Metabolic value theory

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INRAE

Advanced School on Quantitative Principles in Microbial Physiology: from Single Cells to Cell Communities

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The beginning: this talk on one slide

• Resource allocation in cell metabolism is difficult to understand because it concerns coordinated choices of fluxes, metabolite concentrations, and enzyme levels.

• In metabolic optimality problems, all variables depend on each other, and the solution depends on details across the entire network

• Local laws for optimal states can be formulated by introducing new local variables describing "economic values"

• These values can be defined as shadow prices or equivalently, in the case of kinetic models, as metabolic control coefficients

• The same "economic laws" can be derived from (different types of) kinetic, flux analysis, and cell models

• The laws look like a "second thermodynamics", putting constraints on flux directions, and can be used as constraints in flux analysis (e.g. to detect and remove futile cycles)

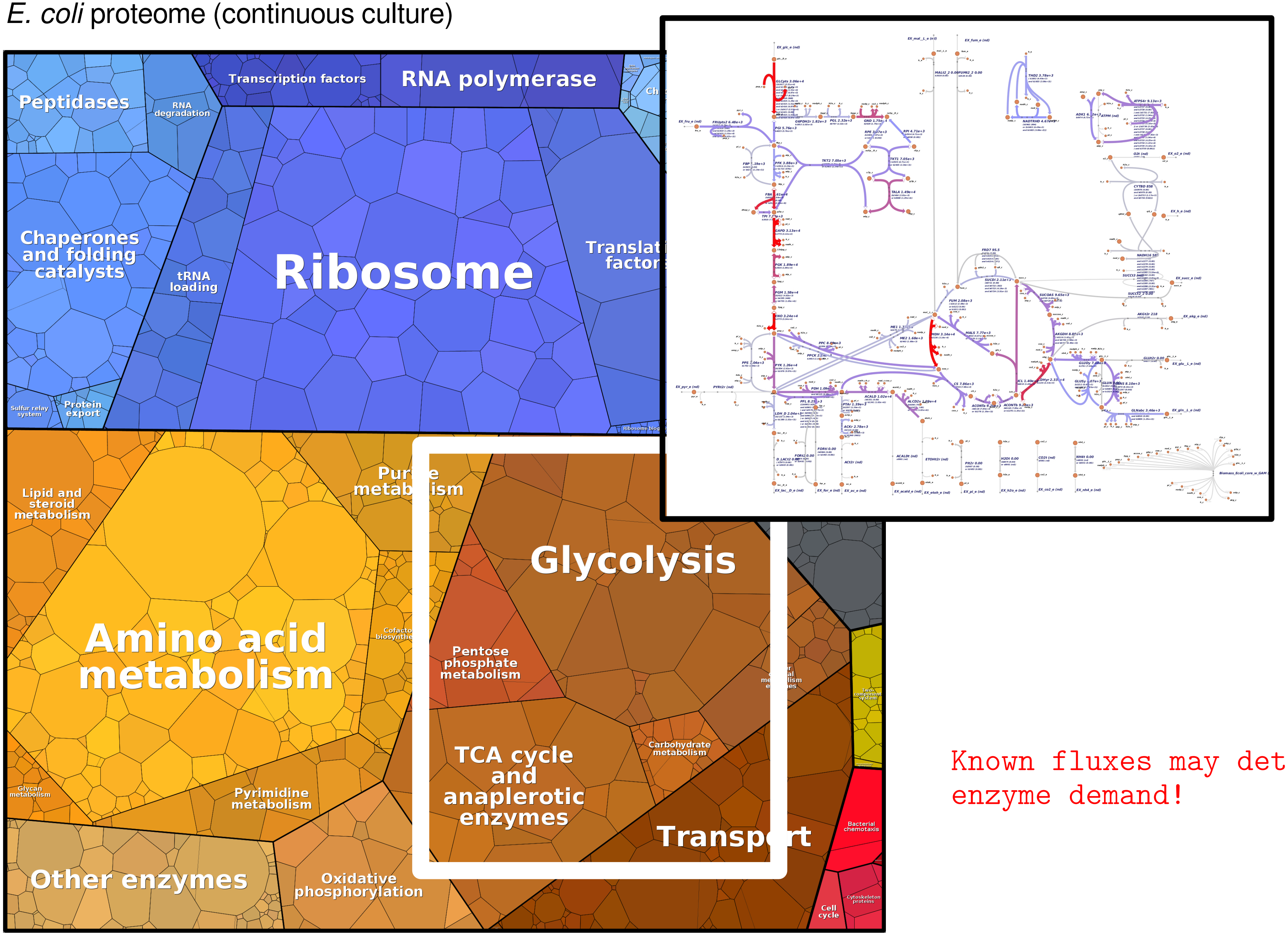
• The balance equations can be interpreted as conservation laws, indicating a "conserved flow of marginal value" in optimal states

• Deviations from optimality can be described by "economic stresses", which should be avoided

• The formalism gives a precise meaning to some economic metaphors that we use to talk about cells

How can we understand enzyme levels in cells?

E. coli proteome (continuous culture)



Known fluxes may determine enzyme demand!

Data : Valgepea et al. (2013)

Factorised rate laws can tell us what determines enzyme demand

Enzymatic rate

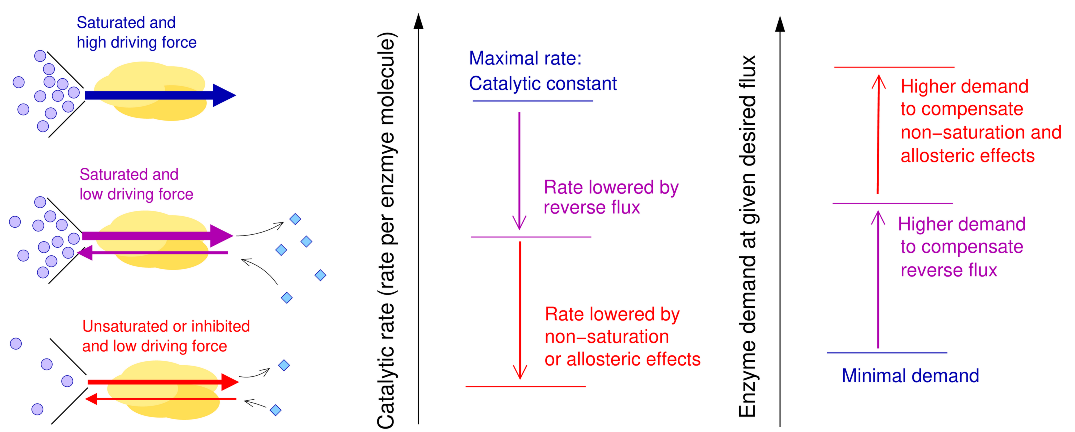
rate · enzyme level · forward catalytic constant · reversibility factor · saturation factor · regulation factor

$$v = E \cdot k^{+}_{\mathrm{cat}} \cdot \underbrace{[1-\mathrm{e}^{-\theta}]}_{\eta^{\mathrm{rev}}} \cdot \underbrace{\frac{s/K_{\mathrm{S}}}{1+s/K_{\mathrm{S}}+p/K_{\mathrm{P}}} \cdot \frac{1}{1+x/K_{\mathrm{I}}}}_{\eta^{\mathrm{kin}}}$$

Enzyme demand

enzyme cost · minimum enzyme cost · enzyme burden

$$q = h_{\mathrm{E}} \cdot E = \overbrace{h_{\mathrm{E}} \cdot v \cdot \frac{1}{k^{+}_{\mathrm{cat}}}}^{\text{minimum enzyme cost}} \cdot \underbrace{\frac{1}{[1-\mathrm{e}^{-\theta}]}}_{1/\eta^{\mathrm{rev}}} \cdot \underbrace{\frac{1+s/K_{\mathrm{S}}+p/K_{\mathrm{P}}}{s/K_{\mathrm{S}}} \cdot [1+x/K_{\mathrm{I}}]}_{1/\eta^{\mathrm{kin}}}$$

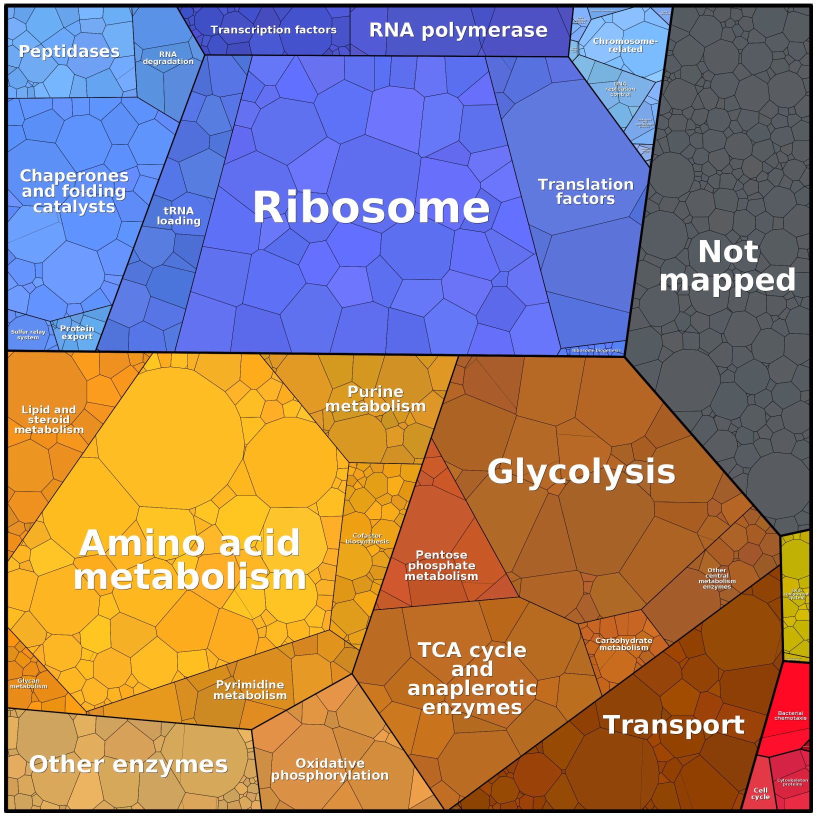


Known fluxes do not suffice to determine enzyme demand!

We also need metabolite concentrations (or some simplifying assumptions)

Noor et al. (2016), PLoS Computational Biology 12 (10): e1005167.

So how can we predict enzyme abundances?



So how to compute the enzyme levels?

This requires that fluxes are known!

Simply compute fluxes by FBA?
But FBA ignores kinetics!

To know the enzyme efficiencies, metabolite concentrations must be known!

We can obtain them by Enzyme Cost Minimisation .. but then we need the fluxes!

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But FBA ignores kinetics!

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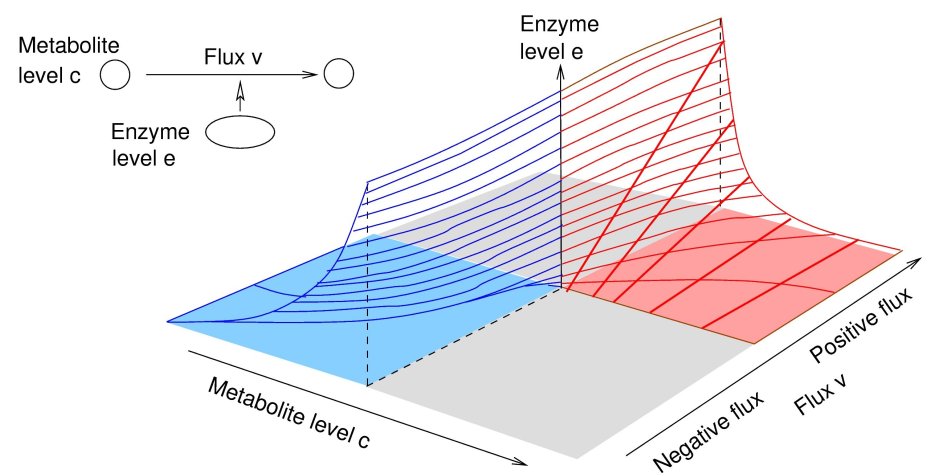
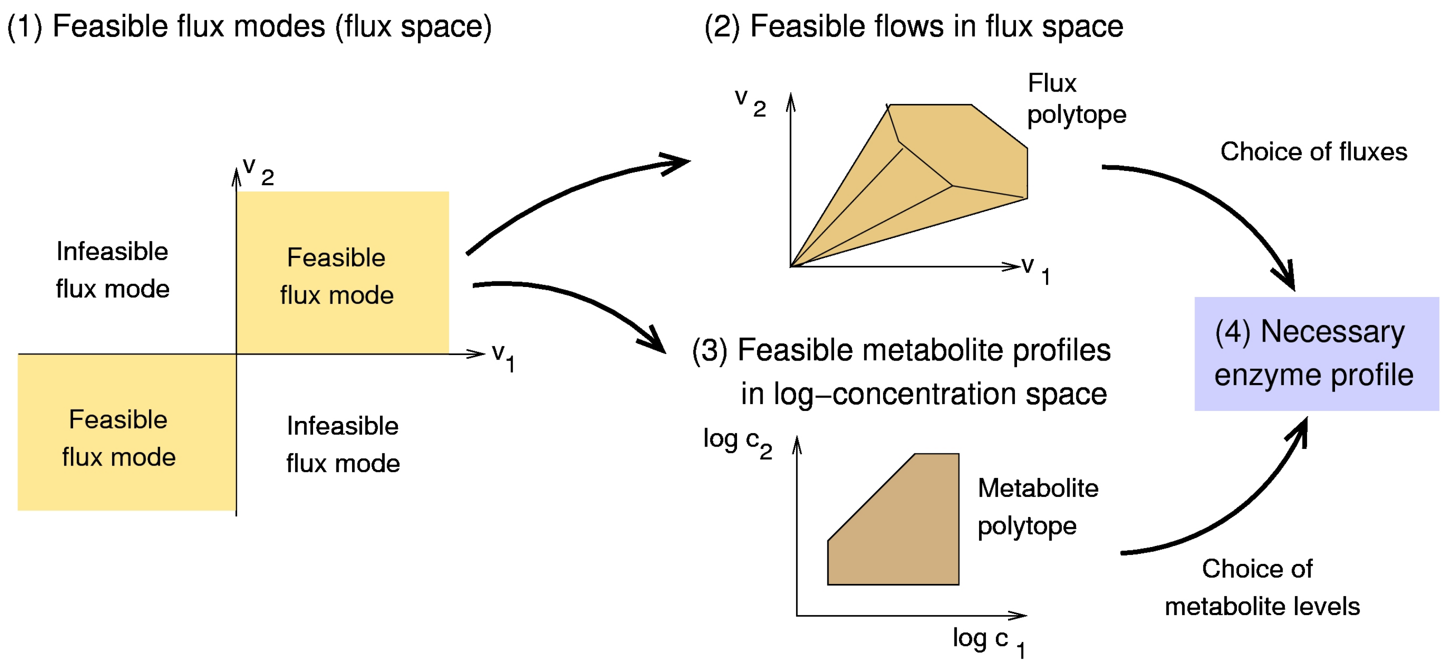
How can we optimise all fluxes, enzyme levels, and metabolite levels at the same time?



Metabolic states can be obtained by screening flux and metabolite profiles

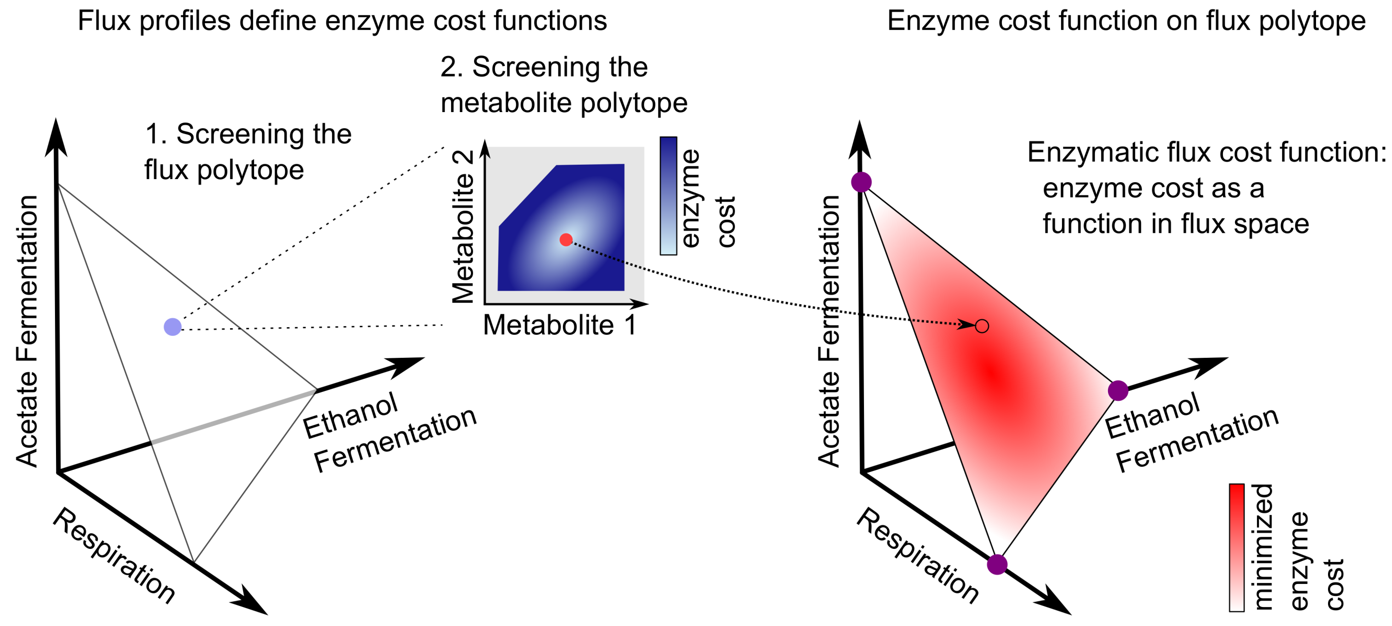


Construction of metabolic states

- All feasible states (and no others) can be constructed
- Feasible states can be parameterised by fluxes and logarithmic metabolite levels
- Thermodynamic correctness is ensured by construction
- Framework for sampling, optimisation, and definition of effective cost and benefit functions

Liebermeister W. (2018), Flux cost functions and the choice of metabolic fluxes; arXiv
Liebermeister W. (2018), Optimal metabolic states in cells; bioRxiv

Optimal metabolic states can be obtained by nested optimisation



Optimality problem for metabolism: minimise enzyme demand at a given biomass production rate

Nested optimisation

Optimise fluxes v (s.t. given biomass flux v_{BM}):

Optimise concentrations c (given fluxes v):

Set enzyme levels e = e(v,c)

→ Compute enzyme cost h(e)

← Outer optimisation: FCM (concave)

← Inner optimisation: ECM (convex)

The optimal flux profiles are polytope vertices (in some cases, Elementary Flux Modes)

Wortel *et al.* (2018), PLoS Computational Biology 14(2)

But still .. isn't there another way to see this?

The problem:

Metablic optimality problems are very unintuitive and require a network-wide optimisation!

In practice, the entire network is not even known!

Generally, in order to optimise one part of the system, optimal solutions for all other parts need to be known!

Instead of optimizing enzyme levels globally, can we understand enzyme investments locally, without simulating the entire cell?

Now, instead, a completely different view:

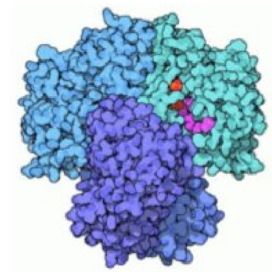
Compare how much enzymes "cost" to how much they contribute to metabolic performance

A economic concept of investments and values!

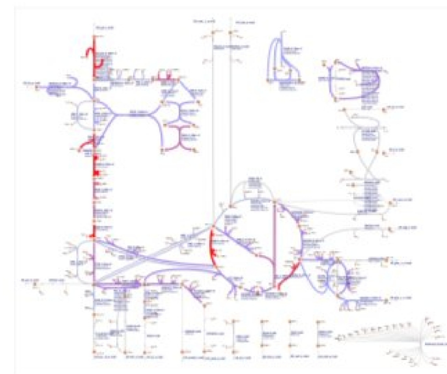
Let's see enzyme abundances as investments that need to be justified by a benefit!

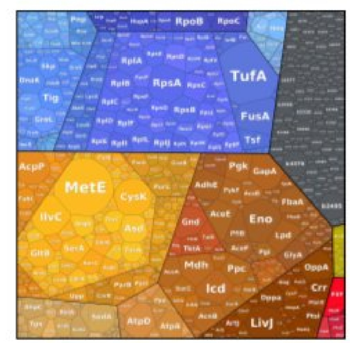
Can we describe optimal states from a local perspective?

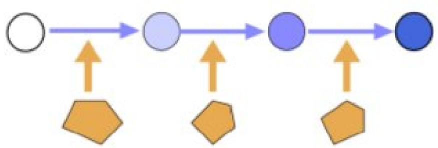
Molecule properties and interactions



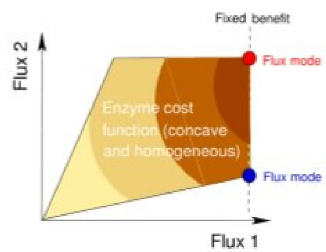
Cellular networks and omics data





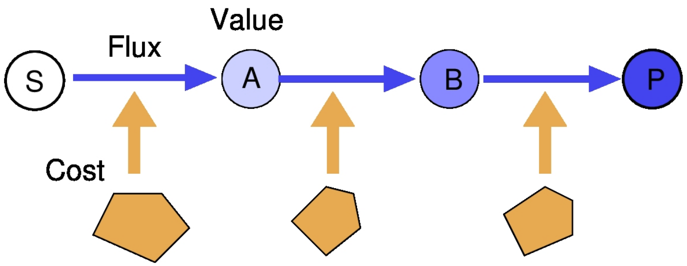


Metabolic values and local economic laws on the network



Optimality problems in abstract spaces

An example of such a theory:
the enzyme-control rule for optimal metabolic states



Flux control coefficients C_l^v describe the global effects of enzymes on fluxes

Enzyme-control rule (Heinrich and Klipp 1999):
In states of maximal enzyme efficiency (maximal flux at a given total enzyme amount), enzyme concentrations and flux control coefficiente are proportional

$$e_l^* \sim C_l^v \qquad \text{that is} \qquad e_l^* = e_{\text{tot}}^* \; C_l^v$$

We can see this as a balance between investment (in enzymes) and benefit (provided by enzymes)

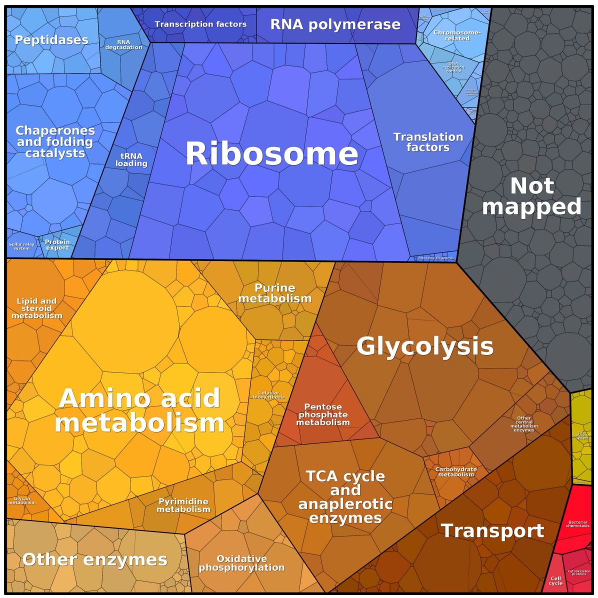
Enzyme-control rule for models with general density constraint (Noor and Liebermeister 2023):

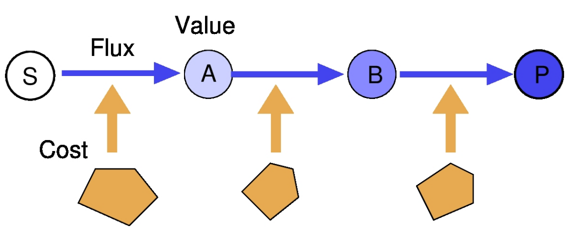
$$e_l^* = e_{\text{tot}}^* \; C_l^v - J^* \frac{b}{a} \sum_i C_l^{s_i *}$$

(where a and b are density weights for enzymes and metabolites)

Brown (1991), J. Theor Biol
Heinrich and Klipp (1999), BioSystems
Noor and Liebermeister (2023), bioRxiv

The enzyme control rule follows from optimality conditions in constrained optimisation





Metabolic optimality problem (Klipp and Heinrich 1999):

Maximise a steady pathway flux v^{st} at a fixed enzyme budget

Maximise $v^{\mathrm{st}}(e)$ s.t. $\sum_l e_l = e_{\mathrm{tot}}$

Solve the problem with Lagrange multipliers:

Lagrangian $\mathcal{L} = v^{\mathrm{st}}(e) - \lambda(\sum_l e_l - e_{\mathrm{tot}})$

Optimality condition $0 = \frac{\partial \mathcal{L}}{\partial e_l} = \frac{\partial v^{st}}{\partial e_l} - \lambda = C_l^v \, \frac{v}{e_l} - \lambda$

Relation between enzyme levels and flux control

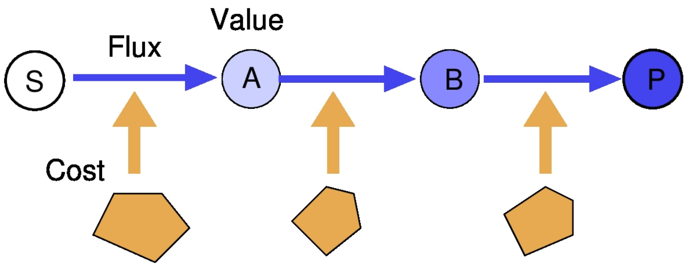
$\frac{C_l^v}{e_l} = \frac{\lambda}{v} = \mathrm{const}$ across all reactions!

Enzyme levels and flux control coefficients must be proportional!

Higher "investment" (enzyme) → higher "use value" (flux control)

E. Klipp and R. Heinrich (1999) BioSystems

The enzyme-control rule implies an enzyme-elasticity rule relating enzyme levels and elasticities around each metabolite



Enzyme-control rule:

$$e_l^* \sim C_l^v$$

Connectivity theorem (in systems without moiety conservation):

$$\forall i : \quad \sum_l C_l^{J_j} \; E_{c_i}^{v_l} = 0$$

Enzyme-elasticity rule

$$\forall i : \quad \sum_l e_l^* E_{c_i}^{v_l} = 0$$

So optimal enzyme levels and elasticities around a metabolite are inversely proportional!

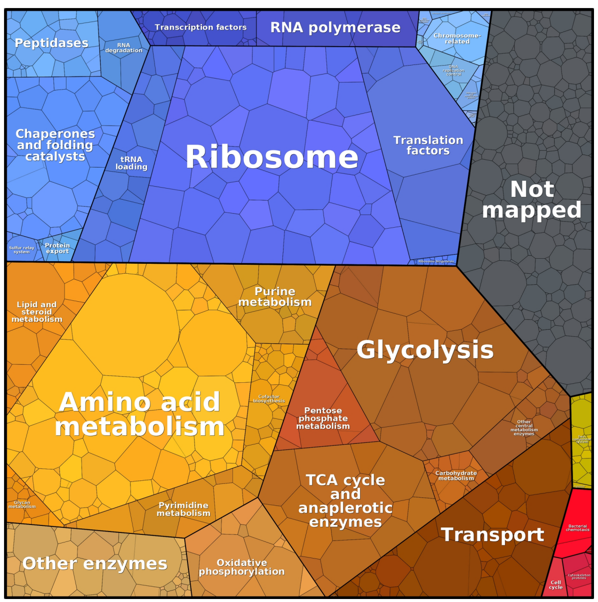
$$\forall i : \quad \frac{e_{i+1}}{e_i} = \frac{|E_{c_i}^{v_i}|}{|E_{c_i}^{v_{i+1}}|}$$

Noor and Liebermeister (2023), Biorxiv

How can we generally describe metabolism in terms of investments and use value?

If we assign investements and use value to enzymes, then ..

- Do metabolites also carry a use value?
- How are all these values related?
- How much enzyme should cells invest in producing valuable metabolites?



We will assume metabolic problems with cost and benefit and would like to equate, for each enzyme

Enzyme investment
= Enzyme-enabled global flux benefit
= Local value production (in the reaction)

Hence

- We see (weighted) protein abundances as an "investome"!
- We describe a global benefit as a local value production!

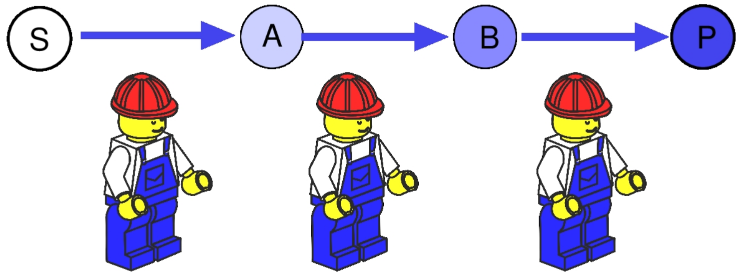
`All this should follow mathematically from existing metabolic optimality problems!`

Enzyme investments and metabolite value

Labour value

The "natural value" of a commodity is the number of working hours put into its production

Labour values increase along a production chain



Value production balance in metabolism

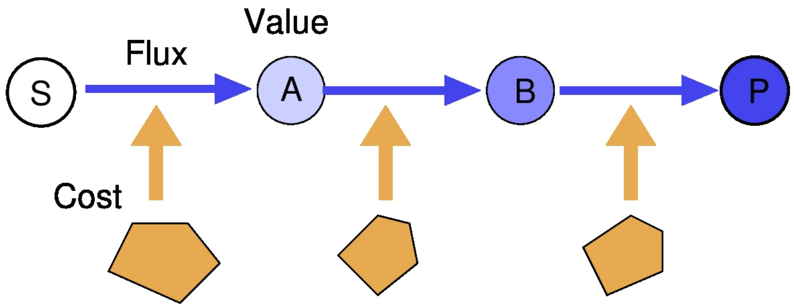
Value production = enzyme investment!

$$\Delta w_r \cdot v = h_e \ e > 0$$

Economic potentials w_r

$$w_{ri} = \sum_l \Delta w_{r_l} = \sum_l \frac{h_{e_l} \ e_l}{v}$$

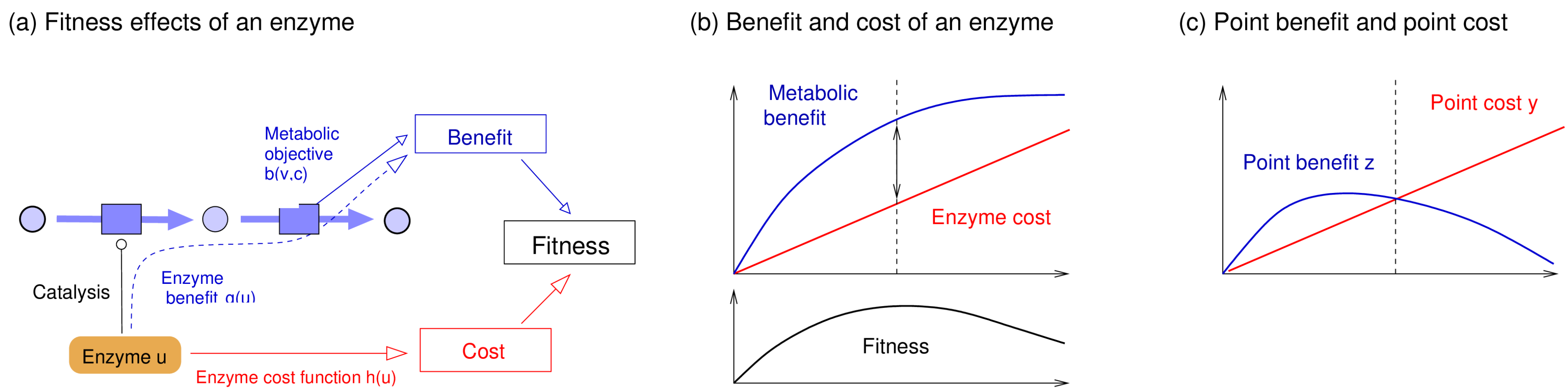
The economic potentials increase along the pathway flux



Can such values be found in an entire network?

Any ideas?

Optimality conditions for enzymes in more general metabolic models



Optimality problem

Maximise $f(e) = b(v(e)) - g(c(e))$ - $h(e)$ = $q(e)$ - $h(e)$

Optimality conditions for active enzymes

Value-price balance

$$\frac{\partial q}{\partial e} = \frac{\partial h}{\partial e}$$

Enzyme value = Enzyme price

Importance-investment balance

$$\frac{\partial q}{\partial e} \cdot e = \frac{\partial h}{\partial e} \cdot e$$

Enzyme point benefit = Enzyme point cost

where

$$\frac{\partial q}{\partial e} = [b_v^T\ C^v - g_c^T\ C^c]\frac{v}{e}$$

with metabolic control coefficients C^v, C^c

Can you spot the hidden enzyme-control rule?

Enzyme benefit principle: dq/de > 0

All active enzymes must have positive control on the metabolic objective!

Liebermeister W. (2014), Enzyme economy in metabolic networks; arXiv:1404.5252

Valid state variations must be fitness-neutral: this leads to the economic variation rules

Writing enzyme values as $w_e = C^g \, \mathrm{diag}(v) \, \mathrm{diag}(e)^{-1}$, with control coefficients C^g, we obtain

Flux and metabolite variation conditions
from (i) cost-benefit balance and (ii) theorems of Metabolic Control Analysis

Flux condition
(from summation theorem)

$$(b_{\mathrm{v}} - a_{\mathrm{v}}) \cdot \delta v = 0$$

for any "legal" (stationary) flux variation vector

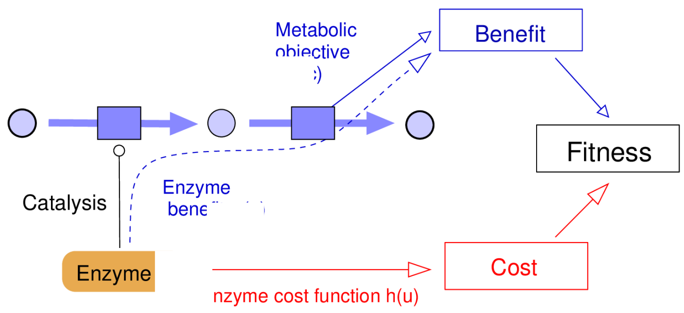
Metabolite condition
(from connectivity theorem)

$$(g_{\mathrm{c}} - E_{\mathrm{c}}^{\mathrm{T}} a_{\mathrm{v}}) \cdot \delta c = 0$$

for any "legal" (moiety-conserving) concentration variation vector

Direct fitness derivatives

Virtual variations



with "direct" economic variables

Flux gain $b_v = db/dv$

Flux burden $a_v = dh/de \; e \,/\, v$

Metabolite load $g_c = dg/dc$

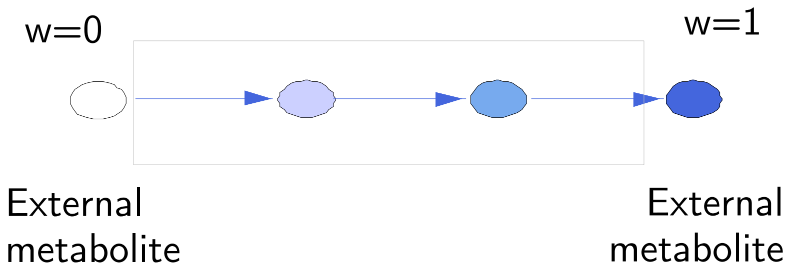
Elasticity $E_c = dv/dc$

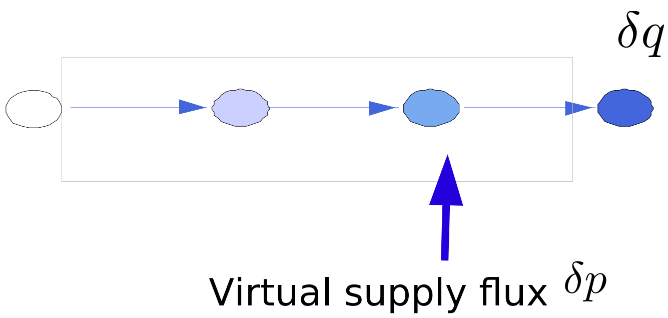
Liebermeister W. (2014), Enzyme economy in metabolic networks; arXiv:1404.5252

Economic values and metabolic control: economic potentials and value production balance

Definition of economic potentials

Metabolic objective: net production of external metabolites





External economic potential

Prefactor in production objective
q(e) = 1 * production rate

Internal economic potential

Control coefficient $w = \frac{\delta q}{\delta p}$

Condition for enzyme-optimal states (maximal g(e)-h(e))

Optimality condition for active enzymes:

$$\frac{\partial q}{\partial e} \cdot e = \frac{\partial h}{\partial e} \cdot e$$

Enzyme point benefit = Enzyme point cost

Reformulation as local balance equation

$$\Delta w \cdot v = \frac{\partial h}{\partial e} \cdot e$$

Economic potential difference x Flux = Enzyme price x Enzyme level

Liebermeister W. (2014), Enzyme economy in metabolic networks; arXiv:1404.5252

Generally, economic values can be defined by Lagrange multipliers

Optimality problem "Metabolic performance minus enzyme cost"

Minimise fitness f(v,c,e) = b(v)-g(c)-h(e) s.t.
N v = 0 (stationary fluxes)
b(v) = b' (fixed flux benefit)
v = e k(c) (rate laws)

Optimisation with Lagrange multipliers ("shadow prices")

Lagrange function: $\mathcal{L} = b(v) - g(c) - h(e) + w_{\mathrm{r}}^T\ N_R\ v + w_{\mathrm{v}}^T (v(v,e) - v) + w_{\mathrm{cm}}^T\,(c_{\mathrm{cm}} - G\ c)$

Abbreviations $b_{v_l} = \frac{\partial b}{\partial v_l},\quad g_{c_i} = \frac{\partial g}{\partial c_i},\quad h_{e_l} = \frac{\partial h}{\partial u_l},\quad E^{v_l}_{c_i} = \frac{\partial v_l}{\partial c_i},\quad E^{v_l}_{e_l} = \frac{v_l}{e_l},$

Optimality conditions

By taking derivatives with respect to v, c, and e and setting them to 0, we obtain the economic rules

Economic rules

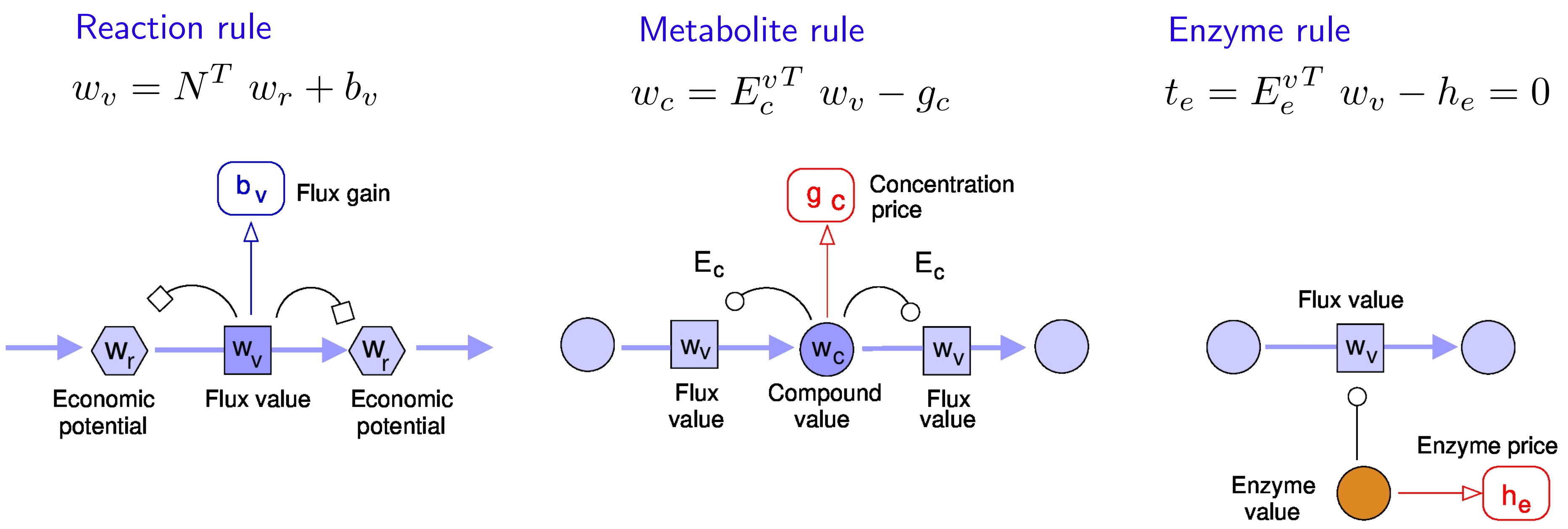
$w_v = N^T\ w_r + b_v$	"Reaction rule"
$w_c = E_c^{vT}\ w_v - g_c$	"Metabolite rule"
$0 = t_e = E_e^{vT}\ w_v - h_e$	"Enzyme rule"

Economic variables

		w_v	Flux value
b_v	Direct flux value	w_r	Economic potential
g_c	Concentration price	w_c	Concentration value
h_e	Enzyme price	t_e	Enzyme tension

Liebermeister W. (2018) The value structure of metabolic states; bioRxiv doi:10.1101/483891

Economic values of network elements are linked by economic rules



Economic rules

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Economic variables

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h_e	Enzyme price	t_e	Enzyme tension

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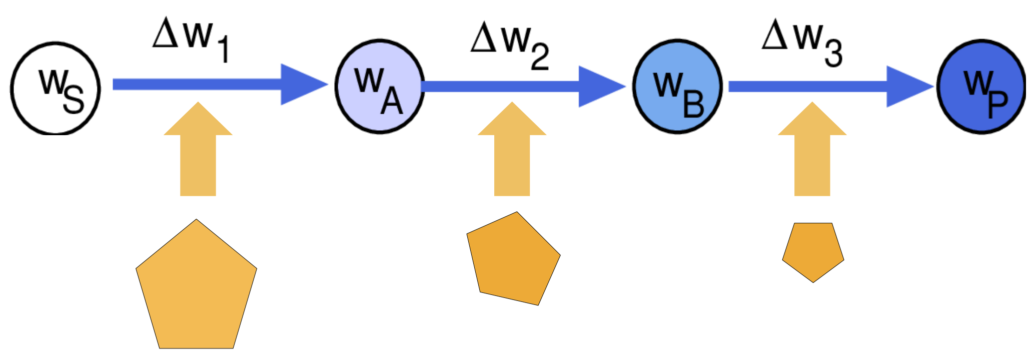
Economic balance for reactions: investment = value production

A local law for enzyme costs, fluxes, and economic potentials



Value production balance (assuming no direct flux gains)

$$\Delta w_r \cdot v = h_e \cdot e > 0$$

Economic potential difference

Flux

Enzyme investment

Derivation from economic rules

Enzyme rule $\rightarrow \quad 0 = \frac{v}{e}\, w_v - h_e$

Reaction rule $\rightarrow \quad \Delta w_r + b_v = w_v$

Taken together:

"Value production=investment"

$$[\Delta w_r + b_v]\ v = h_e\ e$$

"Flux value = Flux burden"

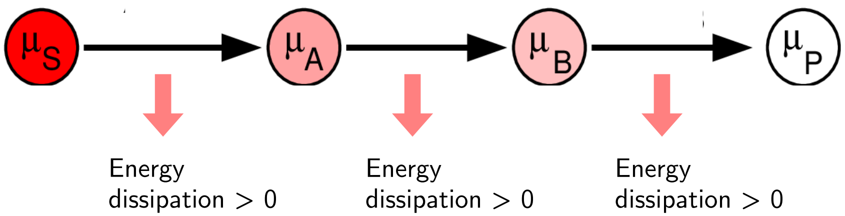
$$\Delta w_r + b_v = h_e\ \frac{e}{v} = a_v$$

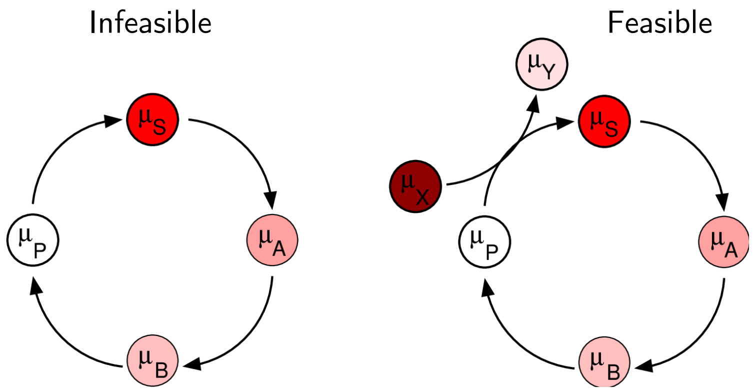
Thermodynamic and economic laws

Positive Gibbs free energy dissipation

$$-\Delta\mu \cdot v > 0$$

Sign constraint: $\mathrm{sign}(v) = \mathrm{sign}(-\Delta\mu)$





Liebermeister W. (2014), How enzyme economy shapes metabolic fluxes; arXiv:1404.5072

Thermodynamic and economic laws

Positive Gibbs free energy dissipation

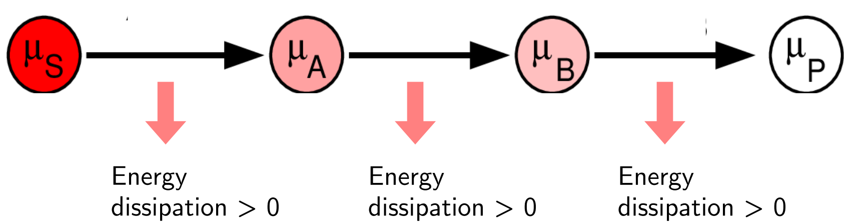
$$-\Delta\mu \cdot v > 0$$

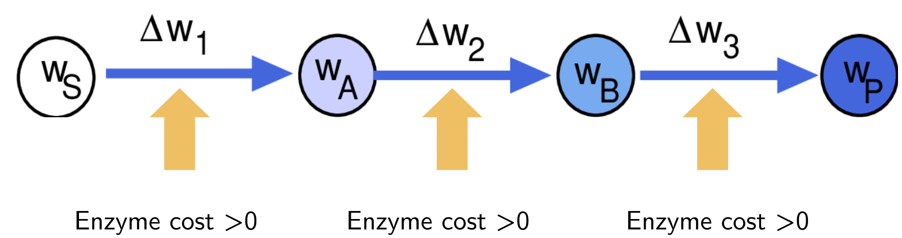
Sign constraint: $\mathrm{sign}(v) = \mathrm{sign}(-\Delta\mu)$

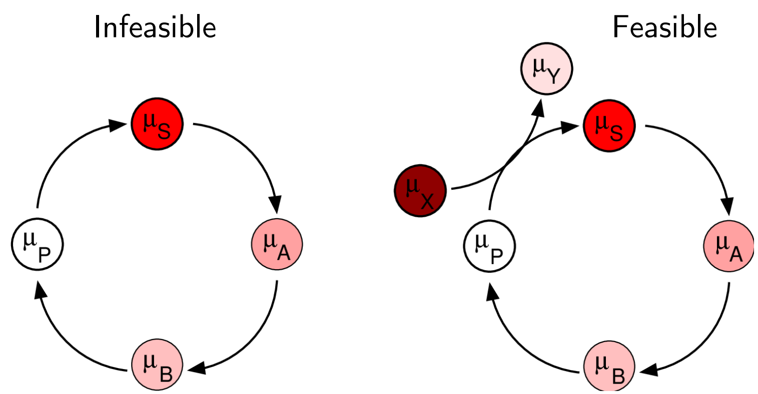
Enzyme point benefit = enzyme point cost

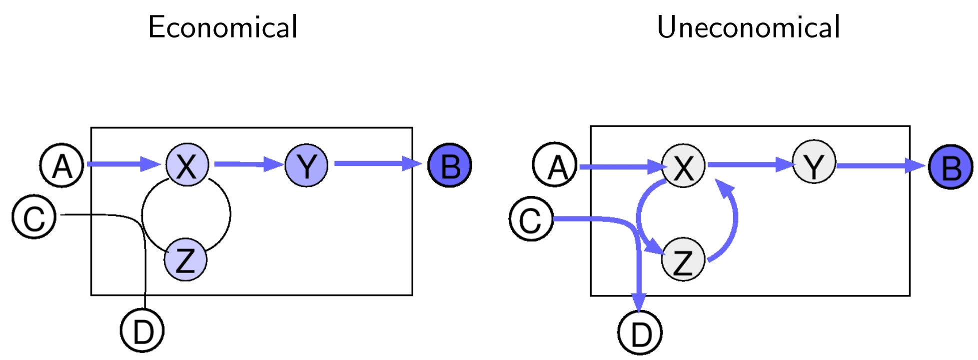
$$\Delta w_r \cdot v > 0$$

Sign constraint: $\mathrm{sign}(v_l) = \mathrm{sign}(\Delta w_l)$









In fact, the derivation is quite similar: both laws stem from a maximality principle

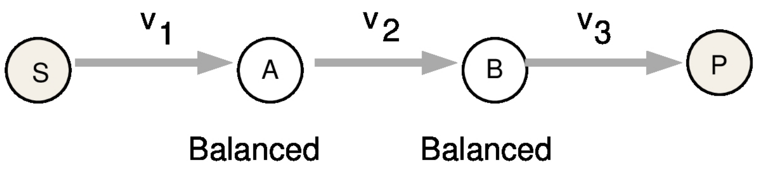
Liebermeister W. (2014), How enzyme economy shapes metabolic fluxes; arXiv:1404.5072

Value balance analysis can predict fluxes that ensure local value production

Flux Balance Analysis

$Nv = 0$ (stationarity)

.. plus other constraints and optimisation:
flux bounds; bound on linear enzyme demand,
maximisation of production rate ..

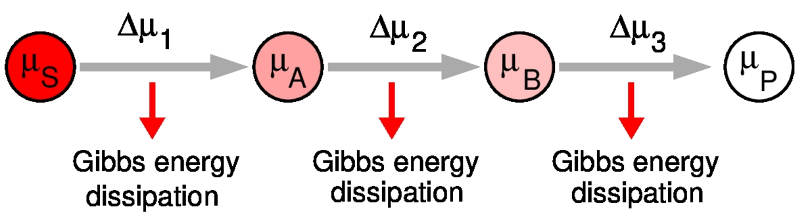


Energetic constraints ($\rightarrow$ "Energy Balance Analysis")

Energy dissipation: $\sigma = \Delta\mu \; v > 0$

with chemical potentials $\mu = \mu^{\circ} + RT \ln c$

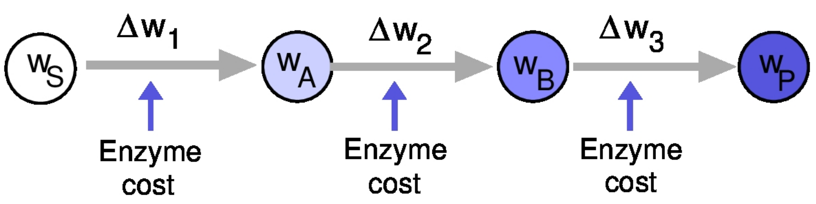
$\rightarrow$ Flux sign constraint: $\mathrm{sign}(v) = -\mathrm{sign}(\Delta\mu)$



Economic constraints ($\rightarrow$ "Value Balance Analysis")

Enzyme investment $h_e^* = h_e \; e = \Delta w_r \; v > 0$

$\rightarrow$ Flux sign constraint: $\mathrm{sign}(v) = \mathrm{sign}(\Delta w)$



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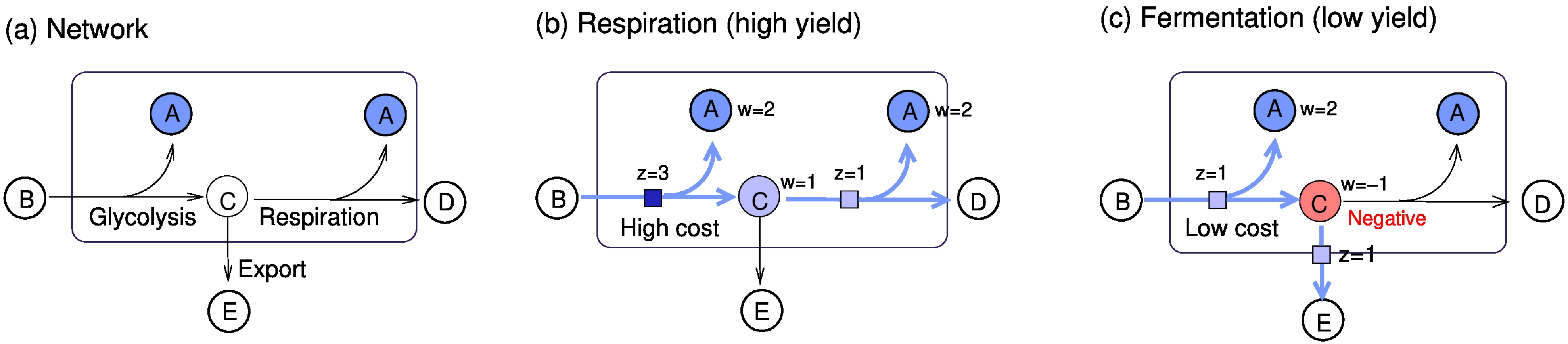
Enzyme investments determine downstream metabolic strategies



A highly discussed question: how do cells "choose" between respiration and fermentation?

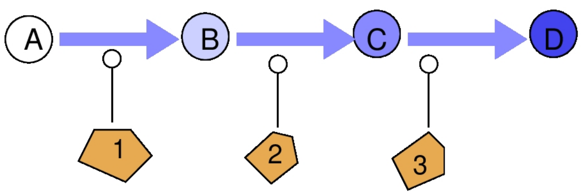
Conclusions from the reaction balance equation:

- Metabolite usage depends on prior investment!
- Substrate investments have similar effects as enzyme investments!

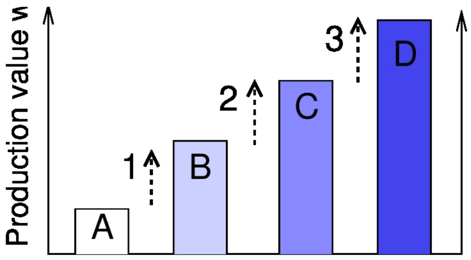
Liebermeister W. (2014), How enzyme economy shapes metabolic fluxes; arXiv:1404.5072

Investments and value production in optimal states can be described as a conserved flow of value

Value production rates



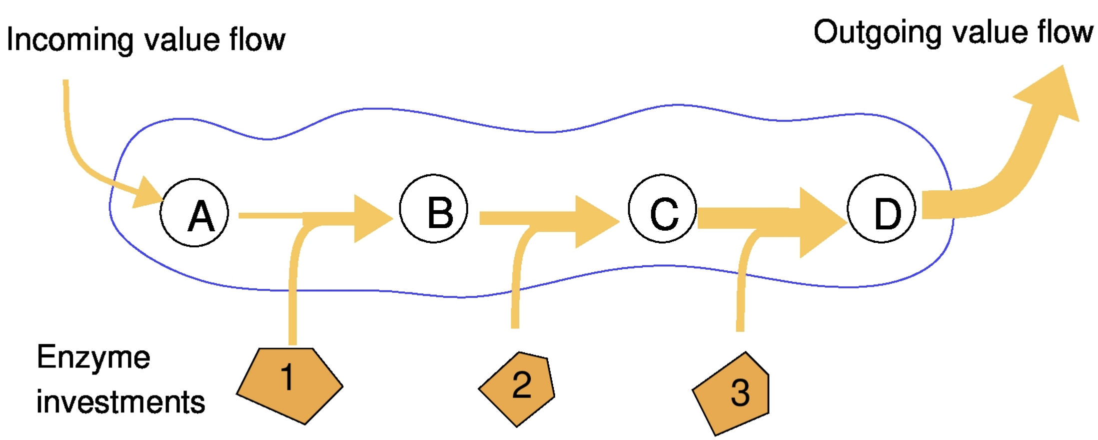
Economic potentials

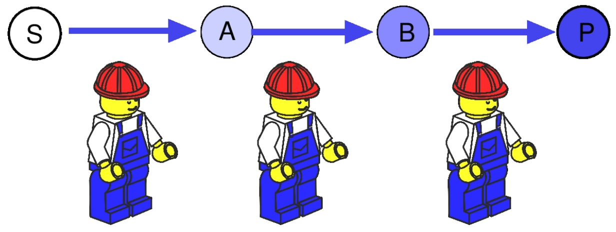


Value production balance

$$\Delta w_r \cdot v = h_e \cdot e > 0$$

Enzyme investments and value flows





How can we describe non-optimal states?
Non-optimal enzyme levels lead to economic "tensions"

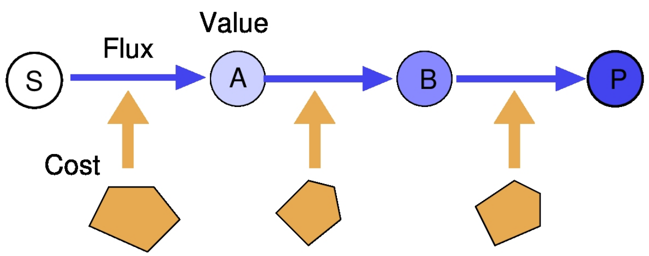
Optimal states: enzyme use value and price must be balanced

$$\frac{\partial f}{\partial e_l} = \frac{\partial q}{\partial e_l} - \frac{\partial h}{\partial e_l} = 0$$

Non-optimal states are characterised by "economic tensions"

$$t_l = \frac{\partial f}{\partial e_l} = \frac{\partial q}{\partial e_l} - \frac{\partial h}{\partial e_l} \neq 0$$

(f: fitness) (q: benefit) (h: cost)



Value production imbalance

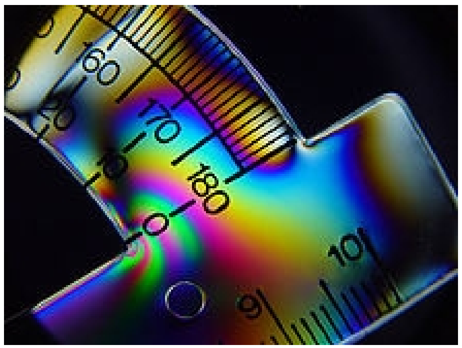
$$[\Delta w_{r_l} + w_{v_l}^{dir}] \; v = h_{e_l} e_l + t_l$$

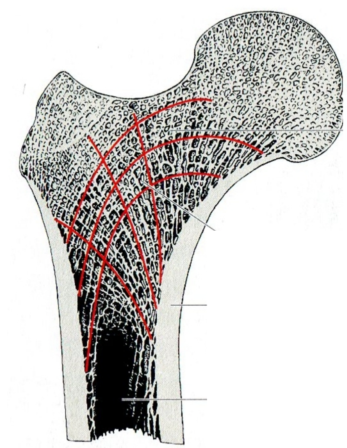
Tensions indicate a mismatch between value production and enzyme investment

Higher enzyme levels tend to decrease an enzyme's control → the tension should decrease!

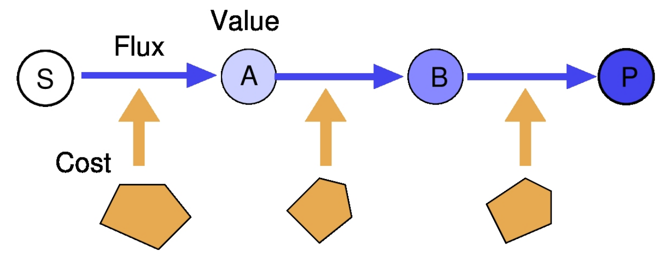
Economic tensions resemble mechanical stresses: an analogy to biomechanics

Wolff's law: bones are shaped by adding and removing material depending on mechanical stresses

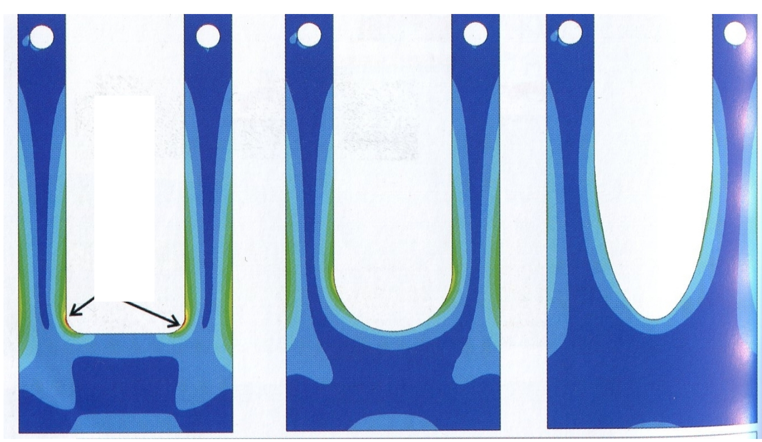




Economic tensions indicate a need to increase or decrease the enzyme levels



C. Mattheck: Mechanical stresses indicate a need to re-enforce a shape (or to save material)



How to find an optimal state?

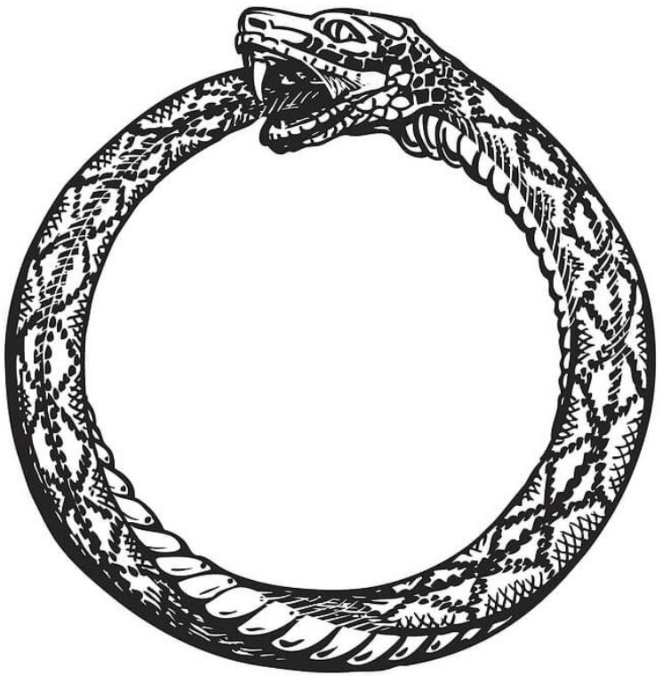
Hypothetical regulation mechanism:
Sense tensions and adapt enzymes!

Tension $t_l > 0 \rightarrow$ increase the enzyme level!

Tension $t_l < 0 \rightarrow$ decrease the enzyme level!

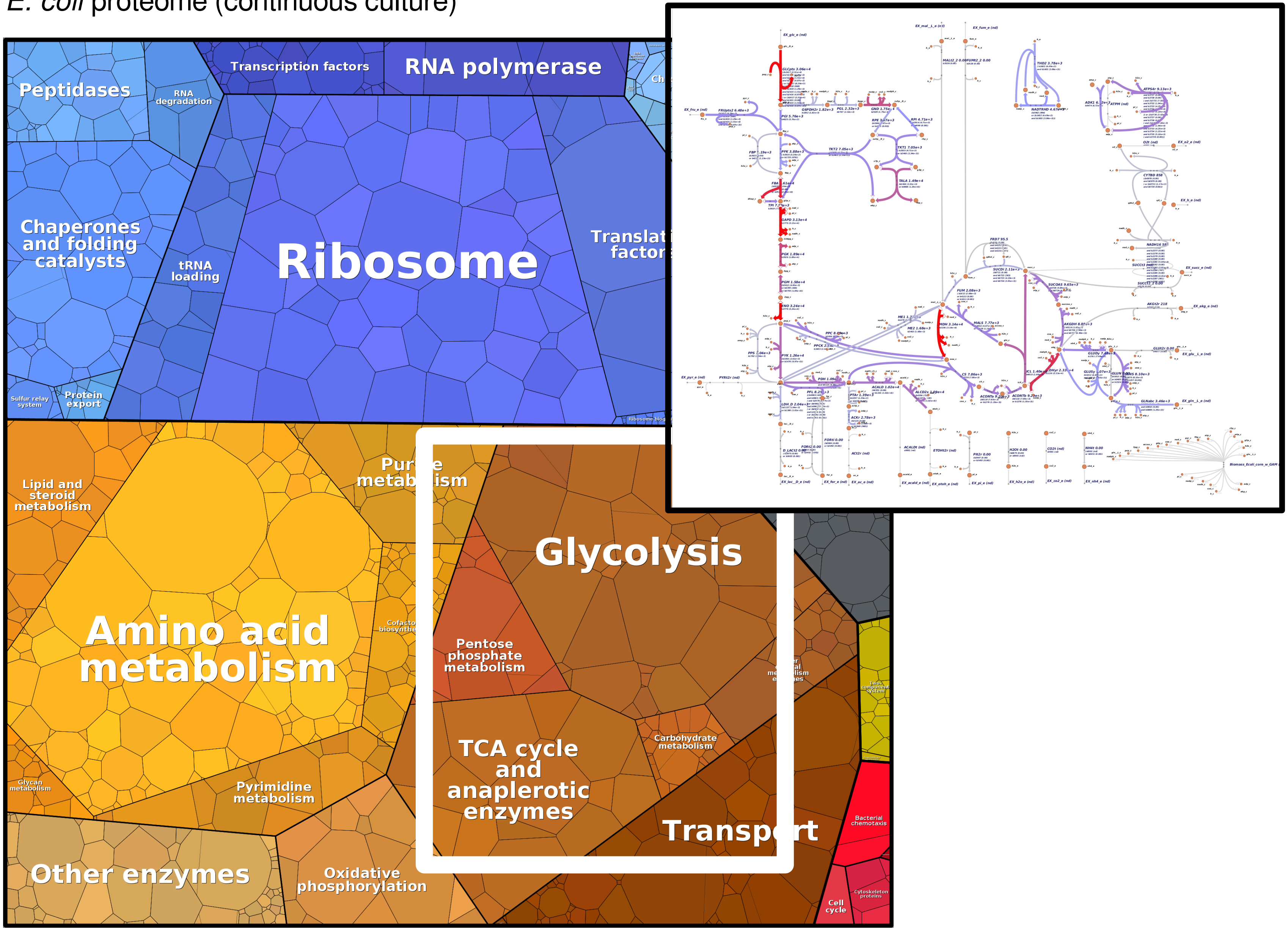
... until all tensions vanish?

Closing the circle: what did we learn?

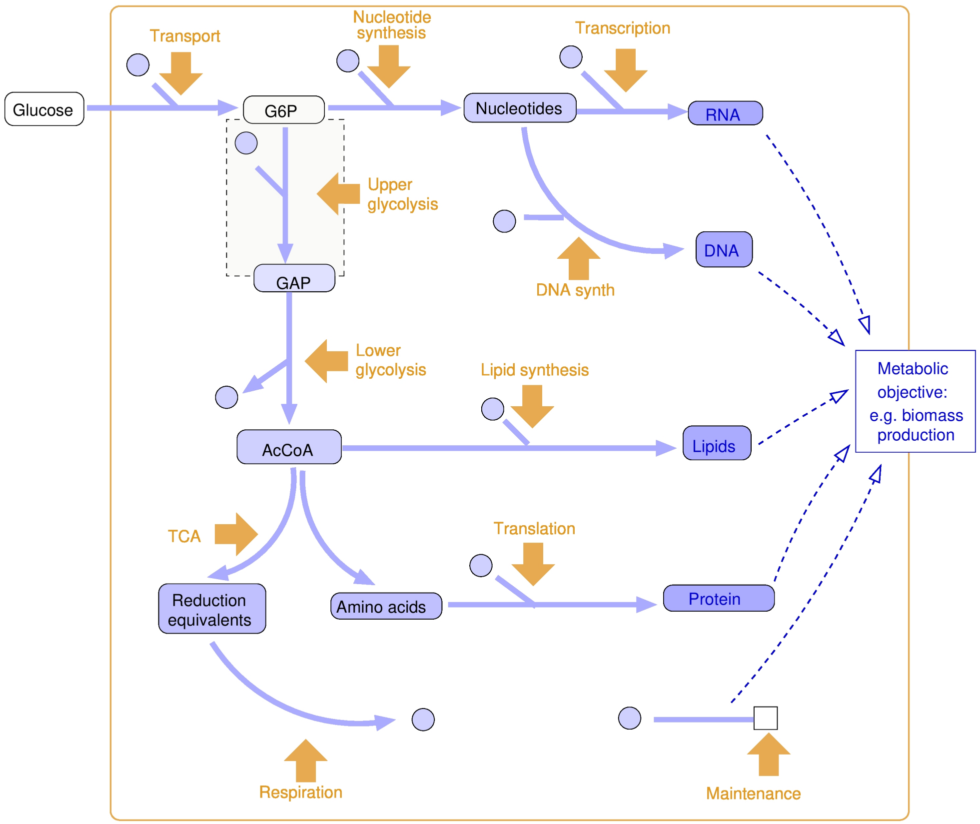


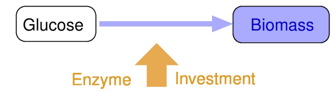
Closing the circle: what did we learn?

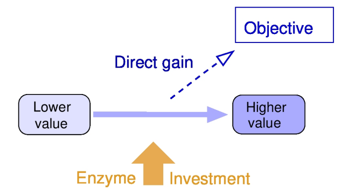
E. coli proteome (continuous culture)

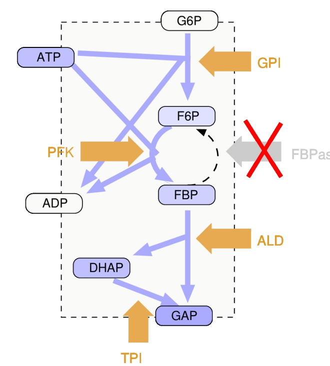


Closing the circle: what did we learn?









To understand enzyme levels, we ask what's their function; what they do in metabolism

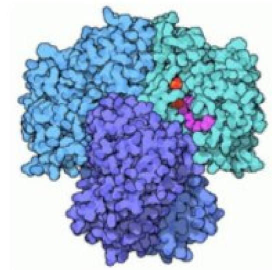
Flux Balance Analysis predicts stationary flux distributions (and some methods consider enzyme usage)

In these methods, enzyme usage must be "justified" by production of valuable compounds

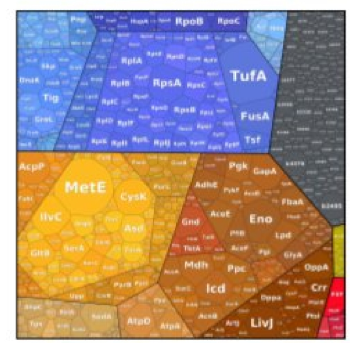
Metabolic value theory applies this logic locally, everywhere in the network by defining "metabolite values"

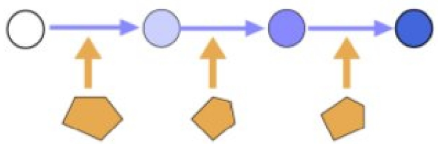
Closing the circle: what did we learn?

Molecule properties and interactions

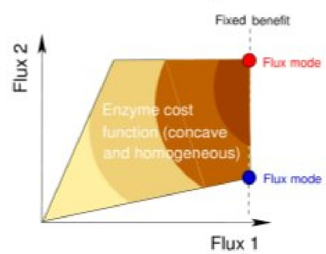


Cellular networks and omics data





Metabolic values and local
economic laws on the network



Optimality problems in abstract spaces

Liebermeister W. (2018) The value structure of metabolic states; bioRxiv doi:10.1101/483891

The end: this talk on one slide

• Resource allocation in cell metabolism is difficult to understand because it concerns coordinated choices of fluxes, metabolite concentrations, and enzyme levels.

• In metabolic optimality problems, all variables depend on each other, and the solution depends on details across the entire network

• Local laws for optimal states can be formulated by introducing new local variables describing “economic values”

• These values can be defined as shadow prices or equivalently, in the case of kinetic models, as metabolic control coefficients

• The same “economic laws” can be derived from (different types of) kinetic, flux analysis, and cell models

• The laws look like a “second thermodynamics”, putting constraints on flux directions, and can be used as constraints in flux analysis (e.g. to detect and remove futile cycles)

• The balance equations can be interpreted as conservation laws, indicating a “conserved flow of marginal value” in optimal states

• Deviations from optimality can be described by “economic stresses”, which should be avoided

• The formalism gives a precise meaning to some economic metaphors that we use to talk about cells

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