Hierarchy of Dominant Paths in Multiscale Networks

Dynamic and static limitation in reaction networks, revisited

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with

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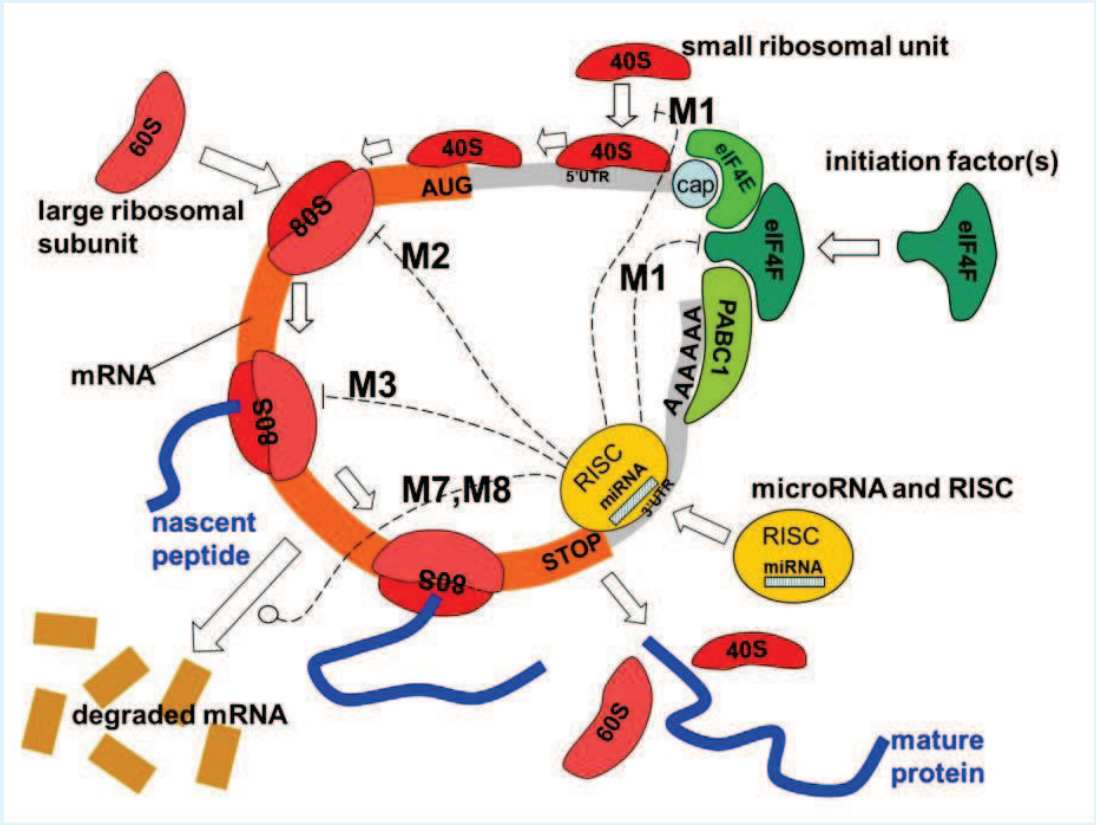
Plan

1. microRNA detective story: plot
2. Google test of model reduction approaches
3. Dominant paths in linear and pseudo-monomolecular networks
4. Simple examples
5. microRNA detective story: denouement
6. Dominant paths in nonlinear networks: an outline.

microRNA detective story

Interaction of microRNA with protein translation process



MicroRNAs (miRNAs) are key regulators of all important biological processes, including development, differentiation and cancer.

Many contradictory findings about deciphering the mechanisms used by miRNAs have been published that stimulate active debate in this field.

Mechanisms of microRNA actions M1-M9:

M1: Cap-40S Initiation Inhibition

M2: 60S Ribosomal Unit Joining Inhibition

M3: Elongation Inhibition

M4: Ribosome Drop-off (premature termination)

M5: Co-translational Nascent Protein Degradation

M6: Sequestration in P-bodies

M7: mRNA Decay (destabilisation)

M8: mRNA Cleavage

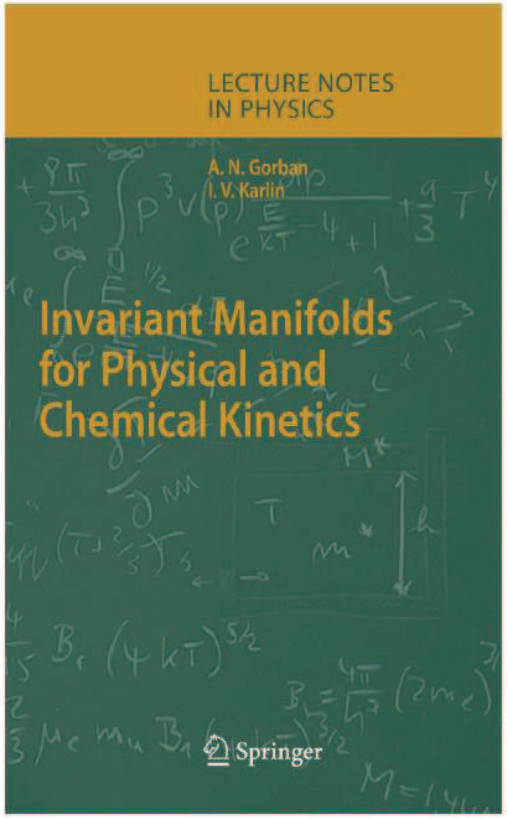
M9: Transcriptional Inhibition through microRNA-mediated chromatin reorganization following by gene silencing

How people use model reduction approaches

"Vox populi, vox Dei"

Google gave on 22 June 2013:

- for "quasi-equilibrium" – 215,000 links;
- for "quasi steady state" 290,000 and for "pseudo steady state" 675,000; 965,000 together;
- for "slow manifold" 21,000 only, and for "invariant manifold" 58,600;
- for "singular perturbation" 321,000 links;
- for "model reduction" even more, 405,000;
- but for "limiting step" – 1,130,000!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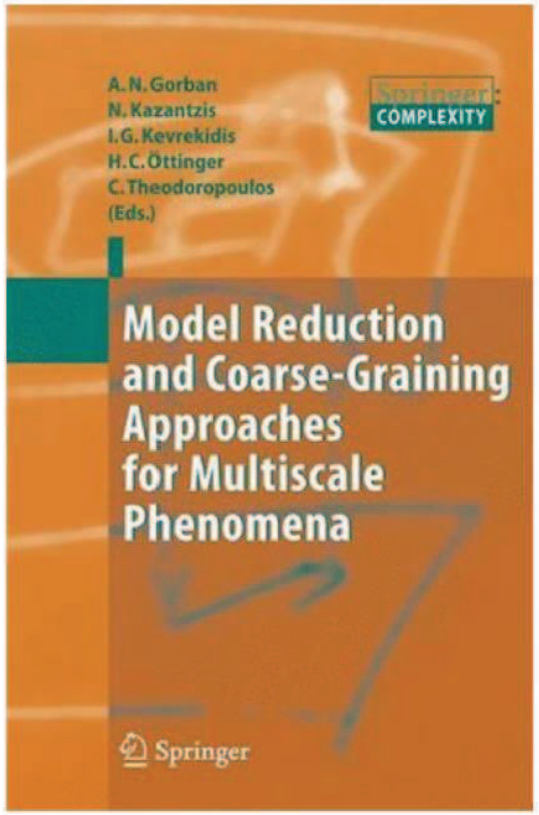
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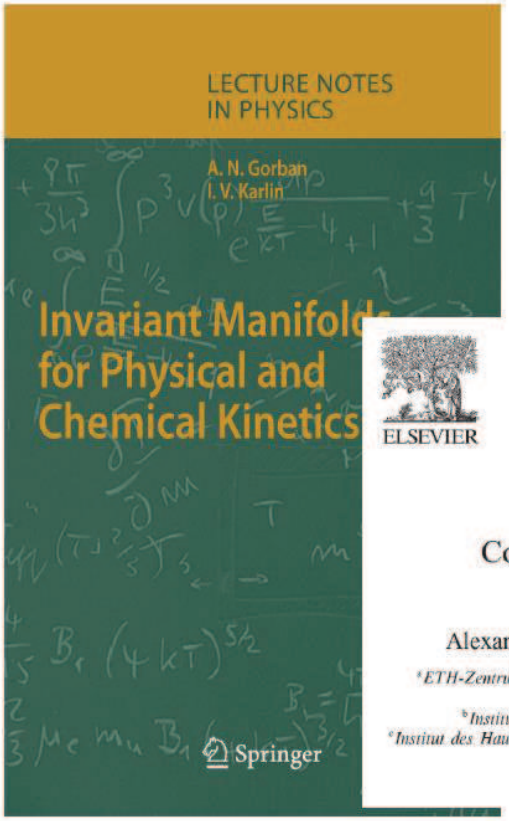

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Constructive methods of invariant manifolds for kinetic problems

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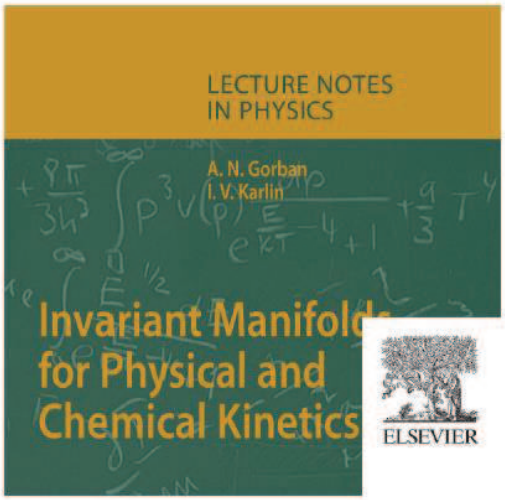

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Method of invariant manifold for chemical kinetics

Alexander N. Gorban[a,b], Iliya V. Karlin[a,*]

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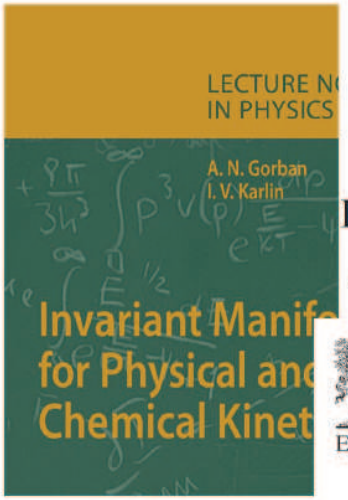

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Invariant grids for reaction kinetics

Alexander N. Gorban[a,b,c], Iliya V. Karlin[a,b,*], Andrei Yu. Zinovyev[b,c]

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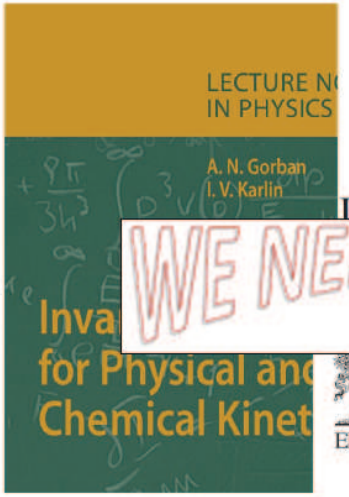

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Limiting step

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.

The most known reason: the bottle neck. Existence of "dominant reagents" in nonlinear reactions can also lead to self-simplification: If for reaction $A + B \to C$ we have $c_A \gg c_B$ then c_A is almost constant and all interesting dynamics is in c_B change. In such a case, we can consider $A + B \to C$ as a linear reaction $B \to C$ with constant proportional to c_A.

We should not always expect one limiting step.

Hierarchical dominant paths in multiscale networks

PLAN

1. Dominant path in multiscale linear networks

2. Gluing cycles and hierarchy of dominant paths

3. Heuristics for nonlinear networks

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

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

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 **catalytic cycle**:

$$\underline{\mathrm{S}} + A_1 \to A_2 \to \ldots \to A_n \to A_1 + \underline{\mathrm{P}}$$

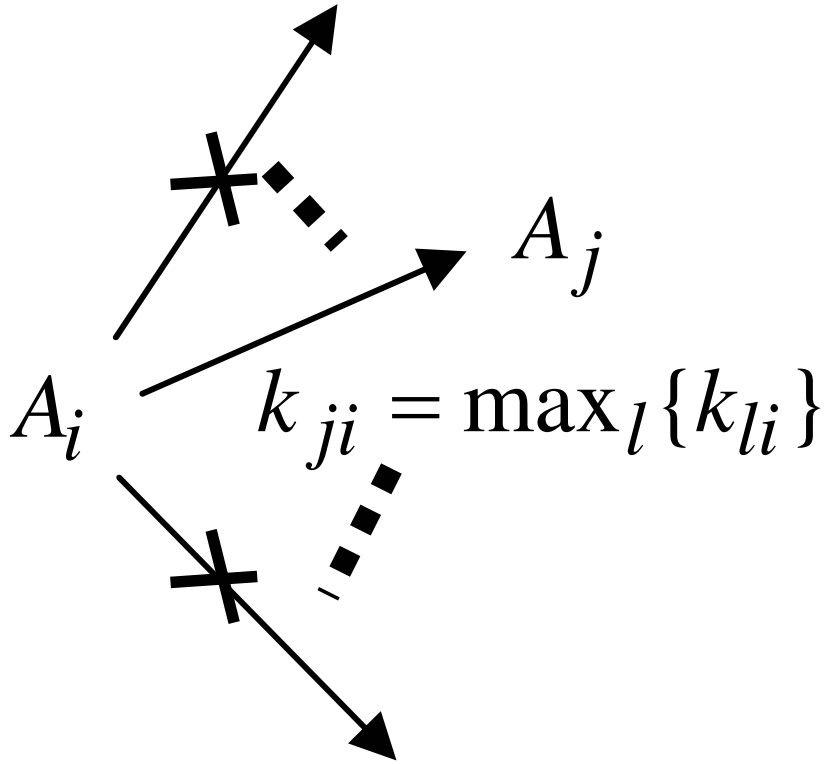
$$A_1 \to A_2 \to \ldots \to A_n \to A_1$$

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

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

At least, in each diverging fork we can select the largest constant.

Let us select the fastest reaction in each diverging fork



The small parameter: $\varepsilon = \max_{l \neq j} \{k_{li}/k_{ji}\}$

Integration of orderings

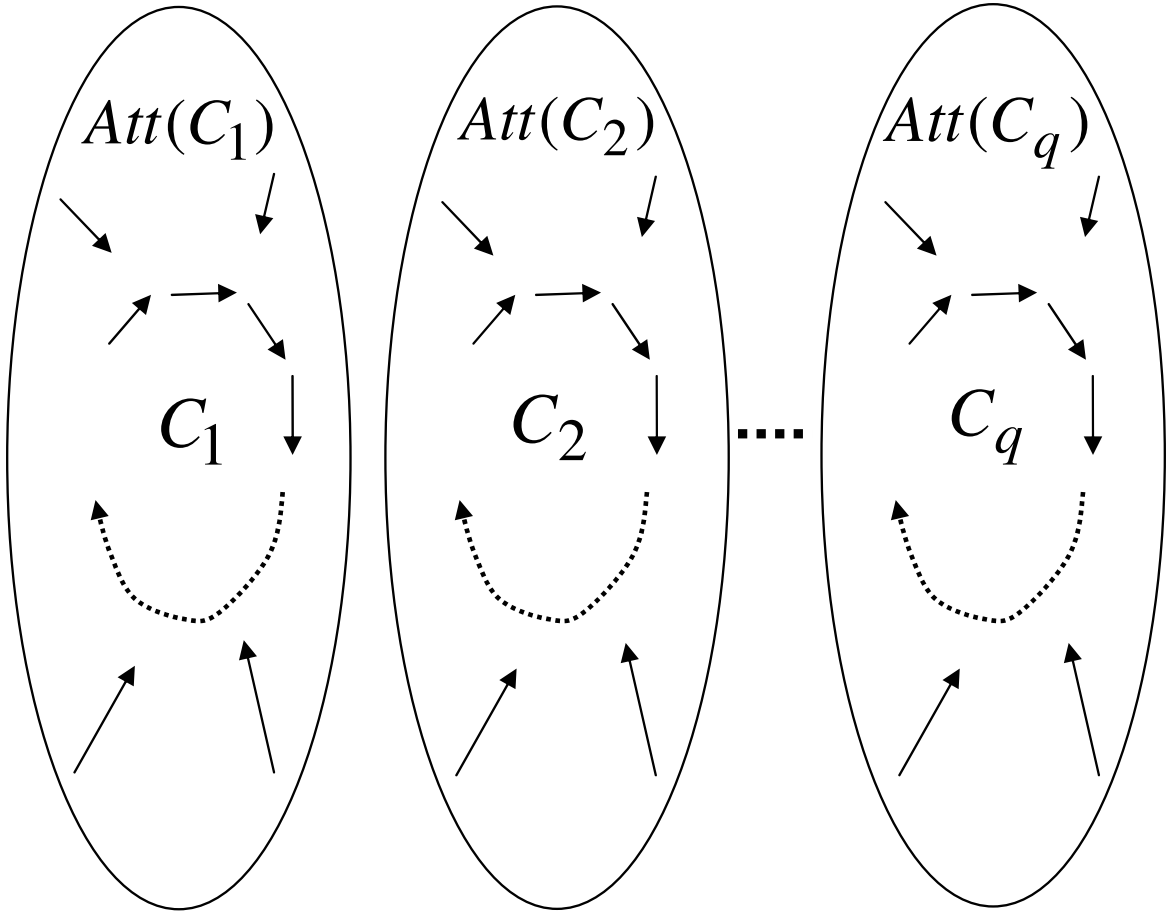
1. Auxiliary discrete dynamical systems

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 $A_i \to A_j$.

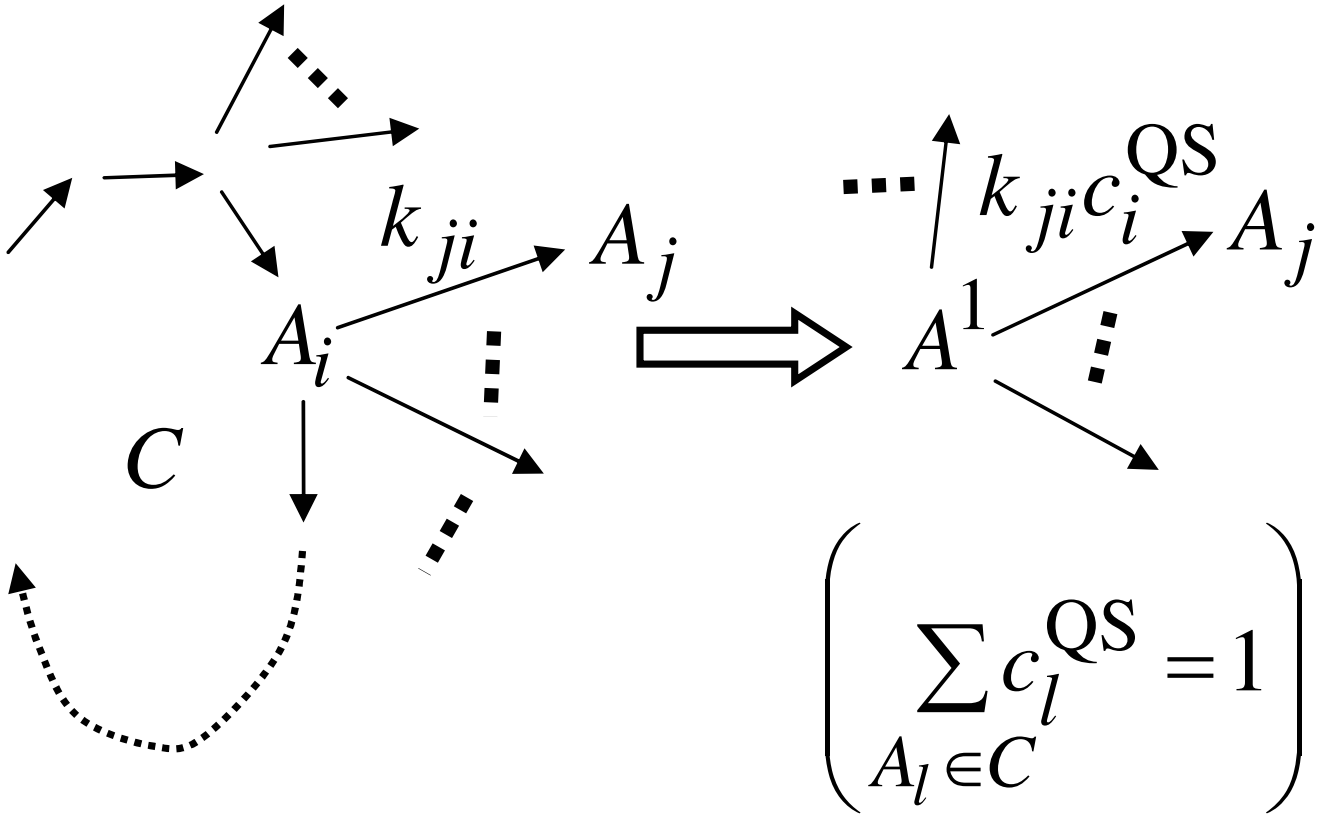
ϕ determines *auxiliary dynamical system* on a set $\mathcal{A} = \{A_i\}$.

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

Decomposition of discrete dynamical systems



Gluing cycles



Then iterate with the smaller number od vertices!

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, $\mathcal{A}^1 = \mathcal{A} \cup \{A^1, A^2, ...\} \setminus (\cup_i C_i)$.

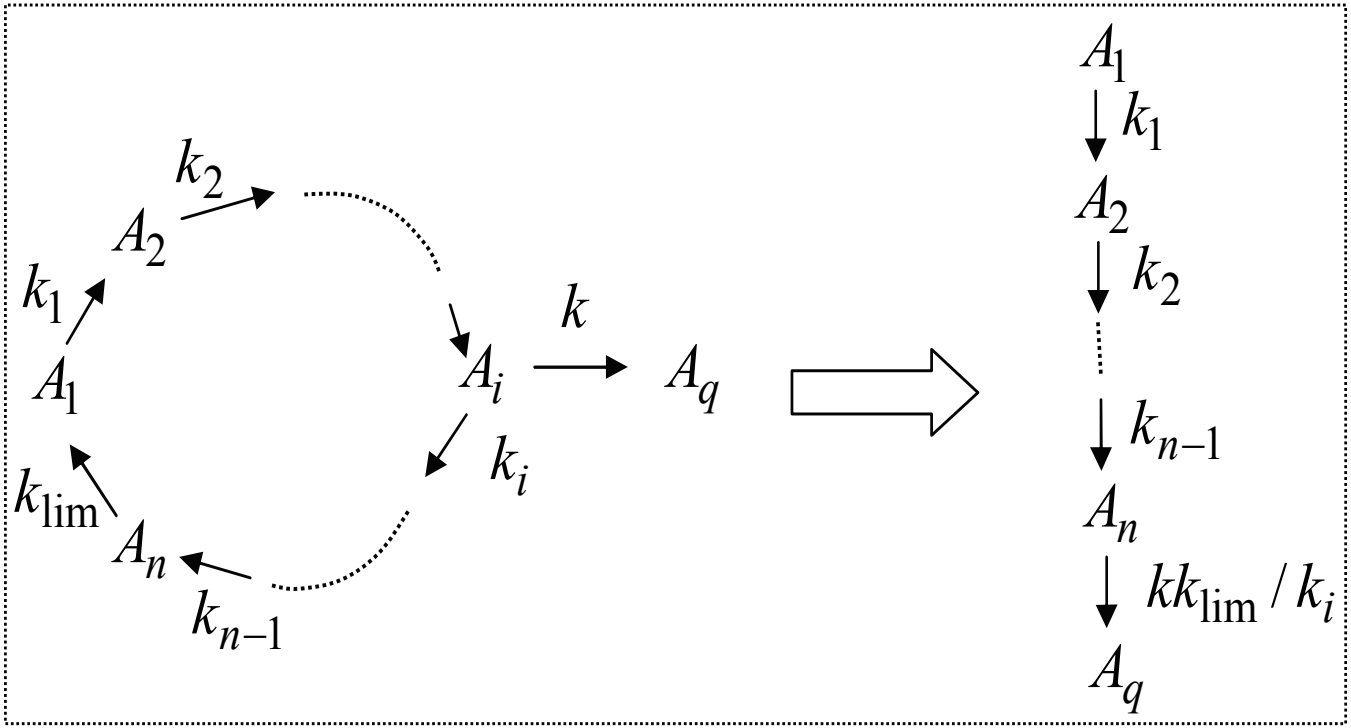
B. For each C_i, we find a normalized stationary distribution due to internal reactions of C_i. Due to limitation, $c_j^* \approx \kappa_{\mathsf{lim}\ i}/\kappa_j$, $A_j \in C_i$.

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 $k_{qj}c_j^*$.

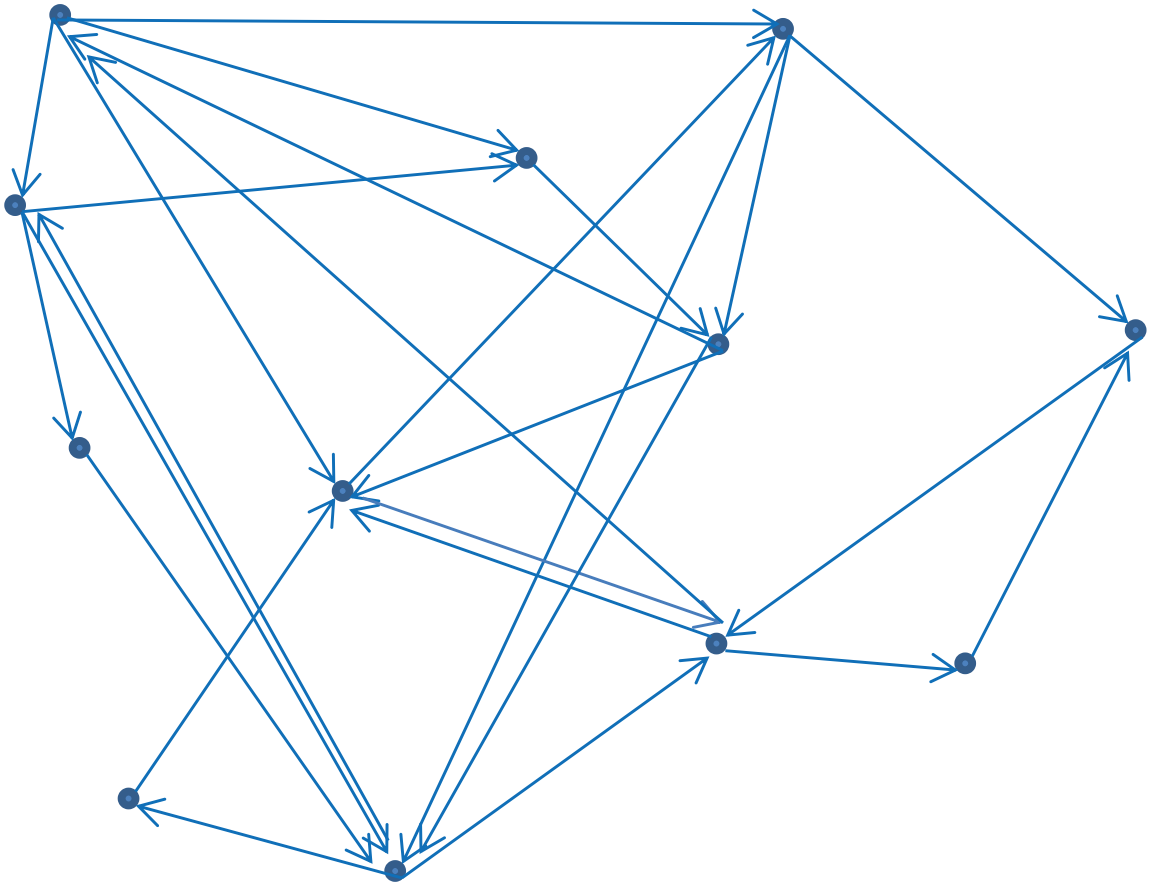
We prepared a new reaction network. Iterate.

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.

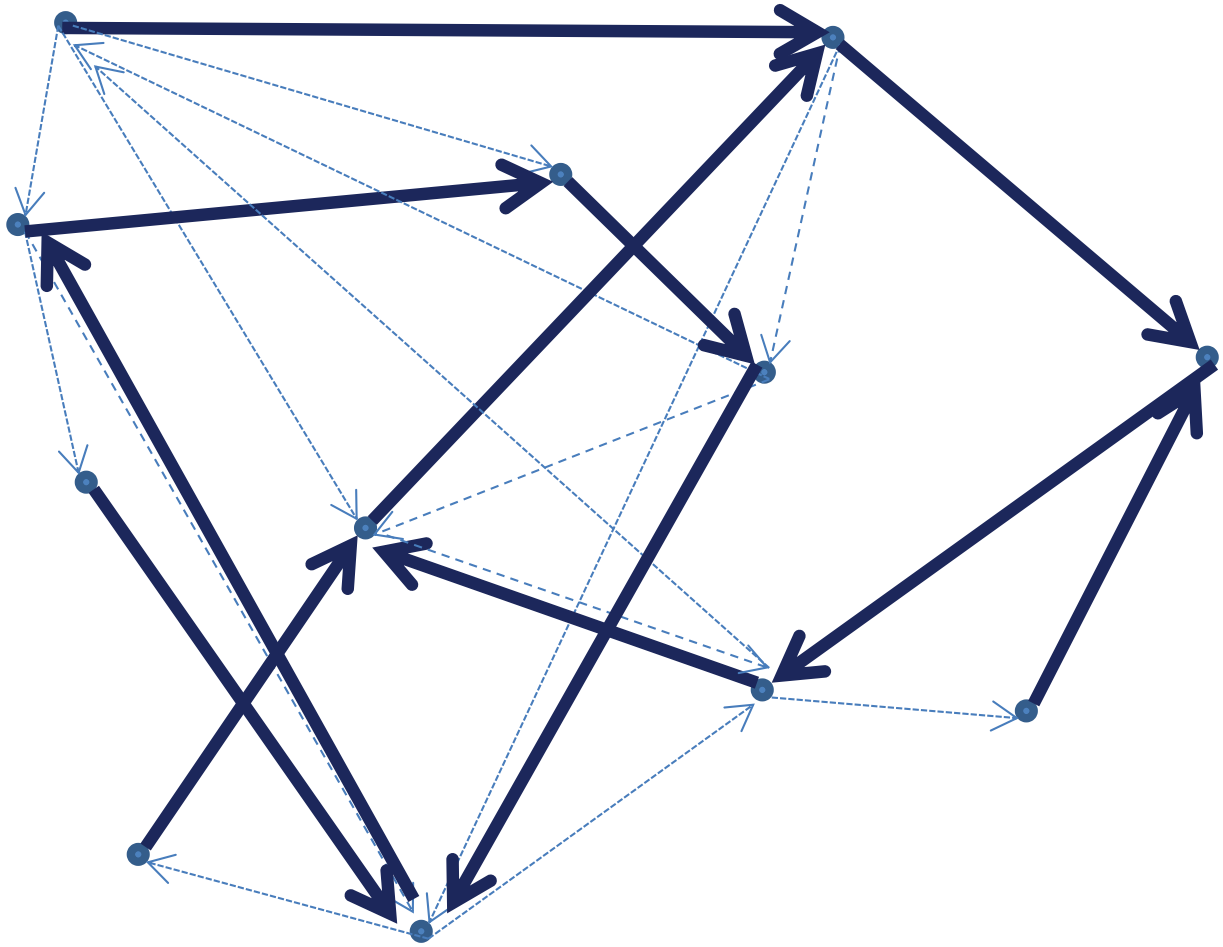
Cycles surgery on the way back



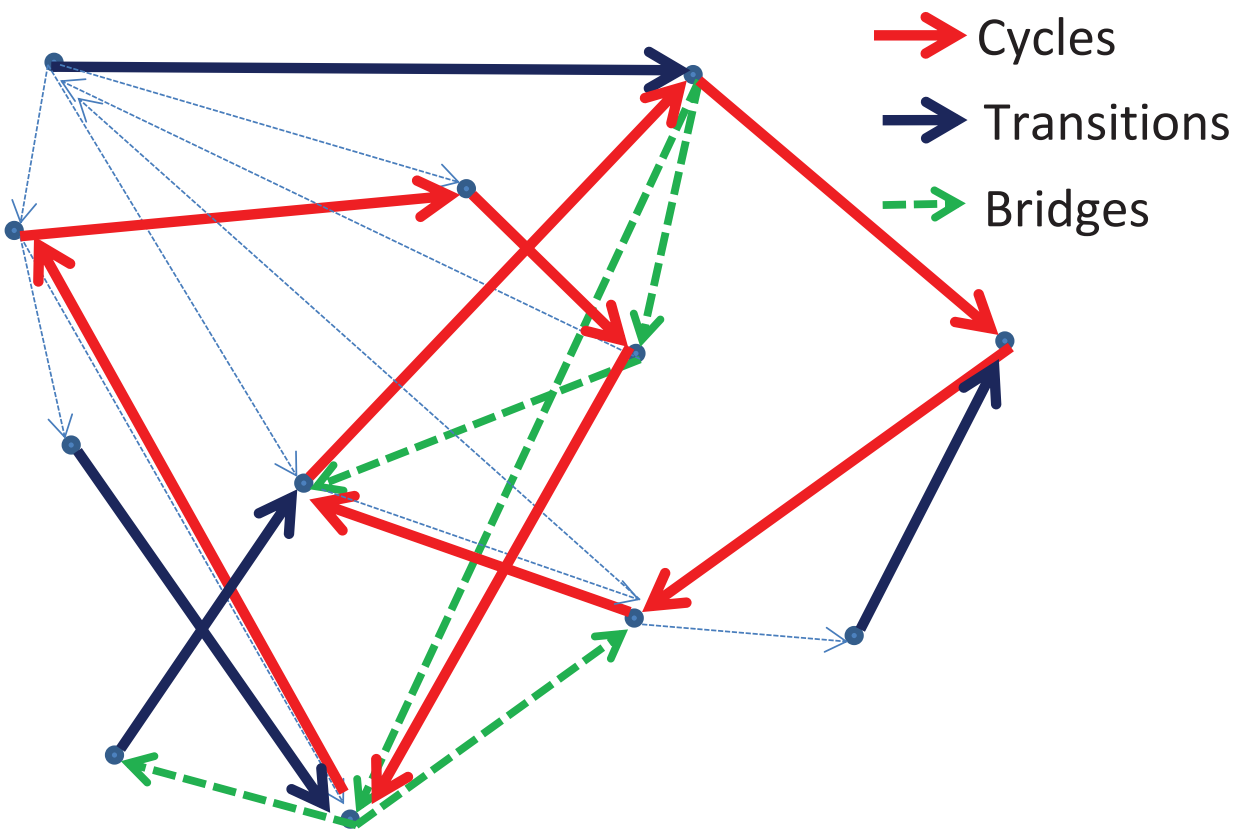
Example. 1. The network



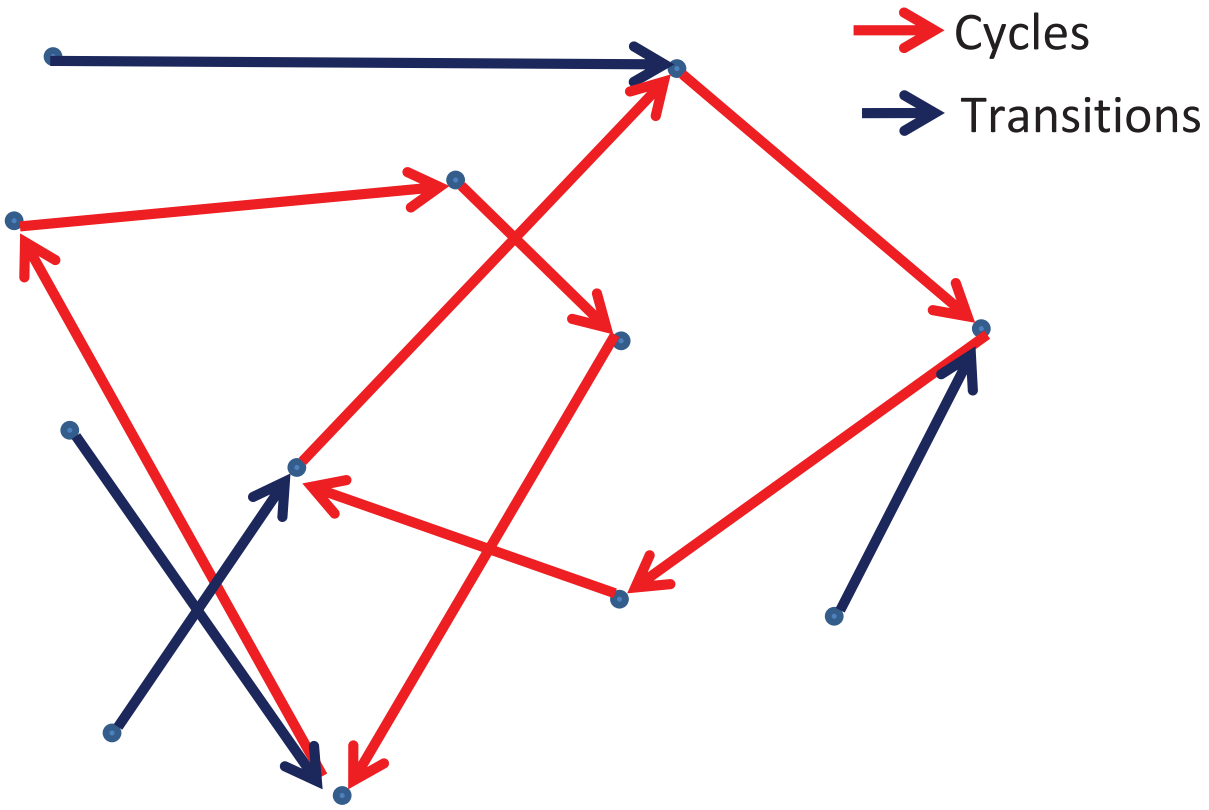
Example. 2. Dominance in diverging forks



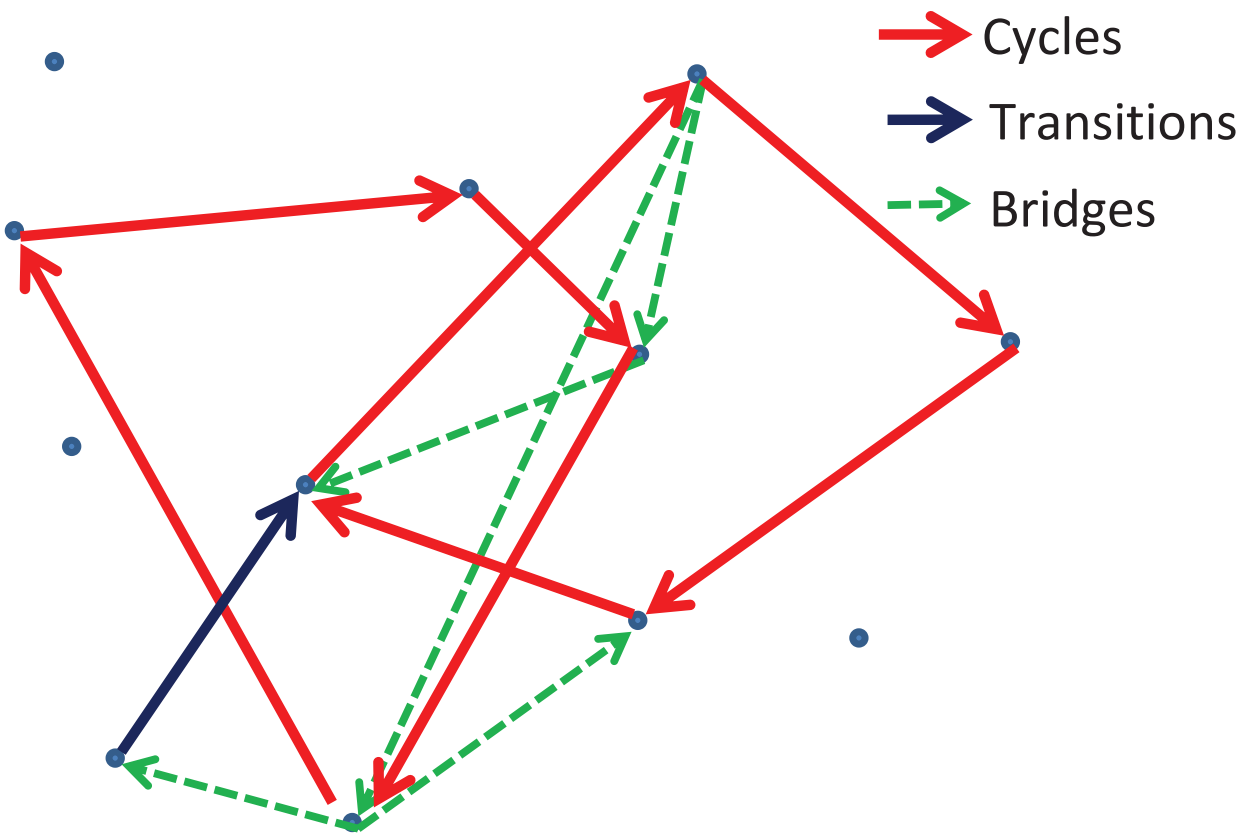
Example. 3. Typology of links



Example. 4. Cycles and attractions



Example. 5. Bridges between attractors



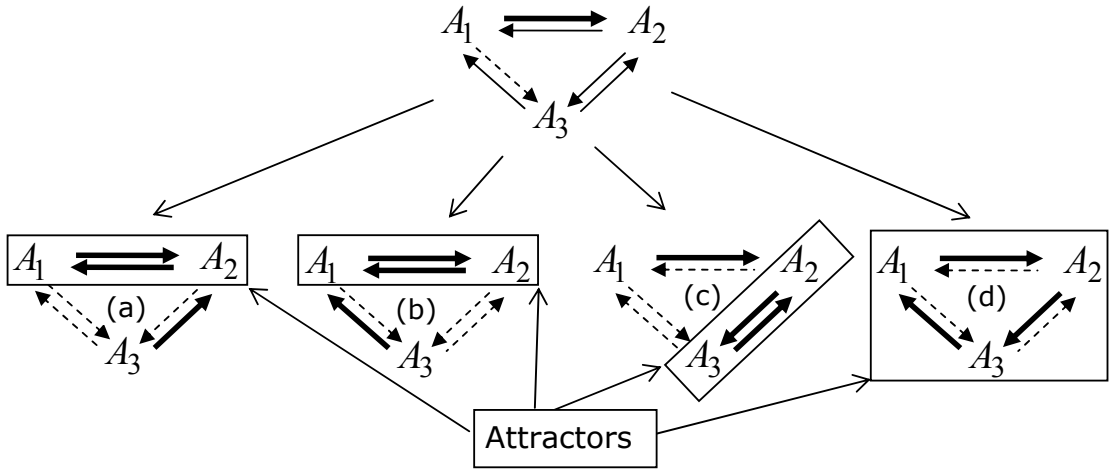
Glue cycles, iterate and get the hierarchical multiscale dominant path.

Theorem. The error of approximation of the eigenvalues and eigenvectors of K by the hierarchical multiscale dominant path tends to 0 with

$$\varepsilon = \max_i\{\max_l\{k_{li}/k_{ji} | j = \arg\max_q\{k_{qi}\},\, l \neq j\}\}$$

It is possible to define from a kinetic experiment the reaction rate constants from the dominant path only because other constants do not affect kinetics.

First of all, let us describe all possible auxiliary dynamical systems for the triangle



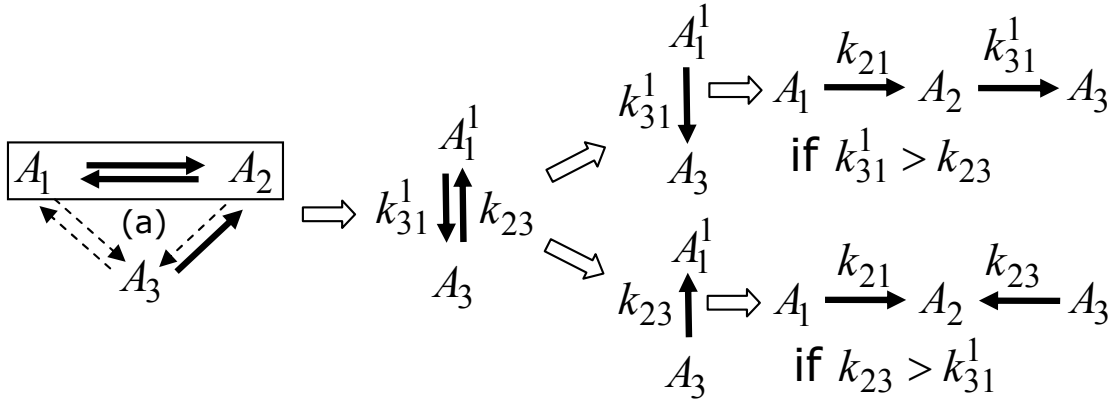
(a) $k_{12} > k_{32}$, $k_{23} > k_{13}$;

(b) $k_{12} > k_{32}$, $k_{13} > k_{23}$;

(c) $k_{32} > k_{12}$, $k_{23} > k_{13}$;

(d) $k_{32} > k_{12}$, $k_{13} > k_{23}$.

Largest rate constant — solid bold arrow.



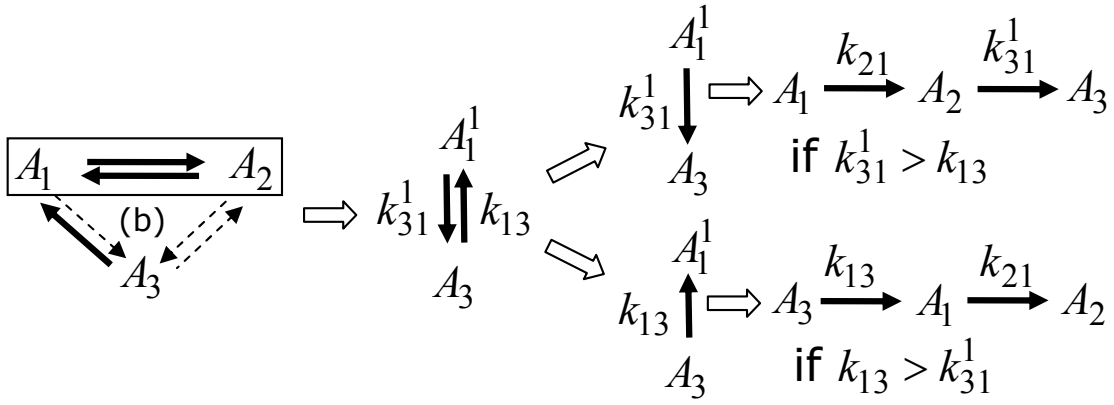
(a)

$k_{31}^1 = \max\{k_{32},\, k_{31}k_{12}/k_{21}\} > k_{23}$, the dominant system $A_1 \to A_2 \to A_3$,

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

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

$$\begin{array}{lll} \lambda_0 = 0\,, & r^0 \approx (0,1,0)\,, & l^0 = (1,1,1)\,; \\ \lambda_1 \approx -k_{21}\,, & r^1 \approx (1,-1,0)\,, & l^1 \approx (1,0,0)\,; \\ \lambda_2 \approx -k_{23}\,, & r^2 \approx (0,-1,1)\,, & l^2 \approx (0,0,1)\,. \end{array} \qquad (2)$$



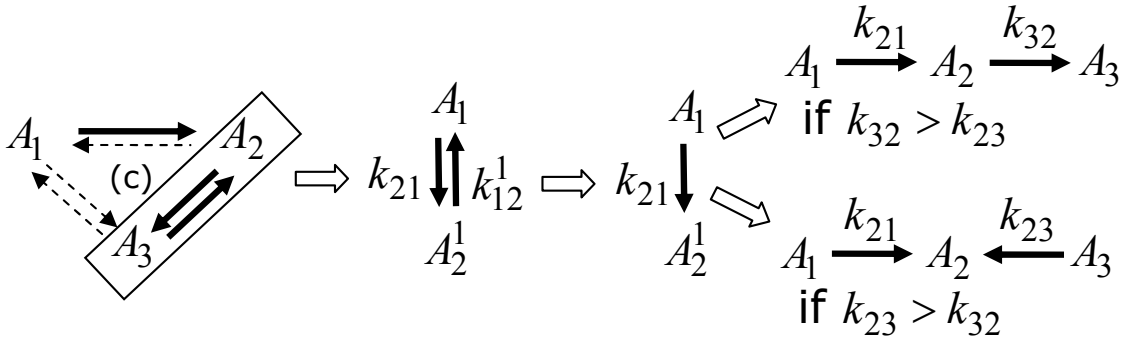
(b)

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

$$\begin{array}{lll} \lambda_0 = 0\,, & r^0 \approx (0,0,1)\,, & l^0 = (1,1,1)\,; \\ \lambda_1 \approx -k_{21}\,, & r^1 \approx (1,-1,0)\,, & l^1 \approx (1,0,0)\,; \\ \lambda_2 \approx -k_{31}^1\,, & r^2 \approx (0,1,-1)\,, & l^2 \approx (1,1,0)\,; \end{array} \qquad (3)$$

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

$$\begin{array}{lll} \lambda_0 = 0\,, & r^0 \approx (0,1,0)\,, & l^0 = (1,1,1)\,; \\ \lambda_1 \approx -k_{21}\,, & r^1 \approx (1,-1,0)\,, & l^1 \approx (1,0,0)\,; \\ \lambda_2 \approx -k_{13}\,, & r^2 \approx (0,-1,1)\,, & l^2 \approx (0,0,1)\,. \end{array} \qquad (4)$$



(c)

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

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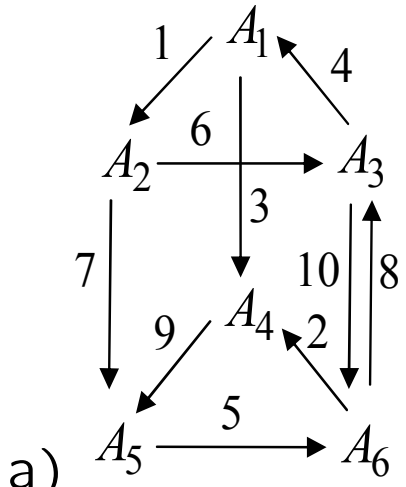
$k_{23} > k_{32}$, the dominant system $A_1 \to A_2 \leftarrow A_3$,

$$\begin{array}{lll} \lambda_0 = 0\,, & r^0 \approx (0,1,0)\,, & l^0 = (1,1,1)\,; \\ \lambda_1 \approx -k_{21}\,, & r^1 \approx (1,-1,0)\,, & l^1 \approx (1,0,0)\,; \\ \lambda_2 \approx -k_{23}\,, & r^2 \approx (0,-1,1)\,, & l^2 \approx (0,0,1)\,. \end{array} \qquad (6)$$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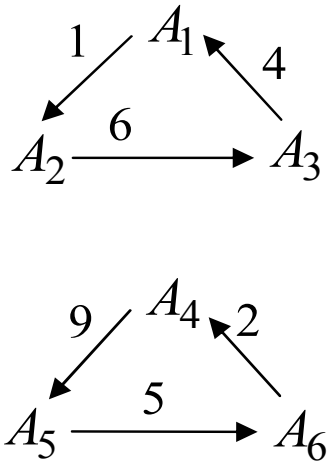
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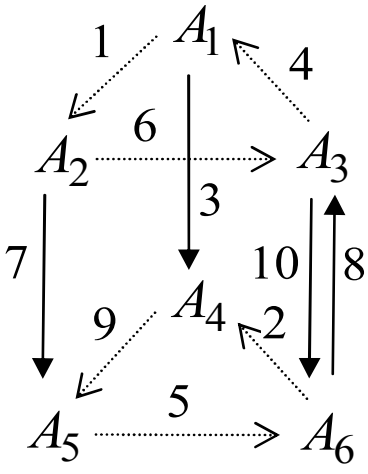
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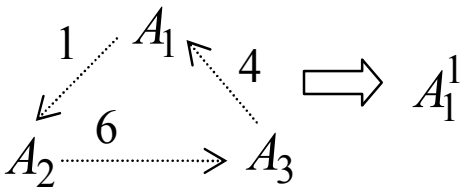
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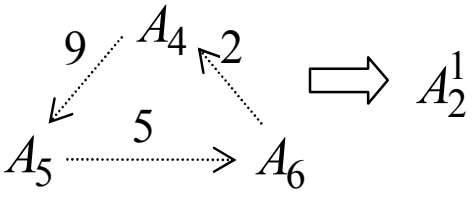
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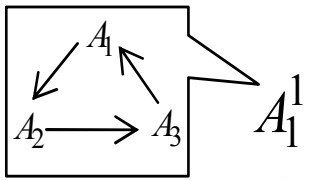
d)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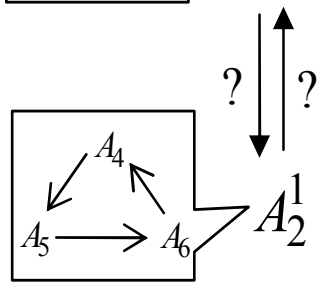
A_1^1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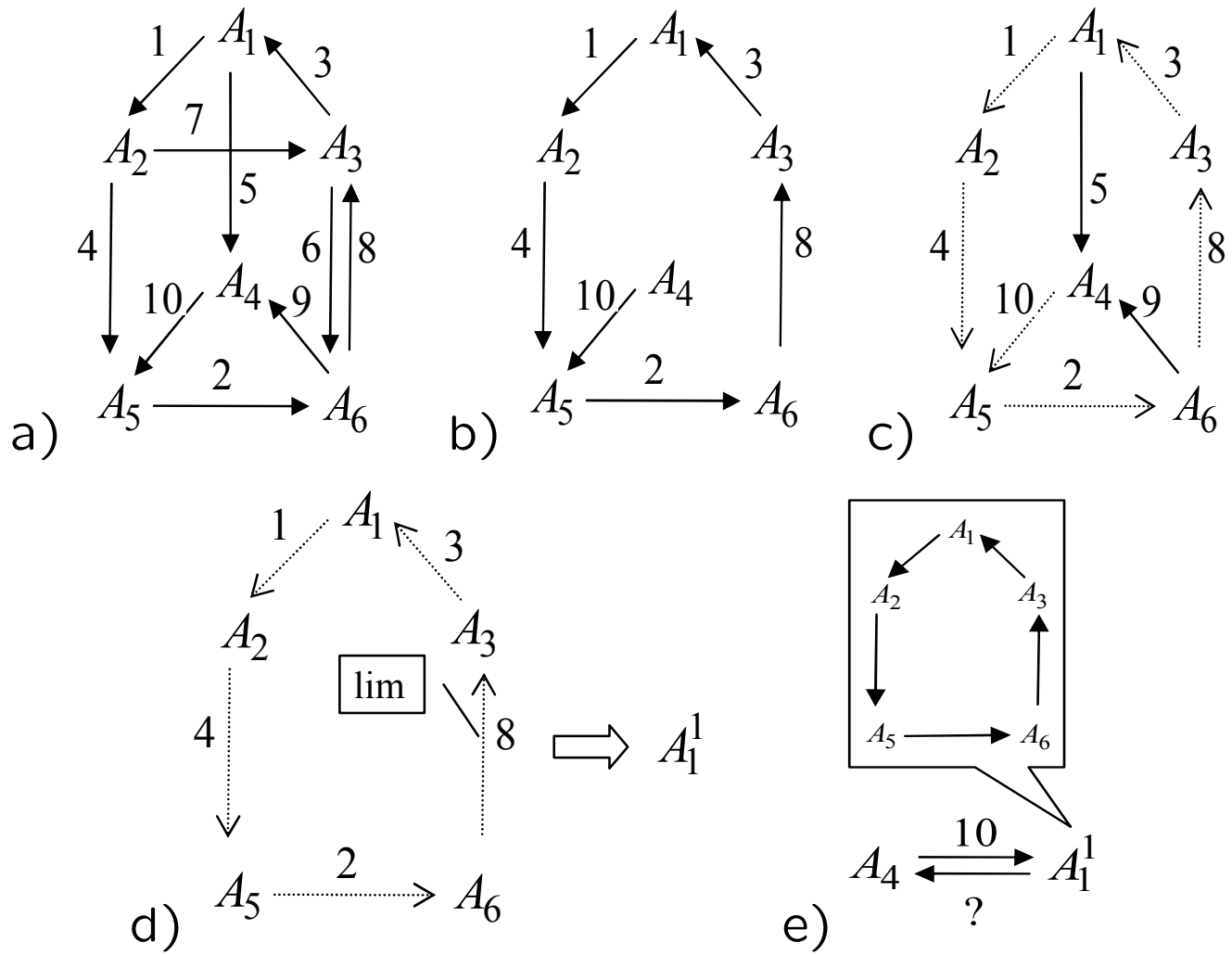
A_4
A_5
A_6
A_2^1

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)

RNA
A PUBLICATION OF THE RNA SOCIETY

Kinetic signatures of microRNA modes of action

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[3]Institut Curie, Service Bioinformatique, F-75248 Paris, France
[4]Ecole des Mines ParisTech, F-77300 Fontainebleau, France
[5]INSERM, U900, Paris, F-75248, France
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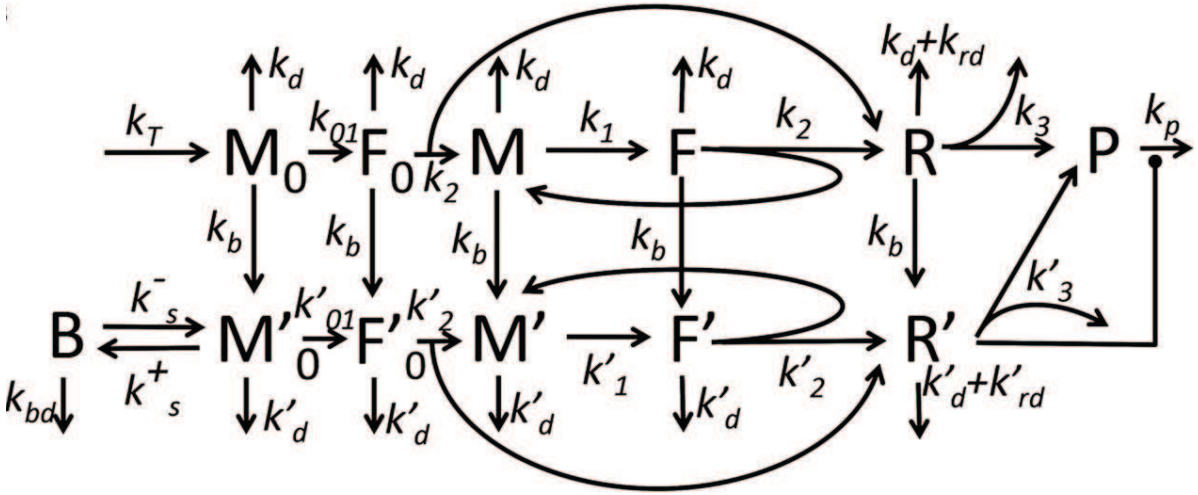
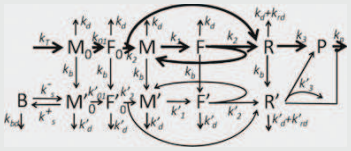
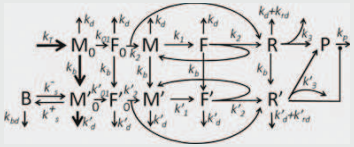
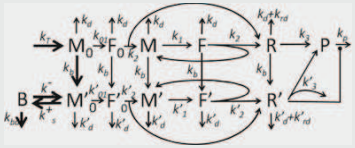
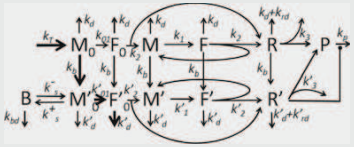
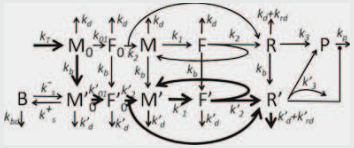
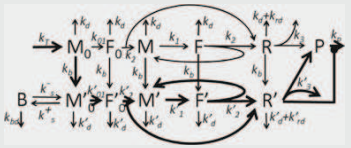
1. Based on the existing data, we develop a model in which all proposed mechanisms of microRNA action may coexist.
2. We have found sensitive parameters and dominant mechanisms of the translation process for various conditions. ....


k_d
k_d
k_d
k_d
k_d+k_{rd}
k_T
k_{Q1}
k_1
k_2
k_3
k_p
M_0
F_0
M
F
R
P
k_2
k_b
k_b
k_b
k_b
k_b
k^-_s
k'_{Q1}
k'_2
k'_3
B
M'_0
F'_0
M'
F'
R'
k^+_s
k'_1
k'_2
k_{bd}
k'_d
k'_d
k'_d
k'_d
$k'_d+k'_{rd}$

Dominant path	Biological interpretation	Corresponding miRNA-mediated translation repression mechanism(s)
	M_0F_0MFRP Normal translation with negligible effect of miRNA	None
	$M_0M'_0$ The dominant effect is degradation of mRNA by miRNA.	M1: Cap inhibition M7: Decay M8: Cleavage
	$M_0M'_0B$ mRNA is captured in P-bodies.	M6: Sequestration of mRNA in P-Bodies
	$M_0M'_0F'_0$ mRNA translation is stuck after initiation, before the assembly of the ribosome.	M2: 60S subunit joining inhibition
	$M_0M'_0F'_0M'F'R'$ mRNA is stuck with ribosomes on it and destroyed, or mRNA translation is prematurely aborted.	M3: Elongation inhibition M4: Ribosome drop-off
	$M_0M'_0F'_0M'F'R'P$ Protein synthesis in the presence of miRNA with low mRNA degradation	M1: Cap inhibition M2: 60S subunit joining inhibition M3: Elongation inhibition M5: Cotranslational protein degradation mechanisms

References

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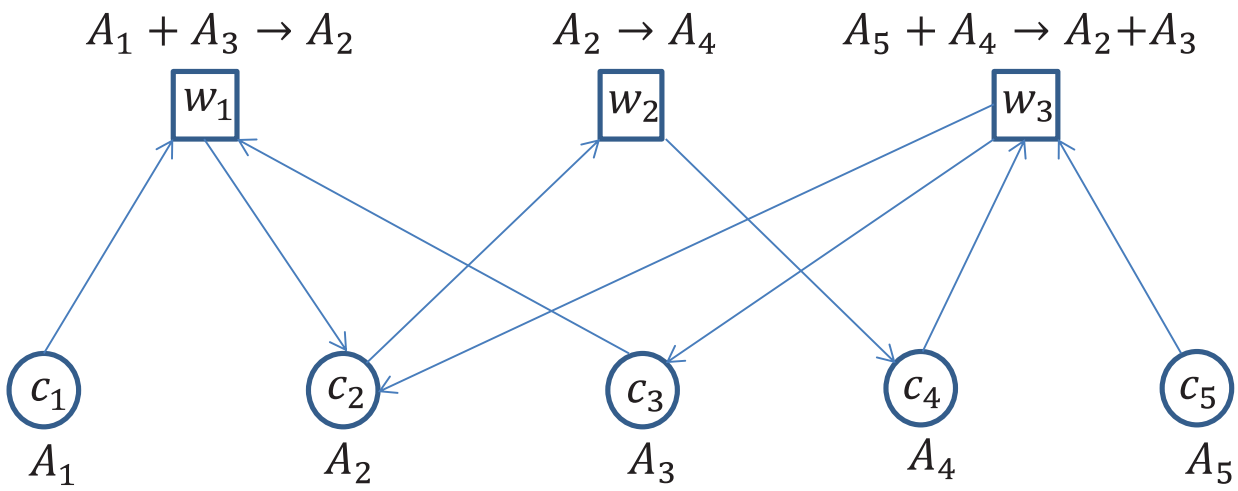
3. O. Radulescu, A.N. Gorban, A. Zinovyev, and A. Lilienbaum Robust simplifications of multiscale biochemical networks, BMC Systems Biology 2008, 2:86.
4. A. Zinovyev, N. Morozova, N. Nonne, E. Barillot, A. Harel-Bellan, A.N. Gorban, Dynamical modeling of microRNA action on the protein translation process, BMC Systems Biology 2010, 4:1

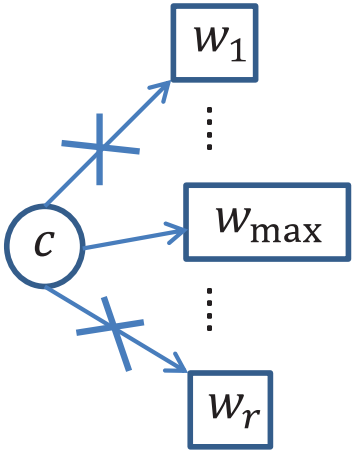
5. A. Zinovyev, N. Morozova, A.N. Gorban, and A. Harel-Belan, Mathematical Modeling of microRNA-Mediated Mechanisms of Translation Repression, in MicroRNA Cancer Regulation: Advanced Concepts, Bioinformatics and Systems Biology Tools, Advances in Experimental Medicine and Biology Vol. 774, Springer, 2013, pp. 189-224.
6. N. Morozova, A. Zinovyev, N. Nonne, L.-L. Pritchard, A.N. Gorban, and A. Harel-Bellan, Kinetic signatures of microRNA modes of action, RNA, Vol. 18, No. 9 (2012) 1635-1655

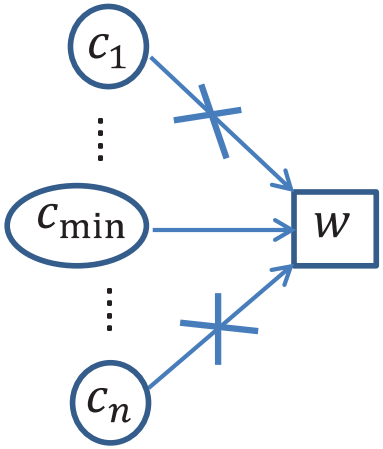
Volpert's graph for nonlinear reactions



Simplification of "forks" for nonlinear reactions

$$\dot{c} = -w_{\max} + (\text{positive terms})$$





$$w = const \times c_{\min}^{\alpha}$$

The main difficulty: the result of the operation depends on constants AND concentrations and might change in time.

What did we talk about from the mathematical perspective?

1. A discrete version of the Wentzel–Freidlin theory;

2. A Lusternik–Vishik–Lidskii perturbation theory for Markov chains;

3. A tropical asymptotic of chemical kinetics.