A Hybrid Discrete-Continuum Approach for Modelling Microcirculatory Blood Flow

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Abstract

In recent years, biological imaging techniques have advanced significantly and it is now possible to digitally reconstruct microvascular network structures in detail, identifying the smallest capillaries at sub-micron resolution and generating large three-dimensional structural data sets of size > 10^6 vessel segments. However, this relies on *ex vivo* imaging; corresponding *in vivo* measures of microvascular structure and flow are limited to larger branching vessels and are not achievable in three dimensions for the smallest vessels. This suggests the use of computational modelling to combine *in vivo* measures of branching vessel architecture and flows with *ex vivo* data on complete microvascular structures to predict effective flow and pressures distributions. In this paper, a hybrid discrete-continuum model to predict microcirculatory blood flow based on structural information is developed and compared with existing models for flow and pressure in individual vessels. A continuum-based Darcy model for transport in the capillary bed is coupled via point sources of flux to flows in individual arteriolar vessels, which are described explicitly using Poiseuille's law. The venular drainage is represented as a spatially uniform flow sink. The resulting discrete-continuum framework is parameterised using structural data from the capillary network and compared with a fully discrete flow and pressure solution in three networks derived from observations of the rat mesentery. The discrete-continuum approach is feasible and effective, providing a promising tool for extracting functional transport properties in situations where vascular branching structures are well defined.

Keywords: Microcirculation, Darcy flow, homogenisation, capillary networks, blood flow

1. Introduction

Normal tissue function is critically dependent on an adequate blood supply. In particular, the vascular system must supply oxygenated blood within a small distance of every point in a tissue, to meet cellular metabolic demands. This is achieved via a hierarchical network of vessels, whose branches with diameters below ~100 μm form the microcirculation and are classified as arterioles, capillaries or venules. The arterioles and venules form dichotomous branching structures with a hierarchy of vessel diameters, and respectively supply and drain the interconnected, mesh-like capillaries, which have diameters below 10 μm. The structures of microvascular networks determine distributions of blood flow and solute transport, and therefore strongly influence the function of the tissues that they supply.

Current *ex vivo* biological imaging techniques allow detailed reconstruction of microvessel network structures, providing 3D data sets with more than 10^6 segments in some cases (Cassot et al, 2006). Examples of these techniques include vascular casting with high-resolution imaging such as micro-computed tomography, confocal imaging based extended-volume imaging systems, and optical imaging of cleared tissue with fluorescent probes, all combined with automated post-processing technologies. A number of studies have used such data to quantify microvascular structures in tissues including brain, retina, heart, lymph node, placenta and solid tumours (Cassot et al, 2006; Lee & Smith, 2008; van den Wijngaard et al 2013; Konerding et al, 1999; Konerding et al, 2001; Chan et al, 2012; Lee, 2009; Folarin et al , 2010; Mayerich et al, 2011; Kelch et al, 2015; d'Esposito et al 2018, Plitman et al 2016, Pearce et al 2016).

The interpretation of such data sets in terms of functional physiological properties remains a major challenge. One obstacle is that *in vivo* measurements of vascular structure and blood flow in all individual microvessels are not generally feasible (Srinivasan et al, 2013). Therefore, mathematical models that link blood flow and mass transport to microvascular network structure provide a key tool for analysing these data sets and extracting functional properties. Indeed, mathematical modelling of blood flow and mass transport is a fundamental aim of the international Physiome Project (http://physiomeproject.org). Two main types of models for this purpose have emerged, here referred to as discrete and continuum.

Discrete models can be used if the complete network structure, including capillaries, is defined explicitly. The flow properties of the network can then be represented mathematically by assigning a conductance, i.e. a ratio of flow rate to pressure drop, to every segment based on Poiseuille's law. Conservation of blood flow at vessel junctions together with flow or pressure boundary conditions (BCs) at the boundary segments of the network lead to a system of linear equations, which can be solved for the node pressures and segment flows (Lipowsky & Zweifach, 1974;

Lorthois et al, 2011). Empirically-determined relationships (Pries & Secomb, 2005) are frequently used to define blood viscosity in Poiseuille's law, as a function of vessel diameter and haematocrit. This approach has been extended to allow estimation of flows with incomplete BCs (Fry et al, 2012), and Bayesian analysis techniques have been employed to quantify the effects of measurement uncertainties (Rasmussen et al, 2017). Even so, predictions of discrete models are inevitably affected by measurement errors and incomplete BCs, and discrete approaches are not feasible if the network structure is incompletely known or is so large that a complete solution is not computationally practical. Numerous approaches have sought to incorporate further haemodynamic (for example, (Secomb et al., 2001)) and topological (e.g. vessel tortuosity (Penta & Ambrosi 2015)) detail into these discrete approaches, with associated increase in computational cost of the model simulations. Although we not incorporate these features in this work, there is ample opportunity for model extension in the future, if the computational cost is justified by the potential for new physiological insights.

Continuum models provide a more approximate approach that can be used when discrete models are not feasible. In this approach, the local transport properties of the capillary network are analysed, and the capillary network is represented in the model by a homogeneous medium with corresponding properties. (Chapman et al, 2008) and (Shipley & Chapman, 2010) developed continuum models for fluid and mass transport through the leaky vasculature and porous interstitium of a solid tumour using mathematical homogenisation methods. In (Chapman et al, 2008) a discrete network of capillaries is homogenised to give a continuum description in terms of a vascular density. In (Shipley & Chapman, 2010) a multiple-scales approach is used to exploit the separation of length scales between individual capillaries and the tissue as a whole, assuming a periodic microstructure. Both approaches result in equations describing a double porous medium with coupled Darcy flow through the interstitium and vasculature. The Darcy fluid permeability tensors capture the dependence of tissue-scale perfusion on the micro-scale geometry and flow characteristics. In the limit of zero vessel leakage relevant to healthy tissues, the interstitial and vascular models are decoupled. More recent work has incorporated further complexity into these averaged frameworks, including haemodynamic complexities such as heterogeneity in blood rheological parameters (Penta et al, 2015). Continuum models have been employed using structural data from the rat myocardium (Lee, 2009; Smith et al, 2014) and human cortex (El-Bouri & Payne, 2015). However, the application of these continuum models involves several challenges (Peyrounette et al, 2018). Firstly, the vasculature contains hierarchical networks with a range of spatial scales, where vascular branching structures in particular may not be well represented in terms of two length scales (capillary scale and tissue scale). Secondly, the models assume a highly interconnected network, such that vessel pressures at nearby spatial locations are correlated. Thirdly, the parameters of the continuum models may be difficult to estimate.

Measurements of blood pressure within systemic microvessels show that most of the arterial-venous pressure drop (75% or more under control conditions) occurs in the arterioles (Chilian et al, 1989; Pries et al, 1995), with a smaller drop in the capillaries and a minimal drop in the venules. Furthermore, the arterioles are the primary site for local control of blood flow, by active contraction or dilation of vascular smooth muscle in their walls. It follows that the arterioles are dominant in determining spatial and temporal variations of flow and pressure in the microcirculation. This behaviour is not well represented by the continuum models described above. This suggests a need for models that include the arteriolar network structure, even if the complete vascular structure cannot be modelled explicitly.

In this study, we develop a coupled discrete-continuum model for microcirculatory blood flow, taking advantage of the arterio-venous asymmetry of the pressure distribution in the systemic circulation (Pries et al, 1995). Blood flows and pressures in the tree-like arteriolar network are modelled using a discrete model, which is coupled via local sources to a continuum description of blood flow in the capillary bed, using a Green's function approach. The venular system is treated using a uniformly distributed pressure-dependent sink term (although we note the opportunity to expand the framework to explicitly model the venular network as required). The model is intended for application in cases where the arteriolar network geometry is mapped out, but the capillary geometry is not fully resolved or is too extensive to be modelled using a discrete approach. For observed networks in the rat mesentery, model predictions are compared with their equivalents obtained from a discrete model for the complete network including capillaries and venules.

2. Mesentery networks and discrete flow solutions

The mesentery is a thin sheet of tissue containing essentially 2D microvasculature. Structural and some blood flow data for networks in the rat mesentery were obtained by Pries et al. (Pries & Secomb, 2005; Pries & Gaehtgens, 1986; Pries et al, 1990; Pries et al, 1995) and flow was analysed using a discrete model. Three such networks (Networks 1, 2 and 3, Figure 1) are used in the present study.

Classification of vessels as arterioles, venules or capillaries is required for the approach presented here. Histological classification according to vessel wall structure (Henrikson et al, 1997) is not available for most imaging methods. Classification algorithms based on flow direction (Roy et al, 2012) or structural information (Cassot et al, 2006; Smith et al, 2015) have been developed. Since data on flow direction are not generally available for large network structures, the structure-based method of Smith et al. (Smith et al, 2015) is used here, specifically their Algorithm 2 for networks with multiple inlets and outlets. This method identifies the topological transitions between the branching arteriolar and venular structures, and the interconnected loops of the capillary bed, and

was shown to be more robust to parameter variations than alternative structure-based algorithms (for example that of (Cassot et al, 2006)). The resulting classification of vessels in the mesentery networks is included in Figure 1 and summary data are provided in Table 1.

The method for network flow calculation (Pries & Secomb, 2005) is as follows. We define N as the set of all nodes, comprised of the sets of interior nodes I and boundary nodes B (defined as nodes connected to only one segment), S as the set of all segments, n, n_I and n_B as the number of nodes in N, I and B respectively, and n_S as the number of segments in S. The flux q_j in segment j is calculated using Poiseuille's Law:

$$q_j = \sum_{k \in N} M_{jk} p_k, \text{ for } j \in S, \tag{2.1}$$

where p_k is the pressure at node k, and

$$M_{jk} = \begin{cases} +\pi\, d_j^4 / 128\, \mu_j l_j & \text{if } k \text{ is the start node of segment } j \\ -\pi\, d_j^4 / 128\, \mu_j l_j & \text{if } k \text{ is the end node of segment } j \\ 0 & \text{otherwise} \end{cases}, \tag{2.2}$$

where d_j and l_j are the diameter and length of segment j, and μ_j the associated viscosity obtained using the *in vivo* law of (Pries & Secomb, 2005). At interior nodes, conservation of flux is satisfied, while at boundary nodes, flux or pressure BCs are applied. At least one pressure BC is required for a unique solution. These conditions are combined to obtain

$$\sum_{k \in N} K_{ik} p_k = -q_{0i} \text{ for } i \in I \cup B. \tag{2.3}$$

Here, K_{ik} is defined by

$$K_{ik} = \sum_{j \in S} L_{ij} M_{jk}\,, \tag{2.4}$$

where

$$L_{ij} = \begin{cases} -1 & \text{if } i \text{ is the start node of segment } j \\ +1 & \text{if } i \text{ is the end node of segment } j \\ 0 & \text{otherwise} \end{cases}. \tag{2.5}$$

If a flow boundary condition is given at node $i \in B$, then q_{0i} is the inflow (or outflow if negative). If a pressure BC is given at node $i \in B$, then $-q_{0i}$ is replaced by the pressure condition and the ith row of K is replaced by δ_{ik}. If $i \in I$, then $q_{0i} = 0$. Equation (2.3) yields a sparse linear system for the node pressures p_k that may be solved using standard numerical methods.

Blood flow directions were recorded in all segments of the three mesentery networks considered, but blood flow velocities were recorded only in Network 1, derived from centre-line velocity measurements (Pries et al, 1994). The measured flow values from Network 1 were not used directly here because these flows did not satisfy conservation of flux at nodes due to measurement inaccuracies. In order to obtain flow solutions by the discrete method, for comparison with the results of the hybrid method, the flow estimation method of (Fry et al, 2012) was applied to all three networks. Motivated by the need to estimate flow rates in networks with incomplete boundary value

data, this method minimises the sum of squared deviations from target pressure and shear stress values in each segment across the network. One pressure boundary condition was enforced at the venous outlet of each network (p_m = 13.8 mmHg), while at arteriolar inlets, flow boundary conditions were assigned by assuming an empirical linear relationship between vessel diameter (d, in μm) and velocity (v, in mm/s): $v = 0.4d - 1.9$ (Pries et al, 1995; Pries et al, 1990) and multiplying by the vessel cross-sectional area to obtain a flow value. This linear relationship is based on experimental measurements of pressure, red cell velocity and diameter in cat mesentery vessels with diameters in the range 7 to 58 μm, and serves as a useful approximation arteriolar inlet flow boundary values, which has been used on similar-sized vessels of other networks. To determine segment viscosities, the *in vivo* viscosity law (Pries et al, 1994) was employed with uniform haematocrit of 0.4 (this assumption facilitates model development, but we note the framework could incorporate heterogeneous haematocrit distributions using established empirical relationships such as those established in (Secomb et al, 2001) in future). The target pressure was set to 31 mmHg (Fry et al, 2012).

The target shear stress ($\tau_{0,j}$, dyn/cm^2) in each segment was assigned as a function of the mean segment pressure (p_j in mmHg, the average of the pressures at the ends) (Pries et al, 1998):

$$\left|\tau_{0,j}\right| = 100 - 86 \cdot \exp\left[-5000 \cdot (log_{10}(log_{10} p_j))^{5.4}\right]. \qquad (2.6)$$

The sign of the target shear stress in each segment was set according to the recorded flow directions, rendering unnecessary the use of an iterative process for determining flow directions (Fry et al, 2012). The value of the parameter k_τ in the flow estimation method, which specifies the weighting of shear stress terms, was chosen by minimising the normalised root mean square deviation from the flow solution obtained with all measured BCs applied in Network 1. This k_τ value was then used for all three networks.

3. Discrete-continuum flow model

Here we describe the hybrid discrete-continuum model and methodology for parameter assignment. This framework is summarised in a flow diagram in Figure 2.

In the hybrid discrete-continuum model, a discrete model for flow and pressure in the arterioles is coupled to a continuum description of flow and pressure in the capillaries and venules. This coupling is achieved via local sources of flow into the continuum domain, positioned at the terminal branches of the arterioles (see Figure 1). To avoid singular behaviour in the pressure field, these inflows are distributed over discs of radius r_0, which provide the coupling between the discrete network and the continuum. In a recent 3D discrete-continuum model (Peyrounette et al, 2018), a more detailed analysis of this coupling was presented, taking into account the local capillary network at the terminal branches of the arterioles. Such local effects can be represented here through the value of r_0. Outflow via the venules is accounted for by a pressure-dependent drainage

term. This drainage is applied throughout the domain, including the regions occupied by the coupling discs.

In the continuum model for the capillary network, Darcy's law describes the coupling between blood velocity and pressure

$$\boldsymbol{u} = -\kappa \nabla p, \tag{3.1}$$

where $\boldsymbol{u}$ is the volume-averaged blood velocity, p is the pressure, and κ is the uniform, isotropic conductivity of the network. This description can be derived by averaging Stokes flow in representative capillary sub-regions via homogenisation methods (Chapman et al, 2008; Shipley & Chapman, 2010; Smith et al, 2014). Conservation of mass yields

$$\nabla . \boldsymbol{u} = -\kappa \nabla^2 p = \sum_{j=1}^{N_t} q_j^{out} d(r) - \beta(p - p_v), \tag{3.2}$$

where the first term on the right-hand side represents discrete sources of flow from the arteriolar network into the capillary domain and the second term represents the spatially distributed drainage into the central venous system. In the arterial source term,

$$d(r) = \begin{cases} 1/\pi\, r_0^2 D & \text{for } r \le r_0 \\ 0 & \text{otherwise} \end{cases}, \tag{3.3}$$

and represents a unit flow source distributed over a disc of radius r_0, where $r = |\boldsymbol{x} - \boldsymbol{x}_j|$, $\boldsymbol{x}_j$ (j = 1,…,N_t) are the source points, q_j^{out} are the source strengths and D is the thickness of the tissue. The source points $\boldsymbol{x}_j$ include the ends of arteriolar vessels and also capillary side-branches of arterioles. In the venous drainage term, p_v is the uniform venous sink pressure and β represents the spatially averaged conductance of the venous network. Equation (3.2) is subject to the condition that the pressure tends to p_v far from the flow sources. The substitution $\bar{p} = p - p_v$ gives

$$-\kappa \nabla^2 \bar{p} + \beta \bar{p} = \sum_{j=1}^{N_t} q_j^{out} d(r) \text{ and } \bar{p} \to 0 \text{ as } |\boldsymbol{x}| \to \infty\ . \tag{3.4}$$

The Green's function, $G(\boldsymbol{x}; \boldsymbol{x}^*)$ corresponding to (3.4) solves the adjoint problem

$$-\kappa \nabla^2 G + \beta G = d(r) \text{ and } G \to 0 \text{ as } |\boldsymbol{x}| \to \infty \tag{3.5}$$

and the solution of (3.2) is then expressed as

$$p(\boldsymbol{x}) = p_v + \sum_{j=1}^{N_t} G(\boldsymbol{x}, \boldsymbol{x}_j) q_j^{out}. \tag{3.6}$$

Hence the final capillary pressure field is given by a superposition of Green's functions weighted by the corresponding source strengths, representing contributions from each source. In polar coordinates, (3.5) can be written as

$$\frac{-\kappa}{r}\frac{d}{dr}\left(r\frac{dG}{dr}\right) + \beta G = d(r) \text{ and } G \to 0 \text{ as } r \to \infty, \tag{3.7}$$

with continuity of $G(r)$ and its flux at $r = r_0$,

$$G|_{r=r_0^-} = G|_{r=r_0^+}\ , -\kappa\left(r\frac{dG}{dr}\right)\Big|_{r=r_0^-} = -\kappa\left(r\frac{dG}{dr}\right)\Big|_{r=r_0^+}, \tag{3.8}$$

and $G(r)$ well-defined at $r = 0$. The solution of (3.7) is given by

$$G(r) = \begin{cases} \frac{1}{\pi r_0^2 \beta D} + AI_0(\lambda r) & \text{for } r \le r_0 \\ BK_0(\lambda r) & \text{for } r \ge r_0 \end{cases}, \quad (3.9)$$

where A and B are integration constants to be determined, I_0 and K_0 are modified Bessel functions of the first and second kinds, and

$$\lambda = \sqrt{\beta/\kappa}\,. \quad (3.10).$$

Applying the continuity of $G(r)$ and its flux at $r = r_0$ conditions (3.8) yields the solution

$$G(r) = \begin{cases} \frac{1 - CK_1(\lambda r_0) I_0(\lambda r)}{\pi r_0^2 \beta D} & \text{for } r \le r_0 \\ \frac{CI_1(\lambda r_0) K_0(\lambda r)}{\pi r_0^2 \beta D} & \text{for } r \ge r_0 \end{cases}, \quad (3.11)$$

where

$$C = \frac{1}{I_0(\lambda r_0) K_1(\lambda r_0) + I_1(\lambda r_0) K_0(\lambda r_0)}. \quad (3.12)$$

3.1 Computational implementation of the discrete-continuum model

To calculate the pressure field, we assume that the arteriolar network structure, arteriolar inlet pressure p_a and the background venous pressure p_v are known, whereas the pressures and flows at the source nodes are unknown. From eq. (3.6), the pressure at $\boldsymbol{x}_i$ is

$$p_i^{out} = p_v + \sum_{j=1}^{N_t} M_{ij}^{tiss} q_j^{out} \text{ for } i = 1, \dots, N_t, \quad (3.13)$$

where

$$M_{ij}^{tiss} = G(r_{ij}) \text{ and } r_{ij} = \left| x_i - x_j \right|. \quad (3.14)$$

The discrete model described in §2 is used to calculate the pressures at the outflow nodes of the arteriolar network, as functions of the unknown flow conditions at the interface between the arteriolar and capillary networks:

$$p_i^{out} = p_a - \sum_{j=1}^{N_t} M_{ij}^{net} q_j^{out} \text{ for } i = 1, \dots, N_t, \quad (3.15)$$

where the matrix $\boldsymbol{M}^{net}$ characterises the pressure-flow relationship in the arteriolar network. The source nodes include capillary side-branches of arterioles. At these points, short dummy segments of length 5 μm and diameter equal to the minimum segment diameter in the arteriolar network are added for convenience, so that all source points are then terminal nodes of the arteriolar network. A sequence of discrete flow calculations is performed to calculate M_{ij}^{net} for j = 1,…,N_t. In each case, if a node is a boundary node for the full network, the BC on pressure or flow for the full network is imposed. The flow at source node j is set to 1 and the flows at all other source nodes are set to zero so that, (3.14) gives

$$M_{ij}^{net} = p_a - p_i^{out}. \quad (3.16)$$

Matching the pressure values from the continuum and discrete solutions, (3.13) and (3.15), yields

$$\sum_{j=1}^{N_t} [M_{ij}^{net} + M_{ij}^{tiss}] q_j^{out} = p_a - p_v, \quad (3.17)$$

which may be solved for q_j^{out}.

3.2 Parameter values

Parameter definitions are summarised in Table 2. We assume that the tissue thickness is D = 20 μm (a different assumed value would give equivalent results except for a rescaling of β and κ). The radius over which sources are distributed is r_0 = 20 μm, chosen so that the sources do not overlap and hence act independently on the continuum solutions. A sensitivity analysis to variations in r_0 is performed in §4.4. The arteriolar inflow pressure p_a is chosen for each network to match that in the discrete solution, and $p_v = 2.6$ mmHg is equal to the average of literature values for the central venous pressure in rats (Cui et al, 2008; Le Marquer-Domagala & Finet, 1995). The calculation of $\boldsymbol{M}^{net}$ also requires information on the flows at the non-source boundaries of the arteriolar network. We use the discrete solutions in the full mesentery networks to provide these values.

The conductivity κ of the capillary network to fluid transport, and rate of drainage β from the capillary into the venous network are not known *a priori*. The conductivity κ is estimated using the 'micro-cell' homogenisation approach (Smith et al, 2014), parameterised using the capillary data for each of the mesentery networks. Periodic hexagonal grid networks were generated with hexagon edge lengths scaled to match the capillary length densities, and non-uniform segment diameters were sampled from a log-normal distribution using the mean and standard deviation from each of the mesentery data sets. Segment viscosities were determined by the *in vivo* viscosity law (Pries et al, 1994) with a uniform haematocrit of 0.4. One thousand such networks were generated and the micro-cell problem solved on each to obtain a mean conductivity representative of each mesentery network (Smith et al, 2016).

With κ given, a root finding algorithm was employed to identify the value of λ as defined in eq. (3.10) (and hence β) for which the difference in the sum of source fluxes between the network flow solution and the Darcy flow solution was zero. Once all parameters were estimated, the source fluxes were calculated using (3.16). Contour plots of pressure were generated from pressures at a grid of points in the spatial domain calculated using (3.6). All computations were carried out using MATLAB 2016a (Mathworks, Inc., Natick, Massachusetts, USA).

4. Results

4.1 Discrete model

Figure 3 shows the pressure and flow distributions in each mesentery network, calculated using the discrete model with the flow estimation method. Each network displays haemodynamic properties consistent with expectations for the microcirculation, with vascular pressures decreasing from the arterioles to the capillaries and then venules. The predicted pressure drop is largest for

Network 1 (84 mmHg), with lower values for Network 2, 3 (42 and 58 mmHg, respectively). Arterioles and capillaries exhibits wide pressure ranges. Figure 4 shows their overlapping pressure distributions. Venular pressures are restricted to the lower end of the pressure range, with low means and standard deviations (Table 2), justifying the averaging of the venular network in the discrete-continuum model.

Flow predictions of the discrete model are shown in Figure 3. Flows are largest in the larger-diameter arterioles and venules, and the majority of capillaries have low flows. In general, flows are largest in Network 2 (a maximum of 1158 nL/min) compared to Networks 1, 3 (maxima of 686 and 727 nL/min, respectively), with larger flows in Network 2 for a smaller pressure drop consistent with the larger network conductivity for that network. The discrete model simulations have 1.6%, 11.8% and 7.4% segment flow directions reversed compared to *in vivo* observations of flow directions.

4.2 Discrete-continuum model

The arteriolar networks with locations of the source points are shown in Figure 1. The number of sources (including arteriolar and capillary side branches), capillary network conductivities, and values of the venous drainage parameter, β, are provided in Table 2; the latter of which are calculated by matching of the sums of the source fluxes predicted by the discrete-continuum method with those from the fully discrete approach. Contour plots of the pressure and velocity distributions in the capillary network are shown in Figure 5. Predicted capillary pressures decay with distance away from the arteriolar sources, consistent with expected bulk pressure drops across the vasculature. For each network, the minimum pressure was achieved at the boundaries of the tissue domain; these minimum pressures were between 3 and 7 mmHg, corresponding to drainage into the central venous system.

Figure 6 shows comparisons of discrete-continuum and discrete predictions of pressures at the nodal locations of each network, for both capillaries and venules. As with the discrete model, the capillary locations (green) in the discrete-continuum model encompass wide pressure ranges, whereas venule locations (blue) are clustered in the lower end of the pressure spectrum. In network 1, the mean pressure at the terminal arterioles in the hybrid model was similar to that in the discrete model, but in networks 2 and 3, the hybrid model predictions of mean pressure were higher than the discrete model predictions by 32% and 53% respectively. The coefficient of determination (R^2) between the discrete-continuum and discrete pressure predictions at the source locations is approximately 0.89, 0.61 and 0.68 for Networks 1, 2, and 3, respectively, indicating good correlation between the two models in predicting microcirculatory pressures. Discrepancies in predicted pressures between the two models were largest in regions where arterioles and venules were in close spatial proximity but not closely connected topologically (data not shown). Such

discrepancies likely arise from the representation of the venular network as a spatially uniform flow sink rather than as a discrete network.

Blood flow velocity predictions of the discrete-continuum model are highest for Network 2, which has the largest network conductivity (Figure 5). Whereas the continuum pressure decays with distance from the arteriolar sources, the spatial organisation of these sources results in local gradients of the pressure field and spatial patterning in the continuum velocity field (for example localised regions of low or high flow), which depends on the local distribution of sources. An analysis of the difference in the discrete and discrete-continuum velocity directions (not shown) indicates that areas of high correlation in velocity directions were distributed seemingly randomly across the regions considered, with the flow directions in the discrete model strongly dictated by the local network geometry. The R^2 values between the discrete-continuum and discrete flow predictions at the source locations are approximately 0.27, 0.52 and 0.28 for Networks 1, 2 and 3 respectively. For all three networks, the SD of the flows was approximately 50% lower in the hybrid model than in the discrete model.

4.3 Sensitivity analysis

To compare the discrete and hybrid models, we analysed the sensitivity of predicted pressures and flows evaluated at the arteriolar source locations to perturbations in key parameters. In the discrete model, ±10% variations were applied to the parameter k_T in the flow estimation algorithm, the venular outflow pressure p_0 and the flow BCs. The results (Table 4) showed similar trends as in previous studies (Smith, 2013; Sweeney et al; 2018). The source pressure and flow rates were not sensitive to changes in k_T. Increasing p_0 elevated predicted source pressures. Large variations in mean source pressures were observed as a result of altering flow BCs. As a result, mean flow rates significantly changed at the source locations due to redistribution of network flow.

In the discrete-continuum model, ±10% variations were applied to the conductivity κ, source radius r_0 and flow BCs at nodes located at the boundaries of each network (Table 5). The mean of the source flows was fixed in the sensitivity analysis because this quantity was used to determine the rate of venous drainage, β. Perturbing κ and r_0 by ±10% had minimal effects in all networks. As in the discrete model, the predictions were sensitive to modification of the flow BCs.

The source radius r_0 is a key parameter in the discrete-continuum model because it affects the pressure field in the continuum resulting from a given arteriolar sources. Further sensitivity analyses were performed to determine the effects of changing r_0 on (a) the difference in predicted means of pressures at arteriolar source locations, and (b) the R^2 of pressures (results are shown in Figure 7). With increasing r_0, the magnitudes of pressure differences between the two models

increase, but the R^2 values improve. The chosen value of r_0 = 20 μm achieves near maximal R^2 values while minimising the magnitude of the pressure differences.

5. Discussion and conclusions

Recent developments in imaging methods are providing data on extensive microvascular structures, but comprehensive measurements of blood flow and pressure are generally infeasible. Mathematical models that predict tissue-scale transport processes based on such structural data have potential to provide insights into normal and pathophysiological tissue function, and guide drug development and dosing regimens. Motivated by these goals, we have developed a hybrid discrete–continuum method for estimating microcirculatory blood flows and pressures from data on network structure and subjected it to rigorous testing by comparing results with those obtained from simulations of the complete network structure.

The hybrid discrete-continuum approach presented here has several advantages. Relative to a purely continuum approach, the inclusion of the arteriolar network results in strong spatial gradients and heterogeneity in microvascular pressure and flow fields. Relative to a fully discrete approach, the representation of capillaries and venules by a continuum greatly decreases the anatomic data that is needed for the model. Predicted intravascular pressures at arteriolar source points are well correlated with predictions from the discrete model. The inclusion of arterioles allows for explicit simulation of effects of local flow regulation, which is mainly achieved by control of arteriolar diameters.

The comparisons with the fully discrete model reveal some limitations of the hybrid approach. The use of a continuum representation for capillaries and venules tends to smooth the results, leading to lower levels of heterogeneity in pressure and flow variables than are predicted by the discrete model. Pressures at the arteriolar source points predicted by the hybrid model are generally higher than obtained using the discrete model, and the discrepancy varies among networks tested. Source flows predicted by the hybrid model show relatively low correlations with the discrete predictions. While the discrete model itself is not definitive, being based on flow estimations with incomplete boundary conditions, these findings nonetheless indicate that the hybrid model is only partially successful in providing quantitative predictions and in representing the flow heterogeneity within and among microvascular network structures.

The application of this discrete-continuum approach is appropriate in cases where the complete network structure is not available. It is assumed that the complete network structure of the arterioles is available. Also, the capillary network structure in a sample region of the tissue is needed, together with specified pressures feeding the arteriolar network and draining the venular

network, and an estimate of overall tissue perfusion (flow per volume). In such cases, the following procedure would be used.
(1) Calculate the capillary network conductivity κ by using data on the vessel radii and lengths to parameterise the micro-cell homogenisation approach (Smith et al, 2014).
(2) Couple a discrete model for flow in the arterioles to a continuum model for transport in the capillary bed, via flow sources into the continuum domain.
(3) Represent the venular network by a sink term distributed throughout the continuum domain.
(4) Solve the coupled system of equations for the pressures at the arteriolar source locations. Estimate the coefficient β by matching perfusion with the prescribed value.

In summary, hybrid discrete-continuum models represent a promising approach to meeting the challenge of relating observations of microvascular structure to the resulting functional properties of tissues (El-Bouri & Payne, 2015; Smith et al; 2016). Such models can readily be extended to fully three-dimensional vascular structures with depth-dependent (Schmid et al; 2017) or anisotropic (Smith et al; 2014) capillary network properties, to incorporate more sophisticated descriptions of vessel tortuosity (Penta & Ambrosi, 2015) and network haemodynamics (e.g. Secomb et al, 2001), and combined with simulations of oxygen transport (Secomb et al; 2004; Secomb 2016) and models of flow regulation (Sweeney et al, 2018; Fry et al, 2013) to gain insight into the physiological processes underlying the control of blood and oxygen supply to tissues.

Competing interests

We have no competing interests.

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