Title: Comprehending Biochemical Network Dynamics through Automatic Inference of State Transition Diagrams

Debprakash Patnaik[1], Vandana Sreedharan[2], Yang Cao[1], and Naren Ramakrishnan[1]
[1]Department of Computer Science, Virginia Tech, Blacksburg, VA
[2]Genetics, Bioinformatics, and Computational Biology Program, Virginia Tech, Blacksburg, VA

Abstract

The development process for biochemical network models follows the traditional pipeline of biochemical network → ODE model → numerical simulation → time series data→system dynamics. Understanding how small changes in the original network propagate to cause qualitative differences in dynamics are key issues in model comprehension, iterative model improvement, and validation. We present an automatic approach to summarize time series data from simulations into state transition diagrams capturing the system dynamics. By using clusters of species concentrations to define the "states" and transitions between these states to define the system trajectories, we show how we can reconstruct key dynamical features such as linear state progressions, attractions toward stable states, and even higher level features such as bistability and oscillations. We demonstrate applications to studying the yeast cell cycle progression both in wild-type cells and in mutants which cause cell cycle arrest at different stages. Our algorithm identifies key cell cycle states, transitions between them, and deviations in these transitions among mutants in a completely unsupervised manner. We also analyze a catalog of bistable networks to unravel the system transitions leading upto stable fixed points. Finally, we show how key behavioral features inferred from the state transition diagrams can be connected back to the network topology in a way that cannot be directly inferred from the ODE model or the raw time series dataset. Our approach for network comprehension thus opens up an important algorithmic approach to the toolkit of the systems biologist.