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## Authors
Sodt, Alex J
Head-Gordon, Teresa

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# An Implicit Solvent Coarse-Grained Lipid Model with Correct Stress Profile

**Alex J. Sodt and Teresa Head-Gordon***

*Department of Bioengineering, University of California, Berkeley*

*Berkeley, California 94720 USA*

We develop a coarse-grained parameterization strategy for lipid membranes that we illustrate for a DPPC bilayer. Our coarse-graining approach eliminates the high cost of explicit solvent but maintains more lipid interaction sites. We use a broad attractive tail-tail potential and extract realistic bonded potentials of mean force from all-atom simulations, resulting in a model with a sharp gel to fluid transition, a correct bending modulus, and overall very reasonable dynamics when compared to experiment. We also determine a quantitative stress profile and correct breakdown of contributions from lipid components when compared to detailed all-atom simulation benchmarks, which has been difficult to achieve for implicit membrane models. Such a coarse-grained lipid model will be necessary for efficiently simulating complex constructs of the membrane, such as protein assembly and lipid raft formation, within these non-aqueous chemical environments.

*Corresponding author

## INTRODUCTION

Considerable physical insight into the protein folding process has been gained from computer simulation with "minimalist" protein models[1-3]. Minimalist protein models integrate out the atomic detail of individual amino acid residues, often only retaining an $\alpha$-carbon trace to represent the protein chain. This level of coarse-grain modeling has proved appropriate for protein folding studies, explaining why native sequences fold more rapidly and more reliably relative to poorly designed or arbitrary heteropolymer sequence[4, 5], qualitatively reproducing differences in folding kinetics of small and large proteins[6], and have been used to clarify the role of native state topology and minimal energetic frustration in the determination of folding rate and mechanism[7-15]. A simplifying feature of these coarse-grained protein models has been the implicit treatment of the aqueous solvent environment, which is absorbed in the effective potentials among the bead residues, solvent frictional forces, and random collisions exerted on the moving chain described by Langevin dynamics.

However, a significant and functionally important fraction of proteins reside natively within a very different environment, i.e. the lipid bilayer of the cell membrane as opposed to the extracellular or cytosol regions. These so-called transmembrane (TM) proteins are involved in a wide variety of biological processes, including channels that regulate cellular ion concentration, receptors involved in signal transduction, and membrane transport proteins which assist non-TM proteins to traverse the lipid bilayer. Given the large spatial and time scales of the membrane bilayer environment which mediate TM protein interactions, mesoscale lipid models may be even more fruitful in providing physical insight and qualitative description of experimental observables than their coarse-grained aqueous protein counterparts. Even so, the membrane bilayers themselves also assemble and are stabilized by a surrounding aqueous environment, requiring a decision in the coarse-graining process for lipid chemistry as to whether the solvent environment will be implicitly or explicitly described[16].

The successes of explicit solvent coarse-grained lipid models have been recently reviewed by Venturoli et al[17]. Coarse-graining strategies such as that used in the MARTINI model[18, 19] seek to retain many of the same features of the all-atom solvent and lipid models such as explicit Coulomb forces. It has been used to study protein insertion and assembly in the bilayer, as well as the properties of lipid mixtures including the addition of cholesterol, to name a few applications. Dissipative particle dynamics (DPD) simulations, which conserve local angular momentum even while employing random/frictional forces, allow for investigation of even larger length and time scales, and have been used to investigate, for

example, the effects of tail stiffness on bilayer properties[20], the effects of non-ionic surfactants[21], and the hydrophobic matching of embedded proteins[22]. It should be noted that the computational time spent on explicit solvent interactions and forces is the dominant contribution for these coarse-grained lipid model simulations.

However, in spite of their cost reduction, implicit solvent models might be expected to have a more difficult time reproducing the correct physical behavior of lipid bilayers than if an explicit solvent is employed. Simple Lennard-Jones interactions for the tail-tail interactions do not appear to adequately stabilize the biologically relevant fluid phase, leading to models that crystallize or don't form stable bilayers, and alternative efforts employing many-body potentials[23-25] or anisotropic interactions[26] did not fundamentally overcome this problem. However, in 2003 Farago employed a simple three-site lipid model with six interaction types, and was able to obtain a fluid bilayer[27]. Deserno and co-workers investigated how a broad, attractive tail-tail potential could stabilize the fluid phase[28, 29], presumably because of the entropic gain of the expanded minimum. Brannigan et al. developed a lipid model with an interface bead at the head-tail intersection whose interactions have a less-steep curvature and were also able to simulate the fluid phase and aspects of an all-atom stress profile[30]. The recent review by Brannigan and co-workers provides a nice summary of mesoscale lipid models in the context of an implicit model for aqueous solvent[31].

In this work, we present a new implicit solvent lipid model for dipalmitoylphosphatidylcholine (DPPC) based on a parameterization strategy that should be readily extendable to other lipid types. The primary idea is that in order to develop a membrane bilayer model with solvent represented implicitly, we require a more explicit representation of the lipid itself, with the number of interaction sites intermediate between all-atom simulations and the mesoscale models developed previously[16]. In this approach we have combined the simplicity of the lipid-lipid interactions of previous implicit solvent models, but with more realistic geometric parameters derived from all-atom simulations. We show that we not only observe a gel-fluid phase transition, but our bilayer has a stress profile that gives good quantitative agreement with all-atom stress profiles without needing to incorporate interface beads. The bending modulus of our model is within the (broad) range of experimental uncertainty, so the model shows promise for describing large lipid formations with substantial curvature, i.e. vesicles. We quantify the accelerated timescales of the bilayer interior by calibrating against the parent all-atom simulation, allowing us to determine a scaling factor that shows our model reproduces the diffusion constant as determined by experimental measurements. The timescales for the undulation modes of the

bilayer have wavelength scaling that is too fast overall, perhaps a limitation of a solvent-free model that would not describe direct water-lipid interactions important for some relaxation processes.

## METHODS

### *Simulation protocol*

We use constant-temperature Langevin dynamics with friction parameter $\zeta$ = 0.05 to simulate the average properties of the DPPC lipid bilayer. Bond lengths are held rigid by using the RATTLE algorithm[32]. All simulations are performed in reduced units, with mass $m$, energy $\varepsilon_H$, and $k_b$ all set equal to unity. The timestep used for propagation was $0.0025\tau$ (and $0.01\tau$ for the long time bending modulus calculations). While the small time step is important to avoid simulation artifacts in the calculation of the pressure tensor[33], we found that the resulting curves were virtually the same using either $0.0025\tau$ or $0.01\tau$, in which data was collected for over $1500\tau$. Periodic boundary conditions were applied, and interactions followed the minimum-image convention as the model incorporates no long-range forces. To best approximate a biological membrane, simulations were performed with zero lateral surface tension (isotropically scaling the x and y box lengths together), using the algorithm of Kolb and Dunweg[34]. The position and velocity scaling appropriate for the zero-tension algorithm was applied to the center-of-geometry positions of the molecules. For the all-atom DPPC trajectories, we used three 50 nanosecond segments from Klauda et al., and the simulation protocol is described therein[35, 36].

### *Calculated properties*

We calculate time autocorrelation functions of lipid tail bending angles in order to quantify the accelerated time scale of our coarse grained model. The bending angle autocorrelation function is a time average of the fluctuations of the angle from its average value, normalized by the average fluctuation, where angle brackets denote an average over time $t'$

$$C_{\theta\theta}(t) = \frac{\left\langle (\theta(t'+t) - \bar{\theta})(\theta(t') - \bar{\theta}) \right\rangle}{\left\langle (\theta(t') - \bar{\theta})^2 \right\rangle} \tag{1}$$

We evaluate the diffusion constant from the mean square displacement (MSD) of the lipid segments using the Einstein relation

$$D_t = \frac{1}{2M} \lim_{t \to \infty} \frac{d}{dt} \left\langle |\mathbf{r}(t) - \mathbf{r}(0)|^2 \right\rangle \tag{2}$$

where $\mathbf{r}(t)$ is the position vector of each CG center at time $t$ and M is the dimensionality.

We also compute the bending modulus of the DPPC bilayer as described by Cooke and Deserno[28, 29]. The average lipid tail position is averaged and interpolated on a 16 by 16 grid, and the average power fluctuations are measured and compared to the continuum model[37, 38]:

$$E = \frac{1}{2}\int dxdy[\kappa(\Delta h)^2 + \Sigma(\nabla h)^2] \tag{3}$$

where $\kappa$is the bending modulus and $\Sigma$is the lateral tension, and *h(r)* is the height of the average tail positions. It is defined by the Fourier transform.

$$h(r) = \sum_q h_q \exp(iq \cdot r) \tag{4}$$

where $h_q$ is the reciprocal space representation of the bilayer height, $q$ is the frequency, and using the equipartition of energy, the power spectrum is given by

$$\left\langle h_q^2 \right\rangle = \frac{k_b T}{L^2[\kappa q^4 + \Sigma q^2]} \tag{5}$$

where L is the lateral box length.

To accelerate the slow relaxation time scales of the long wavelength modes we use the mode-excitation Monte Carlo (MEMC) steps of Farago[39] in addition to our Langevin propagation (see [40] for an exposition on using Monte Carlo moves in addition to molecular dynamics to sample slow degrees of freedom). Monte Carlo moves are attempted every 20 time-steps, with MEMC steps of the form

$$\Delta z = \sum_i \varepsilon_i \cos(q_x^i r_x + q_y^i r_y + \alpha_i) \tag{6}$$

where $\boldsymbol{q}$ is of the form $\frac{2\pi}{L}(n_1, n_2)$, $n_1, n_2 = 0,1,2,...$ and where $n_1^2 + n_2^2 \le 9$, so that the slowest modes are accelerated. The amplitude of the steps, $\boldsymbol{\varepsilon_i}$, is chosen to maximize the steps of the low energy, long wavelength modes and is proportional to $n^{-1}$ ($n^{-2}$ proportional amplitudes resulted in disproportionately rejected long wavelength steps) with amplitude chosen to achieve an optimal Monte Carlo move acceptance ratio, adapted from [39]. We also increase the Langevin friction/noise parameter to 0.5 from 0.05 for the bending modulus calculations to even more rapidly equilibrate the large

wavelength modes. For large enough wave vectors $q$, we fit the undulation amplitude spectrum to Eq. (5) with the tension and bending modulus as adjustable parameters.

Finally, we evaluate the stress profile as described by Goetz and Lipowsky[41], which was based principally on the analysis of Schofield and Henderson[42]. Additionally, as we are using constraints, we include contributions from the constraints and kinetic energy anisotropy, similarly to the work of Lindahl and Edholm[43]. We use the velocity Verlet propagation algorithm such that our contribution from the constraint to the stress profile is $m_i \frac{\Delta v_i}{\Delta t}$, where $\Delta v_i$ is the vector modification to the velocity of particle $i$ (which has unit mass in our model) due to the RATTLE constraints during the time step. We then plot the lateral minus normal pressure as a function of position along the bilayer normal, z. As the pressure is not a well-defined local property, some amount of ambiguity is inevitable, which has been discussed previously[41, 42].

***DPPC Lipid Model***

Our coarse-grained model of DPPC molecules first reduces groups of three or four methylene moieties of the hydrocarbon tails to a single site (fifteen alkyl carbons are reduced to a total of 4 beads), while the ester, phosphoric acid, and choline groups each constitute a single site, each positioned at the center-of-geometry of the original all atom model for each group (Figure 1). The total coarse-grained lipid-lipid interaction potential is described as bead interactions between lipid segments of the general form

$$V_{lipid-lipid} = V_{bend}(\theta) + V^{like}_{head-head}(r) + V^{unlike}_{head-head}(r) + V_{head-tail}(r) + V_{tail-tail}(r) \quad (7)$$

where $V_{bend}(\theta)$ corresponds to the internal lipid geometry potential of the lipids, $r$ is the distance between lipid bead centers, and the remaining terms in Eq. (7) are through-space isotropic interactions between different lipid segments. The bonds are constrained to the $r_0$ values listed in Table 1 for bonded centers based on the labeling scheme of Figure 1.

The DPPC model extracts its internal geometry potential from an all-atom simulation of the fluid phase by collecting the distribution of individual lipid geometries within a bilayer, then Boltzmann inverting them to extract a potential of mean force for all bending potentials. The resulting bending potentials are computed as

$$V(\theta) = -k_b T \ln[\rho(\theta)\sin^{-1}(\theta)] \tag{8}$$

where $\rho$is the density of $\theta$ angles observed between three coarse-grained centers during a trajectory of an all-atom simulation, and which is weighted by the volume factor $\sin^{-1}(\theta)$. The region near the minimum of the potential of mean force is used to define the equilibrium angle $\theta_0$, and the curvature near the minimum is used to define the force constant $k_\theta$. The functional form for $V_{bend}(\theta)$ was chosen to have their second derivative at $\theta_0$ to be $k_\theta$, and to have a zero derivative at $\theta = \pi$. For bending potentials with equilibrium geometry corresponding to $\theta_0 = \pi$, the functional form used in the coarse grained model is

$$\begin{aligned} V_{bend}(\theta) &= k_\theta\,[\cos(\theta)+1] \qquad \theta > \frac{\pi}{2} \\ &= -k_\theta\left(\theta - \frac{\pi}{2}\right) \qquad \theta \le \frac{\pi}{2} \end{aligned} \tag{9}$$

For bending potentials with equilibrium geometry corresponding to $\theta_0 \neq \pi$, the functional form used in the coarse grained model is

$$V_{bend}(\theta) = -k_\theta \cos^{-1}\left(\frac{\theta_0}{2}\right)\left[\cos\left(\theta - \frac{\theta_0}{2}\right) + \theta \sin\left(\frac{\theta_0}{2}\right)\right] + C \tag{10}$$

Because $V_{bend}(\theta)$ is a potential of mean force, it includes in addition to bond angle deformations other geometric components such as dihedral potentials, local 1-4 electrostatics and even constraint forces from the all-atom simulation. Therefore we do not need to define a CG dihedral angle potential to differentiate between gauche and trans conformations, and so a dihedral potential has been ignored in our model Table 2 reports the bending potential parameters based on the labeling scheme of Figure 1.

The head group interactions (for DPPC the phosphoric acid and choline groups) are approximated as a repulsive potential for like-charged group interactions (similar to our protein model)

$$V^{like}_{head-head}(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} + \left(\frac{\sigma}{r}\right)^{6}\right] \tag{11}$$

where $\sigma$ is the effective bead size and $\varepsilon$ is the interaction strength; the model was insensitive to using $r^{-12}$ or the Weeks Chandler, Andersen[44] functional forms; the same functional form is used to

approximate the head-tail interactions, $V_{head\text{-}tail}(r)$. The standard Lennard Jones potential is used for oppositely charged head group interactions.

$$V_{head-head}^{unlike}(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] \tag{12}$$

The tail-tail interactions, however, require more care in their parameterization to be able to differentiate the bilayer fluid phase from the gel phase. In this case, the work of Cooke, Kremer, and Deserno[29] found that spatially extending the basin of lipid-lipid interaction was able to successfully recover the fluid phase. We have used the particular functional form for the lipid tail hydrocarbon and ester interactions due to Cooke and Deserno[28]

$$V_{tail-tail}(r) = \begin{cases} 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] & r < r_c \\ -\varepsilon & r_c < r < r_c + w_f \\ 4\varepsilon\left[\left(\frac{\sigma}{r - w_f}\right)^{12} - \left(\frac{\sigma}{r - w_f}\right)^{6}\right] & r_c + w_f < r < w_{cut} \end{cases} \tag{13}$$

where $w_{cut}$ is the interaction cutoff, $w_f$ is the stretch parameter to flatten the LJ basin, and $r_c = 2^{1/6}\sigma$. The stretch parameter $w_f = 0.25\sigma$ was optimized to obtain a reasonable value for the change in area per lipid from the gel to fluid phase. The interaction strengths $\varepsilon$ used in Eqs. (11)-(13) were varied to reproduce, approximately, the area per lipid distribution in the all-atom simulation (data not shown), while $\varepsilon$ was also tuned to a value that places the gel-fluid phase transition just below T=1.0, with T=1.0 set as a rough approximation of physiological temperature. The interaction distance cutoff was set to $w_{cut} = 6\sigma$. All lipid-lipid interaction parameter values for the DPPC lipid model are reported in Table 3.

## RESULTS

### *Internal Bilayer Timescales*

The energy scale of our coarse-grained model is tuned to the gel-fluid phase transition. This leaves the timescales somewhat undetermined, as the well-depth of the tail-tail interaction now represents not just the forces between the constituent atoms of the tails, but also the essentially bilayer-specific hydrophobic interactions with respect to the implicit solvent. If the time unit is determined by straight

unit conversion, the timescales would be a factor of 13.3 times faster. Instead, we characterize the timescale of our model by matching the relaxation times of the lipid tail bends of the all-atom simulations to the relaxation times simulated by the coarse-grained model. The dynamics at the bilayer surface are likely to be much faster than in the bilayer interior, as there is no water to prevent rapid movements of the positively charged head group, so we restrict ourselves to the tail motions. In Figure 2a we plot the time correlation function (Eq. 1) of the all-atom model with sites corresponding to the reduced representation, and the same in Figure 2b for the coarse-grained simulation for the bends 5-6-7, 6-7-8, 9-10-11, and 10-11-12. Dividing three independent 50 ns all-atom simulations into five 10ns parts each (to estimate error bars) and fitting the autocorrelation time to exponential decay (with $\Delta t$ between 50 ps and 500 ps), yields tail bending relaxation timescales of 726 +/- 70, 570 +/- 64, 778 +/- 63, and 654 +/- 50 ps, for bends 5-6-7, 6-7-8, 9-10-11, and 10-11-12, respectively. The corresponding timescales for the coarse-grained simulation were 39.3 +/- 2.47, 20.8 +/- 1.77, 29.6 +/- 2.23, and 21.3 +/- 2.29 $\tau$, for the same bends. We find that, by interpretation of the bending relaxation timescales of the all-atom simulations, the coarse-grained time unit, $\tau$, is 24 +/- 1.6 ps, a factor of almost two in acceleration of the timescale compared to a direct mapping of the units.

***Lipid Model Properties***

Table 4 reports the area per lipid and tail bend order parameter values against temperature, for our DPPC model. The transition from the gel to fluid phase at T~0.95 exhibits a marked increase in the area per lipid values, with the area approaching that of the parent all-atom simulation between around T=1.05 and T=1.10 (~65 $Å^2$). The experimental value of real phospholipid membranes is between 55 and 75 $Å^2$.[45] Along with the change of the tail-bend distribution indicating alkane melting (Table 4) these properties are prime indicators of the presence of a gel-fluid phase transition in our model.

Table 4 also reports the diffusion coefficients as a function of temperature. We convert the diffusion constant into real units assuming a coarse-grained time unit tau of 24 ps (see section above on internal bilayer timescales). The coarse-grained diffusion constant nicely matches the reported experimental values of the DPPC diffusion constant[46], approximately 1e-7 $cm^2$ $s^{-1}$. Lipid flip-flop, the exchange of lipids between the inner and outer leaflets of the bilayer, has been characterized experimentally to have a very slow timescale (hours) in model membranes, although when catalyzed it is much faster[47]. An all-atom simulation predicts that the barrier for DPPC flip-flop is 75 kJ/mol[48], a value that matches well the experimental prediction of the barrier[49]. As we do not observe any flip-flop events in our simulations (with total simulation time on a millisecond time scale), we do not estimate the rate from

our model since obviously the activation barrier is quite high. More coarsely grained simulations do observe lipid flip-flop events[28], consistent with a dramatic lowering of the activation energy for flip flop and hence very large acceleration of the timescale.

The bending modulus or bending stiffness measures the energetic cost per unit area of imposing a local curvature. Figure 3 shows the log-log plot of the power spectrum vs. $q$. A least-squares fit at low values of $q$, using $\kappa$ and $\Sigma$ in Eq. (5) as adjustable parameters, determined a bending modulus value of our coarse-grained DPPC bilayer of ~18.9 $k_bT$, nicely in the region of the experimental values of ~8-40 $k_bT$, whose broad value range depends on the experimental technique[50]. We also evaluated the relaxation rates of the undulation modes of our DPPC model. The bending modulus relaxation timescale is too fast, with the longest relaxation mode faster by ~3 in our model when compared to experiment. Furthermore the experimentally measured time correlation function scaling with wavelength $q$ for DPPC[51]

$$I(q,t) \propto exp[-f(q)t] \tag{13}$$

measures $f(q) \propto q^{2.5+/-0.5}$, which is intermediate between a free membrane with a thick water layer where $f(q) \propto q^3$ and a membrane dominated by strong coupling between the leaflets where $f(q) \propto q^2$. Because our model lacks explicit solvent, our model corresponds more closely to scaling consistent with the friction between layers with $f(q) \propto q^{1.5}$. Furthermore, we may be measuring a residual tension that is affecting the dynamical relaxations, and it might be necessary to use an alternate surface tension definition to eliminate this free-energy tension[52]. Alternatively, relaxing the bond constraint and using the full tension (rather than center-of-mass tension) in the pressure control algorithm may reduce the residual tension and alter the scaling.

The stress profile of a membrane bilayer reflects the internal forces that enforce the lipid bilayer structure[43]. Figure 4a shows the total CG lipid model stress profile ($\frac{1}{2}p_{xy} - p_z$) plotted against the distance from the midplane of the bilayer along the normal direction, and in Figure 4b we break down the stress contributions from the nonbonded interactions of the choline, phosphoric acid, and tail groups as well as geometric contributions arising from SHAKE constraint forces, bond angle deformations, as well as anisotropy of the kinetic energy component of the pressure. Positive stress corresponds to repulsive interactions that expand the membrane and negative stress to attractive interactions that contract the system.

Our stress profile shows the positive pressure in the lipid tail interior seen in all atom simulations[43, 53], and with approximately the same magnitude (oscillations around 225 bar for our coarse grained model, and oscillations around approximately 100 bar for the all-atom model in [43]). The oscillations of the positive stress in the bilayer interior are consistent with the degree of coarse-graining in our model, that is, oscillations on the order of a bead-width. At the head/tail interface of the stress profile is a region of negative stress, acting to reduce the projected area of the bilayer. The negative stress in the interface region peaks at approximately -600 bar and acts over a region of approximately 0.75 nm, quantitatively consistent with Lindahl and Edholm[43]. The stresses in the head group region are slightly weaker than for the all-atom model, but are consistent with a peak of positive stress at the surface of the bilayer.

When comparing the interaction breakdown of the stress profile found from all-atom simulations[43] to that determined from our CG model in Figure 4b, we see that lack of electrostatics is not a limiting feature in our model. In Figure 7 of [43] that describes the all-atom stress profile, the electrostatics do not contribute in the hydrophobic tail region, and the attractive long-ranged electrostatics largely cancel the repulsive short-ranged (so called 1-4) interactions in the head group region. Thus the remaining Lennard-Jones non-bonded interactions of the CG and all-atom model are consistent in giving positive stress in the tail region due to tight packing and resulting steric repulsions and negative stresses arising from net cohesive forces from the headgroup interactions. From a free energy perspective, the fluidic center of the membrane would like to entropically expand but is held together by the attractions among the head groups, which is an alternative way of analyzing the stress profile. Also consistent between the all atom simulations and our CG model is the largely negative stress contribution from the geometric terms in the tail region and positive stresses in the headgroup region. This agreement is not surprising based on our parameterization strategy in which the CG bond angle potential is a free energy description of the all-atom SHAKE bond constraints, bond angles, dihedral angle potentials, and local 1-4 electrostatic forces that contribute to positive stress near the bilayer surface.

## DISCUSSION

The stress profile is a particularly important property of a lipid bilayer, because the lipid packing stress is thought to closely influence the structure and function of membrane-embedded channels, for example, by accommodating macromolecular conformations that expand or contract normal to the bilayer, or tangentially at the bilayer midpoint[54]. In particular, it has been shown that the lipid packing

environment affects the folding of bacteriorhodopsin[55]. The stress profile is difficult to measure at high resolution experimentally[56], and thus has been studied by a number of all-atom simulation studies[43], including variations in cholesterol concentration[53], lipid type[57], and chain unsaturation[58]. Since the stress profile has been a target of a number of coarse-grained lipid models, and given the experimental uncertainties in determining a quantitative stress profile, stress profiles derived from all atom simulations provide a benchmark for mesoscale membrane models.

The explicit solvent coarse-grained generic amphiphiles by Goetz and Lipowsky[41] has many of the correct features of the stress profiles of all-atom simulations, but has a significant negative peak at the bilayer midpoint, with the implicit solvent coarse-grained model of Brannigan et al. showing a similar result[30] when their sign convention is adapted to our lateral minus normal sign convention. The recent implicit solvent lipid model of Izvekov and Voth[59] displays some of the same stress features as its parent all-atom model, including reduced stress at the bilayer interior, and a large negative stress near the bilayer/head group interface (again their sign convention is adapted to our lateral minus normal convention), but many of the features near the head-group area are reversed from their all-atom counterpart. Perhaps the disagreement arises from known simulation artifacts in the calculation of the pressure tensor for "soft" mesoscale models, or possibly due to the integration error that accumulates from an ill-defined timestep[33]. Efficient DPD simulations have reproduced a qualitatively correct stress profile; in a review of membrane models, Venturoli et al. reproduce a stress profile[17] that has the same features as the all-atom simulation. Finally, detailed explicit solvent coarse-grained simulations, such as the MARTINI forcefield[19] and a LJ/Gay-Berne lipid model[60] nicely reproduce all-atom stress profiles. We consider the stress profile of our implicit solvent coarse-grained model to be among the best in terms of computational cost in accuracy, with accuracy rivaling the MARTINI model but with the computational expense of an implicit solvent model.

## CONCLUSION

Recently, several groups have successfully developed and applied systematic methodology for implicit solvent coarse-graining for lipid bilayers. Izvekov and Voth[59] have adapted their variational coarse-graining, (which creates a many-body potential for a coarse-grained unit by fitting forces from a finer grained model) to the case of implicit solvent lipid models. As well, Boltzmann-inversion procedures may also be employed systematically to create a coarse-grained from a finer grained model. Given a radial distribution function, $g(r)$, perhaps derived as a coarse-grained coordinate from a finer

simulation, there is a unique mapping to a pair potential $v(r)$ [61-63]. This idea has been applied, for example, to form systematic descriptions of polyvinyl chains[64] using iterated Boltzmann inversion[65, 66]. More recently, a two-dimensional bilayer model has been developed using the inversion technique that includes chain disorder as an internal state[67, 68], predicting cholesterol-rich bilayer domains. Such models are attractive because they provide natural definitions for interactions, rather than a heuristic approach. However, the potential may depend strongly on the temperature (for example, across a phase transition the measured distributions, upon which the potentials are determined, change dramatically).

All-atom force fields are parameterized using *ab initio* quantum chemistry methods, and are modified to reproduce condensed-phase experimental information that quantum chemistry cannot describe affordably. In turn, all-atom simulations of lipid bilayers offer a useful parameterization scheme for coarse-grained lipids models, providing a bridge to the limited structural, dynamical and thermodynamic information offered by experiment or detailed atomistic trajectories. For example, in this work we use the distribution of individual lipid geometries from an all-atom simulation to extract a potential of mean force, which we use directly to parameterize the geometric structure of our coarse-grained DPPC lipid model. By combining information from all atom simulations and varying a few model parameters to optimize the area per lipid within the coarse-grained model, our coarse-grained lipid model of DPPC nicely reproduces essential properties of the fluid membrane, such as the stress profile, bending modulus, and diffusion constant, with an estimation of the coarse-grained timescale derived from the all-atom calculation. The flip flop of an individual lipid is never observed during our simulations, qualitatively consistent with our model having a large energetic barrier to moving the headgroup through the membrane core with subsequent lipid reorganization, unlike highly coarse-grained models that typically have negligible barriers to lipid transfer between leaflets. The lack of explicit solvent has limitations in certain dynamical properties such as membrane undulation relaxation modes that are dominated by the timescales of coupled bilayers, although further investigation to remove any residual tension may improve agreement with experiment in the future.

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**REFERENCES**

1. K. A. Dill and H. S. Chan, Nature Structural Biology **V4** (N1), 10-19 (1997).

2. T. Head-Gordon and S. Brown, Current Opinion in Structural Biology **13** (2), 160-167 (2003).
3. J. N. Onuchic, Z. LutheySchulten and P. G. Wolynes, Annual Review of Physical Chemistry **V48**, 545-600 (1997).
4. D. K. Klimov and D. Thirumalai, Proteins-Structure Function and Genetics **26** (4), 411-441 (1996).
5. L. A. Mirny, V. I. Abkevich and E. I. Shakhnovich, Proceedings of the National Academy of Sciences of the United States of America **V95** (N9), 4976-4981 (1998).
6. M. Cieplak, T. X. Hoang and M. S. Li, Physical Review Letters **83** (8), 1684-1687 (1999).
7. S. Brown, N. Fawzi and T. Head-Gordon, Proc Natl Acad Sci U S A **100**, 10712-10717 (2003).
8. S. Brown and T. Head-Gordon, Protein Science **13** (4), 958-970 (2004).
9. C. Clementi, P. A. Jennings and J. N. Onuchic, Journal of Molecular Biology **V311** (N4), 879-890 (2001).
10. N. L. Fawzi, V. Chubukov, L. A. Clark, S. Brown and T. Head-Gordon, Protein Science **14** (5), 1380-1380 (2005).
11. N. L. Fawzi, E. H. Yap, Y. Okabe, K. L. Kohlstedt, S. P. Brown and T. Head-Gordon, Acc Chem Res **41** (8), 1037-1047 (2008).
12. J. E. Shea, J. N. Onuchic and C. L. Brooks, Proceedings of the National Academy of Sciences of the United States of America **V96** (N22), 12512-12517 (1999).
13. J. M. Sorenson and T. Head-Gordon, Proteins-Structure Function and Genetics **V46** (N4), 368-379 (2002).
14. J. M. Sorenson and T. Head-Gordon, Journal of Computational Biology **7** (3-4), 469-481 (2000).
15. J. M. Sorenson and T. Head-Gordon, Journal of Computational Biology **9** (1), 35-54 (2002).
16. S. V. Bennun, M. I. Hoopes, C. Xing and R. Faller, Chem Phys Lipids **159** (2), 59-66 (2009).
17. M. Venturoli, M. M. Sperotto, M. Kranenburg and B. Smit, Physics Reports **437**, 1-54 (2006).
18. S. J. Marrink, A. H. d. Vries and A. E. Mark, J Phys Chem B **108**, 750-760 (2004).
19. S. J. Marrink, H. J. Risselada, S. Yefimov, D. P. Tieleman and A. H. de Vries, J Phys Chem B **111** (27), 7812-7824 (2007).
20. M. Kranenburg, J.-P. Nicolas and B. Smit, Phys Chem Chem Phys **6**, 4142-4151 (2004).
21. R. D. Groot and K. L. Rabone, Biophys J **81** (2), 725-736 (2001).
22. M. Venturoli, B. Smit and M. M. Sperotto, Biophys J **88** (3), 1778-1798 (2005).
23. J.-M. Drouffe, A. C. Maggs and S. Leibler, Science **254**, 1353-1356 (1991).
24. H. Noguchi and G. Gompper, Phys Rev Lett **93** (25), 258102 (2004).
25. Z. J. Wang and D. Frenkel, J Chem Phys **122** (23), 234711 (2005).
26. G. LaPenna, E. K. Foord, J. W. Emsley and D. J. Tildesley, J Chem Phys **104**, 233-241 (1996).
27. O. Farago, J Chem Phys **119**, 596-605 (2003).
28. I. R. Cooke and M. Deserno, J Chem Phys **123** (22), 224710 (2005).
29. I. R. Cooke, K. Kremer and M. Deserno, Phys Rev E Stat Nonlin Soft Matter Phys **72** (1 Pt 1), 011506 (2005).
30. G. Brannigan, P. F. Philips and F. L. Brown, Phys Rev E Stat Nonlin Soft Matter Phys **72** (1 Pt 1), 011915 (2005).
31. G. Brannigan, L. C. Lin and F. L. Brown, Eur Biophys J **35** (2), 104-124 (2006).
32. H. C. Andersen, Journal of Computational Physics **52** (1), 24-34 (1983).
33. A. F. Jakobsen, O. G. Mouritsen and G. Besold, J Chem Phys **122** (20), 204901 (2005).
34. A. Kolb and B. Dünweg, J Chem Phys **111**, 4453-4459 (1999).
35. J. B. Klauda, B. R. Brooks, A. D. MacKerell, Jr., R. M. Venable and R. W. Pastor, J Phys Chem B **109** (11), 5300-5311 (2005).

36. J. B. Klauda, N. V. Eldho, K. Gawrisch, B. R. Brooks and R. W. Pastor, J Phys Chem B **112** (19), 5924-5929 (2008).
37. P. B. Canham, J Theor Biol **26** (1), 61-81 (1970).
38. W. Helfrich, Z Naturforsch C **28** (11), 693-703 (1973).
39. O. Farago, J Chem Phys **128** (18), 184105 (2008).
40. L. J. LaBerge and J. C. Tully, Chemical Physics **260**, 183-191 (2000).
41. R. Goetz and R. Lipowsky, J Chem Phys **108**, 7397-7409 (1998).
42. P. Schofield and J. R. Henderson, Proc. Royal Soc. London A **379**, 231-240 (1982).
43. E. Lindahl and O. Edholm, Biophys J **79** (1), 426-433 (2000).
44. J. D. Weeks, D. Chandler and H. C. Andersen, Journal of Chemical Physics **54** (12), 5237-+ (1971).
45. J. F. Nagle and S. Tristram-Nagle, Biochim Biophys Acta **1469** (3), 159-195 (2000).
46. W. L. Vaz, R. M. Clegg and D. Hallmann, Biochemistry **24** (3), 781-786 (1985).
47. R. D. Kornberg and H. M. McConnell, Biochemistry **10** (7), 1111-1120 (1971).
48. D. P. Tieleman and S. J. Marrink, J Am Chem Soc **128** (38), 12462-12467 (2006).
49. T. Pomorski and A. K. Menon, Cell Mol Life Sci **63** (24), 2908-2921 (2006).
50. D. Marsh, Chem Phys Lipids **144** (2), 146-159 (2006).
51. W. Pfeiffer, S. Konig, J. F. Legrand, T. Bayerl, D. Richter and E. Sackman, Europhys. Lett **23**, 457-462 (1993).
52. O. Farago and P. Pincus, J Chem Phys **120** (6), 2934-2950 (2004).
53. M. Patra, M. Karttunen, M. T. Hyvonen, E. Falck, P. Lindqvist and I. Vattulainen, Biophys J **84** (6), 3636-3645 (2003).
54. S. M. Bezrukov, Curr Opin Coll Int Sci **5**, 237-243 (2000).
55. A. R. Curran, R. H. Templer and P. J. Booth, Biochemistry **38** (29), 9328-9336 (1999).
56. R. H. Templer, S. J. Castle, A. R. Curran, G. Rumbles and D. R. Klug, Faraday Discuss (111), 41-53; discussion 69-78 (1998).
57. J. Gullingsrud and K. Schulten, Biophys J **86** (6), 3496-3509 (2004).
58. S. Ollila, M. T. Hyvonen and I. Vattulainen, J Phys Chem B **111** (12), 3139-3150 (2007).
59. S. Izvekov and G. A. Voth, J Phys Chem B **113** (13), 4443-4455 (2009).
60. M. Orsi, D. Y. Haubertin, W. E. Sanderson and J. W. Essex, J Phys Chem B **112** (3), 802-815 (2008).
61. J. T. Chayes and L. Chayes, J. Stat. Phys **36**, 471-488 (1984).
62. J. T. Chayes, L. Chayes and E. H. Lieb, Commun. Math. Phys. **93**, 57-121 (1984).
63. R. L. Henderson, Phys Lett A **49**, 197- (1974).
64. G. Milano and F. Muller-Plathe, J Phys Chem B **109** (39), 18609-18619 (2005).
65. D. Reith, M. Putz and F. Muller-Plathe, J Comput Chem **24** (13), 1624-1636 (2003).
66. A. P. Lyubartsev and A. Laaksonen, Phys Rev E Stat Nonlin Soft Matter Phys **52**, 3730-3737 (1995).
67. T. Murtola, E. Falck, M. Karttunen and I. Vattulainen, J Chem Phys **126** (7), 075101 (2007).
68. T. Murtola, M. Karttunen and I. Vattulainen, J Chem Phys **131** (5), 055101 (2009).

## TABLES

***Table 1. Bond distance parameters for the DPPC lipid model. LB-X refers to lipid bead centers that make up the bond constraint at the fixed distance $R_0$.***

| *LB-1* | *LB-2* | $R_0$ |
|---|---|---|

| | | |
|---|---|---|
| Chol | Phospho | 1.173 |
| Phospho | T1 | 1.333 |
| Phospho | T2 | 1.626 |
| T1 | T3 | 0.677 |
| T3 | T4 | 1.130 |
| T4 | T5 | 1.314 |
| T5 | T6 | 1.290 |
| T2 | T7 | 0.721 |
| T7 | T8 | 1.140 |
| T8 | T9 | 1.286 |
| T9 | T10 | 1.266 |

**Table 2.** ***Bending potential parameters for the DPPC lipid model.*** LB-X refers to lipid bead centers that make up the bond angle deformations around the equilibrium angle $_0$ with force constant $k$ .

| ***LB-1*** | ***LB-2*** | ***LB-3*** | $\theta_0$ | $k_\theta$ |
|---|---|---|---|---|
| Chol | Phospho | T1 | 121.0 | 5.78 |
| Chol | Phospho | T2 | 120.0 | 0.22 |
| T1 | Phospho | T2 | 43.0 | 97.57 |
| Phospho | T1 | T3 | 180.0 | 3.85 |
| Phospho | T2 | T7 | 110.0 | 19.61 |
| T1 | T3 | T4 | 155.0 | 6.62 |
| T3 | T4 | T5 | 180.0 | 4.64 |
| T4 | T5 | T6 | 180.0 | 4.64 |
| T2 | T7 | T8 | 150.0 | 7.70 |
| T7 | T8 | T9 | 180.0 | 4.64 |
| T8 | T9 | T10 | 180.0 | 4.64 |

**Table 3.** ***Parameters for the DPPC lipid-lipid interactions.*** LB-X refers to lipid bead center types that make up the pair interactions, is the interaction strength parameter, and is the spatial unit (equivalent to 3.78Å), and $w_f$ is the stretch parameter used in Eq. (13).

| ***LB-1*** | ***LB-2*** | $\varepsilon$ | $\sigma$ | $w_f$ |
|---|---|---|---|---|
| Chol | Chol | 1.00 | 1.17 | – |
| Phospho | Phospho | 1.00 | 1.17 | – |
| Chol | Phospho | 3.00 | 1.17 | – |
| Chol/Phos | Tail | 1.00 | 1.17 | – |
| Tail | Tail | 0.75 | 1.42 | 0.25$\sigma$ |

**Table 4.** *Evidence for gel to liquid transition for the coarse-grained DPPC model.* Diffusion constant (with error estimation), area per lipid, and tail order parameter, as a function of temperature.

| **Temperature** | **Diffusion constant** | **Area per lipid (nm$^2$)** | **Tail order parameter** |
|---|---|---|---|

| | **($cm^2/s$ x$10^7$)** | | |
|---|---|---|---|
| 0.4 | 0.0206 (0.005) | 47.8 | 0.768 |
| 0.6 | 0.0198 (0.006) | 49.6 | 0.791 |
| 0.75 | 0.009 (0.004) | 51.8 | 0.747 |
| 0.8 | 0.0134 (0.005) | 52.2 | 0.767 |
| 0.85 | 0.024 (0.014) | 52.8 | 0.777 |
| 0.9 | 0.036 (0.011) | 53.0 | 0.806 |
| 0.95 | 0.062 (0.03) | 53.7 | 0.805 |
| 1.0 | 2.2 (0.1) | 57.0 | 0.744 |
| 1.05 | 2.7 (0.1) | 58.9 | 0.700 |
| 1.1 | 3.76 (0.14) | 60.9 | 0.642 |
| 1.15 | 4.76 (0.2) | 63.5 | |
| 1.2 | 5.32 (0.2) | 66.3 | 0.519 |
| 1.3 | 7.87 (0.3) | 73.5 | 0.403 |

**FIGURE CAPTIONS**

**Figure 1.** *Coarse grained model of dipalmitoylphosphatidylcholine (DPPC) phospholipids.* Labels are used to define the interaction model.

**Figure 2.** The time autocorrelation functions of the bending angles (Eq. 1). We quantify the time scale of the bilayer dynamics by calibrating against the tail bending relaxation times of the parent all-atom simulation.

**Figure 3**. *Log-log plot of the power spectrum vs. q*. A least-squares fit over low values of q, using $\kappa$ and $\Sigma$ in Eq. (5) as adjustable parameters, determined that the bending modulus of our coarse-grained DPPC bilayer is is $18.9 k_b T$ at T=1.0, in good agreement with experiment.

**Figure 4.** (a) The lateral stress profile (normal minus tangential stress) against the distance from the midplane of the bilayer along the normal direction and (b) broken down into phosphate (P), choline (C), and tail (T) non-bonded contributions from Eqs. (11)-(13). The remaining geometric contributions include SHAKE constraint forces, bond angle deformations, as well as anisotropy of the kinetic energy component of the pressure.