

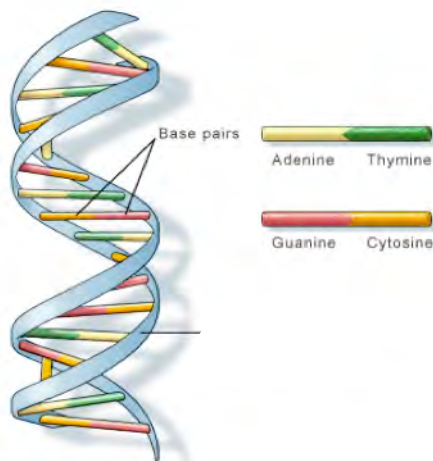
A Mathematical Model for Nucleosome Positioning

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The Colorado State University FEScUE Program (www.fescue.colostate.edu) brings together undergraduates and faculty in mathematics, statistics, and the life sciences to work in interdisciplinary research clusters. In the following, Drew Neavin, a CSU biology major and participant in this program, describes an ongoing FEScUE project based on research in the lab of CSU Biochemistry Professor Jeff Hansen.

Genetic research has been of increasing interest to scientists over the past couple of centuries. Over this time, scientists have made many discoveries including the basic structure of DNA which is a double helix with nitrogenous base pairs connecting the two helices. There are four different bases – Adenine, Thymine, Guanine, and Cytosine. The chemical characteristics of these bases allow that Adenine can only base pair with Thymine while Guanine can only base pair with Cytosine. This is illustrated in Figure 1 below. Mapping of the entire human genome in 2003 (1) was a huge accomplishment for the scientific community, but is just the first step in understanding how genes play into the functioning of human beings and other organisms. One budding area of study regarding genetics is the study of nucleosome positioning.

Illustration of DNA



U.S. National Library of Medicine

Figure 1: This figure shows the DNA double helix with its base pairs. This figure was obtained from the U.S. Library of Medicine (9)

predict nucleosome positioning would be a very helpful tool to those studying human genetics. Current models are becoming increasingly complex and need to match laboratory data. There are multiple components that play into nucleosome positioning that must be understood and addressed to create an accurate model. Such a model would need to include parameters such as thermodynamics, the intrinsic curvature and bending of DNA sequence, the strength of nucleosome positioning, and stretching and contracting of DNA, which all

Nucleosome core particles, made up of about 1.8 turns of DNA or about 146 base pairs wrapped around a nucleosome (2), determine the storage of DNA.

A nucleosome is a protein made up of eight subunits called histones, as can be seen in Figure 2. Nucleosomes can determine the regulation of genes through the amount of accessibility to various lengths of DNA. Additionally, the chemical interactions with other nucleosomes, with linking histones, and with the DNA itself help regulate the positioning of the nucleosome. Therefore, it is extremely important to transcription of the DNA and, ultimately, protein synthesis. Knowledge of nucleosome positioning is crucial before larger steps towards understanding and solving genetic diseases can be pursued.

A model that helps

Nucleosome Core Particle

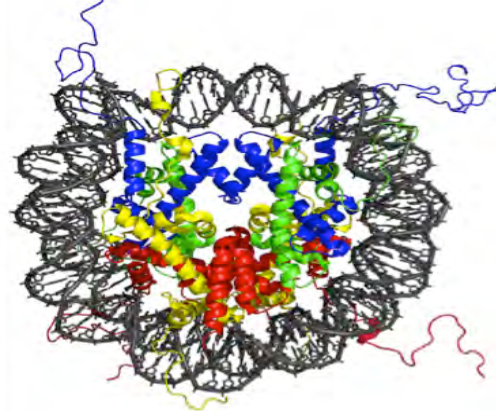


Figure 2: This is a nucleosome core particle that consists of the nucleosome (the lighter, colored parts in the center), made up of eight subunits, that has DNA wrapped around it (the darker, outside part). This picture was obtained from the dissertation by P. Yuan (5)

influence the positioning of nucleosomes. In a recent model by Stolz and Bishop (8), these are implicated into the model as parameters: Tilt, Roll, Twist, Shift, Slide and Rise.

These parameters describe different possible movements of 2 base pairs of the DNA with relation to each other. These can all be seen below in Figure 3. Roll describes the hinging motion away from the y-axis while Slide displaces the base pairs with relation to one another along the y-axis. Tilt is the same movement as Roll and Shift is the same movement as Slide but along the x-axis. Rise creates a larger distance between the two base pairs along the z-axis and Twist rotates the base pairs with relation to the z-axis.

Another component of nucleosome positioning that must be considered in a model is the variability of the exact location of a nucleosome on a length of DNA. While some nucleosomes have very specific positioning places, others can be located anywhere over a certain range of base pairs. This is defined as fuzziness, where promoter nucleosomes can be positioned anywhere along the DNA length that still covers the promoter region (3).

Nucleosome positioning in and of itself is interesting and intricate due to the various patterns and conflicting data, but it is also important to keep in mind that it has larger implications in the overall structure of chromatin, which is the structure produced from many nucleosome core particles winding together closely as seen in Figure 4. It has been shown that the bending of DNA at nucleosomes forms chromatin, therefore the positioning of nucleosomes ultimately determines how DNA is stored (3).

The capability to predict locations of nucleosomes on a DNA strand without doing as many experiments would save geneticists time and money. A model that takes into account many of the factors that have been discussed in this paper and has been shown to have a high rate of accuracy has been created by Stolz and Bishop (8). As expected, this model is extremely complicated and has gone through testing and is continually being refined with new data from laboratory experiments.

This model allows for a user to input a sequence of DNA and it will return the most plausible location of the nucleosome and also the energy level at each base pair. The lower the energy level, the more likely a nucleosome would naturally position in that spot.

A model that is able to accurately predict nucleosome positioning is a large step in understanding more about DNA storage in this field of study, and will ultimately lead to a better understanding of transcription, protein synthesis, and the intricate workings of genes in general.

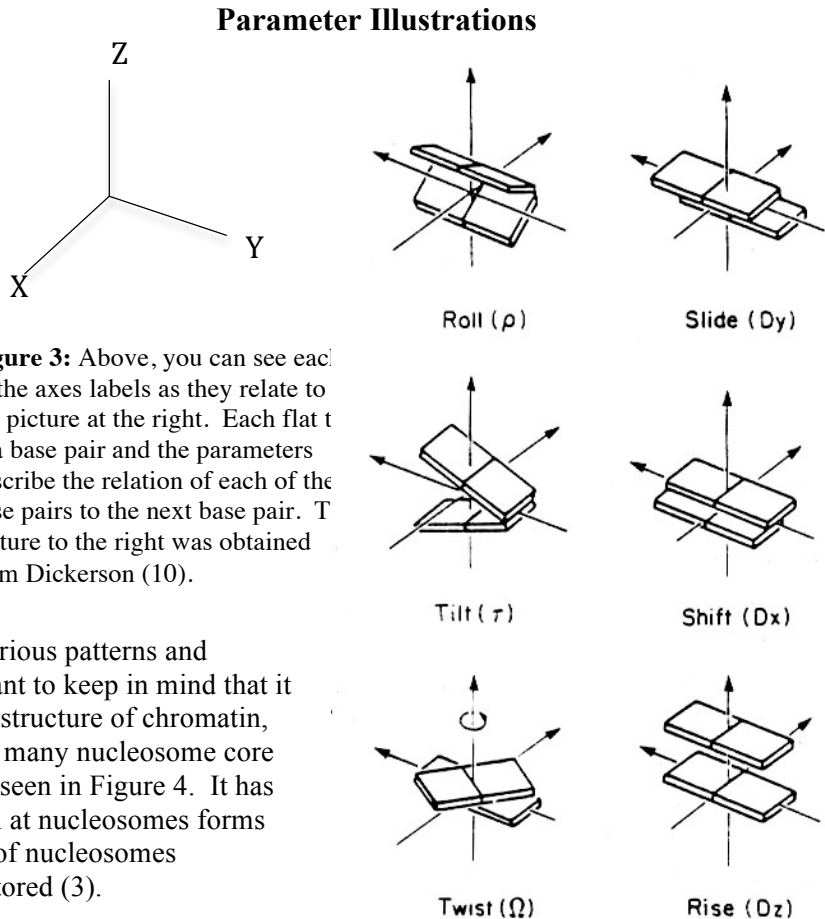


Figure 3: Above, you can see each of the axes labels as they relate to the picture at the right. Each flat is a base pair and the parameters describe the relation of each of the base pairs to the next base pair. The picture to the right was obtained from Dickerson (10).

Illustration of Chromatin

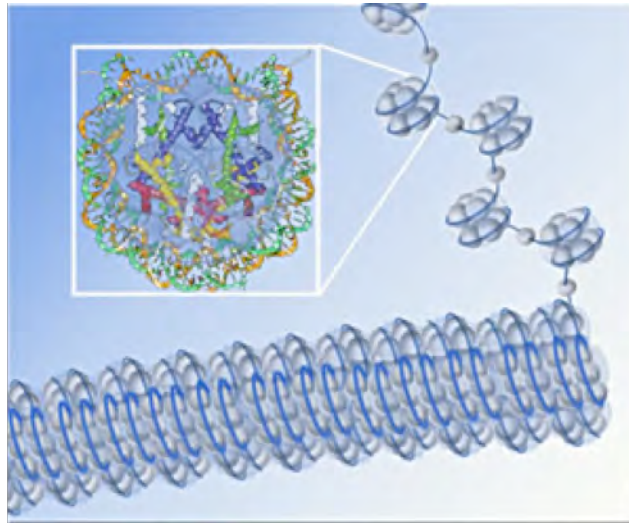


Figure 4: This is an illustration of chromatin. In the upper left hand corner, you can see a singular nucleosome core that makes up chromatin which can be seen along the bottom (7).

References

1. Janson-Smith D, Twyman R. 2010, Human Genome Project. [Online]. Available from: <http://genome.wellcome.ac.uk/node30075.html>. Accessed 2010 9 November.
2. Bates AD, Maxwell A. DNA Topology. 2nd ed. 2005.
3. Arya G, Maitra A, Grigoryev SA. A Structural Perspective on the Where, How, Why, and What of Nucleosome Positioning. *Journal of Biomechanical Structure & Dynamics* [Internet]. 2010; 27(6): 803-820. Available from: <http://www.jbsdonline.com>.
4. Vignali M, Workman JL. Location and function of linker histones. *Nature Structural & Molecular Biology* [Internet]. 1998; 5: 1025-1028. Available from: http://www.nature.com/nsmb/journal/v5/n12/full/nsb1298_1025.html.
5. Yuan P. Role of Sir3 N-terminus in yeast transcriptional silencing. Diss. State University of New York at Stony Brook. San Francisco: GRIN GmbH, 2008. Available from: <http://www.grin.com/en/doc/263458/role-of-sir3-n-terminus-in-yeast-transcriptional-silencing>.
6. Annunziato A. DNA packaging: Nucleosomes and chromatin [Internet]. 2008; Nature Education. Available from: <http://www.nature.com/scitable/topicpage/dna-packaging-nucleosomes-and-chromatin-310>.
7. Asf1: A Protein in the Thick of Things [Internet]. Berkeley Lab News Center. 2007 Aug. 2011. Available from: <http://newscenter.lbl.gov/feature-stories/2004/04/30/asf1-a-protein-in-the-thick-of-things/>.
8. Stolz RC, Bishop TC. ICM Web: the interactive chromatin modeling web server. *Nucleic Acids Research* [Internet]. 2010; 38(2): 254-261. Available from: http://nar.oxfordjournals.org/content/38/suppl_2/W254.full
9. What is DNA?. Genetics Home Reference - Your Guide to Understanding Genetic Conditions. U.S. National Library of Medicine [Online]. 8 Aug. 2011; 11 Aug. 2011. Available from: <http://ghr.nlm.nih.gov/handbook/basics/dna>.
10. Dickerson RE. LMB Progress Report '97/'98. Laboratory of Molecular Biophysics Department of Biochemistry University of Oxford [Online]. 11 Aug. 2011. Available from: http://biop.ox.ac.uk/www/lab_journal_1998/Dickerson.html.