Impact of stoichiometry representation on simulation of genotype-phenotype relationships in metabolic networks.

Genome-scale metabolic networks provide a comprehensive structural framework for modeling genotype-phenotype relationships through flux simulations. The solution space for the metabolic flux state of the cell is typically very large and optimization-based approaches are often necessary for predicting the active metabolic state under specific environmental conditions. The objective function to be used in such optimization algorithms is directly linked with the biological hypothesis underlying the model and therefore it is one of the most relevant parameters for successful modeling. Although linear combination of selected fluxes is widely used for formulating metabolic objective functions, we show that the resulting optimization problem is sensitive towards stoichiometry representation of the metabolic network. This undesirable sensitivity leads to different simulation results when using numerically different but biochemically equivalent stoichiometry representations and thereby makes biological interpretation intrinsically subjective and ambiguous. We hereby propose a new method, Minimization of Metabolites Balance (MiMBl), which decouples the artifacts of stoichiometry representation from the formulation of the desired objective functions, by casting objective functions using metabolite turnovers rather than fluxes. By simulating perturbed metabolic networks, we demonstrate that the use of stoichiometry representation independent algorithms is fundamental for unambiguously linking modeling results with biological interpretation. For example, MiMBl allowed us to expand the scope of metabolic modeling in elucidating the mechanistic basis of several genetic interactions in Saccharomyces cerevisiae.