Internal lipid bilayer friction coefficient from equilibrium canonical simulations

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Abstract
A fundamental result in the theory of Brownian motion is the Einstein–Sutherland relation between mobility and diffusion constant. Any classical linear response transport coefficient obeys a similar Einstein–Helfand relation. We show in this work how to derive the interleaflet friction coefficient of lipid bilayer by means of an adequate generalisation of the Einstein relation. Special attention must be paid in practical cases to the constraints on the system center of mass position that must be enforced when coupling the system to thermostat.

In 1905 Einstein [1] and Sutherland [2] obtained a relation \( D = k_B T \nu \) between the diffusion coefficient \( D \) of a Brownian particle, its mobility coefficient \( \nu \) (ratio between average drift velocity and drift force) the absolute temperature \( T \) and the Boltzmann constant \( k_B \). Similar relations were later established for all the usual transport coefficients (viscosity, thermal conduction, ...), the Einstein–Helfand relations [3]. These expressions provide an alternative way to the Green–Kubo relations for the determination of the transport properties, based on the averaged mean square deviation (MSD) of well chosen dynamical observables. The use of Helfand expressions in molecular dynamics (MD) simulation is however not always practical due to system periodic boundary conditions (PBC) [4, 5].

A natural question arises as to determining lipid bilayer friction properties in a similar way, i.e. by writing and computing the MSD of a carefully chosen dynamical observable. Such result would be valuable as an alternative to out-of-equilibrium simulation techniques, which are diversely implemented in the commonly used simulation packages.

Lipid bilayers are of central interest in biophysics. They result from the self-assembly of amphiphilic lipid molecules [6, 7] and display a very typical structure consisting of two leaflets forming a lamella with molecules in opposite directions, the outside hydrophilic part exposed to water and the hydrophobic part hidden from it (figure 1). Lipid bilayer systems are important due to their intimate connection with biological membrane systems [8].

The interleaflet friction coefficient parameter \( b \) is one of the two main friction coefficients acting within a sheared lipid bilayer. It expresses the proportionality between the relative sliding velocity \( v_s \) of the leaflets and the transverse stress \( \tau \) that arises from such motion, \( \tau \) being equal to \( b v_s \). Due to their fluid character lipid bilayers also possess a transverse shear viscosity \( \eta_b \) which expresses the friction associated to in plane \( xy \) shear motions. The shear viscosity can be conveniently computed by means of out-of-equilibrium or Kubo like approaches [9–11]. By contrast Kubo approaches to the interleaflet friction are not efficient, in part because they are dominated by the low viscosity solvent contribution. Most approaches are based on pulling leaflets with external forces [12, 11, 13] or other out of equilibrium molecular dynamics techniques [10, 14]. The interleaflet friction \( b \) parameter is involved in many remodeling and membrane fluctuation mechanisms [15–17]. It is also hard to determine it experimentally, and recent work indicates values comprised between \( 4 \times 10^7 \) and \( 1.8 \times 10^8 \) Pas m\(^{-1}\) [18]. We aim in this work at proposing a simple approach to the determination of this coefficient \( b \) from an equilibrium molecular dynamics simulation.
A model bilayer system comprising two apposed leaflets and a single water solvent slab is expected to maintain its self-assembled structure for the longest available simulation times. Two-tails standard lipid molecules are too little soluble in water [6, 7] to escape from the bilayer, and have very long leaflet exchange characteristic times [8, 19]. Therefore the only molecular motions expected in such a case are the in-plane self diffusion of lipid molecules and bulk diffusion of water molecules. Let us then decompose the system into three apposed subsystems: upper lipid leaflet (S1), lower lipid leaflet (S2) and solvent (S3). Denoting \( x_i \) the respective horizontal coordinates of the subsystems, one faces the problem of finding a relation between the average displacements covariance matrix \( D_{ij}(t) = \langle (x_i(t) - x_i(0))(x_j(t) - x_j(0)) \rangle, i, j = 1, 2, 3 \), with brackets \( \langle \cdot \rangle \) standing for the canonical equilibrium trajectories average, and the desired friction coefficients.

Simulated molecular systems must be coupled to thermostats to generate representative canonical trajectories and keep the system internal energy constant. A number of popular momentum preserving thermostat such as Nose-Hoover chains or V-rescale thermostat requires in turn that the center of mass of the trajectories and keep the system internal energy constant. A number of popular momentum preserving thermostat such as Nose-Hoover chains or V-rescale thermostat requires in turn that the center of mass of the trajectories and keep the system internal energy constant. A number of popular momentum preserving thermostat such as Nose-Hoover chains or V-rescale thermostat requires in turn that the center of mass of the trajectories and keep the system internal energy constant. A number of popular momentum preserving thermostat such as Nose-Hoover chains or V-rescale thermostat requires in turn that the center of mass of the trajectories and keep the system internal energy constant. A number of popular momentum preserving thermostat such as Nose-Hoover chains or V-rescale thermostat requires in turn that the center of mass of the trajectories and keep the system internal energy constant. A number of popular momentum preserving thermostat such as Nose-Hoover chains or V-rescale thermostat requires in turn that the center of mass of the trajectories and keep the system internal energy constant. A number of popular momentum preserving thermostat such as Nose-Hoover chains or V-rescale thermostat requires in turn that the center of mass of the trajectories and keep the system internal energy constant. A number of popular momentum preserving thermostat such as Nose-Hoover chains or V-rescale thermostat requires in turn that the center of mass of the trajectories and keep the system internal energy constant.

In what follows, we adopt this convention throughout.

The continuous hydrodynamic description of a lipid bilayer system consists in replacing each leaflet by a solid thick slab, and water by a fluid slab at fixed vertical positions (figure 1). This assumes a low water permeability of the membrane on the one hand (verified in practice) and a system center of mass fixed. We assume \( xy \) planar isotropy and restrict ourselves to the \( x \) component of the displacements. The hydrodynamic system is characterized by two masses \( m_1 = m_2 = m \) and two velocity scalars \( V_1, V_2 \) associated to the leaflets, along with a mass density \( \rho \) and a continuous velocity field \( V(z) \) for the water slab. The water mass \( m_w \) and center of mass \( V_w \), follow from integrating \( \rho \) and \( V(z) \) along \( z \). The solvent flow is assumed to be linear parabolic at all times, a situation covering the Couette and Poiseuille velocity profiles. In the absence of sliding, the flow is completely parametrized by \( V_1, V_2 \) and \( V_w \), considered as the slow variables of the many particles system. When connecting these hydrodynamic variables to molecular simulations, it is necessary to account for possible PBC jumps in the molecular displacements, and to consider continuous, unwrapped trajectories.

Subsystems are possibly acted upon by forces \( F_1, F_2, F_3 \) in the \( x \) direction. Mechanical insulation requires \( F_1 + F_2 + F_3 = 0 \) while the stationary system center of mass imposes \( m_1 V_1 + m_2 V_2 + m_3 V_3 = 0 \). As explained in [13], the equations of motions of the 3 subsystems read, in the absence of water-lipid bilayer sliding,

\[
\begin{align*}
    m_1 \dot{V}_1 &= \left( \frac{b A}{L_w} - \frac{2 \eta A}{L_w} \right) (V_2 - V_1) + \frac{6 \eta A}{L_w} (V_3 - V_1) + F_1; \\
    m_2 \dot{V}_2 &= \left( \frac{b A}{L_w} - \frac{2 \eta A}{L_w} \right) (V_1 - V_2) + \frac{6 \eta A}{L_w} (V_3 - V_2) + F_2; \\
    m_3 \dot{V}_3 &= \frac{6 \eta A}{L_w} (V_1 + V_2 - 2 V_3) + F_3,
\end{align*}
\]

(1)
where \( A \) is the area of the slab, \( \eta \) the Newtonian viscosity of the solvent and \( b \) the interleaflet friction coefficient. The relation expresses that internal forces between components are proportional to the system area, and linearly dependent on the mutual velocity differences.

The purpose of the Letter is to establish an Einstein-Helfand relation for the frictions coefficients \( b \) and \( \eta/L_w \). For this purpose we generalize the Langevin-Smoluchowski (overdamped) stochastic equation of motion 

\[
d(mv) = -\zeta dv + \sqrt{2m(k_B T/dW(t))} \text{ of a Brownian particle } (m \text{ mass, } v \text{ velocity, } \zeta \text{ friction coefficient, } t \text{ time, } dW \text{ differential of a normalized Wiener process}) \tag{2}
\]

However, due to the use of a thermostat, a momentum conservation constraint 

\[
\text{The total vanishing impulsion constraint modifies the energy equipartition theorem, as the thermal energy } k_{BT} \text{ of two degrees of freedom is shared by the three subsystems according to their respective inverse masses.} \]

The total mass is recovered, \( \text{TT} \) representing the real transpose of vectors and matrices. This implies [24]

\[
A \cdot \langle pp^T \rangle + \langle pp^T \rangle \cdot A^T = BSB^T. \tag{5}
\]

However, due to the use of a thermostat, a momentum conservation constraint \( U^T p = 0 \) holds, with \( U = (1, 1, 1) \). The friction matrix \( A \) is only of rank 2 as \( U^T A = 0 \) (so does \( A M U = 0 \)).

The total vanishing impulsion constraint modifies the energy equipartition theorem, as the thermal energy \( k_{BT} \) of two degrees of freedom is shared by the three subsystems according to their respective inverse masses. A calculation (Supplementary data) gives

\[
\langle \mathbf{v}^T \rangle = k_B T \left[ M^{-1} - \frac{U U^T}{m_t} \right], \tag{6}
\]

with \( m_t = m_1 + m_2 + m_3 \) the total mass. The impulsion covariance matrix follows immediately, given \( M^F = M \):

\[
\langle pp^T \rangle = M^F \langle \mathbf{v}^T \rangle M = k_B T \left[ M - M \frac{U U^T}{m_t} M \right]. \tag{7}
\]

Combining equations (5) and (7) along with the constraints \( A M U = 0 \) and \( U^T A^F = 0 \) leads to a simple expression for the random force correlations

\[
BSB^T = k_B T (A M + M A^T) = 2 k_B T A M. \tag{8}
\]

Meanwhile, the long times (damped) displacement covariance matrix can be obtained by integrating equation (2), leading to a displacement vector \( \Delta x = (x(t) - x(0)) \) in terms of the vector of Wiener processes \( (W(t)) \), given by \( A M \Delta x = B W \) and thus \( A M \Delta x \Delta x^T (A M)^T = B W W^T B^T \). Taking the thermal average leads to

\[
A M (\Delta x \Delta x^T) A M = B S T = 2 k_B T A M t. \tag{9}
\]

Equation (9) formally solves the problem, by connecting the covariance displacement matrix on the left hand side with the friction matrix \( A M \) on the right hand side. It represents the desired Einstein-Helfand expression for the lipid bilayer frictions. Nevertheless, the expression is not useful as such, due to \( A M \) being a rank 2 matrix. It cannot be explicitly inverted to yield the desired displacement covariance matrix alone on the left hand side of an equation. Equation (9) takes actually a Moore-Penrose pseudo-inverse matrix form.
In the case of interest, it is possible to express the covariance matrix using the orthogonal change of basis

\[
O = \frac{1}{\sqrt{3}} \begin{pmatrix}
1 + \sqrt{3} & 1 - \sqrt{3} & 1 \\
2 & 2 & 2 \\
2 & -1 & -1 \\
1 & 1 & 1
\end{pmatrix}, \quad O^T J A M O = A \begin{pmatrix}
b + \frac{10\eta}{L_w} & 8\eta/L_w & -b \\
8\eta/L_w & b + \frac{10\eta}{L_w} & 0 \\
0 & 0 & 0
\end{pmatrix}.
\]

Parameterizing the displacement covariance matrix \( D \) with Voigt indices \( 4, 5, 6, D_1 = D_2 \) and \( D_4 = D_5 \)

\[
\begin{pmatrix}
(\langle \Delta x_i \Delta x_i \rangle) & \langle \Delta x_i \Delta x_j \rangle & \langle \Delta x_i \Delta x_k \rangle \\
\langle \Delta x_j \Delta x_i \rangle & (\langle \Delta x_j \Delta x_j \rangle) & \langle \Delta x_j \Delta x_k \rangle \\
\langle \Delta x_k \Delta x_i \rangle & \langle \Delta x_k \Delta x_j \rangle & (\langle \Delta x_k \Delta x_k \rangle)
\end{pmatrix} = 2 \begin{pmatrix}
D_1 & D_2 & D_3 \\
D_2 & D_1 & D_3 \\
D_3 & D_3 & D_1
\end{pmatrix},
\]

leads to the explicit inverse relation

\[
3k_BT \begin{pmatrix}
1 & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & 1
\end{pmatrix} = \begin{pmatrix}
b + \frac{10\eta}{L_w} & 8\eta/L_w & -b \\
8\eta/L_w & b + \frac{10\eta}{L_w} & 0 \\
-L_w & -b & 0
\end{pmatrix} \begin{pmatrix}
2(D_1 - D_b + D_3 - 2D_4) & (2D_b - D_1 + D_4 - 2D_4) \\
(2D_b - D_1 + D_3 - 2D_4) & (2D_b - D_1 + D_3 - 2D_4)
\end{pmatrix}.
\]

Equation (12) is a \( 2 \times 2 \) matrix generalization of the Stokes-Einstein relation, and constitutes the main result of this Letter. It is easy to establish two further relations between the covariance parameters

\[
m_nD_3 + 2mD_4 = 0; \quad m(D_1 + D_b) + m_nD_4 = 0,
\]

showing that only two independent degrees of freedom are left in the displacement covariance matrix to match the two independent degrees of freedom of the friction matrix \( b \) and \( \eta/L_w \). Equation (13) follows from the time integration of \( v_i \mathcal{M} U = 0 \), proving that the displacement vector \( \Delta x(t) \) stays orthogonal to \( \mathcal{M} U \). Note that the presentation of equation (12) is not unique, due to an \( O(1) \) degeneracy associated with the choice of the orthogonal matrix \( O \), whose sole effect is to rotate the 2 coordinates in 12.

We now check that the Brownian description proposed predicts correctly the behavior of a simulated lipid membrane system (coarse-grained Martini model [25], 512 lipids, 10\( \mu \)s simulated, see Supplementary data for details). Predictions for the velocity covariance matrix can be assessed by estimating the deviation \( \mathcal{E}_{\text{exp}} \) from the expected result, using the matrix norm \( \|X\|_F = \text{tr}(XX^T) \) (see equation (7)):

\[
\mathcal{E}_{\text{exp}} = \frac{1}{k_BT} \left[ \mathcal{M}^{-1} - \frac{UU^T}{m_t} \right] - \langle vv^T \rangle \|v\|_2/\|\langle vv^T \rangle\|_2.
\]

We find good agreement with the prediction as \( \mathcal{E}_{\text{exp}} \approx 1.8 \times 10^{-5} \) is of the order of two parts per thousand. Using the same data and the Einstein-Helfand relation (12) we obtained respectively \( b = 2.54 \times 10^6 \text{ Pa s}^{-1} \) and \( \eta = 8.1 \times 10^{-4} \text{ Pa s} \), with an estimated relative accuracy of the order of 0.05 (see Supplementary data for details). Figure 2 shows the covariance matrix of mean squared displacements that corresponds to this case. This compares favorably with the reported values, for the same system and conditions, of \( b = 2.55 \pm 0.10 \times 10^6 \text{ Pa s}^{-1} \) and \( \eta = 8. \times 10^{-4} \text{ Pa s} \) [13]. In this approach, the water thickness \( L_w \approx 3.5 \text{ nm} \) was estimated by subtracting to the vertical \( L_z \) simulation box size the average thickness of an homogeneous water slab with the same number of molecules (Luzzati argument). The current approach does not enable to disentangle the respective contributions of \( \eta \) and \( L_w \) in a single simulation. However, it is perfectly feasible to simulate a series of systems with identical number of lipids but increasing amounts of water, and perform a regression analysis as a function of \( 1/L_w \). In addition, the viscosity of the solvent is usually well known and can be obtained by standard simulation techniques such as the Green-Kubo integral of the transverse stress components [22]. We note that as expected, the friction coefficient associated to the CG dynamics is smaller than the experimental value \((\sim 4 \times 10^6 \text{ Pa s}^{-1}) \) by at least one order of magnitude [15, 16, 18]. Coarse-graining seems to have the effect of smoothing the interface between leaflets. However, even atomistic models fail to reproduce experimental values of \( b \) by a factor of 2 at least [18].

To conclude, we have introduced an original equilibrium fluctuation relation between the center of mass mutual diffusion coefficients of a simulated lipid membrane with periodic boundary conditions and the viscous dissipation coefficients (interleaflet friction and solvent viscosity) relevant to the motion in the bilayer plane. This result assumes that no lipid exchange takes place, and that solvent penetration into the membrane can be neglected. It is consistent with the use of a thermostat where the center of mass of the whole system is forced to be static. It is based on a macroscopic long range and long times hydrodynamic description of the mutual bilayer components displacements. It also disregards any sliding of the solvent at the bilayer interface, usually considered as negligible as a first approximation. The diffusion parameters introduced in the discussion depends on the area of the simulated system, very much like the Stokes sphere mobility depends on its radius. A
compromise must be found between increasing the system size to reach some hydrodynamic limit, and keeping it small enough to prevent Helfrich undulations \[26\] and preserving enough leafllet Brownian diffusion. Our method should also be valid for more complex lipid compositions provided the bilayer remains homogeneous. With very little extra-cost in terms of simulation and analysis, this result is poised to become a standard characterization of realistic numerical membranes, provided they are simulated long enough for the leafllet center of mass displacements to be estimated, i.e. long enough for the mean-squared displacements to have reached their asymptotic linear in time behaviors.

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Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

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