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i-BioS: A system for Inverse Biological Virtual Screening Based on Inverse Docking Approach

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Short Abstract: In the present work we develop a new system for inverse docking studies. Our system, called i-BioS (Inverse Biological virtual Screening), is based on Surflex docking program. It was able to reproduce some of the biological activities of violacein and found new ones, associated to its anti-oxidant character.

Long Abstract:

In a competitive environment such as the pharmaceutical industry, getting first on the market is vital. Despite the long and massive investments on promising technologies such as HTS and combinatorial chemistry, the cost of bringing a successful drug to market is estimated between U$900 million (1) and U$1.7 billion (2) per single successful drug marketed. These loads on the costs of all the failures, around 60-70% can be attributed to failures during the various stages of drug discovery and development. One of the major bottle neck is the selection of lead candidates which will prove successful in pre-clinical and clinical development. Within drug discovery, most failed compounds have problems associated with their ADME or toxicity profile.

The great demand on improving the efficiency of drug discovery has created a need for a new paradigm that enables the use structural information in the combinatorial chemistry and medicinal chemistry process. A variety of tools have been developed to identify lead candidates in extensive collections of compounds, like virtual screening and high throughput docking. Additionally, it is becoming clear that successful prediction of drug-like properties at onset of drug discovery will payoff later in drug development (3).

Recently, an innovative approach called inverse docking had been introduced as a chemoinformatics tool to predict a priori several characteristics of lead candidates. (4,5). From a database of biological and therapeutic targets, one could (i) identify unknown and secondary therapeutic targets for a drug, (ii) predict the potential toxicity and side effects of an investigating drug, and (iii) probe the molecular mechanisms of action of bioactive compounds.

As the docking technique has reached the position of established technique, the crucial step for applying the inverse docking is the correct selection of the biological and therapeutics targets. Therapeutic effects of a drug generally result from its interaction with one or more proteins or nucleic acids critical in a disease process, the therapeutic targets. The adverse reaction of a drug in the human body is often induced by its interaction with some of the proteins critically important. Identification of the interaction with these proteins, known as toxicity and side effect targets, has potential application in facilitating the prediction of side effects and toxicity of an investigative drug in early stage of drug development.

The inverse docking approach has been applied by a few groups in the world in order to make a virtual screening of biological and pharmacological properties of molecules of interest. The Bioinformatics & Drug Design group (BIDD) (6) has developed the INVDOCK software. (4) The Laboratoire de Bioinformatique du médicament group (7) developed the sc-PDB, (5) a database of targets for inverse docking studies, comprising a collection of more than 4000 active sites from the PDB.

In the present work we use all protein structures in sc-PDB to develop a new system for inverse docking studies. Our system, called i-BioS (Inverse Biological virtual Screening), is based on Surflex docking program (8) from Biopharmics LLC (9). After obtaining the targets collection, the Reduce program (10) was used for adding all hydrogens atoms with optimization of the orientations of polar hydrogens. Subsequently, each target was submitted to Surflex in order to generate the protomol representation of actives sites. The position of the binding site was determined by coordinates of ligand molecules in the sc-PDB.

The protomol files were archived and we have designed a script which connect the protomol files, the Surflex docking module and the OpenEye Omega software (11). Omega is used to generate 3D conformation structure of the query molecule. The user can input a molecule in the system in a variety of formats such as smiles, SDF or mol2. After the conformer generation the script calls the Surflex program and calculates the geometry and docking energy for the complexes of input molecule with all proteins in the database. The output is a rank of the proteins, with the most probable targets at the top.

We have applied i-BioS system to study the potential targets of violacein, a pigment isolate from Chromobacterium Violaceum, a bacterium found in the Black River, an affluent of the Amazon River. Violacein presents a variety of biological effects, such as anti-cancer, anti-protozoa and anti-viral activities. Using our i-BioS system we were able to reproduce some of these biological activities and found new ones, mainly those associated to its anti-oxidant character. Other results will be discussed concerning applications of i-BioS to guide the biological screening of a selection of natural products isolated by phytochemistry groups from Brazil.

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