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Random walks and chemical networks

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Abstract: We consider continuous time random walks in the orthant with bounded jumps, the rates however are not bounded - they have a polynomial dependence on the coordinates of the point. The case when the rates are bounded corresponds in applications to the queueing theory, more exactly to markovian communication networks. The goal of this paper is to discuss the situation for polynomial rates, we show that the boundaries do not play role, but new effects and complicated behaviour can arise due to hierarchies of time scales.

Key-words: random walks, chemical kinetics, networks, metabolism

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Marches Aléatoires et Réseaux Chimiques.

Résumé : On considère des marches aléatoires avec des taux de transitions polynomiaux dans un orthant représentant un graphe de réactions chimiques. On étudie des changements d'échelle canoniques et non canoniques ainsi que les éventuelles transitions de phases.

Mots-clés : marches aléatoires, réseaux chimiques, métabolisme

1 Introduction

We consider continuous time random walks in the orthant Z_+^N with bounded jumps, the rates however are not bounded - they have a polynomial dependence on the coordinates of the point. The case when the rates are bounded corresponds in applications to the queueing theory, more exactly to markovian communication networks. Very rich behaviour in this case, due to the boundaries, was reviewed in [6]. The main ingredient in random walks with bounded transition rates was the so called fluid (or Euler) scaling limit. The goal of this paper is to discuss the situation for polynomial rates, where the boundaries do not play role, but new effects and complicated behaviour can arise due to different time scales.

The case we consider here corresponds to networks of chemical reactions. Markov processes describing chemical reactions were introduced by physicists, see [1]. One can find other physical references in the review [5] but much earlier paper [1] was not known to the author of this review. The accent in this review was on explicitly solvable cases, see also [4] rather than on general structure of such processes.

The Markov processes introduced here occupy an intermediate position between non-equilibrium statistical physics (where no rigorous results are expected in this case) and deterministic ODE of classical chemical kinetics.

We assume that the number N of molecular types and the number R of reaction types are fixed, but the numbers n_v of molecules of type v may tend to infinity, for all v or only for some. Under such limiting behaviour we study the scaling limits, assuming that the coefficients κ_r of the polynomial are scaled in some way. We think that a clever choice of scalings for κ_r can model some effects in the network of cell metabolic pathways.

1.1 Preliminary definitions

Graph of chemical reactions We write the equation of a chemical reaction as

$$a_1 A_1 + \dots + a_k A_k = b_1 B_1 + \dots + b_l B_l \quad (1)$$

where a_i, b_j are integers (stehiometric coefficients), A_i - input chemical substances (molecules), B_j - output substances.

Graph Γ of chemical reactions is a graph with a local structure. Vertices are of two kinds: some correspond to a substance (molecule, atom, ion, molecular complex, DNA promoter site etc.), others correspond to reaction types. Edges connect substance (or molecular) vertices with reaction vertices, each edge is directed. Edge from substance to reaction means that the substance is the input of the reaction, edge from reaction to substance means that the substance is an output of the reaction. To each reaction vertex r a positive number κ_r is prescribed. Let $I(r), O(r)$ be the sets of molecular vertices, having at least one ingoing edge or outgoing edge to the reaction edge r correspondingly. Edges can be multiple, this corresponds to the multiplicities a_i, b_j .

Moreover, to each molecular vertex corresponds the rate λ_v of the input flow of substance v and the rate μ_v of the output flow of substance v . The network is called closed if $\lambda_v = \mu_v = 0$ for all v , otherwise it is called open.

Random walk in Z_+^N If Γ is finite then a countable continuous time homogeneous Markov chains can be defined on Z_+^N , where N is the number of substance vertices. The coordinate $n_v(t)$ of a point $(n_1(t), \dots, n_N(t)) \in Z_+^N$ is the number of molecules of type v at time t .

Each r defines transitions

$$n_v \rightarrow \begin{cases} n_v - d_-(v, r), & v \in I(r) \\ n_v + d_+(r, v), & v \in O(r) \\ n_v, & v \notin I(r) \cup O(r) \end{cases} \quad (2)$$

where $d_-(v, r), d_+(r, v) > 0$ are the multiplicities of the ingoing or outgoing edge correspondingly. If $v \in I(r) \cap O(r)$ then the transition is $n_v \rightarrow n_v + d_+(r, v) - d_-(r, v)$. These transitions have rates K_r where we consider mainly the case

$$K_r = \kappa_r \prod_{v \in I(r)} n_v^{d_-(v, r)} \quad (3)$$

Intuitively this corresponds to the fact that the number of collisions for a unit of time is proportional to the number of particles: complicated space picture, which is behind the scene, is hidden in κ_r .

For open networks there are also transitions $n_v \rightarrow n_v + 1$ and $n_v \rightarrow n_v - 1$ with rates λ_v and μ_v correspondingly.

Conservation laws For a closed network this chain is reducible: its irreducible components are finite and defined on some subsets of Z_+^N . They are defined by the equations

$$M_j = \sum_v n_v m_{vj} \quad (4)$$

where for each molecule i m_{ij} is the number of atoms of type j in i , and M_j are some constants. This is clear as we have the conservation laws for separate reactions: for any r and any j

$$\sum_{i \in I(r)} d_-(r, i) m_{ij} = \sum_{i \in O(r)} d_+(r, i) m_{ij} \quad (5)$$

2 Deterministic scaling limit

Assume that at time $t = 0$ all $n_v = n_v(0; M)$ depend on a large parameter $M \rightarrow \infty$ so that $\frac{n_v}{M^{\beta(v)}} = c_v(M)$, where $c_v(M) \geq 0$ are called concentrations and $\beta(v)$ are scaling parameters. In this section we take all $\beta(v) = 1$. Then one can always assume that

$$\sum_v c_v(M) = 1 \quad (6)$$

We want to study the process $(n_1(t; M), \dots, n_N(t; M))$ for fixed t and $M \rightarrow \infty$.

The coefficients κ_r can have a different dependence on M . First of all, κ_r are defined up to some common factor (time scale). Next, the ratios $\frac{\kappa_r}{\kappa_{r'}}$ in different models can change due to complicated dependence on many factors: the sizes of molecules, space organization of the cell, details of geometric folding of polymers (tertiary structure) etc. Moreover, we can consider subnetworks of the whole network, that gives even more possibilities for this dependence. We assume in this class of models that $\kappa_r = \kappa_r^{(M)}, \lambda_v^{(M)}, \mu_v^{(M)}$ are functions $\kappa_r(c_v, M), \lambda_v(c_v, M), \mu_v(c_v, M)$ of M and concentrations c_v .

In the following theorem we assume that $\kappa_r = M^{-m(r)+1}a_r$, where a_r are constants and $m = m(r)$ is the degree of the corresponding monomial. We call such scaling canonical.

Theorem 1 *Consider a closed network and assume that for the initial time moment $t = 0$ for any v there exist the limits*

$$c_v(0) = \lim_{M \rightarrow \infty} \frac{n_v(0; M)}{M} \quad (7)$$

Then for any v and for any $t > 0$ there exists the following limit in probability

$$c_v(t) = \lim_{M \rightarrow \infty} \frac{n_v(t; M)}{M} \quad (8)$$

where $c_v(t)$ are positive numbers satisfying the equations

$$\frac{dc_v(t)}{dt} = \sum_{r:v \in O(r)} d_+(r, v)a_r \prod_{w \in I(r)} c_w^{d_-(w, r)}(t) - \sum_{r:v \in I(r)} d_-(v, r)a_r \prod_{w \in I(r)} c_w^{d_-(w, r)}(t) \quad (9)$$

Proof. For some examples the proof can be found in [2], in fact for the general case the proof could follow the same lines. We give the proof for more general case in the next section. Here we give another approach, which is simpler, more intuitive and can be used in more complicated situations to quickly guess the answer.

Let

$$t_1 < t_2 < \dots < t_J \quad (10)$$

be random jump moments on the interval $[t, t + \Delta t]$. We have

$$\frac{c_v(t + \Delta t, M) - c_v(t, M)}{\Delta t} = \frac{n_v(t + \Delta t, M) - n_v(t, M)}{M \Delta t} = \frac{\sum_{j=1}^J \xi_{j,v}}{M \Delta t} \quad (11)$$

where $\xi_{j,v}$ is the projection of the j -th jump onto the v -direction in Z_+^N . The rate of the r -jump at time t is $b_r(t, M)M$, where $b_r(t, M) = a_r \prod_{w \in I(r)} c_w^{d_-(r, w)}(t, M)$. They are of order 1, due to our scaling. For small time Δt the total number J_r of r -jumps is $b_r M(\Delta t + o(\Delta t))$. In fact, we can prove that for any $\varepsilon > 0$ the probability of the event

$$(1 - \varepsilon)b_r M \Delta t < J_r < b_r M \Delta t(1 + \varepsilon) \quad (12)$$

tends to 1 as $M \rightarrow \infty$. In fact, we have a "weakly" inhomogeneous Poisson process of jumps on the interval Δt , where

$$b_r(t_j, M) = b_r(t, M) + O(\Delta t) \quad (13)$$

Thus this complicated process can be majorized (stochastic monotonicity) with a homogeneous Poisson process with rate $b_r M(1 + \varepsilon)$ and minorized with a homogeneous Poisson process with rate $b_r M(1 - \varepsilon)$.

Thus we have proved the "law of large numbers"

$$\frac{\sum_{j=1}^J \xi_{v,j}}{M \Delta t} = \frac{\sum_r (J_r S(r) + O(\Delta t))}{M \Delta t} \sim \sum_r b_r(r, t) S(r) \quad (14)$$

where

$$S(r) = \sum_{r:v \in O(r)} d_+(r, v) - \sum_{r:v \in I(r)} d_-(v, r) \quad (15)$$

In this proof we used only the mere existence of the limits of concentrations

$$c_v(t) = \lim_{M \rightarrow \infty} \frac{n_v(t, M)}{M} \quad (16)$$

2.0.1 Comments

Limiting conservation laws For the system of differential equations we have the limiting linear conservation laws

$$b_j = \sum_v c_v(t) m_{vj} \quad (17)$$

In fact, $b_j = \lim_{M \rightarrow \infty} \frac{M_j}{M}$, that exists by definition of M_j .

Boundary behaviour Consider the closed orthant R_+^N and its open faces $\Lambda(I) = \{(x_1, \dots, x_N) : x_i > 0, i \in \Lambda, x_i = 0, i \notin \Lambda\}$ where Λ is any subset of $\{1, \dots, N\}$.

For closed networks the limiting deterministic dynamical system has the following simple properties. If the initial vector of concentrations belongs to Λ then there are two possibilities. The first one is that the trajectory of the limiting dynamical system belongs to Λ (Λ is invariant), that is it never reaches other faces due to the absence of the constant term in the polynomial. The second possibility is that it immediately leaves Λ correspondingly to the drift vector, necessarily to some face Λ' , $\dim \Lambda < \dim \Lambda'$. Then Λ' is invariant.

Thus the limiting dynamical system is a disjoint union of $D \leq 2^N$ dynamical systems. Note also that there are no constant terms in the drift vector, which is an analytic function of the point in R_+^N . In the general case, when there are constant terms, one can intersect faces of smaller dimensions and scattering (nonuniqueness of the drift vector) occurs.

Open networks The latter possibility occurs for general open networks, that is when $\lambda_v, \mu_v \neq 0$. In the general case an assertion similar to Theorem 1 is known (see [6]) to be wrong (there is no deterministic limit), unless we assume some restricted conditions. For example, if $c_v(0; M) > 0$ for all v , or if we assume that μ_v does not have a constant term. Fortunately enough, in some open biological systems however μ_v are proportional to the concentration c_v . It is known also that if the rates are constant then the dynamical system on Λ can be defined for some Λ , then this dynamical system is linear. In despite of this linearity the global behaviour can be extremely complicated.

Explosions We consider such effects in one-dimensional case, that is for reactions



Then for canonical scaling we get

$$\frac{dc(t)}{dt} = \sum_r d_+(r) a_r c^{d_+(r)}(t) - \sum_r d_-(r) a_r c^{d_-(r)}(t) \quad (19)$$

The following criteria of explosion (escape to infinity for finite time) is well-known: the system has explosion iff the leading term has degree not less than 2 and a positive coefficient.

Explosion effect can have a biological meaning - death of the cell.

3 Nondeterministic scaling limit

Here we consider the case when there are two subsystems of molecules I_1 and I_2 . Moreover, we assume that the numbers n_v of particles from the system I_2 are relatively small and not scaled. It is known that there are some proteins, represented by a couple of molecules per cell, having strong influence on the metabolic network.

More exactly, assume that $Z_+^N = Z_+^d \times Z_+^D$, $N = d + D$, and there are d types of "small" molecules with the state vector $\vec{n}_s = (n_1, \dots, n_d)$ and D types of "large" molecules with the state vector $\vec{n}_l = (n_{d+1}, \dots, n_{d+D})$. There are "fast" reactions r which concern only "small" molecules, that is only coordinates of \vec{n}_s may change, the rates of these reactions are

$$M f_r(M^{-1}\vec{n}_s, \vec{n}_l) \quad (20)$$

its jumps we denote by $z_r \in Z^d$, and the reactions R where any coordinate may change with rates

$$g_R(M^{-1}\vec{n}_s, \vec{n}_l) \quad (21)$$

we denote the corresponding jumps by y_R . Here f_r and g_R are given nonnegative functions on $R_+^d \times Z_+^D$, $f_r(\cdot, \vec{n}_l) \in C^1(R_+^d)$, $g_R(\cdot, \vec{n}_l) \in C^0(R_+^d)$.

Define the Markov process $(\vec{c}(t), \vec{n}_l^\infty(t))$ where $\vec{c}(t) = (c_v(t), v = 1, \dots, d)$ are defined by the differential equations

$$\frac{d\vec{c}(t)}{dt} = \sum_r f_r(\vec{c}(t), \vec{n}_l^\infty(t)) z_r \quad (22)$$

and $\vec{n}_i^\infty(t)$ is a jump process on Z_+^D with possible jumps $\pi_D y_R$ and rates $g_R(\vec{c}(t), \vec{n}_i^\infty(t))$, if $\vec{n}_i^\infty(t) + \pi_D y_R \geq 0$. We will need the following assumptions. The main assumption is

(1) The Markov process $(\vec{c}(t), \vec{n}_i^\infty(t))$ is defined for all t .

Formally we need also two other assumptions, but they hold for closed networks:

(2) If $z_r^v < 0$ for some r and some $v = 1, \dots, d$ then $f_r \equiv 0$ on the set $\{c_v = 0\}$;

(3) For any finite M the Markov process $(\vec{c}^{(M)}(t), \vec{n}_i^{(M)}(t))$ is defined for all t .

Theorem 2 *Under the assumptions (1)-(3) the Markov process $(M^{-1}\vec{n}_s^{(M)}(t), \vec{n}_i^{(M)}(t))$ converges as $M \rightarrow \infty$ to the Markov process $(\vec{c}(t), \vec{n}_i(t))$.*

Proof. Vector field in chemical kinetics is a polynomial vector field $v = (v_1, \dots, v_N)$ on R_+^N such that $v_i \geq 0$ if $x_i \geq 0$. Standard uniqueness and existence theorems for ordinary differential equations show that such vector field defines a dynamical system τ_t on the extended space $\tilde{R}_+^N = R_+^N \cup \{\infty\}$. More exactly, for any $x = x_0 \in R_+^N$ define x_t by the equation

$$\frac{dx_t}{dt} = v(x_t) \quad (23)$$

The solution is defined for $0 \leq t < T(x)$ when the solution is defined. Put $x_t = 0$ for $t \geq T(x)$.

Let $L = \bar{C}_0^\infty(R_+^N)$ be the completion of the space $C_0^\infty(R_+^N)$ of continuous functions with compact support in the norm $\|\phi\| = \max \phi$, that is L is the space of continuous functions on R_+^N tending to 0 if $\|x\| \rightarrow \infty$. Then the dynamical system defines a strongly continuous semigroup T^t on the core $D = C_0^\infty(R_+^N) \subset L$ by

$$(T^t \phi)(x) = \phi(\tau_t x) \quad (24)$$

where by definition $\phi(\infty) = 0, \tau_t(\infty) = \infty$. The generator

$$(A\phi)(c) = \sum_i v_i \frac{\partial \phi}{\partial c_i} \quad (25)$$

of the semigroup is also defined on D . The generator in the theorem 1 is

$$(A_M \phi)(\vec{c}) = M \sum_r f_r(\vec{c}) \left(\phi\left(\vec{c} + \frac{z_r}{M}\right) - \phi(\vec{c}) \right) \quad (26)$$

It is clear that $A_M \phi \rightarrow A\phi$ as $M \rightarrow \infty$ for smooth ϕ , where

$$(A\phi)(\vec{c}) = \sum_r f_r(\vec{c}) \frac{\partial \phi(\vec{c})}{\partial \vec{c}} z_r \quad (27)$$

The generator in the theorem 2 is

$$(A_M \phi)(\vec{c}, \vec{n}_i) = M \sum_r f_r(\vec{c}, \vec{n}_i) \left(\phi\left(\vec{c} + \frac{z_r}{M}, \vec{n}_i\right) - \phi(\vec{c}, \vec{n}_i) \right) + \quad (28)$$

$$+ \sum_R g_R(\vec{c}, \vec{n}_i) (\phi(\vec{c} + \frac{\pi_D y_R}{M}, \vec{n}_i + \pi_D y_R) - \phi(\vec{c}, \vec{n}_i)) \quad (29)$$

Again we have $A_M \phi \rightarrow A \phi$ as $M \rightarrow \infty$ where

$$(A \phi)(\vec{c}, \vec{n}_i) = \sum_r f_r(\vec{c}, \vec{n}_i) \frac{\partial \phi(\vec{c})}{\partial \vec{c}} z_r + \quad (30)$$

$$+ \sum_R g_R(\vec{c}, \vec{n}_i) (\phi(\vec{c}, \vec{n}_i + Y_R) - \phi(\vec{c}, \vec{n}_i)) \quad (31)$$

where $Y_R = \pi_D y_R$.

By Trotter-Kurtz theorem (see [2]) the semigroups T_M^t converge to T^t on L . The convergence of finite-dimensional distributions of the corresponding Markov processes (with given initial state) follows. Note that in our case (due to possible explosions) finite-dimensional distributions can be subprobability measures. Similar construction was used in [3].

4 Two dimensional case

Note that in all previous examples the time t was not scaled. If we would scale $\kappa_r = M^{-m(r)+1+p} a_r$, then we should also scale the time $t = M^{-p} \tau$ with macrotime τ . Then

$$c_v(\tau) = \lim \frac{n_v(M^{-p} \tau; M)}{M} \quad (32)$$

Thus it is equivalent to the canonical scaling.

In the general case scalings can be more complicated. Assume that there are N molecules $v = 1, \dots, N$ and R reactions $r = 1, \dots, R$. For each molecule the concentrations can be scaled as $n_v = M^{\beta(v)} c_v$, and rates - as $\kappa_r = M^{\alpha(r)}$ with $\alpha(r) = -m(r) + 1 + p(r)$, the time is allowed to be scaled as $t M^{-p}$. In the general case one should take $p = \max p(r)$, otherwise there will be infinite number of molecules of some type. That is we exclude the possibility $c_v(t) = \infty$ for any t .

If all $\beta(v)$ are non zero then for appropriate time scaling it can occur that for some v we have $\frac{c_v(t)}{dt} = 0$, we call such v inessential. For example if $\max m(r) = 2$ and all κ_r are not scaled at all, then linear terms become inessential. In the scaling limit we get only quadratic terms. This explains some controversies discussed in section 2.2.2 of [4], where various examples are considered using generating functions method.

Assume that $\alpha(r)$ are fixed. For fixed v , is it possible that several arrays $\{\beta_i(w), w = 1, \dots, N; x_i\}$ exist, which give different NONTRIVIAL limits of $n_v M^{-\beta_i(v)} = c_{v,i}(M), t \rightarrow t M^{x_i}$ for all v ? Can we see different life on different time scales? We give simplest examples below. They are based on the fact that some n_v reach a limiting distribution faster than the convergence to the scaling limit for other v .

We shall illustrate this with dimension 2. There are two kinds of molecules with n_1 and n_2 molecules correspondingly.

n_2 is finite The simplest (and basic) example of a non-triangular system is a random walk in a half-strip $\{(n_1, n_2 : n_1 = 1, 2, 3, \dots; n_2 = 1, 2)\}$. The transitions are

$$(n_1, n_2) \rightarrow (n_1 + 1, n_2), K_1 = a_1(n_2)n_1 \quad (33)$$

$$(n_1, n_2) \rightarrow (n_1 - 1, n_2), K_2 = a_2(n_2)n_1 \quad (34)$$

$$(n_1, 1) \rightarrow (n_1, 2), K_3 = \kappa_3(n_2)n_1 = a_3M^\varepsilon n_1 \quad (35)$$

$$(n_1, 2) \rightarrow (n_1, 1), K_4 = \kappa_4(n_2)n_1 = a_4M^\varepsilon n_1 \quad (36)$$

We assume that $a_1(n_2) - a_2(n_2) > 0$ for $n_2 = 1, 2$. Minus sign would give an ergodic situation, that is not interesting. We will not consider neither the case $a_1(n_2) - a_2(n_2) = 0$, nor the case when $a_1(n_2) - a_2(n_2)$ have different signs for $n_2 = 1, 2$.

Note that we took linear rates because if we take for example $K_1 = \sum_{i=0}^2 f_{+,i}(n_2)n_1^i$ then the limiting system does not exist: we have an explosion. We give more examples when condition (1) of the previous section does not hold.

The following result demonstrates an example of a typical phase transition, which occurs in more complicated situations as well.

Theorem 3 *There are three types of behaviour depending on ε . If $\varepsilon < -1$ then for any $t \geq 0$ there exist the limits*

$$\lim n_2(t, M) = n_2(0), \lim c_1(t, M) = c_1(t) \quad (37)$$

Moreover

$$\frac{dc_1(t)}{dt} = c_1(t)(a_1(n_2(0)) - a_2(n_2(0))) \quad (38)$$

If $\varepsilon = -1$ then $(c_1(t, M), n_2(t, M))$ tends to a Markov process $(c_1(t), n_2(t))$, this process is uniquely defined by the transition rates of $n_2(t)$: $\lambda(1 \rightarrow 2) = a_3c_1(t)$, $\lambda(2 \rightarrow 1) = a_4c_1(t)$ and by

$$\frac{dc_1(t)}{dt} = c_1(t)(a_1(n_2(t)) - a_2(n_2(t))) \quad (39)$$

If $\varepsilon > -1$ then for any $t \geq 0$ $n_2(t, M)$ tends in distribution to a random variable ξ with distribution $P(\xi = 1) = \frac{a_3}{a_3 + a_4}$, $P(\xi = 2) = \frac{a_4}{a_3 + a_4}$ and $c_1(t, M)$ tends to some $c_1(t)$ which satisfies the equation

$$\frac{dc_1(t)}{dt} = c_1(t) \left[\frac{a_3}{a_3 + a_4}(a_1(1) - a_2(1)) + \frac{a_4}{a_3 + a_4}(a_1(2) - a_2(2)) \right] \quad (40)$$

We shall do some comments concerning the proof.

If $\varepsilon < -1$, the n_2 -motion is very slow and during time Δt the number of its jumps has order $o(1)$. Note that n_1 -process performs $O(M)$ jumps. The dynamical system of $c_1(t)$ moves smoothly and is completely defined by the initial value $n_2(0)$. n_2 -process will not be seen, it has not been started.

If $\varepsilon > -1$ then the n_2 -motion does $O(M^\delta)$, $\delta > 0$, jumps during time Δt . The dynamical system of $c_1(t)$ moves smoothly correspondingly to averaged parameters of n_2 -process, that is with respect to its stationary distribution. We will not see n_2 -process - it is too fast.

$\varepsilon = -1$ is the critical point. The dynamical system is controlled by discrete process, there is a feedback. The dynamical system of $c_1(t)$ moves smoothly, in random discrete time moments the parameters of this dynamical system change. During time Δt the number of n_2 -jumps has order 1. The proof is similar to the proof of theorem 1 and we will not give details.

Both n_1, n_2 are infinite Now consider the case when both n_1 and n_2 tend to infinity, with canonical scalings $c_v = \lim \frac{n_v}{M}$. We assume 4 reactions (avoiding explosions) and canonical scaling of κ_1, κ_2 , and general for κ_3, κ_4 . More exactly, the transitions are

$$(n_1, n_2) \rightarrow (n_1 + 1, n_2), K_1 = a_1 M^{-1} n_2 n_1 \quad (41)$$

$$(n_1, n_2) \rightarrow (n_1 - 1, n_2), K_2 = a_2 M^{-1} n_2 n_1 \quad (42)$$

$$(n_1, n_2) \rightarrow (n_1, n_2 + 1), K_3 = a_3 M^{-1+\varepsilon} n_1 n_2 + a_5 M^\varepsilon n_2 \quad (43)$$

$$(n_1, n_2) \rightarrow (n_1, n_2 - 1), K_4 = a_4 M^{-1+\varepsilon} n_1 n_2 + a_6 M^\varepsilon n_2 \quad (44)$$

The case $\varepsilon = 0$ corresponds to the canonical scaling, it is the case of theorem 1.

Theorem 4 *If $\varepsilon < 0$ then there are two possible time scales. Without any scaling we have that the limiting concentrations $c_v(t)$ exist and satisfy the following equations*

$$\frac{dc_2(t)}{dt} = 0, \frac{dc_1(t)}{dt} = (a_1 - a_2)c_2(0)c_1(t) \quad (45)$$

If $a_1 - a_2 < 0$ then for the time scaling $t = \tau M^{-\varepsilon}$ we have

$$c_1(\tau) = 0, \frac{dc_2(\tau)}{d\tau} = (a_5 - a_6)c_2(\tau) \quad (46)$$

The case $\varepsilon > 0$ can be considered similarly. Note that for $a_1 - a_2 > 0$ the second assertion of the theorem does not hold. Thus the microscopic time t gives the first stage of evolution, and the macrotime τ defines the evolution on a longer scale. We see that "ergodic" variables n_v define the possibility of several evolution stages (in general it can be more than two such stages) on different scales.

The Brusselator As an example of the real chemical system, consider an open two-dimensional system with two substances X_1 and X_2 with canonical concentrations $c_i = \frac{n_i}{M}$, $i = 1, 2$, correspondingly. X_1 -molecules enter the system from exterior with rate $a_1 M$ and leave the system (to exterior) with the rate $a_4 n_1$. There are two reactions



with the rates $a_2 n_1$ and $a_3 M^{-2} n_1^2 n_2$ correspondingly. The scalings are canonical and we get the well-known system

$$\frac{dc_1}{dt} = a_1 - a_2 c_1 - a_4 c_1 + a_3 c_1^2 c_2 \quad (48)$$

$$\frac{dc_2}{dt} = a_2 c_1 - a_3 c_1^2 c_2 \quad (49)$$

It is also well-known that this system has a stable limiting cycle and an unstable fixed point. From Markov chain point of view the following problem could be interesting. First of all, for fixed M the Markov chain has a unique invariant measure μ_M . The sequence μ_M weakly converges to some measure μ on the limiting cycle of the limiting dynamical system. This means that the fixed point does not play role. Now assume that this system is a part of (and interacts with) another system. Moreover the scalings are such that the Brusselator is a faster system. Then the invariant measure is necessary to get the behaviour of more slow part of concentrations, this is similar to the case 3 in the theorem 3.

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