QUANTUM QSAR AND MOLECULAR QUANTUM SIMILARITY

The Carbó group has been involved in the development of the field of quantum QSAR and molecular quantum similarity since the 1980s.[105] The quantum similarity measure (QSM) between any two molecules, *A* and *B*, can be calculated using the following:

$$z_{AB} = \langle \rho_A \,|\Omega|\, \rho_B \rangle = \iint \rho_A(r_1)\Omega(r_1 r_2)\rho_B(r_2)dr_1 dr_2,$$

where Ω is some positive definite operator (e.g., kinetic energy or Coulomb) and ρ is the electron density. The QSMs can be transformed into indices ranging between 0 and 1 using

$$r_{AB} = \frac{z_{AB}}{\sqrt{z_{AA} z_{BB}}},$$

yielding the so-called Carbó similarity index (CSI). Calculating an array of QSMs or CSIs between all molecular pairs in some data set provides descriptors for quantum QSAR.[106]

A drawback of the CoMFA-based methods is the need to superimpose the molecules in the training set. This is no easy task due to the many degrees of freedom (both rigid and internal motions). However, the alignment of the molecular structures in a common 3D framework provides a convenient method of determining which regions of the molecules impact activity and which regions can be developed to create new compounds with more favorable properties. QSMs have been developed with a Lamarckian genetic algorithm called the quantum similarity superposition algorithm (QSSA) to superimpose the classic CoMFA data set.[107] The QSSA is performed in such a way as to maximize the molecular similarity and does not rely on atom typing as other empirical based methods do.

Accurate and efficient molecular alignment techniques based on first-principles electronic structure calculations represents a significant challenge due to the associated computational expense. Hence, QSMs tend to use approximate electron densities. Fusti-Molnar and Merz[108] recently described a new scheme that maximizes quantum similarity matrixes in the relative orientation of the molecules using Fourier transform (FT) techniques for two purposes: first, build up the numerical representation of true ab initio electronic densities and their Coulomb potentials and, second, apply the Fourier convolution technique to accelerate optimizations in the translational degrees of freedom. Importantly, to avoid interpolation errors, the necessary analytical formulae were derived for the transformation of the ab initio wave functions in rotational coordinates. The new alignment technique was then shown to be generally applicable for overlap, Coulomb, and kinetic energy quantum similarity measures and can be extended from QSM computation to solving the docking problem with ab initio scoring.

Popelier and coworkers have coupled the atoms-in-molecules (AIM) theory of Bader with quantum molecular similarity to produce quantum topological molecular similarity (QTMS).[109] It uses the so-called Bond critical points of predefined bonds in a series of molecules as descriptors followed by multivariate statistical analysis. The series of compounds must have a common core for this method to remain computationally tractable. QTMS has been used to generate models to estimate the pK_a values for a set of aliphatic carboxylic acids, anilines, and phenols.[110]

OUTLOOK

As with any brief review it is difficult to catalog all the most recent advances. But the use of quantum mechanical approaches in drug design problems using both ligand- and receptor-based drug design applications will certainly experience tremendous growth in the coming years. The ability, in principal, for QM to give extremely accurate interaction energies between a receptor and ligand and its ability to generate novel descriptor classes should attract even more attention to the use of QM in structure-based drug design in the coming years. However, for the use of QM to become standard requires the development of even faster QM methodologies and careful validation studies to demonstrate improved performance over classical methodologies. In the case of RBDD the incorporation of entropy and the role of conformational dynamics still represents a significant hurdle for both classical and QM-based methodologies. Future effort to overcome these problems will certainly be a major focus of researchers involved in SBDD.

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