A Constraint Solving Approach to Tropical Equilibration and Model Reduction

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Abstract. Model reduction is a central topic in systems biology and dynamical systems theory, for reducing the complexity of detailed models, finding important parameters, and developing multi-scale models for instance. While perturbation theory is a standard mathematical tool to analyze the different time scales of a dynamical system, and decompose the system accordingly, tropical methods provide a simple algebraic framework to perform these analyses systematically in polynomial systems. The crux of these tropicalization methods is in the computation of tropical equilibrations. In this paper we show that constraint-based methods, using reified constraints for expressing the equilibration conditions, make it possible to numerically solve non-linear tropical equilibration problems, out of reach of standard computation methods. We illustrate this approach first with the reduction of simple biochemical mechanisms such as the Michaelis-Menten and Goldbeter-Koshland models, and second, with performance figures obtained on a large scale on the model repository `biomodels.net`.

1 Preliminaries on Model Reduction by Tropicalization

We consider networks of biochemical reactions with mass action kinetic laws. Each reaction is defined as

$$\sum_i \boldsymbol{\alpha}_{ji} A_i \rightarrow \sum_k \beta_{jk} A_k.$$

The stoichiometric vectors $\alpha_j \in \mathbb{N}^n$, $\boldsymbol{\beta}_j \in \mathbb{N}^n$ have coordinates $\boldsymbol{\alpha}_{ji}$ and β_{jk} and define which species are consumed and produced by the reaction j and in which quantities.

The mass action law means that reaction rates are monomial functions of the species concentrations x_i and reads

$$R_j(\boldsymbol{x}) = k_j \boldsymbol{x}^{\boldsymbol{\alpha}_j}. \tag{1}$$

where $k_j > 0$ are kinetic constants, $\boldsymbol{\alpha}_j = (\alpha_1^j, \ldots, \alpha_n^j)$ are multi-indices and $\boldsymbol{x}^{\boldsymbol{\alpha}_j} = x_1^{\alpha_1^j} \ldots x_n^{\alpha_n^j}$.

The network dynamics is described by the following differential equations

$$\frac{dx_i}{dt} = \sum_j k_j(\beta_{ji} - \alpha_{ji})\boldsymbol{x}^{\boldsymbol{\alpha}_j}. \tag{2}$$

In what follows, the kinetic parameters do not have to be known precisely, they are given by their orders of magnitude. A convenient way to represent orders is by considering that

$$k_j = \bar{k}_j \epsilon^{\gamma_j}, \tag{3}$$

where ϵ is a positive parameter much smaller than 1, γ_j is an integer, and $\bar{k}_j$ has order unity. An approximate integer order can be obtained from any real positive parameter by

$$\gamma_j = \text{round}(\log(k_j)/\log(\epsilon)), \tag{4}$$

where round stands for the closest integer. For instance, if $\epsilon = 1/10$, γ_j will represent the logarithmic value of the parameter rounded to the nearest decade. Notice that in this representation, small quantities have large orders. Furthermore, the smaller ϵ, the better the separation between quantities of different orders, indeed $\lim_{\epsilon\to 0} \frac{k_i}{k_j} = \infty$ if $\gamma_i < \gamma_j$. We are also interested in the orders of the species concentrations, therefore we introduce a vector of orders $\boldsymbol{a} = (a_1, \ldots, a_n)$, such that $\boldsymbol{x} = \bar{\boldsymbol{x}}\epsilon^{\boldsymbol{a}}$. Orders $\boldsymbol{a}$ are unknown and have to be calculated. To this aim, the network dynamics can be described by a rescaled system of ordinary differential equations

$$\frac{d\bar{x}_i}{dt} = (\sum_j \epsilon^{\mu_j} k_j(\beta_{ji} - \alpha_{ji})\bar{\boldsymbol{x}}^{\boldsymbol{\alpha}_j})\epsilon^{-a_i}, \tag{5}$$

where

$$\mu_j = \gamma_j + < \boldsymbol{a}, \boldsymbol{\alpha}_j >, \tag{6}$$

and $<,>$ stands for the vector dot product. The r.h.s. of each equation in (5) is a sum of monomials in the concentrations, with positive and negative signs given by the stoichiometries $\beta_{ji} - \alpha_{ji}$. Generically, these monomials have different orders (given by μ_j) and there is one monomial that dominates the others. In this case, the corresponding variable will change rapidly in the direction imposed by this dominating monomial. However, on sub-manifolds of the phase space, at least two monomials, one positive and one negative may have the same order. This situation was called tropical equilibration in [6]. Tropical equilibration is different from equilibrium or steady state in many ways. Firstly, steady state means equilibration of all species, whereas tropical equilibration may concern only one or a few rapid species. Secondly, steady state means that forces are rigorously compensated on all variables that are at rest, whereas tropical equilibration means that only the dominant forces are compensated and variables may change slowly under the influence of uncompensated, weak forces. Compensation of dominant forces constrains the dynamics of the system to a low dimensional manifold named invariant manifold [7, 5]. As discussed in [6], tropical equilibrations encompass the notions of quasi-steady state and quasi-equilibrium from

singular perturbation theory of biochemical networks, but are more general. Let us provide a formal definition of tropical equilibration (see [6] for more details).

Definition 1. *Two reactions j, j' are tropically equilibrated on the species i iff:*
i) $\mu_j = \mu_{j'}$,
ii) $(\beta_{ji} - \alpha_{ji})(\beta_{j'i} - \alpha_{j'i}) < 0$ *(meaning that the effects of the reactions j and j' on the species i are opposite),*
iii) $\mu_k \geq \mu_j$ *for any reaction $k \neq j, j'$, such that* $\beta_{ki} \neq \alpha_{ki}$.

According to (6) and Definition 1, the equilibrations correspond to vectors $\boldsymbol{a} \in R^n$ where the minimum in the definition of the piecewise-affine function $f_i(\boldsymbol{a}) = \min_j(\gamma_j + < \boldsymbol{a}, \boldsymbol{\alpha}_j >)$ is attained at least twice. Tropical equilibrations are used to calculate the unknown orders $\boldsymbol{a}$. The solutions have a geometrical interpretation. Let us consider the equality $\mu_j = \mu_{j'}$. This represents the equation of a $n-1$ dimensional hyperplane of $\mathbb{R}^n$, orthogonal to the vector $\boldsymbol{\alpha}_j - \boldsymbol{\alpha}_{j'}$:

$$\gamma_j + < \boldsymbol{a}, \boldsymbol{\alpha}_j > = \gamma_{j'} + < \boldsymbol{a}, \boldsymbol{\alpha}_{j'} > \tag{7}$$

For each species i, we consider the set of reactions $\mathcal{R}_i$ that act on this species, namely the reaction k is in $\mathcal{R}_i$ iff $(\boldsymbol{\beta}_k - \boldsymbol{\alpha}_k)_i \neq 0$. The finite set $\mathcal{R}_i$ can be characterized by the corresponding set of stoichiometric vectors $\boldsymbol{\alpha}_k$. The set of points of $\mathbb{R}^n$ where at least two reactions equilibrate on the species i corresponds to the places where the function f_i is not locally affine (the minimum in the definition of f_i is attained at least twice). For simplicity, we shall call this locus tropical manifold [6, 9].

A simple example of biochemical network is the Michaelis-Menten mechanism of an enzymatic reaction. This network consists of two reactions:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_2}{\to} P + E,$$

where S, E, ES, P represent the substrate, the enzyme, the enzyme-substrate complex and the product, respectively.

The system of polynomial differential equations reads:

$$\begin{aligned} x_1' &= -k_1 x_1 x_3 + k_{-1} x_2, \\ x_2' &= k_1 x_1 x_3 - (k_{-1} + k_2) x_2, \\ x_3' &= -k_1 x_1 x_3 + (k_{-1} + k_2) x_2, \\ x_4' &= k_2 x_2. \end{aligned} \tag{8}$$

where $x_1 = [S]$, $x_2 = [SE]$, $x_3 = [E]$, $x_4 = [P]$.

There are two conservation laws: $x_2 + x_3 = e_0$ and $x_1 + x_2 + x_4 = s_0$ The rescaled variables are $x_i = \bar{x}_i \epsilon^{a_i}$, $1 \leq i \leq 4$, $k_1 = \bar{k}_1 \epsilon^{\gamma_1}$, $k_{-1} = \bar{k}_{-1} \epsilon^{\gamma_{-1}}$, $e_0 = \bar{e}_0 \epsilon^{\gamma_e}$, $s_0 = \bar{s}_0 \epsilon^{\gamma_s}$. Let us notice that the last equation can never be equilibrated because it contains only one monomial. The tropical equilibration equations for

the remaining variables read:

$$\begin{aligned}
\gamma_1 + a_1 + a_3 &= \gamma_{-1} + a_2, \\
\gamma_1 + a_1 + a_3 &= \min(\gamma_{-1}, \gamma_2) + a_2, \\
\gamma_1 + a_1 + a_3 &= \gamma_2 + a_2, \\
\min(a_2, a_3) &= \gamma_e, \\
\min(a_1, a_2, a_4) &= \gamma_s.
\end{aligned} \tag{9}$$

The set of integer orders endowed with the minimum and sum operations is a semiring, called min-plus algebra [2] where the minimum is noted $\oplus$ and the sum $\otimes$. Our tropical equilibration problem is solving a set of polynomial equations in this semi-ring.

Let us emphasize an important difference between the calculation of tropical equilibrations and calculation of exact equilibria of systems of polynomial differential equations. If there are exact conservation laws, the set of exact equilibrium equations are linearly dependent, therefore one can eliminate some of them from the system. Because elements in a min-plus semiring do not generally have additive inverses, elimination is not automatically possible in systems of tropical equations. In this case, one should keep all the tropical equilibrium equations for all the variables and add to them the tropical conservation relations.

2 Example of Golbeter-Koshland Switch

A slightly more complicated network is the Goldbeter-Koshland mechanism. This consists of two coupled Michaelis-Menten equations. The mechanism is important because it plays the role of a switch, allowing the propagation of information in signal transduction networks. The detailed mechanism is represented by four mass action reactions

$$S + E_a \underset{k^a_{-1}}{\overset{k^a_1}{\rightleftharpoons}} E_a S \overset{k^a_2}{\to} S^* + E_a, S^* + E_b \underset{k^b_{-1}}{\overset{k^b_1}{\rightleftharpoons}} E_b S^* \overset{k^b_2}{\to} S + E_b.$$

where S and S^* are, for instance, the un-phosphorylated and phosphorylated forms of a substrate, E_a, E_b, are kinase and phosphatase enzymes, respectively.

This mechanism leads to the following system of differential equations:

$$\begin{aligned}
x_1' &= k^a_2 x_5 - k^a_1 x_1 x_3, \\
x_2' &= k^b_2 x_6 - k^b_1 x_2 x_4, \\
x_3' &= k^a_{-1} x_5 + k^b_2 x_6 - k^a_1 x_1 x_3, \\
x_4' &= k^a_2 x_5 + k^b_{-1} x_6 - k^b_1 x_2 x_4, \\
x_5' &= k^a_1 x_1 x_3 - (k^a_{-1} + k^a_2) x_5, \\
x_6' &= k^b_1 x_2 x_4 - (k^b_{-1} + k^b_2) x_6.
\end{aligned} \tag{10}$$

where $x_1 = [E_a]$, $x_2 = [E_b]$, $x_3 = [S]$, $x_4 = [S^*]$, $x_5 = [E_a S]$, $x_6 = [E_b S^*]$.

This system has three conservation laws:

$$\begin{aligned} x_1 + x_5 &= E_0^a, \\ x_2 + x_6 &= E_0^b, \\ x_3 + x_4 + x_5 + x_6 &= S_0. \end{aligned} \tag{11}$$

Equilibrating each equation of (10) and taking into account (11) leads to the following tropical equations:

$$\begin{aligned} \gamma_2^a \otimes a_5 &= \gamma_1^a \otimes a_1 \otimes a_3, \\ \gamma_2^b \otimes a_6 &= \gamma_1^b \otimes a_2 \otimes a_4, \\ (\gamma_{-1}^a \otimes a_5) \oplus (\gamma_2^b \otimes a_6) &= \gamma_1^a \otimes a_1 \otimes a_3, \\ (\gamma_2^a \otimes a_5) \oplus (\gamma_{-1}^b \otimes a_6) &= \gamma_1^b \otimes a_2 \otimes a_4, \\ \gamma_1^a \otimes a_1 \otimes a_3 &= (\gamma_{-1}^a \oplus \gamma_2^a) \otimes a_5, \\ \gamma_1^b \otimes a_2 \otimes a_4 &= (\gamma_{-1}^b \oplus \gamma_2^b) \otimes a_6, \\ a_1 \oplus a_5 &= \gamma_e^a, \\ a_2 \oplus a_6 &= \gamma_e^b, \\ a_3 \oplus a_4 \oplus a_5 \oplus a_6 &= \gamma_s. \end{aligned} \tag{12}$$

The corresponding CSP, described in the next section, is solved instantly and gives the unique solution: $a_1 = 5, a_2 = 4, a_3 = 3, a_4 = 4, a_5 = 7$ for parameter values consistent with the literature: $k_1^* = 1000, k_2^* = 150, k_{-1}^* = 150$.

3 Tropical Equilibration as a Constraint Satisfaction Problem

Given a biochemical reaction system with its Mass-Action kinetics, and a small ϵ, the problem of tropical equilibration is to look for a rescaling of the variables such that the dominating positive and negative term in each ODE *equilibrate* as per Definition 1, i.e., are of the same degree in ϵ.

Note that there are supplementary constraints related to this rescaling when some conservation laws exist for the original system. Finding these conservation laws is another CSP which can be solved efficiently with constraint methods [8]. Here we will assume that the conservation laws are given in input. In our prototype implementation, both the computation of conservation laws and the following equilibration are performed for a given system.

For each original equation dx_i/dt, $1 \leq i \leq n$ is introduced a variable $a_i \in \mathbb{Z}$ that is used to rescale the system by posing $x_i = \epsilon^{a_i} \bar{x_i}$. These are the variables of our CSP. Note that they require a solver handling $\mathbb{Z}$ like for instance SWI-Prolog [11, 10] with the `clpfd` library by Markus Triska.

The constraints are of two kinds. For each differential equation that should be equilibrated is a list of positive monomials M_i^+, and a list of negative monomials M_i^-. The degrees in ϵ of all these monomials are integer linear expressions in the a_i. Now, to obtain an equilibration one should enforce for each i

that the minimum degree in M_i^+ is equal to the minimum degree in M_i^-. This will ensure that we find two monomials (i of Definition 1) of opposite sign (ii) and of minimal degree (iii). This corresponds to the first six tropical equations of (12). We will see how they can be implemented with reified constraints, but for now, let us assume a constraint `min(L, M)` that enforces that the FD variable `M` is the minimum value of a list `L` of linear expressions over FD variables. We have in our CSP, for each $1 \leq i \leq n$, `min(PositiveMonomialDegrees, M)` and `min(NegativeMonomialDegrees, M)`.

The second kind of constraint comes from conservation laws. Each conservation law is an equality between a linear combination of the x_i and a constant c_i. By rescaling, we obtain a sum of rescaled monomials equal to $\epsilon^{\log(c_i)/\log(\epsilon)}\bar{c_i}$. We want this equality to hold when ϵ goes to zero, which implies that the minimal degree in ϵ in the left hand side is equal to (the round of) the degree of the right hand side. Since once again the degrees on the left are linear combinations of our variables a_i, this is again a constraint of the form: `min(ConservationLawDegrees, K)` where `K` is equal to $\text{round}(\log(c_i)/\log(\epsilon))$. This corresponds to the last three tropical equations of (12).

Furthermore, if the system under study is not at steady state, the minimum degree should not be reached only once, which would lead to a constant value for the corresponding variable when ϵ goes to zero, but at least twice. This is the case for the example treated in [5]. The constraint we need is therefore slightly more general than `min/2`: we need the constraint `min(L, M, N)` which is true if `M` is smaller than each element of `L` and equal to `N` elements of that list. Note that using CLP notation, we have:

```
min(M, L) :-  C#>=1, min(M, L, C).
```

In order to enforce that the minimum is reached at least a required number of times, one obvious solution is to try all pairs of positive and negative monomials and count the successful pairs [7]. However, this is not necessary, the `min(L, M, N)` constraint directly expresses the cardinality constraint on the minimums. and can be implemented using *reified constraints* to propagate information between `L`, `M` and `N` in all directions, without enumeration. Using SWI-Prolog notations, the implementation of `min/3` by reified constraints is as follows:

```
min([], _, 0).
min([H | T], M, C) :- M#=<H, B #<==> M#=H, C#=B+CC,
                      min(T, M, CC).
```

This concise and portable implementation will probably improve when the `minimum` and `min_n` global constraints are available (see [1] for a reference). However it already proves very efficient as demonstrated in the next section.

4 Computation Results on Biomodels.net

To benchmark our approach, we applied it systematically to all the dynamical models of the BioModels[1] repository [4] of biological systems, with ϵ set arbitrarily to 0.1. We used the latest release (*r24* from 2012-12-12) which includes 436 curated models.

Among them, only 55 models have non-trivial purely polynomial kinetics (ignoring *events* if any). Our computational results on those are summarized in the following table, where the first column indicates whether a complete equilibration was found, and the times are in seconds.

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

We managed to avoid timeouts by using an iterative domain expansion: the problem is first tried with a domain of $[-2, 2]$, i.e., equilibrations are searched by rescaling in the $10^{-2}, 10^{2}$ interval. If that fails, the domain is doubled and the problem tried again (until a limit of $10^{-128}, 10^{128}$). This strategy coupled with a domain bisection enumeration (`bisect` option in SWI-Prolog) allowed us to gain two orders of magnitude on the biggest models.

Only one of the models (number 002) used values far from 0 in the equilibration (up to ϵ^{40}) and has no complete equilibration if the domain is restricted to $[-32, 32]$. This is because all kinetics are scaled by the volume of the compartment, which in that case was 10^{-16}, translating the search accordingly. We thus do not believe that enlarging the domains even more would lead to more equilibrations. Nevertheless, choosing a smaller ϵ might increase the number of equilibrations.

18 of the 23 models for which there is a complete equilibration are actually underconstrained and appear to have an infinity of such solutions (typically linear relations between variables). For the 5 remaining ones, we computed all complete equilibrations:

Model	# equilibrations	Total time (s)
BIOMD0000000002	36	109
BIOMD0000000122	45	291
BIOMD0000000156	7	0.008
BIOMD0000000229	7	0.7
BIOMD0000000413	29	3.3

5 Discussion

One of the limits of this approach, is that it is not well suited to equilibration problems with an infinite number of solutions. For those, symbolic solutions depending on free parameters are necessary, as done in [6].

[1] `http://biomodels.net`

It is also possible to reduce a system using its conservation laws, and to apply tropical equilibration directly on the reduced system. However, the resulting equilibrations might be slightly different, apparently due to the possible loss of positivity of certain variables. We want to investigate this question further.

In many cases, it makes sense biologically to only look for partial equilibrations. Strategies to decide when such decision has to be made remain unclear. Nevertheless the framework of partial constraint satisfaction and more specifically Max-CSP [3] would allow us to easily handle the maximization of the number of equilibrated variables.

In this paper we discussed only the calculation of the tropical equilibrations and of the unknown orders of the variables. Once the orders of the variables are known, the rapid variables can be identified and the system reduced to a simpler one. The details of the reduction procedure, involving pruning of dominated terms and pooling of fast variables into fast cycles will be presented elsewhere. A simple reduction procedure, involving only pruning is described by Theorem 3.6 of [6].

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