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Comment on "Preserving the Boltzmann ensemble in replica-exchange molecular dynamics" [J. Chem. Phys. 129, 164112 (2008)]

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In a recent paper,[1] the basic concepts of constant temperature molecular dynamics (CTMD) were criticized; replica-exchange molecular dynamics[2] (REMD) was also criticized since studies of REMD employ CTMD techniques. Among the criticisms,[3] I here address the issue regarding general theoretical aspects of Nosé–Hoover[4,5] (NH) and related methods. Specifically, in Secs. VB and VC of Ref. 1, it is stated in mathematical manners that (I) the NH equation is not measure-preserving[6] (MP); (II) the NH and NH chain[7] systems are not ergodic under the Boltzmann–Gibbs (BG) measure; and (III) the Nosé Hamiltonian system (HS) as well as the Nosé–Poincaré[8] (NP) HS is not ergodic. The MP property is the starting point for discussing the ergodic theory,[9] which deals with the transformations that *preserve the structures* of measure spaces. MP also implies maintaining the probability of a set of states at constant value and is critical for inducing the compatibility between the MD equation and the BG distribution, owing to the existence of a measure associate with the BG density factor. The ergodicity explains that the time series via MD leads to the BG ensemble. If statements (I)–(III) are completely true, then the typical CTMD above may not produce the correct BG ensemble, and then the basis of not only the REMD but many other techniques, including generalized-ensemble methods, is undermined, leading to the suspicion of the correctness of many simulation results. This study demonstrates, by a mathematical standpoint, that (I) is misleading, (II) is not proved since the argument in Ref. 1 is incorrect, and (III) is not proved in a meaningful sense and the proof of (III) in Ref. 1 does not imply the failure of the production of the BG ensemble in these two HSs.

Point (I). The NH equation is MP. For analyzing the subjects, I now consider the measure space $(\Omega,\mathcal{M},P)$, where measure P has the following density ρ defined on a domain Ω of $\mathbb{R}^{2n+1}$ (i.e., $P=\rho d\omega:\mathcal{M}\to\mathbb{R}_+$; ρ is the Radon–Nikodym derivative with respect to Lebesgue measure $d\omega$ on $\mathbb{R}^{2n+1}$ and $\mathcal{M}\equiv\mathcal{L}\cap\Omega$, with $\mathcal{L}$ denoting Lebesgue measurable sets in $\mathbb{R}^{2n+1}$): $\rho(\omega)\equiv\exp[-E_{\rm ext}(\omega)/k_BT_{\rm ex}]$, where $\omega\equiv(q,p,\zeta)\in\Omega$ is a phase space (PS) point and $E_{\rm ext}(\omega)\equiv U(q)+K(p)+(Q/2)\zeta^2[Q>0,K(p)\equiv(p|pM^{-1})/2]$. Assume that the potential function U is smooth (e.g., C^2) and ρ is integrable. First, I discuss the exact flow $\{T_t:\Omega\to\Omega|t\in\mathbb{R}\}$ of the NH vector field $X_{\rm NH}:\omega\mapsto(pM^{-1},-\nabla U(q)-\zeta p,(2K(p)-nk_BT_{\rm ex})/Q)$, assuming its completeness. MP means that $P(T_t^{-1}A)=P(A)$ holds for any time $t\in\mathbb{R}$ and any set $A\in\mathcal{M}$; this relation can also be represented[10] in terms of the density by using Liouville equation, div $\rho X=0$. Since $X\equiv X_{\rm NH}$ satisfies this equation, the NH flow $\{T_t\}$ is MP on $(\Omega,\mathcal{M},P)$. To consider a one-step-map numerical integrator (NI) $\Psi:\Omega\to\Omega$ as well, I shall formulate statements via (measurable) map $T:T\equiv\Psi$ in the case of a C^1-diffeomorphic NI and $T\equiv T_t$ in the case of a flow for which each statement should be read in a suitable context, e.g., by adding "for all t." Then, the MP property is "$P(T^{-1}A)=P(A)$ for any $A\in\mathcal{M}$," which is equivalent to "$\int_\Omega fdP=\int_\Omega f\circ TdP\ \forall f\in L^1(P)\cdots(1)$." Using change of variables, $\int_\Omega fdP=\int_\Omega f(\omega)\rho(\omega)d\omega=\int_\Omega(f\circ T)(\rho\circ T)|J_T|d\omega$, where $J_T(\omega)\equiv\det DT(\omega)$ is the Jacobian of T. Equation (1) is thus valid if "$(\rho\circ T)|J_T|=\rho\cdots(2)$."[11]

In contrast, Ref. 1 argues that since "$\int_\Omega fdP=\int_\Omega(f\circ T)\rho|J_T|d\omega=\int_\Omega f\circ T|J_T|dP\cdots(3)$" holds,[12] Eq. (1) is not valid unless $|J_T|=1$; thus, the NH equation is not MP. However, Eq. (3) is based on the misunderstanding that ρ, or $E_{\rm ext}$, is an invariant function (IF),

$$E_{\rm ext}\circ T=E_{\rm ext}\ \cdots[\text{Relation in Ref. 1}]. \tag{4}$$

In the case of a flow, in fact, Eq. (4) is erroneous, which is deduced from $(d/dt)E_{\rm ext}(T_t(\omega))=-nk_BT_{\rm ex}\zeta(t)$. In the case of NI, the map that exactly meets Eq. (4) has never been known, to the best of my knowledge. In fact, the NI considered in Ref. 1 (App. A1) does not satisfy Eq. (4). The correct condition for MP is not $|J_T|=1$, but another condition, e.g., Eq. (2).[13]

Point (II). Basically, the ergodicity is investigated using the *measure that is preserved* by the target map or flow. For MP map T, the ergodicity is defined by the condition that an invariant set is essentially trivial: $[T^{-1}A=A\Rightarrow P(\Omega\backslash A)=0$ or $P(A)=0]$ for all $A\in\mathcal{M}$. This is equivalent to, e.g., condition (A) $(\lim_{m\to\infty}(1/m)\Sigma_{i=0}^{m-1}f(T^i(\omega))=\int_\Omega fdP/P(\Omega)$ (a.e.) for $\forall f\in L^1(P))$ or condition (B) $([P(A),P(B)>0\Rightarrow\exists m\in\mathbb{N},P(T^{-m}A\cap B)>0]$ for $\forall A,B\in\mathcal{M})$. Condition (A) is an expression, suitable for the purpose of MD simulations, such that the long-time average (its existence is ensured at P-a.e. ω for P that is *preserved* by T) of function f equals the space average, weighted by the BG density in the current case. Condition (B) implies that a nontrivial part of B reaches A after m steps for any nontrivial sets A and B.

As stated, the definition of ergodicity and the equivalence between the conditions such as those above are valid *if* the map is MP. Reference 1 nevertheless debates the ergodicity and uses the equivalence, although it affirms that, as seen above, the NH system is *not MP*. This standpoint cannot be adapted for a standard context; however, we can investigate whether or not the following statements in Lemma 5.1 (Ref. 1) are valid: (i) condition (B) never holds for the NH system, and "thus," (ii) the NH system is not ergodic. To justify (i) in Ref. 1, sets $A, B \subset \Omega$ were prepared such that $E_{\text{ext}}(\omega) < c$ if $\omega \in A$ and $E_{\text{ext}}(\omega) > c$ if $\omega \in B$ for a constant c; then, it was inferred that $P(T^{-m}A \cap B) = 0 (\forall m)$ by considering that $\exists \omega \in T^{-m}A \cap B$ implies a contradiction between the relations $E_{\text{ext}}(\omega) = E_{\text{ext}}(T^m\omega) < c$ and $E_{\text{ext}}(\omega) > c$. However, the equality $E_{\text{ext}}(\omega) = E_{\text{ext}}(T^m\omega)$ is, as stated in point (I), not valid, so that (i) is not proved. Thus, (ii) is not confirmed. In the case of a flow, although a discussion on fine details would be needed, the logic presented in the proof of the lemma cannot be directly used since E_{ext} is not an IF. Thus, Lemma 5.1 is yet to be proved. The same explanation applies to the NH chain [Corol. 5.3 (Ref. 1)], and it is not clear if Theor. 5.2 (Ref. 1) based on Lemma 5.1 holds.

Point (III). The focus is the HS defined by the Nosé Hamiltonian $H(q,s,p,p_s)$, where $(q,s) \in \mathcal{Q}$ are the coordinates of an extended system[4] and $(p,p_s) \in \mathcal{P}$ are the conjugate momenta, and the HS defined by the NP Hamiltonian $\tilde{H} = s(H - H_0)$. Lemma 5.4 (Ref. 1) states that these two systems are not ergodic on whole PS, $\Gamma \equiv \mathcal{Q} \times \mathcal{P} \subset \mathbb{R}^{2n+2}$, by using the discussions similar to those done for Lemma 5.1: viz., by contriving sets $A, B \subset \Gamma$ with effort such that the trajectories starting from A do not reach B. Such an effort, however, is not necessarily required here. This is because in the case of a flow, it is clear that *any* HS (with a nontrivial, smooth, complete field) on the *whole* PS domain $\subset \mathbb{R}^{2N}$ ($N = n+1$ in the present cases) is *not ergodic* with respect to Lebesgue measure l on $\mathbb{R}^{2N}$. In fact, an invariant set M with $l(M), l(\Gamma \setminus M) > 0$ is yielded from the fact that the Hamiltonian is an IF. Rather, since no information on the dynamics is obtained by the nonergodicity on the whole Γ, a meaningful formulation of ergodicity should be performed for each constant energy surface (of the extended system), which is $\Sigma_e \equiv \{H = e\}$ for the Nosé case and $\tilde{\Sigma}_0 \equiv \{\tilde{H} = 0\}$ for the NP case, using an induced measure; in fact, the BG distribution can be generated in Σ_e for each e (Nosé)[4] or in $\tilde{\Sigma}_0 = \Sigma_{H_0}$ (NP).[8] Even if we consider the whole PS with a measure μ concentrated on any Σ_e, $\mu(A) = 0$ or $\mu(B) = 0$ is obtained [since $A \cap \Sigma_e = \phi$ or $B \cap \Sigma_e = \phi$ for any e, as shown from $A \subset \{H < d\}$ and $B \subset \{H > d\}$, where d is a constant given, according to the notation in Ref. 1, by $d \equiv \alpha + \beta + \gamma + \epsilon$], which is contradictory to the intent to show the failure of the condition that corresponds to condition (B) on the flow with $P \equiv \mu$. In the case of map T for H, similar discussions for the flow apply as long as it is assumed that $H \circ T = H$. Even if this assumption is not made for map for H or if a map for $\tilde{H}$ is considered, it is far from achieving a meaningful result on an established NI map $T = \Psi$.[14]

To conclude, Lemma 5.4 cannot be proved in a meaningful sense on the basis of the discussion in Ref. 1. The proof[1] of lemma 5.4 does not indicate that these HSs lead to incorrect time averages that affect the production of the intended BG ensemble.

The points (II) and (III) argued in Ref. 1 are very strong in that they mathematically state that the CTMD are not ergodic regardless of the conditions such as the number of degrees of freedom n, the values of parameters (Q, T_{ex}, etc.), and the details of potential function U (except boundedness). The current comment mathematically states that these proofs mathematically done in Ref. 1 are not valid. In contrast, the current comment does not mathematically states that the CTMD are ergodic. In fact, it is, in general, difficult to prove exactly the ergodicity of a given system.[15]

Conclusion. The criticisms[1] against the foundations of CTMD are confusing and cannot be accepted. They are mainly based on incorrect recognition, Eq. (4), and a misunderstanding of the ergodic-theoretical descriptions. Apart from the modification proposed in Ref. 1, the results pertaining to the CTMD should be based on a more rigorous treatment.

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[9] See, e.g., P. Billingsley, *Ergodic Theory and Information* (Wiley, New York, 1960).
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[11] See the material cited in Ref. 3 for an explanation of technical terms.
[12] Referring to other formulas in Ref. 1, I have corrected minor errors, e.g., f has been used instead of $f \circ T$.
[13] See the material cited in Ref. 3 for additional comments to the discussion in Ref. 1.
[14] See the material cited in Ref. 3 for a conclusive remark on point (III).
[15] However, many numerical simulations have suggested that the ergodicity of the CTMD depends on the conditions in such a manner that small and simple system is not ergodic (the results in Fig. 1 in Ref. 1 would be such examples for NP) while large and complicated system is expected to be ergodic (the results in Fig. 6 in Ref. 1 lack the examples for NP or NH). See the material cited in Ref. 3 for an additional remark.