Computational studies of biomembrane systems: Theoretical considerations, simulation models, and applications

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Abstract This chapter summarizes several approaches combining theory, simulation and experiment that aim for a better understanding of phenomena in lipid bilayers and membrane protein systems, covering topics such as lipid rafts, membrane mediated interactions, attraction between transmembrane proteins, and aggregation in biomembranes leading to large superstructures such as the light harvesting complex of green plants. After a general overview of theoretical considerations and continuum theory of lipid membranes we introduce different options for simulations of biomembrane systems, addressing questions such as: What can be learned from generic models? When is it expedient to go beyond them? And what are the merits and challenges for systematic coarse graining and quasi-atomistic coarse grained models that ensure a certain chemical specificity?
1 Introduction

Lipid bilayers and membrane proteins are one important class of biological systems where the relationship between single molecule properties and the behavior of complex nanoscopically structured materials has been under intense investigation for a long time. In the present review we address how approaches combining theory, simulation and experiment may help us gain a better understanding of phenomena in biomembranes. A general overview of theoretical considerations and continuum theory of lipid membranes is given and different modeling and simulation approaches to biomembrane systems are introduced. In particular we introduce several generic lipid simulation models and show, how these models can help us understand material properties of lipid bilayers such as bending and Gaussian curvature modulus, or membrane tension, discuss timely topics such as lipid rafts, membrane-protein interactions, and curvature mediated interactions between proteins. These fundamental theoretical and modeling investigations are important to understand the principles that govern aggregation phenomena in biological membranes that lead to large superstructures such as the light harvesting complex of green plants. In the last section of this chapter we give an overview of multiscale modeling approaches that try to go beyond generic lipid and protein models and attempt at ensuring a certain chemical specificity while still benefiting from the time- and length-scale advantages of coarse grained simulations. Finally we conclude with the example of the light harvesting complex of green plants, for which we show first steps toward a multiscale simulation model that allows to go back and forth between a coarse grained and an atomistic level of resolution and therefore permits immediate comparison to atomic level experimental data.

2 Theory and simulation of lipid bilayers

To provide a basis for both the theoretical ideas and the computational techniques which we will discuss in this chapter, we start by reminding the reader of some essential concepts. Sec. 2.1.1 reviews some basic aspects of the Helfrich Hamiltonian. Sec. 2.2 introduces three coarse-grained membrane models that will be used in the remainder of this chapter. In Secs. 2.3 and 2.4, we discuss the bending moduli and the surface tension of membranes in more detail, and finally comment on multicomponent membranes in Sec. 2.5.
2.1 Basic concepts

2.1.1 Continuum elasticity of lipid membranes

Lipid molecules are amphiphatic: they consist of a hydrophilic head group and typically two hydrophobic (fatty acid) tails. Yet, despite their amphiphatic nature, lipid molecules dissolved in water have an extremely low critical aggregate concentration (nanomolar or even smaller \(271\)), and thus under most common conditions lipids spontaneously aggregate. Since the roughly cylindrical shape of lipids leads to two-dimensional self assembly, thermodynamic considerations \([130]\) show that—in contrast to the finite size of spherical and wormlike micelles—a single macroscopic aggregate containing almost all of the lipids will form: a two-dimensional bilayer membrane. Its lateral dimensions can exceed its thickness by several orders of magnitude.

2.1.2 The Helfrich Hamiltonian

If lipid membranes are subjected to lateral tension, they typically rupture at stresses of several mN/m, with a remarkably low rupture strain of only a few percent \([233]\). At large scales and moderate tensions it is hence an excellent approximation to consider membranes as largely unstretchable two-dimensional surfaces. Their dominant soft modes are not associated with stretching but with bending \([37,113,77]\). Within the well-established mathematical framework developed by Helfrich \([113]\), the energy of a membrane patch \(\mathcal{P}\), amended by a contribution due to its boundary \(\partial \mathcal{P}\) \([114]\), is expressible as

\[
E[\mathcal{P}] = \int_{\mathcal{P}} dA \left\{ \frac{1}{2} \kappa (K - K_0)^2 + \bar{K} K_G \right\} + \oint_{\partial \mathcal{P}} \gamma .
\]

(1)

Here, \(K = c_1 + c_2\) and \(K_G = c_1 c_2\) are the total and Gaussian curvature, respectively, and the \(c_i\) are the local principal curvatures of the surface \([153,41]\). The inverse length \(K_0\) is the spontaneous bilayer curvature, showing that the first term quadratically penalizes the deviation between total and spontaneous curvature. The parameters \(\kappa\) and \(\bar{K}\) are the bending modulus and Gaussian curvature modulus, respectively, and they quantify the energy penalty due to bending. Finally, the parameter \(\gamma\) is the free energy of an open membrane edge and thus referred to as the edge tension.

2.1.3 Refining the Helfrich model

While the Helfrich Hamiltonian provides a successful framework for describing the large-scale structure and geometry of fluid membranes, it is not designed for mod-

\(^1\) Observe that \(1/K_0\) is not the optimal radius \(R_{opt}\) of a spherical vesicle. Minimizing the energy per area with respect to \(K\) shows that instead this radius is given by \(R_{opt} = 2 + \bar{K}/\kappa\).
eling membranes on smaller length scales, i.e., of the order of the membrane thickness. Several more refined continuum models have been proposed to amend this situation. Evidently, continuum descriptions are no longer applicable at the Ångström scale. However, they still turn out to be quite useful on length scales down to a few nanometers.

As one refinement, Lipowsky and coworkers have proposed to introduce a separate, independent “protrusion” field that accounts for short wavelength fluctuations \[163, 164, 99\]. According to recent atomistic and coarse-grained simulations by Brandt \textit{et al.}, these protrusions seem to correspond to lipid density fluctuations within the membrane \[20, 19\]. Lindahl and Edholm pioneered another important refinement, which is to consider the height and thickness variations of membranes separately \[162\]. Continuum models for membranes with spatially varying thickness have a long-standing tradition in theories for membrane-mediated interactions between inclusions \[214, 213, 126, 272, 53, 51, 127, 35, 111, 34, 135\] (see also Sec. 3.1), and they can be coupled to Helfrich models for height fluctuations in a relatively straightforward manner \[21, 22, 307\]. In addition, one can include other internal degrees of freedom, such as local tilt \[86, 87, 16, 182, 305, 304\], as well as membrane tension \[203, 304\].

In this article, we will focus in particular on the so-called coupled monolayer models \[126, 127, 35, 34, 111, 53, 52, 5, 21, 22\], where membranes are described as stacks of two sheets (monolayers), each with their own elastic parameters. Monolayers are bound to each other by a local harmonic potential which accounts for the areal compressibility of lipids within the membrane and their constant volume \[5, 21\]. Li \textit{et al.} have recently compared the elastic properties of amphiphilic bilayers with those of the corresponding monolayers within a numerical self-consistent field study of copolymeric membranes \[161\]. They found that the bilayer elastic parameters can be described at an almost quantitative level by an appropriate combination of monolayer elastic parameters.

\subsection*{2.2 Coarse-grained lipid models}

The multitude of length- and time scales that matter for biophysical membrane processes is mirrored in a wide spectrum of computational models that have been devised to capture these scales. These range from all-atom simulations \[256, 242, 243, 13, 207\] up to dynamically triangulated surfaces \[103, 102, 154, 210\] and continuum models \[7, 33\]. The region in-between is becoming increasingly populated by a wealth of different \textit{coarse-grained} (commonly abbreviated “CG”) models, which capture different aspects of a very complex physical situation, and a number of excellent reviews exists that provide a guide to the literature \[291, 192, 23, 175, 12, 62, 208, 246\].

Besides their chosen level of resolution, CG models can also be classified by the “spirit” in which they approach a physical situation: If the focus lies on generic mechanisms that are thought to be quite universal in their reach, there is no need
to construct models that faithfully relate to every aspect of some particular lipid. Instead, one creates “top-down” models based on the presumed principles underlying the generic mechanisms of interest. For instance, if one wishes to understand how a bilayer membrane interacts with a colloidal particle that is much bigger than the thickness of the membrane, relevant aspects of the situation will likely include the fluid curvature-elastic response of bilayer lipid membranes, but probably not the hydrogen bonding abilities of a phosphatidylethanol head group. If, in contrast, one wishes to understand how mesoscopic membrane properties emerge from specific properties of their microscopic constituents, the aim is instead to construct “bottom-up” models whose key design parameters follow in a systematic way from those of a more finely resolved model. For instance, if one wishes to understand how those hydrogen bonding abilities of a phosphatidylethanol head group impact the mesoscopic phase behavior of mixed bilayers, it will not do to simply guess a convenient head group interaction potential, even if it is eminently plausible. The latter philosophy goes under various names, such as “systematic coarse-graining” or “multiscaling” and again excellent literature and resources exists that cover this field [198, 131, 229, 231, 58, 211, 212, 54, 59, 223, 226, 296, 241, 170].

The top-down and bottom-up approaches are not necessarily mutually exclusive. It is conceivable that certain aspects of the science are systematically matched, while others are accounted for in a generic way by using intuition from physics, chemistry, mathematics, or other pertinent background knowledge. Conversely, this also means that what any given model can qualitatively or quantitatively predict depends greatly on the way in which it has been designed; there is no universally applicable CG model. Stated differently, systematically coarse-grained models will not be accurate in every prediction they make, and generic models can be highly quantitative and experimentally testable. One always needs to know what went into a given model to be able to judge the reliability of its predictions.

In the following, (2.2.1 – 2.2.3), we will review the basics of three particular CG models that will feature in the remainder of this paper. The choice of models is not meant to imply a quality statement but merely reflects our own experience and work.

### 2.2.1 Cooke model

The Cooke model [47, 45] is a strongly coarse-grained top-down lipid model in which every single lipid is represented by three linearly connected beads (one for the head group, two for the tail) and solvent is implicitly accounted for through effective interactions. It is purely based on pair interactions and therefore very easy to handle. Its main tuning parameters are the temperature, and the range $w_c$ of the effective cohesion that drives the aggregation of the hydrophobic tail beads. One might also change the relative size between head- and tail-beads to control the lipids’ spontaneous curvature [46]. The bead size $\sigma$ serves as the unit of length, the potential depth $\epsilon$ as the unit of energy. For the common choice $k_B T / \epsilon = 1.1$ and $w_c / \sigma = 1.6$ lipids spontaneously assemble into fluid membranes with an area per lipid of about
1.2σ² and a bending rigidity κ ≈ 12.8k_BT (but rigidities between 3k_BT and 30k_BT can be achieved without difficulty), and an elastic ratio of \(\kappa / \kappa \approx -0.92\) [123].

### 2.2.2 Lenz model

Like the Cooke model, the Lenz model [250] is a generic model for membranes, but it has been designed for studying internal phase transitions. Therefore, it puts a slightly higher emphasis on conformational degrees of freedom than the Cooke model. Lipids are represented by semiflexible linear chains of seven beads (one for the head group, six for the tail), which interact with truncated Lennard-Jones potentials. Model parameters such as the chain stiffness are inspired by the properties of hydrocarbon tails [73]. The model includes an explicit solvent, which is, however, modeled such that it is simulated very efficiently: It interacts only with lipid beads, not with itself (“phantom solvent” [158]).

The model reproduces the most prominent phase transitions of phospholipid monolayers [73] and bilayers [159]. In particular, it reproduces a main transition from a fluid membrane phase (\(L_\alpha\)) to a tilted gel phase (\(L_{\beta'}\)) with an intermediate ripple phase (\(P_{\beta'}\)), in agreement with experiments. The elastic parameters have been studied in the fluid phase and are in reasonable agreement with those of saturated DPPC (dipalmitoyl-phosphatidylcholine) bilayers. Recently, the Lenz model was supplemented with a simple cholesterol model [187]. Cholesterol molecules are taken to be shorter and stiffer than lipids, and they have a slight affinity to lipids. Mixtures of lipids and cholesterol were found to develop nanoscale raft domains [187], in agreement with the so-called “raft hypothesis” [225]. As a generic model that reproduces nanoscale structures in lipid membranes (ripple states and rafts), simulations of the Lenz model can provide insight into the physics of nanostructure formation in lipid bilayers. This will be discussed in more detail in Sec. 2.5.

### 2.2.3 MARTINI model

The MARTINI model for lipids [178, 177] is a hybrid between a top-down and a bottom-up model: approximately four heavy atoms are mapped to a single CG bead, and these CG beads come in a variety of types, depending on their polarity, net charge, and the ability to form hydrogen bonds. The systematic aspect of MARTINI largely derives from the fact that the non-bonded interactions between these building blocks (shifted Lennard-Jones and possibly shifted Coulomb potentials) have been parameterized to reproduced most of the thermodynamics correctly, especially the partitioning free energy between different environments, such as between aqueous solution and oil. Given a particular molecule, a judicious choice of assignments from groups of heavy atoms to MARTINI beads, together with standard bonded interactions (harmonic, angular, and dihedral potentials) leads to the CG version of a molecule.
The complete MARTINI force field encompasses more than lipids and sterols [178, 177]; it is currently also available for proteins [190], carbohydrates [168] and glycolipids [169]. The far-reaching possibilities for looking at multicomponent systems without the need to explicitly cross-parametrize new interactions have substantially contributed to the attractiveness of this force field. Of course, care must still be taken that one’s mapping onto the CG level is overall consistent and chemically meaningful: Even though the non-bonded interactions are derived from a single guiding principle, which is both conceptually attractive and computationally powerful, there is no guarantee that it will under all circumstances work for one’s particular choice of system and observable, so it is up to the user to perform judicious sanity checks. After all, with great power there must also come – great responsibility [157].

### 2.3 Obtaining material parameters

The Hamiltonian (1) is an excellent phenomenological description of fluid membranes, but it doesn’t predict the material parameters entering it, which must instead come from experiment or simulation. Let us briefly list a number of ways in which this is achieved, both in experiment and in simulation.

The bending modulus $\kappa$ is measured by techniques such as monitoring the thermal undulations of membranes [29, 28, 255, 84, 119], probing the low-tension stress-strain relation [76], X-ray scattering [165, 44, 284, 216], neutron spin echo measurements [224, 279, 238] (note however the caveats raised by Watson and Brown [303]), or pulling thin membrane tethers [15, 49, 252]. In simulations, monitoring undulations [99, 162, 28, 78, 178, 301, 47, 45, 21, 300, 263] or orientation fluctuations [302], measuring tensile forces in tethers [109, 6, 263], and buckling [209, 124] have been used successfully.

The Gaussian curvature modulus $\kappa_G$ is much harder to obtain, since by virtue of the Gauss-Bonnet theorem [153, 41] the surface integral over the Gaussian curvature $K_G$ depends only on the topology and the boundary of the membrane patch $\mathcal{P}$. Hence, one needs to change at least one of them to access the Gaussian curvature modulus. It therefore tends to be measured by looking at the transitions between topologically different membrane phases (e.g. the lamellar phase $L_\alpha$ and the invented cubic phase $Q_{II}$) [266, 264, 265, 281] or the shape of phase-separated membranes in the vicinity of the contact line [10, 259] (even though the latter strictly speaking only gives access to the difference in Gaussian moduli between the two phases). In Sec. 2.3.2 we will briefly present a computational method that obtains $\kappa_G$ from the closure probability of finite membrane patches [123, 125].

To measure the edge tension requires an open edge, and in experiments this essentially means looking at pores [280, 318, 96, 139]. This also works in simulations [78, 178, 301, 47, 45], but it tends to be easier to create straight bilayer edges by spanning a “half-membrane” across the periodic boundary conditions of the simulation box [283, 309, 136, 299].
The spontaneous curvature $K_0$ usually vanishes due to bilayer up-down symmetry, but could be measured by creating regions of opposing spontaneous curvature and monitor the curvature this imprints on the membrane \cite{298}, or by measuring the shape of a spontaneously curved membrane strip \cite{263}.

Since curvature elasticity is such an important characteristic of lipid membranes, obtaining the associated moduli has always seen a lot of attention. Let us therefore provide a few more details on some classical and some more recent computational strategies to measure them. Shiba and Noguchi \cite{263} also provide a detailed recent review.

2.3.1 Bending modulus

The shape of essentially flat membranes stretched across the periodic boundary conditions of a simulation box can be described by specifying their vertical displacement $h(r)$ above some horizontal reference plane, say of size $L \times L$. In this so-called Monge parametrization the bending contribution due to the total curvature term (ignoring for now on the spontaneous curvature $K_0$) is given by

$$\int dA \frac{1}{2} \kappa K^2 = \frac{1}{2} \kappa \int_{[0,L]^2} d^2r \sqrt{1 + (\nabla h)^2} \left( \nabla \cdot \frac{\nabla h}{\sqrt{1 + (\nabla h)^2}} \right)^2, \quad (2)$$

$$= \frac{1}{2} \kappa \int_{[0,L]^2} d^2r \left\{ (h_{ii})^2 - \frac{1}{2} (h_{ii})^2 h_{jj} - 2h_{ii} h_{jj} h_{kk} + O(h^6) \right\}, \quad (3)$$

where the indices are short-hand for derivatives: $h_i = \partial h / \partial r_i$, etc. The first square root expression in Eqn. (2) is the metric determinant that accounts for the increased area element if the surface is tilted. The expression following it is the total curvature in Monge gauge. Evidently the Helfrich Hamiltonian is highly nonlinear in this parametrization! Hence, one frequently expands the integrand for small $h$, as is done in the second line. The first term, $\frac{1}{2} \kappa (h_{ii})^2 = \frac{1}{2} \kappa (\Delta h)^2$ is quadratic in $h$ and thus gives rise to a harmonic theory, which is referred to as “linearized Monge gauge”. The majority of all membrane work relies on this simplified version. However, the higher order terms occasionally matter: They are for instance responsible for the renormalization of the bending rigidity by thermal shape undulations \cite{118,221,85,146}.

Upon Fourier-transforming $h(r) = \sum_q \tilde{h}_q e^{iqr}$ and restricting the functional to quadratic order we obtain the transformed Hamiltonian $E[\tilde{h}_q] = L^2 \sum_q \frac{1}{2} \kappa q^4 |\tilde{h}_q|^2$, which shows that the modes $\tilde{h}_q$ are independent harmonic oscillators. The equipartition theorem then implies that $\langle |\tilde{h}_q|^2 \rangle = k_B T / L^2 \kappa q^4$, and thus fitting to the spectrum of thermal undulations gives access to $\kappa$. Unfortunately, there are several difficulties with this picture (see, e.g., the recent review \cite{249}). The simple expression can only be expected to hold for sufficiently small wave vectors, since at small length scales local bilayer structure will begin to matter. For instance, it is well known that lipid tilt fluctuations contaminate the undulation spectrum \cite{182,305}. The situa-
tion becomes ever more complicated in low temperature phases that exhibit hexatic order \cite{205,155} or permanent tilt \cite{218,217}. In such cases, the fluctuation spectrum shows no sign of a \(\langle |\tilde{h}_{\mathbf{q}}|^2 \rangle \propto 1/q^4\) behavior up to length scales of at least 40 nanometers \cite{308}. The most obvious way out is to simulate larger systems and thus gain access to smaller wave vectors, but unfortunately these modes decay exceedingly slow. For overdamped Brownian dynamics with a friction constant \(\zeta = L^2 \zeta_0\) one finds \(\dot{\tilde{h}}_{\mathbf{q}} = -\partial E[\tilde{h}_{\mathbf{q}}]/\partial \tilde{h}_{\mathbf{q}} = -L^2 \kappa q^4 \tilde{h}_{\mathbf{q}}\), showing that modes exponentially relax with a time constant \(\tau = \zeta_0/\kappa q^4\) that grows quartically with the wave length. Accounting for hydrodynamics turns this into a cubic dependence, \(\tau = 4\eta/\kappa q^3\) \cite{151,29,258,319}, where \(\eta\) is the solvent viscosity, but the situation is still uncomfortable: when Lindahl and Edholm \cite{162} simulated 1024 DPPC lipids in a 20nm square bilayer, their measured value \(\kappa = 4 \times 10^{-20} J\) implies \(\tau \simeq 3.2\)ns for the slowest (and most informative) mode, not much smaller than the overall 10ns total simulation time.

While measuring \(\kappa\) from the undulation spectrum is possible, there is a more basic concern with such an approach: one tries to measure a modulus with a value typically around \(20k_BT\) by using thermal fluctuations of order \(k_BT\) to excited the bending modes, which of course makes it quite challenging to get a signal to begin with. An obvious alternative is to actively bend membranes and directly measure their curvature elastic response. There are clearly many ways to deform a membrane; here we will describe two possibilities which have been proposed in the past as convenient methods for obtaining the bending modulus.

Harmandaris and Deserno \cite{109} proposed a method that relies on simulating cylindrical membranes. Imagine a membrane of area \(A\) that is curved into a cylinder of curvature radius \(R\). Its length \(L\) satisfies \(2\pi RL = A\), and the curvature energy per area of this membrane is

\[
e = \frac{1}{2} \kappa \frac{1}{R^2} = \frac{1}{2} \kappa \left(\frac{2\pi L}{A}\right)^2. \tag{4}\]

Since changing the length of the cylinder at constant area will also change the curvature radius, and thus the bending energy, there must be an axial force \(F\) associated with this geometry. Its value is

\[
F = \left(\frac{\partial eA}{\partial L}\right)_{A} = A \kappa \frac{2\pi L}{A} \frac{2\pi}{A} = \frac{2\pi \kappa}{R}. \tag{5}\]

Hence, measuring both the axial force and the cylinder radius yields the bending modulus as \(\kappa = FR/2\pi\). Notice that within quadratic curvature elasticity the radius of the cylinder does not matter: Both small and large radii will lead to the same modulus. In other words, \(FR\) is predicted to be a constant. Of course, it is conceivable that higher order corrections to the Helfrich Hamiltonian \cite{1} matter once curvatures become really strong. For the present geometry there is only one term, which enters

\[\delta h \equiv \langle h(r)^2 \rangle^{1/2} = L\sqrt{k_BT/16\pi^3}\kappa \approx L/100 \] (assuming \(\kappa \simeq 20k_BT\)), which is a few ångström for typical simulation sizes.\footnote{It is easy to see that \(\delta h \equiv \langle h(r)^2 \rangle^{1/2} = L\sqrt{k_BT/16\pi^3}\kappa \approx L/100 \) (assuming \(\kappa \simeq 20k_BT\)).}
at quartic order, and one would write a modified energy density $e = \frac{1}{2} \kappa K^2 + \frac{1}{4} \kappa_4 K^4$.

This modified functional leads to $FR/2\pi = \kappa + \kappa_4/R^2 \equiv \kappa_{\text{eff}}(R)$, which can be interpreted as an effective curvature dependent bending modulus. Simulations using different models with different levels of resolution have indeed both seen a small dependence of $\kappa_{\text{eff}}$ on $R$ [109, 263]. They find softening at high curvature, which would indicate that $\kappa_4$ is negative. In contrast, Li et al. [161] recently studied the elastic properties of self-assembled copolymeric bilayers by self-consistent field theory in cylindrical and spherical geometry, and found $\kappa_4$ to be positive. The details of non-linear elastic corrections thus depend on specifics of the model under study, but the present studies suggest that as long as the radius of curvature is bigger than a few times the membrane thickness, these corrections are negligible. For example, Li et al. [161] found the deviations from linear to be less than 2% both in the cylinder and sphere geometry, as long as the reduced curvature was less than $K_0 d = 0.6$ (where $d$ is the bilayer thickness).

The cylinder stretching protocol appears to work very well for simple solvent-free membrane models [109, 6, 263], but with more refined models this method suffers from two drawbacks, both related to the equilibration of a chemical potential. First, the cylinder separates the simulation volume into an “inside” and an “outside”. If solvent is present, its chemical potential must be the same in these two regions, but for more highly resolved models the solvent permeability through the bilayer is usually too low to ensure automatic relaxation. Second, the chemical potential of lipids also has to be the same in the two bilayer leaflets, and again for more refined models the lipid flip-flop rate tends to be too low for this to happen spontaneously.

To circumvent this difficulty, Noguchi has recently proposed to instead simulate a buckled membrane as an example of an actively imposed deformation [209]. This solves both problems simultaneously: Neither does the buckle divide the simulation box into two distinct compartments, nor is lipid equilibration across leaflets a big concern, since for symmetry reasons both leaflets are identical (at least for a “ground state buckle”) and thus ensuring that the same number of lipids is present in both leaflets is a good proxy. The theoretical analysis of the expected forces is a bit more complicated compared to the cylinder setup, but it can be worked out exactly even for buckles deviating strongly from “nearly flat”. Hu et al. have recently provided systematic series expansions for the buckling forces in terms of the buckling strain.

If a membrane has originally a length $L$ and is buckled to a shorter length $L_x$, then the force $f_x$ per length along that membrane as a function of strain $\gamma = (L - L_x)/L$ can be written as [124]

$$f_x = \kappa \left( \frac{2\pi}{L} \right)^2 \left[ 1 + \frac{1}{2} \gamma + \frac{9}{32} \gamma^2 + \frac{21}{128} \gamma^3 + \frac{795}{8192} \gamma^4 + \frac{945}{16384} \gamma^5 + \cdots \right].$$

(6)

Notice that the force does not vanish for $\gamma \to 0$, which is the hallmark of a buckling transition. Hu et al. [124] also estimate the fluctuation correction on this result and find it to be very small; they apply this method to four different membrane models.

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3 Observe that the part of the membrane above the buckle and the part below the buckle can be connected through the periodic boundary of the simulation box.
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Fig. 1 Illustration of a buckling simulation using the MARTINI model for DMPC (which uses 10 beads per lipid) [124]. This particular membrane consists of 1120 lipids and is compressed at a strain $\gamma = 0.3$, which gives it an amplitude of approximately 22% of the box length. To suppress membrane deformations in the second direction, the width of the box is chosen much smaller than its length.

ranging from strongly coarse grained to essentially atomistic, and argue that it is reliable and efficient.

2.3.2 Gaussian modulus

To measure the Gaussian curvature modulus $\kappa$ directly, the Gauss-Bonnet theorem [153, 41] forces one to either change the topology or the boundary of a membrane patch. Recently Hu et al. [123, 125] suggested a way to achieve this. Consider a circular membrane patch of area $A$. Being flat, its energy stems from the open edge at its circumference. The patch could close up into a vesicle in order to eliminate the open edge, but now it carries bending energy. If we imagine that transition proceeding through a sequence of conformations, each one resembling a spherical cap of curvature $c$, then the excess energy of such a curved patch (compared to the flat state) is given by [114, 92]

$$\Delta E(x, \xi) = \frac{4\pi}{\kappa + \kappa} \left[ \sqrt{1 - x} - x \right].$$  

(7)

$\Delta E$ is scaled by the bending energy of a sphere and we defined

$$x = \frac{(Rc)^2}{4\pi}, \quad \xi = \frac{\gamma R}{2\kappa + \kappa}, \quad \text{and} \quad R = \sqrt{\frac{A}{4\pi}}.$$  

(8)

For $\xi > 1$ the spherical state ($x = 1$) has a lower energy than the flat state ($x = 0$). If $x$ is viewed as a reaction coordinate, Eqn. (7) describes a nucleation process, since for $\xi < 2$ the transition from the flat to the spherical state proceeds through an
energy barrier of height $\Delta E^* = (1 - \xi / 2)^2$ at $x^* = 1 - (\xi / 2)^2$. Eqn. 7 shows that the functional form of the nucleation barrier depends on parameters such as moduli and system sizes only though the combination $\xi$, and all parameters entering $\xi$ – with the exception of $K$ – can be determined ahead of time by other means. Hence, measuring $K$ amounts to measuring the nucleation barrier (or at least the location of the maximum). Hu et al. 123, 125 do this by a dynamical process: Equilibrated but pre-curved membrane patches with some initial value for $x$ may either flatten out or close up, depending on where on the barrier they start. The probability for either outcome can be computed if $\Delta E$ is known [138] and so $K$ ends up being found through a series of patch-closure experiments.

The results of such simulations show that $K/\kappa$ is close to $-1$, both for the Cooke model and for MARTINI DMPC (see Sec. 2.2 for a further discussion of these models). This is compatible with experiments [266, 264, 265, 281, 10, 259] but disagrees with the only other method that has been suggested for getting the Gaussian modulus. As first pointed out by Helfrich [115], quite general considerations suggest that the second moment of a membrane’s lateral stress profile is also equal to the Gaussian modulus [115, 116, 278]:

$$\kappa = \int dz z^2 \Sigma(z),$$

where $\Sigma(z) = \Pi_{zz} - \frac{1}{2}[\Pi_{xx}(z) + \Pi_{yy}(z)]$ is the position-resolved lateral stress through a membrane, whose integral is simply the surface tension [240]. However, when applied to the Cooke model, Hu et al. find $K/\kappa \approx -1.7$ [123], quite a bit more on the negative side, while applying it to MARTINI DMPC (at 30K) yields $K/\kappa \approx -0.05$, much closer to zero; MARTINI DPPC and DOPC even lead to positive Gaussian moduli. At present it is quite unclear where this discrepancy originates from, but given that the values obtained from the patch-closure protocol are physically more plausible it seems likely that there is a problem with the stress approach. The latter suspicion is also supported by the fact that a more refined theory of bilayer elasticity [101] predicts corrections to the right hand side of Eqn. 9 that depend on moments of order parameter distributions.

### 2.4 The tension of lipid membranes

The Helfrich Hamiltonian, Eq. (1), does not include a surface tension contribution. Free membrane patches can relax and adjust their area such that they are stress-free. In many situations, however membranes do experience mechanical stress. For example, an osmotic pressure difference between the inside and the outside of a lipid vesicle generates stress in the vesicle membrane. Stress also occurs in supported bilayer systems, or in model membranes patched to a frame. In contrast to other quantities discussed earlier (bending stiffness etc.), and also in contrast to the sur-

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4 The requirement that the Hamiltonian (1) is bounded below demands $-2\kappa \leq K \leq 0$. 

face tension of demixed fluid phases, membrane stress is not a material parameter. Rather, it is akin to a (mechanical or thermodynamic) control parameter, which can be imposed through boundary conditions.

The discussion of membrane tension is complicated by the fact that there exist several different quantities which have been called “tension” or “tension like”. For the sake of simplicity, we will restrict ourselves to quasi-planar (fluctuating) membranes in the following. A thoughtful analysis of the vesicle case has recently been carried out by Diamant [66].

The first tension-like quantity in planar membranes is the lateral mechanical stress in the membrane discussed above. If the stress is imposed by a boundary condition, such as, for instance, a constraint on the lateral (projected) area of the membrane, it is an internal property of the membrane system which depends, among other, on the areal compressibility [304] and the curvature elasticity [39, 40, 81, 107, 195, 196, 197, 63]. Alternatively, mechanical stress can be imposed externally. In that case, the projected area fluctuates, and the appropriate thermodynamic potential can be introduced into the Helfrich Hamiltonian, Eq. (1), in a straightforward manner:

\[ G = E - \Gamma_{\text{frame}} A_p = \int dA \left\{ \frac{1}{2} \kappa (K - K_0)^2 + \kappa K_G - \Gamma_{\text{frame}} \frac{dA_p}{dA} \right\} . \]  

Here \( \Gamma_{\text{frame}} \) is the stress or “frame tension”, \( A_p \) is the projected area in the plane of applied stress, and we have omitted the membrane edge term. Let us consider a membrane with fixed total area \( A \). Since in Monge representation, one has \( \frac{dA_p}{dA} = \frac{1}{\sqrt{1 + (\nabla h)^2}} \approx 1 - (\nabla h)^2/2 + O(h^4) \), the last term in Eq. (10) takes the form

\[ \text{const} + \frac{1}{2} \Gamma_{\text{frame}} \int_{A_p} d^2 r (\nabla h)^2 + O(h^4) \]  

(with const = \( -\Gamma_{\text{frame}} A \)). This is formally similar to a surface tension term in an effective interface Hamiltonian for liquid-liquid interfaces. The main difference is that the base \( A_p \) of the integral fluctuates. However, replacing this by a fixed base \( \langle A_p \rangle \) only introduces errors of order \( O(h^4) \) [247].

From Eq. (11), it is clear that mechanical stress influences the fluctuation spectrum of membranes, and in particular, one expects a \( q^2 \) contribution to the undulation spectrum, \( \langle \tilde{h}^2 \rangle^{-1} \sim \Gamma_{\text{frame}} q^2 + \kappa q^4 + \cdots \). This introduces the second tension-like parameter in planar fluctuating membranes, the “fluctuation tension” \( \Gamma_{\text{fluc}} \). According to Eq. (11), \( \Gamma_{\text{fluc}} \) is identical to \( \Gamma_{\text{frame}} \) up to order \( O(h^2) \).

Finally, the third tension-like parameter in membranes has been introduced by Deuling and Helfrich already in 1976 [64], and it couples to the total area of the membrane

\[ E = \int dA \left\{ \frac{1}{2} \kappa (K - K_0)^2 + \kappa K_G + \Gamma_0 \right\} . \]  

In membranes with fixed lipid area, but variable number of lipids, the “bare tension” \( \Gamma_0 \) is simply proportional the lipid chemical potential. For membranes with fixed number of lipids and variable lipid area, the physical meaning of \( \Gamma_0 \) is less clear, but...
it can still be defined as a field that is conjugate to $A$ in a Lagrange multiplier sense. This term also gives rise to a $q^2$ term in the undulation spectrum, with the fluctuation tension $\Gamma_{\text{fluc}} = \Gamma_0 + O(h^2)$ \textup{(304)}.

At leading (quadratic) order in $h$, the three tension-like quantities, $\Gamma_{\text{frame}}$, $\Gamma_{\text{fluc}}$, and $\Gamma_0$, thus have identical values. Nevertheless, they might differ from each other due to nonlinear corrections \textup{(28, 55, 36, 133, 179)}. For instance, the bare tension $\Gamma_0$ is expected to deviate from the frame tension $\Gamma_{\text{frame}}$ due to the effect of fluctuations. The exact value of the correction depends on the ensemble and differs for systems with a fluctuating number of lipids (variable number of undulating modes) or a fixed number of lipids (fixed number of modes). The former case was analyzed by Cai et al. \textup{(36)}, the latter case by Farago and Pincus \textup{(80)} and subsequently by a number of other authors \textup{(128, 274, 89)}. Interestingly, the correction has an additive component in both cases. Hence a stress-free membrane has a finite bare tension.

Whereas the bare tension, $\Gamma_0$, is mostly of academic interest, the fluctuation tension, $\Gamma_{\text{fluc}}$, describes actual membrane conformations. The relation between $\Gamma_{\text{fluc}}$ and $\Gamma_{\text{frame}}$ has been discussed somewhat controversially in the past \textup{(36, 81, 128, 274, 89, 247, 88, 248, 79, 66)}. Cai et al. \textup{(36)} and Farago and Pincus \textup{(81)} have presented a very general argument why $\Gamma_{\text{frame}}$ and $\Gamma_{\text{fluc}}$ should be equal. Cai et al. \textup{(36)} examined the fluctuations of planar membranes with variable number of lipids and fixed lipid area, and proved $\Gamma_{\text{fluc}} = \Gamma_{\text{frame}}$ in the thermodynamic limit, if the membrane is “gauge invariant”, i.e., invariant with respect to a rotation of the “projected plane”. Farago and Pincus \textup{(81)} developed a similar theory for membranes with fixed number of lipids at fixed projected area. Unfortunately, these arguments – albeit appealing – are not entirely conclusive, since the underlying assumptions can be questioned: The thermodynamic limit does not exist for stress-free planar membranes, since they bend around on length scales larger than the persistence length \textup{(28)}. In the presence of stress, it does not exist either, strictly speaking, because the true equilibrium state is one where the membrane has ruptured. Furthermore, high stresses break gauge invariance. Contradicting Cai et al. \textup{(36)} and Farago and Pincus \textup{(81)}, a number of authors have claimed $\Gamma_{\text{fluc}} = \Gamma_0$ \textup{(128, 274, 89)} based on analytical arguments which however also relied on the existence of the thermodynamic limit and on other uncontrolled approximations \textup{(247, 88, 248)}.

Thus the relation between $\Gamma_{\text{frame}}$ and $\Gamma_{\text{fluc}}$ remains an open question, and simulations can point at the most likely answer. For example, if $\Gamma_{\text{fluc}} = \Gamma_{\text{frame}}$, the fluctuation tension should vanish for stress-free membranes, i.e., the undulation spectrum should then be dominated by a $q^4$-behavior. With a few exceptions \textup{(128, 274)}, this has indeed been observed in coarse-grained or atomistic simulations of stress-free lipid bilayers \textup{(99, 162, 176, 301, 21, 307)} or bilayer stacks \textup{(167)}. This would seem to rule out the alternative hypothesis, $\Gamma_{\text{fluc}} = \Gamma_0$. However, it should be noted that the undulation spectra have relatively large error bars and a complex behavior at higher $q$, as discussed in section \textup{2.3.1}. Therefore, the results also depend to some extent on the fit.

To overcome these limitations, accurate simulations of elastic infinitely thin sheets with no molecular detail are useful. Recently, a number of such simulations have been carried out in two spatial dimensions (i.e., one dimensional membranes)
The results are found to depend on the ensemble. Fournier and Barbetta studied a membrane made of hypothetical “lipids” with freely fluctuating areas, only controlled by a Lagrange parameter $\Gamma$. They found that the fluctuation tension $\Gamma_{\text{fluc}}$ displays a complex behavior and neither agrees with $\Gamma_{\text{0}}$ nor with $\Gamma_{\text{frame}}$. Schmid [247] has considered an arguably more realistic situation where “lipids” have fixed area, and either a fixed frame tension is applied, or the “projected area” is kept fixed. These simulations reproduce the difference between $\Gamma_{\text{0}}$ and $\Gamma_{\text{frame}}$ and indicate with high accuracy that the fluctuation tension is given by $\Gamma_{\text{fluc}} = \Gamma_{\text{frame}}$. Farago [79] confirmed these findings in simulations at fixed projected area. Furthermore, he carried out reference simulations of a hypothetical membrane model which lacks gauge invariance, and found that in this case, the fluctuation tension deviates from the frame tension. These studies support the validity of the picture originally put forward by Cai et al. [36]: For rotationally invariant membranes with fixed area per lipid, the fluctuation tension is given by the frame tension.

2.5 Membrane heterogeneity and lipid rafts

In the late 1990 several scientists put forward the suggestion that biomembranes might not be laterally homogeneous but instead contain nanoscopic domains—soon called “lipid rafts”—which differ in their lipid composition and greatly matter for numerous membrane-associated biological processes [1, 268, 31, 30, 32]. This idea quickly replaced the until then prevailing fluid mosaic model [270], according to which the lipid bilayer merely constitutes a two-dimensional passive solvent that carries membrane proteins. It created huge excitement due to many obvious biological implications and possibilities; at the same time it has long been discussed controversially, for instance because it took time to converge on a universally accepted definition of what a raft is [200, 225, 108, 160].

According to the lipid raft concept, biomembranes are filled with locally phase separated, cholesterol-rich, nanoscale “raft” domains, which contribute to membrane heterogeneity and play an important role in organizing the membrane proteins. Two aspects of this hypothesis are well-established: (i) Biological membranes are laterally heterogeneous, and heterogeneity is important for the function of membrane proteins, e.g. in signaling [292]. (ii) Multicomponent lipid bilayers phase separate in certain parameter regions into a “liquid disordered” (ld) and a “liquid ordered” (lo) phase [287, 288]. The hypothetical “raft state” is not phase-separated, but rather a globally homogeneous state filled with nanodomains of sizes between 10 and 100 nanometers. The raft concept is supported by experimental findings, e.g. on the mobility of certain membrane proteins [228]. It has been questioned mainly due to a lack of direct evidence. Rafts are too small to be visualized in vivo by microscopy. Moreover, it was not clear from a theoretical point of view why nanoscale rafts should be stable with respect to macrophase separation. To explain this, it was proposed that rafts might be nonequilibrium structures [286], that rafts might be stabilized by the cytoplasm [313] or by special line-active lipids [269, 26, 311].
Alternatively, it was argued that “rafts” might simply be a signature of critical fluctuations in the vicinity of critical points [289, 232]. Whether a thermodynamically stable nano-structured raft state could exist in simple multicomponent membranes that do not contain special line-active additives has remained unclear until recently. This theoretical question mark could be removed by recent simulations of the two-component Lenz model by Meinhardt et al. [187]. Fig. 2 shows a top view of a configuration which contains microscopic cholesterol rich domains. The simulations were carried out in a grand canonical ensemble where lipids and cholesterol can swap identities, which excludes the possibility that the finite domains simply reflect incomplete phase separation. The lateral structure factor of the membranes exhibits a peak around $q \sim 0.08 \text{nm}^{-1}$. Its existence shows that the clusters are not critical. Hence, raft-like structures can be thermodynamically stable in multicomponent membranes. The characteristic length scale of roughly 12 nm is compatible with the size commonly attributed to lipid rafts in biomembranes [225].

Two comments are in place here. First, it should be noted that typical “raft mixtures” used for studying rafts in model membranes contain at least three components. This is because three components seem necessary to bring about global lateral phase separation [288]. Meinhardt et al. report raft-like structures in a simulations of a coarse-grained model for binary mixtures, but as in experiments, their systems do not show global phase separation between fluid states. Likewise, there is also some experimental evidence that nanoscopic domains may already be present in binary...
mixtures – in particular mixtures of saturated lipids (lipids with high main transition temperature) and cholesterol. Studies based on local techniques such as ESR, NMR, or diffusivity measurements have indicated the existence of immiscible liquid phases \cite{129,244,288}, whereas in fluorescence microscopy, one only observes one homogeneous phase \cite{288}. This suggests that these two-component membranes phase separate on the nanoscale, while remaining homogeneous on the global scale, and that they thus feature many of the intriguing properties attributed to rafts.

Second, the characteristic length scale of the rafts is similar to the wave length of the ripple state in one-component bilayers in the transition region between the fluid and the tilted gel $L_{g'}$ state \cite{141,260}. Experimentally \cite{148,149} and in computer simulations \cite{152,297,159,134,42}, modulated phases are observed in lipid bilayers that exhibit a tilted gel state, and they are not observed in lipid bilayers with an untilted gel state $L_{\beta}$ \cite{148,149,152,69}. For example, in the Lenz model, rippled states occur in the standard setup with a mismatch between head and tail size \cite{159}, but they disappear if the head size is reduced such that the tilt in the gel phase vanishes \cite{69}.

Meinhardt et al. \cite{187} have proposed a joint theoretical explanation for these findings, which is based on the coupled monolayer model (see Sec. 2.1.3). They assumed that monolayers exhibit local phase separation into two phases with different order parameter (composition or other), and that the spontaneous curvature of the monolayer depends on the local order parameter. In the strong segregation limit where different phases are separated by narrow interfaces, they showed that the line tension is reduced in the presence of a mismatch $\Delta K_0$ between the spontaneous curvatures of the two phases. This is because monolayers with a spontaneous curvature, which are forced into being planar by the apposing monolayer, experience elastic stress, and some of that stress can be released at the domain boundaries. The resulting negative contribution to the line tension scales with $\kappa (\Delta K_0)^2$ and should be present wherever $\Delta K_0$ is nonzero. A more detailed calculation shows that the elastic energy is minimized for circular or stripe domains of a specific size, which is of the order of a few nanometers. This elastic mechanism could thus stabilize rafts of finite size for sufficiently large spontaneous curvature mismatch.

Meinhardt et al. also considered the weak segregation limit, where the phase separation is incomplete, the interfaces are broad, and the free energy can be expanded in powers of the order parameter $\Phi$. They showed that the expansion has a Landau-Brazovskii form \cite{24},

$$ F = \int d^2 r \left\{ \frac{g}{2} (\Delta + \Phi_0^2) \Phi^2 + \frac{r}{2} \Phi^2 - \frac{\gamma}{3!} \Phi^3 + \frac{\lambda}{4!} \Phi^4 \right\}, \quad (13) $$

with a characteristic wave vector of the order $q_0 \ll 1/\xi$, where $\xi$ is the in-plane correlation length $\xi = (\kappa t_0^2/K_A)^{1/4}$ ($t_0$ is the monolayer thickness and $K_A$ the areal compressibility). The Landau-Brazovskii model describes phase transitions driven by a short-wavelength instability between a disordered and one or several ordered phases. In mean-field approximation, it predicts a transition from a disordered phase to one of several ordered modulated phases (lamellar or hexagonal). Fluctuations are
known to shift the order-disorder transition and to stabilize a locally structured disordered phase via the so-called Brazovskii mechanism [24]. The correlation length $\xi$ sets the order of magnitude and a lower limit for the characteristic wave length of the structures. Inserting typical numbers for the elastic parameters of DPPC bilayers in the fluid phase, one obtains $\xi \sim 1\text{ nm}$.

The simple theory put forward by Meinhardt et al. accounts in a unified manner for both ripple phases and raft states in membranes. The prerequisites for the formation of such modulated phases is local phase separation (e.g., in the ripple case, between a liquid and a gel phase, or in the raft case, between a liquid disordered and a liquid ordered phase) and curvature stress in at least one of the two phases (typically the ordered one), resulting, e.g., from a size mismatch between head group and tails. In order to reproduce rippled states or rafts, coarse-grained simulation models must meet these criteria. This is often not the case. For example, the standard version of the popular MARTINI model does not have a ripple phase, because the low-temperature gel phase of saturated phospholipids is untilted.

## 3 Membrane-protein interactions

Biomembranes achieve their biological functions through a multitude of membrane-associated proteins. Whereas the membranes were long thought to mainly serve as a more or less inert background matrix for these proteins, the interactions between membranes and proteins have received more and more attention in recent years [181]. Membranes can affect protein function in several ways. The local lipid environment can immediately influence the function of proteins—e.g., by influencing the tilt and relative position of transmembrane domains [11], or by exerting local pressure on proteins [38]. Furthermore, membranes contribute to the effective interactions between proteins [75, 17, 4], and they can be used to tune protein clustering. In mixed membranes, the “raft hypothesis” mentioned in Sec. 2.5 asserts that nanoscale lipid domains in membranes help to organize and control protein assembly [268, 225].

Membrane-protein interactions are controlled by various factors: Local lipid packing, local lipid concentration, membrane distortion, monolayer and bilayer elasticity. Proteins are surrounded by a shell of lipid molecules (the lipid annulus), which mostly interact non-specifically with the protein molecules [156]. Protein-membrane interactions are thus to a large extent determined by the interactions of the annuli with the bulk, and often do not depend strongly on the details of the protein sequences. If membrane proteins locally deform the lipid bilayer to which they are bound, this can induce forces between them that are potentially long-ranged and quite universal in their characteristics. The reason is that the bilayer acts as a field that can transmit local perturbations—and thus forces—to distant regions. This is perfectly analogous to the way in which for instance an electrostatic field mediates interactions between electric charges or curved space-time mediates interactions between masses, except that a membrane seems more tangible than the other examples.
However, once we look beyond fundamental forces towards higher level emergent phenomena, very tangible fields exist everywhere. For instance, a rope can transduce a tensile force along its length, and we can describe this using continuum elasticity as the underlying “field equation”.

Just like ropes, fluid lipid membranes are continuous media at a sufficiently coarse level of description. But their rich physical structure equips them with several properties that can take on the role of a field, for instance:

a) The membrane thickness can be considered as a spatially varying field that couples to the protein content (see Sec. 2.1.3).
b) The lipids can have a spatially varying orientation or tilt order.
c) In mixed membranes the local lipid concentrations can be viewed as a field.
d) The Hamiltonian (1) associates a characteristic energy to a given shape of a membrane, thus rendering its entire geometry a field.

These fields differ quite substantially in their theoretical description—concentrations are scalar variables, orientations are vectors, and differential geometry is at heart a tensor theory—but all of them are known to mediate interactions. For instance, the fact that proteins might prefer one lipid composition over another and thus aggregate is central to an important mechanism attributed to lipid rafts; and tilt-mediated protein interactions have also been studied in multiple contexts. It is even possible to describe all these phenomena within a common language, using the framework of covariant surface stresses. However, in the present review we will restrict to only two particular example, both related to membrane elasticity: in Sec. 3.1 we will discuss interactions due to hydrophobic mismatch, and in Sec. 3.2 we will look at interactions mediated by the large-scale curvature deformation of the membrane.

### 3.1 Hydrophobic mismatch

Proteins distort or disrupt membranes, which in turn act back on proteins. Structural perturbations contribute to protein function and are among the most important sources of membrane-induced interactions between proteins. Unfortunately, perturbations or transformations of lipid bilayers due to proteins are very difficult to probe experimentally. Complementary theoretical and computer simulation studies can help to elucidate the role of the lipid bilayer in processes such as protein aggregation and function.

One major source of membrane-protein interactions that has been discussed in the literature for many decades is hydrophobic mismatch. If the width of the hydrophobic transmembrane domain of a protein is larger than the thickness of the lipid bilayer, the system can respond in two ways: Either the protein tilts, or the membrane deforms. Both responses have biologically relevant consequences. On
the one hand, the orientation of proteins is believed to have a significant influence on their functionality, e.g. in pore formation [276]. Coarse-grained simulations by Benjamini and Smit have suggested that the cross-angle distributions of packed helix complexes are mostly determined by the tilt angle of individual helices [11]. Membrane deformation, on the other hand, induces effective protein-protein interactions and provides one way to control protein aggregation [110, 56, 253]. In experimental tilt measurements, hydrophobically mismatched proteins were sometimes found to tilt; in other cases, the reported tilt angles were surprisingly small compared to theoretical expectations [112, 215, 294]. This was partly attributed to problems with the analysis of experimental NMR (nuclear magnetic resonance) data [275], partly to the presence of anchoring residues flanking the hydrophobic trans-membrane domains, which might prevent tilting through a variety of mechanisms [213, 43, 120, 295].

However, coarse-grained simulations show that the propensity to tilt is also influenced by more generic factors. Venturoli et al. have reported that cylindrical inclusions with larger radius tilt less than inclusions with small radius [290]. Neder et al. have identified hydrophobicity as another crucial factor determining tilt [202]. In systematic studies of a variety of simple inclusions with cylindrical shape and similar radii, embedded in a model bilayer of the Lenz type, they found that the behavior of different proteins mainly depended on their free energy of insertion, i.e., their binding free energy. Weakly hydrophobic inclusions with negative binding free energies (which stayed inside the membrane due to kinetic free energy barriers) react to hydrophobic mismatch by tilting. Strongly hydrophobic inclusions with binding energies in excess of $100k_BT$ deform the membrane. For the probably most common weakly bound inclusions with binding energies around $10k_BT$, the situation is more complicated: upon increasing hydrophobic mismatch, inclusions first distort the bilayer, and then switch to a tilted state once a critical mismatch parameter is reached. Tilting thus competes with the formation of dynamic complexes consisting of proteins and a shell of surrounding, stretched lipids, and the transition between these two states was found to be discontinuous.

In the case where the membrane is deformed, the deformation profiles can be compared to a variety of theories [214, 213, 191, 82, 83, 135, 16]. Both in coarse-grained [290, 307] and atomistic [48] simulations, it was reported that membrane thickness profiles as a function of the distance to the protein are not strictly monotonic, but exhibit a weakly oscillatory behavior. This feature is not compatible with membrane models that predict an exponential decay [214, 213, 135], but it is nicely captured by the coupled elastic monolayer models discussed earlier [5, 21, 307]. Coarse-grained simulations of the Lenz model showed that the coupled monolayer models describe the profile data at a quantitative level, with almost no fit parameters except the boundary conditions [307, 202].

In membranes containing several inclusions, the membrane thickness deformations induce effective interactions between inclusions. These have also been studied within the Lenz model [307, 204] and other coarse-grained models [252, 188]. The comparison with the elastic theory is less convincing, due to the fact that many other factors such as local lipid packing contribute to the effective potential of mean force,
which cannot easily be separated from the pure hydrophobic mismatch contribution [307]. Except for inclusions with very large radii [188], the hydrophobic mismatch contribution to the effective interactions was generally found to be attractive.

### 3.2 Curvature mediated interactions between proteins

#### 3.2.1 The mystery of the sign

A very striking experimental demonstration of membrane curvature mediated interactions was given by Koltover et al. in 1999 [147]. These authors mixed micron-sized colloidal particles with giant unilamellar vesicles to which they could adhere. While in the absence of vesicles the colloidal particles showed no tendency to aggregate in solution, they quickly did once they adsorbed onto the vesicles. Since it was also evident from many micrographs that the colloids induced local bending of the vesicle’s membrane, the experiment strongly pointed towards membrane curvature mediated attractions between the adhering colloids. This, however, was very surprising: While interactions were indeed expected, the force should have been repulsive, as predicted six years earlier by Goulian et al. [105]. Interestingly, the prefactor of this interactions had to be corrected twice [106, 90], but this did not change the outcome: the colloids should have repelled. It was soon understood that objects that cause anisotropic deformations could in fact orient and then attract [71, 70, 91], but the colloids of Koltover et al. were isotropic (as far as one could experimentally tell).

In what follows we will try to provide a glimpse into this mystery. A big part of it has to do with too careless a use of the statement “theory has predicted”. Theory always deals with model systems and makes simplifying assumptions, and this particular problem is fraught with seemingly inconsequential details that could and sometimes do matter.

#### 3.2.2 The nonlinear ground-state—Take I

The relevant field Hamiltonian pertaining to the curvature-mediated interaction problem is Eqn. (1)—minus several terms which will not matter. For a start, the last term involving the edge tension $\gamma$ does not arise in the absence of any membrane edge. The spontaneous bilayer curvature $K_0$ usually vanishes for symmetry reasons. If lipids can flip between the two leaflets, their chemical potential must be the same in both, and if no other symmetry-breaking field is present, this means that $K_0 = 0$. Unfortunately, membrane curvature itself breaks the bilayer symmetry, and any existing lipid composition degree of freedom must couple to the geometry [310, 95, 174, 3, 257, 46]. So let us for now assume that this is not the case and take a note of this first nontrivial assumption. Moreover, in actual biomembranes none of this need be true since active and passive processes can maintain an asymmetric
l lipid composition across the two leaflets [25, 51]. Finally, the term involving the Gaussian curvature can be dropped here, since we will neither encounter edges nor topology changes, and so the Gauss-Bonnet theorem will work in our favor. What remains is the simpler Hamiltonian (2), but this looks quite formidable in Monge parametrization, as this very equation shows. To make any progress with something as forbidding as this appears quite unlikely. And yet, not all hope is lost. For a spherical particle attached to an asymptotically flat membrane the nonlinear shape equation has an exact solution, namely, a catenoid. This is an axisymmetric minimal surface with $K \equiv 0$ and hence obviously minimizes the left hand side of Eqn. (2). If one adds additional lateral membrane tension, the exact shape of the membrane around a single adhering spherical particle can no longer be calculated analytically, but numerical solutions are relatively easy to come by using an angle-arclength parametrization [60]. Unfortunately, we need to know the solution for two particles, and in the absence of axisymmetry this is difficult—even numerically. It has been done [236], but before we discuss this approach, let us first see what results we can analytically wrest from these equations.

Even for the full nonlinear problem the tight link between geometry and surface stress permits one to express mediated interactions as line integrals over the equilibrium membrane geometry. For instance, picture two spherical particles bound to a membrane, held at some mutual distance. If the particles are identical, then this will give rise to a mirror-symmetric membrane shape, and it may be shown that the force between these particles can be written as [195, 196]

$$ F = \frac{1}{2} \kappa \int ds \left\{ K^2 - K_\parallel^2 \right\}, \quad (14) $$

where for simplicity we restricted to the tensionless case. The integral runs across the symmetry curve (the intersection of the membrane with the mirror plane), $K_\parallel$ is the local curvature of that curve and $K_\perp$ the local curvature perpendicular to that curve. The sign convention is such that a negative sign implies attraction. To get an interaction strength out of Eqn. (14) we need these curvatures, for which we need to solve the shape equations after all. Unfortunately, not even the sign of the interaction is evident form Eqn. (14), since the difference of two squares enters the integrals. Had we been curious instead about the interaction (per unit length) between two parallel rods on the membrane, we would have been in a better position: Now $K_\parallel$ would be zero and the interaction would be clearly repulsive (even though we still don’t quite know how strong it is). It seems that in order to make headway, we must solve the shape equation. The only hope to do this in reasonable generality using analytical tools is to linearize them.

### 3.2.3 Linearization and superposition approximation

Linearizing the nonlinear geometric functional means restricting to the first term in the integrand of Eqn. (3). If we add a surface tension $\Gamma$, this means looking at the energy density $\frac{1}{2} \Gamma (\nabla h)^2 + \frac{1}{2} \kappa (\Delta h)^2$, where $\nabla$ and $\Delta$ is the two-dimensional (flat!)
surface gradient and Laplacian, respectively. A functional variation yields

$$\left[ \Gamma \Delta + \kappa \Delta \Delta \right] h(r) = 0 .$$

(15)

This shape equation is of fourth order, but it is linear. Unfortunately, in the present context we must solve it for a two-particle problem with finite-sized particles, and therein lies the rub: the operator in square brackets is not separable in any simple coordinate system, so we have to deal with the fact that this equation is indeed a partial differential equation.

A popular trick to avoid this problem rests on the following reasoning: If the equation is linear, one might first want to look for a solution of the one-particle problem and then simply create the two-particle solution by superposition. We can then apply Eqn. (14) to calculate the force, which in the present example would yield the interaction potential [61]

$$U(r) = 2\pi \kappa \tilde{\alpha}^2 K_0(d/\lambda) \quad \text{with} \quad \lambda = \sqrt{\frac{\kappa}{\Gamma}} \quad \text{and} \quad \tilde{\alpha} = \frac{\alpha}{K_1(r_0/\lambda)} .$$

(16)

Here, $r$ is the distance between the particles, $r_0$ is the radius of the circular contact line at which the membrane detaches from the colloid, $\alpha$ is the angle with respect to the horizontal at which it does so, and the $K_\nu$ are a modified Bessel function of the second kind. This solution is analytical, simple, and wrong. Or more accurately, it only holds when $r \gg \lambda \gg r_0$, a restriction which excludes the interesting tensionless limit in which $\lambda \to \infty$. The mathematical reason is that superposition in the way celebrated here is not allowed: yes, superpositions of solutions to linear equations are still solutions, but superpositions of solutions, each of which only satisfies some part of all pertinent boundary conditions, generally do not satisfy any boundary condition and are thus not the solutions we are looking for. The physical reason why the superposition ansatz in this case fails is because the presence of one colloid on the membrane which creates a local dimple will abet a nearby colloid to tilt, thereby changing the way in which that second colloid interacts with the membrane and, in turn, the first one.

### 3.2.4 Linearization and a full two-center solution

One way to circumvent the superposition approximation is to solve the full two-center problem. This is of course much more tedious, and in fact can only be handled as a series expansion (in which one satisfies the boundary conditions at both particles up to some order in the multipoles and an expansion in the smallness parameter $r_0/r$). This calculation has been done by Weikl et al. [306], leading to

$$U(r) = 2\pi \kappa \left( \frac{\alpha r_0}{\lambda} \right)^2 \left\{ K_0(r/\lambda) + \left( \frac{r_0}{\lambda} \right)^2 K_2^2(r/\lambda) + \cdots \right\} .$$

(17)
Notice that in the case $r \gg \lambda \gg r_0$ this indeed reduces to Eqn. (16), while in the more interesting limit in which the tension vanishes it reduces to

$$U(r) = 8\pi \kappa \alpha^2 \left( \frac{r_0}{r} \right)^4,$$

which is indeed the solution of Goulian et al. [105], amended by the prefactor corrections [106, 109]. In fact, these authors have actually written down the solution for the case of two non-identical particles 1 and 2 with detachment angles $\alpha_1$ and $\alpha_2$. If we also make their radii $r_i$ different, we find [315]

$$U(r) = 4\pi \kappa (\alpha_1^2 + \alpha_2^2) \frac{r_1^2 r_2^2}{r^4}.$$  

Notice that unlike what one might have guessed from Eqn. (18) the potential (and thus the force) is not proportional to the product of the two detachment angles. The actual form of the prefactor, $\alpha_1^2 + \alpha_2^2$, is highly suggestive of an entirely different underlying physics, as we will now see.

### 3.2.5 Linearization using effective field theory

Eqns. (17), (18) and (19) are expansions of the exact solution for large distance. Working out higher order terms appears reasonably forbidding, given that one has to push a difficult multi-center problem to high order. However, there is a way to disentangle the multi-center problem from the interaction problem.

We have seen that the physical reason why the superposition approximation fails is the induced tilting of neighboring colloids. More generally, any finite particle in contact with the membrane will induce extra membrane deformations if the membrane in its vicinity is perturbed. This is simply a polarization effect: Any “incoming” field interacts with the boundary conditions imposed by the particle and these then create new “outgoing” fields. Superposition of fields would work for point particles, but these don’t capture these polarization effects, unless we equip them with the requisite polarizabilities. But this of course we can do. We can write a new Hamiltonian of interacting point particles, where each of them has the same polarizabilities as the actual finite size particles of the situation we actually wish to describe. This works by adding terms to the Hamiltonian which are localized at the position of the particle and which couple to the field in the same way that a local polarizability would. For instance, if a particle at the position $r_\alpha$ has a dipole polarizability $C^{(1)}_\alpha$, we must add the term $\frac{1}{2}C^{(1)}_\alpha h_i(r_\alpha)$ to the Hamiltonian, where the index $i$ is again a derivative. The energy increases quadratically with the gradient of the local field—exactly as for a dipole polarizability. The only remaining question is: where do we get the polarizabilities from? Answer: just like in classical electrostatics, by calculating the response of one particle in a suitably chosen external field and comparing the full theory with the effective point particle theory.
This idea is an example of what is referred to as effective field theory [239], and it has been used for a host of vastly diverse problems, ranging from black holes in general relativity [100, 227] to finite-size radiation corrections in electrodynamics [93]. The first application in the context of fluid soft surfaces was given by Yolcu et al. [316, 317]. For two axisymmetric particles on a membrane Yolcu and Deserno showed that Eqn. (19) extends as follows [315]:

$$\begin{align*}
U(r) &= 4\pi \kappa (\alpha_1^2 + \alpha_2^2) \frac{r_1^2 r_2^2}{r^4} + 8\pi \kappa \left( \frac{\alpha_1}{r_1} - \frac{\alpha_2}{r_2} \right)^2 \frac{r_1^4 r_2^4}{r^6} + \cdots \\
(20)
\end{align*}$$

Notice that the next order correction is also repulsive and in fact vanishes for identical particles (in contrast to some earlier calculations [72] which missed terms that contribute at the same order).

### 3.2.6 Fluctuation mediated interactions

It has long been known that even two flat circular particles on a membrane feel an interaction, since their boundaries affect the fluctuation spectrum of the membrane and thus its free energy. These forces are proportional to the thermal energy $k_B T$ and not to the surface rigidity $\kappa$ and are examples of Casimir interactions in soft matter systems [140]. For circular discs on a tensionless membrane they are attractive and, to lowest order, decay like the 4th power of distance [105, 220, 72, 117].

The true beauty of the effective field theory approach described in the previous section is that it also greatly simplifies force calculations on thermally fluctuating surfaces [316, 317, 315]. For two flat rigid particles of radii $r_1$ and $r_2$ Yolcu and Deserno find [315]:

$$\frac{-U(r)}{k_B T} = 6 \frac{r_1^2 r_2^2}{r^4} + 10 \frac{r_1^2 r_2^2 + r_1^4 r_2^2}{r^6} + 3 \frac{r_1^4 r_2^4 (5 r_1^4 + 18 r_1^2 r_2^2 + 5 r_2^4)}{r^8} + \cdots . \\
(21)$$

The leading order is well known, all higher orders are new. In fact, if one restricts to identical particles, many more orders can be readily written down:

$$\frac{-U(r)}{k_B T} = \frac{6}{x^4} + \frac{20}{x^6} + \frac{84}{x^8} + \frac{344}{x^{10}} + \frac{1388}{x^{12}} + \frac{5472}{x^{14}} + \frac{21370}{x^{16}} + \frac{249968}{x^{18}} + \cdots , \\
(22)$$

where $x = r/r_0$.

So here we have the first example of an attraction. Could these forces explain the aggregation observed by Koltover et al. [147]? This is difficult to say. First, in the case of almost flat membranes, which all these calculations implicitly assume by using linearized Monge gauge, the ground state repulsion (19) overwhelms the fluctuation contribution (21) once $\alpha > \alpha_c = \sqrt{3k_B T/4\pi \kappa}$, and for a typical choice of $\kappa = 20k_B T$ this gives the rather small angle $\alpha_c \approx 6^\circ$. Most likely the colloids in

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5 Unfortunately, in the first paper which discusses this force, Goulian et al. [105] claim that the prefactor is 12, a mistake that is not fixed during the prefactor-fixing in [106].
the experiments by Koltver et al. imposed much bigger deformations, but it is hard
to say what happens to both forces at larger angles. In the next section we discuss the
numerical solution of the ground state problem, but at present no calculations exist
which push the Casimir force beyond the linear regime, except in the case of two
parallel cylinders, for which Gosselin et al. find, rather remarkably, that the Casimir
force is repulsive [104].

3.2.7 The nonlinear ground-state–Take II

The various linear calculations show that two axisymmetric colloids on a mem-
brane should repel. But as the detachment angles $\alpha$ increase, it becomes harder to
justify the linearization. The expansion in Eqn. (3) ultimately rests on the small-
ness of $|\nabla h|$, an expression that should be compared to $\tan \alpha$. But once higher order
terms matter, Monge parametrization not only becomes technically impenetrable;
it is even incapable of dealing with membrane shapes that display overhangs. It is
hence preferable to discard it in favor of a more general numerical surface triangu-
lization.

Reynwar and Deserno [236] have studied the interaction problem for identical
axisymmetric colloids with large angles $\alpha$, using the package “Surface Evolver” by
Brakke [18]. For small angles $\alpha$ the large distance predictions coincide well with
Eqn. (18), but they break down rather abruptly as soon as $r < 2r_0$, which is when the
particles would touch unless they could also tilt out of each other’s way. For large
$\alpha$, the linear predictions substantially overestimate the repulsion. Interestingly,
for the special case $\alpha = \pi/2$ the repulsive force goes through a maximum (around
$r/r_0 \approx 1.8$), and it decreases upon moving the particles even close together until it
vanishes at $r/r_0 \approx 1$. At even closer distances the particles attract. Attractive forces
must exist also for detachment angles smaller than $\pi/2$, but Ref. [236] does not
attempt to find the minimal angle at which this happens. They certainly also exist
for angles bigger than $\pi/2$, even though it might be that there is also a largest angle
for which they exist. In any case, only for $\alpha = \pi/2$ does the attraction persist all the
way to $r = 0$.

A simple close distance approximation can be devised to understand the necessity
of a sign-flip. At sufficiently close distances the two particles tilt so much that they
almost face each other, and the membrane between them assumes a shape similar
to a cylinder, which is capable of transmitting tensile forces as we have seen in
Sec. 2.3. For angles close to $\pi/2$ this theory suggests [236]

$$ \frac{Fr_0}{\pi \kappa} = \frac{1}{x^2} + \frac{1 - \sin \alpha}{x} - 1 + \mathcal{O}(x) \quad \text{with} \quad x = \frac{r}{2r_0 \cos \alpha}. \quad (23) $$

Observe that the first two terms vanish for $\alpha = \pi/2$, which leaves the (attractive)
force $F = \pi \kappa / r_0$, which is half the value transmitted through a cylindrical mem-
brane tube—see Eqn. (5). The missing factor of 2 derives from the fact that this
calculation is not done at constant area but at constant (in fact: zero) tension. The
numerical calculations suggest that indeed $F(r)$ approaches a constant as $r \rightarrow 0$, even though it seems slightly off from the expected value $-\pi \kappa / r_0$.

### 3.2.8 Curvature mediated interactions in simulations

The experiments by Koltover et al. claim that isotropic colloids on membranes experience a surface (presumably: curvature-) mediated attraction. All theories we have discussed so far claim the force is repulsive, unless one goes to pretty large detachment angles. Can simulations shed more light onto the problem? If so, it will not be necessary to represent the bilayer in any greater detail, since only fluid curvature elasticity needs to be captured.

Reynwar et al. have investigated this problem using the Cooke model, amended by simple generic particles with some given isotropic curvature [237]. They showed that indeed strongly membrane-deforming colloids experience attractive pair interactions. Subsequent more detailed studies revealed that these are compatible with the numerical results discussed in the previous section [236]. However, they also showed that a large number of weakly membrane deforming colloids still aggregate—in fact, that they can drive vesiculation of the membrane [237]. This is surprising, since these particles exhibited detachment angles at which the ground state theory clearly insists on a repulsive pair potential.

However, just because the pair potentials are repulsive does not yet prove that aggregation cannot happen, since curvature mediated interactions are not pairwise additive, as first pointed out by Kim et al. [144, 145]. These authors provide a general formula for an $N$-body interaction, and even though it is really only accurate up to the triplet level [315], it does show that the contributions beyond pairs can lower the overall repulsive energy; for instance, they show that certain multi-particle configurations are indeed marginally stable instead of being driven apart. In a later publication Kim et al. [143] show that an infinite number of periodic lattices exists for which summing the non-pairwise interactions preserve zero membrane bending energy. Again, since their non-pairwise form is only accurate up to triplet order, it is not clear whether this result remains true if all orders are considered. Müller and Deserno have alternatively treated this problem using a cell model [194], in which a regular lattice of particles is replaced by a single particle within a cell, plus boundary conditions that mimic the presence of other surrounding particles. They prove that within this approximation the lateral pressure between colloids is always repulsive, even in the nonlinear regime; how well the cell model actually captures a multi-particle assembly is difficult to say, though. Auth and Gompper have also used a cell model approach [8], but they specifically apply it to a curved background membrane. They argue that even if the forces are repulsive, they might be less repulsive—and thus the free energy per colloid smaller—if the background membrane is curved, since this background curvature screens the repulsion between the colloids. This could provide a driving force for creating curved vesicle buds.

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6 They used the same techniques that also led to the exact Eqn. [14], only that in the cell model case the sign is evident from the expression.
from flat membranes studded with isotropic membrane curving colloids, provided the average area density of colloids remains fixed. The latter is usually the case in simulations, and Auth and Gompper show that the sizes of the vesicle which detach from the parent membrane for differently curved colloids is compatible with what Reynwar et al. [237] observe. What would fix this density in real systems is less clear, but it is conceivable that this is yet another situations where rafts come into play: If the membrane-curving particles have to stay within a finite raft, their mutual repulsion can, by virtue of the mechanism discussed by Auth and Gompper, lead to a budding of that raft domain.

In conclusion we see that the situation is substantially more tricky than the seemingly simple questions “do membrane curving particles attract or repel?” leads one to expect. Nonlinearities, multibody interactions, fluctuations, background curvature, boundary conditions, anisotropies, are only some of the “details” which affect the answer to this question. At the moment the situation remains not completely solved, but the results outlined in this section should provide a reliable guide for future work.

4 Multiscale modeling of lipid and membrane protein systems

4.1 Multiscale modeling: approaches and challenges

As we have seen in the previous sections, coarse grained lipid models have been enormously successful at investigating phenomena in lipid bilayers and lipid bilayer/protein systems. In particular, rather coarse, generic models that reduce the lipids to their most essential features and shed almost all chemical specificity have enormously contributed to our understanding of effective interactions, generalized processes, and their driving forces. A different branch of coarse grained models, the already mentioned bottom-up models, has progressed quite dramatically in the past decade as well. These models are not developed as stand-alone models with parameters derived to reproduce some desired experimentally known feature of the system. They are developed in a bottom-up way with the help of an underlying higher-resolution (atomistic) model. Therefore, frequently the terms “multiscale modeling” or “systematic coarse graining” are used. These models allow to stay closer to an atomistic system and to retain more chemical specificity, and due to their bottom-up construction they offer the opportunity to go back and forth between a coarse grained and an atomistic level of resolution using so-called backmapping techniques.

It should be noted though, that this closeness between levels of resolution does come at a cost: upon reducing the number of degrees of freedom the models become strongly state point dependent and it necessarily becomes impossible to accurately represent all properties of the underlying atomistic system with the coarse grained model. In particular the representation of thermodynamic as
well as structural properties is a severe challenge that has been subject of a multitude of studies over the last years [137]. The question of representability and the unavoidable choice of parametrization target properties that has to be made has led to a number of different systematic coarse graining approaches which are often divided into two general categories: (i) methods where the CG parameters are refined so that the system displays a certain thermodynamic behavior (typically termed thermodynamics-based) [206, 178, 177, 189, 63] or (ii) methods where the CG system aims at reproducing the configurational phase space sampled by an atomistic reference system (often misleadingly termed structure-based) [285, 172, 198, 234, 222, 201, 171, 215, 185, 193, 131, 211, 261]. Representability limitations lead to the observation that a structure-based approach does not necessarily yield correct thermodynamic properties such as solvation free energies or partitioning data while thermodynamics-based potentials may not reproduce microscopic structural data such as the local packing or the structure of solvation shells.

Closely related are also the inevitable transferability problems of CG models: all CG models (in fact also all classical atomistic force fields) are state-point dependent and cannot necessarily be – without reparametrization – transferred to different thermodynamic conditions (temperature, density, concentration, system composition, phase, etc.) or a different chemical or molecular environment (e.g. a certain chemical unit being part of different macromolecular chains). Structural and thermodynamic representability and state-point transferability questions are often intimately linked, since the response to a change in state point corresponds to representing certain thermodynamic properties. Intensive research is currently devoted to this problem [267, 2, 199, 293, 132, 264, 27, 185, 193], since the understanding of potential and limitation of coarse grained models is a necessary prerequisite to applying them to complex biomolecular problems and systems such as multi-protein complexes in biomembranes for the following reason: CG models are usually developed based on smaller less complex reference systems – a reference simulation of the actual target system is by construction prohibitive, otherwise the whole coarse graining effort would not be necessary in the first place. Consequently, it is essential to understand transferability among different concentrations, compositions and environments to be able to put these subsystem-based models together and obtain a reliable model for the actual – more complex – target system. In the following we will show for one example – the light harvesting complex of green plants (LHCII) – some aspects of multiscale modeling of membrane protein systems and some of the problems that need to be addressed if one wants to go beyond generic coarse grained models and retain a certain level of chemical specificity.

4.2 The light harvesting complex

The major light-harvesting complex (LHCII) of the photosynthetic apparatus in green plants binds more than half of the plant’s chlorophyll (Chl) and is presumably the most abundant membrane protein on Earth. It has become an intensely
studied model membrane protein for several reasons. Its structure is known in near-atomic detail \[166, 273\], and much of its biochemistry has been elaborated in the past decades \[251\]. Moreover, LHCII spontaneously self-organizes from its protein and pigment components in vitro; therefore, recombinant versions of it can easily be produced and modified almost at will \[312\]. The assembly of LHCII and the concomitant folding of its apoprotein has been studied in some detail \[121, 68\]. Both processes occur spontaneously upon combining the unfolded apoprotein and pigments in detergent solution. In vivo, the assembly of LHCII takes place in the lipid environment of the thylakoid membrane and, most likely, is influenced by the lipid and protein components of this membrane. This is difficult to analyse experimentally since, so far, the self-organisation of LHCII cannot be achieved yet in a lipid membrane environment. Recently, also the disassembly of LHCII and the role of the bound/dissociating pigments in the falling apart of LHCII trimers has become subject of increased interest. These pigments constitute about 1/3 of the total mass of LHCII and, according to the structure, significantly contribute to the stability of the pigment-protein complex. The structural behavior of LHCII has been analyzed by circular dichroism (CD), fluorescence, and electron paramagnetic resonance (EPR) \[312, 122, 68, 67\].

One important aspect of LHCII that specifically relates to other aspects discussed in the present review is the question of how the membrane environment (lipid composition, membrane curvature, etc.) affects the association of LHCII monomers to form trimers and the assembly of these trimers into the antenna complex around the photosynthetic reaction centers. The non-bilayer forming lipid MGDG constitutes half of the thylakoid membrane. This membrane maintains its lamellar structure only with proteins inserted, predominantly LHCII which, due to its concave shape, eases the curvature pressure exerted by MGDG. It has been suggested that this curvature pressure is a driving force for protein interaction in the membrane \[94\], however, since it is not known whether, e.g., the formation of supercomplexes of LHCII trimers eases or increases curvature pressure, it is unclear whether MGDG (or other curvature pressure-increasing lipid components) promote or inhibit the formation of such supercomplexes. Likewise, the composition of the lipid membrane and the membrane properties such as its curvature pressure most likely influence the folding of the LHCII apoprotein and its assembly with pigments.

LHCII commends itself as a useful model to study the influence of the lipid membrane on the assembly and structural behavior of membrane proteins in general because of its known structure, its availability in a recombinant form, and its self-organisation, at least in detergent micelles. Moreover, the Chl molecules bound serve as built-in fluorescence markers for monitoring the structural behavior of the pigment-protein complex. To be able to correlate experimental observations of aggregate formation with predictions from theory, recombinant LHCII has been inserted in liposomes and assayed for complex-complex distances by inter-complex FRET measurements and for aggregate formation by quantitating aggregate-induced fluorescence quenching (data to be published). Moreover, to test the simulation of pigment-protein assembly in the membrane environment, procedures are being es-
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established to dissociate and re-associate recombinant LHCII in liposomes and to use an in-vitro expression system to insert the protein into liposome membranes [314].

A multiscale simulation model to study the LHCII complex requires as a first step model parameters for all components involved. As already mentioned above, it will be neither possible nor useful to parameterize a CG model based on the actual multicomponent (lipid bilayer/protein/pigments) system but one would rather develop models for sensibly chosen subsystems. While typically parameters for the protein and the lipid bilayer can be found in many standard forcefields, a challenging first task is to obtain a reliable model for the pigments – irrespective of the level of resolution. For many biological applications the MARTINI CG forcefield – that has already been described above – has become very popular and successful, in particular for lipid bilayer and protein systems. To employ the MARTINI forcefield for simulations of the pigmented LHCII, a CG description and model parameters for the pigment molecules needs to be added. We have developed a coarse-grained model of the chlorophyll pigments (Chl b and Chl a) which can be embedded into the existing MARTINI force field to study the pigmented LHCII trimer in the future. To do this, Chl b and Chl a were parameterized in the presence of the lipid bilayer. This reference system for parametrization was chosen for two reasons: most importantly, the Chl-lipid interactions are highly relevant for the formation and behavior of the LHCII protein-pigment complex in the lipid bilayer. 50% of the pigment molecules in the plant are bound to the light harvesting complex, with 42 Chl molecules per LHCII trimer. In vitro studies have shown that the folding of the LHCII apoprotein and the pigment binding to the protein are tightly coupled processes. In the LHCII monomer, many Chl pigments are situated in the outer region of the protein, effectively forming an interface between protein and lipids. Consequently the Chl-lipid interactions are most likely important for the assembly and stability of the trimer. A second reason for choosing the Chl-lipid system as reference for which the interactions between the MARTINI standard forcefield and Chl can be tuned is that it is more tractable compared to the fully pigmented LHCII membrane protein complex. The CG model for Chl b and a in the DPPC bilayer was derived based on a combination of a structure-based approach for bonded and a mixed structure-based and partitioning-based approach for non-bonded interaction potentials to fit the thermodynamics-based MARTINI force field. The CG model for Chl molecules follows the degree of coarse graining of the MARTINI forcefield. Somewhat in line with the general MARTINI parameterization philosophy, which focuses on partitioning properties, the non-bonded parameters were chosen such that the distribution of the CG Chl beads between hydrophilic and hydrophobic regions in the bilayer is correctly represented – compared to the atomistic reference simulation. Here, particular attention was paid to the interactions of the polar center of the porphyrin ring with the lipid beads and to the polarity of the aromatic ring which needs to be carefully tuned to obtain the correct distribution between the polar headgroup and the hydrophobic tail regions of the lipid bilayer. The bonded interactions in the CG pigments were derived such that the coarse grained model reproduces the shape and the conformational behaviour of the atomistic Chl molecules – the overall shape of the porphyrin ring and the different conformations of the phytol tail are well represented.
in this CG model. As a last aspect of validation of the CG model we have analyzed the propensity of the Chl pigments to aggregate in the lipid bilayer: It was found that Chl molecules do aggregate, with clusters that from and break multiple times in the course of the simulation, i.e. the aggregation is not overly strong. Qualitatively, these data are corroborated by fluorescence quenching experiments which show that chlorophylls in lipid bilayers have a tendency to aggregate at low lipid:Chl ratios of less than 1250 lipids/chlorophyll. Summarizing, the structural behavior, the distribution of the pigments in the bilayer (which are indicative of a correct balance of hydrophobicity/hydrophilicity) and the pigment association is very well represented in the CG model compared to atomistic simulations and experimental data. [57].

After driving the CG model parameters for the Chl-lipid system, this new model was now combined with the MARTINI model for proteins to perform some first simulations of the pigmented LHCII complex (in trimeric as well as in monomeric form). In addition classical atomistic (explicit solvent) simulations of trimeric and monomeric LHCII in a model membrane have been performed to provide a reference for validation of the CG simulations. The first CG simulations of the LHCII complex have proven to be very promising. Unlike our initial attempts without the careful parameterization of the pigments, the trimeric protein-pigment complex has been structurally stable, most notably without the presence of any artificial elastic network between the protein core and the pigments (see Figure 3). The properties of the complex from the CG model are in excellent agreement with the atomistic ones. In the future, this CG model will be used to study various aspects of LHCII protein/protein interactions in the lipid bilayer that on the one hand go beyond the time- and length scales accessible to atomistic simulations alone and on the other hand require a more chemically realistic description of the protein/pigment/lipid system than in typical generic CG models.

![Fig. 3](image)

Left panel: Top view of an LHCII trimer (colors according to chain or molecule type: blue - chain A, red - chain B, green - chain C, cyan - Chl b, pink - Chl a). Middle and right panels: Contact maps between Chl pigments and protein residues of LHCII trimer drawn as distance maps between the Cα atoms of the proteins (y-axis) and the Mg atoms of all Chl pigments (x-axis) within a 2.5 nm cut-off for 70 ns long atomistic (middle panel) and 100 ns long CG (right panel) simulations. The maps show that the pigments are stably located in their binding sites for both levels of resolution.
5 Conclusions

In the present chapter we have presented an overview of different approaches to study lipid membranes and membrane protein systems. We have reviewed theoretical and simulation approaches, and shown how generic lipid simulation models can be used to understand the principles that determine properties of lipid bilayers such as bending and Gaussian curvature modulus, membrane tension, or fundamental phenomena such as the formation of lipid rafts, or the curvature mediated interactions between proteins. In the concluding section it was outlined how multiscale modeling can in principle go a step further by ensuring a certain chemical specificity while still benefiting from the time- and length-scale advantages of coarse grained simulations – noting though that there are still a number of challenges in the area of systematic coarse graining that need to be addressed to be able to study complex multicomponent systems such as the the light harvesting complex of green plants. For this system we have shown first steps toward a multiscale simulation model that allows to go back and forth between a coarse grained and an atomistic level of resolution and therefore permits immediate comparison to atomic level experimental data.

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