Enzyme Economy in Metabolic Networks

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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.

1. Resource allocation of metabolic enzymes

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

Resource allocation in kinetic models:
Optimisation of enzyme levels for maximal steady-state benefit, minus enzyme cost

Maximise fitness $f(e) = g(e) - h(e)$
with benefit $g(e) = b(v^{opt}(e)) - d(v^{opt}(e))$
Optimality condition for each active enzyme: $0 = \frac{\partial f}{\partial e_1} + \frac{\partial g}{\partial e_2} + \frac{\partial h}{\partial e_3}$

2. Local balances between economic variables

Variation conditions for optimal enzyme allocation

Flow variation condition $(\delta v^c - \delta a)^T \cdot \delta c = 0$
Metabolite variation condition $(\delta d^e - \delta a^e)^T \cdot \delta e = 0$

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 "economic".
The variation condition 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

Economical flux modes and futile submodes

Economical 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 other 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.

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 $\mathbf{N} \mathbf{v} = 0$
(2) Thermodynamics $-\Delta w^e_1 > 0$
(3) Economy $[\Delta w^e + h^e]_1 > 0$

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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 → high-yield strategy
Low transporter cost → 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 and 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

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.

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

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