To see what no one else has seen before

The cell's interior is an exciting, eventful place. All our genes are there, along with the proteins that regulate them. The principles that coordinate life at the molecular level are what interests Johan Elf, professor of physical biology at the Department of Cell and Molecular Biology at Uppsala University. He was the first in the world to witness individual regulatory proteins binding to their target DNA in living cells.

The research team is investigating how gene expression is coordinated by proteins called transcription factors, but also more generally how biomolecules find each other in the cell's busy interior and how the copying of the cell's genetic material is coordinated with cell division. The overall objective is to find general physical principles that describe the constraints for life at the molecular level.

"We apply a very traditional scientific approach. We formulate quantitative predictions based on the current model or models, and then develop sufficiently sensitive methods to test the predictions," explains Johan Elf.

Making predictions that are sufficiently specific to be falsifiable often requires both good physical models and the development of new simulation methods. However, the team's real challenge usually turns out to be to develop accurate measuring approaches. To achieve sufficient temporal and spatial resolution, the team applies methods for studying individual molecules in living cells. The outcome is often not the one expected.

"Provided you can show that the measurement is sufficiently accurate, it is at least as interesting when you do not get the expected result. That is when you really learn something, even though it may be difficult to find a new model that meets all the requirements from previous experiments and that is still physically possible," says Johan Elf.

Using a physics approach to intracellular biology requires a multidisciplinary research team. In Johan Elf's case the team ranges from mathematics and physics, to microbiology, via chemistry and engineering. This makes it hard to classify the research into a classical scientific discipline.

"The boundaries that are often drawn between physics, chemistry and biology are totally artificial and usually arbitrary. We are working on how living matter works and it doesn't matter if this is biology, physics or something else," says Johan Elf.

When asked whether they have any dream projects, he replies that it is the ones they are working on right now and that the most difficult projects are often the most enjoyable. Some have been running for many years, and are now beginning to look as if they will succeed. In Johan Elf's experience, most innovative and worthwhile projects require a tremendous amount of work from dedicated PhD students and researchers. Formulating a scientific question is only a small part of the process. Then comes very demanding and time-consuming work by everyone involved and a project can fail for many different reasons along the way. The challenge is often that so many different seemingly easy things needs to work at the same time in order for a complex project to fly.

"Our projects almost always require people with different competences, such as microbiologists, physicists and engineers, working closely together for a long time. For this reason, having a group of people that like and trust each other is critical for success," says Johan Elf.

Running complicated method development projects involving many people is obviously very expensive. The team size varies between 15 and 20 people, most of them postdocs. This would not be possible without Johan Elf's success with major grant applications. "I have been more successful in funding my research than I could ever have hoped ten years ago" he says, but also stresses that it is important not to measure success in grant money but in the actual scientific discoveries that the money make possible.

"I am extremely grateful to our sponsors for giving us the opportunity to work on fundamental problems. It is a huge responsibility that we take extremely seriously."

Clear organization and planning are important to Johan Elf. He thinks this might be because the research itself is so unpredictable. The major drivers are solving problems and understanding how things work. He is rarely content, however. Just very pleased and satisfied when they manage to solve a problem that seemed daunting at first.