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Intrinsically Bent DNA Structures Models.

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ABSTRACT

After discovery of right handed double helical B- DNA structure few more structures of DNA were discovered including left handed Z- DNA. Researchers found out that variation in DNA structure was due to the variation in base sequence and dinucleotide step parameters. DNA in its most predomient form DNA is straight. But around 1980 it was observed that sequences /structure variation can create a bend /curvature in DNA structure. The bent can be observed either due to the periodic occurrence of ApA and TpT dinucleotides (Wedge Model) or with junction between two contiguous stretches of DNA with different conformation such as A and B DNA structures (Junction Model). The Wedge Model suggested B- structure , but roll and tilt , in an AA/TT dinucleotide steps open to form wedge and cumulative effect of wedges create curved DNA molecule. It has also been shown that sequences other than A tracts can also create bent in DNA. Polarity of the A and T tracts is also important. The tracts T_4A_4 and A_4T_4 showed different bents. In Junction Model there is A- DNA structure – B DNA structure junction and B- DNA is straight but junction of A-DNA and B- DNA helices displace and angle indicating a bent DNA duplex. A recent Hybrid- Solvent Model has suggested that bending in DNA is due to the interaction of environment such as cation with phosphate groups of the back bone. In this report I explain details of Wedge Model, Junction Model and Hybrid Solvent Model.

Keywords: Junction Model, Wedge Model, Hybrid solvent model , Intrinsically bent DNA Structures.

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INTRODUCTION

After postulation of right handed double helical B- DNA structure (Watson *et.al.,* 1953) , few more structures of DNA called 'A' form (Franklin *et.al.,* 1953 a and b) , 'C' form (Marvin *et.al.,* 1961) and 'D' form (Davis *et.al.,* 1963) were characterized. However, discovery of left handed DNA was surprised to biologists who thought that DNA can only be right handed (Wang *et.al.,* 1979, Crawford *et.al.*, 1980). At later stage if was realized that DNA structure is more complicated and base sequences display variation in dinucleotide step parameters. The DNA molecule is not always found in a linear structure inside the nucleus. The DNA sequence may assume three-dimensional conformations depending on its sequence, which may include cruciform shapes, loops, and curves (Calladine *et al.,* 2004). The sequence dependent structure polymorphism of DNA could play an important role in many biological processes.

It is known that proteins induce DNA deformation but the discovery of curvature in kinetoplast DNA of trypanosomes created intersest of many researchers in curved DNA structures (Marini *et.at.,* 1982 and 1984) . The curvature in DNA was due the intrinsic characteristic of the sequence. Marini *et al* found that a restriction fragment of 450 base pairs from *Leishmania tarentolae* on 1% agarose gel , but migrate as it is 1380 base pairs in length on 12% polyacrylamide gel . The other studies on this DNA also showed that this DNA has unusual compact B- DNA structure. This unusual behavior could be due to some feature intrinsic to kinetoplast DNA (Effron *et.al.,* 1984). The analysis of DNA sequence revealed that there is periodic occurrence of ApA and TpT dinucleotides. Later Crother et.al. found that bending in kinetoplast DNA was due to striking pattern of periodically repeating $(dA)_{5\text{-}6}$ tracts , separated by four to six base pairs of G+C rich sequences(Wu *et.al.,* 1984). A probable explanation for the formation of this curvature is the interaction of the A/T base pairs, which allows the formation of a cross link between one oxygen atom of thymine and one nitrogen atom of adenine in two consecutive pairs. This cross link connection allows base pairs with consecutive A/T tracts to maintain a closed structure (Calladine *et al.,* 2004) and promotes a natural curvature of the helix. Researchers have described curvatures in DNA with other combinations of these tracts (Bolshoy *et al.,* 1991) and also some DNA sequences lacking A/T tracts (Fujimura *et.al.,*1988). This curvature can play a significant role in transcriptional activation by affecting promoter geometry. Many transcriptional activators are DNA-bending proteins that can either recognize DNA bases (direct recognition) or specific DNA properties such as flexibility (indirect recognition) (Perez-Martin *et.al.,* 1997). *Escherichia coli* promoters frequently contain an adenine (A)-tract region, mostly centered around the -44 region, which when mutated has been shown to reduce transcription (Plaskon *et.al.,* 1987). In some cases, substitution of an entire promoter region by properly curved DNA can activate *in vitro* transcription (Gartenberg *et.al.,* 1991, Bracco *et.al.,* 1989). More recent work indicates that these sequences function as upstream recognition elements (UP elements), the curvatures of which play an unknown role (Aiyar *et.al.,* 1998). In addition, HIV-1 reverse transcriptase termination of the (-) strand DNA synthesis is thought to occur because of minor groove compression of duplex DNA caused by the A-tracts (Lavigne *et.al.,* 1997).

The natural sequences exhibiting curvature contain A - tracts (a stretch of dA nucleotides) in phase with duplex DNA repeat of 10-11 residue per turn. The each A-tract make a small bend in helix axis and repetition of the A- tracts in phase with duplex DNA results in their co-herent addition. This result in an overall curvature. To prove that the curvature is due the presences of A- tracts in phase with DNA duplex , Crother et. al. synthesized series of polynucleotides containing A- tracts of variable repeat (Koo *et.al.,*1988 , Haran *et.al.,*1994**)**. The synthesized polynucleotide contain A-tracts showed slow mobility on PAGE . This is characteristic of DNA curvature. Based on these observations few models were formulated to explain the A-tract related bending in duplex DNA. The two important models were a) AA wedge model by Trifonov et .al.(Trifonov *et.al.,* 1980) and b) the junction model by Crother et.al. (Levene *et.al.* 1983).

The bend at junction between two contiguous stretches of DNA with different conformations such as A and B – DNA was suggested by Selsing et al. (Selsing *et.al.,* 1979 **,** MacDonld *et.al.,* 2001**)**. Based on this postulate Crother et.al. suggested that the A-tracts adopt a non B-conformation with base pairs in the flanking regions with B- DNA conformation are nearly perpendicular to the helix axis. This creates marked change at the junction of the two regions. On the other hand Trifonov et . al.(Trifonov *et.al.,* 1980) suggested a AA Wedge Model. The Wedge model suggested that DNA has B-configuration throughout but by roll and tilt an AA/TT dinucleotide steps open to form Wedges. And cumulative effect of periodic Wedges results in a curved DNA molecules.

Various X- ray and NMR studies carried out to understand structural behavior of these DNA molecules could not make things conclusive. The NMR studies supported the idea that A tracts have a negative inclination in consensus with the junction model (Milton *et.al.,* 1990) where as X- ray studies indicated that A-tracts donot have such an inclination (Dickerson *et.al.,*1994). Haran et. al (Haran *et. al,* 2004) pointed out that this discrepancy may be due to the effect of organic solvents used to induce crystallization. The real problem to the Wedge model came from the observation that the polynucleotide d(GTTTTAAAAC) migrates with normal mobility on a gel , whereas polynucleotide d(GAAAATTTTC) migrate slowly and appeared to be curved (Hagerman *et.al.,* 1986**)**. Later it has been observed that not only A- tracts but flanking sequences also contributing towards the curvature of DNA(Abagyan *et.al.,* 1990, Milton *et.al.,* 1990, Milton *et.al.,* 1990). Also it was discover that some sequences , entirely lacking in AA dinucleotides can also take up a curved structures (Bruker *et.al.,* 1991). Therefore a more general model for explaining the bending in DNA structure is required.

Recent analyses of DNA bending have proposed a delocalized bend model that incorporates aspects of both wedge and junction models (Crother *et.al.,* 1999). The bend angle for a single helical turn of DNA containing an A-tract has been estimated by various studies to be 11–28° (Crother *et.al.,* 1999). A large number of biochemical studies of A-tract bending have used DNA oligonucleotides containing a single (or two) helical repeats of a sequence containing a single phased (or two or three phased) A-tract ligated together to make a polymer with *n* repeats, so that the small bends in a single A-tract added in phase give rise to a macroscopically observable bending as assayed by gel electrophoresis, circularization assays, or electron microscopy (Crother *et.al.,*1999). Certain characteristics of A-tracts have emerged, i.e., narrow minor groove, generally high propeller twist, and hydration and/or ions in the minor groove, which may be associated with A-tract bending. However, x-ray crystallography has not resolved the issue of the structural origin of bending, because crystal packing, lattice forces, and crystallization agents strongly influence the bending (DiGabriele *et.al.,* 1993, DiGabriele *et.al.,* 1989, Dickerson *et.al.,* 1994, Dlakic *et.al.,* 1996). The A-tracts in crystal structures are straight (Nelson *et.al.,* 1987), inconsistent with wedge models, and therefore it has been proposed that bending must occur at the junctions of A-tract (Dickerson *et.al.,* 1996). High-resolution structure determination of DNA by NMR has been limited both by the relatively low number of short-range restraints that determine the local dinucleotide restraints for the accurate determination of the global bend. Williams and co-workers (Williams *et.al.,* 2000) have suggested a hybrid-solvent model, based on this model interactions between DNA and its environment causes bending (Shui et.al., 1998, Shui et.al., 1998a). It was proposed that cations interact with phosphate groups of DNA and neutralize them. This neutralization causes the helix axix bending. The origins of A-tract curvature have been studied by molecular substitutions by many researchers (Diekmann et.al., 1992, Seela et.al., 1992 , Maki et al., 2003).

Models For Intrinsic DNA Curvature

Junction model : Selsing et.al. (Selsing *et.al*.,1979) described the A-B- junction bent DNA structure by constructing the dinucleotide and trinucleotide models. The dinucleotide model was discarded because this model exhibited poor stacking and had several non bonded interatomic contacts shorter than 2.0A°. This model was not tenable. Therefore trinucleotide four different models duplex model were investigated. All the models had C3 endo sugar rings in the A DNA end residue and C2endo sugar rings in the B- DNA end residue. But the four models were having different sugar ring puckering assigned to the two function bases . The four models were (C3endo , C3 endo), (C2 endo , C2endo), (C2endo C3endo), (C3endo , C2 endo) where the pucker given first in that assigned to the junction nucleotide residue of the strand running 5' to 3' from A-DNA to B-DNA. Out of four models the (C2 endo ,C3 endo) model was preferred since in this model , all interatomic contacts were acceptable . This model in addition best satisfied base stacking and torsion angle restraints and was thus superior in term of all the criterion . The two view of the C2 endo and C3 endo junction model is shown in Figure-1.

The figure-1 shows how well the base pairs at the junction are stacked . The axis of joined A- DNA and B- DNA helices are also shown and it is apparent that these axis are displaced and at an angle , thus indicating a bend in the duplex . This bend is more easily seen in longer helix . Figure-3 . The base stacking model A-B junctions for all base sequences of (C2 endo and C3endo) model are shown in Figure-2. These arrangement shown in Figure-2 a, back to those observed in B – DNA (Arnott *et.al.,* 1975) , The pattern in Figure 2c also closely mimics the stacks found in the crystal structures of ApU (Seeman *et.al.,* 1976) and GpC(Rorenberg *et.al.,* 1976). Figure 2 d, e and f shows the stacks between the B-DNA base pair and function base pair in the

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final model . Those in Figure 2d and e are quite similar to the patterns seen in D- DNA (Arnott *et.al.,* 1974a). Figure 2f is a pattern that is found in DNA form of poly(dA-dA-dT)poly(dA-dT-dT) (Selsing*et.al.,*1975). This purine over purine and pyrimidine over pyrimidine stack in D-DNA may not be especially favourable since poly(dPu).poly(dpy) duplexes are not found to adopt D- DNA form (Arnott *et.al.,* 1974 b , Arnott *et.al.,*1974 c).

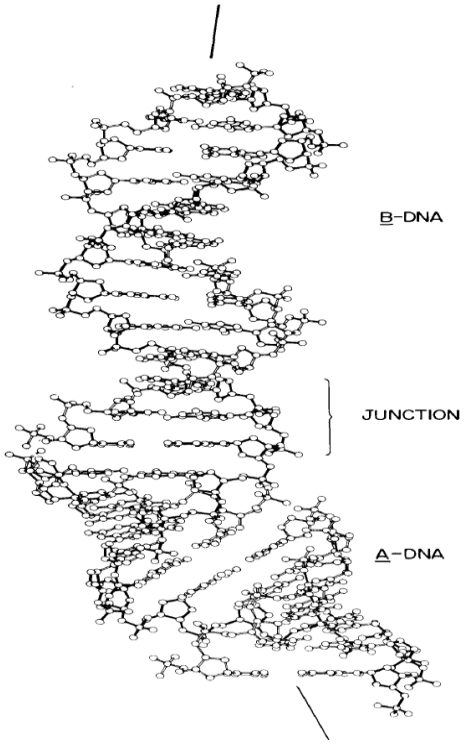

Figure-1 : A projection showing the bend in DNA duplex which results from neighbor A-DNA and B-DNA helical segments . One helical turn of both A- and B- DNA is depicted and the axes of the joined helical are shown. The base pairs encompassing the junction region are indicated . The bonds of the sugar phosphate strand of this duplex are depicted as solid for clarity (Selsing *et al.,* 1979)

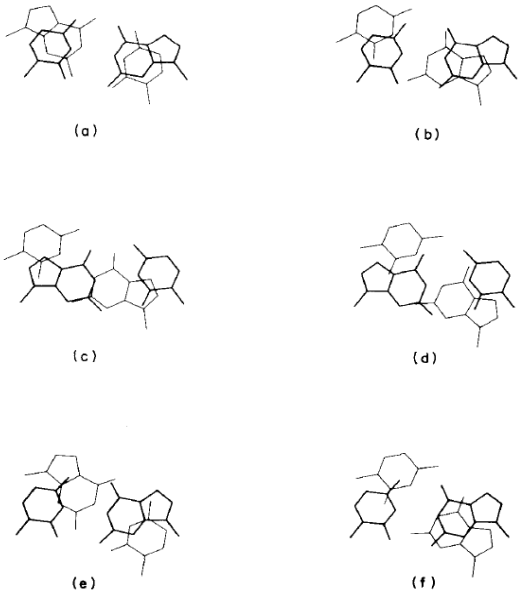

Figure-2 : The base stacking patterns of the model A-B junctions for various base sequences. a,b e and c the stacks between the junction base pair and first neighbor A-DNA base pair , d,e and f, the stacks between the junction base pair and the first neighbouring B-DNA base pairs. The base pair closest to the viewer is accentuated in each projection (Selsing et.al., 1979)

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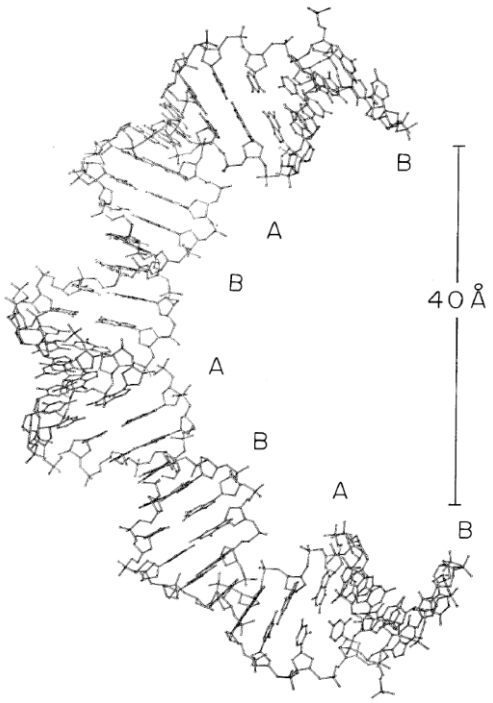

Figure-3 : A computer generated view of a 37 base pair segment of DNA incorporated of six A-B junction. In this figure junction occur at intervals of 4 and 8 residues alternatively . A wide variety of other stacked , curvlinear DNA superstructure can arise with A-B jucntions separated by different intervals (Selsing *et.al.,* 1979).

The model described by Selsing shows that local segment of A DNA could exist in an otherwise B-DNA helix , with two bent junction i regions bordering each A- DNA segment. But A- DNA has 11 fold helix symmetry while B-DNA has 10 fold symmetry, The transition of N base pair in B- DNA helix to the A- DNA form would result in a helical unwinding of roughly 3.3 No with N+2 residues in conformations other than B- DNA. This angle reflects only the unwinding about the helix axis due to the change in helicity of a transition from B-DNA to A-DNA ; depending upon the relative positions of two A-B junction the net unwinding angle may vary by as much as +- 50 ° due to the introduction of bends. A computer generated view of a 37 base pair segment of DNA incorporating six A-B junctions made by Selsing et. al. (Selsing *et. al.* 1979) is shown in Figure-3 . Experimental work (Selsing *et. al.* 1978 , Selsing *et. al.* 1979a) on RNA : DNA and DNA:DNA helix show that junction region between Aand B helices in the block duplex in small while thermal melting and S1 nuclease experiment indicated that the molecules is fully hydrogen bonded and base stacked throughout. The model of Selsing et al was completely consistant with experimental work.

Wedge model : The Wedge model for DNA bending assumes that the AA dinucleotide contains a Wedge angle that causes a deflection in the axis of the DNA double helix (Trifonov *et.al.,* 1980 , Ulanosky *et.al.,* 1986,) The sum of Wedge pointing in the same direction , a condition met by the 10 bp phasing leads to the bending of DNA . As illustrated in Figure-4 the wedge angle can result from a wedge along the tilt axis or a wedge along a roll axis. The principal sequence feature responsible for intrinsic DNA curvature is generally assumed to be runs of adenines. However, according to the wedge model of DNA curvature, each dinucleotide step is associated with a characteristic deflection of the local helix axis. Thus, an important test of a more general view of sequence-dependent DNA curvature is whether sequence elements other than A-A cause the DNA axis to deflect. To address this question, the wedge model was applied to a large body A-tract curvature and non-A tract curves is shown in Figure- 5 . Circularization and gel electrophoretic mobility data on 54 synthetic DNA fragments, A tract curvature and non A tract curves was used to compare the theoretical predictions of the wedge model with experiment. By minimizing misfit between calculated and observed DNA curvature, they found out that the stacks AG/CT, CG/CG, GA/TC, and GC/GC, in addition to AA/TT, have large wedge values. Seven other sequences without AA/TT elements also showed appreciable predicted curvature and was seen by anomalous gel motilities. They estimated , full set of 16 roll and tilt wedge angles together with the known 10 helical twists. From these predicted the general sequence-dependent trajectory of the DNA axis (Bolshoy *et. al.,* 1991)

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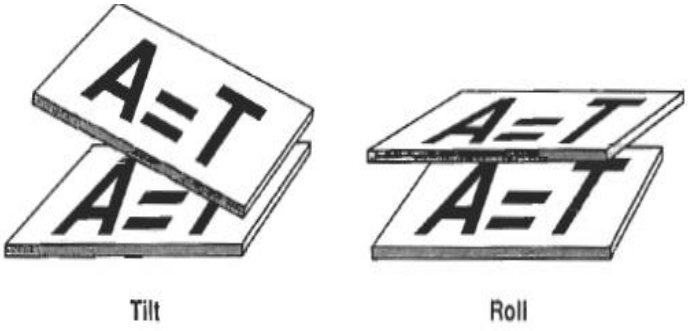

Figure-4 : Different angles of deformation are possible when one base stacks to the other. One angle if the tilt angle , which is the direction of hydrogen bonding. Another is the roll angle , which occurs at 90° to the direction of hydrogen bonding . The tilt angle occurs in the phosphate backbone whereas roll can open the word at either the major or minor groove (Dickerson *et.al.,* 1989).

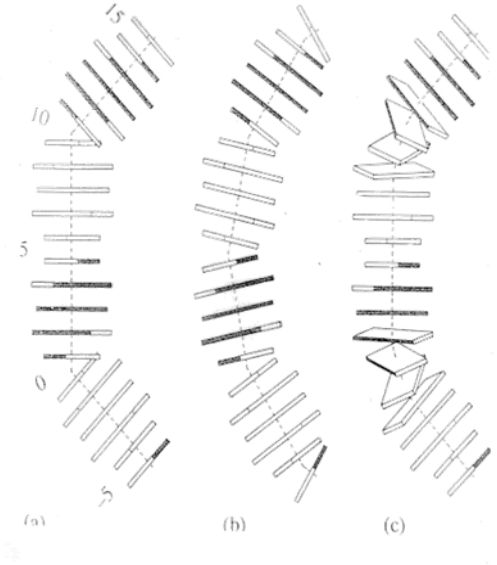

Fig-5 A-tract curvature and non-A tract curves (Lu *et.al.,* 2003) of experimental data by Bolshoy et.al. Bolshoy et.al described the axial path of DNA at each step by three Eulerian angles: the helical twist, the deflection angle (wedge angle), and the direction of the deflection

The A tract story was started by Trifonov and Sussnan (Trifonov *et.al.,* 1980) with the discovered of periodicity of AA . They argued that the AA.TT dimer had an intrinsic Wedge like shape which when repeated in the phase with the helical periodicity of the duplex would introduce systematic intrinsic bending in DNA. (The roll and tilt components of AA*TT wedge , however , were not specified) Marini et.al. interpreted DNA curvature in k- DNA due to periodically repeated of A5 and A6 tracts. The crucial gel electrophoresis experiments carried out by Hagerman (Hagerman *et.al.,* 1986, Hagerman *et.al.,* 1985) , Dickmann (Dickmann *et.al.,* 1992) and Koo ,Wu, Crothers (Koo *et.al.,* 1988 , Koo *et.al.,* 1986) established the following three important features of curved DNA.

I. Properly phased A- tracts are indispensable for strong DNA curvature (e.g. substitution of AAGAA for A5 diminishes the effect drastically)
II. A tract orientation is important A4T4 induced bending differ from that of T4A4
III. Flanking sequences have a limited influence on the magnitude of Incurvature (the gel retardation associated with GA5Gsequence is 10-15% less than that for CA5C).

To account for these results Ulanovsky and Trifonov (Ulanovsky *et.al.,* 1987) refined the AA-wedge model , and specified the values of the Roll and tilt angle of AA*TT dimeric steps. Crother and coworkers further refined the wedge model. (Wu *et.al.,* 1984 , Koo *et.al.,* 1986, Koo *et.al.,* 1987, Crother *et.al.,* 1992). On the other hand Selsing *et.al.* introduced the junction model (Selsing *et.al.,* 1979). The principal difference between the Wedge and Junction model is the cojecture made on the nature of interactions stabilizing the A-tract of interactions stabilizing the(A- tract geometry . The AA- Wedge model is based on the first approximation that the average conformation of any dimeric step (e.g. AC.GT or AA.TT) is independent of its neighbors . In particular the AA*TT dimer is believed to have the same context of both CAAC*GTTG and AAAA*TTTT. By contrast the junction model is based on the assumption that an A-tract (made up of four or more consecutive adenines in the same strand) is stabilized in specific conformation which is somewhat different from the canonical B-form. The latter idea builds upon the concept of junction bending originated by Selising et.al. (Selising *et.al.,* 1979) in their construction of a stereo chemically optimal B/A junction . In other words the AA wedge model is nearest neighbor dimeric model while the junction model postulates co-operative interaction along the DNA chain which make A-tracts different from other sequences.

The difference between the two models leads to difference in the description of DNA deformation. The wedge model consider the dimeric step as the elementary structure unit of duplex and Wedge angle accordingly describe transitions from the ith to (i+1)st base pair (Co-ordinate frames are assigned to each pair) . By contrast the junction model ignores possible irregularities within the A-tracts and non- A tracts and only considers the effective deformation at 5'- and 3'- ends of A-tracts. Subsequent modifications of the Wedge model , in which all 16 dimer are considered donot change the basic tenets (i) the deviation from base pair co-planarity occurs predominantly in AA*TT steps and (ii) that the A-tract occurs naturally in a conformation similar to the B- form. The wedge model also incorporates sequence dependent values of Twist which are based on known solution properties of DNA (Koo *et.al.,* 1990). Among various A_n tracts the bend angle is probably the largest for n=6 , in as much as this case the gel retardation is the strongest. The bend angle for A_6 tract was estimated to be 17-21^o from cyclization experiment (Koo *et.al.,* 1990) . But the experimental bend angle differed by roughly two fold ranging from 13.5 (based on the analysis of 2Dscanning force microscopic image) 28^o (based on early PAGE circulation data). However, the topological measurements of super coiled DNA by Lutter and Co-Worker find the A-tract bend angle to be 22^o at room temperature (Lutter *et.al.,* 1996, Lutter *et.al.,* 2000**7**) . Thus a value of 20+- 2^o was considered to be the best current estimate of DNA bending angle per A6 tract (under standard conditions). As mentioned both AA Wedge model and the junction model ascribe this intrinsic bending to a specific conformation of A- tract with the AA dimer rolled into the minor groove and the base pairs inclined with respect to the local DNA axis. It should be noted that the introduction of 20^o bend per A-tract requires only relatively small distortions in local structures . The roll angles in the A-tract need not differ any more than 5-6 from those of random mixed sequence DNA .

Sequence Requirement for DNA Bending : (Kao *et.al*.,1986) synthesized a large number of oligoncleotides containing various lengths of A tracts that were phased at different different length . These oligonucleotides were conceptually similar to those described by Hagarman (Hagarman *et.al.,* 1985) but were not symmetrical and thus had an A tract in only one strand of the DNA. Polymers with A_{4-9} were bent with bending being optimal for $A_{-6.}$ Koo *et.al.,* polymer with A_3 phased at 10 bp was not significantly bent . (The Hagerman bent sequence with A_3T_3 contained an A_3 tract in both strands that must contribute to bending). A continuous run of As is required for bending since replacement of the central A in A_5 with C G or T destroy the bending . There is no sequence requirement for a particular base 5' or 3' to an A tract for bending although flanking sequences can influence curvature. DNA sequences that do not contain runs of As can also be bent . The bends observed in DNA lacking phased A tracts are usually not a large as A tract bends . These sequences have not been as well studied as A- tract induced bends.

Solution Structures of [d(GCAAAATTTTGC)]$_2$ and [d(CGTTTTAAAACG)]$_2$: From the definition of an A-tract as four or more consecutive A-T base pairs without a TpA step (Hagerman *et.al.,* 1990, Hud *et.al.,* 2003, Crother *et.al.,* 1999), the A_4T_4 sequence consists of a single A-tract element, whereas the T_4A_4 sequence consists of two consecutive A-tract elements disrupted by a TpA step. Instead of using this A-tract definition, Hagerman *et.al.* described A_4T_4 and T_4A_4 as molecular architectures consisting of two A_4-blocks each, where the A_4-blocks are connected at the 3-ends of the A-strands (tail-to-tail) and at the 5- ends (head-to-head), respectively (see Figure 6). Both A_4T_4 and T_4A_4 form well-determined right-handed B-DNA double helices (Figure 6). The most remarkable difference between the molecules is the minor groove profile. The A_4T_4 structure displays a symmetrical and progressive narrowing of the minor groove, reaching a minimal width of -10 Å (closest P–P

distances) at the central ApT step. The T4A4 structure shows the inverse trend, its minor groove is symmetrically widened toward the central TpA step where the maximal minor groove width -13 Å is found (Figs. 6, and 7*a*). Narrowing of the minor grooves of A-blocks was proposed to be a general feature of A-tracts (Hud *et.al.,* 2003, Crother *et.al.,* 1999). The opposite orientations of the A blocks in the two duplexes result in an entirely different environment for the base-stacking interactions at the ApT and TpA steps and is a key factor for A_4T_4 being so different from T_4A_4 in terms of global bending. Most importantly, there is an opposite direction of the local bend at these steps. The ApT step has high negative roll (-12°), providing a local bend toward the minor groove, whereas the TpA step displays high positive roll (11°), resulting in a local bend toward the major groove (Figs. 6and 7*b*). This trend has also been observed in crystal structures of DNA duplexes containing A-tracts (Arnott *et.al.,* 1975, Young *et.al.,* 1995). These two opposite local bends contribute significantly to the different global bends in A_4T_4 and T_4A_4, as can be seen in Fig. 7 and as is discussed below. Both A_4T_4 and T_4A_4 have two additional bends, which occur at the junctions of the A-blocks with the C-G base pairs. Basically, there are two types of these bends. At the 5- end of A-blocks where the minor groove is wide (the case of A_4T_4), the bends occur almost exclusively via positive roll (-12°) toward the major grooves (Figures. 6 and 7). These bends are very similar to the one at the TpA step. At the 3- end of A-blocks where the minor groove is narrow (the case of T_4A_4), the bends take place via a combination of roll and tilt, providing local bends toward the major grooves, and tend to be distributed to the flanking GC-rich sequence as well.

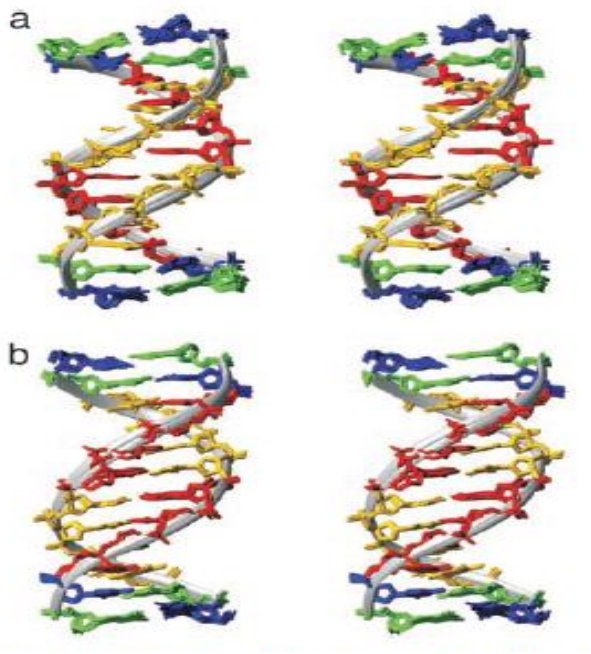

Figure-6 : Superposition of the nine best structures of A_4T_4 (a) and T_4A_4 (b) . The minor groove of the A- tracts is shown in front and ribbon is fitted to the phosphate atoms to highlighted the differences in minor groove widths. Nucleotides are colored blue (G), green (C), red (A) and orange (T) , only non hydrogen atoms are depicted(Stefl *et.al.,* 2004).

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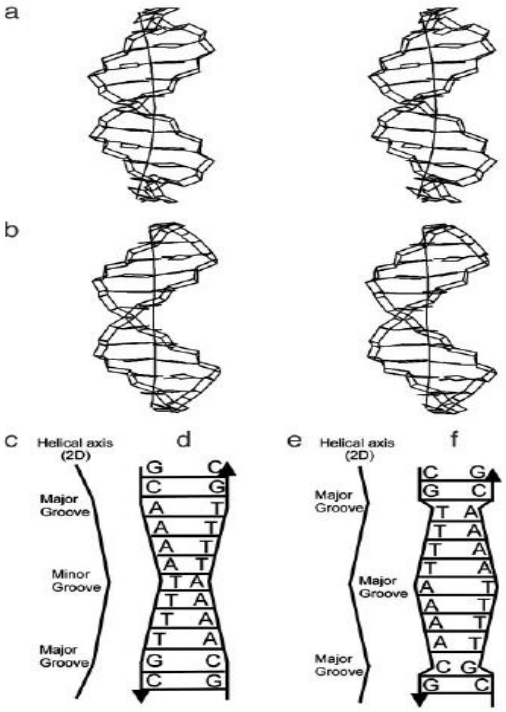

Figure- 7 : Schematic representation of the structures of A_4T_4 (a,cand d) and T_4A_4 (b,e and f) Illustrating the minor groove narrowing and widening and helical axis bending(a&b) . Structures and 3D helical axis calculated by curves 5.3 (Lavery *et.al.,* 1988) . (c and e).Simplified helical axes in 2Dspace ,with direction of local bonds indicated (d &f) Schematics illustrating relative groove widths. (Stefl *et.al.,*2004).

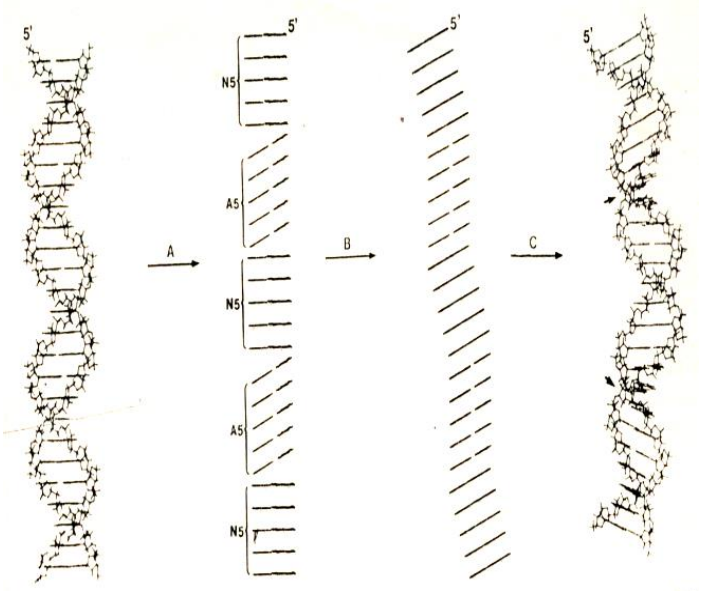

Figure-8 : Schematic illustration of the A – tract induced bending of a DNA segment of sequence $N_5A_5N_5A_5N_5$. In step A , the B- form double helix on the left was unwound its sugar – phasphate back bone removed (for purpose of clarity) and the base pais with in A-tracts tilted or inclined relative to the helix axis in the direction characteristic of poly(dA).poly(dT) (as drawn in the central figures) represent view into the minor groove along the pseudo dyad axis of each base pairs. Had the back bone been shown , they would run lengthwise outside the base pairs forming a ladder – like structure. In step B , local helix axis reorient to facilitate base stacking at the junctions between the structurally dissimilar A_5 and N_5 regions , thus small bends in the helix axis arise from the inclination of the A-T pairs in combination with the requirement for favorable base stacking at junction. When these local bends are positioned in phase with the helix repeat , large global curvature results. This can be seen in step C where (i) the backbone was repacked (ii) 36° twists were applied about the local helix axis between each set of adjacent base pairs and (iii) the entire double helix

was repositioned to put the overall bend in the plane of the page . Note that direction of curvature produced by steps A-C in geometrically equivalent to compression of the minor groove at the centers of the A-tracts (shown by the two small arrows) this is in accord with the bend direction deduced from comparative electrophoresis mobility studies (Koo *et.al.,* 1986, Hagerman *et.al.,* 1986, Ulanovsky *et.al.,* 1987) . In the figure on the extreme right the bend magnitude is 20^{o} per A-tract 10% junction , close the value of 18^{o}/A tract derived from the experiment (Griffith *et.al.,* 1986) in the central two schematic figures, however the bend magnitude are twice those values for visual emphasis (Crother *et.al.,* 1990, Mack *et.al.,* 2001).

A Unifying Model : Based on their understanding of the two models Crother et. al. have built a unifying model as illustrated in the Figure -8 describes as follows , the direction and magnitude of bending are quite accurately predicted if one assumes that base pairs within A - tracts are inclined relative to the helix axis much as they are in model of poly (dA) . poly (dT) , for which substantial experimental support exists. Energy calculations of poly (dA) . poly (dT) indicate that the stacking energies for A.T pairs in this conformation are sub optimal but also that this seemingly unfavorable arrangement promotes formation of net work of hydration in minor groove (linking Thy O2 and Ade N3 atoms on opposite strands) that more than compensates for the lost stacking energy. Removal of this water spine by increased temperature or organic solvents should reduce bending by freeing the -T pairs to adopt a more favorable base stacking arrangement in which they are perpendicular to be the helix axis. The hydration network cannot form GC rich sequence because the guanosine 2- amino group intrudes into the minor groove. According to the model , co-operativity effects should arise at least in part from the relative instability of water spine in short (n= 2-3) A-tracts. Once the A tract has reached a length of 4 this nucleation effect largely overcome. In addition , since minor groove hydration is thought to be disrupting by TpA but not ApT steps , a contiguous array of inclined A.T pairs may run across ApT but not TpA steps . Thus one expects the An and Tn tract in sequences A_nT_n to act in concert as single cooperative unit , whereas those in sequences T_nA_n should behave independently.

The hybrid-solvent model : Both the early models are based on sequence-dependent base-base interactions as the cause of A-tract curvature. (Williams *et.al.,* 2000). Williams and co-workers has proposed a hybrid-solvent model based on interactions between DNA and its environment. In the hybrid-solvent model electrostatic interactions between DNA and the solution cause bending (Shui et.al., 1998, Shui et.al., 1998a).were considered. This model suggests that cations can partition into the minor groove spine of hydration. Once the cation partitioned , can dispersed around DNA in an asymmetric fashion depending on the DNA sequence. Cation organization is DNA sequence dependent. The cation interacts with the functional groups of the DNA bases and backbone. Localization of cations in or around the DNA cause phosphate neutralization. This the localization and neutralization of cations toward one face of the DNA, phosphate result in an asymmetric force on the DNA. This in turn causes narrowing of the minor groove and bending of the helical axis. Williams and co-workers demonstrated, through x-ray crystal structures, localization of Na^{+}, K^{+}, Cs^{+}, Mg^{2+} and Tl^{+} in the A-tract minor groove of the Dickerson dodecamer and narrowing of the minor groove width in response to cation binding (Shui et.al., 1998, Shui et.al., 1998a , Kruger Woods et.al., 2000, Sines et.al., 2000, Howerton et.al., 2001). Egli et.al. has observed Rb+ in the A-tract minor groove of the Dickerson dodecamer (Tereshko et.al., 1999). The localization of monovalent and divalent cations in the minor groove, has been seen by Hud *ad*. in A_{2-5} tracts and which may be the cause of axial bending (Hud et.al., 1997, Hud et.al., 1999, Hud et.al., 2002). Molecular dynamics simulations studies carried out by other researchers supported the above model (Young et.al., 1997 , Young et.al., 1998, McConnell et.al., 2000, Hamelberg et.al., 2000). This model was further supported by phosphate neutralization mechanism with a demonstration of DNA bending as a result of the incorporation of neutral phosphate analogs and cationic analogs (Strauss et al., 1994, Strauss et al., 1996, Strauss et al., 1997, Hardwidge, et.al., 2001). A number of previous studies into the origins of A-tract curvature have made molecular substitutions to test the influence of specific atoms and groups on A-tract structure. Diekmann and McLaughlin substituted inosine-cytosine (I-C) for A-T pairs in order to disrupt bifurcated hydrogen bonds. They found that the effects were generally small, consistent with other localized minor groove effects.

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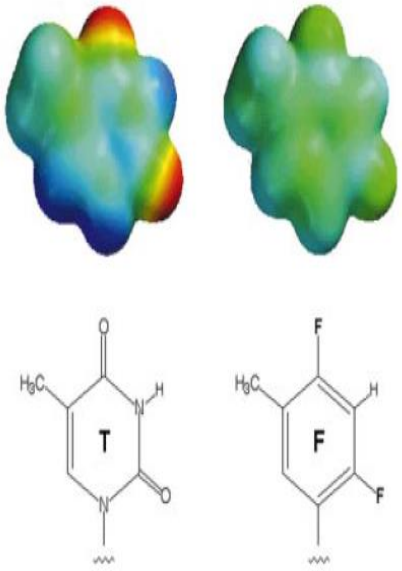

Figure-9. Structures and space filling models of thymine and the non-polar shape mimic difluorotoluene

Calculated electrostatic potentials are mapped on the surface ; red indicates negative potential and blue indicates positive (Maki et al., 2003) being responsible for bending and not bifurcated hydrogen bonds (Diekmann et.al., 1992). Seela and Grein presented a study of substitutions on the purine side of A_5 and A_6 tracts, replacing adenine with analogs lacking minor groove (N3) or major groove (N7) nitrogens (Seela et.al., 1992). Interestingly, both were found to be important in curvature. In the minor groove, removal of N3 at positions 4-6 in an A_6 tract was found to abolish most of the bend, whereas removal at positions 1-3 had little effect. Significantly, such previous molecular replacement studies have probed interactions on the purine side of the A tract but have largely ignored the pyrimidine half. If localized interactions in the minor groove including solvation and cation binding are an important causative factor of curved DNA, then it seems quite possible that thymine O2 might play a central role. Thymine O2 has greater negative charge density than adenine N3, and as such it forms stronger hydrogen bonds to water and is likely to have greater affinity for most cations as well. Moreover, the recent experiments of Williams, Feigon and Beveridge have all pointed to the central role of thymine O2 in cation localization in the minor groove. The effects of substitution of thymines in an A5 tract by 2,4-difuorotoluene deoxynucleoside (F) is a nearly perfect shape mimic (isostere) of thymidine but has fluorine in place of the carbonyls at positions 2 and 4 (Figure 9). Thus, it lacks the hydrogen bonding and metal-ioncomplexation ability of thymidine (Maki et al., 2003) . Using the gel mobility methods of Maher and co-workers (Ross et.al., 1999) the effects on duplex DNA curvature was measured. It was found that substitution of certain thymines in an A tract causes a significant decrease in curvature. These results are found to consistence with localize electrostatic effects at thymine, such as minor groove solvation and cation localization, being primary causes of A-tract curvature.

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