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Wavevector dependence of the effective diffusion coefficient for solutions of macromolecules

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Abstract. The wavevector dependence of the effective diffusion coefficient determined from the initial decay of the dynamic structure factor is calculated correct to first order in the concentration for a system of interacting Brownian particles.

1. Introduction

Intensity fluctuation spectroscopy is widely used to determine diffusion coefficients of proteins and other biological macromolecules. Concentration dependence of the diffusion coefficient is almost invariably observed, reflecting the operation of hydrodynamic and direct potential (hard-sphere and electrostatic) interactions between the molecules in solution. The available theories which give a complete treatment of hydrodynamic and direct interaction effects (Batchelor 1976, Felderhof 1978) refer to the limit of zero wavevector, whereas quasielastic light-scattering techniques probe concentration fluctuations in a single Fourier component of finite wavevector.

In extending either the approach of Batchelor (1976) or that of Felderhof (1978) to finite wavevector, it is necessary to consider the timescale on which the result obtained is likely to be valid. Two characteristic times, the Brownian relaxation time τ_B and the interaction relaxation time τ_I , have been delineated by Pusey (1975, 1978). Batchelor (1976) makes explicit use of the separation of these timescales in his analysis. Marqusee and Deutch (1980) have recently discussed macromolecular self-diffusion and concluded that analyses of the type developed by Batchelor (1976) and Felderhof (1978) refer to events on the 'plateau' timescale $\tau_B \ll \tau \ll \tau_I$. In this paper it is our purpose to extend the analysis of Felderhof (1978) to calculate the wavevector dependence of the effective diffusion coefficient determined from the initial decay of the dynamic structure factor which is observed in quasielastic light-scattering experiments.

Section 2 is concerned with the definition of the diffusion matrix for a system of interacting macromolecules and the derivation of an equation for the time evolution of the local particle number density (Felderhof 1978). In § 3 we introduce an *ansatz* which allows calculation of the wavevector dependence of the diffusion coefficient.

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In § 4 the significance of the result obtained is discussed in relation to other calculations of the diffusion coefficient which may be determined using quasielastic light-scattering spectroscopy.

2. Brownian motion of interacting particles

The Brownian motion of N weakly interacting particles suspended in a low-Reynolds-number fluid may be described (Zwanzig 1969) by a Smoluchowski equation for the temporal evolution of their joint probability distribution $P(\mathbf{X})$:

$$\partial P/\partial t = \nabla \cdot \mathcal{D} \cdot [\nabla P + (1/kT)(\nabla U)P]. \quad (2.1)$$

Here $\mathbf{X} \equiv (\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N)$ is the position of the system in configuration space and $\nabla \equiv \partial/\partial \mathbf{X}$. The coefficient $\mathcal{D}(\mathbf{X})$ is a matrix $(\mathbf{D}_{ij})_{N \times N}$ of diffusion tensors, $U(\mathbf{X})$ is the total potential energy of interaction between the particles, k is Boltzmann's constant and T is the absolute temperature. The terminal velocity $\mathbf{V} \equiv (\mathbf{v}_1, \mathbf{v}_2, \dots, \mathbf{v}_N)$ of the system through configuration space when the particles have steady forces $\mathbf{F}_1, \mathbf{F}_2, \dots, \mathbf{F}_N$ applied to them is governed (Batchelor 1972, 1976) by the mobility matrix $\ell(\mathbf{X})$:

$$\mathbf{V} = \ell \cdot (\mathbf{F}_1, \mathbf{F}_2, \dots, \mathbf{F}_N). \quad (2.2)$$

The diffusion and mobility matrices are related by the generalised Einstein relation (Murphy and Aguirre 1972, Wills 1979)

$$\mathcal{D} = kT\ell. \quad (2.3)$$

The dependence of \mathcal{D} on the configuration \mathbf{X} of the system may, in the dilute limit, be taken into account by pairwise consideration of the hydrodynamic interactions. General expressions for elements \mathbf{b}_{ij} of ℓ when the particles are spheres of radius a immersed in a fluid of viscosity η have been given by Batchelor (1972, 1976), leading to the formula

$$\mathbf{D}_{ab} = D^0 [A_{ab}(r)\hat{\mathbf{r}}\hat{\mathbf{r}} + B_{ab}(r)(\mathbf{I} - \hat{\mathbf{r}}\hat{\mathbf{r}})], \quad a, b \in \{i, j\}, \quad (2.4)$$

where $\mathbf{r} \equiv \mathbf{x}_j - \mathbf{x}_i$ is the pair separation vector, \mathbf{I} is the unit isotropic tensor, $\hat{\mathbf{r}}\hat{\mathbf{r}}$ is the unit dyadic $\mathbf{r}\mathbf{r}/r^2$ and $A_{ab}(r)$ and $B_{ab}(r)$ are coefficients whose values, for 'stick' boundary conditions, are known accurately from theory and by calculation. The free-particle diffusion coefficient D^0 is given by the Stokes-Einstein relation

$$D^0 = kT/6\pi\eta a(1 - \xi) \quad (2.5)$$

where the parameter ξ characterises the boundary condition. It takes values in the range $0 \leq \xi \leq \frac{1}{3}$, the value $\xi = 0$ corresponding to 'stick' and the value $\xi = \frac{1}{3}$ to pure 'slip'. Felderhof (1977, 1978) has given the alternative expressions

$$\mathbf{D}_{ii} = D^0 \mathbf{I} + \mathbf{A}_{ij}(\mathbf{r}) \quad j \neq i \quad (2.6a)$$

$$\mathbf{D}_{ij} = \mathbf{B}_{ij}(\mathbf{r}) \quad (2.6b)$$

and provides extended series expansions (in a/r) for evaluation of $\mathbf{A}_{ij}(\mathbf{r})$ and $\mathbf{B}_{ij}(\mathbf{r})$ with arbitrary boundary conditions. These different conventions for the specification of the pair diffusion tensors \mathbf{D}_{ij} are useful in different contexts, and they are related by the transformations

$$\mathbf{A}_{ij}(\mathbf{r}) = D^0[\mathbf{A}_{ii}(\mathbf{r}) - \mathbf{B}_{ii}(\mathbf{r})]\hat{\mathbf{r}}\hat{\mathbf{r}} + D^0[\mathbf{B}_{ii}(\mathbf{r}) - 1]\mathbf{l}, \quad (2.7a)$$

$$\mathbf{B}_{ij}(\mathbf{r}) = D^0[\mathbf{A}_{ij}(\mathbf{r}) - \mathbf{B}_{ij}(\mathbf{r})]\hat{\mathbf{r}}\hat{\mathbf{r}} + D^0\mathbf{B}_{ij}(\mathbf{r})\mathbf{l}, \quad i \neq j. \quad (2.7b)$$

After assuming pair interactions of the form

$$U(\mathbf{X}) = \frac{1}{2} \sum_{i=1}^N \sum_{j=1}^N u_{ij}(r_{ij}), \quad j \neq i, \quad (2.8)$$

Felderhof (1978) used the N -particle Smoluchowski equation (2.1) to derive an equation for the time evolution of the particle number density $n(\mathbf{x}_1, t)$ in terms of the pair density $n_2(\mathbf{x}_1, \mathbf{x}_2, t)$:

$$\begin{aligned} \frac{\partial n}{\partial t} = & D^0 \nabla_1 \cdot \nabla_1 n + D^0 \nabla_1 \cdot \frac{1}{kT} \int (\nabla_1 u_{12}) n_2 \, d\mathbf{x}_2 \\ & + \nabla_1 \cdot \int \mathbf{A}_{12} \cdot \left(\nabla_1 n_2 + \frac{1}{kT} (\nabla_1 u_{12}) n_2 \right) \, d\mathbf{x}_2 \\ & + \nabla_1 \cdot \int \mathbf{B}_{12} \cdot \left(\nabla_2 n_2 + \frac{1}{kT} (\nabla_2 u_{12}) n_2 \right) \, d\mathbf{x}_2. \end{aligned} \quad (2.9)$$

The tensors \mathbf{A}_{12} and \mathbf{B}_{12} are defined in equation (2.6) and $\nabla_i \equiv \partial/\partial \mathbf{x}_i$. For a system in equilibrium, $n(\mathbf{x}_1)$ and $n_2(\mathbf{x}_1, \mathbf{x}_2)$ are time independent and have the values n_0 and $n_0^2 g_0$ respectively, where the equilibrium radial distribution function $g_0(\mathbf{x}_1, \mathbf{x}_2)$ is given, correct to order zero in n_0 , by

$$g_0(\mathbf{x}_1, \mathbf{x}_2) = \exp(-u_{12}/kT). \quad (2.10)$$

We shall now consider a perturbation solution of equation (2.9) which allows the derivation of the concentration dependence and wavevector dependence of the diffusion coefficient.

3. k dependence of the diffusion coefficient

We denote the equilibrium potential energy of the system by $U_0(\mathbf{X})$ and allow a perturbation potential $\delta U(\mathbf{X})$ of the form

$$\delta U(\mathbf{X}) = \delta u \sum_{i=1}^N \exp(\mathbf{i}k \cdot \mathbf{x}_i), \quad \delta u \ll kT. \quad (3.1)$$

The equilibrium configuration integral is given by

$$Q_0 = \int \dots \int_V \exp\left(-\frac{U_0}{kT}\right) \, d\mathbf{x}_1 \, d\mathbf{x}_2 \dots \, d\mathbf{x}_N. \quad (3.2)$$

When the system is perturbed, the configuration integral is given by

$$Q = \int \dots \int_V \exp\left(-\frac{U_0 + \delta U}{kT}\right) dx_1 dx_2 \dots dx_N \quad (3.3a)$$

$$\approx \int \dots \int_V \exp\left(-\frac{U_0}{kT}\right) dx_1 dx_2 \dots dx_N - \frac{\delta u}{kT} \sum_{i=1}^N \int \dots \int_V \exp(i\mathbf{k} \cdot \mathbf{x}_i) \exp\left(-\frac{U_0}{kT}\right) dx_1 dx_2 \dots dx_N. \quad (3.3b)$$

The first term in equation (3.3b) is Q_0 and the second term is zero provided U_0 depends only on the relative coordinates of the particles as stated in equation (2.8). Thus, any perturbation to the configuration integral will appear in a term of higher order in $\delta u/kT$.

We may now use standard formulae to write explicit expressions for the non-equilibrium particle number density and pair density. Keeping non-zero terms of order $\delta u/kT$, we obtain

$$n(\mathbf{x}_1) = \frac{N}{Q} \int \dots \int_V \exp\left(-\frac{U_0 + \delta U}{kT}\right) dx_2 dx_3 \dots dx_N \quad (3.4a)$$

$$\approx n_0 [1 - (\delta u/kT) \exp(i\mathbf{k} \cdot \mathbf{x}_1)] \quad (3.4b)$$

and

$$n_2(\mathbf{x}_1, \mathbf{x}_2) = \frac{N(N-1)}{Q} \int \dots \int_V \exp\left(-\frac{U_0 + \delta U}{kT}\right) dx_3 dx_4 \dots dx_N \quad (3.5a)$$

$$\approx n_0^2 g_0 \{1 - (\delta u/kT) [\exp(i\mathbf{k} \cdot \mathbf{x}_1) + \exp(i\mathbf{k} \cdot \mathbf{x}_2)]\}. \quad (3.5b)$$

Combining equations (3.4b) and (3.5b), it is possible to specify the perturbation to the pair density in terms of perturbations $\delta n(\mathbf{x}) = n(\mathbf{x}) - n_0$ to the singlet density:

$$n_2(\mathbf{x}_1, \mathbf{x}_2) \approx n_0^2 g_0 + n_0 g_0 [\delta n(\mathbf{x}_1) + \delta n(\mathbf{x}_2)]. \quad (3.6)$$

Substitution of equation (3.6) into equation (2.9) gives rise to an equation for the response of the system to the imposed perturbation:

$$\frac{\partial}{\partial t} [\delta n(\mathbf{x}_1)] = \nabla_1 \cdot D^0 \left(\nabla_1 [\delta n(\mathbf{x}_1)] + n_0 \frac{1}{kT} \int (\nabla_1 u_{12}) g_0 \delta n(\mathbf{x}_2) dx_2 \right) + \nabla_1 \cdot n_0 \left(\int \mathbf{A}_{12} g_0 dx_2 \cdot \nabla_1 [\delta n(\mathbf{x}_1)] + \int \mathbf{B}_{12} g_0 \cdot \nabla_2 [\delta n(\mathbf{x}_2)] dx_2 \right). \quad (3.7)$$

This equation is the same as equation (3.9) of Felderhof (1978) who considered the response of the system to small deviations of the particle number density and radial distribution function away from their equilibrium values. We have now established that it also describes the response to a small perturbation of defined wavelength on the system Hamiltonian.

Equation (3.7) may be used to obtain a diffusion equation in $\delta n(\mathbf{x})$ with a tensor diffusion coefficient $\mathbf{D}(\mathbf{k})$. The expressions for $\delta n(\mathbf{x}_2)$ and $\nabla_2 \delta n(\mathbf{x}_2)$ in terms of $\delta n(\mathbf{x}_1)$ and $\nabla_1 \delta n(\mathbf{x}_1)$ required for this reduction are obtained directly from equation (3.4b):

$$\delta n(\mathbf{x}_2) = \cos(\mathbf{k} \cdot \mathbf{r}) \delta n(\mathbf{x}_1) + (1/k^2) \sin(\mathbf{k} \cdot \mathbf{r}) \mathbf{k} \cdot \nabla_1 \delta n(\mathbf{x}_1), \quad (3.8a)$$

$$\nabla_2 \delta n(\mathbf{x}_2) = \exp(i\mathbf{k} \cdot \mathbf{r}) \nabla_1 \delta n(\mathbf{x}_1). \quad (3.8b)$$

It is worthy of note that in the limit $k = 0$, these expressions correspond to approximations invoked by Felderhof (1978) in his derivation of the concentration dependence of the diffusion coefficient. Consideration of the various terms in equation (3.7) using equations (3.8a) and (3.8b) allows derivation of the wavevector dependence of the diffusion coefficient.

The second term in equation (3.7) is the wavevector-dependent thermodynamic virial correction. Eliminating vanishing terms and integrating over angles, we obtain

$$\nabla_1 \cdot n_0 D^0 \frac{1}{kT} \int (\nabla_1 u_{12}) g_0 \delta n(\mathbf{x}_2) d\mathbf{x}_2 = \nabla_1 \cdot n_0 D^0 \mathbf{C}_V \cdot \nabla_1 [\delta n(\mathbf{x}_1)] \quad (3.9)$$

where

$$\mathbf{C}_V = -4\pi \int [g_0(r) - 1] r^2 \frac{\sin(kr)}{kr} dr \hat{\mathbf{k}} \hat{\mathbf{k}}. \quad (3.10)$$

This part of the diffusion coefficient is anisotropic because a perturbation in the direction of \mathbf{k} gives rise to no thermodynamic force perpendicular to this direction.

From the third term in equation (3.7) we obtain

$$\nabla_1 \cdot n_0 \int \mathbf{A}_{12} g_0 d\mathbf{x}_2 \cdot \nabla_1 [\delta n(\mathbf{x}_1)] = \nabla_1 \cdot n_0 D^0 \mathbf{C}_A \cdot \nabla_1 [\delta n(\mathbf{x}_1)] \quad (3.11)$$

where

$$\mathbf{C}_A = \frac{4\pi}{3} \int [A_{11}(r) + 2B_{11}(r) - 3] g_0(r) r^2 dr \mathbf{I} \quad (3.12)$$

and the scalar coefficients $A_{11}(r)$ and $B_{11}(r)$ are defined in equation (2.4). This part of the diffusion coefficient has no wavevector dependence, because it corresponds to the change in the molecular self-diffusion coefficient due to the presence of neighbouring solute molecules (Wills 1979).

The problem of the divergence in the integral in the fourth term in equation (3.7) may be dealt with by treating \mathbf{B}_{12} as the sum of a short-range part \mathbf{B}_S , an Oseen part \mathbf{B}_O and a dipole part \mathbf{B}_D (Felderhof 1978). After integration over angles we obtain

$$\nabla_1 \cdot n_0 \int \mathbf{B}_{12} g_0 \cdot \nabla_2 [\delta n(\mathbf{x}_2)] d\mathbf{x}_1 = \nabla_1 \cdot n_0 D^0 \mathbf{C}_B \cdot \nabla_1 [\delta n(\mathbf{x}_1)] \quad (3.13)$$

where

$$\mathbf{C}_B = \mathbf{C}_S + \mathbf{C}_O + \mathbf{C}_D$$

$$\begin{aligned} &= \frac{4\pi}{3} \left\{ \iint \left[A_{12}(r) + 2B_{12}(r) - 3 \left(\frac{a}{r} \right) (1 - \xi) \right] g_0(r)_0^{(r)} \frac{\sin(kr)}{kr} r^2 dr \mathbf{I} \right. \\ &\quad + 3a(1 - \xi) \int [g_0(r) - 1] \frac{\sin(kr)}{kr} r dr \mathbf{I} \\ &\quad \left. - \frac{3}{2} a^3 (1 - 3\xi) \int j_2(kr) g_0(r) \frac{1}{r} dr (\mathbf{I} - 3\hat{\mathbf{k}}\hat{\mathbf{k}}) \right\}. \end{aligned} \quad (3.14)$$

The parameter ξ characterises the hydrodynamic boundary condition as in equation (2.5) and $j_2(y)$ is the spherical Bessel function $[(3 - y^2) \sin(y) - y \cos(y)]/y^3$.

It is evident from equations (3.9)–(3.14) that equation (3.7) may be rewritten in the form

$$\frac{\partial}{\partial t}[\delta n(\mathbf{x}_1)] = \nabla_1 \cdot \mathbf{D}(\mathbf{k}) \cdot \nabla_1[\delta n(\mathbf{x}_1)] \quad (3.15)$$

where

$$\mathbf{D}(\mathbf{k}) = D^0[\mathbf{I} + n_0(\mathbf{C}_V + \mathbf{C}_A + \mathbf{C}_B)]. \quad (3.16)$$

Equation (3.15) is a diffusion equation in $\delta n(\mathbf{x}_1)$ and $\mathbf{D}(\mathbf{k})$ is the wavevector-dependent diffusion coefficient specifying the response of a system of interacting solute macromolecules to a small perturbation of wavevector \mathbf{k} . In a quasielastic light-scattering experiment, one observes the decay of fluctuations of wavevector \mathbf{k} in the solute concentration and determines the decay constant Γ defined by

$$\Gamma = \mathbf{k} \cdot \mathbf{D}(\mathbf{k}) \cdot \mathbf{k}. \quad (3.17)$$

Examination of the tensorial character of $\mathbf{D}(\mathbf{k})$ reveals that equation (3.17) may be written in scalar form as

$$\Gamma = k^2 D(k) \quad (3.18)$$

where

$$D(k) = D^0\{1 + n_0[C_V(k) + C_A + C_S(k) + C_O(k) - 2C_D(k)]\} \quad (3.19)$$

The scalars C_i in equation (3.19) are given by the magnitudes of the tensors \mathbf{C}_i specified in equations (3.10), (3.12) and (3.14) regardless of their appended tensorial character. Equation (3.19) demonstrates that the wavevector dependence of the diffusion coefficient for solutions of macromolecules is associated with its concentration dependence (to first order in the concentration), through the thermodynamic virial terms and the correction arising as a result of coupled motions of distinct particles.

4. Discussion

In § 3 we introduced a heuristic *ansatz* (equations (3.1)–(3.6)) which allowed calculation of the wavevector dependence of the diffusion coefficient governing the time evolution of small fluctuations in the particle number density. While a small fluctuation treatment is expected to be valid in the limit of zero wavevector (Felderhof 1978), it is to be expected that nonlinear effects must be considered at $k \neq 0$ (Weissman and Ware 1978). It is thus important to point out that equation (3.6), which is central to the derivation presented here, is correct to first order in the small parameter $\delta u/kT$ introduced in equation (3.1) and ignores correlations in the system which build up dynamically when terms of higher order in $\delta u/kT$ feed back into the lower-order quantities. The result obtained for the diffusion coefficient (equation (3.16)) is therefore valid for events on a timescale shorter than that (τ_I) characterising significant changes in the system configuration. Furthermore, since use of the Smoluchowski equation implies a timescale much longer than the Brownian relaxation time (τ_B), our result is valid on the ‘plateau’ timescale $\tau_B \ll \tau \ll \tau_I$ and should thus be compared with calculations of the effective diffusion coefficient which may be determined from the initial decay of the dynamic structure factor, that is, the first cumulant of the scattered intensity autocorrelation function.

Such calculations have been performed by Pusey (1975, 1978), Ackerson (1976, 1978) and Allison *et al* (1979). Pusey (1975, 1978) did not consider hydrodynamic interactions and the expressions for the hydrodynamic interaction tensors used by Ackerson (1976) and Allison *et al* (1979) predate the work of Batchelor (1972) and Felderhof (1977). However, more recently Ackerson (1978) described a method of calculation for the first cumulant which, in the zero wavevector limit, may be used to give results for the effective diffusion coefficient identical to those of Batchelor (1976) and Felderhof (1978) when exact expressions for the hydrodynamic interaction tensors are used (P N Pusey and R J Tough, personal communication). Equation (3.19) of this paper reduces to the same result in the limit of zero wavevector; at finite wavevector, it represents an improvement over previous calculations of the first cumulant as well as over earlier calculations of wavevector corrections to the concentration dependence of the Fick's law coefficient for mutual binary diffusion (Altenberger and Deutch 1973, Harris 1976, Hess and Klein 1976, Altenberger 1979).

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