Fascinating vesicles?

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Chapter 7

Epilogue

Implications

In this thesis we showed that lipid liposomes can be successfully studied using the MARTINI coarse grained model along with the MFFA boundary approach presented. As shown in chapter 2, the MFFA boundary method has proven to be a useful tool for both the fast formation and equilibration of the vesicle. Future molecular dynamics studies concerning lipid liposomes can definitely benefit from the MFFA boundary method in combination with artificial pores. Whereas the MFFA boundary approach speeds up the computations considerably, the use of artificial pores provides the possibility to determine the equilibrium state of a vesicle. An important insight which we gained from our studies is the fact that simulation and equilibration of lipid vesicles appears far from trivial, as illustrated by the following three findings:

i) Vesicles which are formed by spontaneous aggregation are not necessarily equilibrated. As demonstrated in chapter 3, some optimization processes which take place in the vesicle, such as the transversal demixing of different lipid types, occur on timescales of microseconds, much beyond the actual formation time of the vesicle. As a result of these slow equilibration times, vesicles can still possess a significant pressure difference between their interior and exterior solvent (cf. section 4.3.1) after their formation. Many vesicular systems which have been used in the lit-

erature studies reported so far are likely based on not well-equilibrated systems.

ii) As shown in chapter 3 the optimal population distribution of lipids in the membrane is temperature-dependent. Thus one should take care when simulating a particular vesicle at other temperatures. Strictly speaking, the equilibration has to take place at the temperature of interest. The same applies to modifications in the composition, or to changes in the state conditions in general.

iii) In vesicular systems, the use of standard pressure coupling schemes based on the derivation of pressure from the virial of the whole system is inappropriate when a pressure difference between the interior and exterior solvent is present. In this case both the coupling to the average system pressure as well as scaling the system volume with a constant factor is not correct. A Langevin piston method, as presented in chapter 4, is in such cases required.

Further improvements

The biggest concern of the present boundary methods is the fact that the liposomal membrane undulations can be restricted and correlated. Undulations in the membrane are dependent on the thickness of the solvent layer which embeds the vesicle. As hydrodynamic correlations are long ranged, in practice undulations in the vesicle membrane are artificially correlated and suppressed in simulations by both periodic- and MFFA boundary conditions. With the present molecular dynamics techniques, a correct description of membrane undulations would require an unpractical amount of, computationally expensive, excessive solvent, rendering the actual aim of the simulation unfeasible. Unfortunately,

within the solvent shell approach, the problem of having correlated or suppressed undulations increases with more relevant vesicle sizes. Therefore there is an increasing need to further develop boundary methods with implicit flexibility, which would allow a correct representation of membrane undulations without losing computational efficiency.

Future applications

Within the era of synthetic biology, and the ultimate aim to develop and control artificial cells, computer modeling of vesicular systems will become more and more important. Here we list a few potentially interesting applications for the near future:

i) The fact that the local stress environment in a curved membrane differs from a planar membrane allows the possibility to simulate membrane proteins in different stress environments. Studying membrane proteins embedded in a liposomal membrane may provide useful insights about the specific role of local curvature on structural changes in the protein. The recently developed code to calculate the 3D local pressure field allows a quantitative intepretation of the results.

ii) The ability of coupling pressure both inside and outside the liposome independently using the boundary Langevin piston method along with the ability to locally define the pressure, allows the intriguing possibility to simulate osmotic shocks. This opens the way to study, for instance, the gating mechanism of mechano-sensitive channels under realistic conditions or to investigate the rupture limit of liposomes under stress. In addition, the same setup might also form a useful tool to study stress effects in other systems such as virus capsids.

iii) At present the simulation of raft formation in ternary lipid systems is still beyond the computational limit for atomistic simulations. The coarse grained raft system as presented in chapter 5 can provide realistic configurations as a starting point for all-atom molecular dynamics simulations. To achieve such change of resolution, coarse-grained configurations of a formed raft can be back-mapped to their underlying atomistic counterparts using multi-scaling approaches. This enables to study these systems at the full atomic level of resolution, and, at the same time, can form the basis for further systematic improvements of the coarse-grained methodology.

iv) The detailed structure of domain-containing liposomes can be directly compared with experimental data based on neutron scattering techniques. Under the prerequisite that the experimental studied vesicles are of similar size range and membrane composition, the scattering data can be directly compared with the data reproduced from the simulated liposome. Such a comparison would provide very useful imformation for both the interpretation of the experimental data as well and the refinement of the coarse grained model.