Studying the molecules of life in their natural environment

Jan Pieter Abrahams has a vision for his research in Basel and at the PSI

Since May 2015, the Swiss Nanoscience Institute (SNI) has been sponsoring another professor, who is teaching at Basel University and carrying out research both in Basel and at the Paul Scherrer Institute (PSI). Professor Jan Pieter Abrahams moved to Northwestern Switzerland from the University of Leiden in May 2015. The things that impress him here are the collegiate environment, the availability of first-rate microscopes, and the long-term research strategies in place at his new workplaces in Basel and Villigen. The goal of his research is to analyze the 3D structure of molecules in their natural environment. In pursuit of this challenge, he has already secured funding for an Argovia project and a doctoral position within the SNI's PhD School.

Analyzing molecular structure in situ is key

Large molecules such as proteins are of vital importance to our cells. They are responsible for basic processes like transporting oxygen and fending off pathogens. They play an important role in metabolism and movement and give cells their structure. The 3D structure of proteins is critical to how they function, but it is not yet possible to examine these highly complex forms in their natural environment. The methods available to us today require time-consuming preparation of samples, which can affect protein structure. Until now, the 3D structure of proteins has often been analyzed when they are in crystal form, but in their natural environment in the cells proteins do not normally crystallize. In the cells, most proteins work in tandem with a number of other proteins. It is therefore difficult to arrive at a full understanding of their biological activity if we study them only as isolated molecules.

Developing a new method step by step

Jan Pieter Abrahams's goal is to find a way of analyzing the molecular and atomic structure of proteins and other large molecules without influencing or changing them significantly. He sums up his vision as follows: "I want to look at the molecules of life in atomic detail in their natural state and environment, to gain a better

understanding of how they function and interact." Although there is still no suitable way of doing that, at the University of Basel and the PSI Jan Pieter Abrahams will have the ideal conditions to develop a new method, and the devices that requires, step by step.

Electrons less damaging than light and X-rays

For the time being, Abrahams and his team are continuing to work with protein crystals. Only when they are able to examine the structure of those molecules without difficulty will they move on to natural samples. The researchers are using electron beams to analyze the samples, as these inflict far less damage than X-rays, and visible light is unsuitable. However, they are not using the high-energy electrons to generate images, as with a traditional electron microscope; instead, they are looking at the electron diffraction produced by the sample. This happens because electrons possess wave properties and behave in a similar way to light waves when they hit an obstacle. Using this technique to examine molecules produces a specific diffraction pattern from which the arrangement of atoms in the sample can be inferred. As it requires only one hundredth the number of electrons needed to produce an electron image, it is also much less damaging to the sample. To carry out these analyses, Jan Pieter Abrahams has at his disposal the superb electron microscopes at the Biozentrum's Center for Cellular Imaging and NanoAnalytics (C-CINA), which enable him to examine a sample hundreds of times without damaging it significantly. He is currently still grappling with the problem that the intensity distribution of the diffracted electron wave can be determined, but not its phase. However, he and his team have already found solutions, which they are in the course of publishing.

Developing a better detector through the Nano-Argovia program

If electron diffraction is to be used successfully to analyze big molecules, better detectors will need to be developed. On January 1, 2016, Abrahams and Tim Grüne of the Paul Scherrer Institute launched an Argovia project to do just that. Working alongside colleagues from C-CINA, the PSI and the Swiss firm Dectris, the team will seek to modify a detector developed by Dectris and incorporate it within an electron microscope. Abrahams hopes that this new detector will provide better resolution, allowing the atomic and molecular structure of proteins to be determined more accurately.

New microscope using structured electron waves

For Abrahams, the next step is to develop an entirely new microscope. This will not be able to take images of the sample, like a traditional electron microscope, but will be used solely to analyze electron beam diffraction. Abrahams says of his plans, "This microscope will be less complicated but will produce more precise data for our purposes." In pursuit of this goal, he and Dr Soichiro Tsujino (PSI) have secured funding for a doctoral project at the SNI's PhD school, to be launched in 2016. The aim of the project is to develop a programmable device to produce an electron beam that is no longer generated as a simple wave but already has its own structure. The electron diffraction undergone by a simple wave differs from that undergone by a structured wave, providing scientists with additional information about the arrangement of atoms within the molecule. Commenting on the timescale for the project, Abrahams notes, "I think that in one or two years we will be able to show that the concept works in principle. It will take us longer to make the new microscope a reality."

Off to a good start in Switzerland

Jan Pieter Abrahams only started work at the University of Basel's Biozentrum in May 2015 and has been head of the Laboratory of Biomolecular Research at the PSI since January 2016. However, he has already settled in well and has already launched two SNI projects. When asked about his experiences over the few months, he replies, "I am impressed by the superb facilities here and the way in which colleagues work together across departments. The academic environment in Basel and at the PSI is fantastic. I am really pleased to see the long-term investment that is being made in research here and the links that are being forged between basic sciences and engineering sciences, between biology and physics and the latest technology, to drive research forward."