# Correlated Diffusion of Membrane Proteins and Their Effect on Membrane Viscosity

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ABSTRACT We extend the Saffman theory of membrane hydrodynamics to account for the correlated motion of membrane proteins, along with the effect of protein concentration on that correlation and on the response of the membrane to stresses. Expressions for the coupling diffusion coefficients of protein pairs and their concentration dependence are derived in the limit of small protein size relative to the interprotein separation. The additional role of membrane viscosity as determining the characteristic length scale for membrane response leads to unusual concentration effects at large separation—the transverse coupling increases with protein concentration, whereas the longitudinal one becomes concentration-independent.

## INTRODUCTION

Biomembranes contain a high concentration of proteins, performing key cellular functions (1). Extensive efforts have been directed, therefore, at measuring the dynamics of membrane proteins using various experimental techniques (2). Those studies have concentrated on either single-molecule dynamics (using single-molecule tracking (3,4) and fluorescence correlation spectroscopy (2)) or collective gradient diffusion (using fluorescence recovery after photobleaching (5)). Both the single-particle and large-scale levels are in some contrast with the expected cooperative motion of several proteins at the high concentration relevant to biomembranes, and the crucial role played by small protein aggregates in membranes. Until now experimental investigations of the correlated motion in membranes and monolayers have been limited to rather extended objects, such as domains (6,7) and embedded microspheres (8), although similar two-point microrheological measurements with fluorescent membrane proteins seem feasible (3). Furthermore, in cases where one is interested in membrane properties rather than those of the proteins, two-point microrheology has the advantage of being insensitive to the shape of the inclusion and the local perturbation that it introduces in the membrane (9,10). It seems to be of significant interest, therefore, to account for the correlated Brownian motion of membrane proteins and the associated effects on membrane dynamics.

From a hydrodynamic perspective, a bare, protein-free membrane can be viewed as a quasi-two-dimensional (quasi-2D) liquid, whose molecules (lipids) are free to flow only within the membrane surface, yet exchange momentum with the surrounding three-dimensional (3D) liquid. Hence, flows within a membrane are essentially different from those in both 3D and 2D liquids, in that they do not conserve momentum. As a result, a characteristic length scale $\kappa^{-1}$ emerges, such that over distances much smaller than $\kappa^{-1}$ the membrane keeps its momentum and responds similar to a 2D liquid, whereas beyond that distance momentum is exchanged with the surroundings, and the response is significantly modified.

To gain further intuition for the results that will follow, let us compare this situation in slightly more detail with the ones in momentum-conserving 3D and 2D liquids. In the 3D case, the stress (i.e., momentum flux) emanating from a local perturbation must decay with distance $r$ as $\sigma \sim r^{-2}$ (so that the total flux through an envelope of radius $r$ should remain constant). Since shear stress is related to fluid velocity $v$ as $\sigma \sim \eta_f \nabla v$, where $\eta_f$ is the shear viscosity of the fluid, the velocity response to the perturbation decays as $v \sim (\eta_f r)^{-1}$. More specifically, given a point force $\mathbf{f}$ acting on the liquid at the origin, the steady-state flow velocity $\mathbf{v}(\mathbf{r})$ at position $\mathbf{r}$ is given by (11)

$$\text{3D liquid}: v_i(\mathbf{r}) = G_{ij}(\mathbf{r}) f_j,\ G_{ij}(\mathbf{r}) = \frac{1}{8\pi\eta_f r}\left(\delta_{ij} + \frac{r_i r_j}{r^2}\right), \tag{1}$$

where $\mathbf{G}$ is the Oseen tensor and $i, j = x, y, z$. (Summation over repeated indices is implied throughout this article.) An important consequence of this velocity response is that the correlation (hydrodynamic interaction) between the motions of two particles suspended in the liquid is long-ranged, decaying as $1/r$ (11). Similarly, in a 2D momentum-conserving liquid the stress must decay as $\sigma \sim r^{-1}$, and, thus, the velocity decays as $-\eta_m^{-1} \ln(\kappa' r)$, where $\eta_m$ is the 2D shear viscosity. The resulting well-known logarithmic divergence of this problem (11) requires a cutoff length $\kappa'^{-1}$ (e.g., the system size). The analog of Eq. 1 for the 2D case is

$$\text{2D liquid}: v_i(\mathbf{r}) = G_{ij}(\mathbf{r}) f_j,$$
$$G_{ij}(\mathbf{r}) = \frac{1}{4\pi\eta_m}\left[-\ln(\kappa' r)\delta_{ij} + \frac{r_i r_j}{r^2}\right], \tag{2}$$

where here (and in the rest of the article) $i, j = x, y$. For the intermediate quasi-2D case of fluid membranes we expect the response, and thus the hydrodynamic interaction between

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inclusions, to cross over from the 2D logarithmic decay at short distances to the 3D $1/r$ decay at large distances.

Three major theoretical approaches to membrane hydrodynamics have been presented. In Saffman's pioneering theory (12), the membrane is modeled as a flat slab of viscous liquid, having width $w$ and viscosity $\eta_m/w$. The flow velocity in the membrane is assumed to be two-dimensional, i.e., the velocity profile across the slab width is uniform. The slab has at its two bounding surfaces no-slip contacts with an infinite viscous fluid (water), having viscosity $\eta_f$. The emergent characteristic length—the Saffman-Delbrück length (13)—is given by

$$\kappa^{-1} = \frac{\eta_m}{2\eta_f}. \tag{3}$$

(In asymmetric cases, where the liquids on the two sides of the membrane have different viscosities, one should replace $2\eta_f$ with the sum of those viscosities). Considering a membrane protein as a cylindrical inclusion of radius $a \ll \kappa^{-1}$, Saffman's theory yields the following self-mobility for the protein,

$$B_s = \frac{1}{4\pi\eta_m}[-\ln(\kappa a/2) - \gamma], \tag{4}$$

where $\gamma \simeq 0.58$ is Euler's constant. The self-diffusion coefficient of the protein is simply given, through Einstein's relation, by $D_s = k_BTB_s$, where $k_BT$ is the thermal energy. The weak logarithmic dependence of $D_s$ on the protein size, as predicted by Eq. 4, does not seem to be obeyed in practice (14). It has been argued that the discrepancy might arise from the local disturbance that the protein creates in the membrane (10). Another theoretical suggestion has been to use cylindrical membrane tethers, whose (better-controlled) radius should replace the Saffman-Delbrück length (15). Nonetheless, Eq. 4 has been confirmed in the Brownian motion of small membrane domains (7) and colloidal particles embedded in a fluid monolayer (8). The Saffman theory has been extended to arbitrary values of $\kappa a$ (16) and to the case of membranes supported on a liquid layer of finite thickness (17,18).

In the second approach, introduced by Levine et al. (19–21), the membrane is treated as a viscoelastic film of vanishing thickness within an infinite viscous liquid, taking into account both in-plane and out-of-plane dynamics. The in-plane response of this model, in the limit of a purely viscous, incompressible film, coincides with that of the Saffman theory.

The third theoretical approach considers the membrane as an effective 2D Brinkman liquid (22), i.e., a liquid with an additional phenomenological term that makes it lose momentum over distances larger than a certain given value, $\kappa^{-1}$ (23–28). The mobility of a disk of radius $a$, as calculated from this theory, coincides with Eq. 4 in the limit $\kappa a \ll 1$. However, this approach is essentially different from the first two in that it breaks the translational symmetry along the membrane surface. Thus, while the theories of Saffman and Levine et al. conserve total momentum in 3D, allowing the surrounding liquid to impart momentum back to the membrane at large distances, in the Brinkman-like theory the momentum, once leaving the membrane, is lost. As a result, the large-distance response of this model is qualitatively different, decaying as $1/r^2$ (as required by mass conservation in 2D (29)) rather than $1/r$ (as resulting from momentum conservation in 3D). This approach, therefore, is appropriate at sufficiently short distances, or when translational symmetry is indeed broken. The latter case is relevant, for example, when the membrane is supported on a solid substrate (17,18,23,28,30) or contains immobilized inclusions (31). Actual biomembranes are commonly anchored to an elastic cytoskeleton via immobile proteins and, in such cases, cannot be considered translationally invariant.

Since the lateral size of membrane proteins is typically at least one-order-of-magnitude larger than that of the lipids, they can be considered as suspended in a continuous quasi-2D liquid, thus making the membrane a quasi-2D suspension. In analogy with ordinary suspensions, we expect that the average effect of many such mobile proteins will lead to a modified effective response of the membrane. For example, the presence of hard spheres in 3D suspensions leads to a modified effective viscosity, which is given, up to linear order in the volume fraction of spheres $\phi$, by (32)

$$\text{3D suspension}: \eta_f^{\text{eff}} = \eta_f\left(1 + \frac{5}{2}\phi\right). \tag{5}$$

The analogous result for a 2D suspension of hard disks is (33)

$$\text{2D suspension}: \eta_m^{\text{eff}} = \eta_m(1 + 2\phi), \tag{6}$$

where here $\phi$ is the area fraction of disks. As described above, membranes represent a more complicated intermediate between 2D and 3D liquids, and we expect, therefore, a more subtle, distance-dependent effect of inclusions on its response.

In this work, we extend the Saffmn theory of membrane hydrodynamics (12) to account for the correlated Brownian motion of protein pairs and the effect of protein concentration on that motion. The analysis is restricted to the limit of small protein size, $\kappa a \ll 1$. Since the viscosity of a lipid bilayer is typically $10^3$-fold that of water (34), $\kappa^{-1}$ is typically three-orders-of-magnitude larger than the membrane thickness, i.e., of micron scale. Hence, the limit $\kappa a \ll 1$ should hold for any membrane protein, as originally assumed by Saffman and Delbrück. As regards the interprotein distance, two regimes are addressed—intermediate distances, $a \ll r \ll \kappa^{-1}$, and the asymptotically far region, $r \gg \kappa^{-1}$. We avoid the region $r \sim a$, in which specific effects of protein shape and membrane distortion are expected to be important. Corrections to leading order in $a/r$ are nonetheless derived.

We begin with a presentation of several basic properties of Saffman's hydrodynamic theory, which are useful for our calculations. The resulting coupling diffusion coefficients

of an isolated protein pair are subsequently described. We then proceed to derive the leading corrections to the membrane response, as well as the coupling diffusion coefficients, due to a low concentration of membrane proteins. Finally, we discuss the physical meaning of the results and their practical limitations. While writing this article we have learned of an independent study by Henle and Levine of the effective viscosity of membranes with mobile inclusions (35). The relation between their results and ours is addressed in the Discussion.

## THEORY

### Membrane hydrodynamics

Consider a flat membrane, lying on the $xy$ plane. First, we address the steady-state flow velocity of the membrane at position $\mathbf{r}$, $\mathbf{v}(\mathbf{r})$, in response to a point force, $\mathbf{f}$, applied at the origin and directed along the membrane plane. In Fourier space, $\tilde{\mathbf{v}}(\mathbf{q}) = \int d\mathbf{r} e^{-i\mathbf{q}\cdot\mathbf{r}}\mathbf{v}(\mathbf{r})$, Saffman's analysis yields (12)

$$\tilde{v}_i(\mathbf{q}) = \tilde{G}_{ij}(\mathbf{q})f_j,\ \tilde{G}_{ij}(\mathbf{q}) = \frac{1}{\eta_m q(q+\kappa)}\left(\delta_{ij} - \frac{q_i q_j}{q^2}\right), \quad (7)$$

where $i, j = x, y$. The tensor $\mathbf{G}$ is the membrane-analog of the Oseen tensor of Eq. 1. Inverting to real space, we get

$$G_{ij}(\mathbf{r}) = \frac{1}{4\eta_m}\left\{\left[H_0(\kappa r) - \frac{H_1(\kappa r)}{\kappa r} - \frac{1}{2}(Y_0(\kappa r) - Y_2(\kappa r)) + \frac{2}{\pi(\kappa r)^2}\right]\delta_{ij} - \left[H_0(\kappa r) - \frac{2H_1(\kappa r)}{\kappa r} + Y_2(\kappa r) + \frac{4}{\pi(\kappa r)^2}\right]\frac{r_i r_j}{r^2}\right\}, \quad (8)$$

where $Y_n$ and $H_n$ are, respectively, Bessel functions of the second kind and Struve functions. At short distances, $r \ll \kappa^{-1}$, $\mathbf{G}$ reduces to

$$r \ll \kappa^{-1} : G_{ij}(\mathbf{r}) \simeq \frac{1}{4\pi\eta_m}\left\{-[\ln(\kappa r/2) + \gamma + 1/2]\delta_{ij} + \frac{r_i r_j}{r^2}\right\} + O(\kappa r). \quad (9)$$

This result coincides with the one for a 2D liquid, Eq. 2, with an appropriate definition of $\kappa' \sim \kappa$. At large distances, $r \gg \kappa^{-1}$, $\mathbf{G}$ tends to

$$r \gg \kappa^{-1} : G_{ij} \simeq \frac{1}{2\pi\eta_m}\frac{r_i r_j}{\kappa r^3} + O(\kappa r)^{-2}, \quad (10)$$

which shows the typical $1/r$ decay of 3D flows. Moreover, since $\eta_m \kappa = 2\eta_f$, the large-distance response depends solely on the outer liquid viscosity and is independent of membrane viscosity. (In fact, up to a numerical prefactor, Eq. 10 could be readily derived by requiring that $\mathbf{G}$ decay as $1/r$ and obey 2D incompressibility, $\partial_i G_{ij} = 0$.)

Now suppose that, rather than being a point force, the force is applied to the membrane by a disklike particle of finite radius $a$. To leading order in $a/r$, the membrane flow velocity is given by $v_i(\mathbf{r}) \simeq G_{ij}(\mathbf{r})f_j$. We are interested in the finite-size correction to this flow while still neglecting terms of order $\kappa a$ (as we do throughout this work). The domain of interest, therefore, is $a < r \ll \kappa^{-1}$. In this region the membrane behaves as a 2D liquid, following Eq. 9. Thus, the calculation reduces to a 2D Stokes problem of finding the flow away from a rigid disk, whose solution is

$$a < r \ll \kappa^{-1} : v_i(\mathbf{r}) = G^{(a)}_{ij}(\mathbf{r})f_j,\quad G^{(a)}_{ij}(\mathbf{r}) = G_{ij}(\mathbf{r}) + \frac{a^2}{8\pi\eta_m r^2}\left(\delta_{ij} - \frac{2r_i r_j}{r^2}\right), \quad (11)$$

where $\mathbf{G}$ is given by Eq. 9.

Next, we consider a membrane with a preexisting flow velocity $\mathbf{v}(\mathbf{r})$, and embed in it a circular disk of radius $a$ moving with linear velocity $\mathbf{U}$ and angular velocity $\boldsymbol{\Omega}$. We would like to find the force $\mathbf{F}$, torque $\mathbf{L}$, and force dipole (stresslet) $\mathbf{S}$, which the inclusion exerts on the fluid membrane. For a sphere in an unbounded liquid the linear relations between ($\mathbf{F}$, $\mathbf{L}$, $\mathbf{S}$), on the one hand, and ($\mathbf{v}$, $\mathbf{U}$, $\boldsymbol{\Omega}$), on the other, are given by the first and second Faxén laws (11). In the Appendix, we derive the (approximate) membrane-analogs of these laws, which are

$$\mathbf{F} \simeq \frac{4\pi\eta_m}{\ln(\kappa a/2) + \gamma}\left(\mathbf{v} + \frac{1}{4}a^2\nabla^2\mathbf{v} - \mathbf{U}\right), \quad (12)$$

$$\mathbf{L} \simeq 2\pi\eta_m a^2\left[\left(1 + \frac{1}{8}a^2\nabla^2\right)(\nabla \times \mathbf{v}) - 2\boldsymbol{\Omega}\right], \quad (13)$$

$$S_{ij} \simeq 2\pi\eta_m a^2\left(1 + \frac{1}{8}a^2\nabla^2\right)(\partial_i v_j + \partial_j v_i). \quad (14)$$

Applying the first relation, Eq. 12, to a disk moving in an otherwise stationary membrane ($\mathbf{v} = 0$), we recover the Saffman-Delbrück mobility (Eq. 4). These relations are exact for a 2D liquid (where, in addition, the term proportional to $\nabla^2(\nabla \times \mathbf{v})$ in Eq. 13 vanishes), whereas for membranes their validity is restricted to sufficiently small particles, $\kappa a \ll 1$. (See the Appendix for details.)

### Correlated diffusion

Consider a pair of membrane proteins undergoing Brownian motion while being separated by the 2D vector $\mathbf{r}$. We consider a time period $t$, which is sufficiently short such that $\mathbf{r}$ can be assumed constant, yet sufficiently long to yield Brownian displacements linear in $t$. We further assume that $r$ is much larger than the protein sizes (radii), $a_1$ and $a_2$. The

displacements of the two proteins during time $t$ obey the relations

$$\left\langle \Delta r_{\mathrm{i}}^{\alpha} \Delta r_{\mathrm{j}}^{\beta} \right\rangle = 2D_{\mathrm{ij}}^{\alpha\beta}(\mathbf{r})t\,, \tag{15}$$

where $\Delta r_{\mathrm{i}}{}^{\alpha}$ is the displacement of particle $\alpha$ ($\alpha = 1, 2$) along the axis $i$ ($i = x, y$). The diffusion tensor $D_{\mathrm{ij}}^{\alpha\beta}$ characterizes both the self-diffusion of the particles ($\alpha = \beta$) and the coupling between them ($\alpha \neq \beta$). We define the $x$ axis, without loss of generality, along the line connecting the pair, i.e., $\mathbf{r} = r\hat{\mathbf{x}}$. This choice leads, by symmetry, to $D_{\mathrm{xy}}^{12} = 0$.

The coupled diffusion is then fully characterized by two coefficients: a longitudinal coupling diffusion coefficient, $D_{\mathrm{L}}^{\mathrm{c}}(r) = D_{\mathrm{xx}}^{12}(r\hat{\mathbf{x}})$, and a transverse one, $D_{\mathrm{T}}^{\mathrm{c}}(r) = D_{\mathrm{yy}}^{12}(r\hat{\mathbf{x}})$. The former is associated with the coupled Brownian motion of the pair along their connecting line, and the latter with the coupled motion perpendicular to that line.

For the overdamped dynamics considered here the diffusion tensor in Eq. 15 is simply related to a pair-mobility tensor via the Einstein relation, $D_{\mathrm{ij}}^{\alpha\beta} = k_{\mathrm{B}}TB_{\mathrm{ij}}^{\alpha\beta}$. The mobility tensor $B_{\mathrm{ij}}^{12}(\mathbf{r})$ gives the change in velocity $v_{\mathrm{i}}$ of particle 2 located at $\mathbf{r}$ due to a unit force in the $j$ direction applied to particle 1 at the origin. In the limit $a/r \to 0$ ($a$ being the larger of $a_1, a_2$) this, in turn, is just the membrane-analog of the Oseen tensor, Eq. 8. Hence, we readily identify

$r \gg (a^2\kappa^{-1})^{1/3}$:

$$D_{\mathrm{L}}^{\mathrm{c}}(r) \simeq k_{\mathrm{B}}TG_{\mathrm{xx}}(r\hat{\mathbf{x}}) = \frac{k_{\mathrm{B}}T}{4\eta_{\mathrm{m}}\kappa r}\left[H_1(\kappa r) - Y_1(\kappa r) - \frac{2}{\pi\kappa r}\right]$$

$$D_{\mathrm{T}}^{\mathrm{c}}(r) \simeq k_{\mathrm{B}}TG_{\mathrm{yy}}(r\hat{\mathbf{x}}) = \frac{k_{\mathrm{B}}T}{4\eta_{\mathrm{m}}}\left[H_0(\kappa r) - \frac{H_1(\kappa r)}{\kappa r} - \frac{1}{2}\left(Y_0(\kappa r) - Y_2(\kappa r)\right) + \frac{2}{\pi(\kappa r)^2}\right]. \tag{16}$$

(The domain of validity stated here will be clarified below, when we address the effect of finite particle size.) This result coincides with the in-plane response functions derived by Levine and MacKintosh in the limit of a purely viscous, incompressible membrane (19). It was confirmed in experiments involving colloidal particles in monolayers (8) and rigid circular domains in membrane vesicles (7).

At very large interparticle distances, $r \gg \kappa^{-1}$, Eq. 16 reduces to

$$r \gg \kappa^{-1}: D_{\mathrm{L}}^{\mathrm{c}}(r) \simeq \frac{k_{\mathrm{B}}T}{2\pi\eta_{\mathrm{m}}\kappa r} = \frac{k_{\mathrm{B}}T}{4\pi\eta_{\mathrm{f}}r},$$
$$D_{\mathrm{T}}^{\mathrm{c}}(r) \simeq \frac{k_{\mathrm{B}}T}{2\pi\eta_{\mathrm{m}}(\kappa r)^2} = \frac{k_{\mathrm{B}}T\eta_{\mathrm{m}}}{8\pi\eta_{\mathrm{f}}^2 r^2}. \tag{17}$$

The longitudinal coupling between the two proteins decays asymptotically as $1/r$ and is independent of membrane viscosity. (It is identical, in fact, to the analogous coefficient in a 3D liquid.) The transverse coupling decays only as $1/r^2$, and, curiously, increases with membrane viscosity. When the interparticle distance is smaller than $\kappa^{-1}$ yet still sufficiently large, Eq. 16 becomes

$$\left(a^2\kappa^{-1}\right)^{1/3} \ll r \ll \kappa^{-1}:$$
$$D_{\mathrm{L,T}}^{\mathrm{c}}(r) \simeq \frac{k_{\mathrm{B}}T}{4\pi\eta_{\mathrm{m}}}[-\ln(\kappa r/2) - \gamma \pm 1/2 + (1 \mp 1/3)\kappa r], \tag{18}$$

where the upper (lower) signs correspond to the longitudinal (transverse) coefficient.

Let us now examine the leading effect of finite particle sizes, $a_1$ and $a_2$, and see at what interparticle distance this effect becomes significant. In this domain, clearly, $r \ll \kappa^{-1}$. First, according to Eq. 11 there is a correction of order ${a_1}^2/r^2$ to the flow velocity caused by the forced particle 1. In addition, the first Faxén law, Eq. 12, yields a correction of order ${a_2}^2/r^2$ for the velocity of particle 2 as it is embedded in that flow. Substituting $\mathbf{v}(\mathbf{r})$ of Eq. 11 in Eq. 12 while setting $F = 0$ (particle 2 being force-free), we find the velocity $\mathbf{U}$ of particle 2 to leading order in ${a_1}^2$, ${a_2}^2$. The relation between $\mathbf{U}$ and $\mathbf{f}$ defines a corrected pair mobility tensor, resulting in the coupling diffusion coefficients,

$$a \ll r \ll \left(a^2\kappa^{-1}\right)^{1/3}:$$
$$D_{\mathrm{L,T}}^{\mathrm{c}}(r) \simeq \frac{k_{\mathrm{B}}T}{4\pi\eta_{\mathrm{m}}}\left[-\ln(\kappa r/2) - \gamma \pm 1/2 \pm \frac{a_1^2 + a_2^2}{2r^2}\right], \tag{19}$$

where the plus (minus) sign corresponds to the longitudinal (transverse) coefficient. The coefficients are symmetric under particle exchange $1 \leftrightarrow 2$, as they should be. Comparing Eqs. 18 and 19, we see that the finite-size effect sets in for $r \lesssim (a^2\kappa^{-1})^{1/3}$; hence the domains of validity stated in Eqs. 16–19.

Fig. 1 shows the coupling diffusion coefficients as a function of interparticle distance, along with their asymptotes.

## Effective viscosity

We would like now to calculate the change in membrane viscosity due to the presence of many embedded proteins, to leading (linear) order in protein concentration. The definition of effective viscosity is a subtle point, to which we return in the Discussion. Here we define it using the large-distance flow response of the membrane, i.e., we extract the effective viscosity from $\mathbf{G}(r \to \infty) \to \mathbf{G}^{\mathrm{eff}}$, as it is modified by protein concentration. A similar procedure for a 3D suspension of hard spheres (29) correctly reproduces the known effective viscosity of that system, Eq. 5.

We begin again by applying a point force $\mathbf{f}$ at the origin. The membrane flow velocity at position $\mathbf{r}$ is then given by $v_{\mathrm{i}}^{(0)}(\mathbf{r}) = G_{\mathrm{ij}}(\mathbf{r})f_{\mathrm{j}}$, where $\mathbf{G}$ is given by Eq. 8. Let a disklike protein of radius $a$ be positioned at $\mathbf{r}'$. Due to its finite size it will perturb the membrane flow. The particle is force- and torque-free, and, hence, the leading moment of that perturbation is a force dipole, $\mathbf{S}(\mathbf{r}')$. From our second Faxén-like law, Eq. 14, we have

$$S_{\mathrm{ij}}(\mathbf{r}') = 2\pi\eta_{\mathrm{m}}a^2\left[\partial_{\mathrm{i}}G_{\mathrm{jk}}(\mathbf{r}') + \partial_{\mathrm{j}}G_{\mathrm{ik}}(\mathbf{r}')\right]f_{\mathrm{k}}\,, \tag{20}$$

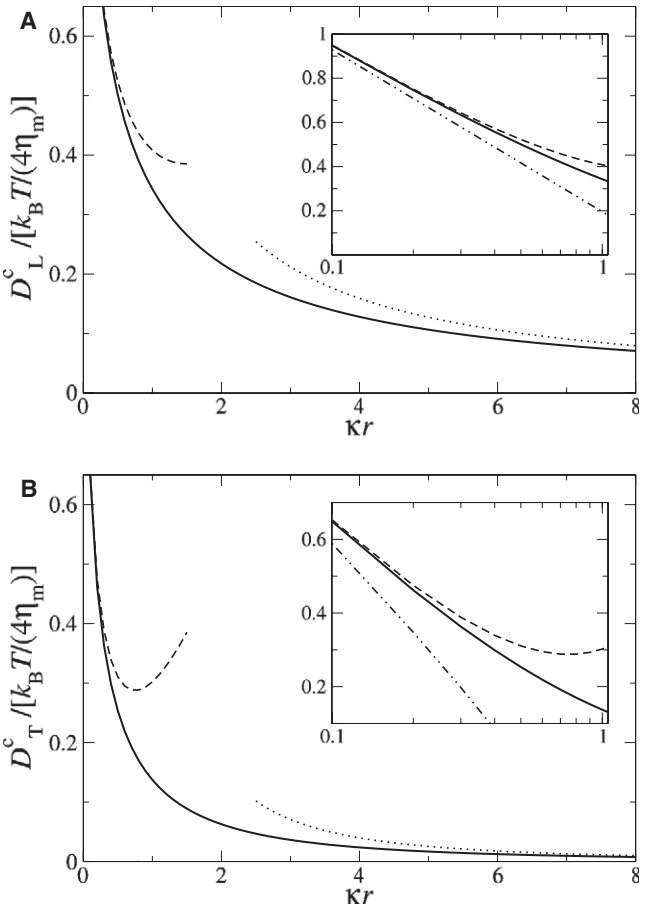


FIGURE 1 Longitudinal (*A*) and transverse (*B*) coupling diffusion coefficients as a function of interprotein distance. The diffusion coefficients are scaled by $k_BT/(4\eta_m)$ and the distance by the Saffman-Delbrück length $\kappa^{-1}$. The results for $r \gg (a^2\kappa^{-1})^{1/3}$ (Eq. 16, *solid lines*) are presented along with their asymptotes for $r \gg \kappa^{-1}$ (Eq. 17, *dotted lines*) and $(a^2\kappa^{-1})^{1/3} \ll r \ll \kappa^{-1}$ (Eq. 18, *dashed lines*). The insets focus on the region of shorter distances, where corrections due to protein size become significant (Eq. 19, *dash-dotted lines*, taking $a_1 = a_2 = 10^{-3}\kappa^{-1}$).

where we have neglected terms of order $a^4$. This force dipole, located at $\mathbf{r}'$, changes the flow velocity at position $\mathbf{r}$ by $\delta v_i(\mathbf{r}) = S_{kj}(\mathbf{r}')\partial_k G_{ij}(\mathbf{r} - \mathbf{r}')$.

Now suppose that many such mobile proteins are present in the membrane, occupying a fraction $\phi$ of its area. The theory being linear, we can superimpose their individual perturbations and average over all possible positions $\mathbf{r}'$. This yields an average correction to the flow velocity,

$$\langle \delta v_i(\mathbf{r}) \rangle = \int d\mathbf{r}' p(\mathbf{r}') S_{kj}(\mathbf{r}') \partial_k G_{ij}(\mathbf{r} - \mathbf{r}'), \qquad (21)$$

where $p(\mathbf{r}')$ is the probability density of finding a particle at $\mathbf{r}'$. To leading order in $\phi$ we may assume a uniform probability density, $p(\mathbf{r}') = \phi/(\pi a^2)$. The convolution in Eq. 21 is then conveniently handled in Fourier space, $\langle \delta \tilde{v}_i(\mathbf{q}) \rangle = [\phi/(\pi a^2)] \tilde{S}_{kj}(\mathbf{q}) i q_k \tilde{G}_{ij}(\mathbf{q})$. Substituting Eq. 7 and the transform of Eq. 20, we find

$$\tilde{v}_i(\mathbf{q}) = \tilde{v}_i^{(0)} + \langle \delta \tilde{v}_i \rangle = \tilde{G}^{\text{eff}}_{ij}(\mathbf{q}) f_j,$$
$$\tilde{\mathbf{G}}^{\text{eff}} = \left(1 - \frac{2\phi q}{q + \kappa}\right) \tilde{\mathbf{G}}. \qquad (22)$$

In the limit $\kappa \to 0$, Eq. 22 reduces to the effective response of a 2D suspension of hard disks, Eq. 6 (33). For finite $\kappa$, because of the $q$-dependent prefactor in Eq. 22, it does not seem at first as if the mobile particles could lead to such a straightforward renormalization of the membrane response, as they do in 2D and 3D suspensions (29). Only in the limit $q \to \infty$ do we simply get $\mathbf{G}^{\text{eff}} \to (1–2\phi)\,\mathbf{G}$ as in the 2D case. In the opposite limit, $q \to 0$, we obtain $\mathbf{G}^{\text{eff}} \to \mathbf{G}$, i.e., the membrane response becomes unaffected by the presence of proteins. A closer inspection reveals, however, that Eq. 22 could be also obtained from $\tilde{\mathbf{G}}$ of Eq. 7 by the following simple substitution (up to linear order in $\phi$):

$$\tilde{G}^{\text{eff}} = \tilde{G}|_{\eta_m \to \eta_m(1+2\phi), \kappa \to \kappa(1-2\phi)}. \qquad (23)$$

Furthermore, since $\kappa = 2\eta_f/\eta_m$, the two substitutions (to linear order in $\phi$) are one and the same. Thus, as in a 2D suspension of hard disks (33), one can write the effective viscosity of the membrane as

$$\eta_m^{\text{eff}} = \eta_m(1 + 2\phi), \qquad (24)$$

provided that this modification is applied to the Saffman-Delbrück length as well.

One should not be confused by the similarity of Eqs. 6 and 24; the effective hydrodynamic response of a protein-laden membrane is not at all similar to that of a 2D suspension. At short distances (yet still much larger than the protein size), substituting $\eta_m \to \eta_m(1 + 2\phi)$ and $\kappa \to \kappa(1–2\phi)$ in Eq. 9 leads to

$$r \ll \kappa^{-1} : G^{\text{eff}}_{ij}(\mathbf{r}) \simeq (1 - 2\phi) G_{ij}(\mathbf{r}) + \frac{\phi}{2\pi\eta_m}\delta_{ij}. \qquad (25)$$

Thus, even in this region of 2D-like behavior, there is an extra term in the membrane response, arising from the modification of $\kappa$. The effect becomes much more dramatic in the large-distance limit, where we have from Eq. 10

$$r \gg \kappa^{-1} : G^{\text{eff}}_{ij}(\mathbf{r}) \simeq G_{ij}(\mathbf{r}), \qquad (26)$$

without any effect of the embedded proteins. As in Eq. 10, the underlying physics is that over large distances, stresses are transmitted through the surrounding liquid. Hence, the response becomes indifferent to the properties of the membrane, be it with or without proteins.

## Concentration corrections to pair diffusion

The results of the preceding section can be readily used to obtain the corrections to the coupling diffusion coefficients due to the presence of many mobile, disklike proteins, occupying an area fraction $\phi$. All we need to do is substitute in

Eq. 16 $\eta_m \to \eta_m(1+2\phi)$, $\kappa \to \kappa(1-2\phi)$, and expand to linear order in $\phi$. This results in

$$r \gg (a^2\kappa^{-1})^{1/3}:$$
$$\delta D_L^c(r) = -\phi\frac{k_BT}{2\eta_m}\left[H_0(\kappa r) - \frac{H_1(\kappa r)}{\kappa r} + \frac{1}{2}(Y_2(\kappa r) - Y_0(\kappa r)) + \frac{2}{\pi(\kappa r)^2}\right]$$
$$\delta D_T^c(r) = -\phi\frac{k_BT}{2\eta_m}\frac{(\kappa r)^2-1}{\kappa r}\left[H_{-1}(\kappa r) + Y_1(\kappa r) + \frac{2}{\pi\kappa r(\kappa r+1)}\right]. \quad (27)$$

Equation 27 gives the concentration corrections to the bare coupling diffusion coefficients given in Eq. 16. Their spatial dependencies are depicted in Fig. 2. The correction to the longitudinal coupling is always negative, whereas the correction to the transverse one becomes positive for $r > \kappa^{-1}$. This is because at such large distances the bare transverse coefficient $D_T^c$ (Eq. 17) increases, rather than decreases, with $\eta_m$.

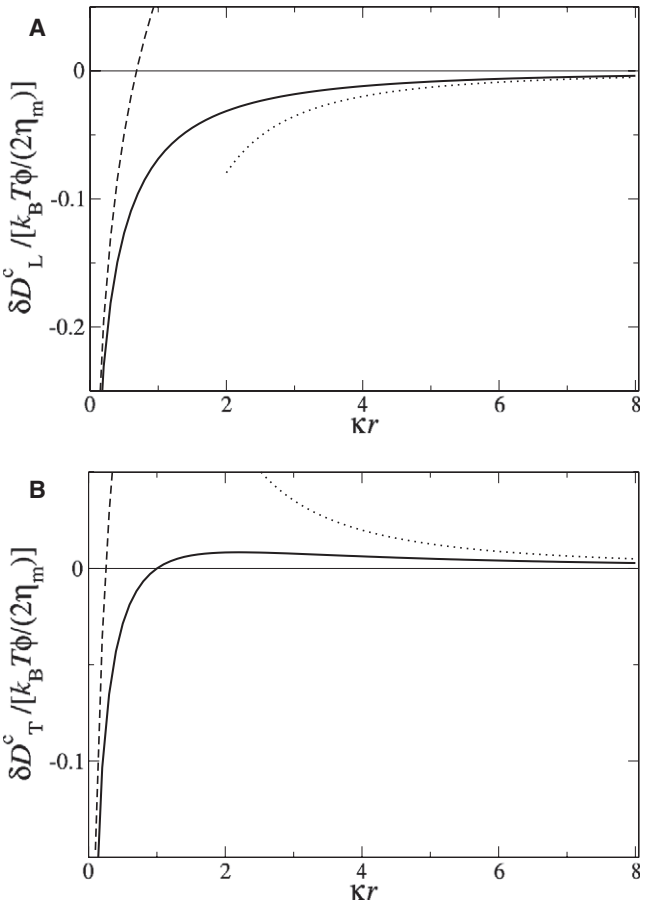


FIGURE 2 Concentration corrections to the longitudinal (*A*) and transverse (*B*) coupling diffusion coefficients as a function of interprotein distance. The corrections to the diffusion coefficients are scaled by $k_BT\phi/(2\eta_m)$ and the distance by the Saffman-Delbrück length $\kappa^{-1}$. The results for $r \gg (a^2\kappa^{-1})^{1/3}$ (Eq. 27, *solid lines*) are presented along with their asymptotes for $r \gg \kappa^{-1}$ (Eq. 28, *dotted lines*) and $(a^2\kappa^{-1})^{1/3} \ll r \ll \kappa^{-1}$ (Eq. 29, *dashed lines*).

At large distances we get the following corrections to Eq. 17:

$$r \gg \kappa^{-1} : \delta D_{L,T}^c(r) \simeq \mp\phi\frac{k_BT}{\pi\eta_m(\kappa r)^2}. \quad (28)$$

Recall that the bare longitudinal coefficient decays at large distances as $1/r$, whereas the transverse one decays as $1/r^2$ (Eq. 17). Hence, according to Eq. 28, the asymptotic behavior of $D_L^c$ is unaffected by the presence of the proteins, $D_L^c \to D_L^c$. This is because at such distances the bare $D_L^c$ is independent of membrane viscosity (Eq. 17). By contrast, the transverse coefficient is affected (increased) by $\phi$ at large distances, $D_T^c \to (1+2\phi)D_T^c$.

At distances much shorter than $\kappa^{-1}$, Eq. 27 becomes

$$(a^2\kappa^{-1})^{1/3} \ll r \ll \kappa^{-1}:$$
$$\delta D_{L,T}^c(r) \simeq \phi\frac{k_BT}{2\pi\eta_m}[\ln(\kappa r/2) + \gamma + 1 \mp 1/2]. \quad (29)$$

Comparing with Eq. 18, we find that the leading term [$\sim\ln(\kappa r)$] is renormalized by $\phi$ as in a 2D liquid, $D_{L,T}^c \to (1-2\phi)D_{L,T}^c$. Yet, the next-order term [$O(1)$] does not follow the same law. This is again because there is another dependence on $\eta_m$ in the length $\kappa^{-1}$.

## DISCUSSION

The theory presented here has yielded several predictions concerning the correlated Brownian motion of pairs of membrane proteins, which can be directly checked in two-particle tracking experiments using Eq. 15. Equation 16 gives the longitudinal and transverse coupling diffusion coefficients as a function of interprotein distance. An equivalent result, in the form of in-plane response functions, has been previously reported (19). It is valid at sufficiently large distances and insensitive to the size and shape of the proteins. For smaller distances, yet still larger than the protein size $a$, we have derived expressions for the coupling diffusion coefficients to leading order in $a/r$ and assuming a disklike shape of the embedded proteins (Eq. 19). Since the finite-size correction is only quadratic in $a/r$, it becomes significant only for distances $r \lesssim (a^2\kappa^{-1})^{1/3}$. For $a \sim 1$ nm and $\kappa^{-1} \sim 10^3$ nm, this crossover length is only ~10 nm. Thus, we expect the finite size of proteins to affect their hydrodynamic coupling only at nanometer-scale distances. We have provided the corrections to the two coupling coefficients due to the presence of other membrane proteins, to leading order in their area fraction $\phi$ (Eq. 27).

Several particular predictions are worth emphasizing.

First, the longitudinal diffusion coefficient decays with distance more slowly than the transverse one. Asymptotically, $D_L^c$ decays as $1/r$, whereas $D_T^c$ decays as $1/r^2$ (Eq. 17).

Second, at such large distances $D_L^c$ becomes independent of membrane viscosity and is, in fact, identical to the longitudinal coefficient in an unbounded liquid. This is because the coupling in this regime is mediated by flows in the surrounding liquid. Thus, the large-distance longitudinal coupling should be the same for different membranes in the same solvent and can be tuned by changing the solvent viscosity. The dominance of stresses in the outer liquid holds for the transverse coupling as well, yet this coupling arises from an effective force dipole, which is proportional to $\kappa^{-1} = \eta_m/(2\eta_f)$ and, therefore, remains membrane-dependent. We note that these asymptotes hold for $r \gg \kappa^{-1} \sim 0.1 - 1\ \mu$m and, hence, may be hard to observe in practice. Nonetheless, the difference in the spatial decays should be seen already at much shorter distances. (See Fig. 1, *A* and *B*.)

Third, the longitudinal coefficient at large distances is predicted to be independent of protein concentration (Eq. 28). This is merely another consequence of the membrane-independence of this coefficient. By contrast, the large-distance transverse coefficient not only depends on protein concentration but increases with $\phi$ (Eq. 28 and Fig. 2 *B*). This unusual result—hydrodynamic interaction enhanced by particle concentration—stems from the aforementioned effective force dipole, which increases with $\kappa^{-1} \sim \eta_m$.

The concept of effective viscosity may have different, not necessarily equivalent, definitions (11). The case of a membrane with mobile inclusions seems to clearly demonstrate this difficulty. If one measured the large-distance longitudinal coupling coefficient as a function of $\phi$, one would find no concentration effect and might infer, therefore, that the proteins do not modify the effective viscosity of the membrane. If the large-distance transverse coefficient were measured, however, an increase with $\phi$ would be found, naively leading to the conclusion that $\eta_m^{eff}$ decreases with $\phi$. A more careful examination of how the large-distance asymptotes of $D_L^c$ and $D_T^c$ depend on $\eta_m$, and how this dependence changes with $\phi$, reveals a concentration dependence identical to that in a 2D suspension, $\eta_m^{eff} = \eta_m(1 + 2\phi)$. (Compare Eqs. 17 and 28.) The calculation by Henle and Levine (35) is based on the same (Saffman) theory, yet follows Einstein's original definition of the effective viscosity as the coefficient relating average stress (or dissipation rate) with strain rate under a given global shear flow (32). They find yet another concentration dependence in the limit $\kappa a \to 0$, $\eta_m^{eff} = \eta_m(1 + 3\phi)$. In the cases of 3D and 2D suspensions, the aforementioned three possible definitions of $\eta_m^{eff}$ give identical results (29). The different behavior of membranes lies in the fact that they do not conserve momentum, i.e., in the appearance of the length scale $\kappa^{-1}$ and its dependence on $\eta_m$.

Thus, the effect of inclusions on membrane viscosity depends on the definition of that transport coefficient and the experiment under consideration. The definition used here relates to how the response of the membrane to local perturbations changes with $\phi$. It is relevant, therefore, to microrheological and particle-tracking experiments. Einstein's definition, as used by Henle and Levine (35), should be appropriate for larger-scale rheological measurements. We have found that the effective response in the presence of proteins is given, as in a 2D suspension, by substituting $\eta_m \to \eta_m^{eff} = \eta_m(1 + 2\phi)$. Yet, unlike 2D suspensions, this substitution should be made also in the Saffman-Delbrück length, $\kappa^{-1} = \eta_m/(2\eta_f) \to \eta_m^{eff}/(2\eta_f)$. The extra dependence of $\kappa$ on $\phi$ leads to a qualitatively different effective response. A clear demonstration is given by the concentration correction to the transverse coupling, $\delta D_T^c$, where the interplay between the $\phi$-dependencies of $\eta_m$ and $\kappa$ leads to a sign reversal of that term (Fig. 2 *B*). Another consequence is the aforementioned independence of the large-distance longitudinal coupling, $D_L^c$, on protein concentration.

We note that a similar absence of a concentration effect on the large-distance response has been observed in another quasi-2D system—a suspension confined between two plates (36,37). The physical origins of the two phenomena, however, are slightly different. In the confined suspension, momentum is lost to the solid boundaries, and the far response arises solely from liquid mass displacement, which is not affected by the presence of particles. In membranes, the far response does arise from momentum diffusion, yet these dynamics take place in the outer liquid and, therefore, are insensitive to the presence of membrane inclusions.

This analysis has involved several rather severe approximations. It should be regarded, therefore, as a first step toward understanding the correlated dynamics of membrane proteins or, alternatively, as a possible means to isolate simple hydrodynamic effects from other, more specific ones.

First, we have focused on the hydrodynamic coupling between proteins, neglecting any direct interaction (38). Such interactions may arise from actual (e.g., electrostatic) potentials or be induced by the perturbations that inclusions introduce in the membrane (10,39,40).

Second, as in previous theories, we have considered a homogeneous membrane, whereas actual biomembranes are believed to contain various heterogeneities and domains (41). A homogeneous hydrodynamic description may still be applicable inside such a submicron domain.

Third, the calculations have been made in the limit of very small particle size, $\kappa a \ll 1$. As the typical values of $\kappa^{-1}$ are micron-scale, this should be a good approximation for practically all membrane proteins. The Saffman theory can be extended to large values of $\kappa a$ as well, yet the calculations become significantly more complicated (16,35).

Fourth, we have treated the membrane as a perfectly flat surface, whereas in practice it is curved and fluctuating. Curvature and bending fluctuations, apart from their aforementioned ability to induce interactions between embedded proteins, may also affect their 2D-projected diffusion as observed in experiments (42–45).

Finally, we have studied the effect of protein concentration to linear order only, assuming $\phi \ll 1$. As in the much simpler case of a 3D suspension of hard spheres, extension to higher orders in $\phi$ should be difficult, involving static and dynamic correlations between particles. Nevertheless, some of our results clearly emanate from more fundamental considerations and should hold for higher values of $\phi$ as well. For example, the $\phi$-independence of $D_{\mathrm{L}}^{\mathrm{c}}(r \gg \kappa^{-1})$ arises from stresses being transmitted through the outer liquid; thus, we conjecture that it is valid to all orders in $\phi$. It is also plausible that, in the limit $\kappa a \ll 1$, expressions of higher order in $\phi$ could be obtained by merely substituting for $\eta_{\mathrm{m}}$ (both directly and in $\kappa$) the effective viscosity, $\eta_{\mathrm{m}}^{\mathrm{eff}}(\phi)$, as calculated for a 2D suspension. These predictions, naturally, will break down at sufficiently high concentration, when the assembly of inclusions crystallizes or jams.

## APPENDIX: FAXÉN LAWS FOR A MEMBRANE

In this Appendix, we calculate the approximate membrane-analogue of the 3D Faxén laws. These laws relate the linear velocity $\mathbf{U}$ and angular velocity $\mathbf{\Omega}$ of a rigid particle, and the flow field $\mathbf{v}(\mathbf{r})$ in which it is embedded, with the moments of force distribution that it exerts on the embedding fluid.

Let the center of a disk of radius $a$ be located at the origin, and let $\mathbf{f}(\mathbf{r}')$ be the distribution of forces that it exerts on the system. This force distribution changes the membrane velocity at position $\mathbf{r}$ by $\int d\mathbf{r}' G_{\mathrm{ij}}(\mathbf{r}-\mathbf{r}')f_{\mathrm{j}}(\mathbf{r}')$, where $\mathbf{G}$ is the membrane-analogue of the Oseen tensor, Eq. 8. Assuming no slip at the particle perimeter, we have

$$r = a: U_{\mathrm{i}} + (\mathbf{\Omega} \times \mathbf{r})_{\mathrm{i}} = v_{\mathrm{i}}(\mathbf{r}) + \int d\mathbf{r}' G_{\mathrm{ij}}(\mathbf{r}-\mathbf{r}')f_{\mathrm{j}}(\mathbf{r}'). \tag{30}$$

We have intentionally left the domain $\mathbf{r}'$ of the force distribution unspecified, since the calculation is insensitive to it; the vector $\mathbf{r}$, however, must be on the particle perimeter, where the no-slip boundary condition is imposed.

Assuming that $\mathbf{v}(\mathbf{r})$ changes very moderately on the scale of $a$, we expand $\mathbf{v}(\mathbf{r}) \simeq \mathbf{v}(\mathbf{0}) + a\hat{r}_{\mathrm{i}}\partial_{\mathrm{i}}\mathbf{v}(\mathbf{0}) + \frac{1}{2}a^2\hat{r}_{\mathrm{i}}\hat{r}_{\mathrm{j}}\partial_{\mathrm{i}}\partial_{\mathrm{j}}\mathbf{v}(\mathbf{0})$. Since both $r$ and $r'$ in Eq. 30 are of order $a$, and we have been assuming throughout this work $\kappa a \ll 1$, we can substitute for $\mathbf{G}$ its short-distance asymptote, Eq. 9. Within these approximations, integrating Eq. 30 over $\mathbf{r}$ yields the analogue of the first Faxén law,

$$\mathbf{F} = \frac{4\pi\eta_{\mathrm{m}}}{\ln(\kappa a/2) + \gamma + O(\kappa a)^2} \times \left[\mathbf{v}(\mathbf{0}) + \frac{1}{4}a^2\nabla^2\mathbf{v}(\mathbf{0}) - \mathbf{U} + O\left(a^4\nabla^4\mathbf{v}\right)\right], \tag{31}$$

where $\mathbf{F} = \int d\mathbf{r}' \mathbf{f}(\mathbf{r}')$.

Next we multiply both sides of Eq. 30 by $\mathbf{r}$ and integrate over $\mathbf{r}$. Separating the resulting tensors into symmetric and antisymmetric contributions, we obtain the analogue of the second Faxén law for the torque and force dipole (stresslet),

$$\mathbf{L} = 2\pi\eta_{\mathrm{m}}a^2\left[1 + O(\kappa a)^2\right]\left\{\left[1 + \frac{1}{8}a^2\nabla^2 + O\left(a^4\nabla^4\right)\right] \times [\nabla \times \mathbf{v}(\mathbf{0})] - 2\mathbf{\Omega}\right\}, \tag{32}$$

$$S_{\mathrm{ij}} = 2\pi\eta_{\mathrm{m}}a^2\left[1 + O(\kappa a)^2\right]\left[1 + \frac{1}{8}a^2\nabla^2 + O\left(a^4\nabla^4\right)\right] \times \left[\partial_{\mathrm{i}}v_{\mathrm{j}}(\mathbf{0}) + \partial_{\mathrm{j}}v_{\mathrm{i}}(\mathbf{0})\right], \tag{33}$$

where $\mathbf{L} = \int d\mathbf{r}'[\mathbf{r}' \times \mathbf{f}(\mathbf{r}')]$ and $S_{\mathrm{ij}} = (1/2)\int d\mathbf{r}'[r'_{\mathrm{i}}f_{\mathrm{j}}(\mathbf{r}') + r'_{\mathrm{j}}f_{\mathrm{i}}(\mathbf{r}')]$. In regular Stokes flows $\kappa = 0$, $\nabla^4\mathbf{v} = 0$, $\nabla^2(\nabla \times \mathbf{v}) = 0$, and the Faxén laws become exact. Thus, Eqs. 31–33 are exact for 2D liquids, where, additionally, the term proportional to $\nabla^2(\nabla \times \mathbf{v})$ in Eq. 32 vanishes. For membranes, however, their validity is restricted to sufficiently small particles, $\kappa a \ll 1$. In addition, the terms of order $a^2$ are valid provided that the considered flow is not too uniform, $|\nabla^2 v/v| \gg \kappa^2$.

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