Chapter 61
An Epistemological Analysis of QSPR/QSAR Models

Jordi Vallverdú
Universitat Autònoma de Barcelona, Spain

ABSTRACT

Computer sciences have deeply changed the way by which we make science or produce knowledge. With the era of computers and the development of computer science, quantum chemists were among the first scientists to explore the potentialities of the new tool, and even to collaborate in its development. In this way, they also became participants in what many dubbed as the Second Instrumental Revolution in chemistry. Deeply involved into this research field, QSAR methods are powerful tools to create knowledge on toxicology and drug design, among others. There are several epistemological questions to be analyzed in order to understand the truth and scientific value of their research results (from in silico to wet laboratories and vice versa).

CHEMISTRY AND COMPUTING: A BRIEF HISTORICAL SKETCH

Computational Chemistry

Computer sciences have deeply changed the way by which we make science or produce knowledge, and this new change affects all different possible research fields (Vallverdu, 2009). When we look at the history of chemistry and the specific moment in which computers came into, we should at the same time to explain the ideas that made possible to analyze chemistry with computers.

DOI: 10.4018/978-1-4666-5125-8.ch061

We must start explaining something elemental: before to have a computational chemistry, it was necessary to create a theoretical chemistry, that is, a mathematical description of chemistry. After, these mathematical models were automated and implemented on computers, leading to the computational chemistry.

As part of the research in the toxicological field, in 1863 A.F.A. Cros noted his Ph.D. thesis that the relationship between the toxicity of primary aliphatic alcohols and their water solubility.

After several improvements made by Dujardin-Beaumetz & Audigé (1875), who indicated that the toxicity of the alcohols mathematically followed their atomic composition, and Hans Horts Meyer & Fritz Baum (1899) discovered a relationship between the lipophilicity of general anaesthetics and their potency. They concluded that lipophilicity was the essential factor in the effectiveness of an anaesthetic. In 1916 Gilbert Newton Lewis proposed that chemical bonding - both the ionic and the homopolar type - could be explained in terms of shared electron pairs (Gavroglu & Simões, 1994). From Lewis research chemistry began its own quest for the elucidation of the nature of chemical bond and bonding.

But quantum mechanics was the key to understand this process. In 1925, Werner Heisenberg published the first paper on quantum mechanics (when we was only 23 years old!). Just one year later, Erwin Schrödinger wrote a series of papers published in the *Annalen der Physik*, where he created the basis for the future computational chemistry, with the great contribution of the so-called 'Schrödinger equation': $H\Psi=E\Psi$. This equation and his several consequences provided a method for calculating how molecules behave. Two years later, in 1927, the Heitler-London paper opened a new era in chemistry, after offering a complete theory on atom bonding, in a German view (reductionist) opposite to that of the Americans Mulliken and Pauling (inclinated towards semi-empirical methods) (Gavroglu & Simões, 1994). The next important step was made in the 1930s, by Nikolai Vasilyevich Lazarev in St. Petersburg who first demonstrated that different physiological and toxicological effects of molecules were correlated with their oil– water partition coefficient through formal mathematical equations in the form: $\log C = a \log_{Poil/water} + b$ (Lipnick & Filov, 1992; Devillers, 2009). Louis Plack Hammet, in 1935, gave rise to the so-called 'σ-π' culture, in the delineation of substituent effects on organic reactions. In this historical moment, at the 1930's end, there were different communities working on quantum chemistry: the pragmatic or trusters in rough semi-empirical approximations (Americans) and the mathematicians (British). The first generation of British quantum chemists, which included J.E. Lennard Jones (1894-1954), D. Hartree (1897-1958) and C.A. Coulson (1910-1974), perceived the problems of quantum chemistry first and foremost as problems in calculation, and by devising novel calculation methods tried to bring quantum chemistry within the realm of applied mathematics (Gavroglu & Simões, 1994, 2002). For the different epistemological approaches to chemistry views of quantum mechanics (valence bond theory –also called the Heitler-London-Slater-Pau method- and molecular orbital theory – the Hund-Mulliken method) read Shaik & Hiberty (2004). As happened also previously with molecular biology, physics came like an elephant into the chemists' culture. In this moment appeared a methodological question: the classic approach of modern chemistry, a 'paper & pencil' discipline, lost its visualization advantages when quantum chemistry appeared as an inherently non-visualizable field. Computers could change in a future this situation, helping human experts to work with fittest cognitive tools to create knowledge.

One decade later, Linus Pauling wrote his 1945 book *The Nature of the Chemical Bond*, affirming that should be possible to describe structural chemistry without the use of advanced mathematics, something that made much easier to apply computers to the chemical analysis (Goodman 2001). In fact, in the 1940's appeared the electronic computers that made possible to elaborate wave equations for complex atomic systems. ENIAC in the USA and Colossus in the UK were the first machines able to compute fast and powerfully large amounts of data (at least for the standards of that moment). As Ana Simões (2007) has clearly explained, with the era of computers and the development of computer science, quantum chemists were among the first scientists to explore the potentialities of the new tool, and