Scientists

Bridging Worlds

Barry Honig

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Barry Honig's development of essential tools for structural biology and his work in the field of computational biology caught our attention. Curious to know more, *BioTechniques* contacted him to find out about the ambitions, character, and motivations that led to his success.

In building your career, what was your most significant obstacle?

My doctorate was in the field of chemical physics, focusing on theoretical spectroscopy. Many concepts in this field were already well understood at the time, so I wanted to move into biology where I could see a new world developing with many open questions. I was introduced to how visual pigments work as a postdoctoral fellow at Harvard University, and enthusiastically adopted a project in this field. But when I finished my fellowship, I encountered a form of cultural bias that still exists to a lesser extent today: physicists and chemists viewed working in biology as a lower level activity while biologists, rightfully, said I wasn't a real biologist. Consequently, I couldn't get a job.

Cyrus Levinthal, who was trained as a physicist and went on to become a biologist, offered me a second chance working in his lab. He did not hire me to do biology, rather to work on environmental problems. Based on the research I did in his lab, I eventually found a job in the chemistry department of the Hebrew University in Jerusalem. A few years later I wanted to move back to the states, but I still had the problem of defining

myself. Was I a chemist? A biologist? What department would I be comfortable in? It was a long struggle, and one I still see today with young people doing interdisciplinary research. In the end, I was fortunate to become part of a new department at Columbia University called biochemistry and molecular biophysics. This has been a wonderful scientific home where nobody really cares about disciplines; the faculty just want to have interesting colleagues.

What has been your most significant scientific contribution?

My most significant contribution has been to successfully integrate computational analysis in various areas of biology. It wasn't always obvious that this would be possible. Early in my career, I discovered the role of charged amino acids in determining how light is detected at the molecular level in visual pigments. I was able to do this by developing software to model the physical and chemical properties of light absorption and the subsequent photochemical processes, and a collaboration with an organic chemist at Columbia, Koji Nakanishi, allowed us to confirm the model and examine the details experimentally.

But the work that I'm probably best known for came after this discovery. After realizing the importance of charges on amino acids in visual pigments, I developed methods to calculate electrostatic properties of proteins and nucleic acids from their 3-dimensional structures. These approaches are applicable to many biological problems, and the software programs I created, DelPhi and GRASP, are widely used today to look at the electrostatic properties of membranes and protein and nucleic acid structures.

What are you working on now?

In the past few years, I have focused on three apparently different biological problems: cell-cell adhesion, transcription factor recognition of specific DNA sequences, and predicting protein interactions on a genome wide scale using structures. In the case of cell-cell adhesion, I want to under-

stand how members of the cadherin family of cell-adhesion proteins, which are similar but subtly different from each other, cause cell recognition and how subsequent adhesion initiates downstream signaling. We are also working on how Hox transcription factors are able to discriminate between nearly identical DNA sequences. We have found that these proteins, as well as many other transcription factors, recognize deviations from the ideal double helix that cause variation in the electrostatic properties of DNA.

Finally, given two protein structures, we want to predict whether they interact. Interactomes have been created by others, but those were not based on protein structures. There are relationships between proteins that don't look alike globally, but their local patterns are similar. We feel that much can be learned from analyzing protein structures and finding common structural patterns that might be lost when looking at the entire structure. We are now able to predict whether two proteins interact or not with a statistical confidence level comparable to that obtained from high throughput experiments.

We approach all of these questions using combinations of crystallography, biophysical measurements, in vitro and in vivo cell assays, an understanding of the biophysical principles involved, and simulations carried out at different levels of granularity. These calculations help us think about the problem, analyze our data, and develop conceptual models. My dream is that computation will not be seen as a separate discipline, but one in a battery of tools that can be used to understand biology. We believe that computation can build a bridge between many different worlds.

Interviewed by Kristie Nybo, Ph.D. Image courtesy of Paul Fetzters.

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