Developing a methodology for protein-ligand docking based on genetic algorithm and rotamer library

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The three-dimensional structure (tertiary structure) of proteins determines their function. The practical uses of this knowledge concern different fields such as biotechnology and pharmaceutical sciences. Combining genetic algorithm, rotamer libraries and molecular dynamics or Normal Modes can constitute a good approach to undertake folding and docking studies. This work presents the first version a method called GANM (Genetic Algorithm Normal Modes). In this version, GANM considers a rigid backbone and a rigid ligand, but flexible side-chains for those involved in ligand binding. The work presents the docking results obtained with the application of this first version of GANM to different protein-ligand systems which are: HIV-1 Protease with DMP323 and nelfinavir as ligand; and DHFR with MTX as inhibitor. The results show the usefulness of using GA combined with a rotamer library to investigate molecular docking. They show a rapid convergence of the algorithm towards lowest energy structures that are close to those observed by X-ray crystallography for the complexes considered. We can observe that the algorithm for rigid docking is more efficient for the complexes: DFHR/MTX and Protease/DMP323. In other side, the semi-flexible simulations was more efficient for the cross-docking cases.

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