually prefer working through SB). To a first approximation, they would support a cellular theory or a tissue organization field theory of carcinogenesis, respectively. The members of the former group are classified as reductionists, in as far as they also assume genetic determinism as their background epistemological framework. The latter group members define themselves as antireductionists because they assume emergentism and organicism as default in accounting for the origin of cancer. A central question is, however, whether the microenvironment is more relevant than genes in the origin and establishment of the phenotype in tumour cells. Both reductionist and anti-reductionists eventually end up claiming that SB might be the solution: reductionists (usually more inclined towards methodological aspects) by focusing on how complex biological systems should be investigated; anti-reductionists (more inclined toward systemic views and epistemological issues) by reflecting on how empirical results question epistemological assumptions in scientific practice (Wolkenhauer and Green, 2013; Bertolaso, 2011).

Convergence on systemic approaches stimulates the philosophical reflection on how explanatory constituent parts of biological systems are identified: what do genes, proteins, and tissues have in common when accounting for maintenance (or disruption) of higher-level properties' robustness? This is not an idealistic view of science. In a society in which science is often driving social commitments, the reflection about how and why some scientific paradigms change and often converge on new conceptual frameworks cannot easily be left aside. Besides useless contrapositions between optimistic and pessimistic views of what science can really do for us, and our society, understanding convergences is an interesting issue for philosophy of SB. As it has been said, "The pessimist is commonly spoken of as the man in revolt. He is not. […] The person who is really in revolt is the optimist" (Chesterton, 1901). Acknowledging, therefore, both the real contribution of molecular and systems biology in the regulation of biological systems, remains one of the main challenges of philosophy of science nowadays. In biological processes, both mechanistic properties, which are better captured by molecular biology, and functional states that are instead object of

inquiry of SB, are involved. However, why both mechanistic and systemic accounts converged on systemic accounts in cancer reseacrh encouraged me to move forward with my research.

How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

Understanding by Relating

Since SB replaced molecular biology in the study of complex biological systems, understanding interactions among parts became the central issue of the biological investigation. ''Reaching such understanding will require a system biology that is defined as the science that deciphers how biological functions arise from interactions between components of living organism. It studies the gap between molecules and life'' (Boogered et al. 2007, p. 6). However, given the on-going revolution forcing the scientific community to elaborate new multilevel and more and more complex models to account for such complex biological dynamics, I focused on a specific aspect of this concern. With the invaluable help of scientists and other philosophers, I started studying *how relevant knowledge emerges* in scientific practice. Taking seriously how paradoxical issues emerge in biological sciences, and the context dependency of biological explanations, led me to consider how explanatory judgments take place in the process of scientific understanding *in terms of facts* more than in terms of events or (molecular) products. The focus in this way is directly on interactions, on emergent properties. Paradigmatic among these properties are the organizational and evolving features of living systems (the main objectives of SB inquiry).

That "[w]e need a theory of explanation that captures several different possibilities" (Woodward, 2014) has already been highlighted when analysing the failure of current models of scientific explanation (DN, statistical relevance, unification, causal-mechanical models, etc.). Any unificationist account, in fact, seems doomed to failure, but how explanatory relevance emerges in scientific practice still remains an open issue. In particular, when spatio-temporally continuous causal processes are at work, no single explanatory tool is either necessary or sufficient. Part of the difficulty is that, to express the relatively fine-grained judgments of explanatory relevance, we need to talk about relationships between properties or magnitudes and our decisions on which facts or features are relevant seem to precede our judgments on causal processes and interactions. The understanding process clearly exceeds a mere psychological upshot or acquisition of knowledge of facts although some relationship among understanding, explanation and contextual factors holds.

On one hand, models of complex biological dynamics usually emerge

as relational dynamic networks with elements that acquire a specific explanatory relevance depending on the level of discussion and on the scientific question posed (Giuliani et al. 2014). That is, *the consideration of the 'relation pattern' as the 'real thing' to be considered by the researcher is the perspective that justifies the peculiar epistemological status of SB*. On the other hand, as Alessandro Giuliani[3] usually poses it, the inescapable premise of a scientific explanation that SB makes explicit is that the essence of the studied phenomenon (for example, the relation between different mutagenicity tests) lies in the mutual correlation between tests emerging from their actual performance in 'real life', i.e. their pattern of response to chemicals, and not on the specific a priori biological construct at the basis of each test.

At this point the notion of *mesoscopic level* can be defined as the scale of network organization at which functionality emerges in responses to higher-level system and environmental constraints. It is at the mesoscopic level that correlations and non-trivial determinism are maximized and where the mesocopic principles of causality and identity - that are relational in nature and have been elewhere defined in terms of 'essentiality-by-location' (Bertolaso et al., 2013; Bertolaso, 2013b) - converge.

Finally, at the crossroads of the mesoscopic and the different scales of explanatory issues, there is what I consider a fundamental epistemological point: the peculiar context dependency of functional explanations in biological sciences. Context-dependencies mainly affect how what is relevant should be understood, *not only in explanatory but also in conceptual terms*. *Relata* and causal relationships in explanatory accounts obviously change under different contextual conditions (pragmatically and through the more trivial notion of context dependency). What is not so obvious is how such *relata* and the causal relevance of their relation conceptually imply each other.

A radically non-reductionist dimension of the notion of *relevance* emerges. I think that SB will still play an important role in appreciating, first of all, the explanatory relevance of *systemic perspectives* that hopefully will allow us to avoid reductionist and relativist perspectives or excessive simplifications driven by mere pluralistic accounts of human understanding and scientific knowledge. Therefore the irreduc-

[3] Since Giuliani took his degree in Biological Sciences in 1982, like other 'optimistic people' he started pursuing a SB road. He adopted a different perspective and new mathematical tools to argue that things are not so complex as they seem but that the problem is actually entailed in the 'mesoscopic principles'. Denis Noble's work should also be mentioned as it has largely inspired Guiliani's as well as my work. Giuliani is currently involved in the analysis of biological experimentation by multidimensional statistics, principal component analysis, and cluster analysis.

ibility of understanding typical of different disciplines is no obstacle but a condition of an integration process of different kinds of human understanding. Moving from physics and chemistry to biological or life sciences more generally, we aim to make explicit the explanatory categories that structure explanations in these fields and to clarify the systemic and relational features of any epistemology and their specificity in the different fields.

What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

What follows from the previous sections is that the philosophical dimension of SB is related to the epistemic assumptions in explaining inter-level regulatory dynamics. A holistic perspective, i.e. an integrated view and interpretation of a complex process, dominates. Downward causation is more relevant in the organization of the experimental strategy than for any bottom-up account. From a scientific point of view this corresponds to a major awareness of the difference between understanding a complex system and the sum of its parts. From a philosophical point of view this points to the relevance of functional explanations in biological sciences. In philosophy of biology the discussion has progressively shifted from the reflection on the epistemological and ontological status of genes and species, for example, to account for specific phenotypes and their differences, to 'what' mechanisms or systems are. On the other hand, in scientific literature we can find statements like these: "Perhaps this rather obsessive attachment to empirical evidence in the biomedical sciences (which looks rather incongruous vis-a-vis the widespread acceptation of Darwin's narrative), is a remainder of late positivism and its fear of metaphysical entities" (Aranda-Anzaldo, 2002). Something in between these positions, and with clear philosophical relevance, still has to be discussed. I mainly think that a wider notion of (functional) evidence (i.e., more comprehensive epistemological tools) is necessary, as the emergence of the discussion on context-dependencies and mesoscopic levels already shows in SB.

A symptom of this necessity is precisely the *tendency to objectify explanatory tools*: mechanisms, functions, networks. Such tools describe relationships whose ontological status is not grasped by 'thing' categories. When we objectify explanatory tools, the risk is to give up the intellectual endeavour of understanding what kind of knowledge is possible, and with the challenge of developing a philosophy of nature that might prove to be useful in understanding why science works. Lack of a philosophy of relations actually justifies, in my opinion, main tensions in current philosophy of science, like the above-mentioned con-

traposition between molecular biology and SB. In Waddington's words (who first dealt with many concepts that are now currently commonly used in SB) there will be a progress "in understanding the nature of the networks of interaction which are involved in the process and which a collection of cells becomes organized into an organ with a unitary character" (Waddington, 1977, p. 21). As O'Malley and Dupré correctly conclude in their paper the "true and distinctive purpose of systems biology" is to understand "this downward causation (or how causality operates at different levels of organisation) and the differences between units acting in aggregation and systematic organization. (…) A substantive answer to this question should cash the definite but sometimes inchoate anti-reductionist intuitions prevalent in contemporary molecular biology. This last question, therefore, builds on the ontological issues to become an epistemological one that lies at the very heart of systems science" (O'Malley and Dupré, 2005, p. 1273).

What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

It has been said that "[s]ystems biology thus encapsulates some of the oldest philosophical tensions in biology and perhaps can be interpreted as just their latest manifestation, an interpretation that must inevitably engender a degree of scepticism about the likelihood that systems biology will lead to their solution" (O'Malley and Dupré, 2005, 1274). I think that one of the oldest tensions in philosophy of (systems) biology deals with understanding the normative character of biological processes. In concrete, the tension between the thing-process issue and the paradoxes emerging in the biology of cancer, clearly question the inadequateness of mereological accounts in answering biological questions. There is no way out from the part-whole dichotomy when ignoring the teleological nature of functional definition, for example, and of context-dependencies of the conceptualization of explanatory parts.

As Giuliani often highlights in our discussions, the crucial point is in the clarification of what scientists intend with the notion of *potential*: "I'll try to explain: a seed of a pine *is not* a pine but it has the 'potential' to become a pine if put in the right environmental conditions. The seed can maintain this potentiality for years (there are cases of germination of grain seeds found in Ancient Egyptian tumbs) and, clearly this potentiality is very specific (a pine seed can only give rise to a pine tree not an oak or an apple tree). This implies in some sense *inside the seed* we have the potential that, *when exploited* will give rise to the tree *but, again*, we have not the possibility to predict all the relevant features of the pine tree by the study of its seed, many actual properties of the pine tree will arise (and can be appreciated) only on the entire plant".

The same happens for drug action: when we speak of 'mechanism' of a given drug we take for granted the 'actual relations among different molecular players' *inside the cell*, already there, before the cell 'meets' the drug whose only work is to 'push a button' to let a peculiar (already wired) interaction to be put in action. This was the concept of pharmacology until recently and the thought of many system biologists that pursue the ideal project of the 'e-cell' or the 'elucidation of all the pathways present in the system' as the avenue to develop new drugs.

In Giuliani's and others' opinion the latter is very unlikely to be true, "like the seed that can 'potentially' become a pine but cannot be considered a complete miniaturized *image* of the pine, a great part of the drug effects in terms of emerging correlations among parts of the system is *induced* by the interaction with the drug and cannot be recognized in the system at rest". This implies the need for consideration of biological entities as dynamical systems whose internal correlation pattern is *not given* but can vary. Quite close to original SB's question about life, there is in fact the need to understand how *dynamics of correlation increase and decrease at the basis of complex systems functioning*. From a methodological point of view, this means going back to a less superficial understanding of the role of *in silico* approaches for preliminary studies and of the modelling of scale variances.

Finally, looking at how Waddington and Kauffmann's or Huang's work, for example, could change our concept of biological information, would be a final and more radical outcome of the revolution SB started years ago. To conclude with another quote I particularly like: "The cause which is blocking all progress today is the subtle scepticism which whispers in a million ears that things are not good enough to be worth improving. If the world is good we are revolutionaries, if the world is evil we must be conservatives. These essays, futile as they are considered as serious literature, are yet ethically sincere, since they seek to remind men that things must be loved first and improved afterwards" (Chesterton, 1901).

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3

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Systems Biology in the Broad Sense

1. How and why were you initially drawn to systems biology?

In 1990, I became an Assistant Professor at the department of microbial physiology, headed by Prof A.H. Stouthamer. In 1994, Stouthamer retired e and Hans V. Westerhoff, who was and is a driven and leading scientist in systems biology, was appointed as his successor. After having finished my research on nitrogen fixation in bacterial symbionts (*Bradyrhizobium-Arachis* symbiosis) and free-living bacteria (*Azorhizobium caulinodans*) that I had started in 1990 under the supervision of Prof. Stouthamer, I began to explore the field of systems biology further.

I was greatly impressed by the work of Peter Jensen, Ole Michelsen and Hans Westerhoff on the control of the H^+-ATPase on growth of *E. coli* (Jensen et al. 1993a; Jensen et al. 1993b). They proved that an enzyme as vital as the H^+-ATPase had virtually no control over the growth rate, which was an astonishing highly counter-intuitive observation, at least for me. I was also impressed by the work of Jannie Hofmeyr and especially by the intensive course on systems biology he gave in Amsterdam in July 1996. Jannie Hofmeyr is a gifted and dedicated teacher and he was able to share his fascination with a systems approach in biochemistry. He convinced me that systems biology was both useful and important. The clear demonstration that there are usually no rate-limiting steps in biochemical pathways, but that control is distributed among the constituent enzymes was an eye-opener for me personally at that time.

Hans Westerhoff, Frank Bruggeman and I started out in 2000 with a special grant from VU University Amsterdam that was assigned to Hans Westerhoff to uncover and study underlying philosophical principles that draw a distinction between systems biology and molecular biology. The three of us studied two general philosophical issues in

collaboration with other groups/persons:

(i) *Reductionism* (together with Jan Treur and Catholijne Jonker from Artificial Intelligence and Huib Looren de Jong from Theoretical Psychology) (see Boogerd et al. 2002; Bruggeman et al. 2002).

(ii) *Emergence* (together with the philosophers Robert Richardson from the University of Cincinnati and Achim Stephan from the Universität Osnabrück) (see Boogerd et al. 2005; Bruggeman, 2005).

At the start of our study, analysis and discussion, I became acquainted with reading und understanding philosophy papers. Initially I found this a laborious process, but after a while it became a highly motivating and very fruitful activity. In retrospect, I am grateful that Hans Westerhoff, who as a systems biologist has a broad and deep interest in a multitude of scientific endeavours, had the vision and the courage to embark on a philosophy of science project that was pretty far from mainstream science and was, and sometimes unfortunately still is, not always appreciated by molecular, or even systems, biologists.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

Remarkably, biologists have not been able to come up with a durable definition of life that was acceptable to the scientific community, likely due to the complex and enigmatic nature of life. Alternatively, they have presented lists with properties defining the hallmarks of life, which is a much easier task. According to Bedau, philosophers even ignored the topic, at least in the last century, but now an increasing number are giving their attention to philosophical problems about life (Bedau, 2011). I think (philosophy of) systems biology should address this daunting task. In this respect, an interesting proposal was done by the ecologist Gerard Jagers op Akkerhuis in his (second) thesis (Jagers op Akkerhuis, 2010). Here he claims to have presented a commonly acceptable definition of life on the basis of a framework (the operator hierarchy) that uses the evolution of complexity from the fundamental particles up to artificial intelligent systems. It remains to be seen whether it will stand the test of time.

A quote from the introductory chapter of our edited (together with Jannie Hofmeyr) book 'Systems Biology (Philosophical Foundations)' from 2007 (Boogerd et al. 2007), which was the first book on the philosophy of systems biology, helps illustrate the general applicability of the systemic approach in science: "Contemporary Systems Biology

is a vigorous and expanding discipline, in many ways a successor to molecular biology and genomics on the one hand and mathematical biology and biophysics on the other (Westerhoff & Palsson, 2004). It is perhaps unprecedented in its combination of biology with a great many other sciences, from physics to ecology, from mathematics to medicine, and from linguistics to chemistry". Thus, systems biology is an interdisciplinary science that requires specialists from various disciplines to communicate (Bruggeman & Westerhoff, 2007) and philosophers are invited to take part in this discourse. Since the systems approach is highly relevant for an ever increasing number of disciplines (including e.g. pharmacology, psychopathology, and psychiatry), I think the philosophy of science can make a valuable contribution by determining whether, and if so, to what degree, overarching philosophical principles can be uncovered within and, more profoundly, across these disciplines.

In 1997, McAllister argued in a critical article concerning the Dutch academic world that (i) the position of the philosophy of science is not strong, (ii) the focus is on the history of philosophy and (iii) philosophers are not in touch with actual developments in scientific research (McAllister, 1997). Although things might be changing for the better, particularly in the field of systems biology (see e.g. Bruggeman, 2007; Callebaut, 2005; 2012; O'Malley & Soyer, 2012; Green & Wolkenhauer, 2012), in my opinion, systems biologists and philosophers alike should spend more time and effort in developing the philosophy of systems biology.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

In the late 20th century, the philosophy of functional biology was the most neglected topic in the philosophy of biology. The philosophy of biology was dominated by evolutionary biology. It was only after the seminal MDC-paper (Machamer et al. 2000) entitled 'thinking about mechanisms' was published that functional biology got some more attention in the philosophy of biology. In the same vein, our edited book on systems biology (Boogerd et al. 2007) can be perceived as an endeavour to start doing justice to the philosophical underpinnings of functional (systems) biology.

As pointed out by the philosopher and biologist Arno Wouters in his insightful and subtle PhD thesis, philosophers of biology and biologists all too often mistakenly take functional explanations for evolutionary explanations (Wouters, 1999). I concur with Wouters who claims that answers to why-questions can also be provided by functional biology, in contrast to the classical view of Ernst Mayr (Mayr, 1961) that why-questions can only be answered by evolutionary biology. One of his functional explanations, which he called 'design explanation', expli-

cates why an item, state, property, or behaviour of an organism is the way it is and not different. In short, it is about biological advantage (Wouters, 2007). This kind of functional explanation is often completely neglected in the philosophy of biology (Wouters, 1999). It is also more often than not misunderstood in biology; it is sometimes mistakenly put into the category of 'capacity explanations' — which are about biological roles, not advantages — in (systems) biology. In contrast, I think that a design explanation, if properly explicated, is a highly relevant concept for the philosophy of systems biology and it deserves more attention than it has received so far.

Theodosius Dobzhansky is perhaps most famous for his statement (1973) that 'nothing in biology makes sense except in the light of evolution'. As an Orthodox Christian geneticist he meant that God used evolution to produce the diversity of life (see Griffiths, 2009). Other philosophers/scientists have positioned themselves in relation to Dobzhansky by neatly paraphrasing his dictum: 'nothing in biology makes sense except in the light of *adaptation*' (see Griffiths, 2009), 'nothing in *an organism* makes sense except in the light of (*functional) context*' (Hofmeyr, 2007; Hofmeyr, 2008) and '*some areas* in biology make sense *without* the light of evolution' (Griffiths, 2009). With due respect, I am myself inclined to go even one step further as my dictum would read: '*many areas in systems* biology make sense *without* the light of evolution'. To avoid misinterpretation, of course I do not wish to challenge evolutionary theory in general (see at questions 4 and 5). In the introduction of our edited book we have argued that in many respects systems biology can do without evolutionary biology, because it addresses the issue of what life is, irrespective of its origin. Certainly in the period of 1980-2005 it was about functional biology rather than evolutionary biology. Although somewhat provocative, this was a valid statement at that time, especially when considering the fact that the mainstream evolutionary theories are indeed backward-looking. Traditional evolutionary biology seeks historical explanations, whereas systems biology looks for contemporary explanations.

It is my personal opinion that the criticism put forward in a review of our edited book (Cain et al. 2008) may be countered in a similar way. Here the authors stated that "the editors explicitly exclude one discipline: evolutionary biology". Although I think this statement is at least partly ungrounded and based on several misinterpretations of the editors' views, in my opinion, we indeed sought to restrain the role of evolutionary theories for molecular systems biology in our book. Much in the same way as Mayr wished to defend the autonomous position of biology against chemistry and physics by claiming that there are two realms in biology, functional and evolutionary biology, of which espe-

cially the latter would warrant the unique position of biology, I think we wished to defend systems biology against the dominancy of molecular biology and evolutionary biology by emphasizing the autonomy of functional biology when appraised in a systemic perspective. My personal point of view in this matter was primarily motivated by the scepsis I share with Wouters about the usefulness of the etiological theory on functions (function as selected effect). Although only a small minority of biologists are working on evolution on a daily basis, it remains the concern of most philosophers of biology (Callebau, 2012). This normative theory dominates evolutionary philosophical thinking, but it does not do justice to how biologists talk of functions in functional biology.

4. What have been the most significant advances in systems biology?

Emphasizing that the following list represents my personal preferences, the most significant advances in systems biology have been:

- Publication of the Recon-2 human metabolic model (Thiele et al. 2013) and the starting up of a personalized healthcare policy.
- Progress in systems medicine and in network-based drug design (e.g. Haanstra et al. 2011.
- Development of evolutionary systems biology (Soyer & O'Malley, 2013).
- Development of comparative systems biology, a combination of bioinformatics and systems biology (Teusink et al. 20109.
- Development of an infrastructure for facilitating systems biology (ISBE) research in Europe (website: project.isbe.eu).
- Further developments in synthetic biology (e.g. Gibson et al. 2010.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

As a matter of fact, in our edited book we only briefly mentioned design explanations, and were primarily focused on mechanisms, mechanistic modelling and mechanistic explanations, because these lie at the heart of the systems biological approach (Boogerd et al. 2013). Yet, this cannot be the whole story. Therefore, I think it is worthwhile to pay more attention to design explanations in systems biology. As Wouters was primarily concerned with zoology (animals) and gave many examples of design explanations in this field of research, his analyses should

be extended to microscopic organisms (microbes). I expect to find a certain degree of commonality, but also to encounter substantial differences between design explanations for the presence of parts (items, components) in animals and microbes and for the processes (activities, behaviours) they engage in.

In 2005, we — together with Robert Richardson and Achim Stephan — introduced a concept of weak and strong emergence that although rooted in biochemical networks was generally applicable to other complex systems in the natural sciences as well (Boogerd et al. 2005). Furthermore, our account of strong emergence is fully compatible with mechanisms and mechanistic (capacity) explanations. Consequently, by means of mathematical models of mechanisms including systemic knowledge, it is possible to reconstruct and calculate strongly emergent behaviour. In principle, the extent to which systemic knowledge is required for reconstruction of the emergent behaviour can be used as a measure of the strength of emergence (Kolodkin et al. 2011; Kolodkin et al. 2012). As a next step, it will be mandatory, however, to show and illustrate the practical usefulness of such a quantifier of emergence.

By accepting a less anthropocentric view on intelligence, a group of authors, including myself, think that emergent properties of microbes such as memory, anticipation, association, adaption and reflection are all manifestations of some sort of microbial intelligence (Westerhoff et al. 2014) and that such a paradigmatic change in perspective might stimulate new areas of investigation in philosophy and the natural sciences.

Although, as said, I am skeptical about the merits of backward-looking evolutionary theories for systems biology, I would like to adjust and fine-tune my position in this respect, because what is needed in my opinion is not so much the common backward-looking evolutionary theories but instead a forward-looking evolutionary approach, in the way explicated by the philosopher Paul Griffiths (Griffiths, 2009). Moreover, I think that such a theoretical predictive approach of evolutionary theory can be adequately complemented and extended by the perspectives of the new discipline of experimental microbial evolution. Both forward-looking evolutionary theories and experimental microbial evolution fit well into systems biology *sensu lato*. The same applies to evolutionary developmental biology (EvoDevo), which became visible as a distinct area of research in the 1980s, and generally speaking, seeks answers to questions at the interface between evolution and development (Müller, 2007). And actually, substantial progress has already been made in the nascent field of evolutionary systems biology (e.g. Loewe, 2009; Soyer & O'Malley, 2013) in the last ten years (O'Malley, 2012). The website of evolutionary systems biology (website: http://evolutionarysystems-biology.org) shows yet another paraphrase of Dobzhansky's dictum and

one that I can subscribe to: 'nothing in biology makes sense except *when properly quantified* in the light of evolution'. Congruent with Maureen O'Malley, I wonder whether it will be the next step toward a new modern synthesis of evolutionary biology (O'Malley, 2012).

The majority of philosophers of biology only discuss phenomena exhibited by higher organisms, mostly animals and occasionally plants (O'Malley, 2013; O'Malley & Dupré, 2007; Wouters, 2013). In particular, the heart of animals and its alleged functions are topics a philosopher cannot escape discussing, at least so it seems. Remarkably, with a few exceptions, philosophers of biology do not discuss prokaryotic or eukaryotic microbes and their behaviours and properties or take them as examples to show the merits of their philosophical case (O'Malley, 2013). I consider this a serious shortcoming of the philosophy of biology that already in its own right warrants an in-depth study of the philosophy of microbes. I applaud therefore the initiative of the philosopher Maureen O'Malley, who recently edited a special issue of the journal 'Biology and Philosophy' dealing with a philosophy of microbes (O'Malley, 2013). In this respect, also her article in Trends in Microbiology (O'Malley, 2009) entitled 'What *did* Darwin say about microbes, and how did microbiology respond?' should be mentioned as a positive exception. Here she refutes the assumption, common under biologists and philosophers of biology alike, that Darwin had nothing to say about microbes.

Systems medicine is making headway in the 21st century in bringing the systems approach to the fore in a field of research that not so long ago used to be dominated by a rather traditional way of thinking (Geenen et al. 2013; Kell & Goodacre, 2014). Also the related field of personalized healthcare (Deisboeck, 2009) has made important progress with the publication of the Recon-1 (Mo et al. 2007) and Recon-2 (Thiele et al. 2013) metabolic models. The same holds for systems toxicology (Geenen et al. 2012). Finally, the transition from the Human Genome Project (HGP) to the Personal Genome Project (PGP) holds promise for the future (Church, 2005), provided that the corresponding ethical issues will be satisfactorily dealt with (e.g. Lunshof & Ball, 2013; Lunshof & Chadwick, 2011).

I concur with the growing insight that much like many physical illnesses, psychiatric disorders are multifactorial systems requiring a pluralist research strategy (Kendler, 2014) and that systems biology should be one of the pillars for modern research in the field of psychopathology and psychiatry (Buitelaar, 2012; McIntosh, 2013; Tretter et al. 2010; van der Stel, 2009). In contrast to psychology, psychopathology (psychiatry) hardly uses the notion of function or dysfunction. As a functional biologist I think that psychopathology will benefit from incorporating the no-

tion of (dys)function. However, in establishing an appropriate concept of function I and others (e.g. Bolhuis et al. 2011) are of the opinion that one should better not take refuge in the popular, but speculative approach taken by mainstream evolutionary psychology. The idea that current psychology can be understood through evolutionary explanations of psychological functions is controversial. This statement applies even more strongly to psychopathology (van der Stel, 2009). Jaap van der Stel based his foundations of psychopathology primarily on the work of the philosopher Mario Bunge. Bunge's general philosophical ideas (e.g. Mahner & Bunge, 1997)) show substantial overlap with the philosophy of systems biology that I endorse. Furthermore, although Bunge and Wouters worked independently on the notion of function, their thoughts about the various kinds of functions in biology are remarkably similar (Mahner & Bunge, 2001; Wouters, 2005; 1999; 2003; 2013). Therefore, I think it deserves further investigation if and to what extent the notions of (dys)function and function attribution as employed in functional biology are applicable to psychopathology and psychiatry.

In summary, I think the following themes needs to be studied in depth in the near future and I expect considerable progress can be made with respect to all four issues:

1. Ascertaining overarching principles within the philosophy of systems biology *sensu lato* will have a strong impact on the orthodox way of thinking in various fundamental and applied sciences.

2. Putting the innovative, but largely neglected idea of design explanations to the fore in systems biology will give credence to this kind of explanation within the philosophy of biology.

3. Shifting from a backward-looking to a forward-looking perspective in evolutionary biology will give novel philosophical insights underlying experimental microbial evolution.

4. Deriving philosophical concepts from functional biology will benefit systems medicine, personalized healthcare, and psychopathology/psychiatry.

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4

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Enactments of Systems Biology

1. How and why were you initially drawn to systems biology?

My first encounter with systems biology was through a course I was invited to teach on interdisciplinary research skills. The course was created for a doctoral training centre for students with a background in mathematics, physics, engineering or computer science to tackle modelling in the life sciences. The doctoral programme was called the Life Sciences Interface Doctoral Training programme, and I went into it with the idea of adapting philosophy of science concepts and principles for use as 'reflective levers' so that tacit assumptions concerning scientific method in these domains could be articulated. I did not have specific knowledge of biological sciences at the time. Shortly afterwards, but also concurrently for several years, I was involved in a project to study the social dynamics of e-science, and I chose the same area as a major case study. My observations of organisational and institutional features of computational and systems biology offered opportunities to study the epistemology of these domains in the practices of the scientists. I was particularly drawn to questions relating to the roles played by very different modes of visualisation in the different disciplines that are meant to be collaborating for a fully functional systems biology project, and the stories told by the visualisations about interdisciplinarity, the clashes of cultures and the pleasures and pains of collaboration. The visualisations also turned out to be good places to explore what was considered to be an observation and good enough evidence in the different disciplines; finally leading onto the ways that the field of biology is being reconstituted. The visualisations were a good entryway to the crucial role of modelling in systems biology; for me they were the interface that allowed me to glimpse the material, technological and organisational complexity of systems biology that has sustained my

fascination.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

Whereas stabilised sciences enact philosophy, systems biology is writing a new philosophical script for enactment. I am deriving my use of the term 'enact' here from Judith Butler's notion of performativity. Butler's concern is with the social and cultural constructions of gender and sexuality and so the immediate relevance of the term to science and philosophy is probably not crystal clear. However, please bear with me. Butler encourages us to distinguish between something that is acted (like an actor acts a role on the stage) and something which is enacted, which is far more diffuse and not deliberate or consciously thought out. To act according to one or other gender role is enacted, not acted: it is a way of acting, of performing, that is informed by sedimented conventions in the socio-cultural milieu. It takes something like drag to bring out or show up the performative aspect of gender. When science is 'business as usual' it enacts a philosophical framework which is a kind of sedimented convention of the field; the tasks and routines associated with that way of doing science enact an implicit philosophical framework – an epistemology of what counts as evidence and reasons for belief; an ontology regarding the constituents of the world as represented by that specific scientific domain; an ethics regarding its import to science, scientists and the wider social world. Systems biology is not science as usual, or it aspires not to be as it deploys technologies that conceptually reshape the research field in some quite radical ways. We might say that systems biology is the drag of biology (or computer science, or mathematics, engineering or the many other sub-disciplines that it involves), in the sense that it shows up the philosophical enactments of the sciences it rests upon. But in another sense, it is also writing a new philosophical script as it goes along.

Epistemologically, systems biology is highly socially and technologically mediated. Such mediation is not novel: but digital and computational technologies are not like other technological instruments and apparatus, and we have not yet fully conceptually assimilated the precise nature of those differences, neither with respect to the forms of social interactions afforded, nor with respect to the forms of scientific representation and intervention they allow. Computational science that involves modelling and simulation is epistemologically challenging in itself, but when we are dealing with physiological processes, there are further epistemological challenges concerning the knowledge process and outcomes of which methodological challenges are only the tip of the iceberg. Computational tools and technologies have also unsettled the ontology of biology, pushing into prominence questions about the components and levels

of biology, about mechanisms and causes, and how – or whether - to draw the borders of systems.

Systems biology also shows up the social and ethical stakes of biology, right across the board. The ethical issues relating to data should systems biology successfully be scaled up to a systems medicine level, and make increasing demands upon patients and citizens to be data providers, will include the well-known issues of anonymity, confidentiality and, consent.; however, there are other deeper questions in the very ethos of systems biology – another form of enactment, the values and virtues that inform how science is done. For example, systems biology sometimes lays claims to a form of community ethos associated with technologies for sharing and standardising data (Leonelli & Ankeny, 2012); we do not yet know how deep this ethos goes, exactly how it is expressed, nor how it interacts with other aspects of the science (such as ownership and authorship). Another aspect of the ethos of the science, which has not been explored, is the implications for scientists themselves. Here I mean 'ethos' in a broader sense including also values entrenched in the mode of doing science, of being a scientist and the relationship to the domain studied implicit in it. The shift to mathematical and computational methods opens up some new ways of doing biology and of being a biologist, but also shuts down others: for example, the intimacy between biologist and organism described in Evelyn Keller's biography of Barbara McClintock (Keller 2003) becomes less defining of what it is to *be* a biologist, to experience biology, and this too is, I think, an aspect of the broad (or deep) ethos of systems biology that has a certain significance for the field of biology. Finally, on a social level, it is an important question how a systems biological reconfiguration of biology - especially if it succeeds in discrediting reductivism - may affect the ideological purposes to which biology is so often put.

In all of these ways, systems biology will be writing a philosophical script as it writes its scientific script. So it might be expected that philosophers - that is, professional philosophers - should be involved with it, to make sure that the script is a good one, a philosophically sound one. However, I am not so sure that this is necessarily the case. Professional academic philosophy needs to reinvent itself if it wants to *participate* in this process. There are other roles available to it besides participation such as commentary and analysis. But to participate in shaping the domain requires setting aside purely philosophical interests and motivations, and the process can sometimes be more conceptually messy than is normal in philosophy. Firstly, thinking of participation as the application of pre-existing philosophical definitions does not work very well, as they often do not fit the domain practices, unless by *a prioristic* stipulation, which is not useful. Secondly, often things are fairly

indeterminate in this emerging domain and could still go in different directions. It is not always clear in advance whether concepts are used imprecisely or even 'messily' because of lack of expertise with philosophical concepts, or because there just is not a precise concept yet, it is emerging. 'Model', 'represent', 'validation', 'certainty', 'evidence', 'cause', 'mechanism', 'process', 'disease', and many others, are examples of terms that are rather indeterminate in the way they are used in practice, and which do not necessarily do better when pinned down to a definition that works well philosophically. The results are not always of interest to philosophy, especially not academic philosophy as currently defined in Anglo-American philosophy. The gains are in surprises and challenges to find ways of thinking philosophically about innovative scientific methods and techniques in ways that can feedback into the science, and which sometimes may also be of interest philosophically. Pragmatically, this also means working on ways of communicating philosophical thinking in scientific contexts; ethically, it means fully taking on board the responsibility that is implied by making an input. The roles of stinging gadfly or enabling midwife for processes that philosophy stands aside from are not really productive for the philosopher participant. And what is the motivation for being a participant? For me, it is the realisation that there is no set or determinate way that systems biology is, it is still fluid enough for participation to make a difference. So many things about the epistemology, ontology and ethics of systems biology are indeterminate, and could develop in different ways. How it turns out is important scientifically, socially and ethically. Philosopher participants stand a chance of contributing to this formation; still, I think this is a role that, for reasons ranging from disciplinary egos to disciplinary boundaries, we are not yet able fully to take on.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

We know that there has been a shift to mathematical and computational techniques in biology that is reflected in the education of biologists; however this is not at all neutral with respect to what the biology of the future will be. By this I do not mean only that biological methods will be different: clearly also understandings of evidence and the concomitant epistemologies will also shift. But along with this there will be shifts in the conception of biological entities and processes. The question for philosophy of biology and systems biology is: what is gained and what is lost through these shifts? How can one do philosophy of biology that takes on board the implications of technologies for biology as a discipline and as a domain?

In his Notes on Nature, originally written in 1956-7 there is the fol-

lowing cryptic remark by Maurice Merleau-Ponty:

> 'It is not possible to speak of Nature without speaking of cybernetics. Maybe this is only an ultra-finalism without mechanism, but we cannot think Nature without taking account to ourselves that our idea of Nature is impregnated with artifice.' (2003:86)

Like so many other intellectuals of his time, Merleau-Ponty was attempting to respond to the challenge of cybernetics, that peculiar mix of technological and scientific thinking that emerged in the 1940s. Even though he was critical of many of the claims made by and on behalf of cybernetics, this quotation shows him fully taking on board the profound rethinking of nature that cybernetics implied. Systems biology is very closely intertwined with computational methods, in fact some would say that they are inseparable and maybe identical – that is, that systems biology just is computational biology. However, there has not been reflection on the implications of this particular technological mode of investigating nature. So far, the reflections on modelling in biology have not considered what a profound shaping of the conception of the biological is brought about by the technologies of modelling, be they 'organic' or computational technologies. I do not mean by this that we should accept the claims bordering on technological determinism of a book such as *Fourth Paradigm: Data Intensive Scientific Discovery* (Hey et al., 2009); however, it does seem that the witnessing of such profound shifts as have been brought about by technologies for sequencing that made the genome project possible, and the range of computational tools and resources that have made systems biology possible in recent history should elicit more reflection on the part of philosophy of biology and of systems biology. Historians of science (such as Hans-Jörg Rheinberger, Peter Galison and Lorraine Daston) attend to the interconnections between technologies and science, and go on to draw epistemological inferences that have not been taken up and elaborated upon by mainstream philosophy of biology. Yet it seems to me that we must try to elaborate epistemologies and ontologies of biology that are able to address the roles of technologies. This is particularly important in view of the specific nature of computational technologies, which are not mechanistic instruments. As Merleau-Ponty noted for cybernetics, these technologies operate according to a profoundly different logic, and it is this that makes them peculiarly able to investigate the form of non-linear causality that is associated with systems biology: but is this

itself one of the ways in which the nature of systems biology is 'impregnated by the artifice' of its computational methods? This is a question that needs reflection.

4. What have been the most significant advances in systems biology?

The development of the advanced computational technologies that got off the ground with the human genome project, and in particular the development of new statistical, mathematical and computational techniques to make it possible to ask questions at a systems level and open different pathways of investigation, will stand to the credit of systems biology. Here once again, its fate and the way it will be viewed historically are bound up with its technologies. Just as systems biology has shown up the enactment of a philosophy (and sometimes many) in the biological sciences, it also shows up the profoundly social character of science. Here the advances in socio-technical infrastructure in systems biology are quite revolutionary for the science. For example, making knowledge and knowledge processes explicit is required for the integration of data that is characteristic of systems biology but at the very same time the computational infrastructure for doing this is a social infrastructure. The drive for ontologies to systematise knowledge in different domains has simultaneously resulted in platforms for communities to develop shared languages and vocabularies, and thereby identify themselves as communities with a shared stake in the development of these infrastructures and the future of their discipline. These socio-technical infrastructures that have sprung up around systems biology have reconfigured biological sciences in a deep and lasting way.

The fact that through these various socio-technological means, systems biology casts into doubt the central dogma of molecular biology, and proposes plausible alternatives to reductivism are hugely important for biology and for philosophy. Causality and levels will never be the same again, and that is a good thing. For me, the most important significance lies in what systems biology may be able to achieve on a socio-cultural level. Biological sciences play a hugely important role in shaping and legitimating ideologies concerning humans, animals, environment and the relations between them. The different forms of reductivism in biology have played out disastrously in the socio-cultural sphere, where we see an ever greater reliance on the most simplistic forms of natural determinism, that is fed by both methodological and ontological reductivism in science, ultimately resulting in a picture of the human and of society that is limited, skewed and simplistic. Even more importantly, it is a picture that is ideologically problematic, outsourcing so much of the life of humans and other animals to some in-

exorable 'natural' bottom-up linear causality. However it is not at all clear that systems biology will indeed fulfill the socio-cultural potential and loosen the grip of different forms of reductivism. One reason for this is that systems biology does present a more complex picture, which for that very reason is harder to communicate in the public domain. Something like 'the selfish gene' is eminently communicable: it contains within itself thousands of possible stories about how selfishness is exemplified in biology that will all be easily assimilable and apparently true to life – in both the biological and social sense. What are the systems stories that will do as well as the 'selfish gene'?

There is tremendous scope for systems biology to make important contributions to medicine and healthcare, not only promising better treatments, but perhaps also to change our relationship to health and disease. This in turn will be one of the places where the possible systems biology 'stories' will make a socio-cultural difference that could affect quite profoundly our experience of health and disease. Connected to human health is animal health and wellbeing and here systems biology may be on the cusp of making a hugely significant advance. If systems biology succeeds in replacing animal studies (models) with computational models, the shifts will be quite dramatic: not only in terms of the numbers of animals used in research, but in the conception of models in biomedical research (non-human animal, animal, computational), clinical trials, and ultimately in a reconfiguring of the ethical discourse around the use of non-human animal research models. But these are not actual advances yet, only promises. The next question calls attention to why we are not yet there.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

The epistemology of computational modelling – specifically the form that it takes in systems biology – continues to be a challenge both to systems biology and its philosophy. Even though non-representationalist accounts of scientific models have been put forward in philosophy of modelling, it is unclear how they will actually work in systems biology. On the surface, they are very well suited for systems biology, as systems by their nature always point to the limits of representation, which closes off a system, or puts a border around it. This will always raise questions about the placement of the closure or border; it is a kind of performative self-questioning. That is good, it is better than pretending that the representational nature of something – like a model – is unproblematic. Except, of course, that the language of representation is still pervasive in the domain. What is the task of the philosopher-

participant here: to try to eliminate talk of representation or to try to enlarge its meaning? The problem is more than one of terminology, but one of the conception of models (including computational models) that spills over into normative questions of the criteria whereby models are found to be acceptable, or, to use another term that is pervasive in the domain, validated. The conception of a validated model as one that represents a target domain by capturing or describing its features is a crucial limitation of the force of systems biology. Take the issue of original conditions that are often held to be required in order to arrive at absolute parameter values that will parameterise equations that are 'representations' of a process; what counts as the original conditions of an ever variable biological process? The very conception of the equations and the computational models yielded through the simulation of the equations, as representations, forces onto the domain a restriction, a border, that already skews it. However, we do not as yet have an alternative epistemic account of the validation of models. The 'models as tools' conception is a respectable alternative, but we do not yet have an account of what, in this domain, is a *good* tool. The reason for this is that, to date, systems biology has been conducted in a largely mathematical and computer science facing way, and has not sufficiently developed viable methodologies for robust experiment facing modelling. This is one of the greatest challenges facing systems biology, and especially, its development into systems medicine. In order to come to be trusted and used for medical purposes, systems biology must find a way of 'talking' to experiments. The conversations have to happen on the level of science and on the social level: that is, systems biologists have to overcome yet another interdisciplinary barrier and enter into real conversations with clinical and medical researchers, which depend on bringing their methodologies together. But so far, there has not yet been sufficient work done on the methodologies for this to happen, in particular, on how to go about making experiments and models comparable. Comparability cannot be taken for granted, in particular in face of the variability of biological systems. Variability has a different significance in biological and biomedical contexts, since in biology it may be safely dealt with through averages, depending on the specific research question, whereas in biomedicine, understanding and coping with variability is a central aspect of treatment.

If systems biology is characterised by its ability to think across levels and to produce multi-scale models, I believe that the underlying problem shared by systems biology and systems medicine, is the variability of biological systems across temporal and spatial scales (as described more fully in Carusi, 2014). There is a pressing need to develop techniques for measuring, modelling, simulating and analysing it; and for

designing experimental systems that do not blackbox it, but instead let it play out so that it can figure in the models of systems biology. This is how the potential of systems biology may well be transformed into a systems medicine worthy of the name.

In considering the shift towards medical applications, in particular if notions such as the 'digital patient' are to be part of systems medicine, the crucial challenges are social, political and ethical. In biomedicine, issues of variability and validation have a social and ethical significance; while trusting a model in biology may have primarily epistemic importance, in biomedicine it has primarily pragmatic and ethical importance (in the sense of responsibility towards patients). Here, it is important not to limit ourselves to the language of impacts of science on society, but first and foremost to recognise that systems biology and systems medicine already have a socio-ethical character, and are already an expression of particular epistemic, ethical and aesthetic values. How it plays out in healthcare, including how the patient is conceived and encouraged to identify her or himself is not just an external effect of the science, but already inscribed in it. The conception of data and model is critical, if systems medicine is going to depend on patients to be data producers, and is promising to generate patient-specific models. Here the epistemology and ethics of modelling come together, and the language of representation that is currently still so firmly entrenched in systems biology, or whatever alternatives are found for it, will certainly have a non-neutral effect on how patients are encouraged to position themselves and understand their own role in systems medicine.

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5

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Systems Biology, Choices Arising

1. How and why were you initially drawn to systems biology?

I have been a systems biologist from the 1960s on, practically from the beginning of my career. This was of course long before the slogan "systems biology" appeared, and long before its precepts were formulated in modern language. The principle reason (then and now) was that I have always been focused on the fundamentals of the genomic control *system* for development. From those early days it was already unequivocally clear to me that development is a direct output of genomic regulatory information (how I had arrived at that is another story). The only ways available to approach directly what I wanted to know was to try to establish the evidential framework of the genomic control system by study of the genome and its populations of differentially expressed transcripts. My first book "Gene Activity in Early Development" was published in 1968 (Davidson, 1968), and it was largely, by today's definitions, devoted to system level observations on developmental biology, in that its premises were that causality in embryonic development must lie (i) in the multiple functions of the encoded *gene regulatory system*; (ii) in the informational characteristics of mRNA populations; (iii) in how the hugely complex genome works to make development happen. These are of course all fundamental propositions emergent from what we would call today biological control system theory. A main focus of the experimental work I began in the 1960s was measurement of RNA population complexities in eggs and embryos: the concept of the *complexity* of a transcript population is intrinsic to system-level understanding, as it essentially amounts to measurement of the dimensions of the sets of informational transactions underlying the developmental process. mRNA and pre-mRNA complexity measurements were the major focus of the work Roy Britten and I collaborated on at Caltech

throughout the 1970s. This work, and much other that we carried on into the 1980s, also provided quantitative measurements of the dynamics of mRNA synthesis and turnover. All of these studies partook as well of another aspect today regarded as a defining characteristic of systems biology, viz. that it was heavily reliant on mathematical and computational data analysis.

In 1969 Britten and I formulated a *gene regulatory network* (GRN) model called "A theory of gene regulation for higher cells" (Britten and Davidson, 1969), which was the initial forerunner of modern GRN models for control of development. This model was system biology in its essence: it was a distributed gene interaction model in which regulatory genes had multiple targets and target genes were expressed in an integrated, regulatory sequence-dependent way, with provision for signal integration. The conceptual output of the model system was a means of explaining on a large scale the spatial expression of cohorts of genes. This model was based on the minimal knowledge then available about populations of nucleic acid species, and on a much deeper store of descriptive knowledge of the events of development, but mainly just on pure logic, given the requirement that a *genomically encoded control system* must exist.

In 1986 the Third Edition of my "Gene Activity in Early Development" was published (Davidson, 1986). In it could (can) be found a comprehensive review of transcript complexity and dynamics as applied to developing embryos of all model systems for which such data were then available, including the results of the previous two decades of systems biology measurements made on sea urchin embryos in our own labs. This work later provided an immeasurable boost to the effort that in our present time has made the GRNs solved for the sea urchin embryo the most comprehensive and authenticated example that we have for any developing system. But it also coincided with the onset of a period that lasted for a about a decade when the power of recombinant DNA technology and *cis*-regulatory analysis diverted our attention away from system level research and toward the crunching of microscopic processes on the single gene level. Unlike the case for most of my contemporaries, however, this diversion remained for us only partial, in that we continued to study development at a system level as best we could. During that time we used clone library arrays to study differential gene expression on a population basis on the one hand, and on the other we continued a decades' long experimental exploration of the sequence organization and sequence content of animal genomes. We were interested, on a genome wide scale, in the nature, frequency, and spatial distribution of repetitive sequence; and in the disposition and length of single copy DNA; as well as in the rules of sequence conservation on a genome level between related species.

Thus there is nothing conceptually new about systems biology to me, except for the endlessly fascinating new experimental results it generates, and their endlessly new conceptual consequences. The basic precept of systems biology, that a defined living process can only be solved if all the moving parts of the system are known and their interactions are discovered, is what animates the major effort of our last 15 years, which has been to solve and to understand the functions of developmental GRNs. The distinguishing features of this now increasingly successful effort with respect to its predecessors over the decades before are a finally adequate knowledge base, the finally adequate technological potency of the methodologies available, and the development of a solid working theory of GRN structure/function. Our current trajectory is not due to the recent advent of novel ideas about system biology, as systems biology has been my own scientific purview for what is now over half a century.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

Two different aspects to this question come to mind. The first has to do with the total change in epistemological landscape brought about by successful application of the precepts of system biology. Developmental biology throughout the 20th century suffered inescapably from Karl Popper's criticism of inductive scientific process, that all it takes is a single instance to the contrary to prove an inductive mechanistic idea wrong. I am not referring here to the majority predilection in 20th century developmental biology to report exclusively empirical descriptions of embryological events, some of which were very broad, but which no matter how detailed, could provide only factual background. Description can be enormously indicative, but cannot complete the process of doing science, since it generates no causal explanations. In the last century those experimental efforts aimed at revealing islands of causality in developmental biology research were invariably focused on single aspects of an overall process, on single genes, or on single instances, on the tractable minute bits of a system that could be satisfactorily taken down to brass tacks in focused experiments. In fact this became a mantra: the only way to learn how anything really works, it was said, is by isolating from the unfathomable overall system what small pieces of it can be experimentally encompassed, such as specific genes or protein species or cell types, in "clean" situations. Popper used the inductive assumption "all swans are white" as his paradigmatic example of the intrinsic problem in inductive logic, wherein the discovery of black swans in Australia provided an example of a previously unexpected falsification. It can be said that Popper's paradigm is appropriately applied

to most 20th century research on developmental gene regulation, for example, as this was always focused on a given gene or factor or small set of genes or factors, and who could be sure if another Australian black swan would not turn up when further genes or factors operating within the same system would be investigated? But genomics has now changed everything, particularly with respect to the fundamental problems of developmental control systems. Thus the foundation principle of systems developmental biology, i.e., that all parts of the system must be included in mechanistic analysis, in principle and in practice offers a waterproof counter to the concern that it is extremely difficult or impossible to know if black swans, i.e., qualitatively different mechanisms, are lurking elsewhere than in the islands of phenomena thus far chosen for causal analysis. Control of developmental processes is mediated primarily in and by the *regulatory genome*, and all the parts of the regulatory genome that are engaged in any given such process can now be determined exactly. Completed GRN analyses show, furthermore, that the causal interactions executed by most of these regulatory elements of the whole system can be defined. An example is our computational demonstration that the sea urchin embryo GRN is sufficient to predictively explain almost all the spatial regulatory transactions underlying a large portion of pre-gastrular embryonic process (Peter et al., 2012). Systems developmental biology is for this reason completely different, in its epistemological condition, from that which preceded it.

The second point to be made is, however, of less encouraging import. We are currently faced with a set of urgent new epistemological issues, which follow from what systems biologists of my persuasion regard as a perversion of scientific practice, and also a perversion of what "systems biology" should actually mean. Nonetheless, the self-described field of "systems biology" has given protective cover, and beyond that, in government and institutional circles a pseudo rationale, to an enormous enterprise, the object of which is to obtain very large, solely observational datasets that are to be interpreted by ex post facto statistical correlations. This type of activity has even been elevated to the status of the shining new universe of "discovery science" (an oxymoron if ever there was) which at last will supplant the "traditional" chains and bonds of prejudiced, expensive, slow, "hypothesis" testing by the means of the experimental method.

The epistemological issue that arises is not attenuated no matter how elegant the instrumentation, how clever the mathematics, nor how massive the datasets. This is whether scientific causality can ever be established without perturbations of the behavior of a system, without experimental tests of logical predictions of the results of perturbation or change in conditions, i.e., without "experimental hypothesis testing".

Or the ancillary epistemological issues: Do we really *need* demonstrations of "scientific causality"? Is not sufficiently dense correlation *sufficient* as a proxy for "scientific" knowledge? How can the limits of solely statistical inference be a priori defined? Another fundamental epistemological problem that "discovery science" generates is an innate contradiction between conclusions based on statistical deduction from an unperturbed dataset, vs. conclusions based on tests of hypotheses generated by consideration of *prior scientific knowledge*. An inbuilt scientific agnosticism and tolerance of ignorance of prior scientific knowledge is characteristic of "discovery science"; while true science intrinsically progresses by conceptually based operations executed *on* prior knowledge, be these operations deliberate revisions, or challenges, or confirmations, or extensions of the prior knowledge.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

I interpret this question to refer to issues of philosophical import pertaining to the practice of biological science in the late 20th century that have been swept under the rug, or otherwise not yet resolved. Not surprisingly the salient examples, in my opinion, devolve from the branch of bioscience that is the newest, implications of which have not been adequately digested or are just beginning to come into focus. I refer here to genomics. I commented above on the violation of scientific method attendant upon the rise of "discovery science", most of which is presented by its perpetrators as outputs of genomics in both institutional and disciplinary senses. But genomics impacts a far broader set of problems, values, and long range scientific guidance issues than this. In my fields of interest, the regulation of developmental processes and the mechanisms of body plan evolution, it is clear that fundamental causal explanation must begin with genomically encoded regulatory information, because that is where these processes are determinatively encoded. This is producing one of the real revolutions resulting from the advent of knowledge of genomes, i.e., genomics. Looking forward, it seems inevitable that scientific initiatives in this field that fail to provide explanations of developmental or evolutionary processes in terms that encompass genomic information will sooner or later be relegated to boutique status. Or they will become extinct, as for reasons of other kinds of obsolescence have so many sub-disciplines of these fields, even in my own lifetime (think of cell physiology, or cytoplasmic inheritance, or cut-and-paste embryology, or for that matter embryology per se, or of what is now in process of happening with transmission developmental genetics). This also means that just as "zoology" no longer exists, many other sectarian or disciplinary entities are all going to be

subsumed in a single intellectual amalgam that will include regulatory molecular biology, information processing, dynamics, development, phylogeny, genomically relevant portions of cell biology and biochemistry, etc. etc. The organizational, science funding, and science educational policy implications of this sea change are not yet explicit, and are only beginning to be explicitly confronted.

Genomics, in the current confusion of headlong data generation, has produced a deep epistemological contradiction, perhaps even a crisis for thoughtful scientific consumers. It is the following: when something is observed to occur in genomes how is its significance to be considered? If it is observed correctly, i.e., it exists as an actual phenomenon, is it to de facto be regarded as significant? That would mean it is a legitimate, indeed an essential enterprise, to carry out experiments on the experiment, in order to determine what fraction of the observation could be due to random noise in the measurement system, or what artefacts lurk that confound meaningful with meaningless signal. An example is the genome wide observation that extremely sensitive methods reveal transcripts present at 0.01 to 0.1 copies per animal cell, representing a large fraction of the genome. There is completely convincing evidence and argument that the vast majority of such are of zero functional consequence, yet we see articles trumpeting that the human genome is 90% copied into mystery transcripts. Is that science? It depends on how we think about the problems genomics throws up: is science description of what can be apparently observed, or is science description of functions and revelations of how processes have been shown to work? Genomics presents unprecedented problems of significance. We know that gene order is extremely flexible and is subject to continuous scrambling in evolution, within very long range conserved syntenic scaffolds (Holland et al., 2008). Gene order on say a megabase scale is not in general a functionally important parameter of animal genomes, as animal genomes operate similarly with similar genes in differing linear orders. But just like functional aspects of genomes, gene order can be deduced, computed, measured, and described. Regions lacking protein coding genes are described in genomics as "gene deserts", a term that from a functional point of view is scarcely felicitous, given that these "deserts" are packed with functionally meaningful cis-regulatory modules (Montavon et al., 2011). These are trivial examples of what in many ways is the general problem of genomics as a new area of science: how to treat *observed* features in respect to description and observation, as opposed to treating them in respect to their *significance* and *function*. It is only the latter that is the essence of the body of scientific knowledge in other disciplines of bioscience.

4. What have been the most significant advances in systems biology?

The most significant impact is that which I addressed above: systems biology provides the conceptual pathway to carrying out biological research so as to obtain a comprehensive framework view of causality in a process. The basis of this argument is the requirement to determine as accurately as possible the interactions of all components of a system of interacting parts, with the corollary that examination of this or that little part alone will never provide a solution to the way the system operates. We now have proof of principle that this indeed works, as in the sea urchin GRN model cited above, and many network level analyses and models of developmental processes are at present formulating what is really a totally new field. The precepts of systems biology are being played out in this new field, which is reviewed and discussed in respect to all aspects of development in the new book of Peter and Davidson "Genomic Control Process" (Peter and Davidson, 2015).

Unfortunately, the news has yet to spread sufficiently in the byways of professional developmental biology, and the journals remain filled with endless sequences of works focused on system subparts, often entitled "X (a gene or a kinase or an miRNA or some other single molecular species) is required for Y" (where Y is a complex process). But by such routes the small part that X plays in the process Y can never really be known because the operation of the system underlying the process remains in the dark, except that it fails if the activity of X is blocked. It is hard to predict how this fundamental epistemological conflict will be resolved. In basic developmental biology research, enlightened funding policy may eventually pull the plug on "X is required for Y" projects, but in applied research, particularly medically oriented research (or research that is purportedly medically relevant) powerful forces continue to mandate this type of approach.

Technological and instrumental advances of major general import can be attributed to the influence of systems biology. The need for measurements on many moving parts of a system at once has utterly transformed research. Thus, *none* of the stock in trade technological approaches we now live with and on, such as QPCR, high throughput sequencing, genome wide assays, transcriptomics, library scale gene perturbation, etc., and all the elegant computational methods for data reduction ancillary to these methods, were with us only 20 years ago. One would have to be blind to history not to acknowledge the potent role systems biology has played in driving the development and proliferation of technologies that have in common their ability to produce accurate data on large numbers of genes or transcripts or sequences at once.

In terms of the practice of basic research, I think that the ideology of systems biology (including here the epistemological strains of systems biology research that preceded the wide use of that name per se) have had a major impact on attitudes toward logic relations in regulatory molecular biology. For much of the 20th century, classical genetics provided the major exemplar of science that generated functional logic relationships. If a mutation of a given gene produced a given effect, we knew that this gene played a causal role somewhere upstream of that effect. Logic so clear was hard to find in any other branch of experimental developmental biology. As focus on the roles of regulatory genes grew from the 1980s onward, and molecular biology afforded identification of genetically defined functions, genetic epistasis relations were ensconced in "swirling arrow" diagrams that purported to show regulatory inter-relationships, "direct or indirect". But it can be said that systems regulatory molecular biology has supplanted this whole approach, powerful and illuminating as it was, with something entirely different. Gene regulatory network analysis has the specific aim of distinguishing between direct and indirect causal relationships, since delineation of the linkages in GRNs requires exactly that form of knowledge. Not only could genetically perceived interrelationships not distinguish direct from indirect relationships, but many functional parts of regulatory systems were for one or another good reason blind to a priori genetic identification. Here again systems developmental biology militated toward molecular instead of genetic methodologies, in its insistence on beginning with as complete as possible parts list. This discussion locates one of the most significant advances with which systems developmental biology must be credited. Systems regulatory biology has resulted in the substitution of causal molecular analysis, the object of which is exact as possible identification and measurement of networks of regulatory interactions, for the prior stock in trade which was epistatic logic pyramids that devolved from genetic observations.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

I interpret "problems" in this question to refer to difficult and infelicitous turns of event that might have devolved from systems biology, and that are of philosophical import; that is, I assume that the question concerns what might be considered the "problematic" consequences of systems biology. The following such problem does not at all *necessarily* follow from the concepts of systems biology, but it has nonetheless turned out to be a major attribute of systems biology as practiced in the USA and Europe. This is the institutionalization of systems biol-

ogy in very large organizational units, such as both academic and .org "institutes". These are supported by combinations of direct funding instruments set up by government, or by very large institute-oriented government support, or by institutionally dedicated endowments. That is, the research generated by these large system biology institutions is not primarily or exclusively supported by small investigator sponsored ad hoc research grants, as is most basic bioscience. The reasons this has occurred are many and various, and proper analysis would require a large scale historical inquiry into current science funding policies, into the dynamics and quality of decision making in institutional scientific centers, and into the relation between top down management of large institutions and the nature of their scientific output. The internal attributes of systems biology that have contributed to this outcome are obvious however: they include the pressure for high powered, expensive instrumentation and computation facilities, for large scale datasets, for large collaborative projects that involve a great many authors many of whom are primarily technological contributors. But it is the consequences of this organizational feature with which I am here concerned rather than its causes. The main consequence has been to push systems biology ever more strongly in the direction of applied science. This is due to feedback relations, which have the canonical property of self-perpetuation. The primary one is the feedback between the size and therefore expense of running large institutions on the one hand, and the availability of relatively enormous amounts of government and private money for support of targeted, applied research of perceived practical (and commercial) benefit on the other. A second feedback relation links large group enterprises with targeted technological objectives defined a priori that are trendy and attract political and organizational support. But targeted technological objectives in research institutions can be antithetical to creativity. I do not here refer to technological creativity, which may flourish in these conditions, but to exploratory conceptual creativity, suffocated by institutional inflexibility, and by institutionally mandated umbrellas of conservative, defined objectives that are usually couched in terms of a proprietary institutional technology.

Much of the mass of large scale systems biology research is medically oriented. This is for the above reasons, but for other reasons as well, in addition to the heavily torqued allocation of resources toward medical ends. Descriptive, large scale correlative compilations of physiological and medical measurements are used to generate valuable diagnostic reference bases, and this requirement synergizes well with the predilections and capabilities unique to systems biology. Furthermore, since we cannot do experiments on humans, the type of high powered correlation analysis that systems biology generates for resolving large

scale datasets provides an apparent substitute for experimental extraction of causal relations. Thus we see repeated claims that computational inference from analyses of unperturbed human cell types of medical significance can reveal their underlying gene regulatory networks (e.g. (Novershtern et al., 2011). In this domain, in other words, sophisticated (and increasingly large and expensive) efforts that are philosophically akin to "discovery science" are powered by systems biology methodologies, operating under the constraints of applications of direct medical relevance.

Let a hundred flowers bloom, as Mao said (with what proved to be entirely malevolent intent); I do not believe that any of the above should be suppressed, as there is no question that these productions of systems biology have yielded unprecedented benefits. The datasets they have produced are of unprecedented usefulness as research resources, and their impact on the technological potency of applied biology, medical and otherwise, is also unprecedented. But I do believe that systems biology is just as much also the path to the future of genomically oriented basic research, and in fact it is the only path that can work. Thus it is an essential lynchpin for the future of basic science. Its precepts always have provided an invaluable, in effect revolutionary guide, for relatively small, entirely independent research enterprises directed at basic causal knowledge, such as my own. Yes, system biology does display a "problematic" tendency toward mega-scale applied science research units. But that is in no way exclusive of the other uses of this cohort of what are essentially *epistemological* precepts for doing bioscience. For systems biology is not only a set of approaches and a technological locomotive, it is also the particular state of mind that, going forward, will successfully orient the most important and meaningful basic research.

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6

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An Affinity to Theories in Biology

1. How and why were you initially drawn to systems biology?

Environmental concerns underlie my early interest in systems. In the 1970s and 1980s it became apparent that environmental issues are often related to a multitude of influencing factors. At that time Frederik Vester (e.g. 1980) began to popularize system thinking in exactly this context. I read several of his books dealing with current issues in ecology and other disciplines, where I found that understanding the behaviour of systems is of paramount importance. I was intrigued by questions such as: Are more complex ecosystems (i.e. systems with a higher number of interacting species) more stable than others? As an ecology student, with a background in mechanical engineering, I attended all the system courses I could find (not very many). It was also the time when the Santa Fe Institute popularized research in the field of complexity. This awakened my interest in applying system approaches in different areas.

Shortly after completing my doctoral thesis in the field of biomimetics I had the luck to get in contact with Rupert Riedl (e.g. 1978, 2000), based on a shared interest in system thinking. Already looking back at a successful career, he wanted to investigate the roots of his system approach in the theory of evolution and how it connects to system theory and evolutionary epistemology. I considered this an interesting endeavour and we started to work on it. Rupert was a student of Ludwig von Bertalanffy in Vienna and a friend of Paul A. Weiss, starting back when they were professors in the US (North Carolina and New York, respectively). Both Bertalanffy (e.g. 1932, 1952) – the father of General System Theory – and Weiss (e.g. 1970, 1973) – an eminent system thinker in biology in the early 20th century – had a huge impact on Riedl's work.

After Rupert passed away, I had no more first-hand information about the history of system thinking in biology. Hence, I had to do some historical research. I found the considerations in theoretical biology – es-

pecially those of Bertalanffy – fascinating. They can teach things that no student of biology gets to hear today. Furthermore, this theoretical biology is tightly connected to system thinking. The organism cannot be understood without considering it as a system, as an organization of tightly interconnected parts and processes.

At the time when I was conducting this research, the field of systems biology gained momentum. It was simply natural to see what was going on there and to compare that with earlier system approaches. In my opinion it was clearly of interest for systems biologists to get to know what ideas others had already come up with (cf. Pouvreau & Drack, 2007; Drack & Wolkenhauer, 2011), even though they lacked the data and tools we have today.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

My personal experience is that younger people in science are often very focused on their research topics and consider philosophy as an oddity about which they know very little. This is very often harmless, but when it comes to more in-depth discussions, I wish that the university curricula in the sciences would provide more space for philosophy. By this I do not necessarily mean metaphysics, but rather that some basic understanding of logic and epistemology would be very useful. At the very least it would be helpful to know that there are different strands (e.g. realists or constructivists) in philosophy and how they are distinct. Students should also be familiar with concepts such as explanation, mechanism, or the character of a model. It seems that the older scientists get, the more they are interested in philosophy. Accordingly, there are also many researchers in systems biology who see the value of interacting with philosophers (Boogerd et al., 2007).

In general, I think philosophy is gaining importance in biology, and biologists nowadays listen to philosophers. A bit unfortunate for biology is that the philosophy of science was for a long time dominated by the influence of physics. Physics was seen as the prototype of science – which in some respects it is – but this approach hindered examining certain crucial characteristics of biology. Hence, many important issues (e.g. the concept of organisation) that are very important for biology in general, and systems biology in particular, were neglected.

Kant outlined many interesting issues involving concepts, such as system, self-organization, teleology, etc. and today these are also relevant for systems biology. Kant mentioned for instance the reciprocal influences among the parts within an organism: the parts of a "thing as a natural product" (organism) "should so combine in the unity of a whole that they are reciprocally cause and effect of each other's form" (Kant,

2010:§65). Here it becomes apparent that philosophy has already addressed questions that are also relevant for science. Looking back at such philosophical considerations is therefore crucial for science in order to get a clear view on basic questions. Of course, this is not relevant for many sophisticated, detailed models in systems biology. Nonetheless, keeping the big picture in mind is definitely an advantage.

Systems biology and a compatible philosophy deal with dynamic events. An atomistic philosophy and scientific approach are not feasible. It is insufficient to study the "atoms" of an object under investigation in isolation and try to combine the results afterwards. The "atoms" behave differently in isolation versus as parts of a system. The dynamic approach in philosophy goes back at least to Heraclitus, and entails a long debate.

Approaching phenomena in which multiple factors are influencing the behaviour of a system is, to my understanding, a core issue of systems biology. In science the usual approach is to change only one parameter at a time and register the outcome. This is not sufficient for understanding system behaviour. Scholars have attempted to tackle this task by introducing *gestalt* or field concepts. Today there is an increasing interest in network-causality, top-down and bottom-up causality. It is important to investigate such concepts also from a philosophical perspective. Finding inconsistencies and contradictions early on is always a good thing, and philosophy can help considerably in this endeavour. What types of explanations are acceptable and what are not?

What I find remarkable in this context is that philosophy of science today is descriptive rather than prescriptive. In the early 20th century some philosophers knew exactly what science is and what not, and how to proceed in research. In several biological disciplines today, they would rightfully criticise research for its questionable theoretical and methodological basis. For instance: Data do not speak for themselves. Hence, a mere data driven approach would just reflect a naïve understanding of science. For such issues philosophy of science is indispensable.

3. What do you consider the most neglected topics and/or contributions in late 20th century (philosophy of) biology?

To my notion, the focus of interest in philosophy of biology in the late 20th century was very much on evolution, leaving aside other philosophically interesting fields in biology. In more recent years there has been, however, a shift from mere consideration of the theory of evolution to other fields as well. Developmental biology and molecular biology have increasingly become a focus of philosophers. There are also philosophical threads where basic concepts are being studied in detail;

e.g. the organism concept – which was largely neglected in the past decades. The basic characteristic of an organism, namely its organization of parts and processes, is reflected more broadly in philosophy today. In the early days of biology and philosophy, many important issues were already tackled, such as the concept of teleology (from Aristotle to Kant and others). Unfortunately, modern research has tended to neglect the discussions of such issues.

Biology has enjoyed a major boost in the last decades on the molecular level, mainly due to novel methods that enabled ground-breaking research on that level. Many highly relevant insights have been gained. At the same time, organismic biology has been marginalized. Systems biology can in this respect play a role as a bridge between the molecular and other levels of the organism. Defining systems biology solely at the molecular level seems to be an unnecessary restriction that limits the impact of the field. Of course one has to consider the history of systems biology, the methods and available data, etc. And it is natural for new tools to be fully applied in science. Nonetheless, one must be aware of what can be done with such tools, and – perhaps more importantly – what cannot be done with them. This is nothing new. With microscopes, people have "seen" many things that turned out to be illusions. Importantly, this is not saying that systems biologists have a narrow view – in fact, systems biology has a broad range from highly abstract approaches (Wolkenhauer & Hofmeyr, 2007) to medical research (Sonnenschein & Soto, 1999). Overall, however, there are research threads that focus very much on the molecular level and others that integrate more to systems biology. Interestingly, the term "systems biology" was, in the late 1960s, coined by Mesarović (1968, 77), and he was sceptical about simply applying engineering principles to biology and about merely considering one level of organization. Certainly, today's systems biology is not a direct descendent of Mesarović's approach, but his thinking is also relevant for what was later independently termed systems biology.

When considering neglected topics in biology as a whole, one definitely needs to mention morphology. Even though it provides the basis for understanding the objects that biologists are dealing with, it is largely ignored – both as a practical field as well as with regard to its theoretical and philosophical underpinnings. Morphologists have provided important results, for instance those pointing to constraints in evolution. This, in turn, is connected to certain unchangeable interdependencies of system parts – both the dolphin and the giraffe have seven cervical vertebra. Such constraints, together with their molecular basis, are being investigated by what is today called "evolutionary systems biology". Accordingly, investigating the organism as if it were an

aggregate of independent parts – a hidden assumption in many works in evolutionary biology – is not well grounded.

Concerning the philosophy of science, I think important work has been done on clarifying the meaning of mechanisms, explanations, and emergence. What I miss is more work on the levels between molecules and the organism; also considered with a perspective from philosophy. Half joking, one could consider this as the vital gap in knowledge between the molecular level and the whole organism; "vital" because this refers to specific biological phenomena in living organisms.

Knowing Bertalanffy's approach, I also find it strange that there is no longer a big effort in building theories in biology. Most researchers are apparently happy with hypotheses that apply to their narrow fields. Sure, the task is not easy, but history shows that it is possible to discover and formulate theories even in biology. Philosophy, to my understanding, should try to integrate findings from all different areas of biology, leading to a big picture, an overview. Here, I think, lies a major potential for philosophical considerations to also fruitfully contribute to biology as a science.

4. What have been the most significant advances in systems biology?

There are numerous important success stories in systems biology. Even though the term did not exist at that time, the approach and method were already present in the Hodgkin-Huxley model dealing with conduction and excitation in nerve cells (Hodgkin & Huxley, 1952). Another important work that also started before the term systems biology was well known, was the modelling of the dynamics in the beating heart by Noble (1962). Here, computers already played a role in calculating the dynamics. The modelling of the cell cycle had a more recent impact (Novak & Tyson, 1993). Clearly, there are more advances involving applying methods of system theory, system dynamics, cybernetics, etc. to biological questions, which can be subsumed under the term systems biology. Many of those methods were already developed decades ago, but could only be applied recently due to today's (relative) simplicity of certain experiments and measurements.

In a broader and perhaps more important sense, there has been a paradigmatic shift due to systems biology: dynamics (in time) has been brought back to biology. Since a majority of the phenomena in biology have their basis in processes, underlining the importance of dynamics cannot be overestimated. It seems that biology has undergone cycles of emphasis from static to dynamic issues and back again. Analogous to the recent shift is a shift from a rather static morphology to a dynamic morphology, or from static gene maps of genes and phenotypes to dynamic interactions among the genes. Similarly, systems biology

again emphasizes the process character, currently mainly on the molecular or cellular level. Processes are, however, present on every level of living beings (cell, tissue, organ, organism, ecosystem) even though they require considering different data. This makes a mere (molecular) data-driven approach too narrow. Moreover, it is becoming increasingly apparent that an interplay of multiple factors has to be considered for understanding certain phenomena. Systems biologists already try to include various factors, such as physical forces or the interactions between tissues. This is a welcome trend.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

On the practical level, one important problem is that certain measurements are difficult to perform. It is relatively easy to measure concentrations of molecules. This already becomes harder when measurements over a time course are necessary. The situation becomes even more complex when spatial inhomogeneities have to be measured. The latter are also a challenge for modelling, because this approach calls for partial differential equations or models with compartments. Many uncertainties or unknowns come into play here. Research becomes even more challenging when factors such as geometric shape or physical forces need to be integrated.

There are also challenges on a conceptual or theoretical level. The comparison of natural and engineered systems, or the transfer of methods and concepts from technology to biology are helpful as heuristics, but also have their limits (Alon, 2007:2, 238). Looking at biological phenomena solely from a physicist, chemist or engineering point of view – and indeed many systems biologists come from such fields – is too narrow for many questions. This is not to say that systems biologists are ignoring specifically vital phenomena, not at all. Nonetheless, looking only through the lenses of the prevailing methods and concepts entails the risk of not recognizing potentially relevant issues. Being driven by available methods, such as molecular data acquisition, rather than conceptual issues, can also result in a constrained mode of explanation. I think that the Chinese boxes-diagram of Weiss (1973: 11) serves as a good illustration for a research program that includes all levels in the hierarchy of the organism viewed as a system. The diagram shows concentric circles including genes in the middle and is surrounded by levels such as tissues and organism, and others in between. There are arrows from each level to the others, and arrows are drawn in both directions, up and down. Each arrow indicates the potential influence of one layer upon another. Such potential influences should be considered in the first

place. They do not necessarily play a role for many questions, but they should definitely be considered for others. Determining whether there is an influence of one layer on the other and what kind of influence that may be (chemical, mechanical, electrical, etc.) is a task for empirical research. "It is a matter for methodical research to replace the arrow symbols of our diagram by concrete information; but to ignore them, erase them mentally, or just give them names, will certainly not do" (Weiss 1973, 13).

Integrating different levels of organization is both a practical as well as a conceptual challenge. Questioning the current boundaries of systems biology seems to be necessary; a task that is critical for science as well as for philosophy of biology. What questions can be tackled with the prevailing conceptual framework and the available data, and where are the limits? One problem when considering only the molecular level is that the organism might be conceived as a micro-precise or micro-mechanistic machine in which all the higher levels are exactly determined by the behaviour of the molecular parts. Weiss demonstrated that this is not the case with examples from embryology, where the variance in the whole system is smaller than the variance of the parts (Weiss, 1973: 41). For questions in other fields of biology, this may play a lesser role, but it should nevertheless be considered. This constant order in the gross despite relatively large freedom of the parts is also an interesting issue for philosophers.

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7

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Interdiciplinarity, Philosophy, and Systems Biology

1. How and why were you initially drawn to systems biology?

My route to systems biology was indirect. I don't think I ever heard the term as an undergraduate (1988-1992) or graduate (1993-1998) biology student. In the US, at least, systems biology didn't emerge as a prominent area until after I had exited the field for philosophy. So it was another decade or so before I encountered systems biology. While training in philosophy, I found it necessary to put my experiences in biology to one side. There was very little connection between the biology research I had done, which was mainly molecular and cellular (with some evolutionary, comparative, and organismal work on the side), and the philosophical concepts and debates I learned about in my second round of graduate study (2000-2007). It actually interfered with learning philosophy of science, to try to relate its ideas to my experiences in biology laboratories. Accordingly, I took a hiatus from all but evolutionary biology during those years of training. Philosophy of biology, I found to my surprise, is to a great extent philosophy of *evolutionary* biology, and even more particularly, philosophy of evolutionary *theory*. So I learned a lot about that area in the course of my philosophical training. But that track didn't lead me to systems biology, although the field was emerging at just that time (early 2000s). I began to look at systems biology in 2010, a few years into my first position as a philosophy professor at Rice University. It was, I think, the first biological field I learned about entirely as an 'outsider' – that is, through reading and talking to practitioners rather than working in it myself. I was fortunate to begin these conversations as Rice was building its program in systems and theoretical biology.

All this autobiographical background may seem extraneous to the question. But it is in fact relevant, because the enormous gap that I found between experimental biology and philosophy of science goes

to the core of why I find systems biology philosophically interesting. Systems biology today is explicitly framed as an integration of different scientific methodologies: experimental molecular/cellular biology, on the one hand, and mathematical modeling informed by principles from physics and engineering, on the other (e.g., Kitano, 2002; O'Malley and Dupré, 2005). Although philosophy of science has been slow to engage ideas from engineering, it has a longstanding emphasis on physics. A great many current debates in (so-called) general philosophy of science are based almost exclusively on episodes from theoretical physics – including recent discussions of models and modeling, laws, explanation, and scientific realism. So there is intellectual kinship, so to speak, between one side of the interdisciplinary merger that is systems biology and mainstream philosophy of science. The other, complementary side of systems biology is very closely related to the fields I initially trained in: molecular and cellular biology. Although technologies have changed, the core aims and methods on the experimental side of systems biology are continuous with those of late 20th century molecular biology (itself an approach that ramifies into many areas of biology, including studies of development, genetics, immunology, virology, and cancer biology). Systems biology, in aiming to integrate these two strands of scientific thought and practice, presents a magnificent opportunity to both broaden philosophy of science and to better understand the relations between biology and physics, theory and experiment.

What drew me to systems biology was, therefore, its interdisciplinary aspect and connection to the sciences I know best. All my research projects are concerned with the gap that divided the two halves of my intellectual life, between philosophy of science and experimental biology. One other feature of my approach to systems biology also bears mention here. My initial engagement with systems biology was as part of a larger project on philosophy of stem cell biology. Philosophers of science had previously been silent on the subject of stem cell research – an instance of the more general disconnect with experimental biology noted above. My goal was to articulate conceptual issues and challenges for stem cell biology from a philosophy of science perspective, showing how new philosophical accounts of models, evidence, causality, and explanation bear on stem cell research today (Fagan, 2013). In the context of that project, I approached systems biology in a deliberately partial way, focusing on its relation to stem cell biology. This stance is likely to be different than that of other philosophers interested in systems biology, in that it places a field of experimental biology squarely in the foreground. This is not to dismiss other approaches to systems biology, but only to note this distinctive feature of my own stance.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

The most basic feature of this relation is implicit in the wording of the question: "inform each other." Any fruitful interdisciplinary connection should be mutual; a 'two-way street.' This point is not specific to systems biology and philosophy, of course, and one might dispute whether there needs to be a genuine interdisciplinary link between these two fields at all. However, in my view philosophy and systems biology have distinctive features that make the prospect of such a relation between them valuable and interesting.

I will first say a bit about how I understand philosophy. (There are probably more views about this than there are philosophers.) In my view, philosophy is abstract reflection about general questions. If you keep asking questions about why things are the way they are, or how things should be, about any topic whatsoever, eventually you're going to be doing philosophy. So every field of knowledge has an intrinsic tie to philosophy; there is no sharp line dividing philosophy from other kinds of inquiry. In this sense philosophy is transdisciplinary, or perhaps anti-disciplinary. Asking and trying to answer basic questions is one of the ways we express our humanity. Creative art is another – or perhaps philosophy is a kind of creative art, consisting in the exercise of reasoning skills to the edge of our abilities. Art or no, philosophy so conceived is something anyone can do, if they're lucky enough to have their physical necessities provided for and some spare time. A few of us do philosophy for a living, but these professional efforts do not exhaust philosophy. They do, however, comprise a mode of philosophy that has the features of a discipline, within which philosophy of science is located. Philosophy of science is the sub-discipline of philosophy that focuses on philosophical questions arising in science: general issues about evidence, explanation, models, theories, *etc*. Exactly what relation philosophy of science should bear to scientific practice itself is a contentious issue, although my own preference (which I expect is shared by other philosophers contributing to this volume) is to engage actual science rather than idealized philosophical constructs.

Systems biology involves new configurations among a number of scientific fields, including molecular biology, physics, computer science, and engineering. These changes raise questions about methods, models, norms, standards, education, and aims – all the components of what Kuhn termed a "disciplinary matrix" (a disambiguation of his more famous term, "paradigm"). Insofar as systems biologists seek to answer these questions explicitly and reflectively, they are engaged in philosophy. Philosophers of science are interested in many of the

same issues, though at a greater remove. Systems biologists approach questions about their disciplinary matrix from an unavoidably interested perspective, and their individual answers are likely to be those that make use of their own skill sets and benefit their own lines of research. The same is true for philosophers of science, of course, but our stake in particular answers for systems biology is lower. So the rise of systems biology creates a situation in which philosophers' and systems biologists' inquiries converge but don't precisely coincide. In the space between these two perspectives is opportunity for fruitful exchange that can enrich both discussions. Philosophers of science, as noted above, can gain a richer understanding of core topics like modeling, explanation, and laws by attending to systems biology. Systems biologists, in turn, can gain broader perspective on the value-laden debates about aims and progress in their field by attending to the work of philosophers of science. In the rest of this section, I discuss a few philosophical ideas that could be useful to systems biologists.

Many systems biologists (and educated people generally) are familiar with Kuhn's accounts of paradigm and scientific revolution. What is less known outside philosophy of science circles is that Kuhn's ideas have been fruitfully modified and extended over the past 50 years. One of Kuhn's important insights concerns the role of shared values in scientific communities. Shared values, encompassing basic background assumptions about knowledge, understanding, evidence, and methods, allow members to refine and deepen their inquiries without the distraction of continuously arguing over fundamentals. But Kuhn saw a community's shared values as part of an indivisible package dominated by a theoretical world-picture: a paradigm providing a rigid monistic framework for doing "normal science" (1962/1996). Paradigm change, according to Kuhn, involves a comprehensive shift from one scientific world-view to another, analogous to a Gestalt shift in perception. This account doesn't have much to offer systems biology, apart from identifying different values as a problem for integrating scientific communities. The idea that scientific fields can productively combine certain aspects of their practice to form a new integrative field of study has no place in Kuhn's account of scientific change. Recent philosophy of science, emphasizing the pluralistic, piecemeal aspect of scientific research, as well as the variety of scientific models and modeling practices, has much more to say. One way this philosophical work can inform systems biology is by making explicit the issues involved in coordinating different scientific communities, and so identifying ways to enhance their integration.

A useful philosophical concept along these lines is the notion of a "boundary object:" an entity (abstract or concrete) that helps transcend

communicative gaps across social worlds (Star and Griesemer, 1989). Boundary objects perform this role by being open to diverse interpretations satisfying different sets of values, yet also retaining a recognizable common core. A model well-suited to play this role for systems biology is Waddington's landscape (1957): a simple diagram representing development as an inclined surface etched with branching valleys (developmental pathways) descending to multiple discrete termini (Figure 1).

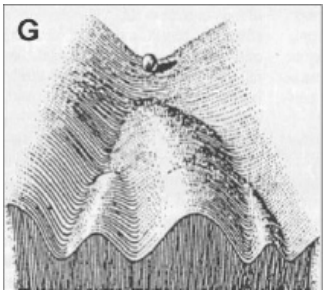

Figure 1. From: The Strategy of the Genes, Waddington CH, 1957, Taylor & Francis, reproduced by permission of Taylor & Francis Books UK.

Waddington's landscape can represent results of both mathematical modeling and experimental manipulation of cell development (Fagan, 2012). One prominent mathematical modeling approach in systems biology begins with a network diagram representing molecular interactions thought to underlie and control cell development. Translated into a system of equations, the model is studied to reveal the network's dynamical behavior, which can be represented as an arrangement of vectors and attractors. Adding a stability dimension to this state space yields a landscape (rendered in 3d for simple networks or via principle components analysis). In this way, systems modelers can derive a landscape 'from the ground up.' The experimental approach, in contrast, begins with many different manipulations of cell development, which reveal causal connections between molecular components and cell phenotypes and behaviors. Results of many such experiments can be grouped together as distinct pathways on a landscape, 'annotated' to correlate cells' developmental potential with their morphological and molecular features. The landscape model is thus a point of contact between the two approaches, and so can provide a shared focus for collaborative effort in understanding cell development. Waddington's landscape is not unique in this regard, but exemplifies the kind of simple model that could help integrate mathematical modeling and experimental methodologies in systems approaches to a variety of biological phenomena.

Another way philosophy can help systems biology achieve its integrative goals is by diagnosing failures and problems. For example, although many experimental biologists are interested in high-throughput data and regulatory motifs, they ignore some theoretical proposals by systems biologists. One such case is a proposed definition of stem cells in terms of dynamical systems models that reproduce characteris-

tic stem cell behaviors *in silico* (Huang, 2011; Furusawa and Kaneko, 2012). Experimental stem cell biologists have consistently ignored these proposals, to the modelers' increasing frustration. This failure to communicate, in my view, is at least partly due to the different standards of explanation endorsed by the experimentalists and modelers in this case (Green et al., 2014). Philosophers of science have proposed a number of different accounts of explanation, which help to clarify the situation. The dynamical systems modelers in this case are committed to something like the traditional covering-law account, which states that a phenomenon of interest is explained by deriving a description of its occurrence from a general law (in this case, principles of dynamical systems theory) and initial conditions. In contrast, experimental stem cell biologists aim at mechanistic explanations, which describe how some overall system (the stem cell) works in terms of its interacting parts (DNA, protein, and other molecules). Philosophical accounts of covering-law and mechanistic explanation, respectively, can identify points of dispute that remain implicit in scientific debates – or, as in this case, prevent debate from even beginning. Value-laden commitments to explanation via derivation from general principles, or via accurate depiction of the details of causal relations, can hamper efforts at integration, if the communities involved do not recognize their differences. Philosophers of science are well-positioned to make these issues explicit and indicate positive solutions. (I return to this issue in the response to Question 5).

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

I will discuss two neglected topics in philosophy of biology, which bear on its relation to systems biology. Philosophy of biology coalesced as a distinct field in the latter 20th century, and from that time has overwhelmingly concentrated on topics pertaining to evolutionary theory. But many biological fields have little connection to evolutionary theory: molecular, cellular and developmental biology, biochemistry, biomedical fields such as virology and immunology, and many others. So there has been a kind of catch-all neglect in philosophy of biology, of 'everything but evolution.'[1] The standard rationale for this pro-evolutionary bias at the expense of other fields is Dobzhansky's maxim, "Nothing in biology makes sense except in light of evolution." This is a very tendentious claim to accept without argument, however, and it

[1] This statement is, like so many other generalizations in biology, an oversimplification. Philosophers of biology have had a lot to say about genes, and the relation between classical and molecular genetics. But evolutionary topics have been dominant, until very recently.

is hardly the case that philosophers of biology view all such claims by scientists as probative for their own inquiries. A more plausible (and nicely reflexive) explanation is the founder effect: the scholars who established philosophy of biology in its current disciplinary configuration worked on evolutionary topics, and this has become entrenched. An unfortunate byproduct of this one-sided engagement with biology is that philosophers of biology can do little to address the deep divide between studies of ecology and evolution on the one hand, and the fields of biochemistry, molecular, cellular, and developmental biology, on the other. These two branches of biology are in my experience largely separate, and the persistent gap impoverishes biology and limits our perspective on a variety of issues (including health and environmental concerns). Yet philosophy, the field arguably best-suited to help bridge this gap, is corralled on one side of it. Philosophical attention to systems biology has helped redress the imbalance and broaden the scope of philosophy of biology. The onset of discussions of evolutionary systems biology, however, raises concerns that the longstanding philosophical bias will reassert itself, with evolution again taking center stage and other biological fields examined only in relation to it (as in 'evo-devo').

A second neglected topic in philosophy of biology - and philosophy of science more generally - is experiment. Philosophy, at least in the Anglophone world, has a longstanding bias toward theory and a correlative tendency to de-privilege experiment. 'Theory' – its structure, laws, and confirmation - was the organizing concept of mid-20th century philosophy of science, which relegated experiment to the means of acquiring data for hypothesis-testing. Hacking's and Franklin's work in the 1980s positioned experiment at the center of key debates in philosophy of science – but only experiments in physics. Experiments in biology have received greater attention since Machamer et al's influential 2000 paper, which proposed causal mechanisms as the centerpiece of a new approach to philosophy of science. Their 'new mechanist' approach is grounded on case studies of molecular biology, cell biology, and neuroscience – so philosophical interest in mechanisms also helps correct for neglect of non-evolutionary topics, discussed above. However, the tendency to privilege theory (particularly mathematical theory) over experiment is still prevalent in philosophy of science, extending to recent work on models and modeling. This raises concerns that philosophers' engagement with systems biology will heavily favor the mathematical modeling aspects, placing experiment in a secondary and neglected role. The situation is complicated by the sociological fact that many systems biologists are trained primarily as modelers, with little background in experimental biology, and are understandably interested in securing a place for their methods in established approaches to bio-

logical questions. The project of promulgating mathematical modeling in biology dovetails with longstanding philosophical biases. Philosophers should attempt to calibrate this situation, rather than falling back into neglect of experiment. Insofar as systems biology is committed to genuinely integrating mathematical modeling and experiment, the standards of experimental approaches cannot be ignored or assumed to be secondary.

4. What have been the most significant advances in systems biology?

Systems biologists will be better able to answer this question. Examples that come to mind are those I have learned from systems biologists: improved understanding of the significance of noise for biological phenomena; engineering of regulatory gene circuits in bacteria, insights into the circadian clock; identification of ATF3 as a regulator of innate immunity; analysis of global properties of networks representing yeast and E. coli metabolism. From my own perspective, I would like to shift the focus of the question a bit, to query the idea of 'significant advances in systems biology.' Much of what has been written on this topic is about *potential* advances: possibilities for future impact and outcomes, rather than concrete scientific achievements. For example: "systems biology is the promise of biology on a larger and quantitatively rigorous scale, a marriage of molecular biology and physiology" (Szallasi et al., 2010, ix), "systems biology…is set to revise many of the fundamental principles of biology, including the relations between genotypes and phenotypes" (Noble, 2010, 1125). Aspirational statements of this sort are entirely appropriate for the early stages of a field. I want to suggest, in addition, that the conceptual orientation that grounds such claims, systems biology's distinct constellation of aims and methods, can itself be considered a scientific advance. Clearly, it is not an advance in the usual sense; it's not an experimental or theoretical result.[2] But a broader notion of scientific progress is worth considering, at least. Systems biology is a positive response to the end of the Human Genome Project, a fruitful reformulation of goals and methods that builds effectively on previous results. It provides a platform and spur for development of new experimental and computational tools, fosters closer connections between science and engineering, and infuses biology with new ideas from other fields. We might well say that a different way of thinking about biology – a new perspective on methods and aims – constitutes an advance.

That said, there is a way of framing systems biology as a conceptual

[2] I am not denying here that systems biology has made such concrete advances. I am examining a slightly different question.

advance that is misleading and should be avoided. It is often stated that systems biology inaugurates a new 'systems-level' approach to biology, in contrast with reductionist molecular studies of isolated molecules and linear causal pathways. For example, the Systems and Synthetic Biology Initiative at Rice University, in a 2010 presentation to university administrators, states that "systems biology introduces a paradigm shift in biology from individual molecular components to their interactions and resulting dynamical properties." The conceptual distinction here, between isolated molecular entities and dynamically interacting components comprising a complex system, is real and important. But it is not true that experimental biology to date has focused on individual molecular components or simple linear causal pathways among them. Immunology, for example, has focused on molecular interactions (e.g., antigen-antibody) since the early 20th century, and relationships between molecular, cellular, and organismal properties have been central to the field for decades. The same is true for studies of cell physiology and organismal development, which incorporate molecular concepts and methods in order to study higher-level systems. This is not to say that systems biology has nothing new to offer biology. What is new is not a focus on dynamically-interacting components of complex systems, however, but rather the methods and concepts deployed to analyze them: high-throughput experimental techniques; mathematical modeling and computer simulation; analogies from electrical and other forms of engineering; *etc*. Failure to recognize the distinction between "what is new, and what is good"[3] in systems biology misrepresents, and thereby alienates, the experimental fields that are natural partners for the mathematical side of systems biology.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

Systems biology is premised on interdisciplinary collaboration of mathematical modeling and laboratory experimentation, and the application to biology of concepts and tools from physics, computer science, and engineering. The project raises a number of philosophical questions: How should concepts and methods from different fields be combined? What standards should govern systems biology? What is the aim of integrative systems biology, and how should we understand its value? All these questions must be resolved, for the field to move beyond the

[3] *Cf*. Samuel Johnson: "Your work, Sir, is both new and good, but what's new is not good and what's good is not new." The situation for systems biology is not so dire; it is just that not all that is good about systems biology is new.

heady stage of hopeful manifestos and begin to deliver on its ambitious promises. To succeed, systems biology needs to integrate effectively with areas of biology that have gone before and are proceeding alongside it; i.e., experimental research in molecular, cell and developmental biology, broadly conceived. How to manage these interdisciplinary or inter-field relationships is a key problem for systems biology, which philosophers can help resolve (albeit with the caveats noted above). Here I will discuss what I see as the main challenges to achieving effective integration, as well as reasons for optimism.

One reason to be optimistic about systems biology's prospects for striking an effective balance among multiple methods is that the field is highly pluralistic and diverse. The label 'systems biology' covers a wide range of projects with diverse influences, ranging from efforts to discover physical laws in biology to using mathematical models to suggest experiments to identify components of molecular mechanisms. Such pluralism is well-motivated, especially in these early days of systems biology. A variety of different ways of integrating experimentation and mathematical modeling, and diverse associated concepts, should be tried out to see what works. Philosophers can play a role here, in characterizing and assessing these different strategies. MacLeod and Nersessian's empirical study of the organization of different systems biology laboratories, and its scientific upshot, is important work along these lines. Their series of papers (discussed elsewhere in this volume) indicates a number of challenges for integrative systems biology, grounded in detailed empirical study. My own work has focused more on systems explanations of biological phenomena, using philosophical accounts of explanation to clarify obstacles to integration and suggest solutions.

There are at least two kinds of obstacle to integrating modeling and experimental approaches in systems explanations of biological phenomena. The first, discussed above, is commitment to different standards of explanation (see response to Question 2). For example, experimental stem cell researchers find (some) dynamical systems models of stem cells deficient, because the latter abstract from molecular details and do not offer guidance for future experiments. The mechanistic explanations that stem cell biologists seek accurately describe certain features of molecular components and interactions. For dynamical systems modelers, however, abstraction from molecular details is an explanatory virtue – the goal is to identify simple general principles that underlie cell behavior. On this view, prevalent among systems biologists, experimental results need to be explained by rendering them predictable according to some general principle. The features that each group prizes in explanations of cell behavior are unsatisfactory for the other. Similar

oppositions arise in the kinds of data needed for each approach to move forward by its own lights. Commitment to different standards makes it difficult for experimental biologists and mathematical modelers to recognize one another's scientific aims and achievements. But even if these differences are made explicit, tradeoffs among the different methods will likely persist. To offset these, points of interdependence between modeling and experimental approaches should be identified, helping to knit the methodologies together despite persistent tensions. For example, to explain cell development, both approaches are needed. Mathematical systems models depend on concrete experiments, both for construction and for prediction. Mechanistic explanations of complex biological systems, based on experiments, depend on mathematical models to explicate the link between interacting molecules and behavior of the whole (Fagan, 2012; 2013). Other cases can easily be found (e.g., Green et al., 2014).

A second obstacle to integrative systems biology is a 'monistic' attitude to explanation and scientific method more generally. Trends in philosophy of science can reinforce this problem (see the response to Question 3 above). Many philosophers share the view that there is one correct account of scientific explanation – whether law-based, mechanistic, unifying, *etc*. Coupled with the traditional philosophical focus on mathematical theories and models, this monism is likely to be expressed as emphasis on theoretical and mathematical modeling aspects of systems biology, with experimental approaches relegated to the role of providing data. It would be unfortunate if philosophy of systems biology reprised the impoverished view of experiment that predominated in mid-20th century accounts of scientific method. On the flipside, it would be unfortunate if experimental biology eschewed new concepts and modeling techniques for understanding biological phenomena. But if the latter are not seen as relevant to or benefiting ongoing experimental inquiries, then systems biology will fail to find a foothold in mainstream biology. It is important for theoretically- and mathematically-inclined systems biologists to recognize that experimental biology is progressing handily by its own lights, unencumbered by the naïve reductionism that is often attributed to it. 'Imperialistic' claims about systems biology that suggest the activity of integration is all one-way, with mathematical models and theoretical concepts (e.g., robustness, modularity) simply imposed on experimental fields, are likely to alienate biologists who might otherwise find the prospect of systems biology exciting – as many philosophers rightly do.

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8

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Problems in Mathematizing Systems Biology

1. How and why were you initially drawn to systems biology?

Perceiving myself as a philosopher of science and mathematics, influenced mainly by Immanuel Kant and his critical philosophy approach, which requires philosophy to keep up with current developments, it was inevitable that I was drawn to systems biology. To be more precise, it is computational systems biology using "mathematical concepts […] to illuminate the principles underlying biology at a genetic, molecular, cellular and even organismal level" (Surridge, 2002, 205) that interests me. It is the ongoing shift *from science to computational sciences* (Gramelsberger, 2011) on which my research has focused for many years, and computational systems biology is an excellent case along with meteorology, physics, chemistry, and other disciplines. However, I have to say that I am less interested in the scientific concepts of biology than in biology's transformation into a computational science, and that biology has long been second to my studies. Originally interested in computer modeling and the simulation of climate change, initially biology became a supplementary, comparative field for studying the conceptual and the infrastructural differences between the two disciplines. Nevertheless, for a few years now biology has drawn me in completely.

The differences between meteorology and biology as computational sciences are huge and I will start by outlining some of the main differences. While meteorology has a long history of using computer models – Lewis F. Richardson computed by hand the first numerical weather forecast in 1922, while Jules Charney, Ragnar Fjørtoft and John von Neumann completed the first weather forecast using electronic computers in 1948 – biology can claim no such history. Of course, computational systems biology is not the first attempt to use mathematics in the field, but it is the first systematic and holistic attempt at the mathemati-

zation of biology as far as I can see.

While meteorology has been the subject of internationally coordinated community activities since the 19th century– the first International Polar Year took place in 1882 and 1883, and since 1990 the international Atmospheric Model Intercomparison Project (AMIP) has compared model experiments for the assessment reports of the Intergovernmental Panel on Climate Change (IPCC)–the situation of modeling and simulation in biology more resembles the new frontier of the 'wild west' (with apologies to biologists). There are thousands of models out there, most of which are not comparable with each other, as modeling is still an individual practice in biology. Each institute, each researcher creates his, or her, own model with slightly different notions and meanings. Biological "models published in peer-reviewed journals are often accompanied by instructions for obtaining the model definitions. However, because each author may use a different modeling environment (and model representation language), such model definitions are often not straightforward to examine, test and reuse" (Hucka et al. 2003, 525). Community efforts like the development of the Systems Biology Markup Language (SBML) have just begun. This makes the field of biology interesting for its nascent community developments, while efforts to establish a community of models have already found some success in meteorology, mainly in the 1990s.

But the most interesting difference for me is the following: The complexity of meteorology as the physics of the atmosphere is by no means comparable to the complexity of biological systems. Current weather and climate models consist of a dynamic core based on seven hydro- and thermodynamic equations in order to compute the main seven variables of the atmosphere (temperature, wind velocity in three directions, air pressure, density, and humidity). Although this dynamic core exhibits complex behavior due to the seven non-linear partial differential equations, a seven variable problem would not help a computational systems biologist much. It would be sufficient for a genetic regulatory network consisting of three genes, four repressor proteins, and their mutual interactions. It is the complexity of biology that makes it such a thrilling case study for philosophy of science and mathematics.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

It is precisely this question of complexity which should provoke extensive philosophical interest–and of course has done so from Kant to this day (Kant ,1790; Bechtel & Richardson, 1993; Krohs & Kroes, 2009). It was Kant who made a clear distinction between biology and physics. Although resolvable into parts, living beings, as he said, exist for the

sake of their whole and therefore cannot fall under the rule of physical laws. This problem in particular drove early biological research on complex systems in Vienna around the 1920s and 1930s. Biologists like Paul A. Weiss and Ludwig von Bertalanffy tried to understand living beings as systems and their behavior as a "Systemreaktion" (Weiss, 1925; von Bertalanffy, 1932; cf. Drack, Apfalter & Pouvreau, 2003). Bertalanffy, who later became the founder of *general systems theory*, aptly remarked in 1968 that "the living cell and organism is not a static pattern or machine like structure consisting of more or less permanent 'building materials' […, but] an 'open system'" (von Bertalanffy 1968, 158). Bertalanffy's open system approach was conceived in distinction to Norbert Wiener's concept of feedback regulation, biologically articulated by Walter B. Cannon as the concept of homeostasis (Wiener, 1948; Cannon, 1929, 1932). For Bertalanffy "the cybernetic approach retains the Cartesian machine model of the organism, unidirectional causality and closed systems" (von Bertalanffy, 1968, 163). However, mathematical models of biological systems employ the same Cartesian machine approach, as for many centuries mathematics has coevolved with physics, but not with biology. Unfortunately, mathematizing biology means physicalizing it. What can be observed at this time is a struggle for adequate mathematical methods (see Question 5).

The problem becomes most prominent in synthetic biology. As the "design principles" (laws) of regulatory networks are not known, the answer is to engineer organisms. Or in other words: To subordinate organisms under a mathematically and technically controllable dynamics (Endy, 2005). Wiener's feedback regulation is experiencing a comeback in terms of non-linear oscillators (Goldbeter, 1975; Elowitz & Leibler, 2000). Thus, instead of understanding biological complexity, synthetic biology focuses on establishing artificial temporal regimes by designing strong prompters, tags, and other wet tools in order to make organisms behave computationally (Gramelsberger, 2013; Kogge & Richter, 2013)– pointing *towards computer aided design (CAD) of useful microorganisms* (Tomita, 2001).

What is missing is a conjoint research endeavor by biologists and philosophers to explore systems understanding and complexity. As far as I know, the system biologist Olaf Wolkenhauer initiated a conjoint research project with philosophers a few years ago, but much more transdisciplinarity would be desirable.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

Most philosophers, like most biologists, are not fond of mathematics and information science. It is no surprise that systems biologists and synthetic biologists usually do not come from biology, but from engineering or physics, respectively. The question is: Which lesson can be learned from this? Particularly because the computer has become the dominant tool in science, most scientific knowledge has been rearticulated in terms of algorithms, almost every measurement device is equipped with computer chips, and so on. The current discussion on "big data"–like most philosophical debates on modeling and simulation–only scratches the surface of the tremendous change science is undergoing in general. Analyzing algorithms and mathematical techniques are not usually part of philosophical studies on big data, modeling, and simulation. Nevertheless, these algorithms and mathematical techniques increasingly shape the epistemic objects of science. To give an instructive example from meteorology: The automatized measurements of the ozone layer did not record the ozone hole for several years, because, according to the algorithms, the values measured were lower than the margin of error. Not until researchers looked "personally" at the raw data did the ozone depletion become noticed. However, the story is a bit more complex, hiding deeper problems associated with the heavily mathematic-laden "nature of the satellite retrieval problems," which are "critically dependent on the availability of prior information" (Bhartia 2009, 216). Nevertheless, once it was finally "discovered," the ozone hole initiated large-scale, international activities in the mid-1980s, culminating in the ban on the production of chlorofluorocarbons. For many environmental scientists and politicians these successful international agreements marked the shift to intergovernmentalism as a role model for global activities to combat anthropogenic climate change.

It is a bit simplistic to say that algorithms deconstructed the epistemic object of the ozone hole, but this example offers a perfect illustration of the influence of today's machine algorithms on science. Another simplification would be to say that in global climate models it is always drizzling, because a climate model is a mathematical object that generalizes and averages everything. Due to generalizing and averaging, fish in ocean models are more like fish soup than anything else. Fish have become interesting for climate researchers because they consume CO_2 carried by plankton. The "fish parameter" articulates rises and drops in CO_2 as a relation between fish and plankton: plankton die at a rate equal to the number of fish squared. Although the examples are simplistic, the message is the following: The meaning and significance

of algorithmically reconstructed objects and phenomena suffer strange transformations due to mathematical techniques. Understanding these transformations is important for understanding the nature of computational science. This holds for mathematical models as well as for CPU-directed measurement methods.

4. What have been the most significant advances in systems biology?

In terms of computational systems biology the most significant advances have been in collecting "quantitative data." The debate about the "data deluge" accounts only for "qualitative data" on phenomena like the functions of genes, pathway maps, and protein interactions. Quantitative data on concentrations of metabolites and enzymes, kinetic parameters and dissociation constants, and flux rates are lacking–not to mention fine-grained and cross-category quantitative measurements. Without adequate quantitative data simulation, results become fictional. Therefore, advances in quantitative measurement methods are urgently required. Electrophysiological techniques (i.e. patch-clamp single-channel recording) as well as fluorescence microscopy have made the collection of quantitative data practicable (Swedlow, 2013). This significance is underlined by the 2014 Nobel Prize in Chemistry for Eric Betzig, William Moerner, and Stefan Hell for their development of super-resolved fluorescence microscopy.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

The most important problem seems to me that mathematizing biology means physicalizing it. What the century-old coevolution with physics means for mathematics and why biology is challenging this coevolution is a core question for philosophy of science and mathematics. I just recently grappled with this problem and tried to discuss it with mathematicians working in the field of systems biology. I will attempt to outline the main line of thought: It was the mathematician Felix Klein who summarized the state of the art of late-19th-century mathematics in 1895, which opened the way to new mathematical concepts and subsequently to the early-20th-century breakthroughs of quantum mechanics and the theory of relativity. He pointed out that the spirit of modern mathematics was borne by the observation of nature. In order to overcome static Euclidian geometry, motion was introduced from physics into mathematics by the invention of calculus by Isaac Newton and Gottfried W. Leibniz in the 17th century. However, as Klein continued, only in his day had the foundations of this new mathematics been established in a rigorous manner by Richard Dedekind's program of

arithmetizing mathematics and by his own program of reunifying geometry using group theory (Klein, 1895). If the outcome of the invention of calculus was that spatial and temporal developments of systems became mathematically describable (differential equations), then the modern version of motion articulated by group theory tremendously expanded the capacities of mathematics to grasp changeable states. It was the "trick" of the late-19th-century mathematics to grasp change not in a static environment, but as invariances in dynamic environments. Quantum mechanics and the theory of relativity are typical, highly abstract theories of invariance and covariance.

However, the concept of motion describing developments introduced from physics into mathematics is a very simple one. This was already recognized by Bertalanffy as well as by current system biologists like Hiroaki Kitano. Defining a system as a complex of interacting elements, physical and biological systems differ from each other in every respect. While in physical systems the elements "are those which are the same within and outside the complex; they may therefore be obtained by means of summation of characteristics and behavior of elements as known in isolation" (Bertalanffy, 1968, 54), in a biological system "large numbers of functionally diverse, and frequently multifunctional, sets of elements interact selectively and nonlinearly to produce coherent rather than complex behaviours" (Kitano, 2001, 206). Elements in physics are neutral entities, on which interactions can be functionally projected. This is different in biology, where the entities involved (genes, mRNA, proteins, metabolites, etc.) change due to their role in a biomolecular network. Furthermore, biological systems are "organized systems" exhibiting a hierarchy of system levels. Finally, the notion of relation is not unidirectional, but bidirectional and multicausal. What Kant called "wholeness" Bertalanffy called "non-summativity." Thus, a biological system cannot be built up like a physical system "step by step, by putting together the first separate elements" (Bertalanffy, 1968, 67). Nevertheless, this is precisely the logic of building up systems mathematically and computing them step-by-step.

For instance, the "virtual self-surviving cell" – the first (*in silico*) minimal cell based on the 1.0 beta version of *E-Cell*, which was accepted as an open source project by the bioinformatics.org in 2000 – was built by combining 127 (105 protein-coding genes and 22 RNA-coding genes) of the 480 genes of *M. genitalium* (Tomita 2001a). The *in-silico* cell can take up and metabolize glucose through the glycolysis pathway and produce ATP as an energy source, which is, in turn, consumed for protein synthesis. All of the activities result from 495 reaction rules for enzymatic reactions, complex formations, transportation, and stochastic processes, which are executed in parallel by telling the *in silico* cell

what to do at each millisecond time step. Thus, the virtual self-sufficient cell can be used to study the temporal patterns of changes and to conduct experiments, e.g. real-time gene knockout experiments, since the advantage of an *in silico* cell is that it is computable, traceable, and interactively accessible.

The question is: Do whole-cell simulations like *E-Cell* introduce the notion of organized complexity to compensate for the physical bias of mathematics? The answer is clearly: No! Whole-cell simulations are collaboratively developed advanced software machineries that interconnect all kinds of computational schemes and strategies. *E-Cell*, for example, combines object-oriented modeling for DNA replication, Boolean networks and stochastic algorithms for gene expression, differential algebraic equations (DAEs) and flux balance analysis (FBA) for metabolic pathways, stochastical differential equations (SDEs) and ordinary differential equations (ODEs) for other cellular processes. Thus, complex systems are built in a bottom-up process by innumerable computational schemes merely bypassing the core challenge of biological complexity by mimicking organized complexity (Gramelsberger, 2013a). The enormous capacities of today's supercomputers turn bypassing into an accessible and attractive strategy. But bypassing through simulation completely misses the decisive point and contributes to physicalization through mathematization. All of the above mentioned computational schemes originally emerged from physics and have been transferred to biology by the modelers–physicists and engineers. Not a single computational scheme or mathematical technique has originated in biology. However, this is the thrilling challenge for biology to inspire a new mathematics.

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9

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Towards a Methodology for Systems Biology

1. How and why were you initially drawn to systems biology?

When finishing my undergraduate studies, I worked on mathematical models simulating the behavior of immune cell populations during allergic reactions. I entered the domain of biology with the mindset of a theoretical physicist. I had been taught that in physics, or at least in theoretical physics, the ideal is to start with only a minimum of specific empirical data, and that models are considered beautiful if they are derived from very general assumptions. I had learned, for instance, that Einstein obtained his groundbreaking theories of relativity by thinking very hard about the conceptual foundations of space and time. Concrete experimental results, such as those produced by the Michelson-Morley-Experiment, may have served as important triggers or tests, but did not enter his theories as proper ingredients. Given this ideal, I assumed that purely theoretical models on their own can do important scientific work in biology as well, and I thought that people in biology prefer experiments mostly because of their aversion towards mathematics. During my PhD at an institution of experimental research in molecular biology and medicine I had to learn about the essential role of experiments, and that models without data are extremely weak in biology.

I was drawn to systems biology because it held the promise to create fruitful interaction of theoretical and experimental modes of inquiry. At a conference on stem cell biology I attended a talk by the systems biologist Sui Huang which made a big impression on me. Huang tried to apply ideas from dynamical systems theory to the field of cellular differentiation, drawing on the work of people like Conrad H. Waddington and Stuart Kauffman who understood cell types as *attractors* of the dynamical network of cellular regulation. In this picture the development of the cell corresponds to the unfolding of the dynamics of this network

and terminally differentiated states correspond to stable equilibria, or attractors, of the system. Differently from Waddington or Kauffman, however, Huang was able to connect these ideas to actual experiments, notably with the use of microarray technology. Using microarrays, the state of the cell over time could be visualized via its transcriptional profile, thereby generating 'holistic snapshots' that showed the coherent behavior of the cell at the system level and suggested the existence of cellular attractor states. Since then I have been intrigued by the question how such coherent, and seemingly simple, emergent behavior can be reconciled with the traditional perspective of molecular biology that focuses on specific localized mechanisms. I think that there is no easy answer to this question, and the gap between the local and the global perspective remains. Probably, it ultimately is an empirical question that will have to be addressed experimentally in some way we cannot yet imagine.

But there are not only those two extreme perspectives. Both ideas, that molecular biology is only looking at individual parts and that systems biology is able to achieve understanding of the "whole", are oversimplified. I started looking at various other approaches in systems biology, and I found that they often rely on very different assumptions about the underlying organization and complexity of living systems. While systems biologists typically argue that the "traditional" approach is overwhelmed by the flood of data produced by genomics experiments, they often do not admit that they cannot directly cope with the full complexity of living systems either. Some systems biologists argue, for instance, that Occam's Razor is not an appropriate guideline for biology at the molecular level and that complex and integrated organization of many molecular players is the rule rather than the exception. However, this is not a stance that can possibly serve as a fruitful research strategy, even taking into account the availability of sophisticated analytical tools and increasing computing power. When taking a closer look at what those same systems biologists actually do in their own research, one realizes that they also have to rely on a variety of simplifying assumptions and idealizations in order to arrive at manageable research problems. The lesson I have drawn from this is that there is not one unique and best strategy to approach the complexity of living systems, at least not with the current state of knowledge. The "traditional" approach represents one particular, and often successful, way of dealing with biological complexity. Discovery in traditional molecular biology has been based on the assumption that the living cell is decomposable into relatively small functional subunits that can be studied largely independently from the systemic context. Another assumption is that these subunits, or mechanisms, are organized in a relatively simple way and can be un-

derstood largely without quantitative reasoning. This is not to say that each and every molecular biologist *actually believes* that these assumptions are justified. Yet without certain simplifying assumptions there is simply no possible starting point for discovery. Drawing on people like Herbert Simon and William Wimsatt, I have used the term "heuristics" for strategies like those, whose role it is to break down the complexity of discovery. What is interesting and new about systems biology, in my opinion, is its potential to propose alternative strategies that *replace* some of the underlying assumptions of the traditional research program with other assumptions that in certain contexts may turn out to be more adequate. The idea underlying my philosophical work was then to analyze and classify systems biology approaches in terms of the sets of heuristic strategies that they apply.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

I think that systems biology represents an interesting case study for the philosophy of science, and that the work of philosophers of science regarding systems biology can be relevant not only for systems biology but for the life sciences in general. Systems biology is interesting in particular because many of its proponents seem to be making a philosophical move themselves, for instance by describing systems biology as representing a "paradigm shift" or as a "holistic" alternative to a conceptually misguided program of "reductionism" etc. A kind of consensus has emerged from the rhetoric that systems biologists put forward, according to which traditional molecular biology has confined itself to the study of the parts of living organisms, whereas systems biology aims at understanding how those parts interact to produce phenotypic properties and behavior. This schematic distinction enables them to equate the two labels of 'molecular biology' and 'systems biology' with competing philosophical perspectives: molecular biologists dissect organisms, list their parts, and try to explain biological function solely in terms of individual molecules or genes. Molecular biology implicitly follows a reductionist perspective by assuming that the whole is captured by the sum of its parts. Systems biologists, by contrast, realize that the interactions between the parts and the systemic context in which the parts are embedded have to be taken into account and take into account that biological systems show emergent behaviors in which 'the whole is more than the sum of its parts.' But while there may be a clash at the conceptual, or rather at the rhetorical, level, the scientific practice tells a somewhat different story. While in theory the opposition between reductionistic molecular biology and holistic systems biology seems clear-cut, in practice everything becomes extremely messy and

intermingled. As I have already discussed above, even within systems biology there is a multitude of different ways of envisaging biological complexity that lead to different styles of doing research. Unfortunately, the oversimplified rhetorical statements have considerable influence on the way in which science is organized and resources are allocated. For instance, the Federal Ministry of Education and Research in Germany invests in large funding schemes to establish systems biology as the "standard method" in the life sciences, even though it is not at all clear what this means. It should be obvious that scientists when commenting on these issues are rarely neutral observers. Especially those who identify themselves as systems biologists have strong interests in justifying and promoting their own perspective. As a consequence, they are prone to equate 'systems biology' with the particular scientific approach they are currently pursuing, and, on the other hand, to give an oversimplified picture of the traditional approach of molecular biology. Philosophers of science, as hopefully unbiased observers, might be able to assist in clarifying these debates and thereby to contribute to a more adequate evaluation of the prospects of systems biology.

Regarding more specific aspects of methodology, there are a number of issues raised by systems biology to which philosophers might contribute (and already have). There is, for instance, the question of "big data" and how to organize, analyze, and integrate large and heterogeneous sets of information. What roles do the statistical tools play that are developed and applied to cope with this information and what are their underlying assumptions? To what extent can we say that approaches based on such tools represent "unbiased" or "data driven" modes of research? Another interesting topic is the impact of computational modeling and simulation on biological research. Do computational models actually explain biological phenomena or are they merely helpful tools that facilitate the discovery of mechanisms? Should we strive for models that include a lot of molecular detail, or are simple "toy models" more valuable? When we simulate complex biological processes at the computer do we actually gain biological understanding even if we cannot follow the inferential process that produces the result? On the other hand, if we work with toy models, do they actually tell us anything about biological reality? And how does the "new" systems biology relate to traditional applications of systems theory and mathematical modeling to biology?

Furthermore, systems biology has introduced, or rediscovered, a number of concepts that are worth being studied from a philosophical perspective. Philosophers can engage in conceptual clarifications, for instance with regard to vague or controversial concepts such as "emergence", but they may also study concepts simply because they are philosophically in-

teresting. One example in this context is the concept of robustness which also provides connections to other fields that are heavily discussed by philosophers of biology such as evo-devo. Systems biology also brings in new metaphors to the study of living systems that are borrowed from fields like engineering, control theory, network theory, or computer science. For some systems biologists these concepts and metaphors mainly serve as tools to simplify or conveniently represent their ideas, while for others they refer to important biological properties or even point towards general "design principles" in biology. The dialectic of this double role played by many such concepts in systems biology provides some particularly fascinating topics for philosophers of science.

It must be mentioned, however, that systems biology is also problematic as a case study for philosophers since it is a very young field most of whose results have not yet stood the test of history. In many regards it is more convenient to study scientific developments from a certain temporal distance and with an idea of where they are going. In particular, one can, with hindsight, analyze the reasons for success or failure of particular approaches or research programs. Since the ultimate fate of current approaches in systems biology is uncertain, philosophers are often forced to take scientists' assessments of their future prospects at face value. However, this is not a problem that arises from systems biology's specific nature, and it basically affects all philosophical investigations of contemporary science.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

Regarding biology in general this question is impossible for me to answer. Biology is such a vast field, and each subfield presumably has neglected topics and contributions of its own. Regarding the areas that I am not entirely ignorant about, I have the feeling that what is generally neglected is the systematic investigation of the biological assumptions underlying some typical patterns of inference. Molecular biologists obviously pay close attention to the details and peculiarities of the mechanisms they are studying, but a lot of their claims are based on problematic generalizations, for instance from animal models to humans, or from conditions of cell culture to the complex physiological context of a multicellular organism. Even though experienced scientists usually have well developed intuitions for assessing the credibility of claims that are derived from results obtained with different techniques, there is, as far as I can see, no systematic method to weight evidence coming from sources of varying reliability. An important reason why the problematic assumptions underlying the practice of biological and biomedical research are rarely studied lies in the way in which science

is organized and funded. It is clearly more popular to study a pathway in a mouse model that is assumed to be relevant for the discovery of novel cancer therapeutics than to systematically investigate the similarity of pathways between mouse and human. Scientists are encouraged to publish results that appear immediately relevant according to external criteria, at the expense of engaging in more careful studies that would create the foundation for more reliable knowledge in the long run. However, the advent of genome wide experiments has the potential to make such systematic studies much easier, and I think that one important role of systems biology should precisely be to investigate the extent to which the assumptions underlying traditional modes of research are justified.

Turning to philosophy of biology, I do not have a straightforward answer either. The early debates in the 1960s and 1970s favored topics from evolutionary biology, while paying less attention to other fields such as molecular or cell biology. However, the philosophy of biology has diversified considerably over the past decades. Along with a general turn towards scientific discovery and practice, philosophers of biology have increasingly studied features of experimental biology, and in particular those features that reveal important differences to the idealized image of science underlying logical empiricism, which had dominated philosophy of science in the first half of the 20th Century. One important lesson to draw from this kind of work is that scientists are not ideal rational agents, but as human beings their cognitive abilities are limited, and these constraints are relevant to an appropriate philosophical analysis of science. Importantly, scientific change is influenced by a wide variety of factors that are not amenable to logic alone and that can only be fully appreciated when taking into account the historical and social dimensions as well. Yet even though in general I am in favor of paying close attention to scientific practice and to the less formal aspects of scientific reasoning and action, I have the impression that there is a tendency in current philosophy of biology to engage with science in a largely descriptive and conceptually not very rigorous manner. Especially when dealing with a young field such as systems biology, where there is an opportunity for fruitful interaction between philosophy and science, philosophers should have the ambition to produce work that can be taken seriously by and is potentially relevant for scientists as well.

4. What have been the most significant advances in systems biology?

It is obviously still very early to properly answer this question. I think that a lot of the research in systems biology is still in an exploratory phase where many different approaches are probed, some of which are more promising than others. In general, research in systems biology has

destabilized some of the assumptions that were commonly held about the organization of biological systems without necessarily providing dignified replacements. But that, in my opinion, is nevertheless progress.

Important scientific results can either increase or decrease the complexity of research problems within a given domain. On the one hand, there are results that lead to a better understanding of complex processes by reducing them to a common pattern. Unification of this kind may lead to concrete strategies and entire research programs of discovering and explaining phenomena. An example for this might be the discovery of the double-helix structure of DNA by Watson and Crick and the subsequent formulation of the central dogma of a unidirectional flow of gene information. On the other hand, there are findings that contradict such unifying schemes, thereby opening up a whole new space of possibilities and revealing aspects of the actual complexity of a domain. This can be exciting but also frustrating at times because such findings often prevent straightforward strategies to tackle certain problems. The discovery of alternative splicing, for instance, has pointed biologists towards new levels of gene regulation and significantly increased the potential complexity to be considered in the study of biological systems.

I have the feeling that in systems biology one can often observe a tug of war between such 'simplifying' and 'complexifying' advances. Network approaches provide interesting examples for both of these. The analysis of large molecular networks using graph theoretical methods seemed to provide a powerful conceptual framework to gain understanding and to obtain manageable representations in spite of the size and intricate connectedness of these networks. The discovery of "hubs" as critical elements in these networks, and more generally of hierarchical structure, opened up the possibility of getting at fundamental principles of biological organization. And in particular the idea of "network motifs" revived the hope that we can explain the behavior of large and complex systems by focusing on smaller units. However, these approaches have been put into question from within systems biology itself. From a methodological perspective it has been argued, for instance, that inferences from presently available data, which only describe subnets of whole networks, can be misleading. Other work has put ideas from network theory to direct experimental test. A particularly fascinating example is the study by Isalan et al. (2008) who managed to rewire the gene regulatory network of *E. coli* in many different ways and found the organism in the majority of cases to remain viable, even when central hubs were affected. This suggested that the bacterial network, at the global level, is much more robust and plastic than expected, which rendered attempts to understand it by focusing on more

manageable substructures problematic.

In general it seems that systems biology is constantly exploring alternative ways of reducing the apparent complexity of living systems, while at the same time questioning these very strategies. Because systems biologists use formal representations, such as equations or graph theoretic concepts, in their reasoning and in the formulation of their results, they are forced to make most of their assumptions explicit. This facilitates a process of mutual correction of different approaches and enables progress towards the ultimate goal of getting at the *actual* organization and complexity of living systems. Instead of citing concrete examples of success in systems biology, I would just like to highlight this generally advancing character of systems biology that has the potential to generate exciting insights into the nature of life.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

I think that there are some very important general problems in systems biology that are at the same time important problems for the philosophy of biology, because they might be productively addressed by philosophers. The most important problem I see is that there are very sophisticated methods in systems biology, but there is no sophisticated methodology. For students and researchers in this field it is very difficult to obtain methodological advice that is not highly technical and suited only to very specific applications of systems biology. In spite of this apparent specialization, I think that many areas of systems biology share important methodological issues and that many problems might be fruitfully expressed and tackled at a more general level. Therefore, a possible task for philosophers might be to contribute to a methodology for systems biology at a general and not too technical level. As Jeremy Gunawardena has highlighted, systems biology will need to start "harmonizing [the] cacophony" of "concepts and techniques that are coming into the subject from the physical sciences and computer science" (Gunawardena, 2010, 42). For example, there seem to be few explicit and generally accepted criteria for what counts as a good mathematical model in systems biology and how to rationally decide between competing alternative models. For reviewers it is often very difficult to judge the value of a model in a manuscript, unless they have very specific expertise. This leads to a flood of mathematical models in scientific articles that are of questionable quality. Obviously, the issues of model construction and model selection are highly context dependent, but there are nevertheless some general aspects whose exploration may lead to helpful guidance for systems biologists. To mention but one is-

sue, in computational modeling there always exists a tradeoff between the complexity that can be integrated into a model and its capacity to act as a good tool for discovery, prediction and understanding. There are principled ways of making this tradeoff for simple statistical models (e.g. the Akaike information criterion for model selection), but the problem essentially remains the same in situations where those solutions are not easily applicable. For this problem it would be extremely helpful to have general standards to guide the actions of researchers, even if those standards might not be perfectly adapted to each individual case of modeling. In general there is a risk that mathematical modeling, very much like statistics, turns into a large toolbox that is unmanageable for all but the most experienced scholars because there is no manual that helps them to choose the right tool.

The prospect for progress in this regard is difficult to evaluate. For philosophers to actually contribute, they must be well acquainted with modeling, data analysis, statistical methods, etc. which is usually not part of their education. For scientists, on the other hand, it often does not pay off to tackle such general methodological problems since the reward for this kind of work is comparatively small. I would predict, however, that in the long run the need for a more standardized methodology will become pressing, and then progress is more likely to occur.

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Exploring the Metabolic Marketplace Through the Lens of Systems Biology

On how I became a systems biologist before there existed a field called systems biology

I began academic life as a temporary junior lecturer in Biochemistry at Stellenbosch University during my Honours year in 1975 (if there is a zero rung on the academic institutional ladder then this must be it). The Biochemistry department was established the year before and the courses inherited from other departments were in dire need of revision. I was thrown into the deep end of the academic pool, being tasked with teaching intermediary metabolism, which I, after only three years of undergraduate study, still understood poorly. Even so, there is no better way to learn a subject than to teach it, and metabolism and enzyme kinetics soon became my favourite parts of the curriculum. However, after a few years I became more and more dissatisfied with the static nature of the way metabolism was typically presented in textbooks: the reaction from substrate A to product B is catalysed by enzyme E with cofactor X; B is then converted to C in a reaction catalysed by…, and so the list goes on. The *rate* of each reaction was treated in a separate chapter of the textbook under the heading of enzyme kinetics. The only connection between maps and dynamics was the statement that each metabolic pathway had a rate-limiting step that completely determined the flux of matter through the path. Although the typical textbook introduction to metabolism described the concept of a steady state in which each metabolite is produced as rapidly as it is consumed, the matter of how the steady-state metabolite concentrations were determined was not discussed at all. In retrospect I perceived, rather dimly, Count Alfred Korzybski's dictum "the map is not the territory", although I encountered this pregnant phrase only much later.

In the late 1970s molecular biology was in full force and recombinant DNA research was all the rage. I, however, had fallen in love with enzymes and was trying to figure out how I could study the dynamics of systems of coupled enzyme-catalysed reactions, not only of two but of many coupled reactions. Coupled enzyme assays were of course standard in enzyme kinetics, but the coupling enzymes had to be in excess so as not to affect the overall rate of the system; the enzyme being studied was thereby artificially made rate-limiting. It was never clear to me that this, as both my biochemistry and organic chemistry textbooks seemed to insist, must always be the case, namely that in any sequence of coupled reactions one step must be rate-limiting. The light went on when I discovered the landmark "The Control of Flux" paper of Henrik Kacser and Jim Burns (Kacser and Burns, 1973). They had developed a quantitative description of how a metabolic steady state responds to perturbations in the activity of the enzymes of the pathway (open input-output systems naturally tend to a state in which all metabolic compounds are produced at the same rate at which they are consumed—in this so-called steady state the rate is more often called a flux). Kacser and Burns showed that there is no requirement for a rate-limiting step in a pathway: control over a steady-state property such as flux or concentration can be shared among all the steps and each contribution can be experimentally quantified and related to the properties of the constituent enzymes. Furthermore, the control distribution is not fixed, but varies as the metabolic state varies. These results have since been experimentally verified over and over.

As so often seems to happen when the time is ripe, two other research groups, that of Reinhardt Heinrich and Tom Rapoport in Berlin and of Michael Savageau in Michigan, had independently developed similar analyses which were all published in the years 1969–1974 (and, as so often seems to happen with views that contradict received wisdom, they were widely ignored). My initial education was completed by Athel Cornish-Bowden, who produced what is still to this day by far the best and most up-to-date book on the kinetics of single enzymes and enzyme systems, now in its fourth edition (Cornish-Bowden, 2012).

So much for my formative years as a theoretical biochemist. In March 1981 Sinclair Research produced the ZX81 computer, the first affordable (for me, at least) home computer. I was hooked and spent many hours learning to program in Basic, sitting in a darkened room with a long cable connecting my diminutive computer to a fuzzy TV screen. These were heady days and I managed to implement a simple algorithm for simulating the time-dependent behaviour of a simple reaction pathway. But it was only in 1984 during my first sabbatical year, spent in part with Athel Cornish-Bowden in Birmingham, UK and in part with

Henrik Kacser in Edinburgh, that I was able to put it all together in the program METAMOD, the first metabolic modelling platform for a microcomputer (produced on the vastly superior—to the ZX81 that is—BBC Microcomputer, fondly known as the Beeb). Subsequently this program evolved, mostly in the hands of Athel Cornish-Bowden, into Metamodel, written in Pascal instead of Basic. It has now been replaced by PySCeS, the Python Simulator for Cellular Systems, written and still actively maintained and expanded by my PhD-student and ex-postdoc Brett Olivier, myself and my colleague Johann Rohwer.

My sabbatical in Birmingham led to an intense and decades-long collaboration with Athel Cornish-Bowden during which we developed not only a radically new view of metabolic regulation (as opposed to the classical view) but also the seeds, through our reversible Hill equation, of an enzyme kinetics suitable for computational systems biology (as opposed to classical enzyme kinetics which had been developed with the aim of studying enzyme mechanism).

The main problem of the classical approach to metabolic regulation was that it focussed only on those parts that manufacture the "end-products" of metabolism, their supply, ignoring the fact that these products are used as substrates for other cellular processes, their demand. For example, amino acids couple their biosynthetic supply pathways to demand processes such as protein synthesis; nucleotides couple their supply pathways to DNA and RNA synthesis, the ATP-ADP-AMP system couples energy-producing to energy-consuming processes. What we were able to show is that the control and regulatory properties that one observes when the supply pathways are studied in isolation change when the supply is embedded in the whole supply-demand system.

Our theory of metabolic supply and demand (Hofmeyr and Cornish-Bowden, 2000) had its origin, as so many new ideas do, in an argument, in this case with the doyen of classical metabolic regulation theory, Daniel Atkinson. His monograph (Atkinson, 1977) on the subject remains the most erudite exposition of the classical view and his energy-charge concept remains a cornerstone of our current understanding of metabolic regulation. But, Atkinson insisted that metabolic control analysis made no useful contribution to our understanding of metabolic regulation, and in our efforts to convince him otherwise we began to realise where the crux of the problem lay. Although the classical approach acknowledged the existence of internal consumer-demand for the products of metabolism it failed to merge supply and demand into a whole picture. In 1991 we published the first of our series of papers on metabolic supply-demand theory using metabolic control analysis to express our arguments (Hofmeyr and Cornish-Bowden, 1991). In this paper we developed the mathematical formalism that has served as ba-

sis for all our subsequent analyses, and also started using a graphical representation (using log-log rate characteristics) of the behaviour of supply-demand systems, a representation which we have since refined into a powerful explanatory tool. Rate characteristics allow one to understand how the steady state responds to perturbations. They also provide a broad picture of how the system behaves over a large range of variation in supply and demand activities. In addition, the slopes at the intersection of the supply and demand rate characteristics (the steady state) are equal to the steady-state elasticities of supply and demand. Elasticities have an analogous interpretation in econometrics: they quantify the sensitivity of a subsystem to variation in a parameter that influences it directly, in this case not price but the amount of commodity (more precisely, the concentration of the supply product).

In this paper, as in all our research, we also made extensive use of computer simulation of reaction networks. An important result of this initial work was the demonstration that in situations where flux is controlled by the demand, the primary function of the supply is the homeostatic maintenance of the concentration of the metabolite that links the supply and demand within narrow ranges at values far from equilibrium. It is the magnitudes of the supply and demand elasticities that determine this functional differentiation of the system: a small demand elasticity ensures flux-control by demand; a high supply elasticity ensures effective maintenance of homeostasis. One can of course imagine the reverse situation in which supply controls the flux (small supply elasticity), while the demand maintains homeostasis (high demand elasticity), or, for that matter, any situation between these extremes. However, it is generally observed that most metabolic supply systems possess elaborate inhibitory feedback mechanisms from their products to upstream supply enzymes; these regulatory mechanisms lead to high supply elasticities. On the other hand, the demand systems for which these products serve as substrates are usually saturated at physiological concentrations of these products (near-zero demand elasticities). On the basis of this we suggested that, contrary to the classical view of metabolic regulation that assigns the role of flux-regulation to product-inhibited enzymes in the supply, the primary role of these enzymes is that of homeostatic maintenance of metabolite concentrations. The control over the fluxes through metabolic pathways lies outside these pathways in the demand processes.

It was therefore by taking demand into account that we turned the classical view of metabolic regulation on its head, and our predictions have now been borne out by many experimental studies (Hofmeyr & Rohwer, 2011). We also realised from both an experimental and a conceptual point of view that regulation can be usefully quantified in terms

of the change in flux relative to the change in metabolite concentration. This measure, which we later generalised in the concept of a co-response coefficient, became an important part of our analysis (Hofmeyr & Cornish-Bowden, 1996).

These results from systems biology have important implications for biotechnology. A major question has always been which enzymes should be increased in order to increase the flux through a metabolic pathway leading to a commercially valuable product. We examined the various manipulation strategies that had been suggested or used for producing an increase in a supply flux to a metabolic end-product such as an amino acid (Cornish-Bowden et al., 1995). The majority of efforts to increase metabolic flux have manipulated the supply side ("pushing" strategies) and are based on the classical view of metabolism. Using computer modelling, we showed that in the face of flux-control by demand the pushing strategies are largely ineffective. As the results of unsuccessful biotechnology efforts are rarely published it is difficult to estimate the costs incurred, but they must be considerable. Our analysis and modelling of metabolic regulation showed that a "pulling" strategy would be much more effective and we suggested some ways in which this could be accomplished. Peter Ruhdal Jensen and co-workers demonstrated experimentally that the pulling strategy works in practice (Koebmann et al., 2002): they showed that the metabolic flux through glycolysis, the pathway that breaks down glucose to produce ATP, is controlled by the demand for ATP. Using recombinant DNA techniques they were able to increase the ATP-demand by introducing an enzyme that wastes ATP, which led to a proportional increase in glycolytic flux by pulling it.

Mathematical and computer modelling clearly played a major role in our investigations of metabolic control and regulation, as it does in much of systems biology. The most important lesson that we learnt was that understanding follows from modelling at the appropriate level of abstraction. Too much detail can hinder understanding. This is a potential problem for the so-called silicon cell or genome-wide models that attempt to include everything but the kitchen sink. No doubt such models can be extremely useful, especially if they have been carefully validated against independent datasets, but it often seems that after the huge task of constructing and parameterising such models has been accomplished nothing much is done with them. This is where supply-demand analysis can come into its own, especially in its generalised form (Rohwer & Hofmeyr, 2008). Rate characteristics of supply–demand can be constructed around each metabolite in the model by fixing the concentration of each metabolite in turn and scanning it as a parameter. The shapes of the resulting rate characteristics, in conjunction with a

comparison of the flux–response coefficients of the supply and demand blocks with the elasticities of the enzymes that interact directly with the fixed metabolite, allow not only regulatory metabolites in the system to be identified and characterised, but also the points where the system is functionally differentiated and which of its metabolites are homeostatically buffered.

This rather lengthy history tries to show that we were doing what I regard as systems biology long before it acquired that name. Our theory explicitly recognises that the evolved properties of any part of a system can only be understood in relation to the whole—it is, therefore, a *systems theory*. While it is perfectly possible to *describe* any part of a system fully in terms of its constituents only, it is impossible to *understand* why that part of the system has the properties it has without considering it in the context of the intact, whole system.

My mantra for systems biology is therefore:

Nothing in an organism makes sense except in the light of functional context (Hofmeyr, 2007)

The foregoing shows that I became a systems biologist by asking systemic questions:

By asking not only how the parts and their interactions determine the emergent behaviour of the whole, but also asking how the properties of the parts are determined by their context within the whole. Metabolic control analysis and supply-demand analysis have proved to be useful tools for addressing such questions.

By realising that not only can a whole be more than the sum of its parts (by exhibiting systemic properties that cannot be attributed to any part), it can simultaneously be less than the sum of its parts (in that the embedding of a part within a whole constrains aspects of the behaviour that it would exhibit when isolated). For example, steady-state fluxes and concentrations are emergent systemic properties that are jointly determined by all the steps in a metabolic system, whereas the activities of the enzymes that catalyse the steps are constrained by the chemical environment in which they find themselves and which is created by the system itself.

By, when asking whether A causes B, always considering ways in which B could cause A through often hidden feedback loops. As Donella Meadows says in her primer on systems thinking (Meadows, 2008): "Watch out! If you see feedback loops everywhere, you're already in danger of becoming a systems thinker!" On the other hand one should realise that sometimes the question may make no sense. In a metabolic steady state, for example, it makes no sense to ask how a metabolite concentration *determines* a flux, or *vice versa*; both are variables that are determined by other system parameters such as enzyme concentra-

tion, which, in turn and depending on how the system is framed, could themselves be variables determined by a more fundamental set of parameters.

What I described above is what I now regard as the first phase in my development as a systems thinker and systems biologist. In fact, for reasons that will become clear, I do not really like to describe myself as a systems biologist anymore: I rather regard myself as a physiologist, more specifically a molecular cell physiologist.

The second phase of my career as systems scientist led me into the world of complexity studies. Twenty years ago I discovered the work of the theoretical biologist Robert Rosen and the world of relational biology opened up for me (Rosen, 1991; Louie, 2009). This in turn led me to the view of organisms as biochemical factories that fabricate themselves (Hofmeyr, 2007), and to the works of John von Neumann on self-reproducing automata (von Neumann and Burks, 1966), Howard Pattee on how a molecule can become a message (Pattee & Raczaszek-Leonardi, 2012), and Marcello Barbieri on biosemiotics, organic codes and code biology (Barbieri, 2012). Rosen had a great influence on my thinking, especially his thoughts on self-fabrication of metabolism-repair systems, on the art of modelling through his modelling relation, and his formalisation of the four Aristotelean causes in terms of category theory, which allows one to unravel complex causal relations in an unprecedented way. Unfortunately these works do not form part of the main systems biology canon and I regard them as the most neglected contributions of the late 20th century to systems biology.

Philosophy and systems biology

I am not a card-carrying philosopher, but to the extent that philosophy can be equated with a worldview—a lens through which to view the world—I am convinced that systems biology needs such a lens, and that this lens is at the same time distinct from and complementary to the reductionistic lens of molecular biology and the historical lens of evolutionary biology. In line with my mantra for systems biology its lens should be that of always taking functional context into account, which is the very essence of the systems approach.

The systems biology lens situates the phenomenon of life somewhere between molecule and autonomous organism. The focus throughout is on organism: life emerges from a system of material components that are functionally organised in such a way that the system can autonomously and continuously produce and repair itself, can distinguish itself from the rest of the world, and can adaptively restructure itself within its genomic constraints in the face of environment fluctuations. Systems biology therefore goes beyond the properties of individual bio-

molecules, taking seriously their organisation into a living whole.

Unfortunately, much of what currently passes for systems biology is what I regard as "system-wide" biology: the idea that understanding will come from measuring the amount of everything that there is to be measured inside a cell under different conditions (DNA, RNA, proteins, metabolites, interactions, etc.). I call this the "omics-delusion". Similarly, system-wide biology attempts to sequence everything that can be sequenced, map all networks, exhaustively model all processes, and visualise everything. It is often only done because, through technological innovation, it is now possible to do so. But the more detailed the map becomes, the more the territory recedes into the distance. In themselves these studies have their own worth, but they do not answer systemic questions such as the ones I listed above. In conjunction with big science, big egos and big money, system-wide biology often leads to what tongue-in-cheek can be called "texas system biology": my <blank> is bigger than yours, where the blank can be filled with, say, dataset, network, hairball graph, computer model, consortium. To a distressing degree much of what passes for systems biology has lost the "systems" part and is just good old reductionistic biology in a new guise.

It is clear that philosophical considerations can and should make an important contribution to keeping systems biology on the right track. There is a well-developed field of systems philosophy based on the pioneering work of Ervin Laszlo (Laszlo, 1972) and Ludwig von Bertalanffy (von Bertalanffy, 1968/1976) and systems biologists would do well to make that required reading for themselves and their students.

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11

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Moving from genetics to systems biology

1. How and why were you initially drawn to systems biology?

A colleague (Anders Blomberg, Gothenburg) asked me in 1999 if I had heard the term systems biology after he read my grant proposals for the local genomics research school. I had not. He thought that what I was proposing fell under this topic. The proposal was granted anyway.

I am an experimental molecular biologist and geneticist by training. My perspective of mathematical modelling in the 1980s and early 1990s was strongly influenced by my doctoral and post-doctoral teachers who thought modelling was pseudo-science. I studied the mechanisms that controlled metabolism in the yeast *Saccharomyces cerevisiae* and models of glycolysis were around at that time. Those earlier models wereonly loosely based on experimental data and I agree that this kind of mathematical model based on purely/mainly theoretical considerations probably was not of great relevance to the research questions we pursued. Usually, as a young student or post-doc one tends to be more open-minded than the boss…But what really irritated me at that time were theoreticians that tried to convince us not to perform a certain experiment because simulations suggested that it would "not work". To employ simulations of mathematical models in order not to do an experiment really did not appeal to my view of biological research. And given the fact that the models where insufficiently based on experimental data I ignored the advice not to do the experiments. Luckily. Meanwhile, I have made peace with glycolytic models because (1) they nowadays are much better supported by data and (2) recent work by the Teusink lab published in Science very nicely confirmed a hypothesis I proposed 20 years ago based on purely experimental observations: trehalose metabolism has the potential to serve as a metabolic buffer to balance between the upper and the lower part of glycolysis, and this may be important for

yeast cells to shift from gluconeogenic to glycolytic metabolism.

Towards the end of the 1990s I had moved on to study signaling pathways, specifically the yeast osmostress-activated Mitogen-Activated Protein Kinase MAPK pathway called HOG (for High Osmolarity Glycerol Response). I was fascinated by the very rapid activation of the pathway following osmotic shock and the fact that activation was transient, declining again after a certain period of time. Apparently, strong feed-back regulation was operating here and I wished to understand the underlying mechanisms of this control. What would be the best approach to truly understand the mechanisms that control signaling pathway dynamics? I found several articles that studied signaling dynamics at a theoretical level and came to the conclusion that the integration of experiments with modelling, simulation, prediction and experimental verification could be a very promising approach. I found articles from Reinhard Heinrich, Berlin, most stimulating in this regard, even though most of these were based on purely theoretical consideration.

My "systems biology" grant proposal provided funding for two PhD students, one on the experimental and one on the theoretical side (with a theoretician as main supervisor). At the same time I made contact with Reinhard Heinrich, who referred me to one of his senior post-docs at that time, Edda Klipp. Thus began a very fruitful collaboration that has been active for the last 15 years and resulted in a series of joint papers, the first of which was published about five years after our introduction.

We jointly worked on just the feedback control of the HOG pathway, involving the two students mentioned above. Additional external funding from the European Commission meant that we both could extend our activities and involve more research staff. We found it difficult to publish our work in such a manner that everybody, especially the experimental and theoretical main workers and principle investigators, would receive the proper appreciation and position on the author list. We submitted separate modelling and experimental papers that were rejected, more than once in fact. When Edda submitted the modelling work to Nature Biotechnology it was not rejected but the journal asked for the experimental data used for modelling to be included in the paper. Thanks to the journal editor we were eventually forced to combine the work and submit a joint paper in 2005, which presented a story of experimentation, modelling, prediction and verification. The story as presented did not exactly reflect the way the work had progressed but it made two major contributions: (1) an early attempt to multi-scale modelling (signaling, gene expression, metabolism, biophysical changes), and (2) an explanation of the feedback mechanism: successful osmoadaptation leads to a situation where the stimulus (high external osmolarity) declines, because the cell increases its internal osmolarity.

That is, feedback control on signaling by adaptation and hence stimulus cessation. The model was simple and effective and backed up very well by experimental data and model simulation. Model simulations could also refute an alternative mechanism proposed purely by experimental work, namely upregulated expression of genes encoding protein phosphatases, negative regulators of signaling. Although the mechanism was intuitively acceptable (and in fact widely cited at that time) it does not seem to bear any relevance for HOG pathway regulation.

Since that time the integration of modelling and experimentation is a main theme in my group's studies on signaling using yeast MAPK pathways and more recently also the AMP-Activated Protein Kinase AMPK pathway.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

According to Wikipedia "Philosophy is the study of general and fundamental problems, such as those connected with … existence and knowledge…, addressing such problems by its critical, generally systematic approach and its reliance on rational argument." There are several ways in which the systems biology approach relates to philosophy in accordance with the definition.

Systems biology attempts to apply the rules of physics and mathematics to achieve a rational understanding of biological phenomena. Biology traditionally is a descriptive science, rather than an exact or mechanistic science. Even molecular biology is generally descriptive in nature. For instance, genetic, molecular as well as cell biological studies over four decades produced a list of components of the central cell cycle machinery. In a number of ways such research also generated information about the relative or absolute numbers of the components, which molecules interact with, or how and when they influence amount or activity of other components of the system. Traditionally, these diverse pieces of information have then been interpreted by scientists on the basis of what has been learned previously about other, similar (sub) systems, the molecules and the principle reactions. In other words, the mechanistic explanations of how the cell cycle (in this example) operates were based on what was found plausible or intuitively acceptable on the basis of the available information and the knowledge and experience of the scientists studying the system. This approach of hypothesis generation (or, eventually, generation of widely accepted facts or knowledge) allowed incorporation of incomplete evidence with a similar weight as strong evidence as well as the substitution of a lack of information with intuition. Most importantly, the illustrations of networks or pathways in text books and papers imply how the system might oper-

ate over time, although commonly only very limited data on a system's dynamics exist. Hence, much of what we believe to "know" about the dynamic operation of molecular systems, such as the cell cycle machinery, is based on interpretation or interpolation rather than on exact experimental evidence or the rules of physics and chemistry. Obviously, molecular processes within a cell must comply with those fundamental natural rules. Therefore, employing mathematical models to describe systems, static or dynamic, and basing those models on the rules of physics and chemistry is an attempt to convert biology from a descriptive to an exact science that mechanistically explains the operation of biological systems. Consequently, systems biology has the potential for a paradigm shift in biological sciences, moving from description to mechanistic explanation.

Systems biology attempts to rationalize a system and identify missing components or connections. A mathematical model of a system, such as the cell cycle machinery, is an attempt to rationalize the known pieces of information and connect those pieces of information employing the rules of physics and chemistry. Commonly, the first modelling attempt is very highly influenced by human interpretation and intuition (see also a discussion about abstraction below). The first model will therefore rarely be able to reproduce the experimental observations, especially not those that were not included in the model design. Such "failing" models are commonly more informative than successful ones, because they point to missing information (for instance a missing component or connection, such as a feedback loop) or to instances where the assumptions made for constructing the model were incorrect. Hence, a mathematical model serves as a test bed for our understanding of the operation of a system. A mathematical model cannot be fooled by our intuition or willingness to interpret; it will faithfully simulate experimental scenarios on the basis of the information that was encoded in the mathematical equations. Failure of a model will therefore guide us to lack of knowledge, data or misinterpretation and hence provide guidance for future experimental research. A model will also be able to predict reasonably plausible mechanisms (plausible on the basis of the rules of physics and chemistry) and refute unreasonable ones, and in this way also guide further research. The systems biology cycle, which has been shown to be amenable to automation, from data/information, model, simulation/prediction, experimental verification and model improvement, is a tool that guides researchers to exact biological mechanisms. The model can also often imply why certain design principles have been employed by nature and how they have been repeatedly used in evolution. In my group we use dynamic mathematical models as a tool to rationalize the available information and to understand regula-

tory mechanisms in the ways described above.

When systems biology employs mathematical models that exactly reproduce biology, is there still a place for the centuries old approach to biological research that relies upon interpretation and intuition based on sound biological knowledge? Within systems biology one of the main intellectual challenges lies within abstraction. At which level of detail can or should a biological system be encoded in mathematical equations? Which reactions should be represented and which ones should be lumped together? Very commonly the level of abstraction is determined by the research question to be addressed by the model as well as the data that are available or the steps/compounds that somehow can be measured experimentally. Generic models, especially generic dynamic models that can be (re)used to address a number of different, or simply any, research question, do not presently exist. This is, because knowledge is incomplete. System abstraction that can identify different processes and parameters in a system, as well as phrasing the relevant questions such that they can be studied with a mathematical model, constitute the philosophical challenges in systems biology.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

There are things where we know that we know them; there are things where we know that we do not know them; and there are things where we do not yet know that we do not know them. Around the millennium shift two major, related questions in biology turned out somewhat unexpectedly to rather fall under the latter category: the genetic code and the mechanism by which genotype confers phenotype.

The elucidation in the 1950s of the three-letter genetic code that encodes the 20 amino acids of proteins as well as the beginning and end of a polypeptide chain certainly was a milestone in biology. With the advent of DNA sequencing technology it allowed researchers to translate a DNA sequence by hand, or with the help of computers, into a polypeptide chain. Computer algorithms allowed for prediction of protein function and to some extent also their structure - based on comparison with proteins of known function or structure. Overall it appeared that we understood and could read the genetic code. This has turned out to be incorrect.

1. The human genome sequence demonstrated that it is not at all straightforward to predict a protein sequence based on the DNA sequence. This is due mainly to alternative start sites as well as (alternative) splicing. Up to today, ca 15 years after the first draft human genome sequence was published, the exact number of proteins encoded by the human genome is still not known.

2. Even a predicted protein sequence does not commonly allow a specific and defined description of the function of the protein, in particular not the physiological role. While very commonly a predicted protein can be functionally classified, for instance with regard to a certain enzyme activity, its role in the cell or organism needs to be studied or verified experimentally.

3. The DNA sequence does not enable the reliable prediction of the expression of a given gene into mRNA and protein because we are still unable to read the chromatin code. Although the DNA sequence encodes the proteins that regulate gene expression and the information where proteins should bind to DNA there are too many levels of regulation to allow for prediction of when and where a protein binds DNA to affect gene expression in the context of the living cell.

4. Next generation sequencing technology revealed that only a small fraction, perhaps 20%, of all transcription of the human genome results in mRNAs encoding protein. Rather, a vast amount of non-coding RNAs are produced. These seem to play roles in epigenetic regulation, regulation of transcription and at various steps of post-transcriptional regulation. Those levels of control, especially at this degree of complexity, were not at all expected only a few years ago and elucidating the molecular and system level mechanisms constitutes an enormous challenge. This regulatory world of non-coding RNA, completely unknown a few years ago, is now being speculated to be a major player in the evolution of complex organisms and hence may explain why, for instance, human and yeast are distinguished by only about a factor of three in terms of the number of protein coding genes.

Taken together, it has turned out that the three letter genetic code determining the amino acid sequence of proteins only is a rather minor piece in the puzzle of the information encoded by the DNA sequence and we are far from being able to decipher that complex code.

Furthermore, we are also far from appreciating the relationship between genotype and phenotype. Very simply, this is because most relevant phenotypes are not determined by a single gene but by several genes/proteins in concert. In other words, the regulatory networks determine phenotype and hence systems biology will play a crucial role in understanding the genotype-phenotype relationship. A major challenge in this context is understanding the underpinnings of disease predisposition in humans. Certain genetic diseases are determined by single mutations

or genomic aberration like chromosome number changes. But predisposition to many other diseases, including cancer and infectious diseases, is determined by a large number of genes/proteins in concert. This, of course, is also true for many relevant phenotypes in other animals, plants and even microorganisms, such as yeast, which hence may play an important role as model organism also in this area of genetic and system research. We are only at the very beginning of the path to understanding how complex phenotypes are determined and systems biology will play a major role in attacking this challenge, although the underlying research may not always be classified under this term: eventually, it is about interactions (of genes or proteins or molecules or cells or organs).

4. What have been the most significant advances in systems biology?

I believe it is rather difficult to point out individual success stories, i.e. specific examples where the integration of experimentation and modelling have resulted in a breakthrough that otherwise would not have been possible. There are many excellent stories employing a systems biology approach that have been published in high impact journals in the last 15 years. But highlighting individual research papers may not be the most appropriate approach when describing the advances in systems biology or those that have been made possible via the systems biology approach.

Systems biology on the one hand is an approach to biology (employing the rules of physics and chemistry and integrating experimentation and modelling). But even more importantly, systems biology is a way of thinking about biological phenomena and mechanisms: that interaction between biological units (molecules, cells, tissues, organisms) are key to understand evolution and mechanisms in biology. This way of thinking has penetrated biology and medicine to a much more significant extent than the term systems biology as such. There is a lot of work being published in high impact journals that at least in terms of the thinking would qualify as systems biology. We often engage in discussions when systems biology might hit mainstream biology and medicine while at present certainly no more than 5% of all labs truly employ a systems biology approach in their research. I would argue that the systems biology way of thinking of biology is nowadays far more wide spread than those 5% might imply. This can be compared with molecular genetics, which probably started with the discovery of restriction enzymes, DNA ligase and the development of gene cloning techniques in the early 1970s. In fact, many labs in the following 10-20 years declined to accept this new approach to research but there is no doubt that the underlying techniques, approaches and the way of thinking became mainstream in biological research by the mid 1980s.

Most labs did not claim to be doing molecular genetics, they rather just employed the approaches to attack their favorite research question. I argue that systems biology is moving in the same direction in becoming mainstream biology in the next ten years or so.

What then will happen with "hard core" systems biology? It certainly will remain a very active field of research with respect to developing the underlying experimental and, in particular, computational techniques and methodologies. As part of the systems or network approach to biology, there are three areas that have recently attracted attention. As already discussed under Question 3, it has become apparent that most relevant phenotypes are not determined by single genes/proteins but rather by complex networks of a large number of genes/proteins. Determining quantitative trait loci (QTLs) in genome-wide association studies has been a major topic in recent years in human, animal and plant genetics. However, it seems that the step from QTLs to the underlying networks that determine phenotype is steep and extremely challenging. The approaches for this next step are not really at hand right now. Although the field of quantitative genetics is not acknowledged to be associated with systems biology it appears that network - and hence systems biology - approaches are eventually needed to determine how genotype determines phenotype.

Thinking about molecular systems and networks has resulted in the realization that most types of data do not reflect the actual behavior of a system. In fact, when studying for instance a metabolic or signaling pathway, what is it we are commonly modelling? In most instances it will be an average behavior over billions of cells, since this is what commonly is measured with invasive methods (all methods that make use of cell extracts). However, it has become clear, that individual cells within a population of genetically identical cells can show significant cell-to-cell variability. This may have a number of different obvious reasons such as different cell cycle stages, different cell age or stochastic variation due to different numbers of molecules between cells in the system under investigation. Therefore methods to determine data from single cells have recently been developed and such data are useful for modelling, last but not least if derived from living cells. Such data can provide "real time" information on the dynamics of a system under study.

Employing single cell data for determination of network structure and dynamics is a major step forward for understanding molecular biological systems and this advance was based on system level thinking. And the same type of argumentation leads to the next step. Advanced imaging technologies have been developed to enable monitoring of single molecule behavior. This then moves the question further: are we

modelling an average behavior over a large number of cells, the average of individual events within a single cell or in fact individual events? What are individual events or individual pathways? For instance, there may be a few hundred or thousand molecules of each protein of a signaling pathway within a given cell. How many individual "pathways" or events do they form at any given moment of time? Can we really dissect individual pathways/events and what does this information tell us about the operation, control, dynamics and evolution of the system? These are exciting thought experiments that may become very relevant with advanced measurement technology.

Another area inspired by systems biology is predictive engineering in synthetic biology. Engineering metabolic and signaling pathways for enabling cells to perform specific tasks in a highly predictive and, in certain scenarios, digital manner, is a field of extremely high potential. In fact it is the merger of two approaches mentioned previously: molecular genetics and systems biology. Engineering of cells guided by mathematical models, similar to the design of cars and aero planes, has major potential for future medicine and biotechnology. We are only at the very beginning of this exciting field.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

In my view there are two important issues and they are not philosophical but very practical and real: (1) education and training as well as (2) access to competence, tools and computing power.

The mindset and principles of systems biology have so far not penetrated education at high school and basic university levels. Therefore, students are generally unaware of the systems biology principles and poorly prepared to enter a higher education program in systems biology. There are several reasons for that and it may take some time to overcome the underlying problems. For instance, teachers do not receive training in systems biology, because teacher education and subsequent training is generally discipline-oriented (i.e. biology or physics or mathematics). Systems biology principles are also not part of common school or university text books for general biology, physics or mathematics education. This will certainly be necessary for spreading systems biology principles and mindset such that they become part of the basic education in the relevant fields (biology, physics, mathematics) at school and university level. There is nothing wrong with discipline-oriented education; one may even argue that sound education in one relevant discipline may be the best foundation for embarking on interdisciplinary programs at a later stage during the studies.

But discipline-oriented education programs clearly must become better in spreading an awareness of the importance of interdisciplinary approaches to biology.

Systems biology is inherently interdisciplinary using approaches and rules from biology, physics, chemistry and mathematics, and even engineering. Education at schools and university is generally discipline-oriented. Hence, the educations systems are directly counterproductive with respect to systems biology. Nevertheless, numerous universities have established interdisciplinary systems biology programs (although often the term is not used in the name of the program), commonly at master's level. Presently, there are discussions ongoing at a European level to harmonize such programs because they are very different in scope and content. It will be important to achieve a common view on the type of skills a student that underwent a systems biology master's program somewhere in Europe should have acquired and what type of tasks s/he should be able to master. For instance:

- An understanding of the type of biological, medical or bioengineering questions that can productively be addressed by integrating experimental data collection with mathematical modelling, simulation and prediction.
- Phrasing (abstracting) research questions such that they become accessible to an integrated experimental/computational approach.
- A good appreciation of the Systems Biology cycle: modelling, simulation, prediction and experimental verification.
- A well-developed ability to communicate scientific questions across experimental and theoretical disciplines and to collaborate across discipline borders.
- Hands-on experience and skills in mathematical modelling using different approaches and a good understanding of the type of modelling that is suitable for different research problems.
- Hands-on experience and skills in a range of experimental techniques and a good understanding of the type of data approaches that are suitable for a given research question.
- Bioinformatics skills such as data handling, management and visualization, including statistical analyses.
- An advanced insight and understanding of the types of scientific argumentation in at least one area of experimental biology, medi-

cine, bioengineering or theoretical/computational biology.

Taken together, the awareness for systems biology principles need to penetrate science education at all levels and true systems biology education should follow similar educational aims wherever it is performed.

Access to competence in mathematical modelling may be a major hindrance for employing a systems biology approach in many research projects. Very commonly, the most successful systems biology studies are based on collaborations between experimentalists, contributing with the biological questions and experimental data and theoreticians, who contribute with skills in modelling, simulation and prediction. Collaboration across disciplines is not a trivial enterprise and very commonly requires skills to communicate across borders. This challenge, as well as the mere availability of matching theoreticians locally may prevent in many cases the integration of modelling and prediction into projects even if the interdisciplinary approaches offer great potential.

Presently, there are efforts ongoing to establish research infrastructures in Europe (as well as here in Sweden) to address this issue. Such infrastructures could serve the research community in different ways:

- Making algorithms and computational tools available via web portals, including tutorials, guidance and support to use those tools.

- Generating pipelines from data generation, data analysis, handling, storage, access to modelling, simulation and prediction.

- Matching expertise and facilitating the establishment of collaborations between experimentalists and theoreticians. This may include also matching additional experimental expertise, for instance to address the lack of certain types of experimental data for a specific project.

- Service modelling, i.e. allocating dedicated staff for certain periods of time to a research project to facilitate the implementation of modelling, simulation and prediction within this project.

Such types of infrastructure would in many ways be different from "standard" research infrastructures, which commonly provide access to "big machines". A systems biology infrastructure would need to provide access to competence and man power, which constitutes specific challenges in setting up such an infrastructure. However, a functional infrastructure, that could also offer training, has the potential to contribute significantly to spreading the systems biology approach in biological and medical research and drive processes towards application in

medicine and biotechnology.

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THE IMPORTANCE OF BEING DYNAMIC: SYSTEMS BIOLOGY BEYOND THE HAIRBALL

1. How and why were you initially drawn to systems biology?

I wonder whether I was actually ever "drawn" to systems biology. On the one hand, it appears in hindsight that this sort of approach has always provided a natural attractor for my thinking. On the other, I am not sure that I would have discovered systems biology if it had not been for a series of personal and historical coincidences.

The first such accident was an aborted attempt at majoring in microbial ecology as an undergraduate student in Zurich in the mid-1990s. My fascination with the intricately interconnected processes constituting the biosphere had provided a large part of my motivation to study biology. I was extremely disappointed to discover that a standard undergraduate diploma thesis in field ecology involved two seasons of sampling with a subsequent (usually rather straightforward) statistical analysis of the data. This sort of correlative and static explanation was not enough for me! It left me intellectually dissatisfied at a very deep and emotional level. Without realizing the implications, I had found my passion for complex mechanistic explanations.

The second accident occurred upon my transfer to the University of Basel, where Walter Gehring was teaching a practical introduction to *Drosophila* genetics. I had been less than impressed by this topic during my time in Zurich, but this course really got my attention. I was happy to get an offer from Professor Gehring to join his laboratory for my 12-month diploma project. My time in the Gehring Lab was equally exciting and frustrating. Ingenious experiments were being performed there but I perceived their interpretation as overly simplistic. A single "master control gene" to make an eye? Evolution through switch-like

mutations in such master regulators? I remained skeptical of such reductionist explanations. This propelled me to look for alternatives that would do justice to the beautiful and exquisite complexity of nature. I found them in Brian Goodwin and Stuart Kauffman, two biologists who could not have been further, intellectually, from my diploma supervisor. Still, I acknowledge Walter Gehring's important influence on my career. Often, mentoring is achieved not by putting students on a certain intellectual trajectory, but by letting them"" search for their own path to enlightenment.

Reading Goodwin and Kauffman was probably my first contact with what we now call "systems biology." Kauffman's book on "The Origin of Order" introduced me to complexity, self-organization, emergent properties, and the computational study of networks. Goodwin's biological structuralism led me to dynamical systems theory, and the idea that genes do not determine anything without their regulatory context. I decided it was time for a radical change in direction.

This leads me to the third accident. To my great delight I learned that Brian Goodwin was setting up a very experimental MSc degree in "Holistic Science" at Schumacher College, in Dartington, Devon. I somehow managed to get funding from the basic-science foundation of a major Swiss pharmaceutical company to study there. The experience was life changing. During my year at Schumacher, I became deeply immersed in process philosophy (in the guise of phenomenology), complexity theory, and dynamical systems. I taught myself to program properly. And most important of all, I learned to keep an open mind. Brian wasn't afraid to speculate and pursue big ideas and unusual concepts. But one aspect of his approach left me dissatisfied: all of it remained purely theoretical. Very few modeling-based studies at that time connected to experimental evidence. None of them managed to do so in an accurate and rigorous manner. I had become completely disconnected from my experimental roots.

It took a fourth accident to reconnect experimental and modeling work. I am greatly indebted to Denis Thieffry, who brought John Reinitz to my attention. I met John at the European Conference on Mathematical and Theoretical Biology in Amsterdam. His talk left an immediate and strong impression. He described his efforts to reverse-engineer the segmentation gene regulatory network of the fruit fly *Drosophila melanogaster*. He was fitting models to (still somewhat improvised) quantitative expression data. This was certainly unusual.[1] It was exactly the

[1] I think it's difficult to underestimate how far ahead of their time John Reinitz, with associates Eric Mjolsness and David H. Sharp, were when developing their connectionist modeling approach in the early 1990s. Doing this sort of science was not at all fashionable at the time. In fact, it was considered to be impossible and outright crazy.

sort of project I was looking for! I told John that I was Walter Gehring's student, and expressed my desire to get into mathematical modeling. He immediately asked me if I wanted to do a PhD with him, only seconds after I had first met him… I needed a moment to recover before inquiring whether he had any additional questions. He suggested that we might as well discuss those over dinner downtown. This dinner in Amsterdam, of which I only retain a hazy recollection, eventually led to me joining John's lab at Stony Brook University in September 2000.

Thus, September 2000 is the exact moment of my proper induction to modern systems biology[2]. With John, I learned to combine quantitative experimental measurements with dynamical systems modeling. He had created a uniquely inter-disciplinary environment in his lab. Everybody was encouraged to try everything, from experiments to programming to mathematical analysis, no matter your background. This did not necessarily increase the publication output of the lab, but created a powerful learning experience through which creative and open minds could flourish. John also taught us to pay attention to details, while never forgetting about the big picture. This shifting bridge between levels of explanation is precisely what distinguishes modern systems biology. It is theory solidly grounded in data. For me, it meant intellectual synthesis as well: John's reverse-engineering approach brought together all the different strands of my scientific interests and skills. Everything fell into place at that time.

There was one more coincidence, maybe the most important one in my career so far. I had joined the Reinitz lab at exactly the right time. John's group, in collaboration with Maria Samsonova in St. Petersburg, had just finished a gargantuan effort to create an amazing and unique quantitative data set of spatio-temporal gene expression patterns in early *Drosophila* embryos. This included developing new methods for data quantification, plus implementing powerful algorithms for model optimization on massive parallel computing clusters. Things were still a bit of a mess, as is usual for such a bleeding-edge effort, but all I needed to do was fit models to the new data set, and analyze the resulting gene circuits. This work led to two papers on the gap gene network of *Drosophila,* which are probably my main contributions to systems biology so far (Jaeger, Blagov, et al., 2004; Jaeger, Surkova, et al., 2004).

Ever since this first encounter with systems biology, I have continued using the Reinitz/Sharp reverse-engineering approach to study the developmental and evolutionary dynamics of the gap gene network in dipteran insects (flies, midges, and mosquitos). I combine this practical

[2] Although it was still not commonly called like that in the early 2000s. We were doing "functional genomics".

data-driven modeling approach with more conceptual theoretical work on the evolution of developmental systems. In my opinion, only such a combination of detailed experimental investigation with integrative dynamical modeling and conceptual innovation will succeed in pushing our understanding of biology to the systems level. This push, in turn, has the potential to yield an entirely different outlook on development and evolution. It could completely transform the way we view and do biology. A paradigm shift is in the air! These are exciting times to be a biologist…

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

To answer this question, I first need to define what I mean by "systems biology". To me, systems biology understands biological phenomena as processes, and studies them in terms of their regulatory dynamics. These dynamics are determined by the structure of the regulatory process, which consists of mechanisms that govern change from a given initial state to produce the output of the system. Systems biology extracts regulatory structures from quantitative data. The rules encoded by these structures can be described by a wide range of formalisms depending on the problem and the amount of detail required from an explanation. What is crucial is not the particular formalism, but a general focus on understanding the regulatory processes that govern biological systems.

This definition explicitly excludes the very common use of the term "systems biology" to denote many kinds of "omics" or big-data science. Such approaches—including genomics, transcriptomics, and proteomics, among others—represent large-scale extensions of traditional genetics and molecular biology. They focus on identifying the molecular components of complex regulatory networks, plus the interconnections among them. The resulting descriptions and models remain static. Their explanatory power when it comes to systems dynamics is limited. Such "omics" approaches are an important prerequisite, but not an integral part of what I call systems biology. Given this definition, it becomes clear that "systems biology" denotes a particular approach or perspective, rather than a well-defined sub-discipline of biology. Systems biology is simply biology with a particular focus on the regulatory dynamics of complex networks. It can be applied to any biological system: organisms, brains (or other organs), tissues, immune systems, gene regulatory networks, physiological systems, metabolism, and even supra-organismic assemblages such as evolving populations, ecological communities, or the biosphere in general.

In light of the above, I see two main points of intersection between systems biology as a general approach and the philosophy of science.

The first concerns process philosophy, the second scientific perspectivism. Process philosophy argues that processes are more fundamental than substance (static things or entities) (Rescher, 1996). In its most pragmatic form, process philosophy states that it is useful and important to study nature in processual terms. In other words, while it is important to know what a system is made of, it is the interactions between its components that define a system's behavior (its dynamical repertoire) and its potential for future change. Things are only of interest as long as they affect other things. Inert entities are irrelevant. Thus, things can only be studied as parts of processes, which is exactly what systems biology is supposed to do. For this reason, process philosophy provides the proper epistemological foundation for the kind of systems biology I am talking about.

In return, systems biology can provide process philosophers with real-world examples of complex regulatory processes and their particular characteristics. From the study of such examples—across all sub-disciplines and scales mentioned above—we may be able to derive general rules, or at least more or less widespread principles, that govern the dynamics of biological regulation. This grounds process philosophy in empirical evidence. In addition, it allows us to develop much-needed novel vocabulary and concepts to talk and think about process. Due to the tendency of Western intellectual tradition to provide explanations in terms of static things[3] we lack common-language terms for the processual aspects of reality. For example, we do not have any intuitive way to deal with the variety of different possible morphogenetic transitions in animal or plant development. There are no commonly used words describing types of transient dynamics, attractors, and bifurcations that underlie these phenomena. Systems biology, given its trans-disciplinary nature, could help provide them.

Systems biology, and the process view in general, can be seen as particular perspectives on nature. Process-based explanations of biological phenomena provide an angle on many problems that is different from traditional substance-based interpretations, e.g. those derived from molecular biology. For instance, many systems biology conferences these days are saturated with explanations in terms of "hairball" graphs (Lander, 2010), showing tremendously complex networks as static representations of nodes and their links. It is interesting to consider in what way such depictions provide an explanation for the system under study, or whether they can be accepted as an explanation at all. In my view, they cannot. They are only the starting point for understanding in terms

[3] Greek and modern atomism, the fundamental particles of physics, or genes as particulate carriers of inherited character traits come to mind.

of the dynamics of the system. However, what I accept as an explanation is subjective. I cannot scientifically prove that the hairball has no explanatory power. In fact, I do acknowledge that it does. I just do not consider its level of explanation satisfactory to me. This personal choice reflects my particular perspective on science.

Scientific perspectivism is a branch of the philosophy of science that attempts to acknowledge this subjective (even constructivist) aspect of science, without having to sacrifice the notion of realism (see, for example, Giere, 2006). Realists assume that the universe exists outside them with a specific causal structure that applies to everything and everyone within it. I would definitely subscribe to this sort of metaphysics. However, individual scientists, and science as a whole in its specific historical context, only ever see a small proportion of all perceivable events or phenomena. Our understanding always remains incomplete and biased by our personal history and societal context. I simply cannot step outside my head to obtain a truly objective bird's eye view of the universe. This implies that even if I ask the same question twice, I will not necessarily end up with the same answer. What kind of explanations I accept as interesting and useful always depends on my current circumstances.

From a perspectivist stance, my process-based view is complementary to, rather than contradicting, substance-based approaches. This philosophical point is important. We could avoid a lot of unnecessary controversies, if scientists were more aware of these issues. This would allow us to focus our attention on more interesting, productive, and also more urgent arguments, some of which I will try to outline in the next sections.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

This is an extremely tricky question to answer. There are many neglected topics and contributions, and I find it difficult to prioritize them. We have already come across the problem of ignoring the fundamentally process nature of biology, and I have argued that a perspectivist stance could avoid many unnecessary controversies. I will not elaborate further on these points. Nor will I pick any additional specific examples for my discussion. Instead, I would like to highlight an underlying tendency in modern science that leads to a whole range of problems being neglected, especially in current biology.

I am talking about the noxious trend—not just in science, but also across society in general—to focus on immediate and quantifiable payoffs. Research impact that cannot be measured after a 2–5 year grant period is simply not noticed, or if it is, it is not sufficiently considered and supported. The idea behind this attitude is imported from the corpo-

rate world, and implies that the more money we throw at a problem, the faster we will solve it. How wonderful would it be if we could skip over the uncertainties of basic research straight to applications with societal and economic impact?

The problem, of course, is that this view of science is fundamentally misguided. Our obsession with productivity and efficiency is a disease. Not only is it impossible to avoid failure, dead-ends, and the serendipity of fundamental scientific discoveries, but our unhealthy focus on producing more and more results in less and less time is actually counterproductive.[4] It makes an increasing number of people feel exhausted, sick, and unhappy. It puts unreasonable pressure on scientists, and yet fails to achieve its aims because nobody can be forced to be imaginative. It makes people lose sight of the meaningful things in life, since it prevents us from taking a step back, from opening up our mind, from reflecting on our situation. In this way, it severely impedes radical breakthroughs that require thoughtful investigation and free exploration. These breakthroughs are an important driving factor for scientific progress. It is impossible to predict them,[5] or even to recognize them, since their impact is often difficult to assess at first sight. A revolutionary discovery can be quite disruptive initially, and its beneficial effects are frequently delayed by years or even decades.[6] In contrast, our current funding and hiring system encourages the steady production of unspectacular incremental—and, dare I say, often dull—research updates, that fatten up many an academic CV. This cannot be right. The system is broken.

This problem affects biology in particular, since we find ourselves at a crucial stage in the history of the discipline. Systems biology can make essential contributions to the paradigmatic shift back from reductionist to integrative and organismic approaches to the life sciences. This important transition will involve tackling quite a number of problems that are conceptually difficult, or otherwise risky, or projects that will take a considerable time to complete and produce specific results. However, our constant rush and push leads us to avoid the difficult questions, even if they're central.

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[4] One is reminded of NASA's "faster, better, cheaper" philosophy that managed to crash space probes into Mars at an ever increasing frequency. This notion of efficiency (and its implied expectation of a free lunch) shows remarkable similarities to the situation in science today. The effects will be predictably and depressingly similar as well.

[5] Rescher (1996) points out that if you could predict future scientific discoveries, you would already have made them!

[6] Think of the laser, positrons, or thermophilic enzymes, all discovered serendipitously by scientists unconcerned with their potential applications, which took decades to have their massive scientific, technological and/or societal impact.

One example of a difficult biological challenge is the need for causal-mechanistic explanations[7] for extremely complex systems. Such explanations are hard, maybe even impossible, to obtain, but they are absolutely required if we are to truly understand physiology, development, evolution, or complex genetic disease (see also question 5). The situation is similar when it comes to understanding the brain, not even mentioning the problems of mind and consciousness. Mechanistic, systems-level understanding of any kind not only requires large-scale experimental efforts, but also conceptual advances. In other words, it requires new ideas, new perspectives, both scientific and philosophical (see question 2). Developing these ideas and perspectives will take time, time that we currently do not allow ourselves to have.

This highlights a second issue with biology today. Researchers in many disciplines—especially those dominated by molecular biology in the past few decades, such as cellular and developmental genetics—fail to appreciate the importance of theory.[8] Nowadays, projects that tackle big problems usually consist of industrial-scale consortia of one sort or another focusing on data collection. Think of large sequencing projects, the ENCODE project to catalogue regulatory elements in the human genome, or current efforts to map the human brain. These large-scale efforts are excessively technology-driven, throwing big money but little thought at major issues. They inevitably disappoint in terms of the insight they provide. The reason for this is simple: if you do not have an interesting question, you are unlikely to get an interesting answer. While we do not necessarily need strictly hypothesis-driven investigation, thoughtful, curiosity-driven research is a must. If we continue the way we are currently going, we run the danger of ending up with massive mountains of big data that nobody can interpret. Systems biology should not reinforce this trend, but rather provide new ways for making sense of life. What we need is a more balanced combination of theory and experimental practice, and more adequate communication between them. The philosophy of biology should certainly be of help in this context. Philosophers and theoreticians have made important contributions to highlight the importance of theory in disciplines where it is generally underrated. Unfortunately, the message is all too rarely heard within the community of experimental biologists. In my view, this must change if systems biology is to achieve its true potential.

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[7] The notion of "causal-mechanistic explanation" used here is somewhat similar to the neo-mechanical philosophy of science, but with a stronger emphasis on dynamics and explicit formulation in mathematical terms (see Jaeger & Sharpe, 2014, for details).

[8] It is important to stress that other disciplines within the life sciences, such as physiology, evolutionary biology, or neuroscience, exhibit a much more mature balance between theoretical and experimental work.

4. What have been the most significant advances in systems biology?

I have defined modern systems biology as a closely-knitted combination of dynamical modeling with experimental data (see question 2). This integrative approach has yielded important new insights into fundamental aspects of biology. For the sake of brevity, I am only able to mention a few outstanding examples.

The first model that used a systems-biology approach to accurately reproduce a biological regulatory process is that of Alan Lloyd Hodgkin and Andrew Huxley, published in 1952. It marks the birth of data-driven systems biology.[9] The Hodgkin-Huxley model simulates the propagation of nerve pulses along the giant axons of squid and cuttlefish. It was later expanded, by Denis Noble and many others, resulting in complex multi-level dynamical models of the heart, which consider gene expression, cellular physiology, tissue geometry, and blood flow patterns. These models have reached a level of accuracy and complexity that enables researchers to simulate heart conditions with the aim of developing and testing new treatments. At a more theoretical level, they show that causation in biological systems cannot be reduced to genetics alone, as multi-level simulations are essential in order to understand the proper physiological and tissue context in which genes exert their effects.

Outside physiology, systems approaches became established much later. We can observe a gradual evolution of purely theoretical dynamical modeling to more data-driven approaches from the 1970s onward. Several success stories resulted from this trend. One remarkable example concerns the robustness of regulatory processes towards genetic and environmental perturbations. Robustness can be seen as the quintessential systems-level characteristic of biological systems. Pioneering work by Naama Barkai, Uri Alon, and others in Stanislas Leibler's group at Rockefeller University in the 1990s revealed that adaptation in bacterial chemotaxis is due to structural properties of the underlying regulatory network, such that the functional output of the process does not depend on precise conditions or parameter values. Similarly, Gary Odell and co-workers discovered that the robust maintenance of segmental boundaries during *Drosophila* development depends on particular feedback mechanisms encoded by regulatory network structure. Further analyses of network models, by Andreas Wagner and others, show that robustness is either a distributed property of whole networks, or can be caused by redundancy of regulatory interactions. In addition, these models revealed the counterintuitive fact that robustness is necessary to explain evolvability—the capacity to change and innovate—in biological sys-

[9] This work also resulted in the only Nobel Prizes that systems biologists have won so far.

tems.

Other success stories include the elucidation of the feedback mechanisms underlying biological oscillations (Goodwin, Novak, Tyson, and others), the clock-and-wavefront model of vertebrate somitogenesis (originally published by Cooke and Zeeman), and various efforts to study the dynamic mechanisms of gradient-based pattern formation. All of these studies provide dynamic explanations of important cellular or pattern-forming processes in terms of regulatory structure. Comparing such structures across cell types, tissues, and organisms in turn allows us to uncover design principles of regulatory circuits; circuits that achieve a wide range of different functions, in a wide range of different biological contexts. In my view, the impressive progress we have made in this field over the past few years is one of *the* major advances in systems biology.

Simulation studies will always remain somewhat limited in their explanatory power. A deeper level of understanding can be achieved by investigating the geometry of the configuration space of dynamical models. For instance, robust systems are evolvable since they exhibit neutral drift along so-called "genotype networks", which allow them to access new adaptive phenotypes more easily. Simulations establish that such genotype networks exist, and that they do indeed lead to the predicted behavior under suitable conditions. However, simulation studies do not tell us *why* genotype networks have the geometrical properties underlying their role in evolvability, how they are arranged in configuration space (Jaeger & Monk, 2014). The complexity of biological systems makes configuration space analysis a daunting challenge. Nevertheless, several theoretical and practical studies have led to interesting insights using this approach: from René Thom's catastrophe theory, which provides the theoretical foundation for the clock-and-wavefront model described above and indicates that only a limited number of different morphological transitions are possible, to Goodwin's structuralist models for the evolution of development, to more recent studies by the groups of Reinitz, Siggia, and others, that characterize pattern-forming processes in terms of attractors and their associated basins. These pioneering efforts promise a whole new kind of understanding of biological regulatory processes.

The reader may have noticed that most examples mentioned so far are from physiology, cell, or developmental biology. The application of systems biology approaches to evolutionary biology remains more limited (see also question 5). These efforts either remain somewhat disconnected from empirical studies, as in the case of the work on robustness and evolvability described above, or are restricted to simulation studies of specific evolving developmental processes (e.g. mammalian

tooth evolution, the evolution of endomesodermal specification in echinoderms, or the evolution of the nematode vulva). It is still too early to assess the wider impact of these investigations, but the fact that we are starting to understand evolutionary dynamics in terms of systems biology is an important advance in itself.

Finally, I need to briefly mention that dynamical systems approaches and simulation studies also lie at the heart of the emerging discipline of synthetic biology with its many significant potential practical implications. A proper discussion of those, however, is far beyond the scope of this essay.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

Throughout my answers I have argued that we need a better understanding of the dynamic mechanisms underlying biological regulatory processes. For me, this is *the* central challenge for systems biology at this point. It will require a conscious shift of focus towards process thinking: more studies of interaction dynamics, less parts lists! It will also require new empirical research efforts—motivated by this shift of focus—that aim at investigating the dynamical repertoires of as many experimentally tractable regulatory processes as possible (Jaeger & Crombach, 2012). This bottom-up approach is the only way to establish whether there actually *are* generalizable principles of biological regulation, and if they exist, what they are like.

The core ingredient of such a research program is a shift from static, correlative, statistical explanations for regulatory processes to dynamic, causal, mechanistic ones (see hairball interpretation, question 2). I do not only want to know how system variables correlate with each other (the hairy connections within the hairball), I want to know which of those connections actually contribute to the regulatory process under study. "Mechanism" (or "mechanistic") does not need to imply that we have to reduce everything to the molecular level (Jaeger and Sharpe, 2014). Quite the contrary: the causally efficient rules governing a system—through its regulatory structure—could be situated at all kinds of scales or levels (see the example of the heart in question 4). Such a multi-level approach is in fact essential to deal with emergent properties such as behavior at the cellular, tissue, or whole-organism level, with trophic interactions in food webs, or with the emergence of thought processes in neuronal nets.

To obtain these kinds of explanations, we need mechanistic models of incredibly complex systems. This requires large efforts to measure relevant systems variables at an acceptable level of accuracy, powerful

numerical algorithms for model optimization and simulation, as well as sophisticated analysis methods able to deal with large and complicated computational systems. While some promising approaches already exist, we cannot solely rely on existing methodology for these tasks. We need to expand our methodological and conceptual toolkit. We may encounter organizational and technological limits, or human limits of comprehension when it comes to complex, feedback-driven, non-linear systems. These limits may be hard to transcend. Drawing a hairball is easy; describing and understanding its dynamics is very, very difficult.[10]

Expanding our methodological and conceptual toolkit will allow systems biology to pay more attention to central biological disciplines that it has neglected so far. This is especially pressing if the potential contribution of systems approaches to such a discipline seems important, timely, and feasible. A good example for this is evolutionary biology. Evolutionary systems biology is still at a very early stage (see question 4). It aims at understanding both how particular regulatory processes evolved, and how their regulatory structure—defined by the associated geometry of configuration space—influences evolutionary dynamics. This could be achieved through the comparative study of reverse-engineered regulatory systems across different groups of organisms, or the *in silico* evolutionary simulation of the possible transitions between observed regulatory structures. Such a structuralist theory of evolving regulatory systems would complement our current knowledge of evolutionary genetics, thereby closing an important gap in our knowledge of how evolution creates novel phenotypes. Again, the main problem is how to deal with the amazing complexity and diversity of biological systems. Considering the potential gain, this is a challenge well worth tackling.

Let me close this essay by summarizing and reiterating that all of the challenges for systems biology that I have discussed here revolve around the crucial and central philosophical question of the limits of our understanding. Clearly, our current computational, mathematical, and conceptual tools are inadequate to deal with the daunting complexity of biological regulatory systems. Important aspects, such as the self-preserving and self-reproducing nature of life are difficult to deal with. Some have even argued that our current mathematical frameworks are entirely inadequate to explain life itself, even in principle. Are there new mathematical theories to be discovered, then? Theories more powerful and suitable than those we have now? And even if such formal-

[10] Understanding goes beyond being able to simulate a process. We want to avoid the kind of systems biology that replaces a complex biological system that we do not understand with a complex computational system that we do not understand.

isms exist, how much can biological complexity be reduced and simplified to render it understandable? Is it more useful to use an analytical or an algorithmic approach? Do you understand life if you can simulate it (although you may not understand the simulation)? These and many other questions await both systems biologists and philosophers of science: Exciting times indeed.

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Extracting Phenomena, Integrating Explanations, and Styling Representations: Some Frontiers for Philosophizing about Biology

1. How and why were you initially drawn to systems biology?

Like many of my philosophical interests, my initial attraction to systems biology was accidental. During the 2010-2011 academic year, my university was developing plans for a partnership with University of Rostock. I received an email notice that there was a systems biologist at Rostock interested in collaborating with a philosopher of science. That is how I met Olaf Wolkenhauer, and he graciously hosted me in his lab for two months during Summer 2011. My prior work in philosophy of science had focused on issues about idealization and confirmation in physics. Olaf and his research group were very generous in trying to explain to me what they were up to as systems biologists, and Olaf also was keen to point me toward topics from his practice that struck him as raising philosophical issues – such as the prominence of diagrams and visualization tools, debates about emergence and what that means "on the ground" for research on carcinogenesis, and the absence of organizing principles or other theoretical foundations for systems biology.

I suppose there were a few reasons I stayed interested in systems biology after leaving Rostock. The first is the willingness of Olaf and his researchers to keep open channels of communication and collaborate for my own research – providing feedback about the science, directions to resources, constructive criticism about possible theses. This has led, so far, to a jointly-authored paper (Jones & Wolkenhauer, 2012) – and I think I am not alone in finding systems biologists to be especially open to collaborating on research projects.

The second reason I stayed interested is that debates involving systems biologists (amongst themselves, or with more traditional biolo-

gists) are not only live but also lend themselves to being understood with minimal biological and mathematical literacy. My few years in college as a physician assistant major (prior to switching to philosophy), together with the math I learned to be able to talk about statistical mechanics, give me enough background knowledge to be able to track the reasoning in biology journal articles, understand computational models (typically differential equations of some kind), and fill in most of the gaps I have about the biology by reading on my own. Whatever the reason, I do not often have the feeling I often had while thinking about philosophical issues in physics, of the mathematics being an obstacle to doing the philosophy. Because the field is relatively new and the debates are live, I also have the feeling that it is possible to say something that is philosophically original.

The third (and maybe final) reason for my continuing interest in systems biology is that it presents philosophical issues that strike me as new and exciting. For example, I have focused most of my attention so far on the role of network visuals (especially node-link diagrams) in helping to amplify cognition of various kinds. This is not a topic much discussed when philosophizing about other sciences, even though visuals are prominent in all disciplines. But I am getting ahead of myself – I have more to say about this under a different question heading. Suffice it to say that being interested in network visuals naturally leads into all sorts of other exciting issues – different kinds of explanation (neither mechanistic nor selectionist), epistemic challenges of curating and sharing models, and criteria for assessing visualization tools, just to name a few.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

For my own approach, philosophy is to systems biology as sport trainers are to professional soccer players. Sports trainers typically sit on the sidelines, watching the game intently, talking to others about what the players are doing, maybe debating with others about various referee calls or tactical decisions; but on occasion the match gets disrupted or stalled, and the trainers get onto the field to interact with the players to engage the problem at hand and give them whatever help they are able to provide.

I see philosophers doing much the same activities with respect to systems biologists. Systems biology is where all the epistemic action is at: there are new practices, methods, strategies, disciplinary integrations, and debates. There is a lot to keep philosophers talking about as they try to understand the epistemic aspects of this activity – so much so, I think, that it is no surprise that we have yet to see an impulse to import

more general and familiar philosophy of science issues (about scientific realism, for example) into the systems biology context. But while philosophers are largely on the sidelines of systems biological activities, I think they are equipped for an advisory or assistant role, too – in clarifying explanatory assumptions, distinguishing explanatory strategies, better formulating the specific phenomena of interest, providing methodological advice – often in the form of lessons extracted from case studies of successful or failed science – and about ways of integrating approaches from different disciplines or ways of conceptualizing model relationships.

I can be a bit more specific about this. Were they to pay more attention to systems biology, philosophers of science would encounter too many of the developments associated with the new era of "big data" and, in the biological context, with the proliferation of –omics technologies. There is some of this in other sciences (maybe climate science). But I think biology stands out as a discipline in which there has been a wild flowering of interdisciplinary approaches – bioinformatics, for example, and applications of informational visualization. This flowering has not kept pace with our understanding. For example, there is a small industry devoted to creating visualization tools for biologists. One of the prominent standards for assessing whether these tools perform well is whether using the tools facilitates insight; but there remains conceptual confusion within the info-vis community about just what counts as an insight, about how to measure or even count insights, and about whether insight is the proper standard for success as opposed to, say, some speed-related standard (see Saraiya et al., 2005.) This is just the sort of issue for which philosophers of science, and maybe even some epistemologists, are especially well equipped to address.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

I am going to rephrase this question to focus on philosophy of biology in the late 20th century and early 21st century. Anyone familiar with the field will know that philosophy of biology has been predominantly focused on evolutionary biology. Some might also share my opinion that philosophy of biology – and perhaps philosophy of science more generally – remains predominantly focused on its own literature, developing or criticizing philosophical views that, in some cases, stretch back for decades with minimal new input from looking at historical or contemporary scientific practice. Certainly this is the impression (and frustration) I have when I look at the textbooks targeted toward undergraduate courses. So I think there are very many neglected topics, and it is hard to rank which of these are most neglected. Because I have

been interested in the cognitive role of visuals in systems biology, I will list some issues related to this topic that merit more attention than they have so far received from philosophers of science. There are a few other neglected topics, too, and while I have not been working on them, I think they are worth thinking about and fertile ground for all kinds of research activities, including interdisciplinary workshops, conference symposia, dissertation projects, and collaborative grant proposals.

Visuals. A neglected topic, of particular interest to me, refers to the benefits that different representation formats, and especially visual formats in contrast to sentential/linguistic ones, provide for epistemically oriented cognitive activities such as hypothesis generation and discovery, data aggregation and organization, model construction and simulation, and explanation of various kinds. Visual representations are so prominent and relevant for biology – and especially, I think, for systems biology approaches – that they are often objects of special interest. There are research organizations, such as the National Center for Biotechnology and Information in the United States and Kanehisa Laboratories in Japan, that support databases for archiving and sharing visuals. Bioinformaticians develop tools for creating, editing, and curating visuals. International consortiums, such as the Systems Biology Graphical Notation (SBGN) project, circulate and refine standards for visual nomenclature (Novere et al., 2009).

Our understanding of the role of visuals in biological practice, from both philosophy and cognitive science, has not kept pace with these developments. This is, I think, an underappreciated area for philosophical inquiry – and an attractive area too, if you enjoy putting visuals into papers and presentations. William Bechtel's research group has done good work in cataloging the kinds of visuals relevant for representing and constructing mechanisms (see Sheredos et al., 2014; Abrahamsen and Bechtel, *forthcoming*.) But there remain very many issues for philosophers. Regarding construction of visuals, there are issues about whether and how visuals amplify cognition in a way that sentential representations do not, about the cognitive affordances and limitations of different kinds of visuals, and about the kinds of assumptions model curators tend to make for the sake of storing and standardizing models and their associated visuals in a way that makes such products accessible and ready for integration. Regarding uses of visuals, there are issues about how practitioners use curated models and visuals (as opposed to originals) when doing their own research, about how to measure the quality of visualization tools, and about the merits and drawbacks for competing notational schemes (say, SBGN diagrams versus molecular interaction maps). This is a fertile area for cognitive science work, too, because much of the existing research on visual representations focuses on visu-

als from mathematics (usually geometry) and physics (usually statics).

Big Data. Beyond my own current interests, I will mention two further topics in general philosophy of biology the neglect of which I find particularly surprising. The first concerns so-called "big data" made available by various –omics technologies. Issues about visualization are relevant here, too. But more generally, I think philosophers of biology have yet to explore adequately the assumptions that go in to using this data, filtering away noise, and constructing stable phenomena to be explained (but see Leonelli, 2014). Moreover, systems biologists usually are very attuned to what's going on with new high-throughput data generating processes – and there is an interesting tension between the kinds of data experimentalists are generating and the kinds of data I think systems biologists wish they could get. This strikes me as an interesting issue for the sociology of science – regarding what drives experimentalists to continue producing data that we're not quite sure how to use. But there seem to be interesting philosophical issues in this area, too – regarding, say, the kind of reasoning systems biologists use to make available data relevant to their models, how data availability affects or constrains choice of model design, and the extent to which data constraints drive different (non-mechanistic, non-selectionist) explanatory strategies.

These issues also lead naturally to issues about how to represent this data. I think this remains relatively neglected by existing, scientifically-informed analyses of representation in biology, because those analyses typically focus on relatively small pathways (or mechanisms) whereas systems biologists often are inclined to use big data to construct relatively large networks. I have tried to broach this issue in the context of using networks to produce topological explanations (Jones, 2014). But this does not scratch the surface of interesting philosophical topics: differences among kinds of networks (see Bachmaier et al., 2013), how clustering works (see Fortunato, 2010), the benefits of modularization (see, for example, Rives and Galitski, 2003), ways of representing networks beyond node-link diagrams (say, as heat map adjacency matrices – see Wilkinson and Friendly, 2009), and cognitive affordances of network thinking (see, for example, Giuliani et al., 2014).

Confirmation. The second generally neglected topic concerns confirmation. Much of the literature in philosophy of biology focuses on conceptual or explanatory issues. This is not a bad thing, because this has led to some important advances in the philosophical discussion. But the focus has tended to push far into the background discussions about confirmation: of mathematical models, of design or organizing principles, and of simulation results. Some of the philosophical literature on robustness touches upon confirmation issues, but so far not in an organ-

ized and deliberate manner. I have done some work (still unpublished), for example, on how biologists use different measures of parameter robustness to rank competing models with respect to comparative plausibility, especially in situations where available evidence either favors no model over others or is jointly inconsistent. But this is kind of a special case, and there seems to be much work to be done in understanding, say, the relation between model validation and model confirmation, or the success criteria for theorem-based organizing principles, or whether models can be validated by data used for parameter tuning (see Carusi, 2014). Established results about confirmation in other sciences might be relevant here; my hunch is that these other results require tailoring to the specific contexts of high throughput data and systems approaches.

Diversity of Models. The third neglected topic concerns the nature and kinds of models. There's a big literature on models in general philosophy of science, and one of the most prominent approaches distinguishes broadly between theoretical models and mediating models. This distinction finds ready application in physics – for example, Newton's laws of motion are theoretical models and specific force laws are mediating models. Of course there are other kinds of models, too: toy models, floating models, data models. Examples of these are also easy to find in physics. What has been neglected, not only by philosophers of biology but also by more general philosophers of science, is whether these categories fit well with the kinds of models one finds in biology and, especially, in systems biology. There is some recent work on mathematical models in systems biology, for example among philosophers developing the idea of dynamic mechanistic explanations (see, for example, Brigandt, 2013). But much work remains to be done in cataloging the many kinds of models to which systems biologists appeal, and this is probably a necessary preliminary to figuring out what insights, if any, systems biological modeling provides for well-known (and usually physics-based) distinctions among kinds of models in science.

4. What have been the most significant advances in systems biology?

I am going to rephrase this question too, to address the most significant advances in philosophy of systems biology. I would say the best advances – at least, the ones I find most interesting – fall into three broad categories: emergence, explanation, and integration.

Emergence. One of the pieces of rhetoric I often hear from systems biologists, especially when asked to reflect on their own work, is that a systems approach to biology differs from more traditional approaches by virtue of being emergentist rather than reductionist. Being familiar with the literature from philosophy of mind, I often have the feeling that what the biologists mean by emergence is not what the philosophers

mean – and, in particular, that the kind of emergence of interest to philosophers is much stronger than the kind of interest to systems biologists. I think philosophers of systems biology have made helpful conceptual contributions here, by clarifying different kinds of emergence and giving the systems biologists a better conceptual toolkit for saying how they think their scientific approach, and how the kinds of systems-level properties they find interesting differ from more traditional biological approaches and more traditional objects of biological inquiry.

That said, there is still work to be done. For example, to take one of Olaf's interests, the tissue organizational field approach to carcinogenesis is prima-facie quite different from the standard somatic mutation approach. The former takes carcinogenesis to be caused by tissue-wide events - the latter by events within individual cells. Advocates of the tissue organization field theory often say that theirs is an approach to cancer as an emergent phenomenon, in contrast to the reductive approach of traditional biologists (see Soto and Sonnenschein, 2006). But, quite apart from the empirical credentials of either approach, there remains conceptual work to be done in clarifying the kinds of tissue-cell relations at issue. For example, are tissue events nothing more than collections of intercellular events? Is appealing to intercellular events compatible with reductionist approaches to carcinogenesis? Is there anything substantial in the idea of downward causation (from tissues to cells), or does this just amount to a kind of agglomeration of causal relations from many cells to one cell? (For some progress, see Malaterre, 2007; Bertolaso, 2011.) There are metaphysical issues here, but I think the more important ones center on clarifying what the tissue organization field theorists are trying to say. Similar issues are relevant for the many other contexts in which systems biologists use the language of emergence.

Explanation. There is often a tight connection between issues about emergence and issues about causation and explanation. In philosophy of biology, the dominant approach to these latter issues focuses on mechanisms and mechanistic explanations. There has been much good work on mechanistic approaches in the life sciences, but – after quite a few conversations with William Bechtel, Sara Green, and others – I think the success of this work has tended to distort the philosophical literature by putting pressure on people to position their work in relation to the literature on mechanism. One of the major contributions from philosophers of systems biology has been to start to move the discussion back toward a focus on what is going on in scientific practice, by bringing to our attention explanations that are quite unlike typical mechanistic ones. These explanations are also not like typical selectionist explanations – and for this reason I think the philosophers of systems biology

are advancing our understanding of scientific explanation by highlighting largely overlooked kinds of biological explanation.

The non-mechanistic, non-selectionist explanations have been given many names – design explanations, topological explanations, explanation via organizing principle, among others (see, for example, Wouters, 2007; Huneman, 2010.) There remains work to be done in figuring out what, if anything unites these kinds of explanation and distinguishes them from mechanistic and selectionist ones. There is a similar discussion in philosophy of physics at the moment, where the project is to identify kinds of non-causal explanation. There the tendency seems to be to contrast causal models with abstract or mathematical ones. But I think philosophizing about explanation in systems biology will show that this is not the most fruitful contrast to make: so-called dynamic mechanistic explanations, for example, are nonetheless abstract and mathematical. In collaboration with Sara Green, I have been trying to conceptualize a third broad category of what we are calling constraint-based explanation. This is a kind of explanation in which formal constraints, rather than mechanistic details, provide the explanatory *oompf*. We think this kind of explanation is especially prominent among systems biologists, and that the focus on formal constraints is what unifies design, optimality, and other otherwise diverse explanatory strategies. We might be mistaken, of course – but this is at least one nice example of how new explanatory approaches in systems biological practice facilitate new philosophical ideas about biological explanation.

Integration. Systems biology is, in essence, an integrative discipline: it does not merely apply, say, network theory to biological systems, but adapts that theory to the particularities of the biological context. A particularly apt example here is Watts and Strogatz's "Collective dynamics of 'small world' networks" (1998), which not only uses network theory to think about how infectious diseases propagate but also introduces into network theory the "small world" property – a property to which mathematicians interested in network theory had hitherto paid little attention. There remains much philosophical work to be done in examining the fruits of this kind of integration. For instance, there is woefully little philosophical literature about networks (as opposed to mechanistic pathways), different ways of representing networks (node-link diagrams, adjacency matrices, heat maps), or the relationship between network elements and network topology. But philosophy of systems biology has at least done the service of turning philosophical attention toward the reality of integration, the problems surrounding integration, and resistances to integration.

This progress has been especially fruitful with respect to explanation. Philosophers of systems biology are doing a good job of identifying dif-

ferent explanatory strategies and addressing how these strategies might complement each other. This is an area where the philosophers can help the systems biologists in the field, as it were – for example, by helping to clarify debates about whether systems biological accounts are properly explanatory (see Green et al., 2014). This is also an area that has rather direct significance for people in other disciplines struggling with integration. I imagine that many theoretically-oriented systems engineers, for example, would be interested in methodological advice about how integration might happen (between, say, network theory, organizational management, and design engineering), about what an integrated approach might look like, and about what has worked and what has not for other systems disciplines (such as systems biology).

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

Issues about the kinds of explanation in systems biology, as well as the differences and compatibilities among these kinds, are starting to receive attention from philosophers. Issues about confirmation, less so – but these issues are difficult in general. I think the best way to continue making progress on these issues will be to start increasing the attention paid to the relata of confirmation and explanation relations, namely, phenomena and "theoretical" representations.

Phenomena. I have mentioned some of the issues about phenomena I think are important, namely, how phenomena are constructed from data, the assumptions that go into this construction, how different kinds of representation (especially visual representation) help to establish or communicate phenomena. But, in large part because of conversations with William Bechtel, I think that being clearer about differences in the way biologists characterize the phenomena in which they are interested – in terms, for example, of actual or possible behavior, general pattern vs. specific detail, qualitative vs. quantitative feature – also would be very helpful for understanding whether, and the extent to which, systems biological approaches actually embody pluralistic explanatory strategies. Progress on this research strikes me as primarily a matter of philosophers taking the time to look closely at the scientific literature, and perhaps receiving some guidance from systems biologists about where to look for the sake of having a varied sample.

Representations. I have also mentioned some issues about representation I think are important, namely, how different formats amplify cognition, as well as the underlying assumptions and kinds of network representations. But there are issues that connect more directly with more familiar topics from philosophy of science. These include identifying

the different kinds of idealization and abstraction systems biologists use for constructing models; and examining how the appeal to certain formal constraints – such as laws of mass action of Michaelis-Menten equations – affects the scope or validity of models. One might also examine ways in which biologists motivate, justify, and correct model assumptions; the strengths and limitations of different modeling approaches for different purposes or for different degrees of data availability; and how model curators introduce or alter model assumptions for the sale of storing and curating models. Progress on this type of research strikes me as quite feasible, if only because philosophers of physics have been successful in pursuing similar issues. Progress here also strikes me as relevant for those in other systems-oriented scientists, such as systems engineers, who are struggling to make sense of what an explanatory or foundational theory would look like for their discipline and what forms newly integrated theories might take.

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14

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Systems biology: Science or Technoscience?

1. How and why were you initially drawn to systems biology?

Since finishing my university education in biology I have been researching epistemic practices and cultures within the life sciences. The experienced fundamental, but unexplained differences between doing ecological field work as opposed to doing molecular biology lab work had left me puzzled and unsatisfied with the very foundations of the scientific discipline I had just earned a degree in. With no fixed curriculum in science and technology studies (STS) offered in Vienna at that time, I underwent a second, self-assembled university education consisting of lectures in philosophy of science and STS, courses in qualitative sociological methodology and active participation in a cultural anthropology working group.

Very much in line with this personal source of motivation, my first STS research project ('Science as Culture', starting in 1999) focused on the enculturation of biology students as compared to students of physics, literature and history. The empirical and analytical work performed therein sensitized me for major differences between more or less distant epistemic communities as they are actualized and conveyed via university curricula, including different ontologies, epistemologies, values and habitual norms. This project also helped me understand what it means to belong or not belong to a certain academic tribe in all its multi-facetted day-to-day reality.

A second research project ('Cultures of Non-Knowledge', 2005-2007) made me focus on the diverse epistemic cultures[1] implicit in ex-

[1] In short, the term 'epistemic cultures' refers to an analysis of science by anthropological means. Scientists are understood as members of a specific research community (or 'tribe'), research is analyzed as a cultural as much as an epistemic practice (for examples of this approach, see Latour, 1987; Becher, 1989; Knorr-Cetina 1999).

pert advice on risk regulation (within the fields of agri-biotechnology and mobile phone use) and their roles in the formation and stabilization of expert dissent. Both these projects – 'Science as Culture' and 'Cultures of Non-Knowledge' – addressed scientific cultures as a mostly given context of individual action. Even though they left room for an understanding of culture as process and enactment, something that is again and again re-interpreted and re-actualized by individual action, they could build on the assumption that the major ontologies, normative settings and boundary drawings[2] of a scientific community were not open for dispute; neither processes of enculturation and socialization nor the enactment of expert authority are typical situations in which such fundamental norms would be open for dispute (at least in the researched cases). Rather, the stability and matter of course character of scientific cultures tend to be over-emphasized in both contexts for didactic as well as strategic reasons.

When Regine Kollek from the University of Hamburg invited me in 2009 to contribute to a research proposal targeting the epistemic culture of systems biology I was both enthusiastic and cautious. The envisioned project would focus on the question of how systems biology deals with complexity and which specific cultural traits, community characteristics and epistemic practices are developed in this context (going beyond the crude observations that the field is multi-disciplinary, combines 'wet' and 'dry' laboratory research in allegedly iterative circles and makes use of mathematical algorithms and computation). It would also provide me with an opportunity to reconstruct the relevance of epistemic cultures within present day-to-day life science research activities (e.g., do systems biologists share specific norms and how do they become relevant in research conduct?). This aspect together with Regine's recognized expertise in both the life sciences and cultural anthropology certainly weighed on the positive side. On the other hand, I was aware of some major challenges of the planned undertaking.

[2] 'Boundary drawing' refers to determining who belongs to a given community (and who doesn't), what makes you belong to it (or not belong to it) and executing the difference between belonging and not belonging to this community. Traditionally, a given epistemic community (e.g., that of molecular biology) would draw a boundary to other epistemic communities (e.g., that of mathematicians) as well as to other, non-epistemic communities or actor fields (e.g. that of politicians or journalists). For synthetic biology, to give a more recent example, drawing a boundary to 'old' and 'inadequate' attempts at introducing engineering to biology within biotechnology has become an important aspect of identity work. Moreover, boundaries are drawn between 'rightful synthetic biology' or 'synthetic biology in a strict sense' (in one interview called "the MIT bubble – that is, MIT plus Imperial College") and other approaches that are (allegedly) unrightfully labelled as synthetic biology.

(1) Day-to-day-research activity does not highlight cultural stability and boundary drawing as did the two former cases of enculturation and expert dissent. (2) Systems biology allegedly stands for a field in a state of emergence and hence of ongoing changes. (3) It very likely represents a new mode of institutionalizing science, including new modes of field formation, characterization and stabilization. (4) The empirical analysis of systems biology is complicated by systems biology's multi-disciplinary and heterogeneous identity. (5) Understanding the basic scientific aspects of systems biology is tremendously challenging in itself due to its multi-disciplinary character, spanning not only cutting edge life science knowledge and methods, but also mathematics and computational science. (6) With systems biology linking local and global realms in particular ways (just as every other research field), the decision where to perform the empirical work becomes difficult and influential. And finally (7), in drafting the specific project proposal, it was unclear how a comparative approach that is methodologically prerequisite for the reconstruction of epistemic cultures should be set up empirically.

Despite these challenges, the research proposal was successful and I was left with searching for ways to deal with them in a constructive way. In fact, the original research project under the title 'Towards a Holistic Conception of Life? Epistemic Presumptions and Socio-Cultural Implications of Systems Biology' (2010-2013) is now being followed by another project focusing on the "(Techno)Epistemic Cultures of 21st Century Life Science" (2014-2018), directly building on the gathered insights. That leaves me with the opportunity to research systems biology for a time span of more than eight years; a fact that thrills me in a positive way most of the time, but sometimes also makes me despair. Like with most qualitative research, one key to success is to translate the aforementioned challenges into epistemic resources, to see the exclamation marks that are already hidden in the question marks. One major thesis I already gathered from the accumulated material is that systems biology as a (techno)epistemic culture shares a lot of its characteristics with other contemporary Big Science research approaches such as modern brain research rather than gaining its identity solely from (a linear advancement of) its historical forerunners. In other words, when looking at its cultural traits, systems biology is *firstly* characterized as a contemporary Big Science endeavor and only *secondly* as relating to a molecular biology tradition. When looking at the various sub-communities within systems biology and the interplay of systems and synthetic biology, the picture of course becomes more complex. These observations also raise the question what kind of category 'systems biology' represents: a discipline, an inter-discipline, a sub-discipline, a research approach or a new paradigm?

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

Speaking from an ethnography of science point of view, It seems to be one of the peculiarities of systems biology that philosophical questions have been raised since iits establishment (that is, around the year 2000) in central scientific fora and that scientists as well as philosophers of science actively contributed to the discussion. The volume of this early philosophical reflection adds to, but also goes beyond the more general trend to accompany the kick-off-phase of newly emerging fields with a rather high percentage of review articles as compared to research papers. In close proximity to the emergence of systems biology, we can observe a rekindling of some old(er) philosophical questions of the life sciences: discourses on vitalist versus mechanistic ontologies, on reductionism versus holism, on Lamarckism vs. Darwinism; conceptual discussions about evolution (that is, 'natural', 'artificial' and 'instrumental' evolution), complexity, emergence and autopoiesis; methodological debates about the integration of qualitative and quantitative, epistemic and technological approaches.

With the active and frequent involvement of philosophy/philosophers, systems biology has been attributed with a nimbus that makes us think of 19th century conceptions of science, when science and philosophy were much closer to each other and science – then labelled as "philosophy of nature" or "Naturgeschichte" – was subsumed under the general category of philosophy. Such an anachronistic re-make of the field's habitus is also facilitated by systems biology's inter- or transdisciplinary ambition (the latter assignment following Stichweh's definition of transdisciplinarity, see Stichweh, 1994) and systems biologist's attempts to overcome the high degree of disciplinary differentiation and segregation that was institutionalized over the past century. A further observation (that has yet to be validated methodologically) adds to this line of thought: systems biology papers tend to quote earlier literature than other comparable scientific papers. Points of reference that date back to the midst of the 20th century are no uncommon features of such publications.

Other, more practical aspects of systems biology also stimulate an active exchange between philosophy and systems biology: systems biology as an inter- or transdisciplinary undertaking is already trained in addressing the burdens of multi-disciplinary collaboration and communication, hence facilitating an exchange with philosophy as yet another field of expertise. Moreover, the attempt alone to address the experienced difficulties and ambiguities of interdisciplinarity leads systems biologists into philosophical territory. And, last but not least, systems

biology is also a project of emancipation from traditional (mostly molecular biology) approaches that can only benefit from addressing specificities from a third point of view. A rekindling of debates on what life is and how it can be grasped scientifically is potential tailwind for its legitimization.

On the other hand, current systems biology clearly is a 21st century undertaking. That means that broadly speaking, philosophical debates are rated as a "nice to have" add on, not as *a sine qua non* of day-to-day research practice. Much of doing systems biology does not necessitate any explicit philosophical reflection and we are far from a situation where philosophers of science are indispensable members of any systems biology project or where philosophy of science represents an obligatory part of any academic career in systems biology. There are no traces to be found of an implicit hierarchy that would subsume science *inter alia* under a broader philosophical ambition. Rather it seems to depend on the individual systems biologist's mindset whether and how far philosophical considerations become influential in scientific practice (and, like in most current science, philosophers are not deemed prerequisite by biologists for "getting philosophical"). If a broader ambition of science is addressed (explicitly or implicitly), then it tends to point towards overarching engineering paradigms rather than philosophical ones, towards changing worlds and constructing new worlds rather than understanding them.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

As outlined above, my own approach is not a strictly philosophical one. Although much of what I do may fall within the realm of a "philosophy of scientific action" or epistemology, other aspects of my work could count as sociology of science or laboratory ethnography. To answer this question in a fruitful way, I will therefore have to widen the scope to all meta-reflection on science as practice, community and/or culture.

The one strand of analysis I have most often been searching for in vain or with unsatisfactory results, consists of historical analyses of the development and re-definition of biology as a discipline from its early beginnings until now. A short and superficial glance at the curricula of the University of Vienna reveals distinct changes in the categorization of biology – from its early beginnings as a "natural history" subsumed initially within medical education and then under the broader category of "philosophy", until its emancipation as a discipline within the canon of natural sciences and finally its recent differentiation into biology and molecular biology, both taught within the faculty of the "life sciences". What were the struggles accompanying these processes of re-labelling?

What triggered the underlying changes in ontology? What did they answer to? What relevance did they have for situated epistemologies and epistemic practices? What is the current reality and state of the category "biology" as seen against this historical background?

Due to many understandable reasons historians/philosophers of science have become rather cautious about any longue durée statements and only a few scholars dare make the jump from micro-histories to macro history or macro histories (here, I think of theorists of science and technology like Dominique Pestre, John Pickstone or Andrew Jamison). As a consequence, there is no broader scholarly debate about the major changes biology underwent and their scientific as well as societal relevance. This scholarly silence stands in stark contrast to existing more exoteric discourses (mostly situated in the contexts of science policy and science communication) that strongly draw on talk about radical shifts and disruptive developments – one only has to think of the alleged convergence of sciences and technologies, the power attributed to a new generation of technosciences[3] or the claim that synthetic biology converts biology into precision engineering.

A second strand that would be highly fruitful for my work is closely related to this first one: it comprises the area where philosophies of science, philosophies of technology and philosophies of engineering overlap. Again, there is some scholarly literature that bridges this existing gap (for example work by Davis Baird, Jean-Pierre Dupuy, Andrew Feenberg, Don Ihde, Alfred Nordmann or Jutta Weber), but it still represents an exception rather than the mainstream I would favor it to be. I also emphasize the plural of philosophies here, because local differences in the conceptions and implementations of science, technology and engineering persist until today, in defiance of all globalization and standardization efforts, and they become highly relevant in the modes in which science, technology and engineering are amalgamated in newly emerging research fields. Synthetic biologists would for instance speak about an "MIT and Imperial College bubble" when it comes to characterizing the state of the art of their field, referring to an engineering paradigm that is (allegedly) specific to the Massachusetts Institute of Technology. Other sources stress the specific cultural background of Japanese research that would blur the boundary between nature and artifacts or science and technology (cp. Steeghs, 2011) and thereby possibly also such distinctions like the one between systems and synthetic biology.

A third strand of questions that should attract more interest in my view comprises the epistemological ramifications of Big Science (cp.

[3] For an outline and illustration of the concept of technoscience, see Nordmann (2006).

Vermeulen et al., 2010), including its high degree of collaborativity, multi-sitedness, digitalization, (alleged) orientation towards external goals and/or orientation towards multiple goals and its high reliance on singular, pre-defined projects. Classical epistemological conceptions of science mostly invoke the idea of an individual thinker who over time gains insights or methodologically supported convictions, following a specific research paradigm, relating to a specific scientific community (most prominently, Ludwik Flecks initial analyses, see Fleck, 1979). With Big Science projects, thinking and thinkers or even individual observers belonging to something like a thought collective seem radically outdated. Research is conceived of as a happening with multiple aims and multiple outputs that accrue at multiple places if only the overall architecture of a project works well enough. Building a scientific career equals surviving being part of as many of such processes as possible without losing too much epistemic credibility while gathering a maximum of citation points. It can be read as a new philosophical stand-point as well as a mirror of the development that current epistemological analyses in STS favor focusing on actor-networks rather than individual thinkers. But whether the development and success of Latour and Callon's Actor-Network-Theory *should* be read and applied not only as the former, but also as the latter, is still open for debate.

4. What have been the most significant advances in systems biology?

Systems biology has been set up as a new research approach, even as a new paradigm of doing research in a specific scientific domain, that is, broadly speaking, modern molecular biology with its high throughput technologies and resulting Big Data. In the wake of preparing for and aiming towards realizing this new approach, the engaged scientists developed new concepts, methods and last but not least new insights and product lines. But what I see in the center of systems biology's achievements is really the acknowledgement of an existing epistemic shortcoming in recent molecular biology and the ensuing attempt to reframe fundamental aspects of doing research in this domain in implicit as well as explicit terms so as to answer to these shortcomings. One could critically assess that not in all cases the epistemic struggle was the first priority and that other stakes were involved in the launch of systems biology – in short, that systems biology was simply a new buzzword and a new strategy to sell more of the same science. Such an interpretation could be tied to relatively meager results when it comes to the fulfillment of initial claims of systems biology's proponents to help solve almost every current societal problem, from hunger to climate change, and it may not be completely unsubstantiated. But still, it does not seem to cover all efforts undertaken by all actors in this context.

Individual researchers and whole research groups took a high risk in investing in an approach that is not guaranteed to "deliver", that necessitates high individual and collective investments (building up new research networks, engaging in multidisciplinary collaboration, acquiring new expertise, questioning well established practices and hierarchies and changing existing curricula) and lures natural scientists out from a rather cozy position of not having to reflect upon the broader epistemic ramifications and ontological presumptions of what they do in their day-to-day work. At least some biologists (as well as philosophers, mathematicians, etc.) sincerely bought into this new project and achieved a lot in re-discussing and re-constructing what it means to do research in the current life sciences and which promising options have not yet been considered adequately. It may rather be a side effect that the attempt to tame Big Data in molecular biology also led to re-addressing the big questions of biology itself, at least punctually: what is specific to the living world as compared to the non-living and what is specific to a science of the living world as compared to a science focusing on the non-living? How does biology address complexity, diversity and evolvability? What is the relation between (the represented) nature, a computer model and something we build brick by brick? How can "wet" and "dry" research be integrated in a meaningful way (and why do we have to integrate them at all)? How can the organization of doing science be adapted to a changing conception of living organisms and/or of how living organisms can be researched?

Hence, from my point of view, the most significant advances made in the context of systems biology are related to a certain audacity to re-frame existing questions and ask new ones – new questions that do not lend themselves to being easily answered (or easily published in the research section of high ranking scientific journals). It may not be the next *in silico* model of a cell, that will be a major achievement of systems biology, but the questions that are raised and discussed while aiming at building such a model.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

Problems that face those doing systems biology research can be divided into two groups: problems that relate to the general situation of current (techno)science, of doing (techno)science and being in (techno)science on the one hand and problems that are specific to systems biology on the other. In the following, I will start each topic with an outline of the general context before focusing in on those aspects specific to systems biology.

(1) In relation to the more general context, one grand question is: ***what is or should be the identity of science*** – i.e., what are its primary, defining orientations along which individual actions can be positioned and quality can be assessed? This first question underwent periods of explicit debate, of historical change and relative stabilization; it is closely related to the characterization of the relation between science and society or science and other societal subsystems. Currently, debates and practical struggles that allude to this theme are very lively in various contexts (such as science funding, quality assessment and science regulation), but tend to address the underlying grand question only implicitly. In rare cases individual stakeholders address it directly, such as in opinions about the current contract between science and society. In other cases, such as the discourse on the character of synthetic biology, specific sub-themes are spotlighted, like the double-identity of research as science as well as engineering or a shift from science towards engineering. But most of these cases fall short of including all available cases and options and/or do not open up a debate on all relating factors and consequences. The prominent science plus/versus engineering discourse in synthetic biology would necessitate an in-depth analysis of what it means to orient (individual and collective) action primarily towards understanding or construction or creation and what the consequences of an amalgamation of orientations in hybrid understanding/engineering activities are (Kastenhofer, 2013; the incompatibility of scientific and technological purposes is also mentioned in Xavier et al. 2014, 488).

(2) Another grand question related to the more general context is raised by major changes in the organization and practice of science: ***how is it possible to perform science under the current organizational and practical conditions*** (project based research, technology and data driven research, collaborative networks, multi-disciplinary and multi-center approaches, etc.) ***and what kind of science results from it?*** Even if science is clearly and primarily oriented towards gaining new insights, how do we conceive of this process in a Big Science context? And where does it leave the individual mind, the individual scientist that feature so centrally in traditional epistemological thought? Of course, there are epistemological approaches that attempt to capture this situation, both within philosophy of science and in science itself. Systems biologists developed their own micro-scale answers, like the scheme of iterative circles connecting exploratory data analysis, hypothesis-testing laboratory experiments and *in silico* model construction. But it might also be time for a more disruptive re-framing of what science is, how knowledge is produced and what it means to know something.

One of the central problems systems biology has chosen to address is

to make sense of high quantities of data about very small entities of living systems with the help of mathematics and computer modelling. In addressing this problem, specific techniques, collaborative patterns and digital constructs gained interest in their own right. Moreover, building a computer model that would enable us to simulate nature in a reliable way, to replace nature in epistemic processes and eventually enable the replacement of nature in processes of material production, somehow emerged as a fascinating vision and objective, with a power to mobilize people and resources far beyond the realm of the life sciences. Again, in the three-step formulation of the central problem addressed by systems biology, we find inscribed a gradient from systems biology being a science, to systems biology representing a technoscience or a technoscientific vision. For the first incarnation of systems biology, a lack of available robust and appropriate data might represent a real bottle neck. Also, and this has been mentioned many times, the integration of different existing approaches (be they called top-down, bottom-up and middle-out or more traditional physiology and quantitative analysis or else) poses a major challenge.

(3) A third grand problem relates to securing quality standards in doing science. Given current situations and contexts of doing science, I want to stress one specific aspect: as science has become ever more multi-disciplinary, multi-sited and collaborative and focuses increasingly on scientific as well technological and societal issues, (successful) communication has become an ever more challenging and crucial component of doing (good) science. Much of this challenge is being addressed in very creative ways, like building up new networks (e.g. in the context of developing new research agendas and funding initiatives), introducing new types of infrastructures (e.g. multi-disciplinary centers, data infrastructures, etc.), experimenting with new formats of education and socialization (e.g. iGEM) or stressing new norms (e.g. "responsible research and innovation" at EU level). Where I see less activity and a growing potential for quality loss is ***the realm of language and within this realm the assessment and maintenance of (a) terminological accuracy and (b) soundness in formulating goals and visions***. The story of the multiple definitions, usages and understandings of terms like "gene" in diverse research fields may be old hat, but it addresses an unsolved and increasingly crucial problem. The same holds true for critique concerning empty promises frequently formulated in science communication. One might hold, that both of these problems are confined to the popularization of science and do not interfere with core science activities. But with a shift of where "core science" takes place in a multi- and trans-disciplinary paradigm of doing science, the related problems cannot be shook off that easily. What do formulations

like "modeling a cell" or "whole-cell modelling" mean? What criteria must be fulfilled in order to be allowed to speak of having "modeled a cell" or having built a "whole-cell model"? What level of performance is realistic in replacing 'material results of an evolution in context' like living cells by material, technologically constructed objects like minimal cells or by digital objects like computer models in epistemic and/or technological terms? What are the diverse meanings of terms such as 'system', 'complexity' or 'reductionist' and 'holistic'? And, on a much more general level, what kind of contribution to solving grand societal problems can we expect from technoscientific undertakings and how is this contribution to be assessed? Admittedly, some of these questions are being addressed in single systems biology review articles and contributions from the philosophy of systems biology, at least the terminological ones (for examples see for instance Xavier et al. 2014 for 'minimal cells' or Krohs and Callebaut, 2007, for 'models of everything'). Although I have found little evidence for a broader uptake of these discussions, I believe that much of the progress in the field of systems biology will depend on such reflection and specification work

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15

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Biological Complexity and the need for Computational Approaches

1. How and why were you initially drawn to systems biology?

A brief description of my academic background may be useful to give a clearer idea of why I became interested in Systems Biology. As a physics student I was working on particle theory. At the same time, in the early 1980s, I was attracted by computer science, particularly by artificial intelligence. Working in parallel in the two different fields, I started to spend more time on computer science. While I love physics, and I still do, I was more and more attracted by computer science because it was a much younger area of study than physics and therefore less well-founded. It was a newer field of study, and highly dynamic. I saw an opportunity in computer science, and I have predominantly worked on artificial intelligence, parallel computing, and robotics (Kitano, 1993; Kitano et al., 1997; Kitano & Hendler, 1994). Artificial intelligence is an area of study with the aim of developing computers that can exhibit human-like intelligence, or of using computers to understand intelligence. After spending a few years on artificial intelligence research, I noticed that artificial intelligence is trying to mimic or to understand intelligence as we know it today, but intelligence is inherently a by-product of evolution. I therefore decided that I should spend a few years trying to understand "life", i.e. the biological systems that underlie intelligence.

By total coincidence, in 1993, I was invited to give a lecture at a one-week long workshop organized by Professor Heisuke Hironaka, a famous mathematician who won the Fields Medal in 1970 for his work on resolution of singularities of algebraic varieties. At the workshop, I met Dr. Shin-ichiro Imai of Keio University, currently a professor at Washington University St. Louis, and Professor Susumu Tonegawa from

MIT who won the Nobel Prize in Physiology and Medicine in 1987. Dr. Imai asked me whether computers or artificial intelligence could make sense of data that appear to be contradictory by identifying undiscovered principles behind these. We discussed whether computational approaches could predict behaviors of biological systems or even uncover mechanisms of biological systems. I was very intrigued by the problems raised and intuitively thought this could be a great problem to tackle. Interestingly, Dr. Tonegawa flatly rejected the idea that computers could predict or help discover anything important in biology because biological systems are so complicated. This was very encouraging because it exactly matches the first law of the Clarke's Three Laws of Prediction that says: "When a distinguished but elderly scientist states that something is possible, he is almost certainly right. When he states that something is impossible, he is very probably wrong" (Clarke, 1962).

I then decided to spend most of my time on biology. I started with the problem of cellular aging - the topic Dr. Imai was working on. Soon, I realized that there are a lot of issues to be solved in biology, especially related to quantitative data acquisition and analysis, systems-oriented thinking, and development of computational approaches. This joint work resulted in a series of papers that essentially made computational predictions on possible mechanisms of aging (Imai & Kitano, 1998; Kitano & Imai, 1998). It should be noted that a possible key role of yeast Sir2 protein in aging control discussed in these articles was confirmed later (Imai et al., 2000).

After spending a couple of years developing new methods for data analysis, I decided that the approach needed a name. One could simply use the term "Computational Biology" or call it "Virtual Biology" because it is biology in virtual space (Kitano et al., 1997). However, I felt that this term did not capture what I wanted to do. So, I asked the question: "what is the central issue that this whole approach wishes to uncover?" The answer was clear. I wanted to understand the systems-level properties of biological systems.

With systems-level properties I do not just mean a high number of genes and proteins. In many biological articles, it is often said that "this gene or protein has XXXX function". I am not happy with such descriptions because genes and proteins do not serve any physiologically meaningful functions in isolation. They have to be embedded into the proper network of interactions. My impression at that time was that systems-oriented thinking was missing in the field and needed to be further reinforced if biology was to really understand the whole picture of life. This is why I coined the term, "Systems Biology". This was around 1996 -1997, when one of the initial projects was computational modeling of *C. elegans'* development (Kitano et al., 1998). I asked Joan

Fujimura, who is a historian of science, if anyone used the term "Systems Biology" in any serious way so that the use of the term could lead to confusion in the field. At that time, we did not find anything conflicting with the use. So, I started using the term, and the notion of Systems Biology gained currency with institutional developments from around 2000 and onwards. Among these were the first International Conference on Systems Biology (ICSB), which I organized in 2000 in Tokyo, followed by California Institute of Technology (2001), Karolinska Institute (2002), etc., and the emergence of the first departments of Systems Biology. Obviously, for me, a major turning point was the publication of two special issues in *Nature* (Kitano, 2002a) and *Science* (Kitano, 2002b).

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

A part of Systems Biology involves the way that people look at nature, especially biological systems, and entails a more holistic view in contrast to the standard reductionist view. It is important to identify and study every gene and protein in these systems. So, I would not discount the value of very powerful reductionist approaches. However, at the end of the day, you need to relate these insights to how the system functions as a whole. This requires us to uncover systems principles behind evolving adaptive complex systems.

It should be noted that the idea of understanding biological systems as systems is not new. It dates back to the work on homeostasis by Walter Cannon (1932), Cybernetics by Norbert Wiener (1948), and General Systems Theory by Ludwig von Bertalanffy (1969). On philosophical ground, systems biology dates back to a series of such studies. At that time, however, these approaches had difficulties in translating the ideas into insights about real and concrete biological systems as this was even before molecular biology emerged, and before researchers had access to modern digital computers.

The beauty of molecular biology is that it enabled us to discuss biological phenomena grounded in the language of molecules. To me this is a major phase shift because physical phenomena have to be grounded at the molecular level, and understanding of biological processes as dynamics of molecules is exactly doing this.

Since then molecular biology, computer science, control theory, as well as other related fields have made significant progress, and we are now able to bridge between biology and physics at a much deeper level than before. Innovations in precision and comprehensive measurement tools, such as genome sequencing systems and high-throughput omics tools, combined with sophisticated computational analysis approaches enable

us to dive deep into the dynamics of biological systems. Systems Biology, in its modern form, picked the right moment to become widely accepted.

One of the issues that I am deeply interested in is to uncover a series of basic principles underlying biological systems. In physics, there are a series of basic theories such as the theory of special relatively, general relatively, electroweak theory, and a series of hypotheses waiting to be verified or falsified. However, biology is a more observationally and experimentally centered field with less emphasis on basic principles. Life forms are so complex and diverse. Biologists, at least to my eye, appreciate diversity rather than principles. Still, I believe there are principles and theories to be discovered in biology. Perhaps, these are different from most of the theories in physics. In physics, we mostly deal with fundamental theories. They define how the world works. The theories of special relatively and quantum physics define how matters, space, and energy are interconnected, and everything on top of it has to be consistent with these principles. Is it possible to pursue a somewhat similar group of theories in biology?

Evolution is one of a very few principles that can be applied to a broad range of biological systems. Aside from that, biology seems to be a vast collection of specific findings and knowledge of cross-species similarities. One should be aware that there are clear differences between physics and biology. One major difference is that biology deals with systems with non-trivial complexity, whereas the basic laws of physics are dealing with elements and their properties rather than systems of these elements. In this sense, biology is similar to engineering. Engineering deals with systems of vast complexity and with a focus on functional properties. There are a series of general theories and principles in engineering formulated for the purpose of properly designing systems and making these work as intended. Importantly, such principles help us understand behaviors of complex systems. Control theory, for example, defines how specific combinations of components form systems that exhibit specific dynamical properties (Doyle, et al., 2009). The Bode Theorem is a theorem that helps us to understand how such systems may behave (Bode, 1945). The theorem says that in the negative feedback circuit (as seen in Figure 1a), there is an inherent trade-off between improving the level of stability at low frequency range and increasing instability at higher frequency ranges (Figure 1b). Stronger feedback further improves stability at low frequency range, but at the cost of increased instability at higher frequency ranges. This is an example of system-level principles because it stems from a specific configuration of components, but not from properties of the components in isolation. Shannon's information entropy may be another principle

at the system level. Complex systems can be designed and understood using a set of such principles. I would call these 'systems principles' or 'structural principles' because these principles relate the structure of systems and their dynamical properties, but are not constrained by specific choices or make-up of the components. My overall view of theories in biology is shown in Figure 2. Fundamental principles are laws of physics and chemistry that govern all elements involved and their immediate interactions. Structural principles are laws of systems that govern how specific configurations of elements give rise to spe-

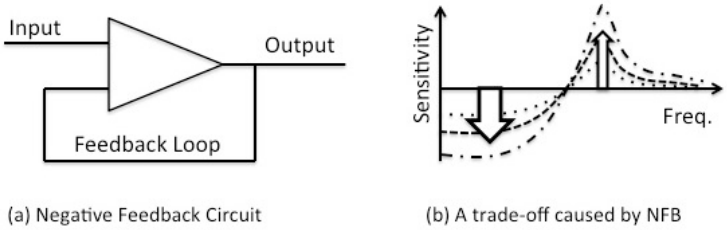

Figure 1: (a) A conceptual diagram of negative feedback circuit, and (b) a trade-off between stability at a low frequency range and instability at a high frequency range

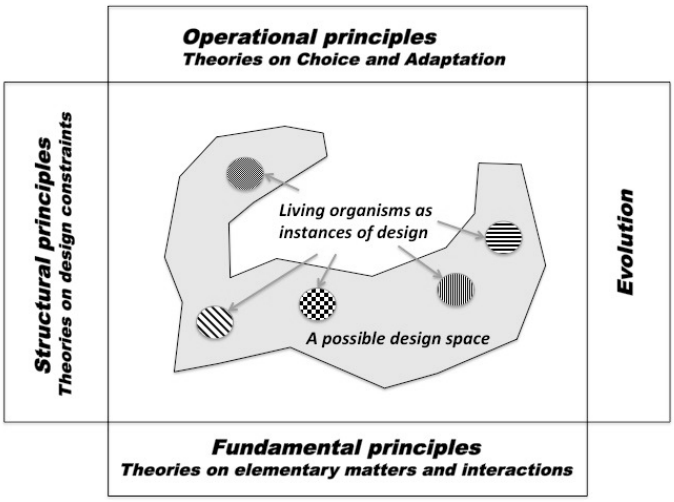

Figure 2: A personal view of structures of principles for biology

cific dynamical properties. Operational principles govern how groups of systems interact and react in environments. This may include game theories, since all of these will be subject to evolutionary selection and adaptation.

One may ask how complex systems ideas relate to biological systems.

The concept of a complex system is vague, but it is often associated with emergent properties. One typical example is self-organized criticality in sand piles (Bak et al., 1988). Similar phenomena can be observed in the Belousov-Zhabotinsky reaction that is related to Prigogine's argument of non-equilibrium dissipative systems (Prigogine & Nicolis, 1971; Prigogine et al., 1974). However, a fundamental difference separating these phenomena and biological systems is evolutionary adaptation. These physical and chemical systems are self-organizing but not subjects of evolutionary adaption. For biological systems, evolution constantly reshapes their form and function. Thus, systems biology is clearly different from complex systems theory.

Systems biology contributes to our view of biology by paying attention to how individual molecules are embedded in larger wholes, but in the light of evolutionary adaptation. At the same time, it does not mean that the concept of non-equilibrium dissipative systems has no place in theory of biological systems. It plays an important role in our understanding of processes of pattern formation that shape biological systems. Figure 3 illustrates how biological systems may be structured and adapt to perturbations. When the influence of external perturbation is small to medium, or within a range of perturbation that the system is already well adapted, systems tend to show a linear response, an adaptive response regulated by feed-back and feed-forward control, or hysteresis. These responses are basically governed by a set of system control loops, as envisioned by Wiener's Cybernetics and partially by Cannon's homeostasis. Let us call this range of dynamic states the "Wiener domain". On the other hand, there are cases where systems are exposed to major perturbations, or where small perturbations lead to major shifts in system status or structural change. Such shifts can be driven by self-organization and some emerging properties as envisioned by Prigogine; hence, let us call this area of systems states the "Prigogine domain." Even in the Prigogine domain, there are underlying feedback regulations that give rise to self-organization. However, it can be distinguished from the Wiener domain due to the degree of structural changes that may be triggered. Both domains contribute to formation of biological systems and regulatory control since both domains must be selected through evolution. While engineering use of control theory has explicitly defined "set points" which system states converge toward, biological systems do not have pre-defined explicit set points. All set points are emerging properties and dynamically moving according to the context of the system, and yet controlled to properly maintain functionalities and resilience of the system. Understanding principles behind such moving target set points are novel theoretical challenges in systems biology that may feed back insights to theories of control and

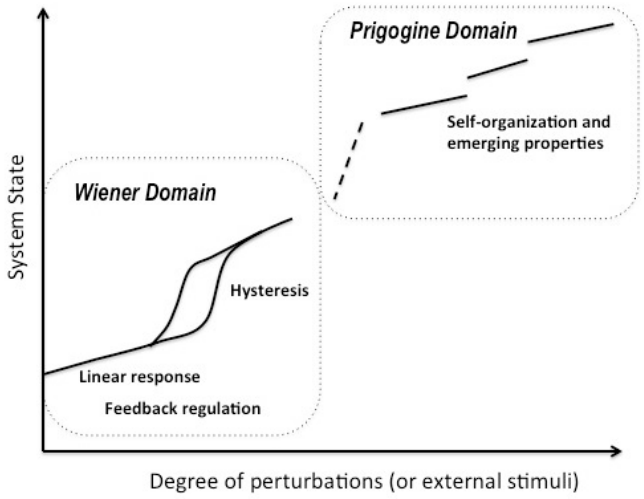

Figure 3: A framework for conceptualizing system formation and adaptation

mathematics of complex systems.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

See my answer to Question 1 and 4.

4. What have been the most significant advances in systems biology?

One of the most important advances is the fact that systems biology, or the systems-oriented approach in biology, is now widely accepted and considered as mainstream in biology. This involves a wider acceptance of mathematical and computational approaches that have been undervalued in the past. There are a series of deeply rooted changes underway as educational institutions increasingly introduce systems biology and related courses that will impact the way that new generations of researchers do biology.

We have made theoretical progress regarding our understanding of several aspects of biological systems such as robustness and fragility, bow-tie networks etc. Understanding the basis for these, and reconceptualizing biological phenomena in new ways, is a first step towards a more comprehensive framework of theories (Carlson & Doyle, 1999, 2002; Csermely et al., 2005; Csete & Doyle, 2002, 2004; Kitano, 2004a, 2004b, 2007a, 2007b).

On the applied research front, some of the work has resulted in suc-

cessful drug discovery programs, for example, Merrimack's MM-121 program (Schoeberl et al., 2009, 2010). Integration with synthetic biology is also important, for example Jay Keasling's work on synthesis of the anti-malarial drug Artemisinin. The company Amyris now produces high-value chemicals through microbial engineering (Hale et al., 2007; Ro et al., 2006).

Development and investigation of a series of large-scale models and high-precision models of key biological processes have been remarkable. Signal transduction, cell cycle, and metabolic networks have been among the main areas of attention, and have potential to be utilized for a range of applications. Already, signaling pathway modeling has been applied to drug discovery with success. Studies using precise computational models help us to understand the dynamics and design principles of biological systems (Chen et al., 2004; Covert & Palsson, 2002; Covert et al., 2001; Duarte et al., 2004, 2007; Novak et al., 1999; Novak & Tyson, 1993; Oda & Kitano, 2006; Oda et al., 2005; Thiele & Palsson, 2010; Tyson & Novak, 2001, 2002).

Furthermore, a series of standard representation formats such as SBML (Hucka et al., 2003), SBGN (Le Novere et al., 2009), BioPax, Mirium etc., have contributed significantly to data and model exchange, model transparency, and open-ended data access. The Garuda platform signifies the transformation from isolated tools to large-scale integration via standard platforms (Ghosh et al., 2011; Kitano et al., 2011).

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

Biological systems are highly complicated, non-linear, and require very high-dimensional and high volume data analysis. In reality, we are as human beings not good at handling such data. How can we understand biological systems in face of this complexity? This is the major challenge for biological and biomedical research. I would claim that a combination of artificial intelligence and human research is the most powerful way to proceed, rather than relying solely on the human brain in trying to understand biology.

In 1997, the IBM Deep Blue computer beat human champion Gary Kasparov in Chess (Hsu, 2004). IBM also developed a computer system called WATSON that won the TV quiz show "Jeopardy!" and a computer program recently outperformed human masters in "Shogi" a Japanese chess (Ferrucci et al., 2010, 2011). IBM's WATSON is now being applied in biological and biomedical contexts to provide medical assistance for diagnosis (Ferrucci et al., 2011).

These examples demonstrate that computers now can outperform hu-

man intelligence capabilities in some domains. At the same time, it is interesting to note that a new kind of Chess game called "Advanced Chess" has emerged after computers outperformed humans in Chess. Advanced Chess allows human and computer to make up a team. Our current understanding is that the computer-human team is stronger than either human-alone or computer-alone. My view is that a similar situation will emerge in biomedical research. The most powerful research team will consist of highly intelligent AI systems and human researchers. Just like we need high-throughput measurement devices and next generation sequencers for any high profile research institution in systems biology today, so will highly intelligent AI systems sooner or later be mandatory for any future high profile research institution.

The reason why I believe AI systems can outperform the human researcher is based on the fact that humans use natural language to think and communicate. When one describes a certain phenomenon, one has to define it. When one describes anything with human language, it inevitably involves errors and a range of inaccuracies. Human language is suitable for daily communication because it is abstract and details can be ignored. But this very nature of human language, hence all human thinking based on natural language, makes it impossible to achieve highly accurate descriptions of and reasoning about biomedical problems. When one describes a given phenomenon or subject "A", it can be described using multiple other words, say X, Y, and Z. But, maybe there are features of A that are not exactly Z, but also have some aspect of W. For example, defining "house", "dinosaur", "ocean", and "lazy" would require a complex combination of words that describes essential and common features of multiple examples of these instances. However, one would quickly notice there are too many exceptions that cannot be covered by a common set of representations, and such exceptions may reach non-trivial proportions. Alternatively, one may wish to create sub-groups of real instances and describe each of these independently. Still, exceptions remain in each subgroup. We can continue to subcategorize each subgroup to improve the accuracy of description. The problem then becomes that we may totally lose track of what each subgroup means. Human beings use imprecise natural language to describe, communicate, and reason. In this lies a fundamental limitation in our cognitive capability to properly describe, classify, and communicate complex phenomena or complex subjects (Figure 4). This has been recognized in the field of general semantics (Korzybski, 1933) and in cognitive linguistics (Lakoff, 1987), but mainly considered as semantic and communication issues, rather than factors limiting human scientific capability. Korzybzki famously claimed that "the map is not the territory". This is very true for the science of complex biological systems.

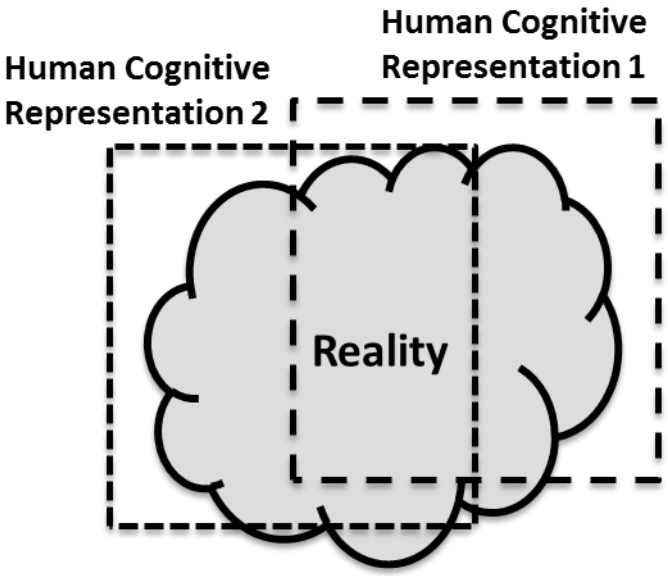

Figure 4: Reality is complex, and humans use imprecise languages to describe it.

Such limitations are explicit in biomedical research from classifications and characterization in basic research to clinical patient stratification and biomarker discovery. Limitations of our cognitive capability are posing a serious bottleneck in our understanding of biological processes, and the best way to overcome this problem involves computational approaches and development of an exact and systematic artificial language. The future of systems biology, and the future of biomedical research in general, depend on the development of artificial intelligence systems, and our ability to work with them.

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16

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SYSTEMS BIOLOGY THROUGH THE CONCEPT OF EMERGENCE

1. How and why were you initially drawn to systems biology?

My research has always had as its single common denominator the aim to try to understand biocomplexity. I first came across the topic of biocomplexity as a subject when I read Nicolis and Prigogine's book on complexity (Nicolis & Prigogine, 1989). At that time, I was a student in the biology department and, inspired, I tried to integrate aspects of different scientific disciplines into my various research objects. Several years later I had graduated from biology, obtained my second master's degree in chemical engineering, and finally learned about systems biology - a science devoted to understanding biocomplexity and to explaining the emergence of complex biological functioning in terms of interactions between macromolecules. I realized that this was the field for me, and in 2005 I joined the newly opened master's program in systems biology at VU UniversityAmsterdam. In 2006, I extended this MSc program into a PhD program and, under the supervision of Hans Westerhoff and Frank Bruggeman, wrote a PhD thesis titled "Emergence of Design". Following my PhD defense, I was employed by the Luxembourg Centre for Systems Biomedicine (LCSB) (http://wwwen.uni.lu/lcsb) and spent two years at the Institute for Systems Biology (ISB) in Seattle (http://price.systemsbiology.net/) as a visiting scholar. I have continued my systems biological studies on the principles of intracellular networks as well as on the philosophical and methodological aspects of the reconstruction of biological emergence *in silico*.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

I think that philosophy (and a specific philosophical paradigm) is exactly what differentiates systems biology from closely related sciences such as molecular biology and computational biology. Indeed, some

people think that systems biology is just a kind of molecular biology - let us say a quantified (computationally based) version of molecular biology - or, on the contrary, that systems biology is just a version of computational biology. I think that a certain philosophical paradigm is what makes systems biology different from these closely related sciences. I believe that systems biology represents a shift in the way we conceptualize systems rather than an extension of previous approaches (Kolodkin et al., 2013; Westerhoff et al., 2009, 2014).

Indeed, systems biology is sometimes perceived as a kind of biology where experiments are accompanied by modeling. But this is not accurate, first of all because building and analyzing models is not specific to systems biology but a fundamental component of any science. In principle, building models is relevant not only for science. In a broad sense, if a *model* simply means a "representation of a limited part of reality by related elements", then a projection of one system (e.g. the real world) to another system (e.g., the formation of a conditional reflex to a stimulus) could be also considered as a kind of "modeling" of reality; Pavlov's dog began to salivate in response to a neutral stimulus preceding the feeding, because previous real world stimuli were reflected in its nervous system. In this broader understanding of what modeling is, unconditional reflexes could also be seen as models, but as models written by adaptation and evolution onto a "hard memory" of species. If we narrow down the definition of modeling with respect to science only, then a model can be defined as a way by which the real object is connected to the reasoning of a scientist, and modeling can be defined as the construction of physical, conceptual or mathematical simulations of the real world. The essence here is that what we call scientific reality - i.e. the way we see the real object (world) – is ultimately just a model of it; it is the interpretation based on our theories. Consequently, biology and systems biology and every other science always have to deal with modeling. If we narrow down the term modeling further to just mathematical modeling or even to exclusively computer modeling of living entities, then this would really just encompass mathematical biology, that is a form of biology that aims to use both experiments and mathematical models. But systems biology means more. Systems biology is not just something plus something. Systems biology is a conceptual approach, a new scientific paradigm. Systems biology is a conceptual approach for understanding biological complexity as such in terms of interactions between macromolecules. Mathematical descriptions and computer simulations are tools for that approach, not the end point (Westerhoff et al., 2009).

I support the definition of systems biology as "a science that aims to understand how biological function that is absent from macromol-

ecules in isolation, emerges when they are components in the system" (Alberghina, 2005; Westerhoff et al., 2009). The philosophical concepts of "emergence" and "system" are central here. This brings philosophy into the center of systems biology, especially philosophical aspects of emergence.

In a metaphysical setting, an emergent property might be defined as a property of a system that satisfies three theses about emergence: (i) the thesis of physical monism, (ii) the thesis of synchronous determinism, and (iii) the thesis or notion of being a systemic (organizational) property (Stephan, 2006). If all of the three theses are satisfied at the same time, then the property may be called an emergent property. The thesis of physical monism restricts the nature of the system's elements, and states that the system consists of only physical entities, denying any supernatural influences. This is how we describe our system *ab initio*: we neglect all supernatural influences *de juro*. The thesis of synchronous determinism restricts the way systemic properties and the system's microstructure are related to each other, and states that there can be no difference in systemic properties without changes in the structure of the system or in the properties of the components: properties of interest (e.g., metabolite concentrations) are underlined by the changes in the system (e.g., changes in components concentrations, reactions rates). The thesis or notion of being a systemic (organizational) property means that a property is not exhibited by elements in isolation.

We suggest classifying emergence into strong emergence and weak emergence. Weak emergence satisfies the three theses stated above. Strong emergence would satisfy all criteria of weak emergence plus an additional one – irreducibility. A systemic property is irreducible " if (i) it is not functionally construable or constructable; if (ii) it cannot be shown that the interactions between the system's parts fill the systemic property's specified functional role; or if (iii) the specific behavior of the system's components, over which the systemic property supervenes, does not follow from the component's behavior in isolation or in simpler configurations" (Boogerd, 2007; Stephan, 2006). Importantly, these varieties of irreducibility are independent of each other. The first variety of irreducibility is epistemological - properties are not functionally construable, because there is a lack of knowledge about the underlying mechanism. This is not the case for systems biological study. In systems biology the emergence is ontological; we built this system ourselves and have knowledge about all components and their interactions. The concept of strong emergence, in which irreducibility of the second type is applied, can be found in the philosophy of mind and means that the specified functional role cannot be reductively explained even when there is full knowledge about the behavior of the parts within the sys-

tem. This is again not the case for systems biology. In systems biology, emergent properties cannot be reduced to the knowledge of the behavior of components in isolation, but we can understand the mechanism when we have a global picture of the system as a whole.

Systems biology focuses on irreducibility of type (iii), when emergence cannot be deduced from the full knowledge of the behavior of the parts and their subsystems in isolation, but we are able to reconstruct the emergence from the knowledge of components. The reconstruction is irreducible because we need to know not only about these components, but also about their relationship to each other. The property might be strongly emergent, yet we might be able to reconstruct it in a mechanistic model. For such reconstruction we not only need complete knowledge of the parts and the subsystems, but also knowledge about how the parts are related in the system. In other words we need to know state-dependent component properties.

The state-dependency of component properties may provide a possible criterion for the strength of emergence: the strength of emergence might be perceived as being proportional to the number of state-dependent properties needed to reconstruct the emergent property. For example, the thermodynamic criterion connected with the flux of energy through a cell could be one important factor contributing to the strength of emergence. When a cell grows or even when it maintains itself, it requires free energy for dissipation (Glansdorff et al., 1974; Westerhoff & Van Dam, 1987) and consequently it requires a high flux through a catabolic pathway such as the pathway converting glucose to pyruvate. We cannot reconstruct the ability of a cell to exist without qualitative information regarding this flux relative to the ambient processes that compromise Life (Boogerd, 2007). The knowledge of steady-state concentrations of intermediates is not enough, because steady-state concentrations could be the same for different values of the flux. A second criterion for determining the strength of emergence may be the number of interactions leading to the emergence. For example, the proliferation of a tumor cell could be considered less strongly emergent than the proliferation of a normal cell, because proliferation of normal cells is determined by more regulatory processes than that of tumor cells. A third criterion may be connected with the occurrence of hysteresis in a system which makes it impossible to predict the system's state without looking at the history of that system, largely because it is difficult to know all relevant details of the present state.

In fact, the concept of emergence was implicitly apparent in molecular biology. When genes related to certain diseases were identified, it was also obvious that they worked in a whole system with other genes. But researchers tried to ignore or reduce biological emergence. From

a more philosophical viewpoint, systems biology is the science that claims to fully account for emergence in living systems.

This brings systems biology into contradiction with the so-called principle of Occams' razor, which again is a philosophical problem. Let us discuss this in more detail. In systems biology, one should assume emergence to be strong rather than weak. If ones wishes to reconstruct an emergent property, one should take into account all knowledge about component properties. This can be formulated as the law of completeness: "If entities A, B, C and D (e.g. proteins) have been discovered in a living system S (e.g. cell, organism, ecosystem) for the fitness of which A, B, C, and D are all known to be essential, and if some properties of system S can be equally well explained either via A, B and C or via A, B, C and D, then the more complex explanation is most likely the correct one", then "[o]ne should not remove things without necessity" (Pluralitas non est eliminanda sine necessitate) (Kolodkin et al., 2012; Kolodkin & Westerhoff, 2011). Interestingly, this contradicts the principle of parsimony, which suggests that, if one considers a phenomenon that can be explained in two different ways - the first explanation requiring entities (terms, factors, transformations etc.) A, B and C, and the second explanation requiring entities A, B, C and D - and if one observes that both explanations give the same result, then entity D is unnecessary and the simpler explanation is most likely the correct one. The parsimony principle basically suggests to "shave away" all assumptions that are unnecessary to explain the phenomenon under study. The axiom is known as Occam's razor: "One should not postulate (pose) more things without necessity" (Pluralitas non est ponenda sine necessitate). But we should note that William of Occam started to use his razor as a tool for the demythologization of the cosmology of antique times. He worked actively to shave away the "soul" and the "will" of cosmic elements and his legacy cleared an avenue for modern science. For instance, shaving away the sacred status of stars liberated astronomers from the fear of being killed by star worshipers and led to the discoveries of Nikolaus Kopernikus. In later times, the statement of Occam was somewhat modified: "Entities should not be increased (multiplied) without necessity" (Entia non sunt multiplicanda praeter necessitatem) (Thorburn, 1918). This provided a good motivation to start viewing the behavior of physical objects as being determined by simple physical laws rather than by divine intervention and thus became very important for the development of physics.

However, Occam's Razor has always been a heuristic method rather than a universal law. There is no proof of the principle: if the simpler explanations are true, this does not imply that those explanations are more realistic because of any universal tendency towards simplicity.

On the contrary, the second law of thermodynamics advocates that there is a tendency towards complexity rather than towards simplicity (Westerhoff et al., 2009). And there are many examples where the more complex explanation turned out to be true: chemiosmotic coupling (Mitchell, 1961), the control of metabolic fluxes (Groen et al., 1982), and general relativity (Einstein, 1961) are but a few of them. Coming back to biology, some years ago it became almost a paradigm that all cellular information is stored in DNA, assuming consequently that if one knows the DNA sequence one can deduce all the properties of the organism. Today it is obvious that this is not true. For example, if one takes a carp's nucleus and puts it into the fertilized but enucleated egg cell of a goldfish, then in most cases the hybrid will die. In rare cases where an embryo manages to develop to an adult organism, the new organism will look like a goldfish (Sun et al., 2005). The reason behind this is that it is the cell as a whole, with all its components including various cytoplasmic molecules (especially proteins), that is responsible for the emergence of life.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

I personally feel that many concepts I am currently using in my systems biological modelling have been theoretically established some years ago within the theory of functional systems by P.K. Anokhin and the theory of stress by H. Selye. Although these are not as such "neglected contributions", we are still reinventing previous discoveries. An astonishing example is close to my own work on Parkinson's Disease (PD). I recently learned that PD had been described in detail by Ferenc Papai in 1690 - more than one hundred years before James Parkinson. However, Ferenc Papai's work was not translated into English, and therefore was not so widely known.

Furthermore, I think that we are currently underestimating the concept of the Virtual (Silicon) Human. Many scientists doubt that this project is realistic, but I believe it is more than a project. It is a new paradigm which will revolutionize not only medicine but the whole of science. I have no qualms about claiming that we will be able to build, ultimately, a computer replica of the whole human body, and I believe that the names of those who were at the source of this concept (e.g. Hans V. Westerhoff) will be recognized appropriately in the history of science.

4. What have been the most significant advances in systems biology?

I personally appreciate the concept of the Virtual Human which suggests that biological emergence could ultimately be reconstructed *in*

silico (Kolodkin et al., 2011). This computer replica of the whole body might be personalized for every patient (Lehrach et al., 2011) and will become a major tool for P4 medicine (Tian et al., 2012). For example, the big problem in pharmacology is related to the fact that there are drugs that can cure the majority of patients but will have fatal consequences for some. According to the current procedure, these drugs are withdrawn from the market. But, if we had a Virtual Human model, we could parameterize this model for an individual patient, simulate an effect of this specific drug for this specific patient, and be able to identify the patient for whom that drug is good and the patient for whom it is not.

From an experimental perspective, I think induced pluripotent stem cell technologies (iPS) will have a very important role to play. These technologies provide amazing opportunities for both practical application (e.g. growth of patient specific organs for transplantology) and for conceptual studies (an iPS cell is in fact a blue-print that can be parameterized/developed into any other cell).

And of course, we cannot underestimate the development of quantification techniques. For example, DNA sequencing is now a routine procedure, transcriptomics is commonly used, and proteomics is becoming more affordable.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

I would identify 10 potential challenges for systems biology:

1. "*All or nothing*". Until now we have had only incomplete models that have been created on rather fragmentary knowledge, but if systems biology's long-term aim comes to fruition, more complete systems biological models will be possible. The impact of complete models will be huge, but it will take a lot of effort to build such models.

2. *High complexity (very strong emergence) of biological systems*. Indeed, some sceptics doubt whether large-scale models of the Virtual Human type are possible. They may point out that in the 1950s and 1960s there were several claims that in the near future it would be possible to model and control the weather. This deterministic approach to modelling weather failed in principle. Instead, chaos theory emerged and we are still not able to fully predict weather patterns, much less to control them (Allen et al., 2013). I think that modeling of humans might be easier than modelling of weather because weather does not have an optimal steady state. We might think that 22 degree Celsius would be optimal for us, but there is no mechanism by which weather should try

to maintain this temperature. But, when we model an organism, there will be a lot of homeostatic mechanisms which drive biological systems towards perfect (or almost perfect) adaptation, to an "ideal" steady state. As a result, we can calculate this attractor of biological optimality, and use the data to model an "ideal" optimally functional organism. The deviation from this optimality (e.g. aging, disease) would then have a mechanism-based explanation.

3. *The number of interactions is huge*. This is related to the previous problem of high complexity and is aggravated by the fact that, compared to physical systems, biological components are highly inhomogeneous. As a result, the interactions between those components cannot be reduced to a single equation (like fluid dynamics equations for homogeneous molecules of water). In biological systems, the diversity of components is much higher and many "laws" govern the interactions between components. As a result, we need to describe every interaction individually. Skeptics might say that when we talk about the entire human body, this number of individual interactions becomes "astronomical" (Noble, 2006). However, taking into account the modular organization of a living system, our rough calculation suggests the number of interactions to be in the order of just 10^5 (Kolodkin et al., 2012; 2013). This is not a small number, but with the foreseen increase in computational power, it should not cause any principal limitation.

4. *Uniqueness*. Every cell, tissue, organ, and organism has a similar composition (in terms of molecules) but is at the same time unique. An individual difference might be observed both on the intracellular level (gene expression, concentration of proteins etc.) and on the level of the emergent cell behavior (membrane potential, cell mobility etc.). In other words, every living system is state dependent to a very high extent. This might cause a problem – do we need to build a separate model for each living system and for each particular situation? The solution could be a blue-print approach. The difference (the information of state-dependency) is not in the model topology (character of interactions) but rather in the particular parameter sets and initial conditions. Consequently, a generic so-called "blue-print" model must be parameterized (tuned) for any particular instantiation. A "silicon pig" in this sense might become a "blueprint model" for an *in silico* human and vice versa.

5. *More than 25,000 dimensions of the model*. There is also a technical problem to building very large - at least 25,000 (number of genes) - dimension models. For this challenge, a "domino approach" may help. The domino approach is based on the fact that there are usually only a

few "key" metabolites or proteins that interconnect different modules in a large model. For example, the most connected metabolite is ATP (Fell & Wagner, 2000). This suggests that we first distinguish between processes involved in ATP production and ATP consumption. Then, using *in vitro* enzyme kinetic assays or modular kinetic analysis (Ciapaite et al., 2005), we can identify how these processes depend on ATP concentration. In this way, we first build a model with the intermediate molecule (ATP) in the middle and several processes around it. This model will predict how activation of the production and consumption processes affects the concentration of the key intermediates and the steady-state fluxes. These model predictions might be compared with results of corresponding experiments. Any failure of the model to predict the observed behavior should throw light on additional processes or additional metabolic intermediates that might be included in the model sequentially, like "domino stones".

6. *Experimental quantification of the components of Life*. By definition, systems biology is a science that claims to account for strong emergence, and to understand how biological function that is absent from macromolecules in isolation emerges when they act as components in the system. This implies that we should know those components and their properties. Unfortunately, our knowledge is still fragmentary. Moreover, science is organized in the way that everybody focuses on a certain research question (story) and not on contributing with a single brick to fit into the collective virtual human project. I remember, many years ago Hans Westerhoff appealed to distributed systematic measuring where "Germany focuses on Liver, UK on the brain etc." I believe a large centralized project of the Virtual Human will be required for the future of science, and that tasks within this project will be distributed among large research centers, each focused on certain measuring techniques and dedicated to providing data to a central modelling facility.

7. *Integration of large amounts of different data*. Often, biological data are obtained from different labs. As a result, the logistics for the integration might not be easy. A potential solution could be based on online modelling, for example using resources similar to the JWS website (Snoep & Olivier, 2002) where users can run computer models in a web browser via an easy-to-use interface (see http://www.jjj.bio.vu.nl/ and http://jjj.biochem.sun.ac.za/info.html). Importantly, the rate laws of every model are fixed, but the kinetic parameters can be changed locally by the user to allow their examination of the system. These changes should not affect the default values stored in the curated database on the server, which are, in fact, the "blueprint model". Upon

obtaining either better kinetic values or values for different physiological conditions, the model can be re-parameterized. Model development, therefore, might become a community approach. At present, the JWS site contains separate models mostly devoted to just a single module of an intracellular network. The next step is to integrate all these modules together into a larger model capable of being reconstructed *in silico*, and subject to hierarchically higher levels of strong emergence e.g. the emergence of a whole cell, and, finally, the emergence of a whole-body organism. As such we should see a convergence of "blueprint modelling" and "domino based approaches", whereby molecular commonalities between individual blueprints are used to join these networks together in the mode of domino tiles. This is the challenge for systems biology if it is to create the silicon human.

8. *Observer effect*. As mentioned above, systems biology rests on precise information about the cell and its biomolecular components. In order to obtain such information, one typically needs to interfere with normal cell functioning. For instance, many studies involve overexpression of a certain protein where the concentration of this protein is altered. The protein is often marked with fluorescent molecules (e.g. GFP), thereby giving it a different size and conformation, and the protein then interacts differently with the transport machinery. Finally, the cell is typically isolated from its tissue and is withdrawn from its normal inter-cellular signalling network that affects cell functioning. If we carefully look at the details, we can usually find at least one way in which experimental intervention changes something in the cell. If the biological object of study is an entire elephant and one measures the temperature of its skin with a very small thermometer, the perturbation caused by the experiment may be minimized. However, if one tries to measure the behaviour of single molecules (the resolution of systems biological study), the perturbation tends to produce an impact on the molecule that is of the same order of magnitude as the molecule itself. This presents a problem particularly in attempts to measure continuous molecular properties quantitatively, and brings to mind the observer effect in quantum mechanics: "Once we have measured the system, we know its current state and this stops it from being in one of its other states"(Schommers & Espagnat, 1989).

9. *Effect of mental processes on physiology*. The anticipated virtual human will be a virtual physiological human, where the physiological behaviour emerges from interactions between molecules. However, mental processes can sometimes intervene with normal physiology (e.g. placebo effect) and this raises an issue of how to compute these

phenomena. Perhaps a "virtual brain" project could shed some light on this challenge.

10. *A science without a scientist*. Another philosophical issue is that the success of systems biology (especially its progress towards the virtual human) would literally mean that we do not have to hold a whole model of the processes we study in our brain any more. The drawback of such *in silico* reconstruction of Life is that we basically delegate our "understanding" to the computer model and this could lead to a new type of science. In its extreme, the human brain will not be necessary at all. The development of artificial intelligence and self-learning algorithms empowered by super-computing (also based on new principles, e.g. quantum commuting) will make the human brain unnecessary for the discovery process. Imagine, a robot that makes a quantitative experiment and delivers data to a super-computer, and this super-computer reconstructs biological emergence and formulates new tasks… This looks like a scientific fantasy, but perhaps we are not so far from its implementation in practice.

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17

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From biological research to a philosophy of systems biology: the ground covered and some challenges that lie ahead

1. How and why were you initially drawn to systems biology?

My investigation of systems biology began about ten years ago, while I was in the process of searching for a dissertation topic. Given that I had turned to the study of philosophy after several years of active engagement with biological research, a project in the philosophy of biology appeared to be a sensible choice. On the other hand, I approached with a certain degree of skepticism the prospect of revisiting the problems of biological practice from which I had sought refuge in a theoretical discipline. But my doubts about whether a biologically oriented project could be philosophically promising were dispelled when, at the suggestion of my dissertation advisor, I reluctantly proceeded to read a special issue of *Science Magazine* which highlighted the features of the then rapidly emerging systems approach in biology. The issue included a brief overview by Hiroaki Kitano (2002), which motivated me to research the subject further.

Although I had not encountered the term "systems biology" before, formal training in genetics had rendered me familiar with many of the problems that this purportedly novel approach aspired to address. It was evident from the outset that systems biology was not perceived in a uniform way by everyone who practiced it or tried to define it. The term meant – and it continues to mean – "different things to different people" (Fischbach & Krogan, 2010, p.1). But the desire to account for the complexity that characterizes biological systems by capitalizing on the use of new technologies for collection and integration of data, computational modeling, and interdisciplinary collaboration, was shared among its proponents (see, e.g., Kitano, 2001; Hood, 2002; Klipp et al.,

2005; Aebersold, 2005; Bruggeman & Westerhoff, 2006). In the human genetics laboratory where I had worked as a graduate student in the late 1990s, the pursuit of similar ambitions was already shaping the experimental agenda. This was a time when high-throughput DNA sequencing techniques and microarrays capable of registering changes in transcriptional regulation for hundreds of genes had just become available. In addition, computational approaches for integrating data were rapidly being developed, thanks to joint contributions from mathematics and computer science. Their implementation facilitated the construction of increasingly refined models of biological systems, thus permitting more accurate predictions of their behavior. Concurrently, a series of sociological changes were taking place in the biological sciences. At Columbia University's Genome Center, for example, the mathematicians and computer scientists who staffed the bioinformatics department had just relocated next to the biology laboratories. Some in the scientific community may have been surprised by developments of this kind. In retrospect, however, it is clear that they were not merely coincidental: they indicated the upgraded role that non-biological disciplines and their methods were destined to play in the way biological inquiry would be conducted in the immediate future.

Working scientists who witnessed these rapid developments in the period that led up to the official birth of systems biology could not help but wonder about their cumulative practical impact. They recognized that innovative techniques could offer solutions to problems for which traditional methods appeared to be insufficient, thus presenting researchers with a path for pursuing objectives that had long remained out of their reach. In short, the immediate response of biologists such as my lab mates to the changing landscape in the discipline consisted in asking about the potential of the new techniques for advancing their experimental projects. I regarded this pragmatic attitude as fully warranted by the nature of the modern scientific enterprise. Doing science, after all, meant first and foremost to produce tangible results. Prioritizing practical considerations would therefore constitute the indicated approach for anyone involved in this activity. But even though as a training scientist I was sympathetic to such a response, it seemed to me that to properly evaluate the promise that the emerging approach held for the fulfillment of biology's most ambitious goals, one would also have to identify its limitations. The latter did not simply amount to determining the scope of problems for which the newly available techniques could provide solutions when tested in practice. It also required defining the theoretical conditions that constrained the range of biological questions that the given methodological orientation would be fit to address. A systematic study of the limitations of biological methodol-

ogy represented, therefore, a direct route from biology to philosophy.

When I was no longer bound by the demands of scientific practice, following this route became a realistic possibility. The philosophical exploration of biology demanded a speculative attitude, but a concrete case to be examined was also needed. For the purposes of a study of this kind, the example of systems biology struck me as particularly appealing. A set of theoretical issues were at the heart of the debate about the optimal manner of implementing the systems approach in the laboratory. Rather than diverting attention from philosophy, then, attending to specific theoretical problems pertaining to the methodology of systems biology could provide the necessary structure for thinking systematically about longstanding epistemological questions.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

Features pertaining to its methodology, practice, history of development, and conceptual origins, render the case of systems biology into a fertile subject of reflection for anyone seeking to examine the relationship between philosophy and biology, and, more generally, philosophy's relationship to science. From the moment of the inception of a research program for the study of complexity in biological systems, its proponents – not only biologists, but also those trained in the non-biological disciplines that systems biology aims to integrate in its framework – were actively engaged in a theoretical discourse regarding its goals and the proper strategy for attaining them. Different visions of systems biology that corresponded to different groups of interlocutors in this discourse had an impact on the implementation of the systems approach, especially at these early stages of its development.

O'Malley & Dupre (2005) observed that in previously published descriptions of the field the various conceptions of systems biology were consistently classified under two distinct, but not mutually exclusive, main streams: one was "pragmatic" while the other was "systems-theoretic." Essentially, this was a division between a perspective adopted by those who placed an emphasis on the role of traditional molecular biology-based methods for the fulfillment of the objectives of systems biology, and another which privileged the role of mathematical, computational, and engineering approaches, but also of concepts from earlier theoretical efforts to study systems in their generality,[1] for achieving the same end. Only one of these two sides draws directly from theoretical

[1] Contributions by Bertalanffy (1968), Rosen (1967), Mesarovic (1968), Ashby (1956), and Wiener (1948), are among those from which the systems-theoretic stream of systems biology has drawn basic concepts.

analyses of the constitution of systems. Nevertheless, they both represent markedly distinct theoretical commitments – frequently due to differences in disciplinary training rather than because of the persuasiveness of philosophical arguments – which have played an important role in shaping the agenda of practicing systems biologists. This observation affirms the influence that idealistic visions of systems biology have had on those who carried out projects under its banner in the laboratory, but it does not yet permit us to make a pronouncement about the potential of philosophy of biology proper to inform its practice.

Interestingly, the methodology of contemporary systems biology seems to be increasingly defined by pragmatic concerns rather than by adherence to abstract theoretical requirements. In fact, a survey of its application reveals a great deal of complementarity and collaboration between the parties that appear to be competing with each other in theoretical debates about systems biology's proper strategic orientation. The systems approach, in other words, is generally not implemented in a purist way in the laboratory. This, of course, is in itself a matter for philosophical reflection. For instance, in a recent paper MacLeod & Nersessian (2013) report on what they call a "bimodal strategy" of practicing systems biology, which couples computational simulation methods and biological experimentation. Rather than following strictly the edicts of a single stream of systems biology, the researcher whose strategy is the focus of their study is guided by the practical demands of her research project. This leads her to adopt a combination of biology-rooted and systems-rooted approaches. For the authors, the description of this researcher's experimental strategy serves as a prelude to a philosophical discussion which focuses on the relative advantages and limitations of her methodological choice.

This example illustrates one of the many ways in which investigation of systems biology informs philosophical inquiry. By serving as an occasion for thinking about biological practice, the paradigm of systems biology helps draw attention to the need for adjusting the agenda of the philosophy of biology, so that it would become capable of addressing the philosophical implications of a range of biology-specific problems stemming from the multidisciplinary and integrative character of the systems approach. The upgraded role of mathematical models in systems biology, for example, indicates that philosophers ought to address questions about the suitability of mathematics for explaining biological phenomena. Similarly, by demonstrating that integration of explanations from different levels of a biological system's organization is essential for systems biology's success, the examination of its practice raises a series of epistemological questions about the limits of mechanism for carrying out the requisite explanatory integration. The

related issue of emergent properties is also highlighted on this occasion, mostly by the failures of systems biology rather than by what it has thus far managed to accomplish. Philosophers of biology, but also those working on metaphysics and the philosophy of mind, can benefit from a discussion of emergence in the context of systems biology. Hence, the philosophy of biology stands to gain from focusing on various aspects of the application of systems biology. But the insights gained could impact the course of system's biology's development, as well. If this scenario were to materialize, the case of systems biology would illustrate paradigmatically what some envision as the ideal relationship between philosophy and science: philosophy's agenda is tested and defined by the pragmatic needs of science and, conversely, the progress of science is facilitated by the theoretical contributions of philosophy. All indications, however, point to the conclusion that whereas philosophical studies of biological practice are having a significant influence on the philosophy of biology, the approach of systems biologists appears to be decidedly pragmatic.

More generally, by shifting the focus on the concept of "system," systems biology has contributed to the most recent reintroduction of the classical philosophical problem regarding the relationship between the whole and its parts, which has preoccupied philosophers since before Aristotle's time. In doing so, it has also helped put in perspective the old debate between holism and reductionism that had never really ceased to occupy an important position in philosophy of science. But, as described earlier, the study of the practice of systems biology has been impacting primarily the agenda of the philosophy of biology, causing it to change its priorities and to expand its scope. One might add that this influence on the philosophy of biology is contributing to its gradual transformation into the kind of discipline that Ernst Mayr had envisioned in *The Growth of Biological Thought* (1982), years before the emergence of the systems approach: a new philosophy of biology that would not dwell on the influence of positivism but would instead become focused on the biologically relevant issues. Finally, one must not discount the importance of the social, political, and ethical impact of the theoretical principles endorsed and the practices promoted by scientific strategies such as systems biology. These themes may not be included in the principal domain of investigation of most philosophers of biology, but critical reflection and analysis of their implications certainly falls under philosophy's jurisdiction.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

Efforts to contribute to the philosophy of biology are often consumed by a concern with the technicalities of biology's application. Consequently, other aspects of the subject matter that are philosophically worth pursuing are either receiving little attention or ignored altogether. The discourse, therefore, often takes the form of extensively descriptive accounts of scientific practice, followed by some critical assessment of the significance of the observations made concerning its mechanics. In this respect, the paradigm adopted might be taken to match closely the model of scientific discourse within biology itself. There is a good argument in favor of this approach: it is said to promote rigor, which is in turn an essential condition for the reputability of the philosophical enterprise. But the role of philosophers cannot be reduced to dealing with problems that scientists themselves are better qualified to resolve. While philosophers of biology stand to benefit from examining biological practice, their responsibility is to ultimately transcend its confines in order to produce insights about biology that are distinct from the scientific insights that biologists routinely produce within their own discipline. The speculative attitude required for accomplishing this was exemplified by theoretical biologists such as Ludwig von Bertalanffy, whose contributions in the 1900s have not received much attention by contemporary philosophers of biology.

Although Bertalanffy (1968) introduced[2] General System Theory (GST) as a paradigm that would extend to all sciences, he conceived the idea that is central to the theory – namely, that all systems share some basic properties – after several years of studying biology. Moreover, the development of a general theory of systems could be attributed, at least in part, to demands for new conceptual tools for addressing the problem of organized complexity in biological systems. The available strategies of reductionist science appeared insufficient for understanding essential features of living beings such as their capacity for self-regulation, self-organization, and maintenance of orderliness. Dissatisfaction with this state of affairs motivated Bertalanffy to articulate GST as a thoroughly scientific holistic alternative whose purpose was to provide formal expressions of the common organizing principles that govern both biological and non-biological systems.

In view of the recent resurgence of interest in problems arising from the complex organization of biological systems, some philosophers of

[2] General System Theory was informally introduced by Bertalanffy at a seminar in the University of Chicago in 1937; thirty-one years, that is, before his comprehensive formal treatment of the subject in the homonymous book.

biology have suggested that it might be time to reevaluate GST's contributions. They have argued that revisiting early theoretical attempts to study systems in their generality could be helpful for informing the methodology and current practice of systems biology. More specifically, they have emphasized the potential of abstract organizing principles, like those postulated by Bertalanffy and other early systematicians, to facilitate explanation in systems biology by generalizing the results obtained through standard mechanistic approaches at a biological system's molecular level (Drack & Wolkenhauer, 2011; Wolkenhauer et al., 2012; Green & Wolkenhauer, 2013). In short, organizing principles could play a complementary explanatory role, alongside causal mechanisms, in the context of systems biology.

Similarly to general systematicians, who strived to study systems in their generality, systems biologists aspire to understand biological systems as systems (Kitano 2001, p.2). The latter, however, have at their disposal new theoretical tools – mathematical and computational – which might allow them to pursue this goal more effectively than the former could ever have done without the equivalent resources. For example, Alon (2006) has shown how basic formal principles, elucidated from the motifs of connectivity that are recurring in small sub-circuits across different regulatory networks, could be articulated in mathematical terms that are simple and concrete enough to be transferrable into the practice of systems biology. While contributions such as Alon's may not suffice for producing the comprehensive understanding which constitutes systems biology's loftiest aspiration, they do illustrate how supplying biologists with general theoretical principles that are practically applicable could gradually move the discipline closer to this goal. Furthermore, they indicate that searching for general system principles need no longer be regarded as a futile theoretical exercise.

4. What have been the most significant advances in systems biology?

In this section, rather than highlighting particular advances in systems biology, I will briefly consider the trajectory of its methodological development, which is in itself a subject of philosophical interest.

The course of development of the systems approach in biology is characterized by progressive diversification of the methods used in its practice. It is not at all clear that this diversity of practices could be attributed to a theoretical program, whose prescriptions are followed deliberately by researchers in the laboratory. On the contrary, it seems to coincide with the recognition that a problem oriented, pragmatic agenda is most productive for systems biology and best suited to its multidisciplinary constitution.

O'Malley & Soyer (2012) provide various examples from the general

context of systems biology in order to show how new insights could be generated by the integration of diverse methods, data, and explanations in the day-to-day practice of science. In one of these examples, the authors consider the strategy employed in a recently published study of vesicle transport in fungi. This is a problem traditionally taken to fall under the jurisdiction of cell biology, which is transformed in this particular case into a problem for molecular systems biology with the import of a mathematical model for the interpretation of biochemical data. By transferring a mathematical explanatory model that had been used for the analysis of systems in physics to cell biology, the transport of vesicles in fungi, which was at first regarded as a deterministic process, is ultimately understood more accurately as stochastic. The reconceptualization of this pragmatic problem through a mathematical cell biology approach, illustrates the explanatory value of integration – in this occasion, an integration of heuristics from different scientific fields. One might also note that the practical needs of the project, rather than abstract theoretical commitments, drive the integration described in this example. A more adequate explanation of the complex biological process under scrutiny is attained as a result.

These observations reinforce a view that has been gaining popularity among philosophers of biology: inquiries that develop around a set of practical problems could produce explanatorily fruitful conditions. Love (2008), for instance, has argued that explanatory integration in biology can be supported by the epistemological framework that emerges when research follows concrete problem agendas. Within this framework, multidisciplinarity arises as a response to the complexity of the problems that researchers encounter in practice. Clearly articulated criteria of explanatory adequacy are to be used for prioritizing the contributions of the various disciplines, or for excluding some of them from the explanatory integration process. These standards, however, cannot be universal. Instead, they are envisioned as context-based, in the sense that they would vary in each particular case depending on the demands of the relevant problem agenda. To demonstrate the applicability and the epistemological advantages of this approach, Love (2008) appeals to a case study from evolutionary developmental biology ("evo-devo"): the project of accounting for the origins of evolutionary innovation and novelty. A case from contemporary systems biology, however, would have served the purpose just as well.

The pragmatic approach to integration advocated by Love and others (see, e.g., Grantham, 2004; also Brigandt, 2010) involves methodological stipulations that are also encountered in a range of recent cases from the implementation of systems biology. More specifically, in response to the complex problems that they set out to address, systems biologists

resort to a diversity of research practices, exploratory questions, and explanatory models. In the same context, heuristics from one field are often employed in the context of another field, as seen in the example of the study of vesicle transport in fungi that was discussed earlier. By establishing connections of this type among them, the fields involved are unified without reduction: their unity can be conceptualized as "interconnection" (Grantham, 2004). Not only is the integration that occurs in this epistemological context non-reductive, but it is also effected by means of specific scientific practices, thus not requiring interfield theories, whose development was regarded as essential for non-reductive unity by Darden & Maull (1977).

Thus understood, the pragmatic approach in systems biology offers a modest non-reductive alternative to the comprehensive explanatory integration sought by system theorists. Systems biologists who organize their research around specific problem agendas seek integration of a narrower scope, within the realm of scientific practice, instead of pursuing the ideal of system-wide understanding. To the extent that it can be correlated with the production of increasingly adequate explanations, the turn to pragmatism constitutes a methodological advance. Notably, by adopting a pragmatic orientation, systems biology is progressing by seemingly retracting from its most ambitious holistic aspirations. But this is only half of the picture: concomitant to the proliferation of the pragmatic paradigm in systems biology is the renewed interest in theoretical efforts for large-scale explanatory integration via general organizing principles. Taken together, these trends present us with an alternative possibility: systems biology need not be seen as destined to proceed by following divergent paths – pragmatic and systems-theoretic – but could be better understood as the locus of integration of contributions from two mutually complementary methodological perspectives that define its application. As such it progresses, albeit in a non-linear way, towards the holistic objective of comprehensive explanatory integration.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

The examination of recent methodological developments in systems biology reveals advances with respect to explanatory adequacy. At the same time, it draws attention to challenges for integration of multiple methods, accounts, and data that is frequently required for producing adequate explanations of complex biological phenomena. The identification of limitations of explanatory integration in systems biology promotes thinking about the conditions required for providing intel-

ligible accounts in science, more generally. As demanded by the occasion, however, I will narrow the scope of the following discussion by concentrating on the philosophical relevance of problems that pertain specifically to mechanistic explanation in systems biology.

Mechanistic explanations are commonly understood as descriptions of interactions among parts, or of other activities within a system, that produce a given phenomenon. Their productive use in the biological context has sparked a lively conversation concerning mechanism among philosophers of biology. The discourse, which has come to be known as the new mechanistic philosophy after Skipper & Millstein (2005) used this term to describe it, developed originally around distinct theoretical accounts of mechanism provided by Glennan (1996) and by Machamer, Darden, & Craver (MDC) (2000). Despite recent amendments to these accounts (e.g., Bogen, 2005; Bechtel & Abrahamsen, 2010; Bechtel, 2011) questions remain about the adequacy of currently available theories for supplying a mechanistic framework that could meet the needs of systems biology.

A particularly important issue that must be addressed for a purely mechanistic strategy to suffice for explanation in systems biology concerns its capacity to accommodate mathematical models. In conjunction with computational approaches, mathematical tools play a central role in the visualization of complex biological systems and in the prediction of their behavior. Frequently mathematics is conceived merely as a language for describing phenomena or objects. Philosophers like Colyvan (2001) and Baker (2005), however, have argued that mathematical formalisms are more than just descriptions: they are explanatory in their own right, and thus the category "mathematical explanation" is genuine. The question relevant to the issue at hand, then, is whether mathematical explanations could be fully integrated into a causal mechanistic framework. If explanation in systems biology is construed as an exclusively mechanistic affair, such condition would seem to be necessary for explanatory adequacy in an approach characterized by the prevalence of mathematical models.

Despite their relative versatility, standard accounts of causal mechanism lack the theoretical tools for incorporating mathematical explanations of complex systems with non-sequential, cyclic organization. According to Bechtel (2011), expansion of the notion of mechanism is needed to overcome this problem. Bogen (2005), as well as Bechtel & Abrahamsen (2010), have taken steps in this direction by articulating conditions of a mechanistic agenda that could include models that do not display regularities or sequential execution of operations. In addition, Bechtel (2011) has emphasized the need to extend the theoretical conception of mechanism sufficiently so as to make it capable of

accommodating mathematical explanations produced by dynamic systems analysis. The progress towards lifting the conceptual obstacles that stand in the way of attaining explanatory integration in systems biology is expected to continue as philosophical debate contributes to the identification of those aspects of available accounts of mechanism that need to be refined or revised. Besides mathematical explanations, other categories, such as evolutionary explanations, currently not expressible in mechanistic terms but frequently encountered in biology, will have to be incorporated into the mechanistic framework, as well, in order to improve its capacity to deal with problems of biological complexity. Nevertheless, one must note that extending or refining the notion of mechanism is not guaranteed to solve the problem of explanatory integration. If achieved at the expense of clarity and precision, expansion could amount to generating mechanisms as complex, and therefore as unintelligible, as the systems that they intend to explain.

Advances in addressing the problem of explanatory integration are not only occurring on the theoretical front. Successful integration of mechanisms from different hierarchical levels of complex biological systems, or of mechanistic models originating from different disciplines, is also taking place in the daily practice of systems biology. In turn, the insights gained from these pragmatic approaches are reapplied in the context of scientific practice where they improve our capacity to manipulate and control biological systems. Despite their reliability, these explanations are partial. Therefore, the goal of comprehensive explanatory integration that constitutes systems biology's highest ambition may not be attained unless all such local explanations are integrated in the context of an all-encompassing mechanism. Alternatively, one might envision a more pluralistic picture of explanatory integration, in which not only mechanisms but also other, non-mechanistic explanations contribute jointly to our understanding of biological phenomena. Determining the conditions for the possibility of integration in either of these cases requires, once again, the input of theory. Despite the progress in explanatory adequacy that manifests itself in the practice of systems biology and the notable advances in thinking about explanation in the philosophy of systems biology, the objective of a comprehensive explanatory integration remains out of reach. Mutually complementary contributions from theoretical and pragmatic approaches promise to produce more reliable explanations, as systems biology continues to develop. But as complete understanding of biological systems continuously eludes us, it appears that the primary benefit from studying problems of explanation in systems biology is philosophical: it puts in context questions of methodology in science, as well as greater epistemological questions concerning meaning and the limits of intelligibil-

ity.

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Complexity Organizing Principles: Prerequisites for Life

1. How and why were you initially drawn to systems biology?

I was not "drawn" to systems biology as such. Systems biology was launched as a new field in 1968, at the Third International Systems Symposium at Case Institute of Technology, Cleveland, Ohio, which I organized to explore how systems theory and biology could benefit from each other. I expected complexity to become the main research topic in the next century, and I wanted to develop theoretical tools for dealing with scientific problems. The motivation was therefore theoretical as well as practical, that is, it had as the objective to provide better methods for understanding as well as controlling complex systems. A part of the symposium regarded conceptual foundations for the new systems biology discipline, focused on relations between biological entities forming a system rather than on the properties of the related entities in isolation. For this purpose, we needed a new general and formal scientific language. I proposed Mathematical General Systems Theory as a candidate for such a language (see Mesarović & Takahara, 1970, 1975). My vision for the new field of systems biology is clarified in my contribution to the symposium proceedings that I edited (Mesarović, 1968). Before we go into the details of my view on systems biology, let me first say a bit more about my background. This is a long story that I here will try to make as short as possible.

I was born Yugoslavia in 1928, where I also took my education up to the level of my PhD. During this period I experienced two sequential regimes before and after Second World War. In both of these regimes, two words – truth and life – lost their meaning and value. Truth was what you were told, while "life" almost lost its value if you were not following the orders. I graduated from the university in mathematics and electrical engineering in order to support my family although my

primary interest was in philosophy (which did not exist in any serious form at the university). After graduation I did my research at the Nikola Tesla Institute in Belgrade and got a teaching appointment at the university in due time to become a Docent, i.e. an academic scholar at associate professor level. My research was theoretical and focused on control of large scale electric power systems. I wrote research papers that were published in international journals, and attended conferences in Heidelberg and Paris.

In 1957, while having breakfast with my wife and my son, I received a letter from the Sloane Foundation informing me that I had been selected to receive the Sloane Foundation MIT grant as well as funding for travel expenses for my family to go with me to the USA. We felt as if we were about to move to another planet. I was very excited about this opportunity, in particular to have the chance to interact with the mathematician Norbert Wiener at the Massachusetts Institute of Technology (MIT). Wiener and his cybernetics became a major source of inspiration for my own work.

After moving to the US in 1958, I became professor at MIT and later associate professor and professor at Case Western Reserve University, Cleveland. I have always been interested in issues related to globalization and environmental problems. In association with the Club of Rome, I was involved in the development of what was called the World Integrated Model (1972). Together with Eduard Pestel, I compiled the findings of a range of analyses on global problems in a book entitled *Mankind at the Turning Point* (Mesarovic & Pestel, 1976). This book became a non-fictional bestseller and has since been translated into 18 languages. In 1999, I became Scientific Advisor on Global Change through UNESCO, and I have served as advisor on issues related to economics, climate change, technology, and sustainable human development.

All of these issues have to do with complexity and the challenges for dealing with complexity. Through my career, I have enjoyed discussions on these issues with politicians, students and colleagues alike. There is a story of a Greek philosopher who said that if somebody would give him access to all the truth in the world under the condition that he cannot tell that truth to anybody, he would not have taken it. It is the same for me, and this is why I became professor.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

Philosophy and systems biology are in a closed loop relationship. Philosophy is why, systems biology is how, and philosophy is then so what? For example, a question is raised in philosophy, and the systems biol-

ogy task is to identify some specific biological problems whose answer provide a response to the philosophical question raised. Or, vice versa, a phenomenon in systems biology is identified and the philosophical implication is then inferred which in turn indicates a class of systems biology phenomena for which an analogous philosophical implication is indicated.

Philosophical questions of randomness in evolution may serve as a good illustration. As a young mathematician, Gödel, shocked the entire philosophical and mathematical establishment by proving that in any formal system, including real number processes, the consistency of the axioms cannot be proven from within this system. What Gödel did can be explained in terms of the difference in grammar and truth. For instance, if a Greek says that all Greeks are liars, his statement may be grammatically correct but can be either true or false. Gödel demonstrated it is important to bear this in mind in our ontological effort to understand the world, i.e. trying to clarify the "what is the case", we are bound to consider epistemological questions ("what we believe to be the case"). We explore the world with models but the syntax of these formal systems comes attached with semantics. That is, there are aspects that remain uncertain from the analysis of the system. Gödel's work is however a triumph as it showed that by modeling models (e.g. formal number systems), we reach higher levels of understanding. My claim is that biology needs Gödel. In Darwin's theory of evolution randomness is required to initiate an evolutionary step but this also implies unpredictability. Biological complexity implies that there will always be some uncertainty but by abstracting from the models we have of biological processes, we can gain insights into general organizing principles. For the current practice in systems biology, this means we must appreciate uncertainty in understanding mechanistic details of biochemical and biophysical processes occurring in cells, and yet, by generalizing pathway models of subcellular mechanisms, through abstraction, we can gain insights into higher level principles of, say, tissue organization.

Another area where philosophy and science intersect is in the debate about the ontology and cause of complex diseases. We can illustrate this with the example of cancer. Traditionally, cancer has been viewed as a disease in which environmental or endogenous events induce mutations to critical oncogenes and tumor supressor genes within a normal cell. However, the evidence is still on the behavioral/observational level (see Question 3), and the question remains whether cancer results from environmental circumstances or is due to failure of coordination processes inherent in the organism. We therefore need a top-down perspective, taking into account how the harmony of healthy states is disrupted in

diseased states. It is truly remarkable how little attention has been paid to harmonization studies of biological systems. An exception is Denis Noble's (2006) book *Music of Life*. Coordination is a generic organizing principle for harmony. I shall elaborate on how systems biology has provided insight into coordination in biological systems in Question 4.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

The most neglected topic in 20th Century philosophy of biology is complexity. This is quite surprising given that already at the launching of systems biology in 1968, Talbot Waterman (professor of biology at Yale University) emphasized Warren Weaver's characterization of biological systems as exhibiting *organized complexity* (Weaver, 1948). Sadly, the challenges for understanding systems with organized complexity have been largely ignored up to the present time. Paul Nurse (a fellow of the Royal Society in the UK who received the Nobel Prize in Medicine in 2001), expressed in his article "Life, logic and information" (*Nature* July 2009) a reminder to scientists as well as philosophers. He stressed that: "Biology stands at an interesting juncture. The past decades have seen remarkable advances in our understanding of how living systems work. These advances have been built mostly on molecular biology: applying the ideas that the gene is the fundamental unit of biological information and that chemistry provides effective mechanistic explanations of biological processes. But comprehensive understanding of many higher-level biological phenomena remains elusive. […].These gaps in our knowledge are accompanied by a sense of unease in the biomedical community that understanding of human disease and improvements in disease management are progressing too slowly" (Nurse, 2008, 424). I believe this is in part due to the failure of recognizing an important distinction between complicated and complex systems.

A complicated system consists of a large number of interacting parts or subsystems with the overall system displaying counterintuitive behavior. That is, the behavior of the whole is not explainable in subsystem levels terms, much like the present global financial system. *A complex system* displays organized complexity, i.e. it is a multilevel system in which functioning and relationships between parts on any given level and between the levels are governed by organizing principles. Saying that a complex system displays organized complexity means that in spite of being complicated – having a considerable number of parts – its functioning is governed by rules such that its behavior is consistent, i.e. it appears organized and in this sense simple. The notion of complexity has been defined in a variety of contexts. The notion of complexity I prefer is motivated by Henry Poincaré's view that

scientific knowledge regards the *relations* between things, rather than the things themselves. Organized complexity is a defining characteristic in systems biology where explicit recognition of the levels from molecules to cells to tissues to organs to organism is essential. A complex biology system – e.g., the human body – is a system of systems in a multilevel, hierarchical, organization-exhibiting structure.

Charles Darwin said that it is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change. Change and dynamics are thus a central characteristic of biological complexity and we can distinguish several principles of response: (i) resilience to external and internal changes (linked to concepts of 'regulation', 'homeostasis', 'robustness'), and (ii) adaptation to external and internal changes (linked to concepts of 'control', 'sensitivity" etc.), and (iii) harmonization of the system's behavior across different levels of structural and functional organization, whereby the system becomes more than the "sum" of its parts looked at in isolation. A complex system is recognized in terms of multi-levelness that can be approached at three ontological levels:

> A. Behavioral Level: Representation or description of phenomena, e.g. how causes/stimuli/inputs map onto effects/responses/outputs in space and time.
>
> B. Functioning Level: Mechanisms which make the system behave as observed
>
> C. Organizing Principles Level: Law-like rules which specify categories of functioning of which a given functioning is identified as one of the instantiations. In systems biology organizing principles are analogous to natural laws in physics and chemistry.

These levels will be clarified below. Complexity is typically considered a "curse", an obstacle to understanding, but luckily we have several strategies to deal with complexity. In response to the increased concern that a lack of understanding of biological complexity is hampering advances in medicine, I propose that the potential of Mathematical General Systems Theory (MGST) should be explored and research should be focused on the search for organizing principles. Using Einstein's dictum that "if you understand it well enough you can explain it simply", we should try to take up this challenge and use mathematical rigor to eliminate alternatives that are not possible. In MGST, 'generality' means reaching important principles through mathematical rigor by identifying what is most essential for the system and expressing this in simple terms. Ludwig von Bertalanffy launched General Systems Theory in the context of biology with the underlying view that mathemat-

ics is useful as an abstract language for generality (Bertalanffy, 1950, 1969). MGST departed from the view of GST in aiming to go beyond representation by modeling of data – to ascertain validity of finding by theorem proving. Validity of certain conclusions at the MGST level leads to validity for a vast number of particularized situations (see also Wolkenhauer, Shibata, & Mesarović, 2011, 2012). Of examples resulting from MGST one can mention the Interaction Balance Coordination Principle (IBCP), which plays a key role in harmonization, and Bounded Autonomy of Levels (see below) (Mesarović, Sreenath, & Keene, 2004; Mesarović & Sreenath, 2006). A well-known and simple example of an organizing principle is the concept of feedback that was formalized by Norbert Wiener in his cybernetic approach. A system which on the behavioral level displays robustness to perturbations may be recognized as having certain feedback mechanisms at the functioning level, and can be categorized at the organizing principles level to be an instantiation of the principle formalized as integral negative feedback (see also Green & Wolkenhauer, 2013). The importance of organizing principles has been largely neglected in modern biology, and I therefore dedicate the following section to clarify how organizing principles advance our understanding of complex, multilevel, biological systems

4. What have been the most significant advances in systems biology?

Systems biology helps to clarify defining features of biological systems. In its most generic form, a complex multilevel system is a system of systems such that the overall system and its subsystems have a distinct behavior, i.e. each level has its own level-specific terms and laws.

Multilevelness, a defining concept in complex systems, is central in most sciences from physics and biology to psychology and the social science, but cross-level causality is not the same in all of them. In biology, the levels are neither independent nor fully coupled. This insight provided the rationality for the formulation of the organizing principle called Bounded Autonomy of Levels (BAL). The BAL principle can be stated as follows: Cross-level relations in a complex biological system are characterized by the existence of domains of functioning on any two levels within which the levels do not interact even though they are interdependent, being the same overall systems. These domains of non-dependence are referred to as BAL domains (see Mesarović & Screenath, 2006). There is a higher degree of biological uncertainty regarding processes across levels compared to causality on one level because processes across levels are highly nonlinearly dependent.

Importantly, we must distinguish between *interdependence* and *interactions*. Interacting subsystems causally impact each other, but subsystems can also be interdependent in the sense that they belong to the

same overall systems without direct interactions in terms of point-to-point mappings between variables. We often need to think of cross-level relations in terms of set-to-set mappings. Although biological systems are interdependent across levels, they are not directly interacting within bounded autonomy domains. For example, we may perturb signaling pathways in various ways that affect causation at this level, but the state of the cell as a whole will not change as long as the perturbations from the signaling pathways lies within the BAL domain. Similarly, mutations of the genome of, say, *E. coli* will often not lead to altered phenotypic states. That is, the system at one level may be resilient to perturbations at another level, but only until the "tipping point" where the state of the cell changes. This is analogous to how action potentials are generated in non-linear fashions from certain voltage values (Noble, 2006, 2012), whereas changes within the BAL domain can be dampened (or can be considered as noise) at the other level. Importantly, causality between levels is two-directional. In the context of mammalian ventricular myocytes the cell voltage depends on ion currents while the cell voltage in turn controls ion flow. Denis Noble has demonstrated that cutting off the cell voltage impact on ion flow shuts down the cell's functioning, an example of top-down causality (see also Noble, this volume). The BAL principle thus shifts the emphasis from attempts to identify specific links or pathways to the identification of the BAL domains or "tipping points" where cross-level effects occur.

Recognition of the BAL principle as a defining characteristic of cross-level causality opens a new direction in complex systems biology research with considerable potential for explanation of causality in a way more consistent with observations while making data-based identification of cross-level relations easier. Aside from shifting the focus from specific pathways to identification of BAL domains, BAL provides a framework for understanding division of labor in biological hierarchies so that harmony resulting in homoeostasis is achieved most economically. The concept of the BAL principles has as its precursor Herbert Simon's famous concept of Bounded Rationality of human behavior in economics and decision making. Simon questioned the assumption of rationality and optimization of human behavior for a range of reasons such as access to incomplete information, time constraints etc. Humans "satisfy" rather than optimize their decision making, i.e. they act with 'bounded' rationality. The BAL principle is reminiscent of Heisenberg's Uncertainty Principle in physics in the sense that it shows the limited precision achieved through approaches based on a one-to-one mapping between all domains across levels. Understanding biological robustness therefore requires identification of BAL domains.

As mentioned in Question 2, another important aspect of living sys-

tems is coordination. Subsystems perform their own functions while being integrated into the functioning of the overall system. This integration is achieved by subsystem *coordination*. Coordination is distinct from control. Control means achieving certain objectives or goals in spite of variability, and it is a top-down directive or order. In contrast, the objective of coordination is not to control but to harmonize, i.e. to influence a set of interacting subsystems in a way that advances the objective of the overall system.

Coordination can be achieved in different ways shown in Figure 1.
A. By endogeneous change of the subsystems themselves, as for example in angiogenesis.[1] There is no recognizable coordination unit.
B. By a distributed coordination process. Again, there is no recognized coordination subsystem which controls the other. This type of coordination is seen in the immune system.
C. By an identifiable coordination subsystem, e.g. at the level of organs.

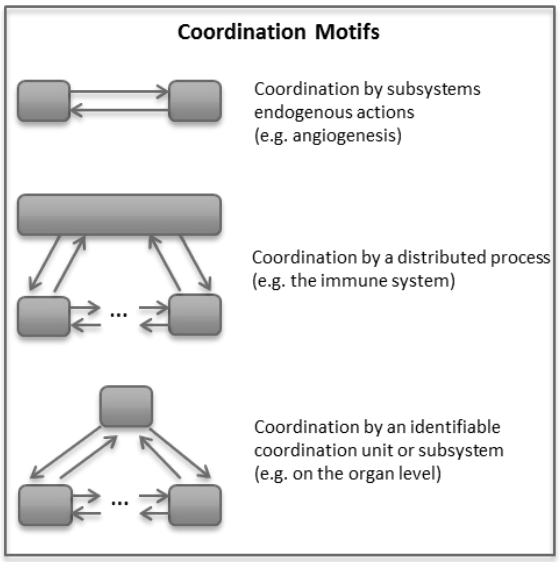

Figure 1. Coordination achieved in different ways.

Coordination as a generic organizing principle is implemented in specific situations by particular organizing principles.

[1] Angiogenesis is a tissue forming process which originally was discovered as a prerequisite for cancer progression but has been identified in a number of other physiological processes as well, including wound healing, growth of neurons in the brain etc.

The Interaction Balance Coordination Principle, IBCP, is an example of a coordination principle that has been studied extensively in multi-level hierarchical systems theory and has wide applications. Stated in simple terms, IBCP is a coordination strategy to detect and account for imbalances in subsystem behavior such that desired states are balanced (Mesarović et al., 2004). By balance it is not meant that the interactions are exactly the same but rather that they are within a satisfactory range. Mathematical analysis has provided proofs of coordinability by IBCP for an exceptionally broad class of systems which makes the principle a strong candidate for explanations of harmony in a range of complex systems. Moreover, these insights have practical implications. For instance, in carcinogenesis the vascular system and tumors are aligned through angiogenesis in the following way; the former grow capillaries to provide the tumor with oxygen and the tumors produce growth factors (Folkman et al., 2000). These interactions are parts of a larger system which exhibits coordination as a distributed system, posing major challenges for our understanding of complex diseases like cancer. In essence, this is why we need systems biology.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

> How odd is it that anyone should not see that all observations must be for or against some view if it is to be of any service.
>
> - Charles Darwin.

With Darwin's quote in mind, I would here like to mention some challenges that may determine the future advance in systems biology. The first may be called the *Brain/Mind Conundrum*. In modern biology, the brain is rightfully recognized as a network of neurons. Neurons are information processing systems, mapping inputs to outputs. But the brain is in many ways different from a computer. The brain is a complex system, i.e. a system of systems. We therefore need to study the brain as a complex system. The brain receives an enormous amount of "data" through neurons but the messages are turned into information only to the extent that neurons interpret these as information. Data-driven science measuring all details alone will not take us to an understanding of how the brain processes information, as we have no clue how to "distill" principles from large amounts of data. As Darwin said, observations must be in service of some kind of theory or guiding principles if they are to make any sense. The current results are highly dependent on

what approach, method, tools, software etc. are used for data analysis, restricting the categories of the system that can be considered. In my view, we need to fundamentally rethink the way we model biological systems and go beyond the "flat earth" perspective of biological networks (Mesarović & Sreenath, 2006). That is, we need to better understand how information is processed and distributed across levels. We need a deeper theory of complex systems.

An intriguing question is the following. Will systems biology come to play a role in all future sciences, analogous to the role that Newton's classical physics played across the entire range of other sciences? I think that systems biology has the potential to influence thinking in all sciences as well as the way we think about societal issues. Shifting from the input/output and complicated system paradigm to the complex multilevel system paradigm also provides a basis for better understanding how financial systems function, or ought to function. The world is multilevel: from global to local, from resources and environment to high finance and politics etc. We therefore need new theoretical frameworks for dealing with complex phenomena. I believe the time is right for a wakeup call.

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Systems Biology Modeling Practices: Reflections of a Philosopher-ethnographer

1. How and why were you drawn to systems biology?

I was coming to the end of an eight-year NSF-sponsored research project in which we conducted ethnographic investigations into the cognitive and learning practices in university biomedical engineering research laboratories. Put succinctly, the major research challenge in the tissue engineering and neural engineering labs we studied was to design, build, and experiment with *in vitro* physical simulation models of *in vivo* phenomena. The "model-systems" comprise biological and engineered materials and are designed to parallel selected *in vivo* phenomena under controlled experimental conditions. The labs were largely populated by "researcher-learners": graduate students and, increasingly over the course of our study, undergraduates. These labs were set in the context of creating a new educational program aimed at developing *hybrid* researchers sufficiently trained as bio-medical-engineers to overcome the obstacles that collaborations between, especially, engineers and biologists had encountered in the early period of development of this field. We characterized the goal of this field as creating an *interdiscipline* – a fully hybrid interdisciplinary field. The objectives of our research were two-fold. From the perspective of cognitive and learning science we wanted to detail the cognitive practices of frontier research in this field, determine the nature of the learning challenges, and also determine good practices that had been developed within the labs to support learning. We then worked with faculty to incorporate our insights about how to facilitate research and learning into the newly developing curriculum. In preliminary research, our at-

tention was directed immediately to the physical simulation models that are the signature research devices for each lab. There has been little discussion of physical models in the philosophical literature, so from the perspective of philosophy of science, I saw this as an opportunity to extend my analysis of model-based reasoning to physical models. And, finally, from the perspective of both cognitive science and philosophy of science this research provided an opportunity to develop further the notion that model-based reasoning is a system phenomenon, with the researcher mental models and external models (in this case physical models) comprising a distributed cognitive system. I have gone into detail since this project formed the background of what drew me to systems biology.

For the next project I wanted to continue with pioneering bioengineering research labs but with the focus on computational modeling and simulation. Systems biology (or "integrative systems biology" as the labs we investigated designated themselves) provided a perfect fit. Not only is computational modeling its central research practice, but it also presents a different variety of interdisciplinarity which is largely based on collaboration between modelers and wet-lab biologists. Thus, facilitating research and learning would require a new analysis and different strategies. Additionally, investigating systems biology research would enable extending the account of model-based reasoning to computational modeling.

We chose two labs to investigate, one that does only computational modeling and collaborates with bioscientists external to the lab and one that also has a fully equipped wet lab for conducting their own experiments in the service of model building ("mixed lab"). The purely computational lab is populated by graduate student and postdoctoral researchers with various engineering and applied mathematics backgrounds. The lab director was trained in theoretical biology. The range of biological systems they investigate is quite extensive, including, yeasts, neural systems, and disease processes such as arteriosclerosis. Initially we had thought the mixed lab would be populated by engineers and biologists, however,, in fact, except for the lab manager (who later transitioned to a grad student) the lab was populated by graduate and undergraduate student engineers, several with bioengineering backgrounds. The lab director was trained first in engineering and then in wet lab research directed towards cell signaling. At first this lab was a combination of hybrid researchers we came to call "bimodal" and pure modelers, but as time went on all the researchers were conducting their own experiments in service of building their models. This lab did have external bioscientists whom the researchers consulted with regularly to sound out their modeling ideas or to gain understanding of the biologi-

cal systems they were investigating, and there were also some external collaborators.

In sum, I was drawn to systems biology because computational modeling and simulation is its primary means of investigation and because studying their practices offered the possibility of both extending my account of model-based reasoning and developing a more nuanced understanding of interdisciplinary research.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

I see the relationship between philosophy of science and the sciences, including systems biology, as mutually informing and potentially collaborative.

From the perspective of philosophy, the fact that systems biology is an emerging field offers the opportunity to gain insight into the practices of a field as they develop in exploratory, incremental, and nonlinear processes. There is the opportunity to cast new light on established philosophical concerns such as modeling and simulation, the relation between reasoning and representation, methodological innovation, and conceptual transfer/formation/change. For example, most of the philosophical accounts of computational modeling and simulation have been based on physics-based sciences. Although it is widely accepted now that the models are not simply derived from theories, still an established theoretical context provides resources that guide and constrain modeling in ways not available to systems biology (more on this in Question 3).

Further, our research provides insights into the affordances and tradeoffs of different strategies for integrating model building and experimentation in systems biology. The two labs we have been investigating have distinct strategies. The purely computational lab had adopted what we called a "unimodal" strategy that relies on collaboration between experimenters and modelers (in this case in different laboratories) (MacLeod & Nersessian, 2013b). Underlying this strategy is the philosophical stance that sophisticated mathematical and computational analysis can overcome complexity and structural uncertainty, making modeling large-scale systems tractable. The combined modeling and wet lab has adopted a bimodal strategy in which modelers perform their own experiments. From the perspective of methodological innovation, the bimodal strategy affords a close coupling between model building and experimentation in which one feeds into and informs the other to an extent not possible when one researcher builds a model and needs to rely on an experimental collaborator to validate its predictions (MacLeod & Nersessian, 2013c). However, a potential major drawback of

the bimodal strategy is that the nature of both the model building and the experimentation is likely to be quite limited. The underlying philosophical stance of this approach is that mathematics and computation are not sufficient to overcome parameter and structural uncertainties, so modeling needs to be tied closely to the experimental data of smaller scale systems.

Each methodological option has advantages and challenges. Each methodological choice indicates an underlying philosophical stance concerning how to manage the complexity of biological systems in light of modeling constraints. Identifying these is not only of philosophical interest, but can help systems biologists further their own understanding of both the reasons for and the consequences of their choice of strategy. What we saw in our labs is that the researchers' choice of strategy often depends on preferences held by lab directors as to the strategy that best achieves certain philosophical objectives concerning what they see as the aims of systems biology and the epistemic standards they wish to apply (MacLeod & Nersessian, 2014).

Thus, there are important connections between philosophical divisions in systems biology and the structure of research. As O'Malley and Dupré (2005) have argued there are, in organization and in research strategy, divisions over the value and aims of systems biology, even though they might not be debated openly. Some systems biologists are relatively pragmatic, and want to use modeling as a tool for the extension of the agenda of molecular biology. Others have a strong theoretical agenda of their own and promote the development of a theory of biological systems and advance the role of mathematics in systems analysis. Better knowledge of methodological strategies, their affordances and limitations, and their philosophical motivations provide insight behind the diversifying structure of the field, and can help lab directors understand the challenges their researchers face, as well as the training and lab organization options available.

3. What do you consider the most neglected topics and/or contributions in late 20th century (philosophy of) biology?

I want to preface my response to this question by noting that I have only recently been engaged with the philosophy of biology. Much of my previous research has been in the philosophy of physics and I came to philosophy of biology through the bioengineering sciences. My perspective on what has been neglected, therefore, comes from my research in the bioengineering sciences. These conduct basic biological research in the context of applications. So, for instance, one of the biomedical engineering labs my research group investigated was in tissue engineering. They conducted pioneering research into endothelial cell

biology in order to understand the role of physical forces in disease processes and later added the agenda of producing a tissue-engineered vascular implant. The systems biology labs we have been investigating are also conducting pioneering biological research on such topics as the response of specific kinds of cancer cells to pharmaceutical treatments.

The first neglected topic has to do with the implications of the move of engineering into biology. One thing our labs share is that most researchers come from engineering rather than biological backgrounds, and bring metaphors and analogies such as electrical circuit analogies and concepts like noise, signal, control, robustness, redundancy, modularity, and information with them to understanding biological systems. The heavy systems engineering and control theoretical perspective forms a significant part of the glue that pieces together the intellectual framework driving systems biology in practice, particularly the belief that system-level understanding is not contingent on a detailed theory of the mechanical interaction of network components (Macleod & Nersessian, 2015). This perspective makes it possible for engineers with little biological background to produce models and simulations that provide novel and significant insights into biosystems phenomena.

As with the labs in our study, engineering models, methods, concepts, technologies and engineers themselves are playing an increasingly prominent role in biological investigation. As a result the emerging "engineering paradigm" has given rise to a complex interplay of different conceptual and methodological frameworks that have yet to be explored in depth by philosophers. Researchers in these fields come from engineering, physics, and other mathematical disciplines or are biomedical engineers trained to understand and build with biological materials. A host of engineering concepts have already entered biology such as robustness, modularity, noise and so forth. But modern systems and synthetic biology go further by transporting wholesale engineering methodologies as tools of biological analysis and representation, and even creating new biological parts and wholes. Although philosophers have addressed issues of reduction, emergence, and explanation arising from this move of engineering into biology, only a few have as yet begun to explore how these engineering perspectives reshape biological investigation and our understanding of biological systems (see, e.g., Knuuttila & Loettgers, 2013; MacLeod & Nersessian 2013a, 2013b).

Lastly, it is widely recognized that engineering has been contributing high-throughput technologies that are being integrated into the data collection process in ways that automate, filter, and control information to isolate underlying systems, processes, and properties of interest. This kind of technological innovation helps fulfill a need for the kind of data necessary to build computational models. What is needed is more

research exploring specifically how the requirements and constraints of computational modeling motivate and guide experimental technological innovation and the role that engineering plays in the construction and control of biological phenomena (Aurigemma et al., 2011).

The second topic concerns the nature of the modeling practices. The kind of modeling in which the researchers in our labs engage is best-described as "mesoscopic" or "mesoscale" or "middle-out modeling" rather than bottom-up (see, e.g., Westerhoff & Kell, 2007; Voit et al., 2012). Mesoscale modeling starts from the presumption that nonlinear and complex system dynamics are emergent properties of network structures that do not require detailed lower level theory (whether physics, biochemistry or molecular biology) to reconstruct and understand (MacLeod & Nersessian, 2015). Our examination of the practices employed in this kind of systems biology modeling underscores the need for philosophers to examine modeling and simulation in the context of theory-development.

Most philosophical accounts of modeling and simulation have been developed for physics-based sciences, where the modeling process starts with established theory, that is, a reservoir of laws, canonical theoretical models, principles of representation (such as boundary conditions) and ontological posits about the composition of phenomena that guide, constrain, and resource the construction of models in diverse disciplines. From Cartwright (1983) on a number of philosophers have argued that we need to be circumspect about the role theory plays in physics and physics-dependent disciplines, and it cannot be said that models are simply derived from theories (see, e.g., Morgan and Morrison, 1999). Nonetheless, in these physics-based fields theory is playing some role and this role is essential, even if it is not as strong as once presumed. Mesoscopic modeling, however, starts without such a reservoir of fundamental biological models, laws, and principles. Modelers need to pull together information and techniques from a variety of sources and integrate the steps so as to find a way of assembling all the elements to produce a stable robust result. This information can take the form of bits of biological theory of molecular interactions, bits of data and research from the literature, and some collaborative assistance from bioscientists. It is assessed in the context of choices about mathematical frameworks (e.g., mass action or generalized mass action and power laws), mathematical techniques of simplification (e.g., steady-state linearizations), and algorithmic parameter estimation techniques (e.g., Monte Carlo simulations) and various other assumptions to get these to work.

At the same time, these processes of incremental model-building and simulation are the means through which the researchers learn to under-

stand their systems, which in turn allows them to make better judgments about what to include and exclude and which tools and techniques help and which will not. Thus there is a complex cognitive dimension to simulation as an essential part of building models of complex systems that lack any core basis of theoretical knowledge that holds across the domain of such systems and could provide or prescribe a starting point for modeling them. Simulation is not just for experimenting on systems in order to "sound out the consequences of a model" (Lenhard, 2007, 181). In mesoscopic modeling simulation is fundamental for assembling and learning the relevant ontological features of a system. Simulation's role as a cognitive resource makes the construction of representations of complex systems without a theoretical basis possible (see also Chandrasekharan & Nersessian, 2011, 2014).

Finally, it should be pointed out that the insights into what needs to be addressed in philosophy of biology outlined above have come from a long-term examination of the actual cognitive practices of bioengineering scientists as they conduct research. From my perspective, the philosophy of science in general needs to be more substantially informed by empirical investigations into science practices – historical and contemporary. This means, among other things, that attention needs to be directed towards a critical reflection on the nature and role of empirical methods. Towards this end we can learn much from the extensive discussions of empirical methods in psychology, anthropology, sociology, and history, while at the same time deliberating on what is desired for philosophical analysis which has normative/evaluative as well as descriptive objectives.

4. What have been the most significant advances in systems biology?

Systems biology is not a homogenous enterprise. Researchers in the field and philosophers identify two broad strands, namely top-down and bottom-up systems biology (see, e.g., Bruggeman & Westerhoff, 2007; Krohs & Callebaut, 2007). Top-down relies upon high-throughput technology which takes repeated simultaneous measurement of large numbers of chemical concentrations within cells, enabling a great quantity of time-series data for many cellular elements to be collected. Computer methods can then be used to "reverse engineer" system structure by sorting through correlations in those elements. Bottom-up (and middle-out) systems biology however simulates systems with dynamical models by drawing upon knowledge of network structure and the kinetic and physicochemical properties of its components. Its data tend to come from molecular biology sources.

There is a lot of focus on advances in the "omics" part of systems biology with high-throughput technologies for data generation, high

performance computing, and statistical data mining practices. Our research drives home the fact that much progress in systems biology is being made with laptop computers in data-poor environments. Thus mesoscopic modeling represents a significant advance. Methodological innovation for managing the complexity of nonlinear systems is an on-going process in these contexts, be it in the form of strategies for adapting problems or for relating modeling and simulation to experimentation. One of the major kinds of advance is the development of novel algorithms for parameter fitting.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

For this question I will focus on what our research has revealed to be a major challenge facing systems biologists: the organization of research and training so as to facilitate collaboration.

Systems biology can be characterized as a *transdiscipline* in that its researchers draw largely on the knowledge, concepts, and methods of a discipline, but address problems that require resources of, or penetration into, one or more other disciplines. Such interdependence is likely to mutually effect changes in understanding, methods, and other practices in regions of the participating disciplines that form part of the problem space. The nature of the problems being formulated and addressed by systems biology creates *interdependence* among researchers in engineering, applied mathematics, computing, and biosciences. In this context, the prefix "trans" signifies that this enterprise seeps into, penetrates, specific prior practices of the mother fields and opens an emergent problem space with multiple possibilities for interaction and integration. I have characterized the problem space of systems biology as an *adaptive problem space* in that, as with the systems it investigates, adaptation of the researchers is a process of continually revising and reconfiguring knowledge, methods, and so forth as they learn and gain experience. Research in adaptive problem spaces is driven by complex interdisciplinary problems, and these require that the individuals themselves achieve a measure of *hybridization* in methods, concepts, models, materials – in how they think and how they act. The question is how much hybridization and how to achieve it.

As we have seen, differences in philosophical perspective on systems biology have led to the different lab organizations of our investigation, and these organizations have implications for training. The bimodal lab director held that her researchers should be trained in modeling and wet lab experimentation at the same time. Another model for bimodal research is sequential training, which she had experienced, but felt had

impeded her progress as a researcher. The modeling-only lab director held that experience in wet lab training was not required for his researchers, and if such training occurred it should be sequentially. What we found is that most graduate and postdoctoral researchers in both labs experienced difficulties in collaborating with bioscientists (the bimodal to a lesser extent), and the bioscientist collaborators we were able to interview also expressed frustrations about collaboration.

At a minimum all researchers irrespective of which lab organization need to develop what Collins & Evans (2002) have called *interactional expertise*. Such expertise required developing a conceptual understanding of the practices of the collaborating field(s) such that one can engage "linguistically" with collaborators. Interactional expertise is contrasted with contributory expertise, where one would be able to engage in the practices themselves. Our studies have shown that in addition to conceptual understanding, researchers also need to develop what I call *epistemic awareness*, that is, to understand that each discipline has presuppositions and commitments regarding what constitutes good research. Collaborating researchers need to be aware of their own epistemic values and those of the other perspective. Effective collaboration requires such things as being aware of the constraints of research in the other field(s) (e.g., what kinds of experiments are feasible) and of what is of value to the collaborator (e.g, the affordances of modeling for integration).

Preparing students for transdisciplinary practice thus requires attending to the development of the requisite expertise and awareness. Our studies suggest that graduate school is where this needs to happen. We have found that our researchers claim functional identities as either modelers or experimentalists, each of which implicates sophisticated skills and knowledge already, which they bring to bear on the lab problems. This deep disciplinary training gives them what they need to begin their graduate work in systems biology. At the same time, they commonly have blind spots to the needs, values, or constraints of the other camp. Modelers need a certain kind of data, which the experimentalists might not value and so will not take the time to perform the experiments. At the same time, the experimentalist might see the modeler as simply reproducing her findings *in silico,* which is not particularly interesting or relevant. These misalignments can lead to a certain stereotyping of one by the other, which is counterproductive

There are varying opinions on how to achieve such expertise and awareness through educational experiences. One much discussed approach is to develop curricula for aspiring systems biologists that have both a substantial mathematics and modeling component and a substantial experimental component (perhaps even at the undergraduate

level). Given the depth of knowledge required in each area to address problems as complex as those of systems biologists aim at, full hybridization is likely a daunting prospect and collaboration is likely to remain the norm. We have been experimenting with other models that we call "small interventions" that offer the potential of big payoffs in facilitating collaboration.

One option for training could be for graduate students to make a temporary excursion of one to two months to the other camp, which is sufficient to get hands-on experience without impeding progress on their own research. Two of our graduate student modelers from engineering backgrounds spent two months learning experimental procedure, conducting their own experiments, and collecting data. In doing so, they began to develop an appreciation for the challenge of gathering data, including the time and financial requirements, and also came to understand why they had been told to model trends in the data rather than specific data points. They also developed the ability to read papers with enhanced understanding of techniques, equipment, and procedures used in lab work. Another benefit was the confidence the modelers developed in talking directly with the experimenters from spending some intense time at the bench top.

In a similar vein, a collaborative laboratory-based graduate course that paired modelers with experimentalists could be designed. The task would be to work on a problem that could benefit from both approaches working in tandem. The need to develop interactional expertise and epistemic awareness would become evident as the team traversed and engaged the same task from two different methodological and epistemological perspectives

On the flip side, if experimentalists were to spend time with modelers, they could better see the possibilities of modeling for prediction, speculation, and experimentation. They could also better understand why the modeler needs certain kinds of data. Further, the experimentalist could become a better consumer of modeling papers for their own work. One possibility here would be to design an integrative modeling course where experimentalists and modelers were again paired to address a problem area. The experimentalist could be very helpful in finding resources for the model and translating them for the modeler. Likewise, the modeler would need to articulate her needs in a way that would allow the experimenter to be a resource. As one experimentalist in a modeling course we developed noted regarding a prior unsuccessful collaboration, she finally understood the questions she needed to be asking her modeler collaborator and what he should have been asking of her.

The kinds of small interventions we propose do not advocate for de-

veloping fully hybrid researchers, but rather for a kind of adaptation that creates symbiosis or mutualism, where both come to appreciate and see the value of the practices of the other. Such educational experiences can promote interactional expertise and epistemic awareness for collaboration in the systems biology problem space where values, practices, and epistemologies differ.

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Systems Biology beyond the genome

1. How and why were you initially drawn to systems biology?

As a research student at UCL in 1960 my supervisor, Otto Hutter, and I had found two types of potassium ion channels in heart cells which we called i_{K1} and i_{K2}. The first is an inward rectifier, passing inward current through the cell membrane much more readily than outward current. The second is called a delayed rectifier. It carries outward current easily but with a slow time course of onset. I wanted to see whether these properties of potassium channels could be combined with the mathematical analysis of sodium ion channels that Hodgkin and Huxley (Hodgkin & Huxley, 1952) had recently published on nerve fibres. So I formulated equations for the two types of potassium channel, and then combined these with a suitably modified version of the HH sodium equations. The answer was very convincing. Membrane potential oscillations emerged that were very similar in shape and time course to those recorded experimentally in the conducting system of the heart. This got me my first publications (Noble, 1960, 1962) and a secure academic post at Oxford University. Systems modelling and experimentation on the heart has since advanced way beyond this early work but the important insights remain correct (Noble, Garny, & Noble, 2012).

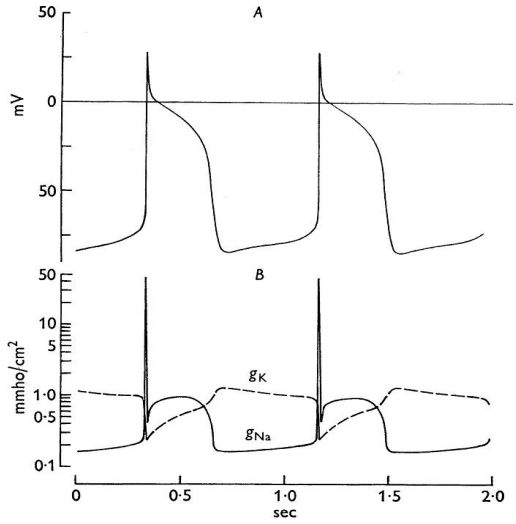

Figure 1. Electrical potential changes (A) and sodium and potassium conductance changes (B) computed from the first biophysically detailed model of cardiac cells. Two cycles of activity are shown. The conductances are plotted on a logarithmic scale to accommodate the large changes in sodium conductance. Note the persistent level of sodium conductance during the plateau of the action potential, which is about 2% of the peak conductance. Note also the rapid fall in potassium conductance at the beginning of the action potential. This is attributable to the properties of the inward rectifier i_{K1}, and it helps to maintain the long duration of the action potential, and in energy conservation by greatly reducing the ionic exchanges involved. (Noble, 1962).

Initially, as taught by my professors at UCL, I regarded this kind of mathematical analysis of a biological process as the ultimate aim of reductionist science. But the more I thought about what I had found I slowly came to a different view.

As Alan Hodgkin had already pointed out in the case of nerve, electrical excitation involving voltage-dependent ion channels can be seen as an example of a multi-scale cycle (called the Hodgkin cycle) in which ion channels contribute charge to determine the cell potential, which in turn influences the channel kinetics themselves. It is characteristic of such cycles that their behaviour requires quantitative analysis since intuition often fails to see the important properties of the whole system. This is one of the main features of the systems approach and the reason why mathematical modelling is necessary.

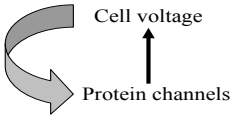

Figure 2 The Hodgkin cycle

The feedback from the cell voltage to the ion channels is also an example of what, in *The Music of Life*, I call 'downward causation' (see also Ellis, Noble, & O'Connor, 2012) since it involves an influence of higher levels (in this case the cell as a whole) on lower-level processes, in this case the ion channels. This kind of process is therefore an example of successful systems biology, although I would not have called it that in 1960. Indeed, I believe that the systems approach to biology long predates the current popularity of the term 'systems biology'. We can trace its history back at least to Claude Bernard, who introduced the principle of homeostasis (the constancy of the internal environment) in 1865 (Bernard, 1865, 1984; see also Noble, 2008a), and even to the philosopher Benedict de Spinoza two centuries earlier in 1665. In a letter to the fledgling Royal Society Spinoza had clearly seen the importance of the constraints that a whole system imposes on its component parts (see Noble, 2011a).

In addition to using the insight of the Hodgkin Cycle, the main integrative insight of my work is that i_{K1} is an energy saving mechanism. The flow of ions down their electrochemical gradients must eventually be reversed by processes that consume energy. By greatly reducing the permeability during the long cardiac action potential, only relatively small ionic currents flow during most of the time, so conserving energy. It is easy to see why channels like i_{K1} were selected during the evolutionary process. This is an integrative functional insight characteristic of the systems approach.

My work in 1960 was done on an early Ferranti Mercury Computer. Computers in those days were far from the machines we know today. They were essentially dedicated, powerful (by the standards of those days) and very expensive calculators used only by people needing to solve mathematical problems that could not be solved by hand. The programs we wrote were on punched paper tape or on magnetic tape, and were fed to the machine through a tape reader. I can't conclude this section without drawing attention to the way in which this way of programming influenced thinking about the role of the genome in biological systems. Monod and Jacob introduced their famous description of the genome as a genetic program using precisely this analogy. Jacob was quite specific about it: "The programme is a model borrowed from

electronic computers. It equates the genetic material with the magnetic tape of a computer." (Jacob, 1982). I think that this analogy is misleading. I will return to it in a later section. I don't think that the genome fulfils the same role. There are no complete algorithms in the DNA sequences.

It will be clear from this answer that I became interested in and was using the systems approach to biology long before the term 'systems biology' became widely used after the year 2000. I may therefore have a significantly different perspective on systems biology from those who have come to it more recently. In any case I see the area as one that has attracted people coming from widely different origins: physiologists, molecular biologists, bioengineers, mathematical and computational scientists, to name a few. We all have our valid views on what it means.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

Philosophy is of course essential to all forms of science, even though many scientists do not acknowledge that dependence and even in some cases vigorously deny it. As Kant clearly saw, we need a metaphysical scheme within which to interpret the world. Physics was reminded of that a century ago when experiencing the revolutions in viewpoint that were required by quantum mechanics and relativity theory. It was in that context that Poincaré pointed out that the biggest philosophical mistakes in science are made by those who claim they are not philosophers (Poincaré, 1902, 1968).

Biology, by contrast, spent most of the twentieth century in the philosophically Laplacian mold of the nineteenth century, as if those revolutions in physics had never happened. The Modern Synthesis (neo-darwinist) view of the central theory of biology, that of evolution, is a gene-centric Laplacian view. The Synthesis is Laplacian in the sense that an "all-seeing, all-knowing, intelligence" could understand everything from knowledge of the genome if the gene-centric view really was correct. Curiously, it was the great quantum mechanics theorist, Erwin Schrödinger, who paradoxically cemented that view by claiming in *What is Life* (Schrödinger, 1944) that biology contrasted with physics in that physics was the study of order from disorder (thermodynamics from stochastic molecular motion) while biology was the study of order from order since he correctly predicted that the genetic material would turn out to be an aperiodic crystal, an excellent description of the polymer with irregular sequences that is DNA. The mistake was to think that it must therefore be read deterministically. That view was cemented even further by the Central Dogma of Molecular Biology (Crick, 1970) which was subsequently misinterpreted to mean that the genome is

strictly isolated from the organism and its environment: a kind of molecular biological version of the original Weismann Barrier. In fact, the genome is read stochastically, is under control by the organism, and is not a determinate fully stable structure.

Many biological scientists today no longer accept the idea of strict genetic determinism, but the spirit of the Modern Synthesis lives on in the privileged attribution of causation to genes and their role in evolution. Genes are no more 'immortal' than the cells on which they depend for their replication. The cells themselves also replicate, by self-templating rather than by sequence copying. Epigenetics has also ensured that the strict distinction between 'replicators' and 'vehicles' is no longer valid. But it never was. Inheriting a complete cell has always been as important as inheriting DNA.

It requires a switch in philosophical viewpoint to see that the ideas of the Modern Synthesis are not compatible with what we actually know about genomes and their relationships with phenotypes and their environments. It was the Nobel laureate, Barbara McClintock, the discoverer of mobile genetic elements, who correctly described the genome as 'an organ of the cell' (McClintock, 1984). In so doing she got the causality in biological systems the right way round (Noble, 2008b). It is the system that tells the genome what to do. Over evolutionary time scales it also reorganizes genomes (Shapiro, 2011).

For a fully systems view of biology therefore we need to replace the Modern Synthesis by a more systems-oriented integrative approach. These ideas have been explored in my recent books and articles (Kohl, Crampin, Quinn, & Noble, 2010; Noble, 2006, 2011b, 2012, 2015; Noble, Jablonka, Joyner, Müller, & Omholt, 2014).

Deconstructing the language of the Modern Synthesis, and particularly its naïve popularizations is a philosophical problem (Noble, 2015). But the outcome is also fully supported by recent experimental findings in epigenetics and in many other areas of biology. It is also relevant to this section to note that it was the great logician of science, Karl Popper, who perceptively spotted some of the key problems with the Modern Synthesis in 1986 (see Niemann, 2014).

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

We have only scratched the surface of the problems of biological complexity. They won't be solved merely by collecting more data. We are awash with data. What is needed is a framework of theory within which we can see our way through the forest of data to find the clues to understanding complexity. I see philosophy as playing a major role here since what is required is a mind-shift away from the naïve reductionist

paradigm that dominated 20th century biology. We need reductionist science. But we don't need the naïve and exclusive philosophy that often accompanies it. Reduction and integration in biology go together, rather as they do also in the mathematics of calculus.

Some of the possible ways forward have been identified in a recent book by Longo and Montevil (Longo & Montevil, 2014), which points the way to some of the important principles, such as the principle of symmetry, that must form the basis of a theory of biology. Embryonic development can be viewed as a series of symmetry breaks. It also treats biological time in an innovative way, it explores the concept of extended criticality (which resembles some of the ideas of Stuart Kauffman), and it introduces the idea of anti-entropy. Organisms can be represented as existing at a continually unfolding state of criticality. If these seem to be strange ideas, recall that the revolution in physics also produced some strange entities both at the micro and macro scales. Those are now part of the very foundations of modern physics. Biology has yet to achieve that. How to do so is a neglected topic. There is a strange resistance to acknowledging the causal role of entities at higher scales and we are still struggling to identify them in mathematically rigorous terms, such as attractors. My view is that the divorce between experimentation and theory in biological science has not served us well. As in physics, the two should go together. They should form a progressive sequence of well-formed rigorous conjectures followed by the critical experiments to test them.

4. What have been the most significant advances in systems biology?

This is a very difficult question to answer since there is no fully agreed definition of what counts as systems biology. The great majority of the major achievements of 20th century physiology, for which many Nobel prizes in physiology and medicine were awarded, should in my view be regarded as achievements of the systems approach. Most successful pharmaceutical products used today owe their origin to this work. By contrast, the number of useful drugs so far produced by genomics alone is very small.[1] This point is central to meeting some of the trenchant criticisms of systems biology since such critics have usually been misled by some of the popularizations of systems biology to think that it is the product only of the twenty first century, following on from the sequencing of the complete human genome at the turn of the century. The systems approach long predates that recent resurgence. Seen as a natural extension of classical physiology, the judgment completely changes.

[1] See e.g. http://www.nytimes.com/2014/11/16/magazine/why-are-there-so-few-new-drugs-invented-today.html?ref=health&_r=0

Achievements such as the Hodgkin-Huxley model (for which Hodgkin and Huxley were awarded a Nobel Prize in 1963), the development of the Physiome Project of IUPS (http://www.iups.org/physiome-project/), and its recent exemplification in the Virtual Physiological Human (www.vph-institute.org) can then all take their place amongst the achievements of the systems approach to biology. There are many more in other areas of physiology.

Examples of success in healthcare include the heart-rate-reducing drug ivabradine (Ferrari et al., 2008), the target for which was discovered in the 1980s as a consequence of precisely the kind of interaction between physiome-type experimentation and modelling that systems biology requires (DiFrancesco, 1981; DiFrancesco & Noble, 1985). The angina treatment ranolazine can also be included since its action depends on synergy between targeting of different receptors and that synergy was revealed fully by computer modelling (Noble & Noble, 2006). I predict that multi-action therapy will become one of the big challenges and potentially big successes of the systems approach. The drug industry has tended to regard multiple actions as undesirable side effects. Most are. But the secret of treating multi-factorial diseases must lie in multi-action remedies. There are desirable as well as undesirable 'side-effects'. Systems approaches could identify the synergies that are beneficial. Screening for multiple targets is also now perfectly possible. If the pharmaceutical industry could adopt this approach at early stages in drug development, as some are now doing, it might have more successes in bringing useful drugs to market.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

The gene-centric view of biology, originating with the frankly reductionist philosophical ideas of Weismann (Weismann, 1893), Schrödinger (Schrödinger, 1944) and Crick (Crick, 1970), led to highly simplified views of the nature of living organisms. Parsimony became the criterion. But parsimony, like beauty, is in the eye of the beholder. What is parsimonious from a molecular viewpoint is simply an incomprehensible forest of data from a systems viewpoint. Parsimony then needs to be viewed from that higher-level perspective, which will necessarily include the ways in which the parts are constrained by the whole. Yet much of the modern trend in systems biology has retained the gene-centric view as its core philosophy. This needs to change.

In particular, we no longer know what we really mean by a gene. The definition has changed fundamentally since the days of Mendel and Johannsen. When Johannsen introduced the word in 1909 (Johannsen,

1909) it was defined as whatever ('ein etwas' – a 'something', 'anything') determined the particular phenotype characteristic that was inherited. By that definition, anything in the organism that contributes to inheritance of the phenotype is, or is part of, a 'gene'. The question of causality is not 'is it the cause?' It is so by definition.

The modern definition is quite different. As a particular sequence of DNA, a 'gene' may or may not be *the* cause of a particular phenotype. Extensive genetic buffering ensures that in most cases it does not. In any case, whether or not that is the case has become an empirical question to be settled by experimentation. In a recent article (Noble, 2015) I have distinguished between the two definitions, using $gene_J$ to refer to Johannsen's original definition and $gene_M$ to refer to the modern molecular biological definition. The difference is illustrated in Figure 3.

Unravelling the philosophical (conceptual) and scientific (empirical) consequences of this confusion seems to me to be the central question to be tackled in the philosophy of systems biology. It is fundamental since answering this question is the way out of the simplistic gene-centric mistakes of the dominant form of twentieth century biological

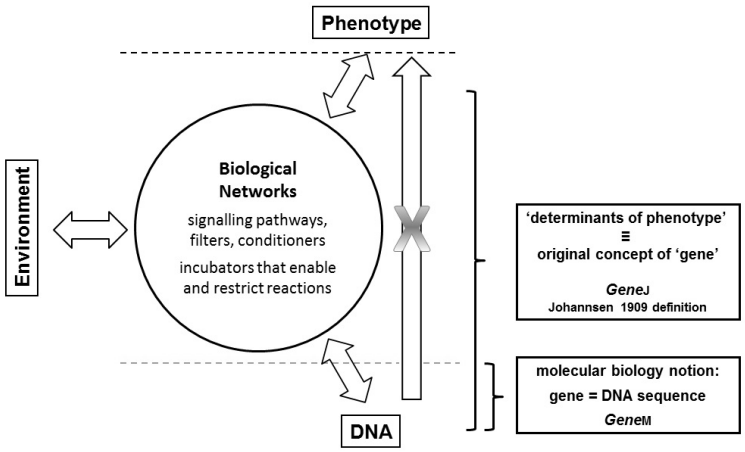

Figure 3. Relations between genes, environment and phenotype characters according to current physiological and biochemical understanding This diagram represents the interaction between DNA sequences, environment and phenotype as occurring through biological networks. Causation occurs in both directions between all three influences on the networks. This view is very different from the idea that genes 'cause' the phenotype (right hand arrow). This diagram also helps to explain the difference between the original concept of a gene as the cause of a particular phenotype (geneJ) and the modern definition as a DNA sequence (geneM). For further description and analysis see (Kohl et al., 2010) .

thought. My own contribution to answering the question has taken the form of proposing a theory of biological relativity (Noble, 2012). This uses the general principle of relativity which consists in distancing ourselves from conceptual frameworks in which we privilege particular frames or causes. In the history of physics this took the form of distancing ourselves from the idea that there is a privileged centre of the universe or a privileged frame from which to view it. Yet twentieth century biology privileged the molecular 'gene' in its theories of causation. There is no reason why nature should have respected such a viewpoint. Nor can it be proved since organisms are open not closed systems. In multi-scale networks, which are the functional networks in organisms that link genotype and phenotype, there can be no *a priori* privileged scale. It is an empirical question to determine at what scale any particular phenotype characteristic is integrated functionally. At the molecular level, most are not. At the cellular level, many are. At the organism level, many more are. Some can only be integrated and understood at a social level, involving populations and their interactions.

This is what I see as the great challenge for the philosophy of systems biology.

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21

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A view on Systems Biology beyond scale and method

1. How and why were you initially drawn to systems biology?

There are many factors that contributed to defining systems biology as a distinct field in biology. Some of them have rather recent origins, such as an enormous advancement of techniques for large scale data acquisition, which opens the door to system level experimental analysis. In addition, systems biology emerged as a consequence of concepts and insights gained from more traditional disciplines in biology and has therefore much more ancient roots. What brought me to systems biology was that genomic sequence analyses revealed that the number and type of genes encoded in the genomes of very different species are too similar to account for the difference in cell type complexity and body plan organization of the respective species. Until not so long ago, major efforts in molecular and developmental biology focused on the characterization of the function of particular individual genes. The analysis often revealed particular genes which upon mutation affect the outcome of a large scale developmental process, such as the development of eyes or limbs in a given species. While indeed such approaches are able to demonstrate the necessity of given genes in a particular process, it reveals little about the particular role that this gene actually plays within the process. Realizing that a large number of genes are actually shared among very different organisms brought a completely different perspective to such endeavors. Because if we have toolkits similar to flies and worms in our genomes, then what makes us look different is not the particular functions of individual gene products, but rather depends on when and where these molecules are expressed and how they interact with each other in order to determine biological function. Therefore we would like to understand not just which genes and molecules are involved in the regulation of a particular process, we also need to understand how these molecules interact to function

in biological processes, and this is one of the major aims of systems biology (Boogerd et al., 2007). This new emphasis required not only the development of techniques to measure interactions among many different molecules, but most importantly, the development of new concepts on how these interactions can be related to function. While the advancement of appropriate and affordable technology has indeed occurred over the last decade, understanding biological functions in terms of interactions appears much more challenging. As a consequence, most available network models represent strictly physical interaction networks, based on the binding interaction among proteins or between proteins and DNA, while a much smaller but growing number of systems biology approaches actually address the functional outcome of given physical interactions.

Every scientific field employs particular tools and concepts to reveal particular aspects of the natural world. It is at the heart of systems biology to consider biological function as the outcome of interactions among multiple molecules. But in many ways, the function of individual molecules and even their interactions with other molecules are, at least at a small scale, also at the center of other fields in biology. So what is so different about systems biology? Is it just a question of scale? Does systems biology by definition involve technologies to assess genome-wide transcriptome data and proteome data sets, if possible in combination with mathematical modeling? I would argue that this field, even though it includes all of the above, goes further than that. Systems biology is not just defined by technology and methods, but by the realization that certain biological processes operate at a level which cannot be understood by accumulating information at the single gene level. It is the biological process itself, not the analysis thereof, which operates at the system level. We have even at this early stage of the field evidence that this is indeed the case, and in the following I will discuss some of the arguments and evidence from my own field to illustrate this further.

I was very fortunate to have entered the field of systems biology by studying gene regulatory networks, as this area provides some of the best experimentally established examples demonstrating the relation between molecular interaction and biological function in multicellular animals. Most of the examples I am using here derive from the insights acquired from gene regulatory network analysis, on the one hand because I know more about these than about other types of biological networks, and on the other hand, because they do provide a number of beautiful examples to illustrate the subtle and profound shift in perspective that may derive from systems biology approaches (Peter and Davidson, in press). To give just a brief overview, the system level functional outcome of gene regulatory networks is the control of when and where

every gene in the genome is expressed. This is of particular importance during development, when gene regulatory networks, by orchestrated control of gene activity, determine the specification of cell fates and the spatial organization of the developing organism. The molecular components in gene regulatory networks are genes encoding transcription factors, which are molecules that control the expression of all genes in the animal genome. The functional interactions in gene regulatory networks are constituted by the direct physical binding of transcription factors to particular DNA sequences within so called *cis*-regulatory modules, associated with given genes, and the contribution of these interactions to the regulation of gene expression. Where any given gene is expressed during development depends on its *cis*-regulatory sequences and on where and when in the developing organism the right combination of transcription factors is present to bind these sequences and regulate gene expression. Since genes encoding transcription factors are regulated in the same manner, the expression of particular combinations of transcription factors is the outcome of how genes encoding transcription factors regulate each other. Gene regulatory networks therefore not only control which sets of genes are expressed together in particular cells, they also control where in the organism these genes are expressed and therefore where organs, body parts and cell types are located. The goal of gene regulatory network analyses is to identify the genomically encoded regulatory interactions among genes encoding transcription factors which account for the establishment of defined cellular functions in defined locations within the animal. In their aim to understand developmental function as an outcome of functional molecular interactions, as well as its scope to encompass the entire genome and entire developing organisms, gene regulatory network analyses provide paradigmatic examples of systems biology approaches.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

Scientific progress requires much more than the accumulation of data. Our ways of thinking about and exploring the natural world, the philosophy of science, have an important role in shaping scientific progress, and systems biology is no exception. There is in all natural sciences a delicate balance between theory and experimental data, and neither by itself is able to satisfy the criteria of scientific progress; both are necessary. To be able to contribute to knowledge, a framework is needed which incorporates what is known and experimentally demonstrated, and which can be used to predict features of the unknown. The advantage of such an approach is that the framework first of all provides a tool to assign meaning to experimental data, by incorporating them into

larger concepts, and second, that the predictions derived from such a framework may be directly testable by experiments to reveal not only the accuracy of our comprehension, but also what was not known so far. However, at present, the rate at which novel technologies are developed and applied appears overwhelming, and the amount of data produced in a very short time is enormous. All too often this fast pace seems to produce an outcome opposite of what the development of new technologies was intended for. Instead of knowing more, we seem to know less. And even worse, it appears almost as if the methods of scientific enquiry that served us for so long are no longer really valid or particularly useful. Instead, knowledge is supposed to emerge directly from the mountains of biological data, unaffected by the bias any idea or preconception might introduce. But the caveats to this view are obvious, since it is very unlikely that we should ever obtain answers if we don't ask any questions. The chance that the ultimate truth will eventually crystallize itself within a sufficiently large amount of biological data is infinitely worse than trying to find the famous needle in the haystack. For as long as we know it is a needle we are looking for, there is indeed a chance to find it. But trying to find an object without any estimate of its size, dimension, material or other general properties seems to be an unnecessarily inefficient and costly enterprise.

Thus, in times when we are flooded with information, in biology and elsewhere, it might be more important than ever to reflect upon the ways by which we acquire and organize information in order to expand current knowledge. Long decades of scientific research have produced so many thoughts and concepts and open questions, many of which can only now be adequately addressed, with the techniques to acquire large scale experimental data at many different levels of biological organization, from nucleic acid to morphology. How current insights can be used to generate a framework concept, and how such framework plus current technology can be used to access what is not yet known is not just of philosophical concern, but of crucial importance for the ability of systems biology approaches to contribute to the solution of some of the long-standing questions in biology, and to formulate new ideas and concepts.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

Now in retrospect it becomes clear that some of the most seriously underestimated aspects of animal biology are those embedded in genomic sequences which are not coding for proteins or RNAs. While considerable attention was given to the identification of individual gene products, new functions of proteins, or RNA molecules, non-coding sequences

were considered much less interesting. But what is encoded in the genome beyond the single gene unit? Nowadays it becomes increasingly clear, that non-coding sequences contain information that is key to the control of animal development and thus animal evolution. But not only that, it appears that the particular design of regulatory sequences in multicellular animals is in itself evidence that biological processes have to be considered at the systems level. In between and flanking the protein coding sequences of a given gene in the genome are usually several *cis*-regulatory modules, relatively short DNA sequences which control gene transcription. The function of *cis*-regulatory sequences is determined by the binding of several transcription factors, the identity of which is determined by small binding sites which occur repeatedly within regulatory sequences. Whether a cis-regulatory module activates or represses gene transcription depends on the combination of transcription factors bound to the module, and the computation performed by the module. When and where *cis*-regulatory modules are active within an organism therefore depends on the availability of the respective set of transcription factors which are required for module function. The output of *cis*-regulatory modules behaves non-linearly in respect to its inputs, since the modules will not be active in the presence of only some of its required transcription factors, or in the presence of the entire set of activators in addition to its transcriptional repressors.

The fact that the regulation of gene expression in multicellular animals depends on multiple transcription factors has crucial consequences. Were transcriptional regulation in multicellular animals linearly dependent on only one transcription factor, their cognate genes would be expressed everywhere the transcription factor is present. With such a system it would be very difficult to control the differential expression of thousands of genes in specific cell types within an animal. However, within single cell organisms this system can actually work well, as demonstrated by the prokaryotic way of regulating gene transcription by only one transcription factor. The combinatoriality of transcriptional control of gene expression has several imports. Because transcription factors in eukaryotes operate combinatorially, individual transcription factors may function in very different developmental contexts. The same transcription factor may contribute to very early developmental processes, such as the specification of progenitor domains, as well as to the differentiation of particular cell types, or it may be involved in the development of very different body parts, such as Pax6 in the development of eyes and pancreas. In each case such transcription factors may execute functions that are specific to that particular context, by regulating different sets of genes. The specificity in each context is provided by the set of transcription factors which are otherwise expressed in each

process. The necessity of transcription factors to operate together with other transcription factors to control gene expression therefore converts gene regulation to a system-level function from the single factor gene regulation that is operative in prokaryotic cells.

Why is this important? I think the fact that *cis*-regulatory sequences operate on combinations of transcription factors is a beautiful demonstration of the importance of considering biological systems beyond the single gene level. Experimental approaches evaluating the function of individual transcription factors and individual signaling molecules, will reveal lists of target genes which may include genes expressed in different locations and at different times, and regulated very differently apart from that one common regulatory input. But in order to determine the context-specific function of transcription factors and signaling molecules, identifying the determinants of this specificity will be very important. In respect to the *cis*-regulatory module, the combination of transcription factors which operate together to regulate its activity can be considered as an informational unit. The same regulatory state may control the expression of many different *cis*-regulatory modules, but interestingly, most *cis*-regulatory modules are specific to a particular regulatory state. Thus the expression of genes in different parts of an animal is usually controlled by separate *cis*-regulatory modules listening to different combinations of transcription factors.

The fact that gene transcription is not regulated on a single-input level has another consequence which offers an explanation why so many different cell types, body parts and animals can be formed using a relatively limited set of transcription factors and an even smaller set of signaling pathways. Combinatoriality thus provides the means for regulatory factors to execute context-specific functions in very different developmental processes. Interestingly, transcription factors are among the most strongly conserved molecules and several experiments have shown that orthologous transcription factors of species as distantly related as *Drosophila* and mice can be swapped and are still fully functional. Were it not for the combinatoriality in gene regulation, how could mice and *Drosophila* have produced such disparate body plans? In the 20th century view which was focused primarily on the functionality of individual molecules such as transcription factors, the behavior of *cis*-regulatory modules and the fundamental import of their functionality on the control of animal development and evolution was not appropriately considered even though experimental *cis*-regulatory data were already available (Small et al., 1992; Yuh and Davidson, 1996). Recognizing the importance of *cis*-regulatory module function requires consideration at the system level. Thus *cis*-regulatory modules provide a very clear demonstration that biological processes may operate at the

system level, using molecules as sets rather than individual units to determine biological function.

4. What have been the most significant advances in systems biology?

I would like to answer this question in terms of evidence for systems biology revealing insights different from other disciplines in biology. Systems biology attempts to understand the functional outcome produced by interactions among multiple molecules. But is this really different from what molecular biology and other fields have been concerned with for a long time? Is it not evident that molecules don't operate in isolation, but that any enzyme modifying another protein will do so by interaction with it? What systems biology addresses is not just the fact that molecules do interact as they perform their functions. Systems biology reveals that the structure of interactions themselves may become the primary determinant of biological function. This might be best illustrated using the insights gained from the analysis of the relationship between network circuit structure and circuit function.

When the architecture of gene regulatory networks underlying seemingly unrelated developmental processes are compared, it becomes apparent that similar network circuitry occurs repeatedly and is associated with very similar functional outcome (Peter and Davidson, in press). For example, the subdivision of an embryonic domain of cells which all express the same regulatory state into two or more domains expressing different sets of regulatory factors and hence destined to different fates, requires some sort of symmetry breaking. Very often, an initial difference among cells is introduced by a signaling molecule, which is only received by some cells of a domain but not by others. The regulatory interactions downstream of that signal furthermore induce the expression of novel genes in the cells responding to the signal. In most studied cases, these target genes include one or several genes producing transcriptional repressors of regulatory genes associated with the fate that will be assumed by the cells of that domain which did not receive the initial signal input. The result of this circuitry is that the initially uniform domain of cells becomes subdivided into cells of alternative fates, a process which occurs repeatedly during development, irrespective of species or body part. In another kind of circuitry, which often is activated downstream of signaling interactions, there are a few regulatory genes expressed together in the same cells, and their transcription factor products activate each other in positive feedback circuitry. Both types of circuit can be found repeatedly, in the gene regulatory networks of various animal species, with the same constellation of regulatory interactions among very different regulatory genes and signaling

molecules giving rise to the same developmental function. What these examples demonstrate is that the control of a particular developmental function depends on network circuitry, on the architecture of the regulatory interactions, but does not rely primarily on the specific properties of given transcription factors, since those are interchangeable. It shows that indeed there is information that is specifically contained in the regulatory interactions, since similar network circuitries that operate a given developmental function have evolved independently in entirely different developmental contexts. What makes the subcircuit specific to a particular developmental context is the identity of regulatory genes involved. But the more general function that these molecules execute can only be accessed on the level of regulatory interactions. Identifying the interactions between these molecules, and their particular developmental function makes clear that the circuitries governing cell fate specification, patterning or cell type differentiation in the development of disparate body parts are remarkably general throughout the metazoan phylogeny.

Thus, to return to the question of this section, I would consider the potential to reveal an entirely different level of biological organization and function as one of the most significant and promising advances that system level approaches offer. Biological systems may indeed, at least in some contexts such as development, operate by means of sets of molecules and the constellations of their interactions, properties which systems biology approaches attempt to reveal.

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

I think there are several aspects to systems biology which will require special attention in order to drive this field forward. Most important, as mentioned above, will be to find approaches to reveal how molecular interactions perform functions, within gene regulatory networks or in other areas of systems biology. As mentioned above, there are several approaches to detect physical interactions between molecules, nucleic acids or proteins, at a large scale. But the resulting networks of physical interactions are usually devoid of functional annotation. Thus at this level such networks do not contribute to our understanding of how a particular biological process operates. But this should be one of the emphases of systems biology approaches, to find functional networks for specific biological processes, even if these networks are much smaller in scale than the physical interaction networks among hundreds or even thousands of components. Sometimes I am asked how many networks I would consider necessary to know in order to learn anything new. In

some ways this question is comparable to asking how many protein coding genes we need to identify in order to understand that genes may code for proteins. We know now that molecules can indeed operate at the system level, as sets of molecules which have functions beyond those of the individual elements, and we know that molecules operate as interacting systems where the interactions can be the major determinant of function. Developmental control by gene regulatory networks shows that this important process operates at the system level, using information contained in sets of molecules, and that the architecture of regulatory interactions serves as determinants for functions. We also have learned many additional principles by which gene regulatory networks operate, a review of which can be found elsewhere. But when it comes to understand how most large scale biological processes are actually controlled, there is still a lot of work to be done, and the principles which we have so far identified will likely be just a small sample of the actual richness of biological systems.

A commonly used approach to understand the development of a body part or any other process is that of studying what it takes to prevent its occurrence. Since there are so many ways with which to interfere with a process, many of which are not even related to the process as such, it will be impossible to reconstruct based on that evidence how the process actually works. Will it be possible for systems biology to overcome this limitation? Can we use systems biology in a constructive way, by assembling bit by bit the molecules and interactions required to operate a large scale function? Biological systems indeed display the properties which could make such endeavors possible. That is, the observation that at many different levels, biological systems deploy individual functional units which are used as modules in more complicated processes could indeed prove extremely useful for analytical purposes. It means that insights gained from the characterization of individual functional modules, such as a *cis*-regulatory module or a network subcircuit, can be characterized individually, at a conceivable scale, and used for assembly of large scale models. In some ways, a recently constructed Boolean model of a large scale gene regulatory network provides a proof of principle to this end (Peter et al., 2012). In this model, the function of individual *cis*-regulatory modules, which were derived from experimental analysis at the *cis*-and trans-level, were used as independent computational units which reproduced the expression of a series of regulatory states in four different embryonic domains. Modularity makes it possible to treat each function independently, assemble them into larger structures and construct system level functions.

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From a Fascination with Arrow Diagrams to Witnessing a Tipping Point in Biology

1. How and why were you initially drawn to systems biology?

High school and college learning in the 1960s and i970s occurred in silos, at least in Germany where I grew up. Languages, geography, religion and history were neatly separated, and students were left on their own trying to figure out that the four actually had enormous influence on each other throughout human history. The natural sciences and math faced an even stronger separation. Math was taught as a general all-purpose tool that could one day be useful if one had to compute the size of an odd-shaped room or the total interest paid on a mortgage. It also scared "normal" people with teasers like two trains traveling towards each other with constant, but different speeds … At the university level, "applied math" was a bad word, because respectable mathematicians worked on problems of Riemann manifolds or Galois Theory. If a math whiz really wanted to stray from purity, physics was an inferior alternative. By the same token, physics was the essentially obligatory minor for a math student, except for a very few esoteric logicians, for whom it was philosophy. By contrast, mathophobes with a scientific bent went into biology. They somehow survived a cookbook class on biostatistical methods, and a few brave souls took "Math for Biologists," which introduced them to exponential and logarithmic functions and the basics of vectors and matrices.

Against this background I became fascinated by several books that came out within a few years of each other and had a crucial concept in common (Meadows & Meadows, 1973; Vester, 1972, 1974, 1975). They used a lot of arrow diagrams and proposed methods from the young field of computing to address pressing world-wide trends in so-

ciety, such as the future exhaustion of minerals and energy, and even the survival of humankind itself. Others proposed that computers could decipher how the brain works. I tried to follow the influence arrows throughout the network diagrams, only to realize that I could not wrap my mind around them, as they had branch points, cycles, and multiple competing influences. Yet, the authors claimed that computers could solve these problems with "simulations," a term that in itself was new to me. In fact, none of my friends had ever actually seen a computer, whether in the form of a pocket calculator or a mainframe.

While few of the predictions in these books materialized in retrospect, the proposition that a complex system could be grasped with math and computers stuck with me. So, in college I tried to combine biology with math as much as possible. I was fascinated with the concepts of cybernetics and developed for my Master's and doctoral projects simple mathematical and computational models, respectively for predator-prey systems in heterogeneous environments and for the formation of scar patterns that formed and remained on the surfaces of budding yeast cells when they produced daughter cells. My models were very primitive by today's standards, but reflected the observations quite well. I even came up with a simple theory for the evolving budding patterns. Although I was allowed to perform these studies, the combination of biology and math was not only not supported, but outright considered ridiculous by most biologists, and even more so by mathematicians. It was argued quite dogmatically that biology was too complicated to use math. Well, as we know now, the dogma has been resoundingly refuted: Biology is too complicated *not* to use math.

Through doggedness and a good dose of happenstance I became a postdoc with Michael Savageau, a deep-thinker and true pioneer of systems biology. Usually hidden from sight in his tiny office or in some library vault, he was designing systematic mathematics for representing and analyzing complex biological phenomena. Although well respected by his colleagues, and consistently funded, I once witnessed how the program director of some NSF math division, upon rejecting our grant proposal, told Mike over the phone that math had been around for a couple of thousand years and that it was not very likely that someone at a medical school would come up with something new. Besides, we asked for a laser printer? Did we want it gold-plated? Small minds, even at high levels, had to ensure that the ocean liner of science did not make abrupt turns.

Undeterred, Mike pressed on, and I followed, working with him on the further development of his Biochemical Systems Theory (BST; (Savageau, 1969)). Mike bemoaned the lack of vision among so many of his contemporaries, but at the same time enjoyed the fact that the

field was not (yet) crowded and we were able to pick low-hanging fruit of our choosing. He was proud of his elegant, homogeneous notation of BST and, while constantly looking for "real" mathematicians willing to explore the intriguing structure and features of BST, he warned that the "first thing these people do is change the notation," a comment that I thought was peculiar but later found to be true. With time I began to appreciate the fading poster on Mike's door, which was rephrasing a quote of the 19th century French writer Victor Hugo that "nothing is as powerful as an idea whose time has come." Indeed, Mike's unwavering vision for the unbounded potential of systems approaches to biology kept us going, and we have been working hard on instilling the same confidence in our students and colleagues, especially in their times of doubt. To sustain this vision was actually not always easy, as we, quite frankly, did not have much to offer. Even the mainframe computers in the early 1980s allowed us to solve systems of merely a few ODEs, and the right data for our purposes simply did not exist or were very hard to come by. As a corollary, the questions we were able to address with our models were mainly sandbox problems, which certainly did not convince successful biologists, let alone physicians, that modeling could ever be a useful tool. Experimentalists taking chances in talking with us were few and far between.

Not much is as sweet as vindication, especially if it comes with the vengeance of a well-defined tipping point. The pivotal time period was the impending completion of the human genome project at the turn of the millennium, along with the emerging high-throughput technologies in molecular biology, such as microarrays. All of the sudden scared by the enormous numbers of data points and the prospect of incomparably more massive datasets, biology started scrambling for computer nerds, at first as data analyzers that "one" hired for the lab, but ultimately as partners in the endeavor of biology, which before our eyes was becoming more and more complicated every year. For me, the most amazing aspect of this historical shift was that it happened within just a few years. Life after the tipping point became much more pleasant for modelers and systems analysts, because many biologists and even physicians began to recognize the need of models.

2. How do you view the relation between philosophy and systems biology, and how can these fields inform each other?

A quick internet search reveals that most definitions of systems biology directly or indirectly include the "emergence" of novel phenomena. Yet, what exactly emergence means seems vague at best. Aristotle already pondered what has become a modern cliché: that a system is more than its parts; that something new is emerging. We understand

that components act synergistically; that a system may start to oscillate, even though none of its components oscillates in isolation; that many relatively simple neurons with well-characterized functionality inexplicably bring forth cognition and thought. It may be up to philosophers to close these types of fundamental gaps. The famous biochemist J.B.S. Haldane declared in 1932 that "the doctrine of emergence … is radically opposed to the spirit of science" (Haldane, 1932). Along the same lines, the modern-day philosopher Mark Bedau asserted that "getting something for nothing" is "illegitimate magic." He proposed a partial solution to the dilemma by defining "weak emergence" as a type of emergence that can only be elucidated through computer simulation (Bedau, 1997). Instructive examples are the *Game of Life* (Conway, 1970) and the emergence of oscillations when a parameter is slightly altered. In complex systems we may not be able to predict or explain these oscillations, but simpler cases allow us to compute and characterize such bifurcations in a rigorous manner. Thus, if math allows a true explanation in simple cases, is it possibly our language of math, let alone our vernacular, that is too restrictive to explain emergence in more complex systems? Is it our thinking that is too limited to explain the emergence of cognition from an assembly of neurons or is its emergence something that simply cannot be explained in terms of cellular function?

A second issue potentially worth discussing among biologists and philosophers is the development of theories. We know that physics, along with its applications in engineering, has been tremendously successful, due to its rigorous theoretical foundation. There is absolutely no doubt that similarly strong theories in biology would have incredible and unforeseeable potential for the treatment of diseases, the microbial production of valuable compounds, and a sustainable stewardship of the environment, to name just three application areas. The question is how we should approach the creation of such theories. Do they have to be extensions of physics? Is it possible in principle to deduce new theories from very large datasets? Can we possibly infer them from mega-simulations? Do we need experiments plus a mental spark of ingenuity to form hypotheses that ultimately become theorems?

Finally, philosophers might join a discussion about the widely accepted 14th century dogma of Ockham's razor, which essentially states that the simpler of two explanations is to be preferred. At first the concept makes much sense, as we certainly do not want to clutter our thinking or theories with details that are not needed. Yet, the more we study biological systems, the more often we find enormous redundancy and could quite easily imagine simpler systems that would perform the same task. Is the observed complexity a violation of Ockham's razor or are the

two completely consistent and only appear to clash because we do not understand all the tasks and constraints that biological systems have to satisfy in order to survive in a rapidly changing, uncertain world?

On the educational side, philosophers, cognitive scientists and psychologists could contribute to the issue of educating newcomers in the complex, transdisciplinary field of systems biology. With such input, we developed an introductory problem-solving systems biology class for graduate students that was radically different from typical modeling courses (Voit, 2013; Voit, Newstetter, & Kemp, 2012). This problem-solving course asked the students to read background information (Voit, 2012) and focused most of the class time on a single, complex disease, such as cystic fibrosis or sickle cell anemia. The course was designed to scaffold the cognitive processes required to gauge systems, diagrams and models, with the overarching goal to instill in the students a "feel for systems," which they could transport into their own research areas without necessarily becoming modelers. Because systems biology is a transdisciplinary endeavor with different languages and scientific cultures, courses of this type require insights into different learning paradigms and cognitive processes.

3. What do you consider the most neglected topics and/or contributions in late 20th Century philosophy of biology?

By any metric, biology of the 20th century has been phenomenally successful, and the insights into the components of life we gained are unprecedented and mind boggling. A noteworthy drawback of this success was that there did not seem to be a reason to look beyond the boundaries of the field. Why should a successful biologist bother with anything else, if so much headway was possible within the dominant paradigm? This paradigm was the dogma of reductionism, which holds that dissecting an organism down to its fundamental building blocks reveals how the organism works. This dogma was so dominant that it smothered ideas of systems thinking and information integration. The fifth edition of the famous text *Molecular Biology of the Cell* has grown to about 1,400 pages, plus a few hundred pages on a CD (Alberts, Johnson, Raff, Roberts, & Walter, 2007). Yet, it is still impossible to predict with reliability how a cell will respond when put into untested conditions. In other words, the enormous success of reductionism inhibited its natural complement of reconstructionism (Savageau, 1991) or, expressed differently, systems biology. Along with this inhibition, biology by and large failed to see the need to search for design and operating principles that would explain classes of observations. A few pioneers did work at this front, but this type of inquiry did not become popular until the 21st century (Alves & Sorribas, 2011; Savageau, 1985).

One aspect of this limited view has been the assertion that "Why" is not a legitimate scientific question. Richard Dawkins, the famous evolutionist, actually called it a "silly" question, arguing that one "why" begets another until scientists run out of answers and must resort to the will of some supernatural deity. Also, questions beginning with "why" have the bad odor of teleology, which comes close to a God-given purpose and ultimate goal. Besides, "why" is reminiscent of creationism and intelligent design. This assessment is puzzling, because it is the very nature of science to be interested in solving puzzles and identifying causes and explanations. In particular, the search for design and operating principles can hardly succeed without asking "why?" in some form or another. After all, the key question in this search is "why is this biological system organized in this particular fashion and not in an alternative manner?"

Addressing future trends in teaching and education, a recent NRC report discussed *A New Biology for the 21st Century* with "the potential to meet critical societal goals" (NRC, 2009). Along with its enthusiasm, NRC warned that the traditional approaches to biology will not suffice and that biology and biological education must be integrated with physics, math, computation and engineering in order to achieve a systems level understanding of biomedical phenomena. This need starkly contrasts the fact that the average biology textbook of 2013 contained just two equations (John Jungck, *pers. comm.*). NRC called the systemic rethinking, combined with the need for new teaching paradigms, "a staggeringly difficult challenge." Numerous other reports came to the same conclusion stating that today's systems biology is woefully underpowered and that innovative system-based strategies can only emerge in due time if a new generation of students, bilingual in the biomedical and computational sciences, is drawn into systems biology through effective education. The development of modalities of this education should be guided by insights from the philosophy of cognition and the learning sciences.

4. What have been the most significant advances in systems biology?

Unfortunately, this section is conspicuously short. Life for systems biologists would be easier if we could point to great successes. If a systems biological study had resulted in a cure for Alzheimer's disease, nobody would need much more convincing that systems biology is important. Alas, we cannot really point to such a success, yet. Yes, we have models of whole cells, at least within some constraints, and models once in a while explain a phenomenon that was puzzling before (Joyce & Palsson, 2007; Karr et al., 2012; Konstorum, Sprowl, Waterman, Lander, & Lowengrub, 2013; Voit, Neves, & Santos, 2006). We

have also succeeded in manipulating microorganisms into exhibiting predicted responses, such as oscillations (Atkinson, Savageau, Myers, & Ninfa, 2003; Elowitz & Leibler, 2000), producing desired compounds in high concentrations (de Graaf, Eggeling, & Sahm, 2001), or making bacteria respond to light signals (Levskaya et al., 2005).

The dearth of monumental successes should not be surprising. Systems biology is often portrayed as an invention of the 1990s and 2000s, which is not quite true. Visionaries like Sir Robert May, Mihajlo Mesarović, Michael Savageau, and Reinhart Heinrich clearly worked on topics of systems biology as early as the 1960s, and pioneers like Ludwig von Bertalanffy in the 1930s and 1940s and Alfred Lotka in the 1920s laid the foundation for much of our thinking today. Even earlier, the physiologists of the 18th and 19th centuries studied the cardiovascular, nervous and gastrointestinal systems, although they did not use much math. Thus, the view that systems biology is a modern outgrowth of molecular biology is rather narrow at best.

Notwithstanding its roots, it was at the turn of the millennium that systems biology moved into the limelight. As part of the buzz, many promises were made of what systems biology would do for us one day, including a deep understanding of health and disease, and the realization of personalized medicine. Systems biology has not lived up to these hallmark promises, and while one must keep in mind that the field is young and has been vastly underpowered, at least in comparison to fields like genetics or molecular biology, the risk of a backlash in public perception is real.

Nevertheless, systems biology has achieved a very important, although somewhat indirect goal. Namely, by asking questions of system connectivity and dynamics, and by focusing on the roles of individual components for the global functioning of cellular systems, systems biology has changed the focus of biological research. The –omics revolution of experimental systems biology has forced the permission to explore what's out there, and thereby reigned in the formerly exclusive right of hypothesis based research. Only twenty years ago, such an exploration was derided as a "fishing expedition" that was not well grounded, had no specific focus, and was therefore not to be published, let alone funded. Now, such studies are often the first stab at investigating and analyzing a complex biomedical question. The successes of these and other high-throughput methodologies have wiped away any doubt that solid data interpretation, through machine learning and pattern recognition, is mandatory. The large datasets and complex patterns within them, in turn, have rendered it evident that sophisticated mathematical and computational systems modeling is needed to combine datasets and to extract information that is not perceivable by the

unaided human mind.

5. What do you consider the most important problems in the philosophy of systems biology and what are the prospects for progress in this respect?

On the research front, the field will have to create a canon of good practices and standard operating procedures. At present, one might say that systems biology still resembles the Wild West, which is exciting and invigorating, but will not be optimally sustainable in the future. The community of practitioners will have to decide what types of questions are important and how they are to be addressed, at least as a default. For instance, should it be allowable to publish a model without a comprehensive sensitivity analysis? Is it desirable, or even necessary, to force practitioners into using a certain modeling language like SBML (SBML, 2001) or does such a mandate choke progress and academic freedom? Should models only be published if they have been rigorously validated, ideally by *de novo* experiments, or would such a requirement slow progress or impede the technical evolution of the field? If there is agreement that the development of theories is desirable, what exactly is the best path? Should theories be based on general design and operating principles? Can the inspiration for theories possibly come from simulations? Could it perceivably come directly from data? Is a solid mathematical understanding of most or all details of a class of problems mandatory before we can even think about theories? In our search for generality, with the ultimate goal of a theory, should we focus on small, highly abstracted systems that we might be able to analyze comprehensively, or should we address large systems and be inspired by biological complexity? Will new theories have the flavor of theories in physics or will they necessarily be probabilistic or otherwise fuzzy, due to the often large uncertainty and variability of biological phenomena?

On an immediate, practical level, the practitioners of systems biology need to study very seriously how to identify the best mathematical representations for biological processes. Strict physics based formulations tend to be too convoluted and difficult, and it appears that the only alternatives are efficacious approximations (Voit, 2008). But how do we select these and how do we ascertain that they are sufficiently appropriate to permit realistic extrapolations toward untested scenarios (Torres & Voit, 2002)? Is it possible to infer adequate representations directly from experimental data? Could data tell us where the approximations might break down or need to be applied in a piecewise fashion?

The educational efforts must target two population groups. One, of course, is the next generation of students and junior practitioners; it will be discussed later. The other important group is the public with

its representatives in positions that determine research directions and funding. As mentioned before, possibly overzealous systems biologists have been promising great advances, which traditional biologists and the public might have interpreted as events of the immediate future. Not delivering on these promises will create the serious risk of push-back that might severely slow down the momentum of systems biology. Thus, the education of colleagues and the public must have the goal of sustaining the current momentum and acceptance of systems thinking. One manner of accomplishing this goal might be the highlighting of smaller successes that hopefully pave the way toward the solution of some of society's grand challenge problems.

Because systems biology is so new, but at the same time seen as very exciting, the demand for new courses dwarfs the number of faculty who feel comfortable teaching a so-far ill-defined topic to heterogeneous groups of students from different backgrounds. This discrepancy immediately leads to the question of how we should best teach the teachers. This question is all but trivial, because it is clear that the education of the next generation of systems biologists is a complex undertaking. Here, cognitive scientists and philosophers could be very helpful by characterizing and explaining the thought processes and different learning modalities that are required to master a complex field like systems biology. It is clear that the traditional paradigm of reductionism must be complemented with true facility in transdisciplinarity, integration, and systems thinking. Gaining such facility will require multi-dialectical individuals who easily translate between modern, often detail-oriented biology and sophisticated mathematical and computational sciences. It must also be explored how newcomers to the field of systems biology best acquire and master what they need to know to become productive. Furthermore, given that information will be available more easily and comprehensively, how should one best teach students to evaluate its quality? It is not even certain what exactly students have to learn to be considered systems biologists. So far there is no "body of common knowledge" or "canon of best practices." If one asked faculty from the various parent disciplines of systems biology to define "their" component of the minimum body of necessary knowledge, no student could possibly satisfy the combined wish list (Voit & Kemp, 2011). Instead, the student of systems biology must become a transdisciplinary thinker and researcher, who has sufficient knowledge in one discipline but understands the basic tenets of one or more other disciplines. While being rooted somewhere in the complex landscape of their discipline, it is imperative that all students of systems biology be trained to develop cognitive flexibility. By the time of graduation, they should have acquired a solid foundation of core competencies throughout the field,

which includes a common language, germane terminologies, fundamental concepts, and the most pertinent techniques of systems biology. In addition, every student will have to develop world-class expertise in one specific (often narrow) area that draws from the parent disciplines and integrates them in a novel fashion. Achieving these goals will require new cognitive and educational strategies but will ultimately be very rewarding.

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23

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From Microscopes to Macroscopes: Advancing biomedical Research Through Systems Approaches

1. How and why were you initially drawn to systems biology?

My first degree was in control engineering, that is, mathematical modeling and simulation of dynamical systems. When I finished my degree in 1994, I noticed that books on cellular biology described networks of interacting genes, proteins and metabolites with a focus on identifying the components that interact, but with little attention to the fact that these networks realize spatio-temporal processes. Not knowing about the experimental challenges involved, I thought that I had found a research gap: The fact is, in order to understand the functioning of cells, including cell differentiation, proliferation and apoptosis, we need to describe them as nonlinear dynamical systems (Wolkenhauer, 2014a). At the time, bioinformatics played a role in identifying and characterizing the molecular components but there was little work on modeling and simulation of intra and intercellular processes. There existed also a large and impressive body of work on modeling metabolic networks, which is why I focused initially on gene regulatory networks and signal transduction pathways. With the emergence of microarray technologies, there was the expectation and promise that one could quantify temporal changes in molecular components. I therefore invested a lot of time understanding the technology, working together with several microarray facilities to establish the technology, all in the hope that I could eventually obtain time course data for modeling regulatory networks as dynamic systems. While microarray data have been useful in differentiating patterns in data, using bioinformatics and machine learning techniques, the applications to dynamical systems theory has been

problematic and in some ways disappointing. To this day, the availability of high quality data that are, reproducibly quantitative and provide comprehensive time courses, can be a limiting factor to what we can or could do with mathematical modeling.

Nonlinear dynamics is one key element of biological complexity but multilevelness, self-organization and emergence are even more challenging aspects that have yet to be more appreciated. As a control engineer I knew that a space shuttle or airplanes are complicated systems but comparing these to what natural systems have on offer, it seems obvious that only biological systems are truly complex. Biological complexity was therefore a big attraction for me to move into the biological sciences. One observation I made, and which annoys me to this day, is that we do not seem to accept complexity and its limitations. In grant proposals and in the press, the impression is given that new technologies put us in a unique position to achieve long awaited breakthroughs. With "impact" being a criterion on most evaluation sheets for grant proposals, scientists have developed a culture that is overoptimistic. In relation to "breakthroughs" in medicine I find this particularly problematic. Biological complexity is creating this marvelous diversity and beauty we find in nature, so why make it appear simpler than it is? In some ways, the emergence of systems biology, and now systems medicine, are recognition of the fact that things are complex and require new and interdisciplinary approaches, but even today we often do not accept our limitations. By reflecting upon limits to what we can and cannot know, by thinking about uncertainty, we may actually be on our way to greater understanding.

I was not so much drawn into biology through what was going on in bioinformatics. It was thus good that systems biology emerged as a new 'field'. I prefer to think of systems biology as an approach, not a discipline. Both, bioinformatics and systems biology are, of course, complementary and in our work we combine bioinformatics approaches, focusing on statistical analyses, database searches etc., with systems biology approaches that are more directed towards modeling and simulations. However, in order to establish systems biology, it was, to begin with, necessary to emphasize differences (Wolkenhauer, 2014b). My favorite description of systems biology describes it as the science that studies how biological function emerges from the interactions between the components of living systems and how these emergent properties enable/constrain the behavior of these components. The emergence of tissue functions from interacting cell populations is a consequence of multilevelness, making it so difficult to understand the (mal)functioning of organs from studying the behavior of single cells. The second aspect of this definition of systems biology emphasizes a shift of focus

from the identification and characterization of molecular components, towards an understanding of functional activity. This development marks the transition from classical bioinformatics and molecular biology, to systems biology. Nonlinear dynamics, multilevelness with self-organization and emergence were and are themes that I have found very attractive because they challenge our state-of-the-art.

Looking at the complexity of cellular systems, it does not take long to realize that the theory of dynamical systems, as useful as it has been in the engineering and physical sciences, has its limitations when it comes to biological complexity. This is also why, after years of data-driven efforts, I have recently argued for more theoretical research in the life sciences (Wolkenhauer, 2013, 2014a). Multilevelness, specifically the need to link cell and tissue level phenomena in biomedical research, provides an exciting challenge for experimentalists and modelers alike. The 'field' is thus evolving and I am as enthusiastic about it, as I was in 1994.

2. How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

I am experiencing an increasing number of contacts with philosophers of science and have found this inspiring and useful for my work. I am convinced that philosophers of science can make a contribution to what is happening now, if they wish to. The reason is that technological developments let us "zoom in" to ever greater details with the consequence that most scientists find it very difficult to "zoom out" and reflect upon their work in a wider context. This zooming out is however very important. We are drowning in molecular details and struggle to integrate these detailed pieces of evidence into a coherent picture about the consequence of molecular interactions at higher levels of tissue organization. Take, for example, disease-motivated research programs into cellular functions. Many projects will focus on selected subcellular networks but how do we integrate the results from various pathways, gene regulation, signaling and metabolism? In most cases this integration takes places in the discussion sections of publications or in review articles. In these discussions we make inferences that go far beyond the experimental context, defined by the technologies used, the experimental model (say a cell line) etc. It is then important to be aware of the consequences and the best way of making inferences and generalizations in light of complexity and uncertainty. Philosophers are experts in taking such a "birds-eye perspective".

There is too little debate on how we go about doing things in the life sciences, as if there are no options and alternative routes to take. For example, review articles, reflecting decades of cancer research, are ad-

mitting that earlier hopes for breakthroughs were not fulfilled. I think it would be worthwhile reflecting on the re-occurrences of hope, raised expectations and subsequent admissions that things turned out to be more complex. Could it be that we pin too much hope on technologies? Could it not be foreseen that advances in the promoted direction would only reveal more layers of complexity? And what about the fundamental way in which we conceive the origin of diseases, like cancer? Could it be that the current, most widely pursued direction is dominating the field so much that it blinds us for alternative ideas? I believe philosophers of science could help with these questions by studying past and present routes to knowledge in the natural sciences and the life sciences in particular. There is no doubt that the availability of technologies has largely determined the questions that are asked in the molecular and biological sciences. Rather than being a means to an end, helping us to answer questions, technologies have opened up directions and generated questions. The role of technologies in driving research directions and questions in biology is quite different to other areas of science and I think it would be worthwhile to reflect upon this. We may approach a situation where data is not the problem and instead of more technologies we should put more emphasis on the development of methodologies, ways of thinking and theoretical tools. For example, it is true that the amount of data being generated, say by deep sequencing and imaging, requires specific IT infrastructures and yet I do not think the main hurdle for progress is the quantity, or even the variety of data types. I think the fundamental problems have less to do with the tools to process data and are related, instead, to the reductionist approach through which we design experiments and interpret the data. In biology, we are dealing with self-organizing and self-referential systems, where the whole (e.g. a tissue) and its parts (cells) reciprocally produce each other; they determine the behavior and functioning of each other. We will thus always run into problems if we then study subsystems in isolation, trying to piece things together afterwards. This example shows that biological complexity is the main hurdle for a better understanding of biological systems and hence the main reason why molecular and cell biology has to change. A living system is complex, not so much due to a large number and variety of components, but because (i) every aspect and component of a living system is subject to constant change and transformation (evolution being the underlying organizing principle); (ii) there are counterintuitive nonlinear relationships between variables interacting in space and time (counterintuitive phenomena that are also limiting the effectiveness of analytical and computational tools); and finally, (iii) living systems consist of multiple levels of organization, manifesting both regressive and progressive causality. It seems quite obvious that

epistemology is the branch of philosophy that could play a role here - a philosophical and historical reflection of fundamental issues seem as important as the study of current practices in the life sciences.

My expectation is that philosophers can help in getting to grips with some of these issues. As a modeler my value to the experimentalist is often my way of thinking, the questions I ask them. Because mathematical modeling requires us to think carefully about what to measure and to be clear about assumptions, this way of thinking can be helpful in a lab where tremendously complex technologies and procedures, and the effort to do the measurements can distract from asking these questions. In a very similar way, the philosopher can ask me questions which will help me to focus and reflect upon my way of doing things. My hope is that philosophers of science will see this opportunity to engage with current research. No doubt, some philosophers will prefer to let us do our thing, waiting until we get old and die, so that they can figure out what the scientists in question thought and where they got it wrong. Hopefully, there are others, brave enough to delve into problems of current topics in the life sciences, taking a chance to engage with scientists that generate experimental data, interpret the data and generate mathematical models. The role and value of models and theory in the life sciences, molecular and cell biology and medical research are areas in which both fields could find fruitful interactions.

3. What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

Unfortunately, I do not know enough philosophy of biology to judge this. When I here speak of biology, I think of molecular and cell biology and, perhaps, research with applications in biotechnology and biomedicine. It seems that until a few years ago, most of the 'philosophical' discussions had to do with evolution, genetics and ethical issues. I now see more and more philosophy of science dealing with recent developments in the life sciences. A comparison with the philosophy of physics is an obvious idea and indeed there are several themes that are relevant to both domains and one finds publications on these issues.

Most important, in relation to systems biology, is probably the role of mathematical models and theory and the processes through which scientists make inferences. The practice of molecular and cell biology is dominated by inferences that go beyond the context that is defined by the experimental setup. Basic examples include the use of experimental models, *in vitro* models, model organisms and the like. Other examples are inferences about cellular functions, like apoptosis, through the study of particular signal transduction pathways. Contexts are also created by the technologies chosen to generate data and while often only one of the

three key classes of cellular processes are addressed (metabolism, gene regulation, signaling), the experimental evidence may be used to make inferences that go beyond the context defined by the experiments. One could argue that most inferences are made by integrating results from a range of studies, with evidence generated in different contexts that do not necessarily integrate well. A cynic might say that the creation of an argument is a form of story telling, knowledge in molecular and cell biology being essentially 'justified belief'. This suggests that the current practice is characterized by some form of 'abductive reasoning', taking the following form: E | C is the evidence from experimental observations O (an aggregate of own experimental data, information from databases and the literature), conditional upon the context C. If no other hypothesis can explain O as well as hypothesis H, through E, then H is the best explanation for E and H is considered valid. The ability of H to explain E | C, its explanatory power is the ability to provide understanding through an iterative process of data-driven modeling and model-driven experimentation. Ultimately, the validity of an argument for or against H is then judged by the scientific community and publications that enrich any particular E with evidence from other sources. The arguments made in such publications are essentially a story being told about H. Now, for H to be accepted and to provide the basis for a more general principle, it should not only explain one set of evidence E for a particular C, but also other experimental observations in different contexts. An interesting epistemological question is then how we arrive at law-like, general principles (Wolkenhauer and Green, 2013).

Rather than being negative about 'neglected' issues, I am encouraged by the opportunities generated for philosophers of biology. Many topics are only emerging now. For example, the need to integrate heterogeneous data from a wide variety of sources and the uncertainty associated with data, are pushing the quest for standardization and ontologies. Standardization is of course essential to ensure the reproducibility of results (experimental and model-based), which are the basis for the integration of data. However, should everything be standardized? For example, when I start a project with an experimental group we will usually conceptualize the system under investigation with some diagram. To begin with, we have no clear idea what the meaning of the arrows we draw could be, what kind of mechanism or interaction may be linked to that arrow. Because the diagrams are often not representing 'what is' (known, considered a fact) but what we believe to be the case (a hypothesis), one requires freedom in how to do things. In other words, vagueness and ambiguity can play an important role. As a project progresses, standards and ontologies become increasingly important. When it comes to the final version of a model and the publication

of results, standardized formats for models, diagrams, operating procedures in the lab etc., they become essential to support the reuse and validation of results within the community. A similar case exists for the use of words in describing cellular systems and their behavior. We speak of "mechanisms", "functioning", "control", "regulation", "signaling", "feedback", "robustness" etc. and there are quite a variety of meanings associated with these terms. I imagine that philosophers of science could help clarify the emergence and use of terminology and by reflecting upon the process by which we make inferences we may actually do things differently, and probably better.

4. What have been the most significant advances in systems biology?

Before systems biology, there were already the fields of theoretical biology and bioinformatics. My guess is that theoretical biology had an image problem when it came to close interdisciplinary collaborations that involved the analysis of experimental data coming from wet-labs. When I started interacting with experimental groups, the words "theoretical" or "mathematical" could not be used, as otherwise it would be difficult to get biologists interested. Bioinformatics paved the way for 'Computational Biology" but in my view it was essential to promote systems biology, not so much as a new field or discipline, but as a new way of thinking. It is fair to say that there was a pre-occupation with single genes and proteins, their molecular characterization as the explanatory foundation for cellular functions, phenotypes and so forth. Cellular networks were appreciated but cellular functions, like apoptosis or cell differentiation are inherently dynamical systems, where spatio-temporal changes of concentrations determine what is happening. If that is accepted, one also must accept as a consequence that cellular functions should then be studied with (Dynamical) Systems Theory. This expertise was not very visible in bioinformatics and it made sense to attract engineers, mathematicians and physicists to study cellular systems. This shift of focus from the identification and molecular characterization of components, towards an understanding of functional activity, is in my view one of the most significant advances in systems biology.

We have made tremendous progress in unraveling cellular networks but when it comes to understanding disease phenotypes we are now making a similar mistake as when systems biology started off: To understand tissues as a whole, we need to study the system as a whole. There is an army of scientists studying subcellular pathways and when you ask them why they study their particular pathway, they argue that it is of key relevance for a cell function (e.g. apoptosis) and that this in turn is important for progress in cancer research. Interesting is the fact that many people will study different pathways for the same rea-

son but quite independently. They then have come up with the notion of "crosstalk" between pathways, which in my view, is only admitting that one cannot understand cellular functions by investigating different pathways in isolation. In the case of diseases like cancer, the progression of the disease is a problem of tissue organization and we must therefore study the tissue as a whole. To claim that experiments on a single signal transduction pathway will help us to explain metastasis is probably in the same league of erroneous thinking as the false hopes people had when they thought single genes can explain diseases. The dilemma is that we currently lack methodologies for such multi-scale or multilevel systems. Just as biologists tend to tailor their research questions to the technologies available in their lab, modelers like to fit the systems in questions into the conceptual framework available. We need thinkers to detect such practices, which are often driven by non-scientific considerations related to money, time, practicalities, or even career progression. I believe these issues have created a culture in which unreasonable expectations are raised about what we can achieve in our research. We should not pretend things are simpler than they are, that things are only a matter of technologies. We should acknowledge uncertainty arising from biological complexity, embrace it and focus more on the development of new methodologies, theoretical tools and new ways of thinking (Wolkenhauer, 2011, 2012). There is no doubt that technologies play a crucial role in generating more and better data but my feeling is that in terms of methodologies a lot more could be done, with potentially great impact.

Significant advances have been made with the help of mathematical modeling. There are numerous examples where biological and biomedical insights were derived from or at least supported by mathematical modeling and computer simulations. I am pleasantly surprised that even in the medical sciences there are now voices that call for more mathematical modeling (Wolkenhauer, 2013).

5. What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

Although I believe that a philosophy of systems biology is important and could help the development of the field, I must recognize that I am not a philosopher and therefore do not really know what suitable problems for philosophers are. As alluded to above, tor me, the most exciting development is the need to integrate data and evidence about subsystems into an understanding of larger systems, as a whole. Diseases are again an excellent example. The root causes of diseases and their progression will rarely be answered on the basis of evidence about

single genes, single pathways, or even single cell behavior. Systems biology has done a great job in progressing our understanding of cellular mechanisms underlying the behavior of cells. We need ideas that generalize mechanisms about specific cellular processes into law-like principles of tissue organization. There are only a few discussions about the development of "theories" in biology. The arguments for a "theory" (explanatory model, hypothesis) are hidden in the discussions of review articles. Along with the need to integrate evidence into "theories", generalization plays a crucial role. As described above, the technologies and methodologies we use create contexts in which experimental evidence is created. If someone describes a mechanism related to some cell function, he may have done the experiments with some cell lines. Of course, the idea is that the same mechanisms, pattern or rule found in that cell line, will apply to other cell lines or other experimental models (model organisms etc.). It is thus common practice to extrapolate from a specific experimental context, but how this could be done in a more effective, or correct way, appears to be an open question. I suppose that philosophers of science could detect patterns in scientific practice, and by comparing what is going on in systems biology with other fields, one could actually help those using systems biology approaches.

I already alluded to biological complexity being something quite special. Self-organization and emergence are classical themes that are still very relevant to systems biology, raising questions about the scientific approach we take when studying tissue level phenomena by means of single subcellular networks and single cells. In (Wolkenhauer and Hofmeyr, 2007) we look at self-organization of cells, and more recently my interest has shifted towards the whole-part relationship in tissues. Using the words of Immanuel Kant, in a tissue every cell owes its presence to the behavior of all the remaining cells, and also functions for the sake of the others. The whole (tissue) and its parts (cells) reciprocally produce each other; determine the functioning of each other. This suggests a fundamental problem for the way we go about studying living systems, and tissues in particular. I consider discussions of related epistemological questions of upmost importance because such discussions could inform decisions we make about the design of experiments, or even how research money is allocated. No doubt, the biological sciences have been largely driven by technological developments but as I have argued here, equally important is how we think about biological systems, how we interpret experimental and model-based results and how we arrive at inferences. In cancer research we currently witness an interesting debate about the genesis and progression of the disease. If you consider cancer a problem of the cell, largely driven by mutations, then new (initially expensive) technologies for deep sequencing may be

the way forward. If, on the other hand, you consider cancer a problem of tissue organization, your experiments may be quite different. It is an interesting thought that decades of research and billions of dollars may be wasted because we 'think' in a certain way. To paraphrase the physicist Werner Heisenberg, we do not observe nature itself, but nature exposed to our method of questioning. As much as we need technologies to advance the biological and medical sciences, equally important are new ways of thinking. My experience is that, unfortunately, this is not sufficiently appreciated, which will generate plenty of material for the philosophy of biology to ponder in future.

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About the Editor

Sara Green has a background in both philosophy and biology. She completed her PhD entitled "Systems Biology and the Quest for General Principles" at the Center for Science Studies, Aarhus University, Denmark in the spring of 2014. This project was conducted within Prof. Hanne Andersen's research group called Philosophy of Contemporary Science in Practice (PCSP), and had the support of Dr. Sabina Leonelli (University of Exeter, UK) as co-supervisor. The PhD project explored the philosophical implications of research strategies in systems biology, with a special focus on so-called organizing or design principles in the life sciences. Sara provided a critical analysis of adaptationist approaches and defended the existence of non-adaptationist applications of engineering approaches to biological organization. At the same time, she has stressed the fruitfulness of systems thinking that goes beyond engineering analogies to study biological systems as dynamic wholes.

Between August 2014 and April 2015 Sara was a postdoctoral fellow at the Center for Philosophy of Science, University of Pittsburgh, USA. Here, her work included analysis of the affordances of different representational strategies used in systems biology to deal with biological complexity. She also developed an interest in the epistemic and social implications of systems medicine, an emerging field that draws on modeling strategies from systems biology. This will be an area that Sara will continue to investigate in her new research project at the Department of Science Education, University of Copenhagen, from June 2015.

Sara works within the field of Philosophy of Science in Practice that aims to understand science as it is practiced and its philosophical and social implications for society, through stronger connection to neighboring fields such as social science, history of science and science proper.