Approach

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Poster Abstracts

The past two decades have witnessed great advances in the computational modeling and systems biology fields. Soon after the first models of metabolism were developed, several methods for the prediction of phenotypes were also put forward. With the ever-growing information provided by such methods, new questions arose. Metabolic Engineering in particular posed some interesting questions. Recently, Schuetz and co-workers proposed that the metabolism of bacteria operates close to the Pareto-optimal surface of a three-dimensional space definedned by competing objectives and demonstrated the validity of their claims for various environmental perturbations[1].

However, phenotype prediction methods have all been developed to operate based on the assumption of a given single-objective, as an example Flux Balance Analysis (FBA) often assumes that the organisms are evolutionarily optimized towards optimal growth. On the other hand, Minimization of Metabolic Adjustment (MOMA) proposes that after a perturbation, the goal of the organisms shifts from optimal growth to the minimization of the global metabolic adjustment relative to the wild-type. Albeit multi-objective approaches focused on the bio-engineering objectives have been proposed[2, 3], none tackles the multi-objective nature of the cellular objectives.

In this work we analyze the inuence of several phenotype prediction methods on the strainsdesigned by metaheuristic algorithms and suggest a multi-objective approach capable of finding designs compliant with the cellular objectives assumed by the various phenotype prediction methods.

Using a recent model of *Escherichia coli* K12[4], we observed the effect of different phenotype prediction methods in the convergence of metaheuristic algorithms performing strain optimization, evolving growth-coupled production mutants in aerobic and anaerobic conditions. A critical analysis of the different mutant ux distributions was performed, and we concluded that, for a selected phenotype prediction method, the strain designs proposed by the optimization algorithms were generally not robust when another method was used to predict their phenotypes.

There is variation in the Biomass-product coupled yield (BPCY) of aerobically succinate producing mutants with glucose as carbon source, when solutions generated with either pFBA (a variation of FBA that minimizes the overall use of enzyme-associated flux[5]) or LMOMA (a linear implementation of MOMA[6]) (box colors) are simulated with the other (x-axis). Besides the great variation in fitness for the different phenotype simulation methods, we veri_ed that in some cases less than 10% of the solutions generated by pFBA are valid in LMOMA (BPCY _ 0:0001).

Assumptions regarding the cellular objectives of an organism when subjected to distinct conditions (environmental, genetic, etc.) are still the object of active discussion. This fact motivated us to develop a method capable of suggesting designs compliant with more than one phenotype prediction method. Solutions generated by our method are simulated using pFBA and LMOMA and plotted by BPCY for both phenotype simulation methods. The ad-hoc clusters reveal a group of interesting solutions (cluster 2). An analysis on the flux distribution of the solutions presented in these clusters is also provided and a rational for robust solution design is derived.

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