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 $X \rightarrow X + \nu_j$, $\nu_j \in \mathbb{Z}^n$.

- 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 $X \to X + \nu_j$, $\nu_j \in \mathbb{Z}^n$.

- 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

$$p_j(x) = \frac{R_j(x)}{\sum_{j=1}^{r} R_j(x)}$$
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 $A_i \rightarrow A_j$ (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

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

Relevance for computational biology:

- Occur as subsystems of larger, nonlinear networks.
- Crude approximations obtained by linearizing networks.
Linear networks with separated constants

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

The eigenvectors of \( K \) specify the dynamics.

Well separated constants

\[ k_{l_1} \gg k_{l_2} \gg k_{l_3} \gg \ldots \]

**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 $A_i \to A_j$.

$\phi$ 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, $\text{Att}(C_j)$: $\mathcal{A} = \bigcup_j \text{Att}(C_j)$. 
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 $l^i_j = \frac{\kappa_j}{\kappa_j - \kappa_i} l^i_j$ 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

\[ l^5 \approx (0, 0, 0, 1, 0, 1, 0) \]

\[ r^5 \approx (0, 0, 0, 0, -1, 0, 0, 1) \]
Sequence of reduced models

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

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

Supagro, Oct 2013
3-rd case: some of $C_j$ are not sinks

Slow reactions leave the cycle.

Pool species in cycles;

Renormalize constants of outgoing slow reactions.

Compare renormalized constants to other constants;

$k_5k_4 / k_3 > k_6$

$k_5k_4 / k_3 < k_6$

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-plus polynomials.

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

Tropical manifold: the set of points where max-plus polynomials are not smooth.

Tropical manifold of \( ay + cx + bx^2 y \) on “logarithmic paper”.
Tropicalized Systems

- Two terms tropicalization (Savageau 2009)

\[ \frac{dx_i}{dt} = \text{Dom}P_i^+(x) - \text{Dom}P_i^-(x) \]

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

\[ \frac{dx_i}{dt} = \text{Dom}P_i(x) \]

where \( \text{Dom} \left[ \sum_{\alpha \in A_i} a_i, \alpha x^\alpha \right] \) =

\( \text{sign}(a_{i, \alpha_{\text{max}}}) \exp[\max_{\alpha \in A_i} \{ \log(|a_{i, \alpha}|) + < u, \alpha > \}] \). 

\( u = (\log x_1, \ldots, \log x_n) \), and \( a_{i, \alpha_{\text{max}}}, \alpha_{\text{max}} \in A_i \) denote the coefficient of the monomial for which the maximum is attained.
Is the heuristics justified?

\[ \frac{dx_i}{dt} = P_i(x) = \sum_{j=1}^{M_i} \bar{k}_{ij} \varepsilon^{\gamma_{ij}} x^{\alpha_{ij}}, \quad (2) \]

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* \( \varepsilon \) *as* \( \varepsilon \to 0 \).

**Theorem** If the system (2) is permanent, then the complete or two terms tropicalization are good approximations: error vanishes like \( \varepsilon^{\gamma} \), and one has orbital topological equivalency between initial and tropicalized trajectories.
Tropical truncation and tropical equilibration

Polynomial kinetics (e.g. mass action law)

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

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

\[ \frac{d\bar{x}_i}{dt} = \sum_{j=1}^{M_i} \epsilon^{\mu_{ij}} \bar{k}_{ij} \bar{x}^{\alpha_{ij}} \]

\[ \mu_{ij} = \gamma_{ij} + \sum_{l=1}^{n} \alpha_{ij}^l a_l - a_i. \]
Tropical truncation

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

$$\frac{d\bar{x}_i}{dt} = \varepsilon^{\mu_i} k_{jj(i)} \bar{x}^{\alpha_{jj(i)}},$$

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

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

\[
\frac{d\bar{x}_i}{dt} = \varepsilon^{\mu_i}(|k_{ij}|\bar{X}^{\alpha_{ij}} - |k_{ij'}|\bar{X}^{\alpha_{ij'}})
\]

The tropically truncated system is binomial (toric system).
Tropical equilibration and model reduction

Lemma 1. We have permanency only if we have tropical equilibration of at least two terms, one positive (production), the other negative (degradation).

Lemma 2. In the case of tropical equilibration of two terms (toric systems), and if $0 = \mu_1 < \mu_2 < \ldots < \mu_{n-1} < \mu_n$ (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

\[ S + E \xrightleftharpoons[k_1]{k_{-1}} ES \xrightarrow{k_2} P + E, \]

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

\[ 0 \leq y \leq e_0, \quad 0 \leq x + y \leq s_0, \quad 0 \leq x. \]
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 $\gamma_{-1} < \gamma_2$

<table>
<thead>
<tr>
<th>No</th>
<th>Condition</th>
<th>Truncated system</th>
<th>Regime</th>
</tr>
</thead>
</table>
| 1  | $a_1 < \gamma_{-1} - \gamma_1$
     | $a_2 = \gamma_e$ | $x' = \varepsilon \gamma_1 + \gamma_e (\bar{k}_1 \bar{e}_0 x + \bar{k}_1 \bar{x} \bar{y})$
     | $y' = \varepsilon \gamma_1 + a_1 (\bar{k}_1 \bar{e}_0 x - \bar{k}_1 \bar{x} \bar{y})$ | QE saturated |
| 2  | $a_1 > \gamma_{-1} - \gamma_1$
     | $a_2 = a_1 + \gamma_e + \gamma_1 - \gamma_{-1}$ | $x' = \varepsilon \gamma_1 + \gamma_e (\bar{k}_1 \bar{e}_0 x + \bar{k}_1 \bar{x} \bar{y})$
     | $y' = -\varepsilon \gamma_{-1} (\bar{k}_1 \bar{e}_0 x - \bar{k}_1 \bar{x} \bar{y})$ | QE linear |
Quasi-steady state approximation

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

<table>
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<tr>
<th>No</th>
<th>Condition</th>
<th>Truncated system</th>
<th>Regime</th>
</tr>
</thead>
</table>
| 1  | $a_1 < \gamma_2 - \gamma_1$  
    $a_2 = \gamma_e$ | $x' = \varepsilon \gamma_1 + \gamma_e (\bar{k}_1 \bar{e}_0 \bar{x} + \bar{k}_1 \bar{x} \bar{y})$  
    $y' = \varepsilon \gamma_1 + a_1 (\bar{k}_1 \bar{e}_0 \bar{x} - \bar{k}_1 \bar{x} \bar{y})$ | $y$ QSS if $a_1 < \gamma_e$ |
| 2  | $\gamma_2 - \gamma_1 < a_1 < \gamma_{-1} - \gamma_1$  
    $a_2 = \gamma_e$ | $x' = \varepsilon \gamma_1 + \gamma_e (\bar{k}_1 \bar{e}_0 \bar{x} + \bar{k}_1 \bar{x} \bar{y})$  
    $y' = -\varepsilon \gamma_2 \bar{k}_2 \bar{y}$ | $x$ QSS if $\gamma_2 > \gamma_1 + \gamma_e$ |
| 3  | $a_1 > \gamma_{-1} - \gamma_1$  
    $a_2 = a_1 + \gamma_e + \gamma_1 - \gamma_2$ | $x' = \varepsilon \gamma_1 + \gamma_e (\bar{k}_1 \bar{e}_0 \bar{x} + \bar{k}_1 \bar{x} \bar{y})$  
    $y' = -\varepsilon \gamma_2 \bar{k}_2 \bar{y}$ | $x$ QSS if $\gamma_2 > \gamma_1 + \gamma_e$ |
| 4  | $a_1 > \gamma_2 - \gamma_1$  
    $a_2 = a_1 + \gamma_e + \gamma_1 - \gamma_2$ | $x' = -\varepsilon \gamma_1 + \gamma_e \bar{k}_1 \bar{e}_0 \bar{x}$  
    $y' = \varepsilon \gamma_2 (\bar{k}_1 \bar{e}_0 \bar{x} - \bar{k}_2 \bar{y})$ | $y$ 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
\[
\bar{z}' = -\varepsilon^{\gamma_2+a_2-\gamma_s}k_2 \bar{y}.
\]

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.

<table>
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<tr>
<th>Found</th>
<th># models</th>
<th>Variables (avg/min/max)</th>
<th>Time (avg/min/max)</th>
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<td>23</td>
<td>17.348/3/ 86</td>
<td>0.486/0.004/2.803</td>
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<td>no</td>
<td>32</td>
<td>17.812/1/194</td>
<td>0.099/0.000/1.934</td>
</tr>
</tbody>
</table>
Cell cycle model

▶ Cell proliferation is regulated by cyclic activity of cyclins

▶ A simple model, Tyson 91

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

\(y_1\) 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

$$
\bar{y}_1' = \varepsilon^{-3+a_2-a_1} k_9 \bar{y}_2 - \varepsilon^{-6} k_8 y_1 + k_6 \varepsilon^{a_3-a_1} \bar{y}_3,
$$

$$
\bar{y}_2' = \varepsilon^{-6+a_1-a_2} k_8 \bar{y}_1 - \varepsilon^{-3} k_9 \bar{y}_2 - \varepsilon^{-2+a_5} k_3 \bar{y}_2 \bar{y}_5,
$$

$$
\bar{y}_3' = \varepsilon^{2+a_4-a_3} k_4 \bar{y}_4 + \varepsilon^{-2+a_3+a_4} k_4 \bar{y}_4 \bar{y}_3^2 - k_6 \bar{y}_3,
$$

$$
\bar{y}_4' = -\varepsilon^{2} k_4' \bar{y}_4 - \varepsilon^{-2+2a_3} k_4 \bar{y}_4 \bar{y}_3^2 + \varepsilon^{-2+a_2+a_5-a_4} k_3 \bar{y}_2 \bar{y}_5,
$$

$$
\bar{y}_5' = \varepsilon^{2-a_5} k_1 - \varepsilon^{-2+a_2} k_3 \bar{y}_2 \bar{y}_5.
$$

Full tropical equilibration

$a_1 = 3, \quad a_2 = 0, \quad a_3 = 2, \quad a_4 = 0, \quad a_5 = 4.$
Tropical equilibrations

Rescaled equations

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

Reduced model

\[ \bar{y}_3' = k'_4 \bar{y}_4 + k_4 \bar{y}_4 \bar{y}_3^2 - k_6 \bar{y}_3, \quad \bar{y}_4' = \varepsilon^2(-k'_4 \bar{y}_4 - k_4 \bar{y}_4 \bar{y}_3^2 + k_1), \]
\[ k_1 = k_3 \bar{y}_2 \bar{y}_5, \quad k_9 \bar{y}_2 = k_8 \bar{y}_1, \quad \varepsilon^3 \bar{y}_1(t) + \bar{y}_2(t) + \varepsilon^2 \bar{y}_3(t) + \bar{y}_4(t) = 1. \]
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 $y_i = \epsilon^{a_i} \bar{y}_i$ and get

$$
\bar{y}_1' = \epsilon^{-3+a_2-a_1} k_9 \bar{y}_2 - \epsilon^{-6} k_8 y_1 + k_6 \epsilon^{a_3-a_1} \bar{y}_3,
$$

$$
\bar{y}_2' = \epsilon^{-6+a_1-a_2} k_8 \bar{y}_1 - \epsilon^{-3} k_9 \bar{y}_2 - \epsilon^{-2+a_5} k_3 \bar{y}_2 \bar{y}_5,
$$

$$
\bar{y}_3' = \epsilon^{2+a_4-a_3} k_4 \bar{y}_4 - \epsilon^{-2+a_3+a_4} k_4 \bar{y}_4 \bar{y}_3^2 - k_6 \bar{y}_3,
$$

$$
\bar{y}_4' = -\epsilon^2 k_4' \bar{y}_4 - \epsilon^{-2+2a_3} k_4 \bar{y}_4 \bar{y}_3^2 + \epsilon^{-2+a_2+a_5-a_4} k_3 \bar{y}_2 \bar{y}_5,
$$

$$
\bar{y}_5' = \epsilon^{2-a_5} k_1 - \epsilon^{-2+a_2} k_3 \bar{y}_2 \bar{y}_5.
$$

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 $a_3 = 2$, $a_4 = 0$ and

$$\bar{y}_3' = k_4' \bar{y}_4 + k_4 \bar{y}_4 \bar{y}_3^2 - k_6 \bar{y}_3$$

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

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

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

Interphase (synthesis)

\[ Y_3 \xrightarrow{k_4} Y_4 \xrightarrow{k_6} Y_4 \]

Mitosis 1 (activation)

\[ Y_3 \xrightarrow{k_4} Y_4 \]

Mytosis 2 (degradation)

\[ Y_3 \xrightarrow{k_6} Y_4 \]
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