SC-XRD

Interview with Manfred Weiss,
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[BAXS] – Hello and thank you for the opportunity to have this conversation with us. First of all, we would like to know how you started your career and your interest in crystallography.

[MW] – My career in crystallography began at the University of Freiburg im Breisgau, in Germany. I was a chemistry student and when I was looking for a diploma thesis, I was offered the chance to work on the crystal structure analysis of porin, a pore-forming membrane protein. At that time, only one membrane protein structure, that of the photosynthetic reaction center was known.

I find the prospect of "seeing" such large molecules atom by atom uniquely exciting. Also, that nature builds up such large molecules, and that they fold themselves, many of them without the need of helper proteins, into their final 3D structure… it's really fascinating.

The porin structure is the one I am most proud of. Further on, there were several difficult ones. Sometimes there was just a tiny part of the structure, e.g. identifying a sodium in the structure of elastase, which everybody had assumed it was a calcium. DapD from M. tuberculosis was another case like this one because we had all the wrong assumptions about it.

I've worked on more than 1,200 structures. Many of them are from screening campaigns and were automatically refined, around 100 were solved by own hands.

[BAXS] - How is the role of X-ray crystallography changing with the emergence of alternative methods in the field of structural biology? How do you see its contribution changing in the future?

[MW] – X-ray crystallography is still the dominant method for structure determination. In the field of macromolecular crystallography, its role has changed, however, mostly due to the advent of the computer program Alphafold2. The software is able to predict the three-dimensional structure of a protein from its amino acid sequence. This essentially takes care of the problem of determining the protein fold. What Alphafold2 cannot do is to define the structure to experimental accuracy. This is still left for the experiment. This level of detail is needed for all questions pertaining to function, or for structure-based drug discovery.

The MX projects submitted to my beamlines are shifting more towards high-resolution chemical biology, with fewer large complexes at moderate resolution. The large complexes will be tackled by cryo-EM.

[BAXS] – What are the challenges you and your team face in your research?

[MW] – For most proteins, the biggest difficulty is still obtaining large and well-diffracting crystals. In particular, now, since the paradigm is shifting from the one crystal – one data set – one structure to many crystals – many data sets – structure plus function and/or dynamics, it is of increasing importance to have good control over the crystallization step.

Having access to a diffractometer in the crystallization lab is important in achieving better control over crystal treatment. Most people throw their crystals into glycerol. Many crystals don't like this. Having the chance to try out 20 different cryo-protectants will enhance the success at the synchrotron dramatically. People very commonly measure crystals that could be improved. Unfortunately, they don't realize this until much later.

[BAXS] – Only a few decades ago, it was unthinkable to have structures solved as quickly as they are today without the need for extensive calculations then made by the scientists themselves. With the continuous progress of artificial intelligence, software, and hardware, users benefit from better and better automation processes. How do you see the role of crystallographers in the context of future technological developments?

[MW] – For years to come, the experiment will beat any calculation or prediction in terms of detail and accuracy. Consequently, there will still be the need for experimental structure determination.

Looking at the "many crystals – many data set – structure plus function and/or dynamics" approach, if data collection in home labs is down to minutes, home labs could be used as data production facilities. Just like with cars, home diffractometers are probably idle 23 out of 24 hours. There is a lot of potential there. It needs automation at every step, a sample reservoir large enough to host enough samples for a night, a weekend or even longer.

[BAXS] – If you could make Bruker a request, what would it be? And one piece of advice?

[MW] – Keep building good X-ray devices and making it easy for the user to use them well.