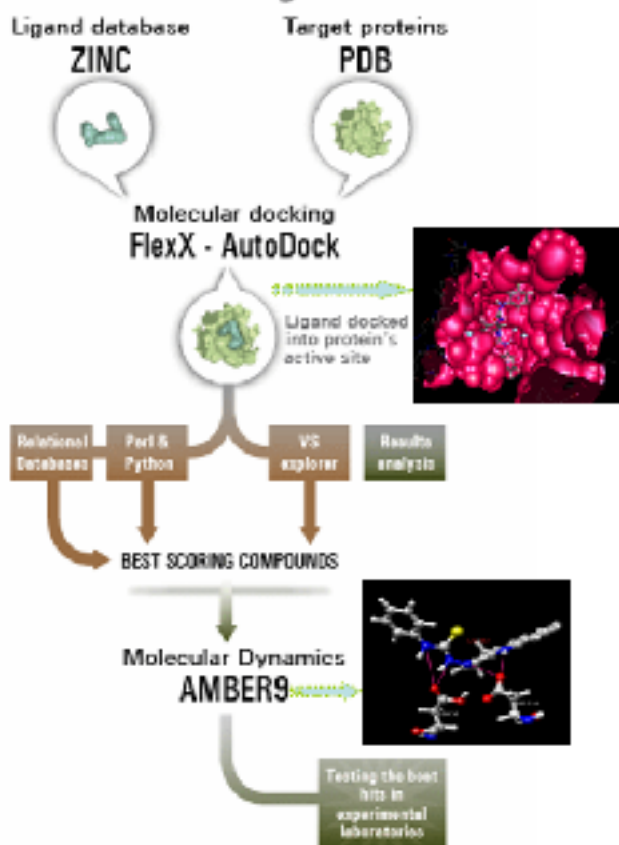


Molecular Dynamics Applications on Grid

The aim of this activity is to use Grid infrastructures to deploy molecular docking and Molecular Dynamics (MD) applications in the perspective of in silico drug discovery against neglected diseases. MD is a form of computer simulation wherein atoms and molecules are allowed to interact for a period of time under known laws of physics, giving a view of the motion of the atoms.

In 2005, the WISDOM collaboration deployed large scale docking computations on the EGEE infrastructure against Plasmepsin targets. The most promising compounds out of 1 million candidates using docking scores were selected. BioinfoGRID contribution to WISDOM focuses on the re-ranking of these best scoring ligands by MD with Amber9 software. Molecular Dynamics address the electrostatic solvation parameters, protein flexibility and other significant parameters which are ignored during the molecular docking step. MM-PBSA and MM-GBSA methods are used to calculate the binding free energy. Depending upon the complexity of the ligand and protein, a single molecular dynamics simulation takes 15-20 minutes.

Virtual screening workflow



Complete workflow employed in WISDOM project

Molecular dynamics procedure involves several steps which are interdependent. Data management is a key issue in molecular dynamics as the output of one particular step serves as an input for the next step. Hence an automated procedure with all the steps to perform is embedded in one script. The refinement and rescoring was set up taking as inputs the docking conformations of the best 5000 compounds resulting from the virtual screening by molecular docking against Plasmepsin. Molecular dynamics deployment is performed on EGEE infrastructure but jobs are submitted only on the Grid nodes with licenses of the Amber software.

The MD rescoring took one week on the EGEE Grid and confirmed the in silico discovery of a new scaffold with positive inhibition activity on plasmepsins. Best 180 compounds are selected based on MM-PBSA and MM-GBSA scores. These 180 compounds are manually visualized and 30 compounds were selected to be tested in wet laboratory to measure their ability to inhibit Plasmepsin activity. The first in vitro results are very promising, as some of these compounds show significant inhibition activity in Haemoglobin degradation.