Mutually consistent metabolic flux and metabolite concentration prediction

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Project Goal:
To develop next generation data-driven metabolic flux and metabolite concentration prediction procedures for microbial metabolic engineering applications.

Systems biology approaches aim to arrive at biological insight by leveraging complimentary insights provided by different –omics datasets. Of particular importance to elucidate cellular metabolism is the accurate and reliable estimation of metabolic fluxes and metabolite concentrations. Here, we develop a procedure mCAFE that integrates measured metabolite concentrations and 13C based amino-acid isotope ratio data to predict mutually consistent estimates of internal fluxes and unmeasured concentrations. Methodologically, mCAFE builds on Metabolic Flux Analysis (MFA) by additionally incorporating a set of constraints that account for the nonequilibrium thermodynamic behavior of each reaction in the model. These constraints explicitly relate the flux ratios of each reaction (i.e., forward/reverse flux) with the ratios of the involved metabolites. We apply mCAFE to predict fluxes and concentrations in a customized model of *Escherichia coli* metabolism using the data available at the Keio multi-omics database and find that the estimates are substantially more reliable than those predicted by MFA respectively. Furthermore, mCAFE recapitulates 65% of the measured metabolite concentrations in a leave-one-out cross validation test therefore confirming its reliability in concentration prediction. Applying mCAFE to 25 different *E. coli* single gene deletion mutants reveals conserved covariances between metabolite concentrations and metabolic fluxes. Finally, mCAFE gives empirical basis for the extent of reversibility of reactions in *E. coli* under different conditions. With the anticipated increase in metabolomics and flux data for different organisms, we expect mCAFE to be the state of the art predictive procedure to harness these datasets to predict reliable estimates of internal fluxes and unmeasured metabolite concentrations.