Attractor Analysis of Asynchronous Boolean Models of Signal Transduction Networks

Andreas Ströhlein
Molecular Networks
Attractor analysis of asynchronous Boolean models of signal transduction networks

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Overview

• Motivation
• Approaches
  – synchronous
  – asynchronous
    • ROA
    • GA
    • DA
• Attractor analysis
• Application
• Conclusion
• References
Motivation

Goal: Predictive tool to uncover the dynamic patterns of a biological system under various internal and environmental perturbations
Approaches

• Modeling

• Nodes = Components of a system
• Edges = Interaction between the nodes
Approaches

• continuous, deterministic approach

• ODEs

• well suited for small and well-characterized systems with known kinetic parameters
Approaches

• many unknown components and parameters

• large scale gene regulatory or signal transduction networks
Approaches

• discrete modeling

• Boolean network models
  – Two states for each node (ON/OFF, 0/1)
Synchronous Modeling

• assumes similar time scales

• synchronous update of the node states

• deterministic

• not taking into account the varieties of time scales associated with different types of biological process
Asynchronous Modeling

• more variability to the update order

• ROA - random order asynchronous

• GA - general asynchronous

• DA - deterministic asynchronous
ROA - Random Order
Asynchronous

• stochastic updates

• at each round of update a random ordered sequence of the nodes is selected and the nodes are updated in that order
GA - General Asynchronous

• at each time step a randomly selected node is updated
DA - Deterministic Asynchronous

- predetermined sequence of updates

- preselected time unit $x$ (multiple of time step) for every node

- node is updated at timepoints $k \times x$ ($k$ being any integer)
Attractor Analysis - Definitions

- **Attractor**
  - fixed point or
  - limit cycle
- **state space**
  - all possible states in the system
- **basin of attraction**
  - all the initial states that end up in a certain attractor
Attractor Analysis of Asynchronous Models

• focus on finding fixed points

• identifying the fixed points reachable from nominal (wild-type) initial conditions

• very little research for cycles and their basins of attraction
Saadatpour et al. 2010

• comprehensive comparison of different models
• one synchronous and three asynchronous models
• investigation of ALL possible attractors and their corresponding basins of attraction
Saadatpour et al. 2010

- theoretical analysis
- solving of scalar equations
- markov chain techniques
- numerical simulations
Predicting Essential Components of Signal Transduction Networks: A Dynamic Model of Guard Cell Abscisic Acid Signaling

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Plants both lose water and take in carbon dioxide through microscopic stomatal pores, each of which is regulated by a surrounding pair of guard cells. During drought, the plant hormone abscisic acid (ABA) inhibits stomatal opening and promotes stomatal closure, thereby promoting water conservation. Dozens of cellular components have been identified to function in ABA regulation of guard cell volume and thus of stomatal aperture, but a dynamic description is still not available for this complex process. Here we synthesize experimental results into a consistent guard cell signal transduction network for ABA-induced stomatal closure, and develop a dynamic model of this process. Our model captures the regulation of more than 40 identified network components, and accords well with previous experimental results at both the pathway and whole-cell physiological level. By simulating gene disruptions and pharmacological interventions we find that the network is robust against a significant fraction of possible perturbations. Our analysis reveals the novel predictions that the disruption of membrane depolarizability, anion efflux, actin cytoskeleton reorganization, cytosolic pH increase, the phosphatidic acid pathway, or K⁺ efflux through slowly activating K⁺ channels at the plasma membrane lead to the strongest reduction in ABA responsiveness. Initial experimental analysis assessing ABA-induced stomatal closure in the presence of cytosolic pH clamp imposed by the weak acid butyrate is consistent with model prediction. Simulations of stomatal response as derived from our model provide an efficient tool for the identification of candidate manipulations that have the best chance of conferring increased drought stress tolerance and for the prioritization of future wet bench analyses. Our method can be readily applied to other biological signaling networks to identify key regulatory components in systems where quantitative information is limited.
Li et al. 2006

- signal transduction network in plants
- model of ABA induced stomata closure as a drought response
Li et al. 2006
Simplification

• Assumption: unregulated nodes are in the ON state

• Simplification of Boolean functions of many nodes

• Stabilization of 26 out of 39 nodes in ON/OFF state after eight update steps
13-node sub-network
11-node sub-network
Synchronous Model

• Three attractors found:
  – fixed point (null fixed point, all nodes in OFF state)
  – two limit cycles of period four

• Conclusion: Same holds for the synchronous model of the whole ABA signal transduction network
Random Order
Asynchronous Model

• Additional state transitions possible

• Simplification of the 11-node sub-network
ROA - Simplification
ROA - Simplification

• Essence of the network captured by three nodes
  – $\text{Ca}^{2+}$
  – $\text{Ca}^{2+}$ ATPase
  – CIS

• Forming a coupled positive and negative feedback loop
ROA - State Transition Graph
8-node sub-network
8-node sub-network

• null fixed point

• Conclusion: 11-node sub-network has only one attractor (null fixed point)

• Same as in synchronous model
Comparison Synchronous Model/ROA

Synchronous:
- Two limit cycles
- Majority of the states in the basins of attraction of the limit cycles

Asynchronous:
- All the states in the basin of attraction of the fixed point

• Spurious oscillations in synchronous models
General Asynchronous Model
Deterministic Asynchronous Model

- many different choices of time units
- null fixed point for all choices
- limit cycles for some choices
Node Perturbations

- Perturbations of nodes lead to a reduced closure probability

- PA and S1P knockouts leading to insensitivity
Conclusion

• Insufficient experimental data to say if findings are biologically significant

• Synchronous models are robust (deterministic) but do not represent the variety of time scales in real biological systems
Conclusion

• Simplification must be done efficiently without loosing information

• Conclusions concerning larger networks are often vague assumptions
Conclusion

• Results depend on the choice of the method
• Overlapping but not identical sets of attractors for different updating schemes
• No optimal choice!