Multi-criterion approaches for the *in silico* optimization of mutant microorganisms

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ABSTRACT

Genetic manipulation of microorganisms to find the optimum set of gene knockouts to create mutants for the production of valuable compounds is, in Metabolic Engineering, a promising, while complex task. Approaches to tackle this problem have been proposed and included MILP-based techniques (OptKnock [1]), that lacked the possibility of including non-linear objective functions. More recently, meta-heuristic approaches like Evolutionary Algorithms (EAs) (OptGene [2]) have been put forward. Although these are more flexible and have provided good results in some cases, they relied on objective functions that aggregate several potentially conflicting optimization goals.
In this work, the problem is interpreted as a Multi-Objective task and an approach based on Multi-Objective EAs (MOEAs) is proposed. The Strength Pareto Evolutionary Algorithm 2 (SPEA2) and the Non-dominated Sorting Genetic Algorithm II (NSGA-II), two state-of-the-art MOEAs were adapted to conduct this task. The optimization goals are to simultaneously maximize the biomass and also the concentration of a desired compound (bi-objective optimization problems). Next, we took the problem further and added two new objectives: minimizing either the number of knockouts in the solution or the sum of all the fluxes present in the model (tri-objective optimization problems).

These algorithms are validated using three real world case studies. The selected organisms are *S.cerevisiae* for the production of succinate and *E.coli* for the production of both succinate and lactate. The results are quite promising when compared with the available single-objective approaches.

Reference List

1 Burgard,A.P., Pharkya,P. and Maranas,C.D. (2003) OptKnock: A bilevel programming framework for identifying gene knockout strategies for microbial strain optimization. Biotechnology and Bioengineering, **84,** 647-657.

2 Rocha,M., Maia,P., Mendes,R., Pinto,J.P., Ferreira,E.C., Nielsen,J., Patil,K.R. and Rocha,I. (2008) Natural computation meta-heuristics for the in silico optimization of microbial strains. BMC Bioinformatics, **9,** 499.