

Wendy Warr Interviews Anton (“Tony”) Hopfinger



Professor Hopfinger gained his PhD at Case Western Reserve University in 1969. He is currently Distinguished Research Professor of Pharmacy at the University of New Mexico, and Professor Emeritus of Medicinal Chemistry in the College of Pharmacy at the University of Illinois at Chicago. His current research interests are 4D-QSAR analysis to develop structure-activity hypotheses for designing new drugs; prediction of ligand-receptor binding thermodynamics; membrane-interaction QSAR analysis for ADMET property prediction; and characterization of molecular similarity and virtual screening. He is an Associate Editor of the *ACS Journal of Chemical Information and Modeling*.

Dr. Warr: What attracted you to QSAR research in the first place?

Prof. Hopfinger: I didn't start out in QSAR research, but rather in developing methods of doing conformational analyses of molecules, including synthetic macromolecules. As my interest grew in medicinal chemistry and pharmacology, the identification of the "active" conformation of a drug from a conformational analysis became of high interest to me. However, I soon came to appreciate what medicinal chemists and pharmacologists already knew. The active conformation is not sufficient to understand and model most structure-activity relationships. Hence, my interests then turned to seeking how I could represent conformational information within the Hansch QSAR paradigm. And that was the start of my interest in QSAR, as well as the start of one of the initial efforts in developing the 3D-QSAR field.

W: I think that I probably first heard your name when MDL was marketing your Chemlab software back in the 1980s. Things have moved on since then, haven't they?

H: Chemlab is probably one of the first two molecular modeling packages to be commercialized in the USA. Interestingly, Chemlab had its origins in providing a way to capture and reuse software developed and/or used in my lab by my graduate students and postdocs. In a sense, I didn't want to "reinvent the wheel" in terms of software each time I got a new student. Today, the choice of software products for use in solving chemical problems is mind boggling in both number and diverse functionality. Unfortunately, and this is solely my subjective view, software products have become so numerous, and with such a major focus on ease of use, that many users are not really aware of what they are using as long it runs for their study. That is, there seems to be less of a concern knowing the hard science behind a calculation now than in the past.

W: You are famous for 4D-QSAR but 5D and even 6D QSAR are now reported. These terms are confusing to cheminformaticians used to talking of 2D and 3D structures. Explain to me in words of one syllable what nD QSAR is.

H: I don't know about "famous" but my group and I have developed a paradigm we call 4D-QSAR that somewhat surprisingly to us can be used in an identical and comparable manner on informatics-based, ligand-based and structure-based QSAR problems. The choice in name "4D-QSAR" may not, in retrospect, have been a good one. The fourth "dimension" in our paradigm is sampling and includes the sampling of conformation, alignment, pharmacophore sites and entropy. The composite information coming from each of these sampled property sets is embedded in the resulting QSAR model. Most of the other nD-QSAR methods consider each of these properties, which we sample as individual dimensions in their QSAR studies. Hence, by way of examples, one would get a 5D-QSAR method if conformational sampling is included, and a 6D-QSAR approach if both conformational and alignment samplings are considered.

W: I note that you review for a huge number of journals in very varied fields. QSAR has a wide range of applications, doesn't it?

H: Yes, the idea of relating a measure of the behavior of a molecule to its inherent properties is increasingly being used throughout the pharmaceutical, materials and chemical sciences. Non-pharmaceutical applications of this approach are generally referred to as quantitative structure-property relationships, QSPRs, a term I had not heard before I used it. QSPR modeling has been around for quite some time, but has never taken off like QSAR modeling has in the pharmaceutical sciences. But that may be changing. Increasingly chemical companies are turning to QSPR modeling as a way of filtering and selecting trial chemicals in new product development. And of course we see the continued growth of QSPR in the ADME – toxicology field.

W: As an Associate Editor of the *Journal of Chemical Information and Modeling (JCIM)*, you wrote our new guidelines on QSAR. These have since been taken up by other journals. Tell us briefly what this means to potential *JCIM* authors.

H: It is extremely important for the continued growth and acceptance of the QSAR/QSPR field that the methods, data and applications reported be validated and be reproducible. My hope, and I think that of my fellow *JCIM* editors, is that the new QSAR guidelines will provide criteria of standardization to achieve validation and reproducibility of QSAR studies.

W: Why isn't there a Hopfinger data set?

H: I don't believe there is a single data set for all applications. For example, to evaluate a method for computing log P would require a different data set than for validating a method to rapidly and effectively do conformational analysis. My strategy has always been to seek out data sets that most meaningfully explore and test a particular theory, method or exploratory idea that we are investigating.

W: Who is your hero, or heroine: the scientist you most admire?

H: I have had the good fortune to work with many excellent scientists over my career. I have tried to let these individuals know my appreciation of, and respect for, what they have done. However, I don't wish to mention names here.

W: Do you have any retirement plans? What hobbies might you have more time for?

H: I don't have any retirement plans. My hope is to continue doing what I am doing, but perhaps morphing with time in terms of how much I do and where I do it. In terms of hobbies, I enjoy non-mainstream movies and model trains. Interestingly, my model train hobby came about in part because it was something of an escape from computers and high technology. But now it has become so high tech that doing QSAR research has almost become an escape from high tech model railroading!

W: In parting, do you have any advice for young modelers?

H: I would tell them to take the time to learn enough physical and theoretical chemistry, enough statistics and enough pharmacology so as to be able to understand and critically question the applicability and reliability of the methods being employed in the software they are using or developing. Obviously this is not generally considered fun to do, but I really think modelers today have gotten too far away from a healthy skeptical and questioning attitude toward computational tools. My anchor point is to remember that we still cannot routinely calculate a reliable IC_{50} value which is the cornerstone measurement in preclinical drug discovery.