Contribution ID: **165** Type: **Oral**

Molecular dynamics refinement and rescoring in WISDOM virtual screenings

Wednesday 13 February 2008 11:55 (20 minutes)

After the docking screening of compounds contained in the ZINC database into the crystal structure, the docking results have been refined using molecular dynamics (MD) in order to validate and optimize the ligand orientation into the binding site of the target. Subsequently, the candidates have been rescored using more accurate scoring functions based on molecular mechanics Poisson Boltzman Surface Analysis (MM-PBSA) and molecular mechanics Generalized Born Surface Analysis (MM-GBSA) approaches. Such procedure was designed and validated on aldose reductase [1] and it is fully automated and able to prepare input files, efficiently refine the structures with MD, and rescore the compounds before the final selection of the best hits.

[1] Ferrari A. Degliesposti G. Sgobba M. Rastelli G. Bioorganic & Medicinal Chemistry 15 (2007) 7865-7877

3. Impact

In the PfDHFR application, the molecular interactions with the most important amino acids in the active site were evaluated as an important criterion for estimating the likeliness of binding, in addition to docking scores. The interaction frequencies with key residues showed an enrichment of interacting compounds on the top of the list, allowing the selection of a subset of 15.000 focused compounds to be processed with MD refinement. After rescoring, two new lists of ordered compounds were obtained and ranked according to MM-PBSA and MM-GBSA free energies of binding. For comparison, known nanomolar inhibitors of PfDHFR were included in the analysis. Interestingly the known inhibitors were on the top of the list, confirming the reliability and the predictive power of the refinement method applied. At the same time, the top-scoring list contained a number of different (not related to already known drugs) compounds which will be very interesting to evaluate for their PfDHFR inhibition.

4. Conclusions / Future plans

Based on the MD results, a subset of best-scoring compounds will be tested for their in vitro inhibition of P. falciparum DHFR.
Further investigation on molecular interactions and binding free energy predictions will be performed on the PfDHFR resistant mutant enzyme.

Provide a set of generic keywords that define your contribution (e.g. Data Management, Workflows, High Energy Physics)

molecular dynamics, virtual screening, grid, drug design

1. Short overview

The Wide In Silico Docking On Malaria (WISDOM) project is focussed on virtual screening of large databases of small molecule compounds through in silico methods deployed on the EGEE grid computing infrastructure. One of the biological targets chosen for these screenings is Plasmodium falciparum Dihydrofolate reductase (PfDHFR), a well validated target for antimalarial drug discovery.

Primary authors: Dr DEGLIESPOSTI, Gianluca (Università di Modena e Reggio Emilia); RASTELLI, Giulio (Università di Modena e Reggio Emilia)

Presenter: Dr DEGLIESPOSTI, Gianluca (Università di Modena e Reggio Emilia)

Session Classification: Life Sciences

Track Classification: Scientific Results Obtained Using Grid Technology