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Coupled Nosé-Hoover Equations of Motions

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Abstract

The Nosé-Hoover equation provides a universal and powerful protocol in computer simulation to realize an equilibrium canonical temperature for a target physical system, and thus fruitful gains are expected in the utility if plural Nosé-Hoover equations are suitably coupled. Here, to realize a *nonequilibrium* temperature, we present coupled Nosé-Hoover equations in which the physical system and a *temperature system* are dynamically coupled. The temperature fluctuations generated by this newly defined temperature system are not ad hoc, and their statistical distribution is completely described. This allows sampling of the physical system that develops at the nonequilibrium temperature. Since the total system is governed by a prescribed distribution, the equilibrium of the physical system is also reconstructed by reweighting. We provide a scheme for setting the distribution of the dynamical inverse temperature as well as statistical relationship between dynamical and physical temperatures. The statistical and dynamical features and the sampling abilities of the current method were demonstrated via distributions, trajectories, dynamical correlations, and free energy landscapes for a model system and a biomolecular system. Our coupled Nosé-Hoover scheme works well, and allows a physical system to be simulated in a nonequilibrium-temperature heat bath with both statistical and arbitrary definitions, which will also facilitate applications to enhanced sampling of physical systems in equilibrium.

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I. INTRODUCTION

The Nosé-Hoover (NH) equation [1, 2] controls the temperature of a target physical system (PS) to describe the equilibrium characterized by the Boltzmann-Gibbs (BG), or canonical, distribution. It is frequently used in molecular dynamics (MD) simulations to reveal the characteristics of PSs in terms of microscopic descriptions [3–5]. Developments of the NH equation include the NH chains [6], Nosé-Poincaré equation [7], Kusnezov-Bulgac-Bauer method [8], configurational temperature NH thermostat [9], and logarithmic oscillators [10]. These methods aim at fast convergence, robust control, efficient sampling, and theoretical developments with respect to Hamiltonian or non-Hamiltonian structures and numerical integration methodologies. Furthermore, these techniques have provided powerful universal protocols in *ab initio* MD [11, 12], nonequilibrium work theorems [13–15], and generalized ensemble methods [16, 17]. Nonequilibrium simulations are also possible, e.g. by appending several thermostats with distinct temperatures for studying heat flow [18, 19].

However, a statistically consistent description for a nonequilibrium physical environment, in which the temperature itself fluctuates locally or globally, has never been provided. Although ad hoc manners for varying the temperature can be designed, they do not provide any information about the probability distribution that the PS obeys, and thus the results are not easily interpreted for comparison with those from experiments.

Utilizing the universal idea of the NH method, here we present a deterministic equation of motion (EOM) describing the PS with a *nonequilibrium temperature*, which is different from the temperature that defines the equilibrium of the PS. The PS interacts with a heat bath in which the temperature, or the inverse temperature, is also a dynamical variable. Specifically, the PS described with n coordinates $x \equiv (x_1, \ldots, x_n)$ and the corresponding momenta $p \equiv (p_1, \ldots, p_n)$ obeys a distribution density $\rho_{\mathrm{E}}(E(x,p),\beta)$, where E is an energy function of the PS and $\beta = 1/k_{\mathrm{B}}T$ is the inverse temperature of the heat bath (k_{B} is Boltzmann's constant). This β is a dynamical variable obeying a certain probability distribution density $f(\beta)$, and forms a *temperature system* (TS). Namely, the physical state (x,p) is realized with a probability density $\rho_{\mathrm{E}}(E(x,p),\beta)$ if the inverse temperature takes the value of β, and β is realized with the probability density $f(\beta)$. By utilizing a conditional probability form, this leads to a joint distribution density of the PS and the TS, described by

$$\rho_{\mathrm{E}}(E(x,p),\beta)f(\beta). \tag{1}$$

Although the target PS is in nonequilibrium, the total system composed of the PS and the TS is in equilibrium characterized by a prescribed distribution, with a density proportional to Eq. (1).

Generalizing the NH method, in order to establish the above scheme, we derive an ordinary differential equation (ODE) that produces the density, Eq. (1), with dynamical variables including the PS variables (x, p) and the TS variable β. The creation of the density is based on the key context of satisfying the equilibrium Liouville equation with respect to all relevant variables such as (x, p) and β. In an actual simulation, the density is described by time averages of target quantities, such as physical quantity functions.

Our purpose is to provide a method for simulating the given PS in a statistically designed, nonequilibrated temperature environment. This results in the following two benefits. First, focusing only on the original PS variables (x, p) in Eq. (1) corresponds to the integration with respect to β, $\rho_{\mathrm{R}}(x, p) \equiv \int \rho_{\mathrm{E}}(E(x, p), \beta) f(\beta) d\beta$, and it becomes the *superstatistics* distribution [20, 21] if $\rho_{\mathrm{E}}(E(x, p), \beta) = \exp(-\beta E(x, p))$. Thus, the current dynamics is compatible with the superstatistics, which describes nonequilibrium complex systems that appear in many attractive physics areas. The superstatistics is intimately related to non-extensive statistical mechanics [22, 23], which has made a strong impact on exploring the foundation of statistical physics and yields a variety of the applications. Second, the current dynamics enables the sampling of states of both equilibrium and nonequilibrium with less effort and without uncertainty. Whereas the temperature replica exchange method [24] requires many state replicas, which undergo a discrete temperature change at an indistinctly prefixed constant frequency, we use a *single* replica of the coupled system, in which the sampling of the physical system is driven by the continuous temperature change with *automatic* fluctuations. An accurate description of the phase-space states in equilibrium can be obtained by a reweighting procedure, which reconstructs an arbitrary distribution on the basis of the prescribed total probability distribution of the arbitrary definition.

The EOM we provide is referred to as a *coupled NH* EOM, which is composed of the NH EOM for the target PS and the NH EOM for the currently introduced TS. Another aim of the current study is to pursue the possibility of the NH scheme, by presenting a method of coupling of two NH EOMs. Considering the fact that the coupled map lattices [25, 26], which couple plural chaotic *maps*, have provided significant impacts on nonlinear dynamics and complex systems, the current scheme for plural chaotic *ODEs* should add a new dimension to the universal NH formalism. It should be noted that the manner of the coupling is nontrivial since the total system must obey the Liouville equation.

In our previous work [27], we derived a general dynamical system, which can lead to the coupled NH EOM, and fully discussed the probability theoretical framework for the ergodic smooth dynamical system, by focusing on the mathematical rigidity. In this paper, we reinforce the physical aspect, including intuitive interpretations of the EOM, closely analyze the specific features that are not necessarily theoretically clear, and provide protocols to assign parameter values for smoothly performing actual simulations. The current simulations of a model system and a biomolecular system validate the theory and reveal the novel and characteristic features of the EOM in detail.

We proceed as follows. First, we describe the form of the total distribution function we want to realize, in order to clarify our specific considerations (Sec. II A). Then we present the coupled NH EOM (Sec. II B) and describe how this EOM creates the total density (Sec. II C). Time averages and space averages for several types of quantities are considered in Sec. II D–Sec. II H 1. We demonstrate the realization of Eq. (1) in Sec. II D and that of ρ_{R} in Sec. II E. A setting method for f, via the assignment of its parameter values, is then discussed in Sec. II H 2. We apply the current methods to a one-dimensional model system and an explicitly solvated protein system (Sec. III). We validate the theory, consider the specific features including the kinetics and system-parameter dependence, and investigate the efficiencies provided by the new scheme (Sec. IV). We conclude our discussions in Sec. V.

II. THEORY

A. Total density

The *coupled NH* EOM is introduced to create the following density:

$$\rho\left(\omega\right) \equiv \rho_{\mathrm{E}}(E(x,p),\sigma(Q))f(\sigma(Q))J(Q)\exp\left[-K_{\mathrm{T}}(\mathcal{P})\right]\rho_{\mathrm{Z}}\left(\zeta\right)\rho_{\mathrm{Y}}\left(\eta\right). \tag{2}$$

Here the primary part, $\rho_{\mathrm{E}}(E(x,p),\sigma(Q))f(\sigma(Q))J(Q)$, consists of the physical quantities (x,p)—with $x \equiv (x_1,\ldots,x_n) \in \mathbb{R}^n$ being the coordinates of n degrees of freedom and $p \equiv (p_1,\ldots,p_n) \in \mathbb{R}^n$ the corresponding momenta—and a newly introduced temperature-related quantity Q, which has m degrees of freedom in general, viz., $Q \equiv (Q_1,\ldots,Q_m) \in \mathbb{R}^m$. These three variables (x,p,Q) are essential variables to describe the desired density, Eq. (1).

The target original PS is represented by an energy function, $E(x,p) \equiv U(x) + K(p)$, namely a potential energy $U(x)$ plus a kinetic energy $(p|\mathbf{M}^{-1}p)/2 \equiv \sum_{i=1}^{n}(\mathbf{M}^{-1})_{ij}p_ip_j/2$, with $\mathbf{M}$ being masses for physical variables. ρ_{E} is a function of the energy $E(x,p)$ and the inverse temperature β, such as the usual exponential function $\exp[-\beta E(x,p)]$, but is not restricted to it. Instead, we impose a natural general condition, $\rho_{\mathrm{E}} > 0$ and $D_1\rho_{\mathrm{E}} < 0$ (D_1 denotes the partial derivative with respect to the 1st variable, viz., the energy). For the following technical reason, here we use a variable Q rather than β, related as $\beta \equiv \sigma(Q)$, in general. $\sigma : \mathbb{R}^m \to \mathbb{R}^m$ is a diffeomorphic map introduced in order to handle the domain of β via mapping $Q \mapsto \sigma(Q) \equiv \beta$, using the variable Q that moves in the *whole* domain $\mathbb{R}^m$ [according to this definition, the inverse temperature becomes a vector, $\beta \in \mathbb{R}^m$; we can flexibly consider it as if β is a parameter set related to a temperature quantity, or treat it in a traditional context such that $\|\beta\| = (\sum_{j=1}^{m}\beta_j^2)^{1/2}$ is used in ρ_{E} such as $\rho_{\mathrm{E}}(E(x,p),\beta) = \exp(-\|\beta\|\, E(x,p))$]. It is helpful to use the whole accessible domain, rather a restricted domain, to easily establish an ODE. By virtue of this, e.g., $\beta > 0$, as expected, can be easily attained by using a 1-dimensional dynamical variable Q that moves for $-\infty < Q < \infty$, if we use σ that transforms both positive and negative values into positive values (like this example, we will use $m = 1$ in the current numerical study; see also Sec. III 1). For this transformation, we need the Jacobian

$$J(Q) \equiv |\det D\sigma(Q)| \tag{3}$$

in an integration of the density, instead of just using $\rho_{\mathrm{E}}(E(x,p),\beta)f(\beta) = \rho_{\mathrm{E}}(E(x,p),\sigma(Q))f(\sigma(Q))$, which will become clearer below [Sec. II D; note $J(Q) = 1$ if we dare to put $Q = \beta$]. That is the reason why $J(Q)$, defined by Eq. (3), appears in Eq. (2). f is the probability density function for β and should be smooth.

The secondary part of Eq. (2) consists of the other three variables $(\mathcal{P},\zeta,\eta)$, which are auxiliary variables to control the total dynamical system, modeled by the NH equations, to generate density (1). First, $\zeta \in \mathbb{R}$ is a control variable for the original PS, and plays the role of a friction coefficient. Second, $\mathcal{P} \in \mathbb{R}^m$ is the momentum corresponding to the temperature coordinate variable Q, and

$$K_{\mathrm{T}}(\mathcal{P}) \equiv \tfrac{1}{2}(\mathcal{P}\,|\,\mathbf{M}_{\mathrm{T}}^{-1}\mathcal{P}) \tag{4}$$

defines the *kinetic energy* for variables $(Q,\mathcal{P})$, with $\mathbf{M}_{\mathrm{T}}$ being their *masses*. Here $(\cdot\,|\,\cdot)$ denotes the inner product. Third, $\eta \in \mathbb{R}$ is a control variable, similar to ζ, but for the

TS rather than the PS. ρ_{Z} and ρ_{Y} in Eq. (2) are 1-dimensional distributions of ζ and η, respectively (they are positive and smooth functions).

Here and throughout the paper, we mention that (x, p, ζ) defines the PS [while we say (x, p) defines the *original* PS if the distinction is needed] and $(Q, \mathcal{P}, \eta)$ defines the TS. This classification seems more natural upon observing the following EOM. The phase space point is thereby represented as $\omega \equiv (x, p, \zeta, Q, \mathcal{P}, \eta)$, and all such points make the total phase space $\Omega \equiv \mathbb{R}^{2(n+m+1)} = \mathbb{R}^n \times \mathbb{R}^n \times \mathbb{R} \times \mathbb{R}^m \times \mathbb{R}^m \times \mathbb{R}$.

B. Coupled Nosé-Hoover equations

Now, we present the following *coupled NH* EOM defined on Ω:

$$\left.\begin{aligned}
&\dot{x} = \mathbf{M}^{-1} p \in \mathbb{R}^n, \\
&\dot{p} = -\nabla U(x) - T(x, p, Q)\,\tau_{\mathrm{Z}}(\zeta)\; p \in \mathbb{R}^n, \\
&\dot{\zeta} = 2K(p) - n k_{\mathrm{B}} T(x, p, Q) \in \mathbb{R}^1, \\
&\dot{Q} = \mathbf{M}_{\mathrm{T}}^{-1} \mathcal{P} \in \mathbb{R}^m, \\
&\dot{\mathcal{P}} = -\nabla \tilde{U}_{E(x,p)}(Q) - \tau_{\mathrm{Y}}(\eta)\; \mathcal{P} \in \mathbb{R}^m, \\
&\dot{\eta} = 2K_{\mathrm{T}}(\mathcal{P}) - m \in \mathbb{R}^1,
\end{aligned}\right\} \tag{5}$$

where

$$T(x, p, Q) \equiv -1/k_{\mathrm{B}} D_1 \ln \rho_{\mathrm{E}}(E(x, p), \sigma(Q)), \tag{6}$$

$$\tau_{\mathrm{Z}}(\zeta) \equiv -k_{\mathrm{B}} D \ln \rho_{\mathrm{Z}}(\zeta), \tag{7a}$$

$$\tau_{\mathrm{Y}}(\eta) \equiv -D \ln \rho_{\mathrm{Y}}(\eta), \tag{7b}$$

and

$$\tilde{U}_\epsilon(Q) \equiv -\ln[f(\sigma(Q)) J(Q) |D_1 \rho_{\mathrm{E}}(\epsilon, \sigma(Q))|]. \tag{8}$$

The first three equations in Eq. (5) form the PS, and the last three form the TS. Coupling between the PS and TS is first seen via the temperature function defined in Eq. (6), $T(x, p, Q)$, which appears in the second and third equations in Eq. (5). The definition of Eq. (6) ensures the positiveness of T due to the condition for ρ_{E} stated above. $T(x, p, Q)$ has the dimension of temperature for all (x, p, Q), and in fact Eq. (6) can be viewed as a definition of temperature generalization, as seen below (cf. Sec. III for more details). We see that (x, p, ζ) forms the NH equations with the *functional* temperature T, instead of the constant external temperature T_{ex}, along with the temperature-dependent friction $T(x,p,Q)\,\tau_{\mathrm{Z}}(\zeta)$ (see below). In addition, $(Q,\mathcal{P},\eta)$ takes the NH form again with the PS-dependent force $-\nabla\tilde{U}_{E(x,p)}(Q)$, along with the unit *temperature*. $\tilde{U}_{\epsilon}(Q)$ plays the role of the *TS potential energy*, which is a function of the temperature coordinate Q and also depends on the energy, $\epsilon \equiv E(x,p)$, of the PS [an example of a specific form of $\tilde{U}_{\epsilon}(Q)$ is available in Sec. III 1]. Coupling between the PS and TS is thus also seen through $\tilde{U}_{E(x,p)}(Q)$.

The friction in the second equation in Eq. (5) seems to be a natural extension of that in the original Nosé-Hoover equation, $\frac{\zeta}{\mathrm{Q_{NH}}}$ ($\mathrm{Q_{NH}}$ is Nosé's mass, a positive parameter with dimension of mass×length^2). This can be seen by setting $\rho_{\mathrm{Z}}(\zeta) = \exp\left[-\zeta^2/2k_{\mathrm{B}}T_{\mathrm{ex}}\mathrm{Q_{NH}}\right]$, with T_{ex} being an external temperature, and by observing the result that $T(x,p,Q)\,\tau_{\mathrm{Z}}(\zeta) = \frac{T(x,p,Q)}{T_{\mathrm{ex}}}\frac{\zeta}{\mathrm{Q_{NH}}}$, where $\frac{T(x,p,Q)}{T_{\mathrm{ex}}}$ is a dimensionless variable. We will use Gaussians for $\rho_{\mathrm{Z}}(\zeta)$ and $\rho_{\mathrm{Y}}(\eta)$ (Sec. II G), and thus recover the linear dependencies of the frictions, viz., $\tau_{\mathrm{Z}}(\zeta)$ and $\tau_{\mathrm{Y}}(\eta)$, on ζ and η, respectively [28].

The physical dimensions of the variables, $[x_i]$, $[p_i]$, and $[\zeta]$, are equal to that in the single NH equation, and $[\tau_{\mathrm{Z}}(\zeta)/k_{\mathrm{B}}] = [\text{energy} \times \text{time}]^{-1}$. For the temperature-system quantities, $[Q_j]$, $[\mathcal{P}_j]$, and $[\mathbf{M}_{\mathrm{T}jk}]$ are not uniquely determined (assuming the uniformity, $[Q_1] = \cdots = [Q_m]$, and so on). However, if one of them is fixed, then the others are determined by two relations, $[Q_j]\,[\mathcal{P}_j] = [\text{time}]$ and $[\mathbf{M}_{\mathrm{T}jk}] = [\mathcal{P}_j]^2$, which come from the fourth and last equations in Eq. (5). Since they are unphysical variables, these peculiar relationships are not problematic. In fact, rather than their direct effect, the effect only through $T(x,p,Q)$, which has a certain physical dimension (viz., temperature, as stated), applies to the PS. Note that $\tilde{U}_{E(x,p)}$ becomes dimensionless and $[\eta] = [\text{time}] = [\tau_{\mathrm{Y}}(\eta)]^{-1}$. We simply treated Q as being dimensionless in our numerical simulation.

C. Realization of the total density

We demonstrate the realization of the density, ρ [Eq. (2)], via the EOM [Eq. (5)]. It can be straightforwardly confirmed that the equilibrium Liouville equation holds

$$\operatorname{div}\rho' X' = 0, \tag{9}$$

where X' denotes the vector field defining Eq. (5), viz.,

$$X'(\omega) \equiv (X'_x(\omega),\ X'_p(\omega), ...,\ X'_\eta(\omega)) \tag{10a}$$

$$\equiv (\mathbf{M}^{-1}p,\ \ - \nabla U(x) - T(x,p,Q)\, \tau_{\mathrm{Z}}\,(\zeta)\ p, ...,\ 2K_{\mathrm{T}}(\mathcal{P}) - m) \tag{10b}$$

and

$$\rho'(\omega) = \rho(\omega)/T(x,p,Q). \tag{11}$$

This means that ρ' (not ρ itself) is an invariant density (viz., $\rho' d\omega$ is an invariant measure) of the flow generated by the ODE, $\dot{\omega} = X'(\omega)$ [Eq. (5)]. Thus, the long time average for any phase space function $g' : \Omega \to \mathbb{R}$ exists from Birkhoff's ergodic theorem, and by assuming the ergodic condition, we have

$$\overline{g'} \equiv \lim_{\tau\to\infty} \frac{1}{\tau}\int_0^\tau g'(\phi(t))dt = \int_\Omega g'(\omega)\rho'(\omega)d\omega \Big/ \int_\Omega \rho'(\omega)d\omega\ , \tag{12}$$

where $\phi : t \mapsto \phi(t) = (x(t), p(t), \zeta(t), Q(t), \mathcal{P}(t), \eta(t))$ is a solution of $\dot{\omega} = X'(\omega)$ [29, 30]. However, this is not the average under the density ρ, but that under ρ'. To gain the average under the density ρ, we proceed as follows. First we apply Eq. (12) to $g'(\omega) = g(\omega)T(x,p,Q)$ for any function $g : \Omega \to \mathbb{R}$, having

$$\overline{gT} = \lim_{\tau\to\infty} \frac{1}{\tau}\int_0^\tau g(\phi(t))T(x(t),p(t),Q(t))dt \tag{13a}$$

$$= \lim_{\tau\to\infty} \frac{1}{\tau}\int_0^\tau g'(\phi(t))dt \tag{13b}$$

$$= \int_\Omega g(\omega)\rho(\omega)d\omega \Big/ \int_\Omega \rho' d\omega\ , \tag{13c}$$

since $g'\rho' = g\rho$ in this case. Second we apply Eq. (13) to $g = 1$ (constant-valued function) and obtain

$$\overline{T} = \lim_{\tau\to\infty} \frac{1}{\tau}\int_0^\tau T(x(t),p(t),Q(t))dt = \int_\Omega \rho(\omega)d\omega \Big/ \int_\Omega \rho' d\omega\ . \tag{14}$$

Thus, dividing Eq. (13) by Eq. (14), we have

$$\overline{gT}\,/\overline{T} = \int_\Omega g(\omega)\rho(\omega)d\omega \Big/ \int_\Omega \rho(\omega)d\omega\ . \tag{15}$$

Here we have assumed that the space-average integrals that appear in Eqs. (13) and (14) are all finite. If we abbreviate the left-hand side (LHS) of Eq. (15) to

$$\overline{\overline{g}} \equiv \overline{gT}\,/\overline{T} \tag{16}$$

and the right-hand side (RHS) to

$$\langle g \rangle \equiv \int_\Omega g\rho d\omega \bigg/ \int_\Omega \rho d\omega \ , \tag{17}$$

then we have, simply,

$$\overline{\overline{g}} = \langle g \rangle \ . \tag{18}$$

This shows the desired results that the average of any function g in the density ρ is represented by a time average, $\overline{\overline{g}}$. Note that, instead of the simple long-time average $\overline{g} \equiv \lim_{\tau\to\infty} \frac{1}{\tau}\int_0^\tau g(\phi(s))ds$, the scaled-time average, Eq. (16), was used to perform our method. This can be understood by noting that we use the field X', rather than $X = X'/T$, and this redefinition is equivalent to a time scaling between the two corresponding ODEs.

Here, we first define the EOM and then prove that it can generate the density. A more natural derivation of the EOM using a general theoretical framework, as well as detailed aspects of the mathematics, are documented elsewhere [27]. We continue to assume the ergodic condition in the following discussions.

D. Average of a function of main variables

We demonstrate in a simple manner the realization of the density, Eq. (1), by evaluating the average of a function of main variables (x, p, Q) or (x, p, β) [recall $\sigma(Q) \equiv \beta$]. Applying Eq. (18) to a function of the form $g(\omega) = B(x, p, \sigma(Q)) = B(x, p, \beta)$ for any B, we have

$$\overline{\overline{B}} = \langle B \rangle \ . \tag{19}$$

Due to its definition, the LHS is

$$\lim_{\tau\to\infty} \frac{1}{\tau}\int_0^\tau B(x(t), p(t), \sigma(Q(t)))T(x(t), p(t), Q(t))dt \bigg/ \lim_{\tau\to\infty} \frac{1}{\tau}\int_0^\tau T(x(t), p(t), Q(t))dt \ . \tag{20}$$

The RHS of Eq. (19) is

$$\int_\Omega B(x, p, \sigma(Q))\rho(\omega)d\omega \bigg/ \int_\Omega \rho(\omega)d\omega \ , \tag{21}$$

for which we will deduce a formula that is suitable for our purpose. Its numerator is

$$\int_{\mathbb{R}^n\times\mathbb{R}^n\times\mathbb{R}^m} B(x, p, \sigma(Q))\rho_{\mathrm{E}}(E(x, p), \sigma(Q))\, f(\sigma(Q))J(Q)\, dxdpdQ \times Z_{\mathrm{Cntr}}, \tag{22}$$

where

$$Z_{\mathrm{Cntr}} \equiv \int_{\mathbb{R}^{m+2}} \exp\left[-K_{\mathrm{T}}(\mathcal{P})\right] \rho_{\mathrm{Z}}\left(\zeta\right) \rho_{\mathrm{Y}}\left(\eta\right) d\mathcal{P} d\zeta d\eta. \tag{23}$$

The integration in Eq. (22) becomes

$$\int_{\mathbb{R}^{2n}\times\mathbb{R}^{m}} B(x,p,\sigma(Q))\rho_{\mathrm{E}}(E(x,p),\sigma(Q))\, f(\sigma(Q))\,|\det D\sigma(Q)|\, dxdpdQ \tag{24a}$$

$$= \int_{\mathbb{R}^{2n}} dxdp \int_{\mathbb{R}^{m}} B(x,p,\sigma(Q))\rho_{\mathrm{E}}(E(x,p),\sigma(Q))\, f(\sigma(Q))\,|\det D\sigma(Q)|\, dQ \tag{24b}$$

$$= \int_{\mathbb{R}^{2n}} dxdp \int_{\sigma(\mathbb{R}^{m})} B(x,p,\beta)\rho_{\mathrm{E}}(E(x,p),\beta)\, f(\beta)\, d\beta, \tag{24c}$$

where we have used a variable transformation in the integration with respect to Q via the Jacobian, $J(Q) = |\det D\sigma(Q)|$. In other words, the Jacobian in Eq. (2) is presented to derive the formula, Eq. (24c). The denominator of Eq. (21) can be obtained by putting $B = 1$ in Eq. (24). Hence, Eq. (21), the RHS of Eq. (19), is

$$\int_{\Omega} B(x,p,\sigma(Q))\rho(\omega)d\omega \bigg/ \int_{\Omega}\rho(\omega)d\omega \tag{25a}$$

$$= \frac{\int_{\mathbb{R}^{2n}} dxdp \int_{\sigma(\mathbb{R}^{m})} B(x,p,\beta)\rho_{\mathrm{E}}(E(x,p),\beta)\, f(\beta)\, d\beta \times Z_{\mathrm{Cntr}}}{\int_{\mathbb{R}^{2n}} dxdp \int_{\sigma(\mathbb{R}^{m})} \rho_{\mathrm{E}}(E(x,p),\beta)\, f(\beta)\, d\beta \times Z_{\mathrm{Cntr}}} \tag{25b}$$

$$= \frac{\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^{m})} B(x,p,\beta)\rho_{\mathrm{E}}(E(x,p),\beta)\, f(\beta) dxdpd\beta}{\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^{m})} \rho_{\mathrm{E}}(E(x,p),\beta)\, f(\beta) dxdpd\beta}. \tag{25c}$$

Namely,

$$\overline{\overline{B}} = \frac{\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^{m})} B(x,p,\beta)\rho_{\mathrm{E}}(E(x,p),\beta)\, f(\beta) dxdpd\beta}{\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^{m})} \rho_{\mathrm{E}}(E(x,p),\beta)\, f(\beta) dxdpd\beta}, \tag{26}$$

indicating the realization of Eq. (1) (consult Ref. [27] for mathematical details). This also becomes the basis for obtaining the averages for the special types of functions treated in Sec. II E, Sec. II F, and Sec. II H. We have assumed that the two integrals in Eq. (25c) are finite and will similarly make a necessary assumption for the integral that we will encounter in an individual space average.

E. Average of a physical quantity

Equation (19) also demonstrates the density creation for physical variables (x,p). Namely, for any physical quantity $A(x,p)$, by substituting $B(x,p,\sigma(Q)) = A(x,p)$ we get

$$\overline{\overline{A}} = \left\langle A \right\rangle, \tag{27}$$

where the LHS is

$$\lim_{\tau\to\infty}\frac{1}{\tau}\int_0^\tau A(x(t),p(t))T(x(t),p(t),Q(t))dt \Big/ \lim_{\tau\to\infty}\frac{1}{\tau}\int_0^\tau T(x(t),p(t),Q(t))dt\ , \tag{28}$$

and the RHS of Eq. (27) is, using Eq. (25),

$$\begin{aligned}
&\int_\Omega A(x,p)\rho(\omega)d\omega \Big/ \int_\Omega \rho(\omega)d\omega && \text{(29a)}\\
&= \frac{\int_{\mathbb{R}^{2n}} dxdpA(x,p)\int_{\sigma(\mathbb{R}^m)} \rho_{\mathrm{E}}(E(x,p),\beta)\, f(\beta)\, d\beta}{\int_{\mathbb{R}^{2n}} dxdp \int_{\sigma(\mathbb{R}^m)} \rho_{\mathrm{E}}(E(x,p),\beta)\, f(\beta)\, d\beta} && \text{(29b)}\\
&= \frac{\int_{\mathbb{R}^{2n}} dxdpA(x,p)\rho_{\mathrm{R}}(x,p)}{\int_{\mathbb{R}^{2n}} dxdp\rho_{\mathrm{R}}(x,p)}, && \text{(29c)}
\end{aligned}$$

with

$$\rho_{\mathrm{R}}(x,p) \equiv \int_{\sigma(\mathbb{R}^m)} \rho_{\mathrm{E}}(E(x,p),\beta)\, f(\beta)\, d\beta. \tag{30}$$

By using an abbreviation,

$$\langle A\rangle_{\mathrm{R}} \equiv \int_{\mathbb{R}^{2n}} A(x,p)\rho_{\mathrm{R}}(x,p)dxdp \Big/ \int_{\mathbb{R}^{2n}} \rho_{\mathrm{R}}dxdp\ , \tag{31}$$

for the *physical*-space average, we have Eq. (27) via the simple expression,

$$\overline{\overline{A}} = \langle A\rangle_{\mathrm{R}}\ . \tag{32}$$

Thus, by solving the ODE, Eq. (5), and calculating the time averages defined in Eq. (28), we realize the density ρ_{R} as represented in Eq. (31). Note that the explicit integration in Eq. (30), viz., the analytic form of $\rho_{\mathrm{R}}(x,p)$, is not needed to generate ρ_{R}, since X' [Eq. (10)] and the time average [Eq. (28)] are defined without the use of ρ_{R}.

The marginal distribution density of x, $\widehat{\rho}_{\mathrm{x}}$, can be obtained via Eq. (32) by defining $A(x,p) = \chi_C(x)$, where $\chi_C(x) = 1$ if $x \in C$ and $\chi_C(x) = 0$ otherwise, with C being each small bin involving a point x^c:

$$\begin{aligned}
\overline{\overline{\chi_C}} &= \langle \chi_C\rangle = \langle \chi_C\rangle_{\mathrm{R}} && \text{(33a)}\\
&= \frac{\int_C dx \int_{\mathbb{R}^n} dp\rho_{\mathrm{R}}(x,p)}{\int_{\mathbb{R}^{2n}} dxdp\rho_{\mathrm{R}}(x,p)} =: \int_C dx\widehat{\rho}_{\mathrm{x}}(x) && \text{(33b)}\\
&\simeq |C|\, \widehat{\rho}_{\mathrm{x}}(x^c). && \text{(33c)}
\end{aligned}$$

In general, the marginal distribution of the ith-component of ω is similarly estimated as $\overline{\overline{\chi_C}} = \langle \chi_C\rangle = \int_C d\omega_i\widehat{\rho}_i(\omega_i) \simeq |C|\, \widehat{\rho}_i(\omega_i^c)$, where $\widehat{\rho}_i : \omega_i \mapsto \int d\omega_1\cdots d\omega_{i-1}d\omega_{i+1}\cdots d\omega_{2(n+m+1)}\rho(\omega_1,\ldots,\omega_{2(n+m+1)}) \big/ \int_\Omega \rho d\omega$ is the target marginal distribution density.

F. Reweighting

We also derive a formula for reweighting to an arbitrary target positive density ρ_{TRG} for the physical system described by (x,p). This can be used to reconstruct an equilibrium distribution, such as the BG distribution, using the current method. Applying Eq. (32) to both functions $A\rho_{\mathrm{TRG}}/\rho_{\mathrm{R}}$ and $\rho_{\mathrm{TRG}}/\rho_{\mathrm{R}}$, we straightforwardly get

$$\overline{\overline{A\rho_{\mathrm{TRG}}/\rho_{\mathrm{R}}}} \bigg/ \overline{\overline{\rho_{\mathrm{TRG}}/\rho_{\mathrm{R}}}} \tag{34a}$$

$$= \left\langle A\rho_{\mathrm{TRG}}/\rho_{\mathrm{R}} \right\rangle_{\mathrm{R}} / \left\langle \rho_{\mathrm{TRG}}/\rho_{\mathrm{R}} \right\rangle_{\mathrm{R}} \in \mathbb{R} \tag{34b}$$

$$= \int_{\mathbb{R}^{2n}} A(x,p)\rho_{\mathrm{TRG}}(x,p)dxdp \bigg/ \int_{\mathbb{R}^{2n}} \rho_{\mathrm{TRG}}(x,p)dxdp \tag{34c}$$

$$=: \left\langle A \right\rangle_{\mathrm{TRG}} . \tag{34d}$$

It follows from $\int_{\mathbb{R}^{2n}} \rho_{\mathrm{TRG}} dxdp > 0$ that Eq. (34b) is well defined. Thus, the average of the function of a physical variable A under the distribution density ρ_{TRG} can be obtained through the weighted long-time averages by

$$\overline{\overline{A\rho_{\mathrm{TRG}}/\rho_{\mathrm{R}}}} \bigg/ \overline{\overline{\rho_{\mathrm{TRG}}/\rho_{\mathrm{R}}}} = \left\langle A \right\rangle_{\mathrm{TRG}} . \tag{35}$$

We will mention some clarifications. Equation (35) is easy to use for reweighting, but it is a formula used when ρ_{R} is explicitly obtained. An alternative formula is discussed in Ref. [27]. Next, some caution regarding the following two issues may be needed in actual computations using these reweighting methods, especially for a small system, although we did not encounter such issues when we used Eq. (35) in the simulations described in Sec. IV. First, the value of the denominators of the scaled time averages in Eq. (35), viz. $\rho_{\mathrm{R}}(x,p)$, may have a very small value, which may occur if the system is small and especially if ρ_{E} is defined by a significantly decaying function. In this case, the time averages eventually have significantly large values, and they behave like noise when the averages are taken for an insufficiently long duration. In such a situation we should discard the data that are larger than the prefixed threshold in practice. Second, in a theoretical sense, $\rho_{\mathrm{R}}(x,p)$ can also have positive infinity as a value for a certain point (x,p). Although all such points have Lebesgue measure zero [27] and just define $1/\rho_{\mathrm{R}}(x,p) = 0$, it is complete if we prepare to avoid the relevant underflow.

G. Average of a function of control variables

The distributions of auxiliary variables, $\mathcal{P}, \zeta$, and η, are directly obtained from Eq. (18). For any function of $\mathcal{P}$, say $h_1(\mathcal{P})$, we have

$$\overline{\overline{h_1}} = \langle h_1 \rangle \,, \tag{36}$$

where

$$\overline{\overline{h_1}} \equiv \lim_{\tau \to \infty} \frac{1}{\tau} \int_0^{\tau} h_1(\mathcal{P}(t)) T(x(t), p(t), Q(t)) dt \Bigg/ \lim_{\tau \to \infty} \frac{1}{\tau} \int_0^{\tau} T(x(t), p(t), Q(t)) dt \,, \tag{37a}$$

$$\langle h_1 \rangle \equiv \int_{\Omega} h_1(\mathcal{P}) \rho(\omega) d\omega \Bigg/ \int_{\Omega} \rho(\omega) d\omega \,. \tag{37b}$$

Here, for the space average,

$$\begin{aligned} &\int_{\Omega} h_1(\mathcal{P}) \rho(\omega) d\omega && (38a)\\ &= \int_{\mathbb{R}^{2n} \times \mathbb{R}^m} \rho_{\mathrm{E}}(E(x,p), \sigma(Q)) \, f(\sigma(Q)) \, J(Q) \, dx dp dQ \\ &\times \int_{\mathbb{R}^m} h_1(\mathcal{P}) \exp\left[-K_{\mathrm{T}}(\mathcal{P})\right] d\mathcal{P} \int_{\mathbb{R}^2} \rho_{\mathrm{Z}}\left(\zeta\right) \rho_{\mathrm{Y}}\left(\eta\right) d\zeta d\eta. && (38b) \end{aligned}$$

Thus, we get

$$\langle h_1 \rangle = \int_{\mathbb{R}^m} h_1(\mathcal{P}) \exp\left[-K_{\mathrm{T}}(\mathcal{P})\right] d\mathcal{P} \Bigg/ \int_{\mathbb{R}^m} \exp\left[-K_{\mathrm{T}}(\mathcal{P})\right] d\mathcal{P} \,, \tag{39}$$

via the cancellation of the quantities; viz., only $\mathcal{P}$-related quantities remain in the space integration average. This is due to the form of Eq. (2), viz., the separation of variables in ρ with respect to $\mathcal{P}_j$, ζ, and η (which implies that these "random" variables are independent). Similarly, for $h_2(\zeta)$ and $h_3(\eta)$, we have

$$\begin{aligned} \overline{\overline{h_2}} &= \langle h_2 \rangle && (40a)\\ &= \int_{\Omega} h_2(\zeta) \rho(\omega) d\omega \Bigg/ \int_{\Omega} \rho(\omega) d\omega && (40b)\\ &= \int_{\mathbb{R}} h_2(\zeta) \rho_{\mathrm{Z}}\left(\zeta\right) d\zeta \Bigg/ \int_{\mathbb{R}} \rho_{\mathrm{Z}}\left(\zeta\right) d\zeta && (40c) \end{aligned}$$

and

$$\begin{aligned} \overline{\overline{h_3}} &= \langle h_3 \rangle && (41a)\\ &= \int_{\mathbb{R}} h_3(\zeta) \rho_{\mathrm{Y}}\left(\eta\right) d\eta \Bigg/ \int_{\mathbb{R}} \rho_{\mathrm{Y}}\left(\eta\right) d\eta \,. && (41b) \end{aligned}$$

In the simulation below, we specifically set

$$\rho_{\mathrm{Z}}(\zeta) = \exp\left[-c_{\mathrm{Z}}\zeta^2\right] , \tag{42a}$$

$$\rho_{\mathrm{Y}}(\eta) = \exp\left[-c_{\mathrm{Y}}\eta^2\right] . \tag{42b}$$

Here c_{Z} and c_{Y} are positive parameters, which could be viewed as a thermostat parameter for the PS and a *thermostat parameter for the TS*, respectively (cf. Sec. II B): c_{Z} governs the heat exchange between the physical system and the (*dynamical*) heat reservoir, and c_{Y} governs the heat exchange between the temperature system and a fictitious heat reservoir for the temperature system.

Note that $\mathcal{P}$, ζ, and η are control variables, not physical variables, so that the inspection of their distributions is not important in a physical sense. However, to validate the creation of the total density ρ [Eq. (2)], they are important and useful: the creation of the correct distributions of these variables means the validity of a necessary condition for the creation of ρ under the ergodic conditions, and their theoretical distributions, as seen above, can be obtained simply regardless of the details of the target PS, such as the complexity and system size. In fact, we use them in this regard for the numerical calculations in Sec. III.

H. Temperature-related quantities

The space average for a function of the inverse temperature β, $h(\beta) = h(\sigma(Q))$, is given by

$$\langle h(\beta)\rangle = \int_{\Omega} h(\sigma(Q))\rho(\omega)d\omega \bigg/ \int_{\Omega} \rho d\omega \tag{43a}$$

$$= \int_{\sigma(\mathbb{R}^m)} h(\beta)f(\beta)Z(\beta)d\beta \bigg/ \int_{\sigma(\mathbb{R}^m)} f(\beta)Z(\beta)d\beta , \tag{43b}$$

assuming that hfZ is integrable, where

$$Z(\beta) \equiv \int_{\mathbb{R}^{2n}} \rho_{\mathrm{E}}(E(x,p),\beta)dxdp \tag{44}$$

is a (generalized) partition function. Equation (43b) can be obtained from Eq. (25), by substituting $B(x,p,\sigma(Q)) = h(\sigma(Q))$. Namely, the average of the inverse-temperature function h, defined by Eq. (43a), becomes the expected value of h in the Z-weighted probability distribution $\propto Zfd\beta$.

Although Z is not given in an explicit form in general, we provide two ideas concerning the calculation of $\langle h(\beta)\rangle$. The first is to provide an approximate estimation of the average, $\langle h(\beta)\rangle$, using a given f. This is the direct problem (Sec. II H 1). The second is to provide an estimation of the function f that gives $\langle h(\beta)\rangle \simeq \gamma$ for any γ given in advance: the inverse problem (Sec. II H 2). This solution means that one can set f, for instance, such that the average of the *dynamical temperature* $1/\beta$ will be the target value γ.

1. Direct problem

Assuming the smoothness of Z and the convexity of $\sigma(\mathbb{R}^m)$ allows the expansion of $\ln Z$ for a certain β_0 and leads to a first order approximation, $Z(\beta) \sim \tilde{Z}(\beta_0)\exp[-(\epsilon(\beta_0)|\beta)]$, where

$$\epsilon(\beta_0) \equiv -\nabla Z(\beta_0)/Z(\beta_0) \in \mathbb{R}^m \tag{45}$$

and $\tilde{Z}(\beta_0) \equiv Z(\beta_0)\exp\{(\epsilon(\beta_0)|\beta_0)\} \in \mathbb{R}$. Note that a higher order approximation can be given via higher-degree polynomials for β and β_0, which will appear in the brackets [ ] and { } of the exponentials, respectively. For the first order approximation, we thus have

$$\langle h(\beta)\rangle \tag{46a}$$

$$\simeq \int_{\sigma(\mathbb{R}^m)} h(\beta)f(\beta)\mathrm{e}^{-(\epsilon(\beta_0)|\beta)}d\beta \bigg/ \int_{\sigma(\mathbb{R}^m)} f(\beta)\mathrm{e}^{-(\epsilon(\beta_0)|\beta)}d\beta =: \langle\langle h(\beta)\rangle\rangle\,. \tag{46b}$$

Considering the fact that f is usually expected to have one maximum value, the value of β_0 as a natural choice for a better approximation is the maximum point of f. Note that the value of $\epsilon(\beta_0)$ can be evaluated numerically as an expected value in a certain ensemble, in principle, as described in Sec. I of Supplemental Material [31]. Thus, if we define the function f then we have an approximated value of $\langle h(\beta)\rangle$, in principle. When $m = 1$, the integrations in Eq. (46b) are over one dimension and so evaluated numerically at least; even when $m > 1$, the integration will be evaluated for a simple form of fh.

2. Inverse problem

Although one can thus find an approximation to the expected value such that $\langle h(\beta)\rangle \simeq \langle\langle h(\beta)\rangle\rangle \simeq \gamma$ from a given f by the aforementioned scheme, it is often more useful to solve the *inverse* problem: set f such that $\langle h(\beta)\rangle \simeq \gamma$ for any given value γ. To address the problem more specifically, suppose we have a given function f that involves an unknown parameter α, denoted as $f = f(\cdot\,;\alpha)$ (the consideration here is so general that it is independent of a specific functional form of f, which will be actually given in Sec. III 1). The inverse problem thus corresponds to seeking the values of α that yield $\langle h(\beta)\rangle \simeq \gamma$. The solution is useful if it is difficult in realistic simulations to determine such parameter values or there is no rigid strategy to adjust f. However, it seems nontrivial to solve this inverse problem, since the function form of ϵ [Eq. (45)], which appears in Eq. (46b), is unknown a priori even for a simple ρ_{E} [$\epsilon(\beta_0)$ at an individual point β_0 can be evaluated in the manner described in Sec. I of Supplemental Material [31], but much effort is required to know the entire functional form].

A simple idea to solve the inverse problem is to eliminate the bottleneck, $\epsilon(\beta_0)$, by introducing a new parameter, U_0, in ρ_{E}. We proceed as follows. Assume that (i) we can set the value of U_0 such that

$$\epsilon(\beta_0; U_0) \equiv -\nabla_{\beta} Z(\beta_0; U_0)/Z(\beta_0; U_0) \simeq 0 \tag{47}$$

for any given β_0. Here, ϵ depends on Z, which depends on ρ_{E}, and now ρ_{E} depends on U_0 so that it is denoted as $\rho_{\mathrm{E}}^{U_0}$ and

$$Z(\beta; U_0) \equiv \int_{\mathbb{R}^{2n}} \rho_{\mathrm{E}}^{U_0}(E(x,p), \beta)\, dx dp. \tag{48}$$

Then we have a simplified relation,

$$\begin{aligned} &\langle\langle h(\beta)\rangle\rangle & \text{(49a)}\\ &\simeq \int_{\sigma(\mathbb{R}^m)} h(\beta) f(\beta;\alpha) d\beta \bigg/ \int_{\sigma(\mathbb{R}^m)} f(\beta;\alpha) d\beta =: \langle h\rangle_f\,. & \text{(49b)}\end{aligned}$$

Accordingly, we see that the inverse problem is solved via

$$\langle h(\beta)\rangle \simeq \langle\langle h(\beta)\rangle\rangle \simeq \langle h\rangle_f = \gamma, \tag{50}$$

by adding two assumptions: (ii) β_0 is described by a certain function of α, such as $\beta_0 = \lambda(\alpha)$ with λ being a known form [e.g., suppose that f is monomodal and so expedient that the maximum-point condition, $Df(\beta_0;\alpha) = 0$, is solved as $\beta_0 = \lambda(\alpha)$]; (iii) Denoting the dependence of $\langle h\rangle_f$ on α by $\Phi(\alpha) \equiv \langle h\rangle_{f(\cdot;\alpha)}$, then the function, Φ, is simple enough so that

$$\Phi(\alpha) = \gamma \tag{51}$$

can be solved with respect to α. Then, α_γ, a solution of Eq. (51), which is expected to be easily solved, becomes also a solution of the inverse problem, viz.,

$$\frac{\int_{\sigma(\mathbb{R}^m)} h(\beta) f(\beta;\alpha_\gamma) Z(\beta;U_0) d\beta}{\int_{\sigma(\mathbb{R}^m)} f(\beta;\alpha_\gamma) Z(\beta;U_0) d\beta} \simeq \gamma, \tag{52}$$

where U_0 is determined from Eq. (47) using $\beta_0 = \lambda(\alpha_\gamma)$; the proof and more details are provided in Sec. II of Supplemental Material [31]. Thus we can find a parameter value $\alpha = \alpha_\gamma$ such that $\langle h(\beta) \rangle \simeq \gamma$ for a given γ.

I. Function settings

To define ρ of Eq. (2), we specifically set the functions, viz., the PS density ρ_{E}, the inverse-temperature distribution density f, and the transform function σ. We will define them in Sec. III I 1 and clarify their physical meanings. In Sec. III I 2 we will demonstrate how these functions can satisfy assumptions (i)–(iii) stated in the preceding subsection. We will also discuss the relevant issue that the average of the physical temperature equals the average of the dynamical temperature.

1. Fundamental functions

One of the most interesting systems is under the BG ensemble with temperature that fluctuates. It can be realized by Eq. (5) with

$$\rho_{\mathrm{E}}(\epsilon, \beta) \equiv \exp\left[-\beta\epsilon\right] \tag{53}$$

and $m \equiv 1$; viz., $\rho_{\mathrm{E}}(E(x,p), \sigma(Q))$ in Eq. (2) becomes $\exp\left[-\sigma(Q)E(x,p)\right]$. In this case, the *dynamical temperature* $1/k_{\mathrm{B}}\sigma(Q)$ simply indicates the BG system temperature (which is not a constant, but now a dynamical variable) and also equals the temperature function defined by Eq. (6), viz.,

$$T(x,p,Q) = 1/k_{\mathrm{B}}\sigma(Q). \tag{54}$$

Namely, taking the conventional BG distribution for ρ_{E}, the "*functional*" (or generalized) temperature $T(x,p,Q)$ gives the dynamical BG system-temperature (it is conventional in that it indicates the BG, but it is new in that it is dynamical). Equation (5) thus represents "BG (canonical) dynamics" + "temperature dynamics."

For the transform σ, we set

$$\sigma(Q) \equiv c \exp\left[Q/l\right] \tag{55}$$

with the positive parameters c and l. This ensures the positivity of the dynamical (BG system) temperature $1/k_\mathrm{B}\beta = 1/k_\mathrm{B}\sigma(Q)$ [this does not contradict Eq. (54), where $T(x,p,Q) > 0$ is ensured by the conditions, $\rho_\mathrm{E} > 0$ and $D_1\rho_\mathrm{E} < 0$]. l governs the dynamical behavior of the dynamical temperature (see below and Sec. IV A), while changes in the value of c only induce the translation of Q (see Sec. III of Supplemental Material [31]).

For f, we use the gamma distribution density $f \equiv f_\mathrm{G}$ defined on $\sigma(\mathbb{R}^1) = (0,\infty)$, i.e.,

$$f_\mathrm{G}(\beta) \equiv c_\mathrm{G}\beta^{\alpha_1-1}\exp\left[-\alpha_2\beta\right]. \tag{56}$$

Here $\alpha = (\alpha_1, \alpha_2)$ are positive parameters, and c_G is the normalization constant so that $\int_0^\infty f_\mathrm{G}(\beta)\, d\beta = 1$. f_G is smooth and decaying as $\beta \to \infty$, and f_G with $\alpha_1 > 1$ is favorably monomodal and also decaying as $\beta \to 0$. The nonequilibrium temperature governed by f_G creates an intriguing environment [32]. Namely, for $E(x,p) + \alpha_2 > 0$, the distribution with respect to (x,p), represented by Eq. (30), is given as

$$\rho_\mathrm{R}(x,p) = \int_{(0,\infty)} \mathrm{e}^{-\beta E(x,p)}\, f_\mathrm{G}(\beta)\, d\beta \tag{57a}$$

$$= \left[1 - (1-q)E(x,p)/k_\mathrm{B}T_0\right]^{1/(1-q)}, \tag{57b}$$

viz., the Tsallis distribution [22, 33, 34] with the renormalized temperature $T_0 \equiv \alpha_2/\alpha_1 k_\mathrm{B}$ and the nonextensive parameter $q \equiv 1 + 1/\alpha_1$. Note that deterministic equations to realize the Tsallis distribution were previously developed [29, 35–38], and here we give an application for realizing the distribution *dynamically* [this does not only mean realizing the distribution $\rho_\mathrm{R}(x,p)$, but also realizing the joint distribution density (1), which also generates $\rho_\mathrm{R}(x,p)$, by *dynamically* fluctuating β; such a realization is not done in those literature], which enables the direct observation of the influence of temperature fluctuations on the PS.

We note that the coupling of the definitions, Eqs. (53), (55), and (56), brings up an interesting feature regarding the potential energy of the TS. Namely, it becomes, up to a constant, the Toda potential [39] for Q as,

$$\tilde{U}_\epsilon(Q) = A_\epsilon \exp(Q/l) - a(Q/l), \tag{58}$$

with "coefficients" $A_\epsilon \equiv c(\epsilon + \alpha_2)$ and $a \equiv \alpha_1 + 1$. The Toda potential has one minimum and represents an unharmonic spring interaction. It has been utilized in the study of nonlinear lattices, and it is relevant to, e.g., integrable systems [40], solitons [41], and thermal conduction [42]. The Q variable receives feedback from the physical system through the energy $\epsilon \equiv E(x,p)$, and makes a nonlinear temperature-control mechanism. l is related to the oscillating motion of Q, as described in Appendix A.

2. Validity of assumptions

For the averages of functions of β (Sec. II H), in order to solve the inverse problem along the line stated in Sec. II H 2, we modify Eq. (53) into

$$\rho_{\mathrm{E}}^{U_0}(\epsilon,\beta) \equiv \exp\left[-\beta(\epsilon+U_0)\right]. \tag{59}$$

This modification yields the change, $E(x,p) \to E(x,p)+U_0$ in Eq. (57) and $A_\epsilon \to c(\epsilon+\alpha_2+U_0)$ in Eq. (58). We stress that Eq. (54) is kept. From a physical viewpoint, U_0 in Eq. (59) can be seen as the shift of the origin of a potential energy, $U \to U+U_0$. While the shift is useless in the BG dynamics, as indicated by the invariance of the dynamics, it can be turned into a useful issue in the current dynamics, as explained below.

To show the validity of assumption (i), we note that

$$\mathbb{R}\ni\epsilon(\beta_0;U_0) = -\int_{\mathbb{R}^{2n}} D_\beta\rho_{\mathrm{E}}^{U_0}(E(x,p),\beta_0)dxdp \bigg/ \int_{\mathbb{R}^{2n}} \rho_{\mathrm{E}}^{U_0}(E(x,p),\beta_0)dxdp \tag{60a}$$

$$= \langle E\rangle_{\mathrm{BG};\beta_0} + U_0 \tag{60b}$$

holds for $\beta_0 > 0$ [cf. Eq. (S1a) and Sec. I of Supplemental Material [31] for more details], where

$$\langle E\rangle_{\mathrm{BG};\beta_0} \equiv \frac{\int_{\mathbb{R}^{2n}} E(x,p)\mathrm{e}^{-\beta_0 E(x,p)}dxdp}{\int_{\mathbb{R}^{2n}} \mathrm{e}^{-\beta_0 E(x,p)}dxdp} \tag{61}$$

is the energy average in the BG distribution at temperature $1/k_{\mathrm{B}}\beta_0$ and it can be estimated by e.g., a preliminary BG dynamics simulation. Hence, we see that Eq. (47) holds by putting

$$U_0 \simeq \mathcal{E}(\beta_0) \equiv -\langle E\rangle_{\mathrm{BG};\beta_0}, \tag{62}$$

which ensures assumption (i).

For the remaining assumptions, we set $\alpha_1 > 1$ and β_0 to be the maximum point of monomodal f_{G}. Note that the optimal β_0 may depend also on h in general [Eq. (46)], but we here consider a simple situation and focus only on f because it appears in both the denominator and numerator in Eq. (43b). Now, hence we have

$$\beta_0 = (\alpha_1-1)/\alpha_2 =: \lambda(\alpha), \tag{63}$$

which is easily computed [viz., (ii) is valid].

We take into account a simple but important problem in Eq. (50): set the average of the dynamical temperature only. This means $h(\beta) = 1/\beta$ and yields

$$\begin{aligned}\Phi(\alpha) &= \langle 1/\beta \rangle_{f_{\mathrm{G}}(\cdot;\alpha)} &\text{(64a)}\\ &= \int_0^\infty (1/\beta) f_{\mathrm{G}}(\beta;\alpha) d\beta \Big/ \int_0^\infty f_{\mathrm{G}}(\beta;\alpha) d\beta &\text{(64b)}\\ &= \alpha_2/(\alpha_1 - 1). &\text{(64c)}\end{aligned}$$

Thus, Eq. (51) is solved for any given $\gamma \in \mathbb{R}$ [(iii) is valid]. Note that to ensure assumptions (i)–(iii), Eq. (55) is not necessary, and only the fact that $\sigma(\mathbb{R}^1) = (0, \infty)$ is used.

Therefore, via the setting of the functions here, we can set an arbitrary value γ for the dynamical-temperature average:

$$\langle 1/\beta \rangle \simeq \langle\langle 1/\beta \rangle\rangle \simeq \langle 1/\beta \rangle_{f_{\mathrm{G}}} = \gamma. \tag{65}$$

The parameters α should be set as $\alpha_2/(\alpha_1 - 1) = \gamma$ and U_0 set via Eq. (62) with a use of Eq. (63).

It should be noted that this scheme is also useful in that it determines the average of not only the dynamical temperature $T_{\mathrm{D}}(\omega) \equiv 1/k_{\mathrm{B}}\sigma(Q)$ but also the physical temperature $T_{\mathrm{P}}(\omega) \equiv 2K(p)/nk_{\mathrm{B}}$. This is due to the relationship

$$\langle T_{\mathrm{P}} \rangle = \langle T_{\mathrm{D}} \rangle . \tag{66}$$

It is in fact a generalization of the well-known relationship in the BG ensemble,

$$\langle K(p) \rangle_{\mathrm{BG};\beta} \equiv \frac{\int_{\mathbb{R}^{2n}} K(p) \mathrm{e}^{-\beta E(x,p)}\, dxdp}{\int_{\mathbb{R}^{2n}} \mathrm{e}^{-\beta E(x,p)}\, dxdp} = \frac{n}{2\beta}, \tag{67}$$

as shown in Appendix B, which also gives the proof of Eq. (66). Considering Eq. (54), relation (66) implies $\langle T_{\mathrm{P}} \rangle = \langle T(x,p,Q) \rangle$, which is expected from the third equation in EOM (5), because we then get $\left\langle \dot{\zeta} \right\rangle = nk_{\mathrm{B}} \langle T_{\mathrm{P}} - T(x,p,Q) \rangle = 0$. Remember that we have obtained $\langle T_{\mathrm{P}} \rangle = \langle T_{\mathrm{D}} \rangle \sim \gamma/k_{\mathrm{B}}$.

III. SIMULATION METHOD

We applied the current method to two systems, a physical model system using a 1-dimensional double-well (1DW) potential, and a realistic protein system, chignolin in explicit solvent. These numerical simulations were performed to address the following three issues.

(i) Validation: Since the current method is designed to produce the target probability distributions, we validated the method by evaluating the generated distributions, including their marginal distributions. This was done for both of the systems as much as possible. See the following two subsections for the technical details.

(ii) Kinetics and parameter dependence: First, the kinetics was revealed by trajectories and correlation functions. In particular, since the aim of the current method is to control the physical temperature, $T_{\mathrm{P}} \equiv 2K(p)/nk_{\mathrm{B}}$, via the dynamical temperature, $T_{\mathrm{D}} \equiv 1/k_{\mathrm{B}}\sigma(Q) = T(x, p, Q)$, in a dynamic manner, the observations of the time developments of both T_{D} and T_{P} are critical. It is also very important to examine the dependence of quantities, including T_{P} and T_{D}, on the newly defined system parameters in the current method, such as c_{Z}, c_{Y}, $\mathbf{M}_{\mathrm{T}}$, and l. This examination was done in detail with the 1DW system, since the essential features can be easily captured in a model system.

(iii) Applicability to sampling: From this viewpoint, it is important to efficiently explore the phase space without the trajectory entrapment due to the ruggedness of the potential energy surface. The temperature fluctuations provided by the current method are expected to surmount this problem. The sampling ability in the current method is investigated with both the 1DW model and protein systems.

The numerical integrator for integrating the EOM, Eq. (5), was constructed from the exact flows of individual decomposed fields [43] for X'. For details see Appendix C.

A. 1DW model system

The 1DW system is defined by an energy function for $(x, p) \in \mathbb{R}^2$ such that

$$E(x, p) = \frac{1}{2}\mathbf{M}^{-1}p^2 + c_U(x^2 - 1)^2,$$

where c_U is the barrier height between the double wells. $\mathbf{M} = 1$ and $c_U = 5$ were used in this study, for which all variables in this model system are dimensionless ($k_{\mathrm{B}} = 1$). Since the exact marginal distribution is available in this system, it is suitable to validate the current method. The 1DW system also provides a simple model that yields the entrapment of the trajectory in either of two wells.

The distributions are evaluated as follows. The 1D marginal distribution densities were calculated for all of the variables: coordinate x, momentum p, and control variable ζ for the physical system, and inverse dynamical temperature $\beta = \sigma(Q)$, momentum $\mathcal{P}$, and control variable η for the temperature system. Here, specifically, the 1D marginal distribution of x is obtained using Eq. (33), where the theoretical distribution density can be estimated by 1D and 2D integrations, and the simulated distribution density was estimated by the LHS of Eq. (33), $\overline{\overline{\chi_C}}/|C|$, with a finite-time approximation. Similar procedures were utilized for p. The theoretical distribution of $\beta = \sigma(Q)$ can be obtained by Eq. (43). The theoretical distributions for the remaining variables, $\mathcal{P}$, ζ, and η, are exactly obtained via Eqs. (39), (40), and (41), respectively. The convergence of the 1D distribution density of x was monitored by the total error, defined by $\Delta(t) \equiv \int_{\mathbb{R}} |\rho_{\mathrm{Theo}}(x) - \rho^t_{\mathrm{Sim}}(x)| \, dx \in [0,\, 2]$, where ρ_{Theo} is the theoretical density and ρ^t_{Sim} is the simulated density evaluated up to time t. To examine more detailed distributions, 2D marginal distribution densities were calculated for (x, p), $(Q, \mathcal{P})$, and (ζ, η). The reweighting to the BG distribution density, $\rho_{\mathrm{BG}}(x, p) \equiv \mathrm{e}^{-\beta_{\mathrm{BG}} E(x,p)}$, was done by Eq. (35) via $\rho_{\mathrm{TRG}} \equiv \rho_{\mathrm{BG}}$.

The simulation parameters are as follows: $c_{\mathrm{Z}} = c_{\mathrm{Y}} = 1$ [Eqs. (42a) and (42b)], $\mathbf{M}_{\mathrm{T}} = 1$ [Eq. (4)], $c = 1$ and $l = 2.24$ [Eq. (55)]. The value of l was to set the oscillating frequency of Q to be $\omega_Q \sim 1$ [see Eq. (A5); and see below for α_1]. Here, c_{Z}, c_{Y}, and $\mathbf{M}_{\mathrm{T}}$ are the parameters that appear in the distributions of ζ, η, and $\mathcal{P}$ [Eqs. (40), (41), and (39), respectively], which are not the main variables, but the control variables. l is not essential to the distribution, but appears in the EOM through the transformation between β and Q. The only theoretically clear fact for these parameters is that they should be positive. Although there may be good strategies to determine their optimal values (if they exist, as discussed in the original NH equation for Nosé's mass), it is more favorable if the method is almost irrelevant to these parameter values, by maintaining the ergodic condition. Thus, regarding c_{Z}, c_{Y}, $\mathbf{M}_{\mathrm{T}}$, and l, we varied the individual values, by 0.1 and 10 times the default values indicated above, in order to investigate the dependence of the method on these parameters. Note that c was omitted in the investigation of this dependence, since it is clear as stated in Sec. III1.

In contrast, for the parameters α_1, α_2 [Eq. (56)] and U_0 [Eq. (59)], which are relevant to the distributions of the main variables x, p, and β, we simply fixed the values as $\alpha_1 = \alpha_2 = 4$ and $U_0 = 0$, regardless of the scheme to assign these values. This is because the theoretical distribution is known for this simple model system, so we do not need to set $\langle h(\beta) \rangle$. The assignment scheme was used for the chignolin system, as described below.

We integrated 10^9 time steps with a unit time of 1×10^{-3}. The initial values were $x(0) = 1$,

$p(0) = 1$, $\zeta(0) = 0$, $Q(0) = 0$, $\mathcal{P}(0) = 1$, and $\eta(0) = 0$.

B. Explicitly solvated chignolin system

Chignolin is a ten-residue designed peptide, which forms a stable (beta)-hairpin in water [44]. To validate the current method and show the improved sampling efficiency for a system with a number of degrees of freedom, this method was applied to the folding process of chignolin in explicit solvent, which has been frequently used for investigating various molecular simulation methods [45–49].

The initial structure of the chignolin molecule was one of the 18 NMR structures in the PDB entry 1UAO [44]. A rectangular simulation box was constructed with a margin of 12 Å to the boundary of the box. The solution system contained 1941 TIP3 water molecules [50], together with two sodium ions for neutralizing the simulation system (total 5963 atoms). After an equilibrium run under the NTP ensemble to allow the simulation box to be relaxed to the size of $40.2 \times 39.8 \times 38.5$ Å^3, a 300-ns MD simulation for Eq. (5) was performed with the timestep of 1 fs, using the AMBER ff03 force field [51]. The simulation was carried out using the class library for multicopy and multiscale MD simulations, μ^2lib [52].

Even in this system, the marginal distributions of the variables, ζ, $\mathcal{P}$, and η can be evaluated for both the theoretical and simulated values, in exactly the same way as that in the 1DW system, as stated in Sec. II G. In contrast, it is difficult to obtain the theoretical distributions of x, p, and β for large systems, in general. Thus, for this system we instead calculated the free energy landscapes, which are concerned with the distributions of (x, p) and provide an indication to the direct relationship to experiments. For β, we measured the average of the dynamical temperature $1/k_{\mathrm{B}}\beta = 1/k_{\mathrm{B}}\sigma(Q)$, where the theoretical value was estimated as described in Sec. II H. The method reweighting to the BG distribution is the same as that in the 1DW case.

The parameters used were $c_{\mathrm{Z}} = 3.3 \times 10^{-2}$ (ps·kcal/mol)$^{-2}$ [Eq. (42a)], $c_{\mathrm{Y}} = 2.1 \times 10^{2}$ ps^{-2} [Eq. (42b)], and $\mathbf{M}_{\mathrm{T}} = 2.4 \times 10^{-3}$ ps^2 [Eq. (4)], which are related to the distributions of the control variables. We set $l = 1.6 \times 10^3$ (no dimension) [Eq. (55)]. Here, l and $\mathbf{M}_{\mathrm{T}}$ were set so that the oscillation of Q has the period $\tau_Q \sim 3$ ps, where τ_Q is approximately estimated as $2\pi/\omega_Q = 2\pi l\sqrt{\mathbf{M}_{\mathrm{T}}/(\alpha_1 + 1)}$ [see Eq. (A5)]; α_1 has been fixed in advance according to the scheme, as specifically described below. τ_Q should not be too small, as compared with the period of the equilibrated oscillations of the molecular system. To choose these values, we considered, as well as the information about the parameter dependence resulting from the study of the model system, a biomolecular simulation context such that the slowest timescale of the T_D motion is comparable to that of the protein motion related to structural change.

We set the values of the parameters α_1, α_2 [Eq. (56)] and U_0 [Eq. (59)], which are related to the distributions of x, p, and β, according to the scheme described in Sec. II H and Sec. III 2. The parameter values of f_G were set by $\alpha_1 = 24691$ (no dimension) and $\alpha_2 = 17173$ (kcal/mol), such that $\Phi(\alpha)$ [Eq. (64)] yields $\gamma/k_\mathrm{B} = 350$ K, which is near the folding temperature. It follows from Eq. (63) that $k_\mathrm{B}\beta_0 = 1/350$ K^{-1}. To set U_0 with Eq. (62), we performed a preliminary BG dynamics simulation at temperature $1/k_\mathrm{B}\beta_0$ and estimated the energy average, $\epsilon(\beta_0) \equiv \langle E \rangle_{\mathrm{BG};\beta_0}$, at approximately -11000 kcal/mol. Thus, we set $U_0 = 11000$ kcal/mol. To check the accuracy of this estimation of $\epsilon(\beta_0)$, we also applied the reweighting method to the BG distribution at β_0, and obtained $\epsilon(\beta_0) = -11012$ kcal/mol, which was quite consistent with the simulation input. We set $c = \langle \beta \rangle_{f_\mathrm{G}} = \alpha_1/\alpha_2 = 1.438$ $(\mathrm{kcal/mol})^{-1}$ [Eq. (55)].

IV. RESULTS

A. 1DW system

Figure 1 shows the 1D marginal distribution densities for all of the variables: x, p, and ζ for the physical system, and $\beta = \sigma(Q)$, $\mathcal{P}$, and η for the temperature system. The simulated distributions agreed very well with the theoretical distributions for the individual variables. The results reweighting to the BG distribution density with $\beta_\mathrm{BG} = 1$ were also satisfactory for x and p, as shown in Figs. 1(a) and 1(b), respectively. These simulated distributions were obtained at time $t = 10^6$. The convergence was also studied. The total error measured by $\Delta(t)$ for the distribution of x, which seems to be the most suitable variable considering the distribution characteristic to this 1DW system as exhibited in Fig. 1(a), demonstrated a marginally small value at $t \gtrsim 10^5$ and then well-converged results at $t = 10^6$ [see Fig. 1(a) in Supplemental Material [31]]. The simulated results of the 2D marginal distribution shown in Fig. 2 successfully reproduced the theoretical distributions: the errors were sufficiently small, as indicated by the standard deviations of the discrepancies between the simulated and theoretical density values, which were 2.3×10^{-3}, 1.6×10^{-3}, and 2.0×10^{-3} for (x,p), $(Q,\mathcal{P})$, and (ζ,η), respectively. These results indicate that a sufficiently accurate distribution was created by the current method.

Figure 3(a) shows the time developments of $T_{\mathrm{D}}=\sigma(Q)^{-1}$ and $T_{\mathrm{P}}=2K(p)$. We see that the overall T_{P} obeys T_{D}: when T_{D} is large, T_{P} is large on average and oscillates with a large amplitude, and vice versa. This behavior seems to be compatible with expectations from the theoretical relationship, $\langle T_{\mathrm{P}}\rangle=\langle T_{\mathrm{D}}\rangle$ [Eq. (66)]. Namely, T_{D} is considered to control the behavior of T_{P} endowed with an oscillation of T_{D} itself. Note that the potential energy of the physical system, $U(x)$, also shows good correlation with T_{P} [Fig. 3(b)]. The conservation of the invariant function [Eq. (C4)] indicates the success of the numerical integration [see Fig. 3(b)].

Regarding the dependence on the values of the parameters c_{Z}, c_{Y}, $\mathbf{M}_{\mathrm{T}}$, and l, we first confirmed that the distribution error $\Delta(t)$, generated by varying the individual parameter value, exhibited well-convergent behavior and became sufficiently small [Fig. 1(b) in Supplemental Material [31]]. This indicates that these parameter-value sets also produced correct distributions under the ergodic condition. The time developments of the phase-space variables were then thoroughly examined, by changing these parameter values in the same manner. In Fig. 4(a) we see that T_{D} does not depend strongly on c_{Z}. This result comes from the fact that T_{D} is the variable of the temperature system, while c_{Z} is a parameter of the physical system [c_{Z} defines the distribution of ζ, which directly controls (x,p)]. $T_{\mathrm{D}}=\sigma(Q)^{-1}$, which is represented by the coordinate, Q, of the temperature system, also does not depend strongly on the temperature-system thermostat parameter, c_{Y}. This is similar to the behavior of the single NH equation (of the physical system), where the coordinate does not strongly depend on the thermostat parameter. As expected, a smaller mass $\mathbf{M}_{\mathrm{T}}$ leads to faster oscillation of T_{D}. Similarly, a smaller l tends to generate faster T_{D} oscillation, a situation for which Eqs. (58) and (55) are concerned. Figure 4(b) shows that T_{P} obeys T_{D} fundamentally while maintaining its original oscillations on the double wells, as observed in Fig. 3, and that the parameter dependence on the T_{P} kinetics is thus similar to that on T_{D}. The trajectories of x imply no direct dependence on the four parameters (Fig. 5). The indirect relationships to T_{P} or T_{D} may come from how frequently the vibrational fluctuation within the wells is amplified to cross the energy barrier between the double wells. A larger T_{P} often seems to induce the crossing, as typically seen around $t = 100$ with $l = 22.4$. This does not contradict the correlation observed between $U(x)$ and $T_{\rm D}$. The trajectories for the other phase-space variables, ζ, η, and $\mathcal{P}$, are also shown in Figs. 2, 4 and 5 in Supplemental Material [31], respectively. Their dependencies on the parameters were almost conceivable from the behavior of the single NH, considering the role of each parameter and the fact that the current method provides the coupling of two NH systems. See Sec. V of Supplemental Material [31] for their details and interesting nonlinear oscillating trajectories in individual cases.

B. Chignolin system

To further verify the current method for a realistic and complex system, the 1D marginal distributions in the 300-ns chignolin simulation were first examined. The distributions for ζ, $\mathcal{P}$, and η in Fig. 6 show good agreement between the exact and simulated values, with the standard deviations of their differences being 1.3×10^{-3}, 1.0×10^{-1}, and 1.0×10^{-1}, respectively. These sufficiently small errors indicate that the simulation reproduces the theoretical distributions for a large system, such as a protein in solution.

The averages of the physical temperature, $T_{\rm P} = 2K(p)/nk_{\rm B}$, and the dynamical temperature, $T_{\rm D} = 1/k_{\rm B}\sigma(Q)$, were estimated. We obtained the simulation result that $\overline{\overline{T_{\rm D}}} = 343.6$ K, which is consistent with the setting obtained from our theoretical finding, $\langle T_{\rm D}\rangle = \langle 1/k_{\rm B}\beta\rangle \simeq \gamma/k_{\rm B} = 350$ K. Furthermore, we confirmed the relation with very high accuracy, such that $\overline{\overline{T_{\rm P}}} = 343.6$ [K] $= \overline{\overline{T_{\rm D}}}$, which corresponds to the theoretical relationship $\langle T_{\rm P}\rangle = \langle T_{\rm D}\rangle$ [Eq. (66)]. These results mean that the parameter assignment scheme of f worked successfully, by the accurately managed sampling with respect to the temperature-related quantities for this realistic system.

The physical temperature $T_{\rm P}$ and the dynamical temperature $T_{\rm D}$ were then investigated in terms of dynamics. Figure 7(a) shows the large fluctuations for both $T_{\rm D}$ and $T_{\rm P} \sim 350 \pm 30$ K, implying large enhancement in the configurational space, which is seen in the large fluctuation of the potential energy $U(x)$ [Fig. 7(b)]. More importantly, a clear correlation is seen for both $T_{\rm D}$ and $T_{\rm P}$, which is strengthened by the results obtained for the total 300-ns run shown in Fig. 7(c), because of $T_{\rm P} \propto K(p)$. Accordingly, $K(p)$ also correlates strongly with $U(x)$ [Fig. 7(d)], which is in contrast to the BG dynamics behavior, in which the dynamics of K and U are almost independent [see Fig. 7(d)]. The observed correlation between T_{D}, K, and U indicates that the large fluctuation of T_{D} regulated by the current method allows the enhanced explosion in (x, p)-space via the nonequilibrated dynamics in it.

The current method together with the reweighting formula allows conformational sampling under the BG ensemble at an arbitrary temperature within the sampled T_{P} range. To clarify this, the free energy surface was calculated along the following two distances between the hydrogen-bonding atoms, Asp3N–Thr8O (d_{38}) and Asp3N–Gly7O (d_{37}), as the appropriate reaction coordinates [46, 47]. These hydrogen bonds are indicators of the formation of the native and misfolded structures, respectively; i.e., the native hydrogen bond between Asp3N and Thr8O is exchanged with a transient hydrogen bond between Asp3N and Gly7O, through the twisting motion of the segment around Gly7 and Thr8 [Fig. 8(a)]. The calculated free-energy profile at 340 K successfully extended over a broad range including energy minima corresponding to the native structure, (d_{37}, d_{38}) $\sim$ (6 Å, 3 Å), and the misfolded structure (d_{37}, d_{38}) $\sim$ (3 Å, 7 Å), indicating enhanced sampling relative to the standard all-atom MD simulation [46, 47].

We also measured the probability of the folded state, p_{fold}, of chignolin in solution, by using the advantage of the current method that the conformational samplings under the BG ensemble are achieved with respect to the overall temperature range. Here, p_{fold} was defined by the probability (under the BG ensemble) that the hydrogen bond between Asp3N–Thr8O is formed; i.e., the corresponding distance is less than 4.5 Å. Figure 8(b) shows the decrease of p_{fold} with temperature, as expected. The folding temperature (the temperature at which $p_{\mathrm{fold}} = 1/2$ holds) was found to be $\sim$ 340 K, which was comparable to the experimental and simulation values (343 K [44, 48]).

V. CONCLUSIONS

We presented coupled NH equations by demonstrating the physical counterpart of the formalism and by analyzing the roles and functions of individual variables and parameters. The coupled NH equations comprise the NH equation of the physical system and the NH equation of the temperature system. This coupling brings the nonequilibrium temperature to the original physical system, by the control of the physical-system temperature T_{P} via the dynamical (functional) temperature T_{D} that is derived by the temperature system. The nonequilibrium temperature is statistically designed with an arbitrarily given distribution density $f(\beta)$, under the ergodic condition of the total dynamical system. We provided both the estimation of the expected values of temperature-variable functions for a given f and conversely the estimation of the parameter values of f such that it yields the desired expected values. We theoretically showed $\langle T_{\mathrm{P}} \rangle = \langle T_{\mathrm{D}} \rangle$ and numerically confirmed the features of the control mechanism. The nonequilibrium temperature is intimately related to the superstatistics and non-extensive statistical mechanics. The functions defined in Eqs. (53), (55) and (56), which assign the BG distribution for a physical system and the gamma distribution for β with $m = 1$, yield the Tsallis distribution for the physical variables (x, p) and the Toda potential for the temperature-system coordinate Q. As these are the results of the simplest case of $m = 1$, we expect more possibilities, as well as capabilities, for the outcomes from $m > 1$.

The current scheme worked well with the 1DW model system and the explicitly solvated chignolin system. The detailed validations in the 1DW revealed that the correct distributions were produced and that this ability was stable, with respect to changes in the system-parameter values within a two order of magnitude range. The dynamics were naturally affected by these parameter values and yielded interesting nonlinear oscillating behavior, while maintaining compatibility with the statistical description. The potential energy of the physical system correlated with T_{P} and T_{D}, implying the effective sampling in the phase space. The present method together with the reweighting procedure calculated the folding free energy landscape of chignolin in a wide range of temperatures, and derived the folding temperature that is comparable to the experimental value.

Note added: After our submission of the first version of this paper, the paper by Gobbo and Leimkuhler was published [53], where a continuous tempering for a physical system is realized. By introducing an extended variable ξ, they define a temperature function $\tilde{T}(\xi)$ that retains the target BG equilibrium temperature within a part of the total extended phase space, $\Omega_{\Delta} \equiv \{(x, p, \xi, \ldots)| \; |\xi| \leq \Delta\}$. To let ξ move diffusively with resulting in its uniform distribution, a help of e.g. metadynamics [54] is needed. This method is reweighting free, and instead the trajectory that can be used as the BG distribution data is not continuous because a part of the trajectory within Ω_{Δ} should be selected. In contrast, our method is self-contained for both the physical and temperature systems and then yields a direct reweighting with continuous trajectories to reconstruct the BG distribution. Furthermore, our general formalism allows applications for any other parameters than the temperature [27].

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Appendix A: Oscillating behavior of Q

We discuss the oscillating behavior of Q [or $(Q, \mathcal{P})$] near an “equilibrium” (stable) point, $Q_0^\epsilon \in \mathbb{R}^m$, where we assume $\nabla \tilde{U}_\epsilon(Q_0^\epsilon) \sim 0 \in \mathbb{R}^m$ for any given ϵ. The expansion of the temperature-system potential energy [Eq. (8)], $\tilde{U}_\epsilon$, with respect to Q yields

$$\tilde{U}_\epsilon(Q) \sim \tilde{U}_\epsilon(Q_0^\epsilon) + D\tilde{U}_\epsilon(Q_0^\epsilon)(Q - Q_0^\epsilon) + \frac{1}{2} D^2 \tilde{U}_\epsilon(Q_0^\epsilon)((Q - Q_0^\epsilon), (Q - Q_0^\epsilon)) \tag{A1a}$$

$$\sim \tilde{U}_\epsilon(Q_0^\epsilon) + \frac{1}{2}((Q - Q_0^\epsilon) \,|\, H_0^\epsilon \,(Q - Q_0^\epsilon)), \tag{A1b}$$

where $H_0^\epsilon \equiv (D_i D_j \tilde{U}_\epsilon(Q_0^\epsilon))$ is the Hessian of $\tilde{U}_\epsilon$ at $Q = Q_0^\epsilon$. By substituting Eq. (A1b) into $\dot{Q}$ and $\dot{\mathcal{P}}$ in Eq. (5), we get

$$\ddot{Q} = -\mathbf{M}_\mathrm{T}^{-1} \, \nabla \tilde{U}_{E(x,p)}(Q) - \tau_Y(\eta) \, \dot{Q} \in \mathbb{R}^m \tag{A2a}$$

$$\sim -\mathbf{M}_\mathrm{T}^{-1} \, H_0^{E(x,p)} \, (Q - Q_0^{E(x,p)}) - \tau_Y(\eta) \, \dot{Q}. \tag{A2b}$$

This seems to be the NH equation of m-dimensional harmonic oscillators with spring constants $H_0^{E(x,p)}$ and equilibrium positions $Q_0^{E(x,p)}$, wherein these two quantities are not constants, but variables depending on the physical system through its energy $E(x, p)$.

In the case of the function setting in Sec. III, we thus have

$$\ddot{Q} \sim -\omega_Q^2 \, (Q - Q_0^{E(x,p)}) - \tau_Y(\eta) \, \dot{Q} \in \mathbb{R}, \tag{A3}$$

where the unique equilibrium point exists for each ϵ, represented by

$$Q_0^\epsilon = l \ln \left[\frac{\alpha_1 + 1}{c(\epsilon + \alpha_2 + U_0)} \right] \tag{A4}$$

and the angular velocity ω_Q is given by

$$\omega_Q \equiv \sqrt{\frac{H_0^{E(x,p)}}{M_T}} = \frac{1}{l}\sqrt{\frac{\alpha_1+1}{M_T}}, \tag{A5}$$

for which the Hessian,

$$H_0^{\epsilon} = \frac{\alpha_1+1}{l^2} > 0, \tag{A6}$$

becomes irrelevant to the physical system energy $\epsilon \equiv E(x,p)$.

Appendix B: Equality of the averages of the physical and dynamical temperatures

We show that

$$\langle K(p)\rangle = \frac{nk_{\mathrm{B}}}{2}\,\langle 1/k_{\mathrm{B}}\sigma(Q)\rangle \tag{B1}$$

holds, where $1/k_{\mathrm{B}}\sigma(Q)$ is a specialized form of the temperature function $T(x,p,Q)$ [see Eq. (54)], due to the choice of Eq. (59) [or Eq. (53)] provided in Sec. III. From Eq. (25), we see that the LHS and RHS of Eq. (B1) are represented, respectively, as

$$\langle K(p)\rangle = \frac{\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^m)} K(p)\mathrm{e}^{-\beta(E(x,p)+U_0)}\, f(\beta)dxdpd\beta}{\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^m)} \mathrm{e}^{-\beta(E(x,p)+U_0)}\, f(\beta)dxdpd\beta} \tag{B2}$$

and

$$\frac{n}{2}\,\langle 1/\sigma(Q)\rangle = \frac{\frac{n}{2}\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^m)} (1/\beta)\mathrm{e}^{-\beta(E(x,p)+U_0)}\, f(\beta)dxdpd\beta}{\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^m)} \mathrm{e}^{-\beta(E(x,p)+U_0)}\, f(\beta)dxdpd\beta}. \tag{B3}$$

Although the individual integrations cannot be explicitly represented in general, due to the complexities of the integrations with respect to x, the equality in Eq. (B1) can be confirmed. Namely, the speculation of the numerators in the RHSs of Eqs. (B2) and (B3) leads to the equality, if

$$\int_{\mathbb{R}^{2n}} K(p)\mathrm{e}^{-\beta E(x,p)}\, dxdp = \frac{n}{2\beta}\int_{\mathbb{R}^{2n}} \mathrm{e}^{-\beta E(x,p)}\, dxdp$$

holds for any β. Thus, by recalling an elementary fact about the kinetic-energy average in the BG ensemble,

$$\langle K(p)\rangle_{\mathrm{BG};\beta} \equiv \frac{\int_{\mathbb{R}^{2n}} K(p)\mathrm{e}^{-\beta E(x,p)}\, dxdp}{\int_{\mathbb{R}^{2n}} \mathrm{e}^{-\beta E(x,p)}\, dxdp} = \frac{n}{2\beta}, \tag{B4}$$

we confirm Eq. (B1). In other words, Eq. (B1) is a *generalized relationship* of Eq. (B4). Notice that the results are irrelevant to the choice of functions σ and f.

Regarding a more general situation, where $T(x,p,Q)$ defined by Eq. (6) is used instead of $1/k_{\mathrm{B}}\sigma(Q)$, we here similarly give a sufficient condition for the validity of

$$\langle K(p)\rangle = \frac{nk_{\mathrm{B}}}{2}\langle T(x,p,Q)\rangle . \tag{B5}$$

Similar to the above, we see that

$$\langle K(p)\rangle = \frac{\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^m)} K(p)\rho_{\mathrm{E}}^{U_0}(E(x,p),\beta)\, f(\beta) dx dp d\beta}{\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^m)} \rho_{\mathrm{E}}^{U_0}(E(x,p),\beta)\, f(\beta) dx dp d\beta},$$

$$\langle T(x,p,Q)\rangle = \frac{\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^m)} T(x,p,\sigma^{-1}(\beta))\rho_{\mathrm{E}}^{U_0}(E(x,p),\beta)\, f(\beta) dx dp d\beta}{\int_{\mathbb{R}^{2n}\times\sigma(\mathbb{R}^m)} \rho_{\mathrm{E}}^{U_0}(E(x,p),\beta)\, f(\beta) dx dp d\beta}.$$

A sufficient condition for the equality, Eq. (B5), is that

$$\int_{\mathbb{R}^n} K(p)\rho_{\mathrm{E}}^{U_0}(U(x)+K(p),\beta) dp = \frac{nk_{\mathrm{B}}}{2}\int_{\mathbb{R}^n} T(x,p,\sigma^{-1}(\beta))\rho_{\mathrm{E}}^{U_0}(U(x)+K(p),\beta)\, dp \tag{B6}$$

holds for all x and β. Using Eq. (6) and performing the surface integrations on Eq. (B6) [where $\mathbf{M}$ in $K(p) = (p|\mathbf{M}^{-1}p)/2$ is assumed to be symmetric and positive-definite matrix, similarly to get Eq. (B4)], we have the following relationship equivalent to Eq. (B6),

$$\int_0^\infty R_0^{x,\beta}(k) k^{\frac{n}{2}} dk = -\frac{n}{2}\int_0^\infty \frac{(R_0^{x,\beta}(k))^2}{R_1^{x,\beta}(k)} k^{\frac{n}{2}-1} dk, \tag{B7}$$

where $R_0^{x,\beta}(k) \equiv \rho_{\mathrm{E}}^{U_0}(k+U(x),\beta)$ and $R_1^{x,\beta}(k) \equiv D_1\rho_{\mathrm{E}}^{U_0}(k+U(x),\beta)$. Note that Eq. (59) satisfies Eq. (B7).

Appendix C: Numerical integration

For integrating Eq. (5), we used the simplest P2S1 scheme [43, 55], which can be given by the following pseudo computer code (h is the unit time step and N_{step} is the total timesteps):

```
Set initial values $(x, p, \zeta, Q, \mathcal{P}, \eta, v)$
CALL atomic interaction $(x, F(x), U(x))$
CALL kinetic energy $(p, K(p))$
$t = h/2$
Do $l = 1,\ N_{\text{step}}$ (time loop)
    $v \leftarrow t\mathcal{Y}(\omega) + v \in \mathbb{R}$
    $\mathcal{P} \leftarrow \exp[-t\tau_{\text{Y}}(\eta)]\mathcal{P} \in \mathbb{R}^m$
    $\eta \leftarrow t[2K_{\text{T}}(\mathcal{P}) - m] + \eta \in \mathbb{R}$
    $\mathcal{P} \leftarrow tF_{\text{T}}(x, p, Q) + \mathcal{P} \in \mathbb{R}^m$
    $Q \leftarrow t\mathbf{M}_{\text{T}}^{-1}\mathcal{P} + Q \in \mathbb{R}^m$
    $p \leftarrow \exp[-tS_1(x, Q, \zeta)]p \in \mathbb{R}^n$
    CALL kinetic energy $(p, K(p))$
    $\zeta \leftarrow [2K(p) - S_2(x, Q)]\, t + \zeta \in \mathbb{R}$
    $p \leftarrow tF(x) + p \in \mathbb{R}^n$
    $x \leftarrow 2t\mathbf{M}^{-1}p + x \in \mathbb{R}^n$
    CALL atomic interaction $(x, F(x), U(x))$
    $p \leftarrow tF(x) + p \in \mathbb{R}^n$
    CALL kinetic energy $(p, K(p))$
    $\zeta \leftarrow [2K(p) - S_2(x, Q)]\, t + \zeta \in \mathbb{R}$
    $p \leftarrow \exp[-tS_1(x, Q, \zeta)]p \in \mathbb{R}^n$
    $Q \leftarrow t\mathbf{M}_{\text{T}}^{-1}\mathcal{P} + Q \in \mathbb{R}^m$
    CALL kinetic energy $(p, K(p))$
    $\mathcal{P} \leftarrow tF_{\text{T}}(x, p, Q) + \mathcal{P} \in \mathbb{R}^m$
    $\eta \leftarrow t[2K_{\text{T}}(\mathcal{P}) - m] + \eta \in \mathbb{R}$
    $\mathcal{P} \leftarrow \exp[-t\tau_{\text{Y}}(\eta)]\mathcal{P} \in \mathbb{R}^m$
    $v \leftarrow t\mathcal{Y}(\omega) + v \in \mathbb{R}$
    $(x, p, \zeta, Q, \mathcal{P}, \eta, v)$ defines variables at $l$ time steps
enddo
```

. (C1)

Here, we set $S_1(x, Q, \zeta) \equiv T(x, p, Q)\, \tau_{\mathrm{Z}}(\zeta)$ and $S_2(x, Q) \equiv n k_{\mathrm{B}} T(x, p, Q)$, assuming that $T(x, p, Q)$ is independent of p, ensured by the function setting in Sec. III 1 [see Eq. (54)]. v is an auxiliary variable to formulate an extended space [43, 55], and

$$\mathcal{Y}(\omega) \equiv -T(x, p, Q)\, \mathrm{div}\, X(\omega), \tag{C2}$$

where $X(\omega) \equiv X'(\omega)/T(x, p, Q)$ and X' is given by Eq. (10). Then, an extended ODE,

$$\dot{\omega} = X'(\omega), \tag{C3a}$$

$$\dot{v} = \mathcal{Y}(\omega), \tag{C3b}$$

can be constructed and it has an invariant function [43], L, defined by

$$L(\omega, v) = -\ln \rho(\omega) + v. \tag{C4}$$

Eq. (C1) is an integration scheme of the extended ODE, Eq. (C3), and the numerical error of the integration can be checked by monitoring the value of equation (C4) in the integration process.

Here "atomic interaction $(x, F(x), U(x))$" is a routine that calculates the atomic force $F(x) \equiv -\nabla U(x)$ and the potential $U(x)$, based on the current coordinates $x \equiv (x_1, \ldots, x_n) \in \mathbb{R}^n$. Note that this part, viz., the evaluation of the potential energy and the force, is the most time consuming [the computational costs is of $\mathcal{O}(n^2)$], but they are only evaluated once at the one stage.

The "kinetic energy $(p, K(p))$" routine calculates the atomic kinetic energy $K(p)$ based on the current momenta $p \equiv (p_1, \ldots, p_n) \in \mathbb{R}^n$. Equation (C1) needs three "CALL kinetic energy" steps. Although these computational costs, each of which is $\mathcal{O}(n)$, can be neglected against the $\mathcal{O}(n^2)$, it may be convenient if we can reduce the cost (considering some sophisticated iteration process for attaining further efficiency). One way to do this is to replace the ordering of the operations $p \leftarrow \exp[-tS_1(x, Q, \zeta)]p$ and $\zeta \leftarrow [2K(p) - S_2(x, Q)]\, t + \zeta$ in Eq. (C1), which retains the evaluation number of the atomic energy and force.

$F_{\mathrm{T}}(x, p, Q) \equiv -\nabla \tilde{U}_{E(x,p)}(Q)$ is the forces for the temperature system, and it needs less computational cost.

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Figure Captions:

FIG. 1. 1D marginal distribution densities for the 1DW model. Simulated and theoretical densities of (a) x, (b) p, and (c) ζ for the physical system, and (d) the inverse dynamical temperature $\beta = \sigma(Q)$, (e) $\mathcal{P}$, and (f) η for the temperature system are shown. The results of the reweighting to the BG distribution densities with $\beta_{\mathrm{BG}} = 1$ are also shown for x and p, as well as the associated theoretical values. All quantities are dimensionless.

FIG. 2. 2D marginal distribution densities for the 1DW model. (a) (x, p), (b) (Q, $\mathcal{P}$) and (c) (ζ, η).

FIG. 3. (a) Time courses of physical temperature $T_{\mathrm{P}} = p^2$ and dynamical temperature $T_{\mathrm{D}} = \sigma(Q)^{-1}$ for the 1DW model. (b) Time courses of potential energy U and invariant L.

FIG. 4. Time courses of (a) physical temperature $T_{\mathrm{P}} = p^2$ and (b) dynamical temperature $T_{\mathrm{D}} = \sigma(Q)^{-1}$ as functions of the following four parameters for the 1DW model. First row: $c_{\mathrm{Z}} = 0.1$ (red), 1 (green) and 10 (blue), second row: $c_{\mathrm{Y}} = 0.1$ (red), 1 (green) and 10 (blue), third row: $\mathbf{M}_{\mathrm{T}} = 0.1$ (red), 1 (green) and 10 (blue), and fourth row: $l = 22.4$ (red), 2.24 (green) and 0.224 (blue). $c_{\mathrm{Z}} = c_{\mathrm{Y}} = 1$, $\mathbf{M}_{\mathrm{T}} = 1$, and $l = 2.24$ are used unless otherwise mentioned. All quantities are dimensionless.

FIG. 5. Time courses of x for 1DW. Color schemes are the same as in Fig. 4.

FIG. 6. Distribution densities of (a) ζ, (b) $\mathcal{P}$ and (c) η for the chignolin system.

FIG. 7. Time courses of (a) T_{P} (black) and T_{D} (red), and (b) U for the chignolin system. Scatter plots of (T_{D}, $K(p)$) in blue and (U, $K(p)$) in magenta are also shown in (c) and (d), respectively. In (d), (U, $K(p)$) obtained by conventional canonical MD is also shown in green.

FIG. 8. (a) Free-energy profile in the plane of two hydrogen-bond distances for the chignolin system, after reweighting to the BG distribution at 340 K. Three representative structures are also shown. (b) Probability of the folded state under the BG distribution as a function of temperature. See text for details.