Q-fit: A method for docking molecular fragments by sampling low energy conformational space

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QFIT is a small molecule docking algorithm for predicting biomolecular-ligand interactions. It uses a new probabilistic sampling method and a conventional molecular mechanics force field for finding small molecular fragments in the binding site of a rigid protein.

The aim is to facilitate the process of finding novel small molecule lead compounds in a fast and efficient way. Potentially these fragments could be connected using combinatorial principles to create *de novo* compounds or used as the base fragment for searching existing chemical databases.

An example of the QFIT program is given in **Figure 1**.

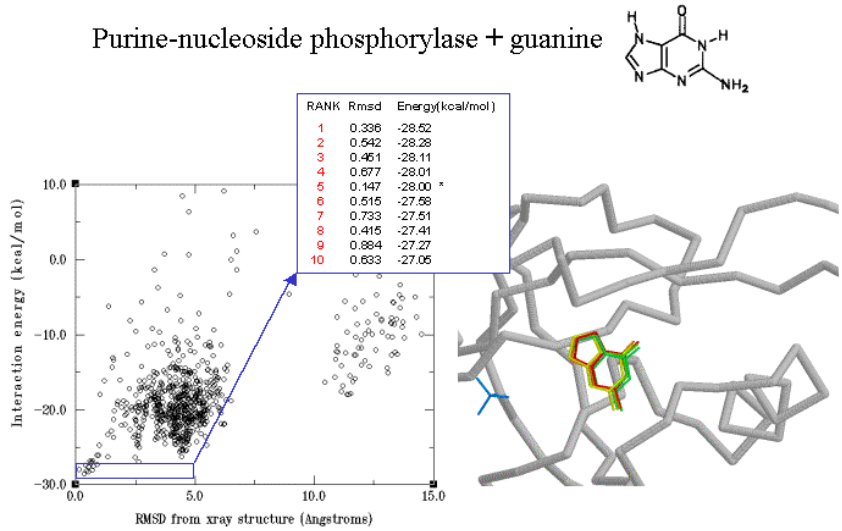

Figure 1. The docking of guanine to purine-nucleoside phosphorylase. The figure shows the RMSD (root mean squared deviation) from the crystal structure versus the interaction energy (more negative is most favourable). The top ten solutions are shown in the box with the minimized crystal structure ranked no. 5. An image of the top five generated solutions in the protein binding site shows that docking reproduces the experimental binding mode of the ligand (in red) with an RMSD of less than 1 Å in all five cases.

The method proves to be very successful in its ability to predict experimental binding modes when using the point interaction model and force field of GRID. The binding modes of several ligand fragments are predicted that have previously proved problematic. The binding modes of ligands used to bench mark several other docking algorithms are reproduced in excellent agreement with experiment. Furthermore, because the probabalistic docking methodology tends to generate low energy conformations first, the time to perform this docking is very fast. Docking of a single ligand fragment including energy minimization can be performed in 10-15 seconds on a desktop PC using conservative parameters for the search depth.

References

Jackson, R. M. (2002). Q-FIT: A Probabalistic Method for Ligand Docking by Sampling Low Energy Conformational Space. Submitted to *J. Computer-Aided Molecular Design*.

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