The study of DNA topology relies heavily on both math and biology to unravel the shape and geometry of complex biological structures and to understand the enzymatic actions that affect DNA topology.

Imagine untangling this gossamer string despite its tight packaging? And how does the tight compaction still allow accessibility for decoding and accurate replication? SF State Associate Professor Mariel Vazquez, a pioneer in mathematical biology, studies DNA compaction in normal cells, as well as DNA rearrangements and other aberrations in cells with erroneous genetic behavior such as breast cancer cells. Her approach comes from pure mathematics and involves computational tools. The outcome, however, could someday help others save lives.
To prevent DNA knots and links, which are to various levels of compaction. Bacterial DNA is circular and is therefore prone to DNA molecule. This may result in catastrophic consequences.

Mathematicians have created tools from computational and analytical knot theory to provide a detailed picture of what DNA looks and acts like when packaged in confined environments, and in turn, how enzymes change the topology of DNA. For example, when packaging DNA in bacteriophage capsids. Colors indicate contiguous DNA regions.

Mariel Vazquez's fusion of math and biology bridges many fields of research. In April 2002, the American Mathematical Society (AMS) Math Awareness Month highlighted the importance of mathematicians to biology.

As researchers realized that enzymes can cut the DNA, transfer it through the break, reseal it, and do that many times. When you take the rubber band inside again, very tightly packed... The enzymes cut the DNA, unravel the shape and geometry of complex biological structures and to understand the enzymatic actions that affect DNA topology. Vazquez applies topology, geometry and computational tools to study the shapes of circular DNA molecules in solution, as well as in confinement, and to understand the way enzymes such as type II topoisomerases allow cells to function smoothly. As this rubber band inside again, very tightly packed... The enzymes cut the DNA, transfer it through the break, reseal it, and do that many times. When you take the rubber band out it is very, very likely to be knotted. "

Javier Arsuaga, Vazquez has developed computer software of various kinds to understand the making and behavior of DNA knots and links. Together with their former postdoc, Rob Scharein, the two have contributed new knot theory software to the widely used computational knot theory program "Knotplot." Vazquez has also authored "TangleView," a Java applet for the topological analysis of site-specific recombination. These programs allow researchers to take experimental data and reproduce and reinterpret it using rigorous mathematical analysis. Using these advanced programs, mathematicians are able to "investigate beautiful mathematical problems that arise from the original biological problems," says Vazquez.

Mariel Vazquez studies the way type II topoisomerases and enzymes with related activity called site-specific recombinases change the topology of DNA. To do so, she employs circular DNA molecules such as the circular chromosomes of the bacterium Escherichia coli (E. coli). Before a bacterial cell divides, its single circular chromosome is replicated, resulting in two interlinked DNA circles. When events such as knotting or linking occur in the circular strands, type II topoisomerases can return the DNA molecules to their native, untangled state. In this way, they function to regulate the topology of DNA by removing unwanted knots and links in preparation for cell division.

In her studies, Vazquez focuses on the cell's ability to faithfully replicate its DNA and to produce unlinked DNA molecules. Vazquez's doctoral advisor from Florida State University, Dr. De Witt Sumners, likes to say that "Mother Nature's solution to the entanglement problem is topoisomerases." The enzyme's activity—passing one strand of DNA through another and allowing torsional stresses to be eliminated—can significantly impact whole-genome sequencing efforts, as researchers often find DNA molecules that are knotted.
Analysis of Site-Specific Recombination: Gin and Xer systems. Next she worked as a Postdoctoral Fellow in Mathematics at UC Berkeley. While there, she split her time between mentoring undergraduate research projects in DNA topology and using math and computers to model the chromosomal rearrangements that result from radiation damage. In 2005, she became an assistant professor at SF State. In her laboratory, she has continued her work on the tangle analysis of Gin systems. Next she worked in the field of Gin and Xer systems. So, the subject of the CAREER award that she obtained earlier this year from the National Science Foundation. Her group also undertakes the computational topology of DNA. As Vazquez and Arsuaga are searching for chromosomal changes associated with recurrent breast cancer in an early stage patients. They are also hoping to identify topological signatures in the DNA that allow an accurate prediction of who is most likely to experience a cancer recurrence. Writing in the journal Bioinformatics in 2002, mathematician Angela Torres states, “The fusion of mathematics and biology will result in a new era of molecular medicine, when the diagnosis, treatment and prevention of disease will be individual-specific and thus more successful.”

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In addition to her research, Vazquez teaches several courses and helps organize professional conferences. Every spring, she teaches a DNA topology course through the SF State math department. She has also organized many conferences and symposia in the last few years. These include the yearly Modern Mathematics Workshop at SAGNAs, SIAM mini-symposium on New Trends in Mathematical Biology at the joint meetings of the American Mathematical Society and the Mathematical Association of America (January 2010), the Fong Symposium at SF State in 2010, the San Francisco International Meeting on DNA Topology (April 2009), and the annual Biology and Mathematics in the Bay Area (BaMBA VI) in November 2010. All of these events, says Vazquez, allow the public to learn the importance of applying fundamental mathematics to important biological problems. Vazquez is convinced that an interdisciplinary approach helps solve such puzzles, and her research group at SF State reflects that conviction. Her group and collaborators typically include chemists, bioengineers, computer scientists, biologists, and mathematicians. “We try to work all together and it is very highly vertically integrated,” she says, meaning that “undergraduates work alongside graduate students, research technicians, research fellows, and faculty members.” This exposure helps biology majors become more comfortable with math and its utility in their research. “Many times, we see biologists who start a research project and soon find that they need to learn statistics…how to program…more math. That’s when they realize that math is not so awful after all. ‘Math can be fun,’ Vazquez says, ‘and it is extremely useful nowadays if you’re a biologist student. Acquiring strong mathematical skills is very important if you want to be competitive.’

Graphics courtesy of Dr. Vazquez.
The College of Science & Engineering is proud to announce that Mariel Vazquez had been awarded a highly prestigious National Science Foundation CAREER grant totaling $600,000. These awards are extremely competitive, with only about two dozen awarded in mathematics each year in the entire country, including just a few per year in biomathematics. The College of Science & Engineering has been remarkably successful with these unusual awards, with 11 of our faculty receiving these awards over the last eight years. The National Science Foundation website includes this description of these awards:

The Faculty Early Career Development (CAREER) Program is a Foundation-wide activity that offers the National Science Foundation’s most prestigious awards in support of junior faculty who exemplify the role of teacher-scholars through outstanding research, excellent education and the integration of education and research within the context of the mission of their organizations.

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DNA topology is the study of knotting, linking and supercoiling of circular DNA molecules. The bacterial chromosome is circular and replication invariably results in the formation of interlinked daughter chromosomes. Error-free unlinking is required to ensure proper segregation at cell division and stable plasmid inheritance. Type II topoisomerases unlink replication links. In Escherichia coli, in the absence of topo IV (a type II topoisomerase credited with chromosome unlinking), the site-specific recombination system XerCD mediates sister chromosome unlinking. This reaction is activated at the division septum by a powerful translocase FtsK, which coordinates the last stages of chromosome segregation. The mechanism by which the XerCD-FtsK complex simplifies the topology of DNA remains unclear. The main objective of the proposed studies is to characterize the topological mechanism of DNA unlinking by the XerCD-FtsK system using knot theory, low-dimensional topology, and computer simulations. There is evidence that after being activated by FtsK, the enzymes XerCD unlink DNA in a stepwise manner. The tangle method will be used to find possible topological pathways of DNA unknotting and unlinking by site-specific recombination on small substrates. A computer model of DNA recombination will be developed, adapted to the Xer-FtsK system, and combined with the analytical results to analyze experimental data obtained from the Sherratt lab. The research is highly interdisciplinary and involves close collaboration with groups in Japan, Canada and the UK. Such collaborations will facilitate state-of-the-art student cross-training. Basic information about DNA topology will be disseminated to the general public, including elementary school children and visitors to the California Academy of Sciences.

DNA replication is the basis for biological inheritance. In bacteria, reproduction starts with replication of the chromosome into two identical daughter molecules, followed by segregation of the newly replicated chromosomes and division of the parent cell into two daughter cells. In circular chromosomes, problems of entanglement during DNA linking complicate the process of chromosome segregation. In Escherichia coli, DNA unlinking is typically mediated by the enzyme topoIV, which is an important drug target for quinolone antimicrobial agents. Understanding DNA unlinking by Xer recombination, in addition to providing a more complete picture of the chromosome segregation process, is highly relevant for drug design. Mathematical and computational tools are very useful for studying the action of enzymes that change the topology of DNA. In this project such tools will be used to characterize all unlinking pathways and to reveal the mechanism of unlinking by Xer. The educational goal is to develop new and effective ways to disseminate knowledge related to DNA topology and its biological significance, as well as to increase public awareness of the critical role of mathematics in understanding biological processes. The proposed plans include the creation of Math Circles for elementary school children in San Francisco and the development of a series of educational materials for public consumption in collaboration with the California Academy of Sciences. This will culminate in the production of an exhibit on DNA topology for the general public in the California Academy of Sciences Museum.