

Hierarchical models in systems biology

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CEA-EDF-INRIA School Model reduction: theory and
applications, 9 October 2007

Outline

- ▶ Introduction : Models of Systems Biology
- ▶ Limitation theory for linear hierarchical models
- ▶ Model reduction for nonlinear hierarchical models
- ▶ Signalling of NF κ B: a case study

Acknowledgements and some references

Alexander Gorban, Department of Mathematics, University of Leicester, UK

Andrei Zinovyev, Service de Bioinformatique, Institut Curie, Paris.

Alain Lilienbaum, Cytosquelette et Développement, CNRS, Paris.

- A.N.Gorban, O.Radulescu, Dynamic and static limitation in multiscale reaction networks, revisited.
- O.Radulescu, A.Zinovyev, A.Lilienbaum, Model reduction and model comparison for NF κ B signaling.
- O.Radulescu et al., Hierarchies and modules in complex biological systems.

Systems biology

Systems biology = approach to physiology and pathology via dynamical models of interaction molecules

Graphs, dynamical systems, complexity, systems control

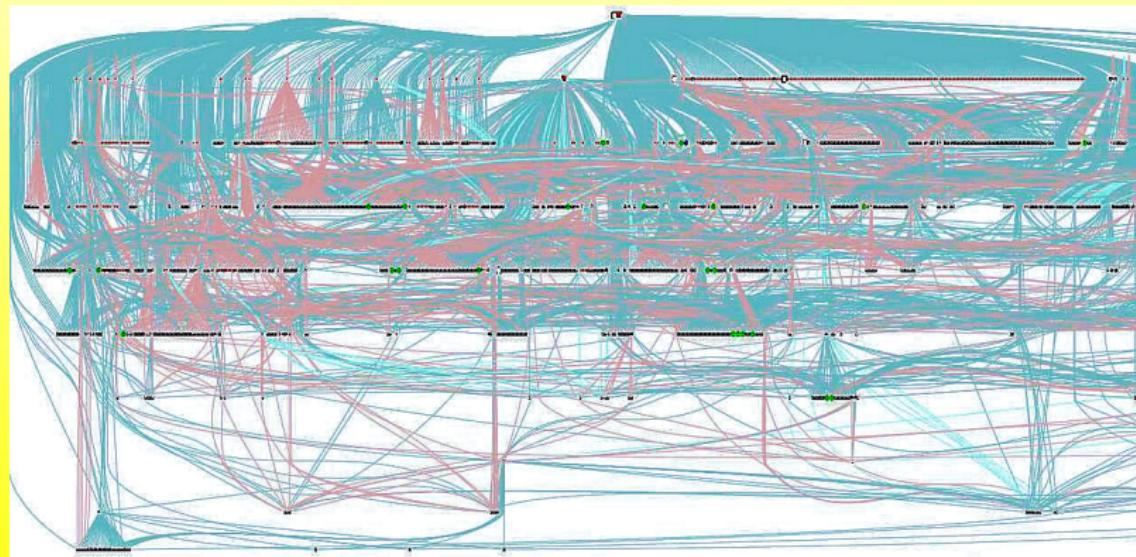
Domains of application: signalling, gene regulation, metabolism

Objectives

- ▶ make sense out of huge data
- ▶ guide experiments
- ▶ design : synthetic biology
- ▶ propose general principles

Make sense out of huge data

Can we understand this?



Guide experiments

In a large scale screening each kinase inactivation experiment costs 100 euros

We have a set of 100 kinases whose putative effect on proliferation is to be tested

We want to test all combinations of two kinases ...

$$100 \times 100 \times 100 = 10^6$$

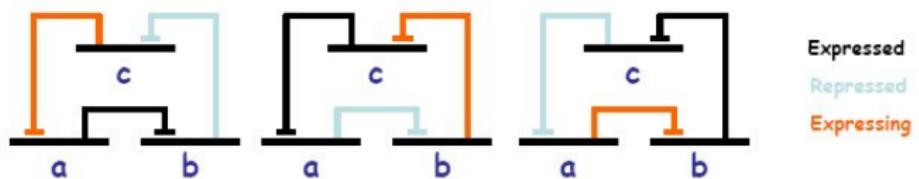
Design, synthetic biology

How to make a switch or an oscillator?

Ex: Bistable Switch

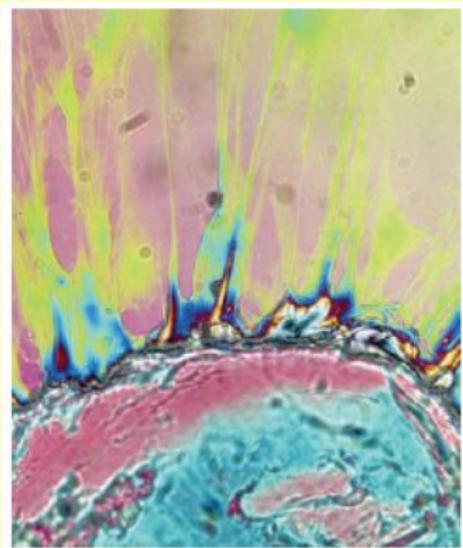


Ex: Oscillator



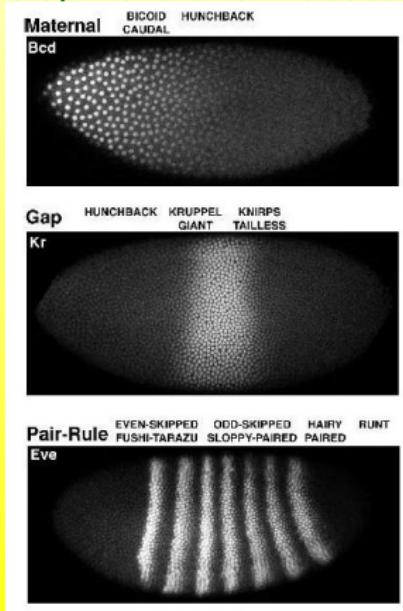
General Principles

Cancer and robustness



Hunt for fragility: weaknesses in tumour growth dynamics could yield new anti-cancer therapies.

Development and Robustness

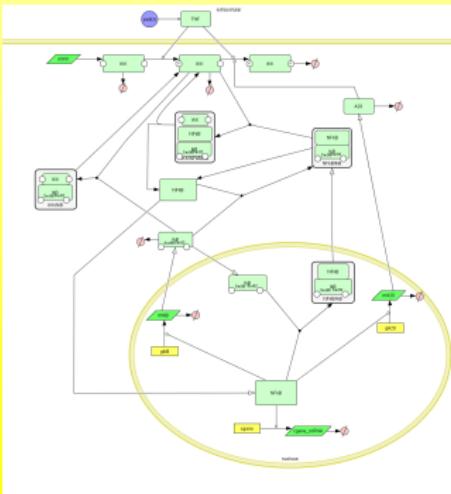


Systems biology standards for biochemical networks

SBML (systems biology markup language)

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</listOfCompartments>
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    </listOfReactants>
    <listOfProducts>
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    </listOfProducts>
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        <apply>
          <times/>
          <ci> mw3a975021_b573_49e6_bb9f_cba57d45785b </ci>
          <ci> mwa320d8ae_3fc8_47d9_9f38_d12a30922b6d </ci>
        </apply>
      </math>
    .....
  </reaction>
</listOfReactions>
```

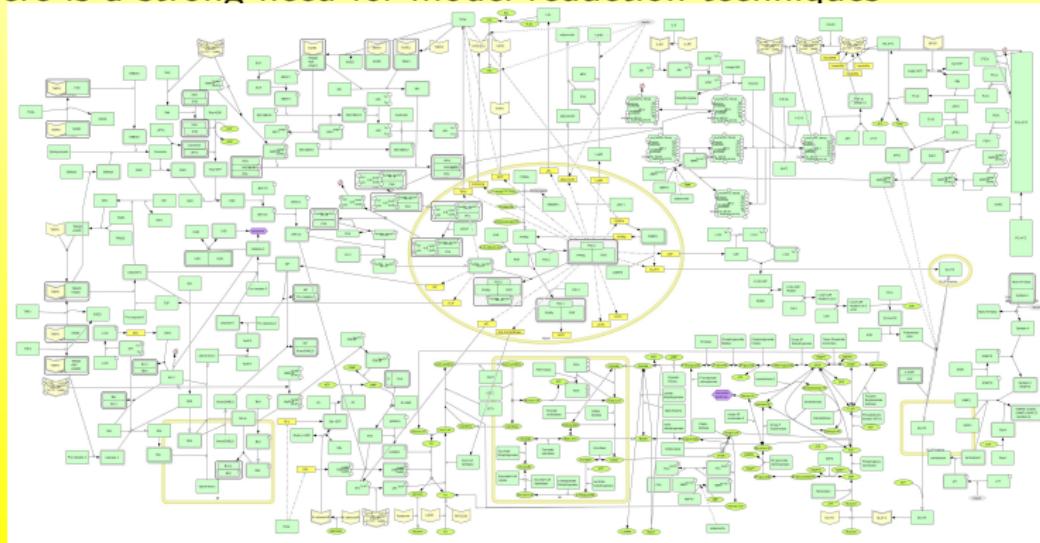
Systems biology graphical notation



Properties of molecular systems

Complexity, hierarchical nature (many well separated timescales, modules)

There is a strong need for model reduction techniques



Biochemical reactions models

- ▶ state $\mathbf{X} \in \mathbb{N}^n$, X_i number of molecules of the species i
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$$R_j^+(\mathbf{x}) = k_j^+ \prod_{i \in \text{reactants}(j)} x_i^{\nu_{ji}^+}, \quad R_j^-(\mathbf{x}) = k_j^- \prod_{i \in \text{products}(j)} x_i^{\nu_{ji}^-}$$

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Stochastic dynamics $\mathbf{X}(t)$ is a jump Markov process, intensity

$\lambda(\mathbf{x}) = V \sum_{j=1}^r (R_j^+(\mathbf{x}) + R_j^-(\mathbf{x}))$ and jump distribution

$p_j^{+/-}(\mathbf{x}) = R_j^{+/-}(\mathbf{x}) / (\sum_{j=1}^r R_j^+(\mathbf{x}) + R_j^-(\mathbf{x}))$

Questions for this lecture

1. Which is the dynamics?
 - ▶ steady state or attractor
 - ▶ time to reach attractor
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 - ▶ time to reach attractor
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2. Which are the critical parameters? Limiting steps?
3. Which are the possible simplifications (model reduction)?
 - ▶ invariant manifolds
 - ▶ quasistationarity
 - ▶ averaging

Linear network of chemical reactions

A_i are reagents, c_i is concentration of A_i .

All the reactions are of the type $A_i \rightarrow A_j$.

$k_{ji} > 0$ is the reaction $A_i \rightarrow A_j$ rate constant.

The reaction rates: $w_{ji} = k_{ji} c_i$.

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Kinetic equation

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

Linear network of chemical reactions

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.

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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** $\Sigma = \{c \mid c_i \geq 0, \sum_i c_i = 1\}$ is positively invariant.

Properties of the dynamics of linear networks

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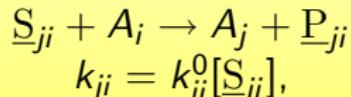
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- ▶ The Jordan cell of \mathbf{K} that corresponds to zero eigenvalue is diagonal – because all solutions should be bounded in Σ for positive time.
- ▶ The shift in time, operator $\exp(\mathbf{K}t)$, is a contraction in the l_1 norm for $t > 0$: for $t > 0$ and any two solutions of (1)
 $c(t), c'(t) \in \Sigma$

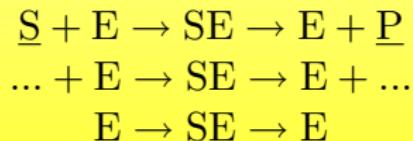
$$\sum_i |c_i(t) - c'_i(t)| \leq \sum_i |c_i(0) - c'_i(0)|.$$

Pseudomonomolecular reactions



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

For example, the Michaelis-Menten system:



Limiting step

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

Let k_q be the smallest constant: $k_q \ll k_i$ ($i \neq q$)

In time scale $\sim 1/k_q$:

$A_1, \dots A_{q-1}$ transform fast into A_q ,

$A_{q+1}, \dots A_{n-1}$ 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

Hierarchical models

Systems biology models need constants and these are most of the time unknown.

We have some ideas about the network structure: reaction graph, influence graph, etc.

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

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

We say that the system has separated constants.

Limiting Step for Irreversible Cycle

Irreversible Cycle $A_1 \rightarrow A_2 \rightarrow \dots A_n \rightarrow A_1$
with reaction rate constants k_i (for $A_i \rightarrow \dots$)

Limiting step $A_n \rightarrow A_1$
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

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

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

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

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

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

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

In particular the largest relaxation time of a cycle $1/k_{n-1}$ is controlled by the second slowest constant.

Dynamic limitation in a cycle, eigenvectors:

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

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

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

$$l_i^i = r_i^i = 1 \text{ and } r_{i-m}^i = l_{i+m}^i = 0.$$

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

$$r_j^i \approx 1, -1, \text{ or } 0; \quad l_j^i \approx 1, \text{ or } 0$$

Eigenvalues and eigenvectors specify dynamics of linear systems

$$c(t) = (I^0, c(0)) + \sum_{k=1}^{n-1} r^k (I^k, c(0)) \exp(-\lambda_k t)$$

Suppose that $c(0)_j = \delta(j, i)$ (charge node i).

- ▶ For systems with separated constants, each time an exponential goes to zero there is a jump $-r^k$ in concentrations, if $I_i^k = 1$.

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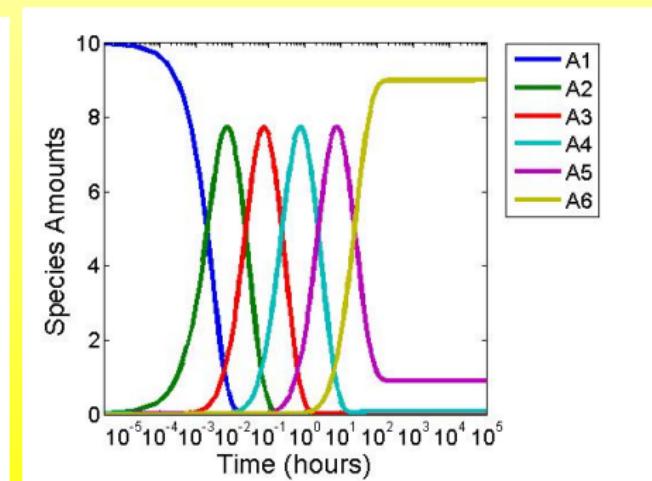
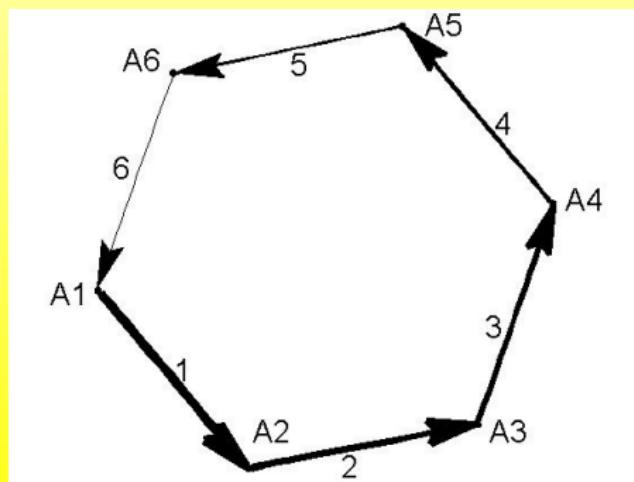
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- ▶ The sequence of jumps $-r^k, I_i^k = 1$ codes the dynamics with initial data in i .
- ▶ The last jump represents the slowest relaxation process, the smallest (in absolute value) eigenvalue.

Jumps in concentrations

$$r_1 = (1, -1, 0, 0, 0, 0), l_1^1 = 1, \dots$$

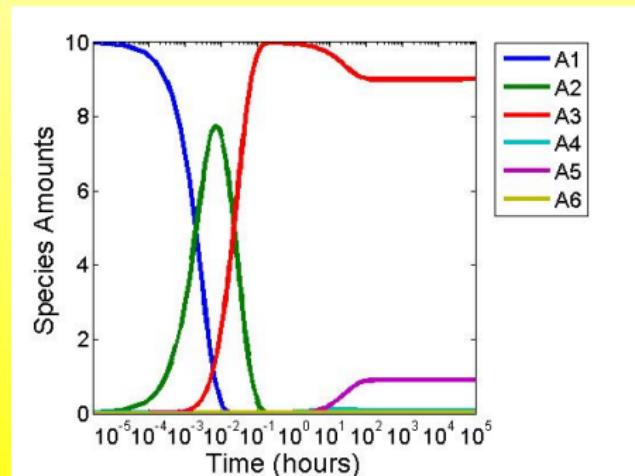
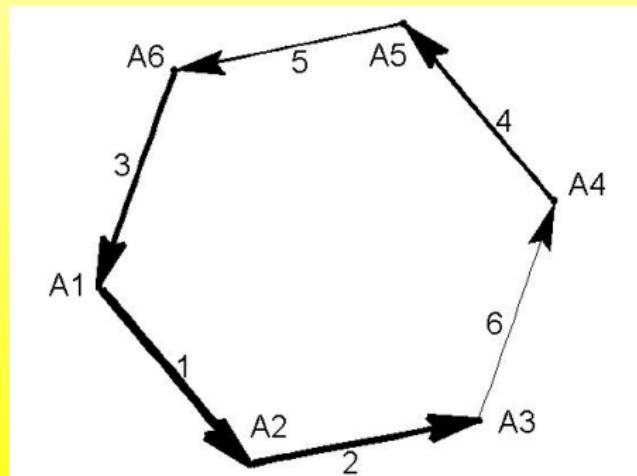
One or few jumps are observable



Jumps in concentrations

Start closer to limiting step

...less jumps



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. Minimal sinks are called *ergodic components*.

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

An important property

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).

Slowest relaxation and ergodicity boundary

Delete reactions one by one, starting with the slowest.

$k_1 > k_2 > \dots > k_r > \dots > k_n$ The first reaction that breaks ergodicity is the ergodicity boundary. We add a conservation law, i.e. a zero eigenvalue.

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$$K = K_{<r}(k_1, k_2, \dots, k_{r-1}) + k_r Q + o(k_{j_r})$$
$$\bar{a}k_r \geq \min_{\lambda \neq 0} \{-Re\lambda\} \geq \underline{a}k_r$$

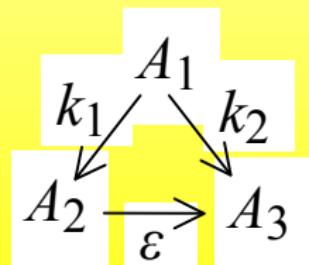
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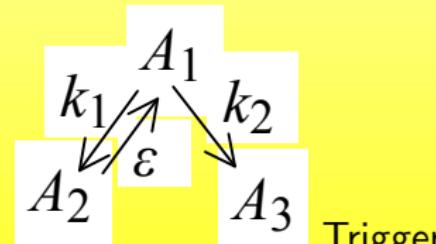
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$$\bar{a}k_r \geq \min_{\lambda \neq 0} \{-Re\lambda\} \geq \underline{a}k_r$$



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



Trigger alternative: $k_1 \ll k_2$, then
 $\min_{\lambda \neq 0} \{-Re\lambda\} \approx \varepsilon$; $k_1 \gg k_2$
 then $\min_{\lambda \neq 0} \{-Re\lambda\} = o(\varepsilon)$

The main goal

Compute approximate dynamics for arbitrary reaction network with well separated constants

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

This was shown to be easy for chains and irreversible cycles.
We build an acyclic reaction network that approximates kinetic of initial network. For this, it is easy to compute right/left eigenvectors.

Auxiliary discrete dynamical systems

For each A_i , $\kappa_i = \max_j\{k_{ji}\}$, $\phi(i) = \arg \max_j\{k_{ji}\}$;

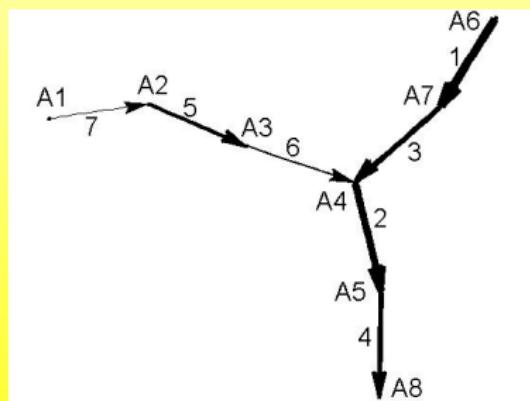
$\phi(i) = i$ if there is no outgoing reaction $A_i \rightarrow A_j$.

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, $Att(C_j)$: $\mathcal{A} = \bigcup_j Att(C_j)$.

1-st case is simple: acyclic auxiliary dynamic systems

All C_j are point attractors.



$r_{\Phi(j)}^i = \frac{\kappa_j}{\kappa_{\Phi(j)} - \kappa_i} r_j^i$ go along the flow $I_j^i = \frac{\kappa_j}{\kappa_j - \kappa_i} I_{\Phi(j)}^i$ go opposite to the flow.

Use $\infty \times 0 = 1$.

For instance:

$$I^1 \approx (1, 0, 0, 0, 0, 0, 0, 0)$$

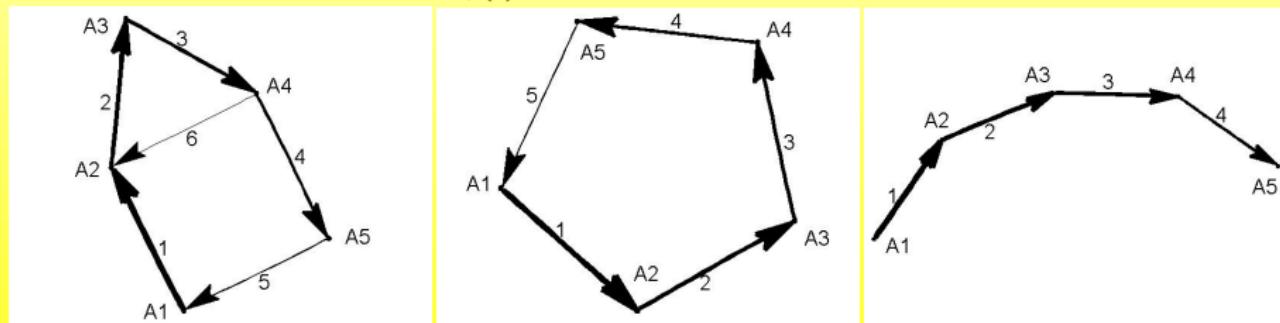
$$r^1 \approx (1, 0, 0, 0, 0, 0, 0, -1)$$

$$I^5 \approx (0, 0, 0, 1, 1, 1, 1, 0)$$

$$r^5 \approx (0, 0, 0, 0, 1, 0, 0, -1)$$

2-nd case: all C_j are sinks in the initial network

Delete the limiting steps from cycles C_j . The obtained *acyclic* reaction network $A_i \rightarrow A_{\phi(i)}$ is the right approximation.



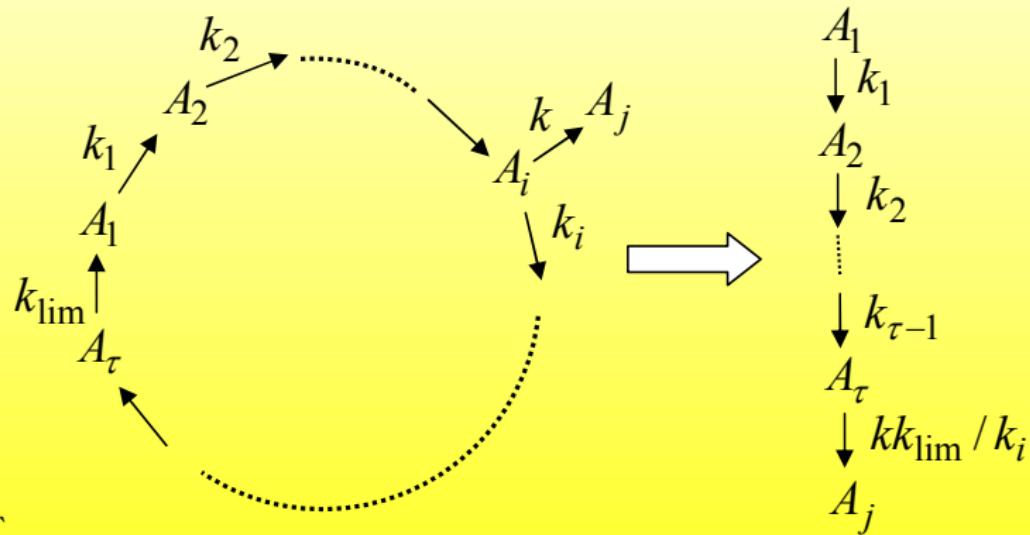
3-rd case: some of C_j are not sinks

- ▶ Replace each such C_i by a new vertex A_i .
- ▶ Inside C_i , the normalized stationary distribution is $c_j^* \approx \kappa_{\lim i} / \kappa_j$, $A_j \in C_i$.
- ▶ Exit constants are renormalized: for each $A_j \rightarrow A_q$ ($A_j \in C_i$, $A_q \notin C_i$) define $A^i \rightarrow A_q$ with the constant $k_{qj}c_j^*$.

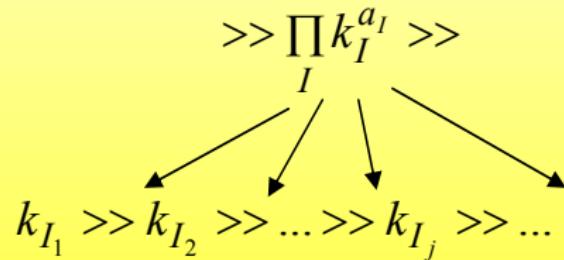
We prepared a new reaction network. Iterate.

- ▶ 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.
- ▶ At each step, some constants are critical (the dominant ones); the dominated ones can change arbitrarily within the constraints of the ordering without influencing the dynamics.

Cycles surgery on the way back



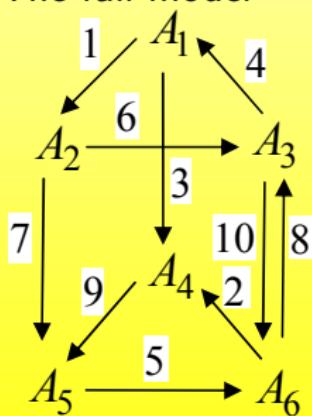
Inclusion monomials in the ordering



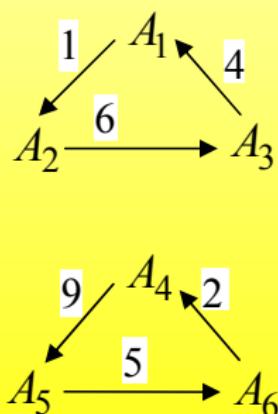
A more complicated example: the prism

The prism is a model used in biophysics (Kurzynski Prog.Biophys.Mol.Biol. 98).

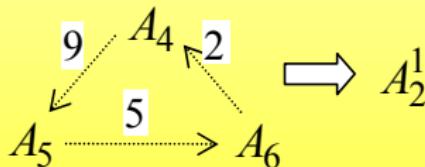
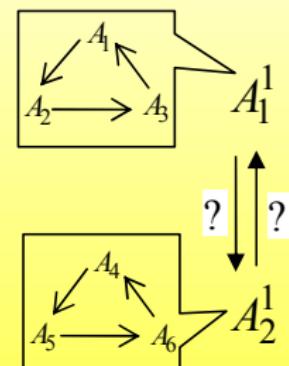
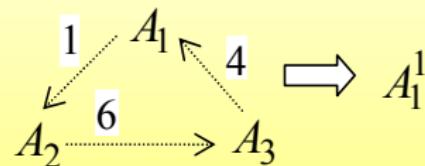
The full model



The auxiliary dynamical system



Glue cycles



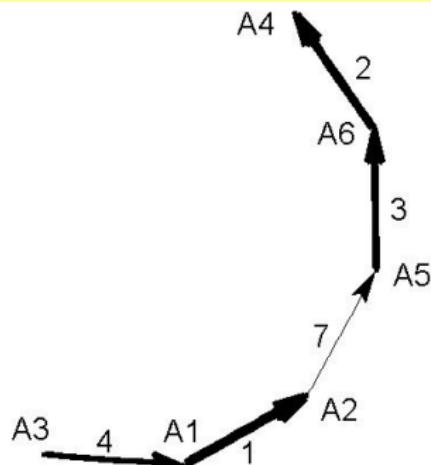
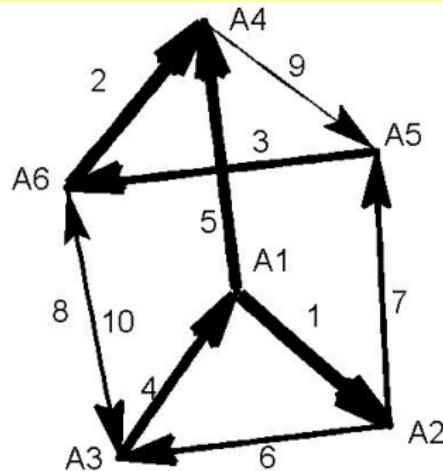
The limiting constant is k_{32} for the upper cycle, k_{54} for the lower cycle.

$$k_{21}^1 = \max\{k_{41}k_{32}/k_{21}, k_{52}, k_{63}k_{32}/k_{13}\}, \quad k_{12}^1 = k_{36}k_{54}/k_{46}$$

six possible orderings, each one a different simplification (different acyclic auxiliary dyn. system or different dominant (critical) parameters)

$$k_{21}^1 = k_{52}, \quad k_{21}^1 \gg k_{12}^1$$

The acyclic auxiliary dyn. syst. is a reaction from A_1^1 to A_2^1 .
Steady state mass is concentrated in A_2^1 . Restore cycles, delete
limiting steps.



Three zero-one laws for multiscale linear networks

1. Steady states (for weakly ergodic networks), recall the example of a cycle.

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SINK1... $\leftarrow A_i \rightarrow \dots$ SINK2

From each vertex almost all flux goes either to SINK1, or to SINK2 (“xor” instead of “or”).

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3. Relaxation eigenmodes (eigenvectors): the dynamics is a sequence of jumps.

CONCLUSION

- We have an algorithm for extraction of the dominant systems from the graph of reactions;
- “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 species;

Model reduction, model comparison

1. **Model reduction** = from one model obtain a less complex one (less variables, less parameters).
 - ▶ **Trajectory based techniques** such as Karhunen-Loëve expansion: find a low dimensional linear space containing the trajectories.
 - ▶ **Singular perturbations**: lumping based on quasistationarity and quasi-equilibrium, approximations to invariant manifold (CSP).
 - ▶ **Averaging**: produce coarse graining variables.
 - ▶ **Invariant or center manifold** calculations: find a non-linear manifold containing the trajectories. Generally these are local methods, the invariant manifold can be made of many pieces.
 - ▶ **Graph contraction** keeping steady state and fluxes at steady state.

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 - ▶ **Graph contraction** keeping steady state and fluxes at steady state.
2. **Model comparison** = given two models of different complexity, construct a mapping between them (map variables, parameters).

Limitation theory for non-linear systems?

- Time scales tend to cluster, or diverge
 - ▶ Singular behavior of the system at bifurcations, no limitation.
 - ▶ Limit cycles and chaotic attractors are possible. Total separation is improbable. For instance Gershgorin theorem implies that kinetics matrices with well separated elements have real eigenvalues.
 - ▶ Invariant manifolds gather several degrees of freedom
- Discrete dynamics on concentrations to be replaced by discrete dynamics on reaction mechanisms?

Quasistationarity

Some species have small concentrations most of the time

$x = \mathcal{O}(\epsilon)$. The system is of the type slow/fast.

$$\frac{1}{\epsilon} \frac{dx}{dt} = f(x, y, \epsilon) \quad (1)$$

$$\frac{dy}{dt} = g(x, y, \epsilon) \quad (2)$$

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If for any y the dynamics (1) has a hyperbolic point attractor, then after a fast transition the system evolves close to the slow manifold M_0 and according to the equation:

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Theorem (Fenichel)

There is an invariant manifold M_ϵ close to M_0 .

A reaction lumping recipe for reaction networks, due to Clarke

/ set **quasi-stationary species**.

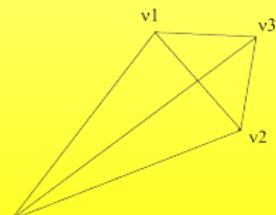
/ are involved in reactions \mathcal{R}_I .

Other species involved in \mathcal{R}_I are T , the **terminal species**.

S_I, S_T are stoichiometry matrices.

Reduction recipe:

1. Solve $\sum_{j \in \mathcal{R}_I} \nu_j R_j(\mathbf{x}_I, \mathbf{x}_T) = 0$ to obtain \mathbf{x}_I as functions of \mathbf{x}_T .
2. Replace R_I by a convex basis.
 - $S_I \gamma = 0$
 - $\gamma_i \geq 0$, if i is irreversible
 - γ has minimal number of nonzero coeffs
3. Eliminate internal cycles, i.e. impose $S_T \gamma \neq 0$.



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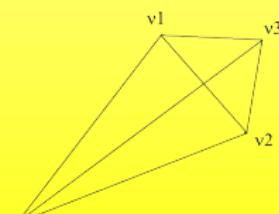
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Remark: no unique recipe, this one has some advantages.

Rate calculations

Limit simplifications of quasi-stationarity equations

- ▶ Solve $\sum_{k \in \mathcal{R}_I} \nu_{k,I} R_k(\mathbf{x}_I, \mathbf{x}_T) = 0$
- ▶ This is a polynomial equation. Obtain dominant order polynomial approximations of the solutions.

Rates of simple submechanisms

- ▶ $\sum_{k \in \mathcal{R}_I} \nu_{k,T} R_k(\mathbf{x}_I, \mathbf{x}_T) = \sum_{i=1}^s S_T \gamma_i R_{\gamma_i}(\mathbf{x}_T)$
- ▶ Suppose that for each simple submechanism i there is a terminal species j such that $S_T \gamma_i$ is unique having nonzero coordinate j .
- ▶ $R_{\gamma_i}(\mathbf{x}_T) = \frac{1}{(S_T \gamma_i)_j} \sum_{k \in \mathcal{R}_I} \nu_{kj} R_k(\mathbf{x}_I, \mathbf{x}_T).$

Averaging

Some species have oscillating behavior, others do not.

$$\frac{dx}{dt} = f(x, y, \epsilon) \quad (1)$$

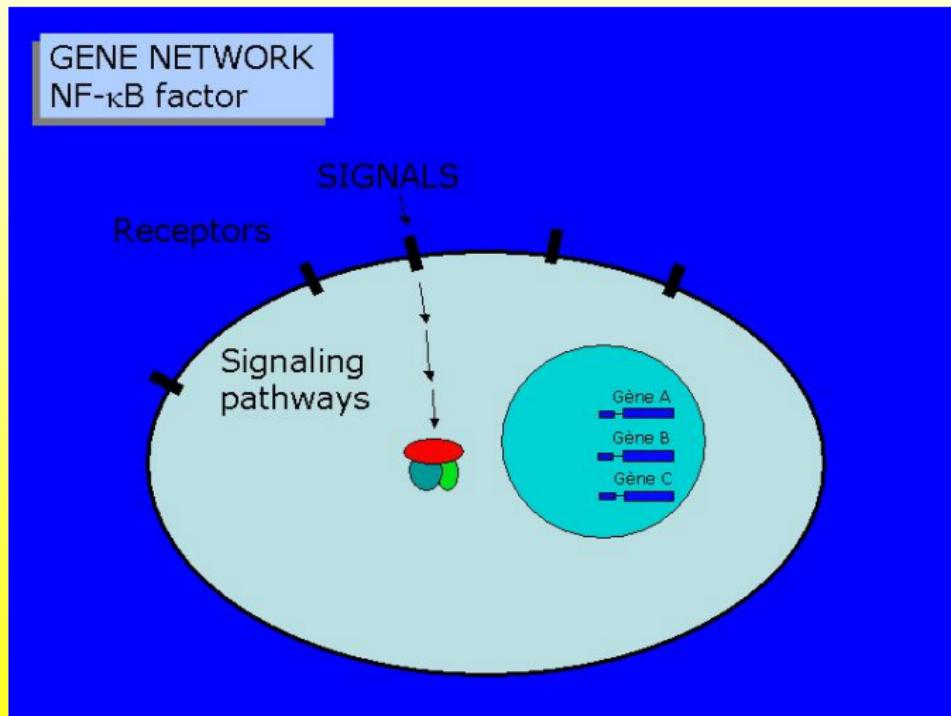
$$\frac{dy}{dt} = \epsilon g(x, y, \epsilon) \quad (2)$$

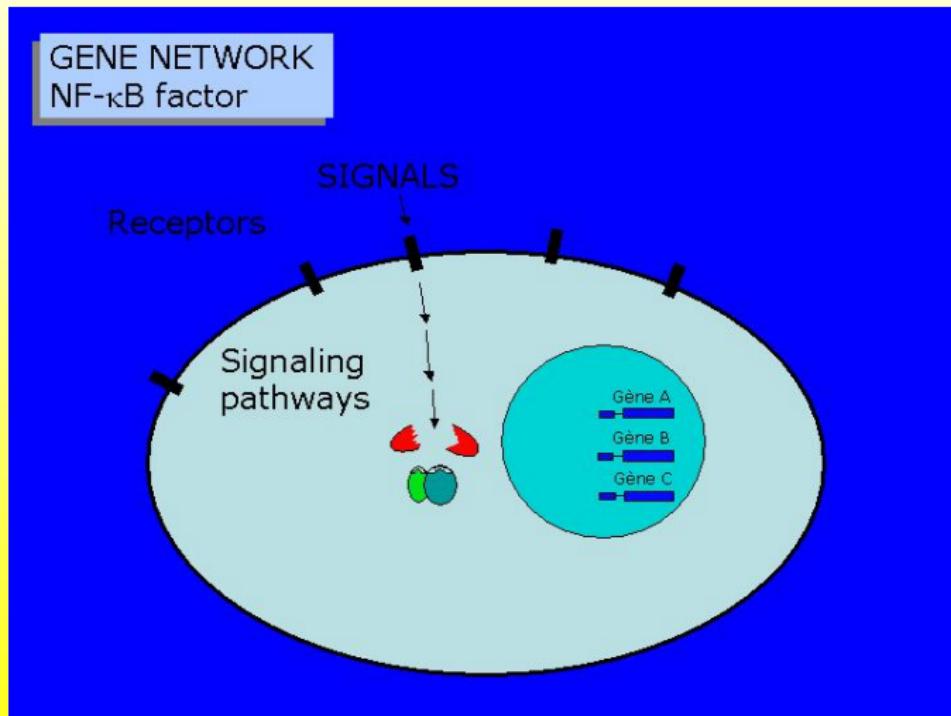
Theorem (Pontryagin, Rodygin)

If for any y the fast dynamics (1) has an attractive hyperbolic limit cycle, then after a fast transition the slow variables average oscillations:

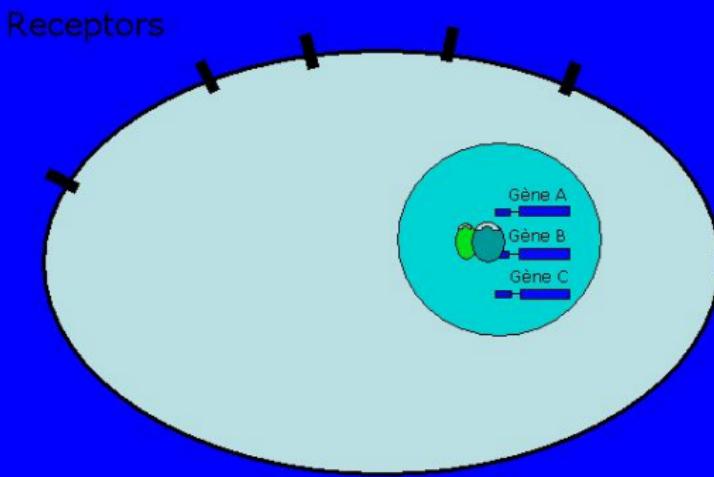
$$\frac{dy}{dt} = \frac{1}{T(y)} \int_0^{T(y)} g(x(\tau, y), y, 0) d\tau$$

Extensions of the theorem in the unstable case by Neishtadt 87, then Sari and Yadi 04 : delayed loss of stability.

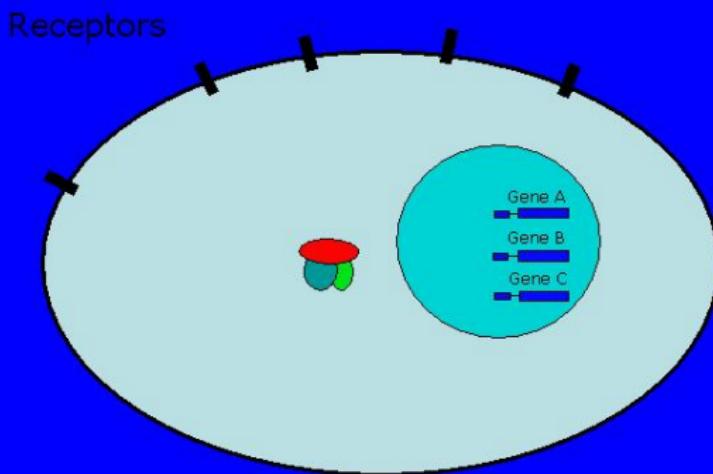


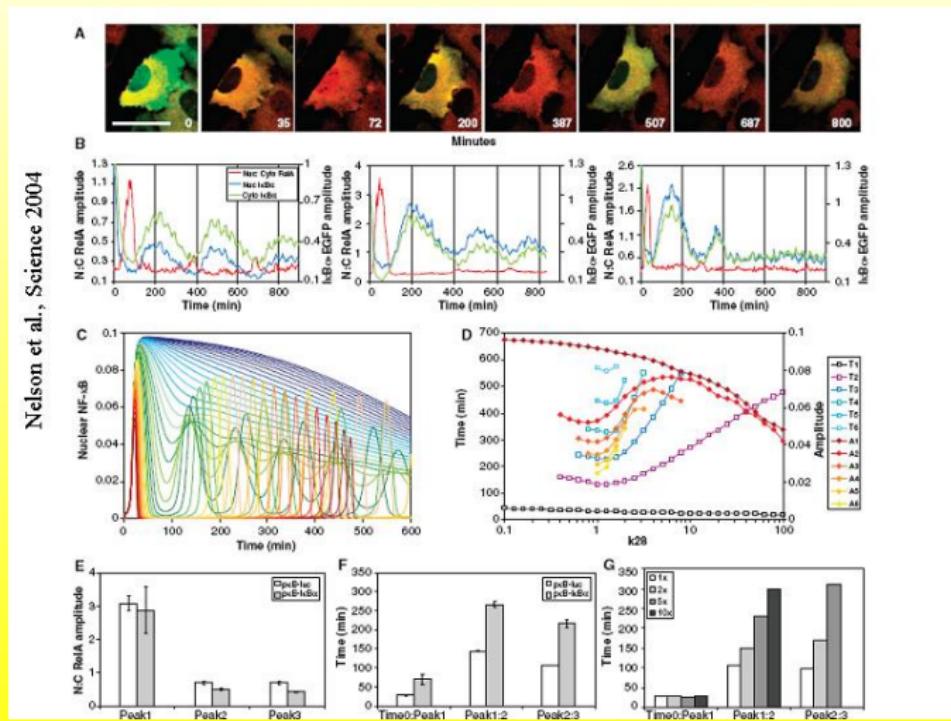


GENE NETWORK
NF- κ B factor

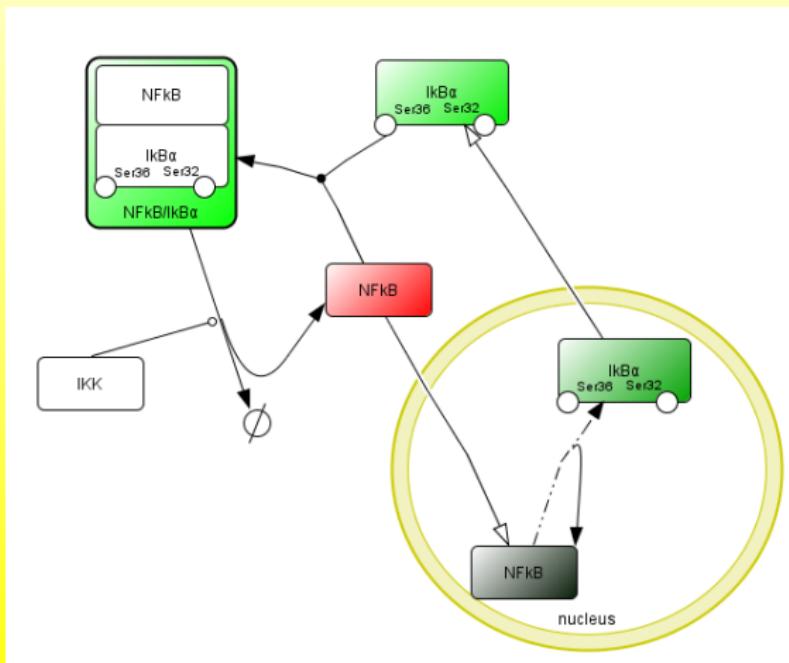


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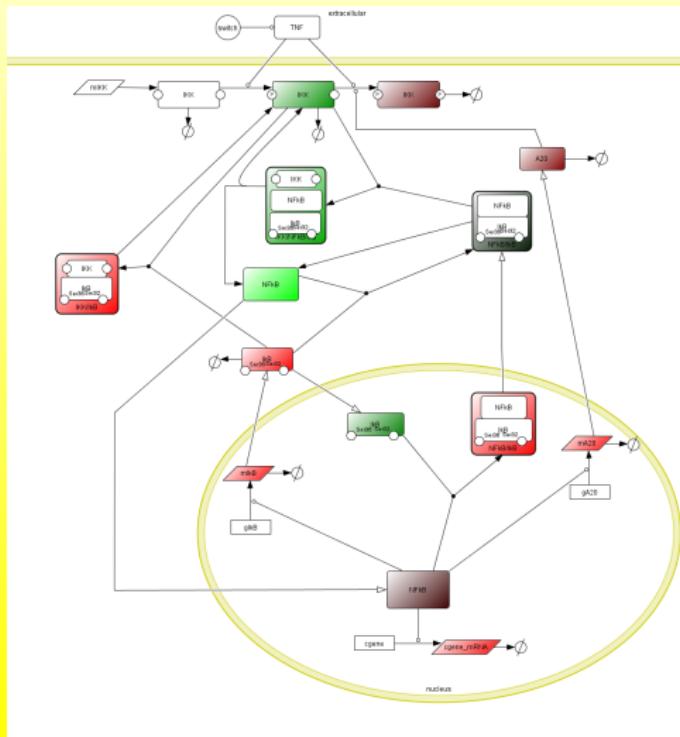




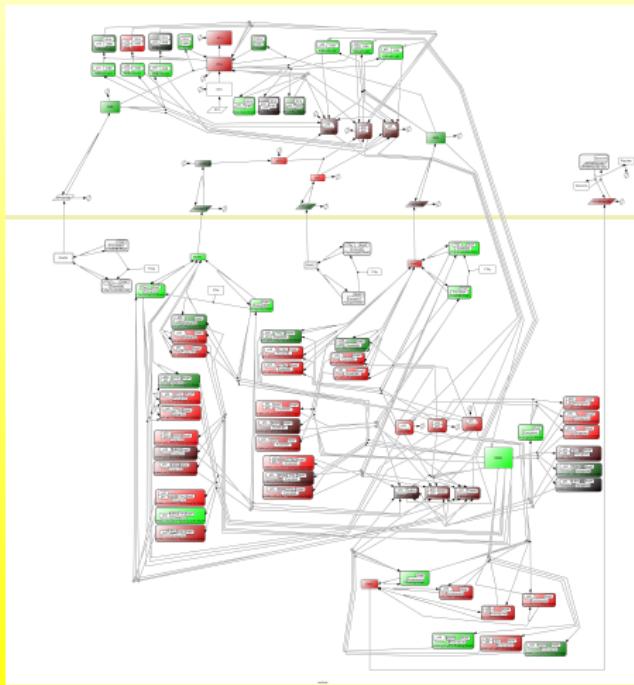
Simplest model



Average complexity model (Lipniacki)



Most complex model

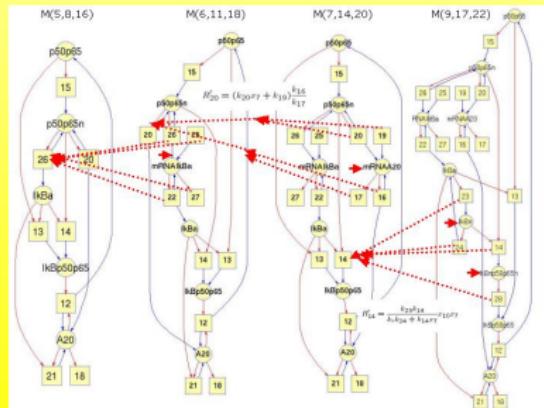


Hierarchies

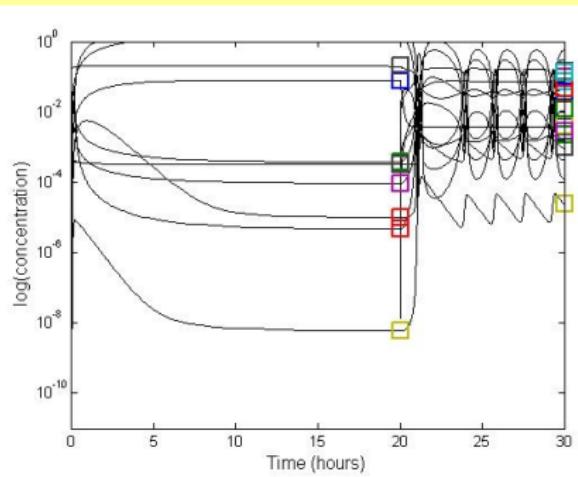
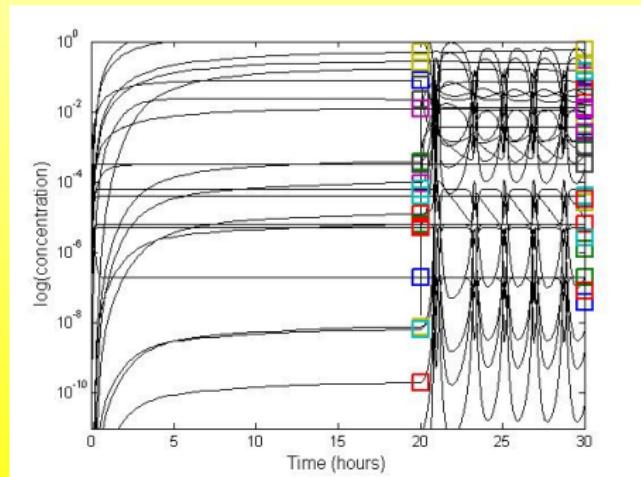
Choose the relevant timescale: period of oscillations.

Multi-step lumping of reactions; at each time use small frontier, large interior subgraphs.

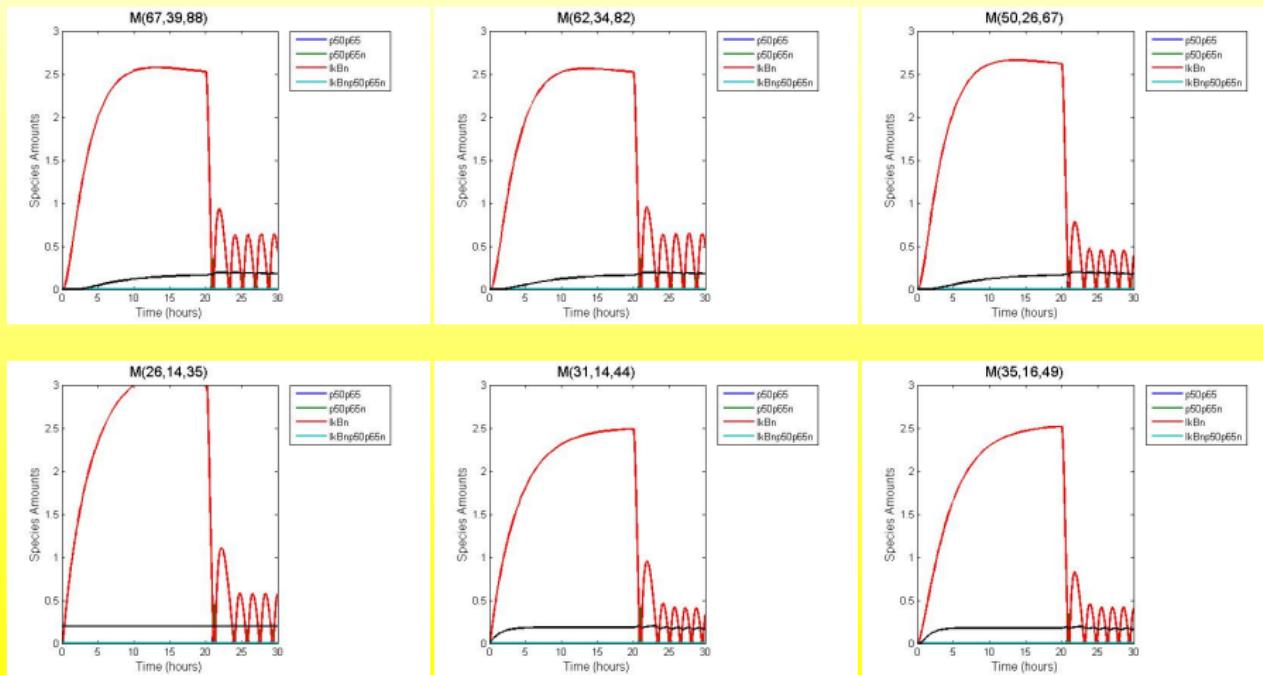
Reduction produces an hierarchy of models and mappings between parameters of models in the hierarchy.



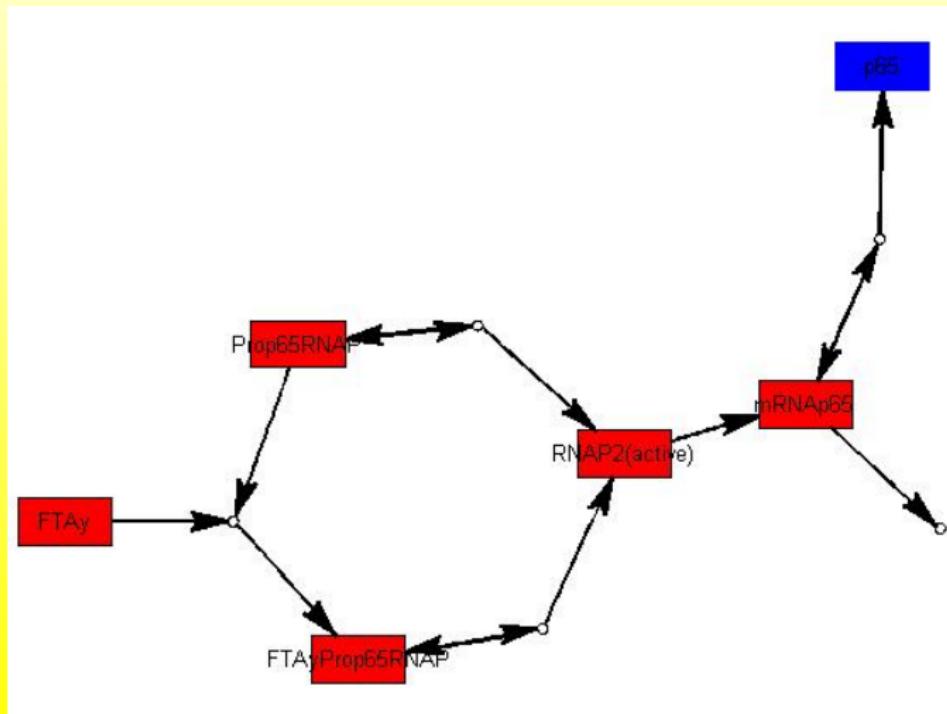
Identification of quasi-stationary species



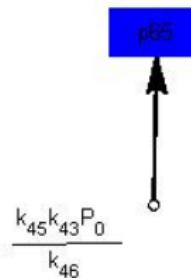
Hierarchy of models, from M(67,39,88) to M(26,14,35)



Production p65



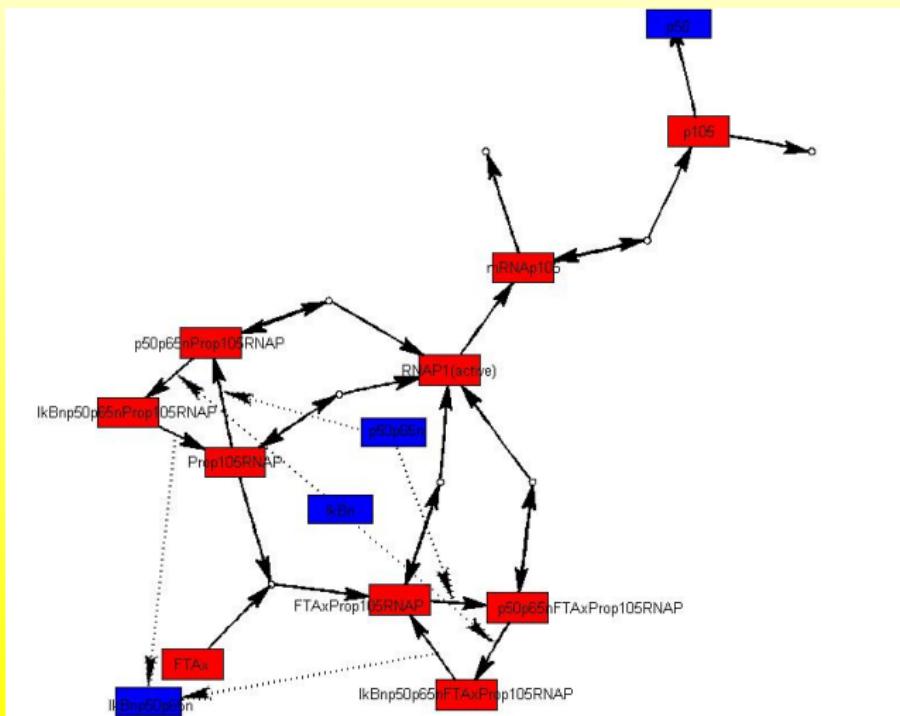
Production p65



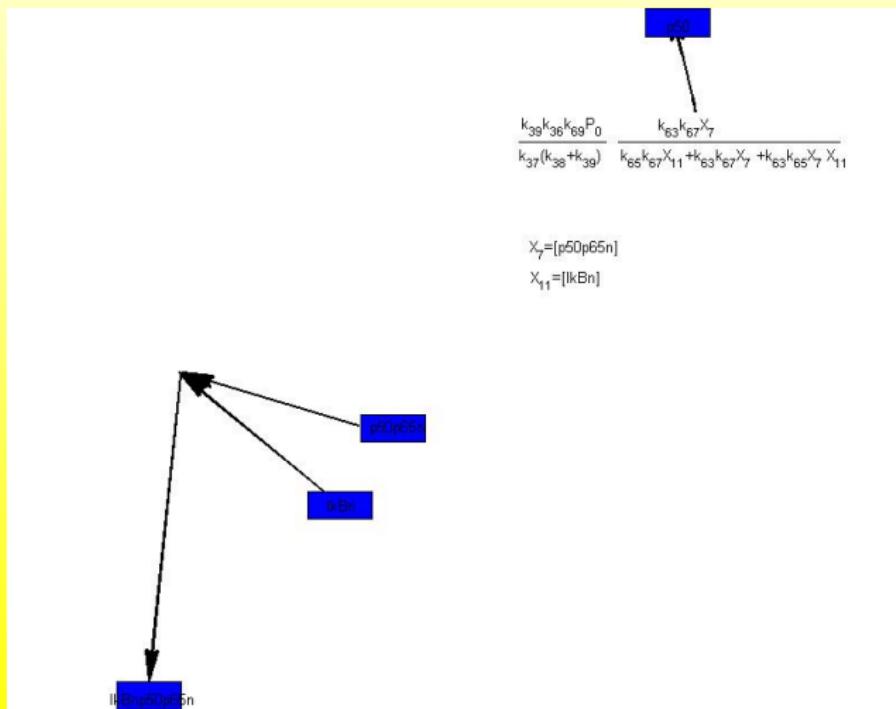
$$\frac{k_{45} k_{43} P_0}{k_{46}}$$

$$F_0 \gg \max(P_0, K_{41})$$

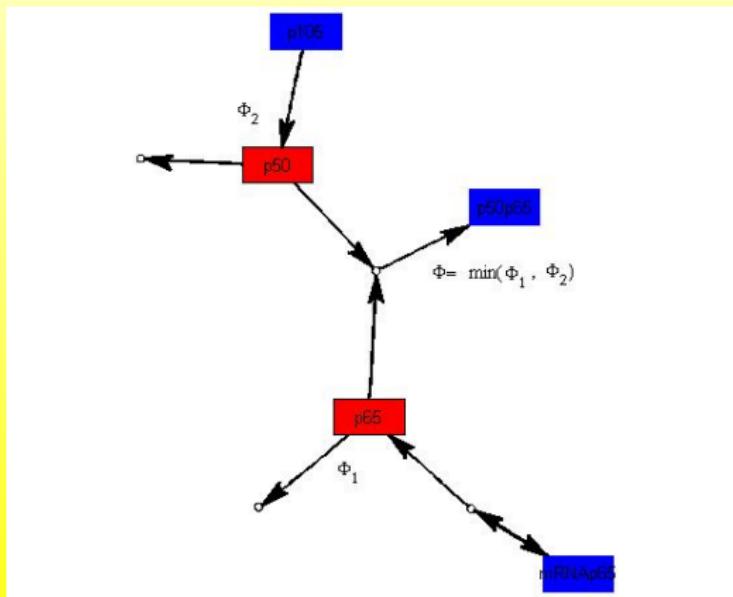
Production p50



Production p50



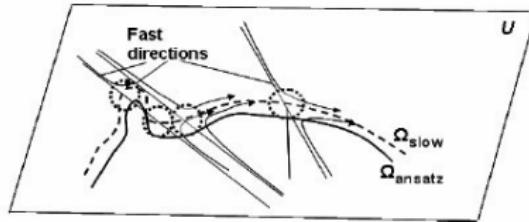
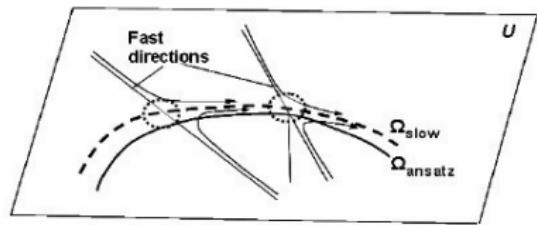
Min-funnel: production p50p65



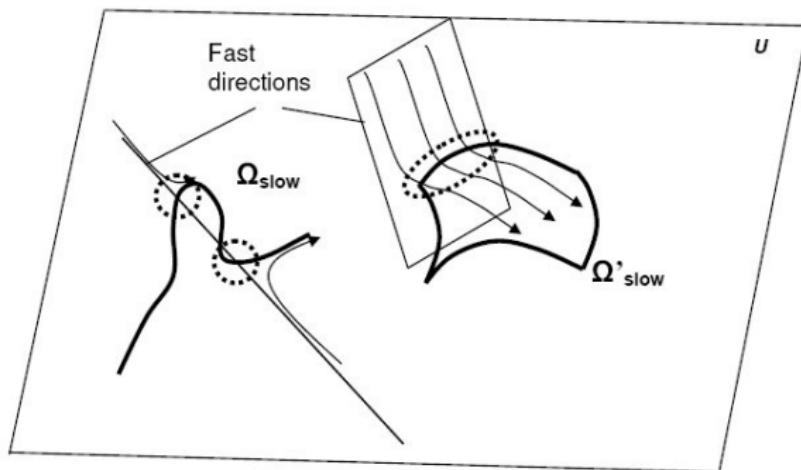
CONCLUSION

- In the non-linear case we coupled quasi-stationarity and averaging to obtain simplified mechanisms;
- We account for the hierarchical nature of the systems by using dominant approximations of the rates;
- Like in the linear case dominant systems give the rough and robust approximation;
- Zero-one laws for multiscale systems occur at the level of rates expression: some parameters (critical) remain, others disappear (only their order matters);
- The method is based on trajectories. The result may change with initial data and order of non-critical parameters;

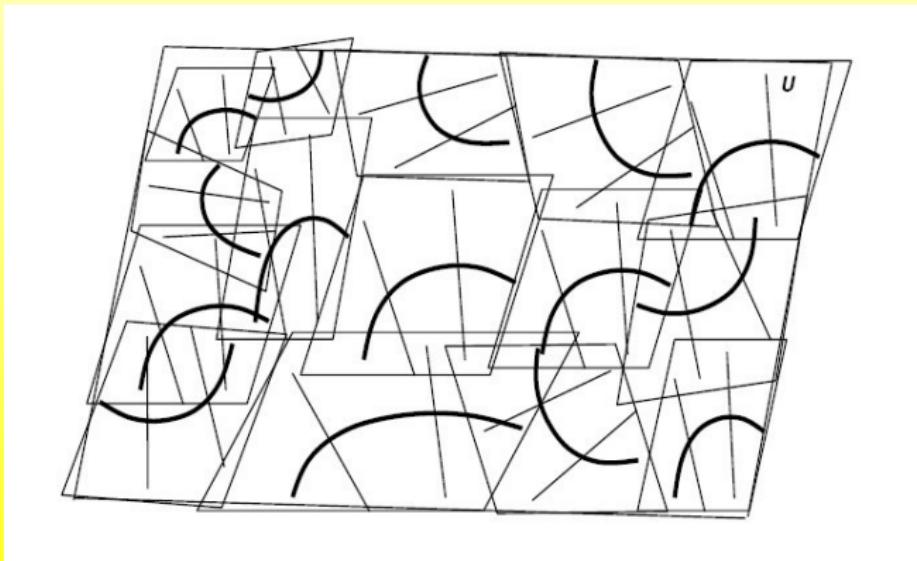
Life is not easy. I. Bifurcations in fast system



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



Crazy quilt, Edredon sauvage



Decomposition (along a trajectory)

