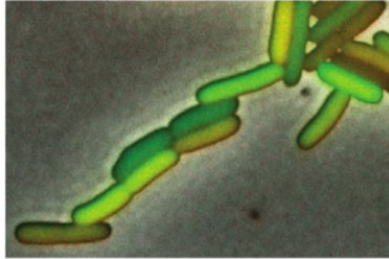
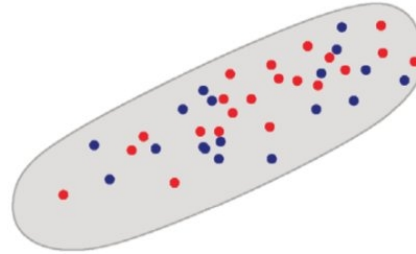


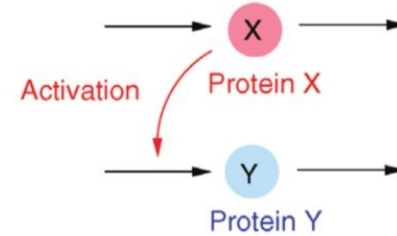
(a) Biological system



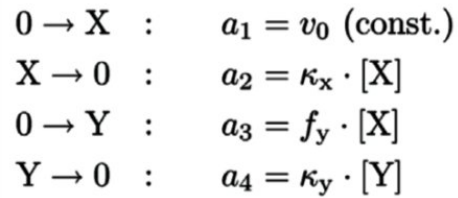
(b) Mental model



(c) Model scheme



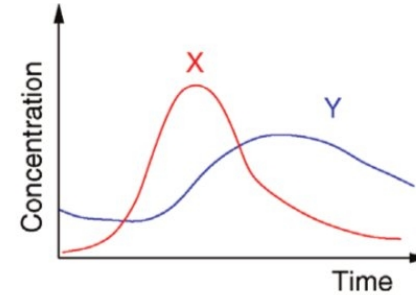
(d) Process model

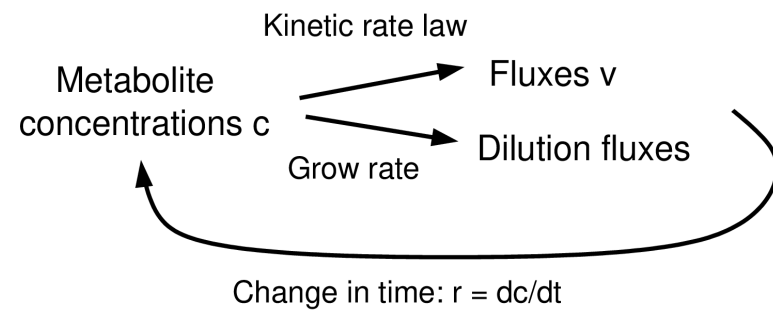
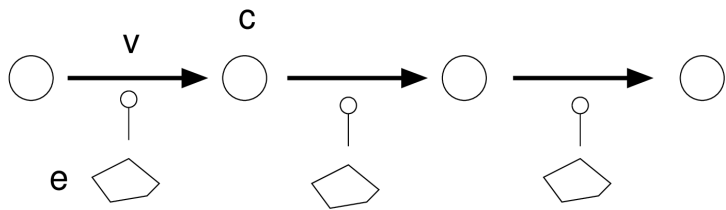


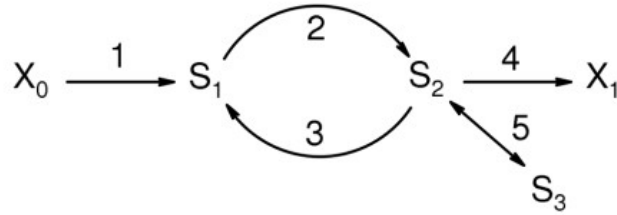
(e) Dynamical model

$$\begin{aligned} dx/dt &= v_0 - \kappa_x x \\ dy/dt &= f_y x - \kappa_y y \\ x(0) &= x_0 \\ y(0) &= y_0 \end{aligned}$$

(f) Quantitative results







Graph

$$\begin{aligned} \frac{dS_1}{dt} &= v_1 - v_2 + v_3 \\ \frac{dS_2}{dt} &= v_2 - v_3 - v_4 - v_5 \\ \frac{dS_3}{dt} &= v_5 \end{aligned}$$

Kinetic model (ODE)

metabolites

reactions

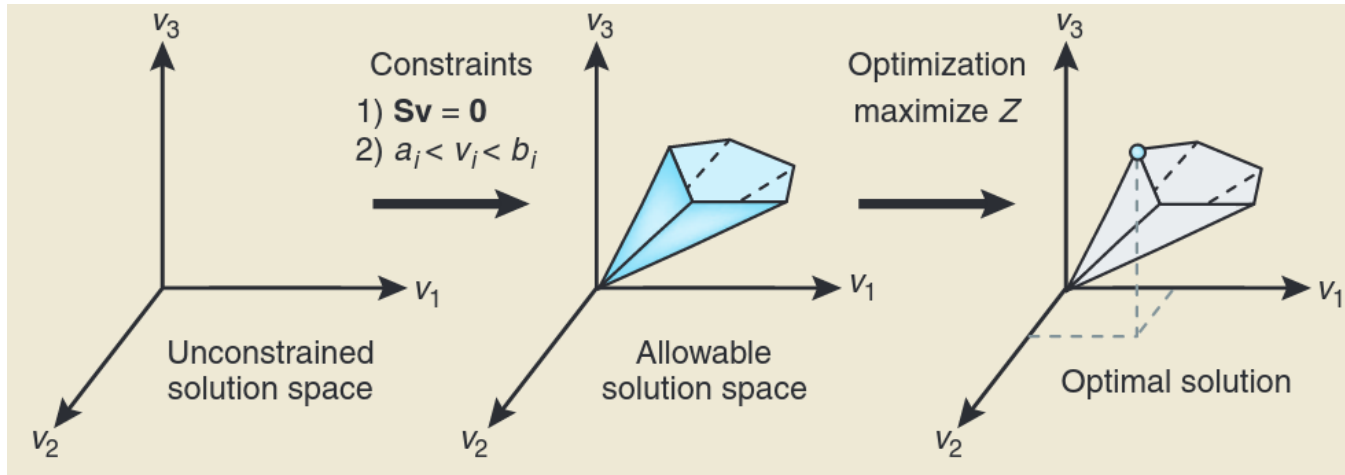
$$\begin{matrix} S_1 \\ S_2 \\ S_3 \end{matrix} \begin{bmatrix} 1 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

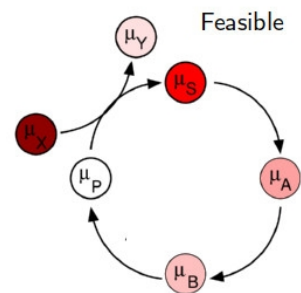
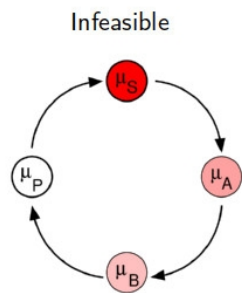
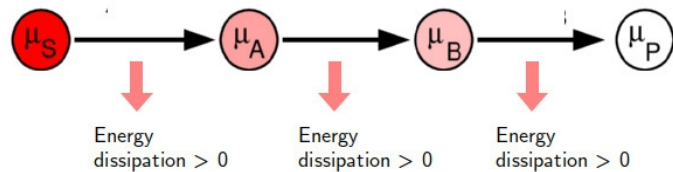
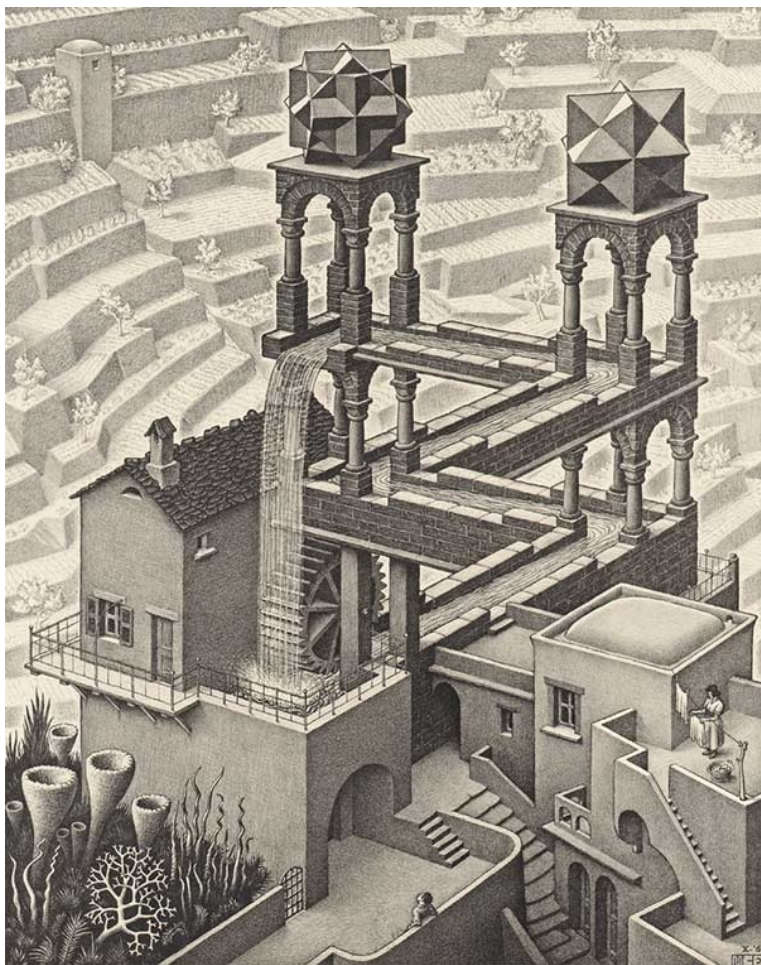
Stoichiometric matrix

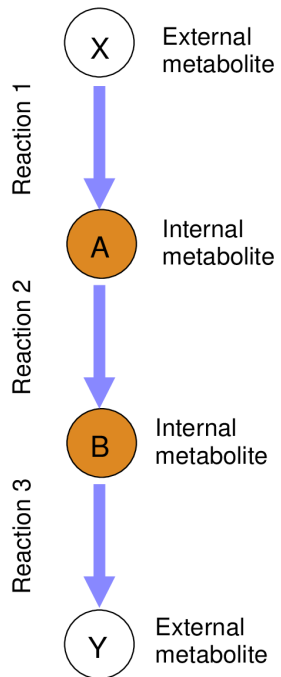
$$\begin{bmatrix} \frac{dS_1}{dt} \\ \frac{dS_2}{dt} \\ \frac{dS_3}{dt} \end{bmatrix} = \begin{bmatrix} 1 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix} \cdot \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix}$$

$$\dot{S} = N \cdot v$$

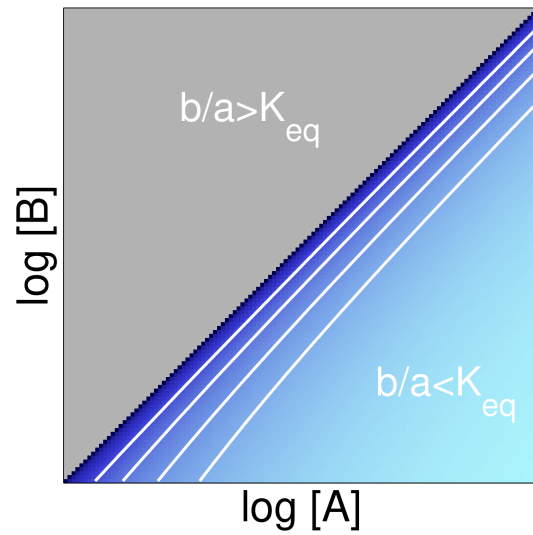
System of differential equations



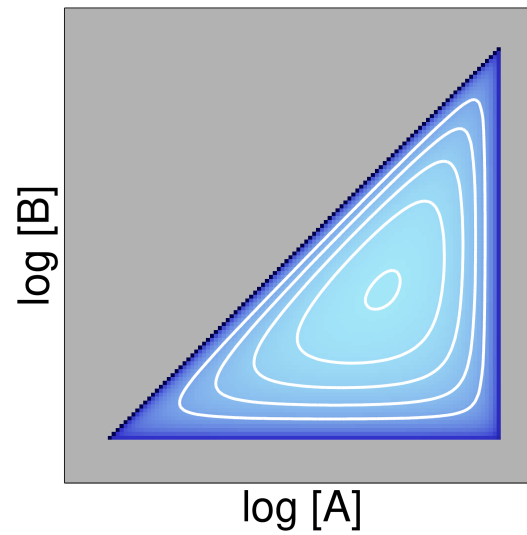


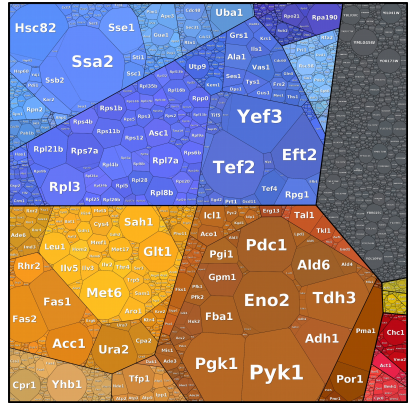
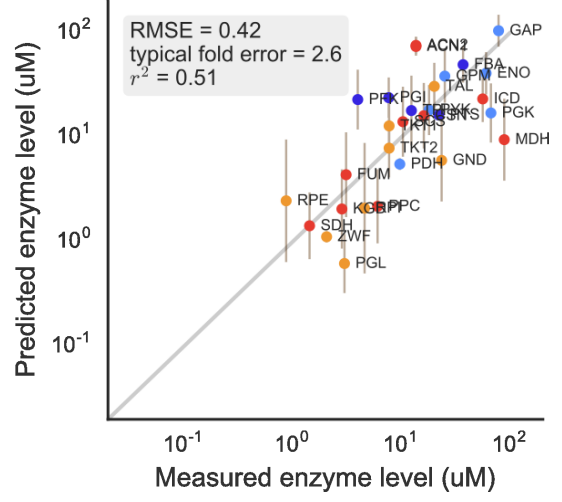
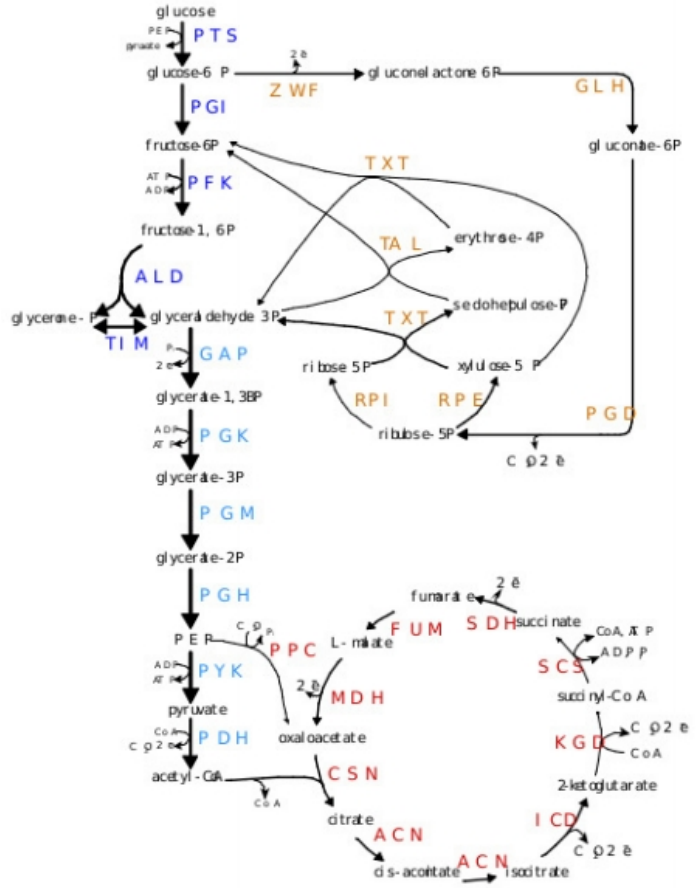


Enzyme demand in reaction 2

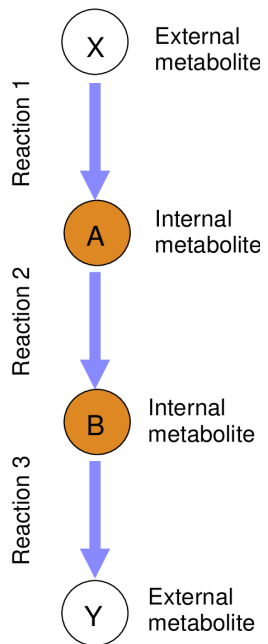


Total enzyme demand

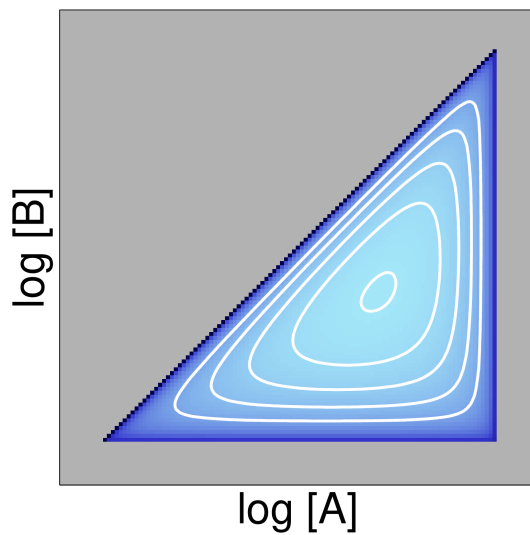




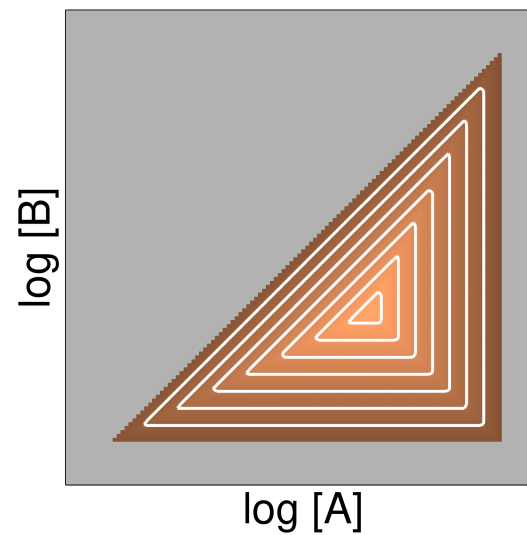


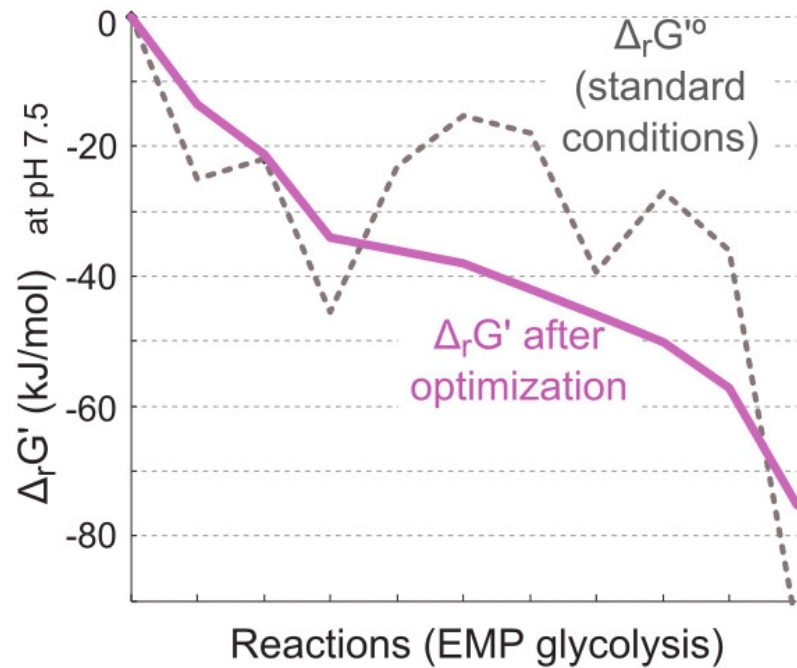
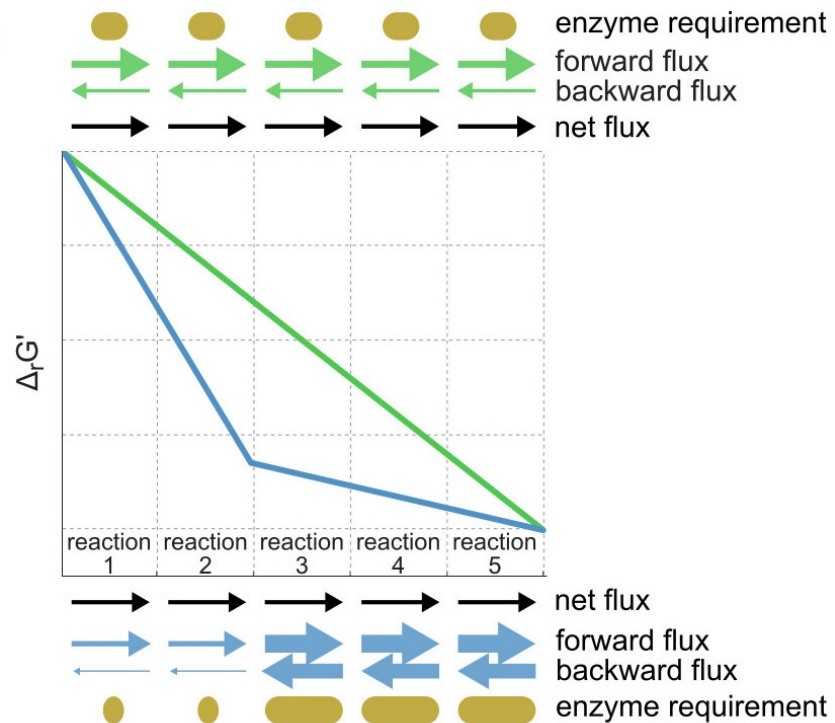


Total enzyme demand

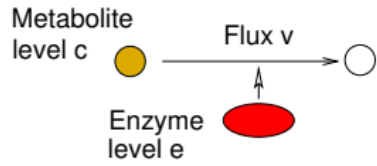


Lowest driving force

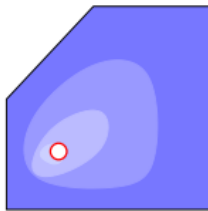




Kinetic model



Metabolite space



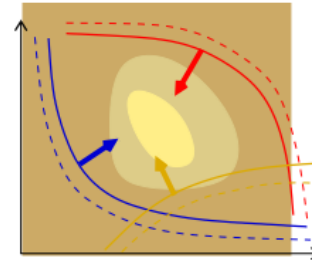
Metabolite levels



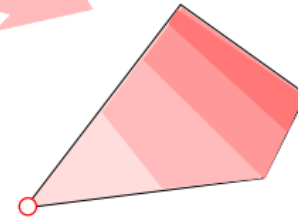
Enzyme levels



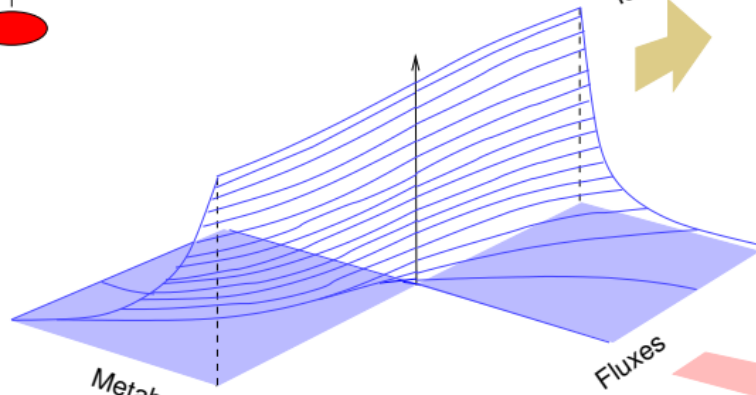
Enzyme space



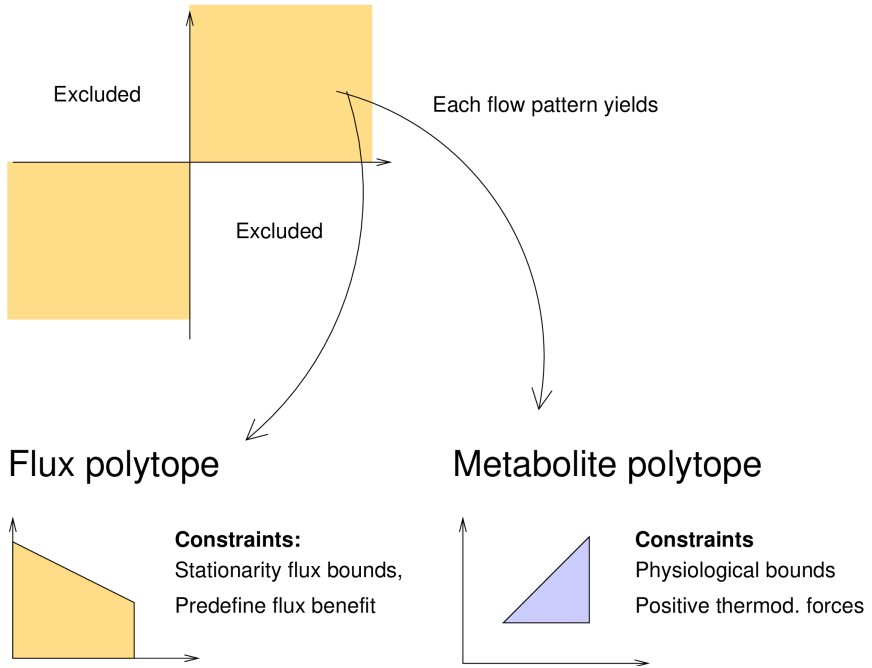
Flux space



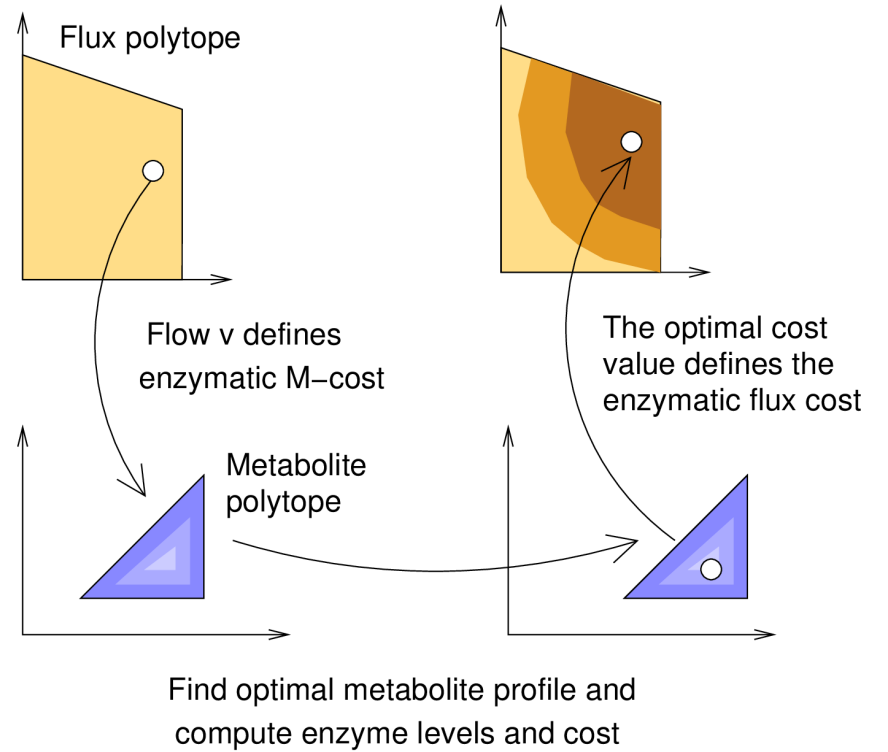
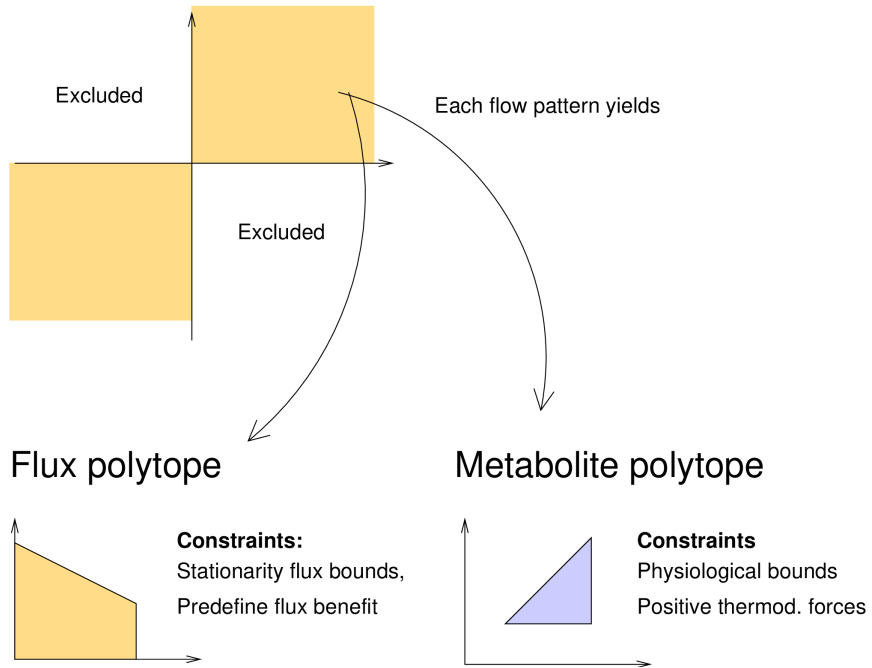
Fluxes



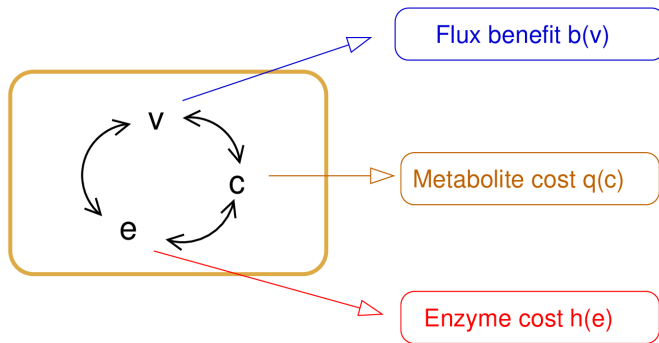
Feasible flow patterns (orthants in flux space)



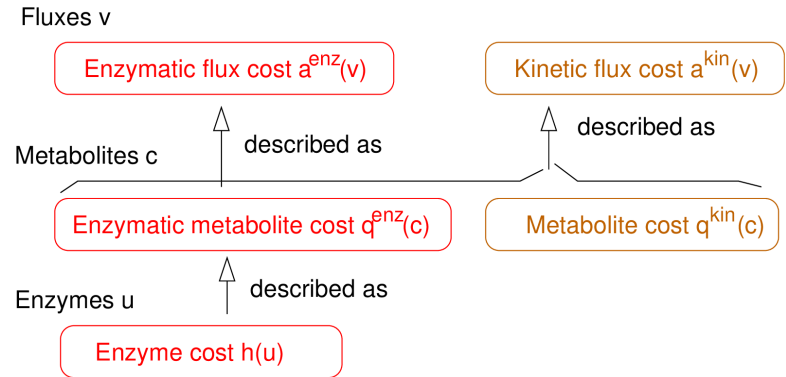
Feasible flow patterns (orthants in flux space)



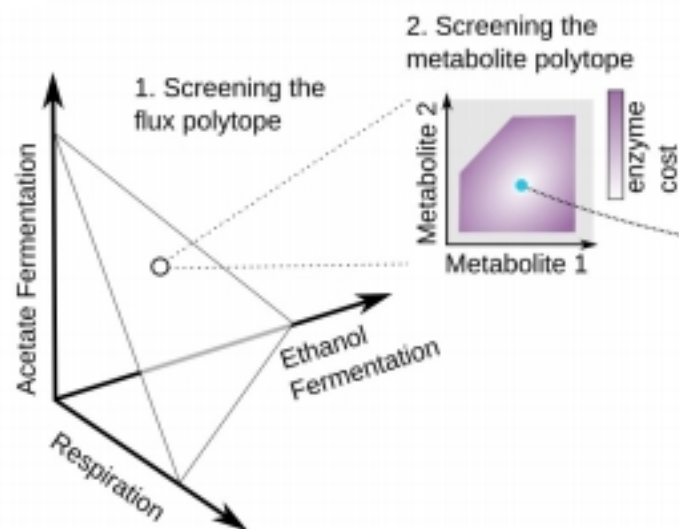
(a) Cost and benefit terms in metabolism



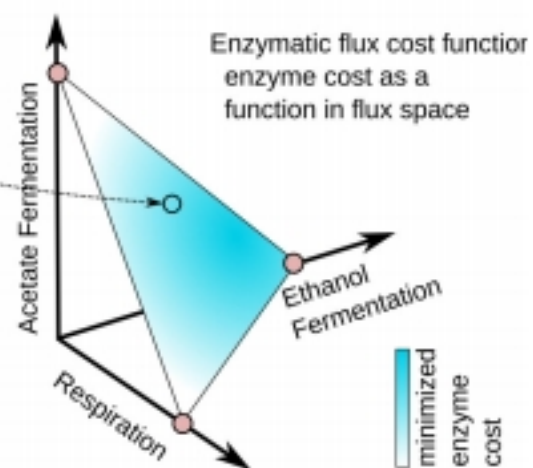
(b) Effective cost functions

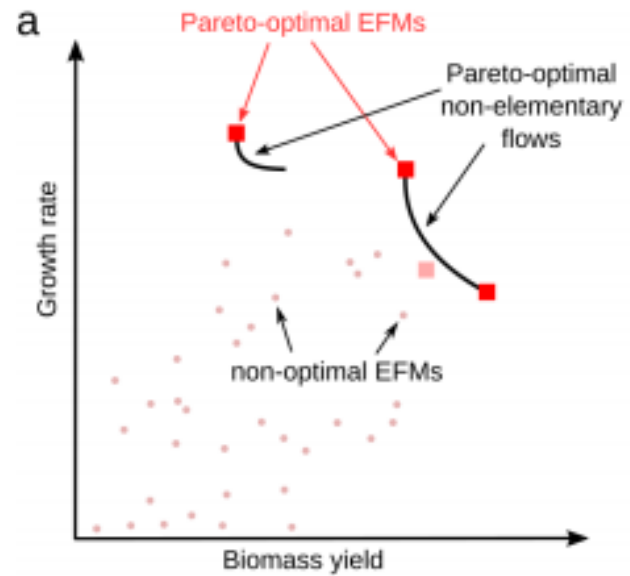
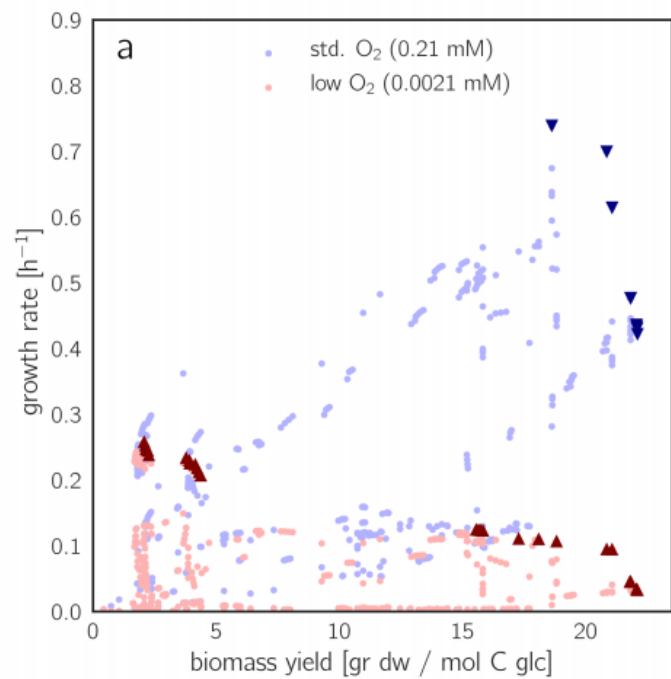


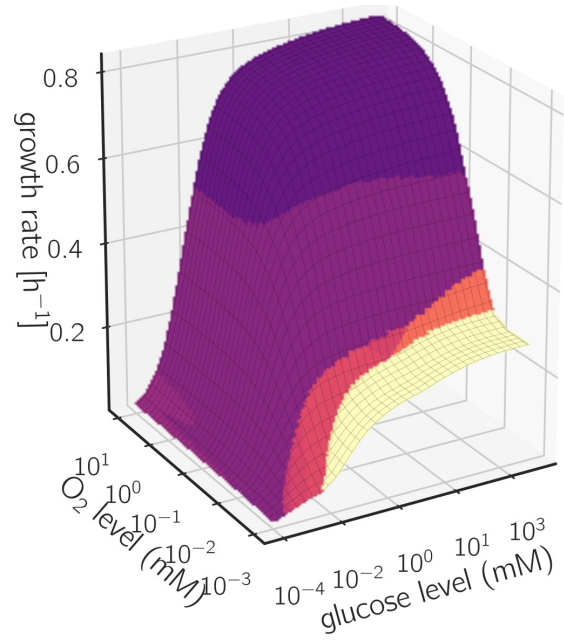
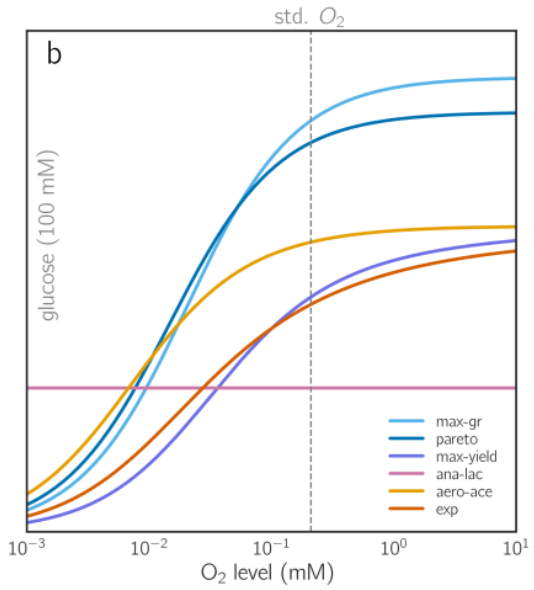
Flux profiles define enzyme cost functions

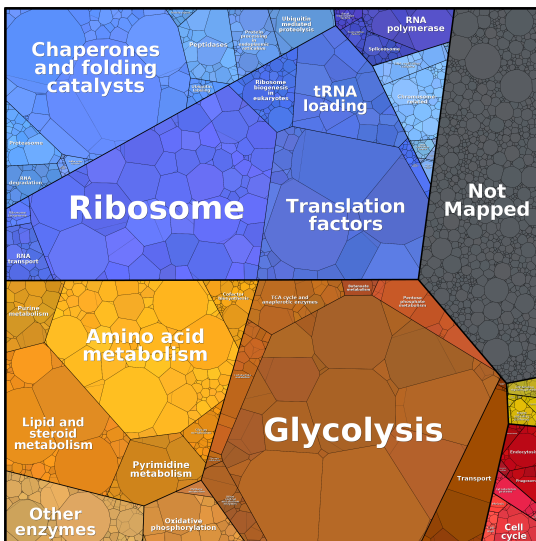


Enzyme cost function on flux polytope



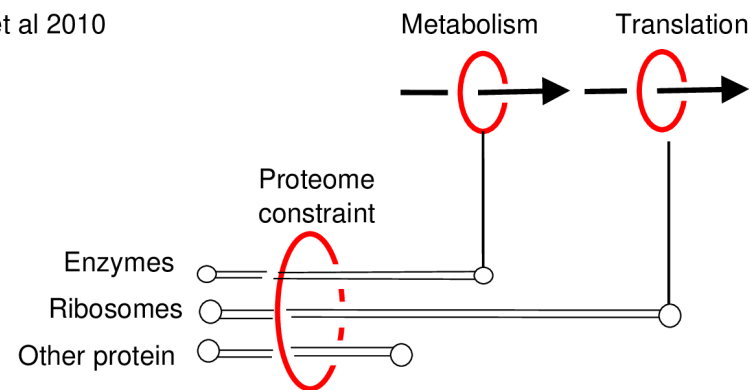
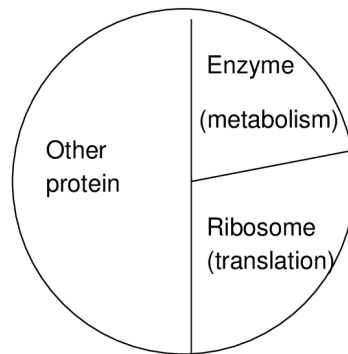


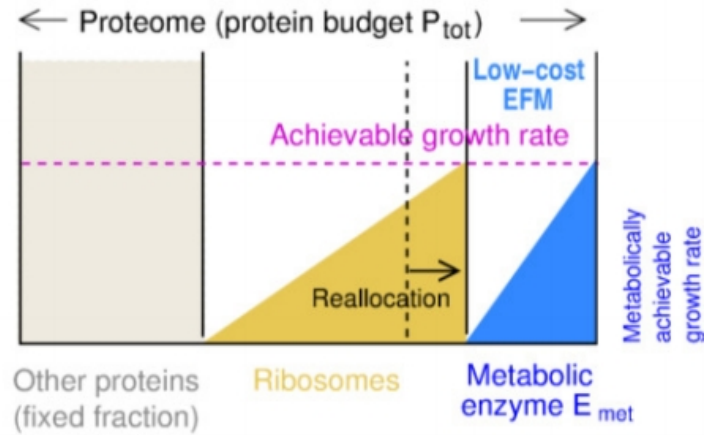
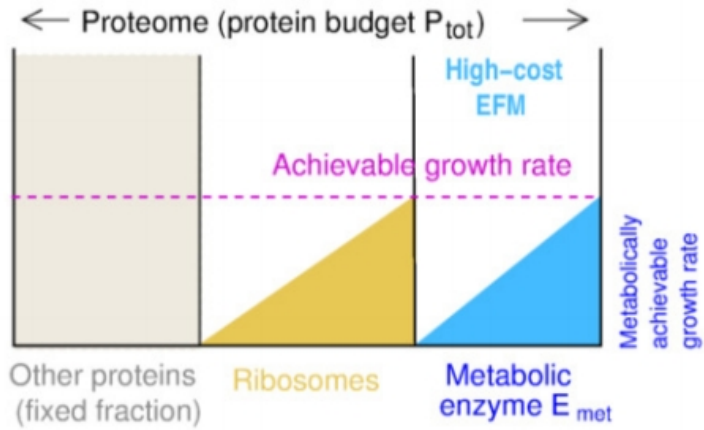




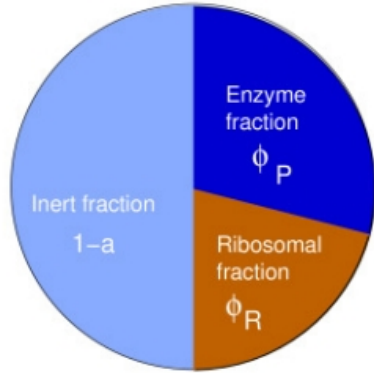
Proteome partitioning

Scott et al 2010





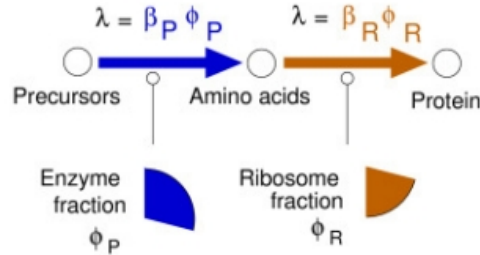
(a) Protein fractions in the sector model



Assumption 1: Enzymes and ribosomes occupy a fixed mass fraction of the proteome

$$a = \phi_P + \phi_R \quad (\text{a: Available proteome fraction})$$

(b) Schematic model of cell growth

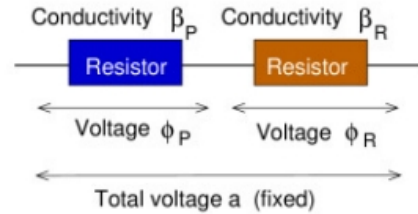


Assumption 2: The growth rate is proportional to each of the two proteome fractions

$$\lambda = \beta_P \phi_P = \beta_R \phi_R$$

β_P Nutrient capacity
 β_R Translation capacity

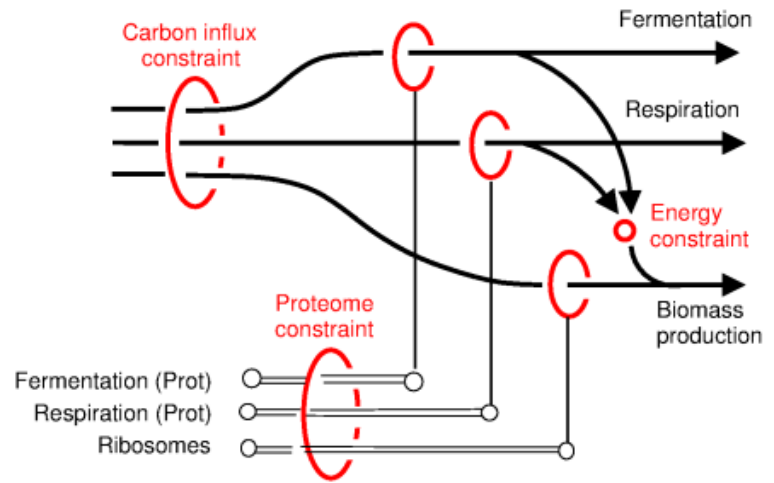
(c) Analogy to electric circuit

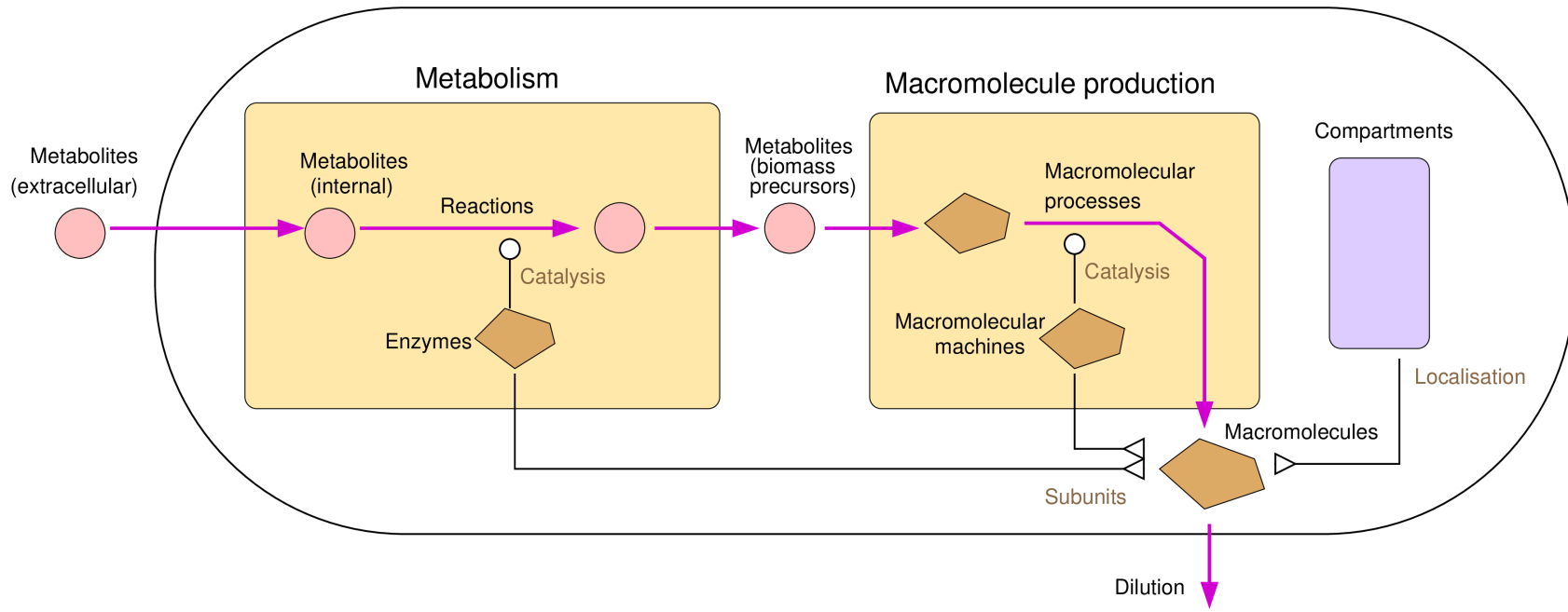


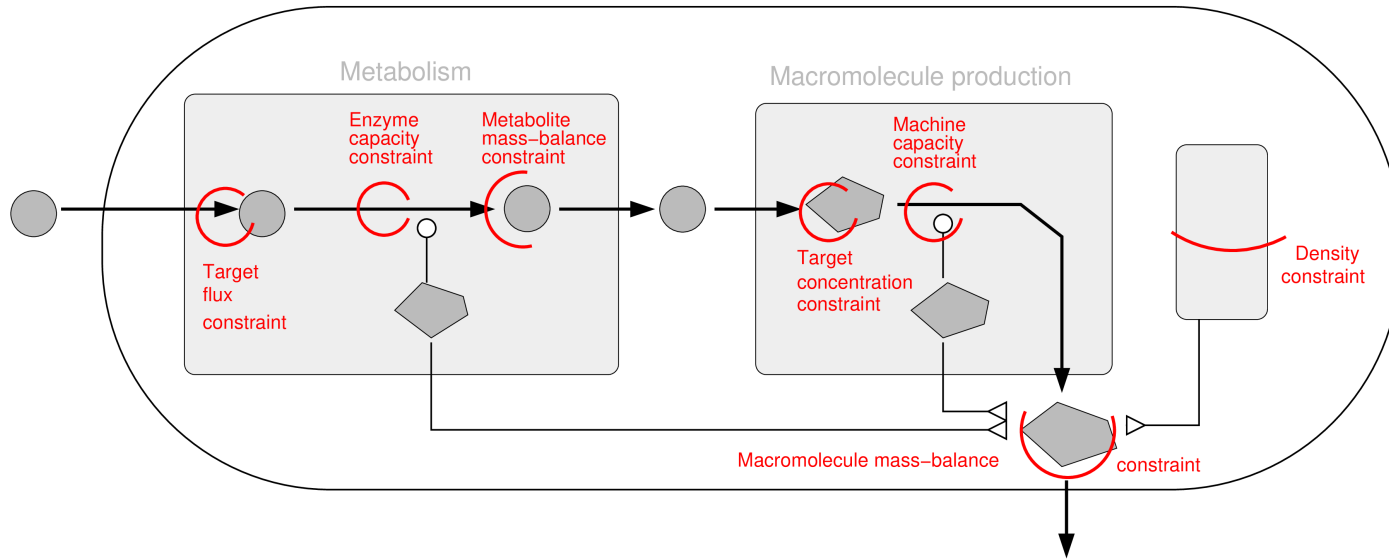
$$\phi_P = \frac{\beta_R}{\beta_P + \beta_R} a \quad \phi_R = \frac{\beta_P}{\beta_P + \beta_R} a$$

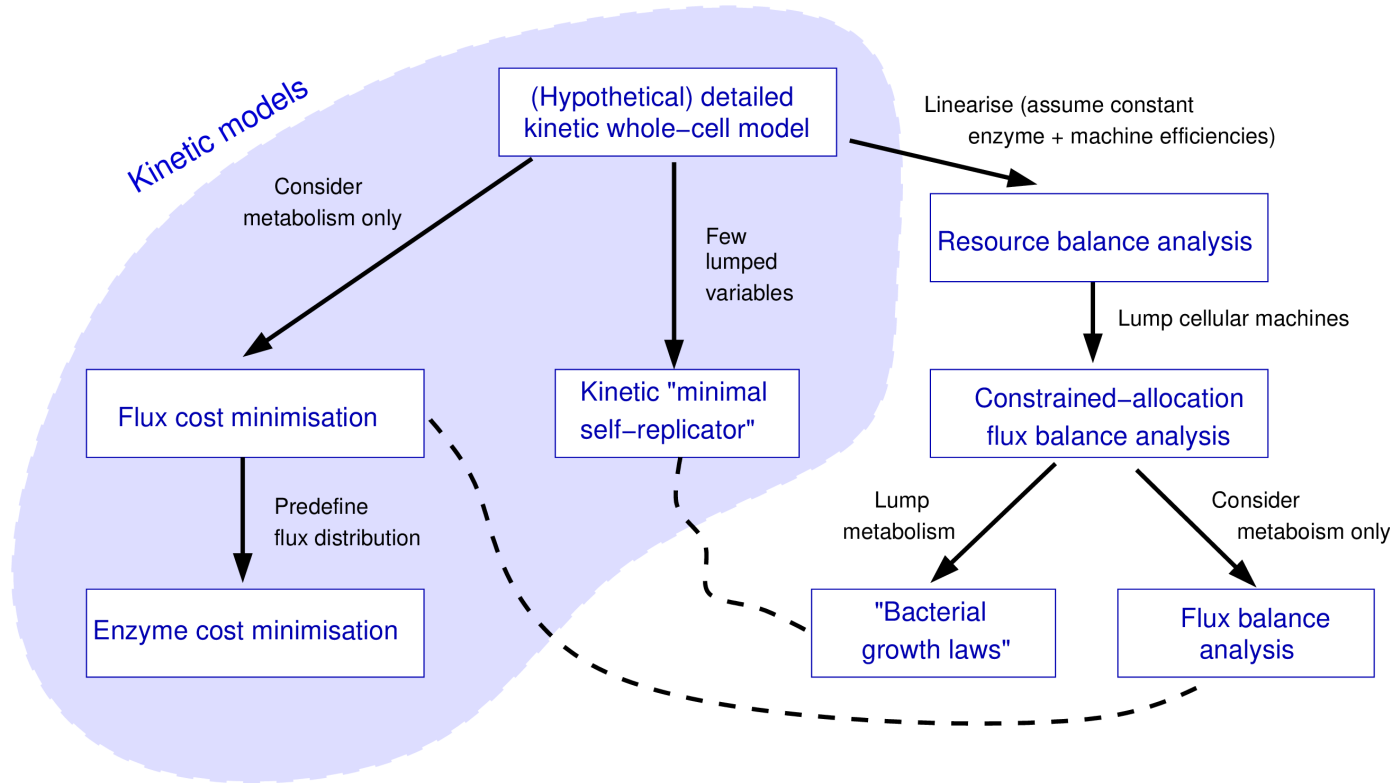
$$\lambda = \frac{\beta_P \beta_R}{\beta_P + \beta_R} a$$

Example: Acetate production in *E. coli*, Basan et al.

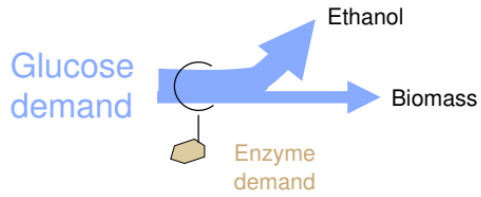








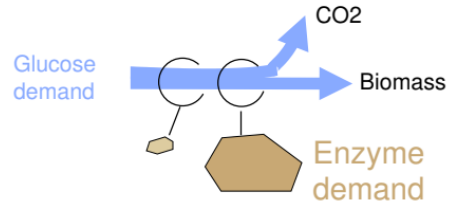
(a) Low-yield (fermentation) strategy



Substrate demand high → Low biomass yield

Enzyme demand low → High growth rate

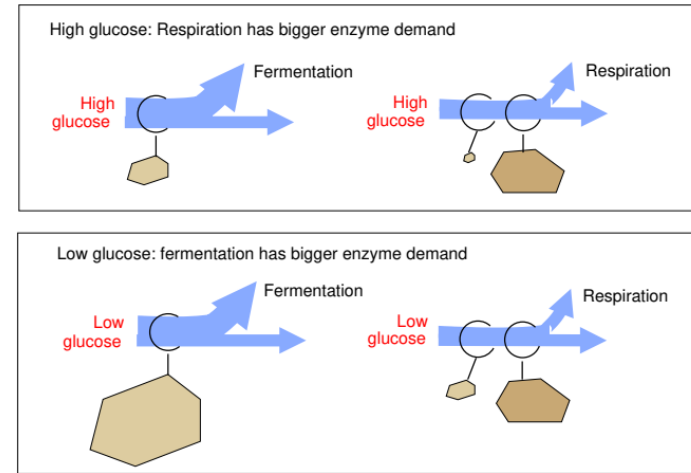
(b) High-yield (respiration) strategy

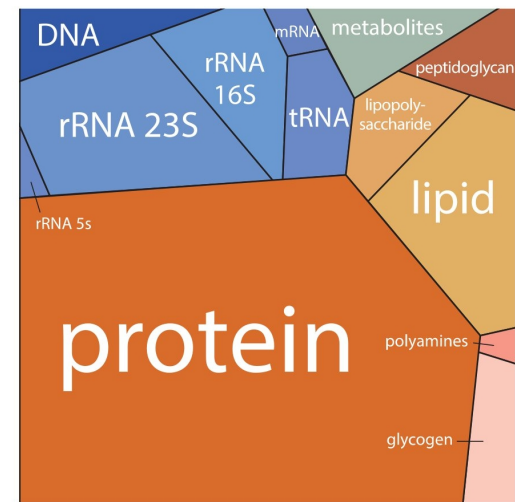
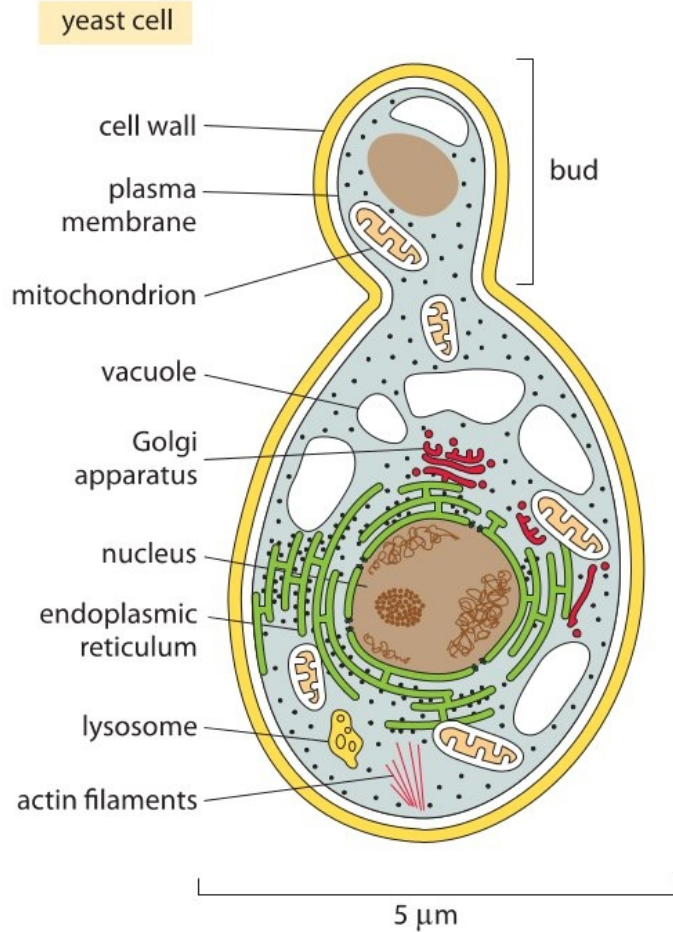
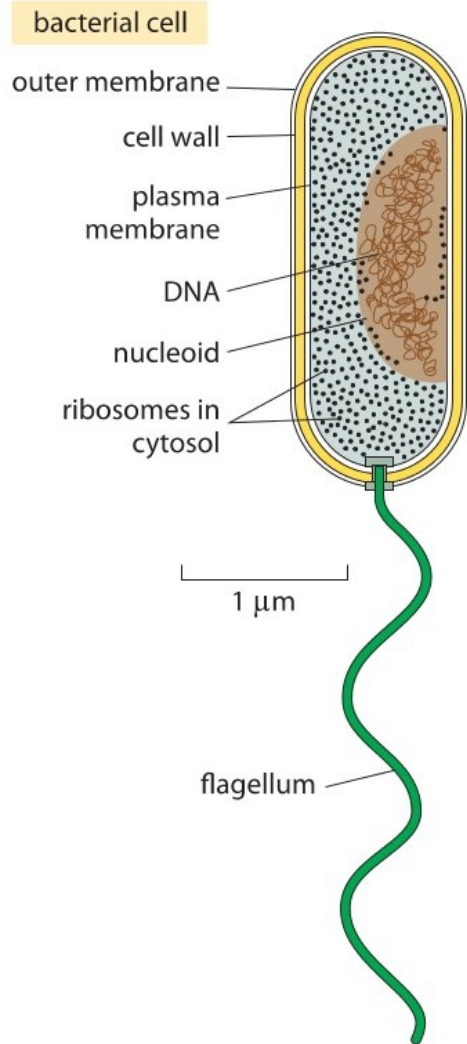


Substrate demand low → High biomass yield

Enzyme demand high → Low growth rate

(c) Enzyme costs at high and low glucose concentrations





property	<i>E. coli</i>	budding yeast	mammalian (HeLa line)
cell volume	0.3–3 μm^3	30–100 μm^3	1,000–10,000 μm^3
proteins per μm^3 cell volume	2–4 $\times 10^6$		
mRNA per cell	10^3 – 10^4	10^4 – 10^5	10^5 – 10^6
proteins per cell	$\sim 10^6$	$\sim 10^8$	$\sim 10^{10}$
mean diameter of protein	4–5 nm		
genome size	4.6 Mbp	12 Mbp	3.2 Gbp
number protein coding genes	4300	6600	21,000
regulator binding site length	10–20 bp		
promoter length	~ 100 bp	~ 1000 bp	$\sim 10^4$ – 10^5 bp
gene length	~ 1000 bp	~ 1000 bp	$\sim 10^4$ – 10^6 bp (with introns)
concentration of one protein per cell	~ 1 nM	~ 10 pM	~ 0.1 – 1 pM
diffusion time of protein across cell ($D \approx 10 \mu\text{m}^2/\text{s}$)	~ 0.01 s	~ 0.2 s	~ 1 – 10 s
diffusion time of small molecule across cell ($D \approx 100 \mu\text{m}^2/\text{s}$)	~ 0.001 s	~ 0.03 s	~ 0.1 – 1 s
time to transcribe a gene	<1 min (80 nts/s)	~ 1 min	~ 30 min (incl. mRNA processing)
time to translate a protein	<1 min (20 aa/s)	~ 1 min	~ 30 min (incl. mRNA export)
typical mRNA lifetime	2–5 min	~ 10 min to over 1 h	5–100 min to over 10 h
typical protein lifetime	1 h	0.3–3 h	10–100 h
minimal doubling time	20 min	1 h	20 h
ribosomes/cell	$\sim 10^4$	$\sim 10^5$	$\sim 10^6$
transitions between protein states (active/inactive)	1–100 μs		
timescale for equilibrium binding of small molecule to protein (diffusion limited)	1–1000 ms (1 μM –1 nM affinity)		
timescale of transcription factor binding to DNA site	~ 1 s		
mutation rate	10^{-8} – 10^{-10} /bp/replication		

macromolecule	percentage of total dry weight	weight per cell (fg)	characteristic molecular weight (Da)	number of molecules per cell
protein	55	165	3×10^4	3,000,000
RNA	20	60		
23 S rRNA		32	1×10^6	20,000
16 S rRNA		16	5×10^5	20,000
5 S rRNA		1	4×10^4	20,000
transfer		9	2×10^4	200,000
messenger		2	1×10^6	1,400
DNA	3	9	3×10^9	2
lipid	9	27	800	20,000,000
lipopolysaccharide	3	9	8000	1,000,000
peptidoglycan	3	9	(1000) _n	1
glycogen	3	9	1×10^6	4,000
metabolites and cofactors pool	3	9		
inorganic ions	1	3		
total dry weight	100	300		
water (70% of cell)		700		
total cell weight		1000		

composition rules of thumb

- carbon atoms $\sim 10^{10}$
- 1 molecule per cell gives ~ 1 nM conc.
- ATP required to build and maintain cell over a cell cycle $\sim 10^{10}$
- glucose molecules needed per cell cycle $\sim 3 \times 10^9$ (2/3 of carbons used for biomass and 1/3 used for ATP)