A Second Generation Mesoscopic Lipid Bilayer Model:

Connections to Field Theory Descriptions of Membranes and Nonlocal Hydrodynamics

Appendix Material

Gary S. Ayton, J. Liam McWhirter, and Gregory A. Voth

Center for Biophysical Modeling and Simulation and Department of Chemistry, University of Utah, 315 S. 1400 E. Rm. 2020, Salt Lake City, Utah 84112-0850

The following three appendices will give additional details to some of the results obtained in the main text.

Appendix A: Detailed Derivation of EM2

The EM2 models originates from a continuum model for the elastic energy of a membrane having a thickness h. This energy can be expressed in terms of bending and bulk expansion/contraction contributions as given in Eq. (2) in the main text.

The first step in deriving the EM2 equations from Eq. (2) in the main text is achieved by formally discretizing the continuum-level field integral. A membrane of area A is initially assumed to be perfectly flat and unstressed. The local density is then defined in terms of “macroscopic” delta functions as given in Eq. (2) in the main text. If the mass density is nearly uniform, then \( \rho(r)/\rho_0 = 1 \) where \( \rho_0 = \langle \rho(r) \rangle = N/(Ah) \), and the average is taken only over the
membrane surface. The next step requires inserting $\rho(\mathbf{r})/\rho_0$ into both terms in Eq. (2) in the main text.

Consider the bending energy component first. If the previous ratio of densities is inserted in the expression for $H_k$, and only uniform bends are treated with $R_i = R_j = R$, then $H_k$ becomes $H_{k,\text{eff}}$, where

$$H_{k,\text{eff}} = \frac{2k_c}{\rho_\Lambda} \sum_{i=1}^{N} \left[ \frac{1}{R_i} \right]^2. \tag{A1}$$

The “eff” stands for effective, because the approximation $\rho(\mathbf{r})/\rho_0 = 1$ has been made. The density $\rho_\Lambda$ is related to $\rho_0$ via $\rho_\Lambda = h\rho_0 = N/A$. Consider a small uniform bend of the entire membrane such that the actual or contour area of the membrane is fixed at the initial area $A$. After this bend the radius of curvature, $1/R_i$, can be found from the average bending deformation about particle $i$. Next, consider two points on the membrane separated by a distance $r_{ij} = |\mathbf{r}_i - \mathbf{r}_j|$, where $\mathbf{r}_i$ ($\mathbf{r}_j$) is the location of particle $i$ ($j$), and the two corresponding normal vectors to the membrane are denoted $\hat{\Omega}_i$, $\hat{\Omega}_j$. The angle between the two normal vectors, due to membrane bending, is given by $\delta \theta_{ij}$. In this way, for small $\delta \theta_{ij}$, $H_{k,\text{eff}}$ can be written as

$$H_{k,\text{eff}} = \frac{2k_c}{\rho_\Lambda} \sum_{i=1}^{N} \left( \frac{\delta \theta_{ij}}{r_{ij}^2} \right)^2,$$

$$= \frac{2k_c}{\rho_\Lambda} \sum_{i=1}^{N} \frac{1}{N_{c,i}} \sum_{j=1}^{N_{c,i}} \frac{(\delta \theta_{ij})^2}{r_{ij}^2}, \tag{A2}$$

$$= \Delta U,$$

where $N_{c,i}$ is the number of “j” EM2 particles within a circle of cutoff radius $r_c$ centered on particle $i$ and lying on the initially flat, unstressed membrane of area $A$. The average $\langle \cdot \rangle$ in Eq.
(A2) is over the j index. This change in energy, \( \Delta U \), due to the imposed bend can be rewritten as a sum of pair interactions, \( \Delta u_{ij} \), such that \( \Delta U = \frac{1}{2} \sum_{i=1}^{N} \sum_{j\neq i}^{N} \Delta u_{ij} \), and

\[
\Delta u_{ij} = \frac{4k_c}{\rho_A N_c} \left( \frac{\delta \theta_{ij}}{r_{ij}} \right)^2 \rightarrow r_{ij} \leq r_c.
\]

(A3)

\[= 0 \rightarrow \text{otherwise}\]

With EM2, a new pair interaction is employed where \( \Delta u_{ij} = u_{ij} - u_{ij}^0 \); \( u_{ij}^0 \) is the pair energy when the membrane is perfectly flat and the new pair interaction is given by

\[
u_{ij}(r_{ij}, \hat{\Omega}_i, \hat{\Omega}_j) = 4\epsilon \phi_{ij}(\hat{\mathbf{r}}_{ij}, \hat{\Omega}_i, \hat{\Omega}_j) \left( \frac{L_{\text{EM2}}}{r_{ij}} \right)^2,
\]

(A4)

where \( L_{\text{EM2}} \) is the fundamental length-scale of the quasi-particle. The actual functional form for \( \phi_{ij} \) can vary but it must satisfy a set of criteria. Most importantly, the leading order expansion of \( \phi_{ij} \) in \( \delta \theta_{ij} \) must be quadratic, i.e., to \( \sim (\delta \theta_{ij})^2 \) so that \( u_{ij} \) can be related to Eq. (A3) for \( \Delta u_{ij} \).

Furthermore, the choice for \( \phi_{ij} \) should result in low energy configurations where the unit vectors \( \hat{\mathbf{\Omega}}_i \) and \( \hat{\mathbf{\Omega}}_j \) are indeed normal to the local membrane surface. For example, consider choosing

\[
\phi_{ij} = \left( \hat{\mathbf{\Omega}}_i \cdot \hat{\mathbf{r}}_{ij} \right)^2 + \left( \hat{\mathbf{\Omega}}_j \cdot \hat{\mathbf{r}}_{ij} \right)^2.
\]

This form employs a spatial dependence similar to a dipole-dipole interaction; however, in this case an aligned configuration of normal vectors that are both perpendicular to \( \mathbf{r}_{ij} \) results in a low energy configuration. This interaction also satisfies the first criteria such that \( \phi_{ij} \equiv (\delta \theta_{ij})^2 / 2 \) for small deformations. In this way, the energy difference for a small bend or value of \( \delta \theta_{ij} \) is given by
\[ \Delta u_{ij} = 4\varepsilon \left( \frac{\delta \theta_{ij}}{2} \right)^2 \left( \frac{L_{EM2}}{r_{ij}} \right)^2. \] (A5)

If the two expressions for \( \Delta u_{ij} \) are compared, the parameter \( \varepsilon \) can be identified as
\[ \varepsilon \equiv 2k_c / \left( \rho^* N_{c,i} \right) \] where \( \rho^* = \rho_A L^2 \). Other possible candidates for \( \phi_{ij} \) may be employed; for example, \( \phi_{ij} = -\hat{\Omega}_{ij} \cdot \hat{r}_{ij} \left[ 1 - \left( \hat{\Omega}_{ij} \cdot \hat{r}_{ij} \right)^2 \right] \), which gives \( \varepsilon \equiv k_c / \left( \rho^* N_{c,i} \right) \).

The bulk elastic component, \( H_{\lambda, \text{eff}} \), can be similarly treated. Consider the substitution of \( \rho(r) / \rho_0 = 1 \) into \( H_\lambda \), for an initially flat, unstressed membrane. After a small uniform expansion of the whole membrane where the membrane remains flat, the effective discretized bulk response is given by
\[
H_{\lambda, \text{eff}} = \frac{1}{2} \sum_{i=1}^{N} \frac{h\lambda}{\rho_A} \left[ \frac{\Delta A}{A_0} \right]_i \equiv \frac{1}{2} \sum_{i=1}^{N} h\lambda A_{i0} \left[ 2\varepsilon_i \right]^2. \] (A6)

The local in-plane strain about particle \( i \), \( 2\varepsilon_i = \left( A_i - A_{i0} \right) / A_{i0} \), must be evaluated where \( A_{i0} = 1 / \rho_A \) is the initial area belonging to particle \( i \). Consider the situation of the initial, unstressed membrane for all particles \( j \) that lie within a small circular area, \( \pi r_c^2 \), of a preset cutoff radius \( r_c \) centered on \( i \). The initial particle separations are \( r_{ij}^0 \). If the number density is nearly uniform, and \( r_c \) is reasonably large then \( \rho_A = N / A \approx N_{c,i} / \left( \pi r_c^2 \right) \). In this way, the effective energy after uniform expansion can be written as
\[
H_{\lambda, \text{eff}} = \frac{1}{2} \sum_{i=1}^{N} \frac{h\lambda \pi r_c^2}{N_{c,i}} \left[ \frac{\Delta A}{A_0} \right]_i. \] (A7)
Now consider the quantity $\xi_i$, defined as

$$
\xi_i = \frac{1}{N_{c,i}} \sum_{j \neq i}^{N_i} 2\pi (r_{ij}^0)^2 \left[ \frac{r_{ij}^2 - (r_{ij}^0)^2}{(r_{ij}^0)^2} \right]^2
$$

$$
\equiv \frac{1}{N_{c,i}} \sum_{j \neq i}^{N_i} 2\pi (r_{ij}^0)^2 \left[ 2 \left( \frac{r_{ij}}{r_{ij}^0} \right) \right]^2
$$

(A8)

where $r_{ij}$ are the interparticle separations after the expansion. If both the fluctuations and magnitude of $\left( r_{ij} - r_{ij}^0 \right) / r_{ij}^0$ are small, then

$$
2 \left( r_{ij} - r_{ij}^0 \right) / r_{ij}^0 \equiv 2 \left( (r_{ij} - r_{ij}^0) / r_{ij}^0 \right) = \left( \Delta A / A_0 \right)_i.
$$

(A9)

The average $\langle \ldots \rangle$ here is over all the $N_{c,i}$ particles $j$ that lie within a distance $r_c$ of i on the initially unstressed membrane. With these substitutions, $\xi_i$ becomes

$$
\xi_i = \left[ \frac{\Delta A}{A_0} \right]^2 \frac{1}{N_{c,i}} \sum_{j \neq i}^{N_i} 2\pi (r_{ij}^0)^2
$$

$$
= \pi r_c^2 \left[ \frac{\Delta A}{A_0} \right]^2,
$$

(A10)

where it has been noted that

$$
\langle r^2 \rangle = \frac{\int_0^{r_c} \int_0^{2\pi} (r^2) r dr d\theta}{\int_0^{r_c} \int_0^{2\pi} r dr d\theta} = \frac{r_c^2}{2}
$$

(A11)

Therefore, the effective energy, $H_{\lambda,\text{eff}}$ can be written as

$$
H_{\lambda,\text{eff}} = \frac{1}{2} \sum_{i=1}^{N} \frac{\hbar \lambda}{N_{c,i}} \xi_i
$$

$$
= \frac{1}{2} \sum_{i=1}^{N} \sum_{j \neq i}^{N_i} 2\pi (r_{ij}^0)^2 \hbar \lambda \left[ 2 \left( \frac{r_{ij}}{r_{ij}^0} \right) \right]^2.
$$

(A12)
The original EM model, which was not derived by discretizing a continuum field theory description of a membrane, matches Eq. (A12) with the substitution of \( 2\pi(t_0^0)^2 / N_c \) with \( 1/\rho_A \), and with \( N_{c,i} = \langle N_{c,i} \rangle \).

**Appendix B: The WCA and BLOBs Mesoscopic Solvents**

EM2 requires an explicit solvent in order to capture the critical hydrodynamic interactions between the elastic membrane and the surrounding viscous solvent, which are in turn necessary for an accurate simulation of the membrane dynamics. There are a large number of coarse-grained representations of fluids at the mesoscale\(^2\)\(^-\)\(^12\) However, in keeping with the multiscale theme of this work, an alternative mesoscopic solvent model has been developed parameterized by simulation “measurements” made on an underlying atomistic-level simulation of the solvent of interest\(^1\)\(^3\), which is denoted as BLOBs. A detailed discussion of the BLOBs coarse-grained fluid model can be found elsewhere\(^1\)\(^3\), here, only the pertinent details will be reviewed.

The BLOBs coarse-grained fluid model utilizes atomistic-level data in order to uniquely parameterize it to a specific solvent at a specific temperature, density, and length-scale of coarse-graining. As such, different parameterizations will result if the underlying solvent of interest is changed, or if the state parameters are altered. Very briefly, an initial MD simulation of the solvent of interest is performed. Then, a single BLOB probe particle (much larger in size than an actual solvent molecule) is embedded in the system, where this probe picks up any local mesoscopic thermal fluctuations that are present. The single BLOB is constructed from the underlying atomistic-level fluid, thus it does not alter the structure or correlations that are present
in the system; however, it does get “driven around” by any local mesoscopic flows that are present.

The forces acting on the single BLOB due to the surrounding fluid can be calculated; thus, a Langevin-like model for the BLOB dynamics can be made. The important quantity is the BLOB force-force time correlation function, expressed as

\[ C_{FF}(t) = \langle F(t) \cdot F(0) \rangle \]

\[ F(t) = \sum_{i=1}^{N_A} f_i(t)p_i(t) \]  \hspace{1cm} (B1)

In this expression, the instantaneous BLOB force, \( F(t) \), is found from the underlying atomistic-level forces, \( f_i(t) \), via the switching function \( p_i(t) \). The switching function has the property of \( p_i(t) = 1 \) if solvent molecule \( i \) is within the BLOB at time \( t \), and is zero otherwise. The summation goes over all \( N_A \) molecules in the system. The BLOB probe itself is a spherical volume with radius \( r_c \) centered at some position \( R(t) \) (which does not have to correspond to the location one of the underlying molecules). As such, the BLOB dynamics, that is the rate of change of the BLOB flow, contains a convective component due to molecules entering and leaving the BLOB region. The resulting behavior of \( C_{FF}(t) \) will also depend on \( r_c \), the radius of the BLOB, which is much larger than the radius of a single solvent molecule. As such, the resulting coarse-grained probe dynamics are dependent not only on the underlying atomistic system, but also on the pre-selected degree of coarse-graining characterized by \( r_c \).

As previously mentioned, the BLOB force-force time correlation function determined from the probing BLOB simulation can be used to construct a Langevin-like model for the system. If the velocity of the BLOB is given by \( U_B(t) \), the corresponding Langevin equation is

\[ \frac{dU_B(t)}{dt} = -\alpha U_B(t) + \frac{F_B(t)}{m_B}, \]  \hspace{1cm} (B2)
where \( m_B \) is the average mass of the BLOB. If the random force \( F_B(t) \) dominates the drag force, 
\[-\alpha U_B(t),\]
in its contribution to the total force-force time correlation function, then \( F_B(t) \) can be related to the \( F(t) \) monitored during the probing BLOB simulation. Typically \( F(t) \) is found not to be truly random, but contains small residual molecular correlations which are reflected by the small, decaying oscillation in \( C_{FF}(t) \) found at long times.

As a brief digression, it should be noted that in Eq. (B2) it is assumed that \( U_B(t) \) is a peculiar velocity, such that 
\[
\sum m_B |U_B|^2 = 3N_D k_B T \quad \text{where} \quad N_D \quad \text{is the number of degrees of freedom.}
\]
If \( U_B(t) \) is not peculiar, i.e., it contains non-equilibrium flow modes for even very slow long wavelength modes, then Eq. (B2) cannot be used. For example, consider a solvent particle that is close to an undulating membrane surface where one of the membrane’s longest wavelength thermal undulation modes takes around a nanosecond or more to bend up then bend down, such that equipartition is satisfied. Now, consider examining the dynamics of a single solvent particle for a shorter time, say 100 picoseconds. In that time-frame, the solvent particle will be “carried” by this very slow undulation mode and as a result its velocity will contain a contribution from the velocity of the slow membrane undulation. If the disparity in time-scales between the particle’s inherent momentum change and the long wavelength membrane undulation is large, then the particle behaves as if it is immersed in an external flow; in this case, Eq. (B2) does not describe the total acceleration of the particle correctly.

Returning to the previous discussion, the total BLOB force, \( F(t) \), is related to or approximated by a random force \( F_B(t) \), whose time correlation function decays linearly according to
\[
\langle F_B(t) \cdot F_B(0) \rangle = C_{FF}(0)(1 - t / \tau). \quad \text{(B3)}
\]
Here \( \tau \) corresponds to the time it takes for \( C_{\text{FF}}(t) \) to decay to zero, and has a value of around 0.04 ps, independent of \( r_c \). In other words, the original \( C_{\text{FF}}(t) \), as calculated from atomistic-level MD, is approximated by a linear decay, originating at the time zero value of \( C_{\text{FF}}(t) \), that is zero a short time \( \tau \) later. As such, within the Markovian approximation, the drag, \( \alpha \), is given by

\[
\alpha = \frac{1}{3m_B k_B T} \left( \frac{C_{\text{FF}}(0) \tau}{2} \right),
\]

(B4)

where \( k_B \) is Boltzmann’s constant and \( T \) is the thermodynamic temperature. Note that \( \delta t_{\text{BLOBs}}=0.04 \) ps is the upper limit for the choice of time-step that can be used during a BLOBs solvent simulation described next. This parameter is strongly related to the initial decay of the atomistic-level force-force time correlation function.

The BLOBs coarse-grained fluid creates a space filling system of \( N_B \) BLOBs particles. It should be noted that an additional conservative, repulsive force must be included in Eq. (B2), because without the conservative force the BLOBs particles would have an equation of state corresponding to an ideal gas. The existence of a pair-wise additive, conservative, and repulsive force between mesoscopic fluid volumes can be justified from Smooth Particle Applied Mechanics (SPAM).\(^{14-16} \) Furthermore, the exact functional form of the repulsive interaction can be varied, since it determines how the mass density of the fluid is distributed.

The equations of motion for the BLOBs fluid can be compactly expressed as

\[
\begin{align*}
\dot{r}_i &= \frac{p_i}{m_B} \\
\dot{p}_i &= F^T_i - \gamma_i p_i, \\
F^T_i &= F^C_i + F^R_i
\end{align*}
\]

(B5)
where $F_i^C$ is the conservative force, $F_i^B$ is the pseudo-random BLOBs force, and $-\gamma_i p_i$ is a Nose-Hoover thermostating term. In the present case, $F_i^C$ arises from a pair-wise additive WCA interaction, expressed as

$$F_i^C = \sum_{j \neq i}^N f_{ij}^C,$$

where

$$f_{ij}^C = -\nabla r_{ij} u_{ij}^C.$$

In this expression, $L$ is the length-scale of the BLOBs particle and $r_{ij}$ is the distance between BLOB $i$ and $j$ in the BLOBs solvent. The BLOBs force, $F_i^B$, generates a highly uncorrelated force with an arbitrary direction (not along the inter-BLOB vector connecting two BLOBs particles, $r_{ij}$), but whose square magnitude recovers the original $C_{FF}(0)$. The BLOBs force is calculated via

$$F_i^B = \sum_{j \neq i}^{Na} f_{ij}^B,$$

where

$$f_{ij}^B = \sum_{k} a_k \sin(k \cdot r_{ij}) k.$$

Here $\{k\}$ is an orthogonal basis set of 6 vectors, $\{k\} = \{(\pm k,0,0),(0,\pm k,0),(0,0,\pm k)\}$ where $k = 2\pi n / L_B$, $n$ is an integer, and $L_B$ is the BLOBs cutoff. Within the sum of $j$ in Eq. (B8), only those $j$ particles within a distance $L_B$ are included; $L_B$ can be different from $L$, the length-scale for the conservative interaction. For large enough $n$, the rapid oscillations in the sinusoidal term
result in nearly random pair forces between the BLOBs particles, yet the instantaneous momentum of the whole BLOBs fluid is conserved since \( f_{ij}^n = -f_{ji}^n \). The coefficient, \( a_k \) is set to

\[
a_k = \frac{1}{k} \sqrt{\frac{C_{FF}(0)}{6\bar{n}_c}}, \tag{B9}
\]

where \( \bar{n}_c \) is the average number of BLOBs particles found within the cutoff distance from a given BLOBs particle.

Appendix C: EM2-Explicit Solvent Equations of Motion

In general, the EM2 membrane, consisting of \( N \) EM2 particles, is immersed in \( N_B \) mesoscopic solvent particles such that the total number of particles is \( N_T = N + N_B \). The equations of motion for the translational dynamics of the coupled EM2-Solvent can be expressed as

\[
\dot{r}_i = \frac{p_i}{m_i}, \tag{C1}
\]

\[
\dot{p} = F_i - \gamma_i p_i,
\]

where \( p_i = m_i v_i \) is the momentum of particle \( i \) (whether it be a solvent or EM2 particle), \( m_i \) is the corresponding mass, \( F_i \) is the total force on \( i \), and \( \gamma_i \) is a drag force. In more detail, the force on particle \( i \) can be written as

\[
F_i = a_i F_i^{EM} + (1 - a_i) F_i^{SOL}, \tag{C2}
\]

where \( a_i = 1 \) if particle is an EM2 particle, and is zero otherwise. The EM and SOL force components are expressed as
\[ \mathbf{F}^{\text{EM}}_i = \sum_{j \neq i} f^{\text{EM}}_{ij} + \sum_{j=1}^{N_b} f^{\text{EM/C}}_{ij}, \]
\[ \mathbf{F}^{\text{SOL}}_i = \sum_{j \neq i} \left[ f^C_{ij} + b_{ij} f^B_{ij} \right] + \sum_{j \neq i} f^{\text{EM/C}}_{ij}, \]  
\[(C3)\]

where \( f^{\text{EM}}_{ij}(\mathbf{r}_{ij}, \hat{\mathbf{\Omega}}_i, \hat{\mathbf{\Omega}}_j) = -\nabla_{\mathbf{r}_{ij}} \left[ H_{k_{ij}, \text{ eff}} \left( \{ \mathbf{r}_{ij}, \hat{\mathbf{\Omega}}_i, \hat{\mathbf{\Omega}}_j \} \right) + H_{k_{ij}, \text{ eff}} \left( \{ \mathbf{r}_{ij} \} \right) \right] \), and \( b_{ij} = 1 \) if a BLOBs force, \( f^B_{ij} \), is included. Details concerning the BLOBs-EM2 interaction will be discussed shortly. The final contribution arises from the EM2-solvent interaction, \( f^{\text{EM/C}}_{ij} \). The drag term, \( \gamma_i \), is determined by a Nose-Hoover feedback; the workings of this feedback depend on whether particle \( i \) is a membrane or solvent particle.

Both the membrane and solvent particles are locally thermostatted using a profile unbiased thermostat (PUT). PUTs have been regularly employed in non-equilibrium molecular dynamics (NEMD) simulations\(^1\)\(^17\) to ensure that the calculation of the local temperature does not include contributions from any external flows that might be present. The concept behind a PUT thermostat is very simple. In order to account for possible flow components in the fluid momentum and/or very slow equipartition modes in a system, the temperature is evaluated using only the high frequency/small wavelength momentum components. This is accomplished by subdividing the system into smaller cells; then, the instantaneous “kinetic” temperature is evaluated using only the local peculiar velocities that are present. The cell size is large enough that a sufficient number of particles is instantaneously present.\(^17\) As such, the low frequency, long wavelength modes are not entered into the calculation of the kinetic temperature. When long wavelength modes are present (for example, the very slow undulation modes in a membrane) they can begin to act like persistent flow modes; if these modes are included in the evaluation of the temperature (to be used in, for example, a Nose-Hoover thermostat), the system will always appear to be a bit “hotter” than it actually is. In the case that a very slow mode is present and
included in this evaluation, the thermostatting mechanism can actually freeze the system. The PUT solves this problem by subdividing the system into a number of smaller cells, subtracting off any local “flow modes”, accounting for the lost degrees of freedom correctly, and then employing the remaining fast velocity modes to calculate the instantaneous kinetic temperature. In this way, the Nose-Hoover equations of motion are expressed as

\[
\dot{\gamma}_i = \frac{a_i}{Q}(T_k^{EM} - T_0) + \frac{(1 - a_i)}{Q}(T_k^{SOL} - T_0);
\]

\[
\sum_{i=1}^{N} m_i \frac{|v_i - u_{EM}|^2}{2} = \frac{3(N - 1)k_B T_k^{EM}}{2};
\]

\[
\sum_{i=1}^{N_{cell}} m_i \frac{|v_i - u_{cell}|^2}{2} = \frac{3(N_{s,cell} - 1)k_B T_k^{SOL}}{2},
\]

where \( u \) is the local flow in a particular cell. The instantaneous kinetic temperature is \( T_k \) while \( T_0 \) is the set, target thermodynamic temperature of interest. For the membrane, just the total flow of the membrane, \( u_{EM} \), is subtracted off as, although the total momentum of the system is zero by definition, the membrane can still “drift” in any direction. Without the PUT, this slow drift will be interpreted as being related to the temperature of the membrane.

For the surrounding solvent, the simulation cell was divided into 4 to 8 smaller cells, depending on the system size, where each cell contained instantaneously \( N_{s,cell} \) solvent particles. Particles are free to cross between cells, as they are only used to determine the local temperature. The local flows of the membrane, \( u_{EM} \), and the solvent, \( u_{cell} \), are given by
The orientation dynamics component of EM2 (i.e., $H_{k,cell}$) can be treated by standard schemes\textsuperscript{18} by introducing a torque defined as

$$\tau_{ij} = -\hat{\Omega}_i \times \nabla \hat{\Omega}_i \Delta u_{ij}(r_{ij},\hat{\Omega}_i,\hat{\Omega}_j),$$

(C6)

where $\Delta u_{ij}(r_{ij},\hat{\Omega}_i,\hat{\Omega}_j) = u_{ij}(r_{ij},\hat{\Omega}_i,\hat{\Omega}_j)$ and $u_{ij}$ is given by Eq. (A4). Since the EM2 membrane is not subject to BLOBs type random forces, standard thermostatting schemes for the rotational component of the dynamics can be employed.

It should be noted that the PUT was not required when the EM2 membrane was immersed in the WCA conservative solvent; however, the PUT did have an effect when the mesoscopic BLOBs solvent was employed. In the latter case, subtracting off the slow flow modes that were coupled to membrane undulations was necessary to recover the correct undulation magnitudes.\textsuperscript{19} This effect can be attributed to the fact that $\langle \gamma_i \rangle > 0$ for $a_i=0$, $b_{ij}=1$, (i.e., the solvent) and the fact that the BLOBs force significantly “slows” the already slow long wavelength undulation dynamics, thus further increasing the disparity in time-scales between the fast and slow modes in the system.
References
