

Optimization of metabolic networks in biotechnology applications

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Computational results

The ethanol production in *Saccharomyces cerevisiae* (model parameters can be found in Polisetty et al., 2008) was maximized under different considerations, that is, involving the modification of different subsets of enzymes. The enzyme activities (K_r) were allowed to change a maximum of 5-fold with respect to their basal state value whereas the metabolite concentrations (X_i) were limited to a 10-fold change. The optimality tolerance was set to 0.20%. Besides, the two different formulations proposed (Big-M and convex hull) were implemented in GAMS 22.9.2, using three different solvers (DICOPT 2x-C, SBB and Alpha-ECP v1.65) to optimize the MINLP on an Intel 1.2 GHz machine. The numerical results of the optimization are presented in *Tables 1 and 2*, where the best solutions obtained for a given number of enzyme manipulations ($ME = 1, 2$ and 8) are shown. Data about the size of the model can be found in *Table 3*.

Table 1. Optimization results allowing the modification of different subset of enzymes using the Big-M formulation.

Best solution modifications			DICOPT		SBB		αECP	
ME	Reactions	K_r	OF	CPU (s)	OF	CPU (s)	OF	CPU (s)
1	HXT	[5.00]	72.68	0.41	72.68	0.80	72.68	21.25
2	HXT, PFK	[5.00, 2.85]	103.66	0.26	103.66	2.41	103.66	17.08
8	All	[5.00, 0.89, 5.00, 0.20, 1.40, 0.20, 5.00, 5.00]	157.59	0.37	157.59	0.05	157.57	20.89

Table 2. Optimization results allowing the modification of different subset of enzymes using the convex hull formulation.

Best solution modifications			DICOPT		SBB		αECP	
ME	Reactions	K_r	OF	CPU (s)	OF	CPU (s)	OF	CPU (s)
1	HXT	[5.00]	72.68	0.42	72.68	0.27	72.68	1000.07
2	HXT, PFK	[5.00, 2.85]	103.66	0.53	103.66	0.39	103.66	18.03
8	All	[5.00, 0.89, 5.00, 0.20, 3.07, 0.20, 5.00, 5.00]	157.59	0.40	157.59	0.03	92.67	27.66

Although numerical results vary significantly from one instance to another, in average, DICOPT and SBB show a better performance as they are able to attain the same or better solutions than Alpha-ECP in lower CPU times. In particular, SBB is the fastest solver in all the instances when convex hull formulation is used for the disjunction. Nevertheless, apart from the aforementioned, no general conclusions can be drawn regarding which of the two formulations object of comparison, Big-M and convex hull, perform better than the other, as no general trends are observed.

Interestingly, a certain degree of degeneracy is observed in the solutions reported, as the same value in the objective function can be obtained through different genetic manipulations (i.e., for $ME = 8$, $K_5 = 1.40$ for Big-M and $K_5 = 3.07$ for convex hull). This is a typical feature in systems biology studies since metabolic networks usually include multiple regulatory loops so that the same response can be attained through different pathways. This point is of particular interest if one aims at reproducing in a real system the results obtained in the optimization as there may be practical implications that make the implementation of one solution advantageous when compared to the others.

Table 3. Model size data.

Big-M		Convex hull	
Equations	73	Equations	81
Continuous variables	14	Continuous variables	38
Discrete variables	24	Discrete variables	24

Interpretation

Discussion of the biological implications of these solutions can be found elsewhere (Guillén-Gosálbez and Sorribas, 2009).

References

- Polisetty, P., Gatzke, E., Voit, E., 2008. Yield optimization of regulated metabolic systems using deterministic branch-and-reduce methods. *Biotechnology and Bioengineering* 99(5), 1154-1169.
- Guillén-Gosálbez, G., Sorribas, A., 2009. Identifying quantitative operation principles in metabolic pathways: a systematic method for searching feasible enzyme activity patterns leading to cellular adaptive responses. *BMC Bioinformatics* 10(386).