

Wolfram Liebermeister

INRA, UR1404, MaIAGE,

Université Paris-Saclay, Jouy-en-Josas, France

Enzyme-optimal metabolic states can be characterised by simple and general laws, formulated in terms of variables called economic potentials [1,2]. The economic potentials represent the usefulness of metabolites in the cell state in question; in enzyme-optimal states, they also reflect the enzyme investments embodied in metabolites. Economic potentials can be defined in kinetic or stoichiometric models, and their balance relations with enzyme costs in reactions or pathways serve as conditions for enzyme optimality.

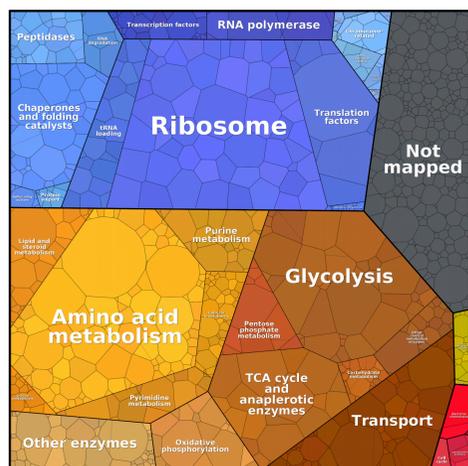
Summary

- The value of metabolites is described by economic potentials
- Economic potentials and fluxes satisfy local balance equations
- The balance equations can serve as constraints in flux analysis

Like the chemical potentials, economic potentials imply constraints on the flux directions: to comply with optimal enzyme allocation, fluxes must be free of futile cycles and lead from lower to higher economic potentials (unless "direct", flux benefits, independent of compound conversion, are taken into account). All flux distributions obtained from FBA with minimal fluxes [3] are economical in this sense and can be realized by kinetic models with optimal enzyme levels. Such models can be systematically constructed from given flux distributions.

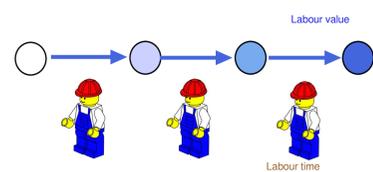
1. Resource allocation of metabolic enzymes

Protein investments in cells

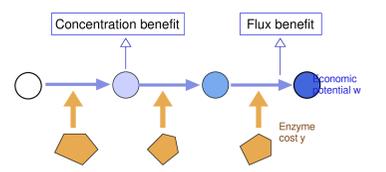


Escherichia coli proteomics data from Valgepea et al. (2013)

Definition of "natural values" (in labour value theory) ..

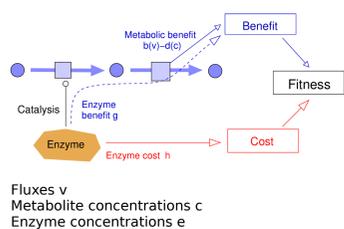


.. inspires the idea of economic potentials ("values" of metabolites)



Resource allocation in kinetic models:

Optimisation of enzyme levels for maximal steady-state benefit, minus enzyme cost



Maximize fitness $f(e) = g(e) - h(e)$
 with benefit $g(e) = b(v^{st}(e)) - d(c^{st}(e))$
 Optimality condition for each active enzyme: $0 = \frac{\partial f}{\partial e_i} = \frac{\partial g}{\partial e_i} - \frac{\partial h}{\partial e_i}$

2. Local balances between economic variables

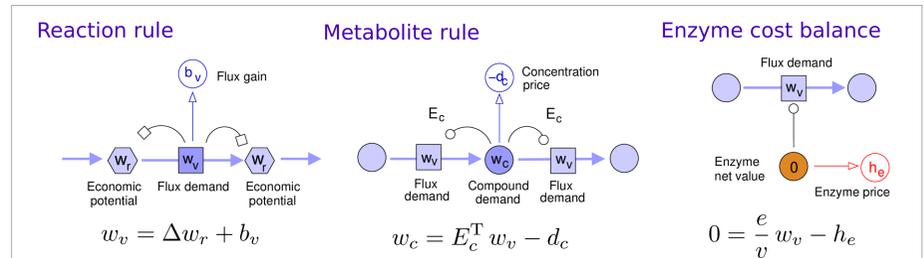
Variation conditions for optimal enzyme allocation

Flow variation condition $(b_v^* - a_v) \cdot \delta v = 0$
 Metabolite variation condition $(d_c - E_c^T a_v) \cdot \delta c = 0$

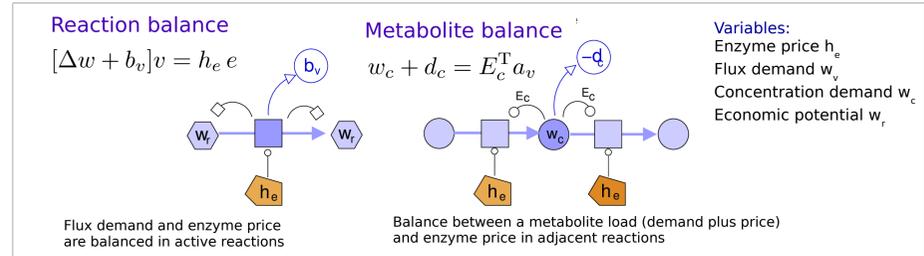
With derivative vectors
 $b_v^* = \frac{\partial b}{\partial v}$ $a_v = \frac{\partial h}{\partial e} \frac{e}{v}$
 $d_c = \frac{\partial d}{\partial c}$ $E_c = \frac{\partial v}{\partial c}$

The variation conditions can be derived as necessary conditions for enzyme-optimal states. They need to be satisfied by any constraint-preserving flux and concentration variations. Flux distributions that satisfy the conditions are called "economical". The variation conditions imply local economic rules and balance equations.

Economic rules for economic potentials and other economic variables



Economic balance equations for states of optimal enzyme allocation



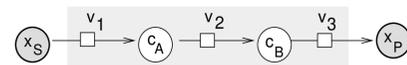
3. Economic constraints for flux analysis

Economic flux analysis

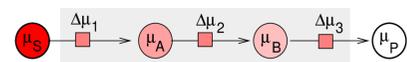
The economic reaction balance provides a link between enzyme costs, economic potentials, and flux directions. In flux analysis it can serve as an extra constraint, in addition to the known thermodynamic constraints on flux directions.

- (1) Stationarity $Nv = 0$
- (2) Thermodynamics $-\Delta\mu_i v_i > 0$
- (3) Economy $[\Delta w_i + b_{v_i}] v_i > 0$

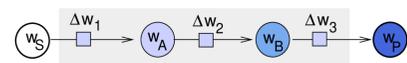
(1) Stationary fluxes / mass balances



(2) Flux leads towards lower chemical potentials μ



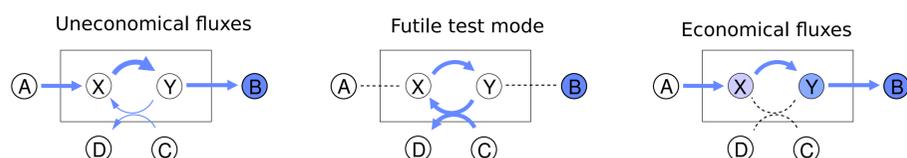
(3) Flux leads towards higher economic potentials w



Economical flux modes and futile submodes

Economic flux analysis excludes uneconomical flux modes. It does so without any knowledge on enzyme kinetics, only based on the pattern of flux directions. There are also two methods to find economical modes: by minimising a weighted sum of fluxes in flux balance analysis, or by detecting and removing futile submodes. Removing futile submodes is analogous to removing thermodynamically infeasible cycles.

Definition (Futile submode): In a flux mode v , a subset M of active reactions that is able to support a futile stationary flux distribution with the same flux signs is a *futile submode*.

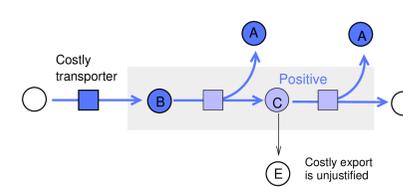


4. A new perspective on metabolic strategies

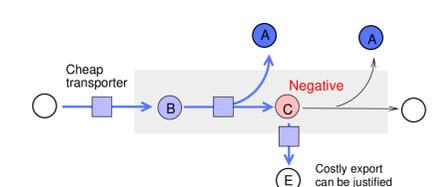
Choice between high-yield and low-yield strategies

Any enzyme investment in a pathway increases the downstream economic potentials. As a consequence, large upstream enzyme investments favour high-yield strategies.

High transporter cost \rightarrow high-yield strategy



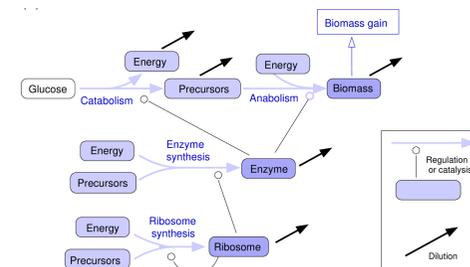
Low transporter cost \rightarrow low-yield strategy



Metabolic economics in whole-cell models

In a whole-cell model, enzymes and ribosomes are treated as regular compounds to be produced an diluted. The aim is to maximise growth, while keeping compounds in physiological ranges. The dilution of a valuable (high-potential) compound can be described by an effective compound cost.

Schematic cell model with dilution



Economic potentials and flux demands

