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Mobility Fluctuations and Electrophoretic Light Scattering from Macromolecular Solutions

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We discuss the origins and the effects of mobility fluctuations of rigid, globular macromolecules on a solution's electrophoretic light scattering spectrum. Assuming a dilute solution, a modified van Hove self-correlation function is calculated via van Kampen's time-ordered cumulant method and the results are compared with less rigorous approaches. The consequences of generalizing to dynamic external fields are briefly considered.

KEY WORDS: Electrophoretic light scattering; stochastic differential equation; mobility fluctuations; van Hove correlation function; dynamic light scattering.

1. INTRODUCTION

Ever since electrophoretic light scattering (ELS) was first applied to the study of macromolecular solutions, speculation has focused on how this novel experimental technique might be employed to extract rate constants for unimolecular reactions involving macromolecules.[1,2] On the theoretical side, the picture is rather simple if the macromolecular shape is spherical, the concentration is low, and the various reactions are "spectroscopically unimolecular." One writes a set of reaction-diffusion equations with an electric field-induced drift which describes the space-time evolution of the probability density of each observable species, with the condition that each density is initially a Dirac delta function:

$$\frac{\partial G_i}{\partial t} = D_i \nabla^2 G_i + \mu_i (\mathbf{E} \cdot \nabla) G_i + \sum_{j \neq i}^{N} (K_{ij} G_j - K_{ji} G_i) \tag{1.1}$$

$$G_i(\mathbf{r}, 0) = \delta(\mathbf{r}), \qquad K_{ij} \geqslant 0$$

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where D is the diffusion coefficient, μ is the mobility, and $\mathbf{E}$ is the external electric field. The G_i are the van Hove self-correlation functions,[3] that is, $G_i(\mathbf{r}, t)$ is the equilibrium ensemble-averaged conditional probability density that a macromolecule of species i located initially at the origin will be at position $\mathbf{r}$ at time t. Note that Eq. (1.1) has the structure of a master equation with diffusion and drift. Since the system is effectively isotropic and unbounded, the spatial Fourier transform of G_i can be identified with the so-called intermediate correlation function, directly obtainable, in principle, from the heterodyne-measured ELS spectrum, which is itself a concentration- and amplitude-weighted sum of the spatial–temporal Fourier transforms of all the G_i (the Wiener–Khintchine theorem). Although this analysis looks impressive and simple on paper, it has so far proven to be impossible to obtain convincing experimenal evidence of even a single reaction-kinetics related spectral feature. Conventional pulse field ELS is apparently not sufficiently sensitive to measure line shapes to the required accuracy.[4] The achievement of better resolution through the use of time-varying fields is currently being vigorously pursued by some in the ELS community[5]; fortunately, it is not difficult to incorporate this effect into our analysis, and some of the theoretical consequences are considered in this paper.

While it is natural to assume that Eq. (1.1) describes the most general case of conformational dynamics, it is quite conceivable that N is large, or even that the transition dynamics is not a Markov process, so that the notion of a set of rate constants is not valid. A previous analysis[6] demonstrated the possibility of a variety of rather distinct "conformational dynamics spectral signatures," which depended strongly on the nature of the underlying stochastic processes, and in this paper we continue our investigation of this model, as follows. Consider a single spherical macroion in solution together with counterions and supporting electrolyte. Suppose that conformational fluctuations have a negligible effect on the hydrodynamic size or shape, but that the molecule's electrophoretic velocity is coupled to its internal dynamics in such a way that the mobility μ fluctuates in time. This might be the case if the surface charge were fluctuating in a low salt environment or if the so-called zeta potential were fluctuating at high salt concentration (the Smoluchowski or large-κ limit, where κ^{-1} is the Debye screening length).[7–9] In other words, we suppose that the ambient electrolyte, which consists of small ions, is able to faithfully track a class of sufficiently slow, electrostatically active conformational fluctuations in the nearby macromolecule, so that we can take the counterions plus suporting salt to be at or near equilibrium for a given macromolecular configuration. As a result of these idealizations, we can replace the N-species system of Eq. (1.1) by a single species with a fixed

diffusion coefficient and a fluctuating, time-dependent mobility. The unimolecular reaction terms may then be recovered as a special case—a Markov process with discrete states.

The point is that by mapping the problem onto a stochastic differential equation with colored, multiplicative noise, we can avail ourselves of the rigorous time-ordered cumulant expansion procedure of van Kampen,[10,11] as well as explore more ambitious, less systematic (in fact, rather ad hoc) techniques, such as the first-order smoothing or first cumulant discard method of Bourret.[12] The problem, therefore, consists of a nontrivial exercise in statistical physics with a close connection to biophysics—the conformational dynamics of solvated globular proteins as observed by ELS.

This paper is organized as follows. In Section 2 we present a projection operator derivation of an exact equation of evolution for the correlation function and introduce the first-order smoothing (B) ansatz. In Section 3 we introduce van Kampen's systematic cumulant expansion and compare to B-smoothing, as well as discuss the exactly solvable Gaussian model. We consider the consequences of assuming a two-state Markov process for mobility fluctuations in Section 4, and in Section 5 we briefly investigate the case of time-dependent external fields.

2. THE MODIFIED VAN HOVE SELF-CORRELATION FUNCTION

Let $\psi(\mathbf{r}, t \mid \mu(0), \mu(t))$ be the probability density that a macromolecule initially at $\mathbf{r} = 0$ with mobility $\mu(0)$ will be located at $\mathbf{r}(t)$ with mobility $\mu(t)$ a time t later. The quantity ψ is therefore a function of the stochastic variable μ as well as the nonrandom variables $\mathbf{r}$ and t. Suppose that ψ satisfies the stochastic Smoluchowski equation

$$\partial\psi/\partial t = D\nabla^2\psi + \mu(t)(\mathbf{E}\cdot\nabla)\,\psi$$

with

$$\psi(\mathbf{r}, 0) = \delta(\mathbf{r}) \tag{2.1}$$

where $\mathbf{E}$ is constant and the equilibrium ensemble average of the fluctuations in ψ and μ vanish. In other words, we have that

$$\begin{aligned} \psi &= \langle\psi(\mathbf{r}, t)\rangle + \delta\psi(\mathbf{r}, t) \\ \mu(t) &= \mu_0 + \delta\mu(\mathbf{t}), \qquad \mu_0 \text{ const} \\ \langle\delta\psi\rangle &= 0, \qquad \langle\delta\mu\rangle = 0 \end{aligned} \tag{2.2}$$

We write Eq. (2.1) in a more compact form,

$$\partial\psi/\partial t = \mathscr{L}_0\psi + \mathscr{L}_1\psi \tag{2.3}$$

where

$$\mathscr{L}_0 = D\nabla^2 + \mu_0(\mathbf{E}\cdot\nabla), \qquad \mathscr{L}_1 = \delta\mu(t)(\mathbf{E}\cdot\nabla)$$

so that $\mathscr{L}_0$ is nonrandom, $\mathscr{L}_1$ is a "centered" random operator ($\langle\mathscr{L}_1\rangle = 0$), and we solve for the modified self-correlation function $\langle\psi(\mathbf{r}, t)\rangle$. First, switch to the integral form of Eq. (2.3),

$$\psi(\mathbf{r}, t) = \exp(\mathscr{L}_0 t)\,\psi(r, 0) + \int_0^t d\tau \exp[\mathscr{L}_0(t-\tau)]\,\mathscr{L}_1(\tau)\,\psi(\tau) \tag{2.4}$$

and introduce the projection operator $\mathscr{P}$ as

$$\begin{aligned} \mathscr{P}\mathscr{L}_0 &= \mathscr{L}_0\mathscr{P}, & \mathscr{P}\mathscr{L}_1\mathscr{P} &= 0 \\ \mathscr{P}\psi(\mathbf{r}, 0) &= \psi(\mathbf{r}, 0), & \mathscr{P}\psi &= \langle\psi\rangle \end{aligned} \tag{2.5}$$

so that the projector $\mathscr{P}$ is an ensemble averaging operator and the initial distribution is nonrandom. Note that the fluctuating part of the distribution is simply the orthogonal projection

$$\delta\psi(\mathbf{r}, t) = (1-\mathscr{P})\,\psi(\mathbf{r}, t) \tag{2.6}$$

A few straightforward iterative manipulations produce

$$\langle\psi(\mathbf{r}, t)\rangle = \exp(\mathscr{L}_0 t)\,\psi(\mathbf{r}, 0) - \mathscr{G}_0\mathscr{D}\langle\psi(r, t)\rangle \tag{2.7}$$

with

$$\begin{aligned} \mathscr{G}_0 f &= \int_0^t d\tau \exp[\mathscr{L}_0(t-\tau)]\,f(\tau) \\ \mathscr{D} &= -\mathscr{P}\mathscr{L}_1 \sum_{n=1}^{\infty} \{\mathscr{G}_0(1-\mathscr{P})\,\mathscr{L}_1\}^n \end{aligned} \tag{2.8}$$

Equations (2.7) and (2.8) constitute a Dyson expansion,[13] which usually appears in the literature as a diagrammatic representation. An exact solution to a Dyson equation is generally not possible, and, with the exception of van Kampen's method, the validity of approximation schemes depends strongly on the specific problem.

For reasons which will become apparent later, we introduce the B ansatz, which amounts to the closure assumption

$$\delta\psi = \mathscr{G}_0\mathscr{L}_1\langle\psi\rangle \tag{2.9}$$

and so

$$\langle \psi \rangle = \exp(\mathscr{L}_0 t)\, \psi(\mathbf{r}, 0) + \mathscr{G}_0 \mathscr{P} \mathscr{L}_1 \mathscr{G}_0 \mathscr{L}_1 \langle \psi \rangle \tag{2.10}$$

Equation (2.9) says that the fluctuating portion of the distribution $\delta\psi(t)$ depends only on $\mathscr{G}_0(\tau)$, on the stochastic operator $\mathscr{L}_1(\tau)$, and on the correlation function $\langle \psi(\tau) \rangle$ at previous times ($\tau < t$). By substituting for $\mathscr{L}_0$ and $\mathscr{L}_1$ from Eq. (2.3) and $\mathscr{G}_0$ from Eq. (2.8), one can cast Eq. (2.10) into the more provocative form

$$\frac{\partial \langle \psi \rangle}{\partial t} = D\nabla^2 \langle \psi \rangle + \mu_0 (\mathbf{E} \cdot \nabla) \langle \psi \rangle + E^2 \int d^3\mathbf{r}' \int_{-\infty}^{t} ds \left[\langle \delta\mu(t)\, \delta\mu(s) \rangle \frac{\partial}{\partial x} G(\mathbf{r} \mid \mathbf{r}', t-s) \frac{\partial}{\partial x'} \langle \psi(\mathbf{r}', s) \rangle \right] \tag{2.11}$$

where the electric field is in the x direction and G is simply the Green's function for diffusion with uniform drift:

$$G(\mathbf{r} \mid \mathbf{r}', t-s) = [4\pi D(t-s)]^{-3/2} \times \exp\left[-\frac{[x - x' + \mu_0 E(t-s)]^2 + (y-y')^2 + (z-z')^2}{4D(t-s)} \right] \tag{2.12}$$

Since the stochastic variable $\delta\mu$ depends only on time and not on spatial coordinates, it is easy to show that the smoothed correlation function $\langle \psi \rangle$ is given exactly by

$$\langle \psi(\mathbf{r}, t) \rangle = C(t)\, G(\mathbf{r} \mid 0, t-0) \tag{2.13}$$

where the fluctuation-dependent factor $C(t)$ is determined by the solution of

$$\frac{dC(t)}{dt} = -E^2 K_x^2 \int_{-\infty}^{t} ds\, C(s) \langle \delta\mu(t)\, \delta\mu(s) \rangle \tag{2.14}$$

where $\mathbf{K}$ is the wave vector associated with the spatial Fourier transform. Now use the time-displacement invariance of an equilibrium correlation function to arrive at

$$\frac{dC(t)}{dt} = -E^2 K_x^2 \int_{0}^{t} ds\, C(s) \langle \delta\mu(0)\, \delta\mu(t-s) \rangle \tag{2.15}$$

where we have assumed that $C(t)=0$ for $t<0$. The convolution theorem of Laplace transforms (variable z) immediately yields

$$\tilde{C}(z)=\frac{1}{z+E^2K_x^2\tilde{\Gamma}(z)}$$
$$\tilde{\Gamma}(z)=\int_0^\infty d\tau\, e^{-z\tau}\langle\delta\mu(0)\,\delta\mu(\tau)\rangle \tag{2.16}$$

and it is now a straightforward matter to investigate the dependence of $C(t)$ on the auxiliary stochastic process $\delta\mu(t)$, as well as the influence of $\delta\mu$ on the ELS heterodyne spectrum via the Wiener–Khintchine theorem.

3. THE VAN KAMPEN EXPANSION AND *B*-SMOOTHING

Unfortunately, despite the simplicity of the previous analysis, it is quite difficult to assess the general validity of the B ansatz. If we are to have full confidence in our results, a more systematic approach to the problem is needed and we therefore turn to van Kampen's time-ordered cumulant expansion.[10,11] First, consider the spatial Fourier transform (wave vector $\mathbf{K}$) of Eq. (2.1):

$$\partial\hat{\psi}/\partial t=[-K^2D+iK_x\mu(t)\,E]\,\hat{\psi} \tag{3.1}$$

This is the simplest example of a more general stochastic equation analyzed by van Kampen:

$$\partial\mathbf{u}/\partial t=[\mathsf{A}_0+\alpha\mathsf{A}_1(t)]\,\mathbf{u}(t) \tag{3.2}$$

where $\mathbf{u}$ is a random vector, A_0 is a nonrandom matrix, $\mathsf{A}_1(t)$ is a random matrix, and α is a scalar expansion parameter. Van Kampen has shown that the statistical or ensemble average of $\mathbf{u}$ with nonrandom initial value $\mathbf{u}(t_0)$ satisfies

$$d\langle\mathbf{u}\rangle/dt=\mathsf{A}_0\langle\mathbf{u}\rangle+\mathsf{K}(t\,|\,t_0)\langle\mathbf{u}\rangle$$

where

$$\mathsf{K}(t\,|\,t_0)=\sum_{m=1}^{\infty}\alpha^m\mathsf{K}_m(t\,|\,t_0)$$

and

$$\mathsf{K}_m(t\,|\,t_0)=\int_{t_0}^{t}dt_1\int_{t_0}^{t_1}dt_2\cdots\int_{t_0}^{t_{m-2}}dt_{m-1}\,\mathsf{C}_m(t,t_1,\ldots,t_{m-1}) \tag{3.3}$$

In Eq. (33), C_m is an mth-order time-ordered cumulant

$$C_m = \langle A_1(t)\, A_1(t_1) \cdots A_1(t_{m-1}) \rangle_P \tag{3.4}$$

where the subscript P signifies cumulant. For example, $C_2(t, t_1)$ is given by

$$C_2(t, t_1) = \langle A_1(t)\, A_1(t_1) \rangle_P = \langle A_1(t)\, A_1(t_1) \rangle - \langle A_1(t) \rangle \langle A_1(t_1) \rangle \tag{3.5}$$

If we denote the correlation time of $A_1(t)$ by τ_c, then to first order in $\alpha\tau_c$, and for times exceeding the initial transient time

$$\frac{d\langle \mathbf{u} \rangle}{dt} = \left\{ A_0 + \alpha \langle A_1(t) \rangle + \alpha^2 \int_0^\infty d\tau\, \langle A_1(t) [\exp(\tau A_0)]\, A_1(t-\tau) \rangle \exp(-\tau A_0) \right\} \langle \mathbf{u} \rangle \tag{3.6}$$

In our case $\delta\mu(t)$ is statistically uncorrelated with $\hat{\psi}(0)$, and so we have, for all times, provided that $|K_x M_0 E \tau_\mu| \ll 1$,

$$\frac{\partial \langle \psi(t) \rangle}{\partial t} = \left[-K^2 D + iK_x \mu_0 E - K_x^2 E^2 \int_0^\infty d\tau\, \langle \delta\mu(0)\, \delta\mu(\tau) \rangle \right] \langle \hat{\psi}(t) \rangle \tag{3.7}$$

where $M_0 = \langle \delta\mu(0)^2 \rangle^{1/2}$ is the amplitude of the equilibrium mobility fluctuations. Note that $|K_x M_0 E \tau_\mu| \ll 1$ can always be experimentally realized, regardless of the magnitude of τ_μ, which is the correlation time for the decay of μ fluctuations. Equation (3.7) implies that the diffusion tensor has been renormalized from isotropic to the anisotropic form

$$\begin{pmatrix} D & 0 & 0 \\ 0 & D & 0 \\ 0 & 0 & D \end{pmatrix} \longrightarrow \begin{pmatrix} D + \delta D_{xx} & 0 & 0 \\ 0 & D & 0 \\ 0 & 0 & D \end{pmatrix}$$

where

$$\delta D_{xx} = E^2 \int_0^\infty d\tau\, \langle \delta\mu(0)\, \delta\mu(\tau) \rangle \tag{3.8}$$

The diffusion coefficient is anisotropically enhanced because the mobility fluctuations interact with the external field to give the macroion rapidly varying random kicks in the **E** direction. The casual observer might conclude that the macromolecule has been distorted by the field, whereas Eq. (3.8) attributes this effect to conformational dynamics.[6]

It so happens that the B-smoothed formulation, as given by Eqs. (2.11)–(2.16), reproduces van Kampen's result (3.8) under virtually identical conditions; i.e., $|\alpha\tau_\mu| \ll 1$. To see this, consider Eq. (2.16) and choose

$$\Gamma(t) = \langle \delta\mu(0)\, \delta\mu(t) \rangle = \gamma\delta(t), \qquad \gamma \text{ const} \tag{3.9}$$

which means that the mobility fluctuation spectrum is white noise. Interpret $\tilde{\Gamma}(z)$ as a Laplace–Stieltjes transform and immediately obtain

$$C(t) = \exp(-K_x^2 E^2 \gamma t) \tag{3.10}$$

which implies

$$\delta D_{xx} = E^2\gamma \tag{3.11}$$

A more interesting picture arises from collapsing the Green's function in Eq. (2.12) as

$$G \to \delta(\mathbf{r} - \mathbf{r}') \tag{3.12}$$

which implies that the macromolecule is virtually stationary during the decay of a μ fluctuation (Brownian limit). Equation (2.11) then says that

$$\delta D_{xx} = E^2 \int_0^\infty d\tau\, \langle \delta\mu(0)\, \delta\mu(\tau) \rangle \tag{3.13}$$

in complete agreement with van Kampen's result.

Now consider the B-smoothed correlation function where $\alpha\tau_\mu$ is arbitrary and $\Gamma(t)$ has the Markov form

$$\Gamma(t) = a \exp(-bt), \qquad a, b > 0 \tag{3.14}$$

From Eq. (2.16) the Laplace transform of $C(t)$ is then

$$\tilde{C}(z) = \frac{z + b}{(z - R_1)(z - R_2)}, \qquad \left.\begin{matrix} R_1 \\ R_2 \end{matrix}\right\} = \frac{-b \pm (b^2 - 4\alpha)^{1/2}}{2}$$

where

$$\alpha = K_x^2 E^2 a \tag{3.15}$$

The correlation function $C(t)$ is therefore given by

$$C(t) = (R_1 - R_2)^{-1} [(R_1 + b)\exp(R_1 t) - (R_2 + b)\exp(R_2 t)] \tag{3.16}$$

Since the R's are in general complex, $C(t)$ decays as the sum of two oscillatory exponentials. An interesting exercise is to go back to the original equation (1.1), take $N=2$, fix D, and take

$$\mu_1 \to \mu_0 + \Delta\mu, \qquad \mu_2 \to \mu_0 - \Delta\mu, \qquad K_{12} = K_{21} \tag{3.17}$$

These limits constitute a dichotomic Markov processes (DMP). After a spatial Fourier transform and a bit of algebra, it is easy to show that Eq. (3.16) and the DMP $C(t)$ are identical, given the proper identification of a and b with the parameters in Eq. (3.17). This connection will be discussed in more detail in the next section. It turns out that the B ansatz is generally exact only for a DMP, which, moreover, can be analyzed via straightforward algebra.

To illustrate the connection between $C(t)$, $\hat{\psi}(\mathbf{K}, t)$, and the heterodyne measured intensity of scattered light $I(\omega)$, we go back to Eq. (3.16) and take the limiting case of infinite correlation time ($b \to 0$) for the μ fluctuations. We now have

$$C(t) = \cos(a^{1/2}t) \tag{3.18}$$

which, via Eq. (2.13) and a Fourier transform, determines $\langle \hat{\psi} \rangle$. The Wiener–Khintchine theorem says that[2]

$$I(\omega) = \frac{1}{2\pi} \int_{-\infty}^{+\infty} \langle \hat{\psi}(\mathbf{K}, t) \rangle \exp(i\omega t)\, dt \tag{3.19}$$

and therefore

$$I_{\omega>0}(\omega) = \text{const} \times \left\{ \frac{DK^2}{[\omega - K_x E(\mu_0 - \sqrt{a})]^2 + (DK^2)^2} + \frac{DK^2}{[\omega - K_x E(\mu_0 + \sqrt{a})]^2 + (DK^2)^2} \right\} \tag{3.20}$$

with another pair of Lorentzians located at the reflection through $\omega = 0$. Equation (3.20) is exactly what one would expect for two noninterchanging species with identical D's and mobilities $\mu_0 \pm \sqrt{a}$.

Suppose the μ fluctuations arise from a stationary Gaussian random process. Then Eqs. (2.1) and (2.2) can be solved exactly as

$$\langle \hat{\psi}(\mathbf{K}, t) \rangle = C(t) \exp[(+iK_x \mu_0 E - K^2 D)\, t] \tag{3.21}$$

with

$$C(t) = \left\langle \exp\left[+iK_x E \int_0^t d\tau\, \delta\mu(\tau) \right] \right\rangle$$

Since $\delta\mu$ is a Gaussian random process, so is $\int d\tau\, \delta\mu$; therefore, $C(\tau)$ can be written

$$C(\tau) = \exp\left[-\frac{1}{2} K_x^2 E^2 \int_0^\tau dt \int_0^\tau ds\, \Gamma(t-s) \right] \tag{3.22}$$

where we have assumed, as before, time displacement invariance for the mobility fluctuations. By choosing

$$\Gamma(t-s) = \gamma\delta(t-s) \tag{3.23}$$

we recover the white-noise result (3.11). By setting

$$\Gamma(t-s) = a \exp(-b\,|t-s|) \tag{3.24}$$

we generate a Uhlenbeck–Ornstein process,[14] which is essentially the only possible stationary Markovian Gaussian random process, in which case

$$C(t) = \exp\{ -(\alpha/b^2)[bt + \exp(-bt) - 1] \} \tag{3.25}$$

where α is given by Eq. (3.15). Here a short correlation time ($b \to \infty$) produces

$$C(t) = \exp[-(\alpha/b)\, t], \qquad b \to \infty \tag{3.26}$$

and we recover a renormalized diffusion tensor as in Eq. (3.11) or (3.13). On the other hand, a very long correlation time ($b \to 0$) produces a result identical to that derived from a static Gaussian distribution of $\delta\mu$'s:

$$C(t) = \exp(-\tfrac{1}{2}\alpha t^2), \qquad b \to 0 \tag{3.27}$$

and the spectrum becomes

$$I(\omega) = \mathrm{Re}\left(\frac{\alpha}{2}\right)^{-1/2} \left\{ \exp\left[\frac{(\lambda - i\omega)^2}{2\alpha}\right] \mathrm{erfc}\left[\frac{\lambda - i\omega}{(2\alpha)^{1/2}}\right] + \exp\left[\frac{(\lambda + i\omega)^2}{2\alpha}\right] \mathrm{erfc}\left[\frac{\lambda + i\omega}{(2\alpha)^{1/2}}\right] \right\} \tag{3.28}$$

where

$$\lambda = -iK_x E\mu_0 + K^2 D$$

For a very large molecule $D \to 0$, λ becomes purely imaginary,

$\mathrm{Re}[\mathrm{erfc}] \to 1$, and the scattered intensity simplifies to the sum of two Gaussians (not Lorentzians):

$$I_{\omega>0}(\omega) \doteq \left(\frac{\alpha}{2}\right)^{-1/2} \left\{\exp\left[-\frac{(\omega - K_x E\mu_0)^2}{2\alpha}\right] + \exp\left[-\frac{(\omega + K_x E\mu_0)^2}{2\alpha}\right]\right\} \tag{3.29}$$

Note that the B smoothing with the same $\Gamma(t)$ gives results quite different from the exact equations (3.25)–(3.28).

4. THE MOBILITY CORRELATION FUNCTION

Up to this point we have tacitly assumed knowledge of the mobility fluctuation correlation function

$$\Gamma(t) = \langle \delta\mu(0)\, \delta\mu(t) \rangle \tag{4.1}$$

without questioning its origins. Here we present what is probably the simplest model that gives a $\Gamma(t)$ decaying as the superposition of simple exponentials: an N-state Markov process. Suppose that $P_j(t)$ is the probability that the macromolecule occupies the jth mobility state at time t conditioned on the initial state distribution. With the Markov assumption we can immediately write a master equation[15]

$$d\mathbf{P}/dt = -\boldsymbol{\Lambda}\mathbf{P}(t) \tag{4.2}$$

where $\boldsymbol{\Lambda}$ is the matrix of transition probabilities λ_{ij}, i.e., $\lambda_{ij}\Delta t$ is the probability of making a jump from state i to j during the time interval $(t, t + \Delta t)$. At equilibrium (steady state) we must have

$$\boldsymbol{\Lambda}\mathbf{P}^{\mathrm{eq}} = 0 \tag{4.3}$$

The matrix $\boldsymbol{\Lambda}$ is singular because $\sum_j P_j = 1$, and so we eliminate $P_1(t)$ and rewrite

$$d\mathbf{P}'/dt = -\boldsymbol{\Lambda}'\mathbf{P}'(t) \tag{4.4}$$

where

$$\begin{aligned} \mathbf{P}'(t) &= [P_2(t) - P_2^{\mathrm{eq}}, \ldots, P_N(t) - P_N^{\mathrm{eq}}] \\ \Lambda'_{ij} &= \Lambda_{ij} - \Lambda_{i1}, \qquad i, j = 2, 3, \ldots, N \end{aligned} \tag{4.5}$$

Equation (4.4) is solved as

$$\mathbf{P}'(t) = \exp(-\boldsymbol{\Lambda}'t)\, \mathbf{P}'(0) \tag{4.6}$$

where the $P_j'(t)$ depend on the initial set of $P_i'(0)$. Write the statistical average of the mobility as

$$\begin{aligned} \langle \mu(t) \rangle &= \sum_{j=1}^{N} \mu_j P_j(t) = \sum_{j=2}^{N} (\mu_j - \mu_1) P_j(t) + \mu_1 \\ \langle \mu(t) - \mu^{\text{eq}} \rangle &= \sum_{j=2}^{N} (\mu_j - \mu_1)[P_j(t) - P_j^{\text{eq}}] \equiv \langle \delta\mu(t) \rangle \end{aligned} \tag{4.7}$$

Equation (4.7) can be written as a scalar product:

$$\langle \mu(t) - \mu^{\text{eq}} \rangle = \boldsymbol{\mu}' \cdot \mathbf{P}'(t)$$

with

$$\mu_j' = \mu_j - \mu_1 \tag{4.8}$$

Now $\Gamma(t)$ can be expressed as

$$\Gamma(t) = \langle \langle \delta\mu(t) \rangle_0 \, \delta\mu(0) \rangle \tag{4.9}$$

where $\langle \cdot \rangle_0$ denotes an average conditioned on the initial value, and this immediately gives

$$\Gamma(t) = \boldsymbol{\mu}' \cdot \exp(-\Lambda' t) \cdot \sigma' \cdot \boldsymbol{\mu}' \tag{4.10}$$

where σ' is the $(N-1) \times (N-1)$ matrix $\langle \mathbf{P}'(0) \cdot \mathbf{P}'(0)^T \rangle$ (T denotes the transpose). Hill has shown that[16]

$$\begin{aligned} \sigma_{ij}' &= -P_i^{\text{eq}} P_j^{\text{eq}}, && i \neq j \\ &= P_j^{\text{eq}}(1 - P_j^{\text{eq}}), && i = j \end{aligned} \tag{4.11}$$

and so for a two-state system we have

$$\Lambda = \begin{pmatrix} \lambda_{12} & -\lambda_{21} \\ -\lambda_{12} & \lambda_{21} \end{pmatrix}, \qquad \Lambda' = \lambda_{21} + \lambda_{12}$$

and

$$P_1^{\text{eq}} = \lambda_{21}/(\lambda_{12} + \lambda_{21}) \tag{4.12}$$

Therefore

$$\Gamma(t) = (\mu_2 - \mu_1)^2 \frac{\lambda_{12}\lambda_{21}}{(\lambda_{21} + \lambda_{12})^2} \exp[-(\lambda_{12} + \lambda_{21})\, t] \tag{4.13}$$

Comparing this with Eq. (3.14), we can identify

$$a=(\mu_2-\mu_1)^2\frac{\lambda_{12}\lambda_{21}}{(\lambda_{21}+\lambda_{12})^2},\qquad b=\lambda_{12}+\lambda_{21} \tag{4.14}$$

Note that the amplitude a depends on the transition probabilities as well as the difference between levels. For the dichotomic Markov case we have

$$\begin{aligned}\mu_2&=-\mu_1=\delta\mu(0), &\lambda_{12}&=\lambda_{21}=\lambda\\ a&=\langle\delta\mu(0)^2\rangle, &b&=2\lambda\end{aligned} \tag{4.15}$$

so now the amplitude is just the mean-square equilibrium mobility fluctuation and the correlation time is the inverse of twice the transition rate.

More generally, $\Gamma(t)$ for an N-state Markov process will decay as the sum of $N-1$ exponentials unless some of the λ_{ij} are identical, in which case fewer exponentials will appear.

Even for $N=3$ the algebra becomes quite tedious, and so we restrict ourselves to a three-state system with identical transition probabilities λ, and simply present the result for $\Gamma(t)$:

$$\Gamma(t)=\tfrac{2}{9}(\mu_1^2+\mu_2^2+\mu_3^2-\mu_1\mu_2-\mu_1\mu_3-\mu_2\mu_3)\exp(-3\lambda t) \tag{4.16}$$

which is quite similar to the two-level mobility correlation function.

V. THE VAN HOVE CORRELATION FUNCTION IN A PERIODIC EXTERNAL FIELD

Thus far we have considered only constant electric fields. However, it is a straightforward procedure to incorporate dynamic fields in van Kampen's treatment. For a time-dependent electric field, Eq. (3.7) becomes

$$\begin{aligned}\frac{\partial\langle\hat{\psi}(\mathbf{K},t)\rangle}{\partial t}=\Big[&-K^2D+iK_xE(t)\,\mu_0\\&-K_x^2\int_0^\infty d\tau\,E(t)\,E(t-\tau)\langle\delta\mu(t)\,\delta\mu(t-\tau)\rangle\Big]\langle\hat{\psi}(\mathbf{K},t)\rangle\end{aligned} \tag{5.1}$$

Choose $\mathbf{E}(t)=\mathbf{E}_0\exp(i\omega_0 t)$ and take for the mobility correlation function the simple exponential (3.14); Eq. (5.1) is easily solved as

$$\begin{aligned}\langle\hat{\psi}(\mathbf{K},t)\rangle=\exp\Big[&-K^2Dt+\frac{K_xE_0\mu_0(e^{i\omega_0 t}-1)}{\omega_0}\\&-\frac{K_x^2E_0^2a(e^{2i\omega_0 t}-1)}{2i\omega_0(i\omega_0+b)}\Big]\end{aligned} \tag{5.2}$$

Note the explicit appearance of the external driving frequency in the "μ_0 average" term as well as in the fluctuation term. At sufficiently low frequencies and for times that are not too long, we can assume

$$\omega_0 t \ll 1, \qquad \omega_0/b \ll 1 \tag{5.3}$$

and thereby recover the renormalized form

$$\delta D_{xx} = E_0^2(a/b) \tag{5.4}$$

while at very high frequencies $\langle \hat{\psi} \rangle$ reflects only isotropic diffusive behavior and decays as a simple exponential. The van Hove function is quite complex in a broad intermediate regime.

Another interesting example is that of an external field with a random phase ϕ:

$$\mathbf{E}(t) \equiv \mathbf{E}(t, \phi) = \mathbf{E}_0 \sin(\omega_0 t + \phi), \qquad 0 \leqslant \phi \leqslant 2\pi \tag{5.5}$$

where ϕ is uniformly distributed between 0 and 2π. The phase average of $\mathbf{E}(t, \phi)$ now vanishes identically

$$\langle \mathbf{E}(t, \phi) \rangle_\phi = 0 \tag{5.6}$$

while the phase-averaged two-time correlation function is given by

$$\langle E(t)\, E(s) \rangle_\phi = \tfrac{1}{2} E_0^2 \cos[\omega_0(t-s)] \tag{5.7}$$

If we assume that the phase and ensemble averages commute, then we can solve Eq. (5.1) for the phase-averaged $\langle \hat{\psi} \rangle$ as

$$\langle \langle \hat{\psi}(\mathbf{K}, t) \rangle_\phi \rangle = \exp\left[-K^2 Dt - \frac{K_x^2 E_0^2 t}{2} \int_0^\infty d\tau \cos(\omega_0 \tau) \langle \delta\mu(0)\, \delta\mu(\tau) \rangle \right] \tag{5.8}$$

which says that the nonrandom or average drift has been filtered out and the fluctuation term consists of the cosine Fourier transform of $\Gamma(t)$.

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