accommodates all main strain design strategies

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Constraint-based modelling methodologies can expedite the strain engineering process by helping in the search for interesting genetic modification targets. Although the search for gene knock-outs is fairly established with *in silico* methodologies, most computational strain design methods still model gene up/down-regulations by forcing the corresponding flux values to pre-calculated levels without considering the availability of resources.

We have developed a new simulation method, Turnover Dependent Phenotypic Simulation (TDPS), which was designed with the goal of simulating quantitatively the phenotype of strains with diverse genetic modifications in a resource conscious manner. Besides gene deletions and down-regulations, TDPS can also simulate the up-regulation of metabolic reactions as well as the introduction of heterologous genes or the activation of "dormant" reactions. In TDPS the flux values through modified metabolic reactions are modelled by taking into consideration the availability of precursor metabolites in the network, which is accomplished by assuming that the production turnover of a metabolite can be used as an indication of its abundance. The developed method is based on a MILP formulation that manipulates the fractions of metabolite turnovers consumed by the modified reactions. Furthermore, TDPS also integrates a new objective function that promotes network rigidity in order to predict the flux phenotype of modified strains. TDPS was validated using metabolically engineered *S. cerevisiae* strains available in the literature by comparing the simulated and experimental production yields of the target metabolite.