Development of a Force Field Topology Database for Detergents for Molecular dynamics simulations with the Amber Force Fields

Stéphane Abel1,2, Anaïs Lorieu1,2, François-Yves Duprapaud1, Fan Wang3, Béatrice de Foresta1,2 and Massimo Marchi
1 Commissariat à l’Energie Atomique, DSV/IBITEC-S/BS25M/LBMS, Saclay, France, 2 UMR CNRS 8221, Saclay, France, 3 Laboratoire des glucides, UFR de Pharmacie & CNRS FRE 3517, Université de Picardie - Jules Verne, Amiens, France. Email: Stephane.Abel@cea.fr

INTRODUCTION

Membrane proteins (MPs) are amphiphilic in nature. As such, to be manipulated and studied in solution, they need to be transferred in a suitable membrane-mimicking environment such as a detergent solution. Unfortunately, there is no systematic way for identifying the ideal detergent for a given MP, and empirical criteria are often used in this undertaking, in contrast to others (e.g. CHARMm or GROMOS). It does not provide any specific parameters for detergent molecules used in membrane protein experiments. As a consequence, studying membrane proteins in micellar environment by molecular dynamics (MD) simulations with Amber is not straightforward. To fill this gap, in this context, we have developed using FRED[2] a complex FF Topology Database (FTTopDB) (i.e. RESP partial charges embedded in a large set of FF terms) for an ensemble of cation and non-cation detergents compatible with AMBER FF and its successive adaptations. Key points of the procedure are the definition of elementary "building blocks" with well-defined conformations as well as the derivation of reproducible RESP-charge values. We have tested our approach in case of the doxylphosphocholine (DPC) detergent, considered as good system to mimic eucaryotic membrane and since it is widely used to study the structure of transmembrane peptides and MPs. Furthermore, DPC micelles have also been used to examine the influence of the micellar environment on the structure and localization of transmembrane peptides of a large ABC MP human multidrug resistance protein MRPM (MRPI).

METHODS

To optimize and derive RESP (Restricted Electrostatic Potential) for detergent molecules, we used the RED server [1] and with the building block approach [2].

The building block approach over the whole molecule approach:
- The optimized geometry of the monomer was optimized and molecular potential energy (MPE) computation
- The optimized geometry of the monomer was defined and controlled.
- Intramolecular hydrogen bonds are discarded from charge derivation to avoid overestimation effects.
- A large set of analog molecules can simulate a given conformation in geometry optimization and in charge derivation stages to obtain a force field library (FTTopDB).
- Need to consider correctly the correct building blocks (not easy).

I. Simplified workflow to derive RESP charges in RED server

A. Centralized parameters

1. Number of centralization

2. Number of intracentralization

3. Centralization value (Å²)

4. RESP charge version

B. RESP charges determination

1. RESP charges determination example

2. RESP charges determination output

C. RESP charges determination output file

II. How to choose the building blocks?

- Few rules to apply depending the chemical bond

  - Peptide bond (same approach used in Dharma et al. [10])

  - Methyl bond

  - Either water or water

III. Representative examples

1. Zwitter (fixed)

2. Ionic

3. Phospholipid

4. Fatty acid

The procedure of the RESP charges determination is a complex task. Many were obtained after about 100 h of calculation. The adequacy of the obtained parameters can be checked by visual inspection, and by two water tests, e.g. for 5 and 10 vs. 10. The time limit is between 1500 - 1500 h.

PARAMETERS VALIDATION

As an example of a peptide, we have examined the case of DPC. We performed simulations of DPC micelles using with 54 monomers using a self-assembled approach.

- All the simulations were performed with GROMACS (v4.5.3) in PBC, in explicit water, at T=300 K and P=1.01 bar using the Nosé-Hoover thermostat [4,5] and the Parrinello and Rahman barostat [6,7].

- Five force fields were compared: AMBER99SB, CHARMM36, GROMOS54A6, GROMOS54A7, GROMOS54A7 with Berger’s parameters [12] and Chiu et al. charges [13] for the three latter FFs. The TIP3P water model was used in the AMBER and CHARMM simulations and the SPC water model in the GROMOS simulations. For CHARMM, AMBER and GROMOS-Berger, electrostatic interactions were treated with PME [14], whereas in GROMOS54A7, GROMOS54A6 runs, the reaction field [15] approach was used instead.

SIMULATIONS WITH PEPTIDES

We have also simulated two transmembrane peptides with a starting helical conformation (TM10b: Ac-S[VGYTVPE][SVMH][PSLAL-SVAAT-A]-am and TM11: Ac-K-N(SGTVS/S[VGSYQ][YIY][TV][PS]-V-LR)-A), from the membrane with the AMBER99SB-ILDN parameters in different environment (e.g. water, in TFE, DPC and dodecyl-ß-maltoside (DDM) [3] with PME. The half - double pair list approach [16] were used to the GLYCAM04 parameters for DDD.

- Peptide structures vs. time and environment.

CONCLUSIONS

- Creation of a detergent FTTopDB for simulations of membrane proteins with the AMBER force fields
- DPC RESP charges within the AMBER force field have been developed and validated by performing a MD of DPC micelles.
- Our charges combined with the AMBER99SB parameters are able to reproduce accurately the DPC micelle properties.
- Starting from a helical conformation for each MRPM peptide, simulations show that, executive of the experiments, in TFE, in DPC or DDM micelles are mainly in modified conformation, whereas in water their structure is unfolded.
- Perspective: Use the same approach of building blocks to develop RESP charges for phospholipids for simulations with microsomes with the AMBER force fields.

REFERENCES