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Tilman Schäffer: Biology and medicine – from the point of view of physics

Tilman Schäffer at the University of Tübingen creates a bridge between physics, biology and medicine. His speciality is innovative microscopic detection methods such as atomic force microscopy. In addition to application, Schäffer is working on improving scanning probe microscopy instrumentation and methods.

Prof. Dr. Tilman Schäffer's thirst for knowledge crosses all disciplinary boundaries. And it is this thirst that brought him into contact with biologists and iridescence when he was doing his master's studies at the UCSB in Santa Barbara (USA) between 1994 and 1996. At the time, a group of Californian biologists was investigating the complex composition of mother-of-pearl (eds. note: also known as nacre) shells of abalone sea snails. Schäffer started working with the biologists and ended up being awarded a doctoral degree for his work on the biomineralisation of abalone nacre in 1998. "Back then, interdisciplinary cooperation was not yet as commonplace as it is today. In addition to the issue I was working on, I was interested in familiarising myself with ideas, photos and terms in the field of biology. Interdisciplinary cooperation is quite a demanding task for people with little experience in their partners' areas of expertise, but individual determination and the efforts of both parties eventually pay off," said Schäffer recalling his first steps in the life sciences. He found the high fracture toughness of nacre, a physical property that offers the animal absolute protection, extraordinarily exciting.

"An abalone shell consists of 97 percent calcium carbonate in the form of calcite and aragonite and 3 percent organic material. "Nacre is composed of different layers of calcium carbonate and lines the shells of abalone snails and many other molluscs. It has a highly orderly arrangement, which in abalone takes the form of pyramids. The crystalline calcium carbonate tablets grow laterally and eventually grow together. Each stratum is separated by bands of protein (organic matrix) around 0.5 nanometres thick," Schäffer explained. The team wanted to find out how a new layer "knows" in which crystalline orientation it has to grow. "We discovered a mechanism based on the growth of mineral bridges that penetrate the pores of the organic layer into the next layer," explained Schäffer who was able to contribute important results using methods from physics, notably atomic force microscopy (AFM). Using AFM, the team of researchers was also able to elucidate the reason for the fracture toughness of snail shells. "The individual molecules can unfold, just like knots on a piece of thread, and fold again. The process is reversible. It is quite a tough binding, and is relatively stable but not the same as a covalent bond," Schäffer explained.

Exploring structures using nano-sized probes

Prof. Dr. Tilman Schäffer puts high-tech microscopy methods at the service of the life sciences.
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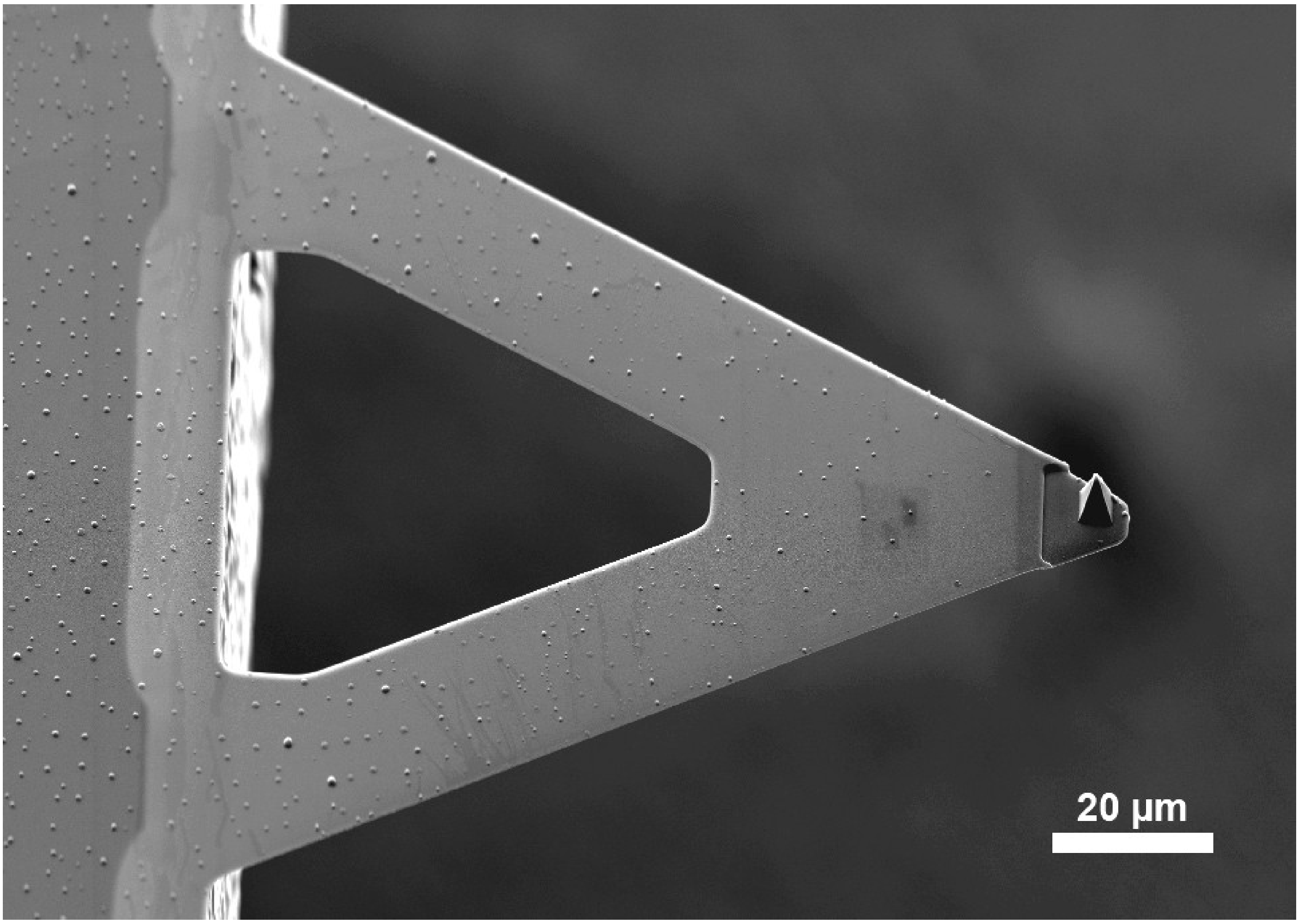
Schäffer has since been using physical methods to examine the mechanics and dynamics of biomolecules. He is not only interested in obtaining research results, but also in developing new methods, improving existing ones and discovering new applications. "For me, the development of

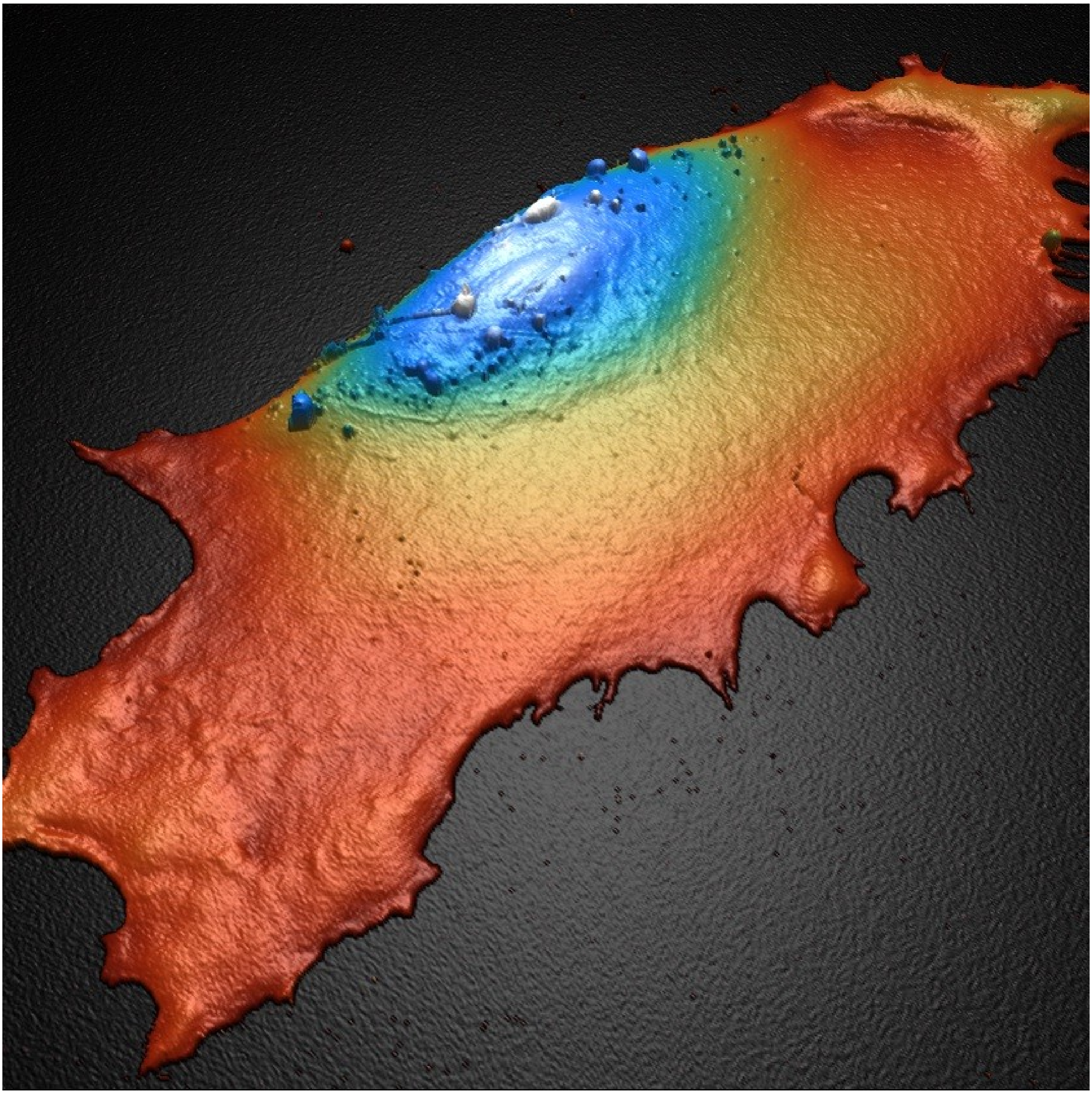


The atomic force microscope is one of Schäffer's preferred examination tools. It is equipped with mechanical probes attached to a flexible cantilever

methods is a very creative process, and I have always enjoyed this kind of work tremendously. Biology provides me with the practical applications," said Schäffer with a smile. His technology of choice is AFM as it offers him many possibilities. Atomic force microscopes are equipped with tiny probes, no bigger than a few nanometres in size and attached to flexible cantilevers. These probes enable the non-destructive detection of individual molecules with a resolution in the nanometer range. "We can use this technology in air, vacuum and liquids. In addition, we can analyse the proteins in their native state, which means that we do not need to stain or dry them. We can also analyse living cells with a high resolution," said Schäffer listing the advantages of AFM.

When he returned to Germany in 1999, Schäffer joined the Department of Molecular Biology at the Max Planck Institute for Biophysical Chemistry in Göttingen where he became the head of a group of researchers focused on AFM. The researchers were focusing specifically on dynamic protein-DNA interactions, and in particular on the binding of p53 to DNA. The p53 protein is a regulatory factor that is a real jack-of-all-trades and is involved in many cellular processes including the transcription of genes as well as in apoptosis and tumour suppression. Due to its crucial role in multicellular organisms, researchers and clinicians are all interested in elucidating the function of the p53 protein. "We have created time-lapse videos of the p53-DNA complex in order to investigate how the protein finds its DNA binding site. We were the first to visualise how the protein binds to DNA. This led to the development of a two-phase model in which p53 diffuses along the DNA until it finds a suitable binding sequence. If the DNA-binding region is mutated, p53 can no longer function as transcription factor and loses its function as tumour suppressor protein," said Schäffer.

Always with an eye on education



This is how cells can be represented using scanning ion conductance microscopy (SICM).

Although he found this kind of research exciting, Schäffer nevertheless was missing something that was quite important to him – teaching. "I have always liked teaching, both as a young student at school as well as during my studies in the USA. I offered my tutoring services voluntarily and completely free of charge. I used to teach on top of my normal research work," Schäffer said. In 2002, Schäffer was offered the position of lecturer in nanotechnological methods in brain research sponsored by the Stifterverband für die Deutsche Wissenschaft and was able to combine both research and teaching. He stayed at the Institute of Physics and Centre for Nanotechnology at the University of Münster until 2007 where he also discovered the field of medicine. "We improved AFM to a degree that enabled us to analyse the mechanical properties of myelinated nerve fibres in neurodegenerative diseases such as Charcot-Marie-Tooth disease (CMT). This provided us with information that enabled us to explore possibilities for the early diagnosis of the disease. We also used AFM with an in vitro model to carry out detailed investigations of the blood-brain barrier in order to find out how the mechanical properties of the single cell layer changed when drugs like hydrocortisone were administered.

After habilitating at the University of Münster, Schäffer went on to look for a professorship as the next logical step in his academic career and was offered the position of professor of applied physics at the University of Erlangen. This position enabled him to continue his life science oriented work, and to develop and improve microscopic methods and instruments as well as establish an own teaching programme. "We built our own instruments, including all components from the electronics to the hard- and software. This might seem like a rather thankless task, but it gave us in-depth insights into the technology of microscopes and helped us improve both methods and technologies," Schäffer said. In terms of application, Schäffer worked with microbiologists and medical experts at the University of Erlangen. "We analysed the ultrastructure and morphology of diphtheria bacteria with the aim of detecting differences between bacterial strains. For example, AFM helped us characterise the rigidity and other mechanical properties of bacterial pili, hairlike appendages on the surface of bacterial cells which play a key role in the invasion of the host," Schäffer said.

Research on living objects – on the molecular level, in real time and contact-free

The diversity of his interests and experiences, combined with the diversity of his examination methods, eventually took Schäffer to Tübingen where he was offered the position of professor of physics and medical engineering. He brings his methodological knowledge to the field of medical engineering, for example by trying to scale up cell mechanics to the tissue and organ level. For this, he uses AFM as well as scanning ion conductance microscopy (SICM). "This is a relatively new method, which is currently only applied by a few research groups around the world. The technique involves the use of pipettes that are up to one hundred times finer than patch-clamp pipettes. We have already reached opening widths of 15 nanometres, but we assume that we will be able to reduce the width of the openings further," said Schäffer. The pipette scans a surface without touching it and measures the current that flows between the opening and the surface. It is worth mentioning that the current depends on the distance between the opening and the surface. "Using this method, we are able to visualise living cells non-invasively and with a high resolution over a period of many hours," Schäffer said. This method gives the researchers new and fascinating insights into the surface structure of cells. Combined with fluorescence microscopy, the method can be used for diagnostic applications in the field of medicine. Schäffer is already working on a project which involves measuring the mechanical properties of cells. This information tells the researchers whether the cell under investigation is a tumour cell or a healthy one. In order to further develop the method, Schäffer's laboratory is also working on cell culturing. And this is an area in which Schäffer and his team have already obtained a great deal of experience.

In Tübingen, Schäffer is also enthusiastically committed to teaching; he has been involved in the medical engineering bachelor's programme and is also closely involved in establishing the planned biomedical technologies master's programme. "I am very interested in making physics a part of the methods used and bringing our way of thinking into the study programme," said Schäffer who also gives lectures for many other courses related to the life sciences and will also in future offer special seminars and lectures for advanced students.

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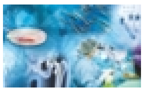

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