ASSESSMENT OF THE CONFORMATIONAL DEPENDENCE OF THE 'MIPHAK' DESCRIPTORS FOR IN-SILICO ADME APPROACHES

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The MiPhaK program generates a number of molecular descriptors based on evaluation of molecular properties on the molecular or solvent accessible surface. The interaction energy between the molecule and a probe atom is calculated all around the molecular or the solvent accessible surface. Subsequently, this three-dimensional map is transformed in a molecular spectrum and then in a set of molecular descriptors. Five probe atoms are available within the MiPhaK program, related to (i) the molecular electrostatic potential, (ii) the H-bond donor/acceptor capabilities, and (iii) the hydrophobicity of the molecule. When used in conjunction with a PLS analysis, the MiPhaK descriptors yielded successfully QSPR models for the prediction of ADME-related properties.

In this work, we engaged ourselves in the assessment of the conformational dependence of our MiPhaK descriptors. Indeed, the impact of the molecular conformation on the predictive ability of any QSPR model should be carefully evaluated for every method based on 3D-derived properties. Quite surprisingly, despite the variety of methods currently available, such an evaluation is only seldom presented.

The MiPhaK methodology, based on the evaluation of an interaction energy spectrum, is particularly suited to this kind of evaluation given the ease of comparison between spectra obtained for different conformers of a same molecule.

The obtained results outline a sensible dependence on molecular conformation for the MiPhaK descriptors related to the molecular electrostatic potential. On the contrary, descriptors related to the H-bond and to the hydrophobic character of the molecule do not show dependence on the molecular conformation, even if the involved molecule has an high conformational freedom. As a further investigation, we carried out a PCA study aimed at evaluating the ability of the MiPhaK descriptors to discriminate between different chemotypes when represented by large conformational ensembles. Also in this case we obtained a different result for MiPhaK descriptors related to the molecular electrostatic potential, which do not cluster together conformations of the same molecule, and those related to the H-bond and Hydrophobic probes, which show a clear conformation-independent behaviour.

In conclusion, our results indicate that the conformational dependency of 3D-derived descriptors should carefully evaluated and that the choice of the appropriate probe atom can be crucial for achieving conformational independency.