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An immersed boundary method for endocytosis

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ABSTRACT

Endocytosis is one of the cellular functions for capturing (engulfing) vesicles or microorganisms. Understanding the biophysical mechanisms of this cellular process is essential from a bioengineering point of view since it will provide guidance for developing effective targeted drug delivery therapies. In this paper, we propose an immersed boundary (IB) method that can be used to simulate the dynamical process of this important biological function. In our model, membranes of the vesicle and the cell are treated as Canham–Helfrich Hamiltonian interfaces. The membrane-bound molecules are modeled as insoluble surfactants such that the molecules after binding are regarded as a product of a "chemical" reaction. Our numerical examples show that the immersed boundary method is a useful simulation tool for studying endocytosis, where the roles of interfacial energy, fluid flow and viscous dissipation in the success of the endocytosis process can be investigated in detail. A distinct feature of our IB method is the treatment of the two binding membranes that is different from the merging of fluid–fluid interfaces. Another important feature of our method is the strict conservation of membrane-borne receptors and ligands, which is important for predicting the dynamics of the endocytosis process.

1. Introduction

Endocytosis [4], the process of the engulfing of molecules, proteins, and other particles into the host cells [1,18], is an essential function for maintaining cellular homeostasis. Fig. 1 is a schematic of the basic steps involved in the process. Endocytosis is used for the transport of neural, metabolic, and proliferative signals [13,25]; the uptake of many essential nutrients; the regulated interaction with the external world; and the ability to mount an effective defence against invading microorganisms. According to the size of the engulfed target, there are four categories of endocytosis pathways, namely, clathrin-mediated endocytosis, caveolae, pinocytosis (cell drinking), and phagocytosis (cell eating). In more recent experiments, it has been suggested that endocytosis can be classified based on whether the process is clathrin-dependent.

It is well known that at the micrometer scale, resistance of water (due to its viscosity) could be significant to hinder the motion of microorganisms. However, existing theoretical studies on endocytosis are based on the energy of the equilibrium state of membranes (static problems) without the consideration of fluid flow [3,9,19,20,27]. Therefore, an important question is how the endocytosis process [16,18] is affected by the presence of water. In this paper we develop a numerical method that can be used to study the roles of fluid (water) as well as membrane properties in the engulfing stage of endocytosis [6,7].

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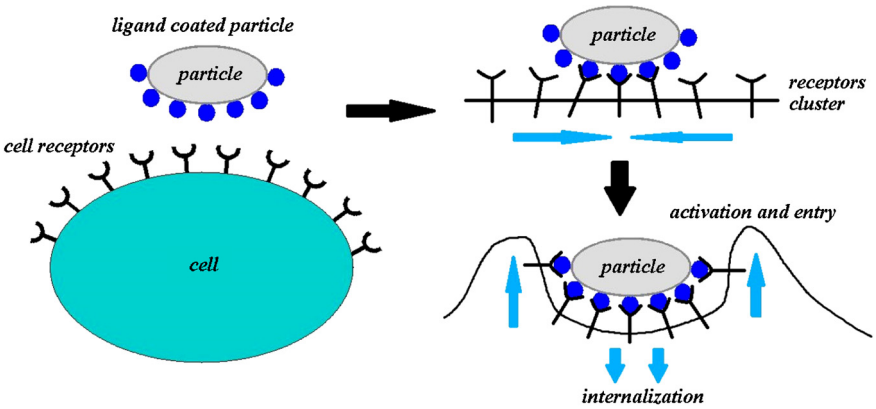

Fig. 1. Schematic diagram of endocytosis.

From the computational point of view, we solve the two-dimensional incompressible Navier–Stokes equations with an immersed cell membrane and a vesicle. We assume that each individual membrane (lipid bilayer) can be represented by an interface with zero thickness while the bound region is composed of an overlap of two interfaces, a "bilayer" or "dual-interface" structure. In our immersed boundary formulation, interfaces are represented by the usual singular delta functions, centered at the immersed boundary points [22,23]. In the basic version of our method, when the immersed boundary points from two different interfaces come close, a rigid connection forms and the two interfaces move with the same velocity. The second version of our method assumes that the receptor molecules and ligands [1,9] on the cell and vesicle membranes move along the interfaces due to molecular diffusion and fluid convection. They are modeled as insoluble reactive surfactants and the interface energy reduction due to the binding of receptors and ligands is proportional to the reacted quantity.

Physically the engulfing process is driven by the reduction of interface energy in the bound region [27]. This mechanism induces changes of both normal and tangential stresses by a jump in the surface energy at the "triple junction", where the two interfaces join. Our numerical results show that for endocytosis to occur, this stress difference cannot be balanced by the buildup of the membrane elastic forces. As a result, it leads to fluid motion and transfer of interface energy to kinetic energy of the fluid and thermal energy (through viscous dissipation). In other words, when interfacial energy is reduced due to binding, only part of it is stored as bending energy in the membranes due to increased curvature in the bound region and near the triple junction. The remainder is utilized to drive the fluid flow in the form of a Marangoni force. Therefore, the equilibrium energy argument only tells part of the story and a complete picture of endocytosis must include the dynamics of the engulfing process. Our paper represents the first step towards the building of a more complete theory.

The rest of this paper is organized as follows. In Section 2, a mathematical model based on the Navier–Stokes equations and molecule concentration equations is presented, and the interfacial forces are derived from the interfacial energy and membrane model. The numerical aspect of the immersed boundary method is given in Section 3. Numerical examples are presented in Section 4. Computation is also carried out to investigate the distribution of energy consumption. We finish our paper with a short conclusion in Section 5.

2. Mathematical model

In this section, we present our mathematical model in an immersed boundary (IB) formulation [22] which consists of fluid, fluid–interface interaction, and receptor and ligand concentration equations. We assume that the fluid is Newtonian and incompressible. The interfacial forces are composed of tension-type forces (adhesion energy and membrane elasticity) and bending forces. For membrane-bound (receptor and ligand) molecules, the reaction (binding) occurs on the edge of the bound region and obeys the law of mass action.

The mathematical model is based on conservation laws, including conservations of mass and momentum of fluid, and conservation of interfacial molecules. Since the membrane is treated as an elastic interface which is embedded in a Newtonian incompressible fluid, the corresponding governing equations are

$$\rho\left(\frac{\partial \boldsymbol{u}}{\partial t} + (\boldsymbol{u}\cdot\nabla)\boldsymbol{u}\right) + \nabla p = \nabla\cdot(2\mu\boldsymbol{D}) + \boldsymbol{f}, \tag{1}$$

$$\nabla\cdot\boldsymbol{u} = 0, \tag{2}$$

where μ and ρ are fluid viscosity and density, respectively, $\boldsymbol{u}$ is the velocity field, p is the pressure, $\boldsymbol{f}$ is the forcing term, and the rate of strain $\boldsymbol{D} = \frac{1}{2}(\nabla\boldsymbol{u} + \nabla\boldsymbol{u}^T)$. For simplicity, we assume that the size of the engulfed target (vesicle) is much smaller than that of the cell. Therefore the problem can be simplified as an initially flat membrane engulfing a circular vesicle, see Fig. 2. The membranes are modeled as elastic interfaces that are immersed in and carried by the fluid. The fluid velocity is continuous at these interfaces. The other condition at the interfaces (membranes) is the balance of the