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Computer Modeling of Red Blood Cell Rheology in the Microcirculation: A Brief Overview

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Abstract—One of the major functions of the cardiovascular system is to deliver blood to the microcirculation where exchange of mass and energy can take place. In the present article, we will provide an overview of the state-of-the-art computational methods for modeling of red blood cell (RBC) rheology and dynamics in the microcirculation. While significant progress has been made in simulation of single-file motion of deformable RBCs in capillaries and of diluted sheared suspensions of RBCs in infinite domains, detailed understanding of the mechanics of blood flow in intermediate diameter microvessels (8–1000 μm) has presented formidable challenges. The difficulties are largely due to modeling the motion of multiple, interacting, highly deformable particles. The current computational tools consist mainly of three-dimensional (3D) boundary-integral methods for single RBC dynamics and deformation; and for rheology of large systems of droplets at large volume fractions using periodic boundary conditions and novel adaptive computational meshes. Further advances will result from combination of these tools to produce new algorithms capable of describing the motion and deformation of large systems of RBCs in microvessels at physiologically relevant volume fractions.

Keywords—Red blood cell, Microcirculation, 3D boundary-integrals, 3D mesh adaptivity.

RED BLOOD CELL DYNAMICS IN THE MICROCIRCULATION

The microcirculation is common to every organ and nurtures the various tissues by providing oxygen and nutrients, and removing waste products. Hence, the physiology of the microcirculation has profound impact on transport phenomena and nutrient exchange, and consequently on human health and disease. A major difficulty in studying the microcirculation is the small dimension of the blood vessels. Experimental data on pressure, velocity, flow, shear stress, mass transfer, etc., are difficult to obtain *in vivo*. Hence, model *in vitro* experiments that obey geometric and dynamic similarity have been very useful. Model experiments, however, are sometimes impractical, tedious or too difficult to carry out. As such, *in silico* mathematical modeling is an attractive alternative. It is the latter computational approach that forms the focus of the present overview.

At the microcirculatory level, the particulate nature of the RBCs becomes important and the blood properties become non-Newtonian. The viscosity, for example, in Poiseuille's law is no longer constant and must be considered as an apparent or relative viscosity (ratio of viscosity of blood to that of water at the same temperature). The apparent viscosity of blood decreases when the vessel diameter is reduced below 1 mm (Fahraeus–Lindqvist effect).[15,27] This decrease in viscosity holds for diameters as small as 8 μm, below which the viscosity increases in the capillaries whose diameters are smaller than or equal to the RBC dimension. This phenomena was coined as the inversion of the Fahraeus–Lindqvist effect.[12,34] The reduction in apparent viscosity is mainly a consequence of the radial migration of the RBCs away from the vessel wall as a result of the hydrodynamic interactions, thus forming a low-hematocrit (defined as the volume of RBC in a unit volume of whole blood) layer therein.[17,31] It has been shown that cells initially on the axis of the tube continue to move along the axis, whereas cells initially released away from the axis tend to deform and move towards the axis. This is a well-established result in microcirculation known as plasma skimming.[28,30] Due to the high-volume fraction of RBCs (ca. 45%), cell–cell and cell–wall hydrodynamic interactions reach an equilibrium. It is likely that the width of the cell-depleted layer is the result of the balance of these two competing mechanisms.[3,31] RBCs' aggregation may also contribute to the decrease in blood viscosity.[4,29]

The mechanics of blood flow in the microcirulation with diameters ranging from 8–300 μm is particularly challenging to approach theoretically and computationally and remains only partially understood. The human RBC is extremely deformable, and its size is comparable to that of the capillary vessel. In pressure-driven single-file flow in capillaries, the dynamics and deformation of the RBCs are dominated by the strong lubrication interactions with the capillary wall. If the deformation is assumed to be axisymmetric, this greatly simplifies the numerical approach.

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In blood flow in the large vessels, RBCs are sufficiently small relative to the vessel diameter and a continuum description is sufficient. However, in microvessels where multiple RBCs span the vessel lumen, shear stresses depend on the radial position; and the RBCs experience hydrodynamic forces from cell–cell and cell–vessel interactions. It is known from 3D simulations of concentrated droplet emulsions[37] that these interactions may even overcome the stresses imposed by the flow at sufficiently large droplet volume fractions (>30%). Thus in intermediate size microvessels, the simplified approaches for the capillary or large vessels are no longer possible.

EARLY COMPUTATIONAL SIMULATIONS OF RED BLOOD CELL RHEOLOGY

Computational simulations of RBC rheology have a long history. In the 1960s and 1970s, a number of theoretical predictions were made based on relatively simple axisymmetric models of RBC by YC Fung, R Skalak, E Evans, G Cokelet, R Hockmuth, A Burton, M Lighthill and many others. Some of the early theoretical results can be summarized briefly as follows: (A) Flexibility of RBC is consistent with the assumption that the interior of the cell is in a liquid state and that the cell membrane is elastic. Surface tension is non-uniform and, though small, is significant; (B) The biconcave geometric shape of the RBCs enables them to deform into a wide variety of shapes without inducing any stress in the cell membrane; (C) In a long capillary blood vessel the velocity profile of the plasma is parabolic, in agreement with Poiseuille's law. Whenever the flow profile is disturbed, it readjusts itself quickly back to the Poiseuille profile; (D) At a branch point the entry flow readjusts itself to Poiseuille flow in a distance about 1.3 times the radius of the capillary tube; (E) Bolus flow of plasma between red cells has only a very minor effect on the oxygen transport; and (F) The resistance of RBC to flow in very narrow capillaries depends critically on the clearance between the cell and the endothelial wall (see review by Fung[16]). These and many other fundamental predictions were made based on simple models of RBC geometry and material properties that set the stage for more advanced computational models as outlined in the next section.

PROGRESS IN 3D SIMULATION OF DEFORMABLE PARTICLES

Major computational difficulties in modeling the motion of multiple, highly deformable 3D particles hydrodynamically interacting with one another and with the vessel walls in nonuniform pressure driven, shear fields have strongly hampered a detailed understanding of the mechanics of blood flow in intermediate size microvessels. To date, quantitative models for blood flow in microvessels taking into account the fluid dynamics and the mechanics of deformation of RBCs have been developed from the increasing knowledge of the mechanical properties of RBCs and novel computational algorithms capable of modeling the coupled fluid–structure interaction and the resulting viscous and elastic stresses. The dynamics have been studied computationally for individual RBCs flowing under simplified conditions in single file in capillaries, and for simple shear flow of dilute suspensions in infinite domains with[2,13,23,26,36] and without[18] RBC elasticity or deformation. Simplified theoretical models for non-dilute suspensions have also been developed.[32,33] Theoretical studies have considered deformable-drop migration from a wall.[5,19] The radial migration of RBCs away from the wall is likely to be highly modulated by RBCs' deformability, as the flow conditions approximate zero-Reynolds-number flow, for which symmetry arguments impose no lateral migration of undeformable particles. For other, approximate approaches, see the recent review by Secomb.[31]

The 3D simulation of large systems of deformable particles under low Reynolds number, such as in the microcirculation, is a major challenge. Numerical methods and techniques have recently been developed to simulate the motion of multiple particles in shear and channel flow using boundary-integral methods for deformable particles[3,6,21,25] and lattice-Boltzmann[1] methods for undeformed rigid particles. These studies have been limited by the lack of adaptive computational meshes. Such meshes are necessary to resolve large deformations of the interfaces and near-contact lubrication hydrodynamic interactions. Both of these occur in the microcirculation where RBCs' volume fractions or hematocrit can reach 45%. The local dynamics of the interfaces and the resulting hydrodynamic stresses are a function of the RBC deformation history because of the viscoelastic properties of the cell membrane. Recently, this major computational obstacle has been overcome by coupling the boundary-integral method to a recently developed 3D adaptive computational mesh.[7] This mesh has been used successfully in several applications, ranging from emulsion droplets in laminar flow,[8,11] in turbulent flow,[9] and in flow through porous media,[22] to growth of microstructure during solidification[10] and alloy formation,[20] and to tumor growth.[35] This triangulated adaptive mesh algorithm[7] is based on local mesh restructuring operations (i.e., edge swapping, triangle insertion/removal, triangle-vertex dynamic spring-like displacement). These operations are performed at every time-step of simulation and lead to a new optimal mesh that corresponds to the global minimum of a spring-like mesh energy function. At the minimum, the local size of triangles is proportional to the smallest of the physical length scales that need to be resolved. In Stokes-flow simulations, this length scale resolves local curvatures of the interfaces and particle–particle separation and lubrication flow. Examples of accurate 3D simulations of near-contact interactions[7] and of flow of a suspension of highly deformable droplets[6] are shown in Figs. 1 and 2.

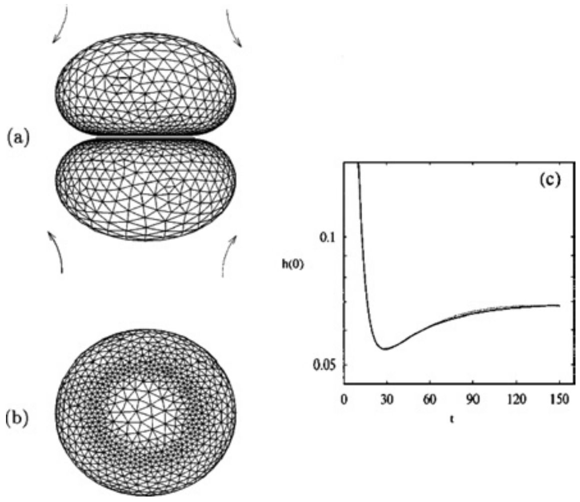

FIGURE 1. 3D adaptive boundary-integral simulation[7] of the impact of two deformable droplets in a compressional flow. (a) The two particles in close contact. (b) The near-contact region of one of the particle surfaces (viewed along the axis of approach), with the development of a ring of finer mesh corresponding to a dimple-like deformed droplet shape. The finest mesh corresponds to the region with the smallest separation. (c) The separation history is compared to an exact result demonstrating high accuracy. Lubrication forces arrest the approach and are accurately resolved by the adaptive mesh.

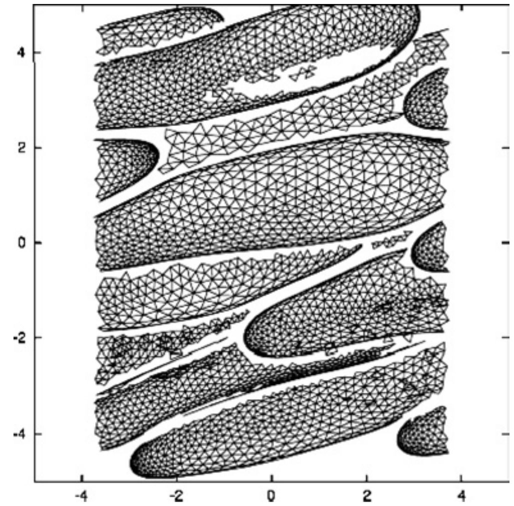

FIGURE 2. 3D adaptive boundary-integral simulation of the shear flow of a concentrated emulsion of highly deformed droplets.[6] Periodic boundary conditions were used; periodic box with 10 drops are shown. Volume fraction ca. 50%. The droplets are extremely deformed by the flow and in close contact with one another. The adaptive mesh accurately resolves deformation and near-contact hydrodynamics.

FUTURE ADVANCEMENTS

Direct computer simulation of the 3D motion and dynamics of multiple, hydrodynamically interacting RBCs in microvessels at realistic flow and hematocrits is now feasible because of the new adaptive methods for studying the 3D motion of very concentrated suspensions of deformable particles with realistic mechanical properties. We propose that in the near future this milestone will be attained by combining the novel adaptive methods for large systems of droplets[6,7] with the novel fluid-structure interaction methods for the flow and RBC's deformable membrane dynamics developed for a single cell.[23,26] Specifically, a successful algorithm will be based on boundary integrals[5,26,35,36] for RBC's deformation that takes into account the interaction with the walls (based on the existing knowledge of fluid and membrane elastic properties[14,24]). These hydrodynamic-elastic equations will be coupled to periodic boundary conditions[6,21,37] to describe large systems of interacting particles in zero-Reynolds-number flow, and to adaptive computational meshes[6,7] to accurately describe RBC's deformation and hydrodynamic interactions.

Through this computational advancement, efficient 3D computer simulations of the RBCs in the microcirculation will be performed to accurately predict the ratio of the particulate to the total flow rate under physiological and pathological conditions. Furthermore, the proposed numerical methods will allow the measurement, *in silico*, of the effect of the microvascular diameter, hematocrit, shear rate, and RBCs' elastic properties on the suspension apparent viscosity of blood in various bifurcations and vessel segments. Finally, in addition to understanding some of the central issues of blood rheology in the microcirculation, the proposed computational methodology will allow the exploration of applications to biotechnology for the analysis of the motion of deformable drug carriers such as liposomes injected in the circulation and to minimize damage of RBCs by the heart-lung machine.

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