Introduction

class – 2 (07.08.24)

LS2103 (Autumn 2024)

IISER Kolkata

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General Information:

1. **Approx. 28 classes, with 8 to10 tutorial sessions**
2. **(-3) marks for not maintaining minimum 80% attendance**
3. **Evaluation:**
   - Internal assessment: Surprise class tests (best 4 out of 5): 20 marks
   - Mid-semester exam: 30 - 35 marks
   - End-semester: 45 - 50 marks
4. **Study Material:**
   - Lectures notes, extra material (to be shared)
   - Philip C. Nelson: *Biological Physics*
   - Phillips, Kondev, Theriot, Garcia: *Physical Biology of the Cell*

What is Biophysics?

Biology – The study of inception, sustenance and the evolution of life, in the context of the environment.

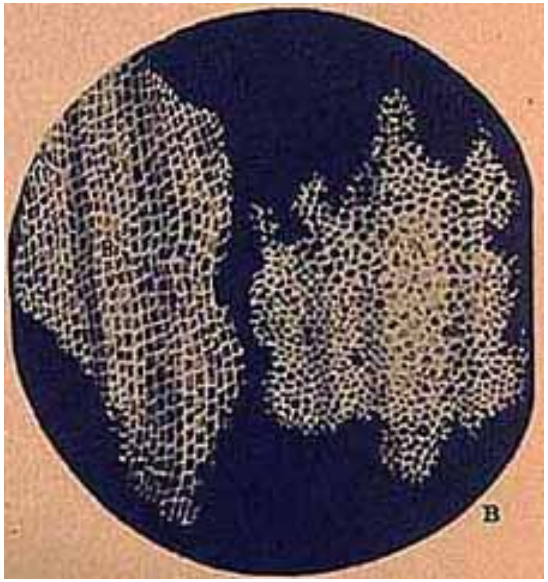
- Mechanistic understanding
- Bridge time, length scales
- Quantitative estimates
- Build falsifiable models, predictions

- Phenomenological problems
- Test physical hypotheses
- Make measurements
- Develop novel protocols

Physics – The study of matter and interactions: force, energy, charge, radiation, etc.

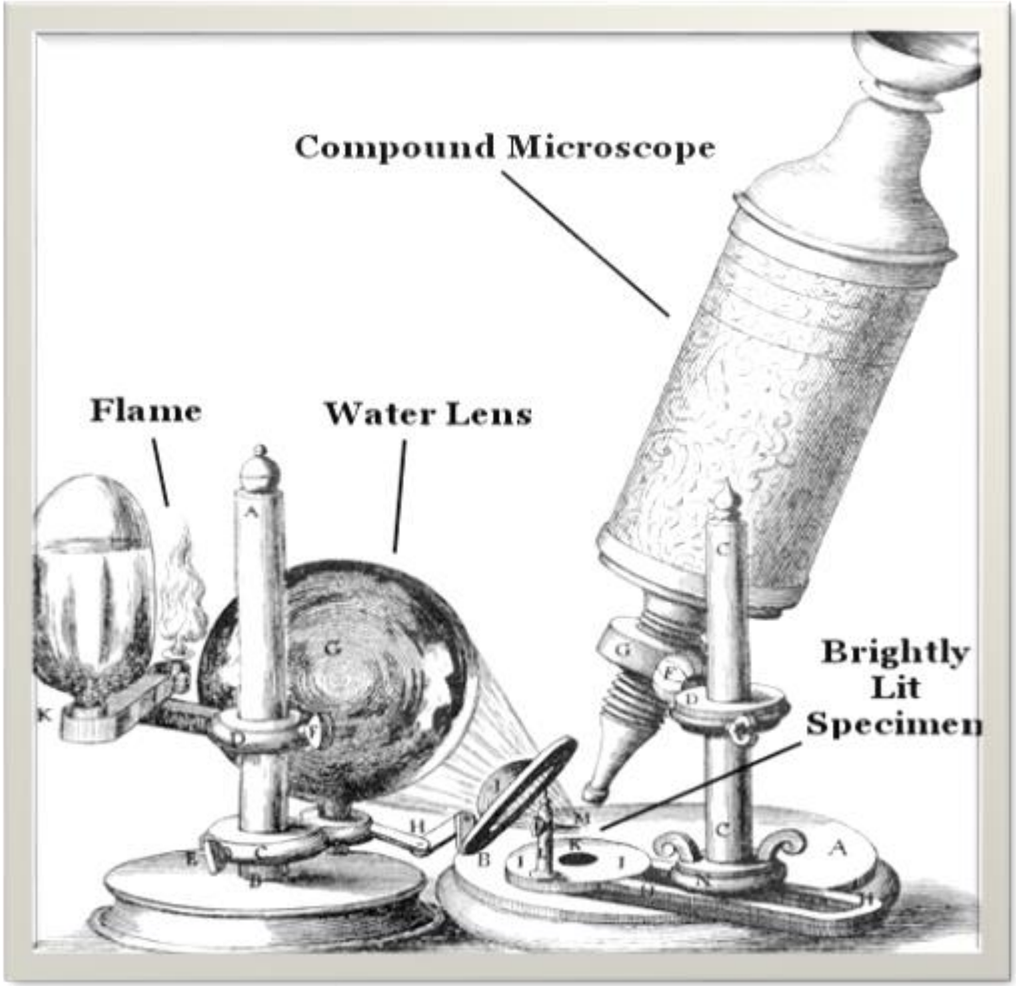
Early Biophysicists

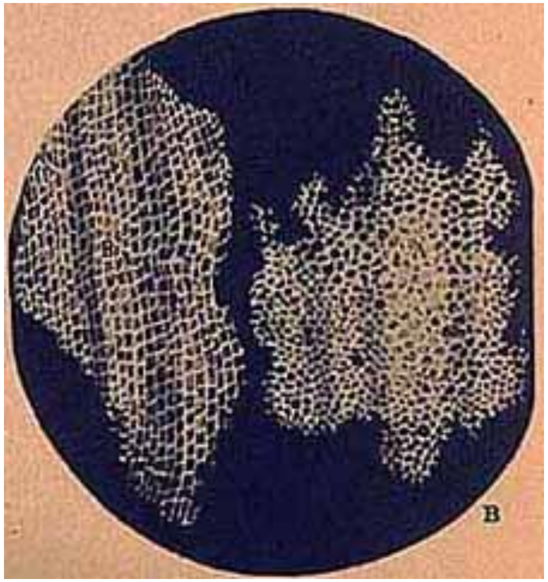
Robert Hooke
(1635 - 1703)



- Discrete "empty" compartments in thin cork layer
- Named them "cells"
  (analogous to dorm rooms in monasteries)
- No apparent connection to life
- Conclusion: spontaneous generation from 'natural' or 'artificial' heat!

Early Biophysicists





(in *Micrographia*, ca. 1665)
50x magnification

Early Biophysicists

Antonie van Leeuwenhoek
(1632 - 1723)

bacteria

Ciliophora

Foraminifera

- Teeming with movement, seemed "alive"!
- Named them "animalcules"
- Wrote series of letters to Royal Society, London
- Hooke asked to verify his observations
- Eventually sets **Cell Theory** in motion

Early Biophysicists

Simple microscope (single lens)
300X magnification

bacteria

Ciliophora

Foraminifera

- Teeming with movement, seemed "alive"!
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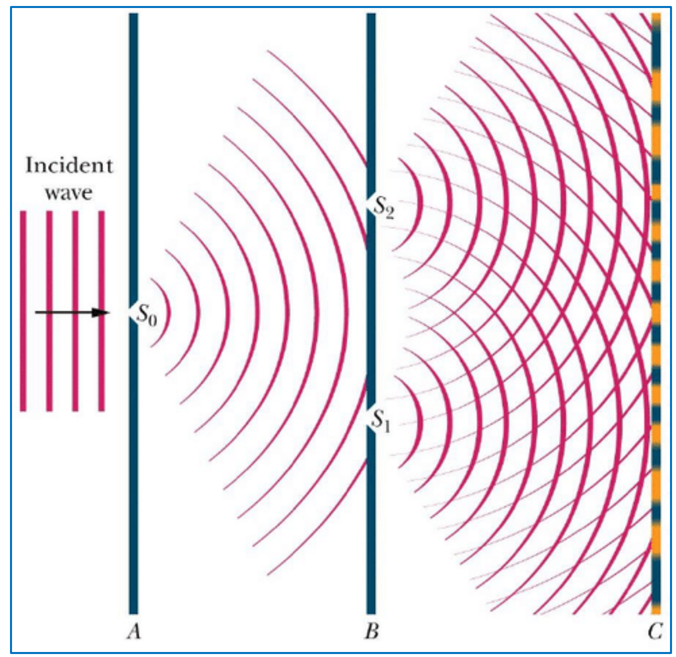
Early Biophysicists

Thomas Young (1773 - 1829)
physician and physicist

Primary interest was in **sense perception**:

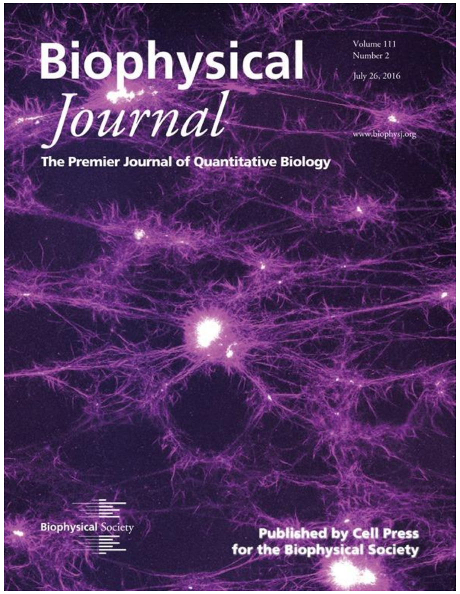
Discovered how the lens of the eye changes shape to focus on objects at differing distances.

Double-slit experiment: Wave nature of light

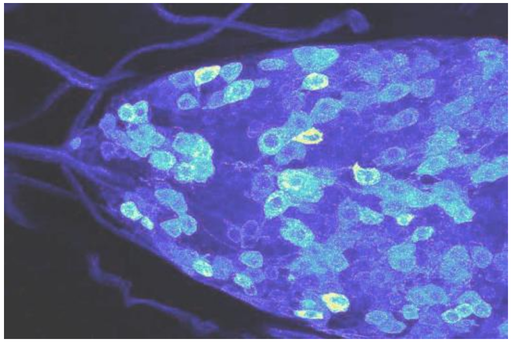


https://www.britannica.com/biography/Thomas-Young#ref35107

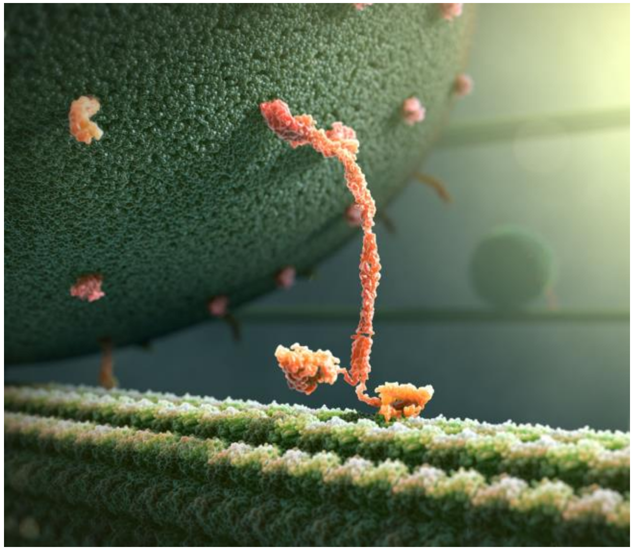
2016, volume 111(2)



Drosophila-neuron image

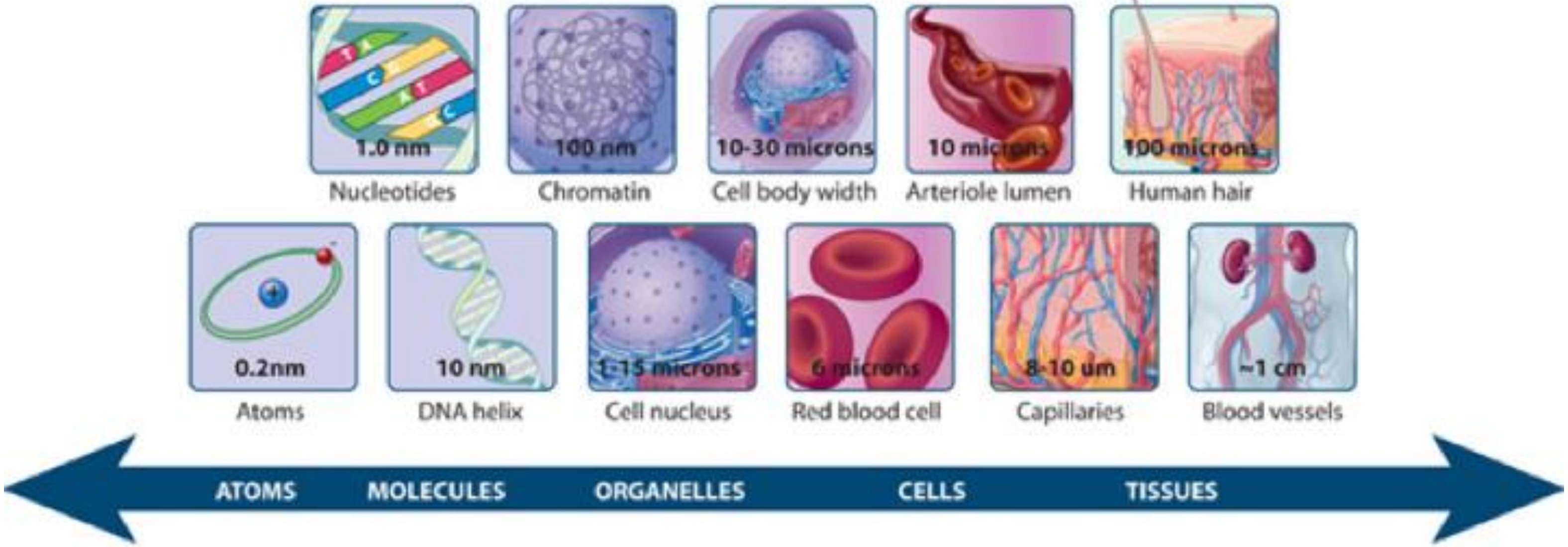


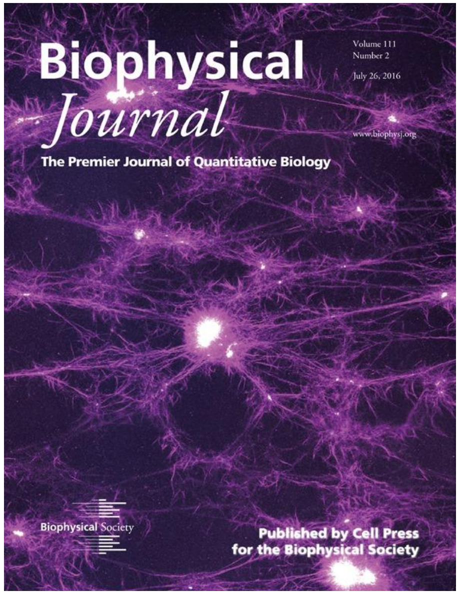
Kinesin 'walking' on microtubule



Biophysics

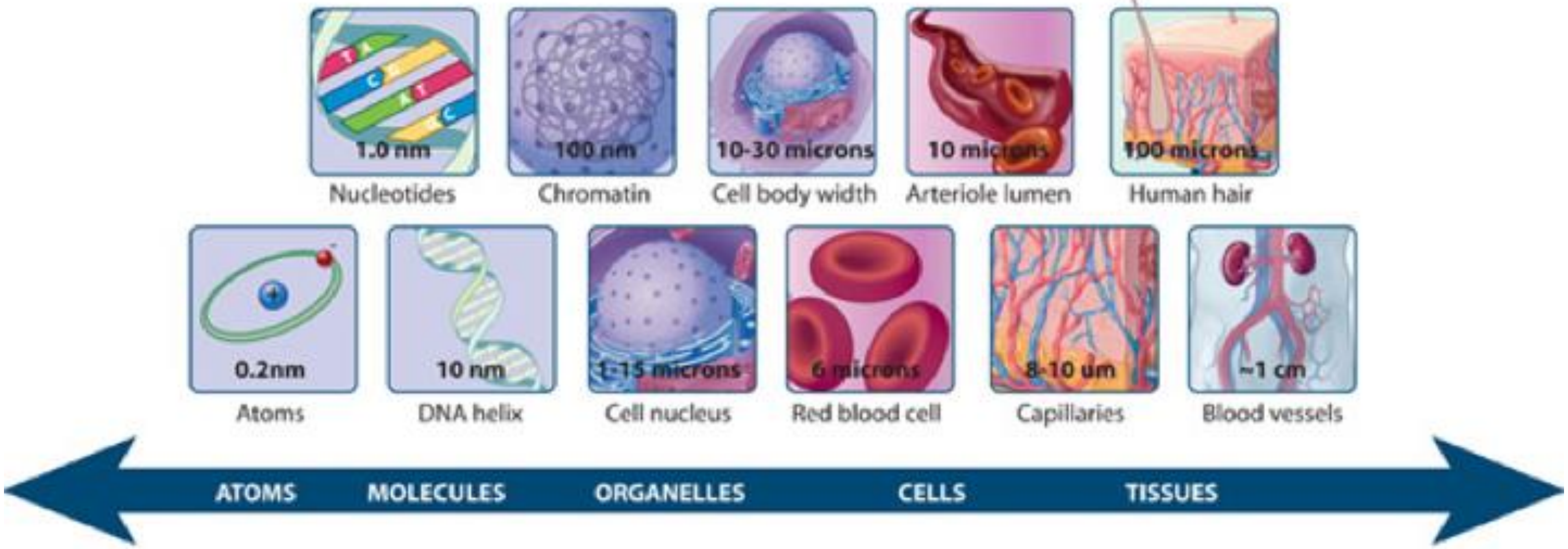
covers biology on wide *length* and *time* scales





- Contractile cytoskeletal network spontaneously formed in mixture of microtubule (*magenta*) and kinesin-5 (*cyan*).
- The network is composed of kinesin-accumulated nodes and bundled microtubule links.

covers biology on wide *length* and *time* scales



Biophysics

Energy processes underlie biology

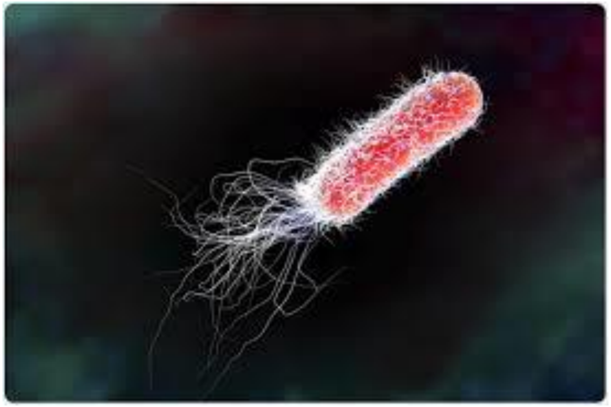


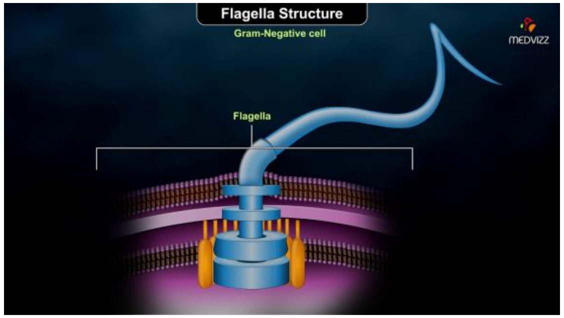
Life forms must continually transduce energy



Bio ⟷ physics

Flow can be turbulent or laminar (in water) depending on the magnitude of forces





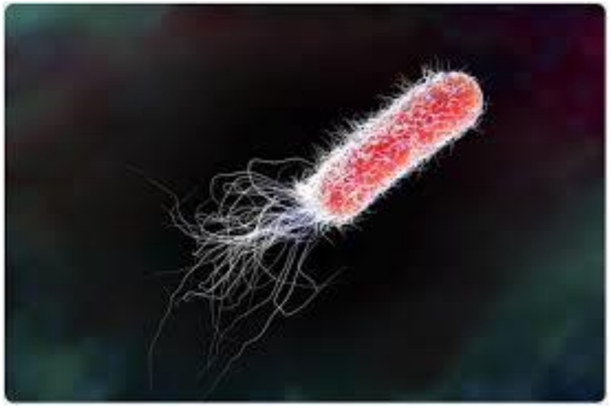
Inner structure converts chemical energy to mechanical energy

Biophysics

What are the scales of energy involved?

Force ~ Newtons

Force ~ picoNewton - nanoNewton



Biophysics

Neutrophil chasing bacteria in the midst of red blood cells (ca. 1950)

https://www.youtube.com/watch?v=5yimbhkTqJo

Can one make a (rough) estimate of the order of magnitudes of forces and energy?

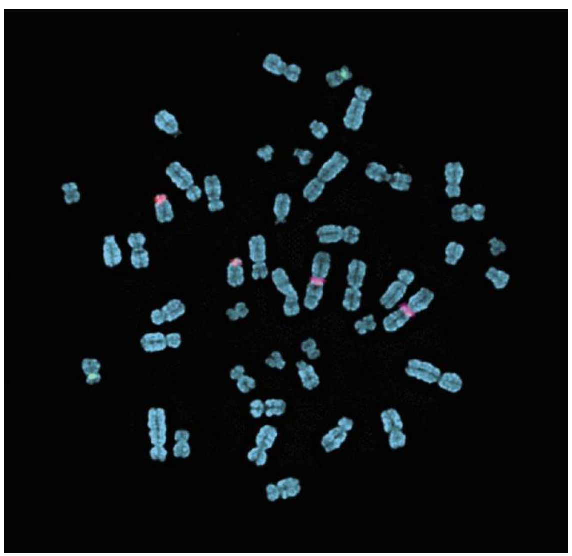
Molecular Basis of Heredity

But what did DNA look like?

"Genetics" was coined in **1905** (by William Bateson), followed by the term "gene" in **1909** (by Wilhelm Johanssen)

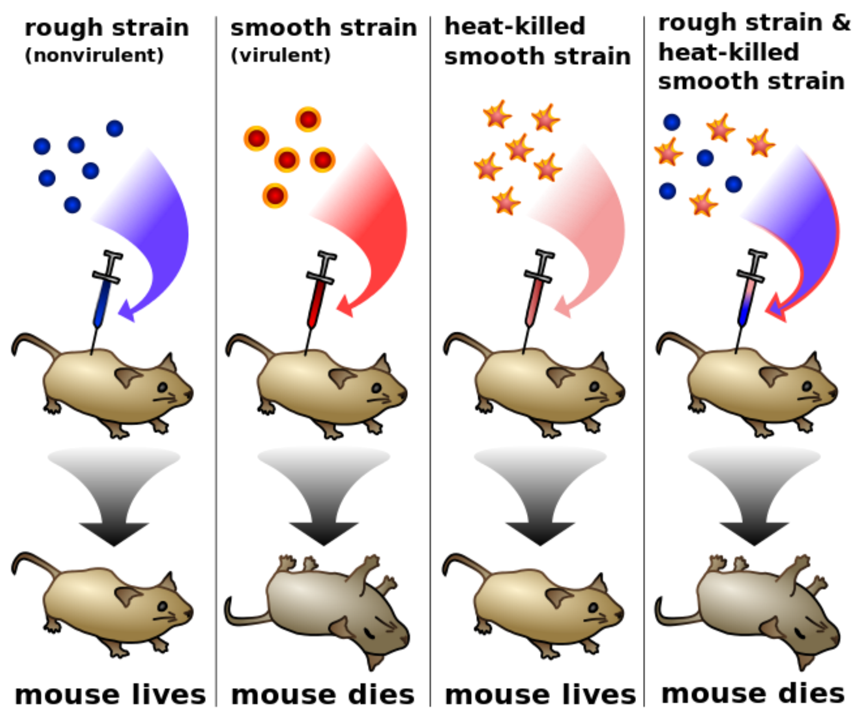
1911:
Thomas Morgan, Alfred Sturtevant

"Genes are arranged on chromosomes"
= protein + nucleic acids



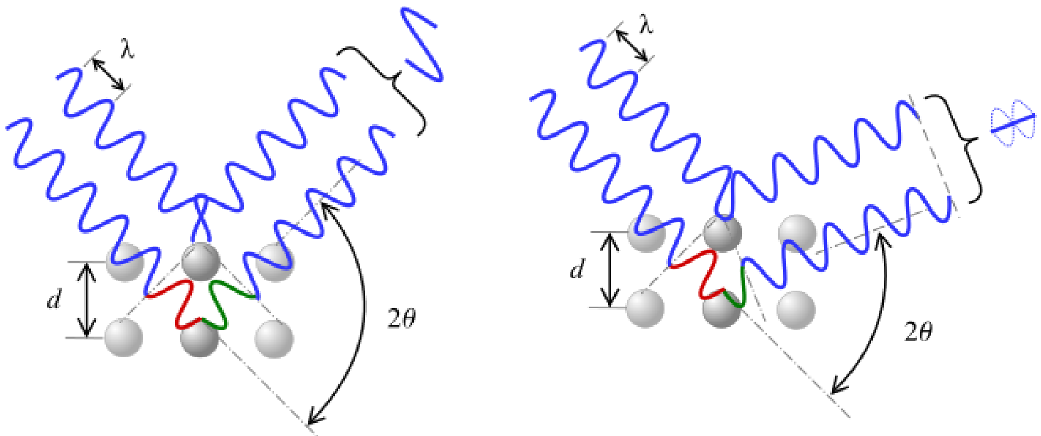
1928:
Frederick Griffith:

DNA could activate pneumococcus bacteria



Molecular Basis of Heredity

The double helix structure

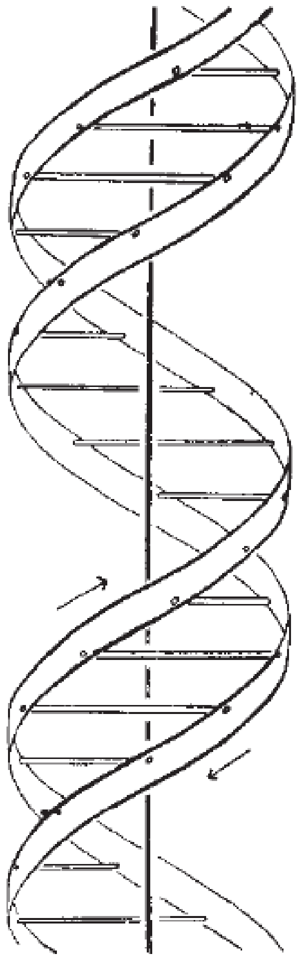


Bragg's Law: $2d\ (\sin\theta) = n\lambda$

Rosalind Franklin
(1920 - 1958)

Molecular Basis of Heredity

The double helix structure



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

No. 4356 April 25, 1953 NATURE

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

[1] Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).

[2] Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).

[3] Von Arx, W. S., Woods Hole Papers in Phys. Oceanog. Meteor., **11** (3) (1950).

[4] Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made

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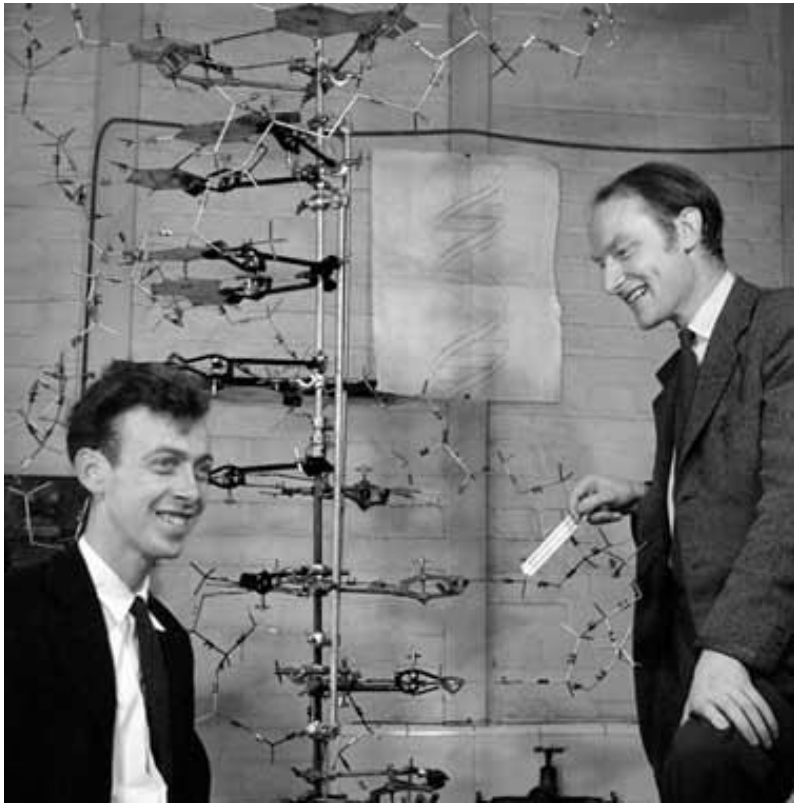
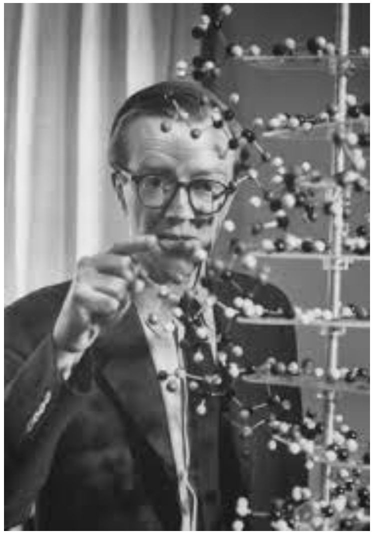
Molecular Basis of Heredity

The double helix structure





Maurice Wilkins
(1916 - 2004)

Rosalind Franklin
(1920 - 1958)

James Watson
(1928-)

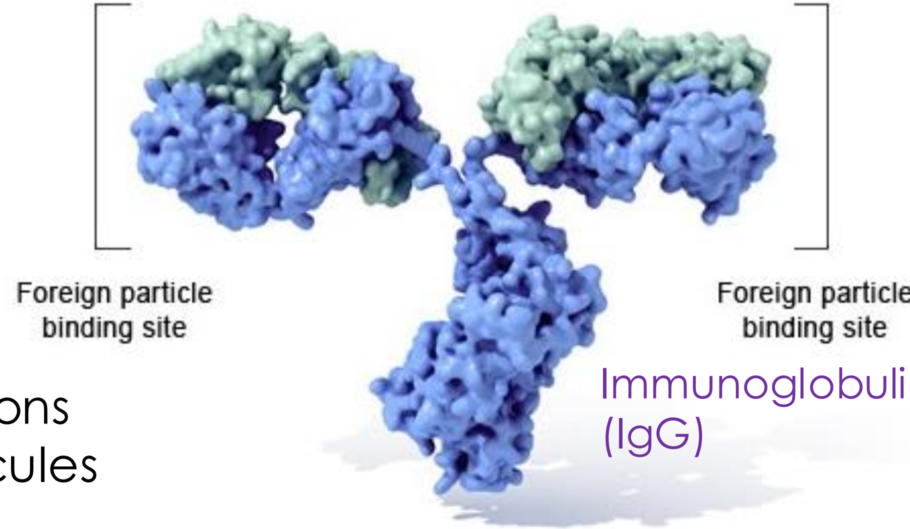
Francis Crick
(1916–2004)

DNA as units of genetic information

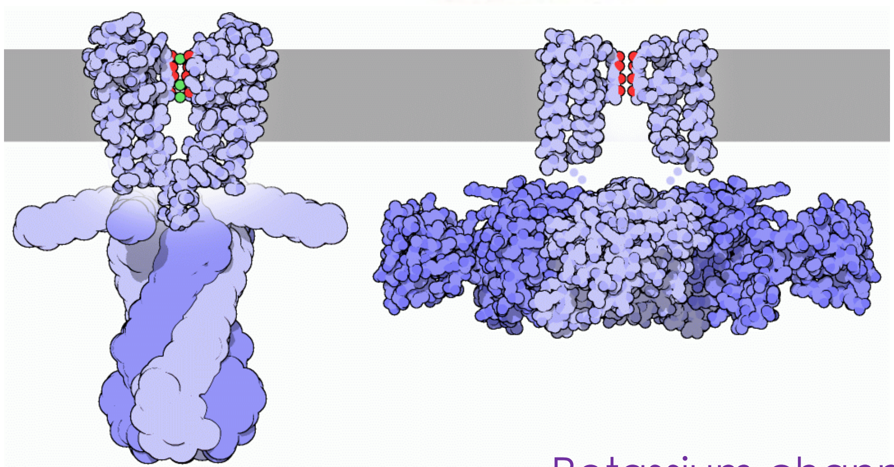
DNA encode PROTEINS, which are the "workhorses of life", *ie.* they are the fundamental biological machinery

Roles include:

- Antibodies
- Enzymes
  - catalysts for chemical reactions
  - manufacturers of new molecules
- Messengers (eg. hormones)
- Structural units
- Channels and Transporters

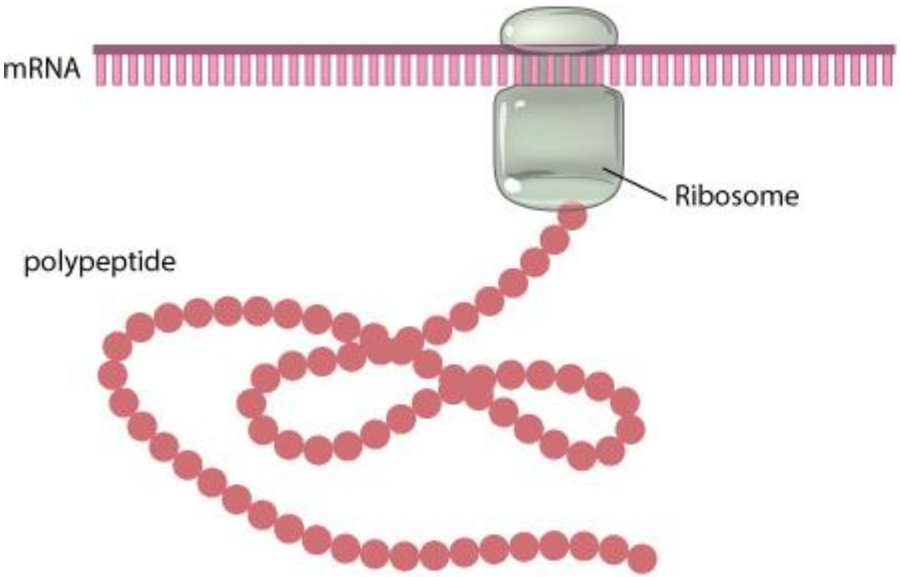


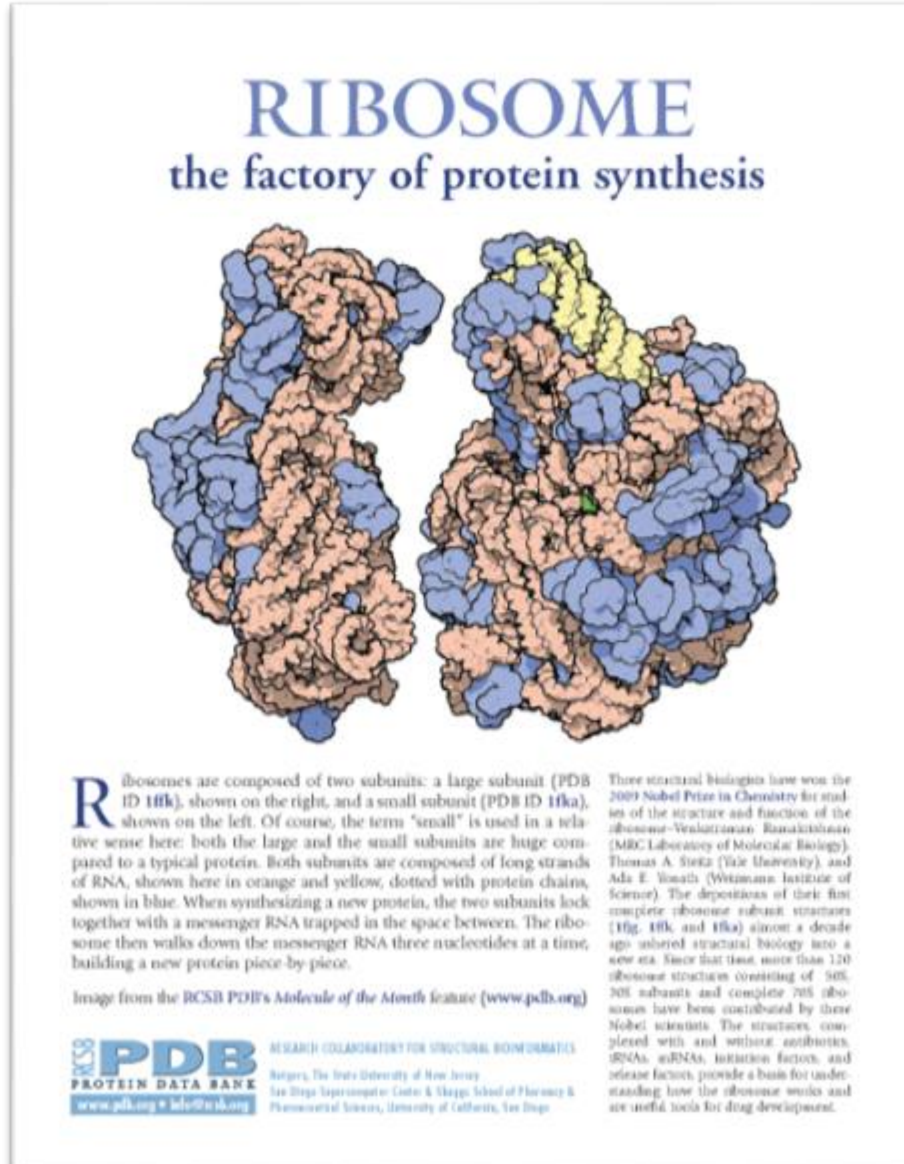
Immunoglobulin G (IgG)



Potassium channels

How are proteins synthesized in the ribosome?





RIBOSOME

the factory of protein synthesis

Ribosomes are composed of two subunits: a large subunit (PDB ID 1ffk), shown on the right, and a small subunit (PDB ID 1fka), shown on the left. Of course, the term "small" is used in a relative sense here: both the large and the small subunits are huge compared to a typical protein. Both subunits are composed of long strands of RNA, shown here in orange and yellow, dotted with protein chains, shown in blue. When synthesizing a new protein, the two subunits lock together with a messenger RNA trapped in the space between. The ribosome then walks down the messenger RNA three nucleotides at a time, building a new protein piece-by-piece.

Image from the RCSB PDB's *Molecule of the Month* feature (www.pdb.org)

Three structural biologists have won the 2009 Nobel Prize in Chemistry for studies of the structure and function of the ribosome—Venkatraman Ramakrishnan (MRC Laboratory of Molecular Biology), Thomas A. Steitz (Yale University), and Ada E. Yonath (Weizmann Institute of Science). The depositions of their first complete ribosome subunit structures (1fjg, 1ffk, and 1fka) almost a decade ago ushered structural biology into a new era. Since that time, more than 120 ribosome structures consisting of 50S, 30S subunits and complete 70S ribosomes have been contributed by these Nobel scientists. The structures, complexed with and without antibiotics, tRNAs, mRNAs, initiation factors, and release factors, provide a basis for understanding how the ribosome works and are useful tools for drug development.

RCSB PDB PROTEIN DATA BANK
www.pdb.org • info@rcsb.org

RESEARCH COLLABORATORY FOR STRUCTURAL BIOINFORMATICS
Rutgers, The State University of New Jersey
San Diego Supercomputer Center & Skaggs School of Pharmacy & Pharmaceutical Sciences, University of California, San Diego

https://pdb101.rcsb.org/learn/flyers-posters-and-other-resources/flyer/the-ribosome

Ribosomal Structure

https://www.nobelprize.org/prizes/chemistry/2009/illustrated-information/

The Nobel Prize in Chemistry 2009
Venkatraman Ramakrishnan, Thomas A. Steitz, Ada E. Yonath

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The Nobel Prize in Chemistry 2009

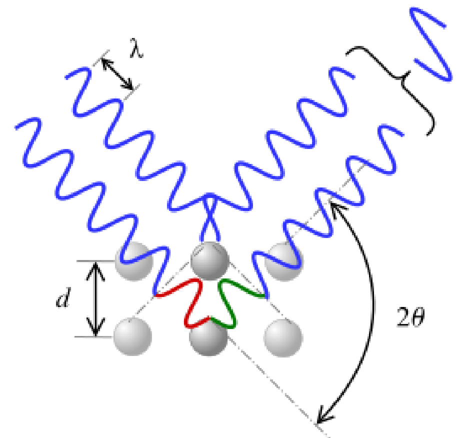
Photo: U. Montan
Venkatraman Ramakrishnan
Prize share: 1/3

Photo: U. Montan
Thomas A. Steitz
Prize share: 1/3

Photo: U. Montan
Ada E. Yonath
Prize share: 1/3

The Nobel Prize in Chemistry 2009 was awarded jointly to Venkatraman Ramakrishnan, Thomas A. Steitz and Ada E. Yonath *"for studies of the structure and function of the ribosome".*

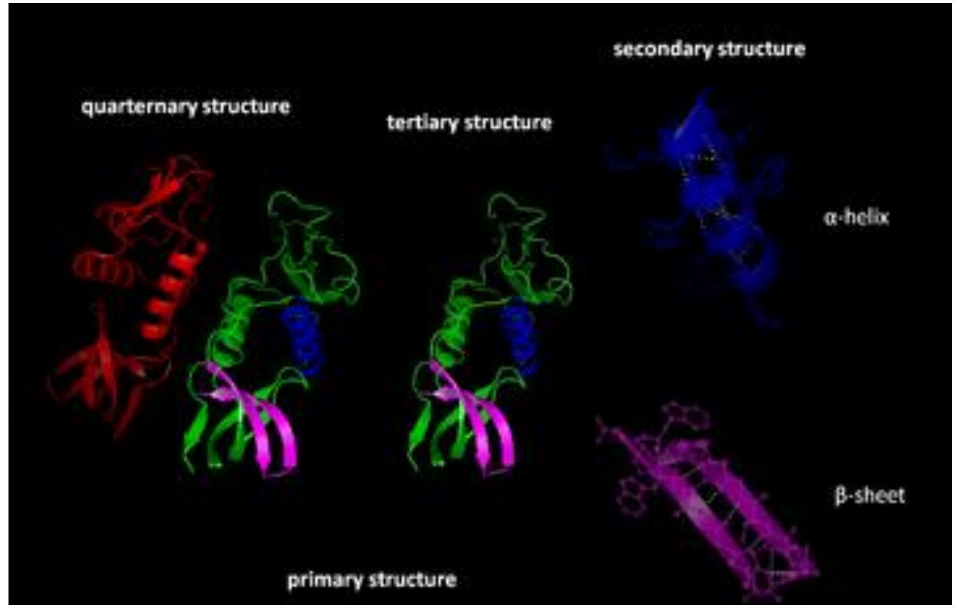
Their method was X-ray crystallography

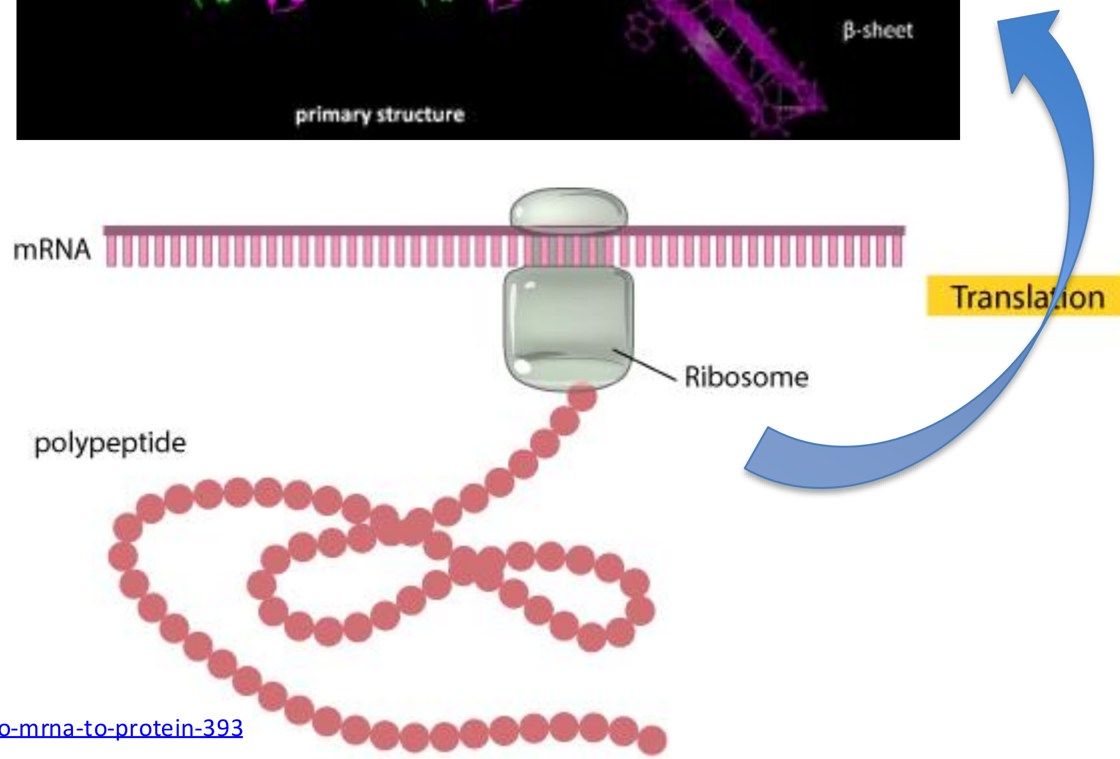


Bragg's Law: $2d\,(\sin\theta) = n\lambda$

Nascently synthesized protein chain usually FOLDS into a functional form

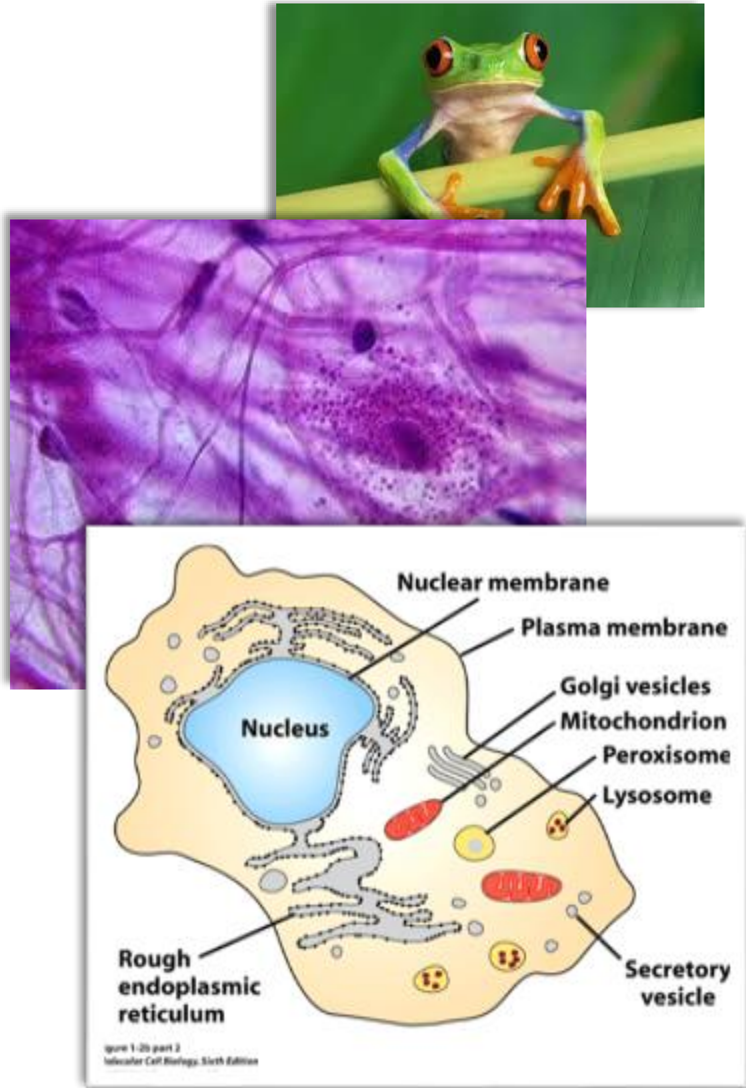
- Folding may be **spontaneous**
- Or it may be **assisted by** other proteins (**chaperones**)
- **The environment (solvent, heat, viscosity, etc) strongly influences the folding *path* and stability of the *final folded structure***
- **The *physics* of *protein folding* is incompletely understood**



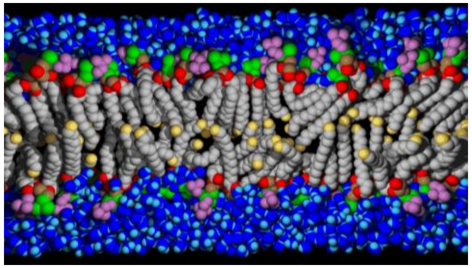


https://www.nature.com/scitable/topicpage/translation-dna-to-mrna-to-protein-393

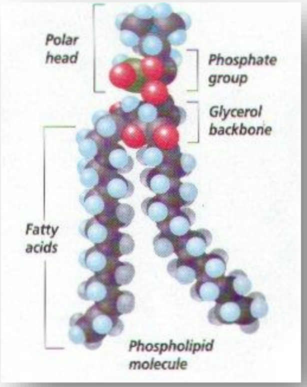
Biological Organization

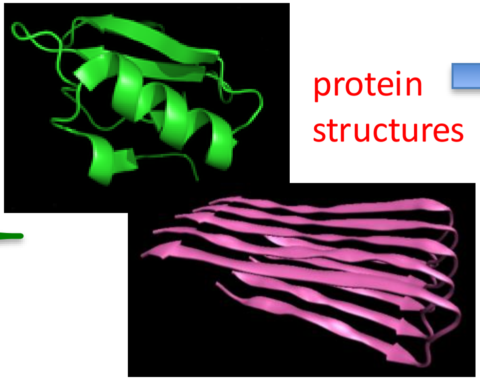


Molecular *Assembly*

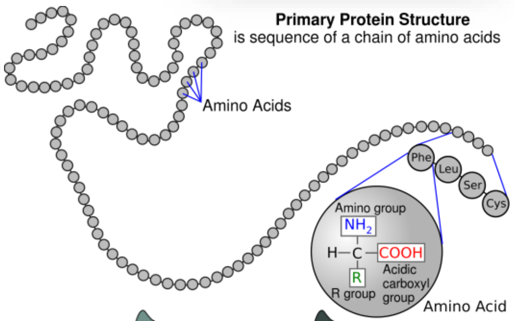


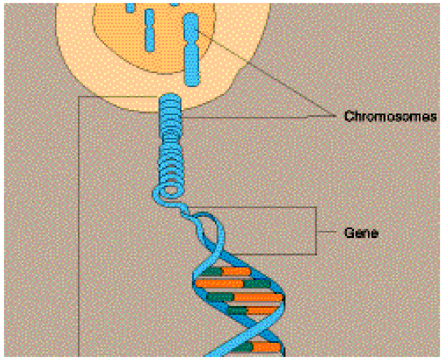
cell membranes



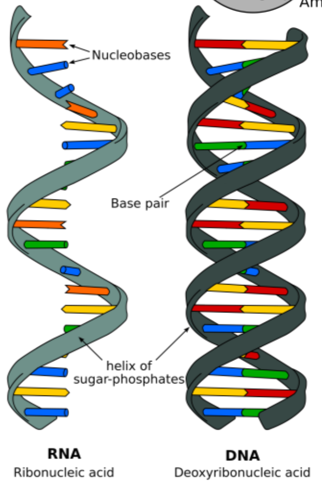


protein structures

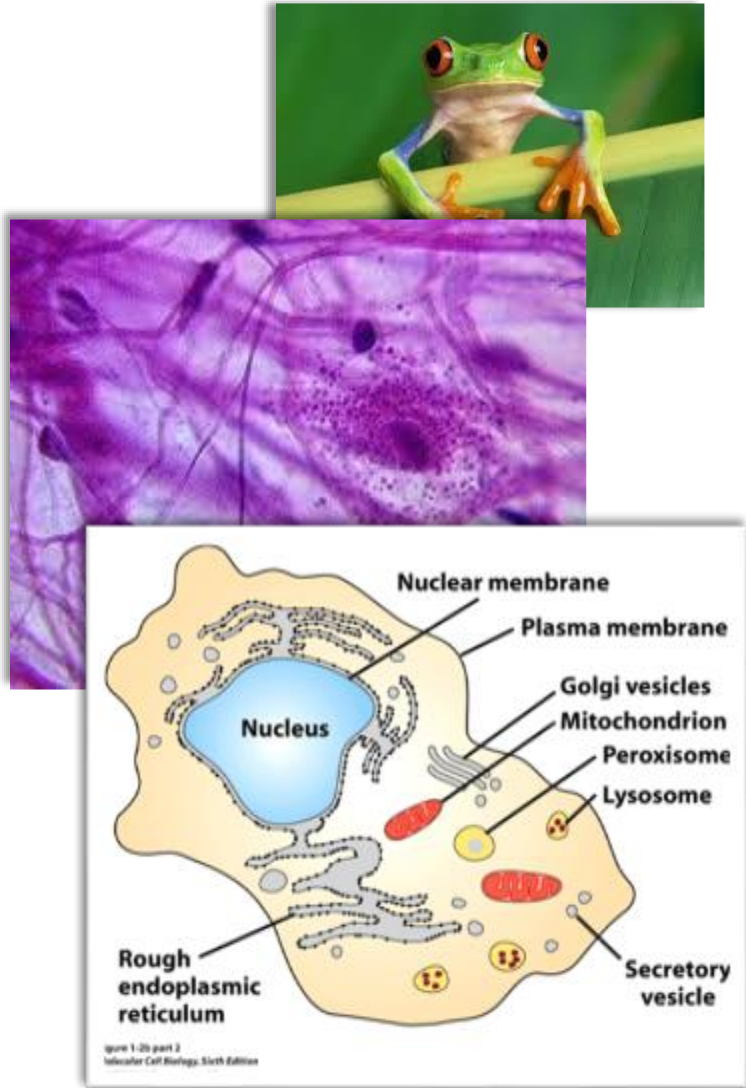


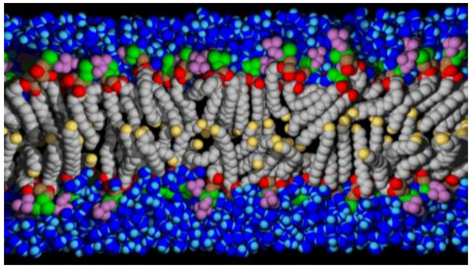


genetic material

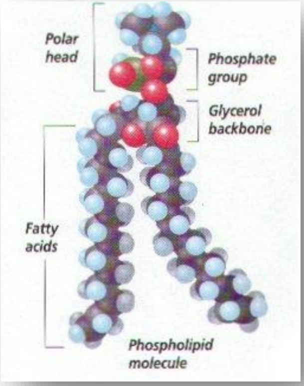


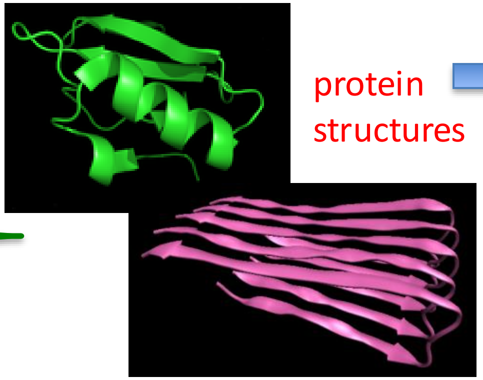
What **Physical Principles** Drive Molecular Assembly?



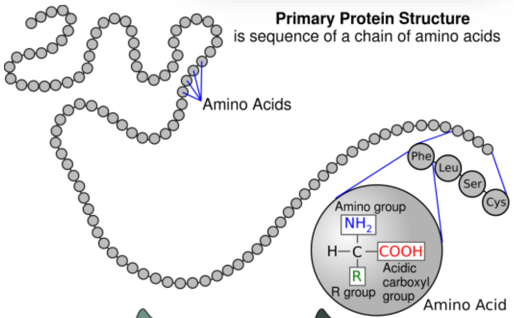


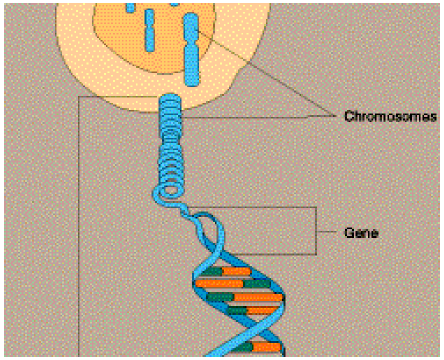
cell membranes



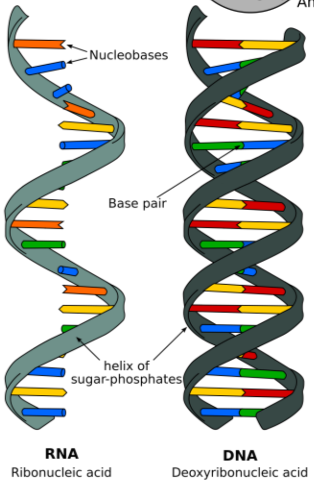


protein structures

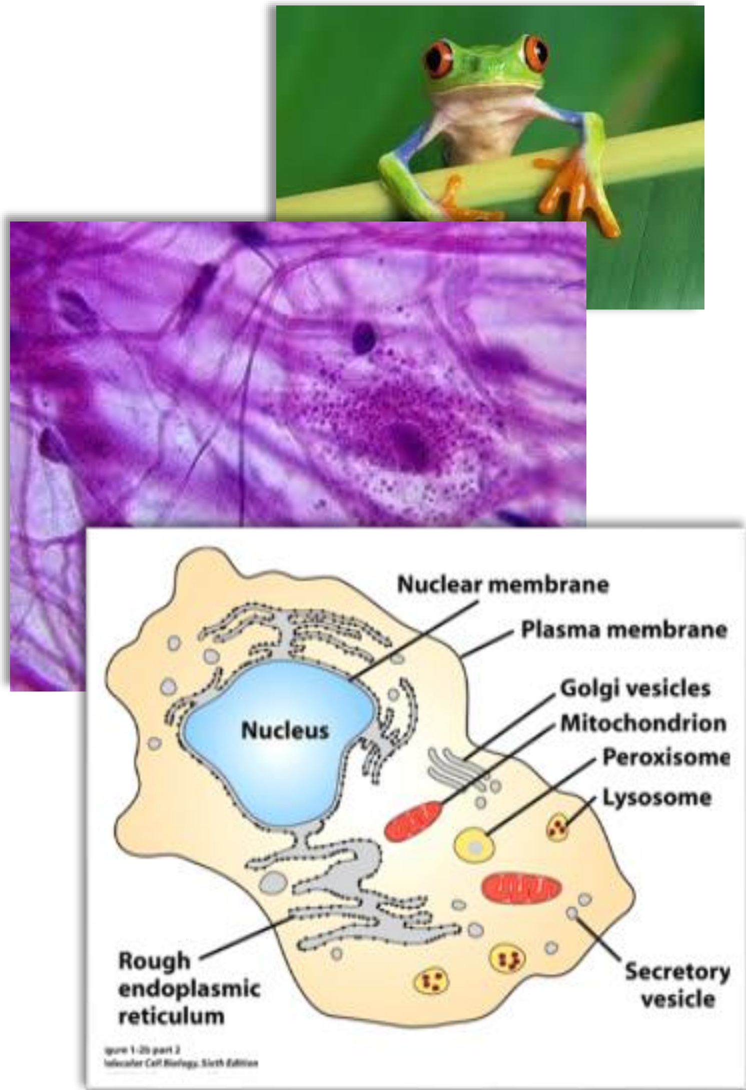




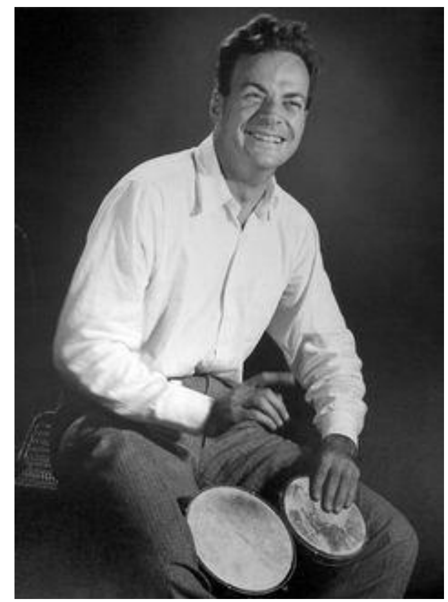
genetic material



What **Physical Principles** Drive Molecular Assembly?



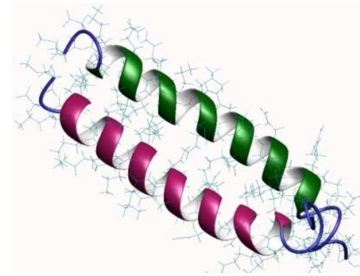
"Everything that *living things* do can be understood in terms of the *jiggling and wiggling of atoms*."

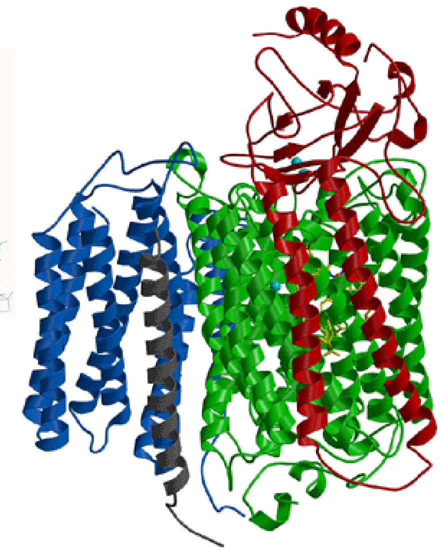


-- Richard Feynman
(1963, *Lectures in Physics*)

Biomolecules

Structure ⟷ **Function**





Dynamical Timescales

Henzler-Wildman & Kern, ***Nature Rev.***, 2007

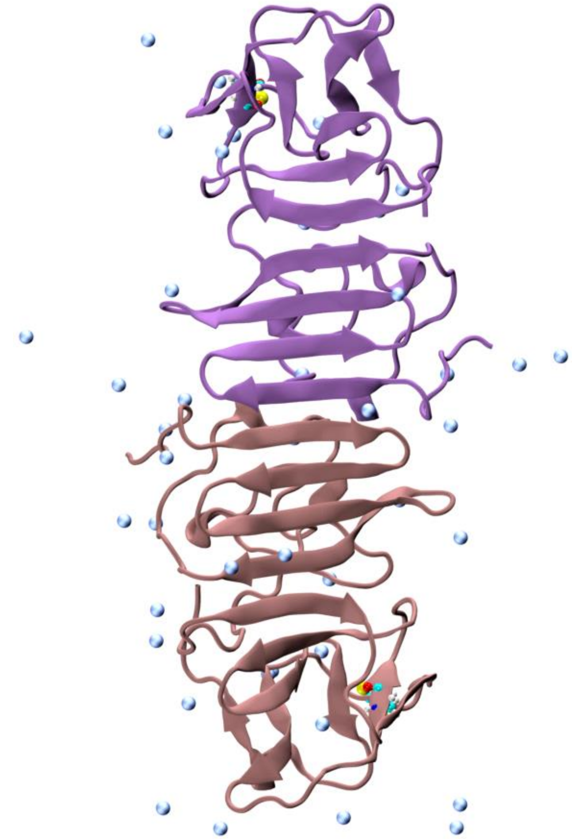
Bond vibration	*Methyl rotations*	*Loop motions*	*Domain motions*	*Protein folding*	
	Sidechain motion				
fs	**ps**	**ns**	**∫s**	**ms**	
10^{-15}	10^{-12}	10^{-9}	10^{-6}	10^{-3}	(s)

Biomolecules

Structure **Function**

Dynamics

Heat, Energy, Temperature, Work, Disorder



Dynamical Timescales

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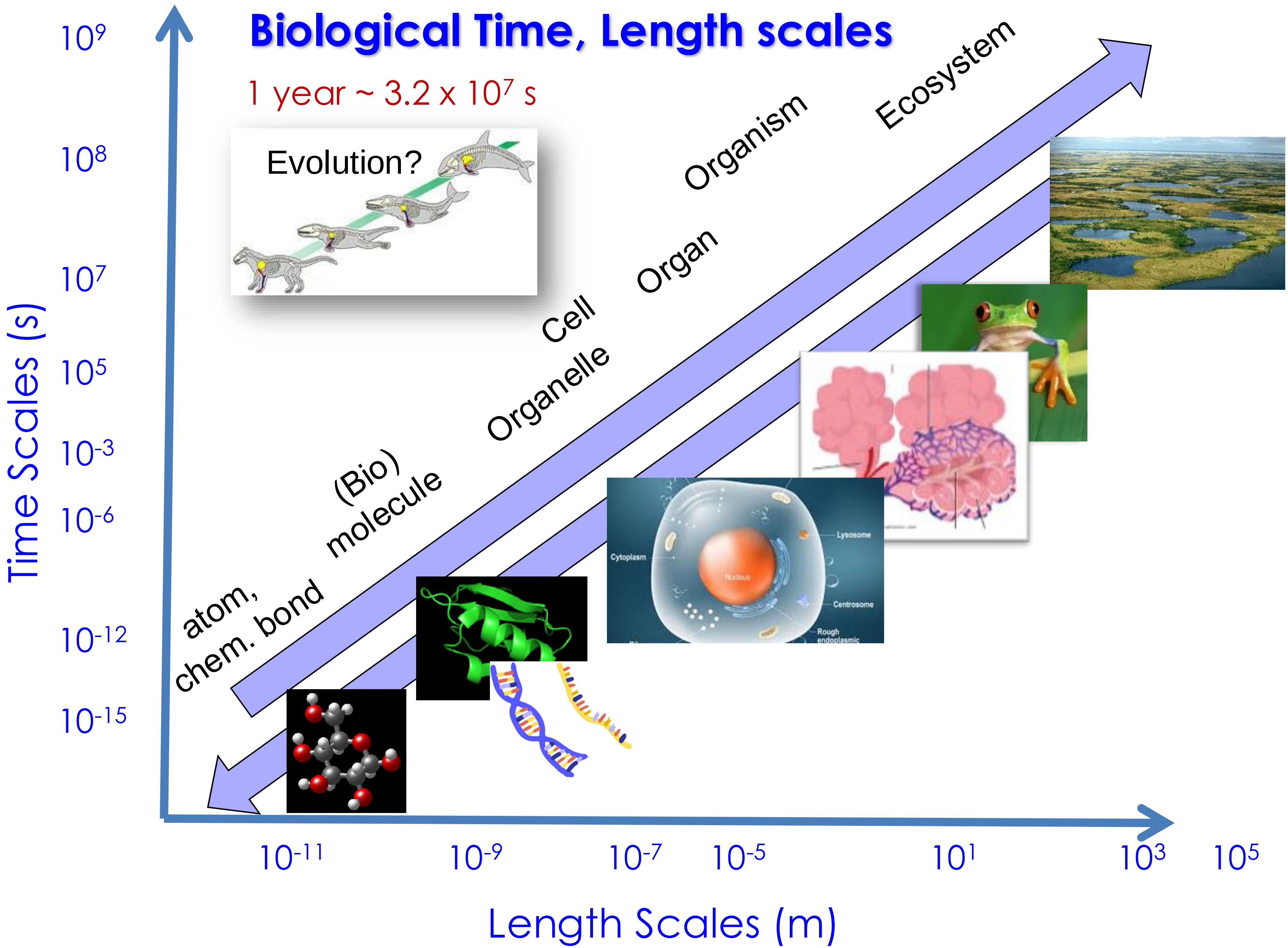
10^{-15}	10^{-12}	10^{-9}	10^{-6}	10^{-3}	(s)

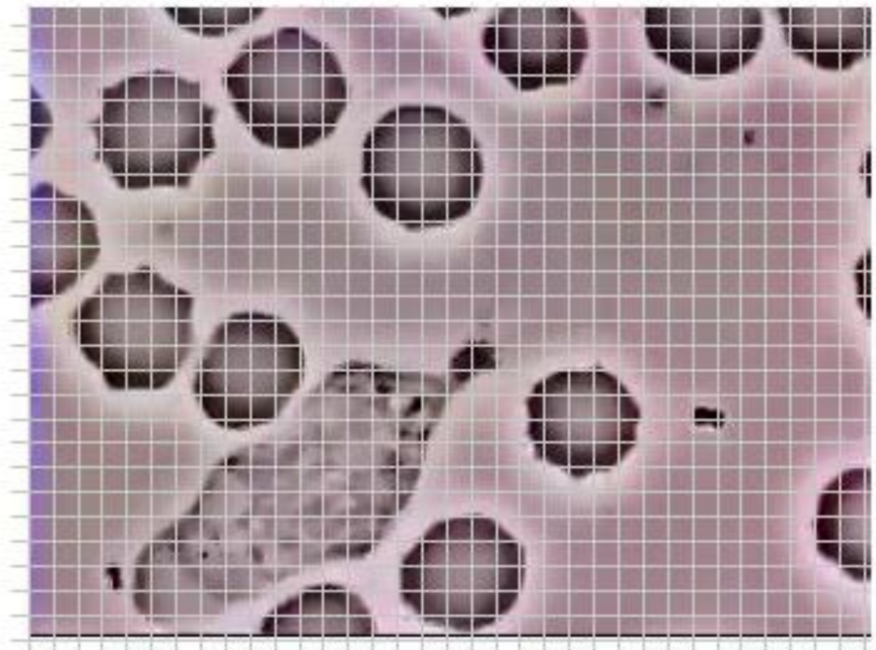


Biological Time, Length scales
1 year ~ 3.2 x 10^7 s
Evolution?
Time Scales (s)
10^9
10^8
10^7
10^5
10^{-3}
10^{-6}
10^{-12}
10^{-15}
atom, chem. bond
(Bio) molecule
Organelle
Cell
Organ
Organism
Ecosystem
Cytoplasm
Nucleus
Lysosome
Centrosome
Rough endoplasmic
Length Scales (m)
10^{-11}
10^{-9}
10^{-7}
10^{-5}
10^1
10^3
10^5

Length, Time and Associated Scales

Neutrophil chasing bacteria in the midst of red blood cells (ca. 1950)

https://www.youtube.com/watch?v=5yimbhkTqJo



Red blood cell ~8 µm

What are the approx. sizes of:

a) the neutrophil,   b) the bacteria it is chasing?

‘Rule of Thumb’: Length Scales

Table 1.1: Rules of thumb for biological estimates.

	Quantity of interest	Symbol	Rule of thumb
E. coli			
	Cell volume	$V_{E. coli}$	$\approx 1\ \mu m^3$
	Cell mass	$m_{E. coli}$	≈ 1 pg
	Cell cycle time	$t_{E. coli}$	≈ 3000 s
	Cell surface area	$A_{E. coli}$	$\approx 6\ \mu m^2$
	Macromolecule concentration in cytoplasm	$c_{E. coli}^{macromol}$	≈ 300 mg/mL
	Genome length	$N_{bp}^{E. coli}$	$\approx 5 \times 10^6$ bp
	Swimming speed	$v_{E. coli}$	$\approx 20\ \mu m/s$
Yeast			
	Volume of cell	V_{yeast}	$\approx 60\ \mu m^3$
	Mass of cell	m_{yeast}	≈ 60 pg
	Diameter of cell	d_{yeast}	$\approx 5\ \mu m$
	Cell cycle time	t_{yeast}	≈ 200 min
	Genome length	N_{bp}^{yeast}	$\approx 10^7$ bp
Organelles			
	Diameter of nucleus	$d_{nucleus}$	$\approx 5\ \mu m$
	Length of mitochondrion	l_{mito}	$\approx 2\ \mu m$
	Diameter of transport vesicles	$d_{vesicle}$	≈ 50 nm

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‘Rule of Thumb’: Length Scales

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I. What is the “surface-to-volume” ratio of *E. coli*?
- Unit?
- How is this expected to scale with size of organism?

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III. Approx. how many times it’s ‘body size’ does *E. coli* cover per second?

- How would you compare this movement with that of “very fast” humans? (Typical Olympic Runner speed ~ 30 km/h)