بسم الله الرحمن الرحيم

BIOCHEMISTRY

فَصَبْرٌ جَمِيلٌ

Lecture 17

Nucleic Acids

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APPROVED

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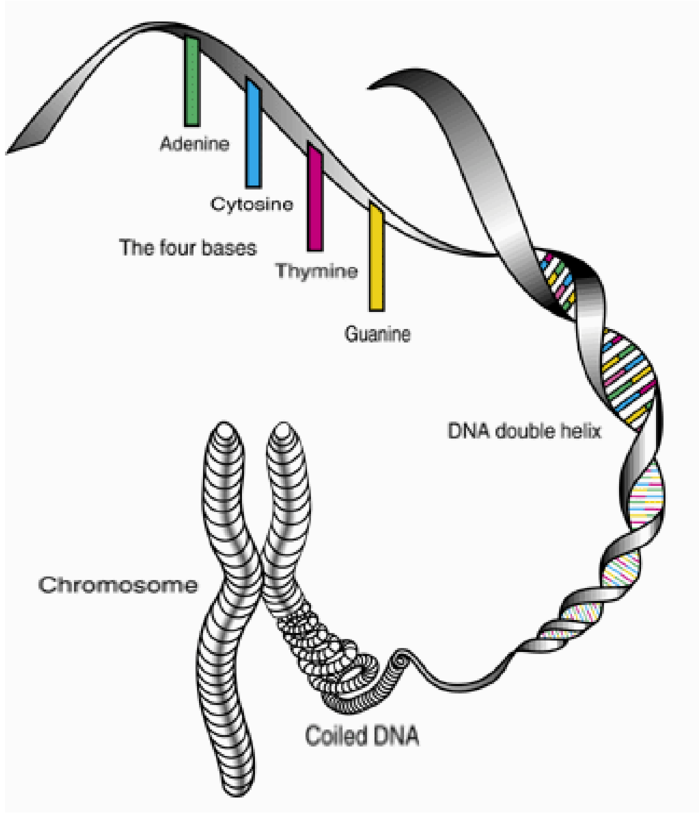
Nucleic acids

Nucleic acids are polymers made of nucleotide monomers chemically connected to each other.

- There are 2 types
  - Deoxyribonucleic acid (DNA)
  - Ribonucleic acid (RNA)
- The primary structure of nucleic acids is linear polymers of nucleotides (monomers) bound to each other via phosphodiester bonds.
- DNA is coiled and can be associated with proteins forming chromosomes.



The genetic material in our body is in the form of chromosomes.
Chromosomes are made of DNA which is a helical structure made of 2 strands (double helix) and each of these strands is made of nucleotides.

Chemical composition and bonds

Nucleotides are made of 3 components:

- **A pentose sugar**

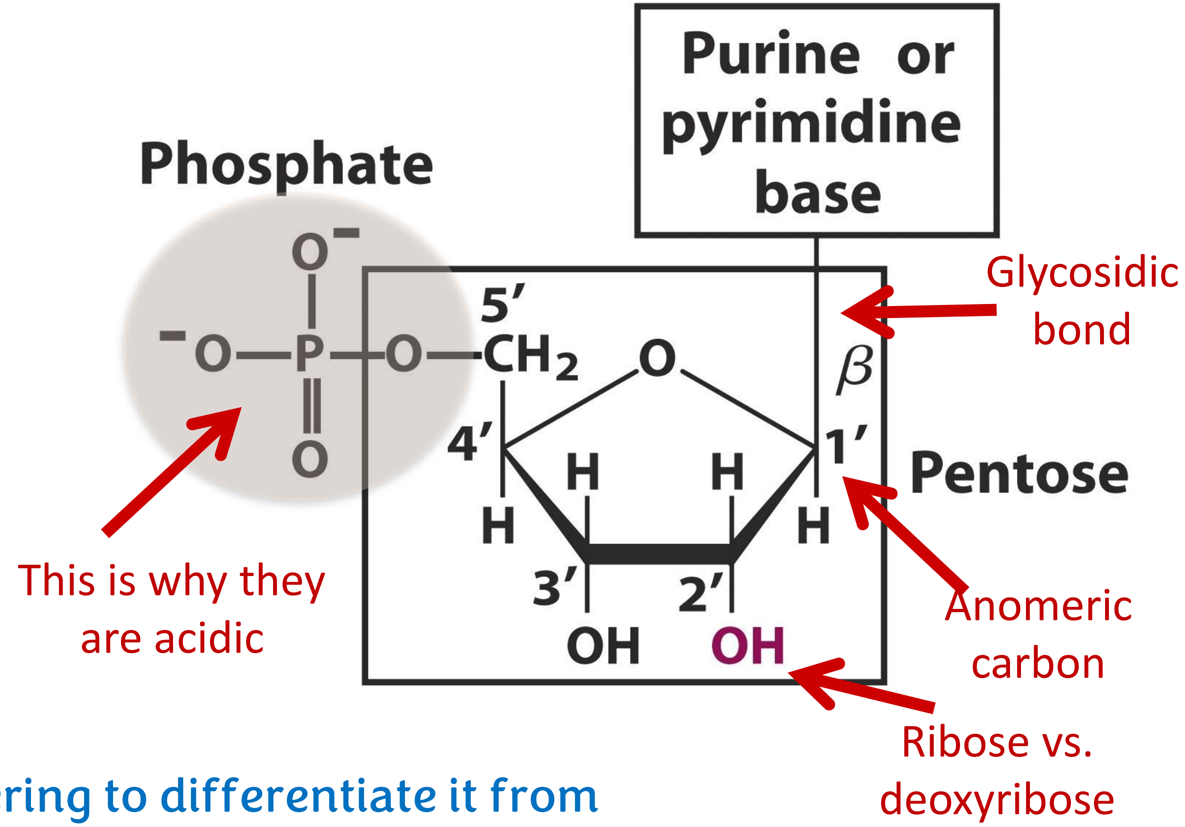
Either a ribose or deoxyribose.

- **A nitrogenous base**

A base which contains nitrogen and is either a purine or pyrimidine.

- **A phosphate group**

It is the reason why DNA and RNA are considered acidic.
They carry a negative charge.



Things you should notice about the structure:

- **The prime symbol** is used with the sugar carbons numbering to differentiate it from the nitrogenous base carbons, so when we say 3' we are talking about carbon number 3 of the sugar.
- **The nitrogenous base** is linked to the anomeric carbon of the sugar with a glycosidic bond.
- **The sugar** is in the β configuration.
- **The phosphate** is linked to carbon number 5 of the sugar.
- **The sugar** is either a deoxyribose(found in the DNA) or a ribose (found in the RNA), to determine, look at carbon number 2, if it is attached to a hydroxyl group then it is a ribose, if it is attached to another hydrogen then it is a deoxyribose.

Nitrogenous bases

There are two types of Nitrogenous bases :

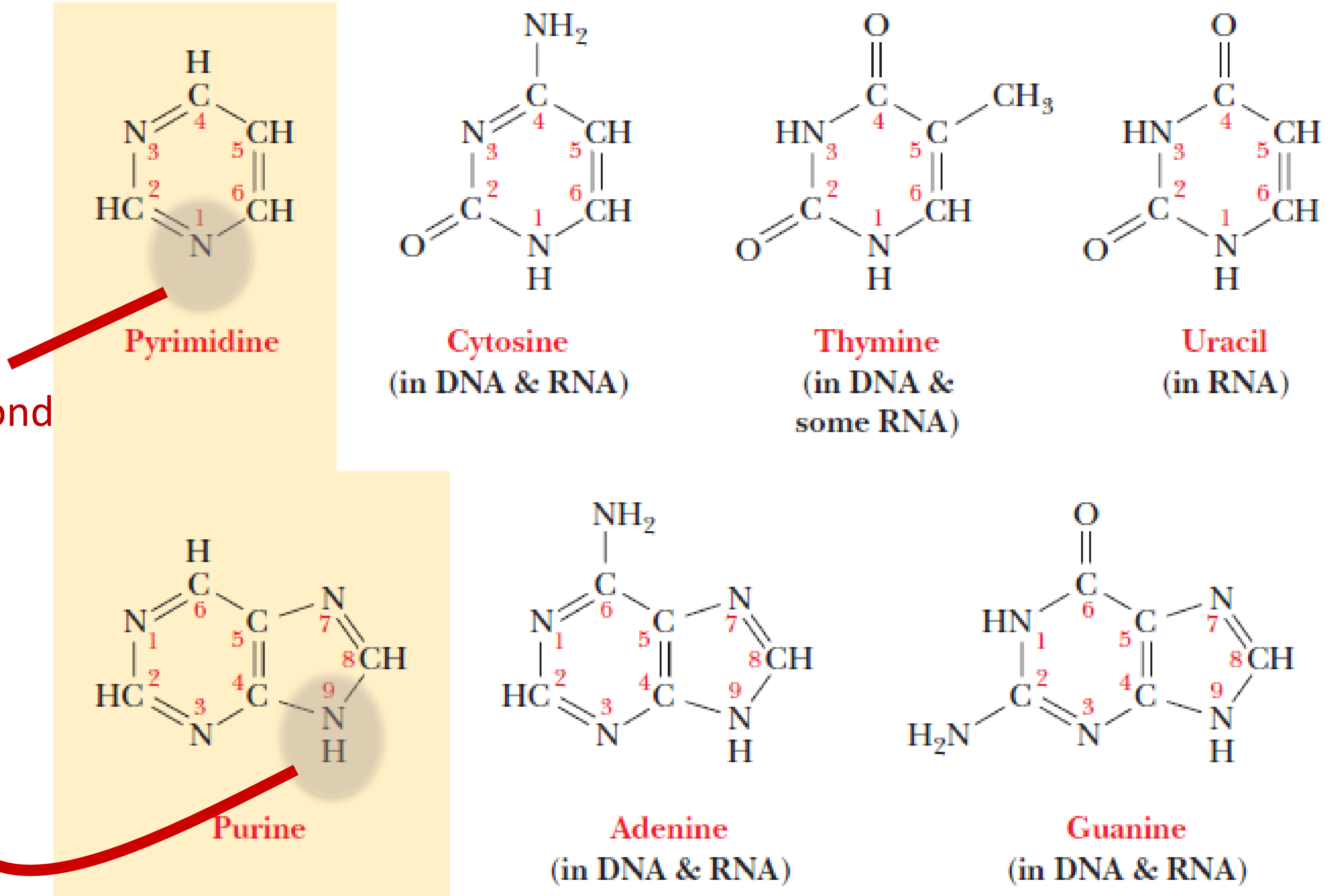
- **Pyrimidines (cytosine, thymine and uracil)**

They are made of a single ring.
Cytosine, thymine and uracil are abbreviated C, T and U respectively.
Uracil is found only in RNA while thymine is found only in DNA.
Cytosine is found in both DNA and RNA.

- **Purines (adenine and guanine)**

They are made of two rings.
Abbreviated A and G.
They are found in both DNA and RNA.

Glycosidic bond

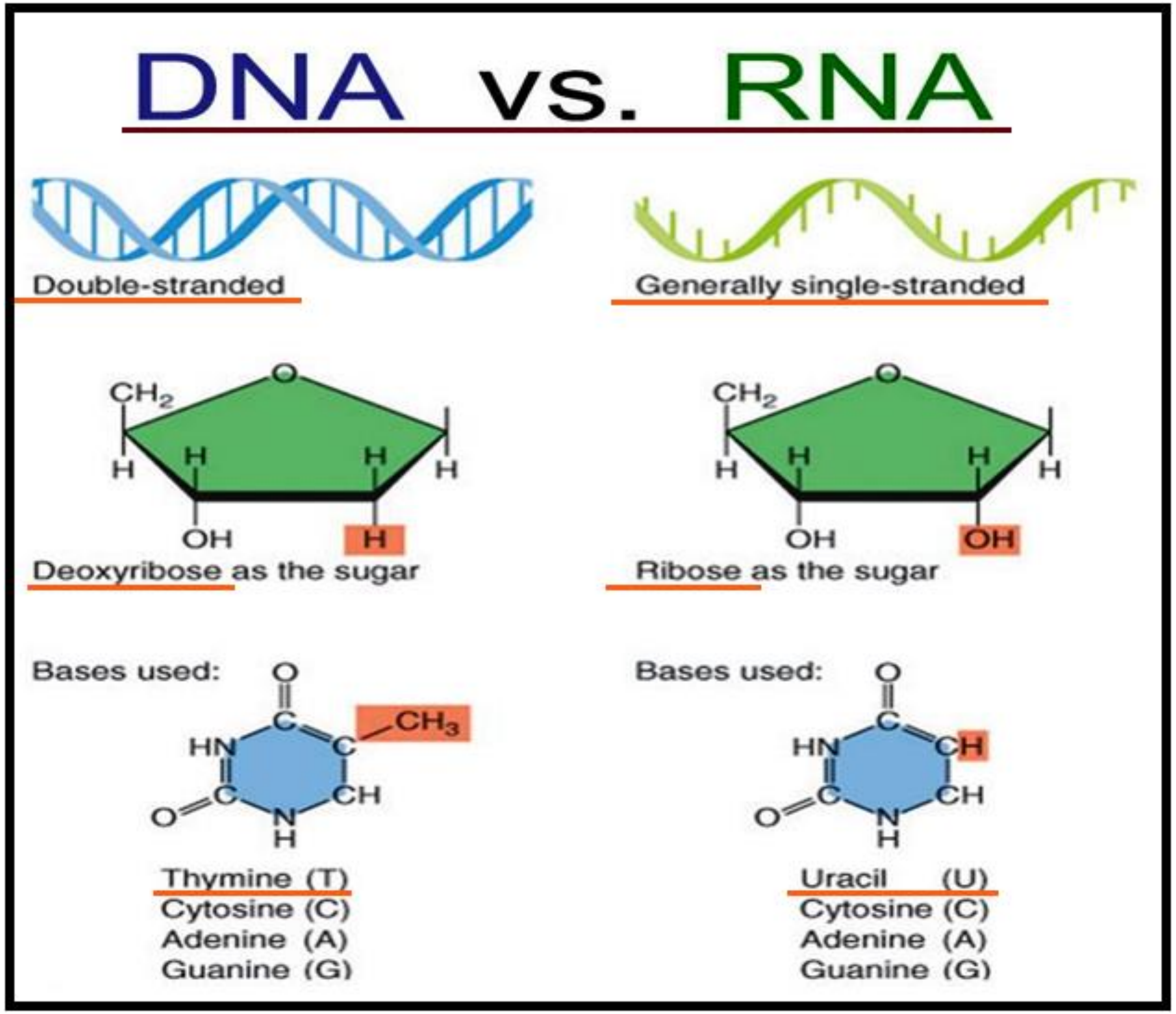


***Notice the difference in numbering the carbons here; there's no (') since these aren't the carbons of the pentose sugar**

Don't worry about memorizing the specific structure of each nitrogenous base, just know how to differentiate between a purine and a pyrimidine.

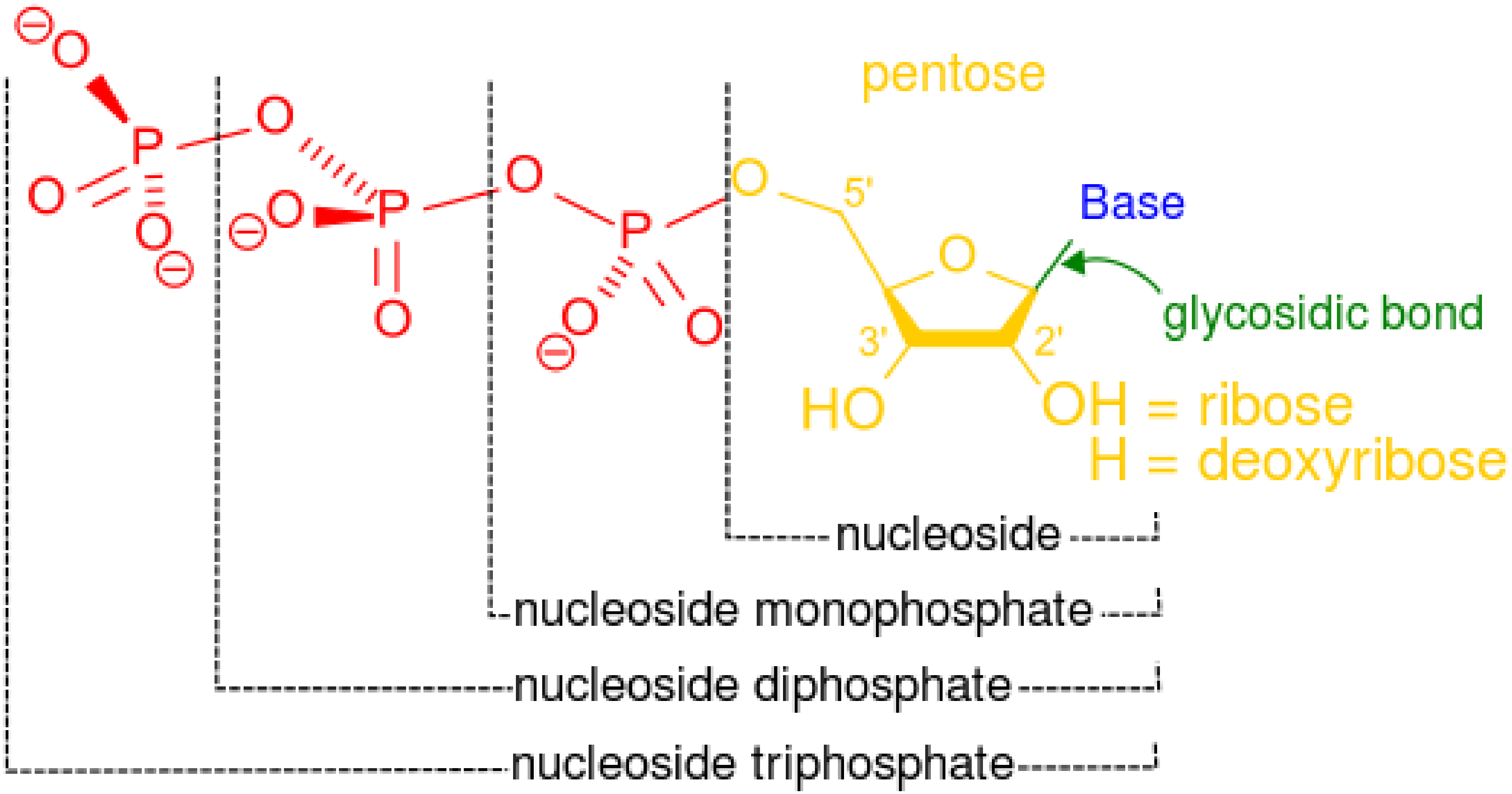
In prokaryotes and eukaryotes (not viruses)

Know the differences between the DNA and the RNA



Nucleotides vs. Nucleosides

As we already said, nucleotides are made of three components, the sugar, the base and the phosphate.
If we have only the sugar and the nitrogenous base the structure is called nucleoside.
Notice that a nucleotide may have more than one phosphate, so if we want to be specific about how many phosphates we have, we use the name nucleoside + (mono di or tri) phosphate.



Nucleotides vs. Nucleosides

Let's discuss how to name a nucleotide.

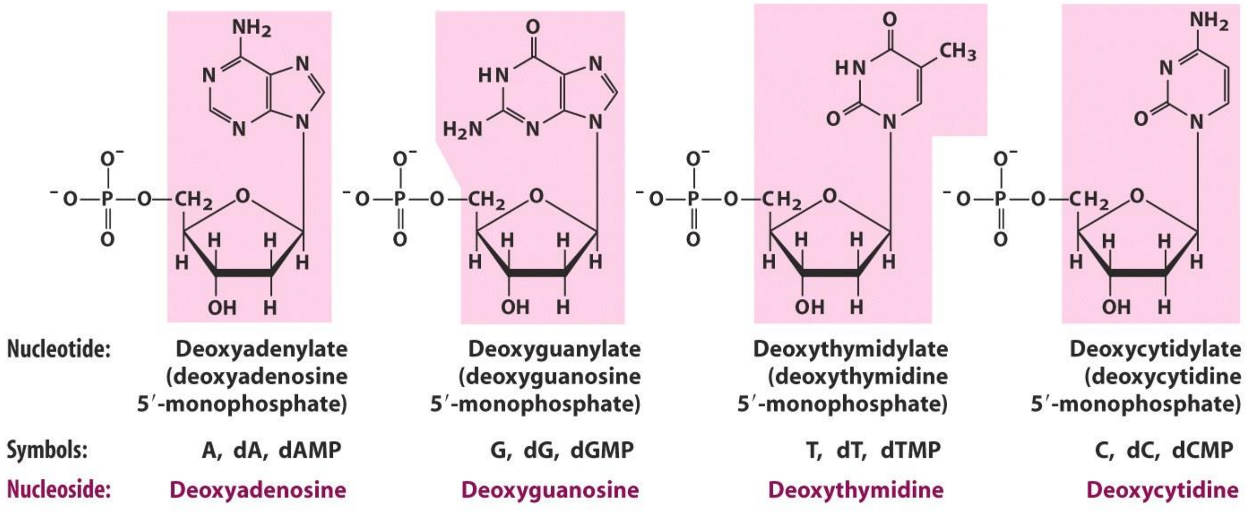
We name the nucleoside by identifying the nitrogenous base. If the base is a purine, we replace the -ine ending with -osine (Adenine→ Adenosine, Guanine→ Guanosine).

If the base is a pyrimidine, we replace the -ine or -il ending with -idine (cytosine→ cytidine, thymine→ thymidine, uracil→ uridine). This is how we name the nucleosides, (the sugar + the nitrogenous base).

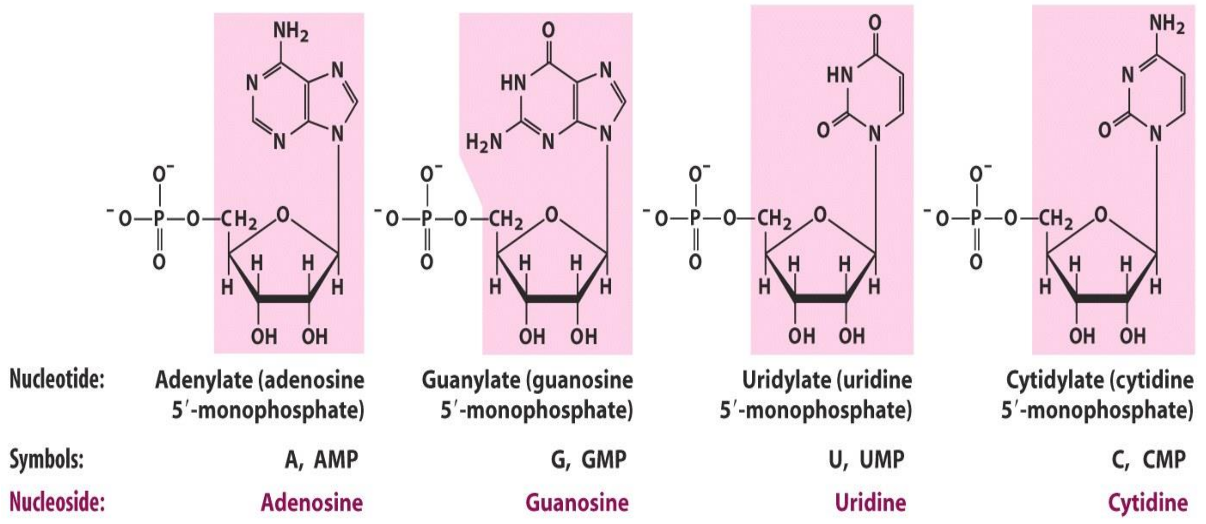
After naming the nucleoside, we add 5' -monophosphate because we have **one** phosphate group attached to the 5' carbon.

If the sugar is a deoxy sugar, we add deoxy as a prefix to the name of the nitrogenous base.

Notice that we have common names e.g. Adenylate; (the suffix -ylate refers to monophosphate molecules).



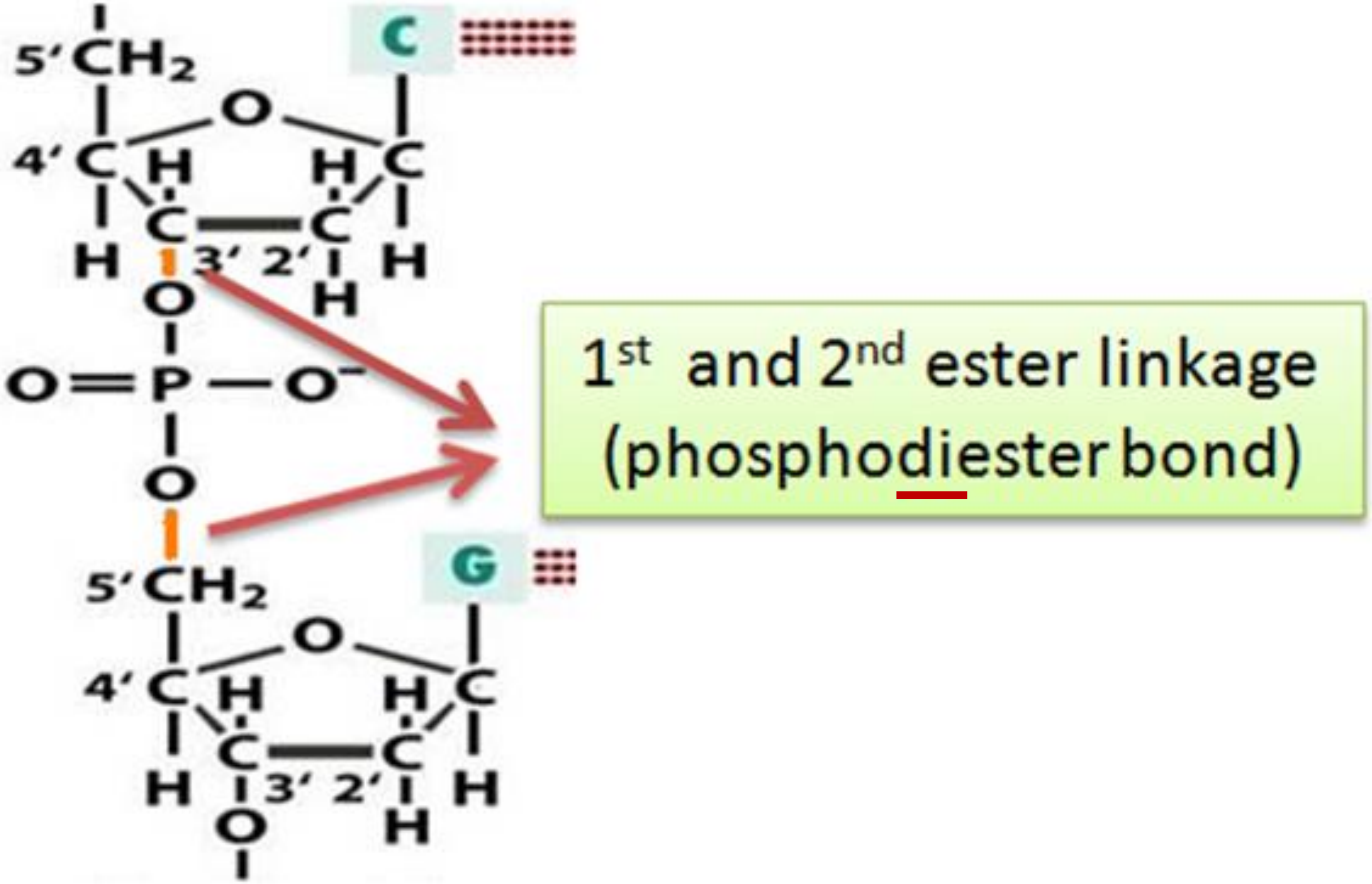
(a) Deoxyribonucleotides



(b) Ribonucleotides

Formation of a nucleic acid polymer

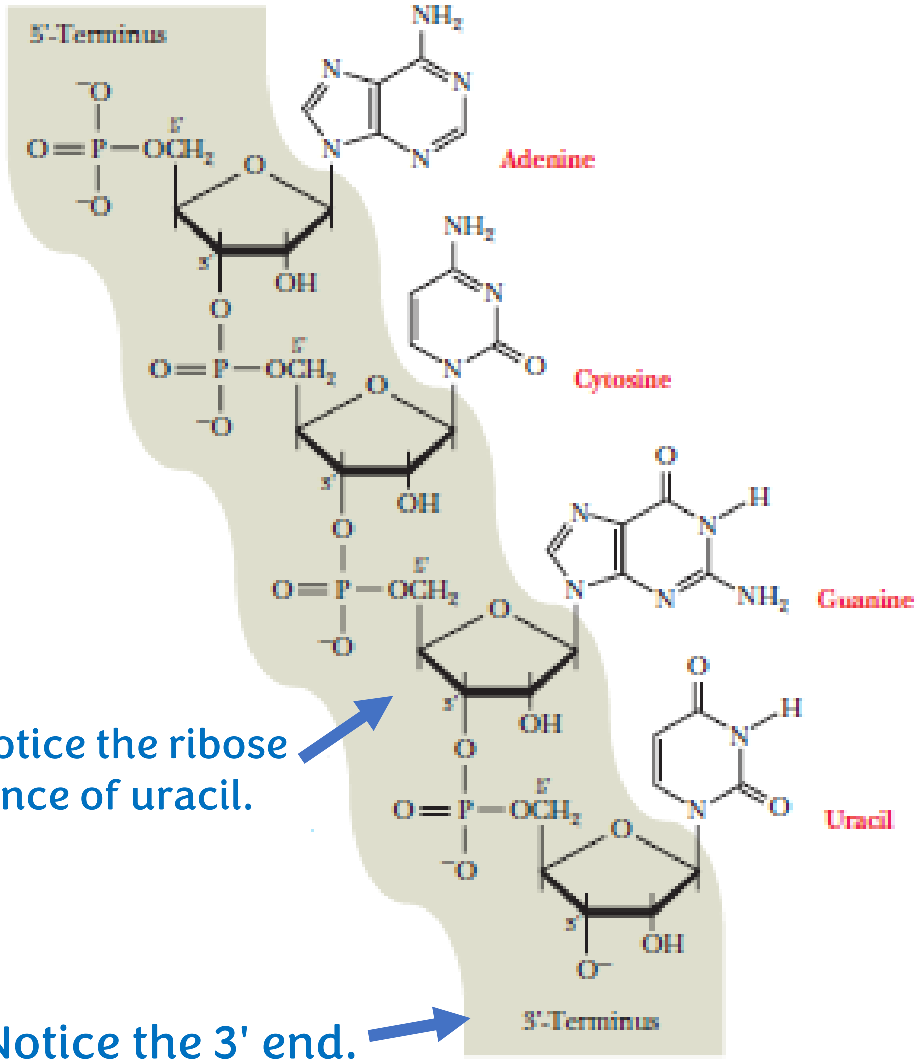
These monomers are linked together by a phosphodiester bond, this bond is always between 3' and 5' carbons.
Phospho**di**ester means that we have two phosphoester groups.(notice the figure below)
We have two ends, a 5' end which is a phosphate attached to 5' carbon and a 3' end attached to hydroxyl group.
We always add nucleotides to the 3' carbon,. This gives us a directionality in the polymerization of the DNA.(always 5' → 3' polymerization)



Nucleic acid polymers

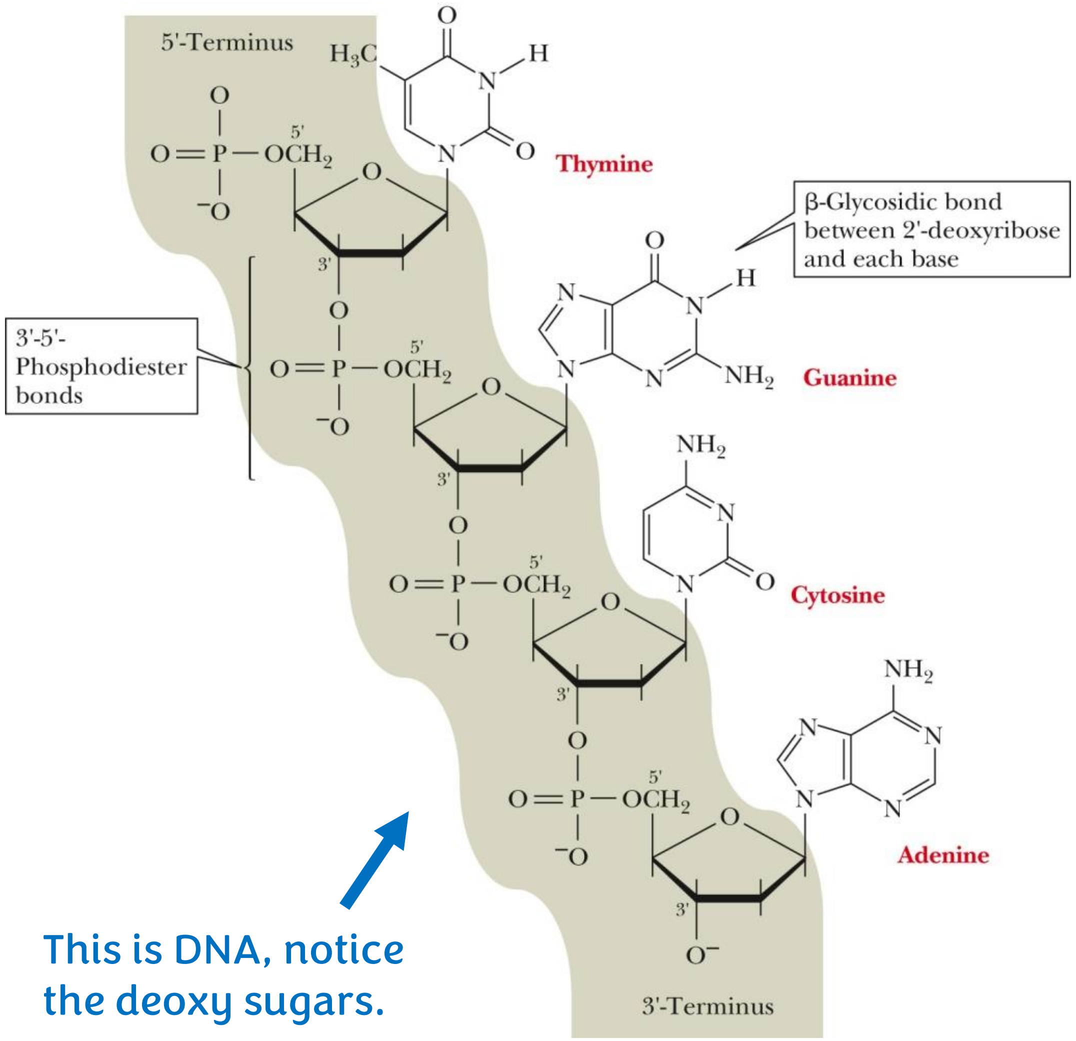
We always write the DNA sequence from the 5' end to the 3' end.
For example, ATGCAAT means that we start with adenine at the 5' end and end with thymine at the 3' end.

Notice the 5' end.



This is RNA, notice the ribose and the presence of uracil.

Notice the 3' end.



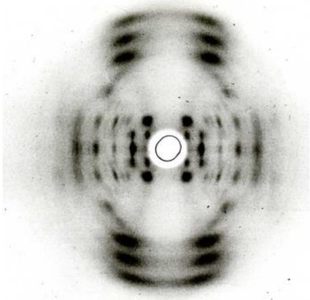
This is DNA, notice the deoxy sugars.

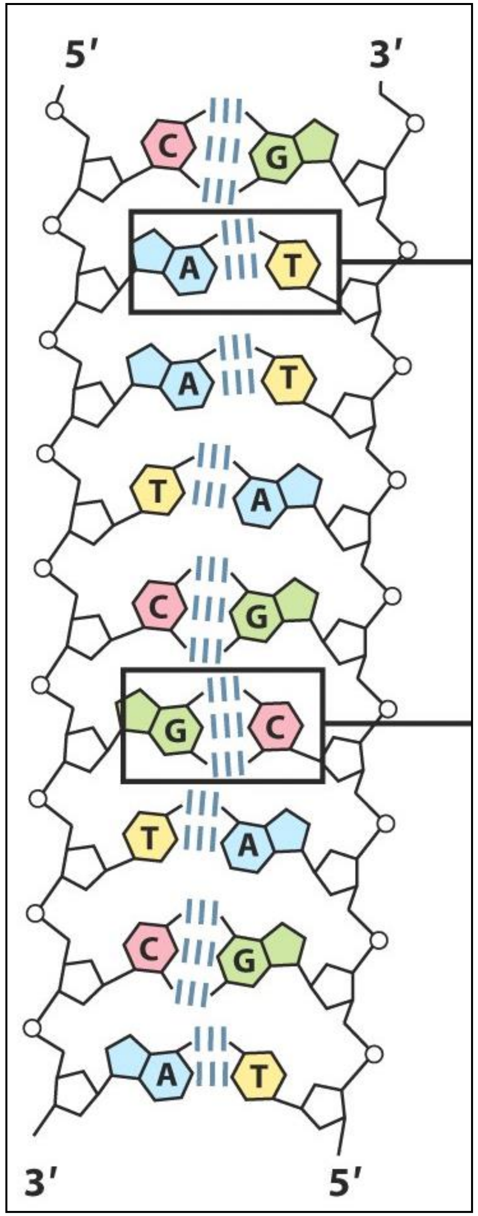
Note on the previous slide

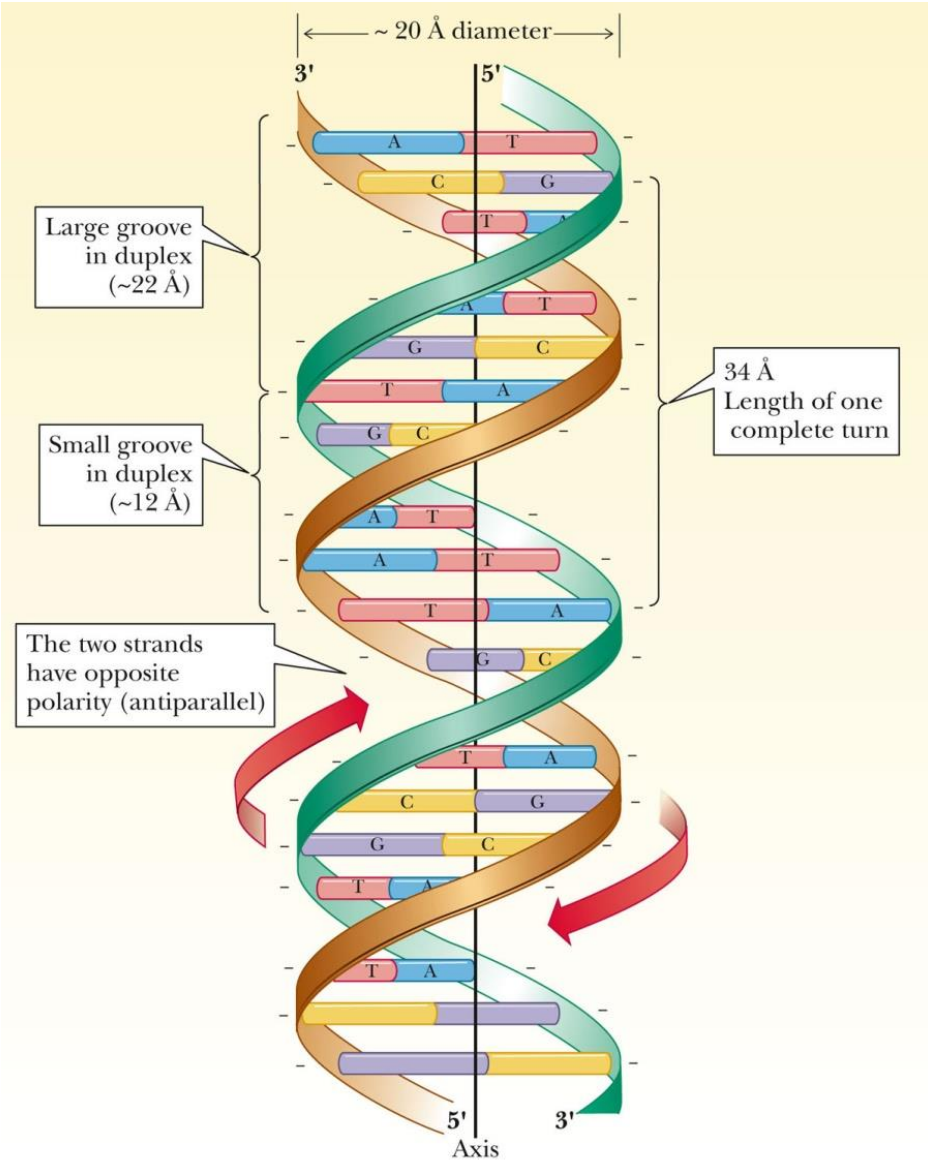
A letter d can be added to indicate a deoxyribonucleotide residue.
For example, dG is substituted for G.
The deoxy analogue of a ribooligonucleotide would be d(GACAT).

DNA structure

- A double helix
- Specific base-pairing
  - A = T; G = C; Pur = pyr
- Complementary
- Backbone vs. side chains
- Antiparallel
- Stability vs. flexibility
- Groovings







Notes regarding the previous slide

DNA structure has the following characteristics:

- **A double helix.**

Meaning that we have two strands of DNA with their nitrogenous bases bonded to each other and these two strands gives a helical structure.

- **The bonding pattern (complementarity).**

Adenine binds with thymine with two hydrogen bonds, guanine binds with cytosine with three hydrogen bonds

- **The sugar-phosphate backbone with their nitrogenous bases directed sideways.**
- **DNA is anti-parallel.**

Which means that if the first strand is directed 5' to 3' from upward to downward the complementary strand will be directed 5' to 3' from downward to upward.

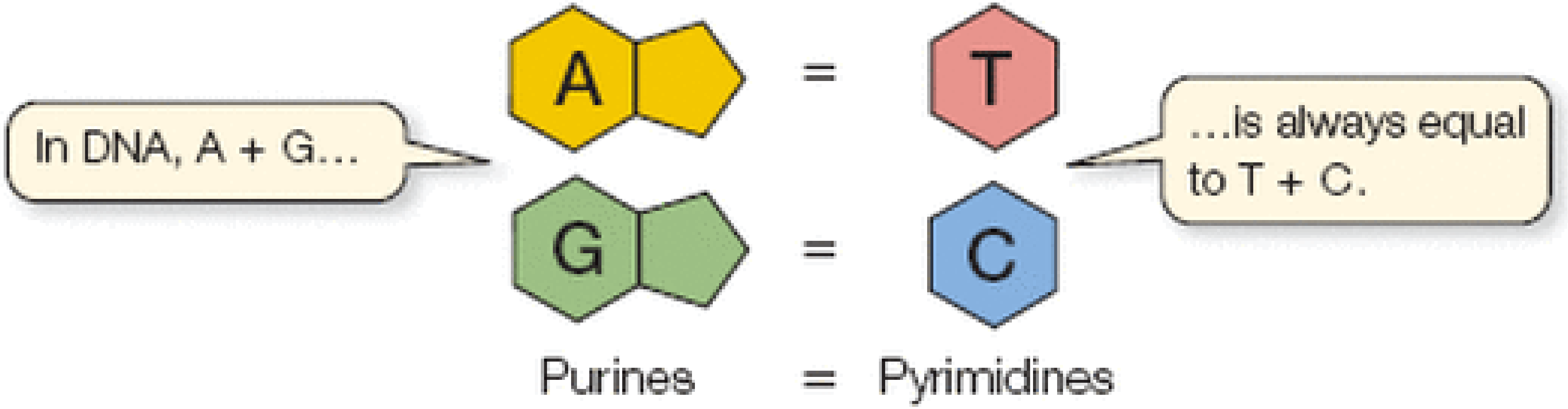
- **It has grooves**

Major and minor grooves are present because the helical structure is not perfect.(illustrated in the next slides)

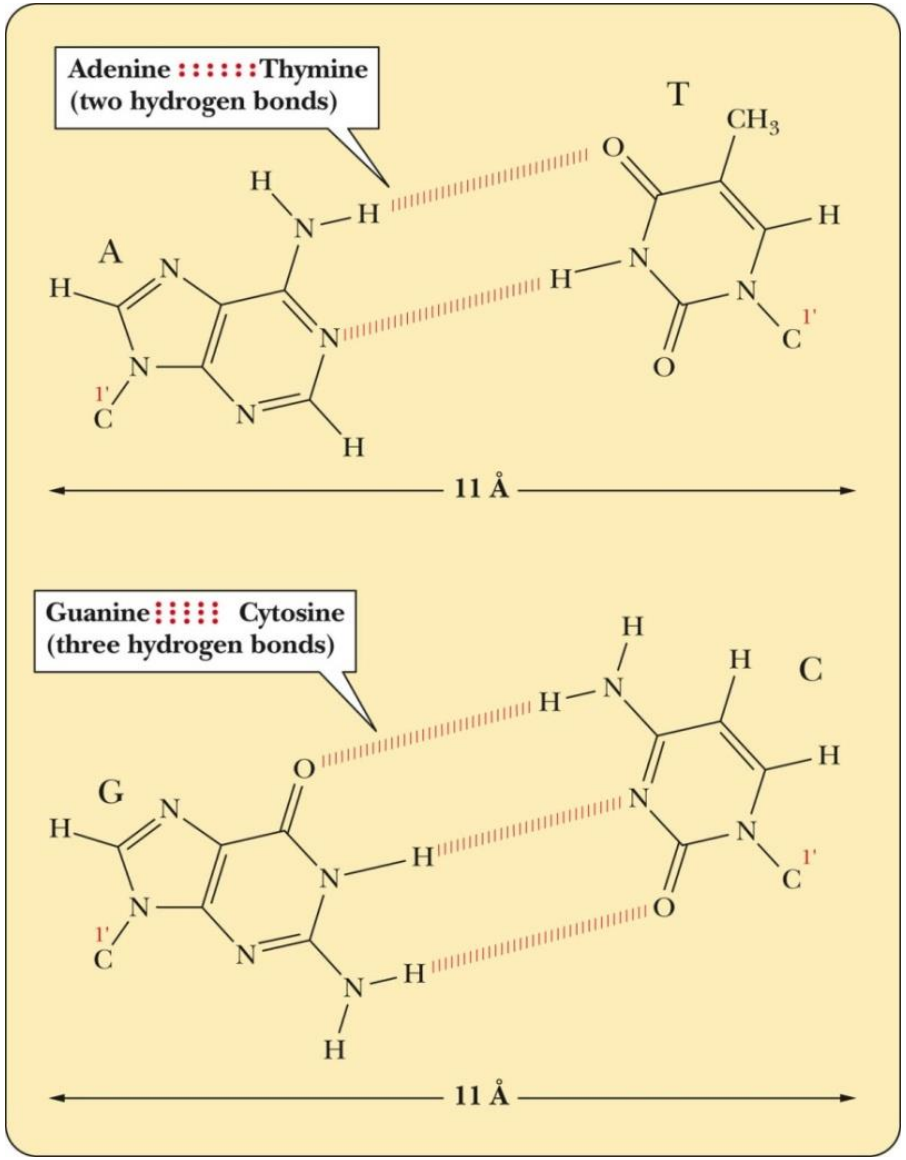
Chargaff's rules

In the DNA,

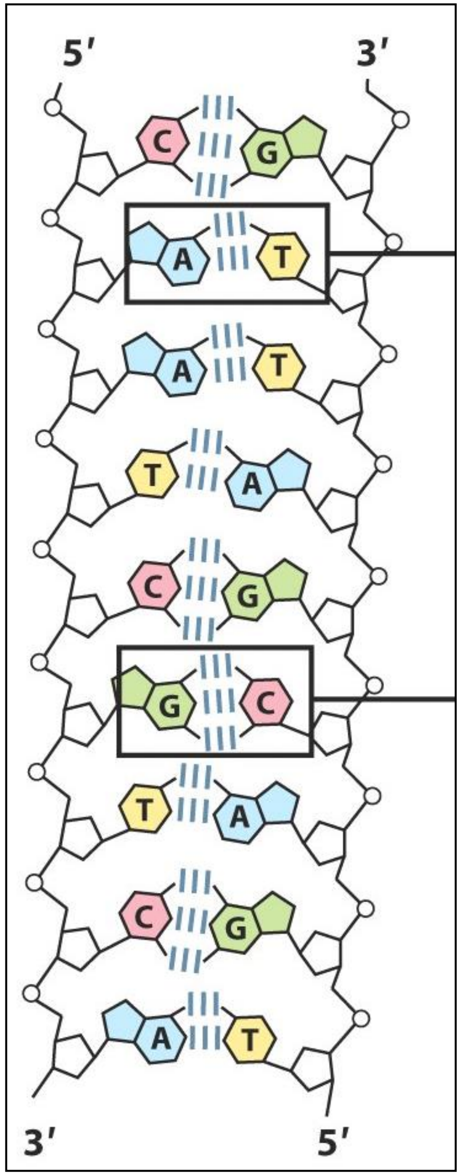
- The number of adenine bases is equal to the number of thymine bases.
- The number of guanine bases is equal to the number of cytosine bases.
- The number of purines is equal to the number of pyrimidines (A+G=T+C).



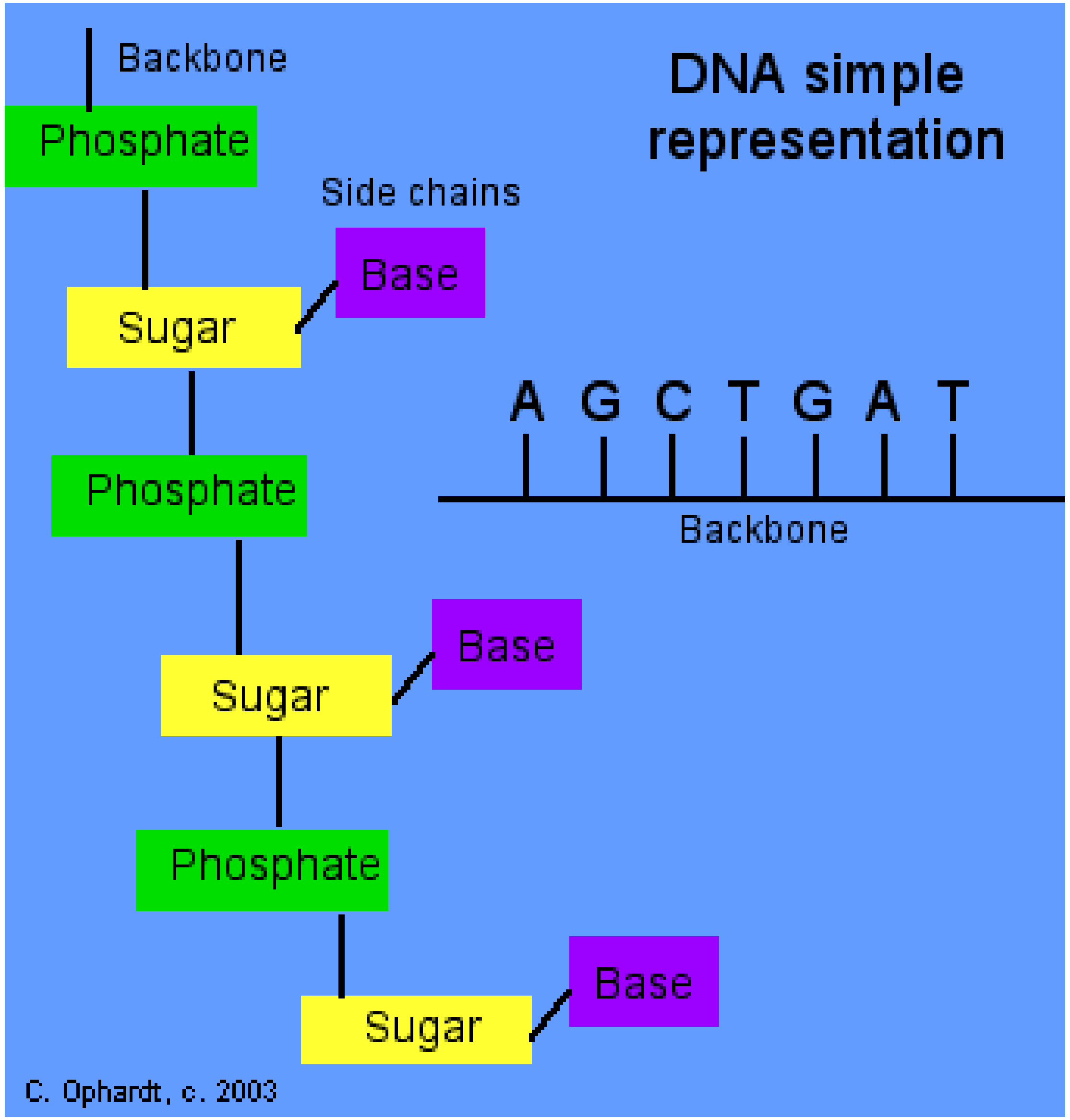
Base pairing



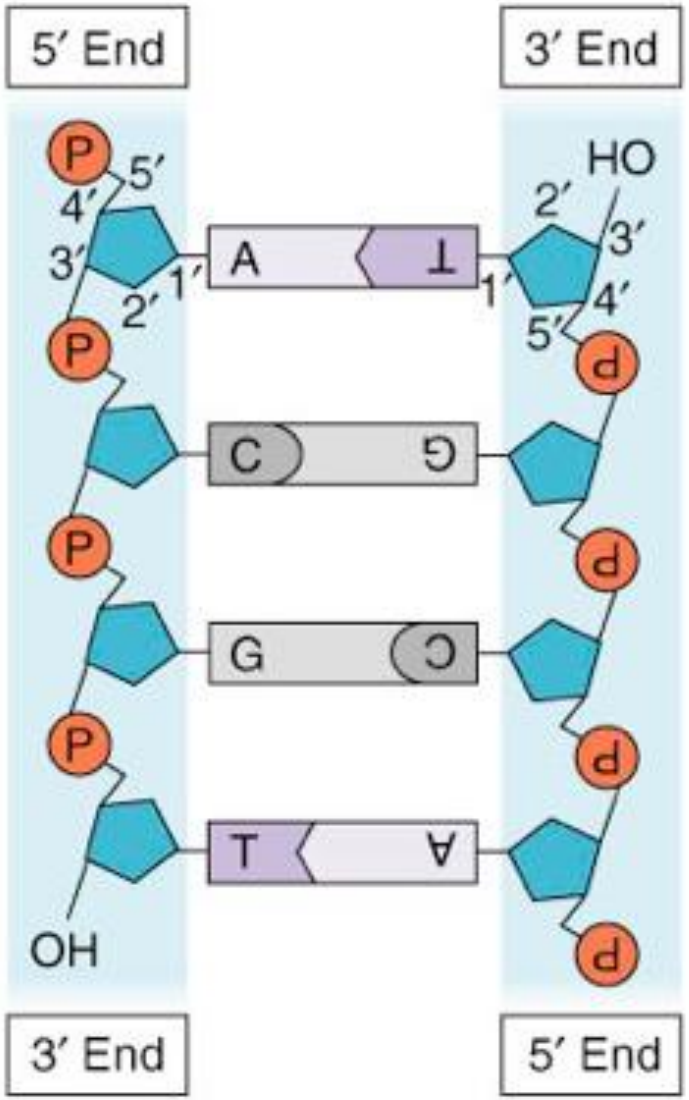
DNA is complementary



Backbone vs. side chains



DNA is anti-parallel



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Writing the sequence of nucleic acids

Writing the sequence of one strand of the DNA is enough since
You could know the sequence of complementary strand from the
bonding pattern.

DNA

5' ...A T G G C C T G G A C T T C A... 3'
3' ...T A C C G G A C C T G A A G T... 5'

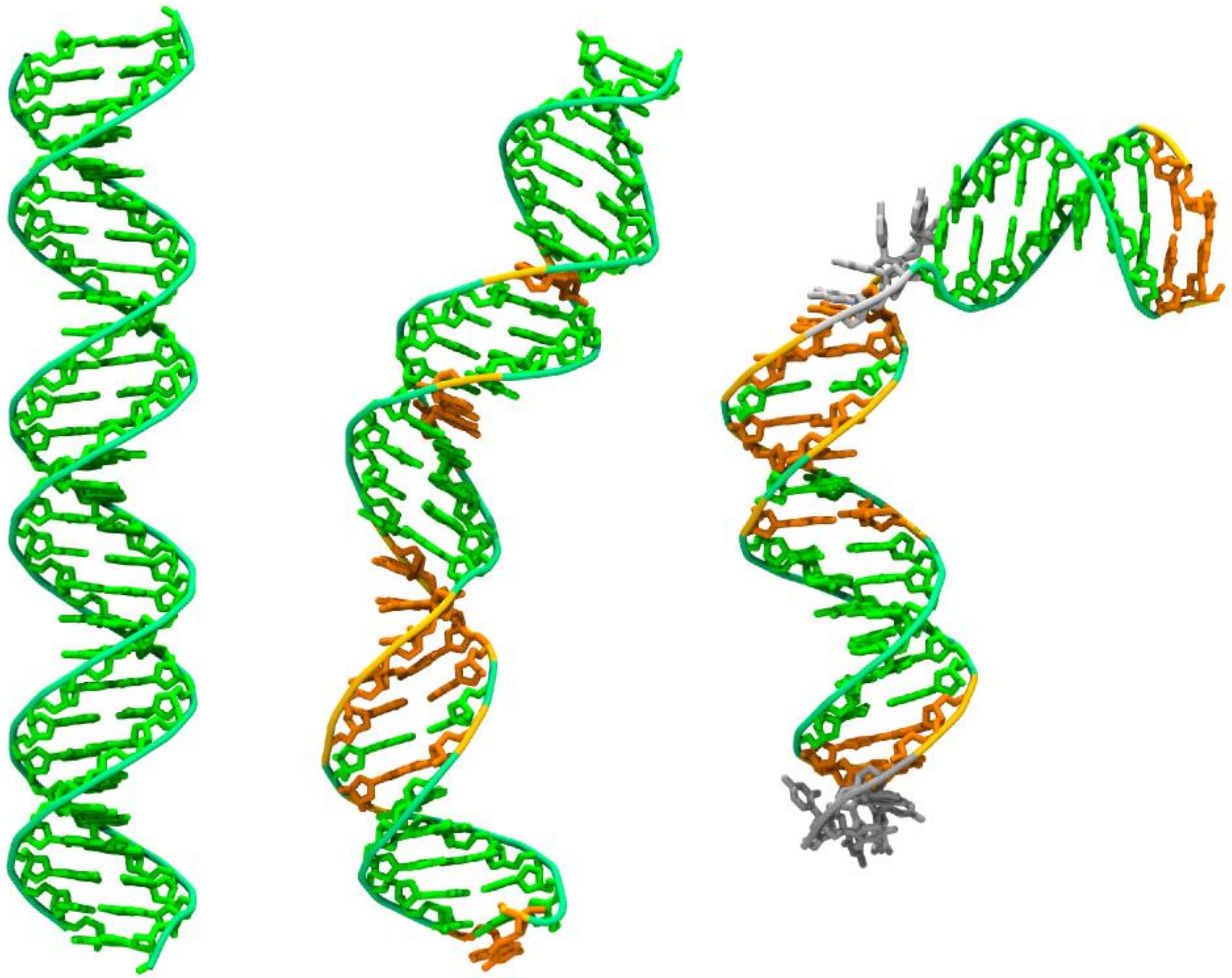
OR A T G G C C T G G A C T T C A.

RNA 5' ...A U G G C C U G G A C U U C A... 3'

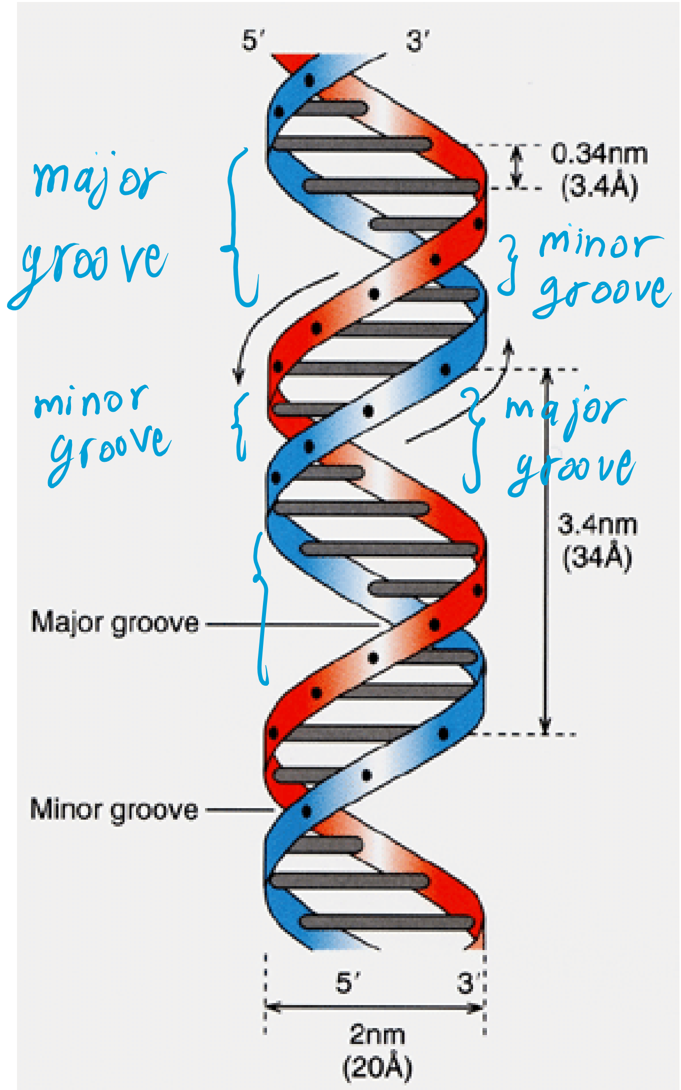
RNA is usually single stranded.
Recall that we always write the sequence of the DNA from 5' to 3'.

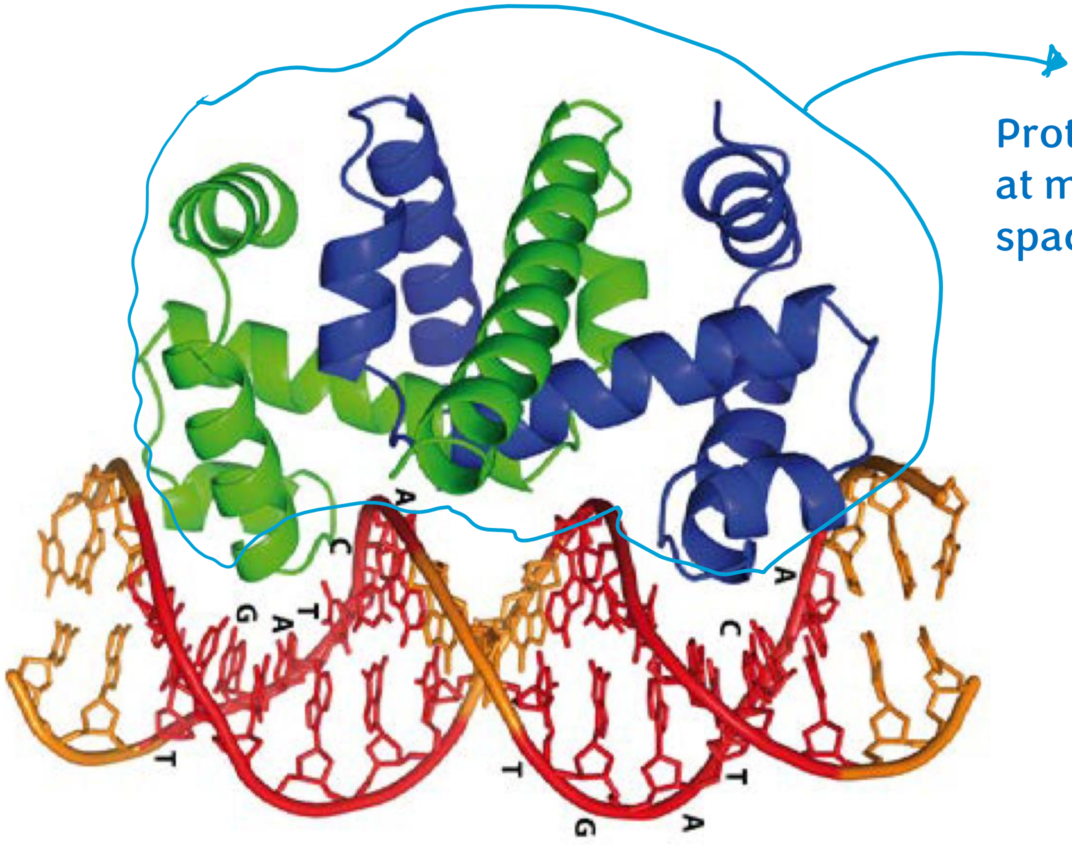
DNA is flexible, yet stable

You can twist it ,but you can't break it
due to its stable structure



DNA grooves





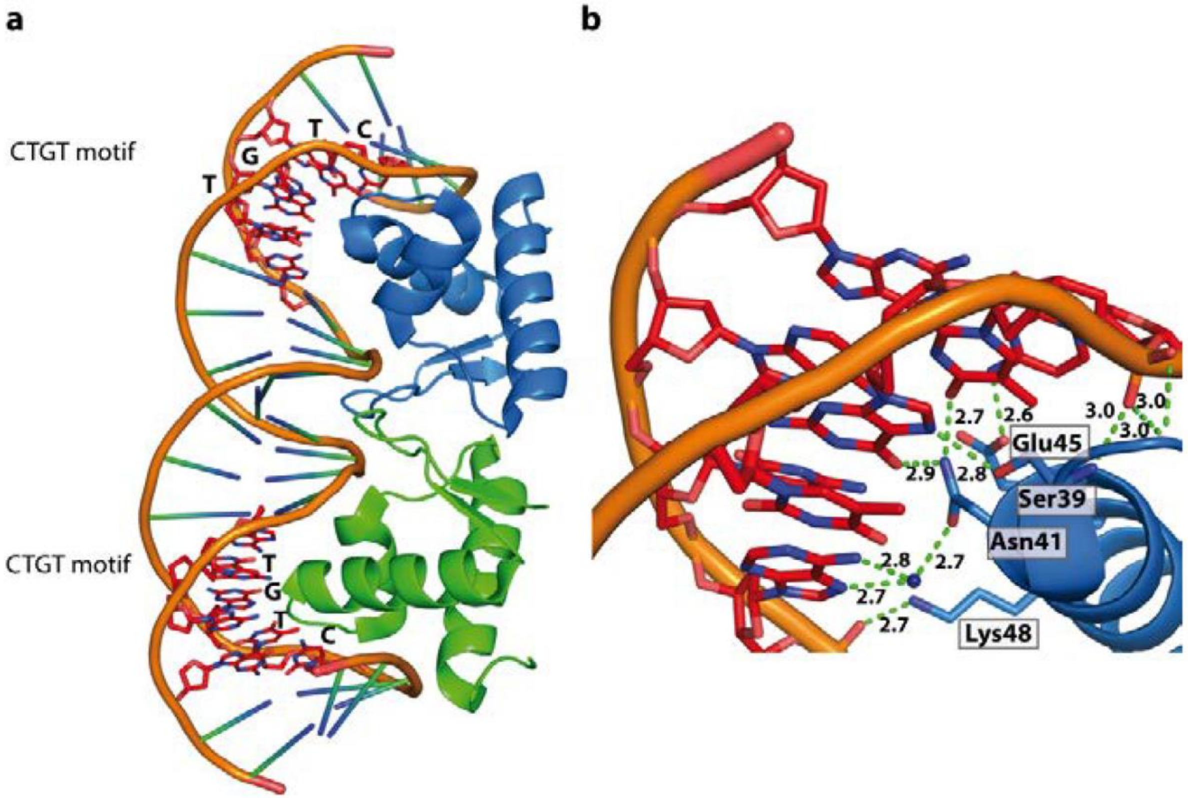
Proteins usually interact with the DNA at major grooves, since there is more space available for the protein to bind.

Each major groove is followed by a minor groove.
Each major groove faces a minor groove (on the other side of the helix).

DNA-protein interaction

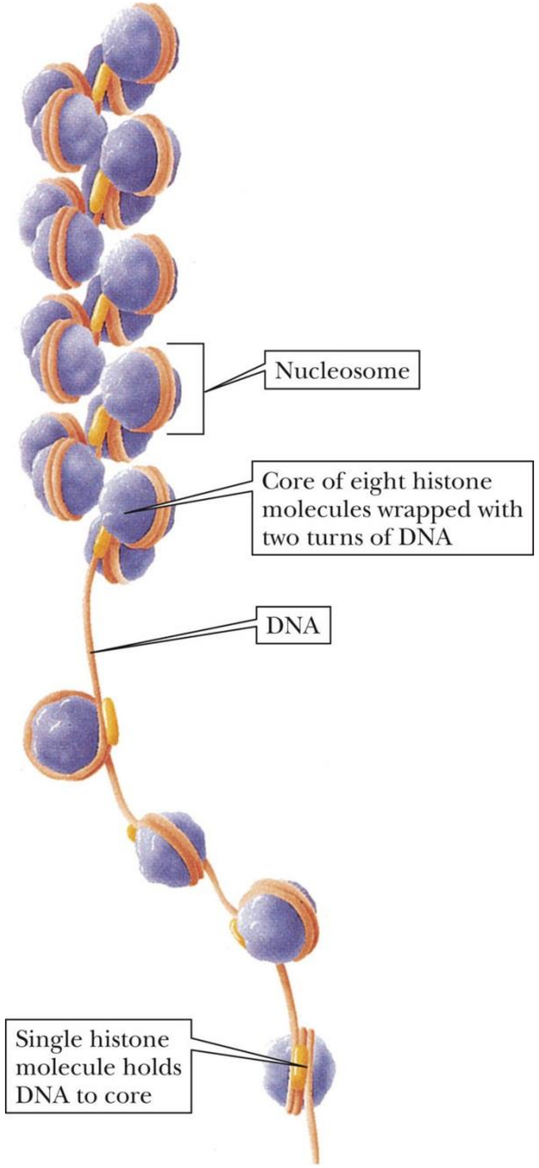
Interactions between the DNA and proteins occur between the amino acids and the nitrogenous bases.

The interactions are very specific because specific amino acids make specific interactions at specific regions of the DNA according to the sequence of nitrogenous bases.



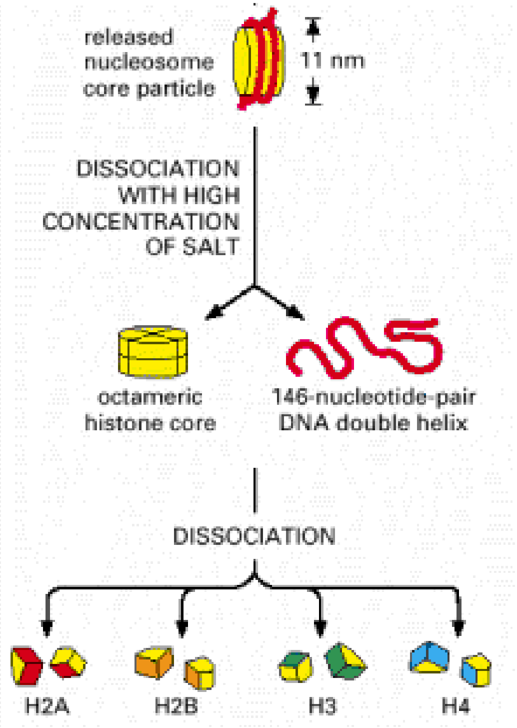
In eukaryotes…

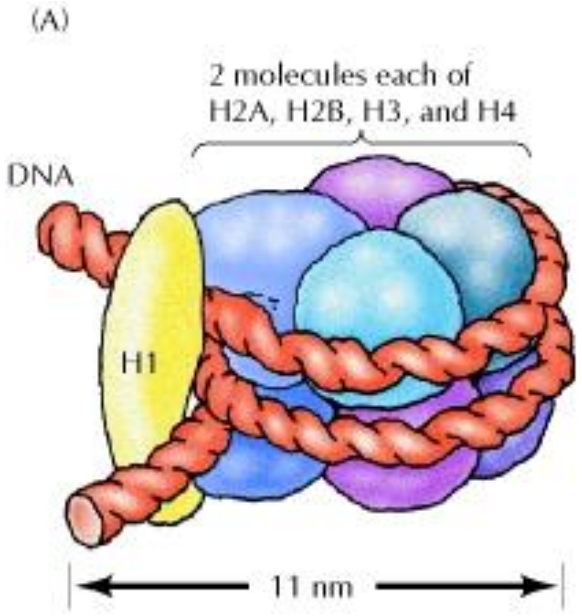
- In eukaryotes, DNA is coiled (around a group of proteins called histones) to package the large DNA.
- Eukaryotic DNA is complexed with a number of proteins, principally histones, which package DNA.
- Chromatin = DNA molecule + proteins.
- The basic structural unit of chromatin is known as a nucleosome.

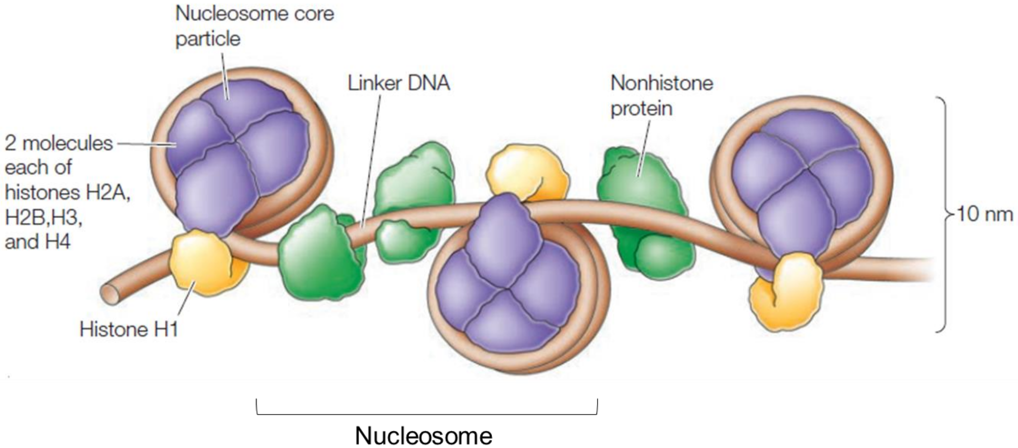


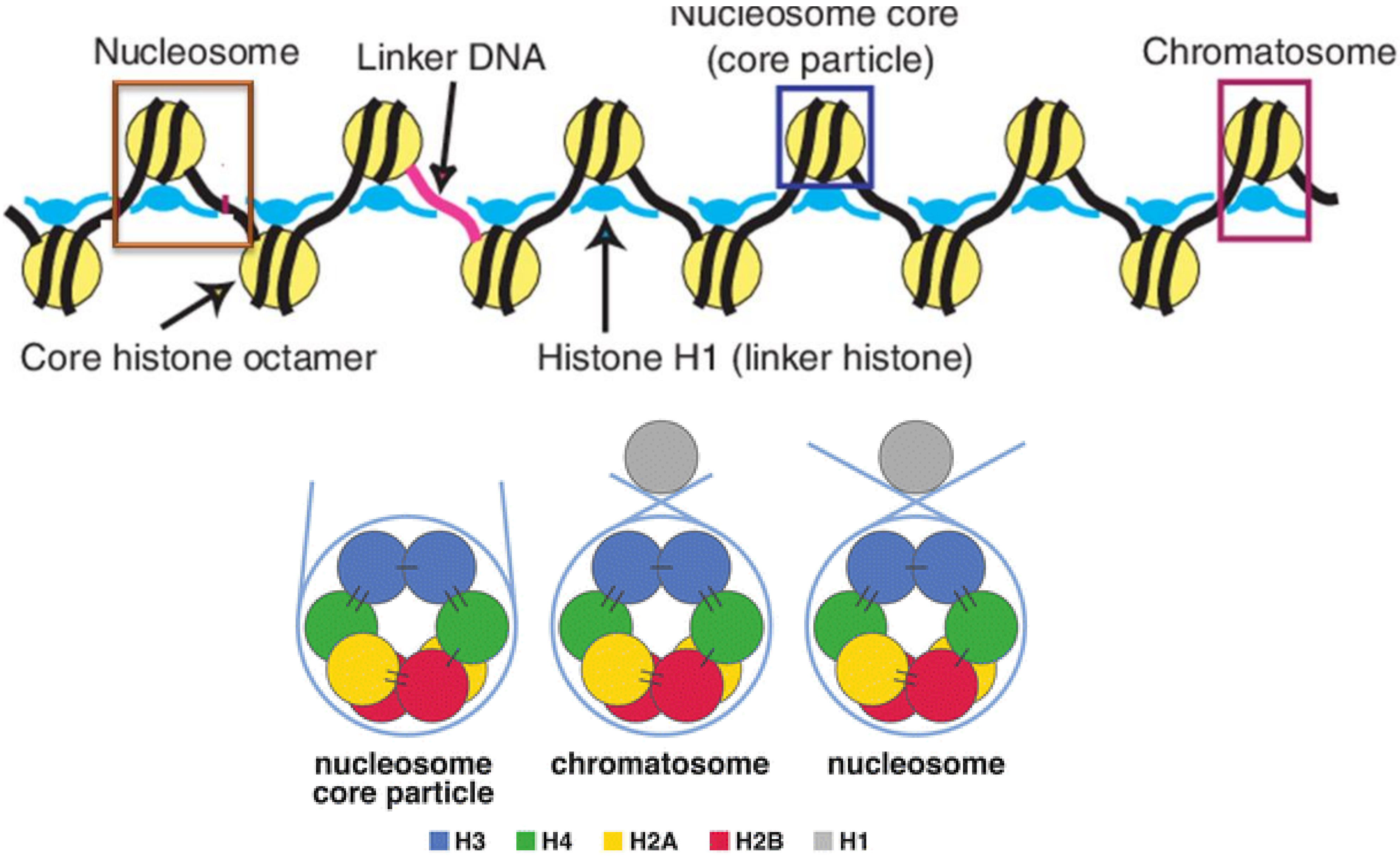
Nucleosomes

- A nucleosome consists of DNA wrapped around a nucleosome core particle, linker DNA, and histone H1.
- The histone core particle is an octamer (two molecules of histones H2A, H2B, H3, and H4) and the DNA wrapped around it.
- A linker DNA connects two nucleosome core particles.
- Histone H1 is bound to the octamer and wrapped DNA (a chromatosome).
- Histones are positively charged facilitating DNA interaction and charge neutralization.

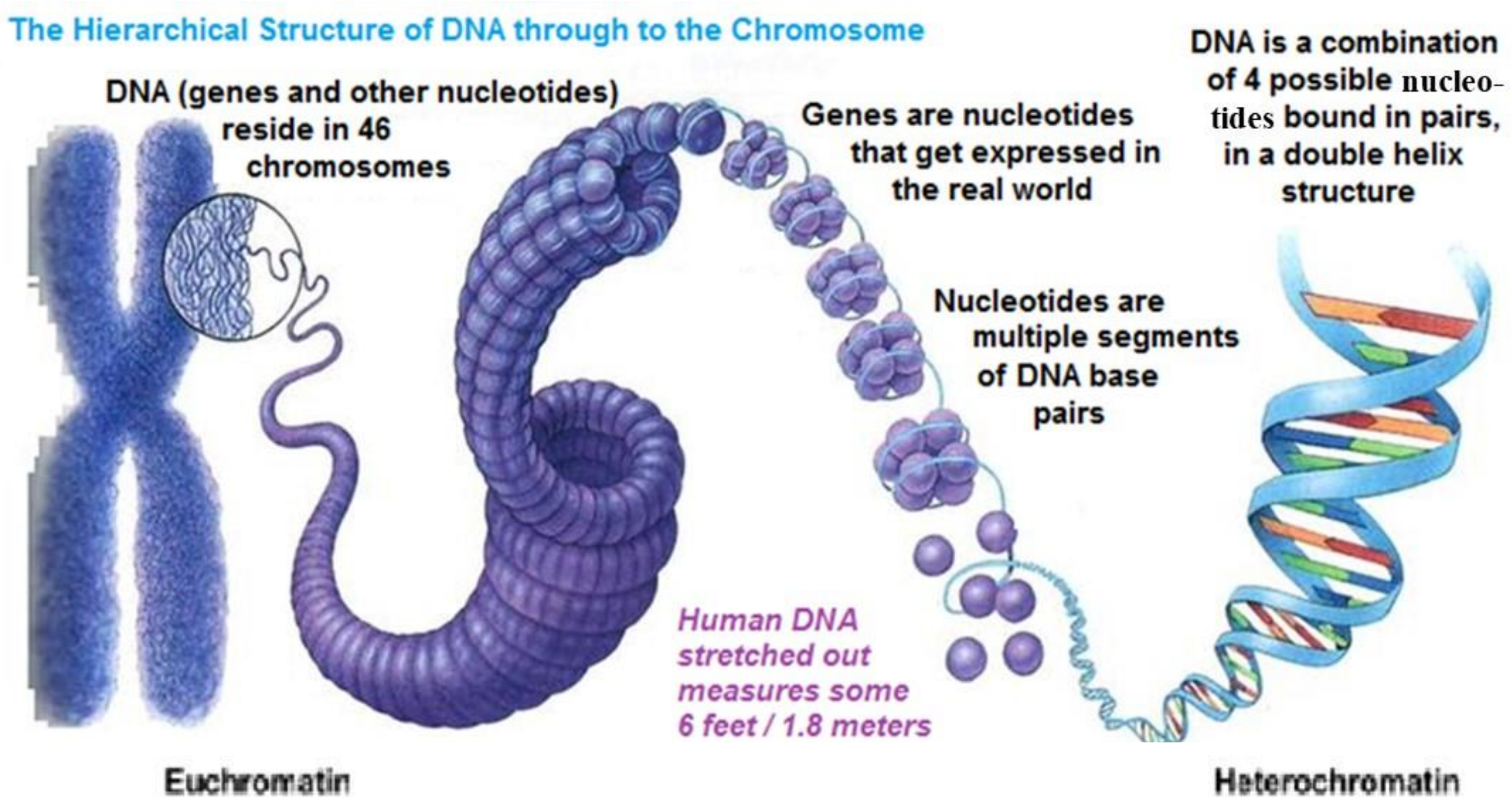


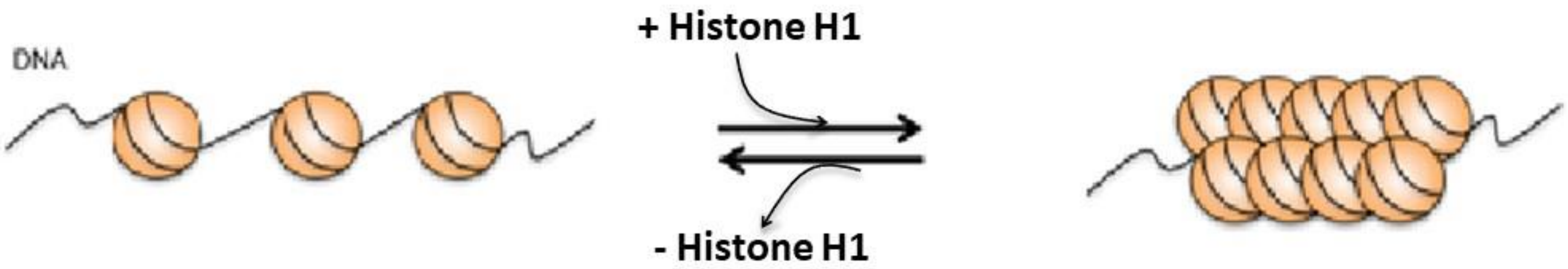





Nucleosome
Linker DNA
Nucleosome core
(core particle)
Chromatosome
Core histone octamer
Histone H1 (linker histone)
nucleosome
core particle
chromatosome
nucleosome
H3
H4
H2A
H2B
H1

Histones package chromosomes





The length of the DNA in each diploid cell is 2 meters, the total length of the DNA in all the cells of a human is equal to the distance of traveling from earth to sun and backwards 500 times!

Histone (H1) helps in packing DNA.

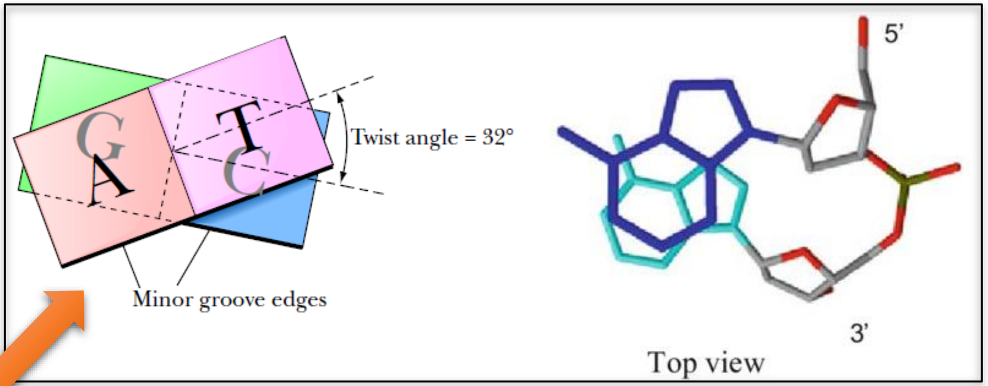
H1 transforms DNA from Euchromatic (loose DNA) → heterochromatic DNA (condensed DNA)

DNA coiling in eukaryotes:

- We have 5 types of histone protein: H1, H2A, H2B, H3 and H4.
- A pair of each type of histone protein (except H1) join to form an **octamer** (histone core).
- DNA is wrapped twice around the octamer, forming **nucleosome core particle**.
- H1 which isn't a part of the octamer seals the nucleosome core particle, this locks and stabilizes the structure and that gives us a **chromatosome.**
- Between each two chromatosomes, there is linker DNA segment which links two chromatosomes together, the structure which consists of the chromatosome and the linker DNA segment around it is called **Nucleosome.**
- The overall structure interacts with other proteins giving us **chromatin**.
- There are proteins (other than histones) which interact with the DNA of eukaryotes, but they are neither as abundant nor as well studied as histones.
- H1 isn’t always present in chromatin.

Proteins interact with the DNA by electrostatic interactions between their positive R groups and the negative phosphate groups of the DNA.

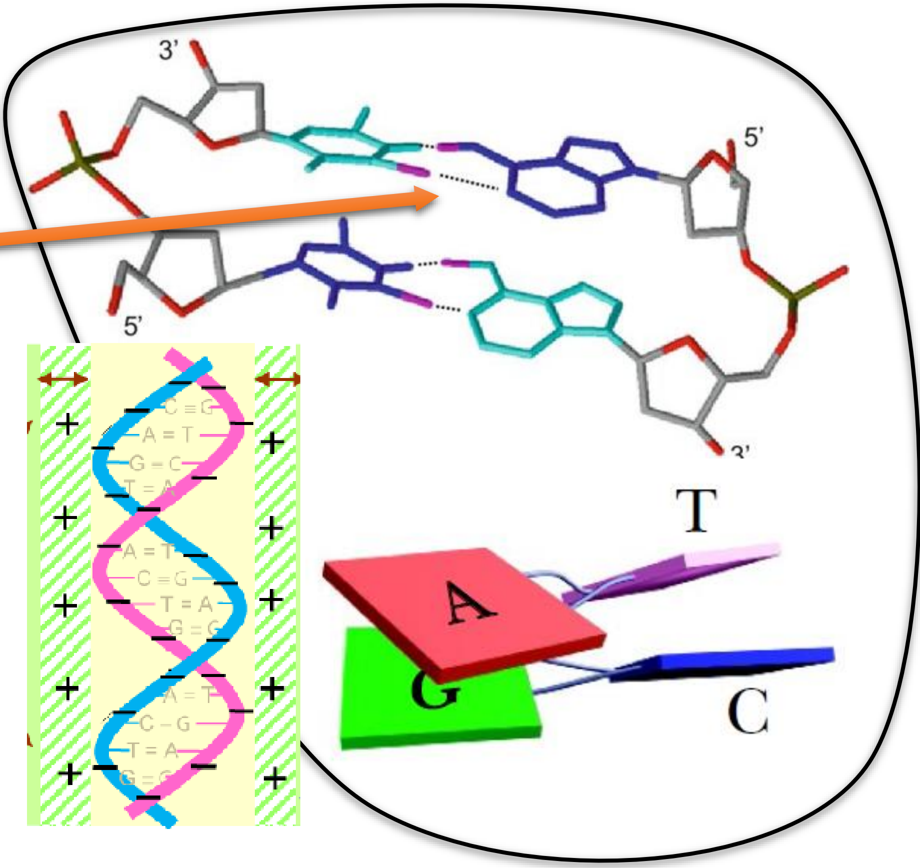
DNA-stabilizing forces



- Hydrogen bonds between complementary bases
- **Hydrophobic stacking:** The hydrophobic rings of the bases interact with each other via hydrophobic interactions and van der Waals interactions.
- Helical twists: Each base pair is rotated with respect to the preceding one for maximal base pairing.

  DNA pairs are not perfectly aligned on top of one another; they are twisted as shown in the figure at the top right. This gives the DNA its helical shape.
- Propeller twists: The bases twist for **optimal base stacking**. Both bases of each pair are twisted as shown in the figure at the bottom right.
- DNA-binding proteins (e.g., histones)
- Ions such as Na^+ or Mg^{2+} (and histones) reduce the repulsion created by the negatively-charged phosphates of the DNA.

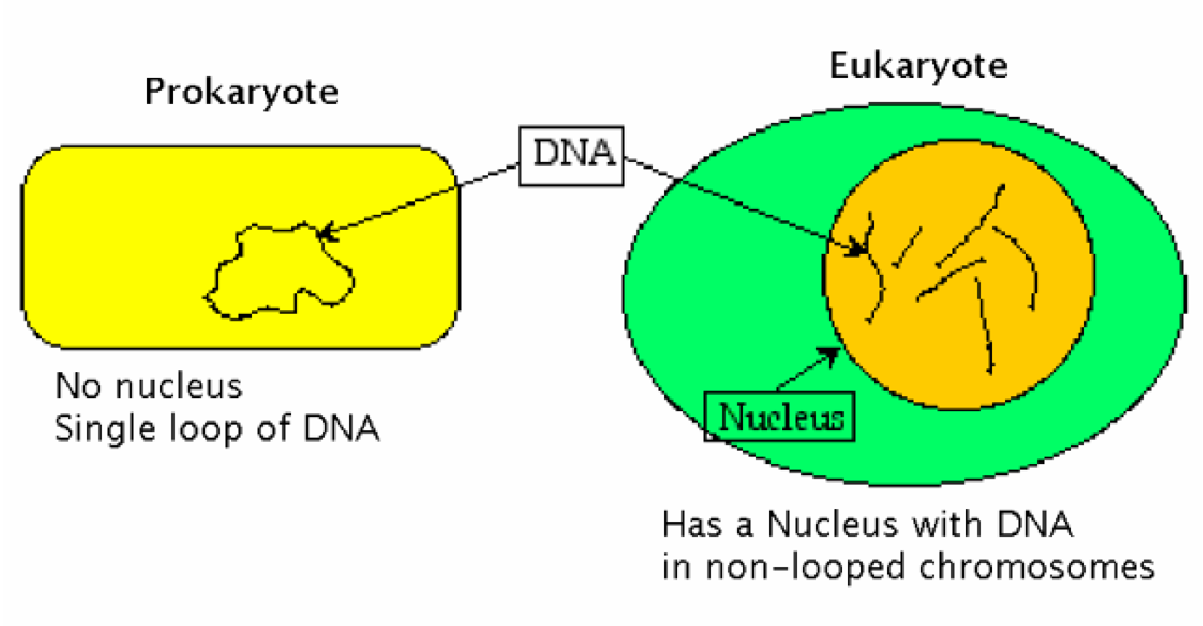
These positive ions neutralizes the negative charge of the phosphate groups, which in turn stabilizes the DNA.



This video could be helpful, click here

The genome of prokaryotes versus eukaryotes

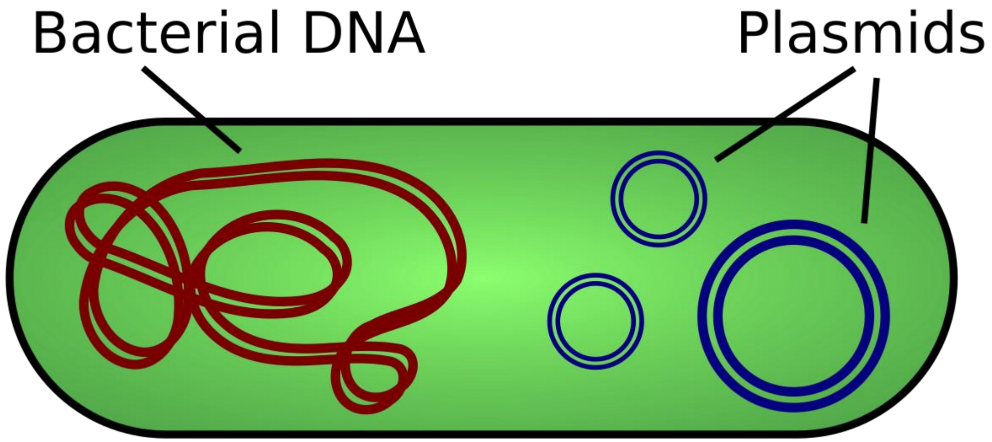
- Genome: the total genetic material of a living being (bacteria vs. human), a species (monkey vs. human), an individual (me vs. you), or a cell (brain vs. liver), etc.
- Prokaryote: an organism that lacks a nucleus or other organelles.
- Eukaryote: an organism that has a true (clearly defined) nucleus.



Bacterial chromosome and plasmids

The genetic materials of bacteria is of 2 types:

1. The chromosome: One circular chromosome of double-stranded DNA.
    - The entire chromosome of the bacterium Escherichia coli is composed of a single circular double-stranded DNA molecule, contains > 4×10^6 base pairs (length of 2 mm) carrying 4200 genes.



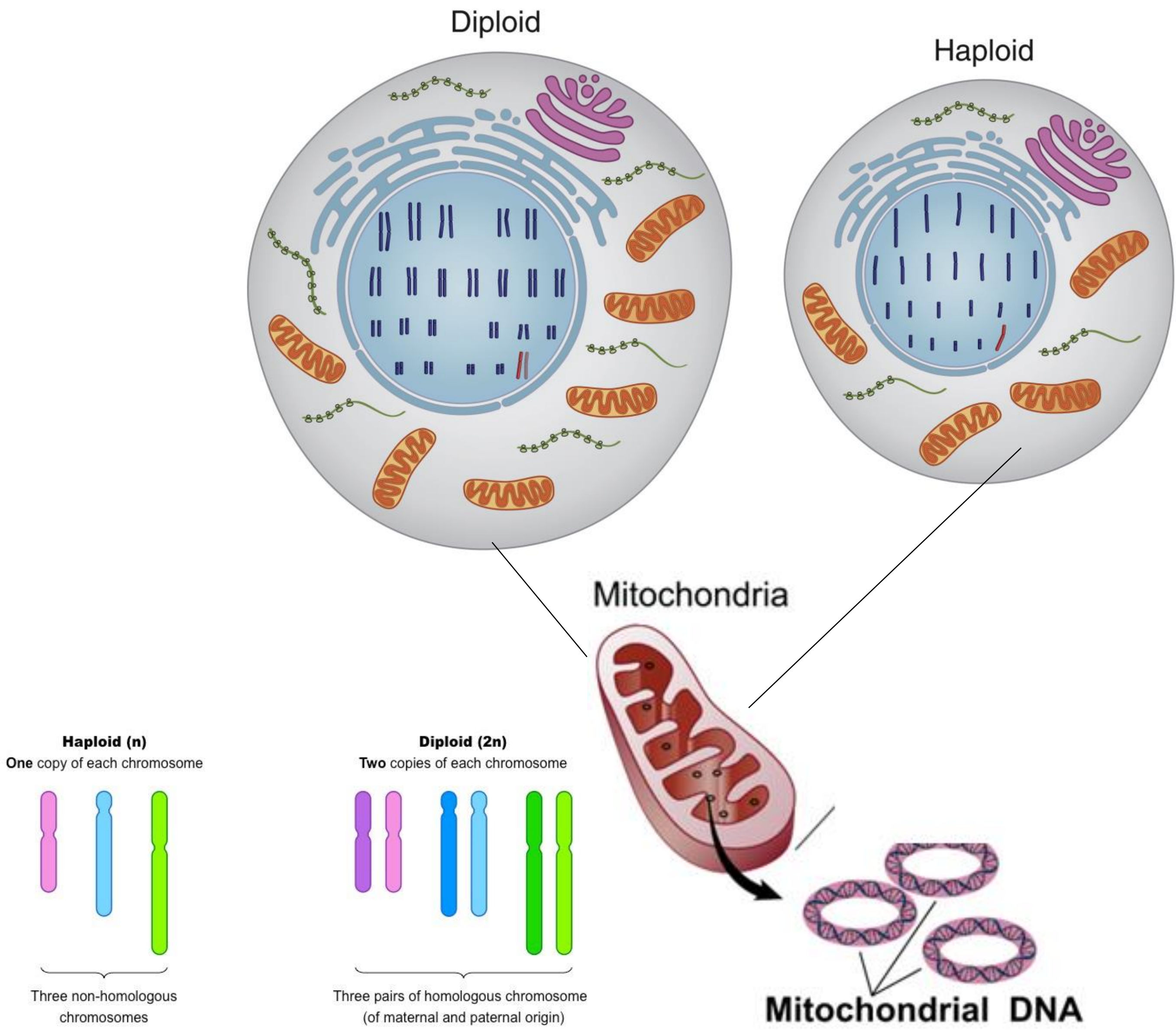
2. **Plasmids** (also found in bacteria, but are different from the bacterial chromosomal DNA), they

1) Small, circular DNA molecules
2) can replicate autonomously independent of the genomic chromosomes
3) not infectious like viruses,
4) can carry genes, some of which confer resistance to antibiotics
5) exist as different types but one plasmid type per cell,
6) can exist as multiple copies.
7) can transfer among bacterial cells.

Human genomes

- The genetic material of humans is of 2 types:
  - The nuclear genome:
    organized as linear chromosomes that consists of ~$3\text{x}10^9$ nucleotides in haploid cells (sperm and egg) with a length of 1m per cell and that carry ~20000 genes.
    - Our somatic cells are diploid.
  - The mitochondrial genome, which constitutes less than 0.1% of the total DNA in a cell (~16500 bp) and encodes 37 genes.

The mitochondrial DNA is circular.



Extra information regarding the previous slide :)

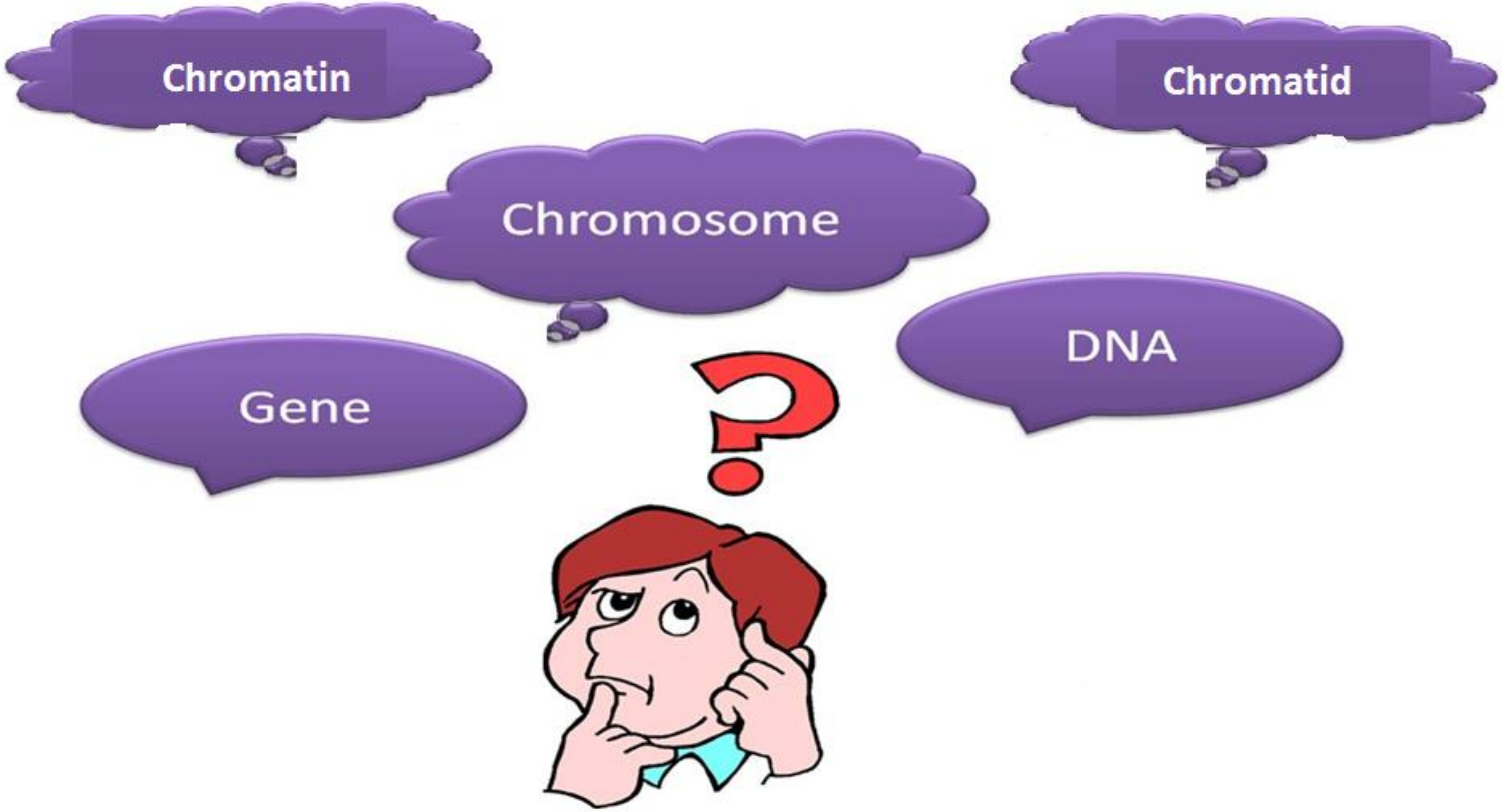
This is **not** included for exam purposes.
Do **not** bother yourself with it!
Read it for **fun** ☺

Endosymbiont theory

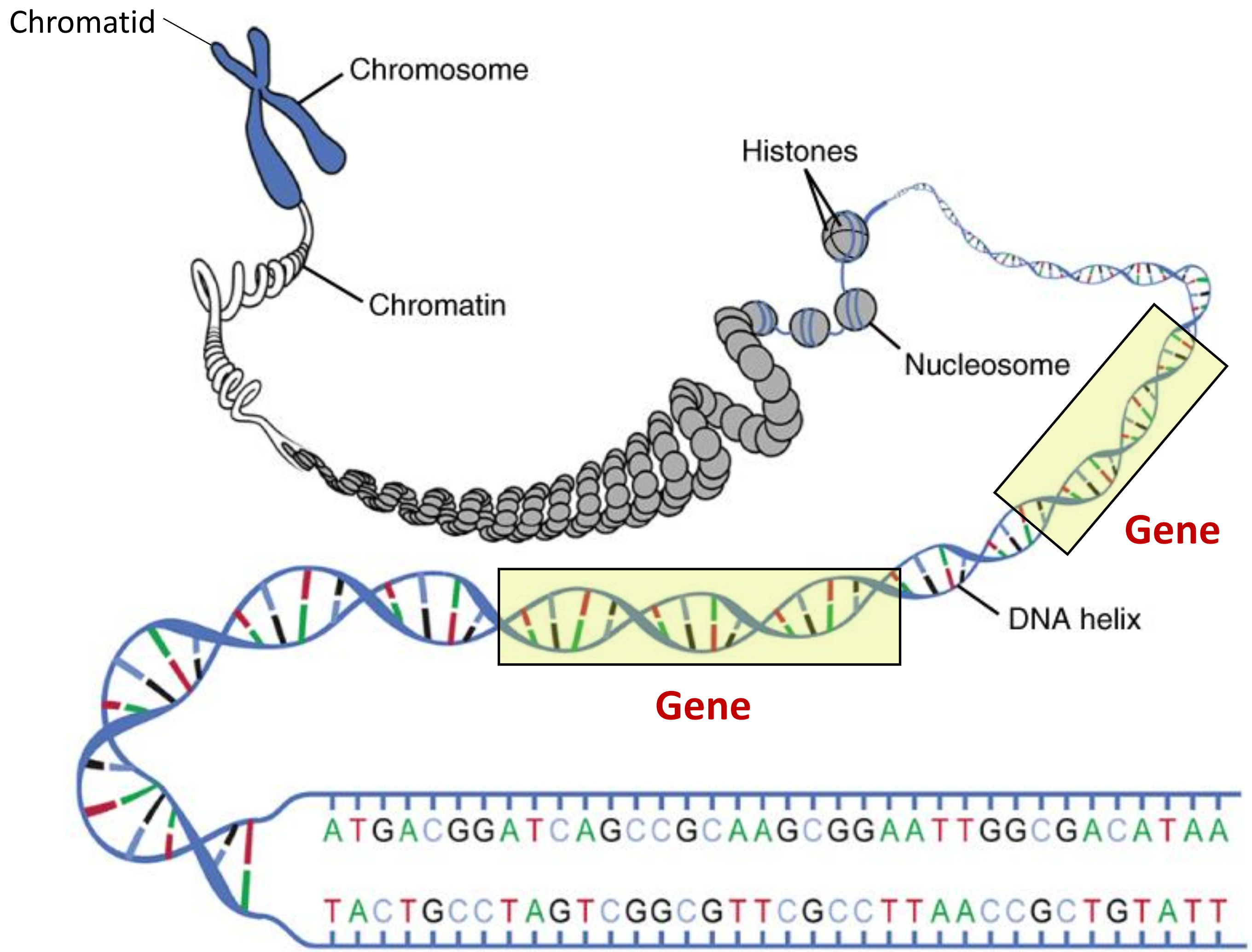
The mitochondrion and the chloroplast are both organelles that were once free-living cells. They were prokaryotes that ended up inside of other cells (host cells). They may have joined the other cell by being eaten (a process called phagocytosis), or perhaps they were parasites of that host cell.

Rather than being digested by or killing the host cell, the inner cell survived and together they thrived. It's kind of like a landlord and a tenant. The host cell provides a comfortable, safe place to live, and the organelle pays rent by making energy that the host cell can use. This happened a long time ago, and over time the organelle and the host cell have evolved together. Now one could not exist without the other. Today they function as a single unit, but we can still find evidence of the free-living past of the organelles if we look closely.

Terms to know

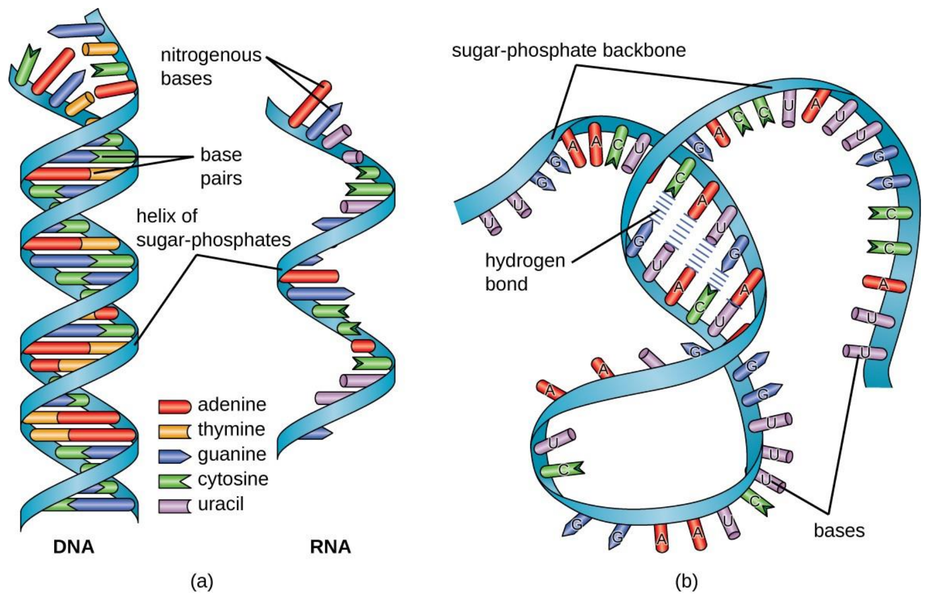


Proffessor said that these concepts will be discussed later on, not in this course, but most of them are mentioned here, so they must be so familiar to you.


Chromatid
Chromosome
Histones
Chromatin
Nucleosome
Gene
DNA helix
Gene
ATGACGGATCAGCCGCAAGCGGAATTGGCGACATAA
TACTGCCTAGTCGGCGTTCGCCTTAACCGCTGTATT

RNA

- It consists of long, unbranched chains of nucleotides joined by phosphodiester bonds between the 3'-OH of one pentose and the 5'-PO_4^- of the next.
- The pentose unit is a ribose (it is 2-deoxyribose in DNA).
- The pyrimidine bases include uracil and cytosine (thymine and cytosine in DNA).
- In general, RNA is single-stranded (DNA is double-stranded) but can form double-stranded regions. If complementary.



DNA: exists in the nucleus; serves as the genetic material

RNA (many types): exist in the nucleus and in the cytosol each has different structure and therefore different function

RNA does not have a precise structure, but it can fold on itself forming hydrogen bonds within the same molecule, if complementary bases meet.

Some RNAs can act as enzymes, known as ribozymes.

Types of RNA

Memorize the first 6 types

Symbol	Non-Coding RNAs	Functions
tRNA	Transfer RNA	mRNA translation (structural)
rRNA	Ribosomal RNA	mRNA translation (structural)
miRNA	micro RNAs	Post-transcriptional transposon repression
piRNA	Piwi-interacting RNA	DNA methylation, transposon repression
siRNA	Short interfering RNA	RNA interference
snoRNA	Small nucleolar RNAs	RNA modification, rRNA processing
PROMPT's	Promoter upstream transcripts	Associated with chromatin changes
tiRNAs	Transcripton initation RNAs	Epigenetic regulation
lincRNAs	Long intergenic ncRNA	Epigenetic regulators of transcription
rasiRNA	Repeat associated small interfering RNA	Involved in the RNA interference (RNAi) pathway
eRNA	Enhancer-like ncRNA	Transcriptional gene activation
T-UCRs	Transcribed ultraconserved regions	Regulation of miRNA and mRNA levels
NATs	Natural antisense transcripts	mRNA stability
PALRs	Promoter-associated long RNAs	Chromatin changes
tasiRNA	Trans-acting siRNA	Represses gene expression
lncRNA	Long noncoding RNA	Regulation of gene transcription

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V1 → V2	35	Don’t memorize	Memorize the first 6 rows
V2 → V3			

Additional Resources Used:

رسالة من الفريق العلمي:

1. Marry Campbell Biochemistry
   (pages : 231 -236)
2. https://www.youtube.com/watch?v=Q2aKY2e92yM&ab_channel=ErikLindahl

كان حبيبنا صلى الله عليه وآله وسلم يقول مستعيناً باالله عز وجل :
"اللَّهمَّ أنتَ عَضُدي ونصيري بِكَ أحاولُ وبِكَ أصاولُ وبِكَ أقاتِلُ"

وقال امرؤ القيس :
فلو أن ما أسعى لأدنى معيشةٍ
كفاني، ولم أطلب قليلٌ، من المال

ولكنما أسعى لمجدٍ مؤثلٍ
وقد يدرك المجد المؤثل أمثالي

وأن المجد ليليق بأمثالكم، فثابروا.