Towards a biologically relevant description of phenotypes based on pathway analysis

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In metabolic systems, the cellular network of reactions together with constraints on reversibility of enzymes determine the space of all possible steady-state 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 precise description of cellular phenotypes through pathway analysis. The first step is based on a modified version of the concept of control effective flux (CEF) [1] and only requires the stoichiometric network. The second step is based on thermodynamic feasibility of reactions and requires measurements of concentrations and thermodynamic properties of the metabolites.

CEFs represent the importance of each reaction for efficient and flexible operation of the entire metabolic network. We modified the concept to take into account the reaction directionality within the modes by splitting up the reversible reactions. We observed that directionality of the largest CEF - forward reaction at least two times larger than backward or vice versa- matches well with the measured reaction directions for growth on glucose, glycerol, and acetate as the sole carbon source. We also found that the modified CEFs are good predictors of intra-cellular fluxes for the central carbon metabolism of *Escherichia coli* and *Saccharomyces cerevisiae*. The proposed method allows a reduction of up to 51% out of 2706 modes for *E. coli* and up to 81% out of 191,083 modes for *S. cerevisiae*, so that only pathways are contained that carry flux matching the measured directions.

An alternative reduction can be obtained by assigning reaction directionalities on thermodynamic grounds using anNET [2] and removing the pathways that contain infeasible reactions. The feasibility of the remaining pathways was checked by taking into account irreversibility of the pathways. Depending on the available measurements and its uncertainties, a reduction of up to 31% in the computed pathways was obtained for particular conditions, though no further reduction compared to the CEFs method. Overall, the largest reduction in the number of pathways was obtained using the stiochiometric network as the only input, thus without the requirement for measurements, towards a biologically relevant description of phenotypes.

References


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