MIPSIM: similarity analysis of molecular interaction potentials
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Abstract
Summary: MIPSIM is a computational package designed to analyse and compare 3D distributions of molecular interaction potentials (MIP) of series of biomolecules.
Availability: MIPSIM software is freely distributed to non-profit academic institutions through its web site: http://www1.imim.es/mipsim. Other organizations must contact the developers. GAMESS (http://www.msg.ameslab.gov/GAMESS/GAMESS.html) and GRID (peter@biop.ox.ac.uk) are external software required to perform some of the MIPSIM computations. They are obtained under conditions similar to MIPSIM’s.
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Introduction
The modelling of the relationships between molecular structures or properties and biological functions or activities is a current challenge in biochemical, physiological and pharmacological research, as well as a useful tool for drug discovery and development. A first strategy for such a modelling is the direct simulation of the ligand-receptor interactions, which implies the knowledge of the 3D structures of both ligands and receptors. A second strategy consists in considering only the similarities between a series of its ligands, trying to find the relationship between molecular and binding data. When the relationship is derived from 3D distributions of molecular properties and it is quantitatively modelled, the approach is called 3D-QSAR (Lozano et al., 1999). A molecular property that is especially used and useful is the Molecular Electrostatic Potential (MEP) (Murray et al., 1992). We previously developed a computational system (MEPSIM) for the analysis and comparison of MEP distributions (Sanz et al., 1993). MIPSIM is a new related system that incorporates innovative algorithms and functionalities like the consideration, in addition to the MEP, of other Molecular Interaction Potentials (MIP).

Function evaluators
The MIPSIM package has been designed to use external software for MIP computation. Currently, MIPSIM makes calls to the GAMESS package (Schmidt et al., 1993) for the quantum mechanical computation of MEP, and the GRID program (Goodford, 1985) for MIP calculations. MIPSIM distribution also includes an interface with the statistical package GOLPE (Baroni et al., 1993), with the purpose of using MIPSIM results in the generation of 3D-QSAR models.

MIPSIM modules
MIN module
The aim of this module is to characterize the points around a molecule where MIP reaches a minimum value in comparison with those of its surroundings. First, MIN computes the MIP values in the points of a homogeneous 3D grid containing the molecule. Then, MIN looks for those points having smaller values than all the surrounding ones. Finally, an optimization algorithm refines the minima values and positions. The output provided by MIN is a description of the minima consisting of their values and Cartesian co-ordinates. When the relationship is derived from 3D distributions of molecular properties and it is quantitatively modelled, the approach is called 3D-QSAR (Lozano et al., 1999). A molecular property that is especially used and useful is the Molecular Electrostatic Potential (MEP) (Murray et al., 1992). We previously developed a computational system (MEPSIM) for the analysis and comparison of MEP distributions (Sanz et al., 1993). MIPSIM is a new related system that incorporates innovative algorithms and functionalities like the consideration, in addition to the MEP, of other Molecular Interaction Potentials (MIP).

COMP module
This module compares pairs of molecules on the basis of their 3D MIP distributions computed in a common grid of points defined around the molecules. The similarity measure (a correlation coefficient) depends on the relative position (alignment) of the molecules...
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Fig. 1. InsightII visualization of MIPSIM analyses of theophylline. (a) Minima search in a MIP distribution (probe: alkylic OH); spheres indicate minima positions; in this example, minima suggest possible H-bonds. (b) One of the maximum similarity alignments of two molecules of theophylline on the basis of their HF/3-21G MEP; this alignment, found by MIPSIM in addition to the obvious structural matching, indicates the possibility of several binding modes of this compound.

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References