Pressure control using stochastic cell rescaling

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Molecular dynamics simulations require barostats to be performed at constant pressure. The usual recipe is to employ the Berendsen barostat first, which displays a first-order volume relaxation efficient in equilibration but results in incorrect volume fluctuations, followed by a second order or Monte Carlo barostat for production runs. In this paper, we introduce stochastic cell rescaling, a first-order barostat that samples the correct volume fluctuations by including a suitable noise term. The algorithm is shown to report volume fluctuations compatible with the isobaric ensemble and its anisotropic variant is tested on a membrane simulation. Stochastic cell rescaling can be straightforwardly implemented in existing codes and can be used effectively both in equilibration and in production phases.

I. INTRODUCTION

Molecular dynamics (MD) simulations can be used to characterize the dynamical properties of microscopic systems by simulating their evolution according to the Hamilton equations of motion. However, the Hamilton equations are valid only for isolated systems and need to be amended to describe the coupling with external baths. Most common cases are thermostats and barostats. The former are used to transfer heat so as to properly control temperature. The latter are used to transfer mechanical work, thereby allowing for external pressure, stress, or surface tension to be controlled.

Pressure control in MD was first introduced in the pioneering work of Andersen using an extended Lagrangian formalism. This framework was then extended to allow periodic cells of arbitrary shapes. A number of variants of these methods have been published with either improved integration schemes, small modifications to control errors when the number of simulated particles is small, or generalization to liquid interfaces. The volume degree of freedom can also be coupled to a stochastic thermostat in a so-called Langevin piston approach. All the methods mentioned so far associate an inertia to the volume, resulting in a second-order differential equation for its time evolution, which is stochastic for Langevin piston algorithms. An alternative approach is to use a Monte Carlo procedure to resample the volume every few steps of MD. The Monte Carlo barostat is simpler to implement, since it does not require the calculation of the virial, but it is sometime considered less efficient than virial-based barostats. This barostat based on a first-order differential equation is the weak coupling or Berendsen barostat. This barostat intuitively changes the volume by an increment proportional to the difference between the internal and external pressure and is very efficient in equilibrating the system. However, it does not sample a predictable ensemble. The usual rule of the thumb is thus to use the Berendsen barostat for equilibration, followed by either a second-order barostat or a Monte Carlo barostat for production (see Fig. 1).

In this work, we propose a new scheme that is based on a first-order differential equation but, at variance with the

![Fig. 1. Graphical representation of protocols for a constant-pressure simulation. In the traditional pipeline (middle panel), an equilibration run using a first-order Berendsen barostat is followed by a production run using a second-order barostat. Indeed, using a second-order barostat on a non-equilibrated system might lead to oscillations and instabilities (upper panel). The here introduced stochastic cell rescaling algorithm relaxes straight to the correct volume and then produces correct fluctuations (lower panel). It can thus be used both for equilibration and production runs.]

Berendsen scheme, samples the correct isothermal-isobaric ensemble (see Fig. 1 lower panel). To achieve this result, we add a suitably designed stochastic term to the Berendsen barostat, in the spirit of what was done in the stochastic velocity rescaling algorithm to amend the Berendsen thermostat. The resulting algorithm can also be seen as a high-friction variant of the Langevin piston barostat. We derive and test several possible integration schemes and provide a reference implementation for all of them in an educational MD code. One of the integration schemes is also implemented and tested in a modified version of the popular MD code GROMACS. The algorithm produces correct volume fluctuations for a wide range of the control parameters in a Lennard-Jones fluid and

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in liquid water. The method is also tested on the calculation of solvation free energies, for which a recent paper suggested incorrect results arising from use of the Berendsen barostat and its semi-isotropic version is tested on a membrane simulation.

II. METHODS

A. Stochastic cell rescaling

We consider a system composed of \( N \) atoms with coordinates \( q_i \) and momenta \( p_i \), contained in a box of volume \( V \). For compactness, in the following we indicate the vector of all coordinates and momenta as \( q \) and \( p \), respectively. According to Hamilton equations, \( p \) and \( q \) evolve as

\[
\frac{dp_i}{dt} = -\frac{\partial U}{\partial q_i}, \quad \frac{dq_i}{dt} = \frac{p_i}{m_i}
\]

where \( t \) is the time, \( m_i \) is the mass of the \( i \)-th particle, and \( U \) the potential energy of the system, which depends on the positions \( q \).

To obtain ensemble averages in the NPT ensemble, where the number of particles, the external pressure, and the temperature are constant, the volume \( V \) has to be allowed to fluctuate so as to sample states with probability

\[
\mathcal{P}(p,q,V) \propto e^{-\frac{K + U + P_0 V + C}{\beta T}}.
\]

Here, \( K = \sum p_i^2/(2m_i) \) is the kinetic energy of the system, \( P_0 \) is the external pressure, \( k_B \) is the Boltzmann constant and \( T \) is the temperature. Equation (2) can be equivalently written as

\[
-k_B T \log \mathcal{P}(p,q,V) = K + U + P_0 V + C
\]

where \( C \) is an arbitrary constant.

The goal of a barostat is to induce changes in the volume \( V \) that preserve the NPT distribution. These changes are typically made at constant scaled positions \( s = q/\sqrt{V} \), so that Cartesian positions \( q \) have to be uniformly scaled. Many algorithms implement this change at constant scaled momenta \( \pi = p/\sqrt{V} \) as well, thus scaling Cartesian positions \( q \) and momenta \( p \) with inverse factors [35]. This scaling preserves the phase-space volume and originally stems from the use of a Hamiltonian formalism in the Andersen barostat. In other methods, this scaling factor is modified by a small correction that vanishes as the number of atoms in the simulated box grows. However, provided one evaluates the compression factor properly, scaling momenta is not strictly necessary, as suggested in Ref. [21]. In the derivation below, we will assume that momenta are scaled with an inverse factor with respect to positions. A similar algorithm can be derived assuming that momenta are not scaled (see Sec. II B).

To obtain a continuous trajectory, we consider changes of \( V \) obtained by the solution of a first-order differential equation. The most general first-order differential equation for the single variable \( V \) with a preassigned stationary distribution \( \mathcal{P}(V) \) is stochastic and has the following form:

\[
dV = D \frac{\partial \log(D \mathcal{P})}{\partial V} dt + \sqrt{2D} dW.
\]

Here \( dW \) is a Wiener noise and the equation is written using Itô stochastic calculus. \( D \) is an arbitrary function of the volume \( V \) that can be interpreted as a diffusion coefficient. The stationarity of distribution \( \mathcal{P} \) can be demonstrated by considering the associated Fokker-Planck equation

\[
\frac{\partial \mathcal{P}}{\partial t} = -\frac{\partial}{\partial V} \left( D \frac{\partial \log(D \mathcal{P})}{\partial V} + \frac{1}{2} \frac{\partial^2}{\partial V^2} (2D \mathcal{P}) \right) = 0.
\]

By inserting Eq. (3) in Eq. (4) with simple manipulation, the most general stochastic differential equation for \( V \) preserving the isothermal-isobaric distribution can be shown to be in the form

\[
dV = -\frac{D}{k_B T} \left( \frac{\partial K}{\partial V} + \frac{\partial U}{\partial V} + P_0 - \frac{k_B T}{V} \right) dt + \sqrt{2k_B T} \beta T V dW.
\]

We notice that the term \( \frac{\partial U}{\partial V} \) is meant to be taken at fixed scaled coordinates and corresponds to the negative of the contribution of the potential energy to the internal pressure. The term \( \frac{\partial K}{\partial V} \) instead has to be computed at fixed scaled momenta, thus defining \( K = V^{-2/3} \sum \pi_i^2/(2m_i) \). We thus have \( \frac{\partial K}{\partial V} = -\frac{2K}{3V} \), and this term corresponds to the negative of the kinetic contribution to the internal pressure. The center-of-mass contribution to the internal pressure might be optionally included (see Supporting Information, Sec. I).

We then arbitrarily set \( D = \frac{\beta T V k_B T}{\tau_p} \), where \( \beta T \) is an estimate of the isothermal compressibility of the system and \( \tau_p \) is a characteristic time associated to the barostat. The resulting differential equation is

\[
dV = -\frac{\beta T V}{\tau_p} \left( \frac{\partial K}{\partial V} + \frac{\partial U}{\partial V} + P_0 - \frac{k_B T}{V} \right) dt + \sqrt{\frac{2k_B T \beta T V}{\tau_p}} dW.
\]

This equation on \( V \) can be converted to an equivalent equation on the strain \( \varepsilon = \log(V/V_0) \), where \( V_0 \) is a reference volume that is needed to have the correct dimensionality [32] and can be arbitrarily set to \( V_0 = 1 \text{nm}^3 \). By means of the Itô chain rule, one obtains

\[
d\varepsilon = -\frac{\beta T}{\tau_p} (P_0 - P_{\text{int}}) dt + \sqrt{\frac{2k_B T \beta T V}{\tau_p}} dW,
\]

where \( P_{\text{int}} = \frac{2K}{3V} - \frac{\partial U}{\partial V} \). The interpretation of Eq. (5) is straightforward. The deterministic term increases or decreases the volume when the internal pressure is respectively larger or smaller than the external one. Thanks to our definition of \( D \), this term is equivalent to the one used in the popular Berendsen barostat. The stochastic term, however, allows volume fluctuations to be properly controlled. Equation (5) can be also derived by taking the high-friction limit of a Langevin piston algorithm with a volume-dependent friction, provided the additional drift is taken into account correctly (see Supporting Information, Sec. II). Equation (5) can then be coupled with Hamilton equations (1) and (2) and with a thermostat to sample the isothermal-isobaric ensemble. The increment in the volume logarithm leads to a rescaling of the cell matrix. We thus refer to this scheme as stochastic cell rescaling.
B. Working with unscaled momenta

The derivation reported in the previous Section assumes that volume changes are operated at constant scaled positions \( s \) and momenta \( \pi \). It is possible to keep scaled positions \( s \) and physical momenta \( p \) fixed, instead, resulting in an algorithm where momenta are not scaled when volume changes. In this case, an extra factor \( V^N \) has to be inserted in Eq. 2 that in turn results in the use of the external temperature in evaluating the ideal gas pressure contribution in \( P_{\text{int}} \). At the same time, the gradient of the kinetic energy with respect to the volume used in Eq. 4 would be zero. It can be seen that this change simply leads to the need to compute the internal pressure using the average kinetic energy instead of the instantaneous one

\[
\beta \beta_{T} = \frac{\sqrt{2Nk_{B}T}}{3V^{3/2}} \approx \frac{\sqrt{\tau_{K}N\sigma_{V}^{2}}}{3\tau_{P}V^{3/2}}.
\]

In the last step we exploited the fact that \( \beta_{T} = \frac{\sigma_{V}^{2}}{(V/\sqrt{k_{B}T})} \), where \( \sigma_{V}^{2} \) are the fluctuations of the volume, and we approximated \( V \) with its average value \( \langle V \rangle \). Since in condensed phases we expect the relative volume fluctuations to be smaller than \( \sqrt{1/N} \), and we assumed \( \tau_{K} \ll \tau_{P} \), the contribution of the additional noise is negligible. This is the case for most of the practical applications considered here, with the used thermostat settings. However, in general settings, the two sources of noise might be comparable. It is thus important to implement stochastic cell rescaling so that, if the internal pressure is computed using the instantaneous kinetic energy, momenta are scaled with the correct factor whenever the volume changes.

C. Effective energy drift

Stochastic cell rescaling is based on the use of Hamilton equations 14 and 15 and of the stochastic differential equation 5 both satisfying detailed balance. When they are integrated with a finite time step algorithm, however, detailed balance is violated. This violation can be monitored during the simulation 30,39 and used to determine if the time step and the other simulation parameters were chosen correctly, to verify that forces are correctly computed as the negative derivatives of the energy function, or to compute the acceptance for a so-called Metropolized integrator. 10 This contribution can be interpreted as the work performed by the integration algorithm on the system 14. In the case of pure Hamilton equations, this drift corresponds exactly to the change in the total energy of the system. When a thermostat is used, its contribution to the drift has to be added14,30,10. Similarly, the barostat will contribute to the drift.

In order to compute the contribution of the barostat to the drift, it is necessary to compute the relative probabilities of generating forward steps, where \( \epsilon \rightarrow \epsilon' \), and backward steps, where \( \epsilon' \rightarrow \epsilon \). We notice that the prefactor of the stochastic term in Eq. 5 depends explicitly on \( \epsilon \). As discussed in more details in Supporting Information, Sec. III, this dependence might increase detailed-balance violations. By performing a change of variable to \( \lambda = \epsilon^{3/2} \sqrt{V_0} = \sqrt{V} \), instead, by means of the Ito chain rule, 33 one obtains the following differential equation

\[
d\lambda = -\frac{\beta_{T} \lambda}{2\tau_{P}} \left( P_{0} - P_{\text{int}} - \frac{k_{B}T}{2V} \right) dt + \frac{k_{B}T \beta_{F}}{2\tau_{P}} dW.
\]
It is important to recall that the effective energy drift quantifies how much detailed balance is violated. However, detailed balance is not a necessary condition for reaching the target stationary distribution. In addition, it has been shown that this drift might overestimate the errors observed in sampling the configurational degrees of freedom.

### D. Integration of the equations of motion

We considered three different ways to integrate Eqs. [1a] [1b] and [1c]. In all of them, it is possible to postpone the calculation of the virial to every $N_P$ steps in a multiple-time-step fashion, in order to speed up the calculation. In the last two algorithms, it is possible to define the effective energy drift (see Sec. II C). More details are reported in Supporting Information, Sec. V.

**Euler integrator.** The volume is evolved by propagating its logarithm using a finite time step approximation of Eq. [5]. Positions and velocities are then evolved using velocity Verlet. For forces are not recomputed after the volume change. As a consequence, the obtained trajectory is not reversible.

**Reversible Euler integrator.** The volume is evolved by propagating its square root using a finite time step approximation of Eq. [7]. Positions and velocities are then evolved using velocity Verlet. Forces are recomputed after the volume change. As a consequence, the obtained trajectory is reversible. However, this is paid with an extra force calculation every $N_P$ steps. In order to quantify the effective energy drift, the virial needs to be recomputed after the volume change.

**Trotter-based integrator.** The volume is evolved by propagating its square root using a finite time step approximation of Eq. [7]. Positions and velocities are then evolved using velocity Verlet simultaneously with volume change using a Trotter splitting. There is no need to recompute forces after the volume change. However, in order to quantify the effective energy drift, the virial needs to be computed also at the step immediately after the one at which scaling was applied. The obtained trajectory is reversible.

For simplicity, we decided to use Eq. [5] in the Euler integrator, where the effective energy drift would not be well-defined anyway, whereas we used Eq. [7] for the reversible implementations. All the three schemes can be implemented either scaling or not scaling velocities upon volume change (see Sec. II D). For each of the integrators, Table I summarizes the cost in term of how many force and virial calculations are required on average for each simulation step. These integrators, similarly to those discussed in Ref. [17], can in principle be used with an arbitrarily large $N_P$, provided that $\tau_p$ is also chosen large enough.

### E. Semi-isotropic version

Eq. [5] can be generalized to cases where $\varepsilon$ is a matrix representing the deformation of the system. We here derive the equations required to sample the constant surface-tension ensemble $NP\gamma T$, where the equilibrium probability reads

$$\mathcal{P}(p,q,A,L) \propto e^{-\frac{K_e U + P_0 A - \gamma A}{k_BT}}.$$  \hspace{1cm} (8)

Here $A$ is the area of the simulation box in the xy plane, $L$ is its height, and $\gamma_0$ is the surface tension multiplied by the number of surfaces.

We arbitrarily set the diffusion coefficients for $A$ and $L$ as $D_A = \frac{2\beta_T A^3 \kappa T}{3W_P}$ and $D_L = \frac{\beta_T L^3 \kappa T}{3W_P}$, respectively. By defining the variables $\varepsilon_{xy} = \log(A/A_0)$ and $\varepsilon_z = \log(L/L_0)$, and following a procedure similar to the one above, these equations of motion are obtained:

$$d\varepsilon_{xy} = -\frac{2\beta_T}{3\tau_p} \left[ P_0 - \frac{\gamma_0}{L} \left( P_{\text{int,xx}} + P_{\text{int,yy}} \right) \right] dt + \sqrt{\frac{4k_BT \beta_T}{3V \tau_p}} dW_{xy}$$ \hspace{1cm} (9a)

$$d\varepsilon_z = -\frac{\beta_T}{3\tau_p} \left( P_0 - P_{\text{int,zz}} \right) dt + \frac{2k_BT \beta_T}{3V \tau_p} dW_z$$ \hspace{1cm} (9b)

Here $P_{\text{int,xx}}$, $P_{\text{int,yy}}$, and $P_{\text{int,zz}}$ are components of the internal pressure tensor and the two noise terms $dW_{xy}$ and $dW_z$ are explicitly written with different subscripts to remark that they have to be drawn independently. For an extensive derivation of Eqs. [9] see Supporting Information, Sec. VI.

By taking the sum of the two equations above and setting $\gamma_0 = 0$, one obtains Eq. [5]. This means that, if no external tension is applied, the dynamics of the volume in the semi-isotropic case will be identical to the isotropic case. In principle, it is possible to tune separately the compressibility of the system in the $xy$ and $z$ directions (see Supporting Information, Sec. VII, for the special case where cell height $L$ is kept constant), or even to choose a non-diagonal diffusion matrix for the $A$ and $L$ variables. This choice would only affect the timescale at which $A$ and $L$ equilibrate, leaving the sampled distribution unchanged.

### F. Computational details

Simulations of the Lennard-Jones fluid were performed using a modified version of the SimpleMD program. A system of $N = 256$ particles was simulated in a cubic box with a time step of 0.005 for $10^7$ steps, accumulating statistics every 10

| Integrator     | Reversible | $N_{\text{forces}}$ | $N_{\text{virial}}$ |
|---------------|------------|---------------------|---------------------|
| Euler         | no         | 1                   | $1/N_P$             |
| Reversible Euler | yes       | $1 + 1/N_P$         | $2/N_P$             |
| Trotter       | yes        | 1                   | $\min(1,2/N_P)$     |

**TABLE I.** Computational overhead for the discussed integrators. Integrators are named as discussed in the main text. $N_P$ is stride for the propagation of the barostat. $N_{\text{forces}}$ and $N_{\text{virial}}$ are the average number of times forces and virial need to be calculated for every MD step, respectively. For all the integrators, the equation of the barostat is propagated every $1/N_P$ steps.
steps. Forces were truncated at distance 2.5. Temperature was set to \( T = 1.5 \) and controlled with a stochastic velocity rescaling thermostat \(^{30}\) with relaxation time \( \tau_T = 0.05 \). Pressure was set to \( P_0 = 1 \) and controlled using stochastic cell rescaling with a range of control parameters. All parameters are reported in reduced Lennard-Jones units. All the reported quantities were computed discarding the initial \( 2.5 \times 10^6 \) steps.

Simulations of the liquid water, host-guest and guest only, and the membrane systems were performed with a modified version of GROMACS 2019.4 \(^{31}\). The liquid water system comprised 2850 waters in a rhombic dodecahedron box. The TIP3P model \(^{28}\) was used to represent the water molecules. A short equilibration run lasting 500 ps was first conducted in the \( NVT \) ensemble. The production phase consisted of three sets of \( NPT \) simulations using the Parrinello-Rahman \(^{31}\), Berendsen \(^{32}\) and stochastic cell rescaling barostats, respectively. In each set, a range of control parameters was explored, using 1 bar as reference for isotropic pressure coupling in all cases. All simulations lasted 10 ns and statistics were saved every 200 steps (0.4 ps). The reference temperature was 300 K in all runs and was controlled through a stochastic velocity rescaling thermostat \(^{30}\) with a relaxation time \( \tau_T = 0.1 \) ps. A Verlet cut-off scheme was employed for neighbor searching, updating the neighbor list every 10 steps. All shown results were obtained discarding the first 2 ns of simulation.

A smaller water box, comprising 900 TIP3P water molecules, was employed to perform the physical validation tests indicated in Refs. \(^{37}\) and \(^{48}\). To conduct these tests, the physical_validation package, an open-source and platform-independent Python library (https://physical-validation.readthedocs.io) in which they are implemented, was used. For each barostat (Berendsen, Parrinello-Rahman and stochastic cell rescaling), two simulations of 10 ns each were run at the reference pressure of 1 bar and 301 bar, respectively, with \( N_P = 10 \) and \( \tau_P = 1 \) for Berendsen and Parrinello-Rahman and \( \tau_P = 0.5 \) for stochastic cell rescaling. All GROMACS input files were taken and adapted from the examples/water_ensemble subfolder coming with the package.

Free energy differences for the host-guest (OA-G3) and guest only (G3) systems were computed from expanded ensemble simulations in solution, conducted using coordinates, topology, and set-up provided by Ref. \(^{32}\). A detailed description of the simulation parameters can be found therein. Briefly, decoupling of the guest was achieved by completely turning off charges first and then removing Van der Waals interactions in both the host-guest and guest only systems. The entire procedure comprised a total of 40 lambda windows. A velocity Verlet integrator was used with a time step of 2 fs. The expanded ensemble simulations were divided in two stages: an initial equilibration stage to adaptively estimate the expanded ensemble weights and the following production phase in which the weights were kept fixed. For the host-guest system, 60 ns were required for the equilibration of weights with Berendsen and stochastic cell rescaling, while for the guest only systems about 30 ns were necessary in all cases. From the production stage, free-energy differences were computed with the multistate Bennett acceptance ratio (MBAR) method \(^{40}\) using the alchemical_analysis tool version 1.0.2\(^{30}\) along with pymbar version 3.0.5. The free energy associated to the presence of the restraints on the center of mass in the decoupled state was computed as \( \Delta G_{\text{restr}} = -\frac{1}{2} \log \left( \frac{2\pi \hbar^2 k}{k} \right) + \log V_{\text{mol}} = 16.73 \text{ kJ/mol}, \) where \( k = 1000 \text{ kJ/(mol-nm)}^2 \) is the coupling constant and \( V_{\text{mol}} = 1.66 \text{ nm}^3 \) is the volume corresponding to the one molar standard state.

Replica exchange simulations for decoupling of the guest only in solution were performed using 40 replicas corresponding to the windows employed to turn off charges and removing Van der Waals interactions in the expanded ensemble simulations, thus resulting in a Hamiltonian replica-exchange protocol. Two variants of the system with varying size of the box were considered: the same used for the expanded ensemble simulations, taken from Ref. \(^{32}\) where a distance of 1.2 nm from all guest heavy atoms in all directions was applied, and a smaller one where such distance was set to 0.8 nm. A leap-frog integrator was used with a time steps of 2 fs and exchanges between replicas were attempted every 400 steps (0.8 ps). Production runs were conducted for a total of \( 5 \) ns/replica and were used to compute the free-energy differences through Bennett’s acceptance ratio method (BAR) \(^{33}\) as implemented in the gmx bar module of GROMACS. Decoupling of the guest E20 (donepezil, extracted from PDB ID: 1EVE) was conducted according to the same set-up. Ligand parameters were determined using the General Amber Force Field (GAFF)\(^{54}\) following the RESP procedure\(^{55}\) to determine the molecule charges. During the simulations, the conformation of the ligand was kept fixed by restraining the root-mean-square displacement from the crystal conformation computed after superimposing the two structures. To this end, the RESTRAINT feature of the bias module of PLUMED\(^{54}\) was used, setting a force constant of 209200 kJ/(mol-nm\(^2\)) for the harmonic restraint.

The membrane system was built as described in the “KALP\(_{15}\) in DPPC” (the KALP model peptide in a lipid bilayer of dipalmitoylphosphatidylcholine) tutorial\(^{53}\) which protocol was based on a previous work\(^{50}\) and used the GROMOS96 53A6 force field\(^{57}\) extended to include Berger lipid parameters\(^{58}\). The procedure included usage of the InflateGRO methodology\(^{59}\) to pack the lipids around the embedded protein. After solvation, a system comprising 126 DPPC lipid and 4182 SPC water molecules\(^{60}\) was obtained. Energy minimization and equilibration of the system were conducted as described in detail in the tutorial. As for the liquid-water system, the production phase consisted of three sets of \( NPT \) simulations using the Parrinello-Rahman, Berendsen and stochastic cell rescaling barostats. A reference pressure of 1 bar was employed for semi-isotropic pressure coupling in all cases, along with \( \tau_P = 2 \) ps and a compressibility of \( 4.5 \times 10^{-5} \text{ bar}^{-1} \). The temperature was set to 323 K and was controlled through the Nose-Hoover thermostat\(^{66}\) with a relaxation time \( \tau_T = 0.5 \) ps, coupling separately a first group comprising the protein and DPPC lipids and a second one including the solvent and ion molecules. All simulations lasted 100 ns and statistics were saved every 200 steps (0.4 ps). All shown results were obtained analyzing the second half of the trajectory.
In all simulations, statistical errors were determined using block analysis with a variable number of blocks and conservatively using the largest estimate for the error.

### III. NUMERICAL TESTS

#### A. Lennard-Jones fluid

We tested stochastic cell rescaling on the simulation of a Lennard-Jones fluid in the NPT ensemble. We first performed a range of simulations at constant volume, computed the average internal pressure, and integrated it so as to obtain a reference distribution for the volume \( V \). The predicted volume fluctuations correspond to an isothermal compressibility \( \beta_T \approx 0.3 \). This value is used as an input in the simulations performed with the barostat. The distribution of the volume obtained using barostat parameters \( N_P = 1 \) and \( \tau_P = 1 \) is perfectly overlapping with the reference one (see Fig. S1).

We then evaluated the robustness of the results by monitoring volume average and fluctuations when changing barostat parameters, testing the three discussed integrators (Fig. 2). We first fixed \( N_P = 1 \) and investigated the dependence of the results on \( \tau_P \) (Fig. 2a). Any \( \tau_P \geq 0.1 \) report results consistent with the reference. As expected, the statistical error on the volume and on its fluctuations grows with \( \tau_P \). This suggests that, in order to equilibrate and sample the volume variable as quickly as possible, \( \tau_P \) should be chosen as small as possible. The autocorrelation time of \( V \) can be seen to be close to \( \tau_P \) when \( \tau_P \) is large enough (see Fig. S2). The relationship between stochastic cell rescaling and the Langevin piston approach can be appreciated by comparing the autocorrelation function of the volume in a Langevin piston with decreasing values of the barostat mass (see Fig. S3). We then fixed \( \tau_P = 1 \) and investigated the dependence of the results on \( N_P \) (Fig. 2b). \( N_P \geq 10 \) resulted in a volume variance observably larger than its reference value. Interestingly, the three introduced integrators resulted in very similar accuracy when used with the same parameters.

For the two integrators that allow an effective energy drift to be defined, we computed this drift for all the chosen sets of parameters (Fig. 2c). As long as \( \tau_P \geq 1 \) and \( N_P = 1 \) the drift was of the order of \( 10^{-6} \) energy units per step, comparable to the one obtained in NVT simulations. By testing different values of \( N_P \), we observed that the drift steadily grew with \( N_P \). This drift can be used to estimate if the violations of detailed balance induced by the barostat are exceeding those that are present also in absence of the barostat.

All the reported results were obtained using the formulation in which momenta are scaled when volume changes (see Sec. II B). Results obtained without scaling momenta were equivalent and are reported in Fig. S4.

#### B. Liquid water

We then tested stochastic cell rescaling on the simulation of a box of TIP3P water molecules. These simulations were done using GROMACS, which includes an implementation of the Parrinello-Rahman algorithm that is known to report results in the NPT ensemble and can thus be used as a reference. We also tested the Berendsen algorithm, that neglects the noise term and is expected produce incorrect volume fluctuations. In the comparison between the Parrinello-Rahman and the two other schemes, one should consider that there is not an equivalence in the definition of \( \tau_P \). Thus, results at the same \( \tau_P \) cannot be directed compared.

We first analyzed the dependence of volume averages and fluctuations as a function of \( \tau_P \), setting \( N_P = 1 \) (Fig. 3). Volume averages were always consistent in the three schemes, but the Parrinello-Rahman implementation showed some instability for the smallest choice of \( \tau_P = 0.1 \). Volume fluctuations obtained with Parrinello-Rahman and with stochastic cell rescaling were consistent and lead to an estimate of the isothermal compressibility equal to \( \beta_T = \frac{\sigma^2}{V k_B T} \approx 1.05 \times 10^{-2} \).
We then tested the impact of the barostat algorithm on the calculation of the solvation and absolute binding free energies for small molecules. This is a relevant case since the incorrect volume fluctuations produced by the Berendsen barostat were recently suggested to significantly affect absolute binding affinities. We here used the same settings reported in Ref. 32 and in particular the same extended ensemble protocol, on a host-guest system (OA-G3) and on a guest-only system (G3). Since the extended ensemble protocol is not compatible with the Parrinello-Rahman implementation present in GROMACS, we only report results obtained with stochastic cell rescaling and Berendsen algorithms. The solvation free energies obtained with different barostats are close to each other (see Table II). Their differences, which enter in the calculation of the absolute binding free energy, agree within the respective statistical error. We remark that the absolute binding free energies reported in Table II did not include corrections for finite size effects, and should not be compared quantitatively with those reported in Ref. 32. However, these corrections are expected to be independent of the choice of the barostat.

In order to better investigate the possible effects of incorrect
TABLE II. Free-energy differences (kJ/mol) for decoupling of the
guest 5-hexenoic acid in host-guest (OA-G3) and guest only (G3)
simulations in solution performed with the Expanded Ensemble
method. \(\Delta G\) in the standard state is computed subtracting the con-
tribution of the restraint acting on the guest in the decoupled state.

| Method                      | \(\text{OA-G3}\) | \(\text{G3}\) | \(\Delta G\) |
|-----------------------------|------------------|--------------|-------------|
| Berendsen                   | 433.1 ± 0.6      | 389.0 ± 0.5  | -27.3 ± 0.7 |
| Stochastic cell rescaling   | 432.6 ± 0.6      | 387.9 ± 0.5  | -28.0 ± 0.7 |

TABLE III. Free-energy of solvation (kJ/mol) computed from decou-
puling simulations of the guest (G3) and ligand E20 in solution per-
formed with the Hamiltonian Replica Exchange method. The simul-
ations of G3 were performed at varying box sizes: a larger one defined
with a 1.2 nm distance (-d 1.2) from the guest in all directions, and a
smaller one with a 0.8 nm distance (-d 0.8).

| Method                        | \(\text{G3-d 1.2}\) | \(\text{G3-d 0.8}\) | \(\text{E20}\) |
|-------------------------------|------------------|-----------------|-------------|
| Berendsen                     | 389.40 ± 0.05    | 389.65 ± 0.10   | 172.02 ± 0.14 |
| Parrinello-Rahman             | 389.35 ± 0.17    | 389.03 ± 0.12   | 172.28 ± 0.13 |
| Stochastic cell rescaling     | 389.41 ± 0.06    | 389.31 ± 0.14   | 172.70 ± 0.13 |

volume fluctuations on the calculation of solvation free ener-
gies, we tested the guest-only system in a replica-exchange
protocol that is compatible with the Parrinello-Rahman baro-
stat implemented in GROMACS. In this case, the size of the
water box was decreased so as to amplify the impact of the
barostat algorithm (see Table III). For all the tested settings,
the discrepancy between the results obtained with the Beren-
dsen, stochastic cell rescaling, and Parrinello-Rahman barostats
were below a fraction of kJ/mol. We notice that the reported
estimate of the statistical error is likely an underestimation
since it does not take into account the exchange of coordi-
nates between the replicas. Tests performed with a larger lig-
and (E20), representative of typical drug molecules pursued in
medicinal chemistry frameworks, confirm that differences are
small (<1 kJ/mol) and likely not correlated or weakly corre-
lated with the choice of the barostat.

D. Membrane simulation

We finally tested the impact of the barostat algorithm on the
equilibration of a model membrane, including a short trans-
membrane protein. In this case we employed the anisotropic
version of the stochastic cell rescaling, Berendsen, and
Parrinello-Rahman algorithms, where no external tension is
applied to the membrane. Whereas the simulations are prob-
able too short to properly equilibrate this system, it is clear
that stochastic cell rescaling and Parrinello-Rahman provide
consistent results, whereas the Berendsen barostat leads to a
suppression of the fluctuations both in the membrane surface
and in the cell size in the direction orthogonal to the mem-
brane (Table IV). Time series for the simulated trajectories
are reported in Fig. S7.

IV. DISCUSSIONS

In this work, we introduced a barostat named stochastic
cell rescaling that is driven by a first order differential equa-
tion on the volume. The formulation makes it very similar to
the popular Berendsen barostat but includes a noise term
to enforce the correct volume fluctuations. Being based on a
first-order differential equation, the method can be used effec-
tively in equilibration phases. The tested systems range from
simple fluids to macromolecular constructs and are modeled
using intra and inter-molecular interactions as well as con-
straints. A version suitable to control surface tension is also
presented and tested on a membrane system. In all tested
cases, the fluctuations obtained with a reference implementa-
tion of the Parrinello-Rahman algorithm were reproduced for
a broad range of choices of the relaxation time of the barostat.
Our algorithm can be implemented using either the instanta-
neous kinetic energy or its average value, resulting in very
similar behaviors in the tested cases. The choice between the
two formulations can be guided by practical reasons, such as
the ease of their implementation in a given MD code.
The algorithm can be easily modified to make usage of the molec-
ular virial (see, e.g., Refs. [12, 13, 17, 22] and 23) provided that
molecular positions and, optionally, velocities are scaled in-
stead of atomic ones. Stochastic cell rescaling can in principle
be combined with any thermostat to sample the isothermal-
isobaric ensemble. In particular, in the membrane simulation
presented here we tested its usage in combination with the
Nose-Hoover thermostat, whereas in the other simulations
we used stochastic velocity rescaling. In general, our recom-
endation would be Langevin dynamics if a local thermo-
stat is desired to independently thermalize all degrees of free-
dom, or stochastic velocity rescaling, if a global thermostat is
preferred so as to avoid slowing down particle diffusion.

Similarly to the Berendsen barostat, our scheme has a single
control parameter, \(\tau_v\), that controls the equilibration rate,
but has to be complemented with an estimate of the isother-
mal compressibility of the system \(\beta_T\). For the simulation of
solvated systems, this compressibility is largely dependent on
the properties of the solvent, so that in typical applications one
can just use an estimate of its value for water. For other sys-
tems, it can be estimated by computing volume fluctuations
\(\sigma_V\) in a test run and using the relationship \(\beta_T = \frac{\sigma^2_V}{V^2 \rho_T T}\). In any
case, only the ratio \(\beta_T / \tau_v\) between these two parameters en-
ters the algorithm, implying that an incorrect estimate of \(\beta_T\)
by, for instance, a factor two would result in an error in the
control of the relaxation time of the barostat of a factor two.
Given the robustness of the results as a function of \(\tau_v\), we con-
sider this as a minor drawback. We notice that this holds also
for the original Berendsen barostat.

The relationship between stochastic cell rescaling and the
Berendsen barostat is very similar to the relationship between
stochastic velocity rescaling and the Berendsen thermostat.
Importantly, the probability distribution of the kinetic energy is
known \textit{a priori}, allowing the equations of the stochastic
velocity rescaling thermostat to be solved exactly. On the
contrary, the probability distribution of the volume depends in
Stochastic cell rescaling can be seen as a first-order version of the Langevin piston algorithm, and indeed it can be obtained by choosing a piston inertia small enough and a friction coefficient correspondingly large (see Supporting Information, Sec. II). The analogy between the Langevin piston and the Berendsen barostat was already pointed out in Ref. 18, although resulting in a first-order equation that was suggested to be difficult to implement. Since the original Langevin piston algorithm was based on the Andersen thermostat, where absolute changes of the volume are driven rather than relative ones, the first-order equation suggested in Ref. 18 differs from Eq. 5 and its deterministic part thus differs from the one used in the Berendsen barostat. The advantage of the present formulation is that it can be straightforwardly implemented in any code supporting the Berendsen barostat, whereas a standard Langevin piston implementation should be built on top of a second-order barostat. In addition, stochastic cell rescaling works by construction in the high-friction limit and it is thus expected to be always stable in equilibration phases, still retaining the correct fluctuations in production runs.

A number of papers have shown artifacts related to the use of the Berendsen thermostat, see, e.g., Refs. 47, 48, 66–68 including broken reversibility and incorrect fluctuations. The artifacts on the reversibility are relatively small, and the largest issue is the underestimation of energy fluctuations, that has an effect on replica-exchange simulations where the incorrectly distributed energies are used to compute acceptance probabilities. The Berendsen barostat, similarly, is known to result in incorrect volume fluctuations (see, e.g., Refs. 47, 48, 68, and 70), and thus should not be used to evaluate compressibilities. The incorrect volume fluctuations could also introduce significant artifacts in replica-exchange simulations where replicas are simulated at different pressure or surface tension. In these cases, a barostat reproducing correct volume fluctuations has to be considered as mandatory. We here tested the result of free-energy calculations required to estimate ligand affinities, that were recently reported to be dependent on barostating details and, in particular, to display measurable artifacts induced by the use of the Berendsen barostat. According to our results, all the tested barostats, including the Berendsen one, were leading to equivalent results in this specific application. This suggests that the discrepancies observed in Ref. 32 might be a consequence of some other implementation detail, and that artifacts of the Berendsen barostat on the properties of solvated molecules that are not directly correlated with volume fluctuations might be small. Nevertheless, we recommend stochastic cell rescaling as a better alternative since, thanks to the additional noise, it is guaranteed to sample the correct distribution.

The semi-isotropic version of stochastic cell rescaling was tested on a membrane simulation. These tests are more qualitative, since it is difficult to obtain statistically converged results on this system within the simulated time scales. Further tests will be necessary to see if pathological behaviors appear when the fraction of one phase is much larger than the fraction of the other phase, or when the difference in compressibility between the two phases is larger. It will be important to verify how stochastic cell rescaling compares with Parrinello-Rahman and anisotropic Martyna-Tobias-Klein algorithms in these difficult cases. A more flexible formulation where all the elements of the cell matrix can be adjusted will be the subject of a later work.

In summary, stochastic cell rescaling provides a simple first-order barostat that can be equally used in equilibration and production runs and can be adopted as a drop-in replacement of the Berendsen barostat, with minimal implementation changes that allow the isothermal-isobaric fluctuations to be properly sampled.

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The data that support the findings of this study are openly available at http://doi.org/10.5281/zenodo.3921866.

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