Numerical Optimization Algorithms and Software for Systems Biology: A globally convergent algorithm for computing stable non-equilibrium steady state concentrations in genome-scale networks.

Ronan M.T. Fleming (ronan.mt.fleming@gmail.com)*[1], Ines Thiele[1], **Michael A. Saunders**[2.]

1 Center for Systems Biology, University of Iceland, Iceland.
2 Department of Management Science and Engineering, Stanford University

www.hi.is/~rfleming

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 Eschericia coli. (b) Validate and interpret flux and concentration prediction in Eschericia 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.

Abstract: Concerning project goal 3(a): At the core of computational systems biology lies a paradox. All of the currently available genome-scale modeling methods can only model chemical reaction rates, but not the abundance (or concentration) of the molecules involved in these reactions. At the same time, the vast majority of experimental omics data are measures of the abundance of some molecule, rather than the rate. The reason for this paradox is that modeling steady state reaction kinetics has been limited to small systems of chemical reactions as the inherently nonlinear systems of equations at the core of such models have been intractable to solve. We present the first globally convergent algorithm for simultaneously computing stable non-equilibrium steady state molecule concentrations and reaction rates. We leverage this algorithm to simultaneously predict stable steady state concentrations and reaction rates in E. coli, which are numerical consequences of various hypotheses regarding the manner in which evolved kinetic parameters may be optimal with respect to optimization of various cellular system objectives.