

Supplementary information

Multi-objective optimization of enzyme manipulations in metabolic networks considering resilience effects

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Mathematical model of anaerobic fermentation in *S. cerevisiae*

Saccharomyces cerevisiae is the most commonly used yeast, which is well studied and widely used in industrial application. The reasons for selecting this metabolic systems are that ethanol fermentation using *S. cerevisiae* is a well established technology and the detailed knowledge about the glucose uptake rate and the formation rate of ethanol in *S. cerevisiae* is available. This GMA model was developed by Curto et al. [1] for analyzing the anaerobic ethanol fermentation of *S. cerevisiae* at steady state. It consists of 5 nonlinear ordinal differential equations and 8 nonlinear rate equations. The maximum reaction rates can be found from an online model database (JWS).

Model equations

$$\begin{aligned}\frac{d[glc]}{dt} &= v_{HXT} - v_{GLK} \\ \frac{d[g6p]}{dt} &= v_{GLK} - v_{PFK} - v_{TPS} \\ \frac{d[f6p]}{dt} &= v_{PFK} - v_{TDH} - \frac{1}{2}v_{GOL} \\ \frac{d[pep]}{dt} &= 2v_{TDH} - v_{PYK} \\ \frac{d[atp]}{dt} &= 2v_{TDH} + v_{PYK} - v_{GLK} - v_{TPS} - v_{PFK} - v_{ATPase}\end{aligned}$$

Rate equations

The rate equations are represented as the following power-law form:

$$\begin{aligned}v_{HXT} &= 0.8122[g6p]^{-0.2344}[HXT] \\v_{GLK} &= 2.8674[glc]^{0.7464}[atp]^{0.0243}[GLK] \\v_{PFK} &= 0.5228[g6p]^{0.7318}[atp]^{-0.3941}[PFK] \\v_{TDH} &= 0.076029[f6p]^{0.6159}[atp]^{0.1308}[TDH] \\v_{PYK} &= 0.09471[f6p]^{0.05}[pep]^{0.533}[atp]^{-0.0822}[PYK] \\v_{TPS} &= 0.000904[g6p]^{8.6107}[TPS] \\v_{GOL} &= 0.09272[f6p]^{0.05}[pep]^{0.533}[atp]^{-0.0822}[GOL] \\v_{ATPase} &= [atp][ATPase]\end{aligned}$$

where each reaction is denoted as follows: v_{HXT} (sugar transport system), v_{GLK} (hexokinase), v_{PFK} (phosphofructokinase), v_{TPS} (glycogen synthetase), v_{TDH} (glyceraldehyde 3-phosphate dehydrogenase), v_{GOL} (glycerol 3-phosphate dehydrogenase, proportional to PYK), v_{PYK} (pyruvate kinase), and v_{ATPase} (ATPase). The rate of ethanol production is given directly by the flux through the pyruvate kinase reaction. State variables in the model are the concentrations of internal glucose $[glc]$, glucose-6-phosphate $[g6p]$, fructose-1,6-diphosphate $[f6p]$, phosphoenol pyruvate $[pep]$, and ATP $[atp]$. Independent variables with constant values are: effective hexose transport $[HXT]$, hexokinase/glucokinase $[GLK]$, phosphofructokinase $[PFK]$, glyceraldehyde dehydrogenase $[TDH]$, pyruvate kinase $[PYK]$, glycogen and trehalose production $[TPS]$, glycerol production $[GOL]$, and ATPase $[ATPase]$.

References

1. Curto R, Sorribas A, Cascante M: **Comparative characterization of the fermentation pathway of *Saccharomyces cerevisiae* using biochemical systems theory and metabolic control analysis: Model definition and nomenclature.** *Mathematical Biosciences* 1995, **130**:25–50.