FANTASTIC Mr. Frank

by Catherine Somzé / photography Jonathan Auch

Professor Joachim Frank

Over the past few years, the quality of visualizations of bio-molecular processes has evolved in spectacular ways. When news of the Zika virus outbreak arrived, it was illustrated with lavish images of its shape and surface, unveiling how it might harm us. Although people in our image-saturated culture might take such detailed visualizations for granted, the technology that makes the imaging of these previously-unseen phenomena possible came to its current height of perfection just a few years ago. For its invention, German-born bio-physicist Joachim Frank (Siegen, 1940), together with his colleagues Jacques Dubochet and Richard Henderson, were awarded the Nobel Prize in chemistry.

In single-particle cryo-electron microscopy, a three-dimensional image of a molecule is reconstructed from thousands of images, each showing a single molecule ("particle") frozen in a thin layer of ice, captured using an electron microscope and an electron-recording camera. Like all innovations, its development did not happen overnight, and only became possible once its constitutive technologies had matured enough. At least three different components had to be available for cryo-electron microscopy to deliver highly detailed images: direct electron detection cameras that are much more sensitive than photographic film, computational technology for image sorting and three-dimensional reconstruction, and the freezing process to capture molecules of all types in mid-movement. In this issue, Mr. Frank talks to *ZOO* in exclusivity about his contribution to the invention, his career, and the surprising importance of art in his life.

Catherine Somzé: Why is cryo-electron microscopy such a groundbreaking discovery?
Joachim Frank: Modern medicine is based on our knowledge of molecules. Before the invention of cryo-electron microscopy, only a certain number of molecules could be visualized and therefore studied. Many molecules resisted preparation for visualization (for instance because they disintegrated or got squashed). Thanks to cryo-electron microscopy, all molecules can be studied now, which means we can start understanding how mutations in disease may interfere with their function; think of the many types of heart disease, and even Alzheimer's. It's the first step towards developing new drugs and curing them. Everything has become possible now!

CS: You won the Nobel Prize together with Jacques Dubochet and Richard Henderson. What was your specific contribution to the study?
JF: What I have been working on over many years is to find out how to reconstruct the structure of a molecule by putting individual projections of many randomly oriented, single molecules all together. Since this requires mathematical and computational techniques that didn't exist when I started in the 1970s, I had to sort of create them.

CS: Did you expect your work to be of such vital importance when you started?
JF: I had a first inkling in 1986, when we got the first 3D image of a molecule from images of a negatively stained sample (i.e. each molecule is embedded in a little puddle of heavy-metal salt) using my reconstruction technique, that it could be a substantial contribution, or that it could be perceived as such. At the time, Jacques Dubochet had developed the cryo-method, which is a way of freezing the molecules that are swimming around in water in a thin layer of ice. Now my reconstruction technique could be used on a much better sample, and the one technique got into a sort of handshake with the other. But the real turning point was in 2012, when the first commercial single electron counting cameras came out. I could never have imagined that the visualization would reach atomic resolution.

CS: The Nobel Prize is the crown jewel of a scientific career. Did you ever dream of winning it?
JF: I don't think there is anybody who doesn't dream about it, right?! [Laughs.] I had this hope but, then, after the "resolution revolution" took place, there were many people who didn't appreciate the beginnings of this whole development. There were all kinds of portrayals about the development of the technology that I couldn't recognize. They were really strange, distorted histories that didn't take our contributions into account. People just didn't have a lot of background knowledge, or they kept it at a certain level.

CS: So the Nobel Prize acknowledges the true history of the development?
JF: And that's really the job of the committee. They receive nominations and then they have to dig very far, and study the literature and contact experts in order to find out the true intellectual development.

CS: You were born slightly after the outbreak of WWII, and you obtained your PhD in Munich. How was it to study in Germany in those years?
JF: I didn't have anything to compare it to. After the PhD, I had the opportunity to go to the United States for a couple of years as a postdoc funded by a fellowship, so only then could I compare science in Germany to science in the United States. And the main difference was that, in Germany, you were nothing. You couldn't speak up, at least at that time. In the States, on the contrary, students were taken seriously.

CS: Do you think it has changed?
JF: I think it has. Europe as a whole has been integrated and there has been a lot of influence from the Anglican side of science on Germany. Nowadays, research institutes are meeting places – they have people from everywhere, and in many cases, English is the language being spoken inside the institute. But I do have to say that I've never returned to anything more than temporary functions at a German institution.

CS: The United States acknowledged your capacities early on.
JF: That's a very funny story. I was among the first people who did image processing with electro-microscopy, so there wasn't lots of literature around, and somehow an editor got hold of what I was doing and asked me to write a review article on the topic. That was in 1972, and I had only written a few original articles. But from one day to the other, I became seen as an expert in the field and was offered a position as a senior research scientist without any teaching obligations. I was essentially left alone with sufficient money. I could develop ideas. It was wonderful!

CS: Your contribution to science is in the field of visualization. What is your relation to art?
JF: I'm a very visual person, so I'm thinking visually. I see this as a trait. I've always been very interested in photography. I've always taken many photographs.

CS: What kind of photography?
JF: It's the photography of the incident. It's always something on the margins — the focus is always something on the periphery. It could be a little plant growing next to a lamp post. By choosing the right angle and the right frame, you can animate something so that a plant can be seen as struggling and completely isolated; you can empathize with it.

CS: But the pictures you share with us here seem rather staged, especially *Circe Waiting for Ulysses.*
JF: It isn't. I took it with a zoom lens in Monemvasia, on the Peloponnese. The woman was looking out over the sea and I took the picture as she appeared in the corner of my eye. This is also how I consider my whole career. Somehow I've always been attentive to things happening at the periphery. I seriously consider unexpected things that would normally be dismissed. In my life, I have experienced that the most valuable things come from outside of the beaten path.

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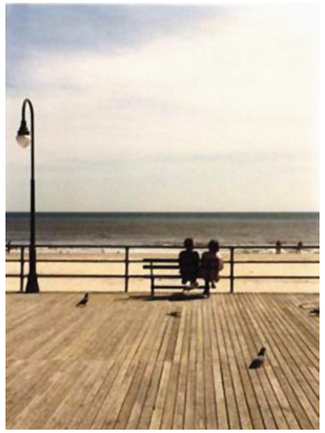

CS: Could you give an example of that in your career?
JF: Right at the beginning, when we were trying to create 3D reconstructions of entire molecules based on many single projections, it was obvious to everyone that one needed some type of a sorting technology — an algorithm — to do that. At the time, a student from Europe asked to join my team. We were in the computer room of the Wadsworth Center, the place where I worked, and people who would come into that room came from all disciplines — biochemists and people working in the field of laboratory medicine — a branch of quantified medicine. Then, once when I was looking at someone who was bent over the printer, out of that printer came what appeared to be clusters of numbers. I didn’t know this guy at that time, but he turned out to be someone in laboratory medicine. He was analyzing measurements of blood samples from patients using a program that cluster them according to their similarity. I walked up to my student and said ‘Stop everything you are doing, we have found the solution!’ Patients and their measurements in laboratory medicine were equivalent to our single-particle projections of molecules and their pixels. All we had to do was to feed our data to this laboratory medicine program and it worked out immediately!

CS: Did you ever consider a career in the arts?
JF: I did, very often. I was always put off by the competitiveness and pettiness of what I saw in the scientific world. Very often at conferences I felt isolated – I couldn’t really be myself. I felt like an outsider and sometimes, when I had real bad disappointments in research, I would imagine myself in the world of art. But then, it’s very sobering to see many people struggle in that field. So I never considered it seriously. My father, and I don’t know whether I was influenced by him, always regarded artists as breadless parasites of society because they didn’t do anything, from his point of view. I could understand the breadless part because I’ve seen many breadless people in the art world, including my uncle, who originally had some success but obviously couldn’t sustain himself, and had a job in high school as the primary source of income.

CS: Your scientific reconstructions capture molecules from all possible angles, whereas your artistic photography is about the untimely. How do both practices relate to each other?
JF: Science has a very exact protocol, which doesn’t allow me a lot of freedom. I need another world where I can escape to, and where I have unlimited freedom. I love photography, and I also write fiction. Art is what keeps me going.