

LNCS 3516

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Computational Science – ICCS 2005

**5th International Conference
Atlanta, GA, USA, May 2005
Proceedings, Part III**

3 Part III

 Springer

Commenced Publication in 1973

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5th International Conference
Atlanta, GA, USA, May 22-25, 2005
Proceedings, Part III



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Library of Congress Control Number: 2005925759

CR Subject Classification (1998): D, F, G, H, I, J, C.2-3

ISSN	0302-9743
ISBN-10	3-540-26044-7 Springer Berlin Heidelberg New York
ISBN-13	978-3-540-26044-8 Springer Berlin Heidelberg New York

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Printed in Germany

Typesetting: Camera-ready by author, data conversion by Scientific Publishing Services, Chennai, India
Printed on acid-free paper SPIN: 11428862 06/3142 5 4 3 2 1 0

Modelling Dynamics of Genetic Networks as a Multiscale Process

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Abstract. A key phenomenon in the dynamics of genetic networks is the cell cycle. In the study of this phenomenon, an important task is to understand how many processes, acting on different temporal and spatial scales, interact in the cell.

In this paper we deal with the problem of modelling cell cycles. We start our analysis from the Novak-Tyson model and apply this deterministic model to simulate relative protein concentrations in several different living systems, including *Schizosaccharomyces pombe* to validate the results. Then we generalize the model to account for the nonlinear dynamics of a cell division cycle, and in particular for special events of cell cycles. We discuss the obtained results and their implications on designing engineered regulatory genetic networks and new biological technologies.

1 Introduction

Cells process information in complex ways. During the cell cycle, an eukaryotic cell duplicates all of its components and separates them into two daughter cells. This process is composed of four phases: G1 phase in which size of the cell is increased by producing RNA and synthesizing protein, S phase in which DNA are replicated, G2 phase in which the cell continues to produce new proteins and grows in size, and M (mitosis) phase in which DNA are separated and cell division takes place [1], [3]. From the outset, we are in a situation where we have to deal with different biological events with different spatial and temporal scales.

The problem of modelling dynamics of genetic networks, including those for cell cycles, has been actively addressed in the past decades [2]. New improved models have been recently developed with increasing capability to predict competitively experimental results [3]. The Novak-Tyson model for a cell cycle in [3] contains over 40 parameters that are of the same units but vary from less than 10^{-2} to 35. A stochastic generalization of that model was presented in [4].

In the present work, we start our analysis from the Novak-Tyson model and apply this deterministic model to simulate relative protein concentrations in several different living systems. Then, we generalize the model to account for the nonlinear dynamics of a cell division cycle, and in particular for special

events of cell cycles. We show that the effects of such fluctuations may have important implications on designing engineered regulatory genetic networks due to the sensitivity of the model to parametrization processes.

2 Mathematical Models of Cell Cycles

Based on the original Novak-Tyson model, in this section, we develop a new model that accounts for fluctuations of concentrations in response to the multi-scale character of cellular activities.

2.1 The Novak-Tyson Model

With $x_1(t) = Cdc13_T(t)$, $x_2(t) = preMPF(t)$, $x_3(t) = Ste9(t)$, $x_4(t) = Slp1_T(t)$, $x_5(t) = Slp1(t)$, $x_6(t) = IEP(t)$, $x_7(t) = Rum1_T(t)$, $x_8(t) = SK(t)$ and $MPF(t)$ denoting the relative concentrations of the corresponding proteins, and $x_9(t) = M(t)$ the mass of the cell in the cell cycle, the equations and parameters in the Novak-Tyson model are given in Table 1 where the time t for variables x_i , $i = 1, 2, \dots, 9$; MPF , TF , $Trimer$ and Σ is dropped.

Table 1. The Novak-Tyson Model. All constants have units min^{-1} , except the J 's and K_{diss} which are dimensionless

$\frac{d}{dt}x_1 = k_1x_9 - (k'_2 + k''_2x_3 + k'''_2x_5)x_1$	(1)	$k_1 = k'_2 = 0.03, k''_2 = 1.0, k'''_2 = 0.1;$
$\frac{d}{dt}x_2 = k_{wee}(x_1 - x_2) - k_{25}x_2$		$k'_3 = 1.0, k''_3 = 10.0, J_3 = 0.01,$
$\quad - (k'_2 + k''_2x_3 + k'''_2x_5)x_2$	(2)	$k'_4 = 2.0, k_4 = 35.0, J_4 = 0.01;$
$\frac{d}{dt}x_3 = (k'_3 + k''_3x_5) \frac{1-x_3}{J_3+1-x_3} - (k'_4x_8 + k_4MPF) \frac{x_3}{J_4+x_3}$	(3)	$k'_5 = 0.005, k''_5 = 0.3, J_5 = 0.3,$
$\frac{d}{dt}x_4 = k'_5 + k''_5 \frac{MPF^4}{J_5^4+MPF^4} - k_6x_4$	(4)	$k_6 = 0.1, k_7 = 1.0, k_8 = 0.25,$
$\frac{d}{dt}x_5 = k_7x_6 \frac{x_4-x_5}{J_7+x_4+x_5} - k_8 \frac{x_5}{J_8+x_5} - k_6x_5$	(5)	$J_7 = J_8 = 0.001; k_9 = 0.1, k_{10} = 0.04,$
$\frac{d}{dt}x_6 = k_9MPF \frac{1-x_6}{J_9+1-x_6} - k_{10} \frac{x_6}{J_{10}+x_6}$	(6)	$J_9 = J_{10} = 0.01; k_{11} = 0.1, k_{12} = 0.01,$
$\frac{d}{dt}x_7 = k_{11} - (k_{12} + k'_{12}x_8 + k''_{12}MPF)x_7$	(7)	$k'_{12} = 1, k''_{12} = 3, K_{diss} = 0.001;$
$\frac{d}{dt}x_8 = k_{13}TF - k_{14}x_8$	(8)	$k_{13} = k_{14} = 0.1; k_{15} = 1.5, k'_{16} = 1,$
$\frac{d}{dt}x_9 = \mu x_9$	(9)	$k'_{16} = 2, J_{15} = J_{16} = 0.01;$
$Trimer = \frac{2x_1x_7}{\Sigma + \sqrt{\Sigma^2 - 4x_1x_7}}$	(10)	$V_{awe} = 0.25, V_{iwe} = 1,$
$MPF = \frac{x_1}{(x_1-x_2)(x_1-Trimer)}$	(11)	$J_{awe} = J_{iwe} = 0.01;$
$TF = GK(k_{15}x_9, k'_{16} + k''_{16}MPF, J_{15}, J_{16})$	(12)	$V_{a25} = 1, V_{i25} = 0.25,$
$k_{wee} = k'_{wee} + (k''_{wee} - k'_{wee})GK(V_{awe}, V_{iwe}MPF, J_{awe}, J_{iwe})$	(13)	$J_{a25} = J_{i25} = 0.01; k'_{wee} = 0.15,$
$k_{25} = k'_{25} + (k''_{25} - k'_{25})GK(V_{a25}MPF, V_{i25}, J_{a25}, J_{i25})$	(14)	$k''_{wee} = 1.3, k'_{25} = 0.05, k''_{25} = 5;$
where $\Sigma = x_1 + x_7 + K_{diss}$ and		$\mu = 0.005.$
$GK(a, b, c, d) = \frac{2ad}{b-a+bc+ad+\sqrt{(b-a+bc+ad)^2-4ad(b-a)}}.$		

2.2 The Generalized Model with Fluctuations

Since a cell cycle involves nonlinear changes of the protein concentrations related to multiple spatial and temporal scales, the regulation of cellular activities

contains a degree of uncertainty [3], [4]. Specifically, at the G1 phase, *Ste9* and *Rum1* are activated while *Slp1* and *Cdc13_T* are reducing rapidly. From the results of the deterministic model and experimental observations, the magnitudes of *Ste9*, *Cdc13_T* and *Slp1* are large enough to introduce fluctuations and the fluctuations of their derivatives are expected. *SK* is also active at the latter part of the G1 phase. During the S phase which is shorter than G1 and G2 phases but much longer than M phase, the magnitudes of *Cdc13_T* and *preMPF* are large enough to generate fluctuations of their changing rates. During the G2 phase, the magnitudes of *Cdc13_T* and *preMPF* continue to increase. In the M phase, the magnitudes of *Cdc13_T*, *preMPF* and *slp1* changes rapidly and are large enough to introduce fluctuations. *IEP* is also active in the M phase.

If the magnitude of the relative concentration of a protein $x_i(t)$ is beyond certain value (we use 0.3 for such a value in this paper), we need to modify the right hand sides (RHSs) of equations (1)–(9). Based on the experimental results (see Fig. 1) and taking into account that the period of the cell cycle is about $T = 138.63$ minutes [3], we suggest to multiply the RHSs of equations (1)–(9) by the functions $f_1(t)$, $f_2(t)$, \dots , $f_9(t)$ respectively, where

$$f_j(t) = \begin{cases} 1 + r, & kT \leq t \leq kT + \alpha_j \text{ or } kT + \beta_j \leq t \leq (k+1)T; \\ 1.0, & \text{otherwise,} \end{cases} \quad j = 1, 5; \quad (15)$$

$$f_\ell(t) = \begin{cases} 1 + r, & kT + \gamma_\ell \leq t \leq kT + \lambda_\ell; \\ 1.0, & \text{otherwise,} \end{cases} \quad \ell = 2, 3, 6, 8; \quad (16)$$

$$f_4(t) = f_7(t) = 1.0; \quad f_9(t) = 1 + r, \quad (17)$$

k is a nonnegative integer, r is a control parameter that provides us with the amplitude of fluctuations, $\alpha_1 = 3$, $\beta_1 = 20$, $\alpha_5 = 15$, $\beta_5 = T - 5$, $\gamma_2 = 10$, $\lambda_2 = T$, $\gamma_3 = 0$, $\lambda_3 = 20$, $\gamma_6 = T - 10$, $\lambda_6 = T$, $\gamma_8 = 10$ and $\lambda_8 = 20$. Note that the choice of $f_i(t)$ for $i = 1, \dots, 9$ is not unique, but the above choice for $r = 0$ is consistent with experimentally confirmed results of [3].

3 Computational Experiments

Both models, described in the previous section, have been implemented in MATLAB. We applied stiff solvers to deal efficiently with numerical difficulties caused by variability of model parameters. The initial conditions in all experiments are $x(0) = (0.45, 0, 1.0, 0, 2.1, 0, 0.05, 0, 1.0)$. In our first set of experiments, we use the deterministic Novak-Tyson model. The results with this model are presented in Fig. 1. Here and in all figures that follow we present two cycles. We observe that the relative concentrations of proteins are qualitatively the same as those obtained in [3], given differences of initial conditions. Replacing k''_{wee} (parameters k''_{wee} and k''_{25} are responsible for rate of tyr-phosphorylation and dephosphorylation) by 0.3 in the above model as suggested in [3], we get a model for the cell cycle of *Wee1⁻* mutants. The results obtained in this case are presented in Fig. 2. We can see that the relative concentrations of *Cdc13_T*, *MPF* and *preMPF*

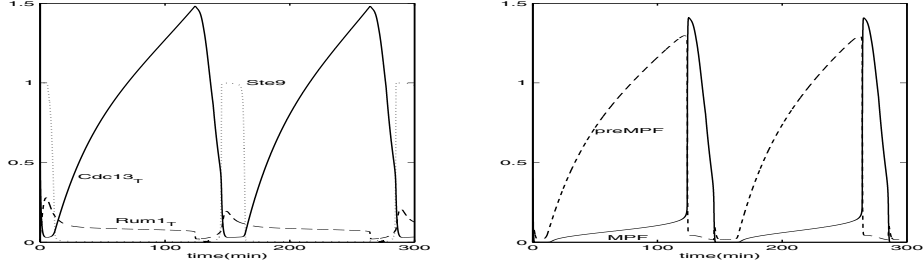


Fig. 1. Numerical simulation of the model in Section 2.1

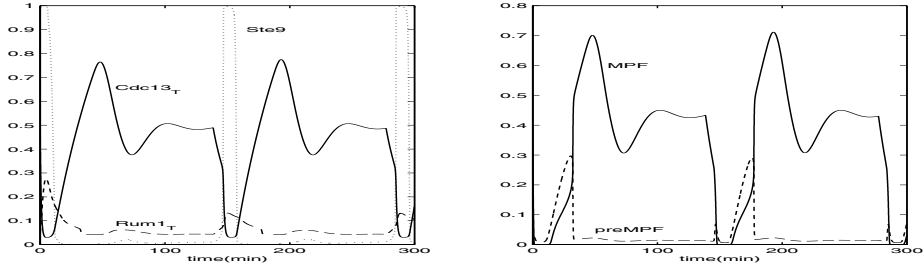


Fig. 2. Numerical simulation of the model with $k''_{wee} = 0.3$

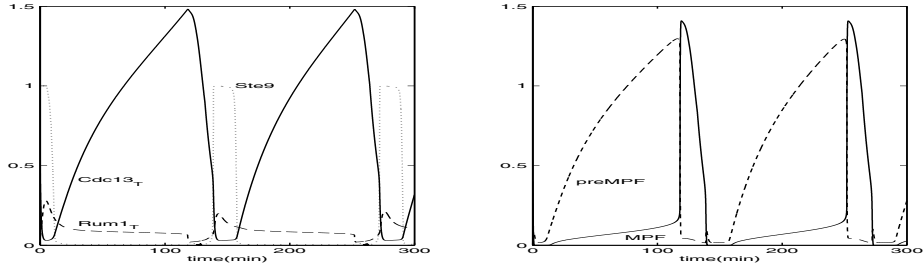


Fig. 3. Numerical simulation of the generalized model with $r = 0.05$

in Fig. 2 are quite different from those in Fig. 1. We have also analyzed the situations with $k''_{wee} = 0.3$ and $k''_{25} = 0.02$, as well as with $k''_{25} = 0.02$, keeping k''_{wee} the same as in our first model. In both cases, noticeable changes in relative *MPF* were observed.

In our second set of experiments, we use the generalized model given in Section 2.2. Setting sequentially $r = 0.001$, $r = 0.005$, $r = 0.01$ and $r = 0.05$ in (15)–(17), we obtained cell cycles with reduced cycle times. The results for two cycles for $r = 0.05$ are shown in Fig. 3. They demonstrate that it is possible to regulate the cell cycle by adjusting the perturbation control parameter r .

4 Conclusions

In this paper, we proposed a new model of cell cycle processes. The model takes into account special events during the cell cycle. The developed methodology can also be used to guide investigations on multiscale phenomena in designing engineered regulatory genetic networks and new biological technologies.

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Table of Contents – Part III

Workshop on “Simulation of Multiphysics Multiscale Systems”

Multiscale Finite Element Modeling of the Coupled Nonlinear Dynamics of Magnetostrictive Composite Thin Film <i>Debiprosad Roy Mahapatra, Debi Prasad Ghosh, Gopalakrishnan Srinivasan</i>	1
Large-Scale Fluctuations of Pressure in Fluid Flow Through Porous Medium with Multiscale Log-Stable Permeability <i>Olga Soboleva</i>	9
A Computational Model of Micro-vascular Growth <i>Dominik Szczerba, Gábor Székely</i>	17
A Dynamic Model for Phase Transformations in 3D Samples of Shape Memory Alloys <i>D.R. Mahapatra, R.V.N. Melnik</i>	25
3D Finite Element Modeling of Free-Surface Flows with Efficient $k - \epsilon$ Turbulence Model and Non-hydrostatic Pressure <i>Célestin Leupi, Mustafa Siddik Altinakar</i>	33
Cluster Computing for Transient Simulations of the Linear Boltzmann Equation on Irregular Three-Dimensional Domains <i>Matthias K. Gobbert, Mark L. Breitenbach, Timothy S. Cale</i>	41
The Use of Conformal Voxels for Consistent Extractions from Multiple Level-Set Fields <i>Max O. Bloomfield, David F. Richards, Timothy S. Cale</i>	49
Nonlinear OIFS for a Hybrid Galerkin Atmospheric Model <i>Amik St.-Cyr, Stephen J. Thomas</i>	57
Flamelet Analysis of Turbulent Combustion <i>R.J.M. Bastiaans, S.M. Martin, H. Pitsch, J.A. van Oijen, L.P.H. de Goey</i>	64
Entropic Lattice Boltzmann Method on Non-uniform Grids <i>C. Shyam Sunder, V. Babu</i>	72

A Data-Driven Multi-field Analysis of Nanocomposites for Hydrogen Storage	
<i>John Michopoulos, Nick Tran, Sam Lambrakos</i>	80
Plug and Play Approach to Validation of Particle-Based Algorithms	
<i>Giovanni Lapenta, Stefano Markidis</i>	88
Multiscale Angiogenesis Modeling	
<i>Shuyu Sun, Mary F. Wheeler, Mandri Obeyesekere, Charles Patrick Jr</i>	96
The Simulation of a PEMFC with an Interdigitated Flow Field Design	
<i>S.M. Guo</i>	104
Multiscale Modelling of Bubbly Systems Using Wavelet-Based Mesh Adaptation	
<i>Tom Liu, Phil Schwarz</i>	112
Computational Study on the Effect of Turbulence Intensity and Pulse Frequency in Soot Concentration in an Acetylene Diffusion Flame	
<i>Fernando Lopez-Parra, Ali Turan</i>	120
Application Benefits of Advanced Equation-Based Multiphysics Modeling	
<i>Lars Langemyr, Nils Malm</i>	129
Large Eddy Simulation of Spanwise Rotating Turbulent Channel and Duct Flows by a Finite Volume Code at Low Reynolds Numbers	
<i>Kursad Melih Guleren, Ali Turan</i>	130
Modelling Dynamics of Genetic Networks as a Multiscale Process	
<i>Xilin Wei, Roderick V.N. Melnik, Gabriel Moreno-Hagelsieb</i>	134
Mathematical Model of Environmental Pollution by Motorcar in an Urban Area	
<i>Valeriy Perminov</i>	139
The Monte Carlo and Molecular Dynamics Simulation of Gas-Surface Interaction	
<i>Sergey Borisov, Oleg Sazhin, Olesya Gerasimova</i>	143
Workshop on “Grid Computing Security and Resource Management”	
GIVS: Integrity Validation for Grid Security	
<i>Giuliano Casale, Stefano Zanero</i>	147