Alex Mogilner: Math illuminates biology

Mogilner uses modeling to probe and explain the behavior of cells and their cytoskeleton.

Sometimes, genetic maps and laboratory experiments cannot provide scientists with enough information to understand a complicated biological problem. At other times, a researcher may have a plausible explanation for some process but no practical way to validate these ideas in an animal or cell culture. These are just some of the scenarios when mathematical modeling offers biologists a precious avenue to discovery.

Alex Mogilner uses the tools of mathematics to help explain and explore the biology of cells and other natural systems. His theoretical models have investigated the assembly of the mitotic spindle (1), the behavior of the actin cytoskeleton (2, 3), and the generation of cell shape and its relationship to cell motility (4, 5). We called him at his lab (currently at the University of California, Davis) to discuss how theoreticians can help biologists reach a better understanding of cell biology and what new questions he plans to probe in the future.

A MOVE ABROAD

Growing up, did you have any role models?

Growing up in Russia I was really fascinated with the theoretical physics of the early twentieth century, when quantum mechanics was invented. I read the biographies of physicists like Niels Bohr, Albert Einstein, Lev Landau, and others. It was really inspiring how much they did.

Did you want to emulate them?

Yes. I started with solid state physics and mathematical physics, and that was very interesting for a while. But later, when I moved to Canada, I realized that wasn't really what I wanted to do for the rest of my life.

How did you move to Canada from Russia?

Before perestroika, it was almost unthinkable to even travel abroad, let alone work. But when perestroika started and this became possible, I got very excited about the possibility of seeing the world, and it seemed like the best thing to do was to go abroad to work as a researcher or maybe do another degree. At the time I was already very close to defending my PhD in Russia, so I started to look for postdocs and found one in Winnipeg, Canada. I spent a year in Winnipeg as a postdoc before I decided I wanted to work on biological problems instead.

I didn't feel I was a genius like Bohr or Einstein, and I didn't feel like spending my whole life solving secondary problems and waiting to get lucky to solve something more significant. I saw that in biology there were many problems toward which a normal person like me could contribute. I guess I was too scared at that moment to try to become an experimental biologist, so it seemed to me that a good solution would be to do mathematical biology, to build on the strengths I already had. So I moved to Vancouver and joined Leah Edelstein-Keshet's group.

> "I start by trying to understand what the biological question is that has to be answered."

And you did another PhD, at UC Berkeley…

I read a famous paper in *Biophysical Journal* in 1993 by George Oster, Charlie Peskin, and Garrett Odell on the concept of the thermal ratchet. I was so enamored by the beauty of this paper that I contacted George Oster and asked him if I could come work with him on this type of problem. I was very lucky that he agreed.

MODELER'S MANTRA

How do you approach constructing a model for a biological problem?

I start by trying to understand what the biological question is that has to be answered, and then I think about whether math is going to be any help in answering this question. Modeling has many different uses.

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Alex Mogilner

In some cases we might think that we qualitatively understand what is happening: how cells divide, for example, or how they move. Modeling can basically verify or refute this understanding with numbers. That is a very important use of modeling but maybe not the most exciting one. What is actually more exciting is to create a mathematical model for a hypothesis in order to simulate and make predictions that can then be tested in biological systems.

So, for example, over the past two decades most of my work has concerned either the mitotic spindle or cell movements. In the mitotic spindle there's this great question: how does the cell have enough time to assemble the spindle before metaphase onset? One cannot simply intuit the answer to this question; instead, the process must be modeled on a computer until the solution is found.

In our work on spindle assembly, my brilliant student Roy Wollman simulated how much time is needed to assemble the spindle by the random search and capture process, it turned out that the model predicted that you need an order of magnitude longer than the time it's observed to take. That's because it's very easy for spindle microtubules to capture the first few chromosomes but capturing the last one takes a really long time if it is simply a stochastic process. Therefore, the search cannot be completely random. The cell must use some mechanism to accelerate the search, and we considered some of these potential

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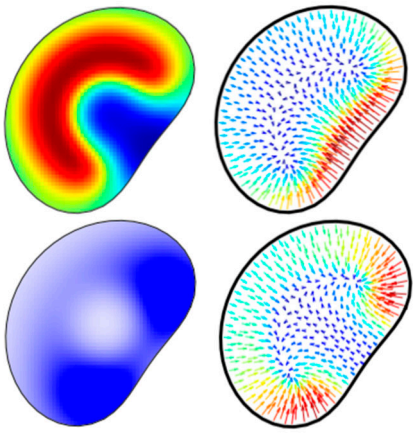

IMAGE COURTESY OF KUN-CHUN LEE

(Clockwise from top left) Simulation of adhesion strength, actin flow, traction forces, and myosin distribution within a keratocyte lamellipodium.

mechanisms with our models. This result was very influential for the field.

More and more papers include some kind of modeling these days…

Models are pretty fashionable, and a good model usually increases the chances for a paper to get into good journals, which of course is of paramount importance these days. Quite often, though, the model is kind of a window dressing. It's simply there to enhance the chance for a paper to get published. But I think for a really good collaboration both sides must be very interested in solving the question, and both of them must see the clear use of modeling. The modelers must not focus on holding to their own agenda to promote some elegant theoretical concept and just illustrate it with a biological phenomenon. On the other hand, while biologists don't necessarily need to understand the nitty-gritty of the math, they do need to understand what modeling is and how it works so they can participate in model development—not just delegate it to modelers and be done with it.

Another important thing is to be willing to go back and forth many times. Biologists have to be ready to test some of the interesting predictions of the model. This is quite a commitment because it requires the design and execution of experiments, which is time consuming and costly. And modelers have to be ready to change their model many times because some of the initial assumptions no doubt will turn out to be wrong, so it is sometimes necessary to scrap some of it. It takes many theory–experiment loops to reach a satisfactory understanding.

THE SHAPE OF THINGS TO COME

You have collaborated with many biologists…

Some of my most satisfying work was with Julie Theriot's group at Stanford. We worked on fish keratocytes, which are a favored system for studying cell motility. The questions we wanted to address were: what explains the beautiful fan-like shape of these cells, and is this correlated at all with their speed of movement? Also, what is the physics of the self-organizing actin treadmill that propels movement of these cells?

> "For a really good collaboration both sides must be very interested in solving the question."

This collaboration was a perfect example of when theory and modeling go hand in hand. I got together with Julie, her student Zach Pincus, and her postdoc Kinneret Keren, and we all began kicking around ideas. We were eventually able to connect the distribution of actin density around the periphery of the cell with the shape of the cell and with its speed, and what was really beautiful was that the formulae we came up with almost didn't depend on any parameters. And we could confirm them experimentally.

I've continued working with Julie's group on many other questions related to cell movement. What I really want to understand now is how the cell polarizes and initiates motility. A related question is, how do cells turn? How do they integrate signals from the environment to decide where to go?

And where will you be doing this work?

I've been very happy at UC Davis, but in the fall I will be moving to New York University, where I'll have a joint appointment at the Courant Institute and Department of Biology. I'm very excited about this because I may have the chance to work with Charlie Peskin, who was one of the authors of that famous *Biophysical Journal* paper from 1993.

Will you be teaching there?

Yes. I'll be teaching both math and biology courses. I think it is becoming increasingly important for biology students to have some courses in the curriculum, beyond standard calculus and physics, to give them some quantitative background. The problems these courses address could be geared toward biological modeling. There is also a need for specialized courses on computational simulation that address how to cycle between a simulation and wet lab experiments. It's much easier than it sounds; I'm currently teaching an undergraduate course like this at UC Davis that's going very well.

What plans do you have for this year, besides the move?

I am completely addicted to traveling. I choose some exotic location and go there for a few weeks to trek around. This year I have been thinking about visiting Ladakh in Northern India. It's a remote and beautiful place that would be wonderful to see.

1. Paul, R., et al. 2009. *Proc. Natl. Acad. Sci. USA*. 106:15708–15713.
2. Mogilner, A., and G. Oster. 2003. *Biophys. J.* 84:1591–1605.
3. Mogilner, A., and B. Rubinstein. 2005. *Biophys. J.* 89:782–795.
4. Keren, K., et al. 2008. *Nature*. 453:475–480.
5. Barnhart, E.L., et al. 2011. *PLoS Biol.* 9:e1001059.

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Mogilner pauses for a drink of chicha (corn beer) during a trek in Cordillera Blanca in Peru.