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People & Ideas

Sophie Dumont: Mastering the uncanny mechanics of living systems

Dumont brings biophysics to decode spindle architecture and dynamic function.

Sophie Dumont is modest when speaking about her own accomplishments, even though she has studied with some of the best and most creative minds in biophysics and cell biology. But it was a lowly breakdown of her Volkswagen hatchback in graduate school that steered her toward studying biophysics at the cell biology level.

As a graduate student with Carlos Bustamante at University of California, Berkeley, Dumont determined how much force it takes to mechanically unfold complex RNA structures (1) and followed how helicase enzymes use ATP to unwind RNA molecules in real time (2).

As a postdoctoral fellow with Tim Mitchison at Harvard Medical School in Boston, Dumont switched from single-molecule studies to probing the mechanics of one of the cell's most complicated and enigmatic structures, the spindle. By subjecting cellular structures to different forces, she probed how spindle length is regulated (3) and how kinetochores grab and move at the same time (4), both age-old questions.

She continued investigating spindle and kinetochore mechanics after setting up her own laboratory at the University of California, San Francisco, in 2012. Her group recently demonstrated how spindles robustly and rapidly repair themselves after laser ablation (5).

In a recent conversation with *JCB*, Dumont explained why the emergent properties of cellular structures differ from those of buildings, and discussed her wanderlust for far-flung places and cultures.

PUSH AND PULL

How did it feel doing single-molecule experiments, describing physical actions that drive biological activity?

I loved my time doing those experiments. People were starting to use optical tweezers to answer lots of new and very creative questions for different enzymes and nucleic acids. When you sit there at the instrument and you see this one helicase, you get to know one molecule "personally"—and that's amazing. These experiments are, however, hard. Most of the time, they don't work.

For example, it took me a year to find the first helicase walking along and unwinding RNA. Before that, I was troubleshooting conditions to make the helicase happy and do its job. You have to believe that the experiment's going to work and keep trying new things. When it finally starts working, it's a good day. That opens up so many possibilities.

Why did you turn toward cellular biophysics for your postdoc?

At the end of grad school, I had the idea that cells would be fun to study because we understand fewer things about how they function, and I wanted to work on a more complex system.

I stumbled upon a landmark paper by Bruce Nicklas published in *JCB* in 1969 (http://dx.doi.org/10.1083/jcb.43.1.40), using chromosome micromanipulation to look at the role of tension in chromosome reorientation. It was absolutely random. My old car broke down, and I took it to the garage near campus. I guess another scientist had previously been in the waiting room, because there was a book containing that paper. I picked it up and started reading. I went on to read every paper that Nicklas had written and I thought, "This is what I want to do."

> "I liked... that the cell seemed to be responding to this mechanical force."

This particular problem of cell division combined many of my interests. There's this beautiful problem of self-organization and building all these structures like the kinetochore and the spindle. Division is also a very mechanical process. So I thought this would be a nice playground for me. The Nicklas paper suggested that mechanical force could have an impact on the decisions a cell makes when it divides. This mechanical idea was very clear to me, and very exciting.

PHOTO COURTESY OF MANU PRAKASH

Sophie Dumont

What was so captivating about that paper?

That paper is amazing, and still, to this day, our methods are not much better. Nicklas took a glass microneedle and used it to exert force on a chromosome during division. He saw that the cell could delay chromosome reorientation because it made a decision that was influenced by him yanking on a chromosome with a microneedle.

I liked that very simple idea that the cell seemed to be responding to this mechanical force. But how does the cell know that force is being exerted? And what does it do with this information?

I viewed the world in a very mechanical and physical way at the time—and probably still do now. Cell division was a biological problem that I could actually grasp.

DYNAMIC INTEGRITY

As a postdoc, how did you make headway on the problem of how kinetochores hold on to dynamically shifting MTs?

The broad question is how the kinetochore holds on to a MT tip that is growing and shrinking all the time. It's a nontrivial problem!

I decided to label two different kinetochore subunits in live cells, and measured their relative positions as kinetochores moved, and as different forces acted on them. The measurement is simple conceptually, but technically difficult. After you measure the distance between the two probes, you can ask, is the distance the same or not when the MT is growing or shrinking? We found that the distance is larger, or that this kinetochore linkage is more stretched out, when the MT is growing.

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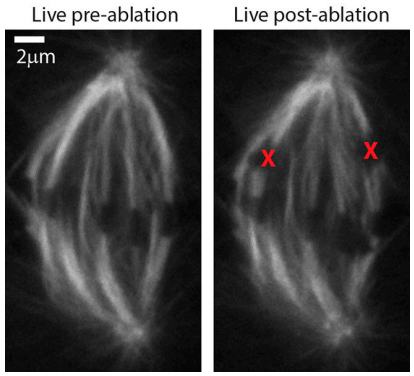

IMAGE COURTESY OF MARY ELTING AND CHRISTINA HUESCHEN (5).

Dumont and colleagues probe the spindle's robustness by laser ablation.

We inferred that the kinetochore grabs on to MTs using two different interfaces—a passive and an active interface, or "hand." In the model we proposed, both active and passive hands engage during MT shrinking, while in the growing state only the passive hand holds on. Whether this is true, and what the contacts between the kinetochore and the MT might be, are still not known.

What inspired your own lab to shoot lasers at spindles?

The idea was simply to ask how the spindle maintains its architecture so robustly. We started cutting spindles using laser ablation and asking how they respond to these cuts. If the spindle repairs the cuts, how does it do so? How do molecules know that a cut has occurred, where it is, and how to repair it? Beautiful previous work suggested that the spindle would somehow repair itself, and we were surprised by how rapidly and robustly that happened, and by how specifically key molecules localized to the cut sites.

The spindle fixes itself within a minute by pulling the cut MT toward the nearest pole?

Yes. Because the response was very robust, it gave us a way to probe repair forces in a quantitative manner. We also combined the ablation experiments with live imaging of dynein and NuMA, which we found were rapidly and specifically recruited to where we cut. They somehow grab on to the freshly created MT minus-ends and hold on to them while walking to the pole on nearby MTs.

It also points to a more general question: How does the cell coordinate distant events in the spindle? Somehow, global information about the spindle has to be obtained from local signals. From reading very local cues, how can the spindle figure out what's happening far away and respond in an integrated fashion? This is a big puzzle about the spindle: it is dynamic and flexible, but, at the same time, it has to have structural, mechanical integrity over long periods. How do you maintain that structure with parts that are so small, dynamic, and flexible?

PLAYING WITH SQUISHY MECHANICS

Should we stop imagining cellular molecules as Legos that snap together to build something?

This is the heart of what excites me. This building that I'm sitting in was built with building blocks that are dead, and engineers can predict the structural features of the building before assembling it. We're quite good at designing, for example, earthquake-resistant buildings.

> "[The spindle] is dynamic and flexible, but, at the same time, it has... integrity over long periods."

When building things in biology, we have a very hard time saying, "I'm going to build this structure from this list of blocks and it's going to have these mechanical properties." There are a few reasons it's so challenging. One is that the parts in biology consume energy—and that makes it hard to predict what mechanics and structures will emerge. Another challenge is that there is a lot of spatial heterogeneity—cellular structures take different architectures in different places. Yet another challenge is that cellular structures can evolve over time.

That is why, although the questions we're asking are quite simple, we don't have answers yet. For sure, we don't have simple answers.

Do you have any insights to share with those just starting up their own labs?

Just focus on the science and have fun. That's the most important thing. There are new demands on your time as faculty, and I just try to ignore some things and focus on science. I didn't have any big strategy. I just do what I love, so most days I just do science and chat with lab members.

What do you do for fun outside the lab?

I love traveling and exploring places I know less about. Some of my favorite trips have been to Iran and Uzbekistan, and other places around there. Iran is a beautiful and welcoming place, and the locals were very curious about what I do as a scientist. We would end up talking about cells and spindles in the streets or in markets. In Uzbekistan, I loved the architecture and crafts, like artisan puppets, with their costumes and faces saying it all. When traveling, I just live in the moment, from day to day, soaking it all in, and taking photos.

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PHOTO COURTESY OF NICOLAS ALTEMOSE

Members of the Dumont lab pose for a photo.