Simple twists of fate

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A novel Brandeis University study this week in *PLoS Biology* reports on some of the molecular gymnastics performed by a protein involved in regulating DNA transcription. Using state-of-the art tools, researchers observed the shape and behavior of individual DNA molecules bent into tight loops by Lac repressor, a protein from the bacterium *E.coli* that switches on and off individual genes.

The study brings scientists an important step closer to understanding the phenomenon of gene regulation, a process elemental to biology from maintaining cell stability in bacteria such as E. coli to helping facilitate the most complex processes of human development and disease. The research was carried out by former Brandeis Ph.D. student Oi Kwan Wong in collaboration with scientists from Wake Forest University and the University of North Carolina.

To switch some genes on or off, a protein has to bind to two different places on the gene simultaneously, creating a loop from the DNA. Although such loops are common, many of their features are poorly understood. Using atomic force microscopy and tethered particle motion (TPM), a technique pioneered at Brandeis, the researchers were able to look at single molecules of DNA to infer the shape of the loop, which is not visible. They discovered that many earlier models of loops were probably wrong because they required the DNA to bend and twist in ways incompatible with the behaviors the scientists observed in the single DNA molecules.

Atomic force microscopy enabled the researchers to view the shape of

the DNA molecules, while TPM revealed the behavior of the DNA molecules. In the TPM experiments, a tiny plastic bead only a millionth of inch in diameter was attached to the end of a DNA molecule. By computer analysis of the bead movements seen in a microscope, the scientists were able to monitor the DNA as it looped and unlooped, revealing the details of the molecule's behavior.

But in addition to these sophisticated techniques, the researchers found a simple yet ingenious way to visualize just how the protein bent and twisted DNA: by creating three-dimensional models of the DNA loops using binder clips and tape. That simple trick helped the scientists determine which models were possible and which were unlikely.

"What we demonstrated in this paper is that, contrary to what many scientists thought, the structure of the protein is flexible and can take on different shapes, helping to minimize DNA bending or twisting in loops, and thus, maximize stable gene regulation," explained Wong's Ph.D. advisor, biochemistry professor Jeff Gelles. "We believe the protein has the ability to change its shape to accommodate different sized loops and different amounts of DNA, helping cells maintain genes in a switched on or switched off state."

"We think it is possible that the characteristics of this genetic switch are examples of a general phenomenon that helps explain gene regulation," said Gelles. Poor gene regulation is implicated in many diseases and cancers, and understanding how it works in even a simple bacterium may pave the way for the development of antibiotics.

"The key is that the protein can change shape "on the fly" to accommodate different kinds of loops, or different spacing between different parts of the DNA. This is the way that the protein may have evolved to make gene regulation more reliable," said Gelles.

Source: Brandeis University