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The Use of Molecular Dynamics Simulations to Predict Thymine Dimer Formation in Histone Bound DNA

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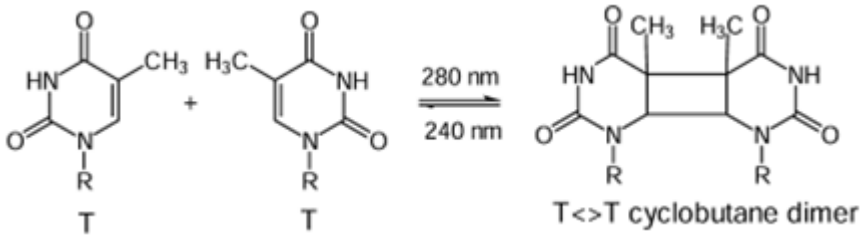
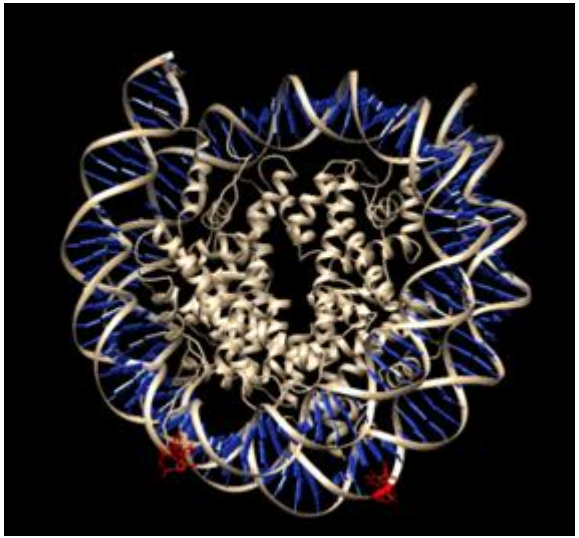
Thymine Dimers in DNA



(Beukers, Eker, & Lohman, 2007)



Visualization made using Chimera

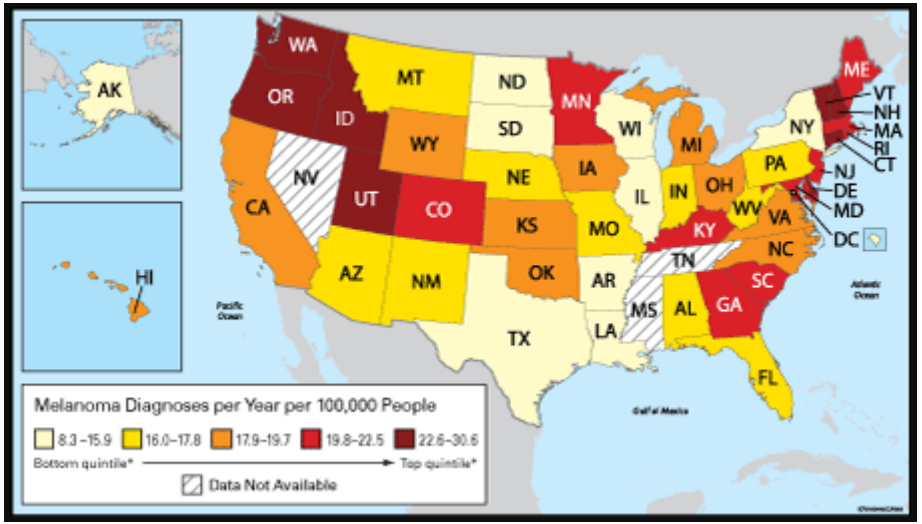
Dimers can lead to

-Interference of DNA replication

-Apoptosis

-Cancer

(Schreier, et al., 2007)



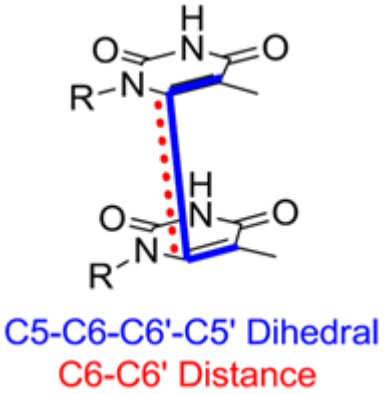
(Skin Cancer Facts For Your State)

In order for the reaction to occur

-Distance needs to be below 3.5Å (Johnson & Wiest, 2007)

-Distance needs to be below 4.2Å (Ramamurthy & Venkatesan, 1987)

-Dihedral angle needs to be 27° ± 3° (Johnson & Wiest, 2007)



(Johnson, 2011)

(Pearlman, Holbrook, & Kim, 1986)

Dimers can increase the bending of the DNA molecule

-Can affect the probability of future thymine dimer formation

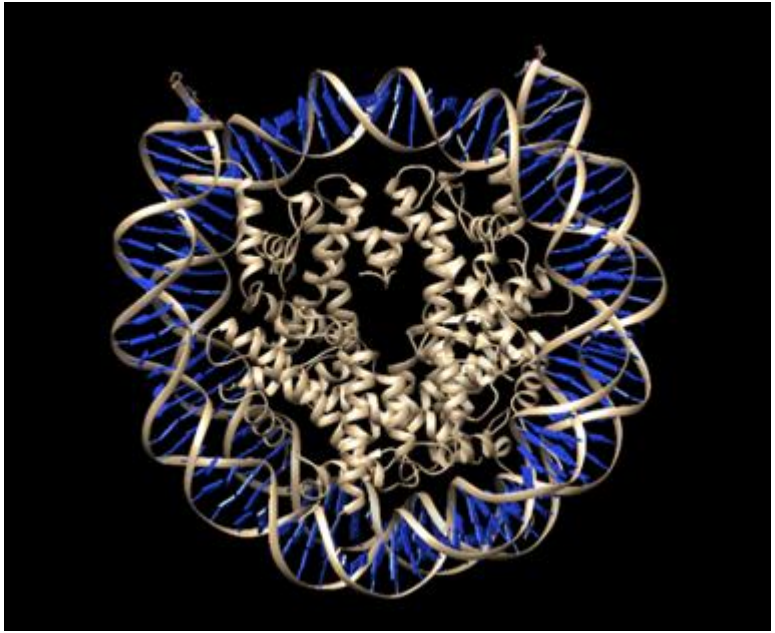
(Finch, Davis, & Rokita, 2013)

Hypothesis

-Location of neighboring thymines around the histone can affect the probability of future thymine dimer formation

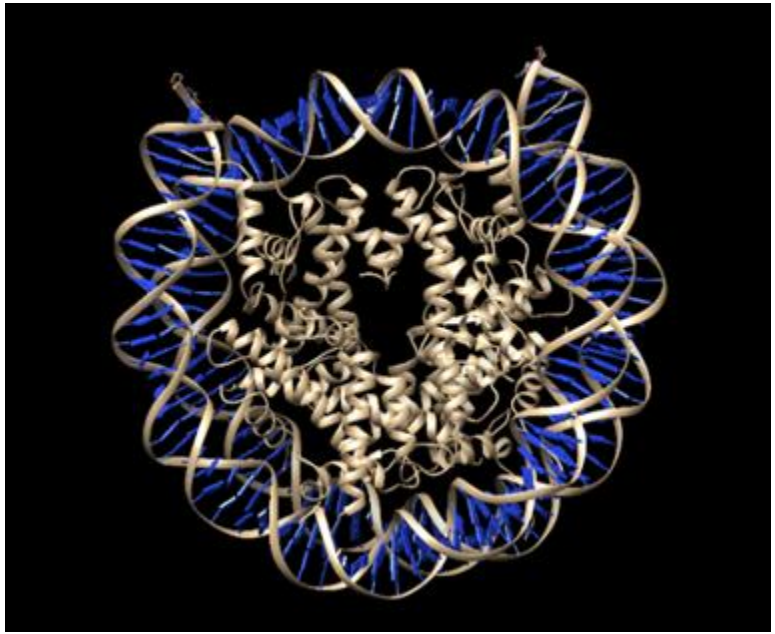
-Presence of a thymine dimer can increase the formation of subsequent thymine dimers within the DNA

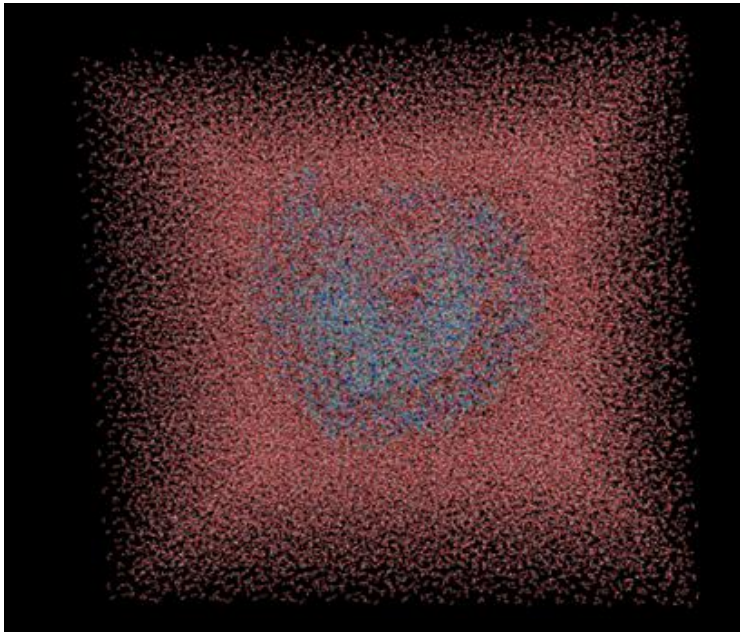
DNA around a Histone



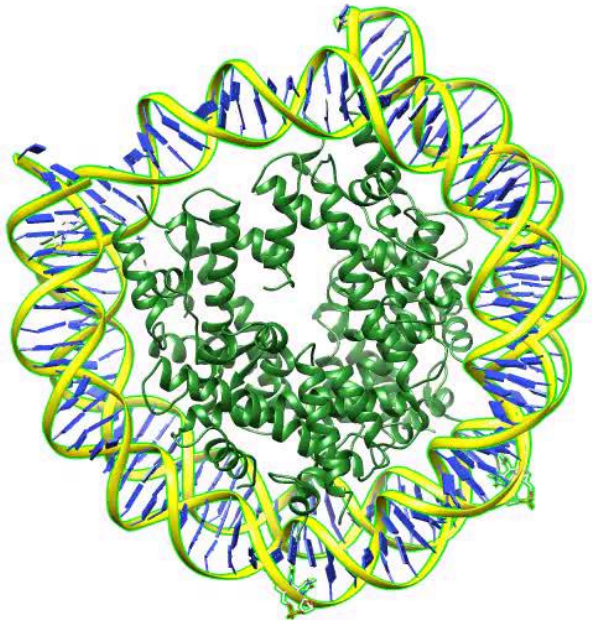
Visualization made using Chimera

Molecular Dynamics





Visualizations made using Chimera



With Dimers

Movies made using VMD

Two systems were created

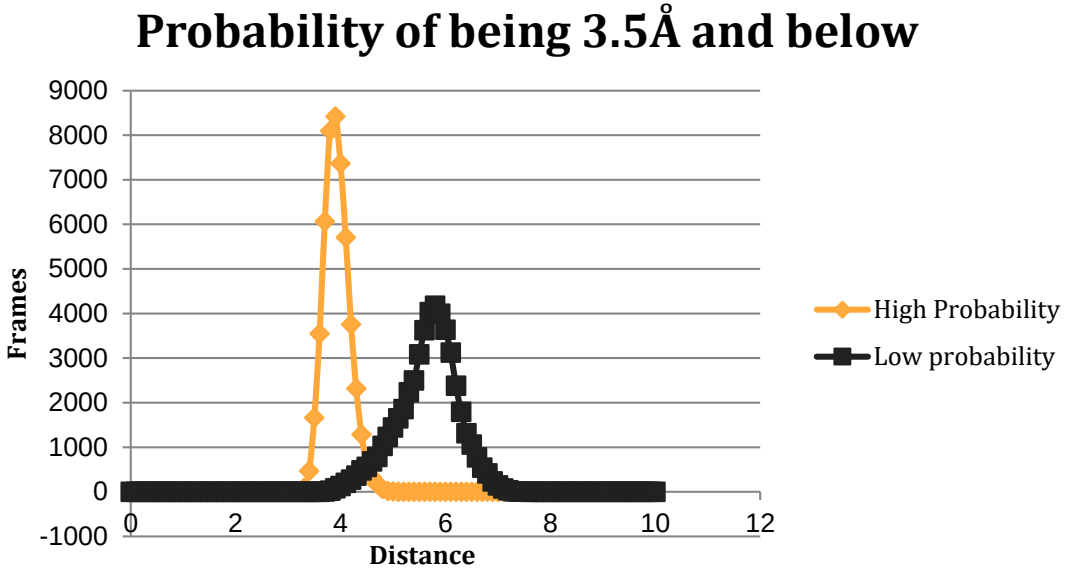
System	Dimensions (Å)	Number of atoms	Number of Neighboring Thymines
NoDimer PDB ID: 5B24	149.78 x111.71 x154.02	217,910	28
Dimer PDB ID: 3AFA	153.77 x103.14 x152.78	204,189	24

Simulations

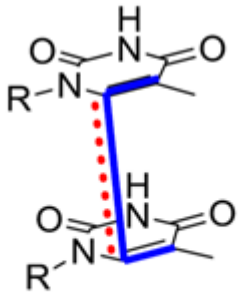
-Amber16, NAMD, VMD, Chimera, X3DNA

-50ns simulations were run for both systems

Analysis

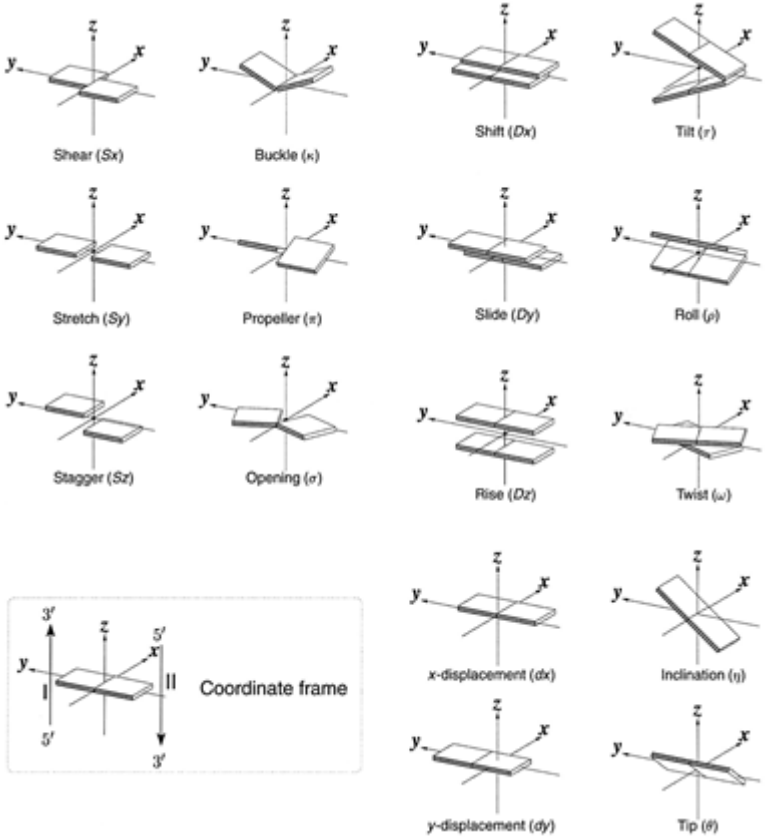


Histograms were created to see how often the neighboring thymines were in the proper orientation



C5-C6-C6'-C5' Dihedral
C6-C6' Distance

(Johnson, 2011)



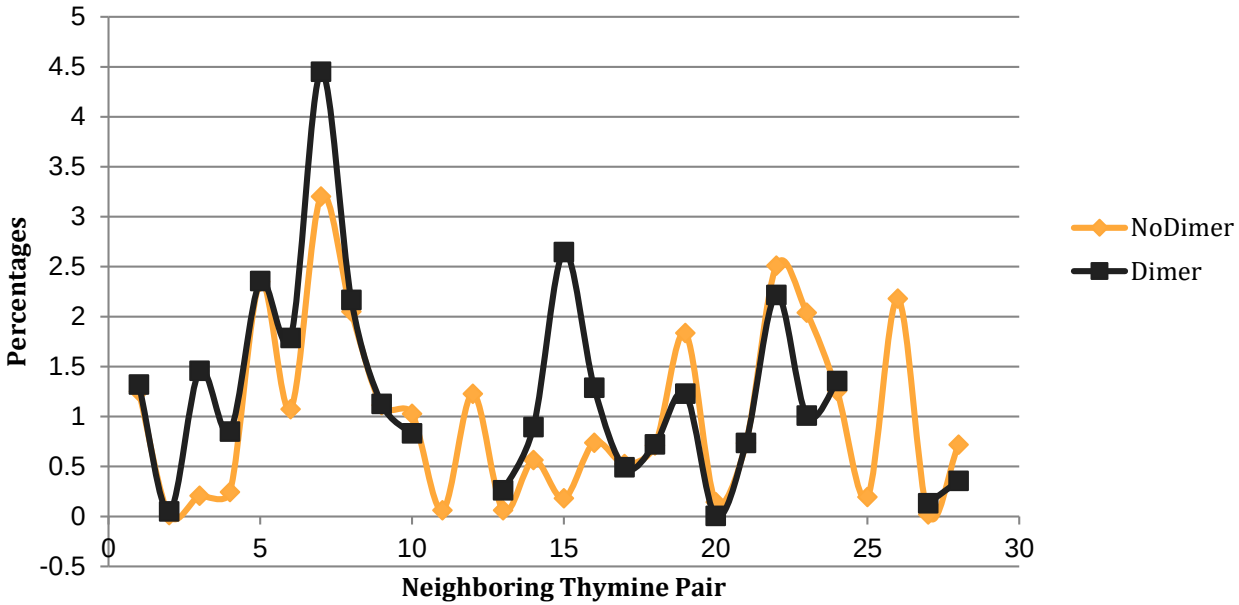
(Lu & Olsen, 2003)

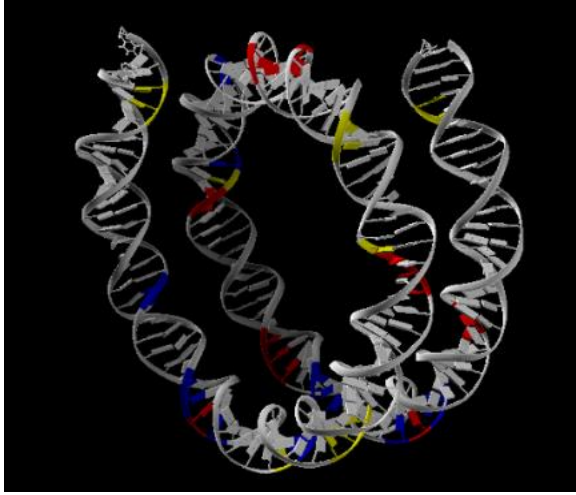
Data for both systems taken over 50ns

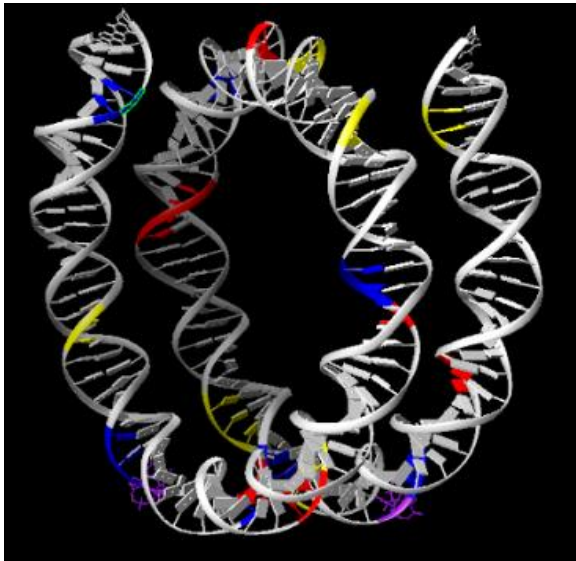
No Dimer	3.5 Å and Below				4.2 Å and Below				Dihedral Angle
	C5C5	C5C6	C6C6		C5C5	C5C6	C6C6		
Maximum	3.20	0.93	0.31		86.55	71.65	47.80		39.56
Minimum	0.01	0.00	0.00		7.92	6.74	3.35		2.59
Average	1.01	0.28	0.08		56.22	40.93	24.00		20.08

Dimer	3.5 Å and Below				4.2 Å and Below				Dihedral Angle
	C5C5	C5C6	C6C6		C5C5	C5C6	C6C6		
Maximum	4.45	1.18	0.31		90.36	76.32	51.01		36.95
Minimum	0.01	0.00	0.00		3.42	2.40	1.45		4.52
Average	1.24	0.32	0.09		62.38	46.00	26.60		19.56

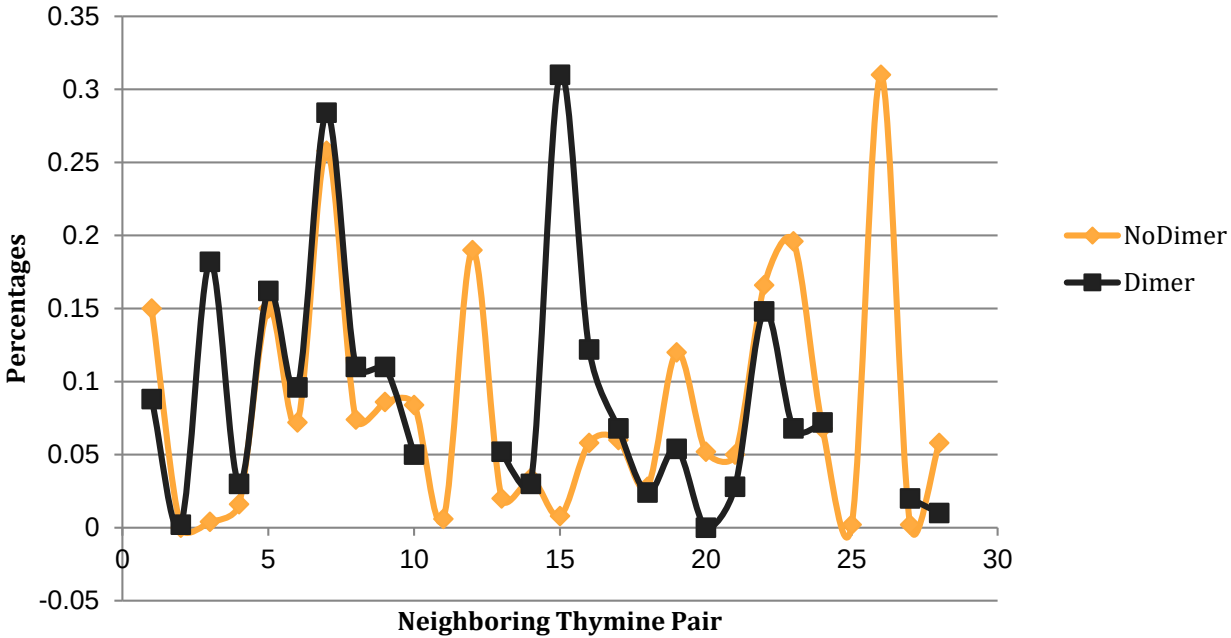
Comparison of Percentages 3.5Å and below C5C5 bond

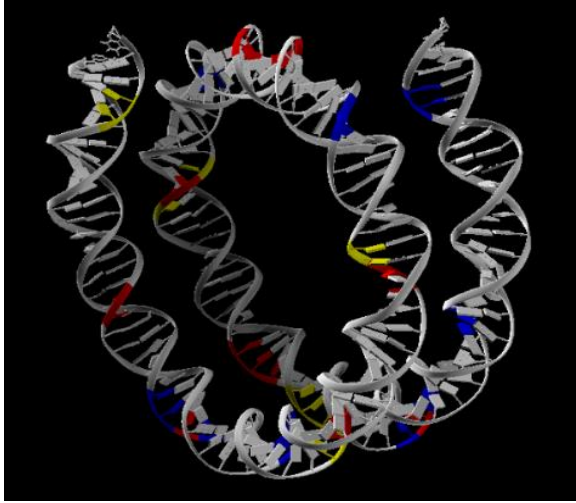


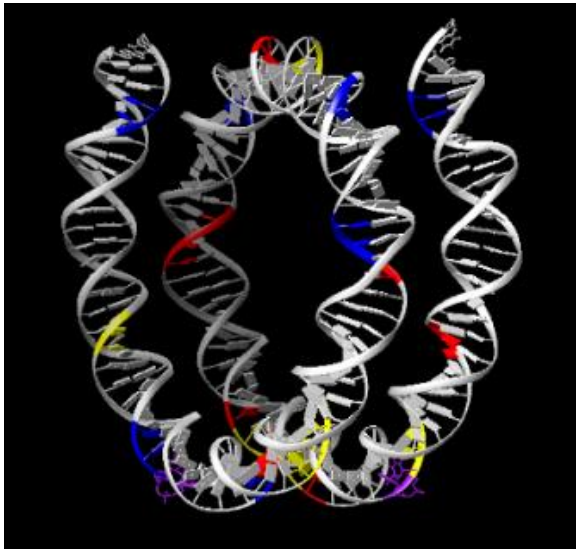


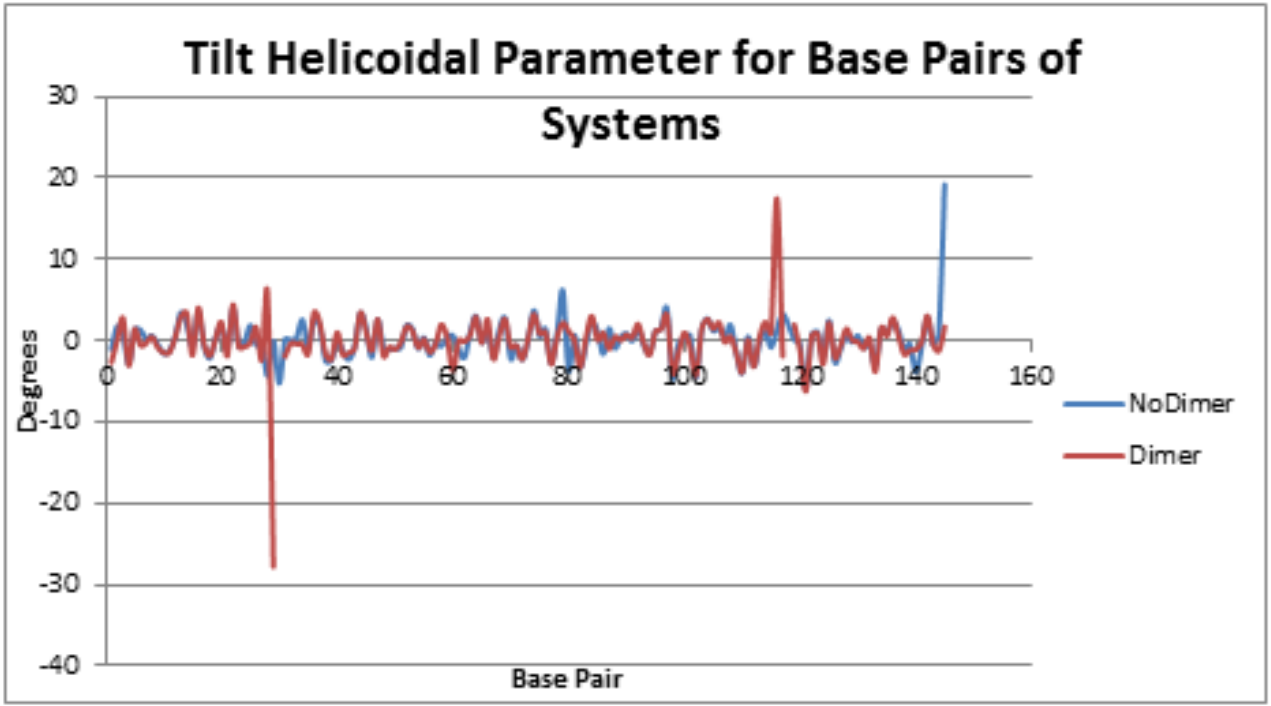


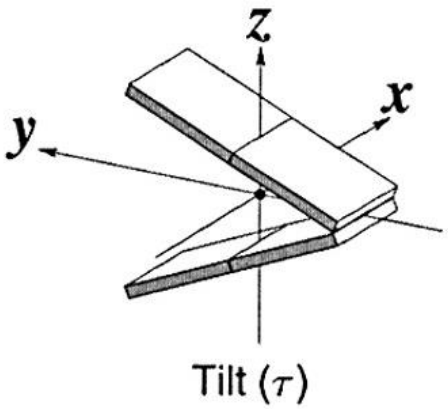
Comparison of Percentages 3.5Å and below C6C6 bond



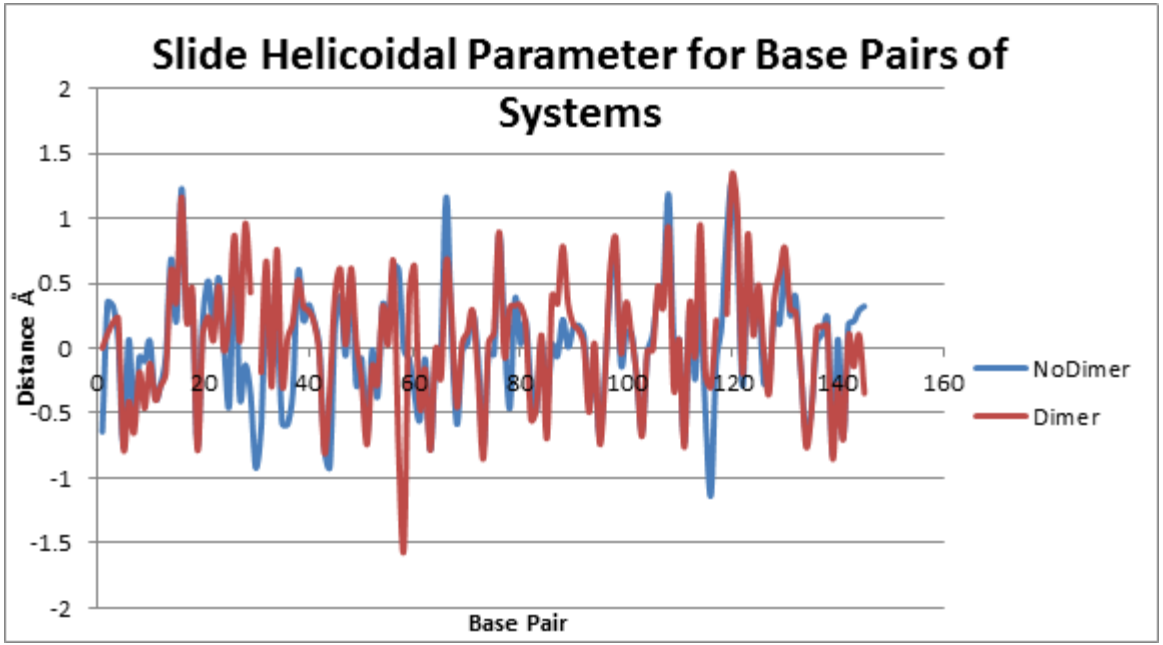


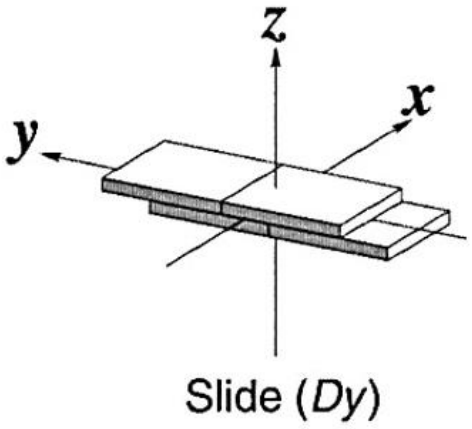






(Lu & Olsen, 2003)





(Lu & Olsen, 2003)

	NoDimer	Dimer
Buckle	0.415151	-0.1035
Inclination	2.852866	3.428711
Opening	-0.23803	0.630925
Propeller	-12.2353	-12.5959
Rise	3.371568	3.385457
Roll	1.239438	1.577406
Shear	-0.01142	0.002419
Shift	0.000128	-0.00281
Slide	0.009082	0.060986
Stagger	-0.02034	-0.00334
Stretch	-0.02764	-0.02578
Tilt	0.149996	-0.02948
Tip	-0.1805	0.114391
Twist	34.81735	35.00886
Xdisplacement	-0.39398	-0.35585
Ydisplacement	0.016326	-0.03016

System averages of helicoidal parameters over 50ns

Conclusion

-Our data suggests that the presence of a dimer within the system may lead to an increased probability of future thymine dimer formation

-Some trends for where there are areas of higher probability and of lower probability are located

Acknowledgments

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Citations

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