

PERSPECTIVES & OPINIONS

| Eric Betzig

A MICROSCOPIST'S VIEW

*A GROUP LEADER AT JANELIA FARM HOPES
TO DO FOR BIOLOGY WHAT THE HUBBLE SPACE
TELESCOPE DID FOR ASTRONOMY.*

Paul Fetters

PHYSICIST ERIC BETZIG MADE A dramatic contribution to the imaging field in the 1980s and 1990s with his work on the near-field microscope. This technology, which shattered the theoretical “diffraction limit” imposed on spatial resolution by the wavelength of light, imaged small structures at higher resolutions than scientists thought possible. Techniques to peer inside living cells at similar high resolutions are still too slow, however. So when Betzig comes to the Janelia Farm Research Campus, opening this fall, he plans to develop a new method—“optical lattice microscopy”—to rapidly image the constant activity within living cells.

Which fields of biology stand to benefit most from improvements to microscopy?

EB: Basically, the interfaces between cell biology and molecular biology. We understand the genetic sequences by which proteins are made, and we understand, in many cases, the structures of the proteins. What we *don't* understand in sufficient detail is when they're expressed, or not expressed, within the cell; how that relates to environmental factors; what other proteins are present within the cell right then; how the proteins interact with one another; and how those areas of interaction are localized to drive the cell and its function.

Conventional optical microscopy cannot provide high-enough resolution to address these questions. But if the techniques that are at the edge right now pan out, we've only seen the tip of the iceberg. I make an analogy with astronomy: When people at the turn of the last century looked at Mars through telescopes with inadequate resolution to see any detail, the fuzzy lines they saw started them thinking about built canals and Martian civilizations.

Similarly, when you crack open any issue of *Cell* or *Biophysical Journal*, you see tons of interpretive studies based on relatively low-resolution cell images. Oftentimes, the interpretations are necessarily speculative. But as we begin to get higher resolutions, better dynamics, and the ability to access deeper tissue, we're going to get vast improvements in understanding. With factor-of-two or -four increases in each of those areas, we'll be creating this multidimensional space of information that can grow by orders of magnitude. All these systems that we've looked at before very blurrily we will now see in greater detail. It's going to be like the difference between using those old telescopes and using the Hubble Space Telescope.

Which aspects of optical microscopy need to be improved?

EB: The first is new contrast mechanisms: To find out more about the cell optically, you need a wider and better set of labels. Single molecules are basically exquisite reporters of their local environment, and

you can optimize them so that the fluorescence of a labeling molecule is sensitive to a parameter of interest. Techniques like fluorescence lifetime imaging give you contrast based on how long it takes for a photon to be emitted from the molecule, which can act, say, as a pH sensor or a viscosity sensor. So this is an ongoing area of interest: both on the chemistry side, in how to create new and better labels, and on the technology side, in how to get the information from the photons.

On a biological level, there are dynamics happening on all time scales, from the femtosecond to the many, many tens of seconds. There's a whole continuum of processes happening, and you want to be able to study as many as you can. So the second goal is to increase the dynamics.

The reason we do optical microscopy (as opposed to electron microscopy)—despite the limited resolution—is that we want to be able to look at living cells without pumping in so much energy that we perturb them. But the more energy you pump into trying to interrogate your sample, the greater the chance of perturbing it. The third goal, then, is to achieve the greatest dynamics possible so that we can look at things in real time, yet do so noninvasively.

Of course, the fourth area would be high resolution: trying to get to the diffraction limit and push beyond it. And finally, deep-tissue imaging: We need to do better than diffraction-limited resolution, which confines us to really thin and idealized samples, and actually push into the brain and other areas. Those are the five main issues that I see people working on in the field of optics.

Is there an ideal goal?

EB: In terms of resolution, once you get to the molecular level, that's pretty much it; there's not much more to do there. But in terms of dynamics, you can always ask for more. In terms of slicing and dicing your signal and getting different contrast, you can always ask for more. In terms of how deep you can go, you can always ask for more. There's loads of room for improvement.

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(JOAN STEITZ)

somewhere else,” says Steitz. If this turns out to be the case, the RNA portion of a snRNP would be considered a ribozyme.

By this time, Steitz had already advanced up the Yale ladder to become a full professor. Her lab subsequently discovered a second spliceosome that eliminates a rare class of “black sheep” introns that have atypical sequences at their splice sites.

And with her discovery of another kind of snRNP particle, small nucleolar RNPs (snoRNPs), she proved that the term junk DNA was a misnomer. Introns, the so-called noncoding regions of DNA, sometimes code for the small nucleolar RNA found in a snoRNP. These molecules (pronounced snow-RNPs by Steitz) chemically modify ribosomal RNA and are essential to its function.

Currently, Steitz is exploring viral snRNPs as well as the welter of effects splicing has on the downstream life of an RNA message. “For instance,” she says, “we know that in the process of splicing proteins are put on RNA that are important for getting the RNA out of the nucleus to the cytoplasm.”

While her work is on the bench side of science, others are translating her findings in the clinic in ways Steitz finds “absolutely amazing.” A recent paper in *Science* details a way to use aberrant splicing to prevent the ravages of muscular dystrophy in dog models. “Basically, they designed a snRNP to undo the drastic consequences of a mutation,” Steitz marvels. “I think that is just extremely cool!”

THE PLEASURE OF HER COMPANY

→ Apart from the official kudos Steitz has received, including the National Medal of Science, postdocs and graduate students in her lab say it’s a genuine pleasure to be there. They rave, for example, about her “really great parties.” At their most recent Halloween bash, Joan was the Statue of Liberty and Tom was Uncle Sam. And Doudna recalls delightful afternoons spent sailing with Steitz and her husband, drinking wine, discussing science—or the wind. “Working as a postdoc under Joan was such a fantastic experience,” says Baserga, “that I spent the first several years on my own wishing I were still there.”

While science itself is clearly Steitz’s first priority, education is her second. “I adore teaching undergraduates and consider it a privilege to interact with the fabulous students at Yale,” she says. Her

recent participation in a committee that wrote the National Academy of Sciences report titled “Bio 2010” inspired her to completely revamp a course for advanced undergraduates that teaches them, by group participation, how to read the literature. “Almost every time I lecture at another university, someone comes up to me and says, ‘I took your biochemistry course back in 19xx, and it was terrific.’ What more can one wish for?”

Another passion is a desire for women scientists to be appreciated as men’s equals. Steitz stands firmly by her 2001 comment in *The New York Times* that a woman scientist needs to be twice as good for half the pay, although, Thomas Cech points out, she doesn’t picket for change but rather leads by example. Steitz spends time on oversight issues to remedy remaining inequality problems—time she would far rather devote to her science.

She bristles when asked about Harvard President Larry Summers’ recent suggestion that women have less innate scientific ability. But she’s certainly circumspect in her reply: “What he said, and the sequelae at Harvard and throughout the nation, is the best thing to happen for women in science since the MIT report.” She is referring to the report out of MIT in the late 1990s that found women scientists at that institution suffered significant discrimination in terms of pay and stature. After that report was made public, remedial changes were initiated at many universities. Steitz says she is optimistic that Summers’ comments will again prompt positive change for women in science. Regarding his continuation as Harvard’s president, post-gaffe: “That’s something I find very interesting,” replies Steitz without expression.

It’s not hard to imagine how she would respond to Dr. Famous today if he questioned her place in and dedication to science. She might show him her weighty CV and invite him sailing with her beloved son and husband to remind him that a career in science does not exclude a happy family life—even without the station wagon. ■

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(ERIC BETZIG)

Do you have thoughts on how to speed up progress?

EB: Well, that gets into the wider philosophical issues of how research is done, which Janelia will try to address in some ways. In particular, I’m hopeful that the innovative engineering group within Janelia will help, at least for stuff we start

to develop internally.

The problem with the near-field microscope—a device I was using fairly successfully—was that there was no mechanism for turning it into a good turnkey instrument. And it’s still too embryonic for most biologists to consider using. There are hundreds, if not thousands, of examples in science and technology of good ideas that just languish because of the gulf that exists between the conception/demonstration of an idea and something that’s economically viable.

My hope is that Janelia will be a step in the right direction, because mechanisms will be in place there to take ideas that have been shown to work from a proof-of-principle standpoint to the point where they might be broadly applied. Right now, that’s pretty damn rare. —Interview by Jennifer Michalowski ■

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(NEVER TOO YOUNG FOR SCIENCE)

tools, observing, drawing conclusions, and making predictions.

Evaluations show that the children’s vocabulary for the names and functions of science tools increased significantly over a 5-month period during the 2005 program and that most were able to select the appropriate tool to solve a new problem. The results “tell us that children not only know how to use the tools but are also more likely to transfer that knowledge into a new situation,” says Garner.

“When we looked at outcomes,” adds CLS president Keith Verner, a former HHMI grantee at the Penn State College of Medicine, “we saw increases that were not dependent on a particular teacher or a particular class. We believe it was the program itself that made the difference.”

Loudoun County’s Scovel agrees, and notes, “We don’t want to repeat what children will learn in kindergarten, but we want to build skills they can use in kindergarten and beyond.” —Judith B. Saks ■

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(EVOLUTION/RELIGION DEBATE)

nonbeliever like myself or a believer like Father Wiseman. It seems to me that [science and religion] are two separate things.” He added, “The Bible is not a work of science.”

“I find it beyond ironic that society depends on DNA evidence for questions of life and death,” Carroll remarked, “yet we’re not willing to contemplate the DNA record of natural history and evolution.” —Jennifer Boeth Donovan ■