Comment on ''Efficient stress relaxation in molecular dynamics simulations of semiflexible *n*-alkanes'' [Phys. Rev. E. 58, 6766 (1998)]

M. Marchi[1] and P. Procacci[2]
[1]*Section de Biophysique des Protéines et des Membranes, DBCM, DSV, CEA, Centre d'Études de Saclay, F-91191 Gif-sur-Yvette Cedex, France*
[2]*Dipartimento di Chimica, Università degli Studi di Firenze, Via Gino Capponi 9, I-50121 Firenze, Italy*
(Received 19 April 1999; published 23 January 2001)

Contrary to the findings of Mülders, Toxvaerd, and Kneller [Phys. Rev. E **58**, 6766 (1998)] (MTK), we are unable to discern any difference in the behavior of long chain alkanes simulated by molecular dynamics at constant pressure using either atomic or molecular scaling schemes. This result confirms our previous study [M. Marchi and P. Procacci, J. Chem. Phys. **109**, 5194 (1998)] on hydrated proteins published at the same time as the MTK's paper. This Comment indicates that errors in the calculation of the pressure tensor might be responsible for at least a part of the MTKs results.

DOI: 10.1103/PhysRevE.63.028701 PACS number(s): 02.70.Ns, 31.15.Qg, 36.20.−r

More than ten years ago Ciccotti and Ryckaert demonstrated that atomic and molecular pressure virials are equal on average for nondissociating molecules [1]. In a recent study Mülders Toxvaerd, and Kneller [2] (MTK) have presented results supporting the view that coupling the intramolecular degrees of freedom [the so-called atomic scaling (AS)] to the volume dynamics ''strongly improves the relaxation energy and volume for long chains'' with respect to the alternative choice of molecular scaling (MS). In particular, it was found that for long chain alkane molecules the faster relaxation of constant pressure molecular dynamics (MD) simulations based on AS is responsible for differences in the computed thermodynamic observables if compared to MS simulations. As a side effect, during the MS run the atomic pressure was computed to differ from the molecular pressure by an almost constant offset of about 150 atm. These findings do not agree with those we reported in an investigation published on Ref. [3]. In that study, R-RESPA (reversible reference system propagation algorithm) [4] multiple time step algorithms for dynamics in the *NPT* ensemble were developed for different pressure scaling schemes and applied to a complex biomolecular system (a molecule of bovine pancreatic trypsin inhibitor protein hydrated by 1142 water molecules). While, in agreement with Ref. [1], we found that the choice of scaling technique did not affect the thermodynamic observables; no significant differences were detected on the time-dependent relaxation dynamics of the observables. This is in sharp contrast with results in Ref. [2].

Various explanations might be given for these discrepancies, such as the poor statistics in the MS scheme (as pointed out by MTK, only 240 degrees of freedom are coupled to the barostat), to the intrinsic nonergodic nature of the system under investigation, or, finally, technical problems in the implementation of the MD simulations. Thus, in order to understand the differences between our two independent investigations we have carried out a series of constant pressure simulations on a 80 dotriacontane molecule system (the same studied in Ref. [2]) with our constant pressure AS and MS algorithms. For these simulations, we have adopted the united atom CHARMM19 [5] parameters set to describe the bonded and nonbonded potential between dotriacontane molecules. No bond constraints were included in our model at this stage. For the MS scheme 240 degrees of freedom were coupled to the barostat while for AS they were 7680, including intramolecular ''breathing'' motions, responsible, according to MTK, for the fast relaxation of AS simulations.

The preparation of the sample follows a procedure similar to that reported in Sec. III of Ref. [2]: We first performed a simulation in the constant volume and temperature (*NVT*) at 500 K for 100 ps, then brought the system to 300 K and further equilibrate for an additional 100 ps. We begin our run from a box of 80 dotriacontane in an all-trans conformation with a box side length of 40.67 Å. After equilibration, we started two separate simulations in the constant pressure and temperature ensemble (*NPT*), with $P=0.1\,\mathrm{MPa}$ and $T=300\,\mathrm{K}$, each lasting 800 ps and using AS and MS, respectively. The integration of the equations of motion was done using the *NPT* multiple time step RESPA algorithms [6] developed by us in Ref. [3]. The piston mass used in all constant pressure simulations was of 1057 a.m.u.

Our results are shown in Figs. 1 and 2. In the former, we compare atomic and molecular pressures computed during the MS (upper panel) and the AS (lower panel) simulations. In the latter we show the relaxations of two observables, the cell volume and the Lennard-Jones (*L-J*) energy, for the two *NPT* scaling schemes. For clearness of the plot, the data in Fig. 2 have been smoothed by removing high-frequency noise (of time period higher than 3 ps) with a Savitsky-Golay standard filter [7]. These results disagree strikingly with those of MTK. In particular, both simulations carried out with the AS and MS schemes compute the same averaged atomic and molecular pressure. We do not observe in any way the offset of about 150 atm between atomic and molecular pressure computed during the MS simulation of MTK. Indeed, in our two simulations the atomic and molecular pressures equilibrate immediately and at the same value (the external pressure) independently on the scaling scheme used in the simulations. Thus, this behavior brings to the calcula-

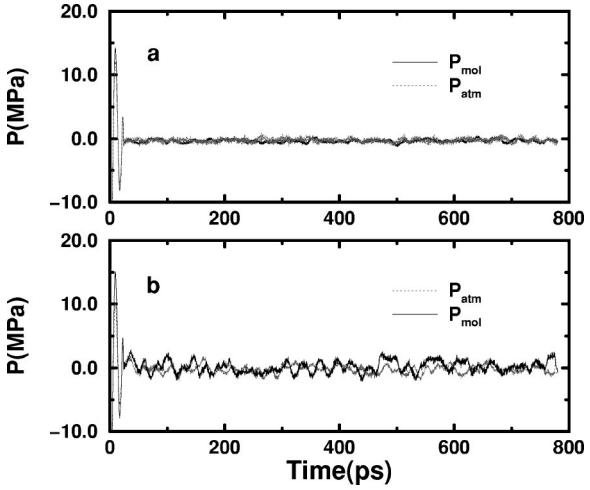

FIG. 1. Evolution of the molecular (continuous lines) and atomic (dotted lines) pressures in NPT MD simulations. Simulations in (a) and (b) use molecular and atomic scaling R-RESPA integrators, respectively.

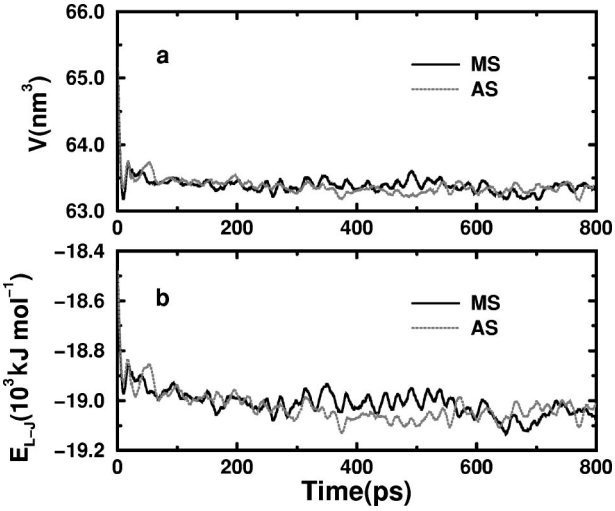

FIG. 2. Relaxation of the total cell volume (V) and Lennard-Jones energies (E_{L-J}) as a function of simulation time for simulations using MS and AS integration schemes.

tion identical thermodynamic observables (within error bar) that relax with approximately the same dynamics (see Fig. 2). As a further contrast, we also observe a rather rapid relaxation of those observables compared with their very slow decay in pointed out by MTK.

To further examine the contrast of our results with those of in Ref. [2], we have carried out additional simulations on *n*-decane and dotriacontane in the *NPT* ensemble by modifying the CHARMM19 force field *L-J* parameters and the stretching equilibrium distance to those of the isotropic Toxvaerd potential of Ref. [8] used by MTK. If, on the one hand, we confirmed our previous results as far as relaxation dynamics of observables and equivalence of atomic and molecular virial, we were unable to obtain the averaged volume within the error bar of that computed for *n*-decane and dotriacontane by MTK. Our averaged volume obtained with the same *L-J* cutoff of 16 Å as MTK is in both cases about 4% smaller than theirs. These results are troublesome, given that we were instead able to successfully reproduce the literature value of the molecular volume of alkanes determined by Monte Carlo for an all atom OPLS force field [9,10]. The introduction of bond constraints in the MS simulation did not affect significantly the computed observables and the relaxation dynamics.

Using more complex torsional potentials, such as the Smith and Jaffe [11] parametrization used by MTK, we found results for the thermodynamics averages similar to those obtained with the CHARMM19 potential and still at variance with those of Ref. [2]. Additionally, we found a slower volume relaxation, probably due to the higher torsional barrier of this potential with respect to CHARMM19, but still much faster than the MTK result. We stress also that even for this potential MS and AS are found to yield identical relaxation rates and equilibrium averages.

Our disagreement with Ref. [2] might be in part due to a probable error in their calculation of the molecular pressure. Indeed, the relation used by MTK to compute the molecular virial is correct only for molecules of small size compared to the box dimensions. In general, this equation is wrong for molecules whose largest intramolecular distance is greater than half the box side length. Their expression reads

$$\sum_{\gamma} \mathbf{R}_{\gamma} \cdot \mathbf{F}_{\gamma} = \sum_{i\gamma<j\delta}{}' \ (\mathbf{r}^{\mathrm{NL}}_{i\gamma,j\delta} - \overline{\mathbf{r}}_{i,\gamma} + \overline{\mathbf{r}}_{j,\delta}) \cdot \mathbf{f}_{i\gamma,j\delta} \qquad (1)$$

where, $\mathbf{r}^{\mathrm{NI}}_{i\gamma,j\delta}$ is the interatomic distance between atom i of molecule γ and atom j of molecule δ, the superscript NI meaning that atomic nearest image conventions have been used and $\overline{\mathbf{r}}_{i,\gamma}$ is the coordinate relative to the center of mass of atom i of the molecule γ. Here, the prime in the sum on the right-hand side means that only contributions from *different* molecules are included. In the case of large molecules some interactions between atoms of the molecule γ, because of periodic boundary conditions, are effectively interactions between distinct images of the same molecule. Thus, to obtain the correct expression for the molecular virial in Eq. (1) the prime should be removed from the sum on the right-hand side. This will give the equation first reported in Ref. [12]. Such an equation reduces to the MTK molecular virial for small molecules.

Finally, we notice that in Ref. [2] the MS volume of dotriacontane is larger than that computed with AS (see their Table IV). This is clearly inconsistent with their Fig. 7. There the AS pressure obtained during a MS run is computed 150 atm higher than the MS pressure. Naturally, a higher atomic pressure means that in a simulation with AS at 1 atm the system volume will *expand* while in the actual AS calculation of MTK the volume *contracts*. This is an additional clue indicating that flawed computation might be playing a significant role in the MTK main results.

To conclude, contrary to the major findings of Ref. [2], we are unable to discern any difference in the behavior of long chain alkanes simulated by MD at constant pressure

using AS and MS schemes. Although we cannot exclude that additional factors such as metastability have some role in the pressure response observed by MTK, our investigation strongly indicates that errors in the calculations of the pressure tensor are likely to be mostly responsible for MTK's findings.

[1] G. Ciccotti and J.-P. Ryckaert, Comput. Phys. Rep. **4**, 345 (1986).
[2] T. Mülders, S. Toxvaerd, and G. R. Kneller, Phys. Rev. E **58**, 6766 (1998).
[3] M. Marchi and P. Procacci, J. Chem. Phys. **109**, 5194 (1998).
[4] M. Tuckerman, B. J. Berne, and G. J. Martyna, J. Chem. Phys. **97**, 1990 (1992).
[5] B. R. Brooks, R. E. Bruccoeri, B. D. Olafson, D. J. States, S. Swaminanthan, and M. Karplus, J. Comput. Chem. **4**, 187 (1983).
[6] We point out that the convenient group scaling scheme described by MP in Ref. [3] becomes identical to an AS scheme if the system does not include hydrogen atoms as is the case here.
[7] W. H. Press, S. A. Teukolsky, W. T. Vetterling, and B. P. Flannery, *Numerical Recipes in Fortran*, 2nd ed. (Cambridge University Press, Cambridge, 1992), Chap. 14, p. 644.
[8] S. Toxvaerd, J. Chem. Phys. **93**, 4290 (1990).
[9] W. L. Jorgensen, D. S. Maxwell, and J. Tirado-Rives, J. Am. Chem. Soc. **118**, 11224 (1996).
[10] With a spherical cutoff of 13 Å we obtain a molecular volume of 166 (1.9) Å for liquid butane against a value of 164 (1.5) Å in Ref. [9]. The maximum error (3σ) is given between brackets. We point out that the Monte Carlo simulation of Ref. [9] employed a Lennard-Jones long-range correction while our calculation did not. It is expected that such a correction will reduce the computed molecular volume of a few tenths of a percentage point.
[11] G. Smith and R. L. Jaffe, J. Chem. Phys. **100**, 18 718 (1996).
[12] D. N. Theodorou, T. D. Boone, L. R. Dodd, and K. F. Mansfield, Makromol. Chem., Theory Simul. **2**, 191 (1993).