NewsBytes

DNA Shows Surprising Flexibility

For decades, scientists have believed that DNA of short lengths (150 base pairs or fewer) behaves as a relatively stiff rod—able to quiver a bit, but rarely forming a circle or tight angle without help from outside forces. But a new simulation, reported in the December issue of *Biophysical Journal*, puts a kink in this theory.

"We observed fairly sharp bends that are inconsistent with classical theory. We see DNA bending quite a bit," says **Alexey Onufriev, PhD**, assistant professor of computer science and physics at Virginia Tech. "If this idea holds up, it may be a paradigm shift in how we think about protein-DNA complexes."

DNA's flexibility on this length scale has implications for DNA packaging, gene transcription, and gene regulation. For example, in the nucleosome (the fundamental unit of DNA packaging), 147 base-pair segments of DNA wrap 1.65 times around a core of proteins. DNA also twists in and out of loops to turn certain genes off and on. Under the old theory, scientists had to reach for *ad hoc* explanations, such as helper proteins, to explain how unbendable DNA could manage these feats.

Onufriev and doctoral student **Jory Z. Ruscio** modeled a nucleosome worth of DNA (147 base pairs) at the atomic level. The key to their simulation was use of the "implicit solvent" method; rather than modeling every molecule of water, they modeled water as a continuous mass. This method saves enormous computing power and speeds up the simulation by about 100-fold by removing water's viscosity—the property that makes it so hard to move quickly in swimming pools, Onufriev says. "Whatever happens conformationally happens fast," he says.

At the same time, water's thermodynamic properties are perfectly preserved. "We cannot ask any questions like what are the diffusion coefficients, because those would be skewed. But we can ask thermodynamic questions—is this conformation more preferable than the other one?" Onufriev says.

This innovation plus use of Virginia Tech's super computer, System X, allowed Onufriev and Ruscio to explore DNA's range of motion on a longer length and time scale than any atomic-level simulation before them.

Their simulation showed that DNA of 147 base pairs wiggles and bends much more than traditional theory predicts—and at a much lower energy cost than expected. The bonds of the double helix remained intact in all simulations, so their results are not an artifact of the DNA simply unraveling to create soft spots.

Onufriev's results agree nicely with two independent threads of experimental evidence that have recently emerged, says **Philip Nelson, PhD**, professor of physics at the University of Pennsylvania. A 2004 paper showed that DNA of 100 base pairs spontaneously forms circles in physiological conditions; and, using atomic force microscopy, Nelson's team recently showed that DNA of this length kinks more frequently than the old theory predicts.

The emerging picture finally makes it clear how nucleosomes, DNA regulatory loops, and viral packaging are possible, Nelson says. "No *ad hoc* mechanisms for promoting tight bending are needed."

"This is one of those beautiful moments where simulation and theory and experiment all converge," he says.

—By Kristin Cobb, PhD

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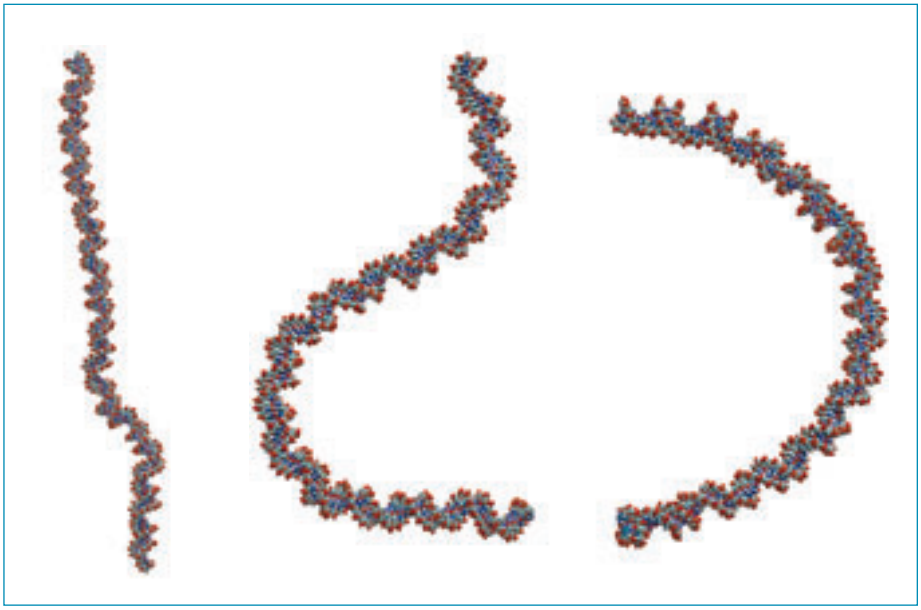
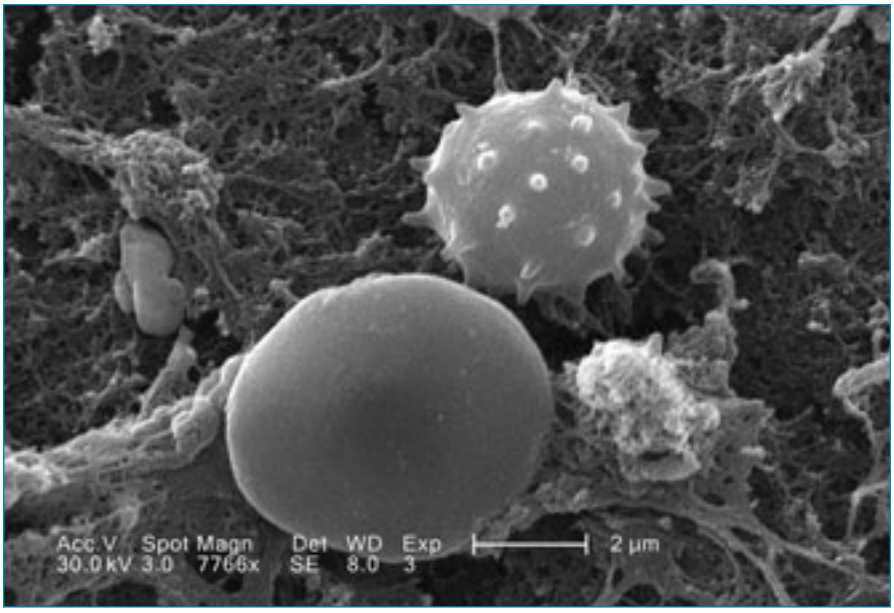


Three different images showing the simulation of DNA's flexibility over a length of 147 base pairs. Courtesy of Alexey Onufriev.

The Geometry of Adhesion

A single cell caught up in the flow of blood, air, or water often depends on its ability to latch onto passing surfaces—in short, its ability to stick. That's why researchers in Germany created a model



The knobby surface of a white blood cell (top) facilitates sticking, and the smooth surface of a healthy red blood cell (bottom) discourages it. Scanning electron micrograph courtesy of CDC/Janice Carr.

that addresses what geometry makes some cells stickier than others. According to their model, reported in *Physical Review Letters* in September 2006, a cell that efficiently initiates adhesion is dotted with elevated receptor patches–knobby protrusions tipped with receptor molecules. The taller the patches, the better.

"Once you start thinking about it, it's obvious." says **Christian Korn**, a PhD candidate in theoretical physics at the Max Planck Institute of Colloids and Interfaces and one of the authors. "You need these protrusions."

Cell adhesion requires two steps: encounter and docking. Korn and **Ulrich Schwarz, PhD**, a theoretical biophysicist and assistant professor at the University of Heidelberg, modeled the encounter step—to identify the cells that are best at initiating adhesion.

To create the model, the researchers simulated spheres sporting receptor patches and flowing above a flat surface with the corresponding ligands. The stickiness of cells was measured by how long it took for the first receptor-ligand encounter to occur. Korn and Schwarz then varied the number, size, and height of the receptor patches to discover the optimum receptor patch geometry. Plastering the cell with as many receptor patches as possible—akin to fully wrapping a bouncy ball in tape—is not the best strategy, they found. "The cell can have only 1% of the surface covered with receptors, and it works almost as efficiently as if it were 100% covered," Korn says. In addition, increasing the lateral size of the patches –placing bigger bits of tape on the ball—doesn't make much difference. Yet increasing the height of those receptor patches—using raised stickers instead of tape—helps the receptor patches find their target ligands sooner compared to lower receptor patches on a cell of the same size.

The researchers point to similar geometry repeated across vastly different systems in nature. Wrinkled white blood cells, which often need to dock close to an infection, place their receptor patches on the tips of finger-like microvilli. Red blood cells, in contrast, are surfboard smooth. But when a red blood cell becomes infected with malaria, it also grows knobs and new receptors on its surface to slow its progress toward destruction in the spleen. Even sticky pollen grains and wandering diatoms in the ocean, Korn says, display spiky geometry.

For experimentalists now probing such systems, says **Cheng Zhu, PhD**, a professor of biomedical engineering at Georgia Tech, the model is interesting, but only part of the equation. "Their model may explain cases where encounter is the limiting step," he says. "Without the complete equation, it's difficult to say how this might affect data interpretation in cases where docking is limiting."

Korn is now extending the model to include binding as well as encounter. He is optimistic that his model will continue to uncover general characteristics of sticky cells. "The big strength of theoretical modeling," he says, "is that you can get the big picture because you focus on a few essential aspects."

—By Louisa Dalton

Biological Evidence for Turing Patterns

In the 1950s, computer science pioneer Alan Turing suggested an elegantly simple mechanism for how biological patterns such as scales, feathers, and hair might form. Now, more than fifty years later, biologists have used a computer model and transgenic mice to confirm mathematical predictions of the Turing model of pattern formation within a specific biological system: mouse hair development.

"It's the most convincing biological (as contrasted with chemical) experiment to date that claims to support the Turing mechanism," says **Irving Epstein, PhD**, a chemistry professor at Brandeis University. The work appeared online in the journal *Science* in November 2006.

Turing's 1952 proposition goes like this: Two molecules—an activator that enhances its own production, and an inhibitor that slows the production of the activator—diffuse and react. If the inhibitor diffuses sufficiently faster than the activator, repetitive patterns may spontaneously emerge.