Collective diffusion coefficient of proteins with hydrodynamic, electrostatic and adhesive interactions

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A theory is presented for $\lambda_C$, the coefficient of the first-order correction in the density of the collective diffusion coefficient, for protein spheres interacting by electrostatic and adhesive forces. An extensive numerical analysis of the Stokesian hydrodynamics of two moving spheres is given so as to gauge the precise impact of lubrication forces. An effective stickiness is introduced and a simple formula for $\lambda_C$ in terms of this variable is put forward. A precise though more elaborate approximation for $\lambda_C$ is also developed. These and numerically exact expressions for $\lambda_C$ are compared with experimental data on lysozyme at pH 4.5 and a range of ionic strengths between 0.05 M and 2 M.

I. INTRODUCTION

Fick’s first law states that the particle flux is equal to minus the collective diffusion coefficient times the gradient of the particle concentration. For colloids or macromolecules in solution, this collective (also called cooperative or mutual) diffusion coefficient is often determined experimentally with the help of dynamic light scattering. If one extrapolates this coefficient to a vanishing concentration of particles, it reduces to the single-particle diffusion coefficient since the interactions between the particles are presumably negligible then. At non-zero volume fractions, particle interactions, such as those of electrostatic and hydrodynamic origin, influence the diffusion. At low enough concentrations, where three- and higher body interactions may be disregarded, the parameter $\lambda_C$ characterizes the departure from the single-particle result.

The concentration dependence of the collective diffusion coefficient of proteins has been studied extensively in experiments, for example in the case of hemoglobin, bovine serum albumin, β-lactoglobulin, ovalbumin and lysozyme. On the theoretical side, a fair number of papers deal with the diffusion of interacting colloidal particles in solution. Apart from giving insight into the diffusion as such, the coefficient $\lambda_C$ is also important because it could yield information about the complex pair interaction between protein molecules. Moreover, it has been argued that $\lambda_C$ may be an alternative parameter useful in diagnosing under what conditions proteins would crystallize.

In Ref. we approximated globular proteins in water with added monovalent salt by hard spherical particles that interact through a short-range attraction and a screened electrostatic repulsion. We appropriately replaced this system by one of spherical particles with sticky interactions only. At infinite dilution the effective stickiness is readily determined by equating the respective second virial coefficients of the two systems. In the effective stickiness, part of the bare adhesion is balanced against the electrostatic repulsion.

In the next section, we formulate a theory for the coefficient $\lambda_C$. We first introduce the interaction used previously to compute protein solution properties and give expressions for the effective stickiness. We then outline the formal expression for $\lambda_C$ due to Felderhof and place this system by one of spherical particles with adhesive interactions only. At infinite dilution the effective stickiness is readily determined by equating the respective second virial coefficients of the two systems. In the effective stickiness, part of the bare adhesion is balanced against the electrostatic repulsion.

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II. THEORY

A. Effective interaction

We model the globular proteins as spherical particles of radius $a$ with a total charge $Zq$ per particle that is uniformly distributed over its surface. Here $q$ is the elementary (proton) charge. For convenience, we scale all distances by the radius $a$ and all energies by $k_BT$ where $k_B$ is Boltzmann’s constant and $T$ is the temperature. We approximate the interaction between two proteins by a steric repulsion plus a short-range attraction of scaled range $\delta \ll 1$ and constant absolute magnitude $U_A$. A far-field Debye-Hückel potential. The latter describes the Coulomb repulsion that is screened due to the presence of monovalent salt of ionic strength $I$. The effective number of charges associated with the far field is computed in the Poisson–Boltzmann approximation. See Refs.
and for further details. The total interaction $U_T(x)$ between the two particles with center-of-mass separation $r$ is thus of the form

$$U_T(x) = \begin{cases} \infty & 0 \leq x < 2 \\ U_{DH}(x) - U_A & 2 \leq x < 2 + \delta \\ U_{DH}(x) & x \geq 2 + \delta \end{cases} \, , \quad (1)$$

$$x = \frac{r}{a} \, . \quad (2)$$

Here, the Debye-Hückel interaction is given by

$$U_{DH}(x) = 2\xi e^{-\mu(x-2)} x \, . \quad (3)$$

where $\xi = \frac{Q}{6} (\frac{Z \mu}{\pi a^2})^2$ and $\mu = \kappa a$. The Debye length $\kappa^{-1}$ is defined by $\kappa^2 = 8\pi Q I$ and the Bjerrum length by $Q = q^2 / \epsilon k_B T$, which equals 0.71 nm in water at 298 K ($\epsilon$ is the permittivity of water); $\mu = 3.28a\sqrt{T}$, if the radius $a$ is given in nm and the ionic strength $I$ in M. We suppose 1-1 electrolyte has been added in excess so $I$ is the concentration of added salt only. We have derived a perturbative expression for the effective charge $qZ_{eff}$ in the Poisson-Boltzmann approximation

$$Z_{eff} = Z - \frac{\mu^2}{6} \left( \frac{Q}{a} \right)^2 \left( \frac{Z}{1+\mu} \right)^3 e^{3\mu} E_1(3\mu) \, . \quad (4)$$

Here, $E_1(x)$ is the exponential integral defined by $E_1(x) = \int_{-1}^{\infty} dt \, t^{-1} e^{-t}$. Eq. (4) is numerically consistent with a different form recently proposed by Aubouy et al.\textsuperscript{32} which is also valid at large values of $Z$.

We want to replace the system of particles interacting through the complicated interaction\textsuperscript{[1]} by a system of particles interacting through a simpler potential, the adhesive hard sphere (AHS) potential of Baxter\textsuperscript{35}

$$U_{AHS}(x) = \begin{cases} \infty & 0 \leq x < 2 \\ \ln \frac{12\pi \omega}{2+\omega} & 2 \leq x \leq 2 + \omega \\ 0 & x \geq 2 + \omega \end{cases} \, . \quad (5)$$

Here, $\tau$ is a positive constant which signifies the strength of the effective adhesion and the limit $\omega \downarrow 0$ has to be taken appropriately after formal integrations. In order to replace the original system by this simpler system, we want to find the correspondence between the parameter $\tau$ in the AHS potential and the parameters $\xi$, $\mu$, $\delta$ and $U_A$ in the original interaction Eq. (1). In this case, we do this by matching the respective second virial coefficients, which ensures that the free energy of the two systems at small concentrations are identical. We emphasize that in the general case, at arbitrary concentrations, we have to match the complete free energies of the respective systems\textsuperscript{32,33}; it is then incorrect to focus on the second virials as has often been done in the past.

### B. Stickiness parameter

We already determined the stickiness parameter $\tau$ in a previous paper\textsuperscript{32}. Here we reproduce the main results.

The second virial coefficient $B_2$ is given by

$$B_2 = \frac{1}{2} \int_V dr \left( 1 - e^{-U(r)} \right) \, , \quad (6)$$

where $U(r)$ is the pair potential scaled by $k_B T$, and $r$ is the unscaled position vector connecting the centers of mass of the two particles. For the pair interaction of Eq. (1), $B_2$ may be expressed by

$$B_2 = B_2^{HS} \left( 1 + \frac{3}{8} J \right) \, , \quad (7)$$

where we introduce the following integrals

$$J \equiv \int_2^\infty dx \, x^2 \left( 1 - e^{-U_T(x)} \right) \equiv J_1 - (e^{U_A} - 1) J_2 \, , \quad (8)$$

$$J_1 \equiv \int_2^\infty dx \, x^2 \left( 1 - e^{-U_{DH}(x)} \right) \approx \frac{4(\mu + \frac{1}{2})}{\mu^2} \frac{\xi}{1 - \frac{\alpha}{2} \xi} \, , \quad (9)$$

$$J_2 \equiv \int_2^{2+\delta} dx \, x^2 e^{-U_{DH}(x)} \approx 2 \delta \left[ e^{-\xi} + \left( 1 + \frac{\delta}{2} \right)^2 e^{-\frac{x}{4\tau}} e^{-\mu \xi} \right] \, . \quad (10)$$

Here, $B_2^{HS} = 16\pi a^3 / 3$ is the value of $B_2$ if the proteins were solely hard spheres and $\alpha = e^{-T} / \sqrt{2}$. We equate Eq. (7) with the second virial coefficient of the AHS model

$$B_2 = B_2^{HS} \left( 1 - \frac{1}{4\tau} \right) \, , \quad (11)$$

which results in a stickiness parameter $\tau$ given by

$$\tau = \frac{2}{3J} \, . \quad (12)$$

From Eqs. (11) and (8) we see how part of the original attraction is compensated by repulsive electrostatics.

### C. General expression for $\lambda_C$

For small volume fractions $\phi$ of spherical particles, the collective diffusion coefficient $D_C$ may be written as

$$D_C = D_0 \left( 1 + \lambda_C \phi + O (\phi^2) \right) \, , \quad (13)$$

where $D_0$ is the diffusion coefficient in the dilute limit. The linear coefficient $\lambda_C$ may be split up into five contributions\textsuperscript{31}

$$\lambda_C = \lambda_V + \lambda_O + \lambda_D + \lambda_S + \lambda_A \, . \quad (14)$$
These terms have been studied for some time\textsuperscript{23,24,25,26}, there is a virial correction because a fluctuation in the osmotic pressure drives diffusion

\[
\lambda_V = 3 \int_0^\infty \! dx \, x^2 \left( 1 - e^{-U(x)} \right),
\]

and four terms arising from the mutual friction between two hydrodynamically interacting spheres. An Oseen contribution

\[
\lambda_O = 3 \int_0^\infty \! dx \, x \left( e^{-U(x)} - 1 \right),
\]

and a dipolar contribution

\[
\lambda_D = 1,
\]

express the long-range hydrodynamic interaction between two particles 1 and 2 whereas the short-range part of the hydrodynamic interaction comes into play in the term

\[
\lambda_S = \int_2^\infty \! dx \, x^2 e^{U(x)} \left( A_{12}^{tt} + 2B_{12}^{tt} \right).
\]

Finally, the modification of the single-particle mobility is expressed by

\[
\lambda_A = \int_2^\infty \! dx \, x^2 e^{U(x)} \left( A_{11}^{tt} + 2B_{11}^{tt} \right).
\]

Here, \( A_{11}^{tt} \), \( A_{12}^{tt} \), \( B_{11}^{tt} \) and \( B_{12}^{tt} \) are dimensionless hydrodynamic functions given in terms of the translational mobility matrix for two spheres centered at \( \vec{R}_1 \) and \( \vec{R}_2 \) (\( \vec{r} = \vec{R}_1 - \vec{R}_2 \)) and acquiring velocities \( \vec{V}_1 \) and \( \vec{V}_2 \) as a result of the forces \( \vec{F}_1 \) and \( \vec{F}_2 \) acting on the spheres

\[
\begin{aligned}
\vec{V}_1 &= \mu_{11}^{tt}(1,2) \cdot \vec{F}_1 + \mu_{12}^{tt}(1,2) \cdot \vec{F}_2, \\
\vec{V}_2 &= \mu_{21}^{tt}(1,2) \cdot \vec{F}_1 + \mu_{22}^{tt}(1,2) \cdot \vec{F}_2.
\end{aligned}
\]

In the notation of Cichocki and Felderhof\textsuperscript{23}, we have

\[
\begin{aligned}
\mu_{11}^{tt}(1,2) &= \frac{1}{6 \pi \eta a} \left[ \vec{I} + A_{11}^{tt}(r) \frac{\vec{r} \times}{r^2} + B_{11}^{tt}(r) \left( \vec{I} - \frac{\vec{r} \times}{r^2} \right) \right]; \\
\mu_{12}^{tt}(1,2) &= \frac{1}{6 \pi \eta a} \left[ A_{12}^{tt}(r) \frac{\vec{r} \times}{r^2} + B_{12}^{tt}(r) \left( \vec{I} - \frac{\vec{r} \times}{r^2} \right) \right],
\end{aligned}
\]

where \( \eta \) is the viscosity of the solvent and \( \vec{I} \) is the unit tensor. The mobility tensors in Eq. \textsuperscript{24} are given by interchanging the labels in Eqs. \textsuperscript{22} and \textsuperscript{23} while taking into account the symmetry relations

\[
A_{12}^{tt}(r) = A_{11}^{tt}(r); \quad B_{12}^{tt}(r) = B_{21}^{tt}(r).
\]

Recall that the particles have a hard-core interaction for \( x < 2 \) so \( \exp -U(x) \) vanishes for \( x < 2 \). We then sum Eqs. \textsuperscript{15}-\textsuperscript{19} and conveniently rewrite \( \lambda_C \) as follows

\[
\lambda_C = c_0 + c_1 \int_2^\infty \! dx \, x^2 \left( 1 - e^{-U(x)} \right) + R.
\]

The constant \( c_0 \) equals the value \( \lambda_C \) would adopt if the spheres were hard but without any other interaction

\[
c_0 \equiv 3 \int_0^2 \! dx \, x^2 - 3 \int_0^2 \! dx \, x + 1 + \int_2^\infty \! dx \, x^2 \left( h(x) - \frac{3}{x} \right) = 3 + \int_2^\infty \! dx \, x^2 \left( h(x) - \frac{3}{x} \right).
\]

Here, \( h(x) \) is the sum of scalar mobility functions

\[
h(x) \equiv A_{11}^{tt}(x) + A_{12}^{tt}(x) + 2B_{11}^{tt}(x) + 2B_{12}^{tt}(x).
\]

The residual term \( R \) in Eq. \textsuperscript{20} depends on the actual interaction

\[
R \equiv \int_2^\infty \! dx \, x^2 \left( 1 - e^{-U(x)} \right) (h(x) - h(2))
\]

though it would vanish if the interaction \( U \) were adhesive and purely of the Baxter type (see Eq. \textsuperscript{5}). The second term on the right hand side of Eq. \textsuperscript{25} is proportional to the constant

\[
c_1 = 3 - h(2)
\]

and the integral is related to the second virial coefficient \( B_2 \) by (see Eqs. \textsuperscript{7} and \textsuperscript{8})

\[
\int_2^\infty \! dx \, x^2 \left( 1 - e^{-U(x)} \right) = \frac{8}{3} \left( \frac{B_2}{B_2^{HS}} - 1 \right).
\]

The resulting expression for \( \lambda_C \) is

\[
\lambda_C = c_0 + \frac{8c_1}{3} \left( \frac{B_2}{B_2^{HS}} - 1 \right) + R
\]

which we can evaluate once we know \( h(x) \) given by Eq. \textsuperscript{25}.

\section{Hydrodynamics}

The function \( h(x) \) was discussed by Batchelor\textsuperscript{37} in his theory of the diffusion of hard spheres. The sum \( A_{11}^{tt} + A_{12}^{tt} \) pertains to the mobility of a pair of spheres moving in the direction of their line of centers whereas \( B_{11}^{tt} + B_{12}^{tt} \) is related to their mobility when they move perpendicular to that line. (Note that in Ref. \textsuperscript{37} \( A_{11} \equiv A_{11}^{tt} + 1, B_{11} \equiv B_{11}^{tt} + 1, A_{12} \equiv A_{12}^{tt} \) and \( B_{12} \equiv B_{12}^{tt} \)). In the latter case, because the spheres are couple-free, the spheres must rotate as the pair translates. At small separations \( x - 2 \ll 1 \), lubrication forces with a logarithmic singularity \( \ln^{-1}(x - 2) \) are then expected to develop on general grounds\textsuperscript{38}. Goldman et al\textsuperscript{39} proposed a form for the singularity which we will test below.

Batchelor\textsuperscript{37} computed \( h(2) = 1.312 \) on the basis of numerical work on the mobilities of touching spheres\textsuperscript{40,41}. Cichocki and Felderhof\textsuperscript{23} evaluated \( c_0 = 1.454 \) (Eq. \textsuperscript{20}) by numerically summing their series expansions of the
hydrodynamic interactions while keeping track of a logarithmic singularity at close separations. Here we reanalyze \( h(x) \) and go well beyond previous computations\(^ {36,42} \) in order to gain more insight into the nature of the singularity and to calculate the residual \( R \).

We assume the interaction \( U(x) \) is of short range so we focus only on \( h(x) \) for \( x < 2 \lesssim 1 \). First, we get an expression for \( A_{11}^h + A_{12}^h \) as an infinite sum from the results of Stimson and Jeffery\(^ {43} \) who expressed the hydrodynamic problem in terms of bipherical coordinates. (Note that there is an error in their paper as pointed out in, for example, Ref.\(^ {44} \) in which one may find a similar expression for \( A_{11}^h - A_{12}^h \) in case one needs \( A_{11}^h \) and \( A_{12}^h \) separately). Calculating \( B_{11}^h \) and \( B_{12}^h \) is more involved. We use the numerical scheme by O’Neill and Majumdar\(^ {45} \) which is similar to that of Goldman et al.\(^ {46} \) (Note that there are a few typographical errors in Ref.\(^ {45} \)). In their Eq. (3.9) \( d \) should be \( d_1 \), the expression for \( v \) in Eq. (4.1) should have a minus sign, \( \xi, \phi \) and \( \psi \) in Eqs. (4.3)-(4.5) should be replaced by \( \xi, c\phi \) and \( c\psi \) respectively, and \( \sinh^2(\beta) \) in Eq. (5.10) should be \( \sinh^3(\beta) \). Also, to obtain \( D_2(A_n, B_n) \) (Eq. (3.29)) from \( D_1(A_n, B_n) \) (Eq. (3.28)) the signs of \( \delta_{n-1}, \delta_n \) and \( \delta_{n+1} \) should be reversed as well (we only checked the case of spheres of equal size). Their Table I is correct, however, for spheres of equal size, apart from the value for \( g_{12}(1, 0, 1) \) which should read -0.1017 instead of -1.1017.

In order to investigate the regime of lubrication for a pair of spheres moving under the action of applied forces normal to their line of centers, we performed the numerical analysis down to \( r/a - 2 = 10^{-10} \) which implies two million terms in the series expansions are needed. We attempted to speed up the iteration by adapting the recurrence relationships introduced more recently by O’Neill and Bhatt\(^ {48} \) for a sphere moving near a wall to the case of two spheres. However, this did not turn out to be useful as it is for the wall configuration.\(^ {47} \) One way of circumventing series expansions could be to elaborate on the trial functions initially used by Fixman in his variational theorem for the mobility matrix\(^ {48} \) but we did not investigate this.

Goldman et al.\(^ {46} \) were the first to give a comprehensive analysis of the mobility of a pair of identical spheres of arbitrary orientation. They numerically solved the Stokes and continuity equations using expansions in terms of bipolar coordinates to high order. For moving spheres whose line of centers is perpendicular to the applied force, the force consists not only of a term arising from pure translation but also a term stemming from pure rotation of the spheres. The latter involves a torque on one sphere diverging as\(^ {49} \)

\[
T_r \sim \frac{3 \ln(x - 2)}{160\pi n^2 a^3} \tag{32}
\]

at very small separations where \( \Omega \) is its angular velocity. Eq. (32) was derived by extending the nontrivial lubrication theory of Ref.\(^ {44} \) in which inner and outer regions have to be matched. Eq. (32) ultimately leads to the following analytical expression for \( h(x) \) valid at small separations

\[
h(x) = h(2) - \frac{0.47666}{\ln(x - 2) + c_2} + O(x - 2). \tag{33}
\]

The coefficient 0.47666 is computed from the numerical tables presented in Ref.\(^ {39} \). We have added a constant \( c_2 \) to the logarithm because we expect the next higher order term in Eq. (32) to be a constant judging by the earlier analysis of the sphere-wall problem.\(^ {49} \) In Fig. 1 we have fitted Eq. (33) to the numerical results discussed above, letting \( h(2) \) and \( c_2 \) be adjustable. The intercept \( h(2) = 1.30993 \) turns out to be close to the value 1.312 quoted above for touching spheres which lends credence to the validity of the asymptotic expression that we propose. Moreover, the resulting coefficient \( c_2 = -4.694 \) and the concomitant shift in Eq. (32) are consistent with the numerical values of the torque \( T_r \) at small separations as presented in table 3 of Ref.\(^ {39} \).

Next, we derive an expression for the residual term given by Eq. (28). First, we propose an initial estimate \( h_0(x) \) for \( h(x) \). We have plotted the numerical values of \( h(x) \) as a function of \( x \) in Fig. 2. As a result of the lubrication regime, \( h \) has a maximum as displayed in the inset. However, \( h(x) \) is only a strongly varying function for \( x < 2.04 \). We therefore simply force a linear fit to the data for \( h \) at \( x = 2.1, 2.2 \) and \( 2.3 \)

\[
h_0(x) \approx 1.3670 - 0.4745(x - 2). \tag{34}
\]

We then insert this estimate into Eq. (28) and add a correction term so as to derive an expression for \( R \) accurate
enough for our purposes.

\[
R \approx -0.147 \left( \frac{B_2}{B_{HS}} - 1 \right) \\
+ 0.4745 \int_{2}^{\infty} dx x^2 (x-2) \left( 1 - e^{-\mu(x)} \right) \\
+ 9 \times 10^{-4} \left( 1 - e^{-U(2)} \right).
\]  

(35)

The first term on the right comes from the fact that the linear interpolation gives \( h_0(2) = 1.3670 \) whereas the real value is \( h(2) = 1.311 \). Since the interaction usually does not change appreciably for \( 2 < x < 2.04 \), it is straightforward to write an estimate for the error—the third term—owing to the deviation of Eq. (35) from the exact function \( h(x) \) (see inset Fig. 2). In our case the error term turns out to be an order of magnitude smaller than the first two terms.

![FIG. 2: The hydrodynamic function \( h(x) \) as a function of the dimensionless separation \( x \equiv r/a \) between the centers of two spheres. The straight line signifies \( h_0(x) \) given by Eq. (34).](image)

E. Determination of \( \lambda_C \)

It is clear from Eq. (28) that \( R \) would vanish if the actual interaction were a pure AHS potential. If we then insert Eq. (11) into Eq. (31), we obtain \(^{20} \)

\[
\lambda_C = c_0 - \frac{2c_1}{3r}.
\]

(36)

Inspection of the various terms in Eq. (35) reveals that \( R \) is often much smaller than unity when the interaction is given by Eq. (1). Hence, a possibly convenient approx-

imation to the coefficient \( \lambda_C \) is from Eq. (12)

\[
\lambda_C = c_0 + c_1 J = c_0 + \frac{8c_1}{3} \left( \frac{B_2}{B_{HS}} - 1 \right)
\]

(37)

where \( J \) may be evaluated numerically or approximately with the help of Eqs. (8)-(10).

The full expression for the dynamical coefficient is written as

\[
\lambda_C = c_0 + c_1 J + R,
\]

(38)

using Eqs. (11) and (34). Now \( R \) from Eq. (35) is reexpressed as

\[
R \approx -0.055J + 0.4745K - 9 \times 10^{-4} \left( e^{U_A-\xi} - 1 \right).
\]

(39)

in view of Eqs. (1) and (3). Here we have introduced the function \( K \) for which we derive a convenient approximation.

\[
K \equiv \int_{2}^{\infty} dx x^2 (x-2) \left( 1 - e^{-\mu(x)} \right) \\
\equiv K_1 - (e^{U_A} - 1) K_2,
\]

(40)

where

\[
K_1 \equiv \int_{2}^{\infty} dx x^2 (x-2) \left( 1 - e^{-U_{DH}(x)} \right)
\]

(41)

and

\[
K_2 \equiv \int_{2}^{2+\delta} dx x^2 (x-2) e^{-U_{DH}(x)}.
\]

(42)

In the same spirit as in Ref. 32 we approximate \( x \left( 1 - e^{-U_{DH}(x)} \right) \approx 2e^{-\mu(x-2)} - 2\alpha\xi^2 e^{-2\mu(x-2)} \), with \( \alpha = e^{-\xi-(1-\xi)} \). We then have

\[
K_1 \approx \frac{\xi (\mu + 1) (4 - \alpha\xi)}{\mu^3},
\]

(43)

where we have neglected the small term \( \alpha\xi^2/2\mu^3 \). In the case of lysozyme at pH 4.5, the deviation of Eq. (43) from the exact result is smaller than about 3% for \( I \geq 0.05 \) M and smaller than about 1% for \( I \geq 0.3 \) M. For the second integral we use the trapezoid approximation

\[
K_2 \approx 2\delta^2 \exp \left[ -\frac{\xi e^{-\mu\delta}}{1 + \delta/2} \right].
\]

(44)

For lysozyme at pH 4.5 with \( \delta = 0.079 \) (see below), this approximation deviates less than about 5% from the exact value for \( I \geq 0.05 \) M and less than about 3% for \( I \geq 0.2 \) M.
III. Comparison with experiment

We compare our predictions of $\lambda_C$ as a function of the ionic strength $I$ with experimental results for lysozyme at room temperature and at a pH of about 4.5. The added salt is NaCl and in most cases a small amount of Na acetate has been added as buffer. The reason for choosing lysozyme under these conditions is that we have previously evaluated the range and strength of the short-range attraction and a lot of experimental data on the collective diffusion coefficient are available in the literature (see Fig. 3).

Lysozyme has a moderate aspect ratio of about 1.5 and we approximate it by a sphere of radius $a = 1.7$ nm. The dimensionless parameter $\mu$ is then given by $\mu = 5.58v_{\text{Z}}$, where the ionic strength $I$ is given in M, and $\xi = 0.209(\bar{Z}/(1+\mu))^2$. Here we follow our discussion in Ref. 32 and use the adjusted charge on the lysozyme sphere $Z = Z_{\text{eff}} - 1$ instead of the effective charge $Z_{\text{eff}}$. Values of $Z$, $Z_{\text{eff}}$ and $\bar{Z}$ as a function of ionic strength can be found in Table I as well as the corresponding quantities $\mu$ and $\xi$. For the range $\delta$ and strength $U_A$ of the attraction we use $\delta = 0.079$ and $U_A = 3.70$ which were computed on the basis of a wide variety of data on the second virial coefficient22.

We next employ three methods to predict $\lambda_C$ theoretically. In the first, we compute $\tau$ by equating the respective second virial coefficients of Section II.B (see Eqs. (8) and (10)). We then calculate $\lambda_C$ from Eq. (39) using $c_0 = 1.454$ and $c_1 = 1.688$. In the second method we use Eq. (58) to determine $\lambda_C$, where $R$ is evaluated with the help of Eq. (39). In both cases the approximations for $J$ and $K$ given by Eqs. (8-10) and Eqs. (10), (14) and (11) were used (see Table I and Fig. 3). Note that there are no free parameters so the curves in Fig. 3 are predictions not fits. For comparison, we also calculate $\lambda_C$ from Eq. (14) exactly, that is by performing the integrals in Eqs. (14-17) numerically with the help of a highly accurate interpolation formula for $b(x)$ (see Table I). Finally, in Fig. 3 we have also plotted data of $\lambda_C$ measured by several experimental groups.

IV. Discussion

In Section II.E we have outlined two approximate methods to calculate $\lambda_C$. As one can see from Table I, both the direct method incorporating an approximation for the residual $R$ and the method relying solely on the stickiness $\tau$ via the second virial yield results that are often close to the exact numerical computations. The direct method is, of course, somewhat more accurate. The $\tau$ method breaks down below 0.2 M. Note that in the important regime $I > 0.2$ M pertaining to protein crystallization, $R$ is much smaller than the absolute magnitude of $\lambda_C$. This may explain why $\lambda_C$ is a useful parameter to characterize the onset of crystallization22.

In Fig. 3 it is clear that there is a large degree of scatter which may be attributed to the systematic variation in sets of data from the various groups, especially at large ionic strengths ($I > 0.4$ M). We do not know what is the cause of this. In one experiment, we often see considerable scatter in a plot of the diffusion coefficient versus the protein solubility which might explain the extreme downturn of several data in Fig. 3 at about 0.5 M. Fig. 3 also shows that our predicted curves lie fairly neatly in the midst of the swarm of data. We emphasize again that we have no adjustable parameters in our calculations except for a slight downward adjustment of the effective charge (see also the discussion in Refs. 32 and 33). The model is thus not inconsistent with the experimental data though we will have to await more experiments under conditions which are better controlled before one may reach a more definitive conclusion. In a similar vein, it is not possible to claim that the neglect of electrolyte friction assumed here is entirely warranted.

In summary, we have approximated proteins by spherical particles interacting by a hard-core and electrostatic
TABLE I: Values of the actual charge $Z$ of hen-egg-white lysozyme (from Ref. [5]), the effective charge $Z_{\text{eff}}$ (see Eq. (4)), the lowered effective charge $\overline{Z} = Z_{\text{eff}} - 1$, and dimensionless interaction parameters $\xi$ and $\mu$ as a function of the ionic strength $I$. The pH equals 4.5 and $\xi$ has been calculated using the lowered effective charge $\overline{Z}$. $R$ has been calculated from Eq. (43), $\tau$ from Eq. (42), $\lambda_C$ (via $\tau$) from Eq. (50) and $\lambda_C$ (direct) from Eq. (59). In all cases approximations for $J$ and $K$ given by Eqs. (8), (10) and (10), (43), (44) were used. The computation of the numerically exact $\lambda_C$ is explained in the text.

| $I$ (M) | $Z$ | $Z_{\text{eff}}$ | $\overline{Z}$ | $\xi$ | $\mu$ | $R$ | $\tau$ via $\tau$ | $\lambda_C$ direct | $\lambda_C$ exact |
|--------|-----|------------------|----------------|------|------|-----|----------------|-----------------|-----------------|
| 0.05   | 9.5 | 8.8              | 7.8            | 2.52 | 1.25 | 4.267| 16.63         | 15.66           |
| 0.10   | 9.8 | 9.2              | 8.2            | 1.84 | 1.76 | 1.382| 5.30          | 5.14            |
| 0.15   | 10.0| 9.4              | 8.4            | 1.48 | 2.16 | 0.744| 0.742         | −0.06           | 0.68            |
| 0.20   | 10.1| 9.6              | 8.6            | 1.27 | 2.50 | 0.514| 0.286         | −2.48           | −1.97           |
| 0.25   | 10.2| 9.7              | 8.7            | 1.10 | 2.79 | 0.408| 0.193         | −4.38           | −3.97           |
| 0.30   | 10.2| 9.8              | 8.8            | 0.984| 3.06 | 0.354| 0.155         | −5.81           | −5.46           |
| 0.40   | 10.3| 10.0             | 9.0            | 0.752| 3.74 | 0.302| 0.109         | −8.82           | −8.53           |
| 1.0    | 10.4| 10.2             | 9.2            | 0.409| 5.58 | 0.323| 0.0734        | −13.87          | −13.55          |
| 1.5    | 10.4| 10.3             | 9.3            | 0.295| 6.83 | 0.349| 0.0655        | −15.72          | −15.38          |
| 2.0    | 10.4| 10.3             | 9.3            | 0.229| 7.89 | 0.367| 0.0616        | −16.82          | −16.46          |

Repulsion together with a short-range attraction. An analysis of the two-particle statistics and hydrodynamics leads to a reasonable prediction of the ionic-strength dependence of the linear coefficient $\lambda_C$. At high ionic strengths, when $B_2$ is negative, the residual $R$ is relatively small so there is then an interesting direct relationship between $\lambda_C$ and $B_2$ (Eq. [57]), which could be tested experimentally.

1. S.S. Alpert and G. Banks, Biophys. Chem. 4, 287 (1976).
2. A.P. Minton and P.D. Ross, J. Phys. Chem. 82, 1934 (1978).
3. R.S. Hall, Y.S. Oh and C.S. Johnson, Jr, J. Phys. Chem. 84, 756 (1980).
4. K.J. LaGattuta, V.S. Sharma, D.F. Nicoli and B.K. Kothari, Biophys. J. 33, 63 (1981).
5. S. Beretta, G. Chirico, D. Arosio and G. Baldini, J. Chem. Phys. 106, 8427 (1997).
6. I. Tinoco, Jr. and P.A. Lyons, J. Phys. Chem. 60, 1342 (1956).
7. T. Raj and W.H. Flygare, Biochemistry 13, 3336 (1974).
8. G.D.J. Phillips, G.B. Benedek and N.A. Mazer, J. Chem. Phys. 65, 1883 (1976).
9. J.L. Anderson, F. Rauh and A. Morales, J. Phys. Chem. 82, 608 (1978).
10. C. Le Bon, T. Nicolai, M.E. Kuil and J.G. Hollander, J. Phys. Chem. B 103 10294 (1999).
11. S.J. Gibbs, A.S. Chu, E.N. Lightfoot and T.W. Root, J. Phys. Chem. 95, 467 (1991).
12. B. Nyström and R.M. Johnsen, Chem. Scripta 22, 82 (1983).
13. A.Y. Mirarefi and C.F. Zukoski, J. Cryst. Growth 265 274 (2004).
14. M. Muschol and F. Rosenberger, J. Chem. Phys. 103, 10424 (1995).
15. J. Zhang and X.Y. Liu, J. Chem. Phys. 119, 10972 (2003).
16. M. Skouri, J.P. Munch, B. Lorber, R. Giegé and S. Candau, J. Cryst. Growth 122, 14 (1992).
17. W. Eberstein, Y. Georgalis and W. Saenger, J. Cryst. Growth 143, 71 (1994).
18. C. Leggio, L. Galantini, E. Zaccarelli and N.V. Pavel, J. Phys. Chem. B 109, 23857 (2005).
19. W.S. Price, F. Tsuchiya and Y. Arata, J. Am. Chem. Soc. 121, 11503 (1999).
20. O. Annunziata, D. Buzatu and J.G. Albright, Langmuir 21, 12085 (2005).
21. P. Retailleau, M. Riès-Kautt, A. Ducruix, L. Belloni, S.J. Candau and J.P. Munch, Europhys. Lett. 46, 154 (1999).
22. J. Narayanan and Y.X. Liu, Biophys. J. 84, 523 (2003).
23. B.U. Felderhof, J. Phys. A 11, 929 (1978).
24. C. van den Broek, F. Lostak and H.N.W. Lekkerkerker, J. Chem. Phys. 74, 2006 (1981).
25. T. Ohtsuki and K. Okano, J. Chem. Phys. 77, 1443 (1982).
26. B. Cichocki and B.U. Felderhof, J. Chem. Phys. 93, 4427 (1990).
27. U. Genz and R. Klein, Physica A 171, 26 (1991).
28. D.N. Petsev and N.D. Denkov, J. Coll. Int. Sci. 149, 329 (1992).
29. N.D. Denkov and D.N. Petsev, Physica A 183, 462 (1992).
30. D.N. Petsev, N.D. Denkov and K. Nagayama, Chem. Phys. 175, 265 (1993).
31. J. Gapinski, A. Wilk, A. Patkowski, W. Häußler, A.J. Banchio, R. Pecora and G. Nägele, J. Chem. Phys. 123, 054708-1 (2005).
32. P. Prinsen and T. Odijk, J. Chem. Phys. 121, 6525 (2004).
33. P. Prinsen and T. Odijk, J. Chem. Phys. 125, 074903 (2006).
34. M. Aubouy, E. Trizac and L. Bocquet, J. Phys. A: Math. Gen. 36 5835 (2003).
35. R.J. Baxter, J. Chem. Phys. 49, 2770 (1968).
36. B. Cichocki and B.U. Felderhof, J. Chem. Phys. 89, 1049 (1988).
37. G.K. Batchelor, J. Fluid Mech. 74, 1 (1976).
38 G.K. Batchelor and J.T. Green, J. Fluid Mech. 56, 375 (1972).
39 A.J. Goldman, R.G. Cox and H. Brenner, Chem. Eng. Sci. 21, 1151 (1966).
40 M.D.A. Cooley and M.E. O’Neill, Proc. Camb. Phil. Soc. 66, 407 (1969).
41 A. Nir and A. Acrivos, J. Fluid Mech. 59, 209 (1973).
42 D.J. Jeffrey and Y. Onishi, J. Fluid Mech. 139, 261 (1984).
43 M. Stimson and G.B. Jeffery, Proc. Roy. Soc. A 111, 110 (1926).
44 H. Brenner, Chem. Eng. Sci. 16, 242 (1961).
45 M.E. O’Neill and S.R. Majumdar, Zeit. angew. Math. Phys. 21, 164 (1970).
46 M.E. O’Neill and B.S. Bhatt, Q. J. Mech. Appl. Math. 44, 91 (1991).
47 M. Chaoui and F. Feuillebois, Q. J. Mech. Appl. Math. 56, 381 (2003).
48 M. Fixman, J. Chem. Phys. 76, 6124 (1982).
49 A.J. Goldman, R.G. Cox and H. Brenner, Chem. Eng. Sci. 22, 637 (1967).
50 V. Mikol, E. Hirsch and R. Giegé, J. Mol. Biol. 213, 187 (1990).
51 D.E. Kuehner, J. Engmann, F. Fergg, M. Wernick, H.W. Blanch and J.M. Prausnitz, J. Phys. Chem. B 103, 1368 (1999).