Review

Mesoscale modeling: solving complex flows in biology and biotechnology

Zachary Grant Mills, Wenbin Mao, and Alexander Alexeev

George W. Woodruff School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA

Fluids are involved in practically all physiological activities of living organisms. However, biological and biorelated flows are hard to analyze due to the inherent combination of interdependent effects and processes that occur on a multitude of spatial and temporal scales. Recent advances in mesoscale simulations enable researchers to tackle problems that are central for the understanding of such flows. Furthermore, computational modeling effectively facilitates the development of novel therapeutic approaches. Among other methods, dissipative particle dynamics and the lattice Boltzmann method have become increasingly popular during recent years due to their ability to solve a large variety of problems. In this review, we discuss recent applications of these mesoscale methods to several fluid-related problems in medicine, bioengineering, and biotechnology.

Mesoscale modeling techniques

Computational modeling of fluid flows has become an important tool that is successfully utilized in solving practical engineering problems. However, the commonly used numerical methods based on the continuum approximation may not always be readily adapted to describe transport processes, micromechanics, and chemical interactions that take place in biological and bioengineering systems at the microscale. By contrast, atomistic scale simulation techniques, such as molecular dynamics (MD) and Monte Carlo (MC) simulations [1], can track the motion of individual molecules and allow the precise reconstruction of the molecular architecture and properties. However, these atomistic methods are prohibitively expensive from the computational point of view even for present-day powerful supercomputers, when it comes to probing the dynamic behavior of micrometer-sized systems that are of practical interest in biotechnological applications.

In this situation, particle-based mesoscale methods are attracting increasing attention as a promising means for tackling challenging problems in bioengineering and biotechnology (Table 1). These methods possess the unique ability to model relatively large physical systems, and, at the same time, effectively capture the essential features of the micro- and nanoscale structure, architecture, and relevant interactions.

Corresponding author: Alexeev, A. (alexander.alexeev@me.gatech.edu).
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In this review, we present several recent examples in which two of the currently most popular mesoscale computational methods, namely dissipative particle dynamics (DPD) [2] and the lattice Boltzmann method (LBM) [3], are utilized to examine biologically relevant flows. Although other mesoscale methods [4,5], such as multiparticle collision dynamics, stochastic rotation dynamics, smooth particle hydrodynamics, and lattice gas and lattice chain models, may also offer unique advantages for modeling specific biomedical systems, they will not be discussed in this short review.

Similar to MD, DPD uses a set of interacting particles or beads. The dynamics of this many-body system is assessed by time integration of Newton's equation of motion. DPD beads, representing clusters of molecules or fluid pockets, interact via conservative, dissipative, and random forces that give rise to normal and shear stresses and random thermal motion [2].

In contrast to MD, DPD uses soft interaction potentials allowing for a greater integration time step, which in turn enables simulations of the dynamic processes that take place over extended times. Furthermore, all interactions between DPD beads are pairwise, thereby exactly conserving the total momentum of the system. The latter property is critical for recovering the proper hydrodynamic behavior even using a relatively small number of beads in the simulations [6].

DPD beads interconnected by bending and stretching springs can be readily used to create macromolecules and polymer networks with different architectures, whereas clusters of DPD beads that are firmly attached to each other can be used to construct rigid objects with various geometries, such as nanoparticles and nanorods. By selectively tuning interactions between individual DPD beads, the effective affinity of molecules can be modified to model specific polymeric systems [7]. Additionally, long-range electrostatic interactions can be introduced into the model [8].

Although the use of soft DPD potentials is beneficial for the increased simulation speed, these potentials allow DPD beads to overlap, which can result in chain intersections when modeling dense polymer melts [9]. This coarse-graining problem can be mitigated via the use of repulsive bond–bond potentials that allows one to properly capture polymer micromechanics and entanglement [10].

LBM simulates fluid behavior using a set of 'fluid particles' that synchronously move along a lattice that is fixed in space [3]. The motion of the particles is described using a distribution function, time evolution of which is governed by the discrete Boltzmann equations. The simulation

Table 1. Advantages and disadvantages of microscale, mesoscale, and macroscale simulation techniques[a,b]

	Modeling approach	Examples of methods	Advantages	Disadvantages
Microscale	*Ab initio* methods and atomistic methods that model complete molecular structure	Density functional theory, molecular dynamics, Monte Carlo methods	• Explicitly model molecular architecture and interactions • Comprehensive information about modeled system • Readily simulate complex heterogeneous systems	• Small physical domains and short time scales • Computationally expensive • Extended simulations to eliminate statistical noise
Mesoscale	Particle-based methods in which particles represent clusters of molecules or fluid pockets	DPD	• Exactly conserves mass and momentum • Designed to model hydrodynamics • Captures basic features of molecular architecture • Effective for modeling of multicomponent systems	• Require mapping to specific physical system • Soft interaction potentials allow particles to overlap • Computationally expensive • Reduced resolution compared to molecular dynamics • Limited to low Schmidt number
		LBM	• Efficient for flows in complex geometries and with particles • Computationally efficient including massive parallel computing • Models multi-phase systems • Eliminates statistical noise • Easy to implement	• Range of viscosities is limited by method stability • Typically used for incompressible laminar flows • Difficult to implement certain boundary conditions
Macroscale	Methods based on discretization of continuous form of transport equations	Finite difference/ volume/element, volume of fluid, level set, immersed boundary methods	• Well-established methods • Computationally efficient • Model large physical systems • Typically formulated using primitive variables	• Require *a priori* knowledge of transport coefficients • Disregard internal molecular architecture • Reconstruction of interfaces can be complicated

[a]Among different mesoscale methods, only DPD and LBM are listed because they are the focus of this review.

[b]Note that some of the listed disadvantages can be overcome by appropriate modifications or combinations of methods.

algorithm includes two steps. The first step simulates the propagation of particles to the neighboring nodes, whereas the second step simulates collisions among particles situated at the same lattice node. The algorithm is then repeated. The collisions are evaluated using a collision operator that describes fluid relaxation towards a local equilibrium. Resulting hydrodynamic properties, such as fluid density, momentum, and stresses, are calculated using the moments of the distribution function.

The simplicity and locality of the LBM algorithm makes this method especially attractive for massive parallel computing, typically required to model large multicomponent systems [11]. By incorporating additional distribution functions, LBM can be extended to model multiphase and multicomponent fluids, including phase transition, mixing, chemical reactions, and heat transport [12–15]. Incorporating thermal fluctuations in LBM or combining the method with Brownian dynamics (BD) yield an effective tool for modeling the transport of nanoparticles and polymer chains in out-of-equilibrium fluid flows [16–18].

One of the major advantages of the LBM over conventional computational fluid dynamic (CFD) methods is its ability to handle effectively flows in complex geometries and particulate flows [19,20]. In LBM, a fluid–solid boundary condition is typically implemented using the so-called bounce back rule or its modifications [21]. That is, when a fluid particle collides with a moving or stationary solid wall, it is reflected back providing no slip and no penetration boundary conditions. Back flow effects associated with the transport of solid particles suspended in a flowing fluid can be also incorporated via a local body force that satisfies the global force and momentum balances [22].

Blood flow and cell interactions

Modeling fluid flows that transport suspended particles help us to understand better the hemodynamics and various physiological and pathological conditions associated with blood flow [23]. Such simulations, however, are rather complicated due to the two-way coupling between multiple finite-sized biological particles and unsteady fluid flow in blood vessels that typically have complex geometry and bifurcations. Furthermore, compliant cells constantly change their shapes due to the local hydrodynamic stresses and the interactions with the vessel walls and other particles, thereby adding to the flow complexity [24]. LBM has been used extensively by researchers to probe the dynamics of blood flows in different conditions (Figure 1A).

LBM has been used to simulate large populations of deformable RBCs suspended in a flow [25]. An immersed boundary (IB) approach for coupling between cells and fluid flow has been developed to examine the behavior of individual cells within dense RBC suspensions [26]. Cell deformation, organization, and clustering in RBC suspensions flowing in a microchannel have a significant influence on the dynamic and rheological behaviors of the flow [27–29]. LBM simulations have demonstrated that the cell-free layer near vessel walls is influenced by both the deformability of the cells and the aggregation strength, whereas the viscosity of the cell suspension has a significant influence mostly during the flow transition. Similar conclusions were obtained using DPD simulations [30].

The effect of cell deformability and plasma viscosity on the cell trajectories in bifurcating microvessels was investigated using LBM [31]. It was shown that an increase in cell rigidity or a decrease in viscosity results in the cell