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IMAGING:

X-ray Crystallography Without Crystals

Robert F. Service

For much of his career, David Sayre has been seeing spots and doing everything he can to get rid of them. Sayre, an x-ray crystallographer now retired from IBM, makes images of materials using x-rays, which can reveal fine detail down to the arrangement of atoms in a molecule. But this ultrahigh-resolution imaging technique only works on crystals, in which many copies of a molecule are lined up in a regular array. When x-rays are targeted at such a crystal, they bounce off the atoms and interact to produce a set of diffraction spots, which researchers can mathematically reconstruct into an image of the molecule. Now Sayre and colleagues in the United States and the United Kingdom have done away with the need to form molecules into a crystal and diffract x-rays into spots. In this week's issue of *Nature* they report creating the first diffraction image from a noncrystalline sample, a feat that could revolutionize the imaging of the vast array of materials that cannot be crystallized, providing ultrahigh-resolution images of everything from cells to individual protein molecules.

"It's really a brilliant experimental achievement," says Eaton Lattman, an x-ray crystallographer at The Johns Hopkins University in Baltimore. Sayre and his colleagues--Jianwei Miao and Janos Kirz at the State University of New York (SUNY), Stony Brook, and Pambos Charalambous at Kings College in London--used their new technique to produce images of an array of tiny gold dots with a resolution of 75 nanometers. That doesn't match the resolution available from crystalline samples, which can be hundreds of times finer, but it's already better than the best optical microscopes. And Miao told *Science* the team has already improved the resolution to about 65 nanometers and expects to do considerably better.

The technique is an outgrowth of conventional x-ray diffraction, which requires knowing two properties of the diffracted x-rays to make an image. The first is the intensity of the diffraction spots--easily determined with a photon counter. The second property is the relative timing of the waveforms of the x-rays, known as their phase. Figuring out the phase is more troublesome, traditionally requiring researchers to compare the diffraction pattern from a pure crystal with one from a similar crystal in which heavy metal atoms substitute for some components of the crystal. The signals from the metal atoms provide reference points from which

the phase of the other x-rays can be worked out.

That's all well and good for working with orderly crystals. But with noncrystalline samples, x-rays don't produce the clear diffraction patterns studded with sharp and isolated spots. Instead, they generate splotchy patterns. The key is that in these splotches, the intensity varies smoothly from one pixel in the diffraction image to the next in a manner related to the phase. In the early 1980s, other researchers suggested that it might be possible to use that information to work out the phase of x-rays diffracted from such samples. So, the SUNY-Kings College team created an algorithm that is designed to extract an image from this fuzzy diffraction data by first making a wild guess, assessing its accuracy, making adjustments, and then repeatedly trying again.

The program starts with the intensity data in the splotchy diffraction pattern and combines this with random phase information generated by the computer to churn out an approximate image of the target responsible for the diffraction. It then adjusts this image by comparing it to a set of known mathematical constraints. Next, it reconverts the revised image back into the corresponding diffraction intensity data and phase information. It combines the new phase information with the original intensity data to generate a new picture. Repeating this cycle about 1000 times, the computer homes in on a final image.

The new algorithm is designed to work with low-energy, "soft" x-rays, which are ideal for imaging biological materials. Such samples vary greatly in the amount of soft x-ray photons they diffract at different wavelengths, says Ian Robinson, a physicist at the University of Illinois, Urbana-Champaign. So, researchers should be able to create high-resolution, high-contrast composite images of cells by combining separate images taken at different soft x-ray wavelengths, he says. Down the road, adds Louise Johnson, a biochemist at Oxford University, the technique could make it possible to image single protein molecules, eliminating the need to crystallize them first, often a major hurdle for protein crystallographers. But generating enough diffraction data from a single molecule will require new x-ray sources billions of times brighter than today's.

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