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Computational models of blood diseases

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

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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.

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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 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

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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 quasi-steady 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