SELECTION OF THERMODYNAMICALLY FEASIBLE AND ACTIVE PATHWAYS

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Although the network of metabolic reactions, together with constraints of (ir)reversibility of enzymes, determines the space of all potentially possible phenotypes, in actuality the cell does not invoke the large majority of those in given conditions. We propose a method in two steps to obtain a more accurate description of cellular phenotypes through pathway analysis. The first step requires measurements of the concentrations and thermodynamic properties of the metabolites; the second step measured exchange rates. The importance of this lays in the fact that the internal fluxes are not independently distributed but strictly constrained by external fluxes through the pathways. The case study considers the central carbon metabolism of *Escherichia coli* using five datasets from literature. As the pathway modelling method, we chose generating vectors (GVs), the smallest subset of pathways, instead of elementary modes, the largest set, because any steady state flux pattern can be expressed as a nonnegative linear combination of GVs and for its associated lower computational intensity [1]. First, we applied thermodynamics analysis [2] to check for thermodynamic inconsistencies in the dataset and model. We removed the blacklisted metabolites before further analysis. Then, we assigned reaction directionalities based on thermodynamic feasibilities (in addition to (ir)reversibilities of the enzymes) in given environmental conditions and recomputed the pathways (which is necessary since the set of GVs is not unique). Finally, feasibility of these pathways was tested taking into account irreversibility of the pathways as well. With this approach, a reduction of up to 61% in the computed pathways was obtained for particular phenotypes. Second, we used a controlled random search algorithm to select an active subset of feasible pathways that describes a particular phenotype based on exchange rates (oxygen uptake rate, carbon evolution rate, glucose uptake rate, specific growth rate, and acetate formation or consumption rate) [1]. The algorithm is based on an iterative search procedure and was run several times to find the active pathways. The original model containing 295 GVs could be reduced to a system of one to three pathways giving a good correlation with the measured datasets.

References

[1] Soons Z. et al. (2010), Comput. Appl. Biotechnol.. Leuven.

[2] Zamboni N. et al. (2008), BMC Bioinformatics 9.