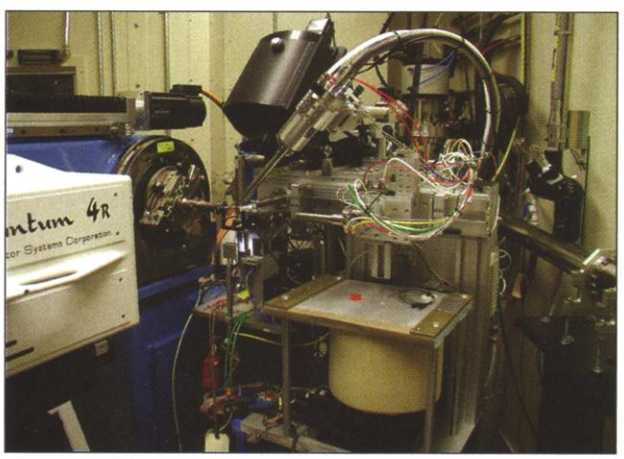
STRUCTURAL BIOLOGY

Robots Enter the Race To Analyze Proteins

BERKELEY, CALIFORNIA—Structural biologists are about to get a helping hand in their effort to map the three-dimensional arrangement of atoms in proteins. Earlier this week, researchers at the Advanced Light Source (ALS) here were scheduled to begin using a new robot to automate the laborious process of mounting protein crystals in a synchrotron's x-ray beamline and then collecting and analyzing the data. Once fully operational, the robot could boost the number of protein structures that can be solved at a beamline nearly 10-fold to about 1000 per year. A similar setup is also gearing up at the European Synchrotron Radiation Facility in Grenoble, France. With these and other robotic systems now on the drawing boards, the throughput of protein structures is poised to make a revolutionary jump.



Hands off. Robot crystallographer at the Advanced Light Source's new x-ray beamline promises to solve protein structures 10 times as fast as humans can.

"We would like it to be so automated, you could walk away from it for days or weeks at a time," says Thomas Earnest, who is overseeing the installation of the new robotic beamline at the ALS. The automation is needed, says Earnest, because the current speed of x-ray crystallography is a bottleneck for genomics programs trying to reveal the genetics, structure, and function behind each of the body's more than 30,000 proteins. If researchers are to have a hope of doing that anytime soon, they need to industrialize the process of solving protein structures, Earnest says.

Initially, however, the robotic beamline's primary mission will be to speed drug discovery. The beamline's $2.4 million price tag has been split between the San Diego biotech company Syrrx and the Genomics Institute of the Novartis Research Foundation (GNF) in La Jolla, California. Research teams at GNF led by chemists Ray Stevens and Peter Schultz have already automated earlier steps in the crystal-making process of purifying proteins from bacteria and coaxing them into crystals. With the robotic beamline now set to go on line, "we're finally seeing everything come together," Stevens says. Once complete, Syrrx and GNF plan to use the automated systems to look at the way hundreds of different small drug candidates bind inside the active sites of different proteins, information that they can then use to design better binding compounds, Stevens says.

High-throughput studies of a wider variety of proteins should be close behind. Like all ALS beamlines, the new facility will dole out 25% of its beam time to general users (Syrrx and GNF will get the other 75%), and Earnest says teams at several other synchrotrons have already started looking into duplicating the robotic beamline at their facilities. Some groups are working to automate not only sample handling and data collection, as at ALS, but also the work of creating the proteins, purifying them, growing crystals, and processing and analyzing the x-ray data. "To be successful in high-throughput crystallography, all the pieces have to work together," says Keith Hodgson, director of the Stanford Synchrotron Radiation Laboratory in Palo Alto, California.

Although the ALS robot can't do everything, it's an important piece, Hodgson says. It houses a liquid nitrogen–cooled Dewar loaded with 64 separate protein crystals ready for analysis. Researchers sitting at a terminal outside the experimental hutch simply type in the order of crystals they want to study. The robot selects the first crystal, removes it from the Dewar, mounts it, centers it in the beam, and fires brief test pulses to find the optimal alignment for collecting data. Then, depending on the quality of the crystal, either the software instructs the beamline instruments to collect a full set of x-ray data, by tracking how the beam of x-rays ricochets off repeating planes in the crystal, or it simply moves the machine on to the next crystal.

Eventually, Earnest says, the ALS team plans to incorporate additional software packages that then automatically process and analyze the data, spitting out final

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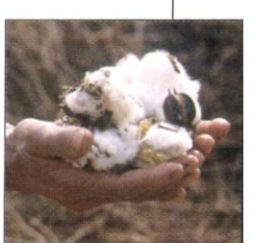
ScienceScope

Fishing for Change Fisheries scientists are bracing for what could be a stormy passage through Washington, D.C. Congress last week began work on renewing the Magnuson-Stevens Act, a 25-year-old law that aims to protect marine life from overfishing.

The law, however, has produced spotty results, experts told the House Resources Committee at a 4 April hearing. "For the fourth year in a row, the number of fish stocks that are [already] overfished, experiencing overfishing, or both has increased," noted Lee Crockett of the Marine Fish Conservation Network, which unites more than 100 science, environmental, and fishing groups. To reverse that trend, he and other advocates say Congress needs to strengthen the law—from improving habitat protection requirements to placing stricter limits on the killing of nontarget species.

Some fishing industry groups, however, say lawmakers should give existing rules—last updated in 1996—more time to work. Current law, they note, has already helped some fisheries, including New England cod and scallop populations, rebound from disaster. Expect to hear plenty from both sides over the next year, as Congress is likely to take its time weighing the arguments before acting.

GMOs Thai-ed Up Thailand has become the first Asian country to ban the release into the environment of genetically modified crops. The 3 April decision orders the agriculture ministry "to halt all genetically engineered crop field trials" and to set up a panel of scientists, farmers, and consumers to draft a biosafety law.



The action would halt ongoing field trials of Bt cotton by Monsanto, although a Bangkok spokesperson says that the government has not yet notified the company. First-year results of its Bollgard variety were "very promising," she added.

Jiragorn Gajaseni, head of Greenpeace's Southeast Asia office, hopes the decision will "encourage [other Asian countries] to follow suit." In 1999 the Thai government banned the import of genetically modified seeds for commercial cultivation but allowed imports for research purposes.

Contributors: Dennis Normile, Jeffrey Mervis, David Malakoff, Pallava Bagla

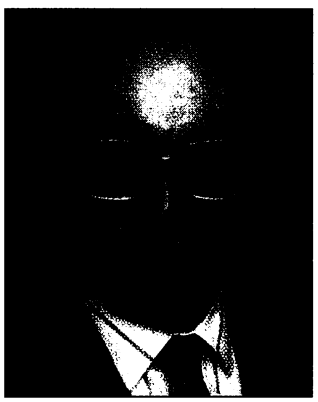
structure in the end. "The ultimate goal is crystals in, structures out," he says. He expects that it will be another 2 years before the full process is complete.

–ROBERT F. SERVICE

STRUCTURAL BIOLOGY

A Plan to Release Data Within Six Months

AIRLIE HOUSE, VIRGINIA—In the 1990s, gene sequencers were under the gun to make their raw data public as rapidly as possible. Now, it's the turn of the gem-cutters of biology—the people who decipher the shape of protein molecules—and some are not too comfortable with the notion. Last week, international leaders of the field rejected a proposal that labs now gearing up to roboticize the study of proteins give away structural coordinates immediately, or within 3 weeks of completion. Instead, at a meeting at an estate here in Virginia's horse country, they agreed to speed up data release, but on a timetable that will allow for the filing of patent applications.



Raising the pace. NIH's Marvin Cassman plans for accelerated data release from U.S. labs.

The plan for immediate data release was drafted at a meeting a year ago in Hinxton, U.K., home of the Wellcome Trust's genome center.* Many said it reflected the ideals of British scientists, who were among the leaders in pushing for rapid release of genome data. But several members of the Airlie group said the proposed short deadlines wouldn't allow enough time to refine and validate structural information. Others, noting that structural data may be valuable for drug design, argued frankly that too-rapid data release would impede patenting. In the end, the group endorsed the release of "most" protein structures from high-throughput labs "as rapidly as possible," with a maximum delay of 6 months for proteins of "special interest." Today, the rule is that investigators release coordinates when they publish a structure.

The strongest opposition to the Hinxton plan came from Japanese delegates, who said it can take many months to process proteins and prepare U.S. patent filings. Toichi Sakata, representing the agency that funds Japanese structural biology—the Ministry of Education, Culture, Sports, Science, and Technology—indicated that Japanese taxpayers want a return on investments in protein analysis in the form of intellectual property. The Japanese group proposed the 6-month limit.

Once the Japanese had spoken, senior European and U.S. scientists said they liked the 6-month delay, too. Udo Heinemann of the Max Delbrück Center for Molecular Medicine in Berlin saw a "fundamental difference" in the way structural genomics is carried out in Europe and the United States. He said his funding agency views his work as being closer to drug development than basic biology. Joel Janin of the Laboratory of Structural Enzymology and Biochemistry in Gif-sur-Yvette, France, felt that "the average European group's view is probably closer to the Japanese position" than the Hinxton model. And biophysicist Stephen Burley of the Rockefeller University in New York City said, "I'm not sure that there's agreement within U.S. groups" that protein structure data are commercially "precompetitive."

A minority objected to the 6-month rule but didn't dissent. "This is a complete reversal" of earlier goals, said Cyrus Chothia, a theoretician of structural biology at the Medical Research Council Laboratory of Molecular Biology in Cambridge, U.K. He chided his colleagues for what he saw as a retreat from data sharing. One meeting organizer detected signs of gambler's fever in the patent discussion: "It reminds me of the lottery," he said. "Very few people will win, but everyone dreams they will."

Participants did agree, however, to increase data sharing and avoid duplication by exchanging lists of "target" proteins in advance. And they outlined a new system of fast peer review and electronic publication, bypassing paper journals to get results out quickly. But they declined to adopt a plan advanced by the U.S. National Institute of General Medical Sciences (NIGMS), part of the National Institutes of Health (NIH), to create a central, public Web site at NIH listing targets claimed by each lab. NIH will do this for its own grantees. One group that specifically opposed listing its own targets is a private consortium led by the Wellcome Trust, which is recruiting about 10 company sponsors for a program to solve and publish 200 protein structures per year (*Science*, 30 March, p. 2531). A trust attorney explained that the companies do not want to tip competitors to potential research plans, but are willing to give away structures once they've been completed.

NIGMS director Marvin Cassman ascribes the difference between the Hinxton and Airlie meetings to the fact that "last year, structural genomics was pie in the sky; this year, the pie is on the plate," and everyone is looking for a slice. NIGMS is leading the effort to speed up protein analysis, having awarded $150 million in structural genomics grants to seven centers last year (*Science*, 29 September 2000, p. 2254). The centers funded under this program are likely to be held to more rigorous data-release standards than the rules adopted at Airlie, Cassman said. NIGMS official John Norvell explained that relatively few families of proteins are represented in the public databases at present, and NIGMS is pushing its centers to identify new proteins at the rate of about 200 per year by 2006. –ELIOT MARSHALL

ASTROPHYSICS

Galaxy Mappers Detect Wiggly Cosmic Order

BALTIMORE, MARYLAND—A wiggly pattern in the way galaxies are arrayed has yielded a new recipe for the early universe. Last week, at meetings on both sides of the Atlantic Ocean,* astronomers working on the ambitious Two Degree Field (2dF) galaxy survey announced that they had seen subtle variations in the distribution of matter at different scales. The discovery provides a new method of calculating the amounts of different types of matter in the cosmos shortly after the big bang.

"That would be extremely exciting if they've seen it," says Max Tegmark, a physicist at the University of Pennsylvania in Philadelphia. Knowing the ratio of ordinary "baryonic" matter to unseen dark matter in the universe is key to deciding among competing cosmological models, Tegmark says.

Deep space. Galactic voids and clusters mapped by the Two Degree Field survey trace ripples from the big bang.

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The 2dF survey, which uses the 4-meter

* The First International Structural Genomics Meeting took place in Hinxton, U.K., in April 2000; the second, at Airlie House near Warrenton, Virginia, 4 to 6 April, 2001. The third will be in Berlin.

* "The Dark Universe," Baltimore, Maryland, 2–5 April; Royal Astronomical Society National Astronomy Meeting, Cambridge, United Kingdom, 2–6 April.