Exploring Vesicle Fusion with Dissipative Particle Dynamics

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Computer models of biophysical processes are important both for understanding their generic features and for visualizing their dynamics **[1]**. Many interesting phenomena occur on length and time scales beyond the reach of traditional Molecular Dynamics (MD), and this has led to the development of so-called *mesoscopic* simulation methods. We have been using Dissipative Particle Dynamics (DPD) to construct improved models of amphiphilic membranes and explore the pathway of vesicle fusion. We have recently published an invited review of simulation methods applied to these soft matter systems **[2]**. Natural membranes, such as the cellular plasma membrane, are a complex mixture of many types of lipid molecule and protein. We have continued to study the material properties of amphiphilic membranes as models of lipid bilayers. The effects of molecular architecture **[3]** and a mixture of two molecule types with different tail lengths and intermolecular interactions **[4]** have been simulated using DPD (**Fig. 1**) by Gregoria Illya (now a post-doc at the MPI for Polymer Research in Mainz). The elastic properties of a membrane composed of two lipid species was also simulated **[5]** using coarse-grained Molecular Dynamics by Alberto Imparato (now a post-doc at the Politecnico di Torino in Torino, Italy). The two techniques produced similar results, indicating that the membrane properties are robust against changing the details of the simulation techniques.

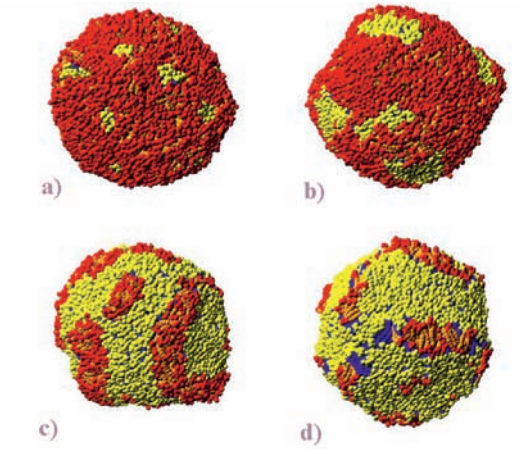

Fig. 1: Phase separation in a vesicle composed of two kinds of lipid with different hydrophobic tail lengths as a function of the longer-tailed lipid concentration (from [4]). The shape of the domains differs from those formed in planar bilayers containing the same lipid types and concentrations because the curvature of the vesicle influences the domain growth. The number fractions of the longer-tail lipid (shown with yellow heads) are as follows: a) 0.1, b) 0.3, c) 0.7, and d) 0.9. The shorter-tail lipids are shown with red heads.

A quite different class of vesicle-forming amphiphiles consists of diblock copolymers, such as poly(ethylene oxide)-polyethylethylene (PEO-PEE). These materials are important for applications such as drug delivery because they form vesicles that are more robust than lipid vesicles, and are not recognised as foreign by the human immune system. In collaboration with the groups of Professors M. Klein and D. Discher at the University of Pennsylvania, we have created a DPD model of PEO-PEE membranes and vesicles and calibrated the DPD parameters using MD simulations on smaller systems **[6]**. This illustrates one way of extending the more accurate, but far more computationally-expensive, MD technique to molecules and system sizes closer to biologically-relevant processes. One application, performed by the Discher group using our DPD code, is to the behaviour of stable pores in the nuclear membrane **[7]**.

Vesicle fusion is a vital cellular function, but the molecular rearrangements that occur when intact membranes approach, merge and fuse cannot yet be observed in experiments. We have extended our previous model **[8]** of tension-induced fusion in two independent ways. The first method replaces the global tensions in the membranes with local forces exerted by transmembrane barrel "proteins" that transduce forces into the membranes (**Fig. 2**).

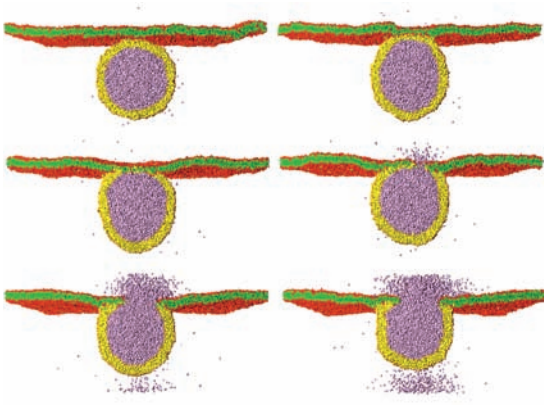

Fig. 2: Sequence of snapshots showing the fusion of a 28 nm diameter vesicle (yellow/orange beads) to a (100 nm)^2 planar membrane (green/red beads). Time proceeds across each row (from [2]). Both membranes are tensionless, and their fusion is driven by local forces exerted by membrane-spanning barrel "proteins". Six barrels are positioned in each membrane in an hexagonal arrangement. A specific force protocol is applied to the barrels to drive the membranes to fuse. After the system has equilibrated, oppositely-oriented bending moments are created in each membrane for 80 ns to bend them towards each other. When the membranes' proximal leaflets have touched, the bending moments are removed and the system is allowed to evolve for 32 ns in order for the two proximal leaflets to merge somewhat. An external force is then applied to the barrels in both membranes so as to raise the tension in the encircled contact zone. The force has a magnitude Fext = 0.4 k_BT/a_0 and is directed radially outward (a_0 is the bead diameter). It is applied in this instance for 64 ns. Once the pore has appeared, it initially expands under the pressure of the inner solvent flowing outwards, but as the membrane relaxes back to its tensionless state it shrinks.

The second method retains the global tensions as the control parameters, and uses a systematic exploration of new parameter sets to develop a more accurate representation of the membrane's mechanical properties (**Fig. 3**). One such parameter set **[9]** was introduced by Lianghui Gao (a post-doc now in Beijing, China) and shows that finite-size effects must be carefully assessed before the model can be compared with experimental systems. This result is important for the development of simulations of many soft matter systems. Lianghui Gao and Andrea Grafmüller, a PhD student, have independently produced two new membrane parameter sets that reveal more details about the pathway of tension-induced vesicle fusion. Key features of these parameter sets are that the membrane is less stretchable than before, and the relation between its tension and area per molecule is linear over the whole range of tensions for which the membrane is intact.

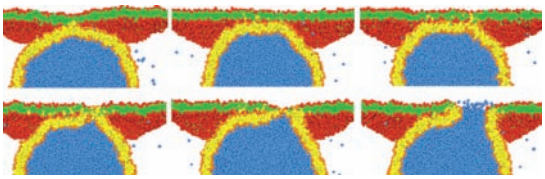

Fig. 3: Fusion pathway of a 30 nm diameter vesicle (yellow/orange beads) to a (50 nm)^2 planar membrane (green/red beads) driven by tension. Time proceeds across each row (from [10]). The stages of fusion are: adhesion of vesicle to membrane (snapshot 2); flip-flop of lipids from the vesicle to the planar membrane (snapshot 3); formation of a disordered, irregularly-shaped contact zone (snapshot 4); transformation of part of the contact zone into a hemifused lamella state (snapshot 5); rupture of the hemifused patch and growth of the fusion pore (snapshot 6).

Andrea Grafmüller has used one of the new parameter sets **[10]** to simulate the fusion of a vesicle to a planar membrane (**Fig. 3**). Both small, 15 nm diameter, and large, 30 nm diameter, vesicles have been followed as they interact with a planar membrane patch that is 50 x 50 nm^2. These simulations have revealed that the fusion of a relaxed vesicle to a tense membrane passes through two energy barriers. The first corresponds to the time required for individual lipid molecules to flip-flop from the (relaxed) vesicle to the (tense) planar membrane; and the second to the appearance of the fusion pore in a bean-shaped disordered region created by the mingling of vesicle and planar membrane lipids. This result may be important for interpreting fusion experiments as most theoretical models to date assume a single energy barrier in the fusion pathway.

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