Poster I-29

VSM-G: the Virtual Screening Manager platform for computational Grids. Use for the identification of putative ligands of the Liver X Receptor

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Short Abstract: The VSM-G platform performs high throughput virtual screening based on both ligand- and receptor-based algorithms running on computational grids. A central molecular funnel composed of successive filters allows the screening of large molecular libraries for compounds prioritization in experimental assays. Illustrations will deal with the LXRß target protein involved in cholesterol regulation.

Long Abstract:
The search for novel therapeutics is time-consuming and expensive, so that any method able to speed up the process is welcome. In the last several years, virtual screening techniques have evolved from a side-show curiosity to a central partner in many drug development strategies. Virtual screening provides numerous advantages, including the speed with which one can screen a large molecular library and a relatively small capital investment to get started compared to the cost of an in vitro HTS program. Presently, virtual screening methods are proving to be a good complement to high-throughput screening experiments, by limiting the number of molecules to be tested and therefore the cost of screening campaigns aimed at identifying putative lead compounds. In such a context, we have developed a Java-based standalone platform, called VSM-G. Its main goal is the prioritization of compounds for experimental testing, by performing high throughput virtual screening. To satisfy this task as efficiently as possible, the software integrates a chain of tools combining both ligand- and receptor-based strategies. The former is implemented as modules such as substructure search to pre-screen molecular databases in order to restraint the number of compounds to consider subsequently. This optional operation may precede the central element of the platform, a multi-step screening funnel which presents several layers of filtering. This approach consists in the succession of different selection methods used sequentially for evaluating the possible affinity of each compound with the protein targets. This stepwise process starts with first geometrical considerations for ligand-cavity matching followed by more efficient flexible docking algorithms and ending with molecular dynamics simulations. At each step a fair percentage of non appropriate molecules may therefore be eliminated, so that the system is able to handle several million compounds, eventually yielding to a small set of putative leads. The capability of screening several million compounds against several hundred biological targets, within a reasonable time, rests on a grid module that spreads the calculations over computational grids composed of PC clusters. The poster describes the basic elements of the platform and showcases its capabilities through an example of relevant biological interest concerning a particular nuclear receptor, namely the Liver X Receptor LXR β. This case illustrates a general effort towards the discovery of new pharmaceuticals for treating cardiovascular diseases by targeting this

receptor involved in cholesterol regulation.