

# US structural genomics effort needs physicists for success

An impending boom in structural genomics is placing increased demands on US synchrotrons — promising jobs for physicists willing to work with biologists in deciphering the three-dimensional shapes of thousands of proteins.

In the United States, the field is being catalysed by a five-year, \$150-million initiative by the National Institute of General Medical Sciences (NIGMS). This pilot programme is funding seven consortia to find the fastest and best ways to solve thousands of structures (see *Nature* 407, 549; 2000). If successful, NIGMS officials predict they could decipher between 10,000 and 30,000 structures in 10 years — representing most families of protein folds that exist in nature.

But for this ambitious experiment to succeed, structural biologists will have to rely on, and work with, physicists. This is especially true in the case of synchrotron light sources. These facilities produce intense, highly focused light that can be used to probe the atomic structure of proteins and other materials. Each synchrotron siphons off light produced by the high-speed particles into several ‘beamlines’, each of which can be equipped with different detectors to probe the properties of various materials. Synchrotrons are considered to be one of the best tools for deciphering protein structures.

At the moment, physicists are in demand for developing new facilities, staffing existing ones, and finding ways to automate many aspects of the protein structure discovery process. But there are only five national synchrotron light sources in the United States — less than half the number in Europe. And many US structural biologists and synchrotron staffers say there is not enough US synchrotron capacity to support existing work, much less the high volumes needed to make the kind of dent in the proteome the structural genomics initiative seeks. “There aren’t enough beamlines for it to grow fast enough,” says Bob Sweet, a structural biologist at Brookhaven National Laboratory’s National Synchrotron Light Source. “There’s a ceiling. We’re going to hit that ceiling in three to five years if we don’t get more beamlines.”

Although there are no solid proposals to build new synchrotron facilities in anticipation of a structural-biology boom, there are several plans at various stages of approval to add more beamlines devoted solely to structural biology. Those initiatives call for adding between 12 and 15 biology beamlines in the next five years to the 40 or so already dedicated to the discipline. If those beam-

lines get approval, several physicists will be needed to develop, and then staff, each of them.

Sweet suspects that adding beamlines to existing facilities may be a short-term fix at best. New facilities may be needed, but the decision will have to be made soon to proceed, as construction of a new synchrotron light source takes up to six years. “We must decide now what we need in six to ten years,” he says. “Otherwise we’ll be in the dark.”

Kevin D’Amico, who has about 20 years of synchrotron experience, now earns a living as a consultant on how to build beamlines devoted to biology. He is currently working with Structural GenomiX, a San Diego biotech company that is building its own beamline at Argonne National Laboratory’s Advanced Photon Source (APS).

D’Amico sees the niche for beamline developers as fairly narrow, with demands in the tens, rather than the hundreds. Qualifications include spending several years working at a synchrotron facility — the same qualifications needed for someone to run either a beamline or an entire facility.

## Staff shortage

Gerd Rosenbaum, director for the Southeastern Regional Collaborative Access Team at Argonne, agrees. “The demand will be greater for people to staff and operate beamlines,” says Rosenbaum, who is overseeing development of a new beamline at the APS. “We have a serious shortage of trained staff at all beamlines — not just the biological ones.”

Rosenbaum notes that the profession of X-ray crystallographer as a speciality in structural biology is dying out, as the tools for using X-rays to study protein structures are becoming easier for a wider community to use. But to make that tool effective, facilities need to attract and retain highly skilled, multidisciplinary teams of people. Teams that support crystallography are made up of structural biologists, computational experts and physicists.

All of these people must, of course, be well-versed in their own discipline, as well as able to communicate with their colleagues in other fields. For example, a physicist employed at a biology beamline must master the instrumentation associated with the experiments as well as understand the intricacies of scanning different kinds of proteins.

Having well-trained staff in place at each beamline will make the operation more efficient when outside users come in to do experiments, or when more users take the ‘Fed-X-ray crystallography’ approach. In



## Wages may make it hard to attract scientists to synchrotrons

Low salaries and high housing costs — this combination is making recruiting synchrotron staff difficult at some facilities in the United States and Britain.

Finding physicists and engineers to work at the Stanford Synchrotron Radiation Laboratory (SSRL) is an uphill battle because the university cannot offer wages that match those of companies in Silicon Valley, says Peter Kuhn, assistant professor at the SSRL. “You try to attract the best scientists and, at the same time, you’re competing with private industry.” That competition turns into a losing battle when potential staffers face the inflated value of real estate in Palo Alto.

The competition is further imbalanced when synchrotrons lack facilities. At the SSRL, beamlines are being added faster than offices can be constructed, so many staff are housed in trailers near the ring. Eventually, the SSRL will have the offices it needs, as the university builds the infrastructure needed to support its expanding interests in biology.

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▶ that approach, users mail in their samples, beamline staff generate the data, and the users analyse it remotely in real time, communicating with the synchrotron staff about whether or not more reads are necessary or if any adjustments need to be made.

Rosenbaum says institutional or cultural obstacles now make it difficult to attract and retain synchrotron staffers. Beamline operators, he says, are “consumed” by their users, and seldom work on their own projects. As a result, many find it hard to get first authorship on papers, making it difficult for them to earn the credentials necessary for a tenure-track position later in their careers. Without a stable staff, beamlines do not run as efficiently as they should, he says. Rosenbaum says the problem applies to synchrotrons throughout the world and extends beyond structural biology.

Sol Gruner, director of the Cornell High Energy Synchrotron Source (CHESS), says that his facility also has several openings.

Gruner notes that staff support at the facilities is more important than having the latest technology.

Although Gruner recruits computational specialists, structural biologists and physicists, he says the physicists—the people responsible for generating the light and seeing that it hits the sample—are the hardest to find.

That difficulty could reflect a general shortage of physicists in the United States. There are fewer physicists looking for work than biologists or chemists (see *Nature* 409, 445; 2001). The shortage may be especially pronounced at synchrotrons because qualified people must possess multidisciplinary skills. “You’re talking about a small group of people who are very much in demand for their versatile talents,” says Gruner. ■

Paul Smaglik is NatureJobs editor.

♦ <http://biosync.sdsc.edu>

♦ <http://www.nigms.nih.gov/funding/psi.html>

♦ <http://www.x12c.nsls.bnl.gov/StrGen.htm>

succeed, automating the whole process, from protein production to crystallization and data acquisition, will become crucial because of the large number of proteins.

Beyond increasing automation and hiring more people, Japanese synchrotrons could be improved by focusing more on service, several users say. There is widespread agreement that both existing and future synchrotron research facilities in Japan must spend more time reflecting the needs of their users and prioritizing beam-time allocation. Some facilities within Japan are well known for their lack of user support. And users from the biology community are increasingly demanding standardization of the equipment and ease of use.

Physicists such as Tsuneaki Miyahara, a professor in the department of physics at the Tokyo Metropolitan University, disagree, arguing that it is important to teach scientists how to improve instrumentation, rather than just how to use it. “Younger scientists generally do not want to go into the details of instrumentation, which might crucially impact on the future development of synchrotron radiation research in Japan,” says Miyahara.

But it is not just hardware specialists that are needed. Structural biologists spend most of their time on model development and verification, says Miyano. The software tools that are needed for this purpose are coming mostly from the United States. “Without a long-term strategy to develop adequate software capacities, the situation seems critical,” says Miyano. ■

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### Web links

SPring-8 ♦ <http://www.spring8.or.jp>

RIKEN Structural Genomics Initiative

♦ <http://www.rsgi.riken.go.jp>

KSR ♦ <http://www.wal.kuicr.kyoto-u.ac.jp>

KEK Photon Factory ♦ <http://www.kek.jp>

UVSOR ♦ <http://vsor-ntserver.ims.ac.jp>

HISOR ♦ <http://www.hsrc.hiroshima-u.ac.jp>

Ritsumeikan University SR Center

♦ <http://www.ritsumei.ac.jp/se/d11/index-e.html>

New Subaru

♦ <http://www.lasti.himeji-tech.ac.jp/NS/Index.html>

## Staffing shortage threatens Japan's structural genomics

Synchrotron radiation facilities in Japan are suffering from a chronic staff shortage. Despite considerable funding increases in some application areas—such as structural genomics and nanotechnology—demand for beamline specialists, experimentalists, technicians and specialized software engineers is outstripping supply.

The bold move a few years ago to put structural genomics at the top of the agenda of the newly established RIKEN Genomic Sciences Center in Yokohama caused a stir within Japan's genetics research community. Although critics of the new centre pointed out that more emphasis should be put on genome sequencing, the centre's designated director, Akiyoshi Wada, argued that focusing efforts on structural genomics would constitute a more viable strategy for a “late-comer” in the genomics field.

With SPring-8, the world's largest synchrotron radiation facility, opening its doors for research in October 1997 in Harima, the timing for a structural genomics initiative was well chosen. A third-generation synchrotron radiation facility in the hard X-ray range, SPring-8 was planned and constructed jointly by RIKEN and the Japan Atomic Energy Research Institute (JAERI).

RIKEN presently occupies two of the four beamlines dedicated to structural biology at SPring-8. Using ‘multiwavelength anomalous diffraction’ and a device called a trichromator, Japanese scientists have successfully tackled the structural basis of glutamate receptors in the central nervous system, and the structure of various proteins includ-

ing bovine rhodopsin.

Funding for structural genomics has been exploding in Japan over the past two years. But, according to insiders, virtually all synchrotron radiation facilities remain inadequately staffed and user support is limited. According to Masashi Miyano, who directs the structural biology group at RIKEN's Harima research centre, the number of beamline staff at SPring-8 is about one-third that of the staff at comparable facilities outside Japan.

Automation may eventually provide part of the answer—especially for ambitious projects in structural genomics. One initiative, headed by Seiki Kuramitsu, a professor in the graduate school of science at Osaka University, aims to elucidate the structure and function of all proteins in the extreme thermophile *Thermus thermophilus*. For this project to

## NMR versus synchrotron radiation

The completion of the world's largest nuclear magnetic resonance (NMR) facility at the campus of the RIKEN Genomic Sciences Center in Yokohama is an important step forward for Japan's structural genomics programme. NMR spectroscopy is a potential rival to synchrotron radiation in protein-structure analysis and, with RIKEN's new facility, Japanese scientists hope to play a key role in developing new instrumentation tools for structural genomics. Initially, the new facility will have 16 machines, and this number is expected to increase to 200 at its completion in 2002. Among others, the facility will host the world's most powerful NMR device.

Although some scientists are sceptical about whether NMR spectroscopy will ever replace crystallography as a research tool in structural biology, others argue that much could be done to improve NMR techniques, and that experimental performance could surge with the availability of new, more powerful instruments.

Yoshiyuki Yokoyama, who is responsible for RIKEN's structural genomics effort, believes that X-ray crystallography and NMR spectroscopy have their perspective advantages and that combining both techniques is likely to be the most beneficial strategy. “X-ray crystallography and NMR spectroscopy are complementary technologies,” he says. ■

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