QnAs with William Bialek

Beth Azar

Science Writer

William Bialek works at the interface of physics and biology, searching for predictive mathematical theories that can quantify and explain diverse biological phenomena. A member of the National Academy of Sciences, Bialek is the John Archibald Wheeler/Battelle Professor in Physics at Princeton University, a member of Princeton's multidisciplinary Lewis-Sigler Institute for Integrative Genomics, and Visiting Presidential Professor at the Graduate Center of the City University of New York. Much of Bialek's work is motivated by the observation that many biological systems perform near certain fundamental limits set by physical laws. He talks with PNAS about his latest work.

PNAS: As a theoretical physicist, what drew you to biology?

Bialek: As a student, I went to biology seminars and found the subjects that they were talking about incredibly interesting but the way they talked about them unsatisfying. Then I would go to the physics department and listen to seminars, and it was the other way around: the way of thinking was incredibly engaging, but the particular subjects they were talking about didn't always grab me. So I wondered whether you could think about the phenomena of life in the language of physics. And I'm still trying to do that.

PNAS: Your work is described as an effort to understand diverse biological phenomena through unifying theoretical principles. Can you explain?

Bialek: In physics we can start with fairly general principles, derive their consequences, and then see those consequences in particular systems. Most biological phenomena are not understood in this way. We understand a lot of particulars, but we don't have a very predictive theoretical framework. For example, we might have a model of how gene expression is regulated. However, one would also like to know whether there is some underlying principle that explains how genetic regulatory networks are organized. Then you could start with that principle and derive some things that have to be true about particular systems.

PNAS: Your early work focused on the nervous system, but more recently, you have

begun to examine embryonic development. What is the connection?

Bialek: I'm interested in the problems of signals, noise, and information transmission. That's a theme, and I continue to work on both neural and genetic networks. When I moved to Princeton [in 2001], my colleague David Tank moved at the same time. We were chatting about what we might do together and we both were curious about how things we understood at the level of the nervous system worked if you dropped down to the level of single cells. Instead of thinking about neural networks, you could think about genetic networks; instead of thinking of information being transmitted along neurons, you could think about it being transmitted from transcription factors to gene expression, and so on. As we were talking, Eric Wieschaus walked into the room. We caught him up and he said: "I'm not sure exactly what you want to do, but let me explain why you should do it in flies."

PNAS: Your early work on *Drosophila* development showed that the responses of a single gene to maternal signals are highly precise. Your Inaugural Article continues to examine how embryonic cells know where they are in the embryo by monitoring the expression of a group of four genes. Could you elaborate?

Bialek: Instead of asking about one gene, we're asking about a collection of several genes together and how the combination of their expression levels encodes a cell's position in the embryo. We can ask how much information all these things carry together. And, indeed, there is something special about their relation to one another, making sure the information is uniformly distributed along the length of the embryo. We argue that this uniformity is a signature of optimization in the transmission of positional information.

PNAS: You found that the expression levels of the four genes carry enough information to determine a cell's location along the anterior-posterior axis of the embryo with an error of just 1%. What does that finding tell us about the physical properties of development?

William Bialek. Image courtesy of the International Centre for Theoretical Physics.

Bialek: This finding takes the qualitative notion of "positional information" and makes it mathematically precise. We can say that this combination of molecules, by virtue of their concentration, tells the position of each cell with a certain accuracy. Once you do that, you see that there really is quite a lot of information available very early. You can almost say exactly where it is just by knowing the expression levels of these four genes. I think that there is a general feeling that everything is terribly noisy and unreliable, and it all sort of miraculously comes together at the end. Instead, it is turning out to be extraordinarily precise even in the very first steps of the process.

PNAS: How close are you, with this work, to unifying principles for development?

Bialek: We are very far from saying that we have a principle that organizes our understanding of this class of networks. On the other hand, this shows that you can go in and start measuring a lot of the relevant quantities. Nothing tells you that you have the right principle, but things could have gone wrong already, and they haven't. Here we are fortunate that not only did we learn how to measure things that the theory suggested would be interesting, but there are aspects of the data that look the way the theory says they should look. Now, does that mean the theory is right? No, it means it's productive.

This is a QnAs with a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 16301.