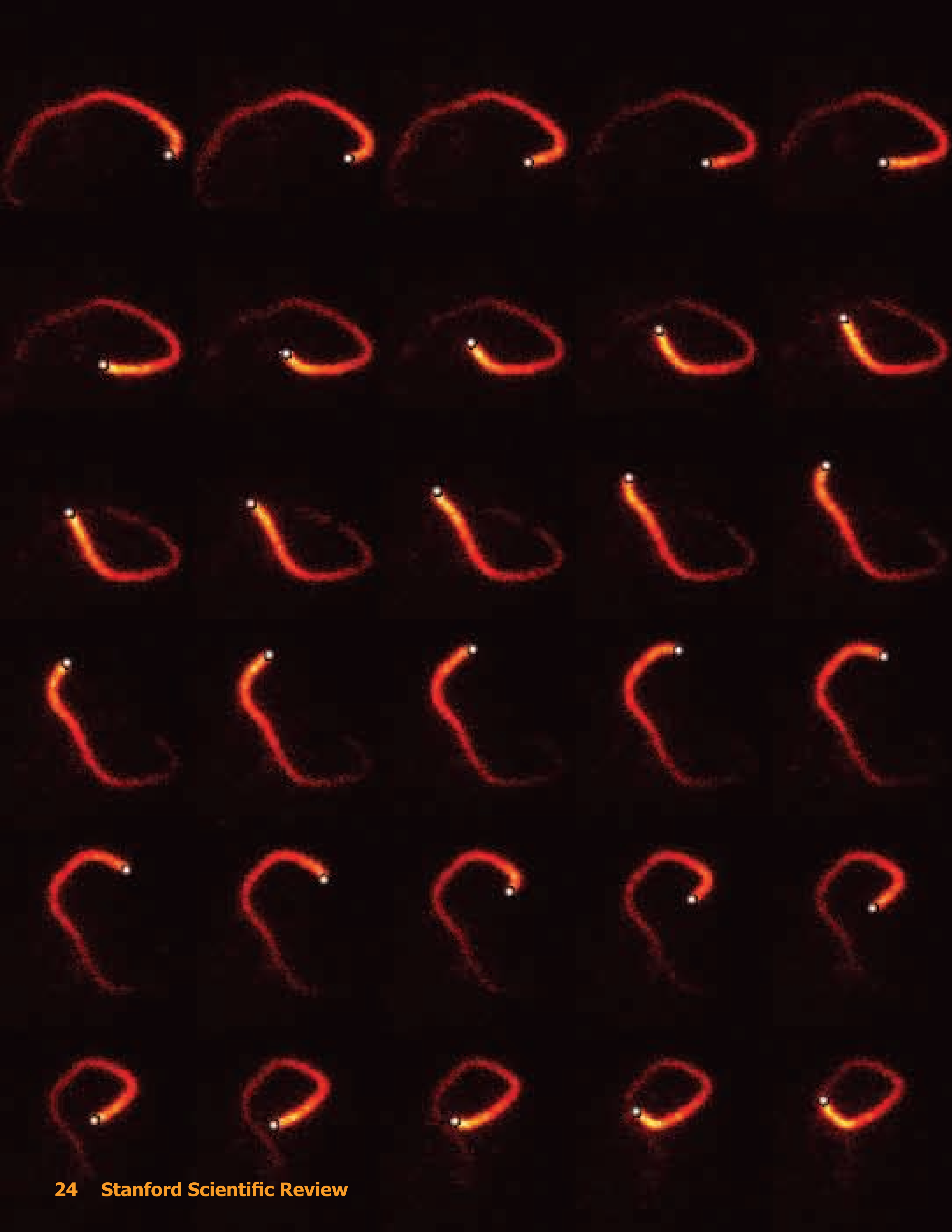

Chasing Pathogens

An interview with MacArthur Fellow Julie Theriot

by Susan Zhang

The MacArthur Fellowship is nicknamed the "genius award" because it is awarded annually to about twenty of the world's most innovative thinkers. In September of last year, Julie Theriot was one of two Stanford faculty members to earn the distinction, granting her $500,000 to pursue her research in biology. An Assistant Professor in the Department of Biochemistry and Department of Microbiology and Immunology, Theriot was recognized for her research in the movement of bacteria within host cells. By applying principles of physics and math to study a biological process, Theriot's lab was able to model actin-based motility in two bacterial models. The *Stanford Scientific Review* interviewed Julie Theriot on October 28, 2004, about her research and perspective on interdisciplinary science.

What were your first research interests in science?

In high school I had worked in a high-energy experimental physics laboratory, but when I got to MIT, I wanted to try different things. The first lab I had worked in was actually a chemical engineering laboratory, but I found that I didn't quite have the taste for engineering...[as far as] the differences between science and engineering, I think if you ask ten different people you'll get ten different answers, but for me the way I encapsulate it is that for science, the goal is to try to understand how something works; for engineering the goal is to try to manipulate the way something works to make it work better or more efficiently, and I just wasn't interested [in that aspect]. The project we were doing was trying to slightly improve the efficiency of a protein renaturation process, and it just really didn't get my imagination going, so I only worked there for a couple of months.

< **Motility of ActA protein-coated beads** driven by actin polymerization. In this serial image sequence (one shot every 30 seconds) of a .5-micron bead coated with the ActA protein of *Listeria monocytogenes*, the bead is superimposed over a photo of the fluorescent actin "comet tail" which propels the bead forward, just as it would propel *Listeria*. (Image courtesy of Julie A. Theriot.)

After that I took a course in neurobiology, and it just blew my mind. I love everything about neurobiology, and one of the professors was working on cellular neurobiology, trying to understand how acetylcholine receptors are clustered at the neuromuscular junction. I thought that was a really interesting problem, so I asked him if I could work in his lab - I worked there for about 2.5 years. I guess in a global sense, it was not that different from what I'm doing now, in that what we're looking at is the way that structures are organized in cells, but the specific kinds of issues we were looking at were of course very different.

How did your earlier research lead you to investigate actin-based motility?

When I started graduate school at UCSF, I had very broad interests in many aspects of biology. I rotated in many labs, and it was all very interesting, but the lab of one of the Assistant Professors, Tim Mitchison, was a very stimulating environment; he was a fountain of ideas, and I ended up asking if I could join his lab. At the time [he] was focused almost entirely on looking at microtubule dynamics, particularly in mitosis. I wanted to do something different, and Tim had had ideas of applying the same approaches to actin, so I started off working with actin.

How do you envision the future of such work in seeking to fuse physics and cellular biology?

I think it's going to be the next big thing. Now, we're living in the post-genome era. Not too long ago it was the pre-genome era. Back then, when I was in grad school, people were focused on identifying genes and trying to find all the genes involved in a process. And now, the kinds of large-scale experiments that are fairly routine to do make it pretty easy to get at least a preliminary parts list of all the things that are likely to be important in the process they're looking at. And so now the question is what to do with all that information, and how to understand how they actually work together. There are of course many different approaches to doing that.

For cell biology, there's the disconnect between what you can do in vitro with purified proteins in the biochemical sense, versus the way they actually work inside of cells because the physical environment in a cell is just totally different from a test tube. Proteins are many orders of magnitude more concentrated, and there's all this compartmentalization within the cell; there are physical limitations to the ways that molecules can interact with each other in a cell. And to really understand how individual proteins work, we can take them in captivity and play with them and see what they do, but then to look at them in their wild environment, the cell is just a very different ball of wax. If you think about this logically, it's totally obvious, but it's something that's only very gradually being accepted in the cell biology research community. Since we've gotten the molecular identification pretty well down – we know how to profile chemical actions of protein – the next thing that we don't have general principles for is the physics of how they interact inside cells.

What is your opinion of the interdisciplinary science programs developing at Stanford, like BioX?

I think it's a good thing. I think it's generally true that most new big changes in understanding come about when two disciplines collide, but there has to be a balance between focused in-depth expertise and breadth. The best scientists I know are very broad thinkers in that they have the vocabulary of many different fields, and can understand concepts in many different fields, but they still have a couple of areas of very deep expertise. Having just breadth, in the absence of depth, doesn't do you any good.

In your own college career, you double-majored in biology and physics. Do you believe undergraduate scientific education should be more interdisciplinary? Would you recommend that students studying biology be well-versed in physics and vice-versa?

If you want to be a physician, you have to understand thermodynamics, flux, and aqueous organic chemistry because that's how drugs work, and you have to understand quantitative measurements and their limits. On the flipside, I've collaborated a lot with physicists. At the level of research labs in physics, any of them who ever get a taste of biology love it because of these wonderful problems - incredibly complex systems that have very peculiar physical behaviors - and that's what they need. The approaches in physics are very powerful, but if you don't have a question to apply it to, what are you going to do? And so, I would think that from pure self-interest, anybody who's interested in condensed matter physics, or physics of complex systems, almost by definition should be taking a lot of biology classes because that's where the problems are.

^ Three stills from a video of *Listeria monocytogenes* bacteria moving in a cytoplasmic extract. On the left is the phase-contrast sequence to show the bacterium moving. On the right is a simultaneously recorded fluorescence sequence, showing the distribution of fluorescently-labeled actin. (Images captured from a Quicktime movie by David Fung, a former member of the Theriot lab)

When I was an undergraduate, as I was double majoring in biology and physics, I took a lot of math and chemistry classes. It was a lot of work, but I'm so glad that I did it because you have that base of knowledge for anything you do. But again, the problem is that you don't want to have people who are a mile wide and an inch deep; you want to have people who have some broad appreciation of these other fields, but they still have to do in-depth investigation of their own. I would be in favor of all science curricula becoming more rigorous, and including more exposure to other fields, but the only way to do that would be to have students take more classes. And I don't think there's anything wrong with that. We live in a civilization, and civilization is so great because you don't have to work everything out for yourself; you can rely on knowledge that others have accumulated. And there's just a whole lot more known about stuff than there was twenty or ten years ago. And if you want to be on the front edge of the wave of science moving forward, you just have to learn more now than what I had to learn when I was your age, because there's more stuff. **S**

Susan Zhang, a freshman, has a knack for turning in forms late and a strange fascination with Tangerine Altoids, which she considers both a blessing and a curse. She likes literature, music, math, and chemistry, but hasn't yet decided on a major.