

Poster III-17

On Appropriateness and Use of Different Scale Models for Pathway Performance Optimization of *Escherichia Coli* Genetic Circuits

Zafiriou, Evangelos^{*}, Du, Jianfeng, Li, Jun, Bentley, William E.

Chemical Engineering Department, University of Maryland, College Park, MD, USA

We consider the pathway performance optimization of two *Escherichia coli* genetic circuits. The first determines the emergence and decay of the heat shock transcription factor, σ^{32} , upon heat shock. Earlier work showed the upregulation of the heat shock response concomitantly with the overproduction of recombinant protein, and this can be detrimental towards maximizing yield. The second genetic circuit that has an interplay with the σ^{32} circuit, involves cell-to-cell communication or “quorum sensing.” It describes the synthesis and perception of autoinducer-2 (AI-2, the signal molecule). Quorum sensing is emerging as an interspecies global regulator involved in establishing virulence of pathogenic bacteria.

A characteristic of such genetic circuits is that molecules are present in both very low and very high quantities, which raises the question as to the appropriate scale for modeling and simulating the system. We have used a simulation environment (Mobius) for stochastic Petri nets (SPN). However, using stochastic Petri nets (SPN) directly as part of an optimization of the system presents problems. SPN use is equivalent to the representation of the system via its Chemical Master Equation (CME), which describes the reaction network in continuous time but with discrete variables (discrete state space). This is a Markov jump process, and if optimization variables are present, we have a Markov decision process (MDP). Solving an MDP problem is extremely difficult for anything but the smallest problems.

Our approach is to use Langevin-type models as approximations of SPNs suitable for use in an optimal control problem. This models the system at a scale between the CME and that of deterministic ODEs, which are computationally fastest. The system is described as:

$$dx/dt = f(x) + g(x) n(t) \quad (1)$$

where $f(x)$ corresponds to the deterministic ODEs. The stochastic nature of the system can be thought of as random noise due to the small number of molecules for some species. This is represented through the noise term $n(t)$. We calculate its variance to match information generated via SPN simulation, thus incorporating information from the simulation at the CME scale. The deterministic part of (1) is used in a first attempt at optimization and the robustness of the solution evaluated for the stochastic system. The next step involves solving the optimal control problem subject to uncertainties that correspond to the variance information on $n(t)$.

We have extended the σ^{32} network to include modeling the activity of the recombinant protein. The extended network is shown to be a good match to experimental results reported in earlier work, where antisense RNA was used to downregulate the σ^{32} -mediated response and increase the activity of recombinant protein. It is possible experimentally to initiate the σ^{32} antisense expression after the protein expression. A simple optimization goal is the timing of the expression of σ^{32} antisense. Although total protein production is lower when the antisense is expressed, the higher specific activity in cultures with σ^{32} antisense results in a larger amount of biologically active recombinant protein.

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