

**Fundamentals of central dogma/
Nucleic acids structure and organization**

Molecular Genetics definition:

The branch of biology that deals with the nature of biological phenomena at the genetics level through the study of:

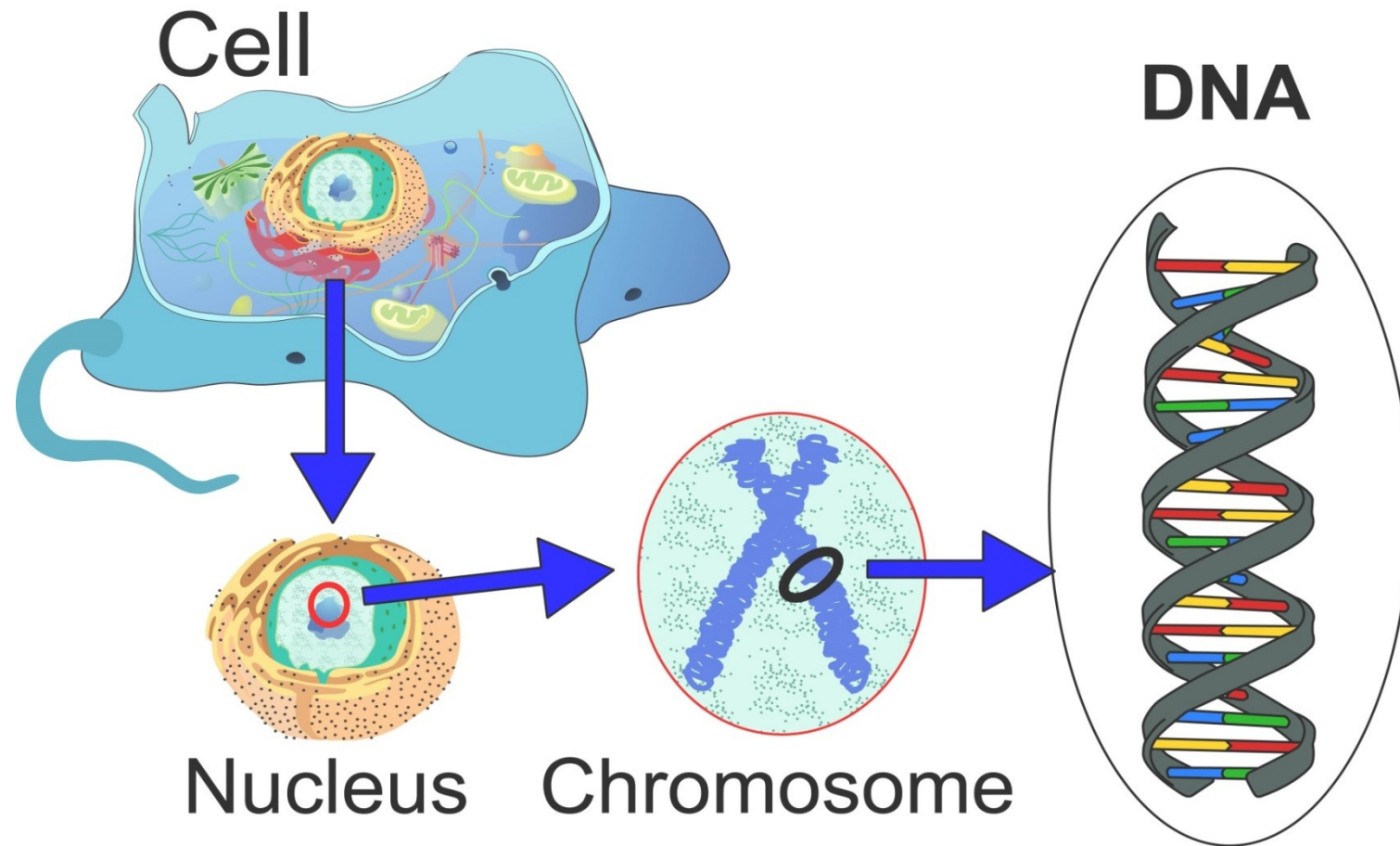
- DNA and RNA, proteins, and other macromolecules involved in genetic information and cell function.**

Functions of nucleic acids

- DNA is the chemical basis of **heredity** and may be regarded as the reserve bank of genetic information.
- Nucleic acids store and transfer cellular information and transfer energy in all living organisms.
- The DNA is organized into genes, the fundamental units of genetic information.
- Every aspect of cellular function is under the control of DNA.

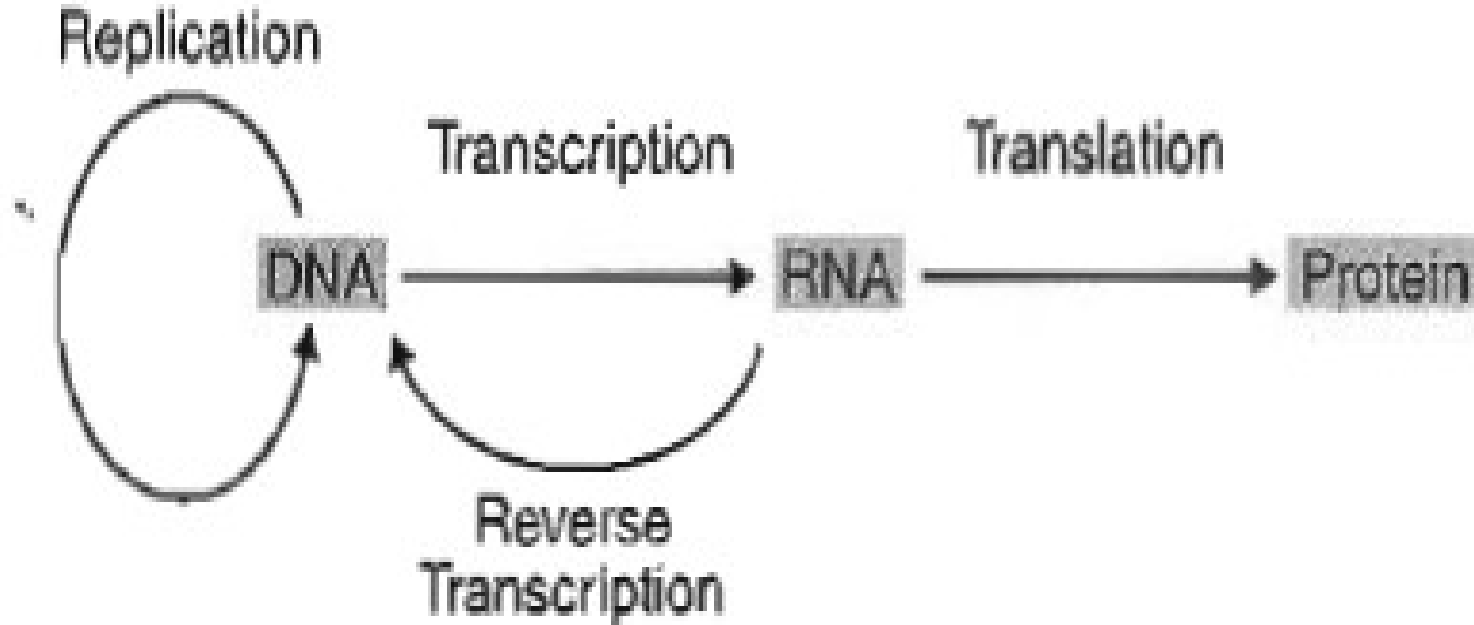
Genetic information

- The entire genetic content of a cell is known as its genome, and the study of genomes is genomics.
- In eukaryotic cells but not in prokaryotes, DNA forms a complex with histone proteins to form chromatin, the substance of eukaryotic chromosomes.
- A chromosome may contain tens of thousands of genes
- Many genes contain the information to make protein products; other genes code for RNA products.
- DNA controls all of the cellular activities by turning the genes “on” or “off.”



The Central Dogma Of Molecular Biology

- The major steps involved in handling genetic information are illustrated by the central dogma of molecular biology

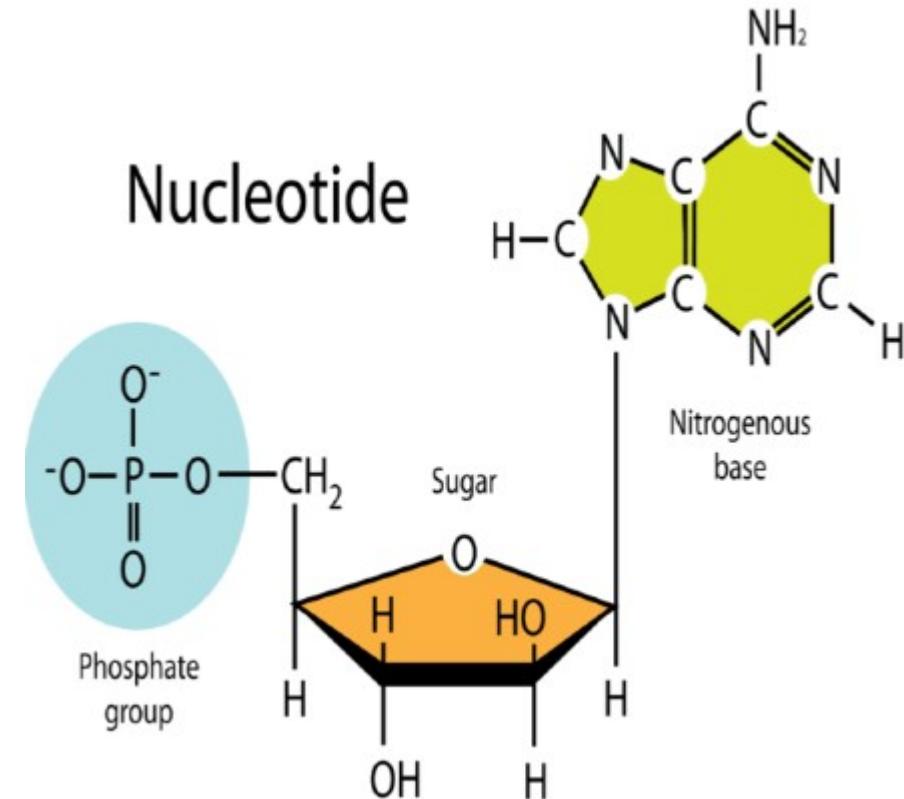


The Building Blocks of DNA

- Double helical structure (Watson & Crick, 1953)
- Three components: 5-carbon deoxyribose sugar, 4 heterocyclic nitrogenous bases & phosphate group

1 sugar + 1 base + 1 phosphate = nucleotide

1 sugar + 1 base = nucleoside



- The heterocyclic nitrogenous bases in DNA are:

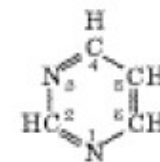
Adenine (A)

Guanine (G)

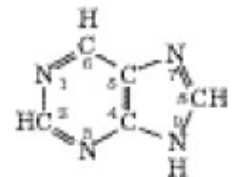
Cytosine (C)

Thymine (T)

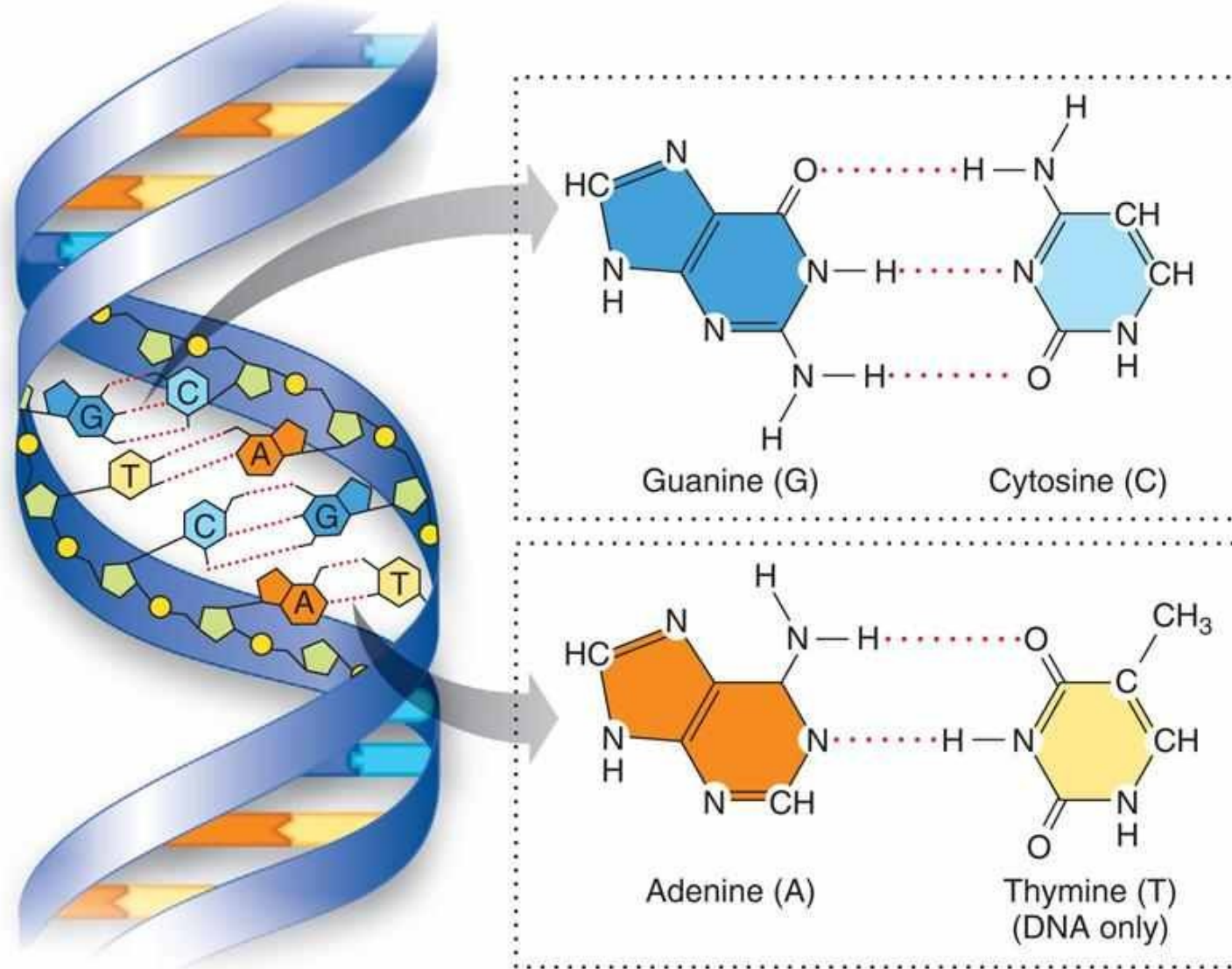
- A & G are purines: Two interlocked heterocyclic rings
- C & T are pyrimidines: One heterocyclic ring



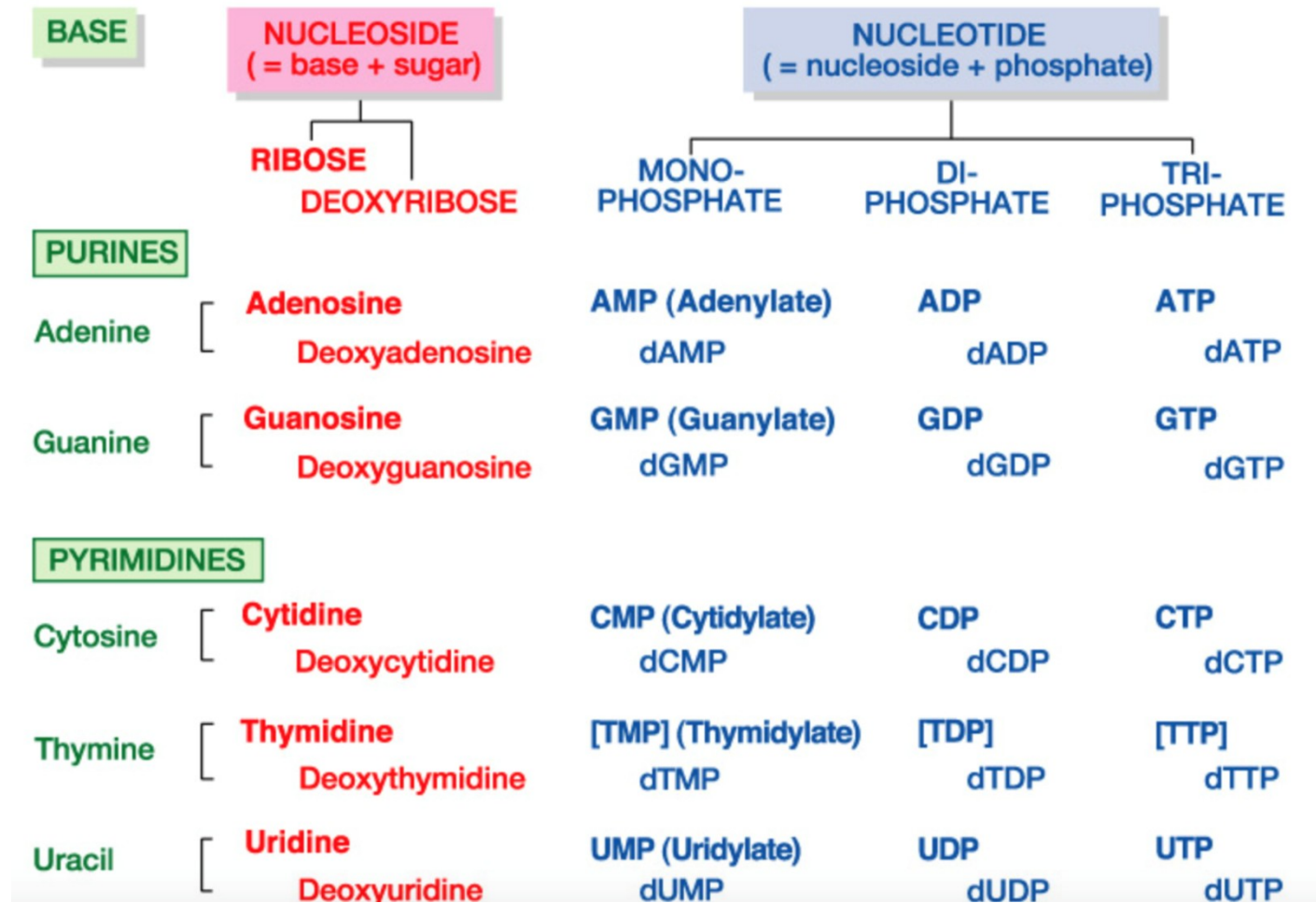
Pyrimidine

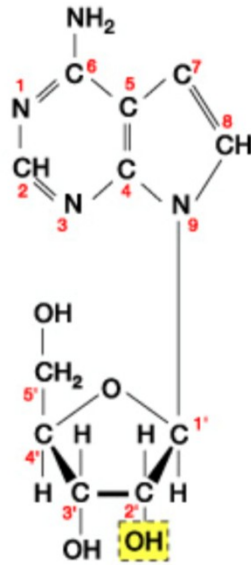


Purine

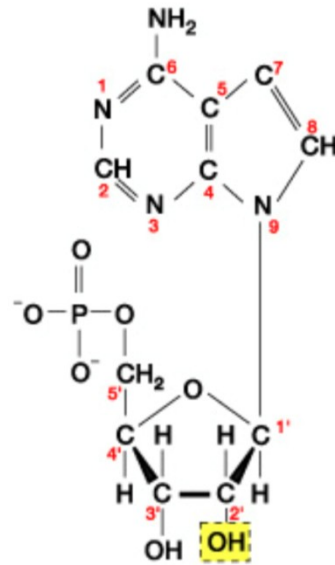


DNA structure with base pairs: G with C and A with T

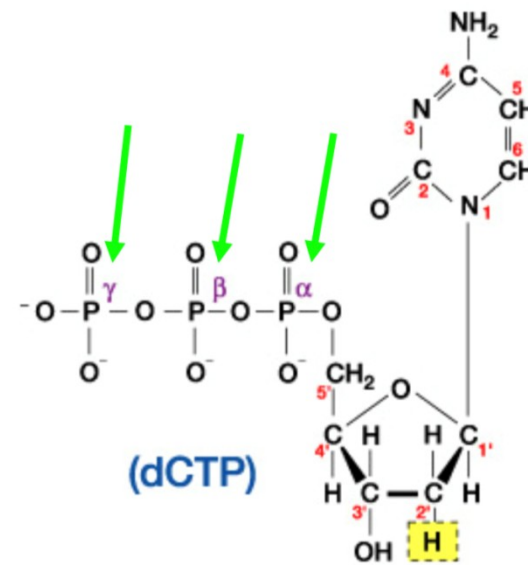




Adenosine



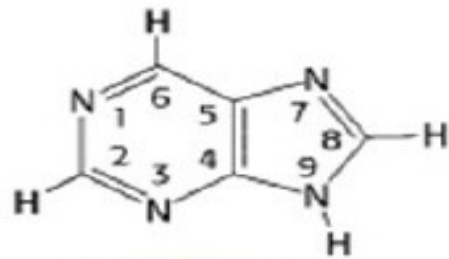
Adenosine 5'-monophosphate (AMP)



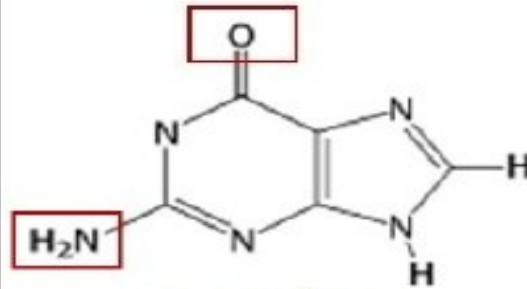
2'-Deoxycytidine 5'-triphosphate (dCTP)

Nitrogenous bases

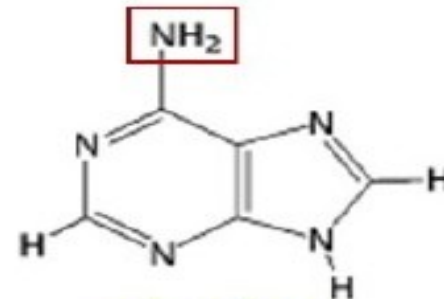
Nucleobases: **Purine** vs **Pyrimidine**



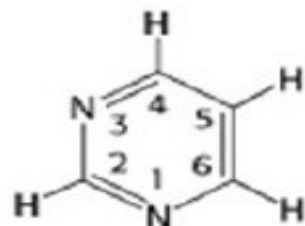
purine



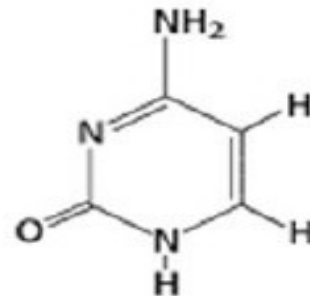
guanine



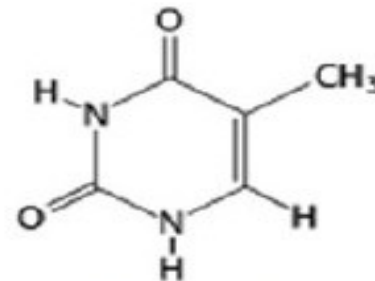
adenine



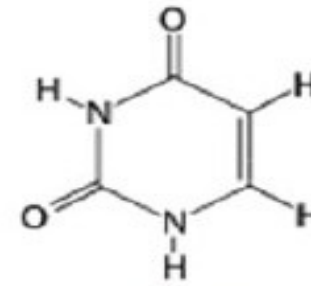
pyrimidine



cytosine



thymine



uracil

Covalent Bonds

- Join nucleotides to each other
- Strong
- Require energy to create & break
- Not affected by environment

Non-Covalent Bonds

- Hold the two chains of DNA together
- Weak (≥ 10 x weaker than covalent)
- Doesn't require chemical energy
- Affected by environment
- Very important in replication, transcription, codon-anticodon recognition & in secondary structure of nucleic acids

- 1926: Levene & Simms
Tetranucleotide structure
- 1953: Pauling & Corey
Triple helix
Phosphates on inside, bases on outside

Watson & Crick model

- Double stranded helix
- External backbone of sugar-phosphate molecules
- Ladder of bases in the centre

Evidence used by Watson & Crick

- Chargaff: base composition of DNA

50:50 purine/ pyrimidine

A=T & C=G

(A+T):(C+G) varies

- Franklin: x-ray diffraction of shape of molecule

DNA was helical

Confirmed Astbury's finding that periodicity of helix was

3.4 nm

The molecule was of unvarying thickness

Features of the Watson & Crick Model

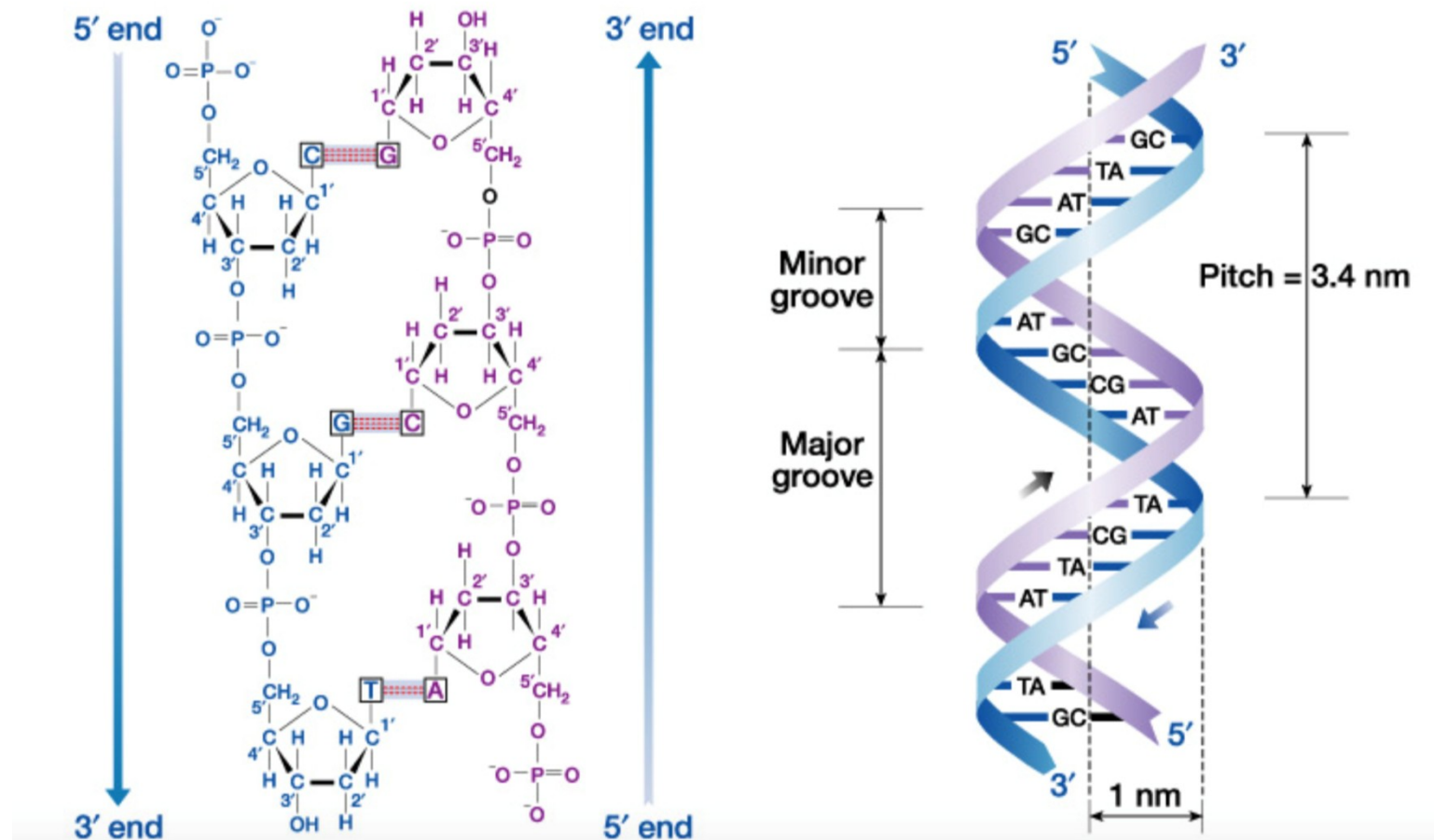
- Two long polynucleotide chains are coiled around a central axis, forming a right-handed double helix
- The two chains are anti-parallel
- The bases of both chains are flat structures, perpendicular to the axis, stuck on one another 0.34 nm apart, on the inside of the structure
- The nitrogenous bases of the opposite chains are paired by hydrogen bonds, in DNA only A=T and C≡G occur
- Adenine pairs with thymine by 2 hydrogen bonds
- Guanine pairs with cytosine by 3 hydrogen bonds

- Each complete turn of the helix is 3.4nm long, with 10 bases per turn in the helix
- The two sugar-phosphate backbones are not equally spaced from one another along the helical axis, resulting in grooves of unequal size between the backbones
- The double helix is 2nm in diameter

Nucleic Acids and 5'-3' prime

- Nucleic acids are polymers of nucleotides joined by 3',5' - phosphodiester bonds; that is, a phosphate group links the 3' carbon of a sugar to the 5' carbon of the next sugar in the chain.
- Each strand has a distinct 5' end and 3' end, and thus has polarity.
- A phosphate group is often found at the 5' end, and a hydroxyl group is often found at the 3' end.
- The base sequence of a nucleic acid strand is written by convention, in the 5'~3' direction (left to right).

- In eukaryotes, DNA is generally double-stranded (dsDNA) and RNA is generally single-stranded (ssRNA).
- Exceptions occur in certain viruses, some of which have ssDNA genomes and some of which have dsRNA genomes.

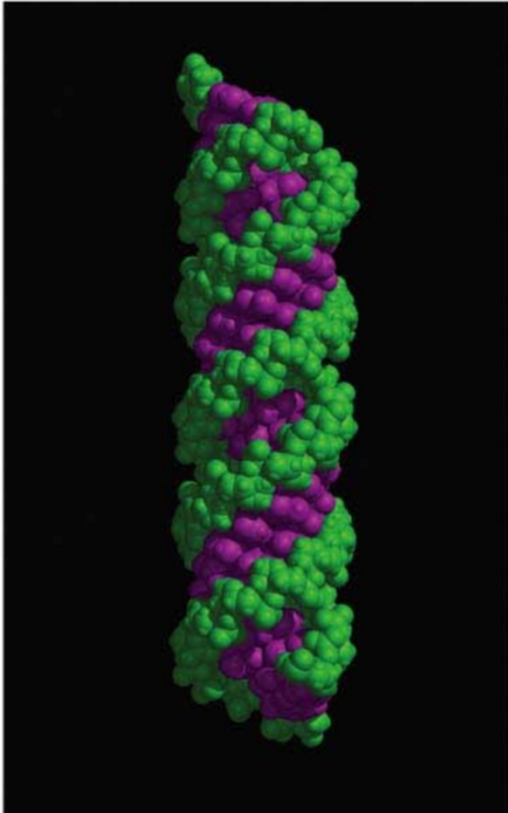


Alternative forms of DNA helix

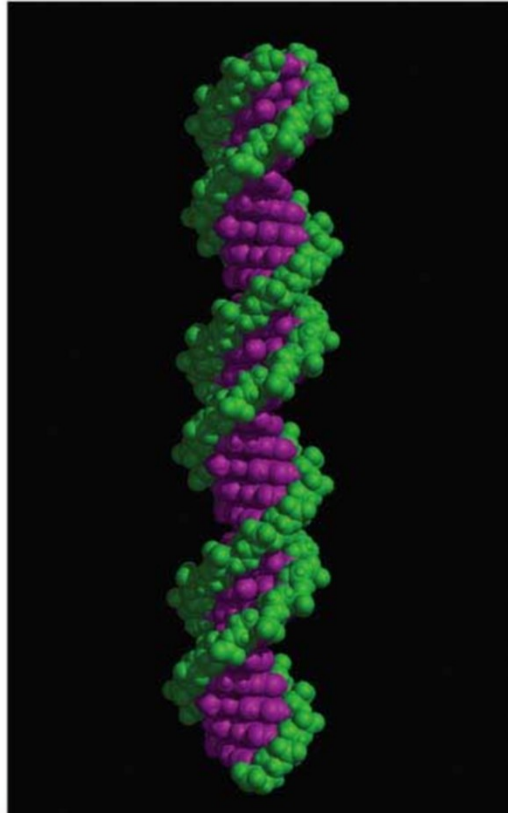
- B-DNA: the form described by Watson & Crick
- A-DNA
 - Occurs under high salt or dehydration conditions
 - 11bp/ turn
 - 2.3nm wide
 - Right-handed helix
 - Bases are off-set from the perpendicular
 - Major & minor grooves altered
 - Does not occur *in vivo*

- Z-DNA
 - Left-handed helix
 - 1.8nm diameter
 - 12bp/ turn
 - Zig-zag shaped
 - Major groove almost non-existent
 - May possibly occur *in vivo*
- P-DNA
 - Long, narrow
 - Phosphates on inside
- C-, D-, E- also hypothesised

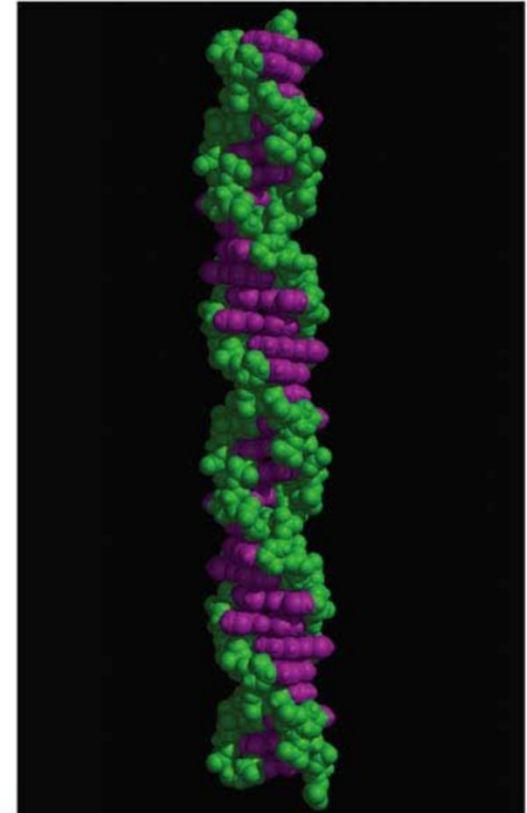
A-DNA



B-DNA



Z-DNA

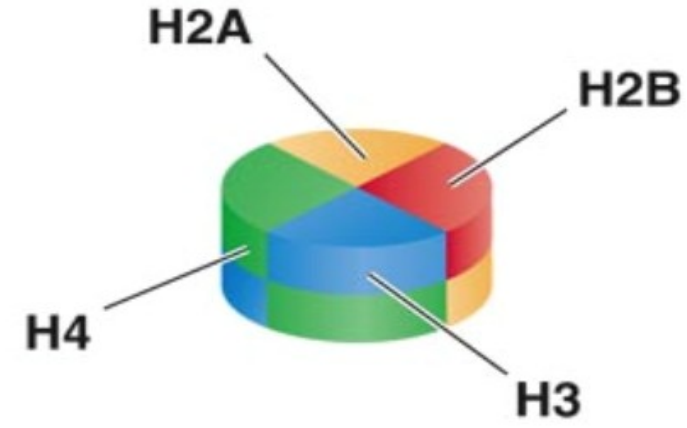


- Human genome $\approx 3.2 \times 10^9$ bp
- Diploid $\therefore 6.4 \times 10^9$ bp
- 1bp = 0.34nm
- 1 cell contains $0.34 \times 6.4 \times 10^9 = 2.17\text{m}$
- Nucleus 5 - 10 μm diameter

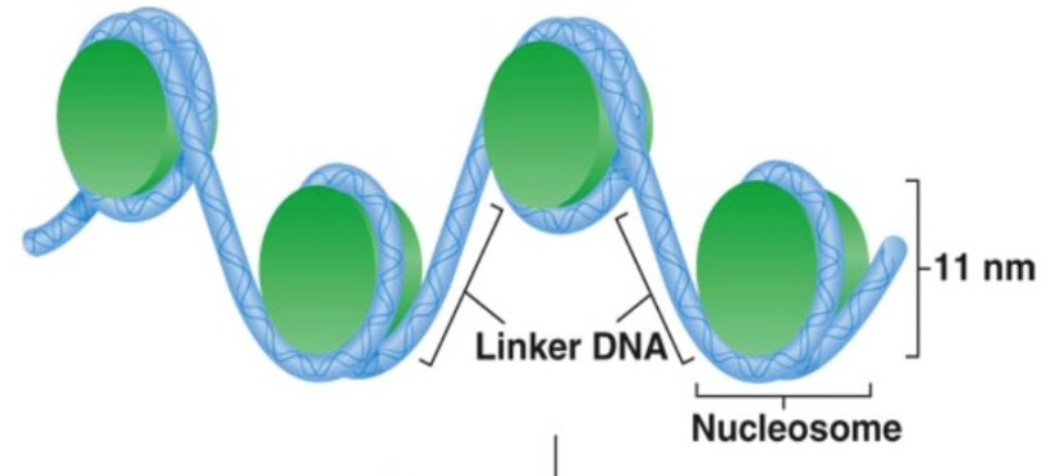
How does DNA fit into a cell?

Nucleosomes “beads on a string”

- Central core of 8 histone proteins: 2x H2A, H2B, H3, H4
- 146bp DNA wraps 1.65 times around the core
- Each nucleosome is an $\approx 11\text{nm}$ diameter x 6nm high cylinder
- A short piece of unwrapped DNA acts as a spacer
- Histone 1 (H1) creates further condensation



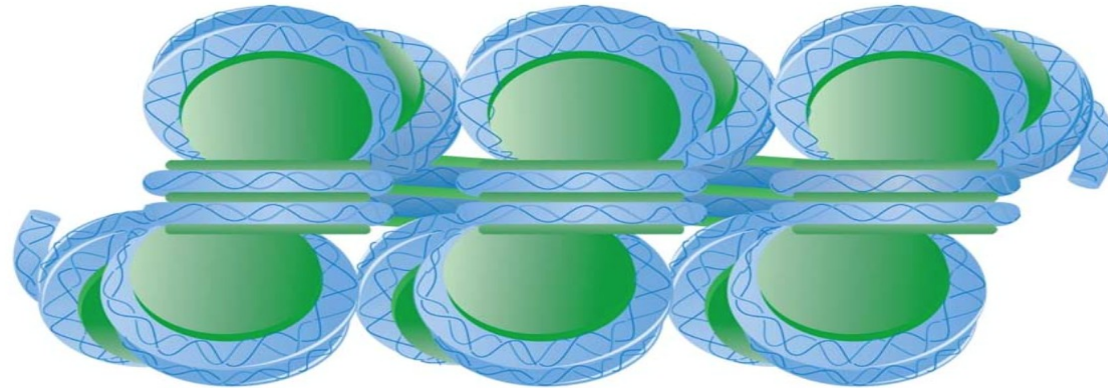
Histone

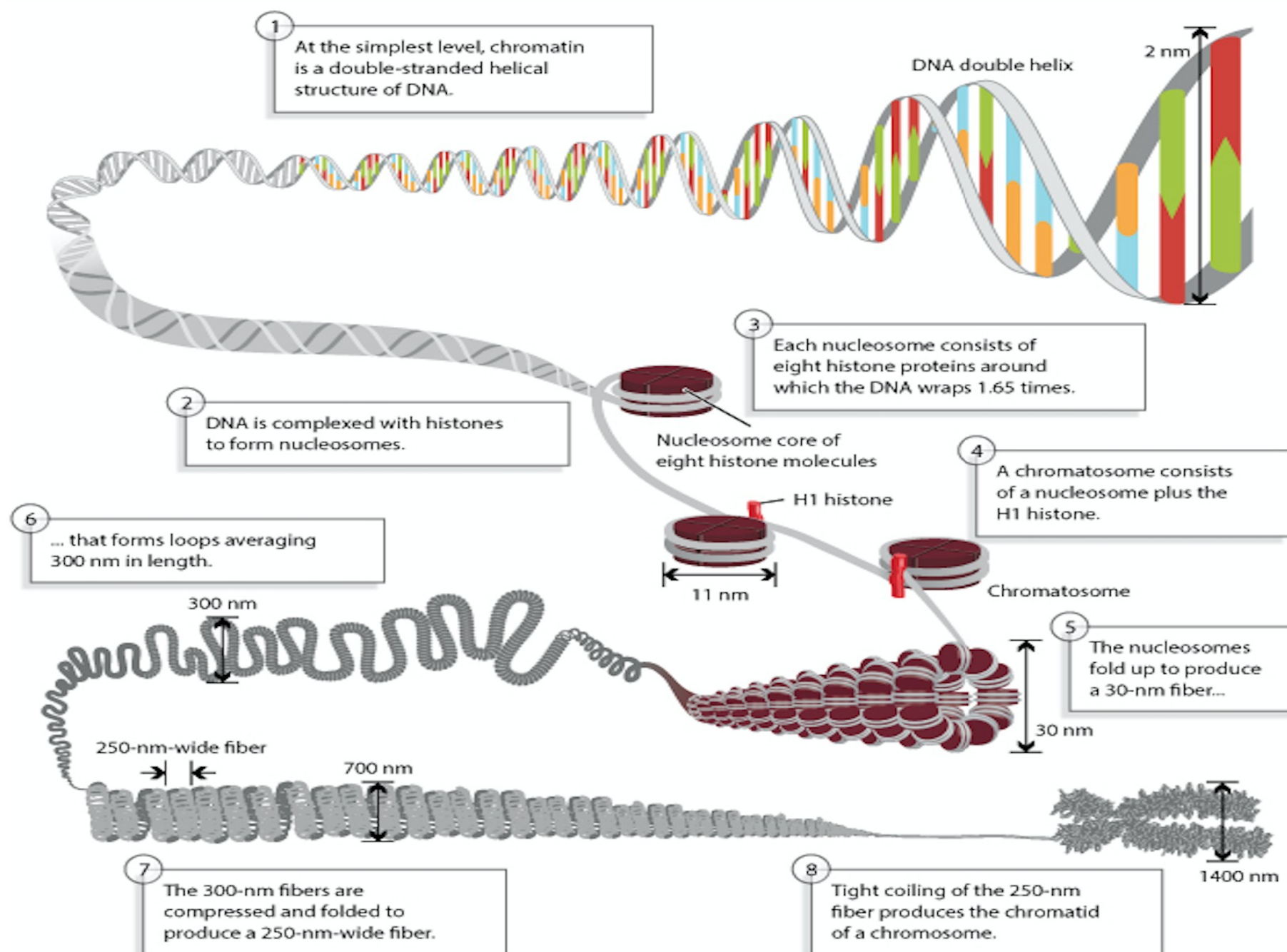


Chromatin

Chromatin Fibres “Solenoids”

- Nucleosomes are wound into compact bundles
- 30nm diameter
- 6 nucleosomes per complete turn





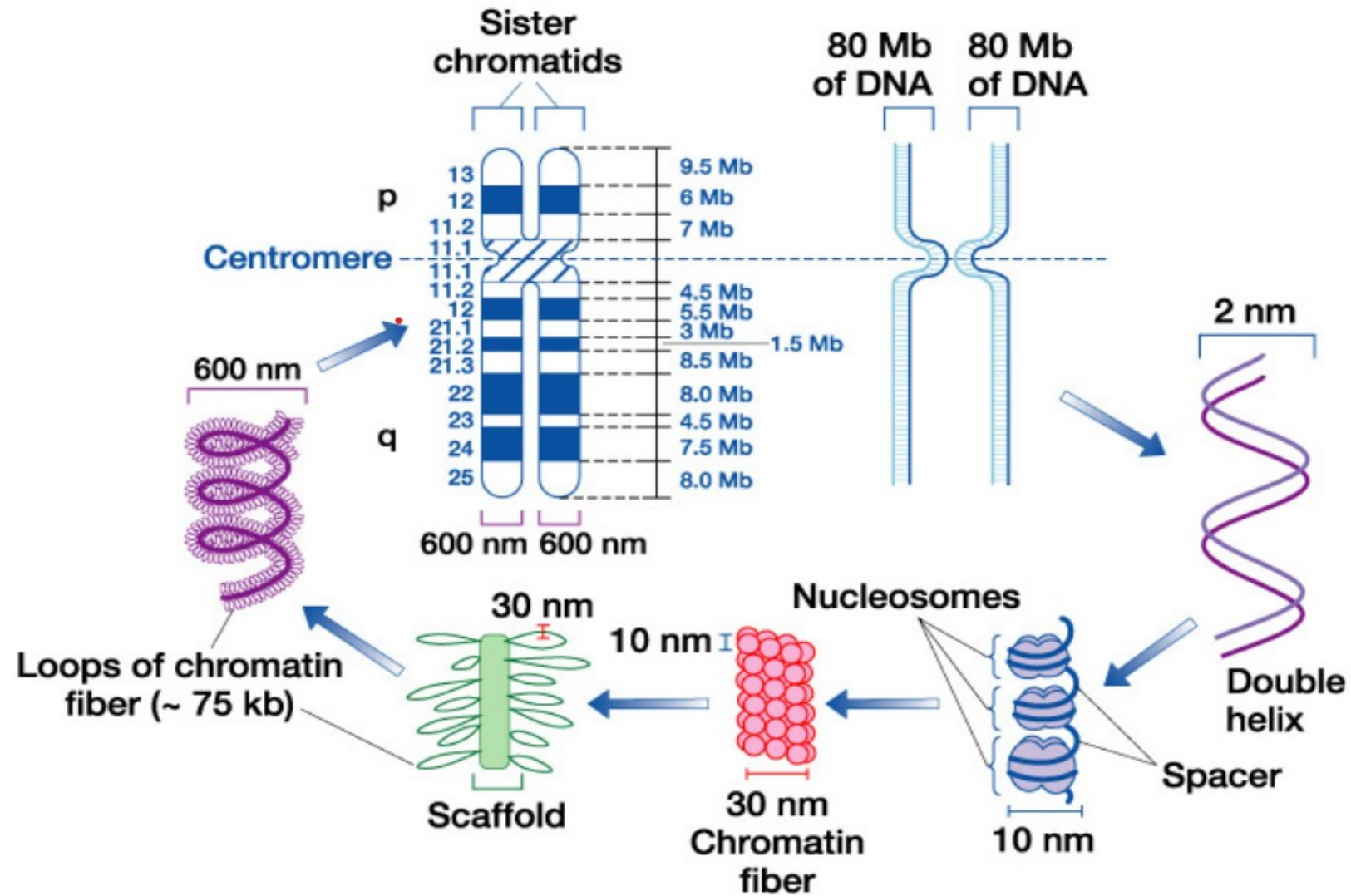


Figure 2-3 Human Molecular Genetics, 3/e. (© Garland Science 2004)

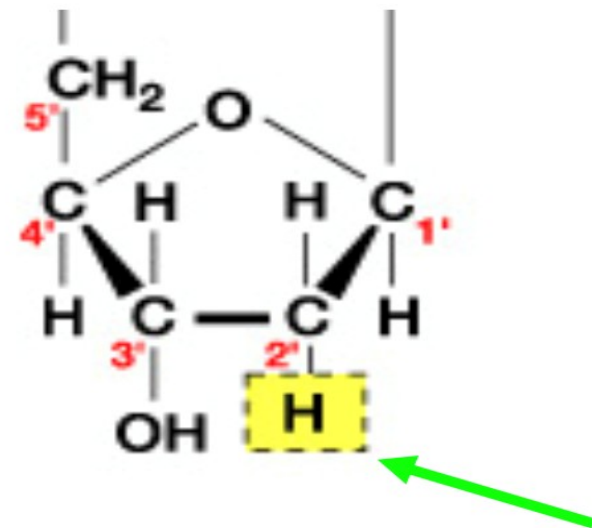
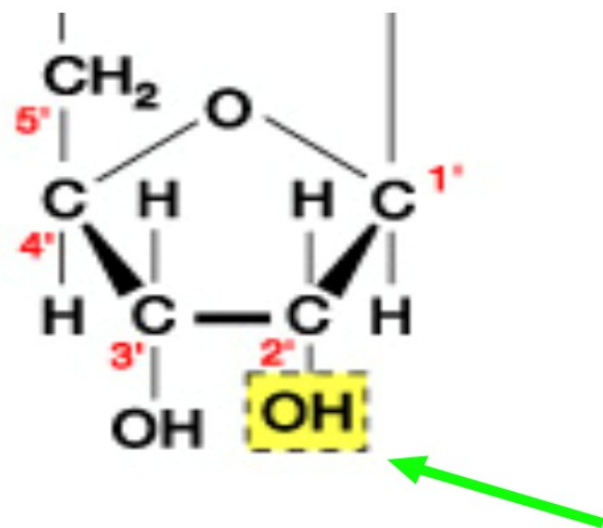
Location of DNA

- In prokaryotes, DNA is not separated from the rest of the cellular contents.
- In eukaryotes, however, DNA is located in the nucleus, where it is separated from the rest of the cell by the nuclear envelope.
- Eukaryotic DNA is bound to proteins, forming a complex called chromatin.
- During interphase (when cells are not dividing), some of the chromatin is diffuse (euchromatin) and some is dense (heterochromatin), but no distinct structures can be observed.

- However, before mitosis (when cells divide), the DNA is replicated, resulting in two identical chromosomes called **sister chromatids**.
- During metaphase (a period in mitosis), these condense into discrete, visible chromosomes.

Structure of RNA

- RNA is similar to DNA. Like DNA, it is composed of nucleotides joined by 3 to 5-phosphodiester bonds, the purine bases adenine and guanine, and the pyrimidine base cytosine.
- However, its other pyrimidine base is uracil rather than thymine. Uracil and thymine are identical bases except that thymine has a methyl group at position 5 of the ring. In RNA, the sugar is ribose, which contains a hydroxyl group on the 2'-carbon
- RNA chains are usually single-stranded and lack the continuous helical structure of double-stranded DNA. However, RNA still has considerable secondary and tertiary structure because base pairs can form in regions where the strand loops back on itself.
- **Is RNA antiparallel?**



Types of RNA

RNA molecules play a variety of roles in the cell. The major types of RNA are:

- 1) **Ribosomal RNA (rRNA)**, which is the most abundant type of RNA in the cell. It is used as a structural component of the ribosome. Ribosomal RNA associates with ribosomal proteins to form the complete, functional ribosome.
- 2) **Transfer RNA (tRNA)**, which is the second most abundant type of RNA. Its function is to carry amino acids to the ribosome, where they will be linked together during protein synthesis.
- 3) **Messenger RNA (mRNA)**, which carries the information specifying the amino acid sequence of a protein to the ribosome. Messenger RNA is the only type of RNA that is translated. The mRNA population in a cell is very heterogeneous in size and base sequence, as the cell has essentially a different mRNA molecule for each of the thousands of different proteins made by that cell.

- 4) **Heterogeneous nuclear RNA (hnRNA or pre-mRNA)**, which is found only in the nucleus of eukaryotic cells. It represents precursors of mRNA, formed during its posttranscriptional processing.
- 5) **Small nuclear RNA (snRNA)**, which is also only found in the nucleus of eukaryotes. One of its major functions is to participate in splicing (removal of introns) mRNA.
- 6) **Ribozymes**, which are RNA molecules with enzymatic activity. They are found in both prokaryotes and eukaryotes.