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Self-assembly of a filament by curvature-inducing proteins

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HIGHLIGHTS

- We introduce a model for the attachment of curvature-inducing proteins on a membrane.
- The stability of the filament shape is characterized by the protein recruitment parameters.
- The dynamics of protein aggregation leads to the formation of regions of high and low curvatures.
- Phase-coarsening eventually leads to a filament with uniform curvature.

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ABSTRACT

We explore a simplified macroscopic model of membrane shaping by means of curvature-sensing BAR proteins. Equations describing the interplay between the shape of a freely floating filament in a fluid and the adhesion kinetics of proteins are derived from mechanical principles. The constant curvature solutions that arise from this system are studied using weakly nonlinear analysis. We show that the stability of the filament's shape is completely characterized by the parameters associated with protein recruitment and establish that in the bistable regime, proteins aggregate on the filament forming regions of high and low curvatures. This pattern formation is then followed by phase-coarsening that resolves on a time-scale dependent on protein diffusion and drift across the filament, which contend to smooth and maintain the pattern respectively. The model is generalized for multiple species of BAR proteins and we show that the stability of the assembled shape is determined by a competition between proteins attaching on opposing sides.

1. Introduction

Self-assembly is a ubiquitous phenomenon that exists over a large range of length scales in systems both physical and biological in nature. Examples range from the astronomically large, such as the formation of galaxies and planetary systems [1], to the nano-scale, such as the technology of DNA origami [2]. In its most basic definition, such self-assembling systems are: (i) comprised of parts or components that exhibit interaction; (ii) at thermodynamic nonequilibrium initially, but tend to equilibrium; (iii) thermodynamically closed [3,4]. Self-assembly is a process of energy minimization that ends in a final, well-defined structure that is uniquely determined by the properties of the interacting components which remain unchanged during the transition to thermodynamic equilibrium. Global order in the system is encoded in the initial set-up and the specific relationships that exist between components; no additional energy is necessary to drive the process [5].

An interesting example of self-assembly is found in the shaping of biological membranes, in particular lipid bilayers, that occur at the cellular level. Such objects are important building blocks which not only coat parts of the cell, such as the nucleus and the endoplasmic reticulum [6], but also form independent biological objects within the cell, such as vesicles and tubules which are necessary for the intra-cellular transport of wastes, nutrients, and proteins [7,8].

The primary mechanism believed to be responsible for the highly curved geometries observed involves the recruitment of membrane-shaping proteins from the cellular fluid, such as the BAR (Bin/Amphiphysin Rvs) and ENTH (Epsin N-Terminal Homology) protein families [9–12]. Such proteins bind directly onto the bilayer by means of electrostatic interactions and bend it by the insertion of amphipathic helix functional groups [13,14], with the magnitude of the induced curvature dependent on the depth of insertion into the lipid monolayer [15] and the number of attaching proteins [16]. Moreover, the BAR and ENTH families

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act as sensors of curvature [17,18], meaning that the shape of the membrane determines the adhesion kinetics of the proteins. In other words, we have a system where the curvature of the membrane regulates the concentration of attached proteins, and vice versa, in an interacting process [19].

Previous investigations on the subject have been from two perspectives; namely, computational, involving large-scale coarse-grain simulations [20–22], and theoretical, which consider the minimization of membrane free energies or electrical potentials to determine the nature of equilibrium configurations. In the former, many interesting aspects of BAR proteins have been found, including the linear aggregation of proteins, leading to membrane tubulation [23,24], and membrane fissioning, leading to closed tubular networks [25]. From a theoretical point of view, the effects of single BAR proteins, in the context of electric fields and potentials [26], and a continuum of them attaching to the lipid bilayer have also been studied, but not to the same extent as computational models. In particular, equilibrium configurations of the self-assembled system, and the role that BAR proteins play in the stability of these final shapes, are considered. Early research on the subject studied not the formation of vesicles or other independent biological objects, but rather the oscillations that can exist on the cell-membrane known as *circular dorsal ruffles* [27,28]. It is found that BAR proteins provide a stabilization of the geometry; a point which has been further investigated in the context of flat membrane geometries [29] and pearling instabilities in cylindrical geometries [30].

As a starting point to understand this phenomenon, we derive the simplest, non-trivial system that allows us to explore the interplay between an underlying geometry and curvature-sensing proteins. We focus on the shaping of a filament and derive a macroscopic model for time-dependent self-assembly using concepts from continuum and statistical mechanics. The result is a thermodynamically consistent system of equations in terms of experimental parameters that allows us to further explore the role of the filament mechanics, the adhesion kinetics of the attaching proteins, and the interactions between these components.

2. Mathematical model

Our mathematical model is based on the following assumptions: (i) We consider a thermodynamically closed system in 2D space which only contains the main continuum, the curvature-inducing proteins, and the interactions between these. There is no forcing or energy input from the outside environment; (ii) We take the continuum to be a 1D filament; explicitly, an elastic rod which is inextensible and unshearable with constant length L that is parameterized with an arc-length coordinate $s \in [0, L]$. This geometry is a simplification of the 2D lipid bilayer without transverse mechanical effects and area dilation, despite the membrane being able to endure strains of 2%–3% [31]. The dependent variable of interest is the filament curvature $\kappa(t, s)$ at time t; (iii) The continuum freely floats in a fluid which is populated with a single type of BAR protein modeled as a thin filament with constant curvature. The proteins induce curvature along one principal direction which is always aligned with that of the main filament and they have a thermodynamically favorable target curvature κ_t. The number of bound proteins per unit length is given by $c(t, s)$.

Additionally, we make two important thermodynamic assumptions. (iv) We suppose that protein–membrane interactions are at thermodynamic equilibrium with respect to energy exchange between these components. A number of theoretical models have made this same assumption [30,28] as well as computational models [32]. In the latter case, results predicted by simulations have been experimentally verified [25], which suggests that this assumption is valid when studying qualitative aspects of the mathematical model.

(v) There are three stages in the protein attachment corresponding to the unbound, transition, and bound states. An unattached protein floating in the cellular fluid is assumed to have zero bending energy (unbound state), but when the protein attaches to the main filament, it deforms itself to match the curvature of the filament and acquires bending energy dictated by bending stiffness B_{BAR} (bound state). We suppose there is an intermediary step to attachment whereby the protein acquires bending energy determined by bending stiffness B_{ts}, which is not necessarily the same as B_{BAR}, and we assume that this transition state is sufficiently long-lived such that thermodynamic equilibrium is reached.

We now derive equations describing the time-evolution of $\kappa(t, s)$ and $c(t, s)$.

2.1. Equations for filamentary mechanics

We model the membrane cross-section as a Kirchhoff elastic filament whose motion is confined to a plane [33,34]. The position of the filament's centerline is denoted by $\mathbf{r}(t, s)$ and the curve is geometrically described by a local director basis $\{\mathbf{d}_1, \mathbf{d}_2, \mathbf{d}_3\}$ which is right-handed and orthonormal. The vectors $\mathbf{d}_3$ and $\mathbf{d}_1$ are the tangent and normal Frenet vectors respectively, whilst $\mathbf{d}_2$ points perpendicularly outwards from the plane and is constant with respect to both t and s (see Fig. 1). To complete the geometric description, we introduce a strain vector $\mathbf{u} = \kappa\mathbf{d}_2$ and spin vector $\mathbf{w} = w_2\mathbf{d}_2$, with w_2 being a measure of the angular velocity of the director basis, so that we have the following kinematic relations:

$$\frac{\partial \mathbf{r}}{\partial s} = \mathbf{d}_3, \tag{1}$$

$$\frac{\partial \mathbf{d}_i}{\partial s} = \mathbf{u} \times \mathbf{d}_i, \tag{2}$$

$$\frac{\partial \mathbf{d}_i}{\partial t} = \mathbf{w} \times \mathbf{d}_i. \tag{3}$$

Defining the velocity of the rod in the local basis $\mathbf{v} = v_1\mathbf{d}_1 + v_3\mathbf{d}_3 = \partial\mathbf{r}/\partial t$, we use (1)–(3) to obtain geometric constraints for v_1 and v_3:

$$0 = \frac{\partial v_1}{\partial s} + \kappa v_3 - w_2, \tag{4}$$

$$0 = \frac{\partial v_3}{\partial s} - \kappa v_1, \tag{5}$$

as well as a compatibility relation, given that $\partial^2\mathbf{d}_i/\partial s\partial t = \partial^2\mathbf{d}_i/\partial t\partial s$:

$$\frac{\partial \kappa}{\partial t} = \frac{\partial w_2}{\partial s}. \tag{6}$$

Considering the mechanics of the continuum, we suppose that the only contribution to the applied force comes from fluid drag, which is proportional to the velocity of the filament $\mathbf{v}$. More specifically, the applied force per unit length is $\mathbf{f} = \mathbf{f}_1\mathbf{d}_1 + \mathbf{f}_3\mathbf{d}_3 = -\eta_1 v_1\mathbf{d}_1 - \eta_3 v_3\mathbf{d}_3$, where η_1 and η_3 are the drag coefficients per unit length in the normal and tangential directions. Given that we are interested in motions that occur at low Reynolds numbers, it is reasonable to assume that the inertial terms can be neglected so that the resulting dynamics are first order in time [35]. Furthermore, we use slender body theory to simplify the applied force so that $\eta_1 = 2\eta_3$, where $\eta_3 = 2\pi\mu/A\ln(L/r)$ for a filament of length L, cross-sectional area A, and radius $r \ll L$ which is submersed in a fluid of dynamic viscosity μ [36]. Introducing the resultant force $\mathbf{n} = n_1\mathbf{d}_1 + n_3\mathbf{d}_3$ and moment $\mathbf{m}$, we balance linear and angular momenta to obtain two equations of motion [37]:

$$\frac{\partial \mathbf{n}}{\partial s} + \mathbf{f} = \rho A\frac{\partial^2 \mathbf{r}}{\partial t^2}, \tag{7}$$