NewsBytes

New Technology Reveals the Genome's 3D Shape

Try taking a human hair as long as Manhattan and cramming it—unsnarled—inside a marble. This is the challenge faced by a 2-meter-long strand of DNA as it folds into its compact array of 23 chromosomes within a cell's nucleus. Previously, scientists only theorized about how DNA squeezes inside a nucleus without becoming a hopelessly tangled mass. Now a new technique called Hi-C reveals that DNA packs knot-free into its chromosomal patterns by assuming a rare geometric shape observed in snowflakes, crystals and broccoli.

"We've developed a powerful new technique to look at chromosomes at an unprecedented resolution," says **Job Dekker, PhD**, cell biologist at the University of Massachusetts and coauthor of the study in the October 9, 2009 issue of *Science*. "What we found constitutes a breakthrough in our understanding of chromosome folding."

At the small scale, DNA wraps around proteins called histones and assumes its classical double-helix shape. At the large scale, chromosomes cluster in discrete sections within the nucleus called "territories." "Between the scale of chromosome territories and the scale of histones, effectively nothing has been known about the structure of the genome," says first author **Erez Lieberman-Aiden**, a graduate student in the lab of **Eric Lander, PhD**, professor of biology at the Broad Institute in Cambridge, Massachusetts.

Hi-C reconstructs an unbiased 3-D map of the entire genome. First, scientists soak a complete set of chromosomes in formaldehyde, which acts like glue to stick together parts of the genome that are close in 3-D space. Then they chop the DNA into a million pieces and perform massive parallel sequencing on the interacting fragments. Mapping software compares the sequences of attached fragments with a human genome reference sequence; based on the results, the scientists compute which parts of the folded DNA physically interact with each other.

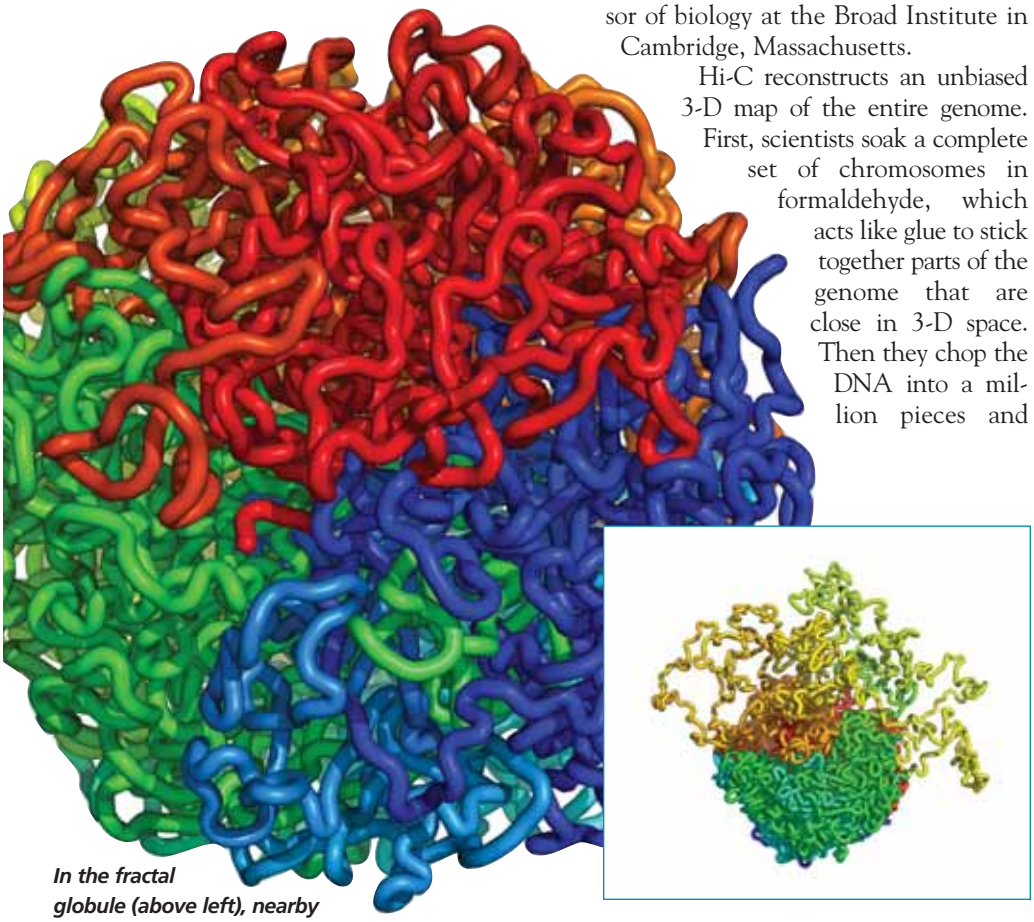
The team found that active, gene-rich and inactive, gene-poor sections cluster in separate parts of the nucleus. The active chromatin segments are like easily accessible papers spread out across a desk, whereas the inactive portions are densely packed, like folders in a file cabinet.

Simulations revealed that DNA assembles into dense fractal globules—structures that look alike at different levels of magnification, such as the intricate geometrical form of a crystal. Genes are easily accessible, but when they're not in use, the structure spontaneously collapses into a tight, knot-free bundle.

"This is the first spatial map of the genome," says **Tom Misteli, PhD**, cell biologist at the National Cancer Institute in Bethesda, Maryland. "It's a technical breakthrough that opens the doors to doing all sorts of interesting experiments."

Future experiments will investigate how the 3-D shape of DNA morphs depending on the activity of genes and disease states, like cancer. As genome sequencing becomes cheaper, Dekker says, it should be possible to obtain higher spatial resolution and even to reconstruct the shapes of individual genes.

—By Janelle Weaver, PhD



In the fractal globule (above left), nearby regions on a chain of DNA—indicated using similar colors—are packed into nearby regions in 3D space. The accessible DNA chain unravels easily (above right) because the globule lacks knots. Images courtesy of Leonid A. Mirny and Maxim Imakaev, reprinted from Lieberman-Aiden, E., et al., Comprehensive Mapping of Long-Range Interactions Reveal Folding Principles of the Human Genome, Science, *326(5950): 289-293 (2009), with permission from AAAS.*

How DNA Goes A'Courtin'

Until now, scientists have known little about how complementary single strands of DNA court one another before binding to form the classical double helix. But now, molecular dynamics simulations have identified that the binding—or hybridization—mechanism depends largely on the sequence of the DNA: Ordered sequences will meet and then slither lengthwise to find the correct match; but sequences that are random will connect at key sites then rapid-

ly assemble along the molecule's length.

"One would have thought that random sequences would have more difficultly hybridizing, and that is not necessarily the case," says **Juan J. de Pablo, PhD**, professor of chemical and biological engineering at University of Wisconsin, Madison. The work was published in the October 5 issue of the *Proceedings of the National Academy of Sciences*.

Scientists have previously tried to simulate the pathways by which DNA strands combine, but the models they used included too much detail to enable sufficiently long computations, de Pablo says. So De Pablo's group developed a highly simplified model, tested on experimental data, to capture essential details of the interactions between the base pairs of complementary strands of DNA. The researchers then simulated the process by which the single strands interact using molecular dynamics and Monte Carlo simulations, taking multiple "snapshots" of the double helix as it assembled. To the team's surprise, the path to a successful union depended crucially on the sequences of the molecules.

When the sequences of both single strands are ordered or repetitive, any two sites of base pairs can come together and the two strands slowly "slither" lengthwise until complementary base pairs match along the entire chain, says de Pablo. When the sequences are random, however, single sites located toward the center of the strands unite early. "The moment they come together, then the molecule just assembles perfectly and it does so very quickly," de Pablo says.

The results could influence the design of technologies that depend on the hybridization process, such as gene chips, de Pablo says. To engineer more efficient and reliable hybridization, researchers could use random sequences, which bind more efficiently and with fewer errors.

"This is an interesting step forward," says **Nadrian Seeman, PhD**, professor of chemistry at New York University. "No one had taken the time to track the pathway previously." Seeman has used the principle of random sequencing in his own hybridization studies, and he finds it reassuring to see it vindicated by the simulation data. "It does tell people who are designing sequences to avoid repetition in the sequences," he says.

—By Jane Palmer, PhD

Modeling Bacterial Comets

Rocketing within and between human gut cells, *Listeria monocytogenes*—a motile, foodborne bacterium—leaves a comet-like tail of actin protein behind it and makes us sick. Scientists have long wondered how actin allows the bacterium to puncture through multiple cells and evade the human immune system. A new computational model shows how rapidly accumulating actin at the back of the bacterium produces that force.

"Our simulation helps us understand the basic physical properties and mechanisms by which actin can produce force," says biophysicist **Mark Dayel, PhD**, a postdoctoral researcher at the University of California, Berkeley, and lead author of the paper published in the September 2009 issue of *PLoS Biology*. "We now have an explanation of why you get a switch from the initial pulse to smooth motion."

L. monocytogenes comes from contaminated produce or milk and infects epithelial cells in the gut. Using a membrane protein called ActA, the bacterium moves by continuously building a network of actin filaments from pieces of the host's cytoskeleton. To observe this system in action, scientists have reproduced the bacterial movement *in vitro* by coating tiny beads with ActA and putting them in a cell solution. Initially, actin fibers build from the surface of the bead, pushing old actin outward and forming a shell. But when the shell gets too big, it cracks and the bead bursts out, propelled forward by

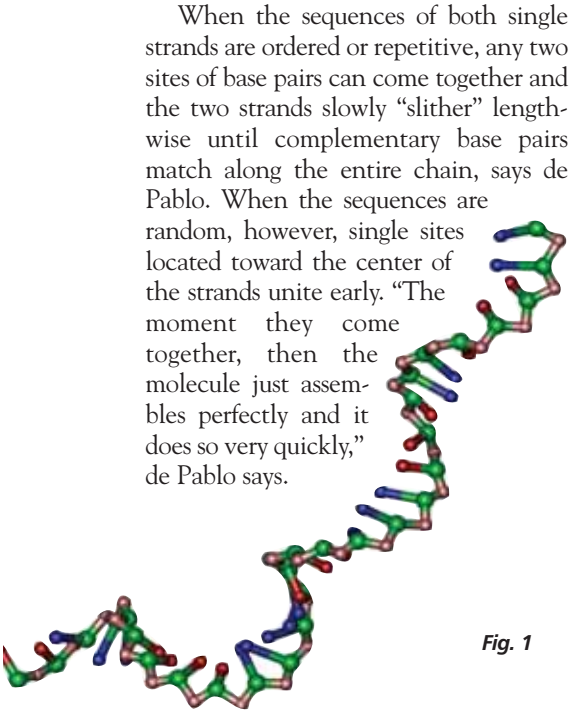


Fig. 1

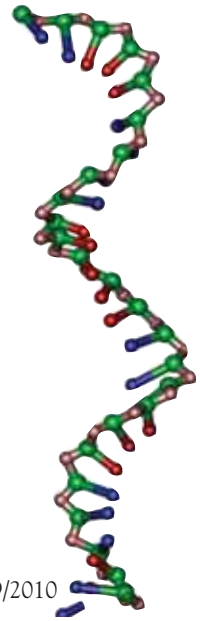


Fig. 2

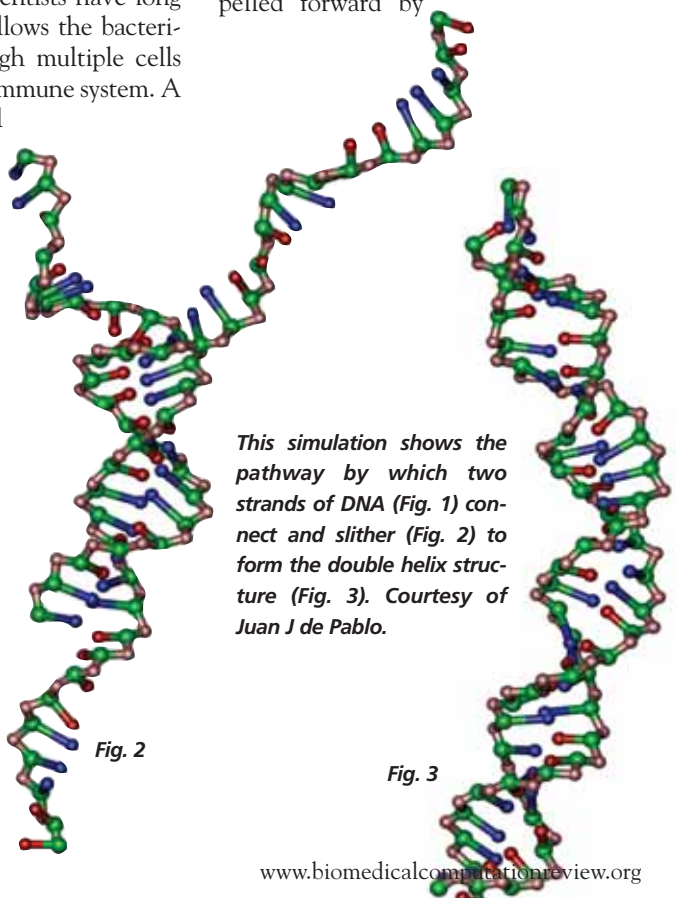


Fig. 3

This simulation shows the pathway by which two strands of DNA (Fig. 1) connect and slither (Fig. 2) to form the double helix structure (Fig. 3). Courtesy of Juan J de Pablo.