Complementarity and clustering in a simple model mixed bilayer

Kunal Khanna, Ted T. Chang, and James T. Kinds

Department of Chemistry, Emory University, Atlanta, Georgia 30032

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Clustering and other nonrandom lateral mixing effects in multicomponent lipid bilayers are of interest for their potential importance to the organization of cell membranes. Atomistic simulations of bilayer mixtures face challenges due to the slowness of lipid diffusion on the typical time scale of $10^{-8}$ s. Even when converged results on bilayer mixtures can be obtained, as through the use of coarse-grained molecular models, the competing interactions that influence miscibility may be difficult to disentangle. Minimal models are therefore useful to identify the effects of various factors.

One effect, the presence or absence of transbilayer correlations in bilayer organization, has been a topic of relatively few experimental studies. Based on neighbor analysis experiments, Zhang et al. recently suggested that in a bilayer containing lipids with tail lengths differing by only two carbons, the two species tend to be positioned complementarily across the bilayer, presumably to reduce steric repulsion between long tail groups on opposing leaflets.

We have studied a simple mixed-bilayer model designed to exhibit such translayer complementarity to determine its effect on the clustering within each leaflet. A cartoon demonstrating the model is shown in Fig. 1(a). Each lipid is represented by a hard cylindrical rod with cross-sectional diameter $\sigma$, the “head” of which is constrained to lie on one of two parallel planes separated by the bilayer thickness $d$ and the orientation of which is fixed normal to the planes. In isolation, each plane behaves as a two-dimensional (2D) hard-disk (HD) fluid, irrespective of the lengths of the rods. The system composition is evenly divided between short ($S$) and long ($L$) rods. Rod lengths are not explicitly defined, except insofar as the long-rod length $l_L > d/2$ (i.e., the rod extends beyond the midplane) and the short-rod length $l_S < d - l_L$. Therefore, the two HD systems are coupled, as $L$ rods are subject to hard-disk overlap restrictions with respect to $L$ rods on the opposite leaflet. The model belongs to the class of nonadditive mixed hard-disk fluids with four types of disks; $S$ disks are assigned a diameter of zero for interactions with all opposite-layer disks.

Monte Carlo simulation was used to sample the ensemble of bilayer configurations with equal numbers of $S$ and $L$ disks and a fixed and equal number of disks per leaflet, while the composition of each leaflet was allowed to fluctuate. In 95% of Monte Carlo (MC) steps, a lateral translation of a single disk by up to 0.05$\sigma$ in $x$ and $y$ was attempted. In the remaining “swap” moves, an $L$ disk is selected at random. If there is a unique $S$ disk within a circle of radius $\sigma$ directly across from the $L$ disk, a trial swap of positions and leaflets is attempted. The swap is accepted if there are no translayer overlaps and if the same uniqueness condition is met for the reverse move. Intralayer swaps were not used because acceptance probabilities were too low at high area fractions. A square, fixed-area simulation cell with 2D periodic boundary conditions containing 2491 rods on each layer was initialized with disks placed on both planes in matching hexagonal arrays in rows of alternating $L$ and $S$ disks. (No significant effects were observed upon variation of the starting configuration.) The number of neighbor pairs, defined as pairs of disks on the same plane with distance $r < 1.3\sigma$, formed between $L$ and $S$ disks as well as the radial distribution functions $g_{LL}(r)$, $g_{SS}(r)$, and $g_{LS}(r)$ within and between leaflets were calculated from simulations of $6 \times 10^7$ MC steps over a range of surface coverage from area fraction $\eta = 0.5-0.75$.

Significant demixing of long and short rods can be seen in a simulation snapshot at area fraction $\eta=0.625$ [Fig. 1(b)]. Radial distribution functions $g(r)$, calculated for the $L-L$, $S-S$, and $L-S$ combinations are qualitatively similar to the function obtained for the simple hard-disk fluid at the same area fraction [Fig. 2(a)]. The peaks corresponding to second and third nearest neighbors are at slightly lower $r$ than the HD reference in the long-long correlation function and are at slightly higher $r$ in the short-short correlation function, while nearest- and next-nearest-neighbor peaks are noticeably suppressed in the $L-S$ correlation function. The probability of

![FIG. 1. Top: Cartoon of bilayer rod model. Bottom: Snapshots showing lateral positions of $L$ and $S$ disks (solid and shaded, respectively) of both leaflets at $\eta=0.625$.](image-url)
**FIG. 2.** (a) Radial distribution function $g(r)$ from Monte Carlo simulations at $\eta=0.625$ for simple hard-disk fluid (solid). (b) Mixed bilayer $g(r)$ normalized to hard-disk reference. Legend for both panels: $L-L$, long dash; $S-S$, short dash; $L-S$, mixed dash.

$L-L$ pairs at contact is greater than that of $S-S$ pairs. Taken together, these observations suggest a short-ranged demixing into $L$ and $S$ domains, with $L$ domains more compact than $S$ domains. The comparison with the HD fluid is highlighted when the correlation functions are displayed normalized to the hard-disk $g(r)$ in Fig. 2(b). A depletion of $L-S$ pairs at short range is apparent. As the model is athermal and as interactions between like and unlike rods in the same plane are identical, the only effect that may cause clustering is the cross-layer packing effect among $L$ rods. The free area of each $L$ rod is restricted by nearby $L$ rods on the opposing leaflet; the local concentration of such rods is reduced, and the translational entropy of $L$ rods is increased when $L$ and $S$ rods group in complementary opposing clusters. (Similar packing considerations have been discussed in the context of the nematic-smectic-A transition of parallel hard rods). The antiphase oscillations in the $L-L$ and $S-S$ functions indicate a tightening and loosening of the local-neighbor shell structures of the long- and short-rod domains respectively, consistent with more compact $L$ domains. This effect can be explained by the additional lateral pressure from $L$ rods on the opposite leaflet.

The effects of packing fraction on demixing, as indicated by the ratio of like- to unlike-type neighbors and the values of $g(r)$ at contact according to pair type, are plotted versus $\eta$ in Figs. 3(a) and 3(b). The preference for neighbors of like type rises with coverage up to $\eta=0.65$, with a sharp drop at higher coverage. Contact probabilities for like and unlike lipids follow a similar trend. As area fraction increases, packing considerations become more important and the degree of demixing tends to rise. However, rather than continue towards phase separation, with $L$- and $S$-rich phases segregated into opposing leaflets, the tendency to cluster falls off above $\eta=0.65$. This fall coincides with an ordering transition to a state with a sixfold symmetry, which is indicated in Fig. 3(c) by the rise in the global bond-orientational order parameter defined as $\psi=|\langle e^{i\phi_{ij}} \rangle|$ (where $\phi_{ij}$ represents the angle between the displacement vector connecting neighbor pair $i$ and $j$ and an arbitrary reference vector). Ordering begins at a lower $\eta$ for the coupled bilayer than for the simple HD fluid, for which Weber et al. calculated a transition density of $\eta=0.706$. The shift of the transition to a lower area fraction when the two leaflet HD systems are coupled comes from the additional surface pressure in the system from the repulsions of long rods across the bilayer. The characterization of such an ordering transition is nontrivial; a scaling analysis as used to establish that the ordering in a “simple” HD system
proceeds from liquid to solid via a hexatic intermediate phase has not been attempted here. Bilayer ordering is accompanied by a rise in one-to-one position correlations between $S$ and $L$ disks across the bilayer, as measured in the value of the corresponding radial distributor function at $r=0$, shown in Fig. 3(d), corresponding to a “locking-in” of the structures of the two layers. An $L$ disk positioned directly opposite an $S$ disk will have little or no effect on $L$ disks in the opposite layer, which already must avoid the $S$ disk. The entropic advantage from reducing translayer contacts of $L$ disk, which drives demixing of $L$ and $S$ disks within each plane, is therefore reduced by translational ordering.

In summary, a simple model illustrates an entropic lateral demixing effect arising from transbilayer lateral repulsions in a bidisperse mixed bilayer. The effect diminishes as the layers undergo an ordering transition. The phenomenon depends on an anticorrelation between the positions of lipids of different tail lengths on opposing leaflets of a bilayer, as has been proposed to account for recent experimental results; however, compared with these model results, a much lower degree of lateral clustering—only a 10% preference for like neighbors—was seen experimentally for this system. This model will miss important effects arising from attractions between head groups and tail groups, conformational isomerism of tails, lipid tilt, and bilayer thickness fluctuations, but it illustrates that translayer steric effects may significantly influence the miscibility and lateral organization of lipids of different lengths.

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