TURNING POINT Insight into decision-making helps neuroscientist advise on policy **p.713**

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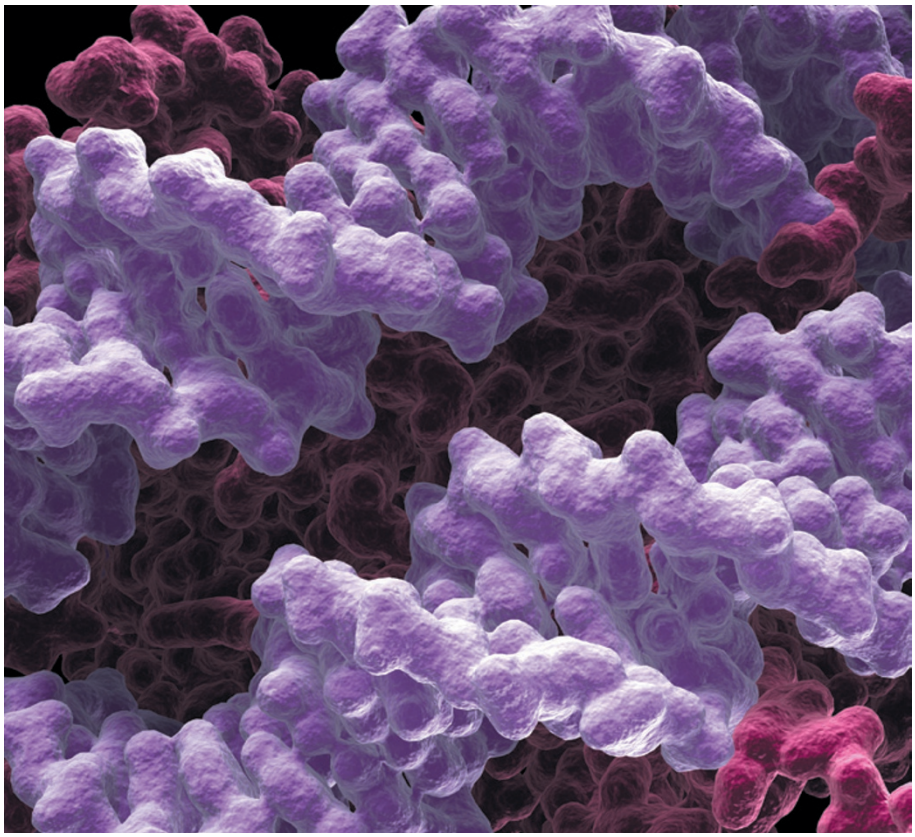


A digital model of a nucleosome, drawn with the use of X-ray crystallography data.

STRUCTURAL BIOLOGY

More than a crystallographer

Researchers trained in X-ray crystallography are still in demand, but must diversify their skill sets to be competitive.

BY LAURA CASSIDAY

Karolin Luger was bitten by the crystallography bug during a biophysics lecture in 1986. "One person gave a talk on X-ray crystallography," she recalls. "The lecture was not that good, but the diffraction patterns were so beautiful that I thought, 'I really want to learn how to do this.'" She learned. As a postdoc, she was first author of a paper that reported the crystal structure of a DNA–protein complex called the nucleosome (see K. Luger *et al. Nature* **389,** 251–260; 1997).

Now a Howard Hughes Medical Institute investigator at Colorado State University in Fort Collins, Luger still uses X-ray crystallography to study chromatin, the DNA–protein complex that packages genomes tightly inside cells. But like most in her field in recent years, she has expanded her toolkit to include other methods.

Twenty years ago, many academic labs existed just for X-ray crystallography. Collaborators would send in samples of their molecules of interest, and labs would crystallize them and solve their structures. Nowadays, labs are much more focused on specific scientific questions, and X-ray crystallography is just one of a suite of tools that they use. Technology has improved so much that the procedure is usually no longer a full-time scientific pursuit. As 'pure' crystallography jobs dwindle, people who are trained in the technique must broaden their expertise to encompass skills such as protein expression and purification, biochemical assays and cell biology.

In fact, many crystallographers now refer to themselves as structural biologists, reflecting the variety of techniques that they use to probe molecular structure. They may have PhDs in biophysics, biochemistry, bioinformatics or computational biology, and find work in academia or industry. But they are united by a desire to 'see' the invisible molecules that make up cells. Those structures, often breathtaking in their beauty and intricacy, provide important clues about functions or sites that might serve as drug targets.

CRYSTALLIZING THE HISTORY

X-ray crystallography has been around for about a century, since scientists realized that atoms in a crystal could diffract X-rays, producing a pattern of spots on a detector. The angles and intensities of the diffracted beams reveal the structure of molecules.

Until recent decades, only specialists with years of training and expensive equipment could perform X-ray crystallography. But in the 1990s, the technique became much more accessible. As synchrotrons — large, ring-shaped particle accelerators that produce powerful X-rays — spread across the globe, researchers could take or send their crystals to the synchrotron facilities, where resident experts guided them in collecting data and interpreting results. The automation of crystallization, improvements in methods for solving structures and a boost in computing power greatly sped up the process, giving researchers time for other scientific pursuits.

Increased competition for research grants also forced crystallography labs to become ▶

more well rounded. Instead of just solving one structure after another, researchers must now link the structure of a molecule to its function through biochemistry and cell-biology experiments. "It's no longer enough to conjecture about the function of a particular protein. You have to test it," says Wayne Hendrickson, who specializes in biochemistry and molecular biophysics at Columbia University in New York.

The story of major crystallography projects such as the Protein Structure Initiative (PSI), supported by the US National Institute of General Medical Sciences (NIGMS), encapsulates the evolution of the field. The PSI has solved more than 5,300 distinct protein structures and spurred innovations in crystallographic methods. Last year, however, NIGMS director Jon Lorsch, acting on the counsel of an advisory panel, decided that the project had run its course, and it will terminate on 30 June 2015 (see *Nature* **503,** 173–174; 2013).

Critics argued that many of the structures that the PSI has solved have little relevance to important biological and medical problems, and that PSI scientists did not adequately poll the biological community to select interesting targets. In addition, such 'big science' programmes consume precious funds that, in the minds of some, would be better spent on individual researcher grants.

Despite the PSI's closure, Hendrickson, whose lab specializes in membrane proteins and was part of the initiative, says that it is too early to gauge the impact on crystallography job prospects. "It will depend on whether PSI centres like ours are able to gain alternative means of support to keep things going," he says. His centre, the New York Consortium on Membrane Protein Structure, is applying to other research organizations and foundations for grants.

TRIAL AND ERROR

Crystallography work increasingly requires a good scientific question rather than just solving structures — something Sheena D'Arcy knows well. As a graduate student, she worked in a crystallography-only lab. "For my postdoc, I wanted a lab that was a bit more driven by scientific questions," she says. She is now working with Luger, using crystallography — and other methods — to study how DNA is packaged into chromatin.

Early in her postdoc, D'Arcy recognized the value of approaching a problem with multiple techniques. She wanted to obtain a crystal structure of nucleosome assembly protein 1 (Nap1), which helps to package DNA in the cell. But she could not get the protein complex to crystallize. And so, while still working on crystallization on the side, she tried an alternative technique — hydrogen–deuterium exchange mass spectrometry. That provided important insights into the structure, and D'Arcy published a paper on it (S. D'Arcy *et al. Mol. Cell* **51,** 662–677; 2013). She says that anyone who is interested in structural biology should consider learning this technique, as well as nuclear magnetic resonance (NMR) spectroscopy.

FRESH APPROACHES

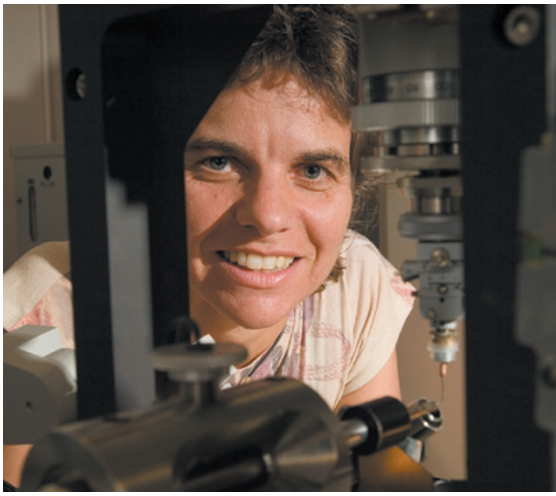
Now that synchrotrons are widespread, crystallography labs no longer need their own expensive X-ray facilities. Luger's lab does retain an X-ray generator for quickly screening crystals and training students; the device is powerful enough to collect publication-quality data from well-ordered crystals that diffract well, but non-ideal crystals or those that are quickly degraded by X-rays are sent to a synchrotron, says D'Arcy. The team has access to a beamline — a path of X-rays coming off the accelerator — at the Advanced Light Source synchrotron at Lawrence Berkeley National Laboratory in Berkeley, California.

The crystallography purist who prefers not to dabble in other techniques might consider a career as a beamline scientist, loading crystals for researchers and overseeing them as they collect data. As well as permanent positions, many synchrotrons offer training programmes in crystallography. They also offer summer programmes and internships for students, postdocs and other researchers who want to learn the technique but lack their own X-ray facilities.

The European Synchrotron Radiation Facility (ESRF) in Grenoble, France, offers a six-week Summer Bachelor Programme for undergraduates, which includes lectures, tutorials, lab work and site visits. The Cheiron School at the SPring-8 synchrotron in Harima, Japan, has ten-day training sessions for graduate students, postdocs and young scientists who wish to pursue careers in fields that involve synchrotron radiation. And the Advanced Photon Source in Argonne, Illinois, presents an annual two-week National School on Neutron and X-ray Scattering, in which graduate students attend lectures and tutorials and conduct short experiments.

"Taking the time to sit down and teach yourself the theory and computer programs is going to pay in the long run."
Sheena D'Arcy

Alexei Bosak began working at the ESRF as a postdoc and is now a beamline scientist. His duties are split between his own research interests in materials science (he has beam time reserved for his own experiments) and the research of ESRF users. "The people come, and we have to make them happy running the experiments," Bosak says. "Sometimes we are less involved, and sometimes we are more involved. But quite frequently a collaboration results."



Karolin Luger, a researcher in X-ray crystallography.

JOHN EISELE, COLORADO STATE UNIVERSITY

NEXT GENERATION

Structural biologists are developing methods to expand the capabilities of conventional X-ray crystallography, with potential implications for future practitioners. In November 2013, the US National Science Foundation (NSF) awarded a US$25-million Science and Technology Center Grant to the University at Buffalo in New York and seven partner institutions to fund the BioXFEL research centre. The centre will further the use of recently developed tools called X-ray free-electron lasers (XFELs) that produce much shorter and more intense pulses of X-rays than synchrotrons (see page 604).

According to Eaton Lattman, a structural biologist at Buffalo and director of the BioXFEL, XFELs can analyse crystals that are 1,000 times smaller than those required for conventional X-ray crystallography. "This opens up a whole new universe of protein molecules for crystallography that we couldn't do before because we couldn't grow big enough crystals," he says. The intense X-ray pulses can also capture frozen images of molecular motion, opening the door for dynamic studies and molecular movies.

The BioXFEL centre will make use of an existing facility at the SLAC National Accelerator Laboratory in Menlo Park, California, among other facilities. A smaller XFEL facility began operating in Harima, near the SPring-8 synchrotron, in 2011. And a larger one is scheduled to open in Hamburg, Germany, in 2015.

Lattman anticipates that the NSF grant will result in a "modest number" of new jobs at member institutions. "Right now, we're really limited by the amount of beam time that is available," he says. "If we start to see more countries around the world building XFEL facilities, then I think we'll see growth in the field comparable to what we saw for traditional crystallography in the 1990s." For now, the field of XFELs

needs technical improvements, such as better data-processing software and specimen delivery systems.

EXPERTS NEEDED

Ironically, the very diversification in skills now required to obtain an academic job has arguably turned many structural biologists into jacks of all trades, masters of none. Today's researchers are accustomed to sending crystals to synchrotrons for analysis, and computer programs perform the analytical work. "To solve a straightforward structure, you really don't have to understand the theory and the maths, and that's a bit of a pity," says Luger. "I'm a little worried that we're running out of people who know how to handle problems or complex situations."

Bosak notes that positions related to crystallography are frequently available at ESRF, and that they are hard to fill. "It's very difficult to find a good crystallographer these days," he says. Beamline scientists must have a thorough understanding of crystallography theory and instrumentation, skills that many modern training programmes do not emphasize. This means that a crystallographer with the right skill set can find that he or she is in demand.

There is also a growing list of contract companies that specialize in crystallography. Firms such as Proteros Biostructures in Planegg, Germany; Shanghai Medicilon in China; and Emerald Bio in Bedford, Massachusetts, provide full-service crystallography to clients, many of which are pharmaceutical companies. The firms employ scientists at bachelor's, master's and PhD levels to carry out all steps of crystallography, from protein design to structural analysis. But pharmaceutical companies such as Merck, based in Whitehouse Station, New Jersey, and Novartis, based in Basel, Switzerland, still have their own crystallography programmes centred on structure-based rational drug design, which also employ scientists at all levels. These companies are potentially a better fit for those who wish to focus on a specific protein or biological process rather than a plethora of them.

D'Arcy advises students with an interest in X-ray crystallography to take the time to learn its theoretical underpinnings and all the techniques involved. "Don't let people do things for you," she says. "There are a lot of senior people who know how to do things, and there's always a time crunch to get data — you get crystals, and you just want to see the structure. Taking the time to sit down and teach yourself the theory and computer programs is going to pay in the long run — because you really learn when things go wrong." ■

Laura Cassiday *is a freelance writer based in Hudson, Colorado.*

TURNING POINT
Nicholas Wright

As a student, Nicholas Wright pursued interests in biology and public policy, securing four degrees and a fellowship in the department of government at the London School of Economics (LSE). He now uses his neuroscience training and insights into human decision-making to inform nuclear-security policy as a fellow at the Carnegie Endowment for International Peace in Washington DC.

CARNEGIE ENDOWMENT FOR INTERNATIONAL PEACE

Did you always have dual interests?
Yes. I went straight to medical school at University College London (UCL), but I also did a year at Imperial College London studying health policy and management, which proved a turning point. While there, I did research in Chile on how best to incorporate scientific findings into clinical medicine. I learned that, to be effective, public policy must always take cultural and organizational factors into account; and I learned how best to ask questions so that they are relevant to public policy.

How did you combine your interests?
At the end of my medical degree, I went to a series of lectures by economist Richard Layard from the LSE, who talked about what neuroscience might be able to tell us about economic and social decision-making. I read up on neuroscience and decided to do a master's degree. My research into functional magnetic resonance imaging (fMRI) dispelled the hypothesis that only one area of the brain specializes in reading. The technique surpassed my expectations and proved itself to be a new source of information that could be relevant to public policy.

How did you delve into decision-making?
It wasn't by chance. After my postgraduate medical exams, I did a PhD project to study how risk perception influences decision-making, hoping to apply the concepts to issues of public policy. I worked with the Wellcome Trust Centre for Neuroimaging at UCL and stayed on as a fellow doing fMRI after I finished my PhD.

How did you position yourself for a policy job?
During a year-long fellowship at the LSE, I built up my contacts, planned events with policy-makers and created a narrative about my experience. Several policy-oriented job opportunities in Washington DC came up, but a position at the Carnegie Endowment for International Peace was most exciting.

What appealed to you about that post?
There was a lot of great work done in the 1970s on applying decision-making and cognitive psychology to nuclear strategy, but much less had been done recently. The ideas coming out of neuroeconomics hadn't yet been applied to international relations, so there was enormous potential for doing interesting work that could have a positive impact on the world.

Has your work had real-world impact?
In January, a colleague and I published an article called 'The neuroscience guide to negotiations with Iran' in *The Atlantic*. We combined insights from neuroscience, behaviour and history to better understand Iranian motives in the ongoing nuclear talks. For example, conciliatory gestures are more effective when they're unexpected. Neuroimaging experiments detail how the brain computes the difference between what is expected and what actually happens, and the more surprising the reward or punishment, the more impact it has on decision-making. Last year, Iranian President Hassan Rouhani unexpectedly used social media to engage on political issues, raising hopes for a diplomatic breakthrough. We argued that neuroscience provides a new, important source of evidence relevant to nuclear talks with Iran. Our article was read by US and UK defence policy-makers, and I have been asked to continue providing briefs to the US Department of Defense.

Do policy-makers value a science background?
In the world of public policy, there are so many competing priorities that there is a limit to how much science can be used. Winston Churchill once said that scientists "should be on tap, but not on top". Although science is not the only consideration, I am on tap to provide it. ■

INTERVIEW BY VIRGINIA GEWIN