CHAPTER 3

Dynamic and Static Limitation in Multiscale Reaction Networks, Revisited

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Abstract

The concept of the limiting step gives the limit simplification: the whole network behaves as a single step. This is the most popular approach for model simplification in chemical kinetics. However, in its elementary form this idea is applicable only to the simplest linear cycles in steady states. For simple cycles the nonstationary behavior is also limited by a single step, but not the same step that limits the stationary rate. In this chapter, we develop a general theory of static and dynamic limitation for all linear multiscale networks. Our main mathematical tools are auxiliary discrete dynamical systems on finite sets and specially developed algorithms of "cycles surgery" for reaction graphs. New estimates of eigenvectors for diagonally dominant matrices are used.

Multiscale ensembles of reaction networks with well-separated constants are introduced and typical properties of such systems are studied. For any given ordering of reaction rate constants the explicit approximation of steady state, relaxation spectrum and related eigenvectors ("modes") is presented. In particular, we prove that for systems with well-separated constants eigenvalues are real (damped oscillations are improbable). For systems with modular structure, we propose the selection of such modules that it is possible to solve the kinetic equation for every module in the explicit form. All such "solvable" networks are described. The obtained multiscale approximations, that we call "dominant systems" are computationally cheap and robust. These dominant systems can be used for direct computation of steady states and relaxation dynamics, especially when kinetic information is incomplete, for design of experiments and mining of experimental data, and could serve as a robust first approximation in perturbation theory or for preconditioning.

1. INTRODUCTION

Which approach to model reduction is the most important? Population is not the ultimate judge, and popularity is not a scientific criterion, but "Vox populi, vox Dei", especially in the epoch of citation indexes, impact factors and bibliometrics. Let us ask Google. It gave on 31st December 2006:

- for "quasi-equilibrium" — 301,000 links;
- for "quasi-steady state" 347,000 and for "pseudo-steady state" 76,200, 42,3000 together;
- for our favorite "slow manifold" (Gorban and Karlin, 2003, 2005) 29,800 links only, and for "invariant manifold" slightly more, 98,100;
- for such a framework topic as "singular perturbation" Google gave 361,000 links;
- for "model reduction" even more, as we did expect, 373,000;
- but for "limiting step" almost two times more — 714,000!

Our goal is the general theory of static and dynamic limitation for multiscale networks. The concept of the limiting step gives, in some sense, the limit simplification: the whole network behaves as a single step. As the first result of our chapter we introduce further detail in this idea: the whole network behaves as a single step in statics, and as *another* single step in dynamics: even for simplest cycles the stationary rate and the relaxation time to this stationary rate are limited by different reaction steps, and we describe how to find these steps.

The concept of limitation is very attractive both for theorists and experimentalists. It is very useful to find conditions when a selected reaction step becomes the limiting step. We can change conditions and study the network experimentally, step-by-step. It is very convenient to model a system with limiting steps: the model is extremely simple and can serve as a very elementary building block for further study of more complex systems, a typical situation both in industry and in systems biology.

In the IUPAC Compendium of Chemical Terminology (2007) one can find two articles with a definition of limitation.

- Rate-determining step (rate-limiting step) (2007): "These terms are best regarded as synonymous with rate-controlling step".
- Rate-controlling step (2007): "A rate-controlling (rate-determining or rate-limiting) step in a reaction occurring by a composite reaction sequence is an elementary reaction the rate constant for which exerts a strong effect — stronger than that of any other rate constant — on the overall rate".

It is not wise to object to a definition and here we do not object, but, rather, complement the definition by additional comments. The main comment is that usually when people are talking about limitation they expect significantly more: there exists a rate constant which exerts such a strong effect on the overall rate that the effect of all other rate constants together is significantly smaller. Of course, this is not yet a formal definition, and should be complemented by a definition of ''effect'', for example, by ''control function'' identified by derivatives of the overall rate of reaction, or by other overall rate ''sensitivity parameters'' (Rate-controlling step, 2007).

For the IUPAC Compendium definition a rate-controlling step always exists, because among the control functions generically exists the biggest one. On the contrary, for the notion of limitation that is used in practice, there exists a difference between systems with limitation and systems without limitation.

An additional problem arises: are systems without limitation rare or should they be treated equitably with limitation cases? The arguments in favor of limitation typicality are as follows: the real chemical networks are multi-scale with very different constants and concentrations. For such systems it is improbable to meet a situation with compatible effects of all different stages. Of course, these arguments are statistical and apply to generic systems from special ensembles.

During the last century, the concept of the limiting step was revised several times. First simple idea of a ''narrow place'' (a least conductive step) could be applied without adaptation only to a simple cycle of irreversible steps that are of the first order (see Chapter 16 of the book Johnston (1966) or the paper of Boyd (1978)). When researchers try to apply this idea in more general situations they meet various difficulties such as:

- Some reactions have to be ''pseudomonomolecular''. Their constants depend on concentrations of outer components, and are constant only under condition that these outer components are present in constant concentrations, or change sufficiently slow. For example, the simplest Michaelis–Menten enzymatic reaction is E+S→ES→E+P (E here stands for enzyme, S for substrate and P for product), and the linear catalytic cycle here is S→ES→S. Hence, in general we must consider nonlinear systems.
- Even under fixed outer components concentration, the simple ''narrow place'' behavior could be spoiled by branching or by reverse reactions. For such reaction systems definition of a limiting step simply as a step with the smallest constant does not work. The simplest example is given by the cycle: $A_1 \leftrightarrow A_2 \rightarrow A_3 \rightarrow A_1$. Even if the constant of the last step $A_3 \rightarrow A_1$ is the smallest one, the stationary rate may be much smaller than $k_3 b$ (where b is the overall balance of concentrations, $b = c_1 + c_2 + c_3$), if the constant of the reverse reaction $A_2 \rightarrow A_1$ is sufficiently big.

In a series of papers, Northrop (1981, 2001) clearly explained these difficulties with many examples based on the isotope effect analysis and suggested that the concept of rate-limiting step is ''outmoded''. Nevertheless, the main idea of limiting is so attractive that Northrop's arguments stimulated the search for modification and improvement of the main concept.

Ray (1983) proposed the use of sensitivity analysis. He considered cycles of reversible reactions and suggested a definition: *The rate-limiting step in a reaction* *sequence is that forward step for which a change of its rate constant produces the largest effect on the overall rate*. In his formal definition of sensitivity functions the reciprocal reaction rate ($1/W$) and rate constants ($1/k_i$) were used and the connection between forward and reverse step constants (the equilibrium constant) was kept fixed.

Ray's approach was revised by Brown and Cooper (1993) from the system control analysis point of view (see the book of Cornish-Bowden and Cardenas, 1990). They stress again that there is no unique rate-limiting step specific for an enzyme, and this step, even if it exists, depends on substrate, product and effector concentrations. They also demonstrated that the control coefficients

$$C_{k_i}^W = \left(\frac{k_i}{W}\frac{\partial W}{\partial k_i}\right)_{[S],[P],\ldots}$$

where W is the stationary reaction rate and k_i are constants, are additive and obey the summation theorems (as concentrations do). A simple relation between control coefficients of rate constants and intermediate concentrations was reported by Kholodenko et al. (1994). This relation connects two type of experiments: measurement of intermediate levels and steady-state rate measurements.

For the analysis of nonlinear cycles the new concept of *kinetic polynomial* was developed (Lazman and Yablonskii, 1991; Yablonskii et al., 1982). It was proven that the stationary state of the single-route reaction mechanism of catalytic reaction can be described by a single polynomial equation for the reaction rate. The roots of the kinetic polynomial are the values of the reaction rate in the steady state. For a system with limiting step the kinetic polynomial can be approximately solved and the reaction rate found in the form of a series in powers of the limiting-step constant (Lazman and Yablonskii, 1988).

In our approach, we analyze not only the steady-state reaction rates, but also the relaxation dynamics of multiscale systems. We focused mostly on the case when all the elementary processes have significantly different timescales. In this case, we obtain "limit simplification" of the model: all stationary states and relaxation processes could be analyzed "to the very end", by straightforward computations, mostly analytically. Chemical kinetics is an inexhaustible source of examples of multiscale systems for analysis. It is not surprising that many ideas and methods for such analysis were first invented for chemical systems.

In Section 2 we analyze a simple example and the source of most generalizations, the catalytic cycle, and demonstrate the main notions on this example. This analysis is quite elementary, but includes many ideas elaborated in full in subsequent sections.

There exist several estimates for relaxation time in chemical reactions (developed, e.g. by Cheresiz and Yablonskii, 1983), but even for the simplest cycle with limitation the main property of relaxation time is not widely known. For a simple irreversible catalytic cycle with limiting step the stationary rate is controlled by the smallest constant, but the relaxation time is determined by the second in order constant. Hence, if in the stationary rate experiments for that cycle we mostly extract the smallest constant, in relaxation experiments another, the second in order constant will be observed.

It is also proven that for cycles with well-separated constants damped oscillations are impossible, and spectrum of the matrix of kinetic coefficients is real. For general reaction networks with well-separated constants this property is proven in Section 4.

Another general effect observed for a cycle is robustness of stationary rate and relaxation time. For multiscale systems with random constants, the standard deviation of constants that determine stationary rate (the smallest constant for a cycle) or relaxation time (the second in order constant) is approximately n times smaller than the standard deviation of the individual constants (where n is the cycle length). Here we deal with the so-called order statistics. This decrease of the deviation as n^{-1} is much faster than for the standard error summation, where it decreases with increasing n as $n^{-1/2}$.

In more general settings, robustness of the relaxation time was studied by Gorban and Radulescu (2007) for chemical kinetics models of genetic and signaling networks. Gorban and Radulescu (2007) proved that for large multiscale systems with hierarchical distribution of timescales the variance of the inverse relaxation time (as well as the variance of the stationary rate) is much lower than the variance of the separate constants. Moreover, it can tend to 0 faster than $1/n$, where n is the number of reactions. It was demonstrated that similar phenomena are valid in the nonlinear case as well. As a numerical illustration we used a model of a signaling network that can be applied to important transcription factors such as NFkB.

Each multiscale system is characterized by its structure (the system of elementary processes) and by the rate constants of these processes. To make any general statement about such systems when the structure is given but the constants are unknown it is useful to take the constant set as random and independent. But it is not obvious how to chose the random distribution. The usual idea to take normal or uniform distribution meets obvious difficulties, the timescales are not sufficiently well separated.

The statistical approach to chemical kinetics was developed by Li et al. (2001, 2002), and high-dimensional model representations (HDMR) were proposed as efficient tools to provide a fully global statistical analysis of a model. The work of Feng et al. (2004) was focused on how the network properties are affected by random rate constant changes. The rate constants were transformed to a logarithmic scale to ensure an even distribution over the large space.

The log-uniform distribution on sufficiently wide interval helps us to improve the situation, indeed, but a couple of extra parameters appears: $\alpha = \min \log k$ and $\beta = \max \log k$. We have to study the asymptotics $\alpha \to -\infty$, $\beta \to \infty$. This approach could be formalized by means of the uniform invariant distributions of $\log k$ on $\mathbb{R}^n$. These distributions are finite-additive, but not countable-additive (not σ-additive).

The probability and measure theory without countable additivity has a long history. In Euclid's time only arguments based on finite-additive properties of volume were legal. Euclid meant by equal area the scissors congruent area. Two polyhedra are scissors-congruent if one of them can be cut into finitely many polyhedral pieces which can be reassembled to yield the second. But all proofs of the formula for the volume of a pyramid involve some form of limiting process. Hilbert asked in his third problem: are two Euclidean polyhedra of the same volume scissors congruent? The answer is "no" (a review of old and recent results is presented by Neumann, 1998). There is another invariant of cutting and gluing polyhedra.

Finite-additive invariant measures on non-compact groups were studied by Birkhoff (1936) (see also the book of Hewitt and Ross, 1963, Chapter 4). The frequency-based Mises approach to probability theory foundations (von Mises, 1964), as well as logical foundations of probability by Carnap (1950) do not need σ-additivity. Non-Kolmogorov probability theories are discussed now in the context of quantum physics (Khrennikov, 2002), nonstandard analysis (Loeb, 1975) and many other problems (and we do not pretend provide here is a full review of related works).

We answer the question: What does it mean "to pick a multiscale system at random"? We introduce and analyze a notion of multiscale ensemble of reaction systems. These ensembles with well-separated variables are presented in Section 3.

The best geometric example that helps us to understand this problem is one of the Lewis Carroll's Pillow Problems published in 1883 (Carroll, 1958): "Three points are taken at random on an infinite plane. Find the chance of their being the vertices of an obtuse-angled triangle." (In an acute-angled triangle all angles are comparable, in an obtuse-angled triangle the obtuse angle is bigger than others and could be much bigger.) The solution of this problem depends significantly on the ensemble definition. What does it mean "points are taken at random on an infinite plane"? Our intuition requires translation invariance, but the normalized translation invariant measure on the plain could not be σ-additive. Nevertheless, there exist finite-additive invariant measures.

Lewis Carroll proposed a solution that did not satisfy some of modern scientists. There exists a lot of attempts to improve the problem statement (Eisenberg and Sullivan, 1996; Falk and Samuel-Cahn, 2001; Guy, 1993; Portnoy, 1994): reduction from infinite plane to a bounded set, to a compact symmetric space, etc. But the elimination of paradox destroys the essence of Carroll's problem. If we follow the paradox and try to give a meaning to "points are taken at random on an infinite plane" then we replace σ-additivity of the probability measure by finite-additivity and come to the applied probability theory for finite-additive probabilities. Of course, this theory for abstract probability spaces would be too poor, and some additional geometric and algebraic structures are necessary to build rich enough theory.

This is not just a beautiful geometrical problem, but rather an applied question about the proper definition of multiscale ensembles. We need such a definition to make any general statement about multiscale systems, and briefly analyze lessons of Carroll's problem in Section 3.

In this section, we use some mathematics to define the multiscale ensembles with well-separated constants. This is necessary background for the analysis of systems with limitation, and technical consequences are rather simple. We need only two properties of a typical system from the multiscale ensemble with well-separated constants:

(i) Every two reaction rate constants k, k', are connected by the relation $k \gg k'$ or $k \ll k'$ (with probability close to 1);
(ii) The first property persists (with probability close to 1), if we delete two constants k and k' from the list of constants, and add a number kk' or a number k/k' to that list.

If the reader can use these properties (when it is necessary) without additional clarification, it is possible to skip reading Section 3 and go directly to more applied sections. In Section 4 we study static and dynamic properties of linear multiscale reaction networks. An important instrument for that study is a hierarchy of auxiliary discrete dynamical system. Let A_i be nodes of the network (''components''), $A_i \to A_j$ be edges (reactions), and k_{ji} be the constants of these reactions (please pay attention to the inverse order of subscripts). A discrete dynamical system ϕ is a map that maps any node A_i in a node $A_{\phi(i)}$. To construct a first auxiliary dynamical system for a given network we find for each A_i the maximal constant of reactions $A_i \to A_j$: $k_{\phi(i)i} \geq k_{ji}$ for all j, and $\phi(i) = i$ if there are no reactions $A_i \to A_j$. Attractors in this discrete dynamical system are cycles and fixed points.

The fast stage of relaxation of a complex reaction network could be described as mass transfer from nodes to correspondent attractors of auxiliary dynamical system and mass distribution in the attractors. After that, a slower process of mass redistribution between attractors should play a more important role. To study the next stage of relaxation, we should glue cycles of the first auxiliary system (each cycle transforms into a point), define constants of the first derivative network on this new set of nodes, construct for this new network an (first) auxiliary discrete dynamical system, etc. The process terminates when we get a discrete dynamical system with one attractor. Then the inverse process of cycle restoration and cutting starts. As a result, we create an explicit description of the relaxation process in the reaction network, find estimates of eigenvalues and eigenvectors for the kinetic equation, and provide full analysis of steady states for systems with well-separated constants.

The problem of multiscale asymptotics of eigenvalues of nonself-adjoint matrices was studied by Vishik and Ljusternik (1960) and Lidskii (1965). Recently, some generalizations were obtained by idempotent (min-plus) algebra methods (Akian et al., 2004). These methods provide a natural language for discussion of some multiscale problems (Litvinov and Maslov, 2005). In the Vishik–Ljusternik–Lidskii theorem and its generalizations the asymptotics of eigenvalues and eigenvectors for the family of matrices $A_{ij}(\varepsilon) = a_{ij}\varepsilon^{A_{ij}} + o(\varepsilon^{A_{ij}})$ is studied for $\varepsilon > 0$, $\varepsilon \to 0$.

In the chemical reaction networks that we study, there is no small parameter ε with a given distribution of the orders $\varepsilon^{A_{ij}}$ of the matrix nodes. Instead of these powers of ε we have orderings of rate constants. Furthermore, the matrices of kinetic equations have some specific properties. The possibility to operate with the graph of reactions (cycles surgery) significantly helps in our constructions. Nevertheless, there exists some similarity between these problems and, even for general matrices, graphical representation is useful. The language of idempotent algebra (Litvinov and Maslov, 2005), as well as nonstandard analysis with infinitisemals (Albeverio et al., 1986), can be used for description of the multiscale reaction networks, but now we postpone this for later use.

We summarize results of relaxation analysis and describe the algorithm of approximation of steady state and relaxation in Section 4.3. After that, several examples of networks are analyzed. In Section 5 we illustrate the analysis of dominant systems on a simple example, the reversible triangle of reactions: $A_1 \leftrightarrow A_2 \leftrightarrow A_3 \leftrightarrow A_1$. This simplest example became very popular for the lumping analysis case study after the well-known work of Wei and Prater (1962). The most important mathematical proofs are presented in the appendices.

In multiscale asymptotic analysis of reaction network we found several very attractive *zero-one laws*. First of all, components eigenvectors are close to 0 or ± 1. This law together with two other zero-one laws are discussed in Section 6: ''Three zero-one laws and nonequilibrium phase transitions in multiscale systems''.

A multiscale system where every two constants have very different orders of magnitude is, of course, an idealization. In parametric families of multiscale systems there could appear systems with several constants of the same order. Hence, it is necessary to study effects that appear due to a group of constants of the same order in a multiscale network. The system can have modular structure, with different time scales in different modules, but without separation of times inside modules. We discuss systems with modular structure in Section 7. The full theory of such systems is a challenge for future work, and here we study structure of one module. The elementary modules have to be solvable. That means that the kinetic equations could be solved in explicit analytical form. We give the necessary and sufficient conditions for solvability of reaction networks. These conditions are presented constructively, by algorithm of analysis of the reaction graph.

It is necessary to repeat our study for nonlinear networks. We discuss this problem and perspective of its solution in the concluding Section 8. Here we again use the experience summarized in the IUPAC Compendium (Rate-controlling step, 2007) where the notion of controlling step is generalized onto nonlinear elementary reaction by inclusion of some concentration into ''pseudo-first-order rate constant''.

2. STATIC AND DYNAMIC LIMITATION IN A LINEAR CHAIN AND A SIMPLE CATALYTIC CYCLE

2.1 Linear chain

A linear chain of reactions, $A_1 \rightarrow A_2 \rightarrow \ldots A_n$, with reaction rate constants k_i (for $A_i \rightarrow A_{i+1}$), gives the first example of limitation Let the reaction rate constant k_q be the smallest one. Then we expect the following behavior of the reaction chain in timescale $\sim 1/k_q$: all the components $A_1, \ldots, A_{q-1}$ transform fast into A_q, and all the components $A_{q+1}, \ldots, A_{n-1}$ transform fast into A_n, only two components,

A_q and A_n are present (concentrations of other components are small), and the whole dynamics in this time scale can be represented by a single reaction $A_q \to A_n$ with reaction rate constant k_q. This picture becomes more exact when k_q becomes smaller with respect to other constants.

The kinetic equation for the linear chain is

$$\dot{c}_i = k_{i-1}c_{i-1} - k_i c_i \tag{1}$$

where c_i is concentration of A_i and k_{i-1} for $i = 1$. The coefficient matrix K of this equation is very simple. It has nonzero elements only on the main diagonal, and one position below. The eigenvalues of K are $-k_i$ ($i = 1, \ldots, n-1$) and 0. The left and right eigenvectors for 0 eigenvalue, l^0 and r^0, are:

$$l^0 = (1, 1, \ldots, 1), \;\; r^0 = (0, 0, \ldots, 0, 1) \tag{2}$$

all coordinates of l^0 are equal to 1, the only nonzero coordinate of r^0 is r^0_n and we represent vector-column r^0 in row.

Below we use explicit form of K left and right eigenvectors. Let vector-column r^i and vector-row l^i be right and left eigenvectors of K for eigenvalue $-k_i$. For coordinates of these eigenvectors we use notation r^i_j and l^i_j. Let us choose a normalization condition $r^i_i = l^i_i = 1$. It is straightforward to check that $r^i_j = 0$ ($j<i$) and $l^i_j = 0$ ($j>i$), $r^i_{j+1} = k_j r_j/(k_{j+1} - k_i)$ ($j \geqslant i$) and $l^i_{j-1} = k_{j-1} l_j/(k_{j-1} - k_j)$ ($j \leqslant i$), and

$$r^i_{i+m} = \prod_{j=1}^{m} \frac{k_{i+j-1}}{k_{i+j} - k_i}; \qquad l^i_{i-m} = \prod_{j=1}^{m} \frac{k_{i-j}}{k_{i-j} - k_i} \tag{3}$$

It is convenient to introduce formally $k_0 = 0$. Under selected normalization condition, the inner product of eigenvectors is: $l^i r^j = \delta_{ij}$, where δ_{ij} is the Kronecker delta.

If the rate constants are well separated (i.e. any two constants, k_i and k_j are connected by relation $k_i \gg k_j$ or $k_i \ll k_j$,

$$\frac{k_{i-j}}{k_{i-j} - k_i} \approx \begin{cases} 1, & \text{if } k_i \ll k_{i-j}; \\ 0, & \text{if } k_i \gg k_{i-j} \end{cases} \tag{4}$$

Hence, $|l^i_{i-m}| \approx 1$ or $|l^i_{i-m}| \approx 0$. To demonstrate that also $|r^i_{i+m}| \approx 1$ or $|r^i_{i+m}| \approx 0$, we shift nominators in the product (3) on such a way:

$$r^i_{i+m} = \frac{k_i}{k_{i+m} - k_i} \prod_{j=1}^{m-1} \frac{k_{i+j}}{k_{i+j} - k_i}$$

Exactly as in Equation (4), each multiplier

$$\frac{k_{i+j}}{(k_{i+j} - k_i)}$$

here is either almost 1 or almost 0, and

$$\frac{k_i}{(k_{i+m} - k_i)}$$

is either almost 0 or almost -1. In this zero-one asymptotics

$$\begin{aligned}
&l_i^i = 1,\ \ l_{i-m}^i \approx 1 \\
&\qquad \text{if } k_{i-j} > k_i \text{ for all } j = 1,\ldots,m, \text{ else } l_{i-m}^i \approx 0; \\
&r_i^i = 1,\ \ r_{i+m}^i \approx -1 \\
&\qquad \text{if } k_{i+j} > k_i \text{ for all } j = 1,\ldots,m-1 \\
&\qquad \text{and } k_{i+m} < k_i, \text{ else } r_{i+m}^i \approx 0
\end{aligned} \tag{5}$$

In this asymptotic, only two coordinates of right eigenvector r^i can have nonzero values, $r_i^i = 1$ and $r_{i+m}^i \approx -1$ where m is the first such positive integer that $i+m<n$ and $k_{i+m}<k_i$. Such m always exists because $k_n = 0$. For left eigenvector $l^i, l_i^i \approx \ldots l_{i-q}^i \approx 1$ and $l_{i-q-j}^i \approx 0$ where $j>0$ and q the first such positive integer that $i-q-1>0$ and $k_{i-q-1}<k_i$. It is possible that such q does not exist. In that case, all $l_{i-j}^i \approx 1$ for $j \geqslant 0$. It is straightforward to check that in this asymptotic $l^i r^j = \delta_{ij}$.

The simplest example gives the order $k_1 \gg k_2 \gg \cdots \gg k_{n-1} : l_{i-j}^i \approx 1$ for $j \geqslant 0$, $r_i^i = 1$, $r_{i+1}^i \approx -1$ and all other coordinates of eigenvectors are close to zero. For the inverse order, $k_1 \ll k_2 \ll \cdots \ll k_{n-1}$, $l_i^i = 1$, $r_i^i = 1$, $r_n^i \approx -1$ and all other coordinates of eigenvectors are close to zero.

For less trivial example, let us find the asymptotic of left and right eigenvectors for a chain of reactions:

$$A_1 \xrightarrow{5} A_2 \xrightarrow{3} A_3 \xrightarrow{4} A_4 \xrightarrow{1} A_5 \xrightarrow{2} A_6$$

where the upper index marks the order of rate constants: $k_4 \gg k_5 \gg k_2 \gg k_3 \gg k_1$ (k_i is the rate constant of reaction $A_i \to \ldots$).

For left eigenvectors, rows l^i, we have the following asymptotics:

$$\begin{aligned}
&l^1 \approx (1,0,0,0,0,0),\ \ l^2 \approx (0,1,0,0,0,0), \\
&l^3 \approx (0,1,1,0,0,0),\ \ l^4 \approx (0,0,0,1,0,0), \\
&l^5 \approx (0,0,0,1,1,0)
\end{aligned} \tag{6}$$

For right eigenvectors, columns r^i, we have the following asymptotics (we write vector-columns in rows):

$$\begin{aligned}
&r^1 \approx (1,0,0,0,0,-1),\ \ r^2 \approx (0,1,-1,0,0,0), \\
&r^3 \approx (0,0,1,0,0,-1),\ \ r^4 \approx (0,0,0,1,-1,0), \\
&r^5 \approx (0,0,0,0,1,-1)
\end{aligned} \tag{7}$$

The correspondent approximation to the general solution of the kinetic equations is:

$$c(t) = (l^0 c(0))r^0 + \sum_{i=1}^{n-1} (l^i c(0))r^i \exp(-k_i t) \tag{8}$$

where $c(0)$ is the initial concentration vector, and for left and right eigenvectors l^i and r^i we use their zero-one asymptotic.

Asymptotic formulas allow us to transform kinetic matrix K to a matrix with value of diagonal element could not be smaller than the value of any element from the correspondent column and row.

Let us represent the kinetic matrix K in the basis of approximations to eigenvectors (7). The transformed matrix is $\tilde{K}_{ij} = l^i K r^j$ $(i, j = 0, 1, \ldots, 5)$:

$$K = \begin{bmatrix} -k_1 & 0 & 0 & 0 & 0 & 0 \\ k_1 & -k_2 & 0 & 0 & 0 & 0 \\ 0 & k_2 & -k_3 & 0 & 0 & 0 \\ 0 & 0 & k_3 & -k_4 & 0 & 0 \\ 0 & 0 & 0 & k_4 & -k_5 & 0 \\ 0 & 0 & 0 & 0 & k_5 & 0 \end{bmatrix},$$
$$\tilde{K} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_1 & 0 & 0 & 0 & 0 \\ 0 & k_1 & -k_2 & 0 & 0 & 0 \\ 0 & k_1 & k_3 & -k_3 & 0 & 0 \\ 0 & 0 & -k_3 & k_3 & -k_4 & 0 \\ 0 & 0 & -k_3 & k_3 & -k_5 & -k_5 \end{bmatrix} \tag{9}$$

The transformed matrix has an important property

$$|\tilde{K}_{ij}| \leq \min\{|\tilde{K}_{ii}|, |\tilde{K}_{jj}|\}$$

The initial matrix K is diagonally dominant in columns, but its rows can include elements that are much bigger than the correspondent diagonal elements.

We mention that a naive expectation $\tilde{K}_{ij} \approx \delta_{ij}$ is not realistic: some of the nondiagonal matrix elements $\tilde{K}_{ij}$ are of the same order than $\min\{\tilde{K}_{ii}, \tilde{K}_{jj}\}$. This example demonstrates that a good approximation to an eigenvector could be not an approximate eigenvector. If $Ke = \lambda e$ and $\|e - f\|$ is small then f is an approximation to eigenvector e. If $Kf \approx \lambda f$ (i.e. $\|Kf - \lambda f\|$ is small), then f is an approximate eigenvector for eigenvalue λ. Our kinetic matrix K is very ill-conditioned. Hence, nobody can guarantee that an approximation to eigenvector is an approximate eigenvector, or, inverse, an approximate eigenvector (a "quasimode") is an approximation to an eigenvector.

The question is, what do we need for approximation of the relaxation process (8). The answer is obvious: for approximation of general solution (8) with guaranteed accuracy we need approximation to the genuine eigenvectors ("modes") with the same accuracy. The zero-one asymptotic (5) gives this approximation. Below we always find the modes approximations and not quasimodes.

2.2 General properties of a cycle

The catalytic cycle is one of the most important substructures that we study in reaction networks. In the reduced form the catalytic cycle is a set of linear reactions:

$$A_1 \to A_2 \to \dots A_n \to A_1$$

Reduced form means that in reality some of these reaction are not monomolecular and include some other components (not from the list $A_1, \dots, A_n$). But in the study of the isolated cycle dynamics, concentrations of these components are taken as constant and are included into kinetic constants of the cycle linear reactions.

For the constant of elementary reaction $A_i \to$ we use the simplified notation k_i because the product of this elementary reaction is known, it is A_{i+1} for $i<n$ and A_1 for $i = n$. The elementary reaction rate is $w_i = k_i c_i$, where c_i is the concentration of A_i. The kinetic equation is:

$$\dot{c}_i = w_{i-1} - w_i \tag{10}$$

where by definition $w_0 = w_n$. In the stationary state ($\dot{c}_i = 0$), all the w_i are equal: $w_i = w$. This common rate w we call the cycle stationary rate, and

$$w = \frac{b}{(1/k_1) + \cdots + (1/k_n)}; \;\; c_i = \frac{w}{k_i} \tag{11}$$

where $b = \sum_i c_i$ is the conserved quantity for reactions in constant volume (for general case of chemical kinetic equations see elsewhere, for example, the book by Yablonskii et al., 1991). The stationary rate w (11) is a product of the arithmetic mean of concentrations, b/n, and the harmonic mean of constants (inverse mean of inverse k_i).

2.3 Static limitation in a cycle

If one of the constants, $k_{\min}$, is much smaller than others (let it be $k_{\min} = k_n$), then

$$\begin{aligned} c_n &= b\left(1 - \sum_{i<n}\frac{k_n}{k_i} + o\left(\sum_{i<n}\frac{k_n}{k_i}\right)\right), \\ c_i &= b\left(\frac{k_n}{k_i} + o\left(\sum_{i<n}\frac{k_n}{k_i}\right)\right), \\ w &= k_n b\left(1 + O\left(\sum_{i<n}\frac{k_n}{k_i}\right)\right) \end{aligned} \tag{12}$$

or simply in linear approximation

$$c_n = b\left(1 - \sum_{i<n}\frac{k_n}{k_i}\right), \;\; c_i = b\frac{k_n}{k_i}, \;\; w = k_n b \tag{13}$$

where we should keep the first-order terms in c_n in order not to violate the conservation law.

The simplest zero order approximation for the steady state gives

$$c_n = b, \;\; c_i = 0 \; (i \neq n) \tag{14}$$

This is trivial: all the concentration is collected at the starting point of the "narrow place", but may be useful as an origin point for various approximation procedures.

So, the stationary rate of a cycle is determined by the smallest constant, $k_{\min}$, if $k_{\min}$ is sufficiently small:

$$w = k_{\min} b \ \text{ if } \sum_{k_i \neq k_{\min}} \frac{k_{\min}}{k_i} \ll 1 \tag{15}$$

In that case we say that the cycle has a limiting step with constant $k_{\min}$.

2.4 Dynamical limitation in a cycle

If k_n/k_i is small for all $i<n$, then the kinetic behavior of the cycle is extremely simple: the coefficients matrix on the right-hand side of kinetic equation (10) has one simple zero eigenvalue that corresponds to the conservation law $\sum c_i = b$ and $n-1$ nonzero eigenvalues

$$\lambda_i = -k_i + \delta_i \ (i<n) \tag{16}$$

where $\delta_i \to 0$ when $\sum_{i<n}(k_n/k_i) \to 0$.

It is easy to demonstrate Equation (16): let us exclude the conservation law (the zero eigenvalue) $\sum c_i = b$ and use independent coordinates c_i $(i = 1,\ldots,n-1)$; $c_n = b - \sum_{i<n} c_i$. In these coordinates the kinetic equation (10) has the form

$$\dot{c} = Kc - k_n A c + k_n b e^1 \tag{17}$$

where c is the vector-column with components c_i $(i<n)$, K the lower triangle matrix with nonzero elements only in two diagonals: $(K)_{ii} = -k_i (i = 1,\ldots,n-1)$, $(K)_{i+1,i} = k_i$ $(i = 1,\ldots, n-2)$ (this is the kinetic matrix for the linear chain of $n-1$ reactions $A_1 \to A_2 \to \ldots A_n$); A the matrix with nonzero elements only in the first row: $(A)_{1i} \equiv 1$, e^1 the first basis vector ($e_1^1 = 1$, $e_i^1 = 0$ for $1<i<n$). After that, Equation (16) follows simply from continuous dependence of spectra on matrix.

The relaxation time of a stable linear system (17) is, by definition,

$$\tau = [\min\{Re(-\lambda_i) | i = 1, \ldots, n-1\}]^{-1}$$

For small k_n,

$$\tau \approx 1/k_\tau, \ \ k_\tau = \min\{k_i | i = 1, \ldots, n-1\} \tag{18}$$

In other words, k_τ is the second slowest rate constant: $k_{\min} \leq k_\tau \leq \cdots$

2.5 Relaxation equation for a cycle rate

A definition of the cycle rate is clear for steady states because stationary rates of all elementary reactions in cycle coincide. There is no common definition of the cycle rate for nonstationary regimes. In practice, one of steps is the step of product release (the "final" step of the catalytic transformation), and we can consider its rate as the rate of the cycle. Formally, we can take any step and study relaxation of its rate to the common stationary rate. The single relaxation time approximation gives for rate w_i of any step:

$$\begin{aligned} \dot{w}_i &= k_\tau (k_{\min} b - w_i); \\ w_i(t) &= k_{\min} b + e^{-k_\tau t}(w_i(0) - k_{\min} b) \end{aligned} \tag{19}$$

where $k_{\min}$ is the limiting (the minimal) rate constant of the cycle and k_τ the second in order rate constant of the cycle.

So, for catalytic cycles with the limiting constant $k_{\min}$, the relaxation time is also determined by one constant, but another one. This is k_τ, the second in order rate constant. It should be stressed that the only smallness condition is required, $k_{\min}$ should be much smaller than other constants. The second constant, k_τ should be just smaller than others (and bigger than $k_{\min}$), but there is no $\ll$ condition for k_τ required.

One of the methods for measurement of chemical reaction constants is the relaxation spectroscopy (Eigen, 1972). Relaxation of a system after an impact gives us a relaxation time or even a spectrum of relaxation times. For catalytic cycle with limitation, the relaxation experiment gives us the second constant k_τ, whereas the measurement of stationary rate gives the smallest constant, $k_{\min}$. This simple remark may be important for relaxation spectroscopy of open system.

2.6 Ensembles of cycles and robustness of stationary rate and relaxation time

Let us consider a catalytic cycle with random rate constants. For a given sample constants $k_1, \ldots, k_n$ the ith order statistics is equal its ith smallest value. We are interested in the first order (the minimal) and the second order statistics.

For independent identically distributed constants the variance of $k_{\min} = \min\{k_1, \ldots, k_n\}$ is significantly smaller than the variance of each k_i, Var(k). The same is true for statistic of every order. For many important distributions (e.g. for uniform distribution), the variance of ith order statistic is of order $\sim \mathrm{Var}(k)/n^2$. For big n it goes to zero faster than variance of the mean that is of order $\sim \mathrm{Var}(k)/n$. To illustrate this, let us consider n constants distributed in interval $[a, b]$. For each set of constants, $k_1, \ldots, k_n$ we introduce "symmetric coordinates" s_i: first, we order the constants, $a \le k_{i_1} \le k_{i_2} \le \cdots k_{i_n} \le b$, then calculate $s_0 = k_{i_1} - a$, $s_j = k_{i_{j+1}} - k_{i_j}$ $(j = 1, \ldots, n-1)$, $s_n = b - k_{i_n}$. Transformation $(k_1, \ldots, k_n) \mapsto (s_0, \ldots, s_n)$ maps a cube $[a, b]^n$ onto n-dimensional simplex $\Delta_n = \{(s_0, \ldots, s_n) | \sum_i s_i = b - a\}$ and uniform distribution on a cube transforms into uniform distribution on a simplex.

For large n, almost all volume of the simplex is concentrated in a small neighborhood of its center and this effect is an example of measure concentration effects that play important role in modern geometry and analysis (Gromov, 1999). All s_i are identically distributed, and for normalized variable $s = s_i/(b - a)$

the first moments are: $\mathbf{E}(s) = 1/(n+1) = 1/n + o(1/n)$, $\mathbf{E}(s^2) = 2/[(n+1)(n+2)] = 2/n^2 + o(1/n^2)$,

$$\mathrm{Var}(s) = \mathbf{E}(s^2) - (\mathbf{E}(s))^2$$
$$= \frac{n}{(n+1)^2(n+2)} = \frac{1}{n^2} + o\left(\frac{1}{n^2}\right)$$

Hence, for example, $\mathrm{Var}(k_{\min}) = (b-a)^2/n^2 + o(1/n^2)$. The standard deviation of $k_{\min}$ goes to zero as $1/n$ when n increases. This is much faster than $1/\sqrt{n}$ prescribed to the deviation of the mean value of independent observation (the "law of errors"). The same asymptotic $\sim 1/n$ is true for the standard deviation of the second constant also. These parameters fluctuate much less than individual constants, and even less than mean constant (for more examples with applications to statistical physics we address to the paper by Gorban, 2006).

It is impossible to use this observation for cycles with limitation directly, because the inequality of limitation (15) is not true for uniform distribution. According to this inequality, ratios $k_i/k_{\min}$ should be sufficiently small (if $k_i \neq k_{\min}$). To provide this inequality we need to use at least the log-uniform distribution: $k_i = \exp \Delta_i$ and Δ_i are independent variables uniformly distributed in interval $[\alpha, \beta]$ with sufficiently big $(\beta - \alpha)/n$.

One can interpret the log-uniform distribution through the Arrhenius law: $k = A\exp(-\Delta G/kT)$, where ΔG is the change of the Gibbs free energy inreaction (it includes both energetic and entropic terms: $\Delta G = \Delta H - T\Delta S$, where ΔH the enthalpy change and ΔS the entropy change in reaction, T the temperature). The log-uniform distribution of k corresponds to the uniform distribution of ΔG.

For log-uniform distribution of constants $k_1, \ldots, k_n$, if the interval of distribution is sufficiently big (i.e. $(\beta - \alpha)/n \gg 1$), then the cycle with these constants has the limiting step with probability close to one. More precisely we can show that for any two constants k_i and k_j the probability $\mathbb{P}[k_i/k_j > r \text{ or } k_j/k_i > r] = (1 - \log(r)/(\beta - \alpha))^2$ approaches one for any fixed $r > 1$ when $\beta - \alpha \to \infty$. Relaxation time of this cycle is determined by the second constant k_τ (also with probability close to one). Standard deviations of $k_{\min}$ and k_τ are much smaller than standard deviation of single constant k_i and even smaller than standard deviation of mean constant $\sum_i k_i/n$. This effect of stationary rate and relaxation time robustness seems to be important for understanding robustness in biochemical networks: behavior of the entire system is much more stable than the parameters of its parts; even for large fluctuations of parameters, the system does not change significantly the stationary rate (statics) and the relaxation time (dynamics).

2.7 Systems with well-separated constants and monotone relaxation

The log-uniform identical distribution of independent constants $k_1, \ldots, k_n$ with sufficiently big interval of distribution ($(\beta - \alpha)/n \gg 1$) gives us the first example of ensembles with well-separated constants: any two constants are connected by relation $\gg$ or $\ll$ with probability close to one. Such systems (not only cycles, but much more complex networks too) could be studied analytically "up to the end".

Some of their properties are simpler than for general networks. For example, the damping oscillations are impossible, i.e. the eigenvalues of kinetic matrix are real (with probability close to one). If constants are not separated, damped oscillations could exist, for example, if all constants of the cycle are equal, $k_1 = k_2 = \cdots = k_n = k$, then $(1 + \lambda/k)^n = 1$ and $\lambda_m = k(\exp(2\pi im/n) - 1)$ $(m = 1,\ldots,n-1)$, the case $m = 0$ corresponds to the linear conservation law. Relaxation time of this cycle may be relatively big: $\tau = (1/k)\ (1 - \cos(2\pi/n))^{-1} \sim n^2/(2\pi k)$ (for big n).

The catalytic cycle without limitation can have relaxation time much bigger then $1/k_{\min}$, where $k_{\min}$ is the minimal reaction rate constant. For example, if all k are equal, then for $n = 11$ we get $\tau \approx 20/k$. In more detail the possible relations between τ and the slowest constant were discussed by Yablonskii and Cheresiz (1984). In that paper, a variety of cases with different relationships between the steady-state reaction rate and relaxation was presented.

For catalytic cycle, if a matrix $K - k_nA$ (17) has a pair of complex eigenvalues with nonzero imaginary part, then for some $g \in [0, 1]$ the matrix $K - gk_nA$ has a degenerate eigenvalue (we use a simple continuity argument). With probability close to one, $k_{\min} \ll |k_i - k_j|$ for any two k_i and k_j that are not minimal. Hence, the $k_{\min}$-small perturbation cannot transform matrix K with eigenvalues k_i (16) and given structure into a matrix with a degenerate eigenvalue. For proof of this statement it is sufficient to refer to diagonal dominance of K (the absolute value of each diagonal element is greater than the sum of the absolute values of the other elements in its column) and classical inequalities.

The matrix elements of A in the eigenbasis of K are $(A)_{ij} = l^iAr^j$. From obtained estimates for eigenvectors we get $|(A)_{ij}| \lesssim 1$ (with probability close to one). This estimate does not depend on values of kinetic constants. Now, we can apply the Gershgorin theorem (see, e.g. the review of Marcus and Minc (1992) and for more details the book of Varga (2004)) to the matrix $K - k_nA$ in the eigenbasis of K: the characteristic roots of $K - k_nA$ belong to discs $|z + k_i| \le k_nR_i(A)$, where $R_i(A) = \sum_j |(A)_{ij}|$. If the discs do not intersect, then each of them contains one and only one characteristic number. For ensembles with well-separated constants these discs do not intersect (with probability close to one). Complex conjugate eigenvalues could not belong to different discs. In this case, the eigenvalues are real — there exist no damped oscillations.

2.8 Limitation by two steps with comparable constants

If we consider one-parametric families of systems, then appearance of systems with two comparable constants may be unavoidable. Let us imagine a continuous path $k_i(s)$ ($s \in [0, 1]$, s is a parameter along the path) in the space of systems, which goes from one system with well-separated constants ($s = 0$) to another such system ($s = 1$). On this path $k_i(s)$ such a point s that $k_i(s) = k_j(s)$ may exist, and this existence may be stable, that is, such a point persists under continuous perturbations. This means that on a path there may be points where not all the constants are well separated, and trajectories of some constants may intersect.

For catalytic cycle, we are interested in the following intersection only: $k_{\min}$ and the second constant are of the same order, and are much smaller than other constants. Let these constants be k_j and k_l, $j \neq l$. The limitation condition is

$$\frac{1}{k_j} + \frac{1}{k_l} \gg \sum_{i \neq j,l} \frac{1}{k_i} \tag{20}$$

The steady-state reaction rate and relaxation time are determined by these two constants. In that case their effects are coupled. For the steady state we get in first-order approximation instead of Equation (13):

$$\begin{aligned} w &= \frac{k_j k_l}{k_j + k_l} b; \quad c_i = \frac{w}{k_i} = \frac{b}{k_i} \frac{k_j k_l}{k_j + k_l} (i \neq j, l); \\ c_j &= \frac{b k_l}{k_j + k_l} \left(1 - \sum_{i \neq j,l} \frac{l}{k_i} \frac{k_j k_l}{k_j + k_l} \right); \\ c_l &= \frac{b k_j}{k_j + k_l} \left(1 - \sum_{i \neq j,l} \frac{l}{k_i} \frac{k_j k_l}{k_j + k_l} \right) \end{aligned} \tag{21}$$

Elementary analysis shows that under the limitation condition (20) the relaxation time is

$$\tau = \frac{1}{k_j + k_l} \tag{22}$$

The single relaxation time approximation for all elementary reaction rates in a cycle with two limiting reactions is

$$\begin{aligned} \dot{w}_i &= k_j k_l b - (k_j + k_l) w_i; \\ w_i(t) &= \frac{k_j k_l}{k_j + k_l} b + e^{-(k_j + k_l)t} \left(w_i(0) - \frac{k_j k_l}{k_j + k_l} b \right) \end{aligned} \tag{23}$$

The catalytic cycle with two limiting reactions has the same stationary rate w (21) and relaxation time (22) as a reversible reaction $A \leftrightarrow B$ with $k^+ = k_j$ and $k^- = k_l$.

In two-parametric families three constants can meet. If three smallest constants k_j, k_l and k_m have comparable values and are much smaller than others, then static and dynamic properties would be determined by these three constants. Stationary rate w and dynamic of relaxation for the whole cycle would be the same as for 3-reaction cycle $A \to B \to C \to A$ with constants k_j, k_l and k_m. The damped oscillation here are possible, for example, if $k_j = k_l = k_m = k$, then there are complex eigenvalues $\lambda = k(-(3/2) \pm i(\sqrt{3}/2))$. Therefore, if a cycle manifests damped oscillation, then at least three slowest constants are of the same order. The same is true, of course, for more general reaction networks.

In N-parametric families of systems N+1 smallest constants can meet, and near such a "meeting point" a slow auxiliary cycle of N+1 reactions determines behavior of the entire cycle.

2.9 Irreversible cycle with one inverse reaction

In this subsection, we represent a simple example that gives the key to most of subsequent constructions of "cycles surgery". Let us add an inverse reaction to the irreversible cycle: $A_1 \to \ldots \to A_i \leftrightarrow A_{i+1} \to \ldots \to A_n \to A_1$. We use the previous notation $k_1, \ldots, k_n$ for the cycle reactions, and k_i^- for the inverse reaction $A_i \leftarrow A_{i+1}$. For well-separated constants, influence of k_i^- on the whole reaction is determined by relations of three constants: k_i, k_i^- and k_{i+1}. First of all, if $k_i^- \ll k_{i+1}$ then in the main order there is no such influence, and dynamic of the cycle is the same as for completely irreversible cycle.

If the opposite inequality is true, $k_i^- \gg k_{i+1}$, then equilibration between A_i and A_{i+1} gives $k_i c_i x \approx k_i^- c_{i+1}$. If we introduce a lumped component A_i^1 with concentration $c_i^1 = c_i + c_{i+1}$, then $c_i \approx k_i^- c_i^1/(k_i + k_i^-)$ and $c_{i+1} \approx k_i c_i^1/(k_i + k_i^-)$. Using this component instead of the pair A_i, A_{i+1} we can consider an irreversible cycle with $n-1$ components and n reactions $A_1 \to \ldots \to A_{i-1} \to A_i^1 \to A_{i+2} \to \ldots \to A_n \to A_1$. To estimate the reaction rate constant k_i^1 for a new reaction, $A_i^1 \to A_{i+2}$, let us mention that the correspondent reaction rate should be $k_{i+1}c_{i+1} \approx k_{i+1}k_i c_i^1/(k_i + k_i^-)$. Hence,

$$k_i^1 \approx k_{i+1}k_i/(k_i + k_i^-)$$

For systems with well-separated constants this expression can be simplified: if $k_i \gg k_i^-$ then $k_i^1 \approx k_{i+1}$ and if $k_i \ll k_i^-$ then $k_i^1 \approx k_{i+1}k_i/k_i^-$. The first case, $k_i \gg k_i^-$ is limitation in the small cycle (of length two) $A_i \leftrightarrow A_{i+1}$ by the inverse reaction $A_i \leftarrow A_{i+1}$. The second case, $k_i \ll k_i^-$, means the direct reaction is the limiting step in this small cycle.

To estimate eigenvectors, we can, after identification of the limiting step in the small cycle, delete this step and reattach the outgoing reaction to the beginning of this step. For the first case, $k_i \gg k_i^-$, we get the irreversible cycle, $A_1 \to \ldots \to A_i \to A_{i+1} \to \ldots \to A_n \to A_1$, with the same reaction rate constants. For the second case, $k_i \ll k_i^-$ we get a new system of reactions: a shortened cycle $A_1 \to \ldots \to A_i \to A_{i+2} \to \ldots \to A_n \to A_1$ and an "appendix" $A_{i+1} \to A_i$. For the new elementary reaction $A_i \to A_{i+2}$ the reaction rate constant is $k_i^1 \approx k_{i+1}k_i/k_i^-$. All other elementary reactions have the same rate constants, as they have in the initial system. After deletion of the limiting step from the "big cycle" $A_1 \to \ldots \to A_i \to A_{i+2} \to \ldots \to A_n \to A_1$, we get an acyclic system that approximate relaxation of the initial system.

So, influence of a single inverse reaction on the irreversible catalytic cycle with well-separated constants is determined by relations of three constants: k_i, k_i^- and k_{i+1}. If k_i^- is much smaller than at least one of k_i, k_{i+1}, then there is no influence in the main order. If $k_i^- \gg k_i$ and $k_i^- \gg k_{i+1}$ then the relaxation of the initial cycle can be approximated by relaxation of the auxiliary acyclic system.

Asymptotic equivalence (for $k_i^- \gg k_i,\ k_{i+1}$) of the reaction network $A_i \leftrightarrow A_{i+1} \to A_{i+2}$ with rate constants k_i, k_i^- and k_{i+1} to the reaction network $A_{i+1} \to A_i \to A_{i+2}$ with rate constants k_i^- (for the reaction $A_{i+1} \to A_i$) and $k_{i+1}k_i/k_i^-$ (for the reaction $A_i \to A_{i+2}$) is simple, but slightly surprising fact. The kinetic matrix for the first network in coordinates c_i, c_{i+1} and c_{i+2} is

$$K = \begin{bmatrix} -k_i & k_i^- & 0 \\ k_i & -(k_i^- + k_{i+1}) & 0 \\ 0 & k_{i+1} & 0 \end{bmatrix}$$

The eigenvalues are 0 and

$$\lambda_{1,2} = \frac{1}{2}\left[-(k_i + k_i^- + k_{i+1}) \pm \sqrt{(k_i + k_i^- + k_{i+1})^2 - 4k_ik_{i+1}}\right]$$

$\lambda_1 = -k_{i+1}k_i(1+o(1))/k_i^-$, $\lambda_2 = -k_i^-(1+o(1))$, where $o(1) \ll 1$. Right eigenvector r^0 for zero eigenvalue is (0, 0, 1) (we write vector columns in rows). For λ_1 the eigenvector is $r^1 = (1, 0, -1) + o(1)$, and for λ_2 it is $r^2 = (1, -1, 0) + o(1)$. For the linear chain of reactions, $A_{i+1} \to A_i \to A_{i+2}$, with rate constants k_i^- and $k_{i+1}k_i/k_i^-$ eigenvalues are $-k_i^-$ and $-k_{i+1}k_i/k_i^-$. These values approximate eigenvalues of the initial system with small relative error. The linear chain has the same zero-one asymptotic of the correspondent eigenvectors.

This construction, a small cycle inside a big system, a quasi-steady state in the small cycle, and deletion of the limiting step with reattaching of reactions (see Figure 1 below) appears in this chapter many times in much general settings. The uniform estimates that we need for approximation of eigenvalues and eigenvectors by these procedures are proven in Appendices.

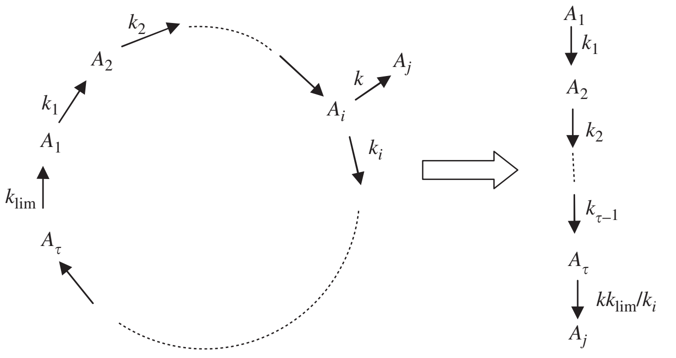

Figure 1 The main operation of the cycle surgery: on a step back we get a cycle $A_1 \to \ldots \to A_\tau \to A_1$ with the limiting step $A_\tau \to A_1$ and one outgoing reaction $A_i \to A_j$. We should delete the limiting step, reattach ("recharge") the outgoing reaction $A_i \to A_j$ from A_i to A_τ and change its rate constant k to the rate constant $kk_{\lim}/k_i$. The new value of reaction rate constant is always smaller than the initial one: $kk_{\lim}/k_i < k$ if $k_{\lim} \neq k_i$. For this operation only one condition $k \ll k_i$ is necessary (k should be small with respect to reaction $A_i \to A_{i+1}$ rate constant, and can exceed any other reaction rate constant).

3. MULTISCALE ENSEMBLES AND FINITE-ADDITIVE DISTRIBUTIONS

3.1 Ensembles with well-separated constants, formal approach

In previous section, ensembles with well-separated constants appear. We represented them by a log-uniform distribution in a sufficiently big interval log $k \in [\alpha, \beta]$, but we were not interested in most of probability distribution properties, and did not use them. The only property we really used is: if $k_i > k_j$, then $k_i/k_j \gg 1$ (with probability close to one). It means that we can assume that $k_i/k_j \gg a$ for any preassigned value of a that does not depend on k values. One can interpret this property as an asymptotic one for $\alpha \to -\infty$, $\beta \to \infty$.

That property allows us to simplify algebraic formulas. For example, $k_i + k_j$ could be substituted by $\max\{k_i, k_j\}$ (with small relative error), or

$$\frac{ak_i + bk_j}{ck_i + dk_j} \approx \begin{cases} a/c, & \text{if } k_i \gg k_j; \\ b/d, & \text{if } k_i \ll k_j \end{cases}$$

for nonzero a, b, c, d (see, e.g. Equation (4)).

Of course, some ambiguity can be introduced, for example, what is it, $(k_1 + k_2) - k_1$, if $k_1 \gg k_2$? If we first simplify the expression in brackets, it is zero, but if we open brackets without simplification, it is k_2. This is a standard difficulty in use of relative errors for round-off. If we estimate the error in the final answer, and then simplify, we shall avoid this difficulty. Use of o and $\mathcal{O}$ symbols also helps to control the error qualitatively: if $k_1 \gg k_2$, then we can write $(k_1 + k_2) = k_1(1 + o(1))$ and $k_1(1 + o(1)) - k_1 = k_1 o(1)$. The last expression is neither zero nor absolutely small — it is just relatively small with respect to k_1.

The formal approach is: for any ordering of rate constants, we use relations $\gg$ and $\ll$, and assume that $k_i/k_j \gg a$ for any preassigned value of a that does not depend on k values. This approach allows us to perform asymptotic analysis of reaction networks. A special version of this approach consists of group ordering: constants are separated on several groups, inside groups they are comparable, and between groups there are relations $\gg$ or $\ll$. An example of such group ordering was discussed at the end of previous section (several limiting constants in a cycle).

3.2 Probability approach: finite additive measures

The asymptotic analysis of multiscale systems for log-uniform distribution of independent constants on an interval log $k \in [\alpha, \beta]$ $(-\alpha, \beta \to \infty)$ is possible, but parameters α, β do not present in any answer, they just should be sufficiently big. A natural question arises, what is the limit? It is a log-uniform distribution on a line, or, for n independent identically distributed constants, a log-uniform distribution on $\mathbb{R}^n$).

It is well known that the uniform distribution on $\mathbb{R}^n$ is impossible: if a cube has positive probability $\varepsilon > 0$ (i.e. the distribution has positive density) then the union of $N > 1/\varepsilon$ such disjoint cubes has probability bigger than 1 (here we use the finite-additivity of probability). This is impossible. But if that cube has probability zero, then the whole space has also zero probability, because it can be covered by countable family of the cube translation. Hence, translation invariance and σ-additivity (countable additivity) are in contradiction (if we have no doubt about probability normalization).

Nevertheless, there exists finite-additive probability which is invariant with respect to Euclidean group $E(n)$ (generated by rotations and translations). Its values are densities of sets.

Let λ be the Lebesgue measure and $D \subset \mathbb{R}^n$ be a Lebesgue measurable subset. Density of D is the limit (if it exists):

$$\rho(D) = \lim_{r\to\infty} \frac{\lambda(D \cap \mathbb{B}_r^n)}{\lambda(\mathbb{B}_r^n)} \tag{24}$$

where $\mathbb{B}_r^n$ is a ball with radius r and center at origin. Density of $\mathbb{R}^n$ is 1, density of every half-space is ½, density of bounded set is zero, density of a cone is its solid angle (measured as a sphere surface fractional area). Density (24) and translation and rotational invariant. It is finite-additive: if densities $\rho(D)$ and $\rho(H)$ (24) exist and $D \cap H = \varnothing$ then $\rho(D \cup H)$ exists and $\rho(D \cup H) = \rho(D) + \rho(H)$.

Every polyhedron has a density. A polyhedron could be defined as the union of a finite number of convex polyhedra. A convex polyhedron is the intersection of a finite number of half-spaces. It may be bounded or unbounded. The family of polyhedra is closed with respect to union, intersection and subtraction of sets. For our goals, polyhedra form sufficiently rich class. It is important that in definition of polyhedron *finite* intersections and unions are used. If one uses countable unions, he gets too many sets including all open sets, because open convex polyhedra (or just cubes with rational vertices) form a basis of standard topology.

Of course, not every measurable set has density. If it is necessary, we can use the Hahn–Banach theorem (Rudin, 1991) and study extensions ρ_{Ex} of ρ with the following property:

$$\underline{\rho}(D) \le \rho_{\mathrm{Ex}}(D) \le \bar{\rho}(D)$$

where

$$\underline{\rho}(D) = \lim_{r\to\infty} \inf \frac{\lambda(D \cap \mathbb{B}_r^n)}{\lambda(\mathbb{B}_r^n)},$$

$$\bar{\rho}(D) = \lim_{r\to\infty} \sup \frac{\lambda(D \cap \mathbb{B}_r^n)}{\lambda(\mathbb{B}_r^n)}$$

Functionals $\underline{\rho}(D)$ and $\bar{\rho}(D)$ are defined for all measurable D. We should stress that such extensions are not unique. Extension of density (24) using the Hahn–Banach theorem for picking up a random integer was used in a very recent work by Adamaszek (2006).

One of the most important concepts of any probability theory is the conditional probability. In the density-based approach we can introduce the conditional density. If densities $\rho(D)$ and $\rho(H)$ (24) exist, $\rho(H) \neq 0$ and the following limit $\rho(D \mid H)$ exists, then we call it conditional density:

$$\rho(D|H) = \lim_{r\to\infty} \frac{\lambda(D \cap H \cap \mathbb{B}_r^n)}{\lambda(H \cap \mathbb{B}_r^n)} \tag{25}$$

For polyhedra the situation is similar to usual probability theory: densities $\rho(D)$ and $\rho(H)$ always exist and if $\rho(H) \neq 0$ then conditional density exists too. For general measurable sets the situation is not so simple, and existence of $\rho(D)$ and $\rho(H) \neq 0$ does not guarantee existence of $\rho(D \mid H)$.

On a line, convex polyhedra are just intervals, finite or infinite. The probability defined on polyhedra is: for finite intervals and their finite unions it is zero, for half-lines $x > \alpha$ or $x < \alpha$ it is ½, and for the whole line $\mathbb{R}$ the probability is 1. If one takes a set of positive probability and adds or subtracts a zero-probability set, the probability does not change.

If independent random variables x and y are uniformly distributed on a line, then their linear combination $z = \alpha x + \beta y$ is also uniformly distributed on a line. (Indeed, vector (x, y) is uniformly distributed on a plane (by definition), a set $z > \gamma$ is a half-plane, the correspondent probability is ½.) This is a simple, but useful stability property. We shall use this result in the following form. If independent random variables $k_1, \ldots, k_n$ are log-uniformly distributed on a line, then the monomial $\prod_{i=1}^{n} k_i^{\alpha_i}$ for real α_i is also log-uniformly distributed on a line, if some of $\alpha_i \neq 0$.

3.3 Carroll's obtuse problem and paradoxes of conditioning

Lewis Carroll's Pillow Problem #58 (Carroll, 1958): "Three points are taken at random on an infinite plane. Find the chance of their being the vertices of an obtuse-angled triangle".

A random triangle on an infinite plane is presented by a point equidistributed in $\mathbb{R}^6$. Owing to the density — based definition, we should take and calculate the density of the set of obtuse-angled triangles in $\mathbb{R}^6$. This is equivalent to the problem: find a fraction of the sphere $\mathbb{S}^5 \subset \mathbb{R}^6$ that corresponds to obtuse-angled triangles. Just integrate .... But there remains a problem. Vertices of triangle are independent. Let us use the standard logic for discussion of independent trials: we take the first point A at random, then the second point B and then the third point C. Let us draw the first side AB. Immediately we find that for almost all positions of the the third point C the triangle is obtuse-angled (Guy, 1993). Carroll proposed to take another condition: let AB be the longest side and let C be uniformly distributed in the allowed area. The answer then is easy — just a ratio of areas of two simple figures. But there are absolutely no reasons for uniformity of C distribution. And it is more important that the absolutely standard reasoning for independently chosen points gives another answer than could be found on the base of joint distribution. Why these approaches are in disagreement now? Because there is no classical Fubini theorem for our finite-additive probabilities, and we cannot easily transfer from a multiple integral to a repeated one.

There exists a much simpler example. Let x and y be independent positive real number. This means that vector (x, y) is uniformly distributed in the first quadrant. What is probability that $x \geqslant y$? Following the definition of probability based on the density of sets, we take the correspondent angle and find immediately that this probability is ½. This meets our intuition well. But let us take the first number x and look for possible values of y. The result: for given x the second number y is uniformly distributed on $[0, \infty)$, and only a finite interval $[0, x]$ corresponds to $x \geqslant y$. For the infinite rest we have $x < y$. Hence, $x < y$ with probability 1. This is nonsense because of symmetry. So, for our finite-additive measure we cannot use repeated integrals (or, may be, should use them in a very peculiar manner).

3.4 Law of total probability and orderings

For polyhedra, there appear no conditioning problems. The law of total probabilities holds: if $\mathbb{R}^n = \cup_{i=1}^m H_i$, H_i are polyhedra, $\rho(H_i) > 0$, $\rho(H_i \cap H_j) = 0$ for $i \neq j$, and $D \subset \mathbb{R}^n$ is a polyhedron, then

$$\rho(D) = \sum_{i=1}^{m} \rho(D \cap H_i) = \sum_{i=1}^{m} \rho(D|H_i)\rho(H_i) \tag{26}$$

Our basic example of multiscale ensemble is log-uniform distribution of reaction constants in $\mathbb{R}^n_+$ ($\log k_i$ are independent and uniformly distributed on the line). For every ordering $k_{j_1} > k_{j_2} > \cdots > k_{j_n}$ a polyhedral cone $H_{j_1, j_2, \ldots, j_n}$ in $\mathbb{R}^n$ is defined. These cones have equal probabilities $\rho(H_{j_1, j_2, \ldots, j_n}) = 1/n!$ and probability of intersection of cones for different orderings is zero. Hence, we can apply the law of total probability (26). This means that we can study every event D conditionally, for different orderings, and then combine the results of these studies in the final answer (26).

For example, if we study a simple cycle then formula (13) for steady state is valid with any given accuracy with unite probability for any ordering with the given minimal element k_n.

For cycle with given ordering of constants we can find zero-one approximation of left and right eigenvectors (5). This approximation is valid with any given accuracy for this ordering with probability one.

If we consider sufficiently wide log-uniform distribution of constants on a bounded interval instead of the infinite axis then these statements are true with probability close to 1.

For general system that we study below the situation is slightly more complicated: new terms, auxiliary reactions with monomial rate constants $k_\varsigma = \prod_i k_i^{\varsigma_i}$ could appear with integer (but not necessary positive) ς_i, and we should include these k_ς in ordering. It follows from stability property that these monomials are log-uniform distributed on infinite interval, if k_i are. Therefore the situation seems to be similar to ordering of constants, but there is a significant difference: monomials are not independent, they depend on k_i with $\varsigma_i \neq 0$.

Happily, in the forthcoming analysis when we include auxiliary reactions with constant k_ς, we always exclude at least one of the reactions with rate constant k_i and $\varsigma_i \neq 0$. Hence, for we always can use the following statement (for the new list of constants, or for the old one): if $k_{j_1} > k_{j_2} > \cdots > k_{j_n}$ then $k_{j_1} \gg k_{j_2} \gg \cdots \gg k_{j_n}$, where $a \gg b$ for positive a, b means: for any given $\varepsilon > 0$ the inequality $\varepsilon a > b$ holds with probability one.

If we use sufficiently wide but finite log-uniform distribution then ε could not be arbitrarily small (this depends on the interval with), and probability is not unite but close to one. For given $\varepsilon > 0$ probability tends to one when the interval width goes to infinity. It is important that we use only finite number of auxiliary reactions with monomial constants, and this number is bounded from above for given number of elementary reactions. For completeness, we should mention here general algebraic theory of orderings that is necessary in more sophisticated cases (Greuel and Pfister, 2002; Robbiano, 1985).

4. RELAXATION OF MULTISCALE NETWORKS AND HIERARCHY OF AUXILIARY DISCRETE DYNAMICAL SYSTEMS

4.1 Definitions, notations and auxiliary results

4.1.1 Notations

In this section, we consider a general network of linear (monomolecular) reactions. This network is represented as a directed graph (digraph): vertices correspond to components A_i, edges correspond to reactions $A_i \to A_j$ with kinetic constants $k_{ji} > 0$. For each vertex, A_i, a positive real variable c_i (concentration) is defined. A basis vector e^i corresponds to A_i with components $e^i_j = \delta_{ij}$, where δ_{ij} is the Kronecker delta. The kinetic equation for the system is

$$\frac{\mathrm{d}c_i}{\mathrm{d}t} = \sum_j (k_{ij}c_j - k_{ji}c_i) \tag{27}$$

or in vector form: $\dot{c} = Kc$.

To write another form of Equation (27) we use stoichiometric vectors: for a reaction $A_i \to A_j$ the stoichiometric vector γ_{ji} is a vector in concentration space with ith coordinate -1, jth coordinate 1 and other coordinates 0. The reaction rate $w_{ji} = k_{ji}c_i$. The kinetic equation has the form

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \sum_{i,j} w_{ji}\gamma_{ji} \tag{28}$$

where c is the concentration vector. One more form of Equation (27) describes directly dynamics of reaction rates:

$$\frac{\mathrm{d}w_{ji}}{\mathrm{d}t}\left(= k_{ji}\frac{\mathrm{d}c_i}{\mathrm{d}t}\right) = k_{ji}\sum_l (w_{il} - w_{li}) \tag{29}$$

It is necessary to mention that, in general, system (29) is not equivalent to system (28), because there are additional connections between variables w_{ji}. If there exists at least one A_i with two different outgoing reactions, $A_i \to A_j$ and $A_i \to A_l$ ($j \neq l$), then $w_{ji}/w_{li} \equiv k_{ji}/k_{li}$. If the reaction network generates a discrete dynamical system $A_i \to A_j$ on the set of A_i (see below), then the variables w_{ji} are independent, and Equation (29) gives equivalent representation of kinetics.

For analysis of kinetic systems, linear conservation laws and positively invariant polyhedra are important. A linear conservation law is a linear function defined on the concentrations $b(c) = \sum_i b_i c_i$, whose value is preserved by the dynamics (27). The conservation laws coefficient vectors b_i are left eigenvectors of the matrix K corresponding to the zero eigenvalue. The set of all the conservation laws forms the left kernel of the matrix K. Equation (27) always has a linear conservation law: $b^0(c) = \sum_i c_i =$ constant. If there is no other independent linear conservation law, then the system is *weakly ergodic*.

A set E is *positively invariant* with respect to kinetic equations (27), if any solution $c(t)$ that starts in E at time $t_0 (c(t_0) \in E)$ belongs to E for $t > t_0$ $(c(t) \in E$ if $t > t_0)$. It is straightforward to check that the standard simplex $\Sigma = \{c | c_i \geq 0, \sum_i c_i = 1\}$ is positively invariant set for kinetic equation (27): just to check that if $c_i = 0$ for some i, and all $c_j \geq 0$ then $\dot{c}_i \geq 0$. This simple fact immediately implies the following properties of K:

- All eigenvalues λ of K have non-positive real parts, $Re\lambda \leqslant 0$, because solutions cannot leave Σ in positive time.
- If $Re\lambda = 0$ then $\lambda = 0$, because intersection of Σ with any plain is a polygon, and a polygon cannot be invariant with respect of rotations to sufficiently small angles.
- The Jordan cell of K that corresponds to zero eigenvalue is diagonal — because all solutions should be bounded in Σ for positive time.
- The shift in time operator $\exp(Kt)$ is a contraction in the l_1 norm for $t > 0$: for positive t and any two solutions of Equation (27) $c(t)$, $c'(t) \in \Sigma$

$$\sum_i |c_i(t) - c'_i(t)| \leq \sum_i |c_i(0) - c'_i(0)|$$

Two vertices are called adjacent if they share a common edge. A path is a sequence of adjacent vertices. A graph is connected if any two of its vertices are linked by a path. A maximal connected subgraph of graph G is called a connected component of G. Every graph can be decomposed into connected components.

A directed path is a sequence of adjacent edges where each step goes in direction of an edge. A vertex A is *reachable* by a vertex B, if there exists an oriented path from B to A.

A nonempty set V of graph vertexes forms a *sink*, if there are no oriented edges from $A_i \in V$ to any $A_j \notin V$. For example, in the reaction graph $A_1 \leftarrow A_2 \rightarrow A_3$ the one-vertex sets $\{A_1\}$ and $\{A_3\}$ are sinks. A sink is minimal if it does not contain a strictly smaller sink. In the previous example, $\{A_1\}$ and $\{A_3\}$ are minimal sinks. Minimal sinks are also called ergodic components.

A digraph is strongly connected, if every vertex A is reachable by any other vertex B. Ergodic components are maximal strongly connected subgraphs of the graph, but inverse is not true: there may exist maximal strongly connected subgraphs that have outgoing edges and, therefore, are not sinks.

We study ensembles of systems with a given graph and independent and well-separated kinetic constants k_{ij}. This means that we study asymptotic behavior of ensembles with independent identically distributed constants, log-uniform distributed in sufficiently big interval $\log k \in [\alpha, \beta]$, for $\alpha \to -\infty$, $\beta \to \infty$, or just a log-uniform distribution on infinite axis, $\log k \in \mathbb{R}$.

4.1.2 Sinks and ergodicity

If there is no other independent linear conservation law, then the system is weakly ergodic. The weak ergodicity of the network follows from its topological properties.

The following properties are equivalent and each one of them can be used as an alternative definition of weak ergodicity:

(i) There exist the only independent linear conservation law for kinetic equations (27) (this is $b^0(c) = \sum_i c_i =$ constant).

(ii) For any normalized initial state $c(0)$ ($b^0(c) = 1$) there exists a limit state

$$c^* = \lim_{t\to\infty} \exp(Kt)c(0)$$

that is the same for all normalized initial conditions: For all c,

$$\lim_{t\to\infty} \exp(Kt)c = b^0(c)c^*$$

(iii) For each two vertices A_i and $A_j (i \neq j)$ we can find such a vertex A_k that is reachable both by A_i and by A_j. This means that the following structure exists:

$$A_i \to \ldots \to A_k \leftarrow \ldots \leftarrow A_j$$

One of the paths can be degenerated: it may be $i = k$ or $j = k$.

(iv) The network has only one minimal sink (one ergodic component).

For every monomolecular kinetic system, the Jordan cell for zero eigenvalue of matrix K is diagonal and the maximal number of independent linear conservation laws (i.e. the geometric multiplicity of the zero eigenvalue of the matrix K) is equal to the maximal number of disjoint ergodic components (minimal sinks).

Let $G = \{A_{i_1}, \ldots, A_{i_l}\}$ be an ergodic component. Then there exists a unique vector (normalized invariant distribution) c^G with the following properties: $c_i^G = 0$ for $i \notin \{i_1, \ldots, i_l\}$, $c_i^G > 0$ for all $i \in \{i_1, \ldots, i_l\}$, $b^0(c^G) = 1$, $Kc^G = 0$.

If $G_1, \ldots, G_m$ are all ergodic components of the system, then there exist m independent positive linear functionals $b^1(c), \ldots, b^m(c)$, such that $\sum_{i=1}^m b^i = b^0$ and for each c

$$\lim_{t\to\infty} \exp(Kt)c = \sum_{i=1}^{m} b^i(c)c^{G_i} \tag{30}$$

So, for any solution of kinetic equations (27), $c(t)$, the limit at $t \to \infty$ is a linear combination of normalized invariant distributions c^{G_i} with coefficients $b^i(c(0))$. In the simplest example, $A_1 \leftarrow A_2 \to A_3$, $G_1 = \{A_1\}$, $G_2 = \{A_3\}$, components of vectors c^{G_1}, c^{G_2} are (1, 0, 0) and (0, 0, 1), correspondingly. For functionals $b^{1,2}$ we get:

$$b^1(c) = c_1 + \frac{k_1}{k_1 + k_2} c_2; \;\; b^2(c) = \frac{k_2}{k_1 + k_2} c_2 + c_3 \tag{31}$$

where k_1 and k_2 are rate constants for reaction $A_2 \to A_1$ and $A_2 \to A_3$, correspondingly. We can mention that for well-separated constants either $k_1 \gg k_2$

or $k_1 \ll k_2$. Hence, one of the coefficients $k_1/(k_1+k_2)$ and $k_2/(k_1+k_2)$ is close to 0, another is close to 1. This is an example of the general zero-one law for multiscale systems: for any l, i, the value of functional b^l (30) on basis vector e^i, $b^l(e^i)$, is either close to 1 or close to 0 (with probability close to 1).

We can understand better this asymptotics by using the Markov chain language. For nonseparated constants a particle in A_2 has nonzero probability to reach A_1 and nonzero probability to reach A_3. The zero-one law in this simplest case means that the dynamics of the particle becomes deterministic: with probability one it chooses to go to one of vertices A_2, A_3 and to avoid another. Instead of branching, $A_2 \to A_1$ and $A_2 \to A_3$, we select only one way: either $A_2 \to A_1$ or $A_2 \to A_3$. Graphs without branching represent discrete dynamical systems.

4.1.3 Decomposition of discrete dynamical systems

Discrete dynamical system on a finite set $V = \{A_1, A_2, \ldots, A_n\}$ is a semigroup $1, \phi, \phi^2, \ldots$, where ϕ is a map $\phi: V \to V$. $A_i \in V$ is a periodic point, if $\phi^l(A_i) = A_i$ for some $l > 0$; else A_i is a transient point. A cycle of period l is a sequence of l distinct periodic points $A, \phi(A), \phi^2(A), \ldots, \phi^{l-1}(A)$ with $\phi^l(A) = A$. A cycle of period one consists of one fixed point, $\phi(A) = A$. Two cycles, C and C' either coincide or have empty intersection.

The set of periodic points, V^{p}, is always nonempty. It is a union of cycles: $V^{\mathrm{p}} = \cup_j C_j$. For each point $A \in V$ there exist such a positive integer $\tau(A)$ and a cycle $C(A) = C_j$ that $\phi^q(A) \in C_j$ for $q \geqslant \tau(A)$. In that case we say that A belongs to basin of attraction of cycle C_j and use notation $\mathrm{Att}(C_j) = \{A | C(A) = C_j\}$. Of course, $C_j \subset \mathrm{Att}(C_j)$. For different cycles, $\mathrm{Att}(C_j) \cap \mathrm{Att}(C_l) = \varnothing$. If A is periodic point then $\tau(A) = 0$. For transient points $\tau(A) > 0$.

So, the phase space V is divided onto subsets $\mathrm{Att}(C_j)$. Each of these subsets includes one cycle (or a fixed point, that is a cycle of length 1). Sets $\mathrm{Att}(C_j)$ are ϕ-invariant: $\phi(\mathrm{Att}(C_j)) \subset \mathrm{Att}(C_j)$. The set $\mathrm{Att}(C_j) \backslash C_j$ consist of transient points and there exists such positive integer τ that $\phi^q(\mathrm{Att}(C_j)) = C_j$ if $q \geqslant \tau$.

4.2 Auxiliary discrete dynamical systems and relaxation analysis

4.2.1 Auxiliary discrete dynamical system

For each A_i, we define κ_i as the maximal kinetic constant for reactions $A_i \to A_j : \kappa_i = \max_j\{k_{ji}\}$. For correspondent j we use notation $\phi(i) : \phi(i) = \arg\max_j\{k_{ji}\}$. The function $\phi(i)$ is defined under condition that for A_i outgoing reactions $A_i \to A_j$ exist. Let us extend the definition: $\phi(i) = i$ if there exist no such outgoing reactions.

The map ϕ determines discrete dynamical system on a set of components $V = \{A_i\}$. We call it the auxiliary discrete dynamical system for a given network of monomolecular reactions. Let us decompose this system and find the cycles C_j and their basins of attraction, $\mathrm{Att}(C_j)$.

Notice that for the graph that represents a discrete dynamic system, attractors are ergodic components, whereas basins are connected components.

An auxiliary reaction network is associated with the auxiliary discrete dynamical system. This is the set of reactions $A_i \to A_{\phi(i)}$ with kinetic constants κ_i. The correspondent kinetic equation is

$$\dot{c}_i = -\kappa_i c_i + \sum_{\phi(j)=i} \kappa_j c_j \tag{32}$$

or in vector notations (28)

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \tilde{K}c = \sum_i \kappa_i c_i \gamma_{\phi(i)i}; \quad \tilde{K}_{ij} = -\kappa_j \delta_{ij} + \kappa_j \delta_{i\phi(j)} \tag{33}$$

For deriving of the auxiliary discrete dynamical system we do not need the values of rate constants. Only the ordering is important. Below we consider multiscale ensembles of kinetic systems with given ordering and with well-separated kinetic constants ($k_{\sigma(1)} \gg k_{\sigma(2)} \gg \cdots$ for some permutation σ).

In the following, we analyze first the situation when the system is connected and has only one attractor. This can be a point or a cycle. Then, we discuss the general situation with any number of attractors.

4.2.2 Eigenvectors for acyclic auxiliary kinetics

Let us study kinetics (32) for acyclic discrete dynamical system (each vertex has one or zero outgoing reactions, and there are no cycles). Such acyclic reaction networks have many simple properties. For example, the nonzero eigenvalues are exactly minus reaction rate constants, and it is easy to find all left and right eigenvectors in explicit form. Let us find left and right eigenvectors of matrix $\tilde{K}$ of auxiliary kinetic system (32) for acyclic auxiliary dynamics. In this case, for any vertex A_i there exists an eigenvector. If A_i is a fixed point of the discrete dynamical system (i.e. $\phi(i) = i$) then this eigenvalue is zero. If A_i is not a fixed point (i.e. $\phi(i) \neq i$ and reaction $A_i \to A_{\phi(i)}$ has nonzero rate constant κ_i) then this eigenvector corresponds to eigenvalue $-\kappa_i$. For left and right eigenvectors of $\tilde{K}$ that correspond to A_i we use notations l^i (vector-raw) and r^i (vector-column), correspondingly, and apply normalization condition $r_i^i = l_i^i = 1$.

First, let us find the eigenvectors for zero eigenvalue. Dimension of zero eigenspace is equal to the number of fixed points in the discrete dynamical system. If A_i is a fixed point then the correspondent eigenvalue is zero, and the right eigenvector r^i has only one nonzero coordinate, concentration of $A_i : r_j^i = \delta_{ij}$.

To construct the correspondent left eigenvectors l^i for zero eigenvalue (for fixed point A_i), let us mention that l_j^i could have nonzero value only if there exists such $q \geqslant 0$ that $\phi^q(j) = i$ (this q is unique because absence of cycles). In that case (for $q > 0$),

$$(l^i \tilde{K})_j = -\kappa_j l_j^i + \kappa_j l_{\phi(j)}^i = 0$$

Hence, $l_j^i = l_{\phi(j)}^i$ and $l_j^i = 1$ if $\phi^q(j) = i$ for some $q > 0$.

For nonzero eigenvalues, right eigenvectors will be constructed by recurrence starting from the vertex A_i and moving in the direction of the flow. The construction is in opposite direction for left eigenvectors. Nonzero eigenvalues of $\tilde{K}$ (32) are $-\kappa_i$.

For given i, τ_i is the minimal integer such that $\phi^{\tau_i}(i) = \phi^{\tau_i+1}(i)$ (this is a *relaxation time* i.e. the number of steps to reach a fixed point). All indices $\{\phi^k(i)|k = 0, 1, \ldots, \tau_i\}$ are different. For right eigenvector r^i only coordinates $r^i_{\phi^k(i)}(k = 0, 1, \ldots, \tau_i)$ could have nonzero values, and

$$\begin{aligned}(\tilde{K}r^i)_{\phi^{\kappa+1}(i)} &= -\kappa_{\phi^{\kappa+1}(i)} r^i_{\phi^{\kappa+1}(i)} + \kappa_{\phi^{\kappa}(i)} r^i_{\phi^{\kappa}(i)} \\ &= -\kappa_i r^i_{\phi^{\kappa+1}(i)}\end{aligned}$$

Hence,

$$\begin{aligned} r^i_{\phi^{k+1}(i)} &= \frac{\kappa_{\phi^k(i)}}{\kappa_{\phi^{k+1}(i)} - \kappa_i} r^i_{\phi^k(i)} = \prod_{j=0}^{k} \frac{\kappa_{\phi^j(i)}}{\kappa_{\phi^{j+1}(i)} - \kappa_i} \\ &= \frac{\kappa_i}{\kappa_{\phi^{k+1}(i)} - \kappa_i} \prod_{j=0}^{k-1} \frac{\kappa_{\phi^{j+1}(i)}}{\kappa_{\phi^{j+1}(i)} - \kappa_i} \end{aligned} \tag{34}$$

The last transformation is convenient for estimation of the product for well-separated constants (compare to Equation (4)):

$$\begin{aligned} \frac{\kappa_{\phi^{j+1}(i)}}{\kappa_{\phi^{j+1}(i)} - \kappa_i} &\approx \begin{cases} 1, & \text{if } \kappa_{\phi^{j+1}(i)} \gg \kappa_i, \\ 0, & \text{if } \kappa_{\phi^{j+1}(i)} \ll \kappa_i; \end{cases} \\ \frac{\kappa_i}{\kappa_{\phi^{k+1}(i)} - \kappa_i} &\approx \begin{cases} -1, & \text{if } \kappa_i \gg \kappa_{\phi^{k+1}(i)}, \\ 0, & \text{if } \kappa_i \ll \kappa_{\phi^{k+1}(i)} \end{cases} \end{aligned} \tag{35}$$

For left eigenvector l^i coordinate l^i_j could have nonzero value only if there exists such $q \geqslant 0$ that $\phi^q(j) = i$ (this q is unique because the auxiliary dynamical system has no cycles). In that case (for $q > 0$),

$$(l^i\tilde{K})_j = -\kappa_j l^i_j + \kappa_j l^i_{\phi(j)} = -\kappa_i l^i_j$$

Hence,

$$l^i_j = \frac{\kappa_j}{\kappa_j - \kappa_i} l^i_{\phi(j)} = \prod_{k=0}^{q-1} \frac{\kappa_{\phi^k(j)}}{\kappa_{\phi^k(j)} - \kappa_i} \tag{36}$$

For every fraction in Equation (36) the following estimate holds:

$$\frac{\kappa_{\phi^k(j)}}{\kappa_{\phi^k(j)} - \kappa_i} \approx \begin{cases} 1, & \text{if } \kappa_{\phi^k(j)} \gg \kappa_i, \\ 0, & \text{if } \kappa_{\phi^k(j)} \ll \kappa_i \end{cases} \tag{37}$$

As we can see, every coordinate of left and right eigenvectors of $\tilde{K}$ (34), (36) is either 0 or ± 1, or close to 0 or to ± 1 (with probability close to 1). We can write this asymptotic representation explicitly (analogously to Equation (5)). For left eigenvectors, $l^i_i = 1$ and $l^i_j = 1$ (for $i \neq j$) if there exists such q that $\phi^q(j) = i$, and $\kappa_{\phi^d(j)} > \kappa_i$ for all $d = 0, \ldots, q-1$, else $l^i_j = 0$. For right eigenvectors, $r^i_i = 1$ and

$r^i_{\phi^k(i)} = -1$ if $\kappa_{\phi^k(i)} < \kappa_i$ and for all positive $m<k$ inequality $\kappa_{\phi^m(i)} > \kappa_i$ holds, i.e. k is first such positive integer that $\kappa_{\phi^k(i)} < \kappa_i$ (for fixed point A_p we use $\kappa_p = 0$). Vector r^i has not more than two nonzero coordinates. It is straightforward to check that in this asymptotic $l^i r^j = \delta_{ij}$.

In general, coordinates of eigenvectors l^i_j and r^i_j are simultaneously nonzero only for one value $j = i$ because the auxiliary system is acyclic. However, $l^i r^j = 0$ if $i \neq j$, just because that are eigenvectors for different eigenvalues, κ_i and κ_j. Hence, $l^i r^j = \delta_{ij}$.

For example, let us find the asymptotic of left and right eigenvectors for a branched acyclic system of reactions:

$$A_1 \xrightarrow{7} A_2 \xrightarrow{5} A_3 \xrightarrow{6} A_4 \xrightarrow{2} A_5 \xrightarrow{4} A_8, \;\; A_6 \xrightarrow{1} A_7 \xrightarrow{3} A_4$$

where the upper index marks the order of rate constants: $\kappa_6 > \kappa_4 > \kappa_7 > \kappa_5 > \kappa_2 > \kappa_3 > \kappa_1$ (κ_i is the rate constant of reaction $A_i \to \ldots$).

For zero eigenvalue, the left and right eigenvectors are

$$l^8 = (1,1,1,1,1,1,1,1,1), \;\; r^8 = (0,0,0,0,0,0,0,1)$$

For left eigenvectors, rows l^i, that correspond to nonzero eigenvalues we have the following asymptotics:

$$\begin{aligned} &l^1 \approx (1,0,0,0,0,0,0,0), \;\; l^2 \approx (0,1,0,0,0,0,0,0),\\ &l^3 \approx (0,1,1,0,0,0,0,0), \;\; l^4 \approx (0,0,0,1,0,0,0,0),\\ &l^5 \approx (0,0,0,1,1,1,1,0), \;\; l^6 \approx (0,0,0,0,0,1,0,0),\\ &l^7 \approx (0,0,0,0,0,1,1,0) \end{aligned} \tag{38}$$

For the correspondent right eigenvectors, columns r^i, we have the following asymptotics (we write vector-columns in rows):

$$\begin{aligned} &r^1 \approx (1,0,0,0,0,0,0,-1), \;\; r^2 \approx (0,1,-1,0,0,0,0,0),\\ &r^3 \approx (0,0,1,0,0,0,0,-1), \;\; r^4 \approx (0,0,0,1,-1,0,0,0),\\ &r^5 \approx (0,0,0,0,1,0,0,-1), \;\; r^6 \approx (0,0,0,0,0,1,-1,0),\\ &r^7 \approx (0,0,0,0,-1,0,1,0) \end{aligned} \tag{39}$$

4.2.3 The first case: auxiliary dynamical system is acyclic and has one attractor

In the simplest case, the auxiliary discrete dynamical system for the reaction network $\mathcal{W}$ is acyclic and has only one attractor, a fixed point. Let this point be A_n (n is the number of vertices). The correspondent eigenvectors for zero eigenvalue are $r^n_j = \delta_{nj}$ and $l^n_j = 1$. For such a system, it is easy to find explicit analytic solution of kinetic equation (32).

Acyclic auxiliary dynamical system with one attractor have a characteristic property among all auxiliary dynamical systems: the stoichiometric vectors of reactions $A_i \to A_{\phi(i)}$ form a basis in the subspace of concentration space with $\sum_i c_i = 0$. Indeed, for such a system there exist $n-1$ reactions, and their stoichiometric vectors are independent. However, existence of cycles implies linear connections between stoichiometric vectors, and existence of two attractors in acyclic system implies that the number of reactions is less $n-1$, and their stoichiometric vectors could not form a basis in $n-1$-dimensional space.

Let us assume that the auxiliary dynamical system is acyclic and has only one attractor, a fixed point. This means that stoichiometric vectors $\gamma_{\phi(i)i}$ form a basis in a subspace of concentration space with $\sum_i c_i = 0$. For every reaction $A_i \to A_l$ the following linear operators Q_{il} can be defined:

$$Q_{il}(\gamma_{\phi(i)i}) = \gamma_{li}, \quad Q_{il}(\gamma_{\phi(p)p}) = 0 \text{ for } p \neq i \tag{40}$$

The kinetic equation for the whole reaction network (28) could be transformed in the form

$$\begin{aligned} \frac{\mathrm{d}c}{\mathrm{d}t} &= \sum_i \left(1 + \sum_{l,l\neq\phi(i)} \frac{k_{li}}{\kappa_i} Q_{il}\right) \gamma_{\phi(i)\ i} \kappa_i c_i \\ &= \left(1 + \sum_{j,l(l\neq\phi(j))} \frac{k_{lj}}{\kappa_j} Q_{jl}\right) \sum_i \gamma_{\phi(i)i} \kappa_i c_i \\ &= \left(1 + \sum_{j,l(l\neq\phi(j))} \frac{k_{lj}}{\kappa_j} Q_{jl}\right) \tilde{K} c \end{aligned} \tag{41}$$

where $\tilde{K}$ is kinetic matrix of auxiliary kinetic equation (33). By construction of auxiliary dynamical system, $k_{li} \ll \kappa_i$ if $l \neq \phi(i)$. Notice also that $|Q_{jl}|$ does not depend on rate constants.

Let us represent system (41) in eigenbasis of $\tilde{K}$ obtained in previous subsection. Any matrix B in this eigenbasis has the form $B = (\tilde{b}_{ij})$, $\tilde{b}_{ij} = l^i B r^j = \sum_{qs} l^i_q b_{qs} r^j_s$, where (b_{qs}) is matrix B in the initial basis, l^i and r^j are left and right eigenvectors of $\tilde{K}$ (34), (36). In eigenbasis of $\tilde{K}$ the Gershgorin estimates of eigenvalues and estimates of eigenvectors are much more efficient than in original coordinates: the system is stronger diagonally dominant. Transformation to this basis is an effective preconditioning for perturbation theory that uses auxiliary kinetics as a first approximation to the kinetics of the whole system.

First of all, we can exclude the conservation law. Any solution of (41) has the form $c(t) = br^n + \tilde{c}(t)$, where $b = l^n c(t) = l^n c(0)$ and $\sum_i \tilde{c}_i(t) = 0$. On the subspace of concentration space with $\sum_i c_i = 0$ we get

$$\frac{\mathrm{d}c}{\mathrm{d}t} = (1 + \mathscr{E})\mathrm{diag}\{-\kappa_1, \ldots, -\kappa_{n-1}\} c \tag{42}$$

where $\mathscr{E} = (\varepsilon_{ij})$, $|\varepsilon_{ij}| \ll 1$ and $\mathrm{diag}\{-\kappa_1, \ldots, -\kappa_{n-1}\}$ is diagonal matrix with $-\kappa_1, \ldots, -\kappa_{n-1}$ on the main diagonal. If $|\varepsilon_{ij}| \ll 1$ then we can use the Gershgorin theorem and state that eigenvalues of matrix $(1 + \mathscr{E})\mathrm{diag}\{-\kappa_1, \ldots, -\kappa_{n-1}\}$ are real and have the form $\lambda_i = -\kappa_i + \theta_i$ with $|\theta_i| \ll \kappa_i$.

To prove inequality $|\varepsilon_{ij}| \ll 1$ (for ensembles with well-separated constants, with probability close to 1) we use that the left and right eigenvectors of $\tilde{K}$ (34), (36) are uniformly bounded under some non-degeneracy conditions and those conditions are true for well-separated constants. For ensembles with well-separated constants, for any given positive $g<1$ and all i, j ($i\neq j$) the following inequality is true with probability close to 1: $|\kappa_i - \kappa_j| > g\kappa_i$. Let us select a value of g and assume that this *diagonal gap condition* is always true. In this case, for every fraction in (34), (36) we have estimate

$$\frac{\kappa_i}{|\kappa_j - \kappa_i|} < \frac{1}{g}$$

Therefore, for coordinates of right and left eigenvectors of $\tilde{K}$ (34), (36) we get

$$|r^i_{\phi^{\kappa+1}(i)}| < \frac{1}{g^k} < \frac{1}{g^n}, \quad |l^i_j| < \frac{1}{g^q} < \frac{1}{g^n} \tag{43}$$

We can estimate $|\varepsilon_{ij}|$ and $|\theta_i|/\kappa_i$ from above as constant $\times$ $\max_{l\neq\phi(s)}\{k_{ls}/\kappa_s\}$. So, the eigenvalues for kinetic matrix of the whole system (41) are real and close to eigenvalues of auxiliary kinetic matrix $\tilde{K}$ (33). For eigenvectors, the Gershgorin theorem gives no result, and additionally to diagonal dominance we must assume the diagonal gap condition. Based on this assumption, we proved the Gershgorin type estimate of eigenvectors in Appendix 1. In particular, according to this estimate, eigenvectors for the whole reaction network are arbitrarily close to eigenvectors of $\tilde{K}$ (with probability close to 1).

So, if the auxiliary discrete dynamical system is acyclic and has only one attractor (a fixed point), then the relaxation of the whole reaction network could be approximated by the auxiliary kinetics (32):

$$c(t) = (l^n c(0))r^n + \sum_{i=1}^{n-1} (l^i c(0))r^i \exp(-\kappa_i t) \tag{44}$$

For l^i and r^i one can use exact formulas (34) and (36) or zero-one asymptotic representations based on Equations (37) and (35) for multiscale systems. This approximation (44) could be improved by iterative methods, if necessary.

4.2.4 The second case: auxiliary system has one cyclic attractor

The second simple particular case on the way to general case is a reaction network with components $A_1, \ldots, A_n$ whose auxiliary discrete dynamical system has one attractor, a cycle with period $\tau > 1$: $A_{n-\tau+1} \to A_{n-\tau+2} \to \ldots A_n \to A_{n-\tau+1}$ (after some change of enumeration). We assume that the limiting step in this cycle (reaction with minimal constant) is $A_n \to A_{n-\tau+1}$. If auxiliary discrete dynamical system has only one attractor then the whole network is weakly ergodic. But the attractor of the auxiliary system may not coincide with a sink of the reaction network.

There are two possibilities:

(i) In the whole network, all the outgoing reactions from the cycle have the form $A_{n-\tau+i} \to A_{n-\tau+j}$ ($i, j > 0$). This means that the cycle vertices $A_{n-\tau+1}$, $A_{n-\tau+2}, \ldots, A_n$ form a sink for the whole network.

(ii) There exists a reaction from a cycle vertex $A_{n-\tau+i}$ to A_m, $m \leqslant n-\tau$. This means that the set $\{A_{n-\tau+1}, A_{n-\tau+2}, \ldots, A_n\}$ is not a sink for the whole network.

In the first case, the limit (for $t \to \infty$) distribution for the auxiliary kinetics is the well-studied stationary distribution of the cycle $A_{n-\tau+1}, A_{n-\tau+2}, \ldots, A_n$ described in Section 2 (11)–(13), (15). The set $\{A_{n-\tau+1}, A_{n-\tau+2}, \ldots, A_n\}$ is the only ergodic component for the whole network too, and the limit distribution for that system is nonzero on vertices only. The stationary distribution for the cycle $A_{n-\tau+1} \to A_{n-\tau+2} \to \ldots A_n \to A_{n-\tau+1}$ approximates the stationary distribution for the whole system. To approximate the relaxation process, let us delete the limiting step $A_n \to A_{n-\tau+1}$ from this cycle. By this deletion we produce an acyclic system with one fixed point, A_n, and auxiliary kinetic equation (33) transforms into

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \tilde{K}_0 c = \sum_{i=1}^{n-1} \kappa_i c_i \gamma_{\phi(i)i} \tag{45}$$

As it is demonstrated, dynamics of this system approximates relaxation of the whole network in subspace $\sum_i c_i = 0$. Eigenvalues for Equation (45) are $-\kappa_i$ $(i < n)$, the corresponded eigenvectors are represented by Equations (34), (36) and zero-one multiscale asymptotic representation is based on Equations (37) and (35).

In the second case, the set

$$\{A_{n-\tau+1}, A_{n-\tau+2}, \ldots, A_n\}$$

is not a sink for the whole network. This means that there exist outgoing reactions from the cycle, $A_{n-\tau+i} \to A_j$ with $A_j \notin \{A_{n-\tau+1}, A_{n-\tau+2}, \ldots, A_n\}$. For every cycle vertex $A_{n-\tau+i}$ the rate constant $\kappa_{n-\tau+i}$ that corresponds to the cycle reaction $A_{n-\tau+i} \to A_{n-\tau+i+1}$ is much bigger than any other constant $k_{j,n-\tau+i}$ that corresponds to a "side" reaction $A_{n-\tau+i} \to A_j$ $(j \neq n-\tau+i+1)$: $\kappa_{n-\tau+i} \gg k_{j,n-\tau+i}$. This is because definition of auxiliary discrete dynamical system and assumption of ensemble with well-separated constants (multiscale asymptotics). This inequality allows us to separate motion and to use for computation of the rates of outgoing reaction $A_{n-\tau+i} \to A_j$ the quasi-steady-state distribution in the cycle. This means that we can glue the cycle into one vertex $A^1_{n-\tau+1}$ with the correspondent concentration $c^1_{n-\tau+1} = \sum_{1 \le i \le \tau} c_{n-\tau+i}$ and substitute the reaction $A_{n-\tau+i} \to A_j$ by $A^1_{n-\tau+1} \to A_j$ with the rate constant renormalization: $k^1_{j,n-\tau+1} = k_{j,n-\tau+i} c^{QS}_{n-\tau+i} / c^1_{n-\tau+1}$. By the superscript QS we mark here the quasi-stationary concentrations for given total cycle concentration $c^1_{n-\tau+1}$. Another possibility is to recharge the link $A_{n-\tau+i} \to A_j$ to another vertex of the cycle (usually to A_n): we can substitute the reaction $A_{n-\tau+i} \to A_j$ by the reaction $A_{n-\tau+q} \to A_j$ with the rate constant renormalization:

$$k_{j,n-\tau+q} = k_{j,n-\tau+i} c^{QS}_{n-\tau+i} / c^{QS}_{n-\tau+q} \tag{46}$$

The new rate constant is smaller than the initial one: $k_{j,n-\tau+q} \le k_{j,n-\tau+i}$, because $c^{QS}_{n-\tau+i} \le c^{QS}_{n-\tau+q}$ due to definition.

We apply this approach now and demonstrate its applicability in more details later in this section. For the quasi-stationary distribution on the cycle we get $c_{n-\tau+i} = c_n\kappa_n/\kappa_{n-\tau+i}$ $(1 \leqslant i < \tau)$. The original reaction network is transformed by gluing the cycle $\{A_{n-\tau+1}, A_{n-\tau+2}, \ldots, A_n\}$, into a point $A^1_{n-\tau+1}$. We say that components $A_{n-\tau+1}, A_{n-\tau+2}, \ldots, A_n$ of the original system belong to the component $A^1_{n-\tau+1}$ of the new system. All the reactions $A_i \to A_j$ with $i,j \leqslant n-\tau$ remain the same with rate constant k_{ji}. Reactions of the form $A_i \to A_j$ with $i \leqslant n-\tau$, $j > n-\tau$ (incoming reactions of the cycle $\{A_{n-\tau+1}, A_{n-\tau+2}, \ldots, A_n\}$) transform into $A_i \to A^1_{n-\tau+1}$ with the same rate constant k_{ji}. Reactions of the form $A_i \to A_j$ with $i > n-\tau$, $j \leqslant n-\tau$ (outgoing reactions of the cycle $\{A_{n-\tau+1}, A_{n-\tau+2}, \ldots, A_n\}$) transform into reactions $A^1_{n-\tau+1} \to A_j$ with the "quasi-stationary" rate constant $k^{\rm QS}_{ji} = k_{ji}\kappa_n/\kappa_{n-\tau+i}$. After that, we select the maximal $k^{\rm QS}_{ji}$ for given j: $k^{(1)}_{j,n-\tau+1} = \max_{i>n-\tau} k^{\rm QS}_{ji}$. This $k^{(1)}_{j,n-\tau+1}$ is the rate constant for reaction $A^1_{n-\tau+1} \to A_j$ in the new system. Reactions $A_i \to A_j$ with $i,j > n-\tau$ (internal reactions of the site) vanish.

Among rate constants for reactions of the form $A_{n-\tau+i} \to A_m$ $(m \geqslant n-\tau)$ we find

$$\kappa^{(1)}_{n-\tau+i} = \max_{i,m}\{k_{m,n-\tau+i}\kappa_n/\kappa_{n-\tau+i}\} \tag{47}$$

Let the correspondent i, m be i_1, m_1.

After that, we create a new auxiliary discrete dynamical system for the new reaction network on the set $\{A_1, \ldots, A_{n-\tau}, A^1_{n-\tau+1}\}$. We can describe this new auxiliary system as a result of transformation of the first auxiliary discrete dynamical system of initial reaction network. All the reactions from this first auxiliary system of the form $A_i \to A_j$ with $i,j \leqslant n-\tau$ remain the same with rate constant κ_i. Reactions of the form $A_i \to A_j$ with $i \leqslant n-\tau$, $j > n-\tau$ transform into $A_i \to A^1_{n-\tau+1}$ with the same rate constant κ_i. One more reaction is to be added: $A^1_{n-\tau+1} \to A_{m_1}$ with rate constant $\kappa^{(1)}_{n-\tau+i}$. We "glued" the cycle into one vertex, $A^1_{n-\tau+1}$, and added new reaction from this vertex to A_{m_1} with maximal possible constant (47). Without this reaction the new auxiliary dynamical system has only one attractor, the fixed point $A^1_{n-\tau+1}$. With this additional reaction that point is not fixed, and a new cycle appears: $A_{m_1} \to \ldots A^1_{n-\tau+1} \to A_{m_1}$.

Again we should analyze, whether this new cycle is a sink in the new reaction network, etc. Finally, after a chain of transformations, we should come to an auxiliary discrete dynamical system with one attractor, a cycle, that is the sink of the transformed whole reaction network. After that, we can find stationary distribution by restoring of glued cycles in auxiliary kinetic system and applying formulas (11)–(13) and (15) from Section 2. First, we find the stationary state of the cycle constructed on the last iteration, after that for each vertex A^k_j that is a glued cycle we know its concentration (the sum of all concentrations) and can find the stationary distribution, then if there remain some vertices that are glued cycles we find distribution of concentrations in these cycles, etc. At the end of this process we find all stationary concentrations with high accuracy, with probability close to one.

As a simple example we use the following system, a chain supplemented by three reactions:

$$\begin{gathered} A_1 \xrightarrow{1} A_2 \xrightarrow{2} A_3 \xrightarrow{3} A_4 \xrightarrow{4} A_5 \xrightarrow{5} A_6, \\ A_6 \xrightarrow{6} A_4, \ A_5 \xrightarrow{7} A_2 \text{ and } A_3 \xrightarrow{8} A_1 \end{gathered} \tag{48}$$

where the upper index marks the order of rate constants.

Auxiliary discrete dynamical system for the network (48) includes the chain and one reaction:

$$A_1 \xrightarrow{1} A_2 \xrightarrow{2} A_3 \xrightarrow{3} A_4 \xrightarrow{4} A_5 \xrightarrow{5} A_6 \xrightarrow{6} A_4$$

It has one attractor, the cycle $A_4 \xrightarrow{4} A_5 \xrightarrow{5} A_6 \xrightarrow{6} A_4$. This cycle is not a sink for the whole system, because there exists an outgoing reaction $A_5 \xrightarrow{7} A_2$.

By gluing the cycle $A_4 \xrightarrow{4} A_5 \xrightarrow{5} A_6 \xrightarrow{6} A_4$ into a vertex A_4^1 we get new network with a chain supplemented by two reactions:

$$A_1 \xrightarrow{1} A_2 \xrightarrow{2} A_3 \xrightarrow{3} A_4^1, \ A_4^1 \xrightarrow{?} A_2 \text{ and } A_3 \xrightarrow{?} A_1 \tag{49}$$

Here the new rate constant is $k_{24}^{(1)} = k_{25}\kappa_6/\kappa_5$ ($\kappa_6 = k_{46}$ is the limiting step of the cycle $A_4 \xrightarrow{4} A_5 \xrightarrow{5} A_6 \xrightarrow{6} A_4$, $\kappa_5 = k_{65}$).

Here we can make a simple but important observation: the new constant $k_{24}^1 = k_{25}\kappa_6/\kappa_5$ has the same log-uniform distribution on the whole axis as constants k_{25}, κ_6 and κ_5 have. The new constant k_{24}^1 depends on k_{25} and the internal cycle constants κ_6 and κ_5, and is independent from other constants.

Of course, $k_{24}^{(1)} < \kappa_5$, but relations between $k_{24}^{(1)}$ and k_{13} are a priori unknown. Both orderings, $k_{24}^{(1)} > k_{13}$ and $k_{24}^{(1)} < k_{13}$, are possible, and should be considered separately, if necessary. But for both orderings the auxiliary dynamical system for network (49) is

$$A_1 \xrightarrow{1} A_2 \xrightarrow{2} A_3 \xrightarrow{3} A_4^1 \xrightarrow{?} A_2$$

(of course, $\kappa_4^{(1)} < \kappa_3 < \kappa_2 < \kappa_1$). It has one attractor, the cycle $A_2 \xrightarrow{2} A_3 \xrightarrow{3} A_4^1 \xrightarrow{?} A_2$. This cycle is not a sink for the whole system, because there exists an outgoing reaction $A_3 \xrightarrow{?} A_1$. The limiting constant for this cycle is $\kappa_4^{(1)} = k_{24}^{(1)} = k_{25}k_{46}/k_{65}$. We glue this cycle into one point, A_2^2. The new transformed system is very simple, it is just a two-step cycle: $A_1 \xrightarrow{1} A_2^2 \xrightarrow{?} A_1$. The new reaction constant is $k_{12}^{(2)} = k_{13}\kappa_4^{(1)}/\kappa_3 = k_{13}k_{25}k_{46}/(k_{65}k_{43})$. The auxiliary discrete dynamical system is the same graph $A_1 \xrightarrow{1} A_2^2 \xrightarrow{?} A_1$, this is a cycle, and we do not need further transformations.

Let us find the steady state on the way back, from this final auxiliary system to the original one. For steady state of each cycle we use formula (13).

The steady state for the final system is $c_1 = bk_{12}^{(2)}/k_{21}$ and $c_2^2 = b(1 - k_{12}^{(2)}/k_{21})$. The component A_2^2 includes the cycle $A_2 \xrightarrow{2} A_3 \xrightarrow{3} A_4^1 \xrightarrow{?} A_2$. The steady state of this cycle is $c_2 = c_2^{(2)}k_{24}^{(1)}/k_{32}$, $c_3 = c_2^{(2)}k_{24}^{(1)}/k_{43}$ and $c_4^{(1)} = c_2^{(2)}(1 - k_{24}^{(1)}/k_{32} - k_{24}^{(1)}/k_{43})$. The component A_4^1 includes the cycle $A_4 \xrightarrow{4} A_5 \xrightarrow{5} A_6 \xrightarrow{6} A_4$.

The steady state of this cycle is $c_4 = c_4^{(1)} k_{46}/k_{54}$, $c_5 = c_4^{(1)} k_{46}/k_{65}$ and $c_6 = c_4^{(1)}(1 - k_{46}/k_{54} - k_{46}/k_{65})$.

For one catalytic cycle, relaxation in the subspace $\sum_i c_i = 0$ is approximated by relaxation of a chain that is produced from the cycle by cutting the limiting step (Section 2). For reaction networks under consideration (with one cyclic attractor in auxiliary discrete dynamical system) the direct generalization works: for approximation of relaxation in the subspace $\sum_i c_i = 0$ it is sufficient to perform the following procedures:

- to glue iteratively attractors (cycles) of the auxiliary system that are not sinks of the whole system;
- to restore these cycles from the end of the first procedure to its beginning. For each of cycles (including the last one that is a sink) the limited step should be deleted, and the outgoing reaction should be reattached to the head of the limiting steps (with the proper normalization), if it was not deleted before as a limiting step of one of the cycles.

The heads of outgoing reactions of that cycles should be reattached to the heads of the limiting steps. Let for a cycle this limiting step be $A_m \to A_q$. If for a glued cycle A^k there exists an outgoing reaction $A^k \to A_j$ with the constant κ (47), then after restoration we add the outgoing reaction $A_m \to A_j$ with the rate constant κ. Kinetic of the resulting acyclic system approximates relaxation of the initial networks (under assumption of well-separated constants, for given ordering, with probability close to 1).

Let us construct this acyclic network for the same example (48). The final cycle is $A_1 \xrightarrow{1} A_2^2 \xrightarrow{?} A_1$. The limiting step in this cycle is $A_2^2 \xrightarrow{?} A_1$. After cutting we get $A_1 \xrightarrow{1} A_2^2$. The component A_2^2 is glued cycle $A_2 \xrightarrow{2} A_3 \xrightarrow{3} A_4^1 \xrightarrow{?} A_2$. The reaction $A_1 \xrightarrow{1} A_2^2$ corresponds to the reaction $A_1 \xrightarrow{1} A_2$ (in this case, this is the only reaction from A_1 to cycle; in other case one should take the reaction from A_1 to cycle with maximal constant). The limiting step in the cycle is $A_4^1 \xrightarrow{?} A_2$. After cutting, we get a system $A_1 \xrightarrow{1} A_2 \xrightarrow{2} A_3 \xrightarrow{3} A_4^1$. The component A_4^1 is the glued cycle $A_4 \xrightarrow{4} A_5 \xrightarrow{5} A_6 \xrightarrow{6} A_4$ from the previous step. The limiting step in this cycle is $A_6 \xrightarrow{6} A_4$. After restoring this cycle and cutting the limiting step, we get an acyclic system $A_1 \xrightarrow{1} A_2 \xrightarrow{2} A_3 \xrightarrow{3} A_4 \xrightarrow{4} A_5 \xrightarrow{5} A_6$ (as one can guess from the beginning: this coincidence is provided by the simple constant ordering selected in Equation (48)). Relaxation of this system approximates relaxation of the whole initial network.

To demonstrate possible branching of described algorithm for cycles surgery (gluing, restoring and cutting) with necessity of additional orderings, let us consider the following system:

$$A_1 \xrightarrow{1} A_2 \xrightarrow{6} A_3 \xrightarrow{2} A_4 \xrightarrow{3} A_5 \xrightarrow{4} A_3, \quad A_4 \xrightarrow{5} A_2 \tag{50}$$

The auxiliary discrete dynamical system for reaction network (50) is

$$A_1 \xrightarrow{1} A_2 \xrightarrow{6} A_3 \xrightarrow{2} A_4 \xrightarrow{3} A_5 \xrightarrow{4} A_3$$

It has only one attractor, a cycle $A_3 \xrightarrow{2} A_4 \xrightarrow{3} A_5 \xrightarrow{4} A_3$. This cycle is not a sink for the whole network (50) because reaction $A_4 \xrightarrow{5} A_2$ leads from that cycle. After gluing the cycle into a vertex A_3^1 we get the new network $A_1 \xrightarrow{1} A_2 \xrightarrow{6} A_3^1 \xrightarrow{?} A_2$. The rate constant for the reaction $A_3^1 \to A_2$ is $k_{23}^1 = k_{24}k_{35}/k_{54}$, where k_{ij} is the rate constant for the reaction $A_j \to A_i$ in the initial network (k_{35} is the cycle limiting reaction). The new network coincides with its auxiliary system and has one cycle, $A_2 \xrightarrow{6} A_3^1 \xrightarrow{?} A_2$. This cycle is a sink, hence, we can start the back process of cycles restoring and cutting. One question arises immediately: which constant is smaller, k_{32} or k_{23}^1. The smallest of them is the limiting constant, and the answer depends on this choice. Let us consider two possibilities separately: (1) $k_{32} > k_{23}^1$ and (2) $k_{32} < k_{23}^1$. Of course, for any choice the stationary concentration of the source component A_1 vanishes: $c_1 = 0$.

(1) Let us assume that $k_{32} > k_{23}^1$. In this case, the steady state of the cycle $A_2 \xrightarrow{6} A_3^1 \xrightarrow{?} A_2$ is (according to Equation (13)) $c_2 = bk_{23}^1/k_{32}$ and $c_3^1 = b(1 - k_{23}^1/k_{32})$, where $b = \sum c_i$. The component A_3^1 is a glued cycle $A_3 \xrightarrow{2} A_4 \xrightarrow{3} A_5 \xrightarrow{4} A_3$. Its steady state is $c_3 = c_3^1 k_{35}/k_{43}$, $c_4 = c_3^1 k_{35}/k_{54}$ and $c_5 = c_3^1(1 - k_{35}/k_{43} - k_{35}/k_{54})$.

Let us construct an acyclic system that approximates relaxation of Equation (50) under the same assumption (1) $k_{32} > k_{23}^1$. The final auxiliary system after gluing cycles is $A_1 \xrightarrow{1} A_2 \xrightarrow{6} A_3^1 \xrightarrow{?} A_2$. Let us delete the limiting reaction $A_3^1 \xrightarrow{?} A_2$ from the cycle. We get an acyclic system $A_1 \xrightarrow{1} A_2 \xrightarrow{6} A_3^1$. The component A_3^1 is the glued cycle $A_3 \xrightarrow{2} A_4 \xrightarrow{3} A_5 \xrightarrow{4} A_3$. Let us restore this cycle and delete the limiting reaction $A_5 \xrightarrow{4} A_3$. We get an acyclic system $A_1 \xrightarrow{1} A_2 \xrightarrow{6} A_3 \xrightarrow{2} A_4 \xrightarrow{3} A_5$. Relaxation of this system approximates relaxation of the initial network (50) under additional condition $k_{32} > k_{23}^1$.

(2) Let as assume now that $k_{32} < k_{23}^1$. In this case, the steady state of the cycle $A_2 \xrightarrow{6} A_3^1 \xrightarrow{?} A_2$ is (according to Equation (13)) $c_2 = b(1 - k_{32}/k_{23}^1)$ and $c_3^1 = bk_{32}/k_{23}^1$. The further analysis is the same as it was above: $c_3 = c_3^1 k_{35}/k_{43}$, $c_4 = c_3^1 k_{35}/k_{54}$ and $c_5 = c_3^1(1 - k_{35}/k_{43} - k_{35}/k_{54})$ (with another c_3^1).

Let us construct an acyclic system that approximates relaxation of Equation (50) under assumption (2) $k_{32} < k_{23}^1$. The final auxiliary system after gluing cycles is the same, $A_1 \xrightarrow{1} A_2 \xrightarrow{6} A_3^1 \xrightarrow{?} A_2$, but the limiting step in the cycle is different, $A_2 \xrightarrow{6} A_3^1$. After cutting this step, we get acyclic system $A_1 \xrightarrow{1} A_2 \xleftarrow{?} A_3^1$, where the last reaction has rate constant k_{23}^1.

The component A_3^1 is the glued cycle

$$A_3 \xrightarrow{2} A_4 \xrightarrow{3} A_5 \xrightarrow{4} A_3$$

Let us restore this cycle and delete the limiting reaction $A_5 \xrightarrow{4} A_3$. The connection from glued cycle $A_3^1 \xrightarrow{?} A_2$ with constant k_{23}^1 transforms into connection $A_5 \xrightarrow{?} A_2$ with the same constant k_{23}^1.

We get the acyclic system:

$$A_1 \xrightarrow{1} A_2, A_3 \xrightarrow{2} A_4 \xrightarrow{3} A_5 \xrightarrow{?} A_2$$

The order of constants is now known: $k_{21} > k_{43} > k_{54} > k_{23}^1$, and we can substitute the sign "?" by "4": $A_3 \xrightarrow{2} A_4 \xrightarrow{3} A_5 \xrightarrow{4} A_2$.

For both cases, $k_{32} > k_{23}^1 (k_{23}^1 = k_{24}k_{35}/k_{54})$ and $k_{32} < k_{23}^1$ it is easy to find the eigenvectors explicitly and to write the solution to the kinetic equations in explicit form.

4.3 The general case: cycles surgery for auxiliary discrete dynamical system with arbitrary family of attractors

In this subsection, we summarize results of relaxation analysis and describe the algorithm of approximation of steady state and relaxation process for arbitrary reaction network with well-separated constants.

4.3.1 Hierarchy of cycles gluing

Let us consider a reaction network $\mathcal{W}$ with a given structure and fixed ordering of constants. The set of vertices of $\mathcal{W}$ is $\mathcal{A}$ and the set of elementary reactions is $\mathcal{R}$. Each reaction from $\mathcal{R}$ has the form $A_i \to A_j$, $A_i, A_j \in \mathcal{A}$. The correspondent constant is k_{ji}. For each $A_i \in \mathcal{A}$ we define $\kappa_i = \max_j\{k_{ji}\}$ and $\phi(i) = \arg\max_j\{k_{ji}\}$. In addition, $\phi(i) = i$ if $k_{ji} = 0$ for all j.

The auxiliary discrete dynamical system for the reaction network $\mathcal{W}$ is the dynamical system $\Phi = \Phi_{\mathcal{W}}$ defined by the map ϕ on the set $\mathcal{A}$. Auxiliary reaction network $\mathcal{V} = \mathcal{V}_{\mathcal{W}}$ has the same set of vertices $\mathcal{A}$ and the set of reactions $A_i \to A_{\phi(i)}$ with reaction constants κ_i. Auxiliary kinetics is described by $\dot{c} = \tilde{K}c$, where $\tilde{K}_{ij} = -\kappa_j \delta_{ij} + \kappa_j \delta_{i\phi(j)}$.

Every fixed point of $\Phi_{\mathcal{W}}$ is also a sink for the reaction network $\mathcal{W}$. If all attractors of the system $\Phi_{\mathcal{W}}$ are fixed points $A_{f1}, A_{f2}, \ldots \in \mathcal{A}$ then the set of stationary distributions for the initial kinetics as well as for the auxiliary kinetics is the set of distributions concentrated the set of fixed points $\{A_{f1}, A_{f2}, \ldots\}$. In this case, the auxiliary reaction network is acyclic, and the auxiliary kinetics approximates relaxation of the whole network $\mathcal{W}$.

In general case, let the system $\Phi_{\mathcal{W}}$ have several attractors that are not fixed points, but cycles $C_1, C_2, \ldots$ with periods $\tau_1, \tau_2, \ldots > 1$. By gluing these cycles in points, we transform the reaction network $\mathcal{W}$ into $\mathcal{W}^1$. The dynamical system $\Phi_{\mathcal{W}}$ is transformed into Φ^1. For these new system and network, the connection $\Phi^1 = \Phi_{\mathcal{W}^1}$ persists: Φ^1 is the auxiliary discrete dynamical system for $\mathcal{W}^1$.

For each cycle, C_i, we introduce a new vertex A^i. The new set of vertices, $\mathcal{A}^1 = \mathcal{A} \cup \{A^1, A^2, ...\} \setminus (\cup_i C_i)$ (we delete cycles C_i and add vertices A^i).

All the reaction between $A \to B (A, B \in \mathscr{A})$ can be separated into 5 groups:

(i) both $A, B \notin \cup_i C_i$;
(ii) $A \notin \cup_i C_i$, but $B \in C_i$;
(iii) $A \in C_i$, but $B \notin \cup_i C_i$;
(iv) $A \in C_i$, $B \in C_j$, $i \neq j$;
(v) $A, B \in C_i$.

Reactions from the first group do not change. Reaction from the second group transforms into $A \to A^i$ (to the whole glued cycle) with the same constant. Reaction of the third type changes into $A^i \to B$ with the rate constant renormalization (46): let the cycle C^i be the following sequence of reactions $A_1 \to A_2 \to \dots A_{\tau_i} \to A_1$, and the reaction rate constant for $A_i \to A_{i+1}$ is k_i (k_{τ_i} for $A_{\tau_i} \to A_1$). For the limiting reaction of the cycle C_i we use notation $k_{\lim\, i}$. If $A = A_j$ and k is the rate reaction for $A \to B$, then the new reaction $A^i \to B$ has the rate constant $kk_{\lim\, i}/k_j$. This corresponds to a quasi-stationary distribution on the cycle (13). It is obvious that the new rate constant is smaller than the initial one: $kk_{\lim\, i}/k_j < k$, because $k_{\lim\, i} < k_j$ due to definition of limiting constant. The same constant renormalization is necessary for reactions of the fourth type. These reactions transform into $A^i \to A^j$. Finally, reactions of the fifth type vanish.

After we glue all the cycles of auxiliary dynamical system in the reaction network $\mathscr{W}$, we get $\mathscr{W}^1$. Strictly speaking, the whole network $\mathscr{W}^1$ is not necessary, and in efficient realization of the algorithm for large networks the computation could be significantly reduced. What we need, is the correspondent auxiliary dynamical system $\Phi^1 = \Phi_{\mathscr{W}^1}$ with auxiliary kinetics.

To find the auxiliary kinetic system, we should glue all cycles in the first auxiliary system, and then add several reactions: for each A^i it is necessary to find in $\mathscr{W}^1$ the reaction of the form $A^i \to B$ with maximal constant and add this reaction to the auxiliary network. If there is no reaction of the form $A^i \to B$ for given i then the point A^i is the fixed point for $\mathscr{W}^1$ and vertices of the cycle C_i form a sink for the initial network.

After that, we decompose the new auxiliary dynamical system, find cycles and repeat gluing. Terminate when all attractors of the auxiliary dynamical system Φ^m become fixed points.

4.3.2 Reconstruction of steady states

After this termination, we can find all steady-state distributions by restoring cycles in the auxiliary reaction network $\mathscr{V}^m$. Let $A^m_{f1}, A^m_{f2}, \dots$ be fixed points of Φ^m. The set of steady states for $\mathscr{V}^m$ is the set of all distributions on the set of fixed points $\{A^m_{f1}, A^m_{f2}, \dots\}$. Let us take one of these distributions, $c = (c^m_{f1}, c^m_{f2}, \dots)$ (we mark the concentrations by the same indexes as the vertex has; other $c_i = 0$).

To make a step of cycle restoration we select those vertexes A^m_{fi} that are glued cycles and substitute them in the list $A^m_{f1}, A^m_{f2}, \dots$ by all the vertices of these cycles. For each of those cycles we find the limiting rate constant and redistribute the concentration c^m_{fi} between the vertices of the correspondent cycle by the rule (13) (with $b = c^m_{fi}$). As a result, we get a set of vertices and a distribution on this set of vertices. If among these vertices there are glued cycles, then we repeat the procedure of cycle restoration. Terminate when there is no glued cycles in the support of the distribution. The resulting distribution is the approximation to a steady state of $\mathcal{W}$, and all steady states for $\mathcal{W}$ can be approximated by this method.

To construct the approximation to the basis of stationary distributions of $\mathcal{W}$, it is sufficient to apply the described algorithm to distributions concentrated on a single fixed point A^m_{fi}, $c^m_{fj} = \delta_{ij}$, for every i.

The steady-state approximation on the base of the rule (13) is a linear function of the restored-and-cut cycles rate-limiting constants. It is the first-order approximation.

The zero-order approximation also makes sense. For one cycle gives Equation (14): all the concentration is collected at the start of the limiting step. The algorithm for the zero-order approximation is even simpler than for the first order. Let us start from the distributions concentrated on a single fixed point A^m_{fi}, $c^m_{fj} = \delta_{ij}$ for some i. If this point is a glued cycle then restore that cycle, and find the limiting step. The new distribution is concentrated at the starting vertex of that step. If this vertex is a glued cycle, then repeat. If it is not then terminate. As a result we get a distribution concentrated in one vertex of $\mathcal{A}$.

4.3.3 Dominant kinetic system for approximation of relaxation

To construct an approximation to the relaxation process in the reaction network $\mathcal{W}$, we also need to restore cycles, but for this purpose we should start from the whole glued network $\mathcal{V}^m$ on $\mathcal{A}^m$ (not only from fixed points as we did for the steady-state approximation). On a step back, from the set $\mathcal{A}^m$ to $\mathcal{A}^{m-1}$ and so on some of glued cycles should be restored and cut. On each step we build an acyclic reaction network, the final network is defined on the initial vertex set and approximates relaxation of $\mathcal{W}$.

To make one step back from $\mathcal{V}^m$ let us select the vertices of $\mathcal{A}^m$ that are glued cycles from $\mathcal{V}^{m-1}$. Let these vertices be $A^m_1, A^m_2, \ldots$ Each A^m_i corresponds to a glued cycle from $\mathcal{V}^{m-1}$, $A^{m-1}_{i1} \to A^{m-1}_{i2} \to \ldots A^{m-1}_{i\tau_i} \to A^{m-1}_{i1}$, of the length τ_i. We assume that the limiting steps in these cycles are $A^{m-1}_{i\tau_i} \to A^{m-1}_{i1}$. Let us substitute each vertex A^m_i in $\mathcal{V}^m$ by τ_i vertices $A^{m-1}_{i1}, A^{m-1}_{i2}, \ldots, A^{m-1}_{i\tau_i}$ and add to $\mathcal{V}^m$ reactions $A^{m-1}_{i1} \to A^{m-1}_{i2} \to \ldots A^{m-1}_{i\tau_i}$ (that are the cycle reactions without the limiting step) with correspondent constants from $\mathcal{V}^{m-1}$.

If there exists an outgoing reaction $A^m_i \to B$ in $\mathcal{V}^m$ then we substitute it by the reaction $A^{m-1}_{i\tau_i} \to B$ with the same constant, i.e. outgoing reactions $A^m_i \to \ldots$ are reattached to the heads of the limiting steps. Let us rearrange reactions from $\mathcal{V}^m$ of the form $B \to A^m_i$. These reactions have prototypes in $\mathcal{V}^{m-1}$ (before the last gluing). We simply restore these reactions. If there exists a reaction $A^m_i \to A^m_j$ then we find the prototype in $\mathcal{V}^{m-1}$, $A \to B$ and substitute the reaction by $A^{m-1}_{i\tau_i} \to B$ with the same constant, as for $A^m_i \to A^m_j$.

After that step is performed, the vertices set is $\mathcal{A}^{m-1}$, but the reaction set differs from the reactions of the network $\mathcal{V}^{m-1}$: the limiting steps of cycles are excluded and the outgoing reactions of glued cycles are included (reattached to the heads of the limiting steps). To make the next step, we select vertices of $\mathcal{A}^{m-1}$ that are glued cycles from $\mathcal{V}^{m-2}$, substitute these vertices by vertices of cycles, delete the limiting steps, attach outgoing reactions to the heads of the limiting steps, and for incoming reactions restore their prototypes from $\mathcal{V}^{m-2}$ and so on.

After all, we restore all the glued cycles, and construct an acyclic reaction network on the set $\mathcal{A}$. This acyclic network approximates relaxation of the network $\mathcal{W}$. We call this system the dominant system of $\mathcal{W}$ and use notation dom mod ($\mathcal{W}$).

4.4 Example: a prism of reactions

Let us demonstrate work of the algorithm on a typical example, a prism of reaction that consists of two connected cycles (Figures 2 and 3). Such systems appear in many areas of biophysics and biochemistry (see, e.g. the paper of Kurzynski, 1998).

For the first example we use the reaction rate constants ordering presented in Figure 2a. For this ordering, the auxiliary dynamical system consists of two cycles (Figure 2b) with the limiting constants k_{54} and k_{32}, correspondingly. These cycles are connected by four reactions (Figure 2c). We glue the cycles into new components A_1^1 and A_2^1 (Figure 2d), and the reaction network is transformed into $A_1^1 \leftrightarrow A_2^1$. Following the general rule ($k^1 = kk_{\lim}/k_j$), we determine the rate constants: for reaction $A_1^1 \to A_2^1$

$$k_{21}^1 = \max\{k_{41}k_{32}/k_{21},\ k_{52},\ k_{63}k_{32}/k_{13}\}$$

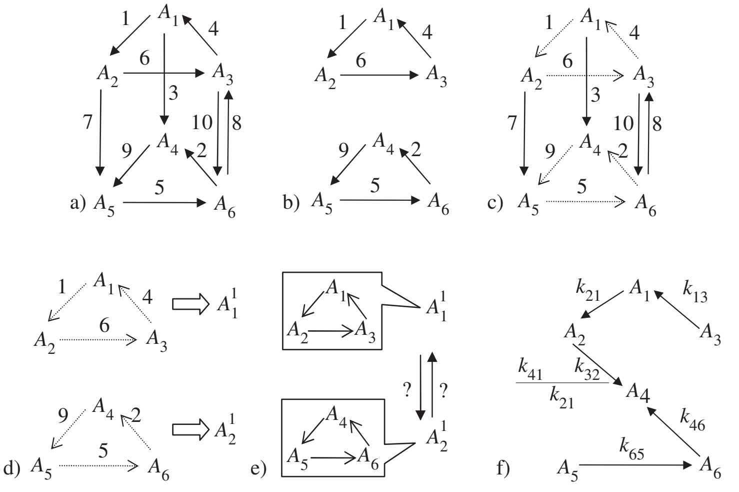

Figure 2 Gluing of cycles for the prism of reactions with a given ordering of rate constants in the case of two attractors in the auxiliary dynamical system: (a) initial reaction network, (b) auxiliary dynamical system that consists of two cycles, (c) connection between cycles, (d) gluing cycles into new components, (e) network $\mathcal{W}^1$ with glued vertices and (f) an example of dominant system in the case when $k_{21}^1 = k_{41}k_{32}/k_{21}$ and $k_{21}^1 > k_{12}^1$ (by definition, $k_{21}^1 = \max\{k_{41}k_{32}/k_{21}, k_{52}, k_{63}k_{32}/k_{13}\}$ and $k_{12}^1 = k_{36}k_{54}/k_{46}$), the order of constants in the dominant system is: $k_{21} > k_{46} > k_{13} > k_{65} > k_{41}k_{32}/k_{21}$.

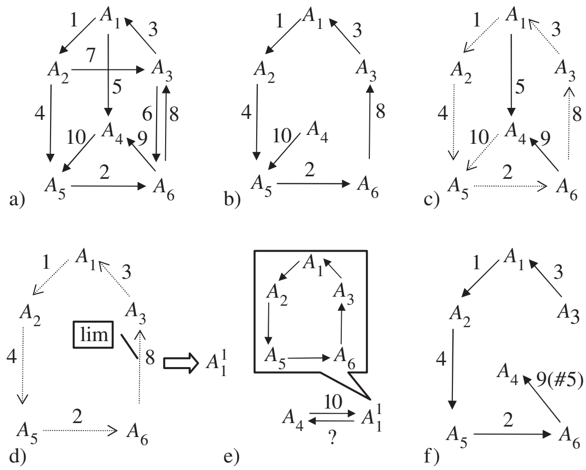

Figure 3 Gluing of a cycle for the prism of reactions with a given ordering of rate constants in the case of one attractors in the auxiliary dynamical system: (a) initial reaction network, (b) auxiliary dynamical system that has one attractor, (c) outgoing reactions from a cycle, (d) gluing of a cycle into new component, (e) network $\mathcal{W}^1$ with glued vertices and (f) an example of dominant system in the case when $k^1 = k_{46}$, and, therefore $k^1 > k_{54}$ (by definition, $k^1 = \max\{k_{41}k_{36}/k_{21}, k_{46}\}$); this dominant system is a linear chain that consists of some reactions from the initial system (no nontrivial monomials among constants). Only one reaction rate constant has in the dominant system new number (number 5 instead of 9).

and for reaction $A_2^1 \to A_1^1$

$$k_{12}^1 = k_{36}k_{54}/k_{46}$$

There are six possible orderings of the constant combinations: three possibilities for the choice of k_{21}^1 and for each such a choice there exist two possibilities: $k_{21}^1 > k_{12}^1$ or $k_{21}^1 < k_{12}^1$.

The zero-order approximation of the steady state depends only on the sign of inequality between k_{21}^1 and k_{12}^1. If $k_{21}^1 \gg k_{12}^1$ then almost all concentration in the steady state is accumulated inside A_2^1. After restoring the cycle $A_4 \to A_5 \to A_6 \to A_4$ we find that in the steady state almost all concentration is accumulated in A_4 (the component at the beginning of the limiting step of this cycle, $A_4 \to A_5$). Finally, the eigenvector for zero eigenvalue is estimated as the vector column with coordinates (0,0,0,1,0,0).

If, inverse, $k_{21}^1 \ll k_{12}^1$ then almost all concentration in the steady state is accumulated inside A_1^1. After restoring the cycle $A_1 \to A_2 \to A_3 \to A_1$ we find that in the steady state almost all concentration is accumulated in A_2 (the component at the beginning of the limiting step of this cycle, $A_2 \to A_3$). Finally, the eigenvector for zero eigenvalue is estimated as the vector column with coordinates (0,1,0,0,0,0).

Let us find the first-order (in rate limiting constants) approximation to the steady states. If $k_{21}^1 \gg k_{12}^1$ then k_{12}^1 is the rate-limiting constant for the cycle $A_1^1 \leftrightarrow A_2^1$ and almost all concentration in the steady state is accumulated inside $A_2^1 : c_2^1 \approx 1 - k_{12}^1/k_{21}^1$ and $c_1^1 \approx k_{12}^1/k_{21}^1$. Let us restore the glued cycles (Figure 2). In the upper cycle the rate-limiting constant is k_{32}, hence, in steady state almost all concentration of the upper cycle, c_1^1, is accumulated in $A_2 : c_2 \approx c_1^1(1 - k_{32}/k_{13} - k_{32}/k_{21})$, $c_3 \approx c_1^1 k_{32}/k_{13}$ and $c_1 \approx c_1^1 k_{32}/k_{21}$. In the bottom cycle the rate-limiting constant is k_{54}, hence, $c_4 \approx c_2^1(1 - k_{54}/k_{65} - k_{54}/k_{46})$, $c_5 \approx c_2^1 k_{54}/k_{65}$ and $c_6 \approx c_2^1 k_{54}/k_{46}$.

If, inverse, $k_{21}^1 \ll k_{12}^1$ then k_{21}^1 is the rate-limiting constant for the cycle $A_1^1 \leftrightarrow A_2^1$ and almost all concentration in the steady state is accumulated inside $A_1^1 : c_1^1 \approx 1 - k_{21}^1/k_{12}^1$ and $c_2^1 \approx k_{21}^1/k_{12}^1$. For distributions of concentrations in the upper and lower cycles only the prefactors c_1^1 and c_2^1 change their values.

For analysis of relaxation, let us analyze one of the six particular cases separately.

1. $k_{21}^1 = k_{41}k_{32}/k_{21}$ and $k_{21}^1 > k_{12}^1$

In this case, the finite acyclic auxiliary dynamical system, $\Phi^m = \Phi^1$, is $A_1^1 \to A_2^1$ with reaction rate constant $k_{21}^1 = k_{41}k_{32}/k_{21}$, and $\mathcal{W}^1$ is $A_1^1 \leftrightarrow A_2^1$. We restore both cycles and delete the limiting reactions $A_2 \to A_3$ and $A_4 \to A_5$. This is the common step for all cases. Following the general procedure, we substitute the reaction $A_1^1 \to A_2^1$ by $A_2 \to A_4$ with the rate constant $k_{21}^1 = k_{41}k_{32}/k_{21}$ (because A_2 is the head of the limiting step for the cycle $A_1 \to A_2 \to A_3 \to A_1$, and the prototype of the reaction $A_1^1 \to A_2^1$ is in that case $A_1 \to A_4$.

We find the dominant system for relaxation description: reactions $A_3 \to A_1 \to A_2$ and $A_5 \to A_6 \to A_4$ with original constants, and reaction $A_2 \to A_4$ with the rate constant $k_{21}^1 = k_{41}k_{32}/k_{21}$.

This dominant system graph is acyclic and, moreover, represents a discrete dynamical system, as it should be (not more than one outgoing reaction for any component). Therefore, we can estimate the eigenvalues and eigenvectors on the base of formulas (35) and (37). It is easy to determine the order of constants because $k_{21}^1 = k_{41}k_{32}/k_{21}$: this constant is the smallest nonzero constant in the obtained acyclic system. Finally, we have the following ordering of constants: $A_3 \xrightarrow{3} A_1 \xrightarrow{1} A_2 \xrightarrow{5} A_4$ and $A_5 \xrightarrow{4} A_6 \xrightarrow{2} A_4$.

So, the eigenvalues of the prism of reaction for the given ordering are (with high accuracy, with probability close to one) $-k_{21} < -k_{46} < -k_{13} < -k_{65} < -k_{41}k_{32}/k_{21}$. The relaxation time is $\tau \approx k_{21}/(k_{41}k_{32})$.

We use the same notations as in previous sections: eigenvectors l^i and r^i correspond to the eigenvalue $-\kappa_i$, where κ_i is the reaction rate constant for the reaction $A_i \to \ldots$ The left eigenvectors l^i are:

$$
\begin{aligned}
&l^1 \approx (1,0,0,0,0,0), \;\; l^2 \approx (1,1,1,0,0,0),\\
&l^3 \approx (0,0,1,0,0,0), \;\; l^4 \approx (1,1,1,1,1,1),\\
&l^5 \approx (0,0,0,0,1,0), \;\; l^6 \approx (0,0,0,0,0,1)
\end{aligned}
\tag{51}
$$

The right eigenvectors r^i are (we represent vector columns as rows):

$$\begin{aligned} r^1 &\approx (1,-1,0,0,0,0), \;\; r^2 \approx (0,1,0,-1,0,0), \\ r^3 &\approx (0,-1,1,0,0,0), \;\; r^4 \approx (0,0,0,1,0,0), \\ r^5 &\approx (0,0,0,-1,1,0), \;\; r^6 \approx (0,0,0,-1,0,1) \end{aligned} \tag{52}$$

The vertex A_4 is the fixed point for the discrete dynamical system. There is no reaction $A_4 \to \ldots$ For convenience, we include the eigenvectors l^4 and r^4 for zero eigenvalue, $\kappa_4 = 0$. These vectors correspond to the steady state: r^4 is the steady-state vector, and the functional l^4 is the conservation law.

The correspondent approximation to the general solution of the kinetic equation for the prism of reaction (Figure 2a) is:

$$c(t) = \sum_{i=1}^{6} r^i (l^i, c(0)) \exp(-\kappa_i t) \tag{53}$$

Analysis of other five particular cases is similar. Of course, some of the eigenvectors and eigenvalues can differ.

Of course, different ordering can lead to very different approximations. For example, let us consider the same prism of reactions, but with the ordering of constants presented in Figure 3a. The auxiliary dynamical system has one cycle (Figure 3b) with the limiting constant k_{36}. This cycle is not a sink to the initial network, there are outgoing reactions from its vertices (Figure 3c). After gluing, this cycles transforms into a vertex A_1^1 (Figure 3d). The glued network, $\mathcal{W}^1$ (Figure 3e), has two vertices, A_4 and A_1^1 the rate constant for the reaction $A_4 \to A_1^1$ is k_{54}, and the rate constant for the reaction $A_1^1 \to A_4$ is $k^1 = \max\{k_{41}k_{36}/k_{21}, k_{46}\}$. Hence, there are not more than four possible versions: two possibilities for the choice of k^1 and for each such a choice there exist two possibilities: $k^1 > k_{54}$ or $k^1 < k_{54}$ (one of these four possibilities cannot be realized, because $k_{46} > k_{54}$).

Exactly as it was in the previous example, the zero-order approximation of the steady state depends only on the sign of inequality between k^1 and k_{54}. If $k^1 \ll k_{54}$ then almost all concentration in the steady state is accumulated inside A^1. After restoring the cycle $A_3 \to A_1 \to A_2 \to A_5 \to A_6 \to A_3$ we find that in the steady state almost all concentration is accumulated in A_6 (the component at the beginning of the limiting step of this cycle, $A_6 \to A_3$). The eigenvector for zero eigenvalue is estimated as the vector column with coordinates (0,0,0,0,0,1).

If $k^1 \gg k_{54}$ then almost all concentration in the steady state is accumulated inside A^4. This vertex is not a glued cycle, and immediately we find the approximate eigenvector for zero eigenvalue, the vector column with coordinates (0,0,0,1,0,0).

Let us find the first-order (in rate-limiting constants) approximation to the steady states. If $k^1 \ll k_{54}$ then k^1 is the rate-limiting constant for the cycle $A_1^1 \leftrightarrow A_4$ and almost all concentration in the steady state is accumulated inside A_1^1: $c_1^1 \approx 1 - k^1/k_{54}$ and $c_4 \approx k^1/k_{54}$. Let us restore the glued cycle (Figure 3). The limiting constant for that cycle is k_{36}, $c_6 \approx c_1^1(1 - k_{36}/k_{13} - k_{36}/k_{21} - k_{36}/k_{52} - k_{36}/k_{65})$, $c_3 \approx c_1^1 k_{36}/k_{13}$, $c_1 \approx c_1^1 k_{36}/k_{21}$, $c_2 \approx c_1^1 k_{36}/k_{52}$ and $c_5 \approx c_1^1 k_{36}/k_{65}$.

If $k^1 \gg k_{54}$ then k_{54} is the rate-limiting constant for the cycle $A_1^1 \leftrightarrow A_4$ and almost all concentration in the steady state is accumulated inside A_4: $c_4 \approx 1 - k_{54}/k^1$ and $c_1^1 \approx k_{54}/k^1$. In distribution of concentration inside the cycle only the prefactor c_1^1 changes.

Let us analyze the relaxation process for one of the possibilities: $k^1 = k_{46}$, and, therefore $k^1 > k_{54}$. We restore the cycle, delete the limiting step, transform the reaction $A_1^1 \to A_4$ into reaction $A_6 \to A_4$ with the same constant $k^1 = k_{46}$ and get the chain with ordered constants: $A_3 \xrightarrow{3} A_1 \xrightarrow{1} A_2 \xrightarrow{4} A_5 \xrightarrow{2} A_6 \xrightarrow{5} A_4$. Here the nonzero rate constants k_{ij} have the same value as for the initial system (Figure 3a). The relaxation time is $\tau \approx 1/k_{46}$. Left eigenvectors are (including l^4 for the zero eigenvalue):

$$\begin{aligned} &l^1 \approx (1,0,0,0,0,0), \;\; l^2 \approx (1,1,1,0,0,0),\\ &l^3 \approx (0,0,1,0,0,0), \;\; l^4 \approx (1,1,1,1,1,1),\\ &l^5 \approx (0,0,0,0,1,0) \;\; l^6 \approx (1,1,1,0,1,1) \end{aligned} \tag{54}$$

Right eigenvectors are (including r^4 for the zero eigenvalue):

$$\begin{aligned} &r^1 \approx (1,-1,0,0,0,0), \;\; r^2 \approx (0,1,0,0,0,-1),\\ &r^3 \approx (0,-1,1,0,0,0), \;\; r^4 \approx (0,0,0,1,0,0),\\ &r^5 \approx (0,0,0,0,1,-1), \;\; r^6 \approx (0,0,0,-1,0,1) \end{aligned} \tag{55}$$

Here we represent vector columns as rows.

For the approximation of relaxation in that order we can use Equation (53).

5. THE REVERSIBLE TRIANGLE OF REACTIONS: THE SIMPLE EXAMPLE CASE STUDY

In this section, we illustrate the analysis of dominant systems on a simple example, the reversible triangle of reactions.

$$A_1 \leftrightarrow A_2 \leftrightarrow A_3 \leftrightarrow A_1 \tag{56}$$

This triangle appeared in many works as an ideal object for a case study. Our favorite example is the work of Wei and Prater (1962). Now in our study the triangle (56) is not obligatory a closed system. We can assume that it is a subsystem of a larger system, and any reaction $A_i \to A_j$ represents a reaction of the form $\cdots + A_i \to A_j + \cdots$, where unknown but slow components are substituted by dots. This means that there are no obligatory relations between reaction rate constants, first of all, no detailed balance relations, and six reaction rate constants are arbitrary nonnegative numbers.

There exist $6! = 720$ orderings of six reaction rate constants for this triangle, but, of course, it is not necessary to consider all these orderings. First of all, because of the permutation symmetry, we can select an arbitrary reaction as the fastest one. Let the reaction rate constant k_{21} for the reaction $A_1 \to A_2$ is the largest. (If it is not, we just have to change the enumeration of reagents.)

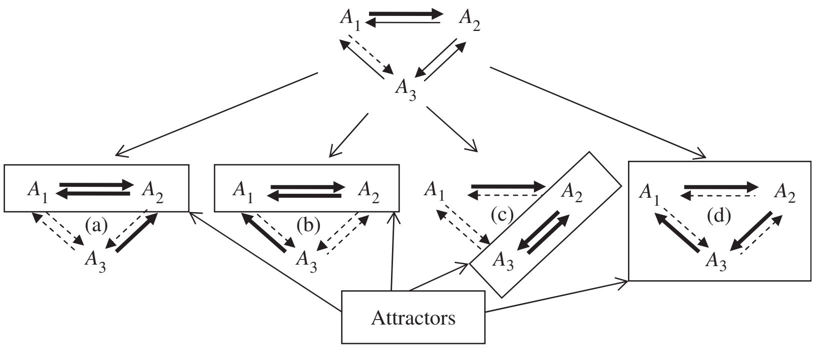

Figure 4 Four possible auxiliary dynamical systems for the reversible triangle of reactions with $k_{21} > k_{ij}$ for $(i,j) \neq (2,1)$: (a) $k_{12} > k_{32}$, $k_{23} > k_{13}$; (b) $k_{12} > k_{32}$, $k_{13} > k_{23}$; (c) $k_{32} > k_{12}$, $k_{23} > k_{13}$ and (d) $k_{32} > k_{12}$, $k_{13} > k_{23}$. For each vertex the outgoing reaction with the largest rate constant is represented by the solid bold arrow, and other reactions are represented by the dashed arrows. The digraphs formed by solid bold arrows are the auxiliary discrete dynamical systems. Attractors of these systems are isolated in frames.

First of all, let us describe all possible auxiliary dynamical systems for the triangle (56). For each vertex, we have to select the fastest outgoing reaction. For A_1, it is always $A_1 \to A_2$, because of our choice of enumeration (the higher scheme in Figure 4). There exist two choices of the fastest outgoing reaction for two other vertices and, therefore, only four versions of auxiliary dynamical systems for Equation (56) (Figure 4).

Because of the choice of enumeration, the vectors of logarithms of reaction rate constants form a convex cone in R^6 which is described by the system of inequalities $\ln k_{21} > \ln k_{ij}$, $(i,j) \neq (2,1)$. For each of the possible auxiliary systems (Figure 4) additional inequalities between constants should be valid, and we get four correspondent cones in R^6. These cones form a partitions of the initial one (we neglect intersections of faces which have zero measure). Let us discuss the typical behavior of systems from these cones separately. (Let us remind that if in a cone for some values of coefficients θ_{ij}, $\zeta_{ij} \sum_{ij} \theta_{ij} \ln k_{ij} < \sum_{ij} \zeta_{ij} \ln k_{ij}$, then, typically in this cone $\sum_{ij} \theta_{ij} \ln k_{ij} < K + \sum_{ij} \zeta_{ij} \ln k_{ij}$ for any positive K. This means that typically $\prod_{ij} k_{ij}^{\theta_{ij}} \ll \prod_{ij} k_{ij}^{\zeta_{ij}}$.)

5.1 Auxiliary system (a): $A_1 \leftrightarrow A_2 \leftarrow A_3$; $k_{12} > k_{32}$, $k_{23} > k_{13}$

5.1.1 Gluing cycles

The attractor is a cycle (with only two vertices) $A_1 \leftrightarrow A_2$. This is not a sink, because two outgoing reactions exist: $A_1 \to A_3$ and $A_2 \to A_3$. They are relatively slow: $k_{31} \ll k_{21}$ and $k_{32} \ll k_{12}$. The limiting step in this cycle is $A_2 \to A_1$ with the rate constant k_{12}. We have to glue the cycle $A_1 \leftrightarrow A_2$ into one new component A_1^1 and to add a new reaction $A_1^1 \to A_3$ with the rate constant

$$k_{31}^1 = \max\{k_{32}, \;\; k_{31}k_{12}/k_{21}\} \tag{57}$$

This is a particular case of Equations (46) and (47).

As a result, we get a new system, $A_1^1 \leftrightarrow A_3$ with reaction rate constants k_{31}^1 (for $A_1^1 \to A_3$) and initial k_{23} (for $A_1^1 \leftarrow A_3$). This cycle is a sink, because it has no outgoing reactions (the whole system is a trivial example of a sink).

5.1.2 Steady states

To find the steady state, we have to compute the stationary concentrations for the cycle $A_1^1 \leftrightarrow A_3$, c_1^1 and c_3. We use the standard normalization condition $c_1^1 + c_3 = 1$. On the base of the general formula for a simple cycle (11) we obtain:

$$w = \frac{1}{(1/k_{31}^1) + (1/k_{23})}, \quad c_1^1 = \frac{w}{k_{31}^1}, \quad c_3 = \frac{w}{k_{23}} \tag{58}$$

After that, we can calculate the concentrations of A_1 and A_2 with normalization $c_1 + c_2 = c_1^1$. Formula (11) gives:

$$w' = \frac{c_1^1}{(1/k_{21}) + (1/k_{12})}, \quad c_1 = \frac{w'}{k_{21}}, \quad c_2 = \frac{w'}{k_{12}} \tag{59}$$

We can simplify the answer using inequalities between constants, as it was done in formulas (12) and (13). For example, $(1/k_{21}) + (1/k_{21}) \approx (1/k_{21})$, because $k_{21} \gg k_{12}$. It is necessary to stress that we have used the inequalities between constants $k_{21} > k_{ij}$ for $(i,j) \neq (2,1)$, $k_{12} > k_{32}$ and $k_{23} > k_{13}$ to obtain the simple answer (58), (59), hence if we even do not use these inequalities for the further simplification, this does not guarantee the higher accuracy of formulas.

5.1.3 Eigenvalues and eigenvectors

At the next step, we have to restore and cut the cycles. First cycle to cut is the result of cycle gluing, $A_1^1 \leftrightarrow A_3$. It is necessary to delete the limiting step, i.e. the reaction with the smallest rate constant. If $k_{31}^1 > k_{23}$, then we get $A_1^1 \to A_3$. If, inverse, $k_{23} > k_{31}^1$, then we obtain $A_1^1 \leftarrow A_3$.

After that, we have to restore and cut the cycle which was glued into the vertex A_1^1. This is the two-vertices cycle $A_1 \leftrightarrow A_2$. The limiting step for this cycle is $A_1 \leftarrow A_2$, because $k_{21} \gg k_{12}$. If $k_{31}^1 > k_{23}$, then following the rule visualized by Figure 1, we get the dominant system $A_1 \to A_2 \to A_3$ with reaction rate constants k_{21} for $A_1 \to A_2$ and k_{31}^1 for $A_2 \to A_3$. If $k_{23} > k_{31}^1$ then we obtain $A_1 \to A_2 \leftarrow A_3$ with reaction rate constants k_{21} for $A_1 \to A_2$ and k_{23} for $A_2 \leftarrow A_3$. All the procedure is illustrated by Figure 5.

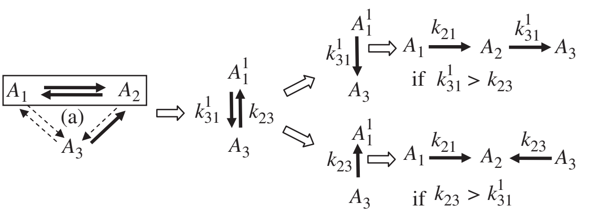

Figure 5 Dominant systems for case (a) (defined in Figure 4).

The eigenvalues and the correspondent eigenvectors for dominant systems in case (a) are represented below in zero-one asymptotic.

1. $k_{31}^1 > k_{23}$, the dominant system $A_1 \to A_2 \to A_3$,

$$\begin{aligned} &\lambda_0 = 0, && r^0 \approx (0,0,1), && l^0 = (1,1,1); \\ &\lambda_1 \approx -k_{21}, && r^1 \approx (1,-1,0), && l^1 \approx (1,0,0); \\ &\lambda_2 \approx -k_{31}^1, && r^2 \approx (0,1,-1), && l^2 \approx (1,1,0) \end{aligned} \tag{60}$$

2. $k_{23} > k_{31}^1$, the dominant system $A_1 \to A_2 \leftarrow A_3$,

$$\begin{aligned} &\lambda_0 = 0, && r^0 \approx (0,1,0), && l^0 = (1,1,1); \\ &\lambda_1 \approx -k_{21}, && r^1 \approx (1,-1,0), && l^1 \approx (1,0,0); \\ &\lambda_2 \approx -k_{23}, && r^2 \approx (0,-1,1), && l^2 \approx (0,0,1) \end{aligned} \tag{61}$$

Here, the value of k_{31}^1 is given by formula (57).

With higher accuracy, in case (a)

$$r^0 \approx \left(\frac{w'}{k_{21}}, \frac{w'}{k_{12}}, \frac{w}{k_{23}}\right) \tag{62}$$

where

$$w = \frac{1}{(1/k_{31}^1) + (1/k_{23}^1)}, \quad w' = \frac{c_1^1}{(1/k_{21}^1) + (1/k_{12}^1)}, \quad c_1^1 = \frac{w}{k_{31}^1}$$

in according to Equations (58), (59).

5.2 Auxiliary system (b): $A_3 \to A_1 \leftrightarrow A_2$; $k_{12} > k_{32}$, $k_{13} > k_{23}$

5.2.1 Gluing cycles

The attractor is a cycle $A_1 \leftrightarrow A_2$ again, and this is not a sink. We have to glue the cycle $A_1 \leftrightarrow A_2$ into one new component A_1^1 and to add a new reaction $A_1^1 \to A_3$ with the rate constant k_{31}^1 given by formula (57). As a result, we get a new system, $A_1^1 \leftrightarrow A_3$ with reaction rate constants k_{31}^1 (for $A_1^1 \to A_3$) and initial k_{13} (for $A_1^1 \leftarrow A_3$). At this stage, the only difference from the case (a) is the reaction $A_1^1 \leftarrow A_3$ rate constant k_{13} instead of k_{23}.

5.2.2 Steady states

For the steady states we have to repeat formulas (58) and (59) with minor changes (just use k_{13} instead of k_{23}):

$$\begin{aligned} &w = \frac{1}{(1/k_{31}^1) + (1/k_{13}^1)}, \quad c_1^1 = \frac{w}{k_{31}^1}, \quad c_3 = \frac{w}{k_{13}}; \\ &w' = \frac{c_1^1}{(1/k_{21}^1) + (1/k_{12}^1)}, \quad c_1 = \frac{w'}{k_{21}}, \quad c_2 = \frac{w'}{k_{12}} \end{aligned} \tag{63}$$

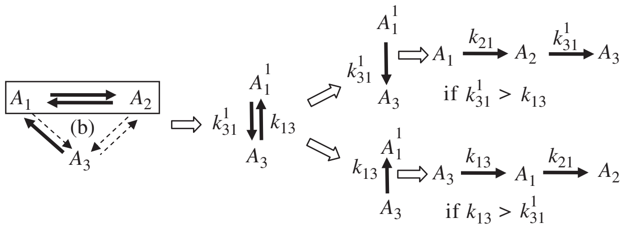

Figure 6 Dominant systems for case (b) (defined in Figure 4).

5.2.3 Eigenvalues and eigenvectors

The structure of the dominant system depends on the limiting step of the cycle $A_1^1 \leftrightarrow A_3$ (Figure 6). If $k_{31}^1 > k_{13}$, then in the dominant system remains the reaction $A_1^1 \to A_3$ from this cycle. After restoring the glued cycle $A_1 \leftrightarrow A_2$ it is necessary to delete the slowest reaction from this cycle too. This is always $A_1 \leftarrow A_2$, because $A_1 \to A_2$ is the fastest reaction. The reaction $A_1^1 \to A_3$ transforms into $A_2 \to A_3$, because A_2 is the head of the limiting step $A_1 \leftarrow A_2$ (see Figure 1). Finally, we get $A_1 \to A_2 \to A_3$.

If $k_{13} > k_{31}^1$, then in the dominant system remains the reaction $A_3 \to A_1$, and the dominant system is $A_3 \to A_1 \to A_2$ (Figure 6).

The eigenvalues and the correspondent eigenvectors for dominant systems in case (b) are represented below in zero-one asymptotic.

(i) $k_{31}^1 > k_{13}$, the dominant system $A_1 \to A_2 \to A_3$,

$$\begin{aligned} &\lambda_0 = 0, && r^0 \approx (0,0,1), && l^0 = (1,1,1); \\ &\lambda_1 \approx -k_{21}, && r^1 \approx (1,-1,0), && l^1 \approx (1,0,0); \\ &\lambda_2 \approx -k_{31}^1, && r^2 \approx (0,1,-1), && l^2 \approx (1,1,0) \end{aligned} \tag{64}$$

(ii) $k_{13} > k_{31}^1$, the dominant system $A_3 \to A_1 \to A_2$,

$$\begin{aligned} &\lambda_0 = 0, && r^0 \approx (0,1,0), && l^0 = (1,1,1); \\ &\lambda_1 \approx -k_{21}, && r^1 \approx (1,-1,0), && l^1 \approx (1,0,0); \\ &\lambda_2 \approx -k_{13}, && r^2 \approx (0,-1,1), && l^2 \approx (0,0,1) \end{aligned} \tag{65}$$

Here, the value of k_{31}^1 is given by formula (57). The only difference from case (a) is the rate constant k_{23} instead of k_{13}.

With higher accuracy, in case (b)

$$r^0 \approx \left(\frac{w'}{k_{21}}, \frac{w'}{k_{12}}, \frac{w}{k_{13}}\right) \tag{66}$$

where w and w' are given by formula (63).

5.3 Auxiliary system (c): $A_1 \to A_2 \leftrightarrow A_3$; $k_{32} > k_{12}$, $k_{23} > k_{13}$

5.3.1 Gluing cycles

The attractor is a cycle $A_2 \leftrightarrow A_3$. This is not a sink, because two outgoing reactions exist: $A_2 \to A_1$ and $A_3 \to A_1$. We have to glue the cycle $A_2 \leftrightarrow A_3$ into one new component A_2^1 and to add a new reaction $A_2^1 \to A_1$ with the rate constant k_{12}^1. The definition of this new constant depends on the normalized steady-state distribution in this cycle. If c_2^*, c_3^* are the steady-state concentrations (with normalization $c_2^* + c_3^* = 1$), then

$$k_{12}^1 \approx \max\{k_{12}c_2^*, k_{13}c_3^*\}$$

If we use limitation in the glued cycle explicitly, then we get the direct analog of Equation (57) in two versions: one for $k_{32} > k_{23}$, another for $k_{23} > k_{32}$. But we can skip this simplification and write

$$k_{12}^1 \approx \max\{k_{12}w^*/k_{32}, k_{13}w^*/k_{23}\} \tag{67}$$

where

$$w^* = \frac{1}{(1/k_{32}) + (1/k_{23})}$$

5.3.2 Steady states

Exactly as in the cases (a) and (b) we can find approximation of steady state using steady states in cycles $A_1 \leftrightarrow A_2^1$ and $A_2 \leftrightarrow A_3$:

$$\begin{aligned} w &= \frac{1}{(1/k_{12}^1) + (1/k_{21})}, \quad c_2^1 = \frac{w}{k_{12}^1}, \quad c_1 = \frac{w}{k_{21}}; \\ w' &= \frac{c_2^1}{(1/k_{32}) + (1/k_{23})}, \quad c_2 = \frac{w'}{k_{32}}, \quad c_3 = \frac{w'}{k_{23}} \end{aligned} \tag{68}$$

5.3.3 Eigenvalues and eigenvectors

The limiting step in the cycle $A_1 \leftrightarrow A_2^1$ in known, this is $A_1 \leftarrow A_2^1$. There are two possibilities for the choice on limiting step in the cycle $A_2 \leftrightarrow A_3$. If $k_{32} > k_{23}$, then this limiting step is $A_2 \leftarrow A_3$, and the dominant system is $A_1 \to A_2 \to A_3$. If $k_{23} > k_{32}$, then the dominant system is $A_1 \to A_2 \leftarrow A_3$ (Figure 7).

The eigenvalues and the correspondent eigenvectors for dominant systems in case (b) are represented below in zero-one asymptotic.

(i) $k_{32} > k_{23}$, the dominant system $A_1 \to A_2 \to A_3$,

$$\begin{aligned} \lambda_0 &= 0, & r^0 &\approx (0,0,1), & l^0 &= (1,1,1); \\ \lambda_1 &\approx -k_{21}, & r^1 &\approx (1,-1,0), & l^1 &\approx (1,0,0); \\ \lambda_2 &\approx -k_{32}, & r^2 &\approx (0,1,-1), & l^2 &\approx (1,1,0) \end{aligned} \tag{69}$$

(ii) $k_{23} > k_{32}$, the dominant system $A_1 \to A_2 \leftarrow A_3$,

$$\begin{aligned} \lambda_0 &= 0, & r^0 &\approx (0,1,0), & l^0 &= (1,1,1); \\ \lambda_1 &\approx -k_{21}, & r^1 &\approx (1,-1,0), & l^1 &\approx (1,0,0); \\ \lambda_2 &\approx -k_{23}, & r^2 &\approx (0,-1,1), & l^2 &\approx (0,0,1) \end{aligned} \tag{70}$$

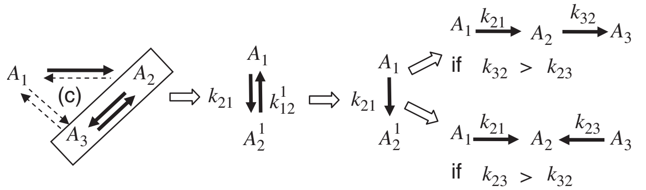

Figure 7 Dominant systems for case (c) (defined in Figure 4).

With higher accuracy the value of r^0 is given by formula of the steady-state concentrations (68).

5.4 Auxiliary system (d): $A_1 \to A_2 \to A_3 \to A_1$; $k_{32} > k_{12}$, $k_{13} > k_{23}$

This is a simple cycle. We discussed this case in details several times. To get the dominant system it is sufficient just to delete the limiting step. Everything is determined by the choice of the minimal constant in the couple $\{k_{32}, k_{13}\}$. Formulas for steady state are well known too: Equations (11)–(13).

This is not necessary to discuss all orderings of constants, because some of them are irrelevant to the final answer. For example, in this case (d) interrelations between constants k_{31}, k_{23} and k_{12} are not important.

5.5 Resume: zero-one multiscale asymptotic for the reversible reaction triangle

We found only three topologically different version of dominant systems for the reversible reaction triangle: (i) $A_1 \to A_2 \to A_3$, (ii) $A_1 \to A_2 \leftarrow A_3$ and (iii) $A_3 \to A_1 \to A_2$. Moreover, there exist only two versions of zero-one asymptotic for eigenvectors: the fastest eigenvalue is always $-k_{21}$ (because our choice of enumeration), the correspondent right and left eigenvectors (fast mode) are: $r^1 \approx (1, -1, 0)$ and $l^1 = (1, 0, 0)$. (The difference between systems (ii) and (iii) appears in the first order of the slow/fast constants ratio.)

If in the steady state (almost) all mass is concentrated in A_2 (this means that $r^0 \approx (0, 1, 0)$, dominant systems (ii) or (iii)), then $r^2 \approx (0, -1, 1)$ and $l^2 \approx (0, 0, 1)$. If in the steady state (almost) all mass is concentrated in A_3 (this means that $r^0 \approx (0, 0, 1)$, dominant system (i)), then $r^2 \approx (0, 1, -1)$ and $l^2 \approx (0, 1, 0)$. We can see that the dominant systems of the forms (ii) and (iii) produce the same zero-one asymptotic of eigenvectors. Moreover, the right eigenvectors $r^2 \approx (0, 1, -1)$ coincide for all cases (there is no difference between r^2 and $-r^2$), and the difference appears in the left eigenvector l^2. Of course, this peculiarity (everything is regulated by the steady-state asymptotic) results from the simplicity of this example.

In the zero-one asymptotic, the reversible reaction triangle is represented by one of the reaction mechanisms, (i) or (iii). The rate constant of the first reaction $A_1 \to A_2$ is always k_{12}. The direction of the second reaction is determined by a system of linear uniform inequalities between *logarithms* of rate constants. The logarithm of effective constant of this reaction is the piecewise linear function of the logarithms of reaction rate constants, and the switching between different pieces is regulated by linear inequalities. These inequalities are described in this section, and most of them are represented in Figures 4–7. One can obtain the first-order approximation of eigenvectors in the slow/fast constants ratio from the Appendix 1 formulas.

6. THREE ZERO-ONE LAWS AND NONEQUILIBRIUM PHASE TRANSITIONS IN MULTISCALE SYSTEMS

6.1 Zero-one law for steady states of weakly ergodic reaction networks

Let us take a weakly ergodic network $\mathcal{W}$ and apply the algorithms of auxiliary systems construction and cycles gluing. As a result we obtain an auxiliary dynamic system with one fixed point (there may be only one minimal sink). In the algorithm of steady-state reconstruction (Section 4.3) we always operate with one cycle (and with small auxiliary cycles inside that one, as in a simple example in Section 2.9). In a cycle with limitation almost all concentration is accumulated at the start of the limiting step (13), (14). Hence, in the whole network almost all concentration will be accumulated in one component. The dominant system for a weekly ergodic network is an acyclic network with minimal element. The minimal element is such a component $A_{\min}$ that there exists an oriented path in the dominant system from any element to $A_{\min}$. Almost all concentration in the steady state of the network $\mathcal{W}$ will be concentrated in the component $A_{\min}$.

6.2 Zero-one law for nonergodic multiscale networks

The simplest example of nonergodic but connected reaction network is $A_1 \leftarrow A_2 \rightarrow A_3$ with reaction rate constants k_1 and k_2. For this network, in addition to $b^0(c) = c_1 + c_2 + c_3$ a kinetic conservation law exist, $b^k(c) = (c_1/k_1) - (c_3/k_2)$. The result of time evolution, $\lim_{t\to\infty} \exp(Kt)c$ (30), is described by simple formula (31):

$$\lim_{t\to\infty} \exp(Kt)c = b^1(c)(1,0,0) + b^2(c)(0,1,1)$$

where $b^1(c) + b^2(c) = b^0(c)$ and $((k_1 + k_2)/k_1)b^1(c) - ((k_1 + k_2)/k_2)b^2(c) = b^k(c)$. If $k_1 \gg k_2$ then $b^1(c) \approx c_1 + c_2$ and $b^2(c) \approx c_3$. If $k_1 \ll k_2$ then $b^1(c) \approx c_1$ and $b^2(c) \approx c_2 + c_3$. This simple zero-one law (either almost all amount of A_2 transforms into A_1, or almost all amount of A_2 transforms into A_3) can be generalized onto all nonergodic multiscale systems.

Let us take a multiscale network and perform the iterative process of auxiliary dynamic systems construction and cycle gluing, as it is prescribed in Section 4.3. After the final step the algorithm gives the discrete dynamical system Φ^m with fixed points A^m_{fi}.

The fixed points A^m_{fi} of the discrete dynamical system Φ^m are the glued ergodic components $G_i \subset \mathcal{A}$ of the initial network $\mathcal{W}$. At the same time, these points are attractors of Φ^m. Let us consider the correspondent decomposition of this system with partition $\mathscr{A}^m = \cup_i Att(A^m_{fi})$. In the cycle restoration during construction of dominant system dom mod($\mathscr{W}$) this partition transforms into partition of $\mathscr{A} : \mathscr{A} = \cup_i U_i$, Att($A^m_{fi}$) transforms into U_i and $G_i \subset U_i$ (and U_i transforms into Att(A^m_{fi}) in hierarchical gluing of cycles).

It is straightforward to see that during construction of dominant systems for $\mathscr{W}$ from the network $\mathscr{V}^m$ no connection between U_i are created. Therefore, the reaction network dom mod($\mathscr{W}$) is a union of networks on sets U_i without any link between sets.

If $G_1, \ldots, G_m$ are all ergodic components of the system, then there exist m independent positive linear functionals $b^1(c), \ldots, b^m(c)$, that describe asymptotical behavior of kinetic system when $t \to \infty$ (30). For dom mod($\mathscr{W}$) these functionals are: $b^l(c) = \sum_{A \in U_l} c_A$ where c_A is concentration of A. Hence, for the initial reaction network $\mathscr{W}$ with well-separated constants

$$b^l(c) \approx \sum_{A \in U_l} c_A \tag{71}$$

This is the zero-one law for multiscale networks: for any l,i, the value of functional b^l (30) on basis vector e^i, $b^l(e^i)$, is either close to one or close to zero (with probability close to 1). We already mentioned this law in discussion of a simple example (31). The approximate equality (71) means that for each reagent $A \in \mathscr{A}$ there exists such an ergodic component G of $\mathscr{W}$ that A transforms when $t \to \infty$ preferably into elements of G even if there exist paths from A to other ergodic components of $\mathscr{W}$.

6.3 Dynamic limitation and ergodicity boundary

Dominant systems are acyclic. All the stationary rates in the first order are limited by limiting steps of some cycles. Those cycles are glued in the hierarchical cycle gluing procedure, and their limiting steps are deleted in the cycles surgery procedures (see Section 4.3 and Figure 1).

Relaxation to steady state of the network is multiexponential, and now we are interested in estimate of the longest relaxation time τ:

$$\tau = 1/\min\{-Re\lambda_i | \lambda_i \neq 0\} \tag{72}$$

Is there a constant that limits the relaxation time? The general answer for multiscale system is: $1/\tau$ is equal to the minimal reaction rate constant of the dominant system. It is impossible to guess a priori, before construction of the dominant system, which constant it is. Moreover, this may be not a rate constant for a reaction from the initial network, but a monomial of such constants.

Nevertheless, sometimes it is possible to point the reaction rate constant that is limiting for the relaxation in the following sense. For known topology of reaction network and given ordering of reaction rate constants we find such a constant (ergodicity boundary) k_τ that

$$\tau \approx \frac{1}{a k_\tau} \tag{73}$$

with $a \lesssim 1$ is a function of constants $k_j > k_\tau$. This means that $1/k_\tau$ gives the lower estimate of the relaxation time, but τ could be larger. In addition, we show that there is a zero-one alternative too: if the constants are well separated then either $a \approx 1$ or $a \ll 1$.

We study a multiscale system with a given reaction rate constants ordering, $k_{j_1} > k_{j_2} > \cdots > k_{j_n}$. Let us suppose that the network is weakly ergodic (when there are several ergodic components, each one has its longest relaxation time that can be found independently). We say that k_{j_r}, $1 \leqslant r \leqslant n$ is the *ergodicity boundary* k_τ if the network of reactions with parameters $k_{j_1}, k_{j_2}, \ldots, k_{j_r}$ (when $k_{j_{r+1}} = \ldots k_{j_n} = 0$) is weakly ergodic, but the network with parameters $k_{j_1}, k_{j_2}, \ldots, k_{j_r - 1}$ (when $k_{j_r} = k_{j_{r+1}} = \ldots k_{j_n} = 0$) it is not. In other words, when eliminating reactions in decreasing order of their characteristic times, starting with the slowest one, the ergodicity boundary is the constant of the first reaction whose elimination breaks the ergodicity of the reaction digraph. This reaction we also call the "ergodicity boundary".

Let us describe the possible location of the ergodicity boundary in the general multiscale reaction network ($\mathscr{W}$). After deletion of reactions with constants $k_{j_r}, k_{j_{r+1}}, \ldots, k_{j_n}$ from the network two ergodic components (minimal sinks) appear, G_1 and G_2. The ergodicity boundary starts in one of the ergodic components, say G_1, and ends at the such a reagent B that another ergodic component, G_2, is reachable by B (there exists an oriented path from B to some element of G_2).

An estimate of the longest relaxation time can be obtained by applying the perturbation theory for linear operators to the degenerated case of the zero eigenvalue of the matrix K. We have $K = K_{<r}(k_{j_1}, k_{j_2}, \ldots, k_{j_r - 1}) + k_{j_r} Q + o(k_r)$, where $K_{<r}$ is obtained from K by letting $k_r = k_{r+1} = \ldots k_n = 0$, Q is a constant matrix of rank 1, and $o(k_r)$ includes terms that are negligible relative to k_r. The zero eigenvalue is twice degenerate in $K_{<r}$ and not degenerate in $K_{<r} + k_r Q$. One gets the following estimate:

$$\bar{a}\frac{1}{k_\tau} \geq \tau \geq \underline{a}\frac{1}{k_\tau} \tag{74}$$

where $\bar{a}$ and $\underline{a} > 0$ are some positive functions of $k_1, k_2, \ldots, k_{r-1}$ (and of the reaction graph topology).

Two simplest examples demonstrate two types of dependencies of τ on k_τ:

(i) For the reaction mechanism Figure 8a

$$\min_{\lambda \neq 0}\{-Re\lambda\} = \varepsilon$$

if $\varepsilon < k_1 + k_2$.

(ii) For the reaction mechanism Figure 8b

$$\min_{\lambda \neq 0}\{-Re\lambda\} = \varepsilon k_2/(k_1 + k_2) + o(\varepsilon)$$

if $\varepsilon < k_1 + k_2$. For well-separated parameters there exists as a zero-one (trigger) alternative: if $k_1 \ll k_2$ then $\min_{\lambda \neq 0}\{-Re\lambda\} \approx \varepsilon$; if, inverse, $k_1 \gg k_2$ then $\min_{\lambda \neq 0}\{-Re\lambda\} = o(\varepsilon)$.

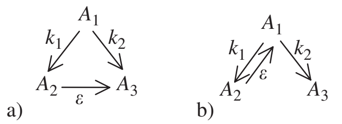

Figure 8 Two basic examples of ergodicity boundary reaction: (a) Connection between ergodic components and (b) Connection from one ergodic component to element that is connected to the both ergodic components by oriented paths. In both cases, for $\varepsilon = 0$, the ergodic components are $\{A_2\}$ and $\{A_3\}$.

In general multiscale network, two type of obstacles can violate approximate equality $\tau \approx 1/k_\tau$. Following the zero-one law for nonergodic multiscale networks (previous subsection) we can split the set of all vertices into two subsets, U_1 and U_2. The dominant reaction network dom mod($\mathscr{W}$) is a union of networks on sets $U_{1,2}$ without any link between sets.

If the ergodicity boundary reaction starts in the ergodic component G_1 and ends at B which does not belong to the "opposite" basin of attraction U_2, then $\tau \gg 1/k_\tau$. This is the first possible obstacle.

Let the ergodicity boundary reaction start at $A \in G_1$ and end at $B \in U_2$. We define the maximal linear chain of reactions in dominant system with start at B: $B \to \ldots$ This chain belongs to U_2. Let us extend this chain from the left by the ergodicity boundary: $A \to B \to \ldots$ Relaxation time for the network of r reactions (with the kinetic matrix $K_{\leq r} = K_{<r}(k_{j_1}, k_{j_2}, \ldots, k_{j_r-1}) + k_{j_r}Q$) is, approximately, the relaxation time of this chain, i.e. $1/k$, where k is the minimal constant in the chain. There may appear a monomial constant $k \ll k_\tau$. In that case, $\tau \gg 1/k_\tau$, and relaxation is limited by this minimal k or by some of constants k_{j_p}, $p > r$ or by some of their combinations. This existence of a monomial constant $k \ll k_\tau$ in the maximal chain $A \to B \to \ldots$ from the dominant system is the second possible obstacle for approximate equality $\tau \approx 1/k_\tau$.

If there is neither the first obstacle, nor the second one, then $\tau \approx 1/k_\tau$. The possibility of these obstacles depends on the definition of multiscale ensembles we use. For example for the log-uniform distribution of rate constants in the ordering cone $k_{j_1} > k_{j_2} > \cdots > k_{j_n}$ (Section 3.3) the both obstacles have nonzero probability, if they are topologically possible. However, if we study asymptotic of relaxation time at $\varepsilon \to 0$ for $k_{i_r} = \varepsilon k_{j_r-1}$ for given values of $k_{j_1}, k_{j_2}, \ldots, k_{j_r-1}$, then for sufficiently small $\varepsilon > 0$ the second obstacle is impossible.

Thus, the well-known concept of stationary reaction rates *limitation* by "narrow places" or "limiting steps" (slowest reaction) should be complemented by the *ergodicity boundary* limitation of relaxation time. It should be stressed that the relaxation process is limited not by the classical limiting steps (narrow places), but by reactions that may be absolutely different. The simplest example of this kind is an irreversible catalytic cycle: the stationary rate is limited by the slowest reaction (the smallest constant), but the relaxation time is limited by the reaction constant with the second lowest value (in order to break the weak ergodicity of a cycle two reactions must be eliminated).

6.4 Zero-one law for relaxation modes (eigenvectors) and lumping analysis

For kinetic systems with well-separated constants the left and right eigenvectors can be explicitly estimated. Their coordinates are close to ± 1 or 0. We analyzed these estimates first for linear chains and cycles (5) and then for general acyclic auxiliary dynamical systems (34), (36) (35), (37). The distribution of zeros and ± 1 in the eigenvectors components depends on the rate constant ordering and may be rather surprising. Perhaps, the simplest example gives the asymptotic equivalence (for $k_i^- \gg k_i, k_{i+1}$) of the reaction network $A_i \leftrightarrow A_{i+1} \to A_{i+2}$ with rate constants k_i, k_i^- and k_{i+1} to the reaction network $A_{i+1} \to A_i \to A_{i+2}$ with rate constants k_i^- (for the reaction $A_{i+1} \to A_i$) and $k_{i+1}k_i/k_i^-$ (for the reaction $A_i \to A_{i+2}$) presented in Section 2.9.

For reaction networks with well-separated constants coordinates of left eigenvectors l^i are close to 0 or 1. We can use the left eigenvectors for coordinate change. For the new coordinates $z_i = l^i c$ (eigenmodes) the simplest equations hold: $\dot{z}_i = \lambda_i z_i$. The zero-one law for left eigenvectors means that the eigenmodes are (almost) sums of some components: $z_i = \sum_{i \in V_i} c_i$ for some sets of numbers V_i. Many examples, Equations (6), (38), (51), (54), demonstrate that some of z_i can include the same concentrations: it may be that $V_i \cap V_j \neq \emptyset$ for some $i \neq j$. Aggregation of some components (possibly with some coefficients) into new group components for simplification of kinetics is the major task of lumping analysis.

Wei and Kuo studied conditions for exact (Wei and Kuo, 1969) and approximate (Kuo and Wei, 1969) linear lumping. More recently, sensitivity analysis and Lie group approach were applied to lumping analysis (Li and Rabitz, 1989; Toth et al., 1997), and more general nonlinear forms of lumped concentrations are used (e.g. z_i could be rational function of c). The power of lumping using a timescale-based approach was demonstrated by Whitehouse et al. (2004) and by Liao and Lightfoot (1988). This computationally cheap approach combines ideas of sensitivity analysis with simple and useful grouping of species with similar lifetimes and similar topological properties caused by connections of the species in the reaction networks. The lumped concentrations in this approach are simply sums of concentrations in groups.

Kinetics of multiscale systems studied in this chapter and developed theory of dynamic limitation demonstrates that in multiscale limit lumping analysis can work (almost) exactly. Lumped concentrations are sums in groups, but these groups can intersect and usually there exist several intersections.

6.5 Nonequilibrium phase transitions in multiscale systems

For each zero-one law specific sharp transitions exist: if two systems in a one-parametric family have different zero-one steady states or relaxation modes, then somewhere between a point of jump exists. Of course, for given finite values of parameters this will be not a point of discontinuity, but rather a thin zone of fast change. At such a point the dominant system changes. We can call this change a *nonequilibrium phase transition*. Here we identify a "multiscale nonequilibrium phase" with a dominant system.

A point of phase transition can be a point where the order of parameters changes. But not every change of order causes the change of dominant systems. However, change of order of some monomials can change the dominant system even if the order of parameters persists (examples are presented in previous section). Evolution of a parameter-dependent multiscale reaction network can be represented as a sequence of sharp change of dominant system. Between such sharp changes there are periods of evolution of dominant system parameters without qualitative changes.

7. LIMITATION IN MODULAR STRUCTURE AND SOLVABLE MODULES

7.1 Modular limitation

The simplest one-constant limitation concept cannot be applied to all systems. There is another very simple case based on exclusion of "fast equilibria" $A_i \rightleftharpoons A_j$. In this limit, the ratio of reaction constants $K_{ij} = k_{ij}/k_{ji}$ is bounded, $0 < a < K_{ij} < b < \infty$, but for different pairs (i,j), (l,s) one of the inequalities $k_{ij} \ll k_{ls}$ or $k_{ij} \gg k_{ls}$ holds. (One usually calls these K "equilibrium constant", even if there is no relevant thermodynamics.) Ray (1983) discussed that case systematically for some real examples. Of course, it is possible to create the theory for that case very similarly to the theory presented above. This should be done, but it is worth to mention now that the limitation concept can be applied to *any* modular structure of reaction network. Let for the reaction network $\mathcal{W}$ the set of elementary reactions $\mathcal{R}$ is partitioned on some modules: $\mathcal{R} = \cup_i \mathcal{R}_i$. We can consider the related multiscale ensemble of reaction constants: let the ratio of any two-rate constants inside each module be bounded (and separated from zero, of course), but the ratios between modules form a well-separated ensemble. This can be formalized by multiplication of rate constants of each module $\mathcal{R}_i$ on a timescale coefficient k_i. If we assume that $\ln k_i$ are uniformly and independently distributed on a real line (or k_i are independently and log-uniformly distributed on a sufficiently large interval) then we come to the problem of modular limitation. The problem is quite general: describe the typical behavior of multiscale ensembles for systems with given modular structure: each module has its own timescale and these time scales are well separated.

Development of such a general theory is outside the scope of our chapter, and here we just find building blocks for the future theory, *solvable reaction modules*. There may be many various criteria of selection of the reaction modules. Here are several possible choices: individual reactions (we developed the theory of multiscale ensembles of individual reactions in this chapter), couples of mutually inverse reactions, as we mentioned earlier, acyclic reaction networks, ...

Among the possible reasons for selection the class of reaction mechanisms for this purpose, there is one formal, but important: the possibility to solve the kinetic equation for every module in explicit analytical (algebraic) form with quadratures. We call these systems "solvable".

7.2 Solvable reaction mechanisms

Let us describe all solvable reaction systems (with mass action law), linear and nonlinear.

Formally, we call the set of reaction solvable, if there exists a linear transformation of coordinates $c \mapsto a$ such that kinetic equation in new coordinates for all values of reaction constants has the triangle form:

$$\frac{\mathrm{d}a_i}{\mathrm{d}t} = f_i(a_1, a_2, \ldots, a_i) \tag{75}$$

This system has the lower triangle Jacobian matrix $\partial \dot{a}_i / \partial a_j$.

To construct the general mass action law system we need: the list of components, $\mathscr{A} = \{A_1, \ldots, A_n\}$ and the list of reactions (the reaction mechanism):

$$\sum_i \alpha_{ri} A_i \to \sum_k \beta_{rk} A_k \tag{76}$$

where r is the reaction number, α_{ri} and β_{rk} nonnegative integers (stoichiometric coefficients). Formally, it is possible that all $\beta_k = 0$ or all $\alpha_i = 0$. We allow such reactions. They can appear in reduced models or in auxiliary systems.

A real variable c_i is assigned to every component A_i, c_i is the concentration of A_i and c the concentration vector with coordinates c_i. The reaction kinetic equations are

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \sum_r \gamma_r w_r(c) \tag{77}$$

where γ_r is the reaction stoichiometric vector with coordinates $\gamma_{ri} = \beta_{ri} - \alpha_{ri}$, $w_r(c)$ is the reaction rate. For mass action law,

$$w_r(c) = k_r \prod_i c_i^{\alpha_{ri}} \tag{78}$$

where k_r is the reaction constant.

Physically, equations (77) correspond to reactions in fixed volume, and in more general case a multiplier V (volume) is necessary:

$$\frac{\mathrm{d}(Vc)}{\mathrm{d}t} = V \sum_r \gamma_r w_r(c)$$

Here we study the systems (77) and postpone any further generalization.

The first example of solvable systems give the sets of reactions of the form

$$\alpha_{ri} A_i \to \sum_{k, k>i} \beta_{rk} A_k \tag{79}$$

(components A_k on the right-hand side have higher numbers k than the component A_i on the left-hand side, $i<k$). For these systems, kinetic equations (77) have the triangle form from the very beginning.

The second standard example gives the couple of mutually inverse reactions:

$$\sum_i \alpha_i A_i \leftrightharpoons \sum_k \beta_k A_k \tag{80}$$

these reactions have stoichiometric vectors $\pm\gamma$, $\gamma_i = \beta_i - \alpha_i$. The kinetic equation $\dot{c} = (w^+ - w^-)\gamma$ has the triangle form Equation (75) in any orthogonal coordinate system with the last coordinate $a_n = (\gamma, c) = \sum_i \gamma_i c_i$. Of course, if there are several reactions with proportional stoichiometric vectors, the kinetic equations have the triangle form in the same coordinate systems.

The general case of solvable systems is essentially a combination of that two Equations (79) and (80), with some generalization. Here we follow the book by Gorban et al. (1986) and present an algorithm for analysis of reaction network solvability. First, we introduce a relation between reactions "rth reaction directly affects the rate of sth reaction" with notation $r \to s$: $r \to s$ if there exists such A_i that $\gamma_{ri}\alpha_{si} \neq 0$. This means that concentration of A_i changes in the rth reaction ($\gamma_{ri} \neq 0$) and the rate of the sth reaction depends on A_i concentration ($\alpha_{si} \neq 0$). For that relation we use $r \to s$. For transitive closure of this relation we use notation $r \succcurlyeq s$ ("rth reaction affects the rate of sth reaction"): $r \succcurlyeq s$ if there exists such a sequence $s_1, s_2, \ldots, s_q$ that $r \to s_1 \to s_2 \to \ldots s_q \to s$.

The *hanging component* of the reaction network $\mathcal{W}$ is such $A_i \in \mathcal{A}$ that for all reactions $\alpha_{ri} = 0$. This means that all reaction rates do not depend on concentration of A_i. The *hanging reaction* is such element of $\mathcal{R}$ with number r that $r \succcurlyeq s$ only if $\gamma_s = \lambda\gamma_r$ for some number λ. An example of hanging components gives the last component A_n for the triangle network (79). An example of hanging reactions gives a couple of reactions (80) if they do not affect any other reaction.

To check solvability of the reaction network $\mathcal{W}$ we should find all hanging components and reactions and delete them from $\mathcal{A}$ and $\mathcal{R}$, correspondingly. After that, we get a new system, $\mathcal{W}_1$ with the component set $\mathcal{A}_1$ and the reaction set $\mathcal{R}_1$. Next, we should find all hanging components and reactions for $\mathcal{W}_1$ and delete them from $\mathcal{A}_1$ and $\mathcal{R}_1$. Iterate until no hanging components or hanging reactions could be found. If the final set of components is empty, then the reaction network $\mathcal{W}$ is solvable. If it is not empty, then $\mathcal{W}$ is not solvable.

For example, let us consider the reaction mechanism with $\mathcal{A} = \{A_1, A_2, A_3, A_4\}$ and reactions $A_1 + A_2 \to 2A_3$, $A_1 + A_2 \to A_3 + A_4$, $A_3 \to A_4$ and $A_4 \to A_3$. There are no hanging components, but two hanging reactions, $A_3 \to A_4$ and $A_4 \to A_3$. After deletion of these two reactions, two hanging components appear, A_3 and A_4. After deletion these two components, we get two hanging reactions, $A_1 + A_2 \to 0$ and $A_1 + A_2 \to 0$ (they coincide). We delete these reactions and get two components A_1 and A_2 without reactions. After deletion these hanging components we obtain the empty system. The reaction network is solvable.

An oriented cycle of the length more than two is not solvable. For each number of vertices one can calculate the set of all maximal solvable mechanisms. For example, for five components there are two maximal solvable mechanisms of monomolecular reactions:

(i) $A_1 \to A_2 \to A_4$, $A_1 \to A_4$, $A_2 \to A_3$, $A_1 \to A_3 \to A_5$, $A_1 \to A_5$, $A_4 \leftrightarrow A_5$ and
(ii) $A_1 \to A_2$, $A_1 \to A_3$, $A_1 \to A_4$, $A_1 \to A_5$, $A_2 \leftrightarrow A_3$, $A_4 \leftrightarrow A_5$.

It is straightforward to check solvability of these mechanisms. The first mechanism has a couple of hanging reactions, $A_4 \leftrightarrow A_5$. After deletion of these reactions, the system becomes acyclic, of the form Equation (79). The second mechanism has two couples of hanging reactions, $A_2 \leftrightarrow A_3$ and $A_4 \leftrightarrow A_5$. After deletion of these reactions, the system also transforms into the triangle form Equation (79). It is impossible to add any new monomolecular reactions between $\{A_1, A_2, A_3, A_4, A_5\}$ to these mechanisms with preservation of solvability, and any solvable monomolecular reaction network with five reagents is a subset of one of these mechanisms.

Finally, we should mention connections between solvable reaction networks and solvable Lie algebras (de Graaf, 2000; Jacobson, 1979). Let us remind that matrices $M_1, \ldots, M_q$ generate a solvable Lie algebra if and only if they could be transformed simultaneously into a triangle form by a change of basis.

The Jacobian matrix for the mass action law kinetic equation (77) is:

$$J = \left(\frac{\partial c_i}{\partial c_j}\right) = \sum_r w_r J_r = \sum_{rj} \frac{w_r}{c_j} M_{rj} \tag{81}$$

where

$$J_r = \gamma_r \alpha_r^\top \mathrm{diag}\left\{\frac{1}{c_1}, \frac{1}{c_2}, \ldots, \frac{1}{c_n}\right\} = \sum_j \frac{1}{c_j} M_{rj},$$
$$M_{rj} = \alpha_{rj} \gamma_r e^{j\top} \tag{82}$$

$\alpha_r^\top$ is the vector row $(\alpha_{r1}, \ldots, \alpha_{rn})$, $e^{j\top}$ the jth basis vector row with coordinates $e_k^{j\top} = \delta_{jk}$.

The Jacobian matrix (81) should have the lower triangle form in coordinates α_i (75) for all nonnegative values of rate constants and concentrations. This is equivalent to the lower triangle form of all matrices M_{rj} in these coordinates. Because usually there are many zero matrices among M_{rj}, it is convenient to describe the set of nonzero matrices.

For the rth reaction $I_r = \{i | \alpha_{ri} \neq 0\}$. The reaction rate w_r depends on c_i if and only if $i \in I_r$. For each $i = 1, \ldots, n$ we define a matrix

$$m_{ri} = \left[0, 0, \ldots, \underbrace{\gamma_r}_{i}, \ldots, 0\right]$$

The ith column of this matrix coincides with the vector column γ_r. Other columns are equal to zero. For each r we define a set of matrices $\mathscr{M}_r = \{m_{ri} | i \in I_r\}$ and $\mathscr{M} = \cup_r \mathscr{M}_r$. The reaction network $\mathscr{W}$ is solvable if and only if the finite set of matrices $\mathscr{M}$ generates a solvable Lie algebra.

Classification of finite dimensional solvable Lie algebras remains a difficult problem (de Graaf, 2000, 2005). It seems plausible that the classification of solvable algebras associated with reaction networks can bring new ideas into this field of algebra.

8. CONCLUSION: CONCEPT OF LIMIT SIMPLIFICATION IN MULTISCALE SYSTEMS

In this chapter, we study networks of linear reactions. For any ordering of reaction rate constants we look for the dominant kinetic system. The dominant system is, by definition, the system that gives us the main asymptotic terms of the stationary state and relaxation in the limit for well-separated rate constants. In this limit any two constants are connected by the relation $\gg$ or $\ll$.

The topology of dominant systems is rather simple; they are those networks which are graphs of discrete dynamical systems on the set of vertices. In such graphs each vertex has no more than one outgoing reaction. This allows us to construct the explicit asymptotics of eigenvectors and eigenvalues. In the limit of well-separated constants, the coordinates of eigenvectors for dominant systems can take only three values: ± 1 or 0. All algorithms are represented topologically by transformation of the graph of reaction (labeled by reaction rate constants). We call these transformations "cycles surgery", because the main operations are gluing cycles and cutting cycles in graphs of auxiliary discrete dynamical systems.

In the simplest case, the dominant system is determined by the ordering of constants. But for sufficiently complex systems we need to introduce auxiliary elementary reactions. They appear after cycle gluing and have monomial rate constants of the form $k_\varsigma = \prod_i k_i^{\varsigma_i}$. The dominant system depends on the place of these monomial values among the ordered constants.

Construction of the dominant system clarifies the notion of limiting steps for relaxation. There is an exponential relaxation process that lasts much longer than the others in Equations (44) and (53). This is the slowest relaxation and it is controlled by one reaction in the dominant system, the limiting step. The limiting step for relaxation is not the slowest reaction, or the second slowest reaction of the whole network, but the slowest reaction of the dominant system. That limiting step constant is not necessarily a reaction rate constant for the initial system, but can be represented by a monomial of such constants as well.

The idea of dominant subsystems in asymptotic analysis was proposed by Newton and developed by Kruskal (1963). A modern introduction with some historical review is presented by White. In our analysis we do not use the powers of small parameters (as it was done by Akian et al., 2004; Kruskal, 1963; Lidskii, 1965; Vishik and Ljusternik, 1960; White, 2006), but operate directly with the rate constants ordering.

To develop the idea of systems with well-separated constants to the state of a mathematical notion, we introduce multiscale ensembles of constant tuples. This notion allows us to discuss rigorously uniform distributions on infinite space and gives the answers to a question: what does it mean "to pick a multiscale system at random".

Some of results obtained are rather surprising and unexpected. First of all is the zero-one asymptotic of eigenvectors. Then, the good approximation to eigenvectors does not give approximate eigenvectors (the inverse situation is more common: an approximate eigenvector could be far from the eigenvector). The almost exact lumping analysis provided by the zero-one approximation of eigenvectors has an unexpected property: the lumped groups for different eigenvalues can intersect. Rather unexpected seems the change of reaction sequence when we construct the dominant systems. For example, asymptotic equivalence (for $k_i^- \gg k_i,\ k_{i+1}$) of the reaction network $A_i \leftrightarrow A_{i+1} \rightarrow A_{i+2}$ with rate constants k_i, k_i^- and k_{i+1} to the reaction network $A_{i+1} \rightarrow A_i \rightarrow A_{i+2}$ with rate constants k_i^- (for the reaction $A_{i+1} \rightarrow A_i$) and $k_{i+1}k_i/k_i^-$ (for the reaction $A_i \rightarrow A_{i+2}$) is simple, but surprising (Section 2.9). And, of course, it was surprising to observe how the dynamics of linear multiscale networks transforms into the dynamics on finite sets of reagent names.

Now we have the complete theory and the exhaustive construction of algorithms for linear reaction networks with well-separated rate constants. There are several ways of using the developed theory and algorithms:

(i) For direct computation of steady states and relaxation dynamics; this may be useful for complex systems because of the simplicity of the algorithm and resulting formulas and because often we do not know the rate constants for complex networks, and kinetics that is ruled by orderings rather than by exact values of rate constants may be very useful.
(ii) For planning of experiments and mining the experimental data — the observable kinetics is more sensitive to reactions from the dominant network, and much less sensitive to other reactions, the relaxation spectrum of the dominant network is explicitly connected with the correspondent reaction rate constants, and the eigenvectors (''modes'') are sensitive to the constant ordering, but not to exact values.
(iii) The steady states and dynamics of the dominant system could serve as a robust first approximation in perturbation theory or as a preconditioning in numerical methods.

The developed methods are computationally cheap, for example, the algorithm for construction of dominant system has linear complexity ($\sim$ number of reactions). From a practical point of view, it is attractive to use exact rational expressions for the dominant system modes (3), (34) and (36) instead of the zero-one approximation. Also, we can use exact formula (11) for irreversible cycle steady state instead of linear approximation (13). These improvements are computationally cheap and may enhance accuracy of computations.

From a theoretical point of view the outlook is more important. Let us answer the question: what has to be done, but is not done yet? Three directions for further development are clear now:

(i) Construction of dominant systems for the reaction network that has a group of constants with comparable values (without relations $\gg$ between them). We considered cycles with several comparable constants in Section 2.2, but the general theory still has to be developed.
(ii) Construction of dominant systems for reaction networks with modular structure. We can assume that the ratio of any two-rate constants inside each module be bounded and separated from zero, but the ratios between

modules form a well-separated ensemble. A reaction network that has a group of constants with comparable values gives us an example of the simplest modular structure: one module includes several reactions and other modules arise from one reaction. In Section 7.7 we describe all solvable modules such that it is possible to solve the kinetic equation for every module in explicit analytical (algebraic) form with quadratures (even for nonconstant in time reaction rate constants).

(iii) Construction of dominant systems for nonlinear reaction networks. The first idea here is the representation of a nonlinear reaction as a pseudomonomolecular reaction: if for reaction $A+B \to \ldots$ concentrations c_A and c_B are well separated, say, $c_A \gg c_B$, then we can consider this reaction as $B \to \ldots$ with rate constant dependent on c_A. The relative change of c_A is slow, and we can consider this reaction as pseudomonomolecular until the relation $c_A \gg c_B$ changes to $c_A \sim c_B$. We can assume that in the general case only for small fraction of nonlinear reactions the pseudomonomolecular approach is not applicable, and this set of genuinely nonlinear reactions changes in time, but remains small. For nonlinear systems, even the realization of the limiting step idea for steady states of a one-route mechanism of a catalytic reaction is nontrivial and was developed through the concept of kinetic polynomial (Lazman and Yablonskii, 1988).

Finally, the concept of "limit simplification" will be developed. For multiscale nonlinear reaction networks the expected dynamical behavior is to be approximated by the system of dominant networks. These networks may change in time but remain small enough.

This hypothetical picture should give an answer to a very practical question: how to describe kinetics beyond the standard quasi-steady-state and quasi-equilibrium approximations (Schnell and Maini, 2002). We guess that the answer has the following form: during almost all time almost everything could be simplified and the whole system behaves as a small one. But this picture is also nonstationary: this small system change in time. Almost always "something is very small and something is very big", but due to nonlinearity this ordering can change in time. The whole system walks along small subsystems, and constants of these small subsystems change in time under control of the whole system state. The dynamics of this walk supplements the dynamics of individual small subsystems.

The corresponding structure of fast–slow time separation in phase space is not necessarily a smooth slow invariant manifold, but may be similar to a "crazy quilt" and may consist of fragments of various dimensions that do not join smoothly or even continuously.

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APPENDIX 1. ESTIMATES OF EIGENVECTORS FOR DIAGONALLY DOMINANT MATRICES WITH DIAGONAL GAP CONDITION

The famous Gershgorin theorem gives estimates of eigenvalues. The estimates of correspondent eigenvectors are not so well-known. In the chapter we use some estimates of eigenvectors of kinetic matrices. Here we formulate and prove these estimates for general matrices. Below $A = (a_{ij})$ is a complex $n \times n$ matrix, $P_i = \sum_{j,j \neq i} |a_{ij}|$ (sums of nondiagonal elements in rows), $Q_i = \sum_{j,j \neq i} |a_{ji}|$ (sums of nondiagonal elements in columns).

Gershgorin theorem (Marcus and Minc, 1992, p. 146): The characteristic roots of A lie in the closed region G^P of the z-plane

$$G^P = \underset{i}{\cup} G_i^P \left(G_i^P = \{z \| z - a_{ii}| \leq P_i\} \right) \tag{83}$$

Analogously, the characteristic roots of A lie in the closed region G^Q of the z-plane

$$G^Q = \bigcup_i G_i^Q \left(G_i^Q \{ z || z - a_{ii}| \le Q_i \} \right) \tag{84}$$

Areas G_i^P and G_i^Q are the Gershgorin discs.

Gershgorin discs G_i^P $(i = 1, \ldots, n)$ are isolated, if $G_i^P \cap G_j^P = \varnothing$ for $i \neq j$. If discs G_i^P $(i = 1, \ldots, n)$ are isolated, then the spectrum of A is simple, and each Gershgorin disc G_i^P contains one and only one eigenvalue of A (Marcus and Minc, 1992, p. 147). The same is true for discs G_i^Q.

Below we assume that Gershgorin discs G_i^Q $(i = 1, \ldots, n)$ are isolated, this means that for all i,j

$$|a_{ii} - a_{jj}| > Q_i + Q_j \tag{85}$$

Let us introduce the following notations:

$$\frac{Q_i}{|a_{ii}|} = \varepsilon_i, \quad \frac{|a_{ij}|}{|a_{jj}|} = \chi_{ij} \left(\varepsilon_i = \sum_l \delta_{li} \right), \\ \min_j \frac{|a_{ii} - a_{jj}|}{|a_{ii}|} = g_i \tag{86}$$

Usually, we consider ε_i and χ_{ij} as sufficiently small numbers. In contrary, g_i should not be small, (this is the *gap condition*). For example, if for any two diagonal elements a_{ii} and a_{jj} either $a_{ii} \gg a_{jj}$ or $a_{ii} \ll a_{jj}$, then $g_i \gtrsim 1$ for all i.

Let $\lambda_1 \in G_1^Q$ be the eigenvalue of A $(|\lambda_1 - a_{11}| < Q_1)$. Let us estimate the correspondent right eigenvector $x^{(1)} = (x_i)$: $Ax^{(1)} = \lambda_1 x^{(1)}$. We take $x_1 = 1$ and write equations for x_i $(i \neq 1)$:

$$(a_{ii} - a_{11} - \theta_1)x_i + \sum_{j, j \neq 1, i} a_{ij} x_j = -a_{i1} \tag{87}$$

where $\theta_1 = \lambda_1 - a_{11}$, $|\theta_1| < Q_1$.

Let us introduce new variables

$$\tilde{x} = (\tilde{x}_i), \quad \tilde{x}_i = x_i(a_{ii} - a_{11}) \; (i = 2, \ldots, n)$$

In these variables,

$$\left(1 - \frac{\theta_1}{a_{ii} - a_{11}}\right)\tilde{x}_i + \sum_{j, j \neq 1, i} \frac{a_{ij}}{a_{jj} - a_{11}} \tilde{x}_j = -a_{i1} \tag{88}$$

or in matrix notations: $(1 - B)\tilde{x} = -\tilde{a}_1$, where $\tilde{a}_1$ is a vector column with coordinates a_{i1}. Because of gap condition and smallness of ε_i and χ_{ij} we can consider matrix B as a small matrix, assume that $\|B\| < 1$ and $(1-B)$ is reversible (for detailed estimate of $\|B\|$ see below).

For $\tilde{x}$ we obtain:

$$\tilde{x} = -\tilde{a}_1 - B(1 - B)^{-1}\tilde{a}_1 \tag{89}$$

and for residual estimate

$$\|B(1-B)^{-1}\tilde{a}_1\| \le \frac{\|B\|}{1-\|B\|}\|\tilde{a}_1\| \tag{90}$$

For eigenvector coordinates we get from Equation (89):

$$x_i = -\frac{a_{i1}}{a_{ii}-a_{11}} - \frac{(B(1-B)^{-1}\tilde{a}_1)_i}{a_{ii}-a_{11}} \tag{91}$$

and for residual estimate

$$\frac{|(B(1-B)^{-1}\tilde{a}_1)_i|}{|a_{ii}-a_{11}|} \le \frac{\|B\|}{1-\|B\|}\frac{\|\tilde{a}_1\|}{|a_{ii}-a_{11}|} \tag{92}$$

Let us give more detailed estimate of residual. For vectors we use l_1 norm: $\|x\| = \sum |x_i|$. The correspondent operator norm of matrix B is

$$\|B\| = \max_{|x|=1}\|Bx\| \le \sum_i \max_j |b_{ij}|$$

With the last estimate for matrix B (88) we find:

$$\begin{aligned} |b_{ii}| &\le \frac{Q_1}{|a_{ii}-a_{11}|} \le \frac{\varepsilon_1}{g_1} \le \frac{\varepsilon}{g}, \\ |b_{ij}| &= \frac{|a_{ij}|}{|a_{jj}-a_{11}|} \le \frac{\chi_{ij}}{g_j} \le \frac{\chi}{g} \ (i \neq j) \end{aligned} \tag{93}$$

where $\varepsilon = \max_i \varepsilon_i$, $\chi = \max_{i,j}\chi_{ij}$ and $g = \min_i g_i$. By definition, $\varepsilon \geqslant \chi$, and for all i,j the simple estimate holds: $|b_{ij}| \le \varepsilon/g$. Therefore, $\|Bx\| \leqslant n\varepsilon/g$ and $\|B\|/(1-\|B\|) \leqslant n\varepsilon/(g\text{-}n\varepsilon)$ (under condition $g > n\varepsilon$). Finally, $\|\tilde{a}_1\| = Q_1$ and for residual estimate we get:

$$\left| x_i + \frac{a_{i1}}{a_{ii}-a_{11}} \right| \le \frac{n\varepsilon^2}{g(g-n\varepsilon)} (i \neq 1) \tag{94}$$

More accurate estimate can be produced from inequalities (93), if it is necessary. For our goals it is sufficient to use the following consequence of Equation (94):

$$|x_i| \le \frac{\chi}{g} + \frac{n\varepsilon^2}{g(g-n\varepsilon)} (i \neq 1) \tag{95}$$

With this accuracy, eigenvectors of A coincide with standard basis vectors, i.e. with eigenvectors of diagonal part of A, $\mathrm{diag}\{a_{11}, \ldots, a_{nn}\}$.

APPENDIX 2. TIME SEPARATION AND AVERAGING IN CYCLES

In Section 2, we analyzed relaxation of a simple cycle with limitation as a perturbation of the linear chain relaxation by one more step that closes the chain into the cycle. The reaction rate constant for this perturbation is the smallest one. For this analysis we used explicit estimates (5) of the chain eginvectors for reactions with well-separated constants.

Of course, one can use estimates (34)–(37) to obtain a similar perturbation analysis for more general acyclic systems (instead of a linear chain). If we add a reaction to an acyclic system (after that a cycle may appear) and assume that the reaction rate constant for additional reaction is smaller than all other reaction constants, then the generalization is easy.

This smallness with respect to all constants is required only in a very special case when the additional reaction has a form $A_i \to A_j$ (with the rate constant k_{ji}) and there is no reaction of the form $A_i \to \ldots$ in the nonperturbed system. In Section 7 and Appendix 1 we demonstrated that if in a nonperturbed acyclic system there exists another reaction of the form $A_i \to \ldots$ with rate constant κ_i, then we need inequality $k_{ji} \ll \kappa_i$ only. This inequality allows us to get the uniform estimates of eigenvectors for all possible values of other rate constants (under the diagonally gap condition in the nonperturbed system).

For substantiation of cycle's surgery we need additional perturbation analysis for zero eigenvalues. Let us consider a simple cycle $A_1 \to A_2 \to \ldots \to A_n \to A_1$ with reaction $A_i \to \ldots$ rate constants κ_i. We add a perturbation $A_1 \to 0$ (from A_1 to nothing) with rate constant $\varepsilon\kappa_1$. Our goal is to demonstrate that the zero eigenvalue moves under this perturbation to $\lambda_0 = -\varepsilon w^*(1+\chi_w)$, the correspondent left and right eigenvectors r^0 and l^0 are $r_i^0 = c_i^*(1+\chi_{ri})$ and $l_i^0 = 1+\chi_{li}$, and χ_w, χ_{ri} and χ_{li} are uniformly small for a given sufficiently small ε under all variations of rate constants. Here, w^* is the stationary cycle reaction rate and c_i^* are stationary concentrations for a cycle (11) normalized by condition $\sum_i c_i^* = 1$. The estimate εw^* for $-\lambda_0$ is ε-small with respect to any reaction of the cycle: $w^* = \kappa_i c_i^* < \kappa_i$ for all i (because $c_i^* < 1$) and $\varepsilon w^* \ll \kappa_i$ for all i.

The kinetic equation for the perturbed system is:

$$\begin{aligned} \dot{c}_1 &= -(1+\varepsilon)\kappa_1 c_1 + \kappa_n c_n, \\ \dot{c}_i &= -\kappa_i c_i + \kappa_{i-1} c_{i-1} \ (\text{for } i \neq 1) \end{aligned} \tag{96}$$

In the matrix form we can write

$$\dot{c} = Kc = (K_0 - \varepsilon k_1 e^1 e^{1\top})c \tag{97}$$

where K_0 is the kinetic matrix for nonperturbed cycle. To estimate the right perturbed eigenvector r^0 and eigenvalue λ_0 we are looking for transformation of matrix K into the form $K = K_r - \theta r e^{1\top}$, where K is a kinetic matrix for extended reaction system with components $A_1, \ldots, A_n$, $K_r r = 0$ and $\sum_i r_i = 1$. In that case, r is the eigenvector, and $\lambda = -\theta r_1$ is the correspondent eigenvalue.

To find vector r, we add to the cycle new reactions $A_1 \to A_i$ with rate constants $\varepsilon\kappa_1 r_i$ and subtract the correspondent kinetic terms from the perturbation term $\varepsilon e^1 e^{1\top} c$. After that, we get $K = K_r - \theta r e^{1\top}$ with $\theta = \varepsilon k_1$ and

$$\begin{aligned} (K_r c)_1 &= -k_1 c_1 - \varepsilon k_1 (1-r_1) c_1 + k_n c_n, \\ (K_r c)_i &= -k_i c_i + \varepsilon k_1 r_i c_1 + k_{i-1} c_{i-1} \ \text{ for } i > 1 \end{aligned} \tag{98}$$

We have to find a positive normalized solution $r_i > 0$, $\sum_i r_i = 1$ to equation $K_r r = 0$. This is the fixed-point equation: for every positive normalized r there exists unique positive normalized steady state $c^*(r)$: $K_r c^*(r) = 0$, $c_i^* > 0$ and $\sum_i c_i^*(r) = 1$. We have to solve the equation $r = c^*(r)$. The solution exists because the Brauer fixed point theorem.

If $r = c^*(r)$ then $k_i r_i - \varepsilon k_1 r_i r_1 = k_{i-1} r_{i-1}$. We use notation $w_i^*(r)$ for the correspondent stationary reaction rate along the "nonperturbed route": $w_i^*(r) = k_i r_i$. In this notation, $w_i^*(r) - \varepsilon r_i w_1^*(r) = w_{i-1}^*(r)$. Hence, $|w_i^*(r) - w_1^*(r)| < \varepsilon w_1^*(r)$ (or $|k_i r_i - k_1 r_1| < \varepsilon k_1 r_1$). Assume $\varepsilon < 1/4$ (to provide $1-2\varepsilon < 1/(1 \pm \varepsilon) < 1+2\varepsilon$). Finally,

$$r_i = \frac{1}{k_i} \frac{1 + \chi_i}{\sum_j (1/k_j)} = (1 + \chi_i) c_i^* \tag{99}$$

where the relative errors $|\chi_i| < 3\varepsilon$ and $c_i^* = c_i^*(0)$ is the normalized steady state for the nonperturbed system. For cycles with limitation, $r_i \approx (1 + \chi_i) k_{\lim} / k_i$ with $|\chi_i| < 3\varepsilon$. For the eigenvalue we obtain

$$\begin{aligned} \lambda_0 &= -\varepsilon w_1^*(r) = -\varepsilon w_i^*(r)(1 + \varsigma_i) \\ &= -\varepsilon w^*(1 + \chi) = -\varepsilon k_i c_i^*(0)(1 + \chi) \end{aligned} \tag{100}$$

for all i, with $|\varsigma_i| < \varepsilon$ and $|\chi| < 3\varepsilon$. $|\chi| < 3\varepsilon$. Therefore, λ_0 is ε-small rate constant k_i of the nonperturbed cycle. This implies that λ_0 is ε-small with respect to the real part of every nonzero eigenvalue of the nonperturbed kinetic matrix K_0 (for given number of components n). For the cycles from multiscale ensembles these eigenvalues are typically real and close to $-k_i$ for nonlimiting rate constants, hence we proved for λ_0 even more than we need.

Let us estimate the correspondent left eigenvector l^0 (a vector row). The eigenvalue is known, hence it is easy to do just by solution of linear equations. This system of $n-1$ equations is:

$$\begin{aligned} -l_1(1 + \varepsilon)k_1 + l_2 k_1 &= \lambda_0 l_1 \\ -l_i k_i + l_{i+1} k_i &= \lambda_0 l_i,\ i = 2, \ldots, n-1 \end{aligned} \tag{101}$$

For normalization, we take $l_1 = 1$ and find:

$$l_2 = \left(\frac{\lambda_0}{k_1} + 1 + \varepsilon\right) l_1,\ \ l_{i+1} = \left(\frac{\lambda_0}{k_i} + 1\right) l_i \quad i > 2 \tag{102}$$

Formulas (99), (100) and (102) give the backgrounds for surgery of cycles with outgoing reactions. The left eigenvector gives the slow variable: if there are some incomes to the cycle, then

$$\begin{aligned} \dot{c}_1 &= -(1 + \varepsilon)\kappa_1 c_1 + \kappa_n c_n + \phi_1(t), \\ \dot{c}_i &= -\kappa_i c_i + \kappa_{i-1} c_{i-1} + \phi_i(t) \text{ (for } i \neq 1) \end{aligned} \tag{103}$$

and for slow variable $\tilde{c} = \sum l_i c_i$ we get

$$\frac{d\tilde{c}}{dt} = \lambda_0 \tilde{c} + \sum_i l_i \phi_i(t) \tag{104}$$

This is the kinetic equation for a glued cycle. In the leading term, all the outgoing reactions $A_i \to 0$ with rate constants $k = \varepsilon k_i$ give the same eigenvalue $-\varepsilon w^*$ (100).

Of course, similar results for perturbations of zero eigenvalue are valid for more general ergodic chemical reaction network with positive steady state, and not only for simple cycles, but for cycles we get simple explicit estimates, and this is enough for our goals.