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Determination of flux directions by thermodynamic network analysis: Computing informative metabolite pools

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Abstract

Network thermodynamics focuses on the energetic analysis of complex metabolic networks. The method connects free Gibbs energies, metabolite concentrations and flux directions by fundamental thermodynamic laws. Here, a new application of network thermodynamics is presented that identifies those metabolite pools that have to be measured in order to determine as many flux directions as possible. For a medium-scaled reaction network such informative metabolite pools are computed with an approach based on Monte Carlo sampling. It turns out that some reactions can be directed with only a few measurements whereas other reactions cannot be directed even with a complete data set. High connectivity in metabolic reaction networks in alliance with concentration ranges make it impossible to intuitively foresee such results. In particular, the impact of measurements of a special type of metabolites being involved in many reactions, so called energetic currency metabolites is investigated.

Keywords: Metabolic networks; Network thermodynamics; Flux directions; Monte Carlo method; Gibbs sampler

1. Introduction

In recent years, metabolomic and fluxomic data become increasingly available in quality and quantity. While metabolic concentrations are directly measurable, quantitative *in vivo* conversion rates of a chemical reaction, so called fluxes, need to be estimated through a model-based, usually iterative interpretation of isotopic labeling patterns observed in metabolites. Basic laws of thermodynamics, however, enable an integrative link between the two constituent levels, namely absolute metabolite concentrations and flux directions, in order to get closer to the whole picture of cellular metabolism. In particular, the second law of thermodynamics states that a reaction (spontaneously) proceeds in the direction of a negative Gibbs free energy change. This means that the sign of the Gibbs free energy change allows for the prediction of the reaction direction with certainty. The Gibbs free energy change, in turn, depends on the concentrations of all participating reactants. Applications of network-based thermodynamics are given by consistency checking of mixed metabolome/fluxome data, computing possible flux direction patterns [2,6], or narrowing the feasible concentration space of immeasurable pools in biochemical reaction networks [5].

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