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All-atom multiscaling and new ensembles for dynamical nanoparticles

Yinglong Miao and Peter Ortoleva^{a)}

Center for Cell and Virus Theory, Indiana University, Bloomington, Indiana 47405

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Viruses and other nanoparticles have mixed microscopic/macroscale character. Thus it is natural to develop an understanding of their dynamics via a multiscale analysis of the Liouville equation following prescriptions introduced for the study of Brownian motion. However, the internal dynamics of the atoms constituting a nanoparticle introduces conceptual and technical difficulties associated with a description involving both the atomistic and nanometer scale properties of these systems and the potential overcounting of degrees of freedom. To overcome these difficulties we introduce a “nanocanonical” ensemble method to facilitate the multiscale analysis of the all-atom Liouville equation. Our approach overcomes technical difficulties associated with the removal of secular behavior, which leads to Fokker-Planck-type equations. Our approach ensures removal of all secular behavior in the N -atom probability density and not just that of a reduced distribution. Being based on a calibrated interatomic force field, our method has the potential to yield parameter-free universal models for nanoparticle dynamics including viral migration in complex media and viral phase transitions and disassembly. © 2006 American Institute of Physics.

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I. BACKGROUND

Multiscale analysis has been the subject of interest over the past century starting with Brownian motion as analyzed by Einstein.^{1–14} In many of these studies, Fokker-Planck equations are derived for structureless particles starting from the Liouville equation. This focus on structureless particles stems in part from the technical challenges of avoiding the overcounting of degrees of freedom, especially as encountered in the process of analyzing the secular (divergent as time becomes large) behaviors that ultimately imply a Fokker-Planck equation. For example, the nanoparticle center-of-mass (c.m.) position and momentum are themselves dependent on atomic variables and are therefore not independent degrees of freedom. Thus one cannot integrate over all atomic configurations without addressing the fact that most of them are not consistent with a given c.m. position of the nanoparticle. In contrast, in the present approach we remove secular behavior from the full N -atom probability density and not solely from an integrated reduction of it. This not only addresses concerns that the integration method for deriving Fokker-Planck equations may leave some secular behavior in the N -atom probability density but also avoids the technical difficulties involved with performing these integrations in a manner that maintains the number of degrees of freedom.

To overcome these difficulties, we introduce slowly varying quantities not as dynamical variables but through Lagrange multipliers which emerge in defining the ensemble that characterizes the lowest order solution to the Liouville equation. We find this approach to be more consistent with the notion of coarse graining; i.e., nanoparticle “position” is more rigorously to be thought of as an averaged quantity and

hence should be characterized via an ensemble of c.m. positions, and similarly for nanoparticle momentum and the N -atom state of the nanoparticle/host system. Thus the nanoparticle c.m. position does not characterize the ensemble of internal atomic states, rather the ensemble average c.m. position does. We show that this view naturally leads to the introduction of a “nanocanonical ensemble” that has formal analogs to the grand canonical ensemble.

The introduction of notions allows for the practical implementation of an approach to complex nanoparticles such as viruses and nanoscale intracellular structures. It has great advantage when considering viruses or other systems involving intranoparticle degrees of freedom. We will emphasize virus and other life-system studies in much of the remainder of this section, although applications in biotechnology and materials science are also envisioned.

Biological systems that involve the dynamics of nanoparticles interacting with a host medium include chromosomes, ribosomes, proteosomes, and viruses. The functioning of these particles cannot be understood in terms of a body without internal structure. For example, a virus can undergo structural phase transitions in response to changes in its surroundings. Ribosomes interact with macromolecules during translation in ways that are sensitive to their detailed molecular structure (i.e., can respond to RNA sequence). Chromosomes make dramatic changes during replication, again a process involving the sensing of atomic-scale details. To simulate these dynamical biochemical processes, a time-dependent formalism that captures both atomic and nanometer scales is required.

Intraviral bodies experience fluctuating dynamics in a constrained space. For example, gold nanoparticles (quantum dots) may be used to probe the assembly, disassembly, or fluctuations of a viral capsid. Nanomaterial synthesis within

^{a)}URL: <http://sysbio.indiana.edu>. Electronic mail: ortoleva@indiana.edu

a viral capsid by the use of viral phase transitions has been demonstrated.^{15,16} The dynamics of these systems reflects the interplay of the fluctuations of the capsid and the internal particles, the interactions between the particles, and the screening or dielectric properties of the medium within the capsid. Thus the entrapped nanoparticles may form long-lived clusters, adhere to the capsid inner surface, and induce capsid phase transitions or disassembly. The all-atom, multi-scale formulation presented here is designed to address these systems whose character emerges via the interplay of atomistic and nanoscale phenomena. Other approaches to nanoparticle modeling (with an emphasis on viruses) are briefly reviewed below to clarify the need for the present approach.

Lumped models reduce the atomic-scale detail to allow for determination of overall structure and some aspects of viral stability and phase transitions.¹⁷ These models do not capture atomic-scale detail; therefore they cannot predict the consequences of an interaction with a drug or cell receptor that may trigger or repress these transitions. They do not allow for an estimation of the effects of pH or salinity on these phenomena. Such models must be recalibrated for each virus and host medium; thus one might question whether the desired answer is built into the computation by calibration so that the predictive power and extension of results from one virus (or even one strain) to another is questionable.

Symmetry-constrained models of a whole-virus capsid have been developed using an all-atom approach.¹⁸ However, a virus likely does not disassemble or make a structural phase transition via a simultaneous and equivalent displacement/rotation of all hexamers, pentamers, or other protein units. Rather initiation of instability is local, starting with a motion or deformation of a single protein or other subunit, and then propagates across the whole virus. Furthermore, as symmetry is imposed, the docking of a single or a few drug molecules at selected sites is a symmetry-breaking process that cannot be investigated by the restricted symmetry approach.

Computational molecular dynamics (MD) is discussed extensively in the literature.^{19–30} MD has been used to model drug/viral protein interactions and their implications for infection. Computational studies were done using stochastic boundary conditions around a single viral protomer^{25,31} and periodic boundary conditions.¹⁸ These studies reveal physical properties of the human rhinovirus (HRV) protomer, such as compressibility, which have been conjectured to be related to the ability of antiviral drugs to inhibit infection, a conclusion not based on whole-virus results, however. While MD is a powerful approach for smaller size, shorter time phenomena, it is apparently not yet practical for whole virus, millisecond to hour time scale modeling.³¹

Normal mode analysis has been used to study whole-virus conformational changes of icosahedral virus capsids.^{32–35} In these studies, various methods are applied to reduce the number of degrees of freedom including the elastic network model and the rotation/translation of blocks (RTB) method. Icosahedral symmetry was used to simplify normal mode calculations via group theory. van Vlijmen and Karplus^{34,35} reported atomic level normal mode calculations of icosahedral viruses with a basis set of molecular dihedral

angles and the uniform rotation/translation of separate capsid proteins under icosahedral symmetry. These calculations provide insights into the conformational changes of icosahedral virus capsids. However, they cannot address the very local and highly nonlinear nature of the drug-virus interaction and the initiation and propagation of a phase transition across a virus and are not appropriate for a viral disassembly study.

In this study, we present a rigorous all-atom theory of nanoparticle dynamics that captures the interplay of their atomic and nanoscale behaviors in a parameter-free and general manner. Being based on a calibrated interatomic force field, our method has the potential to yield parameter-free universal models for nanoparticle dynamics including viral migration in complex media, viral phase transitions and disassembly, and interaction with interfaces and cell membranes.

In Sec. II we introduce the multiscale approach and illustrate the technical challenges it presents for an all-atom analysis of structured nanoparticles. The “nanocanonical” ensemble is developed in Sec. III and is shown to overcome the aforementioned difficulties that otherwise impede the derivation of Fokker-Planck equations for structured nanoparticles. The nanocanonical approach is fully developed in Sec. IV for a structured nanoparticle migrating in, and responding to, a complex host medium. Generalizations and conclusions are presented in Sec. V.

II. LIOUVILLE EQUATION, MULTISCALE FORMULATION

The scaling approach and the challenges involved in the analysis of the Liouville equation for structured nanoparticles are now introduced. Consider an N -atom system comprised of a nanoparticle of N^* atoms and a host medium of $N - N^*$ atoms. To characterize the differences in length, mass, and time scales involved in a nanosystem we introduce a unifying smallness parameter $\varepsilon (\ll 1)$. Thus the nanoparticle c.m. momentum and position are $\varepsilon^{-1}\mathbf{P}$ and $\varepsilon^{-1}\mathbf{R}$. With this, the N -atom probability density ρ is considered to be a function of the scaled c.m. momentum and position, as well as the momenta and positions $\Gamma = \{\mathbf{p}_i, \mathbf{r}_i, i = 1, \dots, N\}$ of the N atoms in the system. A key point is that the multiple distinct dependencies in ρ does not imply a violation of the restriction on the number of degrees of freedom; rather this is to state that ρ has multiple scale character—here the long range migration of the large mass nanoparticle in the presence of the rapidly fluctuating atomic variables Γ .

Using the chain rule, ρ in the above multiscale form satisfies (see Appendix A)

$$\frac{\partial \rho}{\partial t} = (\mathcal{L}_0 + \varepsilon^2 \mathcal{L}_1) \rho, \quad (2.1)$$

$$\mathcal{L}_0 = - \sum_{i=1}^N \left[\frac{\mathbf{p}_i}{m_i} \cdot \frac{\partial}{\partial \mathbf{r}_i} + \mathbf{F}_i \cdot \frac{\partial}{\partial \mathbf{p}_i} \right], \quad (2.2)$$

$$\mathcal{L}_1 = -\frac{\mathbf{P}}{m} \cdot \frac{\partial}{\partial \mathbf{R}} - \mathbf{f} \cdot \frac{\partial}{\partial \mathbf{P}}. \quad (2.3)$$

In this formulation we have introduced the dimensionless parameter ε such that $\varepsilon^2 = m/m^*$ for typical atomic mass m and nanoparticle mass m^* . The net force $\varepsilon \mathbf{f}$ on the nanoparticle can be written in terms of the individual atomic forces \mathbf{F}_i ,

$$\varepsilon \mathbf{f} = \sum_{i=1}^N \Theta_i \mathbf{F}_i, \quad (2.4)$$

where Θ_i is 1 for atoms within the nanoparticle and 0 for host atoms. The net force on the nanoparticle is taken to be small; for the quasiequilibrium states of interest there is much cancellation of the forces on the nanoparticle from those on individual atoms. It is further assumed that external forces are weak. Alternative scalings for nanoparticle mass, momentum, position, and force can also be adopted to investigate other classes of behavior, but the above will serve to illustrate the present methodology. That derivatives in \mathcal{L}_0 are at constant \mathbf{P} and \mathbf{R} , while those in \mathcal{L}_1 are at constant Γ , does not imply that Γ , \mathbf{P} , and \mathbf{R} are independent degrees of freedom; rather they arise due to our attempt to express ρ 's multiscale character. Thus any integration over all states of the system would be over the dependence on Γ , including that in \mathbf{P} and \mathbf{R} .

The multiscale development proceeds by expanding ρ in a series in ε^2 ,

$$\rho = \sum_{n=0}^{\infty} \rho_n(\Gamma, \mathbf{P}, \mathbf{R}, t_0, t) \varepsilon^{2n}, \quad (2.5)$$

where $t_n = \varepsilon^{2n} t$ and $t = \{t_1, t_2, \dots\}$ is the collection of times characterizing the slow behaviors, i.e., that evolve on times of order ε^{-2} , ε^{-4} , and longer.

The lowest order distribution is assumed to reflect the quasiequilibrium nature of the biological phenomena of interest, i.e., ρ_0 is independent of t_0 . Using the chain rule for $\partial/\partial t$ (so that $\partial\rho/\partial t = \partial\rho/\partial t_0 + \varepsilon^2 \partial\rho/\partial t_1 + \dots$), the lowest order problem becomes

$$\mathcal{L}_0 \rho_0 = 0. \quad (2.6)$$

This equation yields solutions which are functions of the Hamiltonian H_0 that generates \mathcal{L}_0 , i.e.,

$$H_0 = \sum_{i=1}^N \frac{p_i^2}{2m_i} + V, \quad (2.7)$$

where V is the N -atom potential. For example, ρ_0 could be the canonical distribution $\exp(-\beta H_0)$ which is normalized by the partition function Q ,

$$Q = \int^* d^{6N} \Gamma \exp(-\beta H_0), \quad (2.8)$$

where $d^{6N} \Gamma = d^3 p_1 d^3 r_1 \dots d^3 p_N d^3 r_N$. The $*$ on the integration implies that \mathbf{R} and \mathbf{P} must be fixed, i.e., for any quantity A ,

$$\int^* d^{6N} \Gamma A = \int d^{6N} \Gamma \delta\left(\mathbf{P} - \varepsilon \sum_{i=1}^N \Theta_i \mathbf{p}_i\right) \times \delta\left(\mathbf{R} - \varepsilon \sum_{i=1}^N \Theta_i m_i \mathbf{r}_i / m^*\right) A. \quad (2.9)$$

Such integrals can be accomplished via Monte Carlo methods and a constant \mathbf{P} , \mathbf{R} -constrained generation of Γ configurations. The $O(\varepsilon^0)$ analysis typically concludes with the introduction of the slowly varying factor $W(\mathbf{P}, \mathbf{R}, t)$, i.e., $\rho_0 = Q^{-1} \exp(-\beta H_0) W$. In Secs. III and IV we demonstrate how the above formulation can be placed on more rigorous footing.

A difficulty with the above formulation is that while solving (2.6) one must keep the delta functions in (2.9) and the constrained integrations as part of the higher order multiscale analysis. For example, a key difficulty arises in analyzing the $O(\varepsilon^2)$ equation,

$$\left(\frac{\partial}{\partial t_0} - \mathcal{L}_0\right) \rho_1 = -\frac{\partial \rho_0}{\partial t_1} + \mathcal{L}_1 \rho_0. \quad (2.10)$$

To solve this equation one must recognize that the right-hand side (RHS) can have contributions from the null space of \mathcal{L}_0 . In this recognition one would like to arrive at an expression for $\partial W/\partial t_1$ by ensuring that the resulting secular behavior (i.e., divergence at large t_0) is removed. The difficulty is that in the classic approach an expression for $\partial W/\partial t_1$ follows from applying $\int^* d^{6N} \Gamma$ to both sides of (2.10) and then using the fact that acceptable probability distributions vanish as $|\mathbf{p}_i| \rightarrow \infty$, and invoking periodic boundary conditions on the \mathbf{r}_i dependence of the probability. In studies of structureless nanoparticles this directly implies $\int^* d^{6N} \Gamma \mathcal{L}_0 A = 0$ for any distribution A and wherein particle $N+1$ is the structureless nanoparticle. This yields the Fokker-Planck equation when computations are carried out to $O(\varepsilon^4)$. The strategy is not clear for the structured nanoparticle wherein the constrained integration $\int^* d^{6N} \Gamma$ must be used to preserve the \mathbf{P} , \mathbf{R} dependence of ρ . This and related difficulties stem from the fact that unlike for the traditional approach, the structured nanoparticle's atomic coordinates are already a complete set of dynamical variables so that either \mathbf{P} , \mathbf{R} are redundant or ignoring their relation to Γ would allow for atomic configurations that are inconsistent with \mathbf{P} and \mathbf{R} . Hence to avoid overcounting the number of degrees of freedom the $\int^* d^{6N} \Gamma$ constrained integrals must be used. But then the boundary conditions on the $\mathbf{p}_i, \mathbf{r}_i$ cannot be readily utilized.

A more fundamental question also arises. Even if one can derive an expression for $\partial W/\partial t_1$ via a Γ integration, the question remains that although secular behavior is removed from a reduced aspect of ρ_1 (e.g., $\int^* d^{6N} \Gamma \rho_1$), it is still not demonstrated that all the secular behavior in ρ_1 itself has been removed. What is needed is an approach wherein the nanoparticle c.m. degrees of freedom, or something related to them, are not independent dynamical variables which must ultimately be related to Γ , and a method that will remove all the secular behavior without resorting to Γ integration. Such an approach is developed in Secs. III and IV.

The N -atom potential $V(\mathbf{r}_1, \dots, \mathbf{r}_N)$ does not explicitly depend on nanoparticle c.m. position \mathbf{R} . This is in contrast with the case of a structureless nanoparticle which can be taken as “atom” $N+1$ whereby \mathbf{r}_{N+1} appears in V explicitly. To resolve this issue, introduce a set of modified coordinates \mathbf{s}_i such that $\mathbf{s}_i = \mathbf{r}_i - \varepsilon^{-1} \mathbf{R} \Theta_i$. Thus the atoms in the nanoparticle are described in the relative frame while those of the host medium are in the laboratory frame. The \mathbf{s}_i are functions of $\mathbf{r}_1, \dots, \mathbf{r}_N, \mathbf{s}_i = \mathbf{s}_i(\mathbf{r}_1, \dots, \mathbf{r}_N)$ and, like \mathbf{R} , are dependent dynamical variables. With this, the potential V can be expressed in the form

$$V(\{\varepsilon^{-1} \mathbf{R} \Theta_i + \mathbf{s}_i, i = 1, \dots, N\}) \equiv U(\mathbf{r}_1, \dots, \mathbf{r}_N, \mathbf{R}), \quad (2.11)$$

so that the explicit dependence of U on the \mathbf{r}_1 is only through relative configuration $\{\mathbf{s}_1, \dots, \mathbf{s}_N\}$. With this the particle derivative of V with respect to \mathbf{R} at constant nanoparticle internal configuration is given by

$$\left(\frac{\partial V}{\partial \mathbf{R}} \right)_{\mathbf{s}_1, \dots, \mathbf{s}_N} = - \frac{1}{\varepsilon} \sum_{i=1}^N \Theta_i \mathbf{F}_i = - \mathbf{f}. \quad (2.12)$$

Finally note that the \mathbf{s}_i are not independent, i.e., $m_1 \mathbf{s}_1 \Theta_1 + \dots + m_N \mathbf{s}_N \Theta_N = \mathbf{0}$. This result forwards the multiscale analysis of the following sections.

III. NANOCANONICAL ENSEMBLES

In Sec. II we considered the nanoparticle to have a particular momentum and position that characterized the lowest order solution to the Liouville equation. However, it would seem more consistent, and is found to have technical advantages, to cast the problem in terms of the dynamics of the ensemble of uncertain nanoparticle states, i.e., to introduce a probability distribution with parameters that characterize the statistics of an ensemble of systems in various nanoparticle states. In the process of developing this notion, we show that the conceptual and technical difficulties encountered in Sec. II are overcome.

To solve the Liouville equation via a multiscale approach, we first seek a quasiequilibrium solution to the lowest order equation,

$$\mathcal{L}_0 \rho_0 = 0. \quad (3.1)$$

As $\mathcal{L}_0 \mathbf{P}$, $\mathcal{L}_0 \mathbf{R}$, and $\mathcal{L}_0 H_0$ vanish, we seek a solution of (3.1) that is a function of H_0 , \mathbf{P} , and \mathbf{R} . The lowest order solution of interest here is constrained such that the ensemble average of the Γ -dependent quantities H_0 , \mathbf{R} , and \mathbf{P} have prescribed values (that may vary on the slow timescale), and hence H_0 , \mathbf{P} , and \mathbf{R} themselves are not fixed. This difference from the approach of Sec. II yields great technical and conceptual advantages.

Using information theory, one obtains the following distribution through the imposition of the aforementioned averages:

$$\hat{\rho}_{\mu, \kappa} = \frac{e^{-\beta H_0 + \mu \cdot \mathbf{P} + \kappa \cdot \mathbf{R}}}{\Xi(\beta, \mu, \kappa)}. \quad (3.2)$$

This lowest order solution depends on the dynamical variables Γ through H_0 , \mathbf{P} , and \mathbf{R} . It is implied by entropy maximization through the introduction of the Lagrange multipliers

β , μ , and κ . We term μ and κ reciprocal quantities in that they will be found to play roles similar to Fourier transform variables, e.g., κ will, through inverse transformation, imply a derivative with respect to c.m. position in a Fokker-Planck equation, and similarly for the reciprocal momentum μ . As is familiar in classical systems, the quasiequilibrium distribution $\hat{\rho}_{\mu, \kappa}$ separates into a momentum and a position factor and similarly for the partition function $\Xi(\beta, \mu, \kappa)$.

The partition function $\Xi(\beta, \mu, \kappa)$ in (3.2) is given by

$$\Xi(\beta, \mu, \kappa) = \int d^{6N} \Gamma \exp[-\beta H_0 + \mu \cdot \mathbf{P} + \kappa \cdot \mathbf{R}]. \quad (3.3)$$

The integration over all atomic degrees of freedom is unrestricted, i.e., one is not burdened with the complexity of restricting the coordinates of the atoms in the nanoparticle to a fixed c.m. location, and similarly for the momenta. In expressions like (3.3) \mathbf{P} and \mathbf{R} depend on all the viral $\mathbf{r}_i, \mathbf{p}_i$. This nanocanonical ensemble ensures that atomic configurations which correspond to large departures of the c.m. coordinates from the specified μ, κ -dependent average values will be improbable.

Let $\langle \dots \rangle_{\mu, \kappa}$ imply a $\hat{\rho}_{\mu, \kappa}$ -weighted average over all configuration Γ : $\langle A \rangle_{\mu, \kappa} = \int d^{6N} \Gamma A \hat{\rho}_{\mu, \kappa}$ for any Γ -dependent quantity A . The averages $\langle \mathbf{P} \rangle_{\mu, \kappa}$ and $\langle \mathbf{R} \rangle_{\mu, \kappa}$ are given by

$$\langle \mathbf{P} \rangle_{\mu, \kappa} = \frac{\partial \ln \Xi}{\partial \mu}, \quad \langle \mathbf{R} \rangle_{\mu, \kappa} = \frac{\partial \ln \Xi}{\partial \kappa}. \quad (3.4)$$

The lowest order equation (3.1) is linear; thus it admits the more general supposition solution

$$\rho_0 = \int d^3 \mu d^3 \kappa \hat{\rho}_{\mu, \kappa} \Psi(\mu, \kappa, t), \quad (3.5)$$

for reciprocal distribution Ψ . As ρ_0 is unit normalized and $\hat{\rho}_{\mu, \kappa}$ is normalized by construction, then

$$\int d^3 \mu d^3 \kappa \Psi(\mu, \kappa, t) = 1. \quad (3.6)$$

With this, ensemble averages indicated by superscript m can be obtained. For example,

$$\mathbf{P}^m = \int d^3 \mu d^3 \kappa \langle \mathbf{P} \rangle_{\mu, \kappa} \Psi(\mu, \kappa, t), \quad (3.7)$$

$$\begin{aligned} \mathbf{f}^m &= \int d^3 \mu d^3 \kappa \int d^{6N} \Gamma \hat{\rho}_{\mu, \kappa} \mathbf{f} \Psi(\mu, \kappa, t) \\ &= \int d^3 \mu d^3 \kappa \langle \mathbf{f} \rangle_{\mu, \kappa} \Psi(\mu, \kappa, t). \end{aligned} \quad (3.8)$$

One may relate $\Psi(\mu, \kappa, t)$ and the nanoparticle momentum-position density W . By definition

$$W(\mathbf{p}, \mathbf{r}, t) = \int d^3 \mu d^3 \kappa \langle \delta(\mathbf{p} - \mathbf{P}) \delta(\mathbf{r} - \mathbf{R}) \rangle_{\mu, \kappa} \Psi(\mu, \kappa, t). \quad (3.9)$$

The definition of the delta function implies

$$W(\mathbf{p}, \mathbf{r}, t) = \int d^{6N}\Gamma \int d^3\mu d^3\kappa \delta(\mathbf{p} - \mathbf{P}) \delta(\mathbf{r} - \mathbf{R}) \times \frac{\exp(-\beta H_0 + \boldsymbol{\mu} \cdot \mathbf{p} + \boldsymbol{\kappa} \cdot \mathbf{r})}{\Xi(\beta, \boldsymbol{\mu}, \boldsymbol{\kappa})} \Psi(\boldsymbol{\mu}, \boldsymbol{\kappa}, t). \quad (3.10)$$

Defining $Q(\beta, \mathbf{p}, \mathbf{r})$ via

$$Q(\beta, \mathbf{p}, \mathbf{r}) = \int d^{6N}\Gamma \delta(\mathbf{p} - \mathbf{P}) \delta(\mathbf{r} - \mathbf{R}) \exp(-\beta H_0), \quad (3.11)$$

one obtains

$$\frac{W(\mathbf{p}, \mathbf{r}, t)}{Q(\beta, \mathbf{p}, \mathbf{r})} = \int d^3\mu d^3\kappa e^{\boldsymbol{\mu} \cdot \mathbf{p} + \boldsymbol{\kappa} \cdot \mathbf{r}} \frac{\Psi(\boldsymbol{\mu}, \boldsymbol{\kappa}, t)}{\Xi(\beta, \boldsymbol{\mu}, \boldsymbol{\kappa})}, \quad (3.12)$$

so that W/Q and Ψ/Ξ are related via a bilateral Laplace transform. The inverse of this relationship casts Ψ/Ξ in terms of an interesting integral of W/Q over imaginary nanoparticle momenta and positions (see Appendix B).

The results (3.12) and (3.5) imply

$$\rho_0 = \frac{e^{-\beta H_0}}{Q(\beta, \mathbf{P}, \mathbf{R})} W(\mathbf{P}, \mathbf{R}, t). \quad (3.13)$$

Note that here W depends on \mathbf{P} and \mathbf{R} , which, in turn, are functions of Γ and hence are dependent dynamical variables. In contrast, \mathbf{p} and \mathbf{r} in (3.10) are not dynamical variables (e.g., $\partial \mathbf{p} / \partial \mathbf{p}_i$ is zero).

As we are interested in developing an equation of motion for W , we adopt (3.13) as the starting point of our analysis rather than the Ψ formulation. This is shown to rather directly lead to an equation for W in the next section wherein we show that this follows by removing secular behavior using a method that does not involve an integration over Γ .

Before proceeding further, we examine the structure of Q in more detail. First we introduce a configurational factor $Z(\beta, \mathbf{R})$ such that

$$Z(\beta, \mathbf{R}) = \int d^3r_1 \cdots d^3r_N \delta\left(\mathbf{R} - \varepsilon \sum_{i=1}^N m_i \mathbf{r}_i \Theta_i / m^*\right) e^{-\beta V}, \quad (3.14)$$

where the \mathbf{R} dependence of V is noted in (2.11). Similarly we introduce a momentum factor Y such that

$$Y(\beta, \mathbf{P}) = \int d^3p_1 \cdots d^3p_N \delta\left(\mathbf{P} - \varepsilon \sum_{i=1}^N \Theta_i \mathbf{p}_i\right) e^{-\beta K}, \quad (3.15)$$

$$K = \sum_{i=1}^N p_i^2 / 2m_i. \quad (3.16)$$

With this, $Q(\beta, \mathbf{P}, \mathbf{R}) = Y(\beta, \mathbf{P}) Z(\beta, \mathbf{R})$. Introducing the new variables $\boldsymbol{\pi}_i$ via $\mathbf{p}_i = \boldsymbol{\pi}_i + \varepsilon m_i \Theta_i \mathbf{P} / m$ and neglecting terms that vanish as $\varepsilon \rightarrow 0$, one finds

$$Y = \int d^3\pi_1 \cdots d^3\pi_N \delta\left(\sum_{i=1}^N \Theta_i \boldsymbol{\pi}_i\right) \exp\left(-\beta \sum_{i=1}^N \frac{\pi_i^2}{2m_i}\right),$$

so that Y , and hence Q , is independent of \mathbf{P} . Thus we write $Q(\beta, \mathbf{R})$ in the developments of the next section. From its definition and (2.12),

$$\partial \ln Q / \partial \mathbf{R} = \beta \mathbf{f}^{\text{th}}, \quad (3.17)$$

where \mathbf{f}^{th} is the scaled net force on the nanoparticle averaged over all atomic configurations consistent with the nanoparticle having c.m. at $\varepsilon^{-1}\mathbf{R}$.

IV. DERIVATION OF THE FOKKER-PLANCK EQUATION

The objective of the present section is to complete the nanocanonical derivation of a Fokker-Planck equation for structured nanoparticles. The starting point is the lowest order solution (3.13). As pointed out at the end of the previous section, Q does not depend on \mathbf{P} and thus is written $Q(\beta, \mathbf{R})$ henceforth. With this we rewrite ρ_0 as

$$\rho_0 = \frac{e^{-\beta H_0}}{Q(\beta, \mathbf{R})} W(\mathbf{P}, \mathbf{R}, t) \equiv \hat{\rho} W. \quad (4.1)$$

By writing (4.1) in this form, we do not take \mathbf{P} and \mathbf{R} to be independent variables. The apparent independence of \mathbf{P} and \mathbf{R} , as in the partial derivatives in \mathcal{L}_0 and \mathcal{L}_1 , is only to highlight the distinct ways (direct in Γ itself and indirect through \mathbf{P} and \mathbf{R}) that ρ depends on the all-atom state Γ . To be sure one could take \mathbf{P} and \mathbf{R} to be dynamical variables and then eliminate six atomic variables (e.g., \mathbf{p}_1 and \mathbf{r}_1). But this would lead to a cumbersome formulation with much tedious bookkeeping and complexity of computation.

An equation for W is obtained via an examination of higher order terms in the Liouville equation. To $O(\varepsilon^2)$ and in light of (2.11) and (2.12) the Liouville equation implies, upon dropping the 0 on t_0 henceforth,

$$\left(\frac{\partial}{\partial t} - \mathcal{L}_0\right) \rho_1 = - \left[\frac{\partial W}{\partial t_1} + \beta \frac{\mathbf{P}}{m} \cdot (\mathbf{f} - \mathbf{f}^{\text{th}}) W + \frac{\mathbf{P}}{m} \cdot \frac{\partial W}{\partial \mathbf{R}} + \mathbf{f} \cdot \frac{\partial W}{\partial \mathbf{P}} \right] \hat{\rho} \equiv G(\Gamma, \mathbf{P}, \mathbf{R}; W) \hat{\rho}, \quad (4.2)$$

where \mathbf{f}^{th} arises from a $\partial Q / \partial \mathbf{R}$ term as in (3.17): in the present context

$$\mathbf{f}^{\text{th}} = \int^* d^{6N}\Gamma \hat{\rho} \mathbf{f}. \quad (4.3)$$

This yields, upon taking ρ_1 to be zero at $t=0$, a solution of the form

$$\rho_1 = \int_0^t dt' e^{\mathcal{L}_0(t-t')} G(\Gamma, \mathbf{P}, \mathbf{R}; W) \hat{\rho}. \quad (4.4)$$

Assembling the above results and using $\mathcal{L}_0 H_0$, $\mathcal{L}_0 \mathbf{P}$, and $\mathcal{L}_0 \mathbf{R}$ vanish, and $e^{\mathcal{L}_0(t-t')} [G(\Gamma, \mathbf{P}, \mathbf{R}; W) \hat{\rho}] = \hat{\rho} e^{\mathcal{L}_0(t-t')} G(\Gamma, \mathbf{P}, \mathbf{R}; W)$ yields

$$\rho_1 = - \left\{ t \frac{\partial W}{\partial t_1} + \int_0^t dt' e^{\mathcal{L}_0(t-t')} \left[\frac{\mathbf{P}}{m} \cdot \frac{\partial W}{\partial \mathbf{R}} + \mathbf{f} \cdot \frac{\partial W}{\partial \mathbf{P}} + \beta \frac{\mathbf{P}}{m} \cdot (\mathbf{f} - \mathbf{f}^{\text{th}}) W \right] \right\} \hat{\rho}. \quad (4.5)$$

Secular behavior is seen in the $\partial W / \partial t_1$ term. However, there are others as well. For example, with the change of variables $t' = t + \tau$ one has

$$\int_0^t dt' e^{\mathcal{L}_0(t-t')} \mathbf{f} = \int_{-t}^0 d\tau \mathbf{f}(\tau) \approx t \mathbf{f}^{\text{th}} \quad \text{for large } t. \quad (4.6)$$

A fundamental hypothesis of statistical mechanics asserts the equivalence of time and ensemble averages in quasiequilibrium systems. This implies

$$\lim_{t \rightarrow \infty} \frac{1}{t} \int_{-t}^0 d\tau \mathbf{f}(\tau) = \mathbf{f}^{\text{th}}, \quad (4.7)$$

where $\mathbf{f}(\tau) = e^{-\mathcal{L}_0 \tau} \mathbf{f}$. Hence secular behavior is removed from ρ_1 if

$$\frac{\partial W}{\partial t_1} = - \frac{\mathbf{P}}{m} \cdot \frac{\partial W}{\partial \mathbf{R}} - \mathbf{f}^{\text{th}} \cdot \frac{\partial W}{\partial \mathbf{P}}. \quad (4.8)$$

Combining the above results, one obtains

$$\rho_1 = - \hat{\rho} \int_0^t dt' e^{\mathcal{L}_0(t-t')} (\mathbf{f} - \mathbf{f}^{\text{th}}) \cdot \left(\beta \frac{\mathbf{P}}{m} + \frac{\partial}{\partial \mathbf{P}} \right) W, \quad (4.9)$$

and $\rho_1 = 0$ as $t \rightarrow \infty$.

Note that these results were obtained without integrating the Liouville equation at $O(\varepsilon^2)$ over Γ and using the fact that ρ vanishes as $|\mathbf{p}_i| \rightarrow \infty$ and is periodic in the \mathbf{r}_i . This traditional method does not guarantee that the full ρ_1 is free of secular behavior. The present method addresses the full time dependence of ρ_1 , ensuring that ρ_1 , and not an integrated reduction of it, has no secular behavior. Furthermore, the technical difficulties due to the fact that the Γ integrals applied must be restricted as in (4.3) in order to preserve the number of degrees of freedom.

To $O(\varepsilon^4)$ one finds

$$\left(\frac{\partial}{\partial t} - \mathcal{L}_0 \right) \rho_2 = - \frac{\partial \rho_0}{\partial t_2} - \frac{\partial \rho_1}{\partial t_1} + \mathcal{L}_1 \rho_1. \quad (4.10)$$

Again with $\rho_2 = 0$ at $t = 0$, we find

$$\rho_2 = \int_0^t dt' e^{\mathcal{L}_0(t-t')} \left(- \hat{\rho} \frac{\partial W}{\partial t_2} - \frac{\partial \rho_1}{\partial t_1} + \mathcal{L}_1 \rho_1 \right). \quad (4.11)$$

Using (4.9) for ρ_1 we obtain

$$\rho_2 = \hat{\rho} \left\{ - t \frac{\partial W}{\partial t_2} + \int_0^t dt' e^{\mathcal{L}_0(t-t')} \left(\frac{\mathbf{P}}{m} \cdot \frac{\partial}{\partial \mathbf{R}} + \mathbf{f} \cdot \frac{\partial}{\partial \mathbf{P}} \right) \times \int_0^{t'} dt'' e^{\mathcal{L}_0(t'-t'')} (\mathbf{f} - \mathbf{f}^{\text{th}}) \cdot \left(\beta \frac{\mathbf{P}}{m} + \frac{\partial}{\partial \mathbf{P}} \right) W \right\} + \dots \quad (4.12)$$

The missing term from $\partial \rho_1 / \partial t_1$ only involves one $\mathbf{f} - \mathbf{f}^{\text{th}}$ term and is seen upon invoking (4.7) to make no secular contri-

bution. Using arguments as for ρ_1 to ensure that ρ_2 has no secular behavior, and the new variables τ and σ such that $t' = t + \tau$ and $t'' = t + \tau + \sigma$, we obtain

$$\frac{\partial W}{\partial t_2} = \lim_{t \rightarrow \infty} \frac{1}{t} \int_{-t}^0 dt \tau e^{-\mathcal{L}_0 \tau} \left(\frac{\mathbf{P}}{m} \cdot \frac{\partial}{\partial \mathbf{R}} + \mathbf{f} \cdot \frac{\partial}{\partial \mathbf{P}} \right) \times \int_{-t-\tau}^0 d\sigma e^{-\mathcal{L}_0 \sigma} (\mathbf{f} - \mathbf{f}^{\text{th}}) \cdot \left(\beta \frac{\mathbf{P}}{m} + \frac{\partial}{\partial \mathbf{P}} \right) W. \quad (4.13)$$

In obtaining this result, we have used the fact that only the \mathbf{f} factors are propagated by the evolution operators as $\mathcal{L}_0 \hat{\rho} = 0$. To complete the analysis, consider the key term

$$t J_{\alpha_1 \alpha_2} \equiv \int_{-t}^0 d\tau e^{-\mathcal{L}_0 \tau} f_{\alpha_1} \int_{-t-\tau}^0 d\sigma (f_{\alpha_2}(\sigma) - f_{\alpha_2}^{\text{th}}), \quad (4.14)$$

where $f_{\alpha_2}(\sigma)$ is the α_2 Cartesian component of \mathbf{f} evolved to time σ . For large but finite t the first integral with the evolution operator $\exp(-\mathcal{L}_0 \tau)$ is approximately t times the ensemble average, i.e.,

$$t J_{\alpha_1 \alpha_2} \approx t \int_{-t-\tau}^0 d\sigma (f_{\alpha_1}(0) (f_{\alpha_2}(\sigma) - f_{\alpha_2}^{\text{th}}))^{\text{th}}. \quad (4.15)$$

Since τ is fixed but t is arbitrarily large, and the integrand vanishes as σ gets large and negative, [i.e., \mathbf{f} and $\mathbf{f}(\sigma)$ are independent random variables for large σ], we obtain

$$J_{\alpha_1 \alpha_2} \approx \int_{-\infty}^0 d\sigma (f_{\alpha_1}(0) [f_{\alpha_2}(\sigma) - f_{\alpha_2}^{\text{th}}])^{\text{th}}. \quad (4.16)$$

Using this result, secular behavior in ρ_2 is removed when

$$\frac{\partial W}{\partial t_2} = \sum_{\alpha_1 \alpha_2=1}^3 \gamma_{\alpha_1 \alpha_2} \frac{\partial}{\partial P_{\alpha_1}} \left(\beta \frac{P_{\alpha_2}}{m} + \frac{\partial}{\partial P_{\alpha_2}} \right) W, \quad (4.17)$$

where the tensorial friction coefficient $\gamma_{\alpha_1 \alpha_2}$ is given by

$$\gamma_{\alpha_1 \alpha_2} \equiv \int_{-\infty}^0 d\sigma [(f_{\alpha_1}(0) f_{\alpha_2}(\sigma))^{\text{th}} - f_{\alpha_1}^{\text{th}} f_{\alpha_2}^{\text{th}}], \quad (4.18)$$

i.e., $\gamma_{\alpha_1 \alpha_2}$ is given by autocorrelation of the force on the nanoparticle. For anisotropic systems, i.e., a virus migrating in a membranous cell interior, $\gamma_{\alpha_1 \alpha_2}$ is a second order tensor reflecting possible preferred migration directions.

Letting $T = t_1$ we recompose the above results to obtain

$$\frac{\partial W}{\partial T} = - \frac{\mathbf{P}}{m} \cdot \frac{\partial W}{\partial \mathbf{R}} - \mathbf{f}^{\text{th}} \cdot \frac{\partial W}{\partial \mathbf{P}} + \varepsilon^2 \bar{\gamma} \cdot \left(\beta \frac{\mathbf{P}}{m} + \frac{\partial}{\partial \mathbf{P}} \right) W, \quad (4.19)$$

in tensor notation.

Application of (4.19) to specific systems requires the use of Monte Carlo methods to estimate the friction coefficient and thermal average force. Note that the above results apply when the thermal average force evolves on the t_2 scale, i.e., for an externally applied force that varies on a time scale much longer than that of atomic vibrations and collisions.

V. GENERALIZATIONS AND CONCLUSIONS

The nanocanonical formulation and integration-free removal of secular behavior allow one to overcome conceptual and technical difficulties encountered in a multiscale analysis of the Liouville equation for structured nanoparticles. These difficulties arise from the need to preserve the number of degrees of freedom in the N -atom system. In Secs. III and IV, the solution is shown to reside in the recognition that coarse graining, by nature, involves a probability distribution for the slow variables that can be built into the lowest order quasi-equilibrium solution through Lagrange multipliers. These multipliers play a role analogous to that of the chemical potential in the grand canonical ensemble (where the number of particles, like the values of slow variables here, is not fixed). Furthermore, the recognition that the introduction of slow variables into the N -atom distribution is simply a way to express its multiscale character, and not to say that these are new dynamical variable, as well as the removal of secular behavior without N -atom momentum-position integration, completes our conceptual scheme.

The nanocanonical methodology can be generalized to complex systems involving nanoparticles with complex internal structure or the interaction of multiple nanoparticles. For example, due to its size, a nanoparticle may experience phase transitionlike behaviors. In this case the associated order parameters, c.m. position, and orientation constitute a set of slow variables denoted R ; with the latter are conjugate momenta P . This theme can be extended to many nanoparticle systems and complex host media like a cell's interior. As for the c.m. variables of Secs. III and IV, one can introduce a nanocanonical ensemble such that

$$\hat{\rho}_{M,K} = \frac{\exp(-\beta H_0 + M \cdot P + K \cdot R)}{\Xi(\beta, M, K)}, \quad (5.1)$$

where

$$\Xi(\beta, M, K) = \int d^{6N} \Gamma e^{-\beta H_0 + M \cdot P + K \cdot R}. \quad (5.2)$$

The transformation $\Psi/\Xi \rightarrow W/Q$ follows directly as in Sec. III, as does the removal of secular behavior without atomic momentum-position integration as in Sec. IV. The result of the multiscale computations is a generalized Fokker-Planck equation. While computations without the present approach would require applying $\int d^{6N} \Gamma$ but with integrations involving complex restrictions (stemming from the many R, P variables that must be respected in order to conserve the number of degrees of freedom). We are pursuing these concepts in an analysis of viral phase transitions and other biological and biotechnical contexts.

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APPENDIX A: DECOMPOSITION OF THE LIOUVILLE EQUATION

The Liouville equation for the N -atom probability density $\rho(\mathbf{p}_1, \mathbf{r}_1, \dots, \mathbf{p}_N, \mathbf{r}_N, t)$ is taken to consist of a nanoparticle of N^* atoms and a host medium of $N - N^*$ atoms. The Liouville equation for this system can be written as

$$\frac{\partial \rho}{\partial t} = - \sum_{i=1}^N \left\{ \frac{\mathbf{p}_i}{m_i} \cdot \frac{\partial}{\partial \mathbf{r}_i} + \mathbf{F}_i \cdot \frac{\partial}{\partial \mathbf{p}_i} \right\} \rho \equiv \mathcal{L}^b \rho, \quad (A1)$$

where $\mathbf{F}_i = -(\partial V / \partial \mathbf{r}_i)_{\mathbf{r}_{j \neq i}}$ is the force on atom i .

Our development starts by considering ρ to be dependent on the nanoparticle c.m. position \mathbf{r}^* and momentum \mathbf{p}^* , as well as individual atomic positions and momenta. Nanoparticle mass m^* and c.m. variables are expressed in terms of atomic variables via

$$\left\{ \begin{array}{c} \mathbf{r}^* \\ \mathbf{p}^* \\ m^* \end{array} \right\} = \sum_{i=1}^N \left\{ \begin{array}{c} m_i \mathbf{r}_i / m^* \\ \mathbf{p}_i \\ m_i \end{array} \right\} \Theta_i, \quad (A2)$$

where $\Theta_i = 1$ (atom i in the nanoparticle), $= 0$ (otherwise). In the multiscale analysis the N -body probability density is taken to have the dependence $\rho^*(\mathbf{p}_1, \mathbf{r}_1, \dots, \mathbf{p}_N, \mathbf{r}_N, \mathbf{p}^*, \mathbf{r}^*, t)$. Upon invoking the chain rule, ρ^* is found to satisfy

$$\frac{\partial \rho^*}{\partial t} = \mathcal{L}^{b*} \rho^* - \left[\frac{\mathbf{p}^*}{m^*} \cdot \frac{\partial}{\partial \mathbf{r}^*} + \sum_{i=1}^N \Theta_i \mathbf{F}_i \cdot \frac{\partial}{\partial \mathbf{p}_i} \right]^* \rho^*, \quad (A3)$$

where a superscript $*$ on an operator implies that $\mathbf{p}_1, \mathbf{r}_1, \dots, \mathbf{p}_N, \mathbf{r}_N, \mathbf{r}^*$, and \mathbf{p}^* are the independent variables. Hence $(\partial / \partial \mathbf{r}_i)^*$ implies an \mathbf{r}_i partial derivative keeping $\mathbf{r}_{j \neq i}$, all \mathbf{p}_j , \mathbf{r}^* , and \mathbf{p}^* constant. Finally,

$$\mathcal{L}^{b*} = - \sum_{i=1}^N \left\{ \frac{\mathbf{p}_i}{m_i} \cdot \frac{\partial}{\partial \mathbf{r}_i} + \mathbf{F}_i \cdot \frac{\partial}{\partial \mathbf{p}_i} \right\}^*. \quad (A4)$$

This concludes the first reformulation.

Next we introduce a scaling ansatz and further definitions. Taking the scaled variables $m^* = \varepsilon^{-2} m$, $\mathbf{p}^* = \varepsilon^{-1} \mathbf{P}$, and $\mathbf{r}^* = \varepsilon^{-1} \mathbf{R}$, and introducing a set of scaled times $t_n = \varepsilon^{2n} t$, $n = 0, 1, \dots$, the N -atom probability density is taken to have the dependence $\rho^{**}(\mathbf{p}_1, \mathbf{r}_1, \dots, \mathbf{p}_N, \mathbf{r}_N, \mathbf{P}, \mathbf{R}; t_0, t_1, \dots; \varepsilon)$. With this and the chain rule ρ^{**} satisfies

$$\sum_{n=0} \varepsilon^{2n} \left(\frac{\partial}{\partial t_n} - \mathcal{L}_n \right) \rho^{**} = 0. \quad (A5)$$

Letting a superscript $**$ on an operator indicates that $\mathbf{p}_1, \mathbf{r}_1, \dots, \mathbf{p}_N, \mathbf{r}_N, \mathbf{P}$, and \mathbf{R} are the independent variables, we find $\partial \rho^{**} / \partial t = (\mathcal{L}_0 + \varepsilon^2 \mathcal{L}_1) \rho^{**}$, where

$$\mathcal{L}_0 = - \sum_{i=1}^N \left\{ \frac{\mathbf{p}_i}{m_i} \cdot \frac{\partial}{\partial \mathbf{r}_i} + \mathbf{F}_i \cdot \frac{\partial}{\partial \mathbf{p}_i} \right\}^{**}, \quad (A6)$$

$$\mathcal{L}_1 = - \left[\frac{\mathbf{P}}{m} \cdot \frac{\partial}{\partial \mathbf{R}} \right]^{**} - \left[\mathbf{f} \cdot \frac{\partial}{\partial \mathbf{P}} \right]^{**}, \quad (A7)$$

and $\varepsilon \mathbf{f} = \mathbf{F}_1 + \dots + \mathbf{F}_{N^*}$ is the net force on the virus and the $**$ are dropped for simplicity here and in the derivations of Secs. II–IV.

APPENDIX B: FOURIER/BILATERAL LAPLACE TRANSFORMATION

Given

$$\hat{f}(k) = \int_{-\infty}^{+\infty} dx e^{kx} f(x), \quad (\text{B1})$$

one may show that the inverse relation reads

$$f(x) = \frac{1}{2\pi} \int_{-\infty}^{+\infty} dk e^{-ikx} \hat{f}(ik), \quad (\text{B2})$$

with $i = \sqrt{-1}$. For two functions $f_1(x)$ and $f_2(x)$ one has

$$\frac{1}{2\pi} \int_{-\infty}^{+\infty} dk e^{-ikx} \hat{f}_1(ik) \hat{f}_2(ik) = \int_{-\infty}^{+\infty} dx' f_1(x-x') f_2(x'). \quad (\text{B3})$$

Results in Sec. III follow upon generalization to six dimensions. For example, one may obtain the inversion formula

$$\frac{\Psi(\boldsymbol{\mu}, \boldsymbol{\kappa}, t)}{\Xi(\boldsymbol{\beta}, \boldsymbol{\mu}, \boldsymbol{\kappa})} = \frac{1}{(2\pi)^6} \int d^3p d^3r e^{-i(\boldsymbol{\mu}\cdot\mathbf{p} + \boldsymbol{\kappa}\cdot\mathbf{r})} \frac{W(i\mathbf{p}, i\mathbf{r}, t)}{Q(\boldsymbol{\beta}, i\mathbf{p}, i\mathbf{r})}. \quad (\text{B4})$$

Thus Ψ/Ξ is related to the integration of W/Q over all imaginary momenta and positions.

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