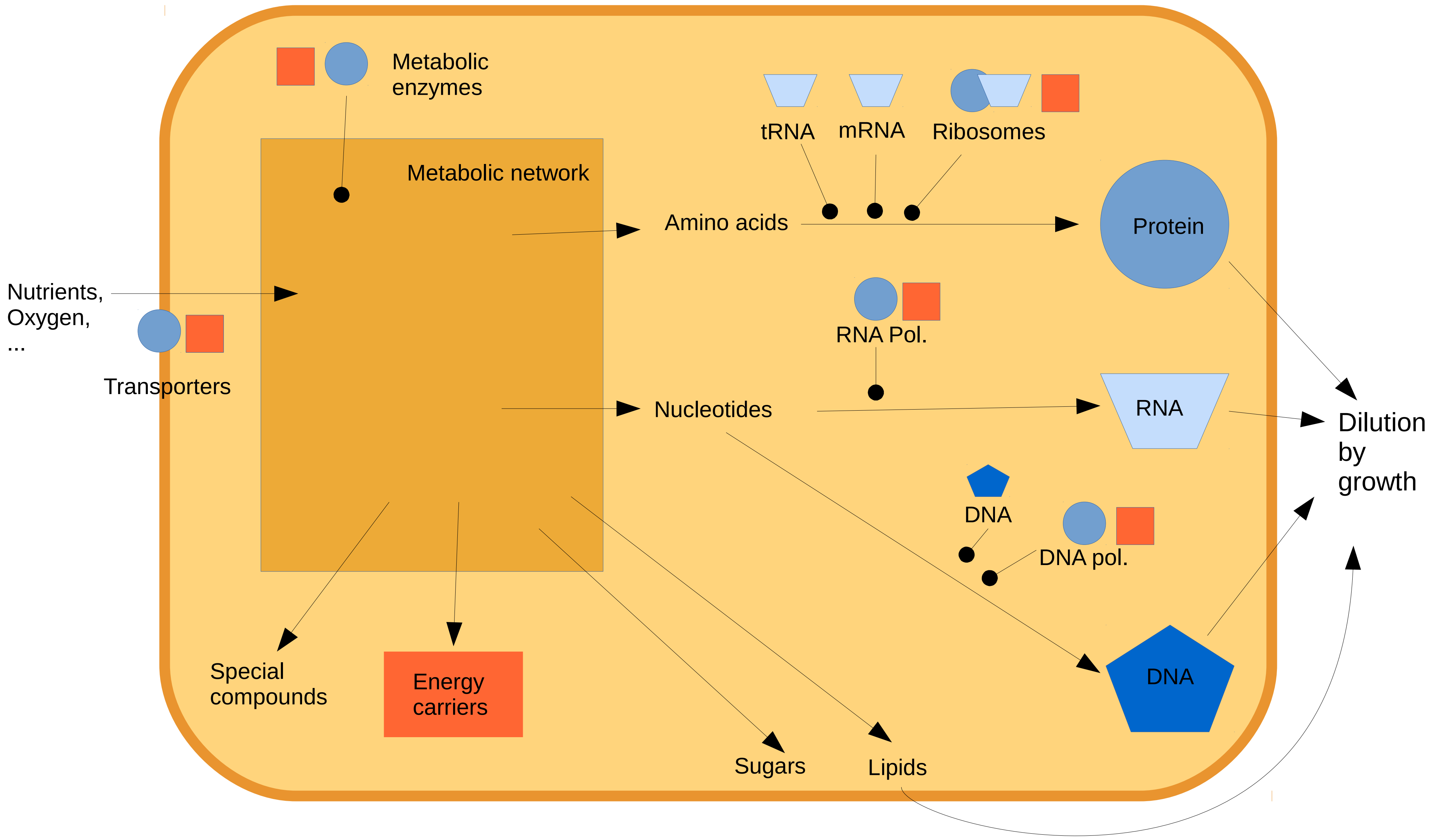
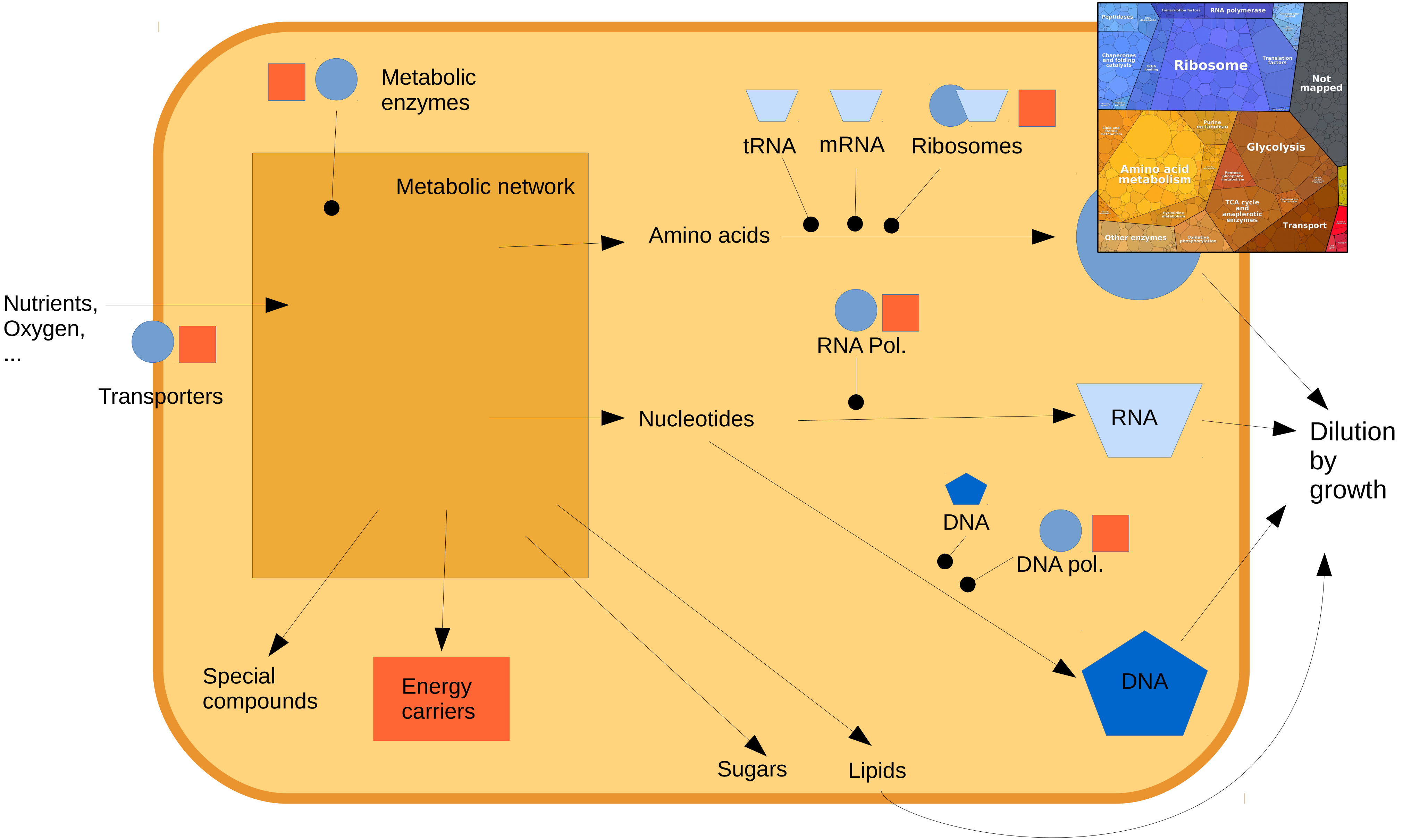
Part 4: Protein cost and resource allocation in cells

The cell as a self-replicating factory

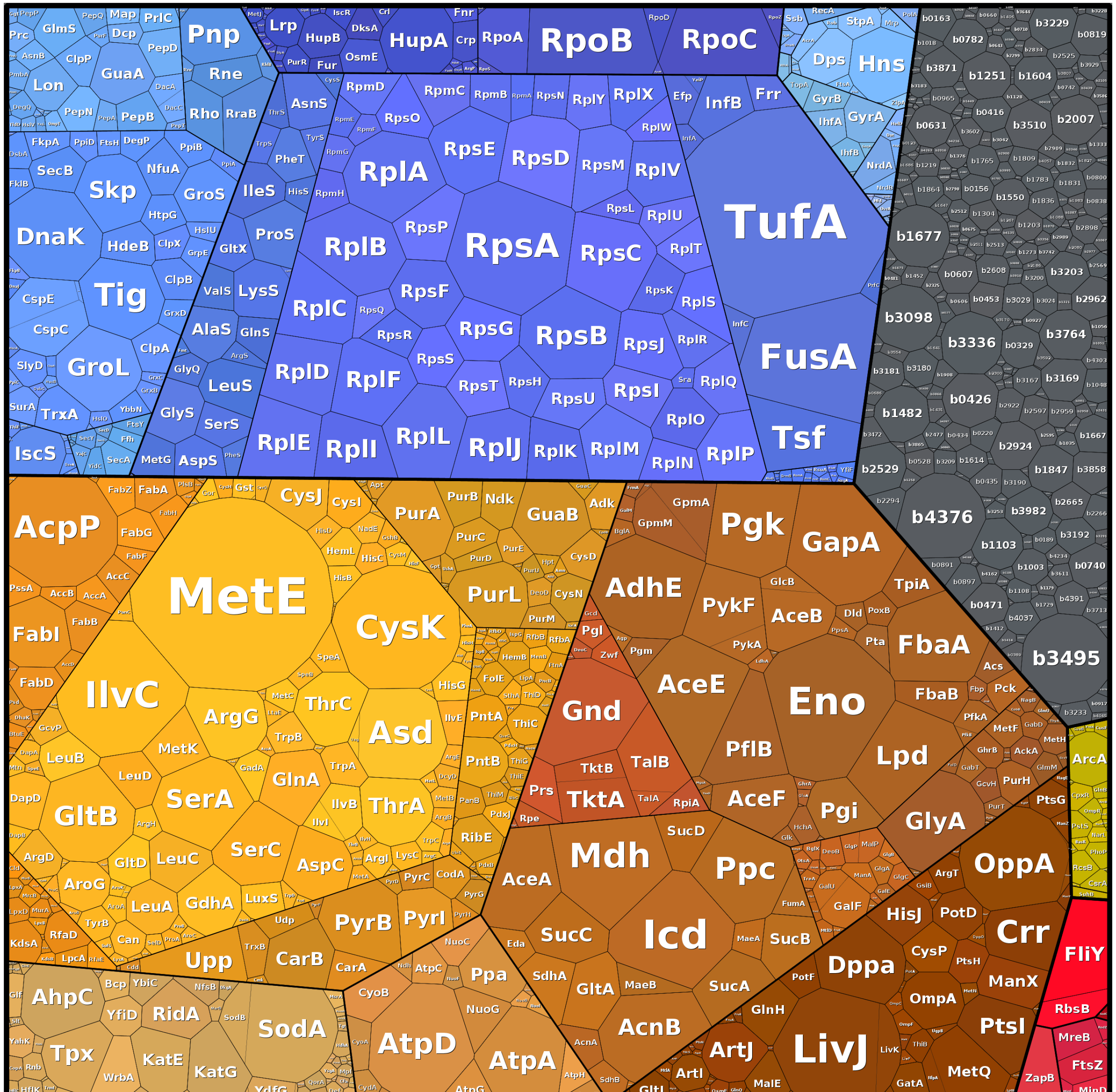


How are proteins allocated to different cell processes?



How do cells "spend their protein budget"?

E. coli proteome (continuous culture)



Data
Valgepea et al. (2013), Mol Biosyst 9 (9)

Visualisation
Liebermeister et al. (2014), PNAS 111 (23)

Proteomaps online service
www.proteomaps.net

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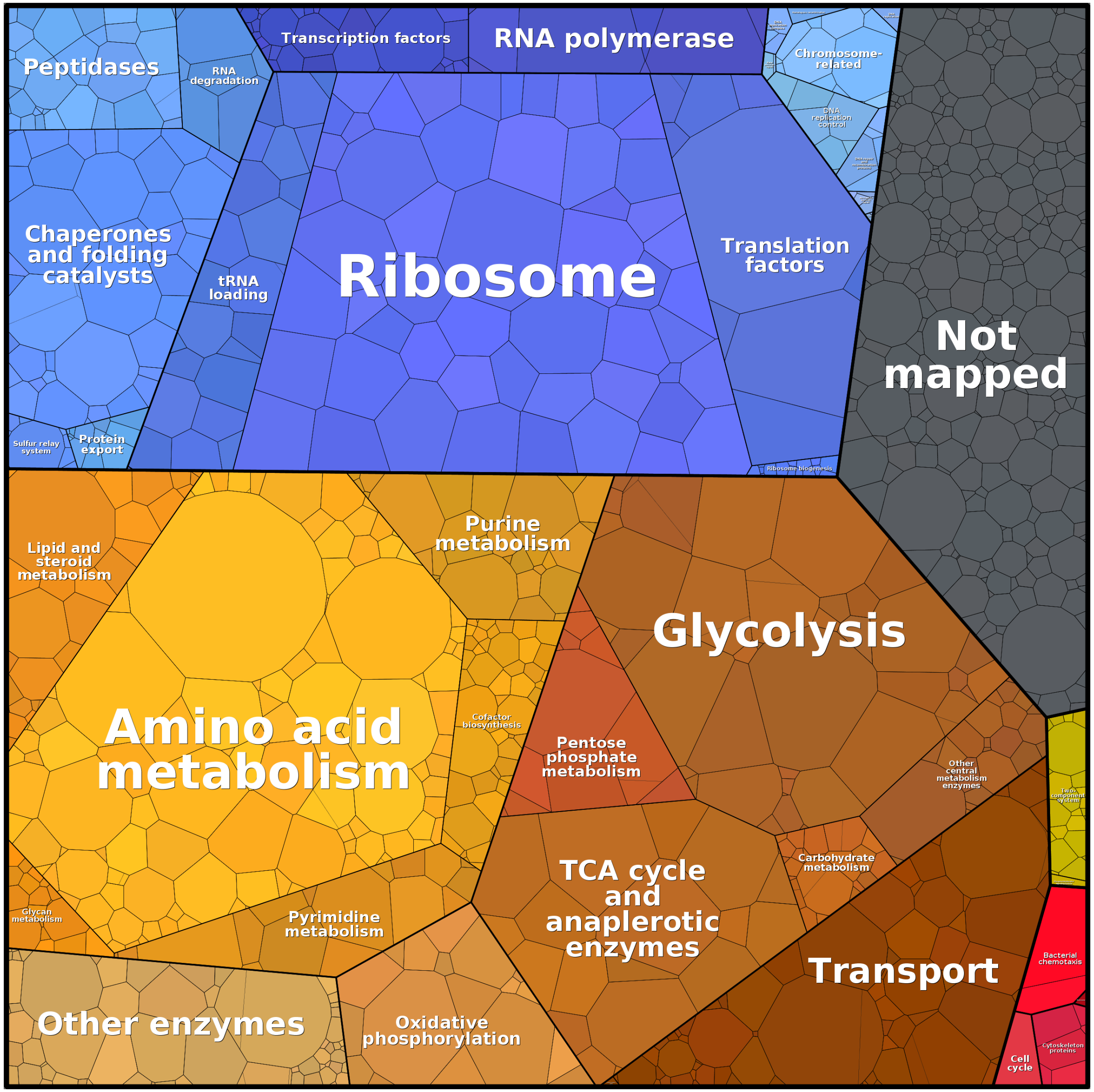

How can we explain .. the different amounts of metabolic enzymes?

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Valgepea et al. (2013), Mol Biosyst 9 (9)

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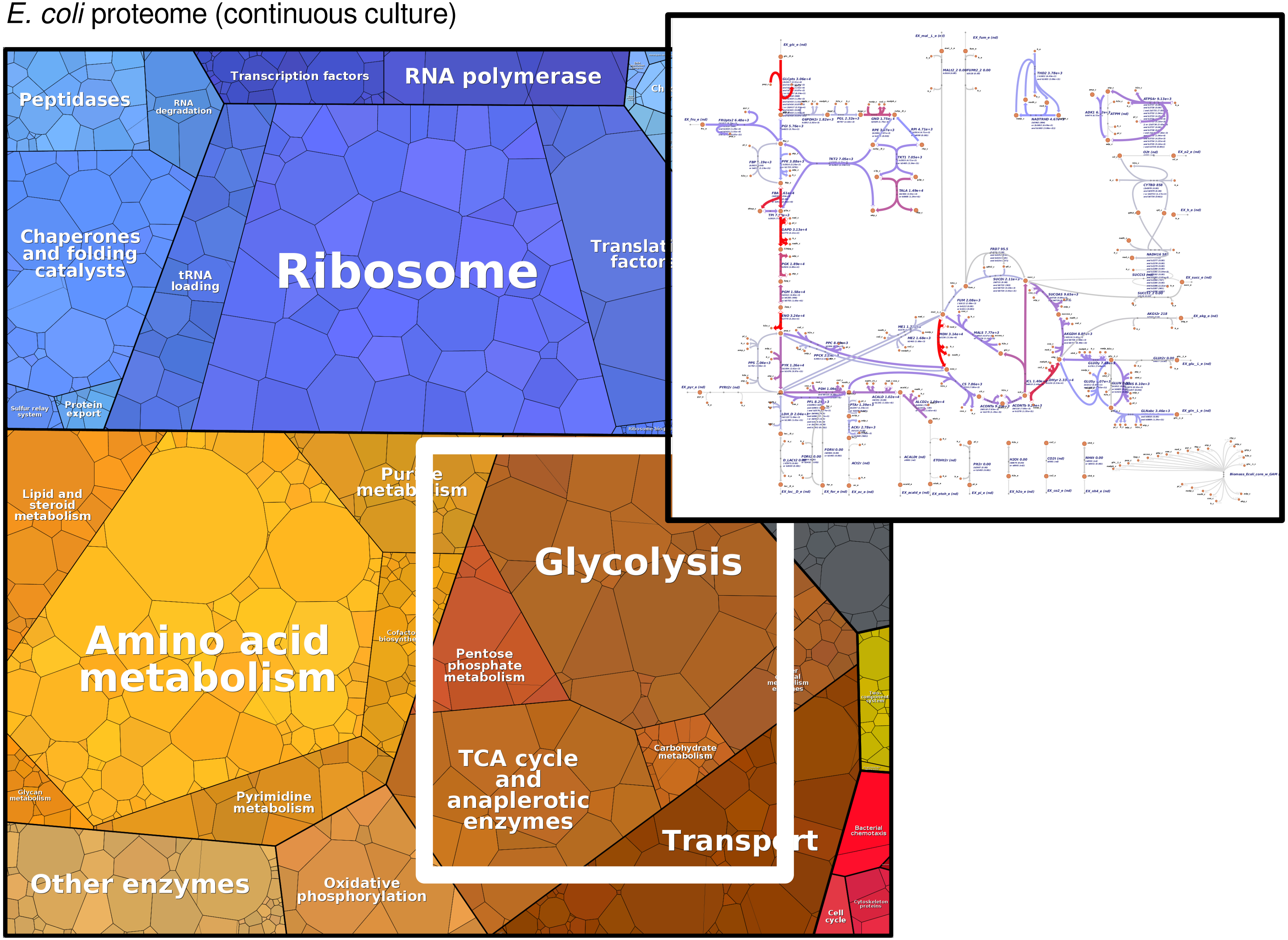

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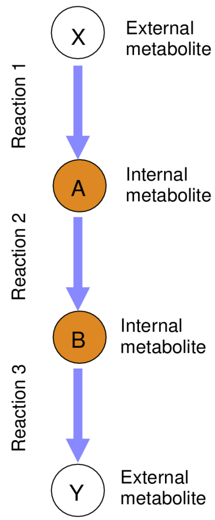
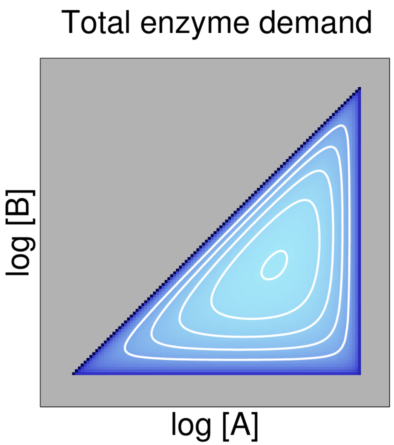
The enzyme cost of metabolic fluxes

Enzyme cost minimisation predicts metabolite and enzyme levels

Example model





Enzymatic rate law

$$v = E\, f(a, b)$$

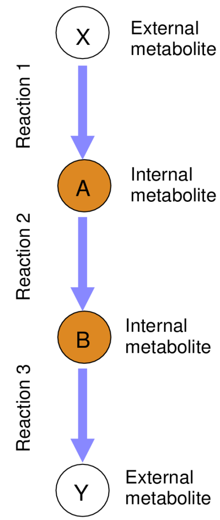
Enzyme cost function

$$\sum_l E_l = \sum_l \frac{v_l}{f_l(a, b)}$$

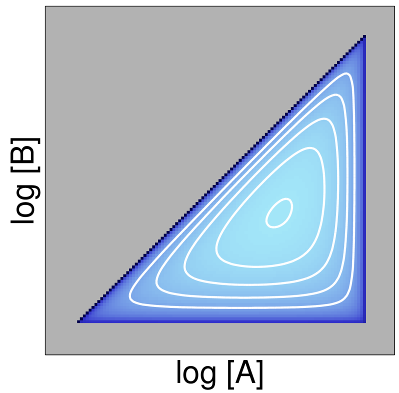
Noor et al. (2016), PLoS Comput Biol 12(10): e1005167

Enzyme cost minimisation predicts metabolite and enzyme levels

Example model



Total enzyme demand



Enzymatic rate law

$$v = E\, f(a, b)$$

Enzyme cost function

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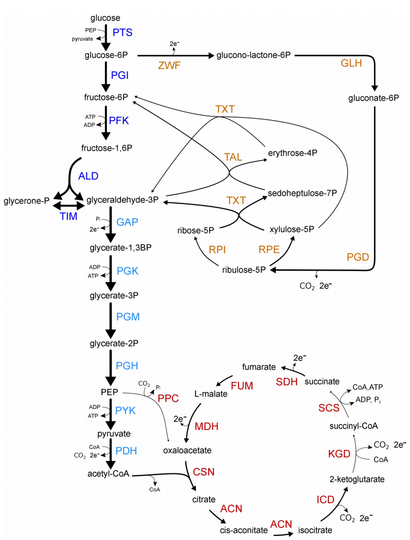
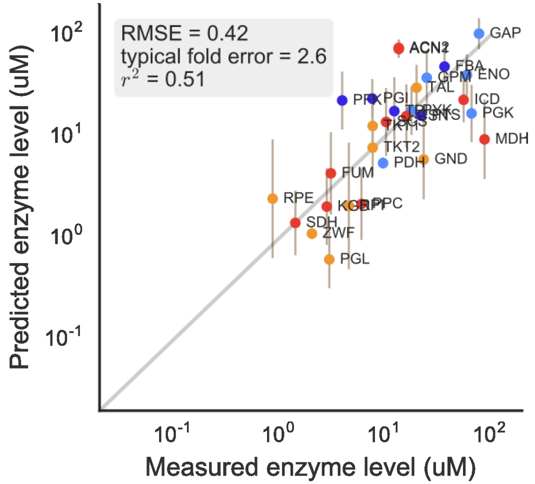
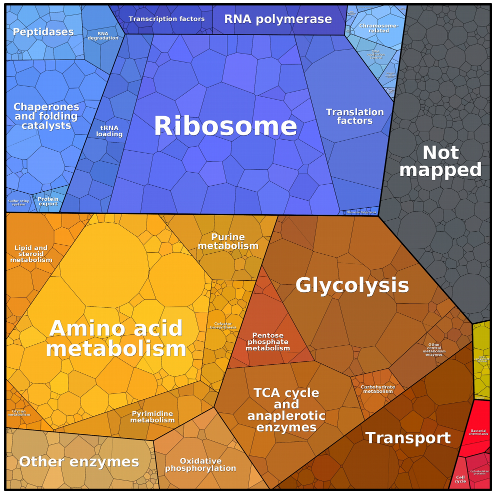
Enzyme predictions for *E. coli* central carbon metabolism

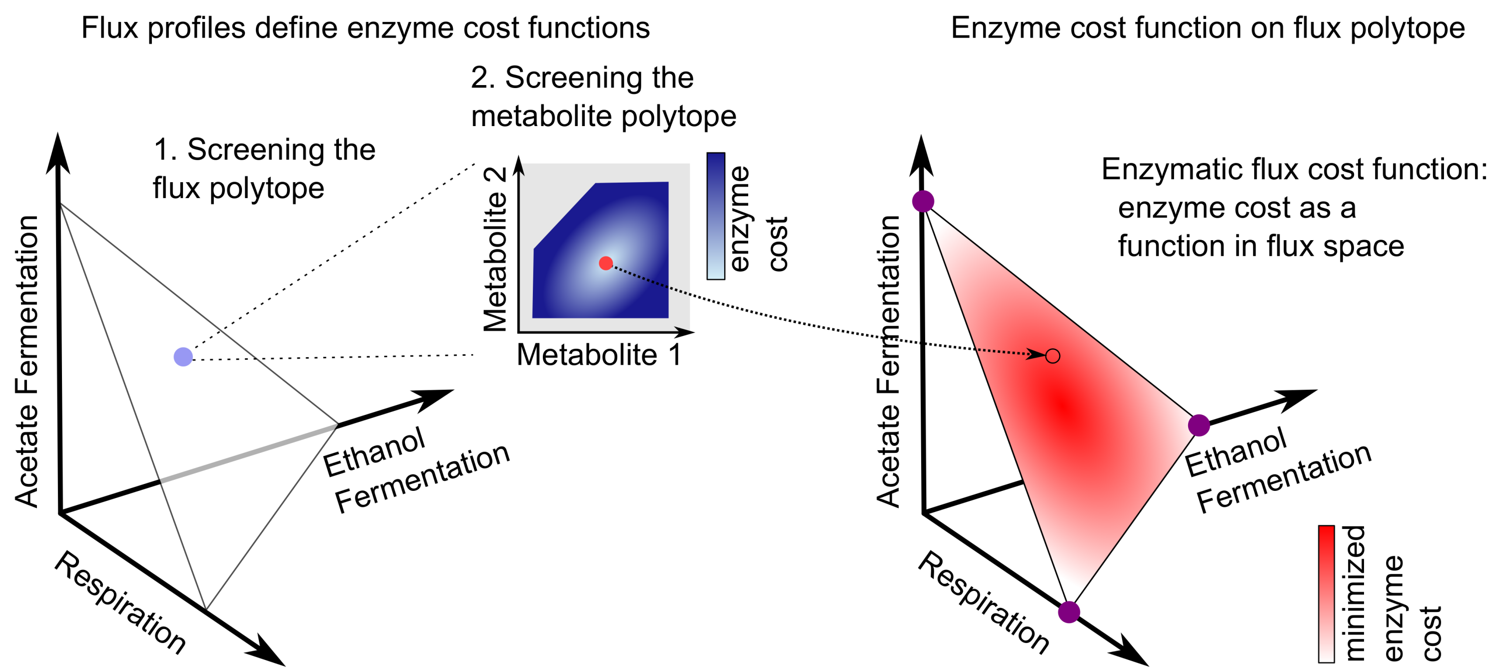






Noor et al. (2016), PLoS Comput Biol 12(10): e1005167

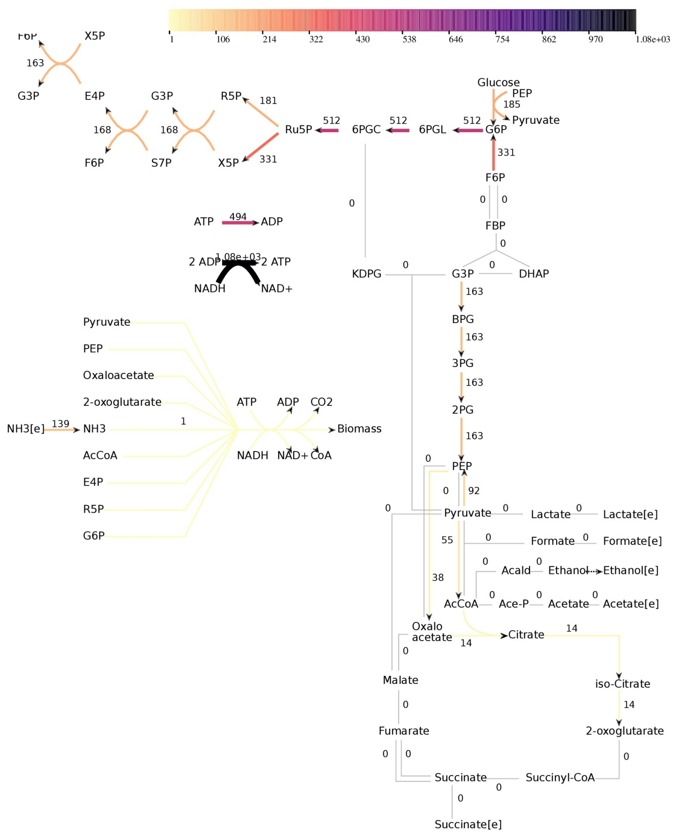
Enzyme cost can be presented as a flux cost function



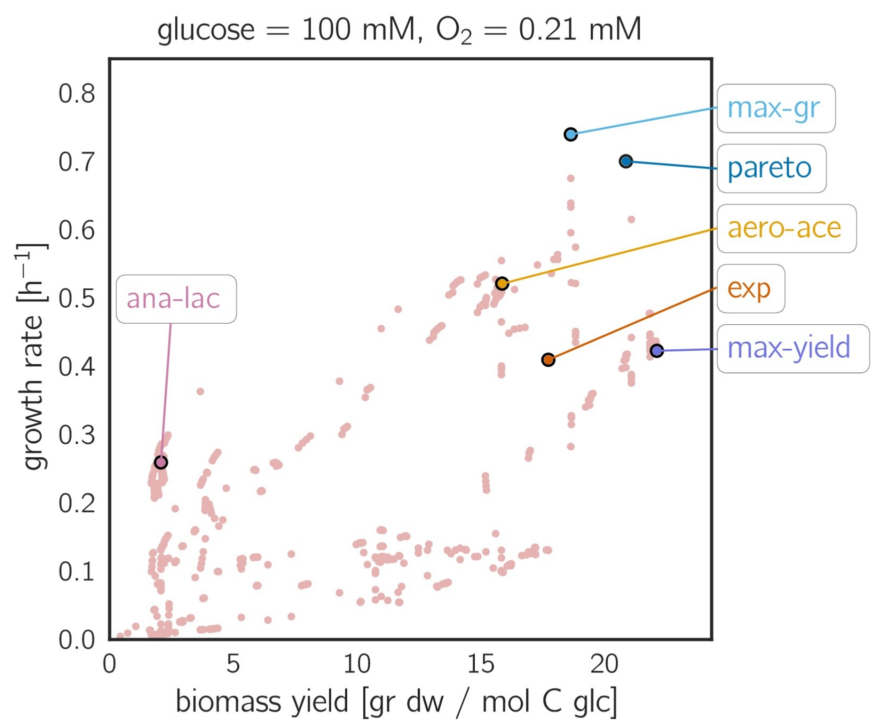
Wortel *et al.*, Preprint at BioRxiv doi.org/10.1101/111161

Elementary flux modes in a model of central metabolism

Model structure (“max-gr” EFM shown by colours)



EFMs in the growth-yield plot



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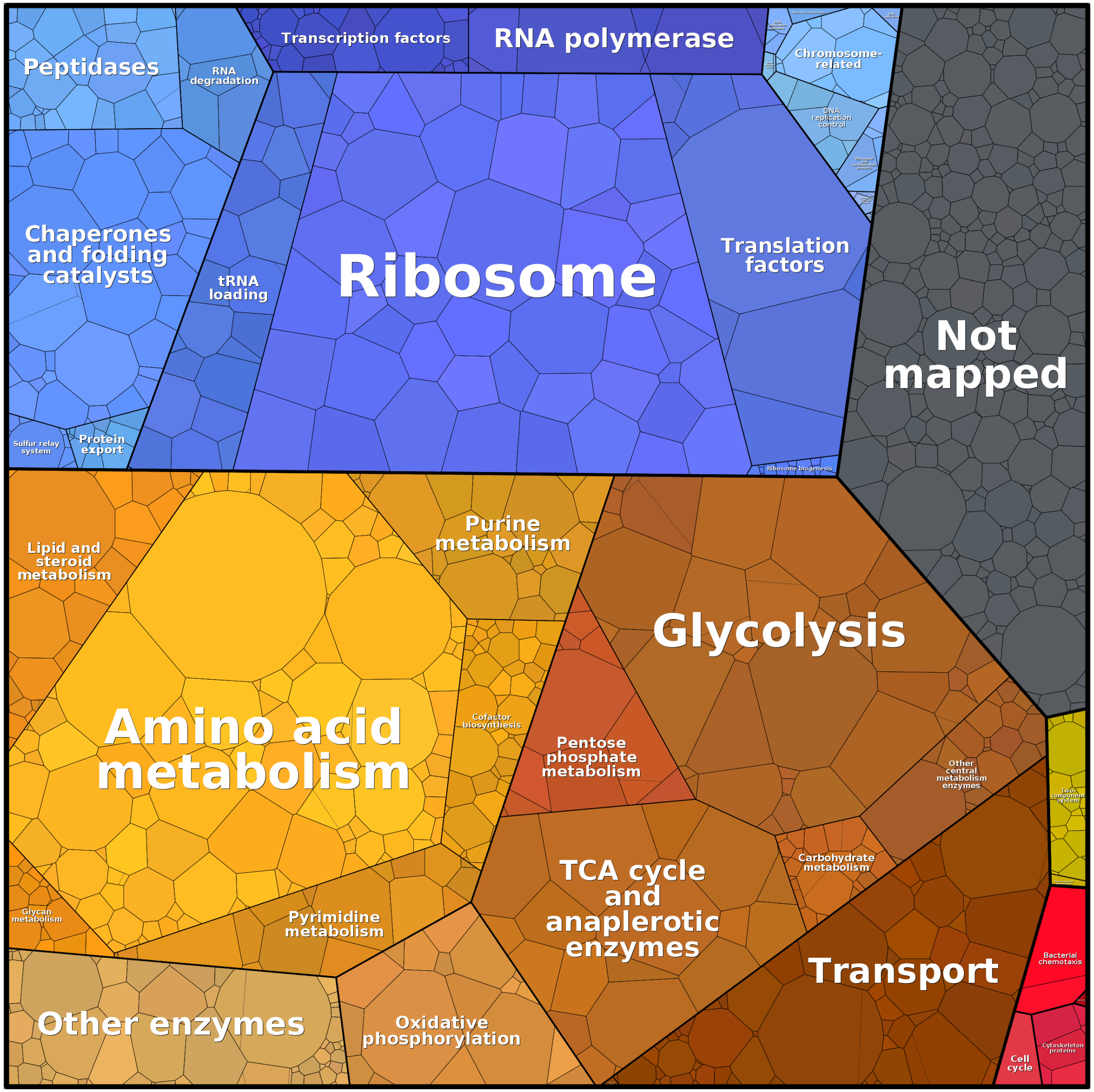
How do cells “spend their protein budget”?

E. coli proteome (continuous culture)



How can we explain .. the ratio of ribosomes / metabolic enzymes?

Data
Valgepea et al. (2013), Mol Biosyst 9 (9)

Visualisation
Liebermeister et al. (2014), PNAS 111 (23)

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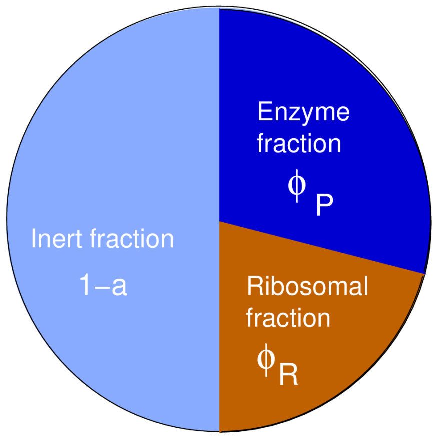
Investments in metabolism or protein production?

“Sector model” of protein investments

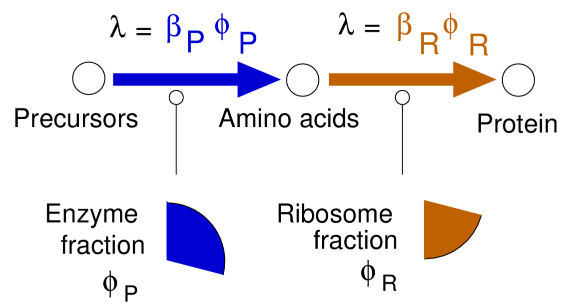
(a) Protein fractions in the sector model



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

$a = \phi_P + \phi_R$ (a: Available proteome fraction)

(b) Schematic model of cell growth



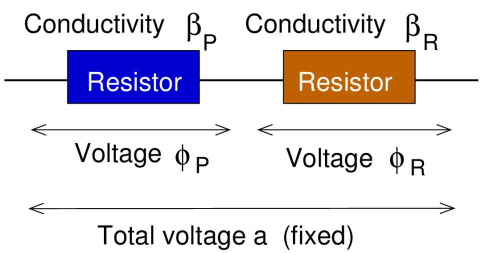
Assumption 2: The growth rate is proportional to each of the two proteome fractions

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

β_P Nutrient capacity

β_R Translation capacity

(c) Analogy to electric circuit

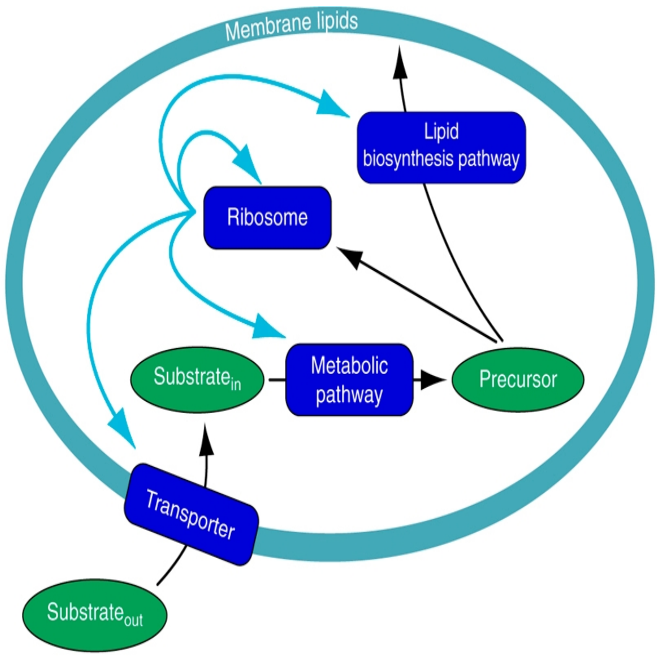


$$\phi_P = \frac{\beta_R}{\beta_P + \beta_R} a \qquad \phi_R = \frac{\beta_P}{\beta_P + \beta_R} a$$

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

Adapted from Scott et al. (2010)

Resource allocation in a simple self-replicating cell

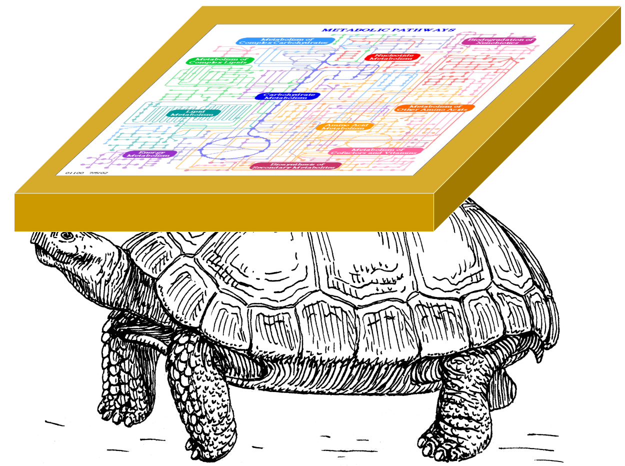


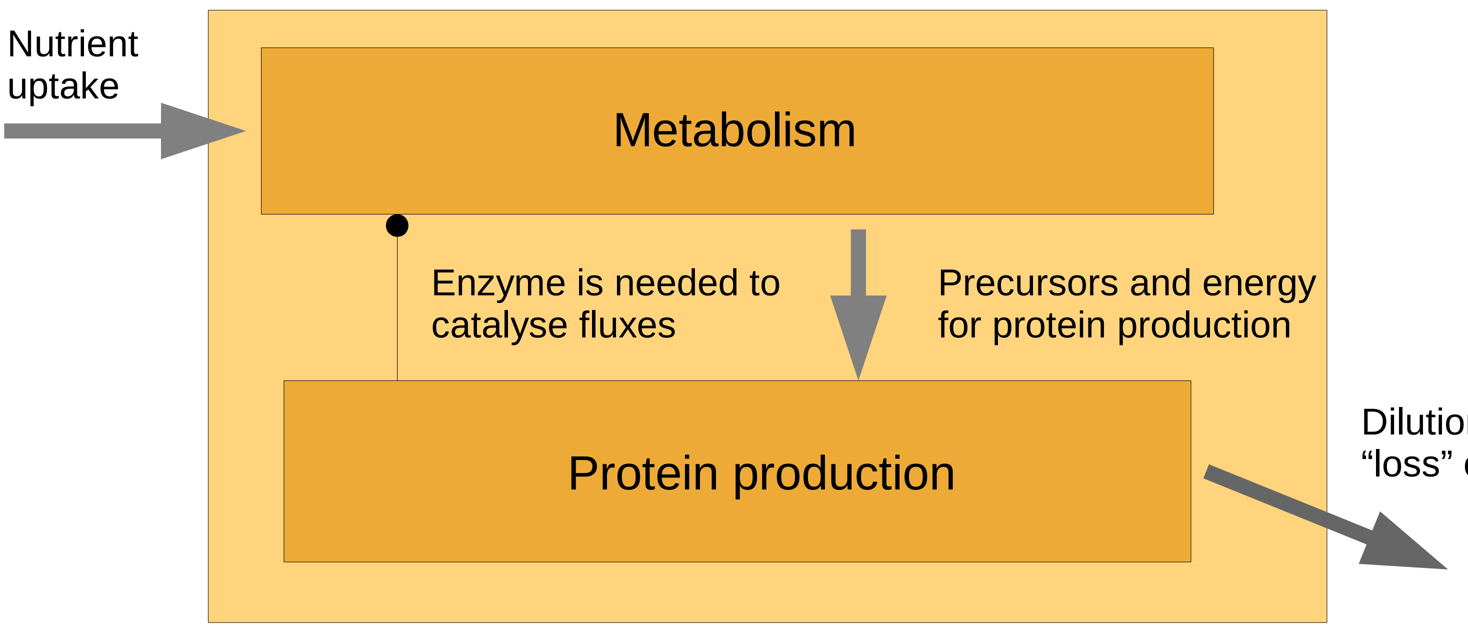
- A “minimal self-replicator” that includes metabolism and enzyme production

- Optimizing resource allocation can explain why cells shift from efficient to inefficient catabolism at high growth rates

Molenaar, D., van Berlo, R., de Ridder, D., & Teusink, B. (2009)
Molecular Systems Biology, 5, 323

Resource balance analysis:
Flux balance analysis, applied to an entire, growing cell

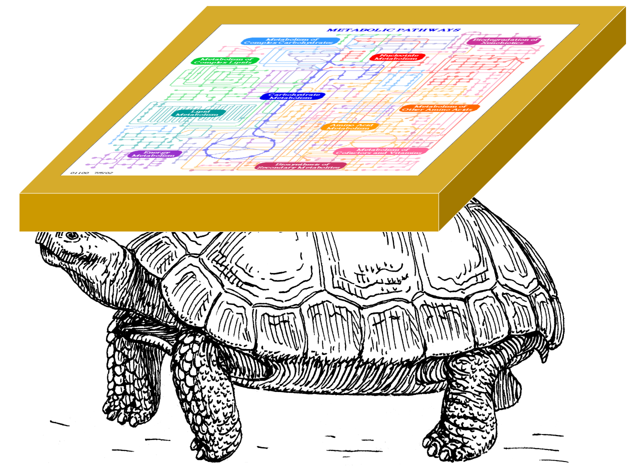




A. Goelzer and V. Fromion. Biochim Biophys Acta, 1810(10):978–988, 2011.

Resource Balance Analysis: Constraints and calculation

RBA implements **three sets of constraints**.



Mass conservation: chemical reactions (metabolic reaction, protein synthesis) and boundary conditions (import/export, creation of biomass).
→ basic Flux Balance Analysis constraint.

Capacity constraints: a reaction flux can only be sustained if there are enough enzymes (or ribosomes, chaperones).
→ sets a price for every metabolic pathway.

Maximal density: every compartment holds a limited number of molecular species.
→ selection of most parsimonious pathways.

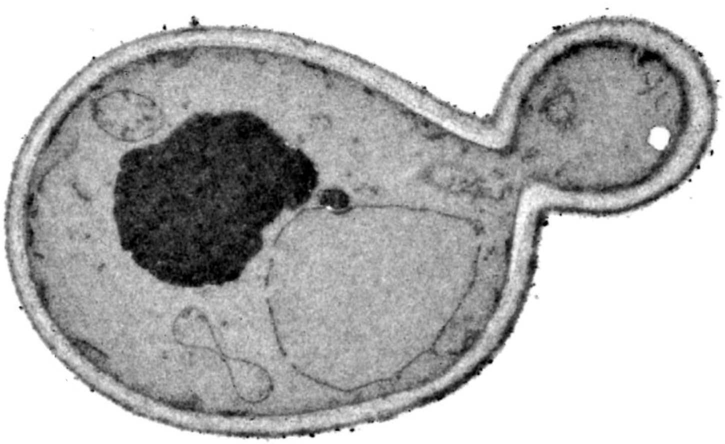
Calculation:

- Fix a growth rate and decide:
  Can a steady (growth) state be maintained? → linear (i.e., FBA-like) problem
- Repeat this many times; find the maximal growth rate at which the problem can be solved

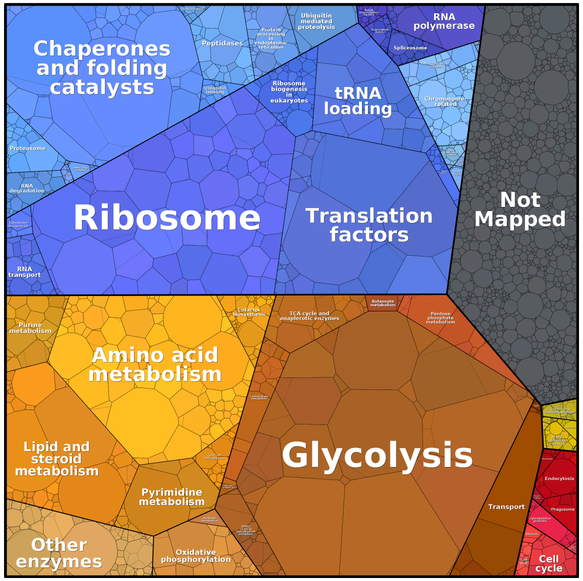
A. Goelzer and V. Fromion. Biochim Biophys Acta, 1810(10):978–988, 2011.

How can a cell reproduce itself?

Budding yeast
(microscope picture of a cell)



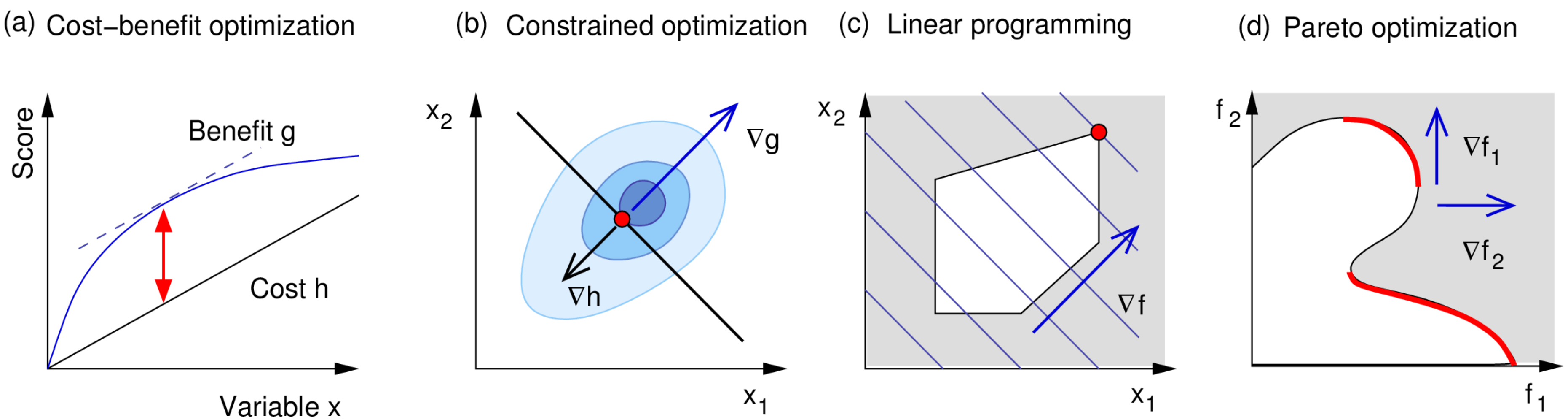
Budding yeast
(relative protein
abundances)



Initial questions for this lecture

- What does a living cell need to do to proliferate, i.e., to reproduce all its components?
- How can it do so in “cost-saving” ways, given physical and biochemical limitations?
- If cells function “optimally”, how will they behave and what will they look like?
- How can we describe all this by mathematical models?

Mathematical descriptions of optimal states



Ingredients for an optimality-based ("economic") cell model

- Network model (with variables to be optimised, and others that depend on them)
- An objective function to be minimised or maximised (biomass production, ..)
- Physical or logical relationships between variables (rate laws, stationarity, ..)
- Constraints, e.g., lower and upper bounds (constraint on protein density, ..)

Objectives and constraints can be exchangeable!
Objectives and constraints can "propagate" through the system!

Conceive a physically impossible superbug!

Conceive a cell or organism that – for the sake of this group work – can defy one fundamental law of physics*.

Try to imagine how such an organism could function, what other restrictions it could bypass, and what other adaptations it would accumulate in its further evolution towards maximal fitness.

Prepare a short (5 minutes) presentation of your group work.

*Alternatively: law of logics; mathematics; etc