Monte Carlo Study of Models of Membrane Proteins

T. P. Connor, D. L. Pagan, A. Shiryayev, J. D. Gunton

Department of Physics
Lehigh University, Bethlehem, PA, USA

ABSTRACT

The crystallization of membrane proteins from solution is sensitive to the role of initial conditions. In order to understand this dependence, we report preliminary results for two models for membrane proteins, each with short range attractive interactions. We determine the fluid-fluid coexistence curve for a square well attractive model in two dimensions at short attractive interaction range $\lambda = 1.1\,\sigma$, where σ is the hard core diameter. We also extend an earlier study of a two dimensional modified Lennard-Jones model.

Keywords: membrane proteins, nano-particles, self-assembly

1 INTRODUCTION

Recent advances in decoding the human genome have identified a huge number of proteins to be investigated. While there are many classes of proteins, one important class is that of membrane proteins, which are confined in or near the cell membrane. High quality crystals, free from defects, are required to determine the structure of these proteins by crystallographic means. Obtaining these crystals depends on understanding the initial conditions that give rise to optimal crystallization. While the structure of many globular proteins has been obtained over the past decade, membrane proteins are notoriously more difficult to crystallize, particularly so in three dimensions [1]. Difficulty arises in isolating interactions between the hydrophilic domains of the proteins in a lattice state. A two-dimensional crystallization in the presence of lipids, when the membrane proteins reconstruct into lipid membranes to form crystals, is a whole new way to determine the structure of the membrane proteins [2], [3]. Many studies [4]–[6] have been aimed at determining the optimal initial conditions for growing high quality globular protein crystals from supersaturated solutions. However, very few studies exist for membrane proteins.

Membrane proteins are nanoparticles that self assemble to form crystals. A typical membrane protein has three distinct domains: two hydrophilic extramembranous domains and the hydrophobic domain that spans the lipid bilayer. These nanoparticles regulate both the flow of ions through the cell and the shape of the actual cell membrane itself. Figure 1 shows an illustration [7] of integral membrane proteins and the cell membrane. The former are characterized as having a small range over which they interact and exhibit a dependence on the strength of the interaction. Until recently no theoretical studies of membrane proteins existed, with research focusing on three-dimensional globular proteins. For the latter, it is known that the details of the actual potential are unimportant, as long as the range of the attractive interaction is sufficiently short. As such, simulations of model globular proteins use different potentials such as the square-well [8], Yukawa [9], and modified Lennard-Jones (MLJ) [10] potentials and yield qualitatively the same results; namely, a metastable fluid-fluid coexistence curve, and a fluid-solid coexistence curve. Recently, a two dimensional MLJ model [10] has been proposed as a generic model of membrane proteins. It was expected that for values of the attractive interaction small in comparison with the protein size, a metastable fluid-fluid region would exist, as has been found in theoretical and simulation studies of globular proteins [4], [10]. Simulations of the two-dimensional model, however, were unable to detect a metastable fluid-fluid coexistence, as the model yielded quite a rapid crystallization. This indicated that the free-energy barrier that has to be overcome to form a crystal nucleus from solution is quite small. The authors were, however, able to esti-

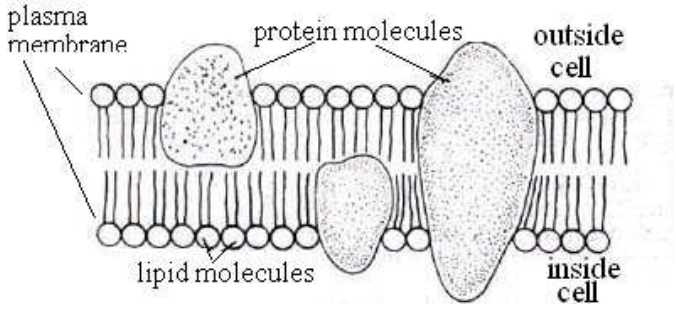

Figure 1: Illustration showing integral membrane proteins and the cell membrane. Not shown are peripheral membrane proteins which are associated with the surface of the plasma membrane.

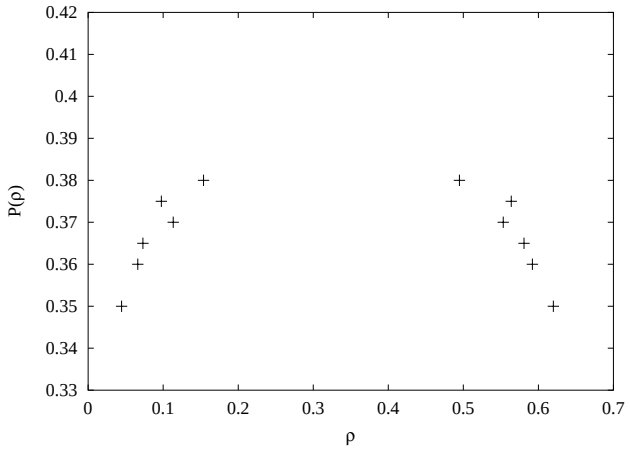

Figure 2: Fluid-fluid coexistence curve determined for the square well model.

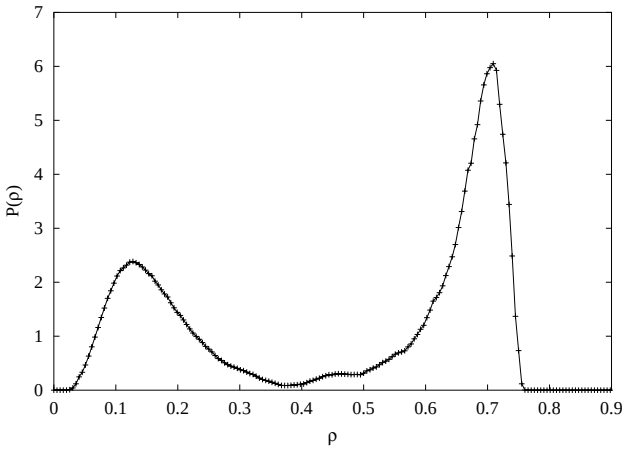

Figure 3: Density distribution obtained in a Monte Carlo simulation of membrane proteins along an isotherm.

mate the fluid-fluid spinodal curve – the locus of points in the phase diagram where the extrapolated value of the inverse isothermal compressibility vanishes.

In another study [11] the phase diagram of a model membrane protein, Annexin V, was determined, using a pairwise, directional interaction potential between proteins.

In this paper we extend these studies of models of membrane proteins by presenting preliminary results for two models with short-range attractions, in two space dimensions. The first is an attractive square well model; the second is the modified Lennard-Jones model, mentioned above.

2 ATTRACTIVE SQUARE WELL MODEL

Our first model is an attractive square well interaction model in two dimensions:

$$V_{SW}(r) = \begin{cases} \infty, & r \leq \sigma \\ -\epsilon, & \sigma < r \leq \lambda\,\sigma \\ 0, & r > \lambda\,\sigma \end{cases} \qquad (1)$$

This model has been studied in three dimensions [8] as a model of globular proteins, but until now has not been studied in two dimensions. To look for coexistence between two phases, we use the Gibbs ensemble Monte Carlo method. Two simulation cells are thermodynamically connected and allowed to exchange volume and particles. To determine coexistence, the conditions $\mu_l = \mu_v$ and $P_v = P_l$ are imposed on both cells, where μ denotes the chemical potential and P denotes the pressure. We sampled the system at various cutoffs to see where coexisting phases could be found. We started with $\lambda = 1.25\,\sigma$, since this is known to be the value in three-dimensions [8] above which no metastable coexistence curve is observed. We subsequently reduced the range of attractive interactions until coexistence was observed. The resulting coexistence curve is shown in Figure 2.

3 MODIFIED LENNARD-JONES MODEL

The second model [10] describes N particles in a two-dimensional box interacting via the modified Lennard-Jones (MLJ) potential

$$V(r) = \begin{cases} \infty, & r < \sigma \\ \frac{4\epsilon}{\alpha^2}\left(\frac{1}{[(r/\sigma)^2-1]^6} - \frac{\alpha}{[(r/\sigma)^2-1]^3}\right), & r \geq \sigma \end{cases} \qquad (2)$$

where σ denotes the hard-core diameter of the particles, r is the interparticle distance, and ϵ is the well depth. The potential was unshifted and truncated at a cutoff distance $r_c = 3.5\,\sigma$, to compare with benchmarks in the literature [10]. The parameter α controls the range of attraction between particles. For $\alpha = 50$ the range of attraction is short compared to the diameter of the particles. In the grand canonical ensemble, the number of particles N is allowed to fluctuate while the chemical potential μ, temperature T, and volume V are fixed. After each Monte Carlo cycle, the joint probability distribution of energy and number density is recorded in the form of histograms. To test for coexistence, the density distribution was examined to determine if any bimodal peaks were present, indicating the presence of two phase at densities ρ_l and ρ_v.

Using these simulations, we attempted to locate a bimodal peak in the density distributions at values of temperature T where a metastable curve was expected

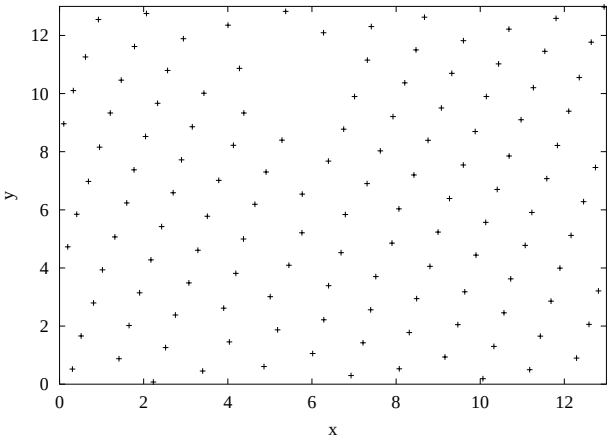

Figure 4: Configuration of the crystal state as obtained by starting the system in a vapor state at $T = .3124$ and $\mu = -2.43$. A regular lattice pattern evolves, along with some 'defects', during a single Monte Carlo simulation.

for the MLJ model. Figure 3 shows a density distribution at $T = .3125$ and $\mu = -2.43$. The bimodal peaks, however, do not correspond to fluid-fluid coexistence, but rather to fluid-solid coexistence. Further investigation reveals that this distribution does not correspond to an equilibrium state; allowing the simulation to continue reveals that the system starts in a fluid phase and subsequently 'crystallizes' into a single solid phase, as shown in Figure 4. A definite lattice structure is observed, confirming the previous findings that there is a low free-energy barrier in the two dimensional MLJ model, as opposed to the MLJ model of globular proteins in three dimensions [5], [12].

4 DISCUSSION

In this work, we report preliminary results for two models of membrane proteins. We were able to determine the fluid-fluid coexistence curve for an attractive square well potential, with $\lambda = 1.1\,\sigma$. Future work is needed to determine whether this is in a stable or metastable region of the phase diagram. We will also study the model for shorter range attractive interactions. Our results to date for the phase diagram of the MLJ model are consistent with the previous study [10].

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