

First Pass Monte Carlo Simulation of Basic Eukaryotic Cell Cycle Regulation Mechanism

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Abstract

The cell cycle and its regulation capture much attention among systems of interest to a wide variety of academic researchers, pharmaceutical industries, and medical initiatives alike. This essential mechanism exceeds in complexity, and thus “quantitative tools are necessary to probe reliably into the details of cell cycle control (Tyson and Novak, 2001)”. Thus far, quantitative efforts have focused on theoretical mathematical models that have been constructed to mimic experimental observations of the system. In light of recent functional improvements to MCell/DReAMM with the release of v.3, the time is ripe to build a first pass spatial model of cell cycle regulation based on the extensive data available from previous mathematical models, with the hope of adding another level of quantitative insight into cell cycle regulatory mechanisms.

Introduction

Careful regulations must control the process of cellular division so that complete replication and proper alignment of the chromosomes occur on a balanced time scale with the duplication of all of the rest of the cellular material. If these processes occur at different rates, the division into daughter cells either fatally damages the chromosomes or the cells become too large or too small to be viable. Tyson and Novak describe a cell cycle that has an irreversible ‘start’ transition between the G1 phase, where a cell spends most of its life, and the S, G2, and M phases where replication, growth, and mitosis occur. The key molecular complexes CycB/Cdk and Cdh1/APC exist in a central antagonism that drives both this start transition and an irreversible ‘finish’ transition that occurs at metaphase during mitosis. In the Tyson/Novak model, the cell mass influences CycB/Cdk and other ‘insensitive helper’ molecules influence both CycB/Cdk and Cdh1/APC to induce the start and finish transitions, respectively.

Using MCell/DReAMM, we will transform the Tyson/Novak sets of non-linear ordinary differential equations (ODEs) into a stochastic model that describes the same characteristic start and finish transitions. The benefit of a stochastic model lies in the potential for new insights into the dynamics of the control networks on a molecular level. Modeling with ODEs necessarily glosses over these dynamics because the basic assumption underlying the fitting of an ODE to a system implies that the reactant molecules exist in a well-mixed state for the duration of the reaction time. However, during molecular interaction inadequate mixing tends to occur at localized regions in space, and the impact of these regions on the balance between a reaction rate and individual molecular diffusion rates may have interesting dynamical implications that a stochastic model could simulate.

Methods

In order to create the stochastic model, we will make use of the improved functionality of MCell v. 3, which now readily handles Michaelis-Menten type reactions occurring among diffusing molecules. In addition, these Michaelis-Menten reactions can be simplified to exclude the intermediary complex for the initial model. Such an omission should achieve a primary qualitative agreement with the Tyson/Novak model at the expense of the molecular dynamics data that we can obtain later by re-including the intermediate state.

First, we face the challenge of reconstructing the molecular reactions from the Tyson/Novak papers. Then, we will convert the reactions to the Model Description Language (MDL) syntax so MCell can interpret and simulate the interactions. Also in the MDL, we will define a simple space, such as a box, within which these reactions occur. Lastly, we must globally scale the reactions rates down to a reasonable time scale. We perform such a reduction because the real-world cell cycle occurs on a time scale on the order of minutes, but good resolution of molecular interaction occurs at simulation time steps on the order of micro- or nano- seconds, making such a real-world simulation unnecessarily computationally expensive without gathering any more meaning from it.

Future Work

The rudimentary model described above would provide the starting point for numerous extensions towards a sophisticated model of cell cycle regulation. As mentioned previously, the simplified Michaelis-Menton reactions may undergo expansions to simulate higher resolution molecular dynamics. We can easily make the simple spatial constraint into a structure reminiscent of an actual cell, and even partition the space into nuclear and cytoplasmic spaces. Eventually, the model may increase in volumetric capacity in proportion to increasing mass to simulate more realistic cellular conditions during division. Also, the format of the MDL allows us to include further regulatory cycles at a later time very easily. Furthermore, minor adjustments to the model could also simulate mutation or disease states, just like what has been done with available mathematical models.

Summary

We intend to build a minimal model for the regulation of eukaryotic cell cycles that produces the same qualitative features of the Tyson/Novak mathematical model for this system. This first model allows for further, incremental improvements that can fill out a more complex, sophisticated model for further use. A computational model of cell cycle regulation should allow us to explore spatial implications for the system and focus on some molecular intricacies that mathematical modeling essentially ignores. With MCell/DReAMM we can track every molecule and what it is doing in discrete space and recover these details.

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