

# In silico metabolic Engineering tool for simulation and optimization of microbial strains accounting integrated metabolic/regulatory information

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## Abstract

Recently, a number of methods and tools have been proposed to allow the use of genome-scale metabolic models for the phenotype simulation and optimization of microbial strains, within the field of Metabolic Engineering (ME). One of the limitations of most of these algorithms and tools is the fact that only metabolic information is taken into account, disregarding knowledge on regulatory events. OptFlux (<http://www.optflux.org>) is an open-source platform that includes several tools to support in silico Metabolic Engineering (ME), including functionalities to load genome-scale metabolic models in several formats, to simulate the phenotype of both wild type and mutant strains using steady-state approaches (e.g. Flux Balance Analysis-FBA[1]) and also to perform strain optimization tasks (e.g. finding the best sets of knockouts for the production of a given metabolite).

In this work, a novel plug-in for this platform is presented, allowing the use of gene regulatory models, represented as Boolean networks. This plug-in links the regulatory model to its corresponding metabolic model, creating an integrated model and allowing its use for the phenotype simulation and strain optimization tasks. This is the first software application that allows the simulation of integrated regulatory/metabolic models.

The phenotype simulation using integrated models is conducted by firstly simulating the Boolean network and, afterwards, identifying the disabled genes in the final state and considering those as knockouts for the metabolic simulation that is conducted using FBA or alternative methods (such as MOMA or ROOM). The user can define the initial state of the Boolean network, use different environmental conditions and also simulate mutants by imposing a set of gene deletions.

The strain optimization operation provides interfaces to identify sets of genes deletions that are able to maximize a given objective function related to the production of a given metabolite with industrial interest. Two meta-heuristic optimization methods (Evolutionary Algorithms and Simulated Annealing) are used in this task[2].

## References

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

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