Faculty of Pharmacy
Biochemistry-2

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Lecturer of Biochemistry

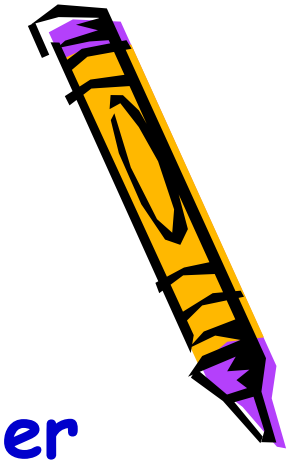
Nucleic Acids

Nucleic Acids

"Molecules of Life"

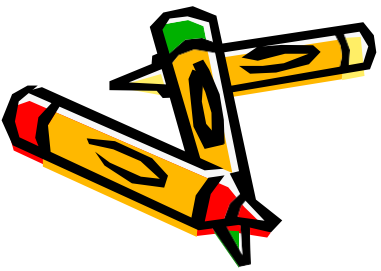
Nucleic acid

- It is an acidic material made in the nucleus of the cell to carry the genetic information in the form of DNA and flows through RNA to ribosomes to produce proteins.
- The building blocks of nucleic acids are called Nucleotides

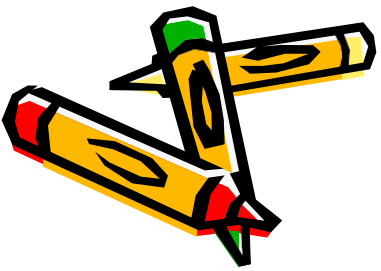


- **Overview:**

- Nucleic acids are not used for either cellular energy or the structural integrity of the cell.
- Nucleic acids are used for the storage &expression of genetic information.



- There are two types of nucleic acids:
  - Ribonucleic acid (RNA).
  - Deoxyribonucleic acid (DNA)

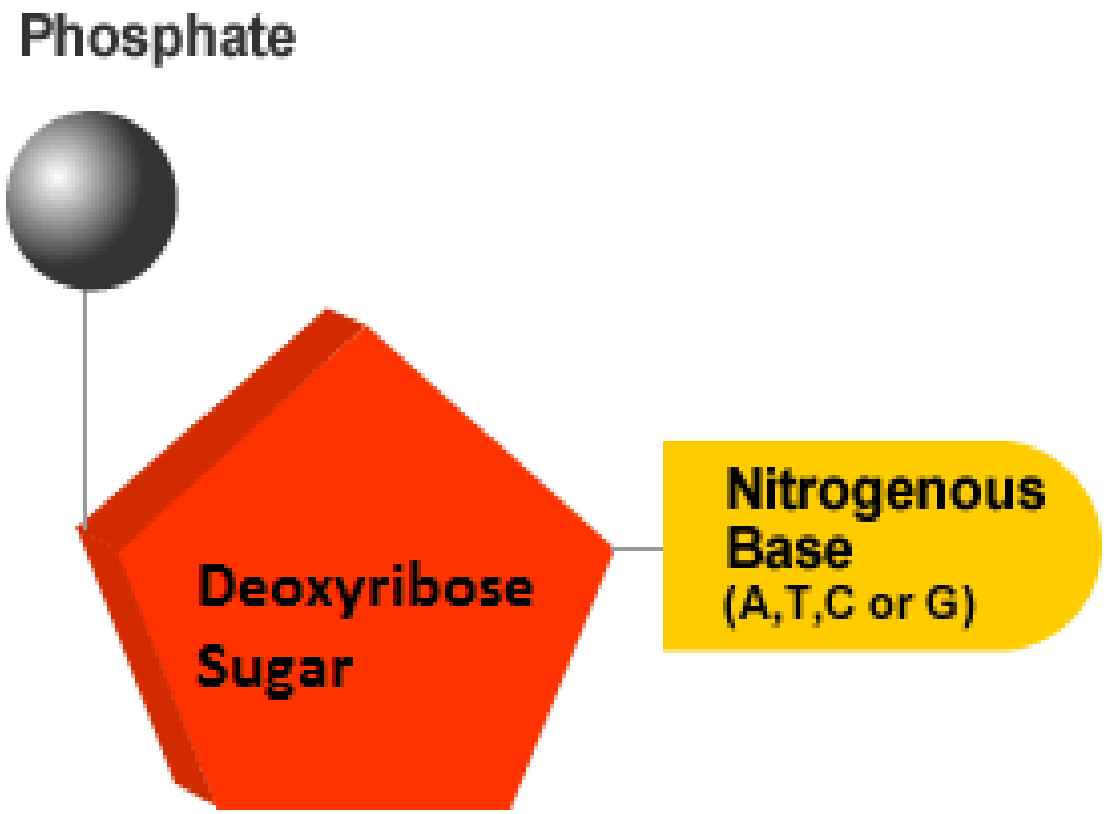


Nucleic Acids

- Nucleic acids are composed of **nucleotides**.
- Each nucleotide is composed of:
  1. Nitrogenous bases.
  2. Pentose sugars.
  3. Phosphate groups.

Nucleotides composition

1. Phosphate group
2. Pentose sugar)ribose or deoxyribose(
3. Nitrogenous base

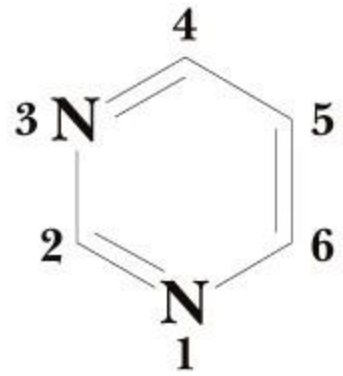


- # Nitrogenous Bases:
- There are five different nitrogenous bases, belonging to 2 families:

1. Purine bases:

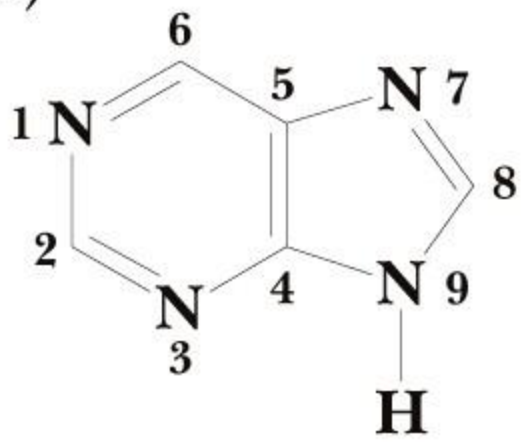
2. Pyrimidine bases:

(a)



The pyrimidine ring

(b)

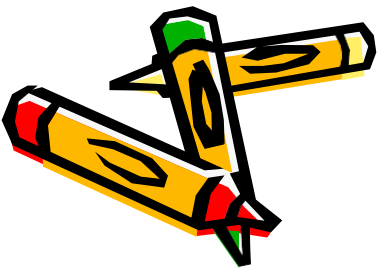


The purine ring system

Nucleic Acids

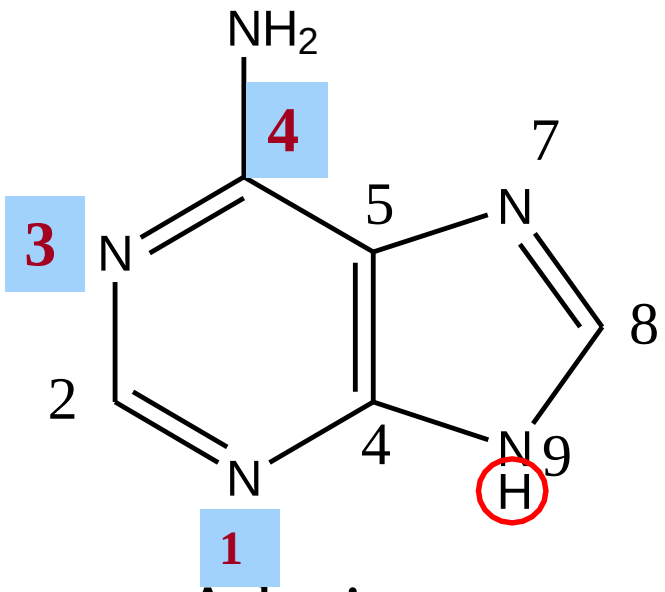
Nitrogenous Bases:

1. Purine bases:
   - Adenine (A)
   - Guanine (G)
2. Pyrimidine bases:
   - Cytosine (C)
   - Uracil (U)
   - Thymine (T)

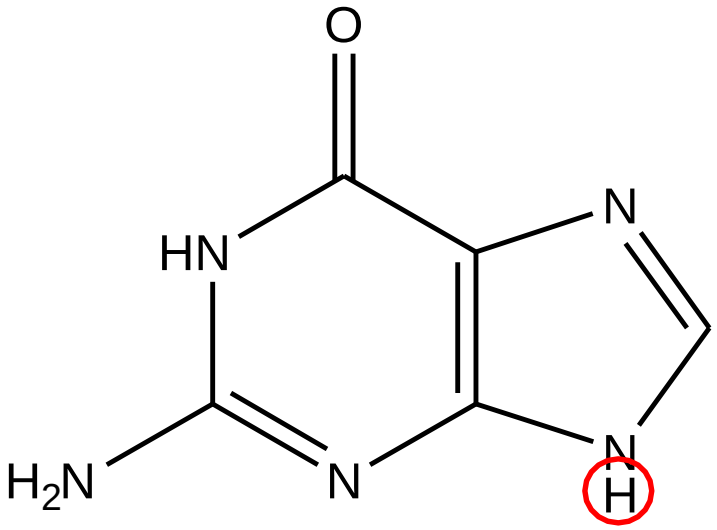


Structure Nitrogenous Bases

.1Purines



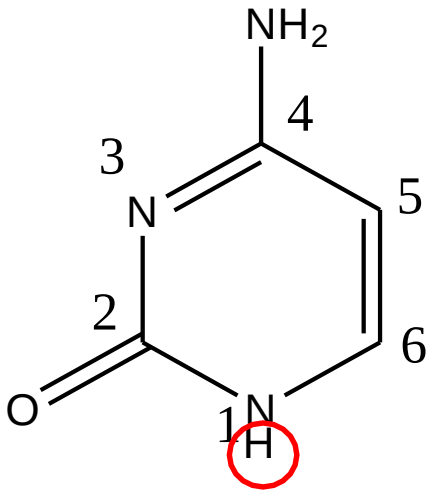
Adenine
(A)



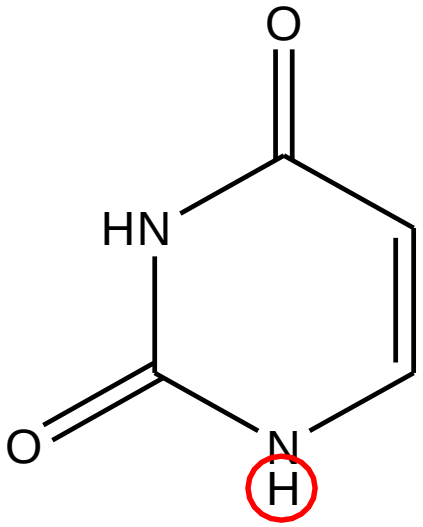
Guanine
(G)

Structure and Nomenclature of Nitrogenous Bases

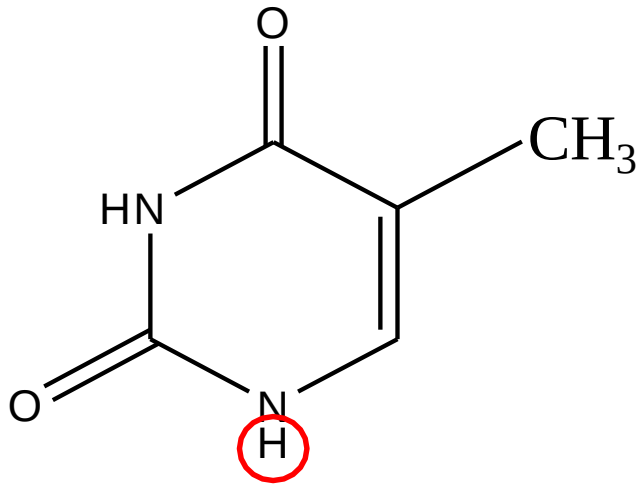
.2Pyrimidines



Cytosine
(C)

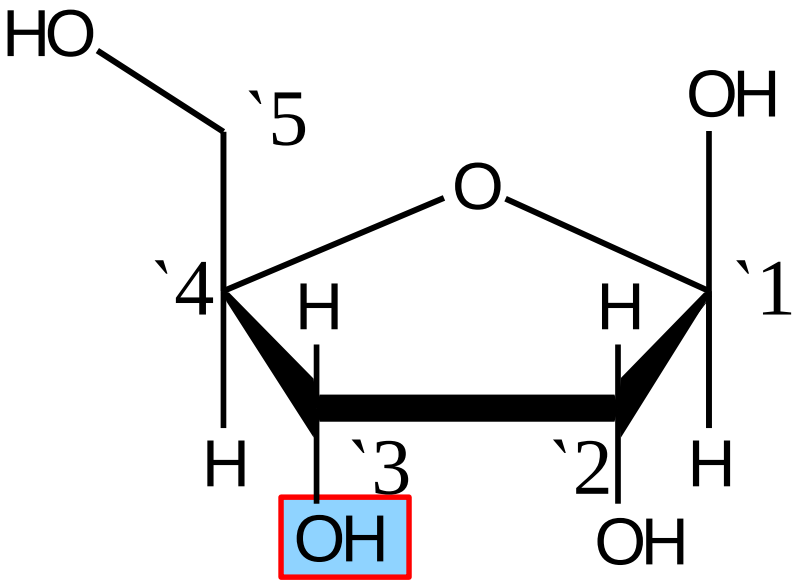


Uracil
(U)

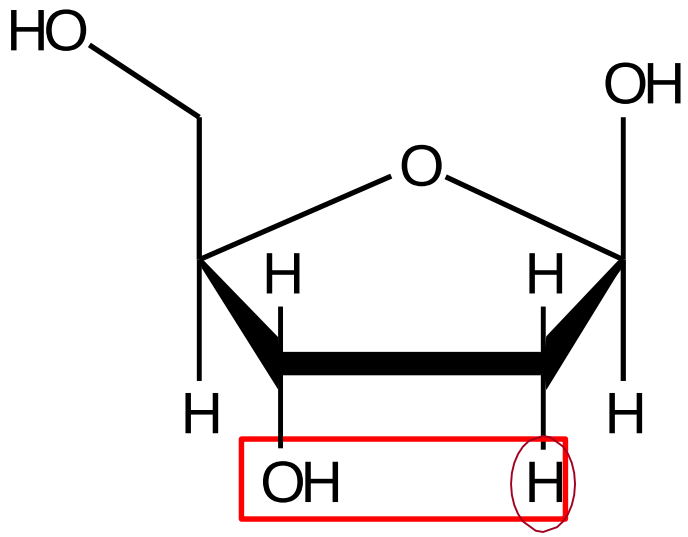


Thymine
(T)

Pentose Sugars

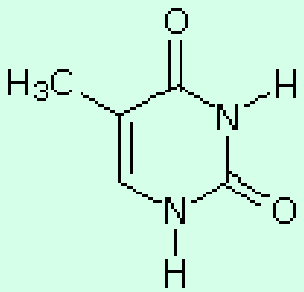
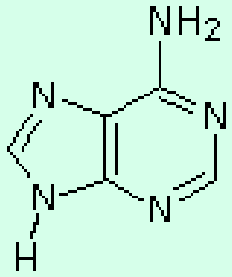
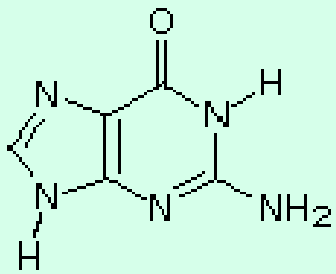
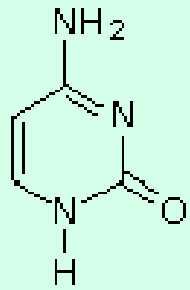
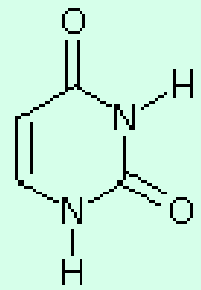
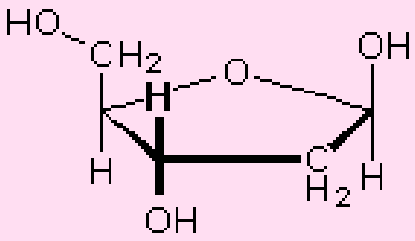
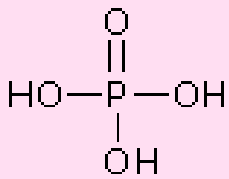
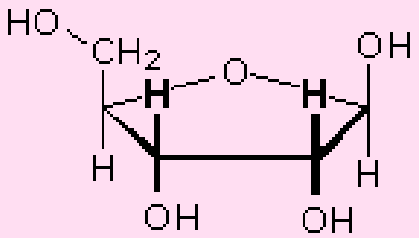


β–D–Ribose



–`2deoxy–β–D–ribose

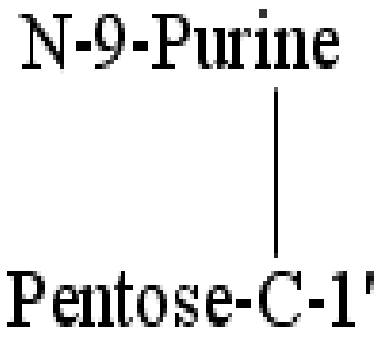
Components of Nucleic Acids

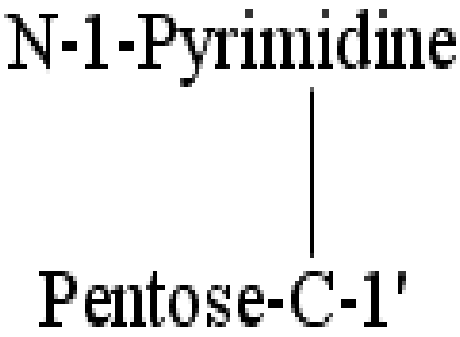
	DNA only	DNA & RNA		RNA only
Nitrogen Bases	 Thymine	 Adenine	 Guanine	 Cytosine	 Uracil
Sugars & Phosphate	 2-Deoxyribose	 Phosphate		 Ribose

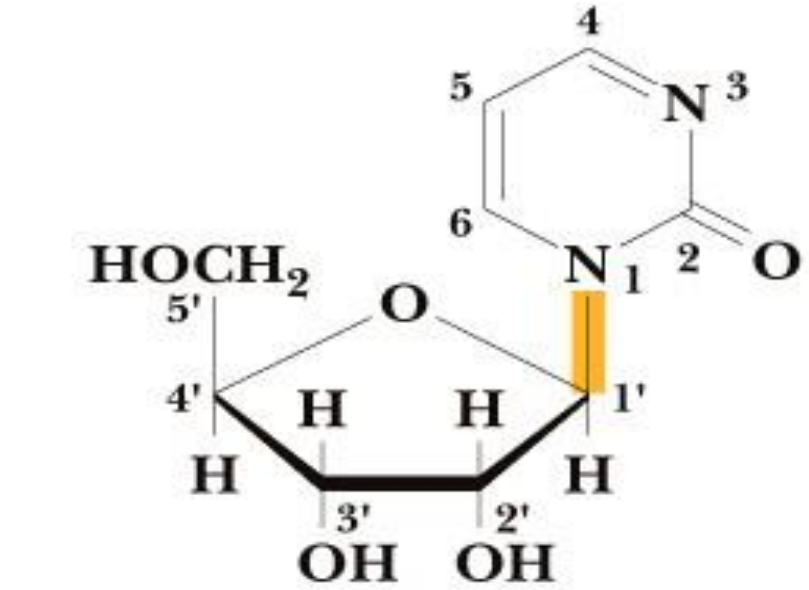
Nucleosides

- **Nucleosides consist of:**
  - **A nitrogenous base.**
  - **A pentose sugar.**
    - **Purine Nucleosides.**
    - **Pyrimidine Nucleosides.**

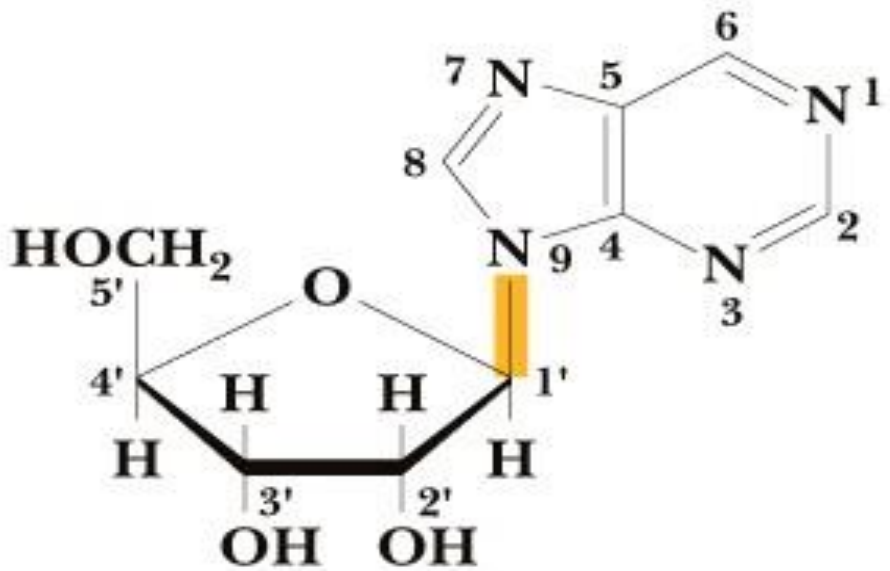
Attachment between nitrogenous bases and sugar





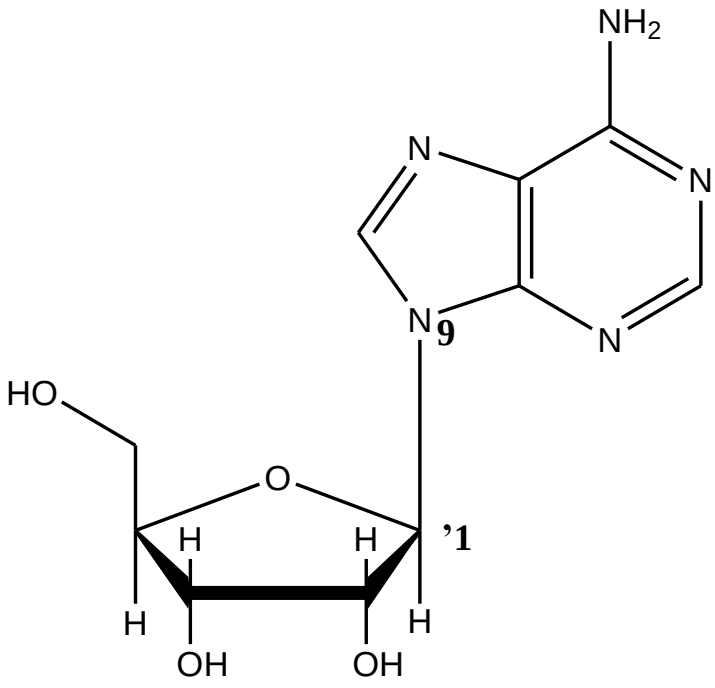


β-N_1-glycosidic bond in pyrimidine ribonucleosides

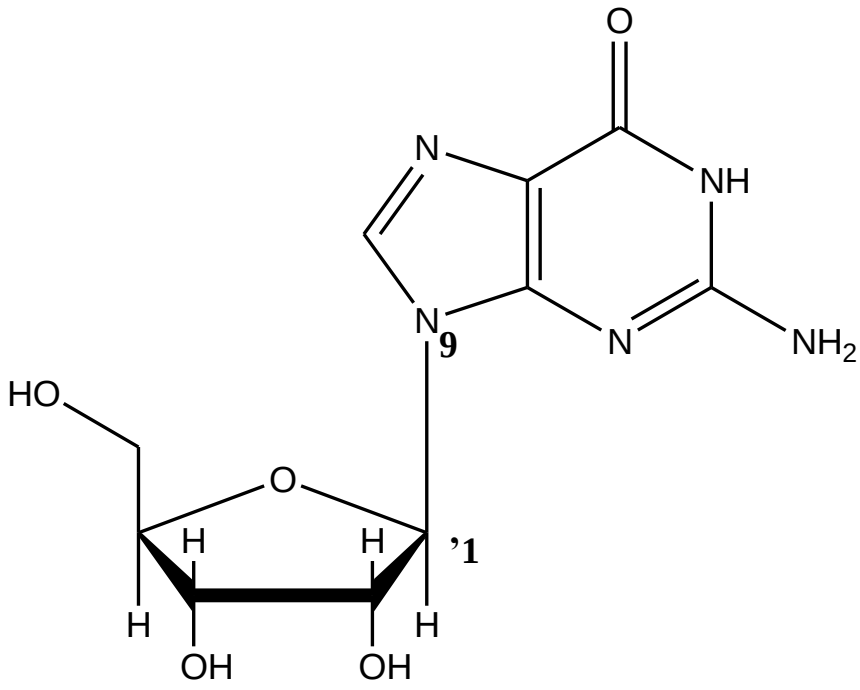


β-N_9-glycosidic bond in purine ribonucleosides

Purine Nucleosides

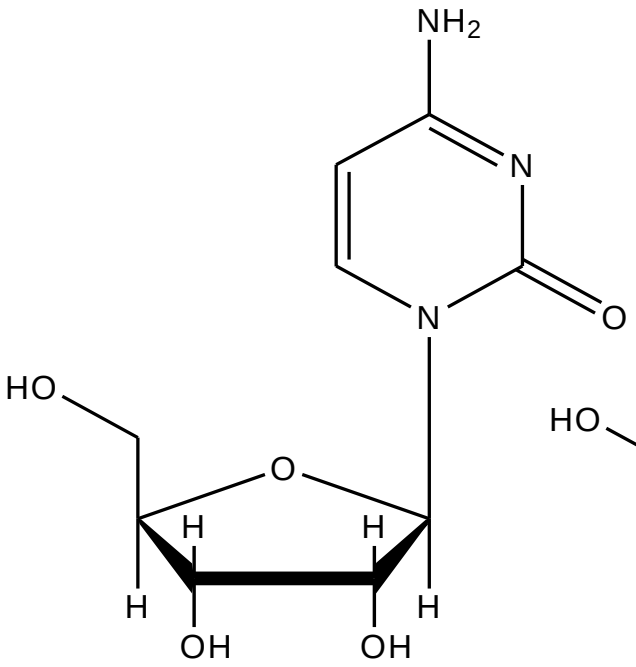


Adenosine

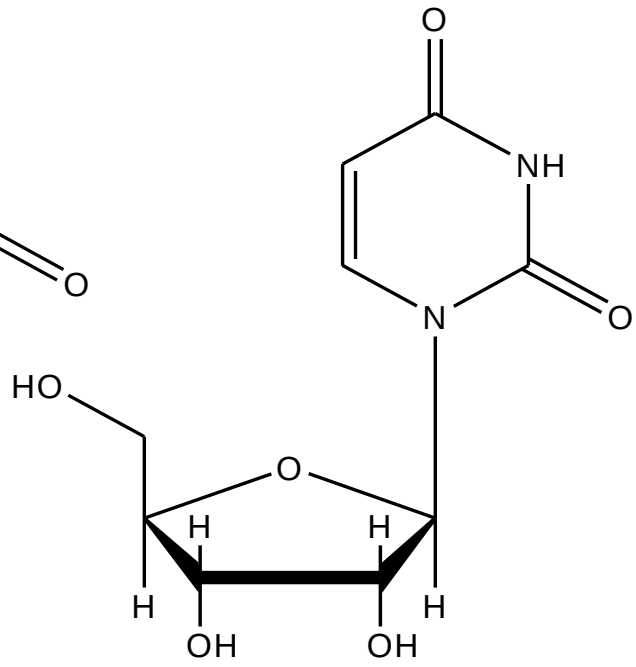


Guanosine

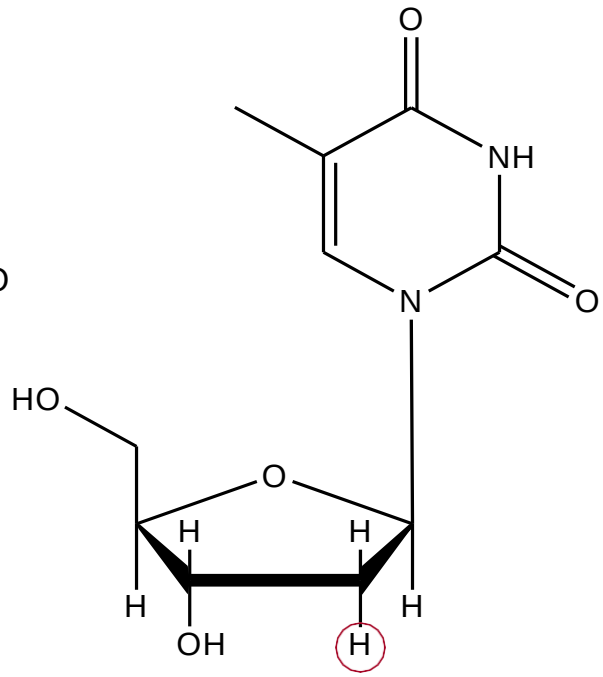
Pyrimidine Nucleosides



Cytidine



Uridine



(Deoxy)
Thymidine

Nucleotides

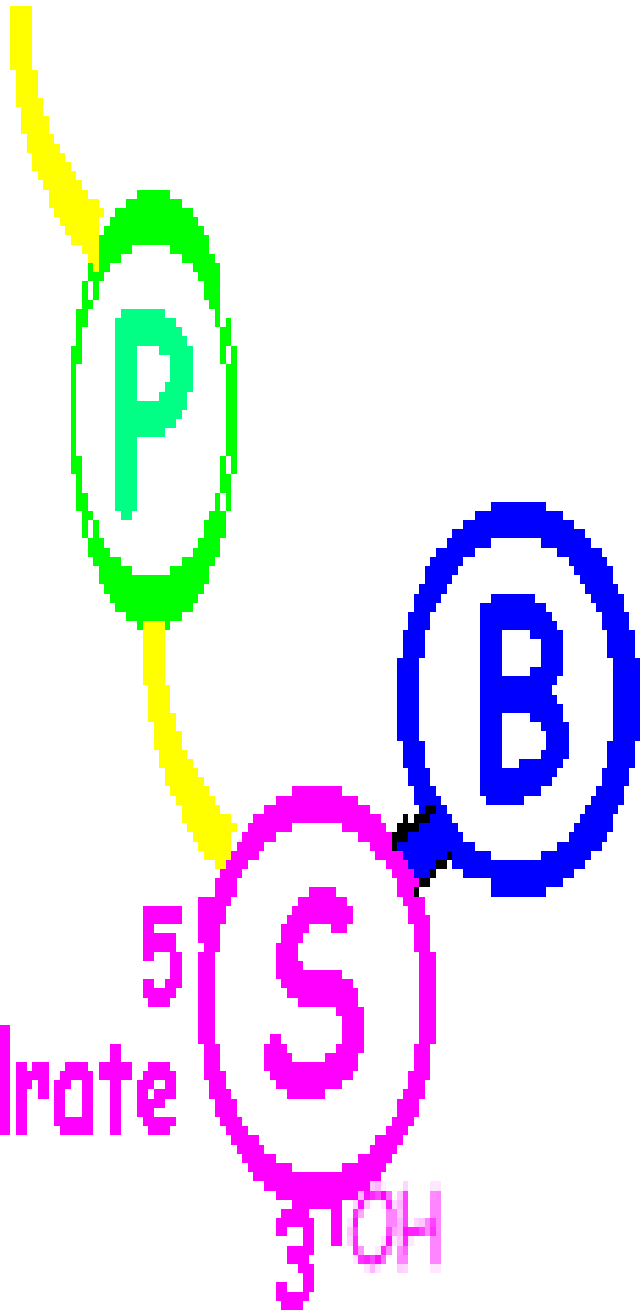
- Nucleotide is consisted of a nitrogenous base with a pentose sugar plus phosphate group

One nucleotide

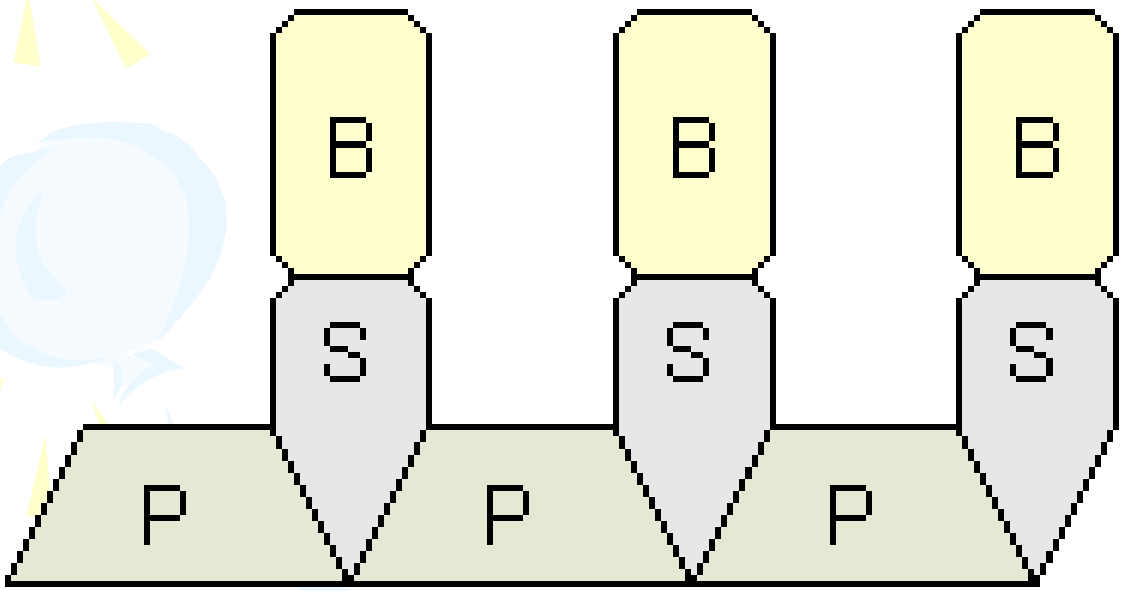
P : Phosphate

B : Organic base

S : "Sugar". Carbohydrate

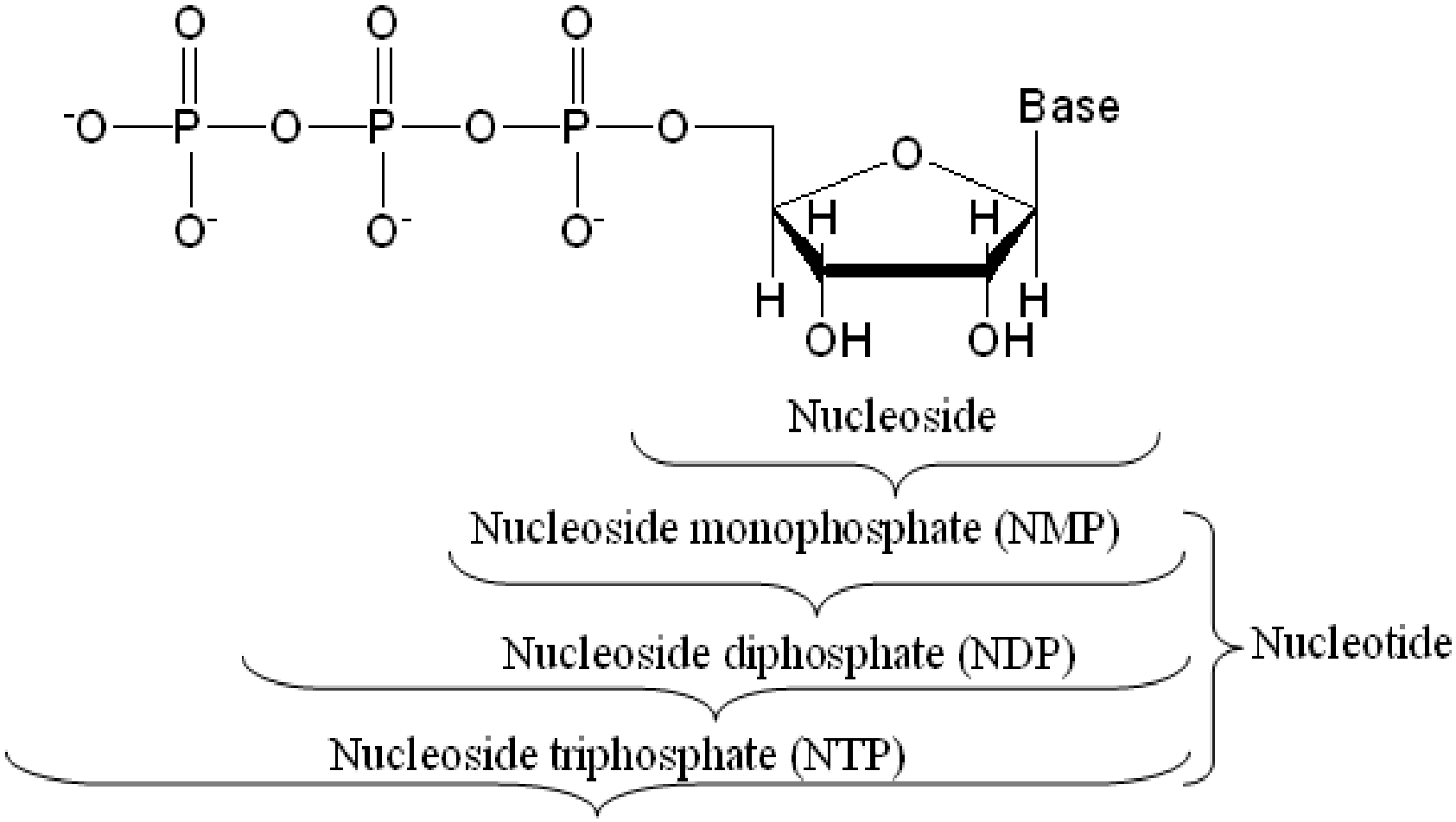


A Trinucleotide

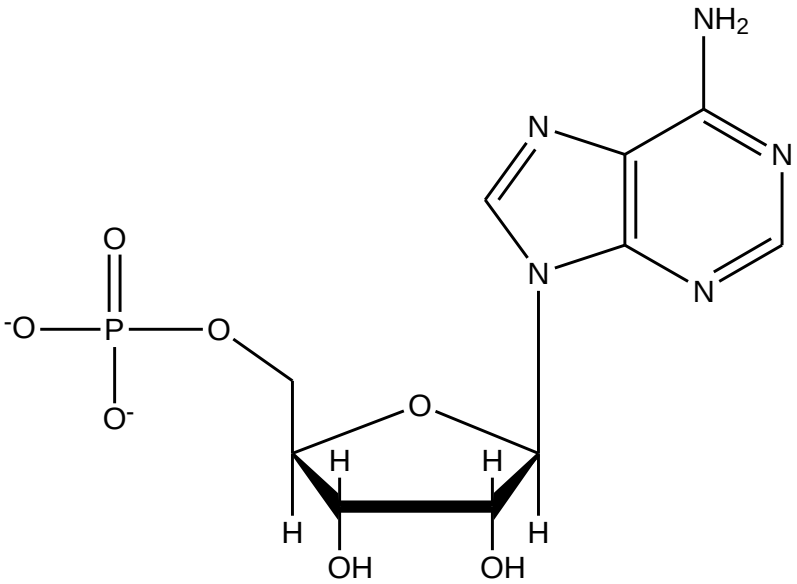


P = phosphate
S = sugar
B = base

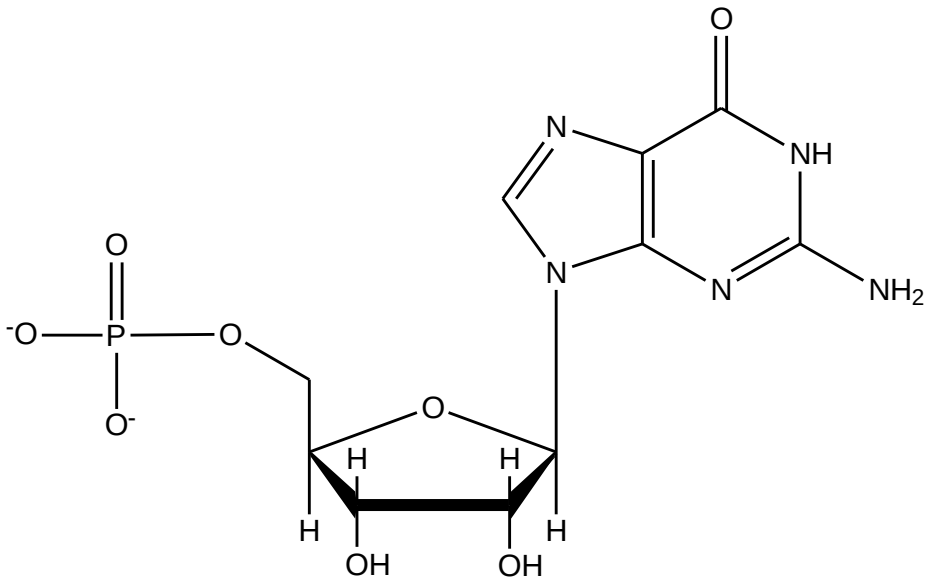
The Major Nucleotides



Nucleotides

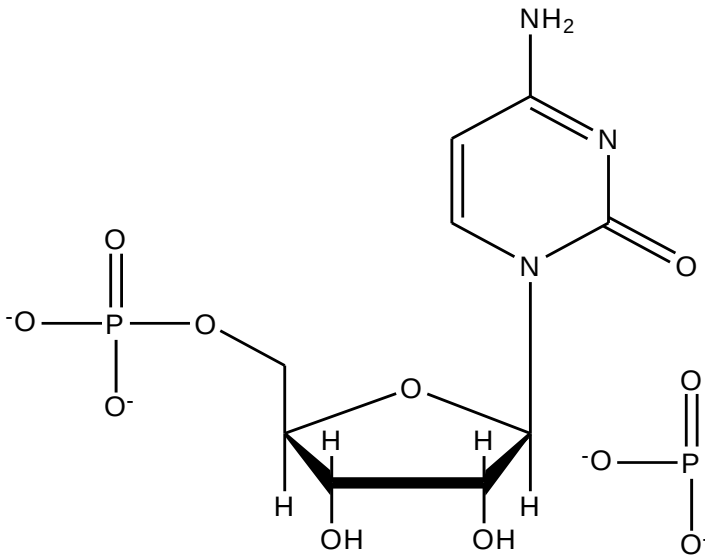


Adenylate

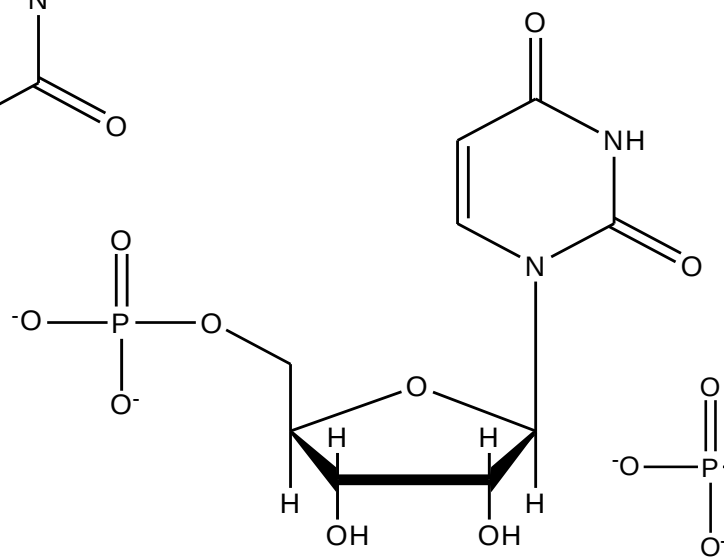


Guanylate

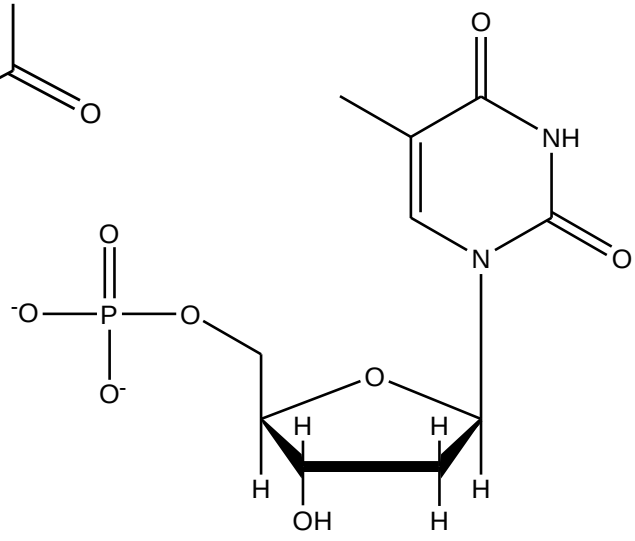
Nucleotides



Cytidylate

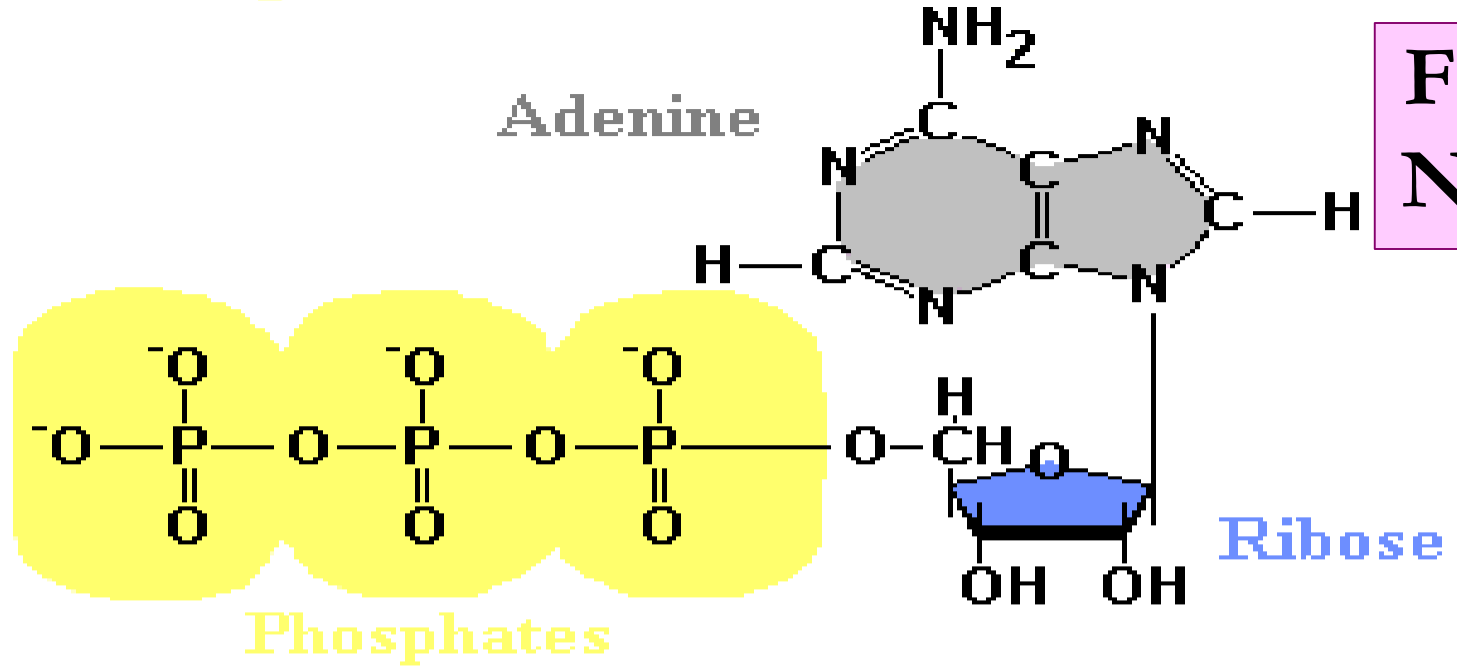


Uridylate

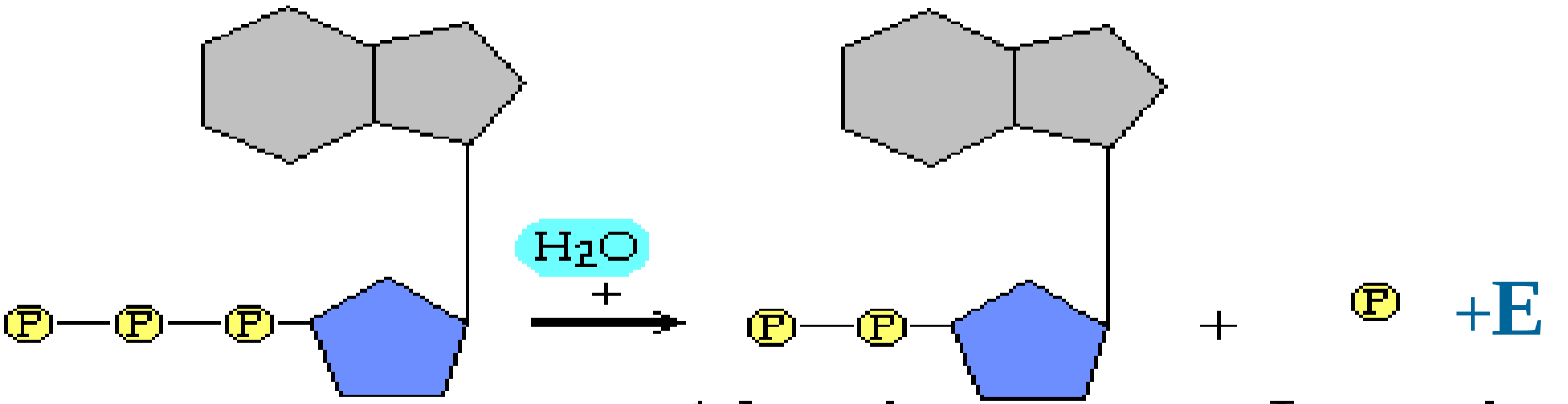


(Deoxy)
Thymidylate

Function of Nucleotides



Adenosine Triphosphate (ATP)

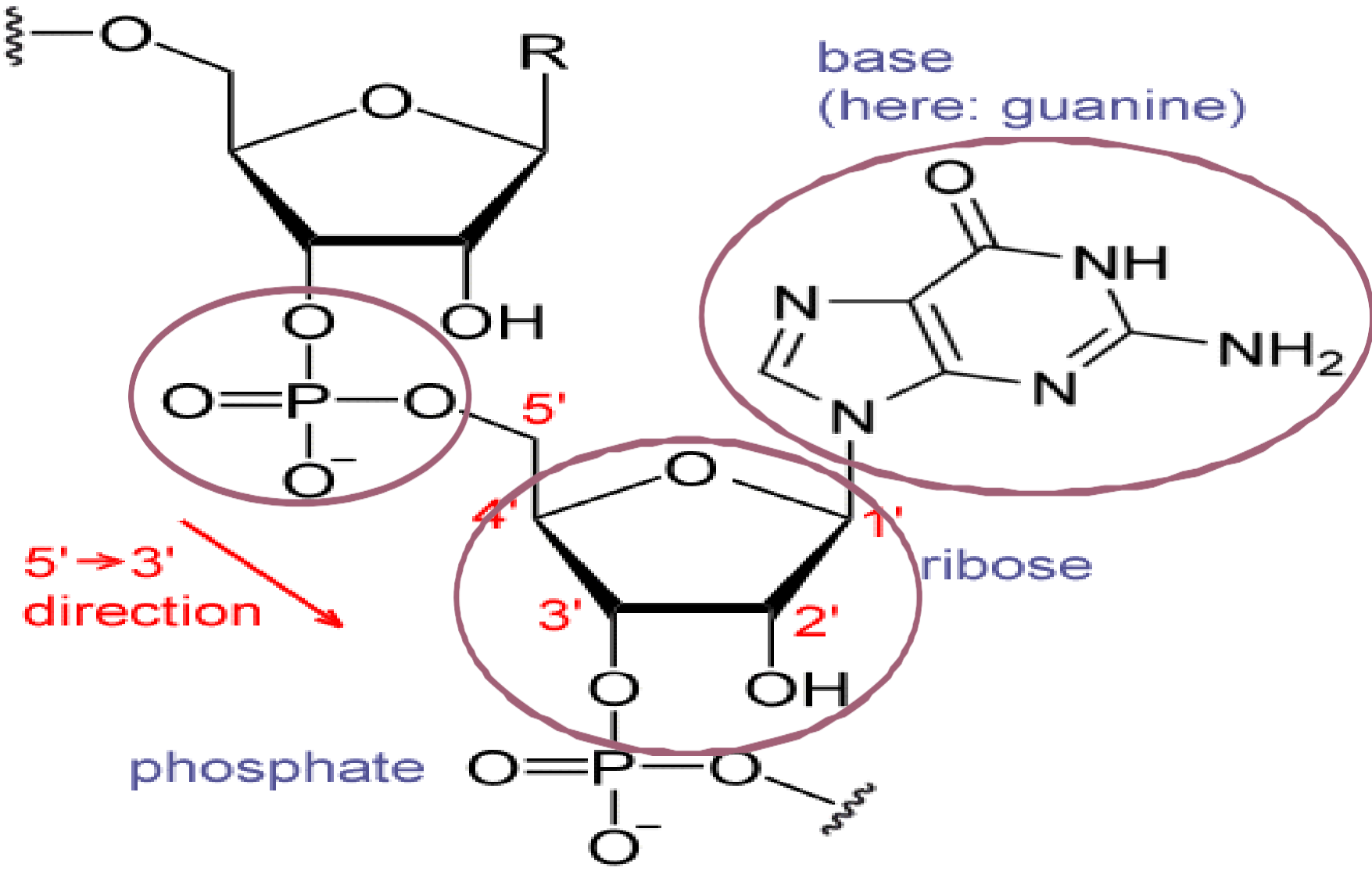


ATP

Adenosine Diphosphate (ADP)

Inorganic Phosphate

Nucleotide structure



Nucleotides bonds

1

Glycosidic bonds (sugar + base(

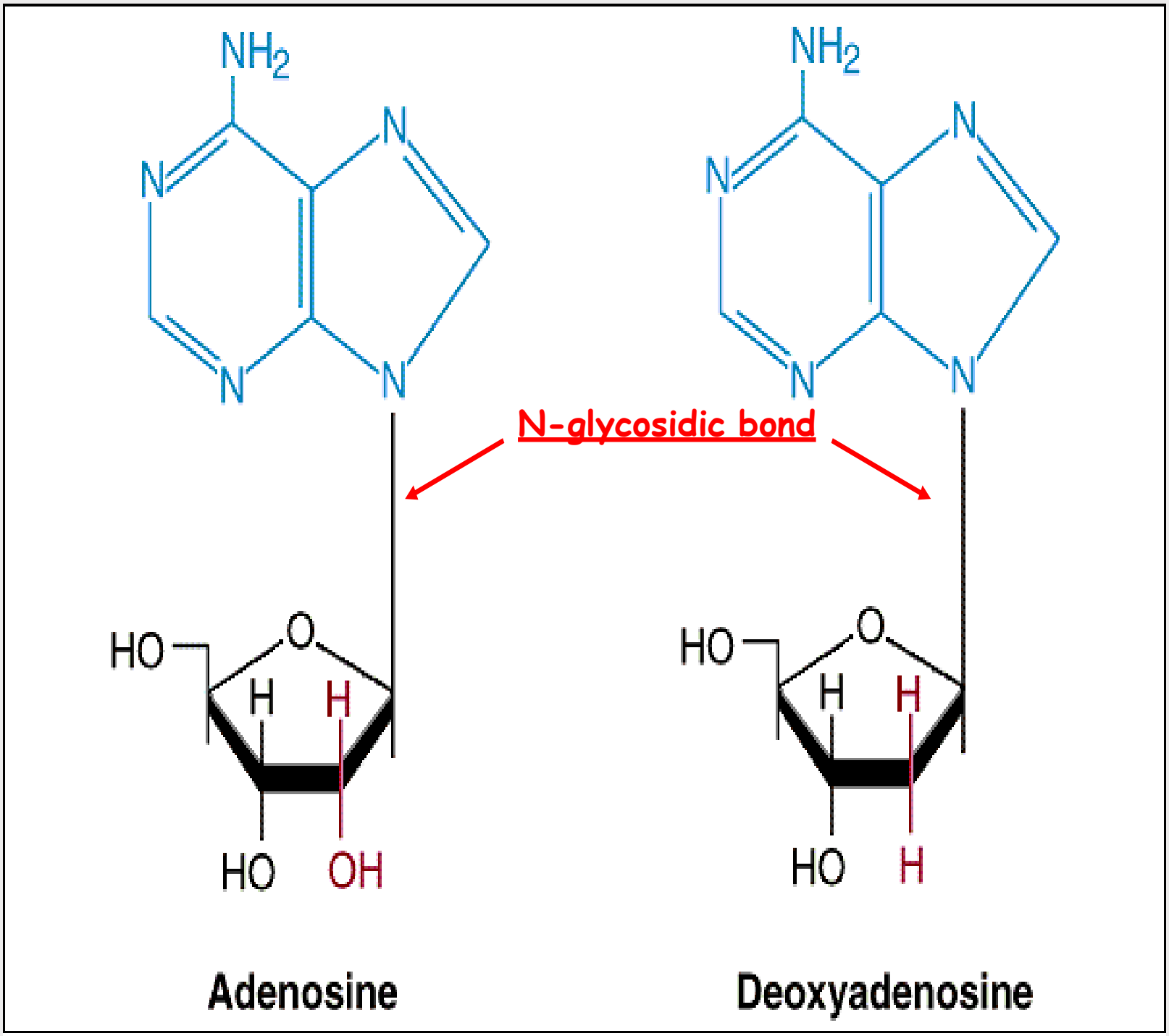
2

Phosphodiester bonds (sugar +phosphate group)

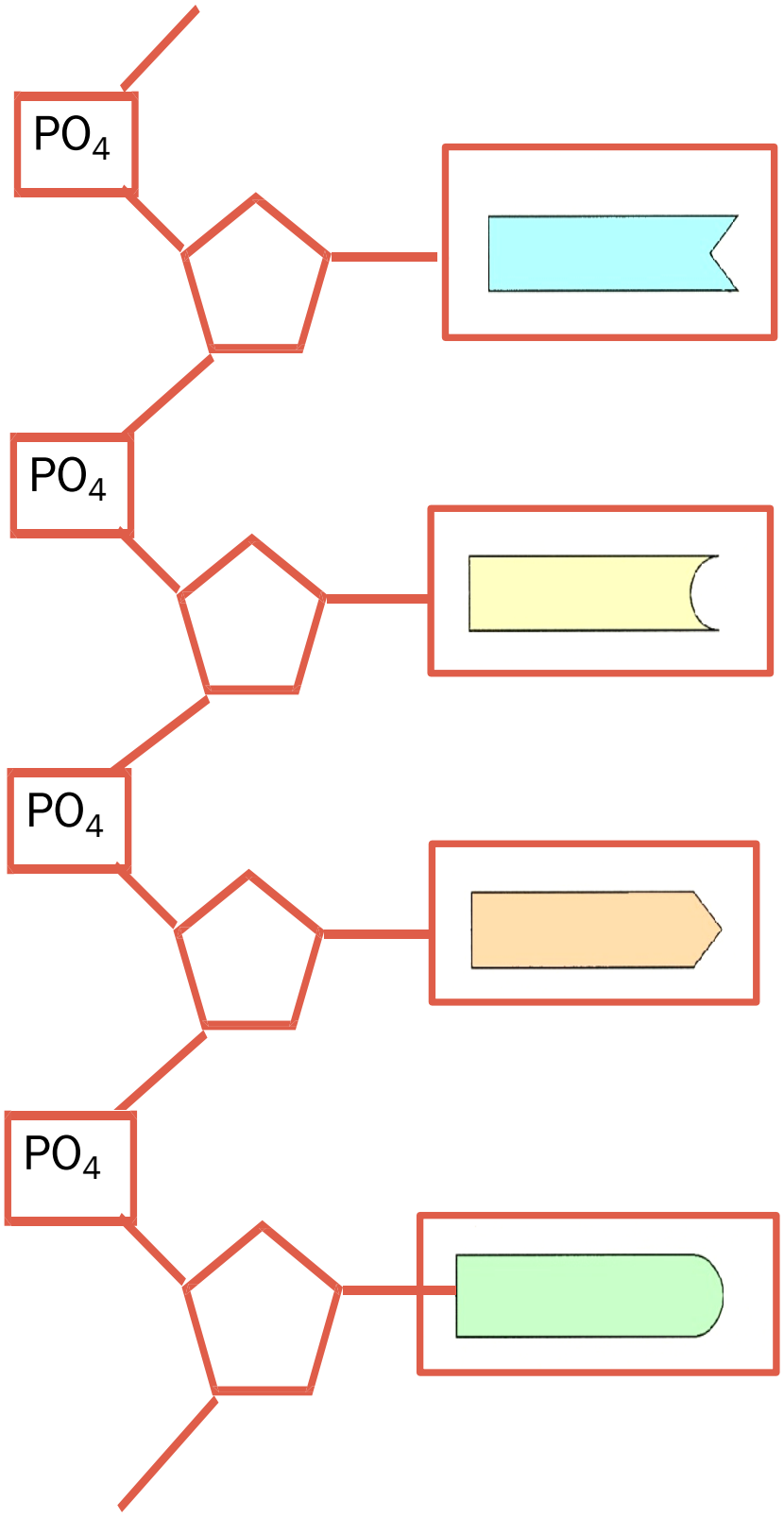
3

Hydrogen bonds
A+T
G+C

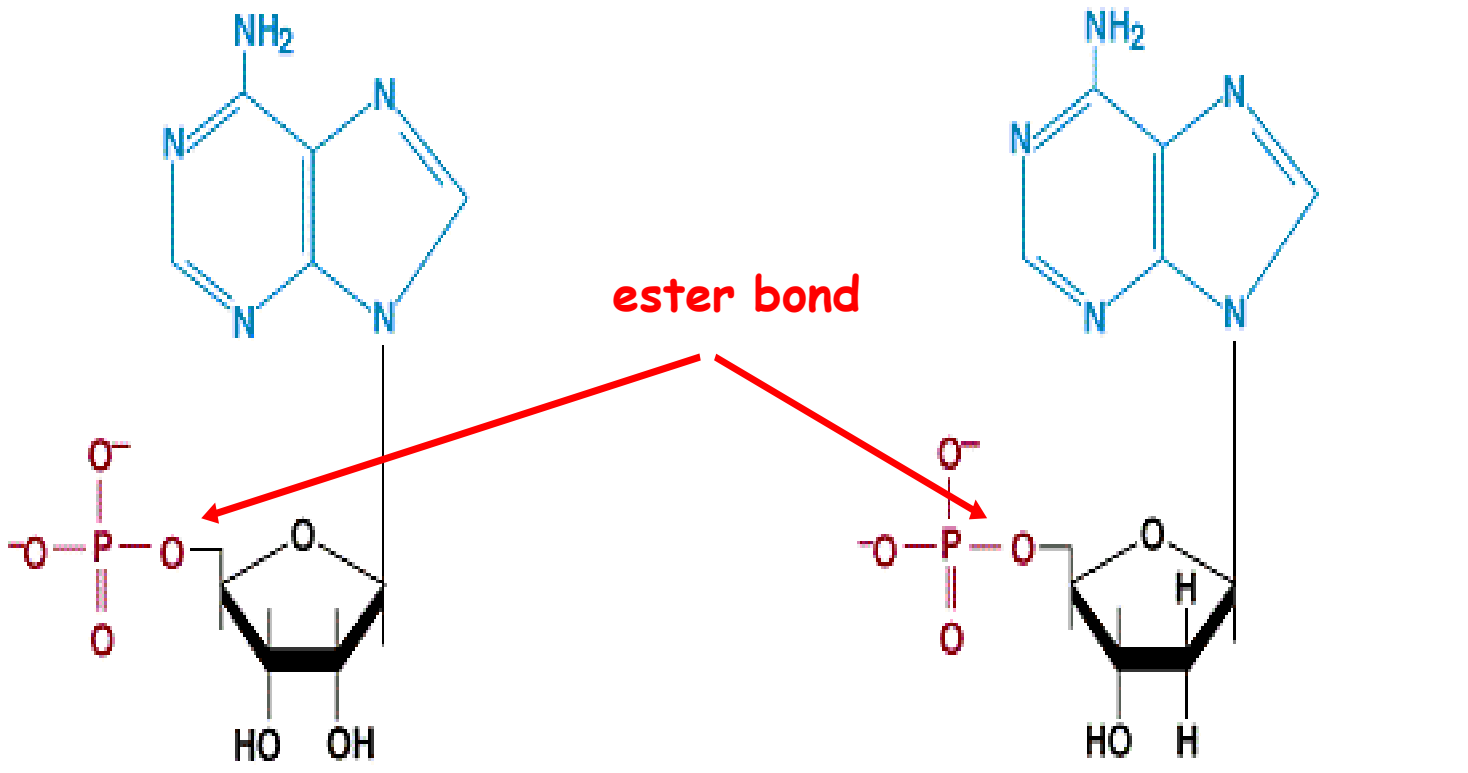
.1Glycosidic bond



2- Phosphodiester bonds



phospodiester bonds join phosphate and sugar into a long chain to act as back bone.



Adenosine 5'-monophosphate (AMP)

Deoxyadenosine 5'-monophosphate (dAMP)

Functions of Nucleotides

A. Adenine Nucleotides (ATP)

B. Guanosine Nucleotides (GTP)

C. Uridine Nucleotides (UTP)

D. Cytidine Nucleotides (CTP)

Functions of Nucleotides

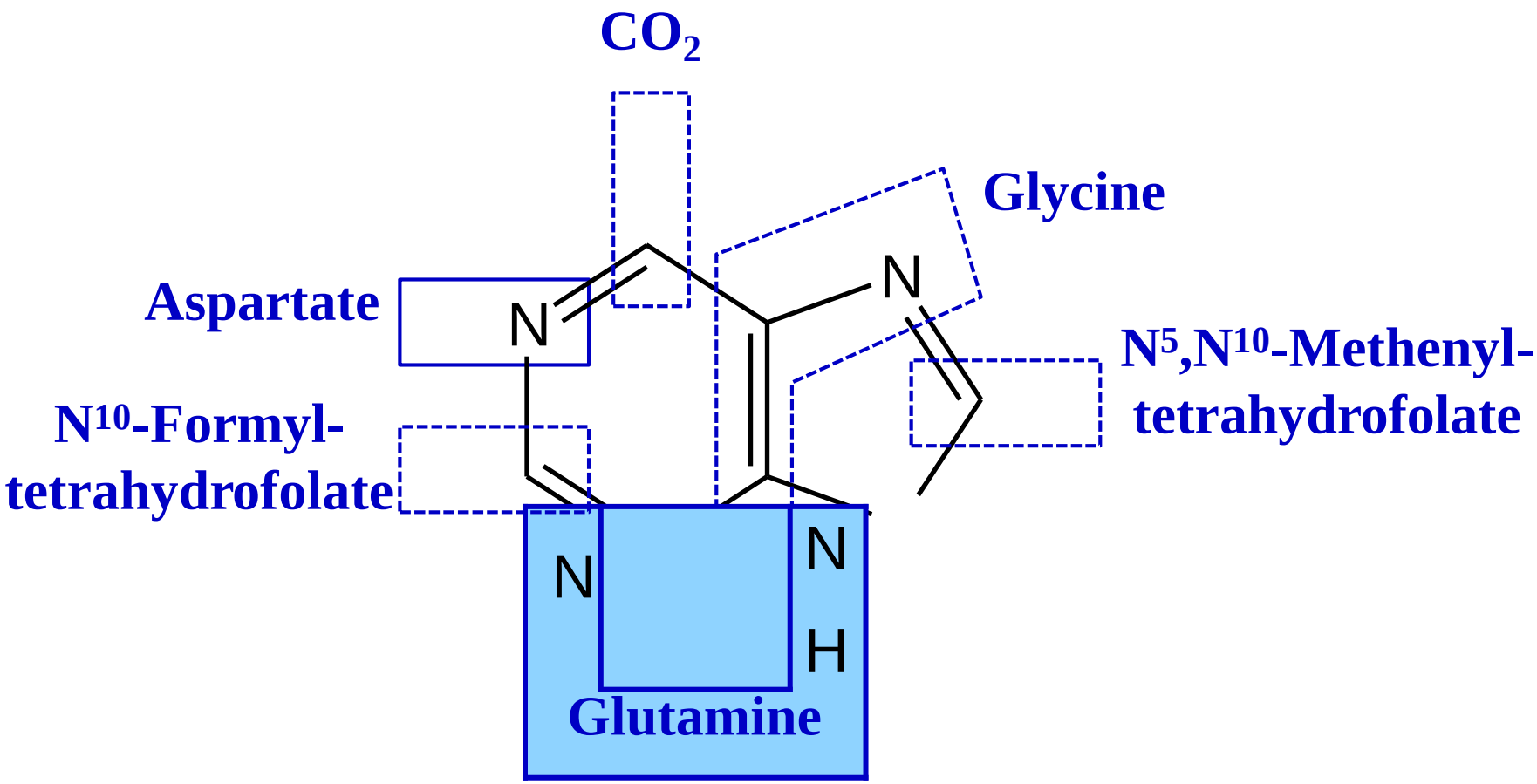
1. Precursor to RNA and DNA.
2. Nucleoside 5‘ – triphosphates are carriers of energy.
3. Bases serve as recognition units.
4. Cyclic nucleotides are 2ry messenger (signal molecules) and regulators of cellular metabolism and reproduction.
5. ATP is central to energy metabolism.
6. GTP drives protein synthesis.
7. CTP drives lipid synthesis.
8. UTP drives carbohydrate metabolism.

De–novo Synthesis of Purine Bases

1. Glycine supplies C–4, C–5 & N–.7
2. Aspartate provides N–.1
3. Glutamine supplies N–3 & N–9 from the amide group.
4. C–8 is provided by the methenyl group of N^5, N^{10}–methenyltetrahydrofolate.
5. C–2 is derived from the formyl group of N^{10}–formyltetrahydrofolate.
6. C–6 is added by carboxylation with CO_2

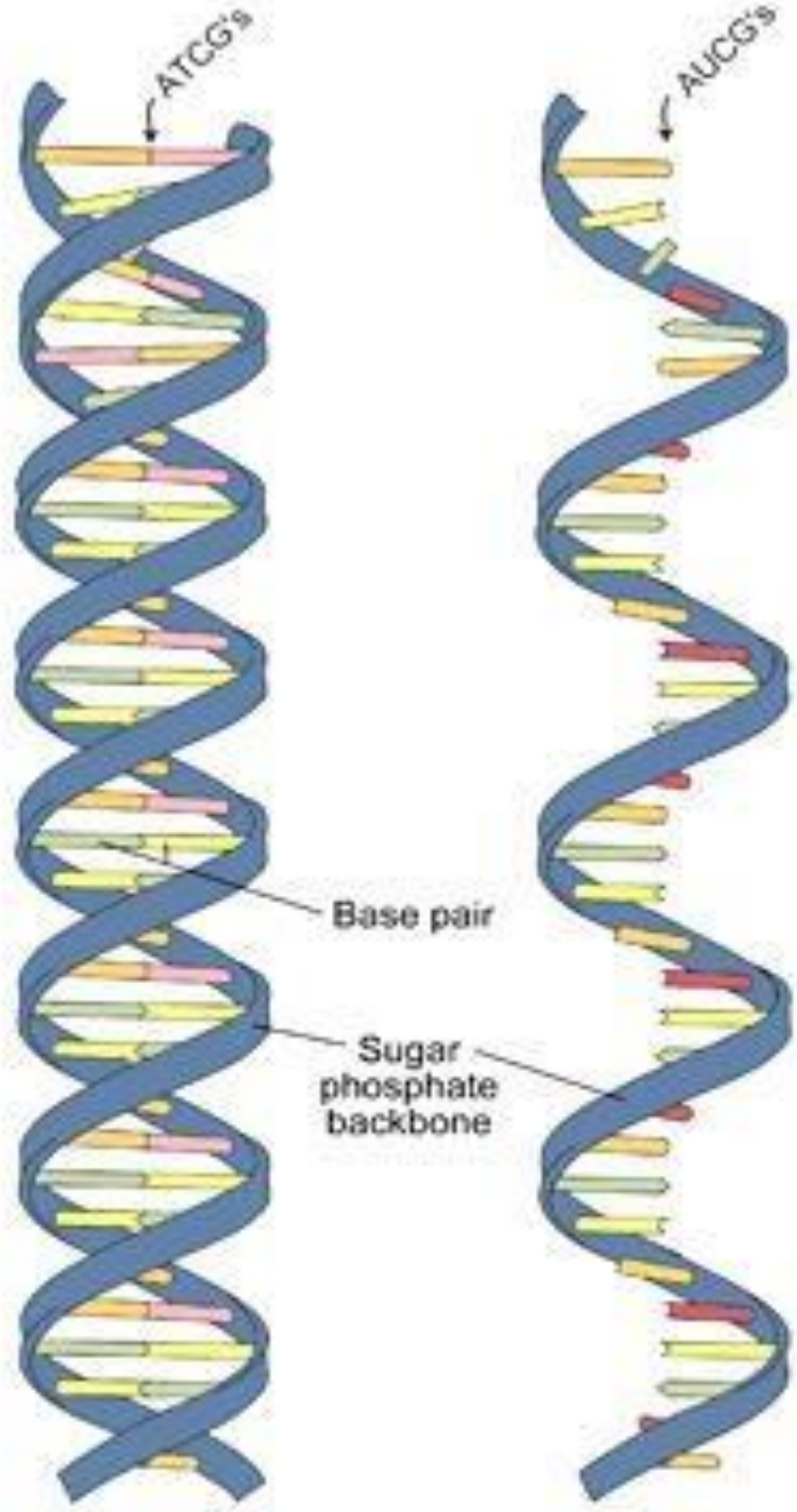
Purine synthesis:

- **Purine Biosynthesis by de–novo pathway:**



Types of Nucleic Acids: DNA & RNA

DNA	RNA
Double strand	Single strand
Contain deoxyribose sugar	Contain ribose sugar
Contain thymine base	Contain uracil base
Found inside nucleus	Found in cytoplasm



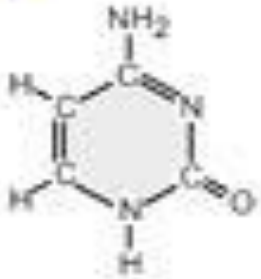
DNA

Deoxyribonucleic acid

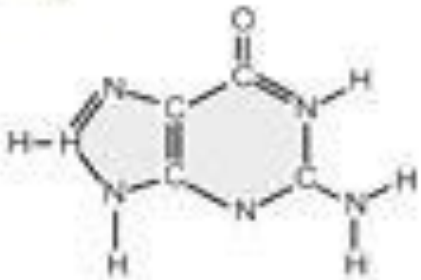
RNA

Ribonucleic acid

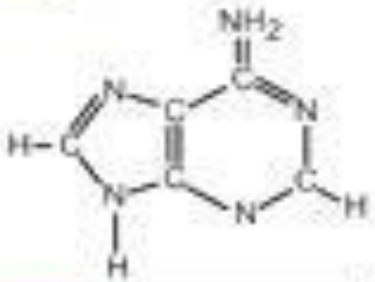
C Cytosine



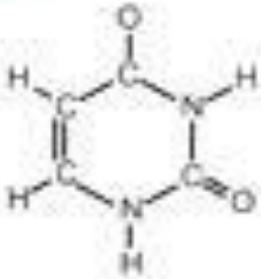
G Guanine



A Adenine



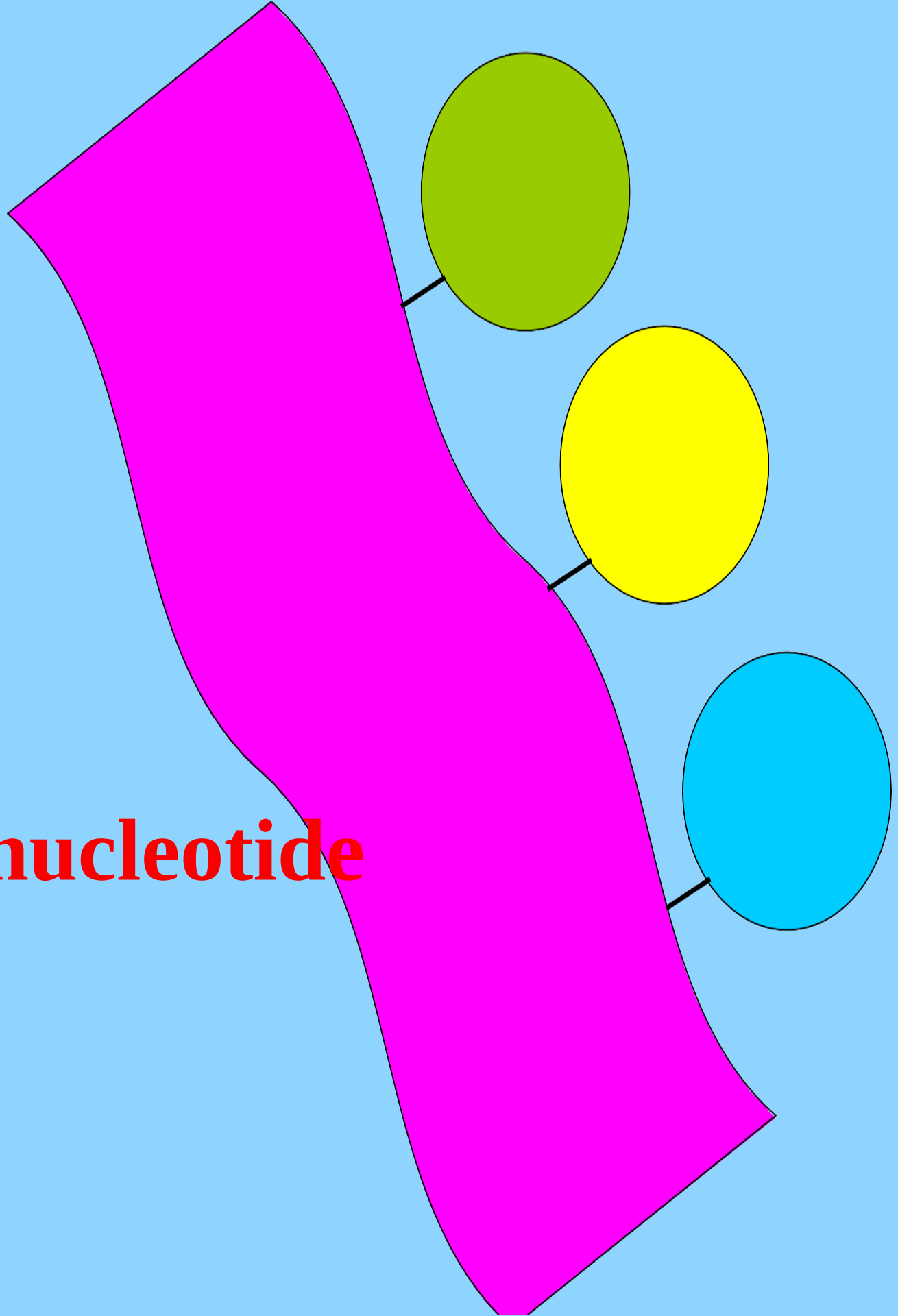
U Uracil



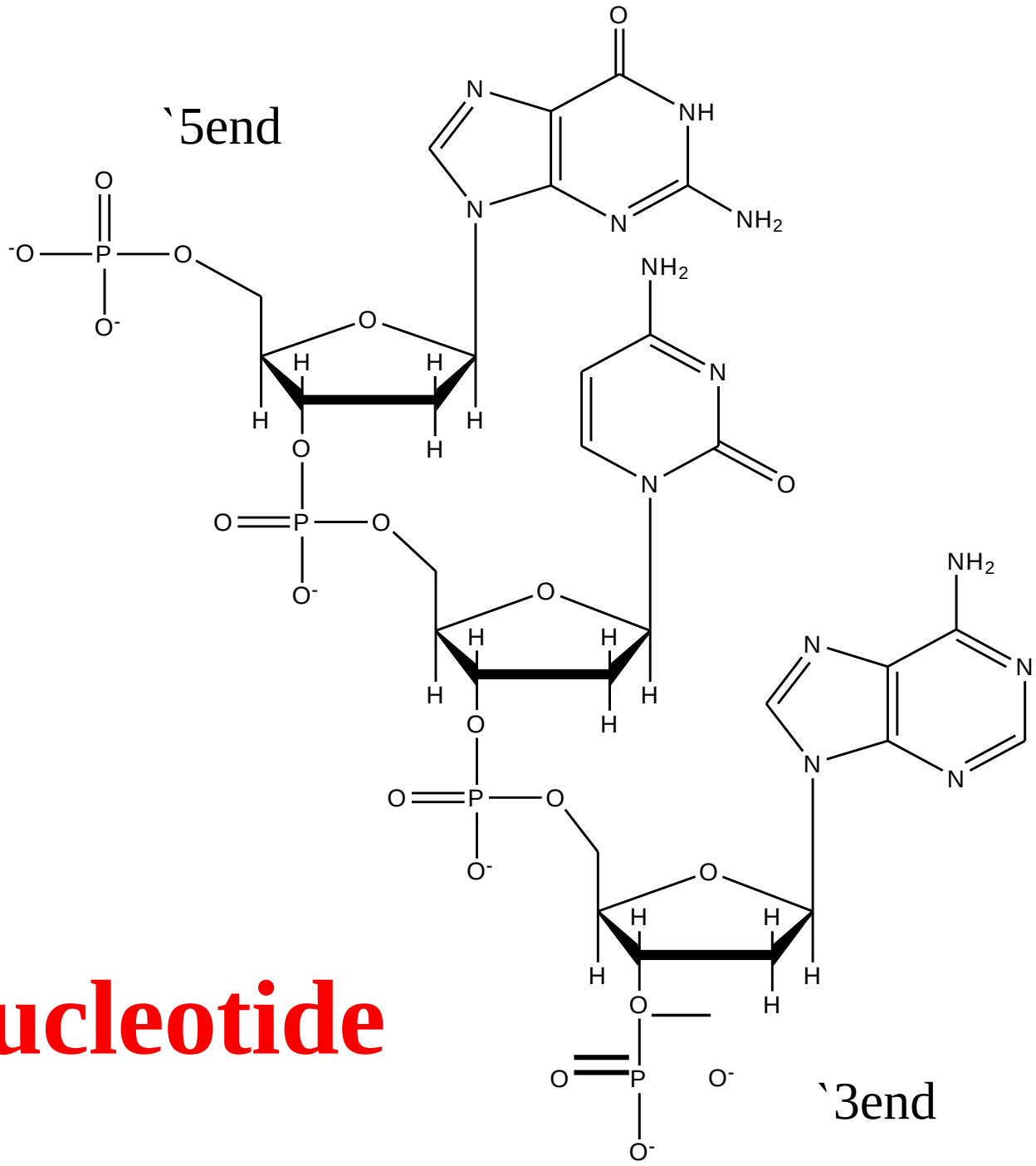
replaces Thymine in RNA

Nitrogenous Bases

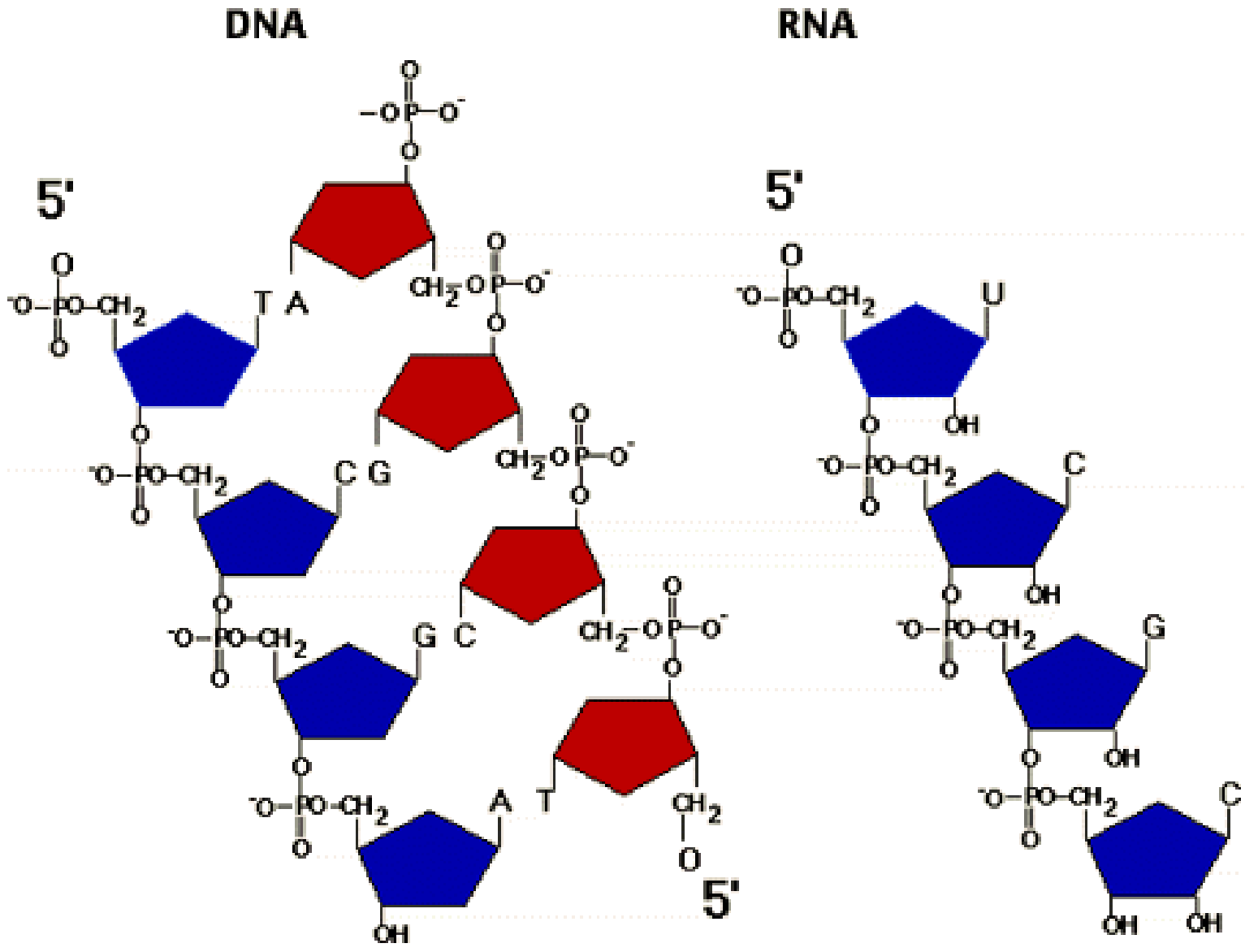
Bases



Trinucleotide



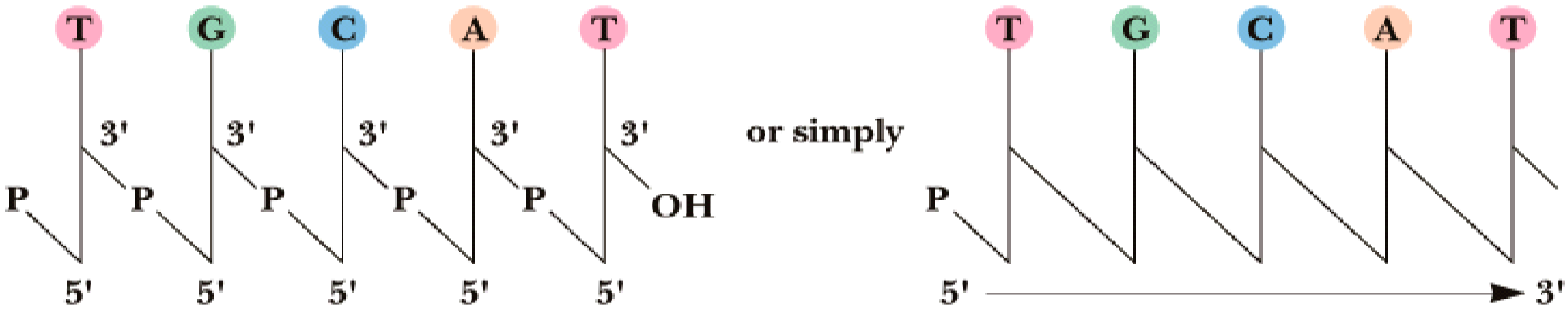
Trinucleotide



Tetranucleotide

Primary Polymeric Structure of DNA Strand:

- It is standard to use the one letter abbreviation for the bases when writing the order of a nucleic acid polymer.
- By convention, DNA sequences are written in the 5` to 3` direction.
- The sequence of the nucleic acid can be written as 5` -pGpCpA-.` 3
- The p is commonly dropped and the sequence is written as 5` -GCA-.` 3

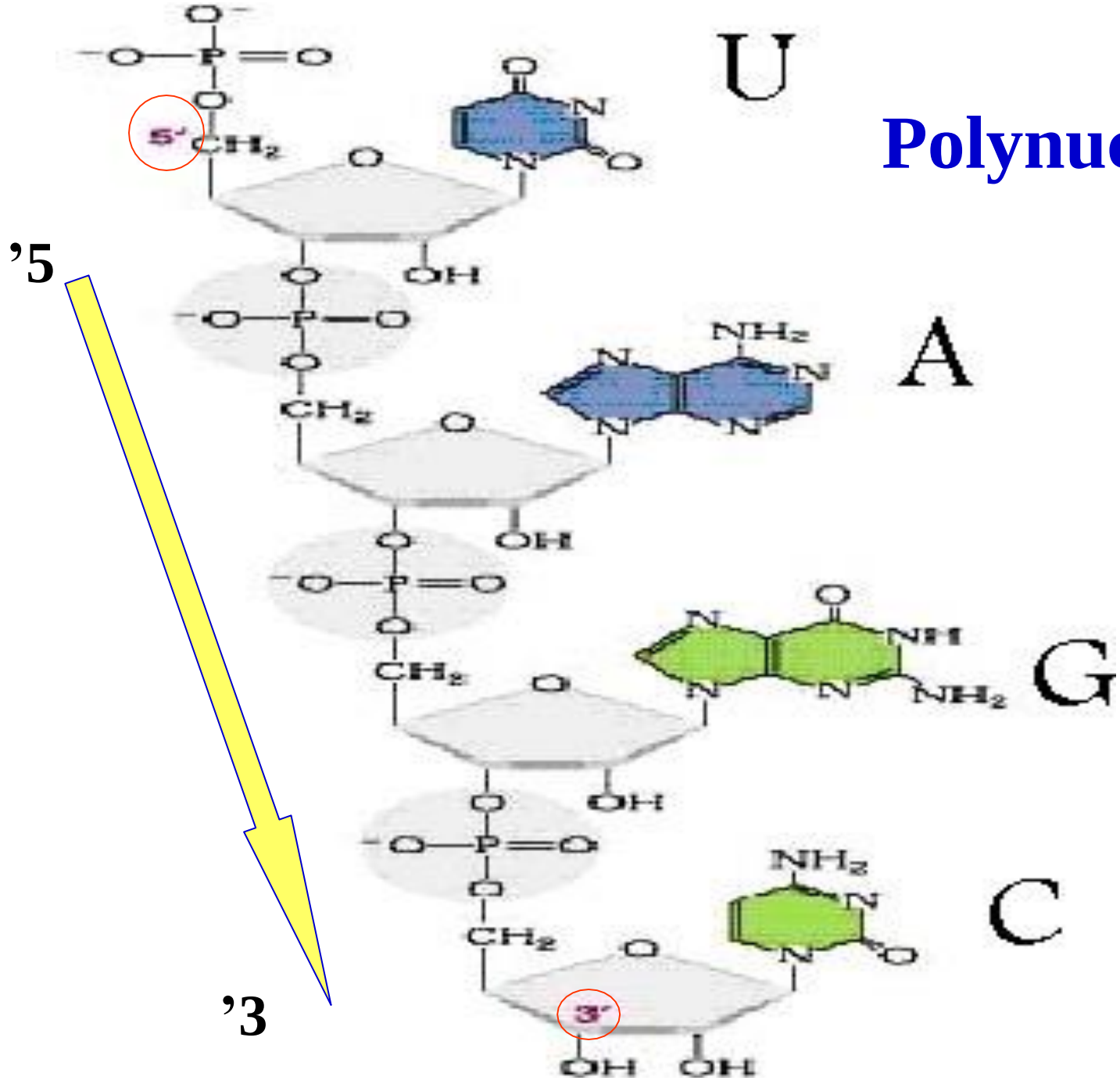


A Polynucleotide

5’–pTpGpCpApT–3’

–’5TGCAT–’3

Polynucleotide

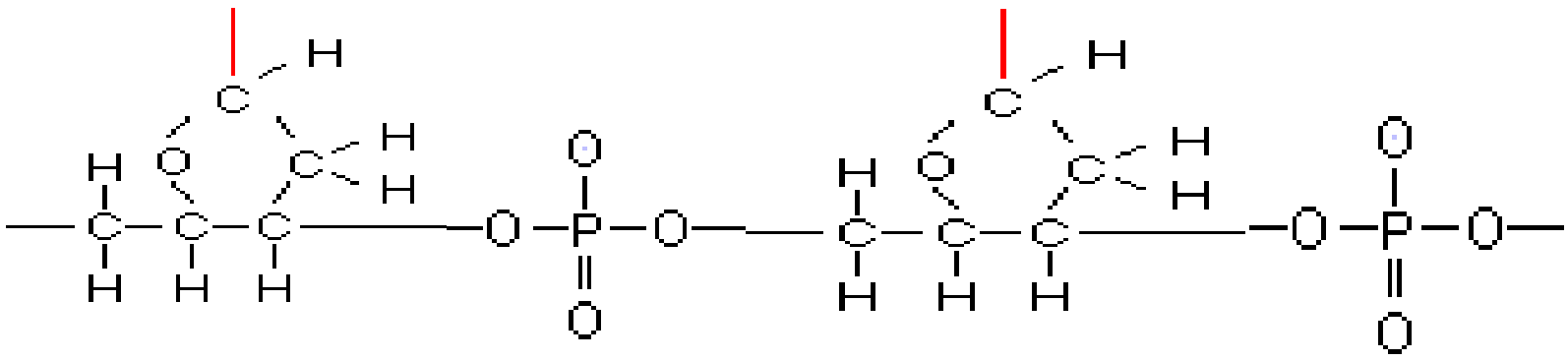


Nucleic Acids

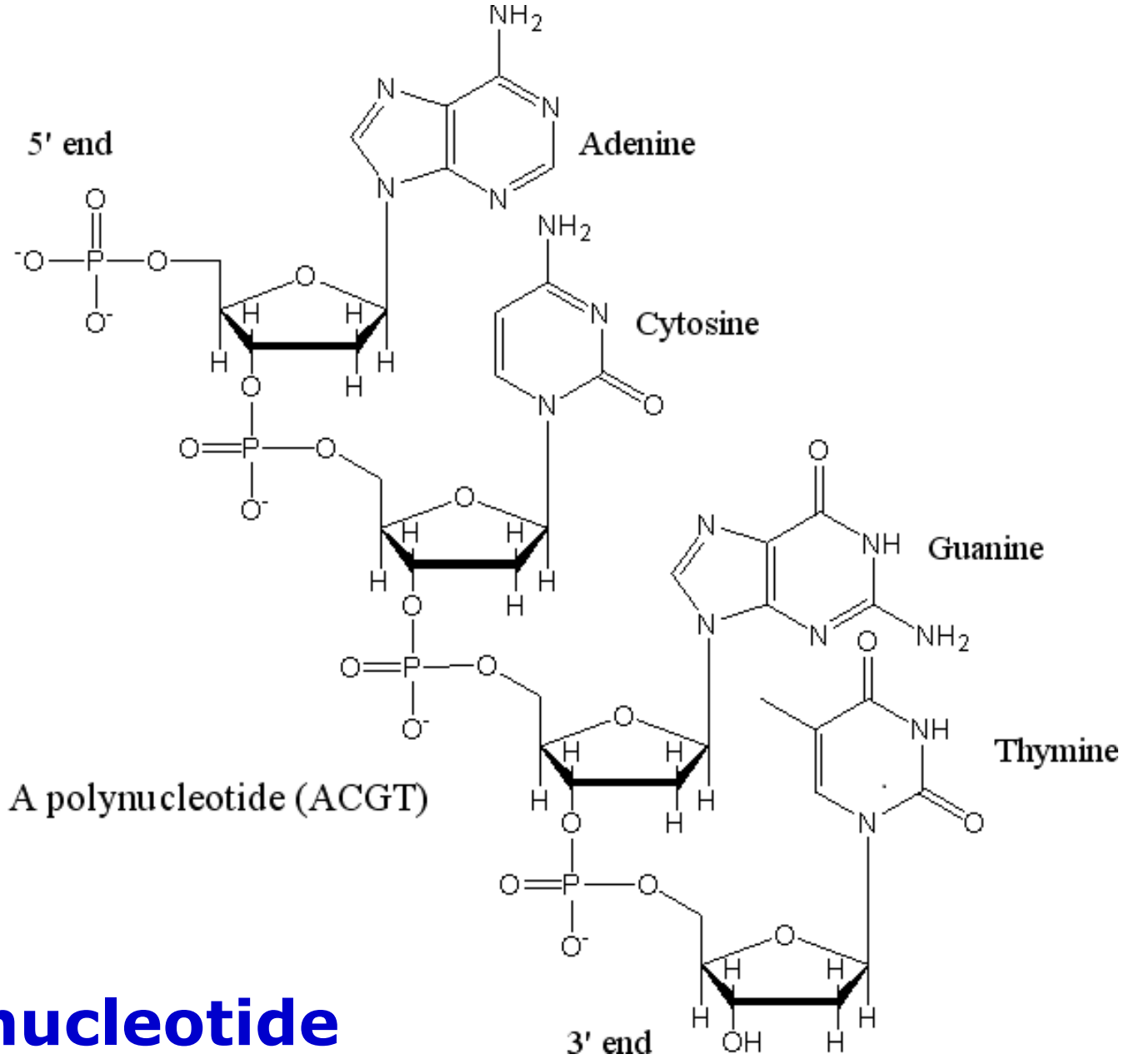
- The nucleic acids are very large molecules (Macromolecules) that have **two** main parts:
  - Main chain.
  - The nitrogenous bases.

Main chain:

- **Sugar and phosphate bonded together in a long chain:**



Sugar	Phosphate	Sugar	Phosphate



A Polynucleotide

5’–pTpGpCpApT–3’

5’–ACGT–’3

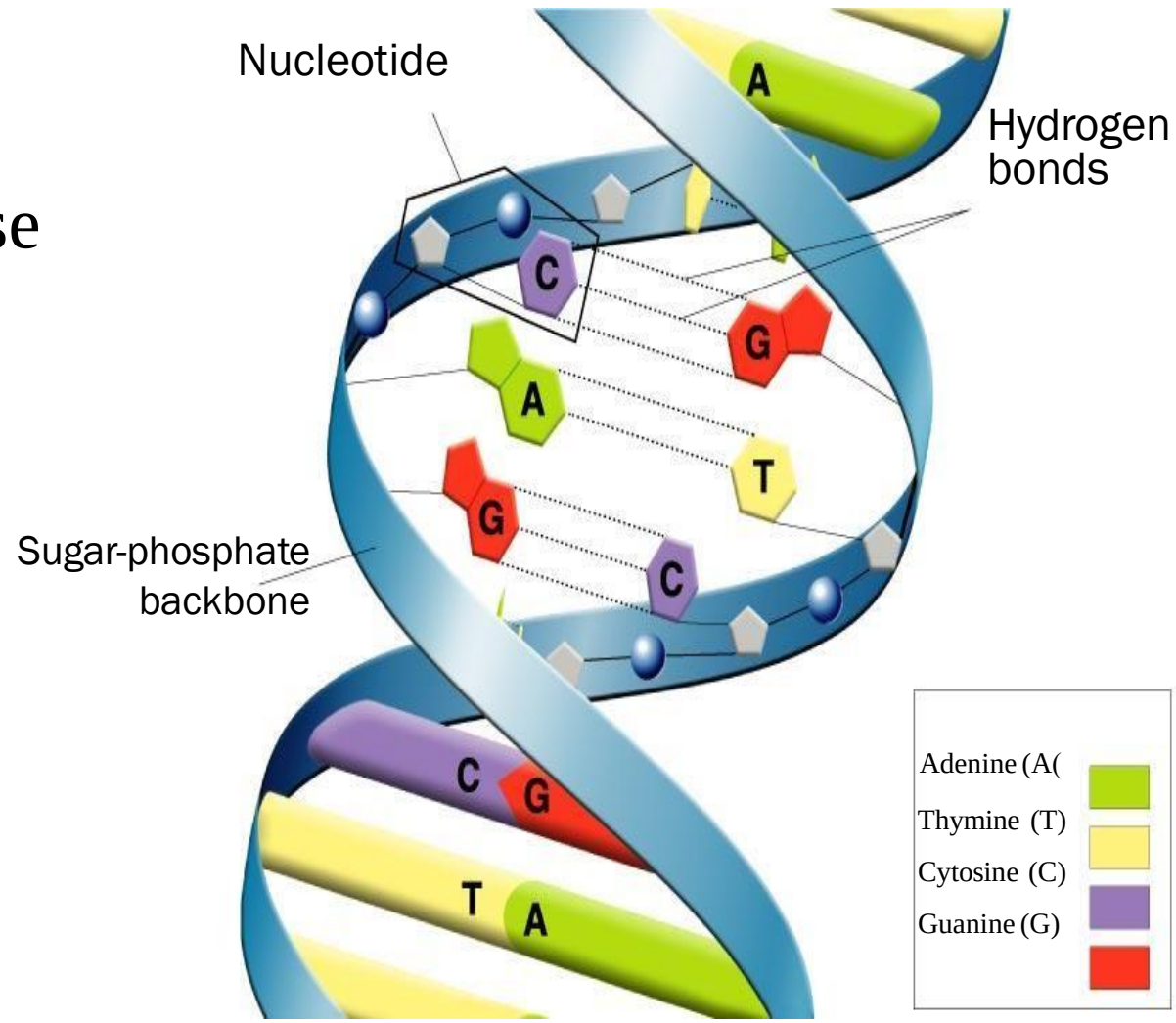
DNA

- DNA usually consists of a double strand of nucleotides.
- The sugar-phosphate chains are on the outside and the strands are held together by hydrogen bonds between the bases.
- The paired strands are coiled into a spiral called Double Helix structure

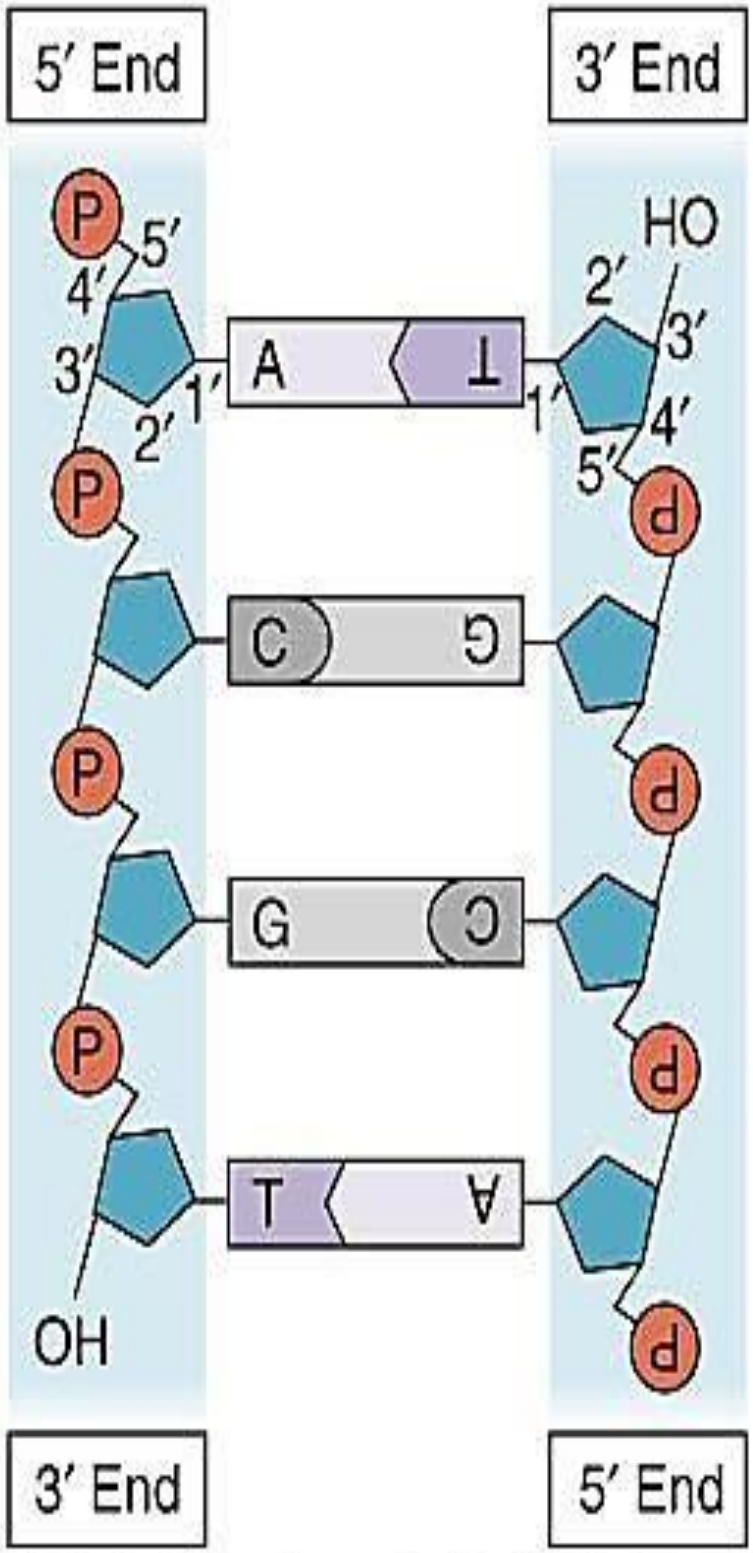
Sugar: deoxyribose

Nitrogenous base:
Thymine, Adenine, cytosine and guanine

Double strand



DNA is in a double strand

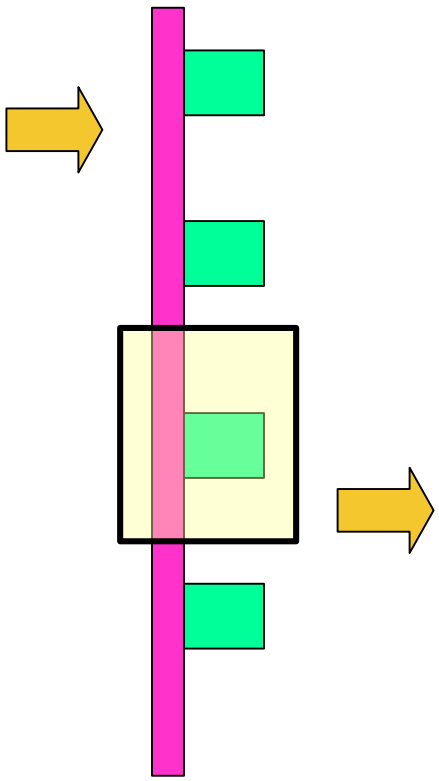


What is DNA made of?

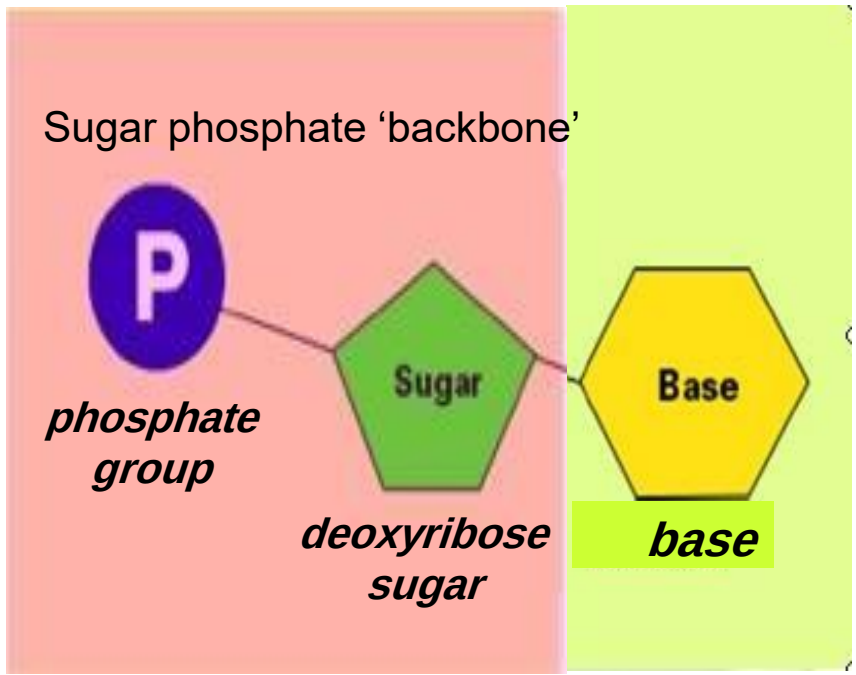
DNA molecule: a long double helix

Double helix ‘untwisted’

One strand of nucleotides



Components of a single nucleotide



Functions of DNA

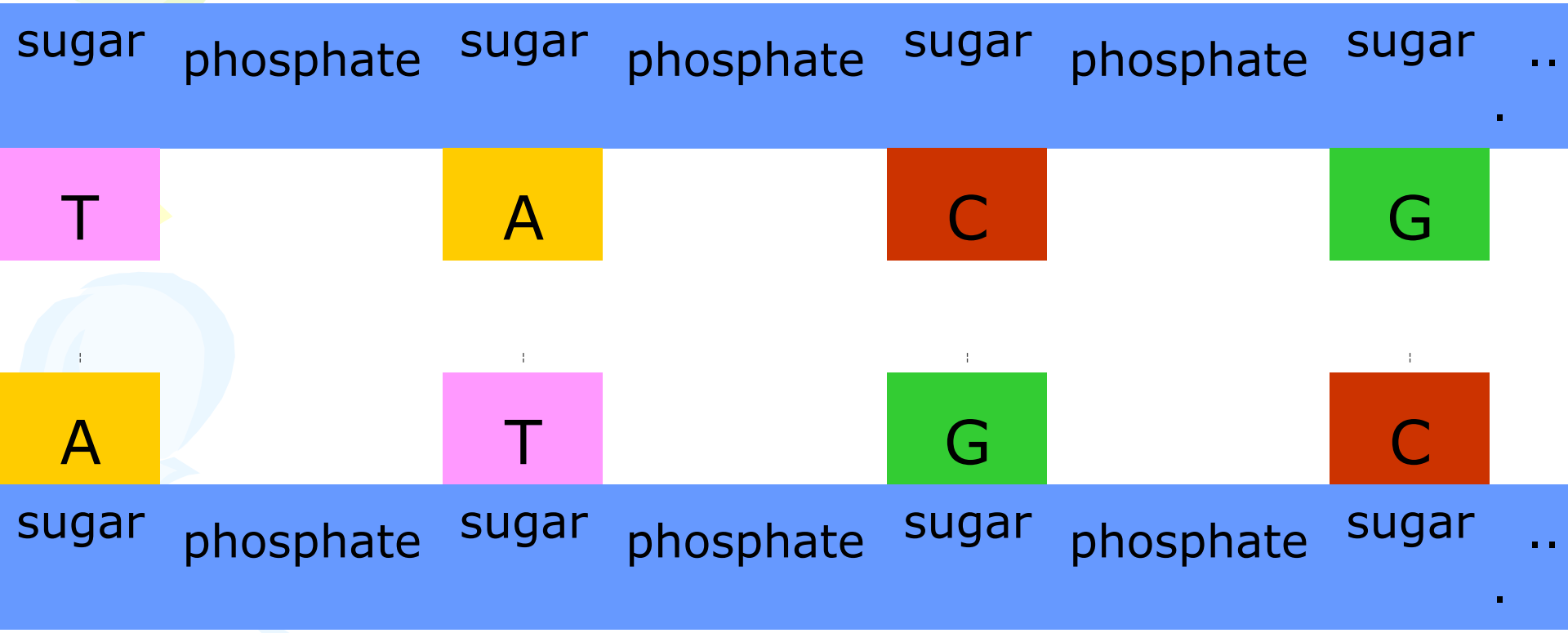
1. DNA synthesis Replication
2. DNA is stored in the nucleus and never leaves the nucleus, then the DNA is converted to RNA in order to move out into the cytoplasm Transcription
3. In the cytoplasm RNA meets up with the ribosome, where it can synthesize proteins Translation

DNA Structure

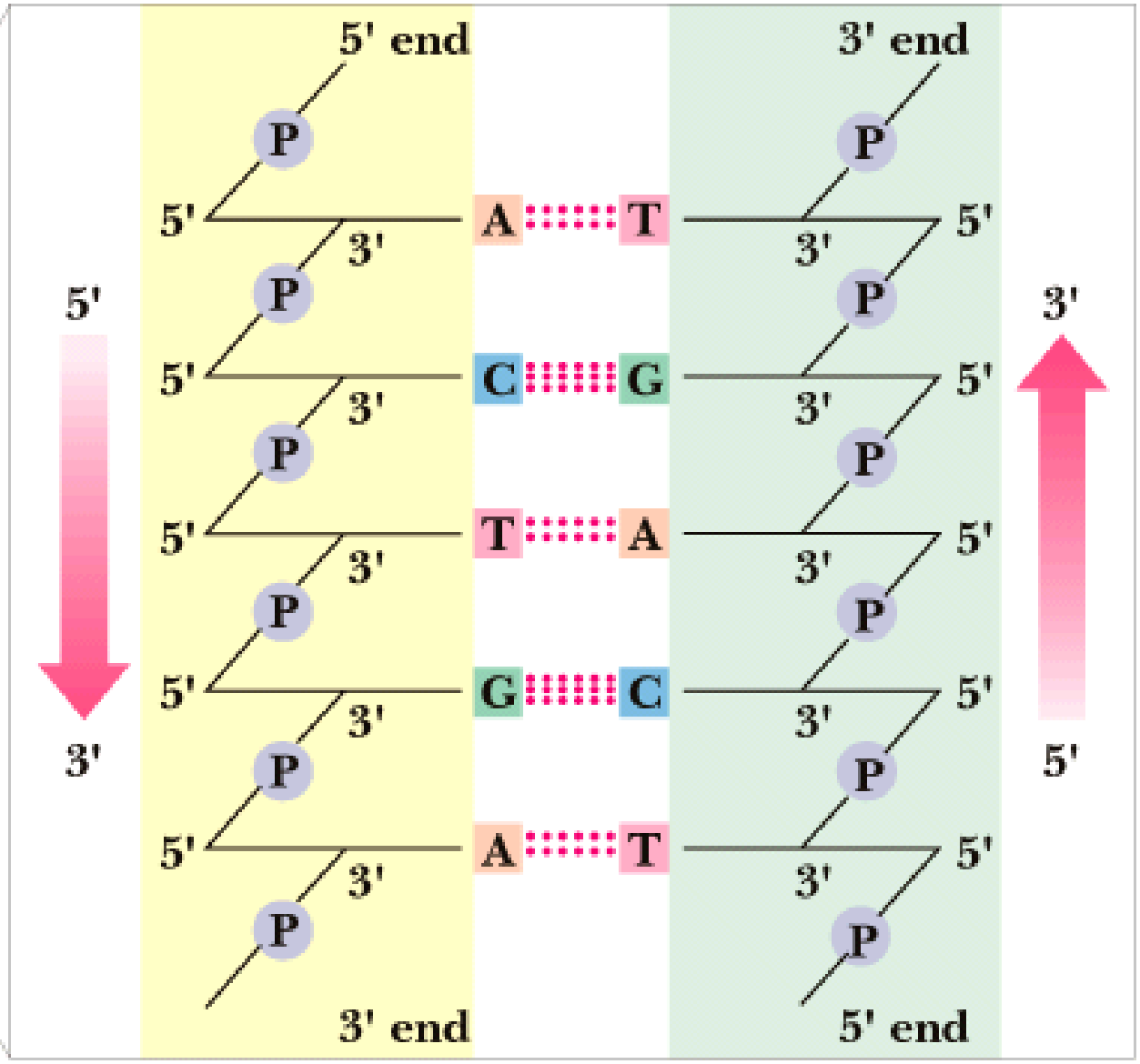
- The complementary base pair:
- Adenine always bonds to thymine with 2 hydrogen bonds (and vice versa)
- Guanine always bonds to cytosine with 3 hydrogen bonds (and vice versa)
- This bonding occurs across DNA molecule leading to a double-stranded system.

- In man, the DNA molecule if fully extended, would have a total length of 1.74 meters.
- If the all DNA in all cells of a man is unwrapped, it could reach the moon ... 6000 times!

The Complementary Base Pair

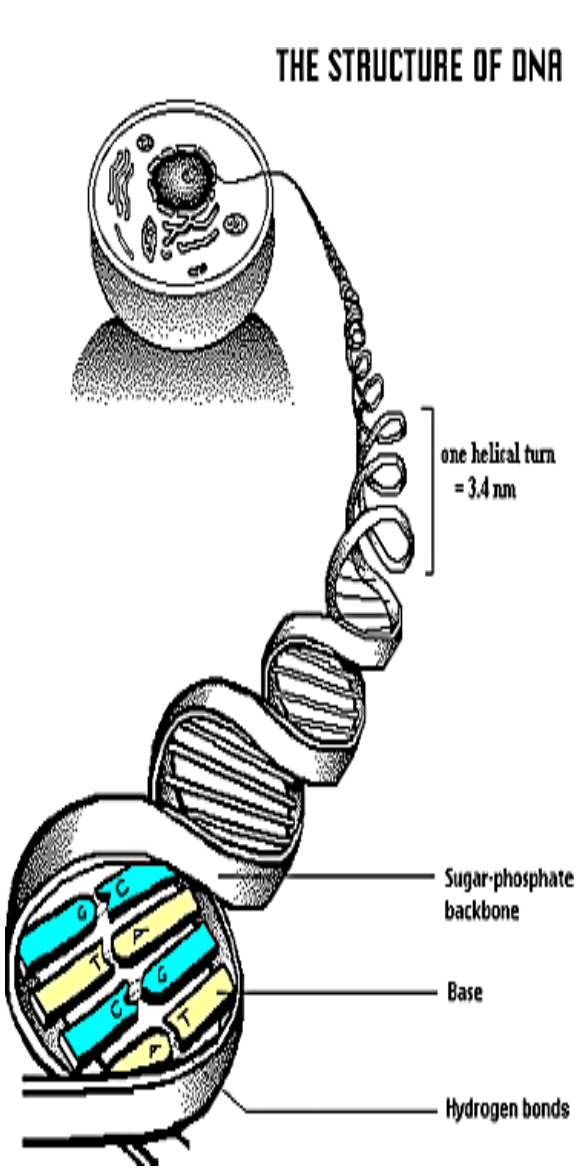


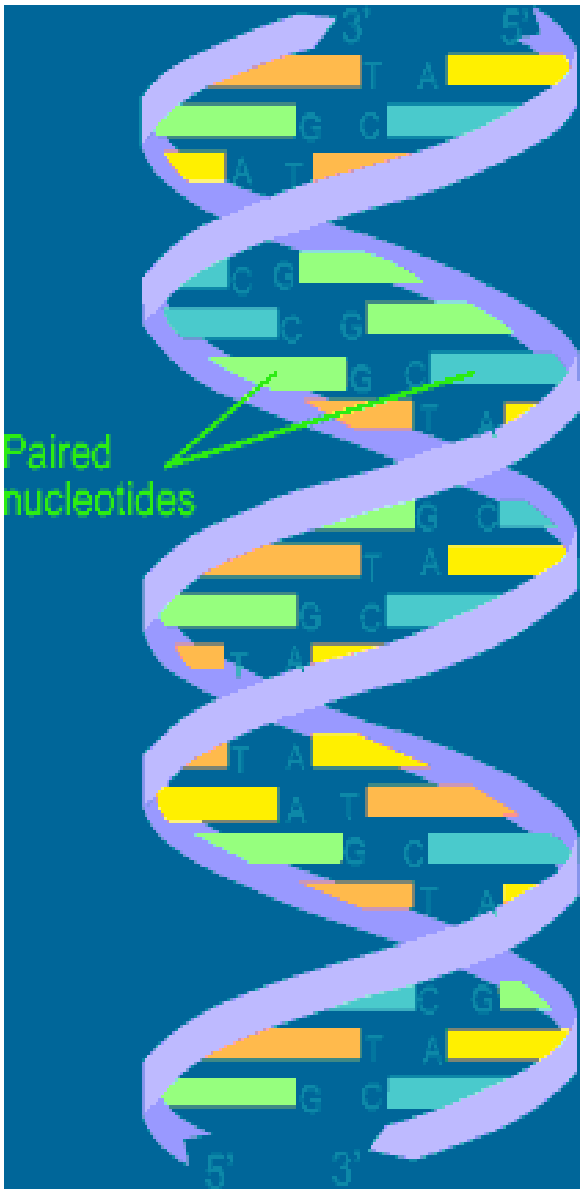
- **Letters A =T & G ≡ C form the “Code of life, Genes“**

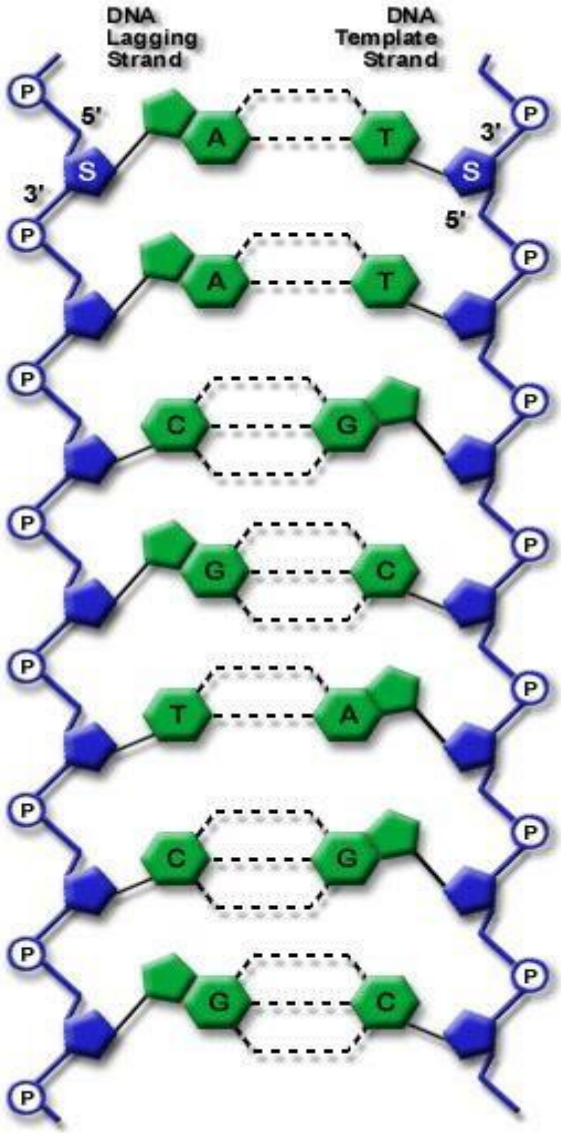


Segment of unwound double helix illustrating the antiparallel orientation of the complementary strands

DNA Structure





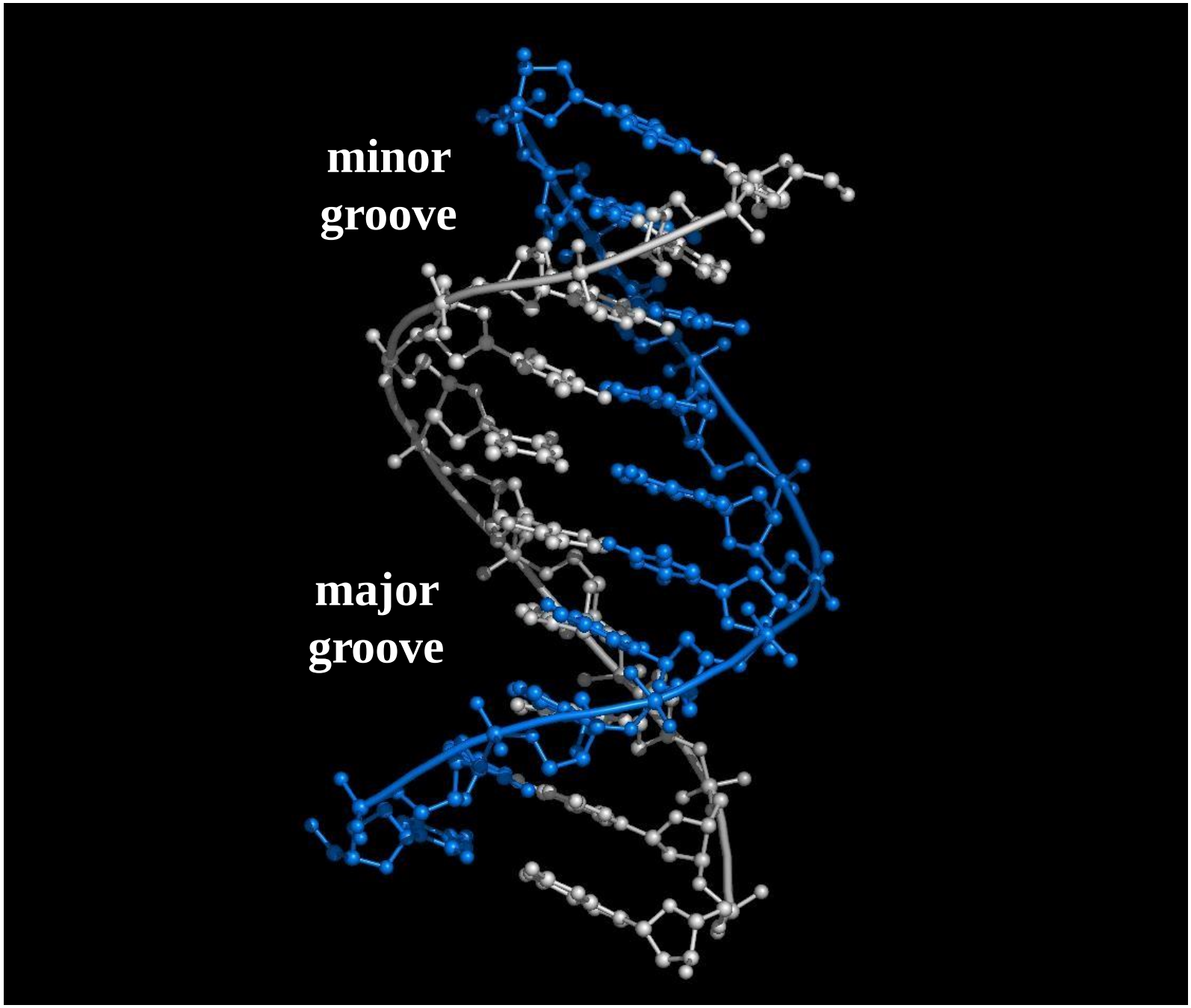


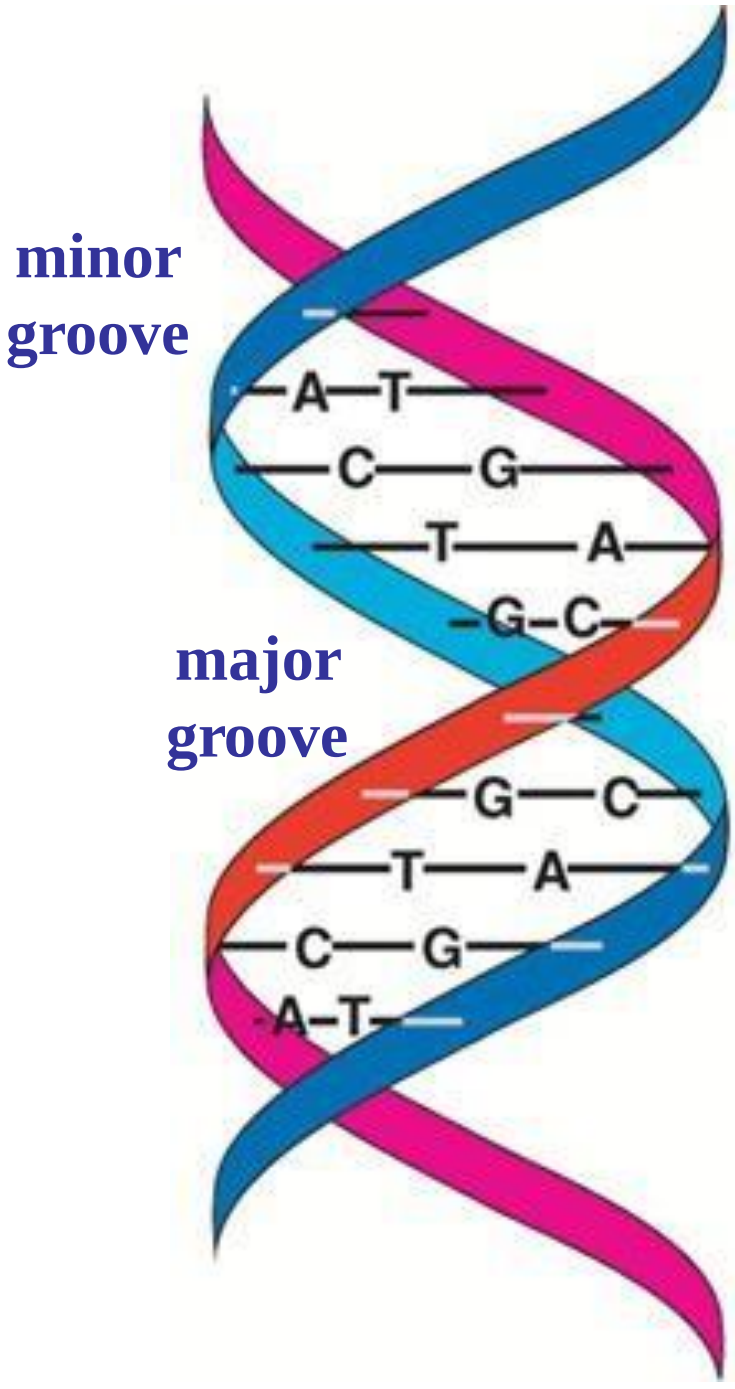
DNA structure

Primary polymeric structure of DNA

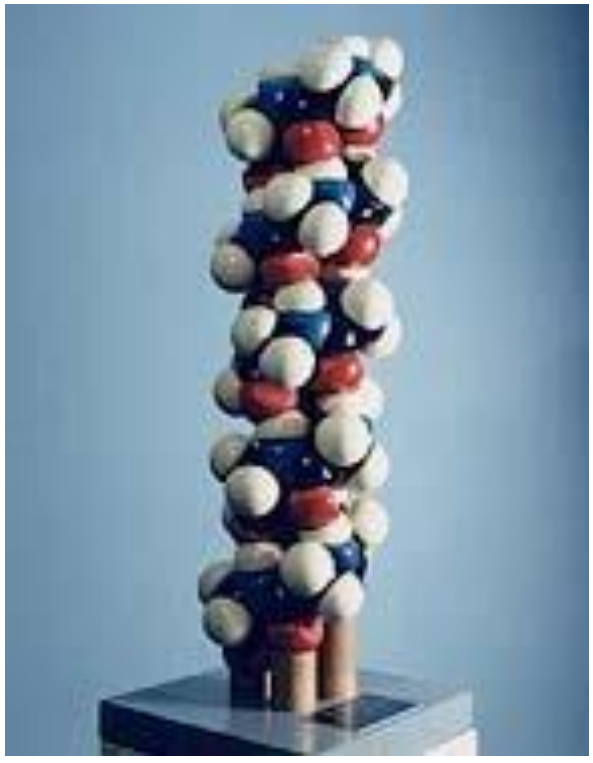
Nucleotides are linked together by phosphodiester bonds between the 3`–hydroxyl on the sugar of one nucleotide through a phosphate molecule to the 5`–hydroxyl on the sugar of another nucleotide.


G
C
A
T


minor
groove
major
groove


minor
groove
major
groove
A
T
C
G
T
A
G
C
G
C
T
A
C
G
A
T

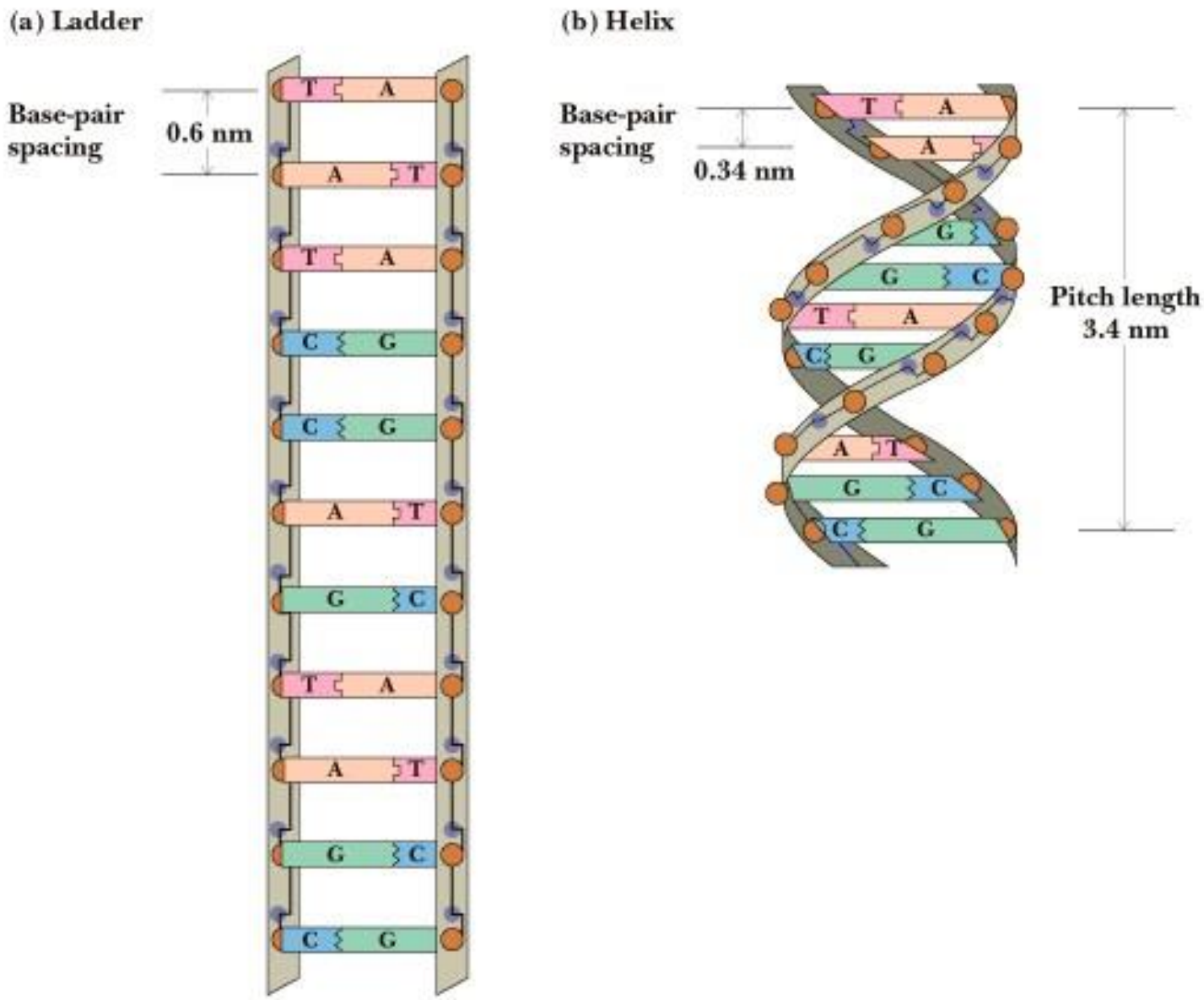
Watson and Crick Model 1953



- In 1953, James Watson and Francis Crick deduced the three dimensional structure of DNA and immediately inferred its mechanism of replication.
- Watson and Crick analyzed x-ray diffraction photographs of DNA taken by Rosalind Franklin and Maurice Wilkins (.(1953

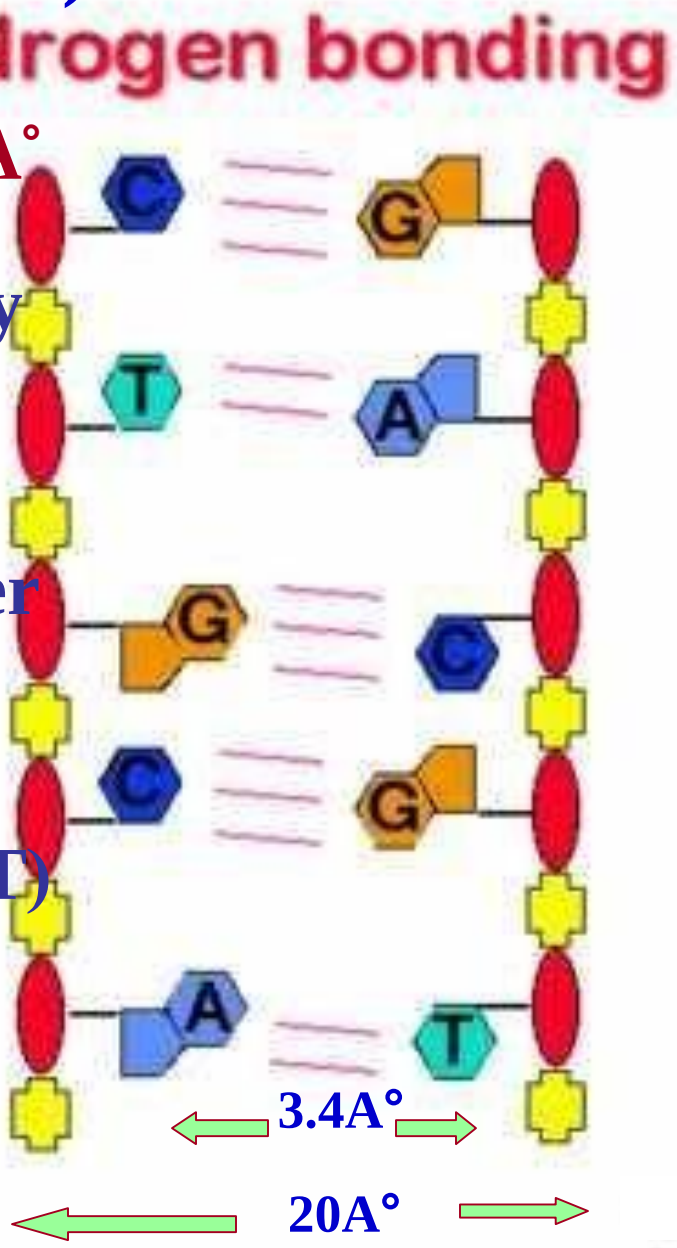
Watson–Crick DNA Double Helix

1. Two helical long polynucleotide chains are paired to each other and coiled around a common axis in a right–handed manner.
2. The two chains run in an opposite directions.
3. Nitrogenous bases are on the inside of the helix,whereas phosphate & deoxyribose are on the outside.


(a) Ladder
Base-pair spacing
0.6 nm
T A
A T
T A
C G
C G
A T
G C
T A
A T
G C
C G
(b) Helix
Base-pair spacing
0.34 nm
Pitch length 3.4 nm
T A
A
G
G C
T A
C G
A T
G C
C G

Watson and Crick Model (1953):

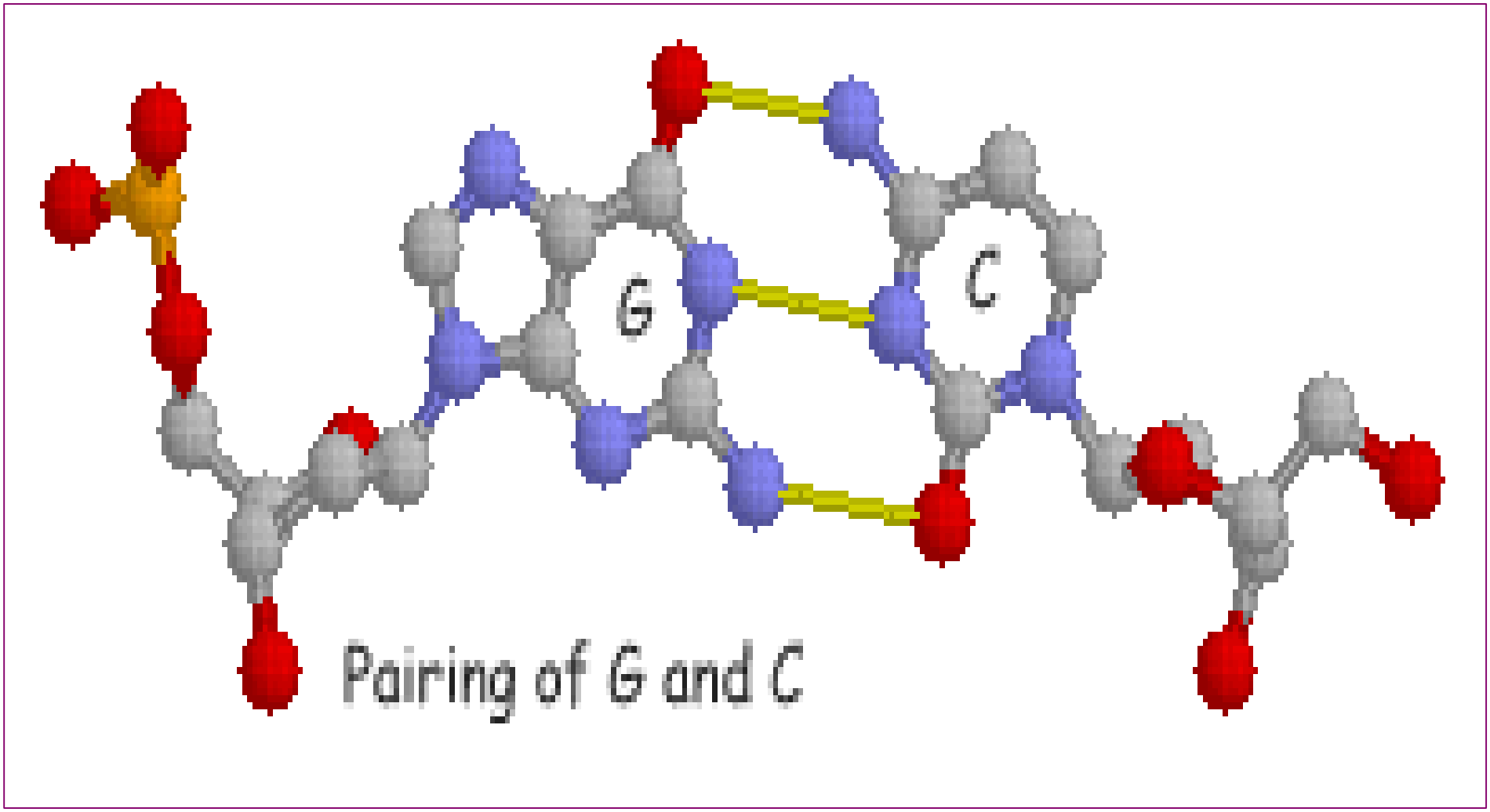
1. The diameter of the helix is 20 A˚
2. Adjacent bases are separated by 3.4 A˚.
3. The two chains are held together by hydrogen bonds:
   i. Adenine (A) = Thymine (T)
   ii. Cytosine (C(≡ Guanine (G)
4. The sequence of bases is not restricted in any way.
5. The sequence of bases carries the genetic information.



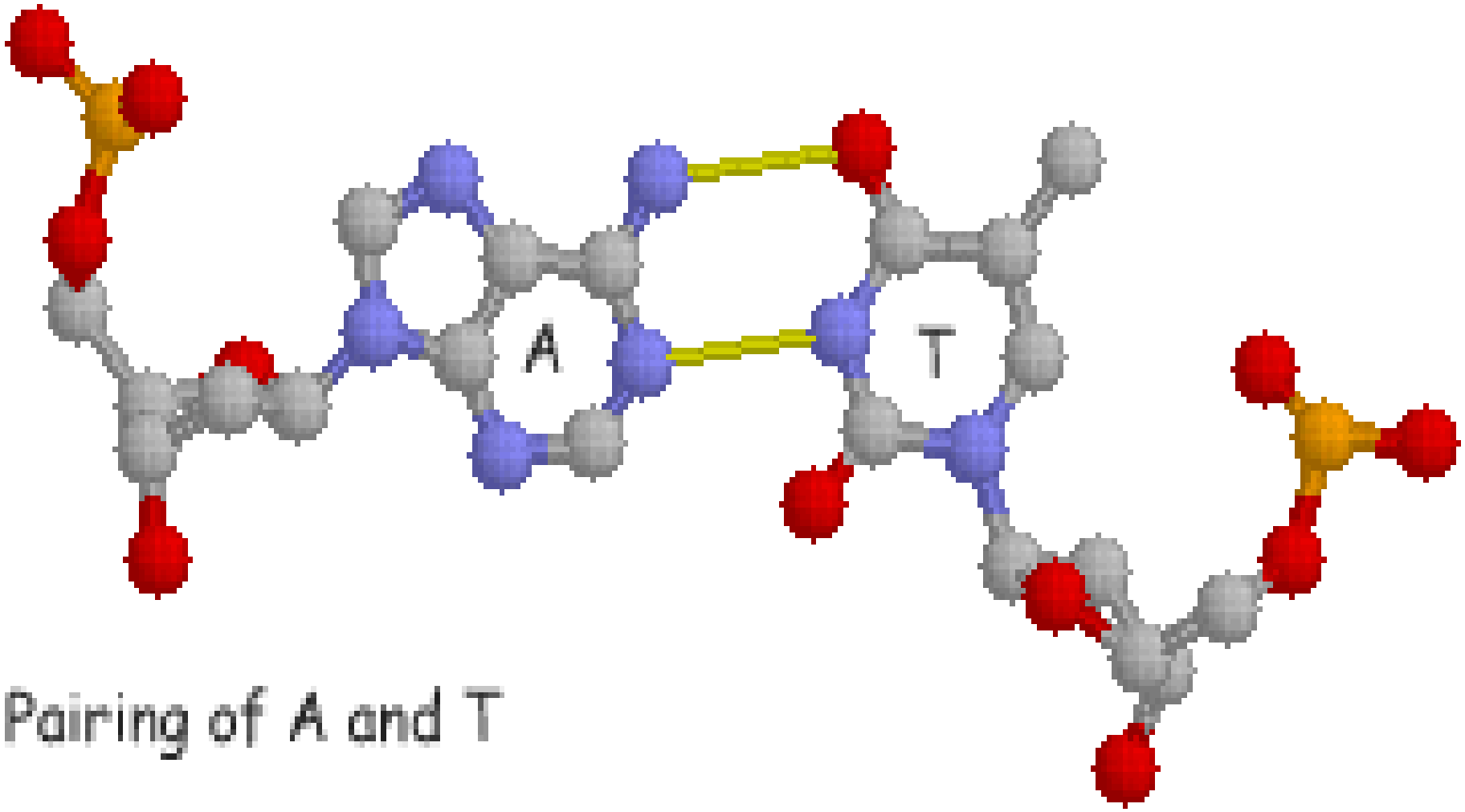
Watson and Crick Model

- The steric restriction due to the limited space between the double–stranded DNA a purine–pyrimidine base pair fits perfectly.
- In contrast, there is insufficient room for two purines.
- There is moor than enough space for two pyrimidines (would be too far apart , i.e. cannot form hydrogen bonds.)

Hydrogen bonds (yellow) between the NH (blue) and O (red(



- **Hydrogen bonds (yellow) between the NH (blue) and O (red(**

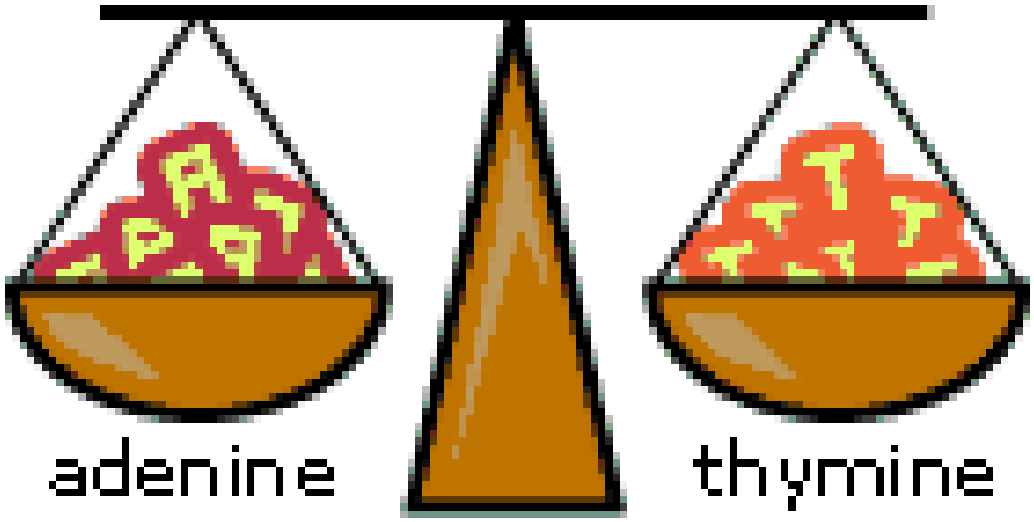


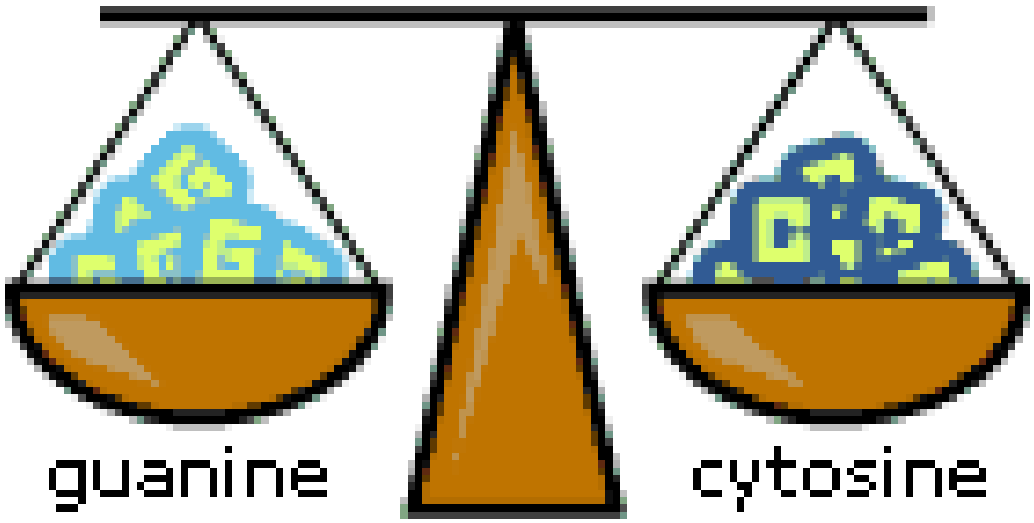
Pairing of A and T

Chargaff's Rules

- **In any sample of double–stranded DNA:**
  1. **The amount of adenine equals the amount of thymine.**
  2. **The amount of guanine equals the amount of cytosine.**
  3. **The total amount of purines equals the total amount of pyrimidines.**

Chargaff's Rules





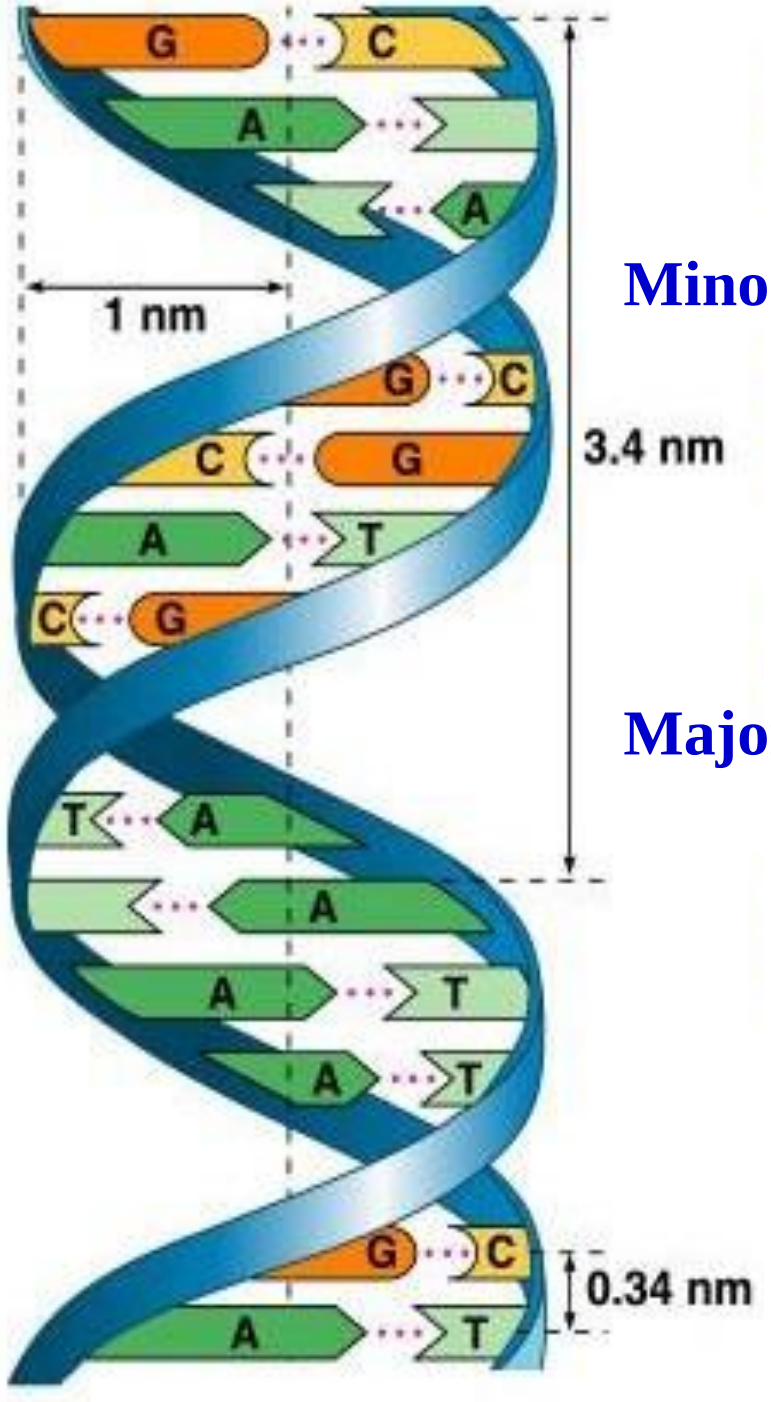
Forms of DNA

1. B – DNA
2. A – DNA
3. Z – DNA

Forms of DNA

.1 B – DNA:

- James Watson – Francis Crick Structure
  - 10residues (base pairs)/turn.
  - Right–handed helix.
  - Bases are perpendicular to the axis
  - e.g.: Chromosomal DNA.



Minor groove

Major groove

Forms of DNA

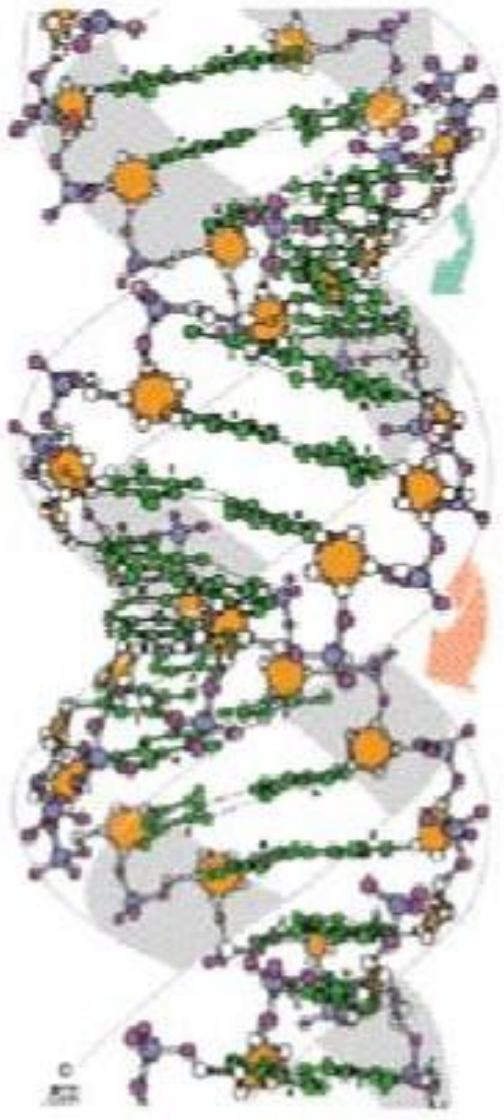
.2 A – DNA:

- **Right–handed helix.**
- **11residues/turn.**
- **No minor groove.**
- **e.g:.**
  1. **RNA–DNA hybrids.**
  2. **RNA–RNA double–stranded regions.**

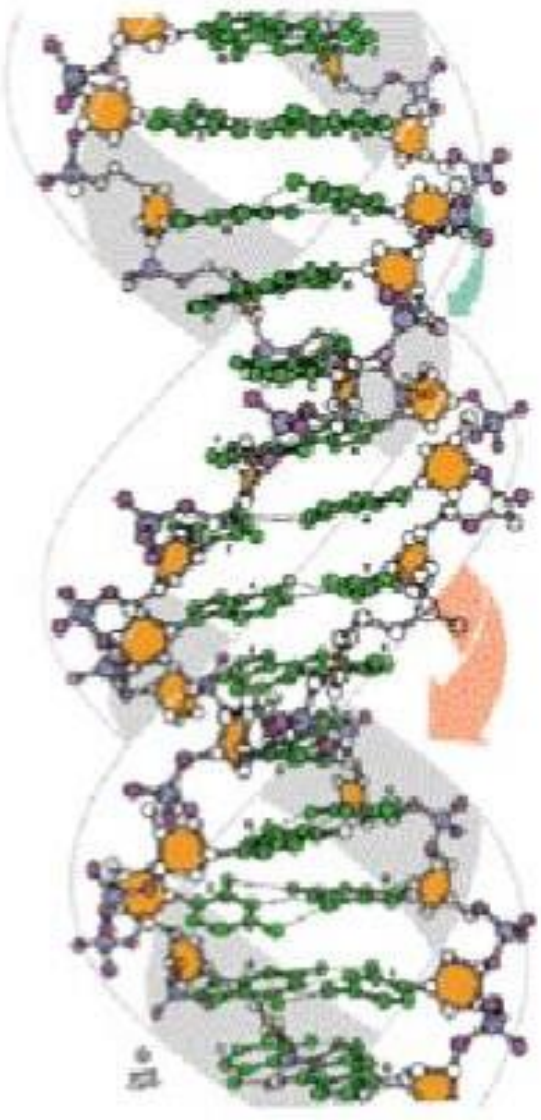
Forms of DNA

.3 Z – DNA:

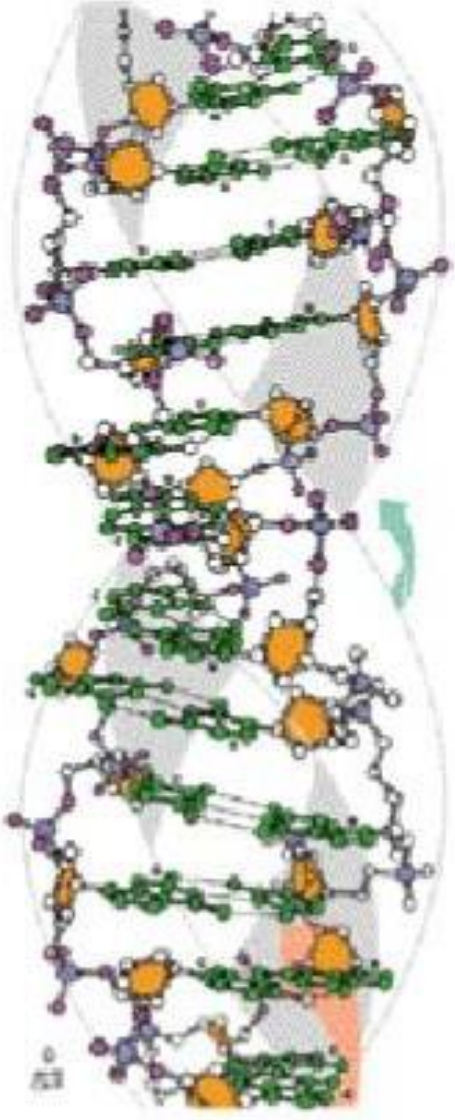
- Left–handed helix.
- 12residues/turn.
- e.g.: Occur naturally in specific regions of DNA (non-chromosomal DNA segments) & may play an important role in regulation of gene expression.



A
DNA



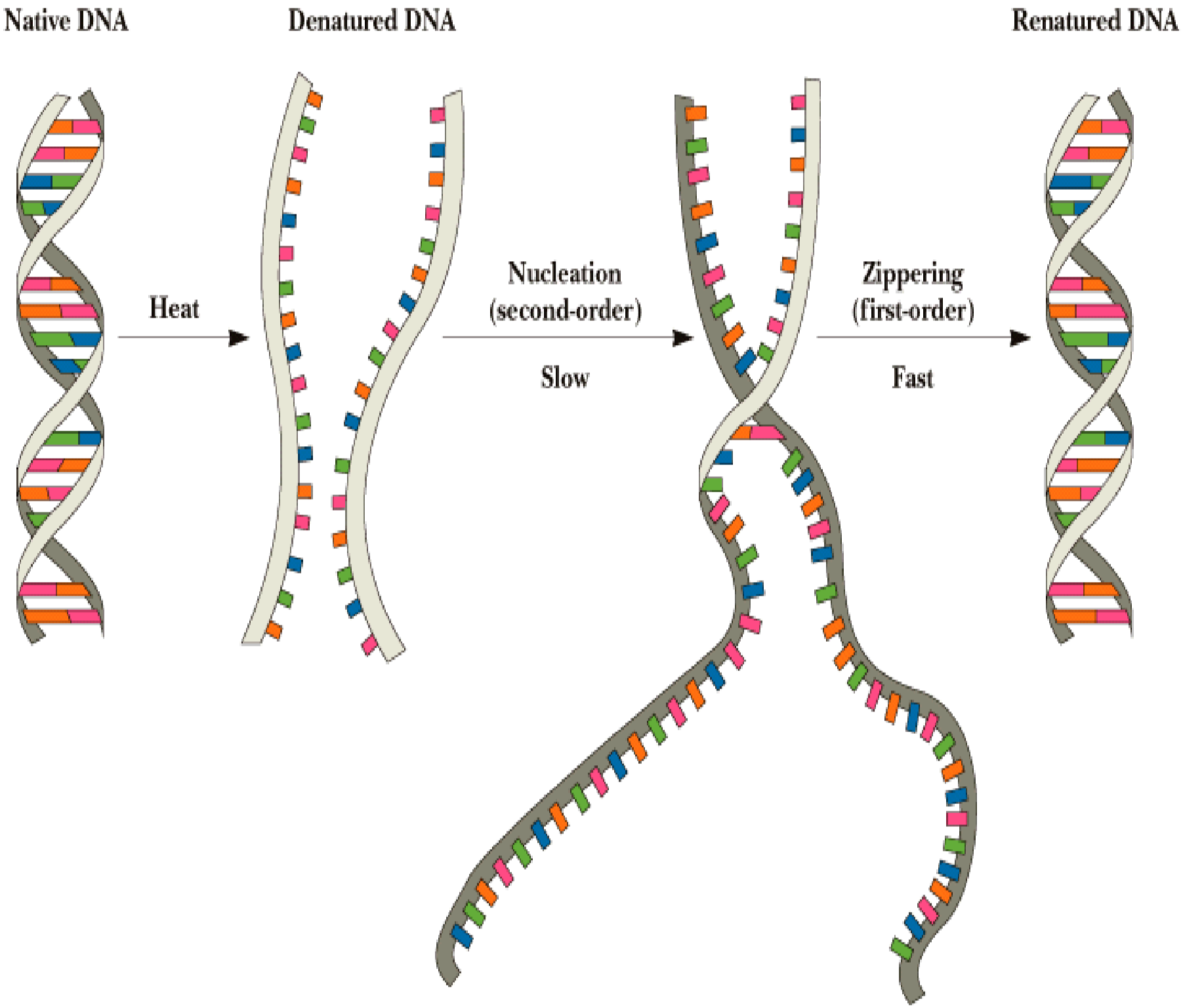
B
DNA



Z
DNA

Separation of the Double Strands of DNA

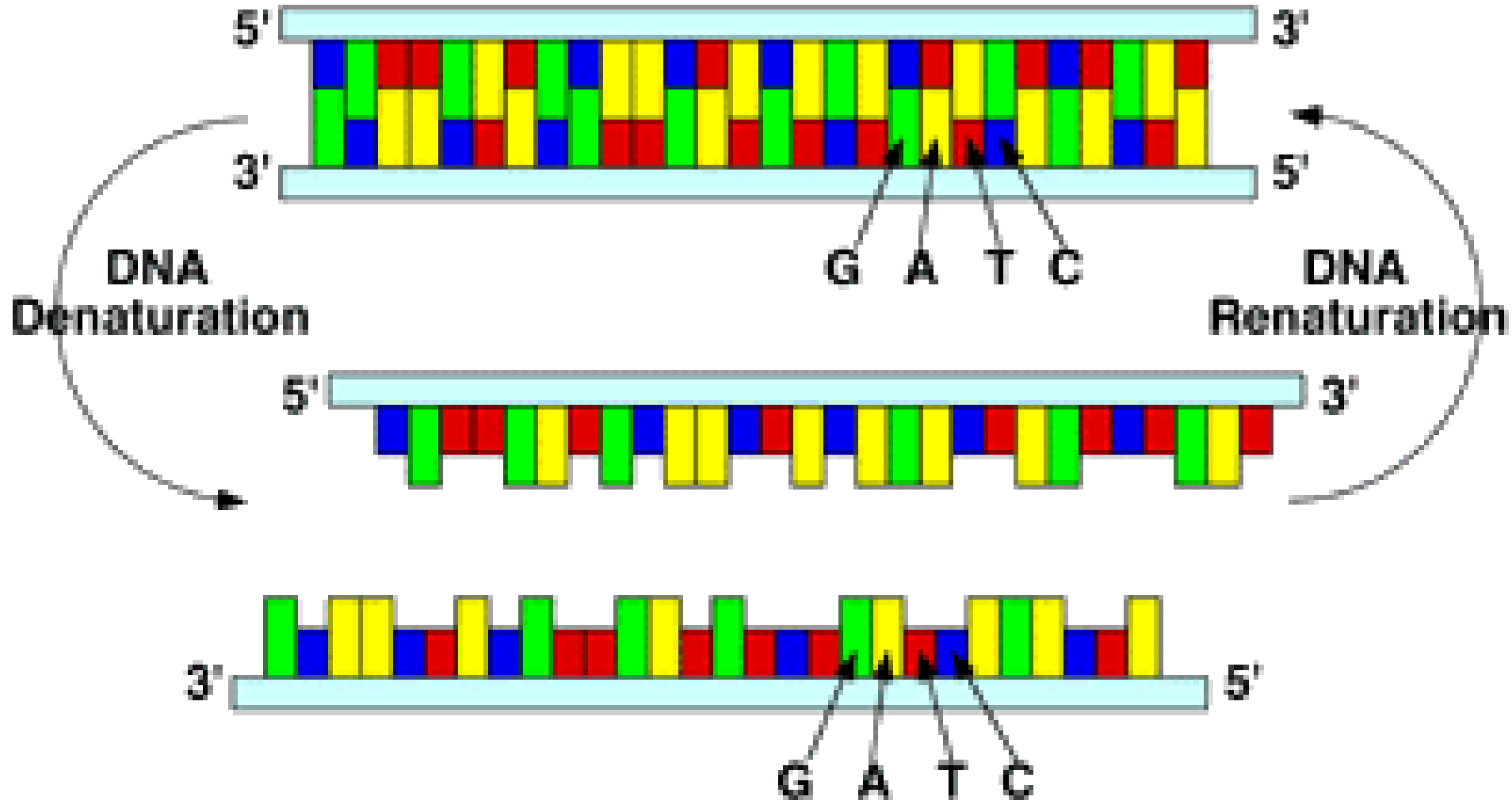
- DNA double–stranded can be disrupted (denatured) by:
  - Either **pH changes** (ionization of nitrogenous bases)
  - Or **increased temperature** (breaks hydrogen bonds)


Native DNA
Denatured DNA
Renatured DNA
Heat
Nucleation
(second-order)
Slow
Zippering
(first-order)
Fast

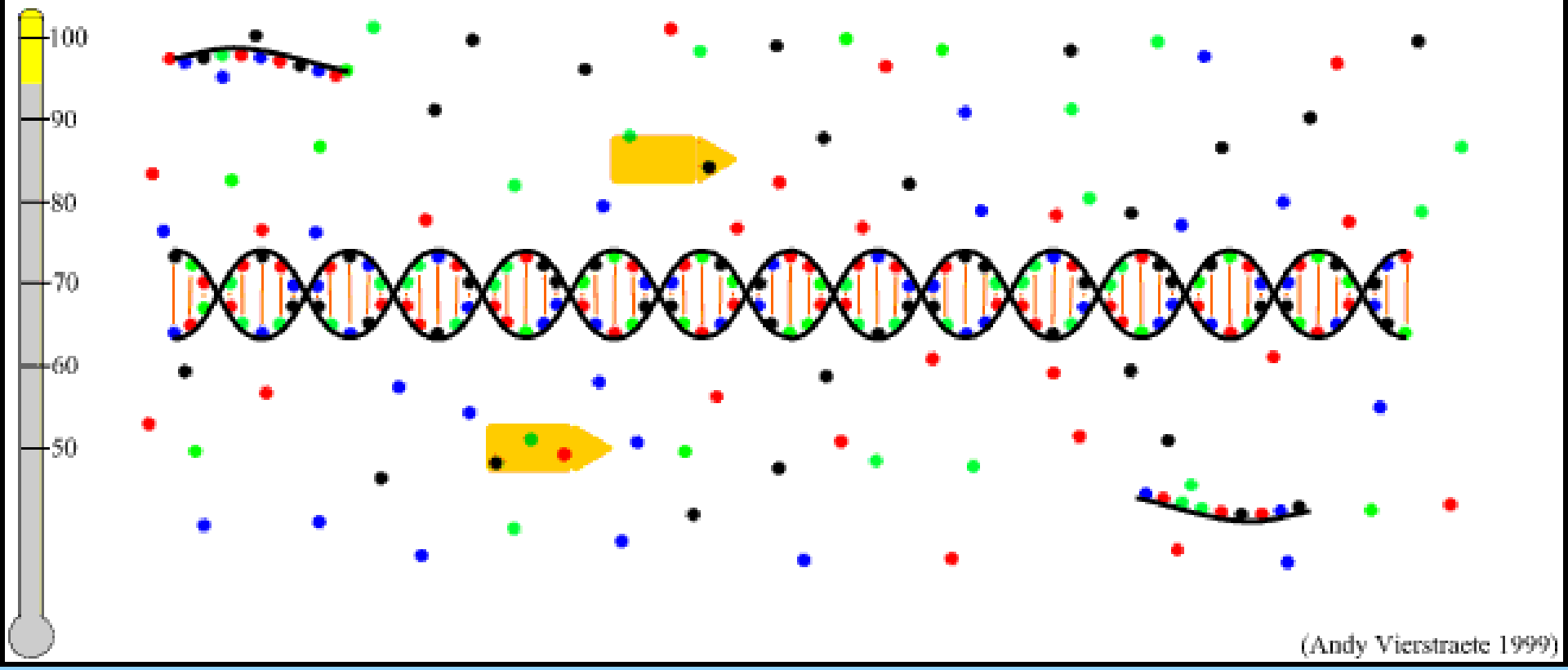
Separation of the Double Strands of DNA

- **Melting temp**. (**Tm**): is the temperature at which **one half** of the helical structure of DNA is lost
- **Denaturation** is the loss of helical structure in DNA
- DNA that contains high concentration of **A** and **T** denature at a lower temp. than that contains higher **G** and **C**

Denaturation/Renaturation



PCR : Denaturation 94°C



Tertiary structure of DNA:

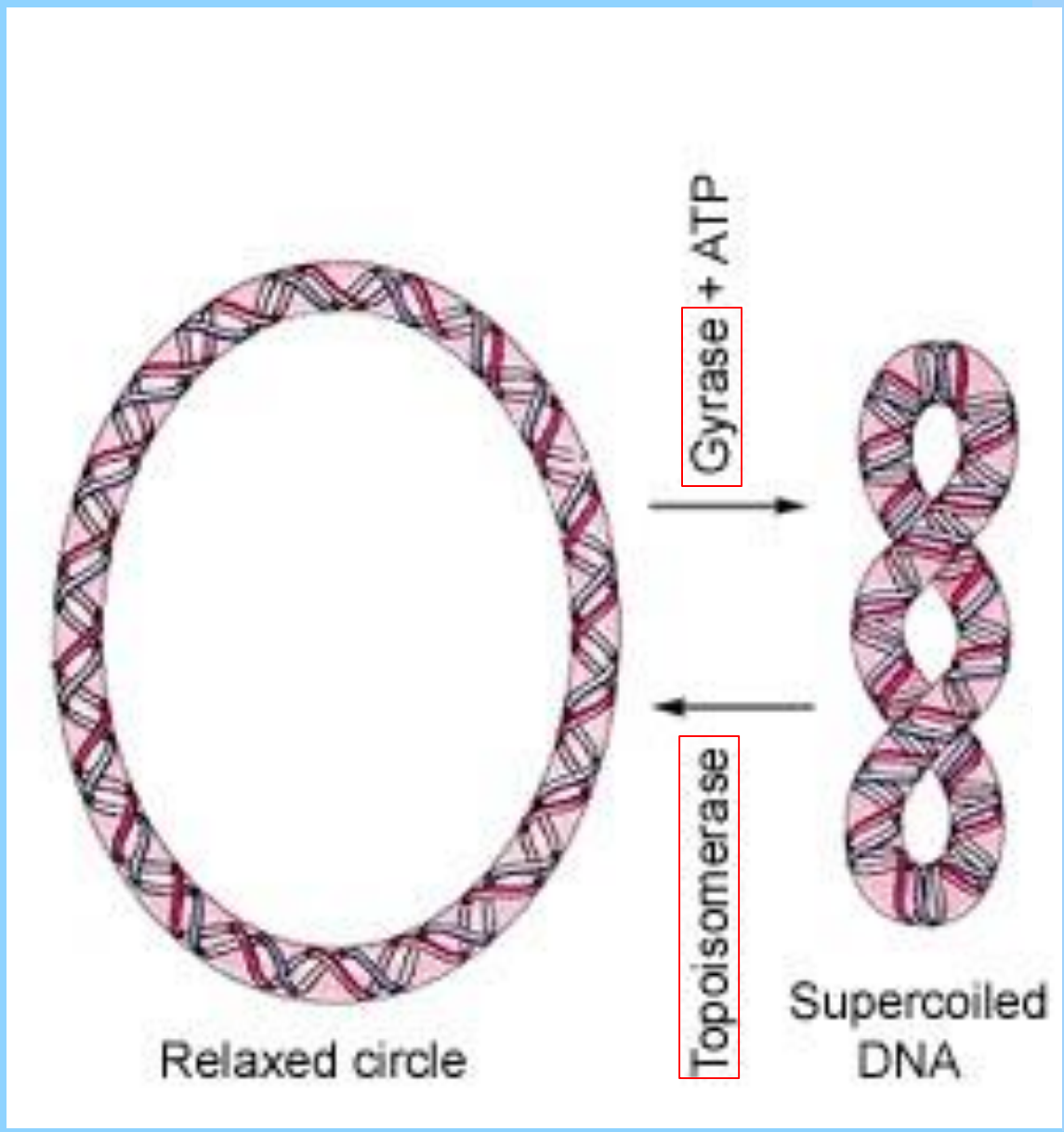
- **Clearly, to get DNA into a cell's nucleus, it must be packed into a more tightly compact form**
- **The structural flexibility of DNA allows it to adopt more compacted structures than simple linear B–form DNA**

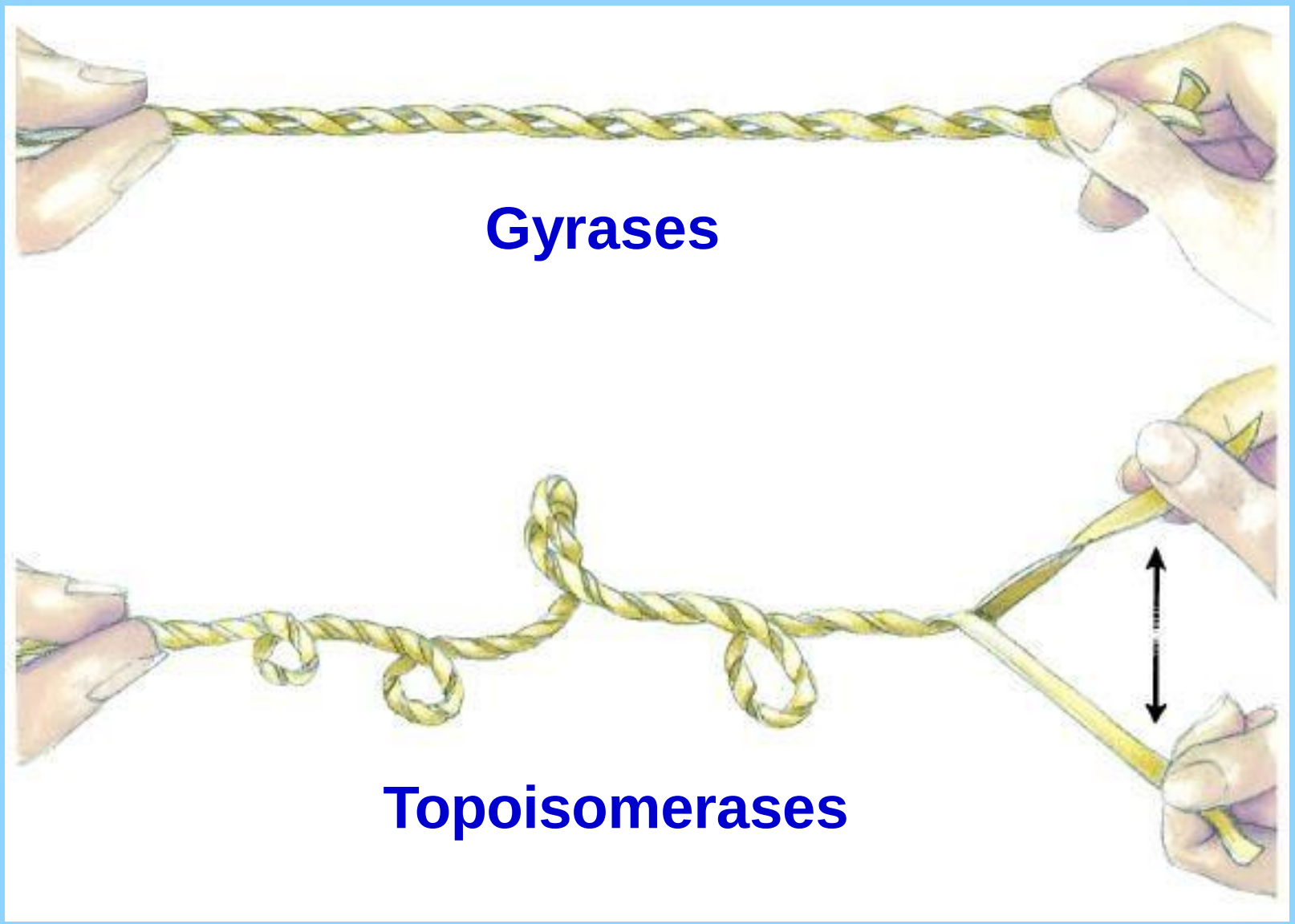
Chromosome Structure

- Human DNA's total length is ~2 meters!
- This must be packaged into a nucleus that is about 5 micrometers in diameter
- This represents a compression of more than !100,000
- It is made possible by wrapping the DNA around protein spools called nucleosomes

Supercoils

- Some DNA are circular, especially in bacteria
- Circular DNA can be twisted into a compact supercoiled or superhelical form
- DNA supercoils can be either right handed (positive) or left handed (negative)
- Supercoils (stretched(have a higher free energy than non – supercoiled (relaxed) DNA
- **Gyrases + ATP** convert non – supercoiled (relaxed) DNA into supercoiled (stretched) DNA
- **Topoisomerases** convert supercoiled (stretched) cellular DNA into non – supercoiled (relaxed) DNA


Gyrase + ATP
Topoisomerase
Relaxed circle
Supercoiled DNA


Gyrases
Topoisomerases

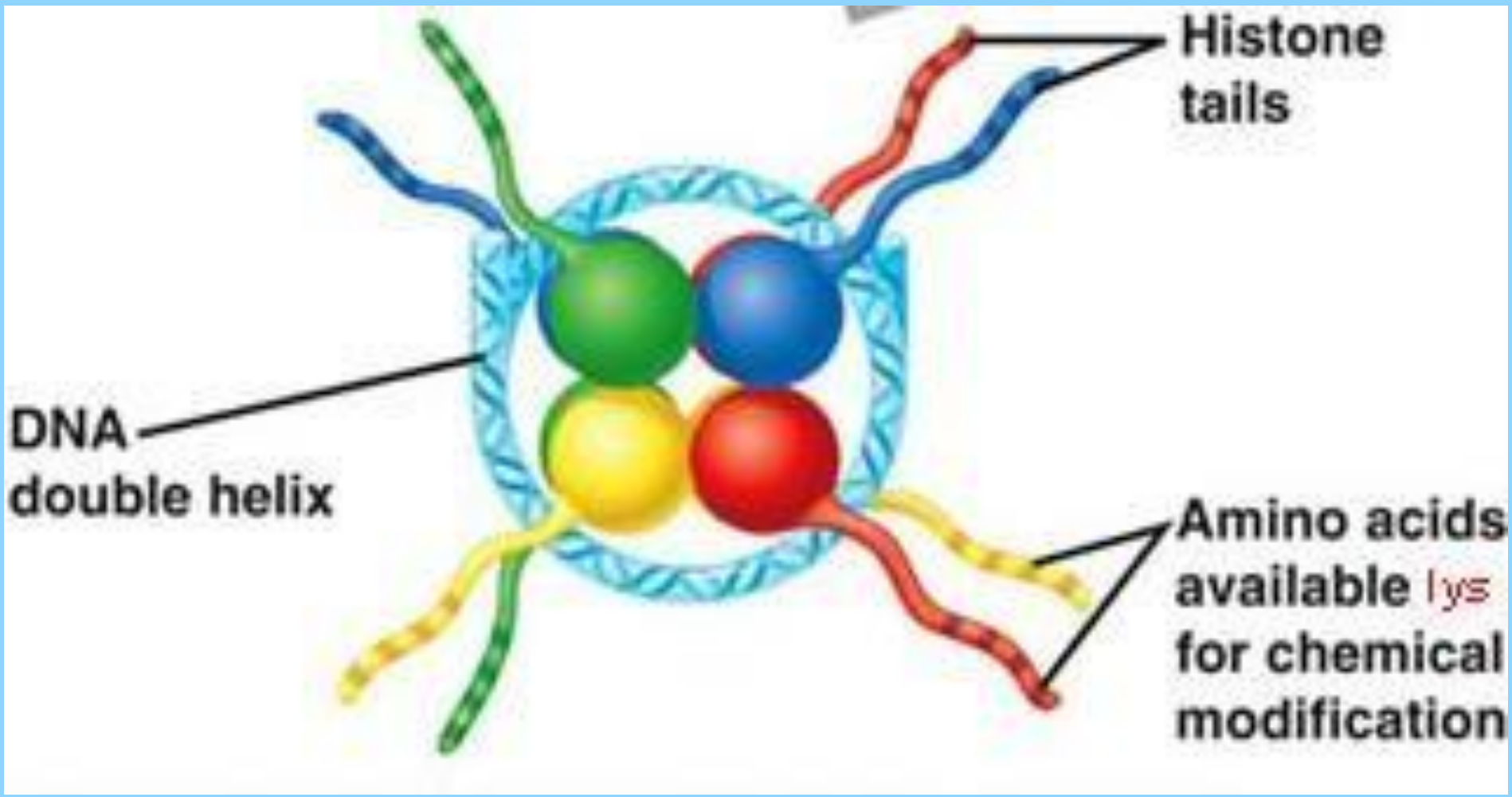
DNA Forms:

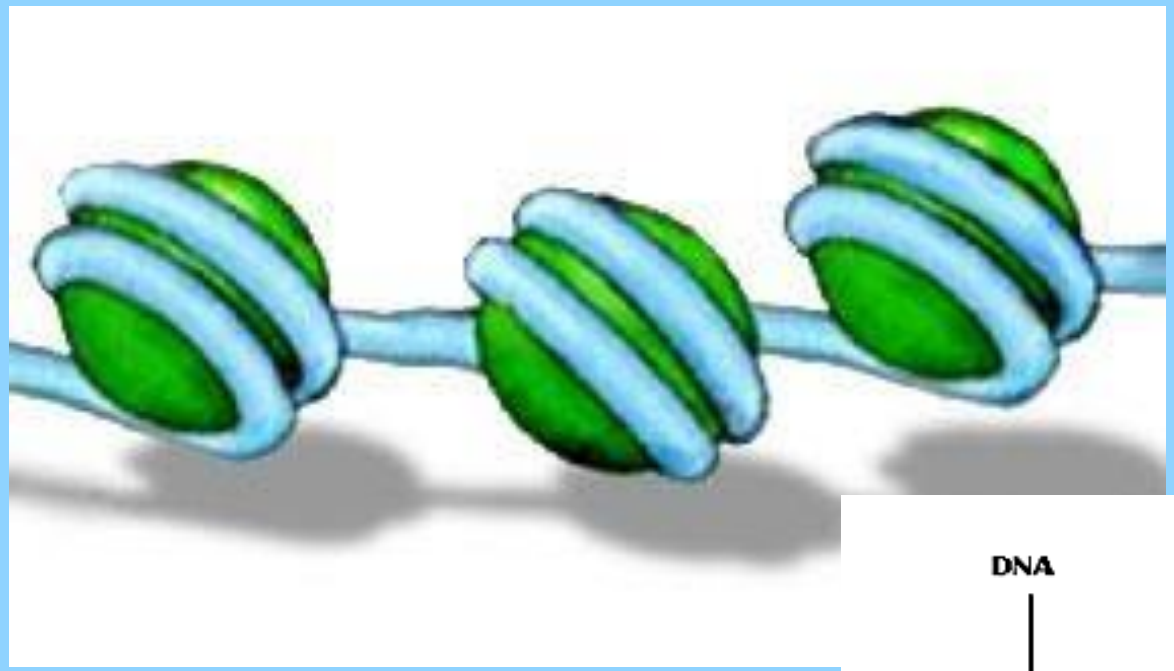
- **DNA is packed in a structure called chromosomes, which are visible under a light microscope**
- **The packing of DNA in a chromosome represents a 10,000 fold shortening of its length from primary B–form DNA**
- **DNA to be accessible to the transcription and replication enzymes, it is packed less densely than in chromosomes, in a structure known as chromatin**

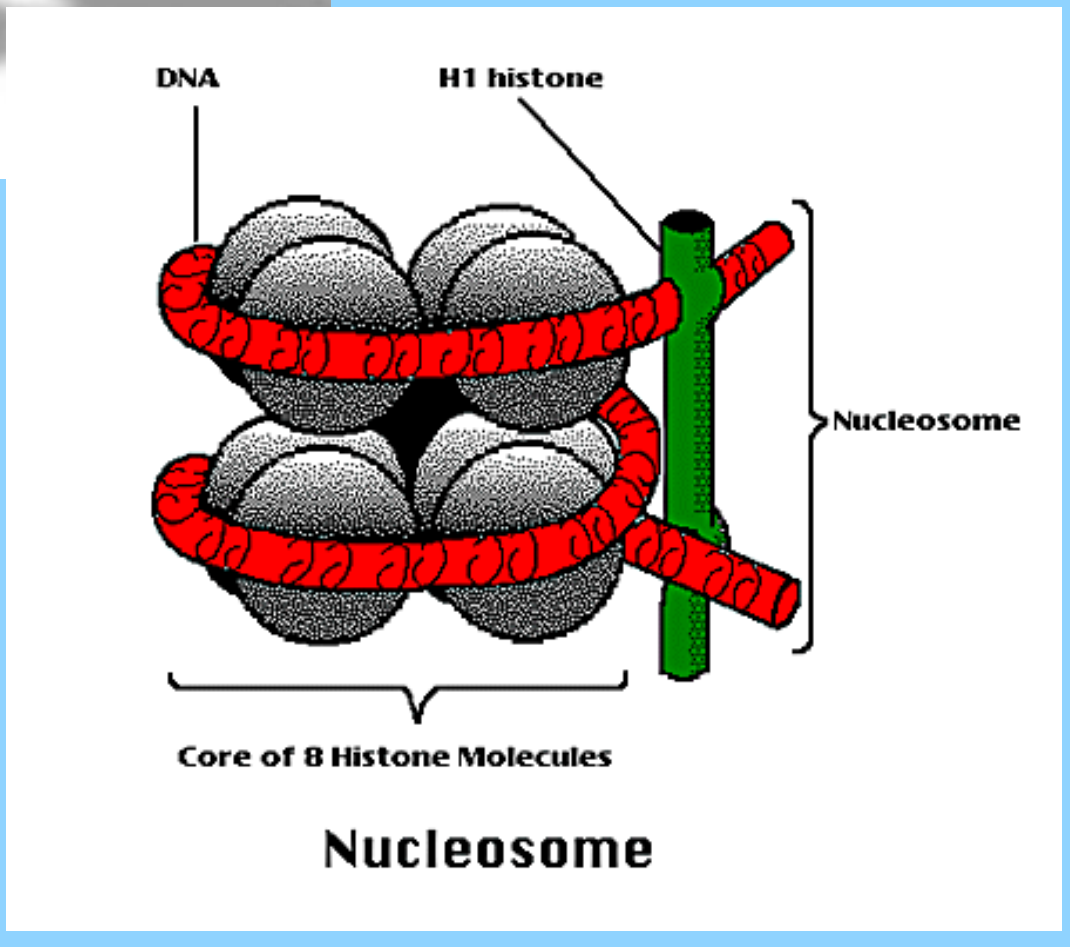
Histones

- **Histones are the major class of proteins associated with chromatin**
- **Histones are basic proteins that bind to the acidic DNA by ionic interactions to form a nucleosome**

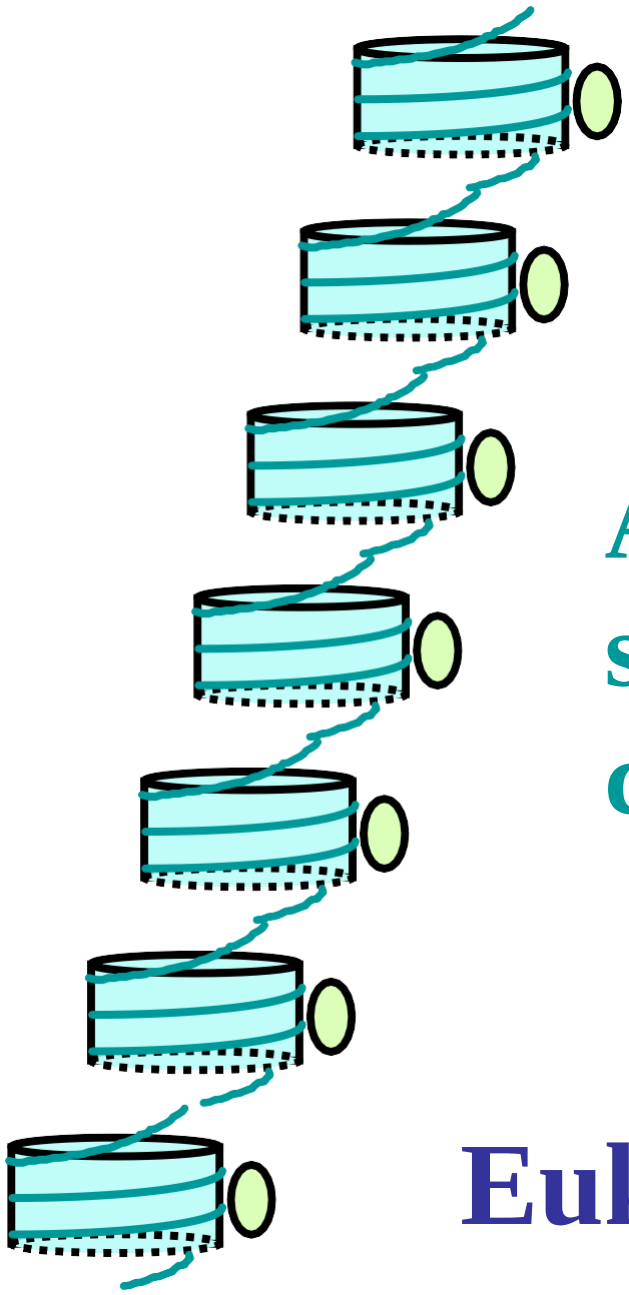
Histones


Histone tails
DNA double helix
Amino acids available lys for chemical modification





Nucleosome



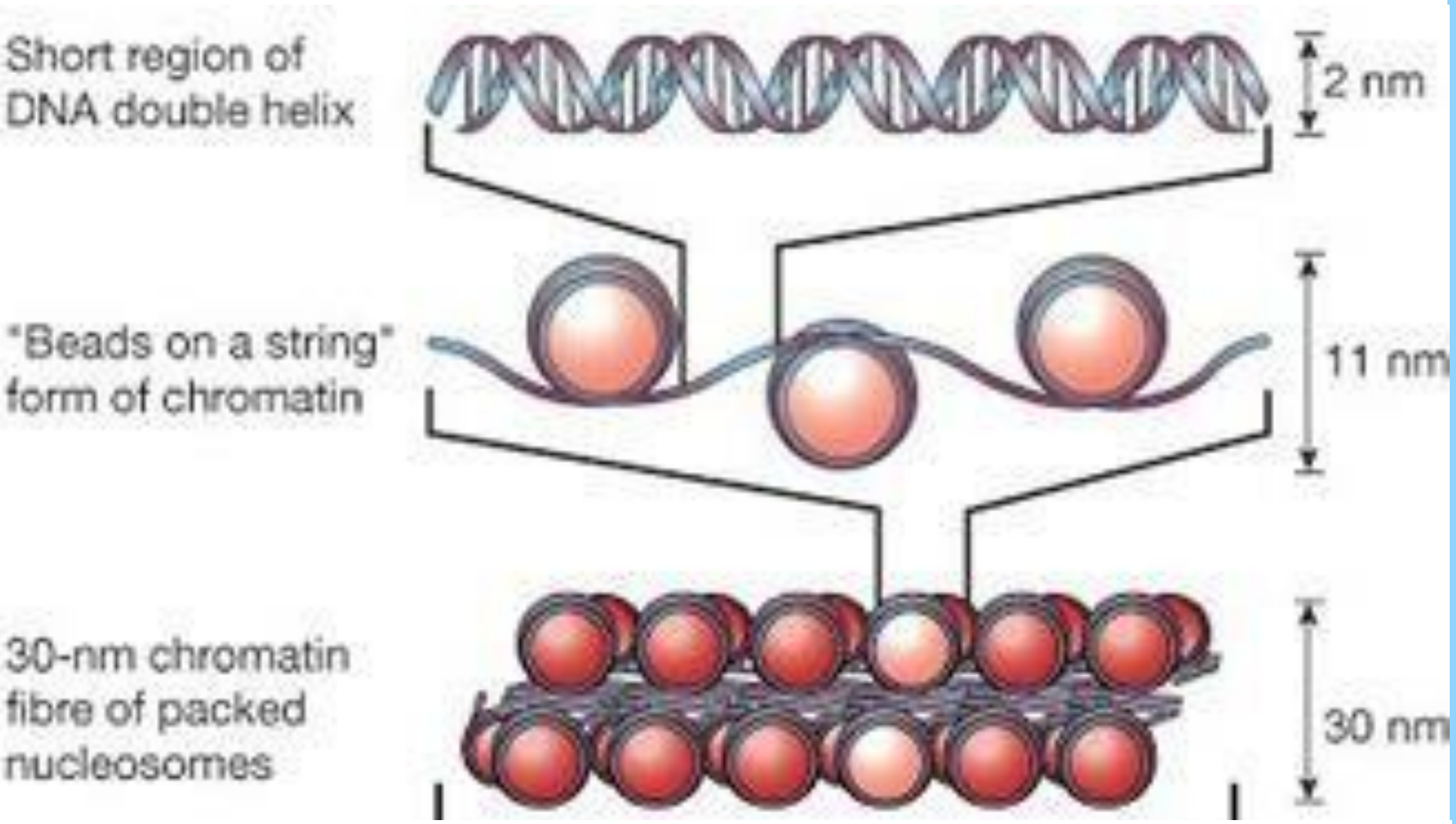
Nucleosomes - like beads on string

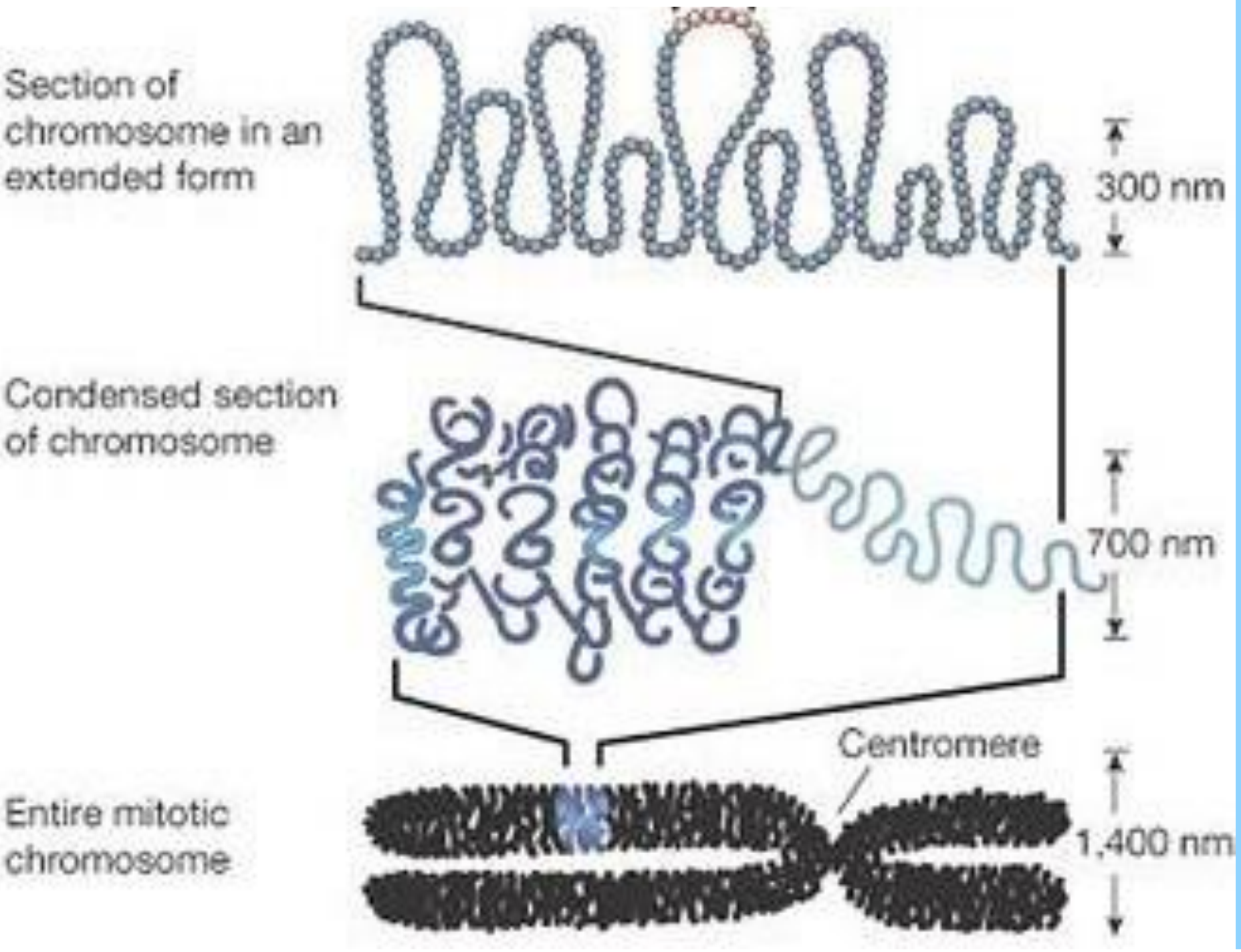
Additional coiling & supercoiling makes compact chromatin

Eukaryotic Chromosome

DNA → Chromatin → Chromosomes

- **DNA double strands condenses with double of its mass of protein to form chromatin which packed as Nucleosomes**
- **Chromatin condenses with a lot of protein 10,000)fold shortening) to from chromosomes**


Short region of DNA double helix
2 nm
"Beads on a string" form of chromatin
11 nm
30-nm chromatin fibre of packed nucleosomes
30 nm


Section of chromosome in an extended form
300 nm
Condensed section of chromosome
700 nm
Centromere
Entire mitotic chromosome
1,400 nm

DNA Multi–scale