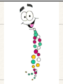
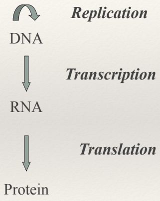
Nucleic Acids

- ECS129
- Instructor: Patrice Koehl

Nucleic Acids



- Nucleotides
- DNA Structure
- RNA
  - Synthesis
  - Function
  - Secondary structure
  - Tertiary interactions
  - Wobble hypothesis



Replication

DNA

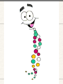
Transcription

RNA

Translation

Protein

Nucleic Acids



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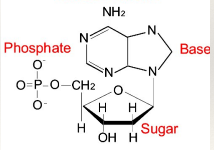
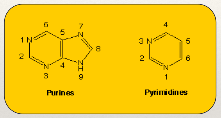
Nucleotide structure



Nucleotides

- Nucleotides are found primarily as the monomeric units comprising the major nucleic acids of the cell, RNA and DNA
- Other functions of nucleotides:
  - serving as energy stores (mainly ATP)
  - controlling numerous enzymatic reactions through allosteric effects on enzyme activity
  - mediators of numerous important cellular processes such as second messengers in signal transduction events

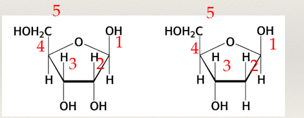
Nucleotides



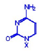
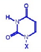
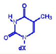
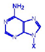
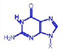
- The nucleotides found in cells are derivatives of the heterocyclic highly basic, compounds, purine and pyrimidine:

Nucleotides

These “bases” are attached to sugar rings: ribose (RNA), deoxyribose (DNA):



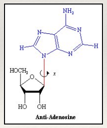
ribose 2-deoxyribose

Base Formula	Base (X=H)	Nucleoside X=ribose or deoxyribose	Nucleotide X=ribose phosphate
	Cytosine, C	Cytidine, A	Cytidine monophosphate CMP
	Uracil, U	Uridine, U	Uridine monophosphate UMP
	Thymine, T	Thymidine, T	Thymidine monophosphate TMP
	Adenine, A	Adenosine, A	Adenosine monophosphate AMP
	Guanine, G	Guanosine, A	Guanosine monophosphate GMP

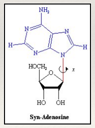
Base conformation

The base can exist in 2 distinct orientations about the N-glycosidic bond.

These conformations are identified as, ***syn* and *anti*.**



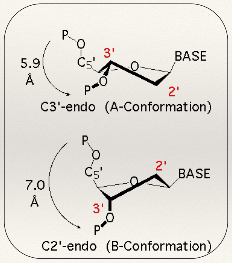
Anti-Adenosine



Syn-Adenosine

The *anti* conformation predominates.

Sugar conformation

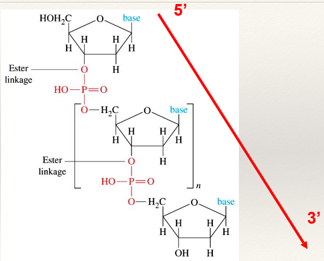


The ribose is a flexible ring that has two preferred conformations in polynucleotides:

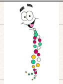
-C3'-endo, found mostly in RNA and in DNA "single strand"

-C2'-endo, found mostly in DNA

Polynucleotides



Nucleic Acids



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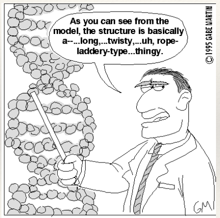
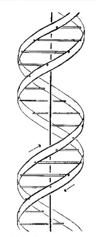
DNA: double stranded helix

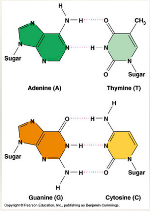


1953: The structure of the DNA molecule is first described.



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

DNA: base pairs



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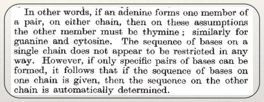
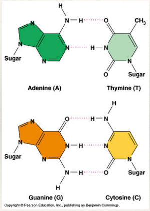

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

Excerpt from Watson and Crick,

Nature, 4356, 737-728 (1953)

DNA: base pairs



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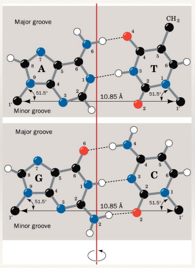
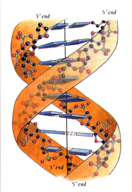
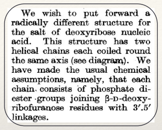
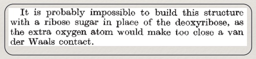
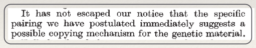


DNA: double stranded helix




We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate di-ester groups joining β-D-deoxy-ribofuranose residues with 3'.5' linkages.


It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.


It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

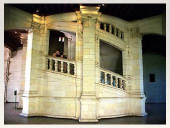
Excerpts from Watson and Crick,

Nature, 4356, 737-728 (1953)

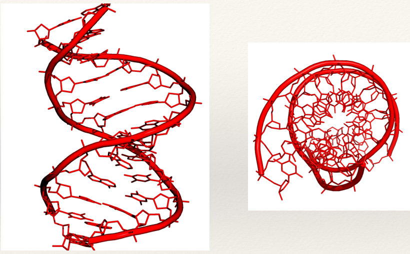
DNA: a style?


Perth, Australia

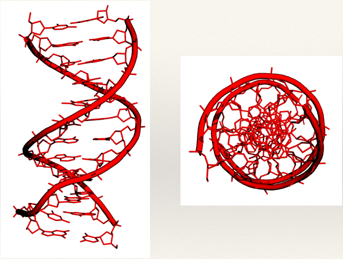

Life Science, UC Davis


Chambord, France

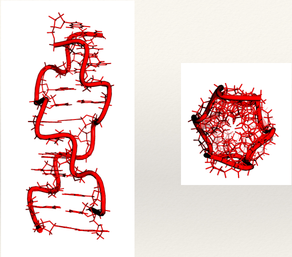
DNA Structures: A-DNA


d(AGCTTGCCTTGAG)•d(CTCAAGGCAAGCT)

DNA Structures: B-DNA

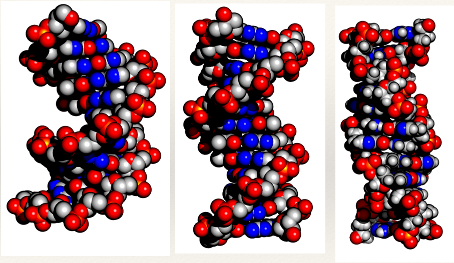

d(CGCGAATTCGCG)•d(CGCGAATTCGCG)

DNA Structures: Z-DNA



d(CGCGCGCGCGCG)•d(CGCGCGCGCGCG)

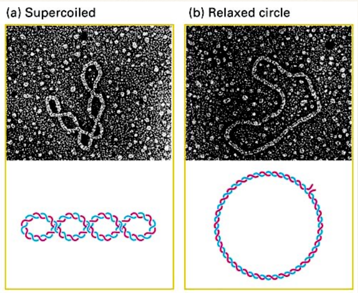
DNA Structures: A, B and Z



DNA Structures: A, B and Z

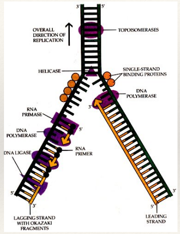
Property	A-DNA	B-DNA	Z-DNA
Helix	Right-handed	Right-handed	Left-handed
Sugar	C3'-endo	C2'-endo	C2' endo (C) C3' endo (G)
Base pairs /turn	11	10	12
Pitch	28 Å	34 Å	44.6 Å
Tilt	20 deg	0	-7 deg
Rise /bp	2.3 Å	3.4 Å	3.7 Å
Diameter	23 Å	20 Å	17 Å

DNA: organization



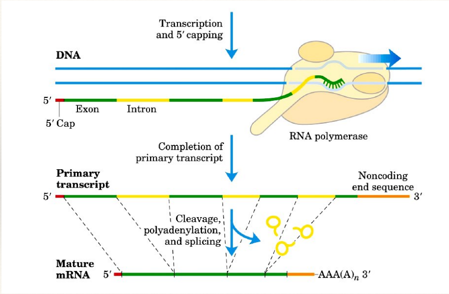
Semi-conservative DNA replication

- Helicase: separates the two DNA strands, starting at replication origins (rich in A-T base pairs)
- RNA primase: inserts a starter of RNA nucleotides at the initiation point
- DNA polymerase binds a complementary leading strand of DNA nucleotides starting at the 3'end of the RNA primer
- Exonuclease removes RNA primer, which are replace with DNA nucleotides by DNA polymerase



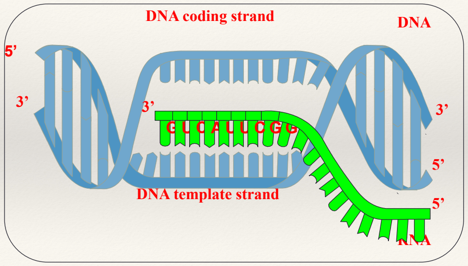
Tutorial : http://www.pbs.org/wgbh/aso/tryit/dna/

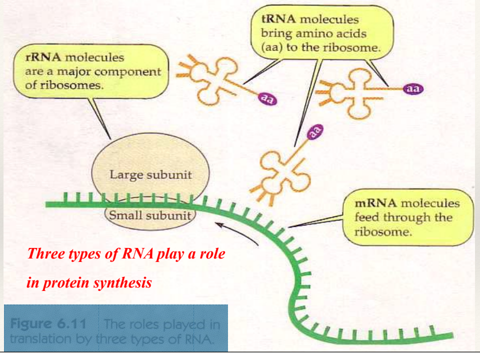
TRANSCRIPTION



mRNA synthesis

The mRNA is formed by adding nucleotide that are complementary to the template strand



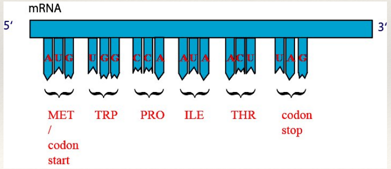


Three types of RNA play a role in protein synthesis

Figure 6.11 The roles played in translation by three types of RNA.

TRANSLATION

- The process of reading the mRNA sequence and creating the protein is called translation
- Protein are made of amino acids (20 different, 9 “essentials”)
- 3 bases or nucleotides make one codon
- Each codon specifies one amino acid : genetic code



GENETIC CODE

2nd base in codon

1st base in codon

3rd base in codon

	U	C	A	G	
U	Phe Phe Leu Leu	Ser Ser Ser Ser	Tyr Tyr STOP STOP	Cys Cys STOP Trp	U C A G
C	Leu Leu Leu Leu	Pro Pro Pro Pro	His His Gln Gln	Arg Arg Arg Arg	U C A G
A	Ile Ile Ile Met/Start	Thr Thr Thr Thr	Asn Asn Lys Lys	Ser Ser Arg Arg	U C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U C A G

GENETIC CODE

The genetic code is universal:

- Virtually all organisms use the same genetic code
- Virtually all organisms use the same 20 amino acids

The genetic code is degenerate:

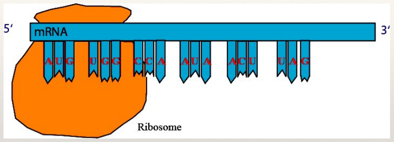
6 codons code for Leu

Some codons have special functions:

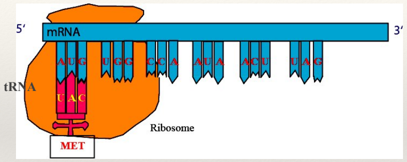
AUG encodes for Met, and is codon start

UAA, UAG and UGA are termination codons

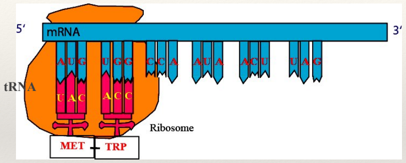
Translation : initiation



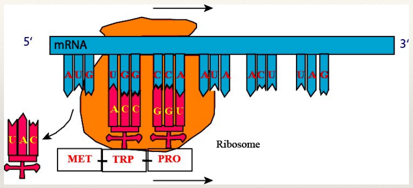
Translation : initiation



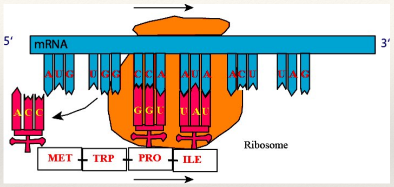
Translation : elongation



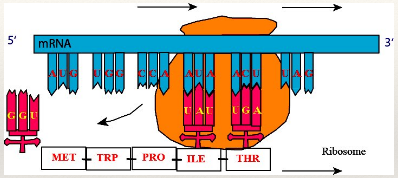
Translation : elongation



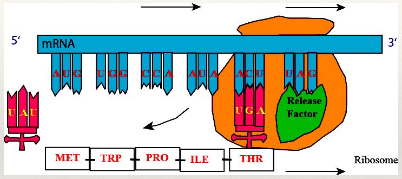
Translation : elongation



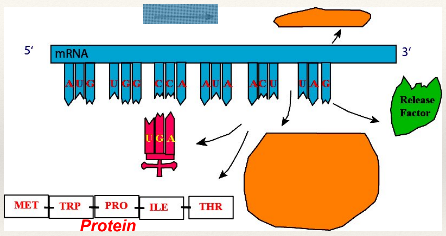
Translation : elongation



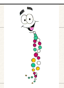
Translation : termination



Translation : termination



Nucleic Acids



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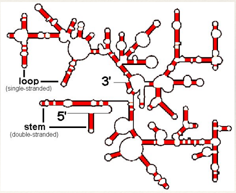
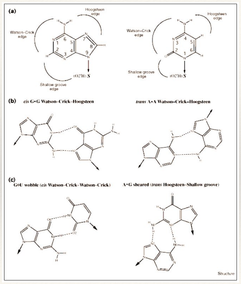


RNA

- RNA versus DNA:
  - ribose instead of deoxyribose
  - Uracyl instead of Thymine
  - mostly single stranded
- Three major RNAs:
  - mRNA (messenger RNA) : DNA transcript
  - tRNA (transfer RNA) : transfer amino acid during protein synthesis
  - rRNA : ribosomal RNA
- Can be active

RNA: non standard base pairs



(Westhof and Fritsch,

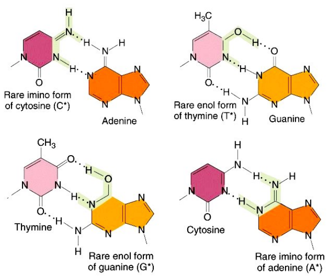
RNA folding: beyond Watson Crick pairing,

Structure, 8:55-65 (2000)

Database of non-canonical base pairs:

http://prion.bchs.uh.edu/bp_type/

RNA: non standard base pairs



RNA secondary structures

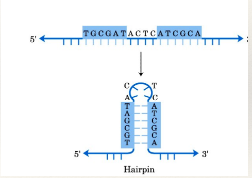
G-C and A-U form hydrogen bonded base pairs and are said to be complementary

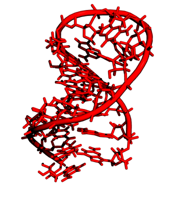
- Base pairs are approximately coplanar and are almost always stacked onto other base pairs in an RNA structure. Contiguous base pairs are called stems.
- Unlike DNA, RNA is typically produced as a single stranded molecule which then folds intra-molecularly to form a number of short base-paired stems. This base-paired structure is called RNA secondary structure.

RNA: Hairpins

Single stranded subsequences bounded by base pairs are called loops.

A loop at the end of a stem is called a hairpin loop. Simple substructures consisting of a single stem and loop are called stem loops, or hairpins.

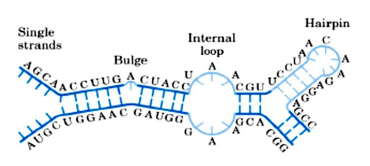




RNA secondary structures

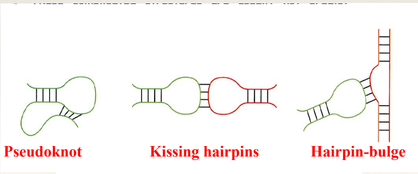
Single stranded bases within a stem form a bulge or bulge loop if the single stranded bases are on only one side of the stem.

If single stranded bases interrupt both sides of a stem, they form an internal (interior) loop.

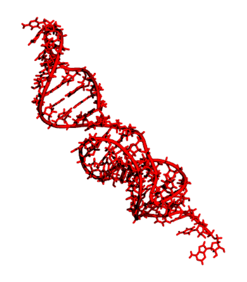


RNA “tertiary interactions”

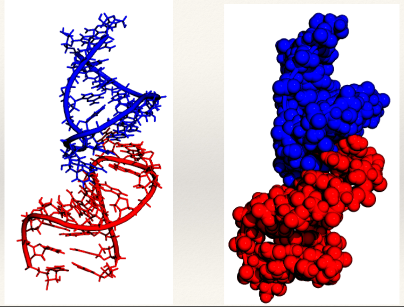
In addition to secondary structural interactions in RNA, there are also tertiary interactions, including: (A) pseudoknots, (B) kissing hairpins and (C) hairpin-bulge contacts.



Pseudoknots

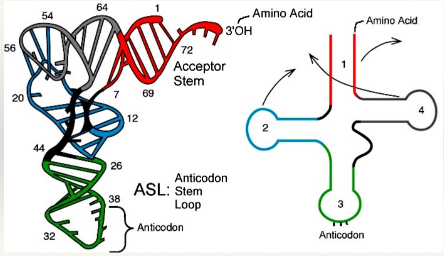


Kissing hairpins

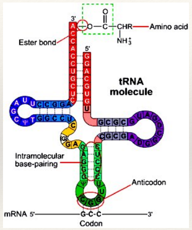


tRNA structure

tRNA: small molecules (73 to 93 nucleotides) with cloverleaf secondary structure



The wobble hypothesis (Crick, 1966)



In 1965, Holley determined the sequence of yeast tRNA(ala): he found the nucleotide Inosine at the 5' end in the anticodon.

The wobble hypothesis (Crick, 1966)

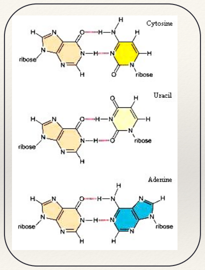
Crick proposed the Wobble hypothesis to generalize Holley's observation:

- *Interaction between codon and anticodon need to be exact at first two positions.*
- *The third interaction can be less restrictive, and can include non standard base-pairing.*

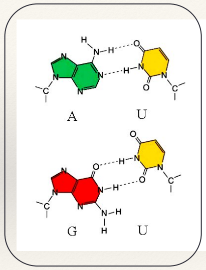
This hypothesis accounts for the degeneracy in the Genetic Code.

5' anticodon base	3' codon base
A	U
C	G
G	C or U
U	A or G
I	A or C or U

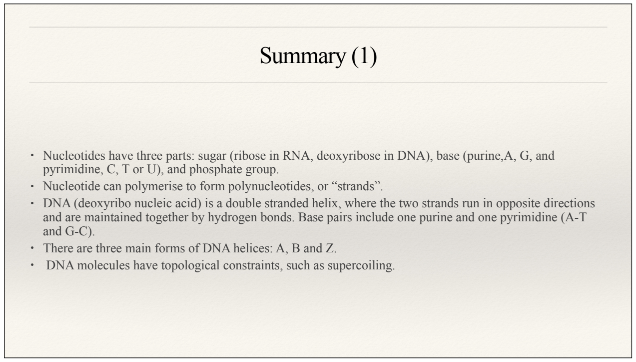
Wobble base pairs



Inosine

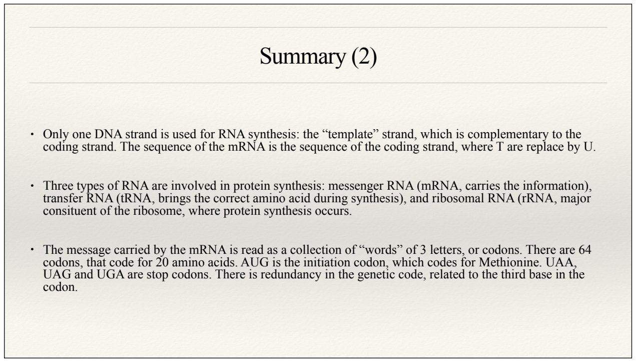


Uracil



Summary (1)

- Nucleotides have three parts: sugar (ribose in RNA, deoxyribose in DNA), base (purine,A, G, and pyrimidine, C, T or U), and phosphate group.
- Nucleotide can polymerise to form polynucleotides, or "strands".
- DNA (deoxyribo nucleic acid) is a double stranded helix, where the two strands run in opposite directions and are maintained together by hydrogen bonds. Base pairs include one purine and one pyrimidine (A-T and G-C).
- There are three main forms of DNA helices: A, B and Z.
- DNA molecules have topological constraints, such as supercoiling.

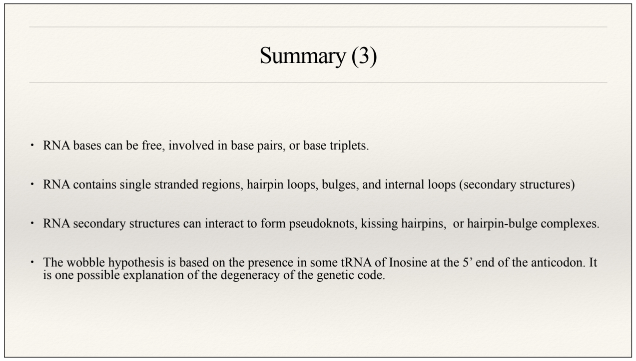


Summary (2)

- Only one DNA strand is used for RNA synthesis: the "template" strand, which is complementary to the coding strand. The sequence of the mRNA is the sequence of the coding strand, where T are replace by U.

- Three types of RNA are involved in protein synthesis: messenger RNA (mRNA, carries the information), transfer RNA (tRNA, brings the correct amino acid during synthesis), and ribosomal RNA (rRNA, major consituent of the ribosome, where protein synthesis occurs.

- The message carried by the mRNA is read as a collection of "words" of 3 letters, or codons. There are 64 codons, that code for 20 amino acids. AUG is the initiation codon, which codes for Methionine. UAA, UAG and UGA are stop codons. There is redundancy in the genetic code, related to the third base in the codon.



Summary (3)

- RNA bases can be free, involved in base pairs, or base triplets.

- RNA contains single stranded regions, hairpin loops, bulges, and internal loops (secondary structures)

- RNA secondary structures can interact to form pseudoknots, kissing hairpins, or hairpin-bulge complexes.

- The wobble hypothesis is based on the presence in some tRNA of Inosine at the 5' end of the anticodon. It is one possible explanation of the degeneracy of the genetic code.