Dominant systems for asymptotic analysis of reaction networks

Dynamic and static limitation in reaction networks, revisited

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Plan

1. Kinetic of linear networks
2. Idea of limitation. Simple examples
3. Model reduction before model creation:
   constant ordering versus constant values
4. Catalytic cycle with limiting step
5. Auxiliary discrete dynamic systems
6. Cycles surgery
7. Example: prism of reactions
8. Conclusion and outlook

Linear network of chemical reactions

A_i are reagents, c_i is concentration of A_i.
All the reactions are of the type $A_i \to A_j$.
$k_{ji} > 0$ is the reaction $A_i \to A_j$ rate constant.
The reaction rates: $w_{ji} = k_{ji} c_i$.

Kinetic equation

$$\dot{c}_i = \sum_{j,\, j \neq i} (k_{ij} c_j - k_{ji} c_i) \text{ or } \dot{c} = \mathbf{K} c, \qquad (1)$$

A **linear conservation law** is a linear function $b(c) = \sum_i b_i c_i$ whose value is preserved by the dynamics.

Example: $b^0 = \sum_i c_i$ is the conservation law.

A set E in concentration space is **positively invariant**, if any solution $c(t)$ that starts in E at time t_0 ($c(t_0) \in E$) belongs to E for $t > t_0$.

The **standard simplex** $\Sigma = \{c \,|\, c_i \geq 0, \sum_i c_i = 1\}$ is positively invariant.

- For all eigenvalues λ of $\mathbf{K}$ $Re\lambda \leq 0$, 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 to rotation group;

- The Jordan cell of $\mathbf{K}$ that corresponds to zero eigenvalue is diagonal – because all solutions should be bounded in Σ for positive time.

- The shift in time, operator $\exp(\mathbf{K}t)$, is a contraction in the l_1 norm for $t > 0$: for $t > 0$ and any two solutions of (1) $c(t), c'(t) \in \Sigma$

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

Pseudomonomolecular reactions

$$\underline{\mathrm{S}}_{ji} + A_i \to A_j + \underline{\mathrm{P}}_{ji}$$

$$k_{ji} = k^0_{ji}[\underline{\mathrm{S}}_{ji}],$$

where $[\underline{\mathrm{S}}_{ji}]$ is concentration of the substrate $\underline{\mathrm{S}}_{ji}$,

$$[\underline{\mathrm{S}}_{ji}] \gg c_i$$

For example, the Michaelis-Menten system:

$$\underline{\mathrm{S}} + \mathrm{E} \to \mathrm{SE} \to \mathrm{E} + \underline{\mathrm{P}}$$

$$\ldots + \mathrm{E} \to \mathrm{SE} \to \mathrm{E} + \ldots$$

$$\mathrm{E} \to \mathrm{SE} \to \mathrm{E}$$

LIMITING STEP

Linear chain of reactions $A_1 \to A_2 \to ...A_n$ with reaction rate constants k_i (for $A_i \to A_{i+1}$)

Let k_q be the smallest constant: $k_q \ll k_i$ $(i \neq q)$
In time scale $\sim 1/k_q$:
$A_1, ...A_{q-1}$ transform fast into A_q,
$A_{q+1}, ...A_{n-1}$ transform fast into A_n,
only two components, A_q and A_n, are present,
the whole chain behaves as a single reaction $A_q \xrightarrow{k_q} A_n$

“Vox populi, vox Dei”

Google gave on 31st December 2006:

- for “quasi-equilibrium” – 301000 links;
- for “quasi steady state” 347000 and for “pseudo steady state” 76200, 423000 together;
- for “slow manifold” 29800 only, and for “invariant manifold” 98100;
- for “singular perturbation” 361000 links;
- for “model reduction” even more, 373000;
- but for “limiting step” – 714000!

To find constants we need to operate with *simple models*.

We need to simplify the *unknown model*.

We have some hypothesis about the network structure

Usually, something is big, and something is small enough, we can guess the constant *ordering* ($I = (i, j)$):

$$k_{I_1} \ll k_{I_2} \ll k_{I_3} \ll ...$$

Irreversible Cycle $A_1 \to A_2 \to \ldots A_n \to A_1$
with reaction rate constants k_i (for $A_i \to ...$)

Limiting step $A_n \to A_1$
with reaction rate constant $k_n \ll k_i$ $(i < n)$

The elementary reaction rate: $w_i = k_i c_i$

The kinetic equation: $\dot{c}_i = w_{i-1} - w_i$ $(w_0 = w_n)$

In the stationary state all the w_i are equal: $w_i = w$.

Static limitation in a cycle

$w = \frac{b}{\frac{1}{k_1}+\cdots\frac{1}{k_n}}$, where $b = \sum_i c_i$

If $k_n \ll k_i$ $(i < n)$ then

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

Dynamic limitation in a cycle, eigenvalues

If k_n/k_i is small for all $i < n$, then the kinetic matrix has one simple zero eigenvalue that corresponds to the conservation law $\sum c_i = b$ and $n-1$ nonzero eigenvalues

$$\lambda_i = -k_i + \delta_i \ (i < n),$$

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

Dynamic limitation in a cycle, eigenvectors:

$l^i\mathbf{K} = \lambda_i l^i$; $\mathbf{K}r^i = \lambda_i r^i$; $(l^i, r^j) = \delta_{ij}$: for $m > 0$

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

$$l^i_{i-m} \approx \prod_{j=1}^{m} \frac{k_{i-j}}{k_{i-j} - k_i};$$

$l^i_i = r^i_i = 1$ and $r^i_{i-m} = l^i_{i+m} = 0$.

If $k_{i_1} \gg k_{i_2} \gg ... \gg k_{i_n} = k_n$ then

$$r^i_{i+m} \approx 1, -1, \text{ or } 0; \quad l^i_{j-m} \approx 1, \text{ or } 0$$

The main goal

For arbitrary reaction network with well separated constants

$$k_{I_1} \gg k_{I_2} \gg k_{I_3} \gg ...$$

we build an acyclic reaction network that approximates kinetic of initial network.

Sinks and ergodicity in reaction networks

A nonempty set V of vertices 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.

For any $c(0) \in \Sigma$ there exists $\lim_{t\to\infty} \exp(\mathbf{K}t)\, c(0)$. A linear network is *weakly ergodic*, if for all $c(0) \in \Sigma$ these limits coincide.

The following properties are equivalent:

i) the network is weakly ergodic.
ii) for each two vertices A_i, A_j $(i \neq j)$ we can find such a vertex A_k that an oriented paths exist from A_i to A_k and from A_j to A_k (it might be $i = k$ or $j = k$).
iii) the network has only one minimal sink.
iv) there is an unique linear conservation law, namely $b^0(c) = \sum_{i=1}^{q} c_i$ (the zero eigenvalue of the matrix $\mathbf{K}$ is not degenerate).

Integration of orderings

1. Auxiliary discrete dynamical systems

For each A_i, $\kappa_i = \max_j\{k_{ji}\}$, $\phi(i) = \arg\max_j\{k_{ji}\}$; $\phi(i) = i$ if there is no outgoing reaction $A_i \to A_j$.

ϕ determines *auxiliary dynamical system* on a set $\mathcal{A} = \{A_i\}$.

Let us decompose this system and find the cycles C_j with basins of attraction, $Att(C_j)$: $\mathcal{A} = \cup_j Att(C_j)$.

Integration of orderings

2. If all C_j are sinks in the initial network, then let us delete the limited steps from cycles C_j. After that, the kinetics of *acyclic* reaction network $A_i \to A_{\phi(i)}$ with constants κ_i approximates the proper kinetics uniformly for any constant values under given ordering.

Example: a "dominant cycle" $A_1 \to A_2 \to ...A_n \to A_1$, if all other reactions $A_i \to A_j$ have constants $k_{ji} \ll k_{i+1\,i}$.

Integration of orderings

3. If some of C_j are not sinks in the initial network, then we glue cycles:

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

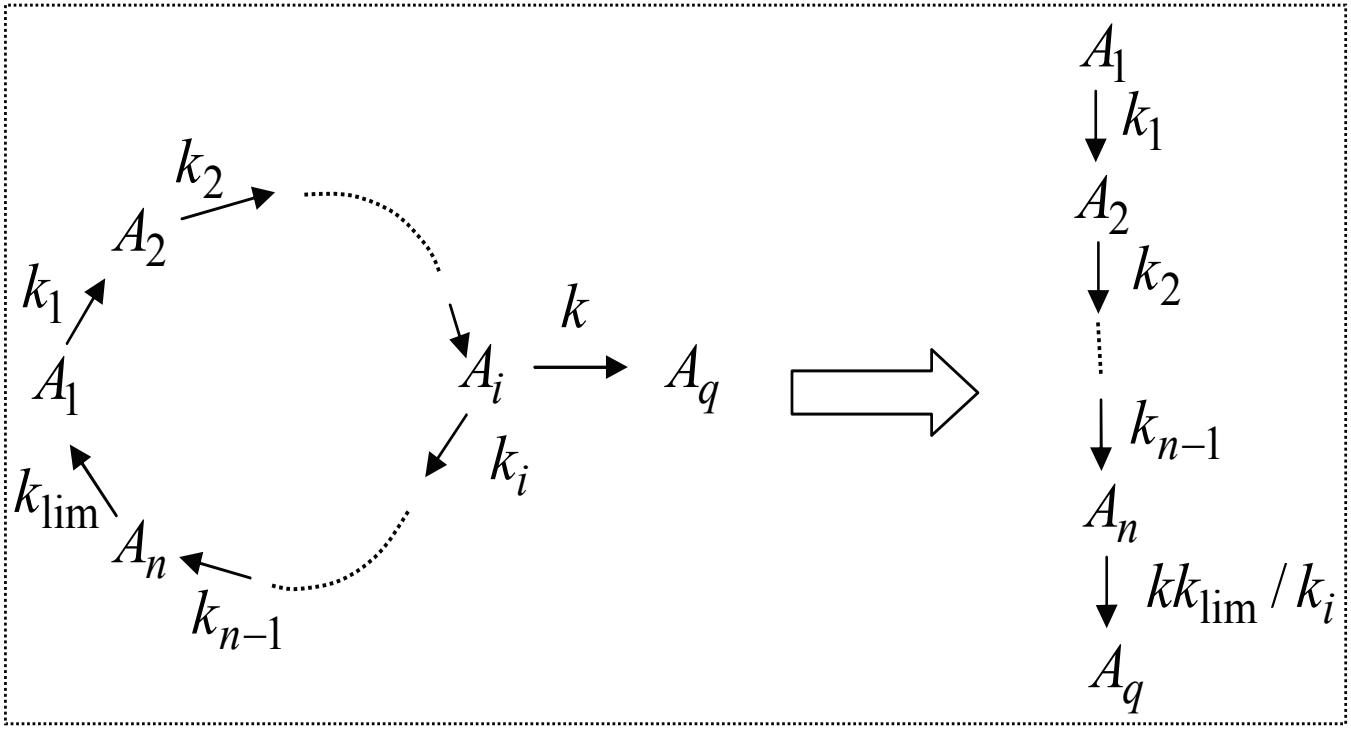
B. For each C_i, we find a normalized stationary distribution due to internal reactions of C_i. Due to limitation, $c_j^* \approx \kappa_{\lim i}/\kappa_j$, $A_j \in C_i$.

C. For each reaction $A_j \to A_q$ ($A_j \in C_i$, $A_q \notin C_i$) we define reaction $A^i \to A_q$ with the constant $k_{qj}c_j^*$.

We prepared a new reaction network. Iterate.

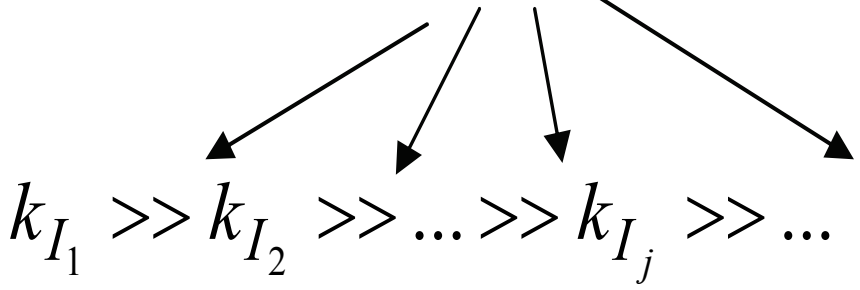
After several steps, we get an auxiliary dynamic system with cycles that are sinks. After that, we shall go back, *restore cycles*, delete limiting steps,... The result is the acyclic dynamic system that approximates kinetics of initial system.

Cycles surgery on the way back

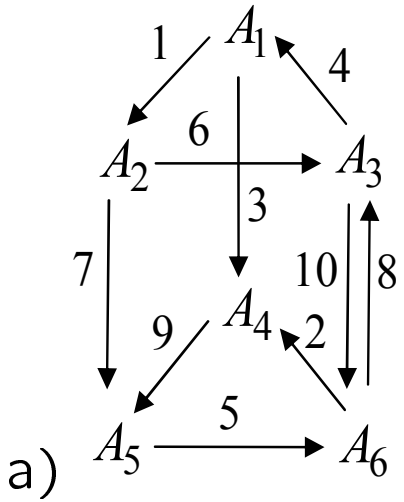


Inclusion monomials in the ordering

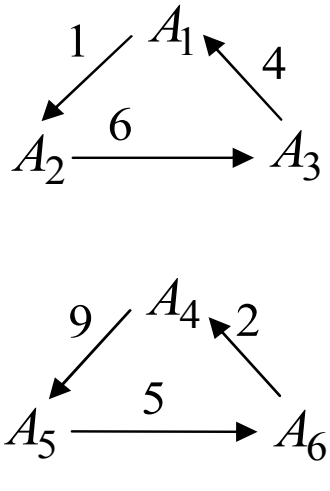
$$>> \prod_I k_I^{a_I} >>$$



$$k_{I_1} >> k_{I_2} >> \ldots >> k_{I_j} >> \ldots$$


1
A_1
4
6
A_2
A_3
3
7
10
8
9
A_4
2
5
A_5
A_6

a)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A_1
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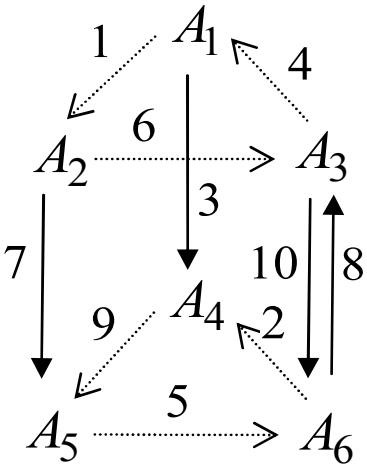
A_2
A_3
9
A_4
2
5
A_5
A_6

b) ; c)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A_1
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A_4
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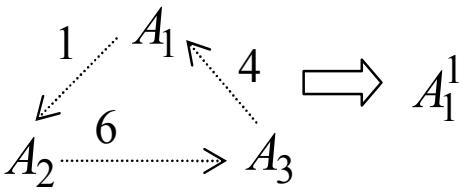
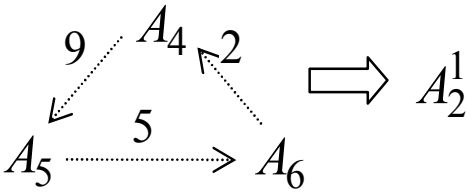
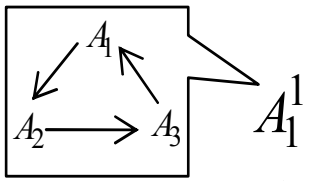
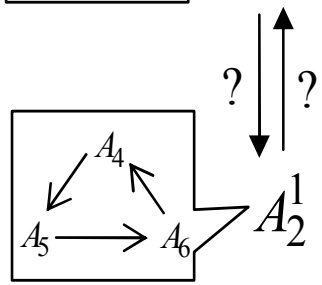
A_5
A_6


1
A_1
4
6
A_2
A_3
A_1^1

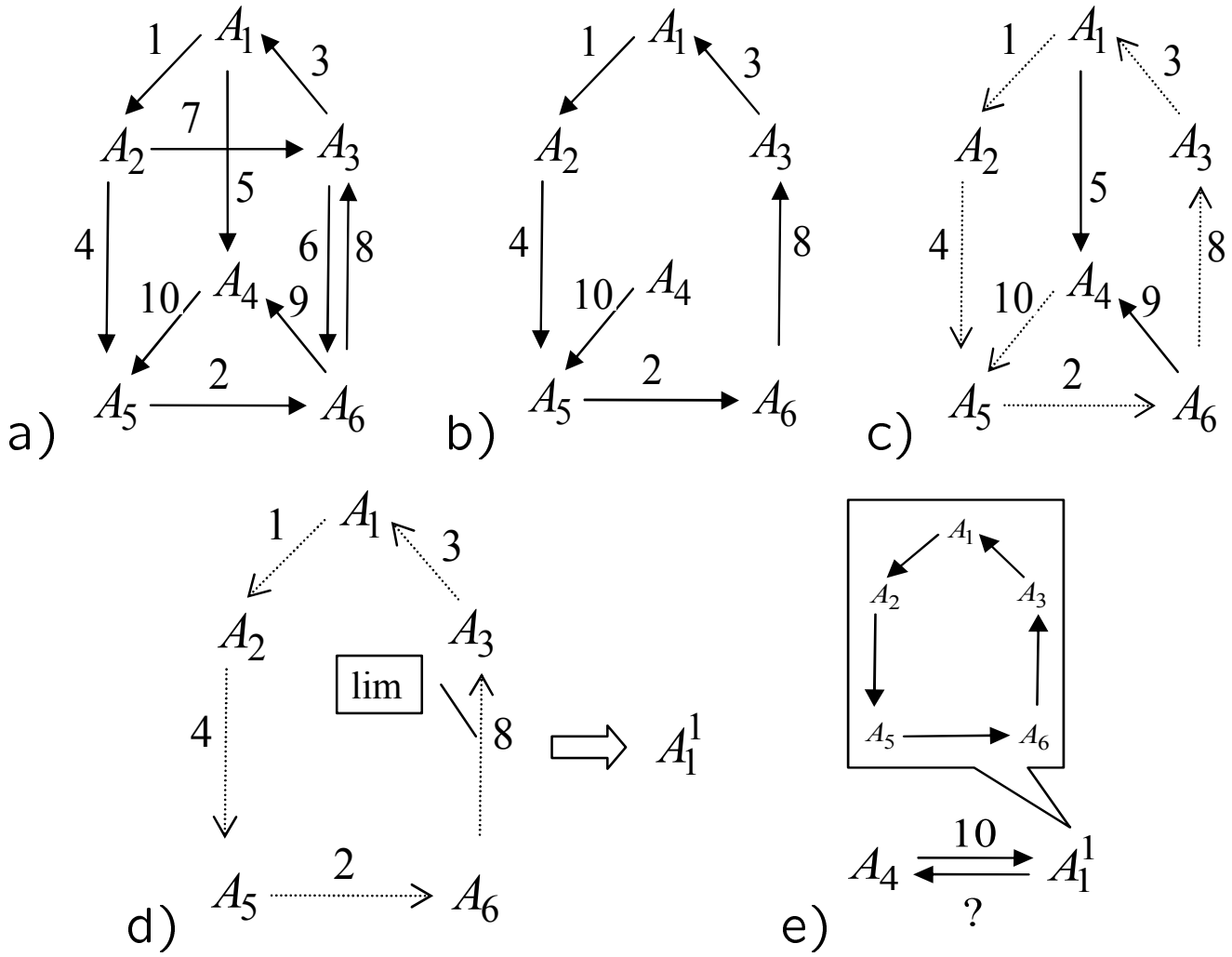

9
A_4
2
5
A_5
A_6
A_2^1

d)


A_1
A_2
A_3
A_1^1


?
?
A_4
A_5
A_6
A_2^1

e)


a)
b)
c)
d)
e)
lim
?

Three zero-one laws for multiscale linear networks

Steady states (for weakly ergodic networks)

Limit states (for non-ergodic networks)
SINK1... $\leftarrow A_i \rightarrow$ ...SINK2
From each vertex almost all flux goes either to SINK1, or to SINK2 ("xor" instead of "or").

Relaxation eigenmodes (eigenvectors)

CONCLUSION

- Dominant systems correspond to faces of the Newton polyhedron for the spectral problem;

- We have the algorithm for extraction of the dominant systems from the graph of reactions without computation of determinants;

- This method can be considered as development of the Vishik-Lyusternik-Lidskii perturbation theory;

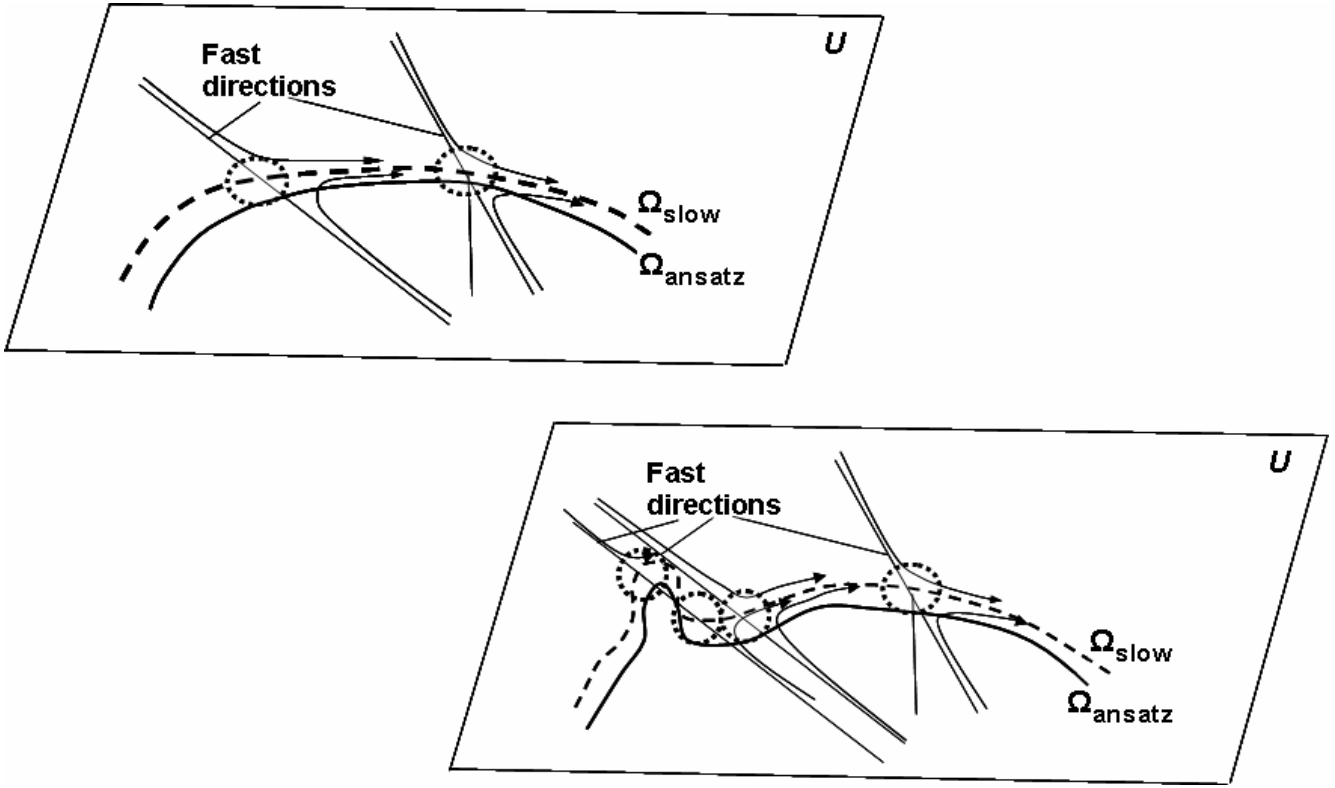
- "Integration of orderings" can be used if the reaction rate constants are known only "by orders";

- Dominant systems give the rough and robust approximation to solution of kinetic equations and can also serve for preconditioning purposes in numerics;

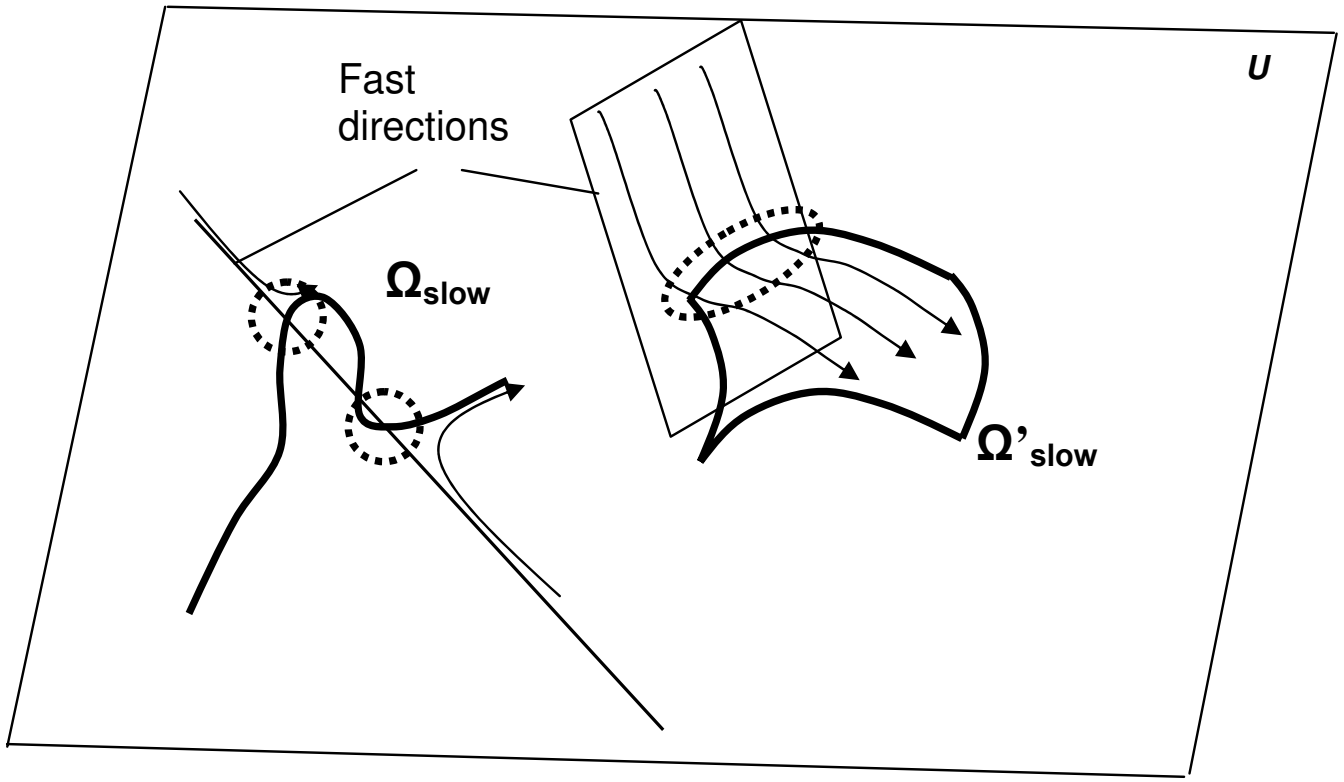
- Zero-one laws for multiscale systems cause the correspondent "phase transitions" and generate new phenomenology of qualitative behaviour for such systems;

- Linear systems - discrete dynamics on the set of components (species); Nonlinear systems - discrete dynamics on the set of small reaction networks.

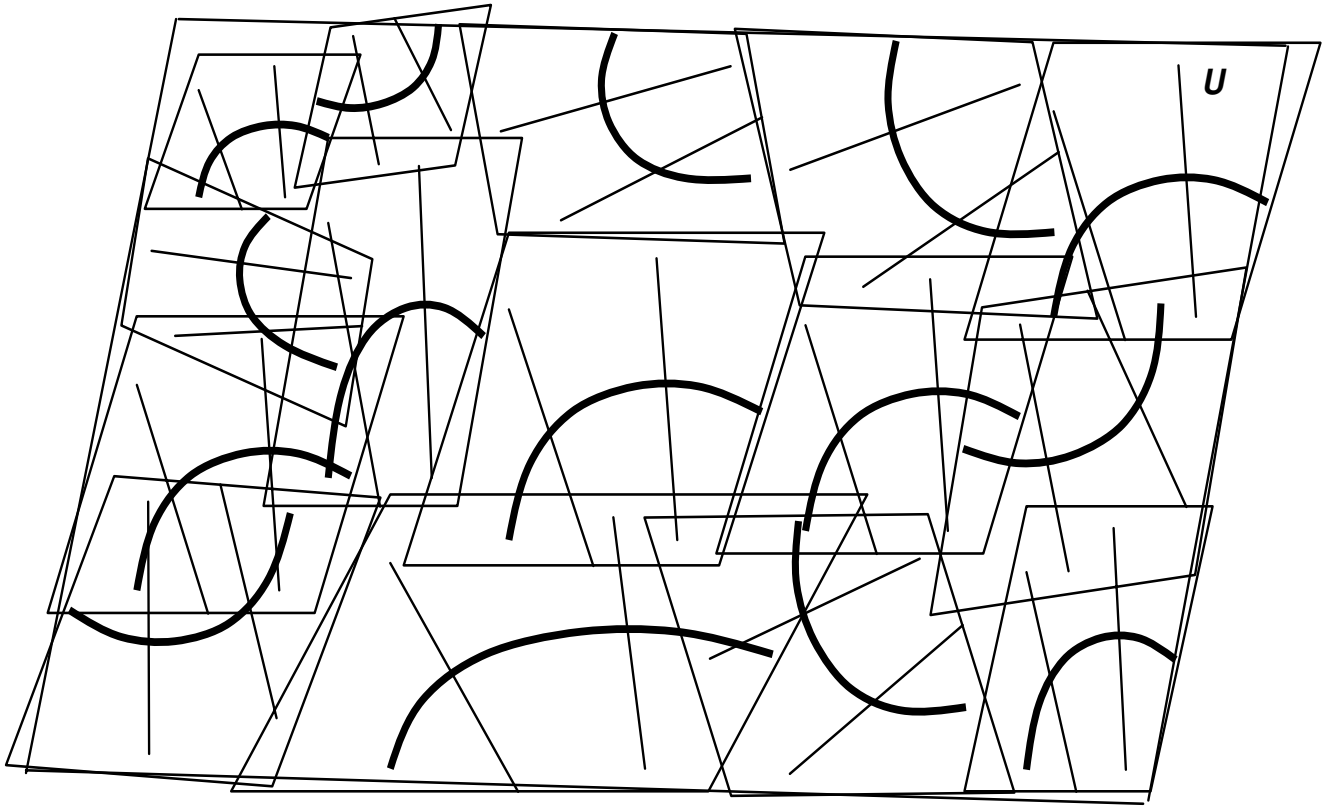
Life is not easy. I. Bifurcations in fast system



Life is not easy. II. Slow manifold is not connected



Crazy quilt of Dynamic Decomposition (total)



Decomposition (along a trajectory)