Introduction

This chapter presents the model of the doped lamellar phase, and the method used to study it: numerical simulations.

1.1 Off-lattice, coarse-grained model

1.1.1 Models of lamellar phases

Molecular dynamics simulations of lipid bilayers which include atomic details have been performed for about three decades [190, 52, 59]. Recent publications report simulations of several hundred of lipids in thousands of water molecules [114, 99]. The available scales in time and space are still limited compared to many biochemical processes, but the performance is increasing enormously, thanks to the parallelization of simulation codes and to faster algorithms. Ten years ago, atomic models permitted to describe the different conformations of molecules in the solid, gel and liquid phases of lipid bilayers [79]. Since then, atomic molecular dynamics simulations have even been used to investigate the interactions of amphiphilic bilayers with other molecules. Due to the complexity of biological membranes, the number of interesting systems which can be simulated is huge: mixtures of lipids, adsorption of peptides, inclusion of cholesterol (see Fig. 1.1 A, from [32]), inclusion of membrane proteins, diffusion of ions, *etc.*

Limiting the accuracy of the calculations by cutting-off the potentials at about 1 nm permits to study a bilayer during longer times (256 DPPC during $0.5 \,\mu s$ [113]) or to simulate more molecules (2000 DPPC for 16 ns [114]).

Coarse-grained molecular models are obtained by neglecting atomic details and keeping only the structure of the molecules. The coarse-grained "molecules" are typically derived from the "realistic" molecules by grouping some atoms together into beads interacting via effective potentials. The electrostatic interactions and the dihedral angle potentials are often neglected. For example, a molecule of hexane C_6H_{14} is possibly coarse-grained into a chain of six "united-atoms" interacting via the popular 6 - 12Lennard-Jones radial pair-potential (6-12 LJ) ([201] and Ref. in it).

$$\mathcal{V}_{\mathrm{LJ}}(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^{6} \right]$$

where ϵ is the potential depth, and σ a typical length for the interaction. The essential



Figure 1.1: A: Atomic model of a bilayer: 108 molecules of DPPC, 5301 molecules of water and 54 molecules of cholesterol [32]. B: Molecular coarse-grained model of a bilayer with ht_4 amphiphiles (one head-bead linked to a chain of four tail beads) [69].

features of Lennard-Jones potentials are a soft repulsion at small distances $(r \leq 2^{1/6}\sigma)$, and a short-ranged attraction $(\mathcal{V}_{LJ} \propto -r^{-6})$.

Shelley *et al.* [174, 173] proposed a coarse-grained model of dimyristoylphosphatidylcholine (DMPC). One amphiphile of more than 100 atoms was reduced to 13 units interacting *via* Lennard-Jones-type potentials (6-12 LJ, but also 4-6 LJ, among others). In this case, the coarse-grained simulations cost about 400 times less computer time than the all-atoms simulations.

Further simplified models describe the interactions between the amphiphilic molecules only qualitatively, but much more generally (see Fig. 1.1 B, from [69]). The main components included in these models are: (i) the amphiphilic structure, (ii) the internal degrees of freedom of the molecules, and (iii) the interactions between amphiphiles and solvent molecules. For example, short amphiphilic oligomers composed of hydrophobic tail-beads linked to hydrophilic head-beads self-assemble into micelles or bilayers, whose shape fluctuations can be studied by numerical simulations [180, 69, 129].

Lattice models also have proven to be very successful to reproduce the phase diagram of amphiphilic solutions [100, 33]. Müller *et al.* explored the mechanical stability of model membranes composed of diblock-copolymers dissolved in bulk homopolymers using lattice Monte Carlo simulations [127, 126], and compared the results to those of self-consistent-field theory.

By neglecting additionally the internal degrees of freedom of the amphiphilic molecules, Leibler *et al.* could simulate a unilamellar vesicle (see Fig. 1.2 A, from [103]).

Finally, a different class of models neglects even the amphiphilic character of the

molecules, to focus on the properties of membranes built by amphiphilic molecules. The membranes are represented as a undulating surfaces. Triangulated elastic surfaces, for instance, have proven to be a good model to study the shape fluctuation of vesicles (see Fig. 1.2 B, from [71]) or the proliferation of pores in bilayers [175, 177].



Figure 1.2: A: Model of a bilayer as an assembly of spheres composed of three parts: one hydrophobic, in the center (yellow), and two hydrophilic at the poles (red and blue) [103]. B: Model of bilayer as a triangulated surface with fluctuating topology [71].

1.1.2 Definition of the model

The model used in this thesis is an extension of a coarse-grained off-lattice model proposed by Grest and Kremer in 1986 [73], which has been used extensively to simulate polymers [97, 47]. It has been extended recently to study the rheologic properties of amphiphilic dimers [182, 75]. The model resembles the one used by Goetz *et al.* [69] (see Fig. 1.1 B): it is a coarse-grained off-lattice molecular model. The amphiphiles are represented by tetrameric chains composed of two hydrophobic tail beads and two hydrophilic head beads, denoted by *hhtt* or h_2t_2 . The polymer is a simple linear chain of hydrophilic beads (see Fig.1.3). Chemical details, long-range interactions or chain stiffness are not incorporated in the model.

The forces derive from radial, short-ranged pair potentials. The beads interact through a soft repulsion and a short-ranged attraction characterized by two parameters: a length defining the range of the interaction σ , and an energy defining the depth of the potential ϵ . The units are the following: for the energies $k_B T$, for the lengths σ , and for the mass of the beads, m. These units lead to the time unit $\tau = (m\sigma^2/k_B T)^{1/2}$.

A bead represents approximatively three alkyl groups, or eventually three water molecules. The orders of magnitude of the units are then $k_BT \simeq 10^{-21} J$, $m \simeq 10^{-25} kg$, and $\sigma \simeq 5 \text{ Å}$ [174]. The time unit is approximatively one picosecond ($\tau \simeq 10^{-12}$ s).



Figure 1.3: Molecules of the model: solvent beads, amphiphiles and polymers. They are composed of four sorts of beads: solvent beads, tail beads, heads beads and polymer beads.



Figure 1.4: Radial pair potentials as a function of the inter-particle distance. A: Potential of interaction between beads that are not connected: $U_{\text{LJ-cos}}$. B: Potential of interaction between connected beads: $U_{\text{LJ-FENE}}$ (solid line). The potentials of non-connected pairs are represented as well (dashed line).

	solvent	head	tail	polymer
solvent	ϵ	ϵ	0	ϵ
head	ϵ	ϵ	0	ϵ
tail	0	0	ϵ	0
polymer	ϵ	ϵ	0	ϵ

Table 1.1: Potential depths for the non-bonded interacting beads. In most cases, $\epsilon = 1.1 k_B T$

Force fields

Unconnected beads interact via the LJ - cos potential, defined by

$$U_{\text{LJ-cos}}(r) = \begin{cases} 4k_B T \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6 + \frac{1}{4} \right] - \epsilon & \text{if } r \le 2^{1/6} \sigma \\ \frac{\epsilon}{2} \left[\cos(\alpha r^2 + \beta) - 1 \right] & \text{if } 2^{1/6} \sigma \le r \le r_c \\ 0 & \text{if } r_c \le r \end{cases}$$
(1.1)

where σ is the unit of length, $\alpha = \pi/r_c^2 - 2^{1/3}\sigma^2$ and $\beta = 2\pi - r_c^2\alpha$. The cutoff is chosen at $r_c = 1.5\sigma$ (see Fig. 1.4 A for an illustration). The minimum of potential $(r \simeq 1.16\sigma)$ and the cut-off $(r = 1.5\sigma)$ are independent of the potential depth ϵ . At $\epsilon = 0$, the potential is strictly repulsive.

The potential depths of the several interactions between unconnected beads are collected in Table 1.1.

Connected beads repel each other with the same soft-core potential as non-bonded beads, but at larger distance, the interaction is attractive through a "finite extendable non-linear elastic" (FENE) potential (see Fig. 1.4 B).

$$U_{\text{LJ-FENE}}(r) = \begin{cases} 4k_B T \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6 \right] - \left(\frac{\kappa r_b^2}{2}\right) \ln \left[1 - \left(\frac{r}{r_b}\right)^2 \right] & \text{if } r \le r_b \\ \infty & \text{if } r_b \le r \end{cases}$$
(1.2)

The parameters used for in this thesis are $r_b = 2.0 \sigma$ and $\kappa = 7.0 k_B T \cdot \sigma^{-2}$, as in [47].

Truncation of the potentials

The potentials of the model are cut off at 1.5σ or 2σ : This permits to optimize the simulation code by using the so-called neighbor-lists and cell-lists [1, 63]. The principle is explained in the following.

If every particle interacts with every other particle of the simulation box, the number of interactions is proportional to N(N-1)/2, where N is the number of bead in the simulation box. If the potential is short-ranged and the density is fixed, the number of interactions increases no longer quadratically, but linearly with N. As most of the time of computation is spent calculating the forces, reducing the cut-off r_c significantly speeds up the calculations.

Still, the number of distances to check remains N(N-1)/2. To speed up the calculations even more, the algorithm uses the so-called neighbor-lists combined with cell-lists [63, 1].

The principle of the neighbor-lists (also named Verlet list) is the following: A list of pairs of particles at the distance r that are close enough to interact is stored $(r \leq r_c)$. For the calculation of the forces, instead of testing N(N-1)/2 distances at each time step, the algorithm directly uses the list of interacting neighbors. The key point is that pairs of particles which are at the distance r slightly larger than the cutoff r_c are also stored in the neighbor-list ($r \leq r_c + d_s$, where d_s is a "distance of security"). Thus the neighbor-list does not have to be updated at each time-step, and much computation time is saved.

Additionally, the construction of the neighbor-lists is optimized by cell-lists: the space is divided into cells, in which the particles are sorted. The lists of cells whose particles may interact is set up only once, at the beginning of the simulation. During the simulation, for each Verlet list update, only the pairs of particles belonging to the pairs of cells registered in the cell-list are checked. The computational time decreases because the construction of the list becomes much cheaper than N(N-1)/2 checks of distances.

Finally, the program is implemented with an optimized domain-decomposition scheme, to run the simulations in parallel [148, 182].

Besides these technical considerations, the truncation of the potentials strongly influences the properties of the system. For instance, the critical temperature of the Lennard-Jones fluid decreases from $k_B T_c/\epsilon = 1.316$ to 1.085 when the potential is cutoff at 2.5 σ and shifted to get a continuous potential [1]. Additionally, as the model does not include long-range interactions, in particular non-screened electrostatic forces, the study is restricted to neutral lamellar phases - or to charged lamellar phases where the long-range interactions are screened by a solvent with a high dielectric constant.

1.1.3 Phenomenology of the model

As the phase diagram of the model is complex, I outline here only the essential features relevant to this thesis. For pedagogical reasons, the details of the simulations are not discussed here (for more details, see Section 1.2).

The solvent: a simple fluid

The solvent beads repel each other at short distance $(r \leq 2^{1/6} \sigma)$, and attract each other at intermediate distance $(2^{1/6} \sigma \leq r \leq 1.5 \sigma)$, as depicted in Fig. 1.4 A. Despite the cutoff of the potential, the pure solvent is similar to a Lennard-Jones fluid. Its phase diagram is expected to be composed of a gas phase, a fluid phase and one or more crystalline phases. For this thesis, the gas phase is not relevant.

To detect approximatively the fluid-to-solid phase transition of the solvent, I studied its density ρ as a function of the potential depth ϵ , with a simulation in the constant-NPT ensemble (see Fig. 1.5). As expected, the density increases when the potential becomes more attractive (increasing ϵ). The abrupt increase of the density indicates the



Figure 1.5: Density of the solvent as a function of the potential-depth in NPT ensemble $(N = 1\,000 \text{ beads}, P = 1\,k_BT \cdot \sigma^{-3}).$

fluid-to-solid transition. Since the transition is first-order, we observe hysteresis when the potential depth is decreased again.

The minimum density at which the solid is observed is about 0.93 beads per unit volume. To ensure that the system remains fluid, one simulates it at a density close to 0.85 beads per unit volume.

Pure amphiphiles: the order-disorder transition

The amphiphiles are represented by chains of two tail beads and two heads beads. The tail-head pairs repel each other at short distance, whereas the head-head or tail-tail pairs additionally attract each other at intermediate distances. If they were not connected to each other, the heads and tails would demix for ϵ larger than $0.6 k_B T$ [182]. In the case of connected chains, increasing the potential depth ϵ drives a self-assembly. For pure amphiphilic systems, two phases have been observed. Two snapshots in Fig. 1.6 represent a pure $h_2 t_2$ system in the disordered phase (small ϵ) and in the ordered liquid crystalline lamellar phase (large ϵ).

Quantitatively, the transition between the two phases can be detected by an abrupt variation of the nematic order parameter S (defined in Section 2.1.2). The transition occurs around $\epsilon = 0.8 k_B T$ (see Fig. 1.6). As the transition is first-order, the system exhibits hysteresis.

To simulate the lamellar phase, I have chosen the value $\epsilon = 1.1 k_B T$. The density 0.85 beads per unit volume corresponds then to a pressure of $3.0 k_B T \cdot \sigma^{-3}$.

More generally, other amphiphilic oligomers $h_n t_m$ may self-assemble into a smectic A. For example, dimers undergo the order-disorder transition at the potential depth $\epsilon = 1.2 k_B T$. I have chosen to simulate tetramers because they are small, symmetric (monolayers have no spontaneous curvature), and their lamellar phase is stable relative