Monte Carlo Simulation of Basic Eukaryotic Cell Cycle Regulation

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Introduction

The cell cycle is an essential process at the core of many important biological events and plays a part in pathologies such as cancer. Many approaches have been taken to understand the complex regulation of this cycle, but until now none have been able to provide insight into its dynamic environment that is highly sensitive to the interaction between chemical signals and physical cell structures.

The standard theoretical approach for quantitatively describing how the cell cycle operates is to model biochemical reactions as systems of differential equations. This approach requires that physically meaningful parameters, like the mass of the cell or its cytoplasmic volume to nuclear surface area ratio, be set as variables that affect the rates of reactions and the movement of molecules. Thus the impact of these physical parameters is adjusted to match experimental results, instead of the changes in the physical environment naturally affecting the chemical reactions in space to reproduce experimental results. The goal of this modeling project focused on attaining cell cycle oscillations in a minimal model system by using a Monte Carlo algorithm implemented in *MCell* to simulate chemical reaction outcomes, and by placing these reactions in a realistic three-dimensional space created with *Blender* and *DReAMM*.

Chemical Basis for the Model

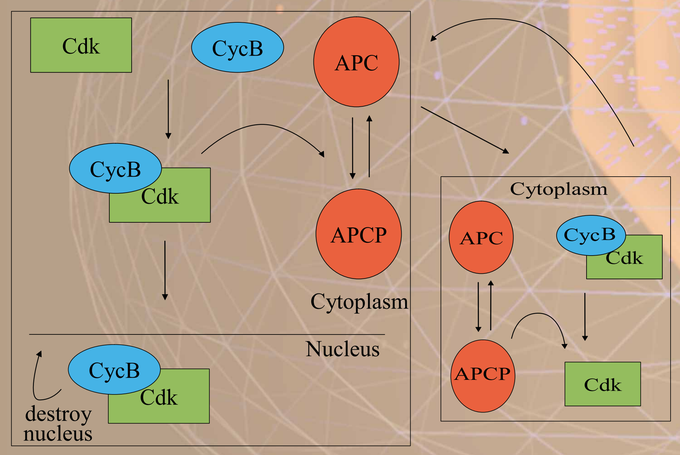


Fig. 1: This chemical network was derived as a simplified version of the networks used by Tyson (2006) and Yang (2006) as the basis for their mathematical models.

The Major Players

Cdk – A kinase that, when active, activates and deactivates key systems of control. Also initiates the breakdown of the nuclear membrane during mitosis (cell division) when active.

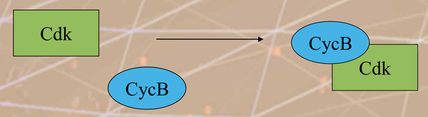
CycB – Activates Cdk. Its creation and destruction is tightly regulated and depends indirectly on Cdk activity.

APC – Activated by Cdk. Promotes the end of mitosis by destroying CycB, thus inactivating Cdk so the nuclear membrane can reform.

Method

The reaction network (Fig. 1) was translated into a specialized code called Model Description Language (MDL) for use in *MCell/DReAMM*.

Fig. 2: CycB + Cdk -> CycBCdk [1e9] : complexBrxn



Rate and Diffusion constants had to be chosen, adjusted, and then scaled to simulate a twenty-four hour cycle within a few minutes of computational time.

A spatial, compartmentalized model had to be built to interact with the reaction mechanisms:

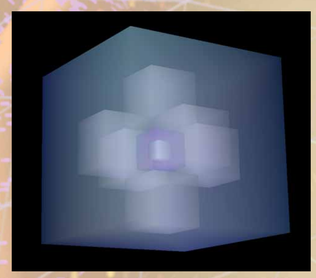


Fig 3: Boxes represent the cell membrane, ER, nucleus, and DNA.

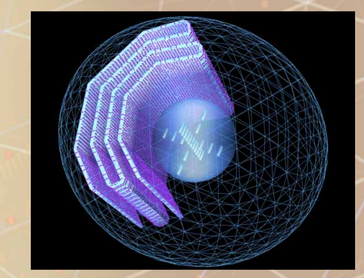
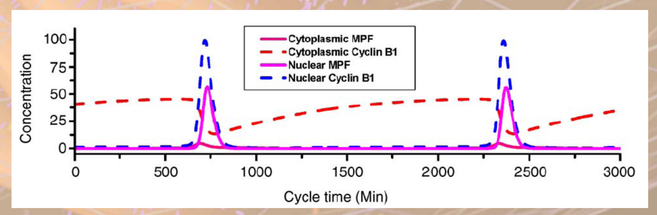
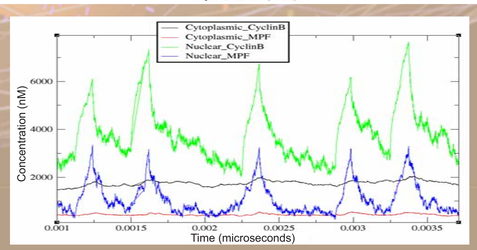


Fig 4: Refined Model with cell membrane, rough ER, nucleus, and chromosomes.

Results

Oscillations that qualitatively mimic experimental and mathematical results have begun to emerge from this model.





Figs. 5 and 6.

The *MCell/DReAMM* model allows physical components like transcriptional signaling for the production of CycB and nuclear membrane degredation to be handled in a more intuitive way than other models. This model indicates that some steps of the process, such as transport of CycB into the nucleus, may not happen as quickly or easily as the mathematical models assume.

Conclusion

Our spatially realistic model of cell cycle regulation succeeds in producing the periodic fluctuations in levels of key regulatory proteins that are observed experimentally and have been modeled mathematically. Preliminary results differ in some key aspects from other currently available models, so there is much work left to do toward validating and improving on this initial model. Some future enhancements include further refinements and additions to the physical cell architecture, the inclusion of greater complexity in the regulatory networks, additional observations of how the model reacts to various spatial and temporal alterations, and using experimental data to determine the ability of the model to predict laboratory outcomes.

Acknowledgements

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Initial model designed with *Blender* v. 2.42 (blender.org).

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