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Phase-field theories for mathematical modeling of biological membranes

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ABSTRACT

Biological membranes are complex structures whose mechanics are usually described at a mesoscopic level, such as the Helfrich bending theory. In this article, we present the phase-field methods, a useful tool for studying complex membrane problems which can be applied to very different phenomena. We start with an overview of the general theory of elasticity, paying special attention to its derivation from a molecular scale. We then study the particular case of membrane elasticity, explicitly obtaining the Helfrich bending energy. Within the framework of this theory, we derive a phase-field model for biological membranes and explore its physical basis and interpretation in terms of membrane elasticity. We finally explain three examples of applications of these methods to membrane related problems. First, the case of vesicle pearling and tubulation, when lipidic vesicles are exposed to the presence of hydrophobic polymers that anchor to the membrane, inducing a shape instability. Finally, we study the behavior of red blood cells while flowing in narrow microchannels, focusing on the importance of membrane elasticity to the cell flow capabilities.

1. Introduction

Like many other organelles at the cell scale, membranes are composite structures that exhibit a bewildering complexity. Their basic ingredient is a lipid bilayer composed by hundreds of different lipid species. The bilayer also contains a dense population of transmembrane proteins, which could represent up to 70% of the total mass of the membrane, and in fact these molecules define the functionality of the membrane (Alberts et al., 1994). Many other proteins are anchored to both sides of the bilayer, and membrane composition is balanced by lipid reservoirs which ensure that the physiological properties of the membrane are maintained. Among others, membranes define the cell frontiers, separating the cytosol from the external environment. They also maintain ion gradients which are necessary to produce ATP, and host the proteins that control cell signaling. Focusing specifically on the structural function, membranes present a delicate interplay with the cortex cytoskeleton, a complex mesh formed by filaments of actin preserving cell inner structure and shape, and provides strength and compactness. This picture represents, however, just a rough description of the membrane composition and function, included here to evidence its extreme complexity. The comprehensive understanding of this fascinating system requires of different level of approaches. At the molecular scale, the detailed running of each microstructure can be analyzed thoroughly from the electrochemical interactions between their molecular components. However, the all-encompassing response of the membrane elements invites to a more general description, and physical theories such as the elastic formalism of plates and surfaces offer a formidable tool to characterize biological membranes. At this point, it is convenient to remark that physicists have focused on the specific study of the human erythrocyte (Sackmann, 1995). This cell is unique among the rest of cells of the organism because it lacks any organelle and inner structure, so that all its physical properties are entirely determined by its membrane, representing a much simpler structure than normal cells. The membrane of the erythrocyte is composed by a lipid bilayer with and underlaying spectrin cytoskeleton which anchors to the cytosolic side of the bilayer. This two-dimensional scaffold has a structural function, preventing the cell from vesiculation and large deformations.

In order to build a physical theory of the membrane, the complexity of the cell membrane suggests to consider the scales of interest. Our scope is to study phenomena at the cell scale, such as cell morphological deformations or mechanical interactions with the environment. In this context, the atomic description is clearly unaffordable: the difficulty of dealing with such a vast number

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of interactions between atoms, even in simple molecules such as lipids, discards any treatment at this scale. Coarse-grained descriptions, which represent each lipid by a number of beads (typically 3–10) that encompass a region of the molecule with similar properties (Marrink et al., 2007; Shillcock and Lipowsky, 2006), offer a path for the study of small sized patches of membranes. The state-of-the-art numerical methods are able to describe the kinetics of typically 10^6 molecules (Marrink and Tieleman, 2013), involving membrane domains of roughly $100\,\text{nm} \times 100\,\text{nm}$, but still far from the macroscopic cell scale, $10\,\mu\text{m} \times 10\,\mu\text{m}$. It is clear that coarse-grained methods are, still, not appropriate if one pretends to study the overall cell response. For this purpose, it is convenient to invoke mesoscopic theories (Deserno, 2009). By considering the membrane as locally homogeneous and introducing a continuum description, each small part of the membrane is characterized by some certain local properties. These properties must be consistent with the local molecular structure of the membrane, so that a connection between the micro and mesoscales should be derived.

This Chapter does not intend to describe in detail the basis of mesoscopic theories in the context of membranes, a subject which has received extensive attention elsewhere (Safran, 1994), but to motivate one of the most relevant methods for studying interface dynamics, the so-called phase field method, as an important tool in the study of membrane elasticity and kinetics. Phase-field models for biological membranes are based on the Helfrich description of membranes (Helfrich, 1973), a modified formulation of the theory of elasticity. We will start presenting this theory and studying its application to lipid membranes, in order to gain some intuition about the physics and elasticity of these structures, and paying special attention to its derivation from the molecular description of the membrane. The main characteristics of membrane elasticity are addressed to be subsequently incorporated to the phase-field model. Then, we will explain the basis of the phase-field methods and how they can be used to model membranes. Finally, we will conclude with some examples of current research on biological membranes that make use of this methodology.

2. The curvature energy

The theoretical study of membranes at the cell scale was first performed by Canham (1970), Helfrich (1973), and Evans (1974). They concentrated on the identification of the relevant elastic properties of the erythrocyte membrane by trying to reproduce its distinctive discocyte shape. The main assumption of their approach is that the cell membrane can be described as a two-dimensional sheet, based on its minute thickness compared to the cell length. Helfrich proposed that from the three main type of deformations that a layer can undergo, shear, tilt and bending, only the last does play a relevant role in the membrane elasticity. Accordingly, he proposed a curvature energy to describe the elasticity of cell membranes,

$$\mathcal{F}_b = \frac{\kappa}{2}\int (C - C_0)^2 dA + \kappa_G \int G dA + \int \gamma dA + \int \Delta p dV, \qquad (1)$$

where $C = (c_1 + c_2)$ and $G = c_1 c_2$ are the total an Gaussian curvatures of the membrane surface given by principal curvatures c_1 and c_2, κ and κ_G are the bending rigidity and saddle-splay modulus, C_0 is the so-called spontaneous curvature that accounts for any asymmetry in the membrane internal structure, whereas γ and Δp generically represent a surface tension and a pressure difference across the membrane. In the Helfrich initial description, these two components are Lagrange multipliers to ensure that cell area and volume, respectively, are conserved. The curvature energy (1) is often expressed in the literature in terms of the mean curvature $H = (1/2)(c_1 + c_2)$, though we follow here the total curvature notation. It is remarkable that the integral of the Gaussian curvature over a surface is a topologic invariant, and consequently it only plays a role in the membrane elasticity in processes comprising topological transformations. For the case of closed membranes, such as cells, the Gaussian term remains constant and for simplicity it can be ignored. The minimization of (1) for an ellipsoidal shape under the appropriate values of area and volume leads to the biconcave discocyte of the RBC as the equilibrium shape. Ensuing studies investigated the properties and minimal shapes of the Helfrich energy and the theory has been refined to incorporate additional mechanisms such as the area-difference elasticity (Sheetz and Singer, 1974). Subsequently, the elastic contribution of the spectrin cytoskeleton which attaches to the lipid membrane was incorporated, with the aim of explaining the entire phenomenology of the human red blood cell (Evans, 1974; Iglic, 1997). The cytoskeleton provides resistance to in-plane deformations and plays a fundamental role in the cell response under certain deformations (such as morphological changes during crenation (Lázaro et al., 2013) or squeezing during optical tweezers experiments, Li et al., 2005), adding a shear-stretching contribution to the membrane elasticity. In our phase-field model we do not consider the cytoskeleton contribution and it therefore applies to problems in which this network is absent (such as in membranes of cell organelles, *e.g.* in the Golgi apparatus) or if it plays a subdominant role, as occurs during blood flow Forsyth et al. (2011).

In the last years, the Helfrich model has been incorporated to different dynamic theories, offering the possibility of studying new and more complicate phenomena. Many of the results of this theory have proven in good agreement with experiments; nice examples include the theoretical prediction of shapes of the stomatocyte–echinocyte transition (Lim et al., 2002), the study of tubulation when polymers are attached to a lipid vesicle and effectively induce a spontaneous curvature (see Section 4) (Campelo and Hernández-Machado, 2008), or the experiments of stretching of red blood cells with optical tweezers (Li et al., 2005). In this section, we first discuss the microscopic basis of the Helfrich theory in order to show the consistency of the mesoscopic approach. We subsequently present the general theory of elasticity and its main results and applications to biological membranes.

2.1. Microscopic realization

Any mesoscopic description assumes that one can define domains of small size compared to the length scale of the system size, so that the variables defined at the mesoscale (*i.e.* at each of these domains) capture the relevant properties of the microscale. With the objective of explaining this fundamental assumption, we present here the simple model proposed by Petrov and Bivas (1984) which, in spite of being highly non-realistic, is useful to naively illustrate the connection between both scales. The model assumes a rough description of the interactions between lipids, and from this simple basis the Helfrich free energy (1) for a bilayer is derived.

The model assumes a harmonic approximation of the free energy per molecule,

$$f_m = \frac{1}{2}k_H\left(\frac{A_H}{A_H^0} - 1\right)^2 + \frac{1}{2}k_T\left(\frac{A_T}{A_T^0} - 1\right)^2 \qquad (2)$$

where $A_{H/T}$ are the areas per molecule of the head/tail, respectively, and $k_{H/T}$ are the harmonic constants related to the respective interactions between each group. A^0 are the preferred areas, related with the equilibrium intermolecular distance in the relaxed monolayer. Still, the effective constants $k_{H/T}$ should be related with the specific bonds between molecules, but this is difficult to address at this simple level of description. If one defines the neutral surface as the point of the lipid where the forces are balanced, and we call A the