Healthcare industry BW

Kay Gottschalk and the physics of cells

You learn a great deal about the physical aspects of cells when you talk to Prof. Dr. Kay-E. Gottschalk. For example, their ability to react as solid and liquid, to adapt their environment to suit themselves and to exert and respond to forces. The 42-year-old has great respect for the smallest of living units, i.e. cells, which he calls smart composite materials. Working on the boundaries of medicine, biology, chemistry and physics, Gottschalk has been professor of bionanomechanics in the Institute of Experimental Physics (director: Prof. Dr. Othmar Marti) at the University of Ulm since 2011.

Professor Kay Gottschalk studies the mechanics of cells.

As self-styled physico-chemist, Gottschalk's work centres on the development of sophisticated physical models for describing cells in his quest to determine, explain and model the mechanics of cells. He is hoping that models of this kind will help biologists to improve their understanding of biological phenomena rather than just producing correlations. "If nothing else, the models will give material scientists useful working insights," says Gottschalk, lowering his sights with more than a slight hint of irony.

Bionanomechanics researchers, including Gottschalk, have already demonstrated the importance of the physics of living cells for tissue engineering and diagnostics applications. Along with some of his former colleagues in the Department of Medicine at the University of Greifswald, Gottschalk has shown that the mechanics of fibroblasts changes in diseased hearts. Another notable example of the importance of the physics of cells is microfluidic blood analysis systems, which also use the mechanics of blood cells. Such a system is due to be placed on the American market in the not-too-distant future.

Gottschalk's academic career is that of a student exploring an emerging field of research and a researcher working in laboratories on three continents and always at the boundaries of the natural and life sciences. Gottschalk was born in Marburg, the son of a physicist, and he spent his first few semesters as a student at the Department of Physical and Theoretical Chemistry at the University of Bonn. He then went on to study at Yale University where he became interested in proteins and started to focus on theoretical structural biology, which, back when the human genome was being sequenced, was something completely new. As a chemistry student, Gottschalk showed great determination and was able to do his degree thesis at Yale where he succeeded in predicting the transmembrane structure of a surface receptor (an integrin) from its amino acid sequence. Many years later his predictions were substantiated experimentally.

A man of action learns to experiment

Gottschalk did his PhD at the Technical University of Munich where he continued to calculate structural models of integrins and other proteins. However, he found the fruitless search for experimenters who could provide experimental evidence for his models increasingly frustrating. Experimental data were lacking and the phase space[1] of potential protein structures was so broad that Gottschalk decided to start doing the experiments himself. This he was finally able to do at the Weizmann Institute of Science in Rehovot/Israel (2002-2005).

It was there that Gottschalk examined protein-protein interactions both experimentally and using computers. He also became acquainted with atomic force microscopy, which can be used to measure such interactions down to the individual molecule level. He then returned to the University of Munich and became group leader (2005-2009) in the laboratory of Prof. Dr. Hermann Eduard Gaub, who pioneered the use of atomic force microscopy of single molecules. The atomic force microscope, with which surfaces can be scanned with a mechanical probe and atomic forces measured at the nanometer scale, brought Gottschalk back to the integrins, transmembrane receptors that exert and sense forces.

Gottschalk studied the mechanics of connective tissue cell integrins and realised that they behaved like "smart materials". He found that the fibroblasts not only directly interacted with their environment, but also altered it to the extent that the mechanics of the fibroblasts changed. Gottschalk calls this interdependence "feedback loops" and explains that knowledge (i.e. the ability

Fibroblasts are not only easy to cultivate, but also perfect for studying the mechanics of cells.

to measure them) of these loops is important for tissue engineering applications. Tissue used to replace cardiac valves needs to take mechanical aspects into account: the cell needs to endure pulling forces without being ripped out of its environment; however pulling too hard on the tissue leads to inflammation. This then triggers signalling cascades, and immune cells are recruited to the site of inflammation, thus destroying the tissue.

[1] Ed. note: Phase space: space where all possible states of a dynamic system are represented.

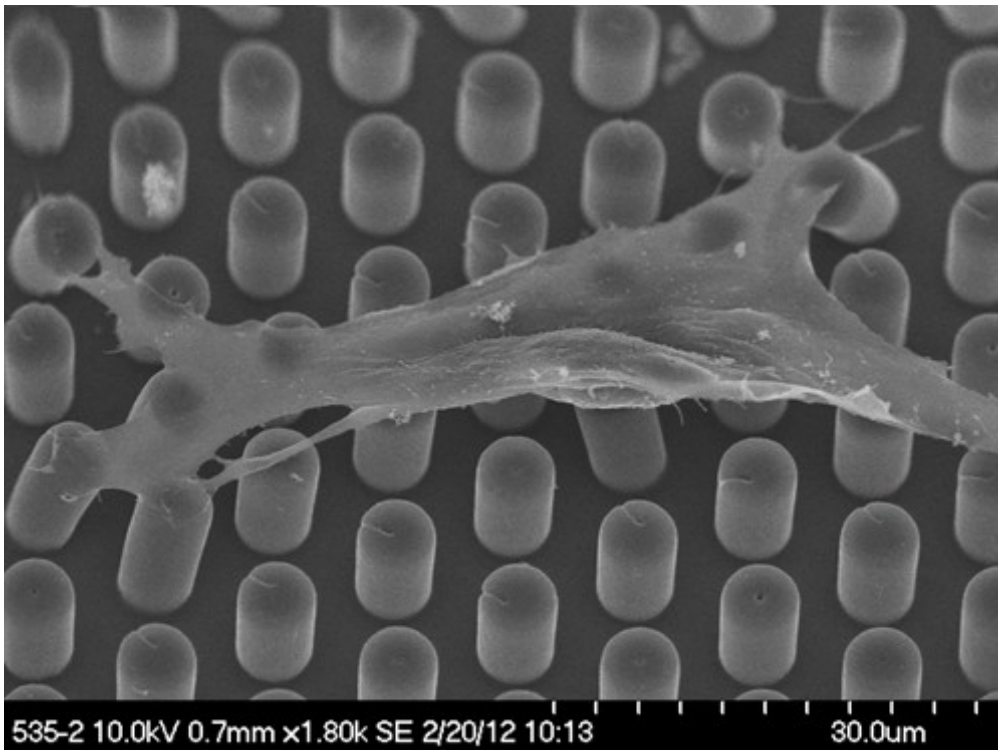
Mechanically induced signalling event

In this context, Gottschalk has found a conclusive explanation for a fascinating physiological phenomenon, i.e. the fact that immune cells (leukocytes) are transported in the blood to the site of inflammation within fractions of a second. Signalling processes induced by diffusion processes would be far too slow, so there had to be a mechanical nano-switch that controlled this rapid regulatory mechanism. What, in fact, makes this possible is integrins on the surface of the leukocytes that switch from the low-affinity (resembling a folded penknife) state to the high-affinity state (resembling an unfolded penknife) when activated (as a result of external forces acting on them). Gottschalk's measurements show that leukocytes become stiffer when they come into contact with inflammatory cytokines, enabling them to respond quickly to integrin-mediated mechanical stimuli; the leukocytes stop rolling and adhere tightly to the epithelium. Gottschalk uses a railing to explain this effect: "It is much easier to grip a railing when it is rigid."

The researchers are currently working on two of a total of 24 integrin subtypes, formed through different subunit combinations and which together form a complex information-processing network.

Along with a mouse geneticist from Munich and a number of other colleagues, Gottschalk is investigating two integrins that bind to the same extracellular matrix protein in order to find out how signals are transduced and extracellular information processed cooperatively. The researchers believe that focussing on two of the 24 integrin subtypes is a good starting point for investigating mechanically induced signal transduction.

Balance between surface tension and adhesion energy

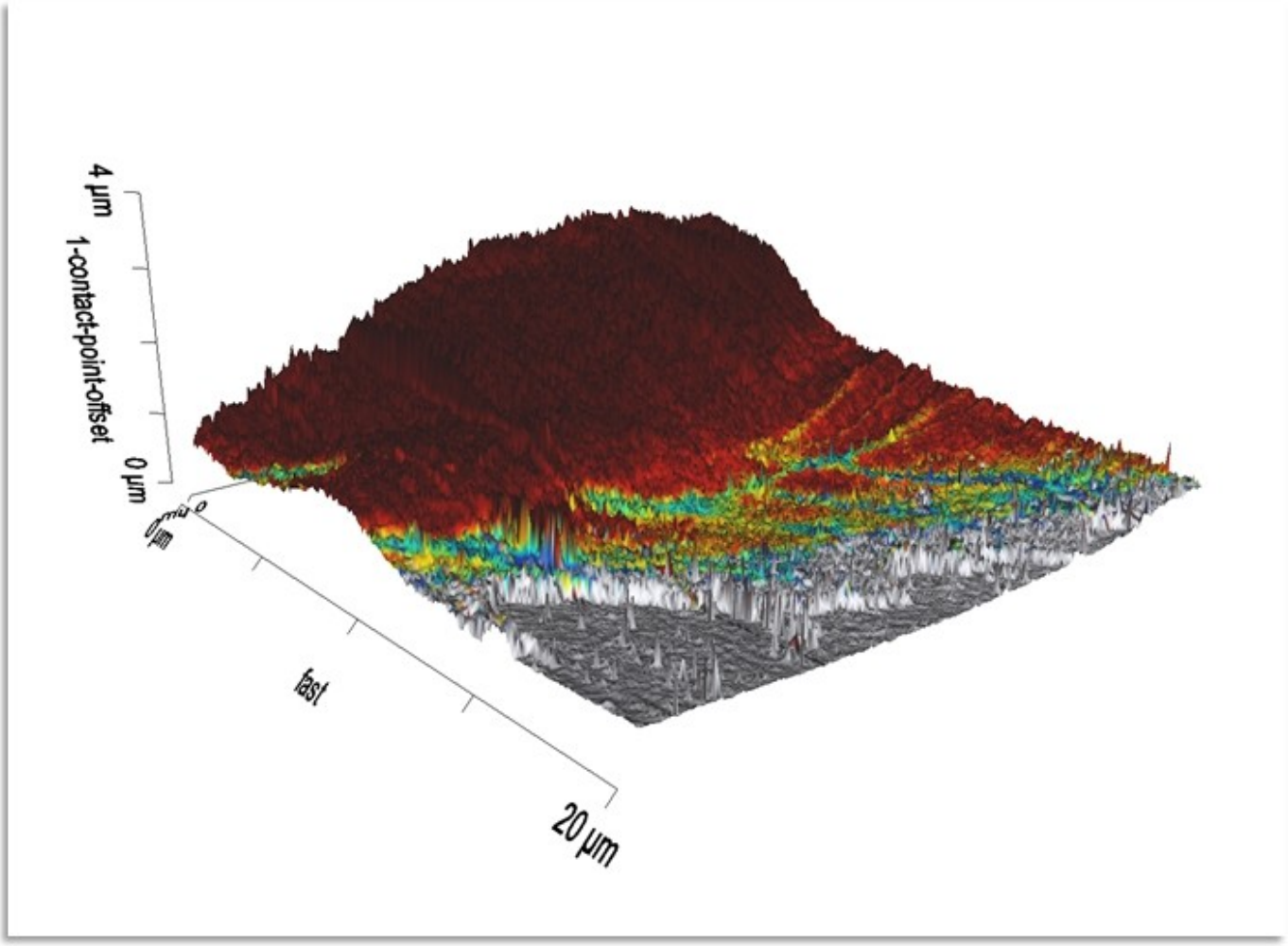


Electron microscope image of a cell on soft silicon columns. The deflection of the columns enables the researchers to measure the forces that a cell exerts. These forces depend on cell type, the state of the cell and the mechanics of the environment.

Biological investigations have provided relatively good insights into the regulation of signalling pathways by mechanical stimuli. However, limited physical information is available on the mechanical behaviour of cells and Gottschalk wants to change this. He explains that the tight binding of a cell to another cell (e.g. endothelial cell) is extremely similar to a drop of water hitting a surface, and that force balances play a key role here. Cellular adhesion energy plays an important role in the interaction between cells and the cells must make use of this energy to actively regulate the surface tension of their membranes. That said, this balancing act needs to take into account the extracellular matrix, the cell membrane and the cytoskeleton. The cell uses different regulatory mechanisms to regulate the adhesion energy via the number and type of surface receptors. Gottschalk believes that cells are able to do this because they behave like smart composite materials that have a high degree of self-adaptation. He is currently generating data that have the potential to demonstrate the ability of cells to adapt to the environment and reveal which surface molecules promote specific cellular functions.

Migrating cells leave their mark

Gottschalk is seeking an in-depth understanding of the material character of cells in order to learn more about cell biology. He is using passive microrheology, a method which was developed by the



Elasticity map of a cell: an atomic force microscope was used to determine the height profile and stiffness of a cell. Cell mechanics provides information about the state of a cell and can be used as a disease indicator.

institute's director Prof. Dr. Othmar Marti. Passive microrheology works as follows: tiny tracers (mm-sized plastic spheres) are added to cell cultures, they are phagocytosed by the cells and incorporated into the cytoskeleton. A high-speed camera is used to capture the motion of the beads, from which the mechanics of the cytoskeleton can be calculated. Gottschalk uses an atomic force microscope to carry out experiments in which pressure is applied to the cell and force-distance relationships are measured. Small columns are used to model the extracellular matrix. Cells that migrate across these columns exert forces that cause the columns to bend. This is visible under the microscope and can be measured.

Gottschalk uses such experiments to describe cells physically. He measures the softness or rigidity of a cell, how much force it can exert, how fast it moves across columns and how all this is related to biological and physical parameters.

Cells without a skeleton tend to wander about

Based on these data, Gottschalk is creating sophisticated physical models to describe reduced cell representations based on biophysical data that he generates himself. He now knows that a cell works if the different cytoskeletal elements (the rather active actin skeleton and the rather passive intermediate filament) are well organised. If one of the elements is not in the correct place, the cells tend to wander around at random. This has not been known in detail up until now.

Life scientists need the support of biophysicists like Gottschalk to help with the quantification of biological effects. He works with mouse geneticists and preclinical lung physiologists such as Prof. Dr. Paul Dietl and Dr. Manfred Frick from Munch, to name just two of his cooperation partners. Gottschalk still derives the data for his models from single-cell experiments. It can therefore be assumed that the elucidation of the dynamics of cell structures (tissues) or organs and the resolution of the different spatial and temporal scales will pose new challenges.

As basic as the research on the mechanics of cells might appear, its medical application is not so far off. The special mechanics of cancer cells can be used for the early diagnostics of cancer, and the feasibility of this approach has already been shown for mucosal cancer. The approach also has the potential to be used for the diagnosis of minor injuries of the knee tissue, and provides a quicker result than cell morphology approaches do. In the medium term, Gottschalk hopes to be able to predict how the mechanics and adhesion behaviour of cells changes upon the reduced expression of a specific signalling protein.

References:

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19-Jan-2015
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