# Petra Schwille: Taking a minimalist approach to membranes

Schwille's group breaks down cell phenomena into their simplest parts.

When Petra Schwille began her scientific career as a physics doctoral student at the Max Planck Institute (MPI) for Biophysical Chemistry in Göttingen, Germany, single-molecule biophysics was a newborn field. The lasers and microscopes tracking DNA–DNA interactions in her advisor Manfred Eigen's group immediately caught her fancy—and improving the precision of biochemical measurements has been a large part of her work ever since.

In 1997, as a postdoc with Watt Webb at Cornell University, she switched to studying the workhorse molecules of the cell, proteins. It was also during this time that giant unilamellar vesicles (GUVs) first made an appearance and Schwille got hooked on working with these and other model membrane systems for their quantifiable physical properties. She established her own group in 1999 at the MPI, Göttingen, and spent a decade as chair of biophysics at Technische Universität Dresden before moving to her current position as the director of cellular and molecular biophysics at the MPI of Biochemistry in Martinsried, near Munich in 2012.

Since 2008, Schwille's laboratory has been pursuing the in vitro reconstitution of bacterial cell division, specifically the MinCDE protein oscillations that direct the division plane of *Escherichia coli* bacteria. Her lab reproduced self-organized protein waves (1) that sense membrane geometry in both two (2) and three dimensions (3). In addition, her group has designed a minimal contractile actin cortex as a first step toward generating a self-dividing cell-like compartment (4). Schwille talked with *JCB* recently about why biologists shouldn't need giant lists of proteins to understand the essence of biological events.

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**Petra Schwille**

## BOILED-DOWN BIOLOGY

***Why do you so often choose to do reconstitution experiments with minimal components?***

It is definitely the physicist's approach to biology, trying to get rid of the complexity, which is not the easiest thing to do in biology. We have these amazing techniques, like fluorescence correlation spectroscopy and single-molecule fluorescence microscopy that give us really high precision. But if we are fishing in a crowded and messy sea of unknown molecules, we can't play to the strengths of these techniques. I don't want to use less sensitive techniques. I would rather try to make the biology more reliable.

***Why did you focus on model membranes?***

When I was setting up my own group, I asked myself what features would a system need to measure it precisely? Model membranes were obviously the first step toward a controllable system.

Of course, some people say, "Well, it may be controllable, but it's not biological because you don't have all the important proteins in there." But then, why should you think you need all that? I'm really interested in the essence of a system. I don't really care so much about its realization in cells. I want to know its core principles.

> "I'm really interested in the essence of a system... I want to know its core principles."

***How did you discover that you could get the* E. coli *MinD and MinE proteins to make "waves"?***

That was an extremely lucky punch. In *E. coli* cells, these proteins oscillate back and forth from one pole to the other. I had a very talented student, Martin Loose, who had the idea to subject these proteins to our model membranes. It just worked. These proteins were amazingly well behaved.

Martin fetched me from my office, and we immediately thought, "My god, this is so cool!" The membrane is like a carpet on a coverslip and the proteins slide over the surface in perfect waves. It's not that the proteins are moving through the membrane, but rather they are attaching to and detaching from the membrane, like people doing the "wave" in a football stadium.

***Movies of these waves are mesmerizing, but what's the biology lesson?***

That, in principle, a system of two proteins and ATP is all you need for protein self-organization and protein gradient formation to position something in the cell. What I find really fascinating about this minimal approach is that you can really nail down how it works. It might not work as precisely or as resiliently as it does in the cell. But to get the general idea of the phenomenon, you don't need so many factors.

And it's such a relief! Everyone who has ever published in a biological journal knows that reviewers keep telling you that you haven't looked at *this* factor and *that* one. I find it completely annoying. I don't want to spend my life checking for all the different factors. I see the necessity in studying complex biological phenomena in their entirety, but it's not my world and I try to stay away from it.

## GEOMETRIC PATTERNS

***How did you show that these proteins could sense the membrane's geometry too?***

Because the membrane is so central to this phenomenon, we thought it might be a good

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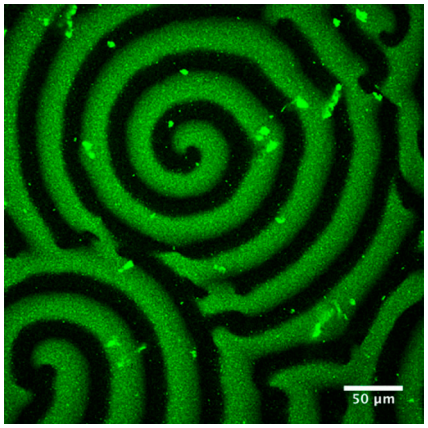


IMAGE COURTESY OF PETRA SCHWILLE

**Spontaneous spiral wave patterns form when MinD, MinE, and ATP are added to a supported membrane.**

idea to first modify the membrane shape. So we cut the membrane into forms. And the waves just go around corners and they go along a serpentine line—the waves just follow the long axis of whatever shape you offer them as long as the dimensions are more or less in line with the wavelength.

***Your group also constructed a model membrane with an actin cortex. What was the idea behind that?***

The starting point was to ask, what is the minimal system required to divide a vesicle compartment? And when you think of that splitting, then you think about contractile rings. My postdoc Sven Vogel aims to reconstitute an actomyosin contractile ring. We are still very far away from that.

But we thought that, to look at a more realistic cell boundary, we would have to equip the membrane with something that supports it. The actomyosin cortex was the simplest representation of that.

We could do single-molecule studies on these little myosin motors when the actomyosin system is attached to the membrane. When we investigated myosin II contraction, we found that it has a very peculiar way of creating force to fragment actin filaments. Myosin broke the actin filaments by buckling them—we didn't expect that.

***Both the Min proteins and the actomyosin cortex are involved in cell division. What intrigues you about that process?***

If you want to know how division is orchestrated, you need to know how the compartment looks. Does the compartment have a specific shape that is easier to divide? Very few cells are really round. There are lots of details known about many different cell division systems, but the core principle of division is still not clear.

I don't believe that we will ever be able to find out what the first cell looked like. We probably don't even have its building blocks anymore. But I do think that the fundamental physical principles, which these molecules probably evoked to do the job, must still be the same.

## COMPARTMENTALIZATION

***How did you recapitulate the Min protein oscillations in 3D?***

That was a big thing because we wanted to have not just the waves on a 2D membrane carpet, which move in one direction, but true oscillations, which ping back and forth, and through this establish a gradient. For a long time, we thought we would have to lock the system in a vesicle. But it was too tedious to encapsulate all the proteins in a vesicle and keep both the proteins and the vesicles happy. And then to start the reaction with ATP at a specific time—that was really a big nightmare.

> "The proteins slide over the surface in perfect waves."

At some point, we had a discussion with some theoreticians and they told us that the most essential requirement is to limit the volume. And then we thought, why not just make little open wells that look like bathtubs? The membrane is everywhere, but not at the top, so we can access the buffer.

After we start the reaction by adding protein and ATP, we cover the well with oil or air. As soon as the volume is limited, there is a competition for molecules in the reaction, and the oscillation starts. It's exactly like in the *E. coli* cell.

***What's your ultimate minimal system?***

What I'd really like to achieve in the next couple of years—or tens of years—is a system that self-regulates the division of a compartment in three dimensions. The system would recognize the shape, geometry, and size, and then divide it in two. What would this system look like? What are the minimal proteins or functional macromolecules? How would they have to act and interact?

***There's a photo of your lab members dressed in traditional Bavarian costumes. Are you from Bavaria?***

I am not from Bavaria, but I have always loved lederhosen. I wore them pretty much all the time from age 6 to 11. Every fall I "force" my lab members to go to Oktoberfest in Bavarian outfits, drink a lot of beer, and eat roast pork and pretzels, because this is simply what you have to do in Munich.

***With a really large group of students and postdocs, how do you stay in touch with each person's project?***

It really depends on the lab member's initiative. Whoever wants to talk to me will always be able to reach me, pretty much around the clock, but I'm not tracking them and breathing down their necks. Unfortunately, this results in most of my brilliant ideas being thoroughly ignored, but also in many great initiatives by my people that I wouldn't have thought of myself.

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2. Schweizer, J., et al. 2012. *Proc. Natl. Acad. Sci. USA*. 109:15283–15288.
3. Zieske, K., and P. Schwille. 2014. *eLife*. 3:e03949.
4. Vogel, S.K., Z. Petrasek, F. Heinemann, and P. Schwille. 2013. *eLife*. 2:e00116.

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**The Schwille lab (some in traditional Bavarian dress) at Starkbierfest, Munich's spring counterpart to Oktoberfest.**