Automated tropical algebra reduction and hybridization of biological models

Oscar O. Ortrega[1,2], Shawn Garbett[1], and Carlos F. Lopez[3,*]

***Short Abstract* — We present TroPyc, a python module integrated into the PySB modeling framework that performs automated reduction and hybridization of biological models. It allows identification of key driver interactions of these complex networks and the most important parameters at different time-scales. Additionally, we validated this module with three different apoptosis models (EARM) and report the key species and parameters of these models. Importantly, this novel approach could find new targets for cancer drugs**

***Keywords* — Systems biology, model reduction, tropical algebra, network analysis.**

I. Purpose

The extrinsic apoptosis reaction model (EARM), is a family of novel and previously published models of extrinsic apoptosis, focusing on variant hypotheses for how the Bcl-2 protein family regulates mitochondrial outer membrane permeabilization (MOMP) [1]. These models possess distinct spatial and temporal dynamic behaviors as well as multiple molecular interactions molecules and interaction sites. Due to this complexity, large models are difficult to interpret yet they are necessary to understand the complexity of systems-level behaviors that lead to cell decision processes. In this work we develop an automated formalism employing algebraic geometry paradigms [2] to identify the important parameters as well as the time-dependent execution where multiple parameters commit a cell to apoptosis. We present the TroPyc Python module that interacts with our PySB modeling framework to perform tropical algebra transformations. TroPyc can hybridize and reduce large biochemical models like EARM into simpler models – also known as– dominant subsystems, that employ a quasi-steady state and quasi-equilibrium approximation to reduce the parameter space and therefore facilitate analysis. As shown in Figure 1, the tropicalization approach enables the extraction of signaling activity in a time-dependent manner, whereas this information is obscured in a typical chemical species dynamic plot.

Acknowledgements: This work was supported by NSF MCB 1411482, NIH K22-CA151918, and the Evans Foundation. OOO was supported by a VISP fellowship

[1]Department of Cancer Biology, Vanderbilt University, 2220 Pierce Ave, Nashville TN.

[2]E-mail: oscar.ortega@vanderbilt.edu

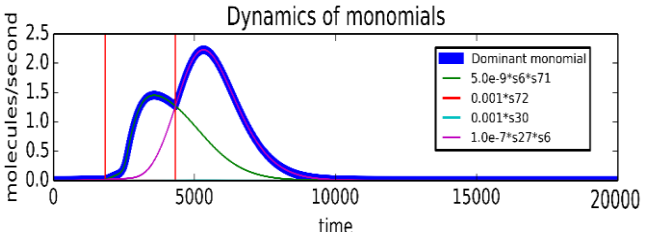

Figure 1. Caspase 3 tropicalization. The red lines identifies the time points where there are sharp transitions between dominant subsystems.

II. Approach

Based on a theoretical analysis by Radulescu *et al* [3], we developed an automated tool to reduce network complexity within the open source PySB framework using tropical algebra. The method consists of a simplification step followed by a tropical algebra calculation step which yields the key driver interactions of a complex network, and the steady state modes that the network can occupy. In addition, state-change drivers can also be identified when comparing multiple network modes. We present validation of the automated algebra tool using three different EARM models: Embedded, direct and indirect [4]. For each model, we identified the driver species in the different time-scales and their related parameter of association or dissociation. Then we validated the relevance of this parameters by changing the parameter value at different time points. We found that when we changed the parameters in time points outside their dominant time-scale, there were no drastic changes in the dynamics of the model. On the other side, when the parameter were changed in time points within their dominance, small changes of the parameter value generated extreme changes in the dynamic behaviors. The results of this analysis could lead to discoveries of new targets for cancer drugs.

References

[1] Lopez, C. F., Muhlich, J. L., Bachman, J. A., & Sorger, P. K. "Extrinsic Apoptosis Reaction Model (EARM)¶." *Extrinsic Apoptosis Reaction Model (EARM) — EARM 2.0 Documentation*. Web

[2] Imre Simon. Recognizable sets with multiplicities in the tropical semiring. Mathematical Foundations of Computer Science (1988), pp. 107–120

[3] Noel V, Grigoriev D, Vakulenko S, and Radulescu O. "Tropical Geometries and Dynamics of Biochemical Networks Application to Hybrid Cell Cycle Models." *Electronic Notes in Theoretical Computer Science* 284 (2012): 75-91.

[4] Lopez, C. F., Muhlich, J. L., Bachman, J. A., & Sorger, P. K. (2013). Programming biological models in Python using PySB. *Molecular Systems Biology*, *9*, 646. doi:10.1038/msb.2013.1

Nothing should be here on page 2! Please limit your abstract to a single page, and create a one-page .pdf file for submission.