Nucleosome Energetics of Highly Occupied Sequences

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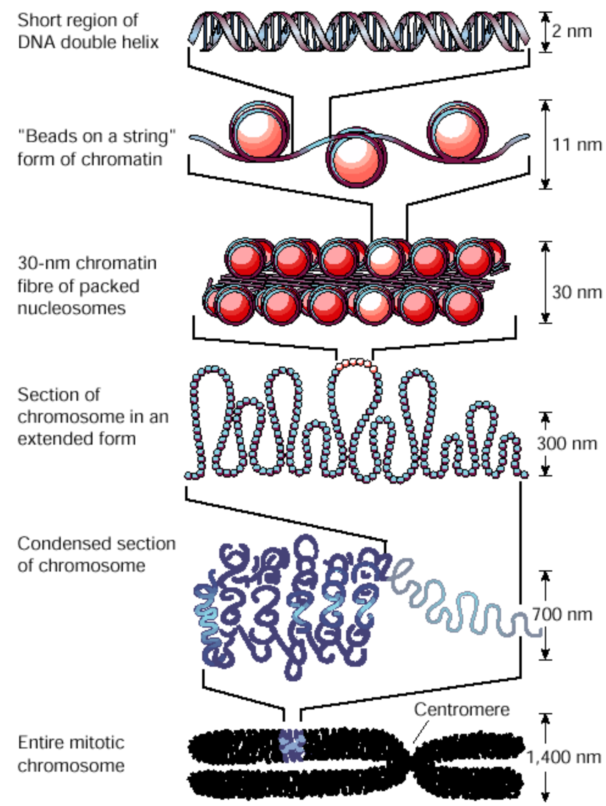
What I did this Summer

- About Nucleosomes
- Molecular Dynamics
- Simulations
- Results and Conclusion

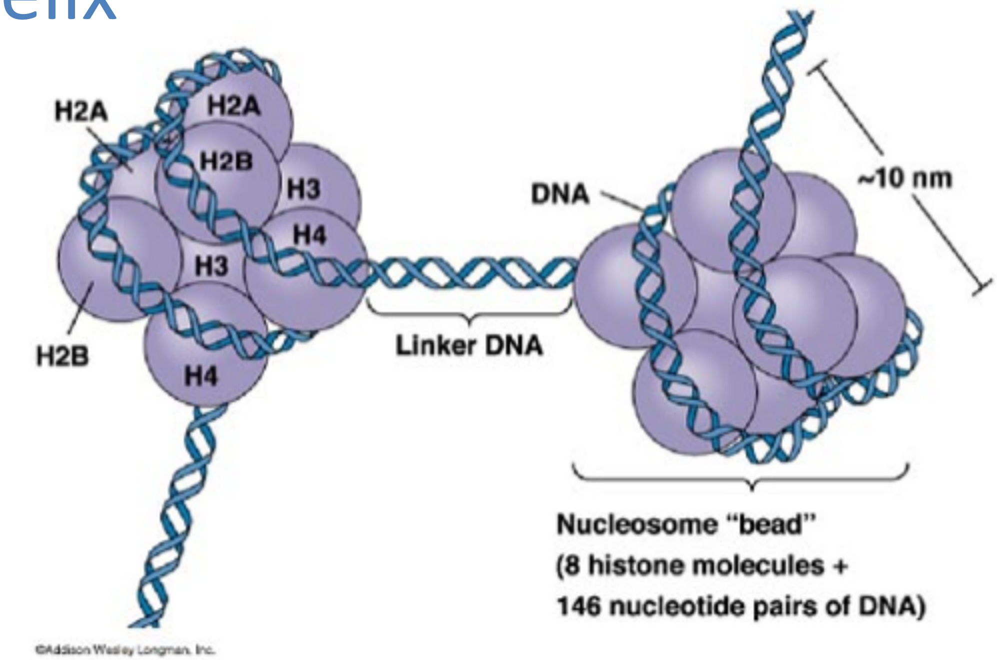
Genetic Material and Packing

- The Human Genome is 3 billion bp long
- This material is condensed into a cell nucleus of 10-20 micrometers



Nucleosomes

- DNA is packed in the nucleus by histones
- Eight histones wrap 147bp long segments of DNA into a left handed superhelix



Nucleosome Location

- Nucleosome Positioning along the genome is vital to behavior of the genetic processes
- Nucleosome location regulates the accessibility of DNA
- Thus affecting the expression of the genome

Nucleosome Location

DNA sequence can influence the location of nucleosomes

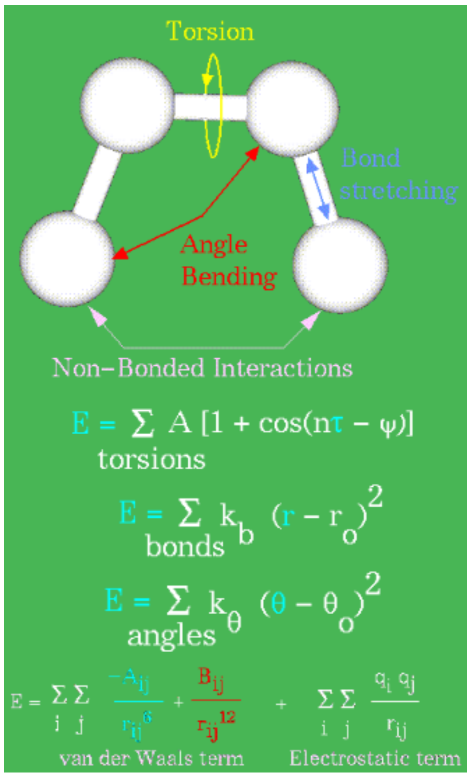
- DNA internal energy
- DNA interaction energy with the environment

It is unclear which energy dominates and how much this affects positioning

The Challenge

- Analyze sequences from each of the sixteen chromosomes in *S. cerevisiae*
- Run molecular dynamics to determine internal and environmental energies

Molecular Dynamics



Molecular Dynamics can simulate changes in a molecule as a function of time or to sample the range of conformations accessible to a molecule at equilibrium

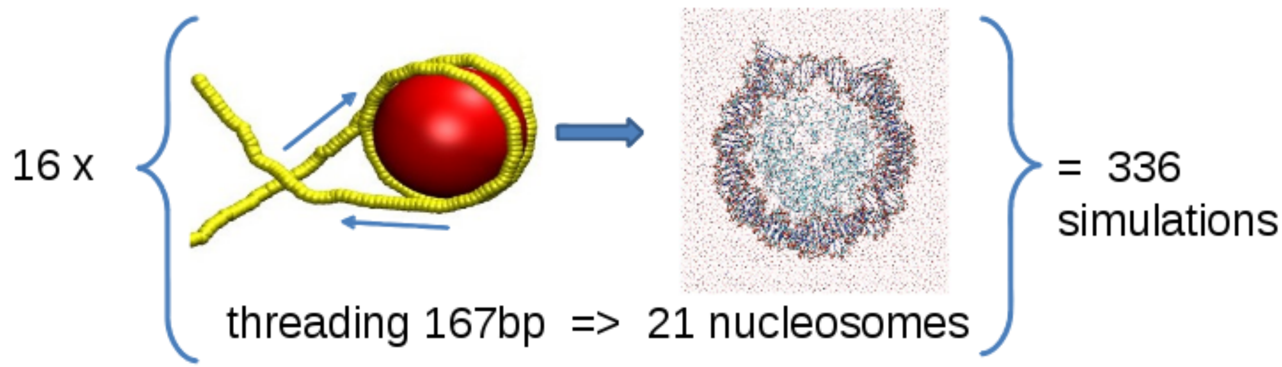
Methods

For each of the 16 sequences

- Extended the sequences to include 20 additional base pairs

  ± 10 from ideal position

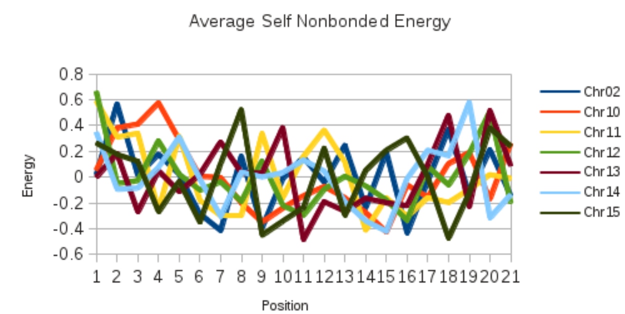
- Models were created by threading the 147bp kernel through 167bp parent sequence

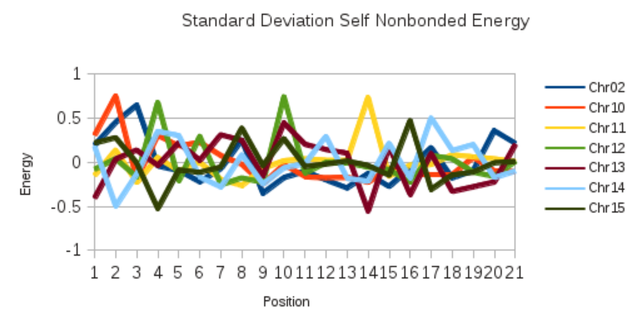


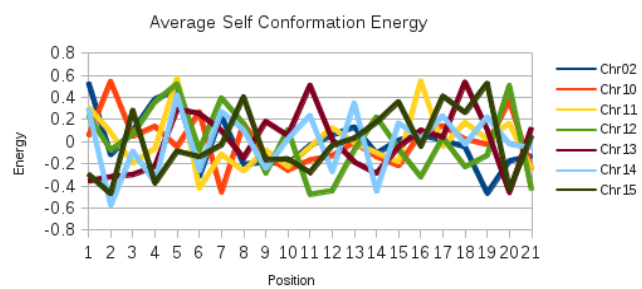
Simulations

- NAMD energy plug-in for VMD was used to calculate energies
- Energies were calculated from simulation trajectories using only the last nanosecond (19-20ns) of given simulations

Results: DNA Self Energy







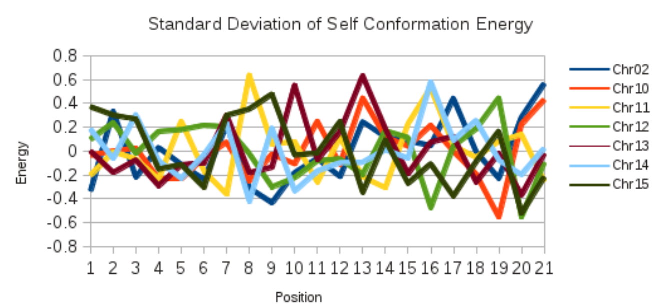


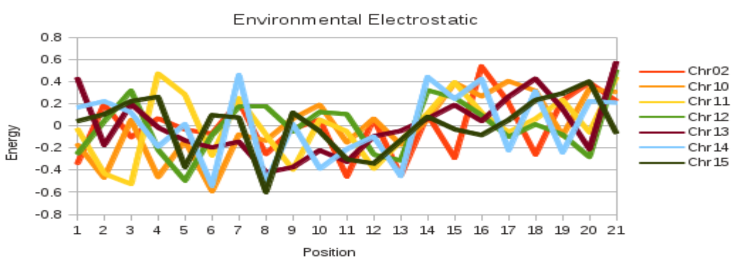
Figure 1. Shows the average self energy of the 127 base pair kernel as observed during simulation time period 19-20ns. The values have been 'normalized by applying the transformation (x-avg)/ (max-min). The DNA conformation energy is a sum of all energy terms.

Figure 2. Shows the standard deviations obtained for the DNA conformation energy.

Figure 3. Shows the average nonbonded interaction energy between DNA and its environment.

Figure 4. Shows the standard deviations obtained for the nonbonded interaction energies displayed in Figure 3.

Results: DNA Environmental Energy



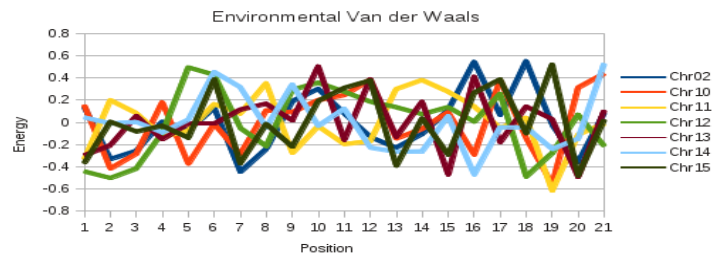


Figure 5. Shows the average Environmental Electrostatic energy normalized by the previously stated method.

Figure 6. Shows the average van der Waals normalized energy.

Results

- Only seven sets out of the sixteen set of simulations have been analyzed.
- Neither the DNA self-energy nor its interaction with the environmental exhibite a clear pattern consistent with a single well positioned nucleosome.
- Both the DNA self energy and the electrostatic interactions between DNA and the environment show some tendency to "curve up" on each plot, suggesting that a shallow minimum may exist.

Conclusions

The data analyzed did not offer any conclusive results including

- The physics regulating nucleosome occupancy and variability in yeast are not governed simply by DNA sequence
- Our simulations may not yet have equilibrated
- Our data must be more carefully analyzed to determine if trends do in fact exist
- Even if DNA sequence does govern positioning we may not be able to see it with the techniques employed here.

Acknowledgements

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Questions, Comments, Pertinent Points?