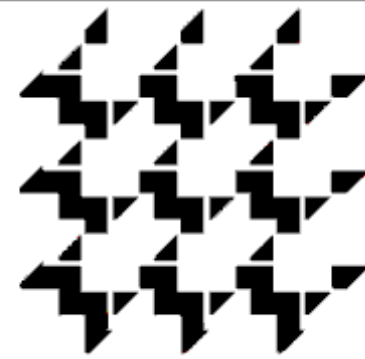


DIMACS

*Center for Discrete Mathematics & Theoretical Computer Science
Founded as a National Science Foundation Science and
Technology Center*



INSIGHTS INTO CHROMATIN PROPERTIES FROM COMPUTER SIMULATIONS

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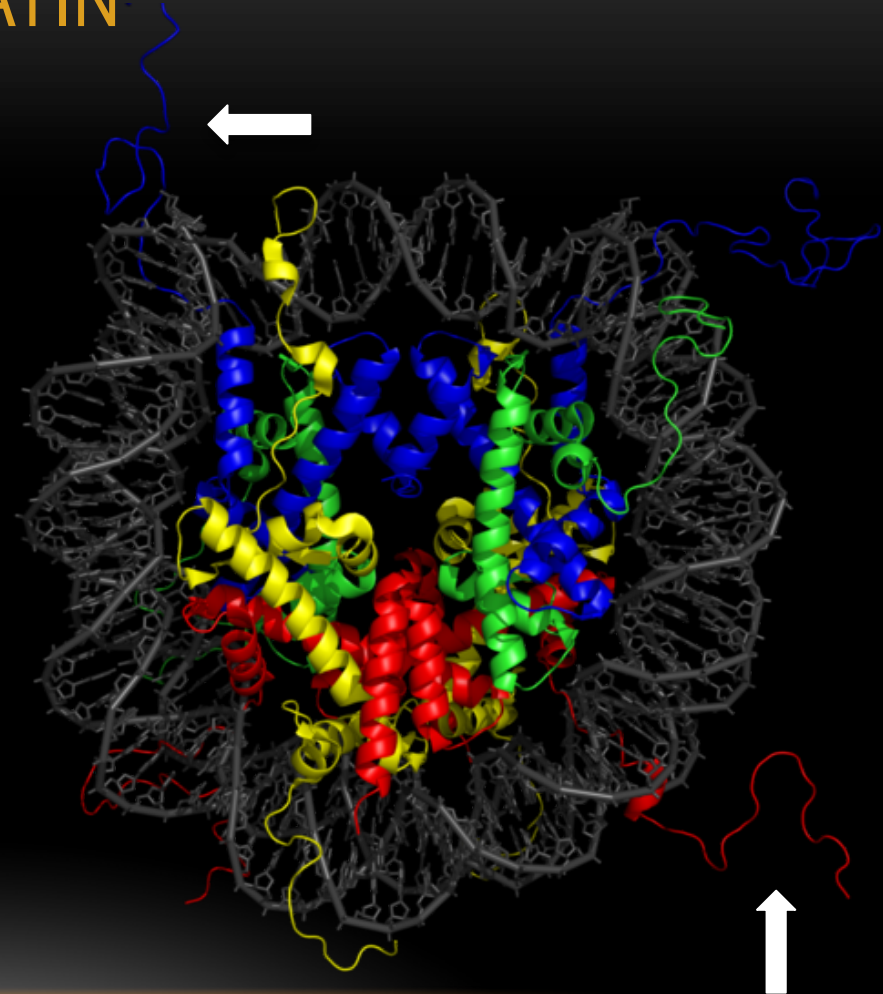
DNA

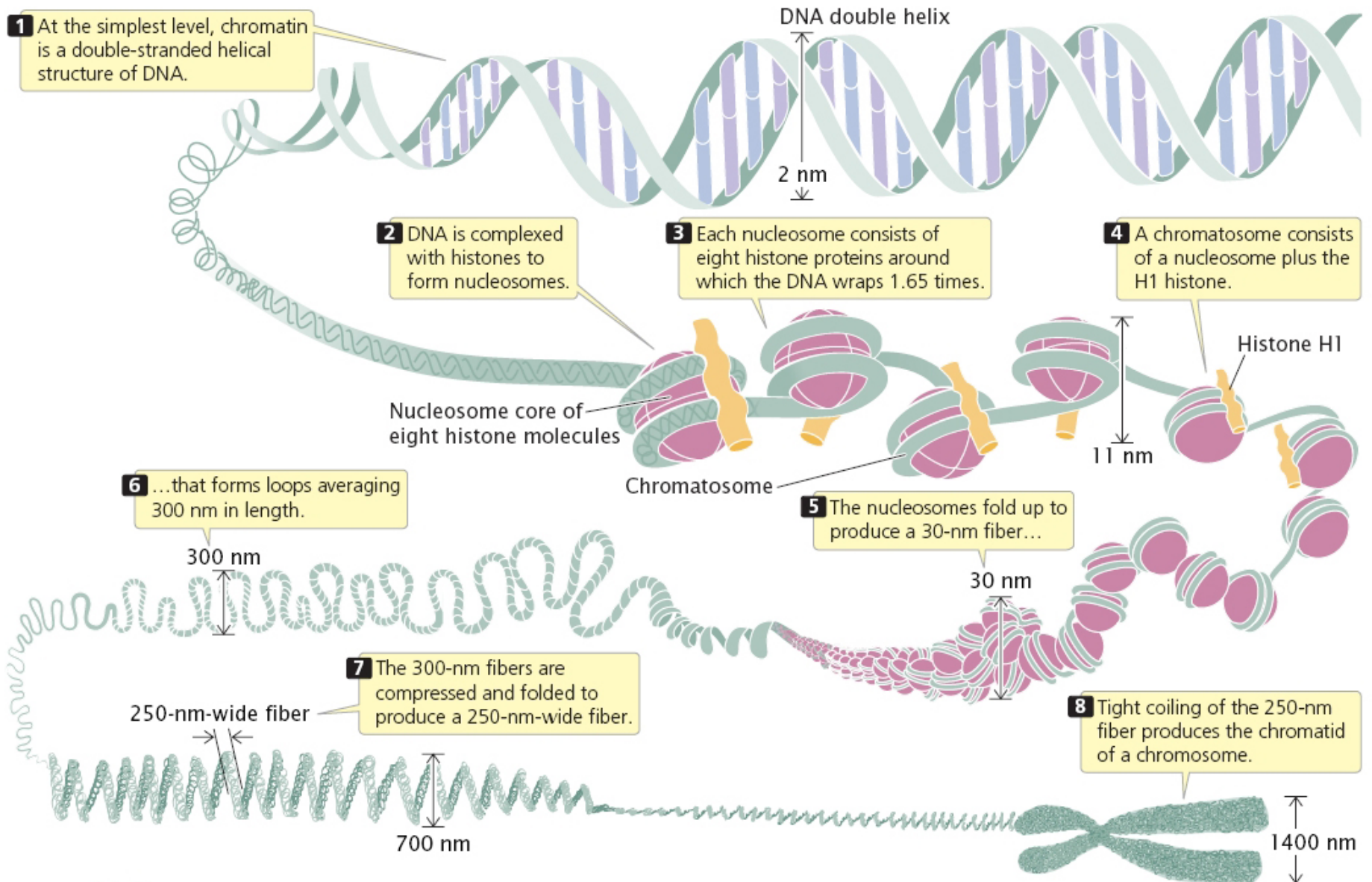
- Identical DNA contained in nucleus of every cell in the body
 - Cell diameter $\approx 10\ \mu\text{m}$
 - **What changes genetic expression to determine cell differentiation?**
- If unwound, human DNA is $\sim 6\ \text{ft}$ in length
 - Estimated 5-50 trillion cells in the human body
 - DNA could reach from here to the sun and back, more than 300 times
 - **How can all of the DNA possibly fit?**



ORGANIZATION - CHROMATIN

- DNA organized into DNA-protein complexes
 - DNA wraps around eight histone proteins to form nucleosomes
 - Histones contain “tails,” highly positively-charged amino acid chain
 - Multiple nucleosomes linked together via linker DNA
 - Packaging of DNA into nucleosomes shortens the fiber length about sevenfold
- Chromatin organization changes drastically during the cell cycle
 - Packing ratio of DNA in metaphase chromosomes is approximately 10,000:1
 - Chromatin fibers repeatedly fold into a hierarchy of multiple loops and coils



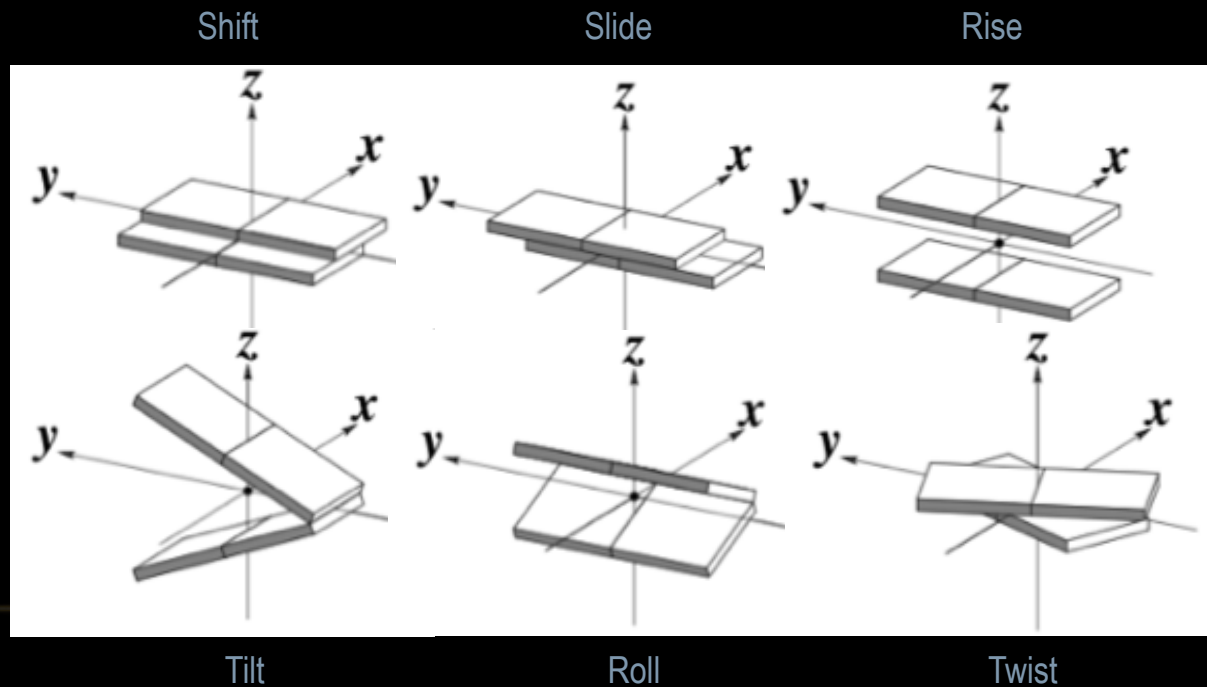


SIMULATION DATA

- Perform Monte Carlo simulations of different chromatin constructs
 - Ex: 7 nucleosomes, no histone tails, 30-bp linkers
 - 13 nucleosomes, histone tails, 35-bp linkers
- Six rigid body parameters describe base-base interactions

Translational:

Rotational:



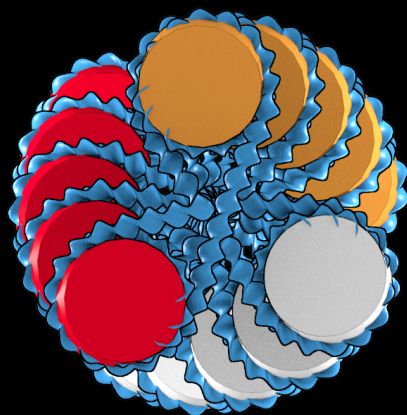
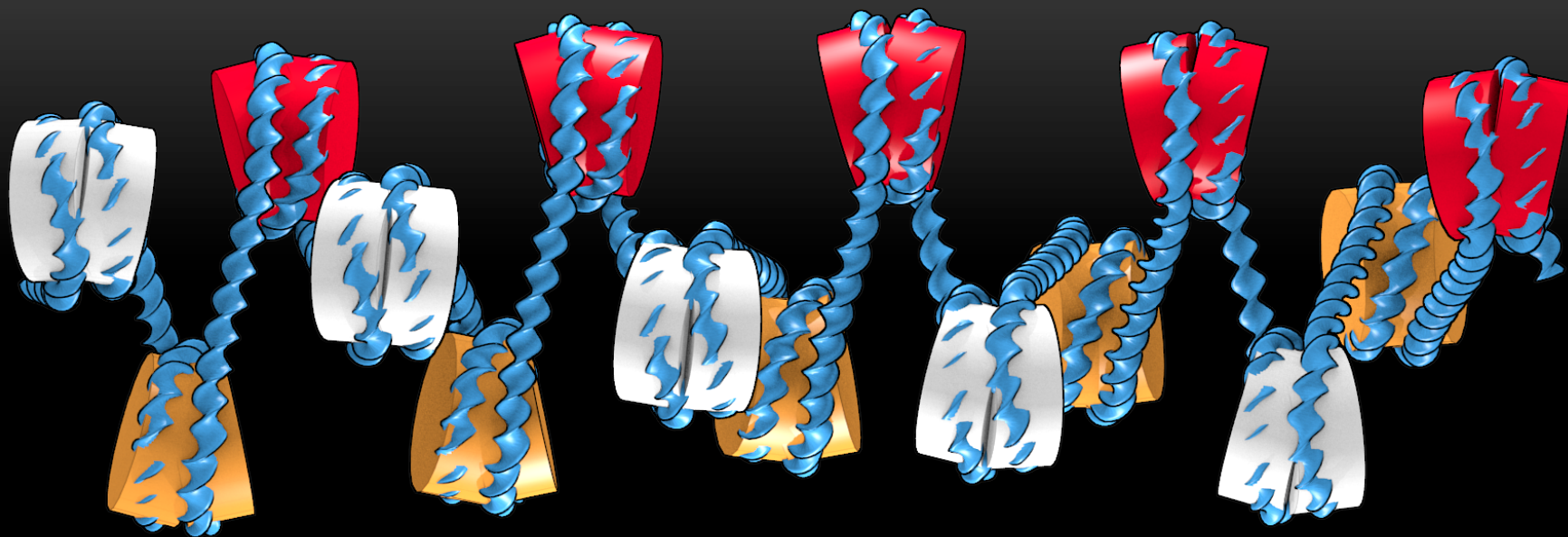
- Simulations data consists of large sets of chromatin configurations (sampling)
 - Analysis of the step parameter statistics
 - Provides geometric information for chromatin fiber
 - Analysis of the relative orientations and positions of the nucleosome local frames
 - Needed to study the electrostatic interactions between nucleosomes

OUTPUT

- Chromatin fiber geometry
 - Geometry around nucleosomes are relatively similar →
overall fiber geometry most affected by linker DNA geometry
 - Bend Angle = $\sqrt{[\text{Tilt}]^2 + [\text{Roll}]^2}$
 - Twist
- Energy at base-pair resolution
- Nucleosome-nucleosome interactions

GEOMETRIC DATA

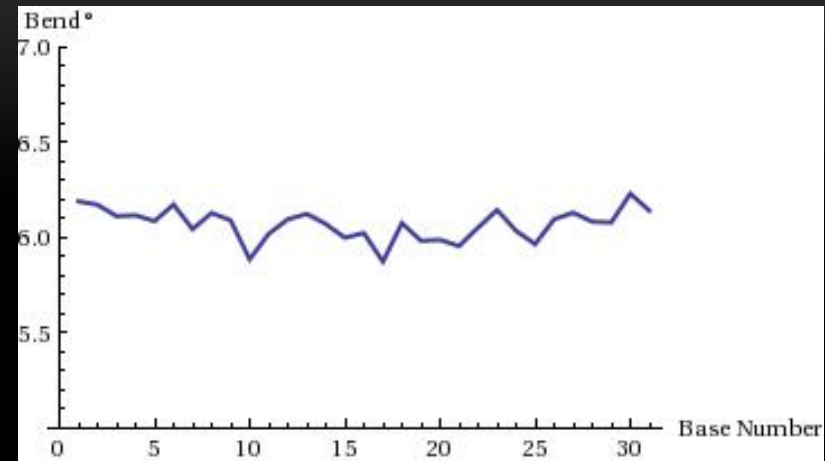
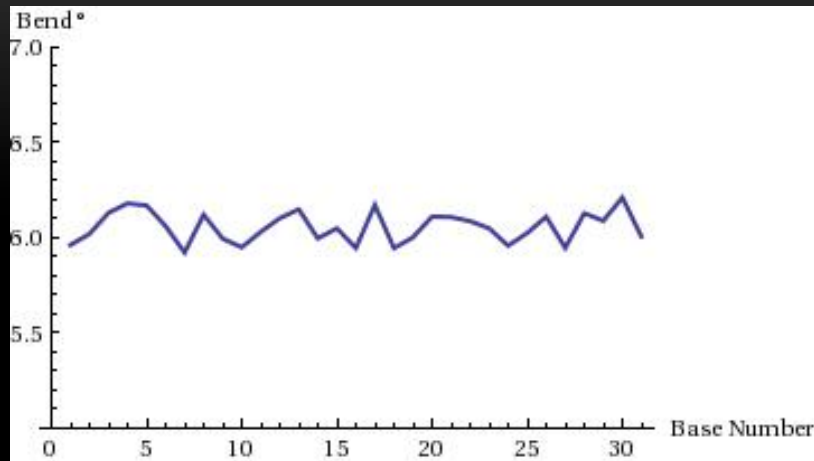
13 NUCLEOSOMES, 30-BP LINKERS:
HISTONE TAILS VS. NO TAILS



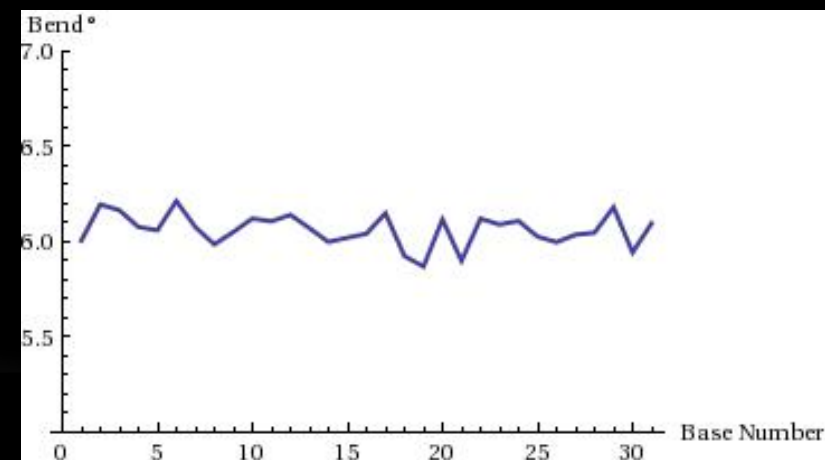
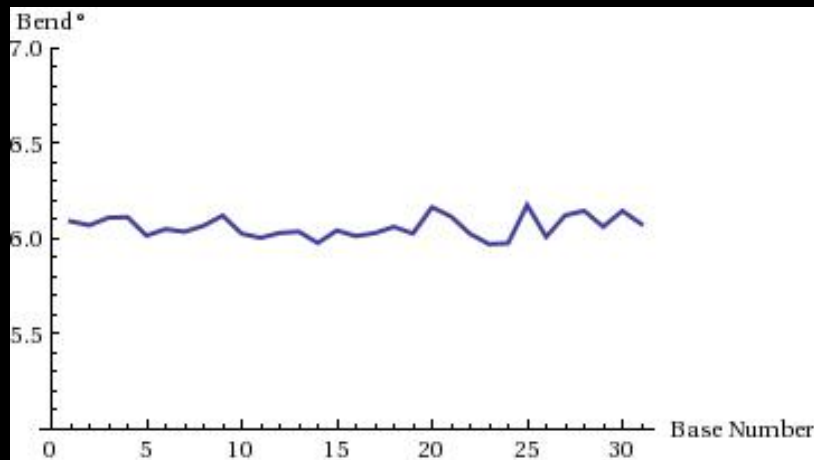
LINKER #7

LINKER #8

BEND ANGLE:
TAILS



BEND ANGLE:
NO TAILS

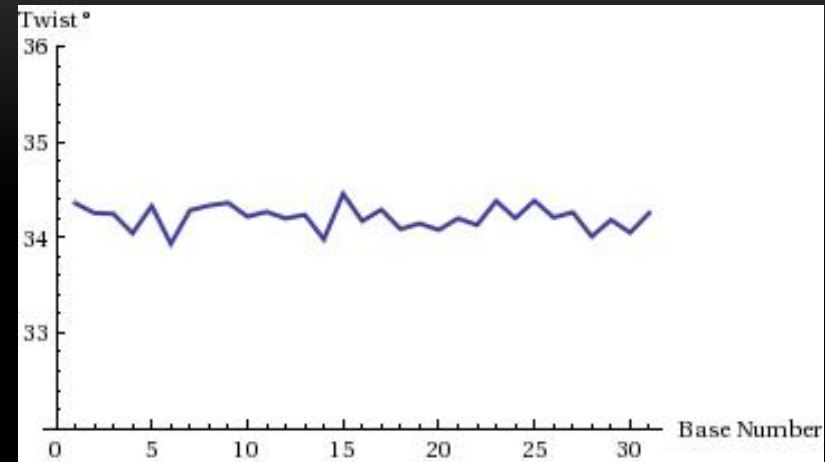
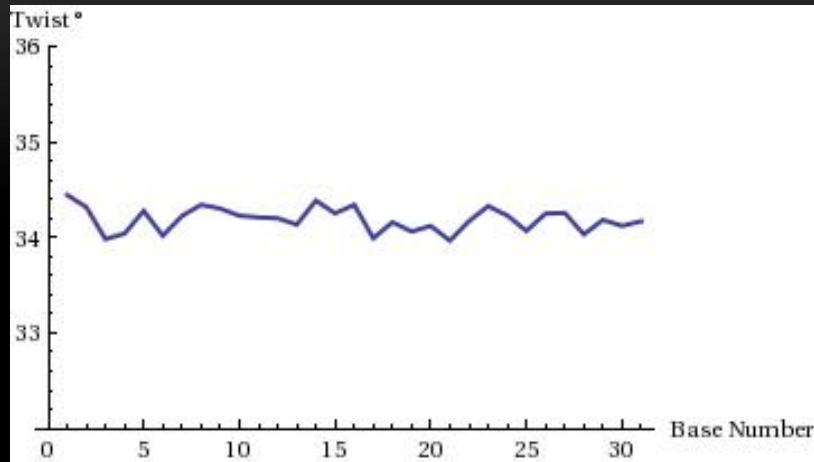


DNA linker curvature between nucleosomes with tails and those without tails is relatively similar. Differences in geometry cannot be inferred from curvature.

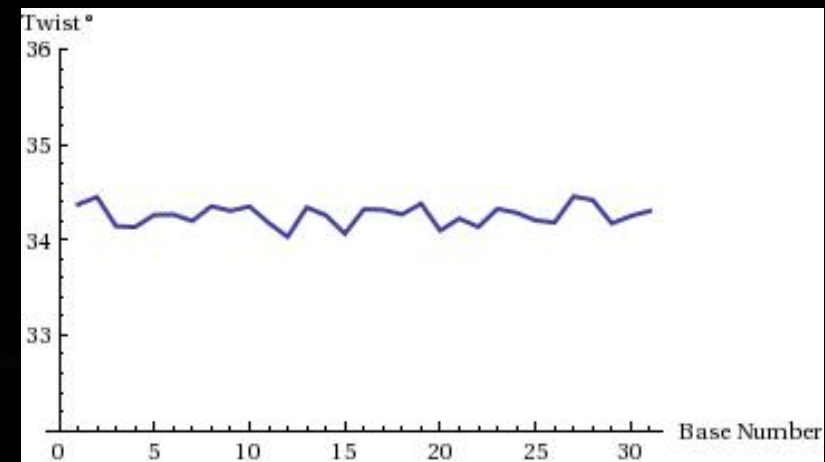
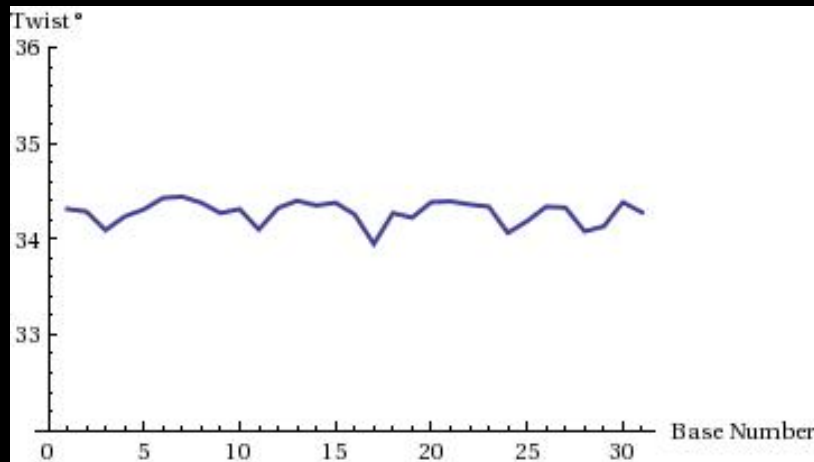
LINKER #7

LINKER #8

TWIST:
TAILS



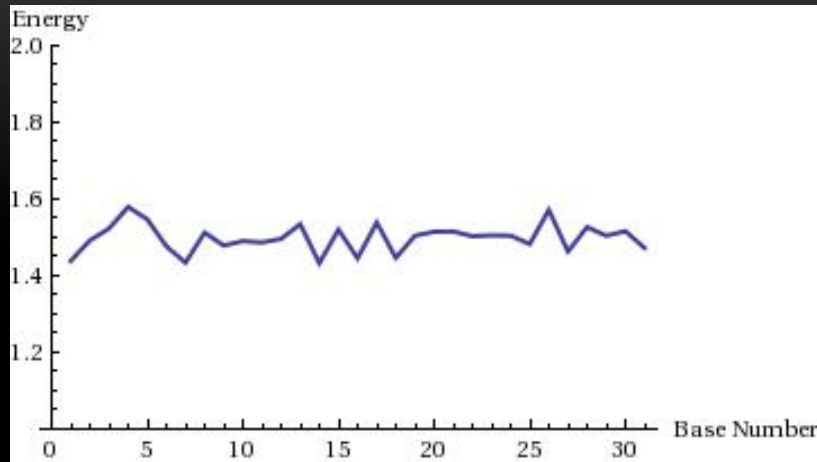
TWIST:
NO TAILS



DNA linker twist between nucleosomes with tails and those without tails is relatively similar. Differences in geometry cannot be inferred from twist.

LINKER #7

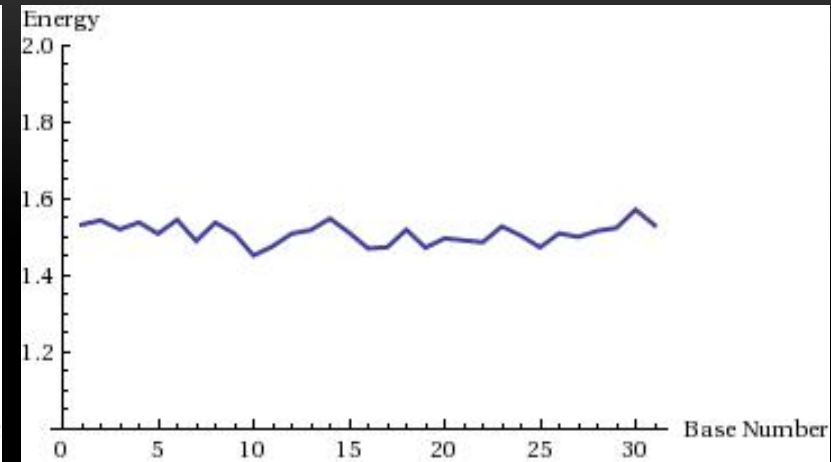
ENERGY:
TAILS



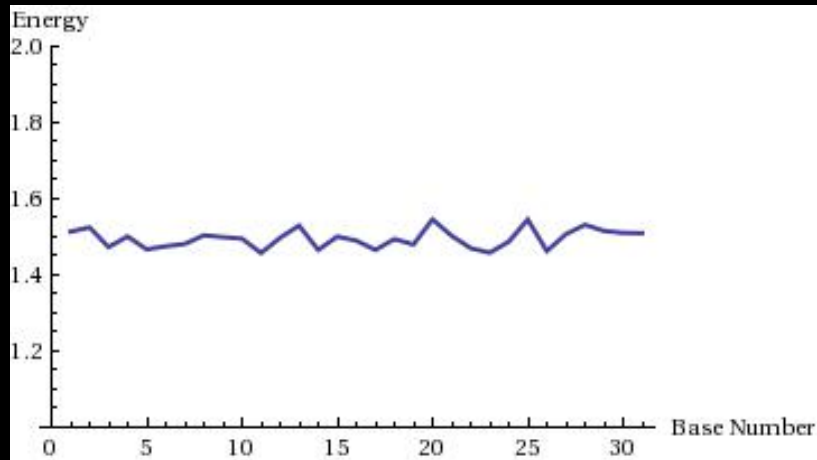
$$E_{\text{TOTAL}}(\text{LINKER}) = 46.4207$$

LINKER #8

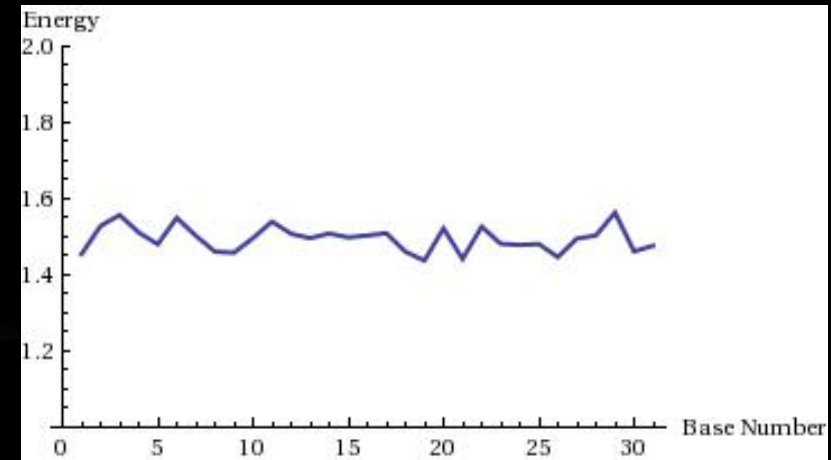
$$E_{\text{TOTAL}}(\text{LINKER}) = 46.793$$



ENERGY:
NO TAILS



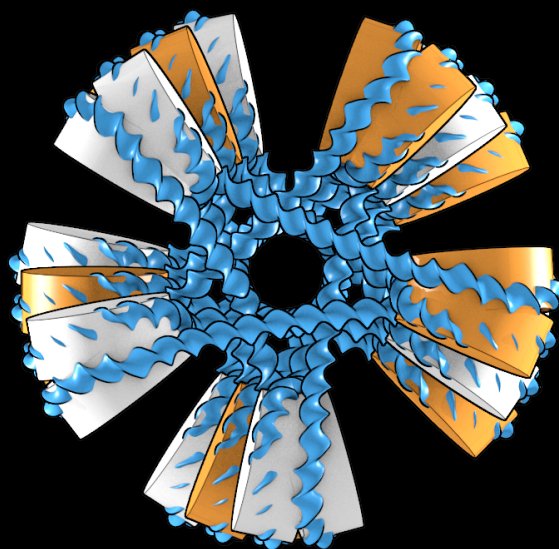
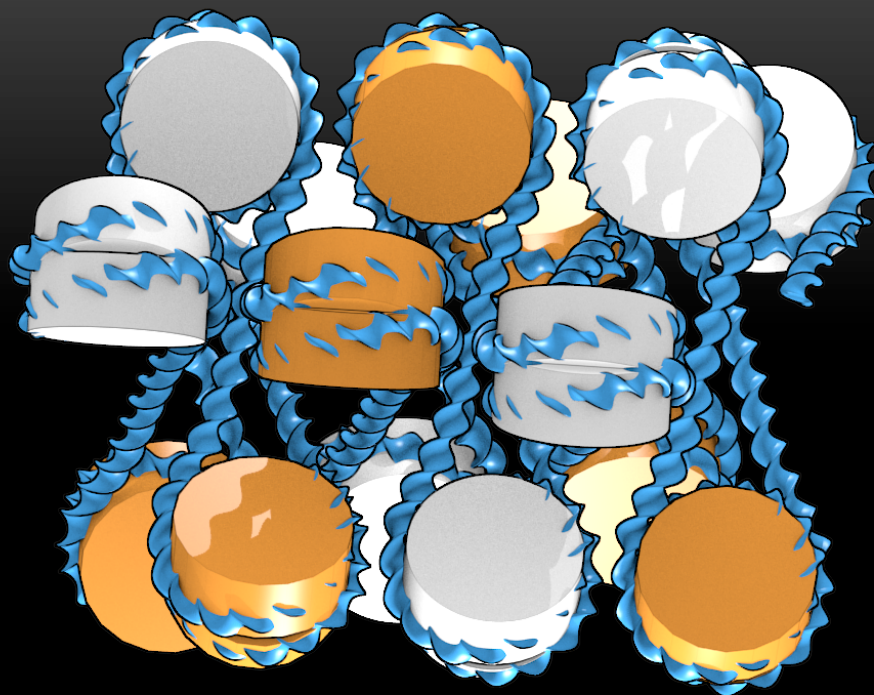
$$E_{\text{TOTAL}}(\text{LINKER}) = 46.3265$$



$$E_{\text{TOTAL}}(\text{LINKER}) = 46.3094$$

DNA linker energy for DNA with histone tails is slightly higher than that without tails. This may infer slight differences in geometry, or it may be attributed to other factors.

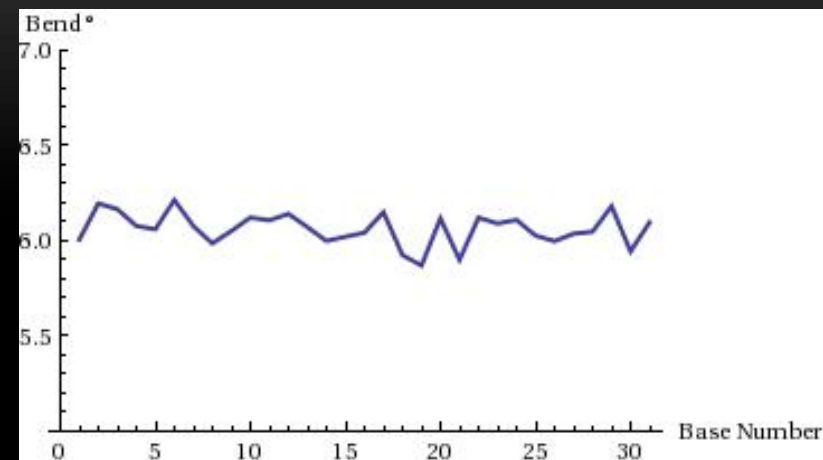
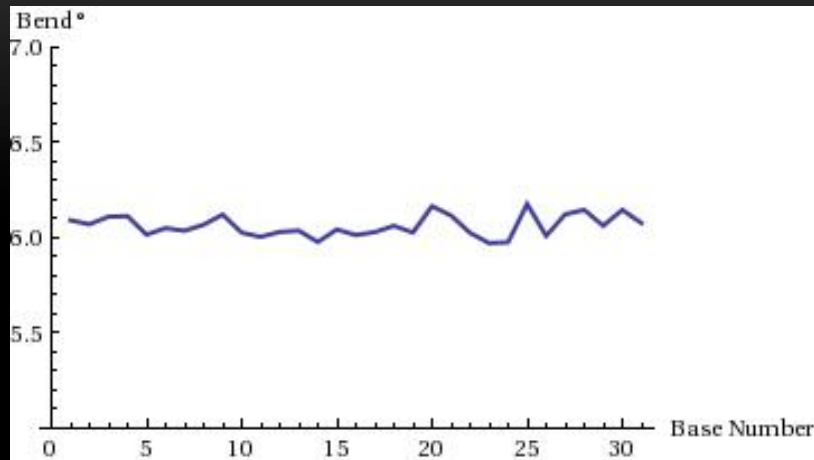
13 NUCLEOSOMES, NO TAILS:
30-BP VS. 35-BP LINKERS



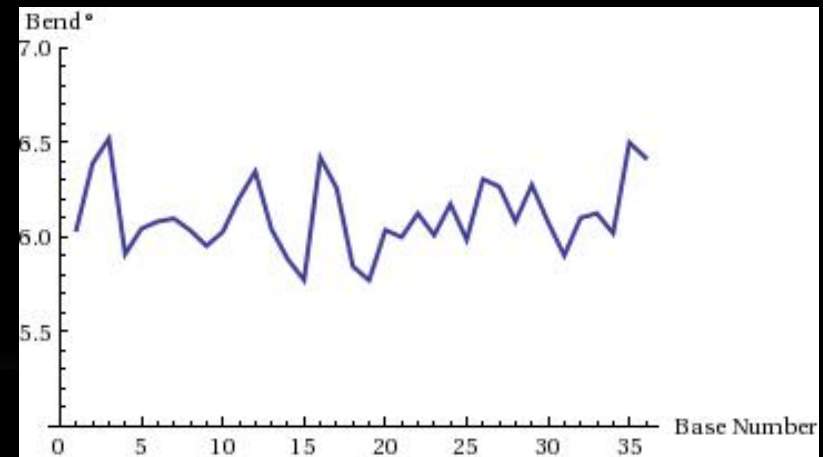
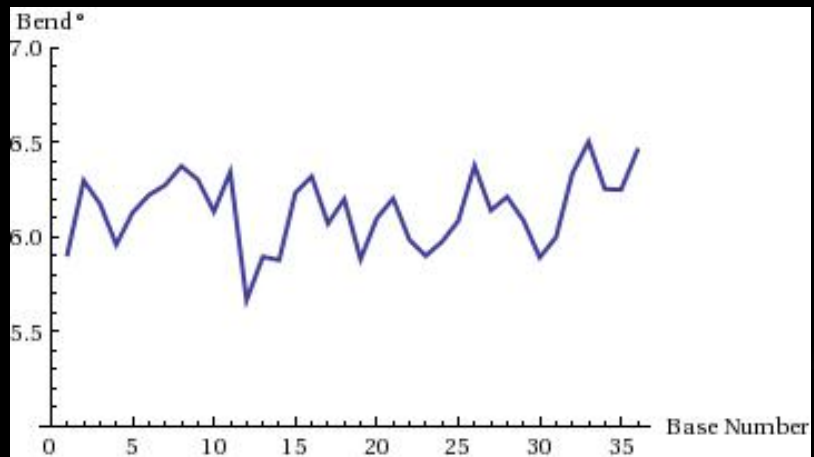
LINKER #7

LINKER #8

BEND ANGLE:
30 BP



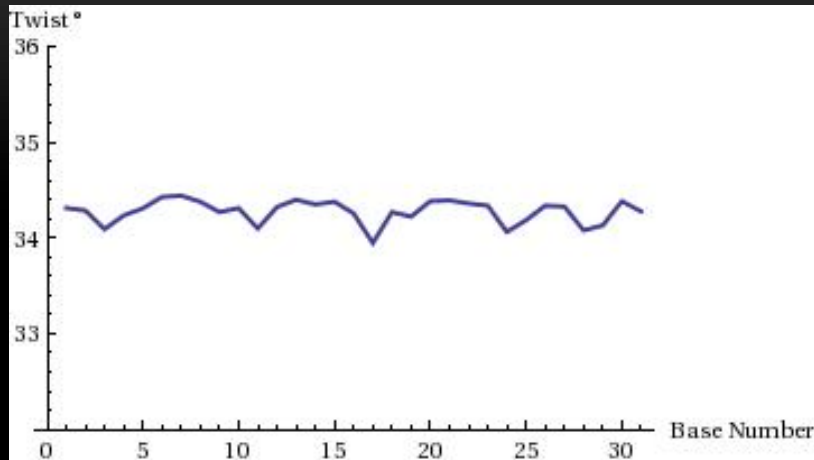
BEND ANGLE:
35 BP



DNA linker curvature for chromatin fiber with 35-bp linkers fluctuates significantly more than that with 30-bp linkers.

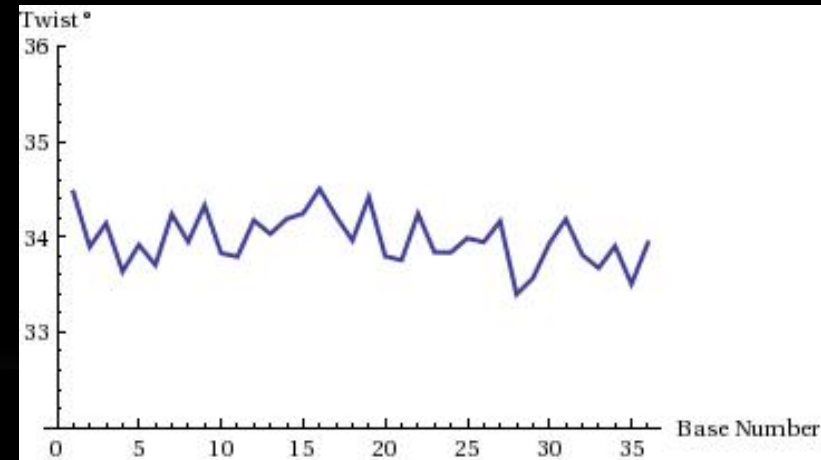
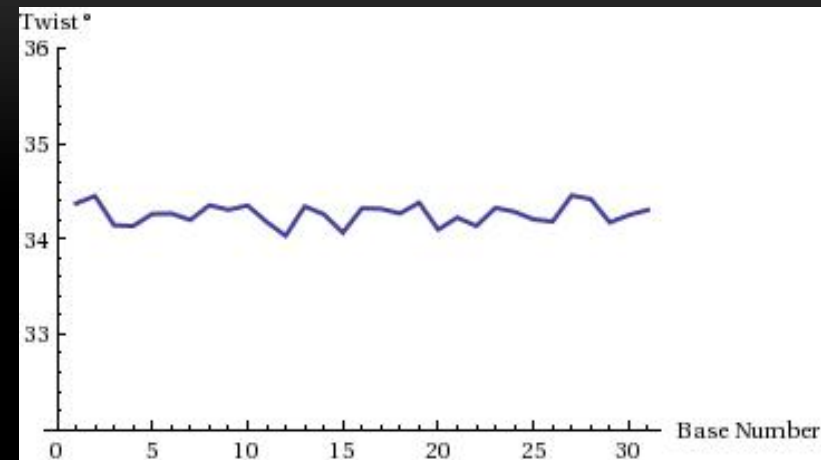
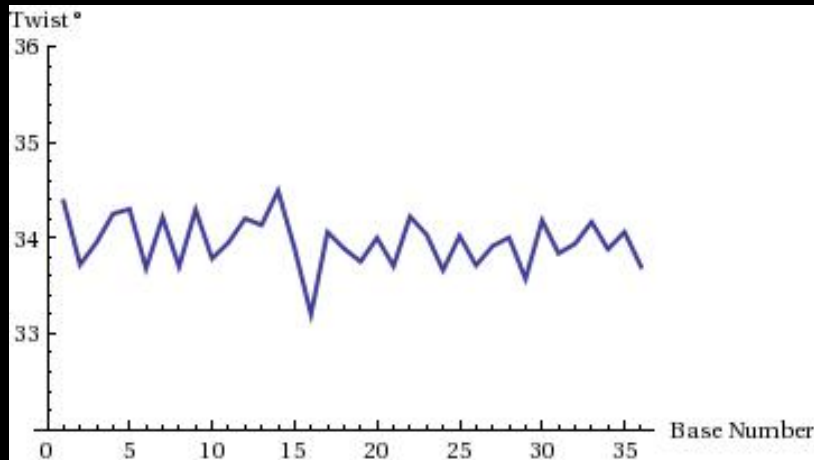
LINKER #7

TWIST:
30 BP



LINKER #8

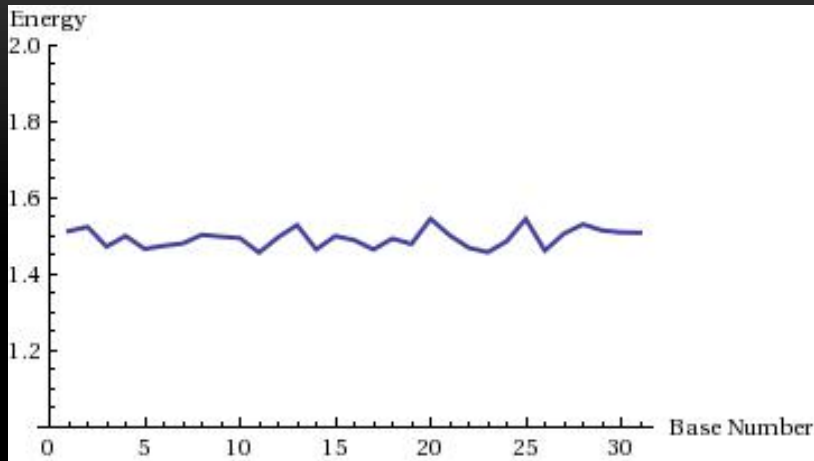
TWIST:
35 BP



DNA linker twist for chromatin fiber with 35-bp linkers fluctuates significantly more than that with 30-bp linkers. This data infers that the chromatin fiber with 35-bp linkers exhibits greater flexibility.

LINKER #7

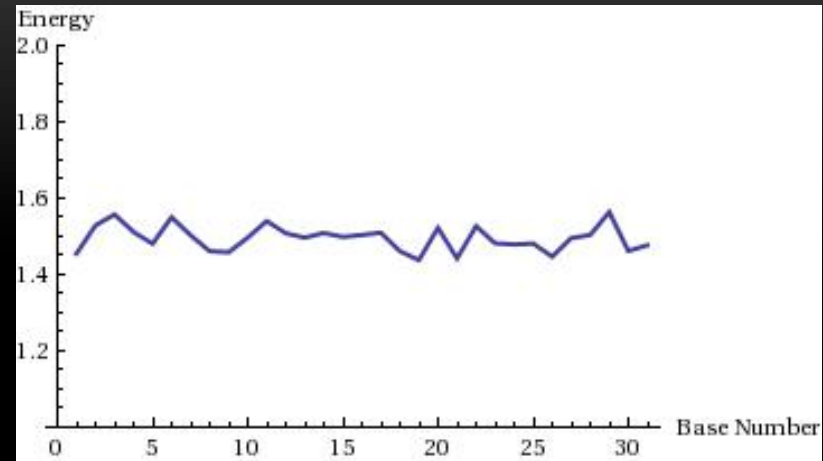
ENERGY:
30 BP



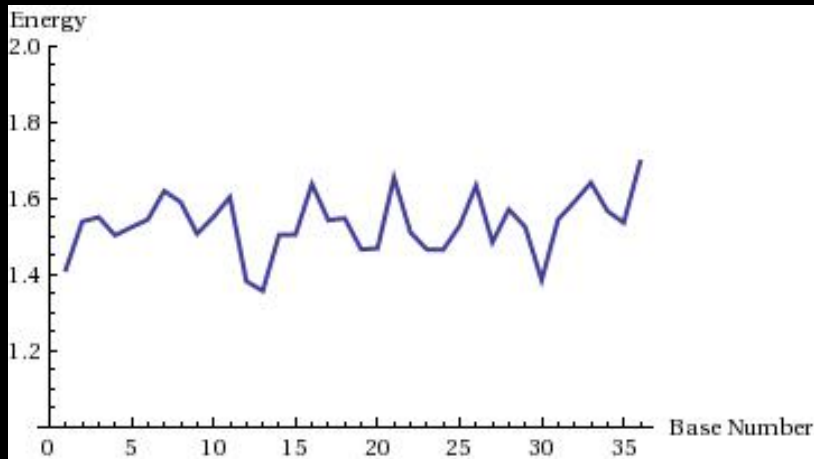
$$E_{\text{TOTAL}}(\text{LINKER}) = 46.3265$$

LINKER #8

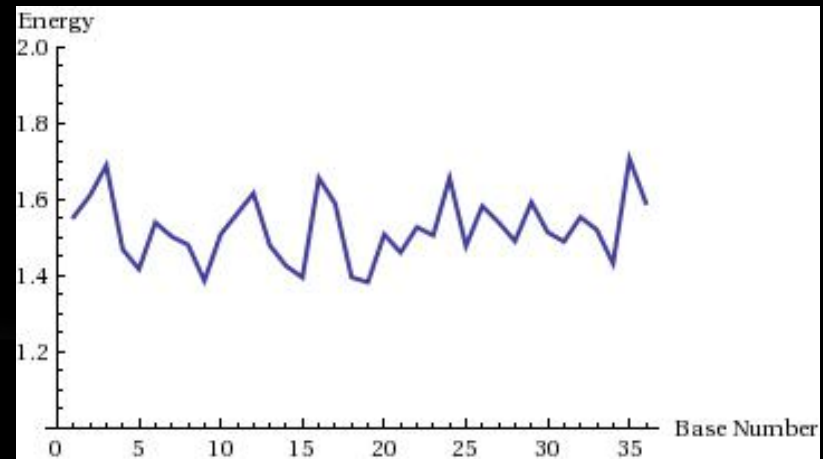
$$E_{\text{TOTAL}}(\text{LINKER}) = 46.3094$$



ENERGY:
35 BP



$$E_{\text{TOTAL}}(\text{LINKER}) = 55.1518$$



$$E_{\text{TOTAL}}(\text{LINKER}) = 54.7961$$

DNA linker energy for chromatin fiber with 35-bp linkers is significantly greater than that with 30-bp linkers. This is a result of chromatin fiber with 35-bp linkers exhibiting a more compacted overall shape.

NUCLEOSOME-NUCLEOSOME INTERACTIONS

- Interaction between nucleosome pairs computer with Debye-Hückel potential equation
- Charges derived from crystal structure (PDB ID = 1KX5)
 - Nucleosome = 30 coarse-grained charges

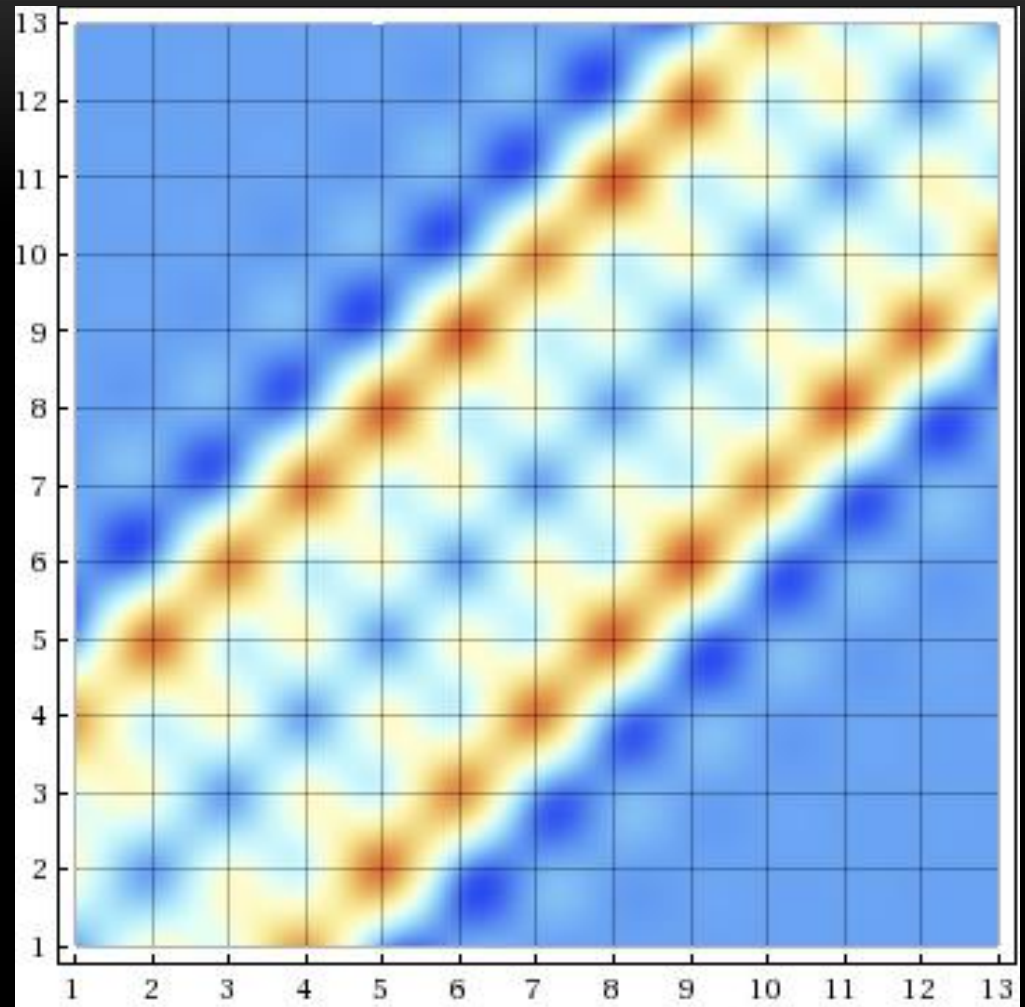
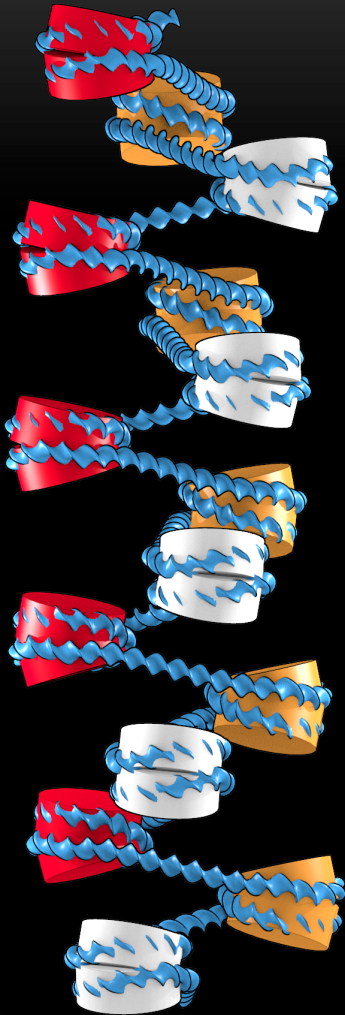
$$E_{el}(\{Q_i\}, \{Q_j\}) = \sum_k \sum_p \phi(Q_i[k], Q_j[p])$$

$$\phi(q_1, q_2, \Gamma_1, \Gamma_2) = (k^* q_1^* q_2)^* [(e^{-|\Gamma_1 - \Gamma_2|/\lambda_D}) / (e_0^* |\Gamma_1 - \Gamma_2|)]$$

q_1 = charge #1 valence, q_2 = charge #2 valence, Γ_1 = charge #1 location, Γ_2 = charge #2 location

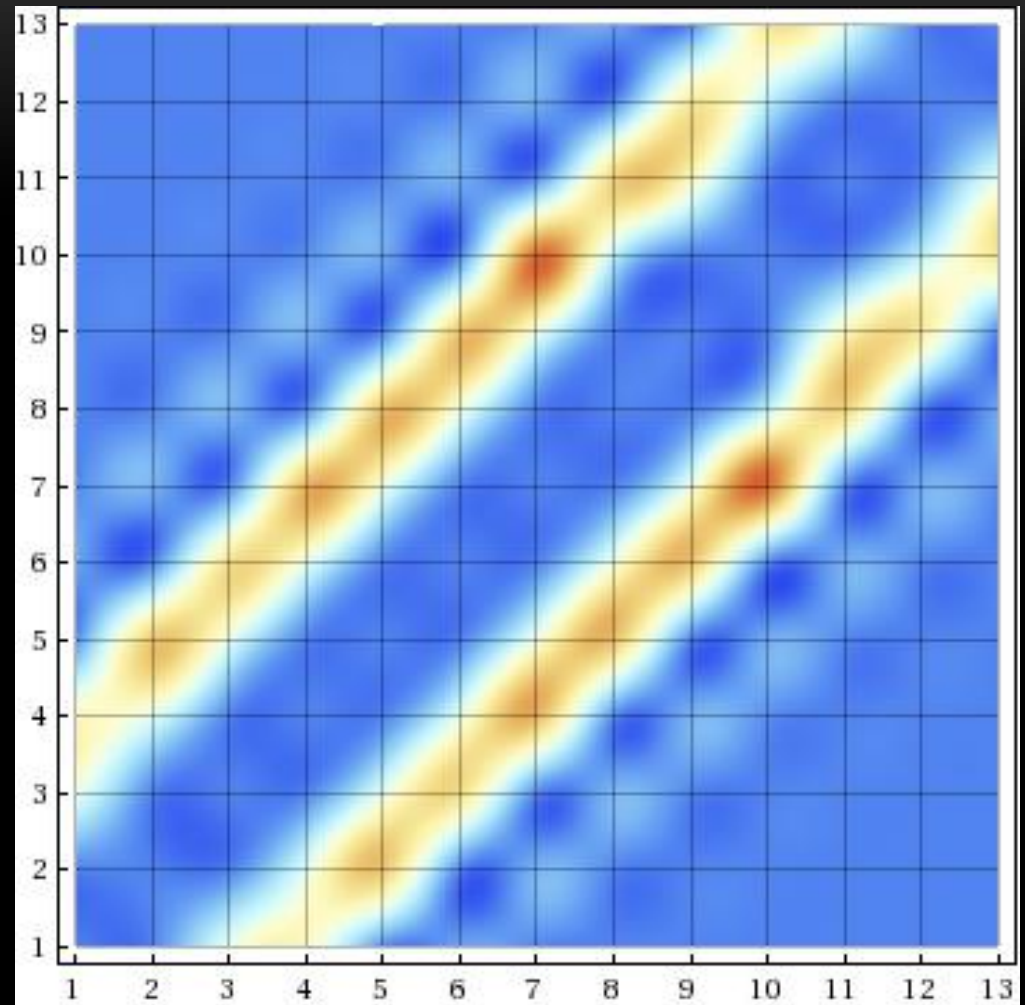
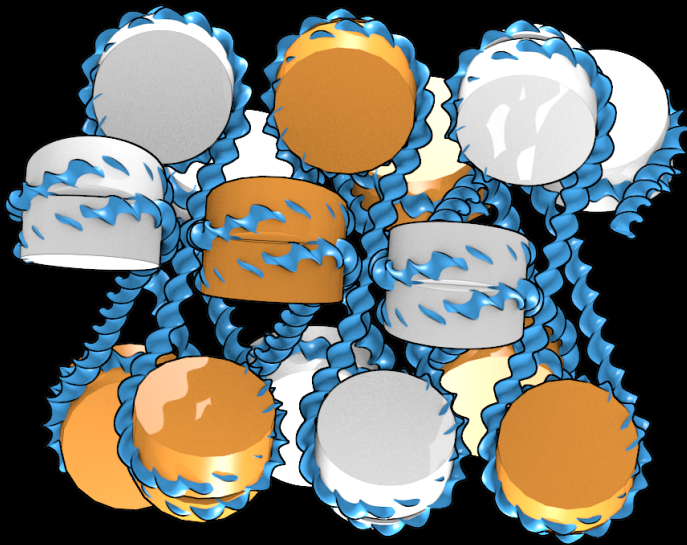
$k = 560.741$, $\lambda_D = 8.33$, $e_0 = 80.00$

13 NUCLEOSOMES, NO TAILS, 30 BP



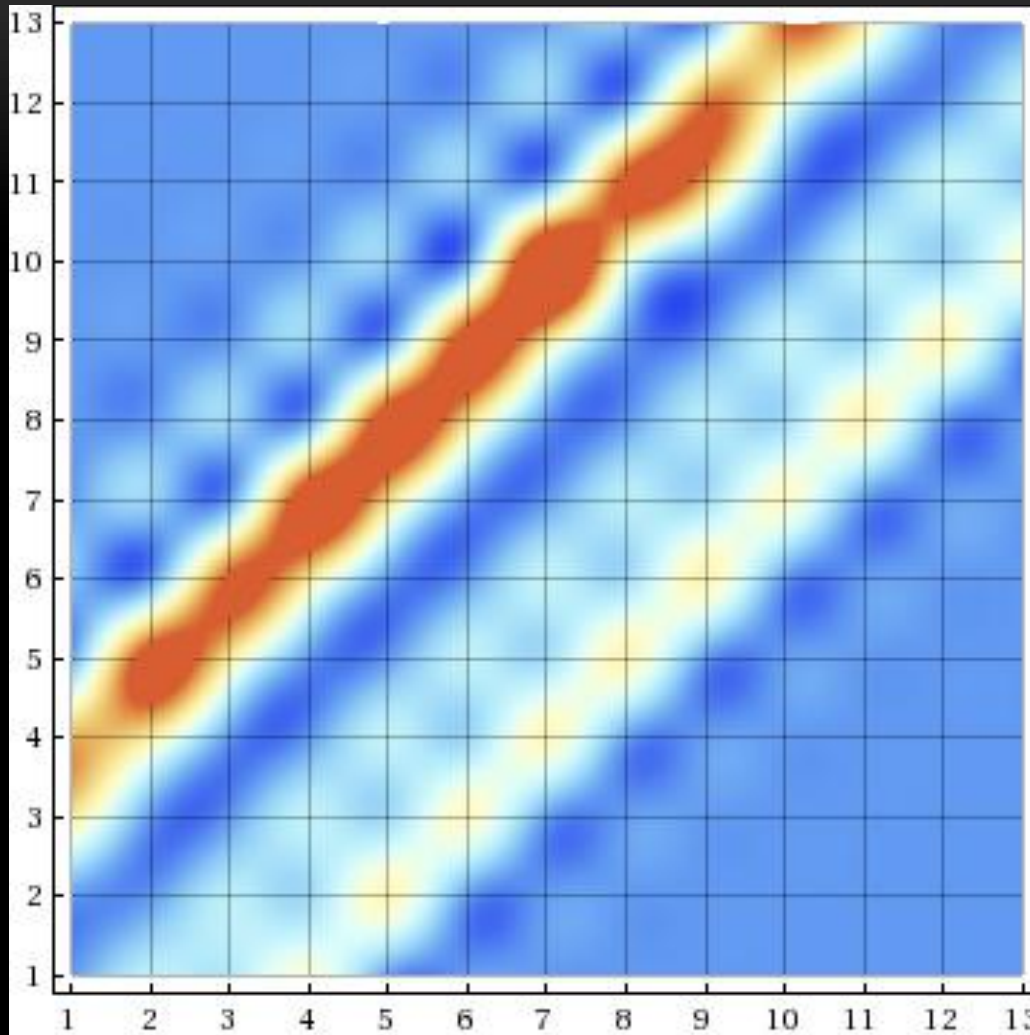
The strongest internucleosomal interactions are between the nucleosome in position i and position $i + 3$, with relatively strong interactions between position i and position $i + 1$. This data is consistent with the fiber geometry.

13 NUCLEOSOMES, NO TAILS, 35 BP



The strongest internucleosomal interactions are between the nucleosome in position i and position $i + 3$, with relatively strong interactions between position i and position $i + 5$. This data is consistent with the fiber geometry.

COMPARING 30 BP VS. 35 BP



This graph compares the internucleosomal interactions between chromatin fiber with 35-bp linkers (above the dark blue middle region) and that with 30-bp linkers (below this region). This comparison demonstrates the following relationship: $35bp(i, i + 5) < 30bp(i, i + 3) < 35bp(i, i + 3)$.