A review of numerical methods for red blood cell flow simulation

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A review of numerical methods for red blood cell flow simulation

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In this review, we provide an overview of the simulation techniques employed for modelling the flow of red blood cells (RBCs) in blood plasma. The scope of this review omits the fluid modelling aspect while focusing on other key components in the RBC–plasma model such as (1) describing the RBC deformation with shell-based and spring-based RBC models, (2) constitutive models for RBC aggregation based on bridging theory and depletion theory and (3) additional strategies required for completing the RBC–plasma flow model. These include topics such as modelling fluid–structure interaction with the immersed boundary method and boundary integral method, and updating the variations in multiphase fluid property through the employment of index field methods. Lastly, we summarily discuss the current state and aims of RBC modelling and suggest some research directions for the further development of this field of modelling.

Keywords: RBC aggregation modelling; RBC deformation modelling; haemodynamics; blood rheology

Introduction

Red blood cells (RBCs) are the most important component of blood for its biological functions and its direct effect on haemodynamics. The major function of RBCs is to deliver oxygen, and this gas exchange process occurs mainly in the microvascular network of arterioles, venules and capillaries. It has recently been demonstrated that RBCs can also synthesise nitric oxide (NO) enzymatically just as endothelial cells do. Exposure of RBCs to physiological levels of shear stress activates the NO synthases and the export of NO from the RBCs into the blood vessel, which may contribute to the regulation of vascular tonus (Ulker et al. 2009).

RBCs in the human circulatory system constitute around 35–50% of the blood volume and are highly deformable partly due to their circular biconcave shapes. Geometrically, undeformed RBCs are 6–8 μm in diameter on their circular discoid plane and 2 μm in average thickness on the biconcave radial plane. They have an average volume of 90 fL and a surface area of about 136 μm² (Mchedlishvili and Maeda 2001; Popel and Johnson 2005). As a result of their major constituency in blood, RBCs affect the blood flow through their viscoelastic rheological properties (Maeda 1996) and by their volume fraction. Furthermore, the features of blood flow and the importance of RBC to RBC interactions in describing overall blood flow may also vary greatly with the vessel diameter. In vessels with diameters larger than 200 μm, the size effect of the RBCs in relation to the vessel diameter can be neglected. In these larger vessels, blood can be modelled as a homogeneous non-Newtonian fluid using a continuum description (Popel and Johnson 2005). However, in vessels with smaller diameters, such as arterioles, venules and capillaries, the size of the RBCs is comparable to the vessel’s internal diameter and a two-phase description of blood as a suspension of RBCs in plasma becomes substantial. Therefore, the detailed quantitative understanding of blood flow in microcirculation requires explicit modelling of RBCs. Such explicit RBC modelling for microcirculation is necessary for describing many physiological processes such as the haemodynamic resistance and its regulation in the microcirculation, transport of oxygen and nutrients, and the body’s immunological and inflammatory responses.

A vital parameter for simulating RBC flow in microcirculation is the mechanostructural characteristics of the RBC. Over the past decades, many researchers have attempted to describe the micromechanics of RBCs, and their studies have generated several mathematical and numerical models. These models are constructed with various degrees of physical relevance, idealisation and sophistication with regard to the cell constitution, geometrical configuration and membrane properties (Pozrikidis 2003). Some of these models utilise a continuum description (Evans and Skalak 1980; Fung 1993; Pozrikidis 2001), whereas others employ discrete RBC representations at the spectrin molecular level (Discher et al. 1998; Li et al. 2005) or at the mesoscopic scale (Dzwinge et al. 2003; Noguchi and Gompper 2005; Tsubota et al. 2006; Dupin et al. 2007; Pivkin and Karniadakis 2008).

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In addition to the structural properties of RBCs affecting blood flow in the microcirculation, RBC aggregation also plays a key role in many important biological processes. In human blood (and many other mammalian species likewise), RBCs aggregate at low shear rates, forming linear or fractal-like structures called ‘rouleaux’ (Baumler et al. 1999; Stoltz et al. 1999; Popel and Johnson 2005). Many previous studies have revealed that the aggregation of blood is influenced by parameters such as the shear rate, haematocrit and the concentration of macromolecules in the plasma or suspending medium (Ben Ami et al. 2001; Rampling et al. 2004). From a pathophysiological understanding, an altered state of RBC aggregation is commonly observed in patients with peripheral vascular disease, where, for instance, elevated aggregation levels are often associated with a higher risk of cardiovascular disease. Elevated RBC aggregation levels also occur after myocardial infarction, ischaemic brain infarcts, in diabetes, and during sepsis. Furthermore, the RBC aggregation tendency can be affected by the cell’s deformability which itself can vary in both physiological and pathological states. The RBC deformability varies between the younger and older RBCs under physiological conditions and can be significantly changed under pathological conditions such as parasitic infection, sepsis, diabetes and genetic defects in the RBCs. In consideration of the aforementioned observations and points, it is clear that understanding the mechanics of RBC aggregation may lead to a more complete understanding of cardiovascular diseases and the pathology of blood.

Apart from the pathophysiological sensitivities of the RBC aggregation phenomenon, the general haemodynamic relevance of RBC aggregation to microcirculatory blood flow is that it leads to an increased blood viscosity, and hence an elevated resistance to blood flow. Although the physiological and pathological importance of RBC aggregation has been realised and extensive experimental investigations have been carried out (Chien et al. 1977; Baumler et al. 1999; Kounov and Petrov 1999; Stoltz et al. 1999; Popel and Johnson 2005; Kim et al. 2006), the underlying mechanisms of the RBC aggregation are still subjects of investigation. The RBC aggregation in blood flow is initiated when the cells are drawn close together by the hydrodynamic forces governing the flow of plasma. If the shearing forces by the fluid motion are small, the cells tend to adhere to one another and form aggregates. Presently, there exist two theories that describe the mechanism of aggregation: bridging between cells by cross-linking molecules (Chien and Jan 1973), and the balance of osmotic forces generated by the depletion of molecules in the intercellular space (Neu and Meiselman 2002).

In the bridging model, RBC aggregation is proposed to occur when the bridging forces due to the adsorption of macromolecules onto adjacent cell surfaces exceed disaggregation forces due to electrostatic repulsion, membrane strain and mechanical shearing (Brooks 1973; Chien and Jan 1973). The depletion model, however, proposes that RBC cell aggregation occurs as a result of lower localised protein or polymer concentrations near the cell surface as compared to the suspending medium (i.e. relative depletion near the cell surface). This exclusion of macromolecules near the cell surface produces an osmotic gradient and thus a depletion interaction (Baumler et al. 1996). Both the bridging and the depletion models have specific limitations but are generally very useful models for describing aggregation phenomena (Armstrong et al. 1999; Baumler et al. 1999). In general, both models assume that the attractive interaction between RBC surfaces occurs when the surfaces are within a close enough range and repulsive interaction occurs when the separation distance becomes sufficiently small. The repulsive interaction represents the steric forces due to the glyocalyx and electrostatic repulsion from the negative charges on the pairing RBC surfaces (Liu et al. 2004).

In this study, we have summarised the methods for the simulation of blood flow in microcirculation. It consists of three parts: (a) methods for RBC modelling, (b) methods for aggregation of RBCs and (c) other supplementary methods required for simulating RBC flow. We hope that this review proves helpful for researchers who intend to embark on the numerical analysis of RBC and blood flow in microcirculation.

RBC deformation model

Shell-based membrane models

One of the representative models based on a continuum description of the RBC is the model developed by Pozrikidis (2001). In his approach, the membrane of an RBC is represented by a highly deformable two-dimensional (2D) shell without thickness. During deformation and membrane displacement, the velocity across the RBC membrane is continuous thereby satisfying the no-slip condition. However, there exists a jump in the interfacial tension \( \Delta F \) across the membrane which is presented in the form:

\[
\Delta F = \Delta F^{\text{m}} n + \Delta F^{\text{p}} q = -\frac{d\tilde{F}}{dt} = -\frac{d}{dt}(\tilde{n} + q\tilde{n}),
\]

where \( \tilde{T} \) is the membrane tension. The membrane tension can be decomposed into the in-plane tension \( \tau \) and transverse shear tension \( q \) as shown in Figure 1, where \( \tilde{n} \) and \( \tilde{q} \) are unit vectors taken in the directions normal and tangential to the membrane surface, respectively.

Pozrikidis’s formulation can be used in conjunction with any constitutive law or laws that describe the in-plane tension \( \tau \) and transverse shear tension \( q \). Accordingly, these various constitutive laws are employed to satisfy the
different requirements of the studied physical phenomenon. In the case of in-plane tension \( \tau \), the neo-Hookean model is the most widely utilised membrane constitutive law because of its simplicity (Bagchi et al. 2005; Bagchi 2007; Zhang et al. 2007, 2008, 2009). Despite being a simple model, it is however sufficient for taking deformability into account (Barthes-Biesel et al. 2002).

In this model, the constitutive law is expressed by the strain energy function (Ramanujan and Pozrikidis 1998) as follows:

\[
W = \frac{1}{2} E_5 \left[ I_1 - \log(I_2 + 1) + \frac{1}{2} \log^2(I_2 + 1) \right],
\]

where \( E_5 \) is the shear elastic modulus of the RBC membrane and \( I_1 \) and \( I_2 \) are the first and second invariants, given by the relations \( I_1 = \lambda_1^2 + \lambda_2^2 - 2 \) and \( I_2 = (\lambda_1 \lambda_2)^2 - 1 \). Terms \( \lambda_1 \) and \( \lambda_2 \) are the principal strains. Equation (2) can also be expressed in terms of principal stretch ratios \( \varepsilon_1 \) and \( \varepsilon_2 \) as follows:

\[
W = E_5(\varepsilon_1^2 + \varepsilon_2^2 + \varepsilon_1^{-2} + \varepsilon_2^{-2}).
\]

Tensions \( \tau_1 \) and \( \tau_2 \) in the principal directions are given by (Barthes-Biesel et al. 2002)

\[
\tau_1 = \frac{E_5}{\varepsilon_1 \varepsilon_2} \left\{ \varepsilon_1^2 - \frac{1}{(\varepsilon_1 \varepsilon_2)^2} \right\}
\]

and

\[
\tau_2 = \frac{E_5}{\varepsilon_1 \varepsilon_2} \left\{ \varepsilon_2^2 - \frac{1}{(\varepsilon_1 \varepsilon_2)^2} \right\}.
\]

For a 2D simulation, the 2D RBC is the equivalent of a three-dimensional (3D) cell subject to stretching in one direction. This leads to the reduction in stress terms: \( \tau_1 \neq 0 \), \( \tau_2 = 0 \) where the subscript ‘1’ indicates the in-plane direction along the membrane and ‘2’ indicates the out-of-plane direction. The deformation \( \varepsilon_2 \) in the out-of-plane direction is not zero but can be expressed in terms of \( \varepsilon_1 \) through equation (5) since \( \tau_2 = 0 \). Consequently, the formulation for a 2D cell model is given by

\[
\tau = \frac{E_5}{\varepsilon_1^2}(\varepsilon_1^2 - 1),
\]

where \( \tau = \tau_1 \) and \( \varepsilon = \varepsilon_1 \).

In addition to elastic deformation, the RBC membrane has been observed to demonstrate area incompressibility in experiments (Hochmuth and Mohandas 1972). The membrane incompressibility can be represented by employing the modulus of area dilatation. The contribution of the modulus of area dilatation can be achieved through two general approaches. The first approach includes the area dilatation term in the strain energy function as proposed by Evans and Skalak (1980). However, Eggleton and Popel (1998) have reported that the Evans–Skalak model requires a large modulus of area dilatation to achieve membrane incompressibility and this resulted in numerical instability. The second approach includes the area dilatation term directly in the stress calculation as demonstrated by Pozrikidis (2003).

As mentioned earlier, Pozrikidis’s approach requires explicit modelling of the two principal tensions. In addition to a constitutive model for the in-plane tension \( \tau \) (Equations (2)–(6)), a constitutive model is required for the transverse shear tension \( q \). The transverse tension is expressed in terms of bending moment \( m \):

\[
q = \frac{dm}{dl} = \frac{d}{dl}[E_B(\kappa(l) - \kappa_0(l))].
\]

where \( E_B \) is the bending modulus, \( \kappa(l) \) the instantaneous membrane curvature and \( \kappa_0(l) \) is the position-dependent mean curvature of the resting shape. An alternate model for predicting the bending resistance is presented by Helfrich’s formulation (Zhongcan and Helfrich 1989) which is as follows:

\[
\Delta F_{\text{bending}} = [E_B(2\kappa + c_0)(2\kappa^2 - 2\kappa_0\kappa) + 2E_B\Delta_{LB}\kappa]\bar{n},
\]

where \( \kappa \) is the mean curvature, \( \kappa_0 \) the Gaussian curvature, \( c_0 \) the spontaneous curvature and \( \Delta_{LB} \) is the Laplace–Beltrami operator.

**Spring-based membrane models**

Apart from the shell-based models employed by Pozrikidis, the spring-based membrane network model has been developed by various researchers. An example of a 3D implementation of the spring network approach is the worm-like chain (WLC) model. In this method, the RBC membrane is discretised by a set of vertex points \( \{\bar{x}_i\} \) to form a 2D triangulated network as shown in Figure 2. The deformation of the membrane is governed by the potential energy of the system which is defined as follows:

\[
V(\{\bar{x}_i\}) = V_{\text{in-plane}} + V_{\text{bending}} + V_{\text{area}} + V_{\text{volume}}.
\]

The in-plane elastic energy \( V_{\text{in-plane}} \) represents the energy from the elastic deformations of the spectrin network. It is
given by

\[ V_{\text{in-plane}} = \sum_j \frac{k_B T l_m (3x_j^2 - 2x_j^3)}{4p(1 - x_j)} + \sum_{\alpha} \frac{C}{A_{\alpha}}, \]

where \( l_j \) is the length of the spring \( j \), \( l_m \) the maximum spring extension, \( x_j \) the spring length ratio given by \( x_j = l_j/l_m \), \( p \) the persistence length, \( k_B T \) the energy unit, \( C \) a constant and \( A_{\alpha} \) is the area of a given element triangulated from the spring network. The first summation term is the attractive WLC potential for individual links. The second summation term is the elastic energy stored in the RBC membrane (Li et al. 2005), and it represents a repulsive potential that balances the WLC term to achieve a non-zero equilibrium spring length for the RBC membrane at a relaxed state (Fedosov et al. 2010). The bending energy \( V_{\text{bending}} \) represents the bending resistance of the lipid bilayer and is defined as follows:

\[ V_{\text{bending}} = \sum_j k_b [1 - \cos(\theta_j - \theta_0)], \]

where \( k_b \) is the bending constant, \( \theta_j \) the instantaneous angle between two adjacent triangles sharing the common edge \( j \) and \( \theta_0 \) is the spontaneous angle. The area and volume conservation constraints are represented through the third and fourth potentials \( V_{\text{area}} \) and \( V_{\text{volume}} \). They account for area incompressibility of the lipid bilayer and incompressibility of the inner cytosol, respectively. Their constitutive relations are expressed as follows:

\[ V_{\text{area}} = \frac{k_a (A - A_{\text{tot}}^0)^2}{2A_{\text{tot}}^0} + \sum_j \frac{k_d (A_j - A_0)^2}{2A_0}, \]

\[ V_{\text{volume}} = \frac{k_v (V - V_{\text{tot}}^0)^2}{2V_{\text{tot}}^0}, \]

where \( k_a, k_d \) and \( k_v \) are the global area, local area and volume constraint coefficients, respectively. Terms \( A \) and \( V \) are the total area and volume of RBC, respectively, whereas terms \( A_{\text{tot}}^0 \) and \( V_{\text{tot}}^0 \) are the specified total area and volume, respectively. Detailed description of the RBC model can be found in Fedosov (2010).

This approach originated from Marko and Siggia (1995) where a simple interpolating model was applied between ideal chain behaviour at very small chain extension and divergent-tension behaviour at large extension. Discher et al. (1998) adopted this model in their 3D RBC micropipette aspiration simulation and Li et al. (2005) utilised this model in their optical tweezers RBC stretching simulation. This method has also been adopted for the RBC membrane model in the dissipative particle dynamics (DPD) simulations by Pivkin and Karniadakis (2008) and Fedosov (2010). The WLC spring model is general enough and can be used together with other simulation methods, such as the lattice Boltzmann and immersed boundary method (IBM).

A different spring-based constitutive model has also been developed by Secomb et al. (2007) where the RBC and its mechanical behaviour are represented by a collection of spring and damper interconnections between nodes on a 2D RBC. The nodes are located along the perimeter of the RBC, with an additional internal node located in the centre of the cell as shown in Figure 3. The outer line segments (external elements) connecting the perimeter nodes to their adjacent nodes are viscoelastic, and are employed to model the RBC membrane’s shear elasticity, bending elasticity and in-plane viscosity. The interior line segments (internal elements) of the cell connecting the perimeter nodes to the internal node are viscous and are employed to represent the viscous resistance of the inner cytosol.
resistance to both cytoplasmic flow and out-of-plane membrane deformation. The perimeter nodes have coordinates given by \( \bar{x}_i = (x_i, y_i) \) with \( i = 1 \to n \), where \( n \) is the number of perimeter nodes used to discretise the RBC membrane boundary. The interior node coordinates are given as \( \bar{z}_0 = (x_0, y_0) \). Correspondingly, line elements are spatially described by their two end-nodes. Quantities associated with an external element are denoted by \( i \) whereby the end-nodes are given as \( (x_i, y_i) \) and \( (x_{i+1}, y_{i+1}) \). Internal elements are described by their end-nodes \( (x_0, y_0) \) and \( (x_i, y_i) \). Equations (14)–(16) present the average tension in an external element, the bending moment acting on an external node and the average tension in an internal element, respectively, which are as follows:

\[
\bar{t}_i = k_i \left( \frac{l_i}{l_0} - 1 \right) + \mu_{\text{m}} \frac{1}{l_i} \frac{dl_i}{df},
\]

\[
m_i = -\frac{k_{\text{b}} \alpha_i}{l_0},
\]

\[
T_i = \mu_{\text{m}} \frac{1}{L_i} \frac{dL_i}{df}.
\]

In the formulation, \( l_i \) is defined to be the length of the \( i \)th external element, \( l_0 \) a reference length, \( k_i \) the elastic modulus, \( \mu_{\text{m}} \) the viscosity of the external elements, \( k_{\text{b}} \) the bending modulus at the perimeter nodes, \( \alpha_i \) the angle between two adjacent external elements, \( L_i \) the length of the \( i \)th internal element and \( \mu_{\text{m}} \) the viscosity of the internal element. The cell interior is assumed to exert a uniform pressure on the membrane in order to restrict the variation of the enclosed cell area as follows:

\[
p_{\text{int}} = k_p (1 - A/A_{\text{ref}}),
\]

where \( A \) is the area of the cell cross section, \( A_{\text{ref}} \) the reference area in the undeformed state or initialised area at the start of the simulation and \( k_p \) is a modelled constant. The value of \( k_p \) should scale appropriately with other forces in order to retain an approximately constant cell area.

In Secomb’s model, the employment of a 2D approach greatly reduced the computational difficulty of the problem. The inclusion of internal viscous elements provides an approximate representation of 3D aspects of cell deformation. Predicted RBC shapes match surprisingly well with the observed shapes despite the limitations of a 2D model. However, this model is expected to be less effective in many practical flow situations where 3D kinematics cannot be overlooked.

Separately, another 2D elastic spring model has been developed by Tsubota et al. (2006a, 2006b) to describe the deformable behaviour of the RBCs. Similarly in this model, the RBC membrane is represented as a series of spring interconnections between adjacent membrane nodes. However, unlike the Secomb model, the viscoelastic property of the RBC interior (cytoplasm) is not described in the RBC model. This is because the cytoplasm is discretised as part of the fluid domain and it is solved by the moving particle semi-implicit fluid solver.

**Membrane viscoelasticity and thermal fluctuation**

The RBC membrane exhibits viscoelastic behaviour during deformation and it can affect the RBC flow dynamics (Mohandas et al. 1980). Puig-De-Morales-Marinkovic et al. (2007) investigated the RBC deformation under oscillatory excitation using optical magnetic twisting cytometry and concluded that elastic stresses dominate at low frequency. Conversely, the viscoelastic behaviour of the RBC membrane becomes apparent at high frequency (>30 Hz). Examples of viscoelasticity implementation for the membrane model can be found in the works presented by Dao et al. (2006), Secomb et al. (2007) and Fedosov et al. (2010).

Apart from viscoelasticity, recent developments by various researchers have also included membrane thermal fluctuations in their numerical models (Noguchi and Gompper 2005; Fedosov et al. 2010). The flickering of the RBC membrane at rest state has been observed by Browicz (1890) and it has been suggested to be a result of Brownian motion or thermal agitation by Parpart and Hoffman (1956). Subsequently, the flickering phenomenon has been referred to as thermal fluctuation (Brochard and Lennon 1975). Recent experiments conducted by Strey and
Peterson (1995) and Popescu et al. (2007) quantified the membrane thermal fluctuation by using phase contrast microscopy and diffraction phase microscopy, respectively. In correspondence to the experiments, results from Noguchi and Gompper (2005) and Fedosov et al. (2010) indicate that the membrane thermal fluctuation can alter the RBC deformation.

**Other RBC models**

Alternatively, other models that describe RBC mechanical behaviour exist and do not fall under the classification of either shell-based or spring-based RBC membrane models. Svetina and Ziherl (2008) used area-difference-elasticity theory to describe the deformation of RBCs. Although it does not explicitly include the shear elasticity of the erythrocyte cytoskeleton, this approach describes the main features of large-scale cell deformations rather well (Ziherl and Svetina 2005). Separately, MacMeccan et al. (2009) have employed the linear finite element method (FEM) to describe the deformation of RBCs. In their model, they simulated several hundreds of 3D RBCs in high volume fraction flows but have not considered the interactions between RBCs. In addition, the FEM approach is limited by a significant increase in computational time when incorporating non-linear RBC properties associated with large membrane deformations.

Separately, several researchers have studied large systems with many RBCs through employing lower fidelity models. Janoschek et al. (2010) and Melchionna (2011) have excluded the deformable characteristic of RBCs by modelling RBCs as rigid bodies suspended in a fluid medium. Similarly, Pan et al. (2011) reduced the complexity of their simulated system by coarse-graining the model used by Fedosov (2010). In these low-fidelity approaches, the relative apparent viscosity values predicted were in reasonable agreement with those reported by Pries et al. (1992).

**RBC aggregation model**

**Bridging hypothesis model**

As introduced earlier, the first model proposed for describing the RBC aggregation dynamics is the bridging hypothesis model. As proponents of the model, Bagchi et al. (2005) adopted the formalism of a ligand–receptor dynamics according to the bridging hypotheses theory. The inter-membrane force $f_m$ due to molecular cross-linking is governed by reaction equations and their reaction rates which are functions of the local distance between the membranes. In the simulation model, the reaction term for a specific segment of a cell membrane is computed by visiting and querying all the other cells to obtain the minimum distance between the cell membrane segment and its neighbouring cells. If the minimum distance between the cell segment and its neighbouring cell segment is less than a threshold length, then this segment pair is given an opportunity to form bonds. Assuming that both cells contribute an equal number of molecules to bond formation, the reaction equation for bond density $n_b$ is given by

$$\frac{\partial n_b}{\partial t} = 2 \left[ k_+ \left( n - \frac{n_b}{2} \right)^2 - k_- n_b^2 \right],$$

where $n$ is the density of the cross-linking molecules on each cell, and $k_+$, $k_-$ are the forward and reverse reaction rate coefficients, respectively. Note that the above equation is slightly different from that of a receptor–ligand interaction, but consistent with the models of Zhu (1991). The reaction rates are computed as proposed by Dembo et al. (1988)

$$k_+ = k_0^b \exp \left[ - \frac{k_0^l (l - l_0)^2}{2K_BT} \right],$$

$$k_- = k_0^b \exp \left[ - \frac{(k_0^b - k_0^l) (l - l_0)^2}{2K_BT} \right],$$

where $|\bar{x}|$ is the distance between the two pairing segments of the two cells, $l_t$ the threshold distance below which the bond formation is initiated, $l = |\bar{x}|$ and $l_0$ are the stretched and unstretched bond length, respectively, $k_0^l$ is the spring constant (force per stretched length), $k_0^b$ is the transition spring constant, $K_B$ is the Boltzmann constant, $T$ is the absolute temperature and $k_0^l$ and $k_0^b$ are the rate coefficients in equilibrium. The bonds behave like stretched springs, and the force per bond is given by

$$f_b = k_0^b (l - l_0).$$

The aggregation force $f_m$ per unit length of the cell membrane is then obtained by the relation:

$$f_m = f_b n_b \frac{\bar{x}}{|\bar{x}|}.$$

Note that in this formulation, the bond density, rate coefficients, bond length and the intermolecular force are not constant and vary along the contact area of the cells. However, these parameters are not available from experiments. Therefore, this model is difficult to use in a complex problem.

**Depletion theory models**

A representative approach for Depletion Theory Aggregation models has been given by Neu and Meiselman (2002).
In their study, they proposed a theoretical model for depletion-mediated RBC aggregation in polymer solutions. In their model, the total interaction energy $W_T$ per unit surface between two infinite plane surfaces is measured. The plane surfaces representing RBC surfaces brought into close contact by the use of polymers such as dextran or polyethylene glycol and the interaction energy $W_T$ is given by the sum of the depletion attractive and electrostatic repulsive energies, with negligible van der Waals interactions

$$W_T = W_D + W_E.$$  \hspace{1cm} (23)

In Equation (23), $W_D$ and $W_E$ are the depletion interaction and electrostatic energies per unit surface, respectively. The depletion energy is modelled in the form:

$$W_D = -2\Pi \left( \Delta - \frac{d}{2} + \delta - P \right),$$ \hspace{1cm} (24a)

when \( \left( \frac{d}{2} - \delta + P \right) < \Delta \),

$$W_D = 0, \hspace{0.5cm} \text{when} \left( \frac{d}{2} - \delta + P \right) > \Delta,$$ \hspace{1cm} (24b)

where $\Pi$, $\Delta$, $d$, $\delta$ and $P$ are the osmotic pressure term, depletion thickness, intercellular distance, RBC glyocalyx thickness (5 nm) and penetration depth, respectively. The osmotic pressure term $\Pi$ and the depletion thickness $\Delta$ are functions of the molecular weight of the polymer and of the polymer concentration $C_p$. The penetration depth $P$ is a function of the polymer concentration calculated as follows:

$$P = \delta(1 - e^{-(C_p/C_b)}),$$ \hspace{1cm} (25)

where $C_b$ is the penetration constant of the polymer in solution.

The electrostatic energy is expressed in the form:

$$W_E = \frac{\sigma^2}{\delta^2 \varepsilon_0 k^3} \sinh(k\delta)(e^{(k\delta - kd)} - e^{-kd}),$$ \hspace{1cm} (26a)

when $d > 2\delta$

$$W_E = \frac{\sigma^2}{\delta^2 \varepsilon_0 k^3} [(2k\delta - kd) - (e^{-kd} + 1)\sinh(k\delta - kd) - \sinh(k\delta)e^{-kd}], \hspace{0.5cm} \text{when} \hspace{0.5cm} d < 2\delta,$$ \hspace{1cm} (26b)

where $\sigma$, $\varepsilon$, $\varepsilon_0$ and $k$ are the surface charge density of RBC, the relative permittivity of the solvent, the permittivity of the vacuum and the Debye–Huckel length, respectively.

The above formulation predicts an optimal polymer concentration for the interaction energy: the interaction energy initially increases with an increase in concentration, reaches a maximum and then decreases as the concentration increases. Furthermore, the interaction energy gradually increases to reach a maximum and then decreases to zero as the two surfaces approach. When the surfaces approach a distance equal to the sum of their glyocalyx thicknesses, they experience a strong repulsive force.

Chung et al. (2007) used Derjaguin’s integral approximation to extend this formulation to surfaces of arbitrary shapes. The result of this approach shows that the attractive forces do not vary significantly across the region in which the interaction energies are effective. This is because the force is a derivative of energy with respect to distance and the energy tail is a linear function of distance.

As mentioned above, the total interaction energy predicted by the depletion theory model is both a function of distance between membranes and polymer concentration. Due to the complexity of total interaction energy computation, Liu et al. (2004) have proposed employing the Morse-type potential energy function to simplify the formulation. In their method, the intercellular interaction energy $\Phi$ is given by

$$\Phi(r) = D_e \left[ \exp \left\{ 2\beta(r_0 - r) \right\} - 2\exp \{ \beta(r_0 - r) \} \right],$$ \hspace{1cm} (27)

where $r$ is the surface separation, $r_0$ and $D_e$ are, respectively, the zero force separation and surface energy and $\beta$ is a scaling factor controlling the interaction decay behaviour. The total interaction force from such a potential is its negative derivative, i.e. $f(r) = -\partial\Phi/\partial r$. The aggregation strength or interaction force between RBCs is represented by amount of surface energy $D_e$ in this model. However, since no experimental value of surface energy is available, one must find suitable value of $D_e$ for the purpose of the simulation.

Methods for multiphase RBC flow

Fluid–structure interaction scheme

In the multiphase description of the RBC flow, the RBC membrane and the suspending fluid (plasma) need to be discretised into separate regions in the computational mesh. Most commonly, an Eulerian mesh is used for describing the fluid domain, whereas a Lagrangian mesh is used to describe the structure domain. The coupling between the Eulerian and Lagrangian meshes is essential in an FSI. Pozrikidis (2003) utilised the boundary integral method to simulate the 3D motion of a liquid capsule enclosed by a membrane in shear flow. Using the boundary integral formulation for Stokes flow (Pozrikidis 1992), he presented that the velocity at a point $x_0$ that lies in the cell
membrane satisfies the integral equation:

\[
\begin{align*}
    u_j(x_0) &= \frac{2}{1 + \lambda} \left[ (u_j^0(x_0) - \frac{1}{8\pi\mu} \int_D \Delta f_j(x_0) G_j(x, x_0) dS(x) - \frac{1 - \lambda}{8\pi} \int_D u_l(x) T_{ijk}(x, x_0) n_k(x) dS(x) \right] \\
    \text{where } D \text{ stands for the membrane, } u_j^0 \text{ is the unperturbed velocity prevailing in the absence of the cell, } \mu_1 \text{ and } \mu_2 \text{ are, respectively, the viscosity of the ambient and cell fluid, } \\
    \lambda = \mu_2 / \mu_1 \text{ is the viscosity ratio, } G_j \text{ and } T_{ijk} \text{ are the Stokes flow Green's functions for the velocity and stress corresponding to the type of flow under consideration, } n \text{ is the unit vector normal to the membrane pointing into the ambient fluid and } PV \text{ denotes the principal value.}
\end{align*}
\]

The strength density of the single-layer potential, \( \Delta f \), is the jump in the hydrodynamic traction across the membrane, defined as

\[
\Delta f = (\bar{\sigma}^1 - \bar{\sigma}^2) \cdot n,
\]

where \( \bar{\sigma}^1 \) and \( \bar{\sigma}^2 \) are the hydrodynamic stress tensors in the ambient and interior cell fluid (Pozrikidis 1992). In the absence of significant membrane inertia, a differential force balance requires

\[
\Delta f = -\bar{L},
\]

where \( \bar{L} \) is the membrane load given in terms of the in-plane and transverse membrane tensions.

Another well-known and popular method for FSI treatment in blood flow simulations is the IBM. It was developed by Peskin (1977) to simulate flexible membranes in fluid flows. The membrane–fluid interaction is accomplished by distributing membrane forces as local fluid forces and subsequently updating the membrane configuration according to the new local flow velocity. The membrane force consists of structural forces generated in the membrane in response to deformation and intercellular forces due to membrane–membrane interaction. In IBM, the membrane force \( \bar{F}_m(x_m) \) at nodes on membrane \( x_m \) induced by membrane deformation is distributed to the nearby fluid nodes \( x_f \) through a local fluid force \( \bar{F}_f(x_f) \) in the form:

\[
\bar{F}_f(x_f) = \sum_m D(x_f - x_m) \bar{F}_m(x_m),
\]

where \( D(x) \) is a discrete delta function which is chosen to represent the properties of the Dirac delta function (N’dri et al. 2003). In a 2D lattice system, \( D(x) \) is given as follows:

\[
D(x) = \frac{1}{4h^2} \left( 1 + \cos \frac{\pi x}{2h} \right) \left( 1 + \cos \frac{\pi y}{2h} \right),
\]

when \(|x| \leq 2h \) and \(|y| \leq 2h\),

\[
D(x) = 0, \text{ when otherwise,}
\]

where \( h \) is the lattice unit. The membrane velocity \( \bar{u}_m(x_m) \) can be updated in a similar way according to the local flow field:

\[
\bar{u}_m(x_m) = \sum_f D(x_f - x_m) \bar{u}(x_f).
\]

In this formulation, there will be no relative velocity between the membrane and the local fluid; therefore, the general no-slip boundary condition is satisfied and no mass transfer through the membrane can occur.

The IBM was originally applied to Cartesian grids but has recently been further extended in immersed FEM, where a Lagrangian finite element solid mesh is described to be moving on top of an Eulerian finite element mesh. The utilisation of finite element meshes for the fluid domain allows for non-uniform meshes with arbitrary geometries and boundary conditions (Sui et al. 2007; Zhang et al. 2007), hence enabling better discretisation and achieving higher accuracy for the simulation model.

**Mesoscopic approach**

The FSI treatment based on the popular Eulerian–Lagrangian approach for blood flow simulation often incurs high computational expense due to a non-trivial coupling between the structural deformation and fluid flow. Alternatively, a Lagrangian–Lagrangian-based mesoscopic approach can lead to sufficient accuracy at an affordable computational cost. Accordingly, several mesoscopic RBC models have recently been developed. Most of them employ a similar idea whereby the RBC cytoskeleton and membrane are represented by a network of springs in combination with bending rigidity and constraints for surface area and volume conservation. Dupin et al. (2007) coupled a discrete RBC to a fluid modelled by the lattice Boltzmann method. Noguchi and Gompper (2005) modelled RBCs and vesicles within the multiparticle collision dynamics framework (Malevanets and Kapral 1999). Pivkin and Karniadakis (2008) employed DPD (Hoogerbrugge and Koelman 1992) for a multiscale RBC model, whereas Fedosov et al. (2010) have extended this model to accurately capture the viscoelastic properties of the RBC membrane and to incorporate the external/internal fluid viscosity contrast – features which were not taken into account in most of the previous models.
Despite the current developments of RBC models, all of the methods above still suffer from high computational expense when several thousand RBCs are required to be modelled. As a consequence, there have been relatively few mesoscopic simulations (Bagchi 2007; Zhang et al. 2009) of blood flow in large vessels (\(D = 100 \, \mu\text{m}\)); because of the computational expense even these few studies are limited to the application of 2D RBC models. In addition, most literature does not include the aggregation of RBCs which will significantly affect the transport behaviour of blood.

**Discussion of numerical modelling**

In summary, we have surveyed and presented some of the methods employed in the simulation of RBC flow. Modelling components essential to capturing the haemodynamics of the RBC flow are CFD models, RBC mechanical deformation and aggregation models, fluid and membrane coupling schemes and a property index updating scheme for distinguishing the separate phases in the blood mixture. These components provide a basic set of tools capable of studying and addressing a breadth of problems related to haemodynamics.

However, as with any numerical approach, the topic of computational efficiency and fidelity ought to be considered. This sensitivity is particularly pertinent to the study of RBC transport behaviour, where feature sizes such as RBC diameters are typically on the micrometer scale. Correspondingly, the scale of discretisation for the numerical model can be on the order of nanometres in order to preserve the accuracy and fidelity of the simulation. This is problematic for studies that are essentially multiscale in nature, such as the study of a capillary network or an organ — the modelled domain in its entirety is several orders larger than the discretisation scale required to capture reasonably correct flow physics. Understandably, the computational cost for such studies will be high. Therefore, strategies such as parallel computing techniques for large multiscale RBC simulations need to be developed in order to study the many practical biological systems. From the perspective of applied models, many studies are trending towards tackling large multiscale problems. Furthermore, the popularity of multicore computing provides a huge potential for more efficient computational algorithms for solving mathematical RBC models numerically.

Another attention-worthy topic in RBC modelling relates back to the essential physiological function of RBCs in blood flow. The gas transport role of discrete RBCs in blood has not been well investigated in the existing literature (Beard and Bassingthwaighte 2001; Chen et al. 2006; Deonikar and Kavdia 2010; Ong et al. 2011). Most gas convection–diffusion transport models thus far have excluded two potentially key attributes of the transport phenomena: first, the discrete representation of advecting RBCs as sources/sinks for gaseous species and second, the non-homogeneous radial distribution of gaseous species in blood. Invariably, the underlying haemodynamics predicted by RBC models constructed from the techniques discussed in this review can significantly affect the gas transport physics. For example,

\[
H(d) = \begin{cases} 
0.0 & \text{when } d < -2h, \\
0.5 \left( 1 + \frac{d}{2h} + \frac{\pi}{2} \sin \frac{\pi d}{2h} \right) & \text{when } -2h \leq d \leq 2h, \\
1.0 & \text{when } d > 2h. 
\end{cases}
\]

A varying fluid property \(\alpha\) can be related to the index \(d\) by

\[
(35) \quad \alpha(\tilde{x}) = \alpha_{in} + (\alpha_{ex} - \alpha_{in})H(d(\tilde{x}))
\]
the local wall shear stress can vary significantly with the dynamics of discrete RBCs and this in turn affects the NO production rate in the endothelium cells. A gas transport model coupled with the haemodynamics model may provide an RBC model with sufficient sophistication to investigate and perhaps even explain several physiological mechanisms for gas exchanges in the microcirculation.

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References
