Getting the rabbit in the hat

Tulane University researchers investigate how tiny units of genetic material fold into long fibers—and impact some of our bodies’ most fundamental processes.

A model of condensed chromatin in which the nucleosomes (blue beads) are closely packed on a length of DNA (tubes). Tight packing limits the range of possible locations for any single nucleosome and thus the fiber assumes a comparatively regular structure.

The human genome’s three billion base pairs, if stretched into a straight chain, would be about one meter long. Yet, by folding itself up, it fits in only a fraction of the volume of a cell’s nucleus. Some very clever origami is required to keep the genome functional in this state instead of just becoming a tangled mess.

But that folding operation—in which short segments of DNA are folded into nucleosomes, forming a fiber-like structure called chromatin—is more than just a means of sneaking a rabbit into a very, very small hat. All genomic processes are somehow impacted by which segments of DNA are wrapped into nucleosomes, the order in which nucleosomes line up, and which face of the nucleosomes’ DNA is directed in and which is directed out.

A team led by Tulane University’s Tom Bishop is beginning to use NCSA’s Abe supercomputer, as well as supercomputers throughout the TeraGrid, to investigate some of the most basic features of how nucleosomes behave.

Most people are familiar with the double helix...
structure of DNA. They’re also familiar with the structure at the other end of the spectrum, when DNA is tightly packaged into chromosomes for segregation to the daughter cells during division. This structure can be seen with a simple microscope. “Somewhere between these two extremes is how DNA exists during most of the cell cycle, thus our interests in nucleosomes and chromatin,” according to Bishop, a research associate professor at Tulane’s Center for Computational Science.

“At this level of folding is where the cellular machinery spends most of its time doing its work based on the DNA blueprints.” He says to think of this work as the “the three Rs and a T of molecular biology”—replication, regulation, repair, and transcription. “Understand these mechanisms and you’ve covered the fundamentals of molecular biology. There’s still much to learn about these mechanisms, but nucleosome stability is likely relevant to all. Our current interest is how stability relates to promoting or restricting the expression of proteins.”

With energy

When DNA folds into fibers of chromatin, the underlying nucleosome structures are all remarkably similar. One hundred and forty-seven base pairs form a spiral staircase around eight proteins called histones. Genetics requires that the sequence vary. Packing requires that the histones be somewhat impartial to the sequence being packed. Nonetheless, sequence differences impact nucleosome behavior.

“They may look identical, but different amounts of energy are required to make each nucleosome,” says Bishop.

This variation in energy determines, in part, the placement of nucleosomes in chromatin fibers and how likely the nucleosomes are to move about in the fiber. It also determines how much energy is required for a cell’s machinery to gain access to DNA inside a given nucleosome.

Nucleosomes with low energy thresholds can more easily be displaced, yielding direct, open access to the DNA blueprints. Nucleosomes with a high energy threshold allow more limited access. Stable nucleosomes perform other tasks. For example, they can help organize the local structure of chromatin and are often associated with promoter complexes that direct the cell machinery toward transcription start sites for particular genes.

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A Blue Waters problem

Tom Bishop’s team models nucleosomes with a simulation code called NAMD. Bishop was one of the code’s earliest users as a graduate student in Klaus Schulten’s Theoretical and Computational Biophysics Group at the University of Illinois at Urbana-Champaign.

As part of the National Science Foundation’s Petascale Computing Resource Allocations program, NAMD is currently being scaled to run on NCSA’s Blue Waters sustained-petascale supercomputer.

Blue Waters will come online in 2011. According to Bishop, more powerful machines like Blue Waters will allow scientists like him to go from simulating single nucleosomes to simulating ensembles of mononucleosomes or short segments of chromatin. Those sorts of simulations will provide further insights into the nucleosome’s behavior and its impact on replication, regulation, repair, and transcription.

“The smallest piece of chromatin is ginormous from an atomic viewpoint; its heterogeneous and sensitive to its solvent environment. To capture such heterogeneities and the solvent environment requires millions of atoms. That’s an ideal problem for Blue Waters,” Bishop says.

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