Combination rules for united-atom lipids and OPLSAA proteins

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Computer simulation of membrane proteins is contingent on the ability of parameter sets to simultaneously direct the time-evolution of proteins, water, and hydrophobic solvents. However, many parameter sets that exist for proteins do not contain parameters for lipids or detergents. Tieleman et al.(1) have reparameterized the dihedral potentials of the united-atom lipid parameters of Berger *et al*(2) in order to permit their combination with the all-atom OPLS protein forcefield(3) within the simulation package GROMACS(4). In this article, we suggest an alternative method for the combination of these force field parameters that is simpler and more inclusive.

In order for distinct force-fields to be compatible, there are two main conditions that must be satisfied. First, it must be possible to simultaneously employ both forcefields according to the rules for which they were designed. Second, there must be correct and bias-free interaction between atomic members of the different force fields. We deal only with the first condition, avoiding a discussion of the appropriateness of combining these two forcefields and focusing entirely on a method by which this combination may be accomplished.

Although in most cases the first condition appears superfluous, this is not necessarily the case. Non-bonded interactions betwen atoms that are separated by exactly three bonds (the so-called 1-4 interactions) are often scaled by some factor from their full strength. The particular scaling factor used differs amongst force fields and thus it is not at all certain that two forcefields can be simultaneously applied while properly scaling the 1-4 interactions of all molecules. The molecular dynamics simulation package GROMACS, for example, permits the specification of particular values for Lennard-Jones (LJ), but not Coulombic, 1-4 interactions. It is this particular property that led to the reparameterization of the lipid dihedral angle energy functions of the Berger lipids such that the nonbonded component of the 1-4 interactions is entirely described by the new dihedral potentials.

While the published reparameterization of dihedral parameters appears to be a valid solution, one would like to avoid reparameterizing every lipid and detergent for which parameters have already been generated using this lipid forcefield. To this end, we suggest a simple trick that can be used within GROMACS to combine the above-mentioned forcefields while properly scaling the 1-4 nonbonded interactions of each. The proposed method makes use of the fact that (i) it is possible to specify a unique value for the LJ component of the 1-4 interactions, and (ii) the scaling factor for the Coulombic component of the 1-4 interactions of one forcefield is an integer multiple of the scaling factor used in the other forcefield (lipids=1.0 and OPLS=0.5). Specifically, the ε values of the 1-4 LJ parameters of the lipids are divided by two in the pairtypes section of the GROMACS input file and the topology file of each lipid is modified such that the list of 1-4 interactions is repeated. The regular OPLS combination rules are then applied. In this way, the LJ and Coulombic 1-4 interactions are both cut in half and then included twice to yield properly scaled 1-4 interactions for both lipids and OPLS protein. We refer to this as the half-ε double-pairlist method.

Figure 1 shows the area per lipid obtained from simulating a bilayer composed of DPPC using a variety of methods to treat the lipid forcefield. The area per lipid derived from the direct use of lipid.itp and ffgmx, a forcefield that does not scale 1-4 interactions, is traced by the red line. Similar results are found when the C6/C12 formulation of LJ interactions is converted to δ/ε while leaving 1-4 interactions unscaled (blue line) and when applying the half-ε double-pairlist method under OPLS (purple line). However, the area per lipid is significantly reduced when the δ/ε formulation of LJ interactions is used while scaling lipid 1-4 interactions according to the rules of OPLS (blue line). In this last set of conditions, the Coulombic 1-4 interactions of lipids are erroneously assigned only half of their full strength.

The half-ε double-pairlist method permits simultaneous molecular simulation of the Berger lipids and OPLS proteins while remaining faithful to the original design of each parameter set. It is also simple

and does not require reparameterization for extention to other lipids and detergents from this lipid forcefield.

Methods

The initial topology for 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) was taken from http://moose.bio.ucalgary.ca/index.php?page=Structures_and_Topologies, as was lipid.itp and the initial structure containing 64 lipids per leaflet solvated by 28.5 SPC waters per lipid. The topology was modified as explained below to achieve the desired scaling of 1-4 interactions. This system was then simulated for 130ns using a time step of 2fs under GROMACS version 3.3.1(4). Lennard-Jones interactions were calculated using a group-based twin-range cutoff calculated every step below 0.9nm and every ten steps for distances between 0.9 and 1.4nm, when the nonbonded list was updated. Coulomb interactions were calculated every step below 0.9nm and long-range coulomb interactions were calculated using the smooth particle mesh Ewald algorithm(5)(6). Simulation in the NPT ensemble was achieved by semi-isotropic coupling to a Berendsen barostat(7) at 1 bar with a coupling constant of 4ps and a compressibility of 4.5e-5 bar^{-1}, and separate coupling of the solute and the solvent to Berendsen thermostats(7) at 323K with coupling constants of 0.1ps. All bonds were constrained with SETTLE(8) (for water) and LINCS(9). Coordinates were saved every 0.1ps.

In order to achieve a final LJ 1-4 scaling of 0.125 and a Coulombic 1-4 scaling of 1.0 for the lipids while scaling protein LJ and coulombic 1-4 interactions by 0.5, the lipid LJ 1-4 parameters were explicitly included with epsilon scaled by an additional factor of 0.5 (total factor of 0.0625), and the list of 1-4 pairs in lipid the topology was duplicated such that these terms are included twice in energy calculations.

This method was originally posted on Gromacs mailing list by Chris Neale:
http://www.gromacs.org/pipermail/gmx-users/2006-May/021416.html
http://www.gromacs.org/pipermail/gmx-users/2006-August/023587.html
http://www.gromacs.org/pipermail/gmx-users/2006-September/023761.html

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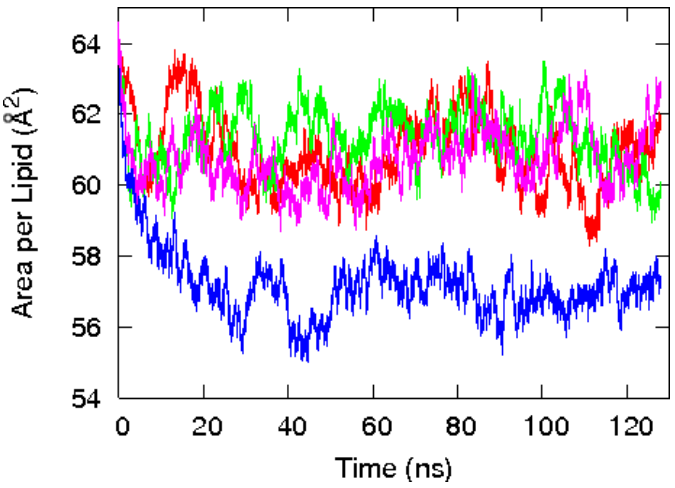

Figure 1: The area per lipid time series at 323K for simulations employing the forcefield parameters of (red) standard ffgmx, (green) ffgmx converted to ε and δ, (blue) standard OPLS, (purple) the half-ε double-pairlist OPLS method.