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# A BIOLOGIST TALKS TO A PHYSICIST

Working alongside people from different fields can help in improving communication skills and identifying gaps in knowledge. **By Kenneth S. Kosik**

As a physician–scientist, many of my colleagues were surprised when I moved my laboratory from the Boston Longwood campus at Brigham and Women's Hospital in Massachusetts to the University of California, Santa Barbara (UCSB), where there is neither a medical school nor a university-affiliated hospital.

More than a few e-mails arrived — some expressed puzzlement, some surprise, some had a wink, but all were punctuated with an exclamation mark.

When I made the move ten years ago, I had wanted to shift my biomedical work closer to the interests of physical-science researchers, to discover broadly applicable principles within the framework of biology, and to grasp the multilayered complexity hidden in nearly every question posed by biologists.

The physical sciences are not lacking in Boston. In fact, they are world class. But my lab was on the 'medical' side of the Charles River, practically an ocean away from the physical-science labs at Harvard University in Cambridge, Massachusetts, on the other side. So, engaging scientists in physics and chemistry, or in computer science and engineering, was challenging — especially for a medical doctor trained rather narrowly in molecular and cellular biology.

My goal was simply to open a conversation and possibly a collaboration with physicists, not to become one. As a relatively small institution with a distinguished faculty in both the physical sciences and engineering, UCSB was, I felt, an ideal place to wade into this territory. Over the ensuing decade, this risky move has resulted in my sharing many graduate students and postdoctoral fellows with computer-science, engineering, physics and chemistry faculty members. These collaborations have greatly broadened the science in all my publications.

I devised a few simple rules to help the biologist in me to cross the divide between the life and physical sciences. In learning to talk to physicists, I discovered that I can communicate better with everyone and clarify for myself what I do and do not understand in my own field.

**Understand what 'I do not understand' means.** When physicists say they do not understand something that you have said about biology, it's possible that you do not understand that topic either.

'Understanding' operates at different planes in different disciplines, and when a physicist seeks understanding, what they hope to grasp might differ from the knowledge that a biologist seeks.

For example, a biologist understands gene transcription by identifying specific transcription factors, their binding sites, the role of RNA polymerase and the genes that get activated.

For the physicist, these crucial facets of transcription – specific gene names and binding sites – are extraneous details. Instead, among the questions they consider important are the probability distributions associated with attracting transcription complexes to specific sites and the quantification of the forces involved in this process.

Clearly, questions of this nature are of keen interest to biologists once we sidestep our love affair with our favourite gene.

**Seek common ground.** When a physicist says they do not understand an aspect of biology, they are not requesting a 'biology 101' explanation. In my experience, when physicists ask a biology question, they want to apply the thinking of physics to biology; specifically, they are searching for universal, mathematical explanations.

Physicists move away from settled questions. In biology, much less seems settled. Emphasizing what you know is less interesting than saying what you need to learn.

Many of the missing pieces in biology are quantitative details, such as the absolute copy numbers of a protein or an RNA in a single cell that kinetically mediates some function, and how the cell keeps track of so many regulatory dials. Do cells perform regular maintenance on a parts-replacement calendar, as is done for aeroplanes, or is damage the only trigger for replacing parts? Does damage tend to occur according to a clock? Identifying these unknowns in biology is more stimulating than recounting textbook-level information.

SONIA FERNANDEZ

Neuroscientist Kenneth S. Kosik.

"The fastest way to make a physicist's eyes glaze over is to recite biological jargon."

**Recognize the posture of false modesty.** I have found that physicists often display a false modesty regarding their knowledge of biology. A physicist will say biology is much more difficult than physics because there is a lot to memorize. They might say: you know an encyclopaedia of detail, and all I know are a few equations.

**Keep in mind the maths shortfall in biology.** For most biological phenomena, we don't have precise equations – unlike in physics. This is not to say that we don't have maths, but our field needs a lot more detailed quantification. This lack is the Achilles heel of biology, and affects even the concepts we use every day.

It is a rare biologist who can explain the negative binomial used in RNA sequencing, parameterize organelle shape and distance scales when assessing active transport and diffusion, or interpret the phase diagrams that correspond to biomolecular condensates – a surging interest in biology.

Deep computational knowledge is a huge asset for biologists, but many have not had the opportunity to hone these skills or even be introduced to them. In my experience, opening a conversation and sharing students with physical scientists is step one towards bridging this gap.

**Don't be flummoxed by physicists' maths.** In discussing their own work, physicists will often reach for a formula. After they write the equation and stare at it as if pondering a Mark Rothko painting, they might proffer an explanation. You can have a productive conversation without the bread-and-butter basics of physics, such as Hamiltonians or modelling an Ising phase transition. Bear in mind that physicists can be more sensitive about the maths than are mathematicians, who are not bound by reality and see the world as a constraint.

Albert Einstein said: "As far as the laws of mathematics refer to reality, they are not certain; and as far as they are certain, they do not refer to reality." The biologist must have substantial comfort with uncertainty. Compared with the good predictions from theory in physics, prediction in vast facets of biology, such as evolution, is more like stock-market cycles – discernible only in retrospect.

**Scale matters.** Consider this matter of perspective: most of the time, what a physicist does is much smaller or much bigger, or much colder or much hotter, than anything we biologists do.

Biologists should know the sizes of macromolecules — the organelles and the cells that they work with — and first consider how they scale (or do not scale) with systems derived from physics.

**Consider precision.** Physicists require much greater certitude to draw a conclusion. They might be a bit smug when you claim significance with a *P* value of less than 0.05. For them, attaining a result with a *P* value of 0.05 is like the chance of hitting a barn door with a baseball: you can't miss it.

**Avoid jargon.** The fastest way to make a physicist's eyes glaze over is to recite biological jargon, such as gene lists and pathways. Come to think of it, it's the fastest way to make anyone's eyes glaze over.

**Skip some details.** Physicists do not want to know about all your controls. They want the concepts, and are willing to assume you have performed the appropriate control experiments and have chosen the correct methods. If you're doing a 'chalk talk' (illustrated presentation) for physicists, be sure to emphasize your ideas more than detailed data and techniques. Physicists make judgements on the basis of clear, cogent, compelling ideas.

**Manage expectations.** Physicists expect you to build your own equipment. If this topic comes up with a theorist, feel free to ignore it. If it comes up with an experimentalist, you will have to concede that you paid a huge mark-up for off-the-shelf equipment.

**Understand optimization versus the 'good-enough' principle.** Biological processes carry evolutionary baggage, and therefore arrive at solutions that might not be optimal. If, for example, you were designing a machine that walks, it might not be best to model it on human walking, which is not necessarily the most efficient way to get somewhere. In the absence of evolution, the physical world is often assumed to operate according to optimized parameters. By contrast, biology operates in what has been called a Waddington terrain: processes function well even when they are not as efficient as possible — as long as they are still good enough to work.

**Consider a physicist's perspective on reductionism.** Reductionist approaches to complex biological systems do not necessarily mean reducing those systems to small units. Systems approaches to biology that involve large numbers of variables can be inherently interesting to physicists because they conceptually resemble problems in statistical mechanics that relate microscopic and macroscopic properties with very large degrees of freedom — and exact solutions are not possible. If a biologist can frame a problem in these terms, it will probably engage a physicist.

**Physicists laugh a lot.** Not only is the humour of physicists arcane, but almost anything unexpected can provide a jocular moment. Theirs are the ultimate inside jokes, which are often not obviously funny. But laugh along anyway — even if you don't find the humour, they won't know the difference.

## The future

To conclude, let me say this path is not for everyone. Knowing yourself is the crucial element. If you are uncomfortable engaging with specialists in fields in which you are not trained, or if you don't want to delve into topics that might not immediately bear a clear connection to your established domain, then the course I took is not for you. However, if you are not only comfortable with this approach, but require stimulation from outside your immediate realm of investigation, there is nothing better than to look in unexpected places.

**Kenneth S. Kosik** is a professor of neuroscience at the University of California, Santa Barbara.

# A PHYSICIST TALKS TO A BIOLOGIST

The fastest way to understand a new discipline is to embed yourself in it. **By Sarah Bohndiek**

It's amazing how many of biologist Ken Kosik's points in his accompanying careers column (page 281) resonate with my experience as a physicist working in the opposite direction. I enjoyed my training in physics largely because it didn't involve rote learning (needed by biologists to get that encyclopaedic knowledge) and it allowed me to derive much of the material from a few key equations and principles.

In his column, Ken notes that when a physicist says they do not understand something in biology, they are not requesting a lengthy 'biology 101' explanation. But I do sometimes want a biology 101 refresher so I can gather a deeper understanding of the biological problem while I think about how to address it.

Ken also talks about being uncomfortable with uncertainty. Personally, I can be quite comfortable with uncertainty when I can take steps to control it; it's just that, in biological systems, I normally have to accept that I can't.

## A deeper understanding

The PhD I received from University College London in 2008 was in radiation physics, with a focus on evaluating the potential of CMOS image sensors (the silicon behind most smartphone cameras) for application in medical X-ray-diffraction studies.

Most of this research took place in a dark room, where I examined the optical response of the image sensors, but because I was in a department of medical physics and bioengineering, I was exposed to a range of biomedical challenges — including cancer detection.

As I progressed through my studies, I realized that I wanted to gain a deeper understanding of cancer itself and how we might exploit its biology so we could use non-invasive imaging to find the disease.

I hadn't studied biology since I was 16, so I started looking for postdoctoral positions in 'friendly' environments — biophysics, bioengineering and so on. But I soon realized that, to truly understand cancer, I needed to break out of my comfort zone and immerse myself in that environment.

My first postdoc was in Kevin Brindle's biochemistry laboratory at the University of Cambridge, UK. I learnt how to hold a pipette, run a magnetic resonance imaging system, conduct animal experiments and design biology studies.

In return, I fixed temperamental magnets, wrote hardware-control code and supervised some of the lab's more physical-sciences-oriented projects. After three years, I had a much greater understanding of cancer biochemistry and how to conduct *in vivo* imaging studies, but I was missing exposure to clinical applications and connection to my previous research home in optics.

My second postdoc, with Sam Gambhir in the department of radiology at Stanford University, California, took me back to my roots. I explored new projects in optics, trying to make imaging with optics faster and cheaper than before and opening new horizons in fields such as endoscopy.

As part of Stanford's Molecular Imaging Program, I saw teams build new technologies in the lab and take them through to first-in-human studies. I was inspired by Sam's dedication to revolutionizing early cancer detection and his incredible passion for transforming technology into clinical trials. That passion still drives me in my current role at the University of Cambridge, UK, where the mission of my interdisciplinary team is to advance our understanding of tumour evolution using next-generation-imaging sciences. We operate between the department of physics and the Cancer Research UK Cambridge Institute, and this gives us access to a community of optical physicists as well as cancer biologists, and a translational pipeline through to clinical application.

## Build synergy

I'm a technology geek at heart. I love to dive into the underlying physics when I design optics and to explore the engineering of new devices; but, for me, the story is never complete without seeing these methods through to application. I feel that the research path I explore today is a synergy of all my experiences.

I am often asked what I learnt as I traversed this path from physics to medicine. The following are the key steps I had to take during my own personal development, which prepared me well to embrace my interdisciplinary career.

**Learn the language.** Just as with a foreign language, the fastest way to become fluent in the language of a new scientific discipline is to embed yourself inside it and practise regularly. For me, learning the language was the most important reason why I moved from physics to biochemistry for my first postdoc.

**Get comfortable being uncomfortable.** I went from being one of the most knowledgeable people in my research field at the end of my PhD to knowing less than most of the first-year PhD students in my new lab. For me, that meant I was doing something right, but you do have to be OK with taking that hit and spending time building a new skill set.

**Don't forget that you bring unique skills.** I had a lot to learn along my journey, but I brought useful skills at each stage. My quantitative mindset was valuable in designing imaging experiments, my engineering skills were useful for fixing broken equipment and my bottom-up physics approach to problems offered a fresh perspective.

**Test biological-research hypotheses.** Sometimes you'll bring a quantitative perspective that enables you to test a hypothesis or embark on a research topic that wasn't accessible before. Don't be afraid to ask the biological question yourself rather than waiting for your collaborators to provide an answer.



**Physicist Sarah Bohndiek.**

> **"A strong element of academic achievement is community recognition and networking."**

**Ask questions.** I had to, and there are no stupid ones. I also attended introductory lectures for first-year undergraduates to fill in gaps in my knowledge. Going back to school and admitting what you do not know is crucial.

**Embrace uncertainty.** I continue to be amazed by the complexity of biology and hence the uncertainty in results. Unfortunately, it's likely that I'll never be as certain about anything in biology as I can be about new discoveries in physics.

**Learn statistics.** Having a quantitative background doesn't necessarily mean you really understand statistics. I had to dive back into statistics to design the best biological experiments.

**Don't lose touch with your roots.** Being able to continually innovate at the interface of physics and biology means staying grounded in the physical sciences, but this can be hard to do when you are in a biological department. To compete for faculty positions, you need to be able to teach your subject, so find ways to keep it fresh in your mind, as I did, for example, by teaching physics in undergraduate or graduate courses.

**Do not blindly accept dogma.** Challenging prevailing ideas in biology using your perspective can bring about revolutions. I greatly admire colleagues who have upturned decades of accepted dogma using quantitative methods that were not even considered by the biological community.

**Perfect your pitch.** Working across disciplines means you'll inevitably be talking at conferences and meetings to groups of scientific non-specialists; the best communicators perfect a balance of generalist and specialist material in presentations and make their language accessible to all.

**Avoid equations during presentations.** It's not just biologists who would prefer not to see them. Illustrate equations with graphs and visuals as much as possible. If you do have to include equations, write them on a board in real time so your audience can follow your guided explanation – don't just flash them up on the screen.

**Find a good mentor.** Finally, and most importantly, I would not be where I am today without my incredible mentors. When you move disciplines, you need people who can help you to integrate into a new community, show you how to navigate a new funding landscape and advise on expectations for junior faculty members, when the emphasis on publication and impact varies dramatically between disciplines.

## The future

More unified training, encompassing physics and engineering applied to biology and medicine, will help to equip the next generation of researchers with the skills they need to operate across these disciplinary boundaries.

I still advocate for specialist training in one field as an undergraduate and then broadening research horizons gradually through advanced academic training.

A strong element of academic achievement is community recognition and networking; moving too rapidly between fields can make it challenging to build a reputation for excellence. Imaging is kind in this respect: regardless of how you form an image, there are many commonalities in the research that mean it is relatively easy to tell a story within your career and maintain connections along that journey.

Building that story and your profile will ultimately be crucial, no matter what path you choose to take.

**Sarah Bohndiek** leads an interdisciplinary team combining physicists, engineers, chemists and molecular biologists at the University of Cambridge, UK.