Constrained optimization sheds light in the metabolic functioning of higher cells

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Objective. To model single-cell organisms by an optimization approach a simple target function suffices since these cells only need to grow and replicate. However, higher organism cells such as the human hepatocyte have a multitude of different functions: self maintenance, substrate supply to other cells of the organism, transformation of waste products to disposable substances, clearance of toxic substances from the blood and detoxification, homeostasis etc. . Thus, the fitness of such a cell can only be measured in the context of the whole organism. Here, we present the steps towards realistic and yet managable models of higher cells.

Flux balance condition

An internal metabolite *j* may neither accumulate nor be consumed

$$\sum_i \mathbf{S}_{ij} v_i = 0$$

Vast complexity of the relations of metabolites, enzymes, and effectors

Multidimensional solution space

Flux balance optimization

maximize	$\Phi(V)$
subject to	<*flux-balance condition*>
	<*system boundary constraints*>

The above optimization problem is a linear program which can be solved very efficiently by modern implementations of the SIMPLEX algorithm.

$\Phi(V)$ is the objective function, e.g. Biomass production.

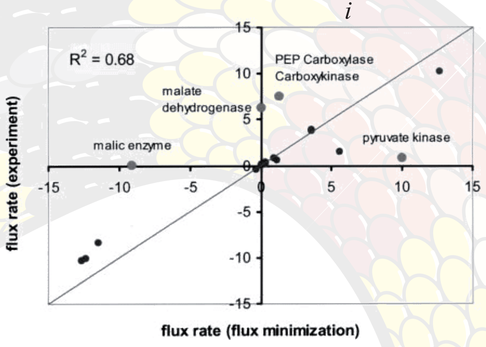
Papoutsakis ET. Biotechnol Bioeng. 1984 Feb;26(2):174-87.
Fell DA, Small JR. Biochem J. 1986 Sep 15;238(3):781-6.

Higher cells do not operate at maximal biomass/substrate efficiency.

Flux minimization

Flux prediction by 1. fixing the metabolic output, and 2. minimzing the objective function:

$$\Phi(V) = \sum_i v_i^+ + K_i^{\mathrm{equ}} v_i^-$$



Correlation between flux values determined by the flux-minimization method and experimentally determined by ^{13}C-labeling in *Methylobacterium extorquens* AM1 (Van Dien et al. .Biotechnol Bioeng. 2003 Oct 5;84(1):45-55.)

Holzhütter HG. Eur J Biochem. 2004 Jul;271(14):2905-22.

Higher cells often operate at the brink of their capacity.

Thermodynamic realizability

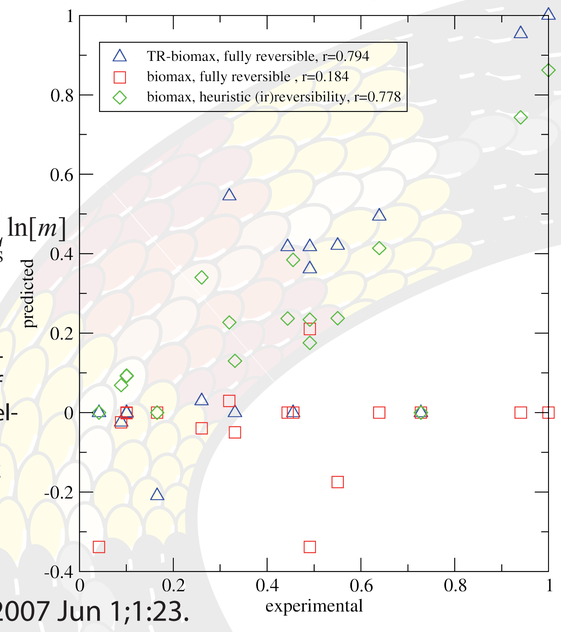
Restricting net flux directions by thermodynamic laws

$$\Phi(V) = \sum |v_i|$$

$$\mathrm{sgn}(v_i) \overset{i}{=} -\mathrm{sgn}(\Delta_r G_i)$$

$$\Delta_r G_i = \Delta_r G_i^0 + RT \sum_{m \in P} \ln[m] - RT \sum_{m \in S} \ln[m]$$

$$c_{\min} \le \ln[m] \le c_{\max}$$



Correlation between predicted and experimentally determined flux values of *Escherischia coli* determined by ^{13}C labeling (Emmerling et al. J Bacteriol. 2002 Jan;184(1):152-64.)—comparison of TR and heuristic settings of irreversibility (Reed JL et al. Genome Biol. 2003;4(9):R54.)

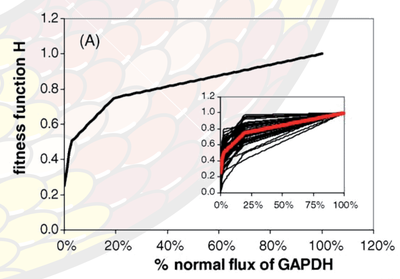
Hoppe et al. BMC Syst Biol. 2007 Jun 1;1:23.

Heuristic settings of irreversibility are too unflexible for higher cells.

Protein synthesis is the dominant energy consumer in the cell.

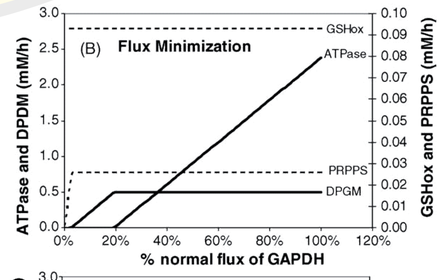
Fitness maximization

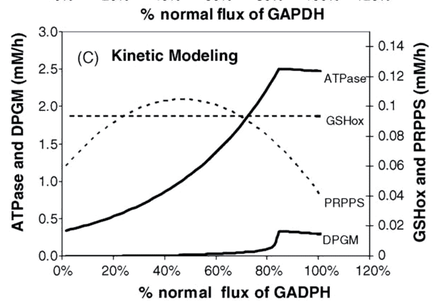
The consideration of a (non-perfect) fitness of the cell allows to model situations where the cell is confronted with a excessive demand on metabolic output, shortage of selected substrates, or decreased capacity of selected enzymes.



$$\Phi(V) = \sum_i \frac{(v_i^+ + K_i^{\mathrm{equ}} v_i^-)}{\sqrt{1 + \left(K_i^{\mathrm{equ}}\right)^2}} - \mathrm{Fitness}$$

$$\mathrm{Fitness} = 1 - \frac{1}{m} \sum_i \alpha_i \max\left\{1 - \frac{v_i}{L_i}, 0\right\}$$





Fitness function (A) and output fluxes (B) of the erythrocyte network as function of the upper boundary placed on the flux through the GAPDH reaction. For the curves shown in the two main panels, the sum of the weighting factors α_i of the fitness function were put to unity. The inset of (C) shows the fitness function at 50 randomly chosen sets of (positive) weighting factors. The curve obtained with for identical weighting factors is shown in bold.

Holzhütter HG. Biosystems. 2006 Feb-Mar;83(2-3):98-107.

Enzyme capacity cost

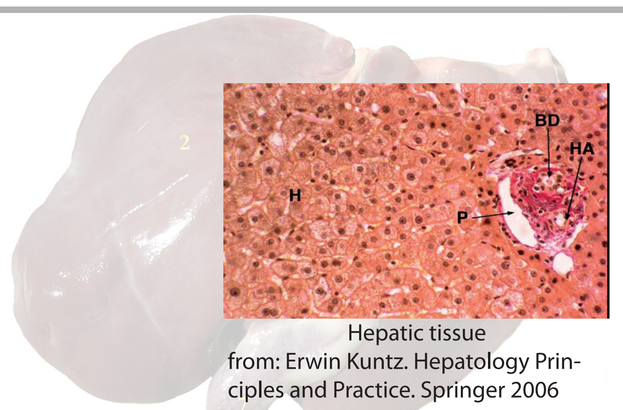
Minimizing the const to supply a certain enzyme turnover

$$\Phi(V) = \sum_j \lambda_j \sum_i \beta_{ij} |v_i| \qquad \lambda_j = \frac{< \text{chain length} >_j}{< \text{turnover number} >_j}$$

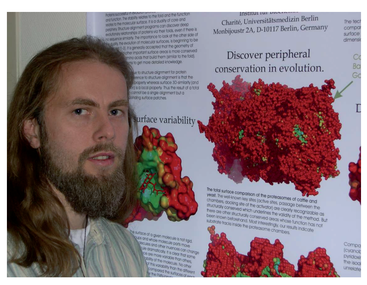
β_{ij} … boolean, whether enzyme j catalyzes reaction i

Holzhütter S, Holzhütter HG. Chembiochem. 2004 Oct 4;5(10): 1401-22. (no consideration of λ_i)

Ongoing project



Hepatic tissue
from: Erwin Kuntz. Hepatology Principles and Practice. Springer 2006



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Conclusions. We are challenged to find a trade-off: on one hand a metabolic model of a higher cell must be sophisticated enough to cope with a higher complexity in their functions, on the other hand the number of model parameters must be small enough to be supported by the available experimental data (often not comprehensive) and it must be simple enough that it allows to obtain concise biochemical knowledge. On top of that, the computation efforts should not impede screening of scenarios and gradual changes of cellular constraints. At the present state of information on higher cells constrained flux-balance models give the most realistic solution.