THE AUTHOR FILE

Mats G L Gustafsson (1960–2011)

A physicist pushed microscopes beyond theoretical limits to provide a better look inside living cells.

Mats Gustafsson, who died of brain cancer April 17, 2011, found thinking in terms of waves just as easy as thinking in terms of three-dimensional space. Rather than considering the nanometer-scale objects in a cell, he would consider bright-dark patterns emitted from the illuminated sample. This allowed him to build microscopes with better resolution than previously considered possible.

Paul Fetters

In conventional microscopy, the wavelength of light limits the size of objects that can be seen clearly. Shine the light in very fine stripes, however, and observable 'fringe patterns' are produced. To the naked eye, these are meaningless, but they contain high-resolution information that a computer can extract. This was the insight that led Gustafsson to invent what is now called structured illumination microscopy (SIM). This technique can reveal details as small as 100 nanometers, half the size conventional microscopy had been thought capable of. SIM has been used, among other things, to make extremely high-resolution videos of living cells and to reveal new details of how DNA is arranged on the edges of the nuclear membrane.

"SIM can follow dynamics beyond the diffraction limit in living cells. That is probably where Mats's greatest legacy will lie," says Eric Betzig, Gustafsson's colleague and collaborator at Janelia Farm Research Campus. Whereas an array of so-called super-resolution microscopy techniques can capture details at even finer resolutions, SIM is both faster and less invasive, making it particularly suited for studying living cells.

Unlike other super-resolution techniques, a beginning graduate student can learn SIM in an afternoon, says John Sedat, who, along with David Agard, was Gustafsson's postdoctoral advisor at the University of California, San Francisco. Gustafsson deserves the bulk of the credit for developing SIM, says Sedat. "He shepherded the technology from initial idea, to proof of principle, to the first biology application, to making it easy to do."

Gustafsson had no training in optics when he joined Sedat's and Agard's laboratories, but he quickly showed an aptitude for integrating diverse fields. SIM is a combination of ideas from astronomy, materials science and optics, says Sedat. "Mats was good at this. It's a beautiful demonstration of the practical and theoretical coming together."

Gustafsson will also be remembered for his ability to ask unusual, useful questions, says collaborator Rainer Heintzmann, a microscopist at Friedrich Schiller Universität Jena in Germany and King's College London. "If you asked him a question that wasn't easy, he'd think a little bit and after some time come up with an answer that made it clear that you hadn't been thinking about the question in the right way."

In addition to SIM, Gustafsson worked on other microscopy techniques, both at University of California, San Francisco and after he joined Janelia Farm as a group leader in 2008. These include nonlinear, higher-resolution versions of SIM, a version of incoherent illumination interference image interference microscopy (I^5M) and a technique that collects images from multiple planes simultaneously. Before his death, Gustafsson had been working on live three-dimensional SIM, which he hoped to combine with his multiplane detection method for even faster noninvasive imaging.

Gustafsson had no shortage of ideas, but he did not publish as many papers as might be expected for someone with his scientific contributions. "If there was a disagreement between experiment and theory, he wouldn't publish until he could work it out," says Heintzmann. That meticulousness meant Gustafsson might share results at conferences several years before the work was published. "He didn't write many papers, but every paper was a bible for that method," says Betzig.

Colleagues remember how quickly Gustafsson could become absorbed in scientific problems. At conference mixers, Gustafsson sometimes preferred math to food; Heintzmann recalls one instance in particular: "We were sitting on the floor in a corner at some party doing some calculations on pieces of paper."

And though the field has become crowded and competitive, Gustafsson never jockeyed for the limelight, says Betzig. "Super-resolution microscopy is filled with a sort of gold-rush mentality," he says. "Mats by example was a silent rebuke to all that. He just knew his technique was good and that he could continue to refine it and that what was real would win out in the end."

© 2011 Nature America, Inc. All rights reserved.