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Computational fluid dynamics in the microcirculation and microfluidics: what role can the lattice Boltzmann method play?

Joseph O'Connor,^{*a} Philip Day,^b Parthasarathi Mandal,^a and Alistair Revell^a

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Patient-specific simulations, efficient parametric analyses, and the study of complex processes that are otherwise experimentally intractable are facilitated through the use of Computational Fluid Dynamics (CFD) to study biological flows. This review discusses various CFD methodologies that have been applied across different biological scales, from cell to organ level. Through this discussion the lattice Boltzmann method (LBM) is highlighted as an emerging technique capable of efficiently simulating fluid problems across the midrange of scales; providing a practical analytical tool compared to methods more attuned to the extremities of scale. Furthermore, the merits of the LBM are highlighted through examples of previous applications and suggestions for future research are made. The review focusses on applications in the midrange bracket, such as cell-cell interactions, the microcirculation, and microfluidic devices; wherein the inherent mesoscale nature of the LBM renders it well suited to the incorporation of fluid-structure interaction effects, molecular/particle interactions and interfacial dynamics. The review demonstrates that the LBM has the potential to become a valuable tool across a range of emerging areas in bio-CFD, such as understanding and predicting disease, designing Lab-on-a-Chip devices, and elucidating complex biological processes.

Introduction

The scientific application of numerical modelling methods, such as Computational Fluid Dynamics (CFD), as precision tools to investigate biological processes has risen dramatically in recent years as confidence and capability in their usage grows and accessibility to higher accuracy techniques increases. As barriers between effective and meaningful cross-disciplinary research are broken down in both academia and industry, the potential for further growth in this discipline is as strong as ever. Efficient parametric studies and patient-specific analyses within practical timescales are just two of the advantages that computational modelling offers over traditional experimental methods. In addition, CFD simulations can provide insight into complex *in vivo* processes that are otherwise experimentally intractable¹. It is then natural that numerical modelling, derived in engineering, has evolved to become an attractive tool to the biomedical scientist. Moreover, with modern computational power increasing as it is, allowing larger and faster simulations than ever before, the use of biological-CFD (BCFD) in this field can only be expected to

grow in the coming years.

A major challenge for BCFD is the vast range of spatial and temporal scales that are typically apparent in most physiological processes. In general, a biological problem will comprise three competing aspects, each to a varying extent: physiology, biology and biochemistry. The physiological features alone, in terms of the range of scales involved, present a formidable challenge. Currently there is no single numerical method capable of resolving all three aspects at all relevant scales, all at once. Over the course of the past 50-60 years a number of different CFD methods have been introduced and developed, each of which is specifically suited to a particular range of scales and physics. Considering for example the biochemical effects and processes occurring at the microscale, the individual molecules must be modelled; while considering the release and transport of an embolus around the body requires simulating a complex network of vessels. Such multiscale activities limit the practical use of CFD for biological flow modelling, as translating certain behaviour at one scale to the resulting effect at another, often distant, scale can be conceptually challenging and is also prohibitively expensive in terms of the computational cost.

Figure 1 portrays the trend in the number of BCFD studies published over the past 15 years based on the appearance of one of three selected common methodologies from the micro, meso, and

^a School of Mechanical, Aerospace and Civil Engineering, The University of Manchester, Manchester, UK, M13 9PL. E-mail: joseph.oconnor@manchester.ac.uk

^b Manchester Institute of Biotechnology, The University of Manchester, Manchester, UK, M1 7DN

Fig. 1 Number of BCFD related articles published per year. Results from Elsevier Scopus database.

Fig. 2 Breakdown of representative scales addressed with each method. Results from Elsevier Scopus database.

macro-scales, respectively*. Examining Figure 1, the increasing adoption of numerical methods over the recent years is clearly evident. It is also interesting to note that in earlier years the use of BCFD was dominated by the pure microscopic and macroscopic methods. Macroscopic approaches, such as the finite volume (FVM), finite element (FEM), and finite difference (FDM) methods, neglect the effects of individual particles/molecules and assume a continuum fluid, allowing simulations spanning large space and time scales compared to other CFD approaches. In contrast, molecular dynamics (MD) provides the ultimate level of detail, but at a huge cost on account of the vast number of molecules required to simulate even the most simple of processes. Figure 1 shows that the lattice Boltzmann method (LBM), a mesoscopic approach, was essentially non-existent in BCFD 15 years ago. However, while the micro and macro-scale methods are still the most popular choices, the LBM has emerged in recent years to share a proportion of the user base and now accounts for approximately 25% of the publications in this area. The LBM is ideally suited to biological flows due to its target length scale and the ease with which it can incorporate additional physics – such as fluid-structure interaction (FSI), interfacial dynamics, particle-particle interactions and intermolecular forces. It is likely that these benefits exhibited by the LBM are the reason for its recent emergence in the field of BCFD.

Figure 2 provides a breakdown of studies associated with a particular biological scale for each of the representative CFD methods†. As expected, the largest relative proportion of studies conducted at the organ level is attributed to the FVM. Also unsurprising is the fact that MD shows the largest relative proportion of studies conducted at the cell level. This figure further highlights the multitude of CFD methods and their differing ranges of

applicability.

The purpose of this review is to highlight the challenges associated with modelling biological fluids, in particular the dynamic range of spatial and temporal scales (e.g. nanometre to metre), flow regimes (e.g. Reynolds, Mach and Knudsen numbers), and multiphysics processes (e.g. biochemical reactions and FSI) present in most biological systems; and to explore the potential benefits that mesoscopic methods, specifically the LBM, can provide. Through a discussion of selected methods, relevant physics and modelling requirements at cell, tissue, and organ level, the LBM is highlighted as a promising tool for a number of applications involving biological flows. Previous studies using the LBM are reviewed and their successes and shortcomings are highlighted. Specific attention is paid to applications in the microcirculation and in microfluidic devices, as the ease with which the LBM can incorporate the additional physics involved in these applications, such as the FSI of deformable convecting particles, makes it an ideal approach. Multiscale methods are neglected here as although they can provide significant insight into certain problems, they also present their own specific challenges; for a discussion on this topic, the reader is instead directed to the literature^{2–4}. The review concludes by introducing some promising opportunities for the LBM, and BCFD in general, and also discusses some current limitations that need to be addressed so that BCFD can continue to develop and sustain its expected growth over the coming years.

Methods & Physics at Different Scales

Modelling Methods

At the microscopic scale the fluid molecule size becomes comparable to the domain size and the continuum assumption, which is used to formulate the Navier-Stokes equations, can no longer be applied⁵. In this scenario, atomistic methods, such as MD, are the preferred choice. Molecular dynamics explicitly calculates the dynamics and interactions of each individual fluid molecule⁶, allowing highly detailed time histories of molecular motion. Additionally, MD is based on a first principles approach – meaning it is theoretically valid for any flow regime⁷. That being said, due

* Scopus search: (PUBYEAR > 1998 AND TITLE-ABS-KEY ("CFD" OR "flow" OR "fluid") AND TITLE-ABS-KEY ("bio*") AND TITLE-ABS ("< method >")), where < method > corresponds to legend.

† Scopus search: (PUBYEAR > 1998 AND TITLE-ABS-KEY ("CFD" OR "flow" OR "fluid") AND TITLE-ABS-KEY ("bio*") AND TITLE-ABS ("< method >") AND TITLE-ABS-KEY ("< scale >")), where < method > and < scale > correspond to x-axis and legend.

to computational demands, MD is currently severely limited in terms of the spatial and temporal ranges it is applicable to; with typical simulated times on the order of nanoseconds⁸. As a result, this restricts the use of MD for many practical applications on account of the high computational cost required to simultaneously consider the necessarily large number of degrees of freedom.

The FVM and its sister, the FEM, are perhaps the most common approaches used in traditional CFD^{9,10}; with the FVM being the method adopted in most industrial CFD packages. Both methods are based on the continuum assumption and have found a broad range of applications in a number of fields; including the biomedical, aerospace, automotive and marine industries, to name a few. The FVM and FEM are mature, well-developed methods that have been active areas of research for many years. Furthermore, they allow simulations spanning much longer spatial and temporal scales than any of the other methods covered in this review. However, both begin to struggle when the continuum assumption starts to break down, and they also have difficulties incorporating particle or molecular interactions. Moreover, the final solution is usually heavily mesh dependant, meaning that a significant amount of time and resources can be spent generating an appropriate mesh before any simulations are performed. This bottleneck in the CFD workflow has been a hot topic for a number of years, and while significant progress has been made it remains so even now^{11,12}. Furthermore, in some cases involving complex geometries it may not even be possible to entirely eliminate poor quality cells – particularly in microfluidic devices with intricate geometries and where spatial scales can range many orders of magnitude¹³.

Mesosopic methods attempt to bridge the gap between the micro and macro-scales. By combining certain aspects of particle-based and continuum methods, mesoscopic methods can exhibit many advantages over the true particle/continuum approaches, particularly for biological flows where many processes are governed by multiphysics interactions and the time and length scales may span larger than the microscale. While there exists a number of mesoscopic methods, or methods which can be applied to the mesoscale, the main focus of this review is the LBM. Other approaches, such as dissipative particle dynamics and multiparticle collision dynamics have been omitted as the majority of the literature for mesoscale applications involving the microcirculation and microfluidics uses the LBM. For a detailed discussion on these other methods the reader is instead directed to the literature^{14,15}.

In the LBM, packets of fluid molecules are represented via a probability function which describes the distribution of molecules at a particular position and time moving with a particular lattice velocity⁵. These fluid packets then evolve according to the lattice Boltzmann equation¹⁶. Through the evolution of each individual probability function, the averaged macroscopic fluid properties can be calculated. Although the LBM has roots in particle kinetics, its principal focus is on the macroscopic fluid behaviour¹⁷. As a result, individual molecular interactions are neglected. However, the driving ethos behind the LBM is that the macroscopic quantities are not governed by individual molecules, but by the cumulative behaviour of many fluid molecules¹⁸. As the LBM combines aspects of both atomistic and continuum models, and

thereby attempts to fuse the advantages of each, the LBM can simulate much larger space and time scales compared to true particle-based methods¹⁹. Additionally, microscopic interactions are handled with relative ease when compared to pure continuum methods. Furthermore, the locality of the LBM scheme means that it lends itself very well to efficient parallel implementation. While it is possible to combine particle and continuum-based methods using a coupled multiscale approach, the LBM allows these advantages to be realised without the complexities and challenges that typically accompany multiscale methods, such as the transfer of information in the interface region²⁰. Also, because most studies involving the LBM are discretised using a regular lattice, generating a computational grid often requires less time and effort than that usually required to generate an appropriate body-fitted mesh. The uniform grid has its own disadvantages however such as when it comes to fully resolving regions of flow with large local gradients (where a finer mesh is required) and representing curved boundaries²¹. Although techniques do exist allowing unstructured formulations of the LBM^{22–24}, the same meshing challenges associated with continuum methods also apply to these approaches.

Relevant Physics & Modelling Requirements

Biological flows are extremely complex, incorporating a broad range of physics across multiple scales. As an example, in large arteries the shear rate of the blood flow is relatively high. This allows the blood to be treated as a Newtonian fluid. However, in smaller vessels where the shear rate is lower it is necessary to consider the non-Newtonian properties of blood and treat it as a shear-thinning fluid. Further still, towards capillary level it is necessary to treat the blood in terms of its constituents: a suspension of cells and biomolecules within a plasma medium²⁵. This highlights the enormous complexity associated with modelling biological flows and why developments in the past have been focussed towards one specific scale or process.

At physical scales relevant to individual cell dynamics and cell-tissue interactions, it is nigh on impossible to apply the continuum assumption. Furthermore, as miniaturisation effects and molecular interactions can no longer be neglected, the flow physics can be dramatically different from the macroscale²⁶. For example, surface area to volume ratio is dramatically increased⁷ and the smaller length scales and velocities involved lead to very small Reynolds numbers (approximately 0.01 for leukocytes²⁷). Additional complexities arise from the fact that many physiological processes involve a strong coupling between the fluid and structural dynamics. Cells typically adapt their own geometry and mechanical properties in response to stresses generated by the fluid²⁸ – such as red blood cells (RBCs)²⁹, platelets³⁰, and endothelial cells²⁸. Also, many cells, including endothelial cells, possess a coating of nanoscale hairs (glycocalyx) that cover the cell membrane and have been shown to increase flow resistance in the microcirculation³¹. Moreover, the presence of the glycocalyx may mean that the standard no-slip boundary condition is no longer acceptable and something more representative, such as a porous layer, may be required³². Finally, many processes involve

Method	Common Applications	Advantages	Disadvantages
Finite Element / Volume	<ul style="list-style-type: none"> Cardiovascular system Arterial flow & pathologies <ul style="list-style-type: none"> aneurysms, stenosis Respiratory flows Medical devices <ul style="list-style-type: none"> heart pumps, valves 	<ul style="list-style-type: none"> Suited to larger space/time scales Mature, well understood, robust <ul style="list-style-type: none"> range of software available Handles macroscopic quantities <ul style="list-style-type: none"> pressure, velocity, temperature 	<ul style="list-style-type: none"> Limited by continuum assumption <ul style="list-style-type: none"> Hard to incorporate microscale Time consuming mesh generation Complex non-linear, non-local equations <ul style="list-style-type: none"> costly for parallel computing
Lattice Boltzmann Method	<ul style="list-style-type: none"> Arterial flow & pathologies <ul style="list-style-type: none"> aneurysms, stenosis atherosclerosis Respiratory flows <ul style="list-style-type: none"> multiphase, air-mucus Cell dynamics & interactions Microfluidics / lab-on-a-chip 	<ul style="list-style-type: none"> Retains particle-based physics Restricted to adjacent points <ul style="list-style-type: none"> efficient parallel computing results in linear equations Simple basic boundary conditions <ul style="list-style-type: none"> higher order can be complex Incorporates physics naturally <ul style="list-style-type: none"> multiphase, molecular interactions, body forces etc. 	<ul style="list-style-type: none"> Stability limitations with basic model <ul style="list-style-type: none"> particularly for high speed flow Generally limited to square lattices <ul style="list-style-type: none"> although extensions do exist Relatively new method compared to finite volume/element <ul style="list-style-type: none"> less experience/robust software
Molecular Dynamics	<ul style="list-style-type: none"> Molecular interactions <ul style="list-style-type: none"> lipids, cholesterol Cell membrane mechanics <ul style="list-style-type: none"> drug delivery Detailed biochemical processes <ul style="list-style-type: none"> protein folding molecular transport 	<ul style="list-style-type: none"> Models individual molecules <ul style="list-style-type: none"> atoms, particles etc. Equations are direct and explicit <ul style="list-style-type: none"> fast to implement and solve Valid for any flow regime <ul style="list-style-type: none"> handles complex physics 	<ul style="list-style-type: none"> Computationally demanding <ul style="list-style-type: none"> needs many degrees of freedom only available to relatively small space/time scales Complex boundary conditions Difficult to obtain target statistics <ul style="list-style-type: none"> long samples required to average out random effects at this scale

Table 1 Various popular CFD methods and their common applications, advantages and disadvantages. The methods are arranged according to the space and time scales they are appropriate for, with the largest scales at the top and smallest at the bottom.

biologically active molecules, making it important to consider the biochemistry as well. Ideally, processes such as signal transduction should be accounted for; however, this dramatically increases the modelling complexity.

The flow physics at the large-scale tissue and organ level can vary significantly depending on the application. Reynolds numbers vary from unity in arterioles³³, up to approximately 3300 in ventricular assist devices (VADs)³⁴, 3600 in nasal flows³⁵, and 4000 in large arteries³⁰. Consequently, the flow can be laminar, turbulent, or in transition. Therefore, since currently there is no model available which can accurately resolve all of these regimes at once^{36,37}, the choice of turbulence model (or lack thereof) requires careful consideration. Also, complex 3D flow fields can arise from unsteady or pulsatile flow, complex geometries, secondary flows, separation and recirculation regions. Usually at this level it is safe to consider the blood as a continuous Newtonian fluid rather than a suspension of cells and molecules or as a shear-thinning fluid. This simplification can also hold true for aerosol deposition in the respiratory system. However, in some circumstances non-Newtonian effects and individual particle/cell dynamics may need to be taken into account. Specifically, in VAD applications at low rotational speeds the shear-thinning

behaviour of blood may start to present itself³⁸ and the non-uniform distribution of RBCs within the device may have an impact on individual cell trauma³⁹. When considering boundary conditions, FSI coupling is also often relevant as physical boundaries are typically motile and deforming. Furthermore, the standard no-slip and prescribed inlet velocity conditions may not be appropriate in applications such as aerosol drug delivery, where setting a pull-flow condition (negative pressure gradient) rather than a prescribed velocity, and correct modelling of the nasal mucosa are important³⁵. While all these complex phenomena vary in their degree of significance, often the largest effect can be through patient-specific variations and physiological state³⁰. Thus, patient-specific modelling, although difficult to obtain⁴⁰, should be undertaken whenever possible. Additionally, other physiological factors, such as posture, exercise³⁵, and disease³³ can have a significant impact on the flow field, making it difficult to obtain consistent and reliable results even with the same patient.

Fig. 3 A representation of various example applications in the vascular system, along with the relevant physical scales involved. The notations L , D and t represent the characteristic length scales in each example. L corresponds to the channel diameter, D_v is the valve leaflet diameter, D_a is the aneurysm diameter, D_c is the cell diameter, D_p is the particle diameter, and t is the glycocalyx thickness. (a) Artificial bileaflet valve. (b) Arterial aneurysm with coil implant. (c) Macroscopic blood behaviour involving many cells. (d) WBC adhesion and rolling during immune response. (e) Cell dynamics and interactions with the vessel wall and glycocalyx layer. (f) Particle sorting in a microfluidic device using actuated artificial cilia (not part of the vascular system but included for reference). The focus of this review is on the smaller-scale applications towards capillary level.

Application of LBM in the Microcirculation & Microfluidics

After reviewing popular BCFD methods and the various challenges and modelling requirements associated with biological flows, the LBM is seen to be a promising technique capable of efficiently simulating complex biological flows in practical timescales, while also incorporating additional physical processes. This is particularly true for the physical scales associated with the microcirculation and microfluidics. As a result, the remainder of this review will focus on previous applications of the LBM in this area. Figure 3 broadly summarises the wide range of physical scales, physiological factors and application areas that are pertinent in the circulatory system, with the focus of this review on the smaller-scale applications.

The Microcirculation

The microcirculation is the part of the circulatory system which involves the smallest blood vessels – arterioles, capillaries and venules. Its main function is the exchange of oxygen, nutrients and waste products between the blood and tissue^{41,42}.

Many common and lethal diseases have been linked to abnormalities in the microcirculation, including hypertension, sickle cell anaemia, diabetes⁴¹, sepsis⁴² and peripheral vascular disease⁴³. The ability to model and understand these microcirculatory processes is therefore of the utmost importance. However, difficulties arise because of the necessity of modelling individual cells/particles/molecules and the resulting FSI⁴⁴. Structural models of the cell need to be formulated and additional effects, such as aggregation and adhesion, need to be accounted for⁴⁵. The LBM is well suited to this due to its particulate nature and ability to incorporate additional physical models. The following section will present and discuss previous applications of the LBM in the microcirculation and highlight some of its successes and shortcomings.

Red Blood Cells.

The modelling of cell dynamics within the microcirculation can be difficult due to the effects of FSI coupling, cell mechanical properties, and cellular interactions. Also, the sheer number of cells present in such applications imposes a significant demand on computational resources. As RBCs typically make up about

45% of blood by volume they are responsible for many of the interesting haemodynamic phenomena that are commonly observed, including the shear-thinning behaviour of blood and the Fahraeus and Fahraeus-Lindqvist effects – which describe the variation of haematocrit and apparent viscosity, respectively, with vessel diameter. Additionally, certain pathological conditions, such as sickle cell anaemia and malaria, directly affect the RBC's mechanics and dynamics, and thus the ability to explicitly model these effects is of critical importance⁴⁶.

The motion of individual RBCs suspended in a fluid can be quite complex and depends on various parameters, including shear rate and membrane compliance. Using a multi-block lattice Boltzmann-immersed boundary (LB-IB) model with an FEM structural mechanics solver, Sui *et al.*⁴⁷ studied the motion of a single RBC with various shapes suspended within a fluid. They found that whereas spherical RBCs tend to undergo tank-treading motion, the dynamics of elongated cells depends on the shear rate; with lower shear rates corresponding to a tumbling motion and higher shear rates leading to a mix of tumbling and tank-treading motion (swinging). Individual RBC dynamics in a pulsating flow have also been studied⁴⁸. Lattice Boltzmann simulations showed that at physiological Reynolds numbers the well known Segré-Silberberg effect, where a suspended particle equilibrates at an off-centre lateral position, vanishes and the final equilibrium position depends on the initial release position and pulsating frequency. However, interestingly, as the frequency approached that of the human heart, the Segré-Silberberg effect reappeared and RBCs released from different positions again moved to the same equilibrium position. This may indicate some physiological reason for the human heart rate, however the simplifications and assumptions used in this study means further analysis is required to gain a fuller understanding of the mechanisms involved.

Dupin *et al.*⁴⁹ developed a 2D LBM approach, based on a modified form of Gunstensen's multiphase model⁵⁰, to study the motion of a large number of RBCs. The original multiphase model was modified in order to prevent the liquid droplets (RBCs) from evaporating and coalescing. On an individual cell level the method cannot be regarded as entirely accurate, one reason being because surface area conservation of the cell membrane was not enforced. However, the model was shown to be a reliable and efficient method for simulating large numbers of deformable cells on a global scale. This multiphase approach was abandoned in further developments to 3D, where instead the cell mechanics were modelled via a spring network and the FSI coupling was achieved via interpolation between the Eulerian (fluid) and Lagrangian (structure) grids. Dupin *et al.*⁵¹ showed that their model could simulate up to 300 deformable cells within a practical timescale and also recover certain haemodynamic phenomena, such as the Fahraeus and Fahraeus-Lindqvist effects^{46,51}.

Zhang *et al.*⁵² developed a 2D LB-IB model to simulate RBCs as deformable liquid capsules, with cell-cell interactions incorporated via a Morse potential (atomic interaction model). Initial results showed that their model could correctly reproduce a number of haemodynamic characteristics such as RBC migration, tumbling and tank-treading motion, and the cell-free layer (CFL) – the plasma-rich near-wall region that arises due to lateral

RBC migration towards the channel centre. Later studies using the same model indicated that the tendency of RBCs to aggregate together is strongly related to the inter-cellular interaction strength and cell deformability^{53,54}. Additional studies demonstrated that, for a single RBC, increased plasma viscosity leads to an increase in RBC migration and tank-treading; effectively reducing the apparent cell stiffness⁵⁵. However, the results showed that this effect was essentially eliminated as the number of cells was increased. Further extensions of this model were made by Xiong and Zhang⁵⁶. Modelling the cell membrane and vessel walls using the immersed boundary method (IBM), they examined the transient wall shear stress (WSS) in a microvessel as single and multiple RBCs flowed past. They found that the peak-valley-peak WSS profile depends on cell length and vessel diameter, and as haematocrit increases the individual cell profiles merge to form a peak-valley profile.

One example of the potential of the LBM to perhaps at some point act as a link between the micro and macro-scales was given by Janoschek *et al.*⁵⁷. They used the LBM and a simplified description of the RBCs, along with potential models gained from MD simulations, to study the collective behaviour of a large number of deformable RBCs. Their 3D model produced efficient simulations of a large number of cells within practical timescales, and incorporated microscopic effects. While simplifications were obviously made to achieve this, the study highlights the possibility that the LBM may prove useful when it comes to linking microscale effects to the macroscale in a qualitative manner, if not quantitatively.

By simulating RBC motion in a bifurcated microchannel, Xiong and Zhang⁵⁸ supported earlier claims^{54,55} that plasma viscosity works to reduce apparent cell stiffness, and that these two properties have opposing effects in terms of cell migration. This study also highlighted the fact that RBCs do not necessarily follow the streamlines of the plasma medium; a common oversimplification which has been made in the past. The relative flux of RBCs in an idealised microvascular bifurcation was studied by Shen and He⁵⁹. They showed, using a 2D LB-IB model, that the RBC flux into each daughter branch depends strongly on the mass flow split, and that for extreme cases there is no RBC flux into the lower-flow branch, even if there is still mass flow in that branch. A similar study examined the effect of haematocrit on the relative flux of RBCs into the daughter branches⁶⁰. Lattice Boltzmann simulations revealed that for normal haematocrit levels the ratio of the RBC flux into the daughter branches is similar to the mass flow split. However, for lower haematocrit values the Segré-Silberberg effect begins to dominate and the off-centre equilibrium position of the RBCs means that the flux ratio of the RBCs into the daughter branch no longer compares to the mass flow ratio. A subsequent study indicated that liposome-encapsulated hemoglobin (LEH) – a possible replacement for RBCs in future artificial blood solutions – may be able to overcome the oxygen bias typically encountered in microvascular bifurcations; where the presence of the CFL tends to result in a significantly reduced RBC flux into the lower flow branch⁶¹. The simulation results showed that, as RBCs tend to force LEH towards the CFL in equilibrium flow, a significant portion of the LEH is convected into the

Fig. 4 RBC and WBC dynamics at a postcapillary expansion without RBC aggregation (a) and with aggregation (b). Coloured contours indicate pressure field. The RBC stack is more effective at pushing the WBC towards the wall and initiating rolling. Profiles show the linear and angular velocities of the WBC with time. Reprinted from ref. 63, Copyright (2005), with permission from Elsevier.

lower flow branch; resulting in a more proportional oxygen bias, even if the majority of RBCs still flow into the larger flow branch. Extending the model to 3D, Hyakutake and Nagai⁶² found that RBC distribution in a bifurcation depends strongly on the angle and diameter of the daughter branches.

The glycocalyx layer (GL) is a coating of nanoscale hairs that cover the membranes of certain cell types, including endothelial cells. The GL has a number of effects and roles within the microcirculation, including increasing flow resistance and transferring mechanical forces to the endothelium. Pontrelli *et al.*⁶⁴ modelled the GL as a porous medium, while also including the sinusoidal shape of the endothelial cells, to investigate the interplay between the GL and RBCs. The results showed that, as an RBC passes, the GL bears most of the WSS; thus protecting the vessel wall. Furthermore, the presence of the GL leads to increased deformation of the RBC. These results indicate that it is crucial to consider wall shape and the presence of the GL in some form, even if not explicitly.

As mentioned previously, certain diseases directly alter the mechanical properties of RBCs and thus can cause abnormalities in their dynamics and function. Dupin *et al.*⁴⁶ used their model to show how sickle cells, with a different stiffness, shape, and size to normal RBCs, can become lodged in a narrowing blood vessel and block upstream healthy RBCs from passing through the narrowed section. A similar study, using a 2D LB-IB model, also showed that the difference in stiffnesses between healthy and diseased RBCs has a large effect on RBC motion and shape, and consequently will have an effect on the overall haemodynamics⁶⁵.

White Blood Cells.

Although the volume fraction of white blood cells (WBCs) is much lower than RBCs, they can still have a significant impact on flow resistance and WSS in the microcirculation. Moreover, their dynamics, interactions, and adhesion to the vessel wall are crucial in immune response. This process has been the subject of a number of studies using the LBM^{27,67}. Using a 3D shear-thinning LBM model to examine the local flow pattern around single and multiple WBCs, simulations revealed that recruitment of the WBC onto the vessel wall is supported by vortices generated from the 3D flow pattern. Additionally, rolling of the WBC along the wall after recruitment is promoted via a torque generated by the flow over the WBC surface. Furthermore, it is thought that the shear stress induced by the rolling motion of the WBC over the endothelium may be large enough to activate additional receptors to enhance the recruitment process²⁷.

To examine the effect that RBCs have on the rolling of WBCs along the vessel wall, Migliorini *et al.*⁶⁸ developed a 2D LBM model for particle suspensions that incorporated the adhesion (receptor-ligand) force between the WBC and vessel wall. At normal haematocrit levels they found that as the RBC collides with the WBC the normal force and torque on the WBC is increased – promoting both WBC adhesion and rolling. It should be noted that even at lower haematocrit values this effect is noticeable; although it is significantly reduced as the CFL is larger. However, while this study was one of the first to incorporate the effect of RBCs on WBC rolling and adhesion, it was limited to one RBC and one WBC and cell deformability was neglected. Building on the previous study, Sun *et al.*⁶⁹ showed that organised rouleaux (stacks of aggregated RBCs) are more effective at directing WBCs towards the vessel wall and promoting WBC adhesion than individually dispersed RBCs. This was supported in future studies by extending the model to incorporate RBC-RBC aggregation⁶³, as seen in Figure 4. Sun and Munn⁷⁰ also showed that the presence of WBCs in a microvessel significantly increases flow resistance. In a later study, by importing a 2D digitised vessel network, the forces, wall stresses, pressure changes and cell trajectories through a real vascular network were calculated⁷¹. A major finding of this study was that as cells pass by they induce pressure and shear stress oscillations at bifurcations (stagnation regions), where the shear stress is usually low. It is thought that this may be one of the main contributing factors in the development of atherosclerosis in these regions. Additionally, Sun *et al.*⁷² used their model to investigate the effect of plasma leakage in an inflamed microvessel. They found that plasma leakage and WBC

Fig. 5 Simulation of deformable RBC and platelet suspension. The small black circles represent the platelets. Initial positions (left) are uniform. After allowing the system to develop (right), it can be seen that the cell free layer forms and the platelets are generally forced into this region. Reprinted from ref. 66, Copyright (2011), with permission from Cambridge University Press.

rolling increases flow resistance, which may lead to overall reduced blood flow through the damaged branch. Furthermore, they found that vessel dilation (e.g during inflammation) works to counter these effects.

Platelets.

Platelets are responsible for clot formation at an injured site or wound. There are a number of pathological conditions that affect platelets; therefore, the ability to model platelet motion and response is an active area of research. Tamagawa *et al.*⁷³ developed an LBM model for examining thrombus formation behind a rearward facing step – a common test case in CFD which involves a discontinuous expansion of the geometry cross section, leading to an area of flow separation and recirculation behind the step. In the context of this study, the rearward facing step geometry was used to emulate the flow separation and reattachment typically encountered in rotary blood pumps. The model was based on an effective distance from the wall (adhesion force) and a shear rate threshold. When these criteria were met the fluid lattice site was transformed into a solid lattice site. The results showed that thrombus formation occurs at the reattachment point behind the step and in the region at the foot of the step in the recirculation zone. The unsteady (pulsatile) results showed similar behaviour, suggesting that it is reasonable to simulate thrombus growth using a steady (non-pulsating) flow.

Crowl and Fogelson studied the lateral distribution of platelets in a microvessel^{66,74}. Their results, shown in Figure 5, revealed that there is an increase in platelet concentration next to the wall within the CFL. Further examination revealed that this phenomenon is caused by the interactions of the RBCs in their equilibrium position. Moreover, as haematocrit is reduced the CFL increases in size and the spike in platelet concentration at the wall reduces and disperses across the CFL. Similarly, Chen *et al.*⁷⁵ demonstrated that increased haematocrit and flow rate leads to an increase in platelet concentration at the near wall region, leading to an increased probability of platelet adhesion. Reasor Jr *et al.*⁷⁶ also studied platelet margination and showed that the rate of lateral motion increases with haematocrit and RBC deformability, and that spherical platelets marginate faster than

disk shaped platelets. Furthermore, the dynamics of platelets in the CFL at different haematocrits have also been studied. At normal haematocrit values platelets slide (rather than tumble) through the CFL, with more of their surface exposed to the vessel wall – possibly maximising their probability of adhesion. Using the method of Crowl and Fogelson, Skorzewski *et al.*⁷⁷ studied the dynamics of platelets in the CFL at a thrombus site. They found that the CFL is narrowed at the thrombus site, leading to a closer contact between the thrombus and platelets; it is thought that this may enhance the likelihood of platelet adhesion and promote further thrombus growth.

Microfluidics

The field of microfluidics deals with flow problems where the characteristic length scale of the domain is on the order of microns. The advantages of working in this regime include smaller sample volumes, faster reaction rates, higher throughput due to parallelisation of components, and the ability to house an entire laboratory on a single chip⁷⁸. Furthermore, the effects of miniaturisation can dramatically alter the flow physics compared to a similar macroscale system (for better and for worse). This, along with the fact that fabrication of such devices is becoming cheaper and easier⁷⁹, is leading to a growing level of research in this area. Common applications in microfluidics include species transport¹³, cell manipulation and analysis⁸⁰, DNA separation⁸¹, and biomarker detection⁸². However, there exists many difficulties in the numerical modelling of such systems. Perhaps the most important is the vast range of relevant scales within such a system, which can be up to seven orders of magnitude (nanometre up to centimetre)¹³. Also, consideration of additional physical processes, such as FSI, heat transfer, electrokinetics and chemical reactions, is often a requirement⁸¹. The LBM is well suited to incorporating these additional physics and therefore is an attractive tool for such applications. The following section will discuss previous studies involving the LBM and microfluidics, and highlight its advantages and disadvantages.

Particle Regulation.

The regulation of particles within a suspending fluid is important in certain microfluidic applications where the manipulation of individual cells or anti-fouling measures are required. One method of achieving this is to design certain geometrical features into the device which can take advantage of the hydrodynamics and particle dynamics effects in order to sort cells/particles by size, stiffness or shape. Kilimnik *et al.*⁸³ investigated the lateral migration of suspended particles within a simple 3D microchannel using a coupled lattice Boltzmann-lattice spring (LB-LS) model. Their results showed that the final equilibrium position of the deformable particles depended on their size, shape and interior fluid viscosity; with smaller, stiffer particles tending to reach an equilibrium position closer to the channel wall. Microchannels with periodically placed diagonal ridges on the upper and lower walls have been demonstrated to provide deformability-based sorting of particles⁸⁴. Simulations revealed that particles with different degrees of compliance were laterally displaced to opposing sides of the channel. Similar results were shown using a deterministic lateral displacement device, for RBC sorting, comprised of an array of pillars with adjacent rows offset from each other⁸⁵. Depending on the lateral stretching of the RBC as it passed around a pillar it was either laterally displaced through the array or formed a zig-zag route through the array. Using the same design as Arata and Alexeev⁸⁴, the ability to sort particles based on size has also been demonstrated⁸⁶.

Another method for particle regulation, inspired by nature, is the use of artificial cilia to influence the flow field in such a way so as to attract or repel certain particles suspended within the fluid. Branscomb and Alexeev⁸⁸ used an LB-LS model to study how an array of unforced elastic cilia embedded within a microchannel can affect particle motion. For a range of cilia deflection angles they found that secondary flows generated by the presence of the cilia resulted in lateral particle motion towards the cilia. They also found that an optimum value for lateral particle velocity occurred at a deflection angle of approximately 45 degrees. Using the same approach, Semmler and Alexeev⁸⁹ demonstrated that rigid cilia embedded at angle in a shear driven flow can repel particles away from the cilia-lined wall against the force of gravity. However, they neglected the attractive force between the particles and channel wall, which has a significant impact in real microfluidic devices. Further studies showed that actuated elastic cilia can be used to regulate particle motion^{87,90,91}. By applying a sinusoidal force to the cilia with varying frequency, it was found that the different beating modes of the filaments induced different flow patterns which could attract or repel suspended particles⁹⁰. Furthermore, by incorporating cilia-particle adhesion, an optimum value for adhesion could be found for propelling particle across the surface of a ciliated layer⁹¹. Using the same approach, it was demonstrated that actuated cilia have the ability to attract or repel particles with various sizes⁸⁷. They found that the competition between adhesion force and the hydrodynamic lift induced by the beating cilia determines the direction of particle motion. Thus the larger particles were directed away from the wall whereas the smaller particles were attracted towards the

ciliated surface, as shown in Figure 6.

Using an LB-LS model, Alexeev *et al.*⁹² showed that by designing patterns into the surface of a microchannel – either geometric, mechanical or chemical – particles can be made to undergo specific directions or instructions. Specifically, a soft substrate resulted in decreased translational velocity of the cell across the surface. Moreover, cells could be made to stop at a specific site (where some sort of analysis could be carried out) and the motion restarted again by increasing the flow rate. A further study showed that designing diagonally striped patterns (mechanical or chemical) into the channel surface could result in a compliance-based particle sorter⁹³. The results indicated that deformable particles were more sensitive to the chemical patterning whereas stiffer cells were more sensitive to the mechanical (surface deformability) patterning. Usta *et al.*⁹⁴ used a similar approach to direct cells through specific routes along a microchannel surface – with different branches characterised by different adhesive and mechanical properties; thus particles, which themselves possessed various adhesive and mechanical properties, would be preferentially attracted to different branches.

Interparticle forces can also be controlled to induce and regulate particle motion. Usta *et al.*⁹⁵ modelled two microcapsules – one filled with nanoparticles that diffuse out of the membrane, and one devoid of any particles. The properties of the nanoparticles were such that as they diffuse into the surrounding fluid and onto the underlying substrate, the adhesive force between the surface and microcapsules was altered. The results showed that this process generated an adhesion gradient which initiated motion of the empty microcapsule. The hydrodynamic response of the capsule's motion initiated a rolling motion of the particle-filled capsule in the same direction – suggesting that hydrodynamics likely plays an important role in chemotaxis⁹⁵. A related study showed that multiple microcapsules can be used to similar effect to form chains of self-organised, autonomous structures capable of carrying out specific biological functions⁹⁶.

Flow Control & Manipulation.

The ability to direct fluid motion or promote scalar transport or mixing is a common problem in microfluidic devices. Alexeev *et al.*⁹⁷ showed, using a 3D LB-LS model, that actuated cilia embedded at an angle in a microchannel can initiate a unidirectional flow along the channel. Furthermore, they found that by varying the Sperm number (or forcing frequency in this case), the direction of the driven flow can be reversed. Additionally, Mills *et al.*⁹⁸ used a similar method to study the ability of actuated cilia to promote heat transport in a microchannel. They found that convective secondary flows generated by the cilia significantly increased heat transfer from the heated wall. Moreover, the optimal Sperm number for promoting heat transfer was found to be very close to the optimum for generating a unidirectional flow⁹⁷ – perhaps suggesting the possibility of optimised multifunctional cilia arrays.

Mixing is an important step in most microfluidic applications involving chemical reactions. However, due to miniaturisation effects, efficient mixing is extremely difficult at these scales. Consequently, a lot of research has gone into designing efficient mix-

Fig. 6 Initial and final positions of particles with varying size suspended within a fluid. Due to interplay between the attractive and lift forces generated by adhesion effects and cilia actuation, particles of a smaller size are attracted to the wall whereas larger particles are repelled. Reprinted from ref. 87, Copyright (2013), with permission from American Chemical Society.

ing strategies for microfluidic devices. An *et al.*⁹⁹ performed a 2D LBM study on an active micromixer comprised of an oscillating/rotating stirrer embedded in the centre of a microchannel, for a range of rotation speeds and Reynolds numbers. They found optimal rotation speeds for various Reynolds numbers, and also showed that the oscillating stirrer was the most efficient method at each optimum rotation speed. Expanding on the previous study, Park *et al.*¹⁰⁰ optimised the oscillating stirrer configuration and found an optimal design with a significantly increased mixing efficiency compared to the initial design. Homogeneous mixing via surface patterning has also been demonstrated¹⁰¹; where two immiscible fluids were mixed as they flowed over wettable and non-wettable patches.

Drug Delivery.

Drug delivery is an important and highly active area of research. Using a 2D LB-LS model, Verberg *et al.*¹⁰² studied the targeted delivery of nanoparticles contained within a microcapsule to a specific site on a channel wall. They found that the nanoparticle Péclet number (ratio of the rate of advection to the rate of diffusion of the particles), adhesion force between the wall and microcapsule, and the microcapsule compliance were all important factors in the rate of adsorption of the nanoparticles by the channel wall. Specifically, low Péclet numbers allowed particles to diffuse onto the wall without being convected downstream by the flow field. Moreover, they found that increased adhesion force and membrane deformability allowed a larger contact area between the microcapsule and wall – increasing the adsorption rate. In a similar study, Verberg *et al.*¹⁰³ also showed that nanoparticle-filled microcapsules rolling along a channel wall can be used for surface repair, and proposed guidelines for flow and capsule parameters. Simulations revealed that when the microcapsule approached the damaged area of the surface (crack), the capsule was forced to stop due to the difference in adhesion properties be-

tween the undamaged and damaged regions. The diffusion of the nanoparticles onto the substrate repaired the surface and the capsule motion was reinitiated. Finally, Jia and Williams¹⁰⁴ demonstrated and validated a model for dissolution of tablets within a fluid medium. The flow field was simulated using the LBM whereas the dissolution of the granule was calculated using a finite difference solver for the convection-diffusion equation. This study demonstrates the LBM's ability to be coupled with other methods and incorporate additional physical processes – highlighting the benefits of using the LBM for these biological applications.

Conclusion, Opportunities & Outlook

In summary, CFD modelling of biological fluids has seen a rapid rise in popularity over the recent years. In particular, although their use is still small compared to other approaches, the growth in popularity of mesoscopic methods, such as the LBM, is noteworthy. In fact, if the current trend holds, in the near future it is likely that such methods will share a very similar proportion of the user base to microscopic and macroscopic methods. Through a discussion of various CFD methods and the relevant physics and modelling requirements at different biological scales, it is clear that the LBM is particularly suited to applications involving the microcirculation and microfluidics. This suitability stems from the LBM possessing attributes of both particle and continuum-based methods, and thus allowing efficient simulations of complex biological flows. After reviewing recent studies involving the LBM, its successes, and its shortcomings, both the extent and limit of the LBM's current capability is apparent, as well as where further developments would be best served.

This review shows that the LBM's approach, by combining aspects of particle-based (microscopic) and continuum-based (macroscopic) methods, renders it ideally suited to biological flows. This is particularly true for the 'midrange' of scales dis-

cussed in this review, where cell-cell interactions occur throughout a network of vessels, or convected matter undergoes a range of body forces. Such dynamics have been shown to be relevant to many important processes of disease (e.g. malaria, sickle cell anaemia, ischaemic stroke), diagnosis (e.g. circulating tumour cell detection) and treatment (e.g. drug delivery and dosage) alike, and is most likely one of the reasons for the LBM's increase in popularity. Furthermore, in these applications the coupling of fluid motion with additional physical models, such as structural deformation, interfacial dynamics, particle-particle interactions and intermolecular forces, is typically a necessity, and can be readily incorporated through the LBM. While it should not be forgotten that the LBM has a number of inherent limitations when compared to macroscale approaches, it can be argued that its advantages outweigh these limitations for this specific range of applications. The LBM is still in its infancy and as its popularity increases and the method begins to mature further, it is likely that its capability will continue to develop and subsequently experience increasing success – leading to further increases in its use and development.

In such a fast-paced and continuously developing field like BCFD, new opportunities and challenges are always appearing. Emerging applications where the LBM, and BCFD in general, could be particularly useful include modelling realistic vascular networks^{105–107} and the FSI of highly deformable structures for flow control, sensing, and propulsion^{108–111}, to name a few; with other developments and opportunities arising continuously. Advances in fabrication processes and experimental techniques should not decrease the need for CFD but instead advocate further development. To take full advantage of the increased throughput, capability, and cost efficiency, CFD should be used in conjunction with these techniques to guide optimal design strategies and provide additional insight into the physical mechanisms involved.

In the next few years it is likely that the use of CFD to model biological fluids will continue to increase at a growing pace, as it has done over the recent years. However, to sustain this growth, further developments and improvements in the methods and models are required. The development of more efficient computational methods that enable simulations of statistically relevant numbers of cells, and multiple cell types, is an ambitious yet necessary goal in order to predict the cause and effect relationship between the micro and macro-scales (as highlighted in this review, work has already begun in this direction). The LBM is an attractive method for this as the locality of the scheme allows it take advantage of the massively parallel architectures that are currently starting to dominate many computing applications. Another important consideration is FSI coupling, as it plays a crucial role in many of the applications discussed in this review. Most FSI methods incur a significant computational cost, and have tended to be limited to two-dimensional studies, since they do not always lend themselves well to parallel implementation. More efficient methods will facilitate three-dimensional simulations; which is clearly important as the assumption of in-plane flow is a drastic oversimplification in many cases. Finally, as evidenced by this review, additional physics such as intermolecu-

lar forces, particle-particle interactions, and particle-wall interactions play an incredibly important role in various biological processes. However, some of these effects are poorly understood and thus simplified or empirical models are typically used to represent them. It is important to gain a better understanding of these effects – through theory, experiment, and simulations – so that they can be incorporated into models and the biochemical reactions and responses can be more physically represented.

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