Scientists

Definitive answers

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Wayne Hendrickson's development of technologies for protein structure determination and his work in the field of x-ray crystallography caught our attention. Curious to know more, *BioTechniques* contacted him to find out about the ambition, character, and motivation that led to his success.

How did you first become interested in crystallography?

While rotating through six biophysics labs as a graduate student at Johns Hopkins University, I became fascinated with solving crystallography puzzles and the definitive character of the answers. With crystallography, you determine the precise location of each atom and I found great sport in the mathematics required; it really seemed like a good home for me.

What led you to focus on technology development?

As a graduate student, I tinkered with one approach to resolving small molecule structures that was being developed by Jerome Karle and Herbert Hauptman at the Naval Research Laboratory in Washington DC. I began postdoctoral studies with Jerry Karle with the idea that we might be able to apply this technique – then being used to resolve small molecule structures such as crystals of organic compounds and small drug-like compounds – to biological studies. I did a number of tests that were disappointing and eventually came to understand theoretically why this wouldn't work. But this caused me to think of other ways to solve this problem, which led to an interest in anomalous scattering and resonance effects.

What has been your most important contribution to your field so far?

We developed a technology called multi-wavelength anomalous diffraction (MAD) phasing for solving the crystal structures of proteins using resonant effects of atoms. This technology takes advantage of the special scattering that occurs when the x-ray energy is near a particular electronic orbital, and it requires an x-ray source that can be readily tuned through a spectrum of possible wavelengths. At the time, commonly used sources emitted characteristic radiations at a single wavelength, but synchrotrons presented the possibility of using a spectrum.

We also devised a method to prepare selenomethionyl proteins, using incorporation by bacteria or other systems. We are able to detect the selenium positions in a protein crystal, which shows us the location of the methionines. From dozens of those selenium centers, we can locate thousands of atoms that make up the protein molecules in the crystal. This is a very effective technique and is now the dominant method for analyzing crystals.

How do you approach technology development?

We develop methods that apply to problems at the forefront of interest or activity, which makes life interesting for me because we end up working on very significant molecular biology questions. The importance of our technology is felt by the people in the field of crystallography, but the impact of the application of these technologies can be even more profound.

For example, in 1984, I moved from the Naval Research Laboratory to Columbia University, which was a pivotal change because it brought me back into biology from a more physics and mathematics aligned environment. HIV was just emerging at the time and people were beginning to understand that it was caused by a virus. One of the important steps forward in HIV research was Richard Axel's discovery of the first known receptor for the virus, CD4. That evolved coincidentally with our development of MAD,

and we began working out many crystal structures, including CD4 binding to the viral envelope glycoprotein, gp120.

What are your current goals?

We work on membrane receptors, including ion channels, and the molecules that signal through them. We are also working on molecular chaperones that assist in protein folding and have a growing interest in misfolding diseases such as Huntingtons. And we are also developing ways to approach proteins without labeling; instead of using selenomethionine, we now look directly at the sulfur atoms in methionine as a first step towards solving structures. In addition, I'm also working at Brookhaven National Laboratory to build a new synchrotron facility, National Synchrotron Light Source II. This facility will produce x-ray beams with more photons per unit area than ever before, and that can be focused down to nanometer levels. There are diverse applications for such beams; for biology, we expect to avoid x-ray damage when looking at very small crystals.

What do you think is the most important open question in the field of crystallography right now?

I would say that the most important issue remaining is to model the movement of a protein. Crystallography gives static pictures. We can learn about protein dynamics using NMR or FRET, but what we would really like to know is the time course of the structural conversion of each part of the protein while it's undergoing a chemical reaction. To model that faithfully, we need computational techniques that can bridge the gap between static images and dynamic functions, as well as multiple crystals that accurately depict the appropriate steps along the path.

Interviewed by Kristie Nybo, Ph.D. Image courtesy of Brian Soda.

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