Creating Pharmacophores from Common Chemical Feature Subsets and its Application to Structure-Based Pharmacophore Modelling

M. Biely\(^1\), G. Wolber\(^1\) and T. Langer\(^1\)

\(^{1}\)Inte:Ligand GmbH, Mariahilferstraße 74B/1, 1107 Vienna, Austria and
\(^{2}\)Computer Aided Molecular Design Group, Institute of Pharmacy, Dpt. Pharmaceutical Chemistry, University of Innsbruck, Austria

INTRODUCTION

Two approaches are commonly used to model a binding site in rational drug design: On the one hand, structure-based design typically characterises one single binding mode and is usually tightly associated with docking methods [1]. Ligand-based design as it can be performed using the software package Catalyst [2], on the other hand, identifies the maximum set of common chemical features, such as hydrogen bond acceptors or donors, positive or negative ionisable points and lipophilic areas from a set of selected active molecules and may consequently represent a broader application scope.

Recently it has been shown that (as an alternative to docking) 3D pharmacophores can be perceived from structural data automatically, showing sufficient selectivity to characterise a single binding mode [3]. In order to classify and prioritise the numerous features which are present in a single complex an automatic overlaying and comparison algorithm has been implemented for broadening their application scope.

METHODS

After the initial manual selection of suitable experimental structural data, the algorithm (figure 1) works fully automatically.

Selection of structural data. As initial set-up it is necessary to select the structural data to be used for pharmacophore creation. It is essential that all used complexes refer to the same target and that the ligand-macromolecule interactions occur at the same location. As an example the PDB entries 1HRN, 1BIL and 1BIM, which represent three different renin inhibitor complexes, are used. Figure 2 shows the ligands and pharmacophores for these entries.

Pharmacophore generation. The first step of the algorithm is to generate pharmacophores for the interactions in each selected complex. LigandScout [3], a programme for deriving pharmacophores from experimental protein-ligand complex data, is used to identify the chemical features in each interaction.

Compatibility graph. To identify those features that are common to all pharmacophores created from the selected complex data, a compatibility graph is constructed. In this graph each node corresponds to a mapping from a feature pair in the first pharmacophore to a feature pair in the second pharmacophore. Such nodes exist for all compatible feature pairs, where compatibility is defined in terms of matching feature characteristics and matching pair length. The length of two pairs match, if the features’ distances are within the defined tolerances. The nodes in the compatibility graph are connected with edges, when the two nodes have exactly one feature pair in common and the other two feature pairs are compatible.

Clique detection. Each clique in this compatibility graph corresponds to a possible overlay of compatible features. Therefore the maximum cliques correspond to the maximum set of chemical features that can be overlaid. The maximum cliques were determined using the efficient clique detection algorithm by Bron and Kerbosch [4].

Feature alignment. For each of the thusly generated subsets of the two pharmacophores, the optimal alignment was determined by analytically calculating the optimal transformation matrix using the algorithm by Kabsch [5]. To prioritise the chemical functionality over the excluded volume information, a weight of 0.1 was used for the excluded volumes, whereas chemical features located on the ligand side were given a weight of 1.0. The optimum common feature model can be derived from the 3D alignment with the lowest RMS.

Calculation of combined features. From the optimum feature mapping determined by the previous steps the features of the combined pharmacophore are placed by averaging the positions of the corresponding chemical features in the two original pharmacophores. Figure 3 shows the result derived from the example PDB entries.

RESULTS

A novel method for overlaying 3D pharmacophores has been presented. It can be used to select and combine chemical features from structure-based pharmacophores, such that a new model is discovered that is significantly broader in its application scope and therefore allows to identify new lead structures for a specific target.

References