People & Ideas

Jagesh Shah: A quantitative approach to cell biology

Shah uses quantitative modeling to build frameworks for understanding complex cellular systems.

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Jagesh Shah

Quantitative approaches are becoming an essential part of modern biology research. For example, systems biologists construct models of complex biological systems to help flesh out conceptual frameworks and to gauge the completeness of our current understanding of those systems (1). Such quantitative approaches come naturally to Jagesh Shah (2).

Shah first trained as an engineer—working on man-made systems—before becoming enthralled by the ones nature built (3). In his lab at Harvard, Shah uses modeling to guide his inquiries into cell behavior (4, 5). We called him to talk about his career and to find out what the mitotic spindle checkpoint and cilia have in common.

COMPUTER ENGINEER

Why did you do your undergraduate and graduate work in engineering?

I was probably inspired by my father, who is an engineer. As a kid I spent a lot of time with him taking things apart and putting them back together. I was interested in how technology works, so, when I went to college, I studied computer engineering. I liked what I was studying academically, but having spent time in industry I didn't want to work there. I wanted to do more theoretical work, so I decided to go to graduate school.

I had taken biology in high school, but I wasn't very excited about it at the time. It wasn't until the early part of graduate school that I really got hooked into biology.

What got you hooked?

For graduate school, I had found a joint program administered between MIT and Harvard where you did your PhD in engineering at MIT and medical school classes at Harvard Medical School. To prepare, I took a freshman biology class, and almost every piece of information transmitted to me by the professors was new to me. It was a transformative experience. As an engineer you could say, "I know how a computer works, and I could in principle build one and explain to you how it works." But then somebody shows you a neutrophil crawling around after a bacterium, and you think, "How the heck does that work?" I was absolutely blown away. I couldn't even imagine writing a program to do the things that a cell does, let alone the program in the cell's nucleus that makes a whole human being. What's the design principle underlying that? At that point, I thought, "This is what I have to do."

ENGINEERING A CAREER

So you changed tracks?

Many people told me, "This is pretty late in the game. How are you going to catch up?" I think that this is where I was lucky to find a mentor who would give me a chance. My PhD advisor was Paul Janmey, a biophysicist who is now at Penn. He was at Harvard when I was a graduate student. He said, "You know what? Here's an opportunity to work on a research project that probably you know nothing about, but I have a sense that you're going to be able to do fine on it."

> "What is it about [the kinetochore] that can cause the entire cell to basically stop?"

I finished my PhD with Paul, where we had worked on cytoskeletal mechanics and motor transport of cytoskeletal elements, and then my wife got a job offer as faculty at the University of California in San Diego. I didn't have a postdoc lined up, but we decided we had to go. So I had a very interesting experience where I used to go visit her and make appointments at various labs. I must've seen 15 labs.

At the time, Don Cleveland and Larry Goldstein had this collaboration where they were looking at how cytoskeletal elements are transported down axons to renew the axonal cytoskeleton. Larry is a geneticist who feels that, whenever possible, all your work should be done in animals, whereas Don is a reductional biochemist. It was an opportunity for me to learn two very different approaches to biology.

I started working on the axonal transport problem, and began doing mouse work, a completely new experience for me. I had a lot of downtime doing this, so I started going to some of Don's other lab meetings. One of these was about mitosis—Don was particularly interested in how the spindle assembly checkpoint works. At one point, the mouse facility shut down because of some infection, and it gave me some time to really dig into a new problem. Given my training in Paul's lab, I had some tools I thought I could use to make measurements in the mitosis system, and again I was lucky because Don and Larry were willing to let me try.

This is one of the problems you're working on in your own lab at Harvard?

One of the earliest hooks for me in the spindle checkpoint problem was a quantitative one: the idea that a single kinetochore has a very small volume relative to the entire cell. It's essentially a 200-nm by 200-nm disc, whereas the cell is much

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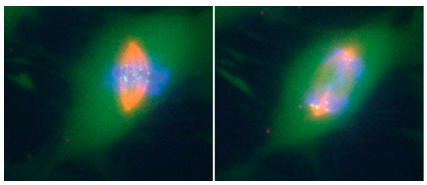

IMAGE COURTESY OF YINGHUA GUAN

A live mitotic cell at metaphase (left) and anaphase (right) stained for tubulin (red), kinetochores (green), and chromosomes (blue).

larger in volume: 6 trillion nm^3. What is it about that tiny catalytic scaffold that can cause the entire cell to basically stop its business—to halt the process of mitosis until a spindle microtubule attaches to it? Another appeal is that a lot of the molecules involved in this process are known. I think to a large extent we can explain most of the behavior we observe with the genes we have, so there is little gene discovery required.

We wanted to dig down deep into the spindle assembly checkpoint and ask: how is the cell so sensitive to the microtubule attachment status of a single kinetochore, and what is the nature of the signal that transmits that information? One way to think about it is that it's like a controlled chain reaction. When no microtubule is attached, a signal is generated at the kinetochore, which can then be propagated and amplified throughout the cytoplasm. We've been trying to model, and experimentally test, what constituents of the cytoplasm help amplify that signal, and our model has taught us that there's actually a fine balance between anaphase inhibition and the ability to remove that inhibition. If we make the inhibition of anaphase really strong, it turns out that anaphase can't be activated. So then the question is, once all the kinetochores are attached to spindle microtubules and that signal is no longer transmitted, how is the cell able to clear away the inhibitory signal and go into anaphase quickly?

I think this is really critical to understand. If we don't identify both the inhibition-promoting and the inhibition-counteracting processes, then, from a systems point of view, we haven't really solved the problem.

REVERSE ENGINEERING

Can you describe a system biologist's approach to a problem like this?

I think what drives a lot of our interest in a problem is the idea of connecting several molecular elements to some physiological question, like how a cell crawls or how a kidney functions. If we have enough of these molecules, can we model a given process with the components we have?

One big question that people ask systems biologists is, why is modeling important? We make models so that we can generate hypotheses that we can test experimentally. The computer model is never complete, but it represents our current understanding of how a system works.

"People ask systems biologists... why is modeling important?"

There are so many approaches for modeling, including statistical approaches like integrative genomics where you're looking at the whole genome. Then there are places where you look at a subset of genes that have been shown to be important in some function and try to understand in mechanistic detail how they all work together to generate that behavior.

To the extent that we can draw a common thread through the things that we work on, it's that the system has something interesting going on underneath the hood that requires a quantitative measurement. That may seem a tenuous thread to some [laughs], but it's an opportunity for us to work deeply on many interesting problems.

Another focus of your lab, intraflagellar transport, does seem like a very different problem…

We got into working on cilia and intraflagellar transport in part because of the early studies of axonal transport that I had done in Don's and Larry's labs. At that time, a set of proteins had been identified in the green alga *Chlamydomonas* that were important for the renewal and regulation of the flagellum and related organelles like cilia. And here was an interesting, quantitative question: How does the cilium, which is far away from the center of the cell, maintain its length or the size of its structure? I thought that we could provide some real insight into this question, and it's what I had my first postdoc work on.

How do you strike a balance between studying these different questions and life outside the lab?

My wife is a scientist, so we have to figure out how to balance our lives. We want to have a life that embraces science but that doesn't consume us. We have two daughters, aged seven and four, and there is no better way to forget about work than by hanging out with them. It just takes your mind to a completely different place—which is good for us and for our science.

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Shah and his wife, Sangeeta Bhatia, share some time away from science with their daughters.