Using Ensembles of Protein Conformations in Structure-Based Drug Discovery

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1. Abstract

Unforeseen conformational changes within a binding site can prevent successful structure-based drug design (SBDD). We have developed a method to generate robust receptor-based pharmacophore models that account for protein flexibility by employing an ensemble of conformations using multiple protein structures. In order to properly overlay different conformations of the same protein based on the rigid regions of the structure, we describe a novel alignment method using a Gaussian-weighted RMSD fit. The algorithm is based on the Kabsch least-squares method and determines an optimal transformation by calculating the minimal weighted deviation between the atomic coordinates. Atoms that barely move between the two conformations will have a greater weighting than those that have a large displacement. Here, we have employed HIV-1 protease (HIV-1p) as a test case to probe the source of the structures by performing conformational analysis of an apo structure across a molecular dynamics (MD) simulation, a bound NMR ensemble, and a collection of bound crystal structures. All MPS pharmacophore models were able to discriminate known HIV-1p inhibitors from drug-like decoys and showed comparable performance. However, the apo model from MD snapshots and the bound model from the NMR ensembles were quite similar and appeared to be the most general yet accurate representation of the hydrophobic pockets of the HIV-1p active site.

2. Background

It is common practice to use a single, static crystal structure in SBDD. However, a protein in solution exists as an ensemble of energetically accessible conformations and is best described when all states are represented. Carlson and coworkers previously developed a method to generate robust receptor-based pharmacophore models that account for protein flexibility. However, a protein in solution exists as an ensemble of energetically accessible conformations and is best described when all states are represented.

3. Incorporating Protein Flexibility: Multiple Protein Structure Method

CONSENSUS CLUSTER

PHARMACOPHORE MODEL

CONFORMATIONS

FLOOD

ENERGY MINIMIZATION

CLUSTER

Activesite of each conformation. Conformational analysis of an apo structure across a molecular dynamics (MD) simulation, a bound NMR ensemble, and a collection of bound crystal structures. All MPS pharmacophore models were able to discriminate known HIV-1p inhibitors from drug-like decoys and showed comparable performance. Here, we have employed HIV-1 protease (HIV-1p) as a test case to probe the source of the structures by performing conformational analysis of an apo structure across a molecular dynamics (MD) simulation, a bound NMR ensemble, and a collection of bound crystal structures. All MPS pharmacophore models were able to discriminate known HIV-1p inhibitors from drug-like decoys and showed comparable performance. However, the apo model from MD snapshots and the bound model from the NMR ensembles were quite similar and appeared to be the most general yet accurate representation of the hydrophobic pockets of the HIV-1p active site.

4. Gaussian-Weighted RMSD Superposition

Implementation of a Gaussian weight into KabschMethod.9

Least squares minimization of the weighted deviation between two atom coordinate sets.

Inherently selects out atom pairs in close proximity.

Key to defining flexible and rigid regions for drug design with MPS models.

Optimal Solution found upon convergence.

Standard RMSD Fit

Weighted RMSD Fit

RAN- (PDB ID: 1BYU)

PDB ID: 1BYP

Translation

CM = \sum_{i=1}^{n} x_{i}^2 + y_{i}^2 + z_{i}^2

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\sum_{i=1}^{n} x_{i}^2 + y_{i}^2 + z_{i}^2

Consensus cluster defined by having parents from >

5. Exploring Sources of Multiple Protein Conformations: HIV-1 Protease as a Test Case

MD Snapshots

11 Structures

NMR Ensemble

28 Structures

Crystal Collection

10 Structures

Backbone of crystal collection shows less conformational variation than the MD and NMR ensembles.

Consensus cluster defined by having parents from >

6. Quantifying Ligand Overlap with DOCK

7. References & Acknowledgements