# A General Framework for Modeling Growth and Division of Mammalian Cells

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***Short Abstract* — A framework for modeling complex cell-biologic processes is presented, based on two constructs: one describing the entire lifecycle of a molecule and the second describing the basic cellular machinery. Use of these constructs allows models to be built in a straightforward manner that fosters rigor and completeness. To demonstrate the framework, an example model of the mammalian cell cycle is presented that consists of several hundred differential equations of simple mass action kinetics. The additional complexity afforded by the framework allows the example model to be calibrated to both large-scale and small-scale observations and allows predictions to be made at both the systems level and the molecular level.**

***Keywords* — Molecule lifecycle, System dynamics, Cell-cycle.**

## I. Purpose

Quantitative modeling of complex biologic processes, such as the eukaryote cell cycle, has been practiced for many decades. (For a general review of cell-cycle modeling, see [1-3] and references therein.) These efforts have produced descriptions of cell-cycle subprocesses (e.g., [4]) and predictions (e.g., [5]; [6] testing of [7]) beyond the realm of the mental models used by many researchers. These models, however, typically involve a small set of regulating enzymes (often fewer than ten) that are independent of the functioning of the entire cell. We have developed a general framework that allows an increase in modeling complexity and tying of pathways to the basic cellular machinery. The framework is demonstrated in a cell-cycle model that allows several novel predictions.

## II. Model Details

The framework involves a construct describing the lifecycle of individual molecules and a construct describing the basic cellular machinery (the base model). The lifecycle construct calculates the creation and destruction of a molecule as well as applicable interactions with other molecules. The base model calculates energy usage, amino acid and nucleotide usage, membrane transport, RNA synthesis and destruction, and overall protein synthesis and destruction. The example cell-cycle model built on the framework calculates the quantities of 33 proteins, and their concomitant 33 mRNAs, over time. The example model exclusive of the base model consists of 387 ODEs and 1100 rate equations.

## III. Conclusions

The example model allows predictions at both the systems level and the molecular level, including the following.

- When redundant pathways can activate a time-critical process, one preferred pathway must inactivate the other redundant pathway(s).
- Explicit growth monitoring is unnecessary during the mammalian cell cycle.
- Pre-translation mRNA regulation (other than splicing and the number of RNA polymerase) is unnecessary during the cell cycle.
- Transcription and translation (i.e., growth) continues during S phase at unimpeded rates.
- For cells capable of division, a ready supply of RNA polymerase must be available during G0.
- For cells capable of division, either a supply of DNA polymerase must be kept inactive during G0 or intense transcription and translation activity must occur and be controlled at a saturation level.
- SCF progressively complexes with Fbw7, Skp2, and Btrc through the cell cycle because of their differences in affinity with SCF and because of autoubiquitination in the absence of substrates.
- Cdc25A and Cdc25B cooperate to instigate the cycB/Cdk1-Cdc25C cascade and the G2/M transition.
- Transcription factors act multiplicatively.

This work also indicates a need for a method to determine the most robust set of rate parameters in a model of coupled ordinary differential equations.

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