A Minimal Cell Model that Incorporates Genetic Regulation

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***Short Abstract* — The question of "What is essential for life?" is one of the most fundamental questions we face. The complete reconstruction of a minimal cell *in silico* is key to fully understanding and identifying underlying regulatory and organizational concepts central to life. The success of whole organism genome sequencing and high-throughput measurements provides an opportunity for system-level analysis of whole organisms, or what has been termed "systems biology". As a systems biology approach, the Minimal Cell Model (MCM) depicts the total functionality of a minimal cell and its explicit response to perturbations in its environment.**

***Keywords* — Bacterial cell models, whole-cell models, hybrid cell models**

I. Purpose

We propose a dynamic modeling framework to integrate genomic detail and cellular physiology within functionally complete 'hybrid' bacterial cell models. An initial step in this approach is the development of a whole-cell coarse-grained model which explicitly links DNA replication, metabolism, and cell geometry with the external environment. A hybrid model can then be constructed from chemically-detailed and genome-specific subsystems, called modules, inserted into the original coarse-grained model. We use the sensitivity analysis of the original coarse-grained model to identify which pseudo-molecular processes should be de-lumped into molecularly detailed mathematical modules to implement a particular biological function.

A minimal cell is a hypothetical entity defined by the essential functions required for life [1]. Although others have the goal of experimentally constructing a minimal cell [2], we seek to identify a minimum number of genes necessary and sufficient for the cell to divide and grow continuously in a rich environment with preformed nutrients and constant temperature and pH. We are constructing a Minimal Cell Model using existing hybrid bacterial cell models as a basis [3]. The model, which contains kinetic, thermodynamic, and stoichiometric constraints, is used as a tool to identify the organizing principles which relate the dynamic non-linear functioning of the cell to the genome sequence.

II. Approach

The project proposed here includes three main parts: 1) Development of novel algorithms for stability and sensitivity analysis of hybrid cell models, 2) Implementation of a system for parameter estimation, and 3) Construction of a genomically and chemically detailed Minimal Cell Model.

III. Results

Using an existing coarse-grained model of *E. coli* [3] as a basis, we have developed a framework for analyzing the stability of hybrid cell models [4] as well as a technique for sensitivity analysis in this class of models using an extension of classical Metabolic Control Analysis [5]. Currently, we are extending a statistical mechanics method for parameter estimation [6] to our models.

References

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