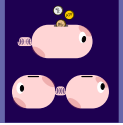

The enzyme cost of metabolic fluxes

Elad Noor & Wolfram Liebermeister

Outline

- Rate versus Yield
- Thermodynamic-focused pathway analysis
- Resource allocation and enzyme cost/demand
- Solutions to the allocation problem
- Example 1: glycolysis in *E. coli*
- Example 2: central metabolism in *E. coli*
- From enzyme allocation to growth rate
- Generalizing to whole networks

Why is there diversity in nature?

- Natural ecosystems $\Rightarrow$ diversity

Credit: Ostrich by Diego Delso, Colibri by The Lilac Breasted Roller

Why is there diversity in nature?

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- Darwin $\Rightarrow$ survival of the fittest

Credit: Official White House Photo by Amanda Lucidon

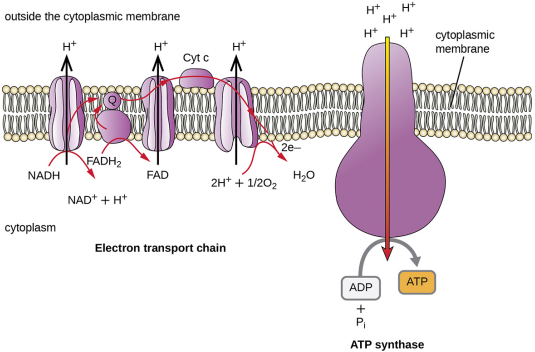
Why is there diversity in nature?

- Natural ecosystems $\Rightarrow$ diversity
- Darwin $\Rightarrow$ survival of the fittest
- Solving the paradox: **tradeoffs!**

Credit: Collage by Kiwi Rex

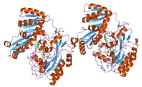
Respiration versus Fermentation

Respiration



Credit: OpenStax College, Microbiology

Fermentation



Lactate dehydrogenase

Credit: Jawahar Swaminathan and MSD staff at the European Bioinformatics Institute

The ATP yield of respiration is much higher than fermentation

Feature	**Respiration**	**Fermentation**
Energy Yield (ATP)	26-32	2
Oxygen required	Yes	No
Membranes required	Yes	No
Involves glycolysis	Yes	Yes
Other pathways	TCA cycle + ETC*	specific fermentation pathway
End products	$CO_2 + H_2O$	lactate / ethanol + CO_2

*Electron Transport Chain

Usually, evolution will maximize the rate, not yield

Glycolysis pathway:

$\mathrm{S} \rightleftharpoons \mathrm{X}_1 \rightleftharpoons \ldots \rightleftharpoons \mathrm{P} \qquad (\Delta G_{\mathsf{driv}} < 0)$

coupled to:

$d\ \mathrm{ADP} \rightleftharpoons d\ \mathrm{ATP} \qquad (\Delta G_{\mathsf{ATP}} > 0)$

What should d be?

*Werner et al. [5]

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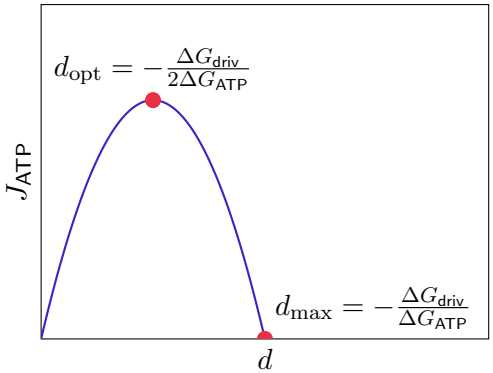
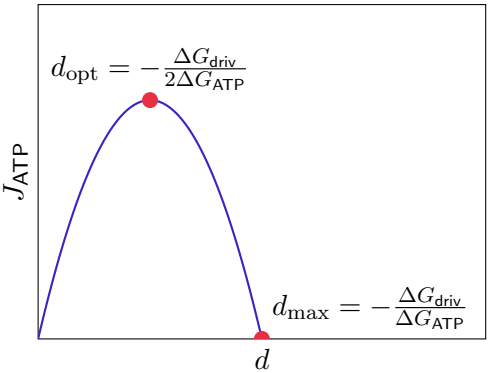


*Werner et al. [5]

Usually, evolution will maximize the rate, not yield

- fermentation (glucose to lactate):
  $d_{\text{opt}} \approx 2$, $d_{\text{max}} = 4$, $d_{\text{human}} = 2$
- fermentation (glucose to ethanol):
  $d_{\text{opt}} \approx 3$, $d_{\text{max}} = 5$, $d_{\text{yeast}} = 2$
- respiration (glucose to CO_2):
  $d_{\text{opt}} \approx 28$, $d_{\text{max}} = 55$, $d_{\text{ecoli}} = 26$

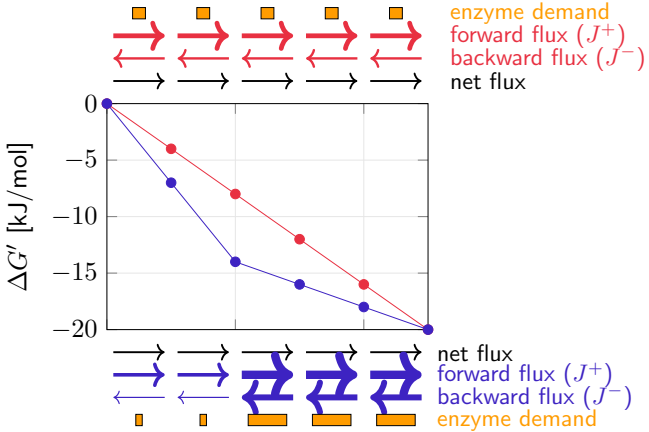


*Werner et al. [5]

Is only considering the *overall* thermodynamic force good enough?

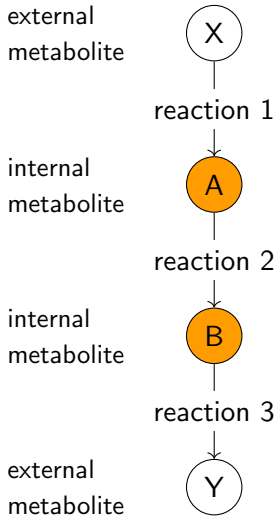
Thermodynamic force affects enzyme efficiency

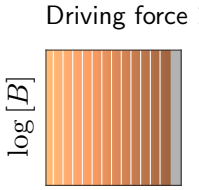
Based on the flux-force relationship*: $\frac{J^+}{J^-} = e^{-\Delta G'/RT}$

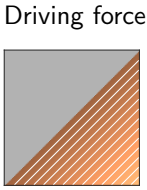


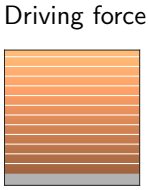
*Noor et al. [3]

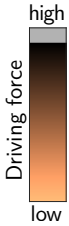
Example with 3-step pathway: Max-min Driving Force

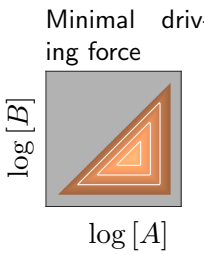












Mechanistic models

Stoichiometric models usually ignore thermodynamics,
while Max-min Driving Force is heuristic.

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while Max-min Driving Force is heuristic.

Is there a mechanistic model that can capture the rate/yield trade-off?

Metabolic pathway efficiency

Genome-scale models typically require linearity, and metabolite concentrations are ignored. Instead one assumes that internal fluxes are*:

1. unbounded

*Noor and Liebermeister [2]

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In reality k_{app} is a function of the metabolic state: $v = e \cdot f(\mathbf{c}; \mathbf{k})$:

- $\mathbf{k}$ – kinetics constants (turnover number, affinity, etc.)
- $\mathbf{c}$ – concentrations of all substrates and products
- $f(\cdot)$ depends also on other factors (e.g. pH, temperature, crowding), but we assume the changes are small

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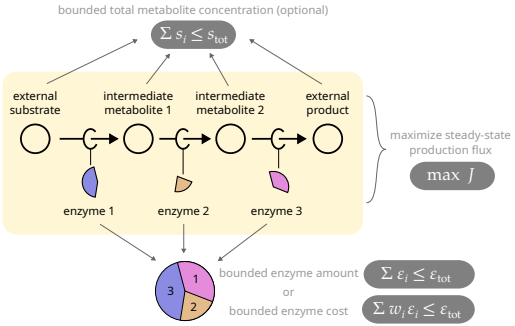
Metabolic pathway efficiency



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Reversible enzyme kinetics based on Haldane

For a reversible enzyme catalyzed reaction*: $S \overset{\mathrm{E}}{\rightleftharpoons} P$

$$v = e \cdot \underbrace{\frac{{k_{\mathrm{cat}}}^{+}\ s/K_{\mathrm{S}} - {k_{\mathrm{cat}}}^{-}\ p/K_{\mathrm{P}}}{1 + s/K_{\mathrm{S}} + p/K_{\mathrm{P}}}}_{k_{\mathrm{app}}}$$

*where s, p, and e are the concentrations of S, P, and E

†where $\Delta_r G' \equiv \Delta_r G'^{\circ} + R\,T\ln(p/s)$ and $\Delta_r G'^{\circ} = -R\,T\ln(K^{\mathrm{eq}})$

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Haldane further showed that the equilibrium constant satisfies the following relationship:

$$K^{\mathrm{eq}} = \frac{{k_{\mathrm{cat}}}^{+}}{{k_{\mathrm{cat}}}^{-}} \frac{K_{\mathrm{P}}}{K_{\mathrm{S}}}$$

*where s, p, and e are the concentrations of S, P, and E

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The Haldane rate law can be rewritten (Noor and Liebermeister [2]) as[†]:

$$v = \underbrace{e \cdot {k_{\text{cat}}}^{+}}_{V_{\max}} \cdot \underbrace{\left(1 - e^{\frac{\Delta_r G'}{RT}}\right)}_{\eta^{\text{for}}} \cdot \underbrace{\frac{\frac{s}{K_{\text{S}}}}{1 + \frac{p}{K_{\text{P}}} + \frac{s}{K_{\text{S}}}}}_{\eta^{\text{sat}}}$$

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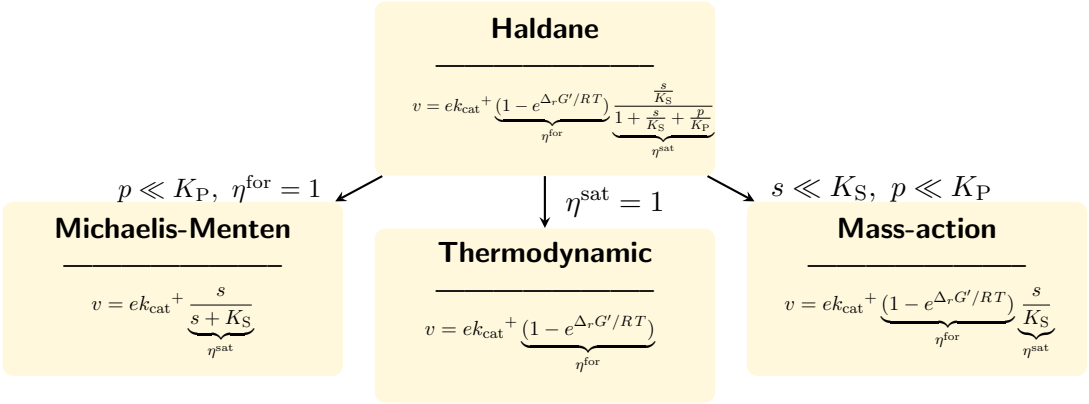
The factorized Haldane rate law and some simplification



Noor and Liebermeister [2]

Unbranched pathway with "thermodynamic" kinetics

$$\mathsf{S}_0 \overset{\mathrm{v}_1}{\rightleftharpoons} \mathsf{S}_1 \overset{\mathrm{v}_2}{\rightleftharpoons} \ldots \overset{\mathrm{v}_n}{\rightleftharpoons} \mathsf{S}_n$$

$$J = e_i \; k_{\mathsf{cat,i}} \left(1 - e^{\Delta_r G'_i / RT}\right)$$

(equivalent to assuming $\eta^{\mathrm{sat}} = 1$)

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$$J = e_i \; k_{\mathsf{cat,i}} \left(1 - e^{\Delta_r G'_i / RT}\right)$$

Optimized flux (approximated) solution*

$$J^* \approx e_{\mathrm{tot}} \cdot \bar{k}_{\mathsf{cat}} \left(1 - e^{\alpha \Delta G'_{\mathsf{tot}} / RT}\right)$$

where: $\bar{k}_{\mathsf{cat}} \equiv \underbrace{\left(\sum_j \frac{1}{k_{\mathsf{cat,j}}}\right)^{-1}}_{\text{pathway specific activity}}$, $\alpha \equiv \left(\sum_j \frac{1}{k_{\mathsf{cat,j}}}\right) \cdot \left(\sum_j \frac{1}{\sqrt{k_{\mathsf{cat,j}}}}\right)^{-2}$, $\Delta G'_{\mathsf{tot}} = \left(\sum_j \Delta_r G'_j\right)$

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$$J^* \approx e_{\text{tot}} \cdot \bar{k}_{\text{cat}} \left(1 - e^{\alpha \Delta G'_{\text{tot}} / RT}\right) \qquad \text{Compare to: } J_{\text{path}} = -L \cdot \Delta G'_{\text{tot}}$$

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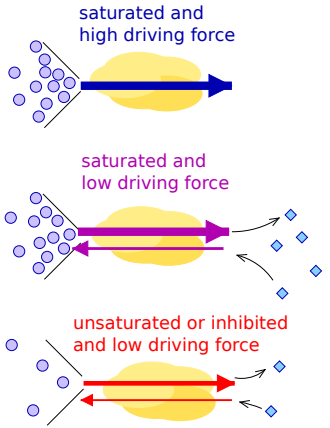
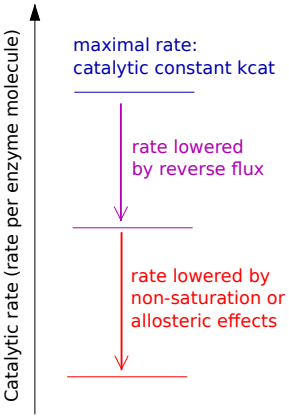
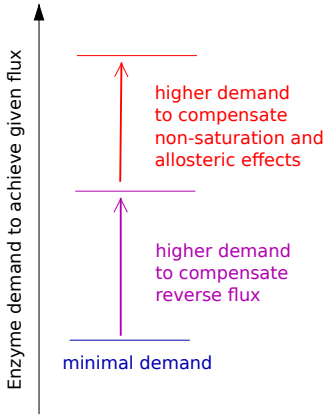
*Noor and Liebermeister [2]

Enzyme efficiency is also affected by saturation







Minimal demand can be expressed as the inverse of the rate law

Reversible Haldane rate law decomposition:

$$v = e \cdot k_{\text{cat}}^{+} \cdot \underbrace{\left(1 - e^{\Delta G'/RT}\right)}_{\eta^{\text{for}}} \cdot \underbrace{\frac{s/K_S}{1 + p/K_P + s/K_S}}_{\eta^{\text{sat}}}$$

And the demand q is defined as the minimum required e for achieving a certain rate v:

$$e = v \cdot \frac{1}{k_{\text{cat}}^{+}} \cdot \underbrace{\frac{1}{1 - e^{\Delta G'/RT}}}_{1/\eta^{\text{for}}} \cdot \underbrace{\frac{1 + p/K_P + s/K_S}{s/K_S}}_{1/\eta^{\text{sat}}}$$

The minimal enzyme cost of a pathway

Given a pathway:

$$\mathrm{S} \rightleftharpoons \mathrm{X}_1 \rightleftharpoons \ldots \rightleftharpoons \mathrm{P}$$

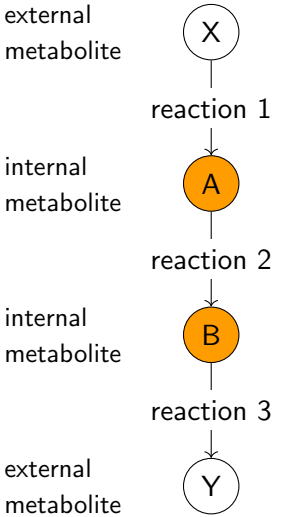
The enzyme cost is defined as:

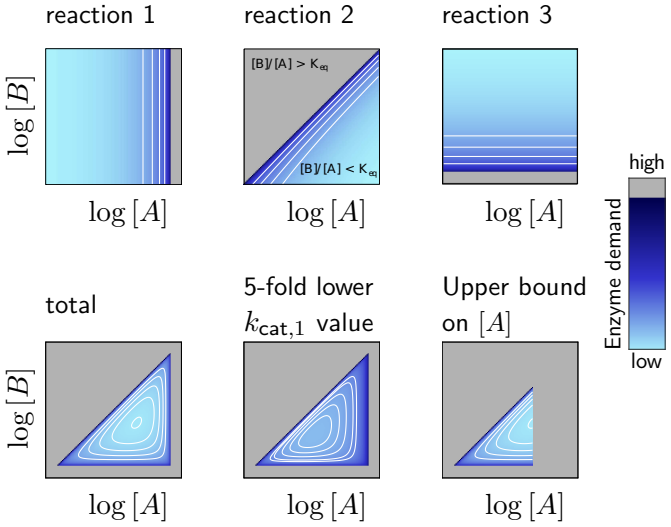
$$e_{\mathsf{tot}} = \sum_i e_i$$

$$e_i = v_i \cdot \frac{1}{k^+_{\mathsf{cat,i}}} \cdot \frac{1}{\eta_i^{\mathsf{for}}(\mathbf{c})} \cdot \frac{1}{\eta_i^{\mathsf{sat}}(\mathbf{c})}$$

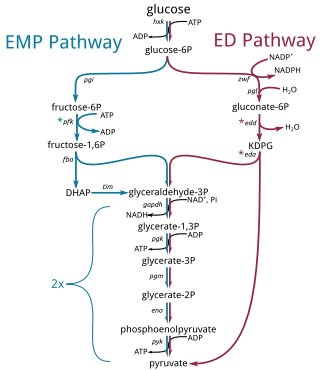
where minimizing e_{tot} over all possible metabolite concentrations $(\mathbf{c})$ gives us the ECM score. This is a convex optimization problem.

Example with 3-step pathway: Enzyme Cost Minimization





How do bacteria choose between two glycolyses?



EMP: Embden-Meyerhof-Parnas, ED: Entner-Doudoroff*

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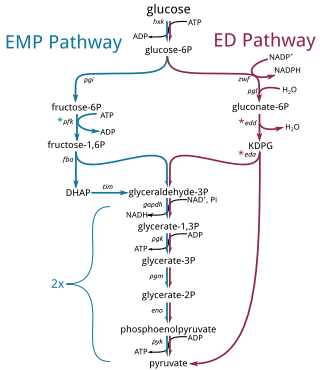

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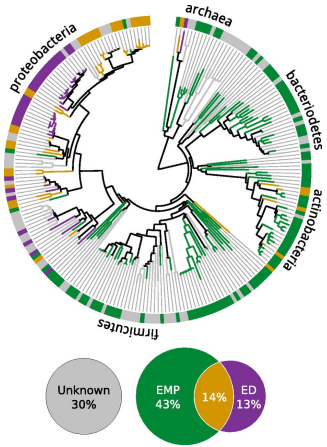

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Overall thermodynamics

Stoichiometry of both glycolytic pathways:

$$\mathrm{Glucose} + 2\,\mathrm{NAD(P)}^{+} + n\,\mathrm{ADP} + n\,\mathrm{Phosphate} \longrightarrow 2\,\mathrm{Pyruvate} + 2\,\mathrm{NAD(P)H} + n\,\mathrm{ATP} + n\,\mathrm{H_2O}$$

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The EMP pathway generates twice as much ATP:

- EMP: $d = 2$ (reminder: $d^{\mathrm{opt}} = 2$, according to Werner et al. [5])
- ED: $d = 1$

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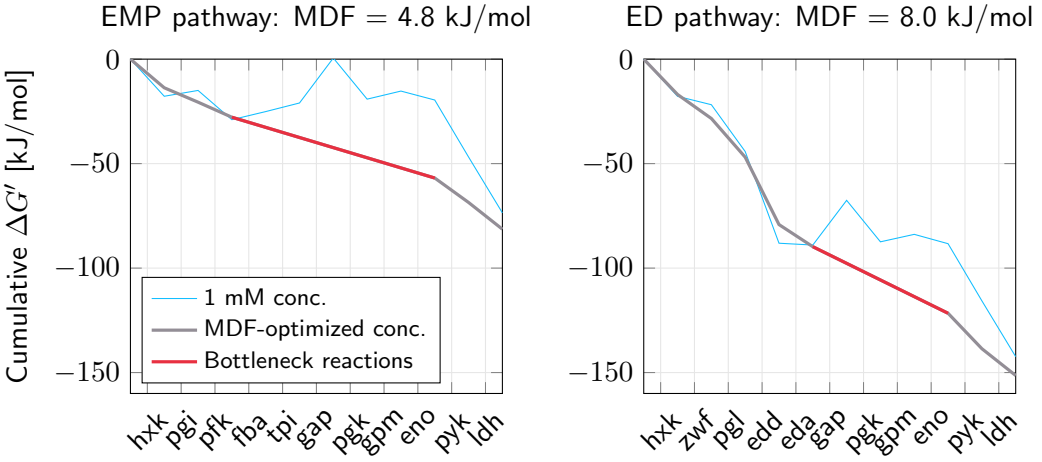
- ED: $d = 1$

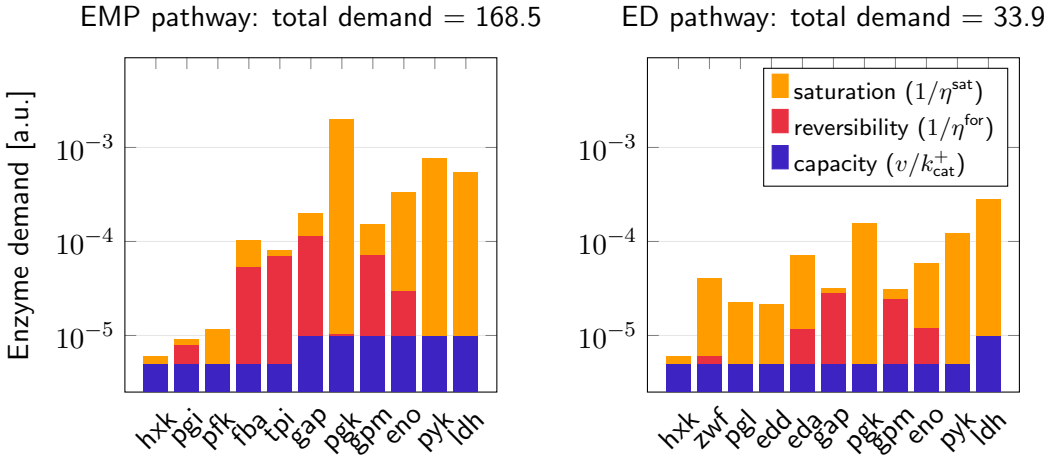
On the other hand, the total driving force of the ED pathway is larger:

- EMP: $\Delta G'_{\mathrm{tot}} \approx -100$ kJ/mol
- ED: $\Delta G'_{\mathrm{tot}} \approx -160$ kJ/mol

ED has a better thermodynamic profile than EMP



ED has a 5-times lower minimal enzyme cost than EMP



More than a single pathway

Can we use ECM more generally to predict enzyme/metabolite concentrations in vivo?

We can calculate the cost of any given flux

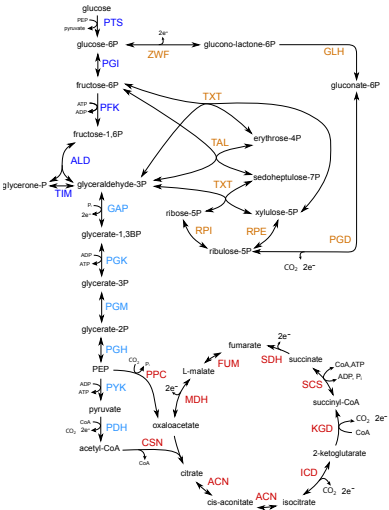
Given any flux (e.g. measured using ^{13}C flux analysis) we can find the minimal enzyme cost based on the kinetic model*

*Noor et al. [4]

We can calculate the cost of any given flux

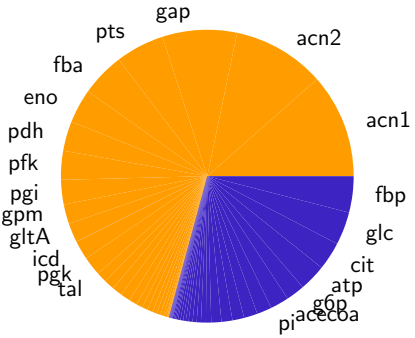
Given any flux (e.g. measured using ^{13}C flux analysis) we can find the minimal enzyme cost based on the kinetic model*

A small model of *E. coli*'s central metabolism – upper glycolysis, lower glycolysis, pentose phosphate pathway, TCA cycle



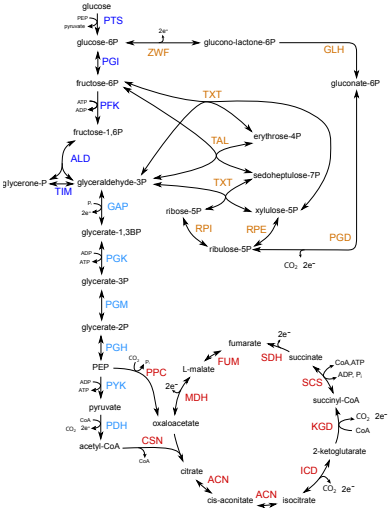
We can calculate the cost of any given flux

Total mass density = 59.3 [g/L]



Enzymes

Metabolites



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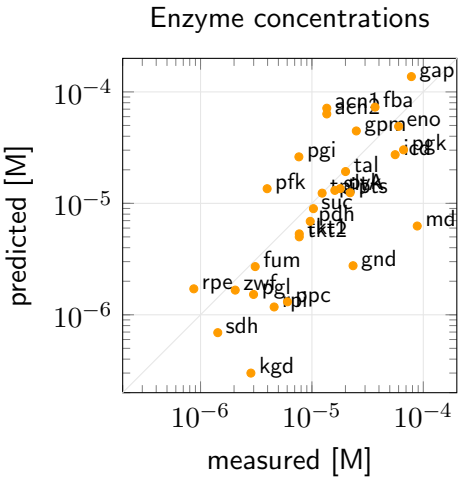

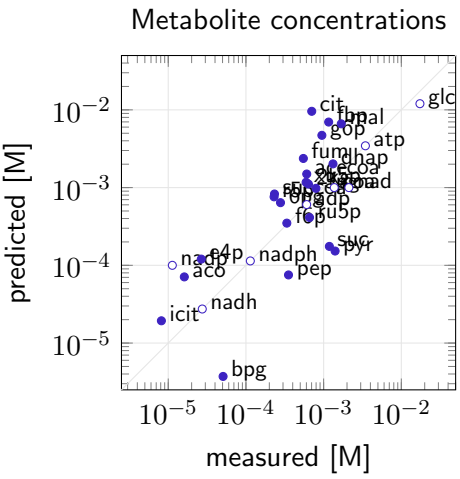

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4. the enzyme cost, allowing $\eta^{\mathrm{sat}} \leq 1$ (convex optimization)

Translating enzyme cost to growth rate

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- But what if we don't know the flux in advance?
- Wortel et al. [6] showed that optimal flux strategies must be Elementary Flux Modes (EFMs)
- Since there is a finite number of EFMs, we can enumerate them and find the one with the lower ECM score

Bibliography

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Please give us feedback about this lecture

Lecture #5: “The enzyme cost of metabolic fluxes”