Protein machines at work visualized in real time

The dynamic nature of individual proteins that interact with each other and with nucleic acid molecules can be studied in real time using powerful single-molecule microscopy techniques. Ultimately, this ability has the potential to provide mechanistic insights into important biological processes, some of which go awry in various human disease states. Carrying out such single-molecule experiments is not trivial, however, and requires skill and perseverance.

Most chemical reactions in our bodies are catalyzed by specialized proteins. How these minuscule but intricate protein machines operate at a molecular level can be studied in real time thanks to powerful microscopy techniques. Even individual molecules can be studied, one at a time, using the imaging approaches that Sebastian Deindl has applied and developed during his time as a postdoc at Harvard University — techniques he now brings to the Uppsala Biomedical Centre. For example, these techniques enable the study of proteins that interact with and manipulate our genetic material.

“These techniques can be extremely powerful. At Harvard, we studied those specialized protein machines that alter how our genetic material is packaged into chromatin, at the level of individual protein molecules” says Sebastian Deindl.

Sebastian’s group also uses so-called structural approaches to investigate what disease-relevant proteins look like at the atomic level. Sebastian will combine this knowledge with the single-molecule fluorescence microscopy to establish how protein structures move and change to function in the cell. These studies are challenging, and it always takes a while to get the knack of it, he says. Designing and setting up these experiments is complicated, and it is also vital to get a sufficiently good signal and resolution so you can see what you want to see. But he has learnt from some of the best: The single-molecule biophysicist Xiaowei Zhuang and the structural biologist John Kuriyan, both pioneers and internationally recognized leaders in their discipline. This invaluable training facilitates his current work to elucidate the molecular mechanisms by which protein machines work in our cells.

“If we can understand the molecular mechanisms that control those protein machines that act on our genetic material, we can go on to understand their roles in human health and disease. Many of the diseases we humans suffer from involve one or more of our vital protein machines not working as they should.”

Sebastian is now in the middle of an intensive effort to build up his research team at SciLifeLab, and has high ambitions for what they would like to achieve. He thinks the Uppsala-Stockholm region is an attractive one, with much to offer.

“We want to advance the technology behind single-molecule imaging so that in the future, we will be able to combine more effectively our knowledge of the structure of protein machines with the way they dynamically change and move in order to work. Our desire is to achieve the ultimate quantitative and mechanistic understanding, by visualizing the work of protein machines in something that could almost be described as molecular movies.”