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NONLINEAR DYNAMICS OF CELL CYCLES WITH STOCHASTIC MATHEMATICAL MODELS

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Cell cycles are fundamental components of all living organisms and their systematic studies extend our knowledge about the interconnection between regulatory, metabolic, and signaling networks, and therefore open new opportunities for our ultimate efficient control of cellular processes for disease treatments, as well as for a wide variety of biomedical and biotechnological applications. In the study of cell cycles, nonlinear phenomena play a paramount role, in particular in those cases where the cellular dynamics is in the focus of attention. Quantification of this dynamics is a challenging task due to a wide range of parameters that require estimations and the presence of many stochastic effects. Based on the originally deterministic model, in this paper we develop a hierarchy of models that allow us to describe the nonlinear dynamics accounting for special events of cell cycles. First, we develop a model that takes into account fluctuations of relative concentrations of proteins during special events of cell cycles. Such fluctuations are induced by varying rates of relative concentrations of proteins and/or by relative concentrations of proteins themselves. As such fluctuations may be responsible for qualitative changes in the cell, we develop a new model that accounts for the effect of cellular dynamics on the cell cycle. Finally, we analyze numerically nonlinear effects in the cell cycle by constructing phase portraits based on the newly developed model and carry out a parametric sensitivity analysis in order to identify parameters for an efficient cell cycle control. The results of computational experiments demonstrate that the metabolic events in gene regulatory networks can qualitatively influence the dynamics of the cell cycle.

Keywords: Cell Cycle Models and Control; Complex Dynamic Systems; Stochastic Effects; Bio-nanotechnology; Cell Engineering and Disease Treatment; Spatio-temporal Interactions; Systems Biology and Systems Science; Coupled Phenomena in Biological Systems; Multiscale Processes.

1. Introduction

Cell cycles are fundamental components of life. They are one of the most important biological processes that provide a key to our knowledge of a large number of genes and networks of protein interactions.[1] They provide an example of complex

dynamic systems[2] in the area of biological sciences in general and systems biology in particular. Their studies assisted us in a better understanding of the multifunctional and multiscale components involved in fundamental disease processes, and finally led us to a realization that an integrated coupled approach in the dynamic analysis of signaling, metabolic and regulatory networks is required.[3]

Cell cycles consist of growth and division of cells which should be in balance for producing a homeostasis of cell size, for responding adequately to the availability of proteins and nutrients, and for other key activities of living organisms. All biological processes, phenomena, and systems are cell-cycle dependent and the understanding of this dependency and its ultimate *control* is one of the most fundamental problems in biological sciences. Indeed, as the key elements in protein interactions, cell cycles provide an elementary dynamics mechanism for all that lives. Extensive research into their influence on neuronal, cardiovascular, and other activities confirm that their understanding and control is critical to disease treatment. At the same time, it is now understood that ultimately a systems science approach is needed for studying cell-cycle associated (coupled) processes as the availability of certain critical proteins can alter substantially or even freeze the cell cycles.

The eukaryotic cell is a key example of a nanomachine where cell cycles are the key to its functioning. During cell cycles, eukaryotic cells duplicate all of their components and separate them into two daughter cells. Every cell cycle is divided into four phases: G1 (gap) phase in which the size of the cell is increased by producing RNA and synthesizing protein, S phase in which DNA is replicated, G2 (gap) phase in which the cell continues to produce new proteins and to grow in size, and M (mitosis) phase in which DNA is separated and cell division takes place.[4,5] The cell cycle involves different biological events on different spatial and temporal scales. It is a complex multiscale process, and although processes with multiple scales appear frequently in many branches of science and engineering,[6–10] the cellular processes have their own specifics and they are always part of a bigger picture. It is known that the activity level of the M-phase Promoting Factor (MPF), a heterodimer which consists of a catalytic (Cdc2) and a regulatory cyclin subunit (Cdc13),[5,11,12] distinguishes the cell cycle between mitosis and interphase. When the amount of cyclin Cdc13 attains a certain value, MPF activity increases abruptly and the cell cycle enters M (mitosis) phase. The amount of cyclin Cdc13 needed for the cell cycle to enter M (mitosis) phase is larger than the amount of cyclin Cdc13 needed for the cell cycle to stay in M phase. This keeps the cell cycle out of the G2 phase. Such a hysteresis type switching behavior plays an important role in living cells.

Nonlinear phenomena such as hysteresis have been attracting an inreasing attention of researchers studying biological organisms.[5,13–20] Although it has been recognized for a long time that stochastic models provide a key tool in the analysis of many systems in biology[21,22] and in the transcriptional regulation modeling,[23–35] most models for cell hysteresis and related nonlinear phenomena, discussed so far

in the literature, are based on deterministic models.[5,15,17,19,36] In this paper, we analyze such nonlinear phenomena with both deterministic and stochastic models, focusing on the cell cycle dynamics, and construct phase portraits of MPF based on the associated models.

During the last decade, substantial research efforts have been directed towards the development of improved models for cell cycles (see, e.g. Refs. 5, 12, 19, 38–48, among many others). Recall, for example, that Novak and Tyson, who presented their deterministic model of regulatory genetic networks for a cell cycle, based their consideration on a system of differential-algebraic equations. The authors provided parameter estimations for their model based on experimental observations[5] and the analysis of a model for eukaryotic cell-cycle regulations has recently been carried out.[49] Although stochastic mathematical models are well accepted for the modeling of other components of life, as well as a variety of complex physical systems with Monte Carlo type simulations,[50,51] nonlinear stochastic mathematical models for cell cycles are at the beginning of their development. Recall that in the description of the dynamics of DNA molecules[52] and similar systems[53] the use of stochastic mathematical models is already quite extensive, while the development of stochastic models describing time-dependent RNA silencing phenomena,[54] RNA-based nanostructures for scaffolding and drug delivery[55] as well as protein interactions has been underway for quite some time. By now, it is clear that due to activities associated with synthesis and degradation by various reactions among other things, we should also account for stochasticity in constructing mathematical models for the dynamics of cell cycles. The Novak–Tyson model has been extended by Steuer who added stochastic noise terms corresponding to fluctuations in living systems.[12] Since then, a number of authors emphasized the importance of stochastic models in this field[10,37,56–58] with mounting evidence pointing to the fact that accounting for stochasticity may lead to qualitatively different behavior of cells. For example, the application of a stochastic model in Battogtokh and Tyson[37] led to a conclusion that in the presence of noise, birthythmicity may lead to miotic arrest. Such new observations are critical in treatment of malfunctioning cells.

In the present paper, a general stochastic framework that allows us to treat living cell fluctuations is proposed. Our major focus is given to three specific stochastic models containing fluctuations related to varying rates of relative concentrations of proteins when the magnitudes of the concentrations exceed a certain threshold. The proposed hierarchy of mathematical models can deal with increasing levels of fluctuations, taking into account the effect of cellular dynamics on the cell cycle.

The paper is organized as follows. After providing a systems biology perspective of the development of mathematical models for cellular processes in Sec. 2, in Sec. 3, we review the deterministic Novak–Tyson model and develop a general stochastic framework for modeling cell cycle dynamics. We complete this section with providing a general formulation of a model that takes into account the effect of cellular dynamics on the cell cycle. Based on these models, in Secs. 4 and 5 we

carry out a series of computational experiments and some representative results of these computations are presented. We carry out a parametric sensitivity analysis and discuss an effective cell control using such parameters. We analyze nonlinear effects in cell cycles, based on the construction of phase portraits for each of the models discussed here. This is followed by a discussion of future development of mathematical models in this field and concluding remarks.

2. Mathematical Models of Cellular Processes from a Systems Biology Perspective

As we already pointed out in the introductory part, an integrated coupled approach in modeling cellular processes is required and this should include regulatory, metabolic, and signaling networks. However, in all biological networks that govern gene expression, signal transduction, and metabolism, stochasticity is a ubiquitous element.[59] As only partial information is available about the cellular processes, the most practical way to approach the problem lies with the development of a hierarchy of mathematical models. Such an approach is typical to the development of mathematical models for many complex physical systems[60–63] and the ideas that have been developed for them are now being applied to biological systems too, including cellular processes.[64]

The starting point of the development of mathematical models for cellular processes usually lies with biochemical reactions in cells where a biochemical noise within genetic circuits is always present due to variability in amplitude, distribution, and propagation of signals. The results of this noise are unavoidable stochastic fluctuations not only in gene expressions, but also in protein concentrations.[65] The latter represent the key variables in all the existing mathematical models for cellular processes. If we assume the Markovian property of biochemical reactions, from the Chapman–Kolmogorov equation it is straightforward to derive the chemical master equation (CME), following the known technique (e.g. Wang *et al.*[66] and references therein):

$$\frac{\partial p(X;t)}{\partial t} = \sum_{i=1}^{M} \{w_i(X-\theta_i)p(X-\theta_i;t) - w_i(X)p(X;t)\}, \tag{1}$$

where p is the probability function for the state of the molecules in the system (cell) denoted by $X = (X_1, \ldots, X_n)$ at time t, $\theta_i = (\theta_{i,1}, \ldots, \theta_{k,n})$ is the change of the state such that $\theta_{i,j}$ is a change in the number of jth molecule by the ith reaction, and $w_i(X)$ is a transition rate from state X to $X + \theta_i$ by ith chemical reaction. A number of numerical algorithms have been developed for the solution of (1). This includes the Gillespie stochastic simulation algorithm, the Gibson–Bruck algorithm, τ-leap approximations, Markov chain Monte Carlo procedures, and a number of others with several software tools such as StochKit available in the literature (e.g. Refs. 66–69 and references therein).

Given the CME (1), by the Taylor expansion of $w_i(X-\theta_i)p(X-\theta_i;t)$ and following standard arguments, we can derive the Fokker–Plank equation, from where we get the Langevin equations for our network:

$$\frac{d\mathbf{x}(t)}{dt} = \mathbf{f}(\mathbf{x}(t)) + \psi(t), \tag{2}$$

where $\psi(t)$ is white noise and in contrast to model (1) (which can be viewed as the description of a discrete Markov process), model (2) is a continuous description of the process (with $\mathbf{x}$ being the concentration of $X(t)$ in the cell volume[66]). This model can be generalized further to the multicellular case in a way similar to Ref. 70.

Compared to the original microscopic model (1), model (2) can be seen as coarse-grained and is sometimes referred to as a mesoscopic model.[57,71] The actual form of such a model can be derived from macroscopic deterministic equations which we discuss next. This allows us to account for finite size effects.

If the system is large, under certain assumptions,[66] we can arrive at deterministic equations discussed in details in Sec. 3.1. As it is well known, when the number of molecules is relatively small, such assumptions become inapplicable as modeling of biochemical reactions as continuous fluxes of matter cannot be justified.[67]

2.1. *Accounting for spatial effects*

It is well known that the cell division mechanism is tightly coupled to the mitosis/growth process and this coupling determines the cell size.[72] The models accounting for such a coupling can be written in the following generic form:

$$\frac{\partial p_q^c}{\partial t} = F_1(p_q^c, p_q^n, k_{s,q}, D_q^c, k_{d,q}^c), \tag{3}$$

$$\frac{\partial p_n^c}{\partial t} = F_1(p_q^n, p_q^c, D_q^n, k_{d,q}^n), \tag{4}$$

where p_q^c and p_q^n are the protein (or protein complex) concentrations of form q in the cytoplasm and nucleus, respectively, $k_{s,q}$ is the protein (of form q) synthesis rate, D_q^c and D_q^n are the diffusion coefficients for that protein in the cytoplasm and nucleus, and finally, $k_{d,q}^c$ and $k_{d,q}^n$ are the protein degradation rates in the cytoplasm and the nucleus, respectively. Several models have been developed recently in this direction in order to account for spatio-temporal interactions,[72,73] but all the models we are aware of used a number of substantial simplifications (e.g. two-compartment, various decoupling assumptions, etc.). Simplifications in modeling cell cycles are inevitable and one of the most generic ways to compensate for that lies through the introduction of a stochastic element into the mathematical model as discussed in Sec. 3.2.

2.2. *Accounting for coupled effects in modeling complex biological systems*

An intrinsic link between the cell division mechanism and the growth process as a function of cell size is just one of many spatio-temporal couplings that will become increasingly important in the development of mathematical models for cell cycles. Another example of coupling is provided by cell polarization and electromechanical effects in cells. Accounting for these effects would also lead to spatio-temporal PDE-based models (e.g. Yi *et al.*[74]). Electromechanical effects in biological systems are ubiquitous. In most cases they require the development of multiscale coupled models of electro-elasticity[75–79] and some such mathematical and computational models have already been developed for cornea, ear and other biotissues, electromotor proteins, cell membranes, protein aminoacids, to name just a few. Time-dependent mathematical models describing electromechanical interactions were analyzed in a series of publications[80–87] with main results on well-posedness, solution regularity, and stability conditions for variational numerical discretizations obtained there. In many systems, including biological, in addition to the electromechanical coupling, thermal effects become important[88–95] and the solution of the full thermo-electromechanical system is required in such cases.[96,97] If the systems interact with other media such as fluids, gas, or acoustic media, an additional coupling should also be incorporated in the corresponding models.[98,99]

2.3. *Reduction procedures for infinite dimensional dynamic systems*

One of the most efficient methodologies to approach the solution of mathematical models describing coupled complex systems is to develop a systematic procedure for model reduction. Such reductions can be carried out via low dimensional reductions on centre manifolds and have been carried out successfully for coupled mathematical models for infinite dimensional dynamic systems.[88,100]

The above procedures are efficient also when the physical systems undergo phase transformations and exhibiting such complex nonlinear behavior as hysteresis.[101] In biological systems such transformations are intrinsic to many cellular processes.[10] In a number of cases, mathematical models for phase transformations can be developed based on the Landau–Devonshire theory[102–107] and efficient numerical techniques have already been developed based on the finite differences,[108,109] finite element approximations for (non-equilibrium thermodynamic) thin films[103,110] and for more general 3D multivariant situations,[102,111–113] the method of lines,[114] finite volume methods,[115,116] and hybrid optimization methodologies.[117] Many of the proposed methodologies are based on the original reduction of the PDE model to a system of differential-algebraic equations, first time proposed for such problems in Melnik

et al.[118] and developed further in Refs. 88, 100, 101, 104 and 119, along with several low dimensional models. Earlier attempts to apply pseudospectral (collocation) methodologies can be found in Refs. 120 and 121. These (essentially energy-based) methodologies, previously applied to physical systems, could be valuable for the treatment of hysteresis, phase transformations, and other nonlinear effects, in biological systems too. It should be noted, however, that the energy landscape approach in the analysis of cell cycles under stochastic fluctuations is only at the beginning of its development.[122]

In what follows, we demonstrate that in the case of cellular processes the stochasticity is important to incorporate into mathematical models not only at the level of biological networks, such as regulatory, metabolic and others, but even in the case when we need to describe (mathematically) relatively simple processes in biological cells.

3. Mathematical Models of Cell Cycles

Based on the deterministic Novak–Tyson model, in this section we propose a stochastic model framework that would allow us to account for fluctuations of concentrations and their rates during special events of the cell cycle.

3.1. *Deterministic modeling of cell cycles*

By analyzing the control system for fission yeast cell cycles, Novak *et al.* developed a mathematical model consisting of parametric differential-algebraic equations that couple relative concentrations of different proteins and the mass of the cell as functions of time (t).[5] In the heart of the model is the activity of M-phase promoting factor, MPF(t), as discussed in the introductory section.

Cell cycles consist of many events and one of the most important is the production of cyclin which in combination with cyclin dependent kinase (or Cdk) leads to the formation of the maturation (or M-phase, as mentioned before) promoting factor. Self-amplification of MPF influences other subsequent events such as DNA replication, followed eventually by the MPF activation of the anaphase promoting complex (APC) which marks the cyclin for degradation, ending the cycle. As we discussed above, in the first approximation, cell division can be viewed as a set of biochemical reactions due to protein interactions. Our discussion here is focused on cellular processes in yeast as a eukaryote with extensive homology to higher organisms and with a large amount of data, from individual genes, proteins and pathways to complete DNA sequences.[123] Recall that in the context of yeast we have to deal with four distinct phases: G_1, S, G_2, and M. G_1 is the growth phase where the cell must grow sufficiently to replicate its building blocks to give rise a new organism. DNA replication and early bud formation take place in phase S. G_2 is the gap phase, and in phase M (metaphase) chromosomes become separated, preparing the way for division. This is followed by M anaphase, as mentioned above (for a schematic

representation of the yeast cell cycle, see, e.g. Klipp[123]). Maturation (M-phase) promoting factor plays a fundamental role in many biological processes, including being a regulator in oocytes during their maturation.[124,125] Due to its key role in the mitosis, it is sometimes called as the mitosis-promoting factor.

Following previous works on the analysis of dynamic processes in yeast with mathematical models, initiated by Novak and Tyson (see Ref. 123 and references therein), the general setup for frequently used deterministic models is as follows. We denote by $x_1(t) = Cdc13_T(t), x_2(t) = preMPF(t), x_3(t) = Ste9(t), x_4(t) = Slp1_T(t), x_5(t) = Slp1(t), x_6(t) = IEP(t), x_7(t) = Rum1_T(t), x_8(t) = SK(t)$ the relative concentrations of proteins of interest. The number of such proteins is problem specific and in the case of fission yeast we deal with eight such proteins plus several others, including M-phase promoting factor. Other proteins can often be incorporated into the model by algebraic, rather than differential, equations. Let further $x_9(t) = M(t)$ be the mass of the cell during the cell cycle at given moment of time t. Then, dynamic interactions between quantities $x_1(t), \ldots, x_9(t)$ can be modelled with the following general system of nonlinear ODEs:

$$\frac{d\mathbf{x}(t)}{dt} = \mathbf{f}(\mathbf{x}(t), t), \tag{5}$$

where $\mathbf{x}(t) = (x_1(t), \ldots, x_9(t))^T$ and $\mathbf{f}(\mathbf{x}(t), t) = (f_1(\mathbf{x}(t), t), \ldots, f_9(\mathbf{x}(t), t))^T$. The type of nonlinearities, defined by the vector function $\mathbf{f}(\mathbf{x}(t), t)$, is problem specific and for fission yeast cells can be modelled by the following relationships:

$$\begin{aligned}
f_1(\mathbf{x}(t), t) &= k_1 x_9(t) - (k_2' + k_2'' x_3(t) + k_2''' x_5) x_1(t), \\
f_2(\mathbf{x}(t), t) &= k_{wee}(x_1(t) - x_2(t)) - k_{25} x_2(t) - (k_2' + k_2'' x_3(t) + k_2''' x_5(t)) x_2(t), \\
f_3(\mathbf{x}(t), t) &= (k_3' + k_3'' x_5(t)) \frac{1 - x_3(t)}{J_3 + 1 - x_3(t)} - (k_4' x_8(t) + k_4 MPF(t)) \frac{x_3(t)}{J_4 + x_3(t)}, \\
f_4(\mathbf{x}(t), t) &= k_5' + k_5'' \frac{MPF(t)^4}{J_5^4 + MPF(t)^4} - k_6 x_4(t), \\
f_5(\mathbf{x}(t), t) &= k_7 x_6(t) \frac{x_4(t) - x_5(t)}{J_7 + x_4(t) + x_5(t)} - k_8 \frac{x_5(t)}{J_8 + x_5(t)} - k_6 x_5(t), \\
f_6(\mathbf{x}(t), t) &= k_9 MPF(t) \frac{1 - x_6(t)}{J_9 + 1 - x_6(t)} - k_{10} \frac{x_6(t)}{J_{10} + x_6(t)}, \\
f_7(\mathbf{x}(t), t) &= k_{11} - (k_{12} + k_{12}' x_8(t) + k_{12}'' MPF(t)) x_7(t), \\
f_8(\mathbf{x}(t), t) &= k_{13} TF(t) - k_{14} x_8(t), \\
f_9(\mathbf{x}(t), t) &= \mu x_9(t).
\end{aligned}$$

Three more proteins are involved in the definition of $\mathbf{f}(\mathbf{x}(t), t)$ where their relative concentrations were denoted by $Trimer(t), MPF(t)$ and $TF(t)$. Furthermore,

some coefficients in the above definition are interdependent with the others, in particular k_{wee} and k_{25}. Therefore, based on experimental observations, system (5) is supplemented by the following algebraic relationships for

$$Trimer(t) = \frac{2x_1(t)x_7(t)}{\Sigma + \sqrt{\Sigma^2 - 4x_1(t)x_7(t)}} \tag{6}$$

$$MPF(t) = \frac{(x_1(t) - x_2(t))(x_1(t) - Trimer(t))}{x_1(t)} \tag{7}$$

$$TF(t) = GK(k_{15}x_9(t), k'_{16} + k''_{16}MPF(t), J_{15}, J_{16}) \tag{8}$$

$$k_{wee} = k'_{wee} + (k''_{wee} - k'_{wee})GK(V_{awee}, V_{iwee}MPF(t), J_{awee}, J_{iwee}) \tag{9}$$

$$k_{25} = k'_{25} + (k''_{25} - k'_{25})GK(V_{a25}MPF(t), V_{i25}, J_{a25}, J_{i25}), \tag{10}$$

where quantities Σ and GK are defined as follows:

$$\Sigma = x_1(t) + x_7(t) + K_{diss}$$

and

$$GK(a, b, c, d) = \frac{2ad}{b - a + bc + ad + \sqrt{(b - a + bc + ad)^2 - 4ad(b - a)}}.$$

The parameters in the model (5)–(10) are determined based on comparisons with experimental results. In what follows, we use all the parameters from Novak *et al.*,[5] summarized in Table 1.

From a mathematical point of view, the model (5)–(10) is a system of differential-algebraic equations with parameters ranging from less than 10^{-2} to 35.

Table 1. Parameters used in the Novak–Tyson model. All constants have units min^{-1}, except the J's and K_{diss} which are dimensionless.

Role	Parameters
*Cdc*13 synthesis and degradation	$k_1 = k'_2 = 0.03, k''_2 = 1.0, k'''_2 = 0.1$
*Ste*9 activation and inactivation	$k'_3 = 1.0, k''_3 = 10.0, J_3 = 0.01, k'_4 = 2.0,$ $k_4 = 35.0, J_4 = 0.01$
*Slp*1 synthesis, degradation activation and inactivation	$k'_5 = 0.005, k''_5 = 0.3, J_5 = 0.3,$ $k_6 = 0.1, k_7 = 1.0, k_8 = 0.25, J_7 = J_8 = 0.001$
IE activation and inactivation	$k_9 = 0.1, k_{10} = 0.04, J_9 = J_{10} = 0.01$
*Rum*1 synthesis, degradation and inhibition	$k_{11} = 0.1, k_{12} = 0.01, k'_{12} = 1, k''_{12} = 3,$ $K_{diss} = 0.001$
SK synthesis and degradation	$k_{13} = k_{14} = 0.1$
TF activation and inactivation	$k_{15} = 1.5, k'_{16} = 1, k''_{16} = 2, J_{15} = J_{16} = 0.01$
*Wee*1 activation and inactivation	$V_{awee} = 0.25, V_{iwee} = 1, J_{awee} = J_{iwee} = 0.01$
*Cdc*25 activation and inactivation	$V_{a25} = 1, V_{i25} = 0.25, J_{a25} = J_{i25} = 0.01$
Rate of tyr-phosphorylation and dephosphorylation	$k'_{wee} = 0.15, k''_{wee} = 1.3, k'_{25} = 0.05,$ $k''_{25} = 5$
Growth rate	$\mu = 0.005$

Hence, from a numerical point of view, its solution requires a special attention, typical for stiff models. From a biological point of view, the model describes wild-type cell cycles of fission yeast. Changing $k''_{wee} = 1.3$ to $k''_{wee} = 0.3$ in this model would result in the model for the so-called $Wee1^-$ mutant cell cycles.[5] Finally, note that replacing $k''_{wee} = 1.3$ and $k''_{25} = 5$ by $k''_{wee} = 0.3$ and $k''_{25} = 0.02$ respectively, we obtain a model for $Wee1^- cdc25\Delta$ mutant cell cycles.[5]

The deterministic models for cellular processes discussed above do not account for stochastic elements in the kinetics of biochemical reactions. A number of attempts to bridge the gap between stochastic and deterministic behaviors of such reactions provided a good starting point for more realistic cell cycle modeling[12,67] which led to the development of models and algorithms we discussed in Sec. 2. In the following section, we discuss a hierarchy of stochastic mathematical models for cell cycles that account for special events. Indeed, although the temporal evolution of cells can be interpreted as a sequence of events,[126,127] not all of such events are deterministic.

3.2. *Stochastic modeling of cell cycles accounting for special events*

All biological processes, and the cell cycles are not an exception, result from the coupled interactions of genes and proteins with an enormous variety of external stimuli, the exact information on which is only partly known. This makes stochastic mathematical models the most natural tool in dealing with the complexity induced by such coupled interactions. In order to control the biological processes such as cell cycles, the ideas of Markov chain network training, neural networks, and evolutionary learning developed for complex systems applications[2,64,128–130] could become increasingly useful in this area too and the first steps in this direction have started to appear.[131] Most details of control issues, however, lie outside of the scope of the present paper, and in what follows we focus only on the influence of a stochastic element introduced into the mathematical models for cell cycles. Such an element can be both detrimental when it drives cells to dramatically different phenotypic states such as cancer and the transition to the genetic competence state, as well as beneficial when it can be used as a stabilization mechanism, for a population to increase its phenotypic variety and help adjusting to changing environments.[59]

Since a cell cycle involves nonlinear variations of the protein concentrations related to many stochastic processes functioning at different spatial and temporal scales, the regulation of cellular activities may not be deterministic.[5,12] In the context of the model considered in the previous sub-section, we note that for wild-type cell cycles of fission yeast, during the G1 phase, $Ste9$ and $Rum1$ are activated while $Slp1$ and $Cdc13_T$ are reduced rapidly. From the results of simulations and experimental observations it is known (see, e.g. Fig. 2 in Novak *et al.*[5]) that the magnitudes of $Ste9, Cdc13_T$ and $Slp1$ can be relatively large to introduce fluctuations

in such a way that some fluctuations of their derivatives may also be expected. Furthermore, SK is also active at a latter stage 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 varying 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 $SLP1$ vary rapidly and are large enough to introduce fluctuations. Finally, IEP is also active in the M phase.

Based on the above observations, we consider the following general stochastic model for wild-type cell cycles of fission yeast

$$d\mathbf{x}(t) = \mathbf{f}(\mathbf{x}(t), t)dt + \mathbf{h}(\mathbf{x}(t), t)d\mathbf{W}(t), \tag{11}$$

where $\mathbf{h}(\mathbf{x}(t), t) = \text{diag}(h_1(\mathbf{x}(t), t), \ldots, h_9(\mathbf{x}(t), t))$ is a diagonal matrix, and $\mathbf{W}(t) = (W_1(t), \ldots, W_9(t))^T$ is a Wiener process[132] such that the term $\mathbf{h}(\mathbf{x}(t), t)d\mathbf{W}(t)$ models fluctuations of the rate of protein concentrations, or in other words, deviations from the deterministic case. Indeed, the system of stochastic differential equations (11) is reduced to model (5) if $\mathbf{h}(\mathbf{x}(t), t) = \mathbf{0}$.

Let us denote by $\mathbf{g}(\mathbf{x}(t), t)dt$ the right hand side of equation (11). As mentioned above, the case of fluctuations absent corresponds to the deterministic Novak–Tyson model (5). In this model the vector function $\mathbf{f}(\mathbf{x}(t), t)$ is only an approximation of real protein interactions due to the presence of many coupled phenomena and processes left behind the scope of this model, including spatial interactions, many activities by synthesis, degradation by various reactions, etc. At the same time, model (11) will allow us to account for the information about the dynamics of cell cycles, left behind the scope of model (5). This is done by introducing a degree of uncertainty. While fluctuations in the solution due to such uncertainty have been studied by other authors (initiated in Steuer[12]), we developed for the first time a hierarchy of mathematical models where such uncertainty is present also in the vector function responsible for protein interactions.

First recall that although biochemical reaction rates and concentrations of proteins are likely best described by stochastic variables, we agree with the authors of Sveiczer *et al.*[133] who argued that it is not necessary to take all possible stochastic variability into account. Note that an abrupt switching of the cell cycle from the G2 phase to the M phase may take place when the amount of cyclin Cdc13 attains a certain value and the cell cycle stays in the M phase even when the amount of cyclin Cdc13 decreases to an amount below that value. Furthermore, the amount of other protein concentrations is only significant at certain periods of the cell cycle. Therefore, it is natural to add the fluctuations when magnitudes of protein concentrations exceed a certain threshold in our models or for the entire cell cycle. Hence, in what follows we will aim at the development of mathematical models (a) with fluctuations in $\mathbf{f}(\mathbf{x}(t), t)$ only, (b) with fluctuations in $\mathbf{f}(\mathbf{x}(t), t)$ and $\mathbf{x}(t)$ both present for certain periods of the cell cycle, and (c) with fluctuations in $\mathbf{f}(\mathbf{x}(t), t)$ for certain periods of the cell cycle and fluctuations in $\mathbf{x}(t)$ for the entire cell cycle.

Other fluctuations of $\mathbf{f}(\mathbf{x}(t), t)$ and $\mathbf{x}(t)$ can be considered to obtain other models, but the above three cases seem to be most typical in practical applications.

As the first step, we approximate functions $W_1(t), \ldots, W_9(t)$ by the Gaussian white noise with zero mean and unit variance (e.g. Kloeden and Platen[132]). From a numerical point of view, it means that in the solution of stochastic differential equations (11) we will use the Gaussian white noise increments as the Wiener path increments $\Delta W_1(t), \ldots, \Delta W_9(t)$ corresponding to $dW_1(t), \ldots, dW_9(t)$. If we define now

$$h_i(\mathbf{x}(t), t) = \begin{cases} \sqrt{r|\mathbf{f_i}(\mathbf{x}(t), t)|} & \text{for } |x_i(t)| > \alpha; \\ 0, & \text{otherwise,} \end{cases} \qquad i = 1, 2, \ldots, 9 \tag{12}$$

with r being a constant that provides an estimate of the amplitude of fluctuations, we obtain our first stochastic model. The model takes into account fluctuations related to the varying rates of relative concentrations of proteins when the magnitudes of the concentrations are beyond a threshold. In computational results reported here we set this threshold to $\alpha = 0.3$. Note that the fluctuations in this model are determined by $h_i(\mathbf{x}(t), t)$ which is related to $\frac{d}{dt}x_i(t)$. This is different from the work by Steuer,[12] where fluctuations were determined by a function that was related directly to $x_i(t)$.

Our next step will be to add term $\sqrt{2D|x_i(t)|}$ to $\sqrt{r|\mathbf{f_i}(\mathbf{x}(t), t)|}$ in (12), where D is a constant that can be used to control the amount of noise. Note that this term was used in Ref. 12 for the entire cycle. A similar idea was used also in Ref. 134 where the authors analyzed the effect of time delay introduced in the activation of anaphase-promoting complex by MPF. In our case, the definition of the fluctuation term in model (11) is given as follows:

$$h_i(\mathbf{x}(t), t) = \begin{cases} (\sqrt{r|\mathbf{f_i}(\mathbf{x}(t), t)|} + \sqrt{2D|x_i(t)|}) & \text{if } |x_i(t)| > \alpha; \\ 0, & \text{otherwise,} \end{cases} \qquad i = 1, 2, \ldots, 9. \tag{13}$$

This defines our second model that takes into account fluctuations related to both, the varying rates of relative concentrations of proteins and the relative concentrations of proteins themselves. This is particularly useful in those cases where the magnitudes of relative concentrations of proteins are beyond a given threshold.

This model can be generalized further if we add term $\sqrt{2D|x_i(t)|}$ to the right hand side of (12). In this case, the definition of the fluctuation term in model (11) becomes

$$h_i(\mathbf{x}(t), t) = \begin{cases} (\sqrt{r|\mathbf{f_i}(\mathbf{x}(t), t)|} + \sqrt{2D|x_i(t)|}) & \text{if } |x_i(t)| > \alpha; \\ \sqrt{2D|x_i(t)|}, & \text{otherwise,} \end{cases} \qquad i = 1, 2, \ldots, 9. \tag{14}$$

The last model takes into account fluctuations related to the varying rates of relative concentrations of proteins when the magnitudes of the concentrations go beyond a

given threshold. Note that in this case, fluctuations are taken into account for the entire cell cycle.

We note also that fluctuations introduced into these new models are related to certain magnitudes of model variables that correspond to specific varying time periods of proteins. In Chen *et al.*[4] the authors analyzed the effect of the cell cycle on gene regulatory networks. In many applications, however, we need to solve an *inverse problem* in a sense that we need to deduce the effect of gene regulatory networks on the cell cycle. Main challenges related to this problem lie with the fact that in gene regulatory networks there may be both regulatory and metabolic activities, and gene expressions in the metabolic parts of gene regulatory networks are very different from those in the regulatory parts. Consequently, the dynamics of the cell cycle will be affected differently during regulatory and metabolic activities of cellular gene regulatory networks. Hence, our mathematical models for the cell cycle should be modified in all cases where it is critical to take into account the behavior of gene regulatory networks. These modifications of systems (5) and (11) can be formalized as follows:

$$\frac{d\mathbf{x}(t)}{dt} = U(t)\mathbf{f}(\mathbf{x}(t), t) \tag{15}$$

and

$$d\mathbf{x}(t) = U(t)\mathbf{f}(\mathbf{x}(t), t)dt + V(t)\mathbf{h}(\mathbf{x}(t), t)d\mathbf{W}(t), \tag{16}$$

respectively, where $U(t) = \text{diag}(u_1(t), \ldots, u_9(t))$ and $V(t) = \text{diag}(v_1(t), \ldots, v_9(t))$ are diagonal matrices. Elements of the matrices $U(t)$ and $V(t)$ are chosen according to the dynamics of the corresponding gene regulatory networks. For instance, they should be chosen differently for the regulatory part and for the metabolic part of the gene regulatory network. Clearly, when $U(t) = I$, (15) is reduced to (5) and when $U(t) = V(t) = I$, (16) is reduced to (11). A more complicated case occurs when one of the relative concentrations, let us say $x_i(t)$, doubles rapidly near $kT + t_{d_i}T$. Here T is the cycle time, $k = 0, 1, 2, \ldots, 0 \leq t_{d_i} \leq 1$. In this case, the choice of elements of $U(t)$ and $V(t)$ can be made as follows:

$$u_i(t) = v_i(t) = \begin{cases} a_i p_i(t/T - k) + b_i, & kT \leq t \leq (k+1)T; \\ 1, & t = (k+1)T, \end{cases} \tag{17}$$

where $p_i(t) = 1/(1 + e^{-\gamma(t - t_{d_i})})$ is a distribution that is centered at $t_{d_i}, a_i = 1/(p_i(1) - p_i(0)), b_i = 1 - p_i(0)/(p_i(1) - p_i(0))$, and γ is a constant.

4. Computational Experiments

In this section we describe three groups of experiments. All models discussed in Sec. 3 have been implemented in Matlab. For comparison purposes, we have also implemented the classical Novak–Tyson model as discussed in Sec. 3.1. We apply Euler's method to deterministic models, discussed in Sec. 3, and stochastic Euler's

method with variable time integrator to our stochastic models. When applying the stochastic Euler's methodology, we use the following formula

$$\mathbf{x}_{n+1} = \mathbf{x}_n + \delta \mathbf{f}_n + \sqrt{\delta}\mathbf{h}_n(\text{randn}, \ldots, \text{randn})^T,$$

where $\mathbf{x}_n = (x_{1n}, \ldots, x_{9n})^T, \mathbf{f}_n = (f_{1n}, \ldots, f_{9n})^T, \mathbf{h}_n = \text{diag}(h_{1n}, \ldots, h_{9n}), \delta$ is the step size of numerical integration, and components of $\sqrt{\delta}(\text{randn}, \ldots, \text{randn})^T$ are Gaussian white noise increments.

Our first group of experiments deals with the models described in Sec. 3.1. In particular, we apply the deterministic Novak–Tyson model to modeling wild-type cells of fission yeast with the following initial conditions: $x_1(0) = 0.02, x_2(0) = 0.01, x_3(0) = 1.0, x_4(0) = 2.1, x_5(0) = 2.1, x_6(0) = 1, x_7(0) = 0.05, x_8(0) = 0$ and $x_9(0) = 1$. These conditions were prompted by Fig. 3 in Novak *et al.*[5] The results of computations based on this model are presented in Fig. 1 where only first two cycles are shown. In Fig. 2 we present the phase portrait of MPF dependent on $Cdc13_T$ during the time interval that covers one cycle. The relative concentrations of proteins in Fig. 1 are qualitatively the same as those previously reported in Novak *et al.*[5]

From Figs. 1 and 2, we conclude that the cell cycle has the property of bistability. This is expected. Indeed, before the amount of $Cdc13_T$ increases to a certain value, MPF activity is low. However, when the amount of $Cdc13_T$ attains that value, MPF activity increases abruptly. Then, MPF activity stays high until the amount

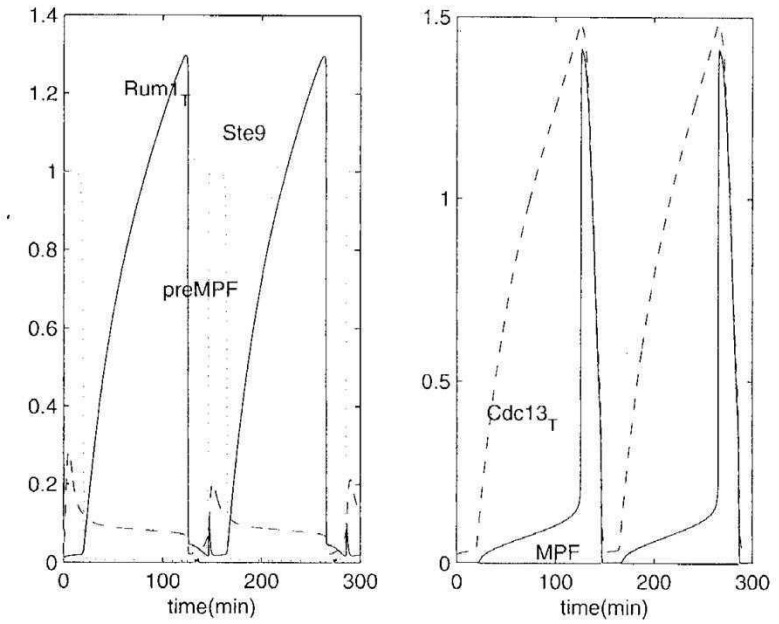

Fig. 1. Protein concentrations with the model from Sec. 3.1 (color online): preMPF/MPF, $\text{Rum1}_T/\text{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

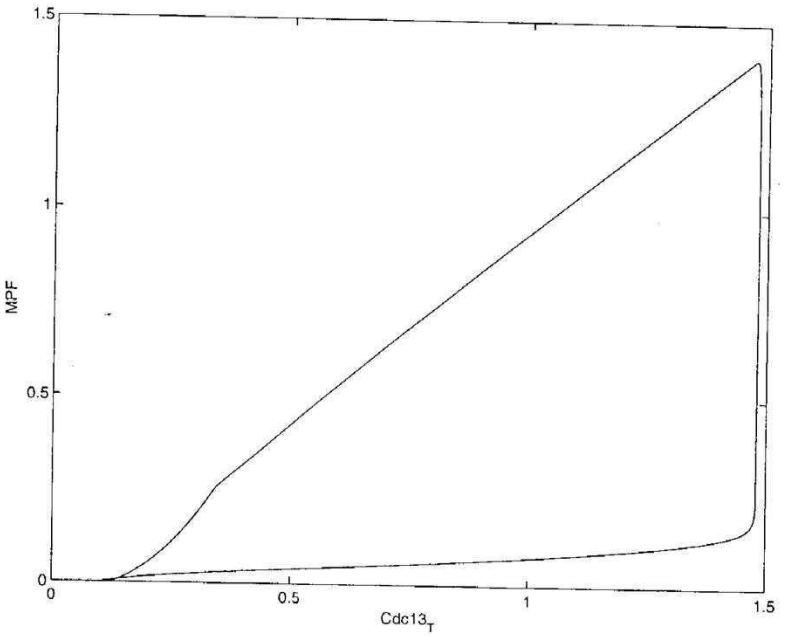

Fig. 2. Phase plot of MPF is dependent on $Cdc13_T$; it is obtained with the model from Sec. 3.1.

of $Cdc13_T$ is reduced to a certain small value. Hence, we observe that for a certain range of $Cdc13_T$ amount, there are two different states of the cell cycle, with low and high MPF activities that correspond to interphase and mitosis, respectively. The amount of $Cdc13_T$ needed to induce mitosis is higher than the amount of $Cdc13_T$ needed to make the cell cycle stay in mitosis. The end result is that this nonlinear phenomenon manifests itself in the fact that the cell cycle stays in mitosis, rather than goes back to interphase, until the amount of $Cdc13_T$ is reduced to a small critical value sufficient to start a new cell cycle. This is consistent with the results previously reported. We move now to the next step in our analysis.

It is known that if we change the values of the parameters k''_{wee} and k''_{25} in the above model from 1.3 and 5 to 0.2 and 3, respectively, we obtain a new model that can be applied to modeling another organism. Inspired by Fig. 3 in Novak *et al.*,[5] we use the following initial conditions: $x_1(0) = 0.01, x_2(0) = 0.001, x_3(0) = 1.0, x_4(0) = 1.1, x_5(0) = 1.1, x_6(0) = 0.5, x_7(0) = 0.2, x_8(0) = 0$ and $x_9(0) = 0.5$. The results of computations are presented in Fig. 3 and Fig. 4. We observe from these figures that the protein dynamics obtained with this new model is quite different from the results obtained with the previous model. It is clear that the deterministic models reported in Sec. 3.1 are very sensitive to parameterization procedures.

The second group of experiments is carried out on the stochastic models developed in Sec. 3.2. Our aim is to analyze the dynamics of the cell cycle when subjected

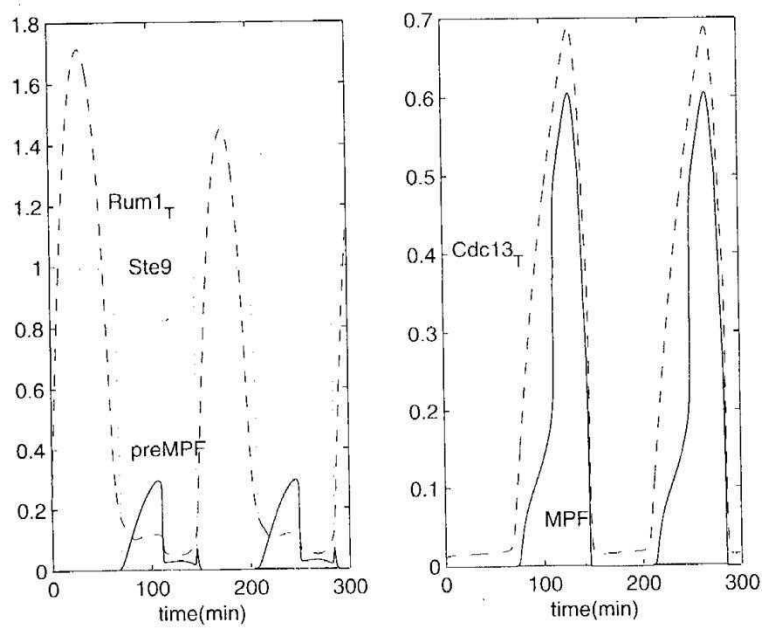

Fig. 3. Protein concentrations with the model from Sec. 3.1 with $k''_{wee} = 0.2$ and $k''_{25} = 3$ (color online): preMPF/MPF, Rum1$_T$/Cdc13$_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

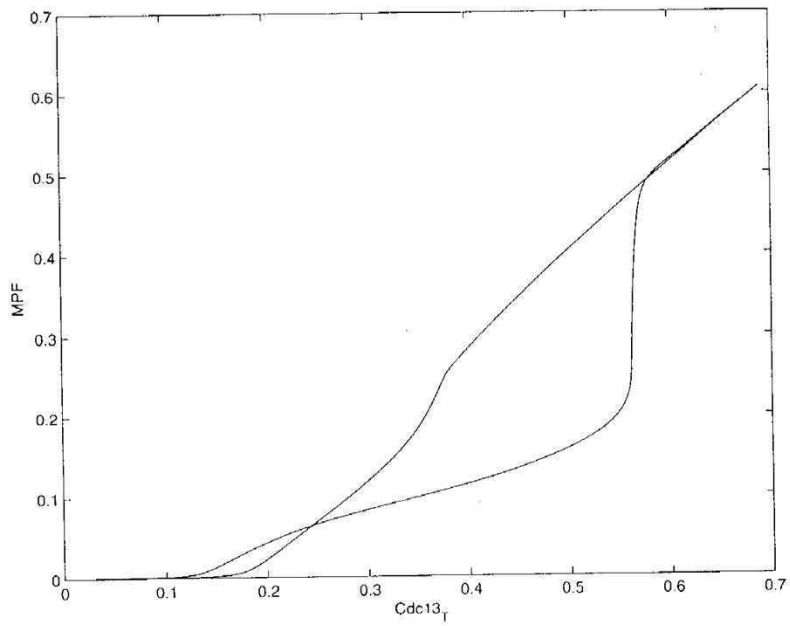

Fig. 4. Phase plot of MPF dependent on $Cdc13_T$ in the model in Sec. 3.1 with $k''_{wee} = 0.2$ and $k''_{25} = 3$.

to different fluctuations, as explained in Sec. 3.2. We use the same initial conditions as before (see Fig. 1). We progressively set $r = 2 \times 10^{-5}, r = 5 \times 10^{-5}$, and $r = 10^{-4}$ in (11), and take (12), (13) with $D = r$, and then (14) with $D = r$. In Figs. 5–7 we present the results of computations, giving relative protein concentrations for each of the above cases (the upper, middle, and bottom plots for the respective values of r as specified above). Furthermore, in Fig. 8 we present the phase portrait of MPF, dependent on $Cdc13_T$, in one cycle. The plot is given for $r = 2 \times 10^{-5}$ in (11) and (13).

For comparison purposes, the results of computation with the stochastic Steuer model,[12] given with the same specified initial conditions, are shown in Fig. 9. Based on the analysis of Figs. 5, 6 and 7, we conclude that the period of the cycle obtained with the stochastic models is not fixed and can be shorter or larger than the cycle period obtained with the corresponding deterministic model. The results obtained with Steuer's model, presented in Fig. 9, led us to a similar conclusion. A closer examination of Fig. 5 reveals that the effect of fluctuations induced by the varying rates of relative protein concentrations gives us a more regular pattern compared to the fluctuations induced by the relative concentrations of proteins themselves. Furthermore, we note that the patterns shown in Figs. 5 and 6 are quite different from the pattern in Fig. 9, while the pattern shown in Fig. 7 is similar to that in Fig. 9. This re-emphasizes the conclusion made in Steuer[12] that the noise can

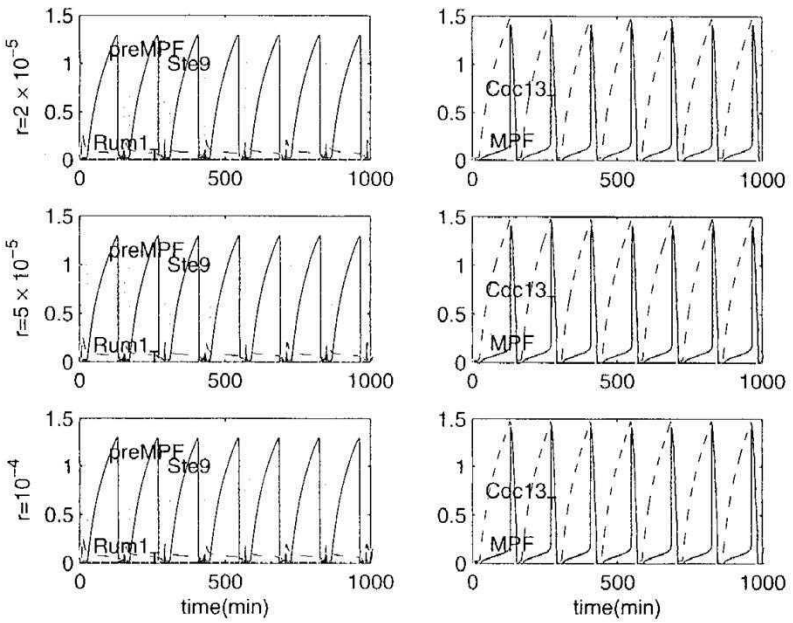

Fig. 5. Protein concentrations with the modified model (11) and (12): $r = 2\times10^{-5}, 5\times10^{-5}, 10^{-4}$ (color online): preMPF/MPF, $\mathrm{Rum1}_T/\mathrm{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

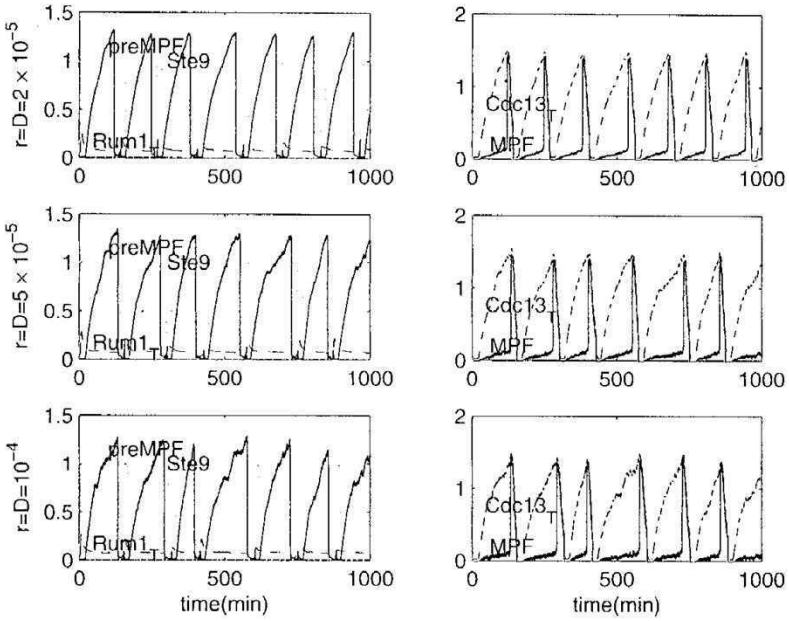

Fig. 6. Protein concentrations with the modified model (11) and (13) with $r = D = 2 \times 10^{-5}$, $5 \times 10^{-5}, 10^{-4}$ (color online): preMPF/MPF, $\mathrm{Rum1}_T$/$\mathrm{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

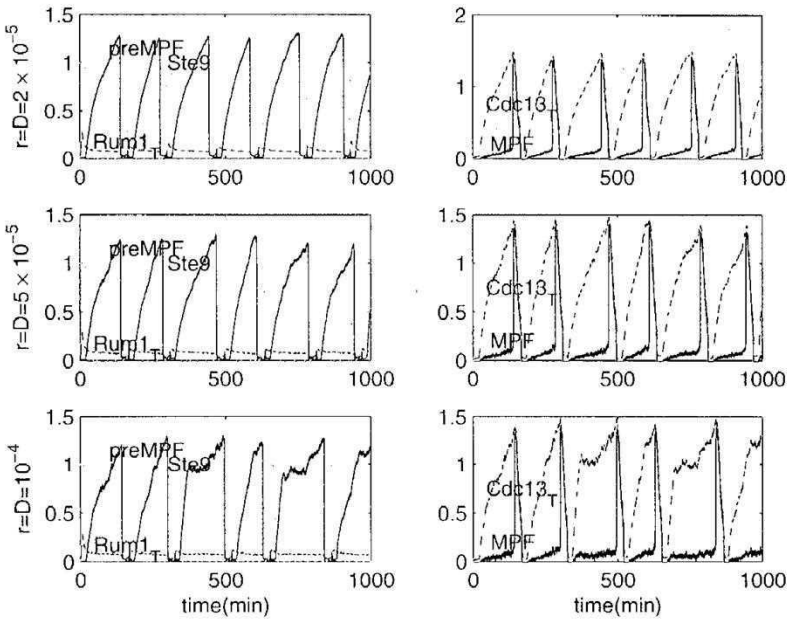

Fig. 7. Protein concentrations with the modified model (11) and (14) with $r = D = 2 \times 10^{-5}$, 5×10^{-5}, 10^{-4} (color online): preMPF/MPF, $\mathrm{Rum1}_T$/$\mathrm{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

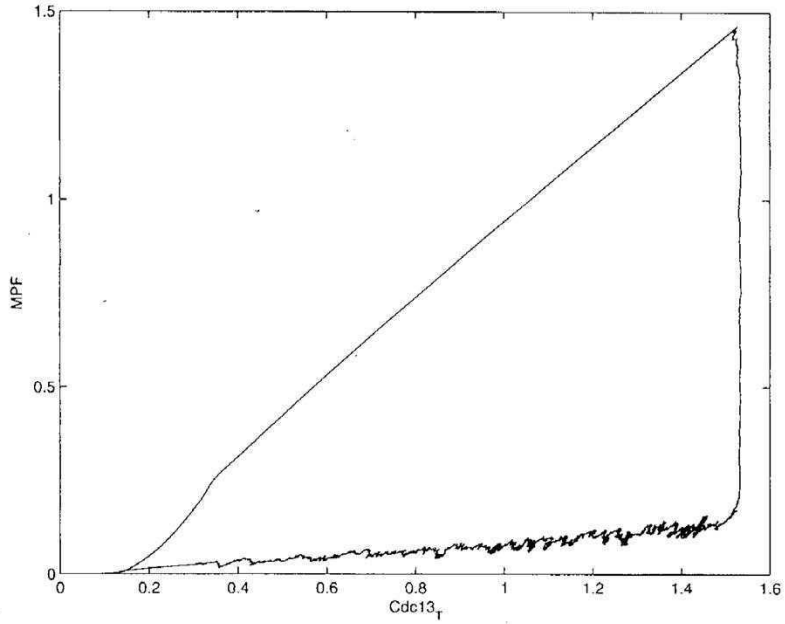

Fig. 8. Phase plot of MPF dependent on $Cdc13_T$ in the modified model (11), (13) with $r = D = 5 \times 10^{-5}$.

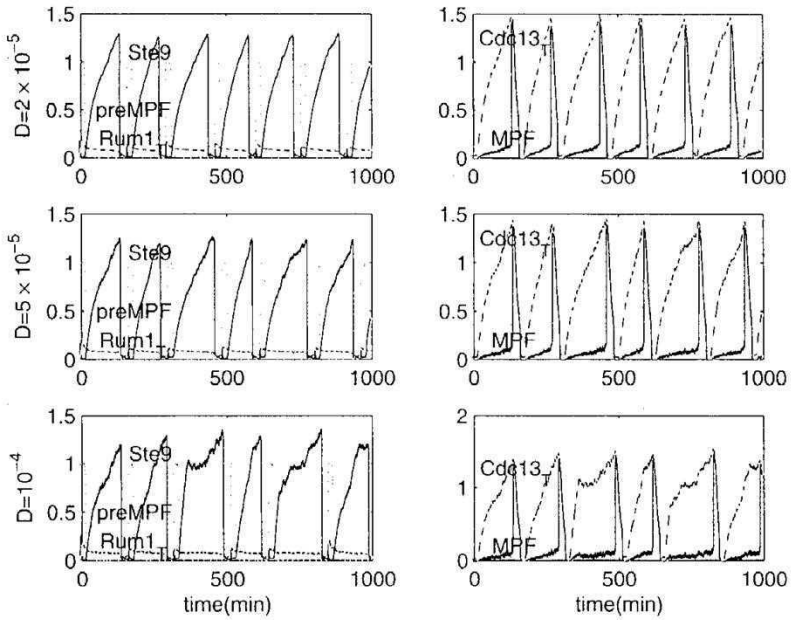

Fig. 9. Protein concentrations with Steuer's stochastic model: $D = 2 \times 10^{-5}, 5 \times 10^{-5}, 10^{-4}$ (color online): preMPF/MPF, Rum1$_T$/Cdc13$_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

be used to regulate the cell cycle. Note also that the analysis of the nonlinear phenomena based on Figs. 6 and 8 leads us to the conclusions similar to those discussed in the context of Figs. 1 and 2. However, Fig. 8 clearly demonstrates the effect of fluctuations on the hysteresis loop that was absent when deterministic models were applied.

Finally, we apply our stochastic model developed in Sec. 3 to the analysis of the effects of metabolic events in gene regulatory networks on the cell cycle. We use (16) with $\mathbf{h}(\mathbf{x}(t), t), r = 2 \times 10^{-5}, r = 5 \times 10^{-5}$ and $r = 10^{-4}$ as it is specified by (12), and U and V as it is specified by (17) ($T = 138.63, t_{d_i} = 0.6$ and $\gamma = 50$). The results are presented in Fig. 10. Comparing Fig. 10 with Fig. 5, we conclude that the dynamics of related gene regulatory networks can qualitatively influence the evolution of cells and can change the cell cycle periodicity.

Our experiments show that when r is more significant than D, the plots with our models are more similar to deterministic models. In the cases where D is more significant than r, the plots with our models are more similar to those obtained with stochastic models such as the one by Steuer. Changing α to larger values will make our models more similar to deterministic models. As can be seen from (17),

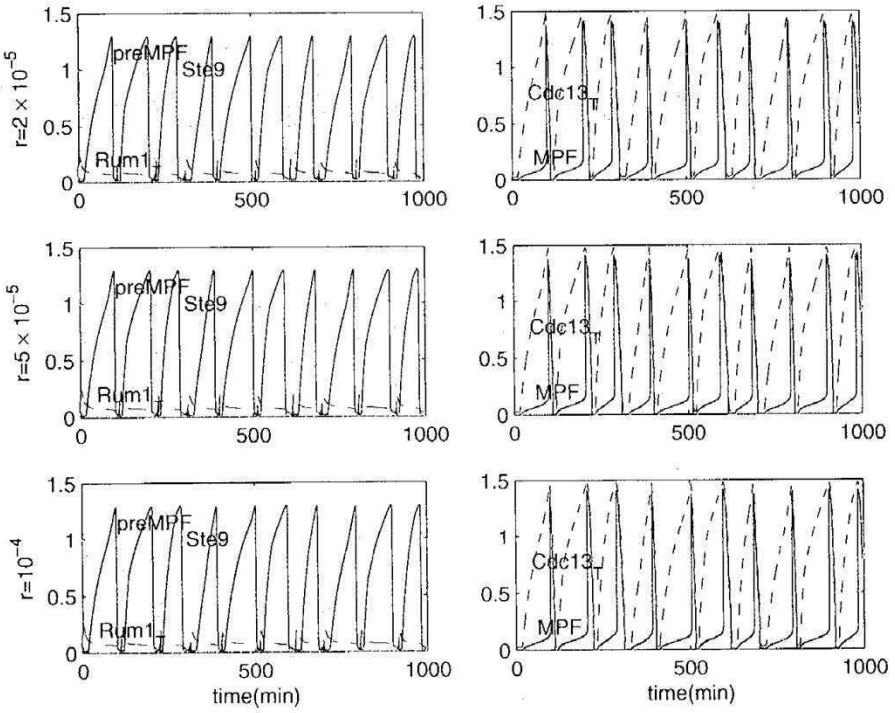

Fig. 10. Protein concentrations with the modified model (16) and $\mathbf{h}(\mathbf{x}(t), t)$ defined by (12), and U and V by (17) (color online): preMPF/MPF, Rum1$_T$/Cdc13$_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

changing t_{d_i} will change the center of the distribution of $p_i(t) = 1/(1 + e^{-\gamma(t-t_{d_i})})$ and changing the value of γ will change the varying rate of $p_i(t)$. It can be expected that when rapid fluctuations in cell cycles are present they will also be affected. The varying rate of such fluctuations will also be different, depending on the values of t_{d_i} and $p_i(t)$. This is confirmed further by additional experiments reported in the next section.

5. Parametric Sensitivity and Cell Cycle Control

Cell cycle control is important for a number of biotechnological and bio-nanotechnological applications, including tissue engineering, where in addition to the complex nature of tissues,[78] we have to account for biocompatibility, genotoxicity tests and other important issues. Human tissues involve coupled complex processes, in particular under their interactions with the environment. Similar to other multiphase and multicomponent complex systems,[2,135,136] coupling the (mass-action) kinetics to other processes, such as thermal and/or accounting for additional effects such as internal viscosity, may be necessary in these situations too.[89,137–139] At this stage, no such results are available in the literature in the context of cell cycle models. The development of such refined models of cell cycles that would take into account spatial (rather than only temporal) interactions in the context of coupled processes would be important for advances in molecular nanotechnology where mechanical and electromechanical systems are developed at the molecular scale. Indeed, it is well understood by now that, e.g. nanoscale cell membrane dynamics is associated with different phenomena of cell's life and one of the most important is cell cycle. The development of new biomaterials such as those based on RNA, for scaffolding and controlled drug delivery techniques and devices[55,140] is another application area where such a control is becoming increasing important.

Recently, cell cycle regulation in eukaryotic cells has been studied in Battogtokh[141] with mathematical models accounting for available experimental data. Further, cell-cycle control systems have been considered in Shen *et al.*[142] where the authors implemented control via a cyclical genetic circuit composed of regulatory proteins with tight coupling to cell division and other important processes. There is a widely accepted consensus that stochastic effects are important in dealing with malfunctioning, such as cancer cells.[143] The importance of stochasticity has been recently emphasized in the context of models for the control of cell proliferation following antigen stimulation, which is at the heart of the adaptive immune response.[144] When the determination of the time at which a stochastic process exceeds a certain threshold is critical, we often arrives at the first passage time problem that arises in many different applications. An efficient methodology for its solution in the multivariate case has recently been developed in Zhang and Melnik (see also references therein).[145] As our main focus in this paper is on the cell and its responses to changing environmental conditions, a degree of uncertainty that

may lead to special events in the cell cycles has been incorporated in the hierarchy of the models developed here. This has been done through a set of parameters. Therefore, in what follows we analyze the parametric sensitivity of a hierarchy of our developed stochastic mathematical models in order to be able to identify those parameters that would allow us an effective cell cycle control.

First, we analyze the protein concentrations with the modified model (11) and (12) decreasing/increasing the value of r on the order of magnitude. Under the given threshold, the qualitative behavior presented in Fig. 5 remains the same even if we further decrease the value of r ten times. Recall that r provides an estimate of the amplitude of fluctuations. Hence, we expect that an increase in r will eventually lead to fluctuation-driven numerical instabilities. Indeed, with the further increase in r, the qualitative behavior of protein concentrations begins to change and already for $r_{\text{new}} = 20r$, we observe fluctuation-driven numerical instabilities indicating a breakdown of this model. In order to avoid that and to provide an efficient control of the cell cycle dynamics, a new model in our hierarchy should be considered where an additional parameter is introduced.

The modified model (11) and (13) contains such an additional parameter D. This leads to a change in the qualitative behavior of protein concentrations when we increase the value of r keeping D the same. In Fig. 11 we present results of such an increase for $r_{\text{new}} = 10r$. As expected, in contrast to Fig. 6, the behavior now becomes similar to the one presented in Fig. 5. As seen from Fig. 12, a more regular

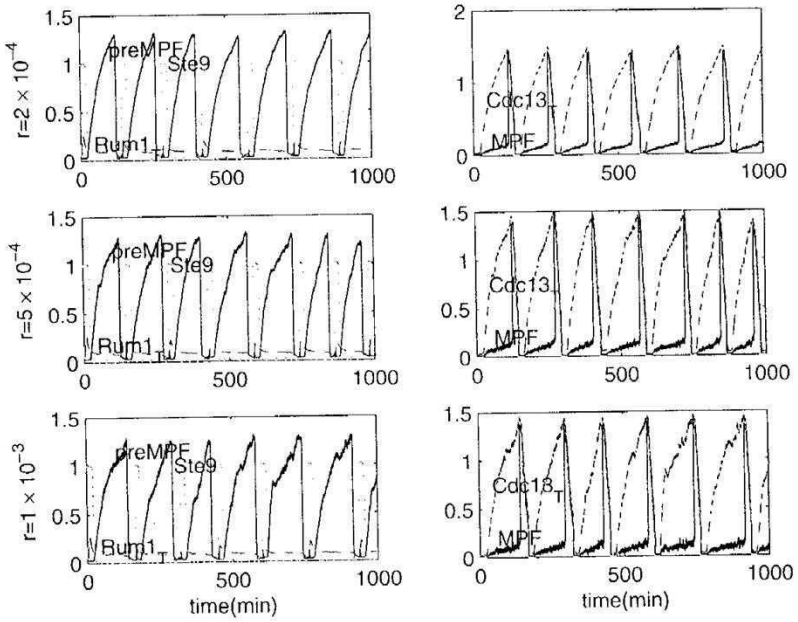

Fig. 11. Protein concentrations with the modified model (11), (13) for $r_{\text{new}} = 10r$ (color online): preMPF/MPF, $\text{Rum1}_T/\text{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

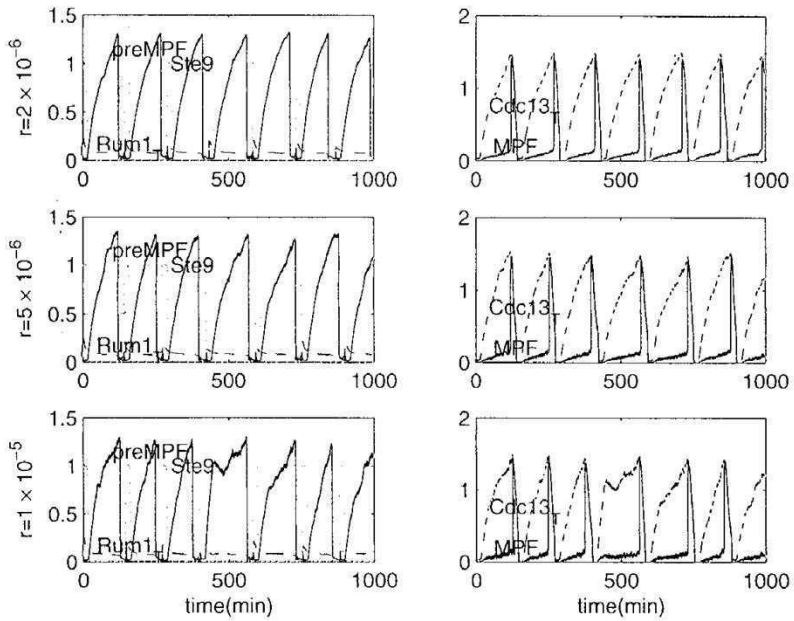

Fig. 12. Protein concentrations with the modified model (11), (13) for $r_{\text{new}} = 0.1r$ (color online): preMPF/MPF, $\text{Rum1}_T/\text{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

behavior is observed also for $r_{\text{new}} = 0.1r$ when protein concentrations are calculated on the basis of model (11), (13). However, the influence of stochasticity in this case can already be observed at the bottom two subplots of preMPF. This is expected as D becomes now more significant parameter compared to r. This is consistent with our conclusions in the end of Sec. 4. When we decrease the value of D in this model, keeping r the same, we observe the behavior changing, accompanying by a shift of the periods, as observed from Fig. 13 plotted for $r = 10^{-4}$. However, the influence of parameter D is still clearly observed on the bottom two subplots of preMPF in Fig. 13. Larger values of D would produce a markedly different picture even for smaller r as demonstrated by Fig. 14, where the influence of stochasticity on the behavior of preMPF can clearly be observed even on the two upper subplots.

Note also that by increasing/decreasing the value of r in 4 times or less, while keeping D the same, we expect from our analysis that the behavior of protein concentrations presented in Fig. 7 will not change drastically. Indeed, recall that the results for this behavior are obtained with the modified model (11), (14). However, due to nonlinearities contained in the right hand side part, further increase in r will lead to numerical instabilities. From our numerical experiments, the upper limit on r to preclude such instabilities is established as $r_{\text{new}} = 5r$.

Similar to our previous analysis, if we decrease D (e.g. four times) in the modified model (11), (14), keeping r the same, the qualitative behavior of cell dynamics approaches to the one presented in Fig. 5. However, the increase in values of

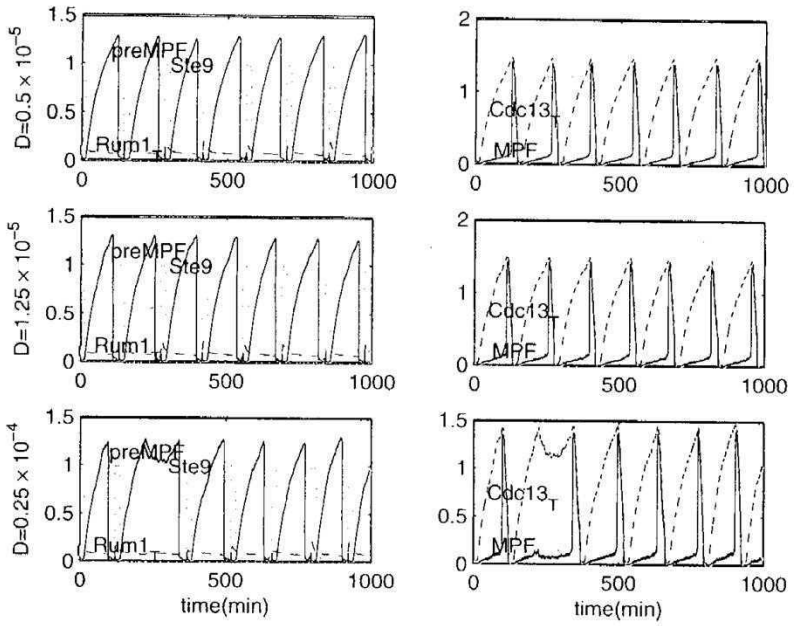

Fig. 13. Protein concentrations with the modified model (11), (13) for $D_{\text{new}} = 0.25D$ (color online): preMPF/MPF, $\text{Rum1}_T/\text{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

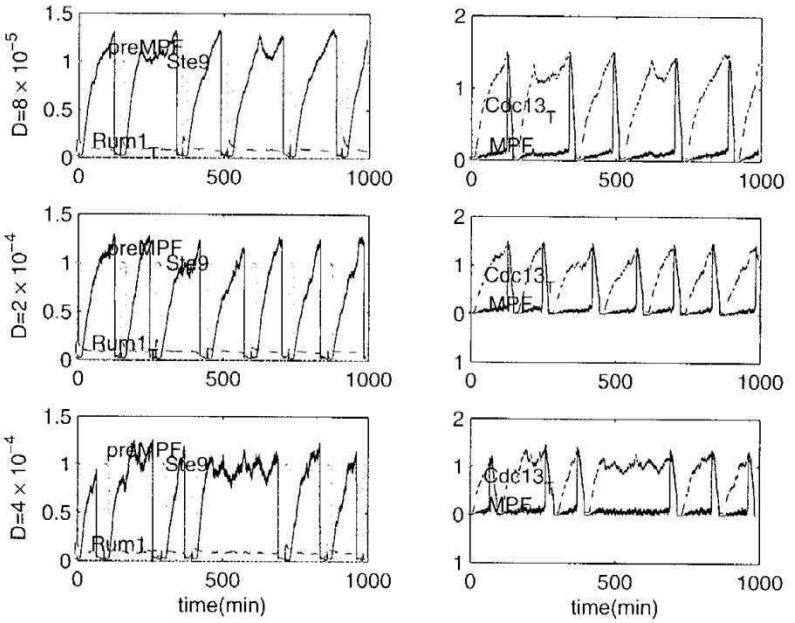

Fig. 14. Protein concentrations with the modified model (11), (13) for $D_{\text{new}} = 4D$ (color online): preMPF/MPF, $\text{Rum1}_T/\text{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

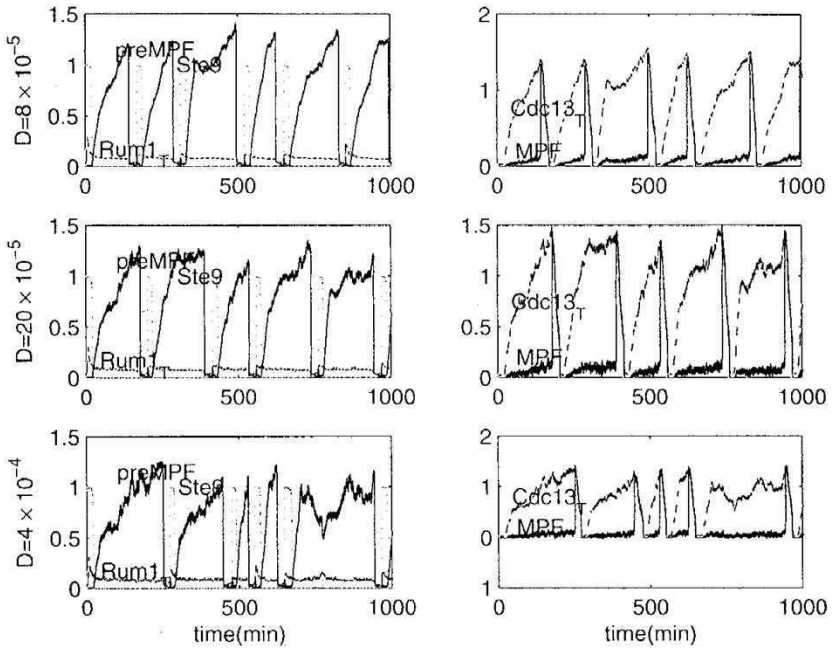

Fig. 15. Protein concentrations with the modified model (11), (14) for $D_{\text{new}} = 4D$ (color online): preMPF/MPF, $\text{Rum1}_T/\text{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

D will lead to qualitative changes. As for model (11), (13), this is expected in this case too due to the increased influence of stochasticity. We demonstrate this increased influence by Fig. 15 where it can clearly be observed for all six sublots of preMPF.

Finally, we analyze the parametric sensitivity of the results obtained with model (16), (17) with respect to parameters γ and t_d. We observe that if we decrease γ, the periodicity is changing. In Fig. 16 we demonstrate the emergence of a new period for $\gamma = 0.05$ (compare this figure with Fig. 10). Note further that the cell cycle periodicity can be controlled more efficiently with parameter t_d. Indeed, we demonstrate this by Figs. 17 and 18 which present protein concentrations with the three times decreased/increase value of t_d, respectively (other parameters were kept the same as discussed in the previous section).

The presented sensitivity analysis of our stochastic models coupled with cell cycle control has a number of important consequences. Among other things, a stochastic factor, intrinsic to the models considered here, can play a role of a stabilization mechanism. Using a simple model, describing the activator-repressor dynamics, the authors of Ref. 65 has recently shown that unstable fixed points in system dynamics can be stabilized by noise.

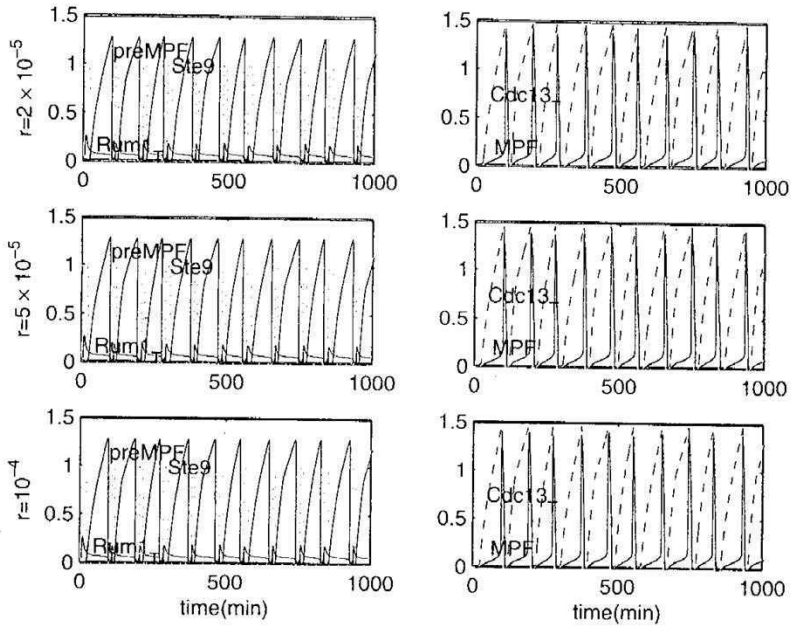

Fig. 16. Protein concentrations with the modified model (16), (17) for $\gamma_{\text{new}} = 0.05$ (color online): preMPF/MPF, $\text{Rum1}_T/\text{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

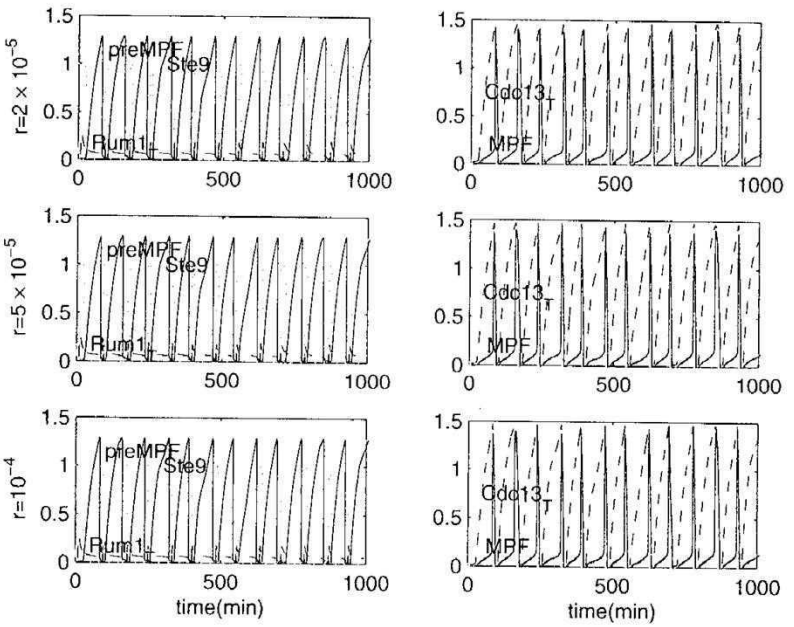

Fig. 17. Protein concentrations with the modified model (16), (17) for $t_d = 0.2$ (color online): preMPF/MPF, $\text{Rum1}_T/\text{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

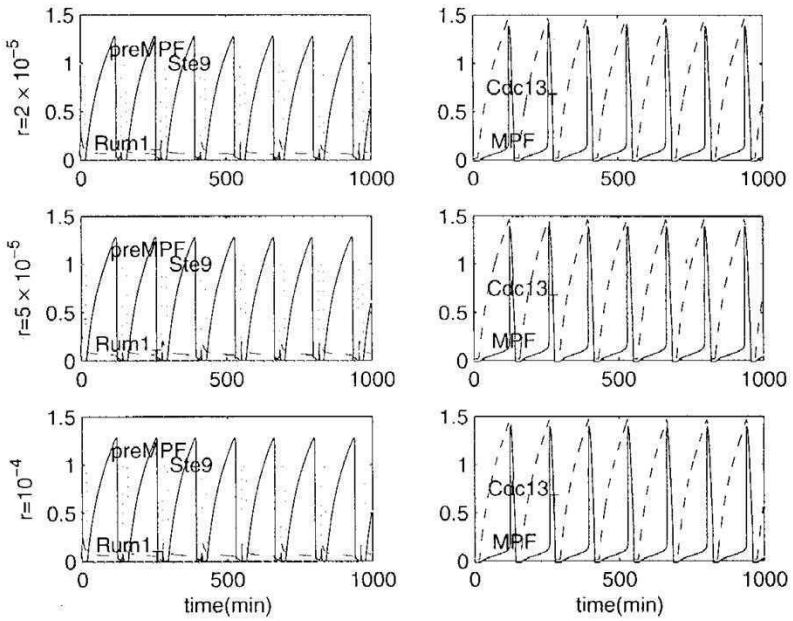

Fig. 18. Protein concentrations with the modified model (16), (17) for $t_d = 1.8$ (color online): preMPF/MPF, $\text{Rum1}_T/\text{Cdc13}_T$, and Ste9 are solid (blue), dashed (red), and dotted (green) lines, respectively.

6. Future Development of Mathematical Models for Cell Cycles and Other Cellular Processes

In Sec. 2 we provided a brief overview of the challenges in the development of more refined mathematical models for cellular processes. Several additional aspects must be taken into account in this development. One of the them stems from the observation that the analysis of time evolution of cellular processes reveals frequently complex behaviors involving multistability and highly oscillatory patterns,[56] where efficient numerical integration procedures developed for highly oscillatory functions could become quite important.[146–149] Furthermore, an accurate description of such behaviors requires taking into account coupled multiscale nature of these processes. Stochasticity is essential in developing mathematical models for such a description due to the fact that random fluctuations in living cells are inevitable under certain conditions.[150] They can restrict the coordination of cellular activities or can introduce phenotypic heterogeneity which may facilitate cellular differentiation in response to changing environmental conditions.[150,151]

The development of more refined mathematical models for cell cycles would be beneficial for such areas as cryobiology/cryosurgery[152,153] (in which case thermal effects need to be accounted for), in the treatment of cancerous and other malignant cells[152] (where coupled effects are essential), for medical applications

of bio-MEMS[154] (in the context of electromechanical effects discussed above), and ultimately for gene network engineering with a range of various applications.[155]

Finally, we note that recent progress has been achieved in developing data driven approaches to modeling cell cycles, including generalizations of the classical Smith–Martin cell cycle model[156] and in developing integrated systems to support research on the cell cycle.[1]

The factors listed above will increase the role of stochasticity in the mathematical modeling of cellular processes because stochastic fluctuations are always present at the level of biochemical reactions where the development of meaningful mathematical models for cellular processes is usually originated from. As we emphasized in this contribution, these stochastic fluctuations should not be eliminated from the mathematical models under various reduction procedures we use to simplify such models. As we demonstrated on simple, but convincing examples, stochasticity remains an important factor to account for even for relatively simple biological systems, involving cell cycles.

7. Conclusions

In the description of the dynamics of cell cycles by mathematical models generically represented by models such as (5), the vector function in the right-hand side is only an approximation of real protein interactions. This is due to the presence of coupled phenomena and processes left behind the scope of such models, e.g. spatial interactions, activities by synthesis, degradation by various reactions, etc. This leads to a situation where part of the information about the dynamics of cell cycles, left behind the scope of such models, should be incorporated in the model by introducing a degree of uncertainty. While fluctuations in the solution due to such uncertainty have been studied by other authors, we developed for the first time a hierarchy of mathematical models where such uncertainty is also present in the vector function responsible for protein interactions. Several main groups of models have been developed. Among them is the group of models that takes into account fluctuations of relative concentrations of proteins during special events of cell cycles. Such fluctuations are induced by varying rates of relative concentrations of proteins and/or by relative concentrations of proteins themselves. As such fluctuations may be responsible for qualitative changes in the cell, we developed a new group of models that accounts for the effect of cellular dynamics on the cell cycle. Finally, we analyzed numerically nonlinear effects in the cell cycle by constructing phase portraits based on the newly developed models and carried out the parametric sensitivity analysis in order to identify parameters for an efficient cell cycle control. The results of computational experiments have clearly demonstrated that the metabolic events in gene regulatory networks can qualitatively influence the dynamics of the cell cycle.

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