Chapter Nine
Nucleic Acids: How Structure Conveys Information

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Information Transfer in Cells

• Information encoded in the nucleotide sequence of DNA is transcribed through RNA synthesis

• Sequence then dictated by DNA sequence

• Central dogma of biology

Replication
DNA replication yields two DNA molecules identical to the original one, ensuring transmission of genetic information to daughter cells with exceptional fidelity.

Transcription
The sequence of bases in DNA is recorded as a sequence of complementary bases in a single-stranded mRNA molecule.

Translation
Three-base codons on the mRNA corresponding to specific amino acids direct the sequence of building a protein. These codons are recognised by tRNAs (transfer RNAs) carrying the appropriate amino acids. Ribosomes are the "machinery" for protein synthesis.
Nucleic Acids

• Levels of structure
  • 1° structure: the order of bases on the polynucleotide sequence; the order of bases specifies the genetic code
  • 2° structure: the three-dimensional conformation of the polynucleotide backbone
  • 3° structure: supercoiling
  • 4° structure: interaction between DNA and proteins

Nucleic Acids

• **Nucleic acid**: a biopolymer containing three types of monomer units
  • a base derived from purine or pyrimidine (nucleobases)
  • a monosaccharide, either D-ribose or 2-deoxy-D-ribose
  • phosphoric acid

• RNA (Ribonucleic Acid)

• DNA (Deoxyribonucleic Acid)
Pyrimidine/Purine Bases

• The structures of pyrimidine and purine are shown here for comparison

Other Bases

• Less common bases can occur

• Principally but not exclusively, in transfer RNAs
Nucleosides

- **Nucleoside**: a compound that consists of D-ribose or 2-deoxy-D-ribose covalently bonded to a nucleobase by a \( \beta \)-N-glycosidic bond
- Lacks phosphate group

![Nucleoside structures](image)

Nucleotides

- **Nucleotide**: a nucleoside in which a molecule of phosphoric acid is esterified with an -OH of the monosaccharide, most commonly either the 3’-OH or the 5’-OH
- Name based on parent nucleoside with a suffix “monophosphate”
- Polymerization leads to nucleic acids. Linkage is repeated \((3',5')\)-phosphodiester bond

*(Biochemical Connections p. 232)*
DNA - 1° Structure

- **Deoxyribonucleic acids, DNA**: a biopolymer that consists of a backbone of alternating units of 2-deoxy-D-ribose and phosphate
  - the 3’-OH of one 2-deoxy-D-ribose is joined to the 5’-OH of the next 2-deoxy-D-ribose by a phosphodiester bond
- **Primary Structure**: the sequence of bases along the pentose-phosphodiester backbone of a DNA molecule
  - base sequence is read from the 5’ end to the 3’ end

DNA differs from RNA

Sugar is 2’-deoxyribose, not ribose.

- Sometimes “d” used to designate “deoxy”
- Writing a DNA strand
  - an abbreviated notation
  - even more abbreviated notations
  - d(GACAT)
  - pdApdCpdGpdT
  - pdACGT
DNA - 2° Structure

- **Secondary structure**: the ordered arrangement of nucleic acid strands
  - the double helix model of DNA 2° structure was proposed by James Watson and Francis Crick in 1953
- **Double helix**: a type of 2° structure of DNA molecules in which two antiparallel polynucleotide strands are coiled in a right-handed manner about the same axis
  - structure based on X-Ray crystallography

Summary – secondary structure of DNA

1. DNA forms a regular right-hand helix, making a complete turn every 3.4 nm with a diameter of 2 nm giving 10 nucleotides per turn.

2. The helix contains 2 anti-parallel polynucleotide chains – bases facing inwards, with a purine always opposite a pyrimidine.

3. Proportion of G always the same as the proportion of C and the proportion of T the same as A.

Chargaff's Law: A=T, G=C
T-A Base Pairing

• Base pairing is complimentary

• A major factor stabilizing the double helix is base pairing by hydrogen bonding between T-A and between C-G

• T-A base pair comprised of 2 hydrogen bonds

G-C Base Pair

• G-C base pair comprised of 3 hydrogen bonds
Other Forms of DNA

- **B-DNA**
  - considered the physiological form
  - a right-handed helix, diameter 11Å
  - 10 base pairs per turn (34Å) of the helix

- **A-DNA**
  - a right-handed helix, but thicker than B-DNA
  - 11 base pairs per turn of the helix
  - has not been found *in vivo*

- **Z-DNA**
  - a left-handed double helix
  - may play a role in gene expression

Comparison of A, B, and Z forms of DNA

- Both A and B-DNA are right-handed helices
- Z-DNA is left handed
- Z-DNA occurs in nature, usually consists of alternating purine-pyrimidine bases
- Methylated cytosine found also in Z-DNA
Other Features of DNA

• **Base stacking**
  - bases are hydrophobic and interact by hydrophobic interactions
  - in standard B-DNA, each base rotated by 32° compared to the next and, while this is perfect for maximum base pairing, it is not optimal for maximum overlap of bases; in addition, bases exposed to the minor groove come in contact with water
  - many bases adopt a propeller-twist in which base pairing distances are less optimal but base stacking is more optimal and water is eliminated from minor groove contacts

Z-form is derivative of B-form

• Produced by flipping one side of the backbone 180° without disturbing the backbone covalent bonds or hydrogen bonds
Propeller Twists

- Bases that are exposed to minor groove contact with water
- They twist in a “propeller twist” fashion
- Results in:
  - less optimal base pair distance
  - more optimal base pair stacking (eliminates presence of water molecules)

DNA - 3° Structure

- **Tertiary structure**: the three-dimensional arrangement of all atoms of a nucleic acid; commonly referred to as supercoiling
- **Circular DNA**: a type of double-stranded DNA in which the 5’ and 3’ ends of each stand are joined by phosphodiester bonds
- **Supercoiling**: Further coiling and twisting of DNA helix.
- **Topoisomerases**
  - Class I: cut the phosphodiester backbone of one strand, pass the end through, and reseal
  - Class II: cut both strands, pass some of the remaining DNA helix between the cut strands, and reseal
- **DNA gyrase**: a bacterial topoisomerase
Super DNA Coiled Topology

• Prokaryotic DNA is circular. It can form supercoils.
• Double helix can be considered to a 2-stranded, right handed coiled rope
• Can undergo positive/negative supercoiling

Properties of naturally occurring DNA molecules

<table>
<thead>
<tr>
<th>Source</th>
<th>Single Strand (SS) or Double Strand (DS)</th>
<th>Circular or Linear</th>
<th>Number of Base Pairs (bp) or Bases (b)</th>
<th>Molecular Mass (Da)</th>
<th>Length (μm)</th>
<th>% (G + C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simian virus 40 (genome)⁴</td>
<td>DS</td>
<td>Circular</td>
<td>5243 bp</td>
<td>3.293 × 10⁶</td>
<td>1.78</td>
<td>40.80</td>
</tr>
<tr>
<td>Bacteriophage φX174 (genome)</td>
<td>SS</td>
<td>Circular</td>
<td>5286 b</td>
<td>1.664 × 10⁶</td>
<td>d</td>
<td>44.76</td>
</tr>
<tr>
<td>Bacteriophage M13 (genome)</td>
<td>SS</td>
<td>Circular</td>
<td>6407 b</td>
<td>1.977 × 10⁶</td>
<td>d</td>
<td>40.75</td>
</tr>
<tr>
<td>Cauliflower mosaic virus (genome)</td>
<td>DS</td>
<td>Circular</td>
<td>8031 bp</td>
<td>4.962 × 10⁶</td>
<td>2.73</td>
<td>40.19</td>
</tr>
<tr>
<td>Adenovirus AD-2 (genome)</td>
<td>DS</td>
<td>Linear</td>
<td>35,937 bp</td>
<td>2.221 × 10⁷</td>
<td>12.2</td>
<td>55.20</td>
</tr>
<tr>
<td>Epstein–Barr virus (genome)</td>
<td>DS</td>
<td>Circular</td>
<td>172,282 bp</td>
<td>1.065 × 10⁸</td>
<td>58.5</td>
<td>59.94</td>
</tr>
<tr>
<td>Bacteriophage T4 (genome)</td>
<td>DS</td>
<td>Linear</td>
<td>168,899 bp</td>
<td>1.062 × 10⁸</td>
<td>57.4</td>
<td>35.30</td>
</tr>
<tr>
<td>Bacterium E coli (genome)</td>
<td>DS</td>
<td>Circular</td>
<td>4.630 × 10⁸ - 7.71 bp</td>
<td>2.869 × 10⁹</td>
<td>1.57</td>
<td>50.80</td>
</tr>
<tr>
<td>Fruit fly (Drosophila melanogaster) (one chromosome)⁵</td>
<td>DS</td>
<td>Linear</td>
<td>~6.5 × 10⁷ bp</td>
<td>~4.3 × 10⁹</td>
<td>~2 cm</td>
<td>~40</td>
</tr>
</tbody>
</table>

¹The term genome designates the total DNA to specify the genetic information for an organism.
²Calculated for double-strand DNA of known sequence: 0.34 nm × the number of base pairs (assumes B form).
³This molecule has not been completely sequenced, so numbers of base pairs, molecular weights, and % (G + C) cannot be given exactly.
⁴The lengths of single-strand DNAs are not well defined; they depend very much on solvent conditions.
Chromatin

• The structure of chromatin

• Each “Bead” is a nucleosome

• Nucleosome consists of: DNA wrapped around histone core

• Recent research has shown that structure and spacing of nucleosomes is important in chromatin function.

Supercoiling in Eukaryotic DNA

• **Histone:** a protein, particularly rich in the basic amino acids Lys and Arg; found associated with eukaryotic DNA
  • five main types: H1, H2A, H2B, H3, H4

• **Chromatin:** DNA molecules wound around particles of histones in a beadlike structure

• Topological changes induced by supercoiling accommodated by histone-protein component of chromatin.
Denaturation of DNA

• Double helix unwinds when DNA is denatured

• Can be re-formed with slow cooling and annealing

[Diagram showing the process of denaturation and renaturation of DNA]

Denaturation of DNA

• **Denaturation:** disruption of 2° structure
  • most commonly by heat denaturation (melting)
  • as strands separate, absorbance at 260 nm increases
  • increase is called hyperchromicity
  • midpoint of transition (melting) curve = $T_m$
  • the higher the % G-C, the higher the $T_m$
  • renaturation is possible on slow cooling
Principal Kinds of RNA

- RNA
  - consist of long, unbranched chains of nucleotides joined by phosphodiester bonds between the 3’-OH of one pentose and the 5’-OH of the next
  - the pentose unit is β-D-ribose (it is 2-deoxy-D-ribose in DNA)
  - the pyrimidine bases are uracil and cytosine (they are thymine and cytosine in DNA)
  - in general, RNA is single stranded (DNA is double stranded)
Similarities and differences between DNA and RNA

- Similar strand structure
- Can define a 5’ and 3’ end
- DNA double stranded, RNA single strand
- 2’ hydroxyl in RNA (causes stability differences)
- Uracil in RNA, thymine in DNA

RNA

- RNA molecules are classified according to their structure and function

**TABLE 9.1**

<table>
<thead>
<tr>
<th>RNA Type</th>
<th>Size</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer RNA</td>
<td>Small</td>
<td>Transports amino acids to site of protein synthesis</td>
</tr>
<tr>
<td>Ribosomal RNA</td>
<td>Several kinds—variable in size</td>
<td>Combines with proteins to form ribosomes, the site of protein synthesis</td>
</tr>
<tr>
<td>Messenger RNA</td>
<td>Variable</td>
<td>Directs amino acid sequence of proteins</td>
</tr>
<tr>
<td>Small nuclear RNA</td>
<td>Small</td>
<td>Processes initial mRNA to its mature form in eukaryotes</td>
</tr>
<tr>
<td>Small interfering RNA</td>
<td>Small</td>
<td>Affects gene expression; used by scientists to knock out a gene being studied</td>
</tr>
<tr>
<td>Micro RNA</td>
<td>Small</td>
<td>Affects gene expression; important in growth and development</td>
</tr>
</tbody>
</table>
tRNA

- **Transfer RNA, tRNA:**
  - the smallest kind of the three RNAs
  - a single-stranded polynucleotide chain between 73-94 nucleotide residues
  - carries an amino acid at its 3’ end
  - intramolecular hydrogen bonding occurs in tRNA
**Ribosomal RNA, rRNA:** a ribonucleic acid found in ribosomes, the site of protein synthesis

- only a few types of rRNA exist in cells
- ribosomes consist of 60 to 65% rRNA and 35 to 40% protein
- in both prokaryotes and eukaryotes, ribosomes consist of two subunits, one larger than the other
- analyzed by analytical ultracentrifugation
- particles characterized by sedimentation coefficients, expressed in Svedberg units (S)

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**The Structure of the Prokaryotic Ribosome**
**mRNA**

- **Messenger RNA, mRNA**: a ribonucleic acid that carries coded genetic information from DNA to ribosomes for the synthesis of proteins
  - present in cells in relatively small amounts and very short-lived
  - single stranded
  - biosynthesis is directed by information encoded on DNA
  - a complementary strand of mRNA is synthesized along one strand of an unwound DNA, starting from the 3’ end
snRNA

- Small nuclear RNA (snRNA) is a recently discovered RNA
- Found in nucleus of eukaryotes
- Small (100-200 nucleotides long)
- Forms complexes with protein and form small nuclear ribonucleoprotein particles (snRNPs)
- snRNPs help with processing of initial mRNA transcribed from DNA