Enzyme Economy in Metabolic Networks

Wolfram Liebermeister

Institut für Biochemie, Charité – Universitätsmedizin Berlin

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

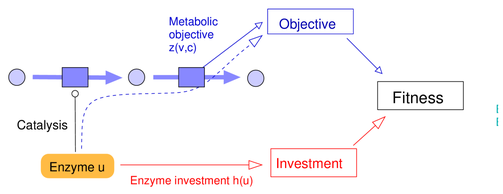
Enzyme-optimal metabolic states can be characterized by simple and general laws, formulated in terms of variables called economic potentials [1,2]. The potentials represent the usefulness of metabolites in the present cell state; in enzyme-optimal states, they also reflect the enzyme investment embodied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

Like chemical potentials, economic potentials imply constraints on the flux directions: to comply with optimal enzyme allocation, fluxes must be free of futile cycles and, in general, lead from lower to higher economic potentials. All flux distributions obtained from FBA with minimal fluxes [3] are proven to be economical in this sense and can be realized by kinetic models with beneficial enzyme levels (i.e. enzymes with positive control over the metabolic objective). Such models can be systematically constructed from given flux distributions.

1. Notions for kinetic models with optimal enzyme levels

Optimal enzyme allocation (enzyme levels u) in kinetic models with objective z(v,c)

Maximize fitness	$f(\mathbf{u}) = g(\mathbf{u}) - h(\mathbf{u})$
with objective function	$g(\mathbf{u}) = z(\mathbf{v}(\mathbf{u}), \mathbf{c}(\mathbf{u}))$
Necessary condition:	$0 = \frac{\partial f}{\partial u_l} = \frac{\partial g}{\partial u_l} - \frac{\partial h}{\partial u_l}$



Gains, enzyme cost, and flux benefit

Enzyme cost	$y_l = (\partial h / \partial u_l)\, u_l$
Concentration gain	$z^{\mathrm{c}}_i = \partial z / \partial c_i$
Flux gain	$z^{\mathrm{v}}_l = \partial z / \partial v_l$
Flux benefit	$b = \mathbf{z}^{\mathrm{v}} \cdot \mathbf{v}$
Splitting the flux gain:	$\mathbf{z}^{\mathrm{v}} = \hat{\mathbf{z}}^{\mathrm{v}} + \mathbf{N}_{\mathrm{ext}}{}^{\mathbf{T}}\, \mathbf{w}^{\mathrm{ext}}$

v = Fluxes
c = Concentrations
u = Enzyme levels
z(**v**,**c**) = Metabolic objective
g(**u**) = Metabolic return
h(**u**) = Enzyme investment
$\hat{\mathbf{z}}^{\mathrm{v}}$ = "Direct flux gain"
$\mathbf{w}^{\mathrm{ext}}$ = "Production gain"

If a flux distribution has a positive flux benefit, it is called "beneficial" (and otherwise "futile").

Condition for optimal enzyme allocation

Flux gain condition	$\mathbf{K}^{\mathbf{T}} \operatorname{diag}(\mathbf{y})\, \mathbf{v}^{-1} = \mathbf{K}^{\mathbf{T}}\, \mathbf{z}^{\mathrm{v}}$
Concentration gain condition	$(\bar{\mathbf{E}}\, \mathbf{L})^{\mathbf{T}} \operatorname{diag}(\mathbf{y})\, \mathbf{v}^{-1} = -\mathbf{L}\, \mathbf{z}^{\mathrm{c}}$

N = Stoichiometric matrix
K = kernel matrix (**N** **K** = 0)
L = Link matrix (**N** = **L** $\mathbf{N}_{\mathrm{R}}$)
$\bar{\mathbf{E}}$ = Unscaled elasticity matrix
E = Scaled elasticity matrix

If a flux distribution can satisfy flux gain conditions with positive enzyme costs y_i, it is called "economical". Uneconomical flux distributions cannot appear in enzyme-optimal kinetic models.

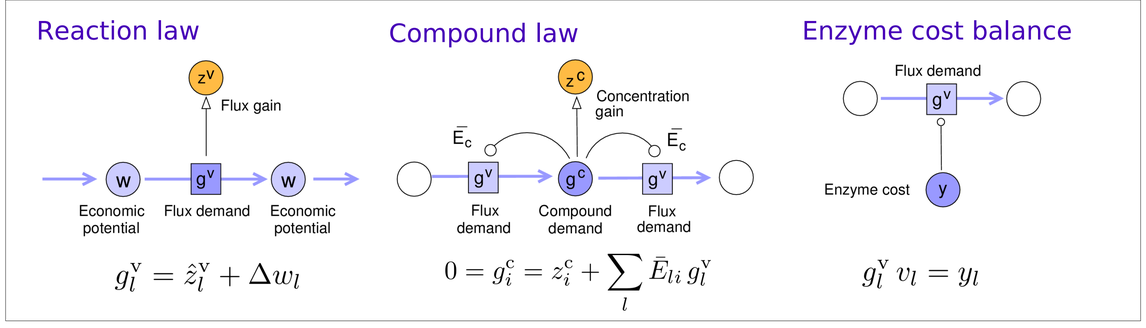
Defining the economic potentials of metabolites

An economic potential w_i describes the marginal benefit that would result from a (virtual and continuous) supply flux φ_i of metabolite *i*.

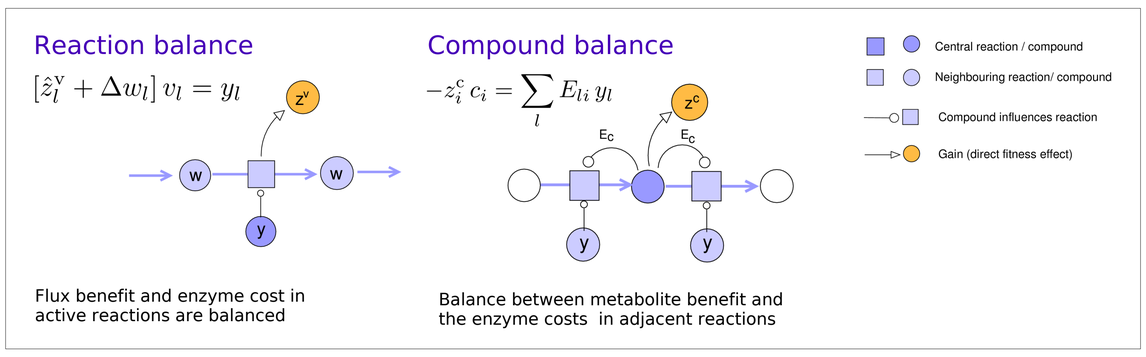
Enzyme demand	$g^{\mathrm{u}}_{i_k}$ → Metabolic response coefficient between return *g* and enzyme *l*
Flux demand	g_i → Metabolic control coefficient between return *g* and enzyme *l*
Concentration demand	g^{c}_i → Response coeff. between *g* and a virtual change in metabolite *i*
Economic potential	w_i → External: w^{ext}_i Internal: control coefficient $w^{\mathrm{int}}_i = \partial g / \partial \varphi_i$

2. Local balances between economic variables

Relationships between demands, gains, economic potentials, and costs



Balance equations for states of optimal enzyme allocation



Consequences of the reaction balance

1. Since enzyme costs y_l must be positive, flux directions follow the flux demands g^{v}_i.
2. If direct flux gain $\hat{\mathbf{z}}^{\mathrm{v}} = 0$ → flux towards higher economic potentials (because $g^{\mathrm{v}}_i = \Delta w_i$)
3. Feasible economic potentials w_i exist if (and only if) the flux distribution is economical.
4. Proportionality of control coefficients and enzyme concentrations [4] follows as a special case.

Extensions of the method

1. Moiety conservation can be handled (with minor changes in the definitions).
2. In models of growing cells, loss of economic potential by dilution leads to effective demands.
3. Economic potentials can also be defined via Lagrange multipliers.
4. Alternative economic potentials can be derived from FBA with flux minimization.

3. Economic constraints for flux analysis

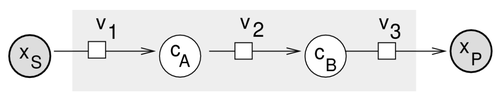
Economic flux analysis

The reaction balance explicitly states connections between flux direction and enzyme investment. It can be used as a constraint in flux analysis.

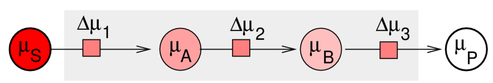
(1) Stationarity	$\mathbf{N}\, \mathbf{v} = 0$
(2) Thermodynamics	$-\Delta\mu_l\, v_l > 0$
(3) Economy	$[\hat{z}^{\mathrm{v}}_l + \Delta w_l]\, v_l > 0$

The flux constraints caused by thermodynamics and enzyme economics are formally analogous and can be handled with the same methods.

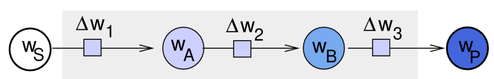
(1) Stationary fluxes / mass balances



(2) Flux leads towards lower chemical potentials μ



(3) Flux leads towards higher economic potentials w

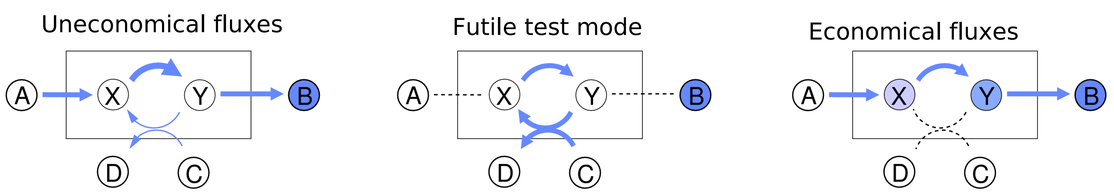


Futile flux modes

Futile cycles can be defined algebraically in the form of futile flux modes:

If a flux distribution contains a subset *M* of active reactions that could support a futile stationary flux distribution with the same flux directions, *M* is called a *futile flux mode*.

Futile flux modes make a flux distribution uneconomical (incompatible with enzyme optimality). They can be detected and removed with the help of elementary futile test modes:



Flux distributions obtained by weighted flux minimization [3] are economical and vice versa.

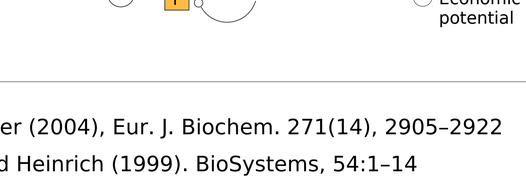
4. The economic balance equations in example models

Choice between metabolic strategies

Choices between high-yield and low-yield strategies can depend on previous investments.

High transporter cost → high-yield strategy

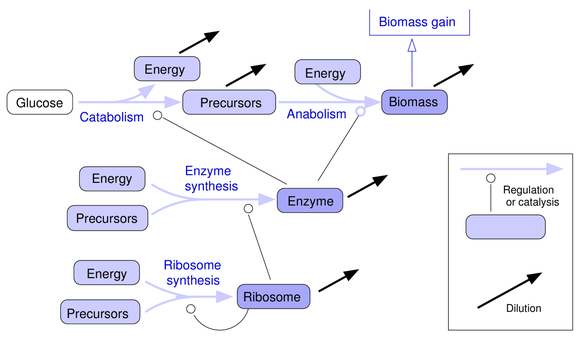
Low transporter cost → low-yield strategy



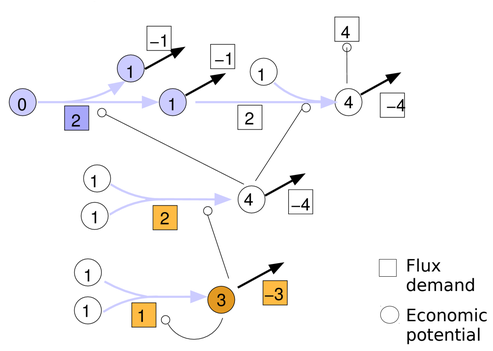
Effective costs and demands in growing cells

If enzymes and ribosomes are treated as regular compounds, the model does not need to contain an explicit cost function. In models of growing cells, dilution fluxes and economic potentials together give rise to effective compound demands.

Schematic cell model with dilution



Economic potentials and flux demands



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[1] Liebermeister (2014), arXiv:1404.5252
[2] Liebermeister (2014), arXiv:1404.5072
[3] Holzhütter (2004), Eur. J. Biochem. 271(14), 2905–2922
[4] Klipp and Heinrich (1999). BioSystems, 54:1–14