Introduction to Biophysics (I)

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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 of single biomolecules
- Biomolecule-nanoparticle interactions
- Superresolution imaging

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What is Biophysics?

- Bio—physics: compare with geo—physics and astro—physics
- Biophysics is an interdisciplinary field that applies the principles and methods of physics to understand how biological systems work.
- It is the place where physics, biology, and often also chemistry merge.
- Biophysics covers all scales of biological organisation, from the molecular or sub-molecular level to the level of organisms and populations of organisms.
- Notable source of innovation
- Biophysics vs Biochemistry vs Biological Physics / Physics in Biology

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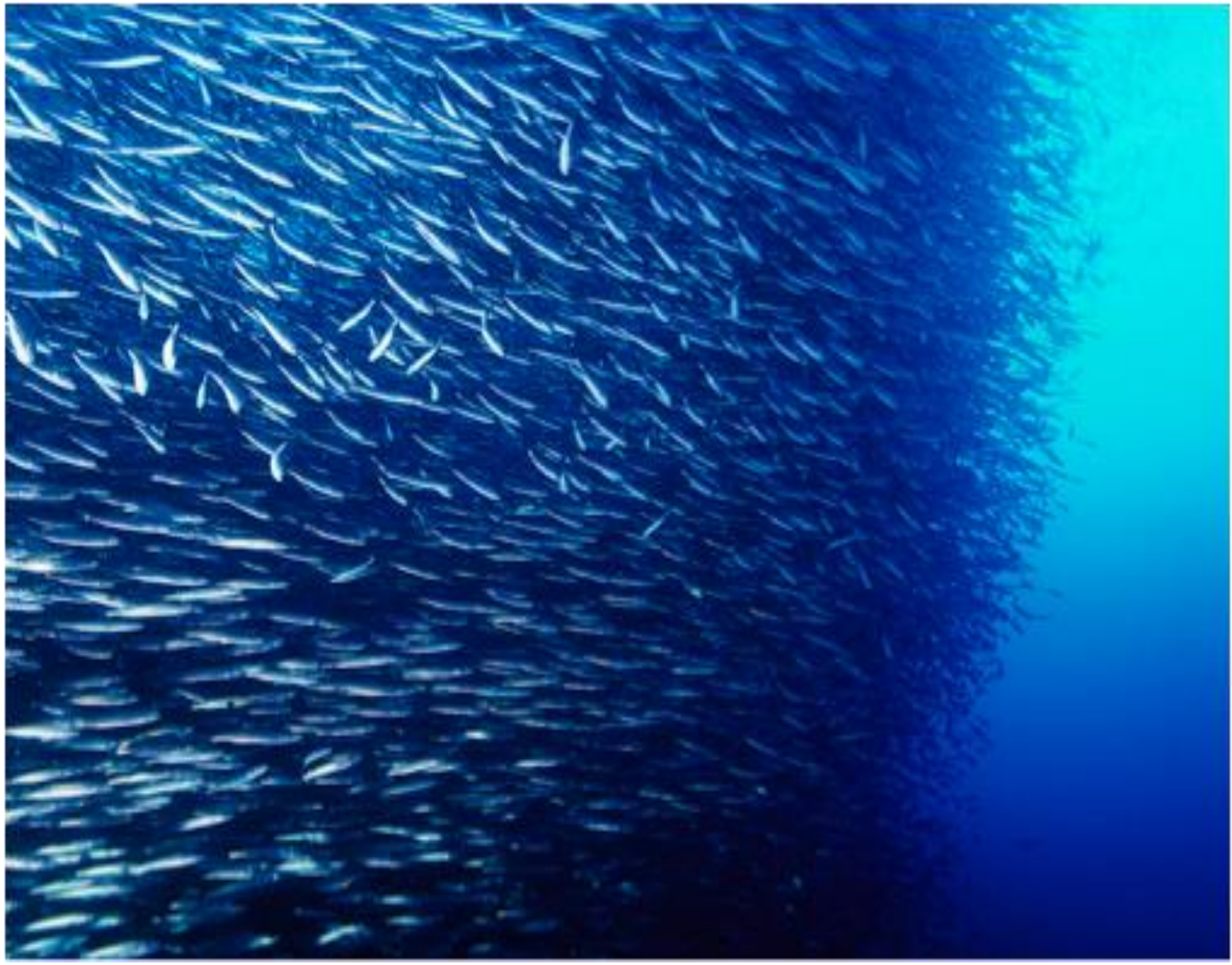
Biophysics is all around us



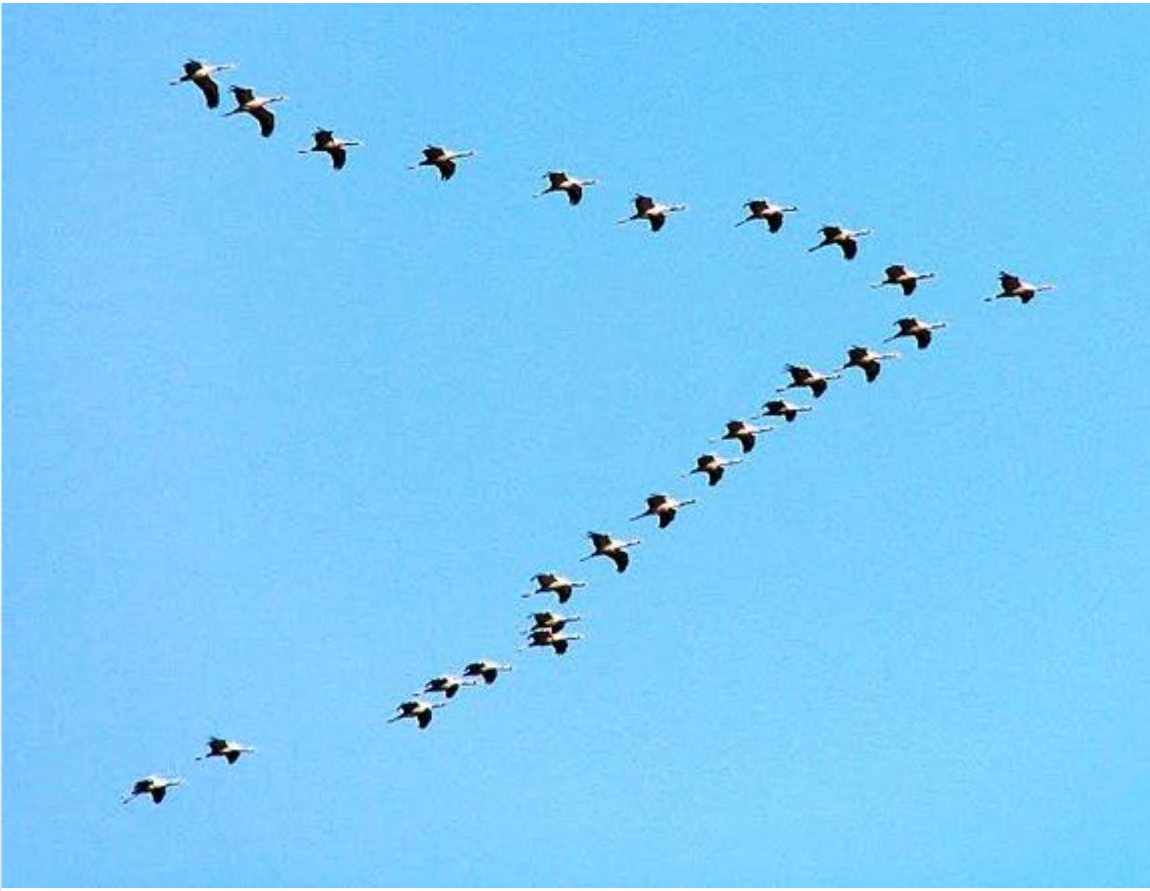


Image credit: Creative Commons

Biophysics is all around us

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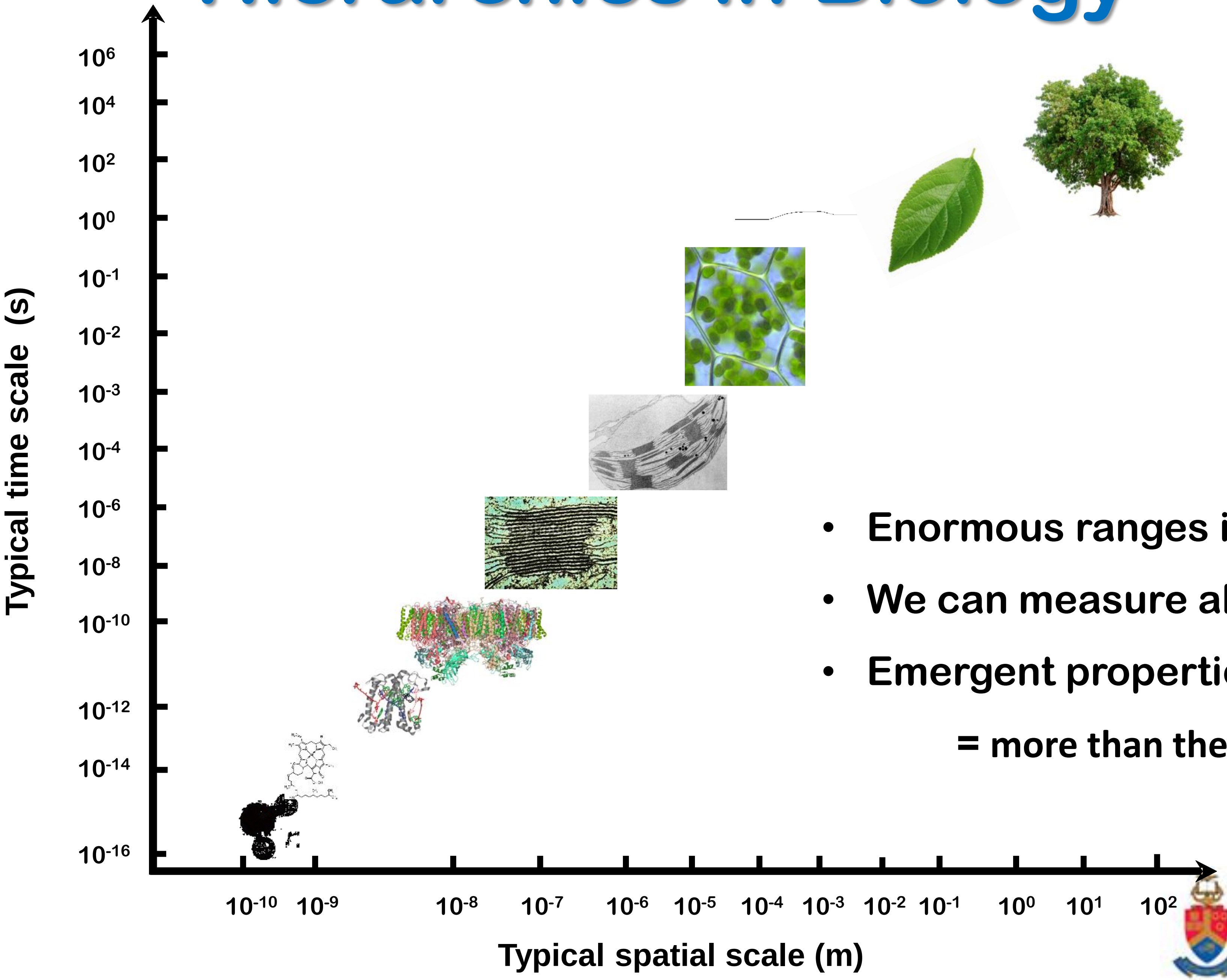
Hierarchies in Biology



- **Enormous ranges in time & space**
- **We can measure all these processes!**
- **Emergent properties**

= more than the sum of their parts

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The Biological Century

- The 21st century has been called the *biological century* because it has already demonstrated unprecedented advances in the biological sciences and related technologies.

- Biological Physics is arguably the most active and rapidly growing area of physics research in the 21st century.

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

3) 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."

Biology is the testing ground for some theories of physics

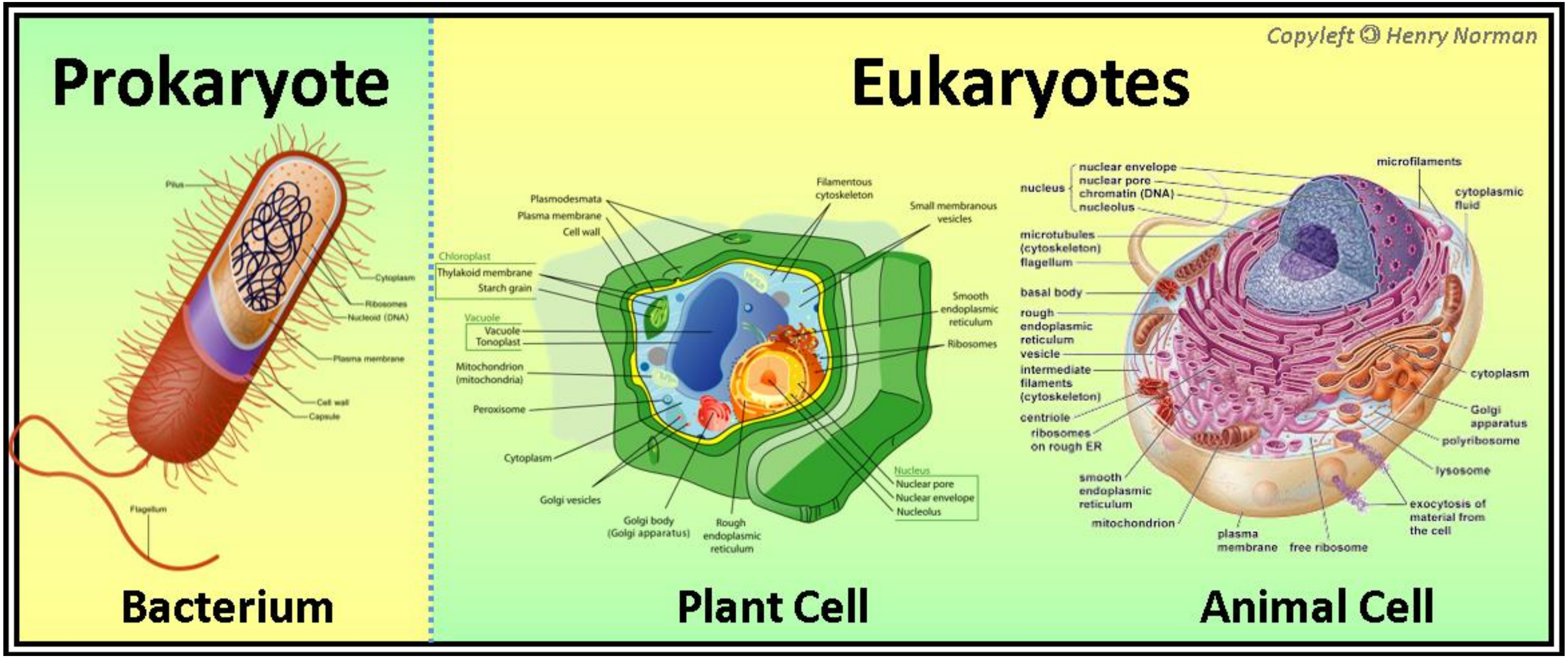
NATURE PHYSICS | VOL 11 | FEBRUARY 2015 COMMENTARY

“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.”

Erwin Schrödinger (in: “What is Life?”): “to avoid a quick decay to equilibrium, a living organism must continually increase the entropy of its surroundings. By digesting food, breathing air and absorbing photons, living organisms channel, or transduce, a continual flow of energy that produces the dissipation required to sustain life away from equilibrium.”

The Biological Cell



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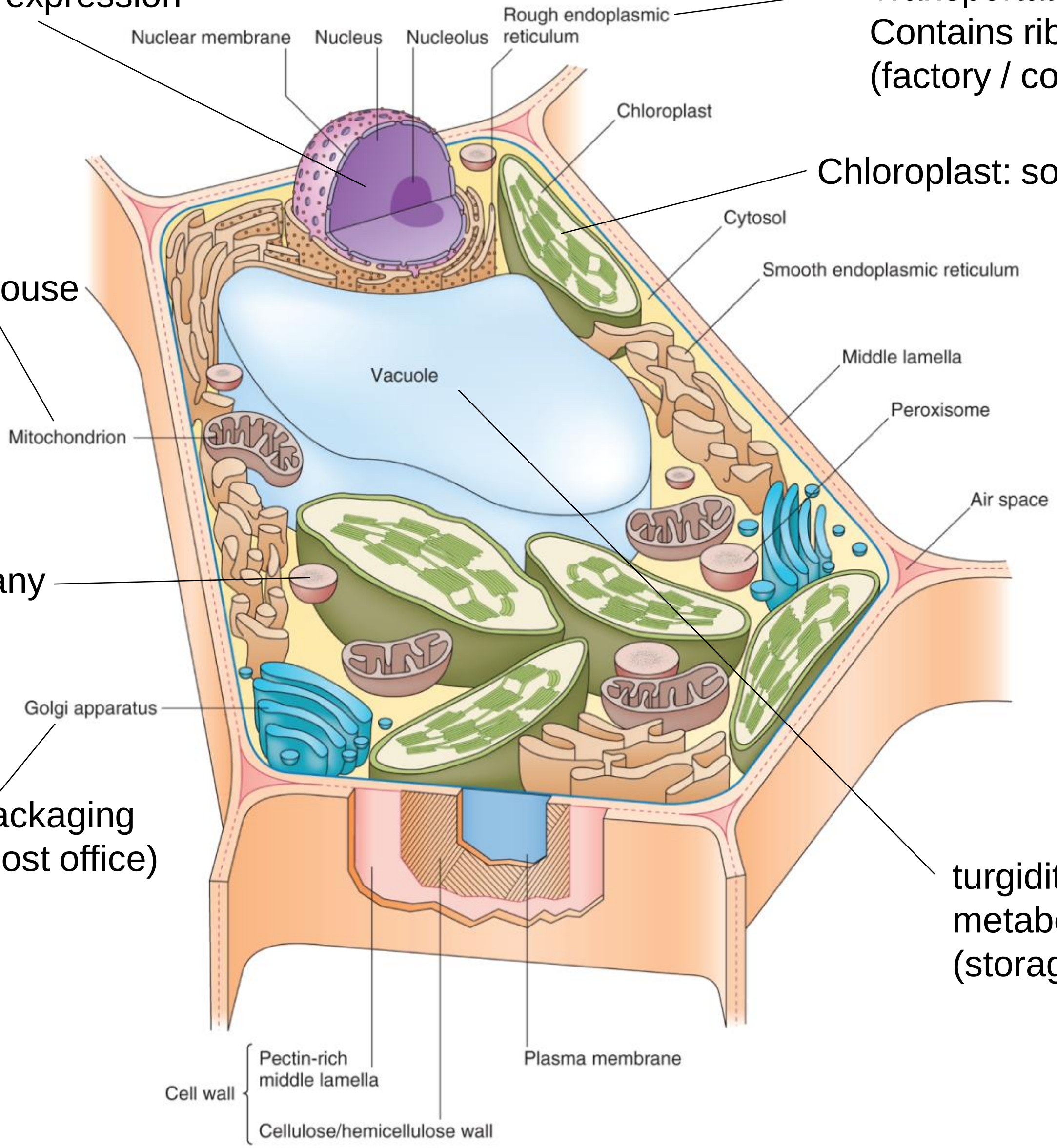
The Plant Cell



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)

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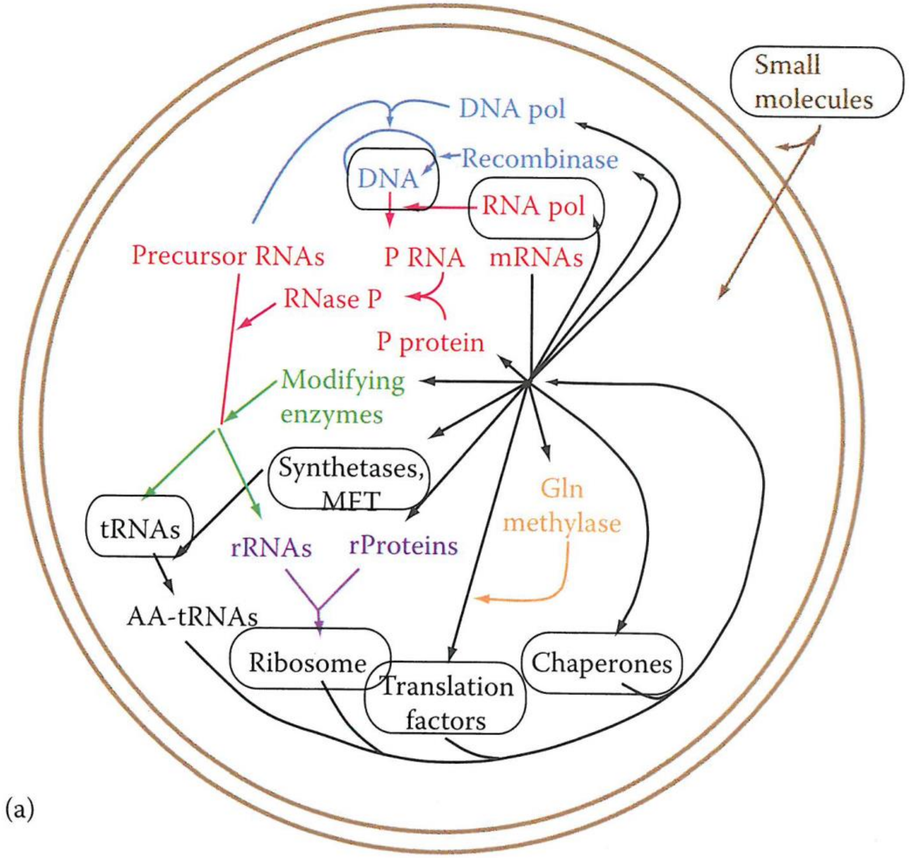
How complex is a cell?

The minimal cell



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

Simplest process = diffusion across the membrane:

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

Reactions with other molecules & feedback mechanisms:

$$\rightarrow \quad \frac{\partial C(x,t)}{\partial t} = -D\frac{\partial^2 C(x,t)}{\partial x^2}$$ ~~+ source & sink terms~~

i.e., **coupled PDEs.**

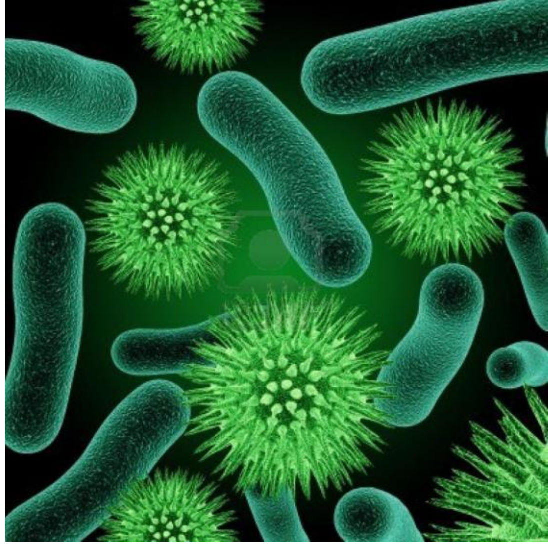
Assume: every line denotes a reaction, described by a PDE.

~30 coupled differential eqs.

Can Mathematica solve this for time-independent processes?

Metabolic pathways

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

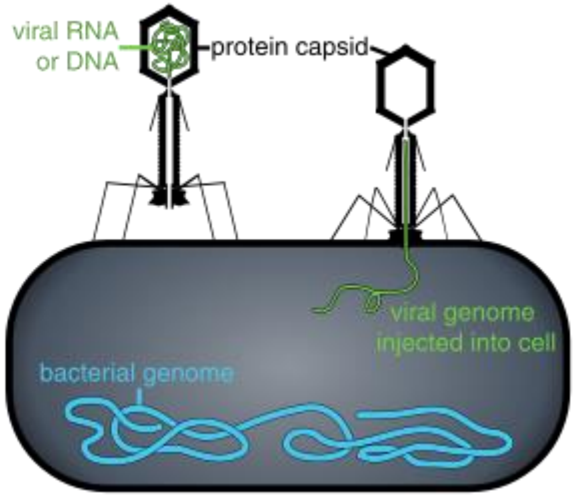
C. 1:1

D. 10:1

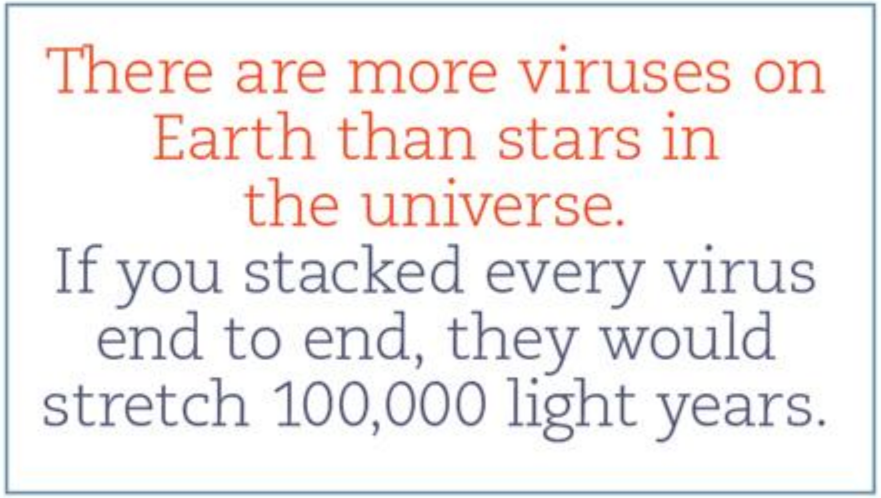
Average size = ~2 μm: 50 μm

Viruses

What is a virus?
Is a virus a living organism?



~10^{31} viruses on the earth!



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.

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

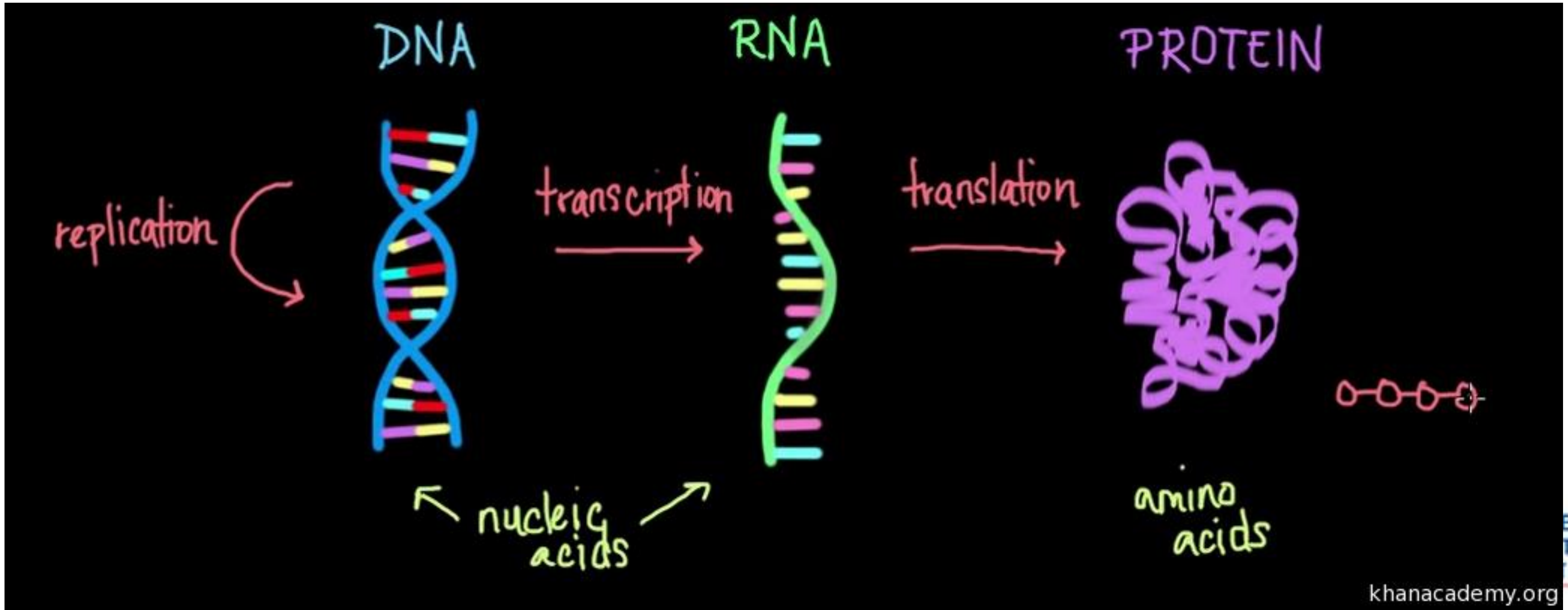
How effective are antiviral drugs?

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

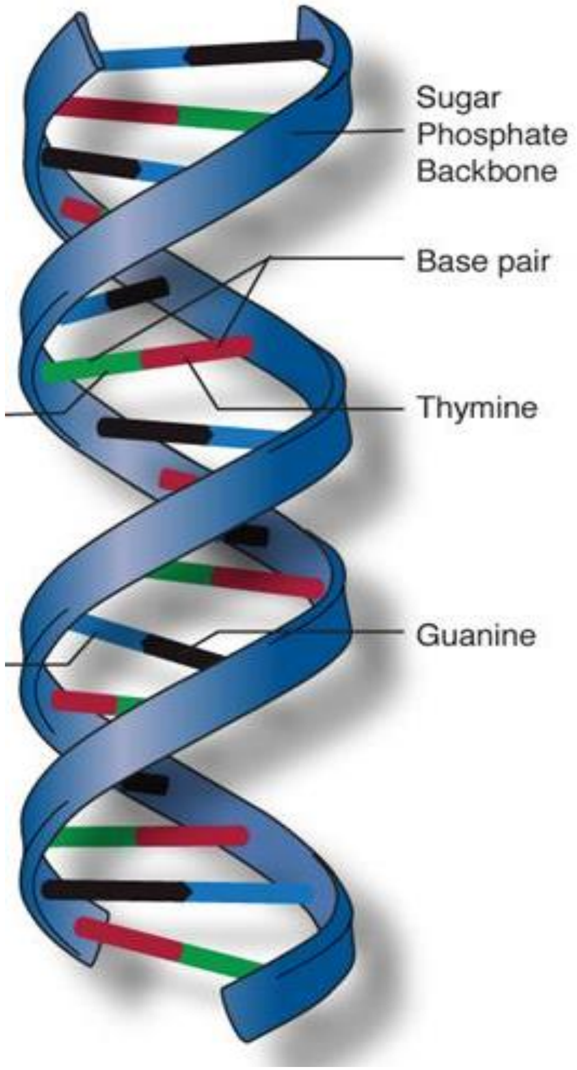
cytoplasm/ER



khanacademy.org

DNA

(deoxyribose nucleic acid)



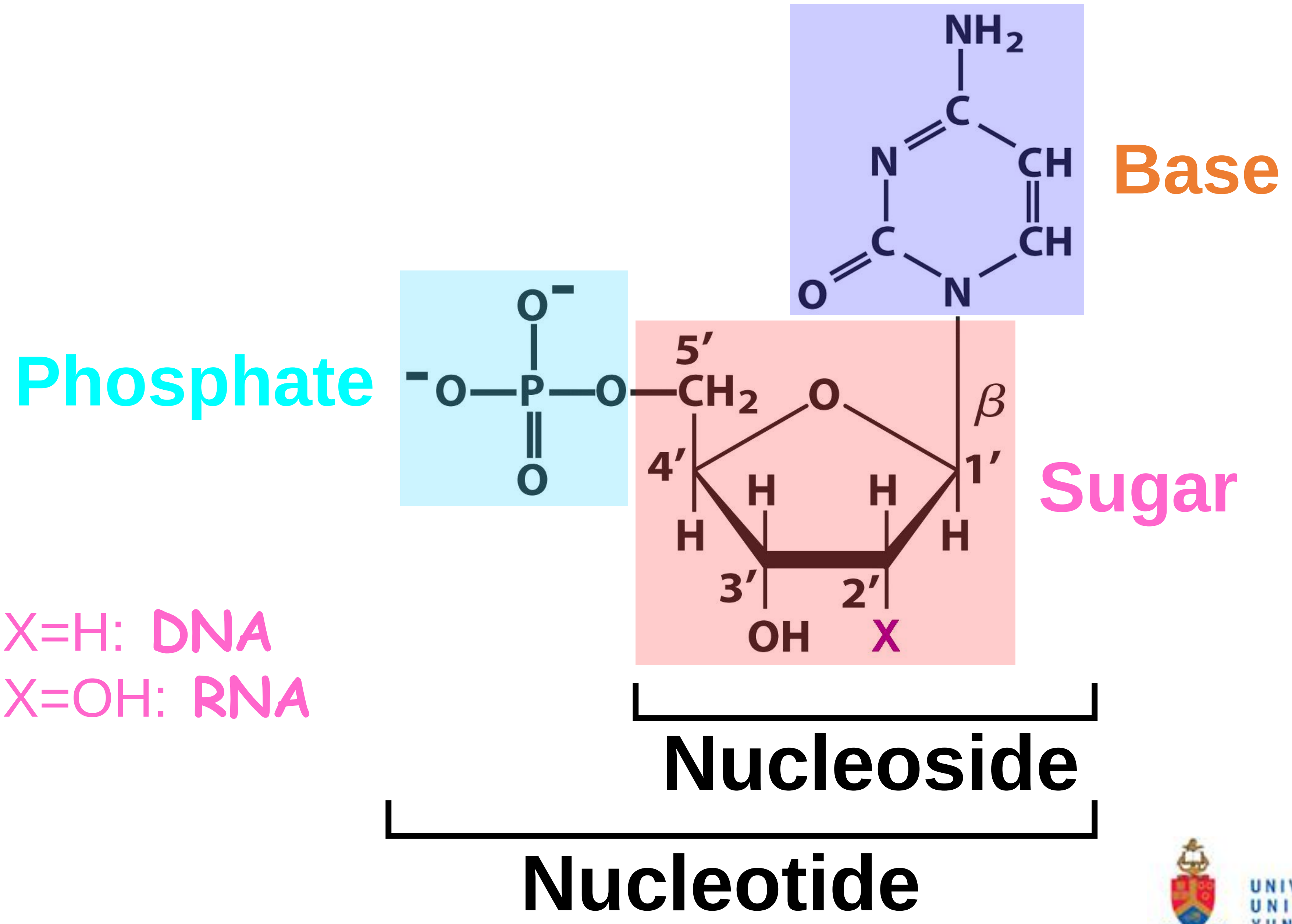
Components of a nucleotide

Base

Sugar

Phosphate

Components of a nucleotide



X=H: **DNA**

X=OH: **RNA**

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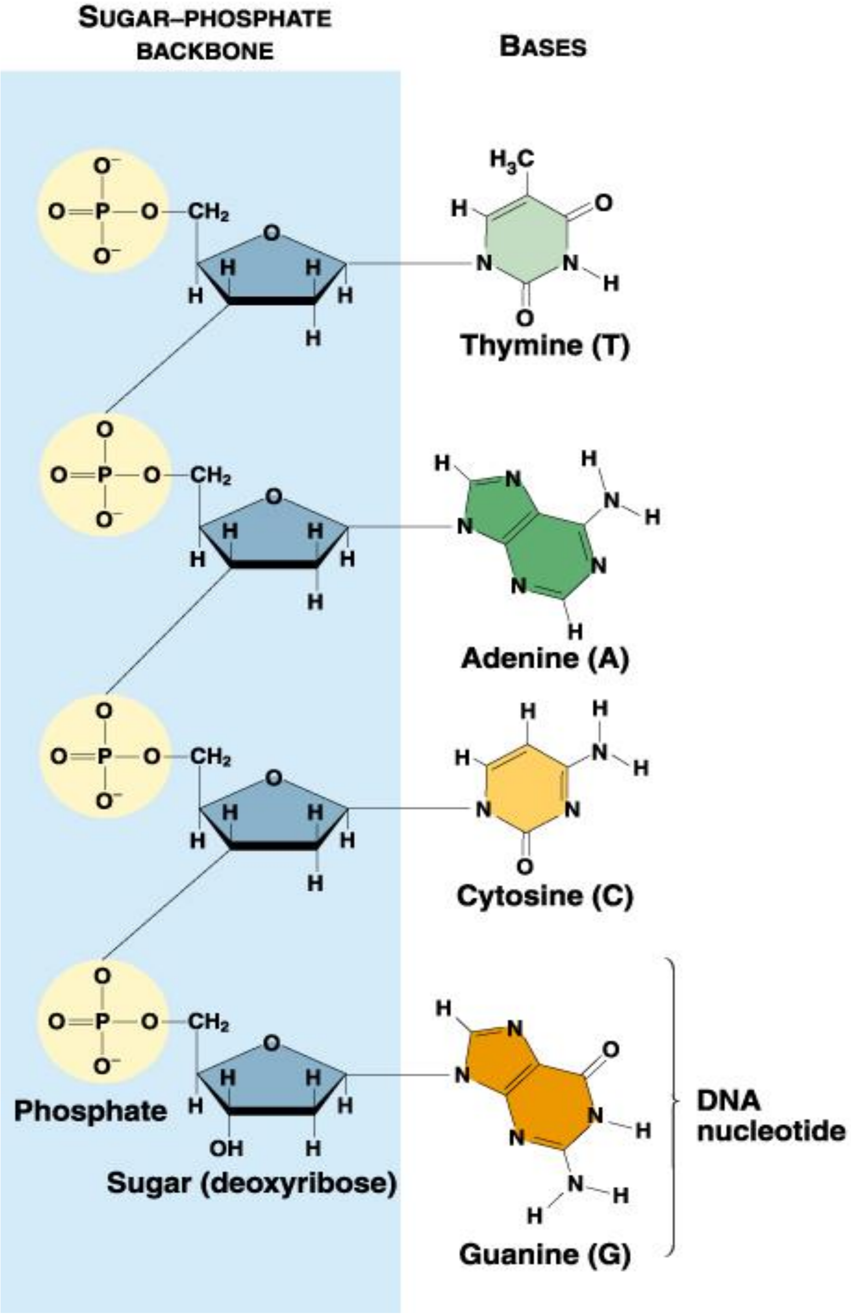
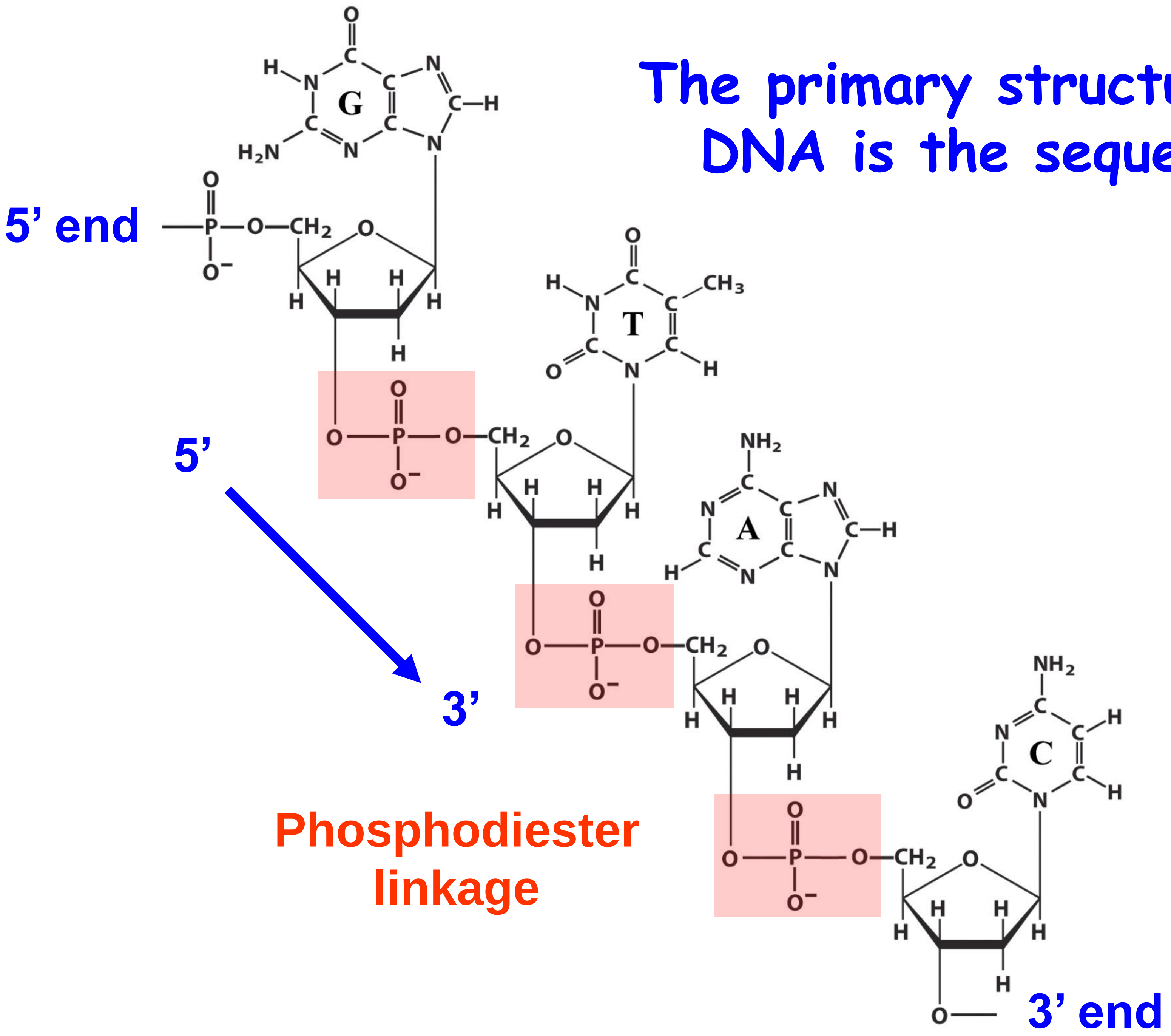
The 4 nucleotides of DNA



The primary structure of DNA is the sequence



5’ end

5’

3’

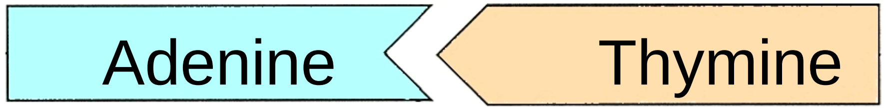
Phosphodiester linkage

3’ end

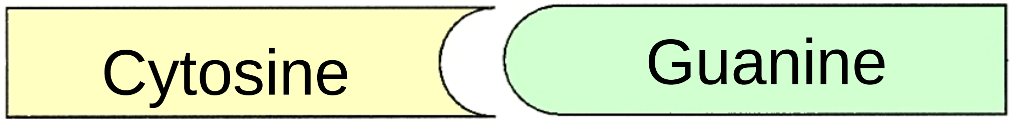
Bonding

The bases always pair up in the same way

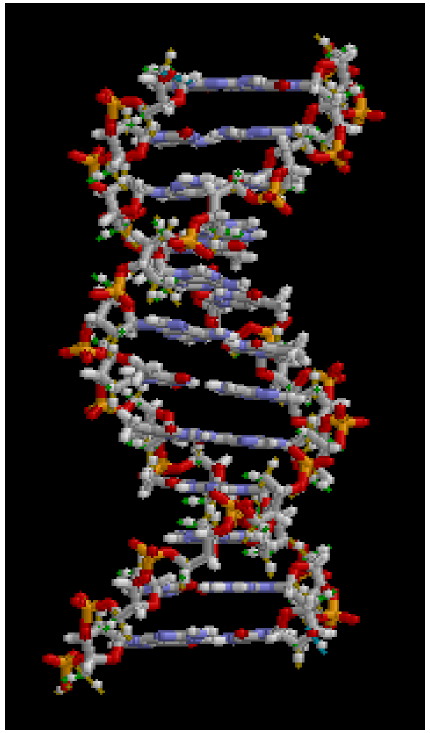
Adenine forms a bond with Thymine



and Cytosine bonds with Guanine

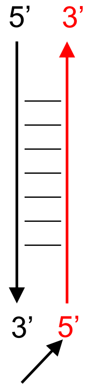


DNA structure

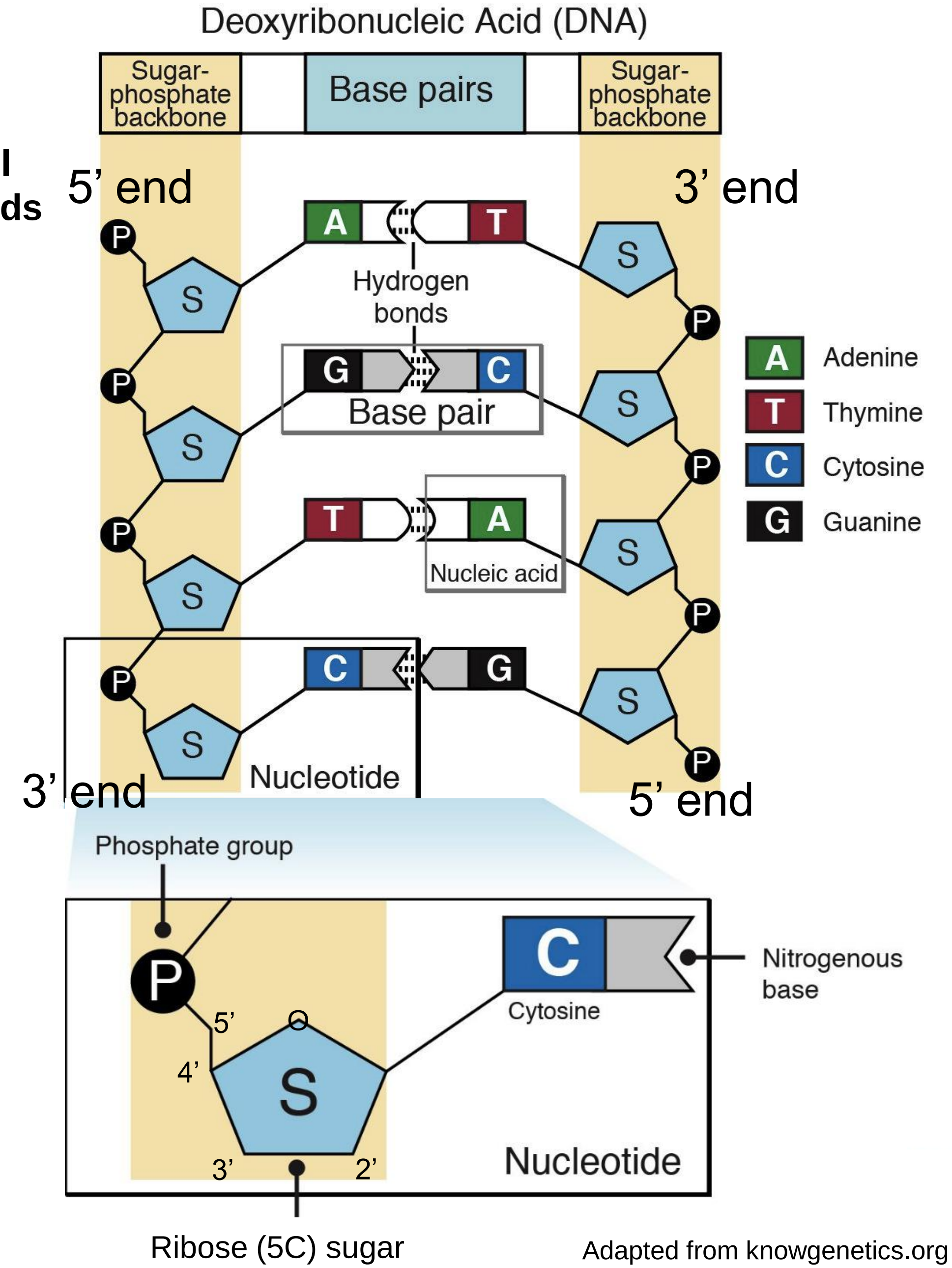


Wiki Commons

Antiparallel double strands



Reverse complementary strand



Adapted from knowgenetics.org

DNA RNA

- **A** always pairs with **T / U**
- **C** always pairs with **G**
- Chain is always polymerised in the 5’ → 3’ direction
- Antiparallel arrangement of strands

DNA structure

- Because of **complementary base-pairing**, it is only necessary (and conventional) to represent the code of *one* strand, always 5’ → 3’

e.g. GATCGCCTAAGCT (single strand)

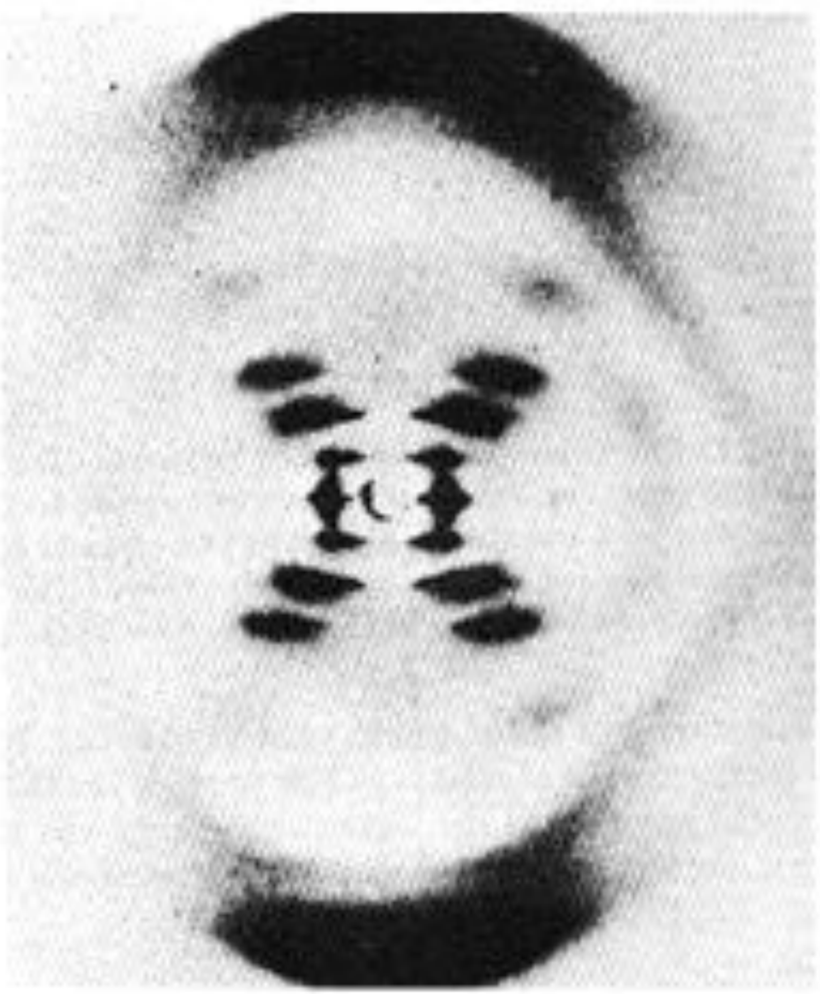
implies

5’-GATCGCCTAAGCT-3’
3’-CTAGCGGATTCGA-5’
(double stranded form)

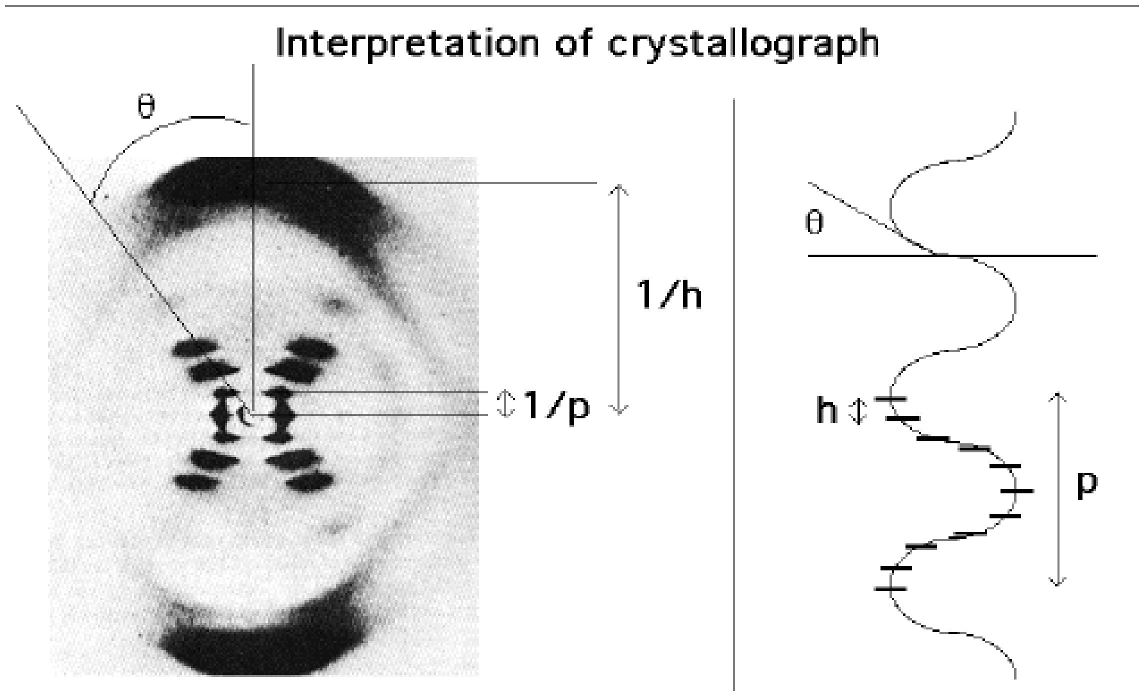
It could also have been written as:

AGCTTAGGCGATC

- By convention, the DNA sequence encoding for a protein is always written as the *sense* strand rather than the *antisense* strand



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

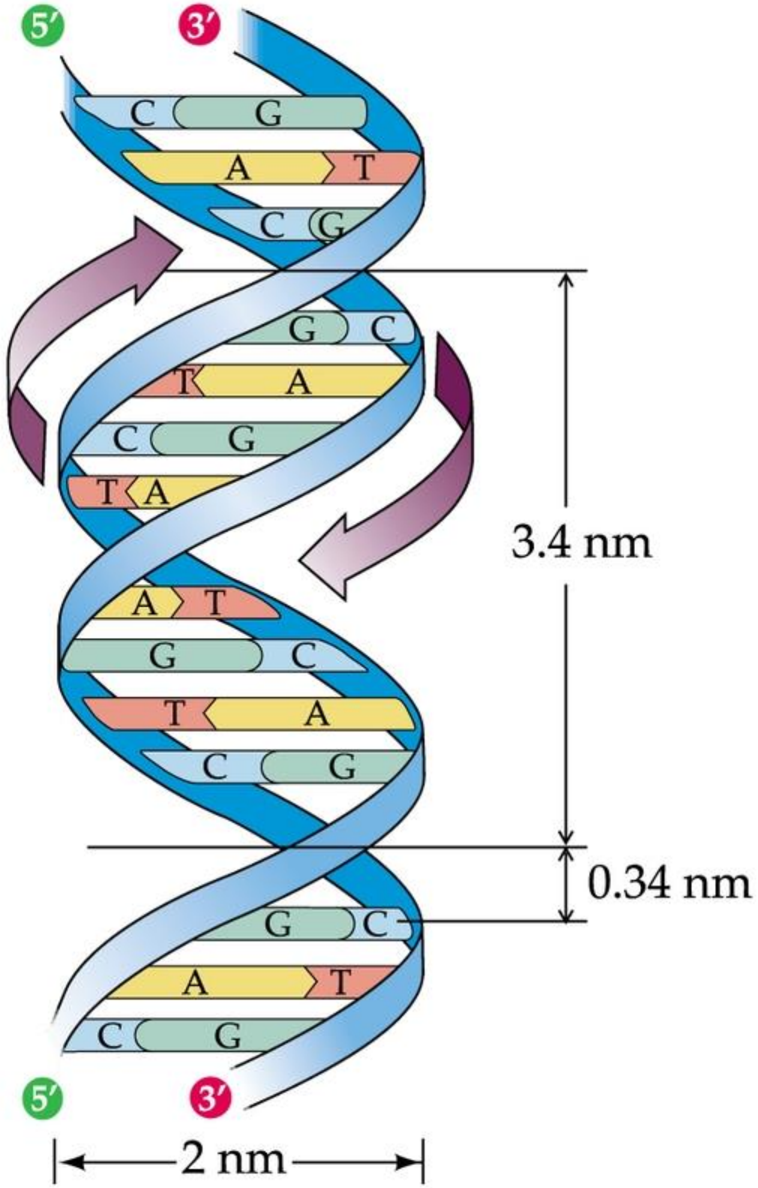


Interpretation of crystallograph

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

h = 3.4 Å (Distance between bases)

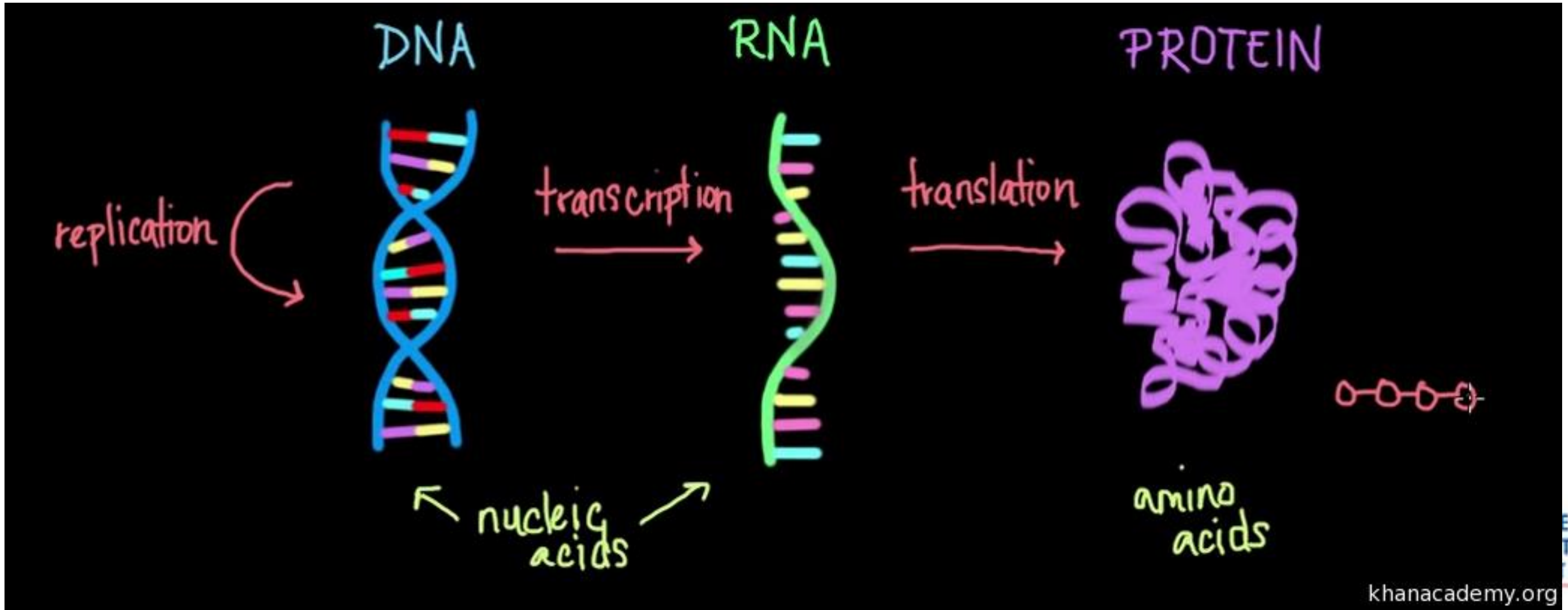
p = 34 Å (Distance for one complete turn of helix; Repeat unit of the helix)



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



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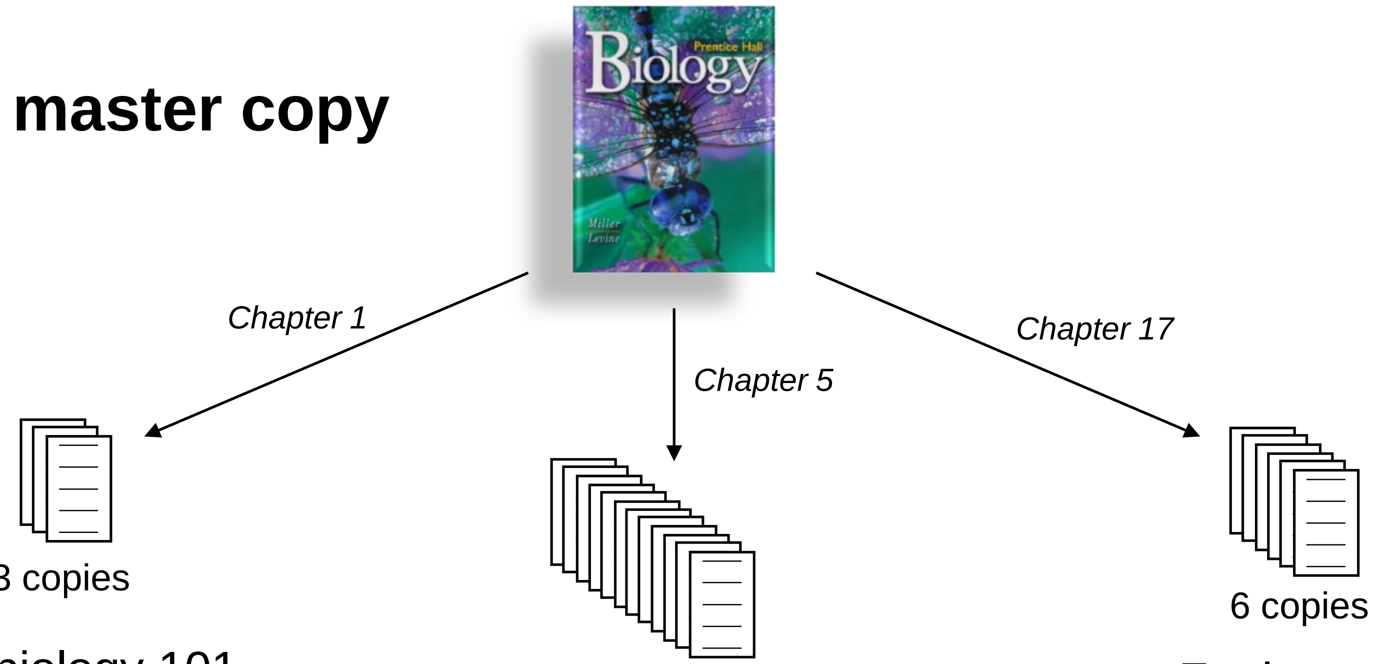
Transcription:
the copying and amplifying phase

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

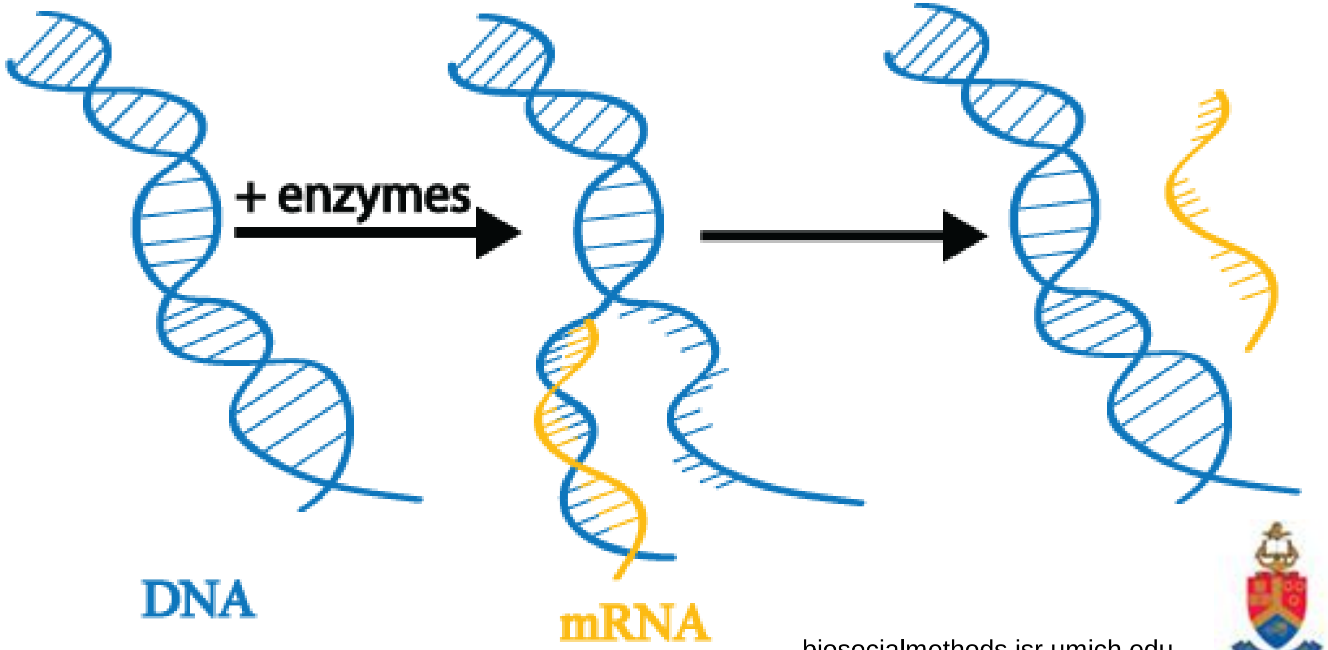
Zoology 101

RNA transcripts

Transcription:
the copying and amplifying phase

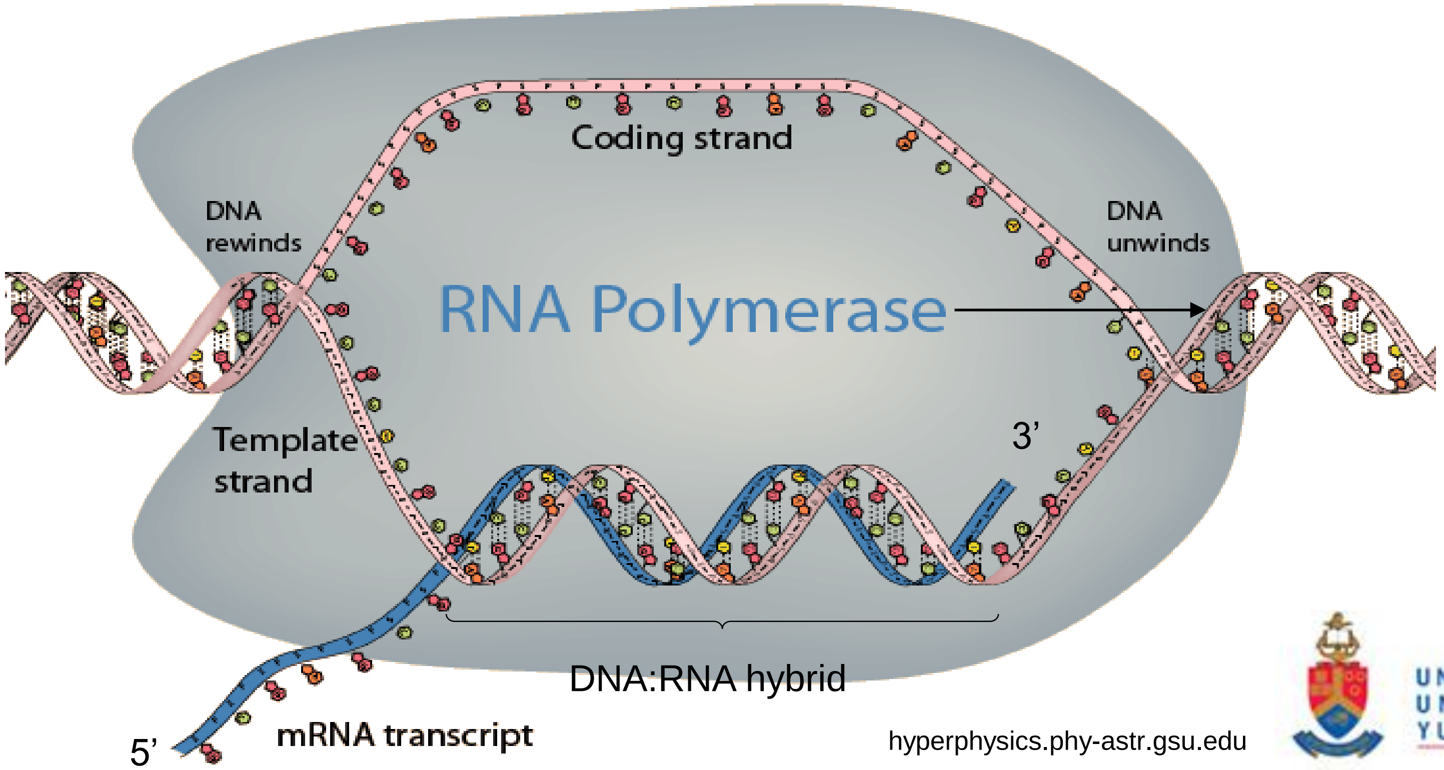
- A segment of the DNA (e.g. a gene coding for a protein) is *transcribed* into a single-stranded **messenger RNA (mRNA)**
- RNA behaves similarly to DNA, but U pairs with A on the DNA strand instead of T

This happens in the nucleus:



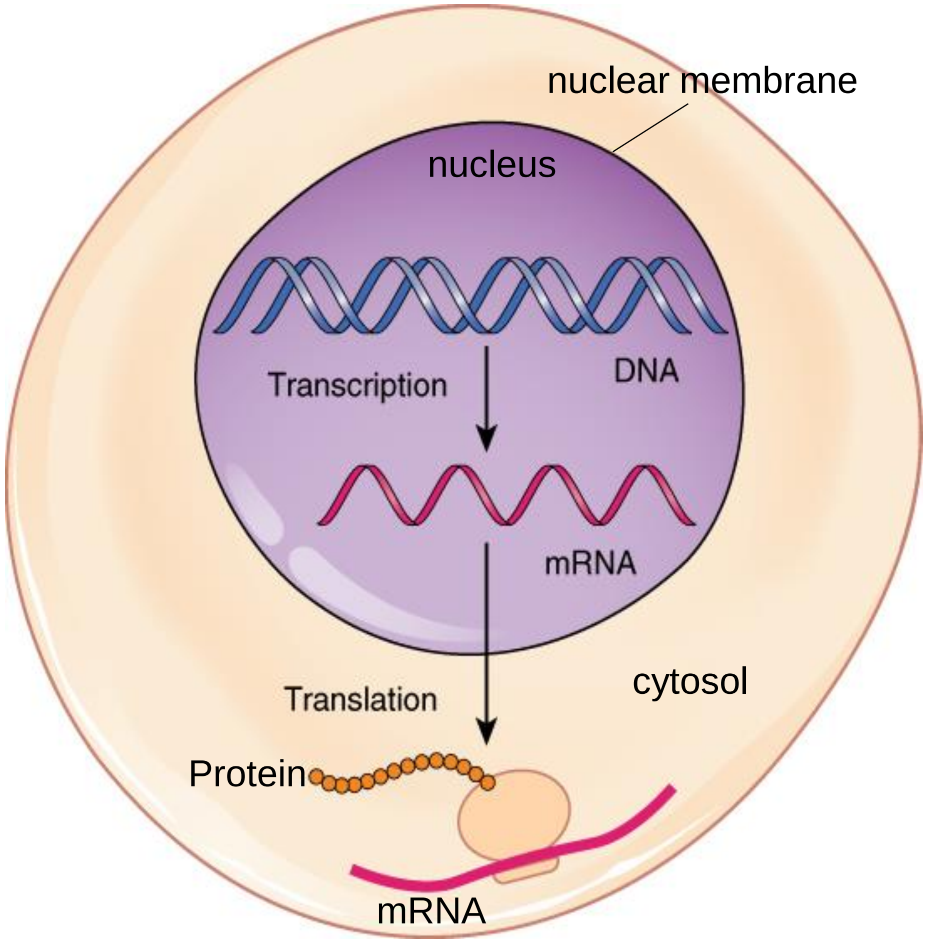
Transcription:
the copying and amplifying phase

- The dsDNA molecule unwinds temporarily, exposing the *antisense* strand which acts as the template for RNA polymerase to synthesize the mRNA
- The mRNA transcript's sequence is exactly the same as the sense-coding strand (aside from T being replaced by U)



hyperphysics.phy-astr.gsu.edu

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**

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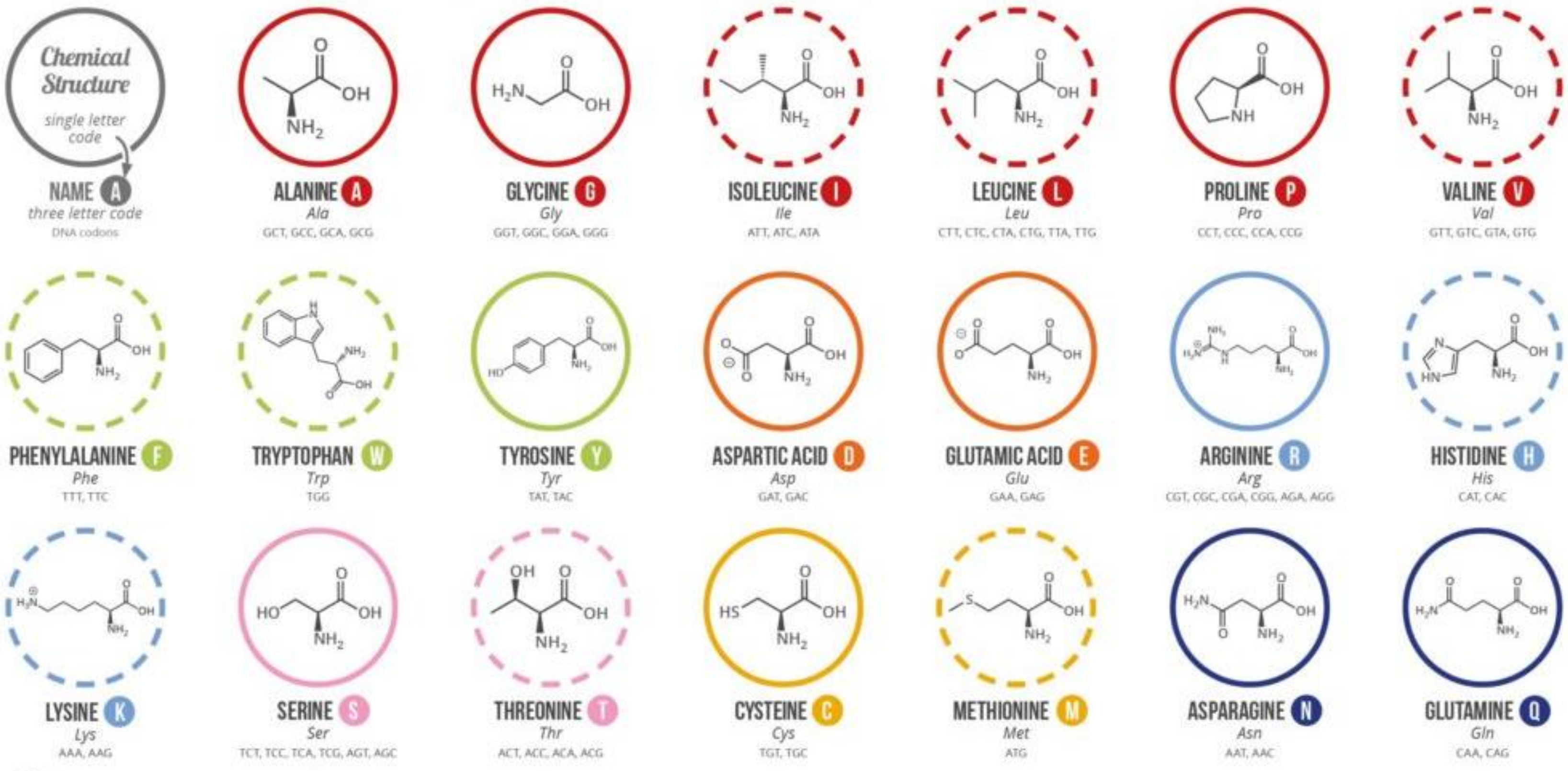
Translation: De-coding a DNA sequence into functional protein

- There are 20 essential amino acids. The sequence in which they are linked to each other will determine the protein's function



Note: This chart only shows those amino acids for which the human genetic code directly codes for. Selenocysteine is often referred to as the 21st amino acid, but is encoded in a special manner. In some cases, distinguishing between asparagine/aspartic acid and glutamine/glutamic acid is difficult. In these cases, the codes asx (B) and glx (Z) are respectively used.

Translation: De-coding a DNA sequence into functional protein

How can four types of nucleotide encode 20 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

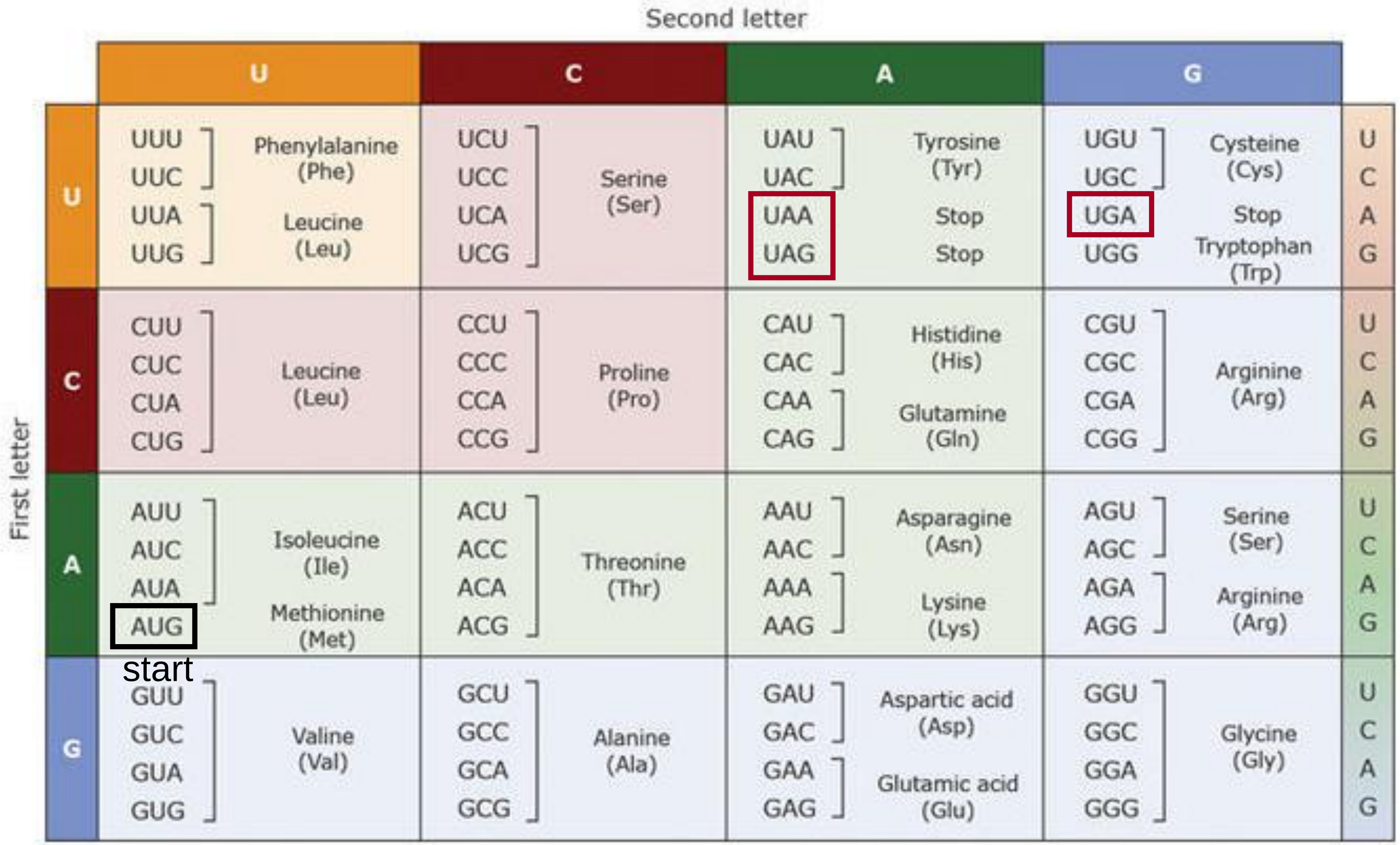
- The codon system of three-letter RNA code corresponding to a single amino acid is universal to all life
- Some amino acids have several possible codons (**code is redundant: reduces error**)
- Some codons represent STOP instructions rather than encoding amino acids

Translation: De-coding a DNA sequence into functional protein

☐ start codon

☐ stop codons

The genetic code

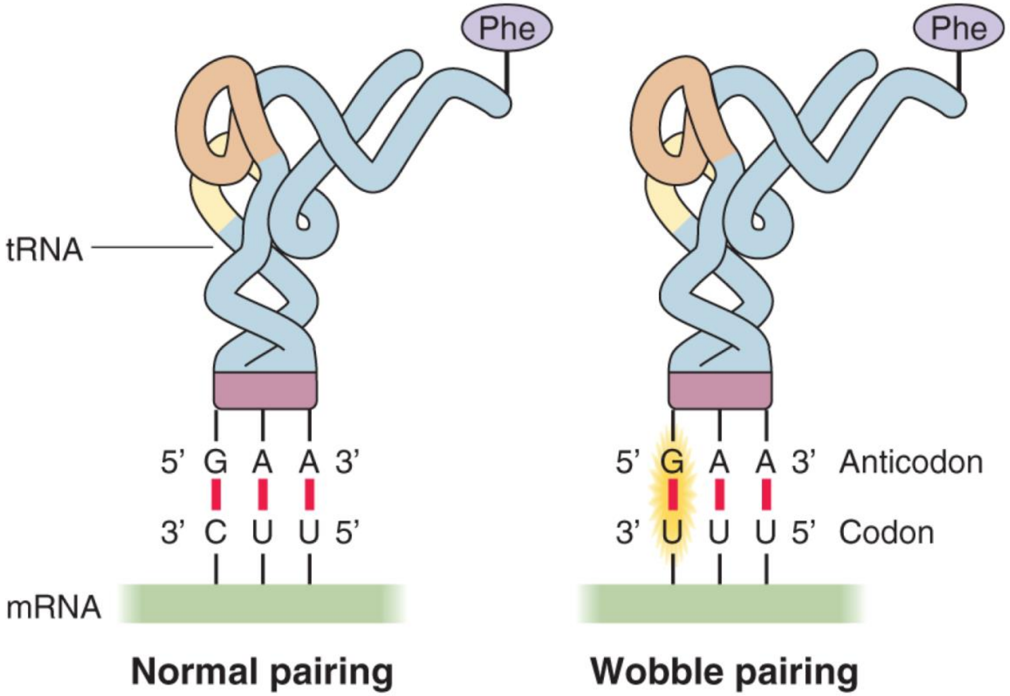


Second letter

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**

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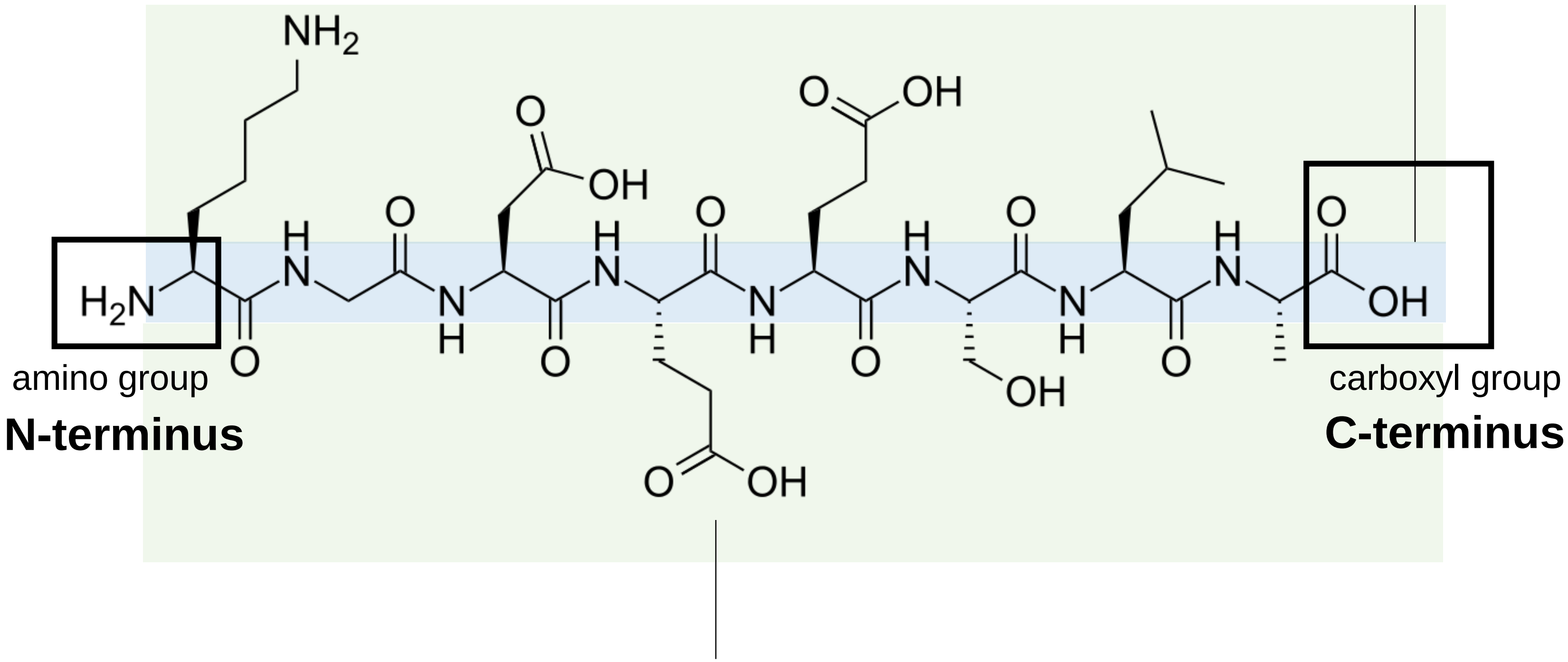
Translation: De-coding a DNA sequence into functional protein

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

Translation:
A closer look at a peptide chain

Backbone of peptide bonds



amino group

N-terminus

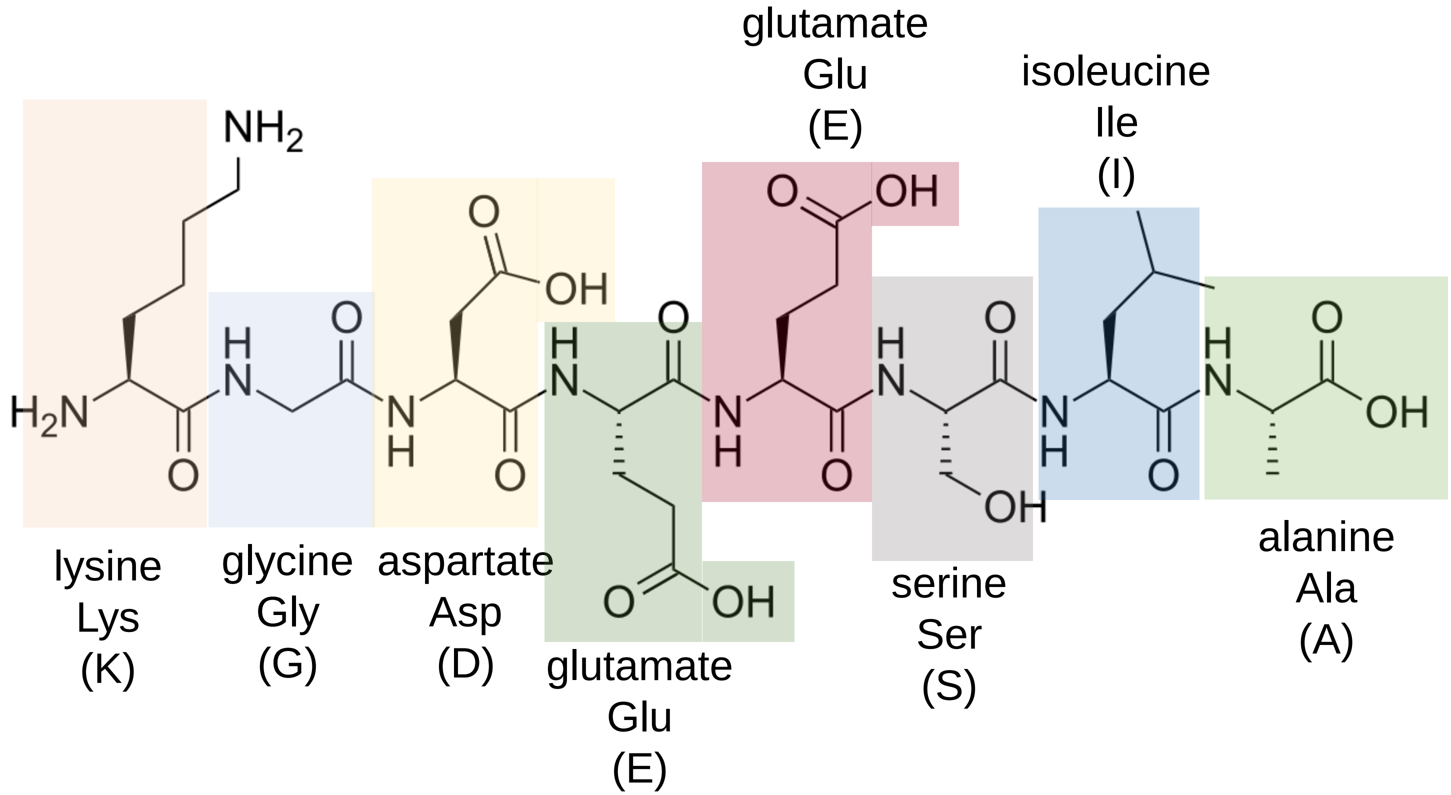
carboxyl group

C-terminus

Side chains (functional groups) of different amino acids

Translation:

A closer look at a peptide chain

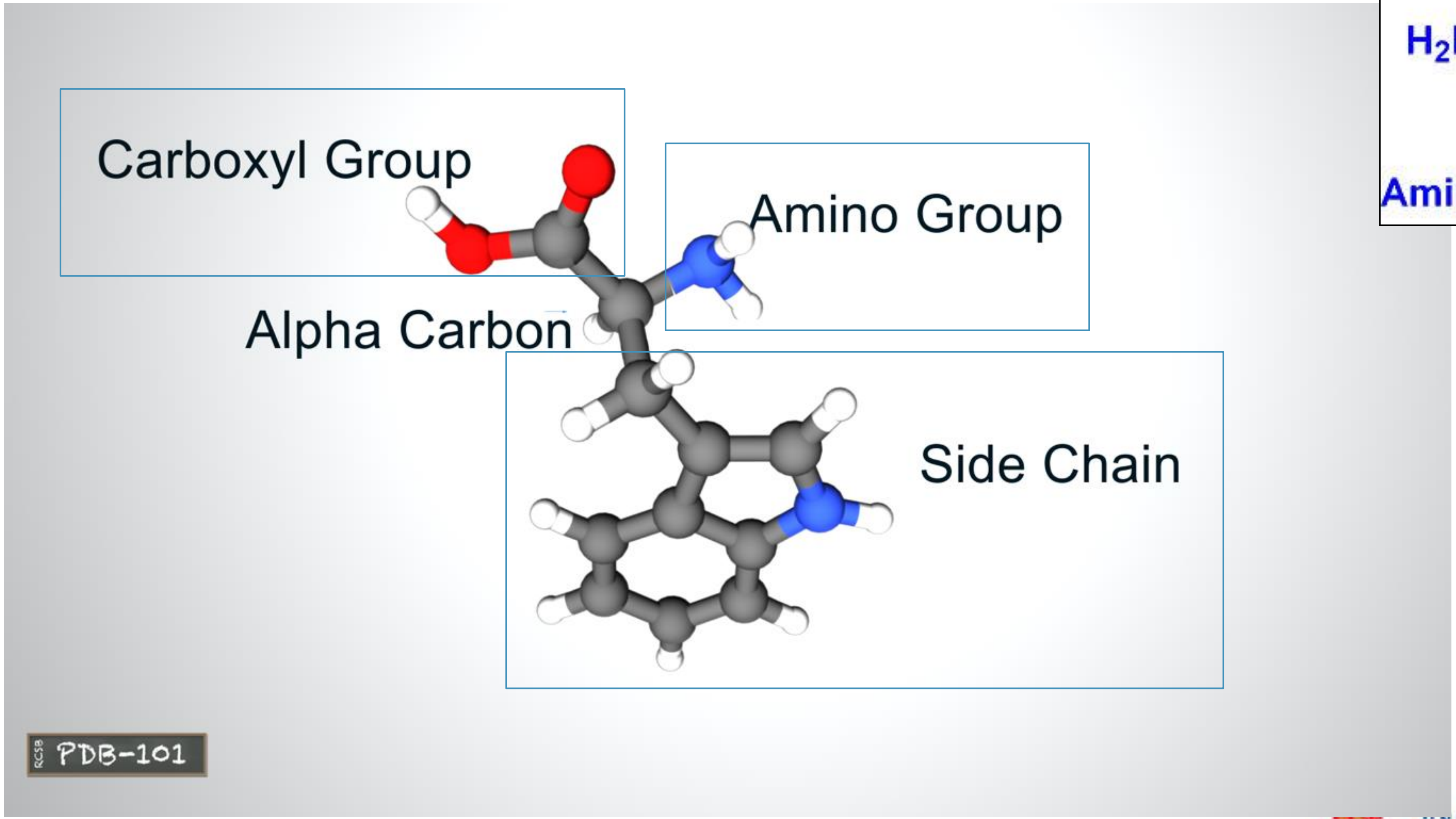


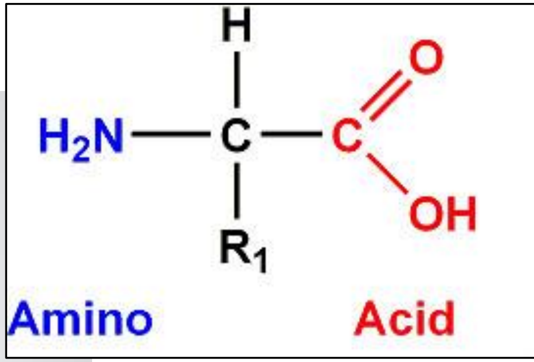
Proteins

- Molecular machines: “Hydrogen atom” of life
- >100 000 types in the human body

The Building Blocks of Proteins

The amino acid





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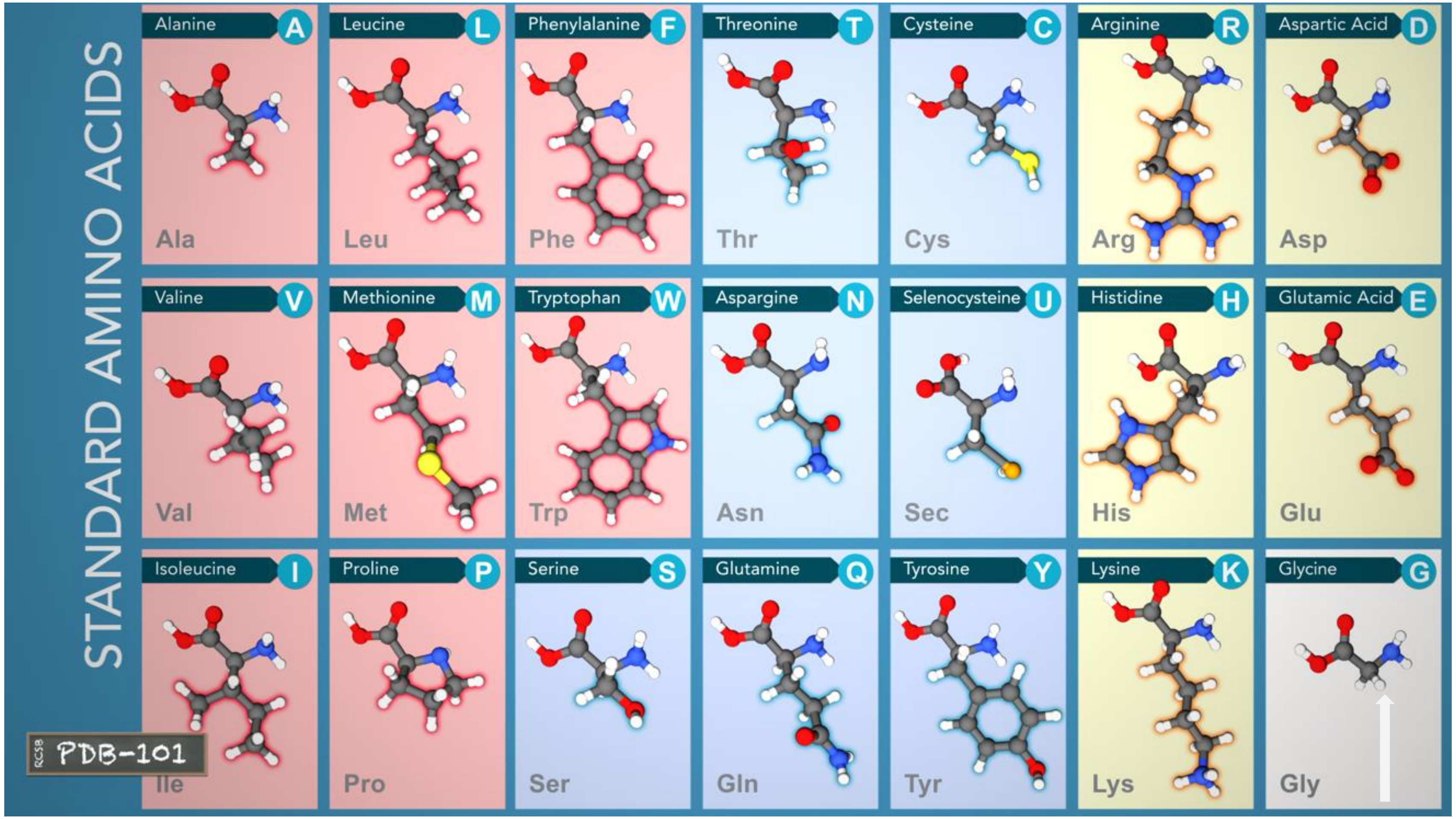
The Building Blocks of Proteins



Hydrophobic

Hydrophilic or polar

Charged

No side chain

The side chain is the only part that varies between amino acids and determines the properties of each amino acid.

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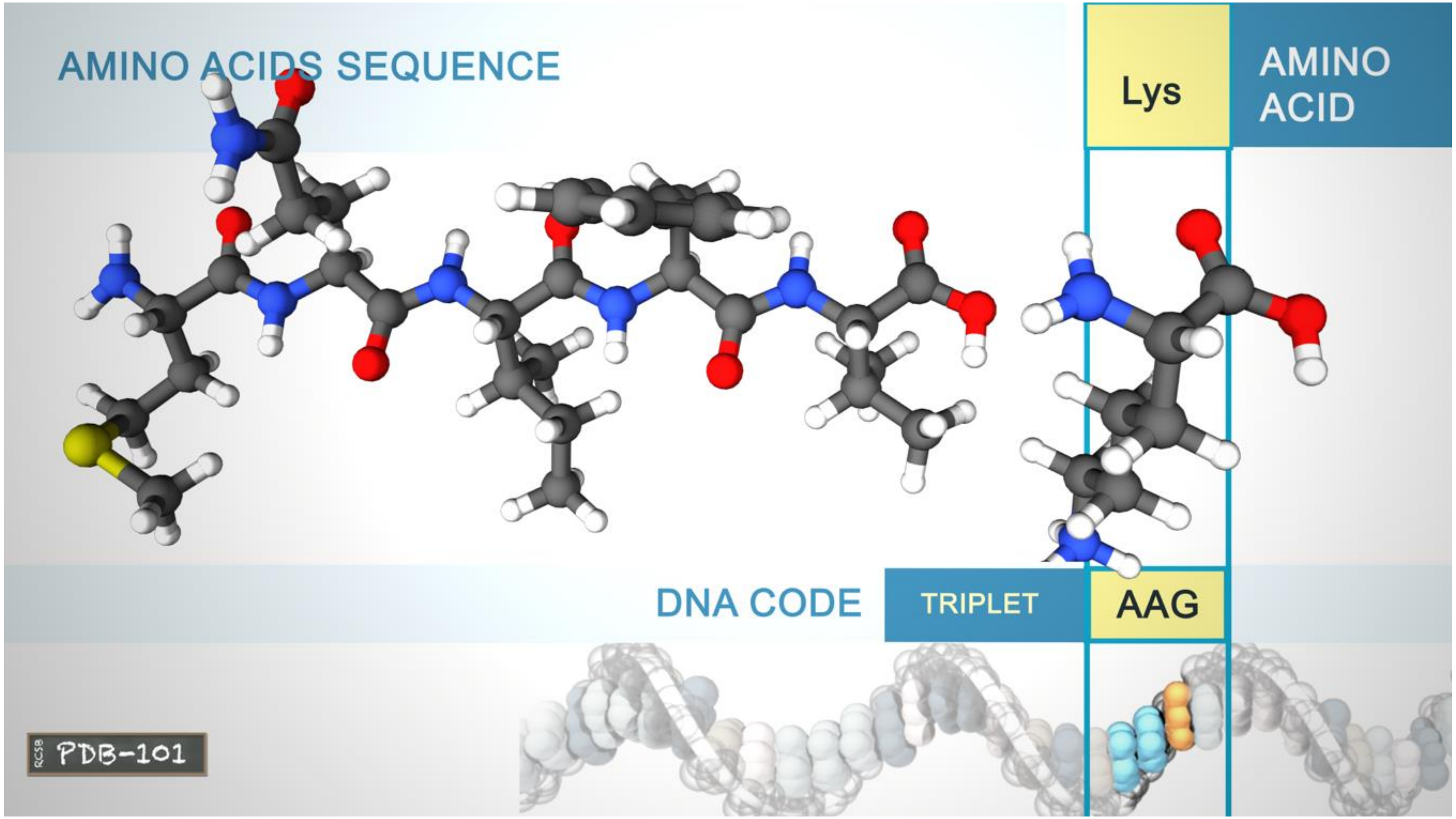
Protein Structure: Primary Structure



The primary structure of a protein is the **linear sequence of amino acids** as encoded by DNA.

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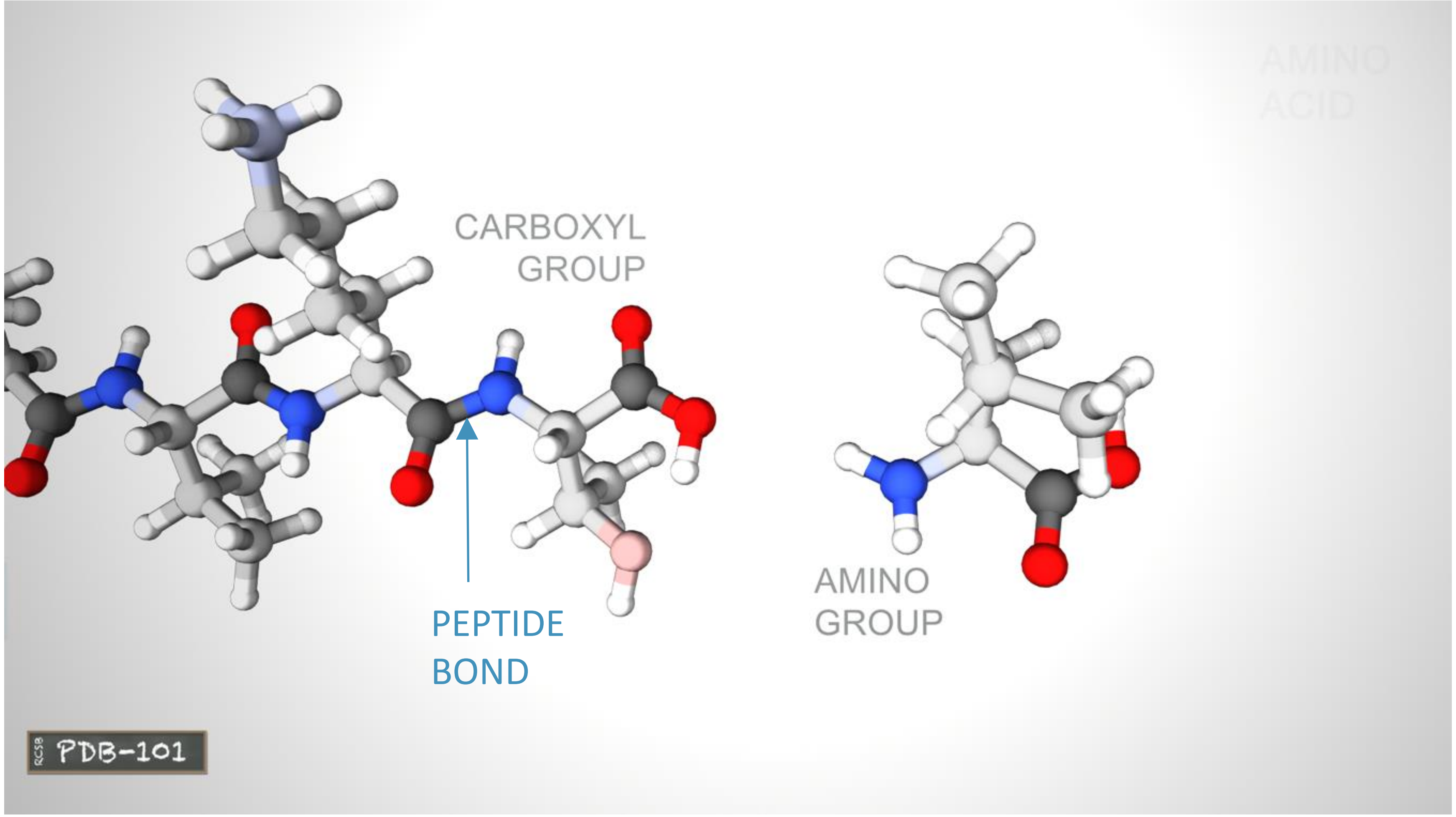
Protein Structure: Primary Structure



The amino acids are joined by **peptide bonds**, which link an amino group and a carboxyl group. A water molecule is released each time a bond is formed.

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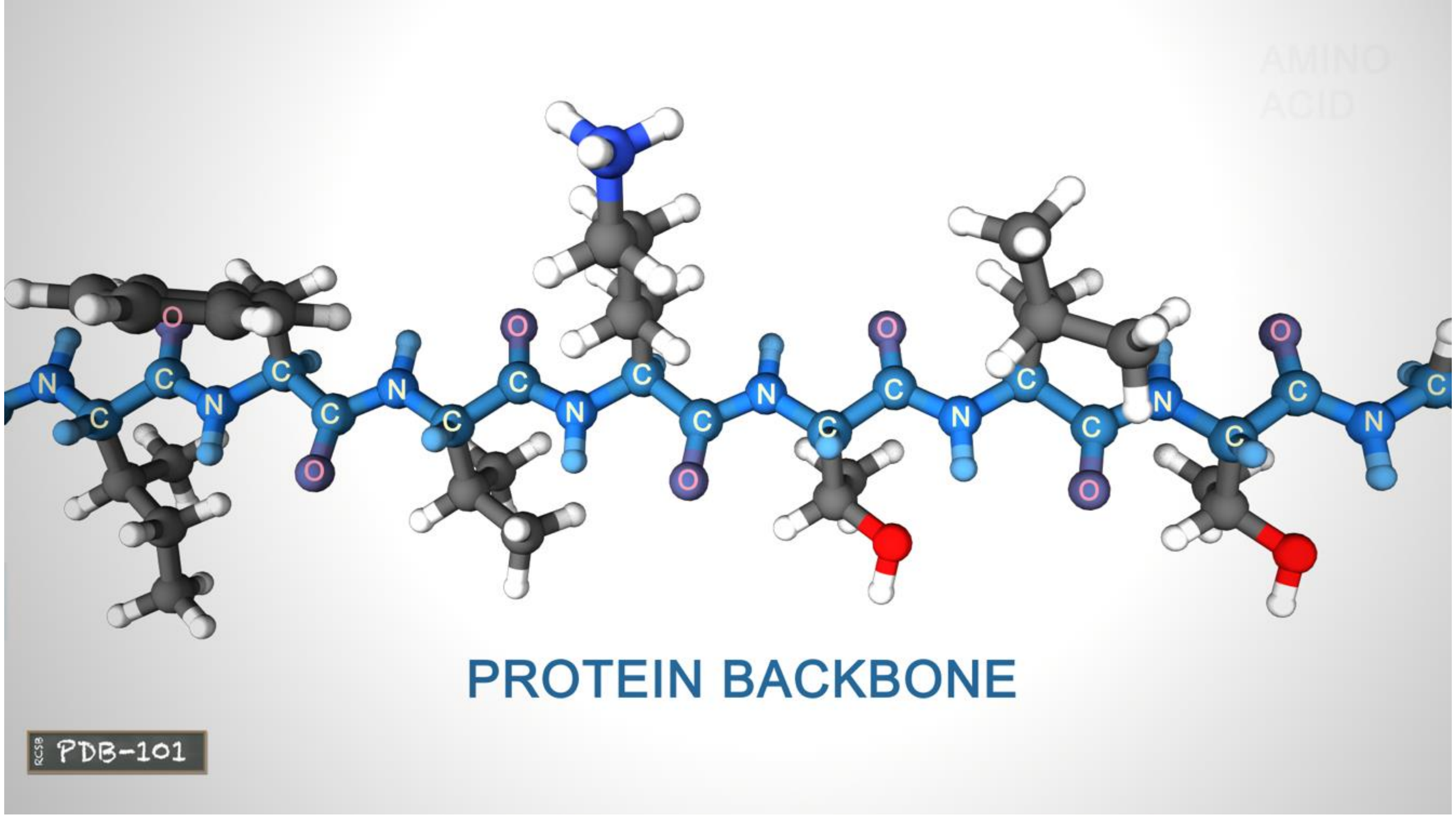
Protein Structure: Primary Structure



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

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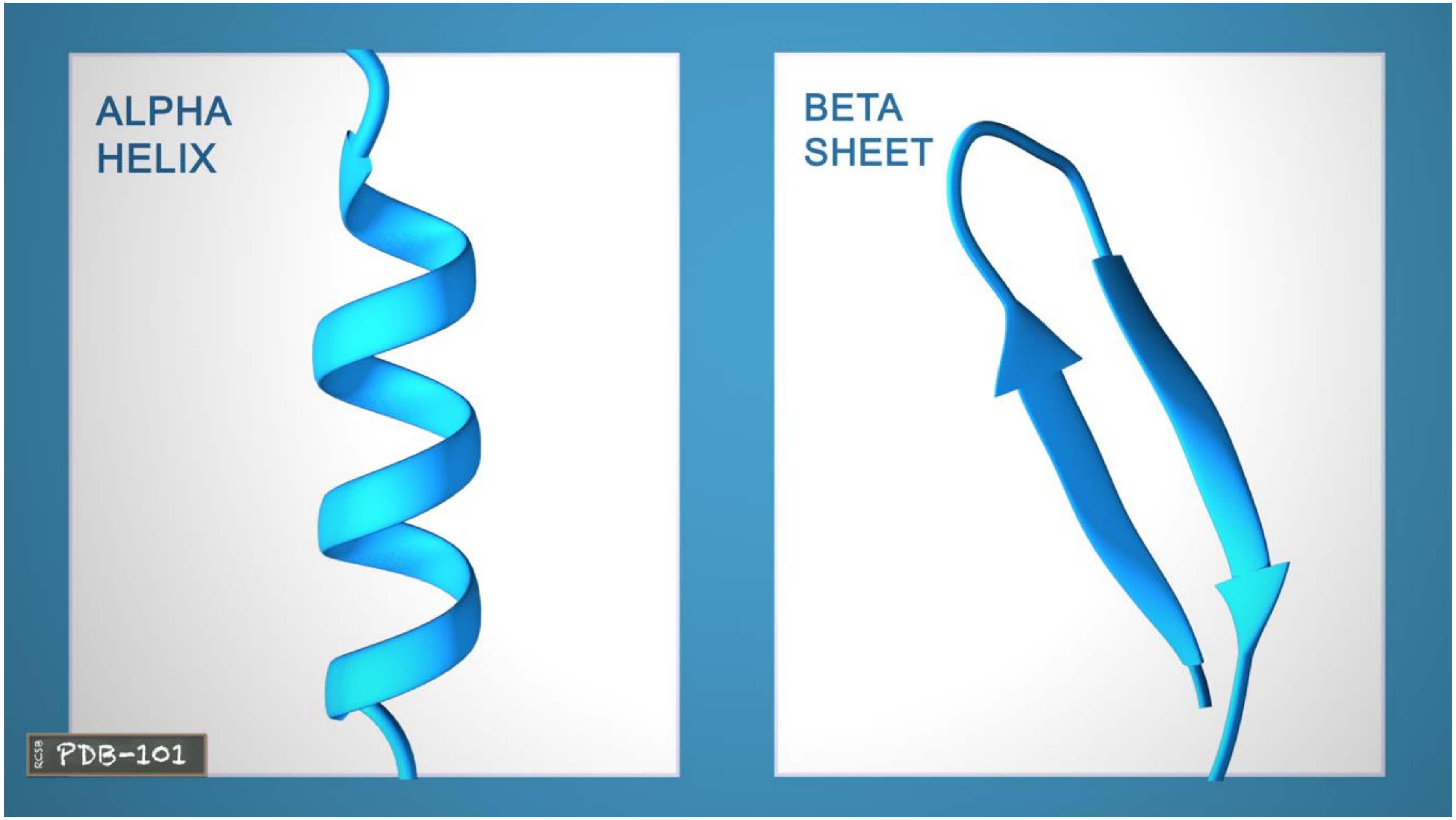
Protein Structure: Secondary Structure



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

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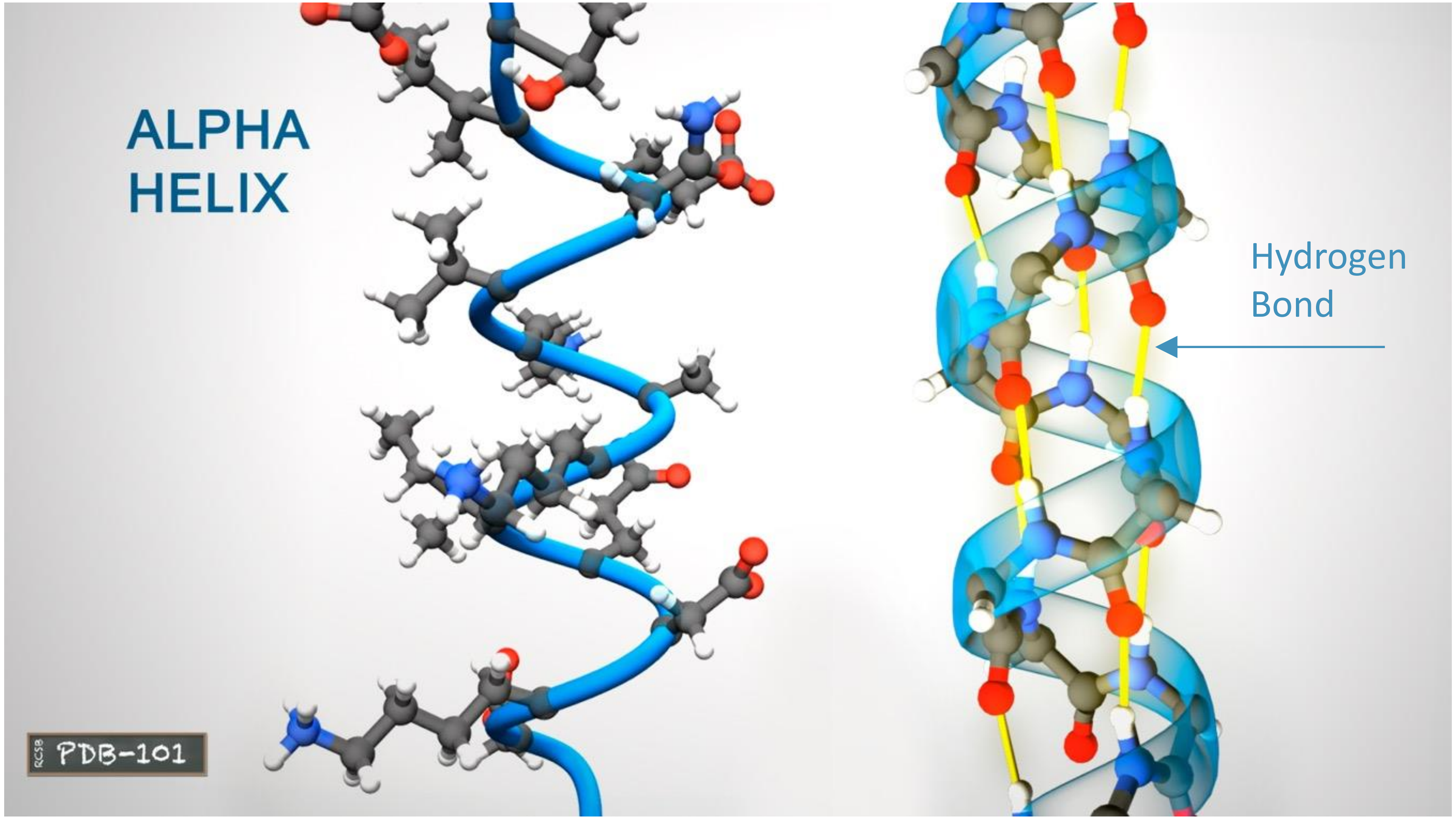
Protein Structure: Secondary Structure



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

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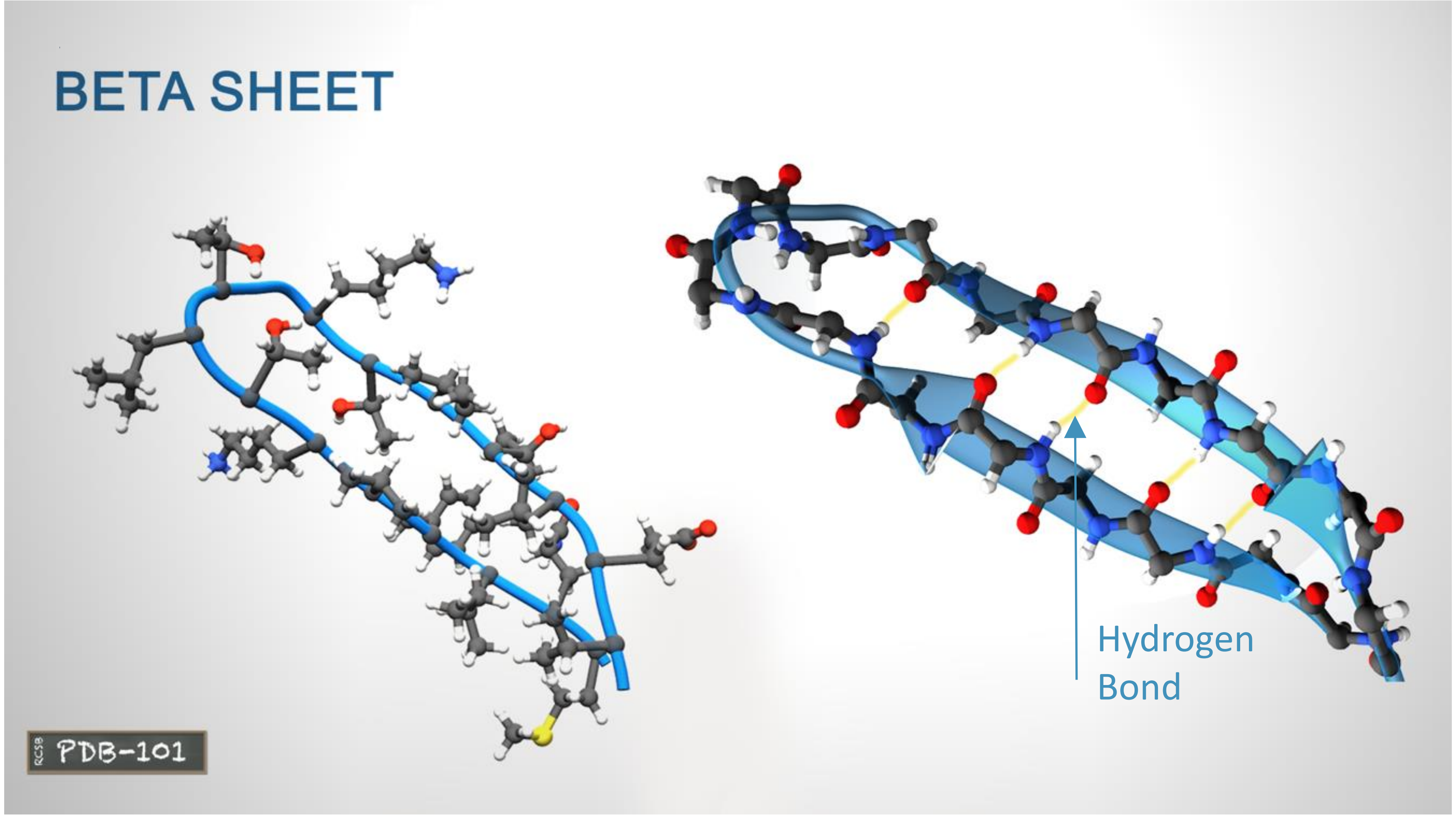
Protein Structure: Secondary Structure



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

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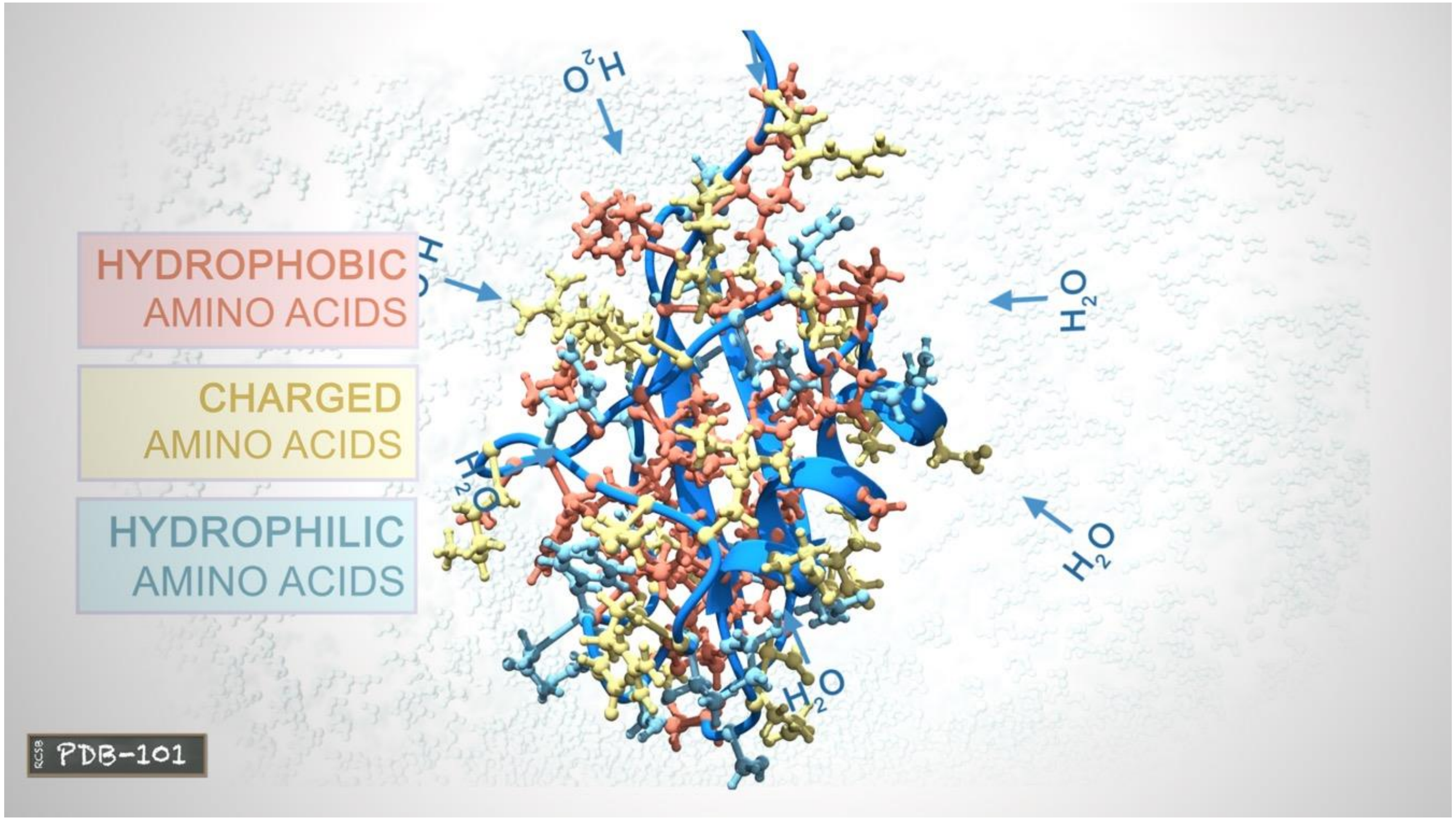
Protein Structure: Tertiary Structure



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.

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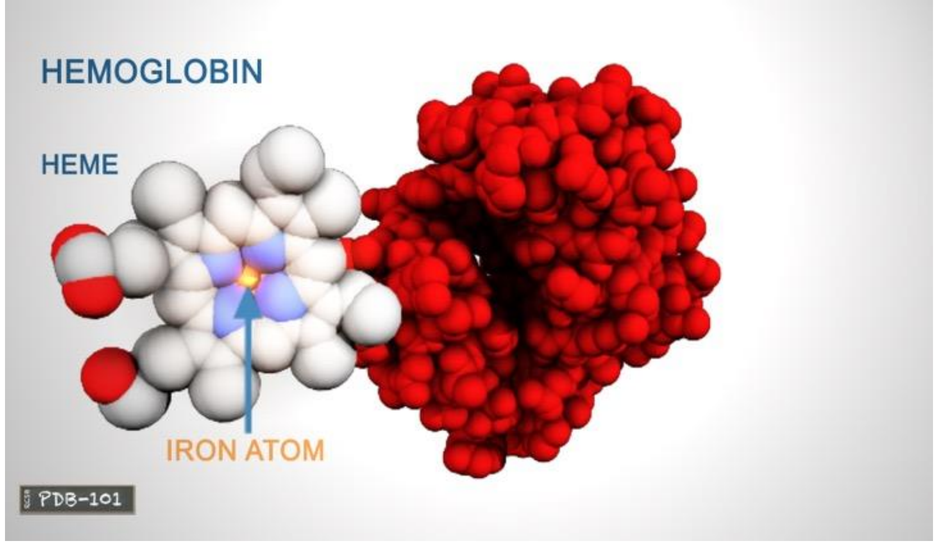
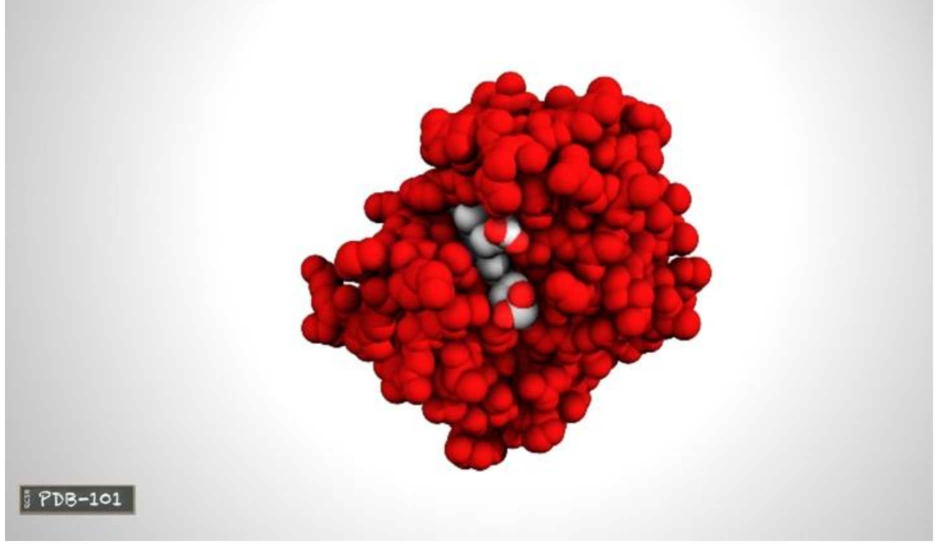
Protein Structure: Tertiary Structure





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.

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Protein folding

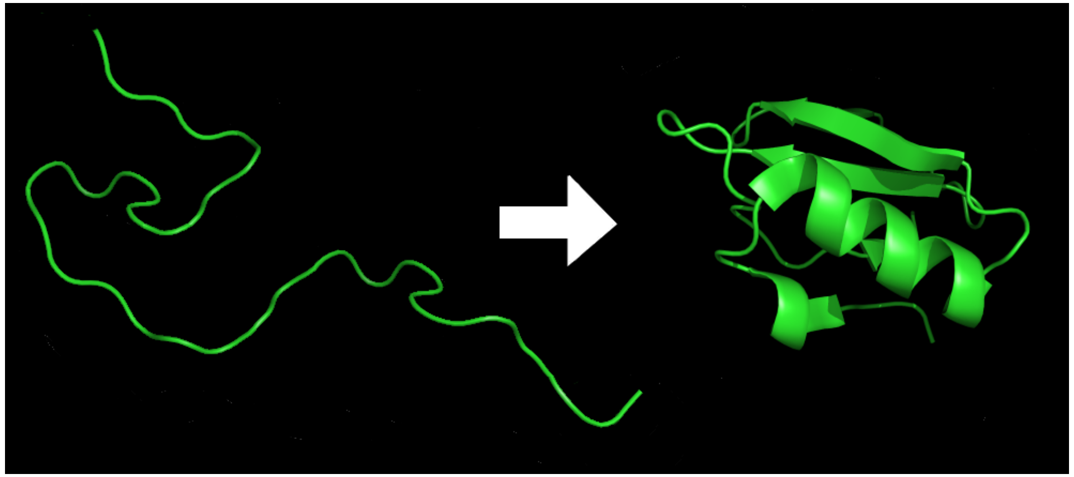


Image credit: Creative Commons license

Driving forces

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

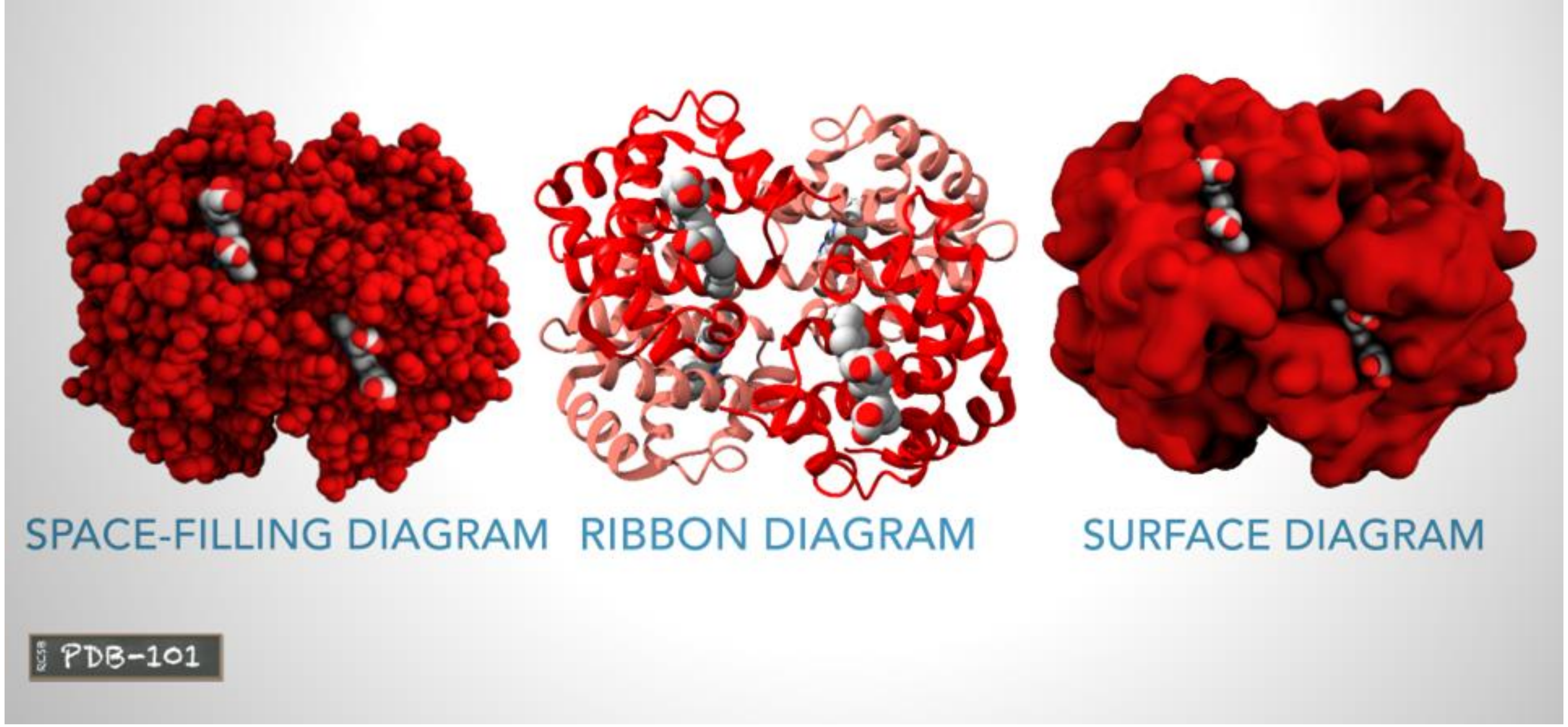
vs Conformational entropy

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.

Protein Representation



Different visual representations of proteins can give us visual clues about the protein structure and function. The **space filling diagram** shows all atoms that are making up this protein. The **ribbon** or **cartoon** diagram shows the organization of the protein backbone and highlights the alpha helices. The **surface** representation shows the areas that are accessible to water molecules.

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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)
- Reaction centre (converts light into chemical energy)

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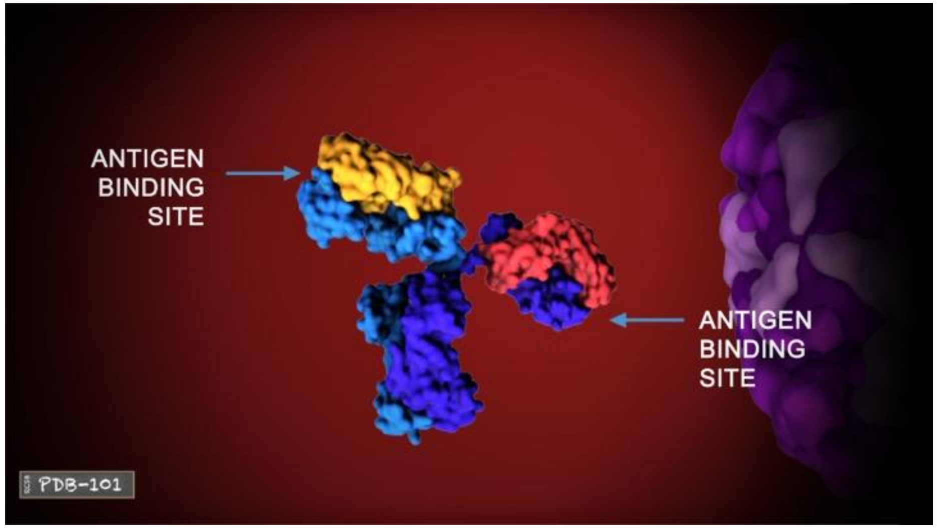
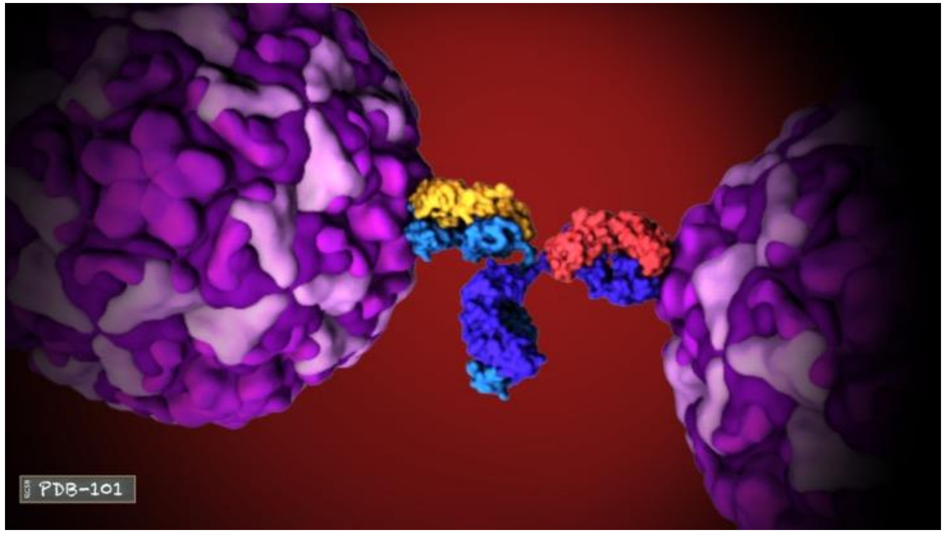
Protein functions: Defense



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.



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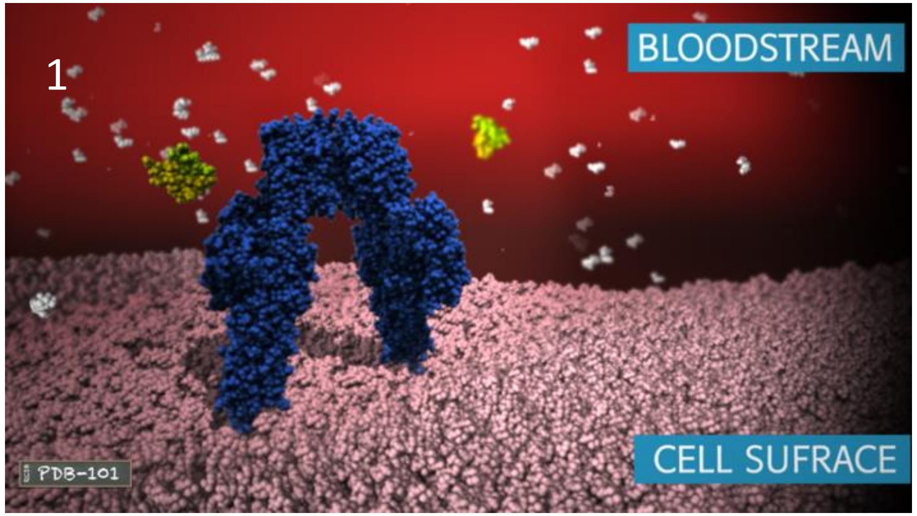
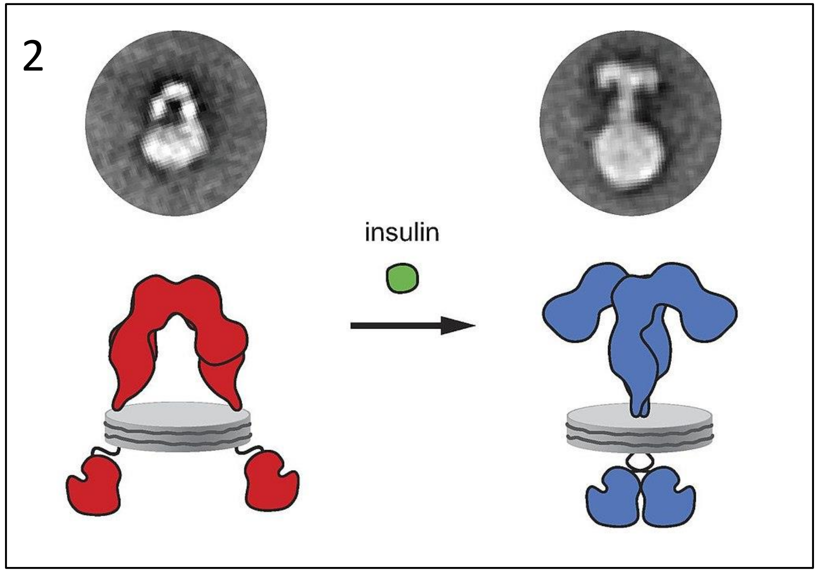
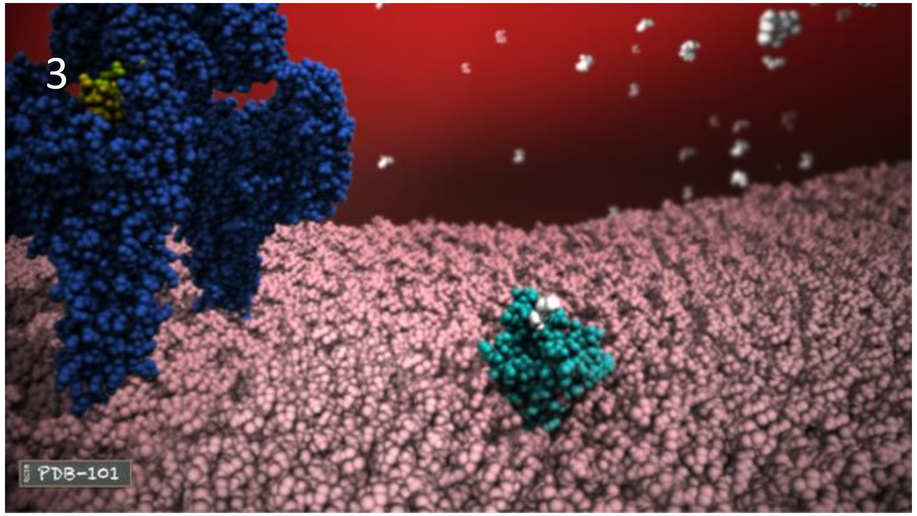
Protein functions: Communication

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.

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Protein functions: Transport

Aquaporin = water channel

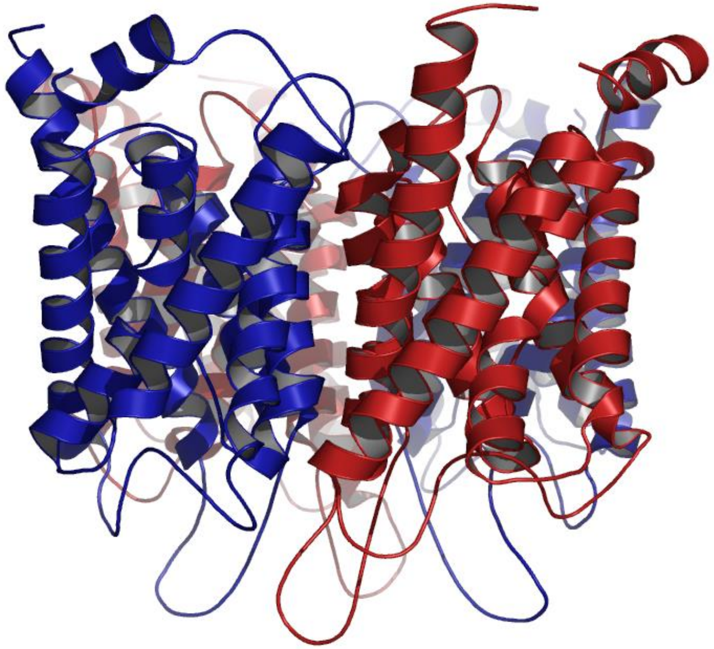


Image credit: Wiki Commons

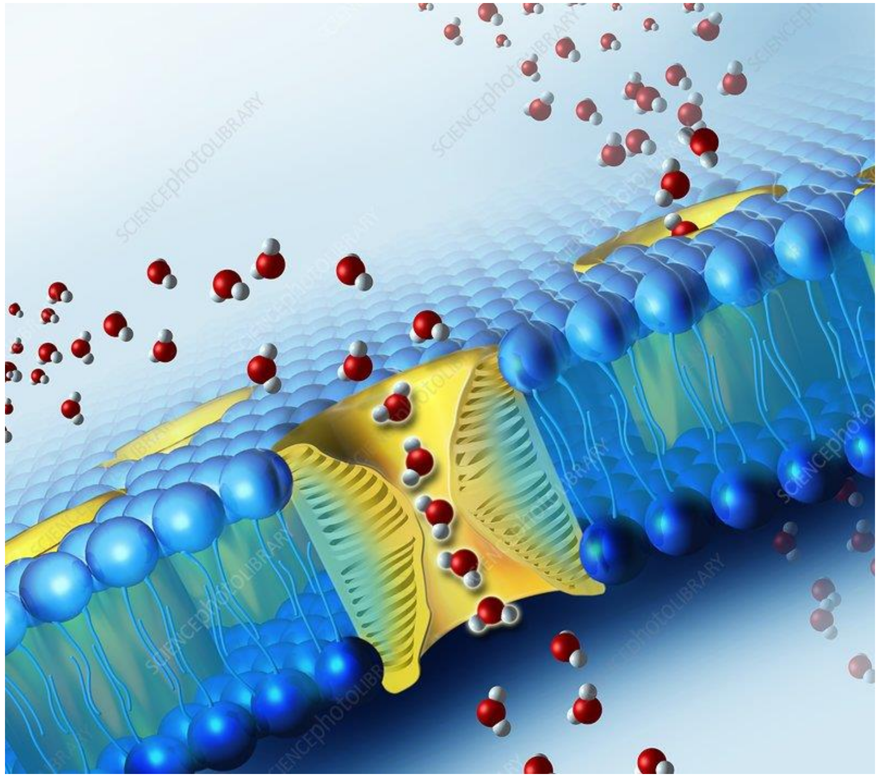
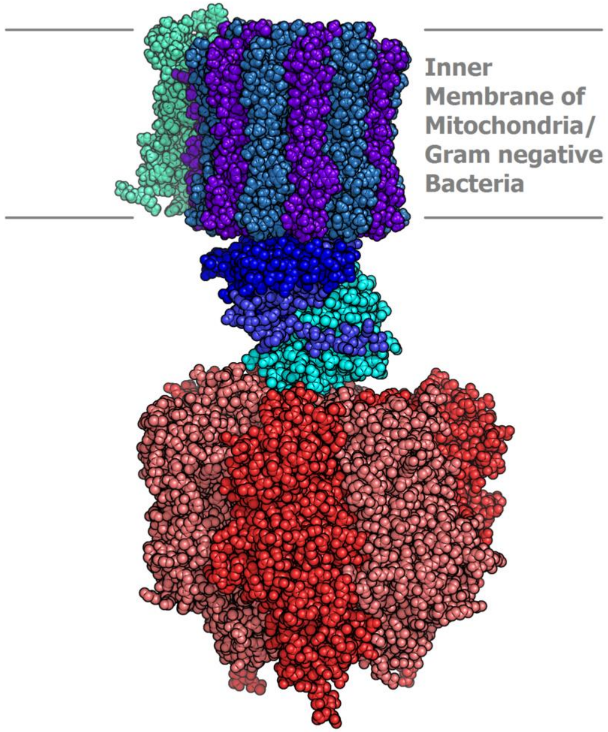
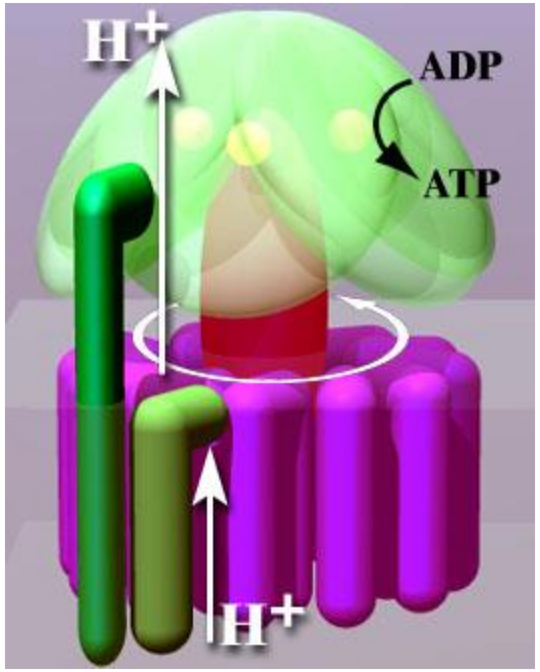


Image credit: Claus Lunau/Science Photo Library

Protein functions: Transport

ATP synthase = proton pump



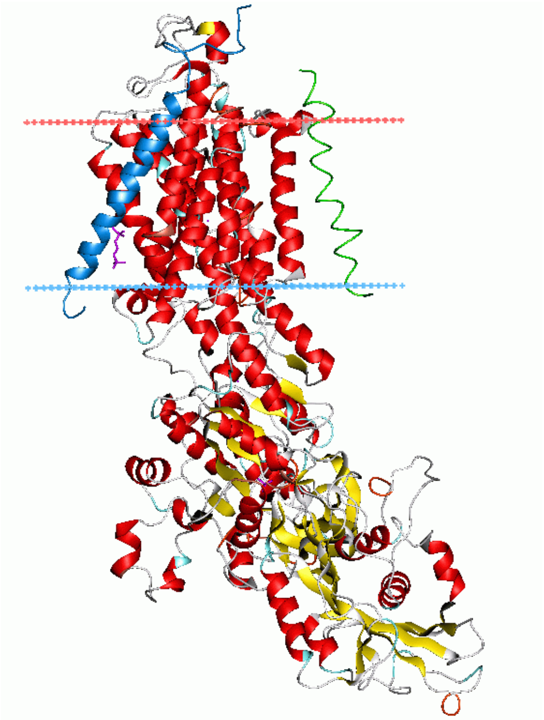


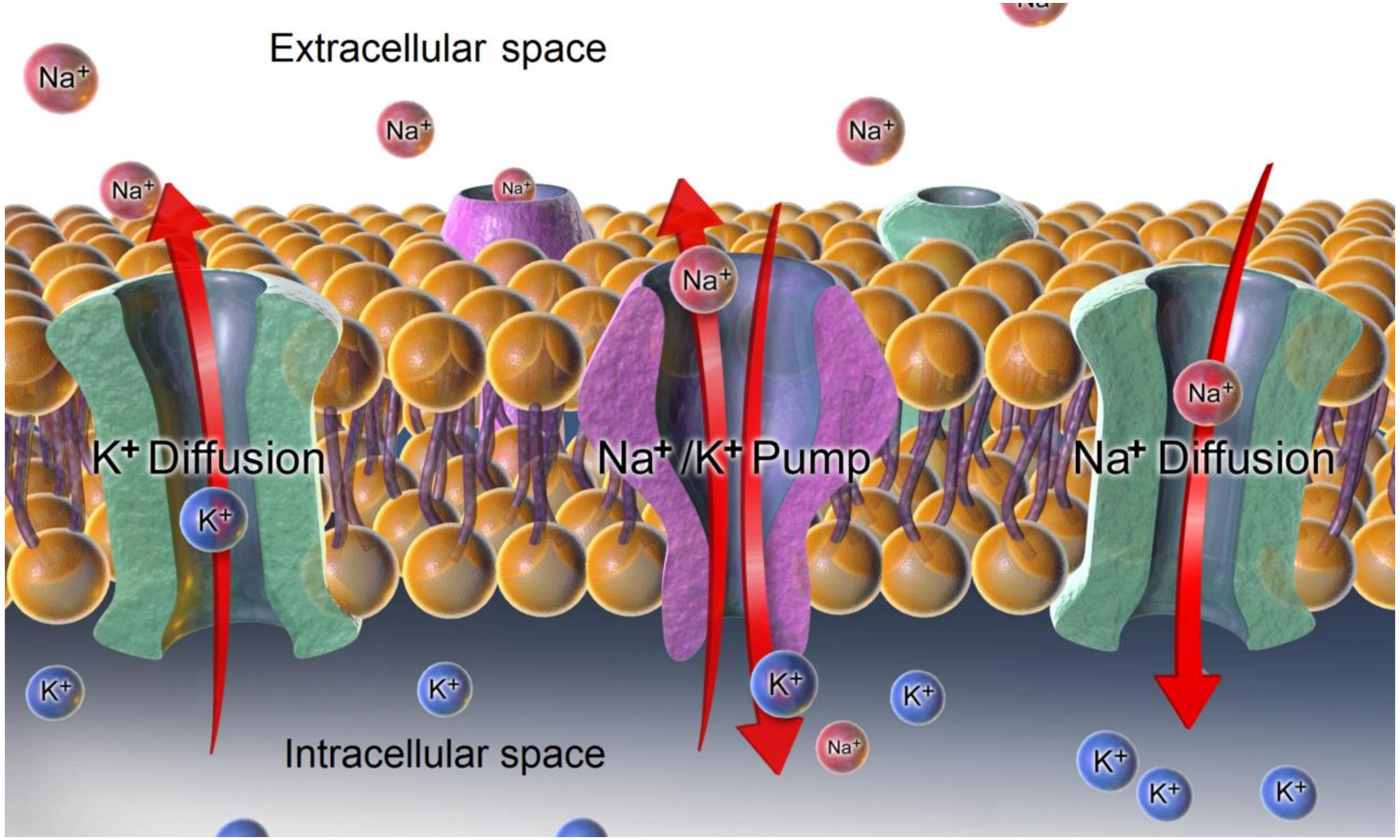
Cool animation: https://www.youtube.com/watch?v=kXpzp4RDGJI

Image credit: Creative Commons

Protein functions: Transport

Sodium & Potassium Channels, and Sodium-Potassium Pump





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

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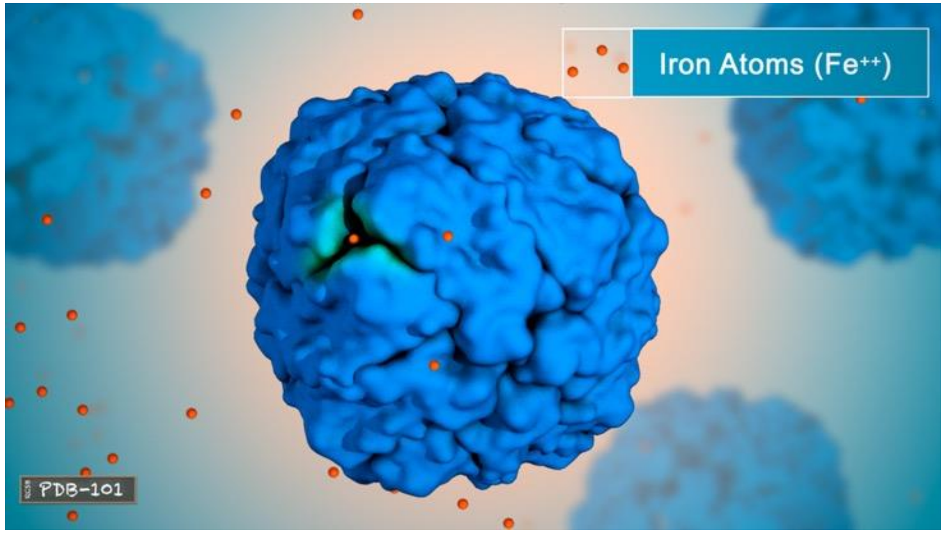
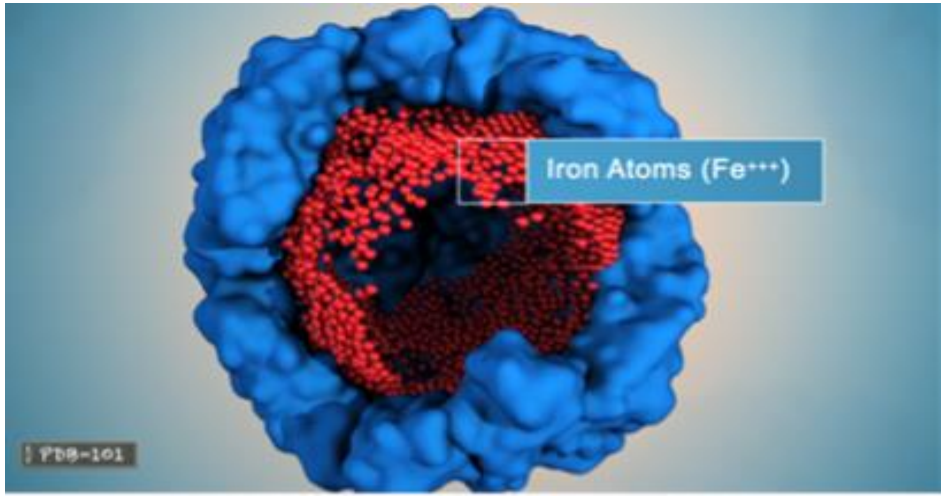
Protein functions: **Storage**





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.

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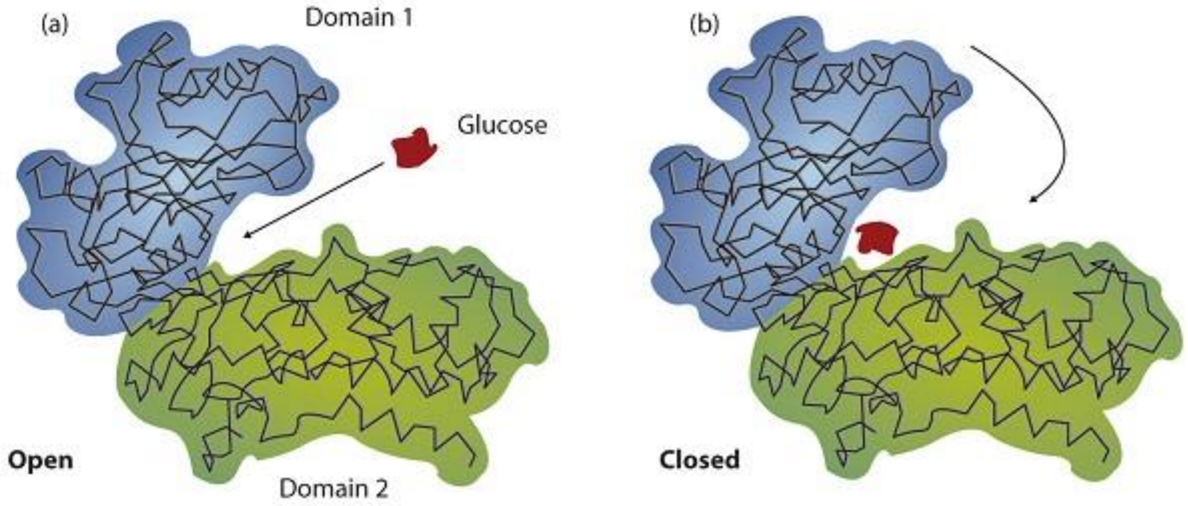
Proteins are dynamic structures

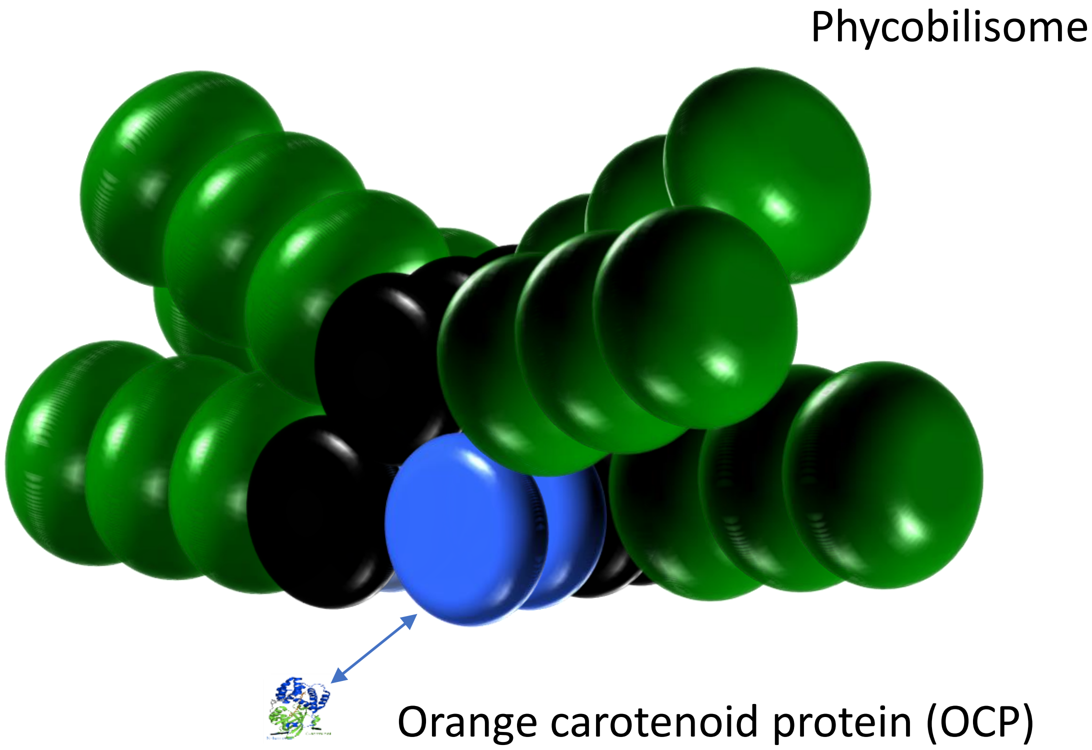


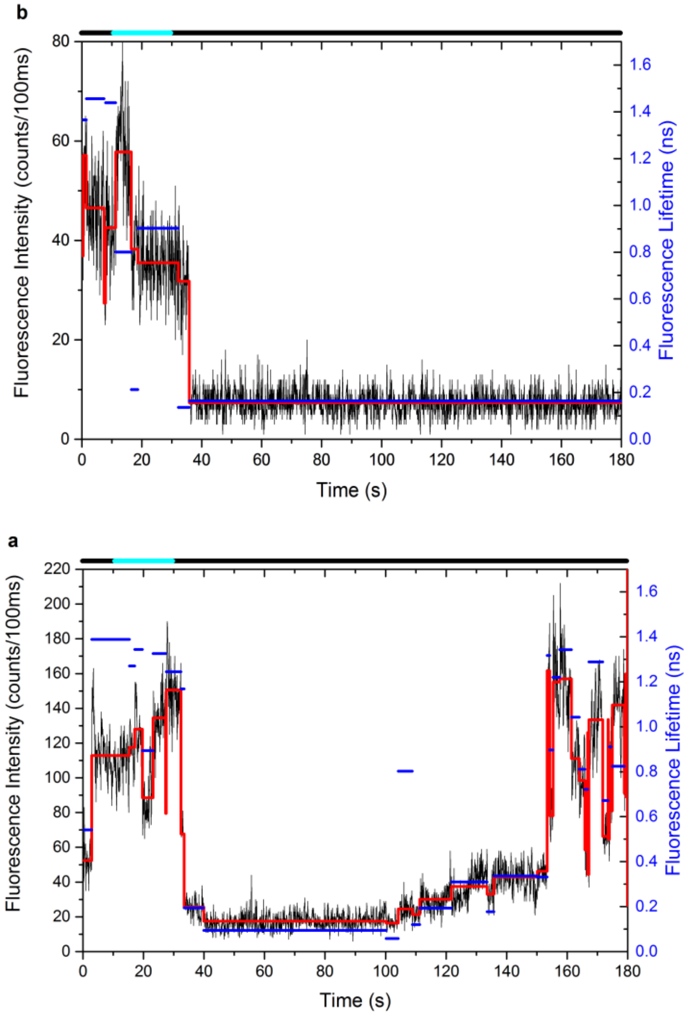
https://chem.libretexts.org/

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

Proteins are dynamic structures

OCP is a blue-light-activated protein that switches off the light-harvesting capability of phycobilisome upon binding.





Gwizdala, Botha, Wilson, Kirilovsky, van Grondelle & TPJK, "Switching an individual phycobilisome off and on" *J Phys Chem Lett* 9:2426-2432 (2018)

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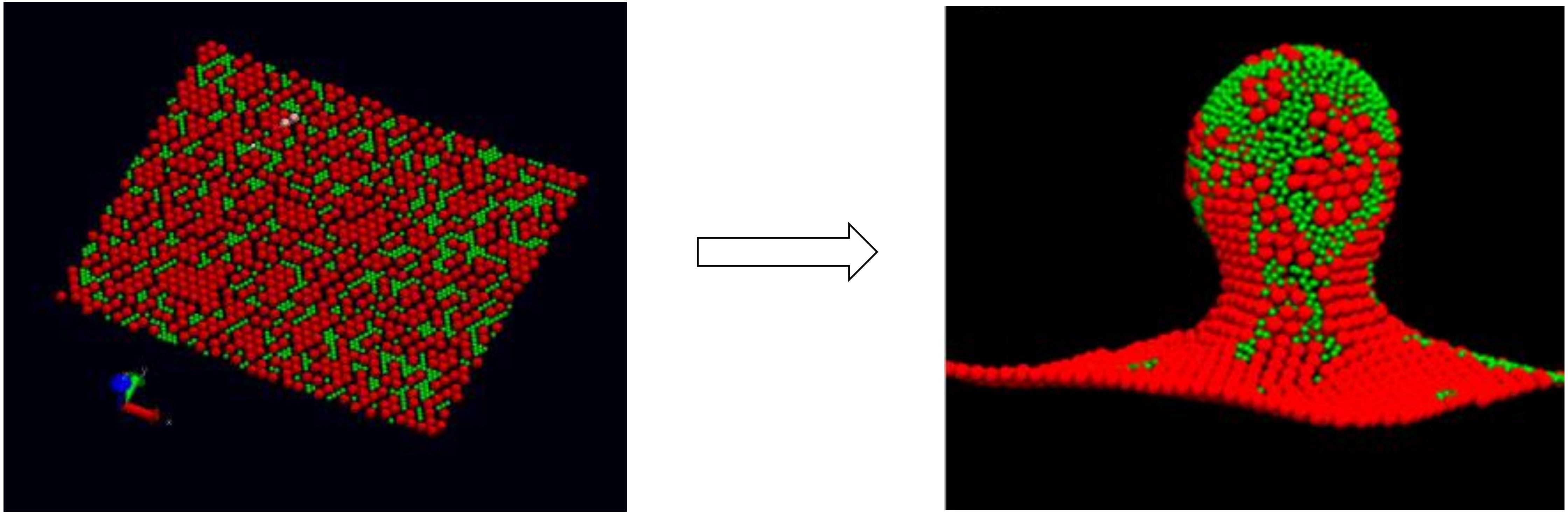
Protein self-assembly due to membrane curvature



RC-LH1 LH2

Helfrich elastic energy $$\mathcal{H} = \frac{1}{2}k_{\mathrm{A}}\frac{(A-A_0)^2}{A_0} + 2k\int_{\mathrm{A}} dA(J-c_0)^2$$

Frese et al. Biophys. J 94, 640 (2008)

Acknowledgements

- Dr Steven Hussey, Dept. Biochemistry, Genetics and Microbiology, University of Pretoria: DNA slides
- PDB Educational Portal: Many protein slides

Some food for thought

“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?”

“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!”

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

Towan Nöthling, PhD student

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A few animations to get you inspired

- The Inner Life of the Cell: https://www.youtube.com/watch?v=FzcTgrxMzZk
- 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

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