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AMMOS: A Software Platform to Assist *in silico* Screening

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Summary: Three software packages based on the common platform of *AMMOS* (Automated Molecular Mechanics Optimization tool for *in silico* Screening) for assisting virtual ligand screening purposes have been recently developed. *DG-AMMOS* allows generation of 3D conformations of small molecules using distance geometry and molecular mechanics optimization. *AMMOS_SmallMol* is a package for structural refinement of compound collections that can be used prior to docking experiments. *AMMOS_ProtLig* is a package for energy minimization of protein-ligand complexes. It performs an automatic procedure for molecular mechanics minimization at different levels of flexibility – from rigid to fully flexible structures of both the ligand and the receptor. The packages have been tested on small molecules with a high structural diversity and proteins binding sites of completely different geometries and physicochemical properties. The platform is developed as an open source software and can be used in a broad range of *in silico* drug design studies.

Keywords: Virtual ligand screening, Structure-based drug design, Molecular mechanics, 3D generation

1. INTRODUCTION

Virtual or *in silico* ligand screening combined with other computational methods is one of the most promising ways to search for new lead compounds, thereby effectively assisting the drug discovery process. Despite considerable progress made in this field, there are very few freely available standalone programs that directly address problems related to structural generation and optimization of compounds in the screening libraries and receptor flexibility for a more accurate prediction of protein-ligand interactions. It has been shown that structural optimization of chemical compounds in the

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libraries prior to screening and post-docking optimization of protein-ligand complexes employed in multi-step structure-based virtual screening approaches help to further improve the overall efficiency of the screening process. To address these points the platform *AMMOS* has been developed as an open source software for: 1) generation and refinement of 3D structures of small molecules in chemical libraries; 2) refinement of predicted receptor-ligand complexes through molecular mechanics optimization procedure allowing partial to full atom flexibility. Three software packages developed on the *AMMOS* platform are shortly presented *DG-AMMOS* for generation of 3D conformations of small molecules using distance geometry, *AMMOS_SmallMol* – for structural refinement of compound collections prior to *in silico* screening experiments, and *AMMOS_ProtLig* – for energy minimization of protein-ligand complexes.

2. DESCRIPTION OF *AMMOS* PLATFORM

For the molecular mechanics optimization, AMMOS makes use of the molecular simulation program *AMMP* [2, 8]. *AMMP* allows to treat standard or non-standard polymer linkages (ensured by the program *PREAMMP* included in the package *AMMP*), unusual ligands or non-standard residues, as well as to complete partial protein structures. *AMMP* incorporates a fast multipole algorithm for the efficient calculation of long-range forces thereby allowing evaluation of non-bonded terms without the use of a cutoff radius and increasing the speed, making calculations comparable to a standard treatment with a 8–10 Å radius cutoff. The *AMMP* force field *sp4* is developed on the basis of the UFF potential set and the AMBER partial charges. Lately, Bagossi et al. [1] proposed the *Mo*dified *P*arameter *S*et for *AMMP* (MOPSA), which has been merged with *sp4* to generate the new standard force field set *sp5*.

The software packages developed on the *AMMOS* platform employ an automatic procedure for energy minimization and have been developed for both *sp4* and *sp5* force field. The packages require as input a compound collection in mol2 format. *AMMOS_ProtLig* additionally needs a protein structure in pdb format and a pre-docked compound collection. The preparation of the small molecules and the protein in ammp format is performed using *PREAMMP* program. Some warning may pop up if unknown atom types or bonds are

present. Minimization performs 2x500 iteration steps with *conjugate gradient* as an optimization method. Experienced users can select other optimization methods among the available ones in *AMMP*, as well as the number of the iteration steps. After the minimization stage, *AMMOS* platform keeps:

1) the new coordinates of the small molecules after generation or minimization in mol2 format.
2) the initial and the final total (or interaction) energies.
3) any warning that may appear during the run.
4) in *AMMOS_ProLig* package the new coordinates of the protein atoms moved after minimization in pdb format and the ranking of all minimized protein-ligand complexes according to the calculated *AMMP* protein-ligand interaction energy.

3. *DG-AMMOS* PACKAGE

DG-AMMOS (Distance Geometry and Automatic Molecular Mechanics Optimization for *in silico* Screening) [3] employs an automatic procedure for generation of 3D conformations of small molecules based on distance geometry. The entire procedure of *DG-AMMOS*, from the input of small molecules (in mol2 format) to the final built molecules (in mol2 format) is shown in Fig. 1.

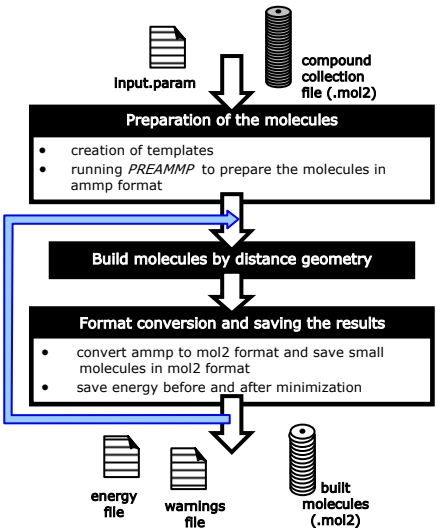

Fig. 1 Schematic diagram of the *DG-AMMOS* procedure

The package *DG-AMMOS* is validated on the Astex dataset, the ChemBridge Diversity database and on a number of small molecules with known crystal structures extracted from the Cambridge Structural Database [3]. A comparison with the free program Balloon and the well-known commercial program Omega generating the 3D of small molecules has been performed. The results show that the *DG-AMMOS* is a very efficient 3D structure generator engine [3]. Thus, it allows fast and reliable generation of 3D conformations of small molecules and can be applied to libraries with a large number of compounds.

4. *AMMOS_SmallMol* PACKAGE

AMMOS_SmallMol [5] employs an automatic procedure for energy minimization of small chemical compounds present in a library. The procedure of *AMMOS_SmallMol*, from the input of small molecules (in mol2 format) to the final minimized compounds (in mol2 format) is shown in Fig. 2.

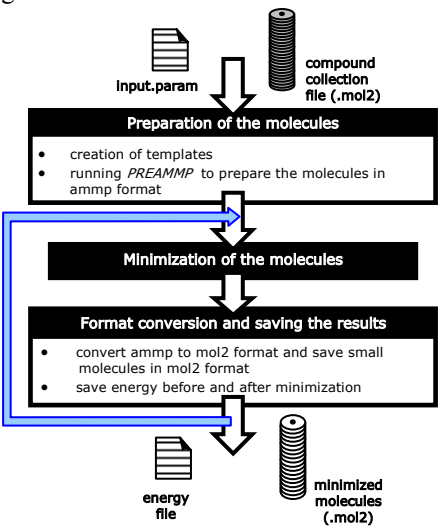

Fig. 2 Schematic diagram of the *AMMOS_SmallMol* procedure

The package performance was evaluated by comparing the structures of small chemical entities minimized by *AMMOS_SmallMol* with those minimized with the Tripos and MMFF94s force fields [5]. The

package was also applied to minimization of small compounds in a chemical library of 37970 single conformer molecules available in ChemBridge diversity set. *AMMOS_SmallMol* can be applied on a huge number of 3D conformations pre-generated with different programs [4, 6, 7].

5. *AMMOS_ProtLig* PACKAGE

AMMOS_ProtLig [5] performs energy minimization of protein-ligand interactions and can be applied on a large number of protein-ligand complexes pre-generated with user-selected docking programs [4, 6, 7]. The entire procedure for energy minimization of protein-ligand complexes, from the input files (the protein and the pre-docked ligand collection) to the output (the final databank of the minimized protein-ligand complexes), is shown in Fig. 3.

AMMOS_ProtLig executes an automatic procedure for energy minimization of pre-docked protein-ligand complexes allowing partial or full atom flexibility of both the ligand and the receptor. Five different possibilities have been elaborated for active/inactive atoms in the protein, while ligands are always flexible:

- *Case 1*: All protein and ligand atoms can move
- *Case 2*: Only the atoms of protein side chains and ligand can move
- *Case 3*: Only the protein atoms inside a sphere around the ligand and the ligand atoms can move
- *Case 4*: Only the atoms of protein side chains inside a sphere around the ligand and the ligand atoms can move
- *Case 5*: Only ligand atoms can move, while the whole protein is rigid

User should select the desired “case” allowing or not movements of the receptor atoms in the *input parameter file*.

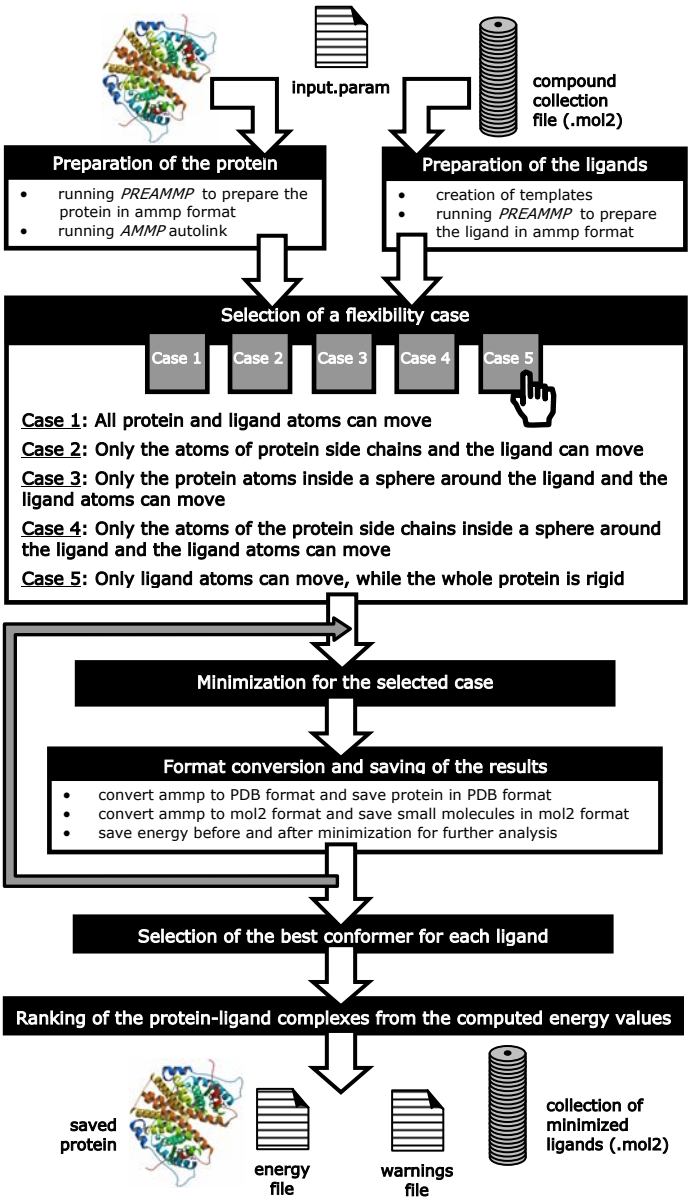

Fig. 3 Schematic diagram of the *AMMOS_ProtLig* procedure

The performance of *AMMOS_ProtLig* was tested for partial to full flexible minimization of protein-ligand complexes obtained from a mutli-step virtual screening [5]. *AMMOS_ProLig* was able to improve the enrichment after a preliminary docking stage with final retrieved 40 to 60% of the active compounds found in the top 3% to 5% of the screened compound collection.

6. CONCLUSIONS

The three open source packages developed on the *AMMOS* platform are fully automatic. They can perform energy minimization of a large compound collection prior to screening, and can also refine docked ligands in the context of a protein structure. *AMMOS* packages execute efficient and fast minimization procedures and can be employed over a large number of compounds or protein-ligand complexes. Applying *AMMOS_ProtLig*, the users can select the energy minimization protocol depending on the projects and, for instance, fix the protein atoms or allow full flexible minimization of both, the ligand and the receptor. Thus, the *AMMOS* packages offer valuable solutions to assist *in silico* screening projects such as optimization of small molecules or energy minimization of protein-ligand complexes.

AVAILABILITY AND REQUIREMENTS

AMMOS packages are written in C and Python and run on Linux. They are also operational on MacOSX system. Detailed installation instructions are provided in the software packages. The source code of *AMMOS* packages is freely available under the terms and conditions of the GNU Public License from http://www.mti.univ-paris-diderot.fr/fr/downloads.html.

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