Computational chemistry

Identifying molecules that might fulfil the stringent criteria necessary to become a drug from the vast number of possibilities has often been likened to searching for a needle in a haystack. Two computational chemists with a focus on drug discovery, Yvonne Martin and Brian Shoichet, discuss what attracts them to working on strategies to cut the haystack down to size.

Yvonne Martin

Recently retired as Senior Volwiler Research Fellow, Advanced Technology Division of Drug Discovery, Global Pharmaceutical Research and Development, Abbott, Chicago, Illinois, USA.

An accidental dinner-party meeting with Corwin Hansch, the father of the concept of quantitative analysis of the relationships between chemical structures and biological activities, was a catalyst for Yvonne Martin's career in computational chemistry in industry. "In high school, I had recognized that I was interested in solving biological problems using chemistry," she recalls. "But at the time that I met Corwin, my involvement in structure–activity relationships was from my pre-Ph.D. work and through my role as a drug metabolism expert at Abbott. During our conversation, I realized that I had to learn more about quantitative structure–activity relationships and bring it to the company."

Since this point, Martin has been involved in computer-assisted drug design at Abbott for more than 30 years. So what has kept her motivated to work in this field for so long? "Simply, it is the continuing challenge to better use the computer to understand structure–activity relationships and to solve problems faced by medicinal chemists in their search for the next new drug," says Martin. "I still remember the day, perhaps 15 years ago, when a chemist came to my office to report on the biological activity of a compound that my models had predicted to be inactive. My heart fell, because he had a big smile on his face and I knew that he was a doubter of the model or he wouldn't have synthesized the molecule. However, his words were: 'You were right. The compound is inactive.' From that time on, he considered the models as he decided which of the possible molecules he should make."

This kind of success with models is an aspect of her role that Martin finds particularly rewarding. "Nevertheless, it is frustrating that we don't yet have computational methods that solve most of the problems faced by a medicinal chemist," says Martin. "For example, we wish computational methods could accurately forecast the affinity of a ligand for a protein, or accurately predict the water solubility of compounds." These problems are sure to keep computational chemists occupied in the future, and there are plenty more ambitious goals if they are addressed, such as predicting how a compound would affect a network of proteins.

An important factor in tackling such challenges as a scientist, in Martin's view, is to publish, and to publish work that is helpful and interesting to others. "Yet another paper on some subject has little impact unless it shows all previous work was flawed or that a superior and simpler approach works better — it is better to publish something completely different or to write a critical review on the topic," she considers. "I've learned that the power of publishing or presenting at meetings is that it introduces you to other scientists who can provide unpublished insights, helpful criticisms and interesting conversations," Martin says. "A second key lesson is to continually expand your horizons to ancillary disciplines that could affect your primary interest, as happened for me with Corwin Hansch."

Brian Shoichet

Professor of Pharmaceutical Chemistry, Department of Pharmaceutical Chemistry, University of California, San Francisco, USA.

For Brian Shoichet, the attraction to the field of computational chemistry began during his chemistry degree at the Massachusetts Institute of Technology, USA, in the 1980s. "I realized that the most interesting examples of molecular recognition occurred among biological macromolecules," he says. "Given my training to that point, I thought I'd go into a field where chemistry could play a role in biological molecular recognition. At the time, computational simulations were having their first flowering, and predicting how small molecules interact with proteins through techniques such as molecular docking seemed very exciting."

So, Shoichet pursued a Ph.D. in molecular docking in the laboratory of Irwin Kuntz, a pioneer in the field, at the University of California, San Francisco (UCSF), USA. With this theoretical grounding, he then made what he considers to be one of the best moves of his career: a postdoctoral position in a protein crystallography laboratory with Brian Matthews at the Institute of Molecular Biology in Eugene, Oregon, USA. "Protein crystallography was going through its golden age," recalls Shoichet, "and I had come to an experimental lab wanting to be exposed to what I naively thought of as 'real data'. In fact, that was my mantra for several months, but once lab mates were used to the novelty of a theoretician wielding a micropipette, they became tired of it. One day, one of my mentors, Walt Baase, turned to me in exasperation and said: 'Data, Brian, is the weakest part of the scientific enterprise. A really good theory trumps data any day.' What he meant was that good experimentalists don't actually trust their data, not before they've looked at it backwards and forwards and sideways, because data can be very misleading and is often, in fact, simply wrong."

This distrust of data has stuck with Shoichet since, and has had a key role in some of the most important discoveries made in his laboratory, including the unexpected finding that many of the false positives that plague industrial high-throughput screening assays are caused by aggregation of the compounds being screened. Odd results like these are one of the aspects that Shoichet finds most exciting in his work. "The challenge comes from distinguishing an observation that has the chance to build into something new and interesting from the vast majority of times when 'Huh, that's weird' means that you or one of your co-workers has messed things up or got things wrong, or you're just confused," says Shoichet.

The field of molecular docking is still some way from realizing its initial promise as a panacea for drug screening, but the excitement that first attracted him to it is still there for Shoichet, who now leads a group at UCSF that mirrors the path he has taken: the research is half theory (molecular docking and inhibitor discovery) and half experiment (enzymology, inhibition mechanisms and crystallography). "We try to work at the interface between the two," says Shoichet, "and occasionally, in moments of bliss, I get into the lab to do experiments myself."