A Study on the Effects of Using Gene-Reaction Rules on in silico Strain Optimization

Paulo Vilaça,[1] Paulo Maia,[1,2] Pedro Evangelista,[1]
Eugénio C. Ferreira,[1] Miguel Rocha,[2] and Isabel Rocha[1]

[1] *IBB-Institute for Biotechnology and Bioengineering, Centre of Biological Engineering,*
[2] *CCTC - Computer Science and technology Center,*
University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal
E-mail {pvilaca, paulo.maia, ptiago, ecferreira, irocha}@deb.uminho.pt
mrocha@di.uminho.pt

Abstract

To identify a set of genetic manipulations that will result in a microbial strain with improved production capabilities of a metabolite / product of industrial interest, is one of the greatest challenges in Metabolic Engineering. This problem represents a complex combination between the development of accurate metabolic and regulatory models / networks, plus the need for appropriate simulation and optimization tools.

To achieve this end, Evolutionary Algorithms (EAs) and Simulation Annealing (SA) have been previously proposed as tools to perform *in silico* Metabolic Engineering [1]. These methods are used to identify sets of reaction deletions, towards the maximization of a desired physiological objective function. In order to simulate the cell phenotype for each mutant strain, including its growth and the by-products secretion, the Flux-Balance Analysis approach is used, assuming that microorganisms have maximized their growth along evolution.

Currently, the available optimization algorithms work only with reaction deletions, i.e. their result is a set of reactions that have to be removed from the metabolic model. Biologically, it is possible to knockout genes, not reactions.

In this work, the transcriptional information is added to the underlying models using gene-reaction rules based on a boolean logic representation. So, for each reaction we have a Boolean expression, where the variables are the encoding genes and including the logical AND and OR operators. The aim is to find the optimal / near-optimal set of gene knockouts necessary to reach a given productivity goal. The results obtained are compared with the ones using the deletion of reactions.

A set of computational experiments were performed, using four case studies and the production of succinate and lactic acid as the metabolite to maximize and E. coli as the selected organism. Genome-scale models including both reactions and gene-reaction rules [2] are used to conduct the necessary FBA simulations.

The results show that several of the results from reaction deletion optimizations are not feasible using the provided gene-reaction rules, i.e. the genes that would need to be removed in order to delete the reaction also lead to the removal of other reactions causing side effects that make the strain unviable.

Nevertheless, basing the optimization algorithms on gene knockouts, we were able to reach solutions where the production of the desired compounds is similar to the ones using reaction deletions.

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