Qualitative dynamics of chemical reaction networks: an investigation using partial tropical equilibrations

Aurélien Desoeuvres¹, Peter Szmolyan², and Ovidiu Radulescu¹

¹ LPHI UMR CNRS 5235, University of Montpellier, Montpellier, France; ovidiu.radulescu@umontpellier.fr
² Technische Universität Wien, Institute for Analysis and Scientific Computing, Vienna, Austria;

Abstract. We discuss a method to describe the qualitative dynamics of chemical reaction networks in terms of symbolic dynamics. The method, that can be applied to mass-action reaction networks with separated timescales, uses solutions of the partial tropical equilibration problem as proxies for symbolic states. The partial tropical equilibration solutions are found algorithmically. These solutions also provide the scaling needed for slow-fast decomposition and model reduction. Any trace of the model can thus be represented as a sequence of local approximations of the full model. We illustrate the method using as case study a biochemical model of the cell cycle.

1 Introduction

Chemical reaction networks (CRN) are models of normal cell physiology and of disease and have multiple applications in biology and medicine. Rather generally, CRNs can be described as systems of polynomial differential equations that result from the mass action kinetics. In applications one would like to characterize these models in terms of attractors, their bifurcations, attraction basins, and of the sequence of states to and on these attractors. These questions belong to the qualitative theory of dynamical systems and are notoriously difficult.

In this paper we introduce a method to describe the qualitative dynamics of mass-action law CRNs, in situations when the dynamics involves processes on several well separated timescales. We have suggested that in these situations, the phase space of the CRN is patched with slow manifolds connected to each other by continuous or discontinuous transitions. Thus, the system stays repeatedly for relatively long time in some metastable state before switching to some other metastable state. In we proposed to use tropical equilibrations as proxies for metastable states and finite-state machines as discrete abstractions for the ODE dynamics of the CRN.

The concept of tropical equilibration comes from algebraic geometry and it is a necessary condition for the existence of real Puiseux series solutions of systems of polynomial equations whose coefficients are powers or Puiseux series of some
scaling parameter $\epsilon$. The concept is naturally related to the problem of finding scalings of differential equations needed in the mathematical theory of singular perturbations for systems with multiple timescales [3].

By revisiting the tropical scaling methodology we realized that the concept of partial tropical equilibrations is better suited to slow-fast decompositions than total tropical equilibrations [1]. The total tropical equilibration condition means that on slow manifolds each polynomial ODE has two dominant monomial terms of opposite signs that can equilibrate each other; the flow generated by the remaining, un-equilibrated monomial terms is slow. However, in slow-fast decompositions only fast variables need to be equilibrated; the dynamics of slow variables is governed by ODEs that may have only one dominant, but slow, monomial term. This leads to the concept of partial tropical equilibration that we investigate here.

We provide an automatic method to compute partial tropical equilibrations, derived from the similar method for total tropical equilibrations based on SMT solvers, SMTcut [1], https://gitlab.com/cxxl/smtcut/-/tree/master/smtcut. Our code is available at https://github.com/Glawal/smtcutpartial. As a case study we discuss a six variables biochemical network describing the cyclic phosphorylation of different substrates in the frog embryo cell cycle, proposed by J.J.Tyson [14]. The partial equilibration solutions of this model are grouped in branches that are geometrically represented as polyhedra in the space of orders of magnitude of the species concentrations. The intersection relations of these polyhedra allow us to define a connectivity graph. We verify numerically that the branches are reasonably well related to slow manifolds and that the allowed transitions from one slow manifold to another are all edges of the connectivity graph. Each branch corresponds to a reduced model that can be computed using the tropical scaling approach. Any trace of the model can be represented symbolically as a sequence of branches or reduced models. Also, any trace can be approximated locally by solutions of the corresponding reduced model. We expect that the global validity of these patched together local approximations as approximations of solutions of the full model can be shown rigorously; this is the subject of ongoing work.

2 Definitions and methods

2.1 Tropical geometry concepts

We briefly recall here how we relate tropical geometry and singular perturbations using what we call tropical scaling. We follow notations from [5]. The reference [5] can be used by the reader as a good introduction to tropical geometry.

We consider differential equations whose r.h.s. are multivariate polynomials $f = \sum c_u x^u$, where $u$ are multi-indices and $c_u$ coefficients. Here, $c_u$ are considered to be functions (rational powers or more generally, Puiseux series) of a positive scaling parameter $\epsilon$. We define the valuation of $c_u$ as the limit

$$\text{val}(c_u) = \lim_{\epsilon \to 0} \log(c_u)/\log(\epsilon).$$  \hspace{1cm} (1)
Another way to introduce valuations is via Puiseux series, i.e. power series with negative and positive exponents. If \( c_u \) is a Puiseux series of \( \epsilon \), then \( c_u \sim \epsilon^{\text{val}(c_u)} \) at the lowest order. As \( \epsilon^{\text{val}(c_u)} \) is the dominant term of \( c_u \) at some fixed \( \epsilon = \epsilon_* \), valuations are obtained from the order of magnitude of \( c_u \) at \( \epsilon = \epsilon_* \). For \( \epsilon_* = 1/10 \), valuations are obtained from decimal orders. With this in mind, \( \text{val}(c_u) \) can always be found from the numerical values of the coefficients (see Section 3).

The valuations of \( x \) are unknown, so they should result from a calculation. The rest of this subsection is about the constraints on the valuations of the variables \( x \), when \( x \) satisfies polynomial equations.

Given a polynomial \( f = \sum c_u x^u \), its tropicalization \( \text{trop}(f) \) is the piecewise-linear function

\[
\text{trop}(f)(w) = \min\{\text{val}(c_u) + u \cdot w\}.
\]

The variety \( V(f) \) is the set of all \( x \) solutions of \( f(x) = 0 \). The tropical hypersurface \( \text{trop}(V(f)) \) is the set of \( w \) where the minimum in \( \text{trop}(f) \) is attained at least twice. A theorem of Kapranov relates the tropical hypersurface to the set of all possible valuations of \( x \) on \( V(f) \), namely \( \text{trop}(V(f)) \) is the closure of \( \text{val}(x) \) where \( x \in V(f) \) \cite{B}. In short, if we know the orders of \( c_u \), the orders of \( x \) satisfying \( f(x) = 0 \) are given by \( \text{trop}(V(f)) \).

Kapranov’s theorem refers to solutions of \( f = 0 \) in the complex field. If we are interested in the valuations of real positive solutions of \( f = 0 \), where \( c_u \) are all real, then one has to consider tropical equilibrations. A tropical equilibration is a \( w \) where the minimum in \( \text{trop}(f) \) is attained at least twice, for at least one positive and at least one negative monomial \cite{B,B}. The tropical equilibrations are thus possible valuations of the real positive solutions of \( f(x) = 0 \).

If \( f = (f_1, \ldots, f_n) \) is a polynomial vector field, we define

\[
\text{trop}(f)(w_1, \ldots, w_n) = (\text{trop}(f_1)(w_1), \ldots, \text{trop}(f_n)(w_n))
\]

The valuations \( \text{val}(x) = (\text{val}(x_1), \ldots, \text{val}(x_n)) \) of the solutions of \( f(x) = 0 \) are in the intersection of the tropical hypersurfaces of the component polynomial \( f_i \). This intersection is called tropical prevariety. By “abus de langage” we call tropical equilibration also an element of the tropical prevariety that is a tropical equilibration for each component.

### 2.2 Partial tropical equilibrations and slow-fast decompositions

In the mathematical theory of slow-fast systems it is usually assumed that the governing equations have the form

\[
\begin{align*}
\frac{dx}{dt} &= f(x, y), \\
\frac{dy}{dt} &= \epsilon g(x, y),
\end{align*}
\]

i.e. the variables are a priori split into the fast variable \( x \) and the slow variable \( y \); here \( 0 < \epsilon \ll 1 \) is a suitable parameter measuring time-scale separation. The CRNs we have in mind are typically not given in this form which is a major obstacle in using slow-fast decompositions in their analysis. We will use partial tropical equilibrations to overcome these difficulties.
We start with an arbitrary splitting of the variables into two groups denoted by $x$ and $y$

\[
\begin{align*}
\frac{dx}{dt} &= f(x, y; k), \\
\frac{dy}{dt} &= g(x, y; k),
\end{align*}
\] (4)

where $f$ and $g$ are polynomial vector fields whose coefficients include the kinetic parameters $k$. Now we search for scalings and conditions leading to time scale separation similar to Eq. (3). To this purpose the model under study is considered to belong to a family of models indexed by $\epsilon$. More precisely, the kinetic parameters $k$ are considered to be powers of $\epsilon$, $k(\epsilon) \sim \epsilon^\gamma$ (this implies that the coefficients of $f, g$ are Puiseux series of $\epsilon$). Then, we consider the solutions of models from this family in the limit $\epsilon \to 0$. The studied model is just a member of the family, obtained for a particular value $\epsilon^*$ of $\epsilon$ and having kinetic parameters $k(\epsilon^*)$. If the value $\epsilon^*$ placing the studied model in the family is small enough, one may expect that the limit solution is a good approximation for the model’s solution.

The tropicalization is useful in the scaling process, because it allows to compute the lowest order terms of the Puiseux series expansions of the polynomials $f$ and $g$. We have

\[
\begin{align*}
\frac{d\bar{x}}{dt} &= e^{\mu_x} \bar{f}(\bar{x}, \bar{y}; \bar{k}) + \text{higher order terms}, \\
\frac{d\bar{y}}{dt} &= e^{\mu_y} \bar{g}(\bar{x}, \bar{y}; \bar{k}) + \text{higher order terms},
\end{align*}
\] (5)

where $\mu_x = \text{trop}(f)(\text{val}(x), \text{val}(y)) - \text{val}(x)$, $\mu_y = \text{trop}(g)(\text{val}(x), \text{val}(y)) - \text{val}(y)$, and $\bar{x}, \bar{y}, \bar{f}, \bar{g}, \bar{k}$ have valuation zero. $\mu_x$ and $\mu_y$ are the timescale orders (in fact orders of reciprocal timescales) for the variations of $x$ and $y$, respectively; smaller timescale orders mean faster variables.

$\bar{f}$ and $\bar{g}$ are called tropically truncated versions of $f$ and $g$.

Let us denote by $\mu_x \ll \mu_y$ the set of inequalities $\{(\mu_x)_i < (\mu_y)_j \forall i, j\}$, meaning that variables $x$ are faster than variables $y$.

If $\mu_x \ll \mu_y$ one shows that the solutions of (5) converge to the solutions of the following reduced system

\[
\begin{align*}
0 &= \bar{f}(\bar{x}, \bar{y}; \bar{k}), \\
\frac{d\bar{y}}{dt} &= e^{\mu_y} \bar{g}(\bar{x}, \bar{y}; \bar{k}),
\end{align*}
\] (6)

under some conditions meaning roughly that the solutions of $\bar{f}(\bar{x}, \bar{y}) = 0$ are hyperbolic attracting equilibria of the equation

\[
\frac{d\bar{x}}{dt} = \bar{f}(\bar{x}, \bar{y}; \bar{k}),
\]

see [3] for the rigorous statement. The first equation of (6) defines the quasi-steady state variety and imposes constraints on $x, y$. Using the tropical approach we transform these constraints into constraints on the order of magnitudes $\text{val}(x), \text{val}(y)$.
As a matter of fact, the valuations of $x$ and $y$ are constrained by

$$\begin{align*}
\{ & \text{(val}(x), \text{val}(y)) \text{ is a tropical equilibration of } f, \\
& \text{trop}(f)(\text{val}(x), \text{val}(y)) - \text{val}(x) < \text{trop}(g)(\text{val}(x), \text{val}(y)) - \text{val}(y). \}
\end{align*}$$

(7)

The first of the equations (7) follows from Kapranov’s theorem because $x$ satisfies $f(x, y) = 0$. The second equation is simply a condition on the timescales.

We call any solution of (7) partial tropical equilibration. Geometrically, (7) defines polyhedral complexes in the space of valuations.

If the system (4) has conservation laws, i.e. linear or polynomial functions $c(x, y)$ such that $\frac{\partial}{\partial x} f + \frac{\partial}{\partial y} g = 0$ identically, one needs to consider the quasi-state equation $f(x, y) = 0$ together with the conservation equation $c(x, y) - c_0 = 0$ where $c_0$ is constant. In this case the problem (7) becomes

$$\begin{align*}
\{ & \text{(val}(x), \text{val}(y)) \text{ is a tropical equilibration of } f \text{ and of } c(x, y) - c_0, \\
& \text{trop}(f)(\text{val}(x), \text{val}(y)) - \text{val}(x) < \text{trop}(g)(\text{val}(x), \text{val}(y)) - \text{val}(y). \}
\end{align*}$$

(8)

We call tropical scaling of a polynomial ODE system, a fixed choice of the valuations of the polynomial coefficients and variables satisfying the partial tropical equilibration constraints. It is very important to keep in mind, that different scalings will be valid in different regions of the phase space and will lead to different reductions.

Like total tropical equilibrations, partial tropical equilibrations (7) can be grouped into branches [10,13]. In a branch, the tropically truncated functions $\bar{f}$ and $\bar{g}$ are fixed. In other words, the dominant terms, corresponding to the min value in trop$(f)$ and trop$(g)$ are the same for all solutions in a branch. Geometrically, a branch is a polyhedral face of the polyhedral complex.

2.3 Coarse graining

The model has continuous parameters and variables which from the mathematical point of view can vary in $[0, \infty)$. Therefore, the valuations and in consequence the scales are in principle continuous. However, to obtain a finite number of useful approximating systems one has to use a suitable selection of discrete (often integer) scales, that cover the relevant domains in parameter- and phase space.

In order to do so, we use logarithmic paper coarse graining. The space of parameters and the phase space are discretized in such a way that any two parameters or two variable values taken from the same cell of a discretizing mesh grid have the same image on logarithmic paper.

In this approach, positive real quantities $x$ are mapped to the logarithmic paper using the application

$$x \rightarrow \frac{1}{d} \text{round}\left( \frac{\log x}{\log \epsilon_*} d\right),$$

(9)

where round is the rounding to the nearest integer, $\epsilon_*$ is a fixed value of $\epsilon$, $d$ is an integer, and $x$ is any positive quantity, e.g. a kinetic parameter, concentration, monomial or polynomial of concentrations. The image of $x$ via the mapping (9) represents the order of magnitude of $x$, which is an integer for $d = 1$ and a rational number from $\mathbb{Z}/d$ when $d > 1.$
Using (9) two values \(x_1\) and \(x_2\) have different images on logarithmic paper if
\[
|\log(x_1) - \log(x_2)| > \frac{|\log \epsilon_*|}{d}.
\] (10)
Equation (10) specifies the cell-size on logarithmic paper. For a given \(\epsilon_*\), the largest cell-size is obtained for integer values \(d = 1\). The cell-size increases when \(\epsilon_*\) decreases. The limit \(d \to \infty\) corresponds to the continuum.

In practice, we want to choose an intermediate cell-size. This should not be too small, to avoid continuous scaling, and not too large, to avoid loss of the structure. Although two parameters are in play, one can not change them independently. As a matter of fact, the value of \(\epsilon_*\) is dictated by singular perturbations; we want this to be small enough. Therefore, the cell-size adjustment is performed by changing \(d\) after the choice of \(\epsilon_*\).

Given \(\epsilon_*\), \(d\) the optimal \(d\) corresponds to the largest cell-size that distinguishes the most robust structural features (geometry of branches of tropical equilibration solutions, differences between orders of magnitude of parameters, concentrations, monomials, see also Section 3.3 and Figure 4).

3 Case study: a cell cycle model

The model presented is a modification of the original Tyson cell cycle model [13]. First, by considering constant concentrations as parameters, the model has been converted to an ODE system with six variables. In order to simplify the analysis we have also removed a variable \(x_6\) that does not interact with the rest of the model. This gives us the following model:

\[
\begin{align*}
\dot{x}_1 &= k_1 x_3 - k_2 x_1 + k_3 x_2, \\
\dot{x}_2 &= k_2 x_1 - k_3 x_2 - k_4 x_2 x_5, \\
\dot{x}_3 &= k_{10} x_4 - k_1 x_3 + k_9 x_3^2 x_4, \\
\dot{x}_4 &= k_4 x_2 x_5 - k_9 x_3^2 x_4 - k_{10} x_4, \\
\dot{x}_5 &= k_6 - k_4 x_2 x_5.
\end{align*}
\] (11)

With the parameter values \(k_1 = 1\), \(k_2 = 1000000\), \(k_3 = 1000\), \(k_4 = 200\), \(k_6 = 3/200\), \(k_8 = 3/5\), \(k_9 = 180\), \(k_{10} = 9/500\), \(k_{14} = 1\), where \(k_{14}\) is the total concentration associated to the conservation law \(k_{14} = x_1 + x_2 + x_3 + x_4\).

3.1 Tropical scaling of the cell cycle model

The reaction rate constants and the concentrations in this model have very different orders of magnitude which suggests dynamics on many well separated time scales. To identify these we rescale the model as a first step of using the procedure described abstractly in Sect. 2:

- Consider \(0 < \epsilon_* < 1\).
- Write \(k_i = \bar{k}_i \epsilon_*^{\gamma_i}\) and \(x_i = \bar{x}_i \epsilon_*^{\alpha_i}\); thus \(\gamma_i = \text{val}(k_i)\) and \(\alpha_i = \text{val}(x_i)\).
The exponents $\gamma_i$ are computed from the numerical values of the parameters. We use $\gamma_i = \text{round}(d \log(|k_i|) / \log(\epsilon_*))/d$ to obtain rational (integer if $d = 1$) exponents. These exponents become valuations when we view the cell cycle model as being part of a family of models with the same structure and with parameters $k_i(\epsilon) = \bar{k}_i \epsilon^{\gamma_i}$ in the limit $\epsilon \to 0$.

Using this scaling we compute the rescaled system

\[ e^{a_1} x_1 = \bar{k}_1 x_3 \epsilon^{\gamma_1 + a_3} - \bar{k}_2 x_1 \epsilon^{\gamma_2 + a_1} + \bar{k}_3 x_2 \epsilon^{\gamma_3 + a_2}, \]
\[ e^{a_2} x_2 = \bar{k}_2 x_1 \epsilon^{\gamma_2 + a_1} - \bar{k}_3 x_2 \epsilon^{\gamma_3 + a_2} - \bar{k}_4 x_2 x_5 \epsilon^{\gamma_4 + a_2 + a_5}, \]
\[ e^{a_3} x_3 = \bar{k}_3 x_2 \epsilon^{\gamma_3 + a_2} - \bar{k}_4 x_3 \epsilon^{\gamma_4 + a_2 + a_5} - \bar{k}_5 x_3 x_5 \epsilon^{\gamma_5 + a_4 + a_5}, \]
\[ e^{a_4} x_4 = \bar{k}_4 x_2 x_5 \epsilon^{\gamma_4 + a_2 + a_5} - \bar{k}_5 x_3 \epsilon^{\gamma_5 + a_4 + a_5} - \bar{k}_6 x_4 \epsilon^{\gamma_6 + a_6}, \]
\[ e^{a_5} x_5 = \bar{k}_5 x_3 x_5 \epsilon^{\gamma_5 + a_4 + a_5}, \]

and the timescale orders of each variable:

\[ \mu_1 = \min(\gamma_1 + a_3, \gamma_2 + a_1, \gamma_3 + a_2) - a_1, \]
\[ \mu_2 = \min(\gamma_2 + a_1, \gamma_3 + a_2, \gamma_4 + a_2 + a_5) - a_2, \]
\[ \mu_3 = \min(\gamma_10 + a_4, \gamma_1 + a_3, \gamma_9 + 2a_3 + a_4) - a_3, \]
\[ \mu_4 = \min(\gamma_4 + a_2 + a_5, \gamma_9 + 2a_3 + a_4, \gamma_10 + a_4) - a_4, \]
\[ \mu_5 = \min(\gamma_6, \gamma_4 + a_2 + a_5) - a_5. \]

In this setting the slow-fast decomposition follows from the timescale orders. Instead of renaming slow variables as \( y_j \) like in Section 2.2, we define instead a subset \( S \subset \{1, \ldots, n\} \) containing indices of the slow components. Thus, all variables \( x_j \) with indices \( j \in S \) are slow and the remaining variables \( x_i \) are faster iff \( \mu_i < \mu_j \) for all \( i \notin S, j \in S \).

Self-consistently, the valuations \( a_i \) are solutions of the partial tropical equilibration problem for a fast/slow splitting with slow variables \( S \) (see the following subsection 3.2 and Appendix 1).

### 3.2 Calculation of the partial tropical equilibrations

The solutions of the partial tropical equilibration problem for \( S \) form a polyhedral complex, each face encoding one combinatorial possibility in the equations. The partial equilibration problem for \( S \) can be decomposed into two kinds of constraints: i) equilibration of fast species and conservation laws, and ii) timescale orders constraints resulting from the slow/fast decomposition.

For example, suppose that we are interested in the partial tropical equilibration when \( S = \{x_3\} \), then the problem is given by:

\[ \gamma_1 + a_3 = \min(\gamma_2 + a_1, \gamma_3 + a_2), \]
\[ \gamma_2 + a_1 = \min(\gamma_3 + a_2, \gamma_4 + a_2 + a_5), \]
\[ \gamma_4 + a_2 + a_5 = \min(\gamma_9 + 2a_3 + a_4, \gamma_{10} + a_4), \]
\[ \gamma_6 = \gamma_4 + a_2 + a_5, \]
\[ \gamma_{14} = \min(a_1, a_2, a_3, a_4), \]
\[ \mu_3 > \mu_1, \mu_3 > \mu_2, \mu_3 > \mu_4, \mu_3 > \mu_5. \]
The first four equations in (14) come for the tropicalization of the polynomial vector field for the fast species \( \{x_1, x_2, x_4, x_5\} \). The fifth equation results from the tropicalization of the linear conservation law \( k_{14} = x_1 + x_2 + x_3 + x_4 \). The remaining equations simply mean that the species \( x_3 \) is slower than all the other.

The real solutions of (14), \( a \in \mathbb{R}^n \), form a polyhedral complex. Coarse graining means that we look for solutions of (14) in \((\mathbb{Z}/d)^n\), in which case we obtain a discrete set of points in the polyhedral complex. To solve this problem we treat each constraint separately. For each constraint, each choice of minima leads to a polytope \( P \). The solution of the problem is the intersection of unions of such polytopes.

The first equation in (14) leads to two possibilities that each gives a polytope. When \( \min(\gamma_2 + a_1, \gamma_3 + a_2) = \gamma_2 + a_1 \), the polytope is given by

\[
\begin{align*}
\gamma_1 + a_3 &= \gamma_2 + a_1, \\
\gamma_2 + a_1 &\leq \gamma_3 + a_2,
\end{align*}
\]

whereas when \( \min(\gamma_2 + a_1, \gamma_3 + a_2) = \gamma_3 + a_2 \), the polytope is given by

\[
\begin{align*}
\gamma_1 + a_3 &= \gamma_3 + a_2, \\
\gamma_3 + a_2 &\leq \gamma_2 + a_1.
\end{align*}
\]

So, for this equation, we get two polytopes. We call this union of polytopes a bag, denoted as \( B_1 \).

The last equation in (14) comes from the timescale constraints and has the form:

\[
\min(\gamma_{10} + a_4, \gamma_1 + a_3, \gamma_9 + 2a_3 + a_4) - a_3 > \min(\gamma_6, \gamma_4 + a_2 + a_5) - a_5,
\]

which gives, if \( \min(\gamma_{10} + a_4, \gamma_1 + a_3, \gamma_9 + 2a_3 + a_4) = \gamma_1 + a_3 \) and \( \min(\gamma_6, \gamma_4 + a_2 + a_5) = \gamma_4 + a_2 + a_5 \) the polytope given by equations:

\[
\begin{align*}
\gamma_1 &> \gamma_4 + a_2, \\
\gamma_1 + a_3 &\leq \gamma_{10} + a_4, \\
\gamma_1 + a_3 &\leq \gamma_9 + 2a_3 + a_4, \\
\gamma_4 + a_2 + a_5 &\leq \gamma_6.
\end{align*}
\]

The partial tropical equilibration problem is then to compute the intersection of these bags. Generally, the problem reads:

\[
A = \bigcap_{i=1}^{n_e} B_i = \bigcap_{i=1}^{n_e} \bigcup_{j=1}^{c_i} P_{ij},
\]

where \( n_e \) is the number of equations in the partial tropical equilibration problem, \( c_i \) is the number of choices for the equation \( i \). As intersections and unions are in finite numbers we can reverse them and get:

\[
A = \bigcup_{i=1}^{n_e} \bigcap_{j=1}^{c} P_{ij} = \bigcup_{j=1}^{c} \bigcap_{i=1}^{n_e} P_{ij},
\]
where $c$ is the total number of choices $c = \sum c_i$, and a branch, which is a face of the polyhedral complex, is given by the intersection of each polytopes for a given choice $\bigcap_{i=1}^n P_{ij}$.

For our example, given $S = \{x_3\}$, most of the choices lead to an empty set. There are thus only two branches (computed with $\epsilon_* = 1/11, d = 1$): $\{x_3\}_{00}$ and $\{x_3\}_{01}$.

If we consider the five variables cell cycle model, there are $2^5 = 32$ possible partial equilibration problems. One of them will not be considered as it consists of no constraints, this is when $S$ is the set of all species.

We have tested the remaining 31 possibilities: the total tropical equilibrations when $S = \emptyset$, and 30 partial equilibrations. Only 9 are non-empty: 8 partial tropical equilibrations and the total one.

Denoting a partial tropical equilibration problem by the associated set of slow species $S$, the list of solutions of all partial equilibration problems is given by

\[ \emptyset, \{x_3\}, \{x_4\}, \{x_5\}, \{x_3, x_4\}, \{x_3, x_5\}, \{x_3, x_4, x_5\}, \{x_1, x_3, x_4, x_5\}, \{x_2, x_3, x_4, x_5\}. \]

The solutions of each partial tropical equilibration problem are grouped in a number of branches. Each branch is denoted by an index number, for instance $\{x_3\} = \{\{x_3\}_{00}, \{x_3\}_{01}\}$.

Although each partial tropical equilibration is a polyhedral complex, their union is generally not a complex. As a matter of fact, the intersection of two polyhedra of different partial tropical equilibrations can be just part of a face. In [13] we have introduced the connectivity graph describing adjacency of branches as faces of the polyhedral complex of total tropical equilibrations: two branches are connected if they share a face. We introduce here a connectivity graph for partial tropical equilibrations. A connectivity graph is a undirected graph whose vertices are partial tropical equilibration branches. The connection between branches is somehow intermediate between adjacency and incidence. Two partial tropical equilibration branches are connected if their intersection has maximum dimension (the dimension of the intersection is equal to the dimension of one of the attached polyhedra).

The figure [11] shows the connectivity graph for all the partial tropical equilibrations of the cell cycle model, quotiented over partial equilibration problems (all branches of one partial equilibration problem are gathered in one node).

Remark: this graph have been made for $\epsilon_* = 1/11$ and $d = 1$. We found that the quotiented graph is robust and does not change for different $(\epsilon_*, d)$ despite the fact that some polytope branches may be different for two different $(\epsilon_*, d)$. Indeed, for $\epsilon_* = 1/11$, $d = 1$, the total tropical equilibration polyhedral complex is a segment plus a half-line whereas for $d = 1000$ it is a point like for $\epsilon_* = 1/29$ and $d = 1$.

### 3.3 Symbolic dynamics by tropicalization

We expect that the traces of the system [11] are most of the time in proximity of partial tropical equilibration solutions. Therefore we can use the tropical equilibrations for symbolic coding of these traces.
In order to test this property, we have simulated for 200 min (using the solver ode3s of Matlab R2021b) 375 numerical traces of (11) starting from the different sets of initial conditions respecting $x_1 + x_2 + x_3 + x_4 = 1$. For each point $x = (x_1, x_2, x_3, x_4, x_5) \in \mathbb{R}^5$ of the numerical trace, we have computed a valuation $a = (a_1, a_2, a_3, a_4, a_5) \in \mathbb{Q}^5$ using $a_i = \text{round} \left( \frac{d \log(|x_i(t)|)}{\log(\epsilon)} \right) / d$. This allows to compute the time-scale order of each species for this point, but also to check if a species is equilibrated or not. With these informations, we can first determine in which partial tropical equilibration the point is (if it lives in a equilibration), and then we can obtain the truncated system, and so, the branch.

Making a projection of these traces on the space $(\log_{\epsilon}^*(x_3), \log_{\epsilon}^*(x_4), \log_{\epsilon}^*(x_5))$ we obtain Figure 2. On this figure, we can see that trajectories are first converging to low dimension manifolds (dimension two or one in projection) that lead to a limit cycle. In Figure 3 we have symbolically coded the points of a particularly long trajectory (marked in red), using the method described above. This figure shows that the trace follows constrained transitions guided by some partial tropical equilibrations. In order to obtain more insight, in Figure 4 we projected the traces on the plane $(\log_{\epsilon}^*(x_3), \log_{\epsilon}^*(x_4))$. We used this “logarithmic paper” representation to show also the tropical equilibration solutions and their polyhedral branches. A tropical equilibration $a = (a_1, a_2, a_3, a_4, a_5) \in (\mathbb{Z}/d)^5$ is represented as a point of coordinates $(a_1, a_2)$ in this representation. Partial tropical equilibration branches are line segments or colored polygonal domains containing tropical equilibration points. As shown in Figure 4b), a large value...
Fig. 2: 375 traces on the space \((\log_{\epsilon^*}(x_3), \log_{\epsilon^*}(x_4), \log_{\epsilon^*}(x_5))\), \(\epsilon^* = 1/11\). In red the trace starting from \((1, 0, 0, 0, 100)\).

Fig. 3: Symbolic coding of the trace starting at \((1, 0, 0, 0, 100)\) (a few very rapid transients states at the beginning of the trace are not represented). On the left side, the marker colors indicate the tropical equilibration branch close to which the trajectory point lies. On the right side, the tropicalization (red line) is represented together with the continuous trace on the limit cycle part (for \(\epsilon^* = 1/11, d = 1\)).

of \(d\) ensures a small cell-size on the logarithmic paper. This ensures a precise representation of the limit cycle, but with a scaling that varies almost continuously and with new polygonal domains. As we are interested only in the robust features of the tropical solutions, we favor the value \(d = 1\) corresponding to Figure 4a).
3.4 Model reduction from partial tropical equilibrations

Each partial tropical equilibration solution provides a scaling of the variables. This scaling is used for identification of slow and fast variables and for automatic model reduction with algorithms introduced in [3, 1]. The algorithms from [3] work when the quasi-steady state equations of fast variables satisfy hyperbolicity conditions. Very often, the hyperbolicity conditions fail because of the existence of exact or approximate conservation laws, which are conservation laws of the full and tropically truncated systems, respectively. We showed in [1] that systems without conservation laws by a change of variables. This extends the applicability of reduction algorithms from [3] to the case when there are conservation laws. We illustrate these techniques on an example and refer the reader to [3, 1] for the complete algorithmic solutions.

Consider the scaling provided by the partial tropical equilibration solution $a = (5, 2, 0, 2, 0)$, computed with $\epsilon_s = 1/11, d = 1$. The rescaled tropically truncated system obtained from the original system of equations (11) reads

\begin{align*}
\dot{x}_1 &= \epsilon^{-6}(k_1\bar{x}_2 - \bar{k}_2\bar{x}_1), \\
\dot{x}_2 &= \epsilon^{-3}(\bar{k}_2\bar{x}_1 - \bar{k}_3\bar{x}_2), \\
\dot{x}_3 &= \epsilon^{0}(k_3\bar{x}_3^2\bar{x}_4 - \bar{k}_1\bar{x}_3), \\
\dot{x}_4 &= \epsilon^{-2}(k_4\bar{x}_2\bar{x}_5 - \bar{k}_9\bar{x}_3^3\bar{x}_4), \\
\dot{x}_5 &= \epsilon^{0}(-k_4\bar{x}_2\bar{x}_5),
\end{align*}

(19)

where the variables $\bar{x}_1, \bar{x}_2$, and $\bar{x}_4$ are fast.

The quasi-steady state approximation can not be applied here because the truncated nonrescaled system describing the fast dynamics

\begin{align*}
\dot{x}_1 &= (k_3x_2 - k_2x_1), \\
\dot{x}_2 &= (k_2x_1 - k_3x_2), \\
\dot{x}_4 &= (k_4x_2x_5 - k_9x_3^2x_4),
\end{align*}

(20)

has a conservation law $x_1 + x_2$ which is an approximate conservation law of the full system (11).

The system (11) has also the exact conservation law $x_1 + x_2 + x_3 + x_4$.

According to the method described in [1], we can eliminate all conservation laws (approximate and exact) by using the following change of variable:

\begin{align*}
x_3 &\leftarrow k_{14} - x_1 - x_2 - x_4, \\
x_2 &\leftarrow x_1 + x_2.
\end{align*}

(21)

After this change of variables we obtain a transformed system of equations that has no conservation laws:

\begin{align*}
\dot{x}_1 &= k_1k_{14} - (k_2 + k_3)x_1 - k_1x_4 + (k_3 - k_1)x_2, \\
\dot{x}_2 &= k_1k_{14} - k_1x_1 - k_1x_4 + k_4x_1x_5 - k_4x_2x_5, \\
\dot{x}_4 &= -(k_9k_7^2 + k_{10})x_4 + 2k_9k_{14}x_2x_4 + 2k_9k_1x_4^2 - k_9x_3^2x_4 - k_9x_3^2x_2 - k_9x_3^2x_4 - k_9x_1x_5, \\
\dot{x}_5 &= k_6 + k_4x_1x_5 - k_4x_2x_5.
\end{align*}

(22)
Fig. 4: a) Tropicalizing each point of the trace for $\epsilon_\ast = 1/11$, $d = 1$, we obtain six points with integer components closest to the limit cycle, each of them corresponding to a partial tropical equilibration: $(0, 0)$ black, $(2, 1)$, $(2, 2)$ green, $(1, 1)$, $(3, 1)$ blue, and $(1, 2)$ red. We use the same color for the points of the trace to indicate which of the 6 points is the closest one. Black lines are intersection of two polytopes. b) For $(\epsilon_\ast = 1/11$, $d = 10)$, we observe that we have more points for the limit cycle, and more polyhedra in the tropical structure. This is due to the coarse graining: the grid cell is smaller for larger $d$.

The rescaled tropically truncated system obtained from the transformed system of equations (22) reads

\[
\begin{align*}
\dot{x}_1 &= \epsilon^{-6}(\overline{k}_3 \overline{x}_2 - \overline{k}_2 \overline{x}_1), \\
\dot{x}_2 &= \epsilon^{-2}(\overline{k}_1 k_{14} - \overline{k}_4 \overline{x}_2 \overline{x}_5), \\
\dot{x}_4 &= \epsilon^{-2}(\overline{k}_4 \overline{x}_2 \overline{x}_5 - \overline{k}_9 k_{14}^2 \overline{x}_4), \\
\dot{x}_5 &= \epsilon^0(-\overline{k}_4 \overline{x}_2 \overline{x}_5).
\end{align*}
\]

The fast variables $x_1$, $x_2$, $x_4$ can be eliminated successively (first $x_1$, then $x_2$ and $x_4$). One gets the reduced model that reads

\[
\begin{align*}
\dot{x}_5 &= -k_1 k_{14}, \\
x_1 &= (k_1 k_3 k_{14})/(k_2 k_4 x_5), \\
x_2 &= (k_1 k_{14})/(k_4 x_5), \\
x_4 &= k_1/(k_9 k_{14}),
\end{align*}
\]

in nonrescaled variables.

The reduced model is one dimensional and describes the decrease at constant rate of $x_5$ as can be observed in the first part of the trace shown in the Figure 3.

We have computed (using $\epsilon_\ast = 1/11$, $d = 1$) all the reduced models for the sequence of partial tropical equilibration solutions obtained from the trace starting at $(1, 0, 0, 0, 100)$ (see Figure 5 for a schematic representation of this sequence). The reduced models are given in the Table S1.
We found that scalings from the same branch lead to the same reduced model. This important property shows the robustness of the reduction because a branch can span several orders of magnitude of the concentrations.

Furthermore, reduced models are nested in the sense that reduced models for scalings on a face of the polyhedral branch are supermodels (contain all the monomial terms) of reduced models originating from scalings at the interior of polyhedral branches.

Finally, all the reduced models for solutions on the limit cycle are submodels of the reduced model obtained from the total tropical equilibration that reads:

\[
\begin{align*}
\dot{x}_2 &= k_1 x_3 - k_6, \\
\dot{x}_3 &= k_{10} x_4 - k_1 x_3 + k_6 x_3^2 x_4, \\
\dot{x}_4 &= k_6 - k_{10} x_4 - k_9 x_3^2 x_4, \\
x_1 &= (k_3 x_2)/k_2, \\
x_5 &= k_6/(k_4 x_2).
\end{align*}
\]

Indeed, as can be seen in Figure 4a), the total tropical equilibration is at the intersection of all polyhedral domains corresponding to partial tropical equilibriations in the limit cycle. This reduced model is in fact two dimensional (\(x_3\) and \(x_4\) are decoupled from \(x_2\)) and can be used to replace in simulation and further analysis the original five dimensional cell cycle model.

Fig. 5: Sequence of partial tropical equilibration solutions on the trace starting with \((1,0,0,0,100)\). The branch symbol is followed by the valuation \(a\). Here the symbol \(\bar{j}\) means \(-j\), e.g. the valuation \((6402 \bar{2})\) denotes \((6,4,0,2,-2)\).

### 4 Conclusion and future work

The tropicalization method decomposes the phase space into polyhedra within which the dynamics of the system is simpler and can be represented by simpler models, with less dynamical variables and parameters. These domains can span several orders of magnitude and therefore the resulting reduced models are robust.
A first possible application of this approach is to find the most robust reduced model, that applies to the largest domain of interest. For the case study discussed in this paper, we found a two variables reduced model covering the entire limit cycle and suitable for describing system's oscillatory dynamics on this attractor.

The validity of the method described in this paper cannot be fully justified by the underlying algebraic process alone and needs to be investigated analytically by methods from dynamical systems theory and perturbation theory. The justification of the method for small to medium size systems, e.g. the cell cycle model used in the case study, in terms of a hierarchy of slow manifolds connected by fast jumps or other transitions at states where normal hyperbolicity is lost, is the subject of ongoing work of the authors. We expect that this will substantially increase the understanding of and the confidence in the method for larger systems.

The method also provides possible ways to approach attractors, in terms of sequences of symbolic states and local reductions. These abstractions can be used to model adaptation behavior of biological systems, described as switching from one attractor to another, passing through transient states of different lifetimes. Our approach provides the timescales of each state and the sequence of variables that are active and relax in each transient. The predicted timescales and relaxing variables are important biologically. In the case of the cell cycle, they could be used to discuss interesting dynamical regimes. In medical applications, network perturbations are used in targeted therapies. Dynamical information is rarely taken into account when designing such therapies. However, as shown in this paper, orders of magnitude of variables and parameters and the associated multiple timescales strongly influence and structure the possible dynamics and response of the system. Thus, together with network topology, orders of magnitude and timescale information must be considered together for predicting the effect of network perturbation.

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Appendix 1. Calculation of partial tropical equilibrations: algorithms and implementation.

The input of our algorithms is a set of polynomial ODE system describing the CRN kinetics:

$$\dot{x}_i = f_i(x),$$ where

$$f_i(x) = \sum_{j=1}^{r} C_{ij} k_j x^{\alpha_j} \in \mathbb{R}[x_1, \ldots, x_n], 1 \leq i \leq n,$$ (26)

$C_{ij}$ are integers representing stoichiometric coefficients and $k_j$ are real, positive kinetic parameters.

Let $0 < \epsilon_* < 1$ and define $\gamma_j := \text{round}(d \log(|k_j|) / \log(\epsilon_*))$.

Following the general approach of the Sections 2.1, 2.2, we tropicalize the polynomials $f_i$:

$$\text{Trop}(f_i) = \min_{j: C_{ij} \neq 0} (\gamma_j + \langle a, \alpha_j \rangle).$$

Let us consider that a $S \subset \{1, \ldots, n\}$ subset represents the slow species of the (26). Then, according to the definition introduced in the Section 2.2, the partial tropical equilibration problem for $S$ consists in finding a vector $a$ such that:

$$\min_{j: C_{ij} > 0} (\gamma_j + \langle a, \alpha_j \rangle) = \min_{j: C_{ij} < 0} (\gamma_j + \langle a, \alpha_j \rangle), \ i \notin S$$ (27)

$$\min_{j: C_{ij} \neq 0} (a_j) = \gamma'_l, \ 1 \leq l \leq n_c$$ (28)

$$\min_{j: C_{ij} \neq 0} (\gamma_j + \langle a, \alpha_j \rangle) - a_i < \min_{j: C_{ij} \neq 0} (\gamma_j + \langle a, \alpha_j \rangle) - a_{i'}, \ i \notin S, \ i' \in S.$$ (29)

The solution of the partial tropical equilibration for $S$ is a polyhedral complex, each maximal polyhedron (called branches and denoted $S_{index}$) being the solution of one set of choices as described below.

Let

$$\rho_i = \text{argmin}_{j: C_{ij} > 0} (\gamma_j + \langle a, \alpha_j \rangle)$$

$$\eta_i = \text{argmin}_{j: C_{ij} < 0} (\gamma_j + \langle a, \alpha_j \rangle)$$

$$\zeta_i = \text{argmin}_{j: C_{ij} \neq 0} (\gamma_j + \langle a, \alpha_j \rangle - a_i)$$

$$\omega_{i'} = \text{argmin}_{j: C_{ij} \neq 0} (\gamma_{i'} + \langle a, \alpha_j \rangle - a_{i'})$$

$$\sigma_l = \text{argmin}_{j: C_{ij} \neq 0} (a_j)$$ (30)

For each $i \notin S$, by fixing $\rho_i$ and $\eta_i$, we get a polyhedron consisting in the equation and inequations

$$\gamma_{\rho_i} + \langle a, \alpha_{\rho_i} \rangle = \gamma_{\eta_i} + \langle a, \alpha_{\eta_i} \rangle$$

$$\gamma_{\rho_i} + \langle a, \alpha_{\rho_i} \rangle \leq \gamma_j + \langle a, \alpha_j \rangle, \ C_{ij} \neq 0$$ (31)

We have also a polyhedron for each $1 \leq l \leq n_c$ by fixing $\sigma_l$, given by the equation and inequations

$$a_{\sigma_l} = \gamma'_l$$

$$a_{\sigma_l} \leq a_j, \ C_{ij} \neq 0.$$ (32)
For each $i \notin S, i' \in S$, by fixing $\zeta_i$ and $\omega_{i'}$, we get a polyhedron consisting in the equation and inequalities

$$\gamma_\zeta_i + \langle a, \alpha_\zeta_i \rangle - a_i \leq \gamma_{\omega_{i'}} + \langle a, \alpha_{\omega_{i'}} \rangle - a_{i'}$$

$$\gamma_\zeta_i + \langle a, \alpha_{\zeta_i} \rangle \leq \gamma_j + \langle a, \alpha_j \rangle, \quad C_{ij} \neq 0$$

$$\gamma_{\omega_{i'}} + \langle a, \alpha_{\omega_{i'}} \rangle \leq \gamma_j + \langle a, \alpha_j \rangle, \quad C_{i'j} \neq 0 \tag{33}$$

For each $i$ in (27), by rolling the choices $(\rho_i, \eta_i)$, we get a union of polyhedra, called bag. For each $l$ in (28), by rolling the choices $(\sigma_l)$, we get a union of polyhedra, also called bag. For each $i, i'$ in (29), by rolling the choices $(\zeta_i, \omega_{i'})$, we get a union of polyhedra, also called bag.

If we note $B_i$ these bags, the problem reads:

$$A = \bigcap_{i=1}^{n_e} B_i = \bigcap_{i=1}^{n_e} \bigcup_{j=1}^{c_i} P_{ij}$$

where $n_e$ is the number of equations in the partial tropical equilibration problem, and $c_i$ is the number of choices for the equation $i$. As intersections and unions are in finite numbers we can reverse them and get:

$$A = \bigcap_{i=1}^{n_e} \bigcup_{j=1}^{c} P_{ij} = \bigcup_{i=1}^{n_e} \bigcap_{j=1}^{c} P_{ij}$$

where $c$ is the total number of choices ($c = \sum c_i$). A branch is then given by $\bigcap_{i=1}^{n_e} P_{ij}$ for one choice $j$.

To solve the tropical equilibration problem, we follow the same process as described in [4], except that we have a different set of bags. We give here how we implement it, the code can be found at [https://github.com/Glawal/smtcutpartial](https://github.com/Glawal/smtcutpartial).

We have tested it on the model (11) under python 3.7, with the solver mathsat, each solution was given under 0.5s, for a total time under 2s. The complexity of finding each tropical equilibration is exponential in the number of variable, due to the combinatorial choice of $S$. And the complexity of solving one equilibration problem is theoretically exponential in the number of bags, but the smt method used, with a preprossessing, allow to reduce this complexity by removing some choices.

As each polyhedron is given by a choice of $(\rho_i, \eta_i, \zeta_i, \omega_{i'}, \sigma_l)$, we can associate to the polyhedron a tropically truncated system $E'$ defined by:

$$\tilde{f}_i(x) = C_{i\rho_i}k_{\rho_i}x^{\alpha_{\rho_i}} + C_{i\eta_i}k_{\eta_i}x^{\alpha_{\eta_i}}, \quad i \notin S$$

$$\tilde{f}_{i'}(x) = C_{i'\omega_{i'}}k_{\omega_{i'}}x^{\alpha_{\omega_{i'}}}, \quad i' \in S$$

$$k_{j} = C_{l\sigma_j}x_{\sigma_j}, \quad 1 \leq l \leq n_c, \tag{34}$$

The tropically truncated system describe the dominant dynamics of each species.

Suppose now that you have a point $x$ coming from a simulation. We can associate to this point a polyhedron of one of the tropical equilibration, if possible, using the following procedure. We compute the species concentration orders $a_i = \text{round}(d \log(x_i) / \log(c_\star))$ and check if these orders are solution of one of the trop-
ical equilibration problem \((27), (28), (29)\). To check if \(a\) is a solution, we need to compute the timescale of each species (that allow a list of \(S\) choice), and to compute orders of each monomials (given by \(\gamma_j + \langle a, \alpha_j \rangle\)), which give us the list of equilibrated species. Then we choose \(S\) as being minimal (each equilibrated species that are faster that non equilibrated species are considered outside \(S\)), this gives us the final choice \((S, \rho, \eta, \zeta, \omega, \sigma)\), denoted \(S_{\text{index}}\), the index being the index of \(P\) in \(rr\) in Algorithm \([7]\).

\[
\text{Algorithm } \text{smcutpartial}(26, S) \\
\quad bb \leftarrow \text{makePolyhedraForPTE}(26, S) \\
\quad rr \leftarrow \text{computePolyhedronDnf}(bb) \\
\quad \text{return } rr
\]

**Algorithm 1:** The algorithm used to find the partial tropical equilibration for \(S\).

\[
\text{Algorithm } \text{makePolyhedraForPTE}(26, S) \\
\quad bb \leftarrow \emptyset \\
\quad \text{foreach } i \in \{1, \ldots, n\} \setminus S \text{ do} \\
\quad \quad bb \leftarrow bb \cup \text{equilibrate}(\dot{x}_i) \\
\quad \quad \text{foreach } j \in S \text{ do} \\
\quad \quad \quad bb \leftarrow bb \cup \text{slowFastPol}(\dot{x}_i, \dot{x}_j) \\
\quad \text{return } bb
\]

**Algorithm 2:** This algorithm makes the list of bags, each bag representing a list of polyhedra, such that each polyhedron is linked to an equilibration for a fast species or a conservation law, or a slow fast decomposition.
**Algorithm 3:** This algorithm computes the bag $b$ linked to an equation of the system, that represent each possible equilibration. It splits negative and positive monomials, computes their tropicalization and makes the bag.

```plaintext
Algorithm equilibrate($\dot{x}_i$)

| $pp, np, b \leftarrow \emptyset$
|-----------------------------|
| \hspace{1cm} foreach $1 \leq j \leq r_i$ do |
| \hspace{1.5cm} $t = \text{trop}(k_j x^{\alpha_j})$
| \hspace{1.5cm} if $S_{ij} < 0$ then
| \hspace{2.2cm} $np \leftarrow np \cup t$
| \hspace{1.5cm} else
| \hspace{2.2cm} $pp \leftarrow pp \cup t$
| \hspace{1cm} foreach $(a,c) \in pp \times np$ do |
| \hspace{1.5cm} $p = \text{makePolyhedron}(a,c,pp,np)$
| \hspace{1cm} $b \leftarrow b \cup p$
| return $b$
```

**Algorithm 4:** $p$ is a polyhedron defined by equation (31) or (32).

```plaintext
Algorithm makePolyhedron($a,c,pp,np$)

| $eq \leftarrow a = c$
|-----------------------------|
| $i eq \leftarrow \emptyset$
| \hspace{1cm} foreach $i \in pp \cup np$ do |
| \hspace{1.5cm} $i eq \leftarrow i eq \cup a \leq i$
| $p \leftarrow \text{make}(eq, i eq)$
| return $p$
```

**Algorithm 5:** This algorithm computes the bag $b$ linked to a slow fast decomposition between two species $x_i$ (fast) and $x_j$ (slow). As the order the species has an impact on the slow fast decomposition, we multiply each monomial in $\dot{x}_j$ by $\frac{1}{x_j}$. Then we split each monomials, compute their tropicalization and make the bag.

```plaintext
Algorithm slowFastPol($\dot{x}_i, \dot{x}_j$)

| $sp, fp, b \leftarrow \emptyset$
|-----------------------------|
| \hspace{1cm} foreach $1 \leq m \leq r_i$ do |
| \hspace{1.5cm} $t = \text{trop}(k_m x^{\alpha_m - a_i})$
| \hspace{1.5cm} $fp \leftarrow fp \cup t$
| \hspace{1cm} foreach $1 \leq m \leq r_j$ do |
| \hspace{1.5cm} $t = \text{trop}(k_m x^{\alpha_m - a_j})$
| \hspace{1.5cm} $sp \leftarrow sp \cup t$
| \hspace{1cm} foreach $(a,c) \in sp \times fp$ do |
| \hspace{1.5cm} $p = \text{makePolyhedronSF}(a,c,sp,fp)$
| \hspace{1cm} $b \leftarrow b \cup p$
| return $b$
```
Algorithm makePolyhedronSF\((a, c, sp, fp)\)

\[
\begin{align*}
eq & \leftarrow \emptyset \\
\text{ieq} & \leftarrow a \geq c \\
\text{foreach } i \in sp \text{ do} & \\
\quad \text{ieq} & \leftarrow \text{ieq} \cup a \leq i \\
\text{foreach } i \in fp \text{ do} & \\
\quad \text{ieq} & \leftarrow \text{ieq} \cup c \leq i \\
p & \leftarrow \text{make}(eq, \text{ieq}) \\
\text{return } p
\end{align*}
\]

**Algorithm 6:** \(p\) is a polyhedron defined by equation [33].

Algorithm computePolyhedronDnf\((bb)\)

\[
\begin{align*}
\text{solver} & \leftarrow \text{getSolveur}(\text{incremental} = \text{true}) \\
f & \leftarrow \text{convertToSMTFormula}(bb) \\
rr & \leftarrow \emptyset, \text{bool} \leftarrow \text{true} \\
\text{while } \text{bool} \text{ do} & \\
\quad \text{\text{solver.addAssertion}(f)} \\
\quad (x, \text{bool}) & \leftarrow \text{solver.solve}(f) \quad (*x\text{ is a point that satisfy the constraints,} \\
\quad \text{\text{bool is false if no } x^*} \\
\quad \text{\text{if } Not(\text{bool}) \text{ then} & \\
\quad \quad \text{Break} \\
\quad \text{else & \\
\quad \quad R & \leftarrow \emptyset \\
\quad \quad \text{foreach } b \in bb \text{ do} & \\
\quad \quad \quad \text{foreach } P \in b \text{ do} & \\
\quad \quad \quad \quad \text{if } x \in P \text{ then} & \\
\quad \quad \quad \quad \quad R & \leftarrow R \cup P.\text{constraints()} \\
\quad \quad \quad \quad \quad \text{Break} \\
\quad \quad \quad f & \leftarrow Not(R) \\
\quad \quad rr & \leftarrow rr \cup R \\
\text{return } rr
\end{align*}
\]

**Algorithm 7:** This algorithm computes the intersection of a set of bags \(bb\). Each polyhedron is transformed to a logical constraint. \(x\) represents a point that satisfy the set of constraints, then, if a such \(x\) is found, it is contained by a polyhedron \(P\) common to each equilibration. We remove this polyhedron from search by adding a constraint and continue the search until there is no feasible point. At the end we get a list of polyhedra \(rr\), that is the tropical equilibration.
Appendix 2. Sequence of reduced models.

Table S1: The sequence of reduced models corresponding to different partial tropical equilibrations along the trace starting at (1, 0, 0, 0, 100), computed with $\epsilon_* = 1/11, d = 1$. A few rapid transient states at the beginning of the trace where not analysed and we start with the partial tropical equilibration solution (6, 4, 0, 2, −2). We indicate the change of variables needed for the elimination of some exact and approximate conservation laws, the truncated rescaled system indicating the local timescales of the variables and the local reduced system in nonscaled variables and parameters. The change of variables is included in the definition of the reduced system.

| Tropical solution | Truncated rescaled system | Change of variables | Reduced system |
|-------------------|----------------------------|---------------------|----------------|
| \(\{x_3\}_{02}\) | \(\begin{align*}
\dot{x}_1 &= e^{-5}(k_1 k_{14} - k_2 \bar{x}_1) \\
\dot{x}_2 &= e^{-4}(k_2 \bar{x}_2 - k_4 \bar{x}_3) \\
\dot{x}_4 &= e^{-5}(k_1 k_{14} - k_2 \bar{x}_1, -k_3 k_4 \bar{x}_4) \\
\dot{x}_5 &= e^{4}(-k_6 \bar{x}_3 \bar{x}_5) \\
\end{align*}\) | \(x_3 \leftrightarrow k_{14} - x_1 - x_2 - 4\) | \(\begin{align*}
\dot{x}_3 &= -k_{14} \\
x_1 &= (k_1 k_{14}) / k_2 \\
x_2 &= (k_1 k_{14}) / (k_2 k_4) \\
x_4 &= k_1 ((k_2 k_4)) \\
\end{align*}\) |
| \(\{x_3\}_{02}\) | \(\begin{align*}
\dot{x}_1 &= e^{-5}(k_1 k_{14} + k_2 \bar{x}_2 - k_4 \bar{x}_3) \\
\dot{x}_2 &= e^{-3}(k_2 \bar{x}_2 - k_4 \bar{x}_3) \\
\dot{x}_4 &= e^{-2}(k_1 k_{14} - k_2 k_4 \bar{x}_4) \\
\dot{x}_5 &= e^{0}(-k_6 \bar{x}_3 \bar{x}_5) \\
\end{align*}\) | \(x_3 \leftrightarrow k_{14} - x_1 - x_2 - 4\) | \(\begin{align*}
\dot{x}_3 &= -k_{14} \\
x_1 &= (k_1 k_{14}) / (k_2 k_4 x_5) \\
x_2 &= (k_1 k_{14}) / (k_2 x_5) \\
x_4 &= k_1 ((k_2 k_4)) \\
\end{align*}\) |
| \(\{x_3\}_{03}\) | \(\begin{align*}
\dot{x}_1 &= e^{-5}(k_1 k_{14} - k_2 \bar{x}_1) \\
\dot{x}_2 &= e^{-2}(k_1 k_{14} - k_4 \bar{x}_3) \\
\dot{x}_4 &= e^{-5}(k_1 k_{14} - k_2 k_4 \bar{x}_4) \\
\dot{x}_5 &= e^{0}(-k_6 \bar{x}_3 \bar{x}_5) \\
\end{align*}\) | \(x_3 \leftrightarrow k_{14} - x_1 - x_2 - 4\) | \(\begin{align*}
\dot{x}_3 &= k_{14} - k_4 \bar{x}_3 \bar{x}_5 \\
x_1 &= -k_4 \bar{x}_3 \bar{x}_5 \\
x_2 &= (k_1 k_{14}) / k_2 \\
x_4 &= (k_1 k_{14}) / (k_2 k_4) \\
\end{align*}\) |
| \(\{x_3, x_5\}_{01}\) | \(\begin{align*}
\dot{x}_1 &= e^{-5}(k_1 k_{14} - k_2 \bar{x}_1) \\
\dot{x}_2 &= e^{-1}(k_1 k_{14} - k_4 \bar{x}_3) \\
\dot{x}_4 &= e^{-2}(k_1 k_{14} - k_2 k_4 \bar{x}_4) \\
\dot{x}_5 &= e^{0}(-k_6 \bar{x}_3 \bar{x}_5) \\
\end{align*}\) | \(x_3 \leftrightarrow k_{14} - x_1 - x_2 - 4\) | \(\begin{align*}
\dot{x}_3 &= k_{14} - k_4 \bar{x}_3 \bar{x}_5 \\
x_1 &= -k_4 \bar{x}_3 \bar{x}_5 \\
x_2 &= (k_1 k_{14}) / k_2 \\
x_4 &= (k_1 k_{14}) / (k_2 k_4) \\
\end{align*}\) |
| \(\{x_3, x_5\}_{01}\) | \(\begin{align*}
\dot{x}_1 &= e^{-5}(k_1 k_{14} - k_2 \bar{x}_1) \\
\dot{x}_2 &= e^{-1}(k_1 k_{14} - k_4 \bar{x}_3) \\
\dot{x}_4 &= e^{-2}(k_1 k_{14} - k_2 k_4 \bar{x}_4) \\
\dot{x}_5 &= e^{0}(-k_6 \bar{x}_3 \bar{x}_5) \\
\end{align*}\) | \(x_3 \leftrightarrow k_{14} - x_1 - x_2 - 4\) | \(\begin{align*}
\dot{x}_3 &= k_{14} - k_4 \bar{x}_3 \bar{x}_5 \\
x_1 &= -k_4 \bar{x}_3 \bar{x}_5 \\
x_2 &= (k_1 k_{14}) / k_2 \\
x_4 &= (k_1 k_{14}) / (k_2 k_4) \\
\end{align*}\) |
| \(\{x_3, x_5\}_{02}\) | \(\begin{align*}
\dot{x}_1 &= e^{-5}(k_1 k_{14} - k_2 \bar{x}_1) \\
\dot{x}_2 &= e^{-1}(k_1 k_{14} - k_2 \bar{x}_1) \\
\dot{x}_4 &= e^{-2}(k_1 k_{14} - k_2 k_4 \bar{x}_4) \\
\dot{x}_5 &= e^{0}(-k_6 \bar{x}_3 \bar{x}_5) \\
\end{align*}\) | \(x_3 \leftrightarrow k_{14} - x_1 - x_2 - 4\) | \(\begin{align*}
\dot{x}_3 &= k_{14} - k_4 \bar{x}_3 \bar{x}_5 \\
x_1 &= -k_4 \bar{x}_3 \bar{x}_5 \\
x_2 &= (k_1 k_{14}) / k_2 \\
x_4 &= (k_1 k_{14}) / (k_2 k_4) \\
\end{align*}\) |
| \(\{x_3, x_5\}_{02}\) | \(\begin{align*}
\dot{x}_1 &= e^{-5}(k_1 k_{14} - k_2 \bar{x}_1) \\
\dot{x}_2 &= e^{-2}(k_1 k_{14} - k_4 \bar{x}_3) \\
\dot{x}_4 &= e^{-2}(k_1 k_{14} - k_2 k_4 \bar{x}_4) \\
\dot{x}_5 &= e^{0}(-k_6 \bar{x}_3 \bar{x}_5) \\
\end{align*}\) | \(x_3 \leftrightarrow k_{14} - x_1 - x_2 - 4\) | \(\begin{align*}
\dot{x}_3 &= k_{14} - k_4 \bar{x}_3 \bar{x}_5 \\
x_1 &= -k_4 \bar{x}_3 \bar{x}_5 \\
x_2 &= (k_1 k_{14}) / k_2 \\
x_4 &= (k_1 k_{14}) / (k_2 k_4) \\
\end{align*}\) |
| \(\{x_3, x_5\}_{02}\) | \(\begin{align*}
\dot{x}_1 &= e^{-5}(k_1 k_{14} - k_2 \bar{x}_1) \\
\dot{x}_2 &= e^{-2}(k_1 k_{14} - k_4 \bar{x}_3) \\
\dot{x}_4 &= e^{-2}(k_1 k_{14} - k_2 k_4 \bar{x}_4) \\
\dot{x}_5 &= e^{0}(-k_6 \bar{x}_3 \bar{x}_5) \\
\end{align*}\) | \(x_3 \leftrightarrow k_{14} - x_1 - x_2 - 4\) | \(\begin{align*}
\dot{x}_3 &= k_{14} - k_4 \bar{x}_3 \bar{x}_5 \\
x_1 &= -k_4 \bar{x}_3 \bar{x}_5 \\
x_2 &= (k_1 k_{14}) / k_2 \\
x_4 &= (k_1 k_{14}) / (k_2 k_4) \\
\end{align*}\) |
| \(\{x_3, x_5\}_{02}\) | \(\begin{align*}
\dot{x}_1 &= e^{-5}(k_1 k_{14} - k_2 \bar{x}_1) \\
\dot{x}_2 &= e^{-2}(k_1 k_{14} - k_4 \bar{x}_3) \\
\dot{x}_4 &= e^{-2}(k_1 k_{14} - k_2 k_4 \bar{x}_4) \\
\dot{x}_5 &= e^{0}(-k_6 \bar{x}_3 \bar{x}_5) \\
\end{align*}\) | \(x_3 \leftrightarrow k_{14} - x_1 - x_2 - 4\) | \(\begin{align*}
\dot{x}_3 &= k_{14} - k_4 \bar{x}_3 \bar{x}_5 \\
x_1 &= -k_4 \bar{x}_3 \bar{x}_5 \\
x_2 &= (k_1 k_{14}) / k_2 \\
x_4 &= (k_1 k_{14}) / (k_2 k_4) \\
\end{align*}\) |
| {x_3, x_4}₀₄ (3, 0, 1, 3, 4) | \[ \dot{x}_1 = \epsilon^{-k}(k_3 \dot{x}_2 - k_2 \dot{x}_1) \]  
| \dot{x}_2 = \epsilon(k_1 \dot{x}_3) \]  
| \dot{x}_3 = \epsilon^0(-k_1 \dot{x}_3) \]  
| \dot{x}_4 = \epsilon^{-1}(k_4 \dot{x}_2 \dot{x}_5) \]  
| \dot{x}_5 = \epsilon^{-2}(k_6 - k_4 \dot{x}_2 \dot{x}_5) \]  
| x_2 \leftarrow x_1 + x_2 \]  
| {x_3}₀₀ (3, 0, 1, 2, 4) | \[ \dot{x}_1 = \epsilon^{-k}(k_3 \dot{x}_2 - k_2 \dot{x}_1) \]  
| \dot{x}_2 = \epsilon^0(k_1 \dot{x}_3) \]  
| \dot{x}_3 = \epsilon^0(-k_1 \dot{x}_3) \]  
| \dot{x}_4 = \epsilon^{-1}(k_4 \dot{x}_2 \dot{x}_5) \]  
| \dot{x}_5 = \epsilon^{-2}(k_6 - k_4 \dot{x}_2 \dot{x}_5) \]  
| x_2 \leftarrow x_1 + x_2 \]  
| {x_3, x_4}₀₄ (3, 0, 2, 2, 4) | \[ \dot{x}_1 = \epsilon^{-k}(k_3 \dot{x}_2 - k_2 \dot{x}_1) \]  
| \dot{x}_2 = \epsilon^0(k_1 \dot{x}_3 - k_4 \dot{x}_2 \dot{x}_5) \]  
| \dot{x}_3 = \epsilon^0(-k_1 \dot{x}_3) \]  
| \dot{x}_4 = \epsilon^0(k_4 \dot{x}_2 \dot{x}_5) \]  
| \dot{x}_5 = \epsilon^{-2}(k_6 - k_4 \dot{x}_2 \dot{x}_5) \]  
| x_2 \leftarrow x_1 + x_2 \]  
| {x_3, x_4}₀₄ (3, 0, 2, 1, 4) | \[ \dot{x}_1 = \epsilon^{-k}(k_3 \dot{x}_2 - k_2 \dot{x}_1) \]  
| \dot{x}_2 = \epsilon^0(k_1 \dot{x}_3 - k_4 \dot{x}_2 \dot{x}_5) \]  
| \dot{x}_3 = \epsilon^0(-k_1 \dot{x}_3) \]  
| \dot{x}_4 = \epsilon^0(k_4 \dot{x}_2 \dot{x}_5) \]  
| \dot{x}_5 = \epsilon^{-2}(k_6 - k_4 \dot{x}_2 \dot{x}_5) \]  
| x_2 \leftarrow x_1 + x_2 \]  
| {x_4}₀₀ (3, 0, 3, 1, 4) | \[ \dot{x}_1 = \epsilon^{-k}(k_3 \dot{x}_2 - k_2 \dot{x}_1) \]  
| \dot{x}_2 = \epsilon^0(k_1 \dot{x}_3 - k_4 \dot{x}_2 \dot{x}_5) \]  
| \dot{x}_3 = \epsilon^0(k_{10} \dot{x}_4 - k_1 \dot{x}_3) \]  
| \dot{x}_4 = \epsilon^0(k_4 \dot{x}_2 \dot{x}_5) \]  
| \dot{x}_5 = \epsilon^{-2}(k_6 - k_4 \dot{x}_2 \dot{x}_5) \]  
| x_2 \leftarrow x_1 + x_2 \]  
| {\emptyset}₀₀ (3, 0, 2, 0, 4) | \[ \dot{x}_1 = \epsilon^{-k}(k_3 \dot{x}_2 - k_2 \dot{x}_1) \]  
| \dot{x}_2 = \epsilon^0(k_1 \dot{x}_3 - k_4 \dot{x}_2 \dot{x}_5) \]  
| \dot{x}_3 = \epsilon^0(k_{10} \dot{x}_4 + k_9 x_3^2 \dot{x}_4 - k_1 \dot{x}_3) \]  
| \dot{x}_4 = \epsilon^0(k_4 \dot{x}_2 \dot{x}_5 - k_{10} \dot{x}_4 - k_9 x_3^2 \dot{x}_4) \]  
| \dot{x}_5 = \epsilon^{-2}(k_6 - k_4 \dot{x}_2 \dot{x}_5) \]  
| x_2 \leftarrow x_1 + x_2 \]  
| {x_4}₀₂ (3, 0, 1, 1, 4) | \[ \dot{x}_1 = \epsilon^{-k}(k_3 \dot{x}_2 - k_2 \dot{x}_1) \]  
| \dot{x}_2 = \epsilon^0(k_1 \dot{x}_3) \]  
| \dot{x}_3 = \epsilon^0(k_9 x_3^2 \dot{x}_4 - k_1 \dot{x}_3) \]  
| \dot{x}_4 = \epsilon^0(-k_9 x_3^2 \dot{x}_4) \]  
| \dot{x}_5 = \epsilon^{-2}(k_6 - k_4 \dot{x}_2 \dot{x}_5) \]  
| x_2 \leftarrow x_1 + x_2 \]