THE AUTHOR FILE

Holger Müller

Building nice, shiny instruments to solve unsolved problems, and the physics of sailing.

I love building stuff,” says Holger Müller, a physicist at the University of California (UC), Berkeley with appointments in the physics department as well as Lawrence Berkeley National Laboratory’s molecular biology and bioimaging division. As a teenager growing up in Munich, Germany, he built radios and amplifiers from electronic components. When he was 14, he applied for his first patent. He did his PhD at Humboldt University, researching optical metrology, and completed a postdoctoral fellowship at Stanford University with Steven Chu.

“I want to build nice, shiny instruments and apply them to solve an unsolved problem,” he says.

One unsolved problem is the graininess and noise in cryo-electron microscopy (EM) images. In these images, the darkest parts are not terribly unlike the brightest. That makes it challenging for labs wanting to see detail. Müller says that Osip Schwartz, postdoctoral fellow in the Müller lab and the new paper’s first author, is wont to say that studying a protein in cryo-EM is much like when an observer on the moon is trying to discern the time on a clock on Earth. “That’s the same size ratio,” says Müller.

Labs want EM-detail but can’t waste time or money on less-than-useful exposures. To improve contrast, it won’t help if researchers simply crank up the electron beam, says Müller, since that would destroy the specimen. His new method, a laser phase plate, improves contrast without needing a higher-energy electron beam current. Adjustments are made after the objective lens.

This solution for cryo-EM grew out of conversations between Müller and his UC Berkeley colleague Robert Glaeser. “Talking to people is a way to catalyze, I think, ideas,” says Müller. Glaeser is co-author on the paper, and someone Müller calls a “cryo-EM guru.”

They decided to improve image contrast by shooting a laser beam at the microscope’s electron beam. “I’m not ashamed to say we spent five years with an approach that ultimately proved not useful,” says Müller. “The laser doesn’t do much to the electron beam unless it’s super powerful,” he says.

Holger Müller in New Zealand.

To get the power, the team built mirrors to bounce the laser back and forth 10,000 times and increase its strength 10,000-fold; they focused the beam with spherical mirrors. Then they needed to mount them in a way to stop the beam from pushing the mirrors out of alignment. It took much trial and error. These days, Müller is setting up a collaborative research and development effort that will help advance the approach so it might become part of commercial cryo-EM instruments.

“Holger Müller is both unbelievably brilliant and ridiculously humble,” says Eva Nogales, a Howard Hughes Medical Institute investigator at UC Berkeley and researcher at Lawrence Berkeley National Laboratory. The cryo-EM field should feel lucky that he decided to address the phase plate issue in EM head-on and find a well-thought-out method for increasing image contrast, she says. “And his solution belongs in a Star Trek episode, it is that cool!”

The approach to phase-shift the electron beam harkens back to research in the 1920s by Dutch physicist and Nobel laureate Frits Zernike. It eventually led Zernike to develop phase-contrast microscopy, which enhances contrast in optical microscopy.

As Müller explains, Zernike knew that our eyes see the brightness and color of light but that we don’t see many of light’s attributes, which can be represented as a waveform squiggle. The squiggle’s amplitude changes when a specimen absorbs some light, which is when a microscopist sees a dark spot. But even when light passes

through a thin specimen, the wave’s cycle can get a nudge, and there’s a phase-shift of the light wave. Zernike improved image contrast by converting this phase-shift into an amplitude change.

Labs have already developed methods to apply Zernike’s insight to EM and they deliver stunning images, says Müller. But these methods have a harder time with imaging campaigns that have hundreds of exposures. The new laser phase plate generates a sustained phase shift of the electron beam and therefore might enable such imaging campaigns, perhaps even let labs make movies and avoid smearing artifacts in their images. To achieve the desired phase shift, Zernike placed a glass plate into the light beam. In EM, labs have used materials such as thin carbon films. “In our case, it’s a phase laser beam but we all use the word ‘phase plate,’” says Müller.

Müller is at home in his native Germany and the US, especially Berkeley. “I love the Bay Area,” he says. And he feels at home in physics and in biology. When presenting something that was previously unknown to biologists, he has noticed they tend to react positively. Once they are sure an observation is not an artifact, their reactions are “wow, that is interesting,” says Müller. In physics, the Schrödinger equation explains all. “If you have an unexplained observation, that means you’re not smart enough to explain it,” he says, laughing.

“I love building stuff.”

Beyond the lab, when he has time, Müller likes to go for a run, sometimes with people in his lab. He recently took his first sailing class and plans to continue. It’s wind, speed and close to the water, “It just occupies all your senses,” he says. “And there is some physics involved.” □

Vivien Marx

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Reference

Schwartz, O. et al. Laser phase plate for transmission electron microscopy. *Nat. Methods* <https://doi.org/10.1038/s41592-019-0552-2> (2019).