Reliable Numerical Methods for FBA and FVA

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Project Goals: 1. Develop algorithms for solving optimization problems involving large stoichiometric matrices. (a) Extend existing sparse linear programming algorithms to enable the solution of such systems, in which the matrix coefficients represent reactions at multiple timescales and thus vary over many orders of magnitude. (b) Develop a convex optimization algorithm for computing thermodynamically feasible reaction fluxes in a general instance of a genome-scale integrated metabolic and macromolecular biosynthetic network. (c) Implement a parallel convex optimizer in to enable sampling of the thermodynamically feasible set. (d) Disseminate software to the systems biology community.
2. Investigate cyclic dependency between metabolic and macromolecular biosynthetic networks. (a) Predict the material and energy cost of macromolecular synthesis in an integrated metabolic, transcriptional and translational model of Escherichia coli. (b) Reconstruct and analyze the macromolecular synthesis network of Thermotoga maritima.
3. Quantify the significance of thermodynamic constraints on prokaryotic metabolism. (a) Simultaneous prediction of metabolic fluxes and concentrations in Escherichia coli. (b) Validate and interpret flux and concentration prediction in Escherichia coli and Thermotoga maritima. (c) Predict thermodynamically favorable pathways for hydrogen production by Thermotoga maritima on a range of substrates. (d) Numerically sample mass conserved, thermodynamically feasible steady state fluxes and concentrations in Escherichia coli.

Poster Abstract: Concerning project goal 1(a):

Integrated networks of organism metabolism and expression are inherently multi-scale because typical fluxes can vary over eight orders of magnitude. Such networks require special methods to analyze them accurately, and naive use of off-the-shelf optimization software for flux balance analysis (FBA) can produce severely inaccurate solutions. We describe methods for obtaining greater reliability.

The multi-scale nature of integrated networks is also problematic for flux variability analysis (FVA). The traditional FVA formulation sacrifices sharpness in the calculated bounds to ensure feasibility of the sequences of linear programs. In practice the bounds can be off by orders of magnitude. We describe an FVA formulation that guarantees both feasible linear programs and sharp calculated bounds.