David Baker

David Baker is a biochemist who is known for his pioneering work in the field of computational protein design and protein structure prediction. His research group focuses on prediction and design of protein structures, protein-folding mechanisms, protein–protein interactions, protein–nucleotide interactions, and protein–ligand interactions. Baker received his Ph D degree in biochemistry at the University of California, Berkeley, USA, and completed his postdoctoral work in biophysics at the University of California, San Francisco, USA. He is currently a professor of Biochemistry and Director of the Institute for Protein Design at the University of Washington, USA. He is also a Howard Hughes Medical Institute investigator and a member of the US National Academy of Sciences. He has received young investigator awards and fellowships from reputed science foundations. He has also received the Irving Sigal Young Investigator award from the Protein Society and the Overton Prize from the International Society of Computational Biology. He is a recipient of the Feynman Prize from the Foresight Institute, AAAS Newcomb–Cleveland Prize, Sackler Prize in biophysics, and the Centenary Award from the Biochemical Society.

During his visit to India during December 2018–January 2019 as the 32nd Raman Chair Professor of the Indian Academy of Sciences, Baker addressed the following questions posed to him:

What got you interested in protein design?

Initially, I started off more with cell biology and how cells are organized. My thesis work with Randy Schekman looked at how proteins moved around in cells. After that, I became more interested in basic questions of biological self-organization; I was fascinated by protein folding, the simplest case of biological self-organization, whereby a polymer has the property to fold into a single unique state that has a function. When I started my own lab, we worked on protein folding experimentally to understand its principles. We encoded the principles from our experimental observations in an algorithm for folding up proteins on the computer. We became reasonably good at predicting the amino acid sequence from the structure and the basic principle was that the given chain of amino acids searches for its lowest energy state on the computer. As this process matured, we realized that rather than starting with an amino acid sequence and finding its lowest energy state, we could start with a brand new structure that accomplishes a specific function and then work backwards to identify an amino acid sequence whose lowest energy state was that structure. That is the protein design problem and how I became interested in it.

You have come up with crowd sourcing protein folding platforms called Rosetta@home and Foldit. How did you envision these projects?

Protein structure prediction or protein design requires a lot of computing power. Initially we just bought computers; however, this turned out to be expensive and we also ran out of space for the computers. We then decided to enlist the general public to help with the computing and that was the start of Rosetta@home. We now send protein structure prediction or design challenges to volunteers all over the world. The work is completed using the idle computing resources from the volunteers' computers and sent back to us. Once we had Rosetta@home set-up, volunteers who watched the protein folding on their computer thought they could do better if allowed to interact with the program. Hence we developed Foldit, an interactive game version that allows the player to enter in, move the protein and guide the search for the lowest energy state. We now have Foldit players designing brand new proteins.

What have been some important outcomes from Foldit?

There have been a number of interesting outcomes from Foldit. The team has developed improved algorithms; solved the crystal structure of a protein designed by Foldit players, a problem that could not be solved before. They have designed new proteins and improved the designed enzymes – a wide range of things, in all.

How has on-going research in your lab been applied to the real world?

In general, when people come to my lab, they try and solve a new problem in protein design that often has application in medicine or nanotechnology. A trend that is on the rise is that once people complete their Ph D or postdoctoral work, they spin out companies that seek to commercialize by getting the designed proteins into the real world. We have quite a few companies now that have come out of the work being carried out in the lab; these companies are designing enzymes that break down gluten for celiac disease; developing vaccines to protect against viruses like respiratory syncytial virus; developing enzymes for use in industrial applications and working in the areas of cancer and autoimmunity.

Your work is highly interdisciplinary. What are the main disciplines that are involved?

Protein folding is a biophysics or a biochemistry problem since it deals with the question – how does a molecule find its lowest energy state? However, to solve it on the computer you have to develop algorithms; that makes it a computer science problem. In a more general sense, it is a physics or physical chemistry problem because you are trying to find the ground state of a complicated molecule and a lot of the analytical methods used are those of physical chemistry. On the other hand, it is also an engineering problem because we are designing new proteins that will solve real-world problems. Finally it is also a genomics problem since we use data from DNA sequences. Thus it is a whole new area altogether.

Regarding the on-going research in your lab, what is it that you are excited about?

I am excited about it all and hoping that there will be several different impacts. Right now we are optimistic about making or being able to make improved therapeutics and vaccines for treating a wide variety of both infectious and chronic diseases.

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