CHARITÉ

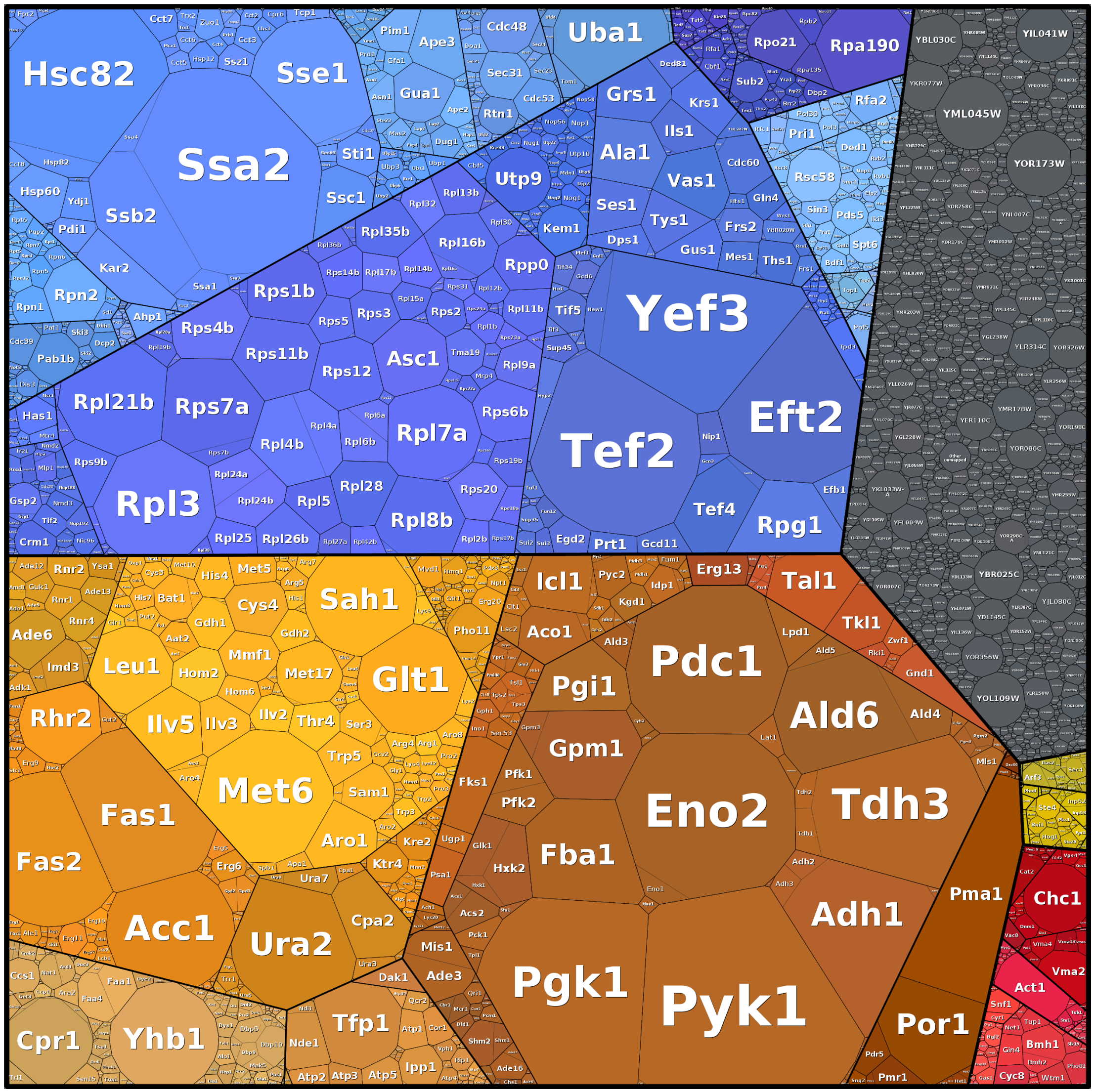
Enzyme economy in metabolic networks

Wolfram Liebermeister

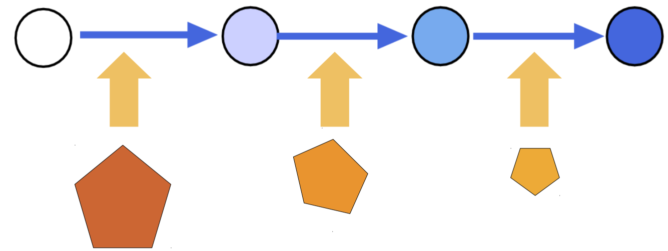
Charité – Universitätsmedizin Berlin

Workshop on the Economy of a Cell:
Resource Allocation, Trade-Offs and Efficiency in Living Systems

1. How can we make sense of enzyme costs?



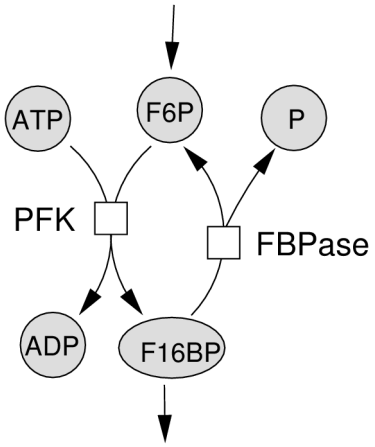
Yeast proteomics data from Nagaraj *et al.* (2012)

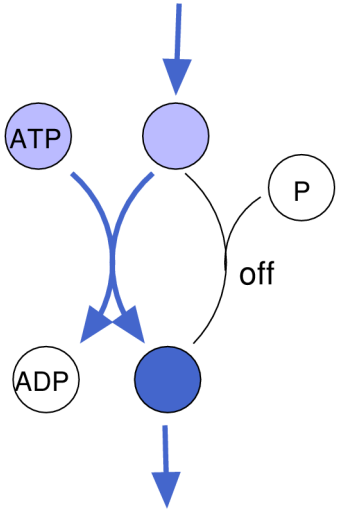


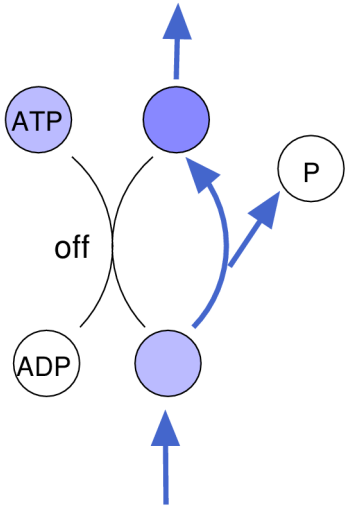
Flux analysis ignores quantitative relations between enzyme levels and fluxes

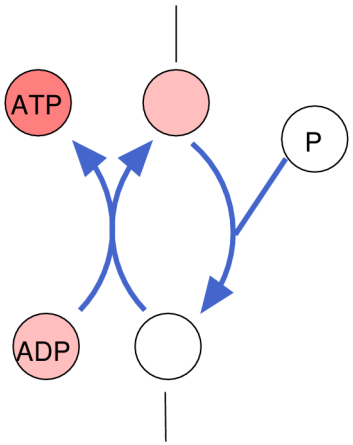
Do we need global models to understand local patterns in enzyme investment?

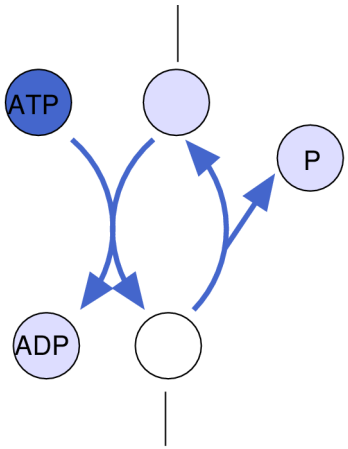
2. How can we make sense of enzyme usage?



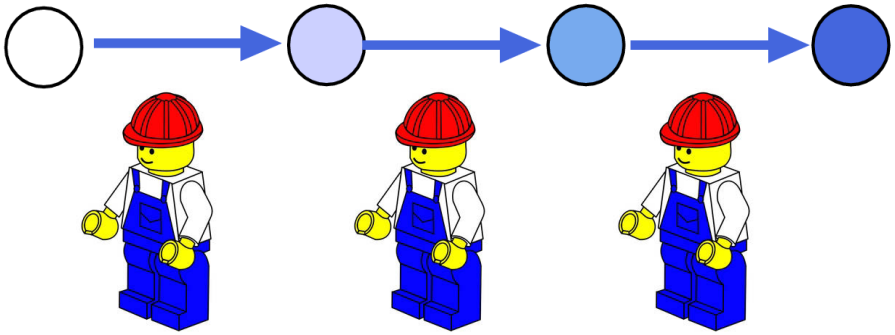








A first intuition: fluxes should lead to value production



Labour value in economics

- Labour value is defined by time invested in the production of a good
- The value increases during production according to invested labour

Analogous postulate for metabolism

- Fluxes should produce valuable metabolites from less valuable ones
- Value of metabolites should increase along the flux
- The value difference (in reaction or pathway) corresponds to enzyme efforts

Economic potentials should also determine the flux directions

Gibbs free energy dissipation

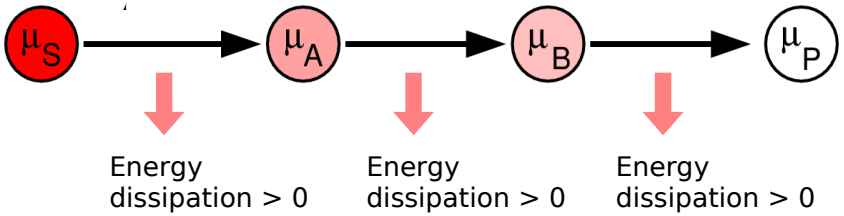
$$-\Delta G \cdot v > 0$$

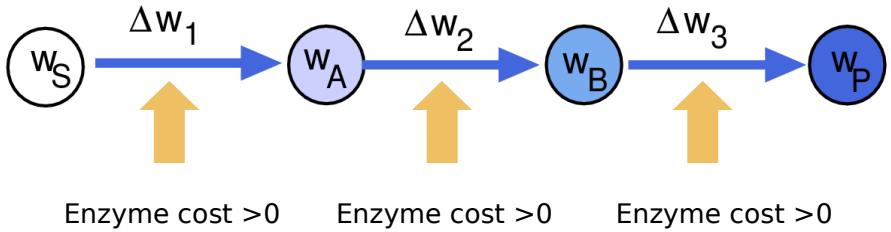
Sign constraint: $\mathrm{sign}(v) = \mathrm{sign}(-\Delta G)$

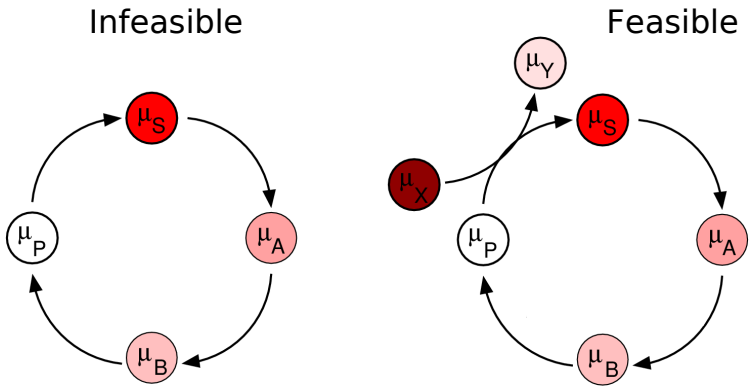
Enzyme benefit = enzyme cost

$$\Delta w \cdot v = y > 0$$

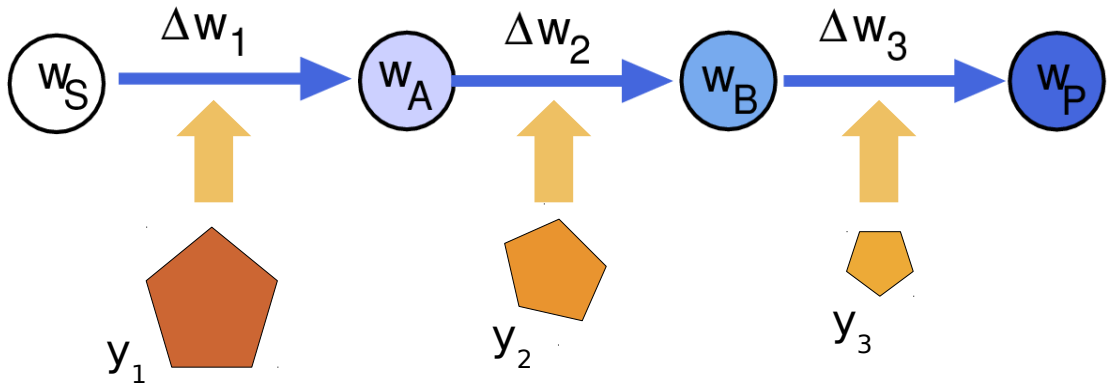
Sign constraint: $\mathrm{sign}(v_l) = \mathrm{sign}(-\Delta \mu_l)$







A condition for enzyme optimality: the reaction balance equation



Reaction balance equation

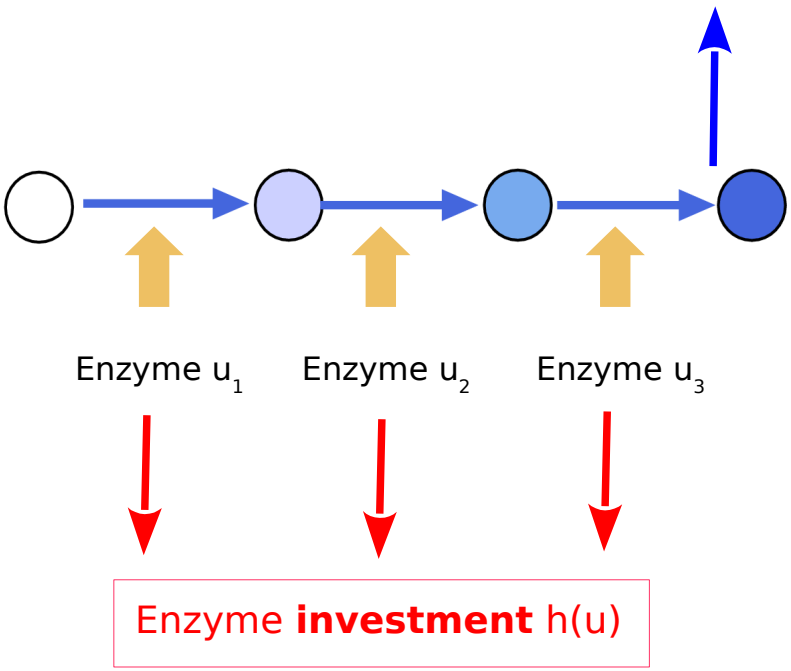
$$\Delta w \cdot v = y > 0$$

“Economic potential difference”

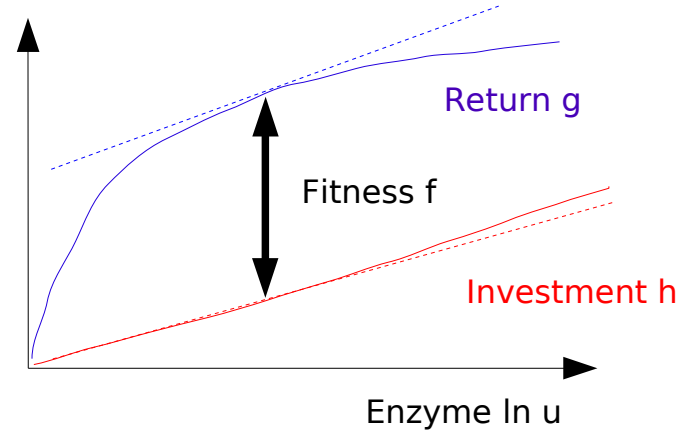
Flux

“Enzyme cost”

Kinetic models with optimal enzyme levels



Fitness f = Return g - Investment h



Optimality condition for active enzymes:

$$\frac{\partial g}{\partial \ln u} = \frac{\partial h}{\partial \ln u} > 0$$

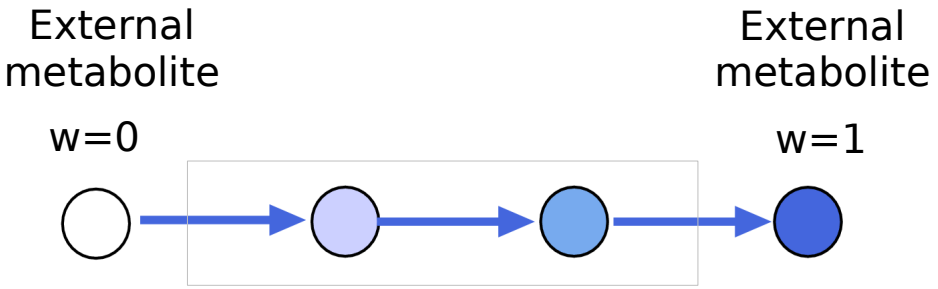
"Enzyme benefit" = "enzyme cost"

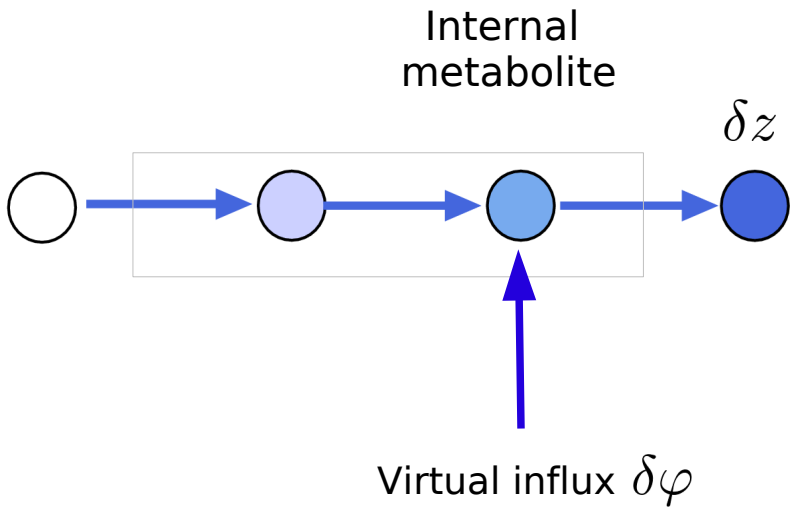
$$\Delta w \cdot v = \frac{\partial h}{\partial u} \cdot u$$

"Economic potential difference" x Flux = "Enzyme price" x Enzyme level

The economic potentials can be defined by control coefficients

Objective:
Production of external metabolites





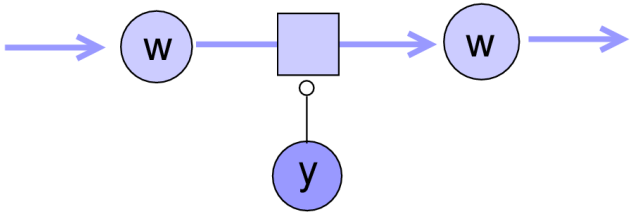
Economic potential:
Directly from production objective

Economic potential:
"Control coefficient" $w = \frac{\delta z}{\delta \varphi}$

Reaction balance … and compound balance

Metabolic objective function:
Net production of some external metabolites

Reaction balance equation



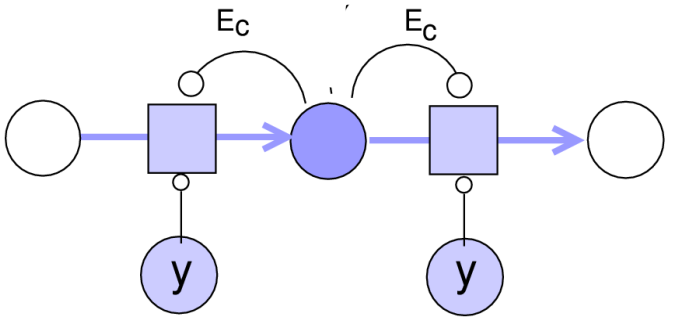
$$\Delta w_l \cdot v_l = y_l > 0$$

Economic potential difference

Flux

Enzyme cost

Compound balance equation



$$0 = \sum_l E_{li}\, y_l$$

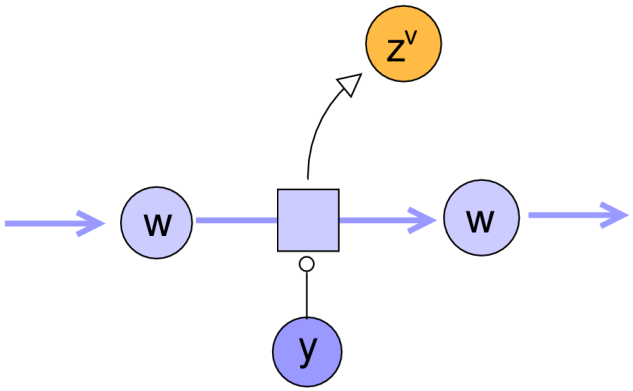
Scaled elasticity

Enzyme cost

General metabolic objectives lead to extra terms

Metabolic objective function:
Some function of the steady-state fluxes and concentrations

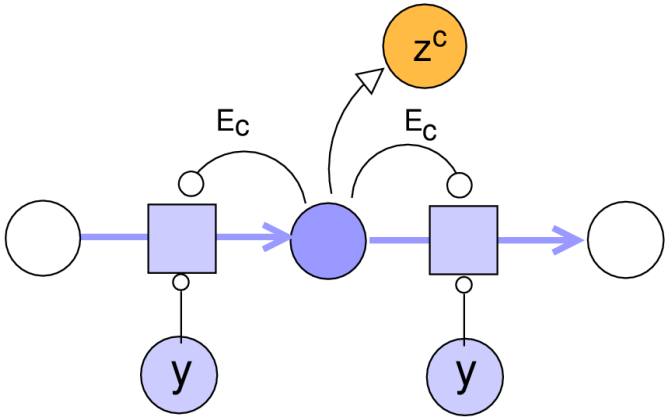
Reaction balance equation



$$[\hat{z_l^{\mathrm{v}}} + \Delta w_l]\, v_l = y_l > 0$$

Direct flux gain | Economic potential difference | Flux | Enzyme cost

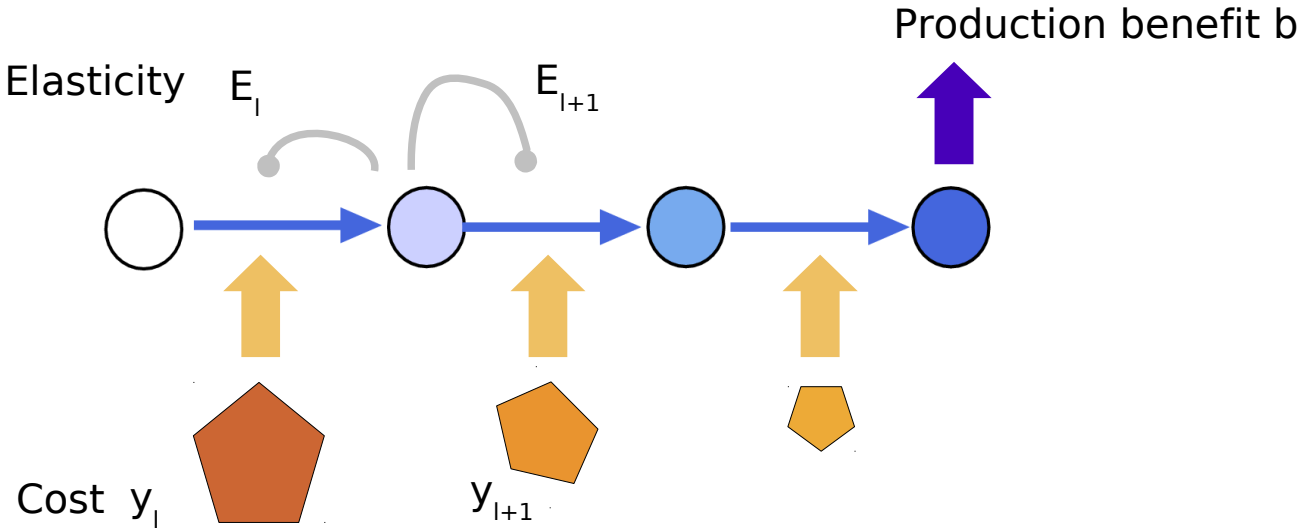
Compound balance equation



$$0 = z_i^{\mathrm{c}}\, c_i + \sum_l E_{li}\, y_l$$

Concentration gain | Concentration | Scaled elasticity | Enzyme cost

Two simple rules for the enzyme costs in a linear pathway



1. Along the pathway: Reaction balance

"Total enzyme cost = Total flux benefit"

$$\sum_l y_l = b$$

2. Around each metabolite: Compound balance

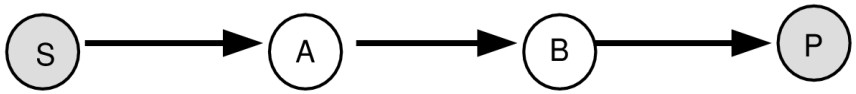
"Enzyme costs scale inversely to elasticities"

$$\frac{y_{l+1}}{y_l} = \frac{\bar{E}_l}{\bar{E}_{l+1}}$$

The economic reaction balance can be used as a constraint in FBA

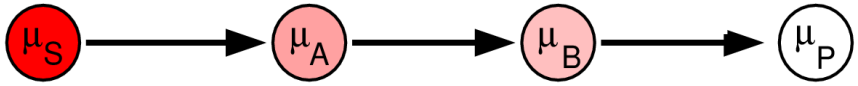
Stationarity

$$N\,v = 0$$



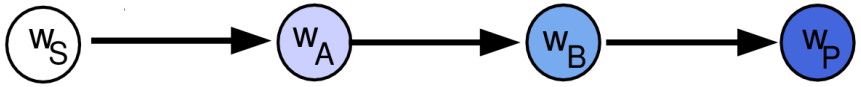
Energy dissipation

$$-\Delta\mu_i \cdot v_i > 0$$



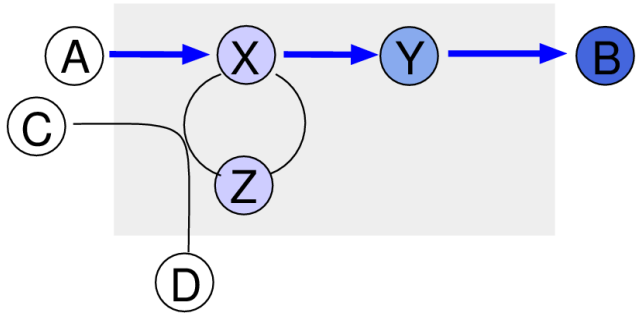
Benefit principle

$$\Delta w_i \cdot v_i > 0$$

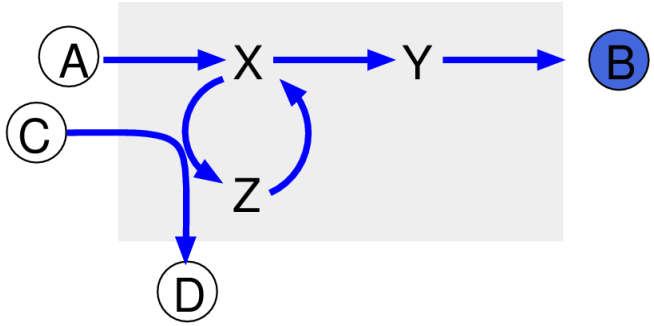


Economical flux distributions must be free of futile cycles

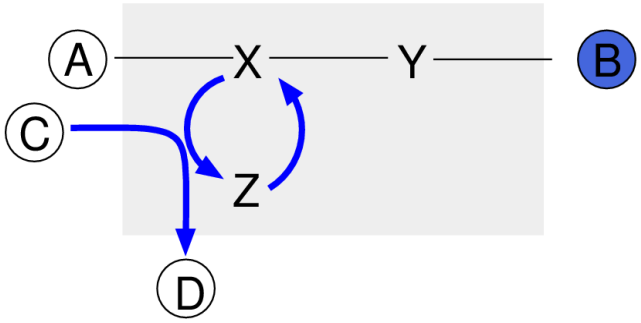
Beneficial, economical flux distribution



Beneficial, but uneconomical flux distribution



Futile test mode



Definition “Futile flux mode”
A set of active reactions in *v* that can support a stationary, futile flux with the same flux directions as in *v*

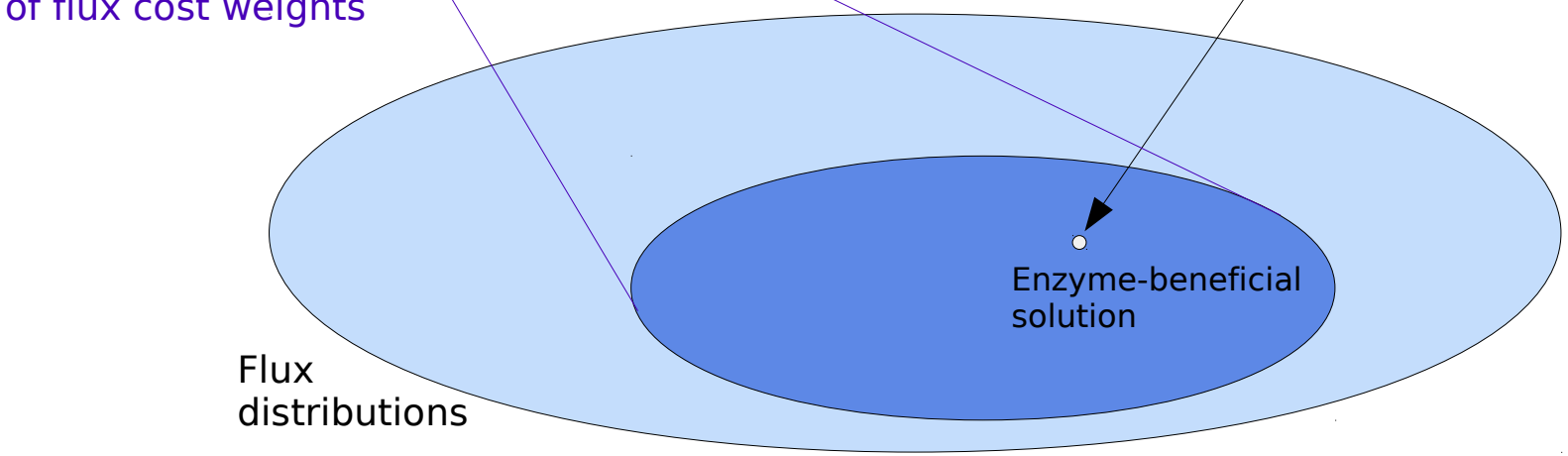
FBA with flux minimisation covers all enzyme-optimal flux distributions

FBA model (weighted flux minimisation)

1. Fixed linear benefit b(v)
2. Minimise flux cost $\sum_l a_l |v_l|$

Kinetic model (optimal enzyme levels)

Kinetic model with beneficial enzyme levels (benefit = cost)



FBA with minimal fluxes and enzyme-optimal kinetic models

FBA model (weighted flux minimisation)

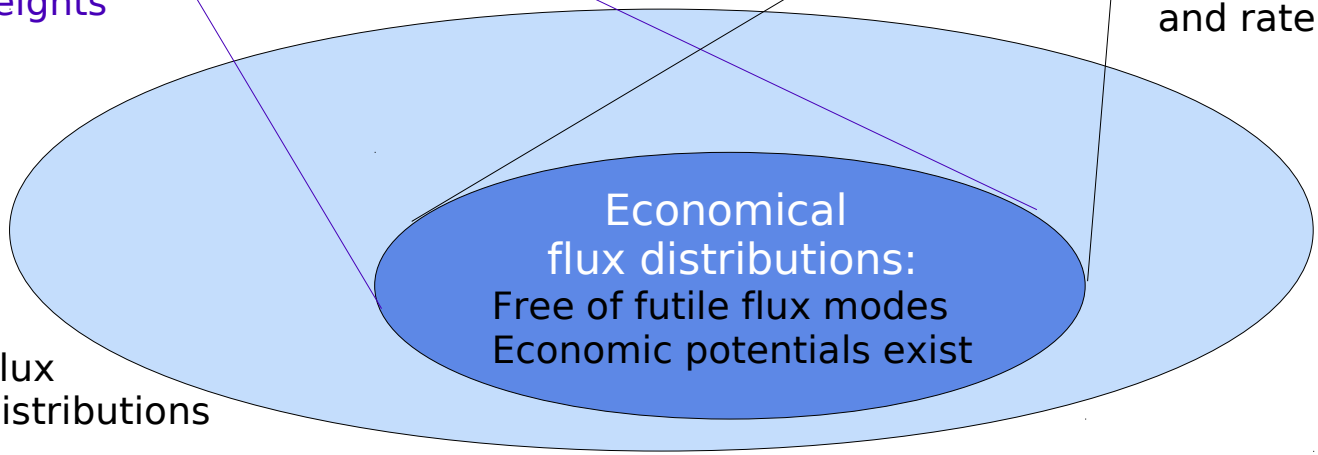
1. Fixed linear benefit b(v)
2. Minimise flux cost $\sum_l a_l |v_l|$

Kinetic model (optimal enzyme levels)

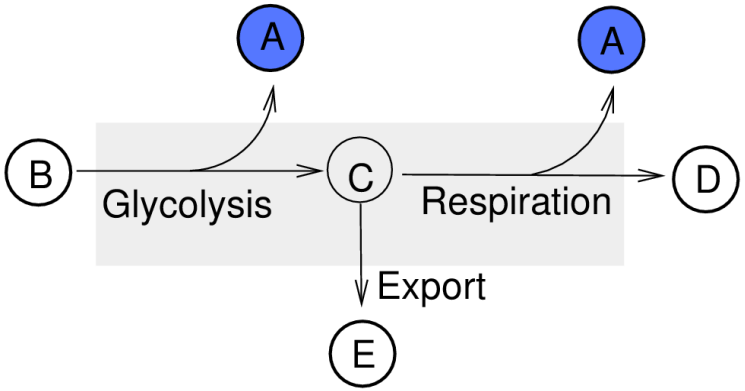
Kinetic model with beneficial enzyme levels (benefit = cost)

All possible choices of flux cost weights

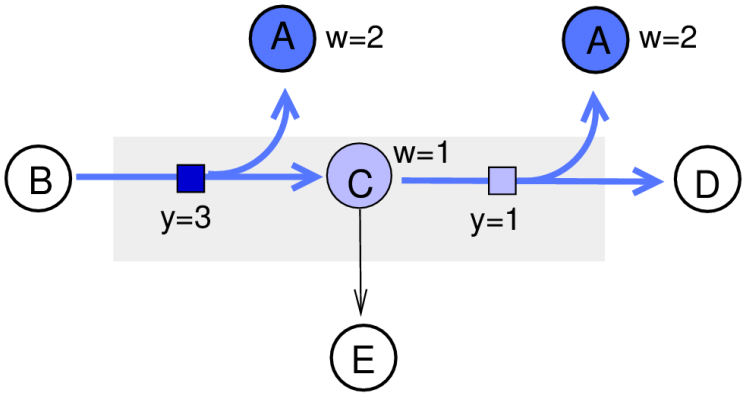
All possible choices of enzyme cost weights and rate laws



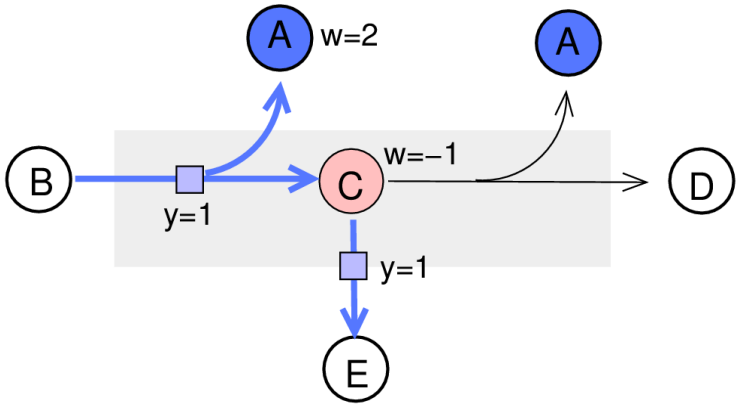
Stefan's minimal model of fermentation and respiration



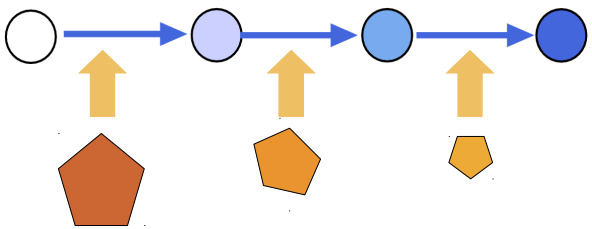
Respiration (high yield)

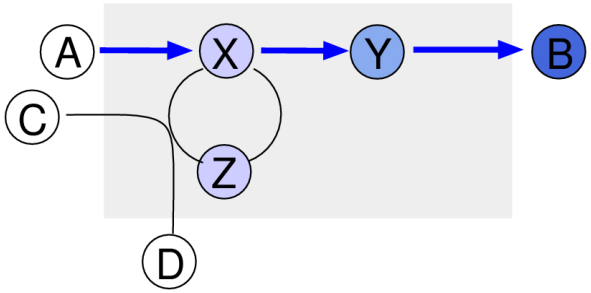


Fermentation (low yield)



Economic variables show enzyme-optimal states from a new angle





- Notions of economic value and cost for metabolic systems
- Local balance relations
- Futile flux modes
- Economic relationships between flux analysis and kinetic models
- Analogies between enzyme economy and thermodynamics

“Enzyme economy in metabolic networks” arXiv:1404.5252

“How enzyme economy shapes metabolic fluxes” arXiv:1404.5072

Acknowledgements

Charité – Universitätsmedizin Berlin
Hermann-Georg Holzhütter
Bernd Binder
Andreas Hoppe

Weizmann Institute of Science
Ron Milo
Elad Noor
Avi Flamholz

Technion – Israel Institute of Technology
Tomer Shlomi
Naama Tepper

DFG Deutsche Forschungsgemeinschaft

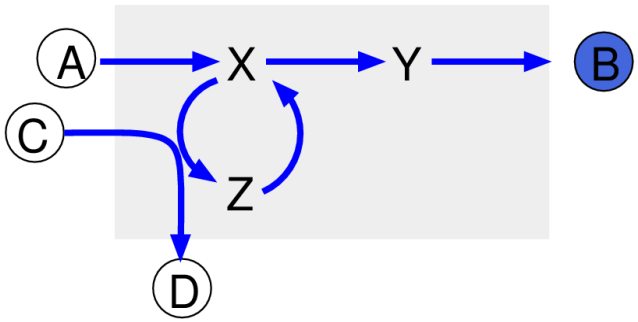
Gain conditions and economical flux distributions

Gain conditions
(from cost-benefit balance $\frac{\partial g}{\partial u_l} = \frac{\partial h}{\partial u_l} > 0$)

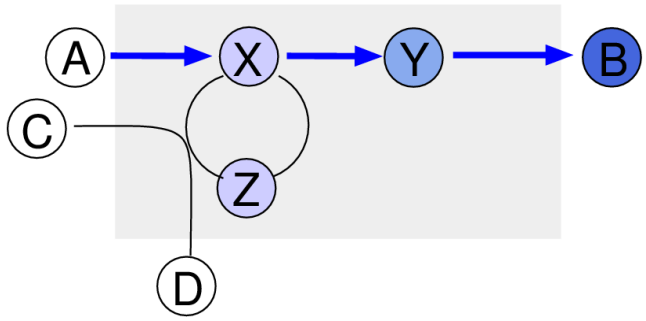
Flux gain condition $\mathbf{K}^{\mathbf{T}} \mathrm{diag}(\mathbf{y})\, \mathbf{v}^{-1} = \mathbf{K}^{\mathbf{T}} \mathbf{z}^{\mathrm{v}}$

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

Flux gain	$z_l^{\mathrm{v}} = \partial z / \partial v_l$
Concentration gain	$z_l^{\mathrm{v}} = \partial z / \partial c_i$
Enzyme cost	$y_l = \partial h / \partial \ln u_l$
Kernel matrix	$\mathbf{K}$
Link matrix	$\mathbf{L}$
Elasticity matrix	$\bar{\mathbf{E}}$



Beneficial flux distribution v
Positive flux benefit $b = \mathbf{z}^{\mathrm{v}} \cdot \mathbf{v} > 0$



Economical flux distribution v:
Flux gain condition can be satisfied with positive costs v

Enzyme-beneficial kinetic models can be constructed from given flux distributions

FBA model

↓ Flux minimization or removal of futile modes

Economical flux distribution

↓ Choose economic variables

Enzyme costs and economic potentials

↓ Choose elasticities / rate laws

Kinetic model in enzyme-beneficial state

Sampled economic potentials in yeast central metabolism