A discrete-particle model of blood dynamics in capillary vessels

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Abstract

We investigate the mechanism of aggregation of red blood cells (RBC) in capillary vessels. We use a discrete-particle model in 3D to model the flow of plasma and RBCs within a capillary tube. This model can accurately capture the scales from 0.001 to 100 μm, far below the scales that can be modeled numerically with classical computational fluid dynamics. 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 plasma is represented by a system of dissipative fluid particles. Modeling has been carried out using 1 to 3 million solid and fluid particles. We have modeled the flow of cells with vastly different shapes, such as normal and “sickle” cells. The two situations involving a straight capillary and a pipe with a choking point have been considered. The cells can coagulate in spite of the absence of adhesive forces in the model. We conclude that aggregation of red blood cells in capillary vessels can be stimulated by depletion forces and hydrodynamic interactions. The cluster of “sickle” cells formed in the choking point of the capillary efficiently decelerates the flow, while normal cells can pass through. These qualitative results from our first numerical results accord well with laboratory findings.

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1. Introduction

Blood is a physiological fluid, which consists of a suspension of polydisperse, flexible, chemically and electrostatically active cells. These cells are suspended in an electrolytic fluid consisting of numerous active proteins and organic substances. For many years blood rheology has been researched experimentally, theoretically, and numerically [1–7]. Blood can be regarded from a fluid dynamical standpoint as a homogeneous fluid for macroscopic blood vessels of a diameter more than two orders of magnitude greater than the size of a red blood cell. Therefore, one can model macroscopic blood dynamics by solving classical hydrodynamic equations. An overview of the most recent numerical methods for modeling vascular flow in macroscale can be found in Quarteroni [3] and in [2,7].

Blood behaves like a nonlinear viscoelastic fluid when subject to dynamical probing. Moreover, blood is thixotropic; that is, its viscoelastic characteristics change with the level of strain and the strain history [1,7]. The mechanical properties of blood are commonly described by the Casson constitutive equation, or can be based on models obtained from experimental viscometric data. The constitutive equations for blood rheology are nonlinear, complex, and not well constrained. Taking into account the complex geometry of blood vessels [8] and the elastic interactions between vessel wall and blood flow, the modeling 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. There are about 1010 blood vessels with diameters of the size of red blood cells (RBC) [1,9]. Because the blood flow in capillaries is stagnant, the majority of deficiencies caused, e.g., by thrombosis occurs in microscopic vessels. These microdefects are very dangerous if they take place over a large volume of vital parts of the organism such as the brain.

Thrombosis is an important defect in the circulatory system. It is a major cause of most heart attacks, stroke, and other severe cardiovascular problems, such as ischemia and angina. The two major components of the thrombotic process are aggregation and coagulation. It is well known that human red blood cells can form aggregates known as...
It is commonly known that shear conditions can accelerate RBC clustering. The choking of flow by necking is one such condition. Geometrical faults in RBC cells caused by blood diseases can be a factor forcing RBC clustering. Numerous studies have been performed in order to investigate the mechanisms of red cell clustering, resulting in two popular hypotheses: the bridging mechanism and the depletion layer hypotheses [1].

These hypotheses can be verified by modeling the feedback dynamics between flow and elastic red blood cells in capillaries. However, this situation cannot be modeled by classical computational fluid dynamics (CFD). Blood in the microscale must be regarded as a two-phase, nonhomogeneous fluid consisting of a liquid plasma phase and a deformable solid phase of blood cells. Consequently, in the capillaries RBCs must be treated as individual “objects” of circular biconcave shape. In the macroscopic models the microscopic phenomena such as interactions between cells resulting from depletion and electrostatic forces, chemical reactions [12], and large density fluctuations in the plasma solution are not present, or they are averaged out. In capillary channels it is necessary to consider all of these interactions including tight interactions between red blood cells and the capillary walls. As shown in [13–15], discrete-particle methods, such as dissipative particle dynamics, the fluid particles model, and the multilevel particle method can be used to modeling complex fluids accurately at scales ranging from 10 nm to 100 µm.

In this work we will present a brand-new idea based on the use of discrete particles for modeling red blood cell 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. The results from calculations involving 1–3 million particles in 3-D are presented in the next section. Finally, we discuss the results and summarize the advantages and drawbacks of this new approach.

2. Numerical model

Physically one can view blood in capillary vessels as a two-phase, nonhomogeneous 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 at the microscale as a continuous medium but rather as an electrolytic suspension with many microstructural components. As shown in [13–16], the mesoscopic scales present in a complex fluid can be accurately modeled by using the discrete particle paradigm.

In the model two types of particles sketched in Fig. 2 are defined according:

1. A fluid particle (FP) represents a portion of plasma fluid or “cluster of fluid suspension.” The interactions between these particles are defined by the collision operator from the fluid particle model (FPM) [17].
Fig. 2. (a) Fluid particle model, (b) RBC model made of “flexible particles,” (c) RBC model after volume rendering, and (d) real image of deformed RBC extracted from http://www.monash.edu.au/pubs/eureka/Eureka_95/clotting.html.

2. A solid particle (SP) corresponds to a “piece of matter”—a single node of elastic mesh of particles, which defines solid components of the vascular system: the capillary walls and red blood cells.

2.1. Interactions among the discrete particles

2.1.1. Plasma

The fluid particle model portraying the dynamics of the plasma fluid is a discrete-particle method. The interactions in the FPM are represented by the collision operator of a finite range. This is unlike in smoothed particle dynamics (SPH) [18] and a broad class of particle methods [19] where the particle interactions are directly based on a regularized stress tensor derived in a canonical manner from the force laws of continuum mechanics. The method is an extension of dissipative particle dynamics DPD [20]. In contrast to DPD,

1. the fluid particles can rotate in space, and
2. the interaction range for FPM can be shorter due to a more realistic interaction potential between fluid particles,

which reduce some of the deficiencies in the DPD model [17], which are usually compensated for by a larger cut-off radius in DPD interactions.

The fluid particles possess several attributes including mass $m_i$, moment of inertia $I_i$, position $r_i$, translational $v_i$, and angular $\omega_i$, velocities, and type (see Fig. 2a). The particles $i$ and $j$ interact with one another by a collision operator $\Omega_{ij}$ standing for the short-range two-body force [14]. This type of interaction is a sum of the conservative force $F_{ij}^C$, two dissipative components $F_{ij}^T$ and $F_{ij}^R$ (translational and rotational), and a Brownian force $F_{ij}^B$.

\[
\Omega_{ij} = F_{ij}^C(r_{ij}) + F_{ij}^T(r_{ij}, v_{ij}) + F_{ij}^R(r_{ij}, \omega_{ij}) + F_{ij}^R(r_{ij}),
\]

where $r_{ij} = r_i - r_j$ is a vector pointing from particle $i$ to particle $j$, $v_{ij} = v_i - v_j$, and $\omega_{ij} = \omega_i + \omega_j$. The Brownian force is a linear combination of random matrices of independent Wiener increments. The equations for forces are derived in [17] and presented in our previous papers [13–16]. We have assumed that if the distance between particles $i$ and $j$, $R_{ij} = |r_{ij}|$, is greater than a cut-off radius $R_{cut}$, the value of $\Omega_{ij} = 0$.

As shown in Español [17], 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.

2.1.2. Red blood cells

Structurally, red blood cells are biconcave discs of diameter $8 \mu m$, $2.5 \mu m$ thick at the edge and $1 \mu m$ thick at the center [1,10]. The biconcave shape of a red blood cell exactly fits its basic role, oxygen transportation in the organism. For example, the surface of a spherical RBC (spherocyte) is $50\%$ less, which considerably reduces the speed of exchange of gases between the RBC and its environment. On the other hand, cells with many appendices would impose additional flow resistance. Therefore, the biconcave shape of the erythrocyte is a dynamical consequence between the maximal structure and the weakest hydrodynamic resistance [1]. It may be derived from a variational principle based on energy considerations and different configurations.

A red blood cell can be conceptualized as a soft bag filled with hemoglobin. A lipid bilayer membrane provides the cell with its shape, strength, and flexibility. The membrane is supported by a complex protein network, which is called the cytoskeleton. The RBC shape depends both on the proper structure of plasmatic RBC membrane and on various kinds of metabolic processes taking place at the plasma/RBC interface [1]. If these processes are disturbed as a result of metabolic diseases, or the blood cell is taken out of plasma, the structure of the RBC can change considerably, forming sickle, spherical, crescent-roll, and other shapes [1,9]. Large-amplitude deformation processes can influence 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]. To obtain a precise RBC model for which its shape will emerge from first principles not only must its internal structure be known—such as the structure of the complex cytoskeleton network—but also all metabolic processes taking place at the RBC/plasma interface should be modeled.

We model only some RBC elastic properties by defining its structure externally, because we know so little about the structure of the protein network and metabolic processes keeping the RBC shape [1] and the cross-scale simulations.
of microscopic metabolic processes. Moreover, modeling the macroscopic flow dynamics is still too demanding for a decent parameter space search and can be handled only on a case-by-case basis.

Red blood cells are known to change shape elastically in response to local flow conditions. Since the rheology of plasma is approximately Newtonian [1], there is little doubt that the non-Newtonian features of human blood come from red blood cells (RBC). The RBC is a highly deformable entity, as demonstrated when cells pass through capillaries within the body, the diameters of which are on the order of 2–4 µm. The interaction of the blood cells with the blood flow becomes the key issue. For these reasons we have assumed in our model that the RBC is made up of a 3-D mesh with particles on springs, which models the cytoskeleton network and hemoglobin. The initially imposed RBC shape can be deformed by the flow elastically. This approximation is sufficient because a qualitative, nonelastic transition from one RBC shape to the other due to stagnant flow in capillary vessels is impossible.

The cells in our model consist of a rectangular 3-D mesh of solid particles (SP) (see Fig. 2). Each SP particle interacts with SP particles in its Moore neighborhood [21] by conservative elastic forces \( \mathbf{F}^C = \mathbf{F}^H \), where

\[
\mathbf{F}^H = \chi \cdot (|\mathbf{r}_{ij}| - a_{ij}) \mathbf{e}_{ij}.
\]  

(2)

Besides the conservative force, the collision operator for SPs includes an additional dissipative component similar to \( \mathbf{F}^T \) for fluid particles. This artificial viscosity prevents the RBC from breaking up numerically due to collisions with 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 the neighboring particle in the Moore neighborhood. The elasticity of the object made of solid particles not only is a function of \( \chi \) but also depends on the type of mesh assumed and its resolution. At a finer resolution the radius of interaction should be extended to the neighboring layers to match the required elasticity. The lack of a self-consistent procedure for computing real material parameters (e.g., elasticity) from interparticle forces is a drawback of this model.

We have assumed that there are no attractive forces between cells; i.e., the particles from different cells (and the channel wall) rebound due to conservative repulsive forces modeled here by the repulsive part of the Lennard–Jones force. In realistic blood the presence of particular plasma proteins, notably fibrinogen and immunoglobulins, plays an important role in the aggregation of blood cells. Many laboratory studies on blood flow suffer from the inability to eliminate thrombin, which activates platelets, as well as preventing fibrin formation, which stabilizes platelet deposits [12]. Neglecting this factor allows us to examine other elements responsible for aggregation, which directly causes the capillary flow, RBC elasticity, and the existence of depletion forces. Depletion forces are volumetric forces of entropic character resulting from the granularity of the plasma suspension represented in the model by fluid particles.

The interactions between fluid particles and RBCs are mimicked numerically by interactions between fluid particles and the solid particles representing red 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 complex systems in which fluid particles interact with a membrane covering the SP mesh, rather than with the separate SP particles. Moreover, coupling the immersed boundary method and the neo-Hookean membrane model [6] with a particle approach could give an approximate formula for matching the interparticle forces parameters to realistic properties of blood cells.

2.1.3. Walls of blood vessels

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 “hallowed out” computationally (see Fig. 2b). The blood vessel consists of several layers of particles to prevent the plasma particles from leaking out of the channel. The wall particles interact with one another with forces similar to solid particles in RBC cells. In contrast to RBC, we have set the Brownian forces for the wall particles to be nonzero in order to avoid excessive energy dissipation from the system and to mimic random deformation due to the wall particles. Interactions between the wall and both plasma and solid particles are repulsive in character and are given by Eq. (1).

2.2. Timestepping and numerical implementation

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

\[
\dot{\mathbf{r}}_i = \frac{1}{m_i} \sum_{j: r_{ij} < \text{cut}} \mathbf{F}_{ij}, \quad \dot{\mathbf{v}}_i = \mathbf{v}_i,
\]  

(3)

\[
\dot{\mathbf{w}}_i = \frac{1}{I_i} \sum_{j: r_{ij} < \text{cut}} \mathbf{N}_{ij}(\mathbf{r}_{ij}, \mathbf{v}_i, \mathbf{w}_i), \quad \mathbf{N}_{ij} = -\frac{1}{2} \mathbf{r}_{ij} \times \mathbf{F}_{ij}.
\]  

(4)

The equations of motion represent stochastic differential equations (SDE) due to the stochastic nature of the Brownian force component. The leapfrog numerical scheme, as in [20], is 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 leapfrog scheme, we have used a higher-order temporal \( O(\Delta t^4) \) scheme for \( \omega \) [16],

\[
\omega_i^{n+1/2} = 2\omega_i^{n-1/2} - \omega_i^{n-3/2} + (\mathbf{N}_{ij}^n - \mathbf{N}_{ij}^{n-1}),
\]  

(5)

while the values of \( \mathbf{v}^{n+1} \) and \( \omega^{n+1} \) are predicted using the \( O(\Delta t^2) \) Adams–Bashforth procedure. As shown in [14],
Fig. 3. (a) A flowchart of the discrete-particle model; (b) geometric decomposition of the particle system into different processors $P_l$ (plasma is invisible).

the hydrodynamic temperature and the hydrodynamic pressures do not exhibit a noticeable drift for around one million timesteps. For simulations requiring more accurate conservation of thermodynamic quantities, another integrator which uses a thermostat should be employed.

2.3. Computational implementation

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 multicomponent system of fluid and solid particles with different interaction ranges we have assumed that cut-off radius $R_{\text{cut}} \sim \max(k(R_{\text{cut}}, k))$. The particular value of $k$ indicates the type of interaction. In these calculations we used the same $R_{\text{cut}}$ for all the interactions excluding wall particle–wall particle and RBC particle–RBC particle interactions (for the same cell), which use invariable neighbor lists. The forces are computed using an $O(M)$ order link-list scheme [22]. The force on a given particle includes contributions from both solid and fluid particles that are closer than $R_{\text{cut}}$ and that are located within the cell containing the given particle or within the adjacent cell. A flowchart of the program kernel is 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 the SPMD paradigm (single program multiple data), commonly used for parallelization of MD code, each processor follows an identical predetermined sequence of operations to calculate the forces acting on the particles within an assigned domain. The code is written in FORTRAN 95 under an MPI environment. The details of the parallel FPM algorithm and speedups obtained on up to 32 processors of IBM SP and SGI-Origin 3800 systems at the Minnesota Supercomputing Institute are described in [16].

3. Results from the modeling

Blood plasma represents a suspension of proteins, enzymes, and other cells (e.g., platelets and leukocytes). We have assumed that its density and viscosity are 2% higher than those of water. From the transport properties of plasma, such as the density, temperature, internal pressure, and viscosity, we derived the model parameters using the equations in the continuum limit [17].
In the model we have also assumed that the capillary diameter is about 1.5 and 3 times larger than the diameter of the cell. The cells were constructed by using the “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.

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

Initially the cells were equally spaced in the tube and positioned parallel to the tube cross-section (see Fig. 6). The concentration of RBC particles in both vessels remains the same. The particles are accelerated in the 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 s. Afterwards they begin to tumble and form clusters, shown in Figs. 7 and 8. We can observe in Fig. 4 that fluid acceleration distinctly decreases. This is due to ejection of the fluid particles from the center of the tube, where the
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.

maximum velocity is found by the RBC solid particles. From Fig. 4 one can see that assuming the same concentration of solid particles, the effective viscosity of the particle system must be higher in narrower vessels.

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 decrease in the tube diameter. Therefore, we have assumed that the total volume of RBC cells is about 10–25% 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 1 mm/s, then the cell-plasma core behaves as a rigid body and blood viscosity is independent on the tube hematocrit. At a lower speed the cells spacing decreases, forming aggregates and the average viscosity between two media is directly proportional to the number of red cells per unit length [1].

In Fig. 6 we show snapshots in which the cells pass through the choking point. In a straight capillary without choking, shown in Fig. 5, 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 decreases, thus stimulating the production of aggregates. In both cases the red cells were initially equally spaced in the tube, as displayed in Fig. 6a. 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 as long as that displayed in Fig. 8a, the aggregation effect can be discerned even more clearly. At small shear and in larger vessels the real blood forms long chains of RBCs. An image (see Fig. 8b) taken from the laboratory is shown as a comparison.

Fig. 8. Aggregation of RBC for free flow in the tube of diameter 25 µm. More than 2 million particles were employed. Approximate shear is 100 s⁻¹. (b) Image of real blood under much smaller shear conditions (5 s⁻¹) with a gap of 0.15 mm. This image was captured on the Linkam CSS450 using whole blood of 40% hematocrit. Figure courtesy of R. de Roeck and M.R. Mackley, Department of Chemical Engineering, University of Cambridge (available at: http://www.cheng.cam.ac.uk/~rmdr2/Nice_Pics.html).
Fig. 9. Schematics showing how damaged cells can strongly influence the blood flow. "V" represents the direction of blood flow.

At higher shear rates the chains break into smaller clusters and the viscosity of blood decreases dynamically [1,10].

We can justify the hypothesis concerning the role played by hydrodynamic and depletion forces in clustering of RBC, because RBC aggregation occurs even though there is an absence of binding forces between the cells in the model. The contribution of hydrodynamic forces to the clustering of cells is caused by the thinning of the stream composed of suspended particles. This hydrodynamical thinning can be observed for capillary flow of granules [15]. However, the granules do not form clot-like structures but rather shapeless elongated forms [14,15].

Depletion forces are excluded volume interactions arising from entropic forces. They represent the natural outcome of the discrete-particle model. The lack of fluid particles between two cells produces an attractive interaction between them due to hydrodynamic pressure. Realistic values of depletion forces depends on how large the physical size of the FPM particle can be. The forces must be of longer range in a colloidal suspension for which the fluid particles can be regarded as relatively large in comparison to colloidal beads. Therefore, we cannot model quantitatively the influence coming from the depletion forces without further experimental constraints.

We believe that the positive feedback between depletion and hydrodynamic forces influences considerably the blood clotting process. In the future this problem should be studied more carefully.

It is not surprising that the choking point in the tube decreases the flow rate and leads to the formation of cell clot close to the neck. However, for normal blood cells from Fig. 7b the clot is able to pass through this point. This is not like in Fig. 7c, where the clot made of deformed crescent-roll shaped cells stops the flow almost completely.

An other sort of critical behavior is shown in Figs. 9 and 10, representing the flow of "sickle" cells, which are characteristic of anemia. As before, we have studied the cells flowing in free and in choked capillary. For sticky, "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). Consequently this phenomenon gives rise to a numerical instability. Figure 10b depicts the situation just before onset of the numerical blowup. From Fig. 11 the viscosity of the "sickle" cell fluid is observed to be greater than that of the fluid with normal biconcave discs.

4. Conclusions

In this paper we have presented a brand-new concept for modeling blood dynamics in capillary vessels. This new approach is based on a paradigm of discrete particles. We show...
Fig. 11. The evolution of the Reynolds number for flows with “sickle” and normal cells. As shown, deoxygenated “sickle” cell blood has a higher viscosity than normal blood.

that a plasma suspension can be modeled by employing fluid particles (FPM), while elastic microstructures, such as red blood cells and larger structures such as the walls of the blood vessel, can be modeled by grids 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 blood plasma suspension can be represented 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 a depleted layer, which results in attractive depletion forces between the cells. This depleted layer hypothesis requires more detailed laboratory studies. Our results 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 that 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 modeling of microscopic multicomponent systems with a granular character. More complicated geometries of the vascular system with elastic walls can be modeled easily. However, the periodicity of the particle system imposes some severe limitations, for example in modeling bifurcating vessels. The low computa-
tional efficiency of the discrete-particle method can be par-
2 tially compensated by greater efficiency in the use of larger
3 parallel systems [16]. The CPU time for computations in-
4 volving 1–2 million particles in 10^4 timesteps is about 2 days
5 on eight processors of an SGI/Origin 3800 system.
6
7 This model is still oversimplified since it uses only two
8 components in blood. However, the discrete-particle ap-
9 proach allows the introduction of additional constituents.
10 It is possible to incorporate a parameter reflecting cell-
11 cell attraction/adhesion, which might arise from fibrinogen
12 at varying concentrations. One would need to include both
13 short-range attraction and some estimates of the tendency of
14 adhesion when two cells squeezing together make a con-
15 tact and sandwich in the fibrinogen. This may be important
16 under normal conditions because the blood fibrinogen level
17 is a high risk factor for inducing large vessel disease. Fur-
18 thermore, there is some possibility that enhanced red cell-
19 fibrinogen binding may be present in “sickle” cell disease.
20 One interesting abnormality of “sickle” cells is a nonuniform
21 negative charge on the surface. One can separately incorpo-
22 rate a parameter, that reflects a lack of charge repulsion, aris-
23 ing from the patchy surface charge.

24 A potential problem is the difficulty in mapping macro-
25 scopic blood properties such as elasticity of the cells into
26 particle interactions. Moreover, more sophisticated proper-
27 ties of red blood cells cannot be reproduced by the model
28 involving a mesh of particles-on-springs. The realistic struc-
29 ture of the RBC membrane, which is composed of a lipid
30 bilayer supported by a scaffolding of cytoskeletal proteins,
31 maintains its local area nearly unchanged [6]. This type of
32 dynamics does not hold for the particles-on-spring model in
33 highly deformed cells. Microscopic chains of chemical re-
34 actions leading, for example, to creation of permanent clots
35 tied by fibrinogen requires more detailed multilevel micro-
36 scopic models involving the implementation of molecular
37 dynamics. There are also serious numerical problems, which
38 may lead to artifacts. For example, the periodic boundary
39 conditions employed in our model can produce stationary
40 waves generating spurious clustering of cells. This draw-
41 back can be partially eliminated by modeling larger systems,
42 i.e., longer blood pipes. However, this will involve still more
43 computational time.

44 Despite these limitations, our present model can still be
45 regarded as an interesting step forward for modeling micro-
46 scopic vascular system. We believe that it may open up new
47 avenues for modeling other problems in blood dynamics in
48 capillary vessels. In Fig. 12 we show potential future appli-
49 cations of the discrete-particle approach. For example, the
50 curvatures and bifurcations of large and medium-sized arter-
51 ies are severely influenced by atherosclerosis. Numerous in-
52 vestigations performed for macroscopic blood vessels [7,23]
53 point to a relationship between the genesis and the progres-
54 sion of the disease with the locally irregular flow field occur-
55 ring in these peculiar zones. We believe that this effect may
56 even be emphasized in capillary vessels in which the mass
57 distribution is not continuous and the shear rate is very high.

Even small wall shear stress can locally disturb mass trans-
8 fer, which is influenced by viscoelastic interactions between
9 RBC and vessel walls and by enhanced particle residence
10 time in flow separation and flow recirculation zones. Other
11 problems involving surface tension, such as droplet break-
12 up and coalescence and the dynamics of capillary pinching
13 of a fluid thread [24,25], can be also modeled efficiently us-
14 ing fluid particles [26,27]. Therefore, our discrete-particle
15 model can open new venues for attacking successfully many
16 scenarios in complex blood dynamics not possible with the
17 classical continuum approach.

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Appendix. Glossary of terms in blood flow (from
26 http://www.academicpress.com/insight/099091997/
27 endothe1.htm)

Term          Definition

Capillary vessels The vessels of diameter from 4 to 10 μm
Endothelial cell A type of squamous epithelium cell that lines the
Endothelium The layer of squamous epithelium that lines the
Fibrin Fibrin is the product of an activated coagulation sys-
Globulin Family of proteins from plasma or serum of blood
Hematocrit Ratio of red blood cells volume/blood volume (in %)
Neutrophils A large leukocyte, containing a lobed nucleus and
Platelet A cytoplasmic fragment that occurs in the blood
Prothrombin A plasma protein that is converted to the active form
Rouleaux Red blood cells appear stuck together like stacks of
Thrombosis Thrombosis refers to the formation of a thrombus
Thrombus A thrombus is an aggregate of a network of fibrin,
References