



Local equivalence of reversible and general Markov kinetics



Alexander N. Gorban*

Department of Mathematics, University of Leicester, Leicester, LE1 7RH, UK

ARTICLE INFO

Article history:

Received 3 July 2012

Received in revised form 4 November 2012

Available online 23 November 2012

Keywords:

Detailed balance

Lyapunov function

Decomposition

Entropy

Uncertainty

ABSTRACT

We consider continuous-time Markov kinetics with a finite number of states and a positive equilibrium P^* . This class of systems is significantly wider than the systems with detailed balance. Nevertheless, we demonstrate that for an arbitrary probability distribution P and a general system there exists a system with detailed balance and the same equilibrium that has the same velocity dP/dt at point P . The results are extended to nonlinear systems with the generalized mass action law.

© 2012 Elsevier B.V. All rights reserved.

1. Introduction

1.1. Detailed balance and beyond

The principle of detailed balance is one of the most celebrated results in kinetics. A kinetic system is represented as a mixture of independent elementary processes (collisions or elementary reactions, for example). Due to the principle of detailed balance, *at equilibrium, each elementary process should be equilibrated by its reverse process*. Kinetics is decomposed into pairs of mutually inverse processes and in many problems we can consider these pairs separately.

We study relations between the systems with and without detailed balance. In this section, we briefly overview the main results of the work. Then, in Section 1.2 we review the history of the problem. We prove the local equivalence theorem for the Markov processes in Section 2 and give there the simple examples. The nonlinear generalizations are presented in Section 3.

In Section 2 we start from the first order kinetics without the detailed balance assumption. The general first order kinetic equation has the form:

$$\frac{dp_i}{dt} = \sum_{j, j \neq i} (q_{ij}p_j - q_{ji}p_i), \quad (1)$$

where q_{ij} ($i, j = 1, \dots, n, i \neq j$) are non-negative. This system of equations (master equations or Kolmogorov's equations) describes dynamics of non-negative variables p_i ($i = 1, \dots, n$). These variables may be considered as probabilities (then $\sum_i p_i = 1$) or concentrations. For the corresponding states or components we use the notation A_i . In this notation, q_{ij} is the *rate constant* for transitions $A_j \rightarrow A_i$.

Let us assume that system (1) has a positive equilibrium $P^* = (p_i^*), p_i^* > 0$:

$$\sum_{j, j \neq i} q_{ij}p_j^* = \left(\sum_{j, j \neq i} q_{ji} \right) p_i^* \quad \text{for all } i = 1, \dots, n. \quad (2)$$

* Tel.: +44 1162231433.

E-mail address: ag153@le.ac.uk.

This is the so-called *balance equation*.

The *detailed balance* condition is much stronger. It assumes that the sums on the left and right hand sides of Eq. (2) are equal term by term:

$$q_{ij}p_j^* = q_{ji}p_i^* \quad \text{for all } i, j = 1, \dots, n, i \neq j. \quad (3)$$

For the number of states $n > 2$, a simple comparison of dimensions demonstrates that there are much more general systems with the given positive equilibrium P^* (2) (dimension is $(n - 1)^2$) than the systems with detailed balance with equilibrium P^* (3) (dimension is $\frac{n(n-1)}{2}$). Surprisingly, for every given distribution P , the set of possible velocities dP/dt for general Markov kinetics with equilibrium P^* is the same as that for Markov kinetics with detailed balance and the same equilibrium. This is the central result of the paper (Theorem 1 in Section 2).

We demonstrate this in two steps. First, we use the representation of a general Markov chain with a given positive equilibrium as a combination with non-negative coefficients of several simple cycles with the same equilibrium.

Second, we demonstrate this equivalence for a simple cycle of transitions with positive constants

$$A_1 \rightarrow A_2 \rightarrow \dots \rightarrow A_n \rightarrow A_1. \quad (4)$$

For the equilibrium P^* the constants of the cycle are $q_{i+1i} = \kappa/p_i^*$ (we use here the standard convention about the cyclic numeration, $n + 1 = 1$).

Thus, if we observe the Markov kinetics at one point then we cannot distinguish general systems from systems with detailed balance because the sets of possible velocities coincide. In particular, they have the same set of Lyapunov functions.

Our main results allow us to decompose any Markov kinetics (or generalized mass action law kinetics with semi-detailed balance) into pairs of mutually inverse elementary processes with the same equilibrium. If the system does not satisfy the principle of detailed balance then this decomposition depends on the state. Nevertheless, in some problems it is still convenient to consider these pairs separately.

In this paper, we give two examples of the application of Theorem 1: the evaluation of logarithmic decrement for general Markov chains and a simple proof of the Morimoto H -theorem for all the Csizsár–Morimoto divergencies. We give also the nonlinear generalization of Theorem 1 for the systems which obey the generalized Mass Action Law (MAL).

The master equation is a source for many other kinetic equations. In particular, in Section 3 we consider complex reactions with intermediate compounds (Fig. 1) under two asymptotic conditions.

- The compounds B_j are in fast equilibrium with the corresponding input or output reagents.
- They exist in very small concentrations compared to other components.

For compound transitions the first order kinetics is assumed because of small concentration of compounds (only first order terms survive). These assumptions allow us to produce the reaction rates for the overall reaction from Fig. 1 in the form of the generalized MAL:

$$r_\rho = \varphi_\rho \exp\left(\frac{\sum_i \alpha_{\rho i} \mu_i}{RT}\right), \quad \varphi_\rho \geq 0 \quad (5)$$

where μ_i is the chemical potential of the component A_i , ρ is the reaction number, $\alpha_{\rho i}$ are the input stoichiometric coefficients (Fig. 1). Both $\alpha_{\rho i}$ and $\beta_{\rho i}$ are non-negative integers. We use notations α_ρ and β_ρ for vectors with coordinates $\alpha_{\rho i}$ and $\beta_{\rho i}$. The positive functions φ_ρ are called the *kinetic factors* whereas $\exp(\sum_i \alpha_{\rho i} \mu_i / RT)$ are the *Boltzmann factors*.

The balance condition of the first order kinetics of compounds (2) transforms in the semi-detailed balance condition (that is known also as the complex or the cyclic balance condition):

$$\sum_{\rho, \alpha_\rho = \mathbf{v}} \varphi_\rho \equiv \sum_{\rho, \beta_\rho = \mathbf{v}} \varphi_\rho$$

for any vector \mathbf{v} from the set of all vectors $\{\alpha_\rho, \beta_\rho\}$. Kinetics with the generalized MAL and the semi-detailed balance conditions give the natural nonlinear generalizations of Markov processes. In particular, the entropy production for these systems at any nonequilibrium state is positive.

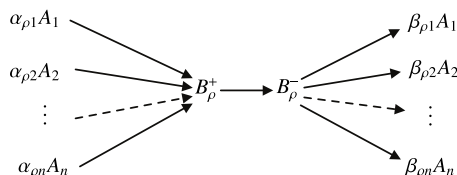


Fig. 1. Elementary reaction with intermediate compounds.

If we assume for the Markov kinetics of compounds that the positive equilibrium is the point of detailed balance (3) then the kinetic factors φ_ρ satisfy the stronger condition of detailed balance:

$$\varphi_\rho^+ \equiv \varphi_\rho^- \quad \text{for all } \rho,$$

where φ_ρ^+ is the kinetic factor for the direct reaction and φ_ρ^- is the kinetic factor for the reverse reaction.

The class of systems with semi-detailed balance is much wider than the class of systems with detailed balance. Nevertheless, locally they coincide: *the set of possible velocities for systems with semi-detailed balance coincide with the set of possible velocities for the systems with detailed balance for given thermodynamic functions and any given state* (Section 3).

The systems with generalized MAL and semi-detailed balance are the nonlinear analogues of the Markov processes and the local equivalence of the generalized MAL systems with detailed and semi-detailed balance is the analogue and a consequence of Theorem 1.

1.2. A bit of history

In 1872, Boltzmann introduced the principle of detailed balance for collisions and used it to prove his H -theorem [1]. Boltzmann's proof of the positivity of entropy production for systems with detailed balance is very transparent because it is sufficient to prove this positivity just for a couple of mutually inverse elementary processes.

In 1887, Lorentz [2] objected Boltzmann: he insisted that some collisions of polyatomic molecules do not have reverse collisions and cannot satisfy the principle of detailed balance. Immediately, Boltzmann realized that there exists a much weaker condition sufficient for the H -theorem [3]. In 1981, it was proven that the Lorentz objections are wrong and the principle of detailed balance is valid for polyatomic molecules [4]. This is not very surprising because the detailed balance follows from microreversibility (or T -invariance of the fundamental equations of mechanics or quantum mechanics). Nevertheless, the Boltzmann discovery is valuable by itself and is used for many kinetic equations.

This condition was rediscovered several times. It is known as the semi-detailed balance condition, the cyclic balance condition or the complex balance condition. In 1952, Stueckelberg proposed a proof of the semi-detailed balance condition for the Boltzmann equation [5]. His proof is based on the Markov model of elementary events. Recently, the Stueckelberg approach has been extended to prove the semi-detailed balance condition for the generalized MAL kinetics [6].

The complex balance condition for chemical kinetics was introduced by Horn and Jackson in 1972 [7] independently of Boltzmann's work. Now it is used for mathematical modelling in chemical kinetics and engineering [8]. Boltzmann's idea about cyclic balance developed in physical kinetics was independently rediscovered in the theory of Markov processes and it is proved that any recurrent Markov process can be decomposed into directed cycles [9].

The principle of detailed balance was crucially important in the development of the Metropolis–Hastings and other Markov chain Monte Carlo algorithms from the very beginning [10]. Technically, it is much easier to use the detailed balance conditions (3) than to follow more intricate balance conditions. Detailed balance was considered as a necessary condition for construction of Monte Carlo algorithms as a “systematic design principle” [11]. It was demonstrated that it helps to reduce the uncertainty of some observables in stochastic numerics [12].

Nevertheless, there are many examples of efficient Monte Carlo computations without detailed balance. Sometimes computational models without detailed balance are constructed because of the physical nature of the systems. For example, the models of inelastic processes in particle physics [13] or in granular media [14] may violate the principle of detailed balance. The general theories of stochastic cellular automata with Gibbsian equilibria but without compulsory detailed balance were developed [15]. It is widely recognized that the balance equation (not the detailed balance) is the necessary and sufficient condition for invariance (stationarity) of the desired equilibrium distribution. Under some more technical irreducibility conditions, the Monte Carlo simulations will converge to this equilibrium [16,17].

The interplay between reversible (with detailed balance) and irreversible Markov chains is non-trivial and important for many applications. Recently, it has been demonstrated that the local deformation of the reversible Markov processes into irreversible ones helps to create efficient computational Monte Carlo algorithms [18].

Much efforts were applied to verification of microscopic reversibility and its consequences, the detailed balance conditions and the Onsager reciprocal relations, in many experimental systems [19–23]. To check experimentally the detailed balance conditions it is necessary to deal with a complex reaction that can be formally equilibrated without detailed balance. If not, then one tests not the detailed balance but just the equilibrium condition as it was mentioned in Ref. [24].

The detailed balance conditions are very natural and appealing. They simplify many computations and proofs. Thus, they are used in many applications and models. For some physical and chemical systems, detailed balance has a solid background, the T -invariance of the fundamental equations, but it is also used beyond the proven microreversibility. When modelling with detailed balance meets some difficulty then the problem about relations between reversible and irreversible systems arises again and detailed balance is substituted by more general conditions. Nevertheless, the convenience, beauty and some intrinsic benefits of the phenomenon, have forced researchers to return to detailed balance if it is possible without a conflict with reality. There are many examples of this “pendulum” in scientific publications: accept detailed balance – criticize detailed balance – go to more general conditions – realize the benefits of detailed balance – return to detailed balance – ...

At the same time, the consequences of the principle of detailed balance are extended to the situations where it was not used before. Thus, recently the multiscale limit of the systems of reversible reactions has been studied when some of the

equilibrium concentrations tend to zero. The extended principle of detailed balance was proved for the systems with some irreversible reaction [25,26].

In Theorem 1, we compare the sets of possible velocities, dP/dt , for two classes of systems: (i) general first order kinetics (1) with the given positive equilibrium P^* and (ii) first order kinetics with detailed balance (3) and the same positive equilibrium.

Understanding the structure of the sets of possible velocities can provide additional information about attainable states of the system which is helpful in the modelling context. There are many other reasons too. It is known that different types of kinetics data bear different degrees of reliability. It would therefore be very attractive to study the consequences of the information of each level of reliability separately [27]. For example, uncertainty about equilibria in the system is usually significantly lower than that of the reaction rate constants. The value of the equilibrium gives us some information about dynamics: the set of possible velocities dP/dt is not arbitrarily wide at a given state and for given equilibrium. For the systems with detailed balance, this set is a polyhedral cone which allows a simple description (Section 2.2). Due to Theorem 1, however, this cone is also the set of possible velocities for the general master equation. Therefore, to distinguish the detailed balance systems from the general ones we have to involve data about dP/dt for several significantly distant distributions P .

Another example is to employ the knowledge of the sets of possible velocities for estimating attainable regions for kinetics. The idea to use the equilibrium information to estimate the attainable sets in kinetics was proposed in 1964 by Horn [28] and developed further in chemical kinetics and chemical engineering [29–33] (for a more detailed review see Ref. [27]). If the sets of possible velocities coincide then the estimated attainable regions coincide too. The knowledge of the sets of possible velocities is also important for the analysis of observability, identifiability and controllability of the systems.

2. Local equivalence of general Markov systems and systems with detailed balance

2.1. Global decomposition into cycles, local decomposition into steps, and the equivalence theorem

Let us start from the master equation (1). The coefficient q_{ij} is the *rate constant* for transitions $A_j \rightarrow A_i$. Any set of non-negative coefficients q_{ij} ($i \neq j$) corresponds to a master equation. Therefore, the set of all master equation (1) may be considered as the non-negative orthant in $\mathbb{R}_+^{n(n-1)} \subset \mathbb{R}^{n(n-1)}$. (The non-negative orthant is the set of all vectors with only non-negative components.)

We assume that system (1) has a positive equilibrium $P^* = (p_i^*)$, $p_i^* > 0$ and the balance condition (2) holds. The sum of these n balance conditions is a trivial identity. Let us delete any single equation from (2), for example, the last one (for $i = n$). Each of the remaining equations includes the variable q_{in} which is not present in other equations ($i = 1, \dots, n-1$). Therefore, for given positive P^* , there are $n-1$ independent conditions on q_{ij} ($i, j = 1, \dots, n, i \neq j$) in (2).

Thus, the balance conditions (2) define for a given positive equilibrium a $(n-1)^2$ -dimensional linear subspace L^* in the $n(n-1)$ dimensional space of q_{ij} ($i \neq j$). A vector of positive coefficients $q_{ij}^* = 1/p_j^*$ satisfies (2) and belongs to L^* . This vector belongs to the interior of the non-negative orthant $\mathbb{R}_+^{n(n-1)}$. Therefore, the intersection $\mathbb{R}_+^{n(n-1)} \cap L^*$ includes a vicinity of q_{ij}^* in L^* and is a $(n-1)^2$ -dimensional cone. Thus, the non-negative solutions of (2) form a $(n-1)^2$ -dimensional closed cone in $\mathbb{R}_+^{n(n-1)}$.

The systems with detailed balance (3) for a given positive equilibrium form a smaller cone. Under these conditions, there are only $\frac{n(n-1)}{2}$ independent coefficients among $n(n-1)$ numbers q_{ij} . For example, we can arbitrarily select $q_{ij} \geq 0$ for $i > j$ and then take $q_{ij} = q_{ji} \frac{p_i^*}{p_j^*}$ for $i < j$. So, for given P^* , the cone of the detailed balance systems (3) can be considered as a non-negative orthant in $\mathbb{R}^{\frac{n(n-1)}{2}}$ embedded in $\mathbb{R}_+^{n(n-1)}$.

If the balance condition (2) holds then system (1) may be rewritten in a convenient equivalent form:

$$\frac{dp_i}{dt} = \sum_{j, j \neq i} q_{ij} p_j^* \left(\frac{p_j}{p_j^*} - \frac{p_i}{p_i^*} \right). \quad (6)$$

With this form of master equation, it is straightforward to calculate the time derivative of the quadratic divergence, a weighted l_2 distance between P and P^* , $H_2(P \| P^*) = \sum_i \frac{(p_i - p_i^*)^2}{p_i^*}$:

$$\frac{dH_2(P \| P^*)}{dt} = - \sum_{i, j, j \neq i} q_{ij} p_j^* \left(\frac{p_i}{p_i^*} - \frac{p_j}{p_j^*} \right)^2 \leq 0. \quad (7)$$

This time derivative is *strictly negative* if for a transition $A_j \rightarrow A_i$ the rate constant is positive, $q_{ij} > 0$, and $\frac{p_i}{p_i^*} \neq \frac{p_j}{p_j^*}$. Hence, if the state P is not an equilibrium (i.e., the right hand side in (6) is not zero) then $\frac{dH_2(P \| P^*)}{dt} < 0$.

Let us introduce the following notation for a given number of states n :

- $\mathcal{Q}_B^n(P^*)$ is the cone of the vectors of non-negative coefficients q_{ij} ($i \neq j$) which satisfy the balance conditions (2), that is, the set of all Markov processes with the equilibrium distribution P^* ;
- $\mathcal{Q}_{DB}^n(P^*)$ is the cone of the vectors of non-negative coefficients q_{ij} ($i \neq j$) which satisfy the detailed balance conditions (3), that is, the set of all Markov processes with detailed balance and the equilibrium distribution P^* .

If a system satisfies the detailed balance condition (3) then the balance condition (2) holds too: it holds term by term, even without summation. Therefore, $\mathcal{Q}_{DB}^n(P^*) \subset \mathcal{Q}_B^n(P^*)$. Moreover, comparing dimension we find that this inclusion is strong. Indeed, $\dim \mathcal{Q}_B^n(P^*) = (n - 1)^2$, $\dim \mathcal{Q}_{DB}^n(P^*) = \frac{n(n-1)}{2}$. If $n > 2$ then $\frac{n(n-1)}{2} < (n - 1)^2$; hence,

$$\mathcal{Q}_{DB}^n(P^*) \subsetneq \mathcal{Q}_B^n(P^*) \subsetneq \mathbb{R}_+^{n(n-1)}. \tag{8}$$

The cone of the systems with detailed balance is, in some sense, much smaller than the cone of the systems with the balance condition: the difference between their dimensions is $\frac{(n-1)(n-2)}{2}$.

Now, let us consider the right hand side vector fields of the systems (1) at the point $P \neq P^*$. For each cone of the coefficients q_{ij} the vectors of the possible velocities, dP/dt , also form a cone. Let us introduce the following notation:

- $\mathbf{Q}_B^n(P, P^*)$ is the cone of the possible velocities, dP/dt , at the point P for $(q_{ij}) \in \mathcal{Q}_B^n(P^*)$;
- $\mathbf{Q}_{DB}^n(P, P^*)$ is the cone of the possible velocities, dP/dt , at point P for $(q_{ij}) \in \mathcal{Q}_{DB}^n(P^*)$.

$\mathbf{Q}_B^n(P, P^*)$ is the cone of all possible velocities for Markov kinetics at the point P if the equilibrium is P^* . $\mathbf{Q}_{DB}^n(P, P^*)$ is the cone of these velocities for Markov kinetics with detailed balance.

Surprisingly, for every given distribution P , the set of possible velocities dP/dt for general Markov kinetics with equilibrium P^* is the same as that for Markov kinetics with detailed balance and the same equilibrium. The following theorem is the central result of this work.

Theorem 1. $\mathbf{Q}_B^n(P, P^*) = \mathbf{Q}_{DB}^n(P, P^*)$.

This means that for every first order kinetic equation (1) with a given positive equilibrium P^* and for every point $P \neq P^*$ there exists a first order kinetic equation with detailed balance and equilibrium P^* that has the same velocity at P . At this point the right hand sides of the kinetic equations coincide.

Therefore, if we observe the Markov kinetics at one point then we can never distinguish general systems from systems with detailed balance. In particular, they have the same set of Lyapunov functions.

Corollary 1. If for a function $H(P, P^*)$, $dH/dt \leq 0$ for any system (1) with equilibrium P^* and detailed balance then $dH/dt \leq 0$ for any system (1) with equilibrium P^* .

The system with detailed balance has $n(n - 1)/2$ dimensions available to match a single n -dimensional velocity vector. Therefore, it is not surprising that the cones $\mathbf{Q}_{DB}^n(P, P^*)$ have non-empty interior (solid cones). But this is not enough to cover any n -dimensional velocity vector using non-negative coefficients q_{ij} . This non-negativity condition defines the borders of the cones and we can a priori just state the inclusion $\mathbf{Q}_{DB}^n(P, P^*) \subseteq \mathbf{Q}_B^n(P, P^*)$. The calculation of dimension does not give a hint about coincidence of these cones.

The proof of Theorem 1 is constructed in two steps. First, we prove that for every P^* and P the cone of possible velocities $\mathbf{Q}_B^n(P, P^*)$ is the convex hull of the velocities at point P of the simple cyclic schemes, $A_{i_1} \rightarrow \dots \rightarrow A_{i_k} \rightarrow A_{i_1}$ ($k \leq n$ and all the numbers i_1, \dots, i_k are different), with the same equilibrium P^* . Second, we prove that it is sufficient to take $k = 2$.

We will characterize $\mathbf{Q}_B^n(P, P^*)$ by its extreme rays. A ray with direction vector $x \neq 0$ is a set $\{\lambda x\}$ ($\lambda \geq 0$). l is an extreme ray of a cone \mathbf{Q} if for any $u \in l$ and any $x, y \in \mathbf{Q}$, whenever $u = (x + y)/2$, we must have $x, y \in l$. If a closed convex cone does not include a whole straight line then it is the convex hull of its extreme rays [34].

Lemma 1. The cone $\mathbf{Q}_B^n(P, P^*)$ does not include a whole straight line.

Proof. If $v \neq 0$ is a possible value on the right hand side of (6) then the derivative of $H_2(P \parallel P^*)$ in direction v is strictly negative (7). Therefore, it is impossible that both v and $-v$ belong to $\mathbf{Q}_B^n(P, P^*)$. \square

Let us consider a simple cyclic scheme, $A_{i_1} \rightarrow \dots \rightarrow A_{i_k} \rightarrow A_{i_1}$ ($k \leq n$ and all the numbers i_1, \dots, i_k are different). For a given positive equilibrium, P^* the coefficients for this scheme belong to a ray:

$$q_{i_{j+1}i_j} = \frac{\kappa}{p_{i_j}^*} \quad (j = 1, \dots, k), \tag{9}$$

where $\kappa \geq 0$ is a constant and we use the standard convention that for a cycle $q_{i_{k+1}i_k} = q_{i_1i_k}$.

Lemma 2. If system (1) has a positive equilibrium P^* then for every A_i either all $q_{ji} = q_{ij} = 0$ or the state A_i belongs to a cycle with strictly positive rate constants.

Proof. Let A_i not belong to a cycle with positive constants. We say that a state A_j is reachable from a state A_k if there exists a non-empty chain of transitions with non-zero coefficients which starts at A_k and ends at A_j : $A_k \rightarrow \dots \rightarrow A_j$. Let $\mathcal{A}_{i\downarrow}$ be the set of states reachable from A_i and $\mathcal{A}_{i\uparrow}$ be the set of states A_i is reachable from. $\mathcal{A}_{i\downarrow} \cap \mathcal{A}_{i\uparrow} = \emptyset$ because A_i does not belong to a cycle. If $\mathcal{A}_{i\uparrow}$ is not empty then in equilibrium all the corresponding $p_j^* = 0$ ($j \in \mathcal{A}_{i\downarrow}$ because there is flow from $\mathcal{A}_{i\uparrow}$ to A_i and no flow back). If $\mathcal{A}_{i\downarrow}$ is not empty then in equilibrium $p_i^* = 0$ because there is a flow from A_i to $\mathcal{A}_{i\downarrow}$ and no flow back. Therefore, if the equilibrium is strictly positive and A_i does not belong to a cycle then $\mathcal{A}_{i\uparrow} = \mathcal{A}_{i\downarrow} = \emptyset$; hence, all $q_{ji} = q_{ij} = 0$. \square

We will use the following simple general statement: let \mathcal{Q} be a cone in \mathbb{R}^m without straight lines, L be a linear map, $L : \mathbb{R}^m \rightarrow \mathbb{R}^k$, and $\mathbf{Q} = L(\mathcal{Q})$ be a cone in \mathbb{R}^k without straight lines. Then for every extreme ray $V \subset \mathbf{Q}$ there exists an extreme ray $W \subset \mathcal{Q}$ such that $L(W) = V$. (In other words, there always exists an extreme ray in the preimage of an extreme ray.) We will apply this statement to $\mathcal{Q} = \mathcal{Q}_B^n(P^*)$ (the cone of all Markov processes with the given equilibrium P^*) and $\mathbf{Q} = \mathbf{Q}_B^n(P, P^*)$ (the cone of the possible velocities at point P for all Markov processes with the given equilibrium). The map L transforms the right hand side of the Kolmogorov equation (1) into its value at point P . This transformation “vector field \mapsto its value at point P ” is, obviously, a linear map.

Lemma 3. Any extreme ray of the cone $\mathcal{Q}_B^n(P^*)$ is a simple cycle with constants (9).

Proof. Let a non-zero Markov chain Q with coefficients q_{ij} belong to an extreme ray of $\mathcal{Q}_B^n(P^*)$. Due to Lemma 2 this chain includes a simple cycle with non-zero coefficients, $A_{i_1} \rightarrow \dots \rightarrow A_{i_k} \rightarrow A_{i_1}$ ($k \leq n$, all the numbers i_1, \dots, i_k are different, $q_{i_{j+1}i_j} > 0$ for $j = 1, \dots, k$, and $i_{k+1} = i_1$). For sufficiently small κ ($0 < \kappa < \kappa_0$), $q_{i_{j+1}i_j} - \frac{\kappa}{p_j^*} > 0$ ($j = 1, \dots, k$). Let Q_κ be the same simple cycle with the coefficients (9). Then for $0 < \kappa < \kappa_0$ vectors $Q \pm Q_\kappa$ also represent Markov chains with the equilibrium P^* . Obviously, $Q = \frac{(Q+Q_\kappa)+(Q-Q_\kappa)}{2}$; hence, Q should be proportional to Q_κ . \square

Due to this lemma, every Markov chain with positive equilibrium is a convex combination of several simple cycles with the same equilibrium. This is the *global decomposition* of a Markov chain into simple cycles. “Global” here means that the same decomposition is valid for all distributions.

Now, we are in position to prove Theorem 1.

Proof. We will prove that any extreme ray of the cone $\mathbf{Q}_B^n(P, P^*)$ corresponds to a simple cycle of length 2 (a step): $A_i = A_j$ with the rate constants (9) $q_{ij} = \frac{\kappa}{p_j^*}$, $q_{ji} = \frac{\kappa}{p_i^*}$.

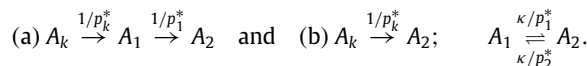
According to Lemma 3, it is sufficient to prove that for any simple cycle with equilibrium P^* and rate constants (9) and for any distribution P the right hand side of the Kolmogorov equation (1) is a conic combination (a combination with non-negative real coefficients) of the right hand sides of this equation for simple cycles of length 2 at the same point P .

Let us prove this by induction on the cycle length k . For $k = 2$ it is true (trivially). For a cycle of length $k > 2$, $A_1 \rightarrow A_2 \rightarrow \dots \rightarrow A_k \rightarrow A_1$, with the rate constants given by (9), the right hand side of Eq. (1) is the vector \mathbf{v}_k with coordinates

$$(\mathbf{v}_k)_j = \frac{p_{j-1}}{p_{j-1}^*} - \frac{p_j}{p_j^*}. \tag{10}$$

Here, without loss of generality, we take $\kappa = 1$, use index j instead of i_j and apply the standard convention regarding cyclic order. Other coordinates of \mathbf{v}_k are zeros.

Let us decompose this \mathbf{v}_k into a conic combination of a vector \mathbf{v}_{k-1} for a cycle of length $k - 1$ and a vector \mathbf{v}_2 for a cycle of length 2. The flux $A_j \rightarrow A_{j+1}$ is p_j/p_j^* . Let us find the minimum value of this flux and, for convenience, let us put this minimal flux in the first position by a cyclic permutation. The target cycle of length $k - 1$ is $A_2 \rightarrow \dots \rightarrow A_k \rightarrow A_2$ with rate constants given by formula (9) ($\kappa = 1$). We just delete the vertex with the smallest flux from the initial cycle of length k . The target cycle of length 2 is $A_1 = A_2$ with the rate constants (9) $q_{21} = \frac{\kappa}{p_1^*}$, $q_{12} = \frac{\kappa}{p_2^*}$. We find the constant κ from the conditions: $\mathbf{v}_k = \mathbf{v}_{k-1} + \mathbf{v}_2$ at the point P , hence, two following reaction schemes, (a) and (b), should have the same velocities, dP/dt :



From this condition,

$$\kappa = \left(\frac{p_k}{p_k^*} - \frac{p_1}{p_1^*} \right) \left(\frac{p_2}{p_2^*} - \frac{p_1}{p_1^*} \right)^{-1}$$

$\kappa \geq 0$ because p_1/p_1^* is the minimal value of p_j/p_j^* . Finally, $\mathbf{v}_k = \mathbf{v}_{k-1} + \mathbf{v}_2$. \square

Further, we omit the index B or DB at the cone: $\mathbf{Q}_B^n(P, P^*) = \mathbf{Q}_{DB}^n(P, P^*) = \mathbf{Q}^n(P, P^*)$.

It is necessary to stress that the decomposition of the right hand side of the Kolmogorov equation (1) into a conic combination of cycles of length 2 depends on the ordering of the ratios p_i/p_i^* and cannot be performed for all values of P simultaneously. Thus, this decomposition is *local*.

2.2. Quasichemical representation and the cones of possible velocities

For systems with detailed balance, the cone of possible velocities, $\mathbf{Q}_{DB}^n(P, P^*)$, is a polyhedral cone. For a given P^* , it is a piecewise constant function of P . The hyperplanes of the equilibria $A_i \leftrightarrow A_j$ divide the standard simplex of distributions into a finite number of polyhedra (*compartments*). In each compartment the dominant direction of every transition $A_i \leftrightarrow A_j$ is fixed and the cone of possible velocities is constant. Now we find that this construction provides the cones of possible velocities for general Markov kinetics and not only for systems with detailed balance. Let us describe these cones in detail.

The construction of cones of possible velocities was described in 1979 [29] for systems with detailed balance in the general setting for generalized MAL, for nonlinear chemical kinetics. These systems are represented by stoichiometric equations of the elementary reaction coupled with the reverse reactions:

$$\alpha_{\rho 1}A_1 + \dots + \alpha_{\rho n}A_n = \beta_{\rho 1}A_1 + \dots + \beta_{\rho n}A_n, \tag{11}$$

where $\alpha_{\rho i}, \beta_{\rho i} \geq 0$ are the stoichiometric coefficients, ρ is the reaction number ($\rho = 1, \dots, m$). The stoichiometric vector of the ρ th reaction is an n dimensional vector γ_ρ with coordinates $\gamma_{\rho i} = \beta_{\rho i} - \alpha_{\rho i}$.

The equilibria of the ρ th pair of reactions (11) form a surface in the space of concentrations. The intersection of these surfaces for all ρ is the equilibrium (with detailed balance). These surfaces of the equilibria of the pairs of elementary reactions (11) divide the space of concentrations into several compartments. In each compartment the dominant direction of each reaction (11) is fixed and, hence, the cone of possible velocities is also constant. It is a piecewise constant function of concentrations (for a given temperature):

$$\mathbf{Q} = \text{cone}\{\gamma_\rho \text{sign}(w_\rho) \mid \rho = 1, \dots, m\}.$$

For example, let us join the transitions $A_i \rightleftharpoons A_j$ in pairs (say, $i > j$) and introduce the *stoichiometric vectors* γ^{ij} with coordinates:

$$\gamma_k^{ij} = \begin{cases} -1 & \text{if } k = i, \\ 1 & \text{if } k = j, \\ 0 & \text{otherwise.} \end{cases} \tag{12}$$

Let us rewrite the Kolmogorov equation for the Markov process with detailed balance (3) in the quasichemical form:

$$\frac{dP}{dt} = \sum_{i>j} w_{ij}^* \left(\frac{p_j}{p_j^*} - \frac{p_i}{p_i^*} \right) \gamma^{ji}. \tag{13}$$

Here, $w_{ij}^* = q_{ij}p_j^* = q_{ji}p_i^*$ is the equilibrium flux from A_i to A_j and reverse.

The cone of possible velocities for (13) is

$$\mathbf{Q}^n(P, P^*) = \text{cone} \left\{ \gamma^{ji} \text{sign} \left(\frac{p_j}{p_j^*} - \frac{p_i}{p_i^*} \right) \mid i > j \right\}. \tag{14}$$

Here, we use the three-valued sign function (with values ± 1 and 0). In Fig. 2, the partition of the standard distribution simplex into compartments, and the cones (angles) of possible velocities are presented for the Markov chains with three states.

A set of distributions U is *positively invariant* with respect to system (1) if for any initial distribution $P(0) \in U$, the solution of (1) $P(t)$ remains in U for $t > 0$. The bold broken lines in Fig. 2 follow along the extreme rays of the angles of possible velocities (clockwise or anticlockwise). They form the borders of a positively-invariant area for all the Markov chains with the given equilibrium P^* .

These borders give, for example, a simple estimate of the logarithmic decrement for Markov chains. For decaying oscillations, the logarithmic decrement is the natural logarithm of the ratio of any two successive amplitudes: $\delta \triangleq \ln \frac{x_1}{x_2}$.

For a complex eigenvalue λ , the period between two amplitudes $T = 2\pi/|\Im\lambda|$ and $\delta = 2\pi \frac{|\Re\lambda|}{|\Im\lambda|}$. For systems with detailed balance, eigenvalues are always real but for the general Markov chains they may be complex. For example, for the simple cycle $A_1 \rightarrow A_2 \rightarrow A_3 \rightarrow A_1$ with the equilibrium equidistribution $p_{1,2,3}^* = 1/3$, and the rate coefficients κ , the nonzero eigenvalues of the linear system (1) are $\lambda = \kappa \left(-\frac{3}{2} \pm i\frac{\sqrt{3}}{2} \right)$ and $\delta = 2\pi\sqrt{3}$.

Let us follow the clockwise border trajectory (Fig. 2) starting from the state A_1 (the corresponding distribution is $P = (1, 0, 0)$). This state belongs to the line of equilibria of the transition $A_2 \rightleftharpoons A_3$. The first step is the equilibration of the transition $A_1 \rightleftharpoons A_2$ (A_3 does not change). After that, the equilibration of the transition $A_1 \rightleftharpoons A_3$ follows (A_2 does not change):

$$\begin{aligned} (1, 0, 0) &\mapsto \left(\frac{p_1^*}{1-p_3^*}, \frac{p_2^*}{1-p_3^*}, 0 \right) \\ &\mapsto \left(\frac{(p_1^*)^2}{(1-p_3^*)(1-p_2^*)}, \frac{p_2^*}{1-p_3^*}, \frac{p_1^*p_3^*}{(1-p_3^*)(1-p_2^*)} \right). \end{aligned} \tag{15}$$

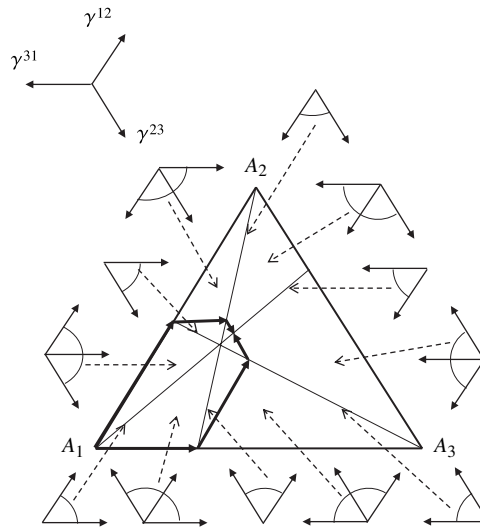


Fig. 2. Partition of the distribution triangle for the Markov chains with three states by the lines $\frac{p_j}{p_j^*} - \frac{p_i}{p_i^*} = 0$ into twelve compartments. The corresponding cones (angles) of possible velocities are presented. The clockwise and anticlockwise borders of the trajectories are represented by bold lines.

As the result of this sequence of equilibrations, when the clockwise border line again approaches the equilibrium line of the transition $A_2 \rightleftharpoons A_3$, the value of p_1 is $\frac{(p_1^*)^2}{(1-p_3^*)(1-p_2^*)}$. After this turn in angle π every trajectory becomes closer to P^* . The contraction coefficient is $\frac{p_1^* p_2^* p_3^*}{(1-p_1^*)(1-p_2^*)(1-p_3^*)}$ or less. The anticlockwise trajectory gives the same contraction. We estimated the logarithmic decrement from below:

$$\delta \left(= 2\pi \frac{|\Re \lambda|}{|\Im \lambda|} \right) \geq 2 \ln \left(\frac{(1-p_1^*)(1-p_2^*)(1-p_3^*)}{p_1^* p_2^* p_3^*} \right). \tag{16}$$

2.3. Two H-theorems

The most general form of the H -theorem for Markov processes was proposed by Morimoto [35]. He used the following H -functions: for each convex function of the positive convex variable $h(x)$ the h -divergence between distributions P and P^* is

$$H_h(P \parallel P^*) = \sum_i p_i^* h \left(\frac{p_i}{p_i^*} \right). \tag{17}$$

At the same time these divergencies were studied by Csiszár [36] and sometimes they are called the Csiszár–Morimoto divergences. These functions were introduced two years earlier by Rényi on the last page of his famous work [37] together with the hint about the H -theorem. For more details see Ref. [38].

The time derivative of the Csiszár–Morimoto function $H_h(P \parallel P^*)$ (17) with respect to the master equation (6) for a general Markov process is

$$\frac{dH_h(P \parallel P^*)}{dt} = \sum_{i,j,j \neq i} q_{ij} p_j^* \times \left[h \left(\frac{p_i}{p_i^*} \right) - h \left(\frac{p_j}{p_j^*} \right) + h' \left(\frac{p_i}{p_i^*} \right) \left(\frac{p_j}{p_j^*} - \frac{p_i}{p_i^*} \right) \right] \leq 0. \tag{18}$$

For a Markov process with detailed balance we use the quasichemical form of the master equation (13) and find immediately

$$\frac{dH_h(P \parallel P^*)}{dt} = - \sum_{i,j,i > j} q_{ij} p_j^* \times \left(\frac{p_j}{p_j^*} - \frac{p_i}{p_i^*} \right) \left(h' \left(\frac{p_j}{p_j^*} \right) - h' \left(\frac{p_i}{p_i^*} \right) \right) \leq 0. \tag{19}$$

The inequality for the general Markov processes (18) follows from Jensen’s inequality in the differential form, $h'(x)(y-x) \leq h(y) - h(x)$. It is valid for left and right limits of h' at any point $x > 0$. The inequality for systems with detailed balance (19) follows from the monotonicity of h' . In full agreement with Corollary 1, the divergences $H_h(P \parallel P^*)$ (17) are Lyapunov functions for systems with detailed balance and for all the Markov processes as well. Theorem 1 has an even stronger corollary.

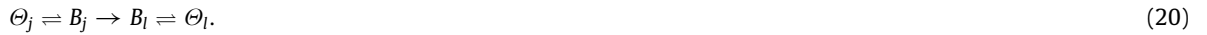
Corollary 2. For every Markov process Q with positive equilibrium P^* and for a distribution $P \neq P^*$ there exists a Markov process Q_{DB} with the same equilibrium that obeys the detailed balance condition and has the following property: for every convex function h the time derivative $dH_h(P \parallel P^*)/dt$ for Q coincides at point P with the time derivative of $H_h(P \parallel P^*)$ at this point for Q_{DB} .

3. Nonlinear kinetics: detailed balance versus semi-detailed balance

The general equations of MAL without any restriction on the reaction rate constants demonstrate all types of non-trivial dynamic behaviour, from multiple steady states to strange attractors [39,40]. It is not a surprise because the MAL systems can approximate with arbitrary accuracy any smooth vector field which preserves the linear conservation laws and positivity of concentrations [41,42].

The systems with semi-detailed balance give the direct nonlinear generalization of the general Markov kinetics. They were introduced by Boltzmann for gas kinetics [3] and generalized later for MAL systems [7,6,8]. The systems with semi-detailed balance are the generalized MAL systems with additional relations between rate constants.

To produce these relations, let us follow the classical work [5] and assume that behind the reaction mechanism (11) there is the reaction mechanism with intermediate compounds B_ρ^\pm illustrated by Fig. 1. Each compound is associated with a formal input or output complex $\sum_i \alpha_{\rho i} A_i$ or $\sum_i \beta_{\rho i} A_i$. Such a complex may participate in several reactions. Let there be k different vectors among $\{\alpha_\rho, \beta_\rho\}$ ($\alpha_\rho = (\alpha_{\rho i})$ and $\beta_\rho = (\beta_{\rho i})$). We denote these different vectors by \mathbf{v}_j ($j = 1, \dots, k$). The correspondent complexes are $\Theta_j = \sum_i v_{ji} A_i$. The reaction mechanism (11) takes the form of the list of transitions $\Theta_j \rightarrow \Theta_l$ and the extended reaction mechanism is the list of transitions

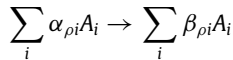


Stueckelberg introduced this representation for the collisions in Boltzmann’s equations and used two asymptotic assumptions.

- The compounds B_j are in fast equilibrium with the corresponding input or output reagents and the reactions $\Theta_j \rightleftharpoons B_j$ in (20) are always close to equilibrium (this is the quasiequilibrium assumption, QE).
- They exist in very small concentrations compared to other components (this leads to the quasi steady state approximation, QSS).

We call the intermediates B_j compounds following the classical work of Michaelis and Menten [43]. In 1913, they introduced the same asymptotic assumptions and representation for an enzyme reaction and demonstrated that in this case the overall catalytic reaction obeys the MAL.

In more general settings, these two assumption, QE and QSS, allow us to produce the reaction rates for the rates of the overall reactions in the form of the generalized MAL. The rate of the reaction



is the product of two factors, a standard Boltzmann factor W_ρ and a kinetic factor $\varphi_\rho \geq 0$:

$$r_\rho = \varphi_\rho W_\rho = \varphi_\rho \exp \left(\frac{\sum_i \alpha_{\rho i} \mu_i}{RT} \right), \tag{21}$$

where μ_i is the chemical potential of the component A_i . The corresponding kinetic equation is

$$\frac{dN}{dt} = V \sum_\rho r_\rho \boldsymbol{\gamma}_\rho, \quad (\boldsymbol{\gamma}_{\rho i} = \beta_{\rho i} - \alpha_{\rho i}). \tag{22}$$

Here N is the vector of composition (N_i is the amount of A_i), and V is the volume.

We use the notation c_i for the concentration of A_i , c is the vector of concentrations, ζ_j is the concentration of B_j . The chemical potentials μ_i of the components A_i are the partial derivatives of the free energy density, $\mu_i = \partial f(c, T) / \partial c_i$. The standard thermodynamic assumption about strong convexity of the function $f(c, T)$ for all T is accepted.

Let us demonstrate how the generalized MAL follows from the QE and QSS approximations (for more details see Ref. [6]). The thermodynamic equilibria for the extended mixture are defined as the conditional minima of the free energy F . The free energy of a mixture of A_i with small admixtures of the compounds B_j is

$$F = Vf(c, T) + VRT \sum_{j=1}^q \zeta_j \left(\frac{u_j(c, T)}{RT} + \ln \zeta_j - 1 \right). \tag{23}$$

The entropic terms $VRT \zeta_j \ln \zeta_j$ in this expression corresponds to the ideal gas equations $p_j = \zeta_j RT$ for the partial pressure of the small admixtures of the compounds B_j . This ideal gas law may be valid not only in gases but for osmotic pressure of small admixtures in solutions (the Morse equation).

The thermodynamic equilibria of B_j are: $\zeta_j^{\text{eq}} = \zeta_j^*/Z$, where Z is a positive number and ζ_j^* is the *standard equilibrium*:

$$\zeta_j^*(c, T) = \exp\left(-\frac{u_j(c, T)}{RT}\right). \quad (24)$$

The thermodynamic equilibrium condition of the reactions $\Theta_j \rightleftharpoons B_j$ under the condition of smallness of ζ_j (QE+QSS) can be solved explicitly:

$$\zeta_j^{\text{qe}} = \zeta_j^*(c, T) \exp\left(\frac{\sum_i v_{ji} \mu_i(c, T)}{RT}\right). \quad (25)$$

The smallness of the concentration of the compounds implies that the rates of the reactions $B_i \rightarrow B_j$ in the extended mechanism (20) are linear functions of their concentrations. Let the rate constants for this first order kinetics be q_{ij} .

In the selected approximations the extended reaction mechanism (20) returns to the form $\Theta_j \rightarrow \Theta_l$. The reaction rate of the transition $\Theta_j \rightarrow \Theta_l$ in the quasiequilibrium approximation is $r_{lj} = q_{lj} \zeta_j^{\text{qe}}$. This is exactly the generalized MAL (21) with

$$\varphi_{lj} = q_{lj} \zeta_j^*, \quad \alpha_\rho = \nu_j, \quad \beta_\rho = \nu_l.$$

At the equilibrium ζ^*/Z , the first order kinetics of compounds should satisfy the general balance condition (2):

$$\sum_j q_{lj} \zeta_j^* = \sum_j q_{jl} \zeta_l^*.$$

Therefore, the kinetic factors φ_ρ satisfy the identity of semi-detailed balance:

$$\sum_{\rho, \alpha_\rho=\nu} \varphi_\rho \equiv \sum_{\rho, \beta_\rho=\nu} \varphi_\rho \quad (26)$$

for any vector ν from the set of all vectors $\{\alpha_\rho, \beta_\rho\}$. This identity is exactly the Markov balance condition (2) for kinetics of compounds with equilibrium ζ^*/Z . It has a very transparent sense: the thermodynamic equilibrium is, at the same time, the equilibrium for the first order kinetics of compounds, i.e. the it satisfies the balance condition (2) for the master equation.

Let us assume that the Markov kinetics of compounds satisfies the detailed balance condition (3) at the thermodynamic equilibrium:

$$q_{lj} \zeta_j^* = q_{jl} \zeta_l^*.$$

Then the kinetic factors φ_ρ satisfy the condition of detailed balance:

$$\varphi_\rho^+ \equiv \varphi_\rho^-, \quad (27)$$

where φ_ρ^+ is the kinetic factor for the direct reaction and φ_ρ^- is the kinetic factor for the reverse reaction.

This detailed balance condition assumes that the sums on the left and right hand sides of Eq. (26) are equal term by term. Therefore, it is stronger than the semi-detailed balance condition.

For linear systems, the semi-detailed balance condition turns into the standard balance condition (2) and the detailed balance condition (27) turns into (3). Of course, the class of systems with semi-detailed balance is much wider than the class of systems with detailed balance. Nevertheless, locally they coincide: *for given thermodynamic functions (23) and any given concentrations and temperature, the cone of possible velocities for systems (22) with semi-detailed balance coincides with the cone of the possible velocities for the systems with detailed balance.*

Indeed, for the given values of concentrations we can perform the following three operations: (i) return from the generalized MAL to the first order kinetic equations of compounds, (ii) use [Theorem 1](#) and find the system of compounds with detailed balance, which has the same velocity at the same point, and (iii) return back, to the generalized MAL. As a result, we get a kinetic system for the components A_j with detailed balance, the same free energy $Vf(c, T)$ (23), and the same velocity at the selected values of concentrations.

4. Conclusion

The definition of detailed balance includes the rates of all transitions at equilibrium but observability of all these rates together is a very special situation. Typically, one can observe the overall system velocity, dP/dt , or just some components of this velocity but not the rates of individual transitions. According to our results, if we know the equilibrium distribution P^* and observe the system velocity at one nonequilibrium point P then we can never distinguish a general system from the systems with detailed balance. This is true for Markov kinetics as well as for the systems with the generalized MAL; detailed balance can never be distinguished from the semi-detailed balance if we know the equilibrium and observe the velocity at one nonequilibrium point. The difference between velocities of the general kinetic systems and the systems with detailed balance is hidden in the correlations between different nonequilibrium states (or, for example, in the continuous pieces of

trajectories). The cone of possible velocities at a nonequilibrium state P is a piece-wise constant function of P , which can be constructed explicitly for the systems with detailed balance (Fig. 2), and the same construction is valid for the general kinetics. These results seem to be rather surprising.

For the nonlinear mass action systems, the systems with semi-detailed balance give the proper analogue of the general Markov kinetics. The conditions of semi-detailed balance were invented for the Boltzmann equation by Boltzmann [3], studied by Stueckelberg [5] and rediscovered for the mass action kinetics by Horn and Jackson [7]. Recently [6], it has been proved that the generalized MAL with the semi-detailed balance condition always follows from the Markov kinetics of compounds in the Michaelis–Menten–Stueckelberg asymptotic. The class of the systems with semi-detailed balance is wider than the class of systems with detailed balance. Nevertheless, for a given equilibrium and for any given value of concentration these two classes have the same sets of possible velocities in the distribution space.

References

- [1] L. Boltzmann, *Lectures on Gas Theory*, U. of California Press, Berkeley, CA, 1964.
- [2] H.-A. Lorentz, Über das Gleichgewicht der lebendigen Kraft unter Gasmolekülen, *Sitzungsber. K. Akad. Wiss. Wien* 95 (2) (1887) 115–152.
- [3] L. Boltzmann, Neuer Beweis zweier Sätze über das Wärmegleichgewicht unter mehratomigen Gasmolekülen, *Sitzungsber. K. Akad. Wiss. Wien* 95 (2) (1887) 153–164.
- [4] C. Cercignani, M. Lampis, On the H -theorem for polyatomic gases, *J. Stat. Phys.* 26 (4) (1981) 795–801.
- [5] E.C.G. Stueckelberg, Théorème H et unitarité de S , *Helv. Phys. Acta* 5 (1952) 577–580.
- [6] A.N. Gorban, M. Shahzad, The Michaelis–Menten–Stueckelberg theorem, *Entropy* 13 (2011) 966–1019. [arXiv:1008.3296](https://arxiv.org/abs/1008.3296).
- [7] F. Horn, R. Jackson, General mass action kinetics, *Arch. Ration. Mech. Anal.* 47 (1972) 81–116.
- [8] G. Szederkényi, K.M. Hangos, Finding complex balanced and detailed balanced realizations of chemical reaction networks, *J. Math. Chem.* 49 (2011) 1163–1179.
- [9] S.L. Kalpazidou, *Cycle Representations of Markov Processes*, in: *Applications of Mathematics*, vol. 28, Springer, New York, 2006.
- [10] N. Metropolis, A.W. Rosenbluth, M.N. Rosenbluth, A.H. Teller, E. Teller, Equations of state calculations by fast computing machines, *J. Chem. Phys.* 21 (6) (1953) 1087–1092.
- [11] M.A. Katsoulakis, A.J. Majda, D.G. Vlachos, Coarse-grained stochastic processes and Monte Carlo simulations in lattice systems, *J. Comput. Phys.* 186 (1) (2003) 250–278.
- [12] Frank Noé, Probability distributions of molecular observables computed from Markov models, *J. Chem. Phys.* 128 (2008) 244103.
- [13] P. Grassberger, A. de la Torre, Reggeon field theory (Schlög'l's first model) on a lattice: Monte Carlo calculations of critical behaviour, *Ann. Phys.* 122 (2) (1979) 373–396.
- [14] D.S. Dean, A. Lefèvre, Possible test of the thermodynamic approach to granular media, *Phys. Rev. Lett.* 90 (2003) 198301.
- [15] J.L. Marroquin, A. Ramirez, Stochastic cellular automata with Gibbsian invariant measures, *IEEE Trans. Inform. Theory* 37 (3) (1991) 541–551.
- [16] V.I. Manousothakis, M.W. Deem, Strict detailed balance is unnecessary in Monte Carlo simulation, *J. Chem. Phys.* 110 (6) (1999) 2753–2756. [arXiv:cond-mat/9809240](https://arxiv.org/abs/cond-mat/9809240).
- [17] M. Athènes, Web ensemble averages for retrieving relevant information from rejected Monte Carlo moves, *Eur. Phys. J. B* 58 (2007) 83–95.
- [18] K.S. Turitsyn, M. Chertkov, M. Vucelja, Irreversible Monte Carlo algorithms for efficient sampling, *Physica D* 240 (45) (2011) 410–414.
- [19] D.G. Miller, Thermodynamics of irreversible processes. The experimental verification of the Onsager reciprocal relations, *Chem. Rev.* 60 (1960) 15–37.
- [20] T. Thornton, C.M. Jones, J.K. Bair, M.D. Mancusi, H.B. Willard, Test of Time-Reversal Invariance in the Reactions $^{16}\text{O}(d, a)^{14}\text{N}$ and $^{14}\text{N}(a, d)^{16}\text{O}$, *Phys. Rev. C* 3 (3) (1971) 1065–1086.
- [21] H. Driller, E. Blanke, H. Genz, A. Richter, G. Schrieder, J.M. Pearson, Test of detailed balance at isolated resonances in the reactions $^{27}\text{Al} + p \rightleftharpoons ^{24}\text{Mg} + \alpha$ and time reversibility, *Nucl. Phys. A* 317 (23) (1979) 300–312.
- [22] C.T. Rettner, E.K. Schweizer, C.B. Mullins, Desorption and trapping of argon at a 2HW(100) surface and a test of the applicability of detailed balance to a nonequilibrium system, *J. Chem. Phys.* 90 (1989) 3800.
- [23] G.S. Yablonsky, A.N. Gorban, D. Constales, V.V. Galvita, G.B. Marin, Reciprocal relations between kinetic curves, *Europhys. Lett. EPL* 93 (2011) 20004.
- [24] E.M. Henley, B.A. Jacobsohn, Time reversal in nuclear interactions, *Phys. Rev.* 113 (1) (1959) 225–233.
- [25] A.N. Gorban, G.S. Yablonsky, Extended detailed balance for systems with irreversible reactions, *Chem. Eng. Sci.* 66 (2011) 5388–5399. [arXiv:1101.5280](https://arxiv.org/abs/1101.5280) [cond-mat.stat-mech].
- [26] A.N. Gorban, E.M. Mirkes, G.S. Yablonsky, Thermodynamics in the limit of irreversible reactions, *Physica A* (2012) [http://dx.doi.org/10.1016/j.physa.2012.10.009](https://doi.org/10.1016/j.physa.2012.10.009). [arXiv:1207.2507](https://arxiv.org/abs/1207.2507) [cond-mat.stat-mech].
- [27] A.N. Gorban, Thermodynamic tree: the space of admissible paths, *SIADS* (in press). [arXiv:1201.6315](https://arxiv.org/abs/1201.6315) [cond-mat.stat-mech].
- [28] F. Horn, Attainable regions in chemical reaction technique, in: *The Third European Symposium on Chemical Reaction Engineering*, Pergamon Press, London, UK, 1964, pp. 1–10.
- [29] A.N. Gorban, Invariant sets for kinetic equations, *React. Kinet. Catal. Lett.* 10 (1979) 187–190.
- [30] A.N. Gorban, *Equilibrium Encircling: Equations of Chemical Kinetics and their Thermodynamic Analysis*, Nauka Publ., Novosibirsk, 1984.
- [31] D. Glasser, D. Hildebrandt, C. Crowe, A geometric approach to steady flow reactors: the attainable region and optimisation in concentration space, *Ind. Eng. Chem. Res.* 26 (1987) 1803–1810.
- [32] D. Hildebrandt, D. Glasser, The attainable region and optimal reactor structures, *Chem. Eng. Sci.* 45 (1990) 2161–2168.
- [33] A.N. Gorban, B.M. Kaganovich, S.P. Filippov, A.V. Keiko, V.A. Shamansky, I.A. Shirkalin, *Thermodynamic Equilibria and Extrema: Analysis of Attainability Regions and Partial Equilibria*, Springer, New York, NY, 2006.
- [34] R.T. Rockafellar, *Convex Analysis*, Princeton University Press, Princeton, NJ, 1997.
- [35] T. Morimoto, Markov processes and the H -theorem, *J. Phys. Soc. Japan* 12 (1963) 328–381.
- [36] I. Csiszár, Eine informationstheoretische Ungleichung und ihre Anwendung auf den Beweis der Ergodizität von Markoffschen Ketten, *Magyar. Tud. Akad. Mat. Kutató Int. Közl.* 8 (1963) 85–108.
- [37] A. Rényi, in: J. Neyman (Ed.), *Proceedings of the 4th Berkeley Symposium on Mathematics, Statistics and Probability 1960*, Vol. 1, University of California Press, Berkeley, CA, 1961, pp. 547–561.
- [38] A.N. Gorban, P.A. Gorban, G. Judge, Entropy: the Markov ordering approach, *Entropy* 12 (5) (2010) 1145–1193. [arXiv:1003.1377](https://arxiv.org/abs/1003.1377).
- [39] G.S. Yablonskii, V.I. Bykov, A.N. Gorban, V.I. Elokhin, Kinetic Models of Catalytic Reactions, in: *Comprehensive Chemical Kinetics*, vol. 32, Elsevier, Amsterdam, The Netherlands, 1991.
- [40] R.M. Eiswirth, K. Krischer, G. Ertl, Nonlinear dynamics in the CO-oxidation on Pt single crystal surfaces, *Appl. Phys. A* 51 (1990) 79–90.
- [41] A.N. Gorban, V.I. Bykov, G.S. Yablonskii, *Essays on Chemical Relaxation*, Nauka, Novosibirsk, 1986.
- [42] K. Kowalski, Universal formats for nonlinear dynamical systems, *Chem. Phys. Lett.* 209 (1993) 167–170.
- [43] L. Michaelis, M. Menten, Die Kinetik der Intervintwirkung, *Biochem. Z.* 49 (1913) 333–369.