Lectures 2 & 3

Patterns of base-base hydrogen bonds-Characteristics of the base pairs

How are double helices assembled??

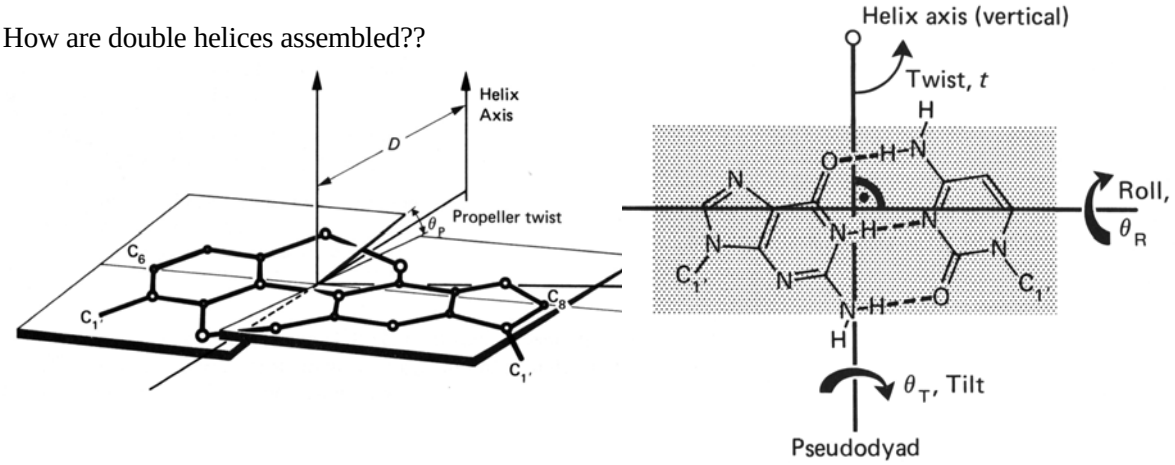

Figure 13

Let us first examine the angular characteristics of base pairs. **Figure 13** diagrams a base pair. The bases in a base pair are usually not coplanar; they instead are twisted about the hydrogen bonds that connect them, like the blades of a propeller. The dihedral angle that defines the non-coplanarity is called the propellor twist angle. To view the angle, hold the base pair such that you are looking down its long axis, the angle is defined as positive when the nearer base rotates clockwise.

If the base pair is imbedded in a helix, then there are several more angular attributes of the base pair that we must consider:

1) D-displacement from the helix axis. By virtue of the symmetry axis we discussed above, in a double stranded nucleic acid, their exists a helix axis which is defined by the average symmetry axes of the base pairs. In some cases, the base pair "slips" from this axis, and this displacment from the axis is measure as distance from the helix axis.

2) Base pair tilt. Despite the propeller twist of a base pair, an average mean plane of the base pair is defined (GRAY AREA IN FIGURE 13). The rotation of this plane about the pseudo-dyad axis defined above is the base pair tilt.

3) Base pair roll. This parameter measures the degree of departure of the mean plane of the base pairs from the perpendicular helix axis on the short axis of the base pairs.

4) Helix twist. Defines the orientation of a base pair with respect to the helix axis. That is how big an arc the base pair traces as it measured from one base pair to the next.

What do these things mean to polynucleotide structure

Propellor twist, base pair roll and displacement are extremely important components in maintaining the stacking interaction of DNA. **Figure 13** shows that in standard Watson Crick B-DNA, the bases are

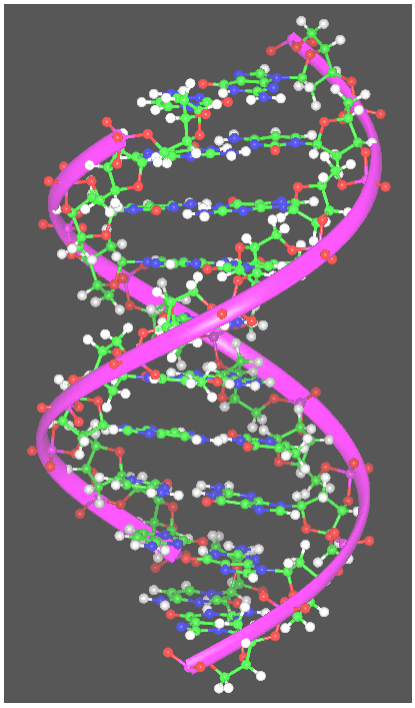

Figure 13

coplanar, no propeller twist and the bases stack readily upon each other. In this type of DNA, the helical twist is 36°, meaning that there are 10.0 base pair/1 turn of helix. However, if any of these parameters are varied the stacking of the base pairs is changed dramatically. For example we lower the temperature or bind a protein. If this change in environment induces an overwinding of the DNA to give 9.33 base pairs per 1 turn of helix (helical twist of 38.6°) and there were no change in either propeller twist, tilt and roll occurred, stacking would be disrupted or worse, the base pairs would crash into one another.

More importantly, and as many things are in nature, more subtly, base pair tilt, roll, helical twist and propeller twist are SEQUENCE dependent, both from the influence of stacking interaction energies and the van der Waals constraints imposed by different base pairs.

Table 2 shows the conformational variations in DNA, dependent both on composition and sequence of the DNA as well as the composition of the surroundings. For example, native DNA can be inter converted between two different families of DNA, B and A, just by changing the humidity. The compositional isomers serve to illustrate the sequence dependence; poly (dA-dT)$_2$ exists A, and B DNA, but poly (dA-A-T).dT-T-A) can exist only as a member of the B-family. These are only a few of the sequence dependent things that can occur in DNA, lets now examine A,B and Z-DNA structure in detail.

Table 2
Principal Crystalline Forms of DNA and RNA in Fibers: Dependence of Form and Relative Humidity (Equivalent to Salt Concentration)[a]

Polynucleotide	Counterion	Relative humidity (%)	Form
Native DNA	Na	75	A
	Na	92	B
	Li	57–66	C
	Li	44	C
	Li	66	B
Poly(dA)·poly(dT)	Na	70	β–B′
	Na	92	α–B′
Poly(dG)·poly(dC)	Na	75	A
	Na	92	B
Poly(dA–dT)·poly(dA–dT)	Na	75	D
	Na	Up to 98	A
	Li	66	B
Poly(dA–dC)·poly(dG–dT)	Na	66	A
	Na	66–92	B
	Na	66	Z
Poly(dA–dG)·poly(dC–dT)	Na	66	C″
Poly(dG–dC)·poly(dG–dC)	Na	95	B
	Na	43	Z
	Na	Up to 92	A
Poly(dA–dA–dT)·poly(dA–dT–dT)	Li	81	B
	Na	66	D
Poly(dA–dG–dT)·poly(dA–dC–dT)	Na	92	B
	Na	Up to 98	A
	Li	98	B
Poly(dA–dI–dT)·poly(dA–dC–dT)	Li	66	C
	Na	66	D
	Na	81	C
Poly(dI–dC)·poly(dI–dC)	Na	92	B
	Na	66	B
Native RNA (reovirus)	Na	75	D

Information content of DNA.

As we discussed in the first lecture, the main function of a nucleic acid is the transfer of genetic information. In the case of DNA, this means not only inter-generational information or passing of the genetic blueprint as well as coding for the general body plan, but it also must contain regulatory information, to help the cell decide when to transcribe a particular gene and when to replicate. These "read-outs" of information are usually made by specific DNA binding proteins. These proteins recognize and bind to DNA sequences that are present in only one or a few copies per genome. Since the DNA of a simple organism like a bacteria contains millions of base pairs, how does the protein recognize a specific sequence--well it "reads" the pattern of H-bond donor and acceptor groups present on a sequence of DNA. The pattern of this information readout must be unambiguous.

The base pairs contain two different surfaces which, when they are contained in double helical DNA are displayed on opposite sides of the molecule. By convention, the sides are defined based on which side is facing where in B-DNA **(Figure 14)**. MAJOR GROOVE-MINOR GROOVE. The information content of the major groove is unambiguous; the minor groove is ambiguous.

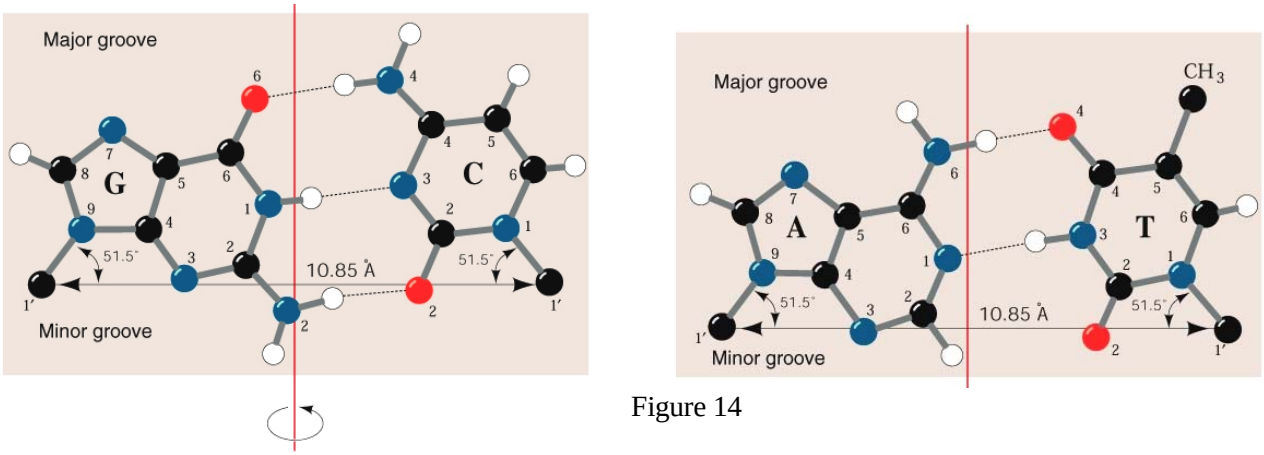

Figure 14

Comparison of A B and Z type DNA.

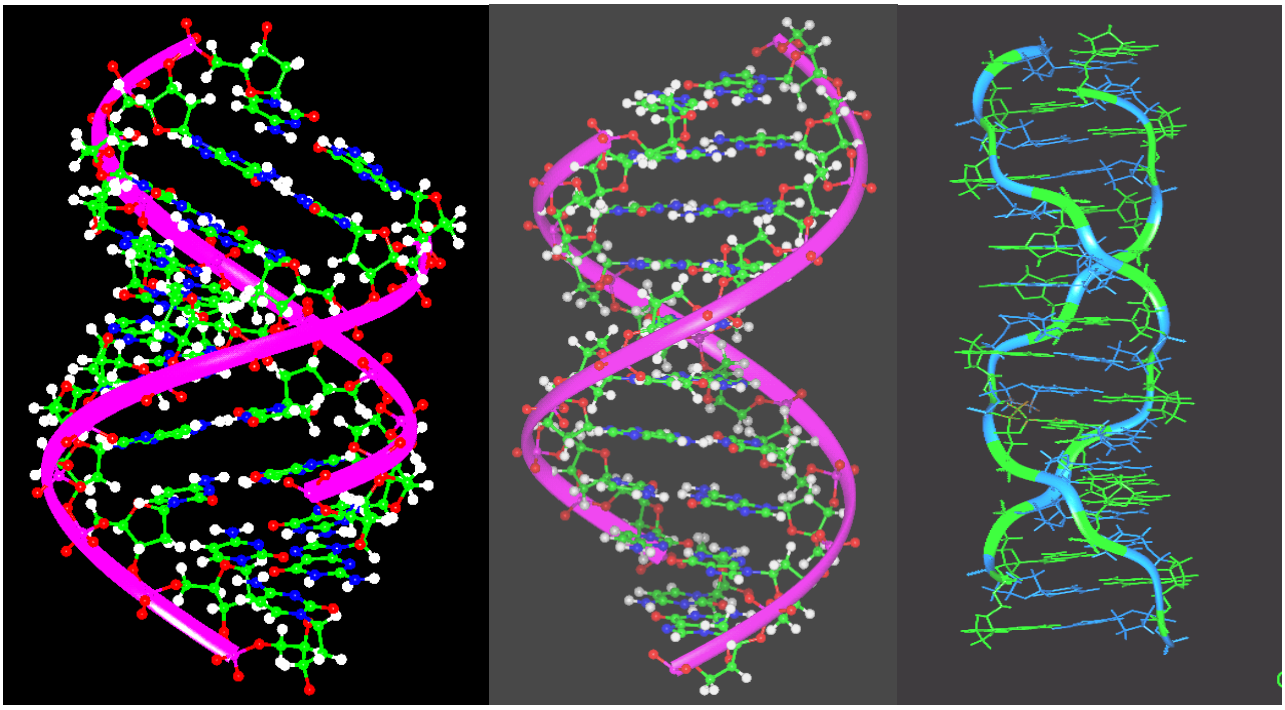

Figure 15

How different are A, B and Z-DNA? Grossly, these two types of DNA are quite different (**FIGURE 15)**. A-DNA is a short stubby helix, while B-helices are rather thin. A-DNA is underwound with respect to B-DNA, having 11 residues/turn of the helix, while B-form has 10-10.5 **(Table 3)**. The most obvious difference is evident if one looks down the helix axis of the DNA. The pseudo dyad axis of B-form base pairs lies almost exactly on the helix axis, therefore the end-on view of B-DNA shows the center of the "cylinder" of B-DNA filled with the base pairs, and the sugar phosphate backbone meanders around the

Table 3 Comparison of Structural Characteristics of A- and B-Type Polynucleotide Double Helices

Family type	A	B
Sugar pucker	$C_{3'}$-*endo*	$C_{2'}$-*endo*
Intrastrand phosphate · · · phosphate distance	5.9 Å	7.0 Å
Dislocation of base-pairs from helix axis	4.4 to 4.9 Å in major groove	−0.2 to −1.8 Å in minor groove
Rotation per nucleotide	30° to 32.7°	36° to 45°
Axial rise per nucleotide	2.56 to 3.29 Å	3.03 to 3.37 Å
Base-pair tilt	Positive, 10° to 20.2°	Negative, −5.9° to −16.4°

outside of it (Figure 16). By contrast the end on view of A-DNA shows that the helix axis is "hollow". The polynucleotide chains wrap around the axis like a ribbon. Both the base pairs and the sugar-phosphate backbone are driven out towards the periphery of the double helix. Moreover, the groove sizes and widths of A and B DNA are dramatically different.

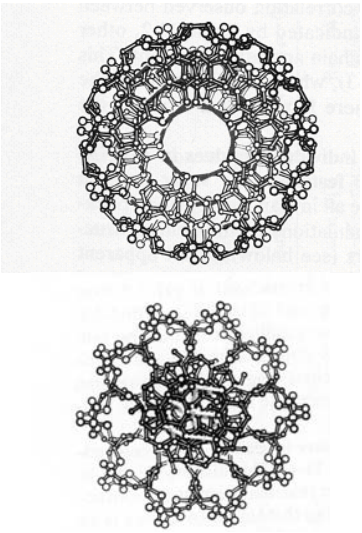

Figure 16

How are these difference generated by the microscopic parameters we discussed earlier

The primary distinction that can be made between A and B type DNA is their differences in preferred sugar pucker and the degrees variability of the backbone torsion angles allowed in each type of DNA. A-DNA contains exclusively C3'-endo type sugar puckers, while B-DNA tolerates the C2'endo family of puckers which includes the lower right quandrant of the pseudorotation cycle, **(FIGURE 6)** from c3'exo to O4' endo. This difference in sugar puckerings causes a variation in the distance between the adjacent phosphates in the same polynucleotide chain; ranging from 5.9 A in C3'endo, to 7.0 A for C2'-endo configurations **(FIGURE 17)**. The decrease P-P distance causes the helical rotation of A-DNA to be less than that of B-DNA. This difference has a consequence in determining the helical arrangements of B and A- DNA, such that these helices are MACROSCOPICALLY different.

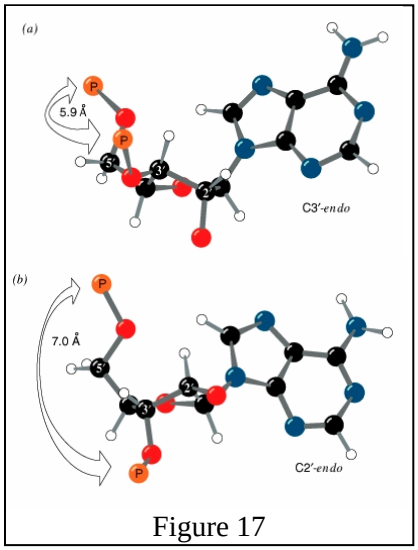

Figure 17

The sugar puckers characteristic of each type of DNA cause the base pairs in the helices to assume different tilt angles with respect to the helix axis. In A-DNA, this tilt, defined as the angle formed between normals to the base pairs and the helix axis is positive in A-DNA, but negative in B-DNA. Looking from the minor groove sides of the bases, tilt in the clockwise direction is positive, and counterclockwise is negative. In B-DNA, the tilt parameter is variable, but is usually quite small, average of about -6^{o}. In A-DNA, tilt is much larger and less variable, +20^{o}.

Outside of the sugar puckering modes and its affect on base pair tilt sense and base stacking, the most important feature distinguishing A from B-DNA is the dislocation of the base pairs (D), from the helix axis. As we have already described, the base pair in B-DNA is astride the helix axis, displacement of ~0.2A. In A-DNA, however, the helix axis is pushed far out into the major groove side of the base pairs with D amounting to 4.4-4.9A **(FIGURE 18)**. This gives A-DNA its hollow appearance from the end-on. In A-DNA the displacement of the helix axis into the major groove gives rise to a very deep and

narrow major groove and a reduced and relatively shallow minor groove (Figure 19). The shallow major groove of A-DNA is only accessible to small molecules, water and metals. In B-DNA the major groove is freely accessible. Since the unambiguous information of a double helix is present in the major groove face of the bases, this limits the utility of A-DNA in storage of regulatory information.

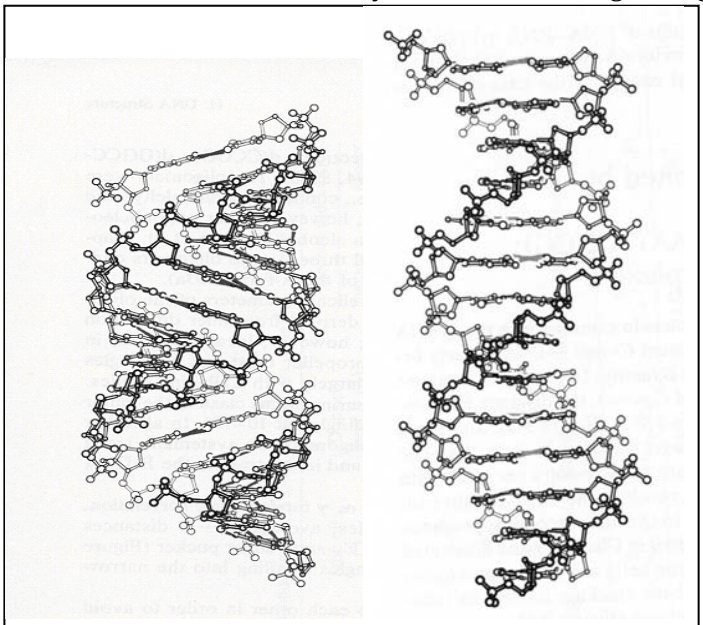

Figure 19

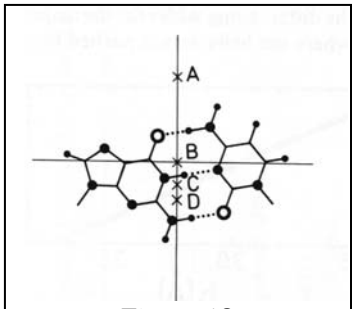

Figure 18