Sensitive Parameters and Tipping Points of Biochemical Networks needed in Precision Medicine

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Introduction

It has been suggested that complex human diseases can be understood by studying the effects of perturbations on the functioning of biochemical reaction networks (BRNs) describing intracellular processes. Additionally, due to inherent robustness of the networks, only a small number of sensitive parameters and tipping points are expected. In this context, we propose a novel computational approach based on tropical geometry to study the qualitative dynamical properties of BRNs that are modeled using non-linear Ordinary Differential Equations (ODEs) and parameterized by orders of magnitudes rather than precise numerical values. We expect that the disease specific changes to the biological system can be associated with a set of alterations in the underlying BRNs (e.g. mutations). In this setting the robustness analysis will be helpful in the mechanistic understanding of disease processes. Furthermore, our method can be applied to define drug target candidates by determining parameters that need to be perturbed to achieve the desired change in system behaviour.

Main Idea

Parameters having less effect (relative to others) on the steady change concentrations of the model variables when perturbed can be considered to be robust.

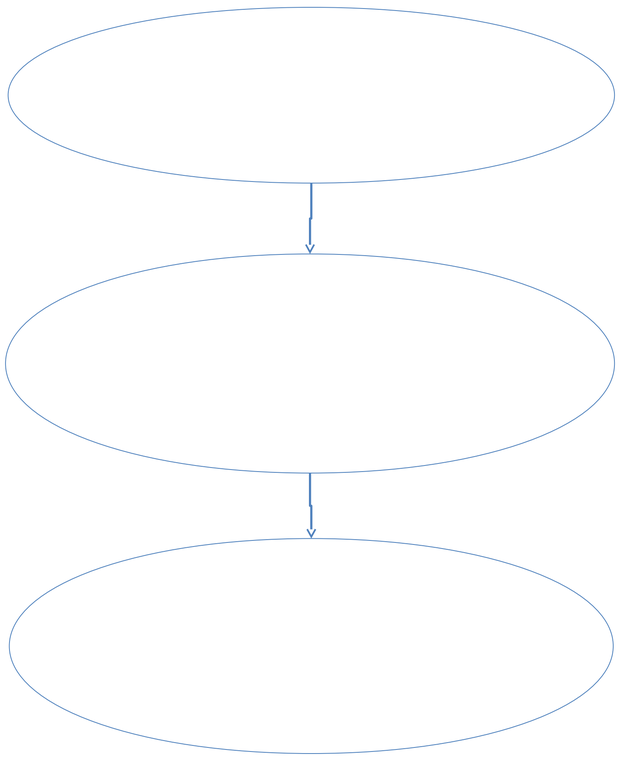
- We computed the steady states "classically" using existing algebraic approaches.
- As an alternative, we approximated the steady states "tropically" using our recently developed technique on tropical geometry (Samal et. al 2015). We denote them as metastable regimes and have showed elsewhere their association with biological phenotypes (Samal et. al 2016).
- The robust parameters determined from both the approaches show a high

Applications in Computational Systems Biology

Our proposed "tropical" approach has the following benefits over the extant approaches:

- Our method **requires parameter orders instead of precise numerical parameter** values and scales to large networks.
- Our method **does not require numerical simulation** of initial values of the model variables to determine multiple steady states.
- The non robust parameters (e.g. sensitive parameters) can be considered as **putative drug targets**.
- Implications in **model fitting and interpretation** by identifying robust and sensitive parameter sets.
- The tropical solutions cover steady states, quasi-equilibrium, quasi-steady states and more generally metastable slow regimes.

Overview of our approach



$$\frac{dx_i}{dt} = F_i(X, P), 1 \leq i \leq n.$$

X set of variables, **x** is single variable.
P set of parameters e.g. kinetic rate or conservation constants.

$$0 = F_i(X, P), 1 \leq i \leq n.$$

Fix nominal values of ***P*** and determine ***X**** for which the above relation holds.
"classically" = Exactly solving for the steady states.
"tropically" = Approximating the steady states based on tropical geometry (meastable regimes).

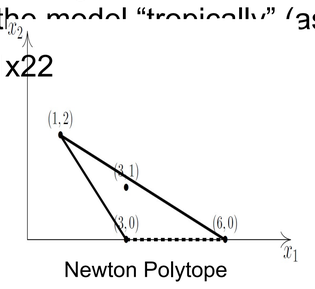
1. Vary ***P*** to ***P'*** and determine ***X*'*** (as per the above step).
2. Compute "distance" between ***X*' and X****
   - The distance is minimum of the pairwise Euclidean in case of multiple steady state solutions.
3. Robust parameter are those where this distance

Solving the Model "Tropically" (Metastable Regimes)

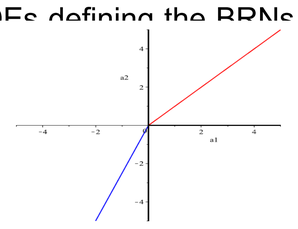
1. The exact steady states were computed by existing implementations of the algebraic techniques in maple programming language. We call this as solving the model "classically".
2. The steady states were approximated using the tropical approach. Here, we call them as metastable regimes. Essentially, the idea is to identify situations when two or several terms of different signs equilibrate each other and dominate all the remaining terms in the right hand side of the ODEs defining the BRNs kinetics. We call this as solving the model "tropically" (as dep

0 = x16 + x13x1 - x13 + x1x22

Input Model



Newton Polytope

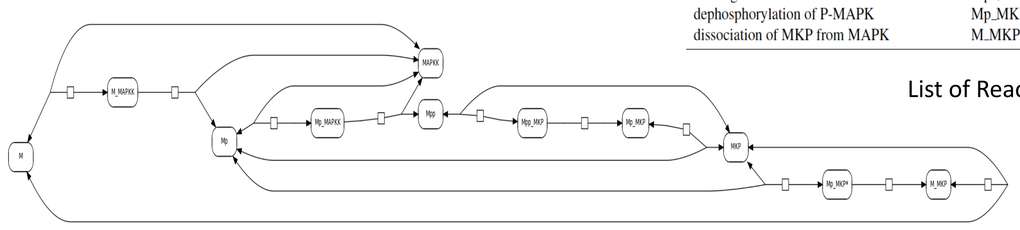


Tropical solutions (metastable regimes) correspond to the half lines (orthogonal to the thick edges of newton polytope)

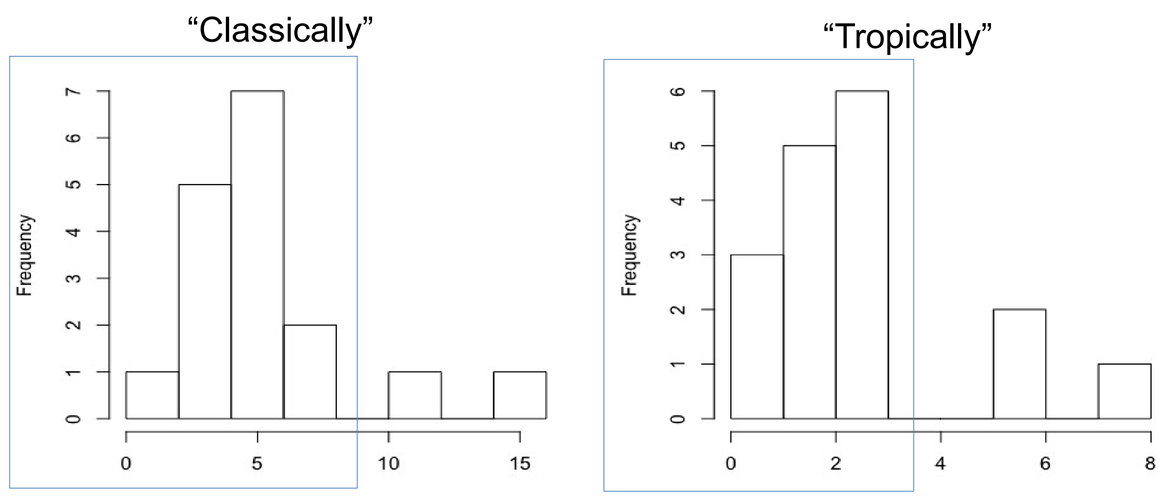
Results

Name	Reaction Equation
binding MAPK and PP-MAPKK	$M + MAPKK \rightleftharpoons M\_MAPKK$
phosphorylation of MAPK	$M\_MAPKK \longrightarrow Mp + MAPKK$
binding PP-MAPKK and P-MAPK	$Mp + MAPKK \rightleftharpoons Mp\_MAPKK$
phosphorylation of P-MAPK	$Mp\_MAPKK \longrightarrow Mpp + MAPKK$
binding MKP and PP-MAPK	$Mpp + MKP3 \rightleftharpoons Mpp\_MKP3$
dephosphorylation of PP-MAPK	$Mpp\_MKP3 \longrightarrow Mp\_MKP3\_dep$
dissociation of MKP from P-MAPK	$Mp\_MKP3\_dep \rightleftharpoons Mp + MKP3$
binding MKP and P-MAPK	$Mp + MKP3 \rightleftharpoons Mp\_MKP3$
dephosphorylation of P-MAPK	$Mp\_MKP3 \longrightarrow M\_MKP3$
dissociation of MKP from MAPK	$M\_MKP3 \rightleftharpoons M + MKP3$

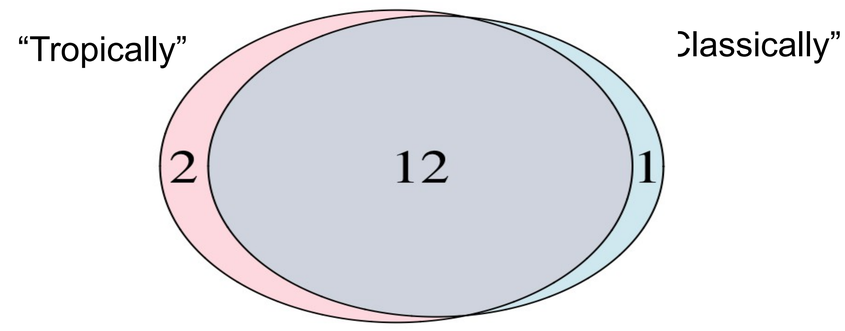
List of Reactions



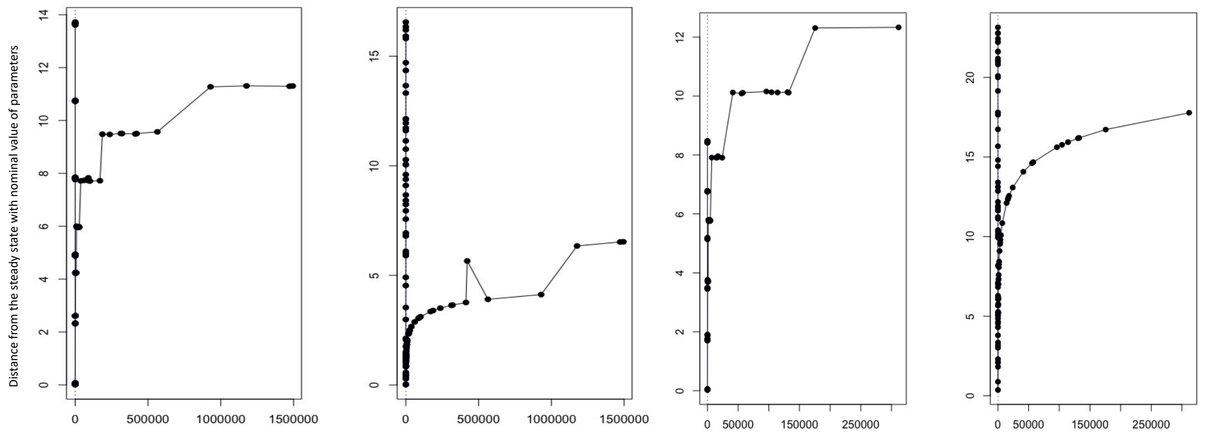
Reaction network of Biomodel BIOMD0000000026 on MAPK Signalling



Distribution of average distances of all the parameters of the model. The distances are determined by perturbing the parameters in log scale and computing the distance between the steady states with perturbed parameters and the steady states with nominal parameter value. Blue boxes are the robust parameters (based on a gap in the distribution).



High overlap among the robust parameters from classical and tropical approaches



Distance between the steady states with the perturbed parameters and the steady states with the nominal value of the parameters.

References

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- Samal, S.S., et al., Geometric analysis of pathways dynamics: Application to versatility of TGF-β receptors. Biosystems, 2016. 149: p. 3-14.

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