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WISDOM: Grid enabled identification of active molecules against targets implicated in Malaria

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The in silico workflow which we employed starts with docking to evaluate the binding energy between a target and a ligand, then selected compounds are refined by Molecular Dynamics (MD). In 2005, against Plasmepsin target, the WISDOM initiative achieved 41 million dockings, using FlexX, in 45 days on 1700 computers which is equivalent to 80 CPU years on one machine. The best 5000 compounds identified were reranked by MD with Amber9 in 7 days equivalent to 124 CPU days on one machine. In 2006, this success led to a second assault against 4 other malaria targets. During 90 days, ˜140 million dockings were achieved which is equivalent to 413 CPU years, representing an average throughput of 80,000 dockings per hour. MD simulations were performed on 15000 docking poses against wild type Dihydrofolate reductase target and 5000 docking conformations against Glutathione-S-transferase target respectively. The total 25 000 simulations lasted for 25 days equivalent to 347 CPU days in one machine.

3. Impact

In silico datas have been valitated experimentally in wet laboratory. 30 compounds coming from MD step were selected manually, based on key interactions, and tested against recombinant aspartic protease Plasmepsin II expressed from the encoding gene. 6 compounds out of 30 showed similar or better inhibitions compared to Pepstatin A, a general inhibitor of aspartic proteases. All tested 30 compounds demonstrated plasmepsin II inhibition activity at nanomolar concentrations. In the meanwhile, 10 compounds out of this 30 were tested in vivo to figure out the impact on Plasmodium falciparum growth as well as the potential toxicity on human cells model. Premilinary results are very promising to go further in drug discovery process. Biological tests will be performed in near future for other targets as well.

URL for further information:

http://wisdom.healthgrid.org/

4. Conclusions / Future plans

Grids have significantly reduced the overall time required for database screening against a particular target. Computing resources from Biomed virtual organization were used exclusively. The molecular docking was deployed on the EGEE grid infrastructure, refinement by Molecular Dynamics on the French regional grid Auvergrid, both using the WISDOM production environment. The successful experimental results reveal the suitable combination of EGEE infrastructure and in silico drug discovery.

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

Malaria,Plasmepsin,virtual screening,docking,molecular dynamics,in vitro,EGEE,Auvergrid,Wisdom

1. Short overview

Malaria is a deadly tropical disease affecting and killing millions of people every year. Malaria is traditionally ignored by the pharmaceutical industries as it is restricted to mainly poor and developing countries and also due to the heavy costs (˜$800 million) involved in the drug discovery activities. Novel and cost effective tools are needed for finding potential new drugs for malaria.

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