The promise (or not) of quantum chemistry in QSAR

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Quantitative Structure-Activity relationships (QSAR) link the (biological) activity of a molecule to its structure, where this structure is expressed in terms of a number of mathematical constructs called molecular descriptors. Via a series of statistical manipulations, the above mentioned link is expressed in some (usually a linear) regression equation. Clearly, if a very good QSAR model can be found, one could dream of predicting (biological) activity for molecules not even synthesized and in this way predict whether such a molecule is worth considering or not.

Unfortunately, and despite the advances made in the last decades, good predictive models that fulfill all requirements that a QSAR model should meet, are not so easy to obtain. One of the sources in which improvement could be sought lies in the molecular descriptors.

It is a direct consequence of quantum mechanics and thus quantum chemistry that there is an ultimate descriptor, namely the wave function or the electron density of the molecule. This entity namely contains all there is to know about the molecule, so including its (biological) activity.

In this lecture we will critically examine whether quantum chemistry really is such a fruitful source of information in QSAR. In this context we will show how quantum chemistry can help to obtain (and justify) different molecular descriptors characterizing e.g., aromaticity or the atom in the molecule and we will show several examples where sometimes quantum chemical descriptors do work, but others where it brings very little added value.