Statistical mechanics of polarizable force fields based on classical Drude oscillators with dynamical propagation by the dual-thermostat extended Lagrangian

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Chetan Rupakheti,¹ Guillaume Lamoureux,² Alexander D. MacKerell, Jr.,³ and Benoît Roux^{1,a)}

AFFILIATIONS

¹Department of Biochemistry and Molecular Biology, University of Chicago, Chicago, Illinois 60637, USA

²Department of Chemistry and Center for Computational and Integrative Biology, Rutgers University, Camden, New Jersey 08102, USA

³Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, Maryland 21201, USA

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a) Author to whom correspondence should be addressed: roux@uchicago.edu

ABSTRACT

Polarizable force fields based on classical Drude oscillators offer a practical and computationally efficient avenue to carry out molecular dynamics (MD) simulations of large biomolecular systems. To treat the polarizable electronic degrees of freedom, the Drude model introduces a virtual charged particle that is attached to its parent nucleus via a harmonic spring. Traditionally, the need to relax the electronic degrees of freedom for each fixed set of nuclear coordinates is achieved by performing an iterative self-consistent field (SCF) calculation to satisfy a selected tolerance. This is a computationally demanding procedure that can increase the computational cost of MD simulations by nearly one order of magnitude. To avoid the costly SCF procedure, a small mass is assigned to the Drude particles, which are then propagated as dynamic variables during the simulations via a dual-thermostat extended Lagrangian algorithm. To help clarify the significance of the dual-thermostat extended Lagrangian propagation in the context of the polarizable force field based on classical Drude oscillators, the statistical mechanics of a dual-temperature canonical ensemble is formulated. The conditions for dynamically maintaining the dual-temperature properties in the case of the classical Drude oscillator are analyzed using the generalized Langevin equation.

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I. INTRODUCTION

Molecular dynamics (MD) simulation methodologies over the last two decades have seen significant developments in empirical force fields that include the explicit treatment of induced polarization.^{1–6} By allowing induced polarization to vary as a function of the molecular environment, these developments offer a significant advantage over widely used additive pairwise force fields. The induced polarization response has the potential to increase accuracy for atomic and molecular species ranging from atomic ions to complex heterogeneous systems such as lipid bilayers. Examples of the application of a polarizable model that yield quantitative

improvements over additive models include calculations of lipid bilayer membrane potential,⁷ ligand–protein binding affinities,⁸ peptide folding,⁹ base flipping,¹⁰ and ion competition around DNA.¹¹ These successes indicate the utility of polarizable models and the significant role they will play in MD simulations.

Dominating the computational requirements of polarizable models is the need to allow the inducible degrees of freedom, $\delta\mu$, to relax for each fixed set of nuclear coordinates in the context of the Born–Oppenheimer approximation,

$$\delta\mu_i = \alpha_i \left(\mathbf{E}_i^{(0)} + \mathbf{E}_i^{(\text{ind})} \right), \quad (1)$$

where $\mathbf{E}_i^{(0)}$ is the static electric field and $\mathbf{E}_i^{(\text{ind})}$ is the induced electric field that depends on the induced dipoles. Traditionally, Eq. (1) is solved iteratively for the set $(\delta\mu_1, \delta\mu_2, \dots)$ until self-consistency is satisfied to a selected tolerance. It is this self-consistent field (SCF) condition, which couples the i th induced dipole $\delta\mu_i$ to all other induced dipoles, that confers the many-body character to polarizable models. However, SCF calculations are computationally demanding, causing slow downs of an order of magnitude or more in polarizable vs additive simulations. Naively relaxing the SCF tolerance to accelerate the calculation is not really a viable option because it introduces uncontrolled lags and noises in the forces that govern the propagation, hereby leading to an ill-defined energy surface underlying the dynamic and equilibrium properties of the system. Numerous approaches have been proposed to accelerate the SCF convergence and design an efficient and accurate dynamical propagator, including time-reversible stable predictor-corrector methods,^{12,13} non-stationary iterative methods with preconditioner,¹⁴ matrix inversion methods,¹⁵ and the treatment of the SCF adiabatic dynamics via mass-zero constrained dynamics as a holonomic constraint.^{16,17} Non-iterative methods attempting to avoid altogether the many-body aspects of SCF induced polarization have also been proposed by limiting the induced dipoles to the first-order approximation determined from the permanent electric fields $\mathbf{E}_i^{(0)}$,^{18–20}

$$\delta\mu_i = \alpha_i \mathbf{E}_i^{(0)}, \quad (2)$$

which is then used to compute forces. This simple idea was exploited to parameterize the so-called inexpensive AMOEBA (iAMOEBA) classical polarizable water model.²¹ The OPTn approach of Brooks and co-workers further expands on this idea by using an n th order perturbation theory (OPTn) to empirically approximate the SCF calculation.^{22,23}

An alternative to the adiabatic SCF propagation is to treat the inducible variables as dynamical degrees of freedom using an extended Lagrangian. Soon after this was first introduced in the context of Car–Parrinello *ab initio* quantum mechanical simulations,²⁴ treatments of classical polarizable models followed with application to point dipoles,²⁵ fluctuating charges,^{26,27} and Drude oscillator (also called the shell or charge-on-spring model).²⁸ Multiple time step algorithms were designed to efficiently treat the rapid dynamics of the induced dipoles.²⁹ A central issue with an extended Lagrangian approach is to remain as faithful as possible to the adiabatic dynamics of the initial model by designing ways to limit the fluctuations of the inducible degrees of freedom. One strategy has been to introduce two independent thermostats, one at a temperature T for the physical degrees of freedom and one at a lower temperature T^* for the inducible degrees of freedom. This led to the polarizable force field based on classical Drude oscillators with the dual-Nosé–Hoover (dual-NH)³⁰ or dual-Langevin-Dynamics (dual-LD)³¹ thermostats. One expansion of this strategy, introduced to better control the energy distribution among the local degrees of freedom, is the temperature-grouped dual-Nosé–Hoover (tgNH) thermostat.³² Another expansion, which seeks to remain more closely faithful to the original adiabatic dynamics, is the inertial extended Lagrangian SCF iteration-free method (iEL/0-SCF).^{33–36}

To be truly useful, a force field must be able to accurately model large and complex condensed phase systems while remaining

sufficiently computationally inexpensive to allow extensive statistical sampling with long MD trajectories. Three principal methods are commonly used to model electronic polarization in atomic and molecular systems, induced dipoles, fluctuating charges, and classical Drude oscillators. Each has advantages and limitations with respect to the potential accuracy and computational requirements, as previously discussed.⁶ Given its computational efficiency and accuracy, the Drude model has a broad range of potential uses for molecular simulations. The extended Lagrangian approach in the context of the classical Drude oscillator model is particularly appealing.³⁰ As the Drude model introduces an auxiliary particle connected to the parent nucleus via a harmonic spring to treat the electronic degrees of freedom, dynamical propagation of the model within standard MD codes is fairly straightforward. As implemented in multiple programs, including NAMD,³¹ CHARMM,³⁷ OpenMM,³⁸ and Gromacs,³⁹ the Drude polarizable force field is approximately four-fold slower than additive models taking into account the use of a 1 fs vs 2 fs integration time step and the overhead associated with the Drude particles (one for each polarizable nucleus that includes all non-hydrogen atoms in the current implementation). The dual-thermostat extended Lagrangian can also be advantageously used in multi-canonical replica-exchange simulations and in alchemical free energy perturbation (FEP) calculations, making it an extremely convenient approach to study complex biomolecular systems. While dynamical transport properties may require more caution, equilibrium structural properties are fairly insensitive to the details of the dual-thermostat.⁴⁰

Ever since the introduction of the dual-thermostat extended Lagrangian propagator in 2003,³⁰ concerns have been expressed that it might not correctly represent the underlying adiabatic SCF potential energy surface of the system. One fear is that the cumulative effect of the dynamical induced degrees of freedom would corrupt the statistical mechanical distribution of states on the SCF energy surface. If this were the case, a number of computational schemes would be compromised by the dual-thermostat propagation. To state the issue in concrete terms, let us consider the ratio of Boltzmann factors,

$$R = \frac{e^{-U'/k_B T}}{e^{-U/k_B T}}, \quad (3)$$

which is a common quantity that is frequently involved in a wide range of algorithms, such as FEP calculation and multi-canonical replica-exchange. The total potential energy of the system is written as

$$U = U_{\text{scf}} + \delta U, \quad (4)$$

where U_{scf} is the true correct SCF energy and δU is some uncorrelated random “noise” arising from the non-SCF behavior of the induced polarization. Keeping the nuclei fixed and averaging over the noise, the ratio R becomes

$$\begin{aligned} \langle R \rangle &= \left\langle e^{-[U' - U]/k_B T} \right\rangle \\ &= \left\langle e^{-[U'_{\text{scf}} + \delta U' - U_{\text{scf}} - \delta U]/k_B T} \right\rangle \\ &= e^{-[U'_{\text{scf}} - U_{\text{scf}}]/k_B T} \times \left\langle e^{-\delta U'/k_B T} \right\rangle \times \left\langle e^{+\delta U/k_B T} \right\rangle \\ &= e^{-[U'_{\text{scf}} - U_{\text{scf}}]/k_B T} \times e^{\sigma^2/(k_B T)^2}, \end{aligned} \quad (5)$$

where σ^2 is related to the mean-square fluctuations of the noise (assuming that the noise is Gaussian with zero average). According to this argument, the result of a calculation relying on an extended Lagrangian simulation of a polarizable model is putatively corrupted by the cumulative effect of spurious errors that undermine the statistical mechanics of the system [we will actually see in Sec. II that FEP and replica-exchange molecular dynamics (REMD) are valid with the dual-thermostat propagator].

Our goal is to address these issues by clarifying the significance of the dual-thermostat extended Lagrangian propagation and follow through its consequences in the context of alchemical free energy perturbation (FEP) calculations and multi-canonical replica-exchange molecular dynamics (REMD) sampling schemes. In the following, we first establish the statistical mechanics of a dual-temperature canonical system. We then apply this analysis to FEP and REMD and explore the conditions for dynamically maintaining the dual-temperature properties in the case of the classical Drude oscillator.

II. THEORY

A. Statistical mechanics of dual-temperature canonical ensemble

Let us consider the potential energy $U(x, y)$, where x and y represent the nuclear and electronic (Drude) degrees of freedom in the system, respectively (although x and y are vectors, boldface symbols are not used to lighten up the notation). In practice, y represents the set of displacements of the reduced-mass Drude-nucleus oscillators,³⁰ but this point will not affect our main argument. The self-consistent field (SCF) energy $U_{\text{scf}}(x)$ corresponds to the function $U(x, y)$ evaluated at $y = y_{\text{scf}}$ satisfying the condition $\partial_y U(x, y) = 0$. In other words, $U_{\text{scf}}(x)$ is determined by minimizing the energy $U(x, y)$ with respect to y while keeping x fixed. Formally, this amounts to a dynamical propagation of the system under a set of holonomic constraints.^{16,17}

To clarify the statistical mechanical significance of the system, we first consider an idealized situation in which the degrees of freedom x and y are perfectly controlled by two separate thermostats at temperatures T and T^* , respectively. While this can be rigorously realized, if the y degrees of freedom are first thermalized at the temperature T^* , we envision that the system will be controlled by a dual-thermostat dynamical propagation scheme. Because the y degrees of freedom are kept close to the SCF solution, deviations are accurately described as a quadratic form

$$\begin{aligned} U(x, y) &= U(x, y)|_{y=y_{\text{scf}}} + \Delta U \\ &= U_{\text{scf}}(x) + \frac{1}{2}(y - y_{\text{scf}})^t \cdot \mathbf{M}^{-1} \cdot (y - y_{\text{scf}}), \end{aligned} \quad (6)$$

where $\mathbf{M}$ represents the covariance matrix for the y degrees of freedom (the inverse of the Hessian second derivative matrix). In principle, the matrix $\mathbf{M}$ depends on x although it is dominated by the stiff harmonic spring with force constant K_D connecting the Drude particle to its parent nucleus (those are the diagonal terms of the matrix). Because those springs are independent of the configuration of the system, the matrix $\mathbf{M}$ is expected to be fairly insensitive to the configuration (x, y) of the system. For example, the second

derivative matrix for one isolated Drude oscillator experiencing a uniform external electric field has the form

$$\{\mathbf{M}\}_{\text{single oscillator}} = \begin{pmatrix} K_D & 0 & 0 \\ 0 & K_D & 0 \\ 0 & 0 & K_D \end{pmatrix}, \quad (7)$$

which is *independent* of the magnitude of the external electric field. Furthermore, the coupling between oscillators is via electric fields that are essentially constant on the length-scale of the nucleus-Drude pair (field gradients are small). Letting $\delta y \equiv y - y_{\text{scf}}$, the conditional probability distribution $P_{T^*}(y|x)$ can be written as a multivariate Gaussian

$$P_{T^*}(y|x) = \frac{e^{-(\delta y^t \cdot \mathbf{M}^{-1} \cdot \delta y)/2k_B T^*}}{[(2\pi k_B T^*)^n \det \mathbf{M}]^{1/2}}, \quad (8)$$

where n is the number of y degrees of freedom. The determinant of the matrix $\mathbf{M}$ is expected to be largely insensitive to the configuration of the system. The joint probability distribution for x and y is

$$P_{T,T^*}(x, y) = P_{T,T^*}(x) \times P_{T^*}(y|x), \quad (9)$$

where $P_{T,T^*}(x)$ is the marginal probability distribution for the x degrees of freedom,

$$P_{T,T^*}(x) = \int dy P_{T,T^*}(x, y). \quad (10)$$

It is useful to define the effective potential $\bar{U}_{T^*}(x)$,

$$\begin{aligned} \bar{U}_{T^*}(x) &= -k_B T^* \ln \left[C \int dy e^{-U(x,y)/k_B T^*} \right] \\ &= -k_B T^* \ln \left[C \int dy e^{-[U_{\text{scf}} + \Delta U]/k_B T^*} \right] \\ &= U_{\text{scf}}(x) - k_B T^* \ln \left[C [(2\pi k_B T^*)^n \det \mathbf{M}]^{1/2} \right], \end{aligned} \quad (11)$$

which plays the role of a potential of mean force for the degrees of freedom x under the condition that the y degrees of freedom were integrated out at temperature T^* (C is a normalization constant). Assuming that the x degrees of freedom are thermalized at temperature T , the marginal probability distribution for the x degrees of freedom is

$$P_{T,T^*}(x) = \frac{e^{-\bar{U}_{T^*}(x)/k_B T}}{\int dx e^{-\bar{U}_{T^*}(x)/k_B T}}. \quad (12)$$

Combining Eqs. (8) and (12) with Eq. (9), we can write the joint probability distribution for x and y as

$$\begin{aligned} P_{T,T^*}(x, y) &= P_{T,T^*}(x) \times P_{T^*}(y|x) \\ &= \frac{e^{-\bar{U}_{T^*}(x)/k_B T}}{\int dx e^{-\bar{U}_{T^*}(x)/k_B T}} \times \frac{e^{-\Delta U/k_B T^*}}{\int dy e^{-\Delta U/k_B T^*}} \\ &= \frac{e^{-U_{\text{scf}}/k_B T} e^{-(\delta y^t \cdot \mathbf{M}^{-1} \cdot \delta y)/2k_B T^*}}{\int dx \int dy e^{-U_{\text{scf}}/k_B T} e^{-(\delta y^t \cdot \mathbf{M}^{-1} \cdot \delta y)/2k_B T^*}}. \end{aligned} \quad (13)$$

Alternatively, this distribution may be expressed as a standard canonical Boltzmann distribution at temperature T for a system with effective potential energy $U_{\text{eff}}(x, y)$,

$$P_{T,T^*}(x, y) = \frac{e^{-U_{\text{eff}}/k_B T}}{\int dx \int dy e^{-U_{\text{eff}}/k_B T}} = \frac{e^{-[U_{\text{scf}} + \eta \Delta U]/k_B T}}{\int dx \int dy e^{-[U_{\text{scf}} + \eta \Delta U]/k_B T}}, \quad (14)$$

where $U_{\text{eff}}(x, y) = U_{\text{scf}}(x) + \frac{1}{2} \eta (\delta y^t \cdot \mathbf{M}^{-1} \cdot \delta y)$, with $\eta = T/T^*$. Once the joint distribution $P_{T,T^*}(x, y)$ is established, then the

statistical mechanics properties of the system are completely and unambiguously defined. On the basis of $P_{T,T^*}(x, y)$, the significance of simulation methods, such as free energy, potential of mean force, and multi-canonical replica-exchange, can be directly examined.

B. Alchemical free energy perturbation

Formally, the alchemical free energy difference of a system as a function of a thermodynamic coupling parameter λ can be written as

$$\begin{aligned} e^{-[G(\lambda') - G(\lambda)]/k_B T} &= \frac{\int dx \int dy e^{-U_{\text{eff}}(x, y; \lambda')/k_B T}}{\int dx \int dy e^{-U_{\text{eff}}(x, y; \lambda)/k_B T}} \\ &= \frac{\int dx \int dy P_{T,T^*}(x, y; \lambda')}{\int dx \int dy P_{T,T^*}(x, y; \lambda)} \\ &= \frac{\int dx e^{-U_{\text{scf}}(\lambda')/k_B T} [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2}}{\int dx e^{-U_{\text{scf}}(\lambda)/k_B T} [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2}} \\ &= \frac{\int dx e^{-U_{\text{scf}}(\lambda')/k_B T} [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2}}{\int dx e^{-U_{\text{scf}}(\lambda')/k_B T}} \frac{\int dx e^{-U_{\text{scf}}(\lambda)/k_B T}}{\int dx e^{-U_{\text{scf}}(\lambda)/k_B T} [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2}} \\ &\times \frac{\int dx e^{-U_{\text{scf}}(\lambda)/k_B T}}{\int dx e^{-U_{\text{scf}}(\lambda)/k_B T} [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2}} \\ &= \left\langle [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2} \right\rangle_{(\text{scf}, \lambda')} e^{-[G_{\text{scf}}(\lambda') - G_{\text{scf}}(\lambda)]/k_B T} \left\langle [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2} \right\rangle_{(\text{scf}, \lambda)}^{-1} \\ &= e^{-[G_{\text{scf}}(\lambda') - G_{\text{scf}}(\lambda)]/k_B T} \frac{\left\langle [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2} \right\rangle_{(\text{scf}, \lambda')}}{\left\langle [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2} \right\rangle_{(\text{scf}, \lambda)}}, \end{aligned} \quad (15)$$

and the resulting free energy difference is

$$G(\lambda') - G(\lambda) = G_{\text{scf}}(\lambda') - G_{\text{scf}}(\lambda) - k_B T \ln \left[\frac{\left\langle [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2} \right\rangle_{(\text{scf}, \lambda')}}{\left\langle [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2} \right\rangle_{(\text{scf}, \lambda)}} \right]. \quad (16)$$

The last term corresponds to a configurational entropy associated with the fluctuations of the orthogonal y Drude degrees of freedom. This contribution is independent of the temperature T^* and does not formally cancel out, even in the limit $T^* \rightarrow 0$. The implication is that the dual-thermostat system does not exactly correspond to the energy surface of the SCF system. This is expected as adiabatic SCF dynamics corresponds to propagation under holonomic constraints.^{16,17} However, this term is expected to be negligible because the determinant of the matrix M is dominated by the stiff harmonic spring connecting the Drude particle to its parent nucleus and insensitive to the configuration of the system [$\ln(1) = 0$], implying that

$$G(\lambda') - G(\lambda) \approx G_{\text{scf}}(\lambda') - G_{\text{scf}}(\lambda). \quad (17)$$

In practice, we typically carry out the FEP calculations within the windowing method directly on the total unmodified potential energy $U(x, y)$,

$$\begin{aligned}
\left\langle e^{-[U(\lambda')-U(\lambda)]/k_B T} \right\rangle_{(T,T^*,\lambda)} &= \frac{\int dx \int dy e^{-[U(\lambda')-U(\lambda)]/k_B T} e^{-U_{\text{eff}}(\lambda)/k_B T}}{\int dx \int dy e^{-U_{\text{eff}}(\lambda)/k_B T}} \\
&= \frac{\int dx \int dy e^{-[U_{\text{scf}}(\lambda')+\Delta U(\lambda')-U_{\text{scf}}(\lambda)-\Delta U(\lambda)]/k_B T} e^{-[U_{\text{scf}}(\lambda)+\eta\Delta U(\lambda)]/k_B T}}{\int dx \int dy e^{-[U_{\text{scf}}(\lambda)+\eta\Delta U(\lambda)]/k_B T}} \\
&= \frac{\int dx e^{-U_{\text{scf}}(\lambda')/k_B T} \int dy e^{-[\Delta U(\lambda')+(\eta-1)\Delta U(\lambda)]/k_B T}}{\int dx e^{-U_{\text{scf}}(\lambda)/k_B T} \int dy e^{-\eta\Delta U(\lambda)/k_B T}} \\
&= \frac{\int dx e^{-U_{\text{scf}}(\lambda')/k_B T} \int dy e^{-(\delta y^i \cdot M_{\lambda'}^{-1} \cdot \delta y + (\eta-1)\delta y^i \cdot M_{\lambda}^{-1} \cdot \delta y)/2k_B T}}{\int dx e^{-U_{\text{scf}}(\lambda)/k_B T} \int dy e^{-\eta(\delta y^i \cdot M_{\lambda}^{-1} \cdot \delta y)/2k_B T}} \\
&\approx \frac{\int dx e^{-U_{\text{scf}}(\lambda')/k_B T} [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2}}{\int dx e^{-U_{\text{scf}}(\lambda)/k_B T} [(2\pi\eta k_B T)^n \det \mathbf{M}]^{1/2}} \\
&= e^{-[G_{\text{scf}}(\lambda')-G_{\text{scf}}(\lambda)]/k_B T} \frac{\left\langle ((2\pi\eta k_B T)^n \det \mathbf{M})^{1/2} \right\rangle_{(\text{scf},\lambda')}}{\left\langle ((2\pi\eta k_B T)^n \det \mathbf{M})^{1/2} \right\rangle_{(\text{scf},\lambda)}} \\
&\approx e^{-[G_{\text{scf}}(\lambda')-G_{\text{scf}}(\lambda)]/k_B T},
\end{aligned} \tag{18}$$

which is the same result as above. The main assumption used here is that the matrix is insensitive to the thermodynamic coupling λ , i.e., $M_{\lambda} \approx M_{\lambda'}$. This assumption is justified on the basis of the argument illustrated by Eq. (7).

In charging free energy calculations based on a nonpolarizable force field, a direct application of the FEP windowing method is adequate. However, in FEP calculations based on the polarizable Drude model, the total potential energy U is not truly pairwise decomposable due to the presence of induced polarization on all the dipoles in the system. For instance, the magnitude of the y degrees of freedom depends implicitly on the parameter λ , which couples the solute to the solvent. A direct application of the windowing method is possible, but it requires a re-calculation of the SCF potential energy U_{scf} for all values of perturbed λ . A naive application of the windowing method as commonly used with additive non-polarizable models

$$\left\langle e^{-[U(\lambda')-U(\lambda)]/k_B T} \right\rangle_{T,T^*,\lambda} \stackrel{\text{wrong}}{=} \int dx \int dy e^{-[U(x,y_{\text{scf}}(\lambda);\lambda')-U(x,y_{\text{scf}}(\lambda);\lambda)]/k_B T} \times P_{T,T^*}(x,y;\lambda) \tag{19}$$

is incorrect because the potential energy $U(x, y_{\text{scf}}(\lambda); \lambda')$ has the fixed charges scaled according to the coupling λ' , while the y polarizable degrees of freedom (the Drude oscillators) remain consistent with the coupling λ . In other words, $U(x, y_{\text{scf}}(\lambda'); \lambda') \neq U(x, y_{\text{scf}}(\lambda); \lambda')$. This could be resolved by re-imposing the SCF conditions on the configuration for all values of λ' , $U(x, y_{\text{scf}}(\lambda'); \lambda')$, but this becomes computationally inefficient and cumbersome. The simplest and most efficient approach to compute the charging free energy is to use thermodynamic integration (TI),

$$\begin{aligned}
\Delta G &= \int_0^1 d\lambda \int dx \int dy \left[\frac{\partial U(x,y;\lambda)}{\partial \lambda} \right] P_{T,T^*}(x,y;\lambda) \\
&= \int_0^1 d\lambda \left\langle \frac{\partial U(y(\lambda);\lambda)}{\partial \lambda} \right\rangle_{(\lambda)}.
\end{aligned} \tag{20}$$

Formally, this works because it proceeds from the derivative of the potential for a single value of λ , hence, bypassing the need to have converged the SCF condition for two values of λ . This approach has been successfully applied by us and others on a range of systems.^{8,41–44}

C. Multi-canonical replica-exchange

A REMD tempering algorithm is constructed from a generalized ensemble comprising multiple systems at different temperatures. Formally, for the exchange probability between two systems to be correct, the proper canonical distribution must be satisfied for both systems. Key to the REMD algorithm is that the ratio of the probability for swapping configuration obeys the proper Boltzmann factor. It is important to note that, in practice, the REMD simulations are carried out by calculating the swapping probability based on the total unmodified potential energy $U(x, y)$. However, the configurations of the n th replica at temperature T_n are distributed according to $P_{T_n,T^*} \propto \exp[-U_{\text{eff}}/k_B T]$. Therefore, to demonstrate that the REMD algorithm is valid for this system, we must show that averaging out the y degrees of freedom is equivalent to carrying out REMD simulations with the SCF energy.

Considering the probability for swapping the coordinates of the nuclei (x) and Drudes (y) of the n th and m th replica at temperature T_n and T_m , we get

$$\int dy_n \int dy_m e^{-[U(x_n, y_n) - U(x_m, y_m)]/k_B T_n - [U(x_m, y_m) - U(x_n, y_n)]/k_B T_m} P_{T_n, T^*}(x_n, y_n) P_{T_m, T^*}(x_m, y_m) \\ = e^{-[U_{\text{scf}}(x_n) - U_{\text{scf}}(x_m)]/k_B T_n - [U_{\text{scf}}(x_m) - U_{\text{scf}}(x_n)]/k_B T_m} \quad (21)$$

For example, this can be shown by carrying the average over the inducible degrees of freedom y_n explicitly,

$$\left\langle e^{-U(x_n, y_n)/k_B T_n + U(x_n, y_n)/k_B T_m} \right\rangle_{(y_n)} = \frac{\int dy_n e^{-U(x_n, y_n)/k_B T_n + U(x_n, y_n)/k_B T_m} e^{-U_{\text{eff}}/k_B T_n}}{\int dy_n e^{-U_{\text{eff}}/k_B T_n}} \\ = \frac{\int dy_n e^{-[U_{\text{scf}} + \Delta U]/k_B T_n + [U_{\text{scf}} + \Delta U]/k_B T_m} e^{-U_{\text{scf}}/k_B T_n - \Delta U/k_B T^*}}{\int dy_n e^{-U_{\text{scf}}/k_B T_n - \Delta U/k_B T^*}} \\ = e^{-U_{\text{scf}}/k_B T_n + U_{\text{scf}}/k_B T_m} \frac{\int dy_n e^{-\Delta U/k_B T_n + \Delta U/k_B T_m} e^{-\Delta U/k_B T^*}}{\int dy_n e^{-\Delta U/k_B T^*}} \\ = e^{-U_{\text{scf}}/k_B T_n + U_{\text{scf}}/k_B T_m} \frac{\int dy_n e^{-\frac{1}{2}(\delta y_n^t \cdot \mathbf{M}^{-1} \cdot \delta y_n)(1/k_B T_n - 1/k_B T_m + 1/k_B T^*)}}{\int dy_n e^{-\frac{1}{2}(\delta y_n^t \cdot \mathbf{M}^{-1} \cdot \delta y_n)/k_B T^*}} \\ = e^{-U_{\text{scf}}/k_B T_n + U_{\text{scf}}/k_B T_m} \frac{[(2\pi)/(1/k_B T_n - 1/k_B T_m + 1/k_B T^*)]^n \det \mathbf{M}}{[(2\pi)/(1/k_B T^*)]^n \det \mathbf{M}}^{1/2} \\ \approx e^{-U_{\text{scf}}/k_B T_n + U_{\text{scf}}/k_B T_m} \frac{[(2\pi k_B T^*)]^n \det \mathbf{M}}{[(2\pi k_B T^*)]^n \det \mathbf{M}}^{1/2} \\ = e^{-U_{\text{scf}}(x_n)/k_B T_n + U_{\text{scf}}(x_n)/k_B T_m}, \quad (22)$$

where the equivalence is verified as long as

$$\frac{1}{k_B T_n} - \frac{1}{k_B T_m} + \frac{1}{k_B T^*} \approx \frac{1}{k_B T^*} \quad (23)$$

While T^* is about 1 K, T_n and T_m are within a range of 300 K–400 K in typical REMD simulations. For this reason, $1/300 \text{ K} - 1/400 \text{ K} + 1/1 \text{ K} = 1/0.9992 \text{ K} \approx 1/1 \text{ K}$. A similar development may be carried out for the average over the y_m degrees of freedom.

III. RESULTS AND DISCUSSION

The analysis above shows that meaningful statistical mechanics of the Drude model within the context of a dual-temperature canonical ensemble is possible as long as the two equilibrium distributions $P_{T, T^*}(x)$ and $P_{T^*}(y|x)$ are well defined. These distributions can be established if one can separately thermostat two sets of degrees of freedom, the nuclei degrees of freedom x , and the Drude oscillators y . For example, such an ideal dual thermostating could be achieved by carrying out interspersed cycles of Metropolis Monte Carlo at two different temperatures on the x and y degrees of freedom. While of limited computational efficiency, such a dual Monte Carlo algorithm would formally generate the two separate equilibrium distributions $P_{T, T^*}(x)$ and $P_{T^*}(y|x)$. This describes an ideal situation where the “warm” nuclei and the “cold” Drude oscillators are thermally isolated from one another. Our interest is to examine the conditions under which this ideal situation can be approximated

via an extended Lagrangian dynamical propagation algorithm operating with two thermostats, and how this compares with an SCF propagation.

A. Drude thermalization

The SCF condition implies that the Drude particles are relaxed to the potential energy minimum near their parent atoms. Under the extended Lagrangian scheme, some deviation from the SCF is expected. Of paramount importance for the statistical mechanical significance of the dual-thermostat extended Lagrangian propagation is the magnitude of the excess potential energy relative to the SCF solution

$$\Delta U = U(x, y) - U_{\text{scf}}(x). \quad (24)$$

Specifically, the average excess energy ΔU relative to SCF must be consistent with the temperature T^* from the distribution $P_{T^*}(y|x)$. Because the y degrees of freedom are kept close to the SCF solution, it is assumed that such deviation can be described by the quadratic form defined in Eq. (8). According to the equipartition partition theorem, the relation between the average excess potential energy per Drude oscillator and the temperature T^* is

$$\langle \Delta u \rangle = \frac{3}{2} k_B T^*, \quad (25)$$

where $\langle \Delta u \rangle = \langle \Delta U \rangle / n$. The excess energy predicted from the simple harmonic analysis is 0.002 98 (T^*/K) kcal/mol. To examine the validity of this analysis, a box of 1981 SWM4 water molecules⁴⁵ was

simulated at constant volume using the dual-thermostat extended Lagrangian propagator. The configurations thus obtained were then post-processed to determine $\langle\Delta u\rangle$, the average excess energy per Drude oscillator. For each configuration, the nuclei were fixed, and the energy was minimized with respect to the Drude particle position to recover the SCF solution. The excess energy per oscillator, Δu , is obtained as the potential energy difference before (extended Lagrangian) and after minimization (SCF). The results assuming different masses for the Drude particles are shown in Fig. 1. The excess potential energy relative to the SCF solution increases linearly in accord with the equipartition prediction. It is also observed that the deviation from the prediction increases as the mass of the Drude particles gets larger. The generally recommended value for the mass of the Drude particle of 0.4 amu leads to a closer match to the theoretical slope. A similar procedure was previously used to examine the deviation from the SCF solution for an ionic liquid, indicating that the deviation represented a small percentage of the total potential energy on average.⁴⁰ For the present system with nuclei at 300 K and Drude oscillators at 1 K, the average potential energy U before minimization is on the order of $-19\,565.6$ kcal/mol, for a relative change $\Delta u/U$ of about 0.06%. The behavior of the energy deviation was also examined for different integration time steps during the extended Lagrangian simulations. As shown in Fig. 2, deviations from the equipartition prediction are noticeable as the time step is increased. This observation also supports the generally recommended value for the integration time step of 1 fs (or less) for polarizable systems with Drude particles.

FIG. 1. Average potential energy deviation from the SCF limit per Drude oscillator ($\langle\Delta u\rangle$) during dual-NH thermostat simulations propagated with different mass of Drude particles and temperatures. The lines represent the excess potential energy calculated for a Drude mass of 0.4 amu (blue), 0.6 amu (orange), and 0.8 amu (green). The dashed line represents the excess potential energy predicted from the harmonic analysis, $\langle\Delta u\rangle = 0.00298 (T^*/K)$ kcal/mol. Simulations were performed on a pre-equilibrated box comprising 1981 SWM4 molecules under periodic boundary conditions with NVT conditions for 4 ns. Constant volume was used for the sake of clarity to focus directly on the thermostat behavior. Long-range electrostatics was treated with particle-mesh Ewald (PME). Extended Lagrangian based MD was used to generate the trajectory using two thermostats and varying the temperatures T^* of the Drude particles. To calculate Δu , the trajectory was post-processed by fixing the nuclei and minimizing the energy with respect to the Drude particle position to match the SCF solution.

FIG. 2. Average potential energy deviation from the SCF limit per Drude oscillator ($\langle\Delta u\rangle$) during dual-NH thermostat simulations propagated with different integration time steps and temperatures. The simulation procedure was the same as described in the caption of Fig. 1 with a Drude mass of 0.4 amu. The lines represent the excess potential energy calculated for a time step of 0.125 fs (red), 0.25 fs (green), 0.50 fs (orange), and 1.0 fs (blue, the same data appear in Fig. 1). The dashed line represents the excess potential energy predicted from the harmonic analysis, $\langle\Delta u\rangle = 0.00298 (T^*/K)$ kcal/mol.

A small excess energy offset remains, both in Figs. 1 and 2, even as the temperature of the Drude oscillator is taken almost to zero. While the origin of this offset is entirely unclear, we suspect that it may be caused by oscillators that are experiencing an anharmonic energy surface relative to the optimal SCF energy minimum. As shown in Fig. 3, there is near perfect agreement between the simulation and the equipartition prediction when all non-bonded interactions are switched off. This suggests that the non-bonded interactions from the surrounding bulk affect the dynamics of the Drude oscillators, leading to deviation from the equipartition theorem prediction. Despite these small deviations, the magnitude of Δu remains largely consistent with an effective quadratic form, and its average remains consistent with the equipartition theorem at a temperature T^* . The deviations are caused, in part, by a combination of factors, including the inaccuracies in the discrete dynamical propagation, anharmonic contributions affecting the Drude oscillators, and the energy transfer between the nuclei thermostated at temperature T and the Drude oscillators thermostated at temperature T^* .

To illustrate the energy transfer or heat flow from the surrounding nuclei to the Drude oscillators, we examine the increase in $\langle\Delta u\rangle$ in the absence of thermostat acting on the Drude oscillators. The same box of SWM4 water molecules was simulated under SCF conditions to record a number of independent configurations. The SCF configurations were then used to start a new trajectory without the thermostat acting on the Drude oscillators, thus allowing them to progressively warm up and thermalize. These un-thermostated trajectories were then post-processed using the protocol. For each configuration, the nuclei were fixed, and the energy was minimized with respect to the Drude particle position to recover the SCF solution. The total excess energy ΔU is obtained as the potential energy difference before (extended Lagrangian) and

FIG. 3. Average potential energy deviation from SCF per Drude oscillator ($\langle \Delta u \rangle$) under varying temperatures with non-bonded interactions turned off. The simulation procedure was the same as described in the caption of Fig. 1 with a Drude mass of 0.4 amu (but without non-bonded interactions) and the time step of 1 fs. The dashed line represents the excess potential energy predicted from the harmonic analysis, $\langle \Delta u \rangle = 0.00298 (T^*/K)$ kcal/mol.

after minimization (SCF). The results are shown in Fig. 4, assuming different masses for the Drude particles. The results show that, in the absence of direct thermostating, the Drude oscillators progressively warm up away from the SCF solution. While this behavior is entirely expected, it is important to realize that the rate of thermalization of the oscillators is actually fairly slow. With a Drude mass of 0.4 amu, the excess energy per oscillator only increases by

FIG. 4. Average excess potential energy Δu per oscillator relative to the SCF limit in simulations initiated from a SCF starting configuration at $t = 0$, the time step of 1 fs, and without a thermostat applied to the Drude oscillators (allowing them to progressively warm up). The lines represent the excess potential energy calculated for a Drude mass of 0.4 amu (yellow), 0.6 amu (blue), 0.8 amu (red), and 1.0 amu (green). The slopes are 0.0005 (kcal/mol)/ns, 0.0071 (kcal/mol)/ns, 0.0379 (kcal/mol)/ns, and 0.1095 (kcal/mol)/ns for the Drude mass of 0.4 amu, 0.6 amu, 0.8 amu, and 1.0 amu, respectively. The estimated relaxation times are >500 ns, 126 ns, 24 ns, and 8 ns for the Drude mass of 0.4 amu, 0.6 amu, 0.8 amu, and 1.0 amu, respectively.

0.000 505 (kcal/mol)/ns. Interestingly, as the mass of the Drude particle is increased, the excess energy rises more rapidly. Because the energy flow from the surrounding nuclei toward the Drude oscillators becomes larger, they warm up more rapidly. The underlying reason is that the effective coupling between the excitations arising from the surrounding bulk and the Drude oscillators depend on the natural frequency of the latter, $\omega_D = \sqrt{K_D/\mu}$. These concepts can be clarified in the context of a generalized Langevin equation, as shown in Sec. III B.

As a final illustration of the ability of the dual-NH propagation to generate a proper statistical mechanical ensemble for the nuclei, we compare the average properties of a system of 1981 SWM4 water molecules from three different simulation methods. The first is a 2 ns MD simulation under the SCF condition with nuclei at 300 K, which is used as a reference. The second is a standard 4 ns dual-NH extended-Lagrangian MD simulation with nuclei temperature T at 300 K. The third is a 3 ns dual-NH REMD simulation comprising five replicas with nuclei temperature T distributed between 300 K and 310 K (300, 302.5, 305, 307.5, 310). For the dual-NH simulations, the Drude oscillator temperature T^* was set at 1 K, and the time step was 1 fs in the NVT ensemble. In the REMD simulation, replica-exchanges were attempted every 100 steps, yielding an acceptance probability varying between 0.24 and 0.49. The O–O, O–H, and H–H radial distribution function for the three types of simulation, shown in Fig. 5, agree very closely. The vaporization enthalpy for SCF, dual-NH, and dual-NH REMD (300 K replica) are -9.8944 kcal/mol, -9.8828 kcal/mol, and -9.8796 kcal/mol, respectively. The standard error estimated from block averages is on the order of 0.003 kcal/mol, yielding ± 0.006 kcal/mol for a 95% confidence interval. The vaporization enthalpy from the dual-NH and SCF simulations differ by about 0.012 kcal/mol, which is small but statistically meaningful, given the estimated standard error and confidence interval. This is indicative of a slight systematic difference between the SCF and dual-NH propagation. On the other hand, the even smaller difference between the average potential energy from the dual-NH and dual-NH REMD simulations, about 0.0032 kcal/mol, is probably not statistically meaningful. As a comparison, the average potential energy for the 310 K replica from the dual-NH REMD simulation is -9.7567 kcal/mol, differing by almost 0.123 kcal/mol from the simulations at 300 K. This demonstrates that the multi-canonical sampling in the REMD simulation is not corrupted by the dual-NH propagation. Importantly, the average potential energy from the three simulations all agree within a factor of less than 0.1%, which supports the notion that the statistical mechanical ensemble for the nuclei at $T = 300$ K is properly realized by the dual-thermostat extended Lagrangian simulations.

B. Generalized Langevin equation analysis

Let us consider the dynamics of one Drude oscillator of natural frequency $\omega_D = \sqrt{K_D/\mu}$, where μ is the reduced mass and K_D is the force constant. We represent the influence of the surrounding in terms of the Generalized Langevin equation (GLE),

$$\mu \ddot{y} = -K_D y - \int_0^t \xi(t-t') \dot{y}(t') dt' + f(t), \quad (26)$$

FIG. 5. Comparison of the O–O, O–H, and H–H radial distribution functions for a system of 1981 SWM4 water molecules at 300 K generated from three different MD simulation methods: SCF (orange solid line), dual-NH extended-Lagrangian (green solid line), and dual-NH REMD with five replicas at $T = 300$ K, 302.5 K, 305 K, 307.5 K, and 310 K (blue dashed line). The results for the dual-NH REMD are taken from the replica at 300 K.

where y is the one-dimensional stretching mode of the oscillator, $\xi(t)$ is the memory function friction kernel, and $f(t)$ is a Gaussian-distributed random force obeying the second fluctuation-dissipation theorem

$$\langle f(t)f(0) \rangle = k_B T \xi(t). \quad (27)$$

Tuckerman and Berne⁴⁶ previously showed that the relaxation time τ of the energy of the oscillator is given by

$$\frac{1}{\tau} = \frac{\tilde{\xi}(\omega_D)}{\mu}, \quad (28)$$

where $\tilde{\xi}(\omega)$ is the cosine Fourier transform of the memory function

$$\tilde{\xi}(\omega) = \int_0^\infty dt \xi(t) \cos(\omega t) \quad (29)$$

evaluated at the natural frequency of the Drude oscillator ω_D . According to this expression, the thermalization rate of the

oscillator depends on the excitations arising from the surrounding bulk at the frequency ω_D . To determine the friction kernel that enters in Eq. (26), we adopted the frozen degree of freedom prescription.⁴⁷ Accordingly, we first generated a trajectory of a periodic box of SWM4 water, in which one tagged water molecule was held fixed at the origin. The oxygen–Drude distance in the fixed water molecule was fixed at a value of 0.2 Å along the HOH vector bisector, which is typical on average for simulations of liquid water based on the SWM4 model.⁴⁵ This trajectory was then post-processed to extract the instantaneous force acting on the tagged Drude oscillator,³⁰

$$F(t) = \left(1 - \frac{m_D}{m_O}\right) F_x^D(t) - \left(\frac{m_D}{m_O}\right) F_x^O(t), \quad (30)$$

where $F_x^D(t)$ is the force acting on the Drude particle and $F_x^O(t)$ is the force acting on its parent oxygen atom. From the time-series of $F(t)$, the memory function is calculated as the time-autocorrelation function,

$$\xi(t) = \frac{1}{k_B T} \langle \delta F(t) \delta F(0) \rangle, \quad (31)$$

where $\delta F(t) = F(t) - \langle F(t) \rangle$ represents the fluctuating part of the time-dependent force. The calculated force autocorrelation function is shown in Fig. 6. It relaxes rapidly within less than 1 ps from a large initial value of 200 [(kcal/mol)/Å]². The cosine Fourier transform of the friction kernel is shown on Fig. 7. According to the GLE analysis, the relaxation time τ for the thermalization of the Drude oscillator depends on the value $\tilde{\xi}$ evaluated at the frequency of the Drude oscillator ω_D (1036 ps^{−1} for a Drude mass of 0.4 amu). However, as observed in Fig. 7, the Fourier transform of the friction kernel in the high-frequency region of the spectrum is too uncertain to yield a useful estimate of the relaxation time. The statistical inaccuracy is due to the accumulation of statistical errors in the calculation of the friction kernel. These limitations notwithstanding, the GLE analysis

FIG. 6. Force–force time-correlation function $\langle \delta F(t) \delta F(0) \rangle$ in [(kcal/mol)/Å]² of the force acting on the Drude oscillator calculated from a MD simulation. The time-dependent fluctuating force $F(t)$ acting on one frozen molecule was extracted from a 1 ns MD trajectory ran with a time step of 1 fs. The correlation function was calculated using a direct moving average.

FIG. 7. Normalized Fourier transform of the friction kernel $\tilde{\xi}(\omega)/\tilde{\xi}(0)$. The static value of the memory function $\tilde{\xi}(0)$ is 92.444 ps kcal/mol Å⁻². In the SWM4 model,³⁰ Drude particles are attached to their parent atoms via a spring of force constant 1000 kcal/mol Å⁻². With a Drude mass of 0.4 amu, the natural frequency of the Drude oscillator ω_D is equal to 1036 ps⁻¹. The inset shows $\tilde{\xi}(\omega)/\tilde{\xi}(0)$ and estimates extracted from Fig. 4 (red triangles).

shows why the rate of energy relaxation from the surrounding real atoms to the Drude oscillators is actually quite slow. This is confirmed by the simulations started from a SCF configurations with no thermostat applied to Drude oscillators (Fig. 4). The relaxation times extracted from Fig. 4 can be exploited to estimate the value of Fourier transform of the friction kernel in the high-frequency region (triangles in the inset of Fig. 7). This analysis suggests that $\tilde{\xi}(\omega)$ must drop by a factor of about 10^{-10} from $\omega = 0$ to $\omega = \omega_D$ for a Drude mass of 0.4 amu. Thus, the slow energy relaxation is fundamentally due to the fact that the high-frequency Drude oscillator couples very poorly to the excitations arising from surrounding bulk.

In ending this discussion, it is important to note that the water model considered here is a special situation. In this model, the O–H bond lengths and the H–O–H bond angle are kept rigidly fixed during dynamics, and there are no high-frequency vibrational degrees of freedom. In more complicated molecules, the parent atom i of the Drude oscillator would be coupled to other atoms through the covalent structure. In the simplest view, the effect of one atom j attached to the parent atom i through a harmonic bond would introduce some time-dependent fluctuating force,

$$\delta F_i(t) = -K_{ij}x_j(t), \quad (32)$$

with

$$x_j(t) = x_j \cos(\omega_j t) + \frac{\dot{x}_j}{\omega_j} \sin(\omega_j t), \quad (33)$$

where ω_j is the vibrational frequency of the atom j . Because the fluctuating force acts on the parent atom i , which is part of the Drude oscillator, it introduces additional dissipative effects, contributing to the memory function $\xi(t)$ that enters the GLE,

$$\langle \delta F_i(t) \delta F_i(0) \rangle = \langle K_{ij} x_i(t) K_{ij} x_i(0) \rangle, \quad (34)$$

$$\approx K_{ij} k_B T \cos(\omega_j t). \quad (35)$$

While this analysis ignores dephasing and other decorrelation effects for the sake of simplicity, it helps to illustrate how an additional coupling to the parent nucleus entering via the covalent structure is expected to introduce additional components to the force autocorrelation function at the frequency ω_j . The amplitude of those contributions would depend on the force constant K_{ij} between the parent atom i and the other atom j . This observation could be formally generalized by considering a full normal mode analysis, though this development will not be pursued here. In biomolecules, harmonic force constants are typically on the order of 400 (kcal/mol)/Å²–500 (kcal/mol)/Å², and vibrational frequencies are typically on the order of 200 ps⁻¹–400 ps⁻¹. While these remain fairly distant from the frequency of the Drude oscillator (which is on the order of 1036 ps⁻¹ here), the increased dissipation affects the local temperature control over the nuclei and the Drude oscillator.

While the dual-NH extended Lagrangian scheme is appropriate in the absence of high-frequency intramolecular modes, systems with high-frequency internal degrees of freedom such as planar improper dihedrals or bond stretches are most susceptible to display some problems. Correcting for this situation by layering independent thermostats upon separate molecular groups is the objective of the dual-temperature-grouped dual-Nosé–Hoover (tgNH) thermostat introduced by Son *et al.*³² They showed that in the presence of high-frequency intramolecular modes, the small internal heat flow from the degrees of freedom of the real atoms to the Drude oscillators generates a stationary temperature gradient affecting the local equipartitioning of the kinetic energy among the different degrees of freedom. As the thermostat acting on the real atoms works to impose a unique global temperature, T , the loss of kinetic energy in the high-frequency motions of the real atoms is compensated by a higher kinetic energy for the low-frequency motions. Such equipartition problems, yielding too high translational kinetic energies for the real atoms, result in overestimated translational diffusion and underestimated bulk densities.³² Roux *et al.* showed that with the dual-tgNH scheme, the heat flow from the real atoms to the Drude oscillators does not affect the apparent temperatures T and T^* , and all measured properties remain very close to the SCF propagation. An alternative solution could be to decrease the mass assigned to the Drude particle to shift the natural frequency of the oscillator ω_D to a higher value, thus further reducing the dynamical coupling with the surrounding atoms. However, this could only be implemented in the context of a multiple time step scheme to remain computationally effective.²⁹ One more avenue is presented by the inertial extended Lagrangian SCF iteration-free method (iEL/0-SCF).^{33–36}

IV. CONCLUSION

The statistical mechanics of a dual-temperature canonical ensemble was formulated to clarify the significance of the dual-thermostat extended Lagrangian propagation in the context of the polarizable force field based on classical Drude oscillators. It was shown how the familiar alchemical free energy perturbation

and replica-exchange simulations executed with the Drude force field with a dual-thermostat extended Lagrangian propagation can remain valid. More generally, the analysis also helps to understand the statistical mechanical foundation of methodologies designed to simulate adiabatic SCF propagation via an extended Lagrangian scheme.^{24–28} Test simulations show that the Drude oscillators warm up very slowly relative to the SCF solution in the absence of direct thermostating. The slow energy transfer was explained on the basis of generalized Langevin equation analysis, showing that the power spectrum of the memory function evaluated at the natural frequency of the Drude oscillator is extremely small (the memory function is related to the force autocorrelation function of the force acting on the Drude oscillator from the surrounding degrees of freedom).

The present analysis mainly focused on the dual-NH thermostat³⁰ although a dual-LD thermostating method can also be used.³¹ While the performance of the dual-NH and dual-LD thermostats is expected to be roughly equivalent in the case of equilibrium properties, it has been shown that the dynamical transport properties are affected by the details of the dual-LD scheme.⁴⁰ While this type of artifacts also arises in the case of nonpolarizable models in standard Langevin simulations with a single temperature, the results should serve as a strong reminder that caution must be exerted in the choice of dual-thermostat for studies of dynamical transport properties.

Practical considerations for performing extended Lagrangian simulations using the classical Drude oscillator model include the time step, Drude particle mass, and issues associated with the risk of polarization catastrophe. The atomic polarization in the Drude model is based on the Drude charge and the force constant on the harmonic spring attaching the Drude particle to the nucleus. Accordingly, it is necessary to assign a mass and force constant that allow for the oscillator motions to occur at a frequency allowing for a reasonable time step. With the Drude force field, the oscillator mass is set to 0.4 amu, a value that is subtracted from the mass of the parent atom, while the force constant in the harmonic spring is set to 1000 (kcal/mol)/Å.⁴⁸ This combination allows for an integration time step of 1 fs while assuring proper decoupling of the slow nuclear degrees of freedom and the fast Drude oscillator degrees of freedom. It is strongly suggested that users of the Drude force field maintain these values when applying the force field.

Polarization catastrophe (i.e., when the Drude particle diverges during the SCF calculation or extended Lagrangian dynamics step) in the context of a finite time step method is a concern when performing simulations. While integration and thermostat parameters may be optimally chosen, the occurrence of close atomic contacts leading to polarization catastrophe during a simulation cannot be fully eliminated. To account for this, a hard-wall condition has been formulated and implemented for simulations using the Drude model.⁴⁹ The hard wall involves reversing the momentum on Drude particles once the distance between the nuclei and the Drude particle is greater than a selected value, typically 0.2 Å. We emphasize that during optimization of the Drude force field, adjustment of the electrostatic parameters (charges, polarizabilities, and Thole screening factor) needs to include considerations to ensure that the Drude particles encounter the hard wall only under exceptional circumstances. Significant number of encounters of the Drude with

the hard wall leads to loss of the adiabatic condition in the extended Lagrangian, thereby altering the thermodynamics of the simulation system.

Such an analysis was carried out in our first paper on the Drude force field.³⁰ Accordingly, both x and y are submitted to a meaningful statistical distribution, $P_{T^*}(x, y)$, such that any sampling algorithm that satisfies and maintains this distribution will work properly. Hence, it is appropriate to apply methods such as replica-exchange with the Drude force field treated with the dual-thermostat formalism.^{50,51}

In summary, the classical Drude oscillator model allows for computationally efficient molecular simulations using a fully polarizable model. The model can be used with a variety of enhanced sampling techniques, such as replica-exchange, steered MD, and metadynamics, and in alchemical free energy perturbation calculations. However, care must be taken when applying the Drude model in charge perturbations due to the need to account for the relaxation of the Drude particles associated with the different charge states. This may be performed using SCF calculations or be avoided by using thermodynamic integration.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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