Thermodynamically constraining a genome-scale metabolic model with von Bertalanffy 2.0

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Project Goals: In flux balance analysis of genome-scale stoichiometric models of metabolism, the principal constraints are uptake or secretion rates, the steady state mass conservation assumption and reaction directionality. Von Bertalanffy 2.0 is an algorithmic pipeline for quantitative assignment of reaction directionality in multi-compartmental genome scale models based on an application of the second law of thermodynamics to each reaction, via estimation of thermodynamic properties using the Component Contribition method.

Reaction directionality in metabolic network reconstructions should be consistent with the second law of thermodynamics, which implies that a reaction can only proceed in a direction associated with a negative chemical potential difference. In biochemical systems, the chemical potential difference is termed the (Legendre) transformed reaction Gibbs energy, which is appropriate for a certain in vivo temperature, pH, ionic strength, electrical potential and metabolite concentrations. In a typical metabolic reconstruction process, reaction directionality is assigned based on thermodynamic data such as experimentally measured equilibrium constants, whenever such data is available. Two problems frequently arise: either no thermodynamic data is available in the literature on the reaction in question or thermodynamic data is available, but only for conditions that differ from in vivo conditions. Quantitative assignment of reaction directionality is possible, even if thermodynamic information does not exist for a particular reaction in question by estimating thermodynamic properties of metabolites and metabolic reactions based on structurally similar metabolites and reactions. Von Bertalanffy 2.0 is an extension to The COBRA toolbox [1] that provides a set of MATLAB functions to that enable quantitative assignment of reaction directionality for all reactions in a multi-compartmental, genome-scale metabolic network reconstructions. This estimation is most accurate for reactions that are structurally most similar to reactions where experimental thermochemical data exists. The methodology for estimation of thermodynamic properties is based on recent advancement in estimation of Gibbs Energy using the Component Contribution method[2]. This method combines estimation via a Group Contribution method with the more accurate Reactant Contribution method by decomposing each reaction into two parts and applying one of the methods on each of them. This method gives priority to the reactant contributions over group contributions while guaranteeing that all estimations will be consistent, i.e., will not violate the first law of thermodynamics. The result is a thermodynamically constrained genome-scale model of a metabolic network with as confidence intervals provided for all estimates. Dissemination via Von Bertalanffy 2.0 is envisaged to facilitate the wide use of thermodynamic data for a better understanding of metabolism.

References

[1] Schellenberger J, Que R, Fleming RMT, Thiele I, Orth JD, et al. (2011) Quantitative prediction of cellular metabolism with constraint-based models: the COBRA Toolbox v2.0. Nature Protocols 6: 1290–1307.

[2] Noor E, Haraldsdóttir HS, Milo R, Fleming RMT (2013) Consistent Estimation of Gibbs Energy Using Component Contributions. PLoS Comput Biol 9: e1003098.

This work was supported by the U.S. Department of Energy, Offices of Advanced Scientific Computing Research and the Biological and Environmental Research as part of the Scientific Discovery Through Advanced Computing program, grant #DE-SC0010429.