THE AUTHOR FILE

Daniel J. Müller

A new way to quantify ligand-binding interactions of individual membrane proteins.

Every morning as he strolls through Basel, Switzerland, biophysicist Daniel Müller passes a 12th-century square and houses that are equally medieval, greets acquaintances, watches people and tunes his senses to the city's mood. He and his cherished, shelter-rescued dachshund, Albert, head to ETH Zürich, Basel, where Albert is a full-fledged lab member and Müller is a faculty member in biosystems science and engineering. Müller is also chair of biophysics and bionanotechnology and has cofounded a research center with 28 research groups devoted to molecular systems engineering.

NCCR Molecular Systems Engineering

Daniel J. Müller

A biological cell is similar to a city in which each inhabitant contributes and maintains city functions, says Müller. He has long wanted to learn how individual membrane proteins contribute to their biological city. He has trained his senses to absorb the city on his walks but lacked approaches to characterize membrane proteins in cells. He has been building, tuning and using technology for this task.

Müller has adapted high-resolution atomic force microscopy to image individual cell surface receptors—G protein–coupled receptors, or GPCRs—and to quantify the way certain drugs or other ligands bind to the receptors. GPCRs are common drug targets, and much research exists on their ligand-binding properties. But the binding is usually characterized in bulk. Such methods detect averaged properties of a population of GPCR molecules but hide each one's individuality, such as whether it is active or inactive.

Atomic force microscopy helps to sense cellular language at a distance, just as a visually impaired person might use a stick to navigate a city sidewalk. An oscillating cantilever, to which a ligand must first be bound, captures dynamic interaction forces at work between ligand and GPCR. Müller and his team also used a new theoretical approach to calculate a map of the ligand-binding free-energy landscape.

Down the road, Müller says, this method could be used in live cells and be combined with cell biological methods and optical microscopy. It could directly quantify cellular response—for example, activation of GPCR-mediated signaling pathways. The approach could tackle some puzzles, such as why a GPCR can have different substates, and help measure how the cell regulates an individual GPCR. "It's all about walking through a city and trying to understand how individuals contribute to the society and vice versa," says Müller.

His urban home now, Basel, is a city he knows well. Müller did his PhD work in physics at the Biozentrum in Basel and Forschungszentrum Jülich in Germany. He completed a short postdoctoral fellowship at Biozentrum before he became a group leader at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany. That post was followed by the chairmanship for cellular machines at the University of Technology, also in Dresden. There he cofounded B CUBE, a bionanotechnology research center.

Müller also launched the company nAmbition to commercialize a robot he previously developed to measure interactions between single molecules. He sold the company to German specialty instrument manufacturer JPK. His entrepreneurial bent arose from his own need for instruments and methods, and he realized other researchers might have use for these tools, too. He has new commercial activities in the works, but it is too early to share details.

Interacting with researchers and nonresearchers alike, walking Albert, letting ideas emerge while stirring coffee—they all help him think about science, says Müller. "I love enjoying the European coffeehouse culture," he says. He also adores opera and theater. Once a year he used to team up with dancers and musicians to bring a combination of science and art to the main stage at Semperoper, the Dresden opera house. One topic was time. A physicist talked about time and the possibility of traveling through it, a philosopher pondered how multitasking dilutes time, a biologist described our internal clock, and dancers interpreted time passing slowly, quickly and endlessly.

"I love enjoying the European coffeehouse culture."

Müller is an aesthete, whose office and home are models of clear design, says friend and colleague Anthony Hyman, who heads the Max Planck Institute of Cell Biology and Genetics in Dresden. "And he brings a similar aesthetic to his experiments," he says. "They are always clearly designed and to the point."

Hyman is especially fond of Müller's inventiveness. "He understands the cell biology and then seeks to make an instrument to test these ideas," says Hyman. "And gets super excited about the idea, just like a kid at Christmas."

Vivien Marx

Alsteen, D. *et al.* Imaging G protein–coupled receptors while quantifying their ligand-binding free-energy landscape. *Nat. Methods* **12**, 845–851 (2015).

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