Three-dimensional numerical simulation of the deformation and the aggregation of human red blood cells

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Abstract

To investigate the deformation and aggregation of the RBCs numerically, mathematical model was established by coupling the interaction between the fluid and the deformable solids. The model includes: 1) A three-dimensional Finite Volume Method solver (CgLes) for incompressible viscous fluid; 2) The combined finite-discrete element method for compute deformation of the RBCs; 3) A JRK model to take account of the adhesion force between different RBCs; and 4) An iterative direct-forcing immersed boundary method to couple the fluid-solid interactions. The computational model was fully verified against published experimental data and the results show good agreement between experimental and simulation results on both the deformation and the adhesion of the RBCs. After verifications of our model, large scale simulations with 49,512 RBCs in a shear flow (with Haematocrit of 45\%) were carried out on High Performance Computers. Simulation results were compared with experimental results and the agreement is favourable. Both the experiment and the simulation show uniform distribution of the RBCs under high shear rate (100/s) and large aggregation structures under low shear rate (10/s).

Keywords: Numerical simulation, red blood cell, aggregation, deformation

1. Introduction

Red blood cells (RBCs, also referred to as erythrocytes) are the most common type of blood cell of human being, occupying about 45\% of the total blood volume for man and 40\% for women. The human RBCs in healthy state are biconcave-shaped disks with a diameter of 6-8\mu m and a thickness of about 2\mu m. The cell membrane is highly deformable to enable RBCs to pass through capillaries and release oxygen\cite{1}. The high deformability of RBCs also leads to the complex rheological behavior of blood flow. Another interesting phenomenon of RBCs is the aggregation under low shear rate, which may alter blood flow property and is meaningful for diagnosis of many diseases. The deformability of RBCs and their tendency to aggregate at low shear rates, forming coin like structures, larger aggregates and networks, affect significantly blood flow and rheology\cite{2-4}; at low shearing flows blood shows viscoelastic and non-Newtonian behaviour. This is more pronounced in the microcirculatory system, comprising the smallest blood vessels (capillaries, arterioles and venules) some with diameters comparable, and even smaller, to the size of the suspended RBCs.

Quantitative understanding of the transport, interaction (including aggregation) and deformation of RBCs is necessary for hematological researches, and may eventually lead to many medial applications, like designing to better stent. However, the numerical simulation of the movement of individual blood cells in either a laminar or turbulent fluid flow is particularly difficult because it not only involves the correct modelling of the fluid flow but also the movement of the cells themselves which, in turn, requires the correct modelling of their dynamics, surface stresses and their surface deformations in response to these stresses.
Interaction of RBCs, including their collision, shielding and aggregation, makes the simulation even more challenging [5-7].

In this research, fluid-solid coupled numerical simulation was carried out for large number of RBCs in shear flow to investigate its mechanism for transport, interaction and aggregation. The mathematical model for the simulations includes a finite-volume based fluid solver for incompressible viscous flow and the combined finite-discrete element method for the interaction and deformation of solid. The immersed boundary method is used to provide a deforming boundary for the fluid and to apply forces to boundary nodes of the solid. The coupled solver is fully parallelized based on spatial decomposition to make large scale simulations possible.

2. Methodology

2.1. Fluid simulation and immersed boundary method

To simulate flow with moving boundaries, we adopt the in-house Computational Fluid Dynamics (CFD) C code called CgLes[8] and a direct forcing algorithm for immersed boundary method[9-10]. CgLes is a highly parallelised three-dimensional fluid solver with second order accuracy in both time and space and the projection method is used to decouple flow velocities and pressure. The Navier-Stokes equations for an incompressible fluid read:

\[
\frac{\partial u}{\partial t} + (u \cdot \nabla)u + \nabla p + \nabla \cdot \nabla u + \nu \nabla^2 u = f
\]

\[
\nabla \cdot u = 0
\]

where \(u\) is the vector of fluid velocities, \(p\) is the pressure normalized with the fluid density and \(f\) is a volume force term. For immersed boundary methods, the force term \(f\) is formulated in such a way as to represent the action of the solid upon the fluid. To demonstrate the application of immersed boundary method, the time-discretized momentum equation is written in the following form:

\[
\frac{u^{n+1} - u^n}{\Delta t} = \text{rhs}^{n+1\over 2} + f^{n+1\over 2}
\]

where \(\text{rhs}^{n+1\over 2}\) regroups the convective, pressure and viscous terms at some intermediate time level between \(t^n\) and \(t^{n+1}\). The force term which yields the desired velocity \(u^{(d)}\) is then expressed as:

\[
f^{n+1\over 2} = \frac{u^{(d)} - u^n}{\Delta t} - \text{rhs}^{n+1\over 2}
\]

The fluid force acting on the boundary nodes, \(f_{solid}^{n}\), is obtained by interpolation from the body forces on immersed boundary points, which are distributed on the surface of the solid:

\[
f_{solid}^{n}(x_{solid}, t) = \int_{s} f(x, t) \delta(x - x_{solid}(x_{solid}, t)) dS
\]

where \(\delta\) is the Dirac delta function.

After solving the solid deformation with the combined finite-discrete element method, the desired velocity of the immersed boundary points, \(U_{IBM}^{n}\), is then updated based on the velocity of boundary nodes on solid surface, also by interpolation:
2.2. Modelling deformations and interactions of red blood cells

To simulate the deformation of solids under the force action of fluid, the combined finite-discrete element method was applied [11]. RBCs are treated as hyperelastic solids, meshed with tetrahedron elements. Because red blood cell is usually considered as hyperelastic material, it can be modelled as Mooney–Rivlin solid. The strain energy density function for an incompressible Mooney–Rivlin material is:

\[
W = C_1(\overline{I}_1 - 3) + C_2(\overline{I}_2 - 3),
\]

where \(C_1\) and \(C_2\) are empirically determined material constants, and \(\overline{I}_1\) and \(\overline{I}_2\) are the first and the second invariant of the unimodular component of the left Cauchy–Green deformation tensor.

Human red blood cells are usually adhesive, which is significant for the formation of RBC aggregations. The adhesion of solid elastic bodies has been extensively studied in the past, and a complete mathematical description has been derived, such as the JKR model (Johnson, Kendall, Roberts, 1964-1971) and the DMT model (Derjagin, Muller, Toropov, 1975). The JKR applies to tips with large curvature radius and small stiffness and proven to be applicable to living cells [13]. The model accounts for the influence of Van der Waals forces within the contact zone. JKR model was adopted in the simulation of RBCs in present study.

2.3. Parallelization of the couple computational model

To simulate macro scale behaviours of red blood cells, like the formation and development of aggregations structures, there should be sufficient quantity of red blood cells involved during simulation. To make simulation of a large quantity of red blood cells possible, e.g. thousands of RBCs, parallelization and optimization of the program is necessary to take advantage of high performance computing facilities. The fluid code CgLes is originally fully parallelized during program designing. The parallelization is based on spatial decomposition by splitting the entire computational domain into blocks. However, the original DEM code is serial. Therefore, we hereby focus on the parallelization and optimization of the DEM code for the solid.

Spatial decomposition was adopted for the parallelization of the DEM code. The decomposition of the entire computational domain shares the same block division with the fluid. The advantage of this scheme is that the fluid block and the solid block for the same physical space are always installed on the same processor. Therefore, no remote data transfer between the fluid and the solid required. Besides, no global data operation is required and all datasets are only running on local processor. The computation is fully scalable in the spatial domain, which makes simulation with very large scales (running on hundreds of cores) possible. Message Passing Interface (MPI) is used for implementation of parallelization in the code.

3. Computational configuration

To investigate the formation and development of RBC aggregations, large scale simulations were carried out with a huge number of RBCs involved. The simulations were setup with same configuration as the experiments by Kaliviotis and Yianneskis [12], in this way, the simulation results can be compared and verified against experimental results. The experiment consisted of two glass plates separated by a gap \(h=0.03\)mm. The lower plate was driven by a stepper motor to shear the blood in the \(z\) direction with a nominal shear rate \(\gamma\) that was controlled by the lower plate rotational velocity \(\omega\). The centre of the viewing window was located at a radius \(R=7.5\)mm from the plate axis of rotation.

The physical domain of experiment is a cylinder with a radius of 9.0mm and a height of 0.03mm, giving a volume of 7.63 mm\(^3\). Nondimensionalized by an average RBC diameter \(D=8\)µm, the domain radius becomes 1125 and the height is 3.75, see Fig.1. The volume is 1.491x10\(^7\). According to packing test of 4,800 RBCs, the nondimensional packing volume of each RBC is 0.3296. Therefore, the total number of RBCs involved in the experiment is 20.44 x10\(^7\) (for haematocrit of 45%). It is almost impossible to simulate the
same number of RBCs with modern computers, even with the most powerful supercomputers nowadays. In fact, it is not necessary to include all of those RBCs during simulation. The computational domain can be deemed large enough as long as the largest structure (aggregation network) is not suppressed by the boundary conditions. The computational domain adopted in our simulations is a simple box with dimensions of 120 (streamwise) x 80 (spanwise) x 3.75 (height) located at the position the same as the view window in experiment. The domain was demonstrated to be sufficient large by a fast descending spatial correlation curve of simulation results. The volume of the computational domain is $3.6 \times 10^4$ and the total number of RBCs contained inside is 49,150.

For parallelization, the computational domain is divided into 8x12=96 blocks during simulation. For simplification, 512 RBCs was assigned to each block, leading to a total RBC number of 49,512. Considering the computational domain is very small compared to the experimental domain and the view window is far away from the center of the rotation, the flow in the computational domain was simplified into a simple shear flow. The bottom plate was set as a stationary nonslip wall boundary, and the top plate was set a nonslip wall moving at velocity the same as the linear velocity of the center point on the top plate. Periodic boundaries were adopted in both streamwise and spanwise directions.

During simulations, all variables are made nondimensional using a Length scale $L$ based on a normal RBC diameter 8.0µm, a density scale $\rho$ based on a density of 1000 kg/m$^3$, and a velocity scale $U$ base on the shearing velocity at the center of the top plate at shear rate 1/s, which is 0.03 mm/s. See Table 1(a) and 1(b) for other parameters used in simulation.

<table>
<thead>
<tr>
<th>Name</th>
<th>Plasma density</th>
<th>Plasma kinetic viscosity</th>
<th>Shear velocity</th>
<th>Reynolds number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimensional</td>
<td>1025 kg/m$^3$</td>
<td>1.46 m$^2$/s</td>
<td>0.03-3.0 mm/s</td>
<td>6.16x10$^{-4}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.16x10$^{-2}$</td>
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<table>
<thead>
<tr>
<th>Name</th>
<th>RBC diameter</th>
<th>RBC density</th>
<th>RBC membrane shear modulus</th>
<th>Gravity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimensional</td>
<td>8.0 µm</td>
<td>1125 kg/m$^3$</td>
<td>6.0x10$^{-5}$ N/s</td>
<td>9.81 m/s$^2$</td>
</tr>
</tbody>
</table>

4. Results and discussions

The simulation under shear rate as high as 100/s show no severe aggregations of the RBCs. Red blood
cells tend to move independently under the entrainment by the flow and uniformly distributed in space, see Fig. 2(a). However, when shear rate decreases from 100/s to 10/s, significant aggregations form, see Fig. 2(b). RBCs aggregate face-to-face to form coin stack like structures, which are called rouleaux.

The formation of rouleaux can be interpreted by the unique discoid shape of the cells. The flat surface of the discoid RBCs give them a large surface area to make contact and stick to each other; thus, forming a rouleau. They occur when the plasma protein concentration is high, and because of them the ESR (erythrocyte sedimentation rate) is also increased. This is a non-specific indicator of the presence of disease.

See Fig. 3 for a comparison of an overall view of the RBC aggregation structure in the experimental and the simulation. The comparisons show apparent similarities of aggregation structure between the experiment and the simulation. Under high shear rate (shear rate=100/s), both the experiment and the simulation show no aggregation of RBCs. To certain extend, the distribution of gaps among RBCs looks different from the experiment to the simulations on the aspect of gaps size and shape. This is partly caused by the method how the images are prepared. For experiment, PIV (particle image velocimetry) technique was used. The view windows was illuminated by letting a laser sheet parallel with the top plate penetrate through the middle of the domain. The image was taken with a CCD camera above the view window. Because the scattering effect of laser light, the laser sheet showed a thickness of 3.5µm with grayscale varying in depth, see Fig. 3(a) and Fig. 3(c). However, as for simulation results, the cut in the middle of the thickness direction are quite clear without any blurring in depth. Let us say the experiment used a soft cut but the simulation used a sharp cut to obtain the image. Besides, the existence of platelets, white cells, and large molecular proteins during experiment also has influence on the image and make it different from the simulation. Even with these influences, the simulate shows quite uniformly distributed gaps and independent RBCs under high shear rate, which agrees well with experimental result. The similarity between the experimental and the simulation results is more obvious for the results under low shear rate (10/s) when severe aggregations occurs, see Fig. 3(c,d). From the overall view, both the results show large aggregation structures of the RBCs. For human blood with haematocrit as high as 45%, this kind of aggregation was widely reported in clinical experiments.

Fig.3. Comparison between experimental and simulation results. a. Experiment at shear rate 100/s; b. Simulation at shear rate 100/s; c. Experiment at shear rate 10/s; d. Simulation at shear rate 10/s; fluid flows from the left to the right; the view window for the experiment has a size of 180µm x 135µm and for the simulation, it is 367 µm x 275µm
5. Conclusion

Three-dimensional computational model was established to simulate the deformation and aggregation of the RBCs numerically. The mathematical model was established by coupling the interaction between the fluid and the deformable solids using continuum mechanics. Deformation and aggregation of individual RBCs up to a number of 49,512 was simulated. Simulation results were compared with experimental data, which show good agreement.

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References