Fixed Points for Stochastic Open Chemical Systems *

V. A. Malyshev
INRIA, France

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1 Introduction

Relation between the existing (mathematical) physical theory and future mathematical biology seems to be very intimate. For example, equilibrium is a common state in physics but in biology equilibrium means death. Biology should be deeply dynamical but this goal seems unreachable in full extent: even in simplest physical situations the time consuming complexity of any study of local dynamics is out of the present state of art. Thus the only possibility would be to consider simpler dynamical models (mean field etc.) but to go farther in their structure. The obvious first step should have been related to chemical kinetics and chemical thermodynamics. Here we present a review of these first results and discuss what should be the second step.

In the first part of this paper we give a short review (in more general terms than in [15]) of the hierarchy of stochastic models, related to physical chemistry. In the basement of this hierarchy there are two models - stochastic chemical kinetics and the Kac model for Boltzman equation. Classical chemical kinetics and chemical thermodynamics are obtained as some scaling limits in the models, introduced below.

If some physical conditions, as reversibility, are assumed for a closed (without matter exchange) system, then we have sufficiently simple behaviour: one can prove convergence to a fixed point. However, in many models of physical chemistry and biology, no reversibility condition is assumed, and the behaviour can be as complicated as one can imagine. Here we have already some gap between physics and biology, and it is necessary to fill in this gap. In the second part of this paper we specify some simple class of open chemical reaction systems, where one can still prove the existence of attracting fixed points. For example, Michaelis-Menten kinetics belong to this class. At the end we present a

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simplest possible model of the biological network. It is a network of networks (of closed chemical reaction systems, called compartments), so that the only source of nonreversibility is the matter exchange (transport) with the environment and between the compartments.

2 Microdynamics

Any molecule of mass m can be characterized by translational degrees of freedom (velocity $v \in R^3$, coordinate $x \in R^3$) and internal, or chemical (for example, rotational and vibrational) degrees of freedom. Internal degrees of freedom include the type $j = 1, ..., J$ of the molecule and internal energy functionals $K_j(z_j), z_j \in \mathbf{K}_j$, in the space $\mathbf{K}_j$ of internal degrees of freedom. It is often assumed, see [11], that the total energy of the molecule i is

$$E_i = T_i + K_j(z_{j,i})$$

We consider here the simplest choice when K_j is the fixed nonnegative number, depending only on j. It can be interpreted as the energy of some chemical bonds.

We consider the set $\mathbf{X}$ of countable locally finite configurations $X = \{x_i, v_i, j_i\}$ of particles (molecules) in R^3, where each particle i has a coordinate x_i, velocity v_i and type j_i. Denote $\mathfrak{M}$ the system of all probability measures on $\mathbf{X}$ with the following properties:

- coordinates of these particles are distributed as the homogeneous Poisson point field of particles on R^3 with some density c,
- the vectors (v_i, j_i) are independent of its coordinate and of the other particles. The velocity v of a particle is assumed to be uniformly distributed on the sphere with the radius defined by the kinetic energy $T = \frac{m}{2}(v_1^2+v_2^2+v_3^2)$ of the particle, thus the pairs (j_i, T_i) are distributed via some common density $p(j, T)$

$$\sum_j \int p(j, T)dT = 1$$

Our first goal will be to define random dynamics on $\mathbf{X}$ (or deterministic dynamics on $\mathfrak{M}$). It is defined by a probability space $(\mathbf{X}^{0,\infty}, \mu)$, where $\mu = \mu^{0,\infty}$ is a probability measure on the set $\mathbf{X}^{0,\infty}$ of countable arrays $X^{0,\infty}(t) = \{x_i(t), v_i(t), j_i(t)\}$ of trajectories $x_i(t), v_i(t), j_i(t))$ on intervals $I_i = (\tau_i, \eta_i)$, where $0 \leq \tau_i < \eta_i \leq \infty$. The measure μ belongs to the set of measures $\mathfrak{M}^{0,\infty}$on $X^{0,\infty}(t)$, defined by the following properties:

- if for any fixed $0 \leq t < \infty$ we denote $\mu(t)$ the measure induced by μ on $\mathbf{X}$, then $\mu(t) \in \mathfrak{M}$;
- the trajectories $x_i(t), v_i(t), j_i(t)$ are independent, each of them is some Markov process (not necessary time homogeneous). This process is defined

by initial measure $\mu(0)$ on M, by birth and death rates, defining time moments τ_i, η_i, and by transition probabilities at time t, independent of the motion of individual particles but depending on the concentration densities $c_t(j,T)$ at time t;

- The evolution of the pair (j,T) for the individual particle in-between the birth and death moments is defined by the following Kolmogorov equations, which controls the one-particle process

$$\frac{\partial p_t(j_1,T_1)}{\partial t} =$$

$$= \sum_j \int (P(t;j_1,T_1|j,T)p_t(j,T) - P(t;j,T|j_1,T_1)p_t(j_1,T_1))dT \qquad (1)$$

defining Markov process with distributions $p_t(j,T)$. The probability kernel P depends however on $p_t(j,T)$ itself, we shall make it precise below.

The dynamics we will describe here is based on some earlier mathematical models and central dogmas of physical chemistry. The simplest way to rigorously introduce measure μ is by the limit of finite volume random dynamics. Initial conditions for this dynamics are as follows: at time 0 some number $n^{(\Lambda)}(0)$ of molecules are thrown uniformly in the cube Λ, their parameters (j,T) are independent and have some common density $p_0(j,T)$, not depending on Λ. Let $n_j(t) = n_j^{(\Lambda)}(t)$ be the number of type j molecules at time t.

Input-Output (I/O) processes Heuristically, our time scale is such that for the unit of time each molecule does $O(1)$ transitions. Then for any macroquantity q of substance its $O(q)$ part may change. One should choose time scales for input-output processes correspondingly.

The (output) rate of the jumps $n_j \to n_j - 1$ is denoted by $\lambda_j^{(o)}$, that is with this rate a molecule of type j is chosen randomly and deleted from Λ. Similarly (input) rate of the jumps $n_j \to n_j + 1$ is denoted by $\lambda_j^{(i)}$, that is a molecule of type j is put uniformly in Λ with this rate. Dependence of both rates on the concentrations can be quite different. To get limiting I/O process after (canonical) scaling one can assume that

$$\lambda_j^{(o)} = f_j^{(o)}\Lambda, \lambda_j^{(i)} = f_j^{(i)}\Lambda \qquad (2)$$

where $f_j, g_j > 0$ are some functions of $c_1^{(\Lambda)}, ..., c_J^{(\Lambda)}$, $c_j^{(\Lambda)} = \frac{n_j}{\Lambda}$ are the concentrations. However, mostly we restrict ourselves to the case when f_j are functions of only c_j. In other words, an individual type j molecule leaves the volume with rate $\frac{f_j^{(o)}(c_j^{(\Lambda)})}{c_j^{(\Lambda)}}$. Denote

$$f_j = f_j^{(i)} - f_j^{(o)} \qquad (3)$$

Stochastic chemical kinetics The hierarchy presented here depends on what parameters of a molecule are taken into account. In stochastic chemical kinetics only type is taken into account. The state of the system is given by the vector $(n_1, ..., n_J)$. There are also R reactions types and each reaction of the type $r = 1, ..., R$, can be written as

$$\sum_j \nu_{jr} M_j = 0$$

where we denote M_j a j type molecule, and the stoihiometric coefficients $\nu_{jr} > 0$ for the products and $\nu_{jr} < 0$ for the substrates. One event of type r reaction corresponds to the jump

$$n_j \to n_j + \nu_{jr}, j = 1, ..., J,$$

Classical polynomial expressions (most commonly used)

$$\lambda_r = A_r \prod_{j:\nu_{jr}<0} n_j^{-\nu_{jr}}$$

for the rates of these jumps define a continuous time Markov process, a kind of random walk in Z_+^J. This dependence can be heuristically deduced from local microdynamics. However, polynomial dependence is not the only possibility, see [32]. Moreover, there can be various scalings for these rates. The scaling

$$A_r = a_r \Lambda^{\gamma_r + 1}, \gamma_r = \sum_{j:\nu_{jr}<0} \nu_{jr}$$

where a_r are some constants and Λ is some large parameter, is called canonical because the classical chemical kinetics equations

$$\frac{dc_j(t)}{dt} = \sum_r R_{j,r}(\vec{c}(t)) \tag{4}$$

for the densities

$$c_j(t) = lim_{\Lambda\to\infty} \Lambda^{-1} n_j^{(\Lambda)}(t)$$

follow in the large Λ limit, with some (see below and [17]) polynomials $R_{j,r}$.

Problem. It is important to give (at least heuristic) local probabilistic models to explain other than polynomial dependence and scalings for the rates. For example for arbitrary homogeneous functions as in [32],

It is assumed that at time $t = 0$ as $\Lambda \to \infty$

$$\Lambda^{-1} n^{(\Lambda)}(0) \to c(0)$$

Chronologically, the first paper in stochastic chemical kinetics was by Leontovich [27], which appeared from discussions with A. N. Kolmogorov. Other references see in [24]. In 70s stochastic chemical kinetics for small R, J was studied intensively, see reviews [22, 9]. At the same time the general techniques to get limiting equations (4) appears in probability theory [33, 6]. Now there are many experimental arguments in favor of introducing stochasticity in chemical kinetics [1, 2, 24].

Stochastic energy redistribution In the classical Kac model [23] the molecules $i = 1, ..., N$ have the same type, but each molecule i has a velocity v_i or kinetic energy T_i. In collisions the velocities (or the kinetic energies) change somehow. There is still continuing activity with deeper results concerning the Kac model, in particular convergence rate, see for example [5].

One should merge Kac type models with stochastic chemical kinetics. Then each molecule i acquires a pair (j_i, T_i) of parameters: type j and kinetic energy T. However this is not sufficient to get energy redistribution. One should introduce also "chemical" energy. As it is commonly accepted, the general idea is that the energy of chemical bonds of a substrate molecule can be redistributed between product molecules, part of the energy transforming into heat. To describe this phenomena in well-defined terms we introduce fast and slow reactions. Fast reactions do not touch chemical energy, that is types, but slow reactions may change both kinetic and chemical energies, thus providing energy redistribution between heat and chemical energy.

Examples of reactions:

1. all chemical reactions are assumed slow - unary (unimolecular) $A \to B$, binary $A + B \to C + D$, synthesis $A + B \to C$, decay $C \to A + B$ etc. In any considered reaction the total energy conservation is assumed, that is the sum of total energies in the left side is equal to the sum of total energies in the right side of the reaction equation;

2. fast binary reactions of the type $A + B \to A + B$, which correspond to elastic collisions and draw the system towards equilibrium;

3. fast process of heat exchange with the environment, with reactions of the type $A+B \to A+B$, but where one of the molecules is an outside molecule.

If there is no input and output, then the Markov jump process is the following. Consider any subset $i_1 < ... < i_{m(r)}$ of $m(r) = -\sum_{j:\nu_{jr}<0} \nu_{jr}$ substrate molecules for reaction of type r.

On the time interval $(t, t + dt)$ these molecules have a "collision" with probability $\frac{1}{\Lambda^{m(r)-1}} b_r dt$, where b_r is some constant. Let the parameters of these molecules be $j_k = j(i_k), T_k = T(i_k)$. Denote

$$T = \sum_{i=1}^{m} T_i, K = \sum_{i=1}^{m} K_{j_i}$$

and T', K' are defined similarly for the parameters $j'_1, ..., j'_m, T'_1, ..., T'_{m'}$ of m' product molecules. The reaction occurs only if

$$T + K - K' \geq 0 \tag{5}$$

and then the energy parameters of the product particles at time $t + 0$ have the distribution defined by some conditional density

$$P_r(T'_1, ..., T'_{m'-1} | T_1, ..., T_m)$$

on the set $0 \le T'_1 + ... + T'_{m'-1} \le T + K - K'$. By energy conservation then

$$T'_{m'} = T + K - K' - \sum_{i=1}^{m'-1} T'_i$$

This defines a Markov process $M_{\bar{A}}(t)$ on the finite-dimensional space (note that $T \in R_+$)

$$Q_{\bar{A}} = \cup_{(n_1,...,n_J)} R_+^{n_1} \times ... \times R_+^{n_J}$$

where the union is over all vectors $(n_1, ..., n_J)$ such that for the array $\bar{A} = (A_1, ..., A_Q)$ of positive integers and for any atom type $q = 1, ..., Q$

$$\sum_j n_j a_{jq} = A_q$$

where a_{jq} is the number of atoms of type q in the j type molecule. In other words, each atom type defines the conservation law $A_q = const$.

Now, using conditional densities P_r, we define the "one-particle" transition kernel

$$P(t; j_1, T_1 | j, T) = \sum_r P^{(r)}(t; j_1, T_1 | j, T) \tag{6}$$

that is the sum of terms corresponding to reactions r. For unimolecular reactions $j \to j_1$ the product kinetic energy T_1 is uniquely defined, thus $P_{j \to j_1}$ is trivial and for some constants u_{jj_1}

$$P^{(j \to j_1)} = u_{jj_1} \delta(T + K - K_1 - T_1),$$

For binary reactions $j, j' \to j_1, j'_1$

$$P^{(j,j' \to j_1, j'_1)} = \sum_{j', j'_1} \int dT' dT'_1 b_{j,j' \to j_1, j'_1} P_{j,j' \to j_1, j'_1}(T_1 | T, T')$$

$$c_t(j', T') \delta(T + K + T' + K' - K_1 - T_1 - K'_1 - T'_1)$$

In particular, for "fast" collisions (which do not change type) we have the same transition kernel but with $j = j_1, j' = j'_1$. We see that $P^{(j,j' \to j_1, j'_1)}$ depend on the concentrations

$$c_t(j, T) = p_t(j, T) c(t)$$

They are defined via the Boltzman type equation

$$\frac{\partial c_t(j_1, T_1)}{\partial t} = f_j(c_j) +$$

$$+ \sum_j \int (P(t; j_1, T_1 | j, T) c_t(j, T) - P(t; j, T | j_1, T_1) c_t(j_1, T_1)) dT \tag{7}$$

which is similar to the Kolmogorov equation but includes also birth and death terms.

All technicalities about the derivation of the limiting processes see in Appendix of [15].

Space dynamics To get thermodynamics we need also volume, pressure etc. Thus it is necessary to define space dynamics and also scaling limit.

In the jump process, defined above, each particle i independently of the others, in random time moments

$$\tau_i(\omega) < t_{1i}(\omega) < ... < t_{in}(\omega) < ... < \sigma_i(\omega)$$

changes its type and kinetic energy (thus velocity). For each trajectory ω of the jump process we define the local space dynamics as follows. It does not change types, energies, velocities, but only coordinates. If at jump moment t of the trajectory ω the particle acquires velocity $\vec{v}(\omega) = \vec{v}(t+0, \omega)$ and has coordinate $\vec{x}(t, \omega)$, then at time $t + s$

$$\vec{x}(t + s, \omega) = \vec{x}(t, \omega) + \vec{v}(\omega)s \tag{8}$$

unless the next event (jump), concerning this particle, of the trajectory ω occurs on the time interval $[t, t + s]$. We assume periodic boundary conditions or elastic reflection from the boundary. We denote this process $X_\Lambda(t)$, the state space of this process is the sequence of finite arrays $X_i = \{j_i, \vec{x}_i, \vec{v}_i\}$. Thus each particle i has a piecewise linear trajectory in the time interval (τ_i, σ_i).

Theorem The thermodynamic limit $X_\infty(t)$ of the processes $X_\Lambda(t)$ exists and its distribution belongs to $\mathfrak{M}^{0,\infty}$.

Proof see in [15].

3 Scaling limit

Now we define more restricted (than $\mathfrak{M}$) manifolds of probability measures on $\mathbf{X}$: the grand canonical ensemble for a mixture of ideal gases with one important difference - fast degrees of freedom are gaussian and slow degrees of freedom are constants K_j, depending only on j.

We consider a finite number n_j of particles of types $j = 1, ..., J$ in a finite volume Λ. Remind that for the ideal gas of the j type particles the grand partition function of the Gibbs distribution is

$$\Theta(j, \beta) = \sum_{n_j=0}^{\infty} \frac{1}{n_j!} \left(\prod_{i=1}^{n_j} \int_\Lambda \int_{R^3} \int_{\mathbf{I}_j} d\vec{x}_{j,i} d\vec{v}_{j,i} \right) \exp \beta(n_j(\mu_j - K_j) - \sum_{i=1}^{n_j} \frac{m_j v_{j,i}^2}{2}) =$$

$$= \sum_{n_j=0}^{\infty} \frac{1}{n_j!} (\Lambda\lambda)^{n_j} \exp \beta(\mu_j - K_j) n_j = \exp(\Lambda \lambda_j \exp \beta \hat{\mu}_j)$$

where

$$\lambda_j = \beta^{-\frac{3}{2}} (\frac{2\pi}{m_j})^{\frac{3}{2}}, \hat{\mu}_j = \mu_j - K_j$$

General mixture distribution of J types is defined by the partition function $\Theta = \prod_{j=1}^{J} \Theta(j, \beta)$. The limiting space distribution of type j particles is the Poisson distribution with concentration c_j. We will need the formulas relating c_j and μ_j

$$c_j = \frac{< n_j >_\Lambda}{\Lambda} = \beta^{-1} \frac{\partial \ln \Theta}{\partial \mu_j} = \lambda_j \exp \beta \hat{\mu}_j$$

$$\mu_j = \beta^{-1} \ln(\frac{< n_j >}{\Lambda} \lambda_j^{-1}) = \mu_{j,0} + \beta^{-1} \ln c_j + K_j, \tag{9}$$

where

$$\mu_{j,0} = -\beta^{-1} \ln \lambda_j \tag{10}$$

is the so called standard chemical potential, it corresponds to the unit concentration $c_j = 1$. We put $c = c_1 + ... + c_J$.

We will need Gibbs free energy G and the limiting Gibbs free energy per unit volume

$$g = \lim_{\Lambda \to \infty} \frac{G}{\Lambda} = \sum \mu_j c_j$$

Define $\mathfrak{M}_0 \subset \mathfrak{M}$ the set of all such measures for any $\beta, \mu_1, ..., \mu_J$, and $\mathfrak{M}_{0,\beta}$ - its subset with fixed β.

In the process defined above the kinetic energies are independent bu may have not χ^2 distributions, that is the velocities may not have Maxwell distribution. We force them to have it by specifying some trend to equilibrium process (elastic collisions) and heat transfer (elastic collisions with outside molecules) processes.

Assume that there is a family $M(a), 0 \leq a < \infty$, of distributions μ_a on R_+ with the following property. Take two i.i.d. random variables ξ_1, ξ_2 with the distribution $M(a)$. Then their sum $\xi = \xi_1 + \xi_2$ has distribution $M(2a)$. We assume also that a is the expectation of the distribution $M(a)$. Denote $p(\xi_1|\xi)$ the conditional density of ξ_1 given ξ, defined on the interval $[0, \xi]$. We put

$$P^{(f)}(T_1|T, T') = p(T_1|T + T')$$

and of course $T_1' = T + T' - T_1$. Denote the corresponding generator $H_N^{(f)}$.

We model heat transfer similarly to the fast binary reactions, as random "collision" with outside molecules in an infinite bath, which is kept at constant temperature β. The energy of each outside molecule is assumed to have χ^2 distribution with 3 degrees of freedom and with parameter β. More exactly, for each molecule i there is Poisson process with some rate h. Denote $t_{ik}, k = 1, 2, ...$, its jump moments, when it undergoes collisions with outside molecules. At this moments the kinetic energy T of the molecule i is transformed as follows. The new kinetic energy T_1 after transformation is chosen correspondingly to conditional density p on the interval $[0, T + \xi_{ik}]$, where ξ_{ik} are i.i.d. random variables having χ^2 distribution with density $cx^{\frac{1}{2}} \exp(-\beta x)$. Denote the corresponding conditional density by $P^{(\beta)}(T_1|T)$. In fact, this process amounts to N independent one-particle processes, denote the corresponding generator $H_N^{(\beta)}$.

Thus we can write the generator as

$$H = H(s_f, s_\beta) = H^{(r)} + s_f H^{(f)} + s_\beta H^{(\beta)}$$

where $H^{(r)}$ corresponds to slow reactions and s_f, s_β are some large scaling factors, which eventually will tend to infinity.

We will force the kinetic energies to become χ^2 using the limit $s_f \to \infty$.

Theorem The limits in distribution

$$\mathfrak{C}_c(t) = \lim_{s_f \to \infty} \mathfrak{X}_c(t), \mathfrak{O}_{c,\beta}(t) = \lim_{s_h \to \infty} \mathfrak{C}_c(t)$$

exist for any fixed t. Moreover, the manifold $\mathfrak{M}_0$ is invariant with respect to the process $\mathfrak{C}_c(t)$ for any fixed rates u, b, h. The manifolds $\mathfrak{M}_{0,\beta}$ are invariant with respect to $\mathfrak{O}_{c,\beta}(t)$.

Thus, in the process $\mathfrak{C}_c(t)$ the velocities have Maxwell distribution at any time moment. For the process $\mathfrak{O}_{c,\beta}(t)$ moreover, at any time t the inverse temperature is equal to β, that is there is heat exchange with the environment. Our individual molecules still undergo Markov process, but simplified. At the same time, the macrovariables undergo deterministic evolution on $\mathfrak{M}_{0,\beta}$.

Markov property - chemical kinetics restoration Note that initially the jump rates depend on the energies, we show that, after the scaling limit, the process restricted on the types will also be Markov. We assume that there are only unary and binary reactions but we do not need reversibility assumption here.

Lemma The process, projected on types, that is the process $(n_1(t), ..., n_J(t))$ is Markov. It is time homogeneous for unary reaction system and time inhomogeneous in general.

Proof. Remind that the jump rates were assumed to have simplest energy dependence, that is collisions occur independently of the energies, but reactions occur only if energy condition (5) is satisfied. Denote $g_\beta(r) = P(|\xi| > r)$ for the χ^2 random variable ξ with inverse temperature β.

Assume $K_1 \leq ... \leq K_J$ and consider first the case of unary reactions. It is easy to see that the process $\mathfrak{O}_{c,\beta}(t)$ can be reduced to the Markov chain on $\{1, ..., J\}$ with rates $v_{jj'} = u_{jj'}$ if $j \geq j'$, and

$$v_{jj'} = g_\beta(K_{j'} - K_j) u_{jj'}$$

if $j < j'$. We used here that the kinetic energy distribution is χ^2 at any time moment.

Similarly for the binary reaction $j, j' \to j_1, j_1'$ we define the renormalized Markov transition rates as

$$c(j, j' \to j_1, j_1') = b_{j,j' \to j_1, j_1'}$$

if $K_j + K_{j'} \geq K_{j_1} + K_{j'_1}$ and

$$c(j, j' \to j_1, j'_1) = b_{j,j' \to j_1, j'_1} P(|\xi_1 + \xi_2| > K_{j_1} + K_{j'_1} - (K_j + K_{j'}))$$

if $K_j + K_{j'} < K_{j_1} + K_{j'_1}$. Here ξ_i are independent and χ^2 with with inverse temperature β. It is crucial here the use of the scaling limit for fast reactions.

Thus, in the thermodynamic limit we get the equations without the energies, that is the classical chemical kinetics

$$\frac{dc_j(t)}{dt} = \sum_r R_{j,r}(\vec{c}(t)) + f(c_j) \tag{11}$$

Example: monotonicity of Gibbs free energy for closed system with only unary reactions Assume now that the continuous time Markov chain on $\{1, ..., J\}$ with rates $u_{jj'}$ is irreducible. We say that this Markov chain is compatible with the equilibrium conditions

$$\mu_1 = ... = \mu_J \tag{12}$$

if its stationary probabiliries π_j, or stationary concentrations $c_{j,e} = \pi_j c$, satisfy the following conditions

$$\ln c_{1,e} + (\mu_{1,0} + K_1) = ... = \ln c_{J,e} + (\mu_{J,0} + K_J)$$

Remark This compatibility condition should appear naturally in local dynamics, but it is not clear how to deduce it in the mean field dynamics. Note that reversibility is not a sufficient condition for the compatibility condition.

To exhibit monotonicity for dynamics one needs special Lyapounov functions in the space of distributions. For Markov chains this is the Markov entropy with respect to stationary measure π_j

$$S_M = \sum p_j \ln \frac{p_j}{\pi_j}$$

see for example [14].

Remind that the equilibrium function - Gibbs free energy $g(t)$ - undergoes deterministic evolution together with the parameters μ_j or c_j. We will show that at any time moment it coincides with the Markov entropy up to multiplicative and additive constants.

Theorem If the compatibility condition (12) holds, then

$$g(t) = \mu c + \frac{1}{\beta C} S_M(t) \tag{13}$$

and monotone behaviour of the Gibbs free energy density follows.

Proof. We have

$$g = \lim_{\Lambda} \frac{G}{\Lambda} = \sum_j c_j \mu_j = \beta^{-1} \sum_j c_j \ln c_j + \sum_j c_j (\mu_{j,0} + K_j) = \tag{14}$$

$$= \beta^{-1} \sum_j c_j \ln c_j + \sum_j c_j (\mu - \beta^{-1} \ln c_{j,e}) = \mu c + \beta^{-1} \sum_j c_j \ln \frac{c_j}{c_{j,e}}$$

where first and second equalities are the definitions, in the third and fourth equalities we used the formula

$$\mu_j = \beta^{-1} \ln(\frac{< n_j >}{\Lambda} \lambda_j^{-1}) = \mu_{j,0} + \beta^{-1} \ln c_j + K_j, \tag{15}$$

where

$$\mu_{j,0} = -\beta^{-1} \ln \lambda_j = -\beta^{-1}(-\frac{d_j}{2} \ln \beta + \ln B_j) \tag{16}$$

is the so called standard chemical potential, it corresponds to the unit concentration $c_j = 1$ for the equilibrium density, see for example [15].

At the same time

$$S_M = \sum p_j \ln \frac{p_j}{\pi_j} = C \sum c_j \ln \frac{c_j}{c_{j,e}}$$

We see that for unary reactions one does not need reversibility assumption.

Monotonicity of Gibbs free energy for closed system with binary reactions For binary reactions a similar result holds (we will not formulate it formally). However, we do not have Markov evolution for the concentrations anymore. Instead, we have the Boltzman equation for the concentrations, that is the so called nonlinear Markov chain on $\{1, ..., J\}$. Then, instead of the Markov entropy one should take the Boltzman entropy with respect to some one-point distribution $p_j^{(0)}$ (see definitions in [17])

$$S_H(t) = -\sum p_j(t) \ln \frac{p_j(t)}{p_j^{(0)}}$$

which coincides with the Markov entropy for ordinary Markov chains. For the monotonic behaviour of the Boltzman entropy, one should assume reversibility or a more general condition - unitarity, called local equilibrium in [17]. Under this condition the monotonicity of the Boltzman entropy was proved in [17]. We get the same formula as (13) if we substitute $-S_H$ instead of S_M.

Remind that under this conditions at the same time $p_j(t)$ form time inhomogeneous Markov chain. In fact, in the long run, that is as $t \to \infty$, the transition rates for one-particle inhomogeneous Markov chain, in the vicinity of the fixed point, is asymptotitcally homogeneous. This shows that binary case is asymptotically close to the unary case.

4 Open thermodynamic compartments

Reversible and nonreversible processes Our systems in finite volume evolve via Markov dynamics. It is not known when and how this dynamics could rigorously be deduced from the local physical laws. However, there are many arguments that reversibility is a necessary condition for this. Reversibility is a particular case of the unitarity property of the scattering matrix of a collision process. It was called local equilibrium condition in [17, 8]).

The reversibility gives strong corollaries for the scaling limits - 1) Boltzman monotonicity and 2) attractive fixed points. We call chemical networks with properties 1) and 2) thermodynamic compartments. Denote the class of such systems **T**. These systems are a little bit more general than the systems, corresponding to the systems with local physical laws (in particular, having convergence to equilibrium property). For example, any unimolecular reaction system belongs to **T**, because, as we saw above, the Markov entropy is the Boltzman entropy here. However, biological systems obviously are not of class **T**. There are different ways to generalize class **T** systems.

The first one is quite common: in chemical and biological systems stochastic processes usually are not assumed to be reversible. However, without the reversibility assumption the time evolution could be as complicated as possible (periodic orbits, strange attractors etc.). That has advantages - one can adjust to real biological situations, and disadvantages - too many parameters, even arbitrary functions. Normally, the rate functions $R_{j,r}$ can be rather arbitrary chosen, typical example where this methodology is distinctly pronounced is [34], connections with physics lost etc. In other words, theory becomes meaningless when one can adjust it to any situation.

Another way could be a hierarchy of procedures to introduce nonreversibility in a more cautious way. Each further step to introduce nonreversibility is as simple as possible and each is related to time scaling, for example, reversible dynamics is time scaled and projected on a subsystem. We start to study here the simplest type of such procedures. In our case the Markov generator will be the sum of two terms

$$H = H_{rev} + H_{nonrev} \tag{17}$$

where the first one is reversible and the other one is not, but it consist only on input and output processes. One of technical reasons to choose such nonreversible hamiltonian is to keep invariance of the manifolds $\mathfrak{M}, \mathfrak{M}_0, \mathfrak{M}_{0,\beta}$.

In principle, another philosophy is possible - large deviation or other rare event conditioning, this we do not discuss here.

Example 1: steady states for open unimolecular systems We consider the case with $J = 2$ and unary reactions only, however the following assertions help to understand how more general open systems can behave. Consider first the thermodynamic limit, and then the stochastic finite volume problem.

In the thermodynamic limit the following equations for the concentrations

$c_j(t), j = 1, 2$, hold

$$\frac{dc_1}{dt} = -\nu_1 c_1 + \nu_2 c_2 + f_1,$$
$$\frac{dc_2}{dt} = \nu_1 c_1 - \nu_2 c_2 + f_2$$

where $\nu_1 = u_{12}, \nu_2 = u_{21}$ and f_j are defined by (3). Possible positive ($c_1, c_2 > 0$) fixed points satisfy the following system

$$f_1(c_1) + f_2(c_2) = 0$$
$$-\nu_1 c_1 + \nu_2 c_2 + f_1(c_1) = 0$$

For example, for constant f_j a positive fixed point exists for any c sufficiently large and equals

$$c_1 = \frac{\nu_2 c - f_2}{\nu_1 + \nu_2}, c_2 = \frac{\nu_1 c - f_1}{\nu_1 + \nu_2}$$

In the linear case, that is for $f_j = a_j c_j$, for the existence of a positive fixed point it is necessary and sufficient that a_j have different signs and $|a_j| < \nu_1 + \nu_2$. Then the positive fixed point is unique and is defined by

$$c_1 = \frac{\nu_2 c}{\nu_1 + \nu_2 - a_1}$$

For faster than linear growth of f_j fixed points cannot exist for large c.

We see from these formulas that the equilibrium fixed point

$$c_1 = \frac{\nu_2 c}{\nu_1 + \nu_2}, c_2 = \frac{\nu_1 c}{\nu_1 + \nu_2}$$

(for the corresponding closed system) is slightly perturbed if f_j (or a_j) are small. Moreover, the perturbed fixed point is still attractive. This is true in more general situations as well.

Now consider the stochastic (finite volume) case.

Proposition Assume that f_j are constants. In a finite volume the process is ergodic if $\sum f_j < 0$, transient if $\sum f_j > 0$ and null recurrent if $\sum f_j = 0$.

Proof. Note that the number of particles is conserved and the number of states is finite if there is no I/O, otherwise the Markov chain is countable: a random walk on $Z_+^2 = \{(n_1, n_2) : n_1 n_2 \geq 0\}$. There are jumps $(n_1, n_2) \to (n_1 - 1, n_2 + 1)$ or $(n_1, n_2) \to (n_1 + 1, n_2 - 1)$ due to reactions, denote their rates $\nu_1 n_1, \nu_2 n_2$ correspondingly. There are also jumps $(n_1, n_2) \to (n_1 \pm 1, n_2), (n_1, n_2) \to (n_1, n_2 \pm 1)$ due to input-output with the parameters $a_j \Lambda$ and $b_j \Lambda$ correspondingly.

Transience and ergodicity can be obtained using Lyapounov function $n_1 + n_2$ and the results from [7]. To prove null recurrence note that for sufficiently large c the system should be in the neighbourhood of the fixed point, which exists for c sufficiently large. Thus one can also use the same Lyapounov function.

General conclusion is that only null recurrent case is interesting. However, models with constant rates are too naive. It is reasonable that there are regulation mechanisms which give more complex dependence of f_j on the rates. Unfortunately, there is no firm theoretical basis to get exact dependence of reaction and I/O rates on the densities.

Example 2: stochastic Michaelis-Menten kinetics The generator for Michaelis-Menten kinetics is of type (17) only in some approximation. This model has 4 types of molecules: E (enzyme), S (substrate), P (product) and ES (substrate-enzyme complex). There are 3 reactions

$$E + S \to ES, ES \to E + S, ES \to E + P$$

with the rates $k_1\Lambda^{-1}n_E n_S, k_{-1}n_{ES}, k_2 n_{ES}$ correspondingly. We can also fix somehow the output rate for P and input rate for S.

If $k_2 = 0$ then, as a zero'th approximation, we have a reversible Markov chain. In fact, there are conservation laws

$$n_E + n_{ES} = m(E), n_S + n_{ES} = m(S)$$

for some constants $m(E), m(S)$. Thus we will have random walk for one variable, say n_{ES}, on the interval $[0, min(m(E), m(S))]$, with jumps $n_{ES} \to n_{ES} \pm 1$. Such random walks are always reversible. The stationary probabilities for this random walk are concentrated around the fixed point of the limiting equations of the classical kinetics

$$\frac{dc_{ES}}{dt} = k_1 c_S c_E - (k_{-1} + k_2)c_{ES} \tag{18}$$

defined by

$$c_{ES} = \frac{c_S}{a + bc_S}$$

for some constants a, b, defined by $m(E), m(S)$. If $k_2 > 0$ but small compared to k_1, k_{-1} then up to the first order in k_2 we have the P production speed

$$\frac{dc_P}{dt} = k_2 c_{ES} = k_2 \frac{c_S}{a + bc_S}$$

We could also look on this kinetics as on the simple random walk. We have to introduce (arbitrarily) output rate for the product P and adjust the input rate of S so that the system become null-recurrent. In fact, due to the conservation law $n_E + n_{ES} = m(E)$ we have random walk on the half strip $\{(n_S, n_{ES})\} = Z_+ \times (0, m(E))$. The null-recurrence condition can be obtained using methods of [7], we will not discuss this here.

5 Network of thermodynamic compartments

Thermodynamic compartments, introduced above, we call networks of rank 1. As we saw they have fixed points, and thermodynamics plays the central role there. It can be some a tightly dependent and/or space localized system of chemical reactions.

Network of rank 2 consists of vertices α - networks of rank 1, and directed edges. Compartments are organized in a directed graph. Directed edge from compartment α to compartment α' means that there is a matter flow from α

to α'. Matter exchange between two compartments suggests some transport mechanism. It is natural that there is a time delay between the moments of departure from α and arrival to α'. The simplest probabilistic model could be the following. Each j type molecule leaves α for the destination α' with rates $f_{j,\alpha,\alpha'}$, similar to defind in (2), and after some random time $\tau(j,\alpha,\alpha')$ arrives to α'. Times $\tau(j,\alpha,\alpha')$ are independent and their distribution depends only on j,α,α'. One can imagine that there is an effective distance $L(\alpha,\alpha')$ between α and α' and some transportation mechanism, which defines effective speed to go through this distance. For example, it can be transport through membrane, which can be represented as a layer $[0,L]\times R^2$ of thickness L. During time $\tau(j,\alpha,\alpha')$ the particle is absent from the network, it has left α but has not yet arrived to α'.

Denote $c_{\alpha,j}$ the concentration of type j molecules in the compartment α. Limiting equations are

$$\frac{dc_{\alpha',j}(t)}{dt} = f^{(i)}_{\alpha',j}(c_{\alpha'}(t)) - f^{(o)}_{\alpha',j}(c_{\alpha'}(t)) + \sum_{\alpha} f_{j,\alpha,\alpha'}(c_{\alpha}(t-\tau(j,\alpha,\alpha'))+$$

$$-\sum_{\alpha} f_{j,\alpha',\alpha}(c_{\alpha'}(t)) + \sum_{r}\nu_{\alpha',jr}R_{\alpha',r}(c_{\alpha'}(t))$$

where $c_\alpha = (c_{\alpha,1},...c_{\alpha,J})$, $f^{(i)}_{\alpha,j}$ is the input rate to α from external environment, $f^{(o)}_{\alpha,j}$ - output rate from α to the external environment. Note that these equations are random due to random delay times τ. In the fisrt approximation one can consider τ constant, however random time delays seem very essential to restore randomness on the time scale, higher than microscopic, in the otherwise deterministic classical chemical kinetics.

Note that the above written equations follow from a similar microscopic model - we will not formally formulate it, because it is obvious from our previous constructions: the corresponding manifold is $\times_{\alpha\in A}\mathfrak{M}_\alpha$, where A is the set of compartments, $\mathfrak{M}_\alpha$ is the manifold for the compartment α.

The following problems and phase transitions can be discussed on the rigorous basis (in progress):

1. The method of thermodynamics bounds in the thermodynamic networks, defined in [31];

2. (Phase transitions due to transport rates) Normal functioning of the network can be close to the system $\{c_{\alpha,j,e}\}$ of equilibrium fixed points in each compartment α. Such situation can be called homeostasis. Homeostatic regulation - keeping the system close to some system $\{c_{\alpha,j,e}\}$. If there is no transport, then the compartments are independent and the fixed points inside them are pure thermodynamic. Under some transport rates the fixed points change in a stable way, they smoothly depend on the transport parameters. However, under some change of the transport rates, the fixed points may change drastically: the system goes to other basin of attraction.

3. (Phase transition due to time desynchronization) It is known now that even a desease can be a consequence of timing errors. For a network of rank 2, for example having cyclic topology (this is called circuit in [30]), assume that the input rates change periodically or randomly in time. The question is that to what process the concentrations converge and with what speed ? This time behaviour could be the next step in the analysis of the structure of logical networks in the sense of [30].

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