Working in the real and the imaginary

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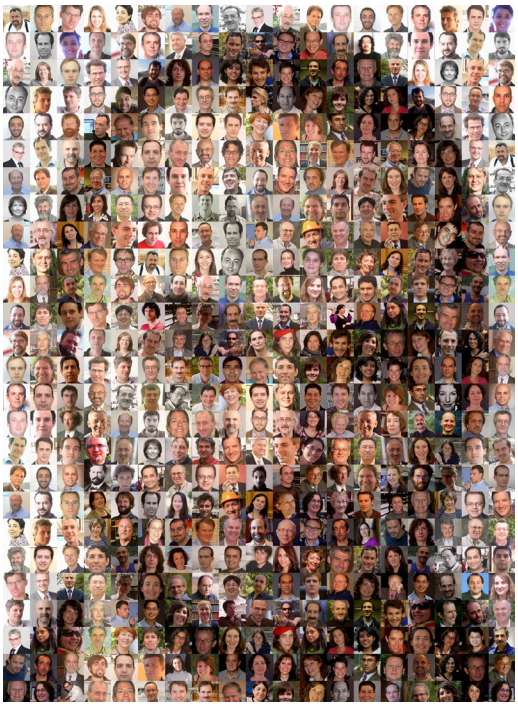
ABSTRACT **The science we practice is shaped by our interactions with people; the enthusiastic teachers, the fascinating mentors, the inspiring colleagues, and the inquisitive students. The science we enjoy takes us into areas we couldn't have anticipated. From time to time, we come back to reality and try to find ways to share our new explorations with our friends and relatives and to convert our insights into collective progress. What could be a better job?**

I am honored and pleased to receive the Early Career Life Scientist Award from the American Society of Cell Biology. It is noteworthy that I was not trained in biology but in physics and chemistry. I have always gazed at cell biology as another planet made of beautiful and crazy things to which I would never have access. However, this prize tells me I have just landed. Exploration can start. Let's put on our spacesuits.

PHYSICS AND CHEMISTRY TOOLS

A physics background doesn't mean having spent hours learning about quantum theory. It is also about instruments, knowing how engines work and having to get your hands dirty. At the Ecole Supérieure de Physique et Chimie de la Ville de Paris, we spent our time in the labs, using all the machines, from the mass spectrometers and the acousto-optic modulators to the rotating evaporator and the milling machine. After synthesizing left and right enantiomers of molecules I can no longer remember, we looked at fluid particles forming circles in standing waves and then generated tortuous diffraction patterns with homemade lasers. I remember seeing some sort of Möbius strip–like shape on an oscilloscope that was monitoring a chaos-generating electric circuit. By having all these tools available, we felt that we could investigate the core principles of any subject.



Manuel Théry: The enthusiastic teachers, fascinating mentors, inspiring colleagues, and inquisitive students of whom I am made.

DO IT YOURSELF

I very much belong to the DIY school of science. I get so much more satisfaction from building rather than buying something. Labeling a protein with a kit is efficient, but it is not as rewarding as doing it with the help of your friendly chemist, a homemade column in a 25-ml pipette, and the UV lamp from the disco dance floor to detect the labeled product. Any small progress is perceived as a real personal advance; you begin to know much better what you are manipulating in your experiments. In the same manner, the bench devices assembled step-by-step morph into large experimental setups. What has impressed me the most are the instruments that have been combined to enable cell manipulation, including micromanipulators, piezo stacks, and photodiodes driven by Labview. I truly believed then, at the Curie Institute, that these setups would open the doors to innovation, not only from a technical standpoint but also from a scientific standpoint, by providing new ways to think about cells. For my friends and me at that time, there was nothing we couldn't build to allow us to play with cells. Pulling, pushing, stretching, squeezing, pressing, blowing, and sucking: we tested everything, we even played the intercellular bridge like the string of a harp!

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FIGURE 1: Pictures taken during the Nuit Blanche, a public all-night art exhibition held 5–6 October 2013. Andreas Christ plated RPE1 cells expressing Lifeact–green fluorescent protein on building-shaped micropatterns. Movies were assembled and music was added by the Groupe LAPS, and the movies were projected back onto the facade of the actual building (www.groupe-laps.org/en).

BACK TO BASICS

The current tendency in pursuing cell biology experiments is to increase complexity. What happens with this tendency is that you acquire tons of images you will never look at and develop automated image-analysis programs that work in a way you don't really understand and that reveal information you could not obtain manually. The positive benefits of this tendency have provided some very interesting insights, and I have been lucky enough to be associated with some of them. However, the papers in the cell cytoskeleton field that have impressed me the most were performed with rudimentary tools and most often depended on careful observation. Most milestones in the cytoskeleton field have been established with simple techniques.

Although I agree that new techniques will take us into new research areas, I still think there are lots of things to do with simple tools, as long as they are cleverly used. One of my favorite examples is the way Ray Rappaport highlighted the rules of mitotic cleavage furrow positioning by piercing a sand dollar egg with a needle. It is also an example that serves a useful answer to some of our article reviewers, in that the experimental setup can be viewed as highly artificial. Yes, the system is not physiological, but Rappaport's needle told us a lot about the way the mitotic apparatus actually works in cells. It would take a book to review the seminal experiments in which a simple, well-thought-out tool has been used to reveal the core mechanism of cell cytoskeleton assembly. But is our knowledge so far advanced that there is no more need for this type of research? Do we necessarily have to develop more complex techniques to try to dig deeper into the complexity of biological mechanisms? I am not so sure. On the other hand, modern tools for cell imaging and manipulation have made inner cell life clearer. They revealed detailed but key features about the actual way the cytoskeleton works. We should not take for granted the basic biological rules laid down in textbooks. So, in parallel to the investigation of complexity with big data, there may be merit in revisiting basic old rules with new tools.

How complete is the current set of basic cell cytoskeleton rules that have been identified? How do cells sense space or measure distances? How do cells set their size or define their shape? Do cells have a center? Is it required for polarity orientation? Is the cell architecture a mere scaffold or does it contain information? How is this information perpetuated in a permanently renewing structure? I often tell students that, in starting to tackle questions like these and to identify any laws, we need equations; and for the equations, we need numbers.

FREE YOUR MIND

My view on the way to progress in science and think about experimental design was dramatically changed when I read the *Introduction à l'étude de la médecine expérimentale* by Claude Bernard (Bernard, 1865, 1957). According to him, all working hypotheses are acceptable as long as they are based on facts established by accurate observation. It may seem obvious, but it opens up a field of possibilities for your imagination. Nothing is too crazy or too foolish to be considered, as long as it is based on rigorous experimental observations. When formulating these hypotheses, it is safe to operate with the spirit that, in the imaginary world, things could be completely different. However, once the experimental results are obtained, you should curb your imaginative and creative impulses and come back to the real world. Forget about your working hypothesis. Conclusions should be drawn from strict observational facts only. These episodes in which the imagination is unleashed give me great pleasure. It is not simply about pushing the boundaries between the real and imaginary, it is about rewiring the real. Even the artists do not have such opportunities. It is our privilege.

PLAY HARD

The adage "work hard, play hard" applies not only to the necessity of a worthy celebration upon the acceptance of a paper. I try to encourage my students to have some good times seeking new ways to put biology problems in another context to offer a fresh look. Our approaches may be funny, but they may also reveal interesting insights. Dress yourself up as a Golgi, and after receiving a big laugh, you will encounter topological problems and will have consider how these problems are solved in cells. Try to walk as a cell (in a swimming pool of Nutella), and the appreciation of the problem of inertia and force balance in a fluid environment with a low Reynolds number will become clearer. I am convinced that serious games are a great way to think about scientific problems. A few years ago, some colleagues and I organized the world cell race. It was a great experience from which we learned as much as we laughed. It had an impact with the public too, and it was blogged about across the world. People threw up a series of good questions: What controls the speed of a cell? Are cancer cells faster than the others? Do small cells move more rapidly than large ones? Do some cells change direction?

Last year we staged a public event to illustrate this question: What is the difference between the architecture of a cell and a building? We achieved this by effectively miniaturizing the front façade of the Saint Louis Hospital, plating cells on it, and video-recording actin dynamics. Videos were then projected back onto the actual building, showing cells attaching stress fibers to windows and gutters. In the crowd, people were discussing the differences between cells and buildings: one was size, of course; but gravity

and dynamics of construction were others. A very young child was puzzled by cell divisions and asked, If they divide, do they become twice as small? If it happens again and again, will there be enough space? I was stunned. The video montage lasted 15 min and was in a loop. Some stayed until 5 a.m., gazing at the giant cells climbing over the hospital. By capturing the imagination of both scientists and the general public, both events showed that we could and we should engage the public more in practical experimental science and hence in the exploration of cell biology.

REFERENCES

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