

Robustness of the fission yeast cell cycle network

Maria Davidich¹, Stefan Bornholdt²,
Institute for Theoretical Physics, University Bremen, Bremen, Germany
Email¹: davidich@itp.uni-bremen.de
Email²: bornholdt@itp.uni-bremen.de

Abstract

We study a Boolean network model of the cell-cycle of fission yeast (*Schizosaccharomyces Pombe*) based on the known biochemical interaction topology. In addition to the central observation that the biological dynamical pattern of protein activities along the cell-cycle is correctly reproduced by such a simple model, we here study the dynamical robustness of the network. In particular, we consider errors in activation of proteins or nodes in the network and find a robust response of the system. Errors persistent in the model match mutations in experiments.

Introduction

A central goal of systems biology is to create predictive models of the regulatory processes in the living cell. Although cell-wide models are still out of reach, predictive models for small modular molecular networks are a matter of active research. There are different mathematical methods that are used for it, reaching from chemical Monte-Carlo simulations to ordinary differential equations. While these methods can provide detailed information about the system's dynamics, recently they have been complemented by more "coarse-grained" approaches that use fewer biochemical parameters but still are able to reproduce the sequence of states in the biological system. As long as exact timing is not of central interest, Boolean networks proved to be a good simple tool for building predictive models for different organisms. Examples for models are the genetic network of *A. thaliana* [1], the cell-cycle networks of *S. cerevisiae* [2], and the mammalian cell-cycle network [3], as well as the segment polarity gene network in *D. melanogaster* [4].

In ref. [5] we constructed a Boolean network model for the fission yeast cell-cycle network and showed that it reproduces the biological time sequence of protein activities. We analyzed the differences and similarities with the corresponding network in budding yeast. Here, we add a robustness analysis of the system.

A discrete dynamical model of the fission yeast cell cycle network

Let us first describe the Boolean network approach to the fission yeast cell-cycle network [5]. From a literature study the proteins that are key-regulators of the fission yeast cell-cycle were identified. These proteins are assumed to be the nodes of the network where each node i can assume two possible states, 1 or 0, denoting whether the protein is active or not. The biochemical reactions between these proteins have been studied in detail over the last years [6]. Our translation into an interaction graph, where all the interactions are reduced to activation and inhibition, is given in Fig.1, where red links correspond to inhibition and green links to activation. This is the starting point for our discrete dynamical network simulation of this network.

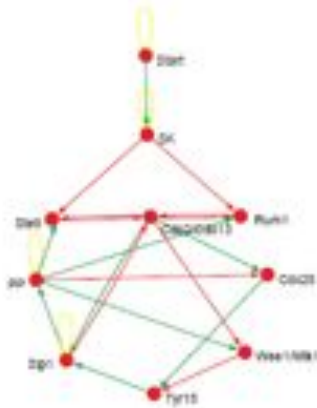


Fig.1 Network model of the fission yeast cell-cycle regulation.

The update rule for the nodes follows the approach in [2], except two special nodes. Slp1 is only activated by a highly active complex Cdc2/Cdc13, which corresponds to both active Cdc2/Cdc13 as well as active Tyr15, since Tyr15 labels the level of activity of Cdc2. This mechanism acts as a barrier for entering mitosis. The second special rule is to add "self-activation" (this node is active if it is not inhibited) to the node Cdc2/Cdc13, as it is otherwise not positively regulated. We also follow [2] by adding "self-degradation" (yellow loops) to those nodes that are not negatively regulated by others, representing the continuous degradation of proteins in the cell, which corresponds to a $\tau_i = -1$. The initial condition correspond to the biological start condition, i.e. all nodes being in the OFF (inactive) state, except for the Start, Ste9, Rum1, and Wee1/Mik1 [7].

Results

The dynamics of this network reproduces the correct time sequence of activation of proteins along the biological cell cycle. The advantage of the model is that the dynamics is based only on the connectivity graph of the network, neglecting all biochemical kinetic parameters. The dynamics of the network is characterized by a dominant attractor that attracts most initial states (71%). This attractor corresponds to the G1 stationary state. All possible basins of attraction of the system are shown in Fig.2, where one can see the state space of all possible network states and all possible dynamical trajectories. The blue arrows show the biological time sequence leading to the G1 fixed point.

An interesting question is how robust the dynamics of the system is under perturbations. In [5] we showed, that under a deviation from the biological pathway by perturbing the activity state of one single protein at one randomly chosen step of the cycle, the system returns to the fixed point G1 in 90 out of 100 possible cases. This can be interpreted as considerable robustness in the fission yeast cell-cycle network, meaning that there is an increased probability to stay in the attractor basin of the biological fixed point when perturbing states along the biological trajectory.

Let us further explore the influence on the dynamics of the cell-cycle of the disturbed biological initial state, starting from all possible initial conditions Hamming distance one from the biological initial state. We find that in seven cases out of nine the system still reaches the G1 fixed point. Those two initial conditions that deviate from biological trajectory coincide with errors of Slp1 and Cdc25 expressions. These two proteins are responsible for the exit of mitosis, and the errors sequences in division of the cell with damaged structure of DNA and thereby death. This also corresponds to the experimental data [8].

Also Wee1 mutations have been investigated recently. Normal functioning of this protein is responsible for the growth of the cell during the G1/S/G2 phases. In case it is damaged (deactivated), the dynamics proceeds to forced mitosis [9]. Such cells are smaller than normal, however they are viable. Modeling this mutation/deactivation of Wee1 with the Boolean network model confirms this, showing that the starting phases are skipped and the process enters mitosis, eventually reaching the G1 fixed point.

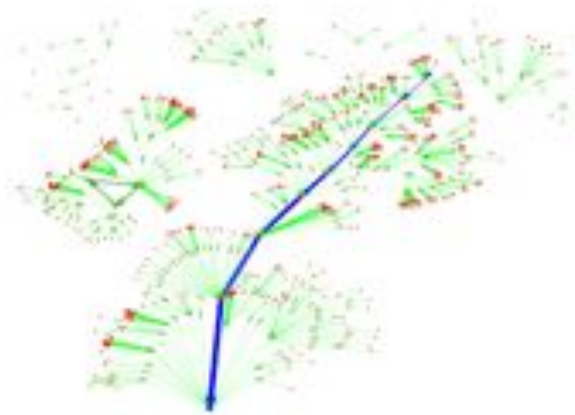


Fig.2. State space of the 1024 possible network states (red dots) and their dynamical trajectories. Each circle corresponds to one network state with each of the ten proteins being in one specific activation state (active/inactive). Arrows between the network states indicate the direction of the dynamical flow from one network state to its subsequent state. The largest attractor tree corresponds to all network states flowing to the G1 fixed point (blue node). The cell-cycle sequence is shown with blue arrows.

To summarize, the Boolean network model of the fission yeast cell-cycle reproduces biological properties of the system, both, the biological trajectory, as well as possible lethal and non-lethal mutations, modeled as perturbations of network states.

References

- [1] Espinosa-Soto C, Padilla-Longoria P, et al. (2004) *Plant Cell* 16: 2923-2939.
- [2] Li F, Long T, et al. (2004) *Proc Natl Acad Sci U S A* 101(14): 4781-4786.
- [3] Faure A, Naldi A, et al. (2006) *Bioinformatics* 22(14): e124-e131.
- [4] Albert R, Othmer HG (2003) *J Theor Biol* 223: 1-18.
- [5] Davidich M, Bornholdt S (2007) www.arXiv.org [q-bio.MN] arXiv:0704.2200
- [6] Correabordes J, Nurse P (1995) *Cell* 83:1001-1009.
- [7] Tyson JJ, Chen KC, Novak B (2003) *Curr Op Cell Biol* 15: 221-231.
- [8] Furnari B, Rhind N, Russell P (1997) *Science*, 227:1495-1497.
- [9] Kim SH, Lin DP, et al., (1998) *Science*, 279: 1045-1047.