A Conversation with Howard Berg

***

S. Bahar

DBP member Howard C. Berg is Herschel Smith Professor of Physics, and Professor of Cellular and Molecular Biology, at Harvard University. As his academic titles suggest, his research is truly interdisciplinary. Among other areas, his research has made pioneering contributions to the study of bacterial locomotion. He is the author of Random Walks in Biology (Princeton, 1993). Berg's most recent book, E. coli in Motion, was published by Springer last year. Howard Berg talked with THE BIOLOGICAL PHYSICIST *about his scientific background, his new book, and his thoughts on interdisciplinary science in general.*

What led you into science in the first place?

My father was a biochemist at the University of Iowa in Iowa City, so I grew up among scientists. But the major spark was the discovery of a cache of 1920's radios in my grandfather's cellar in Wahoo, Nebraska. I became hooked on electronics. This led me to Caltech, where I thought I would become an electrical engineer. I started studying physics, because it appeared more fundamental, and then I became interested in chemistry, inspired by Linus Pauling, who taught the introductory course. I changed majors in my junior year and ended up with a bachelor's degree in chemistry. Along the way, I worked with Victor Neher, building electronics for his cosmic-ray balloons, and with Jerry Vinograd, doing experiments with his Beckman Model E ultracentrifuge. I might have stayed in physics had I been better advised: Willy Fowler was my physics advisor, but he said I needed no advice, because my grades were so good. In retrospect, that was because I lacked a sense of discrimination.

So how did you end up in biology?

That was the product of an extended identity crisis. I studied protein chemistry with Linderstrøm-Lang in Copenhagen and then enrolled in the Harvard Medical School. Within 10 minutes I realized that was a mistake – I was much more interested in basic science – but it took me 2 years to figure out what to do about it. I withdrew, crossed the river, entered Harvard's chemical physics graduate program, and did a thesis with Norman Ramsey on the atomic hydrogen maser. A stint in the Society of Fellows led me back to biology, where I began research on the architecture of the human red cell membrane. I was appointed Chairman of the Board of Tutors in Biochemical Sciences, an undergraduate teaching program, so half of my time belonged to the Dean.

Describe some of the first research you did that you would label "interdisciplinary".

I suppose it was realizing that atomic hydrogen was undergoing free-radical reactions at the surface of the storage bottle in the hydrogen maser. Dan Kleppner and I figured out how to coat the bottle with Teflon, which solved the problem. While in the Society of Fellows, Ed Purcell and I teamed up to develop a new kind of separation technique called sedimentation field-flow fractionation. The test particle for the centrifuge version of this device was a spherical virus called R17, which I got from Joan Steitz, then in Jim Watson's lab. So I did a bit of interdepartmental roaming. It was a few years later, while in the Biology Department, that I got interested in the motile behavior of bacteria. I built a microscope that tracked individual cells of *Escherichia coli* as they swam in three-dimensions. I tried to use the biology instrument shop to build this device, but they threw me out. So I went back to my friends in the physics shop, where I had made parts for Ramsey's second hydrogen maser. I discovered some wonderful 16-mm

films of swimming bacteria, reconstructions of experiments done in the late 19th century by Theodor Engelmann, made by the microbiologist Norbert Pfennig, in Göttingen. I found a projector and showed them to Ed Purcell, on his office wall. He was captivated. His first comment was seminal, "How do they swim in a straight line?!" That was the beginning of our second and more long-lived collaboration.

What led you to write "Random Walks in Biology"?

I had learned a lot about diffusion from Ed Purcell, thinking about sedimenting R17 and swimming *E. coli*. Often, in our discussions, when I tried to write a differential equation on the board, he would tell me that we would do better to ignore the mathematics and think, instead, about the physics. I was not very comfortable with differential equations, anyway, even though George Carrier had done his best. (Carrier began that course with the admonition that the best way to solve a differential equation was to ask someone who knew the answer, the second best way was to guess and then prove the guess to be right, and the third best way was to use the methods he would try to teach. I suppose Matlab and Mathematica have changed that landscape completely, but I haven't caught up.) Neither Ed nor I were comfortable with thermodynamics, which has little to say about the random motion of molecules, in any event. So we thought in terms of the random walk. Once you think about what individual particles are doing, much of the mystery vanishes. Physical chemistry textbooks of that day gave you Fick's first equation (zap) and Fick's second equation (zap again) … but what might they mean?! I got invitations from graduate students to talk about bacterial behavior, notably at the University of Wisconsin at Madison and at Duke. Instead of giving a research seminar, I decided to describe diffusion in terms of the random walk, i.e., to try to teach students something. After a few minutes, one could feel the astonishment in the audience, "I can understand that!" So, there seemed to be a genuine need for such a book. And besides, by writing, I could come to better grips with the subject. The book does derive some relevant differential equations and discuss some solutions of interest, but the emphasis is on what these equations mean in biology, not how they might be solved.

What was the genesis of your new book "*E. coli* in Motion"?

A number of people have been working hard on bacterial chemotaxis for more than 30 years, ever since Julius Adler showed in a classic paper – Chemoreceptors in bacteria. Science **166**: 1588-1597 (1969) – that *E. coli* has specific chemoreceptors, i.e., that cells pursue specific chemicals because they like their taste. Of course, motility and chemotaxis were invented so that cells could find more to eat, but it is taste first, metabolism later. Adler showed that cells are happy chasing substances that taste good, even if they are inedible. I know a lot about the history of this subject – it goes all the way back to 1676, when van Leeuwenhoek first discovered motile bacteria – and about the physics, and somewhat less about the biochemistry and genetics. I thought it would be of interest to summarize this knowledge and to review some of the experiments done along the way. The book is intended for readers who know some science or engineering but who are not trained as microbiologists, readers who would like to learn more about molecular machines. It has the merit of being short.

Do you think there really is an increase in interdisciplinary work now, vs. a decade or two ago?

It seems to be more in the air. There are a plethora of interdisciplinary centers and funding schemes, where one is encouraged to find collaborators in other fields. I find this somewhat off-putting, if not superficial. The best interdisciplinary work is done by people trained in one subject (or even better, more than one) who become immersed in another. Look at the giants of molecular biology: Max Delbrück, Francis Crick, Max Perutz, etc. More recent examples include those pioneering single-molecule biophysics. I think it would be a tragedy if we do not maintain support for individual investigators, chosen by broadly-based peer review.

How would you define "biological physics"? Do you see it as a distinct discipline separate from "biophysics"?

Hans Frauenfelder and I discussed this topic in 1994, in an issue of Physics Today dedicated to physics and biology (February 1994, with our editorial comments on pp. 20-21). Put colloquially, the first is more what biology can do for physics and the second what physics can do for biology. However, I argued that biophysics also includes physics mastered by living things, taught to them by evolution. I think our discussion is still relevant. I feel very strongly that someone interested in an interdisciplinary subject needs to learn more than one language. If you are a physicist, learn some biology, and if you are a biologist, learn some physics. The physicist has a much easier task, because biology is an historical science and thus largely descriptive. It's much easier to learn descriptive subjects once you have mastered analytical ones than the other way around. In short, don't let someone in another culture do your thinking for you.

You have appointments in both Molecular and Cellular Biology and in Physics. Would you call yourself a "biological physicist"?

Perhaps, had I stayed in physics departments and taught physics. However, my laboratory space and teaching responsibilities have been in biology departments, so my working knowledge of physics has declined. (For example, I am no longer able to understand the theoretical section of my Ph.D. thesis: I have not used quantum mechanics for more than 40 years.) So, it's more accurate to say that I am a physicist who does biology, or a biologist who knows some physics. So I guess I am a biophysicist.

What advice would you give to an undergraduate student interested in biological physics?

Study analytical subjects first: applied mathematics, electricity and magnetism, statistical mechanics, and the like. Pick up the more descriptive subjects later: some biochemistry, molecular biology, genetics. So start with physics and then learn some biology. Once you know a bit of both languages, you will be able to take your own measure of the biophysical terrain. Neurobiology is clearly a field of the future, albeit immensely complicated. I think of myself as a neurobiologist, but one who has had the courage to deal only with the simplest single-celled nervous systems.

What about advice for graduate students, postdoctoral fellows, and young faculty members?

One becomes more specialized as one goes along. If you want to do biophysics, use your physics, but immerse yourself in biological problems until you find one that you hope to solve. If you want to do biological physics, i.e., work where the physics itself is paramount, then choose your problems accordingly. To take an example from my field, consider the bacterial rotary motor. If you want to understand how it is assembled and how this assembly is controlled, than do the biochemistry and genetics. If you want to understand its mechanical properties, e.g., the torque that it can generate at different speeds or whether or not it steps, then devise microscopic methods for making such measurements. If you want to understand how the rotation of helical flagella filaments generates thrust or how such helices interact to form flagellar bundles, then grapple with the hydrodynamics. There is a wide range of approaches here from very wet to rather dry. It sounds idealistic and old fashioned, but let curiosity be your guide. Grope about until you find problems that seem really interesting.

Where is your laboratory research headed in the next few years?

We are using fluorescence resonance energy transfer (FRET) to probe interactions between different proteins that constitute *E. coli*'s signal transduction pathway. How do the receptors talk to the flagella, and how, precisely, do the flagellar motors respond? We would like to understand every nut and bolt. Imagine, receptor clusters that count molecules of interest and make temporal comparisons; activation of a diffusible signaling molecule; reversible rotary engines that drive propellers of variable pitch; pistons, rotors, drive shafts, bushings, universal joints; a system with prodigious sensitivity with amplification generated by receptor-receptor interactions. To learn more, see Berg, H.C. Motile behavior of bacteria. *Physics Today*, January 2000, pp. 24-29.

Some recent papers:

Sensory transduction in *E. coli*

1. Sourjik, V. and Berg, H.C. Receptor sensitivity in bacterial chemotaxis. *Proc. Natl. Acad. Sci. USA* **99**, 123-127 (2002).
2. Sourjik, V. and Berg, H.C. Binding of the *Escherichia coli* response regulator CheY to its target measured *in vivo* by fluorescence resonance energy transfer. *Proc. Natl. Acad. Sci. USA* **99**, 12669-12674 (2002).
3. Sourjik, V., and Berg, H.C. Functional interactions between receptors in bacterial chemotaxis. Nature **428**, 437-441 (2004).
4. Vaknin, A., and Berg, H.C., Single-cell FRET imaging of phosphatase activity in the *Escherichia coli* chemotaxis system. *Proc.Natl. Acad. Sci. USA* **101**, 17072-17077 (2004).

Movement near surfaces

5. Darnton, N., Turner, L., Breuer, K., and Berg, H. C. Moving fluid with bacterial carpets. Biophys. J. **86**, 1863-1870 (2004).
6. DiLuzio, W.R., Turner, L., Mayer, M., Garstecki, P., Weibel, D.B., Berg, H.C., and Whitesides, G.M. *Escherichia coli* drive on the right. *Nature*, in press (2005).

Gliding in *Mycoplasma*

7. Miyata, M., Ryu, W.S. and Berg, H.C. Force and velocity of *Mycoplasma mobile* gliding. *J. Bacteriol.* **184**, 1827-1831 (2002).
8. Jaffe, J.D., Miyata, M., and Berg, H.C. Energetics of gliding motility in *Mycoplasma mobile*. *J. Bacteriol.* **186**, 4254-4261 (2004).

Reviews

9. Berg, H.C. The rotary motor of bacterial flagella. *Annu. Rev. Biochem.* **72**, 19-54 (2003)
10. Berg, H.C. *E. coli* in Motion. (Springer- Verlag, NY, 2004).

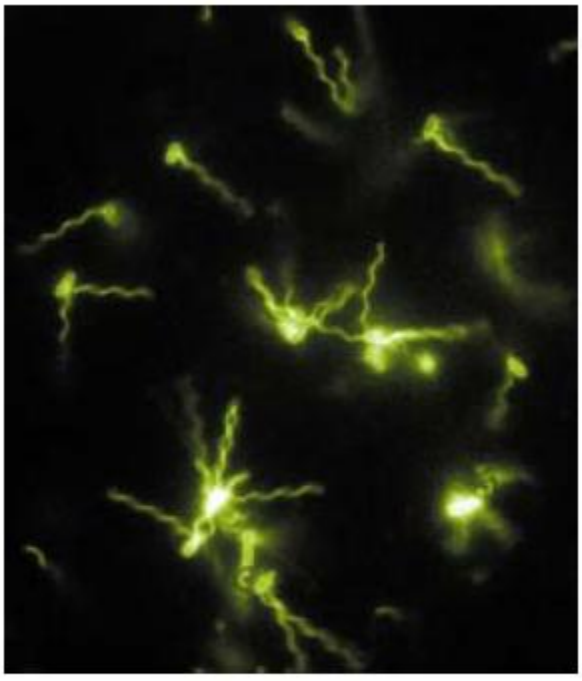

Figure 1. *E. coli labeled with an Alexa Fluor dye and observed in a fluorescence microscope. For movies of such cells swimming, go to the visit* http://www.rowland.harvard.edu/labs/bacteria/index *and click on the "movies" link.*

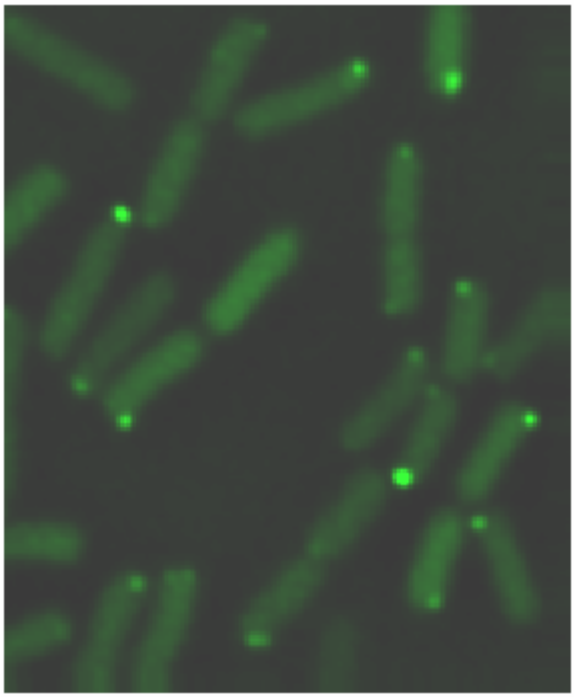

Figure 2. *E. coli has a brain… but it is very small. Cells labeled with a methyltransferase (CheR) yellow fluorescent protein fusion, which binds to chemoreceptors. The receptors form tight clusters, usually at one pole of the cell. Much of the computation involved in sensing changes in the concentrations of attractants in the environment goes on in such clusters, so they are referred to here as brains. When swimming in spatial gradients of attractants, cells make temporal comparisons over a time span of 4 s, so the brain has a short-term memory.*

Howard C. Berg