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CELL CYCLE CONTROL IN EUKARYOTES :
A BIOSPI MODEL

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Cell Cycle Control in Eukaryotes : a BioSpi model

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Abstract

This paper presents a stochastic model of the cell cycle control in eukaryotes. The framework used is based on stochastic process algebras for mobile systems. The automatic tool used in the simulation is the BioSpi. We compare our approach with classical ODE specifications.

Key words: stochastic π -calculus, stochastic simulation, cell cycle, cyclin-dependent kinase.

1 Introduction

In recent years, a major challenge for theoretical molecular biology is to explain the physiology of cell proliferation in a variety of unicellular and multicellular organisms in terms of their underlying molecular control systems. Molecular biologists have uncovered a lot of information about the proteins controlling the cell growth and division in eukaryotes. This wealth of data reflects the complexity of cell cycle regulatory system and consequently the importance of understanding and describing it with a model that suitably simulates the cell cycle behavior.

The most common approach to model the physiology of the cell cycle is to use ordinary differential equations (ODE) that fit the temporal variations of the concentrations of involved proteins. The molecular controls of promotion/inhibition of these proteins has a non-linear oscillatory behavior that requires numerical algorithms for solving the corresponding equations. Simulation tools like BioUML [1], E-CELL [3], Gepasi [4] support modeling of cellular systems, numerical execution and analysis of the ODE based models.

However, modeling with differential equations assumes that systems evolve deterministically in a continuous state space on a continuous time scale: it is

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not always true in biology. The behaviour of a biological system is driven by a complex network of chemical reactions among different molecular species. Although the great usefulness of the differential rate-equations description of chemical kinetics, this approach does not have a robust physical basis. Namely, the time evolution of a molecular system is governed by the laws of quantum mechanics, that establish the only possibility of discrete integer changes in the molecular population levels. Even neglecting quantum considerations and treating the molecular interaction with classical mechanics, it is impossible to make exact predictions about the molecular population levels at a some time without taking into account the precise positions and velocities of all the molecules of the system. In this sense, we can assert that in the N -dimensional sub-space of the species population numbers, a chemical reacting system of classical molecules is not deterministic and its description by means of ODE approach is not suitable.

The probabilistic nature of a biological system at the molecular scale requires new languages able to describe and predict the fluctuations in the population levels. We rely on a stochastic extension [13,14] of the π -calculus [10], a calculus of mobile processes based on the notion of naming. The basic idea of this biochemical stochastic π -calculus is to model a system as a set of concurrent processes selected according to a suitable probability distribution in order to quantitatively accommodate the rates and the times at which the reactions occur.

We use here this framework to model and simulate the cell cycle control in eukaryotes.

Our development can also be interpreted as a comparison between the most common modeling method with ODE and π -calculus representation, in order to point out the ability of this new tool to perform a stochastic simulation of chemical interactions. We also present data obtained from BioSpi [2] simulations.

The paper is organized as follows. In the next section we report a very brief survey of the physiology of the cell cycle. Section 3 describes the molecular interactions that drive the cell cycle and also reports a classical ODE description taken from the literature with its quantitative parameters. Section 4 briefly recalls the basics of the biochemical stochastic π -calculus. Then it shows our specification of the cell cycle control, and finally, it discusses the results of the stochastic simulation. In the last section we show some conclusions.

2 Cell cycle physiology

The cell cycle is the process by which a growing cell replicates all its components and divides into two daughter cells. In eukaryotes the cell cycle is composed by four phases (G1, S, G2 and M), but it is convenient to think of it as the alternation of two states (G1 and S-G2-M) separated by two transition Start and Finish (two state Nasmyth model [11], see Fig. 1). In G1 the

chromosome are not yet replicated and the cell replication-division process is uncommitted. The Start transition occurs when the internal and external conditions are favorable for a new round of chromosome replication and segregation. At this point, the cell irreversibly commits itself to the replication cycle, progressing through the all four stages G1, S, G2 and M, that drive the alternation of synthesis (S) and mitosis (M). In the S phase each DNA molecule is accurately replicated, and the cell increases its mass by duplicating its “hardware” components (proteins, RNA, phospholipid bilayers, carbohydrates, etc.).

The mitotic process is quite complex, occurring in four different sub-processes: prophase, metaphase, anaphase and telophase. In prophase each chromosome consists of two sister chromatids (two identical DNA molecules), tethered together by specific proteins, called cohesins. In early prophase, thin fibers, called microtubules are assembling a bipolar spindle. When aligned, one chromatid of each chromosome is attached by microtubules to one pole of the spindle (metaphase). Triggered by a specific signal, the Finish transition initiates by destroying cohesins and allowing sister chromatids to be pulled to opposite pole of the spindle (anaphase). Thereafter, daughter nuclei form around the segregated chromatids (telophase) and the daughter cell separates. The two new cells are now back in G1 state and the cycle repeats (Fig. 1).

There are also three checkpoints in G1, G2 and M phases to avoid failures. The cell must be large enough and have undamaged DNA to enter S phase. If these two conditions are not satisfied, the cell stops at the G1 checkpoint. Before entering mitosis, at the G2 checkpoint, the cell verifies that DNA synthesis is complete, DNA is undamaged and the size is adequate. Finally, at the M checkpoint, the proper alignments of the chromosomes and the completeness of DNA replication are verified. When these conditions are satisfied, the metaphase checkpoint is lifted and the cell can divide.

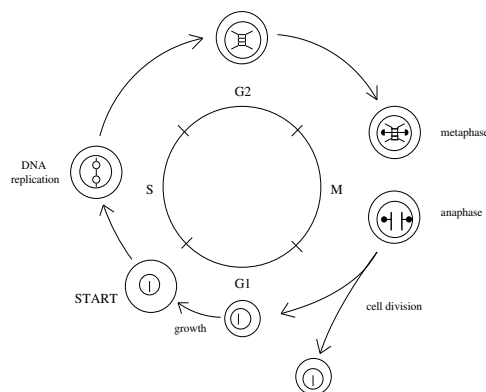


Fig. 1. The phases of the cell cycle

3 Molecular machinery of the cell cycle

The principal components of the complex network of molecular signals regulating the cell cycle are the cyclin-dependent protein kinases (CDKs). The role of these kinases is to phosphorylate certain proteins using ATP as the phosphate donor. CDK requires a cyclin partner in order to be active and to recognize the proper targets. The CDK targets are proteins involved in DNA replication, chromosomes condensation, spindle formation and other crucial events of the cell cycle. For example, by phosphorylating specific nucleotide sequences, where DNA replication can start, the CDKs trigger the DNA synthesis, or by phosphorylating histones (protein involved in DNA packaging), the CDKs initiate the chromosome condensation at G2-M transition.

CDKs activity can be regulated in three ways: by availability of cyclin sub-units, by stoichiometric binding to a cyclin-dependent kinases inhibitor (CKI) and by phosphorylation of CDK sub-units. Most CDKs are present in constant abundance throughout the cell cycle, while the cyclin abundance depends on the rate of cyclin synthesis and degradation, both of which are regulated during the cell cycle as we will see later. The stoichiometric inhibitor CKI of cyclin/CDK dimers also is synthesized and degraded at rates that are regulated during the cell cycle. Finally, CDKs activity can be inhibited by phosphorylation of a specific tyrosine residue. During the cycle the phosphorylation state of CDK varies as the fluctuation of the activity of the tyrosine kinase Wee1 and tyrosine phosphatase Cdc25.

In the Nasmyth model the G1 state is correlated with a low activity of CDKs, while the S-G2-M state is correlated with a high activity of CDKs. At Start, the cyclin synthesis is induced, causing a rise of CDKs activity that continues in the subsequent S-G2-M phases. The initial rise in CDK activity commits the DNA replication, then a further increase is necessary to drive the cell into M phase.

The Finish transition is characterized by the activation of anaphase promoting complex (APC). The APC labels some specific target proteins, which are subsequently destroyed by the cell's proteolytic machinery. The APC is composed by a complex of about a dozen of polypeptides and two auxiliary proteins Cdc20 and Cdh1. The Cdc20 is active at Finish and is involved in the degradation of cohesins at anaphase and in the activation of Cdh1. The combined activity of Cdc20 and Cdh1 is responsible of the cyclin degradation at telophase, allowing the cycle to return to G1 state. The activity of Cdc20 and Cdh1 is controlled by cyclin/CDK dimers, that activate Cdc20 and inhibits Cdh1.

3.1 A simple model of Start and Finish

The control mechanism of the cell cycle modeled by Novak et al. [12] postulates the antagonistic interaction between CDK and APC: the APC extinguishes CDK activity by destroying its cyclin partners, whereas cyclin/CDK dimers

inhibit APC activity by phosphorylating Cdh1 (Fig. 3). The interaction is also mediated by a cyclin-dependent kinase inhibitor (CKI).

The biochemical reactions describing the interaction between cyclin/CDK dimers, APC and CKI are below (parameters values are listed in Tab. 1, where the k 's are the rate constants and the J 's are the Michaelis constants), assuming that the APC cores are in excess and that the total amount of Cdh1 is 1 [12].

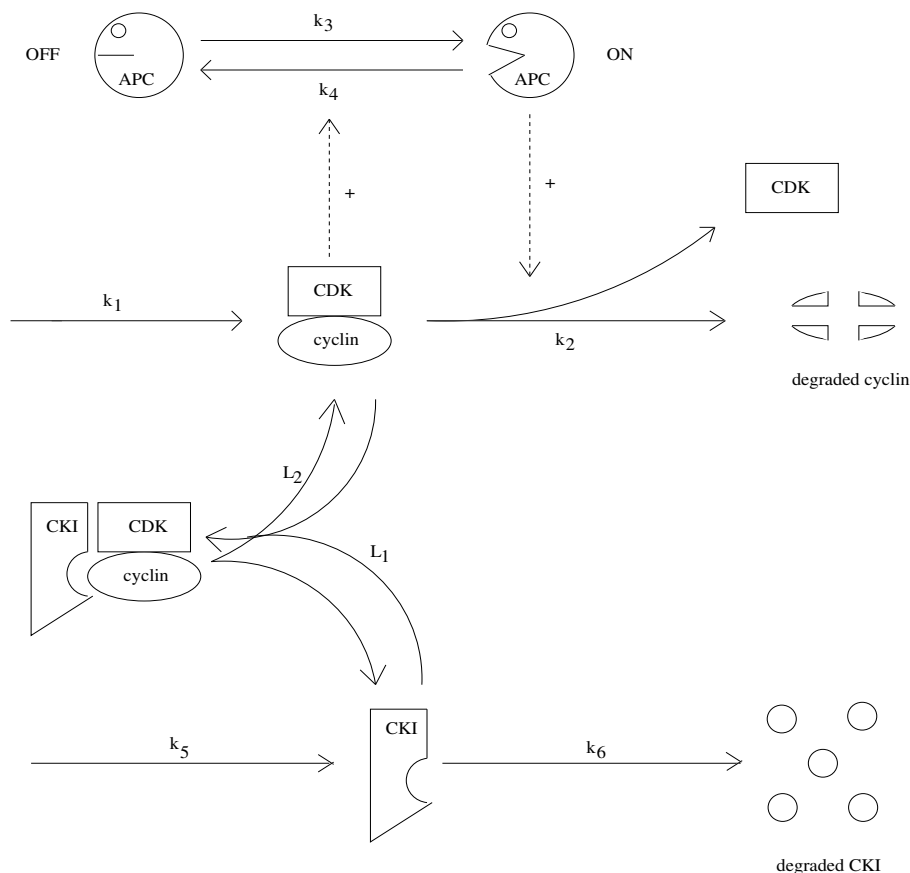


Fig. 2. Cyclin sub-units are synthesized on ribosomes in the cytoplasm and bind rapidly and irreversibly to CDK kinases to form active dimers cyclin/CDK. The cyclin sub-units are degraded periodically by the APC, releasing inactive CDK monomers. The APC is inactivated by cyclin/CDK and re-activated by an “activator”. The k 's are the chemical reaction rates, that for the most part are functions of the dynamics variables. For example, $k_2 = k'_2[inactiveAPC] + k''_2[activeAPC]$, where k'_2 and k''_2 are the enzymatic turnover numbers characterizing the less- and more-active forms of APC, respectively.

Table 1
Parameters values. See [12,6].

Parameters	Values	Parameters	Values
k_1	0.050 min^{-1}	k_8	0.150 min^{-1}
k'_2	0.050 min^{-1}	L_1	200.000 min^{-1}
k''_2	1.000 min^{-1}	L_2	1.000 min^{-1}
k'_3	0.100 min^{-1}	ν'_2	0.050 min^{-1}
k''_3	3.000 min^{-1}	ν''_2	0.150 min^{-1}
k_4	35.000 min^{-1}	J_3	0.040
k'_5	0.005 min^{-1}	J_4	0.040
k''_5	0.200 min^{-1}	m_c	10.000
k_6	0.100 min^{-1}	n	4.000
k'_7	0.150 min^{-1}	μ	0.010
k''_7	9.000 min^{-1}		

$$\frac{dX}{dt} = k_1 - (k'_2 + k''_2 Y)X + (k'_7 + k''_7 X)T - L_1 XZ + L_2 T \quad (1)$$

$$\frac{dY}{dt} = \frac{(k'_3 + k''_3 A)(1 - Y)}{J_3 + 1 - Y} - \frac{k_4 mXY}{J_4 + Y} \quad (2)$$

$$\frac{dZ}{dt} = k_8 + [\nu'_2(1 - Y) + \nu''_2 Y]T - (k'_7 + k''_7 X)Z - L_1 XY + L_2 T \quad (3)$$

$$\frac{dT}{dt} = -[\nu'_2(1 - Y) + \nu''_2 Y]T - (k'_7 + k''_7 X)T + L_1 XZ - L_2 T \quad (4)$$

$$\frac{dA}{dt} = k'_5 + k''_5 \frac{(mX)^n}{J_5'' + (mX)^n} - k_6 A \quad (5)$$

$$\frac{dm}{dt} = \mu m \left(1 - \frac{m}{m_c} \right) \quad (6)$$

where X, Y, Z and T are the concentrations of cyclin/CDK dimers, active Cdh1/APC complex, CKI monomers and cyclin/CDK/CKI trimers; A is the concentration of the Cdc14 phosphatase, that activates Cdh1 at Finish, removing from it the inhibitory phosphate group placed there by cyclin/CDK (Fig. 3). m is the cell “mass” (or size) defined as $m = V_{cyt}/V_{nuc}$, where V_{cyt} and V_{nuc} are the volume of the cytoplasm and the volume of nucleus, respectively. The mass is also time dependent and its evolution is described by eq. (6), where m_c is the maximum size to which a cell may grow if it does not

divide and μ is the specific growth rate when $m \ll m_c$. It is also $m \rightarrow m/2$ whenever the cell divides.

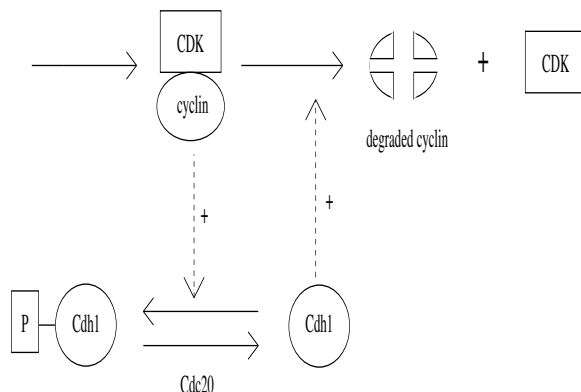


Fig. 3. The sequence of events in the cell cycle can be represented as a negative feedback loop: the cyclin/CDK dimers (X) turn on the activator (Cdc20), which indirectly activates Cdh1, which destroys cyclin sub-units.

At the metaphase-anaphase transition, Cdc14 is activated by Cdc20, which destroys an inhibitor of Cdc14, and it is assumed $A \propto [Cdc14] \propto [Cdc20]$, where the symbol $[-]$ denotes the concentration.

Notice finally that the irreversible transitions Start and Finish are abrupt jumps driven by the rhythmic activation/inhibition of CDK by Cdh1. In equation (2), $Y = [Cdh1]$ represents the active form of Cdh1 protein. When phosphorylated, it becomes inactive. The activity of Cdh1 is constructed as an ultra-sensitive switch between its two forms [8]. At the beginning of the cycle, Cdh1 is active, i. e. $Y \approx 1$. When the X is high enough to compete with $[Cdc20]$, the system changes quickly to $Y \approx 0$.

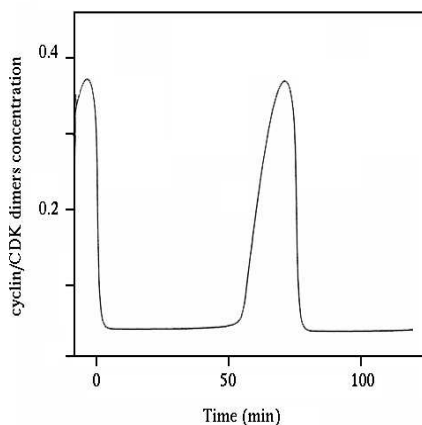


Fig. 4. Simulation of cyclin/CDK concentration variation in time from equations (1) - (6) with the parameters given in Tab. 1. (See [6,12])

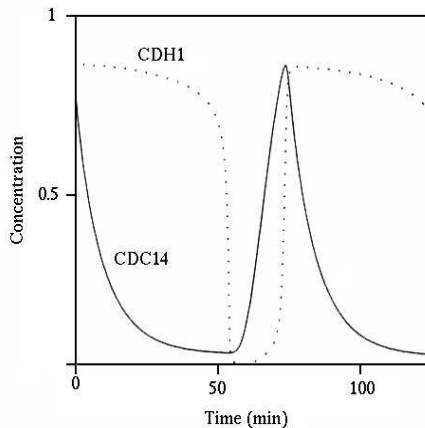


Fig. 5. Simulation of CDH1 and CDC14 concentrations variations in time from equations (1) - (6) with the parameters given in Tab. 1.(See [6,12])

4 Implementation and results

We first recall the syntax and the intuitive semantics of the π -calculus. We then describe our specification of the cell cycle control, and eventually we discuss the simulation results.

4.1 The biochemical stochastic π -calculus

We recall here a simplified version of the calculus in [14] because we need no homodimerization reaction in our specification. Biomolecular processes are carried out by networks of interacting protein molecules, each composed of several distinct independent structural parts, called *domains*. Pair-wise interaction between domains depends on structural and chemical complementarity of particular portions, called *motifs*. Interaction between proteins causes biochemical modification of motifs (e.g. covalent changes). These modifications affect the potential of the modified protein to interact with other proteins. Since protein interactions directly affect cell function, these modifications are the main mechanism underlying many cellular functions, making the stochastic π -calculus particularly suited for their modeling as mobile communicating systems.

Processes model molecules and domains. Global channel names and co-names represent complementary motifs and newly declared private channels define complexes and cellular compartments. Communication and channel transmission model chemical interaction and subsequent modifications. The actual rate of a reaction between two proteins is determined according to a *basal rate*³ and the concentrations or quantities of the reactants. Two different reactant molecules, P and Q , are involved, and the reaction rate is given by

³ The basal rate of a reaction is an empirically-determined constant, which depends on the specific reaction, the temperature, etc.

$Brate \times |P| \times |Q|$, where $Brate$ is the reaction's basal rate, and $|P|$ and $|Q|$ are the concentrations of P and Q in the chemical solution.

The prefix $\pi.P$ of the π -calculus is replaced in the stochastic variant by $(\pi, r).P$ where r is the single parameter of an exponential distribution that characterizes the stochastic behaviour of the activity corresponding to the prefix π . Thus, r corresponds to the basal rate of a biochemical reaction.⁴ Otherwise, the original π -calculus syntax remains intact. The structural congruence \equiv is extended with $A(\tilde{y}) \equiv P\{\tilde{y}/\tilde{x}\}$ (if $A(\tilde{x}) ::= P$ is the unique defining equation of constant A). Similarly to [14] we assume all processes in head normal form. In particular, a process P is in *head normal form* if either it is the null process or $P \equiv \sum_i (\pi_i, r_i).P_i$ and $\forall i \neq j. sbj(\pi_i) \neq sbj(\pi_j)$.⁵ Note, that this condition is justified since we assume at most one occurrence of a given motif in a domain.

The operational semantics of the calculus thereby defines the dynamic behaviour of the modeled system driven by a *race condition*, yielding a probabilistic model of computation. All the activities that are enabled in a state compete and the fastest one succeeds. The continuity of exponential distributions ensures that the probability that two activities end simultaneously is zero.

Since reaction rates depend on the number of interacting processes, the two auxiliary functions, $In, Out : 2^{\mathcal{P}} \times \mathcal{N} \rightarrow \mathbf{N}$ inductively count the number of receive and send operations on a channel x enabled in a process:

$$\begin{aligned} In_x(\mathbf{0}) &= 0 \\ In_x\left(\sum_{i \in I} (\pi_i, r_i).P_i\right) &= |\{(\pi_i, r_i) \mid i \in I \wedge sbj(\pi_i) = x\}| \\ In_x(P_1|P_2) &= In_x(P_1) + In_x(P_2) \\ In_x((\nu z)P) &= \begin{cases} In_x(P) & \text{if } z \neq x \\ 0 & \text{otherwise} \end{cases} \end{aligned}$$

Out_x is similarly defined, by replacing any occurrence of In with Out and the condition $sbj(\pi_i) = x$ with $sbj(\pi_i) = \bar{x}$.

The reduction semantics of the biochemical stochastic π -calculus follows.

⁴ In the original stochastic π -calculus [13] the rate is associated with the prefix. However, in a chemical reaction both reactants share a single basal rate. This is resolved by associating the basal rate with the channel name. For clarity purposes, we continue to specify the rate r in the prefixes throughout the paper, implicitly assuming that two prefixes have the same rate when using the same channel name.

⁵ $sbj(\pi)$ denotes the subject of π , i.e. its output or input link.

$$(\dots + (\bar{x}\langle z \rangle, r).Q) | ((x(y), r).P + \dots) \xrightarrow{x, r_b \cdot 1 \cdot 1} Q | P\{z/y\}$$

$$\frac{P \xrightarrow{x, r_b \cdot r_0 \cdot r_1} P'}{P|Q \xrightarrow{x, r_b \cdot r'_0 \cdot r'_1} P'|Q}, \begin{cases} r'_0 = r_0 + In_x(Q) \\ r'_1 = r_1 + Out_x(Q) \end{cases}$$

$$\frac{P \xrightarrow{x, r_b \cdot r_0 \cdot r_1} P'}{(\nu x)P \xrightarrow{x, r_b \cdot r_0 \cdot r_1} (\nu x)P'}$$

$$\frac{Q \equiv P, P \xrightarrow{x, r_b \cdot r_0 \cdot r_1} P', P' \equiv Q'}{Q \xrightarrow{x, r_b \cdot r_0 \cdot r_1} Q'}$$

A reaction is implemented by the three parameters r_b , r_0 and r_1 , where r_b represents the basal rate, and r_0 and r_1 denote the quantities of interacting molecules, and are computed compositionally via In_x and Out_x while deducing transitions.

4.2 Specification

The system of interacting proteins that regulate the cell cycle illustrated in Fig. 2 has been implemented in the biochemical stochastic π -calculus as follows.

```

SYSTEM ::= CYCLIN|CDK|CDH1|CDC14|CKI|CLOCK
CYCLIN ::= (\nu bb)BINDING_SITE
BINDING_SITE ::= (\bar{l}b\langle bb \rangle, R_4).CYCLIN_BOUND
CYCLIN_BOUND ::= DEGCYC + DEGCKI + CYC_CDK_CKI
DEGCYC ::= (degp, R_1).\overline{degc}.0
DEGCKI ::= (\overline{degd}, R_3).CYCLIN_BOUND
CYC_CDK_CKI ::= (\overline{bind}\langle bb \rangle, R_{11}).\bar{b}b.TRIM
TRIM ::= DIM + NOTHING
DIM ::= (removecki, R_9).(CDK|CYCLIN_BOUND)
NOTHING ::= (donothing, R_{10}).TRIM
CDK ::= (lb\langle cbb \rangle, R_4).CDK_CATALYTIC
CDK_CATALYTIC ::= INACTCDH1 + NEWCDK + INACTCAT
INACTCDH1 ::= (\overline{cdh1r}, R_6).CDK_CATALYTIC
NEWCDK ::= (degc, R_2).CDK
INACTCAT ::= (cbb, R_5).0

CDH1 ::= DEGRCYC + INACT + ACTCDC14
DEGRCYC ::= (\overline{degp}, R_1).\overline{CDH1}
INACT ::= (cdh1r, R_6).\overline{pcdh1r}, R_7).CDH1
ACTCDC14 ::= (\overline{removep}, R_8).\overline{CDH1}

CDC14 ::= (pcdh1r, R_7).CDC14P
CDC14P ::= (removep, R_8).CDC14
    
```

$$\begin{aligned}
CKI &::= DEGRCKI + BINDCYC \\
DEGRCKI &::= (degd, R_3).0 \\
BINDCYC &::= (bind(x), R_{11}).0 \\
CLOCK &::= CLOCK1 + CLOCK2 \\
CLOCK1 &::= (\overline{removecki}, R_9).CLOCK \\
CLOCK2 &::= (donothing, R_{10}).CLOCK
\end{aligned}$$

$$\begin{aligned}
R_1 = 0.005 \quad R_2 = 0.001 \quad R_3 = 0.003 \quad R_4 = 0.500 \quad R_5 = 0.300 \quad R_6 = 0.005 \\
R_7 = 0.009 \quad R_8 = 0.009 \quad R_9 = 0.010 \quad R_{10} = 0.017 \quad R_{11} = 0.020
\end{aligned}$$

The system is composed by six concurrent processes, corresponding to the main five species of proteins, which regulate the cell cycle: CYCLIN, CDK, CDH1, CKI, CDC14 plus the auxiliary process CLOCK whose meaning is explained below. First cyclin sub-units bind to CDK monomers (CYCLIN process) and make them active; then the dimers cyclin/CDK, the activator CDC14 and the CDH1 are involved in a negative feedback loop: cyclin/CDK turns on CDC14, which activates CDH1, which inhibits the cyclin/CDK activity, destroying the cyclin sub-units. The model includes also another possibility of inhibition of cyclin/CDK: the stoichiometric binding with CKI. Instead, we have neglected the inhibition of cyclin/CDK by phosphorylation of CDK sub-units (to keep the model as simple as possible). The events that our code simulates are the dimers cyclin/CDK formation, phosphorylation (de-phosphorylation) of CDH1 by CDC14 and the protein degradation. The binding of cyclin with CDK occurs through the binding site offered by cyclin on the private backbone channel *bb*. All other events occur on global channels each at different suitable rates, following a similar approach to [7]. Phosphorylation (de-phosphorylation) of CDH1 by the catalytic unit of CDK (CDK_CATALYTIC) is mediated by *pchd1r* and *removep* global channels. The stoichiometric binding of cyclin/CDK with CKI is implemented as a local sub-process of CYCLIN process occurring on the channel *bind*.

The different reactions in which the components of the system are involved are implemented as a multiple non-deterministic choice, that is then turned into a probabilistic one by the BioSpi tool (See next section). For instance, the bound state of CYCLIN process (CYCLIN_BOUND), that identifies the cyclin/CDK dimer can undergo three reactions: cyclin sub-unit degradation (DEGCYC), binding with a CKI (CYC_CDK_CKI), to form the trimer cyclin/CDK/CKI (TRIM), or the degradation of CKI sub-unit (DEGCKI). The active form of Cdh1 protein (CDH1) can degrade the cyclin (DEGRCYC), can be inactivated (INACT) by the join with a phosphate group or can be activated by CDC14 (ACTCDC14) that removes from it the phosphor. The trimer CYC_CDK_CKI can be resolved in the dimer cyclin/CDK (DIM) or it can remain itself (NOTHING).

Finally, note that we introduce in the specification the process CLOCK

for technical reasons. It drives the mechanism of sending - receiving on the channels *removecki* and *donothing* in the decomposition of the trimer cyclin/CDK/CDK.

4.3 Simulation

The run of the program produces a trace of the simulated system, that can be subsequently processed to obtain a quantitative time-evolution for each kind of process. The stochastic engine on which BioSpi system is based is the Gillespie algorithm [7] that implements discrete non-deterministic simulations of chemical reactions.

The simulation outputs shown in Fig. 6 are in agreement both with published simulations and data analysis [6,17,16,5,15,9] for the Nasmyth two states model. Our code reproduces the oscillations of the number of processes with the same periods of the differential equation solutions (~ 70 min). This demonstrates that both the ODE model and the π -calculus model are able to simulate the same rhythmic behavior of the cell repeated replication. However the π -calculus model reproduces also the statistical fluctuations of the number of molecules characteristic of a stochastic system at microscopic scale. These fluctuations ripple the shape of the peaks, that instead is sharp in the ODE deterministic model.

Moreover, in our simulation we have used fictitious values for the initial number of processes ($N_0(CYCLIN) = 20$, $N_0(CDK) = 10$, $N_0(CDH1) = 10$, $N_0(CDC14) = 30$, $N_0(CKI) = 10$) because of the lack of experimental measurements. They do not correspond to actual quantities of the related proteins in the cell at the starting of replication. This fact mainly reflects on the height and on the resolution of the peaks in the graphs making more difficult an immediate comparison with the solutions of differential equations. In ODE model the abundance of involved proteins is quantified by its concentration, that is defined as $\frac{N_{proteins}}{V_{nuc}}$, while in BioSpi model we consider purely the number of proteins $N_{proteins}$. Therefore various scale factor, like the volume of the nucleus, re-scale in different way the width of the oscillations in the output of the two models.

5 Conclusions

The continuous deterministic abstraction is an inefficient tool for the description of biological system, because of the inability of the reaction rate equation to describe the fluctuations in the molecular population levels, that could play an important role in the microscopic mechanism governing the macroscopic behavior of the system. Moreover, it is not even guaranteed that the reaction-rate equations provide a sufficiently accurate account of the average molecular population level [7], especially in presence of a complex, non-linear, dynamical system of interactions like the cell cycle machinery. In this context, where the

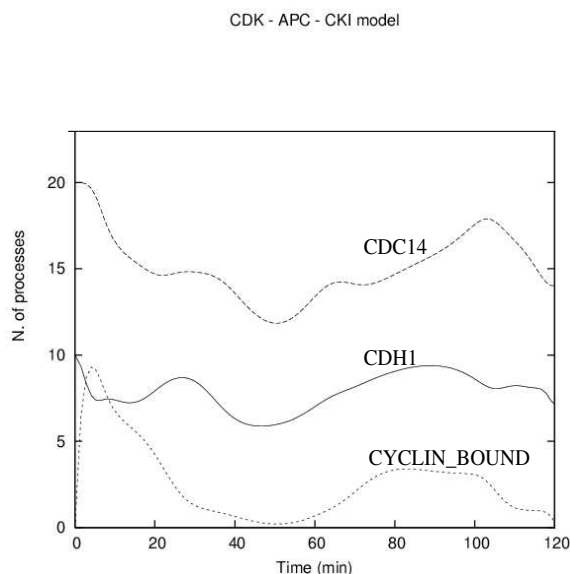


Fig. 6. BioSpi simulation output for the two state Nasmyth model of cell cycle control. Time evolution of absolute number of proteins involved in the process: Cdh1, Cdc14 and cyclin/CDK.

attention of biologists is increasingly being drawn to the microscopic molecular systems, the stochastic π -calculus is a powerful tool for their representation.

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