# Nucleic acids

BIOS 10016

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## Objectives

- Know all definitions associated with nucleic acids.
- Draw and name the nucleosides, nucleotides and Watson-Crick base pairs associated with DNA and RNA.
- Know the numbering schemes for the components of nucleotides.
- Describe and explain the absorbance properties of nitrogenous bases.
- Describe the chemical and structural similarities and differences between DNA and RNA.
- Use Chargaff's rules to predict the composition of DNA molecules.
- Describe the different double helical structures that DNA and RNA can adopt.
- Write out the complementary strand based upon Watson-Crick base pairing.
- Predict the stability of double stranded DNA sequences.
- Identify major and minor grooves in B-DNA.
- Describe how proteins interact with DNA, and why the major groove is often bound.
- Describe the features/forces that stabilize nucleic acid structure.
- Describe the phenomenon and role of supercoils, and the supercoil forms that exist.
- Describe the higher order structures that DNA adopts in cells.
- Describe the roles of messenger, transfer, ribosomal and other non-coding RNAs.
- Describe the features and exceptions to the central Dogma.
- Describe the concepts behind DNA replication:
  - what is the meaning of semi-conservative?
  - the stages involved in the process

- main protein players in prokaryotic and eukaryotic systems and the roles that they play in the process
- mechanism by which nucleotides are added to growing strand

# Nucleic acids, RNA, DNA

## The building blocks of nucleic acids

### Nucleotides

Nitrogenous bases with pentose sugar ($\beta$-D-ribofuranose or $\beta$-D-2'[1]-deoxyribofuranose) with one or more phosphate groups ($\alpha$, $\beta$, $\gamma$). Nitrogenous bases can be **purines** with two rings, 4 nitrogens (adenine, guanine) or **pyrimidines** with one ring (cytosine, uracil, thymine). Nitrogenous bases are heterocycles, aromatic, and flat and absorb UV light (260 nm).

### Nucleosides

Nitrogenous bases with pentose sugar (ribose or deoxyribose) with no phosphate groups.

### Numbering positions on nitrogenous bases

**Pyrimidines**: start with the nitrogen where the sugar is attached, count in a circle toward the next nitrogen.

**Purines**: start with the position opposite the sugar nitrogen, then jump to the next closest nitrogen.

### Nitrogenous base pairings

adenine → thymine (in DNA), 2 hydrogen bonds
guanine → cytosine, 3 hydrogen bonds
adenine → uracil (in RNA), 2 hydrogen bonds

### Nucleotide nomenclature

| Nitrogenous base | Ribose nucleoside | Within a nucleic acid |
|---|---|---|
| Adenine | Adenosine | Adenylate |
| Guanine | Guanosine | Guanylate |
| Cytosine | Cytidine | Cytidylate |
| Uracil | Uridine | Uridylate |
| Thymine | Thymidine | Thymidylate |

## Structure of DNA

### Nucleic acid orientation

- Linear or circular, depending on organism
- DNA - deoxyribonucleotide polymer: dAMP, dCMP, dGMP and TMP

[1]The ' is added to differentiate between the sugar carbon numbering and the nucleotide numbering.

- Linked by phosphodiester bonds between the 5' phosphate of one nucleotide and the 3' hydroxyl of the next (3' $\rightarrow$ 5' linkage)
- RNA - ribonucleotide polymer: AMP, CMP, GMP and UMP
- Conventionally, named and drawn in the 5' to 3' direction (example: 5' ATGC 3')
- Double helix structure of B-DNA was published in 1953 by James Watson and Francis Crick (but it was all because of Rosalind Franklin's X-ray diffraction data!)
- Nobel prize in 1962 along with Maurice Wilkins
- **Anti-parallel, right-handed helix**
- Two grooves: major (wider, deeper) and minor (shallower, smaller)
- 10.5 base pairs per turn
- Watson-Crick base pairing (cytosine to guanine, thymine or uracil to adenine)

**Chargaff's rule for double-stranded DNA**

%C = %G and %A = %T. G to C is more stable because of 3 hydrogen bonds

**Base pair stacking**

- Base pairs stack on each other like books on a shelf
- **Stabilized by London interactions between pi orbitals** ($\pi$-$\pi$ interaction)
- Edges of bases define grooves

**DNA conformations**

B-DNA ist he most common form adopted, but other forms exist:

- A-DNA (dehydrated B-DNA)
  - Right-handed helix
  - Observed in RNA, dehydrated DNA, and DNA-RNA hybrid structures
  - 11 base pairs per turn
  - Pitch: 25.3 Å
- Z-DNA
  - Zigzag conformation
  - Left-handed helix
  - Common for alternating purine/pyrimidine sequences
  - Arises from **torsional strain** imposed by supercoiling

  - 12 base pairs per turn
  - Pitch: 45.6 Å

## Amino acid interactions

- Positively charged amino acids (R, H, K) form salt bridges with $PO_4^-$, elevating protein pI
- Amino acid residues "read" the DNA sequence by recognising H-bond acceptors (A) and donors (D) in the major groove
  - Adenine: $-NH_2$, $N_7$
  - Thymine: $O_4$
  - Guanine: $O_6$, $N_7$
  - Cytosine: $-NH_2$

## Structure stability

- Hydrogen bonds within base pairs
- Hydration (phosphate group and ribose OH are hydrophilic)
- Ionic (phosphate backbone is rich in negative charges, high energy state that can be stabilized by Mg)
- Hydrophobic interactions and base stacking (bases are aromatic - hydrophobic, London force interactions between $\pi$-$\pi$ orbitals result in stacking)

## Supercoiling of DNA

- Positive and negative supercoiling
- Imposed strain causes supercoiling
- Results from attempted unwinding of DNA
- Energy is stored in the supercoil as torque
- A right-handed coil
- The energy helps in the separation of the strands for transcription and replication of DNA

### Positive supercoiling

Results from overwinding, a left-handed supercoil

### Negative supercoiling

Results from underwinding, a right-handed supercoil

## Higher order structures of DNA

- **Nucleosomes**: a complex between DNA and histone proteins
- "Beads on a string" structure
- Positively charged amino acids needed on histone proteins

## RNA - Ribonucleic acids

- A versatile molecule:
  - Protein synthesis
  - Structural roles
  - Catalytic roles
- Differs from DNA:
  - Ribose sugar instead of deoxyribose
  - Uracil nitrogenous base replaces thymine
  - Predominantly exists in single-stranded form
  - Adjacent bases adopt 2° structures: harpins, A-form helices, internal loops, stem loops
  - Adopts 3° and 4° structures, very protein-like
  - Structures are also stabilized by unique base pairs/triplets
- Modification of bases is common

### Types of RNA

**messenger RNA, mRNA** carries genetic information from DNA through to protein synthesis

**transfer RNA, tRNA** molecules transport amino acids to the ribosomes for polypeptide assembly (15% of cellular RNA)

**ribosomal RNA, rRNA** the functional component oand the framework for the ribosome

**ribozyme, catalytic RNA** formation of peptide bonds, associated proteins only play structural roles

## Processes involving DNA

### Central Dogma of genetic information transfer

### DNA transcripted into RNA translated into proteins (and DNA can replicate itself)

- The traditional central dogma is overly simplified since information also flows in the other direction
  - Proteins are involved in regulation
  - RNA molecules involved at all steps
  - Viruses have RNA genomes
  - **RNA world**: the hypothesis that RNA was the first self-replicating molecule
  - Like proteins, RNA molecules can perform many functional roles

### DNA replication

- Process by which DNA is duplicated
- Similar in all organisms
- **Semi-conservative**: new DNA molecules contain one parent and one daughter strand (original strand separates into 2, old strand + new strand)

**Steps:**

1. Initiation:
   - Helicase (important to rip strands apart)
   - Single-stranded DNA binding proteins
   - Primase (allows recognition by polymerase, laying the foundation)
2. Elongation
   - Polymerases
   - Topoisomerases (release supercoiling so processes continue)
3. Termination
   - Ligase
   - Telomerase
   - Tus protein

**DNA replication sites**

- In prokaryotes: 1 site: oriC
- In eukaryotes: multiple origin sites
- Recognised by helicases that destabilise the double-stranded DNA duplex, requires ATP (energy)
- Very energy-intensive process
- Leads to the formation of **replication bubbles** from origins of replication
- **Single-stranded DNA binding (SSB) proteins** stabilize single stranded DNA state
- **Primase** "primes" the open DNA for replication
- Recognises the exposed bases in the replication fork
- Synthesises a short primer sequence on the DNA template (RNA in prokaryotes, RNA-DNA in eukaryotes)

**DNA polymerase**

- Main polymerases: DNA polymerase III (prokayreotes) and DNA polymerases $\delta$ and $\varepsilon$ (eukaryotes)
- Large multi-enzyme complex
- Recognises the RNA-DNA duplex in the replication bubble
- Highly processive, not released until completed replication of DNA
- $\beta$-sliding clamp (encircles DNA and enhances processivity)
- Requires $Mg_2{}^+$, DNA template, primers with a free 3' OH group, and deoxyNTPs (dATP, dCTP, dGTP and TTP)

**5' to 3' synthesis of DNA**

- DNA template read in the 3' $\rightarrow$ 5' direction
- Parental DNA opens
- 5' is the leading strand (continuous), 3' is the lagging strand (discontinuous, happens in **Okazaki fragments**)
- DNA made read in the 5' $\rightarrow$ 3' direction