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A computational approach to modeling cellular-scale blood flow in complex geometry

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ABSTRACT

We present a computational methodology for modeling cellular-scale blood flow in arbitrary and highly complex geometry. Our approach is based on immersed-boundary methods, which allow modeling flows in arbitrary geometry while resolving the large deformation and dynamics of every blood cell with high fidelity. The present methodology seamlessly integrates different modeling components dealing with stationary rigid boundaries of complex shape, moving rigid bodies, and highly deformable interfaces governed by nonlinear elasticity. Thus it enables us to simulate 'whole' blood suspensions flowing through physiologically realistic microvascular networks that are characterized by multiple bifurcating and merging vessels, as well as geometrically complex lab-on-chip devices. The focus of the present work is on the development of a versatile numerical technique that is able to consider deformable cells and rigid bodies flowing in three-dimensional arbitrarily complex geometries over a diverse range of scenarios. After describing the methodology, a series of validation studies are presented against analytical theory, experimental data, and previous numerical results. Then, the capability of the methodology is demonstrated by simulating flows of deformable blood cells and heterogeneous cell suspensions in both physiologically realistic microvascular networks and geometrically intricate microfluidic devices. It is shown that the methodology can predict several complex microhemodynamic phenomena observed in vascular networks and microfluidic devices. The present methodology is robust and versatile, and has the potential to scale up to very large microvascular networks at organ levels.

1. Introduction

Computational modeling of cellular-scale blood flow continues to pose new challenges despite significant progress made in recent years [1,2]. Blood at the cellular-scale behaves as a concentrated suspension that is primarily comprised of red blood cells (RBC), white blood cells (WBC), and platelets. The size of these cells is comparable to a typical vessel radius that is encountered in microcirculation and microfluidic devices. Red blood cells, the major constituent of blood, are extremely deformable particles, and this property is critical to many physiological functions [3–7]. Extreme deformation allows them to squeeze through narrow capillaries in microcirculation without getting damaged. It also causes platelets and WBCs to marginate towards the wall of a blood vessel. The margination of platelets is the first step in the formation of a blood clot, and the margination of WBCs is the first step in the body's defense against bacteria. High fidelity computational

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modeling of RBC deformation in three-dimensions (3D) and its extension to multiple cells in concentrated suspensions remains a non-trivial task. Additionally, the physical properties, e.g. size, shape, and deformability, of RBCs, WBCs, and platelets are widely different. As a result, 'whole' blood behaves as a poly-disperse suspension leading to further difficulty in modeling.

Another major computational challenge in modeling blood flow in microcirculation arises from the geometric complexity and network-like structure of blood vessels. Blood vessels in microcirculation are not simply straight tubes; rather, they continually bifurcate and merge with other vessels resulting in a complex network [3–6]. This network structure is referred to as the microvasculature, and it varies from organ to organ. The architectural complexity increases significantly in tumor microvasculature, where vascular trifurcations and short-length shunts may be present. The influence of the network architecture on the flow of blood cells is expected to be significant, although it is not well understood.

Geometric complexity is also present in microfluidic lab-on-chip devices handling blood. Examples include microchannels with sequential T-bifurcations for cell–plasma separation, channels with repeated expansions and contractions for inertial focusing of cells, and spiraling microchannels for isolating tumor cells [8]. Other examples include artificial vascular networks that are fabricated in an attempt to mimic the real microvasculature [9,10].

To date, most modeling studies on the flow of deformable blood cells have been limited to flow in simple geometries, such as single, unbranched, straight vessels of uniform circular cross-section, and parallel-plate geometry [1,2]. Studies of deformable cells in complex geometry are scarce, and are usually limited to a relatively modest complexity, such as a single bifurcation. The motion of an isolated deformable capsule in 2D bifurcating channels was studied using a finite element model [11], boundary integral simulations [12], and lattice-Boltzmann immersed boundary simulations [13], and in 3D using dissipative particle dynamics [14]. Relatively simpler 2D vascular networks having two to three bifurcations were also considered using lattice-Boltzmann methods [15]. Axisymmetric motion of a single deformable capsule in a hyperbolic constriction was studied using the boundary integral method [16], while 3D capsule motion in constricted microchannels was studied using spectral boundary integral methods [17,18]. The boundary integral method was also used to study the deformation of an RBC squeezing through a narrow passage [19], the motion of a deformable capsule through a square duct with a corner [20], and the interaction of deformable RBCs with platelets flowing in a stenosed capillary vessel [21]. Dissipative particle dynamics has been used to simulate the motion of rigid and deformable particles and cells flowing through cylindrical microchannels, and arrays of posts with different geometrical cross-sections [22,23]. The lattice-Boltzmann immersed-boundary method has been utilized to study the 2D flow of multiple deformable RBCs in stenosed microvessels [24], and the interaction of RBCs and platelets near an intravascular thrombus [25].

Evidently, computational modeling of cellular-scale blood flow in 3D arbitrarily complex geometries, such as physiologically realistic microvascular networks characterized by multiple bifurcations and mergers, or highly complex microfluidic devices, is lacking. To bridge this gap, we present here a 3D direct numerical simulation approach based on the immersed boundary method (IBM) for simulating cellular-scale blood flow in complex geometries. The major strength of immersed boundary methods is that they permit simulation of flows involving arbitrarily complex boundaries without requiring a body-fitted computational mesh [26,27]. A common means of classifying such methods is to consider continuous forcing methods and direct forcing methods. While the continuous forcing methods are well suited for flows with elastic boundaries, such as highly deformable cell membranes [28–31], they are not well suited for simulating rigid boundaries. Direct forcing methods, however, are very well suited for simulating rigid boundaries [26]. In the present problem we consider blood as a suspension of red blood cells (RBC), white blood cells (WBC), and platelets. While the RBCs are extremely deformable, WBCs are relatively less deformable, and inactivated platelets are nearly rigid. Thus, from the immersed-boundary perspective, the problem involves three types of interfaces: deformable interfaces of the RBCs and WBCs that are governed by nonlinear elasticity, moving rigid boundaries of the platelets, and non-moving but geometrically complex boundaries such as vascular network walls. The numerical methodology for the present work builds on the immersed boundary methodologies of both the continuous and direct forcing types, and seamlessly integrates all of these modeling components. Using this approach enables us to simulate geometries that are arbitrarily complex, and not limited to boundaries defined analytically. This permits the simulation of actual physiological geometry, without requiring any simplifications or assumptions, while simultaneously resolving the motion and large deformation of each individual blood cell with high fidelity.

The scientific objective of the present work is to develop a novel numerical technique for simulating the flow of deformable cells and rigid bodies in arbitrarily complex geometries as encountered in diverse types of scenarios ranging from microvascular networks to microfluidic devices. This objective requires that we demonstrate the versatility of the methodology in dealing with diverse types of interfaces and geometries. The numerical methodology is presented in the next section, followed by a detailed validation in §3 against analytical solutions, experimental results, and computational results. Then, in §4 we demonstrate the capabilities of the methodology using several examples, ranging from the flow of deformable RBCs in a physiologically similar microvascular network, to cell motion in a complex microfluidic device. Lastly, in Section 5 we discuss the various features that have been demonstrated with the current technique, and compare our approach to other commonly used methods.