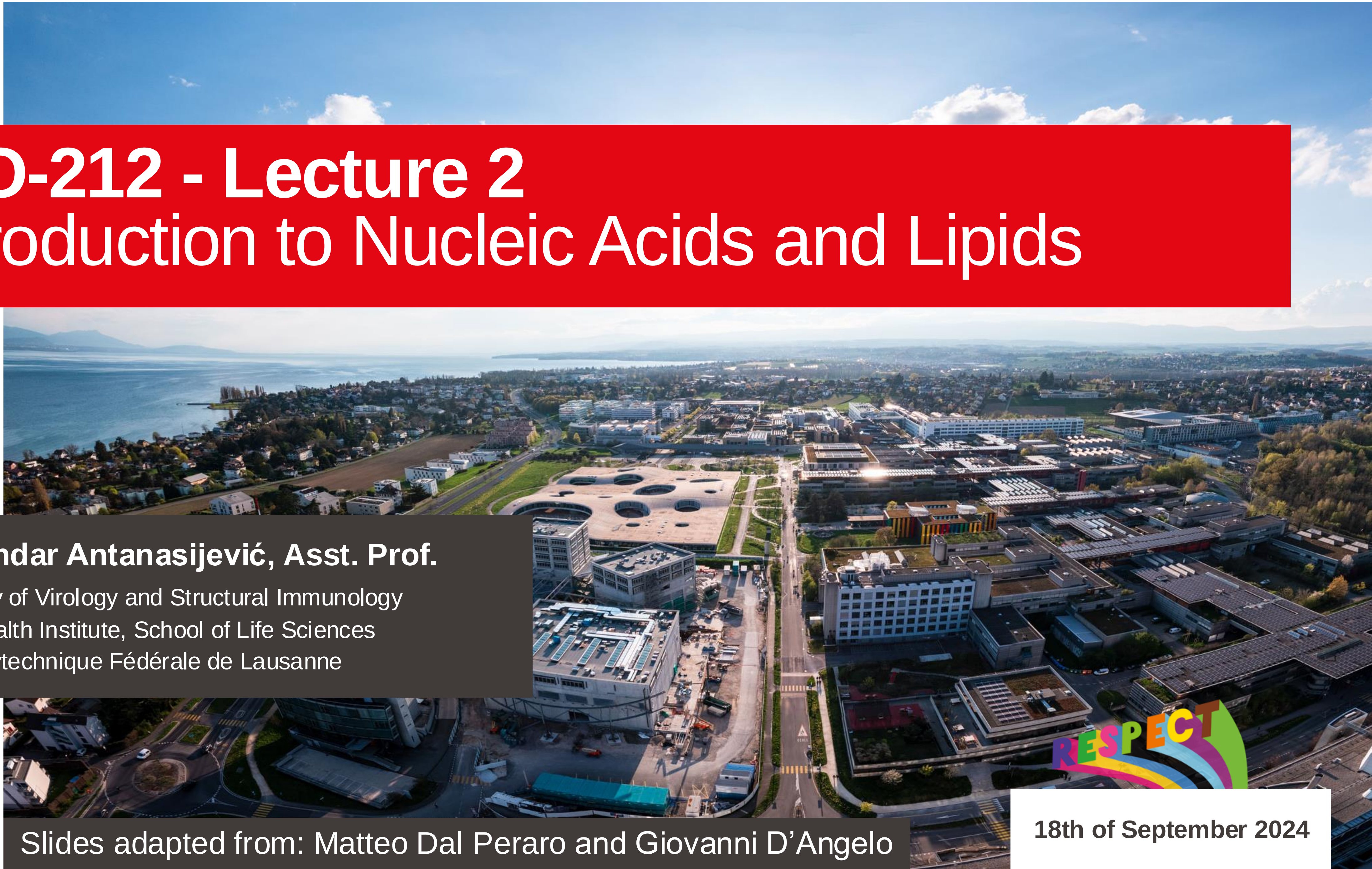
BIO-212 - Lecture 2
Introduction to Nucleic Acids and Lipids



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Slides adapted from: Matteo Dal Peraro and Giovanni D'Angelo

18th of September 2024

EPFL
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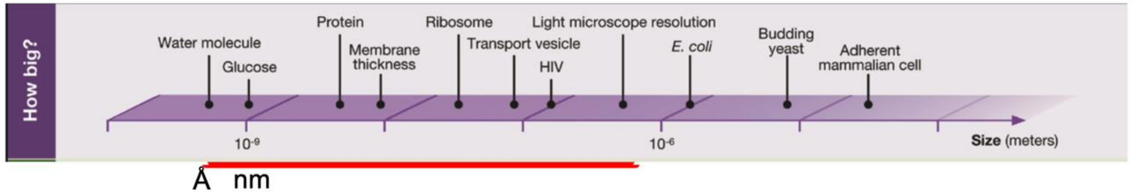
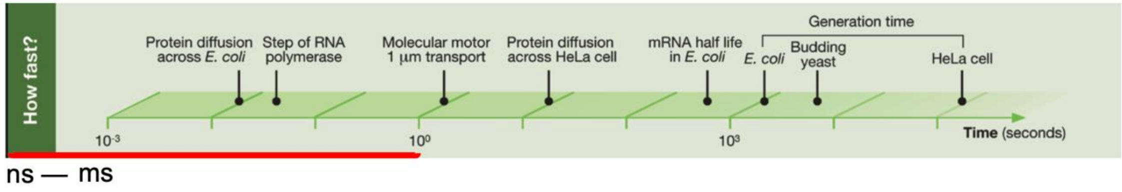
Lecture 1 – Quick Summary

• Biomolecules on the scales of life:

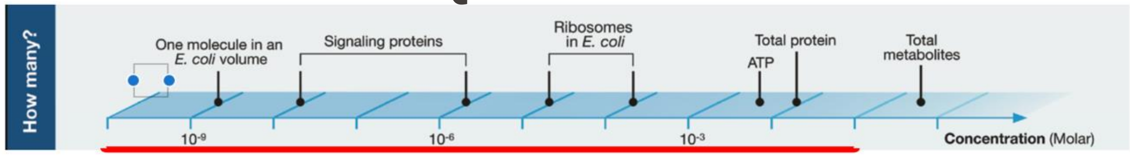
Size



Time

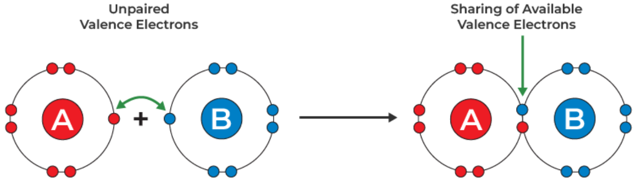


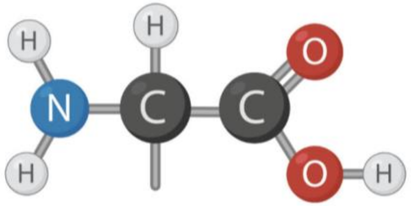
Quantities



• Atomic and molecular interactions in biomolecules

Covalent bonds

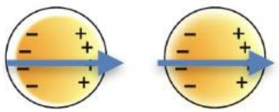




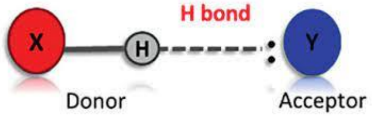
~300-800kJ/mol

Non-covalent interactions

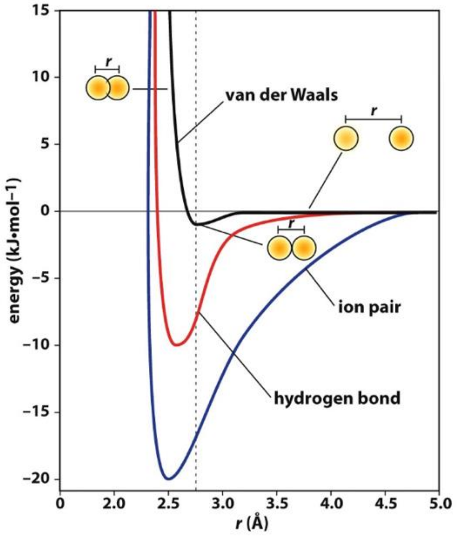
van der Waals interactions



Hydrogen bonds

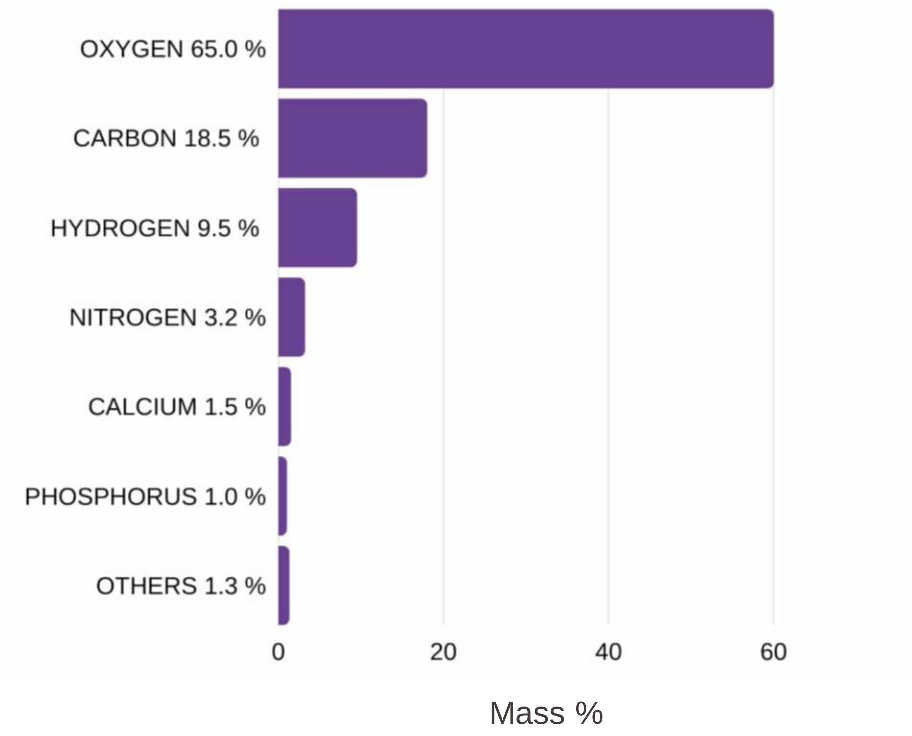


Ionic interactions

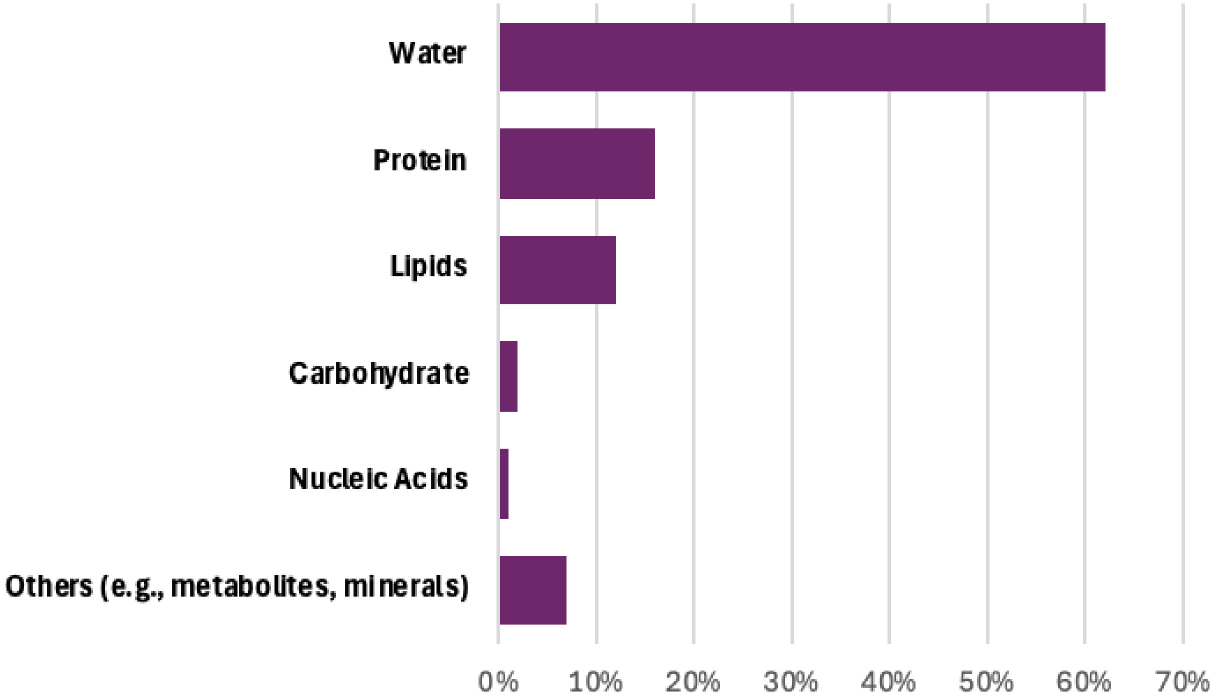


Molecular composition of biological systems

• Atomic composition of human bodies by mass:



• Molecular composition of human bodies by mass:



What is the most abundant molecule by molarity?

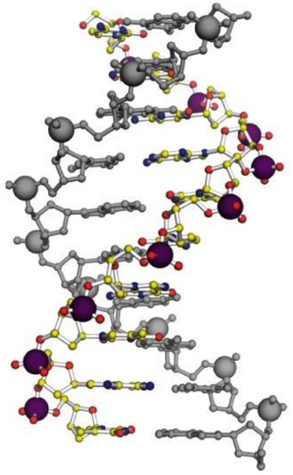
Cell and tissue variation (e.g., bone, adipose cells)

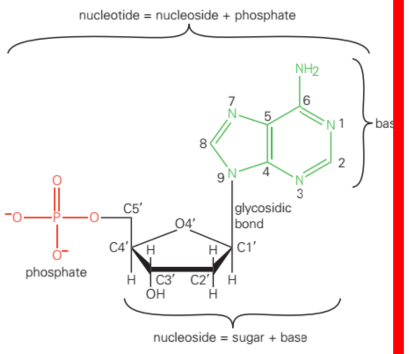
The molecules of Life

Macromolecular Structure

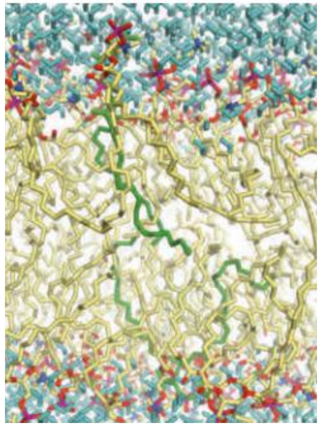
Building Block

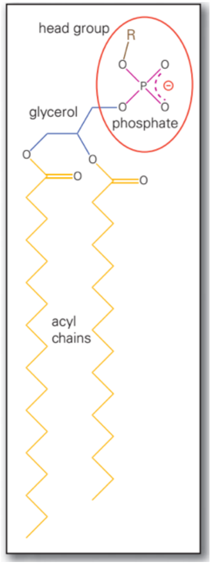
Nucleic Acids



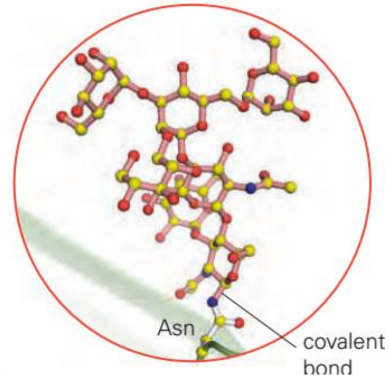


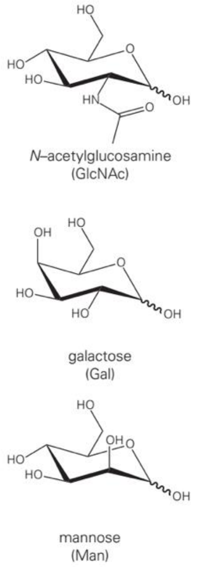
Lipids



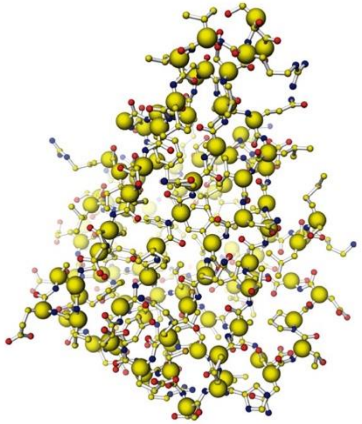


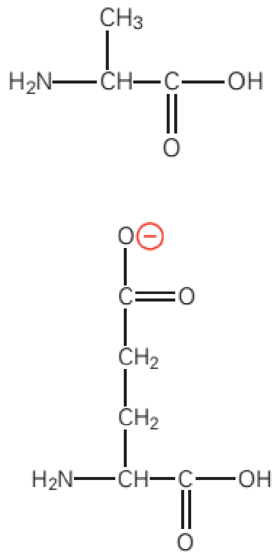
Carbohydrates





Proteins





Nucleic acids in cells (e.g., DNA and RNA)

- The main biological functions are storage, transmission and expression of genetic information

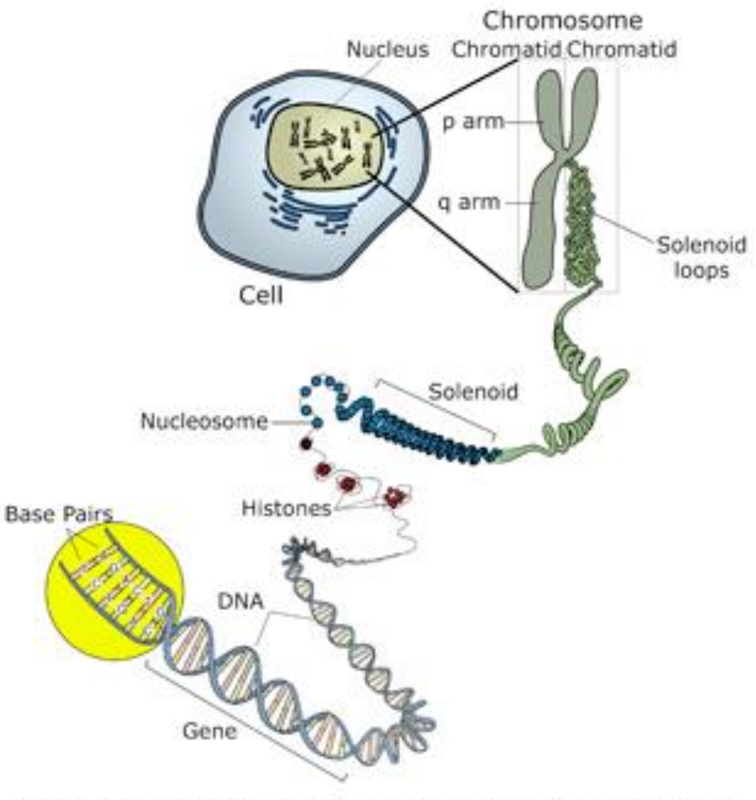
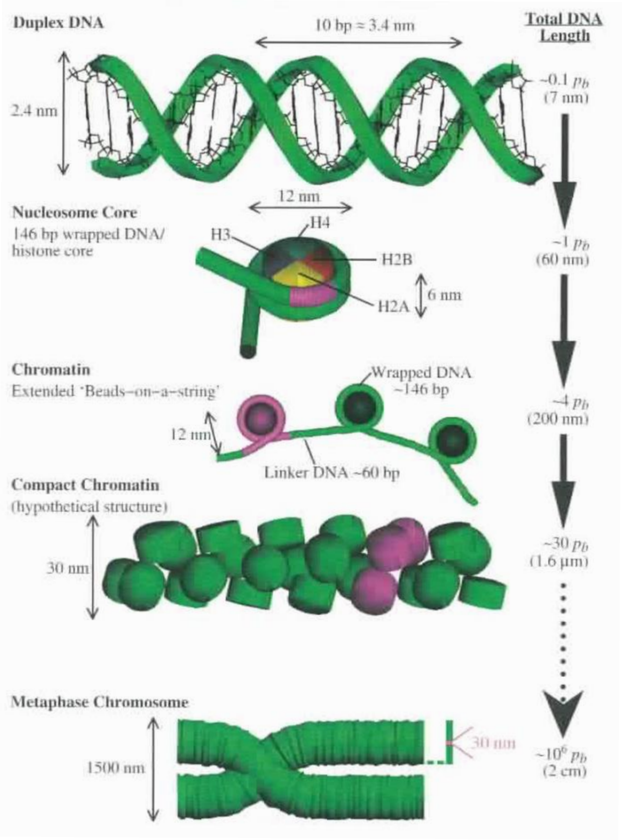


Image adapted from: National Human Genome Research Institute.



Johannes Friedrich Miescher
(1844-1895)

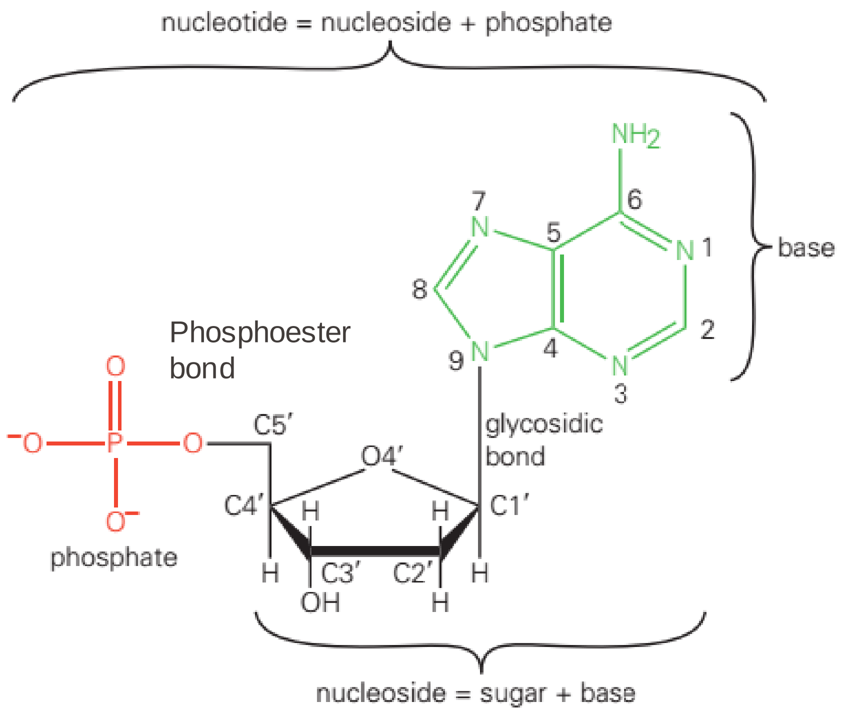
First person to isolate nucleic acids and suggest a role in heredity ("nuclein")

- Nucleotides also serve as energy carriers and signaling molecules, while RNA has many regulatory, catalytic, and sensing roles (particularly important for translation).

Nucleotides – the building blocks of nucleic acids

- DNA and RNA are both polymers of **nucleotides**.

Structure of a nucleotide

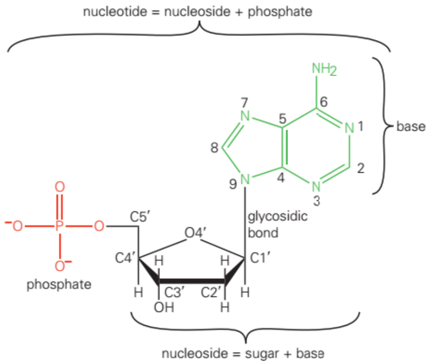


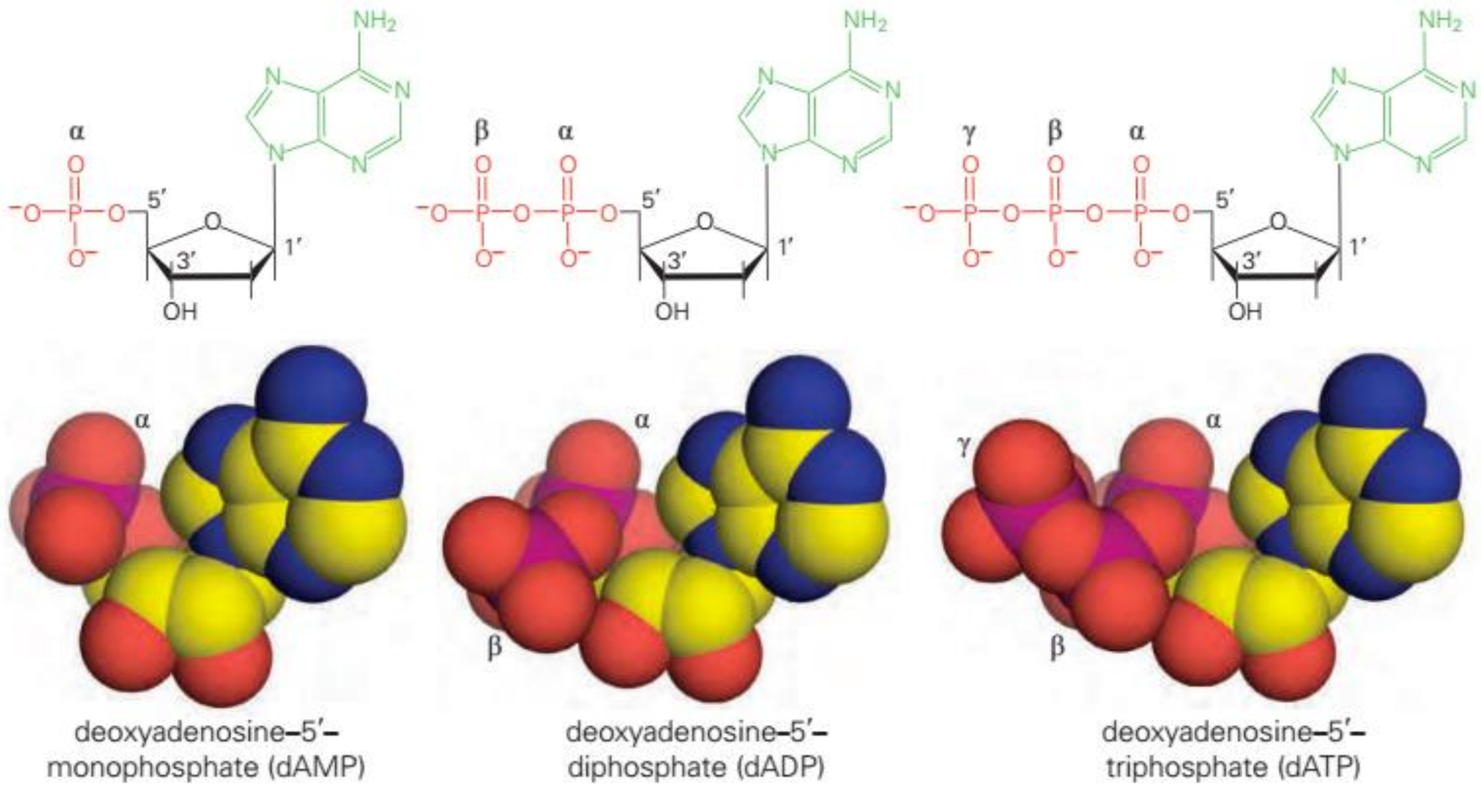
- Key functional groups:
  - Five carbon sugar – **pentose** in black
  - Nitrogen-containing aromatic ring system, i.e. **base** – adenine in green
  - **Phosphate** group in red (ranging from 1 to 3)
- They can be synthesized endogenously and are therefore non-essential nutrients

Nucleic acids – The phosphate group(s)

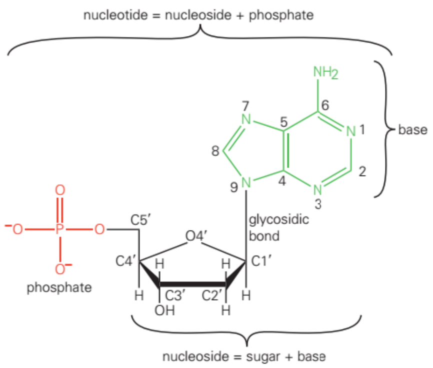
- Nucleotides with one, two or three phosphate groups are referred to as nucleotide mono-, di- or tri-phosphate.

- The three phosphate groups are called alpha, beta and gamma



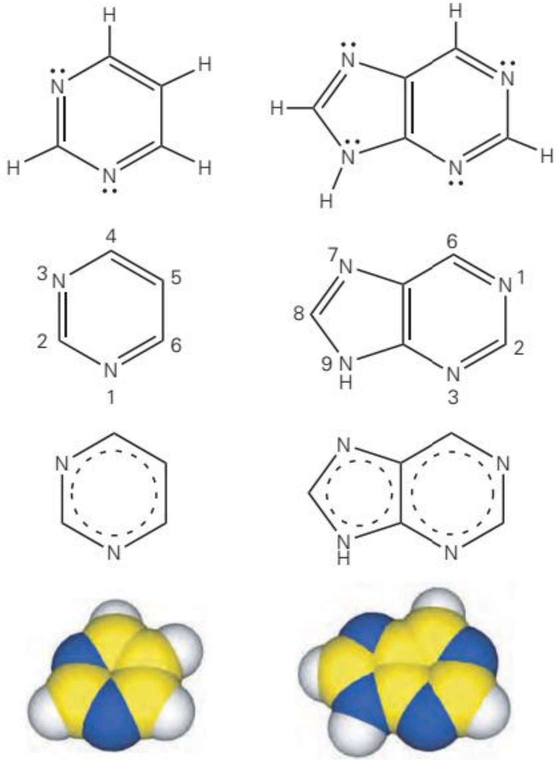


Nucleic acids – The Base



- DNA and RNA are built with 5 different bases

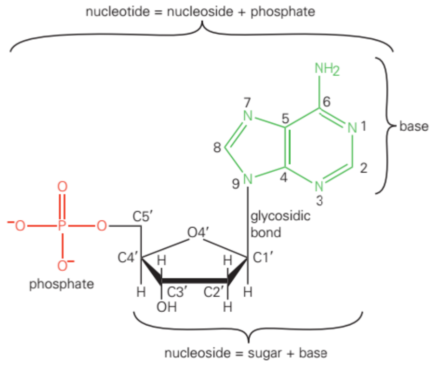
- The name “base” comes from its chemical composition - The ring systems contain lone pairs of electrons in the nitrogens being able to act as electron pair donors – so called Lewis bases



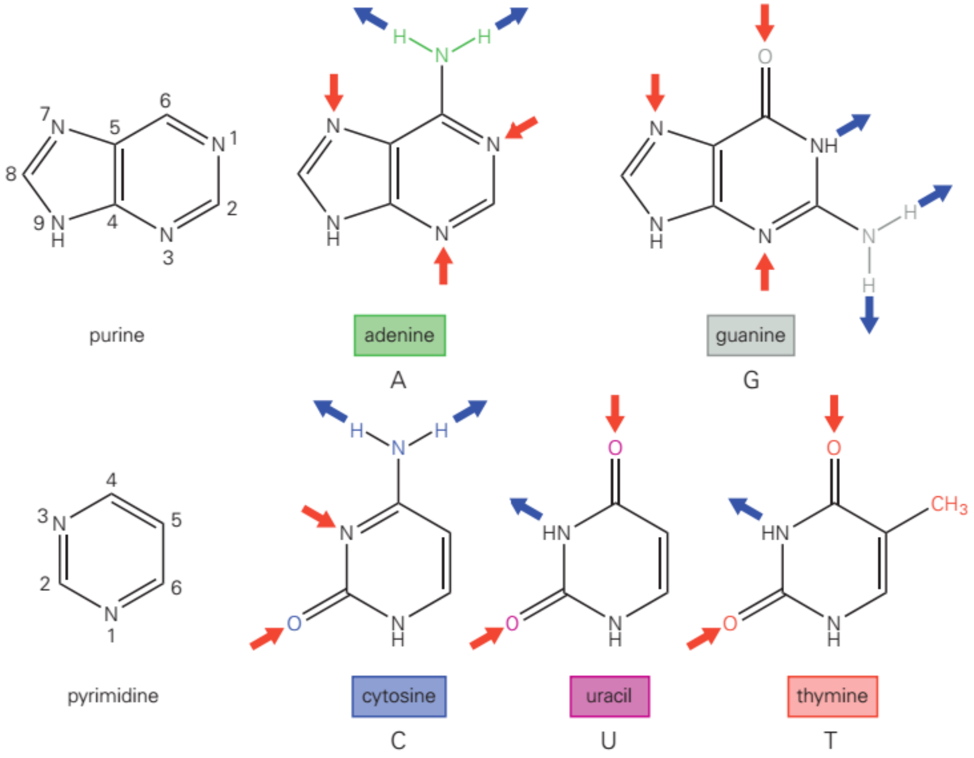
pyrimidine purine

Nucleotide bases in RNA and DNA are substituted forms of two heterocyclic molecules known as **pyrimidine** and **purine**

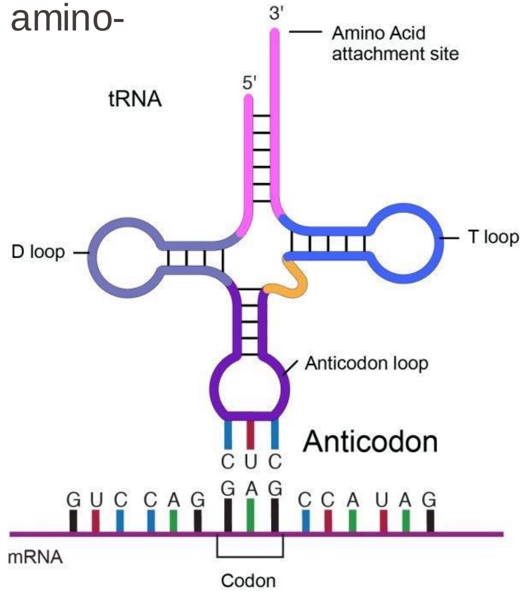
Nucleic acids – The Base



- DNA contains two substituted purines (**adenine** and **guanine**)
- DNA contains two substituted pyrimidines (**cytosine** and **thymine**)
- In RNA **thymine** is replaced by **uracil**



Translation of genetic information into amino-acid sequence

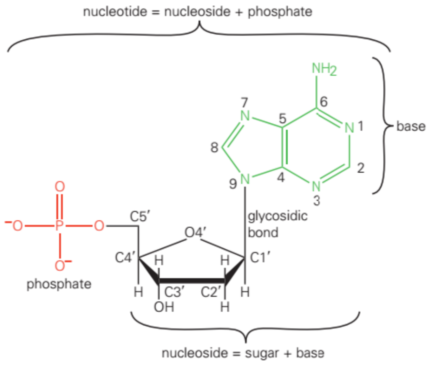


-Blue arrows point to hydrogen bond donor groups

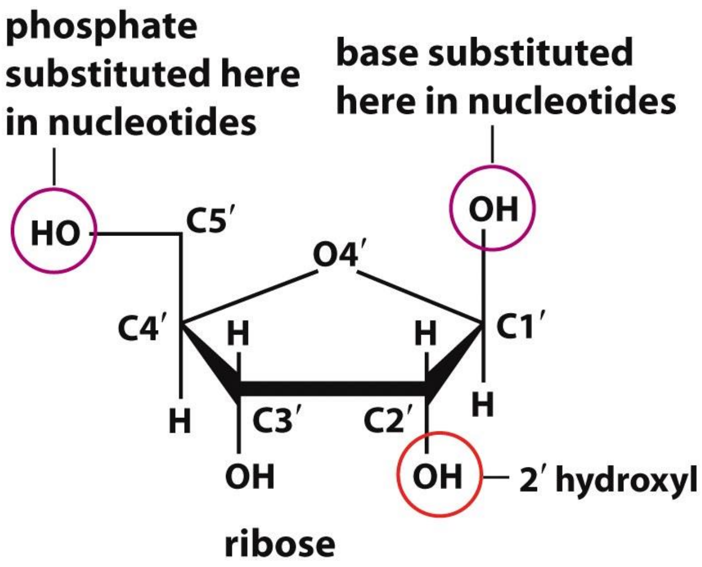
-Red arrows point to hydrogen bond acceptor groups

Key for the ability of RNA and DNA to serve as carriers of genetic information

Nucleic acids – The pentose sugar



- Sugars used in RNA are derived from ribose.
- Sugars used in DNA are derived from 2’-deoxyribose

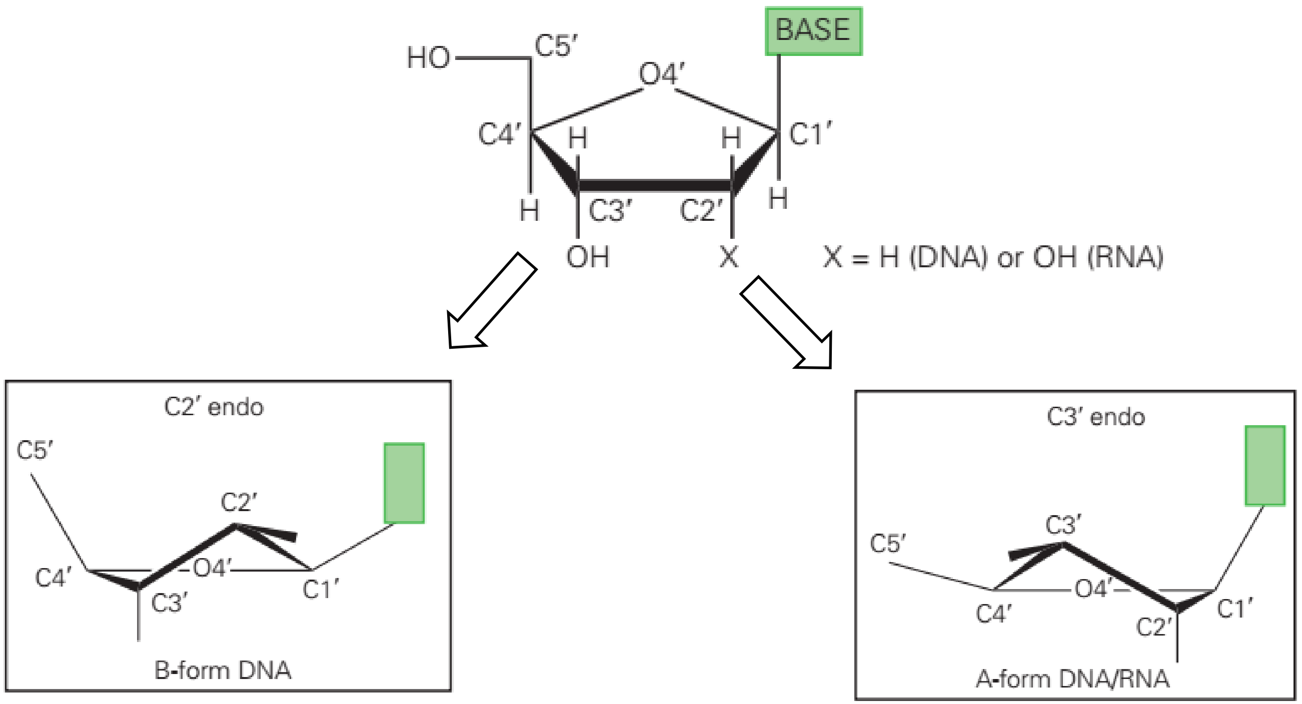


ribonucleotides

2’-deoxyribonucleotides

Nucleic acids – The pentose sugar

- In DNA/RNA molecules the pentose adopts a so-called sugar pucker conformation

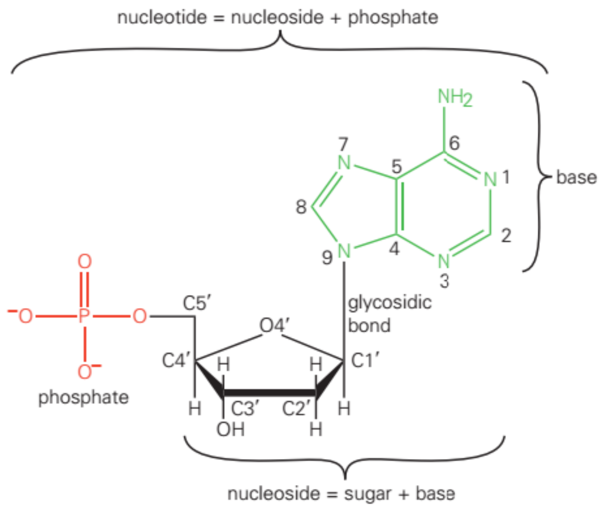


- In energetically favorable conformations four of the atoms of the pentose ring are roughly coplanar and one is out of the plane

Nucleic acids – The Base

- Please note the name distinctions between bases, nucleosides and nucleotides

Base	Nucleosides	Nucleotides
RNA		
Adenine (A)	Adenosine (A)	Adenosine 5'-monophosphate (AMP)
Guanine (G)	Guanosine (G)	Guanosine 5'-monophosphate (GMP)
Cytosine (C)	Cytidine (C)	Cytidine 5'-monophosphate (CMP)
Uracil (U)	Uridine (U)	Uridine 5'-monophosphate (UMP)
DNA		
Adenine (A)	Deoxyadenosine (A)	Deoxyadenosine 5'-monophosphate (dAMP)
Guanine (G)	Deoxyguanosine (G)	Deoxyguanosine 5'-monophosphate (dGMP)
Cytosine (C)	Deoxycytidine (C)	Deoxycytidine 5'-monophosphate (dCMP)
Thymine (T)	Deoxythymidine (T)	Deoxythymidine 5'-monophosphate (dTMP)



Nucleic acids are polymers

• Nucleotides are joined together in DNA and RNA by the formation of a phosphodiester linkage between the 3’ carbon of one nucleotide and the 5’ of another

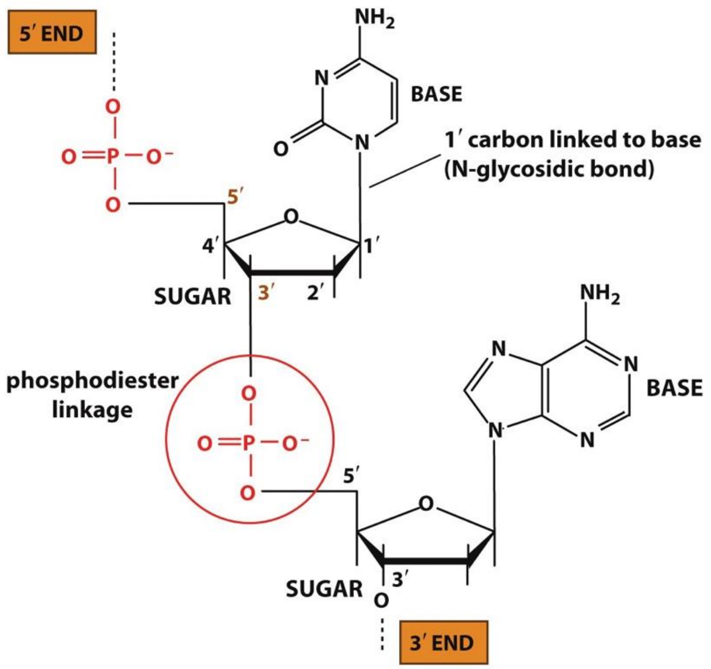


Figure 1.20 The Molecules of Life (© Garland Science 2013)

• The phosphate groups are negatively charged (anion nature)
• Important determinant for the 3D structure of DNA and RNA

Nucleic acids are polymers

• The synthesis of new molecules of DNA and RNA involves the stepwise addition of nucleotide to one end of the chain.
• The triphosphate group is high in energy and its hydrolysis drives the reaction

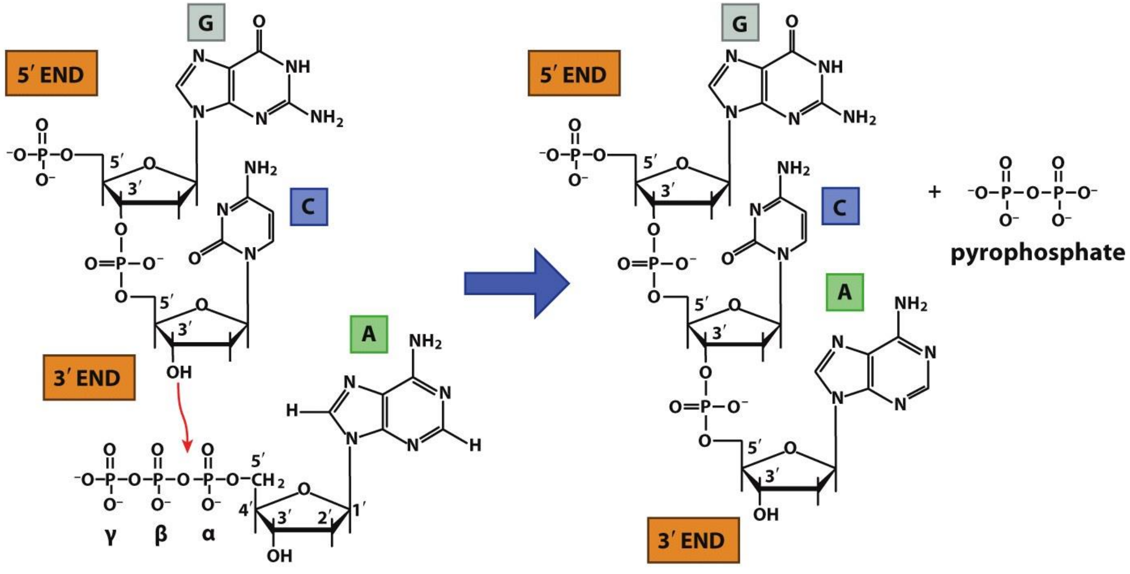


Figure 1.21 The Molecules of Life (© Garland Science 2013)

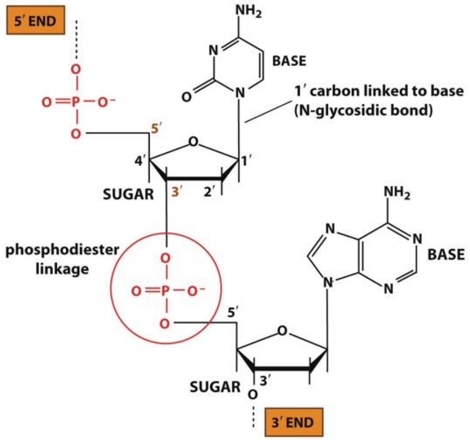


Figure 1.20 The Molecules of Life (© Garland Science 2013)

Nucleic acids are polymers

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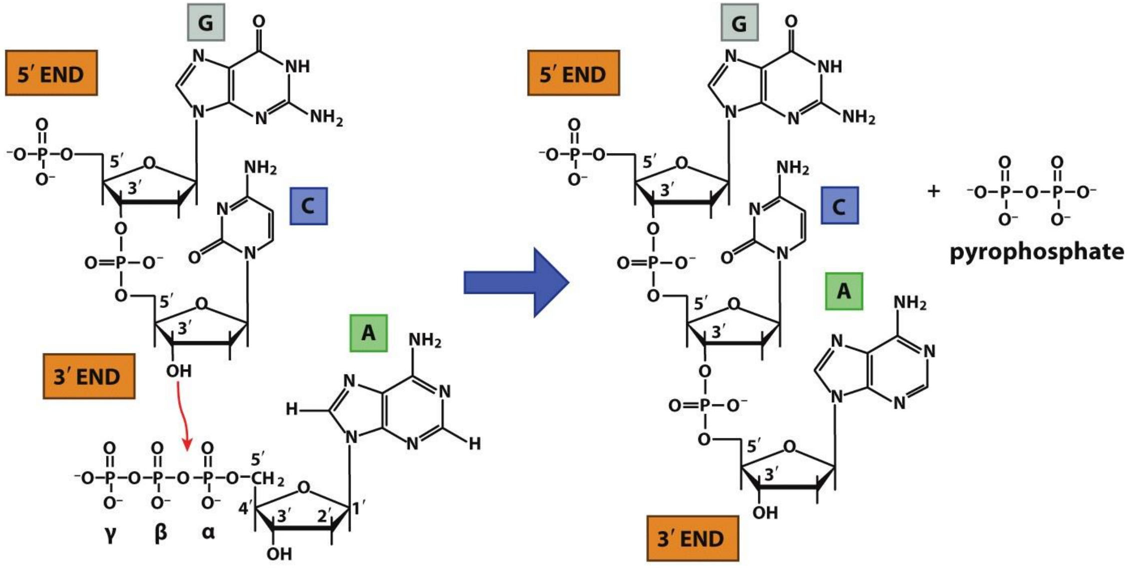


Figure 1.21 The Molecules of Life (© Garland Science 2013)

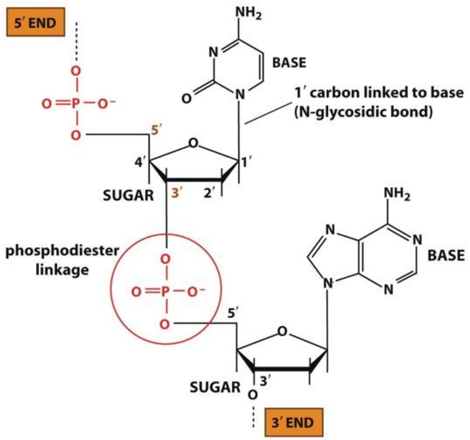


Figure 1.20 The Molecules of Life (© Garland Science 2013)

• DNA and RNA synthesis are template directed – DNA polymerases use a template strand to select each nucleotide to be added to the growing chain
• 3’->5’ phosphodiester linkage imposes directionality
• By convention DNA sequences are written from 5’ to the 3’ end

3D assembly of DNA

- DNA forms a double helix with antiparallel strands

- Two strands together wind up to form a right-handed double-helix

- Bases are on the inside of the helix and the phosphate backbone group are on the outside. Allowing for interactions with ions and water and minimizing repulsion between phosphates

- Base pairing holds the DNA strands together and is strictly complementary

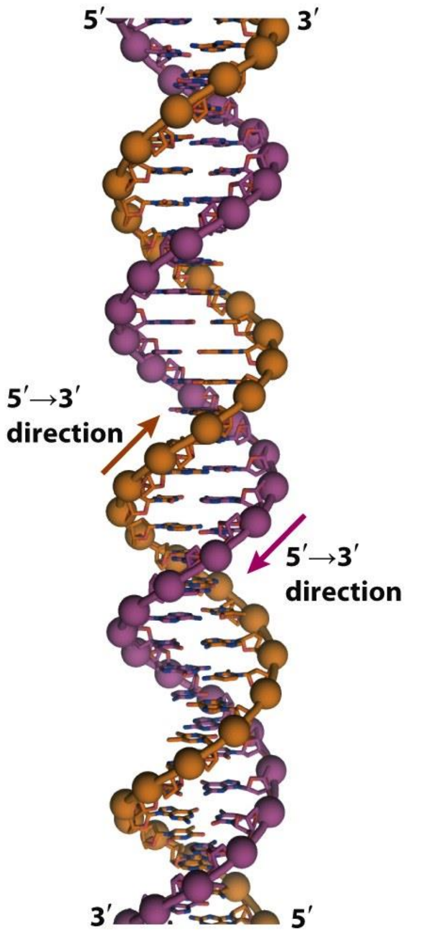


Figure 1.23 The Molecules of Life (© Garland Science 2

Phosphate groups in spheres

2 hydrogen bonds

3 hydrogen bonds

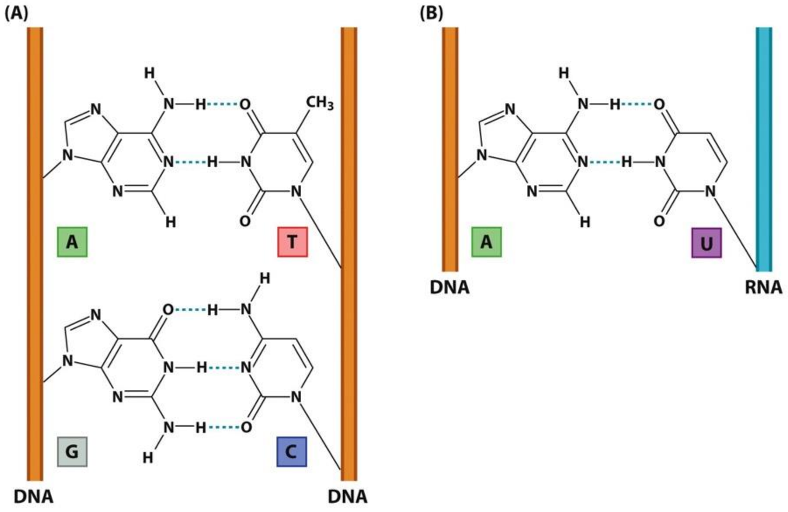
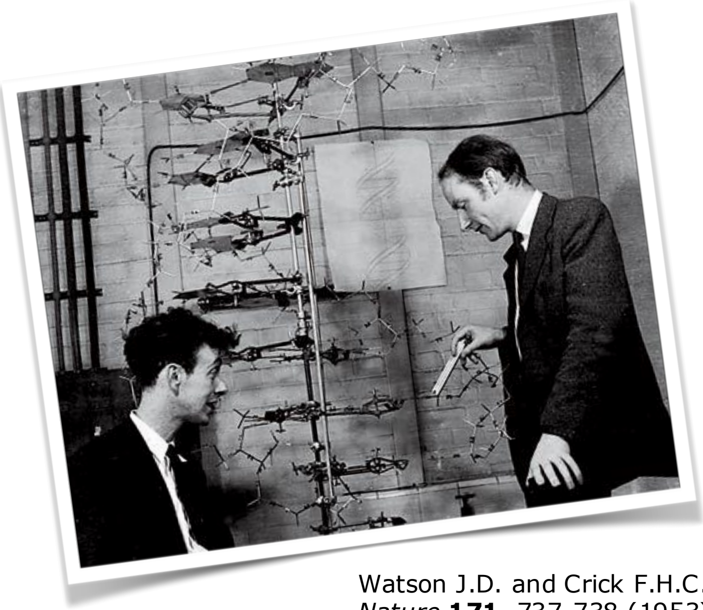


Figure 1.24 The Molecules of Life (© Garland Science 2013)

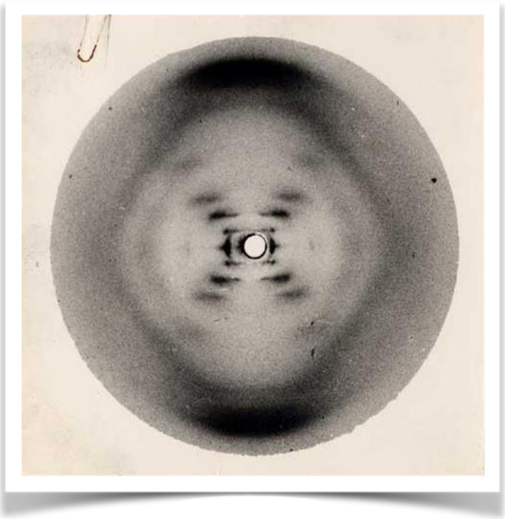
The Watson-Crick base pairs: A-T, G-C and A-U

Rudolf Signer
University of Bern
(purified calf DNA)



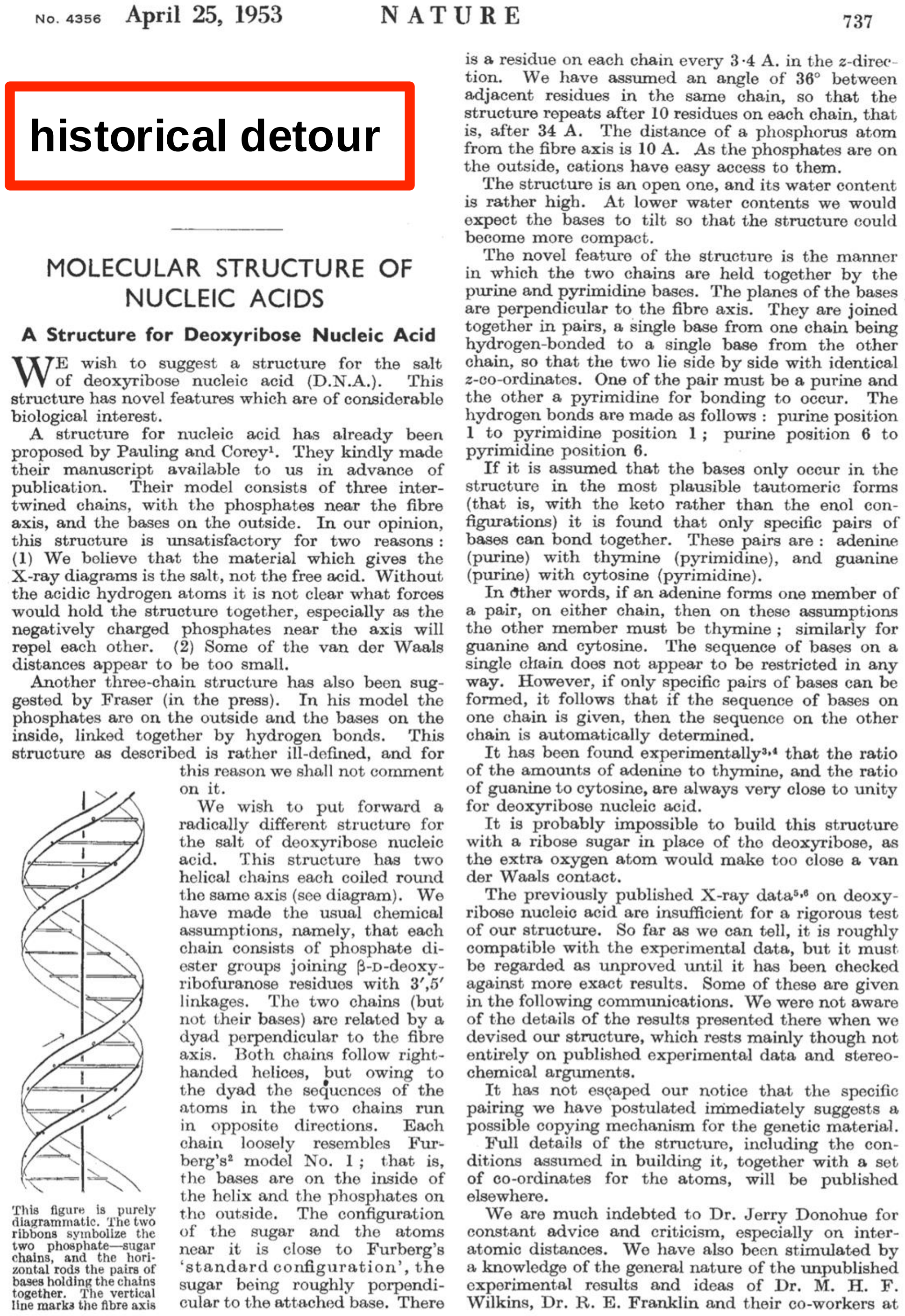
Watson J.D. and Crick F.H.C.
Nature **171**, 737-738 (1953)

Rosalind Franklin
UC London
(x-ray diffraction)



Rosalind Franklin's X-ray image of DNA ("Photo 51")

historical detour



No. 4356 April 25, 1953 NATURE 737

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 their manuscript available to us in advance of publication. Their model consists of three inter-twined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate di-ester groups joining β-D-deoxy-ribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There

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

is a residue on each chain every 3·4 A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereo-chemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on inter-atomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at

James Watson explains DNA base pairing

EPFL

Reprinted from Nature, Vol. 287, No. 5784, pp. 755-758, October 23 1980

Crystal structure analysis of a complete turn of B-DNA

Richard Wing*, Horace Drew, Tsunehiro Takano, Chris Broka, Shoji Tanaka, Keiichi Itakura† & Richard E. Dickerson

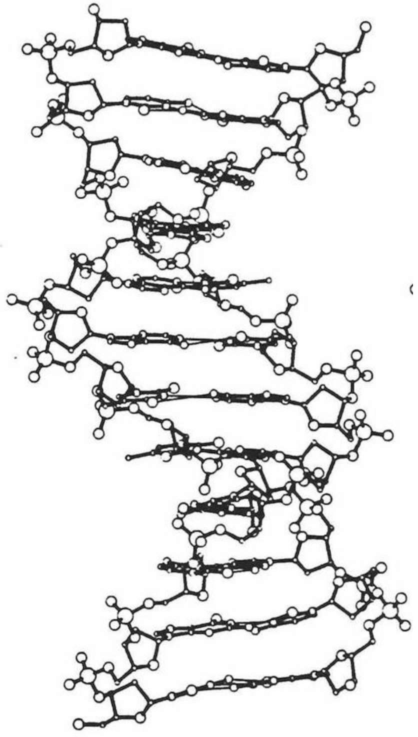
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

DNA is probably the most discussed and least observed of all biological macromolecules. Although its role in biology is a central one, with many examples such as operators and restriction sites where specific base sequences have control functions or interact with specific enzymes, the structures that DNA can adopt have been based until now only on sequence-averaged fibre diffraction patterns. Recent improvements in triester synthesis methods have made possible the preparation of sufficient homogeneous DNA of predetermined sequence for crystallization and X-ray structure analysis. We report here the first single-crystal structure analysis of more than a complete turn of right-handed B-DNA, with the self-complementary dodecamer sequence d(CpGpCpGpApApTpTpCpGpCpG) or CGCGAATTCGCG.

helix axis. Intensities remain strong in all directions out to 2.9 Å, and then exhibit a rapid decline until essentially no data can be obtained beyond 1.9 Å. Of the 5,691 possible reflections to 1.9 Å resolution, 2,818 were found to have an intensity greater than 2σ and were used in the analysis. Two isomorphous heavy atom derivatives were used: *cis*-dichlorodiamino platinum (II) obtained by diffusion, and a 3-Br derivative obtained by *de novo* synthesis of the dodecamer with 5-bromocytosine in the third position along each chain. The 1-Br derivative was crystallized but proved not to be isomorphous, and the 9-Br derivative was synthesized but not needed. Isomorphism in the *cis*-Pt derivative began to fail beyond 4-Å resolution, but the 3-Br derivative remains isomorphous to 2.7 Å.

The present report describes the partially refined structure obtained from multiple isomorphous replacement (MIR) analysis at 2.7 Å (mean figure of merit 57%), followed by Jack–Levitt refinement procedures[3] using 2,725 2σ intensities between 8.0 and 1.9 Å. The current residual error or R factor is 24.8% for a DNA molecule of 486 atoms and 9 initial water molecules. The structure of the DNA itself is essentially correct and is reported now because of its general interest. Refinement will continue with the addition of more solvent and spermine atoms, and some improvement in local nucleotide conformations.

A skeletal drawing of CGCGAATTCGCG is presented in Fig. 1, and a space-filling version from the same orientation in



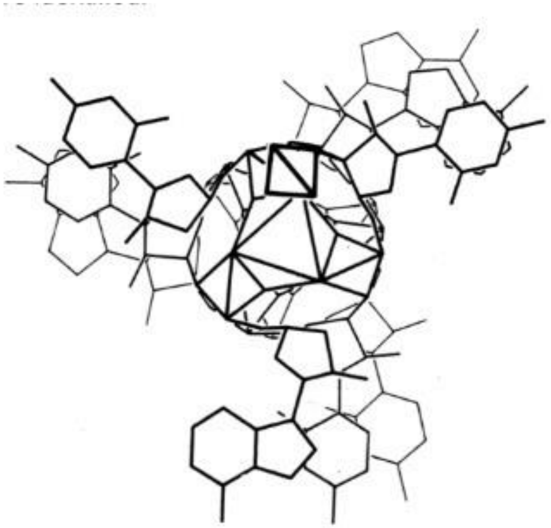


Figure 6, reproduced from: A proposed structure for the nucleic acids. Pauling and Cory (1953) PNAS 39, 84-97.

historical detour

3D assembly of DNA - Interactions

- In addition to hydrogen bonding the double helix is stabilized by **stacking of base pairs**

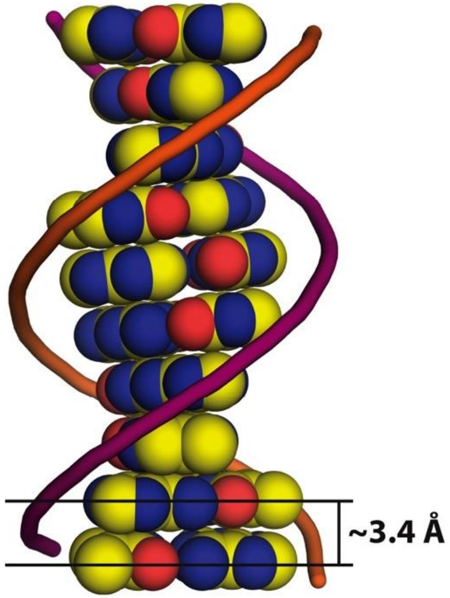
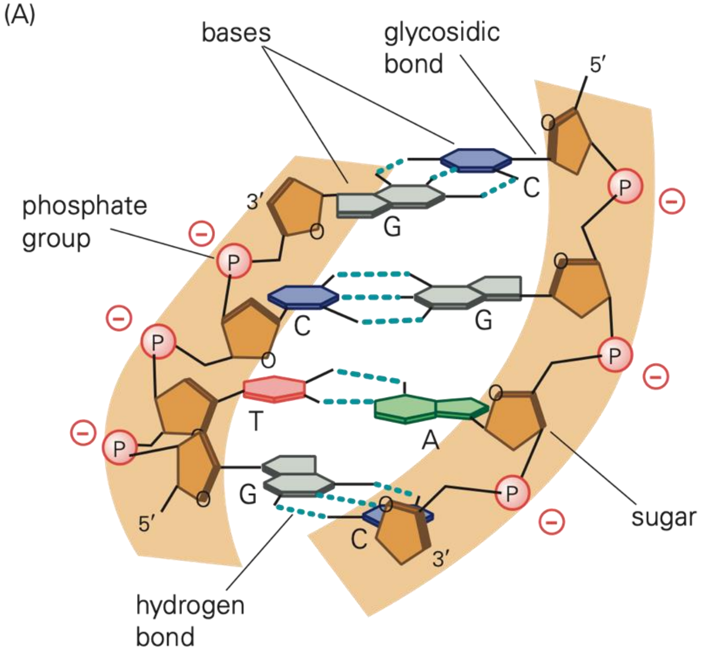


Figure 1.27 The Molecules of Life (© Garland Science 2013)



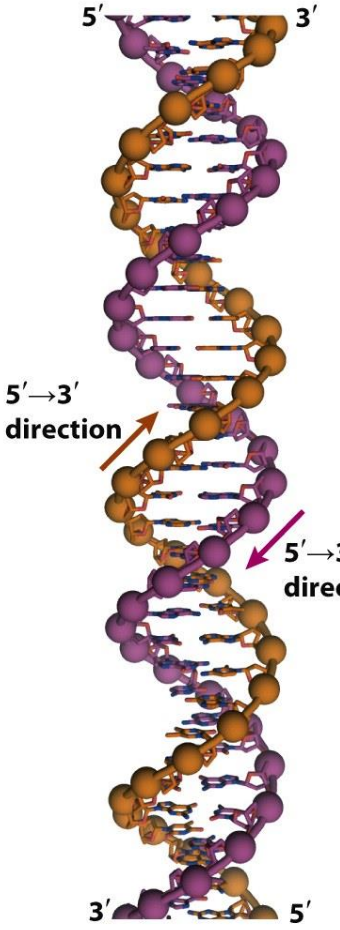


Figure 1.23 The Molecules of Life (© Garland Science 2

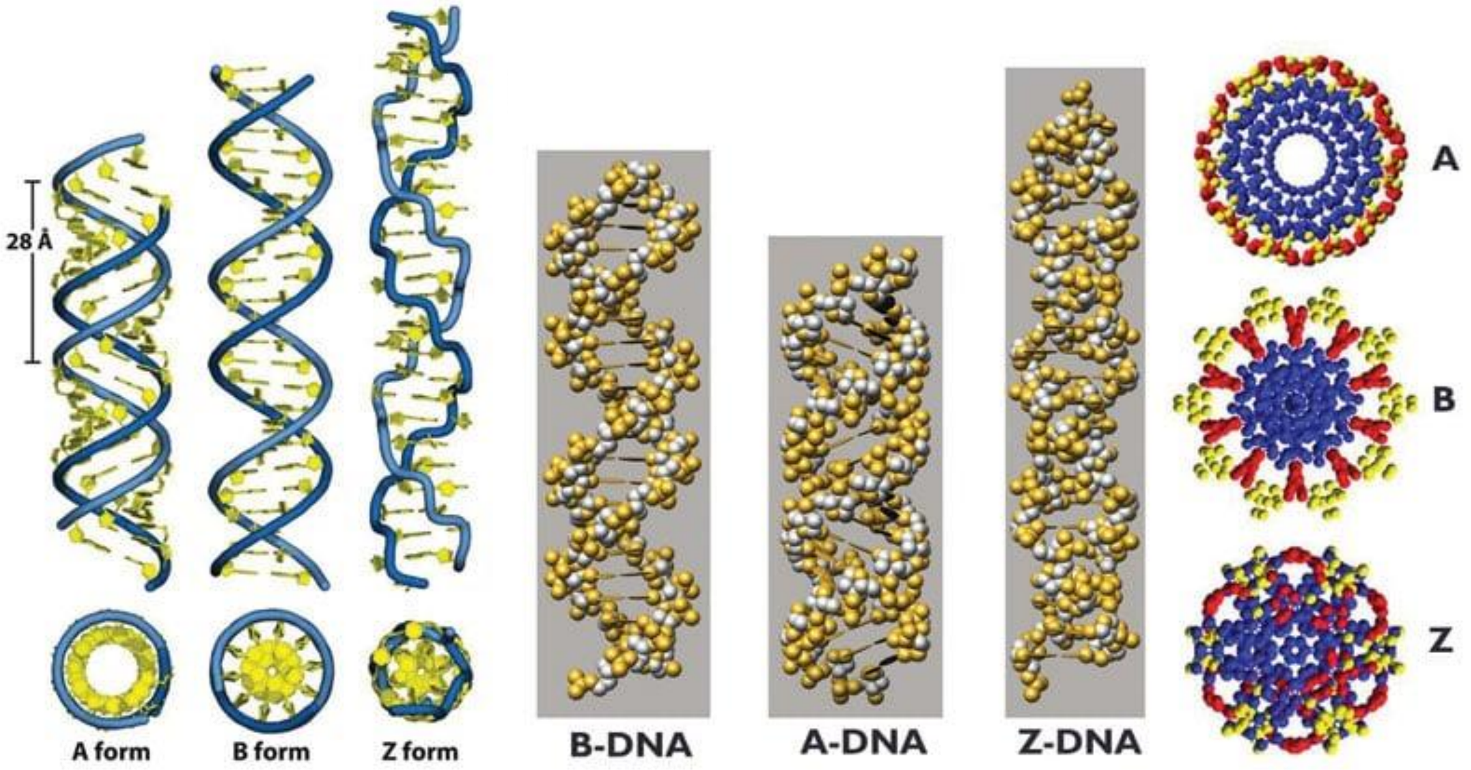
Phosphate groups in spheres

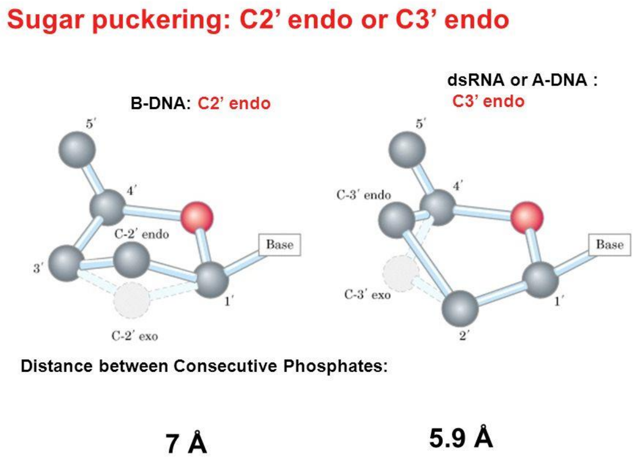
- There is a combination of electrostatic and van deer Waals interactions
- Beautiful example on van der Waals interactions given that the radius of **carbon and nitrogen are 1.7 and 1.6 Å** respectively – the observed **rise per base-pair is 3.4 Å**.

Different DNA assembly forms

- DNA can assemble into 3 major forms: A, B and Z


Rosalind Franklin

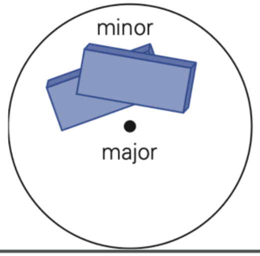
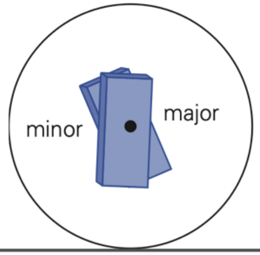
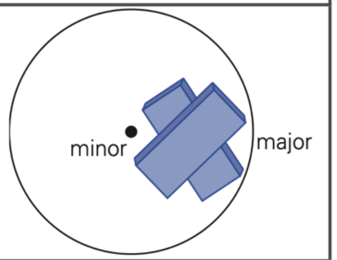




- **The major form in solution is B**, while A and Z are less prevalent (and require special conditions)
- Relative locations of C2' and C3' carbons in deoxyribose are responsible for A and B forms

Different DNA assembly forms

Table 2.1 Structural features of A-, B-, and Z-form helices.

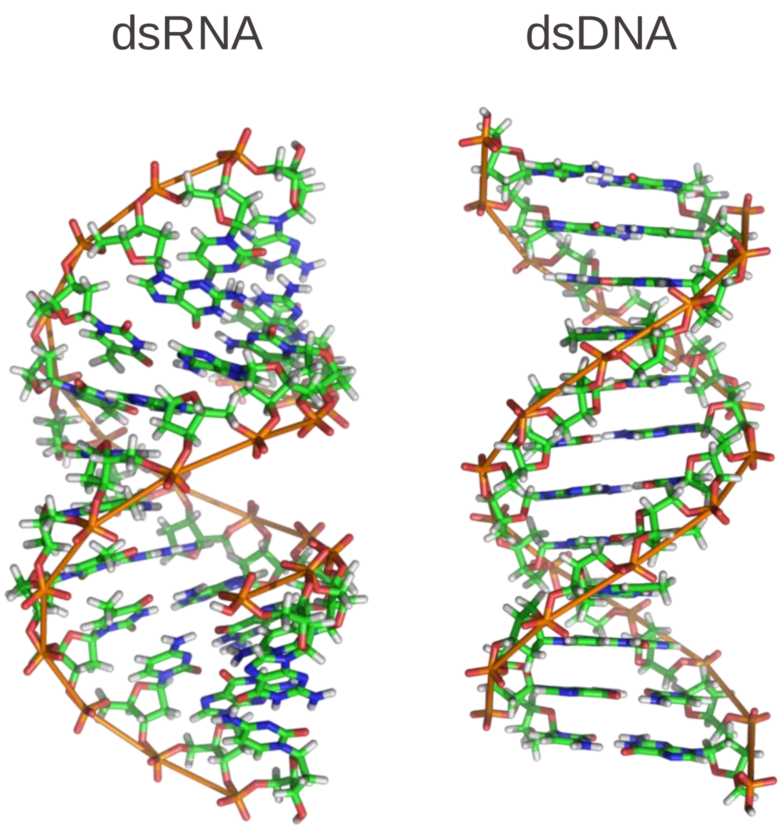
Helical form	A	B	Z
Helical sense	Right	Right	Left
Diameter	~ 26 Å	~ 20 Å	~ 18 Å
Base pairs per turn	~ 11	~ 10	~ 12
Helical twist (rotation per base pair for A and B, per two-base repeat for Z)	~ 34°	~ 36°	~ 60° (CpGp)
Helix pitch (rise per helical turn)	~ 25 Å	~ 33 Å	~ 46 Å
Helix rise (along helix axis; per base pair for A and B, per two-base repeat for Z)	~ 2.3 Å	~ 3.3 Å	~ 7.4 Å (CpGp)
Base tilt (with respect to helix axis)	~ 20°	~ 0°	~ – 9°
Base orientation (with respect to sugar)	Anti	Anti	C anti/G syn
Base pair positions (helix axis indicated by black dot)			
Features of base pair positions	Base pairs displaced from axis; deep major groove, less accessible	Base pairs on axis; both major and minor grooves accessible	Base pairs stick out into the major groove, the minor groove is deep and narrow

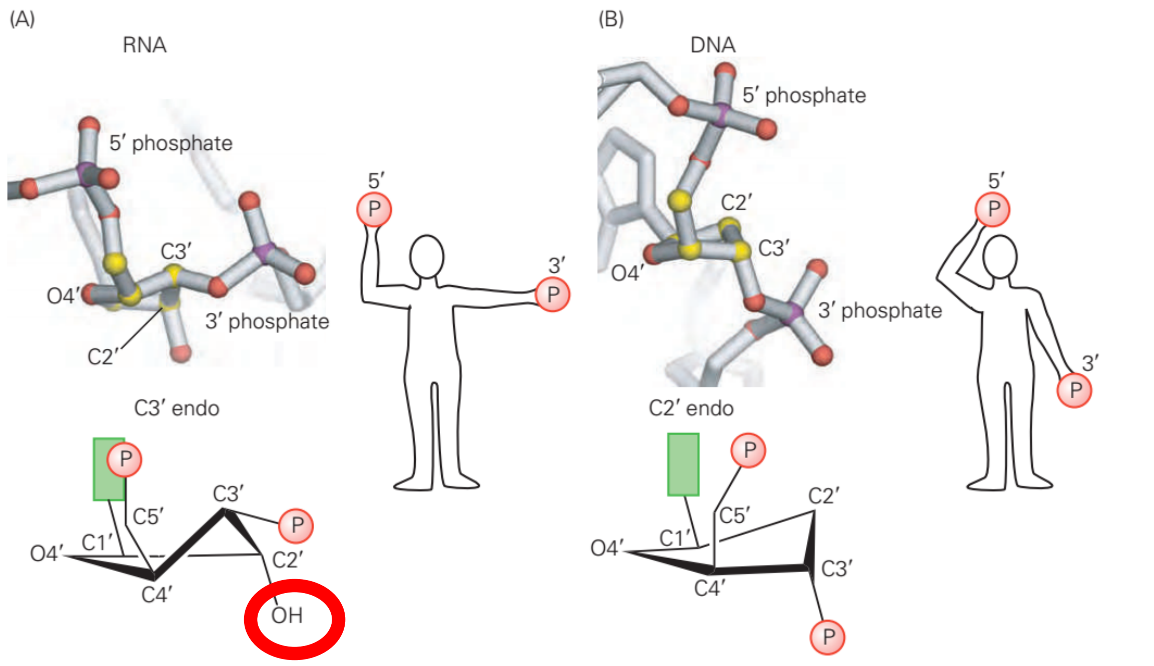
(Adapted from R.E. Dickerson et al., and M.L. Kopka, *Science* 216: 475–482, 1982. With permission from AAAS.)

https://x3dna.org

Differences in assembly of DNA and RNA

- Double-stranded RNA has strong preference towards the A form due to the extra hydroxyl (OH) group



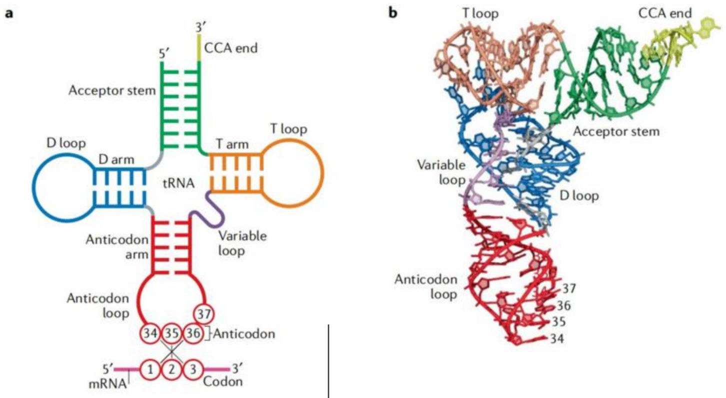


- For RNA the hydroxyl group influences the preferred conformational state of the sugar (C3’ up state) which impacts how it packs into a helix

Differences in assembly of DNA and RNA

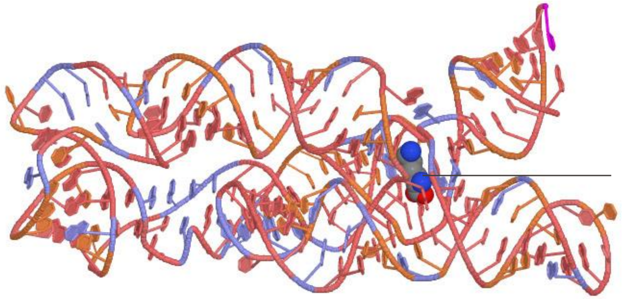
• Due to the unique chemical restraints of the ribose sugar and the single-stranded nature in most cases RNA can take on many diverse forms and, consequently, has more diverse functions compared to DNA

transfer (t) RNA



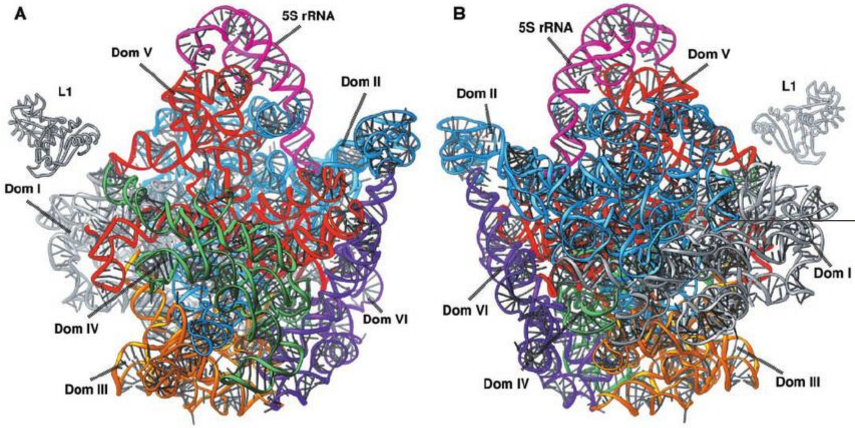
Amino-acid carrier

Riboswitch



Ligand sensing

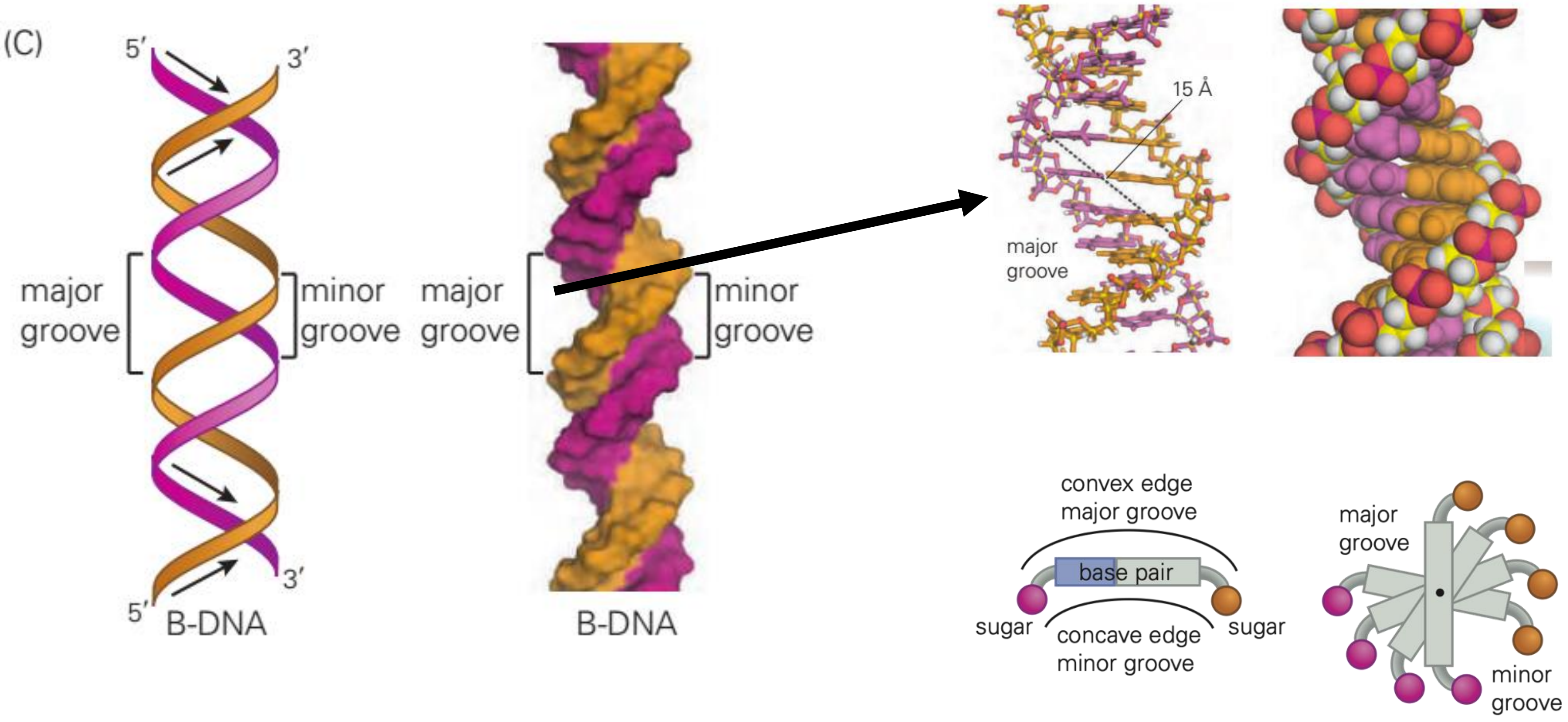
Ribosomal RNA



Catalysis

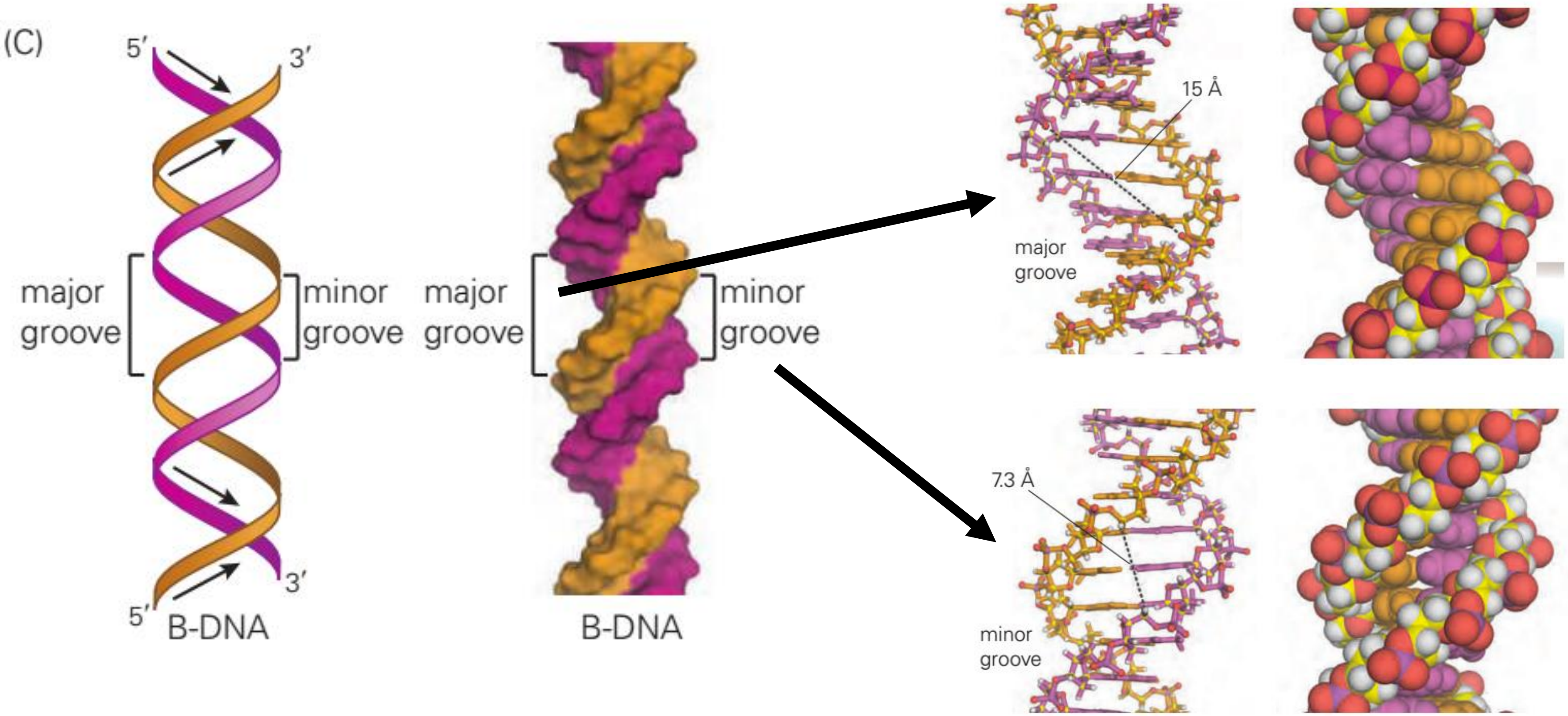
3D assembly of DNA

- One of the most important features of DNA double helices are the grooves.



3D assembly of DNA

- One of the most important features of DNA double helices are the grooves.



- The major and minor groove present very distinct structural features

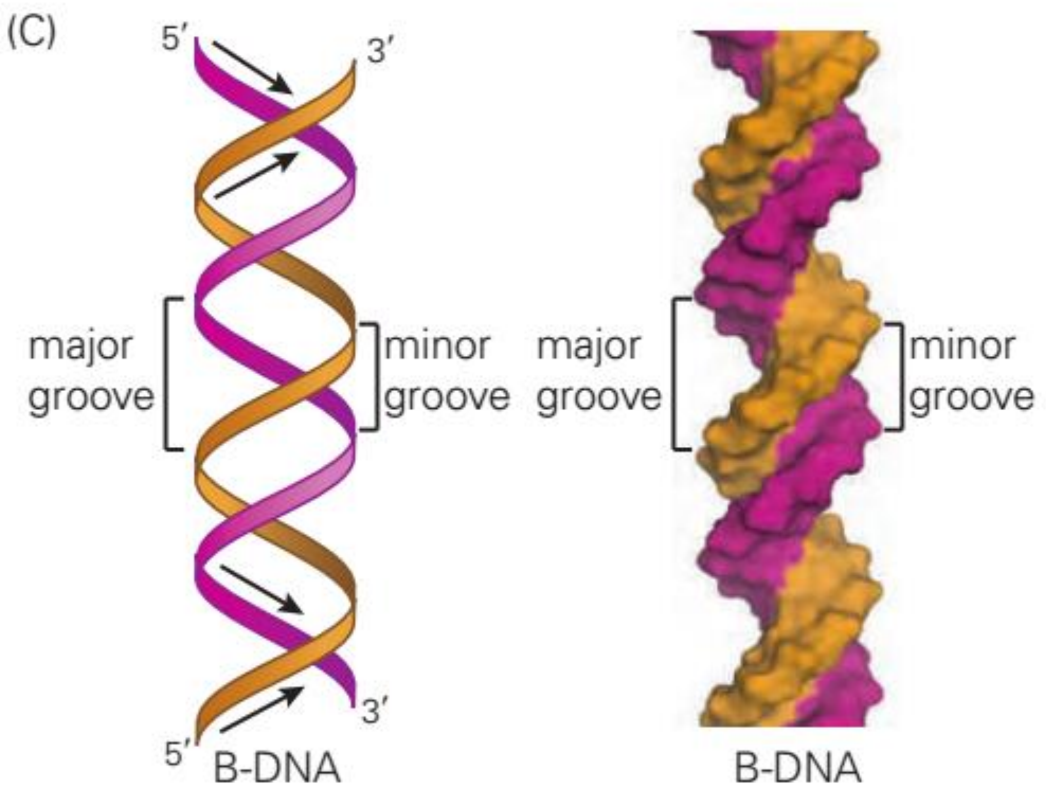
- Very important for the recognition of DNA by proteins.

EPFL

Which of the two grooves has more information on the sequence of underlying bases?

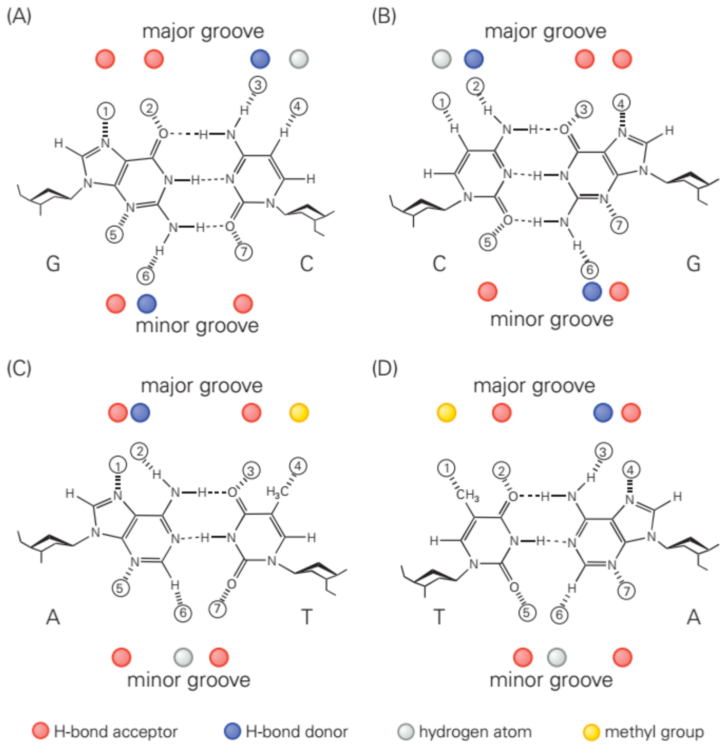
- Minor or Major?

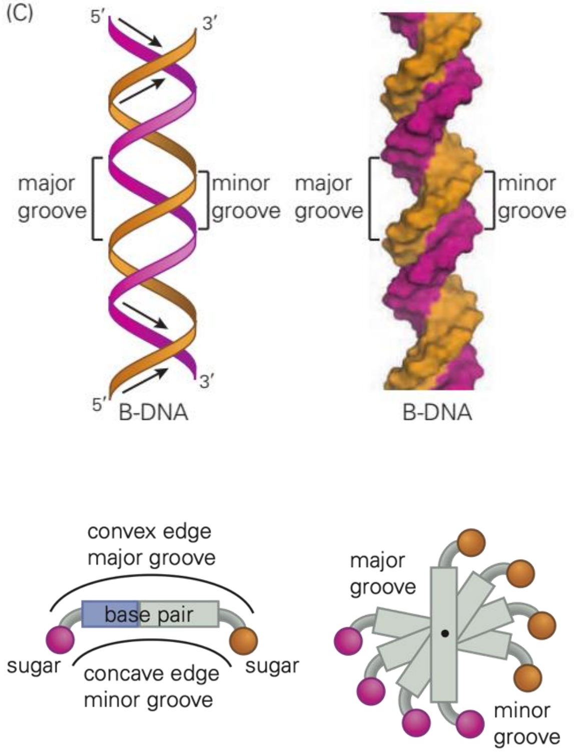
- Why?



3D assembly of DNA

- Potential secondary interaction sites at the edges of Watson-crick base pairs

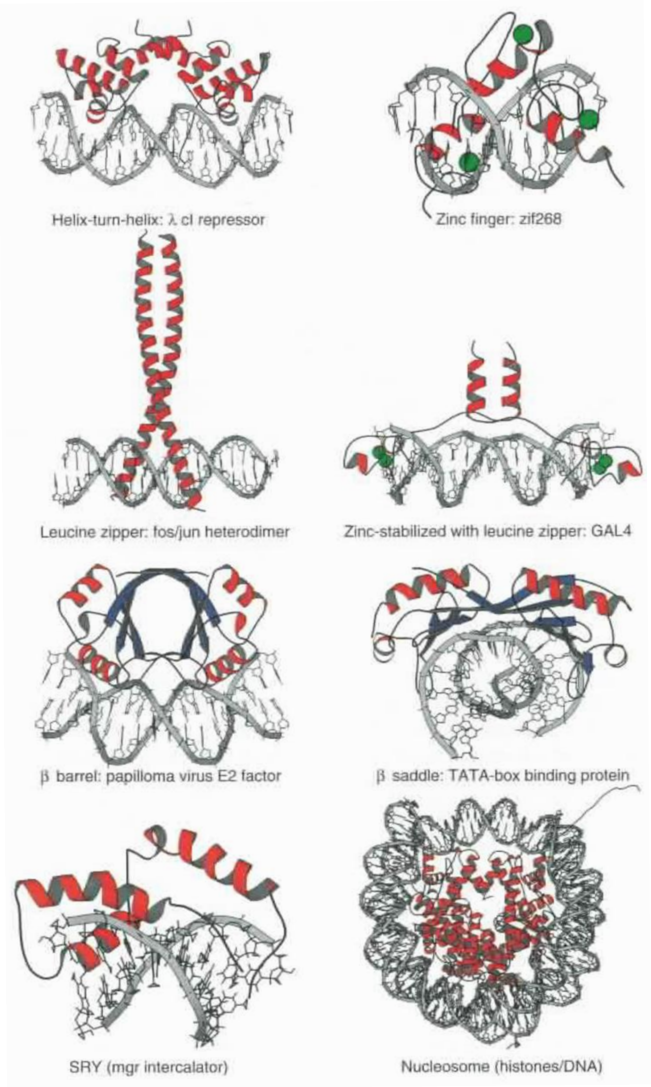




- Four type of interactions are possible.
- The major and minor grooves can be identified by looking at the connections of the base pairs with the sugars. Major groove on the convex edge and the minor groove in on the concave edge.
- Notice the chemical diversity of the major grooves vs the minor grooves.

DNA-binding proteins

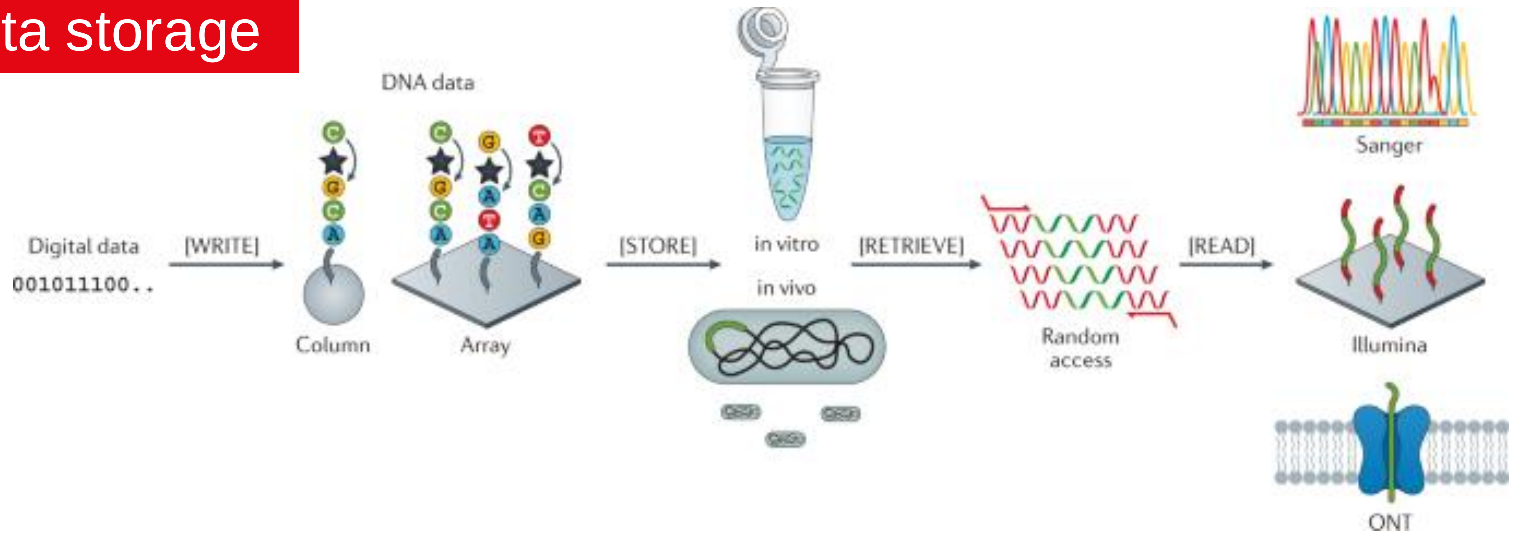
- DNA-binding proteins primarily target the major groove (Mgr) or a combination of major and minor (Mm)



Complex	Binding Motif[a]	Binding Groove[b]	Details of Complex
λ repressor	HTH	Mgr	Canonical HTH; homodimers; 2 helices of Cro dimer cradle Mgr, stabilized by direct H-bond and vdW contacts; little DNA distortion.
CAP repressor	HTH	Mgr	About 90° bend.
trp repressor	HTH	Mgr	Indirect, water-mediated base contacts.
Purine rep.	HTH	Mm	α-helices inserted in mgr.
Yeast MATα2	HTH	Mgr	Homeobox domains bind as monomers.
Zif268	Zn	Mgr	Zinc finger subfamily; each Zn finger recognizes 3 bps.
GATA-1	Zn	Mm	Transcription factors subfamily; single domain coordinated by 4 cysteines.
GAL4	Zn	Mgr	Metal binding subfamily; each of two Zn ions, coordinated by 6 cysteines, recognizes 3 bps.
GCN4	Leu/Zip	Mgr	Canonical; basic region/leucine zipper (α helices) motif; slight DNA bending.
fos/jun	Leu/Zip	Mgr	α-helices resemble GCN4; unstructured basic region folds upon DNA binding.
fos/jun/NFAT	Leu/Zip	Mgr	α-helices bend to interact with NFAT.
MetJ	β-ribbon	Mgr	Two anti-parallel β-strands in Mgr; bends each DNA end by 25°.
papillomavirus E2 DNA target	β-barrel	Mgr	Domed β-sheets form an 8-strand β-barrel dimer interface with 2 α-helices in Mgr; strong tailored fit for every base of the recognition element; bent DNA; compressed mgr; DNA target crystallized without protein.
TBP	β-saddle	mgr	Ten-β-strand saddle binds in Mgr; significant distortion, ≈ 90° bend.
p53 tumor supp.	Loop/other	Mm	Binds to DNA via protruding loop and helix anchored to anti-parallel β-barrel.
SRY	Loop/other	mgr	Isoleucine intercalated into mgr.
NFAT	Loop/other	Mm	Flexible binding loop stabilized by DNA.
histones	Loop/other	Mm	Nonspecific PO_4 interactions.
distamycin (drug)		mgr	Selective to AT bps; binds in mgr without distortion.

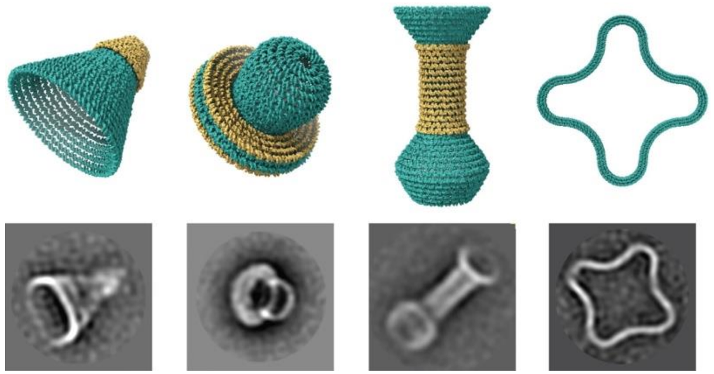
DNA in biotechnology

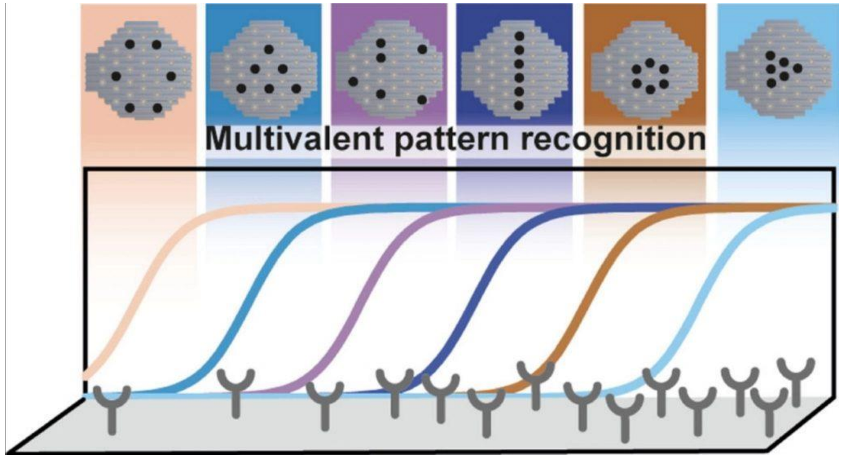
Data storage



Ceze, L., Nivala, J. & Strauss, K. Molecular digital data storage using DNA. *Nat Rev Genet* **20**, 456–466 (2019). https://doi.org/10.1038/s41576-019-0125-3

DNA origami



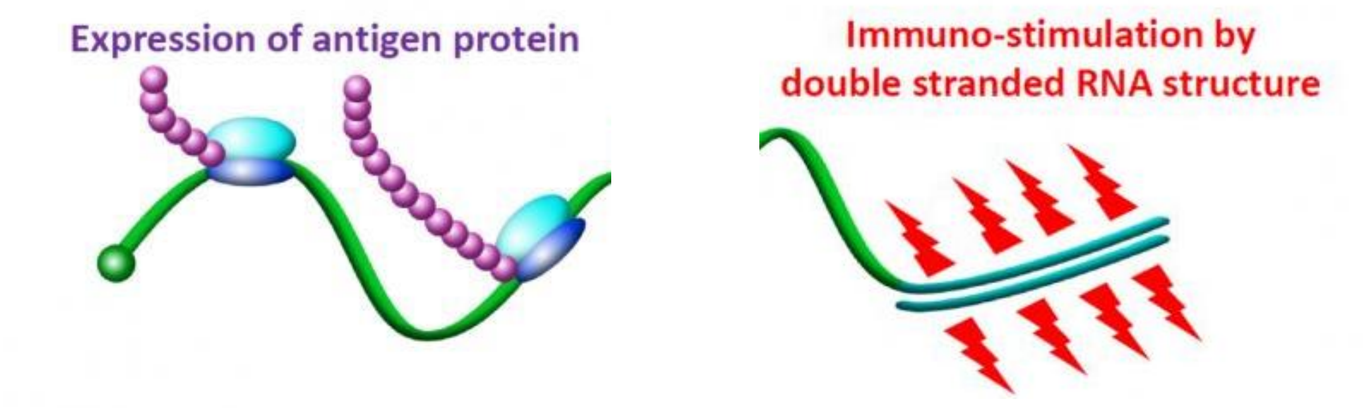


Hale Bila, Kaltrina Paloja, Vincenzo Caroprese, Artem Kononenko, Maartje M.C. Bastings, *American Chemical Society,* (2022) https://pubs.acs.org/doi/10.1021/jacs.2c08529#

https://www.epfl.ch/labs/pbl/

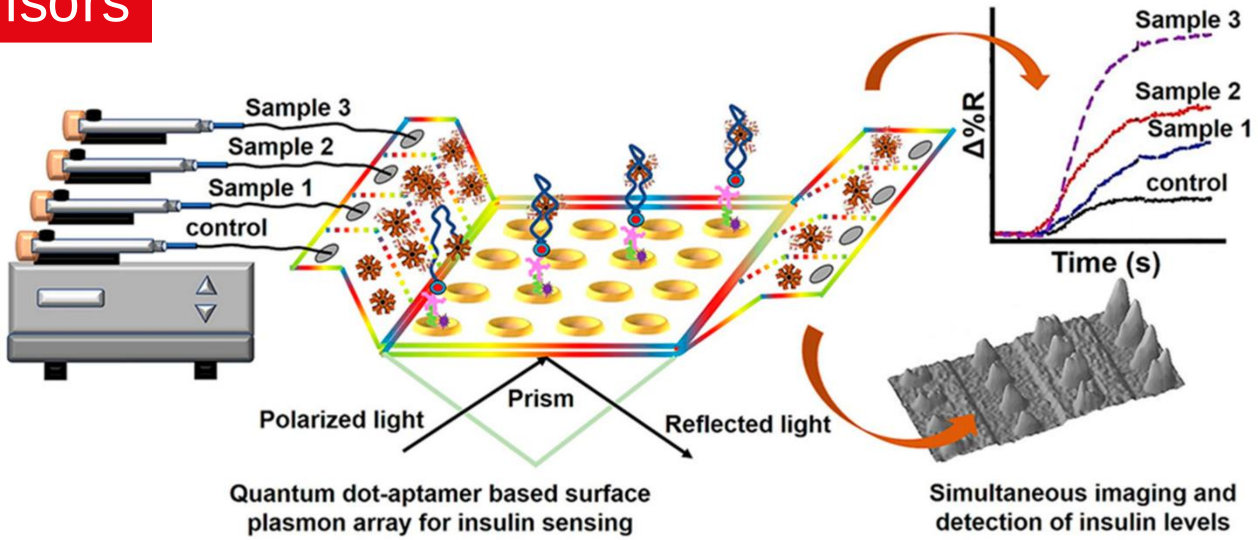
RNA in biotechnology

Vaccines and adjuvants



Abhijeet Girish Lokras, Thomas Rønnemoes Bobak, Saahil Sandeep Baghel, Federica Sebastiani, Camilla Foged, Advanced Drug Delivery Reviews, Vol 213, 2024. https://www.sciencedirect.com/science/article/pii/S0169409X24002412

Biosensors



Nako Nakatsuka, Kelly J. Heard, Alix Faillétaz, Dmitry Momotenko, János Vörös, Fred H. Gage & Krishna C. Vadodaria, Molecular Psychiatry volume 26, pages2753–2763, 2021. https://www.nature.com/articles/s41380-021-01066-5

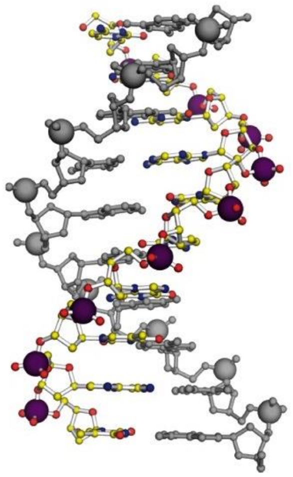
Nucleic acids – Take Home messages

• DNA and RNA are the informational polymers in the cell – encode genetic information in a way that can be read by macromolecular machines, to direct the synthesis of other molecules.
• Nucleotides have pentose sugars attached to nitrogenous bases and phosphate groups.
• The nucleotide bases in DNA and RNA are substituted pyrimidines or purines.
• 4 deoxyribonucleotides in DNA (A,T,G,C) and four ribonucleotides in RNA (A,U,C,G)
• DNA and RNA are synthesized in 5' to 3' direction by sequential reactions that are driven by hydrolysis of nucleotide triphosphates
• DNA forms a double helix with antiparallel strands
• Double helix involves complementary base pairing (A-T and C-G) and is stabilized by, hydrogen bonds, base pair stacking and electrostatic interactions
• B-form DNA allows sequence specific recognition of the major groove by proteins. Each base pair has a unique set of interacting elements in the major groove but not in the minor groove.

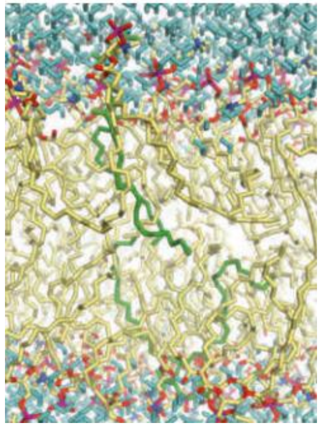
The molecules of Life

Macromolecular Structure

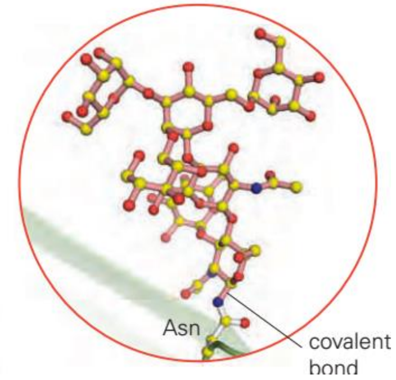
Nucleic Acids



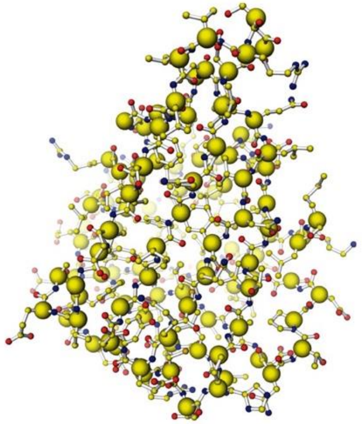
Lipids



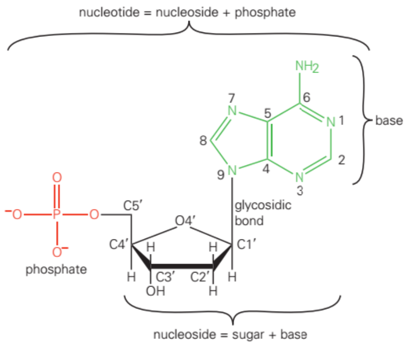
Carbohydrates

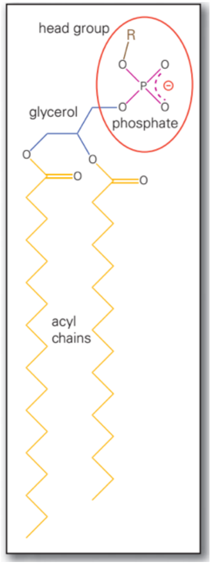


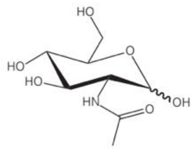
Proteins



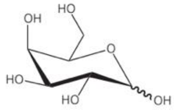
Building Block



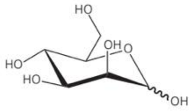




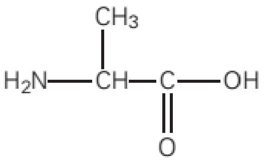
N-acetylglucosamine (GlcNAc)

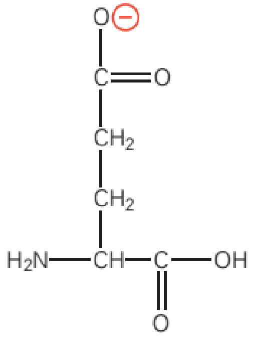


galactose (Gal)

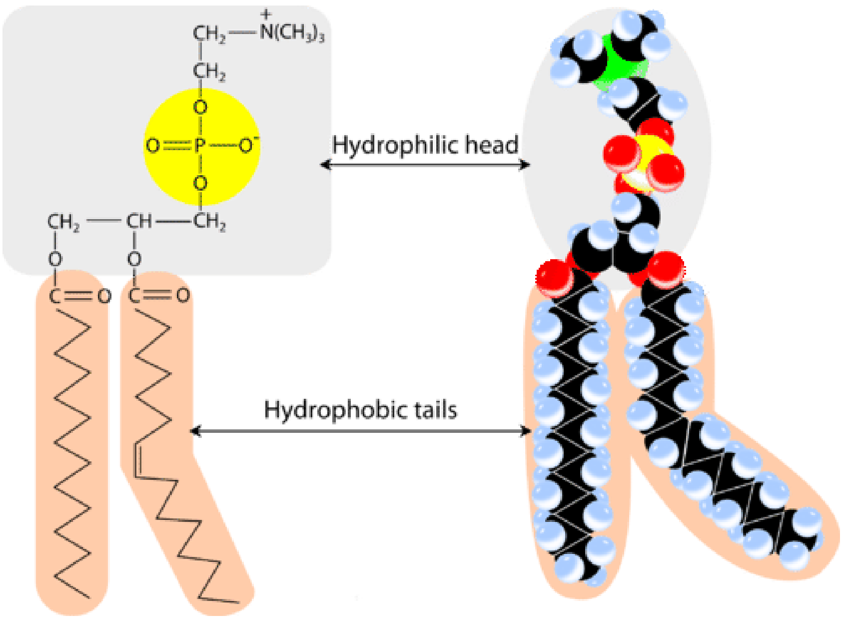


mannose (Man)





What is a Lipid?



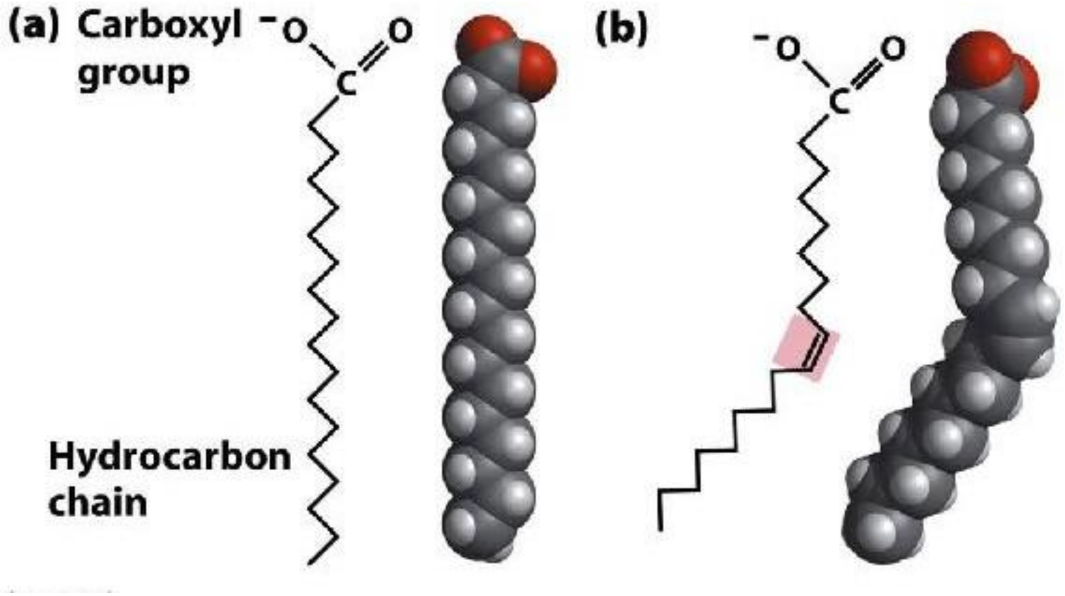
- In biology and biochemistry, a **lipid** is a biomolecule that is soluble in non-polar solvents and does not readily dissolve in water.

- They all contain hydrophobic moieties, and some contain a hydrophilic head group ("amphipathic")

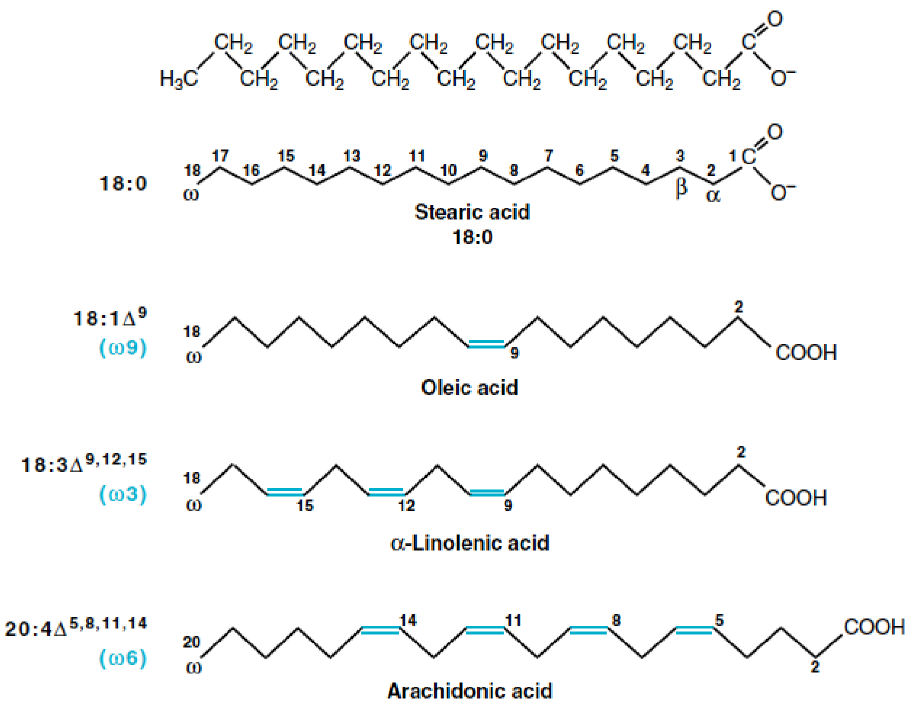
- Three Classes of Lipids Based on Their Functions:
  - **Storage lipids:** Used for bioenergetic purposes and thermal insulation.
  - **Structural lipids:** Used to make membranes.
  - **Bioactive lipids:** Used as hormones and second messengers in signal transduction

Fatty acids

- Naturally occurring monocarboxylic acids



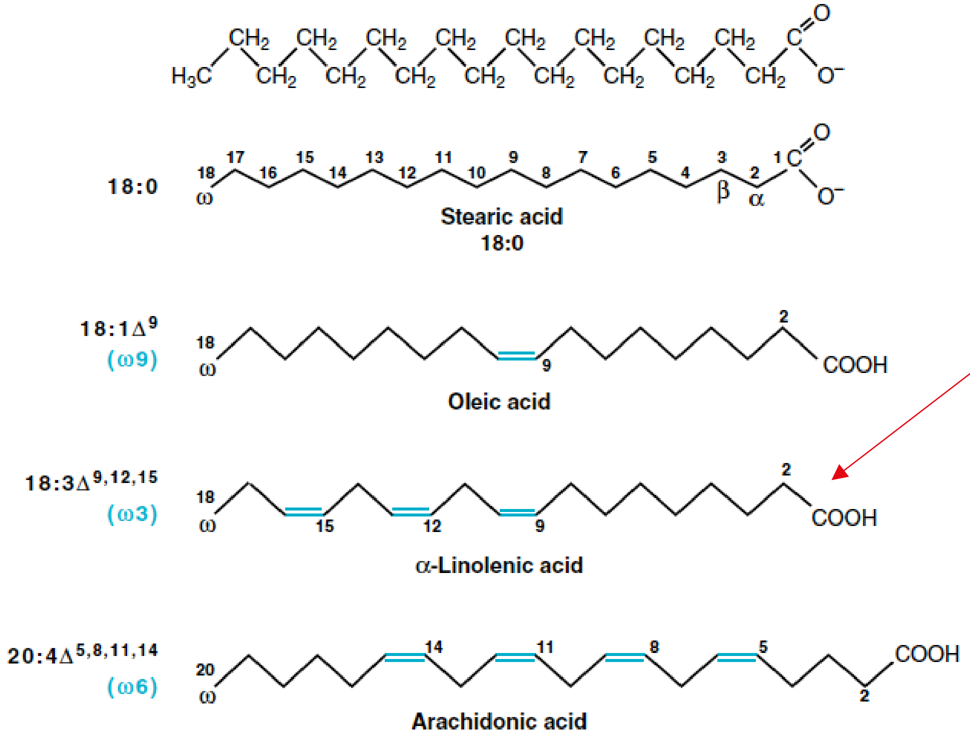
Examples:



- Components of all lipids except sterols
  - **Saturated** -> no double bonds.
  - **Unsaturated** -> one double bond.
  - **Polyunsaturated** (PUFAs) -> more double bonds.

Fatty acid naming convention

- Nomenclature includes the following format: “Number of carbons” : ”Number double bonds”
- Δ^{XYZ} indicates that the double bonds are located at carbon positions XYZ (starting at the carboxyl)
- ω indicates the location of the first double bond starting from the aliphatic (methyl) terminus



Alpha-Linoleic acid

Octadecatrienoic acid

$18 : 3\ \Delta^{9,12,15}\ (\omega 3)$

18 Carbons

3 double bonds

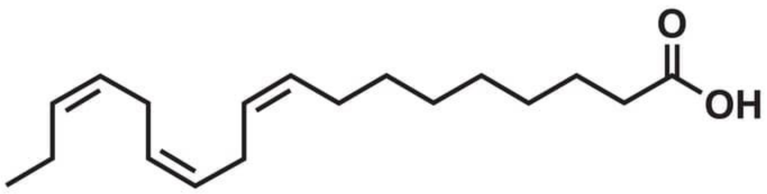
Double bond location

First unsaturated bond from the methyl terminus

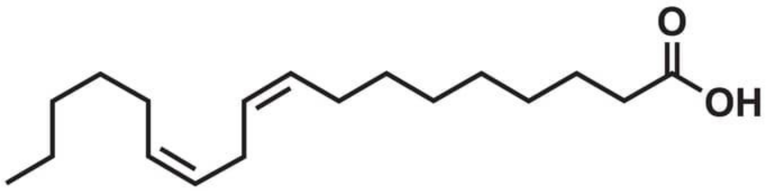
Most common: 16-20 carbons

Fatty acids and nutrition

• Essential vs Non-essential fatty acids



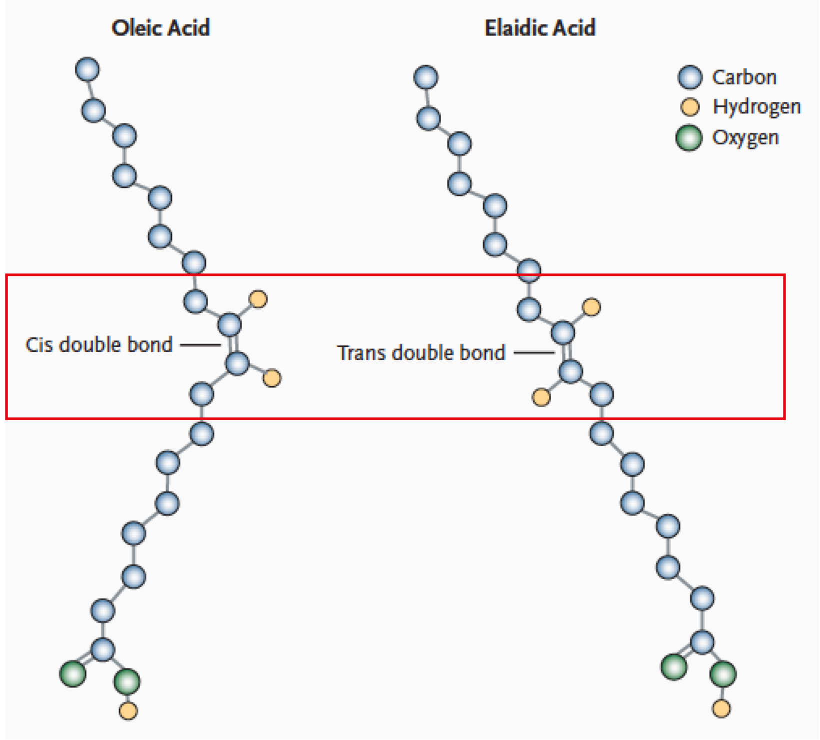
Linolenic Acid (Omega-3)



Linoleic Acid (Omega-6)

• Two essential fatty-acids that cannot be synthesized in humans or other animals: linoleic and linolenic acids
• Acquired through diet (“vitamin F”)
• Omega Fas are found in the membranes of the retina and brain and are important components of heart-healthy diets

• Cis vs Trans fatty acids



• Trans fats are thermodynamically favored but problematic to metabolize by human body
• Found in milk (3%) but largely produced by hydrogenation of vegetable oils for industrial purposes
• Also correlated with coronary diseases caused by low-density lipoprotein (LDL) cholesterol

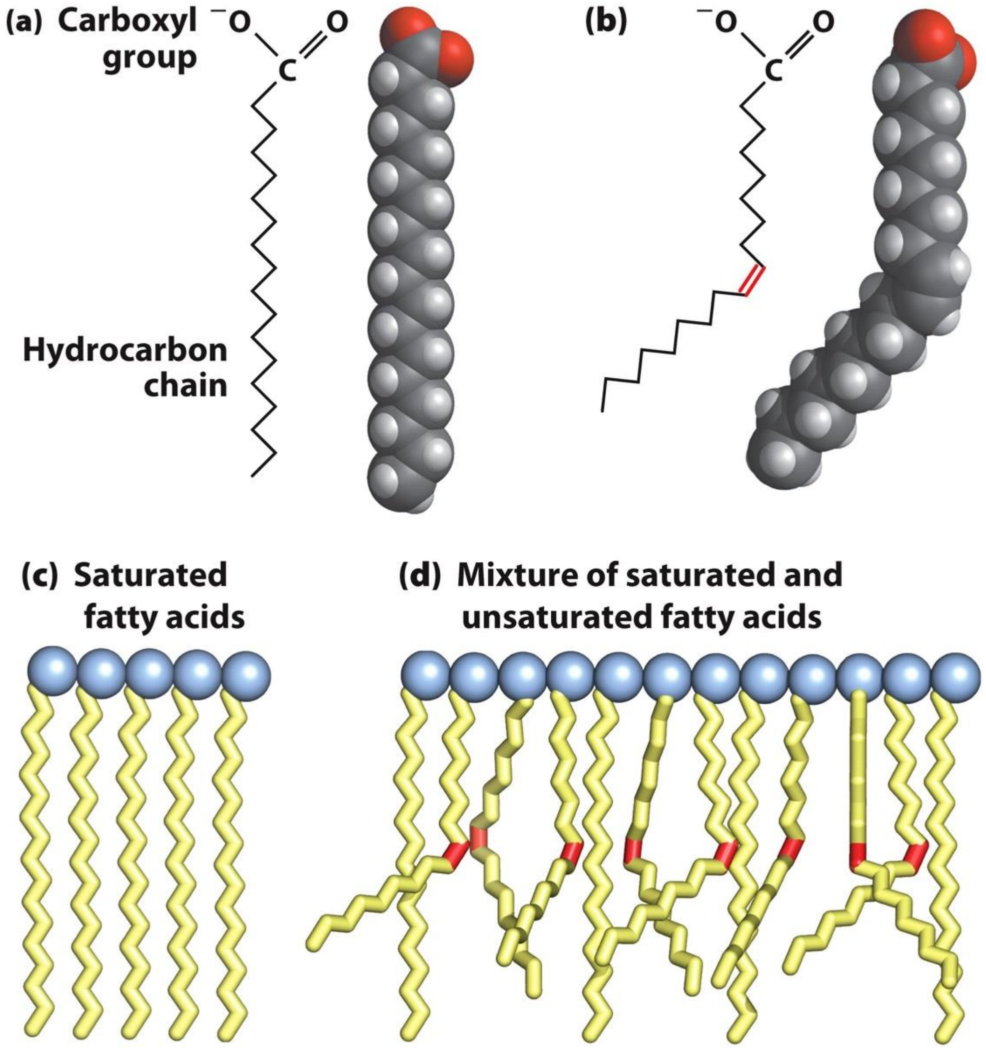
Physicochemical properties of fatty acids

• The hydrocarbon chain accounts for the poor solubility of fatty acids in water.

• Solubility decreases with the increasing chain length and saturation level

• Lauric acid (12:0) has a solubility of 0.063mg/g in water. In contrast, glucose (a carbohydrate) has a solubility of 1’100 mg/g in water **(~17’000-fold difference)**

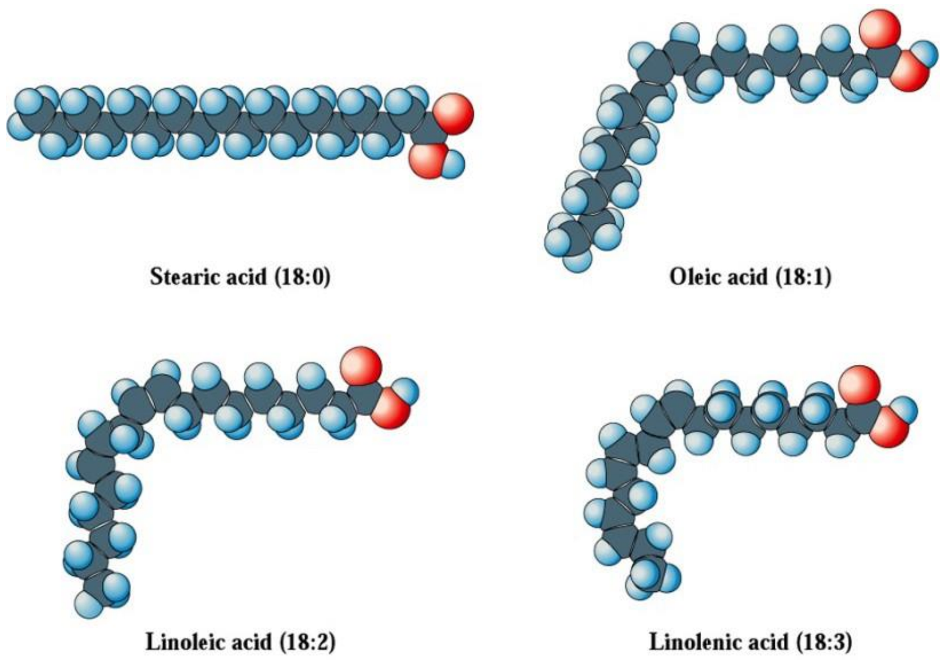
• Albumin in blood can bind and transport FAs

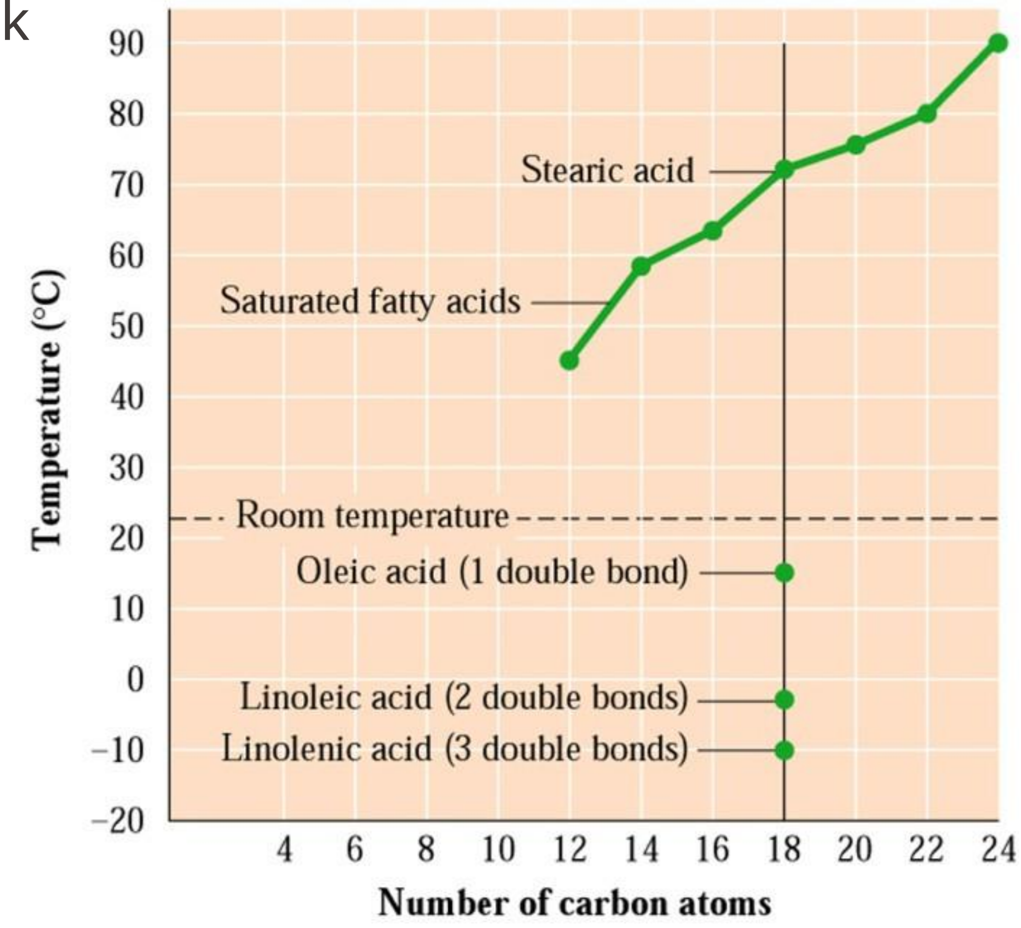


Physicochemical properties of fatty acids

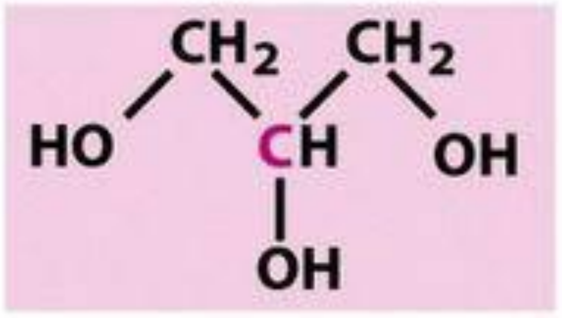
• Melting points **increase with increasing molar mass** (due to van der Waals forces), meaning that the longer the carbon chain in a fatty acid, the higher its melting point.

• Cis-double bonds **lower the melting point** by causing the molecule to become bent and hard to pack with neighboring molecules (lower vdW interactions)

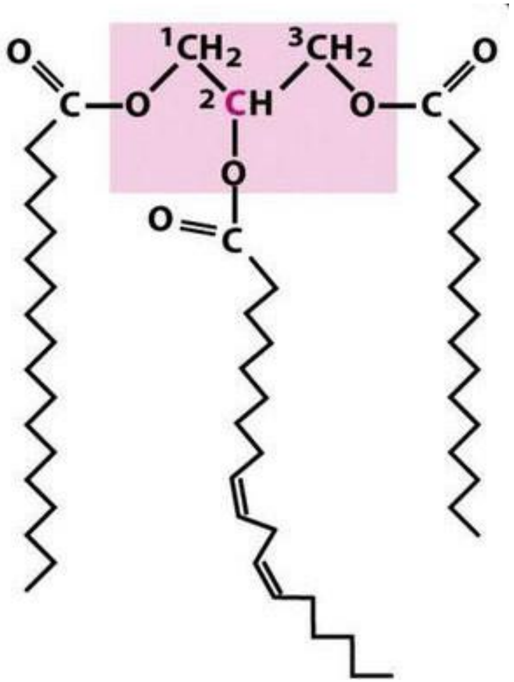




Storage Lipids - Triacylglycerols



Glycerol



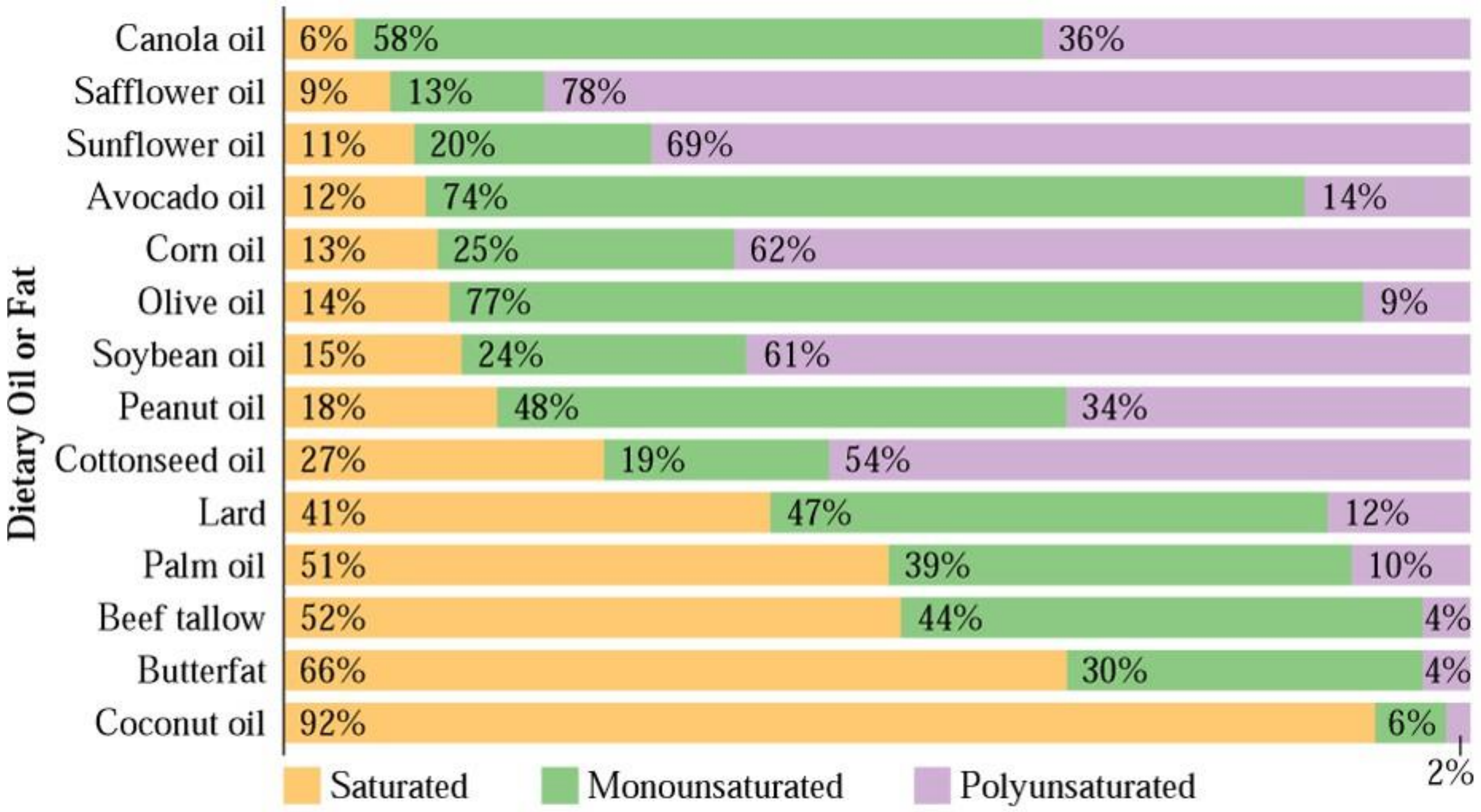
• Triacylglycerols are composed of **three fatty acids** each in **ester** linkage with **a single glycerol molecule**.

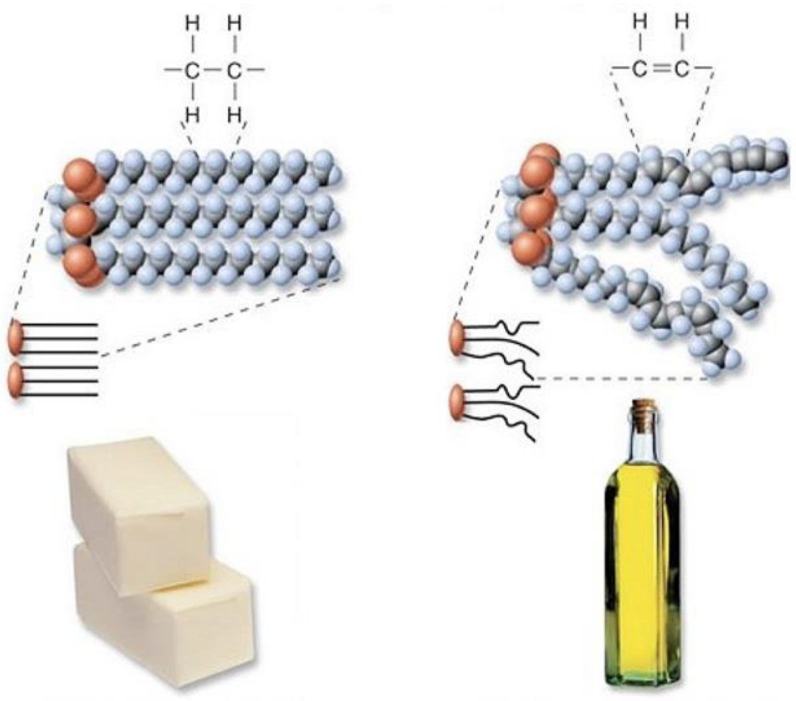
• Those containing the same kind of fatty acid in all three positions are called **simple triacylglycerols** and are named after the fatty acid they contain.

• Simple triacylglycerols of 16:0, 18:0, and 18:1(Δ^9) are called tripalmitin, tristearin, and triolein, respectively. Most naturally occurring triacylglycerols are **mixed** and contain two or more different fatty acids.

Storage Lipids - Triacylglycerols

- The content of unsaturated fatty acids regulates the melting point and the aggregate state of the resulting lipid at room temperature (i.e., solid or liquid)





Butter **Olive oil**

Storage Lipids - Triacylglycerols

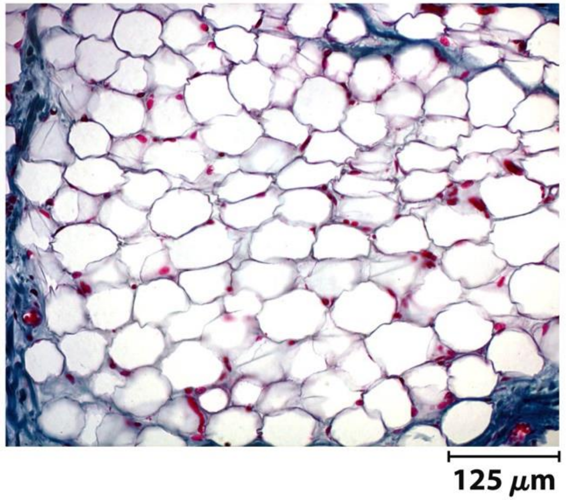
- In the cytosol of most eukaryotic cells, triacylglycerols form oily droplets that serve as **metabolic fuel**.

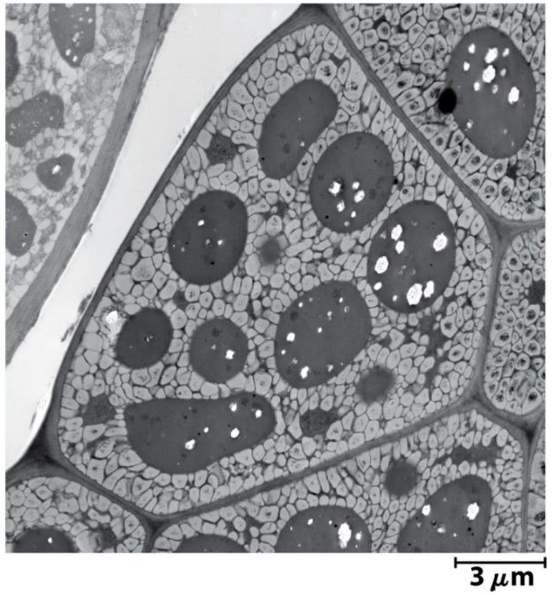
- In vertebrates, there are specialized cells called adipocytes (or fat cells) that store large amounts of these lipids

- Triacylglycerols contain **more energy per gram compared to carbohydrates**. Additionally, they are non-hydrated so there is no extra mass of water.

- In some animals (e.g., seals, penguins, bears) fat stored under the skin **serves as insulation against cold temperatures**

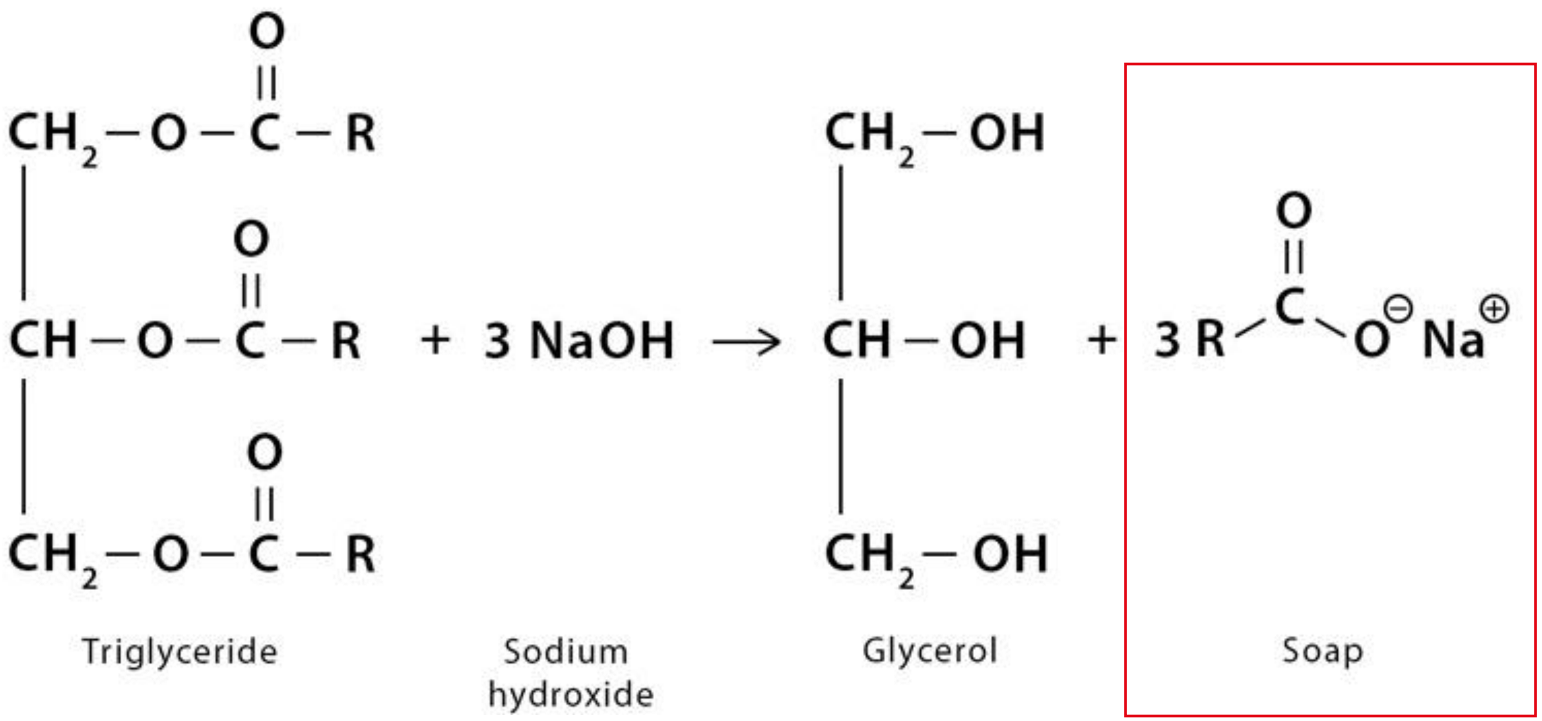
Adipocytes





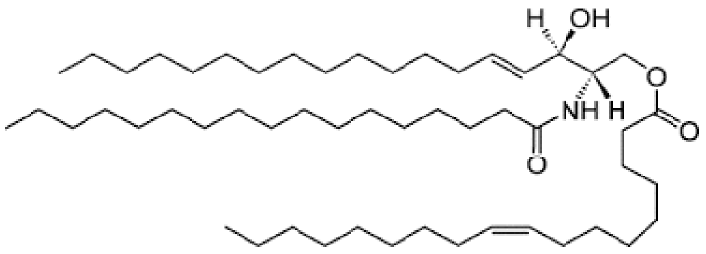
Triacylglycerol hydrolysis - Saponification

- Saponification is a process that involves the conversion of fats, oils, or lipids into soap and alcohol through the application of heat in the presence of an aqueous alkali (e.g., NaOH)

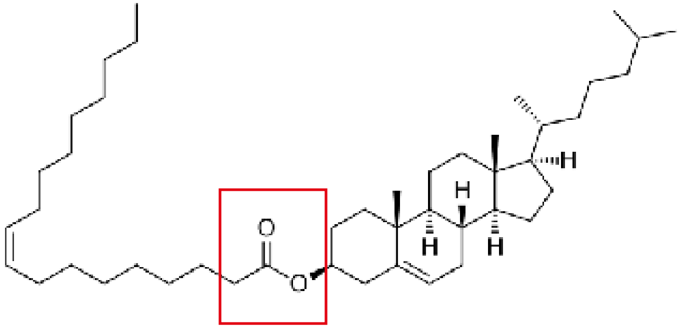


- Soaps are the salts of fatty acids which are monomers with long carbon chains

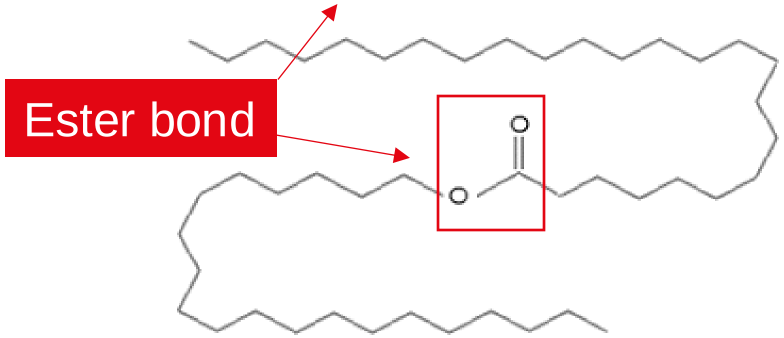
Other Storage Lipids



- **Acylceramides** -> ceramide can be metabolised into acylceramide and stored in lipid droplets



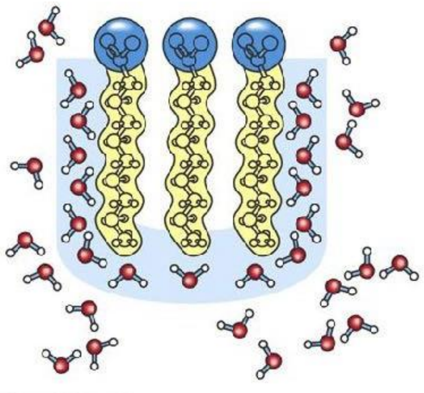
- **Cholesteryl esters** -> A cholesteryl ester is formed through the bonding of the carboxylate group of a fatty acid with the hydroxyl group of cholesterol.



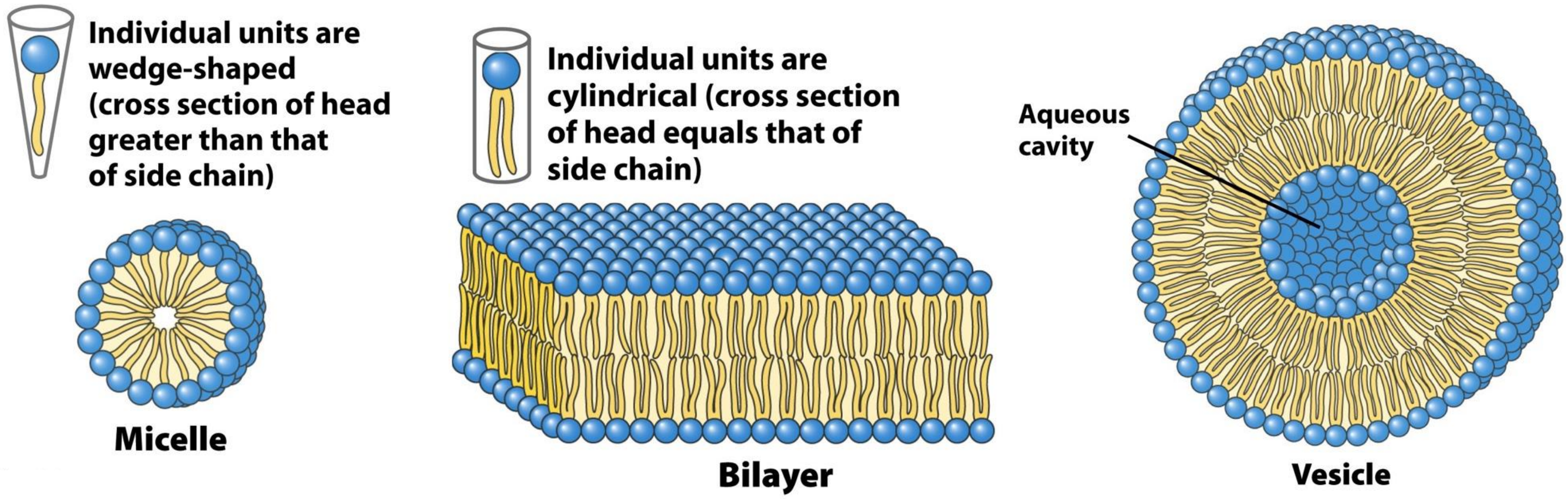
- **Waxes** -> waxes are esters formed by long-chain (C14 to C36) saturated and unsaturated fatty acids with long-chain (C16 to C30) alcohols.

Membrane Lipids

- Membrane lipids are **amphipathic** and contain a hydrophilic head and a hydrophobic tail
- The hydrophobic interactions between **membrane lipids** and their hydrophilic interactions with water guide their arrangement into sheets known as membrane bilayers.



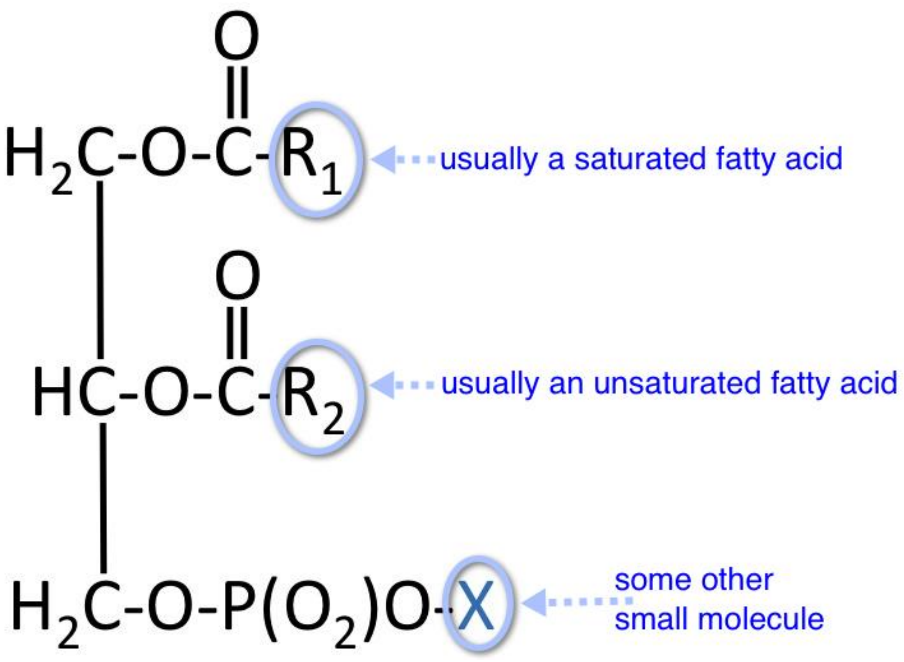
Hydrophobic groups pack and exclude water

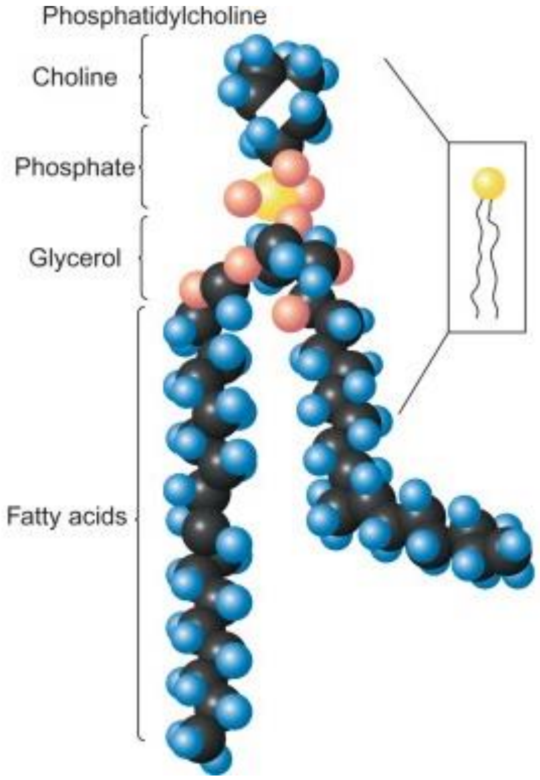


- Cell Membranes are the **barrier** and the **interface** between the cell and the environment. Membranes also define sub-cellular compartments.

Glycerophospholipids

- These lipids consist of **two fatty acids** attached via **ester linkage** to the **first and second carbons of glycerol**, with a **highly polar or charged group** attached through a phosphodiester linkage to the **third carbon**.

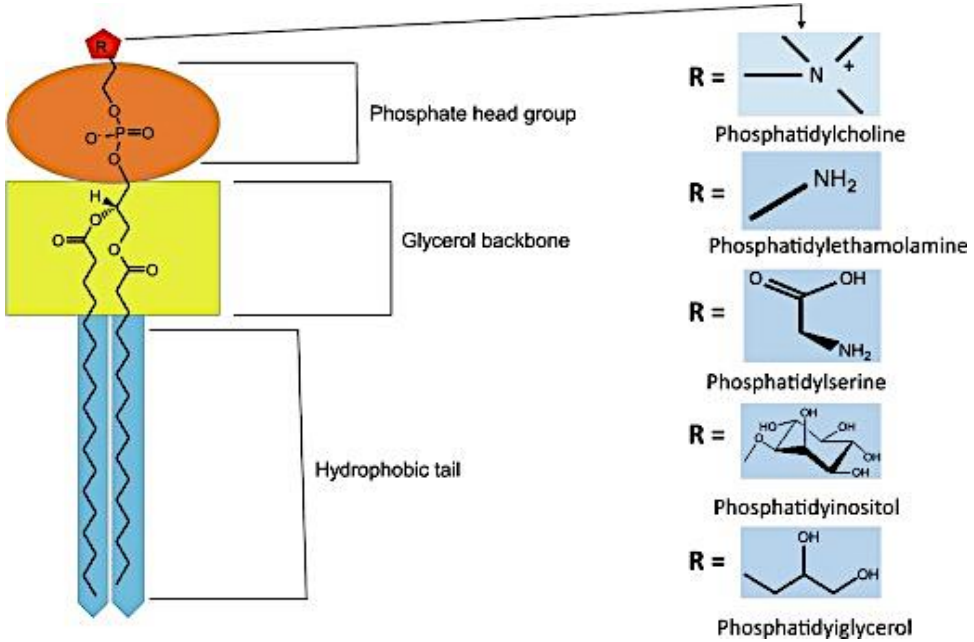




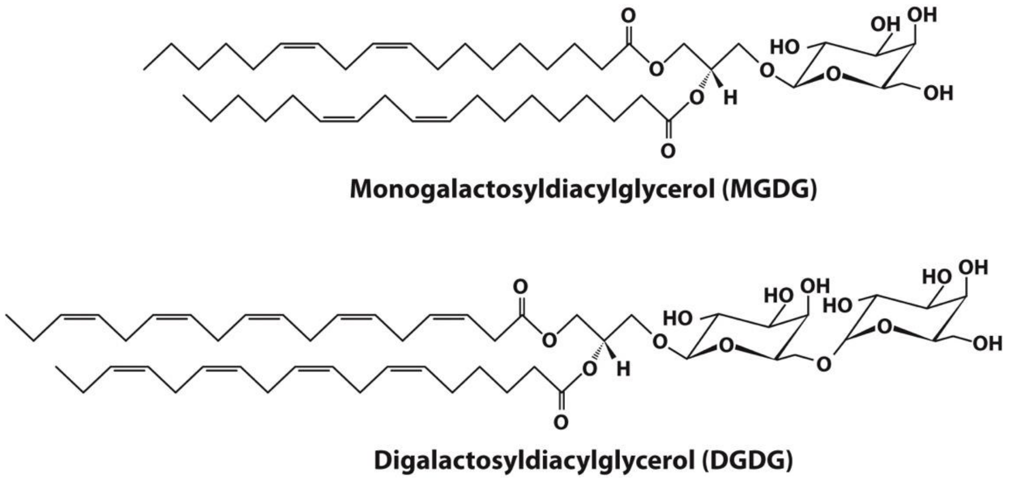
- They represent **the major constituent of cellular membranes, organelles and vesicles**

Glycerophospholipids

- Glycerophospholipids are named based on the **polar head group**
- The head group can be charged (positively or negatively) which plays a significant role in the **surface properties of the membrane**



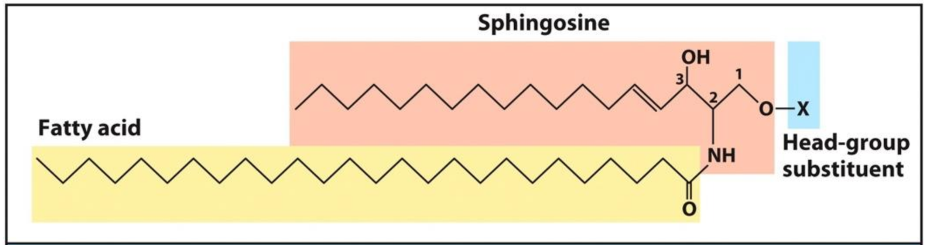
Galactolipids

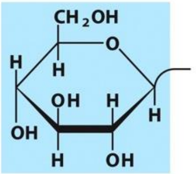
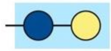
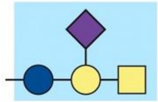


They constitute 70% to 80% of the total membrane lipids in vascular plants, making them **the most abundant membrane lipids in the biosphere.**

Sphingolipids

• Unlike glycerophospholipids, **sphingolipids** contain **no glycerol**. Instead, sphingolipids are composed of one molecule of the **long-chain base** (here sphingosine).



Name of sphingolipid	Name of X—O	Formula of X
Ceramide	—	—H
Sphingomyelin	Phosphocholine	$-\overset{O}{\overset{\Vert}{P}}(O^-)-O-CH_2-CH_2-\overset{+}{N}(CH_3)_3$
Neutral glycolipids Glucosylcerebroside	Glucose	
Lactosylceramide (a globoside)	Di-, tri-, or tetrasaccharide	
Ganglioside GM2	Complex oligosaccharide	

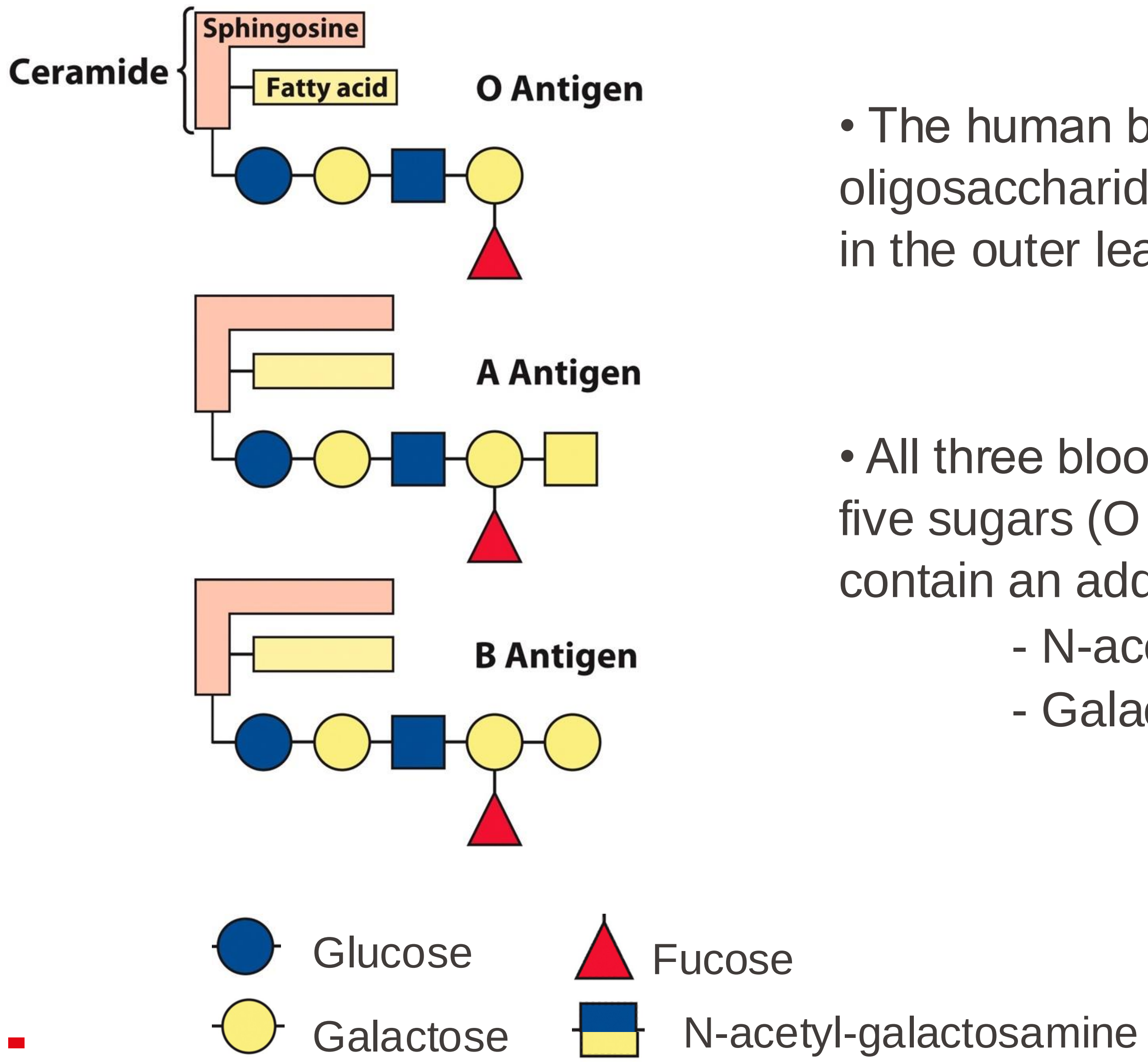
• Depending on the head group they are divided into subclasses (e.g., ceramide, sphingomyelins etc.)

• In addition to constituting cell membranes they play many functional roles, and feature specific tissue distribution

• Sphingomyelins are enriched in plasma membranes of animal cells, particularly in myelin, a membranous sheet that surrounds and insulates neuronal axons

• Glycosphingolipids are found in outer leaflet of cell membranes and play important roles in cell recognition (e.g., neuron development, ABO blood groups)

Blood group antigens determined by sphingolipids

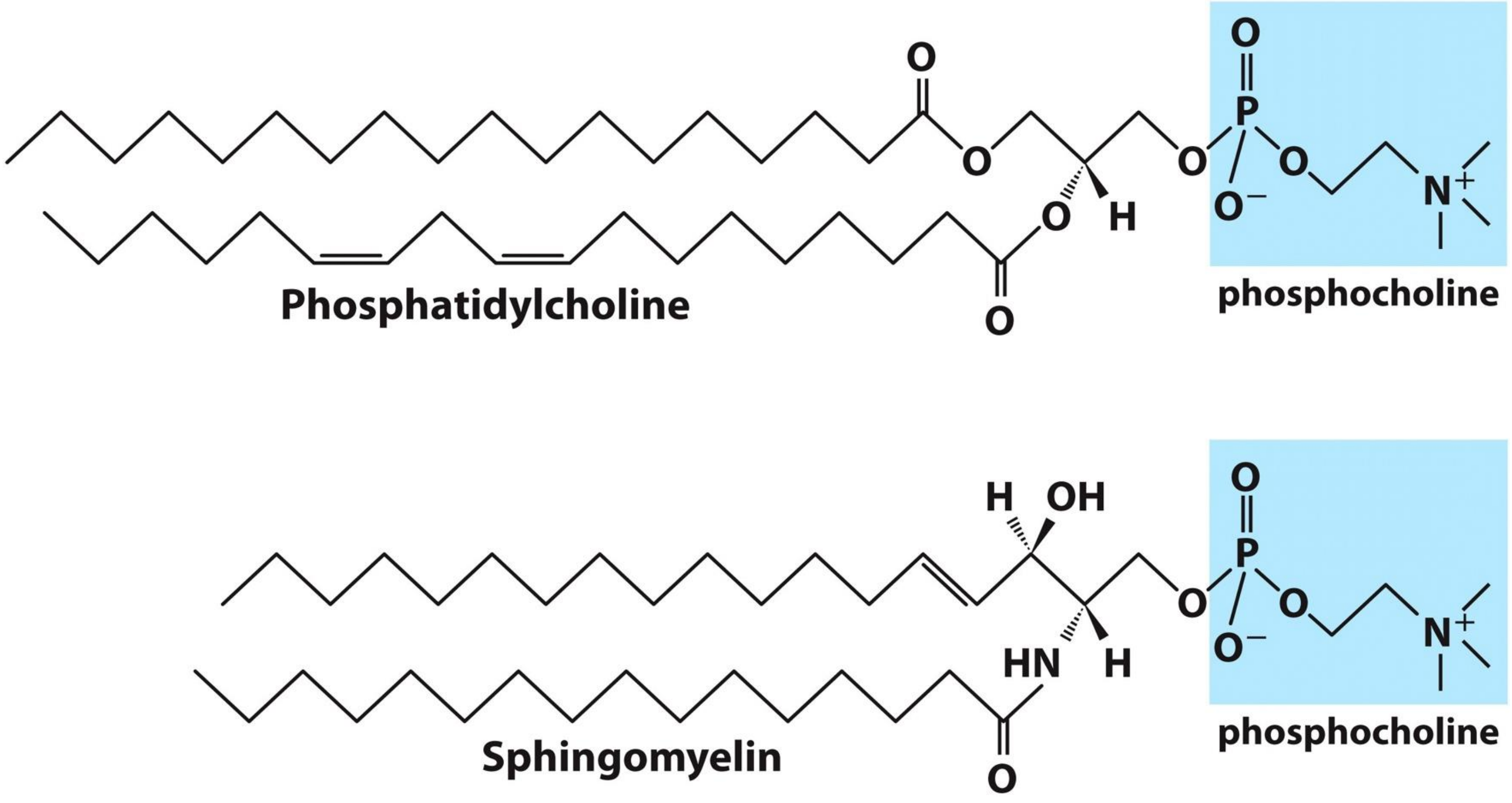


- The human blood groups (ABO) are determined by the oligosaccharide head groups of glycosphingolipids present in the outer leaflet of the red blood cell membrane

- All three blood group antigens contain the same core of five sugars (O group marker), but A and B antigens also contain an additional terminal residue which could be:
  - N-acetyl-galactosamine (A)
  - Galactose (B)

Sphingolipids vs Glycerophospholipids

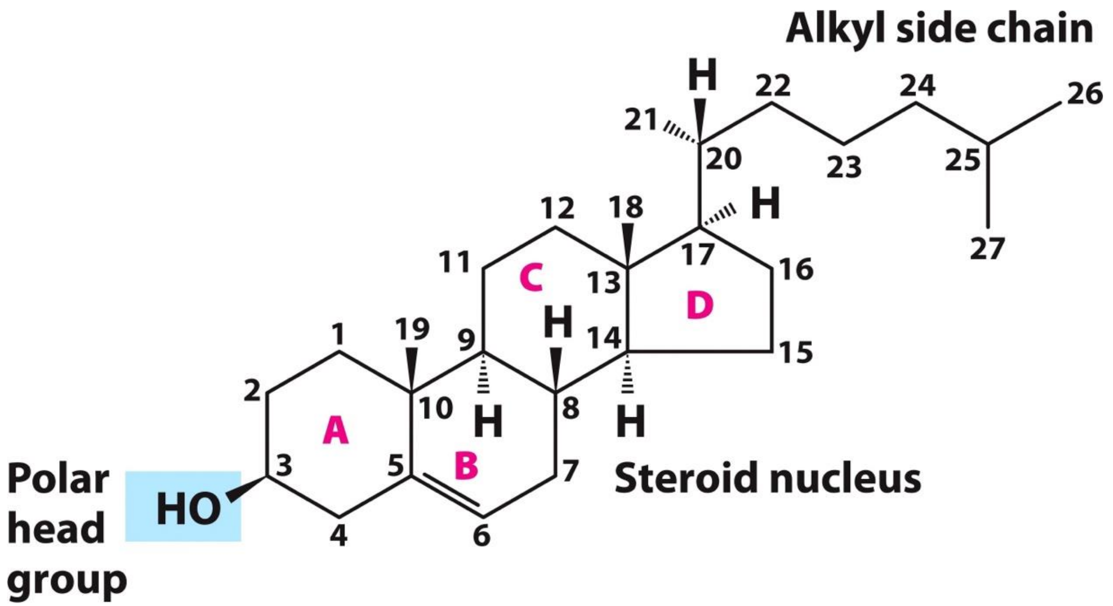
- Structurally they are very similar, but they are synthesized differently and have diverse roles



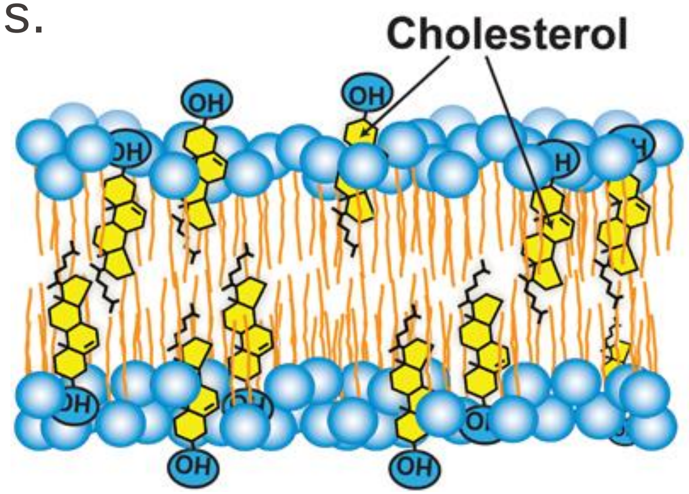
- Defects in sphingolipid metabolism can lead to neurodegenerative diseases (e.g., ALS, HSP) and, if genetic, brain development disorders (e.g., CerTra syndrome)

Sterols

- Sterols consist of a rigid steroid nucleus containing four fused rings, an alkyl side chain of 8 carbons, and a single hydrophilic hydroxyl group attached to C-3 of ring A.
- They are synthesized in humans but also acquired through diet, and they are present in the membranes of most eukaryotic cells.



- The steroid nucleus is nearly planar, and the molecule efficiently packs with the acyl chains of membrane glycerophospholipids and sphingolipids.



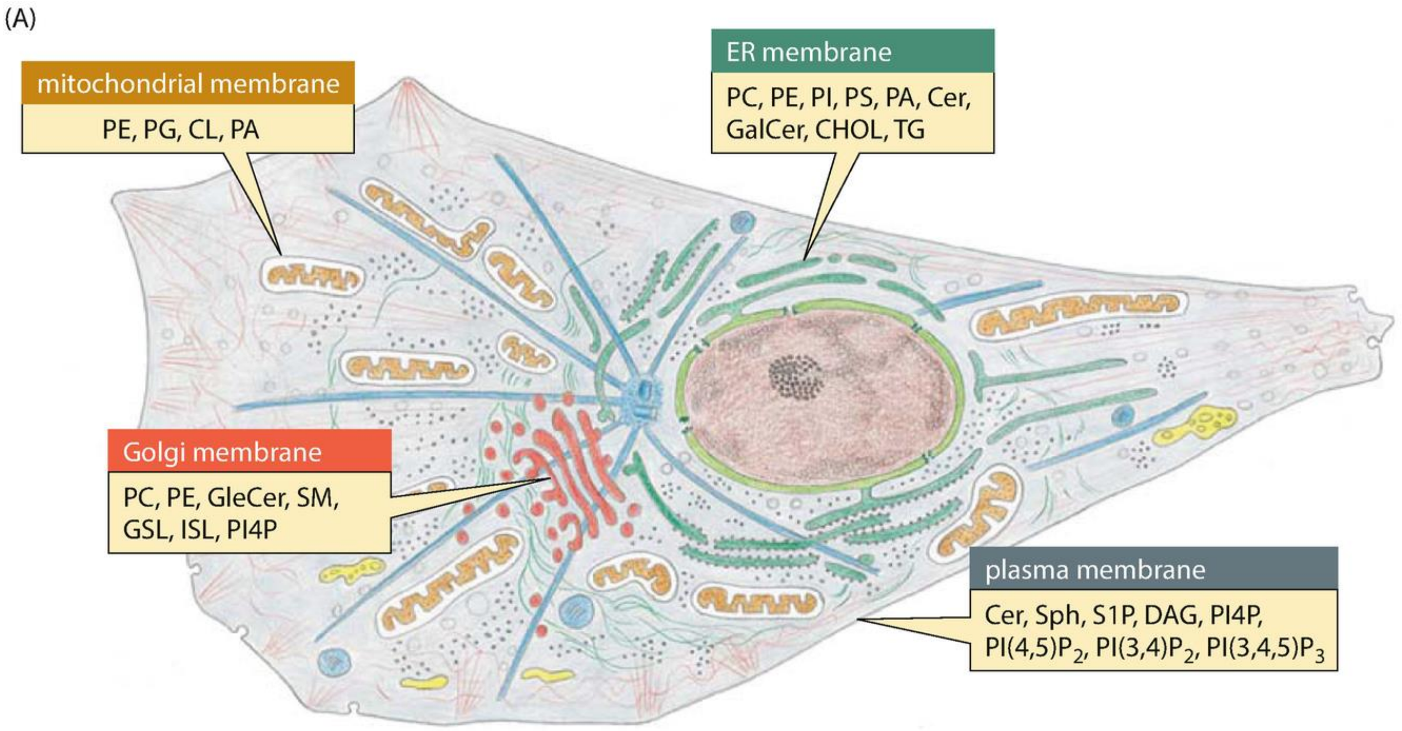
- Cholesterol impacts membrane rigidity/mobility

Lipid composition in different cell compartments

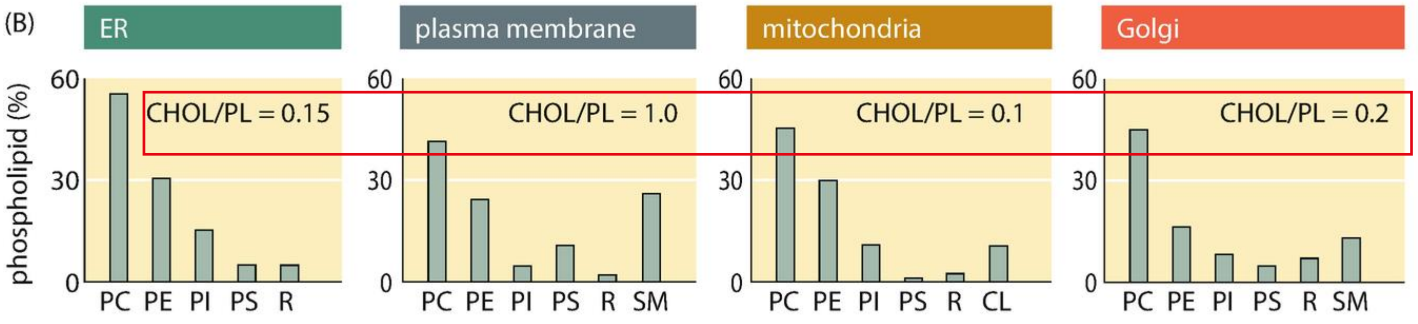
• Phospholipids (PE, PC, PI, PS) are relatively uniform across most membranes

• Sphingolipids (CER, GalCER, Sph) largely present on the plasma membrane but also Golgi and ER

• Cholesterol comprises all membranes but is the highest at the cell membrane where it represents 40-50% of all lipids.

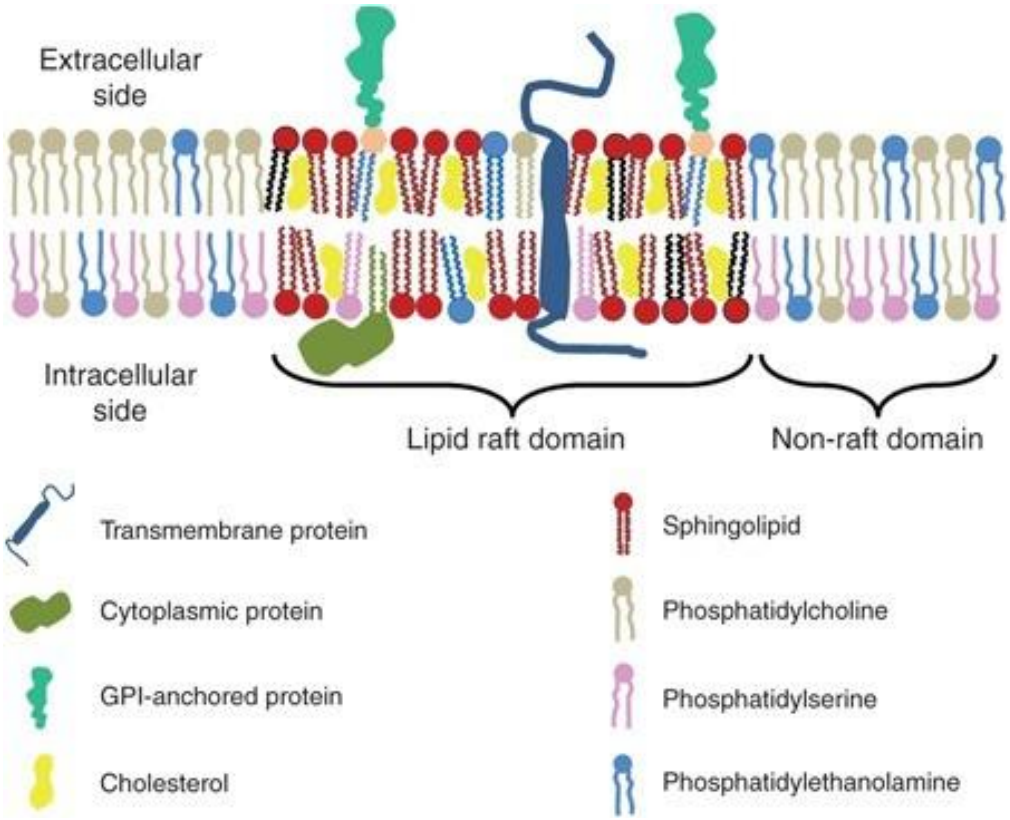


Cholesterol/Phospholipid ratio:



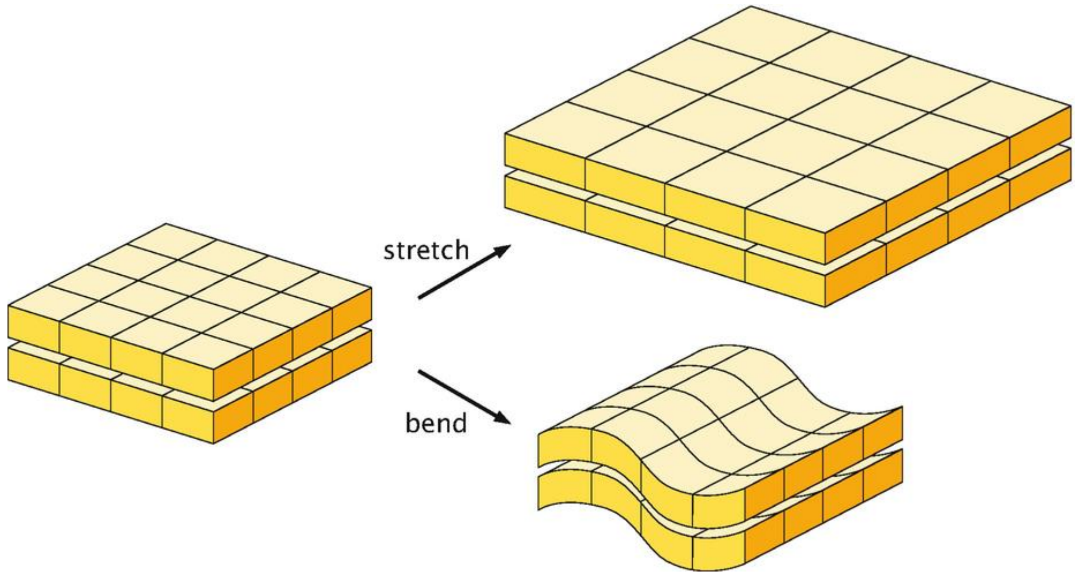
Membranes are asymmetric dynamic structures

- Inner and outer leaflet have different compositions



- **Flippases, Floppases** and **Scramblases** are transmembrane proteins that regulate transport of lipids between leaflets

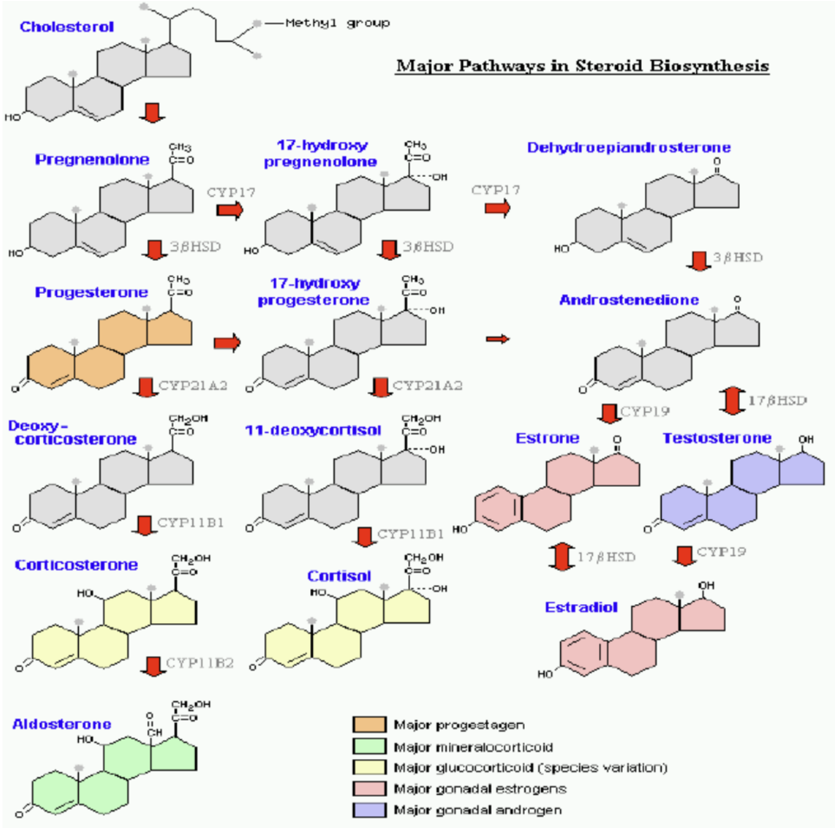
- Membranes are dynamic and pleomorphic

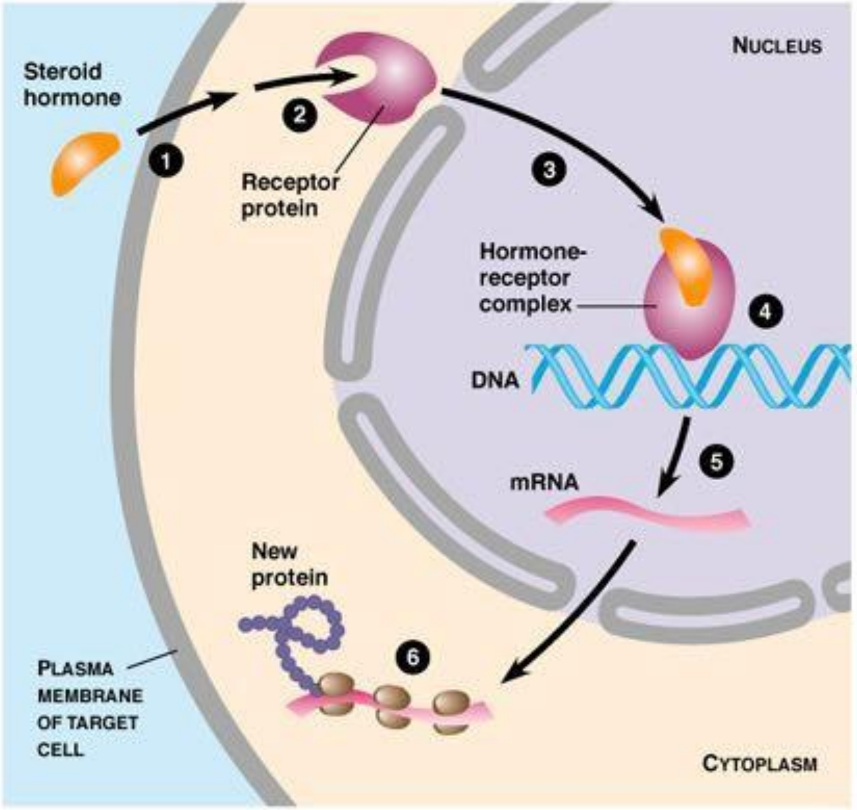


- Membrane flexibility is determined by lipid composition and environmental factors (e.g., mechanical forces)

Bioactive lipids – Steroid hormones

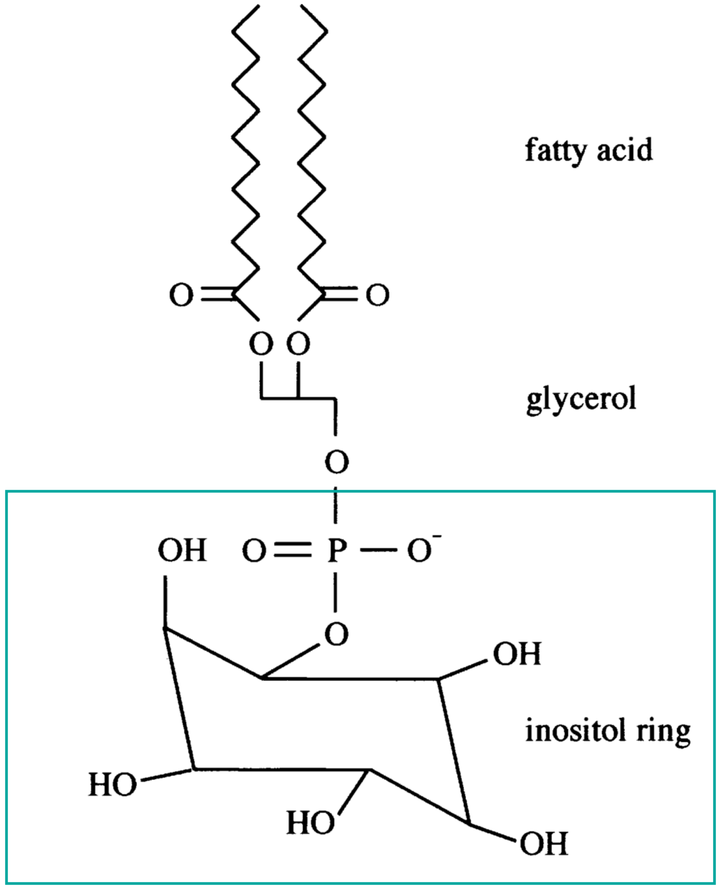
- Bioactive lipids affect cell function in a concentration dependent manner.
- Most commonly they serve as hormones and secondary messengers
- Sterols are precursors of steroid hormones and are therefore also considered bioactive lipids

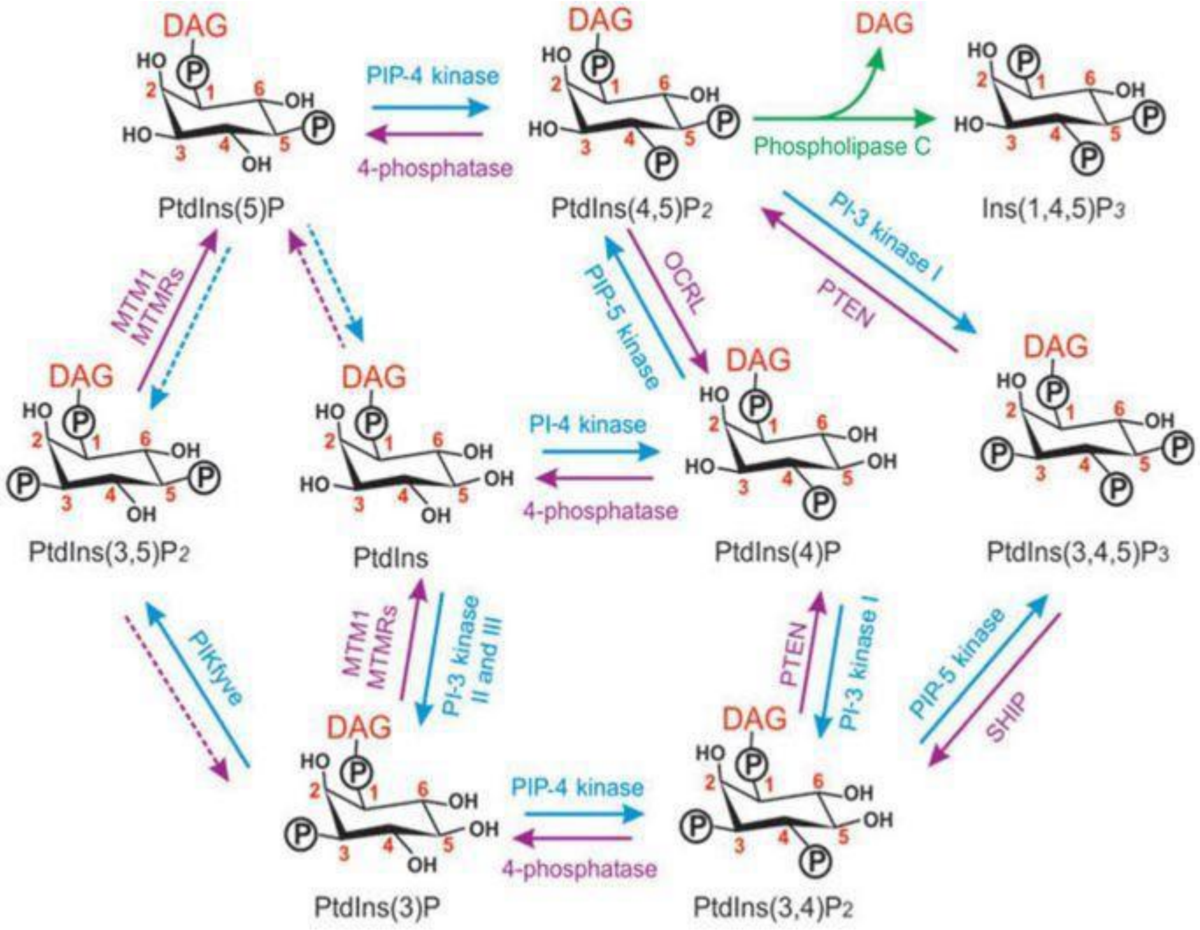




Bioactive lipids – Phosphoinositides (PI)

- Phosphoinositides are minority phospholipids on cellular membranes that have a phosphoglycerol backbone esterified with 2 fatty acids and inositol head group.
- Inositol group can be phosphorylated (P) at one or more sites in a reversible fashion (kinase – phosphatase)



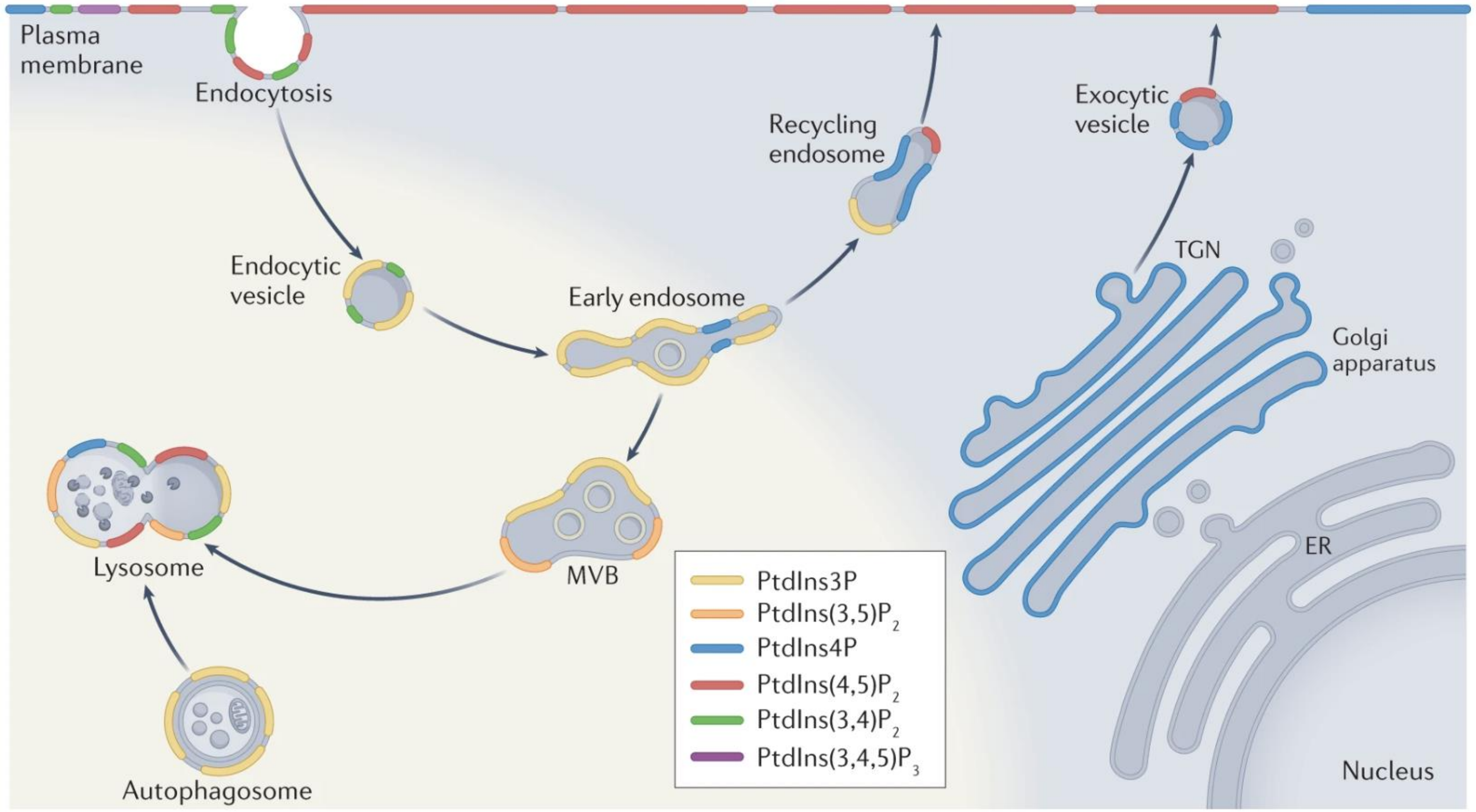


Bioactive lipids – Phosphoinositides (PI)

- Different phosphoinositides populate the membranes of specific intracellular organelles (**PtdIns**)

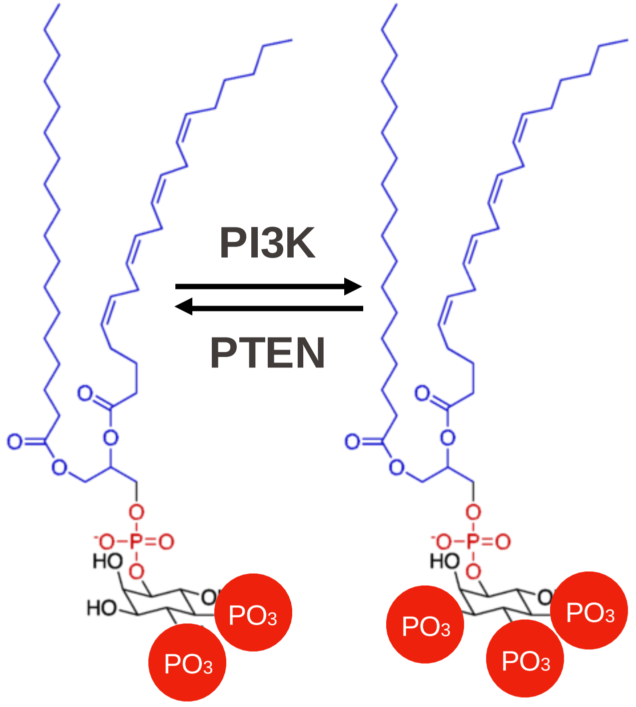
- Differentially phosphorylated PtdIns groups are bound by different cytosolic proteins

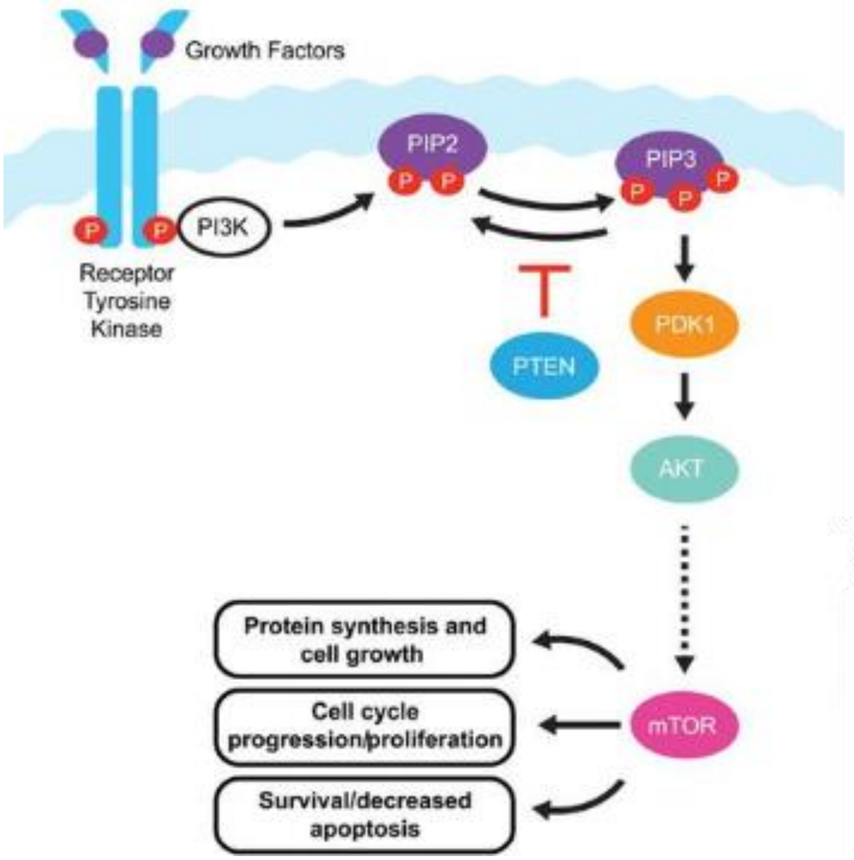
- By this virtue, PtdIns groups **contribute to the identity of intracellular compartments**



Bioactive lipids – PtdIns(3,4,5)P3

- Phosphorilation of PtdIns(3,4)P2 to PtdIns(3,4,5)P3 catalyzed by receptor typrosine kinase is recognized by PDK1 resulting in activation of the downstream signaling cascade and leading to different outcomes to the cell
- In this case, phosphoinositides serve as **secondary messengers**



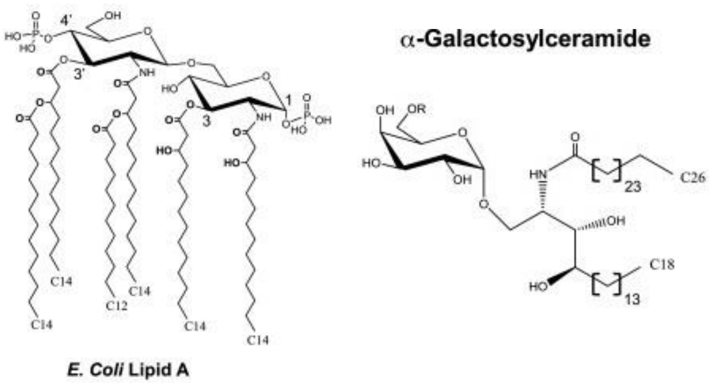


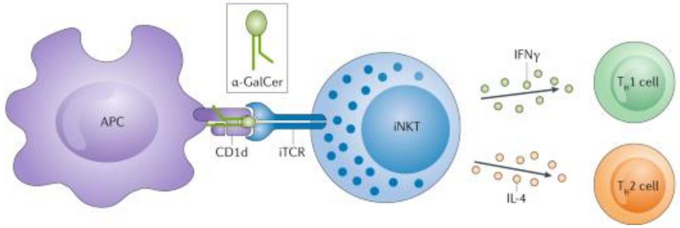
Lipids in bioengineering

- Conventional applications include food, cosmetics, soap, biofuel, chemical feedstock etc.

Immunomodulators

Bacterial glycolipids (LPS)



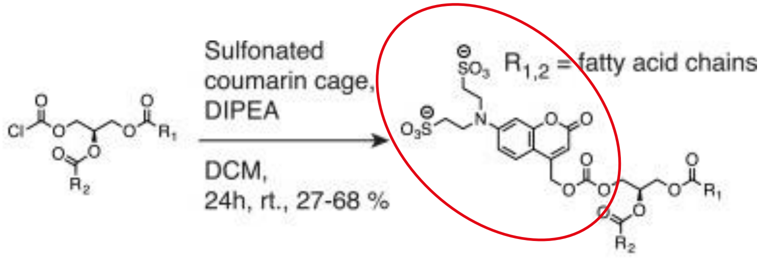


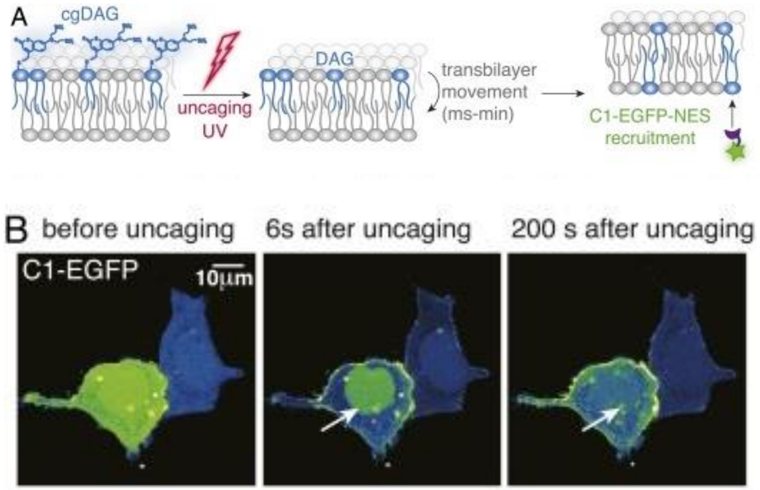
Adjuvant effect

Membrane development

https://www.epfl.ch/labs/dangelo-lab/

Chemical toolkit for biology





https://www.epfl.ch/labs/gr-schuhmacher/

Lipids – Take Home messages

- Lipids are non-water soluble constituents of living organisms
- Lipids may serve as energy stores and thermal insulators
- Lipids constitute the building blocks of biological membranes
- Lipids can serve as first and second messengers in signal transduction
- Lipids are structurally and functionally heterogeneous
- The three main classes of lipids in eukaryotes are glycerophospholipids, sphingolipids and sterols