Solving Knotty Problems in Math and Biology

Mathematicians discovered astonishing connections between two seemingly unrelated fields of math and biologists are using their results to understand the twistings, linkings, and knotting of DNA

A little over a year ago, Vaughan Jones and Joan Birman met in Birman's office at Columbia University. Both are mathematicians, but their fields are so different as to seem totally unrelated. Jones, who is at the University of California at Berkeley, specializes in von Neumann algebras—esoteric mathematical objects that originated with quantum mechanics but since have been abstracted almost beyond recognition. Birman studies knot theory, a branch of pure mathematics related to topology. What brought the two together was Jones's suggestion that perhaps some results he obtained might help answer a fundamental question in knot theory.

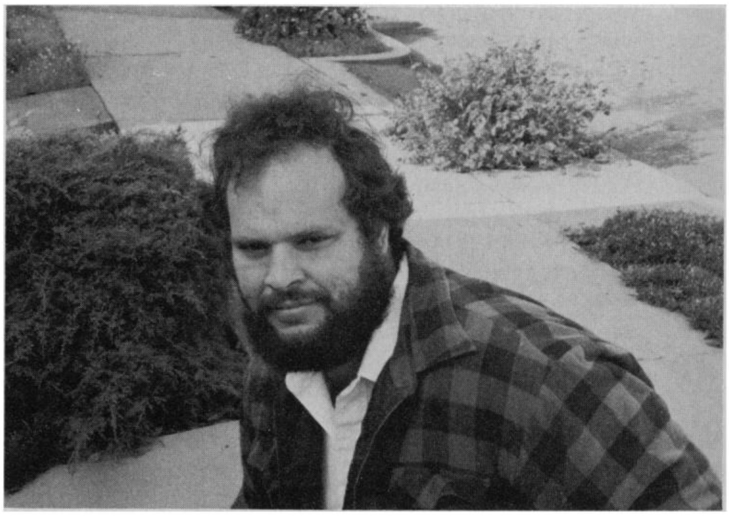
When the two sat down together, the discovery was almost instantaneous. Jones proved that what they both hoped was true—von Neumann algebras are related to knot theory and provide a way to tell very complicated knots apart. "It was wonderful, it was very wonderful, and I'm still thrilled," says Birman.

The result, say mathematicians, is a landmark in recent mathematics whose ramifications are still being worked out. Moreover, it now appears to be of more than theoretical importance. Biologists are beginning to make use of knot theory to understand DNA conformations. The new result is helping them understand how DNA becomes linked like a chain and also knotted during replication and recombination and, as a consequence, how the enzymes producing these knots and links must work.

Von Neumann algebras were discovered in connection with quantum mechanics when physicists needed a new way to talk about "observables." In classical mechanics, observables are such things as energy, position, and momentum. They can be known precisely. But in quantum mechanics, they never can be known precisely, so physicists substituted the mathematical notion of operators for the classical notion of observables.

They also postulated that these operators can be multiplied or added together, making them what mathematicians call an algebra. Finally, in the 1930's, mathematicians Frank Murray and John von Neumann, motivated by mathematics as well as physics, developed what Jones describes as "a very full collection of operators," which became known as von Neumann algebras.

The von Neumann algebras fascinated mathematicians, and, as they began to work with them, they concentrated especially on simple algebras, which they called factors. These are the backbone of all the von Neumann algebras—every algebra can be built up from a collection of factors.



Vaughan Jones

To his great surprise, his work on von Neumann algebras solved outstanding problems in knot theory.

Jones, who started out studying physics and quantum mechanics in his native New Zealand, switched to math in order to concentrate on factors. "They are very beautiful mathematical objects," he says. What particularly intrigued Jones was the notion that factors can have continuous dimensions, meaning that they can have as their dimension not just positive whole numbers, like three-dimensional space, for example, but any number that can be conceived of—1/21, for example, or π, which is not even a rational number. Continuous dimensions, Jones remarks, "are very strange and I was completely fascinated by them."

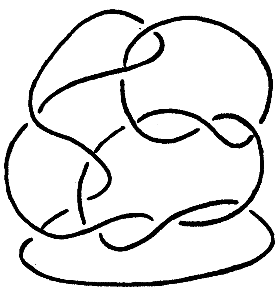
Although von Neumann himself had discovered the notion of continuous dimensions, "one thing that no one had really touched on very much was subfactors," says Jones, which correspond to subsystems of a physical system. For example, if you leave out one particle of a system of interacting particles in quantum mechanics, you will have a subfactor.

Jones came up with the concept of an index for subfactors, which measures their dimensions. Since factors in general can have any dimension imaginable, he fully expected that subfactors would have continuous dimensions also. "What I discovered was sort of amazing. If the dimension of a subfactor is less than 4, it must be precisely $4\cos^2\pi/n$." These strange numbers, "just came out of the proof somehow. It was not entirely understood," says Jones.

Jones then visited some mathematician friends at the University of Geneva and showed them his unexpected result. When they saw how the proof went, a couple of them said that it resembled the braid group, a concept from knot theory. Jones replied that it could not possibly resemble that group. But the very idea that his work with the dimensions of subfactors of von Neumann algebras could have something to do with knot theory led him to Joan Birman's office, where the crucial link between the two fields was made.

Knot theory has a central, fundamental problem: How can you tell whether two knots are the same or different? If you have two knots made of string, can you change one into the other without cutting the string? "Imagine you have a big piece of tangled string and you throw it into the air and let it fall," Jones explains. "It will look different when it lands, but you would find it hard to tell how the knots in the string before you threw it in the air were converted into the knots after it landed. Anyone who's been fishing will understand the problem."

For the past 100 years, knot theorists have made up huge tables of knots, drawing pictures to show which knots are different from others. But this is hardly an ideal solution. What knot theorists really want are properties of knots that they can calculate that are invariant, that uniquely characterize knots. Ideally, such an invariant will always be the same if two knots are the same and will always be different if two knots are different.



Is this knot knotted or not?

It is not always obvious whether a knot is knotted. This "knot" actually is not knotted and is the basis of a magic trick.

The closest anyone came to finding such an invariant was the American mathematician John Alexander. In 1928 he discovered a simple polynomial that is associated with knots and can sometimes determine whether knots are distinct. If the Alexander polynomial is different for two knots, the knots are different. But the problem is that many times the Alexander polynomial is the same for two knots and yet the knots are not the same.

One idea for studying knots was to derive knots from braids. Mathematicians imagine making what they call braids by tying pieces of string to a set of hooks and then winding the strings around each other before tying each piece of string to another hook at the bottom of the braid. An ordinary braid like a braid of hair is a special case of these more general braids. Once a braid is made from strings tangling between two sets of hooks, it can be turned into a knot by bringing the top and bottom set of hooks together and tying the ends of the strings to each other. Sometimes, depending on the braid, there will be a knot, sometimes there will be several knots, and sometimes there will be no knots at all. But, as Alexander showed in the 1920's, this process of making knots from braids allows mathematicians to create any knot they want by making the corresponding braid.

"It seemed like a good idea to use braids to study knots," says Jones, who has become an expert on knots as a consequence of his discovery. "But there is a great deal of non-uniqueness. It is not clear whether you can do a calculation on a braid and get information that only depends on the knot."

What Jones learned from his friends in Geneva, however, is that information on braids appears when he proves his result on the dimension of subfactors. "The braid group somehow appeared in the algebra when I proved my result on the index [dimensions]. It later turned out, by a miracle, that this number, the dimension, is dependent on the knot, not the braid," Jones says. "So you get a function dependent only on the knot." The function was a polynomial.

But the knot connection came only after Jones had learned something about knots. He was no knot theorist and he was not at all sure that this "mysterious way of going about things" actually provided any new information. He sought out Birman to learn about the connections between knots and braids. He was not at all optimistic that his work would lead to anything significant in knot theory. "Braids are related to many things, only one of which is knots," Jones remarks. Since knot theory and von Neumann algebras are so different, the two mathematicians began by spending a day telling each other about their fields.

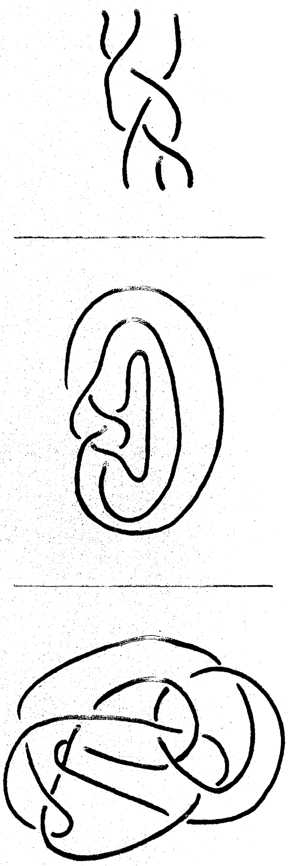
"I'd written a book on studying knots through braids and I suggested we get together and talk," says Birman. When Jones arrived, "at first we thought it was the Alexander polynomial. It looked just like it," Birman recalls. So she asked Jones to calculate his polynomial for the trefoil, which is the overhand knot—the simplest knot that can be tied with string and the knot that is normally used to tie string around a package, for example. There are right-handed and left-handed versions of the overhand knot and, although knot theorists know these versions are different, they find it difficult to prove it. The Alexander polynomials for the two versions are the same.

Jones calculated his polynomial for the right-handed trefoil and its value looked different from the value expected from the Alexander polynomial. Then Birman asked him to calculate his polynomial for the left-handed trefoil. It was not the same polynomial as he calculated for the right-hand knot. "At first, I thought it was a mistake," says Birman. So she had Jones start calculating his polymonial for other knots. "He did many, many specific calculations and there wasn't a false note in it."

Jones's result "was an enormous surprise," Birman remarks. It still does not completely solve the knot theorists' problems because there are some knots that are distinct and that have the same polynomial values. But Jones's polynomial, says Birman, "is more powerful" than Alexander's—it is more likely to distinguish knots that are in fact different.

Yet, says Jones, there were still many loose ends. For one, the mathematics turned out to be unnecessarily complicated. "You start with a knot, go to a braid, then go to a von Neumann algebra and from there you get a dimension." The first thing he learned was that "you don't have to go through the braid." The calculation can be done directly from the knot and is practically the same as the calculation for the Alexander polynomial. This led mathematicians to believe there must be some simple formula to embrace both Alexander's and Jones's polynomials.

Almost immediately, five groups of mathematicians independently and by different methods found a two-variable polynomial



Going from braids to knots

The braid (top) can be converted to a knot (center) by tying its ends together. But going from a knot to a braid can be difficult. For example, try Jones's favorite, the knot at the bottom which was devised by Morwen Thistlethwaite at the Polytechnic of the South Bend in London.

that does the trick. By specifying one variable, you get the Alexander polynomial. By specifying another, you get the Jones polynomial. "So that was wonderful," says Jones. It was the beginning of a flurry of work on simple inductive formulas to distinguish knots.

The knot theorists also are trying to understand what the polynomials really mean—what are they telling mathematicians about knots? They recognize, says Birman, that the polynomials "are encoding data about knots in some terribly complicated way." It is not yet clear just what the encoding pattern is.

In the meantime, this progress in knot theory is having some definite practical consequences in biology. In their attempts to understand the knotting and linking of DNA molecules, many biologists "were becoming very good at knot theory," says Birman. But they are starting to run into problems that simple knot theory and even the Alexander polynomial could not solve.

DNA is packaged very tightly into cells. There is enough DNA in the cells of a person to stretch to the sun and back 50 times, so once it is in cells, it must be coiled, linked like a chain, and knotted in order to fit. Until recently, biologists could only guess at what these knots and links and coils actually look like because DNA is too thin for these structures to show up well under the electron microscope. But recently, Nicholas Cozzarelli of the University of California at Berkeley and his colleagues working with Andrzej Stasiak and his associates at the Institute for Cell Biology in Zurich, Switzerland, found that if they coat the DNA with a protein—rec A—it becomes five times fatter and looks like coiled and knotted sausages under the electron microscope. Now biologists could address fundamental problems of the knot theory of DNA.

> ***"Before Jones, the math was incredibly arcane. The way knots were classified had*** **nothing** ***to do with biology. But now you can calculate things that are important to you."***

The principal observation is that DNA knots and unknots, ties and unties itself and if these procedures do not occur properly, the cell dies. Normally, knots and links appear in DNA during replication and recombination. Then the DNA must be straightened out during cell division. "The biological consequences are profound," says Cozzarelli. "A single link that is not undone is lethal. You have to get rid of all links, supercoils, and knots. If you don't, you die."

So what the biologists want to know is, how are these chain links and knots made—and unmade? The new polynomial has important implications, according to Cozzarelli.

The first major use of the mathematics is to classify DNA knots and links. "It is important to know what to look for," says Cozzarelli. "With complicated knots, there are billions and billions of possible ways they could be made." Biologists cannot fall back on model building, their old standby, because they really need rigorous proofs of how the knots were made. Cozzarelli explains: "It's like doing Rubik's cube. The path from one configuration to another is not obvious. Can two forms be interconverted? Just because you can't do it doesn't mean it's impossible." With the new polynomial, biologists have a way to prove whether two DNA configurations are the same or different.

But Jones's work has a second implication that, Cozzarelli proposes, is where the real future of the result lies. Only two basic operations change the structure of DNA. One is passage—one segment of DNA is broken, another strand is passed through, and the DNA is then closed up. This is how supercoils as well as knots and links are made. The other basic operation is exchange—two pieces of DNA are broken and the DNA from the two strands is switched. "All other motions of DNA can be reduced to these two simple ones," Cozzarelli says.

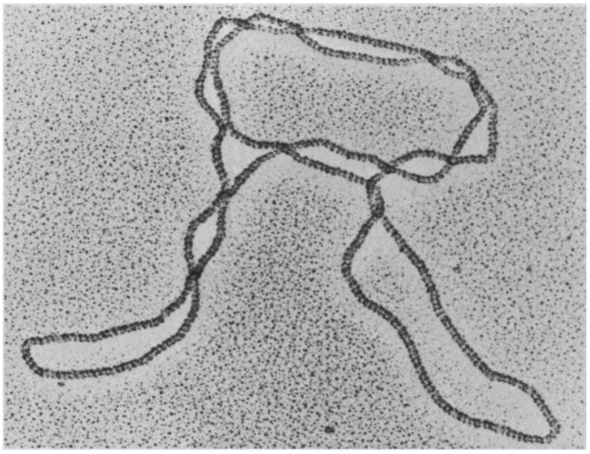
The amazing aspect of the new polynomial is that the two operations it uses are exactly these two operations on DNA. In fact, the mathematical equation roughly says, in biological terms, that if you take a polynomial that describes a knot and add to it a polynomial that describes that knot after it has been broken and the other DNA strand has passed through and then add to that sum the polynomial that describes the DNA after an exchange, the sum must be zero.

"All of a sudden, the math is relevant," Cozzarelli says. "Before Jones, the math was incredibly arcane. The way knots were classified had *nothing* to do with biology. But now you can calculate things that are important to you."

In a recent application of the new mathematics, Cozzarelli and his colleagues Sylvia Spengler and Steven Wasserman along with James White, a geometer at the University of California at Los Angeles, answered the question of whether a model based on four rounds of recombination was correct. "We didn't know if the model was correct or if there was some other way to do it or if you could work backward [from the knot to the original unknotted DNA to get the mechanism]," Cozzarelli says. White proved that the way Cozzarelli suggested the reaction could go was in fact the simplest way and that they could work backward and so they could derive the mechanism.

It is too soon to say where these unexpected connections between von Neumann algebras, knot theory, and molecular biology will lead, but Frank Gilfeather, who is staff director of the National Research Council's state-of-the-art monitoring reviews panel for the mathematical sciences, likes to emphasize that at the very least it illustrates how practical results can come from the most esoteric of research. It is a theme mathematicians know well, and often describe as the unreasonable effectiveness of mathematics. ■ **Gina Kolata**

Nicholas Cozzarelli



How does DNA untie its knots?

This DNA from the bacterial virus lambda is knotted and coiled. Before it can replicate, it must straighten itself out. Using new mathematics results, biologists can determine how knots and chain-like links of DNA are made—and unmade.