Analysis of Reaction Network Systems using Tropical Geometry

Abstract. We discuss a novel analysis method for reaction network systems with polynomial or rational rate functions. This method is based on computing tropical equilibrations defined by the equality of at least two dominant monomials of opposite signs in the differential equations of each dynamic variable. In algebraic geometry, the tropical equilibration problem is tantamount to finding tropical varieties, that are finite intersections of tropical varieties. Tropical equilibrations with the same set of dominant monomials define a branch or equivalence class. Minimal branches are particularly interesting as they describe the simplest states of the reaction network. We provide a method to compute the number of minimal branches and to find representative tropical equilibrations for each branch.

1 Introduction

Networks of chemical reactions are widely used in chemistry for modeling catalysis, combustion, chemical reactors, or in biology as models of signaling, metabolism, and gene regulation. Several mathematical methods were developed for analysis of these models such as the study of multiplicity of steady state solutions and detection of of bifurcations by stoichiometry analysis, deficiency theorems, reversibility, permanency, etc. [1].

All these methods put emphasis on the number and the stability of the steady states of chemical networks. Beyond steady states, metastable states defined as regions of the phase space where the system has slow dynamics are also important for understanding the behaviour of networks. For instance, low dimensional inertial or invariant manifold gather slow degrees of freedom of the system and are important for model reduction. Invariant manifolds can lose local stability, which allow the trajectories to perform large phase space excursions before returning in a different place on the same invariant manifold or on a different one [2]. Such itinerancy phenomena are current in biological networks and it is important to know how metastable states are connected.

We showed elsewhere that tropical geometry methods can be used to approximate such invariant manifolds for systems of polynomial differential equations [3–5]. The slowness of the dynamics on the invariant manifolds follows from the compensation of dominant forces acting on the system, represented as dominant monomials in the differential equations. We have called the equality of dominant monomials tropical equilibration [4, 5]. Tropical equilibrations are different from steady states, because in tropically equilibrated systems one has non-compensated weak forces that drive the system slowly, whereas at steady state net forces vanish. Furthermore, invariant manifolds can be roughly associated to metastable states because they are regions of phase space where systems dynamics is relatively slower. In this paper we introduce methods to compute tropical equilibrations and group them into branches that cover the metastable states of the system. These branches of tropical equilibrations form a complex. The zeroth homology group of this complex indicates the possible transitions between the metastable states.

2 Definitions and settings

We consider biochemical networks described by mass action kinetics

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \sum_j k_j S_{ij} \boldsymbol{x}^{\boldsymbol{\alpha}_j},\ 1 \leq i \leq n, \tag{1}$$

where $k_j > 0$ are kinetic constants, S_{ij} are the entries of the stoichiometric matrix (uniformly bounded integers, $|S_{ij}| < s$, s is small), $\boldsymbol{\alpha}_j = (\alpha_1^j, \ldots, \alpha_n^j)$ are multi-indices, and $\boldsymbol{x}^{\boldsymbol{\alpha}_j} = x_1^{\alpha_1^j} \ldots x_n^{\alpha_n^j}$. We consider that α_i^j are positive integers.

In the case of slow/fast systems with polynomial dynamics such as (1), the slow invariant manifold is approximated by a system of polynomial equations for the fast species. This crucial point allows us to find a connection with tropical geometry. We introduce now the terminology of tropical geometry needed for the presentation of our results, and refer to [6] for a comprehensive introduction to this field.

Let $f_1, f_2, \ldots, f_k$ be multivariate polynomials, $f_i \in \mathbb{C}[x_1, x_2, \ldots, x_n]$, representing all or a part of the polynomials in the right hand side of (1).

Let us now consider that variables x_i, $i \in [1, n]$ are written as powers of a small positive parameter ϵ, namely $x_i = \bar{x}_i \varepsilon^{a_i}$, where $\bar{x}_i$ has order zero (are bounded, uniformly in ϵ). The orders a_i indicate the order of magnitude of x_i. Because ϵ was chosen small, a_i are lower for larger absolute values of x_i. Furthermore, the order of magnitude of monomials $\boldsymbol{x}^{\boldsymbol{\alpha}}$ is given by the dot product $\mu =< \boldsymbol{\alpha}, \boldsymbol{a} >$, where $\boldsymbol{a} = (a_1, \ldots, a_n)$. Again, smaller values of μ correspond to monomials with larger absolute values. For each multivariate polynomial f we define the tropical surface $T(f)$ as the set of vectors $\boldsymbol{a} \in \mathbb{R}^n$ such that the minimum of $< \boldsymbol{\alpha}, \boldsymbol{a} >$ over all monomials in f is attained for at least two monomials in f. In other words, f has at least two dominating monomials.

A *tropical prevariety* is defined as the intersection of a finite number of tropical surfaces, namely $T(f_1, f_2, \ldots, f_k) = \cap_{i \in [1,k]} T(f_i)$.

A *tropical variety* is the intersection of all tropical surfaces in the ideal I generated by the polynomials $f_1, f_2, \ldots, f_k$, $T(I) = \cap_{f \in I} T(f)$. The tropical variety is within the tropical prevariety, but the reciprocal property is not always true.

For our purposes, we slightly modify the classical notion of tropical prevariety. A *tropical equilibration* is defined as a vector $\boldsymbol{a} \in \mathbb{R}^n$ such that $< \boldsymbol{\alpha}, \boldsymbol{a} >$ attains its minimum at least twice for monomials of different signs, for each polynomial in the system $f_1, f_2, \ldots, f_k$. Thus, tropical equilibrations are subsets of the tropical prevariety. Our sign condition is needed because we are interested in approximating real positive solutions of polynomial systems (the sum of several dominant monomials of the same sign have no real strictly positive roots).

3 Branches of tropical equilibrations

For chemical reaction networks with multiple timescales it is reasonable to consider that kinetic parameters have different orders of magnitudes.

We therefore assume that parameters of the kinetic models (1) can be written as

$$k_j = \bar{k}_j \varepsilon^{\gamma_j}. \tag{2}$$

The exponents γ_j are considered to be integer. For instance, the following approximation produces integer exponents:

$$\gamma_j = \mathrm{round}(\log(k_j)/\log(\varepsilon)), \tag{3}$$

where round stands for the closest integer (with half-integers rounded to even numbers). Without rounding to the closest integer, changing the parameter ϵ should not introduce variations in the output of our method. Indeed, the tropical prevariety is independent on the choice of ϵ.

Of course, kinetic parameters are fixed. In contrast, species orders vary in the concentration space and have to be calculated as solutions to the tropical equilibration problem. To this aim, the network dynamics is first described by a rescaled ODE system

$$\frac{\mathrm{d}\bar{x}_i}{\mathrm{d}t} = \sum_j \varepsilon^{\mu_j - a_i} \bar{k}_j S_{ij} \bar{\boldsymbol{x}}^{\boldsymbol{\alpha}_j}, \tag{4}$$

where

$$\mu_j(\boldsymbol{a}) = \gamma_j + \langle \boldsymbol{a}, \boldsymbol{\alpha_j} \rangle, \tag{5}$$

and $\langle , \rangle$ stands for the dot product.

The r.h.s. of each equation in (4) is a sum of multivariate monomials in the concentrations. The orders μ_j indicate how large are these monomials, in absolute value. A monomial of order μ_j dominates another monomial of order $\mu_{j'}$ if $\mu_j < \mu_{j'}$.

The tropical equilibration problem consists in finding a vector $\boldsymbol{a}$ such that

$$\min_{j, S_{ij}>0} (\gamma_j + \langle \boldsymbol{a}, \boldsymbol{\alpha_j} \rangle) = \min_{j, S_{ij}<0} (\gamma_j + \langle \boldsymbol{a}, \boldsymbol{\alpha_j} \rangle) \tag{6}$$

The solutions of this system have a geometrical interpretation. Let us define the extended order vectors $\boldsymbol{a}^e = (1, \boldsymbol{a}) \in \mathbb{R}^{n+1}$ and extended exponent vectors $\boldsymbol{\alpha}_j^e = (\gamma_j, \boldsymbol{\alpha}_j) \in \mathbb{Z}^{n+1}$. Let us consider the equality $\mu_j = \mu_{j'}$. This represents the equation of a n dimensional hyperplane of $\mathbb{R}^{n+1}$, orthogonal to the vector $\boldsymbol{\alpha_j}^e - \boldsymbol{\alpha_{j'}}^e$:

$$\langle \boldsymbol{a}^e, \boldsymbol{\alpha_j}^e \rangle = \langle \boldsymbol{a}^e, \boldsymbol{\alpha_{j'}}^e \rangle, \tag{7}$$

where $\langle , \rangle$ is the dot product in $\mathbb{R}^{n+1}$. We will see in the next section that the minimality condition on the exponents μ_j implies that the normal vectors $\boldsymbol{\alpha_j}^e - \boldsymbol{\alpha_{j'}}^e$ are edges of the so-called Newton polytope [7, 8].

For each equation i, let us define

$$M_i(\boldsymbol{a}) = \underset{j}{\operatorname{argmin}}(\mu_j(\boldsymbol{a}), S_{ij} > 0) = \underset{j}{\operatorname{argmin}}(\mu_j(\boldsymbol{a}), S_{ij} < 0), \tag{8}$$

in other words M_i denote the set of monomials having the same minimal exponent μ_i.

We call *tropically truncated system* the system obtained by pruning the system (4), i.e. by keeping only the dominating monomials.

$$\frac{\mathrm{d}\bar{x}_i}{\mathrm{d}t} = \varepsilon^{\mu_i - a_i}\Big(\sum_{j \in M_i(\boldsymbol{a})} \bar{k}_j \nu_{ji} \bar{\boldsymbol{x}}^{\boldsymbol{\alpha_j}} \Big), \tag{9}$$

The tropical truncated system is uniquely determined by the index sets $M_i(\boldsymbol{a})$, therefore by the tropical equilibration $\boldsymbol{a}$. Reciprocally, two tropical equilibrations can have the same index sets $M_i(\boldsymbol{a})$ and truncated systems. We say that two tropical equilibrations $\boldsymbol{a}_1$, $\boldsymbol{a}_2$ are equivalent iff $M_i(\boldsymbol{a}_1) = M_i(\boldsymbol{a}_2)$, for all i. Equivalence classes of tropical equilibrations are called *branches.* A branch with an index set M_i is *minimal* if there is no other branch with an index set M_i' such that $M_i' \subset M_i$ for all i where the inclusion is strict for at least one i. Because for each index i, the relation (7) defines a hyperplane, the tropical equilibration branches are on intersections of n such hyperplanes. Infinite branches correspond to non-transversal intersections and minimal branches correspond to hyperplanes of maximal dimension.

4 Algorithm

4.1 Pre-processing

We consider examples with polynomial vector field. The kinetic parameters of the equation system are scaled based on Eq. (2).

4.2 Newton polytope and edge filtering

For each equation and species i, we define a Newton polytope $\mathcal{N}_i$, that is the convex hull of the set of points $\boldsymbol{\alpha}_j^e$ such that $\nu_{ji} \neq 0$ and also including together with all the points the half-line emanating from these points in the positive ϵ direction. This is the Newton polytope of the polynomial in right hand side of Eq.(4), with the scaling parameter ε considered as a new variable.

As explained in Section **??** the tropical equilibrations correspond to vectors $\boldsymbol{a}^e = (1, \boldsymbol{a}) \in \mathbb{R}^{n+1}$ satisfying the optimality condition of Definition **??**. This condition is satisfied automatically on hyperplanes orthogonal to edges of Newton polytope connecting vertices $\boldsymbol{\alpha}_{j'}^e$, $\boldsymbol{\alpha}_{j''}^e$ satisfying the opposite sign condition.

Therefore, a subset of edges from Newton polytope is selected based on the filtering criteria which tells that the vertices belonging to an edge should be from opposite sign monomials as explained in Eq.(10).

$$\begin{aligned} E(P) = \{\{v_1, v_2\} \subseteq \tbinom{V}{2} \mid \operatorname{conv}(v_1, v_2) \in F_1(P) \\ \wedge \operatorname{sign}(v_1) \times \operatorname{sign}(v_2) = -1\}, \end{aligned} \tag{10}$$

where v_i is the vertex of the polytope and V is the vertex set of the polytope, $\operatorname{conv}(v_1, v_2)$ is the convex hull of vertices v_1, v_2 and $F_1(P)$ is the set of 1-dimensional face (edges) of the polytope. $\operatorname{sign}(v_i)$ represents the sign of the monomial which corresponds to vertex v_i. Fig. 1 shows an example of Newton polytope construction for a single equation. Further definitions about properties of a polytope and Newton polytope can be found in [7, 8].

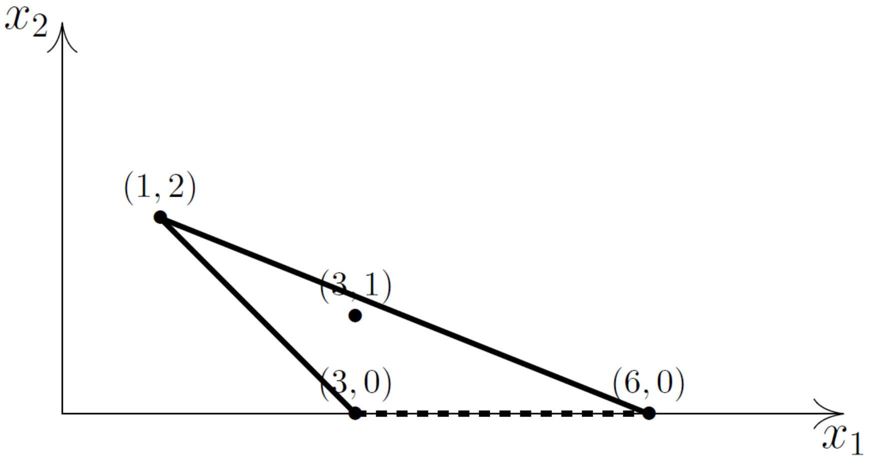

Fig. 1. An example of a Newton polytope for the polynomial $-x_1^6+x_1^3x_2-x_1^3+x_1x_2^2$. In this example, all the monomial coefficients have order zero in ϵ and we want to solve the tropical problem $\min(3a_1+a_2, a_1+2a_2) = \min(6a_1, 3a_1)$. The Newton polytope vertices $(6,0), (3,0), (1,2)$ are connected by lines. The point $(3,1)$ is not a vertex as it lies in the interior of the polytope. This stems to having $\min(3a_1+a_2, a_1+2a_2) = a_1+2a_2$ for all tropical solutions, which reduces the number of cases to be tested. The thick edges satisfy the sign condition, whereas the dashed edge does not satisfy this condition. For this example, the solutions of the tropical problem are in infinite number and are carried by the two half-lines $a_1 = a_2 \geq 0$ and $5a_1 = 2a_2 \leq 0$, orthogonal to the thick edges of the Newton polygon.

4.3 Pruning and feasible solutions

By feasible solution we understand a vector $(a_1, \ldots, a_n)$ satisfying all the equations of the system (**??**). A feasible solution lies in the intersection of hyperplanes (or convex subsets of these hyperplanes) orthogonal to edges of Newton polytopes obeying the sign conditions. Of course, not all sequences of edges lead to nonvoid intersections and thus feasible solutions. This can be tested by the following linear programming problem, resulting from (**??**):

$$\gamma_j(i) + \langle \boldsymbol{a}, \boldsymbol{\alpha_j(i)} \rangle = \gamma'_j(i) + \langle \boldsymbol{a}, \boldsymbol{\alpha'_j(i)} \rangle \leq \gamma''_j + \langle \boldsymbol{a}, \boldsymbol{\alpha''_j} \rangle),$$
$$\text{for all}\, j'' \neq j, j', \nu_{j''i} \neq 0, \quad i = 1, \dots, n \qquad (11)$$

where $j(i), j'(i)$ define the chosen edge of the $i-$th Newton polytope. The set of indices j'' can be restricted to vertices of the Newton polytope, because the inequalities are automatically fulfilled for monomials that are internal to the Newton polytope. For instance, in the exemple of the preceding section, the choice of the edge connecting vertices $(1, 2)$ and $(6, 0)$ leads to the following linear programming problem:

$$a_1 + 2a_2 = 3a_1 \leq 6a_1,$$

whose solution is a half-line orthogonal to the edge of the Newton polygon. The pseudo-code is presented in Algorithm 1 and the pruning method which is heuristic to filter out the infeasible set of edge combinations is presented in Fig. 2. More details in [reference to our unpublished paper ?].

```
Algorithm 1: SolveOrders: Steps of tropical equilibration algorithm
  Input:  List of edge sets $ne_1, ne_2, ..., ne_n$, and the corresponding vertices
  Output: Set of feasible systems (set of inequalities) corresponding to orders of
          the variables $\boldsymbol{a}_1, \boldsymbol{a}_2, ..., \boldsymbol{a}_n$ (tropical equilibration solution set)
begin
    solutionset ={}; integer $k$=1; equation = {}
    SolveOrders(equation, $k$, edge-sets, vertices)
    if $k > n$ then
        return
    for $l = 1$ to number of entries in $ne_k$ edge-set do
        equation(k)* = vertices in $l^{th}$ row
        inequalities* = all other vertices in $ne_1$ to $ne_k$ edge-sets
        if LinearSolve(equation,inequalities) is feasible then
            if $k = n$ then
                add the feasible system (set of inequalities) to solutionset
            SolveOrders(equation, $k + 1$, $ne_1, .., ne_k$, vertices)
*The equations and inequalities are initialised as per Eq. (11)
```

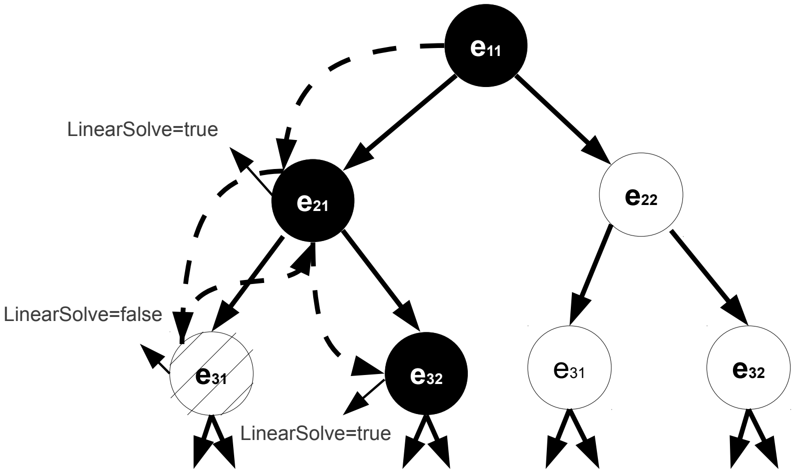

Fig. 2. Pruning strategy. Results using different pruning strategies. The possible combinations of edges are represented in a tree representation. The algorithm starts by testing for feasible solution for first pair of edge sets. If a feasible solution is found, the algorithm proceeds further to other edge sets or it backtracks. In the figure, e_{11} and e_{21} are selected from edge sets ne_1, ne_2 and are checked for a feasible solution satisfying (11). If such a solution exists, it moves to $e_{31}$from the next edge set and again checks for feasible solution, if not then it backtracks to e_{21} and then to e_{32} which results in a feasible solution. Therefore, the subtree with root node e_{31} is discarded from future searches and this improves running time. Likewise the branch e_{11} and e_{22} is explored. This approach is similar to branch and bound algorithm technique. The dashed arrows show the flow of the program.

4.4 Computation of Minimal solution branches

The set of feasible systems that were obtained using Algorithm 1 are actually H-polytopes represented as intersection of finitely many closed half spaces (i.e. either $\leq$ or $\geq$ occurs in the inequality system) and can be represented as

$$P = \{x \in R^n \mid \langle x, b_i \rangle \leq \beta_i, \forall i \in I\} \tag{12}$$

where $b_i \in R^n$ and $\beta_i \in R$ for $i \in I$, where I is an arbitrary index set.

Checking for duplicates The solution set of such H-polytopes are checked for duplicates using the software package polymake [9] using the method *equal_polyhedra*.

Checking for Polytope containment After the distinct polytopes were obtained from the previous step are checked for polytope containment which checks for two given polytopes P and Q if $P \subseteq Q$ is true. This was performed using *included_polyhedra* method in polymake. Those polytopes which are contained in other polytopes are filtered out and the remaining ones were the polytopes corresponding to minimal branches.

Sample point for minimal branches From the polytopes corresponding to minimal branches, the samples points are needed to be computed which correspond to orders of the variables $\boldsymbol{a}_1, \boldsymbol{a}_2, ..., \boldsymbol{a}_n$. For this purpose Satisfiability Modulo Theories (SMT) solver called Microsoft Z3 software [10] was used in python environment. This allowed to express the inequalities as boolean formula and generate the sample point. The tropical solution set can be computed as

$$T_i = \{x \in M_i \wedge x \notin N_i, \forall i \in I\} \tag{13}$$

where x is a tropical solution if it belongs to set M i.e. polytope corresponding to minimal branches and do not belong to N i.e. set of polytopes contained in some polytope in M. I is an index set corresponding to elements of M.

5 Results

33 models were selected from r25 version of Biomodels database [11] having polynomial vector field. The main finding of this paper to compute the minimal branches. A summary of the analysis is presented in Table 1. The analysis is performed to compute all possible combinations of vertices leading to tropical solutions within a maximal running time of 10000 seconds of CPU time. In practice, we restrict this search space using the tree pruning strategy as explained in Sect. 4.3. The analysis was repeated with four different choices for ε values. In such models, the number of variables may not be equal to number of equations as the conservation laws are treated as extra linear equations in our framework.

Table 1. Summary of analysis on Biomodels database. Tropical solutions here mean existence of at least one feasible solution from all possible combination of vertices of the Newton polytope. Timed-out means all solutions could not be computed within 10000 secs of computation time. No tropical solution implies no possible combination of vertices could be found resulting in a feasible solution. Model BIOMD0000000289 has solution at ε values 1/5,1/7 and 1/9 but no solutions at 1/23. Model BIOMD0000000108 has no solutions at all values of ε.

ε value	Total models considered	Models without tropical solutions	Models with tropical solutions	Average running time (in secs)	Average number of minimal branches
1/5	33	1	32	299.38	3.24
1/7	33	1	32	244.12	3
1/9	33	1	32	309.73	3.75
1/23	33	2	31	3179.32	3.84

A semilog time-plot is presented in Fig. 3(a) which plots the log of running time in milliseconds versus the number of equations in the model. In Fig. 3(b) the pruning ratio i.e. the efficacy of tree pruning for ε value of 1/5 is plotted. By pruning ratio is the ratio between number of times the linear programming is invoked with every tree pruning step (cf. Fig. 2) and the possible number of combinations of newton polytope edges without tree pruning (cf. Eq. **??**). This ratio is a measure of efficiency achieved due to pruning.

A semilog plot for minimal solution branches is presented in Fig. 4(a) and a semilog plot in Fig. 4(b) showing the ratio of minimal solution branches to number of feasible systems (obtained from Algorithm 1). It shows a large proportion of feasible systems are either redundant or included in other feasible systems (i.e. inclusion relations).

In order to investigate the effect of different ε values on the number of minimal solutions, a boxplot is presented in Fig. 8(a) for different choices of ε values. In Fig. 8(b) the boxplot shows ratio of minimal solution branches to number of feasible systems (obtained from Algorithm 1) for different choices of ε values

6 Example

7 Discussions

7.1 Robustness of maximal polytopes w.r.t. epsilon

7.2 Effect of epsilon on tropical solutions

7.3 Number of Maximal polytopes versus feasible systems

References

1. Feinberg, M.: Chemical reaction network structure and the stability of complex isothermal reactorsi. the deficiency zero and deficiency one theorems. Chemical

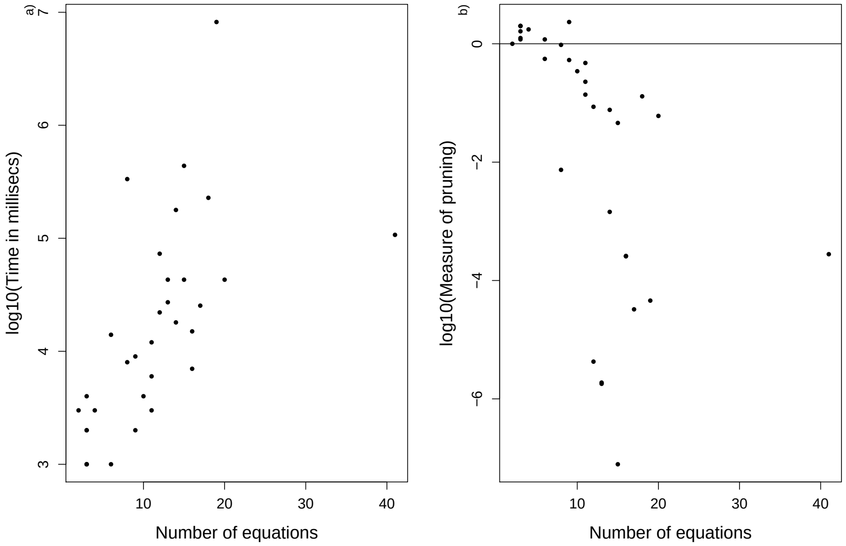

Fig. 3. (a) Plot of running time against number of equations in the model. (b) Pruning ratio for ε value of $1/5$ against number of equations in the model

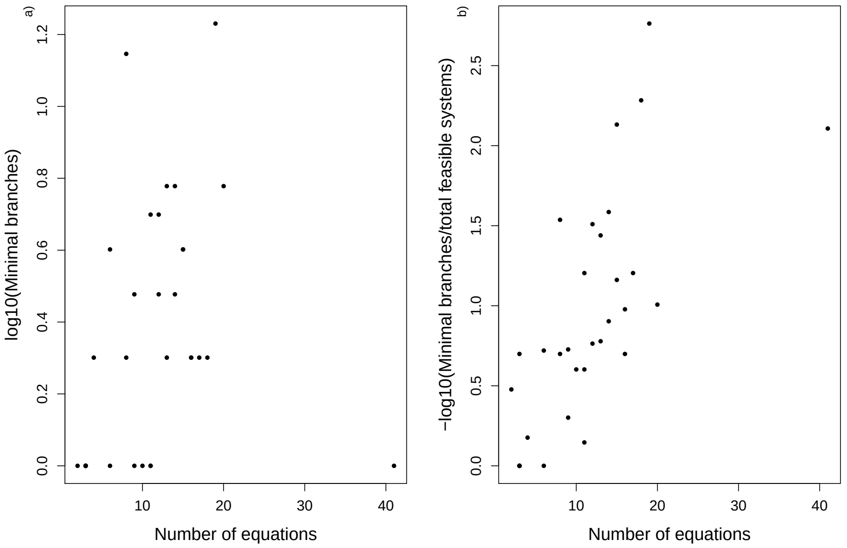

Fig. 4. (a) Minimal branches against number of equations in the model. (b) Ratio of minimal branches to the number of feasible systems i.e. number of feasible edge combinations against number of equations in the model

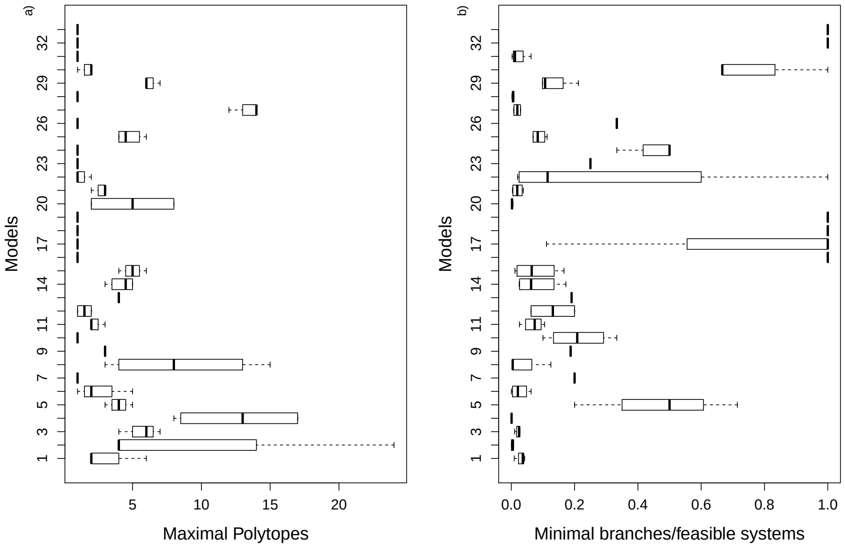

Fig. 5. Boxplots showing (a) Distribution of Minimal branches. (b) Ratio of minimal branches to the number of feasible systems i.e. number of feasible edge combinations. Both distributions are at different ε values: 1/5,1/7,1/9,1/23

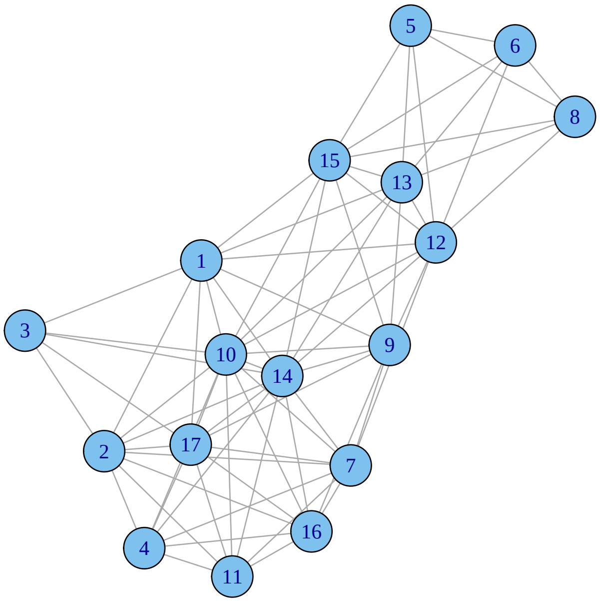

Fig. 6. Graph of connected components for BIOMD0000000028. It has one connected components

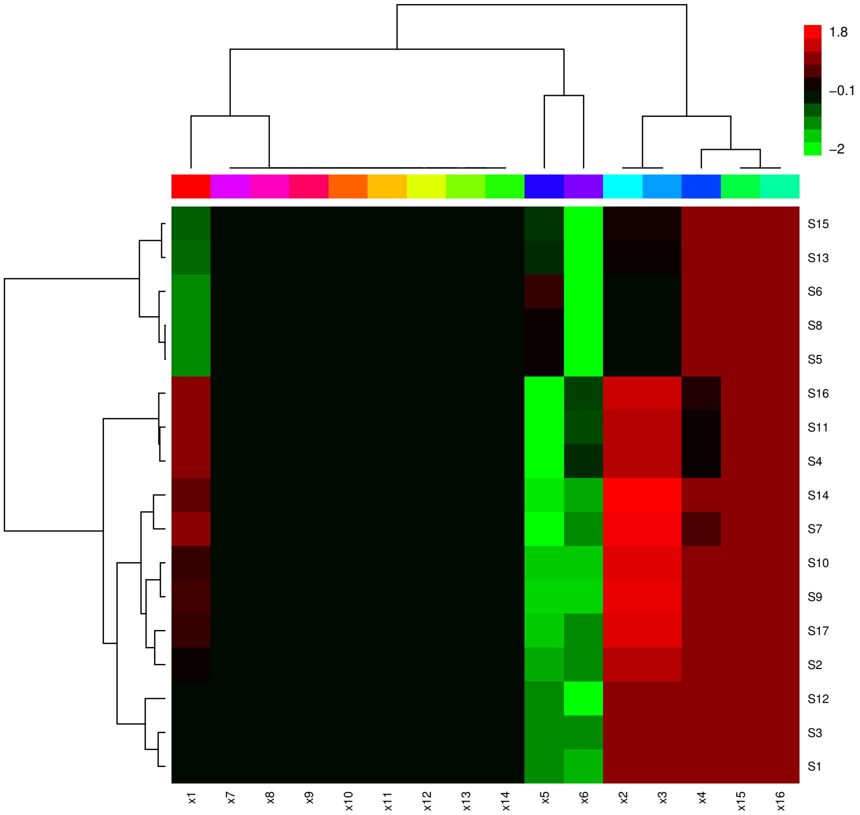

Fig. 7. Heatmap showing the rescaled orders for BIOMD0000000028 with hierarchical clustering for variables (horizontal axis) and tropical solutions (vertical axis). This model has 16 variables and 17 minimal branch solutions. Two clear clusters of variables can be seen as well as two clear clusters for tropical solutions. This may be helpful for data driven identification of slow-fast as an alternative to threshold based fast-slow decomposition

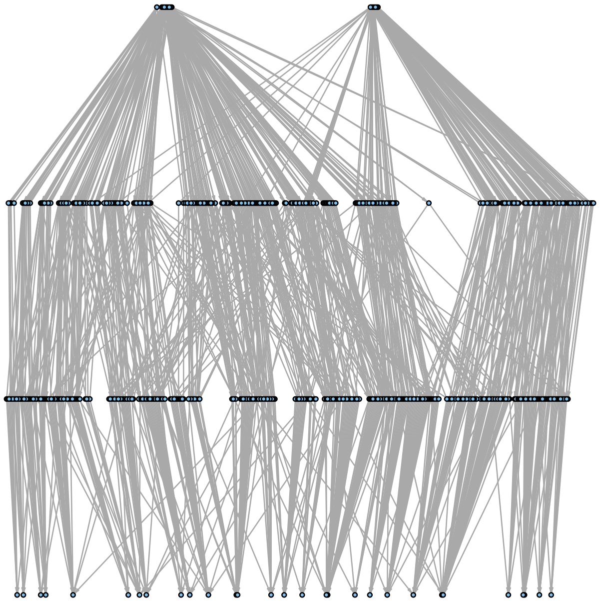

Fig. 8. A directed graph in layered form showing the inclusion relations among the different solution branches. Vertices comprises of solution polytopes and an directed edge between i and j means j is included in i. The topmost layer contain the minimal solution branches, thereafter the bottom layers are ”included” solution branches. The layers of the included solution branches are based on the dimension of the corresponding solution polytope (in descending order). Therefore, included solutions in one layer are of same dimensional solution polytope.

Engineering Science **42**(10) (1987) 2229–2268

2. Haller, G., Sapsis, T.: Localized instability and attraction along invariant manifolds. SIAM Journal on Applied Dynamical Systems **9**(2) (2010) 611–633
3. Noel, V., Grigoriev, D., Vakulenko, S., Radulescu, O.: Tropical geometries and dynamics of biochemical networks application to hybrid cell cycle models. In Feret, J., Levchenko, A., eds.: Proceedings of the 2nd International Workshop on Static Analysis and Systems Biology (SASB 2011). Volume 284 of Electronic Notes in Theoretical Computer Science. Elsevier (2012) 75–91
4. Noel, V., Grigoriev, D., Vakulenko, S., Radulescu, O.: Tropicalization and tropical equilibration of chemical reactions. In: Topical and Idempotent Mathematics and Applications. Volume 616. American Mathematical Society (2014)
5. Radulescu, O., Vakulenko, S., Grigoriev, D.: Model reduction of biochemical reactions networks by tropical analysis methods. Mathematical Model of Natural Phenomena, in press (2015)
6. Maclagan, D., Sturmfels, B.: Introduction to tropical geometry. Graduate Studies in Mathematics **161** (2009)
7. Henk, M., Richter-Gebert, J., Ziegler, G.M.: 16 basic properties of convex polytopes. Handbook of discrete and computational geometry (2004) 355
8. Sturmfels, B.: Solving systems of polynomial equations. CBMS Regional Conference Series in Math., no. 97, American Mathematical Society, Providence, RI (2002)
9. Gawrilow, E., Joswig, M.: Polymake: a framework for analyzing convex polytopes. Polytopes Combinatorics and Computation (2000)
10. De Moura, L., Bjørner, N.: Z3: An efficient smt solver. In: Proceedings of the Theory and Practice of Software, 14th International Conference on Tools and Algorithms for the Construction and Analysis of Systems. TACAS'08/ETAPS'08, Berlin, Heidelberg, Springer-Verlag (2008) 337–340
11. Le Novere, N., Bornstein, B., Broicher, A., Courtot, M., Donizelli, M., Dharuri, H., Li, L., Sauro, H., Schilstra, M., Shapiro, B., Snoep, J.L., Hucka, M.: BioModels database: a free, centralized database of curated, published, quantitative kinetic models of biochemical and cellular systems. Nucleic Acids Research **34**(suppl 1) (2006) D689–D691