Published in final edited form as:

Mol Phys. 2006 October 10; 104(19): . doi:10.1080/00268970600935101.

Equation of state for a coarse-grained DPPC monolayer at the air/water interface

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Abstract

Pulmonary surfactant, a complex mixture of phospholipids and proteins, secreted by the type II epithelial cells in the lungs, is crucial to reducing the effort required for breathing. A lack of adequate amounts of pulmonary surfactant in underdeveloped lungs of premature infants results in infant respiratory distress syndrome (RDS). Surfactant replacement therapy (SRT) is the approved method of mitigating the effects of RDS. The development of new SRT regimens requires a fundamental understanding of the links between surfactant biochemistry and functionality. We use a coarse-grained (CG) model to predict the surface pressure–surface concentration relationship (equation of state) for pure DPPC, which is a major component of endogenous and synthetic pulmonary surfactant mixtures. We show that the model can be efficiently used to predict the equation of state in excellent agreement with experimental results. We also study the structure of the monolayer as a function of the surface tension of the system. We show that a decrease in the applied surface tension results in an increase in order in the head group region and a decrease in order in the tail region of DPPC. This technique may be useful in the prediction of equations of state for surfactant replacements.

1. Introduction

Pulmonary surfactant, a mixture of ~90wt% lipids and ~10wt% proteins secreted by the type II epithelial cells, is essential for the normal functioning of the lungs during the respiration cycle. It helps lower the surface tension by forming a surface-active film at the air/liquid interface thus reducing the effort required for breathing. It also prevents alveolar collapse after expiration. Low amounts of pulmonary surfactant in the alveolar space of neonates results in Respiratory Distress Syndrome (RDS).

The lipid component of pulmonary surfactant comprises of the disaturated phospholipid dipalmitoylphosphatidylcholine (DPPC), unsaturated phosphatidylcholine (PC), phosphatidylglycerol (PG), small amounts of phosphatidic acid (PA), phosphatidylinositol (PI), phosphatidylethanolamine (PE) and the neutral lipid cholesterol. The protein component is made up of the hydrophobic surfactant proteins B and C (SP-B, SP-C) and the hydrophilic surfactant proteins A and D (SP-A, SP-D) [1].

DPPC, the major component of pulmonary surfactant (~40 wt%), is able to form a tightly packed gel phase when compressed at physiological temperatures and reduce the surface tension to near-zero values. The current study employs the coarse-grained (CG) lipid model developed by Marrink *et al.* [2], who demonstrated that their model can be used to study mesoscopic phenomena (time scale ~ μ s, length scale ~ μ m) in lipids and surfactant systems.

They were able to simulate self-aggregation of DPPC into a bilayer with structural properties such as the area per headgroup and bilayer thickness in close agreement with the experimentally determined values. We use the model to simulate a DPPC monolayer at the air–water interface in the $NP_N T$ ensemble [3]. In this ensemble, the unit cell dimensions are changed anisotropically; the cell length normal to the interface is varied to maintain a constant normal pressure (P_N) and the surface area is varied to maintain a constant surface tension (γ). The surface tension can be computed from the components of the pressure tensor as follows:

$$\gamma = \left\langle \left\{ P_{zz} - \frac{1}{2}(P_{xx} + P_{yy}) \right\} \times L_z \right\rangle, \quad (1)$$

where γ denotes the surface tension, P_{ii} denotes the i th component of the pressure tensor and L_z is the unit cell length normal to the monolayer.

A complimentary ensemble in this approach is the $NP_N A T$ ensemble, in which the surface area per molecule (A) is fixed and the surface tension (γ) is allowed to equilibrate. The goal is to obtain the surface tension–surface concentration relationship (equation of state) for the monolayer system. This work is part of a multi-scale modeling approach to the study of the dynamics of pulmonary surfactant during the respiration cycle. As a component of this approach, the surface tension–surface concentration relationship, thus obtained on the mesoscopic scale, will subsequently be integrated with macroscopic simulations of the system [4–6].

In this paper, we first present a review of the relevant published work in the area (section 2). In section 3, we expound the simulation methodology employed in the current study followed by a discussion of the results obtained (section 4). In section 5, we present conclusions based on our observations followed by a perspective on future work.

2. Background

In this section we summarize relevant published work. In section 2.1 we discuss molecular modeling as well as experimental research on pulmonary surfactant functionality. In section 2.2, we present an overview of existing approaches to coarse-grained modeling.

2.1. Pulmonary surfactant functionality

Phospholipid monolayers at the air–water interface are of considerable physiological interest. Mauk *et al.* report molecular dynamics simulations of four different phospholipid monolayers in the $NP_N T$ and the $NP_N A T$ ensemble as well as Langmuir–Blodgett trough experiments [7]. They report good agreement between the pressure–area isotherms obtained from the simulations and from the experiments. Contrary to the observation of Feller and Pastor [8], Mauk *et al.* report results from the $NP_N T$ ensemble to be more reliable than the $NP_N A T$ due to a lack of equilibration to the appropriate pressure in the latter. Dominguez *et al.* have also reported molecular dynamics simulation of DPPC monolayers at the air/water and CCl_4 /water interfaces. They present area per lipid and structural order parameters for their model systems [9].

The commonly held view with respect to surfactant function is that the surface film is able to withstand high surface pressures after expiration through the enrichment of the film with DPPC [10]. Two possible mechanisms have been proposed for DPPC enrichment; selective DPPC adsorption from the underlying subphase that acts as a lipid reservoir to the monolayer and the selective removal or ‘squeezing out’ of other lipid components from the monolayer to the subphase during compression. Both mechanisms are thought to occur [1].

The surfactant proteins are thought to play a major role in the surface film refinement [10]. The reader is referred to the review article by Pérez-Gil and Keough for an overview of the various issues and proposed theories involving the functionality of the surfactant proteins [11].

Recent experimental studies have questioned the classical model [12, 13]. Yu and Possmayer conclude that there is no evidence of lipid selectivity during the formation of surface films by adsorption. Also, there are experimental studies yielding results that contradict DPPC enrichment via the selective removal of non-DPPC lipids [14]. Another possible mechanism termed the theory of SP-B-induced lateral stability has been proposed. The specific interactions of SP-B with the phospholipids are presumed to provide lateral stability to the surface layer thus allowing the layer to withstand high surface pressures [14]. The hydrophobic surfactant protein SP-B has been known to play a critical role in lung function. This was evidenced by studies in which the removal of SP-B via genetic mutation in mice resulted in RDS-like symptoms in neonates [15, 16].

In order to study the behaviour of the components of pulmonary surfactant at the air/water interface, Kaznessis *et al.* have simulated DPPC and DPPG monolayers in the canonical (constant NVT) ensemble at various surface densities [17]. They have presented the effects of surface density and the presence of calcium ions in the sub-phase on the thickness of the monolayer in terms of specific interactions between groups in the two phospholipids. They have also presented electron density profiles and pair distribution functions for key interacting groups in the system. Kaznessis *et al.* have also reported atomistic simulations of systems containing components of pulmonary surfactants, viz. DPPC and DPPG monolayers and the N-terminal region of human surfactant protein-B (SP-B₁₋₂₅) [18]. The simulations were conducted in order to study the nature of interactions of the various amino acid residues and the DPPC/DPPG monolayers.

In a related study, Kandasamy and Larson present 10–20 ns simulations of DPPC monolayers in the presence of SP-B₁₋₂₅ [19]. They observe the formation of hydrogen bonds between the protein and lipid atoms. They conclude that the orientation of the peptide in the monolayer depends on these hydrogen bonds. They also present simulations with mutants of the SP-B₁₋₂₅ peptide. Based on these simulations, they conclude that the first eight amino acids help position the peptide in the monolayer.

2.2. Coarse-grained modeling

The phenomena of interest in biophysical systems are often on a mesoscopic scale (time scale $\sim\mu\text{s}$, length scale $\sim\mu\text{m}$). In order to simulate such systems efficiently and reasonably, researchers are increasingly turning to coarse-grained models [2, 20]. Since the early works of Telo da Gama and Gubbins [21] and Smit [22], several researchers have proposed coarse-grained (CG) models with varying levels of detail. A recent review outlines previous work, summarizes the consequences from coarse-graining and provides a sampling of typical results that can be expected [20]. One approach towards developing reasonable coarse-grained models is to limit the scope of the applicability. Such specific models have been presented for numerous systems: polymer melts by Akkermans and Briels [23], dimyristoylphosphatidylcholine (DMPC) by Shelley *et al.* [24], n-alkanes by Nielsen *et al.* [25], carbohydrates and their water mixtures by Molinero and Goddard [26]. These models were parametrized to reproduce distribution functions and structural properties from fully atomistic simulations as well as experimental measurements of various physico-chemical properties. The n-alkane model of Nielsen *et al.* and the carbohydrate model (denoted M3B) of Molinero and Goddard, in particular, were reported to exhibit excellent agreement with experimental data.

Ayton and Voth have presented the elastic membrane dissipative particle dynamics (EM-DPD) model in which the coarse-graining was extended beyond the usual combined atom approach [27]. Data from atomistic simulations was coupled with longer-range constitutive relationships. They used this model to simulate a dimyristoylphosphatidylcholine (DMPC) bilayer at various surface tensions. They report that the bilayer undulation spectrum and the bending modulus obtained from their simulations are in excellent agreement with the experimental values.

In a remarkable contribution, Marrink *et al.* [2] have presented a new coarse-grained model for lipids and surfactant systems based on the Gromacs force-field. In order to increase versatility over the aforementioned models without sacrificing accuracy, the CG model was parameterized with fully atomistic simulation data from several systems simultaneously. The model was reported to have reproduced experimental and atomistic simulation data for different lipid systems accurately. The applicability, versatility and computational efficiency of the model make it our choice for the current work. The model is discussed in further detail in section 3.

3. Methodology

The simulated monolayer system consists of 144 CG DPPC molecules and ~9000 CG water molecules. A schematic of the simulation cell is depicted in figure 1. The initial x - and z -dimensional cell lengths are also shown. The initial x - and y -dimensional cell lengths are identical. The air phase is modeled as a ~70 Å vacuum space above the monolayer. This space also prevents unrealistic interactions between the water molecules re-entering the simulation cell from above on account of periodic boundary conditions and the DPPC molecules forming the monolayer. The initial monolayer conformation is obtained by replicating a single CG DPPC molecule and incrementally translating the copies in the x - y plane. The monolayer is then energy-minimized with the headgroup fixed for 100 000 steps. A water box is initialized in a face-centered-cubic (fcc) confirmation and equilibrated in the canonical (constant NVT) ensemble for 2 ns.

The program NAMD [28] is used for the simulations with the Gromacs based potential field. The CG model only involves four distinct particle types: apolar, charged, non-polar and polar. The non-polar and charged particles are further divided into four subtypes depending on the ability of the group to form hydrogen bonds. The inter-molecular interactions are represented by a combination of a Lennard-Jones (LJ) and a Coulombic-type interaction (for the charged particles). A schematic of the CG model for DPPC is depicted in figure 2. All the LJ interactions have the same size parameter of 4.7 Å. The energy parameters for the LJ interactions are explicitly set to be one of five levels. This simplicity makes the model extremely versatile for use in the simulation of phospholipid systems. The intramolecular interactions are represented by a combination of bond stretching, bond bending and LJ-type interactions (for second nearest neighbour onwards). The water particles are of the polar type representing four water molecules. For further details of the model and the associated force-field, the reader is referred to Marrink *et al.* [2].

The equilibrated monolayer and water phases were then assembled and equilibrated for 4 ns with a timestep of 10 fs in the $NP_N T$ ensemble using a variant of the extended system formalism [3]. In the method, a flexible simulation cell is employed while allowing anisotropic variations in the size of the cell. The z -dimensional size of the cell, normal to the monolayer, is varied so as to maintain a normal pressure of 1 bar while the x - and y -dimensional sizes are varied to maintain a specified surface tension. Pressure fluctuations resulting from inter-molecular interactions govern the lengths of the simulation cell. Simulation of a system configured in a similar manner has been reported in the $NP_N AT$

ensemble using a fully atomistic force-field [19]. The initial cell has dimensions of $(98 \times 98 \times 264)$ Å and is periodic in all dimensions. This results in an initial interfacial area of 66.0 Å²/molecule. Figure 3 depicts a snapshot of the equilibrated system. The coarse-grained DPPC molecules are shown in the CPK representation while the water groups are represented as semi-transparent spheres. The head group representing the choline moiety is represented with dark spheres. As can be seen from the figure, the equilibrated DPPC molecules in the monolayer have sampled different orientations from the configurational phase space.

Simulations are then performed for 12 ns using a time step of 10 fs in the same ensemble. The intermolecular LJ interactions are truncated beyond a distance of 12 Å. The electrostatic interactions are accounted for using the smooth particle mesh Ewald method [29]. The interpolation is done using a sixth-order B-spline method with a fast Fourier transform grid of $(60 \times 60 \times 200)$ Å. This results in an Ewald parameter of 0.34. The temperature is maintained constant at 323K with a Langevin damping coefficient of 10 ps^{-1} . The Langevin piston period employed is 200 fs with a decay of 100 fs. The Langevin piston temperature is 323 K. The simulations are performed using the multiple time-step algorithm with the electrostatic and non-bonded frequency of two time steps.

The simulations are performed for seven different values of the surface tension ranging from 25 to 55 dynes cm^{-1} in steps of 5 dynes cm^{-1} . The number of water molecules that diffuse from the bottom water phase to the top of the simulation cell on account of periodic boundary conditions was found to be negligible. Other researchers have used a wall-potential to prevent diffusion of the water molecules away from the water phase [17, 30]. However, this approach involves the computationally expensive external force calculation for a water molecule based on its position during the simulation with NAMD and was found to be unnecessary.

4. Results and discussion

The surface areas corresponding to different imposed surface tensions had reached their equilibrium values after 8 ns of simulation time. All the data presented here have been obtained from the analysis of trajectory frames between 8 and 12 ns. The equation of state for surfactant systems is often represented as a plot of the surface pressure as a function of surface area per molecule. The surface pressure can be defined as

$$\pi = \gamma_0 - \gamma, \quad (2)$$

where π denotes the surface pressure, γ_0 denotes the surface tension of pure water (70 dynes cm^{-1}) at the temperature of interest and γ represents the surface tension of the system. Figure 4 shows the surface pressure as a function of surface concentration obtained from our coarse-grained simulations. The corresponding experimental data obtained by Notter [31] are also presented. As can be seen from the figure, a decrease in the applied surface tension, which corresponds to an increase in surface pressure, results in a decreasing surface area per molecule. This result is as expected. In order to be able to reduce the surface tension, the surface-active DPPC molecules have to pack closely at the interface thus causing higher surface concentrations. Figure 4 also shows an excellent agreement between the simulation and the experimental data in the range of surface pressures between 20 and 50 dynes cm^{-1} . This observation underscores the accuracy and versatility of the model in quantitative prediction of physico-chemical properties of biological systems. The accuracy of the force-field is also remarkable on account of the simplicity of the model used for water: a simple LJ interaction site, with no partial charge, hydrogen bonding ability or directional order. This ability coupled with its computational efficiency makes this model highly attractive for

research involving mesoscopic phenomena, which are beyond the scope of fully atomistic molecular dynamics investigations. A caveat is in order for the surface area datum point at an applied surface pressure of 50 dynes cm⁻¹, the surface area/molecule is calculated based on the dimensions of the unit cell and the number of molecules in the system. At 50 dynes cm⁻¹, the monolayer shows a high degree of curvature indicating a folding tendency. On a molecular scale, it can be argued that the surface area experienced per molecule is higher due to this curvature. However, the macroscopic experiments do not account for such atomistic perturbations in the planar monolayer configuration. The simulation at an applied surface pressure of 20 dynes cm⁻¹ was run in triplicate. The equilibrated surface areas were then calculated. The error estimates on the plot are the standard deviations obtained from this analysis and are ~1.2 Å²/molecule.

In an effort to predict the complex phenomena involved in pulmonary surfactant dynamics, Krueger and Gaver have proposed an analytical model that incorporates monolayer collapse and respreading [32]. One of the important parameters in the model is the maximum equilibrium surface concentration (). This parameter represents the monolayer surfactant concentration attainable after equilibration at high bulk concentrations in the absence of compression. The model was parametrized to reproduce experimental data for a large range of conditions. The maximum equilibrium surface concentration () obtained for the model was 4.0e-10 mol cm⁻², which translates to a surface area of 41.5 Å²/molecule. Our simulation results show a plateau in the surface tension–surface concentration relationship between 40 and 45 Å²/molecule indicative of that is in excellent agreement with the model and experimental results.

Figure 5 shows the average end-to-end distance of the DPPC tails as a function of the applied surface tension. Chain 1 has a larger end-to-end distance than chain 2 at all values of the applied surface tension. In general, an increase in the applied surface tension causes a small increase in the chain 1 end-to-end distance. The magnitude of this increase is quite small, however, and may not be statistically significant. The behaviour of the chain 2 end-to-end distance as a function of the applied surface tension is non-monotonic.

The average and standard deviation values for the differences between the average C–C bond length obtained from all the simulations and the equilibrium bond length of 4.7 Å for the three bonds are shown in table 1. The terminology used in the current work is solely for the purpose of simplicity. The C interaction sites referred to earlier represent a moiety in the DPPC molecules comprised of four methyl groups in this coarse-grained model. Likewise, the phosphate and choline moieties in the DPPC molecules will be referred to as the P and N interaction sites, respectively. As can be seen from the table, the bond lengths between the C interaction sites in the DPPC chains are all above the equilibrium distance. Also, the C–C distance is practically independent of the applied surface tension indicated by the low standard deviation (<5%) in these values. The same behaviour is observed for all three bonds in the coarse-grained model employed in the current work.

The average C–C order parameter is plotted as a function of the applied surface tension in figure 6. The C–C order parameter can be defined as

$$S_{CC}^i = \left\langle \frac{3\cos^2\theta_{CC}^i - 1}{2} \right\rangle, \quad (3)$$

where θ_{CC}^i represents the angle made by the vector between C_{i-1} and C_{i+1} and the normal to the monolayer. A highly ordered monolayer configuration results in an order parameter close to unity while a disordered monolayer results in a value of S_{CC} close to zero [33]. The

order parameter for carbon 3 is lower than the value for carbon 2 for all values of the applied surface tension. This result is as expected. The interaction sites away from the head-group region of the DPPC molecule have lower steric and energetic barriers resulting in a larger configuration space and thus a lower order parameter. In general, an increase in the applied surface tension results in an increase in the order parameter. This result is contrary to the observations at the atomistic scale. DPPC is known to reduce surface tensions to extremely low values on account of its ability to pack tightly in a gel phase, which is characterized by high order parameters. The coarse-grained DPPC model does not exhibit this behaviour. The methodology of coarse-graining is known to cause a loss of some detail while retaining the ability to predict macroscopic properties. Our results are consistent with this overall behaviour of these models.

Figure 7 shows the average probability distribution of the P–N angle ($\theta_{\text{P-N}}$) with respect to the normal to the interface for high values of applied surface tension. As can be seen from the figure, the P–N angle has an average value of 90° . The distribution is also diffuse as a function of the applied surface tension. The same distribution is plotted for lower values of the applied surface tension in figure 8. At an applied surface tension of 40 dynes cm^{-1} , a bimodal distribution is observed with peaks at 60° and 120° . A further decrease in surface tension results in the second peak becoming more diffuse. The head-group orientation thus exhibits marked order with a decrease in surface tension.

The average probability distribution of the chain dihedral angle (θ) is plotted in figure 9 for different applied surface tensions. The effect of surface tension on the chain dihedral angle is negligible. For all the applied surface tensions, the *trans* configuration, represented by a 180° dihedral angle, is favoured over the two *gauche* configurations ($\pm 60^\circ$).

5. Conclusions

We have presented the equation of state representing the surface tension–surface concentration relationship for pure DPPC at the air/water interface using the coarse-grained model of Marrink *et al.* that is in excellent quantitative agreement with experimental results available for the system. Each of the datum points presented here requires a simulation time of 300 CPU hours on an AMD Opteron cluster running 2.4GHz processors. A fully atomistic system of similar size would require a computing time of a factor of 50 larger than the coarse-grained simulations presented in the current work. We have thus shown that the coarse-graining methodology provides an efficient and reliable approach to the prediction of physico-chemical properties of biological systems. Extensions to this model will allow simulations of realistic pulmonary surfactant formulations. A detailed understanding of the role of each component obtained from such simulations will greatly facilitate the design of new and efficient pulmonary surfactant regimens.

We have also studied the structure of the DPPC monolayer as a function of the applied surface tension. The average end-to-end distance for chain 1 was shown to be generally longer than for chain 2. The effect of surface tension on the end-to-end distance is not very pronounced. The average C–C bond lengths in the coarse-grained model were shown to be independent of the applied surface tension as well as the position of the bond in the chain. The C–C order parameter generally increased with an increase in surface tension contrary to the observation for atomistic DPPC. The orientation of the P–N bond with respect to the monolayer normal is increasingly ordered with decreasing applied surface tension. Also, the distribution of the dihedral angle of the DPPC tails was shown to be independent of the applied surface tension. The DPPC tails were shown to prefer the *trans* configuration to the two *gauche* configurations. Thus, in general, a decrease in the applied surface tension results

in a more ordered head-group region and a less ordered tail region in the coarse-grained DPPC.

6. Future work

The coarse-graining methodology enumerated by Marrink *et al.* has been shown to be efficient and effective in making quantitative predictions of physicochemical properties of biological systems. The next phase of the current study will focus on extending the method to obtain reasonable models of amino acids. This will enable coarse-grained simulations of realistic pulmonary surfactant mixtures to investigate the functionality of the various components. These models will be optimized and validated using fully atomistic simulations.

Acknowledgments

The research was supported by grant P20-EB001432 from the National Institute of Health and grant NAG3- 2734 from the National Aeronautics and Space Administration. The computational resources were provided by the Center for Computational Science at Tulane University.

7. Nomenclature

A	Surface area per molecule, Å ² /molecule
L_x^{init}	Initial cell length in the x dimension
L_z^{init}	Initial cell length in the z dimension
N	Number of molecules in the system
P_N	Component of the pressure tensor normal to the monolayer surface
P_{ij}	Component i - j of the pressure tensor
S_{CC}^i	Average C-C order parameter for group i
T	Temperature, K
V	System volume, Å ³
	Surface tension, mNm ⁻¹
γ	Surface tension of pure water, mNm ⁻¹
	Maximum equilibrium surface concentration
θ_{CC}^i	Angle made by the vector between C_{i-1} and C_{i+1} with the monolayer normal
$\theta_{\text{P-N}}$	Angle made by the P-N vector with the monolayer normal
	Surface pressure, mNm ⁻¹
	Dihedral angle of the CG DPPC chains

References

1. Veldhuizen EJA, Haagsman HP. Biochim Biophys Acta. 2000; 1467:255. [PubMed: 11030586]
2. Marrink SJ, de Vries AH, Mark AE. J Phys Chem B. 2004; 108:750.
3. Feller SE, Zhang Y, Pastor RW. J Chem Phys. 1995; 103:4613.
4. Ghadiali SN, Gaver DPI. J Appl Physiol. 2000; 88:493. [PubMed: 10658016]
5. Ghadiali SN, Gaver DPI. J Fluid Mech. 2003; 478:165.
6. Zimmer ME IV, Williams HAR, Gaver DPI. J Fluid Mech. 2005; 537:1.

7. Mauk AW, Chaikof EL, Ludovice PJ. *Langmuir*. 1998; 14:5255.
8. Feller SE, Pastor RW. *J Chem Phys*. 1999; 111:1281.
9. Dominguez H, Smondyrev M, Berkowitz ML. *J Phys Chem B*. 1999; 103:9582.
10. Veldhuizen EJA, Batenburg JJ, van Golde LMG, Haagsman HP. *Biophys J*. 2000; 79:3164. [PubMed: 11106621]
11. Pérez-Gil J, Keough KMW. *Biochim Biophys Acta*. 1998; 1408:203. [PubMed: 9813327]
12. Piknova B, Schram V, Hall SB. *Curr Opin Struct Biol*. 2002; 12:487. [PubMed: 12163072]
13. Yu SH, Possmayer F. *J Lipids Res*. 2003; 44:621.
14. Cochrane CG. *Am J Physiol Lung Cell Molec Physiol*. 2005; 288:L608. [PubMed: 15757953]
15. Clark JC, Wert SE, Bachurski CJ, Stahlman MT, Stripp BR, Weaver TE, Whitsett JA. *Proc Natl Acad Sci USA*. 1995; 92:7794.
16. Tokieda K, Whitsett JA, Clark JC, Weaver TE, Ikeda K, McConnell KB, Jobe AH, Ikegami M, Iwamoto HS. *Am J Physiol*. 1997; 273:L875. [PubMed: 9357864]
17. Kaznessis YN, Kim S, Larson RG. *Biophys J*. 2002; 82:1731. [PubMed: 11916834]
18. Kaznessis YN, Kim S, Larson RG. *J Molec Biol*. 2002; 322:569. [PubMed: 12225750]
19. Kandasamy SK, Larson RG. *Biophys J*. 2005; 88:1577. [PubMed: 15738465]
20. Nielsen SO, Lopez CG, Srinivas G, Klein ML. *J Phys: Condens Matter*. 2004; 16:R481.
21. da Gama TMM, Gubbins KE. *Molec Phys*. 1986; 59:227.
22. Smit B, Hilbers PAJ, Esselink K, Rupert LAM, van Os NM. *J Phys Chem*. 1991; 95:6361.
23. Akkermans RLC, Briels WJ. *J Chem Phys*. 2001; 114:1020.
24. Shelley JC, Shelley MY, Reeder RC, Bandyopadhyay S, Klein ML. *J Chem Phys B*. 2001; 105:4464.
25. Nielsen SO, Lopez CG, Srinivas G, Klein ML. *J Chem Phys*. 2003; 119:7043.
26. Molinero V, Goddard WA III. *J Phys Chem B*. 2004; 108:1414.
27. Ayton A, Voth G. *Biophys J*. 2002; 83:3357. [PubMed: 12496103]
28. Kale L, Skeel R, Bhandarkar M, Brunner R, Gursoy A, Krawetz N, Phillips J, Shinozaki A, Varadarajan K, Schulten K. *J Comp Phys*. 1999; 151:283.
29. Essman U, Perera L, Berkowitz ML, Darden T, Lee H, Pedersen LG. *J Chem Phys*. 1995; 103:8577.
30. Alper HE, Bassolino D, Stouch TR. *J Chem Phys*. 1993; 98:9798.
31. Notter, RH. *Lung Surfactants: Basic Science and Clinical Applications*. Marcel Dekker; New York: 2000. p. 59
32. Krueger MA, Gaver DPI. *J Colloid Interface Sci*. 2000; 229:353. [PubMed: 10985814]
33. Ben-Shaul, A. *Handbook of Biological Physics*. Sackmann, E., editor. Elsevier; Amsterdam: 1995. p. 351

Figure 1.
Schematic of the simulation unit cell.

Figure 2.
Schematic of the coarse-grained DPPC model.

Figure 3.
Snapshot of the coarse-grained DPPC monolayer at the air/water interface.

Figure 4. Surface pressure as a function of surface concentration for the coarse-grained DPPC monolayer at the air/water interface at 323 K.

Figure 5.
Average end-to-end distance of DPPC tails as a function of surface tension.

Figure 6.
Average orientation order parameter of the tail groups as a function of surface tension.

Figure 7. Orientation angle probability distribution of the head groups in the monolayer for high values of the applied surface tension.

Figure 8. Orientation angle probability distribution of the head groups in the monolayer for low values of the applied surface tension.

Figure 9. Dihedral angle probability distribution of the lipid chains in the monolayer as a function of surface tension.

Table 1

Average tail bond lengths as percentage change from the equilibrium value.

C-C bond number	Average % change from the equilibrium bond length	Std. deviation in the % change from equilibrium value
1	108.26	0.027
2	108.23	0.045
3	108.26	0.041