

Building Atomistic Models of Asymmetric Lipid Bilayers

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The compositional asymmetry of biological membranes has attracted significant attention over the last decade. Harboring more differences from symmetric membranes than previously appreciated, asymmetric bilayers have proven quite challenging to study with familiar concepts and techniques, leaving many unanswered questions about the reach of the asymmetry effects. One particular area of active research is the computational investigation of composition- and number-asymmetric lipid bilayers with molecular dynamics (MD) simulations.

membrane asymmetry

differential stress

interleaflet coupling

molecular dynamics simulations

lipid bilayers

computational model

1. Introduction

Lipid bilayers are ubiquitous in biology. Constituting the core of cellular membranes, they have long fascinated scientists trying to uncover their multifaceted roles in biological processes. Of particular interest are membrane biophysical properties and their relation to phenomena such as protein-lipid interactions and selective solute permeability [\[1\]\[2\]](#). The effects of lipid composition—one of the major determinants of the bilayer's structural and mechanical properties—have been extensively studied in symmetric model membranes (defined as having two leaflets with identical lipid composition and number density) that can be easily prepared and manipulated [\[3\]](#).

A major discovery in the early 1970s found that the plasma membrane of erythrocytes is compositionally asymmetric, with sphingomyelin and phosphocholine lipids enriched in the outer leaflet, and the aminophospholipids PS and PE largely confined to the inner leaflet [\[4\]\[5\]](#). These observations were later confirmed for the plasma membranes of many eukaryotic cells [\[6\]](#), which necessitated the development of novel experimental and theoretical paradigms for the investigation of membrane asymmetry [\[7\]\[8\]\[9\]\[10\]](#). Central questions in early studies concerned the effects of asymmetry on protein-membrane interactions and interleaflet coupling of phase behavior (**Figure 1**) [\[11\]\[12\]\[13\]\[14\]\[15\]\[16\]\[17\]](#).

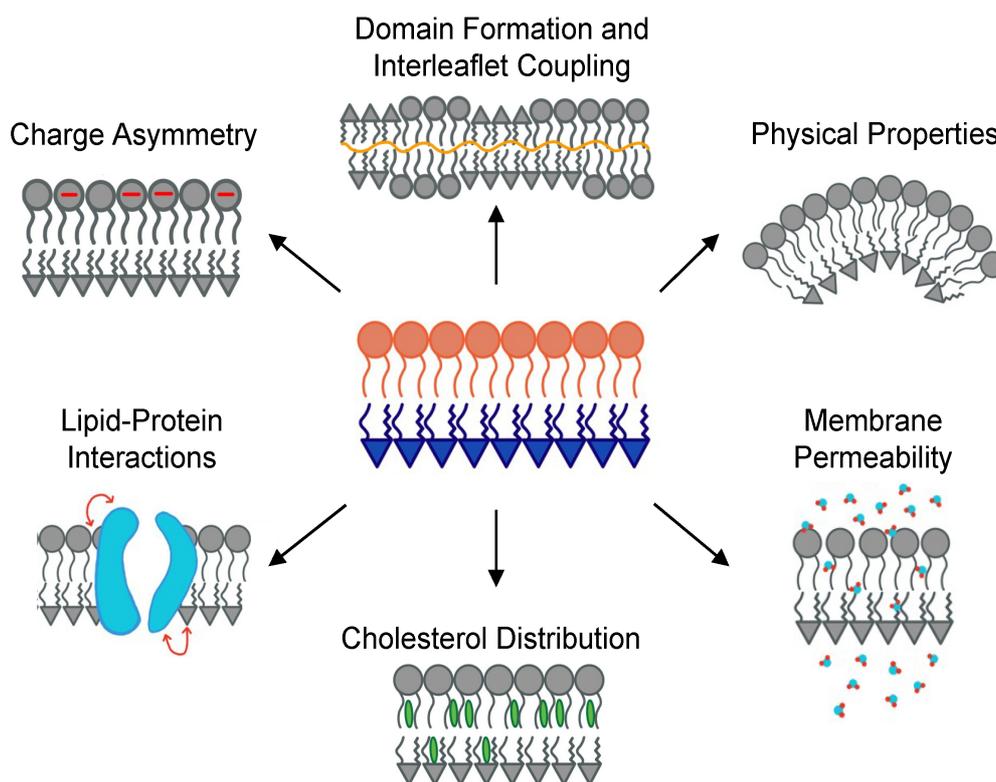


Figure 1. Various properties of asymmetric membranes studied with experiments and simulations. Clockwise from top: Effects of asymmetry on phase separation and interleaflet communication and adjustments; physical properties such as curvature, rigidity, and differential stress; permeability of water and small molecules; distribution of cholesterol between the two leaflets; interaction of membrane proteins with the bilayer; and charge asymmetry.

Offering an atomic resolution that is difficult to achieve with experiments, molecular dynamics (MD) simulations have often provided invaluable insights into the origins of membrane behavior and properties (e.g., [18][19][20][21][22][23]). Therefore, it is not surprising that the computational investigation of membrane asymmetry quickly gained speed alongside the rather challenging experimental characterization of asymmetric model membranes. Inspired mainly by observations in cells, some of the first MD simulation studies focused on the effects of asymmetry on membrane electrostatics and permeability [24][25][26][27], the structural properties of asymmetrically distributed gangliosides [27], and the peculiar confinement of raft-forming mixtures to the outer plasma membrane leaflet [28]. Later, advances in related experimental techniques [7] stimulated the investigation of interleaflet coupling [10][29][30][31][32][33][34][35][36][37][38], cholesterol interleaflet distribution [36][39][40][41][42][43], and protein interactions with asymmetric bilayers [44][45][46][47][48][49][50] (Figure 1).

In an MD simulation, a molecular model is first constructed, and its dynamics are simulated by evaluating interatomic forces from sets of parameters (often experimentally calibrated) and propagating the system in time following Newton's laws of motion. Freely available software packages have been developed to assist with both steps, making MD simulations and their analysis readily accessible [51][52][53][54][55][56][57][58][59][60]. Although an asymmetric bilayer with well-defined leaflet lipid compositions can be built in minutes and generally simulated without major hurdles, it has become clear that one decision in the initial bilayer design—namely, the relative

numbers of slowly-flipping lipids to place in the two leaflets—can be more consequential even than the choice of the specific lipid compositions of the leaflets [\[10\]](#).

2. Protocols for Bilayer Construction

To date, there are four main approaches for the construction of compositionally asymmetric bilayers for MD simulations:

- Ensure equal numbers of lipids in the two leaflets (**EqN**).
- Match the surface areas (or lipid packing densities) of the two leaflets to those from cognate symmetric bilayers (**SA**).
- Eliminate differential stress, i.e., ensure zero leaflet tension (**0-DS**).
- Emulate biological asymmetry (**EmBioAsym**).

Most of these methods require performing at least one simulation to arrive at the desired asymmetric membrane model. Once the relative leaflet compositions and abundances are determined, the bilayer can be simulated with any conventional software to investigate its properties in detail. Below researchers briefly describe each of these approaches and discuss a few studies in which they have been applied.

2.1. Same Number of Lipids (EqN)

Since in symmetric bilayer simulations, the two leaflets generally have equal numbers of lipids (**Figure 2A**), one approach to building asymmetric bilayers is to ensure that same condition (**Figure 2B**). This can be accomplished by building a symmetric bilayer and replacing individual lipids with different ones, or by specifying the same total numbers of lipids in the two leaflets and letting software generate the asymmetric lipid compositions. Here, all lipids are treated identically, thus disregarding any structural differences or packing preferences between species. This approach has been used to study the physical properties of both simpler lipid mixtures [\[27\]](#)[\[30\]](#) and asymmetric plasma membrane models of increasing complexity [\[61\]](#)[\[62\]](#).

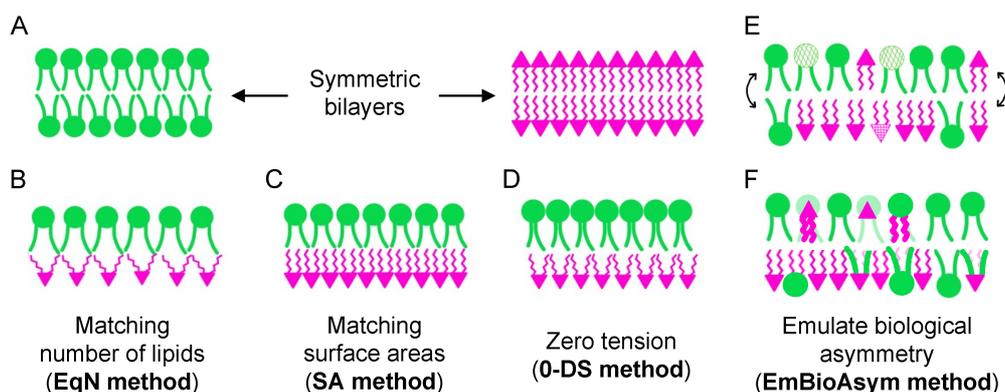


Figure 2. Protocols for the construction of asymmetric bilayers for MD simulations. **(A)** Symmetric bilayers have the same number and type of lipids in their two leaflets. An asymmetric bilayer can be built **(B)** with equal numbers of lipids in the two leaflets (**EqN** method) or **(C)** by ensuring that the relative packing densities (or surface areas) of the two leaflets are initially the same as in cognate symmetric bilayers (the **SA** method). Alternatively, **(D)** iterative simulations and analysis can be used to identify the leaflet number asymmetry that eliminates differential stress (the **0-DS** method) or **(E,F)** advanced simulations can be performed to optimize the leaflet lipid compositions. The latter is achieved by letting a subpopulation of the lipids equilibrate their leaflet concentrations by either **(E)** freely exchanging between leaflets or **(F)** changing their identity, in the presence of constraints keeping other lipids in place (e.g., lipids with patterned headgroups in **(E)** can diffuse only within their respective leaflets).

2.2. Match Surface Areas (SA)

An alternative to the **EqN** method is choosing the relative numbers of lipids in the two leaflets so that at the initial stage of bilayer construction, their average areas per lipid (or surface areas) match those of cognate symmetric bilayers (**Figure 2C**). This can be accomplished by first simulating two symmetric bilayers with the lipid compositions of the asymmetric membrane leaflets, followed by either stitching their leaflets together or using the obtained equilibrium areas per lipid to calculate the respective numbers of lipids and building the asymmetric bilayer from scratch. The latter approach is more general and allows for the construction of asymmetric bilayers of different sizes. This method ensures that the relative packing densities of the two leaflets remain fixed even as the two individual leaflet areas may simultaneously increase or decrease in comparison to their symmetric counterparts. This protocol has been applied to the analysis of the membrane potential [\[24\]\[25\]\[26\]](#), interleaflet coupling [\[29\]\[32\]\[34\]](#), the permeability of plasma membrane models [\[63\]](#), and cholesterol interleaflet distribution [\[39\]\[42\]](#).

To avoid simulating two symmetric bilayers, one can alternatively use reported areas per lipid (APL) for the individual lipids and, if the leaflets contain more than one component, assume ideal mixing and calculate the respective mole-fraction-weighted packing densities. For instance, CHARMM-GUI [\[54\]](#) uses individual lipid APLs to estimate the number of lipids in each leaflet when only lipid composition and lateral box dimensions are provided. This approach was recently used in a study comparing different construction methods for asymmetric bilayers [\[8\]](#).

2.3. Eliminate Differential Stress (0-DS)

Recent experiments have found that preferred lipid packing densities in symmetric bilayers can be altered in asymmetric bilayers, presumably due to the effects of the interleaflet coupling [\[64\]](#). A corollary is that lipid areas in asymmetric bilayers cannot be estimated a priori from their values in symmetric bilayers. It follows that the **EqN** and **SA** methods described above may produce bilayers with differentially stressed leaflets [\[65\]\[66\]](#). To ensure zero leaflet tension (**Figure 2C**), one can follow the protocol outlined in [\[65\]](#), which is based on the following principle. An asymmetric bilayer is first constructed (for example, using the **EqN** or **SA** methods) and simulated until the APL is converged over the last ~200 ns. Then, the lateral pressure profile is calculated from the converged portion and used to obtain the leaflet tension. If the tension is non-zero, the number of lipids is adjusted by either removing lipids from the leaflet with negative tension or adding lipids to the leaflet with positive tension. The exact number of

lipids to add or remove can be chosen on a trial-and-error basis or estimated from the relationship between the bilayer area compressibility modulus and leaflet tension (Equation 3 in [65]). A new asymmetric bilayer is then built from scratch with the updated leaflet lipid numbers and the same steps are repeated (i.e., simulation, calculation of leaflet tension, adjustment, and rebuilding if necessary) until zero leaflet tension is reached. This approach has been used to examine the effects of asymmetry on the mechanical properties of anionic asymmetric bilayers [67] and the ability of gramicidin to scramble lipids [46], as well as the effects of differential stress on the interaction of small molecules with asymmetric membranes [66].

2.4. Emulate Biological Asymmetry (EmBioAsym)

The asymmetry in cell plasma membranes (PM) is maintained via the activity of flippase and floppase enzymes which, when active, move lipids between leaflets against their concentration gradients [68]. Since the lipid specificity of these enzymes is arguably restricted to certain lipid types [69], one hypothesis is that cells regulate their PM lipid organization by restricting the asymmetry of some lipids while letting others equilibrate between leaflets according to their chemical potential. One notable example is cholesterol, a major component of mammalian cell plasma membranes that can rapidly flip between leaflets [6][70][71][72]. Interestingly, while cholesterol is capable of alleviating stresses in the membrane [73], its strong preference for interaction with saturated lipids may dominate over elastic and entropic forces and drive its distribution in a way that *increases* the differential stress [10][36][74]. This illustrates both the natural tendency of a bilayer constituent to equilibrate its distribution based on its chemical potential and the fact that realizing this tendency may produce rather than eliminate stresses in the membrane. In that respect, two methods have emerged to examine the equilibration of lipid redistribution in a simulated bilayer in the presence of imposed asymmetry [8][9].

The first approach involves simulations in the NPT ensemble and utilizes $P2_1$ boundary conditions (**Figure 2E**) [8]. These PBCs allow lipids to sample both leaflet environments by freely exchanging between leaflets during the simulation [75]. To mimic the activity of flippases and simulate asymmetric membranes, the method involves constraining some lipids to stay in one leaflet while allowing others to equilibrate their leaflet concentrations via an interleaflet redistribution [8]. Thus, it is possible to start with a bilayer constructed with one of the methods described above, then restrict some lipids to their respective leaflets and simulate the system with $P2_1$ PBCs to examine the preferred lipid distribution of the unconstrained membrane components in the presence of the imposed asymmetry. Consequently, since the relative numbers of lipids in the two leaflets are not constrained, they can dynamically change during the simulation. As noted by the authors, while opening transient pores in the membrane can also accelerate the exchange of lipids between leaflets, the advantage of $P2_1$ PBCs is that the chemical equilibrium reached by the freely diffusing lipids is a property of the asymmetric leaflets in the absence of any mechanical perturbations such as those imposed by a pore [8].

The second approach starts with a compositionally symmetric bilayer and replaces some of the lipids with new ones to generate the initial asymmetry (if the bilayer contains the same lipid numbers across leaflets, this is equivalent to the **EqN** method). It then proceeds with a simulation not in the NPT ensemble (as discussed above), but instead in a *semi-grand canonical* ensemble that allows dynamic changes in lipid identity (specifically their

saturation or headgroup type) during the simulation (**Figure 2F**) ^[9]. This approach emulates the action of lipid-translocating enzymes by imposing a chemical potential difference between some molecules in one leaflet while letting the leaflet lipid compositions adjust in accordance with the chemical potential of all lipid species subject to the imposed constraints. In these simulations, the lipid number asymmetry is fixed, but the changes in the degree of lipid saturation or type across species dynamically alter the relative packing densities of the leaflets by virtue of their changing lipid compositions. This method is well suited for investigating how some asymmetries might naturally arise from others and has thus helped explain certain experimental observations of the leaflet lipid compositions in erythrocyte membranes ^[9].

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