

# Thermostat Algorithms for Molecular Dynamics Simulations

Philippe H. Hünenberger

Laboratorium für Physikalische Chemie, ETH Zürich, CH-8093 Zürich, Switzerland  
*phil@igc.phys.chem.ethz.ch*

**Abstract** Molecular dynamics simulations rely on integrating the classical (Newtonian) equations of motion for a molecular system and thus, sample a microcanonical (constant-energy) ensemble by default. However, for compatibility with experiment, it is often desirable to sample configurations from a canonical (constant-temperature) ensemble instead. A modification of the basic molecular dynamics scheme with the purpose of maintaining the temperature constant (on average) is called a thermostat algorithm. The present article reviews the various thermostat algorithms proposed to date, their physical basis, their advantages and their shortcomings.

**Keywords** Computer simulation, Molecular dynamics, Canonical ensemble, Thermostat algorithm

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## List of Abbreviations and Symbols

CM      center of mass  
MC      Monte Carlo

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MD	molecular dynamics
NMR	nuclear magnetic resonance
SD	stochastic dynamics
$\delta$	Kronecker delta symbol or Dirac delta function
$h$	Heaviside step function
$k_B$	Boltzmann's constant
$\mathcal{U}$	instantaneous potential energy
$\mathcal{K}$	instantaneous kinetic energy
$\mathcal{H}$	Hamiltonian
$E$	energy (thermodynamical)
$H$	enthalpy
$L$	Hill energy
$R$	Ray enthalpy
$\mathcal{T}$	temperature (instantaneous)
$T$	temperature (thermodynamical)
$T_o$	reference temperature (heat bath)
$\beta$	$\beta = (k_B T_o)^{-1}$
$\mathcal{V}$	volume (instantaneous)
$V$	volume (thermodynamical)
$\mathcal{P}$	pressure (instantaneous)
$P$	pressure (thermodynamical)
$\mathcal{N}$	number of particles ( $n$ -species, instantaneous)
$\mathbf{N}$	number of particles ( $n$ -species, thermodynamical)
$\nu$	chemical potential ( $n$ -species, instantaneous)
$\mu$	chemical potential ( $n$ -species, thermodynamical)
$\mathbf{p}_{\text{sys}}$	system linear momentum
$\mathbf{L}_{\text{sys}}$	system angular momentum
$\mathbf{p}_{\text{box}}$	box linear momentum
$\mathbf{L}_{\text{box}}$	box angular momentum
$N_{df}$	number of internal degrees of freedom
$N_c$	number of geometrical constraints
$N_r$	number of external degrees of freedom
$m_i$	mass of atom $i$
$\dot{\mathbf{r}}_i^o$	real velocity of atom $i$
$\dot{\mathbf{r}}_i$	peculiar velocity of atom $i$
$\mathbf{F}_i$	force on atom $i$
$\mathbf{p}_i$	momentum of atom $i$
$\mathbf{R}_i$	stochastic force on atom $i$
$\gamma_i$	friction coefficient of atom $i$
$\lambda$	velocity scaling factor
$\Delta t$	timestep
$\zeta_T$	temperature relaxation time
$\alpha$	collision frequency (Andersen thermostat)
$\tau_B$	relaxation time (Berendsen thermostat)
$Q$	"mass" of the time-scaling coordinate (Nosé-Hoover thermostat)

$\tau_{NH}$	effective relaxation time (Nosé-Hoover thermostat)
$\mathcal{L}_e$	extended-system Lagrangian (Nosé-Hoover thermostat)
$\mathcal{H}_e$	extended-system Hamiltonian (Nosé-Hoover thermostat)
$E_e$	extended-system energy (Nosé-Hoover thermostat)

## 1

### Introduction

Classical atomistic simulations, and in particular molecular dynamics (MD) simulations, have nowadays become a common tool for investigating the properties of polymer [1] and (bio-)molecular systems [2, 3, 4, 5, 6, 7]. Due to their remarkable resolution in space (single atom), time (femtosecond), and energy, they represent a powerful complement to experimental techniques, providing mechanistic insight into experimentally observed processes. However, direct comparison with experiment requires that the boundary conditions imposed on the simulated system are in adequation with the experimental conditions. The term *boundary condition* is used here to denote any geometrical or thermodynamical constraint enforced within the whole system during the simulation. One may distinguish between hard and soft boundary conditions. A *hard* boundary condition represents a constraint on a given instantaneous observable, i.e. it is satisfied exactly at any timepoint during the simulation. A *soft* boundary condition represents a constraint on the average value of an observable, i.e. the corresponding instantaneous value is allowed to fluctuate around the specified average. The definition of a soft boundary condition generally also requires the specification of a timescale for which the average observable should match the specified value. There exist four main types of boundary conditions in simulations:

1. *Spatial boundary conditions* include the definition of the shape of the simulated system and the nature of its surroundings. In molecular simulations, one typically uses either: (i) vacuum boundary conditions (solute molecule surrounded by vacuum); (ii) fixed boundary conditions (solute-solvent system surrounded by vacuum, e.g. droplet [8, 9, 10, 11, 12, 13, 14, 15]); (iii) periodic boundary conditions (solute-solvent system in a space-filling box, surrounded by an infinite array of periodic copies of itself [16, 17]). In the two former cases, the effect of a surrounding solvent can be reintroduced in an implicit fashion by a modification of the system Hamiltonian. Typical modifications are the inclusion of: (i) solvation forces accounting for the mean effect of the solvent [18, 19, 20, 21]; (ii) stochastic and frictional forces accounting for the effect of collisions with solvent molecules [22, 23, 24, 25, 2]; (iii) forces at the system boundary to mimic a system-solvent interface [8, 9, 10, 11, 12, 13, 14, 15]. Spatial boundary conditions are hard boundary conditions, because they apply strictly to all configurations during a simulation.
2. *Thermodynamical boundary conditions* include the definition of the  $n + 2$  thermodynamical quantities characterizing the macroscopic state of a (mono-plastic)  $n$ -component system (for systems under vacuum boundary conditions, only  $n + 1$  quantities are required because the volume is not defined while

the thermodynamical pressure is zero). These quantities can be selected form pairs of extensive and intensive quantities including: (i) the number of particles ( $\mathbf{N} \equiv \{N_i \mid i = 1 \dots n\}$ ) or chemical potential ( $\boldsymbol{\mu} \equiv \{\mu_i \mid i = 1 \dots n\}$ ) of all species; (ii) the volume  $V$  or pressure  $P$ ; (iii) the energy  $E$  (or a related extensive thermodynamical potential) or temperature  $T$ . The selected set of  $n + 2$  quantities, together with their reference (macroscopic) values, define the thermodynamical ensemble that is sampled during a simulation (Table 1). By default, MD simulations sample microstates in the microcanonical ( $NVE$ ) ensemble. By applying specific modifications to the system Hamiltonian or equations of motion, it is possible to maintain instead a constant temperature, pressure or chemical potential for the different species (or any combination of these changes). The thermodynamical boundary conditions involving extensive quantities should be treated as hard boundary conditions, while those involving intensive quantities should be soft.

3. *Experimentally derived boundary conditions* are used to explicitly enforce agreement between a simulation and some experimental result. These may be applied to enforce, e.g., the reproduction of (average) electron density maps from X-ray crystallography [27, 28, 29, 30], or the agreement with (average) interatomic distances and J-coupling constants from NMR measurements [31, 32, 33, 30]. Since experiments always provide averages over a given time and number of molecules, experimentally derived boundary conditions should be handled as soft boundary conditions.
4. *Geometrical constraints* can also be considered as boundary conditions. A typical example is the use of bond-length constraints in simulations [34, 35, 36, 37, 38, 39], which represent a better approximation to the quantum-mechanical behavior of high-frequency oscillators ( $h\nu \gg k_B T$ ) compared to the classical treatment [40]. Since they are satisfied exactly at every timepoint during a simulation, geometrical constraints represent hard boundary conditions.

The present article is concerned with one specific type of thermodynamical boundary condition, namely the imposition of a constant (average) temperature during MD simulations by means of thermostat algorithms. The simultaneous enforcement of a constant (average) pressure [51, 52, 53, 54, 55, 46, 56, 57, 58, 59, 60, 61, 53, 62, 63, 64, 65, 66, 67, 68, 69, 70] or chemical potential [71, 72, 73, 74] will not be considered here. The discussion is also restricted to systems under either vacuum or periodic boundary conditions, i.e., isolated systems. This implies that the Hamiltonian is time-independent, and invariant upon translation or rotation of the whole system. This Hamiltonian may contain terms accounting for the mean effect of the environment (e.g., implicit-solvation term), as long as it still satisfies the above conditions. The only exception considered here (whenever explicitly stated) is the possible inclusion of stochastic and frictional forces as applied in stochastic dynamics (SD) simulations, or of random collisional forces as applied in the stochastic-coupling (Andersen) thermostat. Finally, it should be stressed that the inclusion of geometrical constraints during a simulation affects the statistical mechanics of the sampled microstates [75]. This is mainly because in the presence of such constraints,

**Table 1.** The eight thermodynamical ensembles, and the corresponding independent and dependent variables. Intensive variables are the chemical potential for all  $n$  species ( $\mu \equiv \{\mu_i \mid i = 1 \dots n\}$ ), the pressure ( $P$ ) and the temperature ( $T$ ). Extensive variables are the number of particles for all species ( $\mathbf{N} \equiv \{N_i \mid i = 1 \dots n\}$ ), the volume ( $V$ ), and the energy ( $E$ ), enthalpy ( $H = E + PV$ ), Hill energy ( $L = E - \sum \mu_i N_i$ ), or Ray enthalpy ( $R = E + PV - \sum \mu_i N_i$ ). Note that grand-ensembles may be open with respect to a subset of species only (e.g., semi-grand-canonical ensemble). The generalized ensemble is not a physical ensemble, because its size is not specified (no independent extensive variable). Isothermal ensembles are discussed in many standard textbooks. Specific references are given for the (less common) adiabatic ensembles

Independent	Dependent	Ensemble
$NVE$	$\mu PT$	Microcanonical [41, 42, 43, 44, 45]
$NVT$	$\mu PE$	Canonical
$NPH$	$\mu VT$	Isoenthalpic-isobaric [46, 47, 48, 45]
$NPT$	$\mu VH$	Isothermal-isobaric (Gibbs)
$\mu VL$	$NPT$	Grand-microcanonical [49, 45]
$\mu VT$	$NPL$	Grand-canonical
$\mu PR$	$NVT$	Grand-isothermal-isobaric [50, 45]
$\mu PT$	$NVR$	Generalized

the kinetic energy of the system cannot be written in a configuration-independent way (unless the constraints are exclusively involved in fully-rigid atom groups, e.g., rigid molecules). This restriction limits the validity of a number of equations presented in this article. However, many results are expected to remain approximately valid for systems involving a small proportion of constrained degrees of freedom, and no attempt is made here to derive forms including explicitly the effect of geometrical constraints.

## 2 Ensembles

An isolated system is characterized by a time-independent, translationally invariant and rotationally invariant Hamiltonian. Integration of the classical equations of motion for such a system leads, in the limit of infinite sampling, to a trajectory mapping a microcanonical ( $NVE$ ) ensemble of microstates<sup>1</sup>. Assuming an infinite numerical precision, this is also what a standard MD simulation will deliver.

The laws of classical mechanics also lead to two additional conserved quantities, namely the linear momentum  $\mathbf{p}_{sys}$  of the system, and the angular momentum  $\mathbf{L}_{sys}$  of

<sup>1</sup> Thermodynamical ensembles are generally defined without the constraint of Hamiltonian translational and rotational invariance, in which case the previous statement is not entirely correct. In the present article, however, the terminology of Table 1 will be (loosely) retained to encompass ensembles where this invariance is enforced. The statistical mechanics of these latter ensembles must be adapted accordingly [76, 77, 78, 79, 80, 81]. This requires in particular the introduction of a modified definition for the instantaneous temperature, relying solely on internal degrees of freedom and kinetic energy (Sect. 3).

the system around its center of mass (CM). In simulations under periodic boundary conditions, the two quantities refer to the infinite periodic system. However, in this case, if the linear momentum  $\mathbf{p}_{box}$  of the computational box is also conserved, the corresponding angular momentum  $\mathbf{L}_{box}$  is not. This is because correlated rotational motion in two adjacent boxes exert friction on each other, leading to an exchange of kinetic energy with the other (internal) degrees of freedom of the system. Note that the physical properties of a molecular system are independent of  $\mathbf{p}_{sys}$ . However, they depend on  $\mathbf{L}_{sys}$ , because the rotation of the system leads to centrifugal forces. For this reason,  $\mathbf{L}_{sys}$  should be added to the list of independent variables defining the ensemble sampled. Whenever  $\mathbf{L}_{sys}$  is not given, it generally implicitly means that  $\mathbf{L}_{sys} = \mathbf{0}$ . The use of  $\mathbf{L}_{sys} \neq \mathbf{0}$  in simulations under periodic boundary conditions (overall uniform rotation of the infinite periodic system) is actually impossible, because it would lead to non-periodic centrifugal forces. Finally, it should be specified that the total energy  $E$  of the system is defined here so as to exclude the kinetic energy contributions corresponding to the overall translation and rotation of the system (so that  $E$  is independent of  $\mathbf{p}_{sys}$  and  $\mathbf{L}_{sys}$ ).

Because the independent variables of the microcanonical ensemble are all extensive, they should be strictly conserved (i.e., time-independent) during the course of a simulation. The corresponding dependent variables, namely the chemical potential  $\mu$ , the pressure  $P$ , and the temperature  $T$ , are not conserved. In a non-equilibrium simulation, these quantities may undergo a systematic drift. In an equilibrium simulation, the corresponding instantaneous observables (denoted by  $\nu$ ,  $\mathcal{P}$ , and  $\mathcal{T}$ ) will fluctuate around well-defined average values  $\mu$ ,  $P$ , and  $T$ . Two important comments should be made concerning the previous statement. First, the instantaneous observables  $\nu$ ,  $\mathcal{P}$ , and  $\mathcal{T}$  are not uniquely defined. The instantaneous temperature is generally related to the total kinetic energy of the system (Eq. (8)), and the instantaneous pressure to the total virial and kinetic energy. However, alternative definitions are available (differing from the above by any quantity with a vanishing equilibrium average), leading to identical average values in equilibrium situations, but to different fluctuations. Second, a microcanonical ensemble at equilibrium could equally well be specified by stating that  $\mathbf{N}$ ,  $V$ , and  $E$  are conserved, and giving the values of  $\mu$  instead of  $\mathbf{N}$ ,  $P$  instead of  $V$ , or  $T$  instead of  $E$  (as long as at least one extensive variable is specified). However, such a specification would be rather unnatural as well as inapplicable to non-equilibrium situations. Furthermore, only the natural variables for defining a given thermodynamical ensemble (Table 1) are either time-independent or characterized by vanishing fluctuations in the limit of a macroscopic system. Finally, it should be stressed that computer simulations cannot be performed at infinite numerical precision. As a consequence, quantities which are formally time-independent in classical mechanics may still undergo a numerical drift in simulations. In microcanonical simulations, this is typically the case for  $E$ , as well as  $\mathbf{p}_{sys}$  and  $\mathbf{L}_{sys}$  (vacuum boundary conditions), or  $\mathbf{p}_{box}$  (periodic boundary conditions).

Unfortunately, the microcanonical ensemble that comes out of a standard MD simulation does not correspond to the conditions under which most experiments are

carried out. For comparison with experiment, the following ensembles are more useful, which involve one or more intensive independent variables (Table 1):

1. In the *canonical ensemble* ( $\mathbf{NVT}$ ), the temperature has a specified average (macroscopic) value, while the instantaneous observable representing the total energy of the system (i.e., the Hamiltonian  $\mathcal{H}$ ) can fluctuate. At equilibrium, the root-mean-square fluctuations  $\sigma_E$  of the Hamiltonian around its average value  $E$  are related to the system isochoric heat capacity,  $c_V$ , through [16]

$$\sigma_E^2 = \langle \mathcal{H}^2 \rangle_{\mathbf{NVT}} - \langle \mathcal{H} \rangle_{\mathbf{NVT}}^2 = k_B T^2 c_V . \quad (1)$$

The fluctuations  $\sigma_T$  of the instantaneous temperature  $\mathcal{T}$  (defined by Eq. (8)) in a canonical ensemble are given by [16]

$$\sigma_T^2 = \langle \mathcal{T}^2 \rangle_{\mathbf{NVT}} - \langle \mathcal{T} \rangle_{\mathbf{NVT}}^2 = 2N_{df}^{-1} T^2 , \quad (2)$$

where  $N_{df}$  is the number of internal degrees of freedom in the system (Eq. (9)). These fluctuations vanish in the limit of a macroscopic system, but are often non-negligible for the system sizes typically considered in simulations.

2. In the *isothermal-isobaric (Gibbs) ensemble* ( $\mathbf{NPT}$ ), the pressure has (just as the temperature) a specified average value, while the instantaneous volume  $\mathcal{V}$  of the system can fluctuate. At equilibrium, the root-mean-square fluctuations  $\sigma_V$  of the instantaneous volume around its average value  $V$  are related to the system isothermal compressibility,  $\beta_T$ , through [16]

$$\sigma_V^2 = \langle \mathcal{V}^2 \rangle_{\mathbf{NPT}} - \langle \mathcal{V} \rangle_{\mathbf{NPT}}^2 = V k_B T \beta_T . \quad (3)$$

The root-mean-square fluctuations  $\sigma_H$  of the instantaneous enthalpy  $\mathcal{H} + P\mathcal{V}$  around its average value  $H$  are related to the system isobaric heat capacity,  $c_P$ , through [16]

$$\sigma_H^2 = \langle (\mathcal{H} + P\mathcal{V})^2 \rangle_{\mathbf{NPT}} - \langle \mathcal{H} + P\mathcal{V} \rangle_{\mathbf{NPT}}^2 = k_B T^2 c_P . \quad (4)$$

Both the instantaneous temperature  $\mathcal{T}$  and the instantaneous pressure  $\mathcal{P}$  will fluctuate around their corresponding macroscopic values, the magnitude of these fluctuations vanishing in the limit of a macroscopic system.

3. The *grand-canonical ensemble* ( $\mu VT$ ) has a constant volume and temperature (as the canonical ensemble), but is open for exchanging particles with a surrounding bath. In this case, the chemical potential of the different species has a specified average, while the instantaneous value  $\mathcal{N}$  of the number of particles can fluctuate. For a one-component system at equilibrium, the fluctuations  $\sigma_N$  of the instantaneous number of particles around its average value  $N$  are related to the system isothermal compressibility,  $\beta_T$ , through [16]

$$\sigma_N^2 = \langle \mathcal{N}^2 \rangle_{\mu VT} - \langle \mathcal{N} \rangle_{\mu VT}^2 = N^2 V^{-1} k_B T \beta_T . \quad (5)$$

The root-mean-square fluctuations  $\sigma_L$  of the instantaneous Hill energy  $\mathcal{H} - \mu\mathcal{N}$  around its average value  $L$  are given by [16]

$$\sigma_L^2 = \left\langle (\mathcal{H} - \mu\mathcal{N})^2 \right\rangle_{\mu VT} - \langle \mathcal{H} - \mu\mathcal{N} \rangle_{\mu VT}^2 = k_B T^2 \left( \frac{\partial L(\mu, V, T)}{\partial T} \right)_{\mu V}. \quad (6)$$

Three other combinations of variables are possible (Table 1), but the corresponding ensembles [45] are of more limited practical relevance. The last combination (generalized ensemble) is not physical, because its size is not specified (no independent extensive variable). Note that although MD samples the microcanonical ensemble by default, the basic Monte Carlo (MC; [82, 83, 84]) and stochastic dynamics (SD; [22, 23, 24, 25, 2]) algorithms sample the canonical ensemble.

Performing a MD simulation in an other ensemble than microcanonical requires a means to keep at least one intensive quantity constant (on average) during the simulation. This can be done either in a hard or in a soft manner. Applying a hard boundary condition on an intensive macroscopic variable means constraining a corresponding instantaneous observable to its specified macroscopic value at every timepoint during the simulation (constraint method). Remember, however, that the choice of this instantaneous observable is not unique. In contrast, the use of a soft boundary condition allows for fluctuations in the instantaneous observable, only requiring its average to remain equal to the macroscopic value (on a given timescale). Typical methods for applying soft boundary conditions are the penalty-function, weak-coupling, extended-system and stochastic-coupling methods [85]. These methods will be discussed in the following sections in the context of constant-temperature simulations. Although there are many ways to ensure that the average of an instantaneous quantity takes a specified value, ensuring that the simulation actually samples the correct ensemble (and in particular provides the correct fluctuations for the specific instantaneous observable in the given ensemble) is much more difficult.

### 3 Thermostat Algorithms

A modification of the Newtonian MD scheme with the purpose of generating a thermodynamical ensemble at constant temperature is called a thermostat algorithm. The use of a thermostat can be motivated by one (or a number) of the following reasons: (i) to match experimental conditions (most condensed-phase experiments are performed on thermostated rather than isolated systems); (ii) to study temperature-dependent processes (e.g., determination of thermal coefficients, investigation of temperature-dependent conformational or phase transitions); (iii) to evacuate the heat in dissipative non-equilibrium MD simulations (e.g., computation of transport coefficients by viscous-flow or heat-flow simulations); (iv) to enhance the efficiency of a conformational search (e.g., high-temperature dynamics, simulated annealing); (v)

to avoid steady energy drifts caused by the accumulation of numerical errors during MD simulations<sup>2</sup>.

The use of a thermostat requires the definition of an instantaneous temperature. This temperature will be compared to the reference temperature  $T_o$  of the heat bath to which the system is coupled. Following from the equipartition theorem, the average internal kinetic energy  $K$  of a system is related to its macroscopic temperature  $T$  through

$$K = \langle \mathcal{K} \rangle = \frac{1}{2} k_B N_{df} T \quad (7)$$

where  $k_B$  is Boltzmann's constant,  $N_{df}$  the number of internal degrees of freedom of the system, and  $\mathcal{K}$  its instantaneous internal kinetic energy. Defining the instantaneous temperature  $\mathcal{T}$  at any timepoint as

$$\mathcal{T} = \frac{2}{k_B N_{df}} \mathcal{K}, \quad (8)$$

one ensures that the average temperature  $\langle \mathcal{T} \rangle$  is identical to the macroscopic temperature  $T$ . This definition is commonly adopted, but by no means unique. For example, the instantaneous temperature could be defined based on the equipartition principle for only a subset of the internal degrees of freedom. It may also be defined purely on the basis of configuration, without any reference to the kinetic energy [87, 88].

In the absence of stochastic and frictional forces (see below; Eq. (17)), a few degrees of freedom are not coupled (i.e., do not exchange kinetic energy) with the internal degrees of freedom of the system. These external degrees of freedom correspond to the system rigid-body translation and, under vacuum boundary conditions, rigid-body rotation. Because the kinetic energy associated with these external degrees of freedom can take an arbitrary (constant) value determined by the initial atomic velocities, they must be removed from the definition of the system internal temperature. Consequently, the number of internal degrees of freedom is calculated as three times the total number  $N$  of atoms in the system, minus the number  $N_c$  of geometrical constraints, i.e.

$$N_{df} = 3N - N_c - N_r. \quad (9)$$

The subtraction of constrained degrees of freedom is necessary because geometrical constraints are characterized by a time-independent generalized coordinate associated with a vanishing generalized momentum (i.e., no kinetic energy). A more formal statistical-mechanical justification for the subtraction of the external degrees of

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<sup>2</sup> A thermostat algorithm (involving explicit reference to a heat-bath temperature  $T_o$ ) will avoid systematic energy drifts, because if the instantaneous temperature is forced to fluctuate within a limited range around  $T_o$ , the energy will also fluctuate within a limited range around its corresponding equilibrium value. To perform long microcanonical simulations (no thermostat), it is also advisable to employ an algorithm that will constrain the energy to its reference value  $E^o$  (ergostat algorithm [86]).

freedom in the case of periodic boundary conditions can be found elsewhere [45]. A corresponding derivation for vacuum boundary conditions has, to our knowledge, never been reported. When stochastic and frictional forces are applied, as in SD, these forces will couple the rigid-body translational and rotational degrees of freedom with the internal ones. In this case all degrees of freedom are considered internal to the system. Thus, Eq. (9) is to be used with  $N_r = 0$  in the presence of stochastic and frictional forces, and otherwise with  $N_r = 3$  under periodic boundary conditions or  $N_r = 6$  under vacuum boundary conditions. Similarly, the instantaneous internal kinetic energy is defined as

$$\mathcal{K} = \frac{1}{2} \sum_{i=1}^N m_i \dot{\mathbf{r}}_i^2, \quad (10)$$

where the internal (also called peculiar) velocities  $\dot{\mathbf{r}}_i$  are obtained from the real atomic velocities  $\dot{\mathbf{r}}_i^o$  by excluding any component along the external degrees of freedom<sup>3</sup>. These corrected velocities are calculated as

$$\dot{\mathbf{r}}_i = \begin{cases} \dot{\mathbf{r}}_i^o & \text{if } N_r = 0 \\ \dot{\mathbf{r}}_i^o - \dot{\mathbf{r}}_{CM}^o & \text{if } N_r = 3 \\ \dot{\mathbf{r}}_i^o - \dot{\mathbf{r}}_{CM}^o - \mathbf{I}_{CM}^{-1}(\mathbf{r}^o) \mathbf{L}_{CM}^o \times (\mathbf{r}_i^o - \mathbf{r}_{CM}^o) & \text{if } N_r = 6 \end{cases}, \quad (11)$$

where  $\mathbf{r}_{CM}^o$  is the coordinate vector of the system center of mass (CM),  $\mathbf{L}_{CM}^o$  the system angular momentum about the CM, and  $\mathbf{I}_{CM}$  is the (configuration-dependent) inertia tensor of the system relative to the CM. The latter quantity is defined as

$$\mathbf{I}_{CM}(\mathbf{r}) = \sum_{i=1}^N m_i (\mathbf{r}_i - \mathbf{r}_{CM}) \otimes (\mathbf{r}_i - \mathbf{r}_{CM}), \quad (12)$$

where  $\mathbf{a} \otimes \mathbf{b}$  denotes the tensor with elements  $\mu, \nu$  equal to  $a_\mu b_\nu$ . Application of Eq. (11) ensures that

$$\sum_{i=1}^N m_i \dot{\mathbf{r}}_i = \mathbf{0} \quad \text{for } N_r = 3 \text{ or } 6 \quad (13)$$

and (irrespective of the origin of the coordinate system)

$$\sum_{i=1}^N m_i \mathbf{r}_i \times \dot{\mathbf{r}}_i = \mathbf{0} \quad \text{for } N_r = 6. \quad (14)$$

Equation (13) is a straightforward consequence of the definition of  $\dot{\mathbf{r}}_i$ . Equation (14) is proved by using  $\boldsymbol{\omega}_{CM}^o \times (\mathbf{r}_i^o - \mathbf{r}_{CM}^o) = \dot{\mathbf{r}}_i^o - \dot{\mathbf{r}}_{CM}^o$  where  $\boldsymbol{\omega}_{CM}^o = \mathbf{I}_{CM}^{-1}(\mathbf{r}^o) \mathbf{L}_{CM}^o$  is the angular velocity vector about the CM. Thus, the linear and angular momenta of the internal velocities vanish, as expected.

<sup>3</sup> It is assumed that the velocities  $\dot{\mathbf{r}}_i^o$  are already exempt of any component along possible geometrical constraints.

Because the instantaneous temperature is directly related to the atomic internal velocities (Eqs. (8) and (10)), maintaining the temperature constant (on average) in MD simulations requires imposing some control on the rate of change of these velocities. For this reason, thermostat algorithms require a modification of Newton's second law<sup>4</sup>

$$\ddot{\mathbf{r}}_i(t) = m_i^{-1} \mathbf{F}_i(t) . \quad (15)$$

In the present context, this equation (and the thermostated analogs discussed below) should be viewed as providing the time-derivative of the internal velocity  $\dot{\mathbf{r}}_i$  defined by Eq. (11). In turn,  $\dot{\mathbf{r}}_i$  is related to the real atomic velocity  $\dot{\mathbf{r}}_i^o$  through the inverse of Eq. (11), namely

$$\dot{\mathbf{r}}_i^o = \begin{cases} \dot{\mathbf{r}}_i & \text{if } N_r = 0 \\ \dot{\mathbf{r}}_i + \mathbf{r}_{CM}^* & \text{if } N_r = 3 \\ \dot{\mathbf{r}}_i + \mathbf{r}_{CM}^* + \mathbf{I}_{CM}^{-1}(\mathbf{r}^o) \mathbf{L}_{CM}^* \times (\mathbf{r}_i^o - \mathbf{r}_{CM}^o) & \text{if } N_r = 6 \end{cases} , \quad (16)$$

where  $\mathbf{r}_{CM}^*$  and  $\mathbf{L}_{CM}^*$  are constant parameters determined by the initial velocities  $\dot{\mathbf{r}}_i^o(0)$ . This distinction between real and internal velocities is often ignored in standard simulation programs. Many programs completely disregard the problem, while others only remove the velocity component along the external degrees of freedom for the computation of the temperature (but do not use internal velocities in the equations of motion). However, as discussed in Sect. 4, this can have very unpleasant consequences in practice. In the following discussion, it is assumed that the equation of motion (Eq. (15) or any thermostated modification) is applied to the internal velocities defined by Eq. (11), while the atomic coordinates are propagated simultaneously in time using the real velocities  $\dot{\mathbf{r}}_i^o$  defined by Eq. (16).

The prototype of most isothermal equations of motion is the Langevin equation (as used in SD; see Sect. 3.2), i.e.

$$\ddot{\mathbf{r}}_i(t) = m_i^{-1} \mathbf{F}_i(t) - \gamma_i(t) \dot{\mathbf{r}}_i(t) + m_i^{-1} \mathbf{R}_i(t) , \quad (17)$$

where  $\mathbf{R}_i$  is a stochastic force and  $\gamma_i$  a (positive) atomic friction coefficient. Many thermostats avoid the stochastic force in Eq. (17) and use a single friction coefficient for all atoms. This leads to the simplified form

$$\ddot{\mathbf{r}}_i(t) = m_i^{-1} \mathbf{F}_i(t) - \gamma(t) \dot{\mathbf{r}}_i(t) . \quad (18)$$

In this case,  $\gamma$  loses its physical meaning of a friction coefficient and is no longer restricted to positive values. A positive value indicates that heat flows from the system to the heat bath. A negative value indicates a heat flow in the opposite direction. Note that if Eq. (18) was applied to the real velocities  $\dot{\mathbf{r}}_i^o$  (as often done in simulation programs) instead of the internal velocities  $\dot{\mathbf{r}}_i$ , the linear and angular momenta of the system would not be conserved (unless they exactly vanish).

<sup>4</sup> It is assumed that the forces  $\mathbf{F}_i$  are exempt of any component along possible geometrical constraints.

Any algorithm relying on the equation of motion given by Eq. (18) is smooth (i.e., generates a continuous velocity trajectory) and deterministic<sup>5</sup>. It is also time-reversible if  $\gamma$  is antisymmetric with respect to time-reversal<sup>6</sup>.

Practical implementations of Eq. (18) often rely on the stepwise integration of Newton's second law (Eq. (15)), altered by the scaling of the atomic velocities after each iteration step. In the context of the leap-frog integrator<sup>7</sup> [89], this can be written

$$\begin{aligned} \dot{\mathbf{r}}_i \left( t + \frac{\Delta t}{2} \right) &= \lambda(t; \Delta t) \dot{\mathbf{r}}'_i \left( t + \frac{\Delta t}{2} \right) \\ &= \lambda(t; \Delta t) \left[ \dot{\mathbf{r}}_i \left( t - \frac{\Delta t}{2} \right) + m_i^{-1} \mathbf{F}_i(t) \Delta t \right], \end{aligned} \quad (20)$$

where  $\lambda(t; \Delta t)$  is a time- and timestep-dependent velocity scaling factor. Imposing the constraint<sup>8</sup>  $\lambda(t; 0) = 1$ , one recovers Eq. (18) in the limit of an infinitesimal timestep  $\Delta t$ , with

$$\gamma(t) = - \lim_{\Delta t \rightarrow 0} \frac{\lambda(t; \Delta t) - 1}{\Delta t} = - \left. \frac{\partial \lambda(t; \Delta t)}{\partial (\Delta t)} \right|_{\Delta t=0}. \quad (21)$$

Note that for a given equation of motion, i.e., a specified form of  $\gamma(t)$ , Eq. (21) does not uniquely specify the scaling factor  $\lambda(t; \Delta t)$ . It can be shown that Eq. (20) retains the original accuracy of the leap-frog algorithm if the velocity-scaling factor applied to atom  $i$  is chosen as [90]

$$\lambda_i(t; \Delta t) = 1 - \gamma(t) \Delta t + \left[ \frac{\gamma^2(t)}{2} + \frac{\gamma(t) F_i(t)}{2m_i \dot{r}_i(t)} \right] (\Delta t)^2. \quad (22)$$

From a thermodynamical point of view, some thermostats can be proved to generate (at constant volume and number of atoms) a canonical ensemble in the limit of infinite sampling times (and within the usual statistical-mechanical assumptions of equal *a priori* probabilities and ergodicity). More precisely, some thermostats lead to a canonical ensemble of microstates, i.e., microstates are sampled with a statistical

<sup>5</sup> The advantages of deterministic algorithms are that (i) the results can be exactly reproduced (in the absence of numerical errors), and (ii) there are well-defined conserved quantities (constants of the motion). In the case of Eq. (18), the constant of the motion is

$$C = \mathcal{K}(t) + \mathcal{U}(t) + 2 \int_0^t dt \mathcal{K}(t) \gamma(t). \quad (19)$$

<sup>6</sup> Considering a given microstate, time-reversibility is achieved if the change  $dt \rightarrow -dt$  (leading in particular to  $\mathbf{r} \rightarrow \mathbf{r}$ ,  $\dot{\mathbf{r}} \rightarrow -\dot{\mathbf{r}}$ , and  $\ddot{\mathbf{r}} \rightarrow \ddot{\mathbf{r}}$ ) leaves the equation of motion for the coordinates unaltered (while the velocities are reversed). Clearly, this condition is satisfied for Eq. (18) only if the corresponding change for  $\gamma$  is  $\gamma \rightarrow -\gamma$ .

<sup>7</sup> The implementation of thermostats will only be discussed here in the context of the leap-frog integrator. However, implementation with other integrators is generally straightforward.

<sup>8</sup> An algorithm with  $\lambda(t; 0) \neq 1$  would involve a Dirac delta function in its equation of motion.

weight proportional to  $e^{-\beta\mathcal{H}}$  where  $\beta = (k_B T_o)^{-1}$ . In this case and in the absence of geometrical constraints, expressing the Hamiltonian in Cartesian coordinates as  $\mathcal{H}(\mathbf{r}, \mathbf{p}) = \mathcal{U}(\mathbf{r}) + \mathcal{K}(\mathbf{p})$ ,  $\mathcal{U}$  being the potential energy, the probability distribution of microstates may be written

$$\rho(\mathbf{r}, \mathbf{p}) = \frac{e^{-\beta\mathcal{H}(\mathbf{r}, \mathbf{p})}}{\int d\mathbf{r} \int d\mathbf{p} e^{-\beta\mathcal{H}(\mathbf{r}, \mathbf{p})}} = \frac{e^{-\beta\mathcal{U}(\mathbf{r})}}{\int d\mathbf{r} e^{-\beta\mathcal{U}(\mathbf{r})}} \frac{e^{-\beta\mathcal{K}(\mathbf{p})}}{\int d\mathbf{p} e^{-\beta\mathcal{K}(\mathbf{p})}}. \quad (23)$$

Integrating this expression over either momenta or coordinates shows that the distribution is also canonical in both configurations (i.e., configurations are sampled with a statistical weight proportional to  $e^{-\beta\mathcal{U}}$ ) and momenta (i.e., momenta are sampled with a statistical weight proportional to  $e^{-\beta\mathcal{K}}$ ). In Cartesian coordinates, such a canonical distribution of momenta reads

$$\rho_p(\mathbf{p}) = \frac{e^{-\beta\mathcal{K}(\mathbf{p})}}{\int d\mathbf{p} e^{-\beta\mathcal{K}(\mathbf{p})}} = \prod_{i\mu} \frac{e^{-\beta(2m_i)^{-1} p_{i\mu}^2}}{\int dp_{i\mu} e^{-\beta(2m_i)^{-1} p_{i\mu}^2}} = \prod_{i\mu} p(p_{i\mu}), \quad (24)$$

where Eq. (10) was used together with  $\mathbf{p}_i = m_i \dot{\mathbf{r}}_i$ . Noting that  $p(\dot{r}_{i\mu}) = m_i p(p_{i\mu})$  and evaluating the required Gaussian integral, this result shows that internal velocities obey a Maxwell-Boltzmann distribution, i.e., the velocity components  $\dot{r}_{i\mu}$  appear with the probability

$$p(\dot{r}_{i\mu}) = \left( \frac{\beta m_i}{2\pi} \right)^{1/2} e^{-(1/2)\beta m_i \dot{r}_{i\mu}^2}. \quad (25)$$

Note that the above statements do not formally hold in the presence of geometrical constraints, but are generally assumed to provide a good approximation in this case. Some other thermostats only generate a canonical ensemble of configurations, but not of microstates and momenta. This is generally not a serious disadvantage for the computation of thermodynamical properties, because the contribution of momenta to thermodynamical quantities can be calculated analytically (ideal-gas contribution). Finally, there also exists thermostats that generate distributions that are canonical neither in configurations nor in momenta.

From a dynamical point of view, assessing the relative merits of different thermostats is somewhat subjective<sup>9</sup>. Clearly, the configurational dynamics of a system will be affected by the timescale of its instantaneous temperature fluctuations, and a good thermostat should reproduce this timescale at least qualitatively. However, the direct comparison between experimental thermostats (e.g., a heat bath surrounding

<sup>9</sup> An objective question, however, is whether the thermostat is able to produce correct time-correlation functions (at least in the limit of a macroscopic system). Since transport coefficients (e.g., the diffusion constant) can be calculated either as ensemble averages (Einstein formulation) or as integrals of a time-correlation function (Green-Kubo formulation), at least such integrals should be correct if the thermostat leads to a canonical ensemble. When this is the case, it has been shown that the correlation functions themselves are also correct at least for some thermostats [91, 86].

a macroscopic system, or the bulk medium around a microscopic sample of matter) and thermostats used in simulations is not straightforward. The reason is that experimental thermostats, because they involve the progressive diffusion of heat from the system surface towards its center (or inversely), lead to inhomogeneities in the spatial temperature distribution within the sample. On the other hand, the thermostats used in simulations generally modify instantaneously and simultaneously the velocities of all atoms irrespective of their locations, and should lead to an essentially homogeneous temperature distribution.

One may nevertheless try to quantify the timescale of the temperature fluctuations to be expected in a thermostated simulation. This timescale can be estimated based on a semi-macroscopic approach [55]. Consider a system characterized by an average temperature  $\overline{\mathcal{T}}$ , in contact with a heat bath at a different temperature  $T_o$ . By average temperature, it is meant that the quantity  $\overline{\mathcal{T}}$  is spacially-averaged over the entire system and time-averaged over an interval that is short compared to the experimental timescale, but long compared to the time separating atomic collisions. The difference between  $\overline{\mathcal{T}}$  and  $T_o$  may result, e.g., from a natural fluctuation of  $\overline{\mathcal{T}}$  within the system. From macroscopic principles, the rate of heat transfer from the heat bath to the system should be proportional to the temperature difference  $T_o - \overline{\mathcal{T}}$  and to the thermal conductivity  $\kappa$  of the system. Thus, the rate of change in the average temperature can be written (at constant volume)

$$\dot{\overline{\mathcal{T}}}(t) = c_v^{-1} \dot{\overline{E}}(t) = \zeta_T^{-1} [T_o - \overline{\mathcal{T}}(t)] \quad (26)$$

with the definition

$$\zeta_T = \zeta^{-1} V^{-1/3} c_o \kappa^{-1}, \quad (27)$$

where  $c_o$  is the system isochoric heat capacity,  $V$  the system volume, and  $\zeta$  a dimensionless constant depending on the system shape and on the temperature inhomogeneity within the system. For a given system geometry (e.g., spherical) and initial temperature distribution (i.e.,  $T(\mathbf{x}, 0)$ ), a reasonable value for  $\zeta$  could in principle be estimated by solving simultaneously the flux equation

$$\mathbf{J}(\mathbf{x}, t) = -\kappa \nabla T(\mathbf{x}, t), \quad (28)$$

where  $\mathbf{J}(\mathbf{x}, t)$  is the energy flux through a surface element perpendicular to the direction of the vector, and the conservation equation

$$\frac{\partial T(\mathbf{x}, t)}{\partial t} = -V c_v^{-1} \nabla \cdot \mathbf{J}(\mathbf{x}, t). \quad (29)$$

Eq. (26) implies that, at equilibrium, the natural fluctuations of  $\overline{\mathcal{T}}$  away from  $T_o$  decay exponentially with a temperature relaxation time  $\zeta_T$ , i.e.

$$\overline{\mathcal{T}}(t) = T_o + [\overline{\mathcal{T}}(0) - T_o] e^{-\zeta_T^{-1} t}. \quad (30)$$

Note that on a very short timescale (i.e., of the order of the time separating atomic collisions), the instantaneous temperature  $\mathcal{T}(t)$  is also affected by important stochastic variations (see Sect. 3.2). Only on an intermediate timescale does the mean effect

of these stochastic fluctuations result in an exponential relaxation for  $\overline{\mathcal{T}}(t)$ . However, because stochastic variations contribute significantly to the instantaneous temperature fluctuations, a thermostat based solely on an exponential relaxation for  $\mathcal{T}(t)$  leads to incorrect (underestimated) temperature fluctuations (see Sect. 3.5).

To summarize, although assessing whether one thermostat leads to a better description of the dynamics compared to another one is largely subjective, it seems reasonable to assume that: (i) thermostats permitting temperature fluctuations are more likely to represent the dynamics correctly compared to thermostats constraining the temperature at a fixed value; (ii) thermostats with temperature fluctuations are more likely to represent the dynamics correctly when these fluctuations occur at a timescale (measured in a simulation, e.g., as the decay time of the temperature autocorrelation function) of the order of  $\zeta_T$  (Eq. (26)), and when the dynamics is smooth (continuous velocity trajectory). These differences will be more significant for small systems, where the temperature fluctuations are of of larger magnitudes (the corresponding root-mean-square fluctuations scale as  $N^{-1/2}$ , see Eq. (2)) and higher frequencies (the corresponding relaxation times scale as  $N^{-1/3}$ , see Eq. (27)).

A summary of the common thermostats used in MD simulations, together with their main properties, is given in Table 2. The various algorithms are detailed in the following sections.

### 3.1 Temperature in the Monte Carlo Algorithm

Although the present discussion mainly focuses on thermostated MD, the simplest way to generate a thermodynamical ensemble at constant temperature is to use the MC algorithm [82, 83, 84]. This algorithm does not involve atomic velocities or kinetic energy. Random trial moves are generated, and accepted with a probability

$$p = \min\{e^{-\beta\Delta\mathcal{U}}, 1\} \quad (31)$$

depending on the potential energy change  $\Delta\mathcal{U}$  associated with the move and on the reference temperature  $T_o$ . Following this criterion, moves involving rigid-body translation and, under vacuum boundary conditions, rigid-body rotation are always accepted because they do not change the potential energy. For this reason, the corresponding degrees of freedom are external to the system. Note also that under vacuum boundary conditions, the centrifugal forces due to the rigid-body rotation of the system, which would be included in a MD simulation, are absent in the MC procedure. Therefore, MC samples by default an ensemble at zero angular momentum. It can be shown that the ensemble generated by the MC procedure represents (at constant volume) a canonical distribution of configurations. The modification of the MC scheme to sample other isothermal ensembles (including the grand-canonical ensemble [92]) is possible. Modifications permitting the sampling of adiabatic ensembles (e.g., the microcanonical ensemble [92, 93, 94]) have also been devised. The MC procedure is non-smooth, non-deterministic, time-irreversible, and does not provide any dynamical information.

**Table 2.** Characteristics of the main thermostat algorithms used in MD simulations. MD: molecular dynamics (generates a microcanonical ensemble, only shown for comparison); MC: Monte Carlo (Sect. 3.1); SD: stochastic dynamics (with  $\gamma_i > 0$  for at least one atom; Sect. 3.2); A: MD with Andersen thermostat (with  $\alpha > 0$ ; Sect. 3.3); HE: MD with Hoover-Evans thermostat (Sect. 3.4); W: MD with Woodcock thermostat (Sect. 3.4); HG: MD with Haile-Gupta thermostat (Sect. 3.4); B: MD with Berendsen thermostat (with  $\Delta t < \tau_B < \infty$ ; Sect. 3.5); NH: MD with Nosé-Hoover thermostat (with  $0 < Q < \infty$ ; Sect. 3.6). MD is a limiting case of SD (with  $\gamma_i = 0$  for all atoms), A (with  $\alpha = 0$ ), B (with  $\tau_B \rightarrow \infty$ ), and NH (with  $Q \rightarrow \infty$ ,  $\gamma(0) = 0$ ). HE/W is a limiting cases of B (with  $\tau_B = \Delta t$ ) and is a constrained form of NH. HG is also a constrained form of NH. Deterministic: trajectory is deterministic; Time-reversible: equation of motion is time-reversible; Smooth: velocity trajectory is available and continuous. Energy drift: possible energy (and temperature) drift due to accumulation of numerical errors; Oscillations: possible oscillatory behavior of the temperature dynamics; External d.o.f.: some external degrees of freedom (rigid-body translation and, under vacuum boundary conditions, rotation) are not coupled with the internal degrees of freedom. Constrained  $\mathcal{K}$ : no kinetic energy fluctuations; Canonical in  $\mathcal{H}$ : generates a canonical distribution of microstates; Canonical in  $\mathcal{U}$ : generates a canonical distribution of configurations. Dynamics: dynamical information on the system is either absent (—) or likely to be unrealistic (—; constrained temperature or non-smooth trajectory), moderately realistic (+; smooth trajectory, but temperature fluctuations of incorrect magnitude), or realistic (++; smooth trajectory, correct magnitude of the temperature fluctuations). The latter appreciation is rather subjective and depends on an adequate choice of the adjustable parameters of the thermostat

	MD	MC	SD	A	HE	W	HG	B	NH
Deterministic	+	—	—	—	+	+	+	+	+
Time-reversible	+	—	—	—	+	+	+	—	+
Smooth	+	—	+	—	+	+	+	+	+
Energy drift	+	—	—	—	+	—	—	—	—
Oscillations	—	—	—	—	—	—	—	—	+
External d.o.f.	+	+	—	—	+	+	+	+	+
Constrained $\mathcal{K}$	—	—	—	—	+	+	+	—	—
Canonical in $\mathcal{H}$	—	—	+	+	—	—	—	—	+
Canonical in $\mathcal{U}$	—	+	+	+	+	+	—	—	+
Dynamics	++	--	++	—	—	—	—	+	++
Eqn. of motion	15		17	41	46	51	52	57	78,79

### 3.2

#### Temperature Relaxation by Stochastic Dynamics

The SD algorithm relies on the integration of the Langevin equation of motion [22, 23, 95, 96, 97, 98, 99, 100] as given by Eq. (17). The stochastic forces  $\mathbf{R}_i(t)$  have the following properties<sup>10</sup>: (i) they are uncorrelated with the velocities  $\dot{\mathbf{r}}(t')$  and systematic forces  $\mathbf{F}_i(t')$  at previous times  $t' < t$ ; (ii) their time-averages are zero; (iii) their mean-square components evaluate to  $2m_i\gamma_i k_B T_0$ ; (iv) the force component  $R_{i\mu}(t)$

<sup>10</sup> More complex SD schemes can be used, which incorporate time or space correlations in the stochastic forces. It is also assumed here that the friction coefficients  $\gamma_i$  are time-independent.

along the Cartesian axis  $\mu$  is uncorrelated with any component  $R_{j\nu}(t')$  along axis  $\nu$  unless  $i = j$ ,  $\mu = \nu$ , and  $t' = t$ . The two last conditions can be combined into the relation

$$\langle R_{i\mu}(t)R_{j\nu}(t') \rangle = 2m_i\gamma_i k_B T_o \delta_{ij} \delta_{\mu\nu} \delta(t' - t) . \quad (32)$$

It can be shown that a trajectory generated by integrating the Langevin equation of motion (with at least one non-vanishing atomic friction coefficient  $\gamma_i$ ) maps (at constant volume) a canonical distribution of microstates at temperature  $T_o$ .

The Langevin equation of motion is smooth, non-deterministic and time-irreversible. Under vacuum boundary conditions and aiming at reproducing bulk properties, it may produce a reasonable picture of the dynamics if the mean effect of the surrounding solvent is incorporated into the systematic forces, and if the friction coefficients are representative of the solvent viscosity (possibly weighted by the solvent accessibility). If SD is merely used as a thermostat in explicit-solvent simulations, as is the case, e.g., when applying stochastic boundary conditions to a simulated system [101, 11, 12], some care must be taken in the choice of the atomic friction coefficients  $\gamma_i$ . On the one hand, too small values (loose coupling) may cause a poor temperature control. Indeed, the limiting case of SD where all friction coefficients (and thus the stochastic forces) are set to zero is MD, which generates a microcanonical ensemble. However, arbitrarily small atomic friction coefficients (or even a non-vanishing coefficient for a single atom) are sufficient to guarantee in principle the generation of a canonical ensemble. But if the friction coefficients are chosen too low, the canonical distribution will only be obtained after very long simulation times. In this case, systematic energy drifts due to accumulation of numerical errors may interfere with the thermostatization. On the other hand, too large values of the friction coefficients (tight coupling) may cause the large stochastic and frictional forces to perturb the dynamics of the system. In principle, the perturbation of the dynamics due to stochastic forces will be minimal when the atomic friction coefficients  $\gamma_i$  are made proportional to  $m_i$ . In this case, Eqs. (17) and (32) show that the root-mean-square acceleration due to stochastic forces is identical for all atoms. In practice, however, it is often more convenient to set the friction coefficients to a common value  $\gamma$ . The limiting case of SD for very large friction coefficients (i.e., when the acceleration  $\ddot{\mathbf{r}}_i$  can be neglected compared to the other terms in Eq. (17)) is Brownian dynamics (BD), with the equation of motion

$$\dot{\mathbf{r}}_i(t) = \gamma_i^{-1} m_i^{-1} [\mathbf{F}_i(t) + \mathbf{R}_i(t)] . \quad (33)$$

Although the magnitude of the temperature fluctuations is in principle not affected by the values of the friction coefficients (unless they are all zero), the timescale of these fluctuations strongly depends on the  $\gamma_i$  coefficients. In fact, it can be shown [54] that there is a close relationship between the friction coefficients in SD (used as a mere thermostat) and the temperature relaxation time  $\zeta_T$  in Eq. (26). Consider the case where all coefficients  $\gamma_i$  are set to a common value  $\gamma$ . Following from Eqs. (8) and (10), the change  $\Delta\mathcal{T}$  of the instantaneous temperature over a time interval from  $t = 0$  to  $\Delta\tau$  can be written

$$\Delta\mathcal{T} = \frac{2}{k_B N_{df}} \int_0^{\Delta\tau} dt \mathcal{K}(t) = \frac{2}{k_B N_{df}} \sum_{i=1}^N m_i \int_0^{\Delta\tau} dt \ddot{\mathbf{r}}_i(t) \cdot \dot{\mathbf{r}}_i(t). \quad (34)$$

Inserting Eq. (17), this can be rewritten

$$\Delta\mathcal{T} = \frac{2}{k_B N_{df}} \sum_{i=1}^N \left\{ \int_0^{\Delta\tau} dt [\mathbf{F}_i(t) - \gamma m_i \dot{\mathbf{r}}_i(t)] \cdot \dot{\mathbf{r}}_i(t) + \int_0^{\Delta\tau} dt \right. \quad (35)$$

$$\left. \times \mathbf{R}_i(t) \cdot \left[ \dot{\mathbf{r}}_i(0) + \int_0^t dt' [m_i^{-1} \mathbf{F}_i(t') - \gamma \dot{\mathbf{r}}_i(t') + m_i^{-1} \mathbf{R}_i(t')] \right] \right\}.$$

Using Eq. (32) and the fact that the stochastic force is uncorrelated with the velocities and systematic forces at previous times, this simplifies to

$$\Delta\mathcal{T} = \frac{2}{k_B N_{df}} \sum_{i=1}^N \left\{ \int_0^{\Delta\tau} dt [\mathbf{F}_i(t) \cdot \dot{\mathbf{r}}_i(t) - \gamma m_i \dot{\mathbf{r}}_i^2(t)] \right. \quad (36)$$

$$\left. + m_i^{-1} \int_0^{\Delta\tau} dt \mathbf{R}_i(t) \cdot \int_0^t dt' \mathbf{R}_i(t') \right\}$$

$$= \frac{2}{k_B N_{df}} \sum_{i=1}^N \int_0^{\Delta\tau} dt [\mathbf{F}_i(t) \cdot \dot{\mathbf{r}}_i(t) - \gamma m_i \dot{\mathbf{r}}_i^2(t)]$$

$$+ 6N_{df}^{-1} N \gamma T_o \Delta\tau.$$

This expression can be rewritten<sup>11</sup>

$$\frac{\Delta\mathcal{T}}{\Delta\tau} = \frac{2}{k_B N_{df}} \sum_{i=1}^N \overline{\mathbf{F}_i \cdot \dot{\mathbf{r}}_i} + 2\gamma [T_o - \overline{\mathcal{T}}], \quad (37)$$

where  $\overline{\mathbf{F}_i \cdot \dot{\mathbf{r}}_i}$  and  $\overline{\mathcal{T}}$  stand for averages over the interval  $\Delta\tau$ . The first term represents the temperature change caused by the effect of the systematic forces, and would be unaltered in the absence of thermostat (Newtonian MD simulation). Thus, the second term can be identified with a temperature change arising from the coupling to a heat bath. This means that on an intermediate timescale (as defined at the end of Sect. 3), the mean effect of thermostatzation can be written

$$\overline{\dot{\mathcal{T}}}(t) = 2\gamma [T_o - \overline{\mathcal{T}}(t)]. \quad (38)$$

Comparing with Eq. (26) allows to identify  $2\gamma$  with the inverse of the temperature relaxation time  $\zeta_T$  in Eq. (26), i.e., to suggest  $\gamma = (1/2)\zeta_T^{-1}$  as an appropriate value for simulations. This discussion also shows that the semi-macroscopic expression of Eq. (26) is only valid on an intermediate timescale, when the stochastic fluctuations occurring on a shorter timescale (i.e., of the order of the time separating atomic collisions) are averaged out and only their mean effect is retained.

<sup>11</sup> In the absence of constraints  $N_{df} = 3N$  due to Eq. (9) with  $N_c = 0$  and  $N_r = 0$  (as appropriate for SD). In the presence of constraints, the derivation should include constraint forces.

### 3.3

#### Temperature Relaxation by Stochastic Coupling

The stochastic-coupling method was proposed by Andersen [55]. In this approach, Newton's equation of motion (Eq. (15)) is integrated in time, with the modification that at each timestep, the velocity of all atoms are conditionally reassigned from a Maxwell-Boltzmann distribution. More precisely, if an atom  $i$  is selected for a velocity reassignment, each Cartesian component  $\mu$  of the new velocity is selected at random according to the Maxwell-Boltzmann probability distribution of Eq. (25). The selection procedure is such that the time intervals  $\tau$  between two successive velocity reassignments of a given atom are selected at random according to a probability  $p(\tau) = \alpha e^{-\alpha\tau}$ , where  $\alpha$  is a constant reassignment frequency. In principle, one can select at random and for each atom a series of successive  $\tau$ -values (obeying the specified probability distribution) before starting the simulation. This series is then used to determine when the particle is to undergo a velocity reassignment. In practice, a simpler procedure can be used when  $\Delta t \ll \alpha^{-1}$  (infrequent reassignments). At each timestep and for each atom in turn, one generates a random number between 0 and 1. If this number is larger than  $\alpha \Delta t$  for a given atom, this atom undergoes a velocity reassignment. This procedure leads to a probability distribution

$$p(\tau)\Delta t = (1 - \alpha\Delta t)^{\tau/\Delta t} \alpha\Delta t \quad (39)$$

for the intervals  $\tau$  without velocity reassignment. This implies

$$\ln \alpha^{-1} p(\tau) = (\tau/\Delta t) \ln(1 - \alpha\Delta t) = -\alpha\tau + O[(\alpha\Delta t)^2]. \quad (40)$$

Thus, when  $\Delta t \ll \alpha^{-1}$ ,  $p(\tau) = \alpha e^{-\alpha\tau}$ , as expected. If the condition is not satisfied, this second method will not work because the probability of multiple reassignments within the same timestep becomes non-negligible.

The equation of motion for the Andersen thermostat can formally be written

$$\ddot{\mathbf{r}}_i(t) = m_i^{-1} \mathbf{F}_i(t) + \sum_{n=1}^{\infty} \delta\left(t - \sum_{m=1}^n \tau_{i,m}\right) [\dot{\mathbf{r}}_{i,n}^*(t) - \dot{\mathbf{r}}_i(t)], \quad (41)$$

where  $\{\tau_{i,n} \mid n = 1, 2, \dots\}$  is the series of intervals without reassignment for particle  $i$ , and  $\dot{\mathbf{r}}_{i,n}^*$  the randomly-reassigned velocity after the  $n^{\text{th}}$  interval. This approach mimicks the effect irregularly-occurring stochastic collisions of randomly chosen atoms with a bath of fictitious particles at a temperature  $T_o$ . Because, the system evolves at constant energy between the collisions, this method generates a succession of microcanonical simulations, interrupted by small energy jumps corresponding to each collision.

It can be shown [55] that the Andersen thermostat with non-zero collision frequency  $\alpha$  leads to a canonical distribution of microstates. The proof [55] involves similar arguments as the derivation of the probability distribution generated by the MC procedure. It is based on the fact that the Andersen algorithm generates a Markov chain of microstates in phase space. The only required assumption is that every microstate is accessible from every other one within a finite time (ergodicity). Note

also that the system total linear and angular momenta are affected by the velocity reassignments, so that these degrees of freedom are internal to the system, as in SD.

The Andersen algorithm is non-deterministic and time-irreversible. Moreover, it has the disadvantage of being non-smooth, i.e., generating a discontinuous velocity trajectory where the randomly-occurring collisions may interfere with the natural dynamics of the system.

Some care must be taken in the choice of the collision frequency  $\alpha$  [55, 102]. On the one hand, too small values (loose coupling) may cause a poor temperature control. The same observations apply here as those made for SD. The limiting case of the Andersen thermostat with a vanishing collision frequency is MD, which generates a microcanonical ensemble. Arbitrarily small collision frequencies are sufficient to guarantee in principle the generation of a canonical ensemble. But if the collision frequency is too low, the canonical distribution will only be obtained after very long simulation times. In this case, systematic energy drifts due to accumulation of numerical errors may interfere with the thermostatization. On the other hand, too large values for the collision frequency (tight coupling) may cause the velocity reassignments to perturb heavily the dynamics of the system. Although the magnitude of the temperature fluctuations is in principle not affected by the value of the collision frequency (unless it is zero), the timescale of these fluctuations strongly depends on this parameter. In fact, it can be shown [55] that there is a close relationship between the collision frequency and the temperature relaxation time  $\zeta_T$  in Eq. (26). Each collision changes the kinetic energy of the system by  $(3/2)k_B[T_o - \mathcal{T}(t)]$  on average, and there are  $N\alpha$  such collisions per unit of time. Thus, one expects

$$\dot{\overline{\mathcal{T}}}(t) = c_v^{-1} \dot{\overline{E}}(t) = (3/2)c_v^{-1} N\alpha k_B [T_o - \overline{\mathcal{T}}(t)], \quad (42)$$

where  $\overline{\mathcal{T}}$  and  $\overline{E}$  stand for averages over an intermediate timescale (as defined at the end of Sect. 3). Comparing with Eq. (26) allows to identify  $(3/2)c_v^{-1} N\alpha k_B$  with the inverse of the temperature relaxation time  $\zeta_T$  in Eq. (26), i.e., to suggest  $\alpha = (2/3)(Nk_B)^{-1} c_v \zeta_T^{-1}$  as an appropriate value for simulations. Note that because  $\zeta_T$  scales as  $N^{-1/3}$  (Eq. (27)), the collision frequency for any particle scales as  $N^{-2/3}$ , so that the time each particle spends without reassignment increases with the system size. On the other hand, the collision frequency for the whole system,  $N\alpha$ , scales as  $N^{1/3}$ , so that the length of each microcanonical sub-simulation decreases with the system size.

### 3.4

#### Temperature Constraining

Temperature constraining aims at fixing the instantaneous temperature  $\mathcal{T}$  to the reference heat-bath value  $T_o$  without allowing for any fluctuations. In this sense, temperature constraining represents a hard boundary condition, in contrast to the soft boundary conditions employed by all other thermostats mentioned in this article. Note that constraining the temperature, i.e., enforcing the relation  $\mathcal{T}(t) = T_o$  (or  $\dot{\mathcal{T}}(t) = 0$ ) represents a non-holonomic constraint. Holonomic constraints are those

which only involve generalized coordinates and time, excluding any dependence on the generalized velocities. Two main temperature-constraining algorithms have been proposed. The first one is due to Woodcock [103], and the second one was simultaneously proposed by Hoover [104] and Evans [105].

In the Hoover-Evans algorithm [104, 52, 51, 105, 106], the quantity  $\lambda(t; \Delta t)$  in Eq. (20) is found by imposing temperature conservation in the form  $\mathcal{T}(t + \frac{\Delta t}{2}) = \mathcal{T}(t - \frac{\Delta t}{2})$ . Using Eqs. (8) and (10), this leads to the condition

$$\begin{aligned} & \frac{\lambda^2(t; \Delta t)}{k_B N_{df}} \left\{ \sum_{i=1}^N m_i \left[ \dot{\mathbf{r}}_i \left( t - \frac{\Delta t}{2} \right) + m_i^{-1} \mathbf{F}_i(t) \Delta t \right]^2 \right\} \\ &= \frac{1}{k_B N_{df}} \sum_{i=1}^N m_i \dot{\mathbf{r}}_i^2 \left( t - \frac{\Delta t}{2} \right). \end{aligned} \quad (43)$$

Solving for  $\lambda(t; \Delta t)$  gives

$$\begin{aligned} \lambda(t; \Delta t) &= \left\{ \frac{\sum_{i=1}^N m_i \dot{\mathbf{r}}_i^2 \left( t - \frac{\Delta t}{2} \right)}{\sum_{i=1}^N m_i \left[ \dot{\mathbf{r}}_i \left( t - \frac{\Delta t}{2} \right) + m_i^{-1} \mathbf{F}_i(t) \Delta t \right]^2} \right\}^{1/2} \\ &= \left[ \frac{\mathcal{T} \left( t - \frac{\Delta t}{2} \right)}{\mathcal{T}' \left( t + \frac{\Delta t}{2} \right)} \right]^{1/2}, \end{aligned} \quad (44)$$

where  $\mathcal{T} \left( t - \frac{\Delta t}{2} \right)$  and  $\mathcal{T}' \left( t + \frac{\Delta t}{2} \right)$  are the instantaneous temperatures computed based on the velocities  $\dot{\mathbf{r}}_i \left( t - \frac{\Delta t}{2} \right)$  and  $\dot{\mathbf{r}}'_i \left( t + \frac{\Delta t}{2} \right)$ , see Eq. (20). Because this quantity satisfies  $\lambda(t; 0) = 1$ , applying Eq. (21) gives

$$\gamma(t) = [N_{df} k_B \mathcal{T}(t)]^{-1} \sum_{i=1}^N \dot{\mathbf{r}}_i(t) \cdot \mathbf{F}_i(t). \quad (45)$$

Inserting into Eq. (18) shows that the equation of motion corresponding to the Hoover-Evans thermostat is

$$\ddot{\mathbf{r}}_i(t) = m_i^{-1} \mathbf{F}_i(t) - [N_{df} k_B \mathcal{T}(t)]^{-1} \left[ \sum_{i=1}^N \dot{\mathbf{r}}_i(t) \cdot \mathbf{F}_i(t) \right] \dot{\mathbf{r}}_i(t). \quad (46)$$

This equation of motion should sample an isothermal trajectory at a temperature determined by the initial internal velocities. Eq. (46) can also be derived directly from Eq. (18) by imposing  $\dot{\mathcal{T}}(t) = 0$ . Using Eqs. (8) and (10) this becomes

$$\dot{\mathcal{T}}(t) = \frac{d}{dt} \left[ \frac{1}{k_B N_{df}} \sum_{i=1}^N m_i \dot{\mathbf{r}}_i^2(t) \right] = \frac{2}{k_B N_{df}} \sum_{i=1}^N m_i \dot{\mathbf{r}}_i(t) \cdot \ddot{\mathbf{r}}_i(t) = 0. \quad (47)$$

Inserting Eq. (18) and solving for  $\gamma(t)$  leads to Eq. (46).

The Hoover-Evans algorithm should in principle ensure a constant temperature at all time points. However, this condition is only enforced by zeroing the temperature derivative. Because the reference temperature  $T_o$  does not appear explicitly in the scaling factor of Eq. (44), numerical inaccuracies will inevitably prevent temperature conservation, and cause the temperature to actually drift in simulations.

In the Woodcock algorithm [103], the quantity  $\lambda(t; \Delta t)$  in Eq. (20) is found by imposing temperature conservation in the form  $\mathcal{T}(t + \frac{\Delta t}{2}) = \frac{g}{N_{df}} T_o$ , thereby making explicit use of the reference temperature. Although  $g = N_{df}$  seems to be the obvious choice, it turns out that  $g = N_{df} - 1$  is the appropriate choice for the algorithm to generate a canonical ensemble of configurations at temperature  $T_o$  (see below). Using Eqs. (8) and (10), this leads to the condition

$$\frac{\lambda^2(t; \Delta t)}{k_B N_{df}} \left\{ \sum_{i=1}^N m_i \left[ \dot{\mathbf{r}}_i \left( t - \frac{\Delta t}{2} \right) + m_i^{-1} \mathbf{F}_i(t) \Delta t \right]^2 \right\} = \frac{g}{N_{df}} T_o. \quad (48)$$

Solving for  $\lambda(t; \Delta t)$  gives<sup>12</sup>

$$\begin{aligned} \lambda(t; \Delta t) &= \left\{ \frac{g k_B T_o}{\sum_{i=1}^N m_i \left[ \dot{\mathbf{r}}_i \left( t - \frac{\Delta t}{2} \right) + m_i^{-1} \mathbf{F}_i(t) \Delta t \right]^2} \right\}^{1/2} \\ &= \left[ \frac{g}{N_{df}} \frac{T_o}{\mathcal{T}' \left( t + \frac{\Delta t}{2} \right)} \right]^{1/2}. \end{aligned} \quad (49)$$

If  $\mathcal{T}(t - \frac{\Delta t}{2}) = \frac{g}{N_{df}} T_o$  (i.e., if the simulation was started with internal velocities corresponding to the reference temperature, or otherwise, after a first equilibration timestep), this quantity satisfies  $\lambda(t; 0) = 1$ . In this case, applying Eq. (21) gives

$$\gamma(t) = (g k_B T_o)^{-1} \sum_{i=1}^N \dot{\mathbf{r}}_i(t) \cdot \mathbf{F}_i(t). \quad (50)$$

Inserting into Eq. (18) shows that the equation of motion corresponding to the Woodcock thermostat is

$$\ddot{\mathbf{r}}_i(t) = m_i^{-1} \mathbf{F}_i(t) - (g k_B T_o)^{-1} \left[ \sum_{i=1}^N \dot{\mathbf{r}}_i(t) \cdot \mathbf{F}_i(t) \right] \dot{\mathbf{r}}_i(t). \quad (51)$$

This equation of motion is rigorously equivalent to the Hoover-Evans equation of motion (Eq. (46)), provided that the initial internal velocities are appropriate for

<sup>12</sup> Note that some simulation programs do not apply the scaling of the velocities by  $\lambda(t; \Delta t)$  at every timestep, but perform the scaling on a periodic basis, or when the difference between the instantaneous and reference temperatures is larger than a given tolerance [107].

the temperature  $T_o$ , i.e., that  $\mathcal{T}(0) = \frac{g}{N_{df}}T_o$ . However, even in this case, the corresponding algorithms differ numerically. Because the Woodcock algorithm explicitly involves the reference temperature  $T_o$  in the calculation of the scaling factor of Eq. (49), its application removes the risk of a temperature drift.

Because maintaining the temperature constant represents a single constraint equation involving a total of  $N_{df}$  velocity variables, it should not be surprising that numerous other choices of equations of motion lead to an isothermal dynamics (also satisfying the two constraints that the system linear and angular momenta are constants of the motion). For example, Haile and Gupta [108] have shown how to construct two general classes of isothermal equations of motion based on generalized forces or generalized potentials. An example of the former class is the Hoover-Evans thermostat. An example of the second class is a thermostat similar (but, contrary to the claim of the authors [108], not identical) to the Woodcock thermostat. The equations of motion of this Haile-Gupta thermostat are

$$\dot{\mathbf{r}}_i(t) = \left[ \frac{g}{N_{df}} \frac{T_o}{\mathcal{T}'(t)} \right]^{1/2} \dot{\mathbf{r}}'_i(t) \text{ and } \ddot{\mathbf{r}}_i(t) = m_i^{-1} \mathbf{F}_i(t). \quad (52)$$

In words, the auxiliary velocities  $\dot{\mathbf{r}}'_i$  are propagated independently in time according to Newton's second law, and the true velocities obtained by multiplying these by the appropriate scaling factor at each timestep. In contrast, in the Woodcock thermostat, the auxiliary velocities  $\dot{\mathbf{r}}'_i$  are obtained at each timestep by increasing the true velocities  $\dot{\mathbf{r}}_i$  by  $m_i^{-1} \mathbf{F}_i \Delta t$ .

It can be shown that the ensemble generated by the (identical) Woodcock and Hoover-Evans equations of motion represents a canonical distribution of configurations (though obviously not of momenta) at temperature  $T_o$ , provided that one sets  $g = N_{df} - 1$  ([104, 53]; see Appendix). This may seem surprising at first sight, but canonical sampling of configurations is only achieved with  $\langle \mathcal{T}(t) \rangle = \frac{N_{df}-1}{N_{df}} T_o \neq T_o$ , i.e., when simulating at a slightly lower internal temperature. The reason is that constraining the temperature effectively removes one degree of freedom from the system. A more consistent approach would be to alter the definition of the instantaneous temperature (Eq. (8)) by changing  $N_{df}$  to  $N_{df} - 1$  in this case. However, since other thermostats may involve different values for the factor  $g$  (see Sect. 3.6), it is more convenient here to stick to a single definition of  $\mathcal{T}$ . On the other hand (and contrary to the author's initial claim [108]), the Haile-Gupta thermostat does not generate a canonical ensemble of configurations ([53, 109]; see Appendix). The equations of motion of temperature constraining are smooth, deterministic and time-reversible. However, the absence of kinetic energy fluctuations may lead to inaccurate dynamics, especially in the context of the microscopic systems typically considered in simulations.

### 3.5 Temperature Relaxation by Weak Coupling

The idea of a thermostat based on a first-order relaxation equation is due to Berendsen [54]. As discussed at the end of Sect. 3, when a system at a given average temperature  $\overline{\mathcal{T}}$  is in contact with a heat bath at a different temperature  $T_o$ , the rate of temperature change is given by Eq. (26). As discussed in Sect. 3.2, this equation is only valid when the average temperature is calculated on an intermediate timescale (short compared to the experimental timescale, but long compared to the time separating atomic collisions). On this timescale, only the mean effect of the stochastic forces acting in SD needs to be considered, leading to the first-order temperature relaxation law of Eq. (26).

The idea behind the Berendsen thermostat is to modify the Langevin equation of motion (Eq. (17)) in the sense of removing the local temperature coupling through stochastic collisions (random noise), while retaining the global coupling (principle of least local perturbation). This prescription is equivalent to assuming that Eq. (26) also applies to the instantaneous temperature  $\mathcal{T}$ , i.e., that

$$\dot{\mathcal{T}}(t) = \tau_B^{-1} [T_o - \mathcal{T}(t)], \quad (53)$$

where the appropriate value for  $\tau_B$  should be the temperature relaxation time  $\zeta_T$ . In this case, the quantity  $\lambda(t; \Delta t)$  in Eq. (20) is found by imposing  $\mathcal{T}(t + \frac{\Delta t}{2}) = \mathcal{T}(t - \frac{\Delta t}{2}) + \tau_B^{-1} \Delta t \frac{g}{N_{df}} [T_o - \mathcal{T}(t - \frac{\Delta t}{2})]$ , where in principle  $g = N_{df}$ . Using Eqs. (8) and (10), this leads to the condition

$$\lambda^2(t; \Delta t) \mathcal{T}' \left( t + \frac{\Delta t}{2} \right) = \mathcal{T} \left( t - \frac{\Delta t}{2} \right) + \tau_B^{-1} \Delta t \left[ \frac{g}{N_{df}} T_o - \mathcal{T} \left( t - \frac{\Delta t}{2} \right) \right]. \quad (54)$$

Solving for  $\lambda(t; \Delta t)$  gives

$$\begin{aligned} \lambda(t; \Delta t) &= \left\{ \frac{\mathcal{T} \left( t - \frac{\Delta t}{2} \right)}{\mathcal{T}' \left( t + \frac{\Delta t}{2} \right)} + \tau_B^{-1} \Delta t \frac{\frac{g}{N_{df}} T_o - \mathcal{T} \left( t - \frac{\Delta t}{2} \right)}{\mathcal{T}' \left( t + \frac{\Delta t}{2} \right)} \right\}^{1/2} \\ &\approx \left\{ 1 + \tau_B^{-1} \Delta t \left[ \frac{\frac{g}{N_{df}} T_o}{\mathcal{T}' \left( t + \frac{\Delta t}{2} \right)} - 1 \right] \right\}^{1/2}. \end{aligned} \quad (55)$$

In general, the algorithm is implemented following the second (approximate) expression. For either of the two expressions, Eq. (21) gives

$$\gamma(t) = \frac{1}{2} \tau_B^{-1} \left[ \frac{g}{N_{df}} \frac{T_o}{\mathcal{T}(t)} - 1 \right]. \quad (56)$$

Inserting into Eq. (18) shows that the equation of motion corresponding to the Berendsen thermostat is

$$\ddot{\mathbf{r}}_i(t) = m_i^{-1} \mathbf{F}_i(t) - \frac{1}{2} \tau_B^{-1} \left[ \frac{g}{N_{df}} \frac{T_o}{\mathcal{T}(t)} - 1 \right] \dot{\mathbf{r}}_i(t). \quad (57)$$

In practice,  $\tau_B$  is used as an empirical parameter to adjust the strength of the coupling. Its value should be chosen in an appropriate range. On the one hand, a too large value (loose coupling) may cause a systematic temperature drift. Indeed, in the limit  $\tau_B \rightarrow \infty$ , the Berendsen thermostat is inactive leading to the MD equation of motion, which samples a microcanonical ensemble. Thus, the temperature fluctuations will increase with  $\tau_B$  until they reach the appropriate value for a microcanonical ensemble. However, they will never reach the appropriate value for a canonical ensemble, which are larger. For large values of  $\tau_B$ , a systematic energy (and thus temperature) drift due to numerical errors may also occur, just as in MD. On the other hand, a too small value (tight coupling) will cause unrealistically low temperature fluctuations. Indeed, the special case of the Berendsen algorithm (Eq. (55)) with  $\tau_B = \Delta t$  is the Woodcock thermostat (Eq. (49)), which does not allow for temperature fluctuations. This shows that the limiting case of the Berendsen equation of motion for  $\tau_B \rightarrow 0$  is the Woodcock/Hoover-Evans equation of motion. Values of  $\tau_B \approx 0.1$  ps are typically used in MD simulations of condensed-phase systems. Note, however, that this choice generally leads to fluctuations close to those of the microcanonical ensemble. With this choice, the Berendsen thermostat merely removes energy drifts from a MD simulation, without significantly altering the ensemble sampled (and thus rather plays the role of an ergostat algorithm).

The Berendsen equation of motion is smooth and deterministic, but time-irreversible. The ensemble generated by the Berendsen equations of motion is not a canonical ensemble ([109]; see Appendix). Only in the limit  $\tau_B \rightarrow 0$  (or in practice  $\tau_B = \Delta t$ ), when the Berendsen equation of motion becomes identical to the Woodcock/Hoover-Evans equation of motion, does it generate a canonical distribution of configurations. In the limit  $\tau_B \rightarrow \infty$ , the microcanonical ensemble is recovered. All intermediate situations correspond to the sampling of an unusual “weak-coupling” ensemble<sup>13</sup>, which is neither canonical nor microcanonical [109]. The reason why the Berendsen thermostat systematically (for all values of  $\tau_B$ ) underestimates temperature fluctuations (and thus does not give the correct thermodynamical ensemble) resides in the transition from Eq. (26) to Eq. (53), corresponding to the neglect of the stochastic contribution to these fluctuations on the microscopic timescale.

### 3.6

#### Temperature Relaxation by the Extended-System Method

The idea of a thermostat based on an extended-system method is due to Nosé [61]. A simpler formulation of the equations of motion was later proposed simultaneously<sup>14</sup>

<sup>13</sup> Assuming a relationship of the form of Eq. (115), it is possible to derive the configurational partition function of the weak-coupling ensemble as a function of  $\alpha$  ([109]; see Appendix). The limiting cases  $\alpha = 0$  ( $\tau_B \rightarrow 0$ ; canonical) and  $\alpha = 1$  ( $\tau_B \rightarrow \infty$ ; microcanonical) are reproduced. Note that the Haile-Gupta thermostat generates configurations with the same probability distribution as the Berendsen thermostat with  $\alpha = 1/2$ .

<sup>14</sup> Eqs. (2.24) and (2.25) in [53] are equivalent to Eq. (6) in [63], provided that one identifies  $\zeta = \dot{s}'/s'$ . These equations are Eqs. (78) and (79) of the present article.

by Nosé [53] and Hoover [63], so that this algorithm is generally referred to as the Nosé-Hoover thermostat.

The idea behind the original Nosé [61] algorithm is to extend the real system by addition of an artificial  $(N_{df} + 1)^{th}$  dynamical variable  $\tilde{s}$  (associated with a “mass”  $Q > 0$ , with actual units of energy  $\times$  (time)<sup>2</sup>, as well as a velocity  $\dot{\tilde{s}}$ , and satisfying  $\tilde{s} > 0$ ) that plays the role of a time-scaling parameter<sup>15</sup>. More precisely, the timescale in the extended system is stretched by the factor  $\tilde{s}$ , i.e., an infinitesimal time interval  $d\tilde{t}$  at time  $\tilde{t}$  in the extended system corresponds to a time interval  $dt = \tilde{s}^{-1}(\tilde{t}) d\tilde{t}$  in the real system<sup>16</sup>. Consequently, although the atomic coordinates are identical in both systems, the extended-system velocities are amplified by a factor  $\tilde{s}^{-1}$  compared to the real-system velocities, i.e.

$$\tilde{\mathbf{r}} = \mathbf{r}, \quad \dot{\tilde{\mathbf{r}}} = \tilde{s}^{-1} \dot{\mathbf{r}}, \quad \tilde{s} = s, \quad \text{and} \quad \dot{\tilde{s}} = \tilde{s}^{-1} \dot{s}. \quad (58)$$

The Lagrangian for the extended system is chosen to be

$$\mathcal{L}_e(\tilde{\mathbf{r}}, \dot{\tilde{\mathbf{r}}}, \tilde{s}, \dot{\tilde{s}}) = \frac{1}{2} \sum_{i=1}^N m_i \tilde{s}^2 \dot{\tilde{\mathbf{r}}}_i^2 - \mathcal{U}(\tilde{\mathbf{r}}) + \frac{1}{2} Q \dot{\tilde{s}}^2 - g k_B T_o \ln \tilde{s}, \quad (59)$$

where  $g$  is equal to the number of degrees of freedom  $N_{df}$  in the real system, possibly increased by one (see below). The first two terms of the Lagrangian represent the kinetic energy minus the potential energy of the real system (the extended-system velocities are multiplied by  $\tilde{s}$  to recover the real-system ones). The third and fourth terms represent the kinetic energy minus the potential energy associated with the  $\tilde{s}$ -variable. The form of the last term is chosen to ensure that the algorithm produces a canonical ensemble of microstates (see below). The Lagrangian equations of motion derived from Eq. (59) read

$$\ddot{\tilde{\mathbf{r}}}_i = m_i^{-1} \tilde{s}^{-2} \tilde{\mathbf{F}}_i - 2 \tilde{s}^{-1} \dot{\tilde{s}} \dot{\tilde{\mathbf{r}}}_i \quad (60)$$

for the physical variables, and<sup>17</sup>

<sup>15</sup> All extended-system variables will be noted with a tilde overscript, to distinguish them from the real-system variables (the real-system variable corresponding to  $\tilde{s}$  is noted  $s$ ).

<sup>16</sup> To simplify the notation, explicit dependence of the different functions on time is generally omitted in this section. The time-dependent functions are  $\tilde{\mathbf{F}}(\tilde{t})$ ,  $\tilde{\mathbf{r}}(\tilde{t})$ ,  $\tilde{\mathbf{p}}(\tilde{t})$ ,  $\tilde{s}(\tilde{t})$  and  $\tilde{p}_s(\tilde{t})$  (together with their first and second time derivatives) for the extended system, and  $\mathbf{F}(t)$ ,  $\mathbf{r}(t)$ ,  $\mathbf{p}(t)$ ,  $s(t)$ ,  $p_s(t)$ ,  $\gamma(t)$  and  $\mathcal{T}(t)$  (together with their first and second time derivatives) for the real system. The dot overscripts indicate differentiation with respect to the extended-system time  $\tilde{t}$  for the extended-system variables, and with respect to the real-system time  $t$  for the real-system variables.

<sup>17</sup> Because the time-average of the time-derivative of a bounded quantity (for example,  $\dot{\tilde{s}}$ ) vanishes, this equation implies

$$\left\langle \tilde{s}^{-1} \sum_{i=1}^N m_i \tilde{s}^2 \dot{\tilde{\mathbf{r}}}_i^2 \right\rangle_{e,v} = \left\langle \tilde{s}^{-1} \sum_{i=1}^N m_i \dot{\mathbf{r}}_i^2 \right\rangle_{e,v} = \langle \tilde{s}^{-1} \rangle_{e,v} g k_B T_o, \quad (61)$$

$$\ddot{\tilde{s}} = Q^{-1} \tilde{s}^{-1} \left( \sum_{i=1}^N m_i \tilde{s}^2 \dot{\tilde{\mathbf{r}}}_i^2 - g k_B T_o \right) \quad (63)$$

for the  $\tilde{s}$ -variable. These two second-order differential equations can be discretized (based on a timestep  $\Delta\tilde{t}$  in the extended system) and integrated simultaneously during the simulation. The successive values of  $\mathbf{r} = \tilde{\mathbf{r}}$  and  $\dot{\mathbf{r}} = \tilde{s} \dot{\tilde{\mathbf{r}}}$  describe the evolution of the atomic coordinates and velocities in the real system at successive time points separated by  $\Delta t = \tilde{s}^{-1}(\tilde{t}) \Delta\tilde{t}$ . This means that the algorithm implemented in this form (referred to as virtual-time sampling) leads to sampling of the real-system trajectory at uneven time intervals. A trajectory with real-time sampling can be achieved either by interpolation at evenly spaced real-time points of the coordinates and velocities issued from virtual-time sampling, or by rewriting the equations of motion in terms of the real-system variables (Nosé-Hoover formulation [53, 63]; see below).

As an alternative to Eqs. (60) and (63), the Nosé equations of motion can be equivalently formulated using a Hamiltonian formalism. In this case, the extended-system conjugate momenta  $\tilde{\mathbf{p}}_i$  and  $\tilde{p}_s$  associated with the physical degrees of freedom and with the  $\tilde{s}$ -variable are defined as

$$\tilde{\mathbf{p}}_i = \frac{\partial \mathcal{L}_e(\tilde{\mathbf{r}}, \dot{\tilde{\mathbf{r}}}, \tilde{s}, \dot{\tilde{s}})}{\partial \dot{\tilde{\mathbf{r}}}} = m_i \tilde{s}^2 \dot{\tilde{\mathbf{r}}}_i \quad \text{and} \quad \tilde{p}_s = \frac{\partial \mathcal{L}_e(\tilde{\mathbf{r}}, \dot{\tilde{\mathbf{r}}}, s, \dot{\tilde{s}})}{\partial \dot{\tilde{s}}} = Q \dot{\tilde{s}}. \quad (64)$$

Comparison with the corresponding real-system momenta<sup>18</sup>, defined as

$$\mathbf{p}_i = m_i \dot{\mathbf{r}}_i \quad \text{and} \quad p_s = Q s^{-2} \dot{s}, \quad (66)$$

shows that the extended-system momenta are amplified by a factor  $\tilde{s}$  compared to the real-system momenta. The extended-system Hamiltonian corresponding to the Lagrangian of Eq. (59) can now be written

where  $\langle \dots \rangle_{e,v}$  denotes ensemble averaging over the extended system (with virtual-time sampling). Considering Eqs. (8) and (10), this result already suggests that the average temperature of the real system coincides with  $T_o$ . Using Eq. (101) and  $\mathbf{p}_i = m_i \dot{\mathbf{r}}_i$ , the above equation can indeed be rewritten

$$\langle \mathcal{T} \rangle_{e,r} = \left\langle \frac{1}{k_B N_{df}} \sum_{i=1}^N m_i \dot{\mathbf{r}}_i^2 \right\rangle_{e,r} = \frac{g}{N_{df}} T_o, \quad (62)$$

where  $\langle \dots \rangle_{e,r}$  denotes ensemble averaging over the extended system (with real-time sampling). From Eq. (102), this latter ensemble average can be identified with a canonical one when  $g = N_{df}$ .

<sup>18</sup> In the absence of thermostat (i.e., when the variable  $s$  is uncoupled from the system), the real-system Lagrangian may be written

$$\mathcal{L}(\mathbf{r}, \dot{\mathbf{r}}, s, \dot{s}) = \frac{1}{2} \sum_{i=1}^N m_i \dot{\mathbf{r}}_i^2 - \mathcal{U}(\mathbf{r}) + \frac{1}{2} Q s^{-2} \dot{s}^2. \quad (65)$$

The momenta of Eq. (66) are derived from this Lagrangian.

$$\mathcal{H}_e(\tilde{\mathbf{r}}, \tilde{\mathbf{p}}, \tilde{s}, \tilde{p}_s) = \frac{1}{2} \sum_{i=1}^N m_i^{-1} \tilde{s}^{-2} \tilde{\mathbf{p}}_i^2 + \mathcal{U}(\tilde{\mathbf{r}}) + \frac{1}{2} Q^{-1} \tilde{p}_s^2 + g k_B T_o \ln \tilde{s}. \quad (67)$$

This function is a constant of the motion and evaluates to  $E_e$ , the total energy of the extended system. The corresponding Hamiltonian equations of motion read

$$\dot{\tilde{\mathbf{p}}}_i = -\tilde{\mathbf{F}}_i \quad \text{and} \quad \dot{\tilde{\mathbf{r}}}_i = m_i^{-1} \tilde{s}^{-2} \tilde{\mathbf{p}}_i \quad (68)$$

for the physical variables, and

$$\dot{\tilde{p}}_s = \tilde{s}^{-1} \left( \sum_{i=1}^N m_i^{-1} \tilde{s}^{-2} \tilde{\mathbf{p}}_i^2 - g k_B T_o \right) \quad \text{and} \quad \dot{\tilde{s}} = Q^{-1} \tilde{p}_s \quad (69)$$

for the  $\tilde{s}$ -variable.

The Nosé equations of motion sample a microcanonical ensemble in the extended system  $(\tilde{\mathbf{r}}, \tilde{\mathbf{p}}, \tilde{t})$ , with a constant total energy  $E_e$ . However, the energy of the real system  $(\mathbf{r} = \tilde{\mathbf{r}}, \mathbf{p} = \tilde{s}^{-1} \tilde{\mathbf{p}}, t = \int \tilde{s}^{-1} d\tilde{t})$  is not constant. Accompanying the fluctuations of  $\tilde{s}$ , heat transfers occur between the system and a heat bath, which regulate the system temperature. As will be seen below (Eq. (78) where  $\gamma = \tilde{\gamma}$  can be identified with  $\dot{\tilde{s}}$ ), the sign of  $\dot{\tilde{s}}$  determines the direction of the heat flow. When  $\dot{\tilde{s}} < 0$ , heat flows into the real system. When  $\dot{\tilde{s}} > 0$ , heat flows out of the real system. It can be proved ([61]; see Appendix) that the Nosé equations of motion sample a canonical ensemble of microstates in the real system, provided that  $g = N_{df} + 1$  (virtual-time sampling) or  $g = N_{df}$  (real-time sampling), and that  $Q$  is finite, this irrespective of the actual values of  $Q$  and  $E_e$ . If the potential energy  $\mathcal{U}(\tilde{\mathbf{r}})$  does not involve terms giving rise to external forces, the total linear and angular momenta associated with the physical degrees of freedom in the extended system, namely

$$\sum_{i=1}^N \tilde{\mathbf{p}}_i = \sum_{i=1}^N m_i \tilde{s}^2 \dot{\tilde{\mathbf{r}}}_i \quad \text{and} \quad \sum_{i=1}^N \tilde{\mathbf{r}}_i \times \tilde{\mathbf{p}}_i = \sum_{i=1}^N m_i \tilde{s}^2 \tilde{\mathbf{r}}_i \times \dot{\tilde{\mathbf{r}}}_i, \quad (70)$$

are also conserved. Because  $\dot{\tilde{\mathbf{r}}}_i = \tilde{s}^{-1} \dot{\mathbf{r}}_i$  (Eq. (58)), this implies that the total linear and angular momenta of the real system are linearly related to  $\tilde{s}^{-1}$  and thus not conserved, unless they vanish. This should be the case if the components of the real velocities  $\dot{\mathbf{r}}_i^o$  along the external degrees of freedom have been removed by application of Eq. (11).

The Nosé equations of motion are smooth, deterministic and time-reversible. However, because the time-evolution of the variable  $\tilde{s}$  is described by a second-order equation (Eq. (63)), heat may flow in and out of the system in an oscillatory fashion [110], leading to nearly-periodic temperature fluctuations. However, from the discussion of Sects. 3 and 3.2, the dynamics of the temperature evolution should not be oscillatory, but rather result from a combination of stochastic fluctuations and exponential relaxation. At equilibrium, the approximate frequency of these oscillations can be estimated in the following way [61]. Consider small deviations  $\delta\tilde{s}$  of  $\tilde{s}$  away from the equilibrium value  $\langle \tilde{s} \rangle_{e,r}$ , where  $\langle \dots \rangle_{e,r}$  denotes ensemble averaging over the

extended system with real-time sampling. Assuming that the interatomic forces have a weak effect on the temperature dynamics (as, e.g., in a perfect gas), the quantity  $\sum_{i=1}^N m_i^{-1} \tilde{\mathbf{p}}_i^2$ , which is solely altered by the action of the forces (Eq. (68)), can be assumed nearly constant. In this case, one may write (with  $g = N_{df}$ )

$$\frac{1}{2} \sum_{i=1}^N m_i \tilde{s}^2 \dot{\tilde{\mathbf{r}}}_i^2 = \frac{1}{2} \sum_{i=1}^N m_i^{-1} \tilde{s}^{-2} \tilde{\mathbf{p}}_i^2 \approx \frac{1}{2} \langle \tilde{s} \rangle_{e,r}^2 \tilde{s}^{-2} N_{df} k_B T_o. \quad (71)$$

Using this result, Eq. (63) may be written (for small  $\delta\tilde{s}$ )

$$\delta\ddot{\tilde{s}} = N_{df} k_B T_o Q^{-1} \tilde{s}^{-1} (\langle \tilde{s} \rangle_{e,r}^2 \tilde{s}^{-2} - 1) \approx -2 N_{df} k_B T_o Q^{-1} \langle \tilde{s} \rangle_{e,r}^{-2} \delta\tilde{s}. \quad (72)$$

This corresponds to a harmonic oscillator with frequency

$$\nu = (2\pi)^{-1} (2 N_{df} k_B T_o)^{1/2} Q^{-1/2} \langle \tilde{s} \rangle_{e,r}^{-1}, \quad (73)$$

where<sup>19</sup>

$$\langle \tilde{s} \rangle_{e,r} = \left( \frac{N_{df}}{N_{df} + 1} \right)^{1/2} \left\langle \exp \left\{ (N_{df} k_B T_o)^{-1} [E_e - \mathcal{H}(\mathbf{r}, \mathbf{p})] \right\} \right\rangle, \quad (75)$$

(...) denoting a canonical ensemble average. Comparison of the approximate oscillation frequency  $\nu$  with the inverse of the temperature relaxation time  $\zeta_T$  (Eq. (26)) may guide the choice of parameters  $Q$  and  $E_e$  leading to a realistic timescale of temperature fluctuations. If the number of degrees of freedom is large and  $E_e$  is close to  $\langle \mathcal{H}(\mathbf{r}, \mathbf{p}) \rangle$ , the average canonical energy corresponding to the real system, Eq. (75) becomes  $\langle \tilde{s} \rangle_{e,r} = 1$ . The latter condition will be satisfied if the algorithm is initiated using real-system velocities taken from a Maxwell-Boltzmann distribution (Eq. (25)), together with  $\tilde{s}(0) = 1$  and  $\dot{\tilde{s}}(0) = 0$ . In this case, comparing Eq. (73) with Eq. (26) allows to identify<sup>20</sup>  $1.2(2N_{df} k_B T_o)^{-1/2} Q^{1/2}$  with the temperature relaxation time  $\zeta_T$ , i.e., to suggest  $Q \approx 1.4 N_{df} k_B T_o \zeta_T^2$  as an appropriate value for simulations. In fact, it may make sense to use an effective relaxation time

$$\tau_{NH} = (N_{df} k_B T_o)^{-1/2} Q^{1/2} \quad (76)$$

instead of the (less intuitive) effective mass  $Q$  to characterize the strength of the coupling to the heat bath.

<sup>19</sup> Considering Eqs. (98) and (101), one has

$$\langle \tilde{s} \rangle_{e,r} = \frac{\int d\mathbf{p} \int d\mathbf{r} \int d\tilde{p}_s \int d\tilde{s} \tilde{s}^{N_{df}+1} \delta[\tilde{s} - \tilde{s}_o]}{\int d\mathbf{p} \int d\mathbf{r} \int d\tilde{p}_s \int d\tilde{s} \tilde{s}^{N_{df}} \delta[\tilde{s} - \tilde{s}_o]}. \quad (74)$$

Inserting Eq. (94), integrating over  $\tilde{p}_s$  for the numerator and denominator, and setting  $g = N_{df}$  leads to Eq. (75).

<sup>20</sup> Because  $\cos(1.2) \approx \exp(-1)$ , it is assumed here that the exponential relaxation time is approximately given by  $1.2/(2\pi)\nu^{-1}$ .

The use of an extended system with a stretched timescale is not very intuitive, and the sampling of a trajectory at uneven time intervals is rather impractical for the investigation of the dynamical properties of a system. However, as shown by Nosé [53] and Hoover [63], the Nosé equations of motion can be reformulated in terms of real-system variables (together with real-time sampling) so as to avoid these problems. The transformation from extended-system to real-system variables is achieved through

$$\begin{aligned}
 s &= \tilde{s}, \quad \dot{s} = \tilde{s}\dot{\tilde{s}}, \quad \ddot{s} = \tilde{s}^2\ddot{\tilde{s}} + \tilde{s}\dot{\tilde{s}}^2, \\
 \mathbf{r} &= \tilde{\mathbf{r}}, \quad \dot{\mathbf{r}} = \tilde{s}\dot{\tilde{\mathbf{r}}}, \quad \ddot{\mathbf{r}} = \tilde{s}^2\ddot{\tilde{\mathbf{r}}} + \tilde{s}\dot{\tilde{\mathbf{r}}}^2, \\
 p_s &= \tilde{s}^{-1}\tilde{p}_s, \quad \dot{p}_s = \dot{\tilde{p}}_s - Q^{-1}\tilde{s}^{-1}\tilde{p}_s^2, \\
 \mathbf{p} &= \tilde{s}^{-1}\tilde{\mathbf{p}}, \quad \dot{\mathbf{p}} = \dot{\tilde{\mathbf{p}}} - Q^{-1}\tilde{s}^{-1}\tilde{\mathbf{p}}_s\tilde{\mathbf{p}}, \\
 &\text{and } \mathbf{F} = \tilde{\mathbf{F}}.
 \end{aligned} \tag{77}$$

Because  $dt = \tilde{s}^{-1}d\tilde{t}$ , these equations are derived using  $d/dt = \tilde{s}d/d\tilde{t}$ , together with the definition of the real-system (Eq. (66)) and extended-system (Eq. (64)) momenta. Based on these expressions, and defining the quantity  $\gamma = s^{-1}\dot{s} = Q^{-1}sp_s$ , the Lagrangian equations of motion (Eqs. (60) and (63)) can be rewritten

$$\ddot{\mathbf{r}}_i = m_i^{-1}\mathbf{F}_i - \gamma\dot{\mathbf{r}}_i \tag{78}$$

and

$$\dot{\gamma} = -k_B N_{df} Q^{-1} \mathcal{T} \left( \frac{g}{N_{df}} \frac{T_o}{\mathcal{T}} - 1 \right). \tag{79}$$

Note that the variable  $\gamma$  is a real-system variable (i.e., a function of the real-system time  $t$ ). The equivalent extended-system variable is  $\tilde{\gamma} = \gamma = \dot{\tilde{s}}$ . If the effective coupling time  $\tau_{NH}$  (Eq. (76)) is used instead of  $Q$ , Eq. (79) becomes

$$\dot{\gamma} = -\tau_{NH}^{-2} \frac{\mathcal{T}}{T_o} \left( \frac{g}{N_{df}} \frac{T_o}{\mathcal{T}} - 1 \right). \tag{80}$$

In a similar way, the Hamiltonian equations of motion (Eqs. (68) and (69)) can be rewritten

$$\dot{\mathbf{p}}_i = \mathbf{F}_i - \gamma\mathbf{p}_i \quad \text{and} \quad \dot{\mathbf{r}}_i = m_i^{-1}\mathbf{p}_i \tag{81}$$

and

$$\dot{p}_s = -k_B N_{df} \mathcal{T} s^{-1} \left( \frac{g}{N_{df}} \frac{T_o}{\mathcal{T}} - 1 \right) - \gamma p_s \quad \text{and} \quad \dot{s} = \gamma s. \tag{82}$$

Equation (81) is easily identified with Eq. (78), and Eq. (82) with Eq. (79). The variable  $s$  is absent from the first set of equations, i.e., its dynamics has been decoupled. In the second set of equations, the evolution of the real-system variables is independent of the actual value of  $s$ , i.e., any choice of the initial value  $s(0)$  will lead to the

same dynamics. Finally, it should be stressed that these equations of motion are no longer Hamiltonian, although the quantity (Eq. (67))

$$H(\mathbf{r}, \mathbf{p}, s, p_s) = \frac{1}{2} \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 + \mathcal{U}(\mathbf{r}) + \frac{1}{2} Q^{-1} s^2 p_s^2 + g k_B T_o \ln s \quad (83)$$

is still a constant of the motion (evaluating to  $E_e$ ). On the other hand, Eqs. (78) and (79) are still Lagrangian, the corresponding Lagrangian being

$$\mathcal{L}(\mathbf{r}, \dot{\mathbf{r}}, s, \dot{s}) = s [ \mathcal{L}_e(\mathbf{r}, s^{-1} \dot{\mathbf{r}}, s, s^{-1} \dot{s}) + E_e ] . \quad (84)$$

To obtain the corresponding Lagrangian equations of motion,  $E_e$  is initially treated as a constant and later expanded using Eq. (83). It appears that Eq. (78) has exactly the form of Eq. (18), i.e., the Nosé-Hoover thermostat has one equation of motion in common with both the Woodcock/Hoover-Evans and the Berendsen thermostats. However, in contrast to these other thermostats where the value of  $\gamma$  was uniquely determined by the instantaneous microstate of the system (compare Eq. (79) with Eqs. (45), (50), and (56)),  $\gamma$  is here a dynamical variable which derivative (Eq. (79)) is determined by this instantaneous microstate. Accompanying the fluctuations of  $\gamma$ , heat transfers occur between the system and a heat bath, which regulate the system temperature. Because  $\gamma = s^{-1} \dot{s} = \tilde{\gamma} = \dot{\tilde{s}}$  (Eq. (77)), the variable  $\gamma$  in the Nosé-Hoover formulation plays the same role as  $\dot{\tilde{s}}$  in the Nosé formulation. When  $\gamma$  (or  $\dot{\tilde{s}}$ ) is negative, heat flows from the heat bath into the system due to Eq. (78) (or Eq. (60)). When the system temperature increases above  $T_o$ , the time derivative of  $\gamma$  (or  $\dot{\tilde{s}}$ ) becomes positive due to Eq. (79) (or Eq. (63)) and the heat flow is progressively reduced (feedback mechanism). Conversely, when  $\gamma$  (or  $\dot{\tilde{s}}$ ) is positive, heat is removed from the system until the system temperature decreases below  $T_o$  and the heat transfer is slowed down.

The second- and first-order Eqs. (78) and (79) can be discretized (based on a timestep  $\Delta t$  in the real system) and integrated simultaneously during the simulation. Note that the Nosé thermostat with  $g = N_{df} + 1$  and virtual-time sampling and the Nosé-Hoover thermostat with  $g = N_{df}$  formally sample the same trajectory. In practice, however, the trajectories are sampled at different real-system time points and will numerically diverge for finite timestep sizes. It can be proved ([63]; see Appendix) that the Nosé-Hoover equations of motion sample a canonical ensemble in the real system provided that  $g = N_{df}$  and that  $Q$  is finite, this irrespective of the actual values of  $Q$  and  $E_e$ . Though interesting, such a proof is not really necessary since the Nosé and Nosé-Hoover formalisms are equivalent. As a by-product of this proof, it is shown that the probability distribution of the  $\gamma$  variable is a Gaussian of width determined by the parameter  $Q$  (Eq. (112)). The Nosé-Hoover equations of motion are smooth, deterministic and time-reversible. However, just as the Nosé algorithm, Nosé-Hoover dynamics may lead to temperature oscillations.

In both algorithms, Some care must be taken in the choice of the fictitious mass  $Q$  and extended-system energy  $E_e$ . On the one hand, too large values of  $Q$  (loose coupling) may cause a poor temperature control. Indeed, the limiting case of the

Nosé-Hoover thermostat with  $Q \rightarrow \infty$  and  $\gamma(0) = 0$  is MD, which generates a microcanonical ensemble. Although any finite (positive) mass is sufficient to guarantee in principle the generation of a canonical ensemble, if  $Q$  is too large, the canonical distribution will only be obtained after very long simulation times. In this case, systematic energy drifts due to accumulation of numerical errors may interfere with the thermostatization. On the other hand, too small values (tight coupling) may cause high-frequency temperature oscillations (Eq. (73)) leading to the same effect. This is because if the  $\tilde{s}$  variable oscillates at a very high frequency, it will tend to be off-resonance with the characteristic frequencies of the real system, and effectively decouple from the physical degrees of freedom (slow exchange of kinetic energy). The choice of the parameters  $Q$  and  $E_e$  can be guided by comparison of the frequency  $\nu$  (Eq. (73)) with the inverse of the temperature relaxation time  $\zeta_T$  (Eq. (26)). Note that if a simulation is initiated with  $s(0) = 1$  and  $\gamma(0) = 0$ , which seems the most reasonable choice, the value of  $E_e$  will match the initial energy of the real system. The numerical integration of the Nosé and Nosé-Hoover equations will not be discussed here. A number of alternative schemes have been proposed in the literature [111, 112, 113, 114, 90].

The constant-temperature Woodcock/Hoover-Evans equation of motion can be retrieved from the the Nosé-Hoover formalism by a slight modification of the extended-system Hamiltonian. This is done by introducing the constraints

$$\tilde{s} = (gk_B T_o)^{-1/2} \left( \sum_{i=1}^N m_i^{-1} \tilde{\mathbf{p}}_i^2 \right)^{1/2} \quad \text{and} \quad \tilde{p}_s = 0 \quad (85)$$

into Eq. (67), leading to the modified Hamiltonian

$$\mathcal{H}_c(\tilde{\mathbf{r}}, \tilde{\mathbf{p}}) = \frac{1}{2} g k_B T_o + \mathcal{U}(\tilde{\mathbf{r}}) + \frac{1}{2} g k_B T_o \ln \left[ (g k_B T_o)^{-1} \sum_{i=1}^N m_i^{-1} \tilde{\mathbf{p}}_i^2 \right]. \quad (86)$$

The corresponding Hamiltonian equations of motion for the physical variables in the extended system are still given by Eq. (68). It can be proved ([61]; see Appendix) that these equations of motion sample a canonical ensemble of configurations in the real system ( $\mathbf{r} = \tilde{\mathbf{r}}, \dot{\mathbf{r}} = \tilde{s}^{-1} \tilde{\mathbf{p}}, t = \int \tilde{s}^{-1} d\tilde{t}$ ) with  $\tilde{s}$  given by Eq. (85), provided that  $g = N_{df}$  (virtual-time sampling) or  $g = N_{df} - 1$  (real-time sampling), irrespective of the constant value  $E_e$  of  $\mathcal{H}_c$ . To show that this situation matches the Woodcock/Hoover-Evans equation of motion, the equation of motion must be rewritten in terms of real-system variables. Evaluating  $\dot{\tilde{s}}$  based on Eq. (85) gives

$$\dot{\tilde{s}} = (g k_B T_o)^{-1} \tilde{s}^{-1} \sum_{i=1}^N m_i^{-1} \tilde{\mathbf{p}}_i \cdot \dot{\tilde{\mathbf{p}}}_i. \quad (87)$$

Applying the transformations of Eq. (77), setting  $\gamma = s^{-1} \dot{s}$ , and inserting Eq. (68) for  $\dot{\tilde{\mathbf{p}}}$ , it is easily seen that the equation of motion in terms of the real-system variables is Eq. (78) together with

$$\gamma = (gk_B T_o)^{-1} \sum_{i=1}^N \dot{\mathbf{r}}_i \cdot \mathbf{F}_i, \quad (88)$$

which is identical to the corresponding factor for the Woodcock (Eq. (50)) and Hoover-Evans (Eq. (45), when  $\mathcal{T}(0) = \frac{g}{N_{df}} T_o$ ) equations of motion. This also shows that the appropriate choice for  $g$  so as to generate a canonical ensemble of configurations using either of these two thermostats is  $g = N_{df} - 1$ .

If, in addition to incorporating the constraint of Eq. (85), the Hamiltonian is changed to

$$\mathcal{H}_h(\tilde{\mathbf{r}}, \tilde{\mathbf{p}}) = \left( gk_B T_o \sum_{i=1}^N m_i^{-1} \tilde{\mathbf{p}}_i^2 \right)^{1/2} + \mathcal{U}(\tilde{\mathbf{r}}), \quad (89)$$

the corresponding Hamiltonian equations of motion for the physical variables in the extended system become

$$\dot{\tilde{\mathbf{p}}}_i = \tilde{\mathbf{F}}_i \quad \text{and} \quad \dot{\tilde{\mathbf{r}}}_i = m_i^{-1} \tilde{s}^{-1} \tilde{\mathbf{p}}_i. \quad (90)$$

Setting  $\dot{\mathbf{r}}_i = \dot{\tilde{\mathbf{r}}}_i$  and  $\mathbf{p}_i = m_i \dot{\tilde{\mathbf{r}}}_i$ , one recovers (using Eq. (85) and identifying  $\dot{\mathbf{r}}'_i = m_i^{-1} \tilde{\mathbf{p}}_i$ ) the Haile-Gupta equations of motion (Eq. (52)). Note that  $\tilde{s}$  no longer acts as a scaling parameter and the extended-system Lagrangian has been changed, so that Eqs. (58) and (64) no longer apply. It can be proved ([53]; see Appendix) that this equation of motion does not sample a canonical ensemble of configurations in the real system, irrespective of the choice of  $g$ .

### 3.7

#### Generalizations of the Previous Methods

An interesting extension of the SD thermostat (Sect. 3.2) is the so-called dissipative-particle-dynamics (DPD) thermostat [115, 116, 117, 118]. This scheme retains a key advantage of the SD thermostat (shared with the Andersen thermostat), namely that it couples atomic velocities to the heat bath on a local basis (as opposed to the global coupling applied by all other thermostats discussed in this article). Local coupling leads to an intrinsically more efficient thermostatization and in turn, permits the use of longer timesteps to integrate the equations of motion (in applications where this timestep is not further limited by the curvature of the interaction function, i.e., when using soft intermolecular potentials). On the other hand, the DPD scheme alleviates two drawbacks of the SD scheme, namely (i) the non-conservation of the system linear and angular momentum, and (ii) the loss of local hydrodynamic correlations between particles. In practice, this is achieved by replacing the frictional and stochastic forces acting on individual atoms in SD (Eq. (17)), by corresponding central pairwise forces acting on atom pairs within a given cutoff distance.

A number of extensions or generalizations of the Nosé or Nosé-Hoover approaches (Sect. 3.6) have also been reported in the literature, following three main directions.

First, more general extended Hamiltonians (including the Nosé Hamiltonian as a particular case) have been shown to also produce canonical phase-space sampling [119, 120, 121, 122, 123, 124, 125, 126, 127]. The additional flexibility offered by these new schemes may be used to overcome the non-ergodic behaviour of the Nosé-Hoover thermostat in the context of small or stiff systems (e.g., single harmonic oscillator) or systems at low temperatures [63, 128, 129, 121, 130, 131, 132]. A number of these variants can indeed produce the correct canonical distribution for a single harmonic oscillator [121, 122, 123, 125, 126]. The most popular of these schemes is probably the Nosé-Hoover chain thermostat [123], where the single thermostating variable  $\gamma$  of the Nosé-Hoover scheme is replaced by a series of variables thermostating each other in sequence.

Second, alternatives have been proposed for the Nosé-Hoover scheme, which are phase-space conserving [133] or even symplectic [127]. One of the latter schemes, referred to as the Nosé-Poincaré thermostat, leads to the same phase-space trajectory as the Nosé-Hoover thermostat with real time sampling, but has the advantage of being Hamiltonian.

Third, generalized equations of motion have been proposed to sample arbitrary (i.e., not necessarily canonical) probability distributions [134, 135, 136, 137]. Such methods can be used, e.g., to optimize the efficiency of conformational searches [134, 135, 137] or for generating Tsallis distributions of microstates [136].

## 4 Practical Considerations

This section briefly mentions two practical aspects related to the use of thermostats in MD simulations of (bio-)molecular systems.

The first problem is encountered when simulating molecular systems involving distinct sets of degrees of freedom with either (i) very different characteristic frequencies or (ii) very different heating rates caused by algorithmic noise. In this case, the joint coupling of all degrees of freedom to a thermostat may lead to different effective temperatures for the distinct subsets of degrees of freedom, due to a too slow exchange of kinetic energy between them. A typical example is the so-called “hot solvent – cold solute problem” in simulations of macromolecules. Because the solvent is more significantly affected by algorithmic noise (e.g., due to the use of an electrostatic cutoff), the coupling of the whole system to a single thermostat may cause the average solute temperature to be significantly lower than the average solvent temperature. A solution to this problem is to couple separately the solute and solvent degrees of freedom to two different thermostats.

The second problem is encountered when using a simulation program that (incorrectly) applies the thermostating directly to the atomic velocities rather than to the internal (peculiar) velocities (Sect. 3). In this case, the system linear and (under vacuum boundary conditions) angular momenta are not conserved, unless they exactly vanish. However, even if these quantities are set to zero at the beginning of a simulation, numerical errors will unavoidably alter these initial values, permitting a flow

of kinetic energy between internal and external degrees of freedom. Unfortunately, it appears that at least some thermostats tend to pump kinetic energy from high-frequency to low-frequency degrees of freedom (thereby violating equipartition). In this case, uniform translational and (under vacuum boundary conditions) rotational motion will tend to build up. For simulations started with vanishing overall momenta, one generally observes a very slow initial rise (often taking nanoseconds) followed by a very sudden burst of translational and rotational kinetic energy. The accumulation of kinetic energy in these degrees of freedom will effectively cool down the internal ones, giving rise to the so-called “flying ice cube effect” [138, 139]. The most obvious remedy to this problem is to remove the overall center of mass motion from the atomic velocities at regular interval during the simulation. However, the application of thermostatization on the basis of internal velocities (Sect. 3) should probably be preferred, because it is more consistent and avoids the introduction of discontinuities in the generated velocity trajectory.

## 5

### Appendix: Phase-Space Probability Distributions

Here, the phase-space probability distributions are derived that correspond to the Woodcock/Hoover-Evans (Sect. 3.4), Haile-Gupta (Sect. 3.4), Berendsen (Sect. 3.5), Nosé (Sect. 3.6) and Nosé-Hoover (Sect. 3.6) thermostats. The derivations are given for all but the Berendsen thermostat, for which the result is merely quoted.

The proof that the Nosé thermostat samples a canonical ensemble of microstates, provided that  $g = N_{df} + 1$  (virtual-time sampling) or  $g = N_{df}$  (real-time sampling), is as follows [53]. The partition function of the microcanonical ensemble generated for the extended system using virtual-time sampling (i.e., using the natural time evolution of the extended system) reads

$$Z_{e,v} = C \int d\tilde{\mathbf{p}} \int d\tilde{\mathbf{r}} \int d\tilde{p}_s \int d\tilde{s} \delta[\mathcal{H}_e(\tilde{\mathbf{r}}, \tilde{\mathbf{p}}, \tilde{s}, \tilde{p}_s) - E_e], \quad (91)$$

where  $C$  is a normalization constant,  $E_e$  the (constant) extended-system energy,  $\delta$  the Dirac delta function, and  $\mathcal{H}_e$  the extended-system Hamiltonian (Eq. (67)). Recasting this expression in terms of the real-system momenta  $\mathbf{p}_i = \tilde{s}^{-1}\tilde{\mathbf{p}}_i$  and substituting  $\mathbf{r} = \tilde{\mathbf{r}}$  leads to

$$Z_{e,v} = C \int d\mathbf{p} \int d\mathbf{r} \int d\tilde{p}_s \int d\tilde{s} \tilde{s}^{N_{df}} \times \delta \left[ \mathcal{H}(\mathbf{r}, \mathbf{p}) + \frac{1}{2} Q^{-1} \tilde{p}_s^2 + g\beta^{-1} \ln \tilde{s} - E_e \right], \quad (92)$$

where  $\mathcal{H}$  is the real-system Hamiltonian, i.e.

$$\mathcal{H}(\mathbf{r}, \mathbf{p}) = \frac{1}{2} \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 + \mathcal{U}(\mathbf{r}). \quad (93)$$

The argument of the delta function in Eq. (92) has a single zero with respect to the  $\tilde{s}$  variable, namely

$$\tilde{s}_o = \exp \left\{ -g^{-1} \beta \left[ \mathcal{H}(\mathbf{r}, \mathbf{p}) + \frac{1}{2} Q^{-1} \tilde{p}_s^2 - E_e \right] \right\}. \quad (94)$$

Using the relationship  $\delta[f(\tilde{s})] = |f'(\tilde{s}_o)|^{-1} \delta[\tilde{s} - \tilde{s}_o]$ , one obtains

$$\begin{aligned} Z_{e,v} &= C g^{-1} \beta \int d\mathbf{p} \int d\mathbf{r} \int d\tilde{p}_s \int d\tilde{s} \tilde{s}^{N_{df}+1} \delta[\tilde{s} - \tilde{s}_o] \\ &= C g^{-1} \beta \int d\mathbf{p} \int d\mathbf{r} \int d\tilde{p}_s \\ &\quad \times \exp \left\{ -(N_{df} + 1) g^{-1} \beta \left[ \mathcal{H}(\mathbf{r}, \mathbf{p}) + \frac{1}{2} Q^{-1} \tilde{p}_s^2 - E_e \right] \right\}. \end{aligned} \quad (95)$$

Integrating with respect to the variable  $\tilde{p}_s$  and using the appropriate Gaussian integral gives

$$Z_{e,v} = C' \int d\mathbf{p} \int d\mathbf{r} \exp[-(N_{df} + 1) g^{-1} \beta \mathcal{H}(\mathbf{r}, \mathbf{p})] \quad (96)$$

with

$$C' = C [(N_{df} + 1) \beta]^{-1/2} (2\pi g Q)^{1/2} \exp[(N_{df} + 1) g^{-1} \beta E_e]. \quad (97)$$

Equation (96) shows that the virtual-time extended-system ensemble average of any quantity  $A$  depending on the real-system coordinates  $\mathbf{r} = \tilde{\mathbf{r}}$  and momenta  $\mathbf{p} = \tilde{s}^{-1} \tilde{\mathbf{p}}$  (and also possibly on  $\tilde{s}$ ), defined as

$$\langle A(\mathbf{r}, \mathbf{p}) \rangle_{e,v} = \frac{\int d\mathbf{p} \int d\mathbf{r} \int d\tilde{p}_s \int d\tilde{s} \tilde{s}^{N_{df}+1} A(\mathbf{r}, \mathbf{p}) \delta[\tilde{s} - \tilde{s}_o]}{\int d\mathbf{p} \int d\mathbf{r} \int d\tilde{p}_s \int d\tilde{s} \tilde{s}^{N_{df}+1} \delta[\tilde{s} - \tilde{s}_o]}, \quad (98)$$

is equivalent to a canonical ensemble average, i.e.

$$\langle A(\mathbf{r}, \mathbf{p}) \rangle_{e,v} = \langle A(\mathbf{r}, \mathbf{p}) \rangle \quad \text{when} \quad g = N_{df} + 1. \quad (99)$$

If real-time sampling is used instead, the probability of any microstate in the ensemble is amplified by a factor  $\tilde{s}^{-1}$  due to the contraction of the timescale. For example, ten microstates at 1 ps interval in the extended system represent 10 ps of real-system time if  $\tilde{s} = 1$  but only 5 ps if  $\tilde{s} = 2$ . Thus, the larger  $\tilde{s}$ , the lower the real-system weight. Consequently, the real-time ensemble average of the quantity  $A$ , defined from Eqs. (98) and (101) as

$$\langle A(\mathbf{r}, \mathbf{p}) \rangle_{e,r} = \frac{\int d\mathbf{p} \int d\mathbf{r} \int d\tilde{p}_s \int d\tilde{s} \tilde{s}^{N_{df}} A(\mathbf{r}, \mathbf{p}) \delta[\tilde{s} - \tilde{s}_o]}{\int d\mathbf{p} \int d\mathbf{r} \int d\tilde{p}_s \int d\tilde{s} \tilde{s}^{N_{df}} \delta[\tilde{s} - \tilde{s}_o]}, \quad (100)$$

satisfies

$$\langle A(\mathbf{r}, \mathbf{p}) \rangle_{e,r} = \langle \tilde{s}^{-1} \rangle_{e,v}^{-1} \langle \tilde{s}^{-1} A(\mathbf{r}, \mathbf{p}) \rangle_{e,v}, \quad (101)$$

irrespective of the value of  $g$ . A straightforward consequence of Eqs. (98) and (101) is that the real-time extended-system ensemble average of any quantity  $A$  is equivalent to a canonical ensemble average, i.e.

$$\langle A(\mathbf{r}, \mathbf{p}) \rangle_{e,r} = \langle A(\mathbf{r}, \mathbf{p}) \rangle \quad \text{when} \quad g = N_{df}. \quad (102)$$

From Eq. (96), the real-system phase-space probability density for the Nosé thermostat (virtual-time sampling) can be written

$$\rho_v(\mathbf{r}, \mathbf{p}) = \frac{\exp[-(N_{df} + 1)g^{-1}\beta\mathcal{H}(\mathbf{r}, \mathbf{p})]}{\int d\mathbf{p} \int d\mathbf{r} \exp[-(N_{df} + 1)g^{-1}\beta\mathcal{H}(\mathbf{r}, \mathbf{p})]}. \quad (103)$$

The proof that the Woodcock/Hoover-Evans thermostat samples a canonical ensemble of configurations provided that  $g = N_{df} - 1$  follows similar lines [53]. It has been seen that this thermostat is identical to the Nosé thermostat with the constraints of Eq. (85) and the Hamiltonian of Eq. (86). In this case, the analog of Eq. (92) reads

$$\begin{aligned} Z_{e,v} &= C \int d\mathbf{p} \int d\mathbf{r} \int d\tilde{s} \tilde{s}^{N_{df}} \delta \left[ g^{-1/2} \beta^{1/2} \tilde{s} \left( \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 \right)^{1/2} - \tilde{s} \right] \\ &\quad \times \delta [\mathcal{H}_c(\mathbf{r}, \tilde{\mathbf{s}}\mathbf{p}) - E_e], \\ &= C g \beta^{-1} \int d\mathbf{p} \delta \left[ \frac{1}{2} \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 - \frac{1}{2} g \beta^{-1} \right] \\ &\quad \times \int d\mathbf{r} \int d\tilde{s} \tilde{s}^{N_{df}-1} \delta \left[ \frac{1}{2} g \beta^{-1} + \mathcal{U}(\mathbf{r}) + g \beta^{-1} \ln \tilde{s} - E_e \right] \\ &= C \int d\mathbf{p} \delta \left[ \frac{1}{2} \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 - \frac{1}{2} g \beta^{-1} \right] \\ &\quad \times \int d\mathbf{r} \int d\tilde{s} \tilde{s}^{N_{df}} \delta \left[ \tilde{s} - \exp \left\{ -g^{-1} \beta \left[ \frac{1}{2} g \beta^{-1} + \mathcal{U}(\mathbf{r}) - E_e \right] \right\} \right] \\ &= C' \int d\mathbf{p} \delta \left[ \frac{1}{2} \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 - \frac{1}{2} g \beta^{-1} \right] \int d\mathbf{r} \exp \left\{ -N_{df} g^{-1} \beta \mathcal{U}(\mathbf{r}) \right\} \end{aligned} \quad (104)$$

The second equality follows from the relationship  $\delta[f(x)] = |f'(x_o)|^{-1} \delta(x - x_o)$ , with  $x = \frac{1}{2} \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2$  and  $x_o = \frac{1}{2} g \beta^{-1}$  and inserting Eqs. (85) and (86). The third equality follows from the relationship  $\delta[f(\tilde{s})] = |f'(\tilde{s}_o)|^{-1} \delta(\tilde{s} - \tilde{s}_o)$ . This partition function is canonical in the configurations if  $g = N_{df}$  (virtual-time sampling). Considering Eq. (101), Eq. (104) shows that the real-time extended-system ensemble average of any quantity  $A$  depending solely on the coordinates is equivalent to a canonical ensemble average if  $g = N_{df} - 1$ . From Eq. (104), the real-system phase-space probability density for the Woodcock/Hoover-Evans thermostat can be written (real-time sampling)

$$\rho_r(\mathbf{r}, \mathbf{p}) = \frac{\delta(\frac{1}{2} \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 - \frac{1}{2} g \beta^{-1}) \exp[-(N_{df} - 1)g^{-1}\beta\mathcal{U}(\mathbf{r})]}{\int d\mathbf{r} \exp[-(N_{df} - 1)g^{-1}\beta\mathcal{U}(\mathbf{r})]}. \quad (105)$$

The derivation of the phase-space probability distribution for the Haile-Gupta thermostat follows similar lines [53]. It has been seen that this thermostat is identical to the Nosé thermostat with the constraints of Eq. (85) and the Hamiltonian of Eq. (89). In this case, the analog of Eq. (104) reads

$$\begin{aligned}
Z_{e,v} &= C \int d\mathbf{p} \int d\mathbf{r} \int d\tilde{s} \tilde{s}^{N_{df}} \delta \left[ g^{-1/2} \beta^{1/2} \tilde{s} \left( \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 \right)^{1/2} - \tilde{s} \right] \\
&\quad \times \delta[\mathcal{H}_h(\mathbf{r}, \tilde{\mathbf{s}}\mathbf{p}) - E_e] \\
&= C g \beta^{-1} \int d\mathbf{p} \delta \left( \frac{1}{2} \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 - \frac{1}{2} g \beta^{-1} \right) \\
&\quad \times \int d\mathbf{r} \int d\tilde{s} \tilde{s}^{N_{df}-1} \delta \left[ g \beta^{-1} \tilde{s} + \mathcal{U}(\mathbf{r}) - E_e \right] \\
&= C' \int d\mathbf{p} \delta \left( \frac{1}{2} \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 - \frac{1}{2} g \beta^{-1} \right) \\
&\quad \times \int d\mathbf{r} \{ g^{-1} \beta [E_e - \mathcal{U}(\mathbf{r})] \}^{N_{df}-1} h[E_e - \mathcal{U}(\mathbf{r})], \tag{106}
\end{aligned}$$

where  $h$  is the Heaviside function. This function arises because  $\tilde{s} \geq 0$ , so that  $E_e < \mathcal{U}(\mathbf{r})$  leads to no solution for  $\tilde{s}$ . Thus, the real-system phase-space probability density corresponding to the Haile-Gupta thermostat (virtual-time sampling) is

$$\rho_v(\mathbf{r}, \mathbf{p}) = \frac{\delta \left( \frac{1}{2} \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 - \frac{1}{2} g \beta^{-1} \right) \{ g^{-1} \beta [E_e - \mathcal{U}(\mathbf{r})] \}^{N_{df}-1} h[E_e - \mathcal{U}(\mathbf{r})]}{\int d\mathbf{r} \{ g^{-1} \beta [E_e - \mathcal{U}(\mathbf{r})] \}^{N_{df}-1} h[E_e - \mathcal{U}(\mathbf{r})]}. \tag{107}$$

Using Eq. (106), it is easily seen that

$$\langle \tilde{s} \rangle_{e,v} = \langle g^{-1} \beta [E_e - \mathcal{U}(\mathbf{r})] \rangle_{e,v}. \tag{108}$$

Thus,  $E_e$  in Eq. (107) can be evaluated as

$$E_e = g \beta^{-1} \langle s \rangle_{e,v} + \langle \mathcal{U}(\mathbf{r}) \rangle_{e,v}. \tag{109}$$

This distribution function is not canonical, irrespective of the value of  $g$  (an alternative derivation of this result can be found in [109]).

The proof that the Nosé-Hoover thermostat samples a canonical ensemble of microstates provided that  $g = N_{df}$  is as follows [63]. Consider the Nosé-Hoover equations of motion, Eqs. (79) and Eq. (81). Because the variables  $\mathbf{r}$ ,  $\mathbf{p}$ , and  $\gamma$  are independent, the flow of the  $(2N_{df} + 1)$ -dimensional probability density  $\rho(\mathbf{r}, \mathbf{p}, \gamma)$  is given by the generalized (non-Hamiltonian) analog of the Liouville equation<sup>21</sup>

$$\frac{\partial \rho}{\partial t} = -\frac{\partial \rho}{\partial \mathbf{r}} \cdot \dot{\mathbf{r}} - \frac{\partial \rho}{\partial \mathbf{p}} \cdot \dot{\mathbf{p}} - \frac{\partial \rho}{\partial \gamma} \cdot \dot{\gamma} - \rho \left[ \frac{\partial}{\partial \mathbf{r}} \cdot \dot{\mathbf{r}} + \frac{\partial}{\partial \mathbf{p}} \cdot \dot{\mathbf{p}} + \frac{\partial}{\partial \gamma} \cdot \dot{\gamma} \right]. \tag{111}$$

<sup>21</sup> The generalized Liouville equation states the conservation of the total number of systems in an ensemble. If  $\Gamma = (\mathbf{q}, \mathbf{p})$ , this conservation law can be written

One can postulate the following extended-system phase-space distribution function

$$\rho_{e,r}(\mathbf{r}, \mathbf{p}, \gamma) = C \exp \left\{ -\beta \left[ \mathcal{U}(\mathbf{r}) + \frac{1}{2} \sum_{i=1}^N m_i^{-1} \mathbf{p}_i^2 + \frac{1}{2} Q \gamma^2 \right] \right\}, \quad (112)$$

where  $C$  is a normalization factor. Using Eqs. (58), (79), and (81) the derivatives involved in Eq. (111) are

$$\begin{aligned} -\frac{\partial \rho}{\partial \mathbf{r}} \cdot \dot{\mathbf{r}} &= \beta \rho \sum_{i=1}^N m_i^{-1} \mathbf{F}_i \cdot \mathbf{p}_i \\ -\frac{\partial \rho}{\partial \mathbf{p}} \cdot \dot{\mathbf{p}} &= -\beta \rho \sum_{i=1}^N m_i^{-1} \mathbf{p}_i \cdot (\mathbf{F}_i - \gamma \mathbf{p}_i) \\ -\frac{\partial \rho}{\partial \gamma} \cdot \dot{\gamma} &= \beta \rho \gamma k_B N_{df} \mathcal{T} \left( \frac{g}{N_{df}} \frac{T_o}{\mathcal{T}} - 1 \right) \\ \rho \frac{\partial}{\partial \mathbf{r}} \cdot \dot{\mathbf{r}} &= 0 \\ \rho \frac{\partial}{\partial \mathbf{p}} \cdot \dot{\mathbf{p}} &= -\rho N_{df} \gamma \\ \rho \frac{\partial}{\partial \gamma} \cdot \dot{\gamma} &= 0. \end{aligned} \quad (113)$$

Using these results and the definition of  $\mathcal{T}$ , it is easily shown that  $\partial \rho / \partial t = 0$  in Eq. (111) provided that  $g = N_{df}$ . This shows that the extended-system phase-space density  $\rho_{e,r}(\mathbf{r}, \mathbf{p}, \gamma)$  is a stationary (equilibrium) solution of Eq. (111) corresponding to the Nosé-Hoover equations of motion. Integrating out the  $\gamma$  variable leads to the real-system phase-space probability density for the Nosé-Hoover thermostat (real-time sampling)

$$\rho_r(\mathbf{r}, \mathbf{p}) = \frac{\exp[-N_{df} g^{-1} \beta \mathcal{H}(\mathbf{r}, \mathbf{p})]}{\int d\mathbf{p} \int d\mathbf{r} \exp[-N_{df} g^{-1} \beta \mathcal{H}(\mathbf{r}, \mathbf{p})]}. \quad (114)$$

which is the canonical probability density if  $g = N_{df}$ . The Nosé-Hoover equations of motion are unique in leading to the stationary extended-system phase-space density of Eq. (112). However, they are not unique in leading to the real-system phase-space density, because the  $\gamma$  distribution (Gaussian in Eq. (112)) is irrelevant here. Finally, it should be mentioned that because the Nosé-Hoover thermostat can be derived from the Nosé thermostat with real-time sampling, the above proof is not really necessary. It is given anyway as a nice illustration of the use of the generalized Liouville equation to derive probability distribution functions for thermodynamical ensembles.

$$\frac{\partial \rho}{\partial t} = -\frac{\partial}{\partial \Gamma} \cdot (\rho \dot{\Gamma}) \quad \text{or} \quad \frac{d\rho}{dt} = -\rho \frac{\partial}{\partial \Gamma} \cdot \dot{\Gamma}. \quad (110)$$

The two forms can be interconverted by expressing  $d\rho/dt$  as a total derivative. If the equations of motion are Hamiltonian, one shows easily that  $d\rho/dt = 0$ . If  $\rho(\Gamma)$  is a stationary (equilibrium) solution, one has  $\partial \rho / \partial t = 0$ .

The derivation of the phase-space probability distribution for the Berendsen thermostat follows again similar lines [109]. The final expression relies on the assumption of a relationship

$$[\langle \mathcal{K}^2 \rangle - \langle \mathcal{K} \rangle^2]^{1/2} = \alpha(\tau_B)[\langle \mathcal{U}^2 \rangle - \langle \mathcal{U} \rangle^2]^{1/2}, \quad (115)$$

between the fluctuations in the kinetic and potential energies in simulations with the Berendsen thermostat. Clearly, such a relationship exists for any system. However, it is unclear whether a common  $\alpha(\tau_B)$  applies to all systems, irrespective of their composition and size. The derivation is then based on finding a stationary solution for the generalized Liouville equation (Eq. (111)). The final (approximate) result is (with  $g = N_{df}$ )

$$\rho_b(\mathbf{r}, \mathbf{p}) = \frac{\rho_p(\mathbf{p}) \exp\{-\beta[\mathcal{U}(\mathbf{r}) - N_{df}^{-1} \alpha \beta^2 [\mathcal{U}(\mathbf{r})^2 - \langle \mathcal{U}(\mathbf{r}) \rangle_b^2]]\}}{\int d\mathbf{p} \rho_p(\mathbf{p}) \int d\mathbf{r} \exp\{-\beta[\mathcal{U}(\mathbf{r}) - N_{df}^{-1} \alpha \beta^2 [\mathcal{U}(\mathbf{r})^2 - \langle \mathcal{U}(\mathbf{r}) \rangle_b^2]]\}}, \quad (116)$$

where  $\rho_p(\mathbf{p})$  is the (unknown) momentum probability distribution. Note that the Haile-Gupta thermostat generates configurations with the same probability distribution as the Berendsen thermostat with  $\alpha = 1/2$  [109].

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