DNA in 'unbiased' model curls both ways

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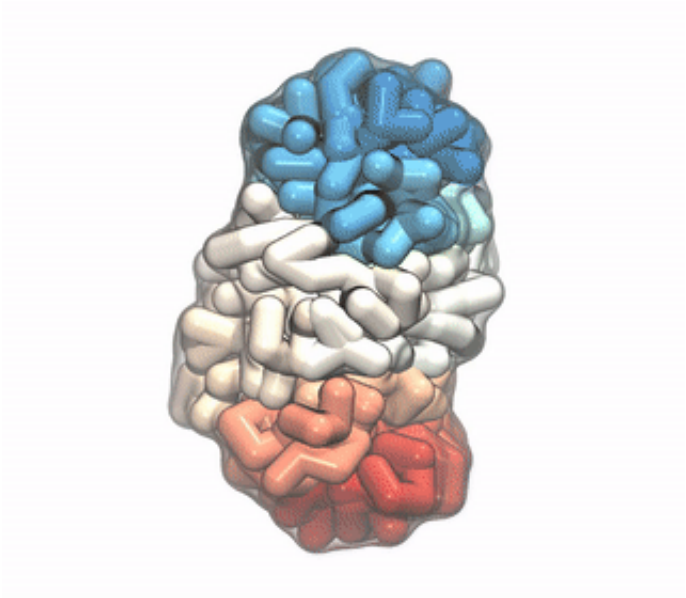

An animated GIF of a coarse-grained model shows DNA forming a helical chromosome during mitosis. Rice University scientists are using computer models to determine the forces that take place as DNA duplicates itself during cell mitosis. Credit: Bin Zhang/Rice University

In 1988, scientists in Switzerland looked through a microscope and saw something they didn't expect: two sections of an X-shaped chromosome spiraling in opposite directions. Now scientists at Rice University have confirmed that such anomalies are indeed possible.

Peter Wolynes, a theoretical biological physicist, and Bin Zhang, a postdoctoral associate, saw the same phenomenon in their sophisticated

computer models of DNA, a finding they said should encourage deeper investigation of a basic biological process. Understanding such processes is important as researchers seek new ways to fight cancer and other diseases.

Their work is described today in *Physical Review Letters*.

Wolynes said biologists are learning much about how a cell functions during interphase—the workaday part of its existence when it makes proteins and regulates other processes necessary to life. They also know much of what happens to a cell in the final stages of mitosis, when it divides.

Between those extremes lie mysteries. At the onset of mitosis, the meter-long strand of DNA in a cell's nucleus condenses into a pinpoint-sized blob. Microscope images show frantic activity as the DNA pushes, pulls and pulses, eventually organizing itself into 23 recognizable, X-shaped chromosomes before splitting.

The Rice scientists developed their simulation software to help understand these hidden phases as DNA folds into chromosomes, which they believe plays a central role in gene regulation, DNA replication and cell differentiation.

The simulation models probable crosslinks between genetic sequences in DNA to see how they interact. The researchers used experimental data that details likely contacts between the sequences. They believe these contacts play a critical part in mitosis, but the details remain hidden inside the compressed blob.

They were surprised when their simulations - based on "unbiased" experimental data - showed superhelices in the chromosomes that emerged from the blob that curled both to the right and to the left,

matching the 1988 observation of sister chromatids (the original chromosome and its centrally joined copy) with opposite helical "handedness."

"That's why this was particularly cool to us," Wolynes said. "The handedness result just sort of fell out of the data even though we weren't looking for it.

"Think of the chromosome at mitosis as a bit like what would happen to a piece of sewing thread if you doubled it up and rolled it between your finger and your thumb," he said. "Depending on how you rolled your fingers, you would get right- or left-turning structures."

The thread itself has a helical arrangement of even smaller fibers, though the twist at one scale doesn't necessarily determine the twist at the larger scales. "But bundles of threads usually get twisted somehow," Wolynes said.

That "somehow" remains one of the mysteries, he said.

Since Crick and Watson described DNA's basic twisted-ladder form, the double helix has always turned to the right - and woe unto those who flipped the image.

But DNA is far more complex. The twisted ladder further coils around histone proteins to form nucleosomes. The strand of nucleosomes twists again, forming a cylindrical coil. And then those coils form coils, the superhelices that fold into recognizable chromosomes.

With the exception of Z-DNA, which turns to the left, it was commonly thought that evolution dictates the helix and its larger-scale structures always go right.

That is possibly still the case, but unlikely, Wolynes said. The Rice model didn't take into account the influence of proteins or other molecules in the nucleus that influence DNA organization, any of which may nudge the coils' chirality into right-handed compliance.

In a subsequent simulation, they increased the agitation of the DNA and saw a quite different result. Raising the temperature in the model forced the DNA to become solidly cylindrical rather than left- or right-handed. "The chirality was lost," Wolynes said. "That raises an interesting question: Does the cylinder form without chirality at first when the chromosome is duplicated and only later pick up its handedness?"

He and Zhang hope their technique will help find the mechanism that gives the superhelix its handedness and determine whether it makes any functional difference.

The study of DNA at Rice's Center for Theoretical Biological Physics is a natural extension of the center's groundbreaking work on proteins, Wolynes said. DNA during interphase is a single long molecule, and molecules and their constituent atoms always seek the easiest path to their natural structures, also known as their lowest energy states. Wolynes and his colleagues have led the study of energy landscapes; they pioneered the model to predict how a protein will find its lowest energy state based on the interaction energies—the "folding funnel"—of its components.

Now the lab has extended these ideas to study entire chromosomes. The task is much more difficult for the chromosome than for analyzing a protein, because there are billions of subunits in a strand of DNA as opposed to hundreds for a protein.

For that reason, the simulations are "coarse-grained" and take into account only a fraction of the atoms rather than the whole set.

Computations are faster this way, yet they retain an accurate view of the entire system because the forces are based on experimental input data, the researchers said. They expect their method will be a useful tool in their continuing study of cellular processes.

Wolynes said the helical formation of the "X" chromatids—the original target of the study—can be traced back to the liquid crystalline nature of DNA. "Liquid crystals are oriented but remain fluid," he said. "The twist transition in the mitotic chromosome resembles what happens when a pixel in a liquid crystal display on your computer changes color."

The National Science Foundation (NSF) supported the research.
Wolynes is the D.R. Bullard-Welch Foundation Professor of Science, a professor of chemistry, of biochemistry and cell biology, of physics and astronomy and of materials science and nanoengineering at Rice and a senior investigator of the NSF-funded Center for Theoretical Biological Physics at Rice. Zhang will join the Massachusetts Institute of Technology as an assistant professor in July.

The researchers used the NSF-supported DAVinCI supercomputer administered by Rice's Ken Kennedy Institute for Information Technology.

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