HIGHLIGHT

Coarse-Grained Models and Collective Phenomena in Membranes: Computer Simulation of Membrane Fusion

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ABSTRACT: We discuss the role coarse-grained models play in investigating collective phenomena in bilayer membranes and place them in the context of alternative approaches. By reducing the degrees of freedom and applying simple effective potentials, coarse-grained models can address the large time scales and length scales of collective phenomena in membranes. Although the mapping from a coarse-grained model onto chemically realistic models is a challenge, such models provide a direct view on the phenomena that occur on the length scales of a few tens of nanometers. Their relevance is exemplified by the study of fusion of model membranes. © 2003 Wiley Periodicals, Inc. J Polym Sci Part B: Polym Phys 41: 1441–1450, 2003

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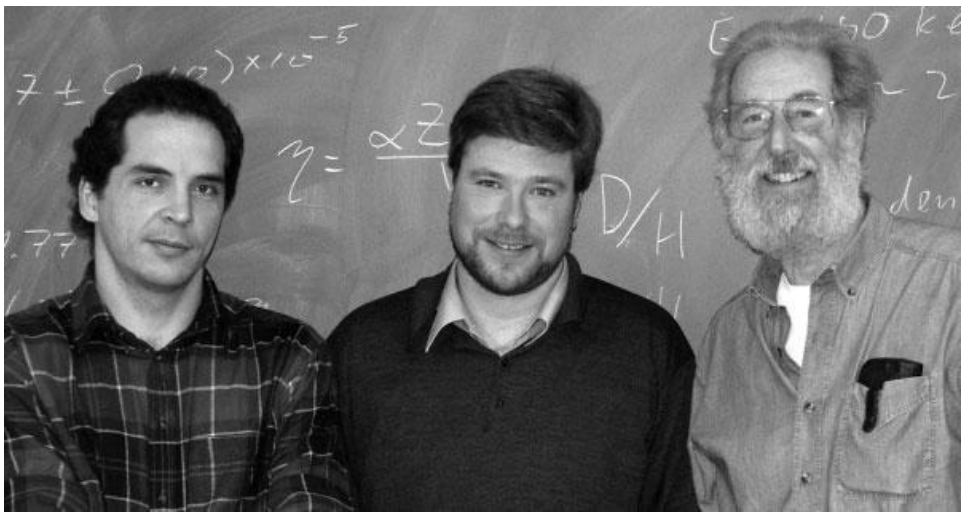

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INTRODUCTION

The behavior of complex molecular systems can be analyzed on different time and length scales. The particular choice of the level of detail, or abstraction, depends on the problem at hand. For instance, one may be interested in single-molecule properties in a large system or, at the other extreme, the macroscopic description of bulk-phase transitions. Just as different experimental techniques are suited for studying different phenomena, theoretical approaches vary in their ability to describe different aspects of complex systems. Biological systems undoubtedly present an example of extreme complexity. They have inspired the development of a wide range of experimental as well as theoretical tools to aid their study. One of the main problems is to link these experimental and theoretical descriptions across the hierarchy of time and length scales. It would be a formidable task even to list all the possible tools available to theorists interested in biological problems. Instead, we consider the theoretical description of lipid bilayer membranes, deceptively simple systems with a very rich behavior on a wide range of scales.

Lipid molecules play an important role in a multitude of chemical and biological processes. By virtue of their amphiphilic architecture, lipids self-assemble into spatially periodic microphases. Lamellar-forming lipids are the basic building blocks of biological membranes. Bilayer membranes serve as semipermeable barriers that organize space into compartments and provide a medium for proteins to function. Lipid molecules are also involved in collective phenomena that change the topology of the compartments by fusion,[1–3] lysis, budding, or pore formation. Despite the fact that these collective phenomena are involved in fundamental biological processes such as fertilization, synaptic release, intracellular traffic, and viral infection, their basic mechanism is not well understood.

Much of the difficulty in obtaining a microscopic view of these collective phenomena can be traced to the length and time scales on which these processes occur—a few tens of nanometers and milliseconds. These scales are not amenable to direct experimental observation or a fully atomistic theoretical study. Indirect experiments, such as those that examine the dependence of the fusion rate on lipid architecture,[4,5] and phenomenological models have made valuable contributions to the understanding and control of these collective processes. A more direct and dynamic picture of these phenomena can be obtained within a framework of coarse-grained simulations. This technique can address the pertinent win-

dow of time and length scales, unattainable by atomistic simulations, with a reasonable computational effort.

We do not discuss collective phenomena within a large single molecule (e.g., conformational changes as they occur in protein folding), nor do we attempt to provide a complete survey about membrane models. We rather give an account of our simulation of fusion of model membranes[6] and place it within the context of other approaches. We briefly discuss the computational models that describe bilayer membranes on different coarse-graining levels, the problems that can be addressed by them, and the connections among the different approaches. We then illustrate the role of coarse-grained models by applying one to membrane fusion. Details of this investigation will be published elsewhere. We close with an outlook and with open questions.

MODELS

Because processes in membranes evolve on vastly different time and length scales, a variety of membrane models has been devised. We divide them roughly into atomistic, coarse-grained, and elasticity models.

Atomistic models describe bilayer properties with chemical accuracy. Molecular architecture and interactions are faithfully modeled including electrostatic interactions, torsional, and bending potentials. Ideally the interactions are derived from *ab initio* calculations. Routinely molecular dynamics simulations are used to examine membrane patches of a few nanometers over timescales of a few tens of nanoseconds.[7,8] This gives information[9] about the bilayer structure, a detailed description of the hydrophobic/hydrophilic interface, the orientation of segments, the role of undersaturation of lipid tails or of the addition of non-lamellar-forming lipids, and the interactions with small inclusions like peptides or cholesterol.[10] Dynamic properties, for example, the lateral self-diffusion of lipid molecules or the transport properties of small molecules across the bilayer, are also accessible.[11] With rare exceptions (see, e.g., ref. 8), the bilayer structure has to be preassembled because the time scale of self-assembly from a homogeneous mixture of lipids and water typically exceeds the simulation time scale. Phase transitions and out-of-plane structures, which occur in budding, are also beyond the scope of atomistic modeling. Nevertheless, it is possible to extract effective material properties, such as tension and elastic moduli, from these simulations.

Coarse-grained models do not attempt to describe the large-scale phenomena starting from the smallest atomic length scale but rather lump a small number of atoms into an effective particle.[12–20] These particles interact via coarse-grained, simplified interactions. Electrostatic and torsional potentials are typically neglected in these models. The reduced number of degrees of freedom and the softer interactions on a coarse scale lead to a significant computational speed-up. Hence, larger systems and longer time scales can be investigated. The objectives of mesoscopic models are twofold. They help to identify interactions that are necessary to bring about collective phenomena on a mesoscopic scale, such as self-assembly. This information yields qualitative insight into the way that parameters on a microscopic level influence the mesoscopic behavior. An example is provided by the means in which the architecture of lipids influences the structure of the self-assembled system. Also, this class of models elucidates the universal behavior on the mesoscopic scale itself (e.g., the role of thermal fluctuations or the existence of phase transitions between self-assembled morphologies). They also are an ideal testing ground for phenomenological concepts. Coarse-grained models can be studied by a variety of techniques—Monte Carlo simulation, molecular dynamics, dissipative particle dynamics,[19,21,22] dynamical density functional theory,[23] and self-consistent field theory.[24–27] The basic problems that limit the predictive power of coarse-grained models are the identification of time, length, and energy scales to be used as compared with the experiment and the identification of the degrees of freedom and interactions to be retained at the coarse-grained scale to incorporate the essential physics of the system.[28] Some of these problems can be addressed by "systematic" coarse-graining procedures[29] (discussed below) or by comparing different coarse-grained models. By doing so, one can gauge the degree of universality and the relevance of interactions. This yields much insight into the mechanisms that underly the phenomena.

Elasticity models are at the other end of the spectrum of theoretical treatments of membranes.[30] The description of particles is dropped altogether, and the membrane is modeled on the level of average material properties. In the simplest case, it is conceived as an infinitely thin, elastic sheet, characterized by a small number of mesoscopic coefficients—tension, spontaneous curvature, and bending rigidity.[31] Despite the apparent simplicity, the statistical mechanics is quite intricate and results in a rich phase behavior.[14,15,32–35] This approach also forms the basis of the phenomenological description of fusion.[36–42] Although these models can address large length scales (e.g., changes of the topological structure of an assembly of membranes), they have difficulty describing the processes that evolve on the scale of the membrane thickness itself and cannot describe those that involve changes in lipid conformations.

The division of models presented above is not absolute. There are approaches that unite techniques from the

different classes, thus providing a smooth transition across the time and length scales. For example, dissipative particle dynamics simulation has been used to investigate an elastic membrane model in which "particles" represent small patches of the membrane.[43]

The coarse-graining of atomistic models is usually a conceptual step, rather than a well-defined quantitative procedure. It relies on the observation that a variety of real physical systems with very different microscopic interactions share the same qualitative behavior on the mesoscopic scale. For example, amphiphilic polymers in aqueous solutions form polymersomes, which exhibit behavior similar to that of liposomes and biological cells.[44,45] This includes, in particular, fusion and rupture of bilayer membranes. In addition, the self-assembled phases in lipid-water mixtures are also found in diblock copolymer melts.

The main goal of "conceptual" coarse-graining is to sacrifice atomistic detail to gain computational advantage while retaining only those architectural distinctions and interactions needed to bring about mesoscopic phenomena of interest. In the case of lipid molecules (or any extended amphiphilic molecules), the latter are considered to be the partitioning of the lipid molecules into a hydrophilic "head" and a hydrophobic "tail" and the strong repulsion between hydrophilic and hydrophobic entities. Even if the interactions on the microscopic scale are extremely complex, they can often be captured qualitatively by simplified interactions on the mesoscopic length scale. Coarse-grained models are well suited to examine the generic, universal features of mesoscopic behavior. By extracting large-scale quantities, such as bilayer thickness, tension, bending rigidity, and viscosity, from a coarse-grained model and comparing those to experimental data one can identify time, length, and energy scales of the phenomena. Unfortunately, a single identification of scale factors cannot reproduce all of those large-scale quantities simultaneously.

The use of coarse-grained models to describe polymeric systems has a long tradition.[29,46–49] In polymer solutions and melts, the elimination of the degrees of freedom is justified by the self-similar structure on a great range of length scales from the statistical segment length to the polymer's radius of gyration. Because of this, the coarse-graining procedure in such systems can formally be performed exactly within the framework of the renormalization group.[50–52] Recent efforts have been directed toward coarse-grained polymer models that not only capture the generic features of polymers on the coarse-grained scale but also retain information about the underlying chemical structure. These "systematic" coarse-graining approaches aim at designing models that bridge the length and time scales from atomistic to macroscopic.[47,53,54] To this end, one chooses a set of structural and thermodynamic quantities of the underlying atomistic systems (e.g., extracted from an atomistic simulation or measured in experiments) and constructs interactions between the coarse-grained degrees of freedom to reproduce those quantities. Typical choices[29,46] include geometrical characteristics of the molecules, the distribution of distances between entities, and thermodynamic properties. Shelly et al.[55] used a very similar procedure to construct a coarse-grained model of phospholipid membranes. This systematic coarse-graining procedure serves a twofold purpose. First, it permits the prediction of properties inaccessible to atomistic simulations. Second, it allows the reintroduction of atomic degrees of freedom and the smaller length scales they entail once the coarse-grained model has equilibrated on a large length scale. Systematic coarse-graining procedures promise the possibility of constructing models tailored to specific systems and problems. Nevertheless, there are caveats. As the interactions on the coarse-grained scale differ qualitatively from the atomistic interactions, they are not transferable,[29] that is, the systematic coarse-graining procedure is specific to a particular state point specified by temperature, pressure, and so forth. Moreover, a small inaccuracy in the free energy on the atomistic scale can give rise to dramatic changes on mesoscopic or macroscopic length scales. This holds *a fortiori* in the vicinity of phase transitions where one encounters a singular dependence on system parameters. Thus, much of the quality of the coarse-graining depends on a careful choice of the set of quantities used for the mapping and the type of interactions in the coarse-grained model.[56]

Notwithstanding the limitations of coarse-grained models, they offer important qualitative insights and test the accuracy of phenomenological concepts. In the following, we illustrate their usefulness in the context of simulating fusion of model membranes. Details of the simulation will be given elsewhere.[6]

EXAMPLE: FUSION OF MODEL MEMBRANES

Two bilayer membranes under tension fuse when brought in close apposition. Although proteins play an important role in overcoming the free energy barrier associated with bringing the two membranes together, the proper fusion event (i.e., the interruption of the bilayer integrity and the formation of a fusion pore) is thought to be determined by the properties of the lipid bilayer itself.[1] Theoretical descriptions have focused almost exclusively on elasticity models, which describe the bilayers by the bending properties of its monolayers. Although the description is successful in rationalizing the dependence of the fusion rate on the lipid architecture

Table 1. Structural and Elastic Properties of Bilayer Membranes

	Polymersomes	Liposomes	Simulation
d_c	80 Å	30 Å (DOPE), 25 Å (DOPC)	$21u$
f	0.39	0.35 ± 0.10	0.34375
$C_0 d_c$	No data	−1.1 (DOPE), −0.29 (DOPC)	−0.68
$\Delta A/A_0$	0.19	0.05	0.19
κ_a/γ_0	2.4	4.4 (DOPE), 2.9 (DOPC)	4.1
$\kappa_b/\gamma_0 d_c^2$	0.044	0.10 (DOPE), 0.12 (DOPC)	0.048

d_c is the thickness of membrane hydrophobic core, f is the hydrophilic fraction, C_0 is the monolayer spontaneous curvature, $\Delta A/A_0$ is the bilayer area expansion (critical value for the experimental systems, and the actual strain used in simulations), κ_a is the bilayer area compressibility modulus, κ_b is the monolayer bending modulus, and γ_0 is the hydrophilic/hydrophobic interface tension (oil/water tension of 50 pN/nm for the experimental systems, and A/B homopolymer tension for the simulations). Data on EO7 polymersomes is taken from ref. 41; and on lipids from ref. 68 and 69. Values of κ_b and γ_0 for the simulated model were calculated by us an in ref. 65.

and membrane tension and is compatible with the mixing of the lipids in the two apposing cis layers, the application of elasticity models relies on two assumptions. First, one has to assume a specific fusion pathway.[36,41,58] The starting point is two tense bilayers in close apposition. Lipids in the facing, proximal, or cis layers rearrange locally and bridge the aqueous gap between the bilayers. This results in the formation of an axially symmetric stalk. In most versions, the stalk then expands radially and the cis layers recede. The distal trans layers make contact and produce an axially symmetric hemifusion diaphragm. Nucleation of a hole in this diaphragm completes the formation of an axially symmetric fusion pore. Second, it is assumed that expansions quadratic in the curvatures are adequate to calculate the properties of highly curved structures that occur when the bilayers join. These approximations have a great influence on the estimate of the free energy of the transition state. In contrast, computer simulations of coarse-grained models prove valuable in providing direct information about the fusion process of model membranes without invoking these additional assumptions.

In our Monte Carlo simulation, we used a coarse-grained three-dimensional lattice model, the bond fluctuation model.[16] Each effective segment is represented by a unit cube that blocks all eight corners from additional occupancy. Hydrophilic and hydrophobic segments repel each other, whereas segments of the same kind attract each other if their distance is smaller or equal than $\sqrt{6}$ in units of the lattice spacing u. Each contact involves the energy $0.17689 k_B T$. "Lipids" consist of 11 hydrophilic and 21 hydrophobic linearly connected segments. The hydrophobic/hydrophilic asymmetry used by us mimics the ratio of head and tail size in biologically relevant lipid molecules. The segments along a molecule are connected by bonds of length 2, $\sqrt{5}$, $\sqrt{6}$, 3, or $\sqrt{10}u$. The solvent is modeled by flexible chains of 32 hydrophilic units, that is, we conceive a hydrophilic chain as a small cluster of solvent molecules.

The model incorporates the relevant aspects of amphiphilic solutions—excluded volume of the segments, connectivity of hydrophilic and hydrophobic segments along the amphiphile, and repulsion between hydrophilic and hydrophobic entities—but we cannot provide a derivation in terms of a "systematic" coarse-graining procedure for a specific biological lipid membrane. Many properties of the model are known, however, and it can be quantitatively compared to the standard Gaussian chain model. The repulsion corresponds to intermediate segregation $\chi N \approx 30$ in terms of the Flory–Huggins parameter χ.[59]

A comparison of the relevant large-scale structural and elastic properties of our simulation model to liposomes and polymersomes is presented in Table 1. Identifying the length scale by the thickness of the hydrophobic region of the bilayer and the energy scale by the tension of the hydrophilic/hydrophobic interface, we obtain agreement for polymersomes (i.e., large vesicles formed by amphiphilic polymers in solution[44]) and reasonable agreement for lipidic vesicles. The simulation model does not differ from the experimental system more strongly than the two distinct systems, which exhibit bilayer fusion, differ from one another. This observation inspires reasonable confidence that our coarse-grained model indeed captures the appropriate interactions to describe the universal aspects of the fusion process.[60]

The simulations of fusion are performed in the canonical ensemble in a cell of geometry $156u \times 156u \times 128u$ with periodic boundary conditions. Two flat, tense, preassembled bilayers of area $156u \times 156u$ and thickness $25u$ are stacked on top of each other with a

spacing of $10u$. A single tense bilayer is stable on the time scale of the fusion event. Each system comprises 3613 amphiphiles and 3708 effective solvent clusters. Thirty-two independent simulation runs are performed. The initial stages of the two runs are presented in Figures 1 and 2 panel A. Two slightly different fusion paths—Figures 1 and 2—are observed in our simulations. During the initial stage of the simulation, the two bilayers collide with one another frequently and sometimes form small local interconnections. For the most part, these contacts are transient. Occasionally we observe sufficient rearrangement of the amphiphiles in each bilayer to form a configuration, the stalk (panels B), that connects the two bilayers. Stalks are metastable, and their lifetime is smaller but comparable to the timescale of fusion, that is, some stalks vanish without proceeding further to a fusion pore. After the stalks are formed, the rate of formation of holes in either of the two bilayers increases, and holes form preferentially in the vicinity of stalks. These configurations are depicted in panels C. The stalks begin to surround the holes to reduce their line tension. Two other events occur to complete the formation of the fusion pore, and they can occur in either order leading to two slightly different fusion paths. In the first, shown in Figure 1, the stalk completely encircles a hole to form the rim of the fusion pore (panel D). This structure looks similar to the radially extended stalk, the hemifusion diaphragm, but it consists of the two monolayers of the upper membrane and not of the two distal trans layers of different membranes as hypothesized by phenomenological approaches.[41,42,58] Formation of the rim is followed by the appearance of a second hole within the diaphragm (panel E) completing the fusion pore. Once the pore has formed, it expands, driven by the reduction in surface tension (panel F). The alternative path is also shown in Figure 2. Before the stalk completely surrounds one hole, a second hole forms in the other bilayer (panel D). The stalk completely encircles both holes (panel E) and aligns them. This completes the fusion pore (panel F).

DISCUSSION AND OUTLOOK

The mechanism of fusion observed in the simulations of our coarse-grained model begins with a stalk, as proposed by other fusion scenarios. The subsequent evolution, however, differs from almost all other mechanisms. In particular, the fusion intermediates we observe in the simulations break the axial symmetry, a possibility that has not been considered in previous studies.

A fusion mechanism similar to the pathway in Figure 2 has been seen independently in simulations of a very different coarse-grained model.[18] In these Brownian dynamics simulations, amphiphiles were described by short rigid rods, and no explicit solvent was used. The apparent insensitivity to details of the simulations model is very important as it suggests that the fusion mechanism is rather universal and that coarse-grained models are adequate to investigate these collective phenomena.

Importantly, the simulations provide a qualitative, yet direct, rationale for experimental observations. Experiments[61,62] observe transient mixing of the lipids between the trans and cis leaves. This process is different from the usual lipid flip-flop that is a very slow process. An increased mixing of the lipids between the two leaves of the same membrane is also observed in the simulations. Part of this is due to an overall thinning of the bilayer caused by the imposed tension that results in flip-flop barrier reduction. In addition, this mixing is facilitated by the formation of transient holes that are promoted by the stalks. There is ample experimental evidence[61–69] that fusion is very frequently accompanied by leakage. Most experiments cannot address the question of whether fusion and transient membrane permeability are indeed correlated in space and time. However, in a recent electrophysiological study,[65,69] it has been convincingly demonstrated that these processes are dynamically correlated. In our simulations, this effect can be easily explained by the formation of transient holes, in the individual bilayers, that play a pivotal role in the fusion mechanism.

The comparison to experiment demonstrates the value of the coarse-grained model that should serve as a good starting point for further investigation of the following issues.

First, knowledge of the free energy barriers along the fusion path is important for controlling fusion and concomitant processes. Although free energy barriers are difficult to measure in simulations, coarse-grained models can be investigated by a variety of computational techniques. For instance, our model can be mapped onto the standard Gaussian chain model for which self-consistent field theory[26,70–72] can be used to calculate the free energy of different intermediates and transition states.

Second, much experimental effort has been directed toward understanding the role of non-lamellar-forming lipids on the fusion rate.[4,5] Their effects also can be addressed with coarse-grained models.

Third, coarse-grained models may also provide input for the approaches on the basis of elasticity theory as one can extract from the former the bending rigidities and spontaneous curvatures required for the latter.[72] Coarse-grained models can also provide direct information about the structure of bilayer junctions. An accurate description of this structure has proven to be crucial in calculating, with elasticity theory, the free energy of the transition state.

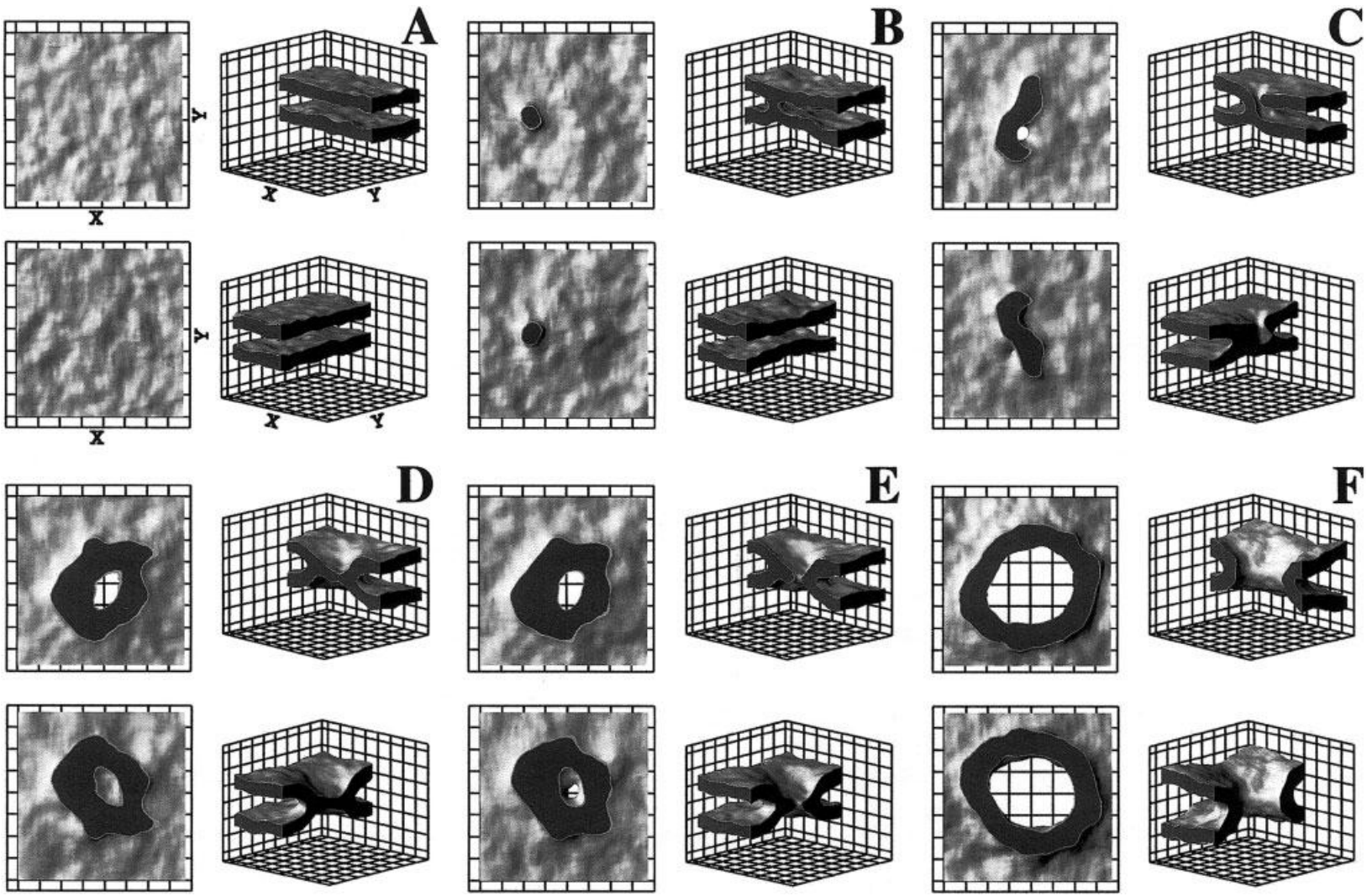

Figure 1. Observed pathway of fusion process. The snapshots were taken from a representative simulation run. Each configuration is shown from four different viewpoints. The hydrophobic core is shown as dark gray; the hydrophilic–hydrophobic interface (defined as a surface on which densities of hydrophilic and hydrophobic segments are equal) is light gray. Hydrophilic segments are not shown for clarity. Top and bottom left subpanels have been generated by cutting the system along the middle x–y plane; the top and bottom halves are viewed in the positive (up) and negative (down) z direction, respectively. Top and bottom right subpanels are side views with cuts made by x–z and y–z planes, respectively. Grid spacing is $20u \approx 1.2\ R_e$.

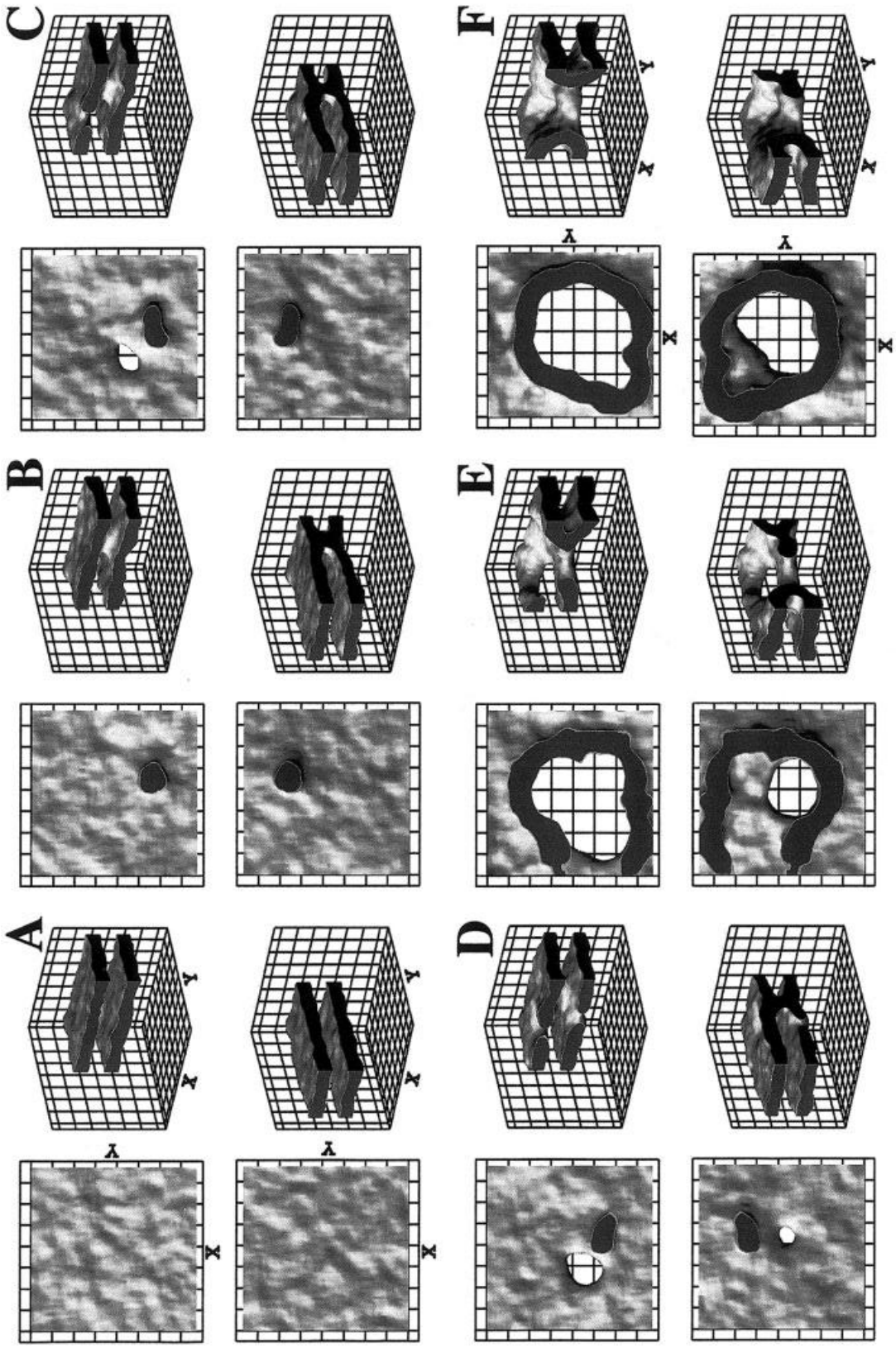

Figure 2. See caption to Figure 1.

Fourth, is the development of models with some chemical specificity. We note that our coarse-grained model reproduces the characteristic data of polymersomes better than that of liposomes (c.f. Table 1). It is important to understand which interactions on the coarse-grained level distinguish between these two systems.

Fifth, mesophase ordering in block copolymer melts has been examined within different dynamical models. It has been suggested[73] that hydrodynamic interactions can strongly affect the kinetics of domain growth. The importance of these effects in the process of membrane fusion or any other collective membrane reorganization is not clear and remains an open problem.

Finally, an understanding of fusion in model membranes might shed light on the role of fusion peptides in biological systems, ultimately providing rational control of this process. Preliminary studies of a very simple model[74] have shown that membrane perturbations caused by model peptides provide sites for small-hole nucleation that, as we have seen, is necessary for the formation of fusion pores.

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