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A multiscale approach to curvature modulated sorting in biological membranes

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ABSTRACT

Combining different theoretical approaches, curvature modulated sorting in lipid bilayers fixed on non-planar surfaces is investigated. First, we present a continuous model of lateral membrane dynamics, described by a nonlinear PDE of fourth order. We then prove the existence and uniqueness of solutions of the presented model and simulate membrane dynamics using a finite element approach. Adopting a truly multiscale approach, we use dissipative particle dynamics (DPD) to parameterize the continuous model, i.e. to derive a corresponding macroscopic model.

Our model predicts that curvature modulated sorting can occur if lipids or proteins differ in at least one of their macroscopic elastic moduli. Gradients in the spontaneous curvature, the bending rigidity or the Gaussian rigidity create characteristic (metastable) curvature dependent patterns. The structure and dynamics of these membrane patterns are investigated qualitatively and quantitatively using simulations. These show that the decomposition time decreases and the stability of patterns increases with enlarging moduli differences or curvature gradients. Presented phase diagrams allow to estimate if and how stable curvature modulated sorting will occur for a given geometry and set of elastic parameters. In addition, we find that the use of upscaled models is imperative studying membrane dynamics. Compared with common linear approximations the system can evolve to different (meta)stable patterns. This emphasizes the importance of parameters and realistic dynamics in mathematical modeling of biological membranes.

1. Introduction

Biological membranes define a mechanical boundary of cells and of substructures inside cells. They provide environments specialized for certain chemical or mechanical processes. The main component of membranes is lipid molecules. In water lipids form, due to hydrophobic interactions, a bilayer structure consisting of two lipid monolayers physically opposed to each other. Since membrane molecules can move freely in lateral direction of the membrane, its lateral behavior can be compared to a two-dimensional (2D) fluid, first described in the 'fluid mosaic' model by Singer and Nicolson (1972). With respect to bending the membrane behaves elastically and in the linear regime is well described by the plate equation (Ciarlet, 1997).

In vivo, biological membranes are composed of many different lipids, proteins and other molecules with different functions (Alberts et al., 2006). Lateral sorting of these components is essential for maintaining the diversity of different membrane systems inside the cell as well as their function (Gennis, 1989). For both, lipids (Baumgart et al., 2003) and proteins (Bonifacino and Lippincott-Schwartz, 2003) lateral phase separation and clustering have been shown. It is widely accepted that membrane curvature modulated sorting is a basal mechanism controlling the spatial organization of lipids and proteins in the absence of specific chemical interactions. However, the exact underlying mechanisms remain mostly unknown (Tian and Baumgart, 2009).

Different membrane model systems, whose geometry, size and composition can be modified in a defined way, have been used to investigate curvature dependent sorting on different scales, experimentally as well as theoretically: experiments with artificial membranes have been performed using unilamellar vesicles (Baumgart et al., 2003; Heinrich et al., 2010; Kamal et al., 2009; Pencer et al., 2008; Roux et al., 2005; Tian and Baumgart, 2009) as well as solid supported membranes (Parthasarathy et al., 2006; Yoon et al., 2006). On the theoretical side, molecular dynamical approaches have been used to investigate the impact of molecular

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parameters (Cooke and Deserno, 2006; Risselada and Marrink, 2009). But these are limited to small spatial and temporal scales due to computational complexity of the corresponding models. To investigate upper scales and to compare experiments with analytical estimates different continuous approaches have been developed (Bozic et al., 2006; Derganc, 2007; Rózycki et al., 2008; Seifert, 1993; Mercker et al., 2011), mainly based on the minimization of a free energy. A curvature dependent free energy of lateral homogeneous membranes has been early described by Helfrich (1973)

$$F_{\text{Helfrich}} = \int \frac{\kappa}{2}(H-H_0)^2 \, d\omega + \int \kappa_G K \, d\omega, \tag{1}$$

where $d\omega$ depicts the surface measure, H the mean curvature and K the Gaussian curvature, both depending on the geometry of the membrane. If C_1 and C_2 are the two principal curvatures, H is defined as their sum and K as their product (see also Fig. 1). H_0,κ,κ_G are the elastic moduli, which are constant if the membrane is lateral homogeneous. H_0 is the spontaneous curvature and represents the preferred curvature in the relaxed state. It is non-zero e.g. if membrane molecules are wedge-shaped. κ and κ_G are the bending rigidity and the Gaussian rigidity (often referred to as the saddle-splay modulus), respectively. Both represent the stiffness of the membrane: in tubular structures (were K vanishes; cf. Fig. 1B) κ penalizes curvatures; in saddle structures (were H vanishes; cf. Fig. 1A) κ_G causes a penalty of curvatures. In general structures both moduli contribute to the energy penalty of curved membranes and most of the geometries appearing in biological membranes exhibit various intermediate structures of tubes, saddle structures and spheres (Fig. 1A–C).

Considering non-homogeneous membranes, it has been shown that gradients in elastic moduli can exhibit a driving force for lateral curvature modulated sorting. Membrane proteins are drawn to regions with curvature adapted to the protein shape (Ramaswamy et al., 2000) and lipids with small bending rigidity are sorted to highly curved membrane regions (Parthasarathy et al., 2006), thus that lateral reorganization reduces the membrane curvature energy. Although various theoretical and experimental studies have been performed to investigate lateral sorting due to gradients in spontaneous curvature (Bozic et al., 2006; Cooke and Deserno, 2006; Derganc, 2007; Kamal et al., 2009; Leibler, 1986; Liang and Ma, 2009; Ramaswamy et al., 2000; Risselada and Marrink, 2009; Seifert, 1993) and bending rigidity (Baumgart et al., 2003; Derganc, 2007; Parthasarathy et al., 2006; Roux et al., 2005; Rózycki et al., 2008), the impact of the elusive Gaussian rigidity on lateral sorting has not been investigated so far. However, experimental studies show that different membrane components can differ distinctly in their Gaussian rigidities (Semrau et al., 2008).

In this study, we investigate theoretically the impact of an inhomogeneous Gaussian rigidity on lateral sorting and compare

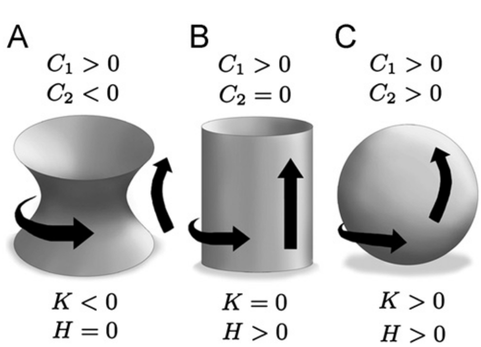

Fig. 1. Principle curvatures C_1,C_2, mean curvature $H = C_1 + C_2$ and Gaussian curvature $K = C_1 C_2$ for different geometries: (A) saddle, (B) tube, (C) sphere.

it with sorting due to gradients in the bending rigidity and spontaneous curvature. Following the experimental approach of Parthasarathy et al. (2006) and Roux et al. (2005), we consider membranes attached to non-planar substrates. Thus by considering a geometrically fixed membrane the complexity is reduced facilitating the extraction of hypotheses to be checked by experimentalists. To do so, a continuous model of lateral membrane dynamics, based on the minimization of a free energy, is derived. Considering a gradient flow of the free energy, we obtain a model in terms of a nonlinear PDE of fourth order, related to the Cahn–Hilliard equation (Cahn and Hilliard, 1958) (cf. Elliott and Garcke, 1996; Elliott and Songmu, 1986 for analytical results). In the following, we show that unique solutions exist and approximate them using a finite element approach. Adopting a multiscale approach, parametrization of the continuous model from the molecular scale has been achieved via upscaling from dissipative particle dynamic (DPD) studies. On the basis of this multiscale modeling approach, simulations are performed comparing dynamics and (metastable) patterns of lateral sorting.

2. Theoretical model

2.1. Continuous approach

Following the ideas of Parthasarathy et al. (2006) and Roux et al. (2005), we consider a curved membrane represented by a fixed smooth Riemannian manifold Γ—in contrast to free membranes typically studied (Baumgart et al., 2003; Heinrich et al., 2010; Kamal et al., 2009; Pencer et al., 2008; Roux et al., 2005; Tian and Baumgart, 2009), where Γ itself is evolving in time. Here, we consider a membrane composed of two different molecule species, e.g. two different lipids or lipids and proteins. The concentration of the two components ϕ^A and ϕ^B in Γ is described by the order parameter $\phi : \Gamma \to [-1,1]$, where $\phi = \phi^A - \phi^B$. That is, if $\phi = 1$ the membrane is locally composed purely of species A and if $\phi = -1$ locally only species B is present.

It has been shown that sorting depends critically on membrane curvature and phase separation (in the absence of specific signals actively influencing lateral dynamics) (Parthasarathy et al., 2006; Roux et al., 2005). Therefore our model is based on the minimization of a free energy $F = F_1 + F_2$ containing both a curvature depending energy F_1 (related to Helfrich, 1973) and a Cahn–Hilliard energy F_2 (Cahn and Hilliard, 1958) modeling lateral phase separation. In detail, both parts read

$$\begin{aligned} F_1 &= \frac{1}{2}\int_\Gamma \kappa(\phi)(H-H_0(\phi))^2 \, d\omega + \int_\Gamma \kappa_G(\phi) K \, d\omega, \\ F_2 &= \tilde{\sigma} \int_\Gamma \left(\frac{\xi^2}{2}(\nabla^\Gamma \phi)^2 + f(\phi) \right) d\omega. \end{aligned} \tag{2}$$

Describing the fact that different components may differ in their mechanical properties (such as shape and stiffness), each macroscopic elastic modulus h ($h \in \{\kappa,\kappa_G,H_0\}$) is taken as a function of the concentration ϕ. Each function h is chosen such that $h(1) = h^A$ and $h(-1) = h^B$, where h^A and h^B are the elastic moduli of the pure components. Furthermore, ξ is a transition length, $\sigma = \tilde{\sigma}\xi$ the line-tension, ∇^Γ the surface gradient and f a double well potential. The function $f : \mathbb{R} \to \mathbb{R}_+$ is of the form $f(\phi) = \frac{9}{32}(\phi^2-1)^2$. Instead of minimizing $F = F_1 + F_2$ directly we adopt a dynamic point of view. Thus assuming local mass conservation lateral dynamics of the two species A and B are determined by the lateral continuity equation

$$\partial_t \phi + \nabla^\Gamma \cdot \vec{j} = 0,$$