RNA as drug target in docking study

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Among the functional components of cells, polypeptides, enzymes, transporters, receptors and ion channels account for the majority of targets in therapeutic intervention. Ribonucleic acids (RNA) has only recently been viewed as a target for small-molecule drug discovery, but the advantages of targeting RNA are quickly being shown compared to traditional protein targets. The ever growing realization of the variety of biochemical roles of RNA in organisms is leading to an increasing appreciation that cellular and viral RNAs provide inviting new targets in drug design to treat both infectious and chronic diseases.

The virtual screening techniques, including automated docking method, could be also applied to RNA targets. However, while automated docking is well established for protein targets, little has been done for optimising ligand-RNA docking process. The crucial problem is still the scoring function. The software Autodock uses an empirical free energy model which was determined based on 31 protein/ligand structures, but this set of parameters is obviously inadequate for RNA/ligand docking process.

The first part of this work was the design of a new parametrization for the free energy model by means of 8 RNA/ligand structures and the corresponding experimental free energies. 248 docking experiments were performed with different values for the contributions of van der Waals, electrostatic, hydrogen bonding, torsion and solvatation effects. We correlated these parameters with both RMSD and ΔGbind for all docking calculations using a layered neural network with back propagation training algorithm. This model obtained from the correlation allowed us to adjust the parameters.

One particularity of RNA is its high flexibility. There are two ways to mimic this flexibility : computing a docking and following it with a molecular dynamic calculation or doing a docking with several conformations of the target. These two approaches were applied to two different targets : RNA 16S bacterial ribosome site and the HIV-1 TAR element. The calculations were correlated with experimental data, and the results showed that the consideration of flexibility is of great interest.