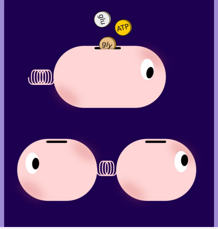
Economic Principles in Cell Biology

Paris, 8-11th July 2024



An inventory of cell components

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Cells as chemicals

99% of cell mass

6	1	7	8	15	16
C	**H**	**N**	**O**	**P**	**S**
Carbon	Hydrogen	Nitrogen	Oxygen	Phosphorus	Sulphur

1% of cell mass: Na, K, Fe, Mo, Cl, Ca…

Bacteria: $CH_{1.77}O_{0.49}N_{0.24}$

Yeast: $CH_{1.61}O_{0.56}N_{0.16}$

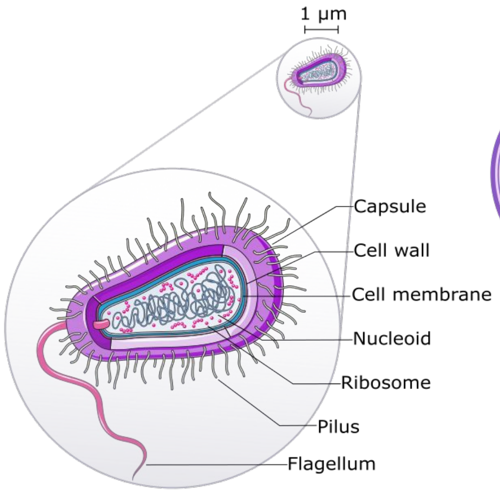
Cells as bags of things

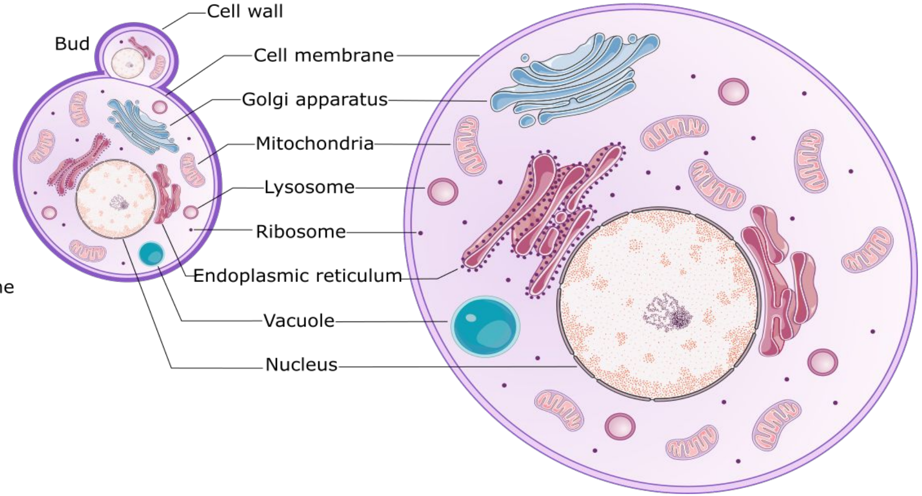
Prokaryotic

- bacteria, archaea
- do not have organelles

Eukaryotic

- yeasts, plant, animal cells
- have organelles



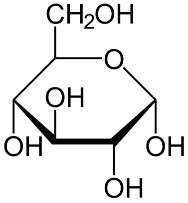


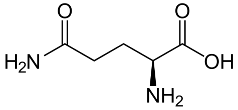
Cells as a collection of biological molecules

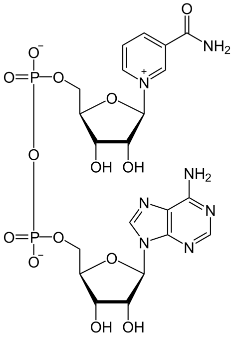
Biological molecules

Small molecules

- < 1000 Da
- mono-/dimers
- metabolites, cofactors…
- various functions

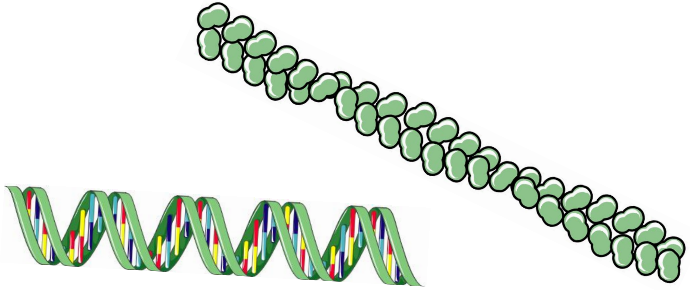




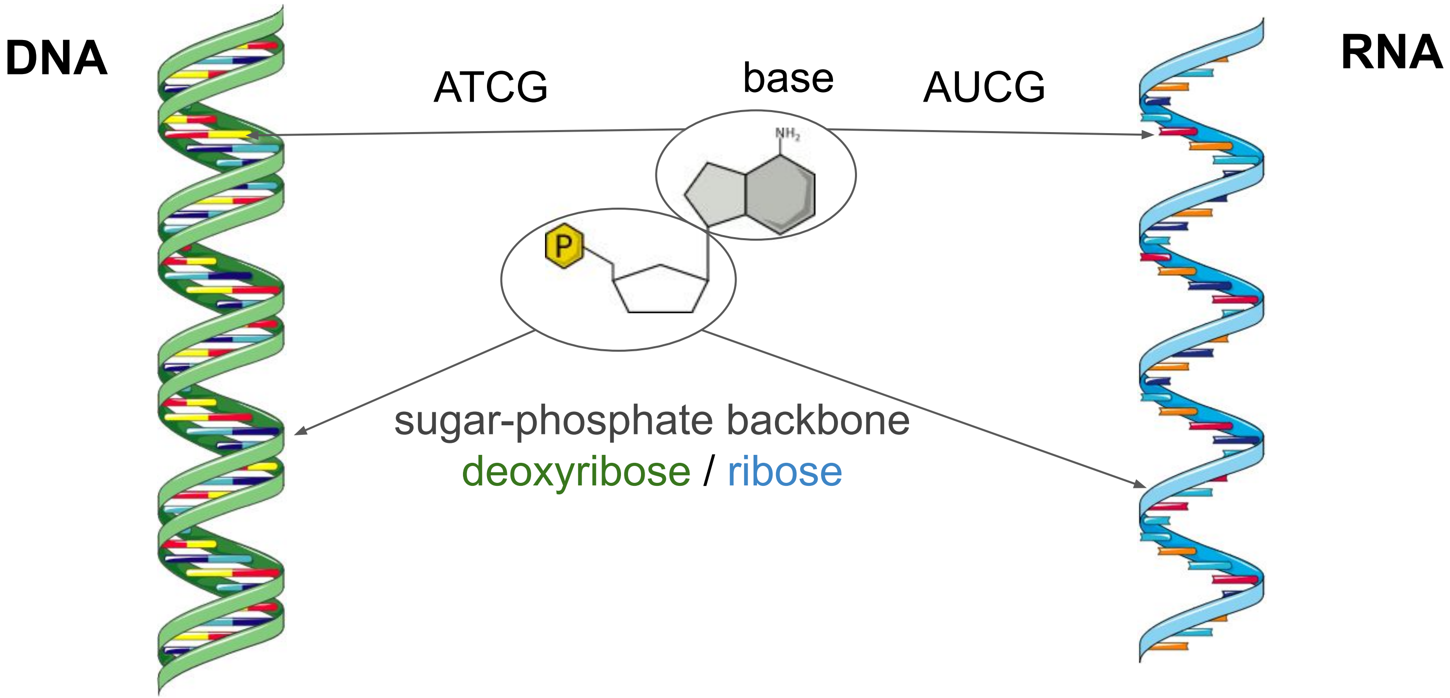


Macromolecules

- polymers
- proteins, nucleic acids, polysaccharides, (lipids?)



Nucleic acids – polymers of nucleotides



Nucleic acids – functions

DNA

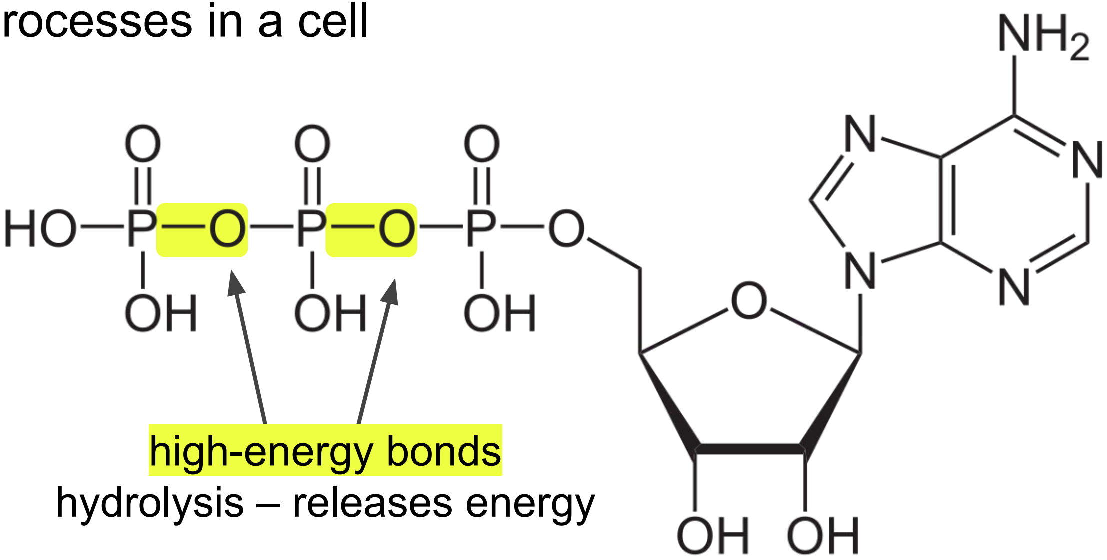
- stores genetic information
- all info to make a new cell

RNA

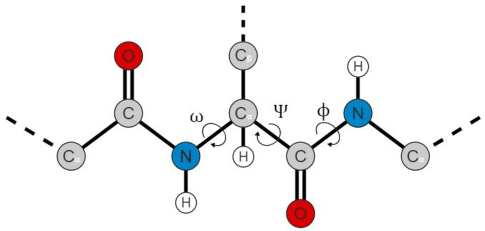
- transcribed from DNA (e.g. ATCG to UAGC)
- **rRNA** – synthesizes proteins (ribosome)
- **mRNA** – template for protein synthesis
- **tRNA** – brings AAs to the synthesis site

Important nucleotide – ATP

- energy currency
- powers processes in a cell

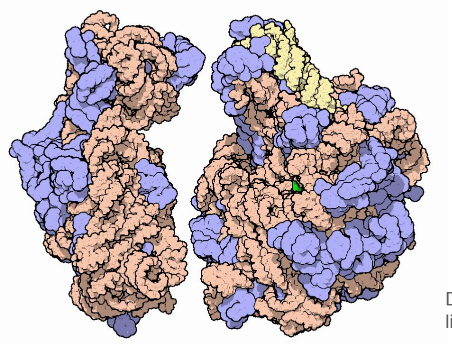


Proteins – polymers of amino acids



- 20 proteinogenic amino acids (AAs)
- 100 AA protein == 20^{100} combinations
- 325 AAs on average in *E. coli*

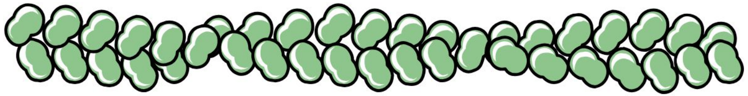
AA chains form 3D structures



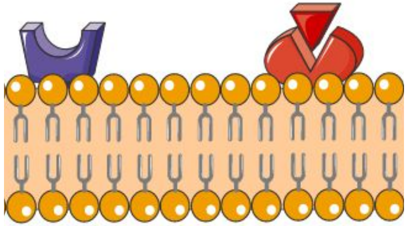
multimers & complexes with other macromolecules

Protein functions

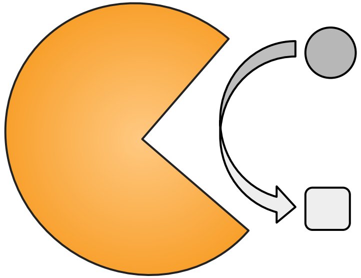
Structural proteins



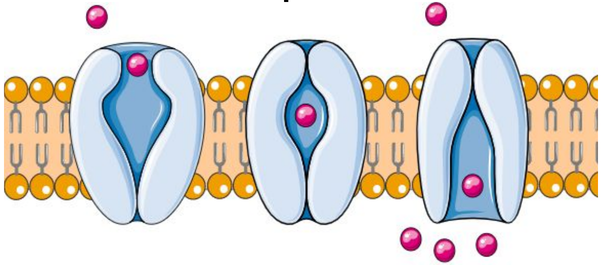
Receptors



Enzymes



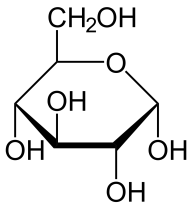
Transporters



Carbohydrates

Monomers/dimers (e.g. glucose)

- carbon & energy source

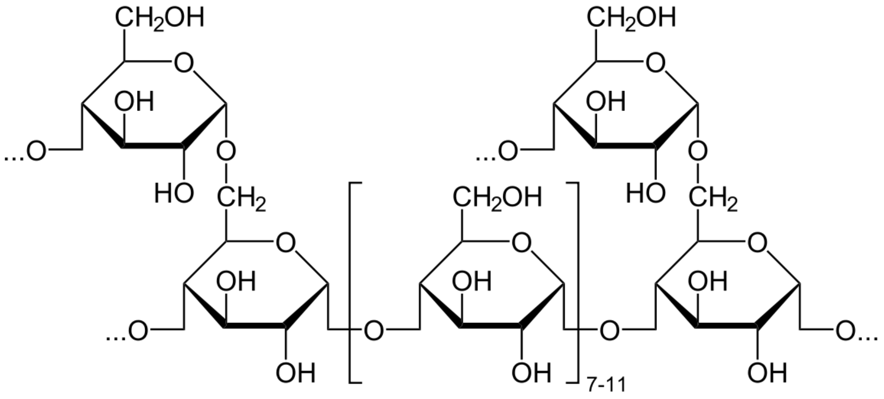


Oligomers

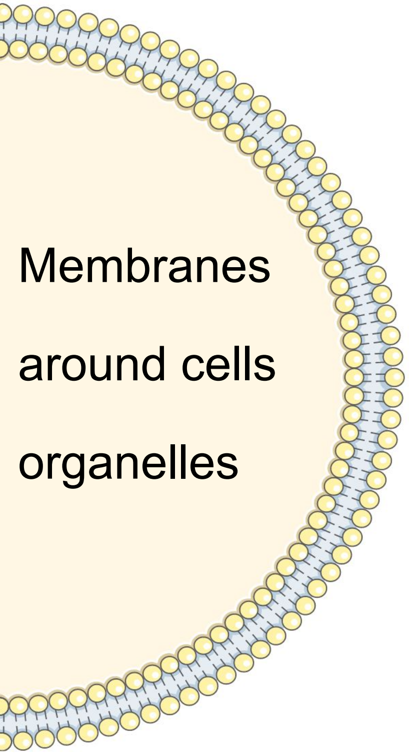
- sensing/reception

Polymers

- storage – glycogen, starch
- structure – mannan, part of cell wall

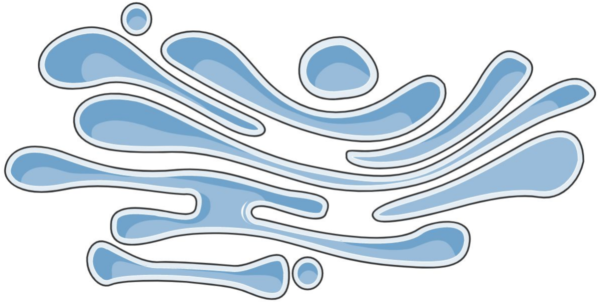


Lipids – diverse hydrophobic compounds

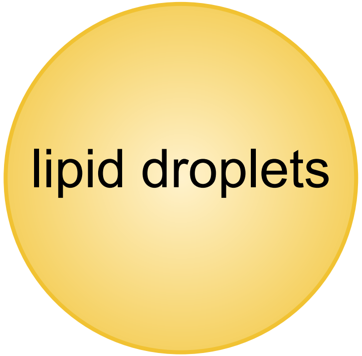


Bilayer membranes

Golgi, ER – protein synthesis & processing



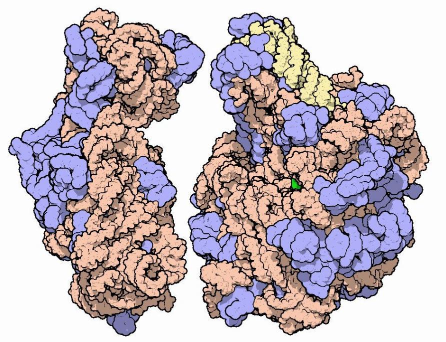
Storage



Biological machines – huge complexes of macromolecules

Ribosome

- complex of rRNA + proteins
- makes proteins



David Goodsell
http://doi.org/10.2210/rcsb_pdb/mom_2000_10
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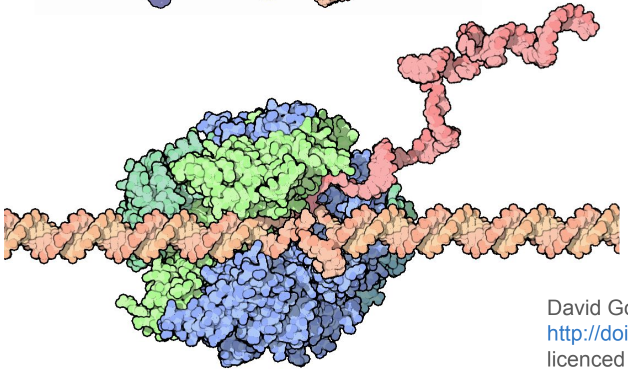
DNA, RNA polymerases

- protein complexes
- synthesis of DNA and RNA



David Goodsell
http://doi.org/10.2210/rcsb_pdb/mom_2003_4
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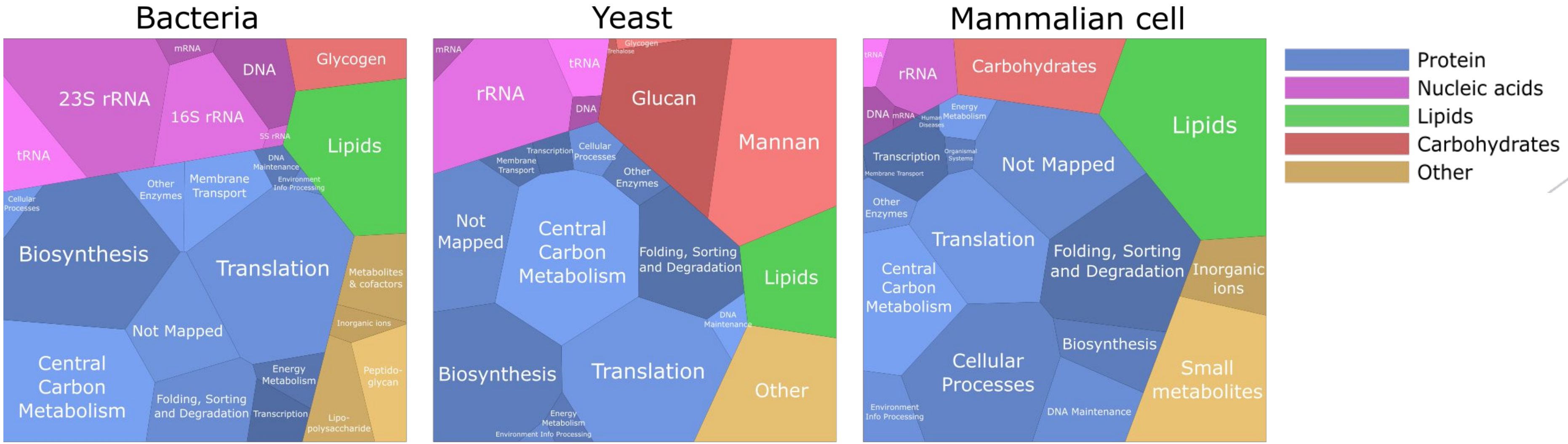
Amounts of cell components

Dry mass composition – similar across cell types

70% water, 30% dry mass



Absolute vs. relative amounts

How many proteins are there in *E. coli* cell?

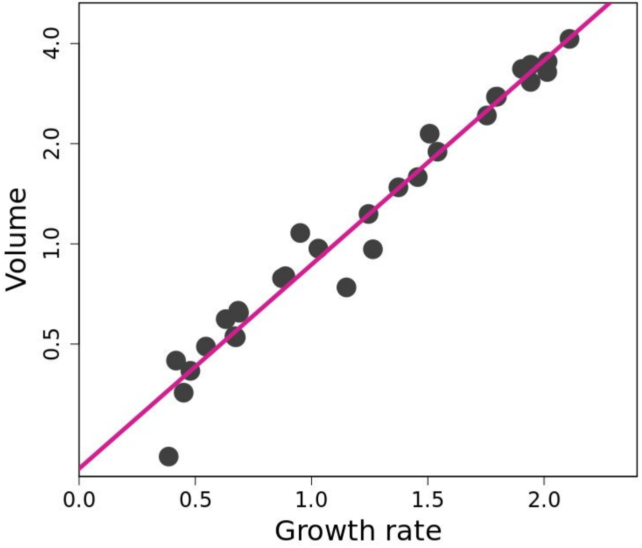
Raise your hand if you think > 10^6

- *E. coli*: 1 μm^3 → 4×10^6
- *S. cerevisiae*: 60 μm^3 → 2×10^8
- Mammalian cell: 3000 μm^3 → 1×10^{10}

Milo, R., & Phillips, R. (2015). *Cell biology by the numbers*. Garland Science.

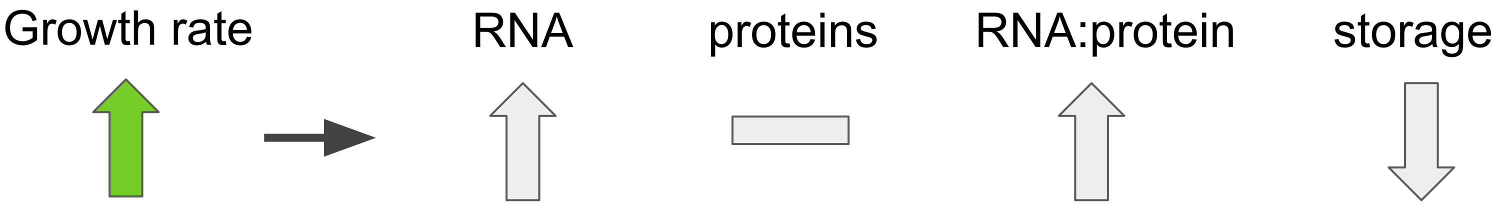
Biomass composition is variable

Nutrient growth law
(Schaechter 1958)



- Cell size, **absolute** DNA, RNA, protein content increase with growth rate
- Bacterial/yeast/mammalian cells
- When growth rate changed by carbon source

Relative composition changes with increasing growth rate



RNA:protein ratio – measure of proteosynthetic capacity

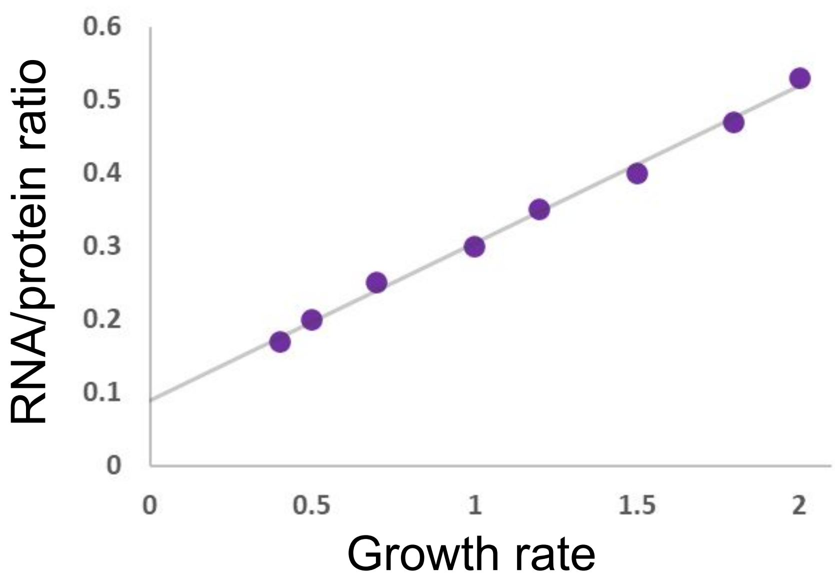
Higher growth rate

↓

more protein synthesis

↓

more ribosomes



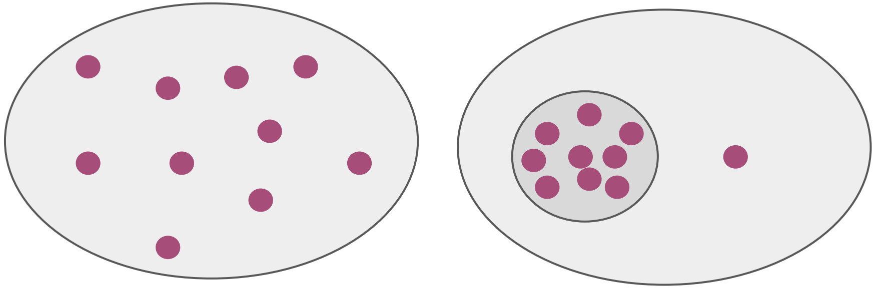
- Ribosome – ⅔ rRNA, ⅓ protein

Other factors that can change composition

- O_2 concentration
- Medium composition
- Mutations
- Temperature

no ‘laws’ for these factors

Composition is not uniform throughout a cell



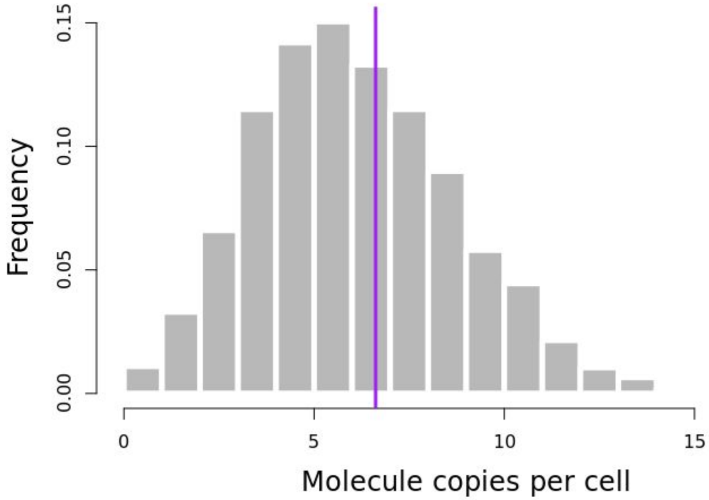
same average concentration

different ‘local’ concentration

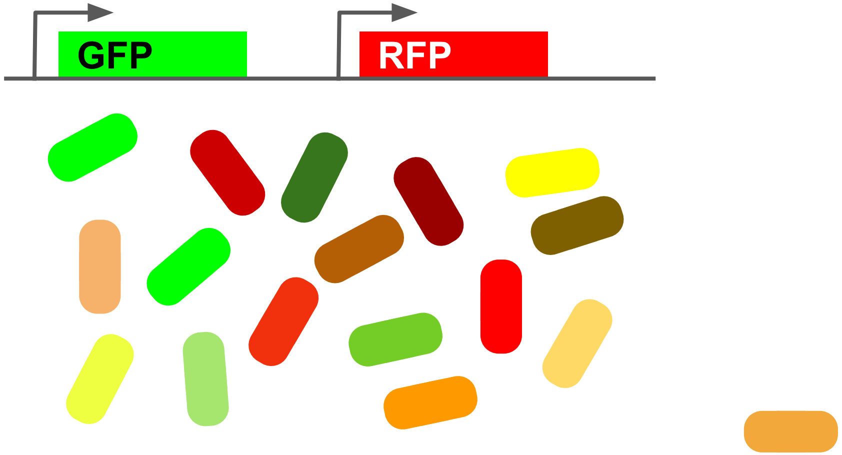
- consequence – different enzyme rates, direction

Populations are not uniform

- processes in a cell – stochastic
- important at low copy numbers



same genome



different phenotype

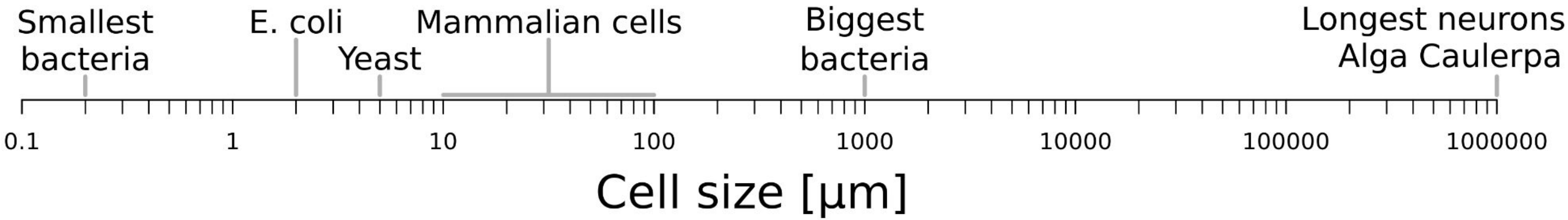
average cell

http://book.bionumbers.org/how-much-cell-to-cell-variability-exists-in-protein-expression/

bet-hedging

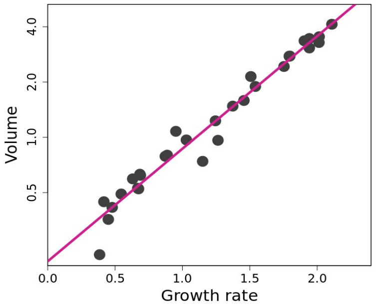
Cell size and density

Cell size – huge variability

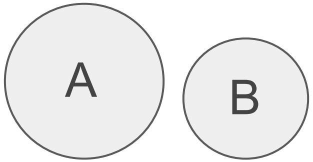


Changes with:

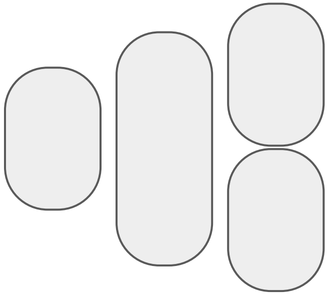
Growth rate



Conditions



Cell cycle



Cell size in multiple dimensions

Name	Unit	E. coli	S. cerevisiae
Cell size	µm	1-2	5
Cell surface area	μm^2	6	70
Cell volume	μm^3	1	60

Shape matters

(A) Hold volume constant

Aspect ratio	1:1	4:1	16:1
Volume	0.5 μm^3	0.5 μm^3	0.5 μm^3
SA / V	6.1 μm^{-1}	7.8 μm^{-1}	16.3 μm^{-1}

Figure from “Harris, Leigh K., and Julie A. Theriot. "Surface area to volume ratio: a natural variable for bacterial morphogenesis." *Trends in microbiology* 26.10 (2018): 815-832.”, licenced under CC BY 4.0

Exercise – buoyant density estimation

What is the buoyant density of a typical bacteria?

	density of component (g/mL)	mass fraction per cell
water	1	0.7
proteins	1.3	0.18
nucleic acids	1.7	0.08
lipids	1	0.03
carbohydrates	1.5	0.01

https://bionumbers.hms.harvard.edu/search.aspx

Buoyant cell density – rule of thumb

1.1 g/mL

Cell density – variable, but the range is small

- 1.05-1.15 g/mL
- some species – variability with growth rate, cell cycle
- increases with osmolarity
- exceptions – fat cells, gassy cells – lower density

Is there an optimal density?

Physical (“hard”) constraints – cannot be bypassed

Temperature, pH, osmolarity

Diffusion limit

- enzyme + substrate have to collide
- no known enzymes above the diffusion limit

Macromolecular crowding

- concentration of macromolecules
- limits cellular processes, e.g. translation

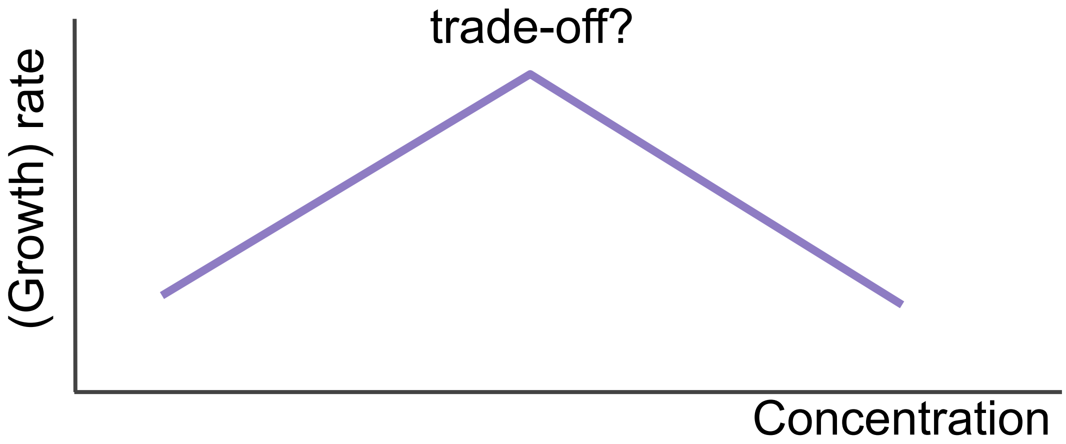
Is there an optimal density?

Too few molecules

Collisions rare

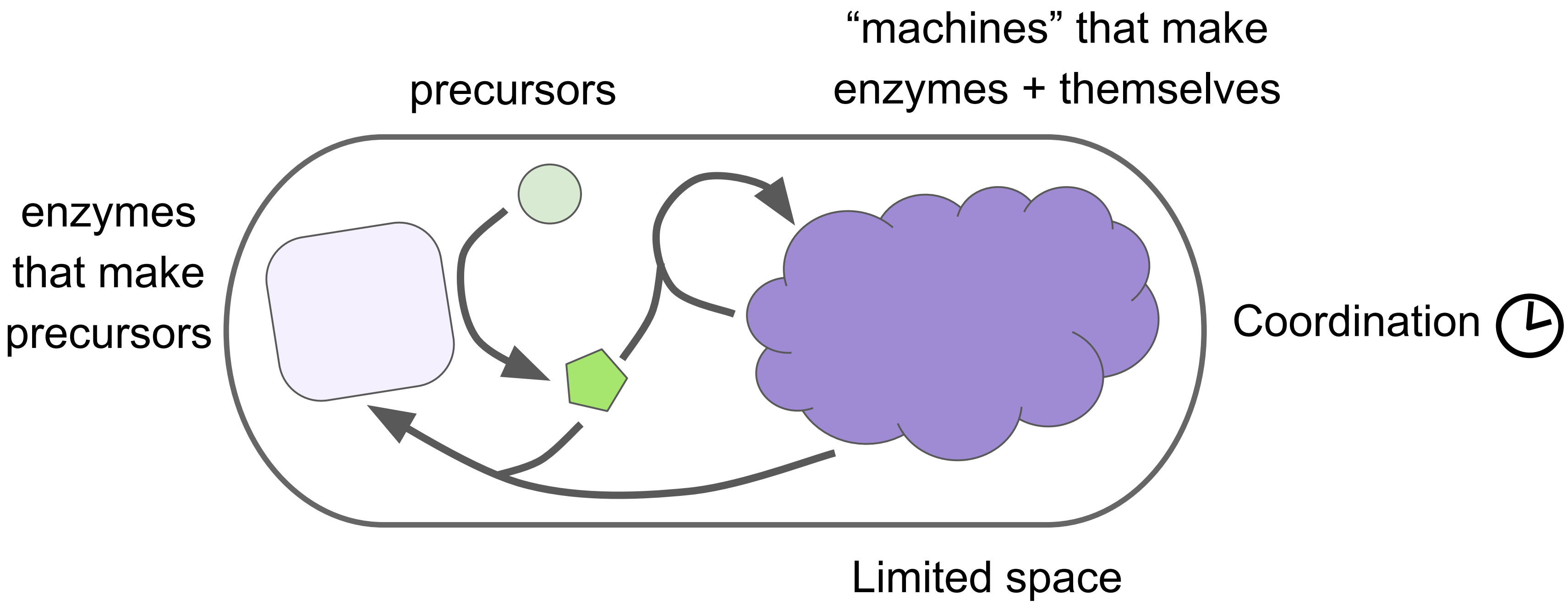
Too many molecules

Crowding – slow diffusion

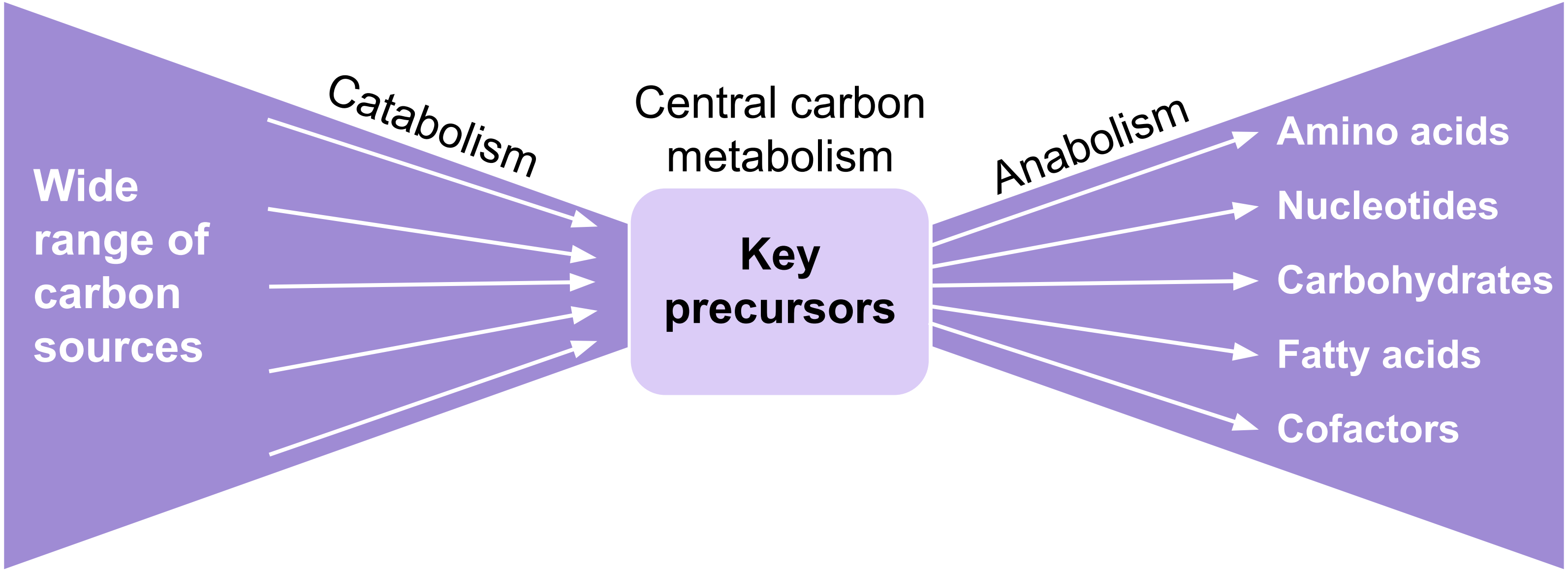


Macromolecule synthesis & resources needed

What does a cell need to grow?



Precursor synthesis – **bow-tie structure** of metabolism

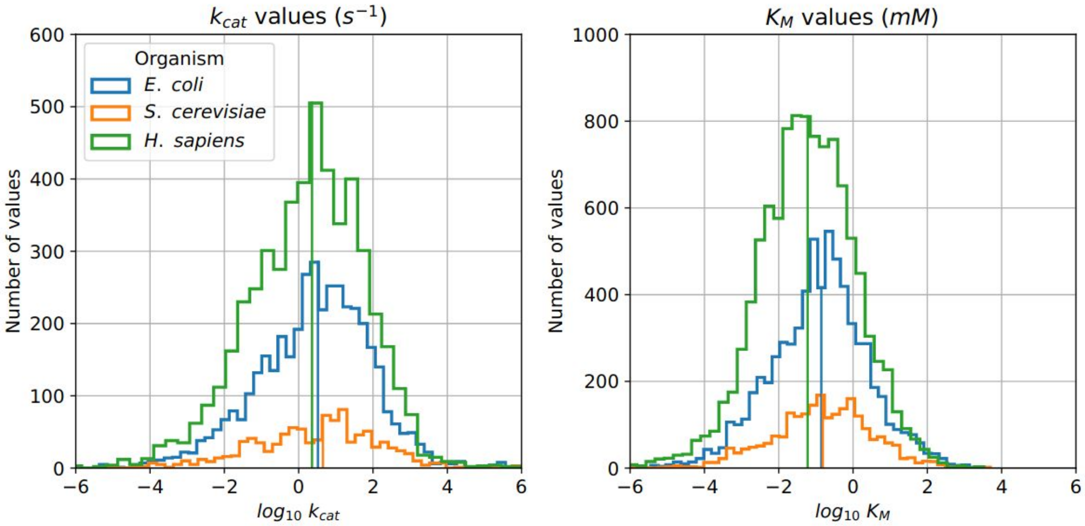


- Growth in various environments
- Many microbes grow on a minimal medium (single source of C, N, S, P)
- Synthesis of precursors competes for the same molecules

Metabolic enzymes – convert nutrients to precursors

main characteristics:

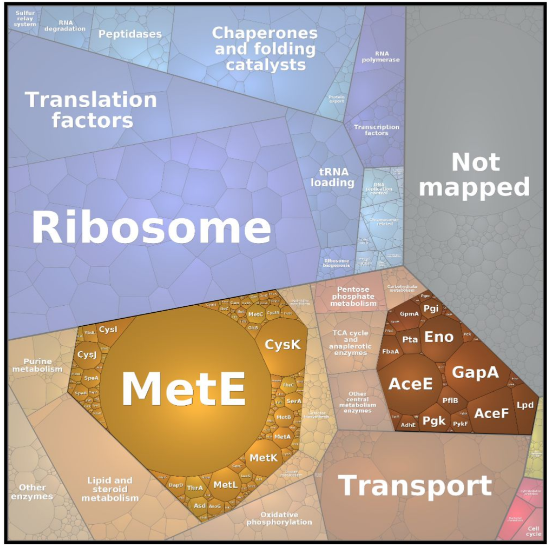
- k_{cat} – turnover number
- K_M – measure of affinity
- k_{cat}/K_M – kinetic efficiency



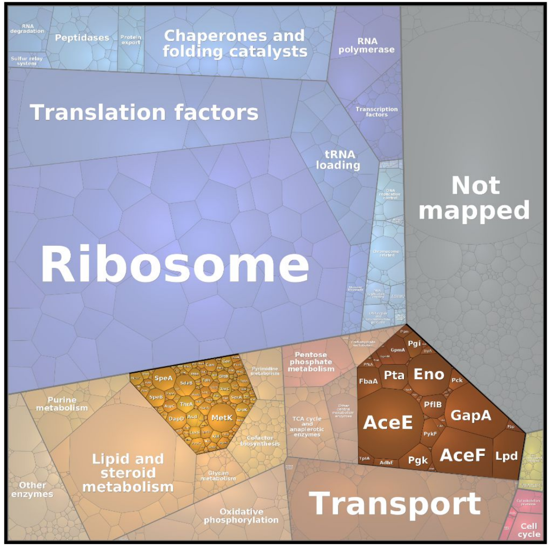
Values from BRENDA database

Different enzymes are needed in different environments

Methionine dropout



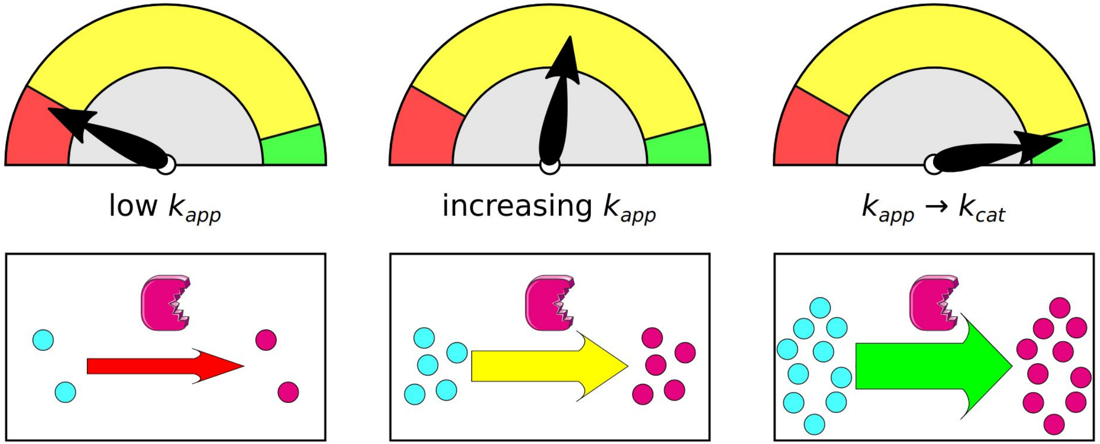
Complete medium



Pathway	Enzyme	Proteome mass fraction (%)		Turnover value k_{cat} (s^{-1})
		Met dropout	Complete	
Glycolysis	Enolase (Eno)	0.53	0.53	192.95
Amino acid biosynthesis	Methionine synthase (MetE)	7.45	0.009	0.12

Enzymes in living cells

- k_{cat} – highest possible efficacy when enzyme is **saturated**
- in cells – we observe **apparent turnover rate k_{app}**



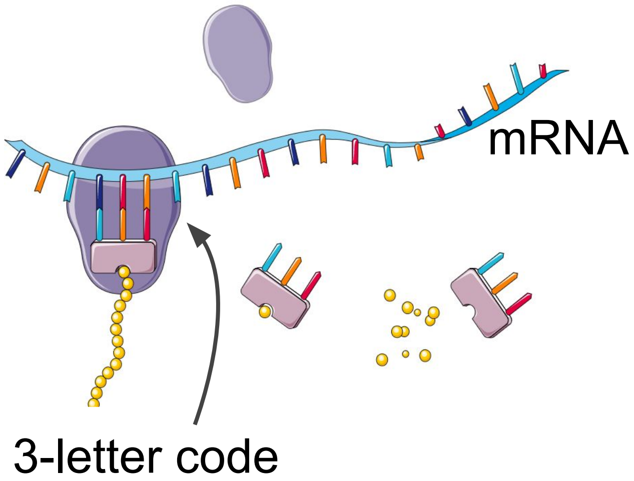
Macromolecule polymerisation

- catalyzed by DNA/RNA polymerases & ribosomes
- their synthesis – significant cost (precursors & energy)
  - average protein in *E. coli* ~ 33 kDa
  - RNA polymerase ~ 400 kDa
  - ribosome ~ 2300 kDa

Processes have to be coordinated

Transcription: *E. coli* 62 nt/s
S. cerevisiae 30 nt/s

Translation: *E. coli* 21 aa/s
S. cerevisiae 10 aa/s



Processes have to be coordinated

- synthesis of many subunits
- e.g. ribosome: 3-4 rRNA molecules and > 50 proteins
- ribosomal proteins – short, similar length

Cell

Quantifying Absolute Protein Synthesis Rates Reveals Principles Underlying Allocation of Cellular Resources

Gene-Wei Li,[1,2,3,*] David Burkhardt,[2,4] Carol Gross,[2,4,5] and Jonathan S. Weissman[1,2,3,*]

Ribosomes are optimized for autocatalytic production

Shlomi Reuveni, Måns Ehrenberg & Johan Paulsson

Nature **547**, 293–297 (2017) | Cite this article

autocatalytic production optimized?

On the Origin of Compositional Features of Ribosomes

Xinzhu Wei, Jianzhi Zhang

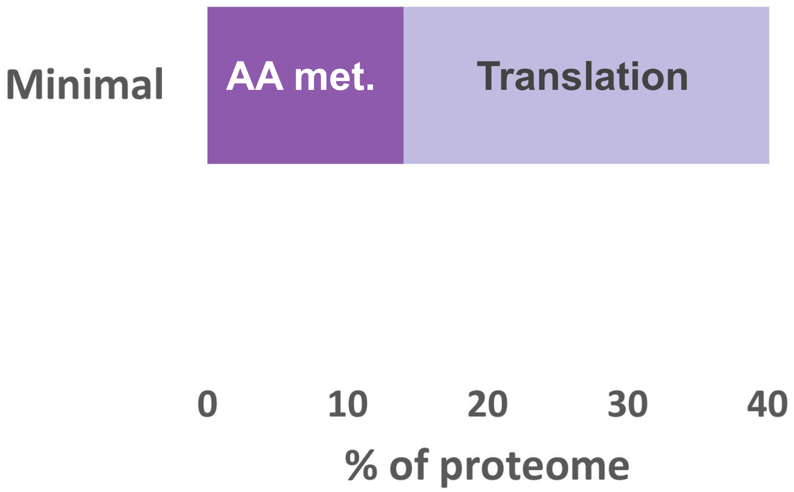
Genome Biology and Evolution, Volume 10, Issue 8, August 2018, Pages 2010–2016, https://doi.org/10.1093/gbe/evy169

Published: 30 July 2018 **Article history** ▾

cellular energy economics optimized?

Physical proteome space is limited

- cells have a finite volume
- most of dry mass – protein (around 50%)
- **optimal allocation** is necessary to achieve high growth rate



for instance, in yeast…

Björkeroth, Johan, et al. *Proceedings of the National Academy of Sciences* 117.35 (2020): 21804-21812.

Biomass composition in mathematical models

- models often focus on proteome
- different levels of detail

  total protein ➢ protein subgroups ➢ individual proteins

- **fixed** vs. **variable** biomass composition

Acknowledgements

Elad Noor

Ohad Golan

Samira van den Bogaard

Wolfram Liebermeister

Milo, R., & Phillips, R. (2015). *Cell biology by the numbers*. Garland Science.

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