Introduction to Biophysics (I)

Tjaart Krüger
Department of Physics
University of Pretoria

E-mail: tjaart.kruger@up.ac.za

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Outline

Lecture 1: Basic concepts

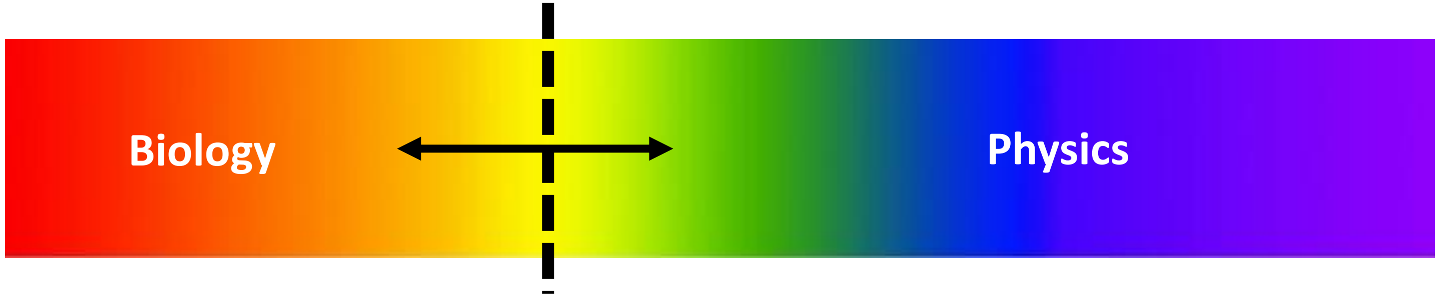
- Introduction
- The biological cell
- Central dogma of molecular biology
- Macromolecules (DNA and proteins)

Lecture 2: Selected theoretical and experimental examples

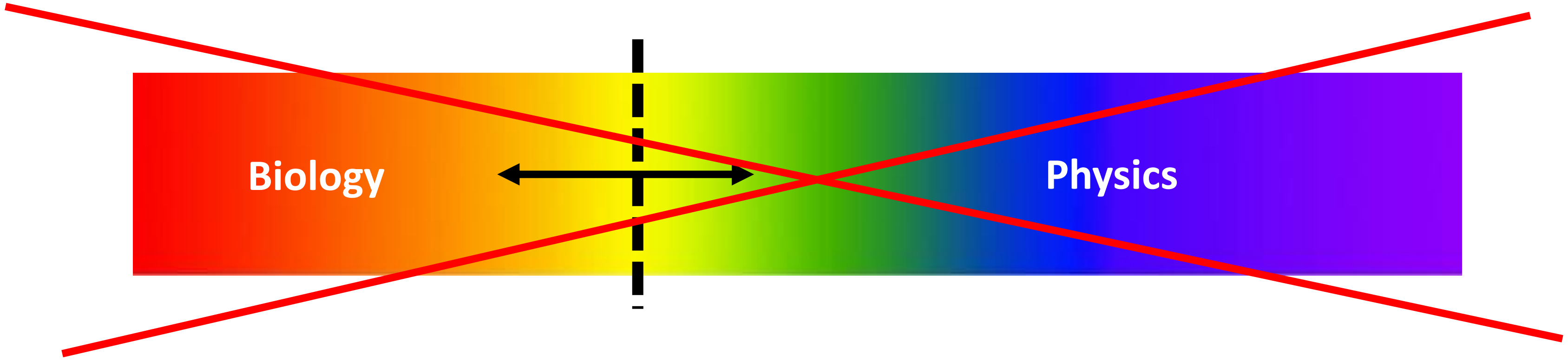
- Quantum biology
- Manipulation and detection of single biomolecules
- Superresolution imaging

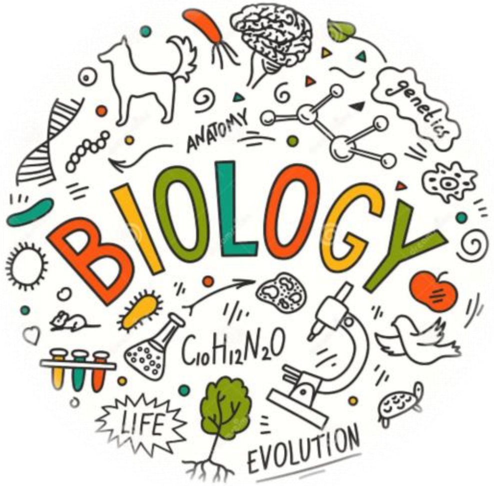
UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

What is Biophysics?



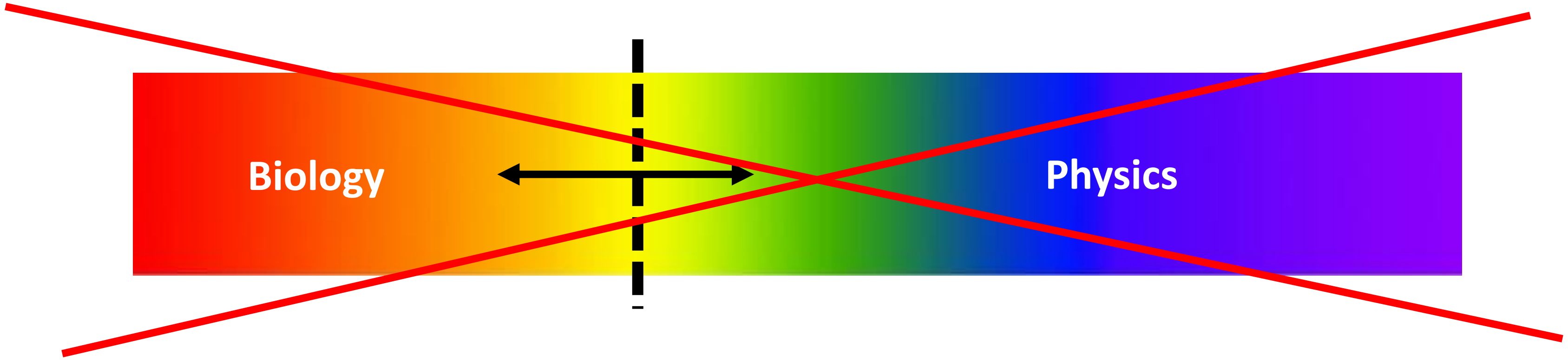
What is Biophysics?

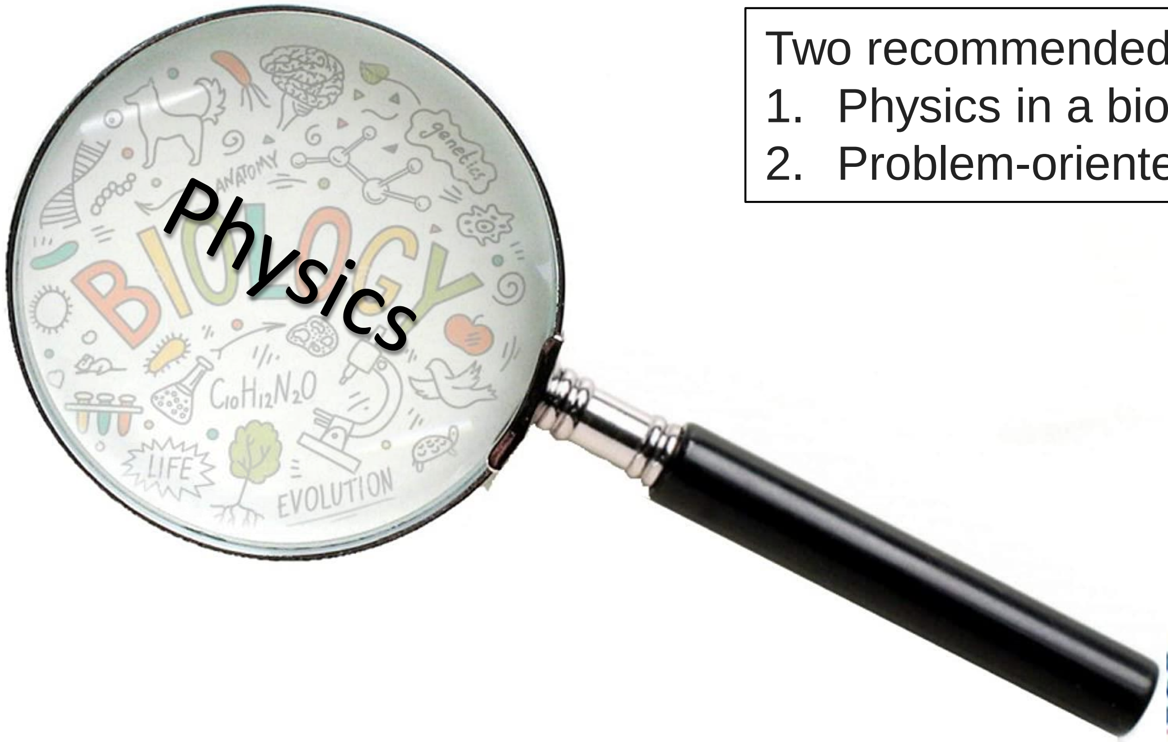




UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

What is Biophysics?

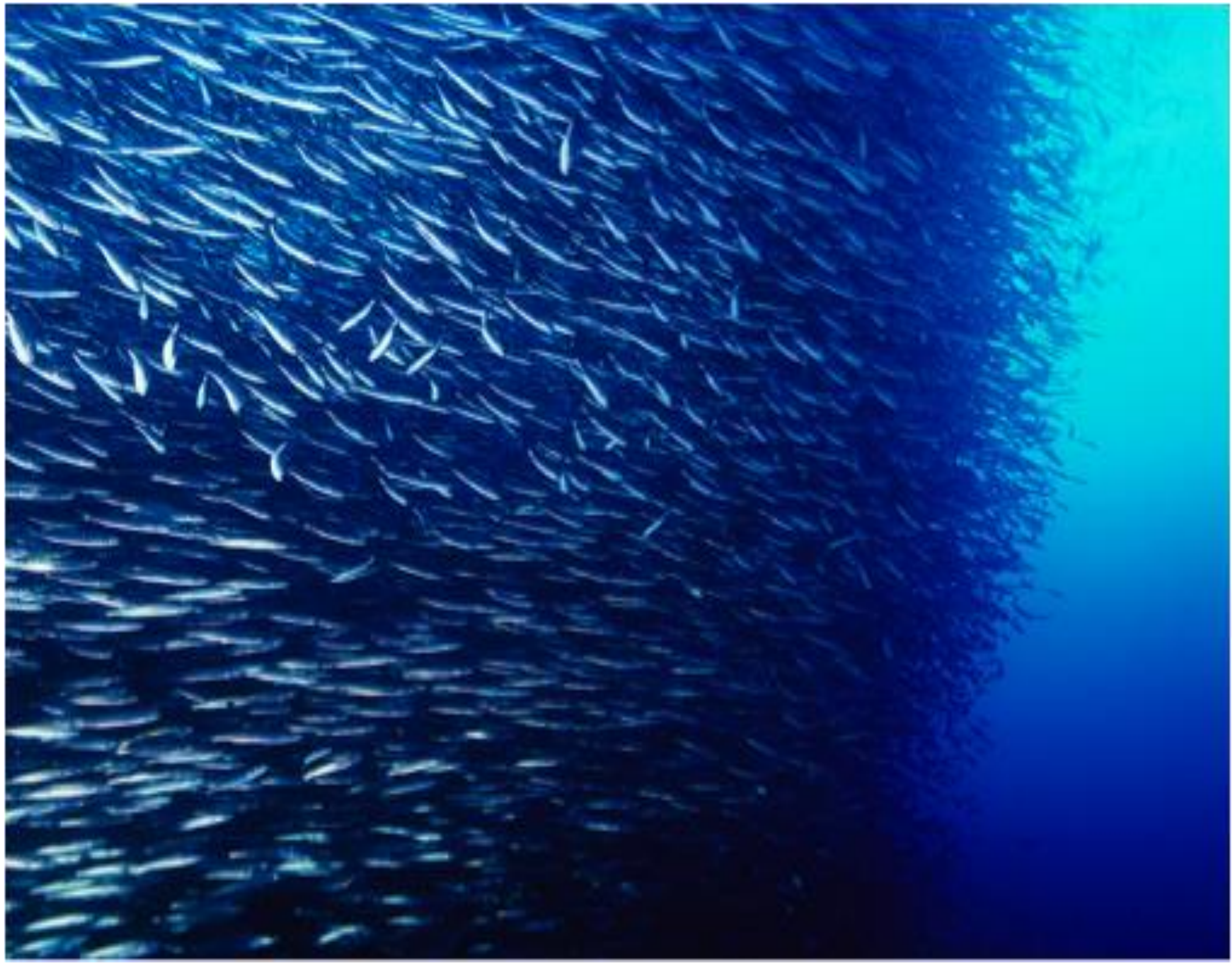




Two recommended approaches:

1. Physics in a biological context
2. Problem-oriented

Biophysics is all around us



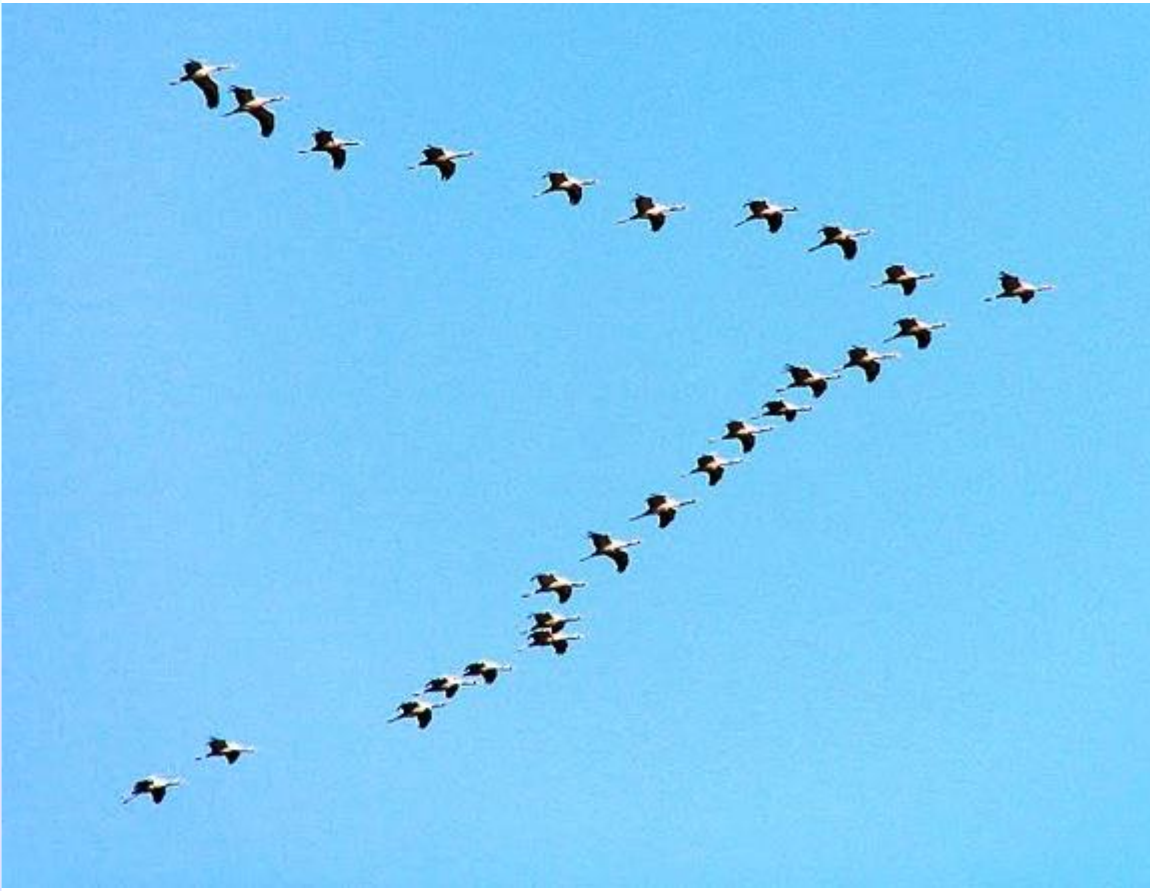
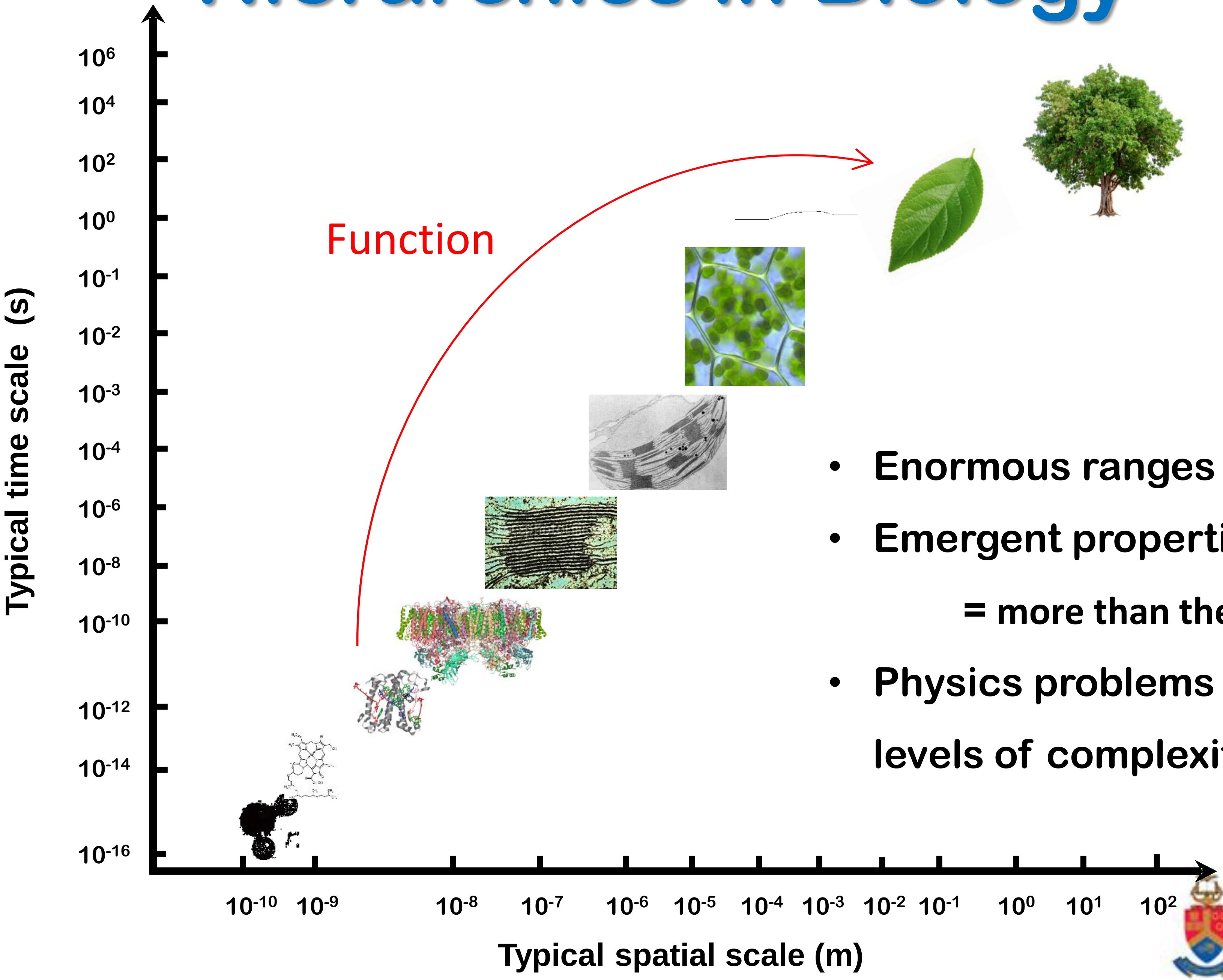


Image credit: Creative Commons

Biophysics is all around us

Image credit: Photo © [orestART / Flickr]() through a Creative Commons license

Hierarchies in Biology



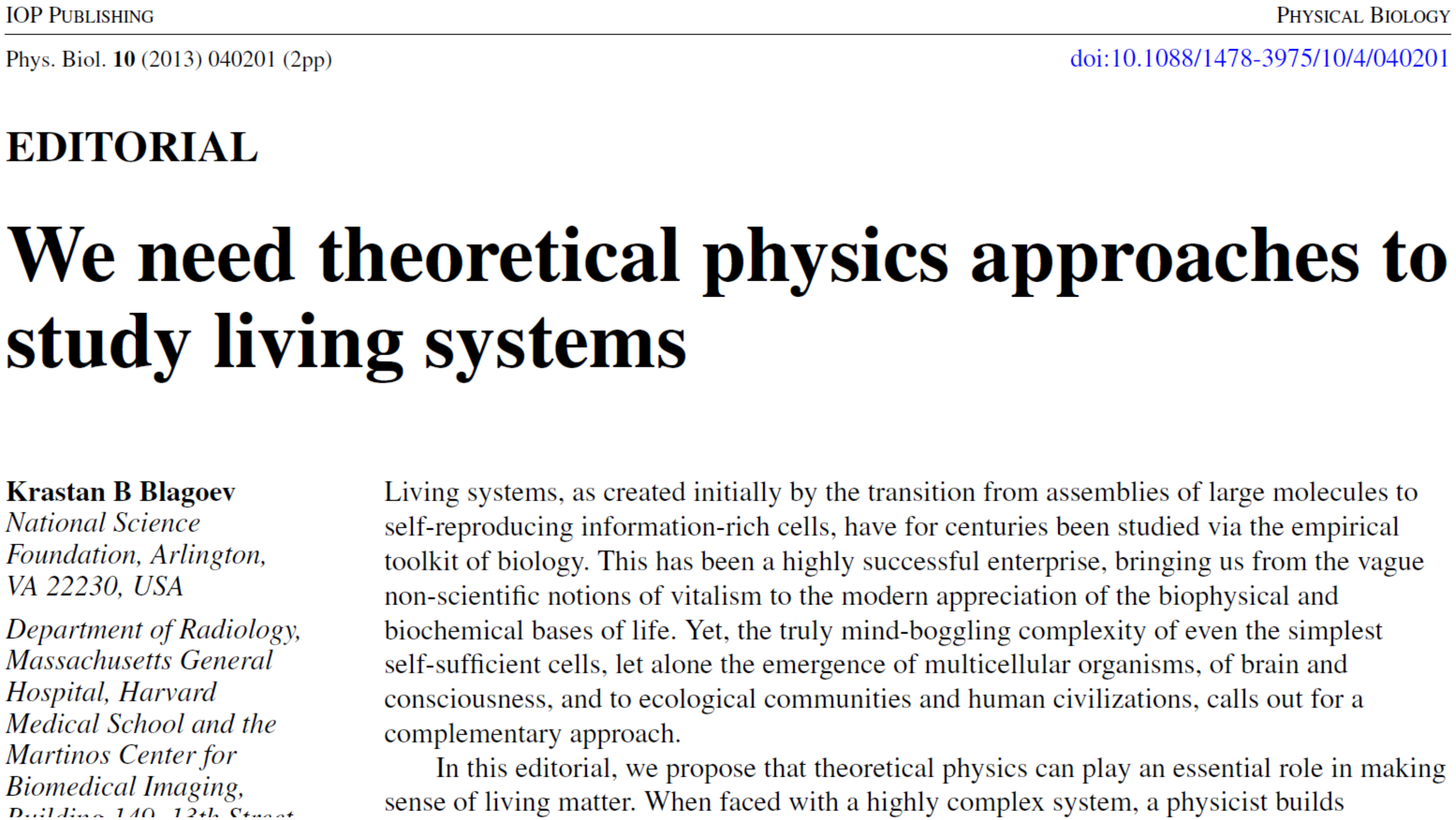
- Enormous ranges in time & space
- Emergent properties

  = more than the sum of their parts
- Physics problems are solved at all levels of complexity

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Why is biophysics important?

1. Physics brings the understanding of biology to a deeper level



IOP PUBLISHING PHYSICAL BIOLOGY

Phys. Biol. **10** (2013) 040201 (2pp) doi:10.1088/1478-3975/10/4/040201

EDITORIAL

We need theoretical physics approaches to study living systems

Krastan B Blagoev
National Science Foundation, Arlington, VA 22230, USA

Department of Radiology, Massachusetts General Hospital, Harvard Medical School and the Martinos Center for Biomedical Imaging, Building 149, 13th Street

Living systems, as created initially by the transition from assemblies of large molecules to self-reproducing information-rich cells, have for centuries been studied via the empirical toolkit of biology. This has been a highly successful enterprise, bringing us from the vague non-scientific notions of vitalism to the modern appreciation of the biophysical and biochemical bases of life. Yet, the truly mind-boggling complexity of even the simplest self-sufficient cells, let alone the emergence of multicellular organisms, of brain and consciousness, and to ecological communities and human civilizations, calls out for a complementary approach.

In this editorial, we propose that theoretical physics can play an essential role in making sense of living matter. When faced with a highly complex system, a physicist builds

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Why is biophysics important?

1. Physics brings the understanding of biology to a deeper level

Teaching assistant: “Dr. Einstein, aren't these the same questions as last year’s [physics] final exam?”

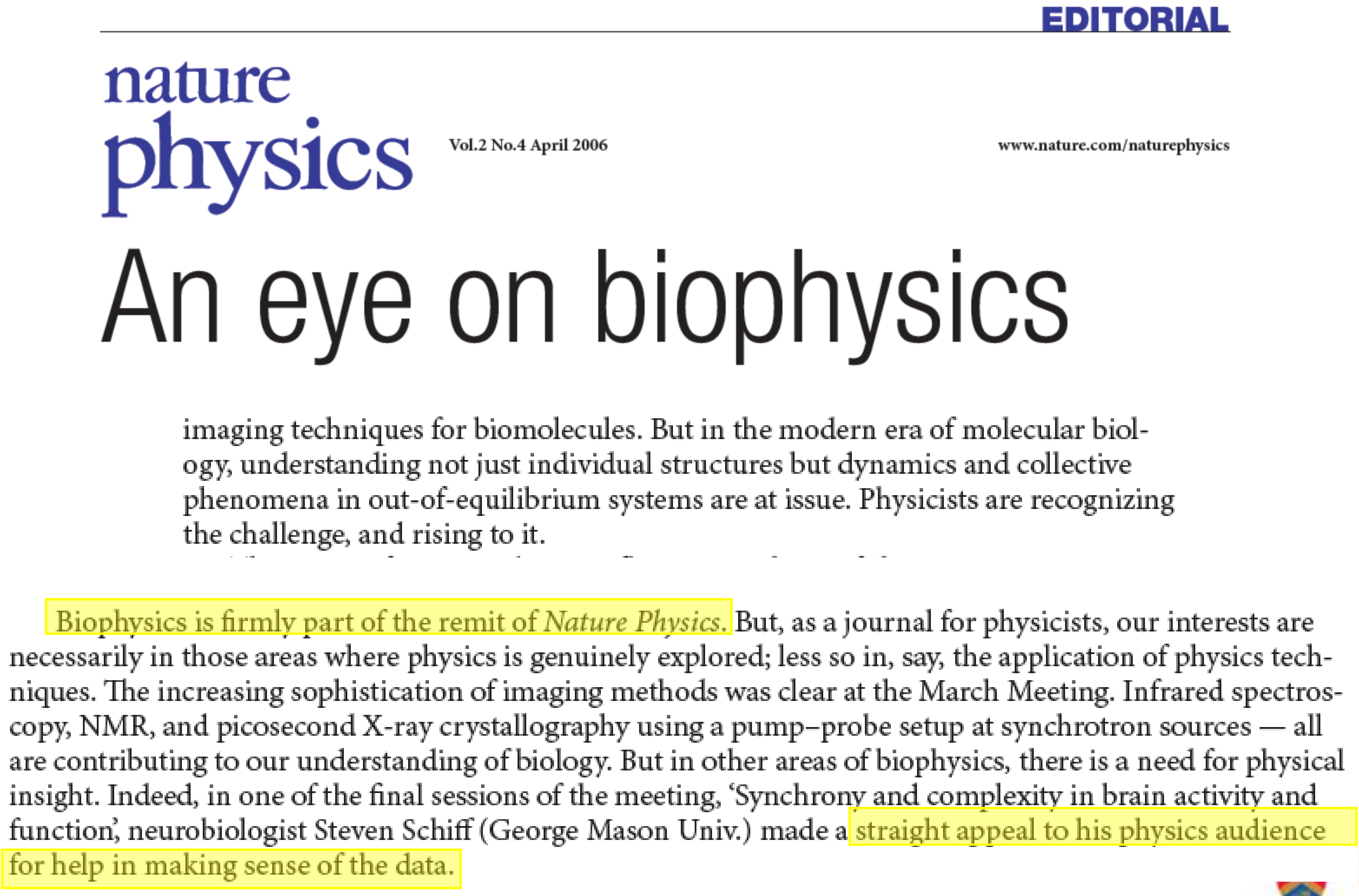
Einstein: “Yes, but this year the answers are different.”

Martin Friede (WHO): “…you will not be able to successfully develop vaccines without biophysics…”

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Why is biophysics important?

1. Physics brings the understanding of biology to a deeper level



EDITORIAL

nature physics

Vol.2 No.4 April 2006

www.nature.com/naturephysics

An eye on biophysics

imaging techniques for biomolecules. But in the modern era of molecular biology, understanding not just individual structures but dynamics and collective phenomena in out-of-equilibrium systems are at issue. Physicists are recognizing the challenge, and rising to it.

Biophysics is firmly part of the remit of *Nature Physics*. But, as a journal for physicists, our interests are necessarily in those areas where physics is genuinely explored; less so in, say, the application of physics techniques. The increasing sophistication of imaging methods was clear at the March Meeting. Infrared spectroscopy, NMR, and picosecond X-ray crystallography using a pump–probe setup at synchrotron sources — all are contributing to our understanding of biology. But in other areas of biophysics, there is a need for physical insight. Indeed, in one of the final sessions of the meeting, 'Synchrony and complexity in brain activity and function', neurobiologist Steven Schiff (George Mason Univ.) made a straight appeal to his physics audience for help in making sense of the data.

Why is biophysics important?

2. Biology offers a testing ground for some theories of physics

NATURE PHYSICS | VOL 11 | FEBRUARY 2015 COMMENTARY

“Diverse Phenomena, Common Themes” by Christopher Jarzynski

> “Biology provides a natural setting for applying and refining the tools of non-equilibrium statistical physics. If an equilibrium state is one in which nothing seems to be happening, then living organisms— which grow, move and multiply— seem to be the exact opposite. Just how does a living organism maintain itself away from equilibrium? Processes such as growth and motion arise from intricate networks of chemical reactions driven by chemical imbalances, that is, chemical potential differences.”

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Why is biophysics important?

3. It drives critical innovative developments

- We’re living in the “Century of Biology”
- Biophysics contributes significantly to
  - Medical science & innovation
  - Environmental management (pollution / climate change)
  - Food security
  - Nanotechnology
  - Even energy security and telecommunications / computing

Why biophysics works for me?

http://www.iop.org/careers/workinglife/articles/page_53286.html

1) **Deborah Fygenson (Associate professor at the University of California, Santa Barbara, US)**

   Research: DNA origami to recreate some of the nanostructures we see in biology.

   For Fygenson, it is the "immediacy" of biophysics that makes the subject so attractive. "It's the potential for impact on human life, the phenomena being close by," she says. "I think that if we start to better understand the physical limitations imposed by biomaterials, we'll have fundamental insights into why biology is constructed the way it is."

   https://www.physics.ucsb.edu/news/announcement/608

2) **Thomas Krauss (Head of the School of Physics and Astronomy, University of St Andrews, UK)**

   Thomas Krauss is a great example of biophysics' interdisciplinary nature. An engineer by training, he spent his early career developing photonics for Internet applications. [e.g. data transmission]

   … Krauss has several interests in the field. One is … the nascent field of "optogenetics" – a process that makes certain nerve cells light-sensitive by infecting them with a virus, so that biologists can learn how they transmit signals at a cellular level. "Combining optogenetics with my interest of controlling light at the nanoscale, you can imagine an array of light emitters firing at neurons, controlling their function at an array type of scale," explains Krauss.

   "I was starting to get bored of telecoms," he adds. "When you do something for 10 years, you start to know most of it. Of course, you never know everything, but the factor of learning gets smaller and smaller. Whereas in biophysics there is so much I have yet to learn."

The Biological Cell

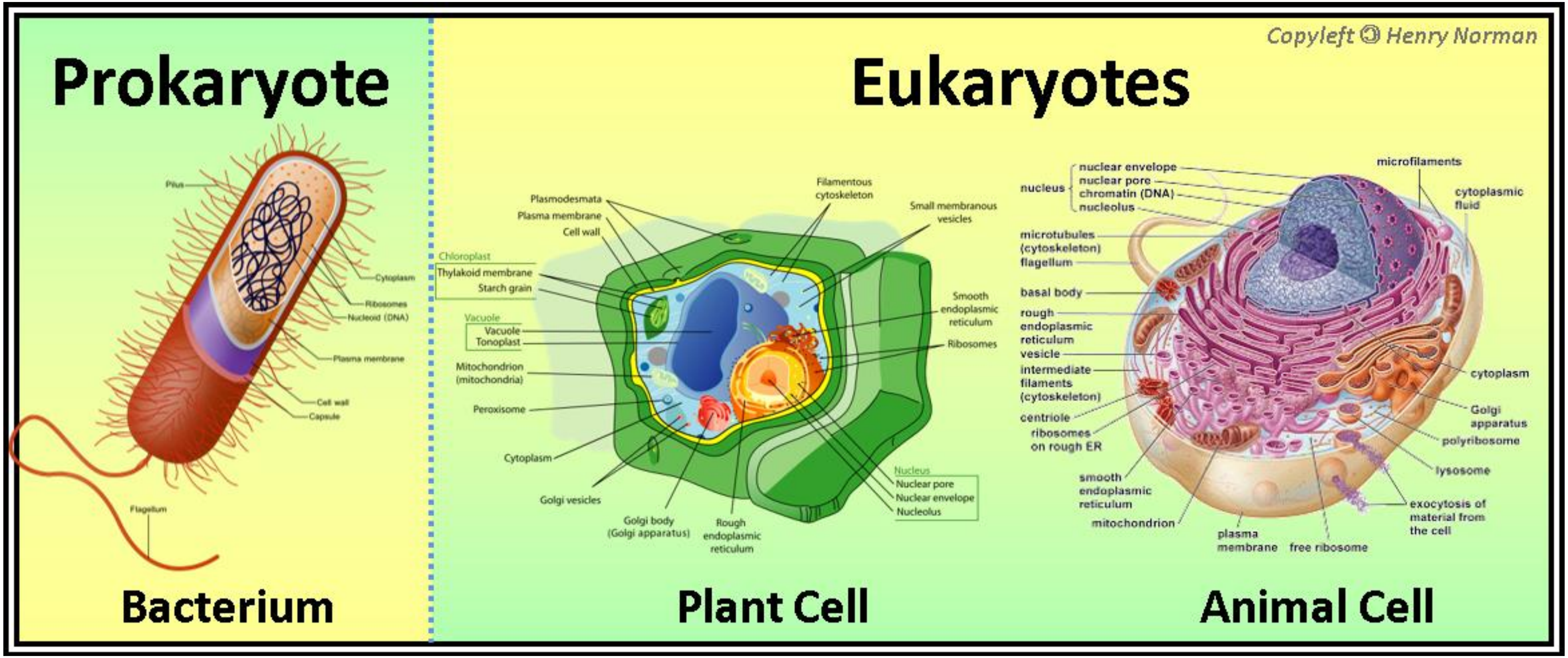


Image credit: Creative Commons

The Plant Cell

DNA and gene expression (City Hall)

Transportation system
Contains ribosomes for protein synthesis (factory / construction site)

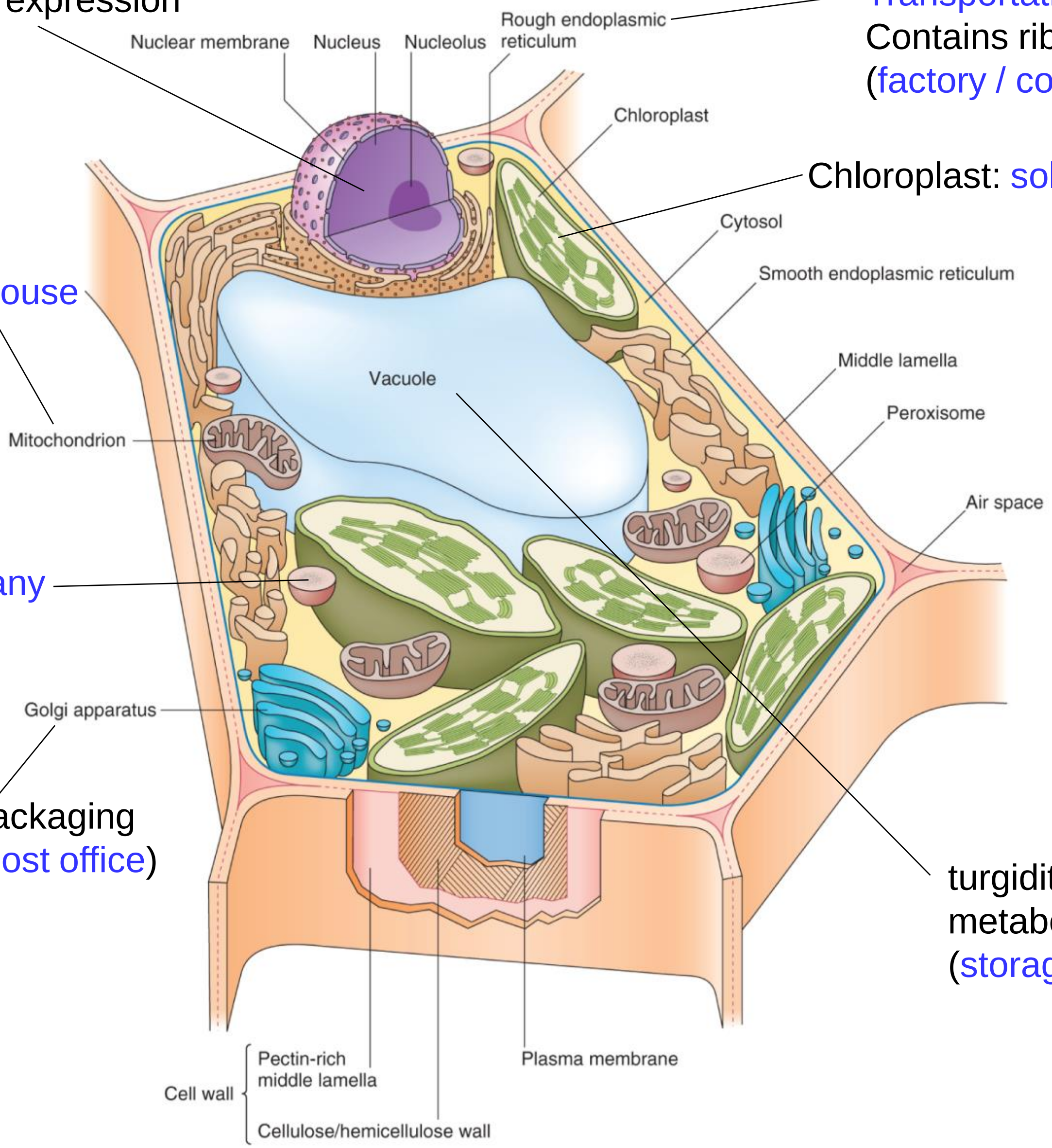
Chloroplast: solar farm

energy powerhouse

Lysosome: garbage company

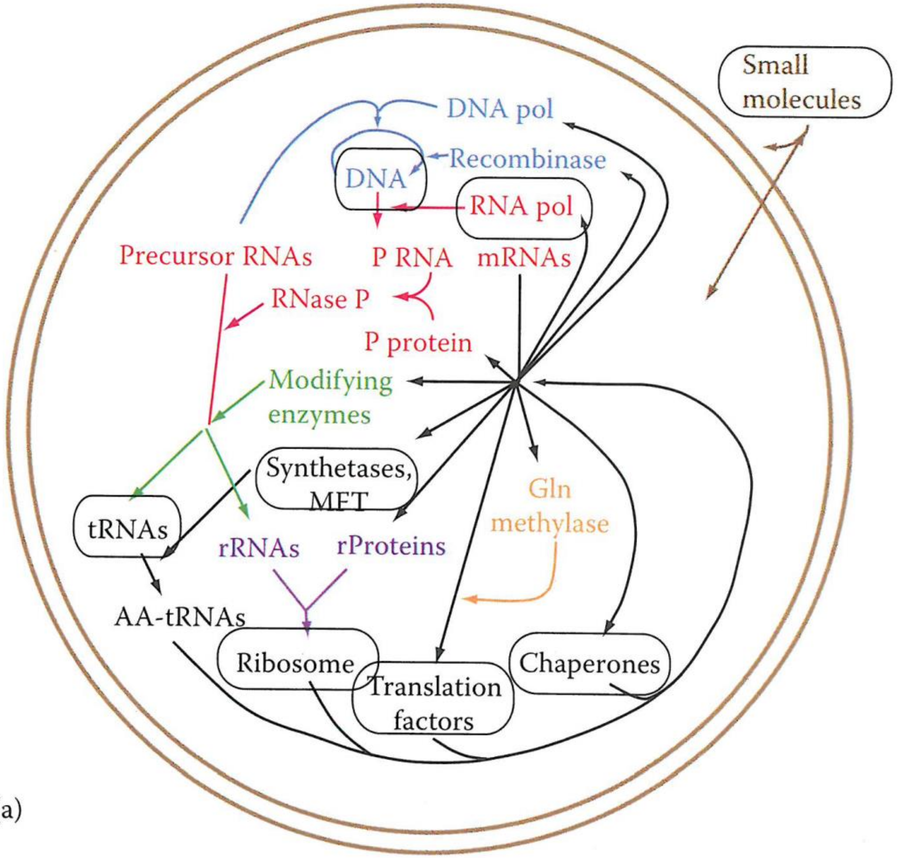
Macromolecule packaging and processing (post office)

turgidity control and metabolite storage (storage unit)



How complex is a cell?

The minimal cell



(a)

From: Quantitative Understanding of Biosystems
An Introduction to Biophysics, Second Edition
By TM Nordlund & PM Hoffmann

Simplest process is diffusion of small molecules:

$$\frac{\partial C(x,t)}{\partial t} = -D\frac{\partial^2 C(x,t)}{\partial x^2}$$

- Boundary conditions
- Reactions with other molecules: source & sink terms
- Feedback mechanisms: **coupled PDEs.**

Assume: every line denotes a reaction, described by a PDE.

~30 coupled PDEs!

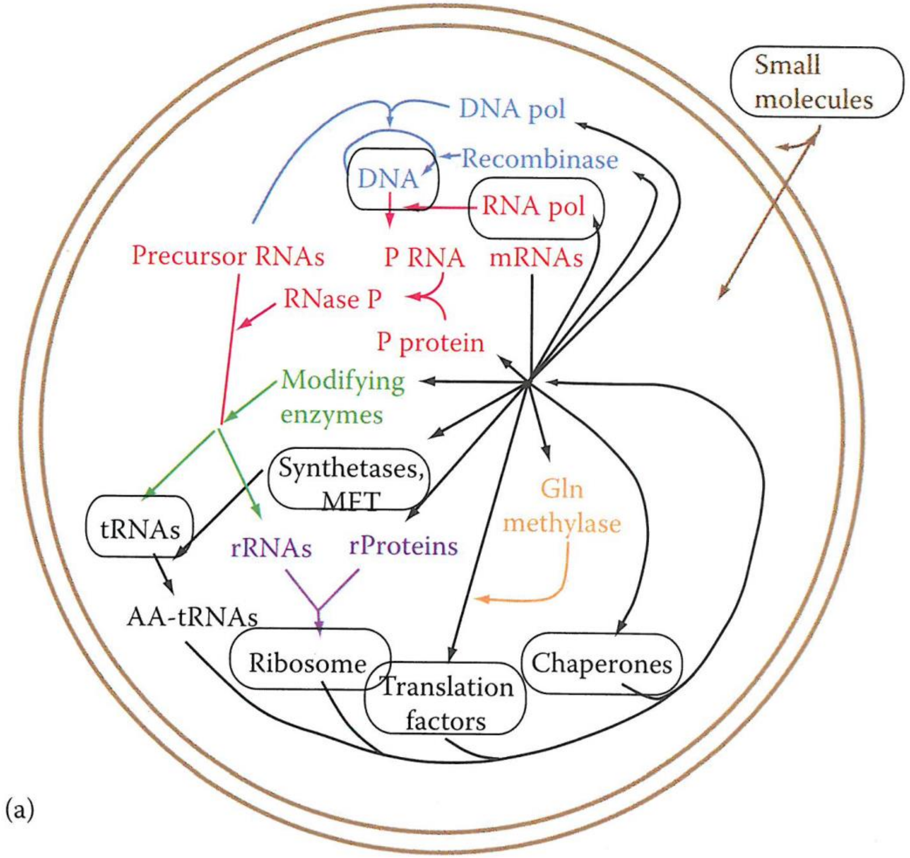
Can Mathematica solve this for time-independent processes?

Metabolic pathways

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

How complex is a cell?

The minimal cell



From: Quantitative Understanding of Biosystems
An Introduction to Biophysics, Second Edition
By TM Nordlund & PM Hoffmann

Simplest process is diffusion of small molecules:

$$\frac{\partial C(x,t)}{\partial t} = -D\frac{\partial^2 C(x,t)}{\partial x^2} \; \xcancel{\text{+ source \& sink terms}}$$

- Boundary conditions
- Reactions with other molecules: source & sink terms
- Feedback mechanisms: **coupled PDEs.**

Assume: every line denotes a reaction, described by a PDE.

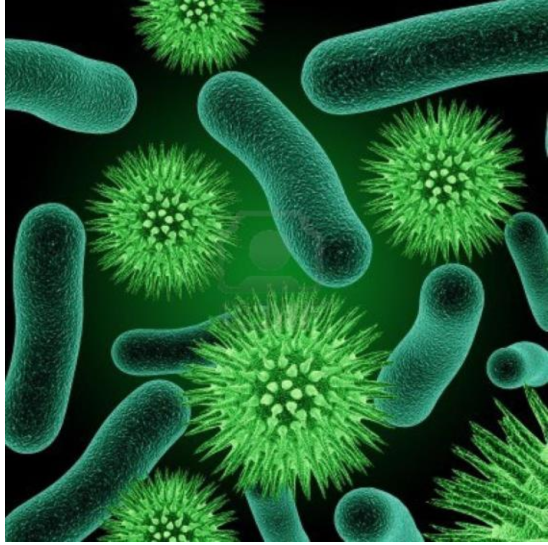
~30 coupled PDEs!

Can Mathematica solve this for time-independent processes?

Metabolic pathways

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Bacteria



~30,000 formally named species

Bacterial library: https://www.usmslab.com/microbiology-lab-resources-library/bacterial-library

What is the ratio of bacterial cells vs. body cells in the human body?

A. 1:100

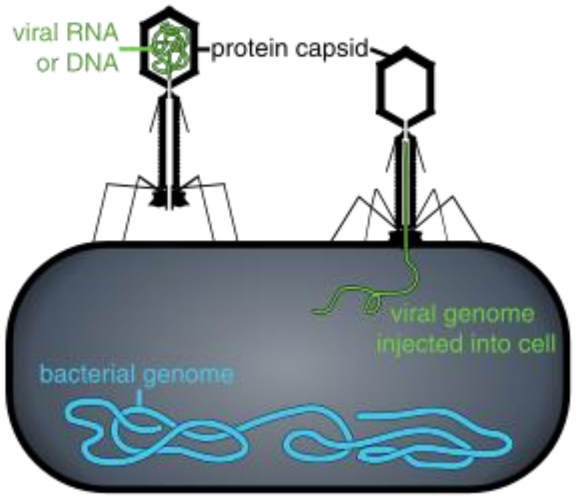
B. 1:10

C. 1:1

D. 10:1

Average size = ~2 µm: 50 µm

Viruses



Nature Reviews Microbiology **9**, 628 (September 2011) | doi:10.1038/nrmicro2644

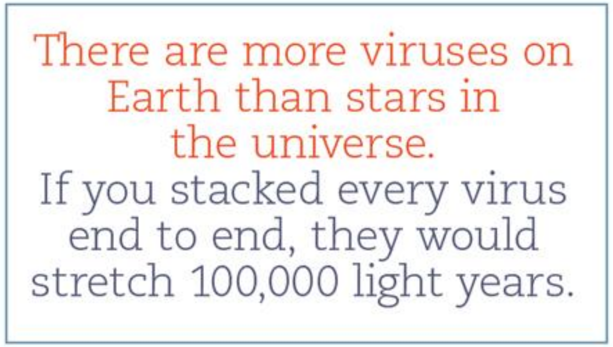
1. Is a virus a living organism?

2. How big are viruses?

~20 – 400 nm

3. How many viruses are there on the earth?

~10^{31} viruses!



There are more viruses on Earth than stars in the universe.
If you stacked every virus end to end, they would stretch 100,000 light years.

4. How effective are antiviral drugs?

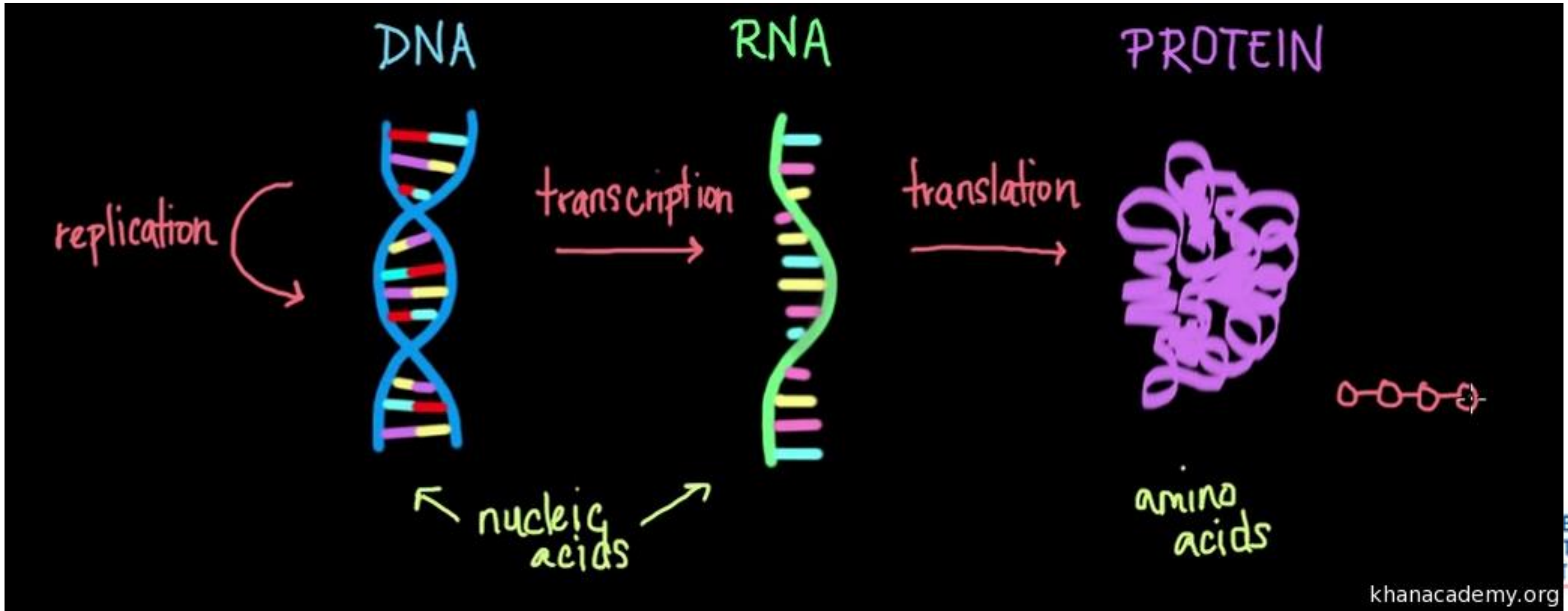
> "…you will not be able to successfully develop vaccines without biophysics…"

Central dogma of molecular biology

- “DNA makes RNA makes protein”
- Encoded instruction (**DNA**) is *transcribed* in an intermediate form (**RNA**) and *translated* to a functional molecule (**protein**)

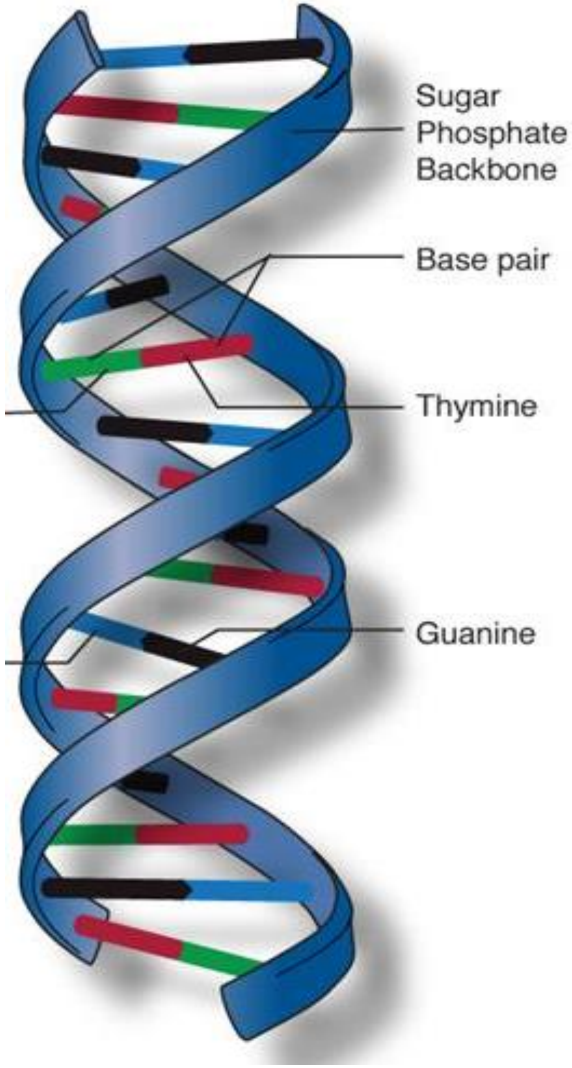
nucleus

cytoplasm/ER

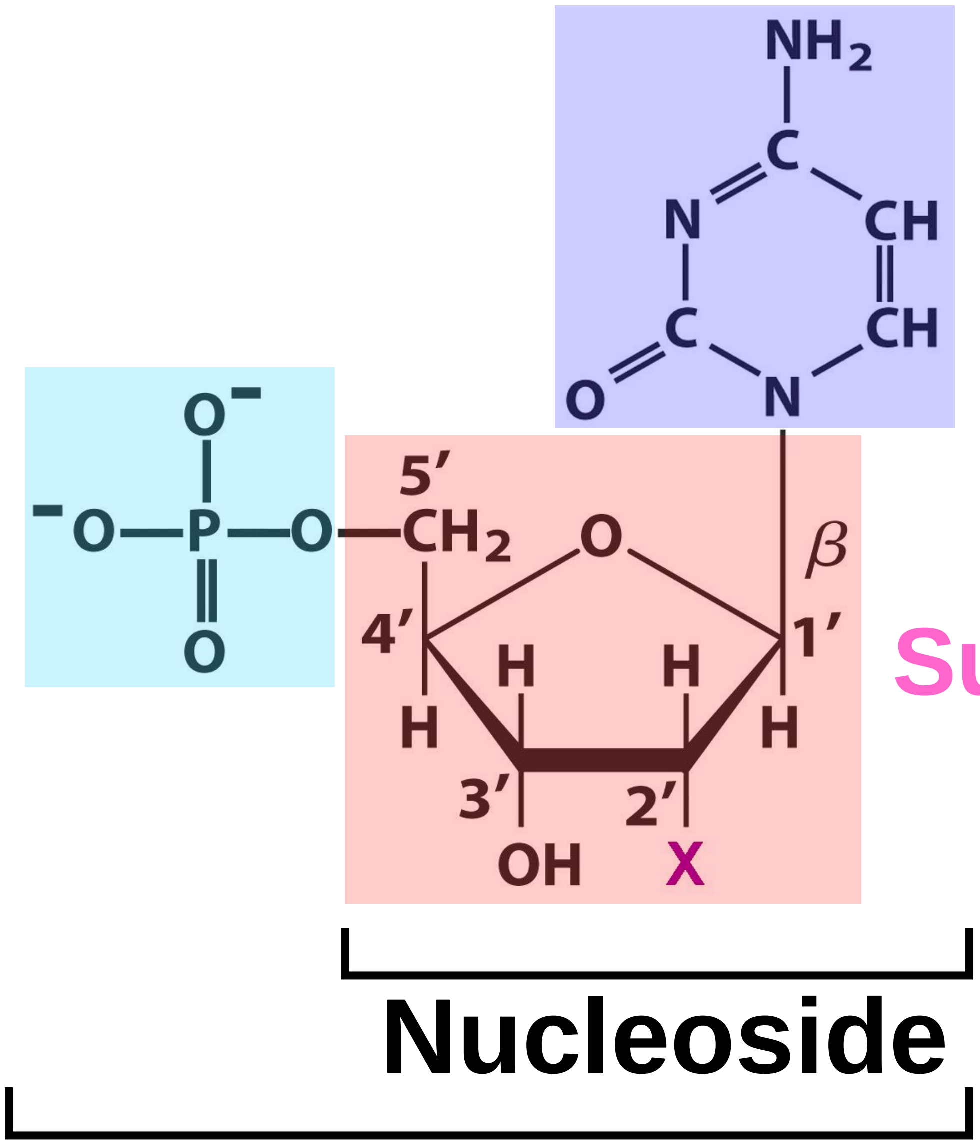


DNA

(deoxyribose nucleic acid)



Components of a nucleotide



Phosphate

Base

Sugar

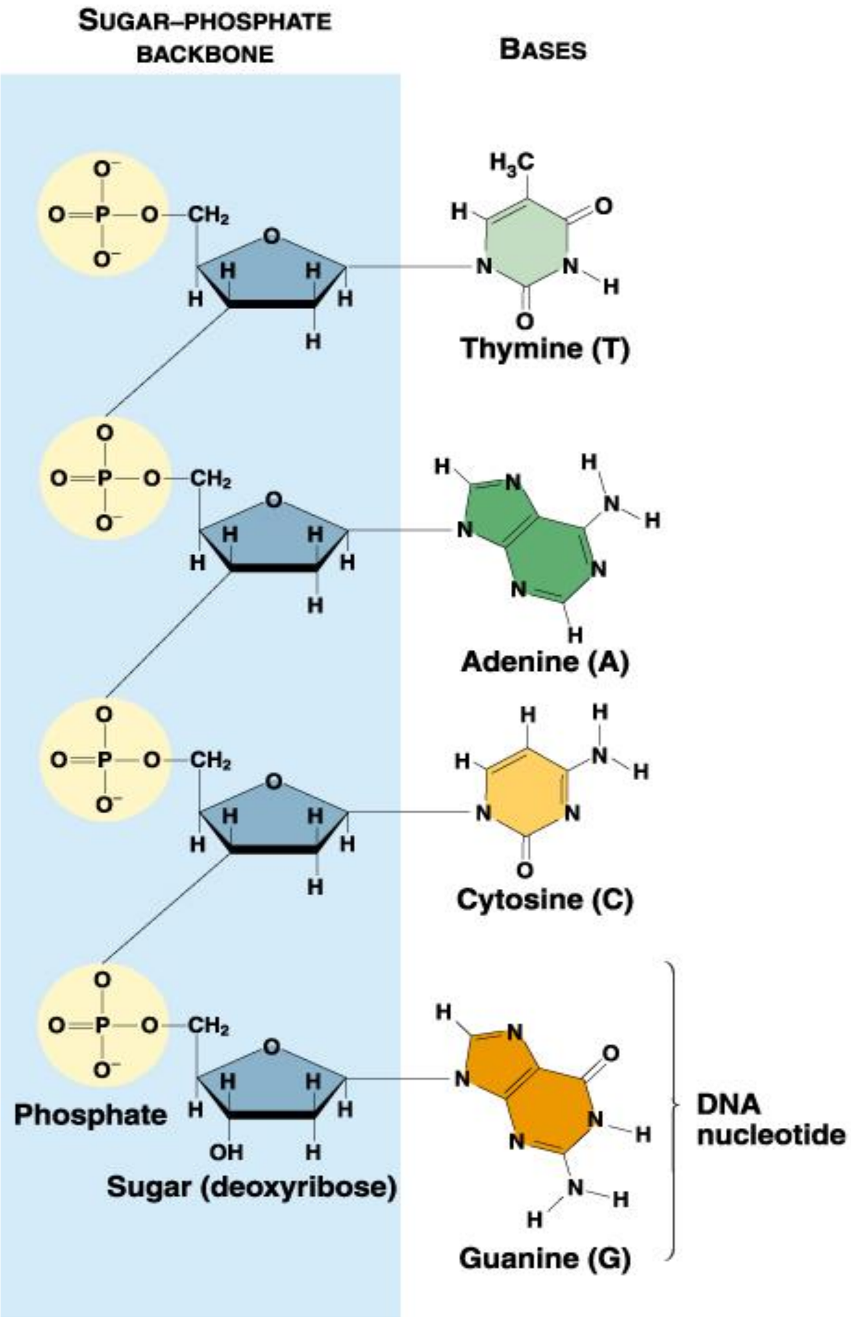
X=H: **DNA**

X=OH: **RNA**

Nucleoside

Nucleotide

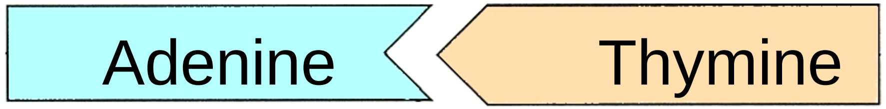
The 4 nucleotides of DNA



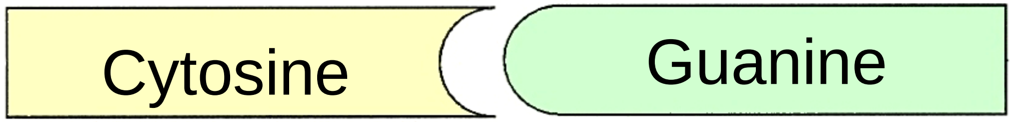
Bonding

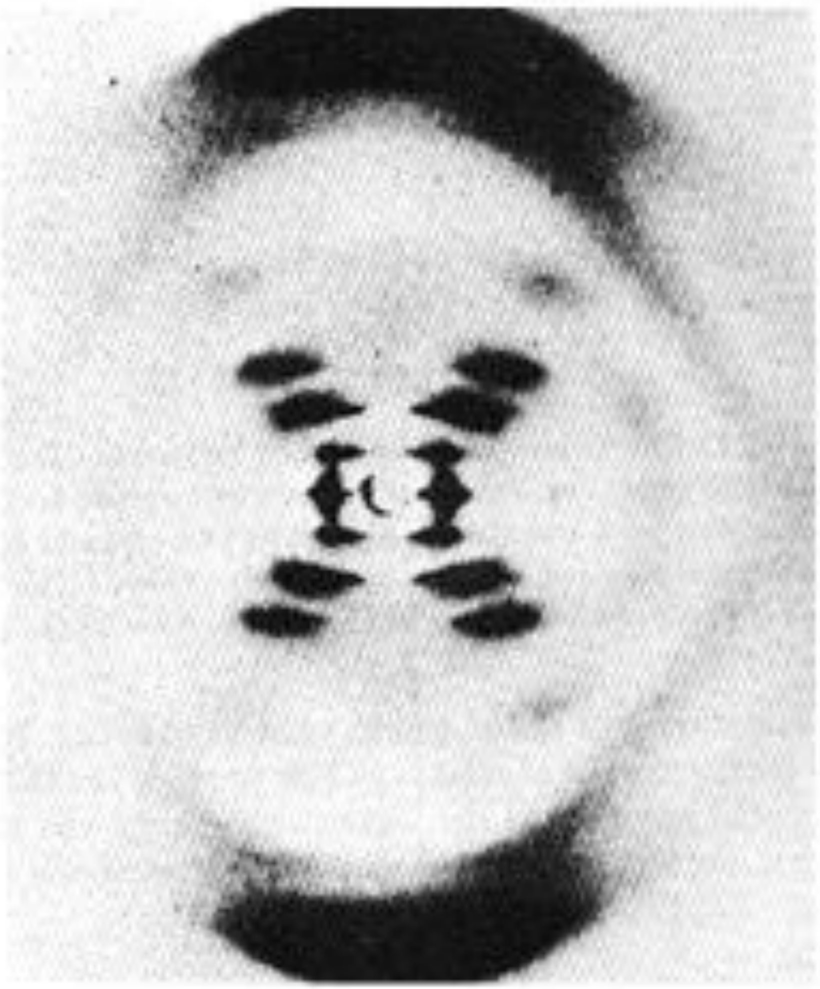
The bases always pair up in the same way

Adenine forms a bond with Thymine

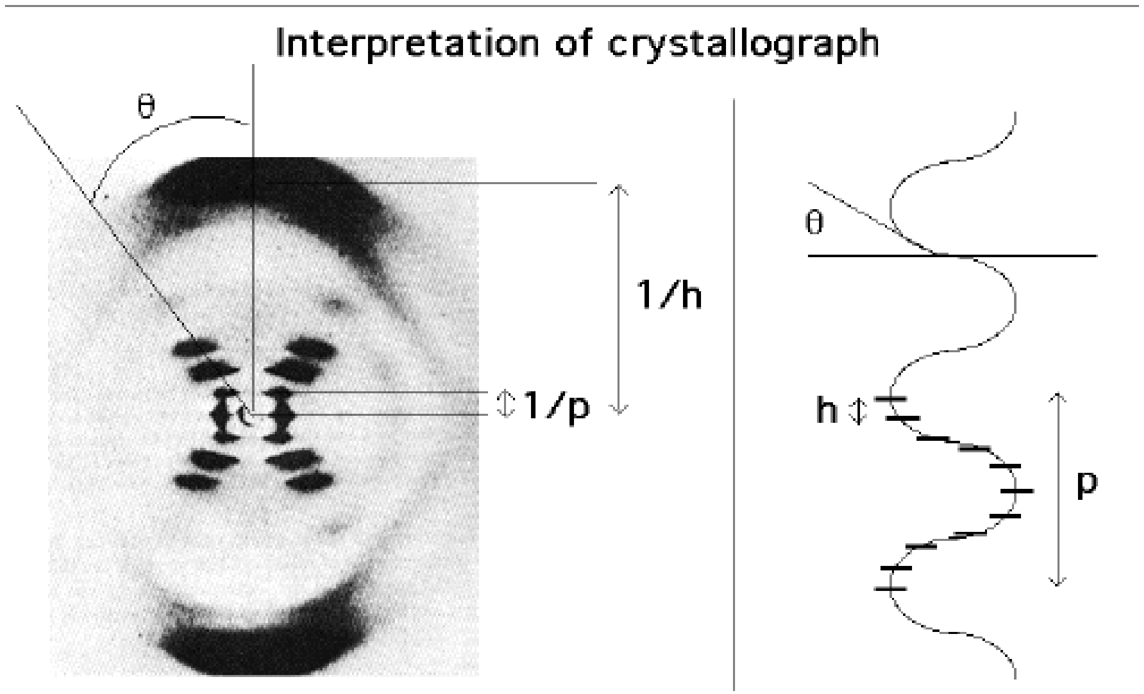


and Cytosine bonds with Guanine





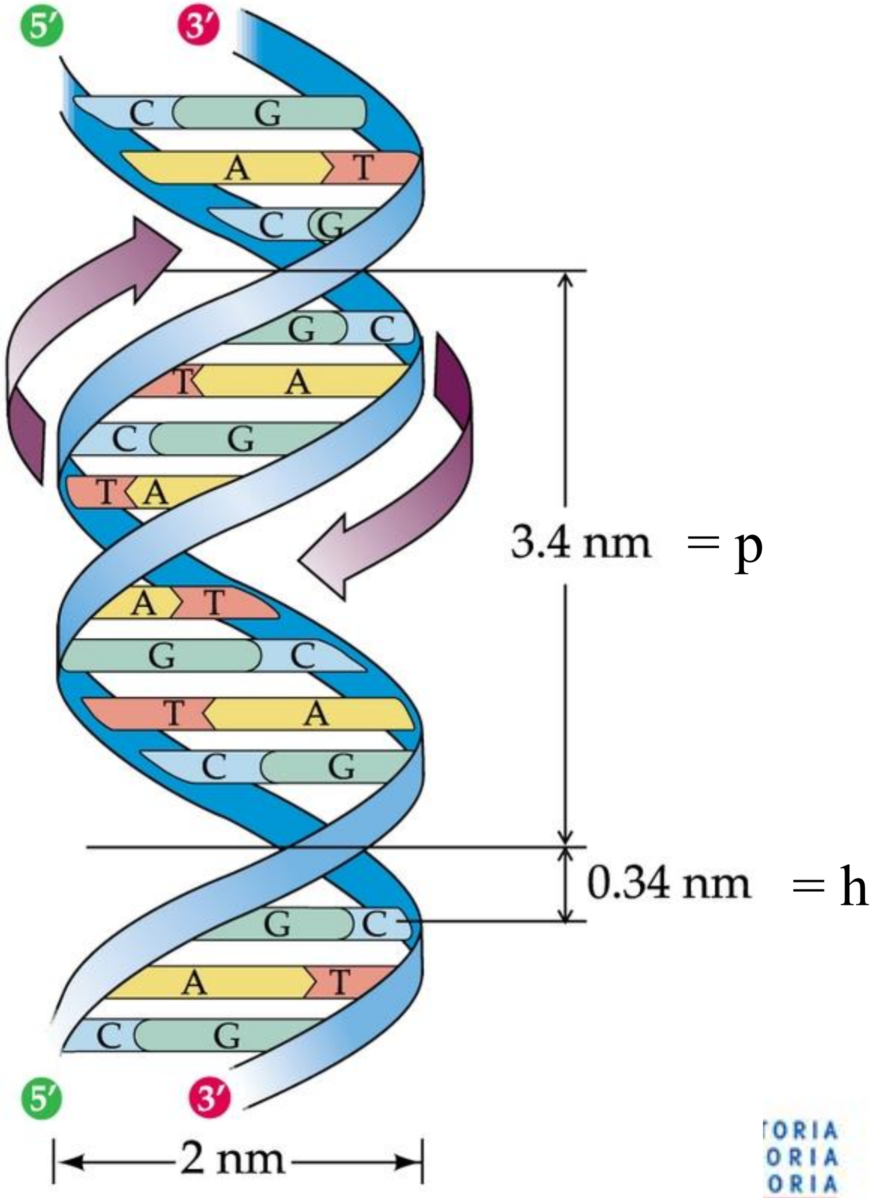
The most important X-ray diffraction pattern in history: DNA



θ - tilt of helix (angle from perpendicular to long axis)

h = 3.4 Å (Distance between bases)

p = 34 Å (Distance for one complete turn of helix; Repeat unit of the helix)

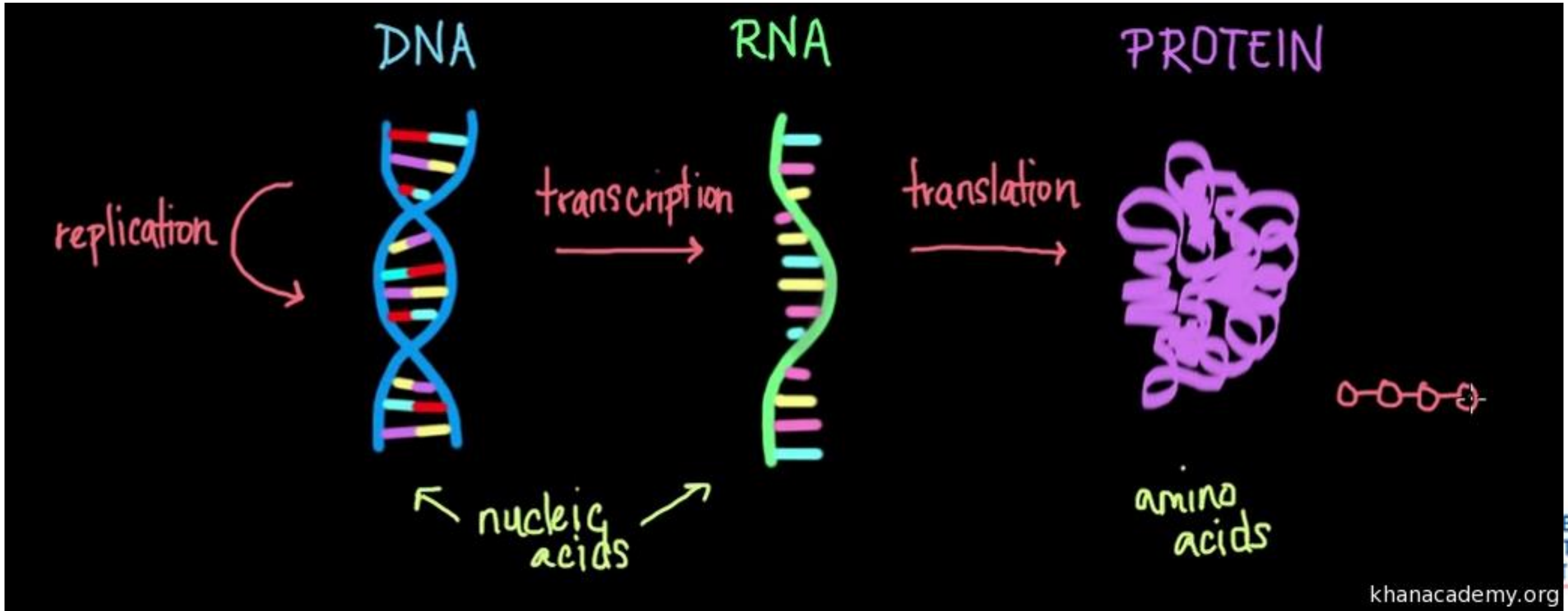


Introduction to molecular biology

- “DNA makes RNA makes protein”
- Encoded instruction (**DNA**) is *transcribed* in an intermediate form (**RNA**) and *translated* to a functional molecule (**protein**)

nucleus

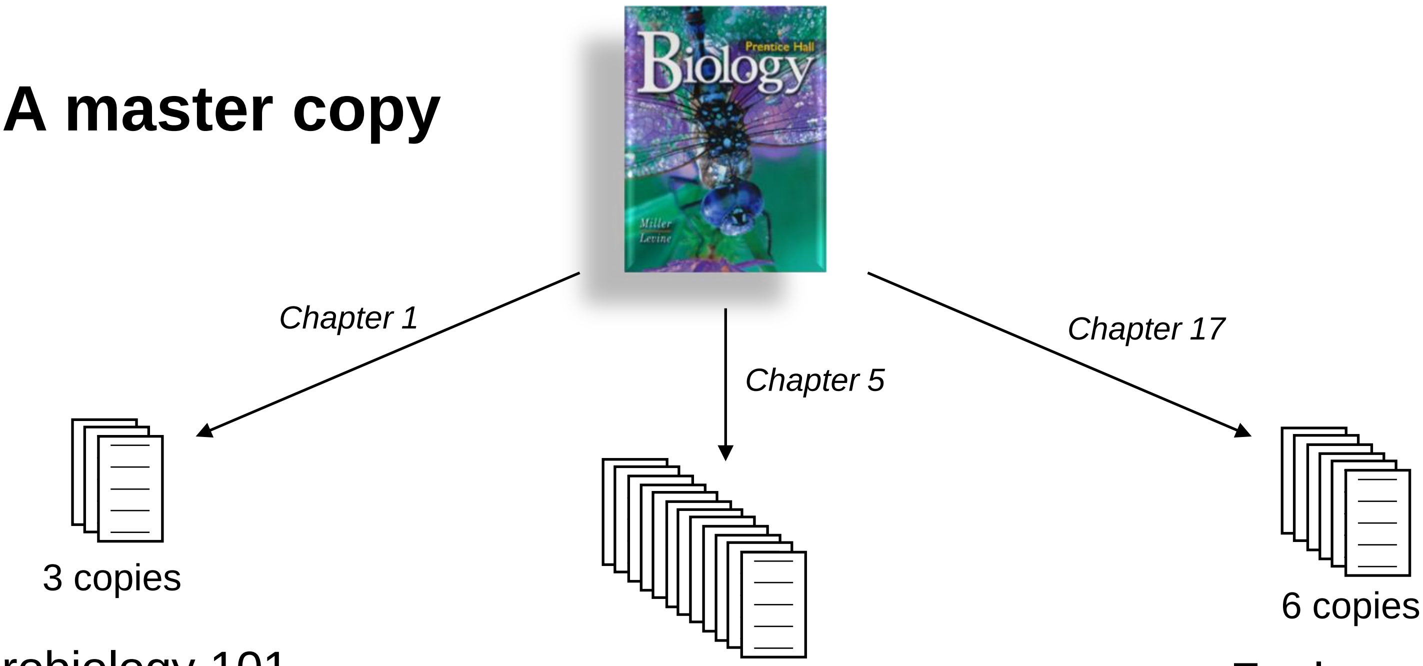
cytoplasm/ER



khanacademy.org

Transcription:
the copying and amplifying phase

Remember the days of photocopying textbooks?



Library copy

DNA master copy

Chapter 1

Chapter 5

Chapter 17

3 copies

Microbiology 101

20 copies

Genetics 101

6 copies

Zoology 101

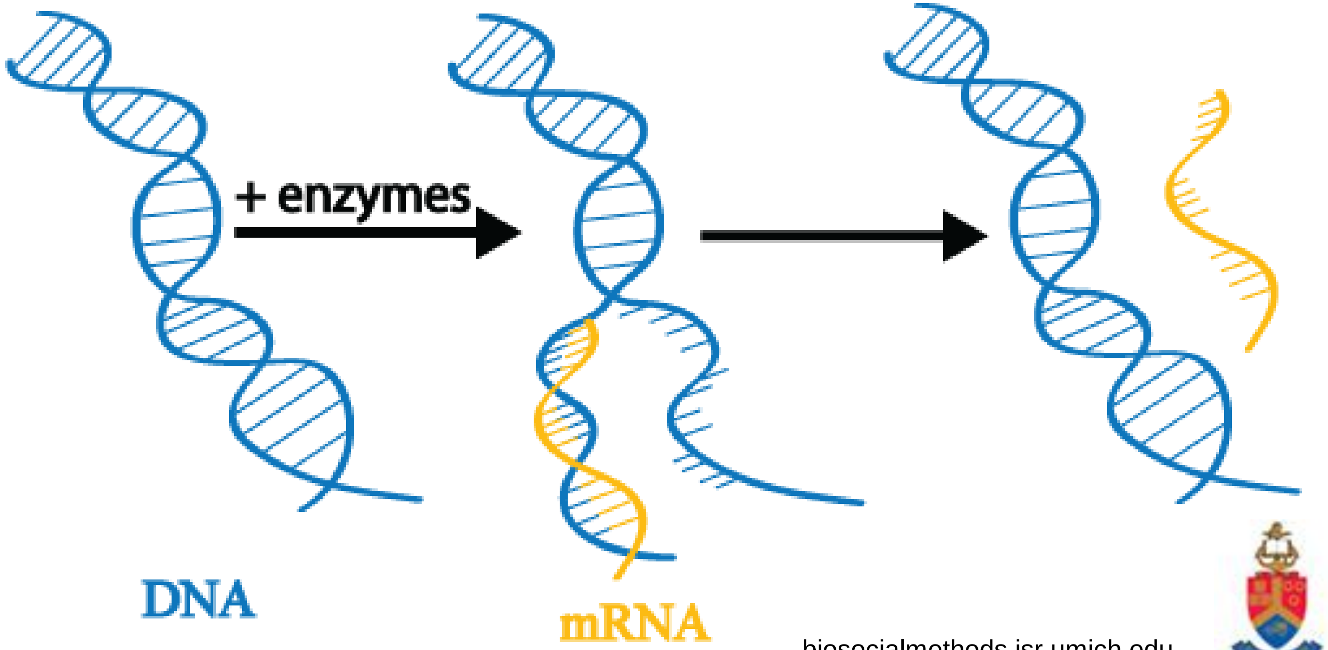
RNA transcripts

Transcription:

the copying and amplifying phase

- A segment of the DNA (e.g. a gene coding for a protein) is *transcribed* into a single-stranded **messenger RNA (mRNA)**
- RNA behaves similarly to DNA, but U pairs with A on the DNA strand instead of T

This happens in the nucleus:

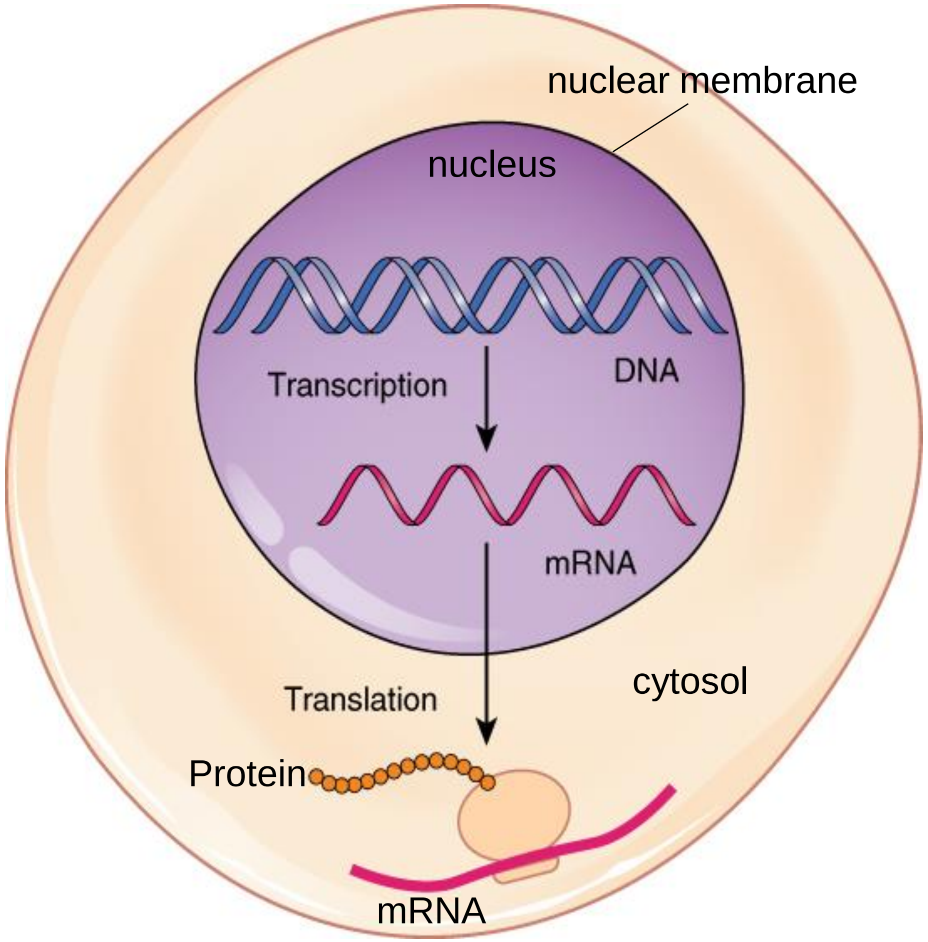


biosocialmethods.isr.umich.edu

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Transcription:

the copying and amplifying phase



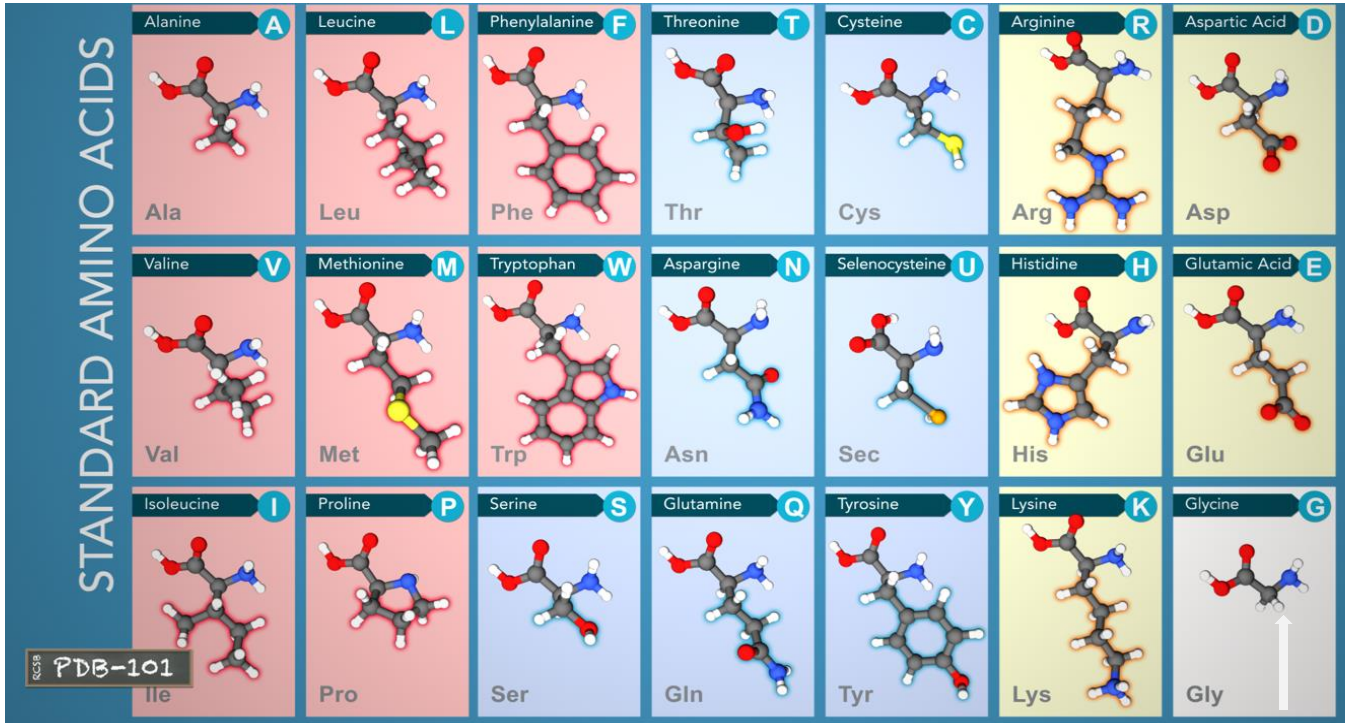
oerpub.github.io

- The mRNA transcript *carries* the code from the nucleus to the cytosol
- Then, the message is *translated* into a protein (amino acid) sequence
- The more mRNA transcripts are produced for a gene, the more protein is produced
- The selective transcription and translation of a specific gene sequence is collectively called **gene expression**

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Translation: De-coding a DNA sequence into functional protein

- There are 21 essential amino acids. The sequence in which they are linked to each other will determine the protein’s function



Hydrophobic **Hydrophilic or polar** **Charged** No side chain

Translation: De-coding a DNA sequence into functional protein

How can four types of nucleotide encode 21 unique amino acids?

1. Single-letter code: 4 possibilities
2. Double-letter code: 4^2 = 16 possibilities
3. Triple-letter code: 4^3 = 64 possibilities

- The codon system of three-letter RNA code corresponding to a single amino acid is universal to all life
- Some amino acids have several possible codons (**code is redundant: reduces error**)
- Some codons represent STOP instructions rather than encoding amino acids

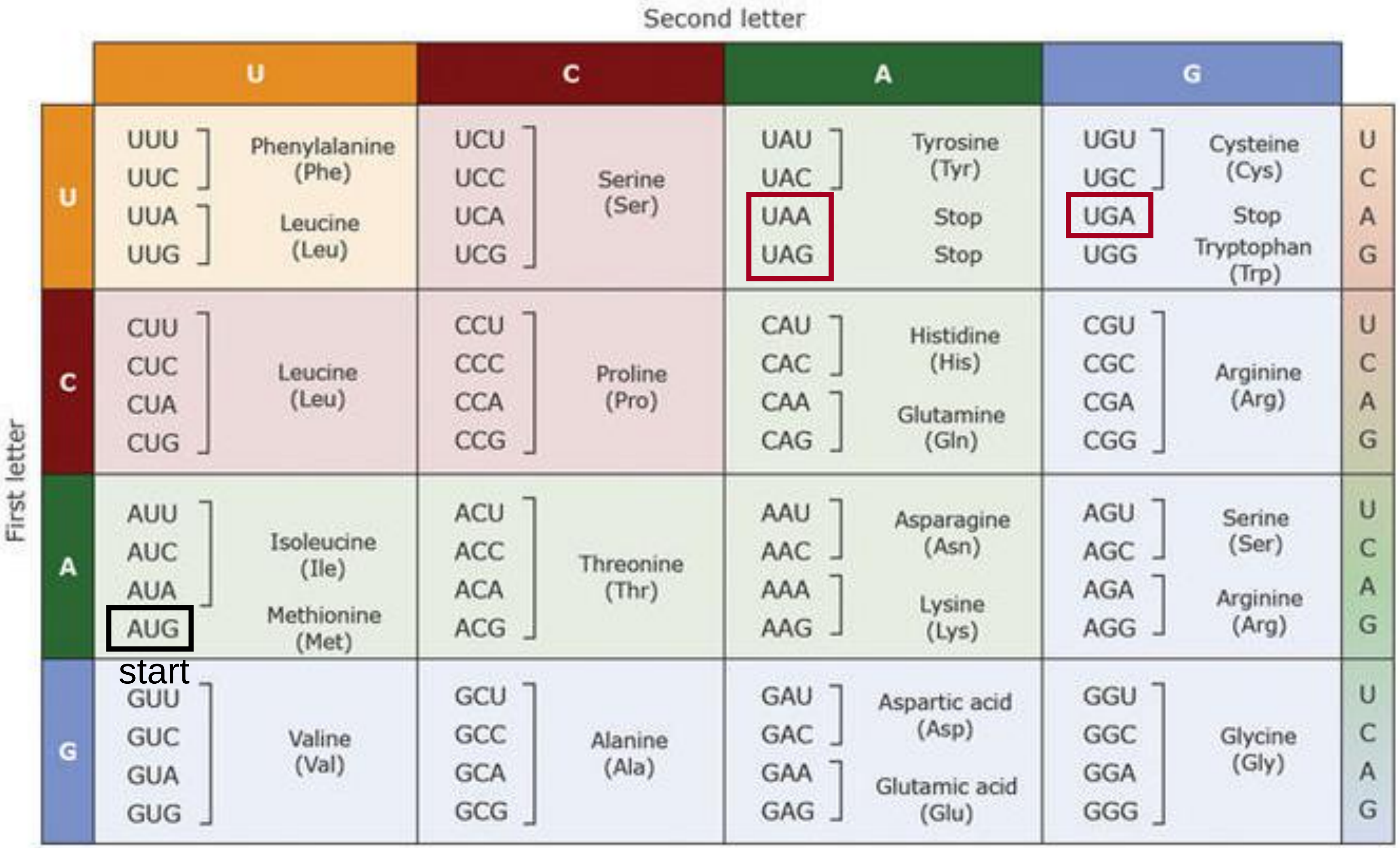
UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Translation: De-coding a DNA sequence into functional protein

☐ start codon

☐ stop codons

The genetic code

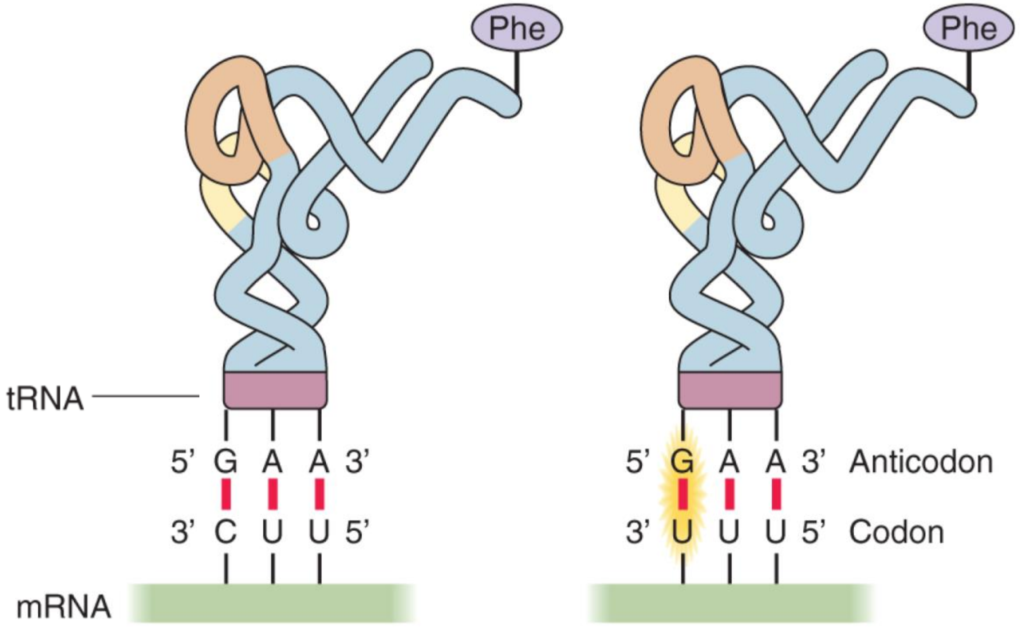


Second letter

First letter	U	C	A	G	
U	UUU UUC Phenylalanine (Phe) UUA UUG Leucine (Leu)	UCU UCC UCA UCG Serine (Ser)	UAU UAC Tyrosine (Tyr) UAA Stop UAG Stop	UGU UGC Cysteine (Cys) UGA Stop UGG Tryptophan (Trp)	U C A G
C	CUU CUC CUA CUG Leucine (Leu)	CCU CCC CCA CCG Proline (Pro)	CAU CAC Histidine (His) CAA CAG Glutamine (Gln)	CGU CGC CGA CGG Arginine (Arg)	U C A G
A	AUU AUC AUA Isoleucine (Ile) AUG start Methionine (Met)	ACU ACC ACA ACG Threonine (Thr)	AAU AAC Asparagine (Asn) AAA AAG Lysine (Lys)	AGU AGC Serine (Ser) AGA AGG Arginine (Arg)	U C A G
G	GUU GUC GUA GUG Valine (Val)	GCU GCC GCA GCG Alanine (Ala)	GAU GAC Aspartic acid (Asp) GAA GAG Glutamic acid (Glu)	GGU GGC GGA GGG Glycine (Gly)	U C A G

Translation: De-coding a DNA sequence into functional protein

- Specialized **transfer RNAs (tRNA)** each link to a specific amino acid (e.g. Phe). Each tRNA will have a unique **anticodon**
- The anticodons pair with each respective codon in the mRNA to bring the corresponding amino acid in place for addition to the growing protein
- Some mismatches are occasionally permitted – this “wobble pairing” allows several different codons to encode the same amino acid



Normal pairing **Wobble pairing**

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

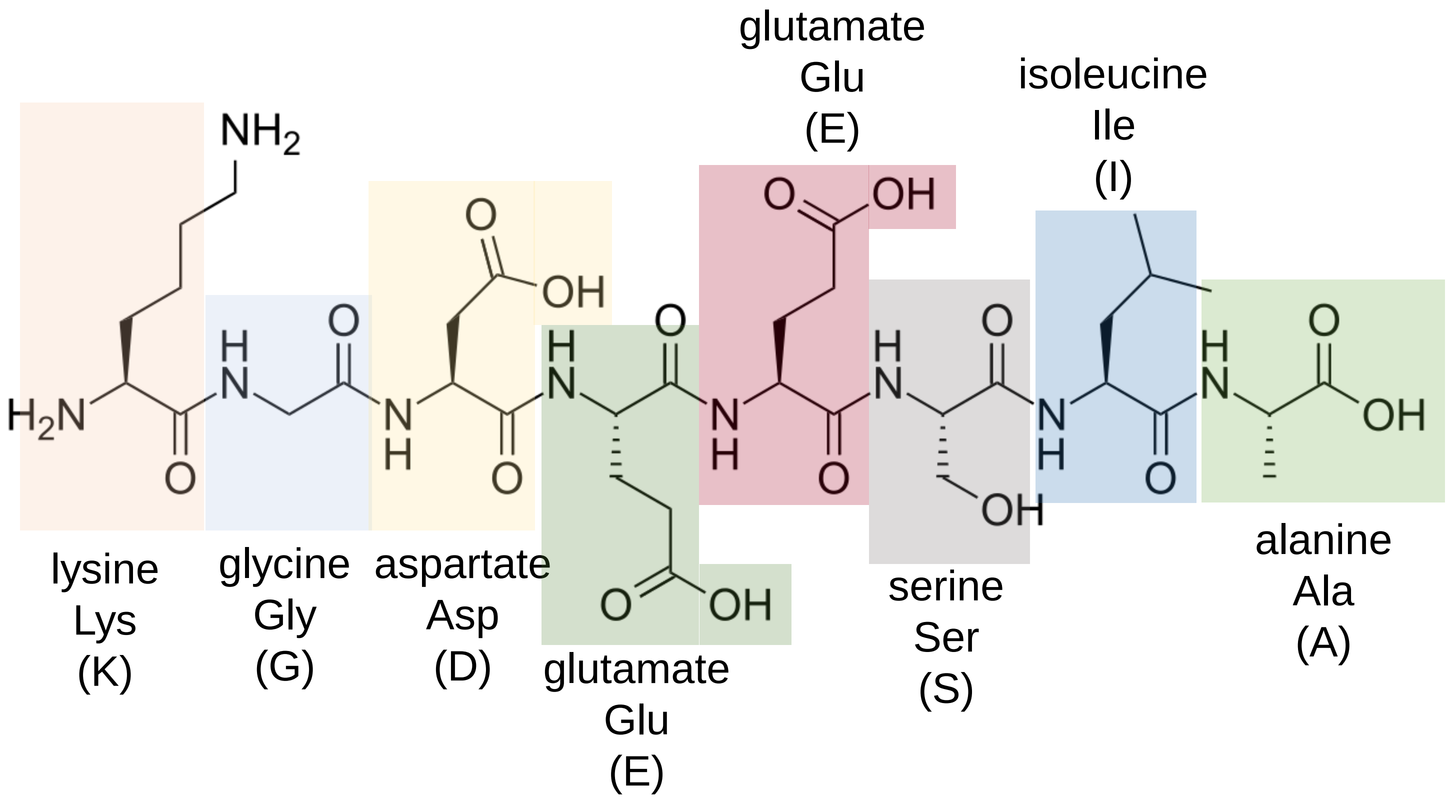
Translation: De-coding a DNA sequence into functional protein

Watch: translation video
https://www.youtube.com/watch?v=gG7uCskUOrA

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

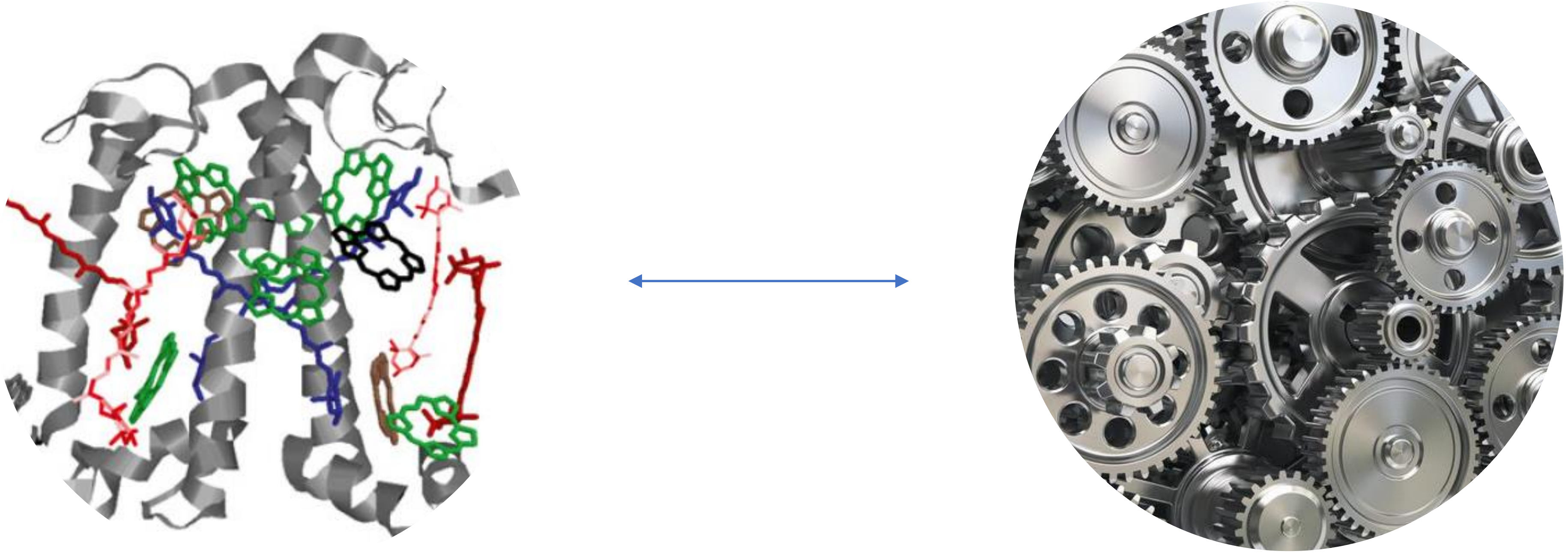
Translation:

A closer look at a peptide chain



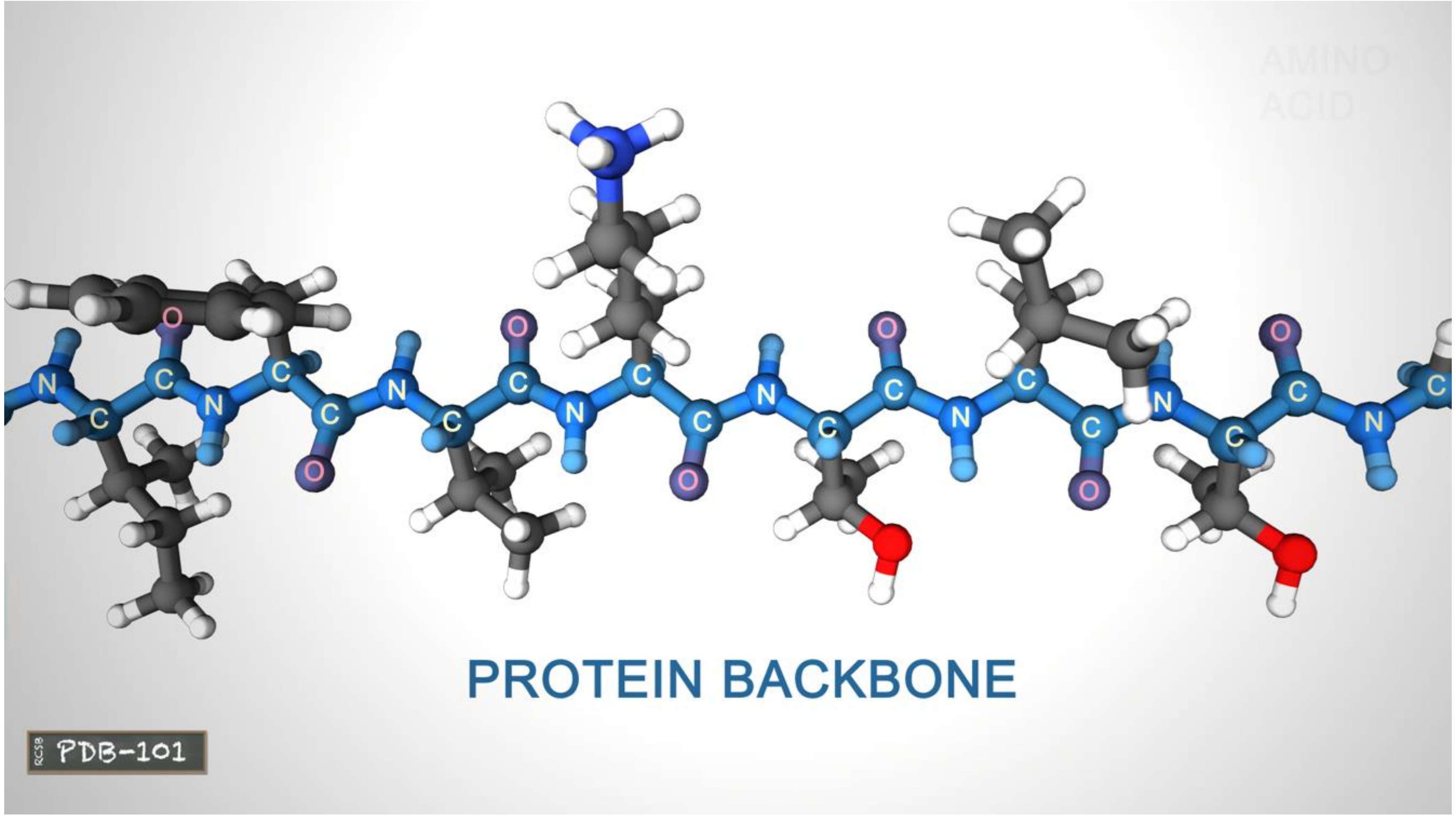
Proteins

"Hydrogen atom" of life



>100 000 types in the human body!!

Protein Structure: Primary Structure

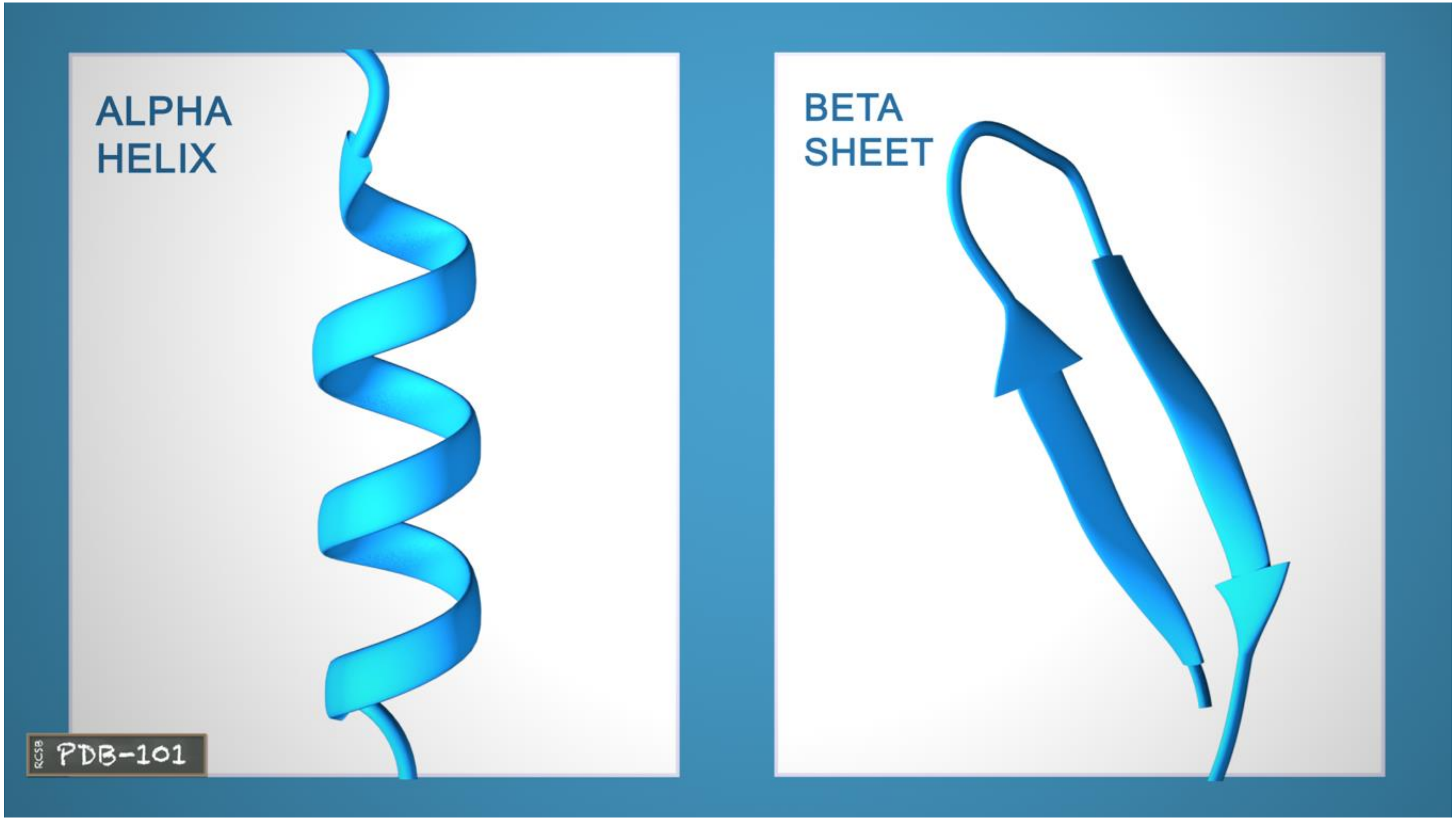


The linked series of carbon, nitrogen, and oxygen atoms make up the **protein backbone**.

pdb101.rcsb.org

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Protein Structure: Secondary Structure

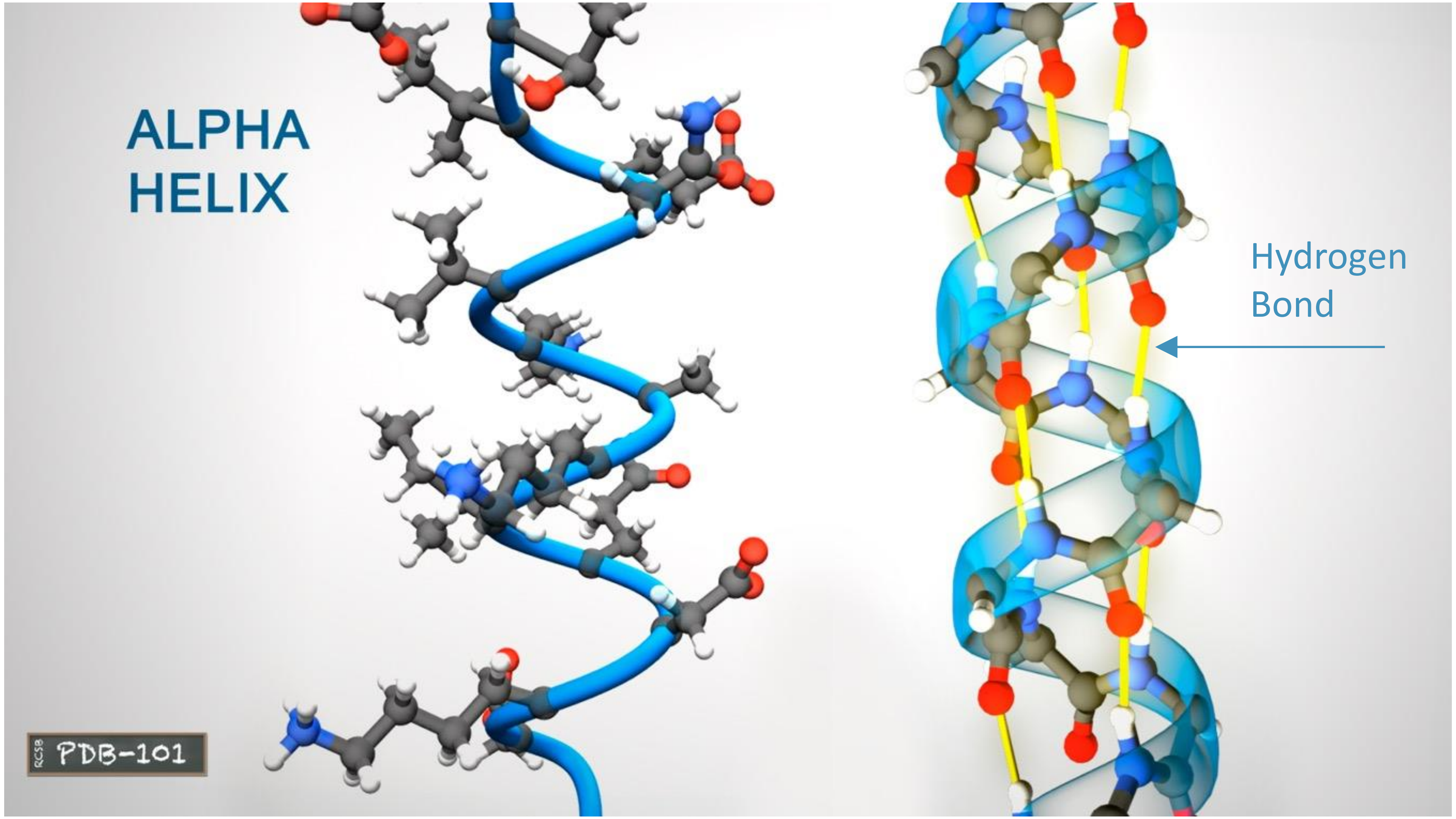


The protein chains often fold into two types of secondary structures: **alpha helices**, or **beta sheets**.

pdb101.rcsb.org

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

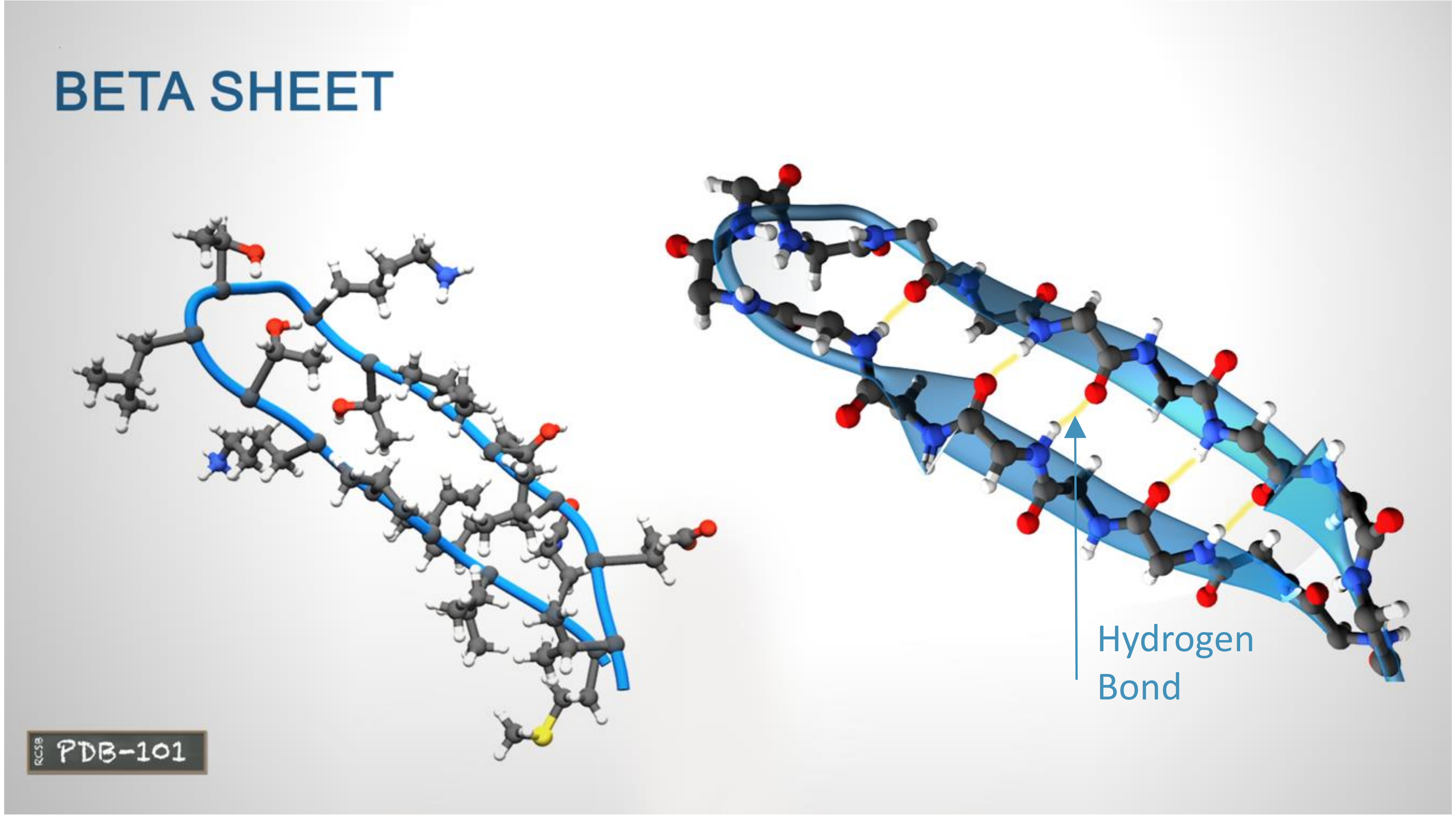
Protein Structure: Secondary Structure



An alpha helix is a **right-handed coil** stabilized by **hydrogen bonds** between the amine and carboxyl groups of nearby amino acids

pdb101.rcsb.org

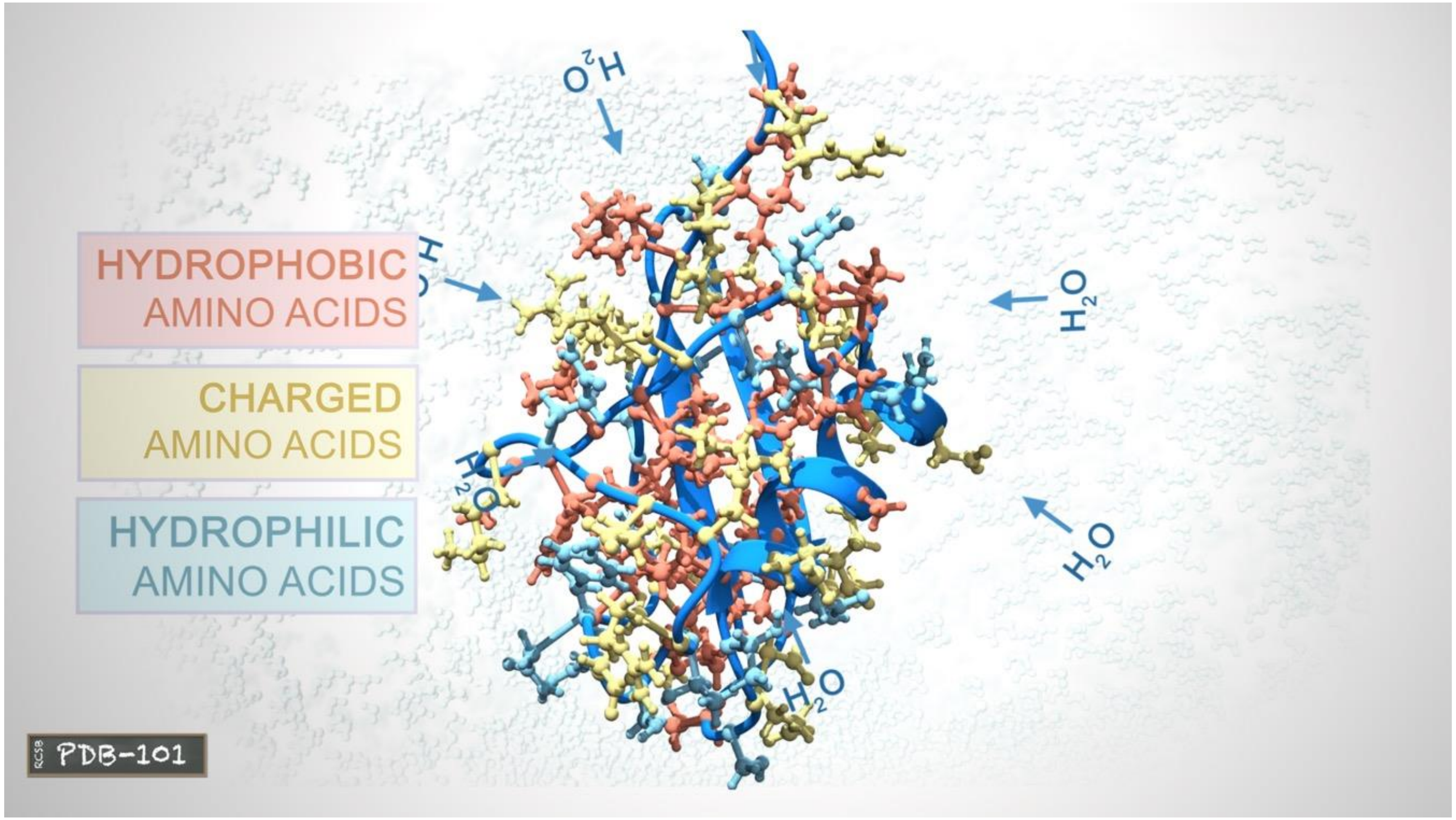
Protein Structure: Secondary Structure



Beta-sheets are formed when hydrogen bonds stabilize two or more adjacent strands.

pdb101.rcsb.org

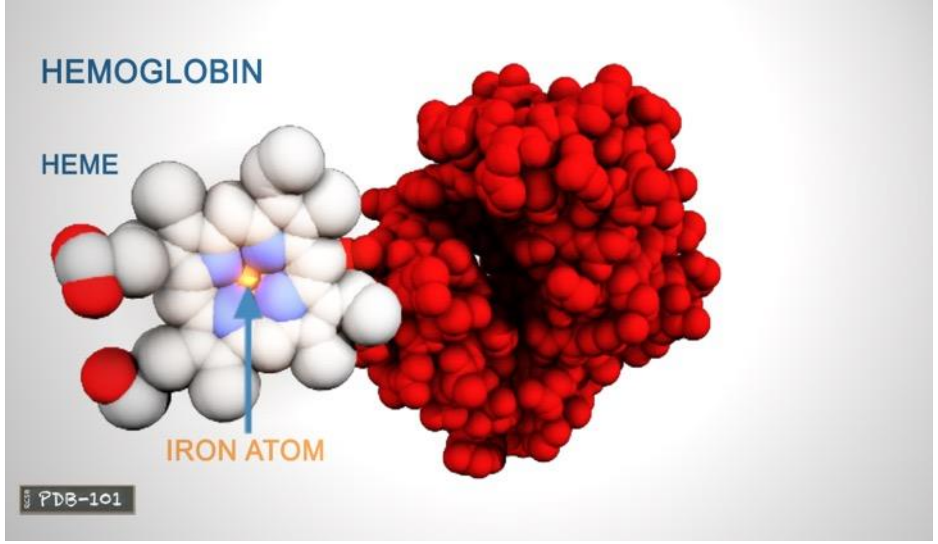
Protein Structure: Tertiary Structure

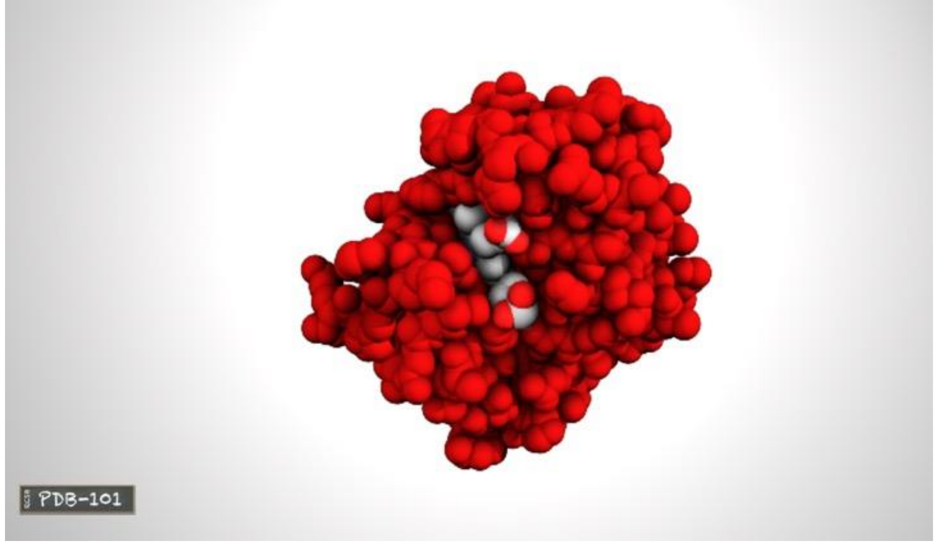


The tertiary structure of a protein is the **three-dimensional shape of the protein chain**. This shape is determined by the characteristics of the amino acids making up the chain.

pdb101.rcsb.org

Protein Structure: Tertiary Structure





pdb101.rcsb.org

The functions of many proteins rely on their three-dimensional shapes.
For example, hemoglobin forms a pocket to hold heme, a small molecule with an iron atom in the center that binds oxygen.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Protein folding

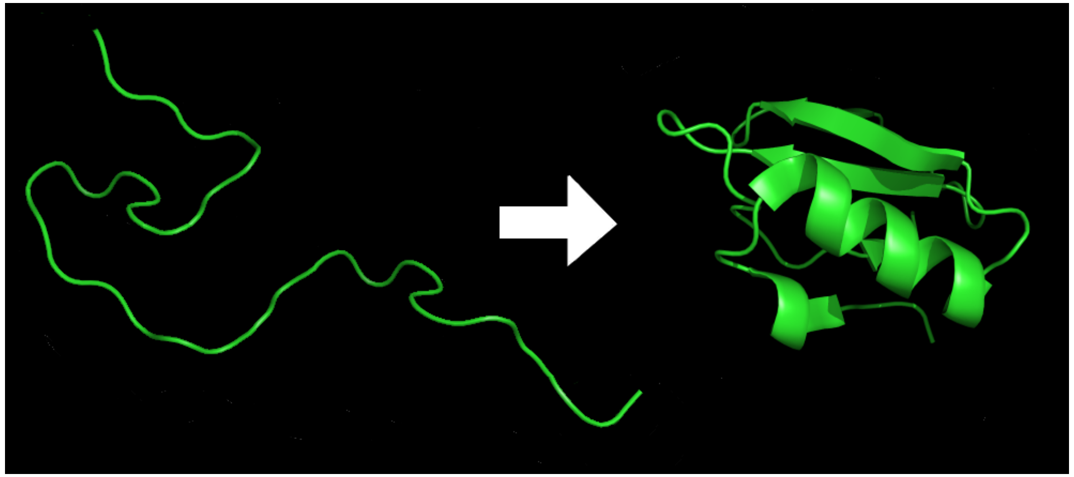


Image credit: Creative Commons license

Driving forces

- Hydrophobic interactions
- Hydrogen bonds
- (other) van der Waals interactions
- Electrostatic interactions
- Disulphide bonds

vs Conformational entropy

Misfolds can lead to severe diseases
E.g. Alzheimer's and Cystic Fibroses

Levinthal's paradox

Imagine that there was only a single bond between each amino acid in a protein of 101 amino acid residues. Imagine that there were only three possible configurations around each of those bonds. This means that the protein could adopt $3^{100} \sim 5 \times 10^{47}$ different conformations.
If the protein is able to sample 10^{13} different bond configurations per second then it would take 10^{27} years to sample all possible conformations of the protein.

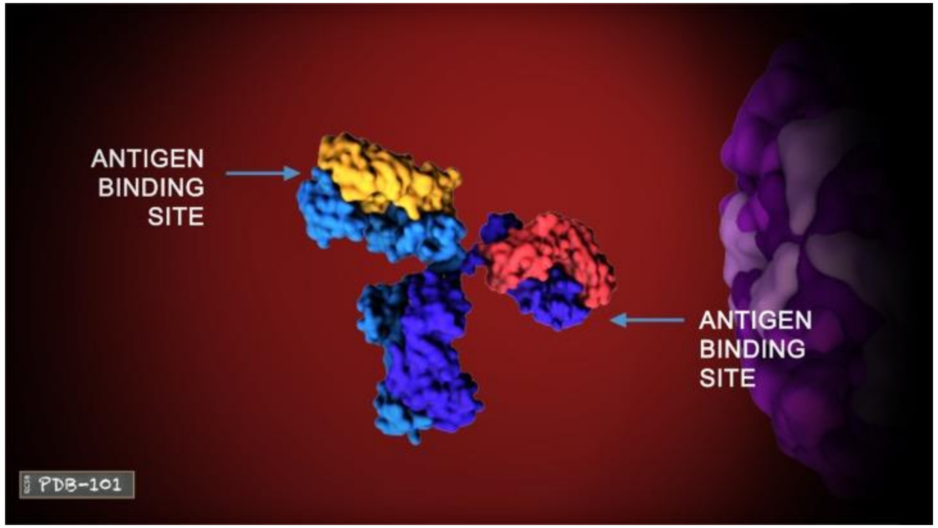
AlphaFold can simulate it!
Quantum Computers will do it even better!

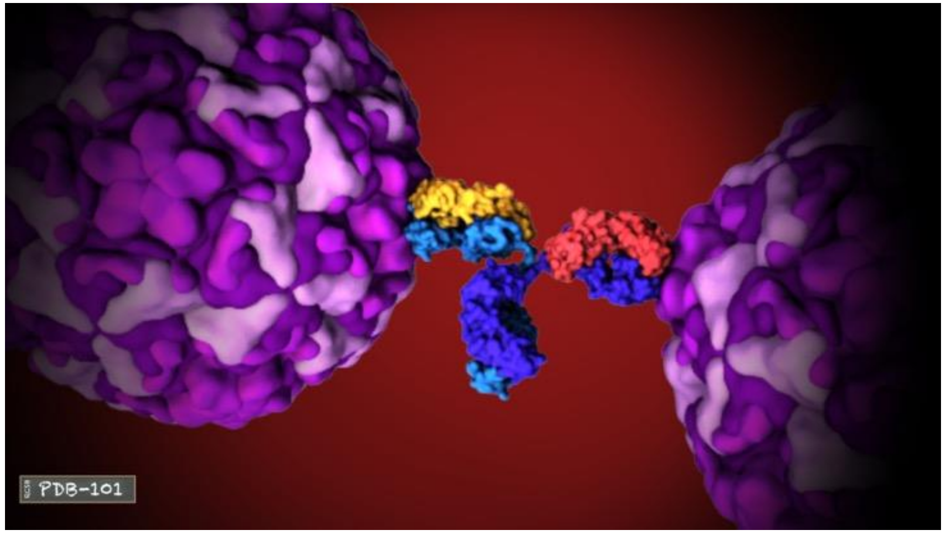
Protein functions

- Catalysing reactions (enzymes)
- Regulation of gene expression
- Building structures (skin, hair, etc.)
- Transport (across membranes or to different cellular compartments)
- Communication (receptors, signalling)
- Storage (bind specific molecules)
- Defense (antibodies bind to viruses or foreign molecules for destruction)
- Motors (generate mechanical forces, leading to torques/displacements)
- Light-harvesting (absorb light and transport photoexcitations)
- Electron and proton tunnelling (e.g. convert light into chemical energy)

pdb101.rcsb.org

Protein functions: Defense



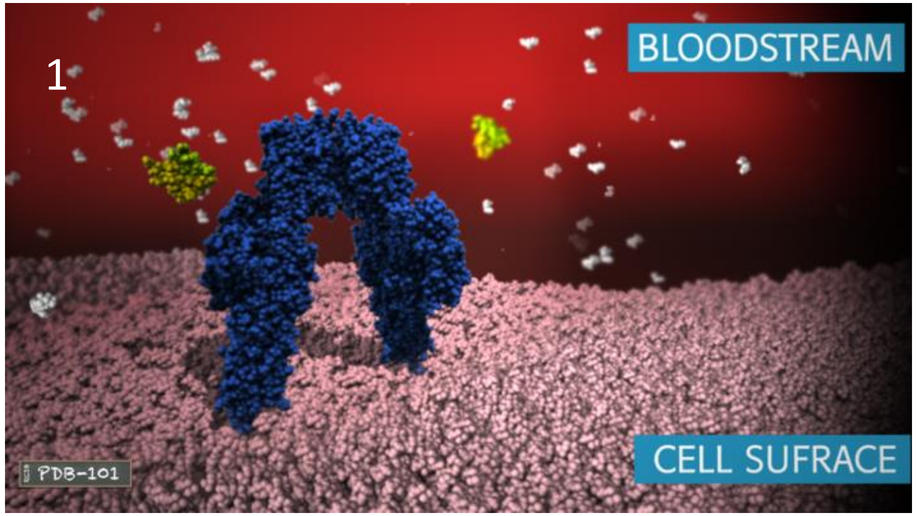


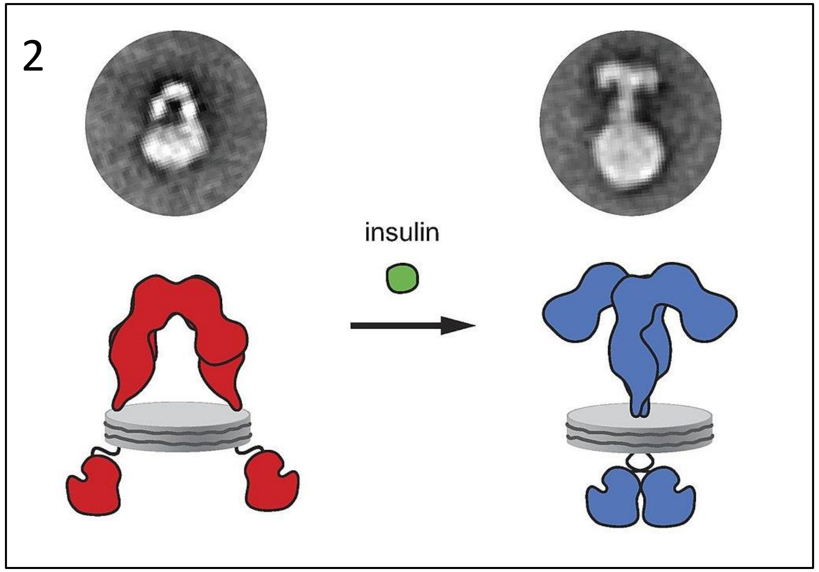
The flexible arms of **antibodies** protect us from disease by recognizing and binding to pathogens such as viruses, and targeting them for destruction by the immune system.

pdb101.rcsb.org

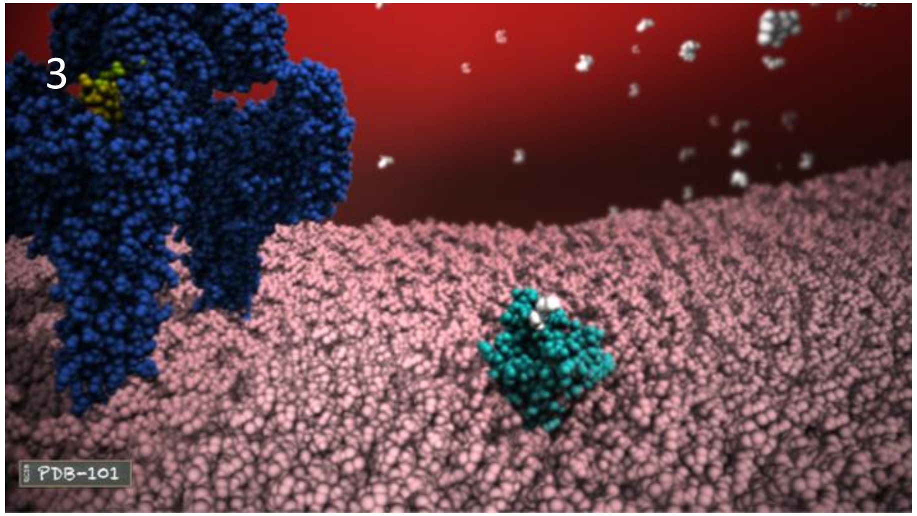
Protein functions: Communication

The **hormone** insulin (yellow) is a small, stable protein that can easily maintain its shape while travelling through the blood to regulate the blood glucose level.





Insulin binds to the insulin receptor (navy blue) and triggers an intracellular signaling pathway.



As a result, the glucose transporter (aqua) comes to the cell surface creating a channel for glucose (white) to enter the cell.

pdb101.rcsb.org

Protein functions: Transport

Aquaporin = water channel

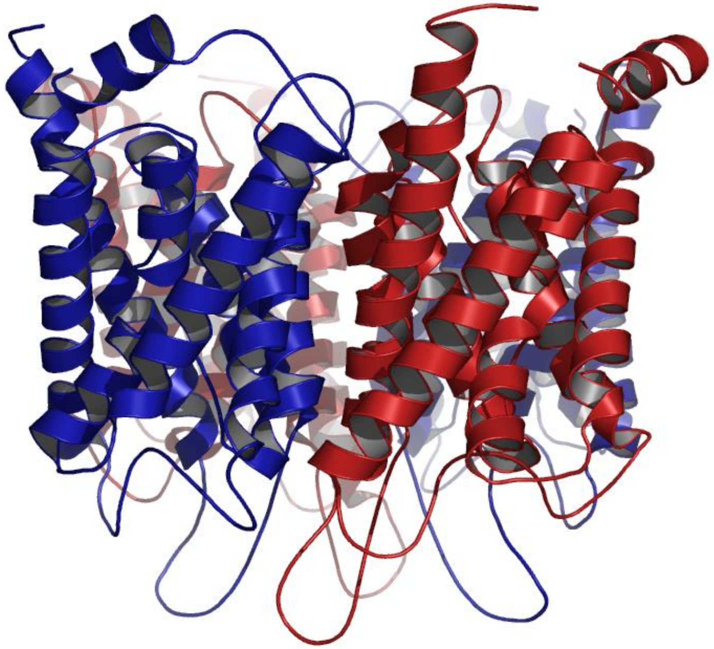


Image credit: Wiki Commons

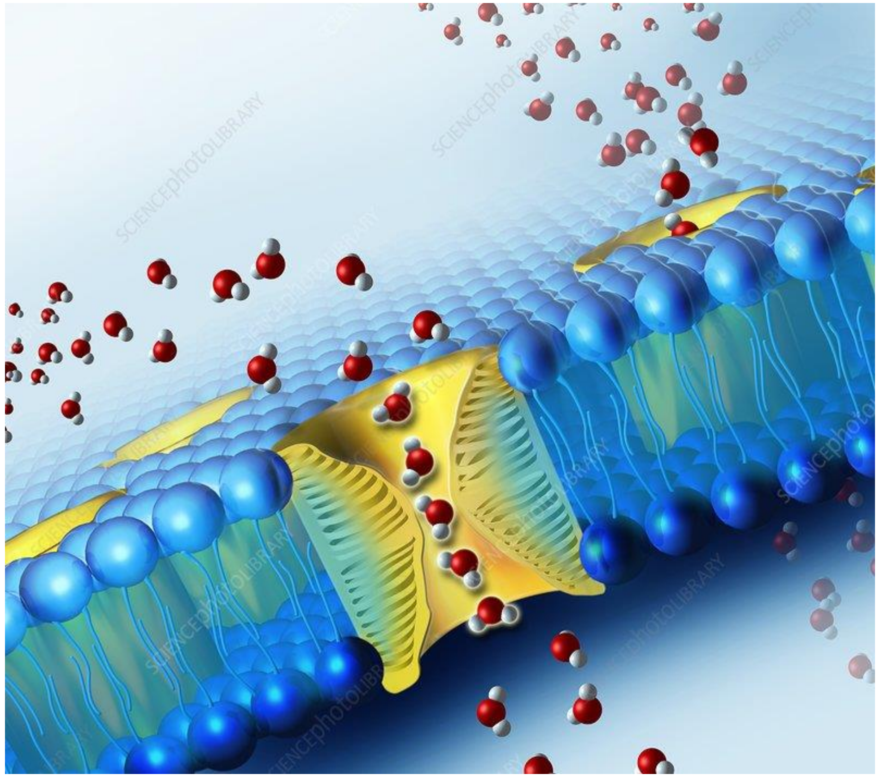
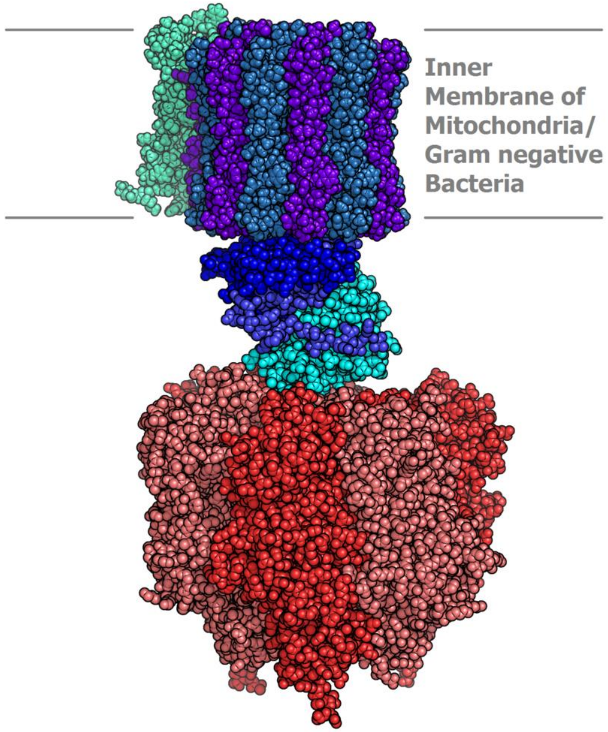


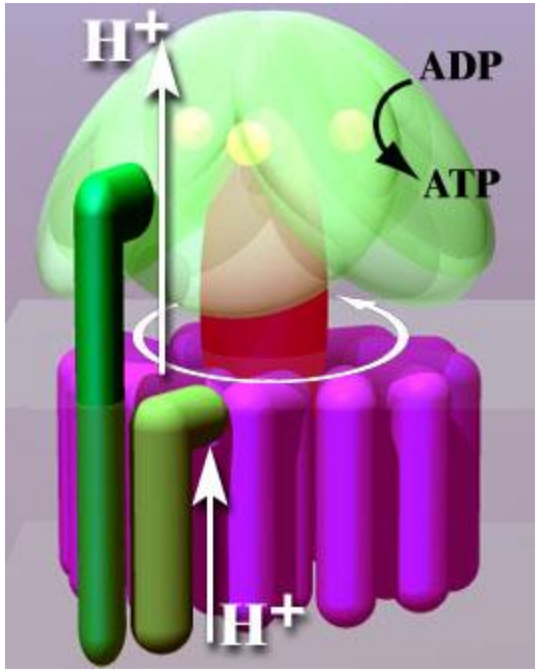
Image credit: Claus Lunau/Science Photo Library

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Protein functions: Transport

ATP synthase = proton pump





Rotates up to 42 000 rpm!

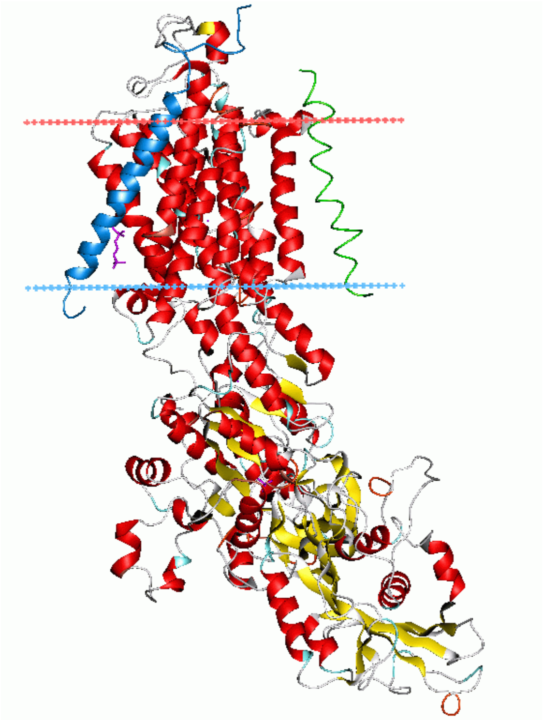
Cool animation: https://www.youtube.com/watch?v=kXpzp4RDGJI

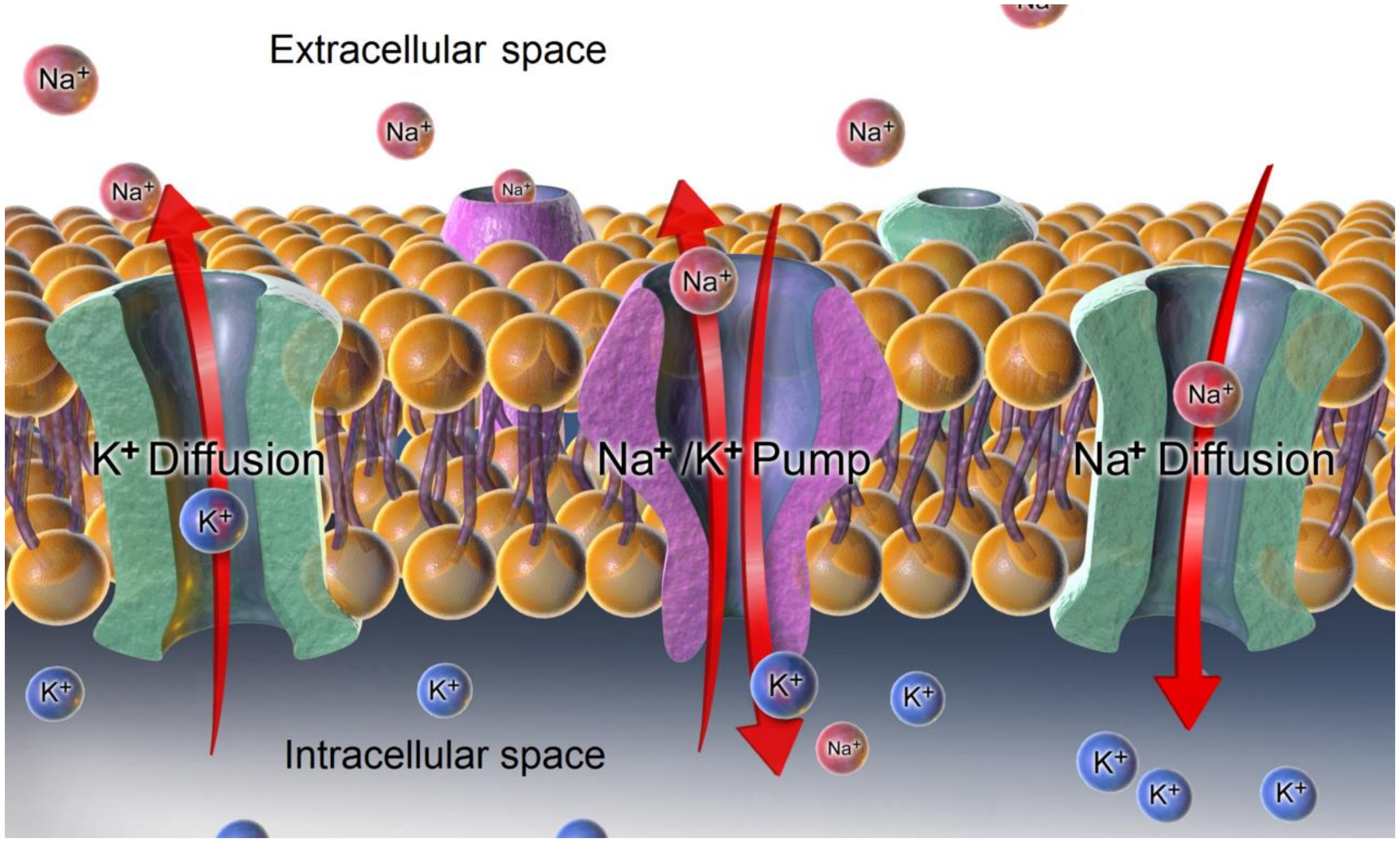
Image credit: Creative Commons

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Protein functions: Transport

Sodium & Potassium Channels, and Sodium-Potassium Pump



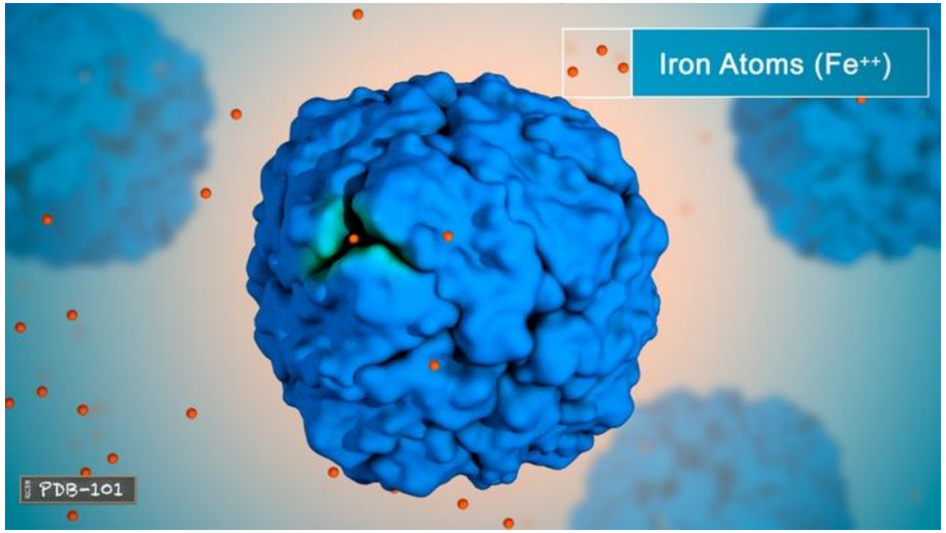


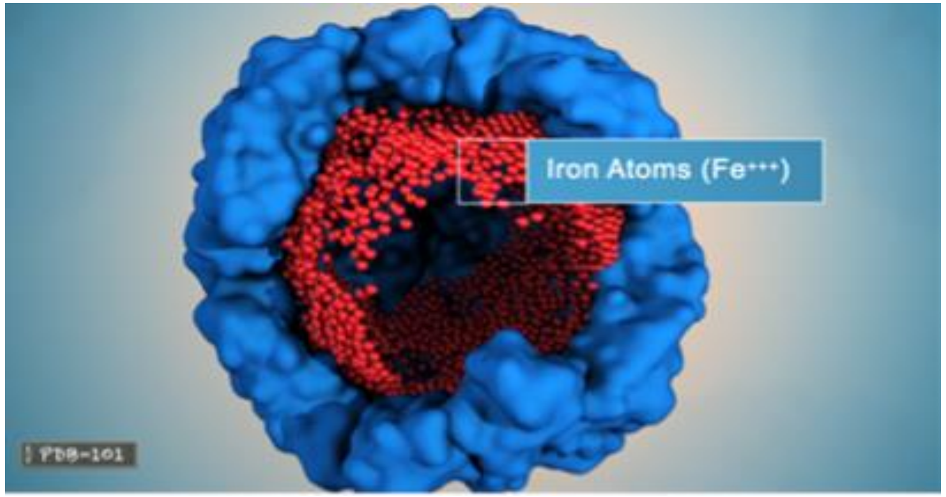
Cool animation: https://www.youtube.com/watch?v=ZKE8qK9UCrU

Image credit: Creative Commons

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Protein functions: Storage





Ferritin **stores** iron. It is a spherical protein with channels that allow the iron atoms to enter and exit depending on the organism's needs.

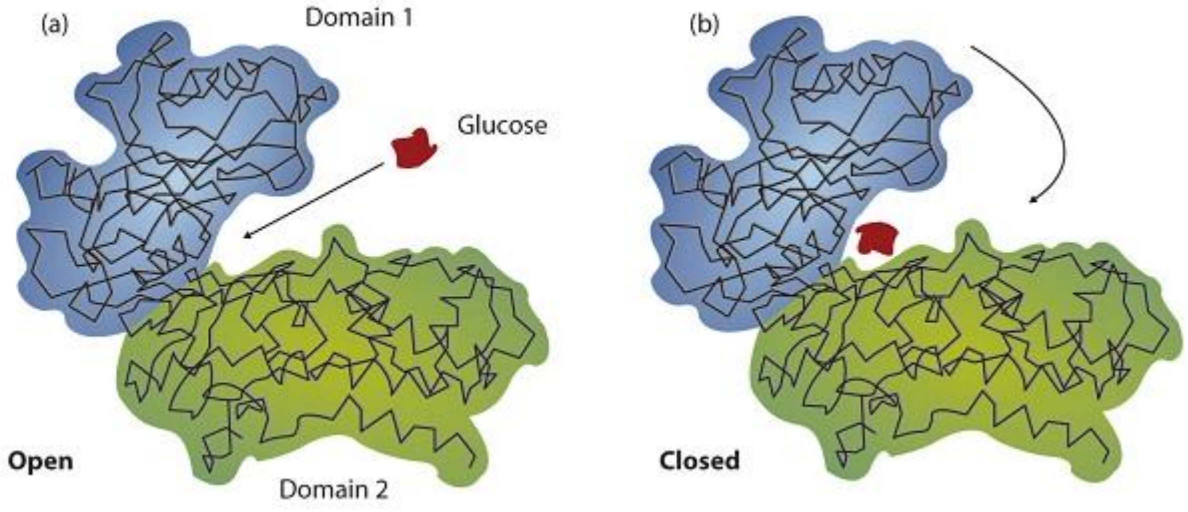
On the inside, ferritin forms a hollow space with the iron atoms attached to the inner wall.

Ferritin stores iron in the non-toxic form.

pdb101.rcsb.org

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Proteins are dynamic structures



https://chem.libretexts.org/

Enzymes switch from an inactive to active conformation upon binding of an activator molecule.

Some food for thought

"Biophysics offers the best of two fields: the complex beauty of Biology and the rigour of Physics."

Towan Nöthling, PhD student

"The more I understand Physics, the more Biology amazes me. The fact that life works – in such exquisite detail, with such remarkable efficiency and elegance, in such a bewildering variety of organisms – is completely mind-boggling!"

"Faced with all these miraculous processes, we will only ask, 'How could anything like that happen at all?' "

Philip Nelson: Biological Physics. Energy, Information, Life

"What a privilege to live in an era where technology enables us to learn about life's processes at such an exceptionally deep level of detail – probably the most fundamental level of detail!"

"Life is a miracle… who can honestly dispute this? How can the reductionist and materialistic frameworks of modern science give a satisfactory explanation for life's processes? Even when taking into account the principle of emergence, how can we explain realities like personality and consciousness? Isn't it then truly remarkable that we can get deep, quantitative information about life's processes using the tools of Physics?"

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

A few animations to get you inspired

- The Inner Life of the Cell: https://www.youtube.com/watch?v=QplXd76lAYQ
- The Inner Life of the Cell: Protein Packing https://www.youtube.com/watch?v=uHeTQLNFTgU
- ATP synthase in action: https://www.youtube.com/watch?v=kXpzp4RDGJI
- The Molecular Basis of Life: https://www.youtube.com/watch?v=fpHaxzroYxg
- Powering the Cell: https://www.youtube.com/watch?v=ahf2HqY_vGg
- Neuronal signalling: https://pdb101.rcsb.org/learn/videos/neuronal-signaling-and-sodium-potassium-pump