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Hybrid continuum–coarse-grained modeling of erythrocytes

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ABSTRACT

The red blood cell (RBC) membrane is a composite structure, consisting of a phospholipid bilayer and an underlying membrane-associated cytoskeleton. Both continuum and particle-based coarse-grained RBC models make use of a set of vertices connected by edges to represent the RBC membrane, which can be seen as a triangular surface mesh for the former and a spring network for the latter. Here, we present a modeling approach combining an existing continuum vesicle model with a coarse-grained model for the cytoskeleton. Compared to other two-component approaches, our method relies on only one mesh, representing the cytoskeleton, whose velocity in the tangential direction of the membrane may be different from that of the lipid bilayer. The finitely extensible nonlinear elastic (FENE) spring force law in combination with a repulsive force defined as a power function (POW), called FENE–POW, is used to describe the elastic properties of the RBC membrane. The mechanical interaction between the lipid bilayer and the cytoskeleton is explicitly computed and incorporated into the vesicle model. Our model includes the fundamental mechanical properties of the RBC membrane, namely fluidity and bending rigidity of the lipid bilayer, and shear elasticity of the cytoskeleton while maintaining surface-area and volume conservation constraint. We present three simulation examples to demonstrate the effectiveness of this hybrid continuum–coarse-grained model for the study of RBCs in fluid flows.

1. Introduction

The human red blood cells (RBCs) are normally biconcave discocytes with a diameter of approximately 8 μm and a thickness of about 2 μm. The mean volume is about 94 μm^3 and the average surface area around 135 μm^2, a value greater than the surface area of a sphere with the same volume. The RBC membrane (∼10 nm in thickness) is composed of a lipid bilayer supported from inside by a two-dimensional (2D) triangular spectrin network of cytoskeletal proteins. A highly elastic membrane, together with a high surface-to-volume ratio, provides RBCs with the ability of large reversible deformation when passing through capillaries. This composite bilayer–spectrin membrane may be treated as an elastic thin shell. Based on this simplified elastic description and the assumption of flat membrane, two fundamentally different approaches have

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been proposed to study RBCs in fluid flows: one more traditional, founded on continuum mechanics, and the other, founded on molecular details, see for recent reviews [1–4].

The classical continuum approach, which was largely inspired by numerical methods developed in mechanical engineering, considers the suspending fluids as well as the RBC membrane itself as a continuous medium. A number of well-established continuum methods have been developed, including boundary integral/element method (BIM/BEM) and several interface tracking methods widely employed in multi-phase flows. These methods have been used to simulate the dynamics of a single RBC in flows as well as the collective behavior of an ensemble of them [4]. From this point of view, the RBC is most often modeled as a hyperelastic capsule (made of a polymerized membrane) [1,4]. However, the fluid nature of the cell membrane was systematically lacking; the near-incompressibility of the membrane was generally taken into account through a high dilatational modulus. Numerical simulations with vesicles (made of lipid bilayer) with bending rigidity can provide insight into the shapes taken by RBCs, either at equilibrium – the typical biconcave shape of RBCs or in flows – bullet, parachute and slipper shapes [1], but shear elasticity and shape memory that are the fundamental mechanical properties of RBCs are missing.

Discrete modeling exploits the microstructural properties of RBCs. Any medium is seen as a huge number of molecules, submitted to thermal agitation and to intermolecular forces. However, to be able to resolve much larger space and time scales involved in the transport of RBCs in fluid flows, coarse-graining of spectrin-level models has to be used, and the level of coarse-graining characterizes the crudeness with which the molecular level of the medium is represented [5]. Mesoscale (whole cell) particle-based methods [6] consider both the lipid bilayer and the spectrin cytoskeleton and the interaction between them. Some cell scale particle-based models keep the trace of the two contributions in the form of a two-component whole cell model [7,8]. In this way, the detachment of the cytoskeleton from the lipid bilayer, which for example can occur in the micropipet aspiration experience or in the flow through a constriction, has been successfully simulated [8].

One could regard the continuum approach as the ultimate state of coarse graining; however, in that ultimate state, the molecular structure is fully integrated and forgotten. There is a need for developing new numerical methods combining the two approaches, thus being able to benefit from advantages of both of them. Indeed, the idea of representing the cytoskeleton as a discrete 2D structure made of a large number of connected springs is very attractive. This is the starting point of the present contribution. Actually, particle-based and continuum-based models work all on the same principle: one mesh (or two coupled meshes if we distinguish between the bilayer and the cytoskeleton) made of triangular elements to represent the RBC membrane. In the particle-based model, the mesh is seen as a discrete network of springs, which tends to a good representation of the spectrin cytoskeleton when the number of vertices reaches the real cytoskeleton structure. In the continuum-based model, the mesh is understood as a finite element discretization of the membrane, in which a two-dimensional mesh, embedded in a 3D domain, is defined by a set of vertices connected by edges. Therefore, the same ingredients are present, providing very similar modeling possibilities in these two approaches.

In this paper, we propose to explore the idea whether the combination of a spring network with a vesicle model could give rise to an accurate and reliable hybrid discrete-continuum RBC model. It is a first attempt to couple a 3D vesicle model with a discrete description of the cytoskeleton. From purely mechanical considerations, such a model could extract the essential mechanical properties of the RBC membrane: fluidity and bending rigidity of the lipid bilayer, and shear elasticity of the cytoskeleton while maintaining surface-area and volume conservation constraint. This is also computationally feasible thanks to an existing continuum vesicle model [9,10]. The argument is that, in the vesicle model, the movements of the bilayer in the normal and tangential directions are treated differently, namely in Lagrangian fashion for the former and with an Eulerian description for the latter. Therefore the tangential movement of mesh vertices (or nodes in a finite element context), which does not change the membrane shape, is fully independent of the tangential movement of the lipids. Actually, the possibility of prescribing the tangential velocities of mesh vertices to any convenient set is used to preserve the mesh quality in a vesicle simulation context. Our idea for an extension towards RBCs is then to prescribe this velocity set to that of the vertices of a spring network. In doing so, the movement of the mesh vertices is constrained to slide along the bilayer. However, this constraint is automatically ensured by the fact that the same mesh is used both for the bilayer and the cytoskeleton, and that the nodes of the bilayer finite-element mesh are also the vertices connected by the edges of spring network. As far as numerical aspects are concerned, one of the major developments involves assigning a spring behavior law to the edges and a drag friction law (based on the lipid/node relative velocity) to the vertices, as well as a way how to incorporate these additional forces into the vesicle model.

In the following sections we first describe the RBC membrane model and outline the numerical methods. We then present three numerical examples to evaluate the proposed hybrid model, followed by a conclusion of the paper.

2. Cytoskeleton elasticity

The membrane model consists of a collection of points $\{\mathbf{x}_n, n \in 1 \dots N\}$, which are the vertices of the RBC surface triangulation, representing the cytoskeleton. The length of the link connecting vertices n and p is defined as $l_{np} = |\mathbf{x}_n - \mathbf{x}_p|$. The spring network induces on each node (or vertex) n of the surface mesh a resulting force given by