

# Hierarchical models in systems biology

Ovidiu Radulescu

IRMAR UMR 6025, University of Rennes 1

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# Outline

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

## Acknowledgements and some references

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

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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 $\kappa$ 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 interacting molecules

Graphs, dynamical systems, complexity, systems control

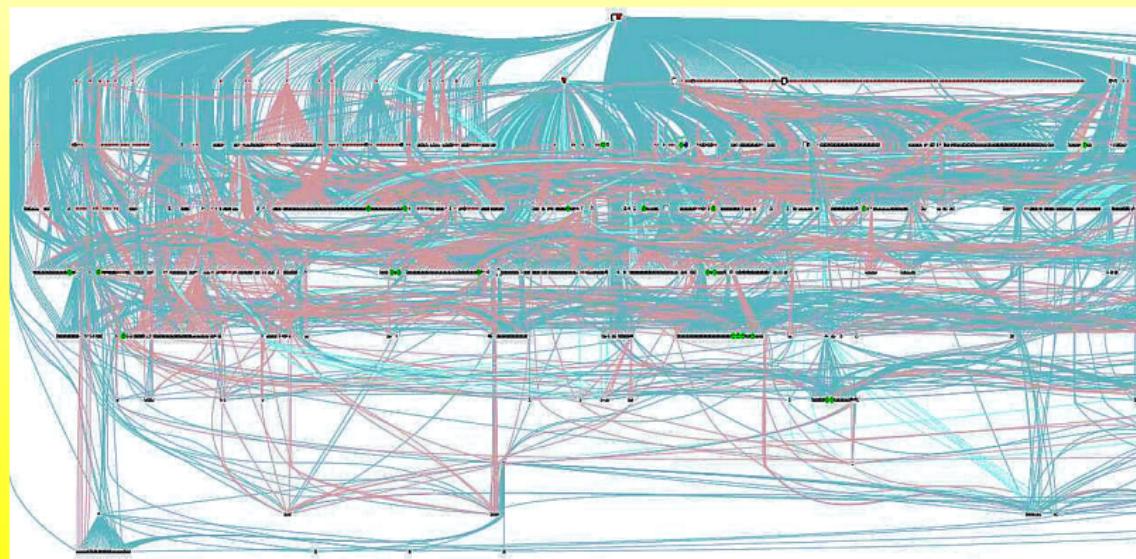
Domains of application: signalling, gene regulation, metabolism

## 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 ...

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

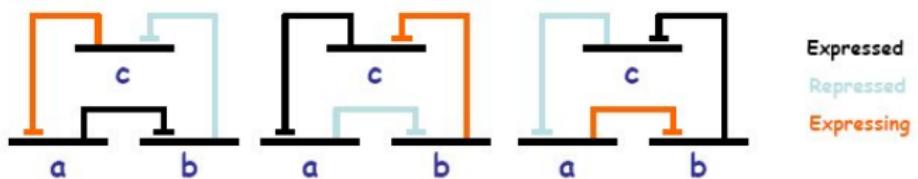
# Design, synthetic biology

How to make a switch or an oscillator?

Ex: Bistable Switch

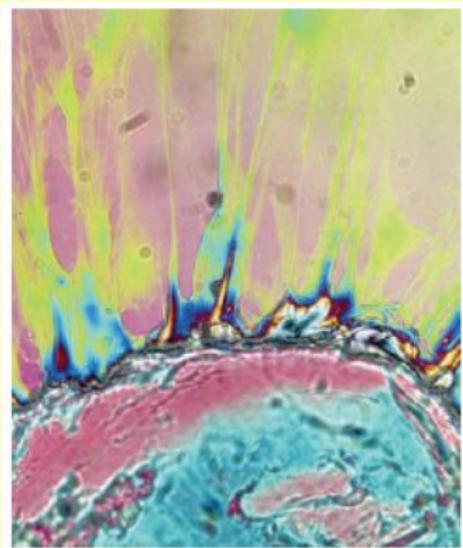


Ex: Oscillator



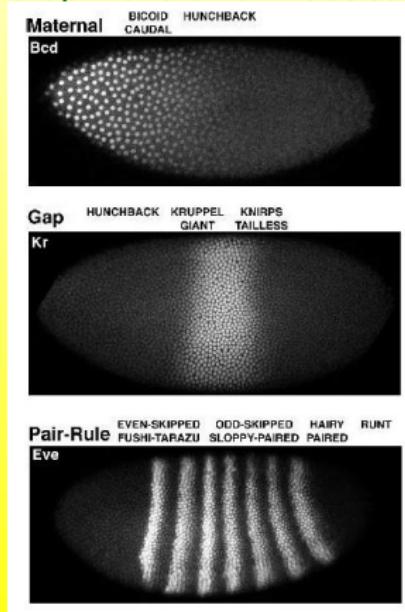
# General Principles

## Cancer and robustness



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

## Development and Robustness

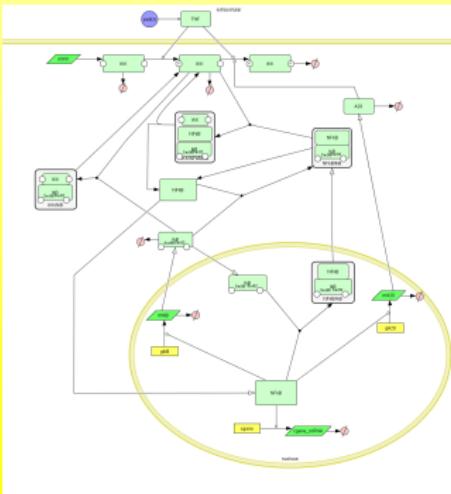


# Systems biology standards for biochemical networks

## SBML (systems biology markup language)

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  <reaction id="mw5c5225fe_b55e_4c43_b823_7815ef9e0bc7" reversible="false" fast="false">
    <listOfReactants>
      <speciesReference species="mwa320d8ae_3fc8_47d9_9f38_d12a30922b6d"/>
    </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>
```

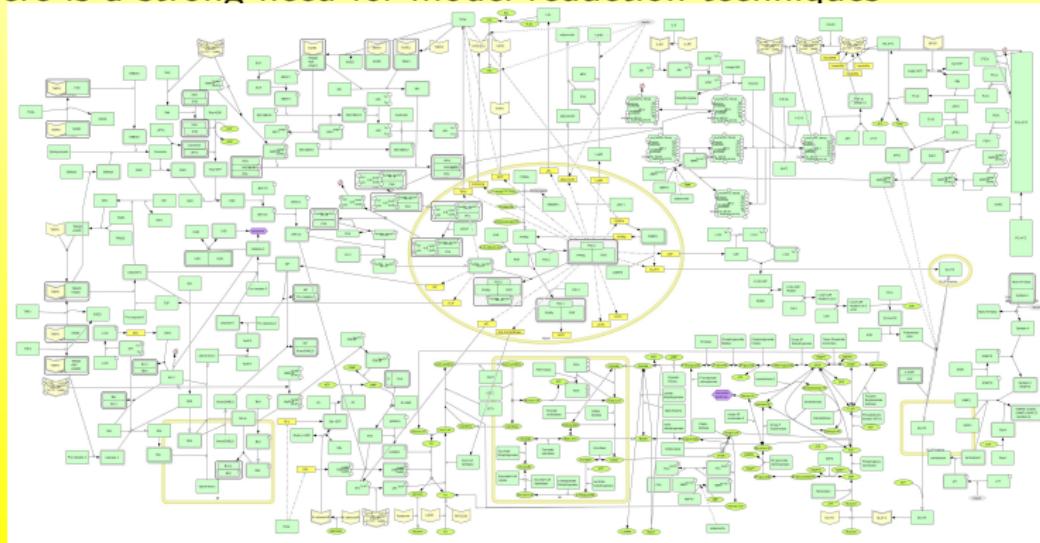
## Systems biology graphical notation



# Properties of molecular systems

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

There is a strong need for model reduction techniques



## Questions for this lecture

- 1.** How to simplify a complex model?
  - ▶ model reduction
  - ▶ model comparison
- 2.** Which are the critical parameters?
  - ▶ Limiting step theory
  - ▶ Idempotent algebra

## Biochemical reactions models

- ▶ state  $\mathbf{X} \in \mathbb{N}^n$ ,  $X_i$  number of molecules of the species  $i$
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Deterministic dynamics  $\frac{d\mathbf{x}}{dt} = \sum_{j=1}^r \nu_j (R_j^+(\mathbf{x}) - R_j^-(\mathbf{x}))$

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

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

## 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

$$\frac{dc_i}{dt} = k_{i0} + \sum_{j \geq 1} k_{ij} c_j - \left( \sum_{j \geq 0} k_{ji} \right) c_i, \quad (1)$$

or in vector form:  $\dot{c} = K_0 + Kc$ .

## 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

**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  $A_q \xrightarrow{k_q} A_n$

## 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

$$\lambda_i = -k_i + \delta_i \quad (i \leq n - 1),$$

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.

# Eigenvalues and eigenvectors specify dynamics of linear systems

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

- ▶ For systems with separated constants, each time an exponential goes to zero there is a jump  $-r^k(I^k, c(0) - c_s)$  in concentrations, if  $(I^k, c(0) - c_s) \neq 0$ .

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- ▶ The sequence of jumps codes the dynamics.
- ▶ The last jump represents the slowest relaxation process, the smallest (in absolute value) eigenvalue.

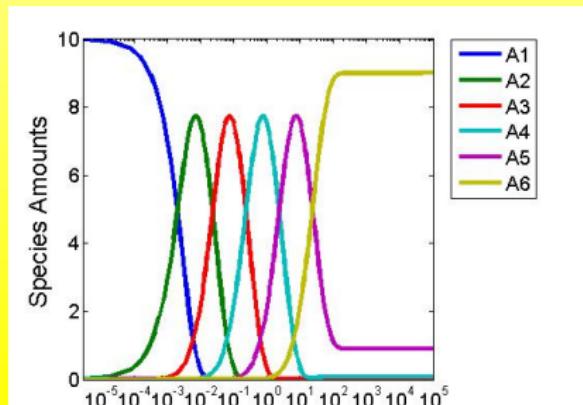
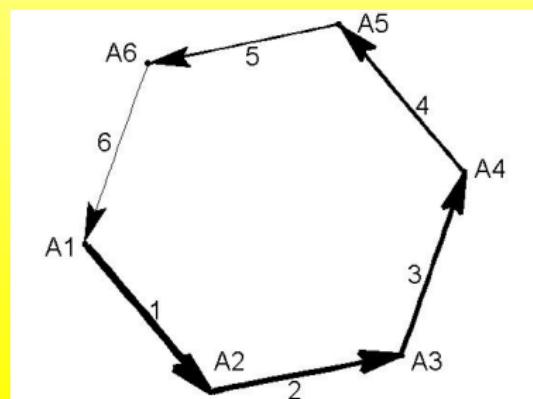
## Jumps in concentrations

Zero-one laws.

The possible values of  $l_i^k$  are 0, 1. The possible values of  $r_i^k$  are -1, 0, 1. Steady states are either zero or concentrated in a point  $(c_s)_i \sim \delta_{i,j}$  (start of limiting step).

Jumps: how many we observe?

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



## Auxiliary discrete dynamical systems

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

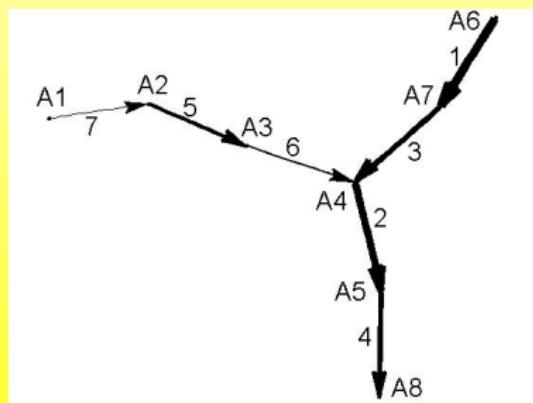
$\phi(i) = i$  if there is no outgoing reaction  $A_i \rightarrow A_j$ .

$\phi$  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.

For instance:

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

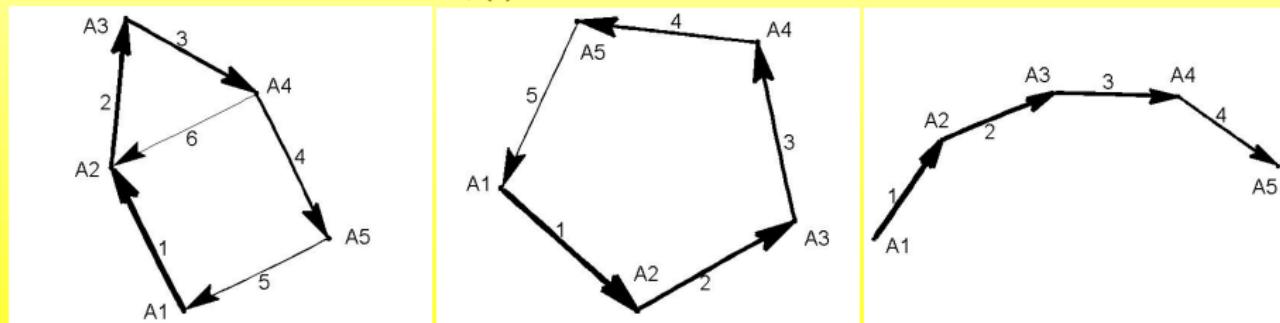
$$r^1 \approx (1, 0, 0, 0, 0, 0, 0, -1)$$

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

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

## 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.



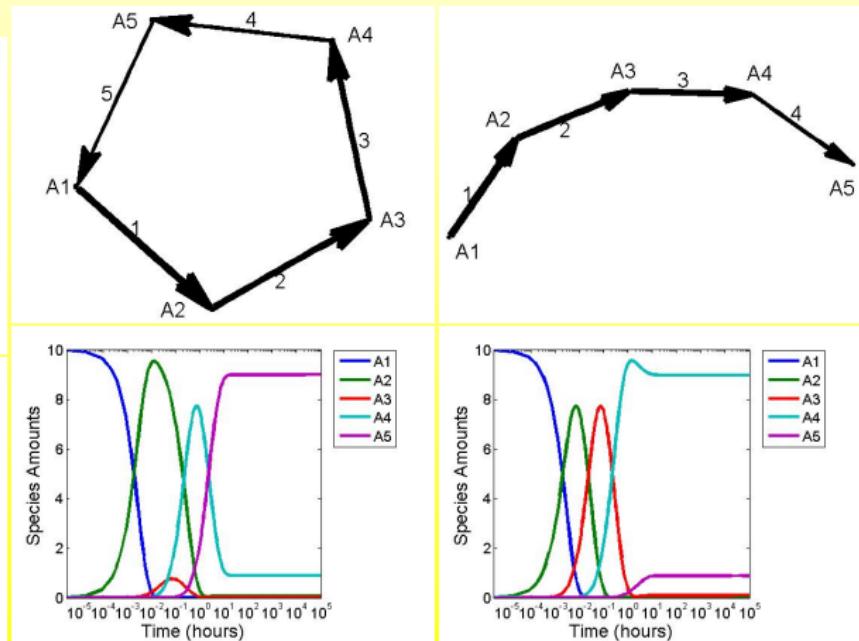
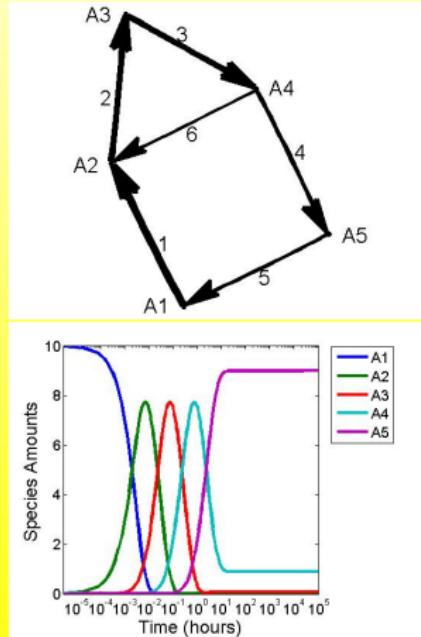
## 3-rd case: some of $C_j$ are not sinks

- ▶ 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.

# An example



# Limitation theory for non-linear systems?

Difficulty: time scales tend to cluster, or diverge

- ▶ Singular behavior of the system at bifurcations, critical slow-down without limitation.
- ▶ Limit cycles and chaotic attractors are possible. Total separation is improbable. For instance Gershgorin theorem implies that kinetic matrices with totally separated elements have real eigenvalues: no oscillations.
- ▶ Invariant manifolds gather several degrees of freedom

# Quasistationarity

Some species have small concentrations most of the time  $x_\epsilon = \epsilon x$ .

The system is of the type slow/fast.

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

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

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**Theorem (Tykhonov)**

*If for any  $y$  the dynamics (1) has a hyperbolic point attractor, then after a fast transition the system evolves according to:*

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## Theorem (Fenichel)

There is an invariant manifold  $M_\epsilon$  close to  $M_0$ .

# Averaging

Some species have oscillating behavior, others do not.

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For any  $y$  the fast dynamics (1) has an attractive hyperbolic limit cycle  $x = \psi(\tau, y) = \psi(\tau + T(y), y)$ , then

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*After a fast transition the slow variables average oscillations:*

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Stationarity equation for non-oscillating variables (to be solved for  $y$ ).

$$\int_0^{T(y)} g(\psi(\tau, y), y) d\tau = 0$$

# A model reduction recipe

/ set of species to be eliminated.

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

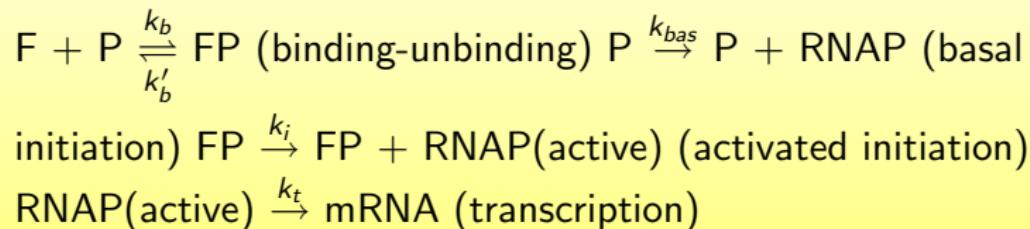
Other species involved in  $\mathcal{R}_I$  are  $T$ , the terminal species.

$S_I, S_T$  are stoichiometry matrices.

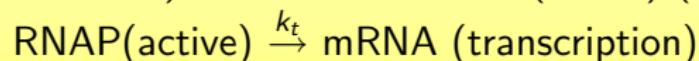
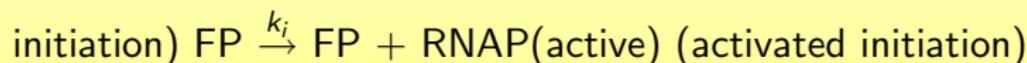
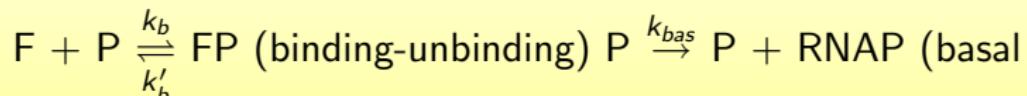
Reduction recipe:

1. Replace  $\mathcal{R}_I$  by linear combinations: convex basis.
  - $S_I \gamma = 0$
  - $\gamma_i \geq 0$ , if  $i$  is irreversible
  - $\gamma$  has minimal number of nonzero coeffs
  - no internal cycles, i.e. impose  $S_T \gamma \neq 0$ .
2. Solve stationarity equations to obtain  $x_I$  as functions of  $x_T$ .
3. Compute rates of new reactions  $\gamma$

## Dominant solutions of polynomial equations, an example



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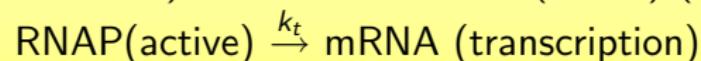
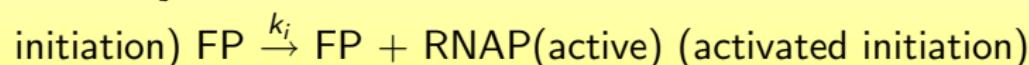
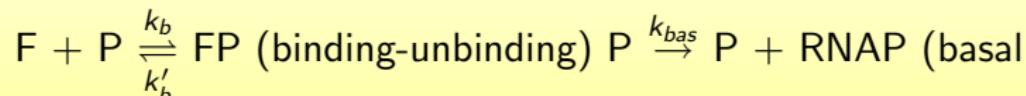


Solve

$$FP = KF_p, \quad F + F_p = F_0, \quad P + F_p = P_0$$

together with  $0 < P_0 \ll F_0, \quad 0 < K \ll F_0$ .

## Dominant solutions of polynomial equations, an example



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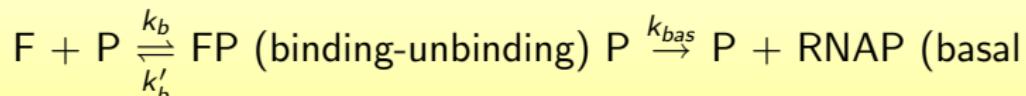
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together with  $0 < P_0 \ll F_0, 0 < K \ll F_0$ .

$$P^2 + (F_0 - P_0 + K)P - KP_0 = 0,$$

$$P = \frac{2KP_0}{(F_0 + K - P_0 + \sqrt{4K + (F_0 + K - P_0)^2})}, \quad P = KP_0/F_0$$

## Dominant solutions of polynomial equations, an example



initiation)  $FP \xrightarrow{k_i} FP + RNAP(\text{active})$  (activated initiation)

$RNAP(\text{active}) \xrightarrow{k_t} mRNA$  (transcription)

Solve

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## Dominant solutions of polynomial equations, an example



initiation)  $FP \xrightarrow{k_i} FP + RNAP(\text{active})$  (activated initiation)

$RNAP(\text{active}) \xrightarrow{k_t} mRNA$  (transcription)

Solve

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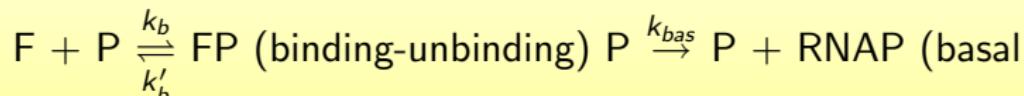
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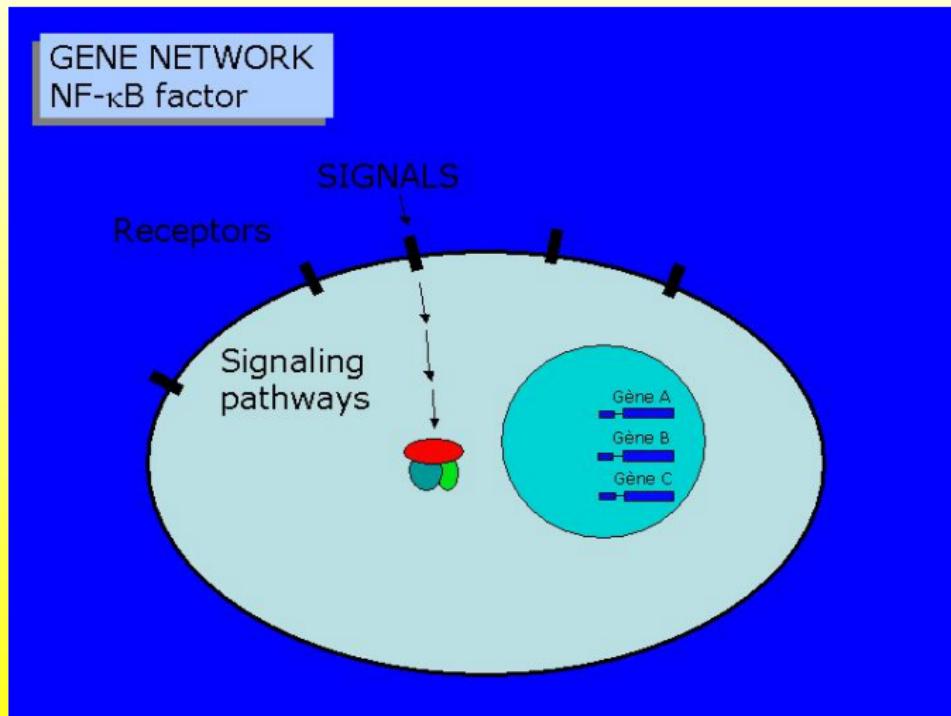
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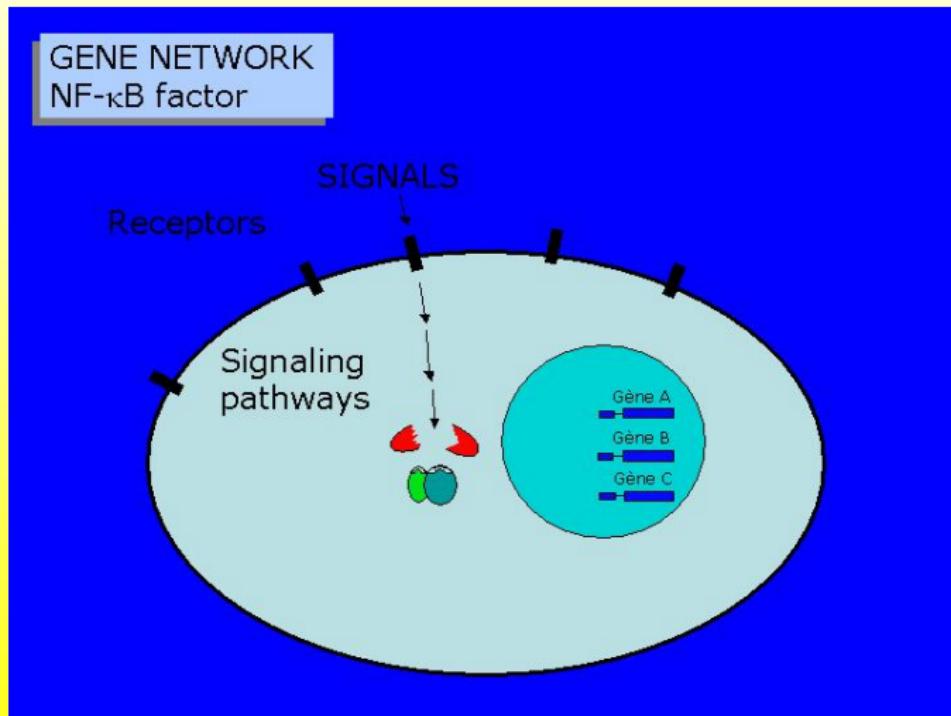
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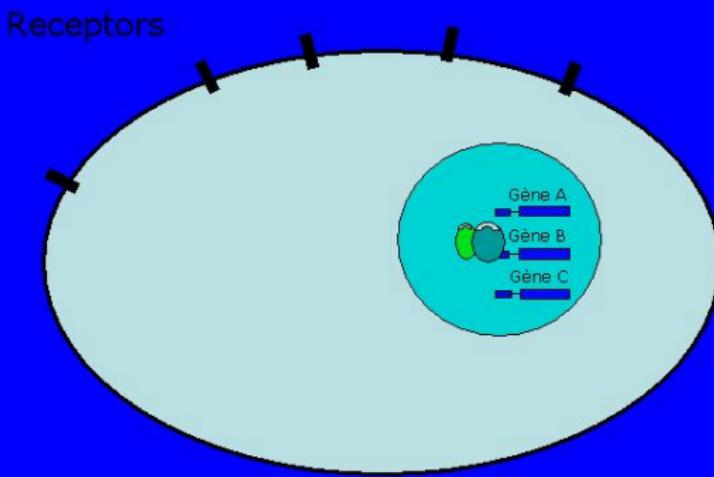
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Non-critical parameters are dominated and disappear.

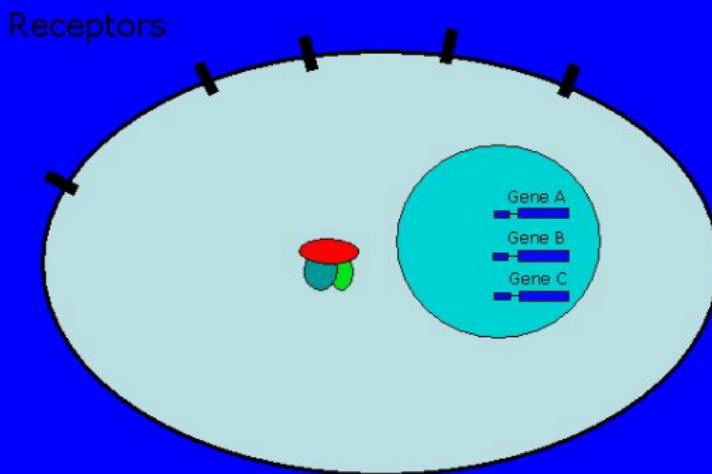


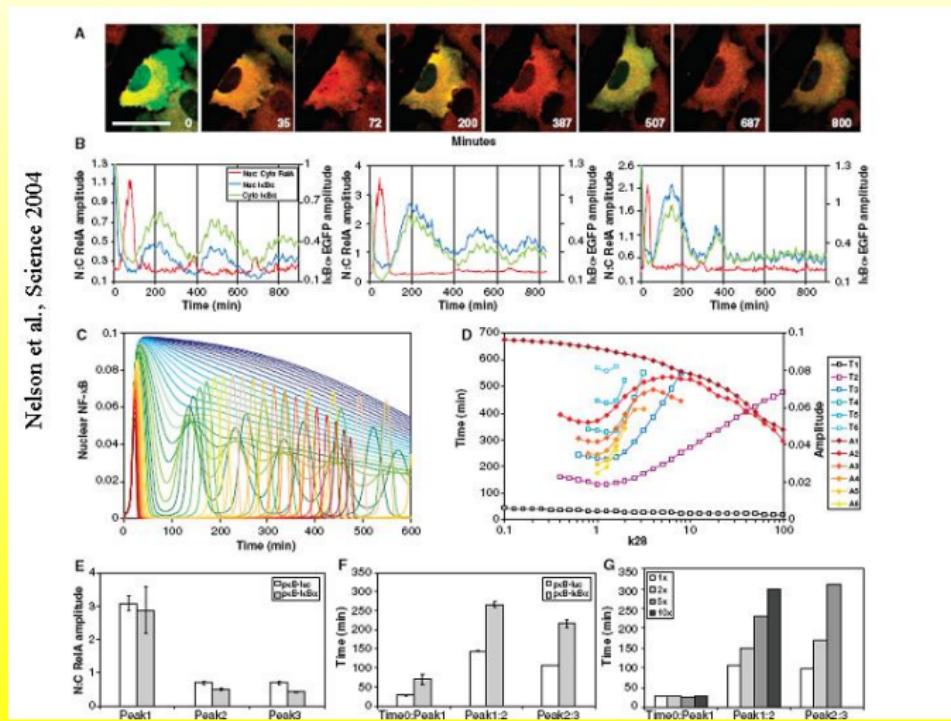


GENE NETWORK  
NF- $\kappa$ B factor

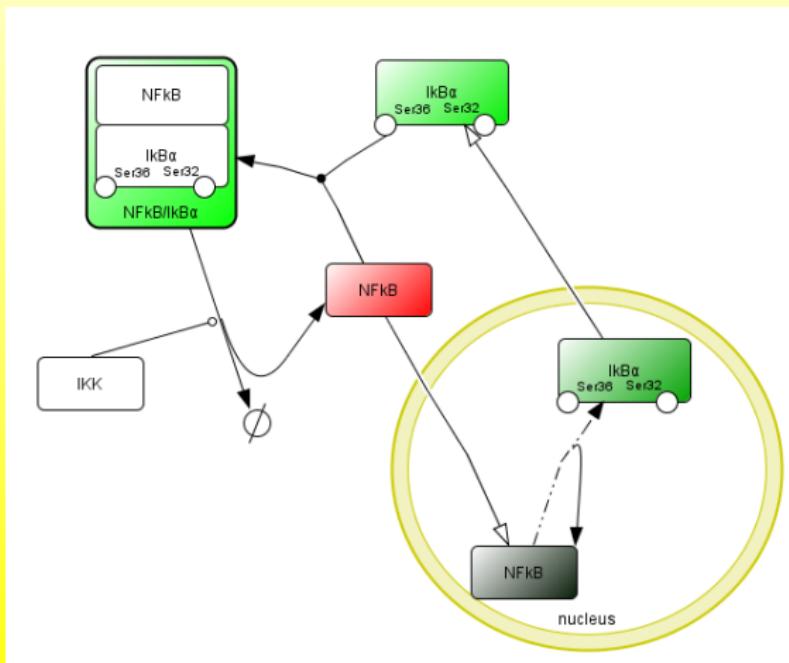


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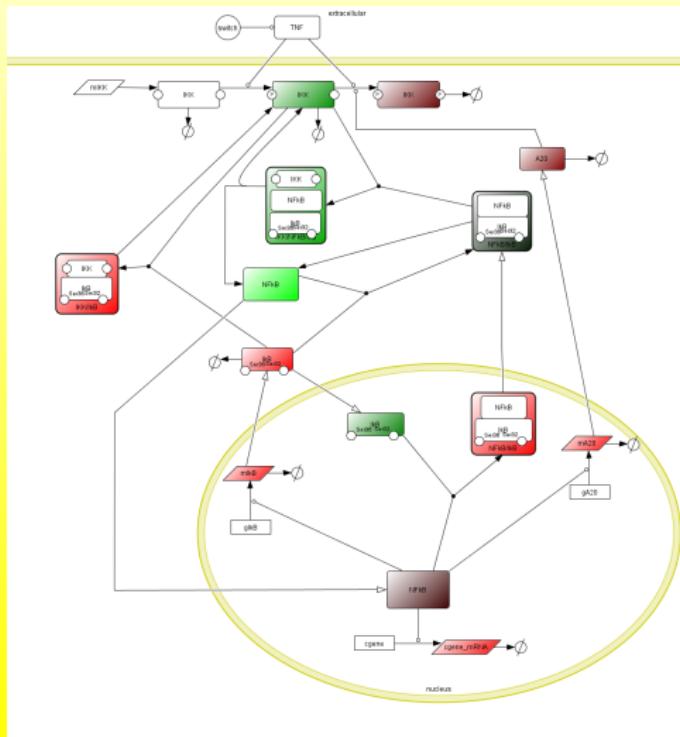




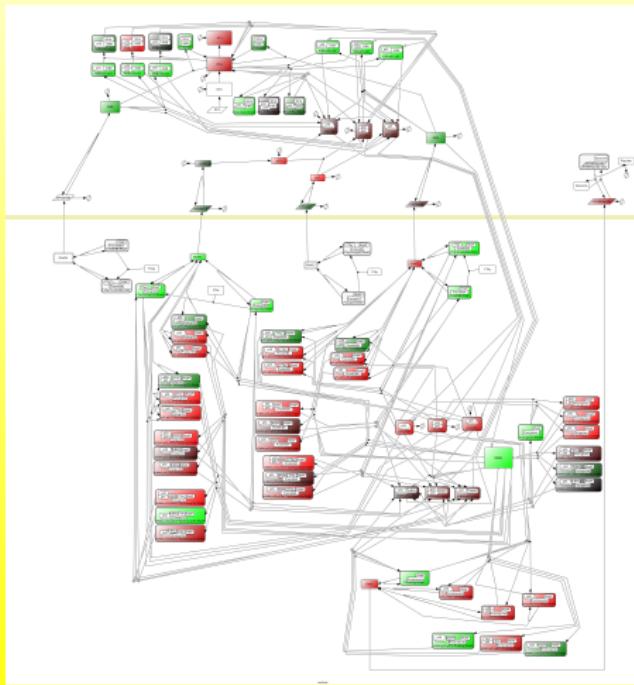
## Simplest model



# Average complexity model (Lipniacki )

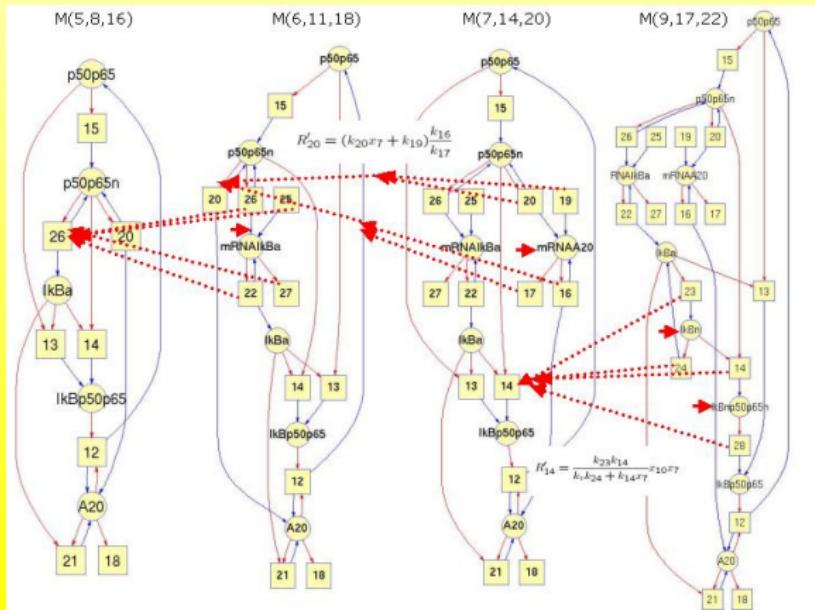


# Most complex model

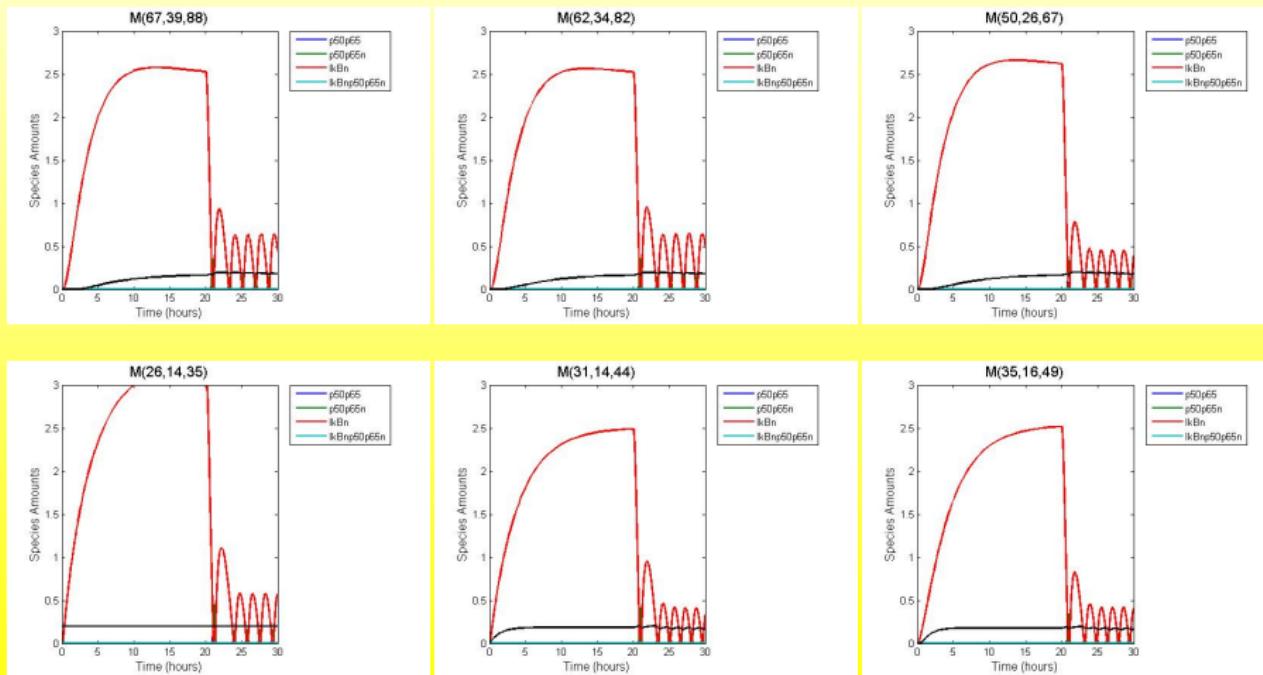


# Hierarchies

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



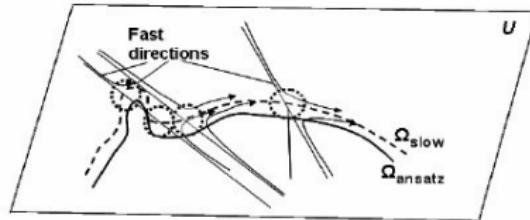
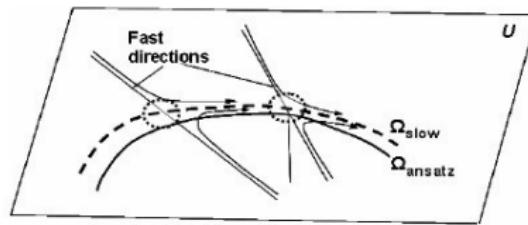
# Hierarchy of models, from M(67,39,88) to M(26,14,35)



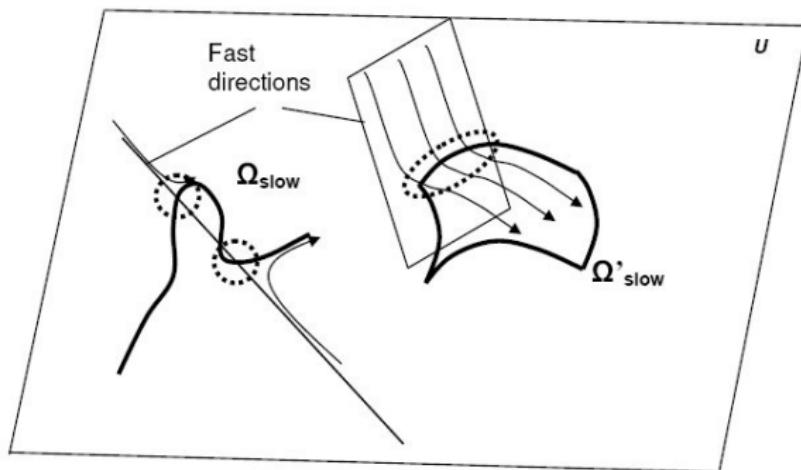
# CONCLUSION

- 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: **limit simplifications**;
- Zero-one laws for multiscale systems occur at the level of rates expression: some parameters (critical) remain, others disappear (only their order matters);

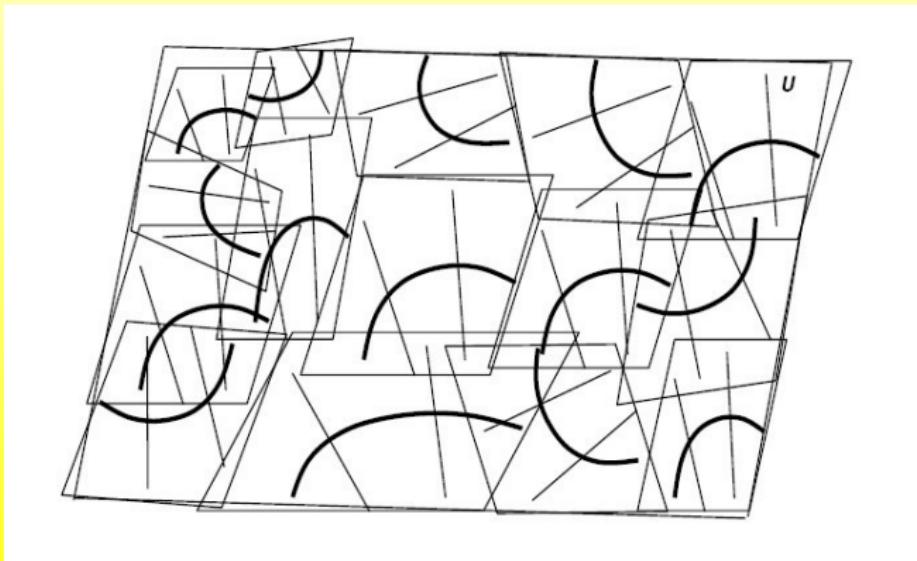
Life is not easy. I. Bifurcations in fast system



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



# Crazy quilt, Edredon sauvage



## Decomposition (along a trajectory)

