Q & A

Cris Kuhlemeier

Cris Kuhlemeier received a PhD in genetics from the University of Utrecht in his native country The Netherlands. After working as a postdoc and assistant professor at The Rockefeller University in New York, he was appointed Professor of Plant Physiology at the University of Bern in Switzerland.

How did you get into plant biology? As a teenager I had no idea what to do. During my last year in high school I had already abandoned my dream of becoming a professional chess player and half-heartedly considered studying history, medicine, political sciences, and exotic languages. There was also the prospect of jail for objecting to military service. After just a few disappointing weeks doing real work in a frozen food factory my parents simply registered me for biology. The atmosphere at the University of Utrecht was so different from the repressive protestant high school up north. There was this excitement about the environment, the protests against the Vietnam war and the dictatorships in Spain and Chile. The Royal Dutch army had in the meantime decided that I was too skinny to be fit for active duty and drafted me "without having to be physically present". Biology itself was less inspiring — the curriculum was rather boring and old-fashioned, lots of the stamp-collecting type of natural history. But I made it through my first year, only failed plant physiology. And I realized that I liked biochemistry and genetics. It was the research work as a master's student that got me excited — I purified translation initiation factors involved in ribosome dissociation under the guidance of a supervisor who rather bluntly explained that science is hard work. After that, I was going to do a PhD on DNA replication of bacteriophage ϕX174, but on my first day of work I was told that since Sanger had sequenced the ϕX genome I was instead going to work on plasmid replication in cyanobacteria. From there it was a logical next step to move into higher plants.

How do you select your research projects? During my PhD I read somewhere that if you work on an organism you should work on something that the organism does well. Plasmid replication in cyanobacteria definitely did not fulfill that criterion. My postdoc work was on transcription. At the time, nothing was known about promoters and transcription factors in plants. Thanks to the emerging transgenic technologies we could do large-scale experiments in real plants. So this was new and exciting and we learned that, even though the individual components were different, the basic mechanisms are conserved between plants, fungi and animals. This also meant that it was probably a good decision to move on. I had become interested in development and decided to work on phyllotaxis, the regular arrangement of leaves and flowers around the stem. Phyllotaxis is a classical problem in botany with interesting quantitative aspects. Nobody had worked on it for decades and we had the field for ourselves until we worked out the molecular mechanism. That took quite a while. Fortunately, one of the many good things about Switzerland is that it generously supports basic science. Another good thing was my new colleagues — they were excellent plant physiologists who were happy to teach me how much more there is to plants than transcription factors. They also patiently corrected my German, and guided me through the bureaucracy. My new interest is the genetics of plant–pollinator interactions. Plants have roots, so they can't move around to find a partner. *Arabidopsis* has solved the problem in a rather boring way by self-fertilization. Most flowering plants, however, have evolved sophisticated mechanisms to recruit animals to help them with outcrossing. We use *Petunia* because it is a classical genetic model system and it has closely related wild species that are pollinated by different animals. We cross the plants and ask which genes make them attractive to bees, moths or hummingbirds.

What is your favorite research article? There are many. Definitely the articles on the crystal structure of the ribosome. The incredible detail is such a change from the clay models of my student days. Now we know that the proteins keep the RNAs in shape, that the ribosome is a ribozyme. And I like the idea that the structure could never have been deduced from the structures of its components. Another inspiration

has been the work of Paul Green on the mechanics of morphogenesis. The concepts have a long history, but until recently geneticists were deeply uncomfortable with them. It is wonderful to see how the two fields are beginning to merge. Finally, the work of John Doebley and colleagues on the origin of maize. Maize does not look like its ancestor teosinte at all, but only five loci can explain most of the difference. It is gratifying when a complex problem turns out to have a simple solution.

How do you see the future of your field? When I first read about PCR, I was sure it would never work. And the human genome project seemed such a waste of good money. So, I better stay close to the present. There is already a clear trend away from *Arabidopsis*, comparable to what happened to *Escherichia coli* in the 1980s — people move on, not because there are no interesting questions left but because exciting new opportunities open up. In our work on the role of mechanics in development we will definitively continue to use *Arabidopsis*. In terms of genetics, this means that the focus must shift from regulatory factors to genes involved in cell wall biosynthesis, cytoskeleton and water movement. Mutations in such housekeeping genes will be highly pleiotropic, but with the advances in conditional expression systems we can hopefully deal with that.

Geneticists have stayed away from non-model plants because they were so hard to work on. The new high-throughput technologies are now lifting that barrier, so we can study the unique biology of a wide variety of species. The impact will be greatest in ecology and evolution, finding the genes that nature selected to adapt to new conditions. In developmental biology, we have ignored the fitness of our mutants as long as the plants were alive enough to work with. Understanding which mutations

can alter traits without compromising fitness in the field will also be relevant for molecular crop breeding.

Why is Europe so critical of GMO crops? As long as it is cheaper to import food than to produce it locally, Western European countries have no need for GMO crops. Where it does matter is Africa. In my scientific opinion, GMO food is safe to eat, GMO crops can increase yield and, when used wisely, are good for the environment. Unfortunately, scientists are helpless in the emotional and politically charged debate. I sincerely hope that one day Greenpeace will conclude that GMOs are not just evil but might, just might, help save the lives of starving children. Greenpeace has great powers of persuasion, and with power comes responsibility.

If you could start again what would you like to work on? Of course, one of the great things of academia is that you can start something new any time, if you really want to. We visited Yellowstone Park last fall and those brilliant thermal pools reminded me how interesting cyanobacteria are. Four billion years ago, cyanobacteria were the dominant form of life — they invented oxygenic photosynthesis and changed the Earth. Today, they thrive in marginal habitats, or as chloroplasts, engulfed and enslaved by colorless proto-eukaryotes. I would like to do single-cell genome sequencing of cyanobacteria and other ancient bacteria from unusual habitats. I would look for enzymes with unusual substrates that had to be taken up from the environment. Such 'reverse ecology' would tell me something about the organic compounds present at the beginning of life. Potential building blocks of a pre-RNA genetic material would be particularly interesting. Cyanobacteria probably drove more ancient life forms to extinction. Or perhaps they didn't? If their genetic material is not PCR-amplifiable, if they are not abundant and grow slowly, nobody would have noticed them. It is hard to imagine the Swiss National Science Foundation funding such a project, but it is fun to think about it. And isn't wild speculation the raw material of science?

University of Bern, Altenbergrain 21, CH-3013 Bern, Switzerland.
E-mail: cris.kuhlemeier@ips.unibe.ch

Essay

Intellectual immigration

The influx of physicists to the realm of biology around 1940 represented the birth of molecular biology. Now, with the sequencing of thousands of genomes and the promise of the $1,000 human genome, we find ourselves returning to physics. The cell is a foreign place, one that requires concepts from physics and statistical mechanics to gain a basic understanding.

Kerry Bloom

Why should we care how long bacteria can swim without energy, or why you can run but not walk through muddy water? The answers to these questions reveal two basic biophysical processes. One is known as Reynolds number (a dimensionless number, the ratio of inertial/viscous force). In a highly viscous environment, mass is irrelevant, and upon loss of energy a bacterium will drift less than the width of a hydrogen atom. Second, non-Newtonian liquids such as muddy water exhibit properties of solids or liquids, depending on the frequency of sampling. The world without gravity (Figure 1, low Reynolds number [1]) is much more representative of life in a cell than our intuition leads. In fact, our intuition fails miserably when we scale down to cellular dimensions. Our world is dominated by inertia — air is our viscosity. The state of constant motion exhibited by all molecules (k_BT = 4.1 pN nm) is completely foreign as we consider our macroscopic world. It is critical that we entrain our intuition with the conditions and experiences encountered by those molecules we yearn to understand. The challenge for 'biologists' is to distrust our instincts, learn a new language, and embrace a world in which there is no gravity, everything is in constant motion and it is thick as molasses. Welcome to the world of the cell.

We turn to the providence of biophysics to provide a basic understanding of the world inside the cell. Let's start with a very simple relationship $\Delta G = \Delta H - T\Delta S$ (Gibbs free energy = Enthalpy – (Temp*Entropy)). In living cells temperature is constant (homeostasis). Thus, we need to look at the Gibbs free energy relation and ask where the sources of energy are. For living matter, the energy source is in enthalpy (ΔH) and the number of conformational states (ΔS). While insights from structural biology cannot be overstated, the number of conformational states and their contribution to biological processes is even more sobering. There are several simple essays that peer into the world of the cell. One is "Life at low Reynolds number" by E.M. Purcell [1]. Purcell describes life in a world dominated by viscosity (Figure 1). In this world, there is no coasting, nuts do not fall off bolts when unscrewed, and walls are not needed to confine biochemical reactions. Second, "There's plenty of room at the bottom" by R. Feynman [2], in which he explains why combustion engines don't work at small scales (heat is dissipated very quickly) and how much room there is at the molecular level. If you take the 'air' out of the atoms in our body, the remaining mass would fit on the head of a pin (*The Tao of Physics*, F. Capra [3]). It's easy to appreciate how our intuition fails in these situations — the challenge is to gain intuition that will guide our quest to understand the mysteries of life.

For a cell biologist, there is not one book that provides the biophysics underlying problems as diverse as the cytoskeleton, chromatin, protein sorting, signaling or nuclear organization (to name a few). Biophysics requires applied math, material science and engineering, physics, polymers, chemistry and biology. There are language and conceptual issues, including diffraction and quantum theory. The tools to tackle complex biological problems such as DNA sequencing, mass spectrometry, and sub-resolution light microscopy generate enormous data sets that bring quantitative and statistical challenges in analysis. In teaching transcription, we now include a discussion of noise and how noise can amplify signals in non-linear processes. In teaching chromosome segregation, we find papers that consider polymer repulsion and the