

The detection of new active site conformations using molecular dynamics and rotamer assignments.

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Protein flexibility is an important, but often neglected aspect of the drug development process. The flexibility of the binding pocket residues of the peroxisome proliferator-activated receptor was investigated using a novel molecular dynamics (MD) protocol. A comparison is made between a standard MD protocol, using water probes in the binding pocket, and a novel protocol, using hydrophobic probes. The ligand-complexed protein is simulated and used as a reference by comparing it to the obtained results of the hydrophobic and water probes trajectories. It is hypothesized that due to the hydrophobic nature of the natural ligands, the MD simulation using hydrophobic probes would result in a more accurate description of the binding pocket dynamics compared to the water probes trajectory.

The raw MD data is described by rotameric conformations, which results in sequence-like descriptions of active site conformations. Clustering and multi-dimensional scaling were used to validate the hypothesis. It was found that the use of a hydrophobic water model increases the sampling of ligand-like pocket conformations. The conversion of MD data to rotameric sequences allows for easy data analysis and intuitive visualizations.

1. Vroling, B, Schaftenaar, G.. The detection of new active site conformations using molecular dynamics and rotamer assignments. , *to be submitted to J. Comput. Aided Mol. Des.*