



Comment to: “Martini straight: Boosting performance using a shorter cutoff and GPUs” by D.H. de Jong, S. Baoukina, H.I. Ingólfsson, and S.J. Marrink

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Comment to : "Martini straight: Boosting performance
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Baoukina, H. I. Ingólfsson, and S.J. Marrink

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Abstract

In a recent study published in this journal, de Jong et al. investigated the efficiency improvement reached thanks to new parameter sets for molecular dynamics simulations using the coarse-grained Martini force-field and its implementation in the Gromacs simulation package [De Jong et al. Vol. 199, pp 1-7, 2016]. The advantages of the new sets are the computational efficiency and the conservation of the equilibrium properties of the Martini model. This article reports additional tests on the total energy conservation for zwitterionic lipid bilayer membranes. The results show that the conclusion by de Jong et al. on the good total energy conservation of the new parameter sets - based on short simulations and homogeneous systems - is generally not valid on lipid bilayer simulations. The energy conservation of the three parameter sets compared in their article (*common*, *new* and *new-RF*) differ if one analyses sufficiently long trajectories or if one measures the total energy drifts. In practice, when total energy conservation is important for a Martini lipid bilayer simulation, one should consider either keeping the *common* set, or carefully testing the *new-RF* set for energy leaks or sources before production use.

Keywords: Computer simulation, molecular dynamics, biological membrane, lipid membrane

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In analytical classical Newtonian dynamics, the total energy of an isolated system is conserved. Total energy conservation is therefore a basic criterion to assess the precision of a molecular dynamics (MD) simulation. While a precise energy conservation is not strictly necessary to investigate the equilibrium structure of a fluid using thermostated simulations, energy sources or sinks may still influence the dynamical properties of the system, such as diffusions, flows, structure fluctuations, or transition mechanisms[1]. Bad energy conservation can also be at the origin of numerical instabilities, i.e. the simulation simply crashes.

In a recent study published in this journal [2], de Jong et al. investigated the efficiency improvement reached thanks to a new parameter set for MD simulations using the coarse-grained Martini force-field [3, 4] and its implementation in the Gromacs simulation Package [5]. Originally, the Martini potentials are based on a shift function that reduces smoothly both Lennard-Jones (LJ) and Coulomb interactions to zero at 1.2 nm, and the associated set of parameters is called *common* in Ref. 2. de Jong et al. developed two new sets of parameters for the MARTINI model labeled *New* and *New-RF*. The *new* set yields modified Lennard-Jones and Coulomb potentials, with straight cutoffs at $r_c = 1.1$ nm. So-called modifiers are also used, ie the complete potentials are shifted by a constant value so that they zero out at the cutoff [6]. In contrast, the *new-RF* set uses reaction-field potential for electrostatics [7]. de Jong et al. have shown that these alternative sets of parameters conserve many properties of the Martini model. They have also analyzed total energy conservation and concluded that "the newly proposed cutoff scheme New-RF appears most suitable for simulations with the Martini force field, and can lead to a significant speedup while keeping energy conservation within reasonable bounds.[...] However, to assure wider applicability, additional testing on specific systems of interest is still recommended." [2].

The present article reports additional assessments of the total energy conservation for zwitterionic lipid bilayer membranes, which are extremely commonly studied with the Martini force-field and the Gromacs package. Our results show that the analysis of energy conservation based on short simulations and homogeneous systems of Ref. 2 is not generalizable to longer simulations, especially for lipid bilayer simulations.

In the following, the model and methods are first described. Then we show that the energy conservation qualities of the *common*, *new* and *new-RF* parameters sets significantly differ if one analyses sufficiently long trajec-

ries or if one measures directly the total energy drifts. Moreover, the total energy drifts of lipidic bilayer simulations can be considerably higher than the ones of homogeneous systems. In practice, when total energy conservation is important for a Martini lipid bilayer simulation, one should consider either keeping the *common* set, or carefully testing the *new-RF* set for energy leaks or sources before production use.

1. Methods

To reproduce some results of [2] and investigate further the impact of structure, the following systems were simulated : bulk water, bulk octanol, water/vacuum interface, water/octanol interface, and hydrated lipid phosphatidylcholine (PC) bilayers. For each of these systems, we have evaluated the energy conservation in the microcanonical ensemble (NVE).

Systems setup. All the systems were simulated with periodic boundary conditions in three dimensions, with Martini version 2.1 [3]. The relative permittivity was set to 15; in combination with an apolar water solvation.

Water and octanol. For bulk water and octanol, a cubic box of $(72 \text{ \AA})^3$ containing respectively 3200 water beads or 1600 octanol molecules was created using the Packmol package [8], then relaxed and subsequently simulated under NPT conditions, as described below. For the water/vacuum system, the previous water cube was simulated in a box of double size in one dimension, creating a layer of vacuum. For water/octanol systems, the water and octanol cubes were appended. To verify whether the temperature drift depends on box anisotropy in an homogeneous system, a bulk water with 6400 water beads was also simulated, with the box size doubled in one dimension.

Planar hydrated bilayers. Three different neutral phosphatidylcholines were simulated, with either 3, 4 or 5 hydrophobic beads of type C1 on both tails, representing respectively 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and 1,2-dibehenoyl-sn-glycero-3-phosphocholine (DBPC). Bilayers of 512 lipids were preformed using the Packmol package [8], and hydrated with 5120 water beads. The initial area per lipid was fixed at 61, 64 and 64 \AA^2 for DLPC, DPPC and DBPC, respectively.

Simulation protocol. Versions 4.6.7 and 2016.3 of the Gromacs software package were used [5]. The later was compiled with mixed floating-point precision (MP) and with double precision (DP). For all systems, we performed successively several simulations to reach equilibrium temperature and pressure without surface tension: (i) an energy minimization (steepest descent with 50000 steps) (ii) a 10 ns NVT simulation with a small timestep ($dt = 1$ fs), (iii) a 10 ns NVT simulation with a normal timestep, (iv) a 10 ns NPT simulation with a Berendsen thermostat, (v) a 1.2 to 100 ns NPT simulation with a Parinello-Rahman thermostat, (vi) a 100 ns NVE simulation. For the water/vacuum system only, the NPT steps (iv) and (v) were replaced by an equal duration NVT simulation. The timestep dt was varied systematically from 10 fs to 30 fs in the steps (iii) to (vi) of the protocol.

The velocity rescale scheme [9] was used with coupling parameters of 1.0 ps^{-1} . For lipid bilayers (DLPC, DBPC and DPPC) the temperature was set to 323 K to ensure simulations of the fluid phase of the membranes. For the non-lipidic systems, and for the DLPC bilayers, the temperature was set to 298 K, to compare with the results of Ref. 2, obtained at this temperature.

A pressure of 1 bar was imposed successively by the Berendsen barostat [10] with a coupling time of 3 ps and a compressibility of $3 \times 10^{-4} \text{ bar}^{-1}$, and the Parinello-Rahman scheme [11] with a coupling time of 12.0 ps. For the anisotropic systems, a zero surface tension was imposed using the semi-isotropic barostat which decouples the box degrees of freedom in z -direction from the ones in x - and y -directions.

Other key parameters include the neighbor list update scheme and frequency, the cut-off radii for the non-bonded potentials, and the exact form of the function nearby the cutoff. We compared various sets of parameters, three of which are identical to the ones by de Jong et al. : *common*, *new* and *new-RF* [2]. One additional set is tested : *new-LR* (Longer- r_c).

1. *Common* Usual parameters in many recent papers. The neighbor list length is 1.4 nm with the neighbor list created using the group-scheme every 10 steps. Potentials and forces are modified, thanks to the Gromacs shifting function between 0.9-1.2 nm and 0.0-1.2 nm for Lennard-Jones (LJ) and Coulomb interactions, respectively.
2. *New* Parameters proposed by de Jong et al. The neighbor list is updated using the Verlet neighbor search (VNS) algorithm with the neighbor list length being automatically determined (**verlet-buffer-drift** at $0.005 \text{ kJ/mol/particle/ps}$)[12, 6]. LJ and Coulomb potentials and

forces are cut off at 1.1 nm, with the potentials shifted to zero at the cut off using the "Potential modifiers" which do not modify the force. The neighbor list is updated every 20 steps.

3. *New-RF* The same as *new* except for the Coulomb interactions a reaction-field potential with $\epsilon_{rf} = \infty$ is used. The potential is smoothly changed to zero at the cut-off by assuming a fixed dielectric constant beyond the cutoff [7].
4. *New-LR* the same as *new* except for the LJ and Coulomb cutoffs which are 1.2 nm. We introduce this new parameter set for lipid bilayers simulations only.

For the microcanonical ensemble, a fixed verlet cutoff of 1.4 nm was used in step (vi) of our protocol (`verlet-buffer-drift` or `verlet-buffer-tolerance` at -1). This choice was conservative, since the cutoff radii used in step (v) were typically 1.17 nm.

Observables. Using the final microcanonical simulation of our protocol (see Sect. 1), we studied the drifts in temperature (\mathcal{DT}) and total energy (\mathcal{DE}^{tot}), and the root mean square deviations (RMSD) of the total and potential energies ΔE^{tot} and ΔE^{pot} . The ratio of the energies fluctuations is noted $r = \Delta E^{tot} / \Delta E^{pot}$. Drifts were calculated by performing a least-squares fit of the time series to a linear function. As implemented in the `g_energy` tool, the drifts are the evolutions of the linear fit during the given measurement time (\mathcal{Dt}). For the results in Tables 1 and 2, the observables were calculated over two different time spans, \mathcal{Dt} , of 0.6 and 10 ns. Average and errors of the drifts and RMSD were then calculated using the numerous values obtained from cutting longer simulations into blocks of 0.6 of 10 ns respectively. The area per lipid, A_L , is simply calculated as $\langle L_x \times L_y \rangle / N_L$, where L_x and L_y are the lateral box dimensions in x and y dimension, angular brackets indicate the time average, and N_L is the number of lipids per monolayer. It is averaged over the last 80 ns of a 100 ns simulation in the NPT ensemble.

2. Results and discussion

An intuitive criterion for acceptable energy conservation is that the total energy fluctuations are small in comparison to other pertinent energies in the system. The observable used in de Jong et al. to quantify this approach is the ratio of the total and potential energies fluctuations $r = \Delta E^{tot} / \Delta E^{pot}$. The criterion of less than 20 % was proposed as acceptable by Winger et

al.[13]. This observable is attractive since it is dimensionless, and can easily be calculated on the relevant time span.

2.1. The ratio of energies fluctuations (r) can vary significantly as a function of the time span of measurement

Before comparing these observables obtained within different publications, we studied how the total energy drifts per time unit $\mathcal{D}E^{tot}/\mathcal{D}t$, and the ratio r depend of the time span of measurement $\mathcal{D}t$ (see Figs.1 and 2). The *common* and *new-RF* sets are compared for bulk water simulations using various time steps.

Figure 1

For all parameters sets and time steps, the total energy drifts per time unit converge towards average values which increase with timestep (see Fig. 1). Fluctuations depending on the time span of analysis $\mathcal{D}t$ exist, but $\mathcal{D}t=10$ ns appears as a reasonable compromise, that allows to measure the total energy drift with sufficient precision to compare parameter sets.

Figure 2

In contrast, Fig. 2 reveals that the time dependence of the ratio r depends on the parameter set. For the *common* set, characterized by low total energy drifts, the ratios converge towards stable values even at small time spans of measurements. But for the *new-RF* set, the ratio r increases continuously with the time span $\mathcal{D}t$, and seems to reach a limit around 2.0 for large time spans (data not shown here). The inset of Fig.2 magnifies the region of small time spans, where one may interpret the initial linear dependency of ΔE^{tot} relative to $\mathcal{D}t$ as the following: If the total energy drift largely dominates over local fluctuations, ΔE^{tot} is expected to be close to proportional to $\mathcal{D}E^{tot}$, which is also proportional to $\mathcal{D}t$.

First, these results show that ratios r obtained from different simulations should be compared on the same measurement time span. In the following, we have chosen to report results for the time span chosen in de Jong et al.[2], i.e. 0.6 ns, and for the time span at which the total energy drift per time unit had practically converged, ie 10 ns. Second, the unpredictable behavior of r for different sets supports the remark of Braun et al. in Ref. 14, stating that the total energy drift per time is more reliable than r , especially when comparing different simulation sets.

The energy conservation analysis performed on a small time span of 0.6 ns, and limited to the energies fluctuations ratio is not sufficient to draw the general conclusion that the three sets are equivalent in terms of energy conservation. As shown on the Fig.1, *common* and *new-RF* sets yield significantly different total energy drifts, which are investigated further in the following.

2.2. Energy drifts are higher with lipid bilayers than with simple liquids

The results for the bulk water, bulk octanol, water/vacuum and water/octanol simulations are shown in Table 1 for a time span of $\mathcal{D}t = 0.6$ ns, to compare with the results presented in Ref. 2. The results by de Jong et al. are reproduced, with temperature drifts of less than 1.0 K, and $r = |\Delta E^{tot}/\Delta E^{pot}|$ between 5 and 10%. Considering the temperature drift, and the ratios r , the *common* and *new* sets indeed give similar results for both homogeneous systems (bulk water and bulk octanol). In line with the results from Braun et al., obtained on microcanonical simulations of all-atom and coarse-grained water models, for simulation lengths of smaller than 1 ns everything looked well behaved [14]. One difference is nevertheless already noticeable even on such small measurement time spans : the absolute value of the total energy drift ($|\mathcal{D}E^{tot}|$) using the *new* set is systematically larger than the values obtained using the *common* set (multiplied typically by 3 to 10).

Table 1

But longer measurement time spans are more precise to study the energy and temperature drifts. For three anisotropic systems, we repeated the same analysis on time spans of $\mathcal{D}t = 10$ ns (see Table 2).

Table 2

The energy conservation remains in reasonable range for all systems using the *common* parameter set. The total energy drift is indeed higher for lipidic bilayer than for the water and octanol simulations, but even in the lipid bilayer simulations, the temperature drifts remain smaller than 1 K, and r values are lower than 15% . Looking at longer microcanonical simulations permits to emphasize that, with the *new* parameter set, the quality of energy conservation strongly depends on the simulated system.

For the water/vacuum system, the *new* parameter set with timestep 30 fs seems still reasonable, but for the lipid bilayer simulations the total energy drifts are larger. In the extreme case, the DLPC at 298 K, the total energy drift per μs reached about 6 times the average kinetic energy ($1/2 \times k_B T$ per degree of freedom). Acceptable values for parameter settings surely depend on the users' goal [13, 15, 16, 14], but this value of total energy drift is so high that we conclude rather generally that for lipid bilayer simulations with MP, the *new* set should be avoided when the *new-RF* set can be used.

2.3. Reaction-Field calculations considerably improve energy conservation, but even with new-RF, care must be taken

Aiming at improving energy conservation using the straight cutoff characterizing the *new-RF* and *new* parameter sets, we pragmatically tested the

impact of a few simulation parameters for our three systems composed of zwitterionic bilayers and the non-polarizable water : (i) the impact of Gromacs version or compilation precision, (ii) the neighbor list generation frequency, (iii) reaction field calculations, (iv) the cutoff of the non-bonded interaction, and (v) the timestep. Energy conservation observables obtained for a timestep of 30 fs and various parameter sets are reported in Table 3.

Table 3

First, because of the VNS implementation algorithm based on groups of particles [6], increasing the frequency for recalculating the Verlet lists did not improve energy conservation (our results, not detailed here, confirmed that the optimum value for `nstlist` is 20 timesteps).

Interestingly, when the reaction field calculations are added, total energy drifts are divided by a factor of 5 to 10 (*new-RF* relative to *new* in Table 3). This improvement of energy conservation is noticeable, all the more so as our simulations contain solely zwitterionic lipids and non-polarizable water. But unfortunately, the total energy drift per μ s of the DLPC simulations remains as high as the average kinetic energy. The *new-RF* set with a timestep of 30 fs may be acceptable in NVT or NPT simulations investigating the structure of lipidic bilayers, but it is to be expected that dynamical properties can depend on the coupling with the thermostat.

Concerning gromacs versions, the results are very similar with the versions 4.6.7 and 2016 of Gromacs (both compiled with MP). Using double precision compilation noticeably divides the drifts by a factor about 2 to almost 10, depending on the system. The gain yielded by higher precision may be limited by the discontinuity of the forces at the cutoff, which does not depend on the precision. Unfortunately, double precision calculations may be incompatible with some GPU (graphics processing unit) acceleration.

We also tested to increase the non-bonded interaction cutoff radius from 1.1 nm to 1.2 nm within the *new-LR* set, as in recent study by Mustafa et al. [17]. Changing the parameters of the cutoff modifies the model (for a detailed example see Ref. 18), we indeed observed water freezing even at 298 K for timesteps of 30 fs (but not for smaller timesteps), and the area per lipid of tension-free hydrated bilayer diminishes by about 3%, i.e. 2 \AA^2 per lipid (see Supplementary Information). Counter-intuitively, such an increase does not significantly improve energy conservation (see Table 3, *new-LR* set). Therefore we did not investigate further in this direction.

Finally, we investigated whether diminishing the timestep would improve total energy conservation for four lipid bilayer simulations. Fig. 3 illustrates the total energy drifts per time unit for dt ranging from 10 to 30 fs, for the

common, *new* and *new-RF* sets.

Astonishingly, the total energy drifts do *not* systematically decrease when dt is diminished to 25 fs or even 20 fs. This non-monotonous behavior reveals that sources other than the numerical integration of Newton’s equation lead to energy leaks in the code. Therefore, diminishing the timestep does not automatically lead to better total energy conservation.

Despite this complexity, diminishing the timestep does not radically change the conclusions drawn previously for $dt = 30$ fs : for the default MP compilation, the *common* set yields lower total energy drifts at all tested timesteps, and the *new-RF* set should be preferred to the *new* set.

The conclusion for the *new-RF* set is less clear and the results are system-dependant. Two different regimes can be distinguished: (i) for $dt \leq 20$ fs, the *common* set conserves the total energy with drift of less than 1% of the average kinetic energy per microsecond, ie better than all other sets; (ii) for $dt \geq 25$ fs, the total energy conservation of the *common* set worsens, approaching the one of the *new-RF* set. At $dt = 30$ fs, the drifts of the *common* set are still 2 to 10 times lower than the ones of the *new-RF* set (see Table 3). In this region, the energy drifts of the *new-RF* set combined calculated with double precision compilation are similar to the one of the *common* set combined with mixed precision compilation, but the results vary depending on the system and on the temperature.

Practical Considerations

The analysis of all energy conservation tests of our lipid bilayer simulations data (see Supplementary Information, Tables S3 to S7) permits to draw practical conclusions concerning the choice of the parameter set.

To optimize the energy conservation quality, while keeping a reasonable performance and a MP compilation, the *common* set with a timestep of 25 fs appears as a safe compromise, with a total energy drift on the order of magnitude of 1% of the average kinetic energy per microsecond.

The *new* set, in combination with a MP compilation, showed poor energy conservation for our microsecond lipid membrane simulations. The *new-RF* set considerably improved energy conservation relative to the *new* set, but on average, its energy conservation quality remained lower than the one of the *common* set. With a timestep of 30 fs, the *new-RF* set can still yield total energy drifts reaching several $k_B T$ per particle per μs , and should be evaluated in each situation. The criterion of $r \leq 20\%$ being possibly not

fulfilled on microsecond time spans, the user should define an acceptable total energy drift per time unit, and choose the combination of parameters that fulfills the criterion accordingly. If the *common* set is no longer available in the future, the total energy conservation of the *new-RF* with double precision calculations set may also be considered as satisfactory after testing.

Conclusions

First, we have compared two observables typically used to perform the total energy conservation analysis of a MD simulation : the ratio of energies fluctuations $r = \Delta E^{tot} / \Delta E^{pot}$, vs. the bare total energy drift per time. For the sets with worse energy conservation, the ratio r depends on the time span of analysis, and should be calculated on relevant simulation times to remain reliable. The measure of the total energy drifts per time unit is more relevant to compare the parameter sets analyzed here, and permits to show significant differences between the *common*, *new* and *new-RF* sets. For the simulations performed with Gromacs default compilation using mixed-precision, the total energy drifts are larger with the *new* or *new-RF* parameter sets in comparison with the *common* parameter set. The *common* set with a timestep of 25 fs appears as a safe option concerning total energy conservation.

Second, our simulation results underline that the quality of the energy conservation does not only depend on the parameter sets, but also on the inner structure of the simulated system. For the systems tested here, and for the mixed floating-point precision gromacs executables, the total energy conservation of lipid bilayer simulations worsens relative to simple liquids. The use of the *new* or *new-RF* parameter sets for lipidic bilayer can lead to considerable amounts of energy flows into or out of the system. Compiling Gromacs v2016.3 with double precision sometimes turned out to improve the energy conservation of the *new-RF* parameter set, but in a timestep- and system-dependent manner. The *new-RF* set with a timestep of 30 fs may be acceptable in isothermal simulations of lipid bilayers investigating the equilibrium structure of the fluid, but the coupling with the thermostat may influence the dynamical properties of the system.

Further investigations on the impact on the energy conservation of Particle-Mesh Ewald (PME) long-range electrostatics calculations, of the reaction field parameters, and of Martini polarizable water solvation [19, 20] in molecular dynamics simulations of Martini biomolecules would be pertinent.

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4. Supplementary Informations

Energy conservation analysis for *common*, *new*, *new-RF* and *new-LR* parameter sets for the timesteps 10, 15, 20, 25 and 30 fs.

- [1] D. J. Bonthuis, K. Falk, C. N. Kaplan, D. Horinek, A. N. Berker, L. Bocquet, and R. R. Netz. Comment on “pumping of confined water in carbon nanotubes by rotation-translation coupling”. *Phys. Rev. Lett.*, 105:209401, Nov 2010.
- [2] Djurre H. De Jong, Svetlana Baoukina, Helgi I. Ingólfsson, and Siewert J. Marrink. Martini straight: Boosting performance using a shorter cutoff and GPUs. *Comput. Phys. Comm.*, 199:1–7, 2016.
- [3] Siewert J Marrink, H Jelger Risselada, Serge Yefimov, D Peter Tieleman, and Alex H de Vries. The MARTINI Force Field: Coarse Grained Model for Biomolecular Simulations. *J. Phys. Chem. B*, 111(27):7812–7824, 2007.
- [4] Siewert J. Marrink and D. Peter Tieleman. Perspective on the Martini model. *Chem. Soc. Rev.*, 42:6801–6822, 2013.
- [5] Sander Pronk, Szilrd Pll, Roland Schulz, Per Larsson, Pr Bjelkmar, Rossen Apostolov, Michael R. Shirts, Jeremy C. Smith, Peter M. Kasson, David van der Spoel, Berk Hess, and Erik Lindahl. Gromacs 4.5: a high-throughput and highly parallel open source molecular simulation toolkit. *Bioinformatics*, 29(7):845, 2013.
- [6] Soren Toxvaerd, Ole J. Heilmann, Jeppe C. Dyre, Mark James Abraham, Teemu Murtola, Roland Schulz, Szilárd Páll, Jeremy C. Smith, Berk Hess, and Erik Lindah. Gromacs: High performance molecular simulations through multi-level parallelism from laptops to supercomputers. *SoftwareX*, 1-2(22):19–25, 2012.

- [7] Ilario G Tironi, Paul E Smith, and Wilfred F Van Gunsteren. A generalized reaction field method for molecular dynamics simulations. *J. Chem. Phys.*, 5451(13):5451—5459, 1995.
- [8] L. Martínez, R. Andrade, E. G. Birgin, and J. M. Martínez. Packmol: A package for building initial configurations for molecular dynamics simulations. *J. Comput. Chem.*, 30(13):2157–2164, 10 2009.
- [9] Giovanni Bussi, Davide Donadio, and Michele Parrinello. Canonical sampling through velocity rescaling. *J. Chem. Phys.*, 126(1):14101, 2007.
- [10] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, A. DiNola, and J. R. Haak. Molecular dynamics with coupling to an external bath. *J. Chem. Phys.*, 81, 1984.
- [11] Michele Parrinello and Aneesur Rahman. Polymorphic transitions in single crystals: A new molecular dynamics method. *J. Appl. Phys.*, 52:7182, 1981.
- [12] Loup Verlet. Computer "experiments" on classical fluids. i. thermodynamical properties of lennard-jones molecules. *Phys. Rev.*, 159:98–103, Jul 1967.
- [13] Moritz Winger, Daniel Trzesniak, Riccardo Baron, and Wilfred F. van Gunsteren. On using a too large integration time step in molecular dynamics simulations of coarse-grained molecular models. *Phys. Chem. Chem. Phys.*, 11:1934–1941, 2009.
- [14] Daniel Braun, Stefan Boresch, and Othmar Steinhauser. Transport and dielectric properties of water and the influence of coarse-graining: Comparing bmw, spc/e, and tip3p models. *J. Chem. Phys.*, 140(6):064107, 2014.
- [15] Siewert J. Marrink, Xavier Periole, D. Peter Tieleman, and Alex H. de Vries. Comment on "on using a too large integration time step in molecular dynamics simulations of coarse-grained molecular models" by m. winger, d. trzesniak, r. baron and w. f. van gunsteren, phys. chem. chem. phys., 2009, 11, 1934. *Phys. Chem. Chem. Phys.*, 12:2254–2256, 2010.

- [16] Wilfred F. van Gunsteren and Moritz Winger. Reply to the 'comment on "on using a too large integration time step in molecular dynamics simulations of coarse-grained molecular models"' by S. J. Marrink, X. Periole, D. Peter Tieleman and Alex H. de Vries, *phys. chem. chem. phys.*, 2010, 12, doi: 10.1039/b915293h. *Phys. Chem. Chem. Phys.*, 12:2257–2258, 2010.
- [17] Ghulam Mustafa, Prajwal P. Nandekar, Xiaofeng Yu, and Rebecca C. Wade. On the application of the martini coarse-grained model to immersion of a protein in a phospholipid bilayer. *J. Chem. Phys.*, 143(24):243139, 2015.
- [18] David van der Spoel and Paul J. van Maaren. The origin of layer structure artifacts in simulations of liquid water. *J. Chem. Theor. Comput.*, 2(1):1–11, 2006.
- [19] Semen O Yesylevskyy, Durba Sengupta, Siewert J Marrink, and Lars V Scha. Polarizable Water Model for the Coarse-Grained MARTINI Force Field. *PLOS Comput. Biol.*, 6(6), 2010.
- [20] Julian Michalowsky, Lars V. Schäfer, Christian Holm, and Jens Smitte. A refined polarizable water model for the coarse-grained martini force field with long-range electrostatic interactions. *J. Chem. Phys.*, 146(5):054501, 2017.

Tables

Sets	Water ^(a)		Water		Octanol		water/vac.		water/octa	
	com.	new	com.	new	com.	new	com.	new	com.	new
\mathcal{DT}	0.2	0.3	0.5	0.5	0.9	-0.2	0.9	0.5	-1.3	-0.3
$ \Delta E^{tot}/\Delta E^{pot} $ (%)	7	12	8	9	6	7	6	6	7	7
$ \mathcal{DE}^{tot}/\mathcal{Dt} $			3	10	1	9	1	4	2	8

Table 1: Energy conservation analysis of simulations in the microcanonical ensemble using the same timespan of analysis as in de Jong et al.[2] ($\mathcal{Dt}=0.6$ ns). Gromacs version is 4.6.7 and the timestep is 30 fs. Temperature drift \mathcal{DT} is in K, and total energy drift \mathcal{DE}^{tot} in $\text{kJ}\cdot\text{mol}^{-1}\cdot\mu\text{s}^{-1}$ per particle. The ratio is obtained with the RMSD ΔE^{tot} and ΔE^{pot} of the total and potential energies respectively. In Ref. [2], the drifts are calculated on the last 0.6 ns from a single 1.2 ns simulations. Our values are averages calculated over 100 measurements on time spans of $\mathcal{Dt}=0.6$ ns, taken from a 100 ns simulation. Typical errors for temperature drifts, ratio and total energy drift are respectively 10^{-2} K, 2%, and 10^{-2} $\text{kJ}\cdot\text{mol}^{-1}\cdot\mu\text{s}^{-1}$ per particle. (a): from de Jong et al. [2].

	Water		Water/Vacc		Water/Octanol		Bilayers	
	common	new	common	new	common	new	common	new
\mathcal{DT}	0.17	3.19					-0.00	8.67
(K)	-0.55	2.00	-0.02	0.22	-0.71	-1.68	-0.07	4.65
							-0.25	4.20
$\Delta E^{tot}/\Delta E^{pot}$	8	40					8	151
(%)	8	30	6	13	7	35	12	108
							12	110
$\mathcal{DE}^{tot}/\mathcal{Dt}$	0.02	6.40					-0.35	23.5
(kJ/mol/ μs /part.)	-0.15	5.20	-0.25	1.46	-0.57	-4.22	-0.76	11.3
							-0.76	10.7

Table 2: Same analysis as in Table 1, but the time span over which the drifts and RMSD are calculated is longer ($\mathcal{Dt}=10$ ns), and lipidic bilayer simulations are included. Results obtained from 100 ns simulations, analyzed on the last 80 ns. For water, the values reported were obtained for two bulk systems of 3200 and 6400 particles. (a): Equilibrium temperature of 323 K.

	Set	Common		New		New-RF			New-
	Gromacs	4.6.7	2016	4.6.7	2016	4.6.7	2016	2016-DP ^(c)	4.6.7
\mathcal{DT} (K)	DLPC ^(b)	-0.00	-0.46	8.67	8.79	1.61	1.53	0.66	-4.35
	DLPC	-0.32	-0.25	4.86	4.91	-0.33	-0.28	-0.19	1.54
	DPPC	-0.07	-0.19	4.65	4.36	-0.69	-0.54	0.44	-1.23
	DBPC	-0.25	-0.65	4.20	4.29	-0.64	-0.86	-0.67	-3.16
$\Delta E^{\text{tot}}/\Delta E^{\text{pot}}$ (%)	DLPC ^(b)	8	8	151	151	47	51	31	136
	DLPC	10	10	107	108	17	17	9	124
	DPPC	12	14	108	106	24	26	8	117
	DBPC	12	14	110	107	27	27	9	128
$\mathcal{DE}^{\text{tot}}/\mathcal{Dt}$ ($\frac{1}{2}\text{kT}/\text{dof}/\mu\text{s}$)	DLPC ^(b)	-0.09	-0.08	6.32	6.22	1.03	1.12	0.60	-5.86
	DLPC	-0.16	-0.15	3.06	3.12	-0.26	-0.26	-0.07	-5.92
	DPPC	-0.19	-0.22	2.81	2.85	-0.41	-0.48	-0.09	-6.17
	DBPC	-0.19	-0.22	2.65	2.76	-0.46	-0.46	-0.06	-6.29

Table 3: Same analysis as in Table 2 for lipidic bilayer simulations only, using various version of gromacs and a timestep of 30 fs. (a) Pure water crystallizes. (b) Equilibration at 298 K instead of 323 K. (c) 2016-DP was compiled with double precision.

Figure Captions

Figure 1. Total energy drifts per time unit $\mathcal{D}E^{tot}/\mathcal{D}t$, for bulk water simulations and timesteps varying from 10 to 30 fs (in $\text{kJ.mol}^{-1}.\mu\text{s}^{-1}$ per particle). The *common* and *new-RF* sets are depicted in dashed red and solid black lines respectively, with thinner lines for larger timesteps. The drifts are obtained over time spans of 1 to 150 ns, taken within the last 180 ns of a microcanonical simulation of 200 ns. Colors available in the online version.

Figure 2. Ratios of energies fluctuations $r = \Delta E^{tot}/\Delta E^{pot}$ for bulk water simulations and timesteps varying from 10 to 30 fs (see legend of Fig. 1). Colors available in the online version.

Figure 3. Total energy drifts $|\mathcal{D}E^{tot}/\mathcal{D}t|$ per μs for various time-steps for our lipid bilayer simulations with Gromacs2016.3 using the *common*, *new* and *new-RF* sets. For the *new-RF* set, the results obtained with Gromacs2016.3 compiled with Double Precision option are also plotted (*new-RF-DP*). Each point corresponds to a simulation (DLPC, DSPC or DBPC at 323 K or 298 K), and the lines depict averages over all the simulations using a given timestep. The energy drifts are represented on a log-scale, and rescaled relative to the average kinetic energy at the corresponding temperature, ie $1/2 \times k_B T$ per degree of freedom (dof). As in Table 2, these are obtained over time spans of 10 ns, from the last 80 ns of a microcanonical simulation of 100 ns. Colors available in the online version.

Figures

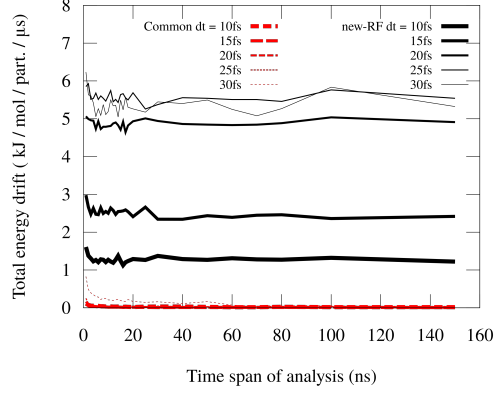


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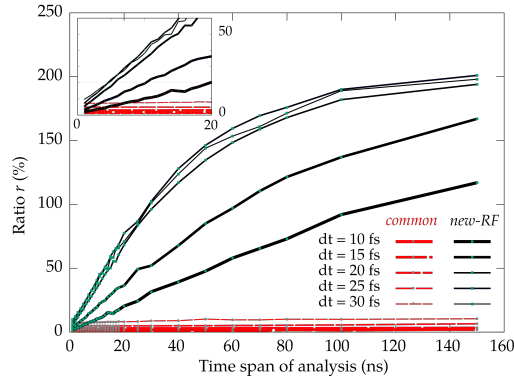


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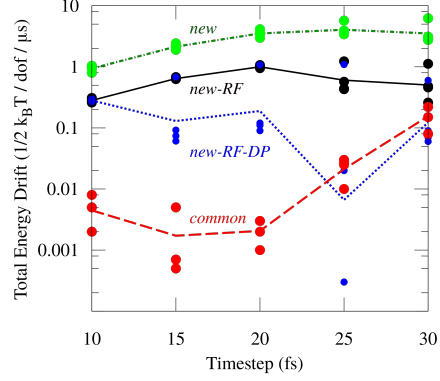


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