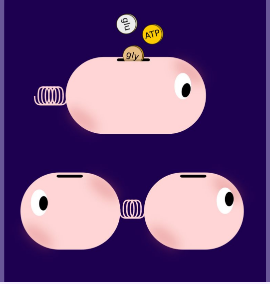
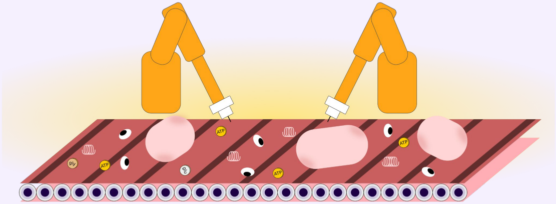
Economic Principles in Cell Physiology

Paris, July 4-6, 2022



What makes up a cell?

Diana Széliová & Pranas Grigaitis



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Cells as chemicals

99% of cell mass

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

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

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

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

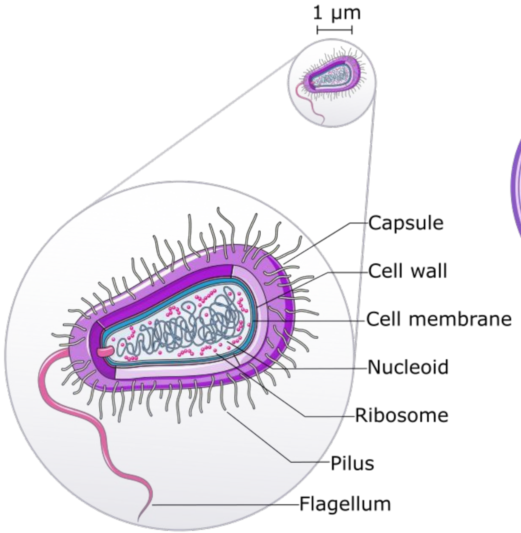
Cells as bags of things

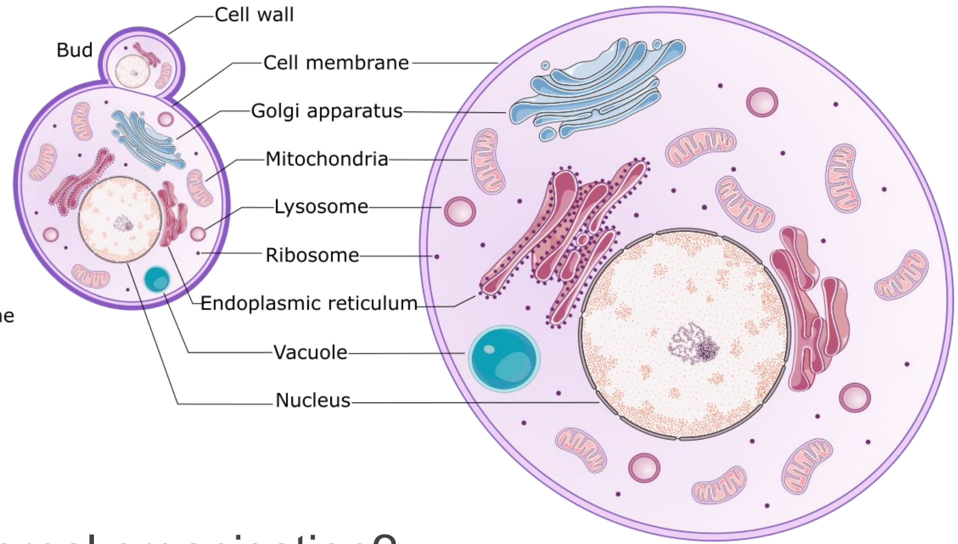
Prokaryotic

- bacteria, archaea
- do not have organelles

Eukaryotic

- yeast, plant, animal cells
- have organelles





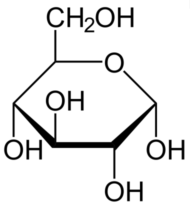
internal organisation?

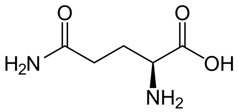
Biological molecules

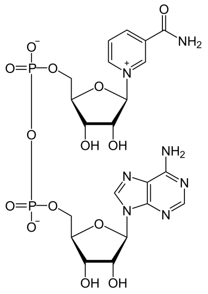
Biological molecules

Small molecules

- < 1000 Da
- mono-/dimers
- thousands of different compounds
- metabolites, cofactors
- various functions

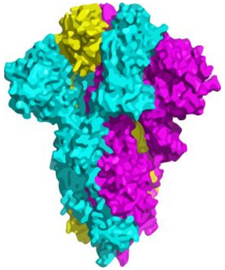




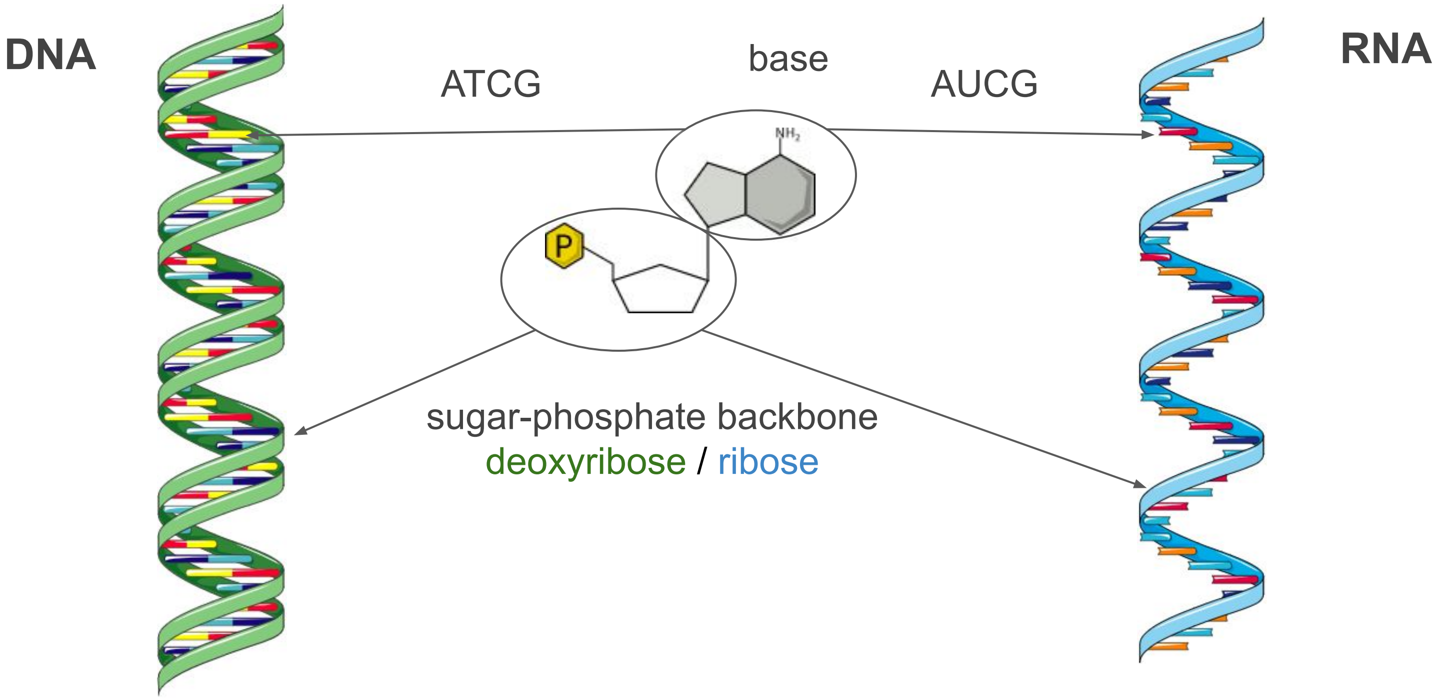


Macromolecules

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



Nucleic acids – polymers of nucleotides



Nucleic acids – functions

DNA

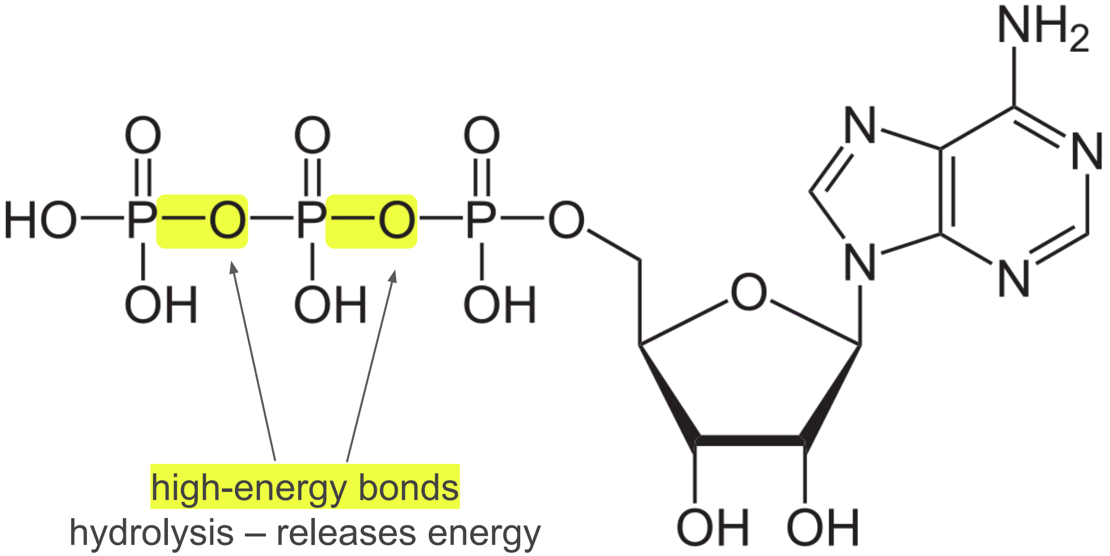
- stores genetic information
- all info to make a new cell

RNA

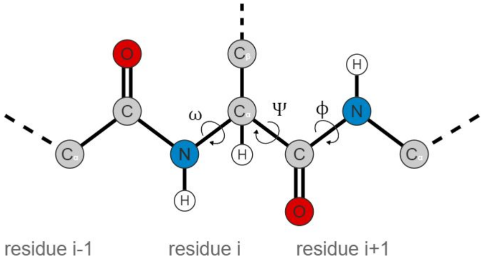
- transcribed from DNA (e.g. ATCG to UAGC)
- **rRNA** – synthesizes proteins
- **mRNA** – template for protein synthesis
- **tRNA** – brings AAs to the synthesis site
- small RNAs

Important nucleotide – ATP

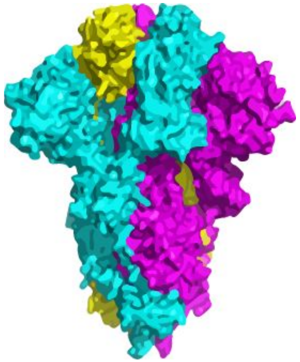
- energy currency
- powers processes in a cell



Proteins – polymers of amino acids

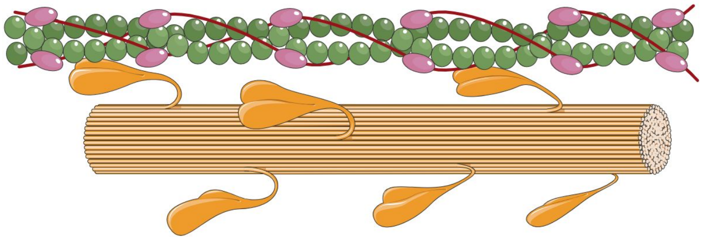


- 20 proteinogenic AAs
- 100 AA protein – 20^{100} combinations
- Poll: Is average protein length in bacteria < 1000 AAs?
- 325 AAs in E. coli
- AA chain folds into 3D structures
- can form multimers

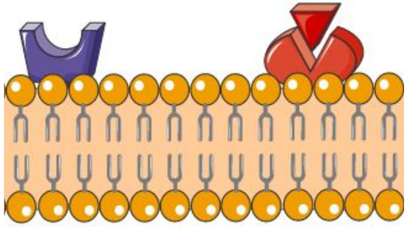


Protein functions

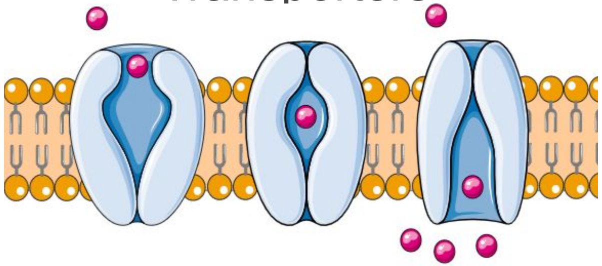
Structural proteins



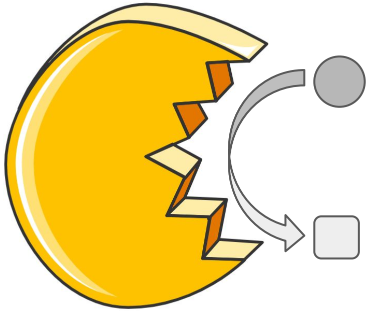
Receptors



Transporters



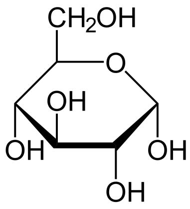
Enzymes



Carbohydrates

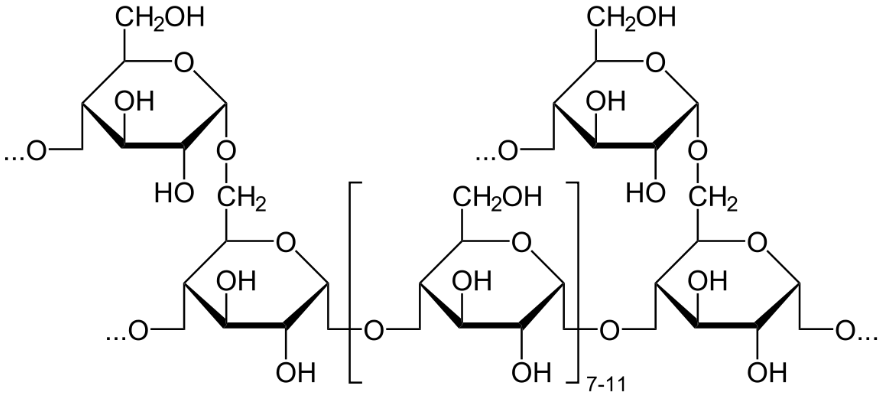
Monomers/dimers (e.g. glucose)

- carbon & energy source



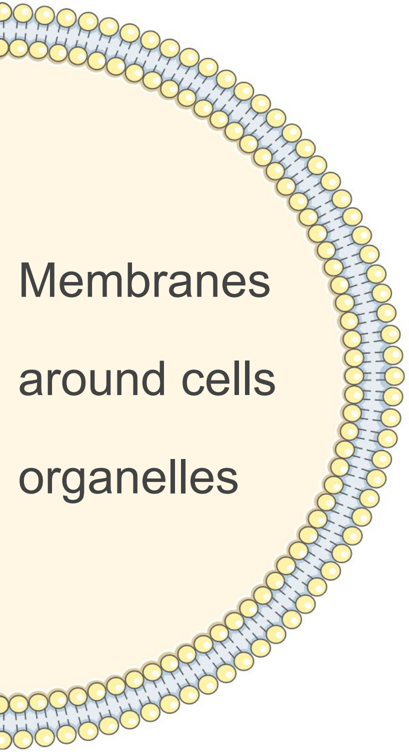
Polymers

- storage – glycogen, starch
- structure – mannan, part of peptidoglycan



Lipids – diverse hydrophobic compounds

Bilayer membranes

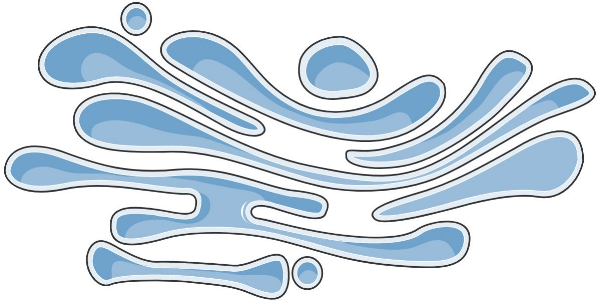


Membranes

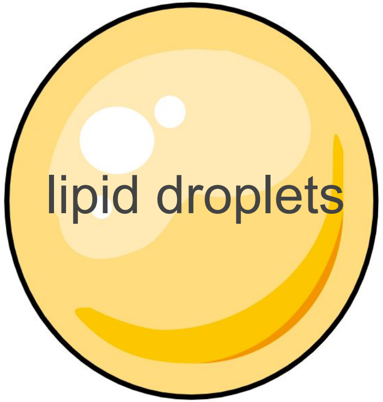
around cells

organelles

Golgi, ER – protein synthesis & processing



Storage

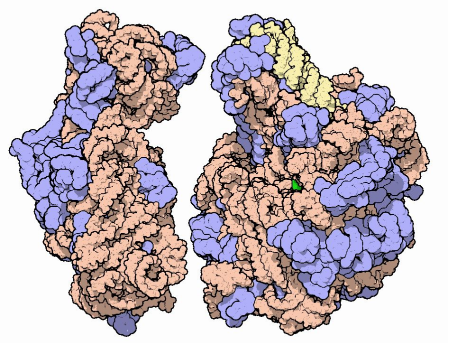


lipid droplets

Biological machines – huge complexes of macromolecules

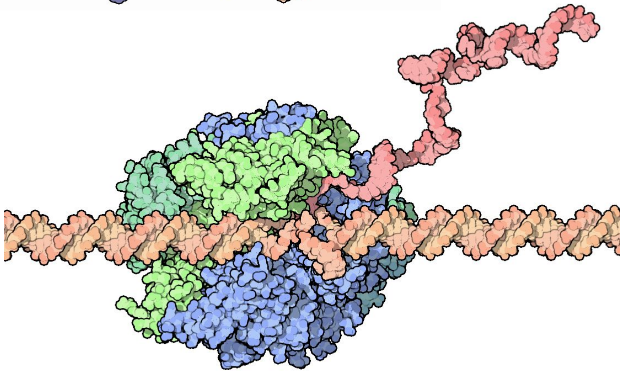
Ribosome

- complex of rRNA + proteins
- makes proteins



DNA, RNA polymerases

- protein complexes
- synthesis of DNA and RNA

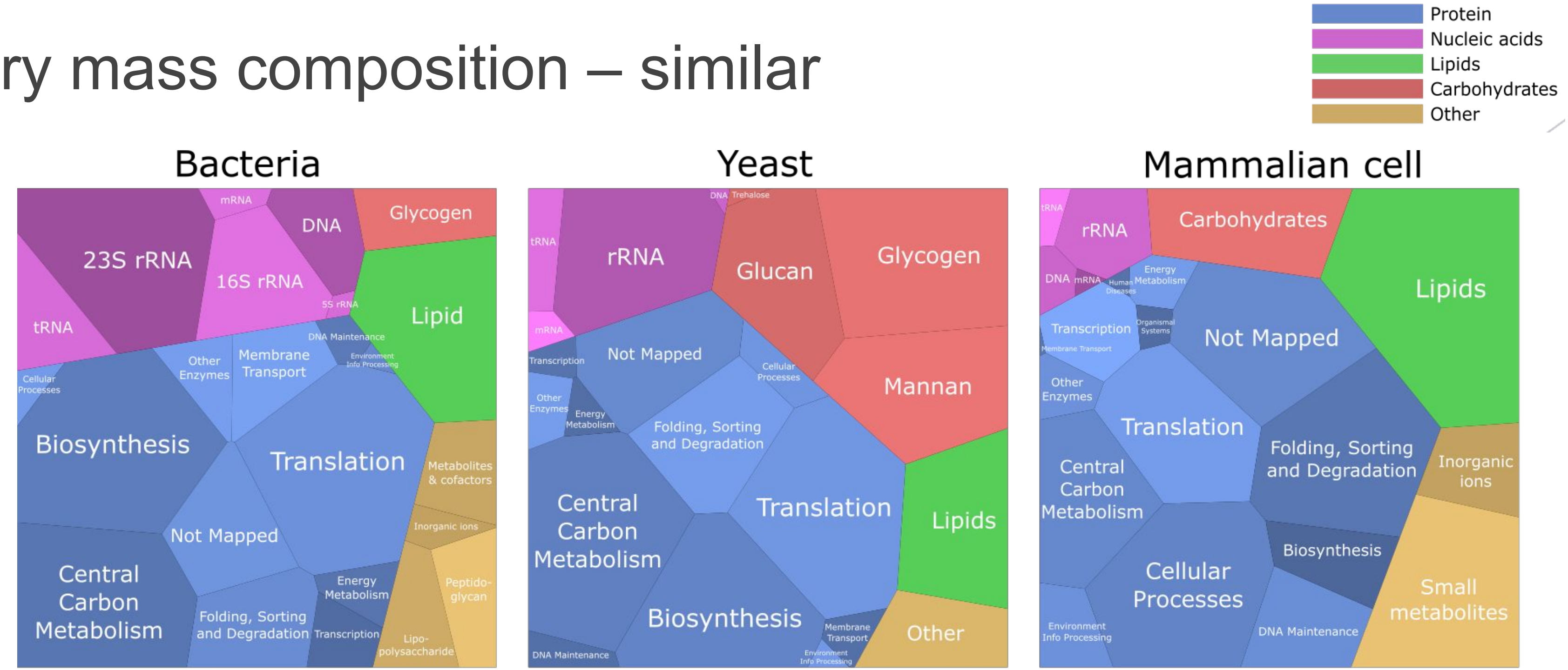


PDB-101: Educational resources supporting molecular explorations through biology and medicine. Christine Zardecki, Shuchismita Dutta, David S. Goodsell, Robert Lowe, Maria Voigt, Stephen K. Burley. (2022) *Protein Science* **31**: 129-140 doi:10.1002/pro.4200

Amounts of cell components

Cells: 70% water, 30% dry mass

Dry mass composition – similar



- engineered yeast cells – up to 80% lipids

Amounts have to be expressed in relation to other quantities

Units:

- number
- mol
- gram

Per:

- cell
- volume
- dry mass
- surface area

Poll:

How many proteins are there in E. coli cell?

Raise your hand if you think > 10^6

Exercise

How many proteins are there per µm^3?

- Protein mass per volume: 0.2 g/ml
- Molecular mass of a protein: 30000 g/mol
- Avogadro number: 6×10^{23} 1/mol
- 1 mL = 10^{12} µm^3

$$\frac{0.2\frac{g}{mL} * 6 * 10^{23}\frac{1}{mol}}{30000\frac{g}{mol}} = 4 * 10^{18}\frac{1}{mL}$$

$$4 * 10^{18}\frac{1}{mL} * 10^{-12}\frac{mL}{\mu m^3} = 4 * 10^{6}\frac{1}{\mu m^3}$$

How many proteins are there per cell?

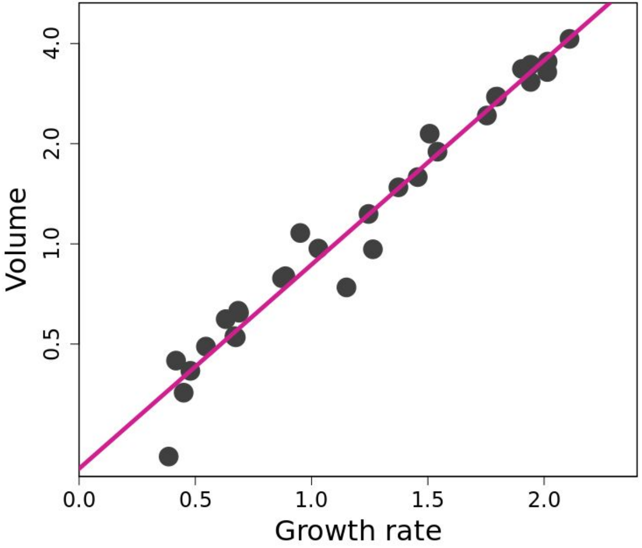
- Cell volumes:
  - E. coli: 1 µm^3 → $4*10^6$
  - S. cerevisiae: 60 µm^3 → $2*10^8$
  - Mammalian cell: 3000 µm^3 → $1*10^{10}$

http://book.bionumbers.org/how-many-proteins-are-in-a-cell/

Variability of cell composition

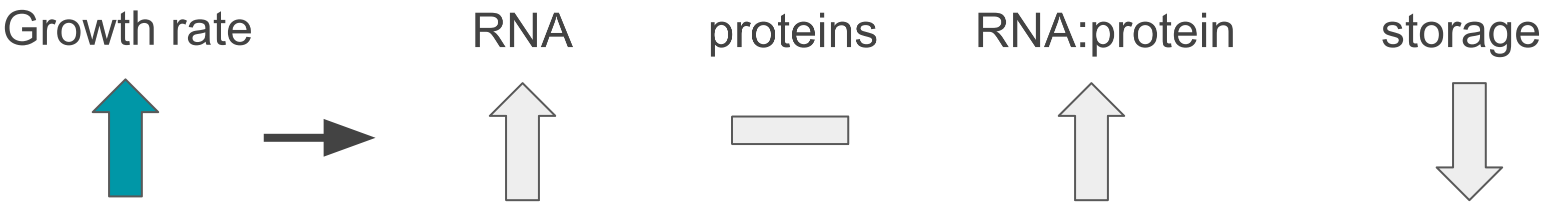
Biomass component amounts change with growth rate

Nutrient growth law
(Schaechter 1958)



- Cell size, **absolute** DNA, RNA, protein content increase with growth rate
- Bacterial/yeast/mammalian cells
- Holds when growth rate modulated by carbon source (not temperature)

Relative composition changes with increasing growth rate



Cells reallocate resources to support higher growth rate

RNA & RNA:protein ratio

- measure of proteosynthetic capacity
- most RNA – involved in protein synthesis

Higher growth rate → more protein synthesis → more ribosomes

Ribosome – ⅔ rRNA, ⅓ protein

More tRNA

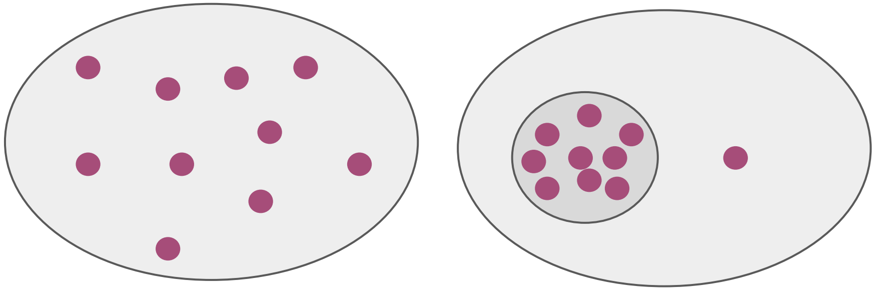
Other factors that change composition but not growth and vice versa

- O_2 concentration
- Medium composition
- Mutations
- Temperature

- AA composition - constant in various conditions (bacteria, yeast, mammals)

Composition is not uniform throughout a cell

- different concentrations in different organelles/areas
- transport – regulated
- different pH, membrane potential
- consequence – different enzyme rates, direction

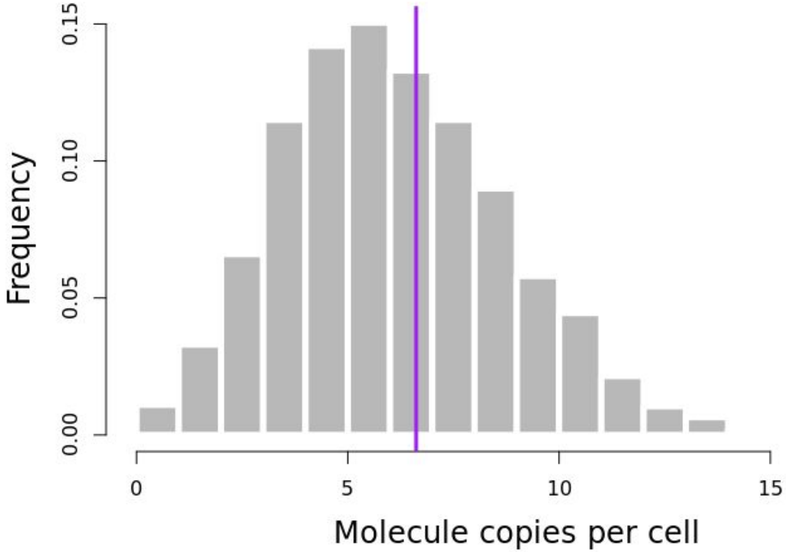


same number of molecules

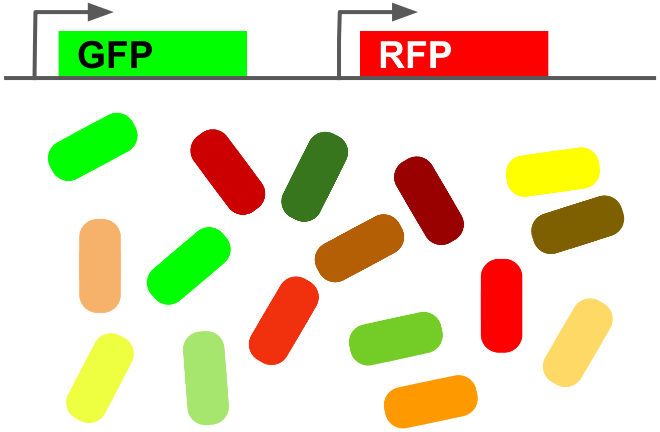
different concentration

Populations are not uniform

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



same genome



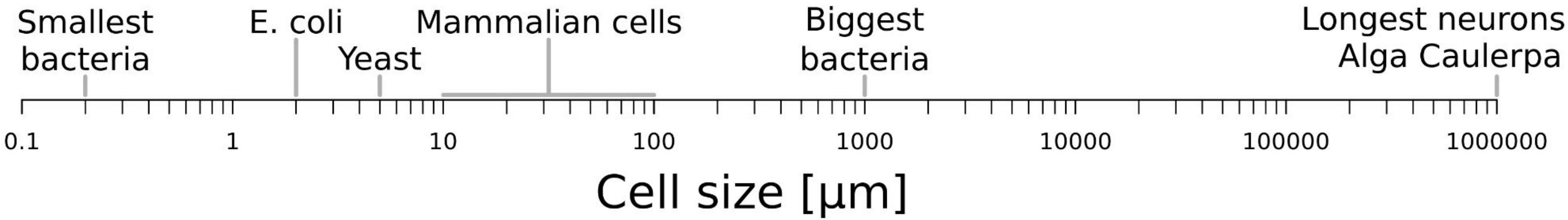
different phenotype

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 (nutrient growth law)
- conditions
- cell cycle

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

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 – constant at different growth rates, during cell cycle
- others – changes during cell cycle, in stationary phase
- 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
- **perfect enzymes** – specific and fast – limited only by diffusion (rare)
- no known enzymes above the diffusion limit

Macromolecular crowding

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

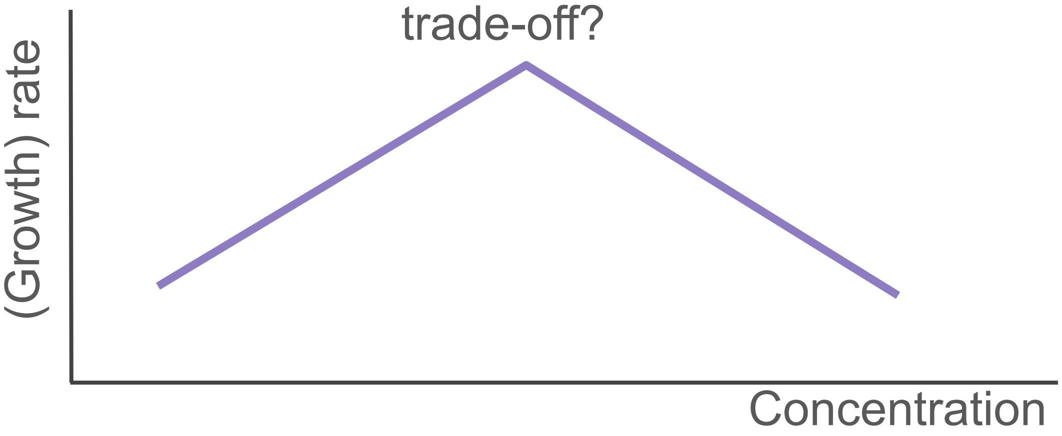
Is there an optimal density?

Too few molecules

Collisions rare

Too many molecules

Crowding – slow diffusion



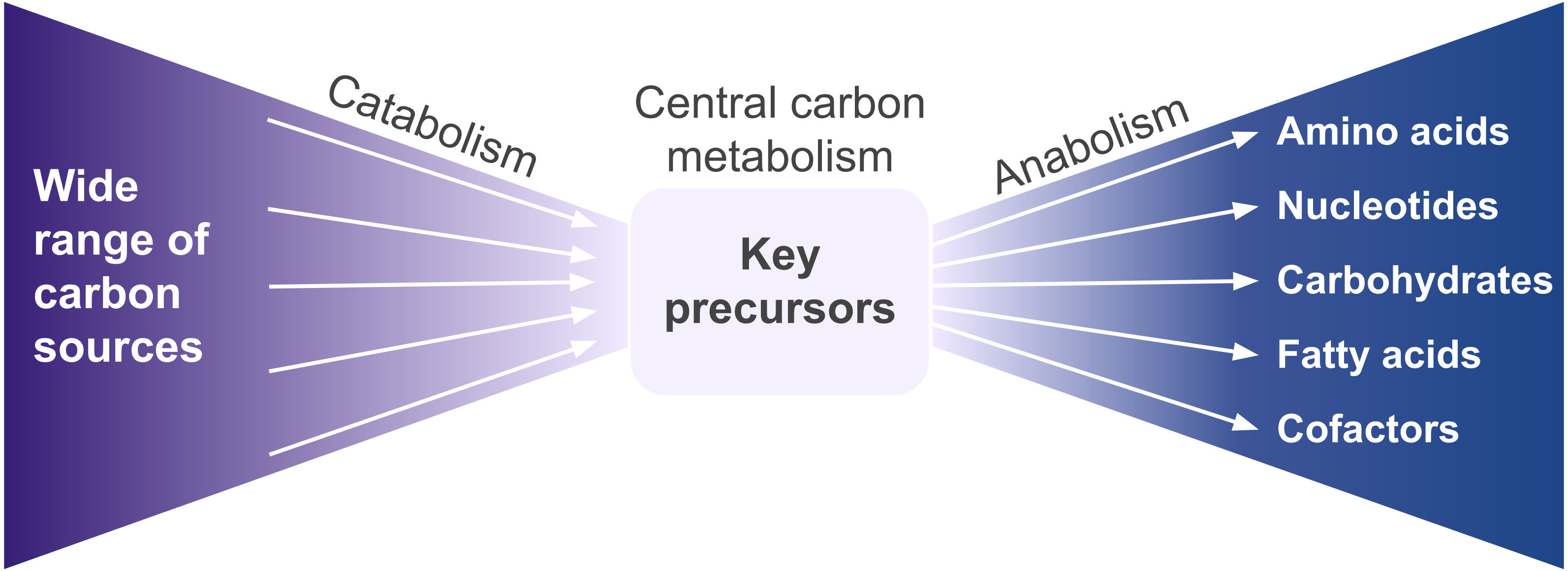
Macromolecule synthesis & needed resources

What does a cell need to grow?

- precursors
- enzymes that catalyze precursor synthesis
- “machines” that synthesize enzymes + themselves

- Processes have to be coordinated
- There needs to be physical space/volume

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



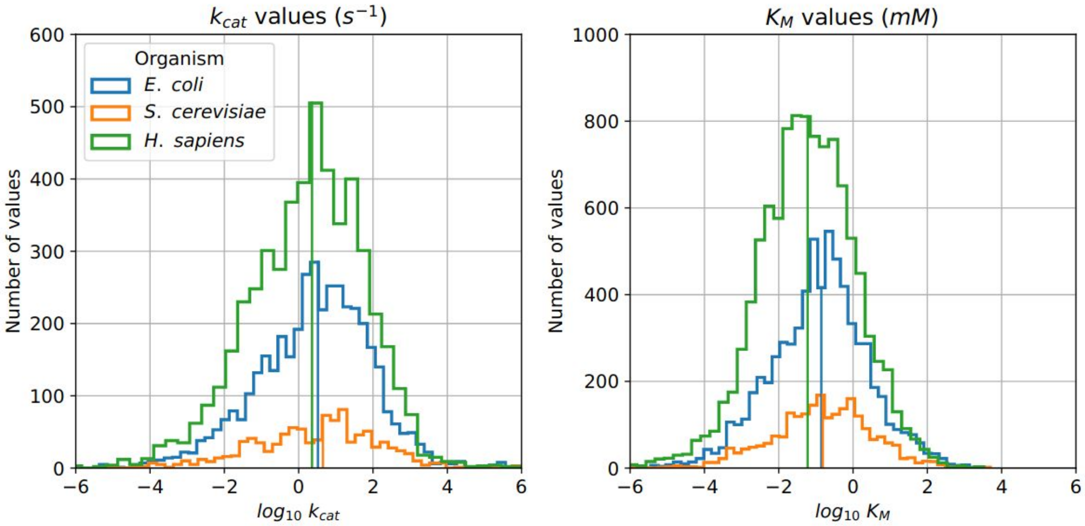
- Allows growth in various environments
- Many microorganisms grow on a minimal medium (Single source of C, N, S, P)
- Synthesis of macromolecule precursors competes for the same molecules

Metabolic enzymes – convert nutrients to precursors

wide variety of sizes and functions

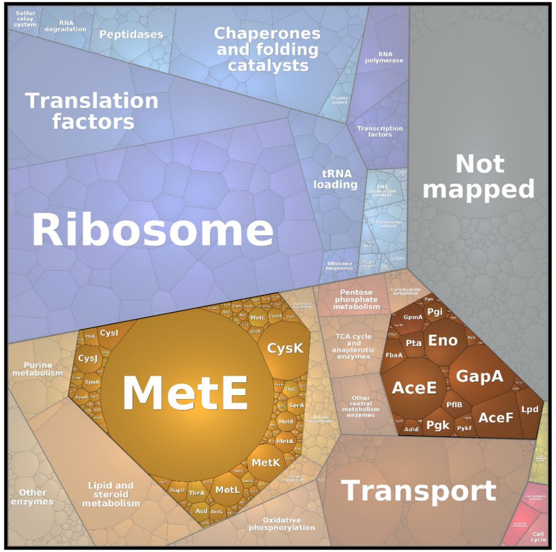
main characteristics:

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

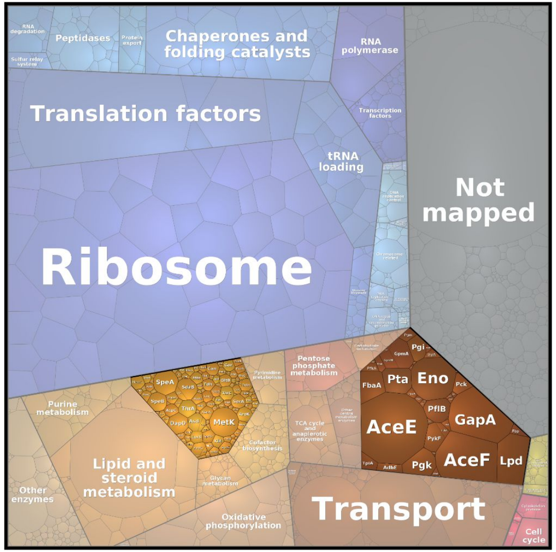


Different enzymes are needed in different environments

Methionine dropout



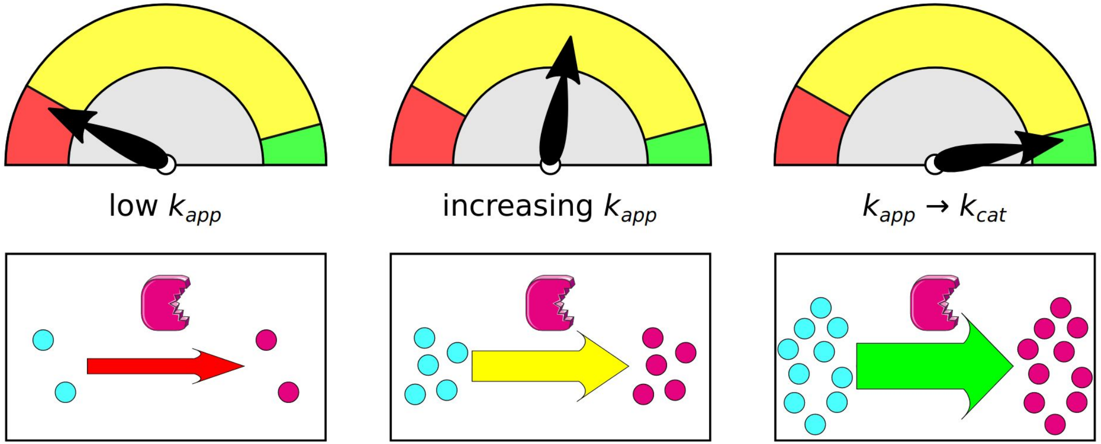
Complete medium



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}**
- enzyme efficiency – k_{app}/k_{cat}



Macromolecule polymerisation

catalyzed by large complexes – DNA/RNA polymerases & ribosomes

Ribosomes:

- synthesis of metabolic enzymes & other proteins
- their own synthesis – significant cost (precursors & energy)
- average protein in E. coli ~ 33 kDa vs. ribosome 2300 kDa

Processes have to be coordinated

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

Ribosomes are optimized for autocatalytic production

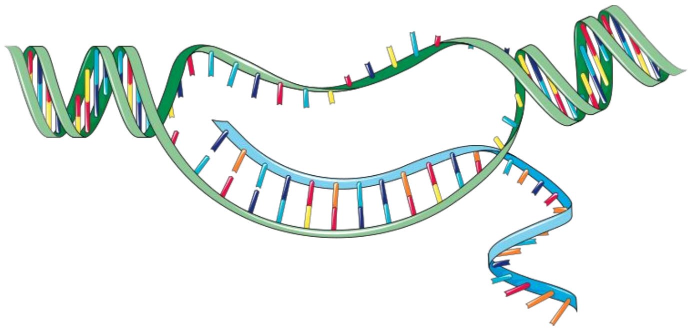
Shlomi Reuveni, Måns Ehrenberg & Johan Paulsson

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

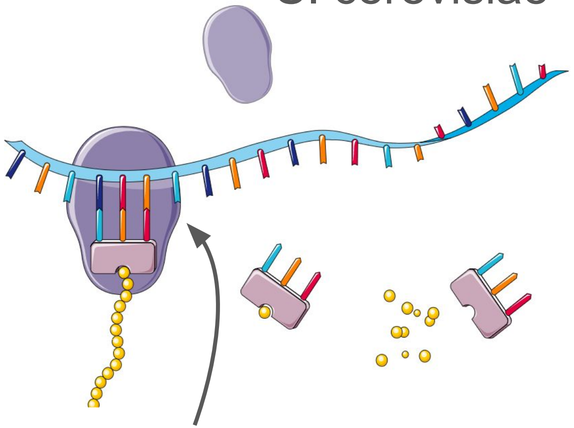
Processes have to be coordinated

- transcription & translation

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



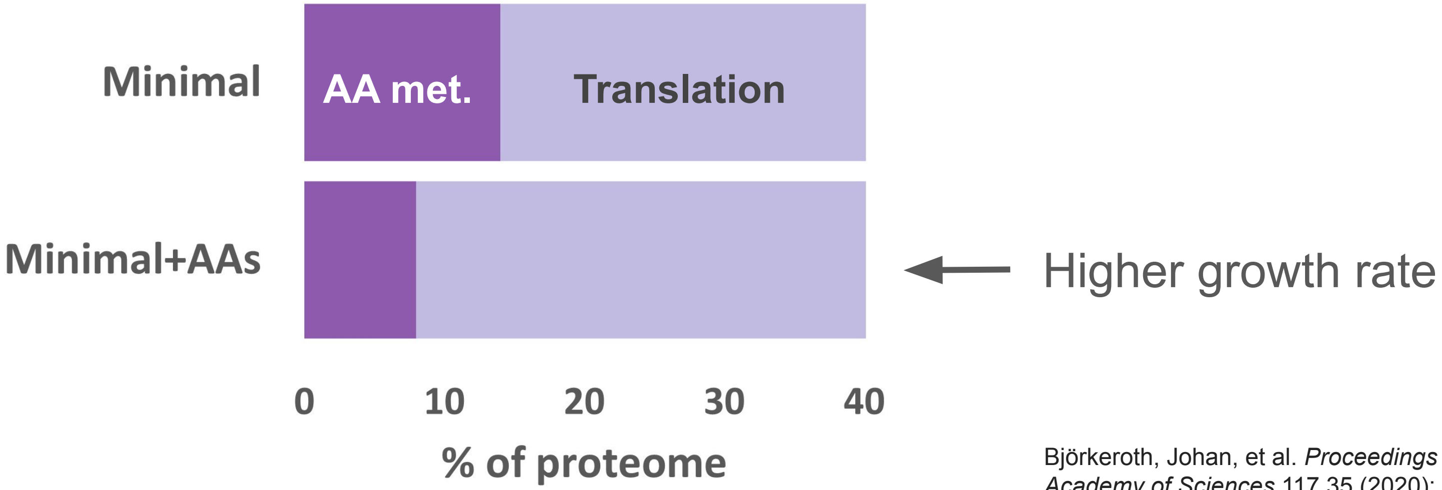
Translation: E. coli 21 aa/s
S. cerevisiae 10 aa/s



3-letter code

Physical proteome space is limited

- cells have a finite volume
- most of dry mass – protein (ribosomal proteins, metabolic enzymes)
- **optimal allocation** is necessary to achieve high growth rate



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

Acknowledgement

Pranas Grigaitis

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Elad Noor

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Thank you for your attention!