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Coarse-grained bond and angle distributions from atomistic simulations: On the systematic parameterisation of lipid models

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ABSTRACT

Coarse-grained (CG) models are popular alternatives to atomistic (AT) force fields as they enable simulations of larger systems at longer timescales. The bottom-up approach is a systematic parameterisation strategy whereby data from AT simulations are used to determine the CG parameters. This is particular straightforward with the bond and angle parameters as a direct Boltzmann inversion can be used. Still, a reference AT force field has to be chosen. In this study, I compare three common AT force fields (Stockholm lipids, Berger and Gromos) and investigate the sampling of bond and angle distributions in two CG models (Martini and Elba). As a test case, I choose a bilayer of POPC lipids. The AT simulations give distributions that agree to a large extent, especially in the fatty acid tails. However, the AT simulations sample distributions that differ from the distributions observed in CG simulations with respect to both location and width. The bond and angle distributions from the AT simulations are then used to re-parameterise the CG force fields. For the Martini model, this significantly alters the physical behaviour of the membrane, which likely is an effect of the mapping. However, for the Elba model the re-parameterised force field gives a membrane that is in some respects closer to the experimental membrane. Implications for CG parameterisation are discussed.

1. Introduction

Molecular dynamic simulations are attractive alternatives to traditional wet-lab experiments as the simulations provide dynamic insight on (bio) chemical systems at an atomistic (AT) resolution [1]. Typically, the atoms are propagated using classical mechanics guided by an empirical potential, viz. a force field. The most accurate force fields model each atom individually but they become computationally expensive when the aim is to study large systems at biological timescales. Therefore, coarse-grained (CG) models have been developed that group atoms into pseudo-atoms or beads, thereby reducing the number of particles that needs to be propagated [2,3]. The least invasive strategy is simply to remove non-polar hydrogen atoms and merge them with the atom they are bonded to, leading to a united-atom force field [4]. A more drastic reduction in the number of particles can be achieved by merging entire groups of atoms into beads. This has been a successful strategy in popular force fields such as Martini [5–7] TraPPE [8], and Elba [9,10].

CG models can be parameterised using several strategies [11]. For instance, matching to macroscopic data from experiments is a common approach for biological CG force fields like Martini and Elba [5,10]. Unfortunately, this procedure is typically ad-hoc in nature, rather than systematic, which is unhelpful if new molecules have to be parameterised by researchers not involved in the original parameterisation. This has also traditionally been the case for AT force fields although recent tools to make unbiased parameterisations have been suggested [12]. A more systematic set of approaches sort under the term bottom-up [13], whereby data from AT simulations are used to derive the CG parameterisation. Several such strategies have been suggested in the literature [14–18]. The most common strategies are force-matching or reconstitution of the pair distribution function [11,13]. The latter can be accomplished with for instance Boltzmann inversion [19], inverse Monte Carlo [15], or Iterative Boltzmann Inversion [16]. Although automatic tools to parameterise CG force fields have been suggested [20–23], they are still less mature and widely used than corresponding tools for AT force fields [24–26].

A critical, and one of the first choices in a systematic bottom-up parameterisation approach is the selection of an AT force field to be used as reference. For biological systems there exists a wide range of force fields [27–30] and it is uncertain what reference to use. A natural question then arises: do the different AT force

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fields give the same CG parameters? What is the sensitivity of the CG model with respect to the AT parameters? Sensitivity issues have been investigated for some time for AT models [31,32] and more recently in CG modelling [33]. In this paper, I will address this question for the small, albeit illustrative case of the parameterisation of bond and angle parameters in a common lipid, POPC (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine). First, there are CG parameters available in both Martini and Elba for this lipid and therefore a direct comparison with AT force fields can be made. Second, by re-parameterising the available CG force fields using data from AT simulations, the effect on the physical properties can be observed. I will conclude the paper by discussing future prospects on parameterisation of lipid force fields using a bottom-up approach.

2. Methods

2.1. System setup

A membrane consisting of 128 POPC and 5120 water molecules were created using the CHARMM Membrane builder web service [34]. This membrane was then simulated with the Stockholm lipids (Slipid) [35], Berger [36], Gromos [37], Martini [6] and Elba [10] force fields. The membrane was minimized using 100 steps of steepest descent followed by 10 ns equilibration at 303 K and 1 bar. Finally, a 250 ns production simulation was run at the same conditions. Two independent repeats were initiated by using different initial coordinates of the system. The simulations are detailed below for each force field. All simulations were run with Gromacs version 5.0.4 [38] except the Elba simulations that were run with Lammps [39].

2.2. Slipid simulations

The time step was set to 2 fs and the Lincs algorithm [40] was used to constrain all bonds. The non-bonded neighbour list was setup with the Verlet scheme [41] and updated every 10th step. Electrostatic forces were treated using particle-mesh Ewald (PME) [42] and the real-space cut-off was 1.2 nm. The van der Waals forces were switched off from 1.0 to 1.2 nm and long-range corrections were added. The 10 ns equilibration simulation was run employing a weak-coupling thermostat [43] with a 0.5 ps coupling constant and a weak-coupling semi-isotropic barostat with a 10 ps coupling constant. The water and lipid molecules were coupled to independent thermostats. The 250 ns production simulation was run with a Noose–Hover thermostat [44,45] and a Parinello–Rahman barostat [46] both using the same coupling constants as in the equilibration simulation.

2.3. Berger simulations

Non-polar hydrogen atoms were removed from the lipids using in-house scripts. The time step was set to 2 fs and all bonds were constraint using the Lincs algorithm [40]. The non-bonded neighbour list was setup with the group scheme [41] and updated every 5th step. Electrostatic forces were treated using PME [42] with a 1.0 nm real-space cut-off. The van der Waals forces were cut-off at 1.0 nm and long-range corrections were added. The thermostat and barostat settings were as in the Slipid simulations.

2.4. Gromos simulations

Non-polar hydrogen atoms were removed from the lipids using in-house scripts. The time step was set to 2 fs and all bonds were constraint using the Lincs algorithm [40]. The non-bonded neighbour list was setup with the group scheme [41] and updated every 2nd step. The electrostatic forces were treated with a generalized reaction field [47] using a 1.4 nm cut-off. The van der Waals forces were cut-off at 1.4 nm and no long-range corrections were added. The thermostat and barostat settings were as in the Slipid simulations.

2.5. Martini simulations

The POPC molecules were mapped to the CG representation and groups of four water molecules were replaced by a CG water bead using in-house scripts. The time step was set to 40 fs and no bonds were constrained. The non-bonded neighbour list was setup with the Verlet scheme [41] and updated every 10th step. Electrostatic forces were treated using a reaction field [47] and a potential shift from 0 to 1.2 nm. The van der Waals forces were switched off from 0.9 to 1.2 nm. The equilibration simulation was run with a weak-coupling thermostat [43] with a 0.5 ps coupling constant and a weak-coupling semi-isotropic barostat with a 10 ps coupling constant. The production simulation was performed with a veloc-

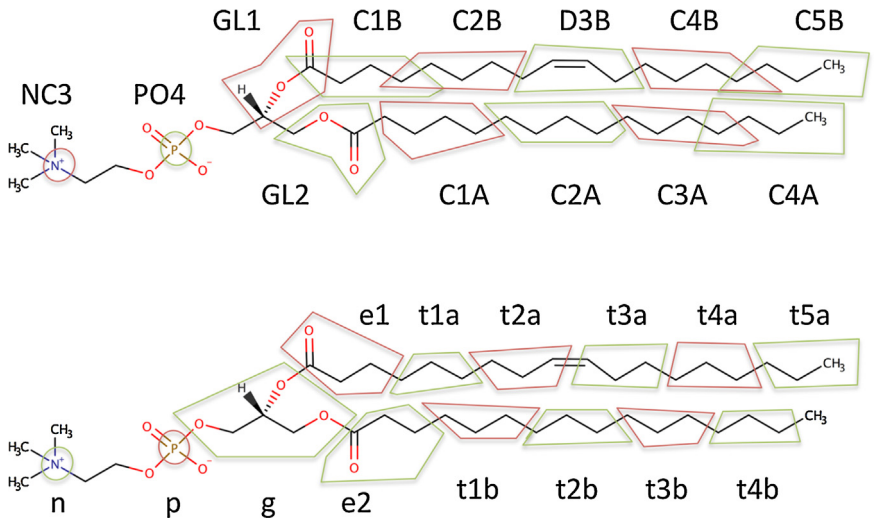

Fig. 1. Atoms to CG bead mapping for Martini (above) and Elba (below). The shape of the region covering the atoms is only for illustrative purposes, all CG beads are spherical. The name of the beads is shown next to each region.