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Multi-scale biological and physical modelling of the tumour micro-environment

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Abstract

Paced by advances in high performance computing, and algorithms for multi-physics and multi-scale simulation, a number of groups have recently established numerical models of flowing blood systems, where cell-scale interactions are explicitly resolved. To be biologically representative, these models account for some or all of: (1) fluid dynamics of the carrier flow, (2) structural dynamics of the cells and vessel walls, (3) interaction and transport biochemistry, and, (4) methods for scaling to physiologically representative numbers of cells. In this article, our interest is the modelling of the tumour micro-environment. We review the broader area of cell-scale resolving blood flow modelling, while focusing on the particular interactions of tumour cells and white blood cells, known to play an important role in metastasis.

Introduction

In recent years, computational models have matured to where they can be used to explore the complex multi-scale (molecular, cell, cell population) and multi-physics (biochemistry, fluid dynamics, structural dynamics) of the tumour micro-environment. Such modelling approaches draw heavily on the breadth of research performed on physiochemical modelling for multi-cell biological systems in general, while necessarily addressing the unique biochemical and dynamic nature of tumour–leukocyte interactions.

Flowing blood models have come to provide understanding of disease states and mechanisms heretofore unapproachable by clinical and experimental observation. Recent examples include sickle cell anemia [1–3], malaria [2,4], haemolysis [5], hemostasis/thrombosis [6,7], aneurism/stenosis [8,9], and cancer metastasis [10–12]. Such models can advance our understanding of disease and potentially lead to improved drug and other (e.g. microfluidics) therapies. Recent reviews by Freund [13], Fedesov et al. [14] and Wang and King [7] summarize the many challenges and methods involved in cell-resolved numerical

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Conflict of interest

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modelling of blood flow. Although the focus of these reviews is on erythrocytes, much of the modelling richness in flowing red blood cells (RBCs) is of relevance to cell-resolved modelling of the tumour micro-environment, as reviewed herein.

The scientific challenges associated with developing these models are significant: complex structural dynamics, stiffly coupled computational fluid dynamics (CFD), rich biochemistry modelling, non-linearities in all of these sub-disciplines, and, high CPU requirements that can render scaling to large systems intractable. Additionally, there are three relevant and disparate space–time scales across which physically reasonable models must span: molecular-scale, cell-scale and cell-population-scale. For example, the protein skeletal structure of the RBC membrane leads to complex and, at best, condition-specific constitutive relations for the dynamics of membrane deformation at the cell-scale [13,15]. Likewise RBC deformation plays importantly in the bulk dynamics and rheology of many-cell flowing systems, most notably white blood cell (WBC), tumour cell (TC) and platelet margination, and the attendant impact on leukocyte rolling/arrest on the vascular endothelium, and on thrombus formation [6,16–19].

We focus here on melanoma metastasis, where the biochemical and dynamic interactions between polymorphonuclear neutrophils (PMNs) and tumour cells are of interest. Phenomenologically, PMNs comprise 50–70% of all circulating leukocytes [20]. Studies have shown that inflammatory signals enhance the ability of circulating melanoma tumour cells to extravasate [21]. The correlation between inflammatory signals and increased melanoma cell metastasis implies that the circulating melanoma cells are able to take advantage of the immune system and use PMNs to assist their extravasation mechanisms. Laboratory experiments have shown that this increased extravasation of melanoma cells arises from the capture of TCs by endothelium cell (EC) adherent PMNs [10,20]. The absence of RBCs in these laboratory studies has enabled measurements leading to a deeper understanding of the dynamics and biochemistry of the PMN mediated extravasation process. Clearly, modelling these RBC-free systems isolates the particular interactions of interest, since the primary physiological role of RBCs in this process is margination. The availability of such *in vitro* adhesion data can serve to calibrate and validate component sub-models without the significant additional complexity of RBC dynamics. Nevertheless, the richness of the modelling involved remains quite high, and includes the tightly coupled effects of adhesion bond biochemistry (PMN–TC, PMN–EC), PMN and TC structural dynamics, and very low Reynolds number fluid dynamics. Accordingly, we here review the state of modelling technology relevant to this tumour micro-environment.

This review is organized as follows: cell-scale fluid dynamics methods for the broader area of cell-resolving blood flow modelling are summarized first. Geometric and structural dynamics modelling of cells in flowing systems are treated next, with emphasis on adherent leukocytes participating in TC capture. The biochemistry of adhesion kinetics models of relevance to PMN–TC and PMN–EC bonding are then presented. Finally, we consider scale-bridging approaches that have appeared for molecular-to-cell and cell-to-cell-population interactions, and present a new approach for predicting adhesion efficiency at the cell-population-scale using a statistical model-of-model technique.

Modelling the tumour micro-environment

Freund [13], Fedesov et al. [14] and Wang and King [7] have recently presented reviews of the state-of-technology in cell-resolved numerical modelling of blood flow. Although our focus here is on the tumour micro-environment, much of the coupled flow, structure and molecular chemistry modelling presented in these RBC focused [13,14] and platelet focused [7] treatments are relevant. In particular the breadth of CFD modelling technology is the same. However, the relevant structural dynamics and biochemistry are quite specific to the particular cell-type and interaction of interest. Accordingly, we review here the general approaches used for CFD analysis of blood flow systems while focusing our structural dynamics and biochemistry modelling discussion on PMN–TC–EC interactions.

Fluid dynamics

Considering the complexity of the biochemistry and structural dynamics in flowing blood systems, the flow itself can be comparatively straightforwardly treated as Newtonian. However, the computational expense of solving the Stokes/Navier–Stokes equations contributes significantly to the overall CPU requirements of a coupled cell-resolved model. Accordingly, research groups have adopted a hierarchy of flow modelling paradigms. In their important early work, Hammer and his group [22–24] adopted a hydrodynamic mobility function to approximate the externally applied hydrodynamic forces on WBCs. Other simplified one-way-coupled approaches based on internal Stokes flow have been used by other researchers as well [5,19]. Such simple flow models enabled these groups to perform elucidative parametric studies on adhesion biochemistry, cell deformation and margination, without undue computational expense.

In cell-resolved modelling, the two-way-coupling between cell/vessel and the flow (or in the case of *in vitro* studies the surrogate carrier fluid) requires at a minimum the solution of the Stokes equation, wherein flow compressibility and convection are dismissed as negligible. This approximation leads to adoption of efficient boundary integral/element methods wherein the flow can be computed as a succession of quasisteady states based on appropriate Green's functions evaluated on discrete surface panels defining the geometry of the individual cells and vessel/chamber walls [25–29]. These continuous field methods are limited in their applicability only by the Stokes assumption of very low Reynolds number, which is appropriate in capillaries and venules, and in the context of the numerous other model approximations in these systems, is probably appropriate for arterioles as well.

Particle based methods are also popularly applied in cell-resolving flowing systems. Here, the Stokes/Navier–Stokes equations are not solved, rather, plasma and cell interiors (assumed fluid) are represented by a number of interacting particles (notionally representative of groups of molecules) whose ensemble behaviour statistically returns the appropriate dynamics of the system. Among other particle based methods (molecular dynamics, smoothed particle hydrodynamics), dissipative particle hydrodynamics (DPD) has been widely used recently in the flowing blood simulation literature [1–3,30,31]. The principal advantage of these methods is that deforming cell membranes can be treated straightforwardly (possibly also using a DPD model) [4,32,33], as can certain molecular-

scale physics (e.g. thermal fluctuations). However these models are generally more computationally intensive than Eulerian approaches discussed next.

Lattice–Boltzman Methods (LBM), like particle based methods, do not treat the integral form of the Navier–Stokes equations. A fixed mesh (lattice) is defined that spans the computational domain, and each mesh volume is seeded with a finite number of fictitious particle populations whose dynamics evolve in time. Many LBM variants exist, distinguished by kinematic and collision rule sets as the particle distributions interact with those in local lattice locations. As with particle methods, viscous flow dynamics emerge statistically in the ensemble of these interactions. These methods can easily accommodate very complex geometries and for time-dependent low Reynolds number systems can be computationally efficient. Accordingly, several groups have developed LBM based cell-resolving blood flow models for rigidly modelled blood cells [34], and also deformable membrane descriptions [8,9,17], when merged with an Immersed Boundary Method (IBM) description of the cells as discussed below.

Interface capturing methods (i.e. Volume of Fluid [VOF], level-set, Immersed Boundary Methods [IBM]) are widely used in multi-constituent multiphase flows, where, as here, the number of discrete constituent interfaces remains tractable to conformal boundary resolution. These Eulerian CFD methods have in common a fixed-mesh approach wherein interfaces/membranes are incorporated into the discrete Navier–Stokes solution on this mesh via source terms representing sub-grid-scale interface/membrane dynamics. The classical IBM approach involves specification of the interface (e.g. bubble/droplet, solid particle/object, blood cell) via a separate unstructured Lagrangian representation. For blood flows, the elastic forces in the cell membrane are coupled to the flow through a force kernel approximation to the membrane stress applied locally as a source term in the Navier–Stokes equations. The membrane kinematics are imposed as appropriately flow advected Lagrangian surface mesh points, and the membrane dynamics are computed through structural mechanics modelling subject to interpolated flow pressure and viscous stress. Many workers have pursued the IBM and hybrid IBM methods for RBC flow simulation [16,17,35–41]. Closely related VOF methods have been applied to WBC adhesion [42]. In these fixed grid Eulerian methods, interface/membrane geometries are defined using local volume fraction ($\alpha = 1$:plasma, $\alpha = 0$:cytoplasm, $0 < \alpha < 1$:membrane) and its derivatives (to define interface direction/curvature). Though quite general in their applicability, membrane mechanics cannot be modelled as richly as in IBM methods or ALE methods (treated below) where the interface is explicitly resolved with its own mesh.

Most modern fluid–structure-interaction (FSI) schemes, as applied in their more conventional engineering venues, adopt the approach of explicitly resolving the structure boundary in a conformal manner. This approach has accuracy advantages in systems where the fluid–structure boundary can be well characterized. However, pursuing this in cell-resolving blood flow systems is not as straightforward since the molecular-scale biology local to the cell membrane surface brings about additional challenges associated with boundary condition specification, cell membrane geometry, and indeed the continuum assumption itself. So although boundary conformal FSI approaches can be developed for

flowing blood systems [10–12,43–45], additional modelling of the flow-membrane interface is unavoidable and needs to be justified in this context, as discussed further below.

Structural dynamics

Whereas the fluid mechanics physics and methods in cell-resolving flowing blood models are independent of the cell type under consideration, the same cannot be said of the structural dynamics. RBCs, WBCs, TCs and platelets have unique molecular and organelle structures that can contribute to significant non-linearity in their cell-scale constitutive dynamics. Freund offers an overview of RBC mechanics and the attendant range of structural dynamics modelling which has been brought to bear for them [13]. As mentioned above, RBCs play an important role in margination of other cells, and the highly deformable nature of RBCs plays directly into this process.

We focus here on PMN-mediated tumour cell adhesion to the endothelium under shear flow conditions, a critical step in metastasis. WBCs are significantly less deformable than RBCs, and indeed, as with simplified flow modelling mentioned above, much important adhesion biochemistry research has been performed with WBCs treated simply as rigid spheres [22–24]. Adherent neutrophils do however deform significantly under higher shear conditions. Specifically, they can elongate up to 140 percent under wall shear rates of 800 s^{-1} , and their EC and TC contact areas increase significantly as well [46]. Therefore, their deformability should be incorporated in cell-resolved models under adherent conditions. To illustrate this, Fig. 1 shows a result from a study by our group where the shear-dependent shapes of adherent PMNs are approximated using side-view microscopy, and these geometries then specified in a CFD model. In the figure, *in vitro* side-view microscopy and μ -PIV visualizations of an endothelium adherent PMN in a flow chamber are shown for a low and high shear condition, along with attendant CFD results which capture the cell shape effects on the velocity field. Also shown are side- and top-view microscopy and μ -PIV images of a PMN–TC aggregate under a low shear condition.

Structural dynamics models of leukocytes first appeared in the 1980s where it became evident that simple homogeneous models and membrane models with a viscous cytoplasm were inadequate in reproducing elastic and time-dependent visco-elastic responses for low and high shear. Dong et al. introduced a model defined by a pre-stressed membrane and a visco-elastic (Maxwell-fluid) interior, that ameliorated some of these shortcomings, especially for small deformations [47]. However, large deformations required much large leukocyte interior viscosities, likely due to the inhomogeneous nature of the cell's internal structure, in particular the comparatively rigid cell nucleus [48]. This led to the postulation of a 3-layer model which added a core region representing the nucleus and its surrounding cytoskeleton [48,49]. This 3-layer model has been adopted by several groups [37,42] and is retained in our research [11,12,45] as illustrated below.

Fluid structure interaction

The most general description of interface-resolving multi-component systems involves boundary conformal meshing of the flow, the particle interior (unless rigid), and the interface/membrane itself. These FSI methods are by definition adaptive moving mesh

schemes, termed Arbitrary Lagrangian–Eulerian (ALE) methods in some contexts. The advantage of these schemes is the potential to model all interface geometry and attendant fluid and structural dynamics as precisely as desired. Also, the distribution of and interaction between adhesion molecules on cell surfaces are straightforwardly handled on mesh conformal membranes. In ‘partitioned’ FSI methods, the respective governing equations are solved exclusively in the appropriate mesh regions with appropriate interface jump and boundary conditions (deflection, stress) applied exactly on the interface surface. A vast literature exists on this class of FSI schemes in large measure because they represent a path to direct numerical simulation of many systems. Today, these methods have significant computer resource requirements associated with high mesh count and mesh adaptation, and are notoriously difficult to parallelize on modern computer architectures. In our view, with evolving algorithmics and parallel computer hardware, membrane/boundary conformal FSI schemes are the future of cell-resolving blood flow modelling.

Figures 2 and 3 show elements of our groups’ recent FSI simulations of PMN–TC interaction and adhesion. Figure 2 shows two timesteps in an adaptive Cartesian-mesh model of a rigid TC interacting with a rigidly modelled deformed adherent PMN, illustrating the membrane conformal and adaptive nature of these simulations. Note that in these very low Reynolds number systems (and near-unity density ratios) the time-dependent terms in the Navier–Stokes equation can be neglected, so mesh topology need not be consistent on successive timesteps. Further details on the mesh adaptation are available in [11,12]. Figure 3 shows successive timesteps in the simulation of a rigid TC interacting with a deforming adherent PMN. In these FSI simulations, commercial mesh generation, CFD, and finite element structural dynamics tools were coupled to in-house adhesion biochemistry and 6DOF modules for TC motion. The Navier–Stokes equations are solved at each timestep on the conformal mesh for that timestep with appropriate moving boundary conditions. The PMN is modelled as a three-component system that includes a visco-elastic cytoplasm, an elastic membrane, and a rigid nucleus. Details of the particular differential models, constitutive relations and numerics associated with the structural dynamics can be found in [11,12]. The adhesion modelling used in these examples are covered in the next section.

Adhesion biochemistry

Dynamic interactions between tumour cells and leukocytes, including their deformation, aggregation and adhesion to the vessel wall arise by virtue of the forces applied to them, including those that arise from fluid pressure and viscous stresses, molecular bond kinetics, and potentially others (repulsive, colloidal).

There is a broad spectrum of molecular-scale biochemical interactions that arise in flowing blood systems. Therefore, we again focus here only on PMN-mediated tumour cell adhesion to the endothelium. Figure 4 shows a simplified representation of the relevant adhesion molecule expressions. Both melanoma cells and endothelial cells express ICAM-1 (intercellular adhesion molecule) on their surfaces, while the EC also expresses E- and P-selectins. PMNs express β -2 integrins, and these can interact, that is, form bonds, with ICAM-1 expressed on both the melanoma and endothelium. This interaction between β -2 and ICAM-1 leads to firm adherence of the PMN to the TC or EC cell. Prior to firmly

adhering to the endothelium wall, the PMN rolls along the wall due to selectin-mediated weak adhesion. These are the relevant adhesion kinetics that need to be modelled.

Modern bond kinetics models build on early work by Bell [50,51], Dembo [52,53], and Hammer [22]. Adhesion kinetics are modelled as probabilistic interactions between receptor and ligand molecules. Adhesion molecules are modelled as springs whose forward (bond formation) and reverse (breakage) rates depend on instantaneous separation distance, and several empirically obtained parameters (equilibrium reaction rates, molecule lengths, spring constants). These under-pinnings have been evolved in the past two decades to incorporate bond/external force directivity [23], microvilli geometry and tension [23,24], two-pathway disassociation [24,54], and cell surface deformation [44,45].

In the context of membrane conformal approaches, a distribution of adhesion molecules is prescribed. Models for adhesion based on cell surface distributions of receptors and ligands first appeared in the early 1990s [22], where Hammer and his coworkers introduced an idealized neutrophil with surface receptor distributions based on modelled geometric parameters (e.g. microvilli) and empirical surface densities. Despite the increased complexity of the surface discretization of a deformed PMN, the same general approach needs to be taken, specifically, the specification of a presumed surface distribution for the various adhesion molecules. If microvilli are not conformally represented in the membrane geometry, prescribed receptor distributions should reflect this, per Hammer's work [22–24]. Also, in the context of TC-PMN collision and tethering, the neglect of explicit microvilli resolution necessitates the incorporation of a fictitious repulsion force [1,8,9,12,19,30,34, 38,44,45]. Lastly, multiple bonds can form and break at any given time step in a TC-PMN collision event/simulation. Accordingly, the space–time distribution of modelled bond interactions should consistently conform to both the membrane surface discretization, and the local probabilistic nature of the bond model [44,45].

Figure 5 shows elements of the authors' recent PMN–TC tethering simulations that capture the nature of the adhesion kinetic modelling. Figure 5a shows the predicted separation distance vs. time between an adherent PMN and a TC that does not bind to the PMN. Comparison is made to the predicted encounter without adhesion modelling. Figure 5b shows the nature of the bonding history - the stochastic behaviour of bond formation/breakage is observed (and can be seen in Fig. 5a as well). Figure 5c illustrates the nature of the generalized bond search/formation algorithm [44,45]. Figure 5d,e shows elements of a rigid PMN–TC encounter where tethering is achieved. Figure 5d shows the predicted path of the TC, and Fig. 5e the final tethered configuration.

Cell-population-scale modelling

The coupled modelling of adhesion-kinetics and cell interactional/structural dynamics, as reviewed above, can be viewed as a multi-scale model (molecular-scale/cell-scale). Other similar examples of molecular-to-cell-scale models include cell/platelet resolved simulation of coagulation [7], and diseased RBC resolved simulation of sickle-cell adhesion [1]. Another class of molecular-to-cell-scale model bridging is associated with membrane and cytoplasm structural mechanics. For example, Boey and Discher [32,33] developed an RBC membrane model based on a viscoelastic spring network, each spring representing a single

group of spectrin molecules, whose fine-through-coarse grain behaviour yields accurate cell-scale rheological properties of the membrane. These spectrin level models of RBCs have been adopted/presented by Fedesov [55], Li et al. [15] and Pivkin and Karniadakis [56], where formal coarse graining adjustments to spectrin (molecular) level network modelling recovers appropriate cell-scale membrane mechanical responses suitable for membrane-scale discretization.

The cell-resolving methods presented in this paper are aimed at deterministic modelling of highly complex biological processes. If one considers extending the reach of these methods to the cell-population-scale, two observations can be made: (1) researchers are now able to model hundreds to thousands of cells simultaneously, depending on simulation dimensionality and pedigree of the sub-models, and such high-compute-power simulations can bring forward many important physiochemical processes (e.g. cell margination, coagulation), (2) the chosen level of modelling complexity leads invariably to compute power scaling limitations to simply increasing the domain size and cell count. So although advances in discipline-coupling algorithms and high performance computing can be expected to advance our community's capability, directly scaling these methods to the modelling of systems of millions to billions of cells may be decades away.

In particular, our group is interested in cancer metastasis, and our local-conditions simulation research has focused on TC-PMN aggregation. We would like to scale the model to the cell-population-scale to be able to answer questions like 'what is the effect of a given drug treatment on TC adhesion efficiency in an elderly individual'. We hypothesize that statistical model-of-model approaches can be brought to bear, thereby reducing compute times by many orders of magnitude compared to direct scaling to the cell-population. Other workers have proposed population balance and stochastic aggregation methods for coagulation and heterotypic cell adhesion and aggregation [57–59]. These methods are both appropriate-for and limited-to aggregation processes. A more general approach is sought as follows.

To date, our group has developed a statistical emulator for the cell-level model of the TC–PMN–EC system to predict binary PMN–TC–EC adhesion outcome, using a generalized Gaussian Process (GP) approach. This model allows us to generate fast approximations of the full set of dynamics models for a single realization of the cell and flow condition, such that it is feasible to predict the adhesion outcomes for many realizations at a reasonable speed. By numerically integrating the predicted outcomes from different conditions over their distribution, the cell adhesion efficiency at the population level ultimately can be computed.

To test the feasibility of this model, we constructed an emulator using the proposed approach, based on a set of adhesion runs using the fully coupled model (albeit with a rigid adherent PMN), where only shear rate and the initial height of the TC above the bottom wall were parameterized. Figure 6a shows predicted TC trajectories for three of the 45 simulation runs used to span this parameter space. As shown in Fig. 6b, the prediction from the emulator matches the response profile of the full simulations very well. Most importantly,

the emulator is more than 1000 times faster than the simulation (<1 min vs. 20 wall-clock-hours).

Although preliminary, this study shows that a suitably trained GP approach can be used to predict adhesion efficiency from a large set of parameter combinations with high computational efficiency and reasonable accuracy. We envision extending this approach to far more complex systems (e.g. RBCs, flowing fibrinogen) with many independent parameters. The ultimate goal of this element of our research is to use the cell-resolving simulation tool to anchor a far more efficient cell-population-scale model for studying tumour cell aggregation.

Conclusions

The accuracy and usefulness of cell-resolving simulations of blood flow will continue to improve, paced by advances in biological and physical models, numerical methods and high performance computing. In this review we summarized the state-of-the-technology of component flow, structure and biochemistry models, with an emphasis on the tumour micro-environment. Future flowing blood models will likely adopt evermore modern membrane resolving fluid-structure-interaction (FSI) methods, and some work in this area by our group was summarized. The scaling of molecular- and cell-scale biophysics to the cell-population-scale holds promise for developing macro-models that are predictive on the clinical-scale, and an offering towards that goal was presented.

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Figure 1.

(a,b) Side-view microscopy and μ -PIV visualizations of an endothelium adherent PMN in a flow chamber for low and high shear conditions ($50, 258 \text{ s}^{-1}$ respectively) [10] (with permission); (c,d) CFD model results for shear rates in (a,b) (prescribed cell shapes) [11]; (e,f) Comparison of measured and predicted velocities for shear rates in (a,b) [11]; (g,h) side- and top-view microscopy and μ -PIV images of a PMN–TC aggregate [27] (with permission).

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Figure 2.

Two timesteps in an adaptive Cartesian-mesh model of a rigid TC interacting with a rigidly modelled deformed adherent PMN [11].

Figure 3.
Successive timesteps in the simulation of a rigid TC interacting with a deforming adherent PMN [11].

Figure 4.
Representation of the relevant adhesion molecule expressions.

Figure 5. Elements of PMN-TC tethering simulations. **(a)** Predicted separation distance vs. time between adherent PMN and a TC [11], **(b)** number of bonds formed vs. time [11], **(c)** generalized bond search/formation [44], **(d)** predicted path of the TC for a PMN-TC tethering event, **(e)** final tethered configuration.

Figure 6.

(a) Predicted TC trajectories for three of the 45 DNS runs used to train the emulator. **(b)** Prediction of the adhesion outcome in a preliminary study with 45 combinations of TC height and shear rate shows a good correspondence between simulation and emulator. Dots represent the full simulation, colored according to adhesion outcomes: no collision between TC and PMN, collision between TC and PMN but no adhesion formed, and adhesion. Contours show the adhesion probability predicted by the emulator, colored according to the value of the probability (right bar). As expected, the probability of adhesion increases with the decrease of height and shear rates. The contour accurately separates adhesion from collision without adhesion.