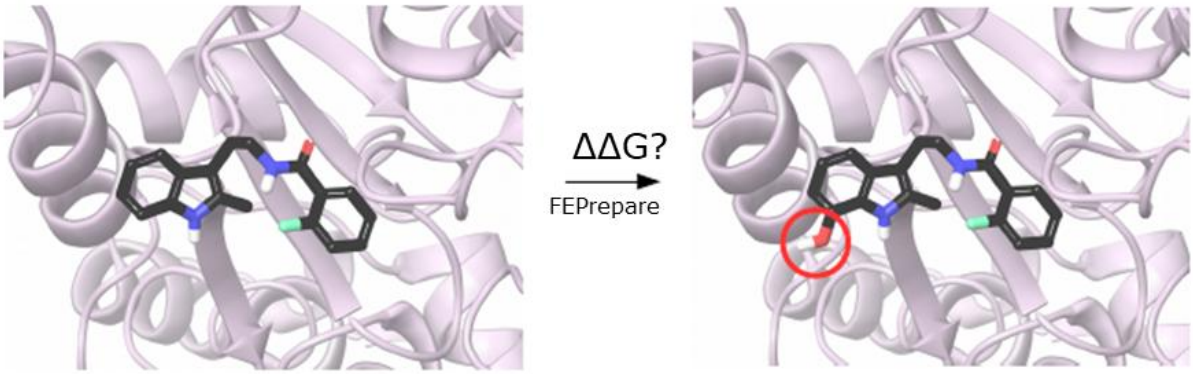
FEPrepare: A set-up tool for NAMD/FEP



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http://feprepare.vi-seem.eu/

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1. INTRODUCTION

One of the most important tasks in drug design is to predict, among a series of lead candidates, which ones will bind more strongly to the therapeutic target. In this direction, relative binding free energy methodologies have been developed, which rely on physics-based molecular simulations and rigorous statistical mechanics to calculate the differences in the free energy of binding between a parent candidate drug and analogues. For example, Free Energy Perturbation (FEP) calculations calculate the free energy difference between an initial (reference) and a final (target) molecule to an average of a function of their energy difference evaluated by sampling for the initial state [1].

Automating free energy perturbation calculations is a step forward to delivering high throughput calculations for accurate predictions of relative binding affinities before a compound is synthesized, and consequently save enormous time and cost.

NAMD [2] is a free parallel molecular dynamics code, designed for high-performance simulations of large biomolecular systems. Although FEP calculations are possible with NAMD, no automated tool has been developed to streamline the process, making the calculations tedious and unfeasible for a large number of molecules. That gave us the motivation to provide an easily accessible web based preparation tool which can produce all the files needed to run a NAMD simulation.

2. METHODOLOGY

In order to run a NAMD/FEP simulation, several inputs need to be created and no algorithm that does so exists. In order to create those files one has to prepare and align the structures from Maestro (or any OPLS that he prefers). Then upload these structures to LigParGen [3] in order to download the topology and the parameter files of the two ligands. Because of an inconsistency to the files that LigParGen provides(pdb, rtf, prm files), new atom names need to be given to all the atoms of both reference and mutant ligand. This is a very time consuming process, this is why the algorithm takes care of it, with a script.

The most tedious file to create, but at the same time most important, is the Dual-Topology file. In the dual-topology approach, both reference and target state atoms exist at the same time, reference state atoms disappear and target state atoms appear. In order to reduce the amount of perturbations during the transformation, we do not just merge the two ligands into one, but rather merge the two ligands into one, keeping the reference ligand the same and adding only the atoms that are being mutated from the mutant ligand. As a result the common part of the two ligands stays the same. The difficult thing is to decide which atoms are being mutated and therefore need to be merged with the atoms of the reference ligand. The algorithm takes into account the difference in the names of the atoms, as well as the difference in their partial charges, in order to figure out which of the atoms should be included in the calculation. Because of the modifications around the area, the summation of the area's charge changes. In relative binding free energy calculations we cannot afford to have different a charge before and after the transformation. To avoid this from happening we distribute the difference of the charges before and after the transformation equally, to all the atoms that take part in our calculation. (Figure 1).

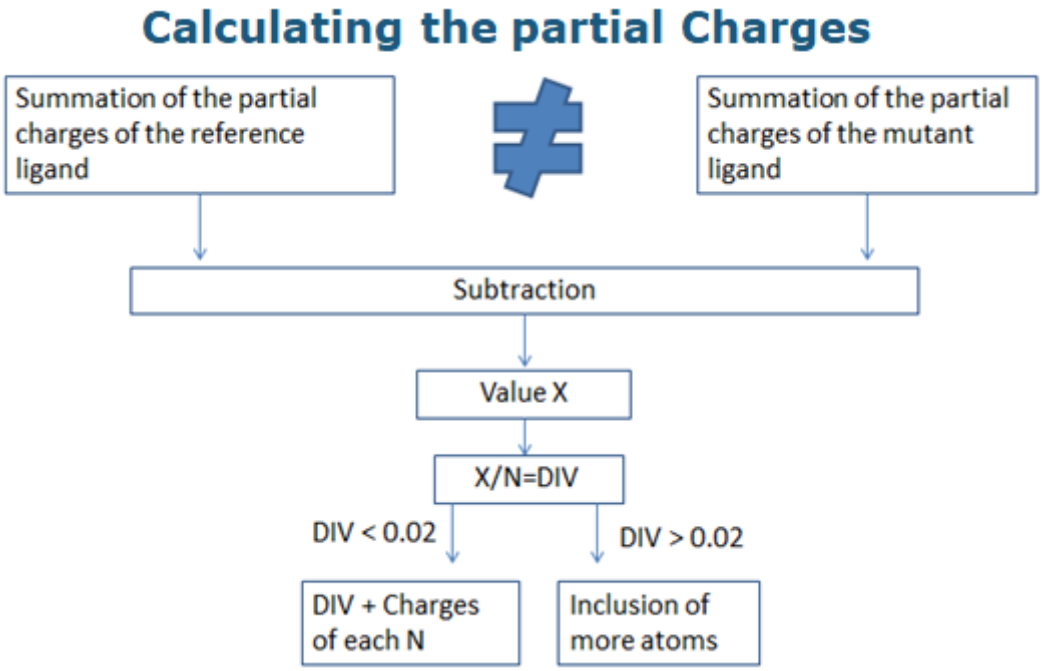

Figure 1: Workflow of the algorithm that distributes the partial charges of the atoms that take part in the mutation

After we have created the Dual-Topology file or as some call hybrid.rtf file we need to merge the atoms of the reference ligand with the atoms of the mutant ligand, that

take part in the calculation, in the hybrid pdb file, and the hybrid prm file as well. A very important file is the Complex pdb file. In order to create the Complex pdb file the algorithm merges the hybrid pdb file with the pdb file of the protein. This file is used as an input to VMD. Since we have automated the whole procedure, there is no reason for the user to use the VMD GUI. The algorithm will do so, and generate the PSF, solvate the system in a water box with limits that are in a 10 A distance from the atom with the greatest coordinate in each direction, and insert counterions to electrically neutralize it, respectively. In addition, the script will measure the values of the minimum, the maximum and the centre of the box. The final PSF and PDB files from the preparation that VMD did are the ionized.psf file and the ionized.pdb file, respectively.

Now, we need to create a FEP file, in which we specify, which atoms disappear, which atoms stay the same, and which atoms appear, during the simulation. These are the atoms selected in the partial charge distribution step. The FEP file is simply a copy of *ionized.pdb* with a slight modification. We need to do the same things for the solvent as well. Of course the algorithm does that too. In the end the user can download all these files as well as all the input files he needs to run his simulation in NAMD such as “par_opls_aam.inp” (OPLS-AA parameters of proteins), “top_opls_aam.inp” (OPLS-AA topology of proteins), “fep.tcl” (iterative tcl script needed for the equilibration runs).

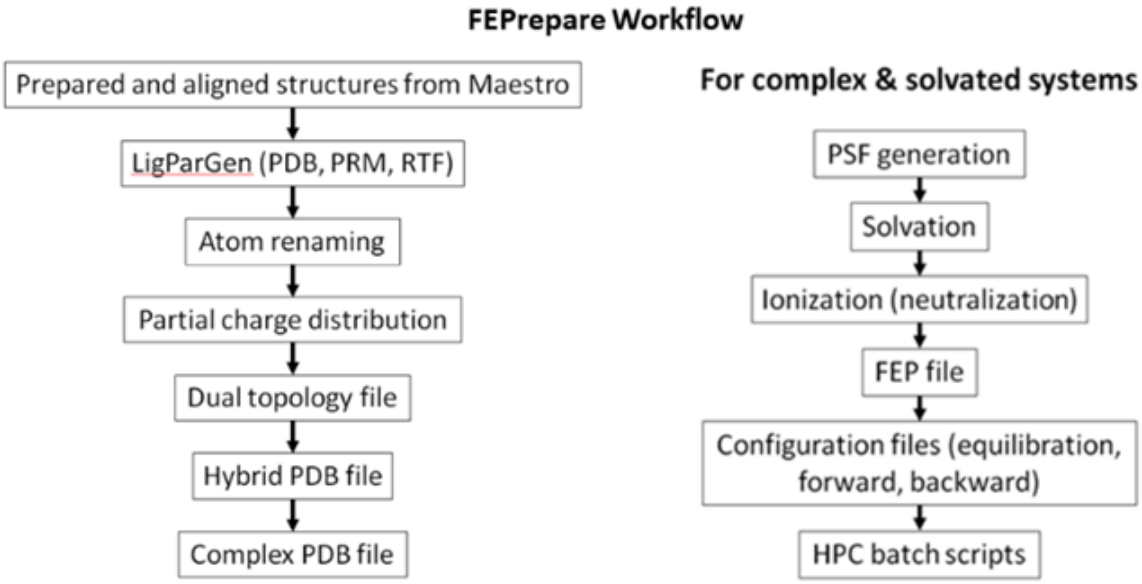

Figure 2: FEPrepare workflow

3. DESCRIPTION OF THE PROGRAM

This tool creates all the files needed to run a NAMD/FEP simulation. It has been implemented as a web-server using Python and PHP and can be accessed at: http://feprepare.vi-seem.eu/

3.1 Input

The topology and parameter files

The inputs that FEPrepare needs are the topology and parameter files for both ligands (reference and mutant) given as .pdb, .rtf, .prm files, and the .pdb file of the prepared and aligned protein.

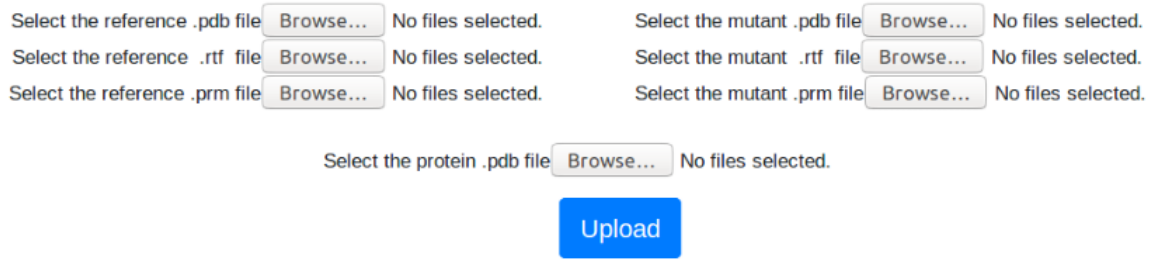

Figure 3: File selection

For example we have chosen ck666 as a reference ligand and ai003 as a mutant ligand. Our protein is Arp2/3. All the files can be downloaded from: http://feprepare.vi-seem.eu/exmple

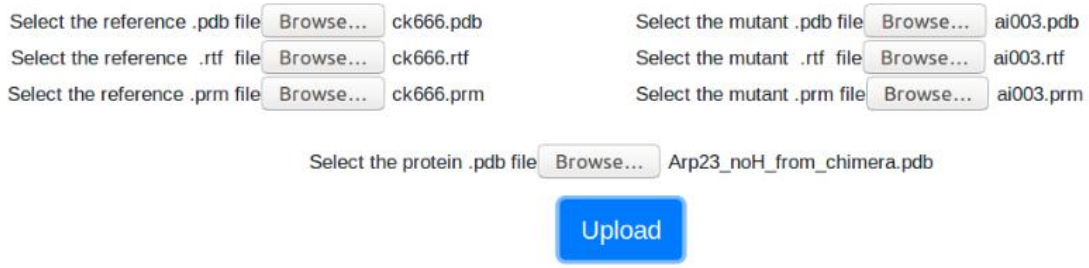

Figure 4: Files selected

After all these required inputs are fulfilled then hit the Upload button.

3.2 Output

As a result you can download the files as a .zip file.

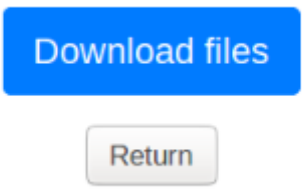

Figure 5: Files needed for NAMD/FEP simulation

BIBLIOGRAPHY

[1] Athanasiou C, Vasilakaki S, Dellis D, Cournia Z. “Using Physics-based pose predictions and Free Energy Perturbation calculations to predict binding poses and relative binding affinities for FXR ligands in the D3R Grand Challenge 2” Journal of Computer-Aided Molecular Design, 2017, in press

[2] Phillips, J C, et al. “Scalable molecular dynamics with NAMD”. Journal of Computational Chemistry 2005, 26, 1781-1802.

[3] L. S. Dodda, I. Cabeza de Vaca, J. Tirado-Rives, and W. L. Jorgensen, "LigParGen web server: an automatic OPLS-AA parameter generator for organic ligands," Nucleic acids research, vol. 45, no. W1, pp. W331-W336, 2017.