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Of Stalks and Diamonds. Simulation Studies of Membrane Fusion and the Role of Fusion Peptides

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Chapter 1

Introduction

God could cause us considerable embarrassment
by revealing all the secrets of nature to us: we should
not know what to do for sheer apathy and boredom.
Johann Wolfgang von Goethe

Membranes composed of lipids define the boundary between interior and outside in all of cellular life, and on top of that establish a complex compartmentalization that is indispensable for a large range of vital functions in all but the most primitive organisms. As such, the study of lipids is a topic of great scientific interest simply by virtue of its importance.

However, their biological relevance is not the only reason to devote time and effort to lipids. While it is the behavior of lipid aggregates that provides cells with the delicate balance between stability and plasticity needed for such tasks as fusion, fission and transport, this behavior is a fascinating topic in its own right, displaying a remarkable contrast between the diversity and complexity of shapes adopted and the relative simplicity of the underlying lipid building blocks.

And, last but certainly not least, lipid polymorphism is a very beautiful topic with a great appeal to the human imagination. If the beauty of science lies in the establishment of order in the phenomena of nature, then lipid polymorphism is one of those areas where the order is especially visible within the manifested phenomena themselves, indicating the richness and complexity of shapes hidden within each individual lipid.

Due to the topic's intimate connection to shape, it is also a topic asking for visualization while being invisible to the human eye. For this purpose, experimental techniques face difficulties, especially when the focus is on the dynamic processes underlying topological changes of the lipid aggregates. Computer simulations, on the other hand, are intrinsically visual techniques, but face different limitations concerning the accessible system sizes and time scales. However, with the steady increase of available computational power and improvements in the efficiency of the methods, simulational techniques can be seen as a powerful tool for the study of lipid aggregates, especially when using simple models for the representation of the molecules and their interactions.

While the intrinsic reliance on models can be seen as a source of concern when it comes to the reliability of conclusions based on simulational data, it is not entirely of disadvantage. In fact, the use of a model eliminates hidden variables, allowing researchers to study a system that is completely known. In principle, it is therefore possible to observe the level of phenomena encountered in direct dependence on the interactions included in the model, making simulations an especially interesting method to use and one well suited for the study of lipid polymorphism.

On the following pages, some attempts at shedding light on the process of membrane fusion will be presented, using molecular dynamics simulations based on a coarse-grained model. In particular, the presentation is organized as follows:

- Chapter 2 will start with a short introduction to the basic concepts needed to understand the work presented and provide the context for the later chapters.
- In Chapter 3, the general feasibility of simulating vesicle fusion with our model is assessed, and evidence for an alternative fusion pathway is presented.
- Chapter 4 investigates the effects of the Influenza HA fusion peptide on stalk formation and the phase diagram of representative mixtures of lipids and water. In addition, the single diamond phase, a previously unreported bicontinuous cubic phase, is described.
- Chapter 5 presents a program for the morphological analysis of coordinate sets representing binary mixtures, using the technique of morphological image analysis to characterize the global geometry and topology of the system in terms of Minkowski functionals. As an extension of this method, the determination of local curvatures is described.
- Chapter 6, finally, deals with a somewhat different topic – the effects of introducing bundling, *i.e.* relative restraints on groups of molecules, to the SPC water model, which is required for the simultaneous representation of water at the fine- and coarse-grained level in multiscaling simulations.
- Chapter 7 concludes the presented work with a summary and outlook.