Tropical approaches to multi-scaleness of chemical reactions
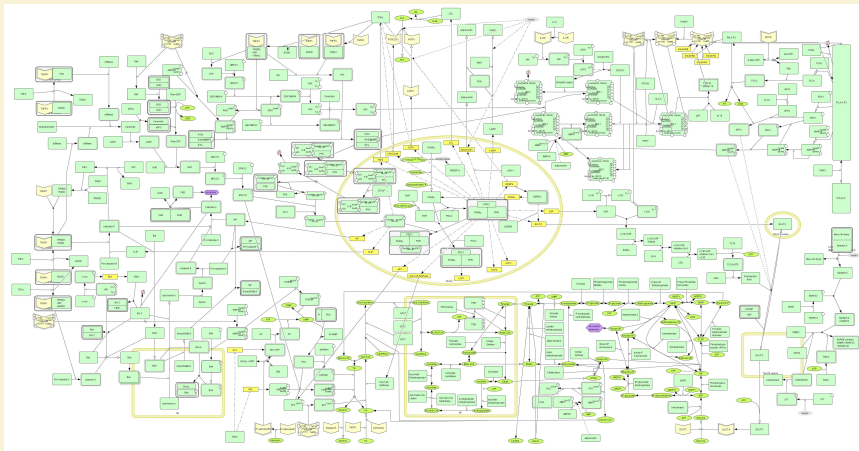
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Outline

- Linear chemical reactions networks with separated constants.
- Non-linear chemical reactions networks with multiple time scales.
- Tropical approaches.

The problem of size

Complex, large scale molecular systems.

Kitano 2004

Dynamics

- State X (numbers of molecules), $x = X/V$ (concentrations), reactions $X \rightarrow X + \nu_j, \quad \nu_j \in \mathbb{Z}^n$.

- Deterministic dynamics

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

Dynamics

▶ State X (numbers of molecules), $x = X/V$ (concentrations), reactions $X \to X + \nu_j, \quad \nu_j \in \mathbb{Z}^n$.
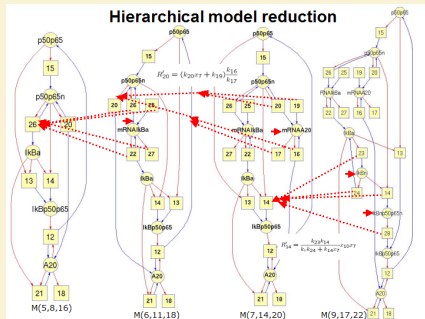
▶ Deterministic dynamics

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

▶ Stochastic dynamics $X(t)$ is a jump Markov process, of intensity
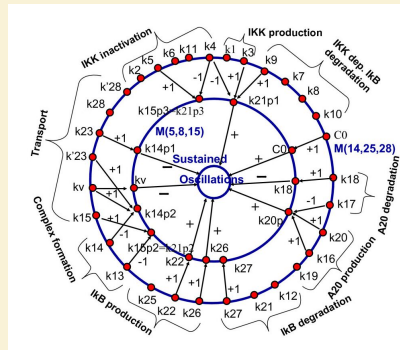
$$\lambda(x) = V \sum_{j=1}^{r} R_j(x),$$

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

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

Model reduction

Hierarchical model reduction

Model reduction: produce models with less variables, equations, parameters

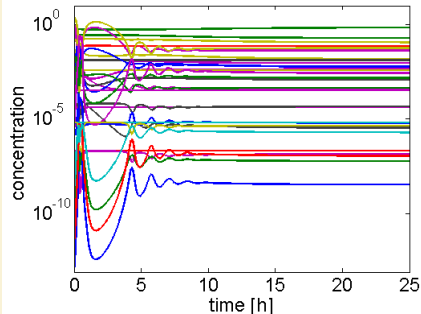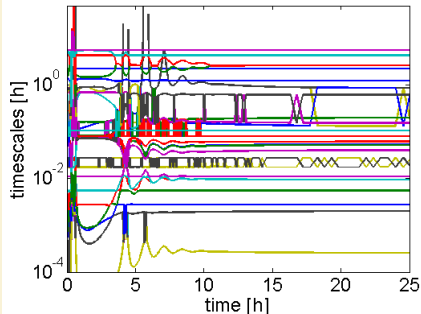Backward pruning: define synthetic parameters that are identifiable

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

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 $A_i \to A_j$ (monomolecular).

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

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

Kinetic equation

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

Relevance for computational biology:

- Occur as subsystems of larger, nonlinear networks.

- Crude approximations obtained by linearizing networks.

Linear networks with separated constants

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

The eigenvectors of K specify the dynamics.
Well separated constants

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

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.
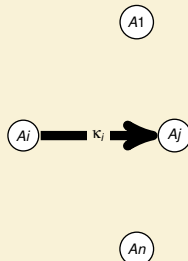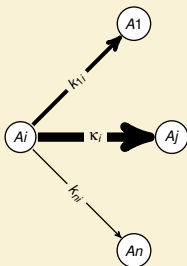
Auxiliary discrete dynamical systems

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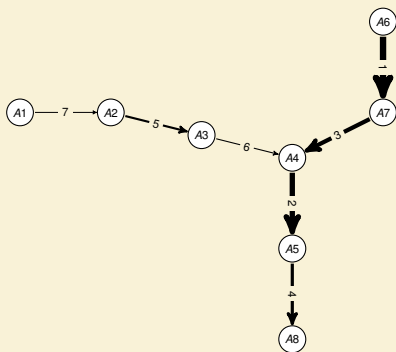ϕ determines *auxiliary dynamical system* on a set $\mathcal{A} = \{A_i\}$.

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.

$r^i_{\Phi(j)} = \frac{\kappa_j}{\kappa_{\Phi(j)} - \kappa_i} r^i_j$ go along the flow $l^i_j = \frac{\kappa_j}{\kappa_j - \kappa_i} l^i_{\Phi(j)}$ go opposite to the flow.

For instance:
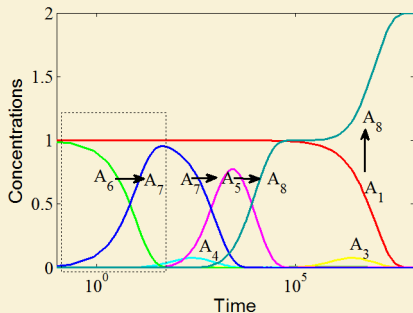
$l^1 \approx (1, 0, 0, 0, 0, 0, 0, 0)$

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

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

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

Sequence of reduced models
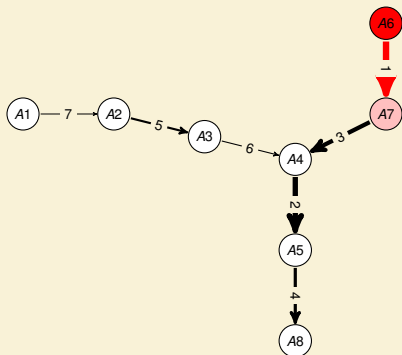
$$l^6 \approx (0, 0, 0, 0, 0, 1, 0, 0)$$
$$r^6 \approx (0, 0, 0, 0, 0, -1, 1, 0)$$
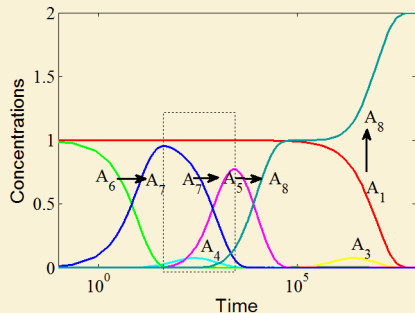
Sequence of reduced models
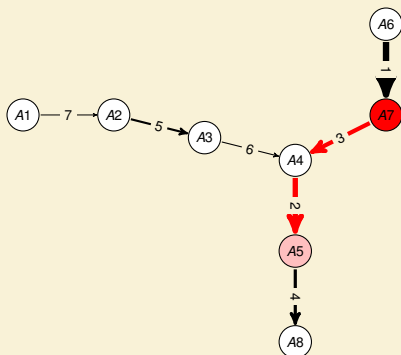
$$l^7 \approx (0, 0, 0, 0, 0, 1, 1, 0)$$
$$r^7 \approx (0, 0, 0, 0, 1, 0, -1, 0)$$

Sequence of reduced models
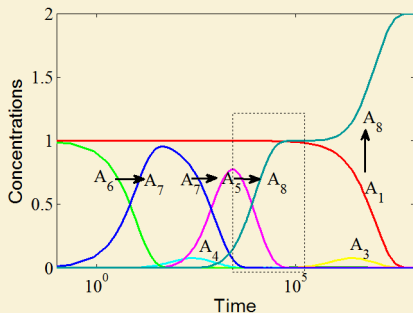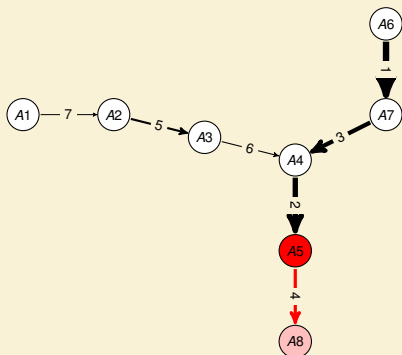
$$l^5 \approx (0,0,0,1,0,1,1,0)$$
$$r^5 \approx (0,0,0,0,-1,0,0,1)$$

Sequence of reduced models
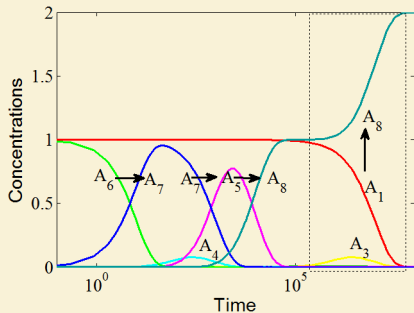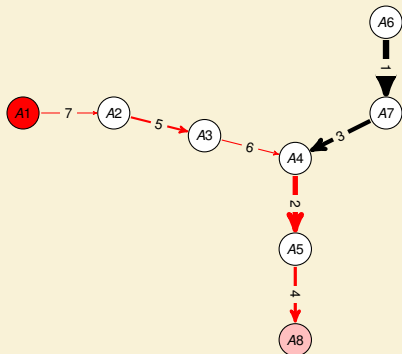
$$l^1 \approx (1,0,0,0,0,0,0,0)$$
$$r^1 \approx (-1,0,0,0,0,0,0,1)$$

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

Delete the limiting steps from cycles C_j. The obtained *acyclic* reaction network $A_i \to A_{\phi(i)}$ is the right approximation.
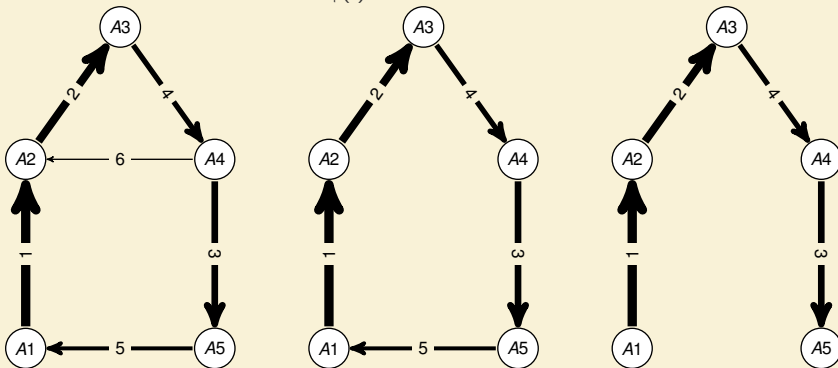
Sequence of reduced models
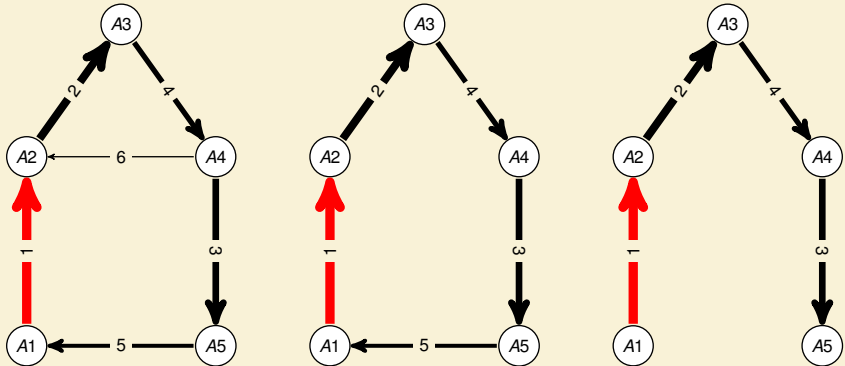
Sequence of reduced models
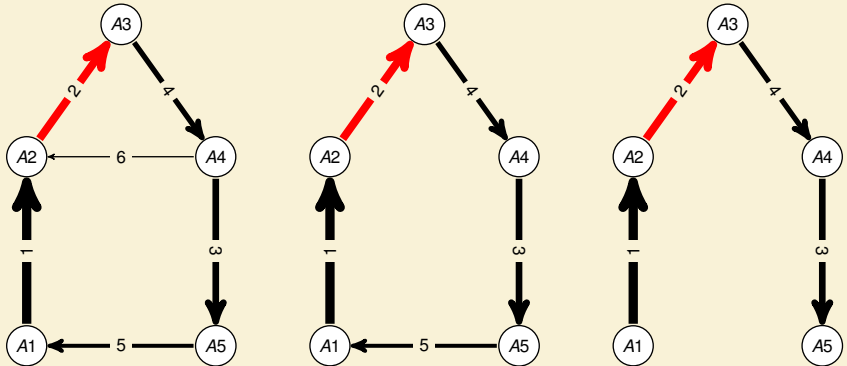
Sequence of reduced models
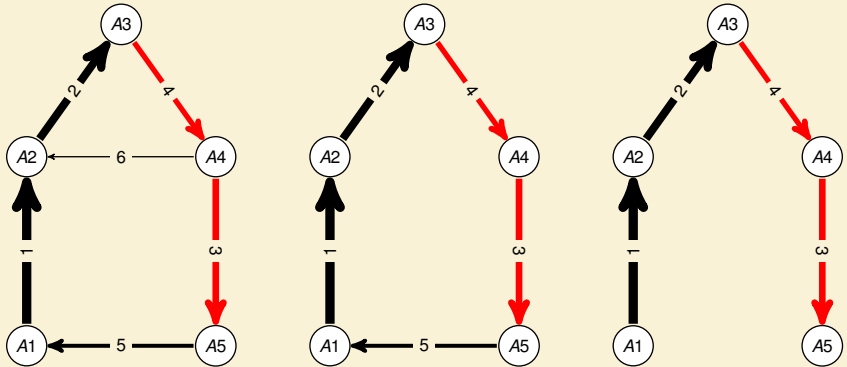
3-rd case: some of C_j are not sinks

Slow reactions leave the cycle.

Pool species in cycles;

$A2 + A3 + A4$

Compare renormalized constants to other constants;

Renormalize constants of outgoing slow reactions.

$k_5 k_4 / k_3$

$k_5 k_4 / k_3 > k_6$

$k_5 k_4 / k_3 < k_6$

Prune, restore cycles
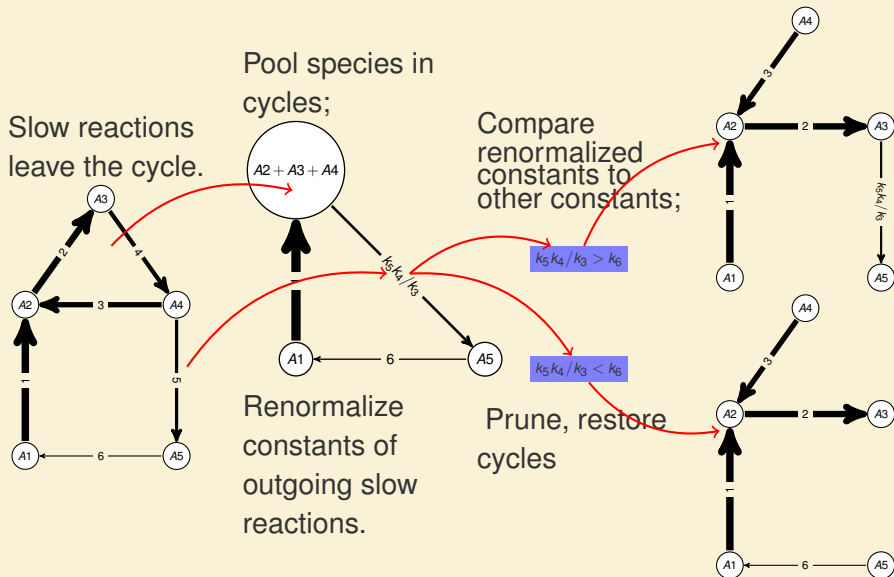
Nonlinear chemical networks

Polynomial kinetics (e.g. mass action law)

$$\frac{dx_i}{dt} = P_i(x) = \sum_{j=1}^{M_i} k_{ij} x^{\alpha_{ij}}$$

$\alpha_{ij} \in \mathbb{N}^n$ are multi-indices, $k_{ij} \in \mathbb{R}$ are kinetic parameters.

- ▶ Timescales are not inverses of parameters in the model. They involve concentrations and can change with time.

- ▶ Exploit some form of equilibration. Use invariant manifolds.

- ▶ Develop a theory of dominance based on tropical ideas.

Litvinov-Maslov tropicalization

Heuristics: replace multivariate polynomials by piece-wise smooth, max-plux polynomials.

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

Tropical manifold : the set of points where max-plus polynomials are not smooth.
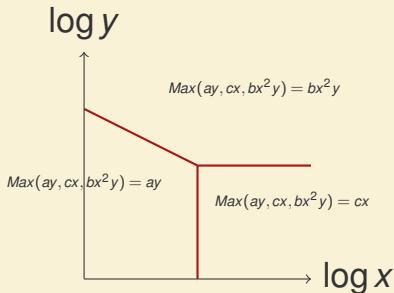
Tropical manifold of $ay + cx + bx^2y$ on "logarithmic paper".

Tropicalized Systems

- Two terms tropicalization (Savageau 2009)

$$\frac{dx_i}{dt} = DomP_i^+(\boldsymbol{x}) - DomP_i^-(\boldsymbol{x})$$

- Complete, or one term tropicalization (Noel et al 2011)

$$\frac{dx_i}{dt} = DomP_i(\boldsymbol{x})$$

where $Dom\left[\sum_{\alpha \in A_i} a_{i,\alpha} \boldsymbol{x}^{\alpha}\right] =$
$sign(a_{i,\alpha_{max}}) exp[max_{\alpha \in A_i}\{log(|a_{i,\alpha}|) + <\boldsymbol{u}, \alpha>\}]$.
$\boldsymbol{u} = (logx_1, \ldots, logx_n)$, and $a_{i,\alpha_{max}}, \alpha_{max} \in A_i$ denote the
coefficient of the monomial for which the maximum is attained.

Is the heuristics justified?

$$\frac{dx_i}{dt} = P_i(\boldsymbol{x}) = \sum_{j=1}^{M_i} \bar{k}_{ij} \varepsilon^{\gamma_{ij}} \boldsymbol{x}^{\boldsymbol{\alpha}_{ij}}, \tag{2}$$

where $\varepsilon > 0$ is a small number.

Definition. *The system* (2) *is permanent, if*

$$C_- < \bar{x}_i(t) < C_+, \text{ for all } t > T_0(x(0)) \text{ and for all } i,$$

where $x_i = \varepsilon^{a_i} \bar{x}_i$ for constants $C_\pm > 0$ and T_0 uniform in ε as $\varepsilon \to 0$.

Theorem If the system (2) is permanent, then the complete or two terms tropicalization are good approximations : error vanishes like ε^γ, and one has orbital topological equivalency between initial and tropicalized trajectories.

Tropical truncation and tropical equilibration

Polynomial kinetics (e.g. mass action law)

$$\frac{dx_i}{dt} = \sum_{j=1}^{M_i} k_{ij} x^{\alpha_{ij}}$$

$\varepsilon > 0$ is a small number. Renormalize concentrations $x_i = \varepsilon^{a_i} \bar{x}_i$ where powers a_i are unknown.

$$\frac{d\bar{x}_i}{dt} = \sum_{j=1}^{M_i} \varepsilon^{\mu_{ij}} \bar{k}_{ij} \bar{\mathbf{x}}^{\alpha^{ij}},$$

$$\mu_{ij} = \gamma_{ij} + \sum_{l=1}^{n} \alpha_l^{ij} a_l - a_i.$$

Tropical truncation

Keep only the minimal powers of ε, ie m_i terms.
For instance, if $m_i = 1$

$$\frac{d\bar{x}_i}{dt} = \varepsilon^{\mu_i} k_{ij(i)} \bar{\mathbf{x}}^{\alpha^{ij(i)}},$$

where $j(i)$ is the index of the unique term with minimum degree in ε,

$$\mu_i = \min_j \left(\gamma_{ij} + \sum_{l=1}^{n} \alpha_l^{ij} a_l \right) - a_i.$$

Tropical equilibration problem

Find a pair (j, j'), $j \neq j'$ such that

i) $\mu_{ij} = \mu_{ij'}$,

ii) $\mu_{ij} \leq \mu_{il}$ for all $l \neq j, j'$,

iii) $k_{ij} k_{ij'} < 0$.

The minimum degree is attained at least twice and the minimal degree terms have opposite signs.

$$\frac{d\bar{x}_i}{dt} = \varepsilon^{\mu_i} \left(|k_{ij}| \bar{\mathbf{x}}^{\alpha^{ij}} - |k_{ij'}| \bar{\mathbf{x}}^{\alpha^{ij'}} \right)$$

The tropically truncated system is binomial (toric system).

Tropical equilibration and model reduction

Lemma1. *We have permanency only if we have tropical equilibration of at least two terms, one positive (production), the other negative (degradation).*

Lemma2. In the case of tropical equilibration of two terms (toric systems), and if $0 = \mu_1 < \mu_2 < ... < \mu_{n-1} < \mu_n$ (total separation) each variable follows

$$\frac{dx}{dt} = b_1(z)x^{\beta_1} - b_2(z)x^{\beta_2}, \quad b_1, b_2 > 0,$$

where z is a slow function of time and we have permanency iff $\beta_1 < \beta_2$.

Theorem. If the above conditions are satisfied, then the system has an attractive invariant manifold. The corresponding equilibration can be used to reduce the model. Fast variables are tropically equilibrated.

Michaelis-Menten enzymatic reaction

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_2}{\to} P + E,$$
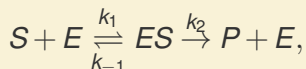
Using the conserved quantities $e_0 = [E] + [ES]$,
$s_0 = [S] + [ES] + [P]$, we get the system

$$x' = -k_1 x(e_0 - y) + k_{-1} y, \quad y' = k_1 x(e_0 - y) - (k_{-1} + k_2)y.$$

where $x = [S]$ and $y = [SE]$,
and some constraints

$$0 \leq y \leq e_0, \, 0 \leq x + y \leq s_0, \, 0 \leq x.$$

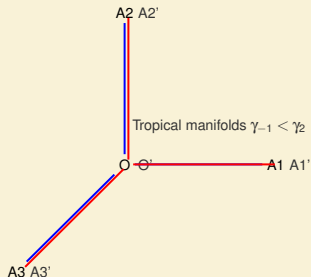# The tropical equilibration problem

After rescalings $x = \bar{x}\varepsilon^{a_1}$, $y = \bar{y}\varepsilon^{a_2}$, $k_1 = \bar{k}_1\varepsilon^{\gamma_1}$, $k_{-1} = \bar{k}_{-1}\varepsilon^{\gamma_{-1}}$, $e_0 = \bar{e}_0\varepsilon^{\gamma_e}$, $s_0 = \bar{s}_0\varepsilon^{\gamma_s}$, we get

$$\bar{x}' = -\bar{k}_1\bar{e}_0\varepsilon^{\gamma_1+\gamma_e}\bar{x} + \bar{k}_1\varepsilon^{\gamma_1+a_2}\bar{x}\bar{y} + \bar{k}_{-1}\varepsilon^{\gamma_{-1}+a_2-a_1}\bar{y},$$
$$\bar{y}' = \bar{k}_1\bar{e}_0\varepsilon^{\gamma_1+\gamma_e+a_1-a_2}\bar{x} - \bar{k}_1\varepsilon^{\gamma_1+a_1}\bar{x}\bar{y} - (\bar{k}_{-1}\varepsilon^{\gamma_{-1}} + \bar{k}_2\varepsilon^{\gamma_2})\bar{y}.$$
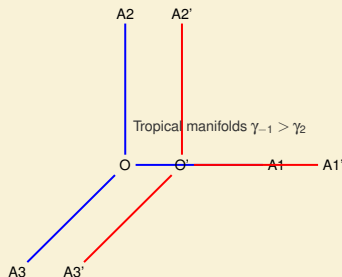
that leads to the equilibration equations

$$\gamma_1 + \gamma_e = \min(\gamma_1 + a_2, \gamma_{-1} + a_2 - a_1),$$
$$\gamma_1 + \gamma_e + a_1 - a_2 = \min(\gamma_1 + a_1, \min(\gamma_{-1}, \gamma_2)).$$

Quasi-equilibrium approximation

Tropical manifolds $\gamma_{-1} < \gamma_2$

No	Condition	Truncated system	Regime
1	$a_1 < \gamma_{-1} - \gamma_1$ $a_2 = \gamma_e$	$x' = \varepsilon^{\gamma_1 + \gamma_e} \left(-\bar{k}_1 \bar{e}_0 \bar{x} + \bar{k}_1 \bar{x} \bar{y} \right)$ $y' = \varepsilon^{\gamma_1 + a_1} \left(\bar{k}_1 \bar{e}_0 \bar{x} - \bar{k}_1 \bar{x} \bar{y} \right)$	QE saturated
2	$a_1 > \gamma_{-1} - \gamma_1$ $a_2 = a_1 + \gamma_e + \gamma_1 - \gamma_{-1}$	$x' = \varepsilon^{\gamma_1 + \gamma_e} \left(-\bar{k}_1 \bar{e}_0 \bar{x} + \bar{k}_{-1} \bar{y} \right)$ $y' = -\varepsilon^{\gamma_{-1}} \left(\bar{k}_1 \bar{e}_0 \bar{x} - \bar{k}_{-1} \bar{y} \right)$	QE linear

Quasi-steady state approximation

A2 A2'

Tropical manifolds $\gamma_{-1} > \gamma_2$

O O' A1 A1'

A3 A3'

No	Condition	Truncated system	Regime
1	$a_1 < \gamma_2 - \gamma_1$ $a_2 = \gamma_e$	$x' = \varepsilon^{\gamma_1 + \gamma_e} \left(-\bar{k}_1 \bar{e}_0 \bar{x} + \bar{k}_1 \bar{x} \bar{y} \right)$ $y' = \varepsilon^{\gamma_1 + a_1} \left(\bar{k}_1 \bar{e}_0 \bar{x} - \bar{k}_1 \bar{x} \bar{y} \right)$	y QSS if $a_1 < \gamma_e$
2	$\gamma_2 - \gamma_1 < a_1 < \gamma_{-1} - \gamma_1$ $a_2 = \gamma_e$	$x' = \varepsilon^{\gamma_1 + \gamma_e} \left(-\bar{k}_1 \bar{e}_0 \bar{x} + \bar{k}_1 \bar{x} \bar{y} \right)$ $y' = -\varepsilon^{\gamma_2} \bar{k}_2 \bar{y}$	x QSS if $\gamma_2 > \gamma_1 + \gamma_e$
3	$a_1 > \gamma_{-1} - \gamma_1$ $a_2 = a_1 + \gamma_e + \gamma_1 - \gamma_{-1}$	$x' = \varepsilon^{\gamma_1 + \gamma_e} \left(-\bar{k}_1 \bar{e}_0 \bar{x} + \bar{k}_{-1} \bar{y} \right)$ $y' = -\varepsilon^{\gamma_2} \bar{k}_2 \bar{y}$	x QSS if $\gamma_2 > \gamma_1 + \gamma_e$
4	$a_1 > \gamma_2 - \gamma_1$ $a_2 = a_1 + \gamma_e + \gamma_1 - \gamma_2$	$x' = -\varepsilon^{\gamma_1 + \gamma_e} \bar{k}_1 \bar{e}_0 \bar{x}$ $y' = \varepsilon^{\gamma_2} \left(\bar{k}_1 \bar{e}_0 \bar{x} - \bar{k}_2 \bar{y} \right)$	y QSS if $\gamma_2 < \gamma_1 + \gamma_e$

Tropical equilibrations and model reduction

TTS at quasi-equilibrium : pruning

$$\bar{x}' = \varepsilon^{\gamma_1 + \gamma_e}(-\bar{k}_1 \bar{e}_0 \bar{x} + \bar{k}_{-1} \bar{y})$$
$$\bar{y}' = \varepsilon^{\gamma_{-1}}(\bar{k}_1 \bar{e}_0 \bar{x} - \bar{k}_{-1} \bar{y})$$

New slow variable $z = x + y$: pooling

$$\bar{z}' = -\varepsilon^{\gamma_2 + a_2 - \gamma_s} \bar{k}_2 \bar{y}.$$

Eliminate x, y, obtain the reduced model
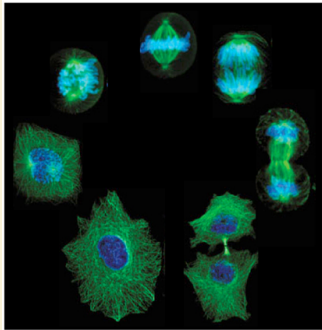
$$z' = -k_2/(1 + k_{-1}/(k_1 e_0))z.$$

Results on Biomodels.net

Two methods : Newton polytope, reified constraints.

436 curated models, 55 have purely polynomial kinetics.

Found	# models	Variables (avg/min/max)	Time (avg/min/max)
yes	23	17.348/3/ 86	0.486/0.004/2.803
no	32	17.812/1/194	0.099/0.000/1.934

Cell cycle model

- Cell proliferation is regulated by cyclic activity of cyclins

- A simple model, Tyson 91

$$
\begin{aligned}
y_1' &= \varepsilon^{-3}k_9 y_2 - \varepsilon^{-6}k_8 y_1 + k_6 y_3, \\
y_2' &= \varepsilon^{-6}k_8 y_1 - \varepsilon^{-3}k_9 y_2 - \varepsilon^{-2}k_3 y_2 y_5, \\
y_3' &= \varepsilon^2 k_4' y_4 + \varepsilon^{-2}k_4 y_4 y_3^2 - k_6 y_3, \\
y_4' &= -\varepsilon^2 k_4' y_4 - \varepsilon^{-2}k_4 y_4 y_3^2 + \varepsilon^{-2}k_3 y_2 y_5, \\
y_5' &= \varepsilon^2 k_1 - \varepsilon^{-2}k_3 y_2 y_5.
\end{aligned}
$$

y_1 cdc2, y_2 p-cdc2, y_3 cyclin-p:cdc2 complex (active MPF), y_4 cyclin-p:cdc2-p complex (inactive MPF), y_5 cyclin.

Tropical equilibrations

Rescale $y_i = \varepsilon^{a_i} \bar{y}_i$ and get

$$
\begin{aligned}
\bar{y}_1' &= \varepsilon^{-3+a_2-a_1} k_9 \bar{y}_2 - \varepsilon^{-6} k_8 y_1 + k_6 \varepsilon^{a_3-a_1} \bar{y}_3, \\
\bar{y}_2' &= \varepsilon^{-6+a_1-a_2} k_8 \bar{y}_1 - \varepsilon^{-3} k_9 \bar{y}_2 - \varepsilon^{-2+a_5} k_3 \bar{y}_2 \bar{y}_5, \\
\bar{y}_3' &= \varepsilon^{2+a_4-a_3} k_4' \bar{y}_4 + \varepsilon^{-2+a_3+a_4} k_4 \bar{y}_4 \bar{y}_3^2 - k_6 \bar{y}_3, \\
\bar{y}_4' &= -\varepsilon^2 k_4' \bar{y}_4 - \varepsilon^{-2+2a_3} k_4 \bar{y}_4 \bar{y}_3^2 + \varepsilon^{-2+a_2+a_5-a_4} k_3 \bar{y}_2 \bar{y}_5, \\
\bar{y}_5' &= \varepsilon^{2-a_5} k_1 - \varepsilon^{-2+a_2} k_3 \bar{y}_2 \bar{y}_5.
\end{aligned}
$$

Full tropical equilibration
$a_1 = 3, \quad a_2 = 0, \quad a_3 = 2, \ a_4 = 0, \ a_5 = 4.$

Tropical equilibrations

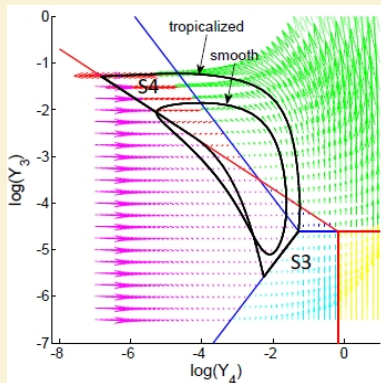Rescaled equations

$$\bar{y}'_1 = \varepsilon^{-6}(k_9\bar{y}_2 - k_8\bar{y}_1) + k_6\varepsilon^{-1}\bar{y}_3, \bar{y}'_2 = \varepsilon^{-3}(k_8\bar{y}_1 - k_9\bar{y}_2) - \varepsilon^2 k_3\bar{y}_2\bar{y}_5,$$
$$\bar{y}'_3 = k'_4\bar{y}_4 + k_4\bar{y}_4\bar{y}_3^2 - k_6\bar{y}_3, \bar{y}'_4 = \varepsilon^2(-k'_4\bar{y}_4 - k_4\bar{y}_4\bar{y}_3^2 + k_3\bar{y}_2\bar{y}_5),$$
$$\bar{y}'_5 = \varepsilon^{-2}(k_1 - k_3\bar{y}_2\bar{y}_5).$$

Reduced model

$$\bar{y}'_3 = k'_4\bar{y}_4 + k_4\bar{y}_4\bar{y}_3^2 - k_6\bar{y}_3, \bar{y}'_4 = \varepsilon^2(-k'_4\bar{y}_4 - k_4\bar{y}_4\bar{y}_3^2 + k_1),$$
$$k_1 = k_3\bar{y}_2\bar{y}_5, k_9\bar{y}_2 = k_8\bar{y}_1, \varepsilon^3\bar{y}_1(t) + \bar{y}_2(t) + \varepsilon^2\bar{y}_3(t) + \bar{y}_4(t) = 1.$$

Tropicalization of the 2D reduced cell cycle model

- ▶ the smooth and tropicalized trajectories are qualitatively similar.

- ▶ y_3, y_4 are excitable, not equilibrated in the same time.

Partial tropical equilibrations

Rescale $y_i = \varepsilon^{a_i} \bar{y}_i$ and get

$$
\begin{aligned}
\bar{y}_1' &= \varepsilon^{-3+a_2-a_1} k_9 \bar{y}_2 - \varepsilon^{-6} k_8 y_1 + k_6 \varepsilon^{a_3-a_1} \bar{y}_3, \\
\bar{y}_2' &= \varepsilon^{-6+a_1-a_2} k_8 \bar{y}_1 - \varepsilon^{-3} k_9 \bar{y}_2 - \varepsilon^{-2+a_5} k_3 \bar{y}_2 \bar{y}_5, \\
\bar{y}_3' &= \varepsilon^{2+a_4-a_3} k_4' \bar{y}_4 + \varepsilon^{-2+a_3+a_4} k_4 \bar{y}_4 \bar{y}_3^2 - k_6 \bar{y}_3, \\
\bar{y}_4' &= -\varepsilon^2 k_4' \bar{y}_4 - \varepsilon^{-2+2a_3} k_4 \bar{y}_4 \bar{y}_3^2 + \varepsilon^{-2+a_2+a_5-a_4} k_3 \bar{y}_2 \bar{y}_5, \\
\bar{y}_5' &= \varepsilon^{2-a_5} k_1 - \varepsilon^{-2+a_2} k_3 \bar{y}_2 \bar{y}_5.
\end{aligned}
$$

From the equilibration of y_1, y_2, y_5 we find
$a_1 = 3$, $a_2 = 0$, $a_5 = 4$.

Partial tropical equilibrations
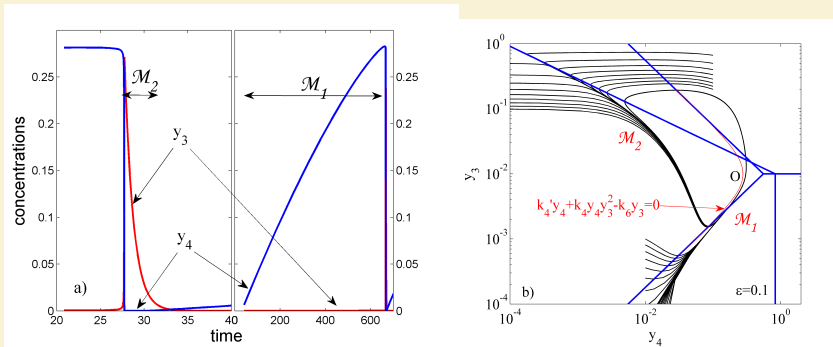
if y_3 is equilibrated, then $a_3 = 2, \quad a_4 = 0$ and

$$\bar{y}_3' = k_4'\bar{y}_4 + k_4\bar{y}_4\bar{y}_3^2 - k_6\bar{y}_3, \; \bar{y}_4' = \varepsilon^2(-k_4'\bar{y}_4 - k_4\bar{y}_4\bar{y}_3^2 + k_1).$$

if y_4 is equilibrated, then $a_3 = 0, \quad a_4 = 4$ and

$$\tilde{y}_3' = \varepsilon^6 k_4'\tilde{y}_4 + \varepsilon^2 k_4\tilde{y}_4\tilde{y}_3^2 - k_6\tilde{y}_3, \; \tilde{y}_4' = -\varepsilon^2 k_4'\tilde{y}_4 + \varepsilon^{-2}(-k_4\tilde{y}_4\tilde{y}_3^2 + k_1).$$
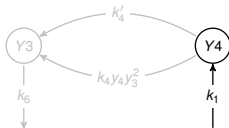
Tropical equilibrations and invariant manifolds

Tropical equilibrations correspond to locally attractive invariant manifolds and slower parts of the cycle.
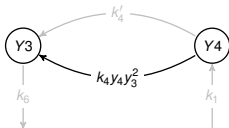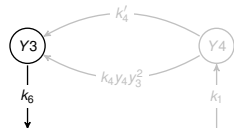
Hybrid cell cycle model
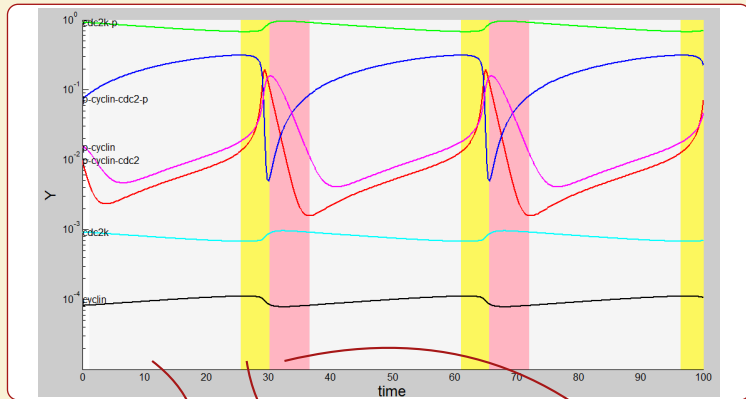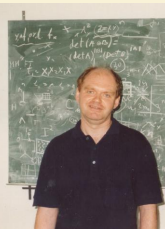
Acknowledgements

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