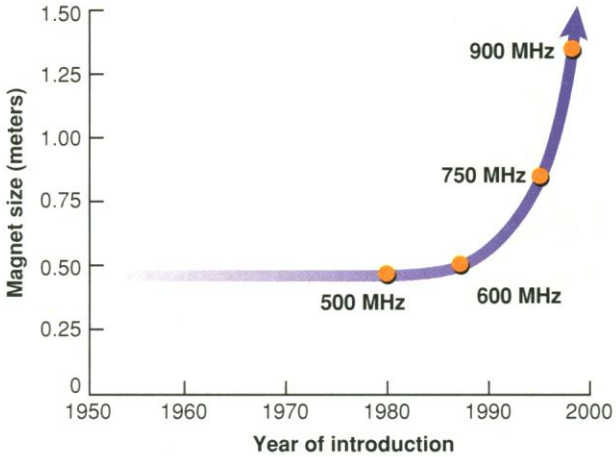
INSTRUMENTATION

NMR Researchers Look to the Next Generation of Machines

Paul Ellis is expecting big things from the machine that will be delivered this summer to his team at the Pacific Northwest National Laboratory (PNNL) in Richland, Washington: He's betting it will launch both a scientific and a cultural revolution. The machine, the first of a new generation of nuclear magnetic resonance spectrometers, should allow researchers to work out the structures of molecules—ranging from large protein-DNA complexes to the surfaces of catalysts—with greater precision than ever before. The cultural revolution will come when these instruments become more widely available: They could transform nuclear magnetic resonance (NMR) studies into a Big Science enterprise.



Leaping forward. Successive generations of NMR machines contain ever-larger magnets, boosting both performance (measured in megahertz, MHz) and cost.

For the past 50 years, NMR machines have been cheap and small enough to allow hundreds of individual investigators to buy and house their own. Next-generation NMRs will be different. With a powerful magnet at its heart, PNNL's new $7 million NMR will stand 7 meters high, be surrounded by a shield made of 113 tons of iron, and hold some 240 kilometers of superconducting wire. "It's not something everybody can have in the basement," says Ellis, an NMR spectroscopist. And many NMR experts believe the high cost of the new machines will force changes in the way NMR technology is funded. Not only will the field require more total money, but grants are likely to go to large centers rather than individuals, forcing traditionally independent scientists to coordinate their research.

"This is a community that is more or less oriented to doing small science," says Bob Eisenstein, assistant director of the Mathematics and Physical Sciences directorate at the National Science Foundation (NSF), who spoke last month at a workshop* to discuss the coming technological turning point in NMR studies. "There are always a lot of birthing pains in making the transition from doing one style of science to another," he adds.

Next-generation NMR machines earn their name from the massive magnets at their core, which boost both performance and cost. To map the structure of atoms in a molecule, NMR exploits the fact that some atomic nuclei behave like tiny bar magnets and align when put into a magnetic field. Researchers then disrupt that alignment slightly and use the telltale oscillation, or precession, of nuclei around the magnetic axes to identify the nature of particular atoms and their positions. But heat weakens the magnetic signal by buffeting many of the aligning nuclei into pointing in the opposite direction. More powerful external magnets help counteract those effects and give a stronger signal, explains Jim Prestegard, a structural biologist and NMR expert at the University of Georgia, Athens.

So over the years, NMR makers have put ever larger magnets into their machines (see graph). Today's top-of-the-line, 750-megahertz (MHz) machines (named for the speed that protons in the machines precess) are outfitted with 17.6-tesla magnets; PNNL's 900-MHz machine will have a 21-tesla magnet. And plans are already on the drawing board for 1000-MHz or 1-gigahertz (GHz) machines, which would require fields of more than 23.5 tesla.

Bigger magnets mean machines that are more sensitive—able to detect faint signals from smaller samples—and have better resolution, or the ability to sort out one nuclear signal from another, a trait important in studying large molecules. "They can propel science into new directions," says Peter Wright, an NMR expert at The Scripps Research Institute in La Jolla, California. For example, the new machines are likely to make a big splash in tackling such problems as identifying the three-dimensional structures of the 100,000 or so human proteins whose genes are currently being sequenced by the Human Genome Project.

When coupled with new NMR techniques developed over the past year, next-generation machines should be able to resolve proteins twice as large as those that can be tackled by current NMR technology—and produce results faster than ever. That's "a tremendous advance," says David Wemmer, an NMR spectroscopist at the University of California, Berkeley, and the Lawrence Berkeley National Laboratory. Researchers could look at how proteins link to other proteins and to DNA—linkages that are at the heart of gene transcription and signal transduction, two of the hottest areas in molecular biology. "The potential return for going to higher fields is greater than ever before," says Prestegard.

In addition to probing the structures of ever-larger proteins, the new machines are also expected to help researchers look at smaller samples than ever before, a feat especially prized by materials researchers. Current-generation machines have given NMR researchers their first glimpses of the structures of surfaces. (Older machines required large chunks of bulk materials rather than the tiny amounts seen on surfaces.) Next-generation machines will likely extend this feat, using faint signals that show up only at high fields to track the behavior of atoms on the surfaces of catalysts and electrons in high-temperature superconductors. "High-field [NMR] experiments can have a significant impact on our understanding of materials chemistry," says Ellis.

But to realize all this scientific potential, these behemoths will have to be accessible. The new machines push current magnet technology to the limit—and they won't come cheap. "The cost of these magnets is going up exponentially" with each new generation, says Wright. The initial 900-MHz machines weigh in at $7 million apiece, compared to about $500,000 for the garden-variety NMR used in hundreds of individual labs today. And getting the larger magnets needed for 1-GHz machines "will certainly require new technology," possibly wires made from high-temperature superconductors, which can better withstand high magnetic fields, says magnet expert Robert Griffin at the Massachusetts Institute of Technology in Cambridge. The price tag for these futuristic machines is expected to top $10 million.

Participants in last month's workshop urged more funding for NMR, pointing out that so far it has been a poor cousin to the rival technique of x-ray crystallography. Through 1994, the United States spent $230 million to equip academic departments with NMR, compared with

* "High Field NMR: A New Millennium Resource," Washington, D.C., 15–16 January.

about $1 billion that the U.S. Department of Energy (DOE) has spent since 1988 to build just two of the premier U.S. x-ray synchrotron facilities and upgrade two others. Crystallography is often faster and better able to decipher bigger molecules, but NMR works on molecules in solution, a more natural state for biological molecules such as proteins. NMR researchers already solve nearly one-quarter of the 900 or so new protein structures completed each year, and the resolution of the new NMRs is expected to be nearly on a par with that of crystallographers, says Wemmer.

Even if new NMR funds materialize, however, "these very high field magnets are getting beyond the ability of individual institutions to acquire [them]," says Wright. And if the PNNL facility and another planned in Florida wind up being the only facilities constructed, "there's no way we'll satisfy all the people who want to use these machines," warns Ellis.

To soften the blow, Jack Crow, director of the National High Magnetic Field Laboratory in Tallahassee, Florida, and others have proposed that funding agencies set up regional centers to house the new machines, an idea that got a thumbs-up from meeting attendees such as Griffin. Researchers could use their own NMR machines to do preliminary work on molecular structures, then travel to regional centers to collect a relatively small amount of data to sharpen the resolution—a practice already used by crystallographers.

Such cooperation has occurred temporarily whenever manufacturers introduce a new line of cutting-edge NMRs, until bulk manufacturing pushes the price lower, says Griffin. But thanks to the high materials cost of the superconductors, next-generation machines are likely to stay pricey—and few in number—for an indefinite period. That will require extended cooperation both among researchers as well as the federal agencies that normally fund NMR research—DOE, NSF, and the National Institutes of Health.

"It's a cultural shift," says Griffin. He and others say that the new machines will transform the NMR community from a collection of independent researchers to a group that carefully reviews—and prioritizes—each other's research to vet access to the high-end machines. One option discussed at the meeting was to extend collaboration even further by wiring up next-generation NMR centers with high-speed data and Internet links. Researchers around the country would then send their samples to a regional lab, log onto the Net at a scheduled time, and run their experiments remotely. But before that shift takes place, say Eisenstein and other agency officials, it will be up to the NMR community to make the case that the change will be worth it.

–Robert F. Service

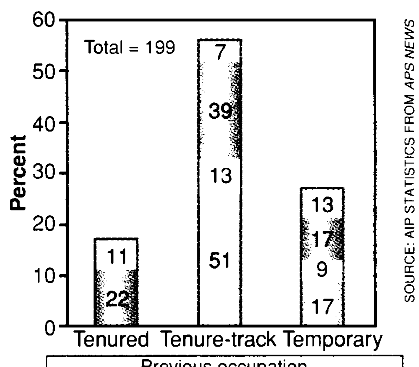
CAREERS

Young Physicists Despair of Tenured Jobs

Physics is the search for universal laws that stand the test of time. But for recent Ph.D.s in the United States, doing physics can be an endless search for a tenure-track faculty opening. Ever since a faltering economy and the end of the Cold War flooded the academic job market with physicists in the late 1980s and early '90s, the bad news about physics careers has kept coming. New studies suggest that in spite of jobs spawned by a resurgent economy, a minuscule percentage of young physicists can expect to move from a postdoc to a plum faculty job—and they are painfully aware of their poor prospects.

The American Institute of Physics (AIP) estimates that during the 1995–96 academic year, when 1438 new physics Ph.D.s were conferred in the United States, only about 50 postdocs—the next step up from a Ph.D.—moved on to tenure-track jobs in Ph.D.-granting physics departments. Although there's no comparable analysis of job movement for previous years, some observers are drawing an obvious conclusion. "The bottom line is that the job problem in physics is not over," says Sherrie Preische of the American Physical Society's (APS's) Executive Office. Because most of the new jobs have appeared in "nontraditional" areas such as engineering and finance, the APS is now boosting efforts to prepare new physicists for careers outside academia.

The AIP's jobs analysis* did reveal some encouraging signs. In 1996, for the first time since the early 1980s, more new Ph.D.s were hired into "potentially permanent" jobs than into postdocs. But most of those jobs were outside physics, in areas such as engineering and computer software. A young physicist seeking an academic post still faced crushing competition. About 400 temporary and permanent faculty jobs were filled in all degree-granting institutions over 1995–96—a figure that has remained "remarkably stable" for years, says Roman Czujko, manager of AIP's education and employment statistics division. But most of those jobs were filled not by postdocs or new Ph.D.s, but by more experienced physicists, often from industrial labs or other physics departments.



Experience counts. Senior physicists got most of the jobs that opened at Ph.D. granting institutions in 1995 to 1996.

The toll on young physicists' morale has been heavy, as Preische found in a separate survey, published along with the AIP's job numbers in the February *APS News*. Fully 70% of the 592 junior members of APS whom she sampled said that their peer group is "pessimistic with regard to career prospects," and 40% "would not advise someone to pursue a career in physics." Glen Crawford, a postdoc at the Stanford Linear Accelerator Center, says he wasn't surprised by these findings. During his physics education, he says, "there was the implicit assumption that you would always be doing physics research. So the prospect of not doing physics can be depressing."

Young physicists need to realize that their skills are much more likely to be exercised outside academia, says Roy Richter, a senior research scientist at General Motors Global R&D Operations and a member of the APS Committee on Careers and Professional Development. Indeed, the APS survey found that junior members who had already made the switch to industry were more content than postdocs were. "The Ph.D. is becoming more like a set of tools that you can then apply to other areas," says James Kakalios, a professor at the University of Minnesota who says his students have been particularly successful in finding work at small companies, such as those that make computer components.

"Physics departments should take note of where their graduates are finding their career paths," says Barrett Ripin of the APS, who helped form the careers committee. To educate departments about career alternatives, the committee is developing resources such as speakers and industry internships, and it plans to hold an open discussion of these programs during the spring APS meeting in Los Angeles next month. As Crawford says, all this might help students realize "that, hey, maybe you're not going to be a professor at Rattlesnake University. Maybe you'll be at Applied Materials."

–James Glanz

* See AIP's 1996 *Initial Employment Report* at http://www.aip.org/statistics/trends/trends.htm for numbers and links to further details.