A Discrete-Particle Model of Blood Dynamics in Capillary Vessels

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Abstract

We investigate the physical mechanism of aggregation of red blood cells (RBC) in capillary vessels, using a discrete particle model. This model can accurately capture the scales from 0.001\(\mu\)m to 100\(\mu\)m, far below the scales, which can be modeled numerically with classical computational fluid dynamics. We use a discrete-particle model in 3D for modeling the flow of plasma and RBCs in a capillary tube. The two situations involving necking and no necking have been considered. The flexible viscoelastic red blood cells and the walls of the elastic vessel are made up of solid particles held together by elastic harmonic forces. The blood plasma is represented by a system of dissipative fluid particles. We have simulated the flow of cells of different shapes, such as normal and “sickle” cells. The cells coagulate in spite of the absence of adhesive forces in the model. The total number of fluid and solid particles used ranges from 1 to 3 million. We conclude that aggregation of red blood cells in capillary vessels is stimulated by depletion forces and hydrodynamic interactions. The cluster of “sickle” cells formed in the necking of the conduit efficiently decelerates the flow, while normal cells can pass through. These qualitative results from numerical simulations accord well with laboratory findings.

\textbf{Keywords:} discrete particles, viscoelastic blood flow, elastic capillary vessels, fluid particle model

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Introduction

As a physiological fluid, blood is a complex suspension of polydisperse, flexible, chemically and electrostatically active cells, which are suspended in an electrolytic fluid consisting of numerous active proteins and organic substances. The rheology of blood has been studied for many years experimentally, theoretically and numerically [1-6]. For macroscopic blood vessels of a diameter more than two orders of magnitude greater than the size of a red cell, blood can be considered as a homogeneous fluid. Therefore, macroscopic blood dynamics can be modelled by solving classical hydrodynamic equations. An overview of the most recent numerical methods for modeling vascular flow in macroscale can be found in Quarteroni, SIAM News, 2001 [3].

Mechanical properties of blood are usually described by a constitutive equation, which is constructed on the basis of experimental viscometric data. The derivation of such an equation applicable for the macroscale is non-trivial. If blood is tested dynamically it would behave like a nonlinear viscoelastic fluid. Moreover, blood is thixotropic, that is, its viscoelastic characteristics change with the level of strain and strain history [1,7]. For example, at a vanishing shear rate the blood behaves like an elastic solid. The constitutive equations are non-linear, complex and not well constrained. Taking into account the complex boundary conditions associated with various geometry of blood vessels and elastic interactions between vessel wall and blood flow, the simulation of realistic hydrodynamic behavior of blood in macroscopic vessels is indeed a very challenging undertaking.

Macroscopic vessels represent only a small fraction of circulatory system, although the largest veins contain 50% of blood. The vascular tissue is made of microscopic – capillary channels. There are about $10^{10}$ blood vessels whose diameters are comparable with the dimensions of the red blood cells (RBC) i.e., 5-10µm [1,6]. Therefore, the majority of defects in circulatory blood system occurs in capillary vessels where blood flows less vigorously than in larger macroscopic vessels.

Fig.1 Rouleaux – aggregates of red blood cells. This figure comes from R de Roeck and M.R.Mackley, Department of Chemical Engineering, University of Cambridge (from http://www.cheng.cam.ac.uk/~rmdr2/research.html#Aggregation [5])

Thrombosis is an important defect in circulatory system. It is a major cause of most heart attacks and of other severe cardiovascular problems, such as ischemia and angina. The two major components of the thrombotic process are aggregation and coagulation. Aggregation involves platelets, a cellular constituent of the blood. The processes of cell-cell and cell-substrate adhesion
within the moving blood are connected with a very complex activation mechanisms involving changes in platelet’s surface membrane and chemical composition of the blood plasma in the neighborhood of injury [1,9]. It is well known that human red blood cells can form aggregates known as rouleaux [1,7] (see Fig.1) whose formation depends on the presence of the proteins fibrinogen and globulin. The slower the blood flow, the smaller is the shear rate and the larger are rouleaux. Necking of the microscopic vessels caused, e.g., by accumulation of cholesterol plagues in the vessel walls, slows down the flow. This stimulates the creation of larger and larger thrombi, resulting in a positive feedback loop, which can eventually choke the flow.

Blood coagulation is a physiological mechanism for stopping leaks in blood vessels. At sites of damaged vascular endothelium, platelets and neutrophils are captured from the flow stream while a protein, “tissue factor”, localized on the vessel wall can bind a specific enzyme to initiate a cascade of coagulation reactions on cellular surfaces, resulting in the conversion of prothrombin to thrombin [1,8,9]. Coagulation involves a network of more than 30 enzyme reactions with numerous forward and feedback loops, presumably for the dual purposes of control and amplification of the initial perturbation. Aggregation and coagulation are independent processes that only interact in the end, when the fibrin mesh forms on the platelet aggregate. A deep understanding of coagulation and aggregation processes is of major medical importance [9].

Both coagulation and aggregation involve the mutual binding of red blood cells (RBC). Binding depends on the following factors:

1) The presence of particular plasma proteins.
2) The imposed flow conditions.
3) The deformation of RBC.

Numerous studies have been performed on investigating the mechanisms of red cell aggregation, resulting in two popular hypotheses: the bridging mechanism and the depletion layer hypotheses [1]. It is commonplace knowledge that shearing conditions can accelerate the aggregation process. The choking of flow by necking is one such the condition. Geometrical faults in RBC cells caused by blood diseases, can be the following factor forcing the aggregation.

Numerical models of blood flow, which are based on macroscopic continuum hydrodynamic equations are not sufficient in the physics for simulating the feedback dynamics between microscopic flow and aggregated microstructures in capillary vessels. Formation of RBC clusters cannot be simulated by the classical computational fluid dynamics (CFD). In the capillaries RBCs must be treated as individual “objects” of circular biconcave shape. Consequently, blood in the microscale must be regarded as a two-phase, heterogeneous fluid consisting of a liquid plasma phase and a deformable solid phase of blood cells. In the macroscopic models the microscopic phenomena such as interactions between cells resulting from depletion and electrostatic forces, chemical reactions [8], large density fluctuations in plasma solution, are not present or they are averaged out because of their coarse-grained nature. In capillary channels it is necessary to consider all of these interactions, including the tight interactions between red blood cells and the capillary walls. As shown in [10,11,13], discrete-particle methods, such as dissipative particle dynamics, fluid particles model and multi-level particle method, can be used for modeling accurately complex fluids in scales ranging from 10nm to 100µm.

In this paper we present a novel idea based on the use of discrete-particles for modelling red blood cells dynamics in capillary vessels. We investigate the mechanism of RBC aggregation in microscopic blood channels employing a fluid particle model. First, we briefly describe the numerical model, focusing on its efficient parallel implementation. Next we go over the results from simulations involving 1-3 million of particles in 3-D. Finally, we discuss the results and summarize the advantages and disadvantages of this new approach.
Numerical model

Blood in capillary vessels can be viewed physically as a two-phase, heterogeneous fluid consisting of a liquid plasma phase and an elastically deformable solid phase filled with blood cells. The plasma, rich in many other blood components such as lipids, enzymes and platelets, cannot be studied in the microscale as a continuous medium but rather as an electrolytic suspension with many microstructural components. As shown in [10-13], the mesoscopic scales present in complex fluid can be accurately modelled using the discrete particle approximation.

In the model two types of particles are defined accordingly:

**Fluid particles (FP)**, which represent a portion of plasma fluid – “lumps of fluid suspension” from Fig.2a. The interactions between these particles are defined by the collision operator from fluid particle model (FPM) [14]. FPM is an extension of the dissipative particle dynamics (DPD) [15] method.

**Solid particles (SP)**, the “pieces of matter” defining nodes of the elastic grid. They represent the solid components of the vascular system, i.e., the vessel walls and red blood cells shown in Fig.2b,c,d.

Interactions among the particles

Fluid particle model (FPM), describing the plasma fluid, differs from the dissipative particle dynamics (DPD) first described by by Hoogerbrugge and Koelman [15]. The fluid particles can rotate in space and can be understood as relatively large mass packets, although they are still particles in the statistical mechanics sense. The interactions between the particles are represented by the collision operator of a finite range (unlike in smoothed particle dynamics (SPH) [16]) and a broad class of particle methods [17] where they are derived in a canonical manner from the force laws of continuum mechanics and are directly based on a regularized stress tensor. In contrast to classical dissipative particle dynamics, the interaction range for fluid particle model can be shorter due to more realistic interaction potential between droplets in FPM. It reduces some of the deficiencies in DPD model [14], which are usually compensated by a larger cut-off radius in the DPD interactions.

The fluid particles possess several attributes including mass $m_i$, position $r_i$, translational $v_i$ and angular $\vec{v}_i$ velocities and type (see Fig2a). The “droplets” interact with each other via a collision operator $\Omega$ standing for the two-body, short-ranged force [14]. This type of interaction is a sum of the conservative $F_C$, two dissipative components $F_T$ and $F_R$ (translational and rotational) and a Brownian force $\vec{F}_B$. Summarizing:

$$\Omega = -V'(r_{ij})\vec{e}_{ij} - \gamma \cdot m(A(r_{ij})\vec{1} + B(r_{ij})\vec{e}_{ij}) \cdot \left( v_j + \frac{1}{2} \frac{r_{ij}}{r_{ij}} \times \vec{v}_j + \vec{v}_i \right) + \sigma \left( \vec{a}(r_{ij})\bar{d}W^s_{ij} + \vec{b}(r_{ij})\frac{1}{D} tr[d\bar{W}] \vec{1} + \vec{c}(r_{ij})\bar{d}W^a_{ij} \right) \cdot \vec{e}_{ij} \tag{1}$$

where: $r_{ij} = r_i - r_j$ is a vector pointing from particle $i$ to particle $j$ and $\vec{e}_{ij} = \frac{r_i}{r_{ij}}, D$ – is the model dimension, $dt$ – is the timestep, $\gamma$ - scaling factor for dissipation forces, $d\bar{W}^s, d\bar{W}^a, tr[d\bar{W}]\vec{1}$ - are respectively the symmetric, antisymmetric and trace diagonal random matrices of independent Wiener increments and $A(r), B(r), C(r), \vec{a}(r), \vec{b}(r), \vec{c}(r), V'(r)$ – are normalized weight functions dependent on the separation distance $r=r_{ij}$. We have assumed that if a distance between particles $i$ and $j$, $r_{ij} = |r_{ij}|$, is greater than a cut-off radius $R_{cut}$, the value of $\Omega=0$.

As shown in Español [14], the single-component FPM system yields the Gibbs distribution as the steady-state solution to the Fokker-Planck equation. Consequently, it obeys the fluctuation dissipation theorem, which defines the relationship between the normalized weight functions.
Since the rheology of the plasma is approximately Newtonian [1], there is little doubt that the non-Newtonian features of human blood come from the red blood cells (RBC). The interaction of the blood cells with the blood flow becomes the key issue. Normal human RBC assumes a biconcave discoid shape with an averaged diameter of 8 µm, thickness of 2 µm [1,7]. Red blood cells are known to change shape in response to the local flow conditions. Deformation affects the physiological function of the red blood cell and its hydrodynamic properties. At a concentration of 50%, a suspension of rigid spheres cannot flow, whereas blood is fluid even at 98% concentration in volume [1].

The cells in our model consist of rectangular grid of solid particles (SP) (see Fig.2). The particles interact with particles in their Moore neighborhood [23] by conservative elastic forces $F^C = F^H$ where:

$$F^H = \chi \cdot (|r_{ij}| - a_{ij}) e_{ij}$$  \hspace{1cm} (2)

Besides conservative force, the collision operator for SPs includes the additional dissipative component similar to $F^T$ for fluid particles. This artificial viscosity prevents RBC from breaking-up due to collisions with the fast particles. In the model we assume that the value of $a_{ij} \in \{1, \sqrt{2}, \sqrt{3}\}$. As shown in Fig.2a, $a_{ij}$ depends on the position of neighboring particle in the Moore neighborhood. The elasticity of the object made of solid particles is not only a function of $\chi$ but also depends on the type of grid assumed and its resolution. At a finer resolution the radius
of interaction should be extended to the neighboring layers for matching to the required elasticity. The lack of a self-consistent procedure for matching the real material parameters (e.g., elasticity) is a drawback of this model. Coupling the immersed boundary method and neo-Hookean membrane model [6] with a particle approach gives an approximate formula for matching interparticle forces parameters to realistic properties of blood cells.

We have assumed that there are no attractive forces between cells, i.e., the particles from different cells (and channel wall) rebound due to conservative repulsive forces simulated here by the repulsive part of the Lennard-Jones force. In realistic blood the presence of particular plasma proteins, notably fibrinogen and immuno-globulins, plays an important role in the aggregation of blood cells. Many laboratory studies on blood flow suffer from inability to eliminate thrombin, which activates platelets, as well as preventing fibrin formation, which stabilizes platelet deposits [8]. Neglecting this factor allows us to examine other elements responsible for aggregation. They are directly caused by the capillary flow, RBC elasticity and the existence of depletion forces.

Depletion forces are volumetric forces with an entropic character, resulting from the granularity of the plasma suspension represented in the model by fluid particles. The interactions between fluid particles and cells are mimicked numerically by interactions between fluid particles and grids of solid particles representing cells. We assume also that the forces between fluid particles and solid particles are similar to those given in Eq.(1) One can consider more complicated systems in which fluid particles interact with surfaces covering the SP grid, rather than with the separate SP particles.

Along the blood vessel wall there is a layer of endothelial cells. These cells cannot move, but they can deform. They respond to the shear exerted on the vessel wall by the flowing blood. The cells form a continuous layer through which any exchange of matter between the tissue and the blood takes place. In the model the blood channel is made of massive particles “hollowed out” computationally (see Fig.2b). The blood vessel consists of several layers of particles to prevent the plasma particles from leaking outside of the channel. The wall particles interact with one another with forces similar to solid particles in RBC cells. In contrast to RBC, the Brownian force for wall particles is non-zero in order to avoid excessive energy dissipation from the system and to simulate the random deformation of wall. Interactions between the wall and both plasma and solid particles are repulsive in character and are given by Eq.1.

Timestepping and numerical implementation

The temporal evolution of the particle ensemble obeys the Newtonian laws of motion:

\[ \dot{\mathbf{v}}_i = \frac{1}{m_i} \sum_{j, r_{ij} < r_{cut}} \Omega \left( \mathbf{v}_i, \mathbf{v}_j, \mathbf{r}_{ij} \right) \]

\[ \dot{\mathbf{r}}_i = \mathbf{v}_i \]  

\[ \mathbf{F}_i = \frac{1}{I_i} \sum_{j, r_{ij} < r_{cut}} \mathbf{N} \left( \mathbf{r}_i, \mathbf{r}_j, \mathbf{r}_{ij} \right) \]

\[ \mathbf{N}_{ij} = -\frac{1}{2} r_{ij} \times \mathbf{F}_{ij} \]  

The equations of motion represent stochastic differential equations (SDE) due to stochastic nature of the Brownian force component. The **leap-frog** numerical scheme as in [15] represents only a crude approximation of the stochastic integrator. It generates serious artifacts, leading to unphysical correlations and monotonically increasing (or decreasing) temperature drift. Due to the large instabilities observed for the **leap-frog** scheme, we have used a higher-order temporal \(O(\Delta t^4)\) scheme for \(\omega\) [10-13]:

\[ \omega_i^{n+1/2} = 2\omega_i^{n-1/2} - \omega_i^{n-2} + \left( N_i^n - N_i^{n-1} \right) \]  

6
while the values of $v^{n+1}$ and $w^{n+1}$ are predicted by using the $O(\Delta t^2)$ Adams-Bashforth procedure. As shown in [11], both the hydrodynamic temperature and hydrodynamic pressures do not exhibit a noticeable drift for one million timesteps. For simulations requiring more accurate conservation of thermodynamic quantities, another integrator, which uses a thermostat, should be employed.

We consider here an isothermal three-dimensional system, which consists of $M$ particles confined in a long cylinder with periodic boundary conditions in the $z$ direction. The flow is directed from top to the bottom. The particle system is accelerated by an external force corresponding to a given pressure gradient. For the multi-component system of fluid and solid particles with different interaction ranges we have assumed that cut-off radius $R_{cut} = \max_k(R_{cut, k})$. The particular value of $k$ indicates the type of interaction. In these simulations we used the same $R_{cut}$ for all the interactions excluding interactions between wall particle-wall particle and RBC particle-RBC particle (for the same cell), which uses invariable neighbor lists. The forces are computed by using $O(M)$ order link-list scheme [18]. The force on a given particle includes contribution from both solid and fluid particles that are closer than $R_{cut}$ and which are located within the cell containing the given particle or within the adjacent cell. The procedures for computing the collision operator and integrating Newton’s equations are displayed in Fig. 3a.

As shown in Fig. 3b, the parallel algorithm is facilitated by geometric decomposition of the tube onto $P$ domains and by mapping them onto $P$ processors. By using SPMD paradigm (single program multiple data), commonly used for parallelization of MD code, each processor follows an identical predetermined sequence of operation to calculate the forces acting on the particles within an assigned domain. This code is written in FORTRAN 95 with a MPI environment. The details of the parallel FPM algorithm and the speedups obtained on up to 32 processors of IBM SP and SGI/Origin 3800 systems at the Minnesota Supercomputing Institute are described in [12].
Results

The FPM method can predict the transport properties of the fluid, thus allowing one to adjust the model parameters such as: density, temperature, internal pressure and viscosity, by using the limit of the continuum equations [14]. The plasma represents a suspension of proteins, enzymes and other cells (e.g., platelets, leukocytes etc.). We have assumed that its density and viscosity is 2% higher than water.

Structurally, red blood cells are biconcave discs of dimensions 8 µm diameter, 2.5 µm thick at the edge and 1 µm thick at the center. They can be envisaged as soft bags containing hemoglobin. The RBC is a highly deformable entity, as demonstrated when cells pass through capillaries within the body, the diameters of which are of the order 2-4 µm. The capillary diameter is about 1.5-3 times larger than the diameter of the cell. The cells were constructed by using “particles on strings” model described in the previous section (see Fig.2). Likewise we have fabricated deformed “sickle” cells and crescent-roll cells representing some blood diseases. We have assumed that solid particles are about 15% heavier than fluid particles (density of blood in 45% of hematocrit is 1.07 g/ml). The pressure gradient inducing the flow is about 3.2-3.5 kPa, i.e., similar to that in the capillary blood vessels [1]. For this pressure the local Reynolds number in a capillary, Re, is around 0.01.

![Graph showing averaged velocity of fluid and solid particles for two tubes with different diameters.](image)

**Fig.4** Averaged velocity of fluid and solid particles for two tubes with different diameters.

In Fig.4 we display the average velocity of fluid particles along the z-direction with time for two simulations with different diameters of the tube, and in Fig.5 are shown two snapshots from the corresponding simulations.

Initially the cells were equally spaced in the tube and positioned parallel to the cross-section (see Fig.5). The concentration of RBC particles in both vessels remains the same. The particles are accelerated in z-direction by a constant force. In the beginning the velocity increases linearly. RBC cells were separated and do not tumble up to about 0.1 sec.. Afterwards they begin to tumble and form clusters shown in Fig.7 and Fig.8. We can observe in Fig.4 that fluid acceleration distinctly decreases. This is due to ejection of the fluid particles by the RBC solid particles from the center of the tube, where the maximum velocity is found. From Fig.4 one can
see that by assuming the same concentration of solid particles, the effective viscosity of the particle system must be higher in the narrower vessels.

**Fig. 5** Snapshots of RBC flowing in tubes of different diameters: 10µm and 25µm, respectively. Time is given in seconds. The current timesteps are specified above the figures. Formation of clusters can be observed.

**Fig. 6** Snapshots of the red blood cells flowing in a narrow tube for small spacing between the cells.
However, as shown in [1], the apparent viscosity of blood flowing in cylindrical vessels decreases drastically with decreasing blood vessel diameter. An explanation of this Fahraeus-Lindquist effect is that the hematocrit in the tube decreases with a shrinkage of the tube diameter. Therefore, we have assumed that the total volume of RBC cells is about 10-35% of the capillary volume (excluding walls) and is smaller than in macroscopic vessels (about 50%). If the spacing between RBC is small (high hematocrit) and the flow velocity is greater than 1mm/s, then the cell-plasma core behaves as a rigid body and blood viscosity is independent of the tube hematocrit. At a lower speed the cells spacing decreases, forming aggregates. The average viscosity between two media is directly proportional to the number of red cells per unit length [1].

In Fig.6 we show the snapshots in which the cells were initially equally spaced in the tube. Without choking and in the presence of the high fluid velocity we cannot observe any differences in cell spacing during the flow process. The cells passing through the choking point block the flow. Consequently the cell spacing shrinks, thus stimulating the production of aggregates. As shown in Fig.7, one can observe the aggregation of cells into irregular clusters for both free and choked flows and both for normal and deformed cells. In the tube, which is twice longer than that displayed in Fig.8a, the aggregation effect can be discerned even clearer. In larger vessels with a small shear deformation the real blood forms long chains of RBCs. A laboratory picture is presented for comparison in Fig.8b. At a higher shear rate the chains break into smaller clusters and the viscosity of blood decreases dynamically [1,7].

Because RBC coagulation occurs, in spite of the absence of binding forces between cells in the model, we can justify the hypothesis about the role played by depletion forces in aggregation of RBC. The contribution of hydrodynamic forces to the clustering of cells is due to thinning of the stream of suspended particles. This hydrodynamic thinning can be observed for capillary flow of granules [13]. However, the granules do not form clot-like structures but rather assume shapeless elongated forms [11,13]. We believe that the positive feedback between depletion and hydrodynamic forces influences considerably the blood clotting process. These two phenomena need further study.

**Fig.7** Snapshots of RBC flow in a tube for a) normal cells and b) crescent roll - distorted cells. About 1.3 million fluid and solid particles were employed.
**Fig.8** Aggregation of RBC for free flow in the tube of 25µm diameter. More than 2 million particles were employed. Approximate shear rate is 100s⁻¹. Below, the image of real blood under much smaller shear conditions (5s⁻¹) with a gap of 0.15 mm. This image was captured on the Linkam CSS450 by using whole blood of 40% haematocrit. Figure courtesy of R de Roeck and M.R.Mackley, Department of Chemical Engineering, University of Cambridge [http://www.cheng.cam.ac.uk/~rmdr2/Nice_Pics.html](http://www.cheng.cam.ac.uk/~rmdr2/Nice_Pics.html).

It is not surprising that the choking point in the tube retards the flow rate and causes the formation of cell clot close to the necking zone. However, for normal blood cells from Fig.7b the clot is able to pass through this point. This is not like Fig.7c, where the clot made of deformed (crescent-roll shaped) cells stops the flow almost completely.
Sticky red cells block the blood flow

If there is no oxygen, an ischemia occurs

**Fig.9** Schematics showing how damaged cells can strongly influence the blood flow. "V" represents the direction of blood flow.

**Fig.10** Snapshots from simulations of “sickle” RBC flowing in the pipe for a) free flow b) flow with the choked point placed at the lower end of the pipe. 2.3 million particles are employed.

Other kind of critical behavior is shown in Figs.9,10 representing the snapshots from simulations of “sickle” cells - characteristic for anemia disease - flowing in free and in choked capillary. For “crescent-roll” RBC and “sickle” cells the probability of clotting increases considerably. As shown in Fig.11, both “sickle” and normal cells block the flow. However, due to the higher elasticity of the normal cells, the flow stabilizes, while the “sickle” cells disrupt the pipe walls (see also Fig.10). This leads consequently to numerical instability. Fig.10b depicts the situation just before onset of the numerical blow-up. From Fig.11 the viscosity of “sickle” cell fluid is observed to be greater than the fluid with normal biconcave discs.
**Fig. 11** The evolution of the Reynolds number for flows with “sickle” and normal cells. As shown, deoxygenated “sickle” cells blood has a higher viscosity than normal blood.

### Conclusions

We have presented here a brand new idea for modelling blood dynamics in capillary vessels. This novel approach is based on the paradigm of discrete particles. We show that a plasma suspension can be modelled by employing fluid particles (FPM), while elastic microstructures, such as red blood cells and larger structures such as walls of the vessel, can be simulated by a grid of solid particles.

We show that the RBC aggregate into clusters, despite the lack of binding forces between cells in the model. The reason is that the plasma suspension is modeled by the particles and considerable fluctuations of local plasma density can be observed. The fluid particles are pushed out from the space between the cells due to flow. The voids form depleted layer, which results in attractive depletion forces between the cells. This depleted layer hypothesis requires more detailed laboratory studies. Our simulations also confirm the medical observations concerning clotting of distorted cells close to the choking point. The "sickle" blood cells are unable to squeeze through the smaller blood vessels (arterioles and capillaries). RBCs, which are “sickle”-shaped, often become stuck in small blood vessels and halt the blood flow.

In contrast to the classical models based on continuum flow equations, the particle model allows for the simulation of microscopic multi-component systems with a granular character. More complicated geometries of the vascular system with elastic walls can be modelled easily. However, the periodicity of the particle system imposes some limitations for simulating branching vessels. The low computational efficiency of discrete particles method can be partially compensated by efficient use of parallel systems [12]. The CPU time for simulations involving 1-2 million particles is about 2 days on 8 processors of SGI/Origin 3800 system.

This model is still oversimplified, since there are only two components in the blood. However, the discrete-particle approach allows for the introduction of additional constituents. It is possible to incorporate a parameter reflecting the cell-cell attraction/adhesion, which might arise from fibrinogen at varying concentrations. One would need to include both short-range attraction and some estimates of the tendency of adhesion, when two cells squeezing together make a contact and sandwich in the fibrinogen. This may be important under normal conditions because the blood fibrinogen level is an indicator of a high risk factor for inducing large vessel disease.
Furthermore, there is some possibility that enhanced red cell-fibrinogen binding may be present in “sickle” cell disease. One interesting abnormality of “sickle” cells is a non-uniform negative charge on the surface. In this case one can separately incorporate a parameter, which reflects a lack of charge repulsion, arising from the patchy surface charge.

**Fig. 12** The diagram presenting the potential scope in the application of the discrete-particle model. The snapshots show volumetric visualization of velocity fields in plasma for two types of choking: in the neck of a capillary vessel and in a bifurcation. Below the snapshot from a 2-D FPM simulation, which shows the potential application of the discrete-particle model in modeling phase separation and coalescence of droplets in blood. This allows one to compute the dynamics including surface tension in blood and plasma.
A potential problem is the difficulty in mapping of the macroscopic blood properties such as elasticity of the cells into particle interactions. Moreover, more sophisticated properties of red blood cells cannot be simulated by the model involving the grid of particles-on-springs. The realistic structure of RBC membrane, which is composed of a lipid bilayer supported by a scaffolding consisting of cytoskeletal proteins, maintains its local area nearly unchanged [6]. This type of dynamics does not hold for the particles-on-spring model in highly deformed cells. Microscopic chains of chemical reactions leading, for example, to the creation of permanent clots tied by fibrinogen, requires more detailed multi-level microscopic models involving the implementation of molecular dynamics. There are also serious numerical problems, which may lead to physical artifacts. For example, periodic boundary conditions employed in our model can produce stationary waves generating spurious clustering of cells. This drawback can be partially eliminated by modeling larger systems, i.e., longer blood conduits. However, this will entail more computational time.

Despite these limitations, our present model can still be regarded as an interesting step put forward for modeling microscopic vascular system. We believe that it may open up new avenues for the simulation of other problems in blood dynamics in capillary vessels. In Fig.12 we show the potential future applications of the discrete-particle approach. For example, the curvatures and bifurcations of large and medium sized arteries are severely influenced by atherosclerosis. Numerous investigations performed for macroscopic blood vessels [19,20] point to a relationship between the genesis and the progression of the disease with the locally irregular flow field occurring in these peculiar zones. We believe that this effect may be even emphasized in capillary vessels in which the mass distribution is not continuous and the shear rate is very high. Even a small shear stress at the wall can locally disturb mass transfer, which is influenced by viscoelastic interactions between RBC and vessel walls and by enhanced particle residence time in flow separation and flow recirculation zones. Other problems involving surface tension, such as droplets break-up and coalescence and the dynamics of capillary pinching of a fluid thread [24, 25] can be also simulated efficiently by using the fluid particle model [26,27]. Therefore, the discrete-particle model is very well suited for attacking many diverse scenarios in complex blood dynamics.

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# Glossary of terms in blood flow
(from http://www.academicpress.com/inscight/09091997/endothe1.htm)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Capillary vessels</td>
<td>The vessels of diameter from 4µm to 100 µm</td>
</tr>
<tr>
<td>Endothelial cell</td>
<td>A type of squamous epithelium cell that lines the interiors of cavities, spaces, and blood vessels.</td>
</tr>
<tr>
<td>Endothelium</td>
<td>The layer of squamous epithelium that lines the cavities of the heart, blood vessels, and lymph vessels.</td>
</tr>
<tr>
<td>Fibrin</td>
<td>Fibrin is the product of an activated coagulation system. It forms in the extravascular space by cleavage of fibrinogen. It is an important component of a blood clot, as well as a thrombus.</td>
</tr>
<tr>
<td>Globulin</td>
<td>Family of proteins from plasma or serum of the blood.</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Ratio of: red blood cells volume/blood volume [in %]</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>A large leukocyte, containing a lobed nucleus and abundant cytoplasmic granules, that stains with neutral dyes.</td>
</tr>
<tr>
<td>Platelet</td>
<td>A cytoplasmic fragment that occurs in the blood of vertebrates and is associated with blood clotting. Also, THROMBOCYTE. Blood cell which initiates the vascular phase of the acute inflammatory response</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>A plasma protein that is converted to the active form thrombin (factor IIa) by cleavage by activated factor X (Xa) in the common pathway of blood coagulation</td>
</tr>
<tr>
<td>Rouleaux</td>
<td>Red blood cells appear stuck together like stacks of coins when observed on a peripheral smear. This is due to the presence of an abnormal protein, such as a paraprotein.</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Thrombosis refers to the formation of a thrombus within the vascular space.</td>
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<tr>
<td>Thrombus</td>
<td>A thrombus is an aggregate of a network of fibrin, platelets, and blood elements trapped by the fibrin net.</td>
</tr>
</tbody>
</table>
References


