Checkpoint Oriented Cell Cycle Simulation Critical Role For Age Distribution Initialization

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ABSTRACT

In this paper we start to validate a computational cell cycle model, developed in a collaborative work between computer scientists and biologists, evaluating the convergence between *in-vitro* and *in-silico* results. Whereas most models are phase-orientated our model deals with a checkpoint orientated paradigm and uses phase orientation as an output to provide the biologists with a relevant view of the simulation result. Throughout this paper, we will show that the initialization state of a multi-cellular culture is a high constraint in the relevance of the results. This initialization state lets emerge computational artifacts as phasing.

Categories and Subject Descriptors

I.6.3 [**Simulation and Modeling**]: Applications

Keywords

Cell Cycle, Multicellular Simulation, Developmental System, Individual Cell-Based Model, Artificial Life, Synthetic Biology

1. INTRODUCTION

The living world reveals its complexity daily. Understanding and assimilating this complexity is of major relevance. With the latest computation capacity explosion, *in-silico* models are positioned to provide new means of studying and exploring complex living systems. Many questions could be tackled with these approaches, specifically when experiments are difficult to address *in-vitro*. System modeling may therefore use fitted methodologies and bottom-up approaches tend to be the general paradigm. They focus on each functional component of the systems and their interactions; and allow to tame the natural complexity and to represent it in model.

Cellular cultures are a set of experiments used by biologists to characterize *in-vitro* specific features of the cell behavior. For instance, in cancer research, the culture is used to evaluate the impact of pharmacological compounds on specific regulatory mechanisms of the cells. Increasing the understanding of the cell cycle is at the heart of cancer research and therefore, the high issues foreseen with *in-silico* simulations of cellular systems let think that prospective search of new therapies could be addressed *in-silico*.

In the different fields of computational and molecular biology, the focus on aspects of the cell cycle differs. Molecular biology models focus on the modeling and simulation of the molecular regulatory network of cycline-dependent kinase (CDK) [2]. These models are molecular-based models and do not account for behavioral considerations at a macro-level, their aims being to focus on the regulatory mechanisms.

The other family of models used to simulate cell proliferation is called Individual Cell-Based Models (ICBMs) [1]. These are a subset of the agent-based models. Agent-based models have mainly proved their relevance in the simulation of different complex systems from social networks to the social behavior of hive insects. Basically, individual cell based models come under two classes: cellular automaton (CA) models and off lattice models [4]. These models generally consider the cell cycle as a single time unit decision and the update frequency is the global scheduler of the cell cycle. Basically, this representation does not allow any consideration on the relevance of the major events occurring during progression in the cell cycle phases.

Whereas molecular-based models accurately express the dynamics of the advancement of cells in each phase of the cell cycle, the individual-based models often do not, due to their meta-description of the cell cycle. Expressing these dynamics reveals interest in simulating *in vitro* cultures where external compounds are introduced to study their effect in the dynamics of advancement. Our goal is to simulate as closely as possible the population response to an external stress expressing the dynamics of progression of the cells at a population scale. For that purpose, we use the simplicity of ICBM representations to describe cellular behavior and to introduce temporal considerations thanks to an accurate description of the cell cycle. This approach led us to build a hybrid representation of the cell cycle with a hand coded regulation network and probabilistic-based cellular processes. In this paper we will show the preliminary results obtained simulating a basic stage of the cell's population dynamics: the exponential growth phase, allowing us to focus on the population dynamics during the different phases. Through these experiments, the problem of age distribution of cells will be ad-

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dressed and more globally the focus will be put on the importance of the initial system state in the results of a simulation.

2. MODELLING CELL BEHAVIOUR

The functional and regulatory level of the cell cycle are disjointed. A weakness of traditional approaches in proliferation simulation is often to focus on only one of these aspects whereas the effective cell behavior depends on the interaction between these two levels. Particularly, from the cell's internal state depends the regulatory pathway followed. For instance a cell that has replicated its DNA will be allowed to continue its proliferative behavior. To represent these mechanisms and their interaction with the greatest accuracy, it is necessary to observe and describe both levels in accurate cell cycle modeling.

A natural population of cells presents heterogeneous features. Owing to the variability of the duration of each cell cycle phase, two cells born at the same time will not divide simultaneously even if environmental conditions were equivalent. In this work, this heterogeneity is represented with a specific set of parameters for each cell. Therefore, the embedded parameters are generated according to a distribution law. The cell cycle model is thus able to produce a population of specific cells and not only a population of clones. If the cell population was composed of clones, the system would suffer from phasing and synchrony in the sequencing of the different phases, each sister cells going to division at the same time.

To represent the cellular activity in a temporal manner and remain at a macroscopic level of representation, we based the cellular process modeling on their scheduling as presented in [3]. In this context, 3 parameters are used for each cellular process: the optimal time of realization, the maximum time before it eventually results in the cell's death, and the probability of success. Using these parameters, we generate a set of parameters which are used for the computation. Our processes are represented over time as Bernoulli processes. The average optimal time determines the number of successes needed to consider the process as achieved and the success rate is used to define the probability of success of one trial.

The multi-agent system built with the previous elements will be used to validate our cell cycle model with experimental data. The next part is dedicated to the simulation of cells population with a comparison between *in-vitro* and *in-silico* results.

3. SIMULATION OF CELL POPULATION

In this part, a specific stage of the cellular proliferation is studied. This stage, called the exponential growth phase, displays particular features that allows the simplification of the environment. During this stage, the proliferation is not inhibited. Several inhibition factors are undergone by the cells. Firstly, the cells need glucose and oxygen to feed themselves but in a 2-D monolayer culture the environment is saturated in growth factors and nutriments. This is explained by the fact that the cell layer is immersed in the culture medium. This characteristics allow the need for the simulation environment of diffusion algorithms or artificial chemistry to be dispensed with.

In *in-vitro* culture, cell proliferation is also constrained by an inhibition factor called the contact inhibition. This inhibition appears when cells reach confluence in their culture medium. Indeed, if its local neighborhood is saturated by other cells, a cell will not proliferate and will enter into quiescence. The exponential growth phase is the proliferation stage, which precedes the confluence. For these considerations, the simulation model can be dispensed with physical model and topological aspects. The cells do not have shapes nor dedicated site on a lattice. The simulation runs without environment.

In this work we show that the model and the simulator are able to reproduce the characteristics of the cell proliferation in an exponential growth phase. The expressivity of the model also induces that prospective research could be done using the simulator. The different experiments proposed highlight the importance of the age distribution in a multicellular simulation. Through this experiments set, the different models of age repartition of cells in the cell cycle are confronted and it is observed, throughout the simulation, that the cell age distribution is not uniform but decreasing as presented in several mathematical modeling.

Another important question addressed in this work is which variability into a cell population. An experiment, with a forced decreasing distribution and a population of clones, shows that it is difficult to highlight that the cells are strictly identical. Nevertheless, the artifact induced by this equivalence has an important impact on a synchronized situation. Indeed, even if a population of clones could be synchronized with the same scenario as a heterogeneous population, the desynchronization remains impossible. It is due to the involved checkpoint that lets all the cells pass through its transition when the synchronized situation is over. From there, the sequencing of the different actions will be totally synchronous and the resynchronization will never occur.

4. CONCLUSION

The preliminary results of this work point out that the model reproduces accurately the dynamics of cell proliferation in an exponential growth phase. The different experiments led in parallel with different initialization protocols show that the system state at the beginning constrains the results. Moreover the problematic of the system state at the initialization is extendable to the simulations of all complex systems. The variability of the results from one set of parameters to another, which is very close in terms of valuation, reveals the complex nature of the cells population. To tackle this complexity, reducing the environmental side-effect to quantify them later may also be extended to all complex systems. The help of *in-silico* experiments in biological science allows the consideration of problems that cannot be addressed *in-vitro*. In this case, the problem of age distribution in the cell cycle that cannot be addressed with *in-vitro* experiments, due to the lack of adapted technologies can be tackled. The issues highlighted through this paper show that the distribution of cell age in a simulation has a tremendous impact and should be regularly studied.

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