Rigid-Body Molecular Alignment Using Quantum-Mechanics-Derived Local Properties

Ahmed El Kerdawy, [a,b] Matthias Hennemann [a,c] and Timothy Clark [a,c,d]

[a] *Computer-Chemie-Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraβe 25, 91052 Erlangen, Germany.*

[b] *Zentralinstitut für Scientific Computing (ZISC), Friedrich-Alexander-Universität Erlangen-Nürnberg, Martensstraβe 5a, 91058 Erlangen, Germany.*

[c] *Interdisciplinary Center for Molecular Materials, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraβe 49, 91052 Erlangen, Germany.*

[d] *Centre for Molecular Design, University of Portsmouth, King Henry Building, Portsmouth PO1 2DY, United Kingdom.*

Molecular alignment is an essential prerequisite for many ligand-based drug design (LBDD) techniques such as 3D-QSAR, pharmacophore elucidation, receptor modeling and 3D similarity searching. [1] Molecular alignment prior to these approaches represents an approximation to the binding orientation of the investigated ligands in the biological target, whose structure is unknown. The quality of the alignment greatly influences the results and performance of these LBDD approaches; for example the results of 3D-QSAR are very sensitive to the manner in which the different ligands are aligned. [2] We now present a workflow for rigid-body molecular alignment using quantum-mechanics-derived electron density (ρ) and molecular electrostatic potential (MEP) calculated on a grid around the ligands to be aligned. The alignment algorithm depends on maximizing the similarity between the template molecule and the other dataset ligands. The similarity between the two molecules' properties on the grid is calculated using Hodgkin's similarity index [3] and the Simplex algorithm [4] is used to maximize the similarity. The use of quantum-mechanics-derived properties makes this alignment protocol more accurate and more efficient in describing molecular steric and electrostatic properties than conventional molecular-mechanics-based methods, which use atom-centered charges and Lennard-Jones potentials. They consider important features for CADD which cannot be described by conventional methods such as σ-holes (responsible for halogen bonding) and polar flattening. Being field based, the method presented is efficient in aligning chemically diverse ligands and finding chemically different ligands with similar binding properties, an important feature for scaffold hopping and finding new chemical entities (NCE) to overcome patent limitations. Although it uses quantum-mechanics-derived properties, the method presented is computationally efficient and so it can not only be used for molecular alignment prior to 3D-QSAR or pharmacophore elucidation campaigns but also for 3D similarity searching in databases.

[1] Lemmen, C. and Lengauer, T. *J. Comput.-Aided Mol. Des.* **2000**, 14, 215–232.
[2] Verma, J. *et al.*, *Curr. Top. Med. Chem.* **2010,** 10, 95-115.
[3] Hodgkin, E. E. and Richards, W. G. *Int. J. Quantum. Chem.* **1987,** 14, 105-110.
[4] Nelder, J. A. and Mead, R. *The Computer J.* **1965,** 7(4), 308-313.