Proceedings of the 8th International Symposium on Mathematical Morphology,
Rio de Janeiro, Brazil, Oct. 10 –13, 2007, MCT/INPE, v. 2, p. 79–80.
http://urlib.net/dpi.inpe.br/ismm@80/2007/05.23.01.03

A structural PGN model for control of cell-cycle Progression

Nestor Walter Trepode[1],
Hugo Aguirre Armelin[2], Michael Bittner[3],
Junior Barrera[1], Marco Dimas Gubitoso[1]
and Ronaldo Fumio Hashimoto[1]

[1] *Institute of Mathematics and Statistics, University of São Paulo, Brazil.* {walter,jb,gubi,ronaldo}@ime.usp.br

[2] *Institute of Chemistry, University of São Paulo, Brazil.* haarmeli@iq.usp.br

[3] *Translational Genomics Research Institute (TGen), Phoenix, AZ, USA.* mbittner@tgen.org

1. Introduction

The cell division cycle comprises a sequence of phenomena controlled by a stable and robust genetic network. A Probabilistic Genetic Network (PGN) is a particular family of Markov chains with some additional properties (axioms) [1, 2]. We applied a PGN to construct an hypothetical model with a dynamical behavior displaying the degree of robustness typical of the biological cell-cycle. The structure of our PGN model was inspired in well established biological facts such as the existence of integrator subsystems, negative and positive feedback loops and redundant signaling pathways. Our model represents genes' interactions as stochastic processes and presents strong robustness in the presence of moderate noise and parameters fluctuations [3, 4]. A recently published deterministic yeast cell-cycle model [5] does not perform as well as our PGN model, even upon moderate noise conditions. In addition, self stimulatory mechanisms can give our PGN model the possibility of having a pacemaker activity similar to the observed in the oscillatory embryonic cell cycle [6].

2. Our structural model for control of cell-cycle progression

The architecture of our cell-cycle control model is depicted in Figure 1, showing the forward and feedback regulatory signals between gene layers ($\mathbf{s}, \mathbf{T}, \mathbf{v}, \mathbf{w}, \mathbf{x}, \mathbf{y}$ and $\mathbf{z}$), that determine the system's dynamic behavior. These gene layers represent consecutive stages taking place along the classical cell-cycle phases G_1, S, G_2 and M, and are comprised by the genes — state variables — expressed during the execution of each stage. They are grouped into the two main parts: *i*) G_1 phase — layer $\mathbf{s}$ — that represents the cell growth phase immediately before the onset of DNA replication (i.e. S phase), during

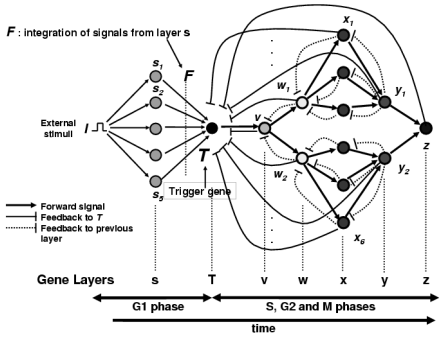


Figure 1. Cell-cycle network architecture.

which the cell responds to external regulatory stimuli (*I*) and *ii*) S, G_2 plus M phases — layers $\mathbf{T}$, $\mathbf{v}$, $\mathbf{w}$, $\mathbf{x}$, $\mathbf{y}$ and $\mathbf{z}$ — that goes from DNA replication to mitosis. The S phase trigger gene T represents an important cell cycle check-point, interfacing G_1 phase regulatory signals and the initiation of DNA replication. The signal F stands for integration, at the trigger gene T, of activator signals from layer $\mathbf{s}$. Our basic assumption implies that the cell cycle control system is comprised of modules of parallel sequential waves of gene expression (layers $\mathbf{s}$ to $\mathbf{z}$) organized around a check point (trigger gene T) that integrates forward and feedback signals. For example, within a module, the trigger gene T balances forward and feedback signals to avoid initiation of a new wave of gene expression while a previous one is still going through the cell cycle. A number of check point modules, across cell cycle, regulate cell growth and genome replication during the sequential G_1, S and G_2 phases and cell duplication via mitosis.

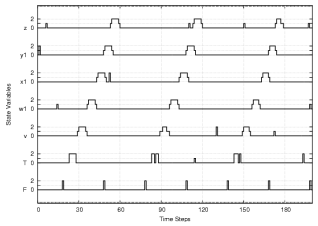
2.1 Experimental results

We simulated both, the yeast cell-cycle model [5] and our structural cell-cycle progression control model, as a PGN with probability $P = 0.99$ and driven by different excitation signals F: a unique activation pulse ($F = 2$), then pulses of F of increasing frequency (decreasing period), i.e. F activator pulses arriving each time more frequently (in each simulation), and, finally, with a constant signal $F = 2$.

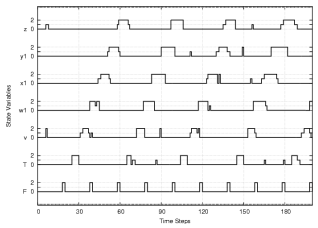
In the yeast cell-cycle model, driven by a single activation pulse, after the cycle should have ended,

Proceedings of the 8th International Symposium on Mathematical Morphology,
Rio de Janeiro, Brazil, Oct. 10 –13, 2007, MCT/INPE, v. 2, p. 79–80.
http://urlib.net/dpi.inpe.br/ismm@80/2007/05.23.01.03

there is a large amount of noise producing spurious waveforms when the system should remain in a stationary state. In the other simulations of this model (increasing frequency activator pulses), the signal waveforms appear to be completely distorted [4].



(a) F = Period 30 oscillator.



(b) F = Period 20 oscillator (model with random delays in the regulatory signals [4]).

Figure 2. Simulation of our three level PGN cell-cycle progression control model with 1% of noise (PGN with $P = 0.99$) when activator pulses of F can arrive before the previous cycle has ended.

In the simulations of our model, a single pulse of F makes the system go through all its cycle stages and, after that, all signals remain at zero level with a very little amount of noise. When the pulses arrive more frequently, a new cycle is started *only* if the previous one has finished (Figure 2). No spurious signal waves are generated by noise nor the forward cell-cycle signal is stopped by it (i.e. all normally initiated cycles are finished). If a very frequent train of pulses triggers gene P before the ongoing cycle is finished, that signal is stopped at the following gene layers by the inter-layer feedbacks. Only a very frequent excitation (period 3, 2 or constant F) is able to take the system out of its normal behavior.

3. Discussion

Our cell-cycle progression control model was able to represent some behavioral properties of the real biological system, such as: (i) sequential waves of gene expression; (ii) stability in the presence of variable excitation; (iii) robustness under noisy parameters: (iii-i) prediction by an almost deterministic stochastic rule; (iii-ii) stochastic choice of an almost deterministic stochastic prediction rule (random delays), and (iv) auto stimulation by means of positive feedback [4]. The presence of numerous negative feedback loops in the model provide stability and robustness. They warrant that, under multiple noisy perturbation patterns, the system is able to automatically correct external stimuli that could destroy the cell. The inclusion of positive feedback can make our model able of exhibiting a pacemaker activity, like the one observed in embryonic cells. The parallel structure of the system architecture represents biological redundancy, which increases system fault tolerance.

Acknowledgments

This work was partially supported by grants 99/07390-0, 01/14115-7, 03/02717-8 and 05/00587-5 from FAPESP, Brazil, and by grant 1 D43 TW07015-01 from The National Institutes of Health, USA.

References

[1] J. Barrera, R. M. Cesar Jr, D. C. Martins Jr, E. F. Merino, R. Z. N. Vêncio, F. G. Leonardi, M. M. Yamamoto, and C. A. de B. Pereira, *A New Annotation Tool for Malaria Based on Inference of Probabilistic Genetic Networks*, CAMDA, 2004, pp. 36–40.

[2] J. Barrera, R. M. Cesar Jr, D. C. Martins Jr, R. Z. N. Vêncio, E. F. Merino, M. M. Yamamoto, F. G. Leonardi, and C. A. de B. Pereira, *Constructing Probabilistic Genetic Networks of Plasmodium falciparum from Dynamical Expression Signals of the Intraerythrocytic Development Cycle*, Methods of Microarray Data Analysis V, 2007, pp. 11-26.

[3] N. W. Trepode, H. A. Armelin, M. Bittner, J. Barrera, M. D. Gubitoso, and R. F. Hashimoto, *Modeling Cell Cycle Regulation by Discrete Dynamical Systems*, GENSIPS 2005: IEEE International Workshop on Genomic Signal Processing and Statistics, 2005.

[4] N. W. Trepode, H. A. Armelin, M. Bittner, J. Barrera, M. D. Gubitoso, and R. F. Hashimoto, *A Robust Structural PGN Model for Control of Cell-Cycle Progression Stabilized by Negative Feedbacks*, EURASIP Journal on Bioinformatics and Systems Biology **2007** (2007), Article ID 73109.

[5] F. Li, T. Long, Y. Lu, Q. Ouyang, and C. Tang, *The Yeast Cell-Cycle Network is Robustly Designed*, PNAS **101** (2004), 4781–4786.

[6] J. R. Pomerening, S. Y. Kim, and J. E. Ferrell Jr., *Systems-Level Dissection of the Cell-Cycle Oscillator: Bypassing Positive Feedback Produces Damped Oscillations*, Cell **122** (2005), 565–578.