amyloid. (Duke University's Allen Roses has argued that ApoE4 contributes to the hyperphosphorylation of tau.) The scientists found that PHF-tau injected along with aluminum resisted breakdown for the longest period. The researchers suggest that aluminum, which binds avidly to phosphate groups, may change PHF-tau's molecular conformation so that it is less accessible to the protein-digesting enzymes.

Trojanowski and Lee's suggestions are "very reasonable, very significant," says Fasman of Brandeis, whose own test-tube experiments have shown that the more phosphate groups that are attached to synthetic neurofilament fragments, the more aluminum ions are able to bind and cross-link neurofilaments, rendering them less soluble. The activity of aluminum may thus be "the crucial step" opening the route to tangle formation, Fasman says.

Other scientists, however, say the "crucial step" may occur even earlier, before phosphatases or aluminum come into play. In the first place, no one knows whether the modest buildups of aluminum found in the brains of Alzheimer's patients contribute to, cause, or result from tangle formation, says neuroscientist Zaven Khachaturian, director of the Office of Alzheimer's Disease Research at the National Institute on Aging. As for the post-mortem stability of PHF-tau, Michel Goedert, a molecular neurobiologist at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, U.K., says it could simply be caused by some other "upstream" events that give the filaments their particularly insoluble structure.

Harvard's Selkoe thinks these upstream events may be genetic and may involve β-amyloid, the main component of the other characteristic Alzheimer's lesion, senile plaques. Increased neuronal secretion of β-amyloid, possibly as a result of a genetic defect, may eventually produce neurotoxic effects that alter the phosphorylation state of tau protein, Selkoe says. (New studies of mice that express the human gene for β-amyloid precursor protein, reported this week in *Nature*, may allow tests of this possibility.) "Many people in the field now believe that tangles are a step in the degeneration of neurons, not the cause," Selkoe says.

Khachaturian points out that Alzheimer's research has long been polarized between labs focusing on β-amyloid and those interested in tau—or the "BAPtists" and the "Tauists." But he notes that both tangles and plaques apparently result from breakdowns in the balance between protein synthesis and degradation in the neuron, and that the new findings may point to a common path during at least part of this process. And perhaps along that common path will lie a way to untangle the puzzle of the disease.

–Wade Roush

MEETING BRIEFS

At Math Meetings, Enormous Theorem Eclipses Fermat

Hardly a word was said about Fermat's Last Theorem at the joint meetings of the American Mathematical Society and the Mathematical Association of America, held this year from 4 to 7 January in San Francisco. For Andrew Wiles's proof, no news is good news: There are no reports of mistakes. But mathematicians found plenty of other topics to discuss. Among them: a computational breakthrough in the study of turbulent diffusion and progress in slimming down the proof of an important result in group theory, whose original size makes checking the proof of Fermat's Last Theorem look like an afternoon's pastime.

Slimming an Outsized Theorem

What use is a proof so long that no one mathematician can plow through the whole thing? That's been a problem facing group theorists for the last decade. The reason is that one of their most important theorems, describing the taxonomy of the mathematical objects known as simple groups, has a proof that runs an estimated 15,000 pages, spread over upwards of a thousand separate papers written in widely varying styles by hundreds of researchers. But the Enormous Theorem, as it's affectionately called, is in for some downsizing. Two mathematicians—Richard Lyons at Rutgers University and Ron Solomon at Ohio State University—are leading an effort to tame it.

As befits this mathematical monster, the job isn't going to be finished in a day. After a dozen years, Lyons and Solomon have completed only a fraction of the job, they told their colleagues at the San Francisco meetings, and they expect the task to stretch well into the next century. It's not just the length of the original proof that's so time-consuming, they say, but the need to rework its logic to simplify and shorten it. The wait should be worth it, however. "We've proved some old theorems in considerably greater generality than they were proved the first time," Lyons notes. When they are finished, the result should be a proof that a single individual can comprehend—which should give comfort to some mathematicians who are now hesitant to base their own work on the Enormous Theorem because they can't read it all.

Many researchers in group theory, as well as "customers" who come across groups in other areas of mathematics, rely heavily on the Enormous Theorem, known more prosaically as the classification theorem for finite simple groups. Groups are fundamental algebraic objects that describe various kinds of symmetry. (The rotations of a pentagon by multiples of 72 degrees make up one example of a finite group.) Simple groups are the building blocks from which other groups are assembled, much as atoms are the building blocks of molecules. And just as chemists organize the elements into eight columns, the classification theorem says each finite simple group belongs to one of four categories: cyclic, alternating, Lie-type, or sporadic. The four categories are as different as Heraclitus's earth, air, water, and fire, but knowing that every finite group represents some combination of just four types of simple groups is itself an enormous simplification.

Part of the reason the original proof turned out to be so long is that the four categories have widely varying properties, so that unifying concepts are hard to come by. Group theorists chipped away at the classification problem for nearly 30 years, from 1950 to 1980, slowly building up an arsenal of techniques and proving results for specific cases. In 1972, Daniel Gorenstein of Rutgers spelled out a 16-point program for attacking the problem, but there were few who thought the effort would be successful until Michael Aschbacher at the California Institute of Technology made a series of breakthroughs in the early 1970s. By 1980, it was clear to the experts that their collective effort had solved all the problems of the classification; Gorenstein declared victory in what he called the Thirty Years' War.

The proof, though, was unlike anything mathematicians had ever called a proof before. A traditional mathematical proof is one that an individual can sit down, read, and check for him- or herself. But the proof of the Enormous Theorem has so many pieces that even the experts who produced it rely on one another for assurance that the pieces—some still unpublished—fit together. As Solomon puts it, "If the generation of people who worked on the proof were to vanish, it would be very hard for future generations to reconstruct the proof out of the literature. It wouldn't be impossible, but it would be quite a scramble."

To some mathematicians, it's worrisome that they can't check the theorem on their own. Shreeram Abhyankar of Purdue University, for example, tries to avoid citing the Enormous Theorem in his work on algebraic geometry. "I still use it as a guideline," he told *Science*. But the state of the proof makes him reluctant to use the theorem directly. Others have fewer qualms. "Very many parts of it are extremely parallel," explains Stephen Smith of the University of Illinois, Chicago, who, with Aschbacher, organized the San Francisco sessions on the classification theorem. As a result, familiarity with the details of one part of the proof gives experts confidence in other parts.

Even so, everyone would be happier with a shorter, more readable proof. Gorenstein, who died in 1992, conceived of a second-generation proof soon after the original was finished. He was joined by Lyons and Solomon, who are still at work on it. Their first installment, published last year by the American Mathematical Society, weighed in at a slim 165 pages, but all it does is establish notation and terminology, outline the strategy of the proof, and give references for those parts of the theorem that the rest of the proof will not address. (Certain key elements have already received thorough second-generation treatment from other mathematicians.) Volume 2, which is nearing completion, will be three or four times as long as the first volume. Lyons and Solomon project a total of 10 volumes in all.

At that rate, the second-generation proof is still going to be gigantic, with estimates ranging between three and five thousand pages. Like marathon runners, Lyons and Solomon are harboring their strength. "We're just trying to keep a steady pace," Lyons told *Science*. Asked about the prospect of a third-generation proof that would bring the classification theorem down to, say, a reader-friendly 50 pages, Smith replied, "I don't see any way that could happen, but we're all hoping that someone'll come along with a brilliant idea. That would be great."

Turbulence Made Universal

Andrew Majda likes to show off his "boring" graphs: three nearly identical straight lines passing almost perfectly through their respective data points. What they demonstrate, though, is anything but boring. The exercise in curve fitting by the Princeton University mathematician represents a remarkable advance in the study of turbulent diffusion, the process that spreads cigarette smoke through a room and salt through the ocean. The agreement between the curves and the points shows for the first time that a mathematical model of turbulent diffusion works equally well across a huge range of scales—from millimeters to thousands of kilometers.

Theorists can predict the course of idealized, simple diffusion, in which random particle motions alone gradually spread a fluid-like "tracer" (which can be anything from heat to a chemical concentration) through a medium (which can be anything from air to porous rock). Turbulent diffusion, in which small-scale, random fluctuations accelerate the diffusion process, is far more common, however. Second-hand smoke is just one example. "If one is serious about investigating global warming scientifically, one has to be able to model turbulent transport," notes Peter Lax at the Courant Institute of Mathematical Sciences in New York City. The problem is, researchers have never been sure how well their models represent the reality of turbulence.

COURTESY OF PAUL E. DIMOTAKIS

A stirring sight. Turbulent mixing during a rocket test firing near Los Angeles.

Mathematicians studying turbulent diffusion do have a differential equation that describes how the diffusing agent varies in time and space. But the equation is difficult, if not impossible, to solve exactly because it includes a random coefficient representing the velocity field—all the currents and eddies in the environment, which also vary in time and space. Nevertheless, there are lots of theoretical predictions of how solutions to the equation should behave. Two long-standing ones imply that, on average, turbulent diffusion looks the same, mathematically, over many different scales in time and length.

In 1926, the English meteorologist L. F. Richardson argued that during turbulent diffusion, the square of the average distance between nearby particles grows in proportion to the cube of time. And in 1941, the Russian mathematician Andrei Kolmogoroff hypothesized that the difference in velocity between two points in space is proportional to the cube root of distance between the two points. Both predictions are examples of what physicists call "universal" laws, because they hold regardless of the scale of time or length.

Researchers had caught glimpses of this predicted universal behavior in experiments. They have also tested the predictions over a small range of scales in computer simulations. These simulations approximate a solution to the diffusion equation by keeping track of the tracer concentration at points of a grid; they then change the values in discrete time steps. In principle, computer models could check the predictions over a larger range of scales by using increasingly fine grids and small time steps, but the amount of computation involved increases exponentially—by as much as a factor of 10,000—with each refinement in scale.

That left theorists with the challenge of checking whether their mathematical models of turbulent diffusion adhere to the predicted universal laws without actually computing over the entire range of scales. "It seems like you're asking the impossible," notes Majda. Nevertheless, that's what he and Princeton colleague Frank Elliott have effectively done.

Using a clever combination of mathematical and computational techniques, Elliott and Majda found a way to run computer simulations that include all scales of a turbulent diffusion process at once. Majda describes it as a numerical laboratory "where you do something you could never dream of, namely putting in all the scales in a problem and actually looking at their effect with enough control so that it's a meaningful experiment."

"It looks like we're cheating," Majda admits. While some researchers with competing methods have questions about his approach, no one has accused him of any underhanded computing. Majda's "boring" graphs confirm that Kolmogoroff's scaling hypothesis is correct over 12 orders of magnitude for one particular model of turbulent diffusion. Other, equally "tedious" graphs confirm Richardson's law over a similar range of scales—far larger than the one or two orders of magnitude obtained in the past. The results are "very impressive," says Lax.

It's unlikely that any turbulent diffusion process in nature takes place on so many different scales at once, Majda points out, but it's nice to know the numerical laboratory can handle problems of that size. The work so far, he says, is "really just a warm-up" for future work that includes studying the physics of cloud formation. Cloud formation, too, involves many different time and length scales, and it is so poorly understood that it holds back long-range weather prediction and stymies global climate models. Any boring graphs Majda comes up with there will no doubt stir up a lot more excitement.

–Barry Cipra