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Numerical simulation of endocytosis: Viscous flow driven by membranes with non-uniformly distributed curvature-inducing molecules

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ABSTRACT

The formation of membrane vesicles from a larger membrane that occurs during endocytosis and other cell processes is typically orchestrated by curvature-inducing molecules attached to the membrane. Recent reports demonstrate that vesicles can form de novo in a few milliseconds. Membrane dynamics at these scales are strongly influenced by hydrodynamic interactions. To study this problem, we develop new diffuse interface models for the dynamics of inextensible vesicles in a viscous fluid with stiff, curvature-inducing molecules. The model couples the Navier–Stokes equations with membrane-induced bending forces that incorporate concentration-dependent bending stiffness coefficients and spontaneous curvatures, with equations for molecule transport and for a Lagrange multiplier to enforce local inextensibility. Two forms of surface transport equations are considered: Fickian surface diffusion and Cahn–Hilliard surface dynamics, with the former being more appropriate for small molecules and the latter being better for large molecules. The system is solved using adaptive finite element methods in 3D axisymmetric geometries. The results demonstrate that hydrodynamics can indeed enable the rapid formation of a small vesicle attached to the membrane by a narrow neck. When the Fickian model is used, this is a transient state with the steady state being a flat membrane with a uniformly distributed molecule concentration due to diffusion. When the Cahn–Hilliard model is used, molecule concentration gradients are sustained, the neck stabilizes and the system evolves to a steady-state with a small, compact vesicle attached to the membrane. By varying the membrane coverage of molecules in the Cahn–Hilliard model, we find that there is a critical (smallest) neck radius and a critical (fastest) budding time. These critical points are associated with changes in the vesicle morphology from spherical to mushroom-like as the molecule coverage on the membrane is increased.

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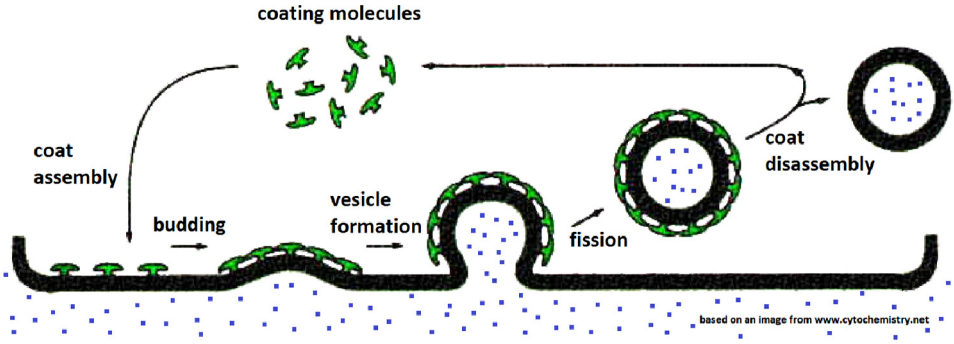

Fig. 1. Schematic of the processes involved in endocytosis. Curvature inducing molecules attach to the membrane and induce out-of-plane deformations. Once enough molecules cover the membrane a vesicle is formed that provides the vehicle to transport extracellular cargo into the cell.

1. Introduction

The biological membranes that surround cells and organelles often undergo shape changes as part of cellular processes. In one class of processes, which includes endocytosis, inter-organelle transport and virus entry [24], a small membrane vesicle is formed from a larger membrane. In others, locally curved membranes enable other mechanical processes such as cytoskeletal protrusion [30]. These events are typically orchestrated by curvature-inducing molecules that dynamically attach to the membrane, such as clathrin and bar-domain proteins (see Fig. 1).

Classical clathrin-mediated endocytosis, which occurs on a timescale of seconds, has been extensively studied, including contributions from mathematical models [4,25,29]. However, recent reports demonstrate that in some circumstances vesicles can form de novo in a few milliseconds [41]. Examples include ultrafast endocytosis at the neurological synapse, in which rapid endocytosis is necessary to complement rapid exocytosis of neurotransmitters [32].

Ultrafast vesicle formation raises a fundamental biophysical question: Membrane dynamics at these scales (millisecond, nanometer) are dominated by hydrodynamic interactions, as the membrane pushes the intracellular and extracellular fluids around to accommodate curvature. What limits do hydrodynamic interactions impose on the speed of endocytosis? How do the resulting intracellular flows affect the arrival rate of soluble curvature-inducing molecules? What are the intermediate dynamic shapes of the membrane and what spatial constraints do these shapes place on membrane-associated molecules, such as clathrin and receptor cargo?

To address these questions, we have developed computational fluid dynamic models of a membrane interacting with intracellular and extracellular fluids. The identity of molecular participants in ultrafast endocytosis remains unknown. Therefore, we consider an abstract curvature-inducing molecule (henceforth CIM) and explore the dependence of vesicle formation on its properties. Known CIMs include proteins such as clathrin, caveolin, COP proteins, BAR domain proteins such as GRAF1 and epsins, as well as lipid modifiers [28]. These range in size-per-molecule from 4 nm for epsin [21] to 50 nm for clathrin [16], and range in spontaneous curvature from zero to 9^{-1} nm^{-1} for synaptotagmin [28]. For recent reviews of CIMs and other modes of biological membrane sculpting, see [23,28,33,36]. For simulation results, we use parameter values in the range of these known CIMs.

Mathematical models have been developed, and numerical simulations have been performed, for vesicles with variable biophysical properties due to the presence of multiple lipid components and embedded proteins using discrete and continuum approaches. See, for example, the review by Elson et al. [14]. Here, we use a continuum phase field approach and extend our previous work for locally inextensible, homogeneous closed vesicles [2] to locally inextensible, heterogeneous membranes with CIMs. Although phase field models for heterogeneous vesicles have been developed previously, e.g., [40,26,18,12,44,17,15,19], none of these approaches considered the effect of fluid flow (and local inextensibility). The effect of flow on the dynamics of locally inextensible, multicomponent vesicles was investigated using a combined boundary integral and surface phase field approach in 2D [35] and in 3D axisymmetric geometries [34]. However to simulate endocytosis, which typically occurs on length scales of nanometers while the overall membrane may be millimeters in length, as in the experiments described above, only a part of membrane can be considered due to computational cost. This geometry is straightforward to implement using the phase field approach developed here. Further, the phase field model can also be extended to incorporate additional physical processes such as adsorption and desorption of CIMs following [37,38] and is independent of dimension, which makes the extension to fully three dimensional geometries straightforward as well.

The outline of the paper is as follows. In Sec. 2 the mathematical model is presented. In Sec. 3 the discretization of the equations and the numerical methods used to solve the discrete system are discussed. In Sec. 4, simulations demonstrating the convergence of the algorithm are presented along with an investigation of the influence of hydrodynamics and the dynamics of CIMs on the results. Finally, in Sec. 5 conclusions are drawn and future directions are discussed. Several technical results are derived in the Appendices.