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BOLTZMANN MAPS FOR NETWORKS OF CHEMICAL REACTIONS AND THE MULTI-STABILITY PROBLEM

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Abstract. Boltzmann Maps are a class of discrete dynamical systems that may be used in the study of complex chemical reaction processes. In this paper they are generalized to open systems allowing the description of non-stoichiometrically balanced reactions with unequal reaction rates. We show that they can be widely used to describe the relevant dynamics, leading to interesting insights on the multi-stability problem in networks of chemical reactions. Necessary conditions for multistability are thus identified. Our findings indicate that the dynamics produced by laws like the mass action law, can hardly produce multistable phenomena. In particular, we prove that they cannot do it in a wide range of chemical reactions.

1. **The biological problem.** In recent years a new picture of the intracellular mechanisms has been drawn. Cells can respond to a wide range of extracellular stimula that induce different behaviors: apoptosis, proliferation, survival, motility and so on. The effectors for signaling are proteins that play several roles: they can be receptors, enzimes, vectors for signal propagation or catalizers. They interact together drawing signaling pathway in which they are identified as nodes. A key feature for these pathways is that they are not isolated: different paths, with completely different biological phenotypes as outputs, can share some nodes or even some functional units. In other words a protein is not focused only on one job, but it can perform different tasks. This important characteristic of the intracellular signaling pathways increases the complexity of signaling description. It is a kind of comunication code between extracellular environment and cell core.

Understanding this code is as interesting as complicated. One should know all proteins involved in the signaling and should understand their roles. Intracellular localization is definitely important. Cells can be divided into different compartments: membrane, cytoplasm, nucleus, cytoscheleton, mitocondria and so on. Proteins that localize in different places cannot directly interact with each other, their interactions

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could be affected by diffusion, and spatial organization of proteins could switch on signalling or could turn it off.

Common approaches to these problems concern topological proprieties of the networks drawn by the interactions, and lead to the concept of robustness, via graph theory. Cutting off one or more edges from a graph, a robust path should still display the same behaviour and mediate the same information. That is quite interesting from a biological point of view but may not be sufficient for a quantitative study of the problem. [2, 8]

Boolean approaches are based on the weighting of edges of networks with "boolean" rates: ± 1 and 0. These approaches, get closer to quantitative analysis [9, 10, 3]. Fully quantitative approaches are based on Lotka-Volterra predator-prey models [11]. Pathways are interpreted as systems of reactions, and each reaction is described by Ordinary Differential Equations (ODEs) for the protein concentrations.

Complicated pathways result in large systems of ODEs characterized by many parameters. Their behaviour depends on the reaction constants, that must be determined experimentally. It is usually difficult and invasive to get a good estimate of such constantss; moreover, their values vary from cell type to cell type.

In this work a different approach is developed, through a generalization of Boltzmann Maps meant to describe the behavior of the concentrations of proteins as functions of the parameters. In this way, it is possible to understand the importance of the reaction constants for the different biological phenotipes. Various models of chemical reactions appear chaotic, while other models appear non chaotic [6, 12, 18, 4, 7, 21], but it is diffcult to understand the extent to which these behaviours pertain to the models, to their approximations, or to the real systems of reactions.

The considerable amount of research performed so far has not clarified to a satisfactory degree various questions, including that of the bistability [1, 5]. In fact, doubts have been raised that the law of mass action is the appropriate starting point to understand these problems of biological interest. In this paper we do one step forward in this direction, indicating that the law of mass action by itself is typically not adequate to produce complex behaviours.

Boltzmann Maps allow us to treat the model without any need for simplifications. The price to pay is that, so far, Boltzmann maps do not describe all networks of reactions that one would like to treat.

This paper is organized as follows. Section 2 describes Boltzmann maps, and sumarizes the results obtained through them. Section 3 generalizes the results to networks of reactions, while Section 4 focuses on a subset of reactions that are called linearly independent. Section 5 illustrates physical aspects of this description. Section 6 summarizes our conclusions.

2. **Boltzmann maps.**

Boltzmann Maps are a class of discrete time stochastic processes [19], that have been adapted to describe the time evolution of chemical reactions [16, 14, 15, 13], by associating given probabilities to the concentrations of the chemicals which take part in a given reaction. They owe their name to the Boltzmann *Stosszahlansatz*, which implies that particles are independent before they interact with each other.

2.1. **Balanced reactions and equal reaction constants.** The first reactions that have been studied in terms of Boltzmann maps have been called "stoichiometrically balanced" and have equal forward and backward reaction constants. We recall their definition and properties, by means of a simple example first, and later we illustrate the general framework.

Definition 2.1. A chemical reaction

$$r_1 A_1 + ... + r_n A_n \underset{k_f}{\overset{k_b}{\rightleftharpoons}} s_1 B_1 + ... + s_m B_m$$

is called *stoichiometrically balanced*, if the sums of its stoichiometric coefficients obey $r_1 + ... + r_n = s_1 + ... + s_m$. If some of the chemicals A_i and B_j coincide, the reaction is called *autocatalytic*.

Consider the following reaction with equal reaction rates for both directions of reaction:

$$2A \underset{k}{\overset{k}{\rightleftharpoons}} A + B. \tag{1}$$

The law of mass action gives the evolution of the concentrations of the chemicals A and B, respectively a and b, in terms of the following system of ODEs:

$$\begin{aligned} \dot{a} &= -k(a^2 - ab) \\ \dot{b} &= +k(a^2 - ab) \end{aligned} \tag{2}$$

This system can be associated with an evolving probability measure P, whose components are the normalized concentrations:

$$P = (P_A, P_B); \quad P_A + P_B = 1; \quad P_A,\ P_B \geq 0$$
$$P_A = \frac{a}{a+b}, \quad P_B = \frac{b}{a+b}$$

and belongs to the simplex of probability measures $\Sigma(\Omega)$ on the sample space $\Omega = \{A, B\}$. Assume that the probability for a particle i to interact with a particle j is, according to the Boltzmann's *Stosszahlansatz*, $p_{ij} = P_i P_j$ where $i, j = A, B$. Then, one can form the four dimensional vector $p = P \otimes P = \sigma(P)$ that describes the two-chemicals probabilities:

$$p = \left(p_{AA}, \quad p_{AB}, \quad p_{BA}, \quad p_{BB}\right) = \left(p_A^2, \quad p_A p_B, \quad p_B p_A, \quad p_B^2\right) \ ,$$

with $p \in \Sigma(\Omega \times \Omega)$, the simplex of probability measures on the sample space $\Omega \times \Omega = \{AA, AB, BA, BB\}$.

After a time interval Δt, during which reactions take place, the concentrations of A and B, hence the probability p, may have changed. If μ is the probability that two particles A react and produce a pair AB in that time interval, $1 - 2\mu$ is the probability that they do not react[2]. Then, the probability to find a couple AA, after a time step, is $(1-2\mu)$ times the probability that two A's are present, p_{AA}, plus the contribution of the reverse reaction, which uses one A and one B to produce two A's. Assume that the reverse reaction occurs with same probability, in the same

[2]The factor two in front of μ is due to the fact that A and A produce AB or BA with equal probability.

interval Δt. Then, calling $p^* = (p^*_{AA}, p^*_{AB}, p^*_{BA}, p^*_{BB})$ the resulting probability, one can write:

$$\begin{aligned}
p^*_{AA} &= (1-2\mu)p_{AA} + \mu p_{AB} + \mu p_{BA} = (1-2\mu)p_A^2 + 2\mu p_A p_B \\
p^*_{AB} &= \mu p_A^2 + (1-\mu)p_A p_B \\
p^*_{BA} &= \mu p_A^2 + (1-\mu)p_A p_B \\
p^*_{BB} &= p_B^2
\end{aligned}$$

The last equation is due to the fact that two B's interaction results always in two B's. Concisely, one may write $p^* = \begin{pmatrix} p^*_{AA} & p^*_{AB} & p^*_{BA} & p^*_{BB} \end{pmatrix} = Tp$, where $T : \Sigma(\Omega \times \Omega) \to \Sigma(\Omega \times \Omega)$, is defined by

$$T = \begin{pmatrix} 1-2\mu & \mu & \mu & 0 \\ \mu & \frac{1-\mu}{2} & \frac{1-\mu}{2} & 0 \\ \mu & \frac{1-\mu}{2} & \frac{1-\mu}{2} & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

and is doubly stochastic if $\mu \in [0, \frac{1}{2}]$. The probabilities of the single chemicals after the time Δt is the conditional expectation onto the first factor of p^*, $P^* = (P^*_A \; P^*_B) = Mp^*$, where $M : \Sigma(\Omega \times \Omega) \to \Sigma(\Omega)$ is defined by

$$Mq = M(q_{AA}, q_{AB}, q_{BA}, q_{BB}) = ((Mq)_A, (Mq)_B) = (q_{AA} + q_{AB}, q_{BA} + q_{BB}) \; .$$

Therefore, one obtains

$$\begin{aligned}
P^*_A &= P_A - \mu(P_A^2 - P_A P_B) \\
P^*_B &= P_B + \mu(P_A^2 - P_A P_B)
\end{aligned}$$

which is the Euler scheme for the numerical solution of Eqs.(2), with $\mu = k(a+b)\Delta t$.

Definition 2.2. Given a sample space Ω, and a doubly stochastic matrix on $\Sigma(\Omega \times \Omega)$, the map $\tau : \Sigma(\Omega) \to \Sigma(\Omega)$, that transforms P into P^*, performing the steps σ, T and M:

$$P \overset{\sigma}{\mapsto} p = P \otimes P \overset{T}{\mapsto} p^* \overset{M}{\mapsto} P^* = \tau(P) \tag{3}$$

is called *Boltzmann Map*.

This definition trivially generalizes to the case in which T acts on $\Sigma(\Omega \times_{i=1}^{n} \Omega)$, for any finite n [16]

This construction suggests some considerations. From the second principle of thermodynamics, the physical entropy of an isolated system, such as the one here described, increases from the initial state to the equilibrium state. Often the thermodynamic entropy is identified with the information theoretic Shannon entropy, defined by

$$\mathscr{S} = -P_A \log P_A - P_B \log P_B = S(P_A) + S(P_B) \; ,$$

although this identification is not always justified. Nevertheless, if $\mathscr{S}$ qualitatively behaves like the physical entropy, one may use it to characterize the evolution of the system. In particular maximizing the Shannon entropy as a function of the probability measure p, one could identify the steady states.

The Shannon entropy would then be a Liapunov functional for the system of ODEs associated with Reaction (1), as indeed verified in [16].

This approach readily extends to systems of m reactions involving n chemicals [16]

$$\alpha_i{}^j C_j \underset{k_i^-}{\overset{k_i^+}{\rightleftharpoons}} \hat{\alpha}_i{}^j C_j \ ; \quad i = 1, \ldots, m \ ; \quad j = 1, \ldots, n \tag{4}$$

if stoichiometric balance holds, i.e. $\sum_{j=1}^n \alpha_i{}^j = \sum_{j=1}^n \hat{\alpha}_i{}^j$, and if $k_i^+ = k_i^-$.[3] Let us introduce the $m \times n$ matrices $\alpha = (\alpha_i{}^j)$ and $\hat{\alpha} = (\hat{\alpha}_i{}^j)$ containing the stoichiometric coefficients of chemicals that appear respectively on the left and on the right hand side of Eq.(4). The rows of α and $\hat{\alpha}$ correspond to reactions while the columns refer to the different chemicals; these form the sample space, $\Omega = \{C_1, ..., C_n\}$. If chemical C_j does not appear on the left of the i-th reaction, $\alpha_i{}^j = 0$ and, similarly, $\hat{\alpha}_i{}^j = 0$ if it does not appear on the right side. A Boltzmann map can be defined for such systems of reactions, through the convex combination τ of the maps of the single reactions, $\tau^{(i)}$, i.e.

$$\tau = \sum_{i=1}^n \lambda_i \tau^{(i)}, \quad \lambda_i \geq 0, \quad \sum_{i=1}^m \lambda_i = 1,$$

where, letting $P \in \Sigma(\Omega)$ be a probability on Ω, each $\tau^{(i)}$ acts as the identity on the components of P concerning the chemicals not affected by the i-th reaction. The map σ of the previous example, is replaced, in each single reaction, by a map σ_i, which forms the product $\otimes_{j=1}^{\nu_i} P_j$, i.e. the product probability in the ν_i-particles space $\Sigma(\times_{i=1}^{\nu_i}\Omega)$, if $\nu_i = \sum_{j=1}^n \alpha_i{}^j = \sum_{j=1}^n \hat{\alpha}_i{}^j$. Similarly T is replaced by the single interaction matrices $T^{(i)}$, constructed with the probabilities that ν_i particles react. Finally, M is replaced by the conditional expectations M_i, which sum over $\nu_i - 1$ components of the joint probabilities on the ν_i-particle space.

Thanks to the properties of doubly stochastic matrices and to the convexity of the entropy, existence, uniqueness, global stability and convergence to the fixed points (or stationary states) have been proven for all systems of stoichiometrically balanced reactions, with $k_i^+ = k_i^-$ for all reactions [16]. These results exclude the possibility that such systems of reactions, as large and complex as one wishes, may enjoy any form of bistability.[4] It is interesting to note that this is a consequence of the following facts:

- the dynamics τ takes palce in a compact and convex state space;
- the Shannon entropy is bounded, strictly convex and a strict Liapunov function for each single raction $\tau^{(i)}$;
- the dynamics due to a single $\tau^{(i)}$ moves the concentrations along a given straight line whose orientation is determined by the stoichiometric coefficients, and which is selected by the initial conditions.

It follows that the convex combination of the single maps has the Shannon entropy as a strict Liapunov function, that the maximum of this function is an equilibrium state, and that this equilibrium is unique and globally attracting. This is in accord with the physics of well stirred (spacially homogenous) and isolated (neither matter nor energy are exchanged with the environment) reactions. Furthermore, because each single reaction makes the Shannon entropy increase, except at the equilibrium

[3] In Eq.(4), Einstein's summation convention is used.

[4] Various equilibria may coexist, but except for the one that maximizes the Shannon entropy, subject to the constraints of the conserved quantities, they are all trivial, in the sense that they correspond to the absence of chemicals needed for the reaction to proceed.

state, it results that the unique fixed point is the only point which is fixed for each reaction, separately. This makes quite easy its identification. Furthermore, the fact that each single $\tau^{(i)}$ reaction moves the probabilities along a line of given orientation and that τ is a convex combination of the $\tau^{(i)}$'s, implies that the full dynamics is confined within a set of dimensionality equal to the number of independent orientations. Therefore lack of stoichiometric balance, or unequal reaction constants are necessary conditions for multistable phenomena.

The generalization of the above results to systems of reactions which are not stoichiometrically balanced, or which have unequal forward and backward reaction constants, is not obvious. Indeed, simple counterexamples show that some fundamental features of the theory outlined above fail to be realized in more general settings. This problem is considered in the next section.

2.2. **Activity-led and X-led general single reactions.** Boltzmann Maps have been devised for *single* reactions which are not stoichiometrically balanced and which have unequal reaction rates [13]. The construction given so far, however, holds for single reactions only and rests on virtual particles, which restore the stoichimetric balance and equalize the possibly different forward and backward reaction rates. We illustrate these ideas on a simple example:

$$A + A \underset{k^-}{\overset{k^+}{\rightleftharpoons}} B, \quad \text{with} \quad k^+ \neq k^- \ . \tag{5}$$

To be treated, this reaction is first transformed into

$$A + A \underset{k}{\overset{k}{\rightleftharpoons}} B + \gamma^-, \tag{6}$$

where the value of k is proportional to k^+ while the concentration of γ^- is fixed so that the product $k\gamma^-$ be equally proportional to k^-. Thus the modified reaction behaves like the original one, with different forward and backward reaction constants. If γ^- is seen as a real chemical, the fact that its concentration is fixed implies a flow of γ^- particles in and out of the reactor. Therefore, Reaction (5) represents an open system and its entropy does not necessarily grow, differently from the previously discussed cases.[5] In this case, even if the Shannon entropy continues to qualitatively behave as the physical entropy, it does not necessarily play the role of a Liapunov functional for the evolution, and shoud be replaced by other quantities [13, 14, 17].

Indeed, in [13, 17, 14], the theory was modified as follows. First, the sample space is taken to be $\Omega = \Omega_A \times \Omega_B \times \Omega_{\gamma^-}$, where $\Omega_d = \{0, 1, 2, 3, \dots\}$ is the infinite sample space of numbers of molecules of chemical d. Let p be a probability measure on the simplex $\Sigma(\Omega)$. Its time evolution is given through a doubly stochastic operator, as in the previous theory, but the vectors of probabilities $p = \{p_{ijk}\}_{i,j,k=0}^{\infty}$ are not identified with the concentrations of the chemicals: their generic component, p_{ijk} say, represents the probability to find i particles of chemical A, j particles of B and k particles of γ^- in a given volume ΔV, which is not specified. The chemical concentrations are obtained as the expected numbers of chemicals, N_A,N_B and N_{γ^-},

[5] In some papers the virtual particles have been interpreted as the heat exchanged by the reaction with a heat reservoir [17]. Even in this case, the system is formally not isolated and the entropy is not a Liapunov function.

in ΔV, and are given by

$$\rho_A = \frac{N_A}{\Delta V} = \frac{1}{\Delta V}\sum_{i=0}^{\infty} i\ p_A(i)\ ; \qquad \rho_B = \frac{N_B}{\Delta V} = \frac{1}{\Delta V}\sum_{i=0}^{\infty} i\ p_B(i) \tag{7}$$

$$\rho_{\gamma^-} = \frac{N_{\gamma^-}}{\Delta V} = \frac{1}{\Delta V}\sum_{i=0}^{\infty} i\ p_{\gamma^-}(i) \tag{8}$$

where

$$p_A(i) = \sum_{j,k=0}^{\infty} p_{ijk}\ , \quad p_B(j) = \sum_{i,k=0}^{\infty} p_{ijk}\ , \quad p_{\gamma^-}(k) = \sum_{i,j=0}^{\infty} p_{ijk}$$

are the marginal probabilities concerning the single chemicals. For a general single reaction of the form:

$$\alpha\ {}^jC_j \underset{k^+}{\overset{k^-}{\rightleftharpoons}} \hat{\alpha}\ {}^jC_j, \qquad\qquad j = 1, \dots, n \tag{9}$$

one needs two virtual chemicals at most, γ^- and γ^+. One virtual chemical suffices if the reaction is not stoichiometrically balanced, since one may add a stoichiometric coefficient for γ^- to balance the stoichiometry. Then taking the γ^- concentration one obtains the desired k^+ to k^- ratio. If, on the other hand, the reaction is stoichiometrically balanced, two virtual chemicals are needed to preserve this balance, and there is one further degree of freedom to obtain the desired value of k^+/k^-. In the following, for sake of generality, we assume that two virtual chemicals have been added to the original reaction:

$$\begin{gathered} \eta\gamma^+ + \alpha\ {}^jC_j \underset{\tilde{k}}{\overset{\tilde{k}}{\rightleftharpoons}} \hat{\alpha}\ {}^jC_j + \hat{\eta}\gamma^-, \\ \alpha\ {}^j\delta_j + \eta\hat{\delta}_+ = \hat{\alpha}\ {}^j\delta_j + \hat{\eta}\hat{\delta}_-\ . \end{gathered} \tag{10}$$

Denote by $\Omega_C = \prod_{j=1}^n \Omega_{C_j}$ the sample space of the real chemicals, with $\Omega_{C_j} = \{0, 1, 2, 3, \dots\}$ for each chemical C_j, and by $(l_1, l_2, \cdots, l_n)$ the configuration of the system with l_1 molecules of chemical C_1, l_2 of chemical C_2 and so on. The full sample space of the balanced reaction is then

$$\Omega \equiv \Omega_C \times \Omega_\gamma \equiv \prod_{d=1}^{n} \Omega_d \times \Omega_{\gamma^+} \times \Omega_{\gamma^-}$$

where $\Omega_\gamma = \Omega_{\gamma^+} \times \Omega_{\gamma^-}$ is the sample space of the virtual chemicals. Let $\Sigma(\Omega)$ denote the simplex of probability measures on Ω, and consider only product measures in it:

$$p = \otimes_{d=1}^{n}\ p_d \otimes p_{\gamma^+} \otimes p_{\gamma^-}$$

where $p_d = (p_d(0), p_d(1), p_d(2), \dots)$ is the collection of probabilities $p_d(i)$ to find i particles of species d in volume ΔV. So the probability to find that the state is

$$(l_1, \dots, l_n, q_+, q_-)\,, \tag{11}$$

is defined by the product:

$$p_{l_1 \cdots l_n q_+ q_-} = p_1(l_1) \cdots\ p_n(l_n)\ p_{\gamma^+}(q_+)\ p_{\gamma^-}(q_-). \tag{12}$$

In order to obtain the kinetic equations for the reaction, [13] assumes that initially p_d obeys $p_d(i) = a_d^i(1 - a_d)$, with $a_d \in [0, 1)$, which is called activity, and is related

to the average (or expected) number of chemicals N_d in ΔV by

$$N_d = \frac{a_d}{1-a_d}, \qquad a_d = \frac{N_d}{1+N_d} \ .$$

To describe the evolution of the probability measure p, caused by the chemical reaction, [13] introduces a doubly stochastic operator $T : \Sigma(\Omega) \to \Sigma(\Omega)$, defined by

$$p^*_{l_1\cdots l_n q_+ q_-} = T_{l_1\cdots l_n q_+ q_-}{}^{a_1\cdots a_n b_+ b_-} p_{a_1\cdots a_n b_+ b_-} ,$$

with the condition that a state like (11) may only evolve in

$$(l_1 - m_1, \cdots, l_n - m_n, q_+ - \eta, q_- + \hat{\eta})$$

or in

$$(l_1 + m_1, \cdots, l_n + m_n, q_+ + \eta, q_- - \hat{\eta}) .$$

Let μ be the probability of such transitions in the unit time. Here, $m_d \equiv \alpha^d - \hat{\alpha}^d$ represents the variation of the number of chemicals in one reaction event. Clearly, the reaction events may take place only if the number of reactants is sufficient, i.e. if

$$l_d - m_d \geq 0, \quad q_+ - \eta \geq 0, \quad q_- - \hat{\eta} \geq 0 \ .$$

In this case, there is a probabilty $1 - 2\mu$ that the reaction event does not occour. Otherwise the no-reaction probability is 1.

Remark 1. At this stage, the concentrations of virtual chemicals may still vary. The way in which they are fixed is explained later.

The probability of the state Eq.(11), after one time step, is then obtained from the probability that the reaction does not take place, times the initial probability, and from the probability that the reaction does take place, times the probability associated with the reaction products. The resulting operator T may be represented by the matrix elements

$$\begin{aligned} T_{l_1\cdots l_n q_+ q_-}{}^{a_1\cdots a_n b_+ b_-} = & (1 - \mu\zeta_+ - \mu\zeta_-)\, \delta_{l_1\cdots l_n q_+ q_-}{}^{a_1\cdots a_n b_+ b_-} + \\ & - \mu\zeta_+ \delta_{l_1 - m_{i1}, \cdots, l_n - m_{in}, q_+ - \eta, q_- + \hat{\eta}}{}^{a_1\cdots a_n b_+ b_-} + \\ & - \mu\zeta_- \delta_{l_1 + m_{i1}, \cdots, l_n + m_{in}, q_+ + \eta, q_- - \hat{\eta}}{}^{a_1\cdots a_n b_+ b_-} \ . \end{aligned} \tag{13}$$

where $\delta_{l_1\cdots l_n q_+ q_-}{}^{a_1\cdots a_n b_+ b_-}$ are Kroneker symbols, whose elements equal one when the values of the upper labels equal those of the lower ones, and are zero otherwise, while the terms $\zeta_\pm$ let the reaction proceed only when the amounts of chemicals are sufficient for that; they are defined as products of Heaviside step funcions:

$$\zeta_+ = \prod_{d=1}^{n} \theta(l_d - \alpha_d)\theta(q_+ - \eta)$$

$$\zeta_- = \prod_{d=1}^{n} \theta(l_d - \hat{\alpha}_d)\theta(q_- - \hat{\eta}) \ .$$

In the case of Reaction (6), T has a set of invariant subspaces, in the simplex $\Sigma(\Omega)$, that are spanned by the probabilities of the following sets of states in Ω:

$$\begin{aligned} &\{(n, j, z), \quad (n-2, j+1, z+1), \quad \ldots, \quad (1, j + \tfrac{n-1}{2}, z + \tfrac{n-1}{2})\}, \quad \text{if } n \text{ is odd}, \\ &\{(n, j, z), \quad (n-2, j+1, z+1), \quad \ldots, \quad (0, j + \tfrac{n}{2}, z + \tfrac{n}{2})\}, \quad \text{if } n \text{ is even}, \end{aligned}$$

where $j, z \geq 0$, $jz = 0$, and none of the entries in the brackets can be negative. For example, let the initial state be $(4, 2, 1)$. Then the corresponding invariant subspace concerns the states

$$\{(6, 1, 0), \quad (4, 2, 1), \quad (2, 3, 2), \quad (0, 4, 2)\}.$$

The smallest subspaces are related to $\{(0, j, z)\}$ and $\{(1, j, z)\}$ and are one-dimensional. The action of T is the identity on the 1-dimensional invariant subspaces; it is represented by

$$\begin{pmatrix} 1-\mu & \mu \\ \mu & 1-\mu \end{pmatrix},$$

on the 2-dimensional subspaces, and by

$$\begin{pmatrix} 1-\mu & \mu & 0 \\ \mu & 1-2\mu & \mu \\ 0 & \mu & 1-\mu \end{pmatrix}$$

on the three dimensional subspaces. Higher dimensional subspaces are acted on by block matrices whose first and last rows are $(1-\mu, \mu, 0, \ldots, 0)$ and $(0, \ldots, 0, \mu, 1-\mu)$ respectively, while the other rows have the form $(0, \ldots, 0, \mu, 1-2\mu, \mu, 0, \ldots, 0)$.

The probability p_d^* to find particles of the species d, after the action of T, which transforms p into p^*, is obtained as the conditional expectation onto the d-th factor $p_d^* = M_d p^*$, defined by

$$p_d^*(l_d) = \sum_{l_1,\ldots,l_{d-1},l_{d+1},\ldots,q_+,q_-} p^*_{l_1,\ldots,l_d,\ldots,l_n,q_+,q_-}, \quad l_d = 0, 1, 2, \ldots \tag{14}$$

In the case of Reaction (6), this results in the probabilities

$$\begin{aligned} p_A^*(0) &= (1-\mu)p_A(0) + \mu\left[p_A(2) + p_A(0)p_B(0) + p_A(0)p_{\gamma^-}(0) + \right. \\ &\quad \left. - p_A(0)p_B(0)p_{\gamma^-}(0)\right] \\ p_A^*(1) &= (1-\mu)p_A(1) + \mu\left[p_A(3) + p_A(1)p_B(0) + p_A(1)p_{\gamma^-}(0) + \right. \\ &\quad \left. - p_A(1)p_B(0)p_{\gamma^-}(0)\right] \\ p_A^*(i) &= (1-2\mu)p_A(i) + \mu p_A(i)\left[p_B(0) + p_{\gamma^-}(0) - p_B(0)p_{\gamma^-}(0)\right] + \\ &\quad + \mu p_A(i-2)\left[1 - p_B(0) - p_{\gamma^-}(0) + p_B(0)p_{\gamma^-}(0)\right] + \\ &\quad + \mu p_A(i+2), \quad i \geq 2, \end{aligned} \tag{15}$$

for the chemical A, and in the probabilities:

$$\begin{aligned} p_B^*(0) &= R_B(0); & p_B^*(j) &= R_B(j), \quad j \geq 1 \\ p_{\gamma^-}^*(0) &= R_{\gamma^-}(0); & p_{\gamma^-}^*(z) &= R_{\gamma^-}(z), \quad z \geq 1 \end{aligned}$$

for the chemicals B and γ, where

$$\begin{aligned} R_d(0) &= (1-\mu)p_C(0) + \mu[p_A(0)p_C(0) + p_A(1)p_C(0) + p_C(0)], \quad \text{for} \quad d = \{B, \gamma\} \\ R_B(j) &= (1-2\mu)p_B(j) + \mu[p_A(0) + p_A(1) + p_{\gamma^-}(0)] + \mu p_B(j+1)[1 - p_{\gamma^-}(0)] + \\ &\quad + \mu p_B(j-1)[1 - p_A(1) - p_A(0)], \qquad \text{for} \quad j \geq 1 \\ R_{\gamma^-}(j) &= (1-2\mu)p_{\gamma^-}(j) + \mu[p_A(0) + p_A(1) + p_B(0)] + \mu p_{\gamma^-}(j+1)[1 - p_B(0)] + \\ &\quad + \mu p_{\gamma^-}(j-1)[1 - p_A(1) - p_A(0)] \qquad \text{for} \quad j \geq 1 \end{aligned}$$

After a time step, Δt, the average expected number of chemicals of specie d becomes $N_d^* = \sum_{i=1}^{\infty} i p_d^*(i)$. In particular, Reaction (6) yields

$$N_A^* = N_A - \mu \left\{ 2[1 - p_A(1) - p_A(0) - 2[1 - p_B(0) - p_{\gamma^-}(0) + p_B(0) p_{\gamma^-}(0)] \right\}$$

where Eq.(15) was used. Recalling that the initial probability has the form $p_d(i) = a_d^i(1 - a_d)$, one obtains

$$N_A^* = N_A - 2\mu(a_A^2 - a_B a_{\gamma^-}) \ . \tag{16}$$

In the limit that $N_d \ll 1$, one has $a_d \approx N_d$, hence Eq.(16) becomes the Euler scheme for the numerical solution of the differential equation implied by the law of mass action, expressed in terms of the average number of chemicals:

$$N_A^* = N_A - 2\mu(N_A^2 - N_B N_{\gamma^-}) \ ,$$

where $\mu = \tilde{k}\Delta t$ and $\tilde{k}$ is the reaction constant of (10). Similarly, for the other chemicals, the action of T produces:

$$N_B^* = N_B + \mu(N_A^2 - N_B N_{\gamma^-}) \ , \qquad N_{\gamma^-}^* = N_{\gamma^-} + \mu(N_A^2 - N_B N_{\gamma^-}) \ .$$

In the time Δt, p most likely loses its original form of product probability, even if it starts as such. Therefore, to continue to express the evolution in terms of activities, [13] first introduced the map M that takes p^* into the product of its marginals, $p_1^* \otimes p_2^* \otimes \cdots \otimes p_{\gamma^+}^*$, and then defined the map $Q_d : \Sigma(\Omega_d) \to \Sigma(\Omega_d)$ as:

$$[Q_d p_d](i) = a_d^i(1 - a_d), \quad 0 \le a_d < 1, \quad i \ge 0$$

with the requirement that N_d be preserved by Q_d, i.e.

$$\sum_{i=0}^{\infty} i[Q_d p_d](i) = \sum_{i=0}^{\infty} i p_d(i) = N_d$$

The action of the map obtained concatenating T, M and the Q_d's (collectively denoted by Q) modifies the concentrations of the virtual chemicals, therefore, [13] finally introduces the map $\xi : \Sigma(\Omega) \to \Sigma(\Omega)$, which acts only on the probabilities of the virtual chemiclas, restoring them to their initial values. The Boltzmann Map for the given single reaction, is then defined as the map acting on product states, which is obtained from the composition of the maps described above; it can be concisely expressed by $\tau = \xi \circ Q \circ M \circ T$.

Definition 2.3. The single reaction map defined by

$$\begin{aligned} p \ = \ & \otimes_{d=1}^n p_d \otimes p_{\gamma^+} \otimes p_{\gamma^-} \ \overset{T}{\mapsto} \ p^* \ \overset{M}{\mapsto} \otimes_{d=1}^n p_d^* \otimes p_{\gamma^+}^* \otimes p_{\gamma^-}^* \\ & \overset{Q}{\mapsto} \otimes_{d=1}^n p_d' \otimes p_{\gamma^+}' \otimes p_{\gamma^-}' \ \overset{\xi}{\mapsto} \ \otimes_{d=1}^n p_d' \otimes p_{\gamma^+} \otimes p_{\gamma^-} = p' = \tau p \ . \end{aligned} \tag{17}$$

is called *generalized Boltzmann Map.*

The Shannon entropy associated to the system described by Reactions (10) is defined by

$$\begin{aligned}\mathscr{S}(p) &= -\sum_{l_1\dots q_-}^{\infty} p_{l_1\dots p_{\gamma^-}} \log p_{l_1\dots p_{\gamma^-}} = \\ &= -\sum_{d=1}^{n}\sum_{i=0}^{\infty} p_d(i)\log p_d(i) - \sum_{i=0}^{\infty} p_{\gamma^+}(i)\log p_{\gamma^+}(i) - \sum_{i=0}^{\infty} p_{\gamma^-}(i)\log p_{\gamma^-}(i) = \\ &= \sum_{d=1}^{n}[(1+N_d)\log(1+N_d) - N_d\log N_d] + (1+N_{\gamma^+})\log(1+N_{\gamma^+}) + \\ &\qquad - N_{\gamma^+}\log N_{\gamma^+} + (1+N_{\gamma^-})\log(1+N_{\gamma^-}) - N_{\gamma^-}\log N_{\gamma^-} = \\ &= \sum_{d=1}^{n} S(p_d) + S(p_{\gamma^+}) + S(p_{\gamma^-})\end{aligned}$$

where the single chemical entropies S have been introduced. The actions of T, M and Q do not decrease $\mathscr{S}$, if Δt is sufficiently small and positive; indeed, they increase $\mathscr{S}$ except at their unique common fixed point. But the action of the map ξ, taking back to their previous values the probabilities of the virtual chemicals, could decrease $\mathscr{S}$, consistently with the picture of an open system. Is there a different Liapunov functional that may characterize the dynamics of τ defined by Eq.(17)? References [13, 17, 19] answer affirmatively this question, observing that

$$\begin{aligned}S(N'_\gamma) &= (1+N'_\gamma)\log(1+N'_\gamma) - N'_\gamma\log N'_\gamma + (1+N'_\gamma)\log(1+N_\gamma) \\ &\quad - N'_\gamma\log N_\gamma - (1+N'_\gamma)\log(1+N_\gamma) + N'_\gamma\log N_\gamma = \\ &= f_{N_\gamma}(N'_\gamma) + (1+N'_\gamma)\log(1+N_\gamma) - N'_\gamma\log N_\gamma\end{aligned}$$

where $\gamma = \gamma^+$ or γ^-, and $f_{N_\gamma}(x) = (1+x)\log\frac{(1+x)}{(1+N_\gamma)} - x\log\frac{x}{N_\gamma}$. The function f_{N_γ} has an absolute minimum in $x = N_\gamma$ and obeys $f_{N_\gamma}(x) \geq 0$, for every $x \in \mathbb{R}^+ \cup \{0\}$. It follows that the Shannon entropy for real chemicals obeys the following:

$$\begin{aligned}&\sum_{d=1}^{n} S(N'_d) = \mathscr{S}(p') - S(N'_{\gamma^+}) - S(N'_{\gamma^-}) \\ &\geq \mathscr{S}(p) - \sum_{q=\{\gamma^+,\gamma^-\}}\Big[(1+N'_q)\log(1+N_q) - N'_q\log N_q\Big] = \\ &\sum_{d=1}^{n} S(N_d) + (N'_{\gamma^+} - N_{\gamma^+})\log\frac{N_{\gamma^+}}{(1+N_{\gamma^+})} + (N'_{\gamma^-} - N_{\gamma^-})\log\frac{N_{\gamma^-}}{(1+N_{\gamma^-})}\end{aligned} \tag{18}$$

where N'_d is the population of the real chemical C_d after a time step, while N'_{γ^+} and N'_{γ^-} are the populations that the virtual chemicals would reach if they were not fixed by the map ξ. The inequality holds because the Shannon entropy is defined over the complete system of real and virtual chemicals, and the virtual ones change like any other chemical under the actions of T, M and Q. Thus $\mathscr{S}(p') = \sum_{d=1}^{n} S(N'_d) + S(N'_{\gamma^+}) + S(N'_{\gamma^-}) \geq \sum_{d=1}^{n} S(N_d) + S(N_{\gamma^+}) + S(N_{\gamma^-}) = \mathscr{S}(p)$, and the only step that may decrease $\mathscr{S}$ is the application of ξ. Exploiting the existence of conserved quantities, such as

$$\eta N_{\gamma^+} + (\hat{\alpha}^d - \alpha^d)N_d = \text{const.}\,, \qquad \text{and} \quad \hat{\eta}N_{\gamma^-} + (\alpha^d - \hat{\alpha}^d)N_d = \text{const.}\,, \tag{19}$$

one realizes that the following function Ψ is a strict, strictly convex Liapunov functional for the reaction:

$$\Psi(N_1,\dots,N_n)=\sum_{d=1}^{n}S(N_d)+b^{\ell}_{\gamma^+}N_\ell\log\frac{N_{\gamma^+}}{(1+N_{\gamma^+})}+b^{k}_{\gamma^-}N_k\log\frac{N_{\gamma^-}}{(1+N_{\gamma^-})},\quad(20)$$

where $b^{\ell}_{\gamma^+}=\frac{\hat{\alpha}^l-\alpha^l}{\eta}$ and $b^{k}_{\gamma^-}=\frac{\alpha^k-\hat{\alpha}^k}{\hat{\eta}}$ are constants determined by the stoichiometric coefficients and N_ℓ and N_k are eiher the populations of any two real chemicals, or of any single one. Using these facts, the same argument of Section 2.1 proves the following, which applies even to non-stoichiometrically balanced reactions with unequal forward and backward reaction rates:

Proposition 1. *Consider a single activity-led reaction, with positive initial concentrations. Its state is asymptotically attracted towards a fixed point.*

The interest of the activity-led reactions lies in the fact that the law of mass action is bound to fail at very high concentrations, where the reaction rates tend to saturate, rather than growing as powers of the concentrations. From this point of view, activity-led reactions provide one saturation mechanism. However, in [13], it was proven that existence of a strict Liapunov function, and global convergence to a unique fixed point, is afforded by a much more general class of reactions, there called X-led. The X-led evolution of a generic reaction like (9) is governed by the map

$$N'_d=N_d-\operatorname{sign}\left(\alpha^d-\hat{\alpha}^d\right)\chi_d\,\mathcal{D}\left(N_1,\dots,N_n\right)\ ,\qquad d=1,\dots,n$$

where χ_d is a constant that depends on Δt and on the stoichiometric coefficients, the disequilibrium parameter is given by

$$\mathcal{D}\left(N_1,\dots,N_n\right)=k^+X_1(N_1)^{\alpha^1}\cdots X_n(N_n)^{\alpha^n}-k^-X_1(N_1)^{\hat{\alpha}^1}\cdots X_n(N_n)^{\hat{\alpha}^n}\quad(21)$$

and the functions $X_i:[0,\infty)\to\mathbb{R}$ can be the concentration, the activity or any other function of the concentration of C_i, which obeys the following conditions:

- X_i is continuously differentiable in $(0,\infty)$;
- $X_i(0)=0$;
- $\frac{dX_i}{dN_i}>0$, for $N_i>0$;
- given an interval $[0,\eta)$ and one natural number m, there is a real number $\omega(m,\eta)>0$ such that $N_i/X_i(N_i)^m\geq\omega(m,\eta)$ for all $N_i\in(0,\eta)$.

In the next section, the theory illustrated in this subsection is generalized to networks of reactions, similarly to what was done for the theory concerning stoichiometrically balanced reactions with equal forward and backward reaction constants. However, it turns out that a straight generalization of the results on existence and uniqueness of the fixed points, and on the global convergence to such fixed points, is not possible in this case.

3. **Networks of reactions.** Consider a system of m reactions in the general form:

$$\alpha_i{}^jC_j\underset{k_i^-}{\overset{k_i^+}{\rightleftharpoons}}\hat{\alpha}_i{}^jC_j,\quad i=1,\dots,m\quad j=1,\dots,n\qquad(22)$$

where stoichiometric balance and equal forward and backward reaction constants are not required. To balance stoichiometrically all the reactions, and to have equal

forward and backward reaction constants in each of them, introduce $2m$ virtual chemicals $\left(\gamma_1^-, \gamma_1^+, \cdots, \gamma_m^-, \gamma_m^+\right)$, so that the reaction becomes:

$$\eta_i \gamma_i^+ + {\alpha_i}^j C_j \underset{k_i}{\overset{k_i}{\rightleftharpoons}} {\hat{\alpha}_i}^j C_j + \hat{\eta}_i \gamma_i^- \ ; \quad i = 1, \ldots, m \ ; \quad j = 1, \ldots, n \tag{23}$$

and the balance conditions $\sum_j {\alpha_i}^j + \eta_i = \sum_j {\hat{\alpha}_i}^j + \hat{\eta}_i$ hold for every i. Here $\{{\alpha_i}^j\}$ and $\{{\hat{\alpha}_i}^j\}$ are the matrices of the stoichiometric coefficients of the Reactions (22), while $\{\eta_i\}$ and $\{\tilde{\eta}_i\}$ are the corresponding vectors for the virtual substances; these arrays have vanishing entries for the chemicals that do not appear in some of the reactions. The sample space, as above, is denoted by

$$\Omega \equiv \Omega_C \times \Omega_\gamma \equiv \prod_{d=1}^{n+2m} \Omega_d,$$

and $\Sigma(\Omega)$ represents the corresponding simplex of probability measures. Again, we only consider product probability measures $p = \otimes_{d=1}^{n+2m} p_d$, where the virtual chemicals probabilities are labelled by $d = n+1, \ldots, n+2m$. This does not suffice for a direct generalization of the theory of Subsection 2.1 to all network of reactions.

3.1. **Compactness of the phase space.** Fundamental ingredients of the proofs that led to the results of Subsection 2.1 are the convexity and compactness of the phase space, which coincided with the closed, bounded and finite dimensional $\Sigma(\Omega)$, and with the strict convexity and boundedness of the Shannon entropy $\mathscr{S}$. In the case of systems of reactions which are not balanced, this boundedness of the Shannon entropy is not guaranteed anymore. For instance, the reactions

$$x_1 \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} x_2 \ ; \qquad x_2 \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} 2x_1 \tag{24}$$

can be separately considered as single reactions, in the theory so far developed, but if they constitute a network of two reactions, they lead to an evolution during which $\mathscr{S}$ may grow without bounds. Indeed, if the two reactions are taken with same weight, the X-led evolution equations take the form

$$\begin{aligned} \dot{N}_1 &= -k_1^+ X_1 + k_1^- X_2 + 2k_2^+ X_2 - 2k_2^- X_1^2 \\ \dot{N}_2 &= k_1^+ X_1 - k_1^- X_2 - k_2^+ X_2 + k_2^- X_1^2 \end{aligned}$$

which have a unique fixed point $(\hat{X}_1 = k_1^+ k_2^+ / k_1^- k_2^-, \hat{X}_2 = (k_1^+)^2 k_2^+ / (k_1^-)^2 k_2^-)$ apart from the trivial one $(0,0)$. In the case that $X_i = N_i$, this non-trivial fixed point attracts the evolution, and results in unbounded growths if either k_1^- or k_2^- vanish, but unbounded growths of the concentrations are obtained even with finite reaction constants. For instance, if the evolution is activity led, $X_i = a_i$, it suffices that either $\hat{X}_1$ or $\hat{X}_2$ be greater than one. However, Reaction (24) is not physically relevant, since it violates the condition of conservation of mass; the concentrations may grow without bounds, making the Shannon entropy, as well as other similar functionals, increase without bounds. This is not the case of stoichiometrically balanced reactions, because they even preserve the total number of particles in the system. One realizes that Reaction (24) has no linear conserved quantities whose coefficients are all positive. Therefore, in the following, we restrict our attention to systems which verify the following:

Condition 1. *When the reactor is closed, the network of reactions preserves one linear combination of all the "concentrations"*

$$\varsigma^{\,j} N_j = M \tag{25}$$

whose coefficients $\varsigma^{\,j}$ *are all positive.*

This condition is independent of the equality, or otherwise, of the forward and backward reaction constants.

Conservation of mass always leads to a conserved quantity of the form of Eq.(25) but this condition is more general: Eq.(25) is a necessary condition for compactness of the phase space, whatever the meaning of this conserved quantity is.

$$N_j(t) \geq 0, \quad j = 1, \ldots, n+\eta$$

for all times t, which, because of the validity of Eq.(25), implies also the bounds

$$N_j(t) \leq \bar{N}_j = \frac{M}{\varsigma^{\,j}}$$

The presence of further linear conserved quantities, of the form

$$\varsigma_j{}^{j} N_j = c_j \ , \qquad j = 1, ..., \tilde{m} \tag{26}$$

where the coefficients $\varsigma_j{}^{j}$ are not necessarily positive anymore, simply reduces further the size of the phase space for the evolution of the concentrations, which we call Λ. This proves the following:

Proposition 2. *Any strictly convex function (e.g. the Shannon entropy) has a unique maximum in* Λ*, if condition in Eq.(25) is satisifed.*

3.2. **Fixed points and reactions dependence.** In the case of Section 2.1, Eq.(25) is always satisified, hence there is a unique maximum for the Shannon entropy in Λ, $\hat{\mathscr{S}} = \mathscr{S}(\hat{p})$, which corresponds to the unique fixed point of the map $\tau = \sum_{i=1}^{m} \lambda_i \tau^{(i)}$. This point is fixed for each single reaction, separately, i.e. it satisifes $\hat{p} = \tau^{(i)}\hat{p}$ for $i = 1, \ldots, m$. This makes rather easy its identification, however large the number of chemicals n or the number of reactions m might be. The search for the fixed points is further simplified by the observation that each single reaction identifies a direction in the phase space of the concentrations, which is given by the intersection of $n-1$ hyperplanes representing $n-1$ conserved quantities, like Eqs.(26). Therefore, the single reaction lives in the line identified by this direction and by the initial condition, indpendently of whether the reaction is density-led or more generally X-led. This implies that the network of reactions lives in a set which is m-dimensional, if all reaction lines are linearly independent, otherwise it lives in a lower dimensional set. Clearly, this dimensionality never exceeds $n-1$, in the physically relevant cases without in- and out-fluxes of matter, because the concentrations are assumed to obey Eq.(25).

Definition 3.1. We call *dependent* or, respectively, *independent* the networks of reactions whose reaction lines are or, respectively, are not linearly dependent.

In the cases of Section 2.1, with $(n-1)$-dimensional set Λ, the fixed point is immediately found to be the uniform distribution $p_u = (1/n, \ldots, 1/n)$, which is the global maximum of $\mathscr{S}$. This is the case whether $m = n-1$ or $m \geq n-1$, as illustrated, for example, in Fig. 1 for the two networks

$$A + B \underset{k_1}{\overset{k_1}{\rightleftharpoons}} 2C \ ; \qquad 2A \underset{k_2}{\overset{k_2}{\rightleftharpoons}} B + C \tag{27}$$

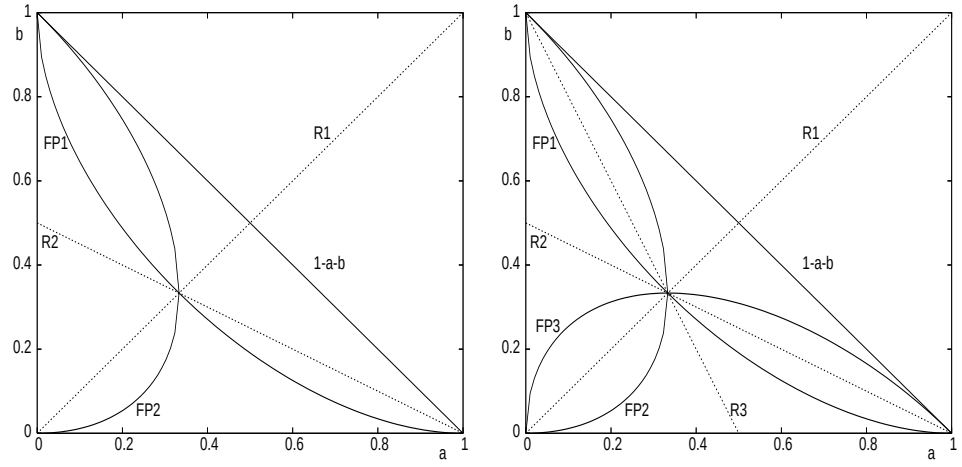

FIGURE 1. The phase space of networks (27) and (28) is the lower-right triangle of the square $[0,1]\times[0,1]$. The single reaction directions are identified by the labels R1, R2 and R3, according to the order of (28). The manifolds of fixed points of the single reactions are correspondingly labelled by FP1, FP2 and FP3. The left panel refers to network (27), the right panel to network (28). In both cases, there is a unique fixed point for the overall dynamics, identified by the intersections of the single reaction manifolds of fixed points. At that point, $\mathscr{S}$ is maximum. In the case of (27), the reaction directions are linealry independent; while they are linearly dependent in the case of (28).

and

$$A+B \underset{k_1}{\overset{k_1}{\rightleftharpoons}} 2C\ ; \qquad 2A \underset{k_2}{\overset{k_2}{\rightleftharpoons}} B+C\ ; \qquad A+C \underset{k_3}{\overset{k_3}{\rightleftharpoons}} 2B \tag{28}$$

whose only conserved quantitiy is the total mass, $p_A+p_B+p_C=1$. The fixed point of both networks is easily found to be $(1/3,1/3,1/3)$ by solving respectively the two systems

$$\begin{cases} p_A p_B = p_C^2 \\ p_A^2 = p_B p_C \end{cases} \qquad \text{and} \qquad \begin{cases} p_A p_B = p_C^2 \\ p_A^2 = p_B p_C \\ p_A p_C = p_B^2 \end{cases} \qquad \text{with } p_C = 1-p_A-p_B \tag{29}$$

and considering that the maximum of $\mathscr{S}$ can only be obtained at a fixed point (because $\mathscr{S}$ is a strict Liapunov functional), and that the maximum of $\mathscr{S}$ is the uniform distribution, if there are no constraints to satisfy.

In the case of linearly dependent networks, this reasoning fails if one of the reactions has unequal forward and backward reaction constants. Consider, for instance,

$$A+B \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} 2C\ ; \qquad 2A \underset{k_2}{\overset{k_2}{\rightleftharpoons}} B+C\ ; \qquad A+C \underset{k_3}{\overset{k_3}{\rightleftharpoons}} 2B\ . \tag{30}$$

Fig. 2 shows that the manifolds of the single reaction fixed points do not have a common intersection.

Another difficulty in the study of networks, with non-balanced reactions, is evidenced by the physical condition of the conservation of mass. Consider, for instance,

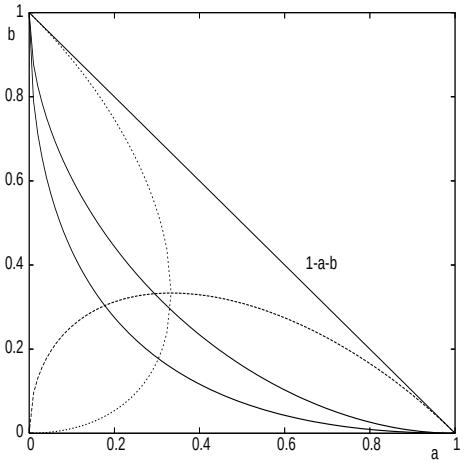

FIGURE 2. The phase space of network (30). Because $k_1^+ \neq k_1^-$ there is no fixed point common to the three reactions separtely. The two continuos curved lines correspond to $k_1^+ = 0.7$ (upper line), and to $k_1^+ = 0.2$ (lower line), while $k_1^- = 1$.

the following network:

$$A + B \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} C \; ; \qquad 2A \underset{k_2}{\overset{k_2}{\rightleftharpoons}} B + C \; ; \qquad A + C \underset{k_3}{\overset{k_3}{\rightleftharpoons}} 2B \tag{31}$$

which is like the previous example, except for the presence of C in place of $2C$, in the right hand side of the first reaction. The difficulty is that each reaction implies one condition on the masses m_A, m_B and m_C of the different chemicals: the first reaction implies $m_A + m_B = m_C$, the second implies $2m_A = m_B + m_C$ and the third implies $m_A + m_C = 2m_B$. These conditions amount to an homogeneous linear system of equations, which has positive solutions only if the determinant of the matrix of coefficients vanishes. In our case, this does not happen: the three equations have only the trivial solution.

In general, networks of balanced reactions are bound to give rise to dependent linear equations for the masses, whether the networks are dependent or not, because the sum of the columns of the relevant coefficient matrix is the vanishing column. If, on the other hand, one reaction is not balanced, the sum of the columns of the coefficient matrix has one non-vanishing entry, and this may result in an independent set of equations, which admit only the trivial solution. This means that the given network, although mathematically viable, is physically impossible. Clearly, for a fixed number of substances, the larger the number of reactions, the more likely it is for a generic network to be dependent and for the equations for the masses to be independent, if stoichiometric balance is not satisfied. Then the network is not physically consistent, and is not of interest in our investigation on chemical kinetics.

The above shows that a generalization to networks of reactions with unequal forward and backward reaction constants, or with non-balanced reactions, of the results for the existence and uniqueness of the fixed points, requires some care, when the reaction lines are dependent. Therefore, we first investigate the restricted case of independent networks.

4. **Independent networks of activity-led reactions.** Consider a network of m reactions, like (23), whose evolution is activity-led. If this network is independent, the real chemicals must be a number $n \geq m+1$, because the conservation of mass always provides one linear relation among the real chemicals concentrations. Therefore, for each different virtual chemical, there is a different linear quantity, which may be added to the Shannon entropy, in order to define a strict Liapunov function for the overall dynamics. This can be understood generalizing the argument for single reactions given in Section 2.2. Take the doubly stochastic operator

$$T = \sum_{i=1}^{m} \lambda_i T^{(i)}, \tag{32}$$

convex combination of the single reaction operator $T^{(i)}$, with coefficients λ_i, where each $T^{(i)}$ is the doubly stochastic operator describing the reaction probabilities for the i-th reaction, extended as the identity on the extra dimensions of the probability space.

Using the operator T in the definition (17) of the Boltzmann map τ, one finds that the corresponding map Υ for the evolution of the particle numbers $\mathcal{N}$

$$\mathcal{N} = (N_1, N_2, ..., N_n, N_{\gamma_1^-}, ..., N_{\gamma_m^+}) \overset{\Upsilon}{\mapsto} \mathcal{N}' = (N_1', N_2', ..., N_n', N_{\gamma_1^-}, ..., N_{\gamma_m^+}).$$

is the convex combination of the single reaction maps $\Upsilon^{(i)}$, $\Upsilon = \sum_{i=1}^{m} \lambda_i \Upsilon^{(i)}$, and is expressed by

$$N_j' = N_j - \sum_{i=1}^{m} \mu_i \left(\alpha_i^j - \hat{\alpha}_i^j\right) \mathcal{D}_i \qquad i = 1, \dots, m \ , \qquad j = 1, \dots, n$$

Here, the virtual chemicals concentrations do not vary in time. Denote by $\tilde{\Upsilon}$ the map corresponding to the same operator T, but without the application of ξ, i.e. corresponding to $\tilde{\tau} = Q \circ M \circ T$. The action of $\tilde{\Upsilon}$ is also a convex combination of single reaction maps, $\tilde{\Upsilon} = \sum_{i=1}^{m} \lambda_i \tilde{\Upsilon}^{(i)}$, and is defined by

$$\begin{aligned} N_j' &= N_j - \sum_{i=1}^{m} \mu_i \left(\alpha_i^j - \hat{\alpha}_i^j\right) \mathcal{D}_i \\ N_{\gamma_i^+}' &= N_{\gamma_i^+} - \mu_i \eta_i \mathcal{D}_i \ , \qquad i = 1, \dots, m \ , \qquad j = 1, \dots, n \\ N_{\gamma_i^-}' &= N_{\gamma_i^-} + \mu_i \hat{\eta}_i \mathcal{D}_i \end{aligned} \tag{33}$$

where $\mathcal{D}_i$ is the disequilibrium parameter of the i-th reaction, and some of the stoichiomentric coefficients may vanish. In particular, α_i^j vanishes if C_j does not appear in the left hand side of the i-th reaction, $\hat{\alpha}_i^j$ vanishes if C_j does not appear in its right hand side. The i-th reaction is called autocatalytic if both α_i^j and $\hat{\alpha}_i^j$ are positive. If $\alpha_i^j = \hat{\alpha}_i^j$, C_j is a catalyst which is neither produced nor depleted by the i-th reaction, hence the i-th reaction gives no contribution to the variation of the concentration of C_j. If the i-th reaction in the network is balanced and has equal forward and backward reaction constants, it is not necessary to introduce virtual chemicals in it, therefore, in general, a network of m reactions has η virtual chemicals, with $0 \leq \eta \leq 2m$. However, for a sufficiently general formalism, it is convenient to attribute two different virtual chemicals to each reaction in the network and, in case they are not needed because the i-th reaction is stoichiometrically balanced and has equal reaction constants, we will take $\eta_i = \hat{\eta}_i = 1$ and $N_{\gamma_i^-} = N_{\gamma_i^+} = 1$.

Similarly to Section 2.2, we replace the concentration of each virtual chemical with the concentrations of real chemicals, in the Shannon entropy, observing that

$$N_j + \sum_{i=1}^{m} \frac{\alpha_i^j - \hat{\alpha}_i^j}{\hat{\eta}_i} N_{\gamma_i^-} = K_j \ , \qquad j = 1, ..., n$$

and that

$$\eta_i N_{\gamma_i^+} + \hat{\eta}_i N_{\gamma_i^-} = K_{\gamma,i} \ , \qquad i = 1, ..., m$$

are constant in time, for the evolution expressed by Eqs.(33). Because $n \geq m + 1$, there are sufficiently many conserved quantities, and they are independent since each of them depends on the concentration of a real chemical which does not appear in any other conserved quantity. Thus, there is a unique solution for the concentrations of the virtual chemicals in terms of the real chemicals concentrations and of conserved quantities:

$$N_{\gamma_i^-} = \sum_{j=r_1,r_2,...,r_m} z_j (K_j - N_j) \ , \qquad i = 1, ..., m \tag{34}$$

where the constants z_j are determined by the stoichiometric coefficients, and the indexes r_ℓ label the real m chemicals which have been chosen. Similarly, one has $N'_{\gamma_i^-} = \sum_j z_j (K_j - N'_j)$, and

$$N'_{\gamma_i^-} - N_{\gamma_i^-} = \sum_{j=r_1,r_2,...,r_m} z_j (N_j - N'_j) \ . \tag{35}$$

Therefore, given the initial conditions, which fix the values of the K_i's, the effect of $\tilde{\Upsilon}$ on the virtual chemicals may be replaced by its effect on the real chemicals, which is the same effect produced by the full map Υ. This can be used in the calculation of the variation of the Shannon entropy, as follows.

Observe that $\mathscr{S}(\mathcal{N}) = \sum_{j=1}^{n} S(N_j) + \sum_{j=1}^{m} [S(N_{\gamma_j^-}) + S(N_{\gamma_j^+})]$, grows under the action of $\tilde{\Upsilon}$, unless $\mathcal{N}$ is fixed for $\tilde{\Upsilon}$. Indeed, each single reaction map increases the sum of the entropies of the virtual and real chemicals of its concern, and acts as the identity on the other chemicals. If the state is fixed for all $\tilde{\Upsilon}^{(i)}$, then it is fixed for $\tilde{\Upsilon}$ and is fixed also for the full Boltzmann map Υ. If $\mathcal{N}$ is not fixed for $\tilde{\Upsilon}^{(i)}$, it is not fixed for the corresponding Boltzmann map $\tilde{\tau}^{(i)}$. Therefore one has $\mathscr{S}(\tilde{\Upsilon}^{(i)} \, \mathcal{N}) > \mathscr{S}(\mathcal{N})$, and

$$\mathscr{S}(\tilde{\Upsilon} \, \mathcal{N}) = \mathscr{S}\left(\sum_{i=1}^{m} \lambda_i \tilde{\Upsilon}^{(i)} \, \mathcal{N} \right) \geq \sum_{i=1}^{m} \lambda_i \mathscr{S}\left(\tilde{\Upsilon}^{(i)} \, \mathcal{N} \right) > \mathscr{S}(\mathcal{N}) \tag{36}$$

In terms of single chemical entropies, one may write

$$\sum_{j=1}^{n} S(N'_j) + \sum_{i=1}^{m} \left[S(N'_{\gamma_i^+}) + S(N'_{\gamma_i^-}) \right] > \sum_{j=1}^{n} S(N_j) + \sum_{i=1}^{m} \left[S(N_{\gamma_i^+}) + S(N_{\gamma_i^-}) \right] \tag{37}$$

where the dashes denote the values after one application of $\tilde{\Upsilon}$. The variation of the entropy of $N_{\gamma_i^-}$, can now be expressed as

$$\begin{aligned} S(N'_{\gamma_i^-}) - S(N_{\gamma_i^-}) &= -\sum_{k=0}^{\infty} p'_{\gamma_i^-}(k) \log p'_{\gamma_i^-}(k) + \sum_{k=0}^{\infty} p_{\gamma_i^-}(k) \log p_{\gamma_i^-}(k) \\ &= \sum_{k=0}^{\infty} p'_{\gamma_i^-}(k) \left[\log p_{\gamma_i^-}(k) - \log p'_{\gamma_i^-}(k)\right] \\ &- \sum_{k=0}^{\infty} p'_{\gamma_i^-}(k) \log p_{\gamma_i^-}(k) + \sum_{k=0}^{\infty} \log p_{\gamma_i^-}(k) \\ &\leq -\frac{\|p'_{\gamma_i^-} - p_{\gamma_i^-}\|_2^2}{2} - \sum_{k=0}^{\infty} p'_{\gamma_i^-}(k) \log p_{\gamma_i^-}(k) + \sum_{k=0}^{\infty} \log p_{\gamma_i^-}(k) \end{aligned}$$

where $\| * \|_2$ is the ℓ_2-norm, and the inequality follows from Kulback's lemma [19]. Recalling that $p_X(k) = a_X^k(1 - a_X)$ in the LTE states, one obtains

$$\begin{aligned} &S(N_{\gamma_i^-}) - S(N'_{\gamma_i^-}) \geq \\ &\frac{\|p'_{\gamma_i^-} - p_{\gamma_i^-}\|_2^2}{2} + \sum_{k=0}^{\infty} \left[p'_{\gamma_i^-}(k) - p_{\gamma_i^-}(k)\right] \left[k \log a_{\gamma_i^-} + \log(1 - a_{\gamma_i^-})\right] = \\ &\frac{\|p'_{\gamma_i^-} - p_{\gamma_i^-}\|_2^2}{2} + \left(N'_{\gamma_i^-} - N_{\gamma_i^-}\right) \log a_{\gamma_i^-} \geq \left(N'_{\gamma_i^-} - N_{\gamma_i^-}\right) \log a_{\gamma_i^-} \end{aligned}$$

Therefore, (37) leads to

$$\begin{aligned} &\sum_{j=1}^{n} S(N'_j) + \sum_{i=1}^{m} S(N'_{\gamma_i^+}) + \sum_{i \neq r} S(N'_{\gamma_i^-}) > \\ &\sum_{j=1}^{n} S(N_j) + \sum_{i=1}^{m} S(N_{\gamma_i^+}) + \sum_{i \neq r} S(N_{\gamma_i^-}) + \left[S(N_{\gamma_r^-}) - S(N'_{\gamma_r^-})\right] \geq \\ &\sum_{j=1}^{n} S(N_j) + \sum_{i=1}^{m} S(N_{\gamma_i^+}) + \sum_{i \neq r} S(N_{\gamma_i^-}) + \left(N'_{\gamma_r^-} - N_{\gamma_r^-}\right) \log a_{\gamma_r^-} \end{aligned}$$

Substituting Eq.(35), one then obtains

$$\begin{aligned} &\sum_{j=1}^{n} S(N'_j) + \sum_{i=1}^{m} S(N'_{\gamma_i^+}) + \sum_{i \neq r} S(N'_{\gamma_i^-}) + \log a_{\gamma_r^-} \sum_i z_i N'_i > \\ &\sum_{j=1}^{n} S(N_j) + \sum_{i=1}^{m} S(N_{\gamma_i^+}) + \sum_{i \neq r} S(N_{\gamma_i^-}) + \log a_{\gamma_r^-} \sum_i z_i N_i \end{aligned}$$

This identifies one strict Liapunov function for $\tilde{\Upsilon}$ which evolves the concentrations of the real chemicals as Υ does, but does not affect the concentrations of the virtual chemicals. Indeed, repeating the same calculations for all virtual chemical concentrations, one finds that

$$\Psi(\hat{\mathcal{N}}) = \sum_{j=1}^{n} S(N_j) + \sum_{j=1}^{n} \tilde{z}_j N_j \ , \tag{38}$$

which is function of the real chemicals $\hat{\mathcal{N}} = (N_1, N_2, ..., N_n)$ only, is a strict Liapunov functional for $\tilde{\Upsilon}$. Here the coefficients $\tilde{z}_j$ depend on the stoichiometric coefficients, as usual. Becasue the virtual chemicals do not appear in Eq.(38), the application of the map ξ does not affect Ψ which is, therefore, a strict Liapunov function for the whole Boltzmann map τ and for the map Υ. This has some consequence, as in the case of balanced reactions with equal forward and backward reaction constants. In particular, the following holds:

- *The compactness and convexity of the space of concentrations Λ, together with the strict convexity of Ψ, implies the existence of a unique maximum of Ψ in Λ;*
- *the fact that Ψ is a strict Liapunov function for Υ, implies that its point of maximum, $\tilde{\mathcal{N}}$ say, is a fixed point of Υ;*
- *then, $\tilde{\mathcal{N}}$ is a stable fixed point;*
- *the fixed points of Υ and of the corresponding continuous time evolution are the same, and the results for the map hold for sufficiently small time steps, i.e. for sufficiently small μ_i's in Eqs.(33), therefore the associated ODE also has a unique, stable fixed point.*

The above arguments can be generalized to the case with more than two fixed concentrations, in a single reaction, so that fluxes of real chemicals can be treated within the same framework. In that case, C_j may be treated like a virtual chemical, as long as there are sufficiently many quantities conserved by the action of Υ. As a matter of fact, the above arguments apply to all networks with as many independent quantities conserved by Υ, as many single reactions with (real or virtual) chemicals with fixed concentrations. Therefore, dependent networks can be considered, as long as the dependence concerns stoichiometrically balanced reactions with equal forward and backward reaction constants. We conclude that:

Remark 2. Multistability is not possible in networks of linearly independent activity-led reactions. These systems have one quantity conserved by Υ for each chemical that is conserved (virtual or real), and the resulting system of equations is linearly independent allowing only one set of solutions for the conserved chemicals in terms of the evolving ones.

Violating this condition is therefore a necessary condition for multistability.

4.1. **Fixed points and their stability.** For the identification of the fixed points, consider first systems which have no fixed concentrations, i.e. systems of stoichiometrically balanced reactions with equal forward and backward reaction constants. The Liapunov functional is the entropy $\mathscr{S}$. Assume that the system is at the equilibrium $\tilde{p}$: $\tau\tilde{p} = \sum_{i=1}^{m} \lambda_i \tau^{(i)}\tilde{p} = \tilde{p}$ and that at least one reaction is not, $\tau^{(i)}\tilde{p} \neq \tilde{p}$. Then, $\mathscr{S}(\tau^{(i)}\tilde{p}) > \mathscr{S}(\tilde{p})$ and

$$\mathscr{S}(\tau\tilde{p}) = \mathscr{S}\left(\sum_{i=1}^{m} \lambda_i \tau^{(i)}\tilde{p}\right) \geq \sum_{i=1}^{m} \lambda_i \mathscr{S}(\tau^{(i)}\tilde{p}) > \mathscr{S}(\tilde{p}),$$

which is in disagreement with the assumed equilibrium. Then, the fixed point $\tilde{p}$ is fixed for τ if and only if it is fixed for each single reaction $\tau^{(i)}$. The corresponding fixed concentration $\tilde{\mathcal{N}}$ is stable, because the entropy cannot decrease, hence the sets $\Lambda_s = \{\mathcal{N} \in \Lambda : \mathscr{S}(\mathcal{N}) \geq s\}$ are invariant closed convex subsets of Λ, with $\Lambda_{\tilde{\mathscr{S}}} = \tilde{\mathcal{N}}$ and $\Lambda_s = \emptyset$ for $s > \tilde{\mathscr{S}}$. Therefore, for every $\epsilon > 0$, there is $s \in [\mathscr{S}_{min}, \tilde{\mathscr{S}})$ such that

Λ_s is contained in the ball of radius ϵ centered at $\tilde{\mathcal{N}}$, $\mathcal{B}_\epsilon(\mathcal{N})$ say, where $\mathscr{S}_{min}$ is the absolute minimum of the Shannon entropy in Λ.

A similar argument holds for the stability of the unique fixed point of a general system of linearly independent reactions, because the Liapunov functional Ψ enjoys properties similar to those of $\mathscr{S}$.

These considerations substantially simplify the search for steady states. For instance, let the evolution be given by Eqs.(33), then the fixed point is not merely identified by the solutions of

$$\sum_{i=1}^{m} \mu_i(\alpha_i^j - \hat{\alpha}_i^j)\mathcal{D}_i(N_1, \dots, N_n) = 0 \ , \quad j = 1, \dots, n \tag{39}$$

but by the system of equations

$$\mathcal{D}_i(N_1, \dots, N_n) = 0 \ , \quad i = 1, \dots, m$$

within the phase space Λ identified by the conserved quantities.

5. **Physical interpretation.** It is important to point out that $N_i(\Delta V)$, the number of particles that we can expect in a volume ΔV, is an extensive quantity, while the probability of finding j molecules of chemical C_i in ΔV, $p_i(j; \Delta V)$ say, is not extensive,[6] but may still depend on ΔV. The activity a_i and the concentration of a chemical, $\rho_i = \frac{N_i}{\Delta V}$, are not extensive as well, but do not depend on ΔV, indeed they ought to be intensive quantities. Introducing $\Delta V_{i,min}$ as the minimum volume that may contain the substance C_i, e.g. the volume of one molecule of C_i, one obtains $\sum_{j=0}^{\infty} j p_i(j; \Delta V_{i,min}) \leq 1$, and

$$\rho_{i,max} = \frac{1}{\Delta V_{i,min}} \tag{40}$$

for the maximum concentration of C_i. To correctly interpret the meaning of the quantities used so far, one should then keep in mind that they must be referred to the volume in which the reactions take place. In particular, the activity a_i should be written as

$$a_i(\Delta V) = \frac{N_i(\Delta V)}{1 + N_i(\Delta V)} \tag{41}$$

which raises the question of which volume has been implicitly assumed in the previous papers on activity-led reactions [16, 13]. Although this may be a conventional choice, which does not affect the results, the question is relevant to identify the low concentration regime, in which the activities approximately equal the densities. Dividing by ΔV, in the numerator and in the denominator of Eq.(41), one obtains

$$a_i(\Delta V) = \frac{\frac{N_i(\Delta V)}{\Delta V}}{\frac{1}{\Delta V} + \frac{N_i(\Delta V)}{\Delta V}} = \frac{\rho_i}{\rho_{i,\text{ref}} + \rho_i} \tag{42}$$

where $\rho_{i,\text{ref}}$ is a reference concentration, that may be taken as convenient. In particular, taking $\Delta V = \Delta V_{i,min}$ implies $\rho_{i,\text{ref}} = \rho_{i,max}$ and $a_i \leq 1/2$. Then, the reactions turn density-led when $\rho_i \ll \rho_{i,max}$, i.e. when $a_i \simeq \frac{\rho_i}{\rho_{i,max}} \ll 1$, or $\sum_{j=0}^{\infty} j p_i(j; \Delta V_{i,min}) \ll 1$. One may then introduce

$$\Delta V_{min} = \max\{\Delta V_{1,min}, \dots, \Delta V_{n,min}\},$$

[6] For instance, $p_i(j; \Delta V)$ is bounded from above by 1.

and refer all quantities to this volume. Quite obviously, the formalism thus produced, will seldom substantially differ from the density-led case, therefore, the results obtained above for activity-led reactions apply to the density-led cases with a high degree of accuracy. The larger ΔV_{min} is, the easier it will be for activity-led evolutions to differ from the corresponding density-led behaviours.

With this in mind, the activity-led evolution of $2A \underset{\tilde{k}}{\overset{\tilde{k}}{\rightleftharpoons}} B+\gamma^-$, for instance, which is given by $N'_A = N_A - 2\mu(a_A^2 - a_B a_{\gamma^-})$, with $\mu = \tilde{k}\Delta t$, may be rewritten as

$$N'_A = N_A - 2\mu \left\{ \left(\frac{\rho_A}{\rho_{A,\text{ref}} + \rho_A} \right)^2 - \left(\frac{\rho_B}{\rho_{B,\text{ref}} + \rho_B} \right) \left(\frac{\rho_{\gamma^-}}{\rho_{\gamma^-,\text{ref}} + \rho_{\gamma^-}} \right) \right\}$$

If, one takes $\Delta V_{min} = \max\{\Delta V_{A,min}, \Delta V_{B,min}\}$ and $\rho_{A,\text{ref}} = \rho_{B,\text{ref}} = \rho_{\gamma^-,\text{ref}} = \rho_{max}$ then $\rho_A, \rho_B, \rho_{\gamma^-} \ll \rho_{max}$ yields, with good approxiation, the evolution

$$\rho'_A = \rho_A - 2\frac{\mu}{\rho_{max}}(\rho_A^2 - \rho_B \rho_{\gamma^-})$$

which is the Euler approximation for the ODE representing the law of mass action. The reaction constants are then given by

$$k^+ = \frac{\mu}{\Delta t \rho_{max}}, \qquad k^- = \frac{\mu \rho_{\gamma^+}}{\Delta t \rho_{max}} .$$

One may easily work out the general expression of the reaction constants, in terms of the parameters.

According to Eq.(41) and Eq.(42), the Liapunov functional Eq.(38) can be written as

$$\Psi(\hat{\rho}) = \sum_{j=1}^{n} \tilde{S}(\rho_j) + \sum_{j=1}^{n} \frac{\tilde{z}_j}{\rho_{max}} \rho_j \tag{43}$$

where $\hat{\rho} = (\rho_1, \rho_2, ..., \rho_n)$ and $\tilde{S}(\rho_j) = S\left(\frac{\rho_j}{\rho_{max}}\right)$. For $2A \underset{\tilde{k}}{\overset{\tilde{k}}{\rightleftharpoons}} B + \gamma^-$ the Liapunov functional becomes:

$$\Psi(\hat{\rho}) = \tilde{S}(\rho_A) + \tilde{S}(\rho_B) + \frac{\rho_A}{\rho_{max}} \log\left(\frac{\rho_\gamma}{\rho_{max} + \rho_\gamma} \right)$$

where ρ_γ is the fixed concentration of the virtual chemicals.

This analysis indicates that the physical meaning of the quantities which we have called "activities" depends on the choice of the reference volume or, equivalently, of the reference density. Indeed, once ΔV_{min} and ρ_{max} have been fixed, the activities become intensive quantities, as they are supposed to be. However, there is a certain degree of arbitrariness in choosing those reference parameters. Indeed, they can be taken arbitrarily small or large, as long as they are positive finite numbers, without affecting the qualitative results obtained so far. Quantitatively, instead, the results do depend on the choice of the reference parameters, therefore, they must be chosen case by case, in such a way that the corresponding physics is properly reproduced.

The most obvious case that needs to be considered, is the density-led case. To obtain $\rho_i \ll \rho_{max}$ for the whole time evolution, so that the dynamics is effectively density-led, it suffices to take $\rho_{max} \gg \rho_{i,max}$ for all $i \in \{1, \ldots, n\}$. Less, indeed, is necessary, because of the conservation of mass: it suffices to take $\rho_{max} \geq \bar{N}_i/\Delta V$ for all i's, where $\bar{N}_i$ is the maximum number of C_i particles, compatible with the initial conditions. Whether a reaction should be density or activity led, or of a different

kind, cannot be decided within the mathematical theory; it is determined by the physical nature of the system. The simulation of the density-led reactions through the activity-led reactions can be made arbitrarily accurate by taking sufficiently large ρ_{max}. This, leads us to the following conclusions:

Proposition 3. *Density-led as well as activity-led networks of reactions, with nonvanishing forward and backward reaction constants, which are independent, or have as many independent conserved quantities as conserved concentrations, have a unique fixed point, which is stable. This holds also for open systems, with fluxes of matter that keep certain concentrations fixed.*

Hence multistability, if possible at all in these cases, requires more than feedbacks and coupling with the outer environment.

Remark 3. For multistability in independent networks, it is necessary to have some vanishing reaction constants, or different couplings with the environment. Alternatively, kinetic laws not consistent with the law of mass action are required.

The possibility that some reaction constants vanish is excluded, in the present framework, by the fact that the corresponding reaction operators, T, would not be doubly stochastic [13]. Some of these cases, have however been investigated, and no multistability has been evidenced [17].

The cases with some vanishing constants of motion, as well as the case of dependent networks will be studied in detail in a future paper. In the next section, we only consider some example, which illustrate what may happen, in general.

6. **Concluding remarks and open questions.** In this paper, systems of reactions have been investigated generalizing previous results about Boltzmann maps [19, 16, 13]. Two families of reactions have been identified: linearly independent and linearly dependent ones. The independent ones have been understood in the cases with non-vanishing reaction rates, thanks to the construction of a strict Liapunov functional. These systems always have just one stable stationary point. Vanishing reaction rates, however, can induce limit cycles, as in the case of the brussellator [18, 17]:

$$\begin{aligned} A &\overset{k_1}{\to} Z \\ B + Z &\overset{k_2}{\to} Y + D \\ 2Z + Y &\overset{k_3}{\to} 3Z \\ Z &\overset{k_4}{\to} E \end{aligned}$$

Here, the chemicals A and B are kept constant while the dynamics of the chemicals Z and Y are decoupled from those of D and E. In the activity-led formalism, the resulting equations for chemicals Z and Y are

$$\begin{aligned} \frac{da_Z}{dt} &= (k_1 a_A - k_2 a_B a_Z + k_3 a_Z^2 a_Y - k_4 a_Z)(1 - a_Z)^2 \\ \frac{da_Y}{dt} &= (k_2 a_B a_Z - k_3 a_Z^2 a_Y)(1 - a_Y)^2 \end{aligned} \tag{44}$$

With parameters $k_1 = 5/16$, $k_2 = 3/8$, $k_3 = 1/4$, $k_4 = 5/64$, $a_A = 1/8$ and $a_B = 1/4$, this evolution has limit cycles but no multistability [17]. Similar conclusions ought to hold for the more general case of X-led reactions, although the existence of

a Liapunov functional for networks of X-led reactions has not been proven. Indeed, the generalization of Eq.(44) to generic X-led reactions

$$\begin{aligned} \frac{dX_Z}{dt} &= \left(\left. \frac{df^{-1}}{dX} \right|_{X_Z} \right)^{-1} (k_1 X_A - k_2 X_B X_Z + k_3 X_Z^2 X_Y - k_4 X_Z) \\ \frac{dX_Y}{dt} &= \left(\left. \frac{df^{-1}}{dX} \right|_{X_Y} \right)^{-1} (k_2 X_B X_Z - k_3 X_Z^2 X_Y) \end{aligned} \tag{45}$$

where $X = f(\rho)$, has the same number of fixed points for all choices of X, because $(df^{-1}/dX)^{-1}$ is bounded away from zero.

Another class of networks, within which multistable behaviours might be found is the class of linearly dependent reactions. These networks do not have the Liapunov functionals of the linearly independent ones, in general. This is reflected, for instance, in the fact that in general the stable stationary points of dependent networks do not lie on the intersection of the manifolds of the stationary points of the single reactions (Fig.3). This leaves open the possibility that multistability be found in dependent networks. Therefore, Thomas' conjecture, which states that

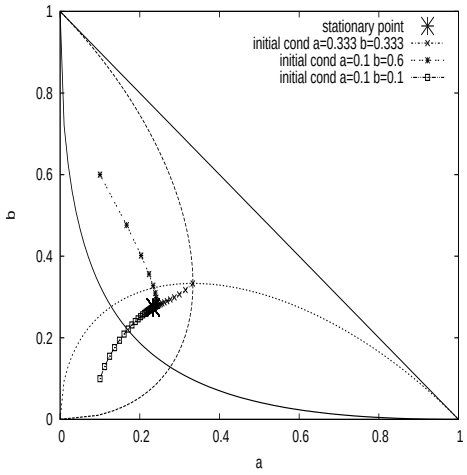

FIGURE 3. Two-dimensional projection of the phase space of Reactions (30), with three evolutions corresponding to different intial conditions (the lines with $*$, $\times$ and $\Box$). The stable stationary point is the point common to all the paths.

feedback loops are necessary for bistability [20], must be associated to one further necessary condition within the framework of density and activity-led reactions: i.e. that reaction networks be dependent.

General linearly dependent networks will be investigated in future works. However, according to our numerical results, it seems that the difference between linearly dependent reaction networks and independent networks is only quantitative and not qualitative. Even linearly dependent reactions seem not to allow multistability. This suggests that the search for multistable behaviours should not be based on the law of mass action, and not even on simple-minded modifications of the law

itself. Approximations starting from the law of mass action which end with multistable behaviors (i.e. Michaelis-Menten or Hill procedures) need to be handled with care, because they may alter the asymptotic behaviours. This observation is further supported by our tests with different (X-led) evolution laws, supposed to mimic e.g. the effects of growing concentrations on the reaction rates. In particular, we have considered cases in which reaction rates saturate (the activity-led reactions), cases in which the reaction rates do not saturate, but grow only loagrithmically with the concentrations, and cases in which the reaction rates do not saturate but grow as the square root of the concentrations. These cases cover a rather wide range of possibilities, beyond those given by the law of mass action. The activity-led case, in particular, looks formally rather close to the Michaelis-Menten evolutions, but shows multistability neither in the independent networks, nor in the dependent networks considered here.

Behaviours such as multistability thus seem to require physical properties, that are unlikely to pertain to the law of mass action and its immediate generalizations. Connections of the theory outlined in this paper with other approaches such as those of Michaelis-Menten and Hill will be the subject of future works.

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