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## Coarse-grained molecular simulations of membrane adhesion domains

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We use a coarse-grained molecular model of supported lipid bilayers to study the formation of adhesion domains. We find that this process is a first order phase transition, triggered by a combination of pairwise short range attractive interactions between the adhesion bonds and many-body Casimir-like interactions, mediated by the membrane thermal undulations. The simulation results display an excellent agreement with the recently proposed Weil-Farago two-dimensional lattice model, in which the occupied and empty sites represent, respectively, the adhesion bonds and unbound segments of the membrane. A second phase transition, into a hexatic phase, is observed when the attraction between the adhesion bonds is further strengthened. © 2014 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4886397>]

Lipid membranes define the boundaries of living cells and function as physical barriers that prevent unwanted uptake (leakage) of different ions and molecules into (out of) the cell.<sup>1</sup> The ability of membranes to adhere to different elements, such as the extracellular matrix (ECM), the cytoskeleton and other membranes, is controlled by adhesion molecules and is crucial for many biological processes.<sup>2</sup> Membrane adhesion bonds may aggregate into large adhesion domains to provide stronger anchoring of the cell to the ECM and other neighboring cells.<sup>3–5</sup> Generally speaking, clustering of membrane adhesion bonds is facilitated by several factors, such as electrostatic and van der Waals interactions,<sup>6</sup> effective forces arising from the action of the cytoskeleton,<sup>7</sup> and membrane-mediated interactions.<sup>8</sup> In this work we put our focus on the latter type of interactions, whose origin is the entropy associated with the thermal undulations of the membrane,<sup>9</sup> and which can be understood heuristically as follows: Consider, for instance, a membrane bound to a solid surface by several adhesion bonds. When comparing to a free (unbound) membrane, the bound one undergoes smaller height fluctuations, thus losing some entropy. However, the aggregation of adhesion bonds into a single adhesion cluster allows the unbound segments of the membrane to fluctuate more freely, which drives the membrane to a lower free energy state. The membrane fluctuations, thus, induce an effective attractive interaction between the adhesion bonds.

During recent years, considerable efforts have been directed toward understanding the biophysical principles that govern the clustering process of adhesion bonds. Traditionally, a lattice model is used, in which the membrane is discretized into patches, which may or may not contain adhesion molecules that bind (via receptor-ligand bonds) the membrane to an underlying surface. Lipowsky and Weikl<sup>10,11</sup> proposed a model in which the system Hamiltonian involves three terms: (i) Helfrich curvature elastic energy, (ii) the energy of the specific ligand-receptor bonds, and (iii) a generic interaction term between the membrane and the surface. A closely related model was introduced more recently by Speck and Vink,<sup>12</sup>

with an additional feature of tethering the membrane at several points (distinct from the adhesion sites) to the cytoskeleton. Both models predict a domain formation through a cooperative binding process, i.e., a process where the binding of a receptor-ligand pair facilitates conditions for the formation of other bonds in its vicinity.

The aforementioned models constitute discrete versions of Helfrich continuum surface model of lipid bilayers. Thus, each lattice site is characterized by two variables  $s_i$  and  $h_i$ . The former parameter characterizes the distribution of adhesion bonds, where  $s_i = 1$  corresponds to a membrane segment that is connected to the surface and  $s_i = 0$  to a segment which is free to fluctuate. The latter parameter,  $h_i$ , represents the local height of the membrane. Analyzing the aggregation behavior of the adhesion bonds by means of computer simulations requires sampling over different distributions of lattice sites, as well as over different height conformations. This may become a computationally expensive task in simulations of large systems. It is, therefore, desirable to develop a model that integrates out the degrees of freedom associated with the height fluctuations and, instead, assigns a potential of mean force between the lattice adhesion sites. Apart from computational simplicity, another advantage of this approach is that it offers direct comparison with the well-investigated two-dimensional (2D) lattice-gas model and, thus, highlights the role played by the membrane-mediated interactions in the aggregation process. Such a lattice model was recently proposed by Weil and Farago (WF).<sup>13</sup> (We note that an opposite approach is taken in Refs. 10, 11, where the positional degrees of freedom  $s_i$  are integrated out by using the mean field solution of the 2D lattice-gas model. This yields an effective membrane-surface interaction energy term in the Helfrich Hamiltonian that depends on the local  $h_i$ .) The WF model combines two attractive energy terms

$$\mathcal{H} = -\epsilon \sum_{i,j} s_i s_j + \sum_i V_i (1 - s_i). \quad (1)$$

The first energy term constitutes the conventional lattice-gas model, where the sum runs over all pairs of nearest neighbor sites. The energy  $\epsilon > 0$  gained for each pair of occupied sites accounts for all the interactions between the adhesion bonds other than the membrane-mediated potential of mean force. The latter potential is represented by the second term in Eq. (1) which, quite unusually, involves summation over the *empty* sites only. The energy of each empty site measures the amount of free energy lost due to the suppression of the thermal height fluctuations of the corresponding membrane segment. Weil and Farago<sup>13</sup> conjectured that this free energy penalty depends on the distance of the segment from the nearest adhesion bond  $d_i^{\min}$ , i.e., the distance to the nearest occupied site, and is given by

$$V_i = \frac{k_B T}{\pi} \left( \frac{l}{d_i^{\min}} \right)^2, \quad (2)$$

where  $l$  is the lattice constant (which should be of the order of a few nanometers – comparable to the thickness of the membrane). Remarkably, the expression for the free energy  $V_i$  (2) is independent of the bending rigidity of the membrane  $\kappa$ . Notice that, in general,  $d_i^{\min}$  depends on the distribution of *all* the occupied sites and, therefore, the second term in Eq. (1) represents a multi-body potential of mean force between the adhesion bonds. This potential is attractive because most of the entropy is lost at the interfacial regions between occupied and empty sites where  $d_i^{\min}$  is small. When only two sites are occupied, the potential between them has a logarithmic dependence on their separation  $r$

$$U(r) = 2k_B T \ln \left( \frac{r}{l} \right). \quad (3)$$

The last result has been obtained independently through scaling arguments, and has been verified by computer simulations of coarse-grained bilayer membranes.<sup>14</sup>

Monte Carlo (MC) simulations of the WF model reveal that the system condenses for  $\epsilon > \epsilon_c > 0$ . The transition value,  $\epsilon_c$ , is smaller than the corresponding value of the standard lattice-gas model at the same density by typically a factor of 2-3. Noticeably,  $\epsilon_c$  is smaller than the thermal energy  $k_B T$  in the WF model, and larger than  $k_B T$  in the standard lattice-gas model. In agreement with previous lattice models that include the membrane explicitly (and not via a potential of mean force),<sup>10-12</sup> the adhesion sites do not form large clusters when  $\epsilon = 0$ , which implies that the membrane-mediated interactions alone are not sufficient to allow the formation of large adhesion domains, but they greatly reduce the strength of the residual interactions required to facilitate such clusters. Following this study, Noguchi<sup>15</sup> suggested that the strength of the membrane-mediated interactions can be enhanced by pinning more than one membrane to the surface. He demonstrated this by simulating monolayers of particles that are pinned to each other by “gap junctions.” In simulations of  $N_{\text{lay}} = 2$  layers, the gap junctions remain dispersed. This result agrees with the prediction of the WF model for  $\epsilon = 0$  since the problem of two surfaces with bending rigidity  $\kappa$  is equivalent to a single membrane with  $\kappa/2$  connected to an infinitely rigid surface. However, when the number of monolayers is  $N_{\text{lay}} >$

2, the gap junctions exhibit a different behavior and condense into a large stable domain. This behavior can be attributed to the fact that the entropy loss caused by the gap junctions is proportional to the total rate of collisions between the layers in the stack,<sup>14</sup> which grows proportionally to the number of *pairs* of colliding surfaces, i.e., to  $(N_{\text{lay}} - 1)$ . Motivated by the results of the molecular simulations, Noguchi<sup>15</sup> also simulated the WF lattice model, with a free energy term which is simply  $(N_{\text{lay}} - 1)$  times larger than  $V_i$  given by Eq. (2). It was found that the WF model yields results in very good agreement with the molecular simulations.

In this paper, we provide yet another evidence for the ability of the WF model to accurately capture the aggregation behavior of adhesion bonds in supported membranes. To this end, we use the model proposed by Cooke and Deserno (CD),<sup>16</sup> in which lipids are modeled as trimmers consisting of one hydrophilic (head) and two hydrophobic (tail) beads. This model is less coarse-grained than the one used by Noguchi<sup>15</sup> and, thus, gives a better representation of lipid membranes which are simulated as bilayers rather than monolayers. A flat plate, which cannot be intersected by the lipids, was placed underneath the lower monolayer at  $z = 0$ , and the attachment of the membrane to the surface was established by restricting  $N_b$  head beads from the lower monolayer to  $z = 0$  and allowing them to move only in-plane. We conducted MC simulations with periodic boundary conditions of a bilayer comprising of  $2N = 2000$  lipids at different densities of adhesive lipids,  $\phi = N_b/N$ . A slight change in the CD model was made where, for pairs of adhesive head beads, the pair potential was switched from head-head to tail-tail. While the former pair potential is purely repulsive, the latter also includes a cosine interaction well whose depth can be tuned (see Eq. (4) in Ref. 16). This attractive part of the pair potential plays the same role played by the standard lattice-gas term in Eq. (1), with  $\epsilon$  denoting the interaction energy between nearest neighbor occupied sites. By setting the depth of the potential well in the molecular model to  $\epsilon$ , and by simulating the WF lattice model with same value of  $\epsilon$ , one can directly compare the two models to each other. This allows us to test the accuracy of the WF model for  $\epsilon > 0$  – an aspect of the model which has not been probed in Ref. 15.

The simulations of the CD model (to be henceforth referred to as the “molecular simulations”), which were conducted at zero surface tension, consist of several types of MC moves, including translation of beads, rotation of lipids, and changes in the cross-sectional projected area of the membrane. To achieve equilibration within a reasonable computing time, two additional move types were also performed. The first move type resolves the problem arising from the slow changes in the amplitudes of the large wavelength bending modes.<sup>17</sup> It involves a collective change in the heights of all the lipids, allowing acceleration and rapid relaxation of these modes. The other process limiting the approach to equilibrium is the slow diffusion of the lipids, especially those pinned to the surface which serve as the adhesion bonds. In order to speed up the aggregation of adhesion domains, one needs to allow the adhesion bonds to “jump” across the membrane. This is accomplished by the second move type, in which two lipids simultaneously experience opposite vertical

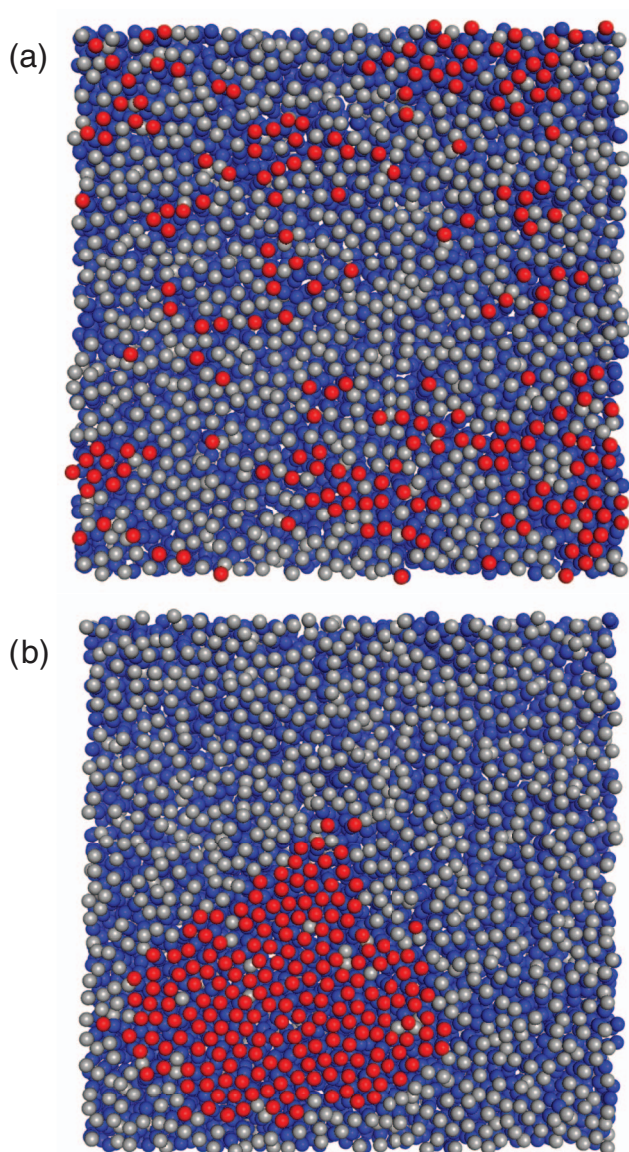


FIG. 1. Bottom view of a membrane with concentration of adhesion bonds  $\phi = 0.2$  for (a)  $\epsilon = 0.4$  and (b)  $\epsilon = 1.2$ . The head and tail beads of the lipids are colored in grey and blue, respectively, while the adhesive beads are colored in red.

translations: the free lipid whose head resides closest to the surface is brought down and attached to the surface, while a randomly chosen pinned lipid is lifted and released.<sup>14</sup>

We simulated membranes with different concentrations  $\phi$  of adhesion bonds, and for different values of  $\epsilon$  (measured in units of the thermal energy  $k_B T$ ). Snapshots of equilibrium configurations corresponding to  $\epsilon = 0.4$  and  $\epsilon = 1.2$  are shown, respectively, in Figs. 1(a) and 1(b). The concentration in both cases is  $\phi = 0.2$ . The distinction between the two configurations is clear: In (a) the adhesion bonds are scattered across the membrane in relatively small clusters, while in (b) they are assembled into one big aggregate. The transition between the gas and the condensed phases of adhesion bonds displayed, respectively, in Figs. 1(a) and 1(b) occurs at intermediate values of  $\epsilon$ . This is demonstrated in Fig. 2, where we plot the average energy of the pair interactions between

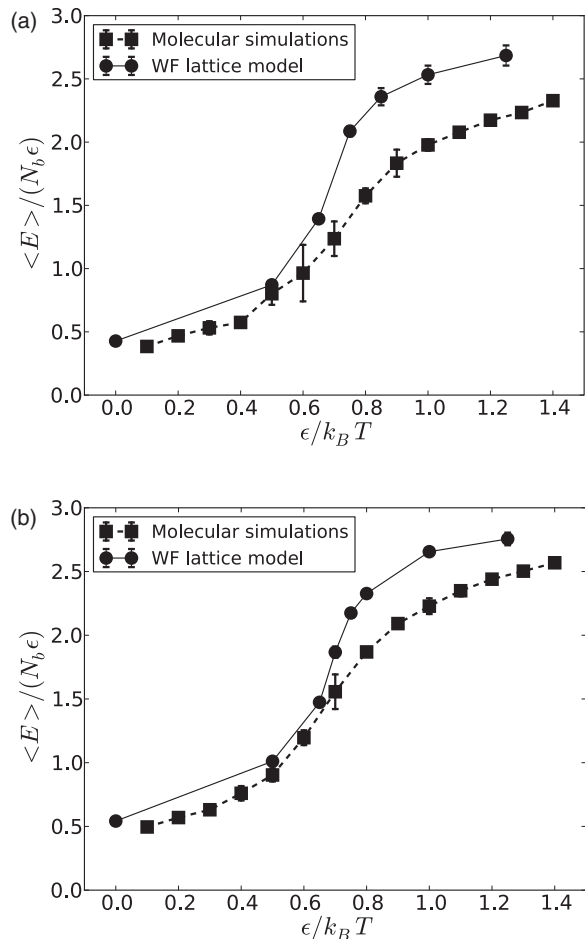


FIG. 2. The average energy of direct interactions between the adhesion bonds (normalized per adhesion bond) as function of the pair interaction energy  $\epsilon$ , for (a)  $\phi = 0.05$  and (b)  $\phi = 0.1$ . Solid squares and circles denote the results of the molecular simulations and of the Weil-Farago 2D lattice simulations, respectively. The solid and dashed lines are guides to the eye.

the adhesion bonds (normalized per adhesion bond),  $\langle E \rangle / N_b$ , as a function of  $\epsilon$ , the (maximum) strength of the pair interaction, for  $\phi = 0.05$  (a) and  $\phi = 0.1$  (b). The simulation results, which are plotted in solid squares (with the dashed line serving as a guide to the eye), suggest that the transition between the phases is of first order. The energy steeply increases around  $\epsilon_c \approx 0.7$  from a low value reflecting the dispersed distribution of adhesion bonds in the gas phase where the number of pair interactions is small, to a high value characterizing a big cluster where the bonds are closely packed and experience a large number of pair interactions. Also plotted in Fig. 2 are the results of lattice simulations of the WF model for identical values of  $\phi$  and for various values of  $\epsilon$  (solid circles with solid line serving as a guide to the eye). The agreement between the molecular simulations and the lattice simulations of the WF model is very good. The lattice model predicts a very similar value of  $\epsilon_c \approx 0.7$  (for both simulated concentrations), and gives very similar values of  $\langle E \rangle / N_b$  in the gas phase ( $\epsilon < \epsilon_c$ ).

A slight discrepancy between the molecular and lattice simulation is observed in the condensed phase for  $\epsilon > \epsilon_c$ , where the WF model appears to give higher values of the mean interaction energy  $\langle E \rangle / N_b$ . This deviation between the

results of the lattice and continuum molecular models is anticipated considering the nature of the models. In the former, the sites are organized on a perfect triangular lattice, and the energy assigned to every pair of nearest neighbor occupied sites is *exactly*  $\epsilon$ . In the latter, on the other hand, the bonds within each cluster do not necessarily have a long range positional order [see, e.g., the snapshot in Fig. 1(b)], and  $\epsilon$  denotes the *depth* of the interaction well. The actual strength of the interaction is expected to be lower than  $\epsilon$  in the continuum molecular model, which explains why it gives lower values of  $\langle E \rangle / N_b$  than in the lattice simulations.

At even higher values of  $\epsilon$ , the close agreement between the lattice and the molecular simulations is regained. This occurs due to another phase transition that the clusters undergo, from disordered liquid-like structures into more ordered organizations, such as the one displayed in Fig. 3(a) for  $\phi = 0.2$  and  $\epsilon = 3.4$ . This phase transition can be understood within the framework of the KTHNY theory, which proposes the formation of a two dimensional hexatic phase with a quasi-long range hexagonal (orientational) order.<sup>18</sup> This transition

is characterized by the bond orientational order parameter

$$\psi_{6j} = \frac{1}{N_j} \sum_{k=1}^{N_j} e^{i6\theta_{kj}}, \quad (4)$$

where the sum runs over the nearest neighbor adhesion bonds  $k$  to a given adhesion bond  $j$  (whose identity is determined by Voronoi tessellation), and  $\theta_{kj}$  is the angle between the line connecting the pair of bonds  $j$  and  $k$  and some fixed axis. Averaging over all the adhesion bonds within the cluster yields the global orientational order parameter

$$\Phi_6 = \left| \frac{1}{N_b} \sum_{j=1}^{N_b} \psi_{6j} \right|. \quad (5)$$

Another quantity undergoing rapid variations at the transition is the self-diffusion coefficient of the adhesion bonds (relative

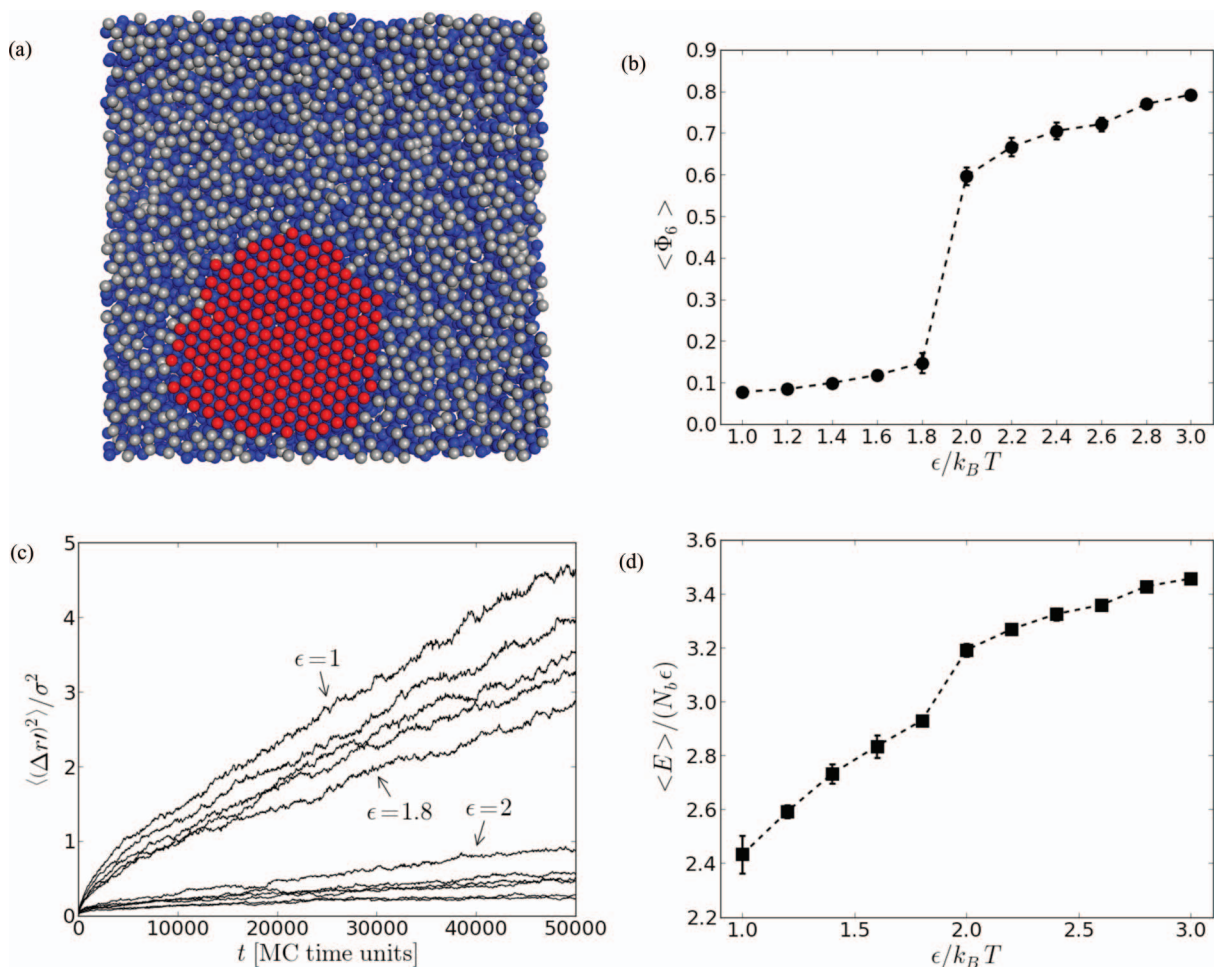


FIG. 3. The molecular simulation results for a membrane with  $\phi = 0.2$  for  $\epsilon > \epsilon_c$ . (a) Snapshot of an equilibrium configuration with  $\epsilon = 3.4$ , depicting an adhesion domain organized in the hexatic phase. Color coding as in Fig. 1. (b) The mean bond orientational order parameter  $\langle \Phi_6 \rangle$  as a function of the pair interaction energy  $\epsilon$ . The transition into the hexatic phase occurs around  $\epsilon_h \approx 1.9$  where a sudden increase in  $\langle \Phi_6 \rangle$  is observed. (c) The mean square displacement of the adhesion bonds vs. the simulations time for different values of  $\epsilon$ . The slope of each curve is a measure for the self-diffusion coefficient of the adhesion bonds within the cluster  $D$ . The results for  $\epsilon = 1, 1.8, 2$  are marked by arrows. (d) The average interactions energy per adhesion bond as a function of  $\epsilon$ .

to the diffusion of their center of mass), defined by

$$D = \lim_{t \rightarrow \infty} \frac{1}{4N_b t} \sum_{i=1}^{N_b} \langle [(\vec{r}_i(t) - \vec{r}_{\text{cm}}(t)) - (\vec{r}_i(t=0) - \vec{r}_{\text{cm}}(t=0))]^2 \rangle \equiv \lim_{t \rightarrow \infty} \frac{\langle (\Delta r')^2 \rangle}{4t}, \quad (6)$$

where  $r_i(t)$  and  $r_{\text{cm}}(t)$  denote, respectively, the position of adhesion bond  $i$  and of the center of mass of the cluster at time  $t$  (measured in MC time units), and  $\langle \dots \rangle$  denotes statistical average. The transition into the hexatic phase is characterized by (i) an increase in  $\Phi_6$ , associated with the emergence of orientational order, and (ii) a sharp decrease in  $D$ , reflecting a lower mobility of the adhesion bonds. In Fig. 3(b), we plot our results for  $\langle \Phi_6 \rangle$ , as a function of  $\epsilon$  for  $\phi = 0.2$ . In Fig. 3(c), the mean square displacement of the adhesion bonds (measured in units of  $\sigma^2$ , where  $\sigma$  is the range of the head-head repulsive potential in the Cooke-Deserno model<sup>16</sup>) is plotted versus the simulation time (measured in MC time units), with the curves, from top to bottom, corresponding to increasingly higher values of  $\epsilon$ . [Each curve in Fig. 3(c) corresponds to a data point in Fig. 3(b).] The curves display a linear increase in  $\langle (\Delta r')^2 \rangle$  with  $t$ , and the slope of each curve is proportional to  $D$ . Both Figs. 3(b) and 3(c) indicate that the transition from disorder-liquid into an ordered-hexatic structure occurs at around  $\epsilon \approx 1.9$ . Another evidence for the fluid to hexatic transition is also observed in Fig 3(d), showing a “jump” in the average interaction energy between  $\epsilon = 1.8$  and  $\epsilon = 2.0$ . Notice that the values of  $\langle E \rangle / N_b$  in the hexatic phase is *higher* the  $3\epsilon$ , which is the maximum possible value in simulations of the WF model on a triangular lattice. This feature is related to the form of the attractive tail-tail pair potential in the molecular simulations whose cut-off range was set to slightly less than  $2.5\sigma$ . This implies that, in a closely packed cluster, each adhesion bond may weakly interact with its next- and next-next-nearest neighbors, which explains why  $\langle E \rangle / N_b$  is larger than  $\epsilon$ .

To conclude, we used coarse-grained molecular simulations to study the aggregation of adhesion domains in supported membranes. Formation of adhesion domains occurs due to two types of attractive interactions existing between the adhesion bonds. These include (i) a many-body potential of mean force induced by the thermal fluctuations of the membrane, and (ii) short-range pair interactions of strength  $\epsilon$ . Upon increasing  $\epsilon$ , the system goes from a “gas” phase where the adhesion bonds are scattered across the membrane in relatively small clusters, into a “condensed” fluid phase, in which they are assembled into large aggregates. At even higher values of  $\epsilon$ , another phase transition is observed from a condensed fluid-like phase into a more ordered hexatic phase, in which the adhesion bonds also

exhibit a considerably reduced diffusivity. Based on our computational observations, we, respectively, identify these transitions as a first-order condensation transition, and a Kosterlitz-Thouless phase transition. To rigorously characterize the nature of the transitions, one would need to perform finite size scaling analysis, but this goes beyond the scope of the current study.

Our simulation results, especially those related to the condensation transition, appear to be in excellent agreement with the recently proposed WF lattice model. This lends credibility to the main idea of the WF model, which is to associate the fluctuation-induced potential between the adhesion bonds, with free energies assigned to the empty sites of the lattice. The empty sites represent the fluctuating segments of the supported membrane, and the free energy assigned to each site measures the free energy loss due to the local restrictions imposed on the membrane thermal undulations. This free energy penalty mainly depends on the distance,  $d_{\text{min}}$ , between an empty site and the closest occupied site (representing an adhesion bond). In the present paper, we investigated tensionless membranes with adhesion bonds directly pinned to the underlying surface. Under these conditions, the WF model assumes that the energy of the empty sites scales proportionally to  $d_{\text{min}}^{-2}$ . In a future publication, we plan to extend the WF lattice model to more general conditions. The extensions of the WF model will be tested against molecular simulations akin to those presented here.

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