Nonequilibrium thermodynamics of non-ideal reaction–diffusion systems: Implications for active self-organization

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ABSTRACT

We develop a framework describing the dynamics and thermodynamics of open non-ideal reaction–diffusion systems, which embodies Flory–Huggins theories of mixtures and chemical reaction network theories. Our theory elucidates the mechanisms underpinning the emergence of self-organized dissipative structures in these systems. It evaluates the dissipation needed to sustain and control them, discriminating the contributions from each reaction and diffusion process with spatial resolution. It also reveals the role of the reaction network in powering and shaping these structures. We identify particular classes of networks in which diffusion processes always equilibrate within the structures, while dissipation occurs solely due to chemical reactions. The spatial configurations resulting from these processes can be derived by minimizing a kinetic potential, contrasting with the minimization of the thermodynamic free energy in passive systems. This framework opens the way to investigating the energetic cost of phenomena, such as liquid–liquid phase separation, coacervation, and the formation of biomolecular condensates.

I. INTRODUCTION

Self-organization of molecules in solution can produce complex spatio-temporal structures that range from self-assemblies to phase separations, encompassing stationary patterns and oscillations. It results from nonlinear effects which can be caused by a variety of mechanisms.

One possible mechanism is based on molecular interactions, typical of *non-ideal* systems, which can lead to self-organization even at equilibrium. When no external energy is provided to sustain self-organization, this mechanism is *passive* and described by a dynamics exhibiting *detailed balance*. The theoretical description for this mechanism is typically provided by Cahn–Hilliard theory of spinodal decomposition[1] and its variants.[2] It can be further understood from a thermodynamic perspective through theories like that proposed by Flory and Huggins[3,4] as a relaxation toward equilibrium.

Another mechanism involves multimolecular chemical reactions in *open* systems, which can also lead to self-organization in the absence of interactions. Predicted by Turing[5] and extensively studied by the Brussels School,[6–8] its experimental validation took nearly four decades.[9] From a thermodynamic viewpoint, this type of self-organization is maintained by the continuous consumption of energy,[10–12] making the mechanism *active* with dynamics that exhibits *broken detailed balance*. While our focus is on molecules in solution, we note that this mechanism also applies to larger spatial structures, such as predator–prey distributions,[13,14] vegetation patterns,[15,16] and spiral patterns of galaxies.[17]

Recent years have seen renewed interest in the study of self-organization due to its crucial role in biological systems, where

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biomolecular condensates[18,19] resulting from liquid–liquid phase separation form membraneless compartments. These condensates have been observed to serve various functions, including storage of molecules,[20] enhancement of reaction rates by concentrating enzymes and substrates,[21,22] and maintenance of macromolecule folding states.[23]

Many studies have attempted to reproduce the dynamics and the concentration profiles of these condensates,[24–27] without characterizing the interplay between passive[28] and active[29,30] mechanisms in their formation and regulation. Indeed, their nonequilibrium nature is not easily discernible from examining the self-organized spatial structures alone. Instead, it requires a more detailed analysis of both diffusion and reaction fluxes, and how these fluxes are related to energy consumption. This critical feature is known as *thermodynamic consistency*.

Understanding the control of self-organized structures by out-of-equilibrium chemical reactions and the resulting dissipation of energy is crucial, especially in the field of biology. Achieving passive control is nearly impossible due to the difficulty in adjusting molecular interactions. Consequently, it is necessary to rely on active mechanisms. However, since biosystems operate within a limited energy budget and energy consumption is crucial for almost all biological processes, efficient regulation is essential. Previous studies have explored the regulation of such structures through simple unimolecular reactions[31,32] or examined their stability in multimolecular reactions,[33] yet a comprehensive framework to analyze the nonequilibrium aspects of self-organization is still lacking. This work addresses this gap by highlighting the critical role of the reaction network topology in defining the relationship between self-organized structures and their thermodynamics.

We develop a general thermodynamic theory for open non-ideal reaction–diffusion systems by integrating the thermodynamic theories of both non-ideal chemical reactions[34,35] and ideal reaction–diffusion systems.[10,11] This unified approach enables us to investigate the energetics of self-organized structures and the interplay between passive and active mechanisms. We examine various classes of reaction networks. For *detailed balanced* ones (open or closed), we show that the dynamics always relaxes to equilibrium while minimizing a suitable thermodynamic potential which plays the role of a Lyapunov function that depends only on the energetics and not on the kinetics. In these passive systems, the resulting self-organized structures do not dissipate. For *pseudo-detailed balanced* reaction networks, we show that the dynamics can be mapped into a detailed-balanced dynamics minimizing a kinetic potential that we identify and that plays the role of a Lyapunov function. Nevertheless, these systems are active, and the resulting self-organized structures dissipate. For *complex balanced* reaction networks (characterized by Arrhenius-like reaction fluxes), such a mapping does not exist, but the dynamics still minimizes a kinetic potential that we construct and that plays the role of a Lyapunov function. These systems are also active, and the self-organized structures they produce also dissipate. Remarkably, even though these systems are active, diffusion processes equilibrate at steady state in both pseudo-detailed balanced and complex balanced networks. However, most active systems do not fall into these classes. Nonetheless, we show that our theoretical framework can be used to systematically analyze the energetics and the dissipation produced by the various active processes generating the self-organized structures.

This paper is structured as follows. We begin in Sec. II by outlining the basic setup. Specifically, we define the representations of chemical reactions in terms of chemical reaction networks and graphs of complexes, which are crucial for the derivations of our results. In Sec. III, we introduce the dynamical description of the concentration fields and explore the concept of detailed balance in Subsection III A. In Subsection III B, we discuss the conservation laws of chemical reaction networks to identify molecule fragments, known as moieties, which are transferred between chemical species through reactions while remaining intact. These moieties will be instrumental in identifying the nonconservative forces that break detailed balance. We turn to thermodynamics in Sec. IV. We first discuss the conditions needed for the dynamics to be thermodynamically consistent. We then use moieties to rewrite the second law of thermodynamics in a way that identifies the thermodynamic forces driving the system out of equilibrium and the thermodynamic potential acting as a Lyapunov function when forces are switched off. In Sec. V, we make use of thermodynamics, along with the representations of chemical reactions in terms of chemical reaction networks and graphs of complexes, to derive our main findings for pseudo-detailed balanced networks and complex balanced networks. We end our study in Sec. VI by analyzing the energetics of various reaction networks using numerical simulations, including a network that is neither pseudo-detailed balanced nor complex balanced. Conclusions are drawn in Sec. VII.

II. BASIC SETUP

We consider non-ideal reaction–diffusion (RD) systems in solution: n_s interacting, reacting, and diffusing chemical species (identified by the labels $i \in \mathcal{S}$) are mixed together with a non-reacting and abundant species called solvent that maintains the temperature T and the volume V constant. We further assume that RD systems are embedded within impermeable walls. The species $\mathcal{S}$ are either chemostatted (labeled $y \in Y$), if exchanged with external reservoirs called chemostats (labeled $y \in Y$ too), or internal (labeled $x \in X$). We use n_y and n_x for the number of chemostatted and internal species, respectively. Due to the exchanges with the chemostats, RD systems are said to be open. Without exchanges, RD systems would be closed.

A. Chemical reaction networks and graphs of complexes

Chemical species are interconverted via chemical reactions $\rho \in \mathcal{R} = \{\pm 1, \pm 2, \dots, \pm n_r\}$ characterized by the following equation:

$$\sum_x \nu_{x,\rho} Z_x + \sum_y \nu_{y,\rho} Z_y \underset{-\rho}{\overset{\rho}{\rightleftharpoons}} \sum_x \nu_{x,-\rho} Z_x + \sum_y \nu_{y,-\rho} Z_y, \quad (1)$$

where Z_i is the chemical symbol of the species i, while $\nu_{i,\rho}$ (respectively, $\nu_{i,-\rho}$) is its stoichiometric coefficient in reaction ρ (respectively, $-\rho$). The set of species $\mathcal{S}$ might include non-reacting species (labeled for instance n_r). All reactions are assumed to be reversible: for every (forward) reaction $\rho \in \mathcal{R}$, reaction $-\rho \in \mathcal{R}$ and denotes its backward counterpart.

On the one hand, chemical reactions (1) can be represented as a hypergraph, known as a chemical reaction network (CRN), by mapping species into nodes and reactions into edges.[36] Its topology is

encoded in the $n_s \times n_r$ stoichiometric matrix $\mathbb{S}$ whose entries (for $\rho > 0$),

$$S_{i,\rho} = v_{i,-\rho} - v_{i,\rho}, \tag{2}$$

specify the net variation of molecule number of species i in reaction ρ. By definition, $S_{i,-\rho} = -S_{i,\rho}$ and $S_{nr,\rho} = 0 \,\forall \rho$.

On the other hand, the set of chemical reactions (1) can also define the so-called graph of complexes. The n_k complexes (identified by the labels $k \in \mathcal{K}$) are aggregates of internal species acting as reactants of a reaction,

$$V_{k(\rho)} = \sum_x v_{x,\rho} Z_x, \tag{3}$$

and the graph of complexes is obtained using the complexes as nodes and reactions as edges,

$$V_{k(\rho)} \underset{-\rho}{\overset{\rho}{\rightleftharpoons}} V_{k(-\rho)}. \tag{4}$$
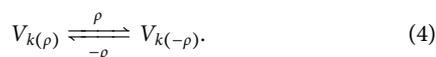
Note that the same complex can be involved in different reactions. For instance, if reactions have no internal species among their reactants, they share the same complex (usually represented by the symbol of empty set, i.e., $\emptyset$, as done in the example in Subsection VI D). The topology of the graph of complexes is encoded in the $n_k \times n_r$ incident matrix ∂ whose entries (for $\rho > 0$),

$$\partial_{k,\rho} = \mathbb{1}_{k,k(-\rho)} - \mathbb{1}_{k,k(\rho)}, \tag{5}$$

specify whether the complex k is a product (positive value) or a reagent (negative value) of reaction ρ (with $\mathbb{1}_{k,k'}$ being the Kronecker delta).

The graph of complexes allows us to divide the set of reactions $\mathcal{R}$ into $2n_e$ disjoint *lumped reactions* identified by the labels $\varepsilon \equiv (k, k') \in \mathcal{E}$, which collect the reactions interconverting the complex V_k into $V_{k'}$. Namely,

$$\mathcal{R} = \bigcup_\varepsilon \mathcal{R}_\varepsilon, \tag{6}$$

with

$$\mathcal{R}_\varepsilon \equiv \{\rho \in \mathcal{R} \text{ such that } V_{k(\rho)} = V_k \text{ and } V_{k(-\rho)} = V_{k'}\}. \tag{7}$$

Note that, if $\rho \in \mathcal{R}_\varepsilon$, then $-\rho \in \mathcal{R}_{-\varepsilon}$ with $-\varepsilon \equiv (k', k)$. By definition, all reactions $\rho \in \mathcal{R}_\varepsilon$ have the same stoichiometric coefficient (respectively, matrix) for each internal species $v_{x,\rho}$ (respectively, $S_{x,\rho}$), labeled $v_{x,\varepsilon}$ (respectively, $S_{x,\varepsilon}$) hereafter. On the other hand, there might be two reactions ρ and ρ' in $\mathcal{R}_\varepsilon$ such that $S_{y,\rho} \neq S_{y,\rho'}$.

We conclude this subsection by introducing a topological quantity, called deficiency, which essentially quantifies the number of "hidden" cycles of CRNs (i.e., cycles that do not have a graphical representation in the graph of complexes) and is known to underlie the emergence of complex behavior in ideal CRNs.[37–42] A cycle is formally defined as a right-null eigenvector $\phi = (\ldots, \phi_\rho, \ldots)$ of the substoichiometric matrix for the internal species $\mathbb{S}_X$,

$$\sum_{\rho > 0} S_{x,\rho} \phi_\rho = 0. \tag{8}$$

It, thus, represents a sequence of reactions (by specifying the number of times each reaction occurs) that upon completion leaves the

molecule number of the internal species unchanged. Some cycles can be represented as loops in the graph of complexes. Indeed, the substoichiometric matrix for the internal species $\mathbb{S}_X$ can be expressed in terms of the incidence matrix ∂ using the composition matrix Γ as

$$S_{x,\rho} = \sum_k \Gamma_{x,k} \, \partial_{k,\rho}, \tag{9}$$
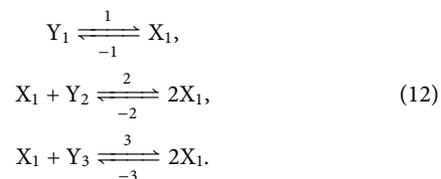
where

$$\Gamma_{x,k(\rho)} = v_{x,\rho} \tag{10}$$

specifies the stoichiometric coefficient of each internal species x in each complex k. Hence, from Eqs. (8) and (9), it follows that any right-null eigenvector of the incidence matrix ∂, defining a loop in the graph of complexes, corresponds to a cycle. However, the converse is not true, and this difference is encoded in the deficiency defined as

$$\delta \equiv \dim \ker(\mathbb{S}_X) - \dim \ker(\partial), \tag{11}$$

where $\dim \ker(\bullet)$ returns the dimension of the kernel of a matrix, i.e., the number of linearly independent right-null eigenvectors.

B. Example

Consider a system composed of one internal species $\{X_1\}$ and three chemostatted species $\{Y_1, Y_2, Y_3\}$ that are interconverted by the following chemical reactions:

$$Y_1 \underset{-1}{\overset{1}{\rightleftharpoons}} X_1,$$

$$X_1 + Y_2 \underset{-2}{\overset{2}{\rightleftharpoons}} 2X_1, \tag{12}$$

$$X_1 + Y_3 \underset{-3}{\overset{3}{\rightleftharpoons}} 2X_1.$$

The first pair of reactions $\{\pm 1\}$ represents the direct interconversion of Y_1 into X_1, while the second (respectively, third) pair of reactions $\{\pm 2\}$ (respectively, $\{\pm 3\}$) represents the interconversion of Y_2 (respectively, Y_3) into X_1 promoted by X_1 in an autocatalytic way. In Fig. 1, we illustrate the CRN and graph of complexes representations introduced in Subsection II A for the chemical reactions in Eq. (12).

Note that the substoichiometric matrix $\mathbb{S}_X$ in Fig. 1 admits two (linearly independent) cycles, namely,

$$\phi = \begin{array}{c} 1 \\ 2 \\ 3 \end{array}\!\!\begin{pmatrix} 0 \\ 1 \\ -1 \end{pmatrix} \quad \text{and} \quad \phi' = \begin{array}{c} 1 \\ 2 \\ 3 \end{array}\!\!\begin{pmatrix} 1 \\ 0 \\ -1 \end{pmatrix}. \tag{13}$$

The former is also a right-null eigenvector of the incidence matrix corresponding to the loop,

$$V_1 \xrightarrow{2} V_2 \xrightarrow{-3} V_1, \tag{14}$$
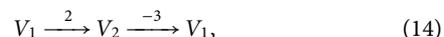
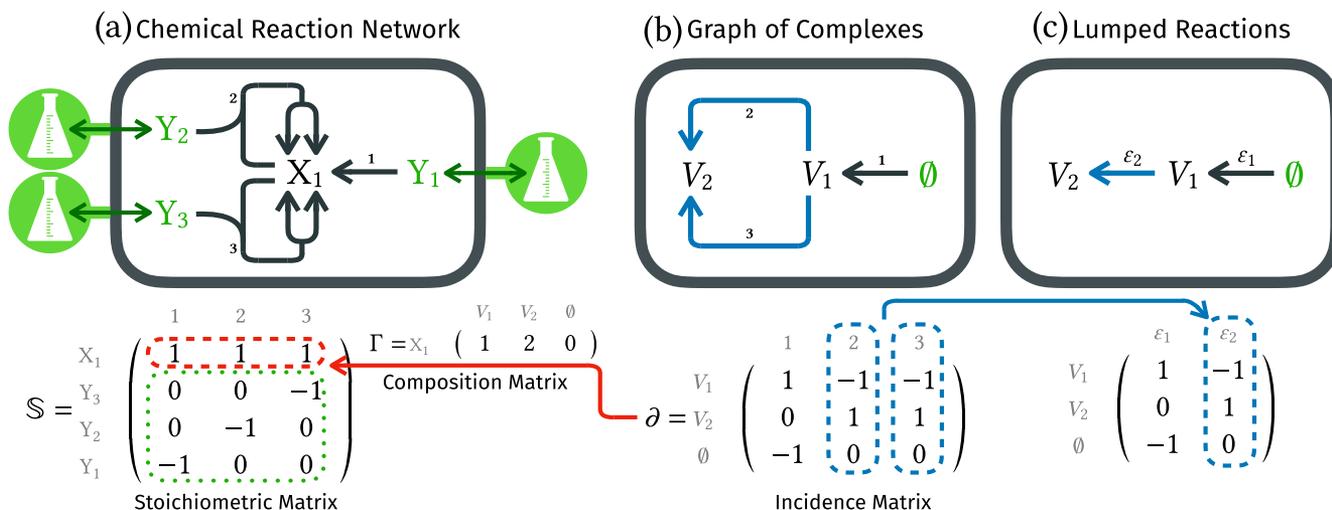while the latter is not. Hence, $\delta = 1$.

FIG. 1. Different representations of the chemical reactions in Eq. (12). (a) CRN representation in terms of a hypergraph where the species $\{X_1, Y_1, Y_2, Y_3\}$ are mapped into nodes, while the reactions $\rho \in \{1, 2, 3\}$ are mapped into edges. The green double-headed arrows represent the exchange processes of the chemostatted species. The topological properties of the CRN are encoded in its stoichiometric matrix $\mathbb{S}$, where the red dashed (respectively, green dotted) line highlights the substoichiometric matrix for the internal (respectively, chemostatted) species $\mathbb{S}_X$ (respectively, $\mathbb{S}_Y$). (b) Graph of complexes representation where the complexes $\emptyset = Y_1$, $V_1 = X_1$, and $V_2 = 2X_1$ are mapped into nodes, while the reactions $\rho \in \{1, 2, 3\}$ are mapped into edges, and the exchange processes are not represented. The topological properties of the graph of complexes are encoded in its incidence matrix ∂. The substoichiometric matrix for the internal species $\mathbb{S}_X$ is related to the incidence matrix ∂ by the composition matrix Γ. The reactions $\rho = 2$ and $\rho = 3$ (highlighted by the blue dashed line) interconvert the same pair of complexes, i.e., V_1 and V_2, and, thus, correspond to a single lumped reaction. (c) Simplified representation of the graph of complexes where the lumped reactions $\varepsilon_1 = (\emptyset, V_1)$ and $\varepsilon_2 = (V_1, V_2)$ are mapped into edges instead of the reactions. Note that all reactions, as well as all lumped reactions, are assumed to be reversible even though only the forward reactions and lumped reactions are represented.

III. DYNAMICS

The abundances of the chemical species $i \in \mathcal{S}$ in every point of space $\boldsymbol{r} \in V$ are specified by the concentration fields $\boldsymbol{c}(\boldsymbol{r}) = (\ldots, c_i(\boldsymbol{r}), \ldots)$ following the RD equation:

$$\partial_t c_i(\boldsymbol{r}) = -\nabla \cdot \boldsymbol{J}_i(\boldsymbol{c}(\boldsymbol{r})) + \sum_{\rho > 0} S_{i,\rho} \, j_\rho(\boldsymbol{c}(\boldsymbol{r})) + I_i(\boldsymbol{r}), \quad (15)$$

where $I_i(\boldsymbol{r})$ is the exchange current of species i with the corresponding chemostat [and thus, $I_x(\boldsymbol{r}) = 0 \, \forall \boldsymbol{r}$]; $j_\rho(\boldsymbol{c}(\boldsymbol{r}))$ is the net current of reaction $\rho > 0$ given by the difference between the forward $\omega_\rho(\boldsymbol{c}(\boldsymbol{r})) \geq 0$ and backward $\omega_{-\rho}(\boldsymbol{c}(\boldsymbol{r})) \geq 0$ reaction flux,

$$j_\rho(\boldsymbol{c}(\boldsymbol{r})) = \omega_\rho(\boldsymbol{c}(\boldsymbol{r})) - \omega_{-\rho}(\boldsymbol{c}(\boldsymbol{r})); \quad (16)$$

$\boldsymbol{J}_i(\boldsymbol{c}(\boldsymbol{r}))$ is the diffusion current of species i. For the sake of compactness, we omit the time-dependence of any function [see for instance the concentration fields in Eq. (15)].

Remark. Note that we implicitly assumed that the concentration fields of the chemical species are large enough that their dynamics becomes deterministic.[43]

A. Steady state

The steady-state solutions of the RD equation (15), i.e., $\partial_t \boldsymbol{c}(\boldsymbol{r}) = 0$, if they exist, can be classified as either equilibrium or nonequilibrium steady states. Equilibrium steady states $\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})$ satisfy

$$j_\rho(\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})) = 0 \quad \text{and} \quad \boldsymbol{J}_i(\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})) = 0, \quad (17)$$

for all $\rho \in \mathcal{R}$, $i \in \mathcal{S}$, and $\boldsymbol{r} \in V$. When the RD dynamics admits well-defined equilibrium steady states, RD systems are said to be *detailed balanced*. Nonequilibrium steady states $\boldsymbol{c}_{\text{ss}}(\boldsymbol{r})$ are characterized by

$$j_\rho(\boldsymbol{c}_{\text{ss}}(\boldsymbol{r})) \neq 0 \quad \text{and/or} \quad \boldsymbol{J}_i(\boldsymbol{c}_{\text{ss}}(\boldsymbol{r})) \neq 0, \quad (18)$$

for some $\rho \in \mathcal{R}$ and/or $i \in \mathcal{S}$.

If the steady-state concentration fields are constant for every $\boldsymbol{r} \in V$, they are said to be *homogeneous* and represented by $\boldsymbol{c}_{\text{eq}}^{\text{h}}$ and $\boldsymbol{c}_{\text{ss}}^{\text{h}}$ for equilibrium and nonequilibrium steady states, respectively. In general, steady-state concentration fields are $\boldsymbol{r}$-dependent and are said to be *inhomogeneous*. Also, equilibrium steady states can be inhomogeneous when chemical species interact (as predicted by the Cahn–Hilliard[1] and Flory–Huggins[3,4] theories).

B. Conservation laws

The conservation laws[10,44,45] of the RD dynamics (15) (labeled $\lambda \in \Lambda$) are linearly independent left-null eigenvectors $\boldsymbol{\ell}^\lambda = (\ldots, \ell_i^\lambda, \ldots)$ of the stoichiometric matrix, namely,

$$\sum_i \ell_i^\lambda S_{i,\rho} = 0 \quad \forall \rho. \quad (19)$$

They physically identify fragments of (or entire) molecules, called moieties, that remain unaltered by the chemical reactions and the diffusion processes: they are transferred from one species to another via the chemical reactions and from one point in space to another via the diffusion processes. Indeed, the moiety abundances, given by

$$L^\lambda[\boldsymbol{c}] = \sum_i \ell_i^\lambda \int_V d\boldsymbol{r}\, c_i(\boldsymbol{r}), \qquad (20)$$

are conserved by the RD dynamics (15) in closed RD systems [i.e., when $I_i(\boldsymbol{r}) = 0 \,\forall i$],

$$d_t L^\lambda[\boldsymbol{c}] = \sum_{\rho>0} \underbrace{\sum_i \ell_i^\lambda S_{i,\rho}}_{=0} \int_V d\boldsymbol{r}\, j_\rho(\boldsymbol{c}(\boldsymbol{r}))$$

$$- \sum_i \ell_i^\lambda \underbrace{\int_V d\boldsymbol{r}\, \nabla \cdot \boldsymbol{J}_i(\boldsymbol{c}(\boldsymbol{r}))}_{=0} = 0, \qquad (21)$$

where we used the definition of conservation law in Eq. (19) and the fact that the volume V has impermeable walls, i.e., $\int_V d\boldsymbol{r}\, \nabla \cdot \boldsymbol{J}_i(\boldsymbol{c}(\boldsymbol{r})) = 0$. Note that there is always at least the conservation law $\boldsymbol{\ell}^m = (\dots, m_i, \dots)$ (with m_i being the molecular mass of species i) since the total mass is conserved by the chemical reactions. Furthermore, the set of conservation laws $\{\boldsymbol{\ell}\}$ is not unique: a linear combination of conservation laws is still a conservation law. Different sets (i.e., different representations) identify different moieties.

In open RD systems, when the Y species are chemostatted, conservation laws are split into unbroken and broken conservation laws,[35,45] labeled $\lambda_u \in \Lambda_u$ and $\lambda_b \in \Lambda_b$, respectively (this splitting will be crucial in Subsection IV D to identify the energetic cost of breaking the detailed balance condition and maintaining RD systems out of equilibrium). The unbroken conservation laws are the largest subset of conservation laws that can be written with null entries for the chemostatted species, i.e., $\ell_y^{\lambda_u} = 0 \;\forall y$ and $\forall \lambda_u$, and hence, $\sum_x \ell_x^{\lambda_u} S_{x,\rho} = 0$. They identify moieties that are carried by the internal species only and, consequently, are not exchanged with the chemostats. The corresponding abundances are still conserved,

$$d_t L^{\lambda_u}[\boldsymbol{c}] = \sum_y \ell_y^{\lambda_u} \int_V d\boldsymbol{r}\, I_y(\boldsymbol{r}) = 0, \qquad (22)$$

despite the RD system being open. The broken conservation laws are the other conservation laws: $\Lambda_b = \Lambda \backslash \Lambda_u$. They identify moieties that are carried by the chemostatted species too and, consequently, are exchanged with the chemostats. The corresponding abundances are, in general, not conserved,

$$d_t L^{\lambda_b}[\boldsymbol{c}] = \sum_y \underbrace{\ell_y^{\lambda_b}}_{\neq 0} \int_V d\boldsymbol{r}\, I_y(\boldsymbol{r}) \neq 0. \qquad (23)$$

Note that open RD systems have always at least one broken conservation law since the total mass is not conserved by the exchange processes and, consequently, $\boldsymbol{\ell}^m$ is broken.

In Subsection IV D, we will use the unbroken conservation laws to quantify the free energy exchanged between RD systems and

chemostats. To this aim, it is important to recognize that chemostatting a species does not always break a conservation law.[10,35] Hence, the set of chemostatted species Y (and the set of the corresponding chemostats) can be split into two disjoint subsets.

The potential species (labeled $y_p \in Y_p$) are the smallest subset of chemostatted species such that all conservation laws $\{\boldsymbol{\ell}^{\lambda_b}\}$ with $\lambda_b \in \Lambda_b$ are broken. Crucially, there is always a representation of the broken conservation laws such that each corresponding moiety is exchanged with only one potential chemostat. Indeed, the matrix (see the graphical representation in Fig. 2) whose entries are $\{\ell_{y_p}^{\lambda_b}\}$ (with $\lambda_b \in \Lambda_b$ and $y_p \in Y_p$) is square and invertible[45,46] and, by labeling $\{\overline{\ell}_{\lambda_b}^{y_p}\}$ the entries of the inverse matrix, the broken conservation laws can be represented in terms of the following linear combination as:

$$\sum_{\lambda_b} \overline{\ell}_{\lambda_b}^{y_p} \, \boldsymbol{\ell}^{\lambda_b}. \qquad (24)$$

The abundance of each moiety in this representation,

$$M_{y_p}[\boldsymbol{c}] = \sum_i \sum_{\lambda_b} \overline{\ell}_{\lambda_b}^{y_p} \ell_i^{\lambda_b} \int_V d\boldsymbol{r}\, c_i(\boldsymbol{r}), \qquad (25)$$

where i runs over all species $\mathcal{S}$, changes [according to the RD equation (15)] only because of the exchanges with one specific potential chemostat,

$$d_t M_{y_p}[\boldsymbol{c}] = \sum_{y_p'} \underbrace{\sum_{\lambda_b} \overline{\ell}_{\lambda_b}^{y_p} \ell_{y_p'}^{\lambda_b}}_{=\mathbb{1}_{y_p,y_p'}} \int_V d\boldsymbol{r}\, I_{y_p'}(\boldsymbol{r}) = \int_V d\boldsymbol{r}\, I_{y_p}(\boldsymbol{r}), \qquad (26)$$

if all chemostatted species are potential species, i.e., $Y = Y_p$. This allows us to label each moiety in Eq. (25) using the label of the chemostat it is exchanged with, i.e., y_p, rather than the label of the corresponding broken conservation law, i.e., λ_b. Note that Eq. (26) specializes Eq. (23) for open RD systems with only potential chemostatted species and with the conservation laws expressed according to the representation in Eq. (24). We emphasize that the representation in Eq. (24) will be the one used to quantify the free energy exchanged between RD systems and chemostats by entering the definition of the thermodynamic potential in Eq. (42).

The force species ($y_f \in Y_f$) are the other chemostatted species: $Y_f = Y \backslash Y_p$. The corresponding chemostats exchange moieties that are already exchanged with the potential chemostats. Indeed, in general, the abundance of each moiety in the representation given in Eq. (24) changes according to

$$d_t M_{y_p}[\boldsymbol{c}] = \int_V d\boldsymbol{r}\, I_{y_p}(\boldsymbol{r}) + \sum_{y_f} \sum_{\lambda_b} \overline{\ell}_{\lambda_b}^{y_p} \ell_{y_f}^{\lambda_b} \int_V d\boldsymbol{r}\, I_{y_f}(\boldsymbol{r}), \qquad (27)$$

using Eqs. (15) and (25) and the splitting $Y = Y_p \bigcup Y_f$. Hence, chemostatting the force species (after the potential species were already chemostatted) does not break any new conservation law but creates a flux of the same moiety between different chemostats. The energetic cost of sustaining these fluxes will enter the definition of the nonconservative work in Eq. (43).
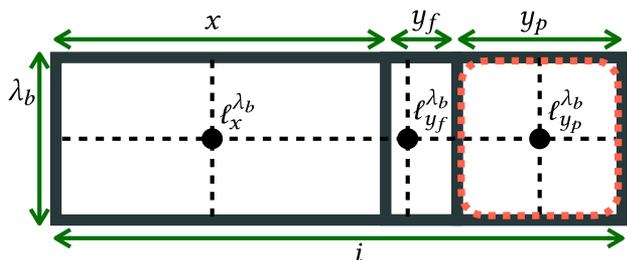
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FIG. 2. Representation of the matrix with entries $\{\ell_i^{\lambda_b}\}$, where λ_b is the row index and i is the column index (namely, the matrix constructed using the broken conservation laws $\{\ell^{\lambda_b}\}$ as rows). The matrix column (respectively, the entries) can be further specialized into those corresponding to the internal species x (respectively, $\ell_x^{\lambda_b}$), force chemostatted species y_f (respectively, $\ell_{y_f}^{\lambda_b}$), and potential chemostatted species y_p (respectively, $\ell_{y_p}^{\lambda_b}$). The submatrix with entries $\{\ell_{y_p}^{\lambda_b}\}$ (red dotted line) is square and invertible,[45,46] and we label $\{\bar{\ell}_{\lambda_b}^{y_p}\}$ the entries of the inverse matrix where y_p is the row index and λ_b is the column index.

C. Example

An RD system with the chemical species and reactions introduced in Subsection II B admits only one conservation law (see the stoichiometric matrix in Fig. 1), i.e.,

$$\ell = \begin{matrix} X_1 \\ Y_3 \\ Y_2 \\ Y_1 \end{matrix} \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \end{pmatrix}. \tag{28}$$
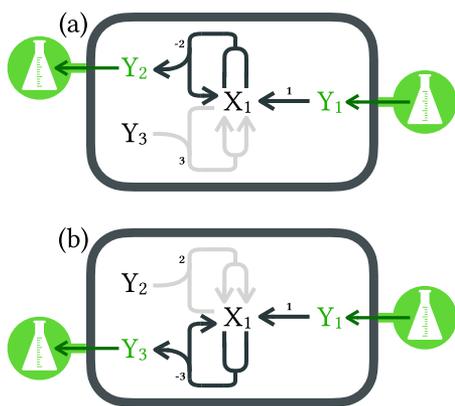

FIG. 3. Illustration of the sequences of reactions transferring the same moiety from a potential chemostat to a force chemostat (for an RD system with the chemical species and reactions introduced in Subsection II B). (a) When only the species Y_1 and Y_2 are chemostatted, the moiety can be injected into the RD system by a chemostat as the species Y_1, transferred via the sequence of reaction $\{1, -2\}$ to the species Y_2, and finally extracted from the RD system by a different chemostat as the species Y_2. (b) When only the species Y_1 and Y_3 are chemostatted, the moiety can be injected into the RD system by a chemostat as the species Y_1, transferred via the sequence of reaction $\{1, -3\}$ to the species Y_3, and finally extracted from the RD system by a different chemostat as the species Y_3. Note that when all three species $\{Y_1, Y_2, Y_3\}$ are chemostatted, the same moiety can be transferred between each pair of chemostats.

This physically means that all species $\{X_1, Y_1, Y_2, Y_3\}$ are made of the same atoms, namely, the same moiety. Therefore, $L[c] = \int_V d\boldsymbol{r}\, (c_{X_1}(\boldsymbol{r}) + c_{Y_1}(\boldsymbol{r}) + c_{Y_2}(\boldsymbol{r}) + c_{Y_3}(\boldsymbol{r}))$ is conserved if no species are chemostatted. By chemostatting just one of the species $\{Y_1, Y_2, Y_3\}$, the conservation law is broken. Hence, any of the species $\{Y_1, Y_2, Y_3\}$ can be chosen as a potential species. We choose Y_1. By chemostatting another species, for instance, Y_2, no conservation law is broken. Hence, Y_2 is a force species and the same moiety is exchanged between two different chemostats as illustrated in Fig. 3. Note that this implies that the matrix with entries $\{\ell_{y_p}^{\lambda_b}\}$ has just one entry corresponding to $\ell_{Y_1}^{\lambda_b} = 1$ and that the conservation law in Eq. (28) is already written in the representation given in Eq. (24).

IV. THERMODYNAMICS

We now develop a nonequilibrium thermodynamic theory for open RD systems of interacting chemical species undergoing the RD dynamics (15) by combining the thermodynamics of noninteracting (i.e., ideal) RD systems[10,11] and interacting (i.e., non-ideal) CRNs.[35]

A. Nonequilibrium free energy

Nonequilibrium thermodynamics presumes that all degrees of freedom other than concentration fields are equilibrated (e.g., the temperature T and the volume V are fixed, while the fields responsible for the interactions, e.g., electrostatic fields, relax instantaneously to mean-field values depending on the concentration fields only). In this framework, the nonequilibrium Helmholtz free energy $F[c]$ of RD systems can be specified by its equilibrium form, but as a functional of the nonequilibrium concentration fields. Furthermore, $F[c]$ can always be written as the sum of an *ideal* and a *non-ideal* contribution,

$$F[c] = F^{id}[c] + F^{ni}[c]. \tag{29}$$

Here, the ideal term $F^{id}[c]$ is the ideal solution Helmholtz free energy, while the non-ideal term $F^{ni}[c]$ accounts for the interactions between the chemical species.

The free energy contribution of each chemical species is specified by the chemical potential as

$$\mu_i(\boldsymbol{c}(\boldsymbol{r})) = \frac{\delta F[c]}{\delta c_i(\boldsymbol{r})} = \mu_i^{id}(c_i(\boldsymbol{r})) + RT \ln \gamma_i(\boldsymbol{c}(\boldsymbol{r})), \tag{30}$$

where $\mu_i^{id}(c_i(\boldsymbol{r}))$ is the ideal chemical potential,

$$\mu_i^{id}(c_i(\boldsymbol{r})) = \mu_i^\circ + RT \ln c_i(\boldsymbol{r}), \tag{31}$$

with μ_i° being the standard chemical potential, R being the gas constant, and $\gamma_i(\boldsymbol{c}(\boldsymbol{r}))$ being the activity coefficient accounting for the interactions,

$$RT \ln \gamma_i(\boldsymbol{c}(\boldsymbol{r})) = \frac{\delta F^{ni}[c]}{\delta c_i(\boldsymbol{r})}. \tag{32}$$

Note that the ideal free energy $F^{id}[c]$ reads[10,11]

$$F^{id}[c] = \sum_i \int_V d\boldsymbol{r}\, \left(\mu_i^{id}(c_i(\boldsymbol{r})) - RT \right) c_i(\boldsymbol{r}). \tag{33}$$

B. Thermodynamic consistency of the RD dynamics

We start by introducing the entropy production rate as

$$\dot{\Sigma}[\boldsymbol{c}] \equiv \dot{\Sigma}_{\text{rct}}[\boldsymbol{c}] + \dot{\Sigma}_{\text{dff}}[\boldsymbol{c}], \tag{34}$$

that quantifies the dissipation resulting from the changes in chemical potentials caused by the two types of processes occurring in the system, namely, reactions and diffusion,

$$T\dot{\Sigma}_{\text{rct}}[\boldsymbol{c}] \equiv -\sum_i \sum_{\rho>0} \int_V d\boldsymbol{r}\, \mu_i(\boldsymbol{c}(\boldsymbol{r})) S_{i,\rho} j_\rho(\boldsymbol{c}(\boldsymbol{r})), \tag{35a}$$

$$T\dot{\Sigma}_{\text{dff}}[\boldsymbol{c}] \equiv -\sum_i \int_V d\boldsymbol{r}\, \nabla\mu_i(\boldsymbol{c}(\boldsymbol{r})) \cdot \boldsymbol{J}_i(\boldsymbol{c}(\boldsymbol{r})). \tag{35b}$$

The central assumption ensuring thermodynamic consistency of the RD dynamics is that the reaction fluxes $\omega_{\pm\rho}(\boldsymbol{c}(\boldsymbol{r}))$ satisfy the local detailed balance condition,

$$RT \ln \frac{\omega_\rho(\boldsymbol{c}(\boldsymbol{r}))}{\omega_{-\rho}(\boldsymbol{c}(\boldsymbol{r}))} = -\left(\sum_x \mu_x(\boldsymbol{c}(\boldsymbol{r})) S_{x,\rho} + \sum_y \mu_y(\boldsymbol{c}(\boldsymbol{r})) S_{y,\rho} \right), \tag{36}$$

resulting from the macroscopic limit[43] of the local detailed balance condition of stochastic thermodynamics[47] when applied to CRNs.[46,48] We further assume that the diffusion current $\boldsymbol{J}_i(\boldsymbol{c}(\boldsymbol{r}))$ of each species is treated within a linear regime and expressed as

$$\boldsymbol{J}_i(\boldsymbol{c}(\boldsymbol{r})) = -\sum_j O_{i,j}(\boldsymbol{c}(\boldsymbol{r})) \nabla\mu_j(\boldsymbol{c}(\boldsymbol{r})), \tag{37}$$

where $\{O_{i,j}(\boldsymbol{c}(\boldsymbol{r}))\}$ are the entries of the positive-definite Onsager matrix $\mathbb{O}(\boldsymbol{c}(\boldsymbol{r}))$.[49] Using these two assumptions in Eqs. (36) and (37), we see that the two entropy production rates in Eq. (35) can be rewritten in a manifestly non-negative form,

$$T\dot{\Sigma}_{\text{rct}}[\boldsymbol{c}] = \int_V d\boldsymbol{r} \underbrace{RT \sum_{\rho>0} j_\rho(\boldsymbol{c}(\boldsymbol{r})) \ln \frac{\omega_\rho(\boldsymbol{c}(\boldsymbol{r}))}{\omega_{-\rho}(\boldsymbol{c}(\boldsymbol{r}))}}_{\equiv T\dot{\sigma}_{\text{rct}}(\boldsymbol{r}) \geq 0} \geq 0, \tag{38a}$$

$$T\dot{\Sigma}_{\text{dff}}[\boldsymbol{c}] = \int_V d\boldsymbol{r} \underbrace{\sum_{i,j} \nabla\mu_i(\boldsymbol{c}(\boldsymbol{r})) \cdot O_{i,j}(\boldsymbol{c}(\boldsymbol{r})) \nabla\mu_j(\boldsymbol{c}(\boldsymbol{r}))}_{\equiv T\dot{\sigma}_{\text{dff}}(\boldsymbol{r}) \geq 0} \geq 0, \tag{38b}$$

where the equality sign is achieved only at equilibrium (17).

The change in free energy (29) in closed RD systems, using Eq. (15) [when $I_i(\boldsymbol{r}) = 0 \,\forall i$] and integrating by parts, gives the second law of thermodynamics for closed RD systems,

$$d_t F[\boldsymbol{c}] = -T\dot{\Sigma}[\boldsymbol{c}] \leq 0. \tag{39}$$

With the additional assumption that the free energy in Eq. (29) is lower bounded, $F[\boldsymbol{c}]$ becomes a thermodynamic potential acting as a Lyapunov function of the RD dynamics (15). This ensures thermodynamic consistency, namely, closed RD systems always relax toward an equilibrium steady state.

Remark. In Eqs. (38a) and (38b), we introduced the densities of reaction $\dot{\sigma}_{\text{rct}}(\boldsymbol{r})$ and diffusion $\dot{\sigma}_{\text{dff}}(\boldsymbol{r})$ entropy production rate,

respectively. They are non-negative for every $\boldsymbol{r} \in V$ and vanish only at equilibrium (17). The density of reaction entropy production rate can be also split into the non-negative contribution of each reaction $\dot{\sigma}_\rho(\boldsymbol{r}) \geq 0$: $\dot{\sigma}_{\text{rct}}(\boldsymbol{r}) = \sum_{\rho>0} \dot{\sigma}_\rho(\boldsymbol{r})$.

Remark. The expressions of entropy production rates in Eqs. (38a) and (38b) together with the local detailed balance condition (36) and $\mathbb{O}(\boldsymbol{c}(\boldsymbol{r}))$ being a positive-definite matrix imply that the thermodynamic equilibrium conditions, $\dot{\Sigma}_{\text{rct}}[\boldsymbol{c}_{\text{eq}}] = 0$ and $\dot{\Sigma}_{\text{dff}}[\boldsymbol{c}_{\text{eq}}] = 0$, are equivalent to

$$\sum_i \mu_i(\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})) S_{i,\rho} = 0, \tag{40a}$$

$$\nabla\mu_i(\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})) = 0, \tag{40b}$$

for all $\boldsymbol{r} \in V$, for all $\rho \in \mathcal{R}$, and for all $i \in \mathcal{S}$. The equilibrium conditions in Eq. (40) can also be derived by minimizing the free energy (29) as done in Appendix A.

C. Chemostats

Thermodynamically, chemostats control the chemical potentials $\mu_y(\boldsymbol{c}(\boldsymbol{r}))$ of the chemostatted species in every point of space $\boldsymbol{r} \in V$, which can, thus, be treated as (in general, $\boldsymbol{r}$- and time-dependent) control parameters, i.e., $\{\mu_y(\boldsymbol{r})\}$. In ideal RD systems, where the chemical potentials are given in Eq. (31), chemostats control the concentration fields of the chemostatted species too: $c_y(\boldsymbol{r}) = \exp((\mu_y(\boldsymbol{r}) - \mu_y^\circ)/RT)$. The exchange current $I_y(\boldsymbol{r})$ in Eq. (15) represents the physical mechanism implementing this control. In non-ideal RD systems, where the chemical potentials are given in Eq. (30), controlling the chemical potentials of the chemostatted species does not univocally determine their concentrations because of the interactions.[35]

D. Second law for open RD systems

Using the expression for the entropy production rate in Eq. (34), together with the splitting of the conservation laws in broken and unbroken as well as the splitting of the chemostatted species into potential and force species, the second law of thermodynamics for open RD systems can now be rewritten as

$$T\dot{\Sigma}[\boldsymbol{c}] = -d_t \mathcal{F}[\boldsymbol{c}] + \dot{W}_{\text{nc}}[\boldsymbol{c}] + \dot{W}_{\text{driv}}[\boldsymbol{c}] \geq 0. \tag{41}$$

This can be checked by direct substitution of the different terms on the right-hand side that we now define together with the RD equation (15).

The semigrand Helmholtz free energy $\mathcal{F}[\boldsymbol{c}]$ is the proper thermodynamic potential of open RD systems. It reads

$$\mathcal{F}[\boldsymbol{c}] = F[\boldsymbol{c}] - \sum_{y_p} \mu_{y_p}^{\text{ref}} M_{y_p}[\boldsymbol{c}] \tag{42}$$

and is obtained, in analogy to equilibrium thermodynamics when passing from the canonical to the grand canonical ensembles, from the Helmholtz free energy (29) by removing the energetic contribution of the matter exchanged with the chemostats. The latter

accounts for the abundances of the moieties $\{M_{y_p}[\boldsymbol{c}]\}$, given in Eq. (25), times a reference value of chemical potentials of the potential species $\{\mu_{y_p}^{\text{ref}}\}$, controlled by the corresponding chemostats. If the potential chemostats impose different values of the chemical potentials $\{\mu_{y_p}(\boldsymbol{r})\}$ in different $\boldsymbol{r} \in V$, then the reference chemical potential $\{\mu_{y_p}^{\text{ref}}\}$ can be chosen arbitrarily among these values. This is equivalent to choosing a reference equilibrium steady state $\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})$ satisfying $\mathcal{F}[\boldsymbol{c}_{\text{eq}}] \le \mathcal{F}[\boldsymbol{c}]$ as discussed in Appendix B.

The nonconservative work rate

$$\dot{W}_{\text{nc}}[\boldsymbol{c}] = \int_V d\boldsymbol{r} \underbrace{\sum_y f_y^{\text{nc}}(\boldsymbol{r}) I_y(\boldsymbol{r})}_{\equiv \dot{w}_{\text{nc}}(\boldsymbol{r})} \tag{43}$$

quantifies the energetic cost for sustaining fluxes of the same moiety between chemostats with different chemical potentials by means of the nonconservative forces,

$$f_y^{\text{nc}}(\boldsymbol{r}) \equiv \mu_y(\boldsymbol{r}) - \sum_{y_p, \lambda_b} \mu_{y_p}^{\text{ref}} \, \overline{\ell}_{\lambda_b}^{y_p} \, \ell_y^{\lambda_b}. \tag{44}$$

These forces emerge in two cases. When $\mu_{y_p}(\boldsymbol{r}) \ne \mu_{y_p}^{\text{ref}}$ (because $\sum_{\lambda_b} \overline{\ell}_{\lambda_b}^{y_p} \ell_{y_{p'}}^{\lambda_b} = \mathbb{1}_{y_p, y_{p'}}$), the forces $f_{y_p}^{\text{nc}}(\boldsymbol{r})$ correspond to diffusive forces that can be present even in the absence of chemical reactions.[10] They arise because the potential chemostats y_p impose values of the chemical potential that are different from the reference equilibrium ones $\mu_{y_p}^{\text{ref}}$ (see Appendix B). When $\mu_{y_f}(\boldsymbol{r}) \ne \sum_{y_p, \lambda_b} \mu_{y_p}^{\text{ref}} \, \overline{\ell}_{\lambda_b}^{y_p} \, \ell_{y_f}^{\lambda_b}$, the forces $f_{y_f}^{\text{nc}}(\boldsymbol{r})$ correspond to chemical forces that can also be present in homogeneous systems.[35] They arise because force chemostats y_f impose chemical potentials that are different from the one they would have if all reactions were equilibrated $\sum_{y_p, \lambda_b} \mu_{y_p}^{\text{ref}} \, \overline{\ell}_{\lambda_b}^{y_p} \, \ell_{y_f}^{\lambda_b}$ (see Appendix B).

The driving work rate reads

$$\dot{W}_{\text{driv}}[\boldsymbol{c}] = -\sum_{y_p} \left(d_t \mu_{y_p}^{\text{ref}} \right) M_{y_p}[\boldsymbol{c}] \tag{45}$$

and quantifies the energetic cost of the time-dependent changes of the reference chemical potentials $\{\mu_{y_p}^{\text{ref}}\}$ (with $y_p \in Y_p$) defining the reference equilibrium to which the open RD system would relax if the nonconservative forces vanished.

Physically, the second law (41) expresses (and quantifies) the different sources of free energy [on the right-hand side of Eq. (41)] that can balance dissipation [on the left-hand side of Eq. (41)] and, hence, maintain open RD systems out of equilibrium. Let us illustrate this point by considering three simple cases.

First, when the chemical potentials of the chemostatted species are independent of time and such that $f_y^{\text{nc}}(\boldsymbol{r}) = 0$ (which also implies homogeneous chemostatting), both work contributions vanish and the second law (41) reduces to $d_t \mathcal{F}[\boldsymbol{c}] = -T\dot{\Sigma}[\boldsymbol{c}] \le 0$. This, together with $\mathcal{F}[\boldsymbol{c}]$ being lower bounded (as shown in Appendix B), implies that the RD system relaxes to equilibrium while minimizing $\mathcal{F}[\boldsymbol{c}]$ that serves as a Lyapunov function. This RD system is, therefore, detailed balanced despite being open. As shown in Appendix B, the specific equilibrium steady state $\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})$ to which the RD system

relaxes is defined by the chemical potentials $\{\mu_{y_p}^{\text{ref}}\}$ and the abundances $\{L^{\lambda_u}[\boldsymbol{c}]\}$. If self-organized structures emerged, i.e., the concentrations $\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})$ are not homogeneous, they would be sustained by a passive mechanism that does not dissipate.

Second, when the chemical potentials of the chemostatted species are dependent on time but $f_y^{\text{nc}}(\boldsymbol{r}) = 0$ still holds, only the nonconservative work rate vanishes from the second law (41), namely, $T\dot{\Sigma}[\boldsymbol{c}] = -d_t \mathcal{F}[\boldsymbol{c}] + \dot{W}_{\text{driv}}[\boldsymbol{c}] \ge 0$, and the RD system is still detailed balanced. Indeed, if the time dependence is very slow, the RD system will quasi-statically follow the changing equilibrium state. For faster time dependence, the RD system will be prevented from reaching equilibrium.

Third, when the chemical potentials of the chemostatted species are independent of time but $f_y^{\text{nc}}(\boldsymbol{r}) \ne 0$, detailed balance is broken and the second law (41) reduces to $T\dot{\Sigma}[\boldsymbol{c}] = -d_t \mathcal{F}[\boldsymbol{c}] + \dot{W}_{\text{nc}}[\boldsymbol{c}] \ge 0$. If the RD system eventually reaches a nonequilibrium steady state, the second law is further reduced to $T\dot{\Sigma}[\boldsymbol{c}_{\text{ss}}] = \dot{W}_{\text{nc}}[\boldsymbol{c}_{\text{ss}}] \ge 0$. In this case, $\dot{W}_{\text{nc}}[\boldsymbol{c}_{\text{ss}}]$ quantifies the net free energy intake by the open RD system that is dissipated to maintain the system in a nonequilibrium steady state.

E. Example

We consider the RD system with the chemical species and reactions introduced in Subsection II B and with the chemostats imposing $\boldsymbol{r}$-dependent chemical potentials $\mu_{Y_1}(\boldsymbol{r})$, $\mu_{Y_2}(\boldsymbol{r})$, and $\mu_{Y_3}(\boldsymbol{r})$. We choose Y_1 as a potential species (as discussed in Subsection III C) and one of the values of $\mu_{Y_1}(\boldsymbol{r})$ as a reference chemical potential $\mu_{Y_1}^{\text{ref}}$. The corresponding nonconservative work rate [whose general expression is given in Eq. (43)] specializes into the sum of three contributions,

$$\begin{aligned} \dot{W}_{\text{nc}}[\boldsymbol{c}] = & \int_V d\boldsymbol{r} \, (\mu_{Y_1}(\boldsymbol{r}) - \mu_{Y_1}^{\text{ref}}) I_{Y_1}(\boldsymbol{r}) \\ & + \int_V d\boldsymbol{r} \, (\mu_{Y_2}(\boldsymbol{r}) - \mu_{Y_1}^{\text{ref}}) I_{Y_2}(\boldsymbol{r}) \\ & + \int_V d\boldsymbol{r} \, (\mu_{Y_3}(\boldsymbol{r}) - \mu_{Y_1}^{\text{ref}}) I_{Y_3}(\boldsymbol{r}), \end{aligned} \tag{46}$$

where we used the broken conservation law in Eq. (28). The first contribution results from applying different chemical potentials to the species Y_1. The second (respectively, third) contribution results from applying different chemical potentials to the same moiety carried by both the species Y_1 and Y_2 (respectively, Y_3) as illustrated in Fig. 3.

Note that the nonconservative work in Eq. (46) is not the excess work introduced in Refs. 50 and 51, even though the two expressions might look similar. The difference between the actual chemical potential and a reference one features both expressions. This reference chemical potential is the steady state one in the excess work, while it takes the equilibrium value imposed by the potential chemostats in the nonconservative work. Furthermore, also a current multiplying the difference between chemical potentials features the expression of both works. This current is the total time derivative of a species concentration in the excess work, while it is the exchange current with the chemostat in the non-nonconservative work. Indeed, the excess work is not directly related to the evolution of the semigrand free energy (42) via the second law (41), but rather

to the evolution of the kinetic potential in Eq. (71) in homogeneous systems.

V. THERMODYNAMIC PROPERTIES OF ACTIVE SELF-ORGANIZATION–EXACT RESULTS

The RD dynamics might reach a steady state where the chemical species are inhomogeneous. We now use the thermodynamic theory introduced in Sec. IV to prove that for two classes of CRNs, namely, pseudo detailed balanced (Subsection V A) and complex balanced (Subsection V B) discussed in Fig. 4, stationary concentration profiles are determined by the minimization of appropriately constructed kinetic potentials acting as Lyapunov functions, when the chemical potentials $\{\mu_y\}$ of the chemostatted species are homogeneous and constant in time. Furthermore, for both classes of CRNs, diffusion processes always equilibrate, which implies that the chemical potentials become homogeneous at a steady state. In addition, for pseudo-detailed CRNs only, the transient dynamics and steady-state concentration fields can be exactly simulated also in reaction–diffusion systems relaxing toward equilibrium with appropriately constructed chemical potentials.

The proofs of this result are derived in Subsections V A and V B by assuming that the chemostatted species are ideal, i.e., they do not interact with the internal species, for the sake of simplicity. We can, thus, treat both $\{\mu_y\}$ and $\{c_y\}$ [related via Eq. (31)] as control parameters. We generalize our result to non-ideal chemostatted species in Subsection V C.

A. Pseudo detailed balanced CRNs

We define CRNs as pseudo detailed balanced when their stoichiometric matrix for the internal species and lumped reactions does not admit any right-null eigenvector. Namely, there is no $\{\phi_\varepsilon\}$ such that

$$\sum_{\varepsilon>0} S_{x,\varepsilon}\, \phi_\varepsilon = 0. \qquad (47)$$

We now show that the RD dynamics of pseudo detailed balanced CRNs is driven by the minimization of a kinetic potential and relaxes to a steady state $c_{ss}(r)$ characterized by a vanishing diffusion
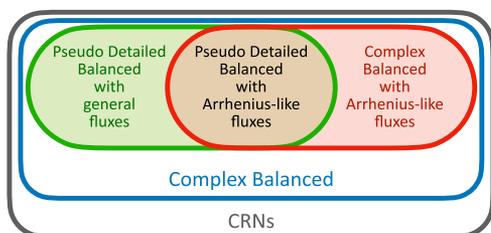

FIG. 4. The gray box represents the set of all possible CRNs endowed with all possible reaction fluxes. The blue box, a subset of the gray box, represents the set of all possible complex balanced CRNs endowed with all possible reaction fluxes. Pseudo detailed balanced CRNs are always a subset of complex balanced CRNs. In Sec. V, we consider pseudo detailed balanced CRNs with reaction fluxes of general form (green oval) and complex balanced CRNs with Arrhenius-like reaction fluxes (red oval).

entropy production rate, i.e., $\dot{\Sigma}_{\mathrm{diff}}[c_{ss}] = 0$, independently of whether the concentration fields are homogeneous or inhomogeneous.

Assumption. We consider reaction fluxes of the general form as

$$\omega_\rho(c(r)) = k_\rho \omega_{\mathrm{in}}(c(r), \{v_{x,\rho}\}) \omega_{\mathrm{ch}}(\{c_y\}, \{v_{y,\rho}\}), \qquad (48)$$

namely, the concentration dependence of each flux $\omega_\rho(c(r))$ is univocally determined by the stoichiometric coefficients via the unspecified functions $\omega_{\mathrm{in}}(c(r), \{v_{x,\rho}\})$ and $\omega_{\mathrm{ch}}(\{c_y\}, \{v_{y,\rho}\})$. The latter depends only on the concentrations of chemostatted species because they are assumed to be ideal. Here, k_ρ is an unspecified constant parameter. For example, mass-action fluxes,[52,53] and Arrhenius-like fluxes satisfy Eq. (48). Note that, while the latter read

$$\omega_\rho(c(r)) = A_\rho\, e^{\frac{\sum_x \mu_x(c(r)) v_{x,\rho}}{RT}}\, e^{\frac{\sum_y \mu_y v_{y,\rho}}{RT}}, \qquad (49)$$

with $A_\rho = A_{-\rho}$ being a constant parameter, the fluxes in Eq. (48) can in general account for a concentration-dependent A_ρ.

Proof. We start by using $S_{x,\rho} = S_{x,\varepsilon}\ \forall \rho \in \mathcal{R}_\varepsilon$ to rewrite the contribution due to the chemical reactions in Eq. (15) for the internal species as

$$\sum_{\rho>0} S_{x,\rho}\, j_\rho(c(r)) = \sum_{\varepsilon>0} S_{x,\varepsilon} \hat{j}_\varepsilon(c(r)), \qquad (50)$$

with

$$\hat{j}_\varepsilon(c(r)) = \sum_{\rho \in \mathcal{R}_\varepsilon} \{\omega_\rho(c(r)) - \omega_{-\rho}(c(r))\} \qquad (51)$$

being the lumped reaction ε net current. By writing now each reaction flux $\omega_\rho(c(r))$ as the product between its symmetric part $s_\rho(c(r)) \equiv \sqrt{\omega_\rho(c(r))\omega_{-\rho}(c(r))} = s_{-\rho}(c(r))$ and its antisymmetric part $\sqrt{\omega_\rho(c(r))/\omega_{-\rho}(c(r))}$ specified by the local detailed balance condition (36), $\hat{j}_\varepsilon(c(r))$ becomes

$$\hat{j}_\varepsilon(c(r)) = a_\varepsilon(c(r))\left\{ e^{-\frac{\sum_x \mu_x(c(r)) S_{x,\varepsilon}}{2RT}} - b_\varepsilon e^{-\frac{\sum_x \mu_x(c(r)) S_{x,-\varepsilon}}{2RT}} \right\}, \qquad (52)$$

where we factorized

$$a_\varepsilon(c(r)) = \sum_{\rho \in \mathcal{R}_\varepsilon} s_\rho(c(r)) e^{-\frac{\sum_y \mu_y S_{y,\rho}}{2RT}} \geq 0, \qquad (53)$$

and the constant quantity is

$$b_\varepsilon = \frac{a_{-\varepsilon}(c(r))}{a_\varepsilon(c(r))} = \frac{\sum_{\rho \in \mathcal{R}_\varepsilon} s_\rho(c(r)) e^{-\frac{\sum_y \mu_y S_{y,-\rho}}{2RT}}}{\sum_{\rho \in \mathcal{R}_\varepsilon} s_\rho(c(r)) e^{-\frac{\sum_y \mu_y S_{y,\rho}}{2RT}}} \geq 0. \qquad (54)$$

This results from the fact that (i) the chemical potentials $\{\mu_y\}$, and the corresponding concentrations $\{c_y\}$, are homogeneous and constant, and (ii) the fluxes in $s_\rho(c(r))$ are univocally determined by the stoichiometric coefficients according to Eq. (48) with $v_{x,\rho} = v_{x,\varepsilon}\ \forall \rho \in \mathcal{R}_\varepsilon$.

We now use the pseudo detailed balanced condition. Since there are no right-null vectors of $S_{x,\varepsilon}$, we can always introduce the constant coefficients $\{\Delta_x\}$ such that

$$\ln b_\varepsilon = \sum_x \Delta_x S_{x,\varepsilon}/RT. \qquad (55)$$

Indeed, given the $n_x \times n_e$ matrix $\hat{\mathbb{S}}_X$ whose entries are $\{S_{x,\varepsilon}\}$ with $x \in X$, $\mathcal{E} \ni \varepsilon > 0$, $\mathrm{rank}(\hat{\mathbb{S}}_X) = n_e$. Therefore, the set of internal species can always be split into two disjoint sets X_I and X_D such that the matrix $\hat{\mathbb{S}}_{X_I}$ (with entries $\{S_{x,\varepsilon}\}$ with $x \in X_I$ and $\mathcal{E} \ni \varepsilon > 0$) is square and invertible. This leads to

$$\Delta_x = RT \sum_{\varepsilon > 0} \ln b_\varepsilon (\hat{\mathbb{S}}_{X_I}^{-1})_{\varepsilon,x} \quad \text{for} \quad x \in X_I, \qquad (56a)$$

$$\Delta_x = 0 \quad \text{for} \quad x \in X_D, \qquad (56b)$$

and allows us to write the lumped reaction ε net current (52) as

$$\hat{j}_\varepsilon(\boldsymbol{c}(\boldsymbol{r})) = \hat{\omega}_\varepsilon(\boldsymbol{c}(\boldsymbol{r})) - \hat{\omega}_{-\varepsilon}(\boldsymbol{c}(\boldsymbol{r})). \qquad (57)$$

Here, we introduced the lumped reaction $\pm\varepsilon$ fluxes that read

$$\hat{\omega}_{\pm\varepsilon}(\boldsymbol{c}(\boldsymbol{r})) \equiv a_{|\varepsilon|}(\boldsymbol{c}(\boldsymbol{r}))e^{\frac{\sum_x \Delta_x S_{x,|\varepsilon|}}{2RT}} e^{-\frac{\sum_x \hat{\mu}_x(\boldsymbol{c}(\boldsymbol{r}))S_{x,\pm\varepsilon}}{2RT}}, \qquad (58)$$

with $|-\varepsilon| = |\varepsilon| = \varepsilon > 0$, and satisfy a pseudo local detailed balance condition as

$$RT \ln \frac{\hat{\omega}_\varepsilon(\boldsymbol{c}(\boldsymbol{r}))}{\hat{\omega}_{-\varepsilon}(\boldsymbol{c}(\boldsymbol{r}))} = -\sum_x \hat{\mu}_x(\boldsymbol{c}(\boldsymbol{r}))S_{x,\varepsilon}, \qquad (59)$$

with the chemical potentials

$$\hat{\mu}_x(\boldsymbol{c}(\boldsymbol{r})) \equiv \mu_x(\boldsymbol{c}(\boldsymbol{r})) + \Delta_x. \qquad (60)$$

Note that Eq. (60) only implies a shift of the standard chemical potentials of the internal species $\{\mu_x^\circ\}$.

Up until now, we just re-wrote the lumped reaction net current $\hat{j}_\varepsilon(\boldsymbol{c}(\boldsymbol{r}))$ entering the RD equation (15) via Eq. (50) as in Eq. (57). However, this rewriting allows us to show that the potential $F_{\mathrm{pdb}}[\boldsymbol{c}]$, obtained from the free energy (29) of the RD system after applying the shift of the chemical potentials in Eq. (60), decreases in time during RD dynamics (15). Indeed, using $\mathrm{d}_t c_y = 0$, its time derivative reads

$$\mathrm{d}_t F_{\mathrm{pdb}}[\boldsymbol{c}] = -T\hat{\dot{\Pi}}_{\mathrm{rct}}[\boldsymbol{c}] - T\dot{\Sigma}_{\mathrm{dff}}[\boldsymbol{c}] \leq 0, \qquad (61)$$

where $\dot{\Sigma}_{\mathrm{dff}}[\boldsymbol{c}] \geq 0$ is given in Eq. (38b) (since $\nabla\mu_y = 0$) and, using Eq. (59),

$$T\hat{\dot{\Pi}}_{\mathrm{rct}}[\boldsymbol{c}] = RT \sum_{\varepsilon > 0} \int_V \mathrm{d}\boldsymbol{r}\, \hat{j}_\varepsilon(\boldsymbol{c}(\boldsymbol{r})) \ln \frac{\hat{\omega}_\varepsilon(\boldsymbol{c}(\boldsymbol{r}))}{\hat{\omega}_{-\varepsilon}(\boldsymbol{c}(\boldsymbol{r}))} \geq 0. \qquad (62)$$

This, together with the fact that $F_{\mathrm{pdb}}[\boldsymbol{c}]$ is lower bounded (since $F[\boldsymbol{c}]$ is lower bounded by assumption, see Subsection IV B), implies that the RD dynamics (15) of pseudo detailed balance CRNs must relax toward a steady state $\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})$ satisfying

$$\hat{\dot{\Pi}}_{\mathrm{rct}}[\boldsymbol{c}_{\mathrm{ss}}] = 0 \quad \text{and} \quad \dot{\Sigma}_{\mathrm{dff}}[\boldsymbol{c}_{\mathrm{ss}}] = 0, \qquad (63)$$

or equivalently

$$\sum_x (\mu_x(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) + \Delta_x)S_{x,\varepsilon} = 0 \quad \text{and} \quad \boldsymbol{J}_i(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) = 0, \qquad (64)$$

for all $\varepsilon > 0$ and for all i.   □

Let us now discuss the meaning and implications of Eqs. (63) and (64).

First, the mechanism underpinning the dynamics of pseudo detailed balanced CRNs as well as the emergence of self-organized dissipative structures is the minimization of $F_{\mathrm{pdb}}[\boldsymbol{c}]$, which plays the role of a Lyapunov function. However, $F_{\mathrm{pdb}}[\boldsymbol{c}]$ is not a thermodynamic potential, but rather a kinetic potential: the chemical potentials (60) encode kinetic properties, namely, the symmetric part of the reaction fluxes $\{s_\rho(\boldsymbol{c}(\boldsymbol{r}))\}$ via $\{\Delta_x\}$ [see Eqs. (55) and (54)].

Second, Eqs. (63) and (64) physically mean that diffusion processes are equilibrated at a steady state. This, together with Eq. (40b) and the fact that $\hat{\mu}_x(\boldsymbol{c}(\boldsymbol{r}))$ and $\mu_x(\boldsymbol{c}(\boldsymbol{r}))$ are related through the constant coefficient Δ_x, see Eq. (60), implies

$$\nabla\mu_i(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) = 0 \quad \forall i, \qquad (65)$$

namely, the chemical potentials of all species are homogeneous.

Third, spatial self-organization at steady state leads, in general, to inhomogeneous reaction fluxes. Indeed, as long as reaction fluxes do not exclusively depend on the chemical potentials, homogeneous chemical potentials do not imply homogeneous reaction fluxes. However, this is not the case for, for example, Arrhenius-like reaction fluxes (49) which become homogeneous when the chemical potentials are homogeneous (see also Subsection VI B).

Fourth, by plugging $\boldsymbol{J}_i(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) = 0$ into Eq. (15), we obtain that the concentration fields $\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})$ are also a steady state of the chemical dynamics for the internal species in every point $\boldsymbol{r} \in V$, i.e.,

$$\sum_{\rho > 0} S_{x,\rho}\, j_\rho(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) = 0. \qquad (66)$$

Since both diffusion and chemical reactions are at a steady state, no oscillations or moving structures (e.g., chemical waves) can emerge.

Fifth, $\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})$ is not, in general, an equilibrium steady state: diffusion processes are equilibrated, i.e., $\dot{\Sigma}_{\mathrm{dff}}[\boldsymbol{c}_{\mathrm{ss}}] = 0$, but chemical reactions are not. Indeed, $\hat{\dot{\Pi}}_{\mathrm{rct}}[\boldsymbol{c}_{\mathrm{ss}}]$ is not the thermodynamic reaction entropy production rate (35a) and $\hat{\dot{\Pi}}_{\mathrm{rct}}[\boldsymbol{c}_{\mathrm{ss}}] = 0$ in Eq. (63) does not imply $\dot{\Sigma}_{\mathrm{rct}}[\boldsymbol{c}_{\mathrm{ss}}] = 0$. The expressions of $\hat{\dot{\Pi}}_{\mathrm{rct}}[\boldsymbol{c}_{\mathrm{ss}}]$ in Eq. (62) and $\dot{\Sigma}_{\mathrm{rct}}[\boldsymbol{c}_{\mathrm{ss}}]$ in Eq. (38a) have a similar structure, given in terms of the lumped reaction fluxes $\hat{\omega}_\varepsilon$ and the actual reaction fluxes ω_ρ, respectively. Yet, $\hat{\dot{\Pi}}_{\mathrm{rct}}[\boldsymbol{c}_{\mathrm{ss}}]$ does not resolve the dissipation of the single reactions $\rho \in \mathcal{R}_\varepsilon$ in the lumped reaction ε, and it is always a lower bound of the $\dot{\Sigma}_{\mathrm{rct}}[\boldsymbol{c}_{\mathrm{ss}}]$ (because of the log sum inequality).

Sixth, by re-writing the lumped reaction net current $\hat{j}_\varepsilon(\boldsymbol{c}(\boldsymbol{r}))$ according to Eq. (57) with fluxes satisfying the pseudo local detailed balance condition (59), the RD dynamics (15) for the internal species is mathematically equivalent to the RD dynamics of a detailed balanced (and hence driven by purely passive mechanisms) RD system. For this reason, we named this kind of CRNs pseudo detailed balanced. Furthermore, Eq. (64) implies that $(\mu_x(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) - \Delta_x)$ can be written as a linear combination of unbroken conservation laws similar to what happens at equilibrium where the equilibrium chemical

potentials can be written as a linear combination of conservation laws [see Eq. (40a) and Appendix A].

We conclude this discussion by showing that the lumped reaction net currents $\hat{j}_\varepsilon(c(r))$ cannot, in general, be written as in Eq. (57) when CRNs are not pseudo detailed balanced. Namely, there are no $\{\Delta_x\}$ satisfying Eq. (55). Indeed, if there were, the existence of a right-null vector of $S_{x,\varepsilon}$ as defined in Eq. (47) would imply

$$\sum_{\varepsilon>0} \ln b_\varepsilon \phi_\varepsilon = 0. \qquad (67)$$

However, Eq. (67) cannot hold in general since $\{b_\varepsilon\}$ is defined using the symmetric part of the reaction fluxes so encoding kinetic properties, while $\{\phi_\varepsilon\}$ is derived from the stoichiometric matrix so encoding topological properties only.

In summary, the nonequilibrium dynamics of pseudo detailed balanced CRNs, as well as the resulting self-organized structures, can exactly be obtained by passive mechanisms too.

B. Complex balanced CRNs

CRNs are said to be complex balanced[54] when there exists a homogeneous steady state c_{ss}^h of the chemical dynamics, i.e., $\sum_{\rho>0} S_{x,\rho} j_\rho(c_{ss}^h) = 0$, such that the sum of the net currents entering into a complex k equals the sum of the net currents exiting from it, namely, $\sum_{\rho>0} \partial_{k,\rho} j_\rho(c_{ss}^h) = 0 \; \forall k$, or equivalently

$$\sum_\rho \mathbb{1}_{k,k(\rho)} j_\rho(c_{ss}^h) = 0 \;\; \forall k. \qquad (68)$$

Deficiency-zero CRNs, where every cycle (i.e., every right-null eigenvector of the substoichiometric matrix for the internal species) is also a right-null eigenvector of the incidence matrix, are always complex balanced. If the deficiency is greater than zero, then CRNs are, in general, not complex balanced (except for a set of kinetic parameters of null measure[41,55]).

We now show that the RD dynamics of complex balanced CRNs is driven by the minimization of a kinetic potential and relaxes to a steady state $c_{ss}(r)$ characterized by a vanishing diffusion entropy production rate, i.e., $\dot{\Sigma}_{dff}[c_{ss}] = 0$, independently of whether the concentration fields are homogeneous or inhomogeneous. We do so by generalizing a previous proof for the existence of a Lyapunov function for homogeneous complex balanced CRNs in dilute solutions undergoing mass-action kinetics.[56]

Assumption. We consider reaction fluxes of Arrhenius-like form (49) and we rewrite them as

$$\omega_\rho(c(r)) = a_\rho \; e^{\frac{\sum_x \mu_x(c(r)) v_{x,\rho}}{RT}}, \qquad (69)$$

with $a_\rho \equiv A_\rho \exp((\sum_y \mu_y v_{y,\rho})/RT) \neq a_{-\rho}$ being a constant parameter accounting (also) for the chemostatted species. Note that, since $v_{x,k(\rho)} = v_{x,\rho}$ by definition of complexes, Eq. (68) becomes

$$\sum_\rho \mathbb{1}_{k,k(\rho)} \left\{ a_\rho - a_{-\rho} e^{\frac{\sum_x \mu_x(c_{ss}^h) S_{x,\rho}}{RT}} \right\} = 0, \qquad (70)$$

when endowed with Arrhenius-like reaction fluxes (69).

Proof. We start by introducing the potential

$$F_{cb}[c] \equiv F[c] - \sum_x \mu_x(c_{ss}^h) \int_V dr \; c_x(r), \qquad (71)$$

and then we show that $F_{cb}[c]$ acts as a Lyapunov function of the RD dynamics (15) with respect to a steady state characterized by homogeneous chemical potentials. Note that the potential (71) is obtained from the free energy (29) via a shift of the standard chemical potentials of the internal species $\{\mu_x^\circ\}$ given by

$$\Delta_x = -\mu_x(c_{ss}^h), \qquad (72)$$

like what is done in Eq. (60) for pseudo detailed balanced CRNs.

By using Eqs. (15) and (69), and $d_t c_y = 0$, the time derivative of $F_{cb}[c]$ reads

$$d_t F_{cb}[c] = -T\dot{\Pi}_{cb}[c] - T\dot{\Sigma}_{dff}[c], \qquad (73)$$

where $\dot{\Sigma}_{dff}[c] \geq 0$ is given in Eq. (38b) (since $\nabla \mu_y = 0$), and

$$T\dot{\Pi}_{cb}[c] \equiv -\int_V dr \sum_{\rho,x} \left\{ (\mu_x(c(r)) - \mu_x(c_{ss}^h)) S_{x,\rho} a_\rho e^{\frac{\sum_x \mu_x(c(r)) v_{x,\rho}}{RT}} \right\}. \qquad (74)$$

We have now to show that $-\dot{\Pi}_{cb}[c] \leq 0$. By using (i) Eq. (2), (ii) multiplying and dividing by $\exp(\sum_x \mu_x(c_{ss}^h) v_{x,\rho}/RT)$, and (iii) $e^a(b-a) \leq e^b - e^a$ for any real number a and b (where the equality sign is achieved if and only if $a = b$), we obtain

$$-\frac{\dot{\Pi}_{cb}[c]}{R} \leq \int_V dr \sum_\rho \left\{ e^{\frac{\sum_x (\mu_x(c(r)) - \mu_x(c_{ss}^h)) v_{x,-\rho}}{RT}} - e^{\frac{\sum_x (\mu_x(c(r)) - \mu_x(c_{ss}^h)) v_{x,\rho}}{RT}} \right\} a_\rho e^{\frac{\sum_x \mu_x(c_{ss}^h) v_{x,\rho}}{RT}}, \qquad (75)$$

where the equality sign is achieved if and only if $(\mu_x(c(r)) - \mu_x(c_{ss}^h)) S_{x,\rho} = 0$. Since $\sum_\rho = \sum_k \sum_\rho \mathbb{1}_{k,k(\rho)}$ and $v_{x,k(\rho)} = v_{x,\rho}$ by definition of complexes, the two integrands in Eq. (75) can be rewritten as

$$\sum_k e^{\frac{\sum_x \mu_x(c(r)) v_{x,k}}{RT}} \sum_\rho \mathbb{1}_{k,k(\rho)} a_{-\rho} e^{\frac{\sum_x \mu_x(c_{ss}^h) S_{x,\rho}}{RT}}, \qquad (76a)$$

$$\sum_k e^{\frac{\sum_x \mu_x(c(r)) v_{x,k}}{RT}} \sum_\rho \mathbb{1}_{k,k(\rho)} a_\rho, \qquad (76b)$$

respectively, and hence, the r.h.s. of Eq. (75) reads

$$-\int_V dr \sum_k e^{\frac{\sum_x \mu_x(c(r)) v_{x,k}}{RT}} \sum_\rho \mathbb{1}_{k,k(\rho)} \left\{ a_\rho - a_{-\rho} e^{\frac{\sum_x \mu_x(c_{ss}^h) S_{x,\rho}}{RT}} \right\} = 0, \quad (77)$$

because of Eq. (70). Thus,

$$d_t F_{cb}[c] \leq 0. \qquad (78)$$

This, together with the fact that $F_{cb}[c]$ is lower bounded (since $F[c]$ is lower bounded by assumption, see Subsection IV B), implies that the RD dynamics (15) of complex balance CRNs must relax toward a steady state $c_{ss}(r)$ satisfying

$$\dot{\Pi}_{cb}[\boldsymbol{c}_{ss}] = 0 \quad \text{and} \quad \dot{\Sigma}_{dff}[\boldsymbol{c}_{ss}] = 0, \tag{79}$$

or equivalently

$$\sum_x (\mu_x(\boldsymbol{c}_{ss}(\boldsymbol{r})) - \mu_x(\boldsymbol{c}_{ss}^h))S_{x,\rho} = 0 \quad \text{and} \quad \boldsymbol{J}_i(\boldsymbol{c}_{ss}(\boldsymbol{r})) = 0, \tag{80}$$

for all $\rho > 0$ and for all i. □

As we did in Subsection V A, we now further discuss the conditions, the physical meaning, and the implications of Eqs. (79) and (80).

First, as for pseudo detailed balanced CRNs, the mechanism underpinning the dynamics of complex balanced CRNs as well as the emergence of self-organized dissipative structures is the minimization of $F_{cb}[\boldsymbol{c}]$ in Eq. (71), which plays the role of a Lyapunov function. However, $F_{cb}[\boldsymbol{c}]$ is not a thermodynamic potential, but rather a kinetic potential: it encodes kinetic properties via the steady state concentrations in $\{\mu_x(\boldsymbol{c}_{ss}^h)\}$ [see Eq. (71)].

Second, as for pseudo detailed balanced CRNs, Eqs. (79) and (80) physically mean that diffusion processes are equilibrated at a steady state. This, together with Eq. (38b), implies that the chemical potentials of all species are homogeneous.

Third, spatial self-organization at a steady state does not lead to inhomogeneous reaction fluxes. Indeed, homogeneous chemical potentials at steady state, together with reaction fluxes of Arrhenius-like form (69), imply that the reaction fluxes are homogeneous too, unlike for pseudo detailed balanced CRNs.

Fourth, as for pseudo detailed balanced CRNs, by plugging $\boldsymbol{J}_i(\boldsymbol{c}_{ss}(\boldsymbol{r})) = 0$ into Eq. (15), we obtain that both diffusion processes and chemical reactions are at steady state in every point $\boldsymbol{r} \in V$. Consequently, no oscillations or moving structures (e.g., chemical waves) can emerge.

Fifth, as for pseudo detailed balanced CRNs, $\boldsymbol{c}_{ss}(\boldsymbol{r})$ is not, in general, an equilibrium steady state even if the diffusion processes are equilibrated, i.e., $\dot{\Sigma}_{dff}[\boldsymbol{c}_{ss}] = 0$.

Sixth, Eq. (80) implies that $(\mu_x(\boldsymbol{c}_{ss}(\boldsymbol{r})) - \mu_x(\boldsymbol{c}_{ss}^h))$ can be written as a linear combination of unbroken conservation laws similarly to what happens at equilibrium where the equilibrium chemical potentials can be written as a linear combination of conservation laws [see Eq. (40a) and Appendix A].

In summary, the nonequilibrium dynamics of complex balanced CRNs, as well as the resulting self-organized structures, shares important features with passive mechanisms, e.g., it is driven by the minimization of (appropriately constructed) potentials and diffusion processes equilibrate.

C. Generalization to non-ideal chemostatted species

We show here that the results of Subsections V A and V B can be generalized to the case with non-ideal chemostatted species. Namely, when the chemical potentials $\{\mu_y(\boldsymbol{c}(\boldsymbol{r}))\}$ [given in Eq. (30) and not in Eq. (31)] are still homogeneous and constant in time, i.e.,

$$\mu_y(\boldsymbol{c}(\boldsymbol{r})) = \mu_y \quad \forall \boldsymbol{r} \quad \text{and} \quad \forall t, \tag{81}$$

but the concentrations $\{c_y(\boldsymbol{r})\}$ are not. Note that this implies that the exchange currents $\{I_y(\boldsymbol{r})\}$ in Eq. (15) represent the mechanisms ensuring that Eq. (81) is satisfied, but $\partial_t c_y(\boldsymbol{r}) \neq 0$ in general.

To do so, we recognize that the exchange currents $\{I_y(\boldsymbol{r})\}$ can always be represented as the (net) result of exchange reactions $\rho_y \in \mathcal{R}_{ex} = \{\pm 1, \pm 2, \ldots, \pm n_y\}$ between the species $y \in Y$ and ideal chemostatted species $\tilde{y} \in \tilde{Y}$ according to

$$Z_y \underset{-\rho_y}{\overset{\rho_y}{\rightleftharpoons}} Z_{\tilde{y}}. \tag{82}$$
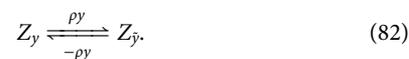
Indeed, as long as the exchange reactions $\rho_y \in \mathcal{R}_{ex}$ are fast enough (compared to the time scale of the other reactions $\rho \in \mathcal{R}$ and of the diffusion processes), they are always equilibrated and, consequently, Eq. (81) is satisfied (with μ_y playing the role of the chemical potential of $\tilde{y}$). This implies that RD systems with non-ideal chemostatted species are equivalent to RD systems with $X \cup Y \cup \tilde{Y}$ species (where $X \cup Y$ are internal species, and $\tilde{Y}$ are ideal chemostatted species) and $\mathcal{R} \cup \mathcal{R}_{ex}$ reactions. As proven in Subsections V A and V B, the latter will relax to a nonequilibrium steady state with homogeneous chemical potentials (i.e., where diffusion processes have equilibrated) if their CRNs are either pseudo detailed balanced or complex balanced and, therefore, also the former will relax to the same steady state. Note that the CRN topology of RD systems with $X \cup Y \cup \tilde{Y}$ species might be different from the one of the original RD systems because of the introduction of the exchange reactions (82).

D. Emergence of spatial structures by diffusive processes

In pseudo detailed balanced and complex balanced CRNs, the steady state spatial structure $\boldsymbol{c}_{ss}(\boldsymbol{r})$ is determined by the minimization of appropriately constructed kinetic potentials obtained by a simple shift of the standard chemical potentials of the internal species $\{\mu_x^\circ\}$. This, together with the equilibration of the diffusion processes at steady state, implies that the chemical reactions are the mechanism determining the total abundances of the chemical species, i.e., $\int_V d\boldsymbol{r} \, \boldsymbol{c}_{ss}(\boldsymbol{r})$, while diffusion is the mechanism determining the spatial structures, i.e., the $\boldsymbol{r}$-dependence of $\boldsymbol{c}_{ss}(\boldsymbol{r})$. Indeed, as proved in Appendix C, the steady-state concentration profiles $\boldsymbol{c}_{ss}(\boldsymbol{r})$ of pseudo detailed balanced and complex balanced CRNs can also be obtained by minimizing the free energy of pure diffusion, $F[\boldsymbol{c}]$ in Eq. (29), when the total abundances are set to values equal to $\int_V d\boldsymbol{r} \, \boldsymbol{c}_{ss}(\boldsymbol{r})$.

In CRNs that are neither pseudo detailed balanced nor complex balanced, this differentiation between the roles of chemical reactions and diffusion no longer holds in general and both mechanisms contribute to determining the spatial structures.

E. Final comment

We note that the equilibration of diffusion processes in complex balanced CRNs endowed with Arrhenius-like fluxes was also recently derived in Ref. 57 with a different approach. Let us now stress the differences between our work and Ref. 57. First, our derivation is a closed derivation at the deterministic level of description of the RD dynamics. Their derivation is based on the stochastic dynamics of complex balanced CRNs. Second, our derivation is consistent with nonlocal terms [e.g., of the form $\nabla c_x(\boldsymbol{r}) \cdot K_{x,x'} \nabla c_{x'}(\boldsymbol{r})$, see Eq. (83) in Sec. VI] in the non-ideal free energy. Their derivation determines the Lyapunov function of the reaction dynamics [the equivalent of $F_{cb}[\boldsymbol{c}]$ in Eq. (71)] by taking the macroscopic limit of the steady-state rate function for *homogeneous* CRNs. Hence,

their Lyapunov function can consistently include only local terms [e.g., of the form $c_x(r)M_{x,x'}c_{x'}(r)$, see Eq. (83) in Sec. VI] in the non-ideal free energy (although they use nonlocal terms in one of the examples). Third, our derivation can be applied to RD systems with non-ideal chemostatted species (see Subsection V C). Their derivation requires ideal chemostatted species.

VI. THERMODYNAMIC PROPERTIES OF ACTIVE SELF-ORGANIZATION–NUMERICAL RESULTS

We now examine the thermodynamic properties (introduced in Sec. IV) of specific RD systems. We first illustrate the exact results obtained in Sec. V for pseudo detailed balanced CRNs and complex balanced CRNs. We then examine a CRN that is neither pseudo detailed balanced nor complex balanced. To do so, we will numerically simulate their RD dynamics (15) to determine the final steady state $c_{ss}(r)$ starting from a homogeneous steady state c_{ss}^h after the concentration of each internal species x is perturbed with a Gaussian white noise of zero average and $(0.1 * c_x^h)^2$ variance. We consider RD systems in a two-dimensional space with periodic boundary conditions. Simulations are performed using the py-pde package developed in Ref. 58.

A. Model

We consider RD systems where the set of internal species includes a nonreacting species, labeled nr in the following, while the chemostatted species are assumed to be ideal, with homogeneous and time-independent chemical potentials.

The non-ideal free energy, accounting for the interactions between the internal species only, is assumed to have the following form:

$$F^{ni}[c] = \frac{RT}{2}\sum_{x,x'}\int_V dr \left[c_x(r)M_{x,x'}c_{x'}(r) + \nabla c_x(r) \cdot K_{x,x'}\nabla c_{x'}(r) \right],$$

(83)

where $\{M_{x,x'}\}$ and $\{K_{x,x'}\}$ are the entries of the two (symmetric) matrices $\mathbb{M}$ and $\mathbb{K}$ describing the mean-field molecular interactions and the cost of forming interfaces, respectively. If $M_{x,x'} > 0$ (respectively, $M_{x,x'} < 0$), then $\mathbb{M}$ represents repulsive (respectively, attractive) interactions between x and x': large concentrations $c_x(r)$ and $c_{x'}(r)$ in the same region increase (respectively, decrease) the free energy, i.e., $c_x(r)M_{x,x'}c_{x'}(r) > 0$ (respectively, $c_x(r)M_{x,x'}c_{x'}(r) < 0$). Similarly, if $K_{x,x'} > 0$ (respectively, $K_{x,x'} < 0$), then $\mathbb{K}$ represents an energetic advantage (respectively, disadvantage) in distributing x and x' in different regions: gradients $\nabla c_x(r)$ and $\nabla c_{x'}(r)$ with an opposite sign at the interface between a region enriched in x and a region enriched in x' decrease (respectively, increase) the free energy, i.e., $\nabla c_x(r) \cdot K_{x,x'}\nabla c_{x'}(r) < 0$ (respectively, $\nabla c_x(r) \cdot K_{x,x'}\nabla c_{x'}(r) > 0$). Note that the non-ideal free energy in Eq. (83) is consistent with the one used in Refs. 59 and 60 and corresponds to one introduced by Cahn and Hilliard[1] if higher orders in gradients are included. The corresponding chemical potentials of the internal species are given by

$$\mu_x(c(r)) = \mu_x^\circ + RT \ln c_x(r) + RT \sum_{x'} \left[M_{x,x'}c_{x'}(r) - K_{x,x'}\nabla^2 c_{x'}(r) \right],$$

(84)

where we also used Eqs. (30) and (33). The chemical potentials of the chemostatted species $\{\mu_y\}$ are treated as control parameter like in Sec. V and are related to the corresponding concentrations $\{c_y\}$ via Eq. (31).

Reaction fluxes are assumed to follow Arrhenius-like forms given in Eq. (69). The entries of the Onsager matrix $\mathbb{O}(c(r))$ in the diffusion currents (37) are assumed to read
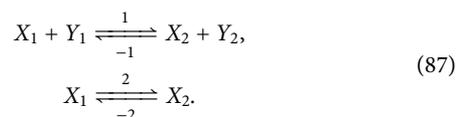
$$O_{i,j}(c(r)) = D_i c_i(r) \mathbb{1}_{i,j},$$

(85)

where D_i is the diffusion coefficient of species i. Hence, the diffusion currents for the internal species are given by

$$J_x(c(r)) = -D_x c_x(r)\nabla\mu_x(c(r)) \ \forall x \in X.$$

(86)

B. Pseudo detailed balanced CRN

We consider an RD system with three internal species $\{X_1, X_2, X_{nr}\}$ and two chemostatted species $\{Y_1, Y_2\}$ which are interconverted via the reactions,

$$X_1 + Y_1 \underset{-1}{\overset{1}{\rightleftharpoons}} X_2 + Y_2,$$
$$X_1 \underset{-2}{\overset{2}{\rightleftharpoons}} X_2.$$

(87)

The CRN (87) has three complexes $V_1 = X_1$, $V_2 = X_2$, and $V_3 = X_{nr}$, and the corresponding graph of complexes reads

$$V_1 \underset{-1}{\overset{1}{\rightleftharpoons}} V_2,$$
$$V_1 \underset{-2}{\overset{2}{\rightleftharpoons}} V_2,$$

(88)

admitting only the lumped reaction from V_1 to V_2 and its backward counterpart from V_2 to V_1. Hence, the stoichiometric matrix for the internal species,

$$\mathbb{S}_X = \begin{matrix} X_1 \\ X_2 \\ X_{nr} \end{matrix} \begin{pmatrix} \overset{1}{-1} & \overset{2}{-1} \\ 1 & 1 \\ 0 & 0 \end{pmatrix},$$

(89)

becomes the matrix

$$\begin{matrix} X_1 \\ X_2 \\ X_{nr} \end{matrix} \begin{pmatrix} -1 \\ 1 \\ 0 \end{pmatrix},$$

(90)

when considering the only lumped reaction. Since the matrix in Eq. (90) does not admit any right-null eigenvector, the CRN (87) is pseudo detailed balanced (see Subsection V A).

We solve the RD dynamics (15) when the mean-field molecular interactions and the cost of forming interfaces are given by the following matrices:

$$\mathbb{M} = \begin{matrix} X_1 \\ X_2 \\ X_{nr} \end{matrix} \overset{\begin{matrix} X_1 & X_2 & X_{nr} \end{matrix}}{\begin{pmatrix} 0 & \chi & 0 \\ \chi & 0 & \chi \\ 0 & \chi & 0 \end{pmatrix}}, \quad \mathbb{K} = \begin{matrix} X_1 \\ X_2 \\ X_{nr} \end{matrix} \overset{\begin{matrix} X_1 & X_2 & X_{nr} \end{matrix}}{\begin{pmatrix} k_1 & k_2 & 0 \\ k_2 & k_1 & k_2 \\ 0 & k_2 & 0 \end{pmatrix}}.$$

(91)

The typical steady-state solution and its thermodynamic properties are shown in Fig. 5. We observe that the concentration fields spatially organize [Fig. 5(a)] into a pattern that is qualitatively

analogous to a complete phase separation obtained at equilibrium: the species X_2 accumulates in a *single droplet*. The chemical reactions are, however, out of equilibrium, i.e., $\hat{\sigma}_{\mathrm{rct}}^{\mathrm{ss}}(\boldsymbol{r}) > 0$ [see Fig. 5(b)], even if the net current along the lumped reaction, namely, $\hat{\jmath}_1(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r}))$ $= j_1(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) + j_2(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r}))$, vanishes as predicted in Subsection V A [see Fig. 5(d)]. Furthermore, in agreement with our derivation in Subsection V A, at steady state, diffusion processes are at equilibrium, i.e., $\dot{\sigma}_{\mathrm{dff}}^{\mathrm{ss}}(\boldsymbol{r}) = 0$, because the chemical potentials are homogeneous [see Fig. 5(c)].

Note that the steady-state density of the reaction entropy production rate in Fig. 5(b) is homogeneous because we used reaction fluxes of Arrhenius-like forms, and therefore, the reaction fluxes become homogeneous at steady state (as explained in Subsection V A).

C. Complex balanced CRN

We consider an RD system with four internal species $\{X_1, X_2, X_3, X_{\mathrm{nr}}\}$ and two chemostatted species $\{Y_1, Y_2\}$ that are interconverted via the reactions as

$$X_1 + Y_1 \underset{-1}{\overset{1}{\rightleftharpoons}} X_2 + Y_2,$$
$$X_2 \underset{-2}{\overset{2}{\rightleftharpoons}} X_3, \qquad (92)$$
$$X_3 \underset{-3}{\overset{3}{\rightleftharpoons}} X_1.$$
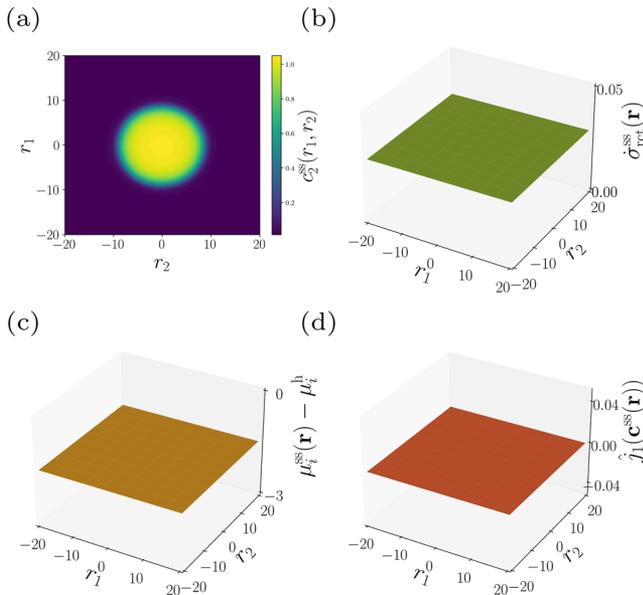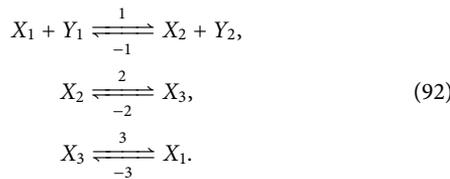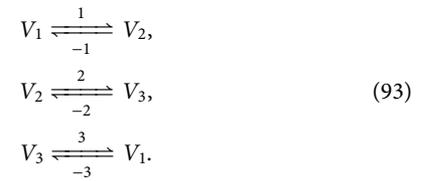

(a) (b)
(c) (d)

FIG. 5. Steady state and corresponding thermodynamic properties of the pseudo detailed balanced CRN (87). (a) Concentration field of X_2. (b) Density of reaction entropy production rate. (c) Difference between the chemical potential of $i \in \{X_1, X_2\}$ [labeled here $\mu_i^{\mathrm{ss}}(\boldsymbol{r})$] and its chemical potential at the homogeneous steady state (labeled here μ_i^{h}). (d) Net current of the lumped reaction, i.e., $\hat{\jmath}_1(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) = j_1(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) + j_2(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r}))$. Simulation parameters in arbitrary units: $RT = 1$, $\chi = 3$, $k_1 = 0.1$, $k_2 = 0.05$, $\mu_1^\circ = 0$, $\mu_2^\circ = -2$, $\mu_{Y_1} = 1$, $\mu_{Y_2} = 0$, $A_\rho = 1 \forall \rho$, $D_x = 1 \forall x$, $c_1^{\mathrm{h}} = 0.087$, $c_2^{\mathrm{h}} = 0.213$, and $c_{\mathrm{nr}}^{\mathrm{h}} = 0.7$.

The CRN (92) has four complexes $V_1 = X_1$, $V_2 = X_2$, $V_3 = X_3$, and $V_4 = X_{\mathrm{nr}}$, and the corresponding graph of complexes reads

$$V_1 \underset{-1}{\overset{1}{\rightleftharpoons}} V_2,$$
$$V_2 \underset{-2}{\overset{2}{\rightleftharpoons}} V_3, \qquad (93)$$
$$V_3 \underset{-3}{\overset{3}{\rightleftharpoons}} V_1.$$

Since the substoichiometric matrix for the internal species

$$\mathbb{S}_X = \begin{array}{c} X_1 \\ X_2 \\ X_3 \\ X_{\mathrm{nr}} \end{array} \begin{pmatrix} \overset{1}{-1} & \overset{2}{0} & \overset{3}{1} \\ 1 & -1 & 0 \\ 0 & 1 & -1 \\ 0 & 0 & 0 \end{pmatrix} \qquad (94)$$

admits only one cycle that is also a right-null eigenvector of the incidence matrix,

$$\partial = \begin{array}{c} V_1 \\ V_2 \\ V_3 \\ V_4 \end{array} \begin{pmatrix} \overset{1}{-1} & \overset{2}{0} & \overset{3}{1} \\ 1 & -1 & 0 \\ 0 & 1 & -1 \\ 0 & 0 & 0 \end{pmatrix}, \qquad (95)$$

the CRN (92) is deficiency-zero [see Eq. (11)] and, therefore, complex balanced (see Subsection V B).

We solve the RD dynamics (15) when the mean-field molecular interactions and the cost of forming interfaces are given by the following matrices:

$$\mathbb{M} = \begin{array}{c} X_1 \\ X_2 \\ X_3 \\ X_{\mathrm{nr}} \end{array} \begin{pmatrix} \overset{X_1}{0} & \overset{X_2}{\chi} & \overset{X_3}{0} & \overset{X_{\mathrm{nr}}}{0} \\ \chi & 0 & \chi & \chi \\ 0 & \chi & 0 & 0 \\ 0 & \chi & 0 & 0 \end{pmatrix}, \quad \mathbb{K} = \begin{array}{c} X_1 \\ X_2 \\ X_3 \\ X_{\mathrm{nr}} \end{array} \begin{pmatrix} \overset{X_1}{k_1} & \overset{X_2}{k_2} & \overset{X_3}{0} & \overset{X_{\mathrm{nr}}}{0} \\ k_2 & k_1 & k_2 & k_2 \\ 0 & k_2 & k_1 & 0 \\ 0 & k_2 & 0 & k_1 \end{pmatrix}. \qquad (96)$$

The typical steady-state solution and its thermodynamic properties are shown in Fig. 6. As for the RD system in Subsection VI B, we observe that the concentration fields spatially organize [Fig. 6(a)] into a pattern that is qualitatively analogous to a complete phase separation obtained at equilibrium: the species X_2 accumulates in a *single droplet*. The chemical reactions are, however, out of equilibrium, i.e., $\dot{\sigma}_{\mathrm{rct}}^{\mathrm{ss}}(\boldsymbol{r}) > 0$ [see Fig. 6(b)], while diffusion processes are at equilibrium, i.e., $\dot{\sigma}_{\mathrm{dff}}^{\mathrm{ss}}(\boldsymbol{r}) = 0$, since the chemical potentials are homogeneous [see Fig. 6(c)] as predicted by our derivation in Subsection VI B.

Furthermore, according to Eq. (80), the difference $(\mu_x(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) - \mu_x(\boldsymbol{c}_{\mathrm{ss}}^{\mathrm{h}}))$ for every internal species can be written as a linear combination of unbroken conservation laws (defined in Subsection III B). This implies that in general

$$(\mu_{X_1}(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) - \mu_{X_1}(\boldsymbol{c}_{\mathrm{ss}}^{\mathrm{h}})) = (\mu_{X_2}(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) - \mu_{X_2}(\boldsymbol{c}_{\mathrm{ss}}^{\mathrm{h}}))$$
$$= (\mu_{X_3}(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) - \mu_{X_3}(\boldsymbol{c}_{\mathrm{ss}}^{\mathrm{h}}))$$
$$\neq (\mu_{X_{\mathrm{nr}}}(\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})) - \mu_{X_{\mathrm{nr}}}(\boldsymbol{c}_{\mathrm{ss}}^{\mathrm{h}})), \qquad (97)$$
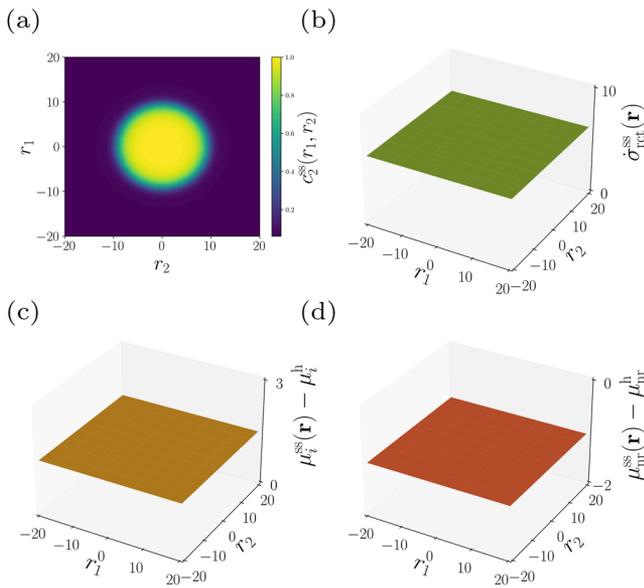
FIG. 6. Steady state and corresponding thermodynamic properties of the complex balanced CRN (92). (a) Concentration field of X_2. (b) Density of reaction entropy production rate. (c) Difference between the chemical potential of $i \in \{X_1, X_2, X_3\}$ [labeled here $\mu_i^{ss}(\boldsymbol{r})$] and its chemical potential at the homogeneous steady state (labeled here μ_i^h). (d) Difference between the chemical potential of X_{nr} [labeled here $\mu_{nr}^{ss}(\boldsymbol{r})$] and its chemical potential at the homogeneous steady state (labeled here μ_{nr}^h). Simulation parameters in arbitrary units: $RT = 1$, $\chi = 3$, $k_1 = 0.5$, $k_2 = 0.1$, $\mu_{1,2}^\circ = 1$, $\mu_3^\circ = 3$, $\mu_{nr}^\circ = 0$, $\mu_{Y_1} = 4$, $\mu_{Y_2} = 0$, $A_\rho = 1 \forall \rho$, $D_x = 1 \forall x$, $c_1^h = 0.007$, $c_2^h = 0.274$, $c_3^h = 0.019$, and $c_{nr}^h = 0.7$.
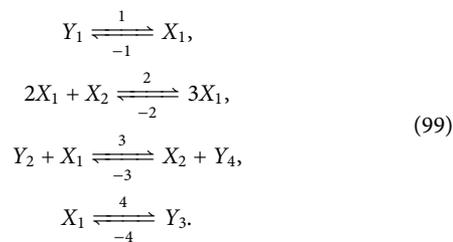
since the stoichiometric matrix for the internal species (94) admits the following left null eigenvectors:

$$
\begin{array}{c}
X_1 \\ X_2 \\ X_3 \\ X_{nr}
\end{array}
\begin{pmatrix} 1 \\ 1 \\ 1 \\ 0 \end{pmatrix}, \qquad
\begin{array}{c}
X_1 \\ X_2 \\ X_3 \\ X_{nr}
\end{array}
\begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \end{pmatrix}. \tag{98}
$$

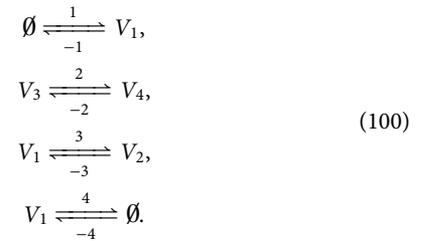The constraint in Eq. (97) is confirmed by the simulation [compare Figs. 6(c) and 6(d)].

D. Brusselator

We consider an RD system of three internal species $\{X_1, X_2, X_{nr}\}$ and four chemostatted species $\{Y_1, Y_2, Y_3, Y_4\}$ that are interconverted via the reactions as

$$
Y_1 \underset{-1}{\overset{1}{\rightleftharpoons}} X_1,
$$
$$
2X_1 + X_2 \underset{-2}{\overset{2}{\rightleftharpoons}} 3X_1,
$$
$$
Y_2 + X_1 \underset{-3}{\overset{3}{\rightleftharpoons}} X_2 + Y_4, \tag{99}
$$
$$
X_1 \underset{-4}{\overset{4}{\rightleftharpoons}} Y_3.
$$

The CRN (99) is known as Brusselator and can be represented in terms of the six complexes $V_1 = X_1$, $V_2 = X_2$, $V_3 = 2X_1 + X_2$,

$V_4 = 3X_1$, $V_5 = X_{nr}$, and $\emptyset = Y_{1,2}$ and the following graph of complexes:

$$
\emptyset \underset{-1}{\overset{1}{\rightleftharpoons}} V_1,
$$
$$
V_3 \underset{-2}{\overset{2}{\rightleftharpoons}} V_4,
$$
$$
V_1 \underset{-3}{\overset{3}{\rightleftharpoons}} V_2, \tag{100}
$$
$$
V_1 \underset{-4}{\overset{4}{\rightleftharpoons}} \emptyset.
$$

The stoichiometric matrix for the internal species

$$
\mathbb{S}_X = \begin{array}{c} X_1 \\ X_2 \\ X_{nr} \end{array}
\overset{\begin{array}{cccc} 1 & 2 & 3 & 4 \end{array}}{
\begin{pmatrix} 1 & 1 & -1 & -1 \\ 0 & -1 & 1 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}} \tag{101}
$$

admits two cycles, i.e.,

$$
\boldsymbol{\phi} = \begin{array}{c} 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{pmatrix} 1 \\ 0 \\ 0 \\ 1 \end{pmatrix} \quad \text{and} \quad
\boldsymbol{\phi}' = \begin{array}{c} 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{pmatrix} 0 \\ 1 \\ 1 \\ 0 \end{pmatrix}, \tag{102}
$$

but only the first one is a right-null vector of the incidence matrix,

$$
\partial = \begin{array}{c} V_1 \\ V_2 \\ V_3 \\ V_4 \\ V_5 \\ \emptyset \end{array}
\overset{\begin{array}{cccc} 1 & 2 & 3 & 4 \end{array}}{
\begin{pmatrix} 1 & 0 & -1 & -1 \\ 0 & 0 & 1 & 0 \\ 0 & -1 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ -1 & 0 & 0 & 1 \end{pmatrix}}. \tag{103}
$$

Hence, the deficiency reads $\delta = 1$ [see Eq. (11)] and, in general, the CRN (99) is neither pseudo detailed balanced nor complex balanced. Namely, any homogeneous steady state $\boldsymbol{c}_{ss}^h$ of the chemical dynamics satisfying $\sum_{\rho>0} S_{x,\rho} j_\rho(\boldsymbol{c}_{ss}^h) = 0$ does not satisfy $\sum_{\rho>0} \partial_{k,\rho} j_\rho(\boldsymbol{c}_{ss}^h) = 0$ too (except for a set of parameters, e.g., $\{A_\rho\}$, $\{\mu_y\}$, $\mathbb{M}$, and $\mathbb{K}$, of null measure[41,55]).

We solve the RD dynamics (15) when the mean-field molecular interactions and the cost of forming interfaces are given by the same matrices as in Eq. (91). The typical steady-state solution and its thermodynamic properties are shown in Figs. 7 and 8, respectively. We observe that the concentration fields spatially organize (Fig. 7) into a pattern that is striking different from the previous ones examined in Subsections VI B and VI C (see Figs. 5 and 6, respectively). In this case, X_1 accumulates in *multiple droplets* and X_2 remains almost homogeneous. Furthermore, both reactions and diffusion processes are out of equilibrium since the chemical potentials are not homogeneous [Fig. 8(a)]: $\dot{\sigma}_{rct}^{ss}(\boldsymbol{r}) > 0$ [Fig. 8(d)] and $\dot{\sigma}_{diff}^{ss}(\boldsymbol{r}) > 0$ [Fig. 8(c)]. This has two main consequences. First, the dissipation due to the chemical reactions, quantified by $\dot{\sigma}_{rct}(\boldsymbol{r})$, is not homogeneous either: reactions dissipate more inside the droplets [Fig. 8(d)]. However, not all reactions contribute in the same way to the total reaction entropy production rate. Indeed, as shown in Figs. 8(e)–8(h), reaction $\rho = 1$ dissipates more outside the droplets, while $\rho = 2, 3$, and 4 dissipate more inside the droplets. Furthermore, $\rho = 2$ (representing an autocatalytic reaction) is the reaction dissipating the most.
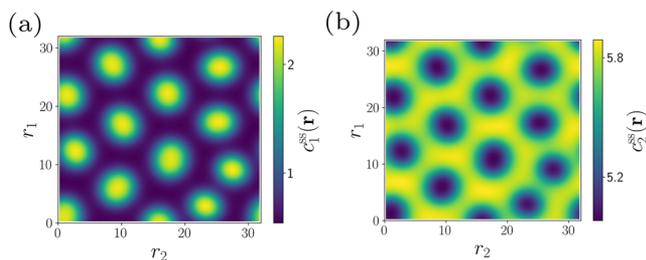
FIG. 7. Steady state concentration fields of (a) X_1 and (b) X_2 of the CRN (99). Simulation parameters in arbitrary units: $RT = 1$, $\chi = 0$, $k_1 = 0.1$, $k_2 = 0.05$, $\mu_x^\circ = 0$, $\forall x$, $\mu_{Y_1} = \ln 2$, $\mu_{Y_2} = \ln 5$, $\mu_{Y_3} = \ln 0.01$, $\mu_{Y_4} = \ln 0.1$, $A_\rho = 1 \forall \rho$, $D_1 = 1$, $D_2 = 10$, $D_{nr} = 1$, $c_1^h = 1.05$, $c_2^h = 5.76$, and $c_{nr}^h = 1.00$.

This physically implies that reactions $\rho = 2, 3,$ and 4 are more out of equilibrium inside the droplets or, equivalently, they occur in a preferential direction (either forward or backward) more inside the droplets than outside [since the entropy production rate is related to the asymmetry in the reaction fluxes via Eq. (38a)]. Second, the diffusion processes are out of equilibrium and dissipate mostly at the interface between the droplets and the bulk as shown in Fig. 8(c). This physically means that diffusion currents are maintained with a preferential direction at the interface between the droplets and the bulk in such a way as to balance the consumption/production of species inside the droplets due to the chemical reactions and sustain the steady state pattern.

Note that the steady-state density of nonconservative work [which satisfies $\dot{w}_{nc}^{ss}(\boldsymbol{r}) = \dot{\sigma}^{ss}(\boldsymbol{r})$] is peaked inside the droplets [see Fig. 8(b)] and, therefore, most of the free energy maintaining nonequilibrium self-organization is provided from inside the droplets (even if the chemostatted species are homogeneous).
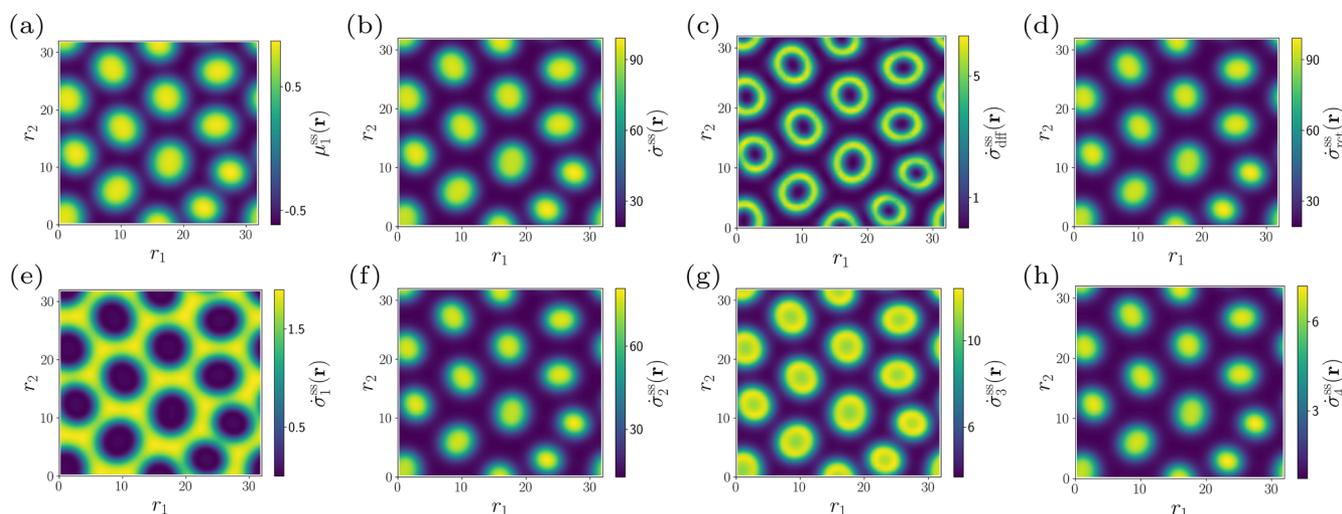
VII. CONCLUSIONS

We provided a general thermodynamic framework to study the energetics of self-organization in open non-ideal RD systems. We showed that it can be used to study, in great detail, with spatial resolution, the contribution of the reactive and diffusive processes to the dissipation of self-organized structures. For special classes of RD systems, our framework allowed us to construct potentials that are minimized by the dynamics (Lyapunov functions) and whose minima correspond to the steady state. Thermodynamic potentials (independent of the kinetics) are found for detailed balance RD systems that relax to equilibrium, while kinetic potentials are found for pseudo detailed balanced and complex balanced CRNs that relax to nonequilibrium steady states. In doing so, we demonstrated that thermodynamics is useful not only to study the energetics of RD systems but also to make inferences on their dynamics.

Our framework addresses the questions posed in the introduction concerning the mechanisms sustaining and controlling self-organization. It reveals how the interplay between passive and active mechanisms is intricately tied to the topology of the underlying CRN. In particular, the mechanisms are purely passive in detailed balanced CNRs (Sec. IV D), where both chemical reactions and diffusion equilibrate. In contrast, pseudo detailed balanced (Subsection V A) and complex balanced CRNs (Subsection V B) exhibit a mix of active and passive traits: chemical reactions dissipate (i.e., they are active), but diffusion equilibrates (i.e., it is passive). In CRNs that are neither pseudo detailed balanced nor complex balanced, both chemistry and diffusion dissipate, and self-organization is purely active. Our framework further uncovers how the control of self-organized structures by chemical reactions is also strongly dependent on the network topology. In the case of pseudo detailed balanced and complex balanced CRNs, the chemical reactions only determine the total concentrations of the species, which diffusion then spatially organizes (Subsection V D). Instead, chemical

FIG. 8. Steady-state thermodynamic properties of the CRN (99). (a) Chemical potential of X_1. (b) Density of entropy production rate $\dot{\sigma}^{ss}(\boldsymbol{r}) = \dot{\sigma}_{dff}^{ss}(\boldsymbol{r}) + \dot{\sigma}_{rct}^{ss}(\boldsymbol{r})$. (c) Density of diffusion entropy production rate $\dot{\sigma}_{dff}^{ss}(\boldsymbol{r})$. (d) Density of reaction entropy production rate $\dot{\sigma}_{rct}^{ss}(\boldsymbol{r}) = \sum_{\rho=1}^{4} \dot{\sigma}_\rho^{ss}(\boldsymbol{r})$ and (e)–(h) its decomposition into the contribution of each reaction $\rho = 1, 2, 3, 4$ as explained in Subsection IV B. Simulation parameters are the same as in Fig. 7.

reactions can directly affect the spatial organization of CRNs that are neither pseudo detailed balanced nor complex balanced.

Our framework is general and applicable to a wide range of systems in both biology and synthetic chemistry. It can distinguish between active and passive mechanisms solely on the basis of the topology of the CRN. However, determining the dissipation of self-organized structures requires knowledge of all diffusion and reaction fluxes, which can be challenging to obtain. From this perspective, our thermodynamic framework demands a more detailed system characterization compared to dynamical frameworks that primarily focus on reproducing self-organized structures.

Furthermore, we emphasize that the crucial feature of our framework is thermodynamic consistency. This is ensured by the local detailed balance condition, which corresponds to the macroscopic limit[43] of the local detailed balance condition of stochastic thermodynamics[47] when specialized for CNRs.[46,48] However, it is important to note that this condition might not hold at scales, such as those of predator–prey distributions, vegetation patterns, and spiral patterns of galaxies. Hence, the direct application of our framework to these systems is not straightforward, and the development of thermodynamically consistent coarse-graining techniques, such as those in Refs. 61 and 62, will be necessary.

Finally, we stress that our local detailed balance condition (36) is in agreement with the general derivation in Ref. 49, where the thermodynamic forces conjugated to the reaction currents are the (stoichiometric-weighted combinations of) chemical potentials $\{\mu_i(\boldsymbol{c}(\boldsymbol{r}))\}$. Other works have used instead the exchange chemical potentials $\{\mu_i^{\text{ex}}(\boldsymbol{c}(\boldsymbol{r}))\}$, namely, the differences between the chemical potentials and the chemical potential of another species chosen as reference. This is only consistent with the local detailed balance condition when dealing with unimolecular (or pseudo-unimolecular) reactions.

Future studies will be needed to extend our framework to fluctuating RD systems[63] and to explore the phenomenology of self-organized structures in non-ideal RD systems following the line of Refs. 64 and 65. Another interesting extension concerns microswimmers that undergo a self-propelled motion;[66–70] here, the challenge is to understand how to properly describe the coupling between chemical reactions, occurring either at the surface of (e.g., Janus colloids in a fuel bath) or within (e.g., bacteria filled by nutrient consumption) microswimmers, and the resulting self-propelled dynamics.

AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Francesco Avanzini: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Timur Aslyamov**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Étienne Fodor**: Conceptualization (equal); Funding acquisition (equal); Project administration (equal); Resources (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (supporting); Writing – review & editing (supporting). **Massimiliano Esposito**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

APPENDIX A: MINIMIZATION OF THE FREE ENERGY

We prove here that the equilibrium steady state $\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})$ of closed RD systems [defined in Eq. (40)] corresponds to the minimum $\boldsymbol{c}^*(\boldsymbol{r})$ of the free energy (29) satisfying the conserved quantities of the RD dynamics (15) (i.e., the abundances of the moieties (20) as discussed in Subsection III B).

We start by recognizing that $\boldsymbol{c}^*(\boldsymbol{r})$ is defined by the minimum $(\boldsymbol{c}^*(\boldsymbol{r}), \boldsymbol{f}^*)$ of the Lagrangian functional,

$$\mathcal{L}[\boldsymbol{c}, \boldsymbol{f}] = F[\boldsymbol{c}] - \sum_\lambda f_\lambda \left(\sum_i \ell_i^\lambda \int_V d\boldsymbol{r} \, c_i(\boldsymbol{r}) - L^\lambda \right), \quad \text{(A1)}$$

with $\boldsymbol{f} = (\ldots, f_\lambda, \ldots)$ being the vector of the Lagrange multipliers and $\{L^\lambda\}$ being the actual values of the moiety abundances. Namely, $(\boldsymbol{c}^*(\boldsymbol{r}), \boldsymbol{f}^*)$ is the solution of the following equations:

$$\left. \frac{\delta \mathcal{L}[\boldsymbol{c}, \boldsymbol{f}]}{\delta c_i(\boldsymbol{r})} \right|_* = \mu_i(\boldsymbol{c}^*(\boldsymbol{r})) - \sum_\lambda f_\lambda^* \ell_i^\lambda = 0, \quad \text{(A2a)}$$

$$\left. \frac{\delta \mathcal{L}[\boldsymbol{c}, \boldsymbol{f}]}{\delta f_\lambda} \right|_* = -\left(\sum_i \ell_i^\lambda \int_V d\boldsymbol{r} \, c_i^*(\boldsymbol{r}) - L^\lambda \right) = 0. \quad \text{(A2b)}$$

Equation (A2) implies that $\boldsymbol{c}^*(\boldsymbol{r})$ satisfies the equilibrium conditions in Eq. (40) and, consequently, $\boldsymbol{c}^*(\boldsymbol{r}) = \boldsymbol{c}_{\text{eq}}(\boldsymbol{r})$. Indeed, using Eq. (A2a),

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$$\sum_i \mu_i(\boldsymbol{c}^*(\boldsymbol{r})) S_{i,\rho} = \sum_i \left(\sum_\lambda f_\lambda^* \ell_i^\lambda \right) S_{i,\rho} = 0, \qquad (A3)$$

by definition of conservation laws [given in Eq. (19)], and $\{\mu_i(\boldsymbol{c}^*(\boldsymbol{r}))\}$ are homogeneous implying that Eq. (40b) is satisfied too.

APPENDIX B: MINIMIZATION OF THE SEMIGRAND FREE ENERGY

We prove here that the equilibrium steady state $\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})$ of open RD systems [defined in Eq. (40)] corresponds to the minimum $\boldsymbol{c}^*(\boldsymbol{r})$ of the semigrand free energy (42) satisfying the conserved quantities of the RD dynamics (15) (i.e., abundances of the moieties corresponding to the unbroken conservation laws (22) as discussed in Subsection III B). We also prove that the equilibrium chemical potentials of the Y_p and Y_f species are solely determined by the reference chemical potentials $\{\mu_{y_p}^{\text{ref}}\}$.

We start by recognizing that $\boldsymbol{c}^*(\boldsymbol{r})$ is defined by the minimum $(\boldsymbol{c}^*(\boldsymbol{r}), \boldsymbol{f}^*)$ of the Lagrangian functional,

$$\mathcal{L}[\boldsymbol{c},\boldsymbol{f}] = \overbrace{F[\boldsymbol{c}] - \sum_{y_p} \mu_{y_p}^{\text{ref}} M_{y_p}[\boldsymbol{c}]}^{= \mathcal{F}[\boldsymbol{c}]}$$
$$- \sum_{\lambda_u} f_{\lambda_u} \left(\sum_i \ell_i^{\lambda_u} \int_V \mathrm{d}\boldsymbol{r}\, c_i(\boldsymbol{r}) - L^{\lambda_u} \right), \qquad (B1)$$

with $\boldsymbol{f} = (\dots, f_{\lambda_u}, \dots)$ being the vector of the Lagrange multipliers and $\{L^{\lambda_u}\}$ being the actual values of the abundances of the moieties corresponding to the unbroken conservation laws. Namely, $(\boldsymbol{c}^*(\boldsymbol{r}), \boldsymbol{f}^*)$ is the solution of the following equations:

$$\left. \frac{\delta \mathcal{L}[\boldsymbol{c},\boldsymbol{f}]}{\delta c_i(\boldsymbol{r})} \right|_* = \mu_i(\boldsymbol{c}^*(\boldsymbol{r})) - \sum_{y_p,\lambda_b} \mu_{y_p}^{\text{ref}} \overline{\ell}_{\lambda_b}^{y_p} \ell_i^{\lambda_b} - \sum_{\lambda_u} f_{\lambda_u}^* \ell_i^{\lambda_u} = 0, \quad (B2a)$$

$$\left. \frac{\delta \mathcal{L}[\boldsymbol{c},\boldsymbol{f}]}{\delta f_{\lambda_u}} \right|_* = - \left(\sum_i \ell_i^{\lambda_u} \int_V \mathrm{d}\boldsymbol{r}\, c_i^*(\boldsymbol{r}) - L^{\lambda_u} \right) = 0, \qquad (B2b)$$

where we used Eq. (25). Equation (B2a) implies that the chemical potentials in the minimum $\boldsymbol{c}^*(\boldsymbol{r})$ of the semigrand free energy (42) read

$$\mu_i(\boldsymbol{c}^*(\boldsymbol{r})) = \sum_{y_p,\lambda_b} \mu_{y_p}^{\text{ref}} \overline{\ell}_{\lambda_b}^{y_p} \ell_i^{\lambda_b} + \sum_{\lambda_u} f_{\lambda_u}^* \ell_i^{\lambda_u}, \qquad (B3)$$

and, therefore, $\boldsymbol{c}^*(\boldsymbol{r})$ satisfies the equilibrium conditions in Eq. (40), i.e., $\boldsymbol{c}^*(\boldsymbol{r}) = \boldsymbol{c}_{\text{eq}}(\boldsymbol{r})$. Indeed,

$$\sum_i \mu_i(\boldsymbol{c}^*(\boldsymbol{r})) S_{i,\rho} = \sum_i \left(\sum_{y_p,\lambda_b} \mu_{y_p}^{\text{ref}} \overline{\ell}_{\lambda_b}^{y_p} \ell_i^{\lambda_b} \right) S_{i,\rho}$$
$$+ \sum_i \left(\sum_{\lambda_u} f_{\lambda_u}^* \ell_i^{\lambda_u} \right) S_{i,\rho} = 0, \qquad (B4)$$

by definition of conservation laws [given in Eq. (19)], and $\{\mu_i(\boldsymbol{c}^*(\boldsymbol{r}))\}$ are homogeneous implying that Eq. (40b) is satisfied too.

Remark. According to Eq. (B3), the equilibrium chemical potentials of the internal species are determined by (i) the reference chemical potentials $\{\mu_{y_p}^{\text{ref}}\}$ and (ii) the abundances $\{L^{\lambda_u}[\boldsymbol{c}]\}$ of the moieties corresponding to the unbroken conservation laws via $\{f_{\lambda_u}^*\}$.

Remark. According to Eq. (B3), the equilibrium chemical potentials of the potential and force species are solely determined by the reference chemical potentials $\{\mu_{y_p}^{\text{ref}}\}$, according to

$$\mu_{y_p}(\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})) = \mu_{y_p}^{\text{ref}}, \qquad (B5a)$$

$$\mu_{y_f}(\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})) = \sum_{y_p,\lambda_b} \mu_{y_p}^{\text{ref}} \overline{\ell}_{\lambda_b}^{y_p} \ell_{y_f}^{\lambda_b}, \qquad (B5b)$$

using $\sum_{\lambda_b} \overline{\ell}_{\lambda_b}^{y_p \prime} \ell_y^{\lambda_b} = \mathbb{1}_{y_p,y_p\prime}$ and $\ell_y^{\lambda_u} = 0$. Thus, if the force species were chemostatted in such a way that $\mu_{y_f}(\boldsymbol{r}) \neq \mu_{y_f}(\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})) = \sum_{y_p,\lambda_b} \mu_{y_p}^{\text{ref}} \overline{\ell}_{\lambda_b}^{y_p} \ell_{y_f}^{\lambda_b}$, open RD systems would not admit an equilibrium steady state, and detailed balance would be broken [as discussed in Subsection IV D using the formulation of the second law given in Eq. (41)]. Similarly, if the potential chemostats imposed different values of the chemical potentials $\{\mu_{y_p}(\boldsymbol{r})\}$ in different $\boldsymbol{r} \in V$, open RD systems would not admit an equilibrium steady state and detailed balance would be broken. If this is the case, we recall that the reference chemical potential $\{\mu_{y_p}^{\text{ref}}\}$ entering the definition of semigrand free energy (42) can be chosen arbitrarily among these values. This is equivalent to choosing a reference equilibrium steady state $\boldsymbol{c}_{\text{eq}}(\boldsymbol{r})$ to which the open RD system would relax if $\mu_{y_p}(\boldsymbol{r}) = \mu_{y_p}^{\text{ref}}$, and the force species were not chemostatted.

APPENDIX C: MINIMIZATION OF THE FREE ENERGY IN PURELY DIFFUSIVE SYSTEMS

We prove here that the steady state $\boldsymbol{c}_{\text{ss}}(\boldsymbol{r})$ of either pseudo detailed balanced CRNs (defined in Subsection V A) or complex balanced CRNs (defined in Subsection V B) corresponds to the minimum $\boldsymbol{c}^\bullet(\boldsymbol{r})$ of the free energy $F[\boldsymbol{c}]$ in Eq. (29) when the total abundances of the chemical species are fixed and equal to $\int_V \mathrm{d}\boldsymbol{r}\, \boldsymbol{c}_{\text{ss}}(\boldsymbol{r})$.

In what follows, we use $F_{\text{pdb/cb}}[\boldsymbol{c}]$ for the kinetic potential of either pseudo detailed balanced or complex balanced CRNs. Namely, the potential obtained from the free energy (29) after applying the shifts $\{\Delta_x\}$ of the standard chemical potentials of the internal species in Eq. (56) for pseudo detailed balanced CRNs or in Eq. (72) for complex balanced CRNs. Furthermore, like in Subsections V A and V B, we assume that the chemostatted species are ideal, homogeneous, and constant in time.

We have to start by recognizing that, in agreement with Subsections V A and V B, $\boldsymbol{c}_{\text{ss}}(\boldsymbol{r})$ is a minimum of the kinetic potential $F_{\text{pdb/cb}}[\boldsymbol{c}]$ satisfying the conserved quantities of the RD dynamics (15) [i.e., abundances of the moieties corresponding to the unbroken conservation laws (22)]. Indeed, the minimum $(\boldsymbol{c}^\bullet(\boldsymbol{r}), \boldsymbol{f}^*)$ of the Lagrangian functional,

$$\mathcal{L}[\boldsymbol{c}, \boldsymbol{f}] = F_{\mathrm{pdb/cb}}[\boldsymbol{c}] - \sum_{\lambda_u} f_{\lambda_u}\left(\sum_x \ell_x^{\lambda_u} \int_V \mathrm{d}\boldsymbol{r}\, c_x(\boldsymbol{r}) - L^{\lambda_u}\right), \quad \text{(C1)}$$

with $\boldsymbol{f} = (\ldots, f_{\lambda_u}, \ldots)$ being the vector of the Lagrange multipliers and $\{L^{\lambda_u}\}$ being the actual values of the moieties abundances corresponding to the unbroken conservation laws, is the solution of the following equations:

$$\left.\frac{\delta \mathcal{L}[\boldsymbol{c}, \boldsymbol{f}]}{\delta c_x(\boldsymbol{r})}\right|_* = \mu_x(\boldsymbol{c}^*(\boldsymbol{r})) + \Delta_x - \sum_{\lambda_u} f_{\lambda_u}^* \ell_x^{\lambda_u} = 0, \quad \text{(C2a)}$$

$$\left.\frac{\delta \mathcal{L}[\boldsymbol{c}, \boldsymbol{f}]}{\delta f_\lambda}\right|_* = -\left(\sum_x \ell_x^{\lambda_u} \int_V \mathrm{d}\boldsymbol{r}\, c_x^*(\boldsymbol{r}) - L^{\lambda_u}\right) = 0, \quad \text{(C2b)}$$

where we used the fact that the chemostatted species are ideal, homogeneous, and constant in time. Equation (C2a) implies that $\boldsymbol{c}^*(\boldsymbol{r})$ satisfies the conditions in Eq. (64) [respectively, Eq. (80)] for the steady state of pseudo detailed balanced (respectively, complex balanced) CRNs with $\{\Delta_x\}$ given in Eq. (56) [respectively, Eq. (72)].

We now consider the minimum of the free energy $F[\boldsymbol{c}]$ in Eq. (29) when the total abundances of the chemical species are fixed and equal to $\int_V \mathrm{d}\boldsymbol{r}\, \boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})$: the minimum $(\boldsymbol{c}^\bullet(\boldsymbol{r}), \boldsymbol{f}^\bullet)$ of the Lagrangian functional,

$$\mathcal{L}[\boldsymbol{c}, \boldsymbol{f}] = F[\boldsymbol{c}] - \sum_x f_x \int_V \mathrm{d}\boldsymbol{r}\, \left(c_x(\boldsymbol{r}) - c_x^{\mathrm{ss}}(\boldsymbol{r})\right), \quad \text{(C3)}$$

with $\boldsymbol{f} = (\ldots, f_x, \ldots)$ being the vector of the Lagrange multipliers, satisfying

$$\left.\frac{\delta \mathcal{L}[\boldsymbol{c}, \boldsymbol{f}]}{\delta c_x(\boldsymbol{r})}\right|_\bullet = \mu_x(\boldsymbol{c}^\bullet(\boldsymbol{r})) - f_x^\bullet = 0, \quad \text{(C4a)}$$

$$\left.\frac{\delta \mathcal{L}[\boldsymbol{c}, \boldsymbol{f}]}{\delta f_x}\right|_\bullet = -\int_V \mathrm{d}\boldsymbol{r}\, \left(c_x^\bullet(\boldsymbol{r}) - c_x^{\mathrm{ss}}(\boldsymbol{r})\right) = 0, \quad \text{(C4b)}$$

where we used again the fact that the chemostatted species are ideal, homogeneous, and constant in time. By comparing Eqs. (C2) and (C4), we can conclude that Eq. (C4) admits a solution such that $\boldsymbol{c}^\bullet(\boldsymbol{r}) = \boldsymbol{c}^*(\boldsymbol{r}) = \boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})$ and $-f_x^\bullet = \Delta_x - \sum_{\lambda_u} f_{\lambda_u}^* \ell_x^{\lambda_u}\ \forall x$. Namely, the $\boldsymbol{r}$-dependence of $\boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})$ for either pseudo detailed balanced CRNs or complex balanced CRNs can be obtained by minimizing the free energy $F[\boldsymbol{c}]$ in Eq. (29) with the constraint that the total abundances of the chemical species are equal to $\int_V \mathrm{d}\boldsymbol{r}\, \boldsymbol{c}_{\mathrm{ss}}(\boldsymbol{r})$.

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