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Network modeling approaches for metabolic diseases and diabetes

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Abstract

Metabolic diseases (MD) are amenable to network-based modeling frameworks, given the systemic perturbations induced by disrupted molecular mechanisms. We present here a brief overview of network modeling methods applied to inborn errors of metabolism (IEM), systemic metabolic conditions (mainly diabetes), and metabolism-related inflammation and autoimmune disorders. Clinical diagnosis and identification of causal agents in IEMs and uncovering the multifactorial mechanisms underlying the development of diabetes and other systemic metabolic diseases are the main challenges being addressed. The review also highlights some of the studies undertaken to investigate the role of the gut microbiome in MD, especially in diabetes. While the network frameworks employed in different modeling approaches have provided novel insights, some technique-specific limitations and overall gaps in general research trends need further attention.

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Keywords

Networks, Metabolic diseases, Diabetes.

Introduction

Metabolism is an essential function in every cell and enervates every process in the body. This, combined with the worldwide prevalence of metabolic syndrome, obesity, and systemic complications of type 2 diabetes (T2D) [1] as well as metabolism-related inflammation and autoimmune disorders, such as type 1 diabetes (T1D), Inflammatory Bowel Disease (IBD), Crohn's disease (CD), and coronary artery disease (CAD), motivates large research endeavors for identifying disease mechanisms, potential novel treatments and also for an effective translation to clinical outcome management. Concomitant with the increased molecular data generation, the development of computational methods and tools has provided means of handling and analyzing this data. In particular, various network frameworks have been adopted to investigate a variety of biological conditions, states, and disease contexts, including metabolic diseases (MD) [2,3].

Network modeling approaches for metabolic diseases and diabetes

The network paradigm naturally fits the architecture of metabolism on different levels. Systemic effects on metabolic fluxes can intuitively be captured by graphs and hypergraphs, with nodes and edges usually being metabolites and reactions. Several network-based modeling approaches have been developed (Box 1). Genes encoding enzymes involved in chemical reactions have been identified and mapped to the reaction networks, thus leading to the establishment of the widely adopted generic genome-scale metabolic reconstructions. Constraint-based modeling (CBM) then works by assuming time-invariant constant concentrations of the intracellular metabolites and allows for example identifying active metabolic pathways based on the fluxes through the system (e.g. ref to Ref. [4]). CBM models can be combined with Ordinary differential equation (ODE) based models, which capture the time-dependent quantitative states of entities, given initial conditions and kinetic parameter values for defining the system under study i.e. glucose-insulin ODE models (GIM) were combined with CBM models to capture the dynamics of glucose (ref to Ref. [5]). On the other hand, directed DNA-protein interactions can be modeled through gene-regulatory networks (GRNs), detailing the transcription factors regulating their target genes [6]. This transcriptional wiring can be a differentiating factor between a healthy and diseased state. Mapping and predicting systemic changes in proteins contributing to disease pathology can be undertaken by leveraging protein−protein interaction networks (PPINs) (e.g. Ref. [7].) Several publicly available PPI databases contain recorded protein−protein interactions from different species.

Box 1. Different network modeling approaches

Constraint-based modeling (CBM): Constrained-based modeling describes the metabolism at steady state by a system of linear equations, represented by a stoichiometric matrix S and flux vector v. At steady state, the product of S*v = 0, and the values of the variables of the flux vector can be calculated [40]. However, the system is underdetermined in most cases; hence, the solution is not unique but is often a set of solutions that are referred to as solution space. Flux Balance Analysis (FBA) that determines the solutions that maximizes the flux through the objective function often biomass production, and among other allows to perform fluxes prediction or simulate *in silico* knockouts (*In silico* KO).

Gene regulatory network models: Gene expression comprises an interplay of several elements, most notably transcription factors (TFs) and their target genes. Thus, a gene regulatory network tries to map these regulatory relationships, resulting in directed networks indicating the asymmetrical relationship between these elements. While a generic network can be derived using co-expression data, several methods are now in place that integrate transcription factor binding sites, their accessibility data in the form of ChiP-seq and ATAC-seq [41].

Weighted gene co-expression network analysis (WGCNA) [42]: It is a commonly used technique for analyzing correlations among genes. It yields correlated gene clusters or modules. These modules are also used to correlate genotype with phenotype. Correlations in gene expression can indicate genes which are co-regulated or pathway level linkages between genes. Strong correlations are given weightage, while weaker correlations are pruned to obtain a network. However, there are computational choices to be made such as the choice of correlation, size of modules, etc. which is often context specific.

Protein–protein interaction network models: Interactions between proteins are identified based on experimental techniques including physical interactions such as yeast two-hybrid, affinity purification mass spectrometry, bioluminescence resonance energy transfer, etc. [43] or genomic interactions such as synthetic lethality [44]) or predicted using different computational approaches such as molecular docking. Several databases manage and curate PPIs, for different organisms, and based on different levels of evidence available for the reported interaction. From generic PPINs, contextualized PPINs are generated in different studies to visualize and investigate different biological questions, such as the contexts and effects of disease-associated proteins. PPINs are generally undirected and contextualized using gene expression data. The neighborhood of known proteins is a rich environment to obtain mechanistic insights, identifying missing links in signaling and estimate the effect of perturbation of proteins.

Bayesian network models: Bayesian networks are directed acyclic graphs (DAGs), with nodes denoting variables and the edges denoting the dependencies between the variables, for example if genes are the nodes, the edges represent the regulatory relationships between them [45]. As the network is a DAG, causal links can be established between the nodes, as opposed to networks containing loops and cycles where isolating effects is difficult.

Ordinary differential equations: Relationships between interacting molecular species are derived from first principles, such as mass-action kinetics and the evolution of the system with time can be simulated. Here, the initial state of the system (such as initial concentrations of the reactants and products), and associated kinetic parameters are essential inputs for the modeling format. Robust models are highly dependent on the availability of accurate parameter values, accessing which can be a challenge. However, predictive ODE models are of immense value in biotech industries and for pharmacokinetic-pharmacodynamic modeling in drug development. Hybrid approaches such as coupling ODEs with CBM models can capture some dynamics of key metabolites such as glucose.

Machine Learning: Machine learning approaches are employed to either cluster (unsupervised) or to find features that allow segregating labeled data (supervised). This can be done as different models learn from a set of training data and apply the resultant specific model on new inputs. For example, analysis of health records of diabetics and non-diabetics/healthy patients yield a diagnostic tool to classify new patient. Clustering can help identify patient sub-groups, thus providing finer distinctions and allowing for more tailored therapeutic approaches. Several different algorithms are used in practice, to obtain either continuous values or class labels, such as regression, tree-based algorithms, and support vector machine among others.

Neural networks: Originally, neural networks were inspired by the structure of the brain, where the different signals processed resulted in an output from interconnected neurons. A neural network consists of an input layer and an output layer at its two ends, with the central architecture of hidden layers (ranging from just one to many). Connections between the input data, and its processing through the different layers results in activation of a specific output, based on the configuration of the model structure and the activated weights among the layers.

These are obtained using several different experimental techniques such as two-hybrid, and affinity-based methods. Correlations between expressed genes can be used to construct co-expression networks. The analysis of such networks also includes identifying modules of genes contributing towards a specific physiological process. Refined methods, such as Gaussian graphical models have been proposed to ensure the removal of spurious correlations (by considering partial correlation coefficients), and Bayesian network modeling to help strengthen the case for causal inference [8]. Table 1 offers an overview of some studies reported recently employing few of the described methods applied to different MD contexts.

Along with the traditional genome-wide association studies (GWAS), gene expression (RNA-seq) and proteomic (MS-based quantification) readouts, metabolomics, lipidomics, functional assays (knockouts, overexpression) are serving as individual or combined data inputs for the above-mentioned computational methods. Each modeling approach thereby has its own capabilities. CBM, due to the conservation of mass principle and the definition of an objective function is often employed for the simulation of single/double gene knockouts. PPINs help in identifying disease genes/proteins and drug targets in the vicinity of known candidates which might lead to translational research

Table 1

Some recent studies using various network-based methodologies applied to metabolic diseases.

Modelling approach/Analysis	Basic principle	Aim	Disease	References
CBM	Contextualization using metagenomic data	Investigate the microbiome-level bile-acid production	IBD	Heineken et al., 2019 [20]
CBM	FBA on microbial communities	Understanding the effect of metformin on gut microbiome		Ezzamouri et al., 2023 [21]
CBM	FBA on microbial communities	Modeling to Infer Metabolic Interactions in the Gut Microbiota	T1D, T2D	Diener et al., 2020 [25]
CBM	Modified FBA to simulate competitive inhibitions	Biomarker prediction for PKU disease	IEMs	Liu et al., 2022 [4]
CBM (+ML)	Flux prediction using expression data	Biomarker prediction, Reporter metabolites	T2D	Hoshea, et 2023 [26]. Varoom et al. [27]
CBM (stepwise simulation)	Flux prediction for fed and fasting states Stepwise increase of lipid oxidation and glucose uptake *In silico* gene KO	Insulin resistance-associated metabolic phenotypes	IR	Nogiec et al., 2015 [28]
CBM + ODE-based GIM model	Dynamic FBA contextualized with expression data	Altered metabolic processes in T1D, effects of exogenous insulin	T2D	Ben Guebila et al., 2021 [5]
CBM + ODE-based GIM model	Dynamic FBA + tissue model reconstructions	Find urine and blood biomarkers for IEMs	IEMs	Martins Conde et al., 2015 [29]
CBM (+ML)	Parsimonious FBA ((RIPTiDe) to prune reactions of a generic genome scale model	Metabolic underpinnings of CD and clarify possible biomarkers and druggable targets	CD	Fernandes et al. [30]
CBM + GWAS	*In silico* KO	Study IEMs	IEMs	Cheng et al., 2021 [31]
GBM	Reconstruction using metagenomics data (metaGeM)	Differences in Species	T2D	Zorrilla et al., 2021 [32]
Co-variance network	Spearman correlation between gene pairs (4 organs) and metabolic parameters	Inferring causal organ/pathways mediating microbiota linked disease contribution	T2D	Li et al., 2022 [19]
Gene regulatory network	TF-target networks inference from single-cell RNA-seq data of beta-cells	Impact of aging on pancreatic beta cells	T2D	Shrestha et al., 2022 [6]
Co-expression, Bayesian networks	Analysis of adipose and muscle tissues from three cohorts of different ancestries	Cell-type specific networks of insulin regulation	IR	Xu et al., 2023 [15]
Gaussian graphical network	Disease specific metabolite network construction using clinical data from various studies	Computational method for improving clinical diagnosis of IEMs	IEM	Thistlethwaite et al., 2022 [9]
Gaussian graphical network	Construction of and community detection in metabolite network	Classifying pleiotropic variants	IEM/T2D	Lotta et al., 2022 [33]
Protein−protein interaction network	Propagation of metabolic enrichment score derived from untargeted metabolomic data through PPIN	Prioritizing candidate genes for IEMs in patient samples	IEM	Graham Linck et al., 2020 [7]
Co-expression (WGCNA)	Integration of proteomic and transcriptomic data for WGCNA	Investigating differences across several types of adipose tissues	IR	Kreig et al., 2022 [34]
Co-expression (WGCNA)	Correlated gene modules associated with the clinical traits in cohorts	Identifying altered methylation and gene expression in children of mothers with T1D	T1D	Knorr et al., 2022 [35]

(*continued on next page*)

Table 1. (*continued*)

Modelling approach/Analysis	Basic principle	Aim	Disease	References
Co-expression (WGCNA)	Topological analysis of co-expression network using betweenness centrality	Identifying genes associated with diabetic skin conditions	T2D	Liu et al., 2022 [36]
Co-expression (WGCNA)	Correlation of changes in gene expression across time-points between individuals	Identifying mechanisms of transition from pre-diabetic condition to diabetes	T2D	Chen et al., 2022 [37]
Co-expression (WGCNA)	Network of 450 variable genes, analysis of modules identifying hub genes	Assessing the effect of time restricted eating on metabolic and hormonal profile and subcutaneous adipose tissue transcriptome in males with obesity	Obesity	Zhao et al., 2023 [38]
Co-expression (WGCNA), Bayesian network	Co-expression networks for 7 tissues (for identifying tissue-specific gene clusters), four probabilistic causal network models (using transcriptomics, genomics, clinical traits, and metabolomics)	Mechanistic understanding of inverse relationship between glucose and lipid metabolism	CAD	Cohain et al., 2021 [8]
Co-expression (WGCNA)	Comparison between gene modules and wiring of (high risk) non-diabetic and diabetic cohorts	Transcriptomic signals from blood, signatures of insulin resistance and glucose intolerance	T2D	Gudmundsdottir et al., 2020 [39]

Abbreviations: CBM - constraint-based modeling, CAD—Coronary Arterial Disease, CD -Chron Disease, FBA - flux balance analysis, GWAS – genome-wide association studies, IBD- Inflammatory Bowel Disease, IR – Insulin resistance, KO - knockout, ML - machine learning, ODE - ordinary differential equations, T1D- Diabetes Type I, T2D - Diabetes Type II, WGCNA - weighted correlation network analysis.

towards improved clinical diagnosis and therapeutic interventions. The computational repertoire has expanded considerably with machine learning (ML) which offers powerful ways of handling the enormous volumes of data available, along with predictive capabilities. The choice of modeling approach is often context-specific, depending on factors such as data availability, the research question, and computational resources.

Metabolic disorders range from an identifiable single mutation (inborn errors of metabolism, IEM) to multifactorial polygenic systemic conditions, T2D being the classical example. Some of the recent applications of network modeling for these conditions are discussed below.

Network approaches for IEMs

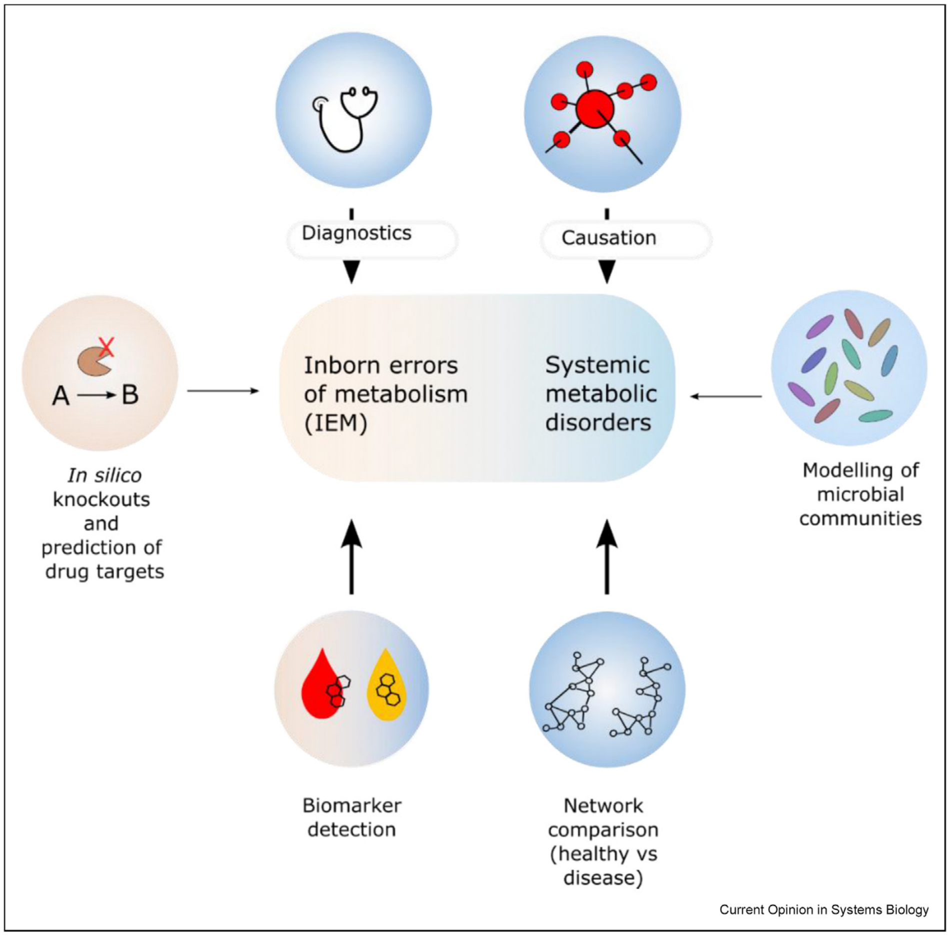
Inborn error of metabolism, although the pathology might sometimes be more complex, are metabolic Mendelian disorders which can be traced to mutation in a single gene. Being cumulatively widespread but individually rare disorders, the lack of patients/data for robust statistical analysis is especially challenging from the perspective of clinical diagnosis and treatment options (Figure 1). Computational methods are supplementing experimental efforts to address the challenges that IEMs pose.

The combination of patient data and prioritization of candidates via network propagation was shown to yield an improved diagnosis of IEMs and neurometabolic conditions [7]. This approach combined untargeted metabolomics data from patients with a PPIN to obtain a prioritized set of putative causal genes likely to yield the observed phenotype. This approach was proposed to facilitate improved diagnosis of IEMs, thus providing patient-specific treatment. A similar concept of employing untargeted metabolomics data for IEM diagnosis assistance was shown to diagnose patients across 16 different IEMs [9]. Here, Gaussian graphical models of control and disease states were constructed using clinical data. The IEM phenylketonuria (PKU) was examined by Liu et al. [4] through the lens of CBM. Based on flux balance analysis (FBA), their model showed that excess phenylalanine was responsible for brain pathology as against reduced blood tyrosine. Their approach included extending and modifying the curated genome-scale model Recon 2.2 [10] to include multiple compartments and competition for metabolite transport. While the diagnosis models often yield identities of disease-linked candidates, FBA returns quantitative insights on differences between healthy and diseased states.

Network approaches for systemic metabolic conditions including diabetes

For systemic, multi-factorial conditions like diabetes, the focus is on finding causal agents mediating pre-

Figure 1



Some of the applications of the network-based approaches discussed in this review. Studies include *in silico* knockouts for identifying essential genes and drug targets, for biomarker detection and improved clinical diagnosis for IEMs. For systemic conditions, comparison of different conditions to uncover condition-specific regulatory wiring, influence of non-genetic factors such as gut microbiome on MD progression, and causal genes/proteins as disease agents are some of the areas where network approaches are being used.

diabetic to diabetic transitions, improving therapeutic options, and ways of synthesizing causal factors in the face of heterogeneity. This is a condition that requires not only population-based statistics but incorporation of patient profiles for personalized treatments [11]. CBM allows the prediction of the metabolic phenotype of a cell, tissue, or organism from genotype data. The advent of context-specific models via the integration of bulk transcriptomics data and single-cell RNA-seq data allows for the building of not only disease-specific and patient-specific models but also for capturing metabolic exchanges between different cell populations in a tissue [12]. Metabolic modelling involving a whole-body model [13] was applied for studying diabetes, of type 1 [5]. Hybrid modeling (GIM) approach was also developed for multi-tissue models coupled to a dynamic ODE-based model which allows for simulations such as tissue-based insulin and glucagon action, insulin-dependent receptor synthesis, and gastrointestinal hormonal regulation of glucose levels, although it is limited to the glycolysis. The coupled model was able to capture the disruption of peripheral glucose concentrations, as well as the effect of injection of insulin on the liver [14].

Networks can provide additional insights when combined with diverse datatypes. In a study of the effect of aging on pancreatic islet beta cells [6], gene regulatory network (GRN) composed of transcription factors indicated the down-regulation of stress response in aging, suspected to influence the development of T2D. Aging also reflected changes in GRN structural and wiring, with the size of TF regulons decreasing over time. Another study of adipose and muscle tissues of three cohorts of different ancestries [15] employed co-expression and Bayesian networks, uncovering cell-specific networks linked to insulin sensitivity/resistance. The co-expression network was used to obtain cell-type specific gene modules enriched in genes correlated with insulin sensitivity, while the Bayesian networks allowed for Casual inference of network driver genes (such as leptin (LEP)) as determinants of insulin resistance (sensitivity).

Thus, models can act as backbones for integrating different datatypes. They can also be used for combining different layers and modeling interactions. Depending on whether the available inputs are static or dynamic, modeling methodologies can be applied (CBM for static, ODEs for dynamic). Different inputs, data processing and models may lead to uncovering different players and pathways involved in metabolic regulation. Where these models converge and diverge needs to be carefully evaluated, however. While strong convergence could indicate conserved mechanisms, divergences may point to patient/population specific features. Careful evaluation of different modeling strategies and the obtained inferences can provide rich insights into this complex, multifactorial condition.

Networks approaches for investigating the relation of microbiome and metabolic conditions

The gut microbiome has been increasingly implicated in maintaining normal health and dysbiosis and changes in gut microbiome have been linked to MD, and associated co-morbidities such as diabetes and cardiometabolic conditions [16,17]. Hence, the link between the gut microbiome and disease alterations is being actively explored. In a study investigating atherosclerosis cardiovascular disease (ACVD), T2D and obesity to identify the role of microbiota in the three conditions, increased tartrate metabolism was highlighted, hypothesizing that tartrate could explain the effect of glutamate on increase in BMI [18]. Li et al. [19] employed a multi-organ network in their study of T2D which attributed insulin resistance in white adipose tissues to specific species of gut microbiota associated with high fat/high sugar diet.

The gut microbiome, unlike for pluricellular organisms like that have many tasks to fulfil, can reasonably be approximated by the optimization of biomass production while constraining the model with the metagenomic data and media composition. On an individual level, metabolic models have been reconstructed for over 7000 microbiome species [20]. However, mechanistic and diagnostic studies require coupling of host and microbial cells, capturing the overall effect. Models are often linked through exchange compartments that allow metabolites exchanges and an optimization function of the community which is a composite of the objective functions of each model. Depending on the study goal, the community can use different objectives functions such ATP maintenance or growth. Nevertheless, it is important is to enforce that every model can grow. The gut microbiome also responds to xenobiotics and drug treatments and is thus a critical determinant of drug availability and treatment effects. Ezzamouri et al. [21] used a community model to study the effect of metformin, one of the most commonly used drugs for diabetes mellitus on the gut microbiome. The study confirmed that the proportion of the different communities in the gut microbiome changed upon four months of metformin treatment. Moreover, bacteria expressing enzymes implicated in pectins and mannose degradation were favored by metformin.

The choice of the approach depends on the research questions and the available data. CBM, which considers the metabolism at a steady state, does not suit the capture of dynamic behaviors. CBM should preferably be chosen to integrate high-throughput omics data when the structure of the network is relevant for research questions such in the case of the prediction of essential genes, metabolic fluxes, fluxes exchanges, and growth. PPI networks can be constructed using generic databases and qualitative data such as known disease-associated genes from literature. This approach is generally useful when quantitative data is unavailable. PPI databases are typically collections of interactions collated from different studies. Thus, these cover a variety of different experimental conditions. However, the biggest drawbacks are noisy data with biased datasets, and the unavailability of standard pipelines. Co-expression networks can be obtained from experimental gene expression data and thus can overcome database biases. However, the parameters required to constrain these networks are often arbitrary. ODE based models can provide quantitative insights on the concentration of various species in a network but are dependent on the availability of reliable parameter values and initial conditions.

Gaps and perspectives

Network-based models can be used to study systemic properties, such as growth rates, specificity, sensitivity genes knockout predictions and essentiality of genes, and propagation of effects in the neighborhood of disease agents. They are useful frameworks for data integration and developing personalized patient profiles. A wide spectrum of omics datasets including patient clinical data has been enabling different modeling approaches, yielding promising results with a perspective to be clinically relevant. The need for pinpointing causal factors rather than statistical associations is one of the common future goals that is being seen in recent studies. Indeed, novel methods of data integration and extracting causal mechanisms are being reported, such as the Transkingdom Network Analysis (TkNA) [22]. TkNA has shown, for example, the reduction in the impact of western diet by two species of *Lactobacillus* by to be improving liver mitochondrial functioning [23]. However, such reports still constitute a minority as we observed during the compilation of this review. Furthermore, each modeling technique requires optimization in specific areas. For CBM approaches, the definition of the objective function for systemic metabolic conditions is challenging, and wider discussions are warranted. Similarly, for GRNs, PPIs, network construction is often subjective. Hence, while individual studies could offer dataset-specific insights, comparison and benchmarking efforts across studies is difficult. Deep learning (DL) methods such as neural networks (NN) also use a network architecture, where the input is passed through a series of node layers, and the output is a result of a specific combination of edge weights connecting the nodes across the different layers. Moreover, graph neural networks (GNNs) are specifically designed to accept networks as inputs and allow learning tasks on them. In this review, DL-based methods have not been emphasized, partly because we found a large fraction to be focused on image analysis and patient classification, very few using multi-omics data for mechanistic investigations. NN methods can improve predictions, but unless backed by transparent explainability, both the predictions and utility in clinical applications will be limited. One way of addressing this limitation is to design models with interpretable architecture obtained from prior knowledge such as pathway information or GO (Gene Ontology) structures. Hybrid methods combining multiple approaches such as CBM with dynamic ODE-based modeling or with the various network modeling and analysis methods could be instructive in obtaining a detailed mechanistic understanding. ODEs, however, require estimates of kinetic parameters. Novel methods are being proposed, for example, NN-based pipelines are being used to estimate parameters and produce biologically relevant metabolic models [24]. Some standardization is required such as standardized data quality checks, processing, and integration methods. While a multitude of assays and data are being generated, integration while dealing with technical noise, batch effects and experimental artifacts is critical. Integrated pipelines for prediction and validation are necessary to determine the accuracy and biological relevance of computational inferences. However, there are active developments under way in the field. Synthesis of insights from different techniques is needed at a frequent interval to ensure community consensus on methods and ultimately improving the translational potential of the delivered outcomes.

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Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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