they can do mathematics merely by creating and looking at the computer-generated designs. Others, like Albert Marden at the University of Minnesota, defend Mandelbrot's approach, saying that "fractal-like situations come up all over science and mathematics."

Still others, such as Robert Devaney at Boston University, give the fight a split decision. Devaney, who works with high school teachers and students to develop new math curricula, says "high school kids love this stuff; they eat it up." Once they get interested in the pretty pictures, Devaney feels, it's easy to pull them into the mathematics behind the pictures.

And there is some real math there. Even Krantz acknowledges that some very important theorems are connected with fractals. But he is irritated by what he sees as a fascination with form over substance. "The fractal gurus spew data out on a computer, then see what they come up with. This is entirely counter to the scientific method, which in mathematics is called the proof. There are no proofs in fractal theory, just pretty pictures."

One thing's for sure: Krantz's article and Mandelbrot's rebuttal have stimulated the mathematical community to debate the value of fractals. "Everywhere I went, people were talking about the articles," says Sheldon Axler, editor of *The Intelligencer*.

Of the many mathematicians he has spoken to at conferences, Axler says a majority sided with Krantz, especially about the lack of mathematical content in fractal theory. "People are a little turned off by the hype. Where's the substance? Where's the theorems? Where's the beef?" Researchers also agree with Krantz in their frustration over having to compete with fractals for funds, Axler says, and some mathematicians have even tried working a mention of fractals into their grant applications. "It seems that if fractals are dabbled into grants, it's easier to get the money," Axler says.

Some mathematicians who have followed the feud over fractals suggest that it is as much a cultural conflict as anything else. "It's not traditional mathematics," says William Thurston at Princeton, and so "a lot of mathematicians are suspicious of fractals." And although the turf battles in mathematics may seem obscure to the outside world, they are very real to mathematicians.

"Mathematics is the most ferocious field in science," Mandelbrot says, "because there is no objective judgment of the value of things." Arguments can get "very bitter," he adds, "but it just stays in the commons and the lounges because no one outside the field knows what they're talking about."

■ ROBERT POOL

Seeing Proteins in 4D

It doesn't take special 4D glasses, just state-of-the-art NMR spectroscopy, to bring new protein structures into view

A "QUANTUM JUMP" in nuclear magnetic resonance (NMR) spectroscopy, achieved by researchers at the National Institutes of Health, could open a new window on complex protein structures. Lewis Kay, Marius Clore, Ad Bax, and Angela Gronenborn at NIH's Laboratory of Chemical Physics report on page 411 of this issue of *Science* that they have literally added an extra dimension to NMR, going from the current three dimensions to four. Their technique, which Bax says "nobody really believed could be done," will make it possible to apply NMR spectroscopy to the structural analysis of much larger proteins than before.

"It's an exciting advance," says Stephen Fesik, a chemist at Abbott Laboratories in Abbott, Illinois, who helped develop 3D NMR. To date, NMR structural determinations have been done mostly on proteins with molecular weights below 10,000, with the largest being under 20,000, Fesik notes. But many proteins are much bigger than that, and the new technique should help bring them into range.

This is good news for scientists who want to learn how protein chains fold and twist in space. That knowledge is needed to understand how enzymes and other proteins work, and it may also aid drug design.

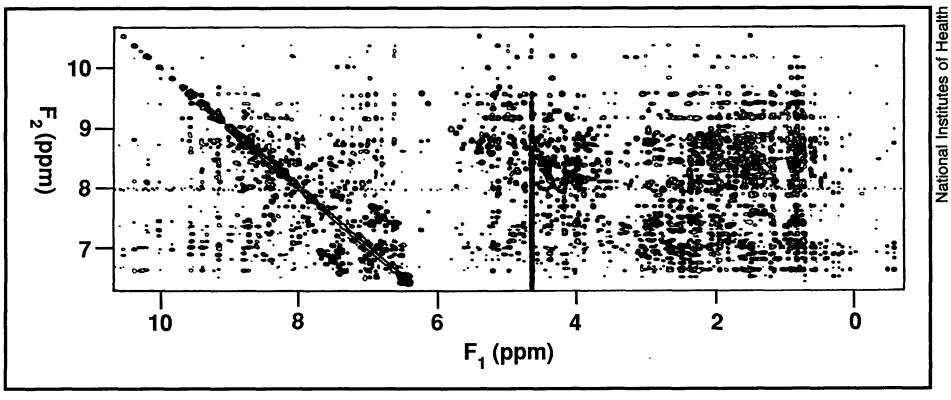
A majority of protein structures now are determined by x-ray crystallography, which can analyze much larger proteins than NMR, but crystallography has several limitations. The major one is that it depends on getting good quality crystals, which is always difficult, and sometimes impossible, for proteins. But NMR spectroscopy works on proteins in solution. It can also reveal details, such as how a protein moves over time, that are invisible to crystallography.

NMR spectroscopy analyzes a molecule by studying its magnetic structure. The nucleus of each hydrogen atom in a molecule, as well as the nuclei of some of the molecule's other atoms, act like tiny magnets, setting up their own magnetic fields and influencing the fields of nearby atoms. By perturbing these fields in various ways and watching how they respond, researchers can get a tremendous amount of data—so much, in fact, that it's hard to sort it all out.

That's where the multiple dimensions come in. The 1D, 2D, 3D, and 4D NMR experiments don't imply a physical image of a molecule in one, two, three, and four dimensions. Instead, they refer to how the data are collected and displayed. If the data were printed words, the different dimensions would correspond to a line of text, a page, a book, and a multi-volume book set.

A 1D NMR experiment, which gives a single "line" of data, is straightforward. First, a powerful magnet aligns the nuclear spins of the atoms in the sample so that they are all pointing the same direction. Then the sample is bombarded with radiofrequency radiation which has the effect of turning all these tiny nuclear magnets on their sides, where they begin to precess, or rotate around the axis of the applied magnetic field. The precessing nuclei generate their own magnetic fields which are detected by a magnetic coil and analyzed.

This allows scientists to get information about the sample because each nucleus precesses at a slightly different frequency, called its resonance frequency, which depends on its immediate surroundings. A proton (hydrogen nucleus) bonded to a carbon atom



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2D is not enough. *For interleukin-1β, the 2D spectrum is impossible to interpret.*

will precess at a different frequency from a proton attached to a nitrogen atom, for example. The resonance frequencies of the protons are displayed on a graph, where the locations of the "peaks" give information about the chemical environment of the protons—say, whether a proton is near a carbon atom or a nitrogen atom. In simple molecules, 1D NMR experiments give enough information to solve the structure.

But in complicated molecules, like proteins, the NMR spectrum is so crowded that it's impossible to tell which proton is which. The solution: add another dimension.

First done in the 1970s, 2D NMR experiments consist of series of 1D experiments in which the precessing spins of the protons interact with one another. A 2D experiment might, for example, consist of 1000 runs, each lasting about a minute, for a total of about 18 hours. By examining the proton interactions, a researcher can tell which pairs of protons lie within about 5 angstroms of each other. Assuming that the researcher knows the sequence of amino acids in the protein, this information is enough to reveal how the protein twists around on itself.

The biggest protein that has been analyzed with 2D NMR, however, is only about 100 residues long, Fesik says. If the protein is much bigger, the peaks in the spectrum—which correspond to pairs of close-lying hydrogen atoms—are so close together that "you can't tell which pair of protons corresponds to a given peak." The 2D spectrum for interleukin-1β, the protein analyzed by the NIH group, looks like someone spilled ink on it (see figure).

Just a couple of years ago, researchers successfully moved from 2D to 3D. One way to do this is to add a step in which the spins of precessing protons interact with the spins of precessing carbon nuclei. This entails running a set of 20 to 30 abbreviated 2D NMR experiments, varying the amount of "mixing" time between protons and carbon nuclei each time. A complete 3D NMR experiment generates a huge amount of data to sift through. It's worth it, though, because this extra information removes much of the ambiguity about the proton locations.

Although the 3D NMR technique has successfully provided structures for proteins of more than 150 amino acids, it, too, has limits. The complexity of the NMR data increases exponentially with the molecular weight of the protein; analyzing a 200–amino acid protein would probably be pushing the limit for conventional 3D NMR. The obvious step was to go to 4D and get information about the location of protons with respect to both carbon and nitrogen atoms, but that meant running 20 or so shortened 3D NMR experiments, adding up to a very long experiment and causing a number of technical problems as a result of the tremendous amount of data generated.

The NIH group, however, was able to find a number of shortcuts to decrease the amount of time needed for a 4D experiment. Last year, they announced that they had managed to cut the time needed for a single full-fledged 3D spectrum to about 5 days, which they've now shortened to about 2. The 4D spectrum reported in this issue took about a week, and now the group says they can do one in 4 days.

Interleukin-1β has only 153 amino acids, but within 2 years the NIH group expects to be doing proteins of up to 300 amino acids. Analyzing a protein that big, will probably take from 4 to 6 months, Clore estimates. Still, that's faster than it sometimes takes to grow high-quality crystals and do crystallography. And 4D NMR also provides extra detail that gives more precise structures.

The NIH group doesn't plan to stop at four dimensions. They're already looking at 5D NMR. Can 6D be far behind?

■ ROBERT POOL

Organic Superconductor Record

A compound created by a team of chemists at Argonne National Laboratory has set a new record for critical temperature in an organic superconductor. It becomes superconducting—loses all electrical resistance—at 11.2 K, more than 10% higher than the previous best by an organic material. Although inorganic copper oxide superconductors have done much better—some become superconducting at temperatures as high as 125 K—the organic superconductors do have certain advantages, such as being lightweight, that could eventually prove important in applications. And, the Argonne researchers say, dramatic improvements in organic superconductors may be possible. Their new material, they say, offers some obvious possibilities for structural modifications that could lead to further increases in the critical temperature.

The best organic superconductors are all based on the compound bis(ethylenedithio)tetrathiafulvalene, which is mercifully shortened to ET in the literature. In 1988, for example, a group of researchers at the University of Tokyo in Japan set the previous record with $(ET)_2Cu(NCS)_2$, which has a critical temperature of around 10 K. And the compound that has now bettered that is $(ET)_2Cu[N(CN)_2]Br$, which was synthesized by a team led by chemist Jack Williams of Argonne.

Why do these complexes superconduct? No one really knows for sure, but part of the answer lies in ET's structure. The molecules are flat and, when the material crystallizes, they stack up one on top of the other like piles of pancakes. They also donate electrons to other molecules—a prerequisite if organic compounds are to conduct electricity. When ET is combined with an appropriate electron acceptor, the transferred electrons can move easily up, down, and between the stacks of molecules, carrying an electric current through the material.

Williams says that the team, which includes Aravinda Kini, Urs Geiser, Hau Wang, Douglas Carlson, and Wai Kwok, all at Argonne, and Myung-Hwan Whangbo at North Carolina State University in Raleigh, found their new material by trying different electron acceptors. They were guided in part, he says, by a correlation that they had noticed earlier—the larger the acceptor molecule that is combined with ET, the higher the critical temperature. "Aside from that, there's little theoretical guidance as to what to do," he says, so it was mostly trial and error.

The new superconductor, which was described in the 11 July issue of *Inorganic Chemistry*, has several similarities to the high-temperature copper oxide superconductors discovered in the past 3 years, Williams notes. Like them, it is a layered material—layers of ET alternate with layers of the electron acceptor, and the current travels mostly along the ET layers. Its electronic structure resembles that of the high-temperature materials in certain ways, and both the organic superconductor and the high-temperature superconductors are hard, brittle materials.

Unlike high-temperature superconductors, the Argonne material is not likely to end up in any commercial applications, but its discovery does have important implications for research, Williams says. The electron acceptor, $Cu[N(CN)_2]Br^-$, is structurally different from any used before, he explains, so there are "lots of obvious substitutions to try" to obtain even higher critical temperatures. How high can organic superconductors go? Williams says it's anybody's guess, but he wouldn't be surprised to see them eventually reach liquid nitrogen temperatures (77 K) and beyond. "We know that high critical temperatures exist [in the copper oxide superconductors], so there's no reason to think they won't exist in other materials." ■ R.P.