Computational Blood Flow Analysis
—New Trends and Methods*

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Abstract

Over the past few decades, a large number of novel numerical methods have been proposed to analyze blood flows and to understand the relationship between vascular diseases and hemodynamics. In this paper, we review recent computational fluid dynamics studies on macroscale hemodynamics such as blood flow in the heart and large arteries, microscale blood flows in small vessels in which blood is assumed to be a suspension of red blood cells in plasma, and single red blood cell motions in an induced flow field. The advantages and disadvantages of numerical methods are discussed, and current trends in these research fields are introduced.

Key words: Review, Hemodynamics, Blood Flow, Computational Analysis, Numerical Method

1. Introduction

Despite the dazzling advances and sophistication of computer technology, the real-world application of this technology seems to have lagged dismally behind. This is particularly true for applying computational biomechanics to the real world, specifically to the human body. Recognizing the complexity of life as revealed by ongoing life science discoveries, we cannot expect adequate computational approaches to biomechanics by simply increasing the size and speed of computer systems. Although fierce competition for cutting-edge ultra-supercomputers continues between the United States and Japan, and the proposed next generation “peta-flops computer” surpasses the last world champion computer, the Japanese Earth Simulator, by twice or even three times in an order, it will not provide so much enhancement regarding the scale of the computational problem that can be solved. The necessary computational power is much more than a couple of orders greater than what is currently possible. Thus, the simple expansion of computational power will not enable the complex problems of life to be solved, as was the dream of earlier days.

Contributing to the complexity of life problems is our growing understanding of the structure of living systems, which are composed of layers of structures and functions analogous to those of the universe. The human body consists of several sometimes undistinguishable layers, from the quantum level to that of the whole body. Most importantly, everything at each level can interact with everything at any other level. These interactions reflect the essence of life. Moreover, an individual does not exist in isolation but as a part of many different groups, such as a family, species, ecosystem, and ultimately the biosphere. Comprehensive approaches must be pursued to properly incorporate these multilayered phenomena in order to understand living systems. If not, biomechanical studies based on computational as well as experimental methods will inevitably fail to lead us to meaningful understanding, and consequently those studies will not yield valid clinical or engineering
Major advances in computer technology during the past decades have enabled the analysis of various phenomena that could not be studied previously by numerical means. Complex biological aspects of the human body have been studied by computational methods. Some of the most successful studies have been those characterizing blood flow. Many investigators, including us, began with fairly simple objects and progressed to more complicated systems, widening the horizon of computational research not only for fundamental understanding but also for direct and indirect clinical applications.

Nevertheless, the same difficult fundamental challenges remain for the application of computational methods to blood flow analysis. These difficulties, particularly as related to the computational biomechanical analysis of the cardiovascular system, can be classified into four major challenges with respect to computational methodology: the complex and individually variable geometry of the cardiovascular system, particularly the vasculature; the complex, flexible, and nonlinear material properties of the conduit walls throughout the cardiovascular system; the pulsatile nature of blood flow and its complex interactions with the former two characteristics; and the non-Newtonian viscous nature of blood, which is not a simple matter of material properties. Each of these individually represents an exigent target in terms of computational mechanics, but the analysis becomes even more difficult when considering their interactions in forming the natural blood flow of the cardiovascular system. Since the time we first used computational fluid dynamics (CFD) and later computational mechanics (fluid and solid interaction studies) to study the cardiovascular system, these challenges continue to be the major obstacles to the application of computational methods.

In addition to the technological tasks above, it is also necessary to consider biological complexities in the analysis of blood flow, especially with respect to disease processes. Most modern analyses of the cardiovascular system are strongly motivated by a desire to understand pathological processes. Among them, atherosclerosis has been and still is the most important disease in terms of the mechanical analysis of blood flow. Together with other vascular disorders, including cerebral and aortic aneurysms and thrombotic diseases, atherosclerosis is typically a chronic disease and takes decades of life to initiate and develop, becoming lethal in the latter half of life. Thus, the entire disease process, from initiation to the last fatal stage, is under the influence of biological responses and adaptations of the living system. Unfortunately, most so-called CFD studies, including our past studies, did not keep this point in mind. A living system, either as a whole or as a subsystem, such as the cardiovascular system, is always under the integrated nervous and humoral control of the whole body, i.e., in homeostasis. Multiple feedback mechanisms with mutual interactions between systems, organs, and even tissues provide integrated control of the entire body. These control mechanisms have different spatial coverages, from the micro- to macroscale, and different time constants, from nanoseconds to decades. Moreover, it is gradually becoming clear that a living system can only be understood in light of its historical evolutionary processes. This point may not be important when analyzing an idealized vascular system, but it will be crucial to understanding and locating total physiological and pathological processes in a whole living system.

In the present review, we look back at the milestones achieved in the field of computational biomechanical analysis, providing some of our recent attempts to tackle the obstacles presented by computational difficulties and fundamental biological knowledge. In section 2, recent CFD studies on macroscale hemodynamics, such as blood flow in the heart and large arteries, are reviewed. We focus in particular on advanced methodology in section 2.1, intracardiac and aortic flow analysis in section 2.2, and applications to pressure wave propagation in section 2.3. In section 3, recent CFD studies on microscale hemodynamics, such as blood flow in small vessels, in which blood is assumed to be a suspension of red blood cells in plasma, and the motion of a single red blood cell in an induced flow field are
reviewed. The advantages and disadvantages of numerical methods are discussed, and current trends in these research fields are introduced.

2. Macroscale fluid mechanics of blood flow

Over the past few decades, numerical methods for computational fluid dynamics (CFD) have progressed. Based on this progress, current trends in computational hemodynamics favor more practical applications for diagnosing cardiovascular diseases and planning related surgery. This section reviews recent CFD studies on macroscale hemodynamics such as blood flow in the heart and large arteries. We focus in particular on advanced methodology, intracardiac and aortic flow analysis, and applications to pressure wave propagation.

2.1. CFD methods in macroscale hemodynamics

Blood is a suspension of different particles, including red blood cells, white blood cells, and platelets, in plasma. In the heart and large arteries, rheological effects of the particles can be ignored, and blood is simplified as a continuous viscous fluid. Using numerical methods for viscous incompressible flows\(^{(1),(2)}\), CFD analyses have provided a great deal of hemodynamic knowledge (see Taylor and Draney\(^{(3)}\)), even with the assumption of a rigid vessel. However, heart valves and arterial walls, which consist of collagen and elastin fibers, smooth muscle cells, and water, exhibit nonlinear elastic (or viscoelastic) deformation, greatly affecting the blood flow pattern. Therefore, in recent years, macroscale blood flow dynamics have often been described using a fluid–structure interaction model. Currently, CFD modeling of fluid–structure interactions is the most important but also the most computationally challenging class of problems. A key issue of the modeling is to couple incompatible descriptions of fluid and structural motions; fluid motion is described in Eulerian coordinates, whereas structural motion is described in Lagrangian coordinates. Generally, two different methodologies are employed to couple these descriptions, arbitrary Lagrangian–Eulerian (ALE) methodology\(^{(4)-(6)}\) and immersed boundary (IB) methodology\(^{(7),(8)}\).

In ALE methods, fluid motion is formulated using ALE coordinates, which are set to be identical to the Lagrangian coordinates of the structural motion at the fluid–structure coupling interface. Thus, fluid meshes require a mesh updating technique such as the elasticity-based mesh control method proposed by Johnson and Tezduyar\(^{(9)}\). Zhang and Hisada developed an ALE finite element method (FEM) with a strong coupling strategy for analyzing fluid–structure interactions with structural buckling and large deformation\(^{(10)}\). Such a strong coupling strategy provides the most stable and accurate fluid–structure coupling because both the geometrical compatibility conditions and the equilibrium conditions are directly satisfied. Watanabe et al. has presented a left ventricle model based on an ALE-FEM and incorporating the molecular mechanism of cardiac excitation and contraction\(^{(11),(12)}\). An ALE-FEM using a velocity–pressure correction procedure was presented by Perktold et al.\(^{(13)}\), and his coworkers applied the method to blood flow simulation in an ascending aorta\(^{(14)}\) and a coronary artery\(^{(15)}\). The deforming-spatial-domain/stabilized space–time (DSD/SST) formulation by Tezduyar\(^{(16)-(18)}\) is an extension of ALE-FEM methods. In the DSD/SST method, the finite element formulation is written over a sequence of space–time slabs, and four-dimensional interpolations are used for the discretization, where the slab represents the slice of the space–time domain between time levels \(n\) and \(n+1\). Deformation of the fluid domain is expressed by the shape of the space–time slabs. For references, see the recent review paper\(^{(19)}\). Applying this method\(^{(20)}\) to cardiovascular dynamics, Torii et al.\(^{(21),(22)}\) successfully performed patient-specific computations for the cerebral artery with aneurysms. Several other methods, for example, Gerbeau et al.\(^{(23)}\), Ramaswamy et al.\(^{(24)}\), and Kim et al.\(^{(25)}\), have been categorized as ALE methods. One disadvantage of the ALE methods is the need for
remeshing. For the realistic geometries of large deformable vessels and heart valves, all of
the ALE methods have difficulty updating the ALE meshes without changing the mesh
topology, and thus alternatively remeshing is performed. However, remeshing can be
time-consuming and expensive, and the interpolation of flow quantities on newly generated
meshes can introduce numerical diffusion.

Another elegant method of fluid–structure coupling is the IB method, which was
developed by Peskin(26)–(28) for the coupled simulation of blood flow and muscle contraction
in a beating heart. The distinguishing feature of the IB method is that the entire simulation
can be performed on Cartesian meshes without mesh updating. The Lagrangian and Eulerian
descriptions are connected by making use of the Dirac delta function. Tension forces at
several control points along the coupling surfaces are imposed and distributed to neighboring
fluid meshes through the delta function. An immersed FEM (IFEM) adopting the extended
IB method was proposed by Zhang et al.(30) to eliminate some drawbacks of the original IB
method. In the IFEM, the structural models are not restricted to fibers, and the finite element
structural model gives a more accurate stress field than the original IB method. Moreover, the
high-order reproducing kernel particle method (RKPM) delta function(31) used in the IFEM
increases the accuracy of the coupling procedure and allows the use of nonuniform meshes
for the fluid domain. Gay et al. presented an IFEM model for the mechanical behavior of
expanding balloon stents in angioplasty(32). The IFEM has been extensively applied to
microscale blood flows such as monocyte deposition, platelet adhesion, and red blood cell
aggregation(33). Fictitious domain (FD) methods(34),(35), similar to the IB method, are based on
treating velocity constraints with Lagrange multipliers. Using a FD method developed by
Baaijens(36), de Hart et al. modeled the fluid–leaflet interaction in the aortic valve(37)–(39). This
model combines the FD and ALE methods(40), and Wolters et al. used it for a patient-specific
analysis of abdominal aortic aneurysms(41).

Both the ALE and IB methods have been used in CFD studies to estimate relevant flow
factors such as wall shear stress (WSS); however, both methods encounter mesh resolution
problems, and very fine meshes are required to obtain accurate WSS fields, as demonstrated
by Prakash et al.(42). Uniformly fine mesh computations require a huge number of meshes and
therefore need an extremely long CPU time to use realistic geometry, especially for multiple
arteries with a variety of vessel sizes. To address this problem, adaptive mesh refinement
(AMR) methodology developed by Berger et al.(43),(44) was recently applied to blood flow
analysis. The AMR method, which allows placing fine meshes only where necessary, can
dramatically improve the boundary layer resolution with computational costs comparable to
those with coarse meshes. In an ALE framework, Cebral et al. constructed patient-specific
models using an AMR technique for the Circle of Willis(45) and a cerebral aneurysm(46). Griffith
proposed an adaptive IB method applicable to heart dynamics(47), and an adaptive FD
method was developed by van Loon et al.(48). Although such AMR applications are just
getting started, the AMR computation offers the promise of further progress in diagnosing
cardiovascular disease and designing cardiovascular devices(49).

2.2. Computational analysis of the intracardiac and aortic flows

Flow in large arteries is a classical problem in biomechanics. Numerous CFD studies
have been performed to relate hemodynamic factors, such as WSS, to vascular lesions(50),(51).
Until recently, the understanding of flow dynamics in arteries and their relationship to the
localized occurrence of vascular disease was limited by the use of simplified geometric
models and idealized flow conditions. Recent developments in imaging technologies and
computer power have enabled image-based CFD in which the anatomically realistic
geometry of a blood vessel is defined from medical images. The imaging modalities that have
been used to provide geometric information for CFD are Doppler ultrasound(52)–(54), digital
subtraction angiography(55)–(57), computed tomography(58),(59), and magnetic resonance
imaging (MRI)\(^{(60)-(64)}\). Among these, recent studies have tended to use MRI because it has the advantage of providing not only blood vessel geometry but also time-resolved velocity images that can be used as boundary conditions and to validate simulated results. Temporal resolution is still a major concern with MRI, although electrocardiographic gating ameliorates this drawback.

Image-based analyses of aortic flow have been conducted by several groups\(^{(58),(60),(62),(65)-(67)}\). A comparison of the CFD results with clinical data of vascular lesion sites has helped identify fluid mechanical factors that cause vascular diseases. Shahcheraghi et al.\(^{(65)}\) demonstrated that the preferential development of early atherosclerotic lesions is coincident with regions of extreme WSS and pressure. Mori et al.\(^{(66)}\) found that the WSS is locally high at the proximal and distal ends of the aortic arch, where aortic aneurysms develop preferentially. Morris et al.\(^{(58)}\) showed that the WSS is maximal at the inner and outer curvatures of the aorta, where thrombus formation is often reported.

Although these studies have demonstrated the potential of image-based patient-specific analysis of aortic flow, the choice of proper inlet flow conditions remains contentious. As Friedman and Giddens\(^{(68)}\) noted, the inflow boundary conditions significantly affect the accuracy and significance of WSS or its temporal and spatial gradients, which are of central interest in this field. Past studies have tended to assume a flat velocity at the inlet, based on measurements using hot film anemometry\(^{(69),(70)}\). Recent MRI measurements\(^{(71)-(73)}\) have demonstrated that the velocity profile of aortic inflow is not flat but rather has a time-dependent three-dimensional structure with complex secondary flows, which are likely attributable to flow dynamics in the left ventricle of the heart.

To our knowledge, the first practical CFD analysis of intracardiac flow was performed by Peskin and McQueen\(^{(74)}\). They introduced the IB method (see section 2.1 for details) to trace the wall–blood interface on a Cartesian grid and made vast contributions toward modeling intracardiac flow\(^{(25)-(27)}\). However, they have devoted themselves mainly to modeling itself rather than the analysis of flow in the heart, which has limited the value of their studies from a biomechanical perspective.

Studies attempting to relate intraventricular flow to cardiac function began appearing in the 1990s. Primarily systolic flow was studied because of its direct relation to the pumping function of the heart. Georgiadis et al.\(^{(75)}\) investigated the effects of eccentricities of the left ventricle on flow ejection and addressed the importance of the sphericality of the ventricular chamber in terms of intraventricular pressure gradients during flow ejection. The reported results, however, seemed to be limited by the use of a potential flow model. The influence of abnormal wall motion on systolic flow was investigated both two-dimensionally\(^{(76)}\) and three-dimensionally\(^{(77)}\) by Schoephorster’s group. More realistic flow simulation was performed by Taylor et al.\(^{(78),(79)}\), who defined the model geometry from a resin-molded canine heart. Later, they extended their study to examine the effect of partial cardiac infarction on intraventricular systolic flow\(^{(80)}\).

Although attempts to numerically model diastolic flow have been relatively few in the past, they have recently increased. Lemmon et al.\(^{(81),(82)}\) simulated intraventricular flow under the abnormal diastolic conditions of delayed ventricular relaxation, delayed ventricular relaxation with increased ventricular stiffness, and delayed ventricular relaxation with increased atrial contraction. Similarly, but with a much simpler model of the wall, a simulation was performed by Vierendeels et al.\(^{(83),(84)}\) to analyze the development of a vortex in relation to the wall stiffness and some clinical indices. The vortex structure in the left ventricle with a dilated cardiomyopathy was investigated by Baccani et al.\(^{(85)}\), who also examined the influence of the mitral valve opening on the ventricular filling flow, focusing on the traveling speed of vortices\(^{(86)}\). Domenichini et al.\(^{(87)}\), members of the same Baccani group, introduced a direct numerical simulation for precisely analyzing a vortex structure, although the validity of the simulated vortex structure seems to be limited by the assumption...
of a quiescent flow at the onset of diastole. Work by Nakamura et al.\(^{(88)}\) presented more
detailed insights into the development process of a vortex; they showed that a pair of vortices
in the long-axis plane, often observed in \textit{in vivo} \(^{(89)}\)–\(^{(91)}\) and in earlier numerical studies\(^{(92)}\),
was a cross section of the annular vortex. They discussed the relationship between the growth
of an intraventricular vortex and a Doppler-derived clinical index for left ventricular diastolic
function, the so-called “flow propagation velocity,” and provided the fluid mechanical basis
of this index. Their subsequent analysis of the utility and limitations of this index showed that
the flow propagation velocity was not sensitive to flow disturbances remaining from
systole\(^{(93)}\) and to ventricular untwisting\(^{(94)}\). Nakamura et al. also addressed the importance
of the opening mode of the mitral valve orifice on vortex formation within the left ventricle
during diastole\(^{(95)}\) and showed that the vortex structure affected left ventricular flow ejection
into the aorta\(^{(96)}\).

Recently, we attempted to model the cardiovascular system from its origin, the left
ventricle. At its start, the left ventricle model was attached to the root of the aorta. Figure 1
shows snapshots of blood flow, expressed by particle tracking, at (a) mid-diastole, (b) early
systole, and (c) end diastole in the heart (left ventricle) and the aorta with three branches. The
simulation successfully demonstrated a series of flow events during the cardiac cycle
observed \textit{in vivo}\(^{(90)}\)\(^{(97)}\). A large vortex that formed within the ventricular cavity during
diastole helped preferentially redirect blood particles to the aorta without a major loss of fluid
momentum, thereby facilitating the ejection of ventricular blood into the aorta during systole.
The impact of the ventricular ejected flow on hemodynamics in the aorta was clarified by
Nakamura et al.\(^{(98)}\), who compared the WSS along the inner curvature of the aorta obtained in
the integrated simulation with the cases in which the aortic flow was calculated using the
parabolic inflow or the flat inflow at the aortic root. This comparison suggested that some
vascular diseases at the ascending aorta might be associated with pathological
hemodynamics in the left ventricle.

Although hemodynamic factors are thought to play an important role in the development
and progression of vascular diseases, the mechanism that explains the relationship between
hemodynamic factors and the development of vascular lesions remains unclear. More
detailed and sophisticated modeling of blood flow in the heart and large arteries, performed
in concert with theoretical and experimental approaches, will lead to new discoveries in
biomechanics that may open the door to the development of innovative engineering concepts
as well as novel medical treatments.

![Fig. 1 Flow in the left ventricle and the aorta. (a) Diastole. (b) Early systole. (c) End systole.](image_url)
2.3. Fluid–solid interaction studies with respect to wave propagation

Pulsatile blood flow due to contraction of the ventricle causes an arterial wall disturbance, which oscillates in the radial direction as a result of wall elasticity and propagates toward the periphery. During the wave propagation, both wave reflection and energy dissipation occur, producing complex waveforms. Despite the extreme complexity of wave propagation in living blood vessels, the hemodynamics of systemic circulation warrant investigating. Young\(^{(99)}\) focused on wave propagation in terms of traveling speed in an ideal elastic tube with no branches, formulating a pulse wave velocity (PWV). This formulation was modified by Korteweg and Moens in 1878 and is known as the Moens–Korteweg equation\(^{(100)}\). According to the Moens–Korteweg equation, the PWV of a long straight elastic tube is

\[
PWV = \sqrt{\frac{Eh}{2\rho r}},
\]

where \(E\) is the Young’s modulus of the wall, \(h\) is the wall thickness, \(\rho\) is the fluid density, and \(r_i\) is the internal radius of the tube.

Since the 1990s, the Moens–Korteweg equation has been preferred for its simplicity in the noninvasive clinical diagnosis of systemic circulation diseases, including hypertension\(^{(101),(102)}\), diabetes \(^{(103),(104)}\), coronary artery disease\(^{(105)}\), and eating disorders\(^{(106)-(108)}\). Many clinicians believe that the mechanical properties of the arterial wall can be detected by measuring PWV and make efforts to statistically relate PWV to vascular disease. However, the validity of a diagnosis based on PWV is still uncertain because no evidence exists validating the application of the Moens–Korteweg equation to living blood vessels. Further investigation of pulse wave propagation is needed to determine the reliability of PWV as a diagnostic tool.

In general, three approaches are used to investigate pulse wave propagation: mathematical and one-dimensional analysis, experiments, and full computational analysis. In this review, we focus on full computational analysis and only briefly discuss the other two approaches.

Mathematical analysis of arterial waveforms has been used in cardiovascular physiology since Womersley\(^{(109)-(113)}\) introduced it in 1955. He used Fourier techniques to summarize the physics of pulsating blood flow in arteries. In the 1960s, Taylor\(^{(114)}\) developed a randomly branching model of the arterial system and demonstrated the input impedance of a randomly branching network of elastic tubes. A thorough introduction to the fundamentals of the mathematical analysis of blood flow as well as studies using one-dimensional analysis has been provided recently by Zamir\(^{(115)}\) and Pedley\(^{(116)}\).

With regard to the experimental approach using living subjects, Frank\(^{(117),(118)}\) revealed that an increase in mean arterial pressure increased PWV, which was subsequently investigated in detail by Bramwell and Hill\(^{(119)}\), who presumed that the dependence of PWV on blood pressure was attributable to the nonlinearity of the mechanical properties of the arterial wall. Anliker et al.\(^{(120)}\) studied the velocity of a discrete wave at various pressures and showed the nonlinear relationships between PWV and aortic pressure. Subsequently, the range of PWV measurements was expanded from large arteries to pulmonary arteries\(^{(121),(122)}\) and coronary arteries\(^{(123)}\). For more details, see Nichols and O’Rourke\(^{(124)}\).

Experimental studies using elastic tubes have also been performed to clarify pulse wave propagation. Newman et al.\(^{(125)}\) demonstrated pulse wave attenuation by using a saline-filled vinyl tube with a length of approximately 90 m, and also showed the impedance ratio of tubes with discontinuities. The influence of the viscoelasticity of the tubes was examined by Gerrard\(^{(126)}\), Ursino et al.\(^{(127)}\) assessed wave propagation with different pressure signals, and Bertram et al.\(^{(128)}\) used nonlinear elastic tubes. Although many studies have been reported using different methods, more detailed models are necessary to describe the complicated wave propagation in living vessels.
We recently attempted a new approach for investigating pulse wave propagation using a full computational method, i.e., a fluid–solid interaction computational method\textsuperscript{(129),(130)}, to assess in detail the influences of the three-dimensional geometries and mechanical properties of the arterial wall. To our knowledge, few full computational studies related to wave propagation have been reported. To reproduce wave propagation, we used compressive Navier–Stokes equations for the fluid region, which is a unique technique for stabilizing the computation. We first showed the accuracy of the computation in terms of PWV in long straight elastic tubes and concluded a good correspondence between the PWV values from the computation and those from the Moens–Korteweg equation for a PWV range of up to 12 m/s, which covers the range of values in human large arteries. We next showed the influence of blood flow on PWV in stenosed arteries. Vena contracta at the stenosis nonlinearly affected the PWV. We also studied the waveforms of the stenosed and aneurysmal arteries of several severities. Figure 2 illustrates wave propagation in an aneurysmal artery. The incident wave from the inlet propagates toward the periphery, and transmitted and reflected waves occur at the aneurysm. We showed that the wavelength of the reflected wave from an aneurysm is greatly affected by the longitudinal length of the aneurysm due to the multiple advancing and retreating waves in the aneurysm. In our investigation of a straight artery with branches, reflected waves from the branches complicated the propagation analysis.

Recent experimental studies have shown that the arterial wall moves the same magnitude in the longitudinal and radial directions\textsuperscript{(131),(132)}. Like blood flow, a longitudinal movement of the arterial wall may cause WSS, which has an important role in the physiology of living blood vessels, and a three-dimensional, full computational technique is needed to evaluate the influence due to longitudinal movements of the arterial wall. In addition, more realistic geometries and mechanical properties must be determined to enable more realistic modeling of the interactions between blood flow and arterial walls in the systemic circulation.

![Wave propagation in an aneurysmal artery.](image)

**Fig. 2** Wave propagation in an aneurysmal artery.
3. Microscale fluid mechanics of blood flow

In this section, we focus on microscale blood flow instead of the macroscale. Recent studies on blood flow in small vessels and motion of a red blood cell in induced flow fields are reviewed.

3.1 Microscale blood flows in small vessels

Blood can be regarded as a homogeneous fluid from a macroscopic perspective; however, blood is actually a suspension of red blood cells (RBCs), white blood cells (WBCs), and platelets in viscous fluid plasma. The mechanical behaviors of these blood components and their mechanical interactions become more critical for smaller vessels in which the cellular size is closer to the vessel diameter. In this section, we review recent computational studies that deal directly with the motions of multiple blood cells on a microcirculation scale of under several hundred micrometers during blood flow.

Given that RBCs occupy 45% of the whole blood volume, the motions of RBCs are important in determining the rheological properties of blood. Extensive in vitro experimental studies have investigated the effects of the mechanical properties of individual RBCs as well as the volumetric ratio of RBCs to whole blood (i.e., the hematocrit, Hct) on blood flow\(^{(133)}\), whereas computational simulations on this topic have originated only recently. This is because earlier numerical methods with fixed grids in Euler coordinates, such as the finite difference method (FDM), finite volume method (FVM), and finite element method (FEM), although very powerful and widely applied to blood flow problems in large vessels (as described in section 2), have several limitations in analyzing the complex geometries, moving boundaries, and multiphysics problems apparent in microscale blood flow. Recently, under the assumptions of Stokes' flow for infinite flow domains, a boundary element method (BEM), which will be discussed further in section 3.2, with adaptive meshes has emerged as a strong tool for detailed investigations of the mechanical behaviors of multiple RBCs\(^{(134)}\). In that study, an adaptive meshing technique combined with fixed grids in Euler coordinates was shown to be useful for analyzing a moving boundary during the motion of multiple RBCs in microscale blood flow.

Using a different approach, Sun and Munn\(^{(135)}\) proposed that the two-dimensional lattice Boltzmann method could simulate blood flow by considering individual RBCs to be suspended in plasma. Even though they assumed RBCs to be rigid, they qualitatively reproduced the experimentally observed motions of multiple RBCs, including the axial migration of RBCs and the appearance of a plasma layer near the vascular wall. With the Boltzmann method, the assembly of virtual particles is considered to represent a working fluid in the simulation region, which allows multiphase flow to be modeled by introducing particular forces among the virtual particles that represent the solid RBCs.

The collective behavior of blood under the influence of the mechanical interactions between RBCs is essential in determining the rheological properties of blood as a mass. Wada et al.\(^{(136),(137)}\) proposed the cell flow model, a type of Eulerian–Lagrangian model from the standpoint of multiscale mechanics and based on the minimum energy principle. Assuming that the macroscopic flow field is not affected by the motion of individual RBCs, i.e., one-way coupling, they determined the macroscopic flow field by theoretical/numerical analysis. Under the given flow field, they determined the motion of elastic deformable RBCs\(^{(137)}\) from the difference in velocity between the RBC and fluid flows. Although this method addresses the details of coupling effects between RBCs and plasma fluid, it allows a practical way of using RBC motions to investigate three-dimensional blood flow properties, such as the axial concentration of RBCs, the distribution of RBCs into daughter vessels, and the non-Newtonian properties of blood rheology, for vessels with diameters of several hundred micrometers. This method is suitable for a vector/parallel computer system such as
the Earth Simulator system because the solving method consists of explicit procedures.

The particle method is a more direct approach for modeling the multiphase flow of blood cells suspended in plasma fluid. In this method, a set of discrete particles representing blood components move in Lagrangian coordinates driven by interaction forces determined by the discretized form of governing equations for the particles. In a blood flow simulation based on a particle method, each particle can represent one discrete physical object (e.g., a platelet) or a set of particles can be generated to represent a part of the physical domain (e.g., a large blood cell such as a RBC or fluid plasma).

Boryczko et al. simulated three-dimensional blood flow of multiple RBCs in a capillary using a discrete particle model and suggested that the combined effects of Hct and RBC deformation have a substantial role in apparent blood flow properties. In that study, the RBC was assumed to be an elastic body, and an internal fluid was not considered. Nevertheless, the simulations reproduced the collective behavior of RBCs and would be expected to be useful tools for determining quantitative relationships between RBC motion and the rheological behavior of blood as a mass. Alternatively, Tsubota et al. proposed a two-dimensional blood flow simulation that combines the MPS method and the RBC membrane spring model and demonstrated the effects of the deformability of individual RBCs, the hematocrit values, and mechanical interactions between RBCs on blood flow properties of the microcirculation. The interaction forces between particles were determined on the basis of Navier–Stokes (N-S) equations to express incompressible viscous flow, and the particles of RBC membrane were connected to neighboring membrane particles by stretching and bending springs. In a recent study, Tsubota et al. substituted the forces induced by the springs to express the elastic RBC membrane into the N-S equations as the external force, thus permitting the coupled analysis of elastic RBC motion and plasma fluid flow. This approach is similar to that proposed by Takano et al., who employed the SPH method as a particle method and quantitatively demonstrated the three-dimensional motion of a single deformable RBC in a shear flow field.

Fig. 3 Numerical simulation of platelet aggregation in blood flow, using the particle method.
The particle method can also be used for analyzing the platelet aggregation in blood flow that causes primary thrombogenesis, in which fluid mechanical factors play an important role. Kamada et al. (145) modeled an individual platelet as a single particle, assuming that the size of each platelet was very small compared with the characteristic size of a blood vessel (see Fig. 3). The adhesion of platelets aggregated to the injured vessel wall was expressed by the spring force (146) acting between platelets and the injured wall. With this spring force, the deformation and collapse of an aggregated thrombus as a solid-like material under plasma flow was successfully predicted. The goal of this model is to reproduce the thrombogenesis phenomenon under various blood flow fields based on the scale of the platelet. Boryczko et al. (147) used a similar particle method approach to construct a model of fibrin aggregation for investigating the effects of RBC entrapment on the dynamics of clotting.

Even though the particle method is a computationally expensive, it allows us to directly analyze a suspension of different blood cells in plasma, needing only to assign suitable interaction forces between particles. It is expected that, combined with a sophisticated macroscale computational technique, this simulation method will be indispensable in understanding the overall properties of blood flow, from cellular motion to the resulting rheological properties of whole blood.

### 3.2. Motion of a red blood cell in induced flow fields

Descriptions of the motion of a red blood cell (RBC) in a simple shear flow, such as a tank-treading motion, or in a capillary can be found in some recent reviews (e.g., Popel and Johnson, 2005 (148); Michel and Curry, 1999 (149)) as well as in some classical reviews (e.g., Goldsmith and Skalak, 1975 (150); Fung and Zweifach, 1971 (151)). In this section, we focus on the numerical methods applied to such problems.

The RBC is usually modeled by a capsule with a thin membrane and containing Newtonian fluids, whereas the white blood cell is often modeled by a capsule containing viscoelastic fluids or by a standard solid (152). The flow around a RBC is assumed to be a Stokes flow, given that the Reynolds number based on the cell diameter and the velocity variation in the cell scale are usually much less than unity. In using a capsule model, the flow field inside and outside a capsule can be described by the Stokes equation and the continuity equation, and the problem is closed with a constitutive equation describing a mechanical behavior of the membrane. The most successful numerical method for addressing this problem is the boundary element method (BEM) first developed by Youngren and Acrivos (153).

In the case of a Stokes flow of Newtonian fluids, the interfacial velocity at a point on the membrane is expressed by the integration of single- and double-layer potentials over all surfaces (154, 155). The main advantage of the integral equation is that all unknown quantities are distributed on the particle surface. In the BEM, the boundary integral equation is approximated by the summation at discrete collocation points on the surface, so that a computational mesh needs to be generated only on the two-dimensional surface, even though the flow problem is fully three-dimensional. The total number of meshes required is much less than with other numerical methods, which leads to a low computational load. Moreover, the BEM can easily deal with an infinite computational domain. In the Stokes flow regime, a flow disturbance due to a point force decays as \( r^{-1} \), where \( r \) is the distance; thus a fairly large computational domain must be generated to avoid numerical errors resulting from the boundary conditions. In the case of the BEM, however, such boundary conditions are automatically satisfied by selecting appropriate kernel functions in the boundary integral equation.

The large deformation of a RBC has been simulated using the BEM, representing a field pioneered by Pozrikidis (156)–(160), who performed computations for a capsule of biconcave unstressed shape over an extended range of dimensionless shear rates and for a broad range of ratios of internal to external fluid viscosities. The membrane used in that study was nearly...
incompressible and exhibited an elastic response to shearing and bending deformation. They clarified the deformation of a cell and the stress exerted on the membrane in simple shear and extensional flows, as well as the migration of a cell in a tube flow. Nevertheless, some problems remain in these simulations. For example, a capsule of biconcave unstressed shape does not show a smooth tank-treading motion because the membrane stiffness is not homogeneous. Lac and Barthes-Biesel recently reported that the pre-stress of a membrane is important in the deformation of a capsule. It may be that an appropriate pre-stress is essential for simulating RBC motion. Future studies are needed to clarify this point.

Although accounting for membrane pre-stress is difficult in simulating single-cell deformation, another challenge exists in modeling the interaction between two RBCs. The cell–cell interaction is not purely a hydrodynamic phenomena, and currently, two accepted theories describe the mechanism of aggregation: the bridging of two cells by cross-linking molecules and osmotic force generated by the depletion of molecules in the intercellular space. Bagchi et al. used a formalism of bond formation, which does not imply a specific molecular mechanism, and simulated the aggregation of RBCs by the front tracking/immersed boundary method. They demonstrated that the rheological properties of cells have marked effects on aggregation. A precise aggregation model needs to be established.

Apart from the rigorous treatment of a RBC, some simplified models are used to express the basic RBC properties. Ishikawa et al. tried to improve a standard Eulerian–Lagrangian method for a dispersed two-phase flow and proposed a bead–spring cell model in which a bead represents the viscous drag and a spring represents the elasticity of the membrane (see Fig. 4). They showed that the model could express the rheological properties of low-hematocrit blood, such as the shear thinning property and the elasticity, even though the computational load was considerably lower than that of the standard BEM. Wada and Kobayashi proposed a mathematical model of a RBC based on the energy principle, in which the cell shape is determined so as to minimize the total elastic energy of the membrane. They showed a stable biconcave shape as well as a cupped shape, depending on the rheological property of the membrane. This model has an advantage in describing RBC deformation especially when the membrane experiences buckling.

Normal blood has a volume concentration of RBCs of about 40–45%, whereas white blood cells occupy 1/600 of the total cell volume, and platelets occupy 1/800 of the total cell volume. Thus, blood can be approximated as a concentrated suspension of RBCs. As the momentum, energy, and mass transport in blood are strongly dependent on the microscopic flow structures, many studies have tried to clarify the RBC motions in blood flow. However, numerical simulation of a concentrated suspension of RBCs has not yet been successful. The main difficulties encountered in this simulation are that the motion of even a single RBC is difficult to simulate, the interactions among RBCs have not been precisely modeled, the number of cells involved is so great that the computational load is enormous, and lubrication flows in the thin intercellular space. Furthermore, the macroscale flow structure due to cell aggregation must be accurately resolved, indicating the divergent scale of flow fields to be addressed. Owing to these difficulties, the numerical simulation of a concentrated suspension of RBCs is currently one of the most challenging tasks in this field of research. Some novel numerical methods, which could be applicable to this problem, were recently reported. We will briefly introduce them.

Some of the methods can efficiently simulate a concentrated suspension of rigid particles. Ladd was able to perform Stokesian dynamics simulations of suspensions with up to 32,000 rigid spheres by a lattice Boltzmann method. The main problem in applying this method to a suspension of RBCs is its adaptation to boundary conditions on the membrane. Sangani and Mo developed a fast multipole method (FMM) and performed Stokesian
dynamics simulations of suspensions with up to 8000 rigid spheres. The FMM is potentially applicable to a suspension of RBCs, but this has not yet been performed. Zinchenko and Davis(172,173) improved the standard boundary element method and were able to simulate up to 200 deformable drops with 1500 mesh points per particle in a simple shear flow. A high efficiency was demonstrated for this method, with gains of two orders of magnitude over the standard boundary element method. This method may be readily applicable to a suspension of RBCs, but again it has not yet been performed.

Several unsolved problems remain related to simulating red blood cell motions. To overcome these difficulties, it will be necessary to improve the modeling of cell behavior as well as the computational methods. We expect this to be accomplished in the near future to provide a better understanding of microcirculation.

Fig. 4 Simulation of low-hematocrit blood flow, using a bead–spring cell model. On the left, a flow field is shown. The figure on the right shows the deformation of a sample cell model.

4. Conclusions

In this paper, we have reviewed a large number of studies on macroscale and microscale hemodynamics. Owing to the advances in computer technology during the past decades, it becomes possible to model and to simulate complex hemodynamic problems, such as the complex and individually variable geometry of the cardiovascular system, the flexible and nonlinear material properties of the conduit walls, the pulsatile nature of blood flow, and the heterogeneous property of blood.

In considering clinical applications, however, the previous researches are not sufficient, and one needs to consider biological complexities in the analysis of blood flow, especially with respect to disease processes. A disease is not just a failure of machine. It is an outcome of complex interactions among multi-layered systems and subsystems. They mutually interact across the layers in a strongly non-linear and multi-variable manner. It is also noteworthy that a living system, either as a whole or as a subsystem, such as the cardiovascular system, is always under the integrated nervous and humoral control of the whole body, i.e., in homeostasis, as mentioned in section 1. Multiple feedback mechanisms with mutual interactions between systems, organs, and even tissues provide integrated control of the entire body. These control mechanisms have different spatial coverages, from the micro- to macroscale, and different time constants, from nanoseconds to decades. Though it has not been fully acknowledged, much longer time scale phenomena such as evolution and differentiation of living system must also be paid full attention if we are to understand the living system per se. In the future analysis, therefore, these biological phenomena need to be included in discussing physiological as well as pathological, i.e. disease processes. We
expect this to be accomplished in the future by integrating new understandings of macroscale and microscale hemodynamics, if we continue to be together with advances of related sciences and technologies.

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