533e Analysis of the Thermodynamic Feasibility of a Genome Scale Metabolic Model

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The sequencing and annotation of the entire genomes of numerous microorganisms has led to the advent of genome scale metabolic models such as the iJR904 model of E. coli developed by Palsson and coworkers. Metabolic flux analysis (MFA) is widely employed to generate the flux distributions that satisfy stoichiometric mass, energy, redox, and charge balance constraints in these models. However, these constraints do not provide insight into which of these flux distributions will be thermodynamically feasible. Some flux distributions will utilize pathways involving reactions that are thermodynamically unfavorable; these pathways will be incapable of producing acceptable concentrations of desired metabolic end products or intermediates. This work focuses on assessing the thermodynamic feasibility of the flux distributions generated by performing MFA on a genome scale metabolic model.

The thermodynamic aspects of the method fully exploit knowledge of the characteristics of living systems, metabolic pathways, and biochemical thermodynamics. A pathway is assessed according to its free energy change, the criterion for spontaneity. Because experimental data on the concentrations of metabolites in a living organism is nearly impossible to obtain; there exists no method to calculate the free energy change of a chemical reaction in a living system. However, because many chemical structures of common metabolites are known a group contribution method can be used to estimate the standard transformed free energy change of every reaction in the model. The central importance of the estimation of individual reactions is critical to the thermodynamic analysis of pathways; therefore the error and accuracy of the group contribution method are given particular critical evaluation. With the estimate of the thermodynamics of each chemical reaction in a pathway the characteristics of the thermodynamic landscape of each pathway in the organism are able to be assessed.

Knowledge of pathway thermodynamics and MFA are combined to assess the feasibility of flux distributions. Alternative pathways to objectives such as growth or growth precursors are examined for thermodynamic bottlenecks. Flux distributions utilizing the most thermodynamically favorable reactions and pathways are discussed with respect to their physiological significance.