

# Reduction of biochemical networks with multiple time scales

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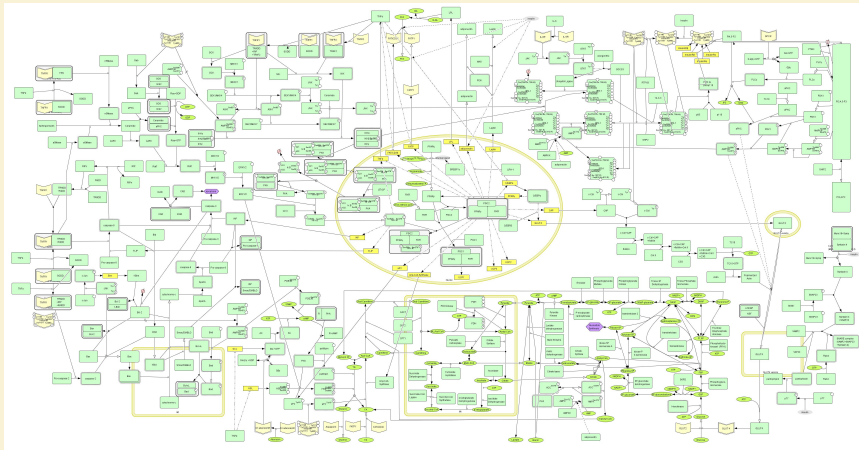
jointly with  
A.N.Gorban,D.Grigoriev,V.Noel,S.Vakulenko,A.Zinovyev

# Outline

- ▶ Model reduction for linear networks with separated constants.
- ▶ Model reduction for non-linear networks with multiple time scales.
- ▶ Tropical geometry and model reduction.

# The problem of size

Complex, large scale molecular systems.



# Dynamics

- ▶ State  $X$  (numbers of molecules),  $x = X/V$  (concentrations), reactions  $X \rightarrow X + \nu_j$ .
- ▶ **Deterministic dynamics**

$$\frac{dx}{dt} = \sum_{j=1}^r \nu_j R_j(x)$$

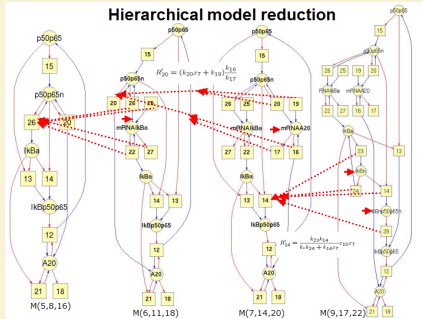
- ▶ **Stochastic dynamics**  $X(t)$  is a jump Markov process, of intensity

$$\lambda(x) = V \sum_{j=1}^r R_j(x),$$

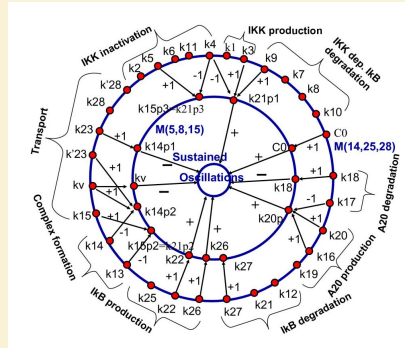
jumps  $X \rightarrow X + \nu_j$ , jump distribution

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

# Model reduction



**Hierarchical model reduction:**  
 produce models with less  
 variables, equations,  
 parameters; use graph rewriting

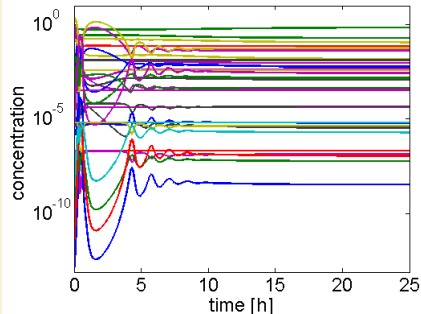


**Backward pruning:** define  
 synthetic parameters that are  
 identifiable

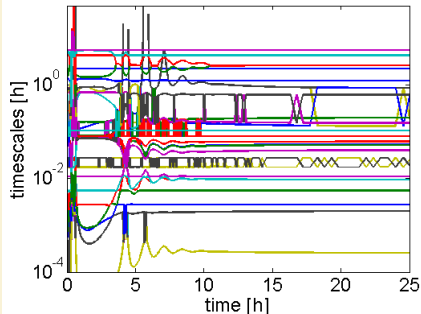
# Multiscale networks

Our methods apply to molecular networks that have many, well separated, time and concentration scales.

Widely distributed concentrations, in log scale



Widely distributed timescales, in log scale



Produced with the model in Radulescu et al BMC Systems Biol. 2008

Our aim: develop reduction methods for multi-scale models with uncertainty.

# Linear networks of chemical reactions: digraphs with linear kinetics

$A_i$  are reagents,  $c_i$  is concentration of  $A_i$ .

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

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

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

Kinetic equation

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

Relevance for computational biology:

- ▶ Occur as subsystems of larger, nonlinear networks.
- ▶ Crude approximations obtained by linearizing networks.

# Linear networks with separated constants

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

The eigenvectors of  $K$  specify the dynamics.

Well separated constants

$$k_{l_1} \gg k_{l_2} \gg k_{l_3} \gg \dots$$

**Integer labeled digraphs:** each reaction arc has an integer label, specifying its position in the sequence of all reactions, ordered by speed; the lowest order is the most rapid.

**Theorem:** *the multiscale approximation of an arbitrary linear network with separated constants is an acyclic, deterministic, integer labeled digraph.*



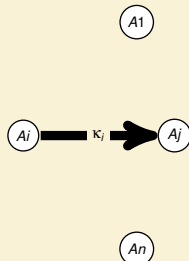
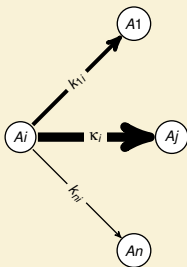
# Auxiliary discrete dynamical systems

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  $\mathcal{A} = \{A_i\}$ .

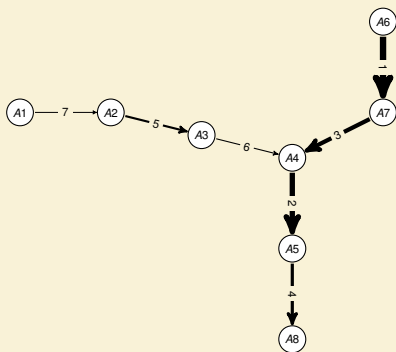
Pruning: keep only the dominating step



The auxiliary dynamical system is further decomposed into cycles  $C_j$  with basins of attraction,  $Att(C_j)$ :  $\mathcal{A} = \cup_j Att(C_j)$ .

# 1-st case: acyclic auxiliary dynamic systems

All cycles  $C_j$  are point attractors.



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

For instance:

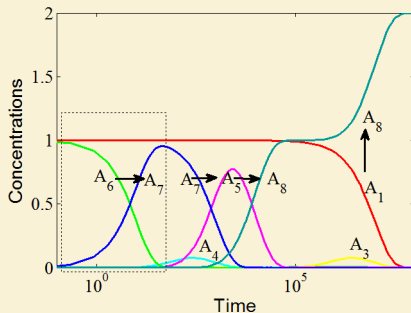
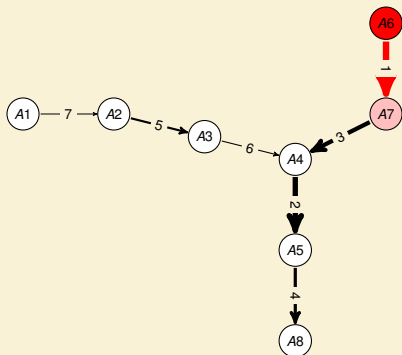
$$l^1 \approx (1, 0, 0, 0, 0, 0, 0, 0)$$

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

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

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

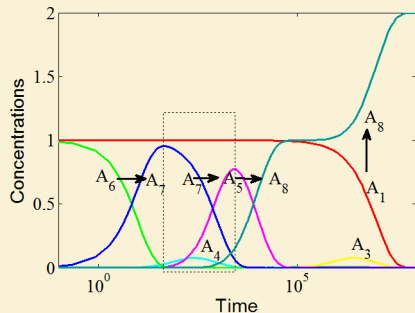
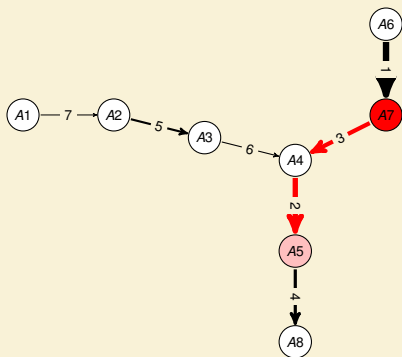
# Sequence of reduced models



$$l^6 \approx (0, 0, 0, 0, 0, 0, 0, 1)$$

$$r^6 \approx (0, 0, 0, 0, 0, -1, 1, 0)$$

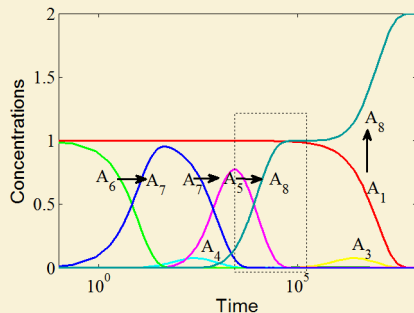
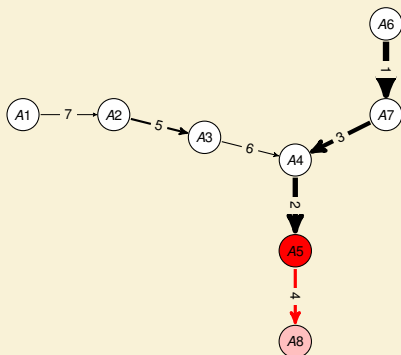
# Sequence of reduced models



$$l^7 \approx (0, 0, 0, 0, 0, 0, 1, 1)$$

$$r^7 \approx (0, 0, 0, 0, 1, 0, -1, 0)$$

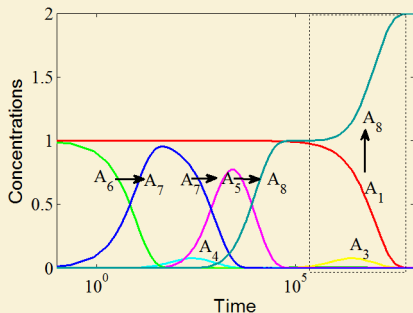
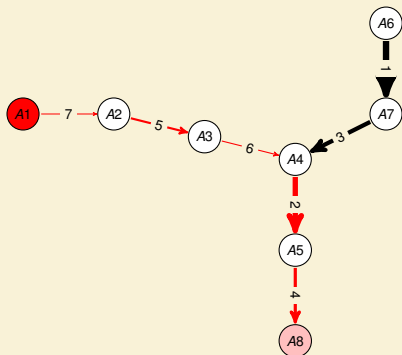
# Sequence of reduced models



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

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

# Sequence of reduced models

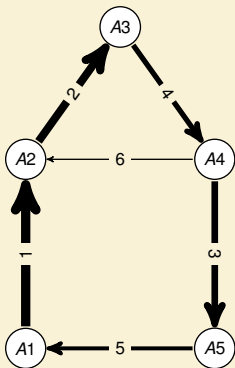


$$l^1 \approx (1, 0, 0, 0, 0, 0, 0, 0)$$

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

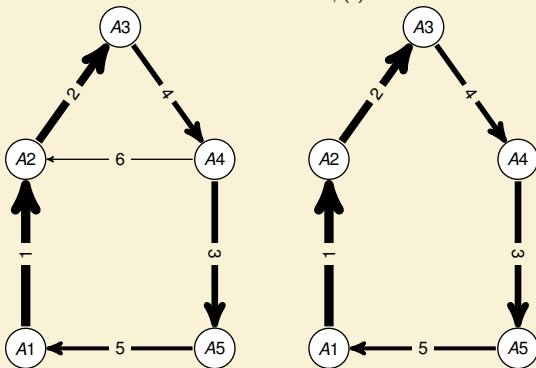
## 2-nd case: $C_j$ are sinks in the initial network

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



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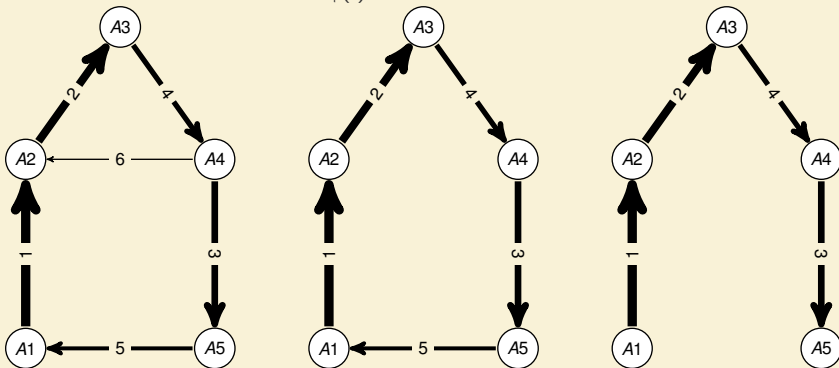
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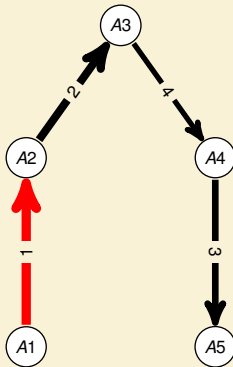
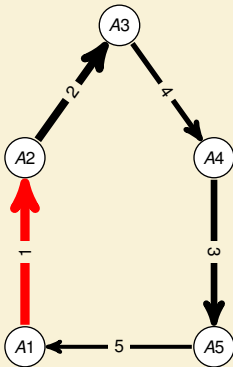
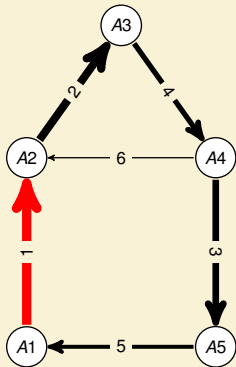


## 2-nd case: $C_j$ are sinks in the initial network

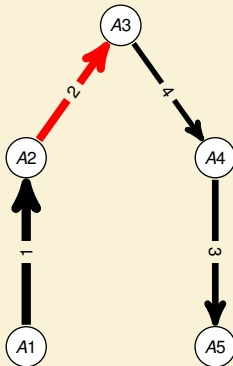
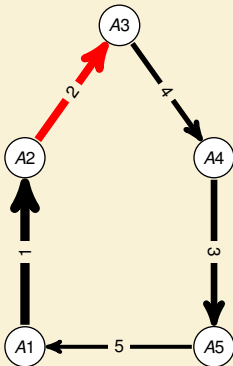
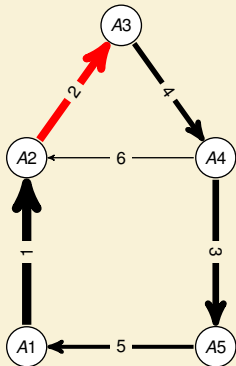
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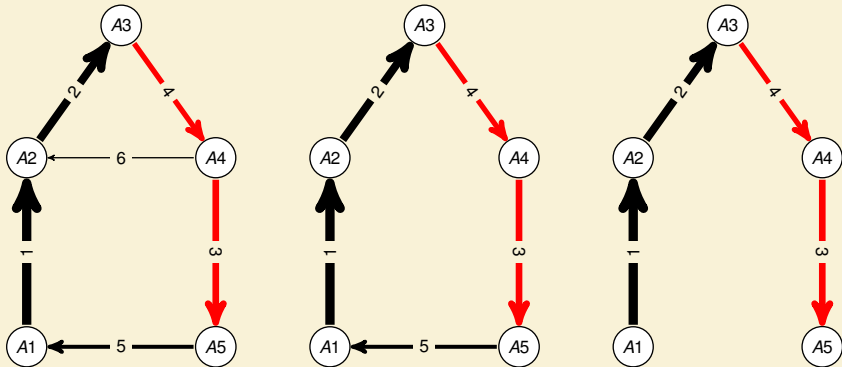
# Sequence of reduced models



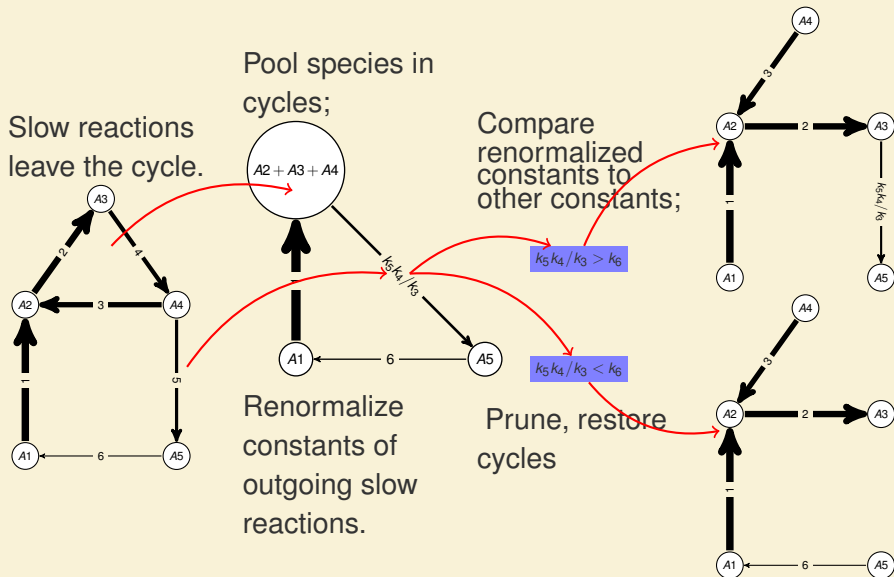
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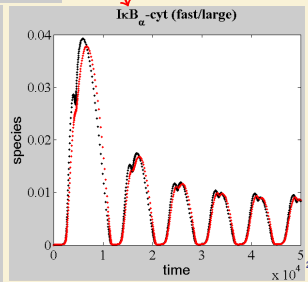
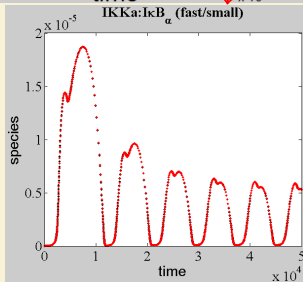
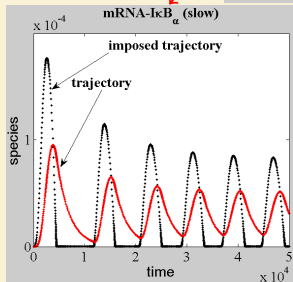
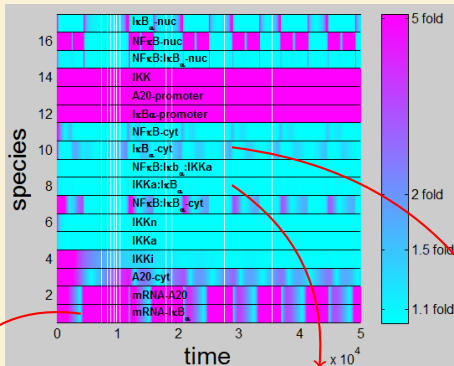
### 3-rd case: some of $C_j$ are not sinks



# Nonlinear networks

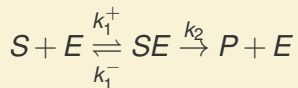
- ▶ Timescales are not inverses of parameters in the model. They involve concentrations and can change with time.
- ▶ Main ideas: quasi-steady state approximation, quasi-equilibrium.
- ▶ Given the trajectories  $c(t)$  of all species solution of  $\frac{dc}{dt} = f(c)$ , the imposed trajectory of the  $i$ -th species is a solution  $c_i^*(t)$  of the equation  $f_i(c_1(t), \dots, c_{i-1}(t), c_i^*(t), c_{i+1}(t), \dots, c_n(t)) = 0$ . **We say that a species  $i$  is slaved** if the distance between the trajectory  $c_i(t)$  and some imposed trajectory  $c_i^*(t)$  is small for some time interval  $I$ ,  $\sup_{t \in I} |\log(c_i(t)) - \log(c_i^*(t))| < \delta$ , for some  $\delta > 0$  sufficiently small.

# Slaved species - NF $\kappa$ B model



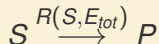
# Small concentration slaved species - quasi-steady state approximation

Example: Michaelis-Menten mechanism.



QSS approximation (Briggs-Haldane): *quasi-steady state species are low concentration, fast species.*

Pooling of reactions.



$$\frac{dP}{dt} = -\frac{dS}{dt} = k_2 ES, \quad k_1 S \cdot (E_{tot} - E) = (k_{-1} + k_2) ES$$

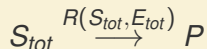
$$R(S, E_{tot}) = k_2 E_{tot} \cdot S / (k_m + S)$$



# Small concentration slaved species - quasi-equilibrium approximation

QE approximation (Michaelis-Menten): *quasi-equilibrium reactions are fast, reversible reactions.*

Pooling of species.  $S_{tot} = S + ES$ ,  $E_{tot} = E + ES$ .



$$\frac{dP}{dt} = -\frac{dS_{tot}}{dt} = k_2 ES, \quad k_1(S_{tot} - ES) \cdot (E_{tot} - ES) = k_{-1} ES$$

$$R(S_{tot}, E_{tot}) = k_2 \frac{2E_{tot}S_{tot}}{(E_{tot} + S_{tot} + k_{-1}/k_1)(1 + \sqrt{1 - 4E_{tot}S_{tot}/(E_{tot} + S_{tot} + k_{-1}/k_1)^2})}$$

$$R(S_{tot}, E_{tot}) \approx k_2 \frac{E_{tot}S_{tot}}{k_{-1}/k_1 + S_{tot}}, \text{ if } E_{tot} \ll S_{tot}$$

# Graph rewriting operations - pooling and pruning of reactions and species

*Let  $S^f$  be the stoichiometric matrix of the fast subsystem: fast reactions for QE; reactions producing or consuming fast species for QSS.*

## Pooling

For QSS define reaction pools, solutions of  $S^f \gamma = 0$ : **routes**.

For QE define species pools, solutions of  $b^T S^f = 0$ :

**conservation laws**.

Impose minimality conditions  $R(\gamma') \subset R(\gamma) \Rightarrow \gamma' = 0 \vee \gamma' = \gamma$

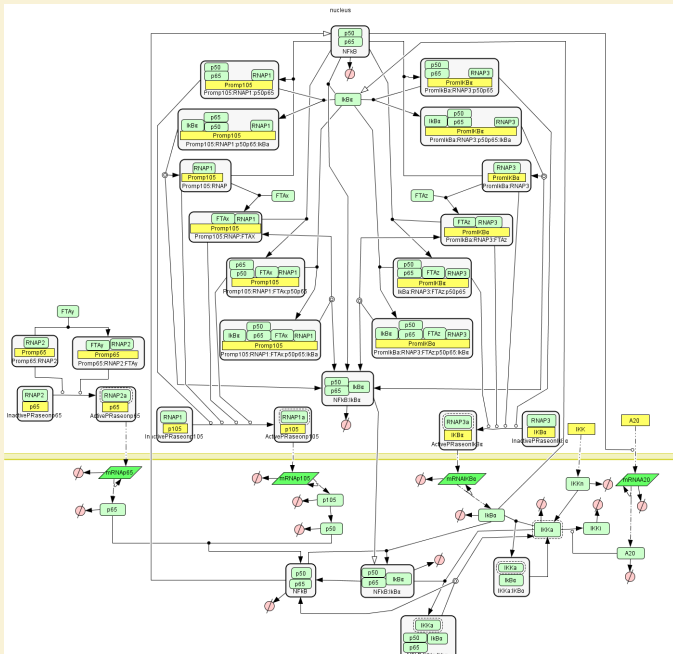
**elementary modes**.

## Pruning

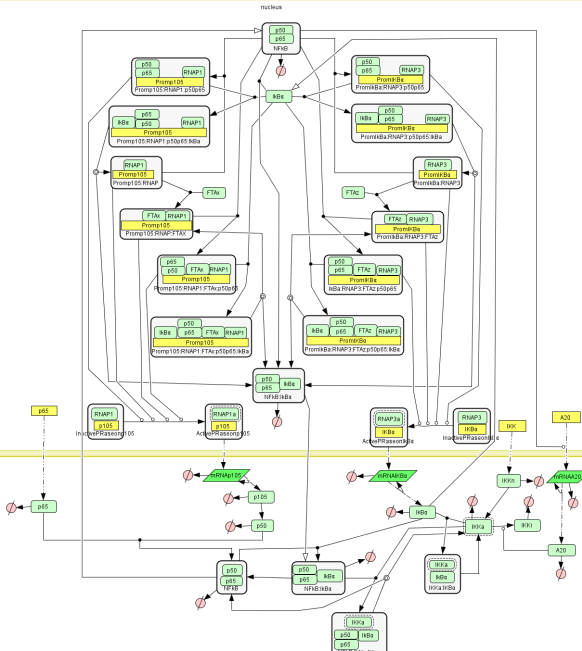
Quasi-steady state species and quasi-equilibrium reactions can be pruned (singular perturbations).

Dominated reactions can be also pruned (regular perturbations).

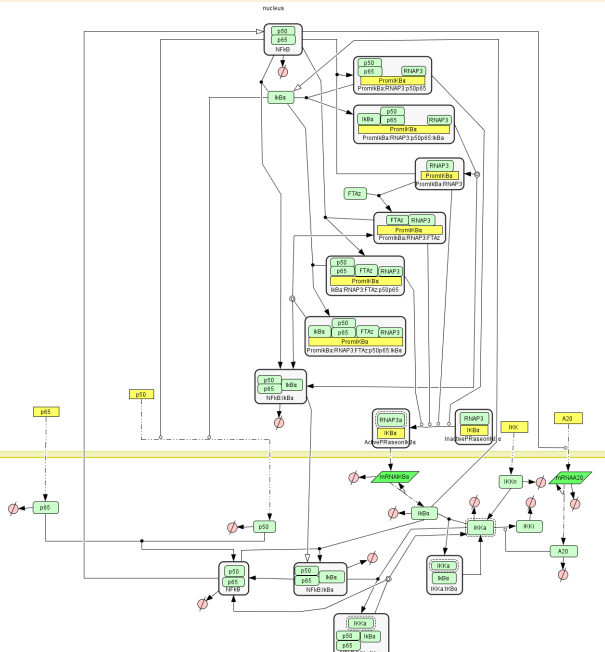
## Hierarchy of NF $\kappa$ B models $M(39, 65, 90)$ , BIOMD0000000227



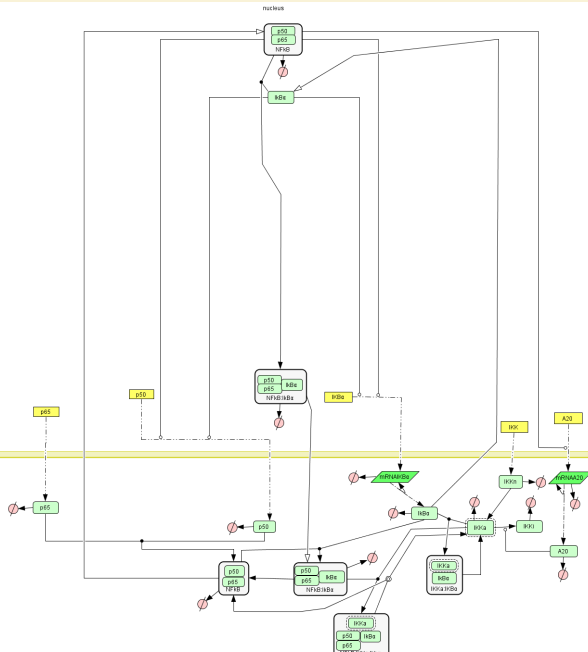
## Hierarchy of NFκB models $M(34, 60, 82)$ MODEL7743631122



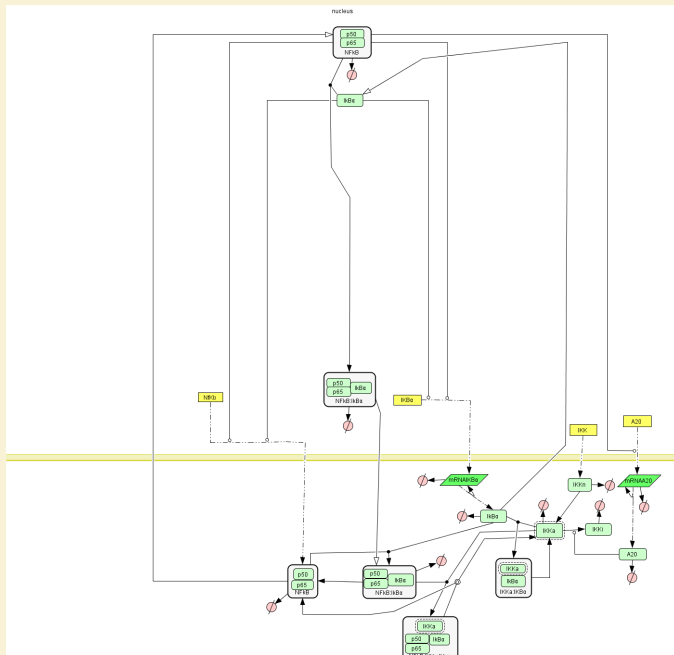
# Hierarchy of NF $\kappa$ B models $M(24, 65, 62)$ MODEL7743608569



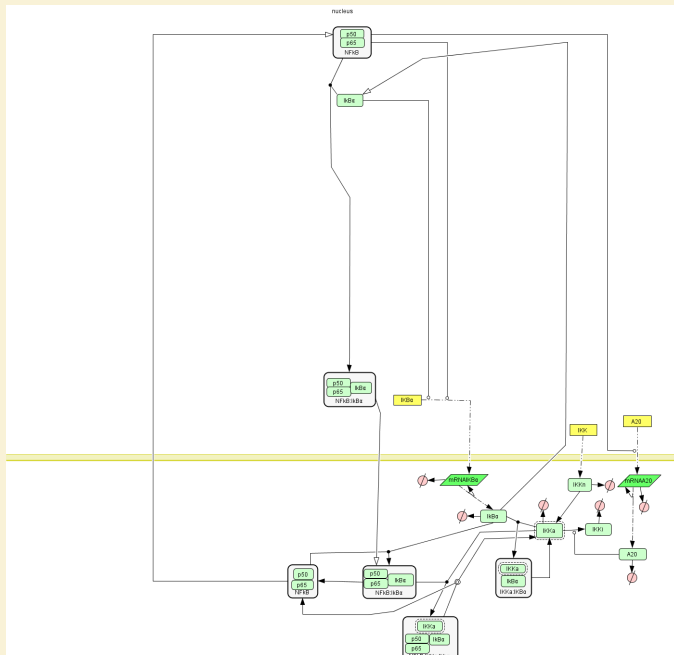
# Hierarchy of NF $\kappa$ B models *M(16,34,46)* MODEL7743576806



# Hierarchy of NF $\kappa$ B models $M(14, 30, 41)$ MODEL7743528808



# Hierarchy of NF $\kappa$ B models $M(14,25,33)$ MODEL7743444866





# Tropical geometry and model reduction

Multi-scale models of computational biology satisfy:

- ▶ vectors fields of ODE models are ratios of multivariate polynomials  $P_i(x) = \sum_{\alpha \in A} a_{\alpha} x_2^{\alpha_2} \dots x_n^{\alpha_n}$ .
- ▶ reduction methods exploit dominance relations between monomial rate terms.
- ▶ the dominant (reduced) subsystem depends on the time-scale, it can change with time (hybrid models).

Tropical geometry offers convenient solutions to:

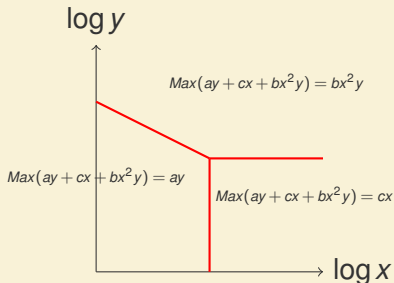
- ▶ solve systems of polynomial equations  $P_i(x) = 0$  with separated monomials.
- ▶ simplify and hybridize rational ODE systems  $\frac{dx_i}{dt} = P_i(x)/Q_i(x), 1 \leq i \leq n$ , with separated monomials.

# Litvinov-Maslov tropicalization

Replace multivariate polynomials by piece-wise smooth, max-plus polynomials.

$$\sum_{\alpha \in A} a_{\alpha} x^{\alpha} \rightarrow \exp[\max_{\alpha \in A} \{ \log(a_{\alpha}) + \langle \log(x), \alpha \rangle \}].$$

The tropical manifold is the set of points where max-plus polynomials are not smooth.



The tropical manifold of the polynomial  $ay + cx + bx^2y$  on “logarithmic paper”.

# Tropicalization of Tyson et al. 91 cell cycle model

2D reduced model.

$$y_3' = k_4' y_4 + k_4 y_4 y_3^2 - k_6 y_3,$$

$$y_4' = -k_4' y_4 - k_4 y_4 y_3^2 + k_1,$$

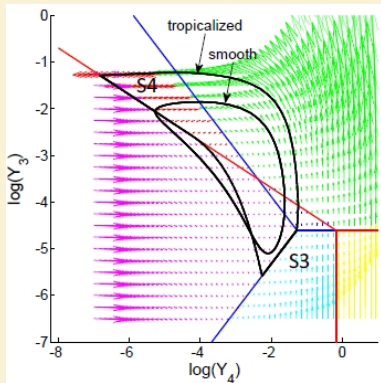
Tropicalization.

$$y_3' = \text{Dom}\{k_4' y_4, k_4 y_4 y_3^2 / C^2, -k_6 y_3\},$$

$$y_4' = \text{Dom}\{-k_4' y_4, -k_4 y_4 y_3^2 / C^2, k_1\},$$

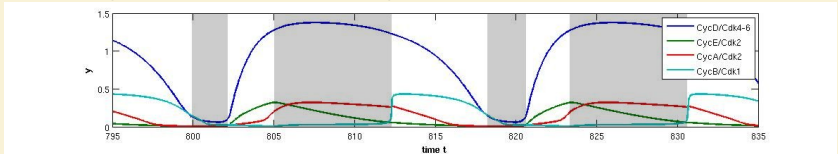
Cell cycle oscillates, also passes from one “mode” to another:

life is hybrid.

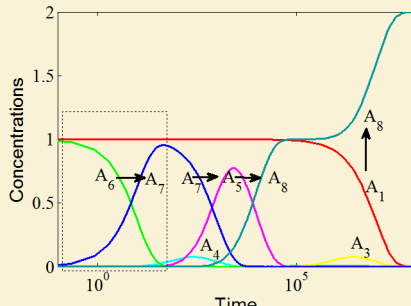


# Tropical geometry and hybridization

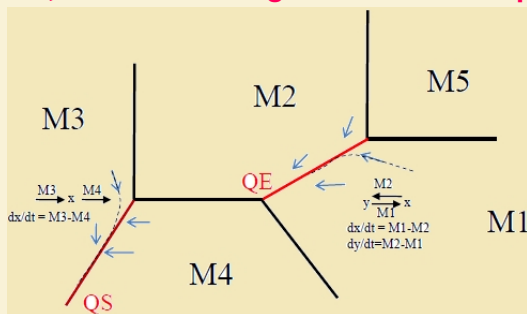
Full or partial tropicalizations can be used as hybrid cell cycle models (Noel et al 2011, 2012).



The dominant subsystem of linear networks with total separation is a full tropicalization.



## QE, QSS and sliding modes of the tropicalization



$$\begin{aligned} dx/dt &= M1 - M2 + M3 - M4, \\ dy/dt &= M2 - M1 + M5 \end{aligned}$$

Some monomials of the polynomial equations  $\frac{dx}{dt} = P(x)$ , can be pruned (are dominated) on the tropical manifold. The pruned version  $\frac{dx}{dt} = \tilde{P}(x)$ , where  $\tilde{P}$  is obtained from  $P$  by removing dominated monomials, corresponds to the fast subsystem of the QE and QSS approximations.

**Theorem:** QE and QSS conditions imply the existence of sliding modes on the tropicalization. Use sliding modes of the tropicalization to detect QE and QSS conditions...in progress!

# Conclusions

- ▶ Network with many, well separated, time scales, can be reduced to simpler networks, in a way that does not depend on the exact values of the parameters, but on their order relations.
- ▶ Tropical geometry is the natural framework for unifying various approaches to this problem.
- ▶ The algorithms are ready to use for backward pruning strategies: find effective, critical parameters.
- ▶ Need some rough estimates of timescales and concentration ranges.

## Some bibliography

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