

Lateral Segregation in Biomimetic Membranes

The main goal of the project is to develop a multiscale description of the self-assembly of block copolymers (as well as other large solutes) in lipid membranes, both of biomimetic and natural types and thus to aid in the interpretation and design of experiments at Argonne. Zapol and coworkers are in the process of performing simulations for a pair of interacting block copolymers in a lipid membrane. These simulations will enable Freed and coworkers to deduce interaction parameters that are the key variables in a coarse scale thermodynamic theory which is under development while the time consuming simulations are in progress.

In order to perform a reliable computational study of lateral segregation, we have focused on performing MD simulations for the interaction between poly(ethylene oxide)-b-poly(propylene oxide) (PEO-PPO) diblock copolymers with DMPC bilayers. Currently, there is no coarse grained parameterization which would describe this copolymer-lipid system. As a first step towards performing these calculations, we are extending an existing coarse grained model for lipids to include PEO-PPO diblock copolymers. The extension developed here is based on a coarse grained lipid-water MARTINI force field [1], developed by Marrink *et al.* In this coarse grained approach, a group of atoms is represented by a single interaction bead. This model was chosen for its ability to reproduce experimental properties of various lipid assemblies, including the fluid bilayer phase. In addition to this beneficial feature, the model's implementation for the current project is relatively straightforward and can be easily extended to include other molecules. The model has been applied to simulate DMPC lipid bilayers in the lipid phase using MD simulations, see Fig. 1.

The polymer-lipid force field under development will include a coarse grained description for the PEO-PPO copolymers and parameters for lipid-copolymer and copolymer coarse grained water interactions. The bonded interactions between neighboring beads in PEO-PPO chains are taken from a recently developed coarse grained representation by Bedrov *et al.* [2] In this treatment, each monomer is represented by a single coarse grained bead. As no interaction parameters between coarse grained polymers and the coarse grained lipid-water system are available, we are currently determining parameters for non-bonded interaction between polymer-water and polymer-lipid coarse grained beads. We have carried out all atom simulations of PEO-PPO in water and will use the results to deduce the non-bonded interactions between coarse grained beads. Once these interactions are derived, we will proceed with CG simulations of aggregated and dispersed polymers in lipid bilayer. The results of the CG simulations will provide key parameters, such as compressibility and bending modulus, required for the thermodynamic model under development by Freed.

A thermodynamic theory for aggregation in binary systems by Wheeler [3] has been used by McConnell and coworkers [4] to analyze their extensive experimental data for aggregation of cholesterol in lipid membranes, a system of considerable biological importance and whose mathematical description at the coarse grained level is identical to that for the block copolymer/lipid system of interest to our joint study. The thermodynamic theory [3,4] invokes a series of assumptions that limit its applicability and leads to the presence of a plethora of

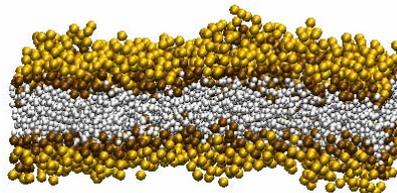


Fig. 1. A snapshot from coarse grained MD simulation of lipid bilayer using MARTINI force field.

adjustable parameters, assumptions that are in the process of being lifted by Freed and coworkers. The first simplifying approximation in the prior theory [3,4] is the assumption that the two components (call them A and B) aggregate in a fixed-cluster two step mechanism, $A + B \leftrightarrow AB$, followed by $nAB \leftrightarrow (AB)_n$, where n is an adjustable parameter. We have extended this model to describe the mathematically more complicated, but the physically more realistic situation in which there is a distribution of aggregate sizes $\{n\}$ as dictated by an equilibrium condition. The calculations consider the phase behavior, the mass distribution of the aggregates and their yield, the specific heat, etc., and these calculated thermodynamic properties are in the process of being compared with the predictions of the fixed-cluster model to assess when the simpler model is adequate for describing experimental data. (Strong differences are already apparent for the temperature dependence of the specific heat.) In the process, we have lifted the second limiting approximation of the prior theory, namely the use of three interaction parameters rather than the six minimally required to describe the “ternary” mixture of A, B, and aggregates of AB. While this may appear to expand the number of adjustable parameters, this situation is reversed by the next step planned in this study, the extension of the theory to describe compressible systems.

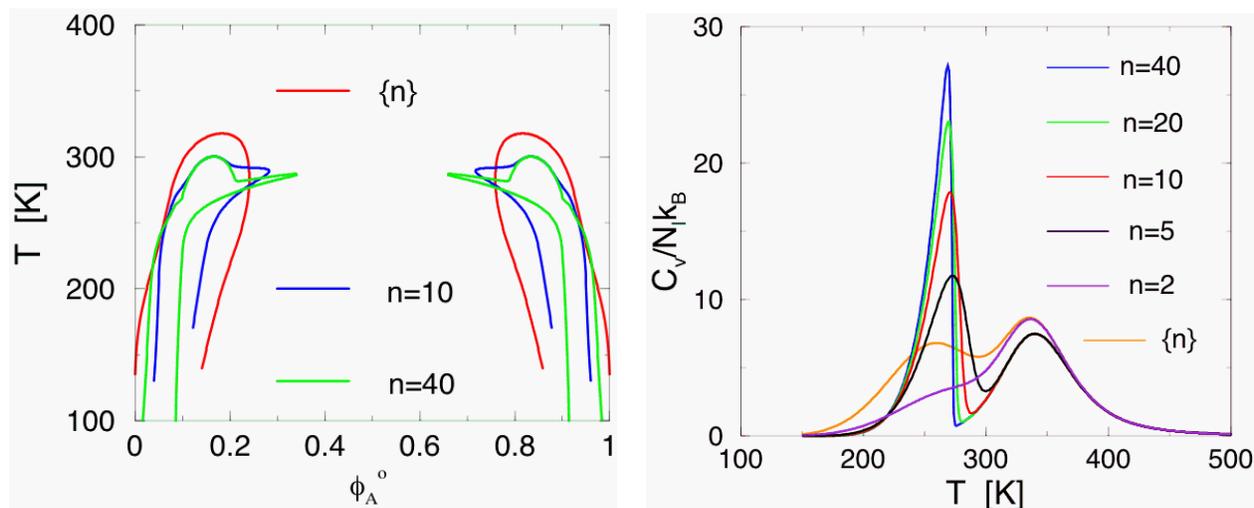


Fig. 2. Comparison of theory for distribution of cluster sizes (red) with fixed cluster size model (sizes specified) for temperature-composition phase diagram (left) and specific heat (right.)

The system compressibility is a crucial physical feature necessary by virtue of the area changes observed on aggregation. The prior studies treat compressibility by introducing the simplifying assumptions that the interaction parameters and the areas per molecule are all linear functions of the surface pressure, with coefficients that provide six extra adjustable parameters. Our planned theory will more realistically describe a compressible system as one in which there is excess free volume, [5] thereby enabling computation of the equation of state for the surface pressure as a function of temperature, concentration, and area, a crucial experimentally accessible thermodynamic property for deducing signatures of the aggregation. Because the model for a compressible system is far more complicated, the initial comparisons with the fixed-cluster version of the theory have been restricted to an incompressible system (as essentially in the prior theory when the *ad hoc* expansions in surface pressure are not invoked).

References:

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