

HOMOGENIZATION OF NONLINEAR BLOOD FLOW IN PERIODIC NETWORKS: THE LIMIT OF SMALL HAEMATOCRIT HETEROGENEITY*

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Abstract. In this work we develop a homogenization methodology to upscale mathematical descriptions of microcirculatory blood flow from the microscale (where individual vessels are resolved) to the macroscopic (or tissue) scale. Due to the assumed two-phase nature of blood and specific features of red blood cells (RBCs), mathematical models for blood flow in the microcirculation are highly nonlinear, coupling the flow and RBC concentrations (haematocrit). In contrast to previous works which accomplished blood-flow homogenization by assuming that the haematocrit level remains constant, here we allow for spatial heterogeneity in the haematocrit concentration and thus begin with a nonlinear microscale model. We simplify the analysis by considering the limit of small haematocrit heterogeneity which prevails when variations in haematocrit concentration between neighboring vessels are small. Homogenization results in a system of coupled, nonlinear partial differential equations describing the flow and haematocrit transport at the macroscale, in which a nonlinear Darcy-type model relates the flow and pressure gradient via a haematocrit-dependent permeability tensor. During the analysis we obtain further that haematocrit transport at the macroscale is governed by a purely advective equation. Applying the theory to particular examples of two- and three-dimensional geometries of periodic networks, we calculate the effective permeability tensor associated with blood flow in these vascular networks. We demonstrate how the statistical distribution of vessel lengths and diameters, together with the average haematocrit level, affect the statistical properties of the macroscopic permeability tensor. These data can be used to simulate blood flow and haematocrit transport at the macroscale.

Key words. homogenization, multiple scales, blood flow, haematocrit

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1. Introduction. The microcirculation is a complex network of vessels whose primary function is to distribute oxygen and nutrients to the tissues and remove waste products. Due to the large number of vessels and their characteristically small diameter, the microcirculation also plays a major role in blood flow resistance. In diseased states, increases in blood-flow resistance can lead to increased blood pressure and risk of cardiovascular events such as stroke [24, 26]; additionally, the abnormal structure of the microcirculatory network in tumors, characterized by many immature leaky vessels and small inter-branching distances, leads to inefficient and inhomogeneous distribution of oxygen, which can manifest as tumor hypoxia [20, 29], and have poor

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consequences in terms of tumor prognosis. Therefore, it is of evident interest to gain a better understanding of how the structure of the microcirculatory network affects blood flow.

State-of-the-art imaging modalities (e.g., [4, 8]) can now generate detailed information about microcirculatory networks with high fidelity and spatial resolution. However, numerical simulations of blood flow and the associated transport of oxygen at the scale of entire tissues is still too computationally intensive to conduct, even for relatively small volumes of tissue. This is especially true when the intrinsic nonlinearities of blood flow (see below) are taken into consideration and when the flow is unsteady.

One solution to the problem of resolution over large volumes of tissue is to *replace* the microscale mass and momentum balances with an upscaled representation. This is particularly effective when microscale information is not critical for the modeling goals. One such methodology that has been applied successfully in a variety of fields across science and engineering is the method of multiple-scale homogenization. A useful feature of this approach is that the microstructural properties of the vascular network are related to the macroscale transport properties in a coherent and predictable way. Thus, homogenization of blood flow in vascular networks can leverage the (nowadays) available microscale data of network structures (e.g., [4, 8]) to generate predictions regarding measurable distributions of flow and oxygen transport at the macroscale (e.g., [14, 27]).

Within the homogenization framework, a representative volume is considered such that a separation of length scales is achieved. In other words, the characteristic length scale of the representative volume is sufficiently smaller than the macroscopic length scale (defining, for example, the tissue comprising an organ). While vascular networks do not always allow definition of a *representative* volume, at the scale of the network of the smallest microcapillaries, this approximation is reasonable due to the homogeneous, space-filling nature of the capillary bed [25]. The equations governing the microscale problem in the representative control volume are asymptotically expanded in powers of the ratio of the micro-to-macro length scales. This procedure results in solvability conditions in terms of governing equations for the propagation of the leading-order solution at the macroscale. In the specific context of low-Reynolds-number, fixed-haematocrit flow in networks, the homogenization process results in a Darcy-type equation relating the flow and pressure gradient through an effective permeability tensor which depends on the geometry of the representative microscale network [7].

Blood flow in the microcirculation (specifically in the small-arteriolar and capillary regions) is slow ($U \sim 1$ mm/s), the characteristic diameter is small ($D \sim 10$ μ m), and a typical value of the kinematic viscosity of blood is $\nu \sim 1$ mm²/s. Consequently, the Reynolds number ($\text{Re} = UD/\nu$), describing the ratio of viscous and inertial terms in the momentum balance, is very small ($\text{Re} \sim 0.01 \ll 1$). For simplicity, blood is often viewed as a Newtonian fluid which, together with the low-Reynolds dynamics, justifies the use of a linear, Stokes-flow model. However, this approximation ignores some of the complexities arising from the particulate nature of blood; red blood cells (RBCs) are deformable particles that occupy a significant proportion of the blood volume (typically $\sim 45\%$ in large vessels, but can be somewhat lower in the microcirculation [3]). The high elasticity of the RBCs, coupled with the shear forces induced by the plasma flow, affect RBC migration in several ways, the most important of which is their tendency to migrate transversely, away from the vessel wall, leaving a cell-free layer in the vicinity of the wall. This transverse migration alters the resistance to blood flow as the haematocrit volume fraction and vessel diameter change,

a phenomenon known as the Fåhræus–Lindqvist effect [10]. To account for this effect in continuum models for blood flow, Pries et al. [34] derived an empirical model for the apparent viscosity of blood as a function of the discharge haematocrit (ratio of RBC flux to total flux) and vessel diameter. The existence of an RBC-depleted layer in the vicinity of the vessel wall introduces an additional complexity of blood flow—a nonlinear biasing of the haematocrit flow at a vessel bifurcation towards the daughter branch with the higher flow, a phenomenon known as “plasma skimming”, which leads to an inhomogeneous distribution of haematocrit in the vascular network [33]. Together, the effects of the haematocrit-dependent viscosity and biased haematocrit splitting at vessel bifurcations result in a highly nonlinear system of equations coupling haematocrit concentrations and flow rates in different vessels of a network.

The aforementioned nonlinearities have been shown to drive the emergence of multiple equilibria and oscillatory dynamics in irregularly-structured vessel networks [1, 21, 22]. Many previous papers on the topic of homogenization of blood-flow (e.g., [6, 9, 30, 37, 38, 41]), assumed a constant haematocrit so that the nonlinearities associated with spatially varying haematocrit were neglected. In this work we maintain the spatial variation of haematocrit, and account for the resulting nonlinear properties of blood in our homogenization methodology. This approach requires the momentum and haematocrit balances to be coupled. We found that if vessel diameters are sufficiently large ($\gg 1 \mu\text{m}$), the splitting phenomenon at vessel bifurcations is subdominant such that, at leading order, the average-macroscopic haematocrit is merely advected by the average flow. In turn, the uniformity of haematocrit at the *microscale* (it changes only on the *macroscopic* length scale) results in a nonlinear Darcy relation between the macroscale flow and pressure gradient, where the permeability tensor depends on the macroscopic haematocrit.

The remainder of this manuscript is structured as follows. In section 2 we describe the model for blood flow in vascular networks. We present the homogenization methodology in two parts: in section 3 we extend the homogenization procedure developed by Chapman and Wilmott [7] for homogenization of flow in networks to account for vessel conductances that are haematocrit-dependent. This yields a Darcy-type equation in which the permeability tensor is a function of the haematocrit. Then, in section 4 we close the system of equations by introducing our approach for homogenization of haematocrit propagation which is based on an assumption of small haematocrit heterogeneity (small deviations from uniform haematocrit). The resulting macroscale homogenized model is summarized in section 5. In section 6 we validate the convergence of the network model to the homogenized description. The permeability tensor, included in the homogenized model, contains details about the structure of the microscale representative network. In section 7 we present results for the permeability tensor as a function of the haematocrit level and the geometrical and topological features of the elementary network (i.e., the representative volume). This paper concludes in section 8 where we summarize our findings and outline possible directions for future research.

2. Model for blood flow in vascular networks.

2.1. Model for blood flow in a single vessel. In this section we explain how we relate the blood flow through a single cylindrical vessel to the pressure difference between its ends (nodes). We denote by p_i^* the pressure at node i and by q_{ij}^* and h_{ij} the flow rate and haematocrit fraction (the ratio of RBC flow to the total flow), respectively, in the vessel connecting nodes i and j . Here, and throughout this manuscript, asterisks denote dimensional quantities.

We begin by describing the flow in a single vessel segment. Thus, for each vessel segment, ij , conservation of fluid mass yields the relation

$$(2.1) \quad \frac{\partial q_{ij}^*}{\partial x^*} = 0.$$

Here, x^* is the coordinate coincident with the vessel axis. Consequently, we have that q_{ij}^* is uniform along each vessel segment (but may vary between segments). Our approach requires that we know both the distribution of pressures among segment nodes, and the haematocrit in each segment. As standard for haematocrit, we assume that it is transported hyperbolically, which is equivalent to assuming that the Péclet number is sufficiently large. Thus, assuming a steady-state flow, conservation of haematocrit is given by

$$(2.2) \quad \frac{\partial}{\partial x^*}(q_{ij}^* h_{ij}) = 0,$$

where $q_{ij}^* h_{ij}$ represents the RBC flux (and where $0 \leq h_{ij} \leq 1$ represents the RBC fraction). By combining (2.1) and (2.2) it is immediately apparent that h_{ij} does not vary with the position in a given vessel.

Since we focus on blood flow in the microcirculation, we assume low-Reynolds-number flow and that the pulsatile variations in flow are sufficiently damped that steady-state flow conditions prevail. Each segment is assumed to be cylindrical, with a uniform diameter, d_{ij}^* , whose length, l_{ij}^* , is much larger than its diameter. Under these assumptions, the flow satisfies Poiseuille’s law,

$$(2.3) \quad q_{ij}^* = -\frac{\pi}{128} \frac{d_{ij}^{*4}}{l_{ij}^* \mu_0^* \mu(h_{ij}, \tilde{d}_{ij})} (p_j^* - p_i^*).$$

Here, the apparent viscosity of blood is given by $\mu_0^* \mu$, where μ_0^* represents the plasma viscosity and μ is a nondimensional function which represents the effect that the haematocrit fraction, h_{ij} , and vessel diameter ($\tilde{d}_{ij} = d_{ij}^*/d_\mu^*$ denotes the dimensionless vessel diameter, with $d_\mu^* \equiv 1 \mu\text{m}$) have on the effective blood viscosity. The vessel diameter is scaled by d_μ^* in the viscosity function for consistency with the functional form proposed by Pries et al. [34] to model the empirical blood viscosity. The explicit expression for the blood viscosity used in this work is detailed in Appendix A and is based on the model of [34].

Upon translating the balances to dimensionless form, we scale diameters of vessels by d_0^* , a representative vessel diameter in the network, which is typically much larger than $1 \mu\text{m}$ ($d_0^* \gg d_\mu^*$); and vessel lengths by a reference length, l_0^* . Additionally, we introduce the macroscopic length scale, Λ_0^* , representing the characteristic size of the full vascular network (i.e., a network containing a large number of vessels), such that we can define a small parameter ϵ as follows:

$$(2.4) \quad \epsilon = \frac{l_0^*}{\Lambda_0^*} \ll 1.$$

The pressure is normalized by the macroscopic pressure difference, Δp_0^* , representing the characteristic magnitude of the pressure difference between the macroscopic boundaries. Accordingly, we scale the flow by $\Gamma_0^* \equiv \pi d_0^{*4} \Delta p_0^*/(128 \Lambda_0^* \mu_0^*)$ to obtain the nondimensional equation

$$(2.5) \quad q_{ij} = -\frac{g_{ij}}{\epsilon} (p_j - p_i),$$

where the nondimensional conductance, g_{ij} , is given by

$$(2.6) \quad g_{ij} = \frac{d_{ij}^4}{l_{ij} \mu(h_{ij}, \tilde{d}_{ij})}.$$

2.2. Model for blood flow in a periodic network. In this work, blood flow is represented as occurring in a network of vessel segments (edges) that are connected at bifurcations (nodes). For closure, we assume periodicity of the network such that it forms a tessellation of periodic unit cells filling the macroscale domain. In studies which analysed the statistical properties of vascular networks [25], the capillary bed was found to have a homogeneous distribution of vessel properties across large length scales. Therefore we can view it as if it is composed of repeated tessellations of a specific microstructure. We note that using microscale periodicity to represent the effective properties of the macroscopic domain is common in the literature and heuristically acceptable in the context of Poisson-type problems, such as those that arise in studies of porous-medium flow [32, 42]. Motivated by the similar nature of porous-medium and network flows, we postulate that the periodic-microcell approach is applicable when considering blood flow in vascular networks.

In line with the microscale periodicity assumption, each unit cell is composed of N nodes, connected *internally* by edges, and is *interconnected* to a number of identical neighboring unit cells. The (spatially uniform) set of relative displacements between identical nodes in neighboring unit cells defines the periodic pattern of the network. Following [7], we denote the relative displacement vector by $\mathbf{r} \circ \mathbf{L}$, where \mathbf{L} is the vector of unit-cell dimensions and \circ marks the Hadamard product; \mathbf{r} indicates the direction of displacement in cell-length units.

In periodic networks, two nodes in neighboring unit cells may be connected via either “inlet” or “outlet” vessels. Within each unit cell, there are exactly N nodes. Any such node may be connected to any of the other $N - 1$ nodes within the unit cell, or to nodes that belong to adjacent unit cells. Thus, in order to fully describe the periodic unit cell, the vessels spanning more than one unit cell must be appropriately identified. For that purpose we follow [7] and denote each vessel by a double-small-letter-subscript, ij , marking its end nodes, together with a superscript \mathbf{r} , where \mathbf{r} represents a displacement vector specifying an adjacent unit cell. Accordingly, the set $\mathcal{N} = \{\mathbf{0}, \mathbf{r}_1, \dots, \mathbf{r}_{N_{\text{adj}}}\}$ defines the set of edge displacements, where N_{adj} is the number of neighboring unit cells. Here, $\mathbf{r} = \mathbf{0}$ will mark a vessel whose coordinates i and j are both within a single unit cell; the remaining N_{adj} elements of \mathcal{N} specify the displacements for the remaining edges that begin with one of the N nodes in the unit cell but terminate in an adjacent unit cell. Figure 1 shows a schematic of a periodic network, where some examples for the convention used to define the different edges are shown.

For simplicity of notation, we will sometimes use a single capital-letter-subscript, J , to denote a vessel so that the transformation between vessel index and its corresponding double-node indices is unique. For example, the haematocrit in vessel J can also be represented as the haematocrit in vessel j_0j_1 where j_0 and j_1 are the end nodes of vessel J , $h_J \equiv h_{j_0j_1}^{\mathbf{r}}$. Its periodic counterpart will be denoted by $h_j \equiv h_{j_1j_0}^{-\mathbf{r}}$.

At this juncture, we specify the system of equations governing the flow in the unit cell. By applying conservation of flow at each node, i , we write

$$(2.7) \quad \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N q_{ij}^{\mathbf{r}} = \sum_{\mathbf{r}} \sum_{j=1}^N g_{ij}^{\mathbf{r}} (p_j - p_i) = 0, \quad \text{for } i = 1, \dots, N,$$

where the summation is over all $\mathbf{r} \in \mathcal{N}$ covering both cell-internal vessels and vessels connected to each of the neighboring unit cells. Here, $g_{ij}^{\mathbf{r}} \equiv 0$ if nodes i and j are not connected under the orientation defined by \mathbf{r} .

In order to close (2.7), the conductance, $g_{ij}^{\mathbf{r}} = g_{ij}^{\mathbf{r}}(h_{ij}^{\mathbf{r}})$, must be evaluated. Accordingly, the distribution of haematocrit in the vessel network must be deter-

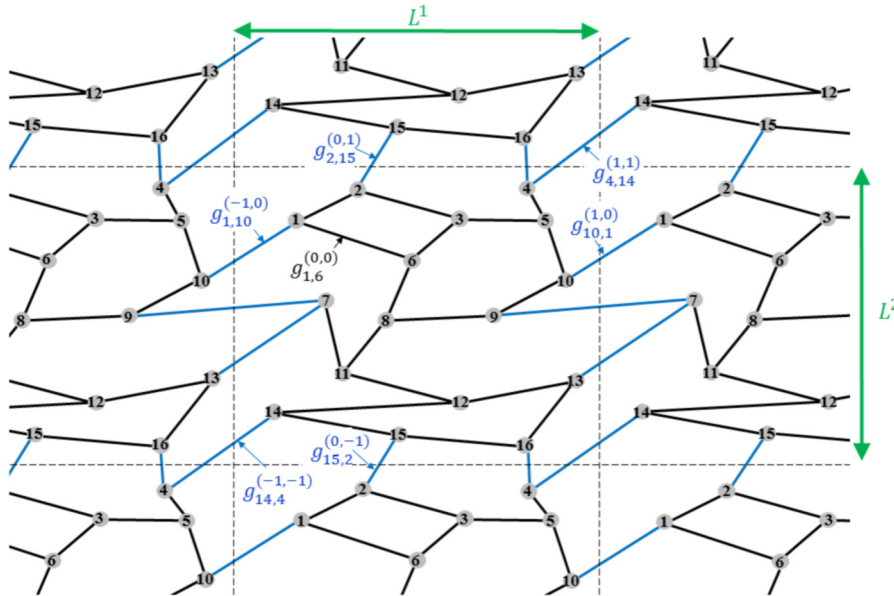


FIG. 1. Schematic of a two-dimensional (2D) periodic network. Each unit cell in this example network is composed of 16 nodes, 18 cell-internal edges (black), and 12 edges spanning more than one unit cell (blue). In this specific example, $\mathbf{L} = (L^1, L^2)$ and $\mathcal{N} = \{(0, 0), (1, 0), (-1, 0), (0, 1), (0, -1), (1, 1), (-1, -1)\}$. Some examples for the convention used to describe the edge conductances, $g_{i,j}^{\mathbf{r}}$, are shown in this figure. (Figure in color online.)

mined. In general, the haematocrit in a vessel depends on the haematocrit and flow in its parent vessel(s) [33]. Therefore, three different types of vessel exist in each unit cell, as illustrated in Figure 2: (i) vessels emerging from bifurcating flow junctions; (ii) vessels originating from converging flow junctions; (iii) vessels originating from nodes in neighboring unit cells (“inlet vessels”). Here, we define the haematocrit in each vessel as

$$(2.8) \quad h_J = F_J(h_{J_p}, q_{J_p}), \quad \text{for } J = 1, \dots, M,$$

where J_p is (are) the parent vessel(s) of vessel J , and F_J depends on the type of the vessel; we postpone its definition to section 4. The number of vessels in the unit cell, M , refers to all the vessels that are connected to at least a single node in the unit cell.

Equations (2.7) and (2.8), together with (2.5) and (2.6), constitute a coupled system of nonlinear equations for p_i ($i = 1, \dots, N$), q_J and h_J ($J = 1, \dots, M$). In this paper we seek to upscale the microscopic unit-cell-level description given by (2.5)–(2.8) to the macroscopic level using the method of multiscale homogenization. The methodology of homogenization of flow in periodic networks was recently formulated by Chapman and Wilmott [7] for the linear case where the vessel conductances are independent of the flow. Here, we generalize the methodology of [7] to a case where the conductances are determined by a viscosity that is *nonlinearly* coupled to the vessel haematocrit; the haematocrit, in turn, depends on the flow through interactions at vessel bifurcations. In section 3 we will follow the scheme of [7] to derive macroscopic equations for the flow in terms of the conductances, $g_{ij}^{\mathbf{r}}$. Then, in section 4 we will derive homogenized equations governing haematocrit propagation through the network so that the conductance can be coupled to the haematocrit through a nonlinear apparent viscosity function.

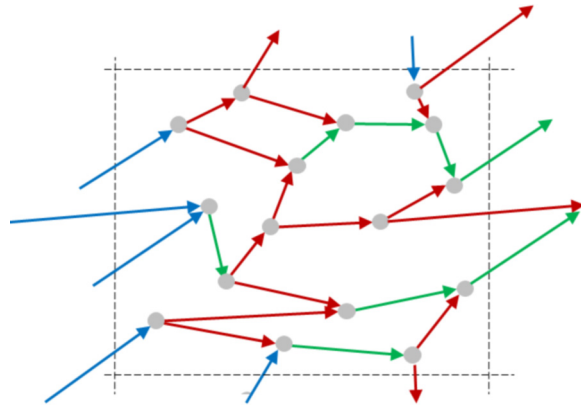


FIG. 2. Examples of different vessel types in a periodic unit cell of vascular networks. In this example, the direction of flow at each edge of the unit cell from Figure 1 was chosen arbitrarily and was denoted by the direction of the arrow. The different vessel types were then marked accordingly: (i) vessels emerging from bifurcating-flow junctions (red); (ii) vessels originating from converging-flow junctions (green); (iii) vessels originating from nodes in neighboring unit cells (blue). (Figure in color online.)

3. Homogenization of the flow.

3.1. Asymptotic solution for the pressure. One critical difference in this problem from the work conducted by [7] is that the conductances, g_{ij}^r , depend upon spatial location through the coupling with the haematocrit (and, hence, ultimately the pressure). While the conductance in each vessel *segment* is constant, the conductance may be different for each such segment. To spatially identify vessel segments, each vessel segment is tagged with the coordinate representing its midpoint. Thus, we have

$$(3.1) \quad g_{ij}^r = g_{ij}^r \left(\mathbf{x} + \frac{1}{2} \epsilon (\mathbf{x}_i + \mathbf{x}_j + \mathbf{r} \circ \mathbf{L}) \right).$$

Here, \mathbf{x} is the origin of the unit cell normalized by the macroscopic length scale, Λ_0^* . The dimensional position of a node within the unit cell, as well as the length of the unit-cell, both scale with the characteristic vessel length, such that

$$\mathbf{x}_i^* = l_0^* \mathbf{x}_i \quad \text{and} \quad \mathbf{L}^* = l_0^* \mathbf{L}.$$

Therefore, the normalization by Λ_0^* yields the $O(\epsilon)$ scaling. For notational convenience, we set

$$(3.2) \quad \bar{\mathbf{x}}_{ij}^r = \mathbf{x} + \frac{1}{2} \epsilon (\mathbf{x}_i + \mathbf{x}_j + \mathbf{r} \circ \mathbf{L}).$$

We are now ready to write the nodal pressures in (2.7) as a function of their spatial locations as follows

$$(3.3) \quad \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N g_{ij}^r(\bar{\mathbf{x}}_{ij}^r) \left[p(\mathbf{x} + \epsilon \mathbf{x}_j + \epsilon \mathbf{r} \circ \mathbf{L}) - p(\mathbf{x} + \epsilon \mathbf{x}_i) \right] = 0, \quad \text{for } i = 1, \dots, N.$$

Sidebar: Expansion of the flow fields and network periodicity. At this juncture, we would like to perform Taylor series expansions for the pressure and conductance in a neighborhood of the cell origin, \mathbf{x} . First, it is important to explain and justify the use of a Taylor series expansion for the conductance which is generally not continuous at vessel bifurcations (also, while the pressure is continuous, its gradient is not). Here, we make the case for the conductance, but the same arguments apply for the pressure.

Consider $g_{ij}^{\mathbf{r}} \equiv \mathbf{G}$, a vector of conductances of all vessels in a single unit cell. Then, the expansion of \mathbf{G} around the cell origin assumes that the change of a specific vessel conductance (a single component in \mathbf{G}) between unit cells is continuous. As such, the discontinuity of the conductance at vessel bifurcations (which manifests by $G_I \neq G_J$, where I and J are two vessels connected at a bifurcation) is not important for the expansion, because we expand each component separately.

The above discussion leads to the explanation of how we impose network *periodicity*. Without loss of generality, we can consider two neighboring unit cells, which are concatenated in the \mathbf{x}^1 direction and numbered n and $n + 1$; the unit cells have a cell-length, ϵL^1 in the \mathbf{x}^1 direction. We accordingly define the x^1 -component of the origin of the n th cell as $(n - 1)\epsilon L$. Then, the conductance of a vessel originating in cell n and terminating in cell $n + 1$ (having an indicator $\mathbf{r}^+ \equiv (1, 0, 0)$) is

$$\begin{aligned}
 (3.4) \quad g_{ij}^{\mathbf{r}^+} \left(n, \bar{\mathbf{x}}_{ij}^{\mathbf{r}^+} \right) &= g \left((n - 1)\epsilon L \mathbf{x}^1 + \frac{1}{2}\epsilon(\mathbf{x}_i + \mathbf{x}_j + L\mathbf{x}^1) \right) \\
 &= g \left(\epsilon \left[\left(n - \frac{1}{2} \right) L \mathbf{x}^1 + \frac{1}{2}(\mathbf{x}_i + \mathbf{x}_j) \right] \right),
 \end{aligned}$$

where $g(\mathbf{x})$ is a continuous and once-differentiable function of the spatial coordinate, \mathbf{x} . Equivalently, the conductance of the *same* vessel can be written as a vessel originating in cell $n + 1$ and terminating in cell n (with an indicator $\mathbf{r}^- = -\mathbf{r}^+$):

$$\begin{aligned}
 (3.5) \quad g_{ji}^{\mathbf{r}^-} \left(n + 1, \bar{\mathbf{x}}_{ji}^{\mathbf{r}^-} \right) &= g \left(n\epsilon L \mathbf{x}^1 + \frac{1}{2}\epsilon(\mathbf{x}_i + \mathbf{x}_j - L\mathbf{x}^1) \right) \\
 &= g \left(\epsilon \left[\left(n - \frac{1}{2} \right) L \mathbf{x}^1 + \frac{1}{2}(\mathbf{x}_i + \mathbf{x}_j) \right] \right),
 \end{aligned}$$

which is identical to the expression in (3.4). Therefore, the *periodicity* condition is given by

$$(3.6) \quad g_{ij}^{\mathbf{r}^+} \left(n, \bar{\mathbf{x}}_{ij}^{\mathbf{r}^+} \right) = g_{ji}^{\mathbf{r}^-} \left(n + 1, \bar{\mathbf{x}}_{ji}^{\mathbf{r}^-} \right).$$

Noting that the number of the unit cell can be simply replaced by the spatial location of its origin, we can write the periodicity condition (3.6) in the form

$$(3.7) \quad g_{ij}^{\mathbf{r}}(\mathbf{x}) = g_{ji}^{-\mathbf{r}}(\mathbf{x}),$$

such that any variation in the conductance of a specific vessel, ij , between different cells is accounted for via the dependence on the spatial location, \mathbf{x} .

Returning now to (3.3) and expanding it in a Taylor series centered on the cell origin, \mathbf{x} , the result is a series in powers of ϵ ,

(3.8)

$$\begin{aligned} & \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N \left[g_{ij}^{\mathbf{r}} + \frac{1}{2} \epsilon \sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}}}{\partial x^s} + \dots \right] \\ & \times \left[p_j - p_i + \epsilon \sum_{k=1}^3 (x_j^k + r^k L^k) \frac{\partial p_j}{\partial x^k} - \epsilon \sum_{k=1}^3 x_i^k \frac{\partial p_i}{\partial x^k} \right. \\ & \left. + \frac{\epsilon^2}{2} \sum_{k=1}^3 \sum_{l=1}^3 (x_j^k + r^k L^k)(x_j^l + r^l L^l) \frac{\partial^2 p_j}{\partial x^k \partial x^l} - \frac{\epsilon^2}{2} \sum_{k=1}^3 \sum_{l=1}^3 x_i^k x_i^l \frac{\partial^2 p_i}{\partial x^k \partial x^l} + \dots \right] = 0. \end{aligned}$$

The expansion of $g_{ij}^{\mathbf{r}}$ reflects the dependence of the conductance on the haematocrit; later, this will be expanded explicitly in terms of the haematocrit. From here forward, unless stated otherwise, functions are evaluated at the cell origin, \mathbf{x} .

To clarify the notation, the nodal pressures are written as a vector, $\mathbf{P} = (p_1, \dots, p_N)^T$. Then, (3.8) can be expressed as a system of N equations in the following compact matrix form:

$$(3.9) \quad A_0 \mathbf{P} + \epsilon \left[\sum_{l=1}^3 B_0^l \frac{\partial \mathbf{P}}{\partial x^l} + A_1 \mathbf{P} \right] + \epsilon^2 \left[\sum_{k=1}^3 \sum_{l=1}^3 C_0^{kl} \frac{\partial^2 \mathbf{P}}{\partial x^k \partial x^l} + \sum_{l=1}^3 B_1^l \frac{\partial \mathbf{P}}{\partial x^l} \right] = O(\epsilon^3),$$

where

$$\begin{aligned} A_0 &= \sum_{\mathbf{r} \in \mathcal{N}} \left[g_{ij}^{\mathbf{r}} - \delta_{ij} \sum_{m=1}^N g_{im}^{\mathbf{r}} \right], \\ B_0^l &= \sum_{\mathbf{r} \in \mathcal{N}} \left[(x_j^l + r^l L^l) g_{ij}^{\mathbf{r}} - \delta_{ij} x_i^l \sum_{m=1}^N g_{im}^{\mathbf{r}} \right], \\ A_1 &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \left[\sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}}}{\partial x^s} - \delta_{ij} \sum_{m=1}^N \sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{im}^{\mathbf{r}}}{\partial x^s} \right], \\ C_0^{kl} &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \left[(x_j^k + r^k L^k)(x_j^l + r^l L^l) g_{ij}^{\mathbf{r}} - \delta_{ij} x_i^k x_i^l \sum_{m=1}^N g_{im}^{\mathbf{r}} \right], \end{aligned}$$

and

$$\begin{aligned} B_1^l &= \sum_{\mathbf{r} \in \mathcal{N}} \left[(x_j^l + r^l L^l) \sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}}}{\partial x^s} \right. \\ & \quad \left. - \delta_{ij} x_i^l \sum_{m=1}^N \sum_{s=1}^3 (x_i^s + x_m^s + r^s L^s) \frac{\partial g_{im}^{\mathbf{r}}}{\partial x^s} \right]. \end{aligned}$$

In these expressions, δ_{ij} is the conventional Kronecker delta tensor. The structure of the matrices A_0 , A_1 , B_0^l , B_1^l and C_0^{kl} depend upon the particular connectivity of the network.

We aim to solve (3.9) in the limit $\epsilon \rightarrow 0$ by seeking an asymptotic expansion for \mathbf{P} of the form

$$(3.10) \quad \mathbf{P} = \mathbf{P}^{(0)} + \epsilon \mathbf{P}^{(1)} + \epsilon^2 \mathbf{P}^{(2)} + \dots$$

At this juncture, the conductances are expanded in the form

$$(3.11) \quad g_{ij}^{\mathbf{r}} = g_{ij}^{\mathbf{r}(0)} + \epsilon g_{ij}^{\mathbf{r}(1)} + \dots$$

The expansion of the conductances will ultimately correspond to the expansion of the haematocrit; this will be explained in further detail in section 3 [see (4.5) et seq.].

Identities. Defining the $[N \times 1]$ vector $\mathbf{u} = (1, \dots, 1)^T$, we have the following identities (these were proved in [7]; for completeness, we reiterate the proofs in Appendix B):

$$(3.12a) \quad A_0 = A_0^T;$$

$$(3.12b) \quad A_0 \mathbf{u} = A_1 \mathbf{u} = \mathbf{0};$$

$$(3.12c) \quad \mathbf{u}^T A_0 = \mathbf{0};$$

$$(3.12d) \quad \mathbf{u}^T B_0^k \mathbf{u} = 0.$$

Substituting from (3.10) and (3.11) into (3.9), and equating the $O(1)$ terms, we have

$$(3.13) \quad A_0(g_{ij}^{\mathbf{r}(0)}) \mathbf{P}^{(0)} = 0.$$

Using (3.12b) and (3.13) we can write

$$(3.14) \quad \mathbf{P}^{(0)} = p(\mathbf{x}) \mathbf{u},$$

showing that, to leading order, the pressure is uniform across the unit cell.

Substituting from (3.14) into (3.9) and equating terms of $O(\epsilon)$ we have

$$(3.15) \quad A_0(g_{ij}^{\mathbf{r}(0)}) \mathbf{P}^{(1)} + \left(A_0(g_{ij}^{\mathbf{r}(1)}) + A_1(g_{ij}^{\mathbf{r}(0)}) \right) p \mathbf{u} + \sum_{l=1}^3 B_0^l(g_{ij}^{\mathbf{r}(0)}) \frac{\partial p}{\partial x^l} \mathbf{u} = 0.$$

Then, using the identity in (3.12b) we have

$$(3.16) \quad A_0(g_{ij}^{\mathbf{r}(0)}) \mathbf{P}^{(1)} + \sum_{l=1}^3 B_0^l(g_{ij}^{\mathbf{r}(0)}) \frac{\partial p}{\partial x^l} \mathbf{u} = 0.$$

From (3.12a) and (3.12b), $A_0^T = A_0$ and $A_0 \mathbf{u} = 0$, such that

$$(3.17) \quad A_0^T(g_{ij}^{\mathbf{r}(0)}) \mathbf{u} = \mathbf{0}.$$

By appealing to the Fredholm alternative, we deduce that since (3.17) holds there is a solution for $\mathbf{P}^{(1)}$ only if

$$(3.18) \quad \mathbf{u}^T \sum_{l=1}^3 B_0^l(g_{ij}^{\mathbf{r}(0)}) \frac{\partial p}{\partial x^l} \mathbf{u} = 0,$$

where (3.12d) guarantees that this condition is satisfied for any p . Then, we can write the $O(\epsilon)$ contribution to the pressure as

$$(3.19) \quad \mathbf{P}^{(1)} = T(\mathbf{x}) \mathbf{u} + \sum_{l=1}^3 \mathbf{w}^l \frac{\partial p}{\partial x^l},$$

where the two terms on the right-hand side represent homogeneous and particular solutions, T is an arbitrary function, and \mathbf{w}^l is any vector satisfying

$$(3.20) \quad A_0(g_{ij}^{\mathbf{r}(0)})\mathbf{w}^l = -B_0^l(g_{ij}^{\mathbf{r}(0)})\mathbf{u}.$$

Substituting from (3.14) and (3.19) into (3.9), and equating terms of $O(\epsilon^2)$, we have

$$(3.21) \quad \begin{aligned} & A_0(g_{ij}^{\mathbf{r}(0)})\mathbf{P}^{(2)} + \left(A_0(g_{ij}^{\mathbf{r}(1)}) + A_1(g_{ij}^{\mathbf{r}(0)}) \right) \sum_{l=1}^3 \mathbf{w}^l \frac{\partial p}{\partial x^l} \\ & + \sum_{k=1}^3 B_0^k(g_{ij}^{\mathbf{r}(0)}) \frac{\partial}{\partial x^k} \left(T(\mathbf{x})\mathbf{u} + \sum_{l=1}^3 \mathbf{w}^l \frac{\partial p}{\partial x^l} \right) + \sum_{l=1}^3 B_0^l(g_{ij}^{\mathbf{r}(1)}) \frac{\partial p}{\partial x^l} \mathbf{u} \\ & + \sum_{k=1}^3 \sum_{l=1}^3 C_0^{kl}(g_{ij}^{\mathbf{r}(0)}) \frac{\partial^2 p}{\partial x^k \partial x^l} \mathbf{u} + \sum_{k=1}^3 B_1^k(g_{ij}^{\mathbf{r}(0)}) \frac{\partial p}{\partial x^k} \mathbf{u} = 0, \end{aligned}$$

where we have used the identity in (3.12b). Then, by the Fredholm alternative, we obtain the following solvability condition:

$$(3.22) \quad \begin{aligned} & \mathbf{u}^T A_1(g_{ij}^{\mathbf{r}(0)}) \sum_{l=1}^3 \mathbf{w}^l \frac{\partial p}{\partial x^l} + \sum_{k=1}^3 \sum_{l=1}^3 \mathbf{u}^T B_0^k(g_{ij}^{\mathbf{r}(0)}) \frac{\partial \mathbf{w}^l}{\partial x^k} \frac{\partial p}{\partial x^l} \\ & + \mathbf{u}^T \sum_{k=1}^3 \sum_{l=1}^3 C_0^{kl}(g_{ij}^{\mathbf{r}(0)}) \frac{\partial^2 p}{\partial x^k \partial x^l} \mathbf{u} + \mathbf{u}^T \sum_{l=1}^3 B_1^l(g_{ij}^{\mathbf{r}(0)}) \frac{\partial p}{\partial x^l} \mathbf{u} = 0, \end{aligned}$$

where the dependence on $g_{ij}^{\mathbf{r}(1)}$ has been eliminated by using the identities in (3.12c) and (3.12d).

We define the symmetric tensor \mathcal{K} ,

$$(3.23) \quad \mathcal{K}^{kl} = \mathbf{u}^T C_0^{kl}(g_{ij}^{\mathbf{r}(0)})\mathbf{u} + \frac{1}{2} \mathbf{u}^T B_0^k(g_{ij}^{\mathbf{r}(0)})\mathbf{w}^l + \frac{1}{2} \mathbf{u}^T B_0^l(g_{ij}^{\mathbf{r}(0)})\mathbf{w}^k$$

and the antisymmetric tensor Ω ,

$$(3.24) \quad \Omega^{kl} = \frac{1}{2} \mathbf{u}^T B_0^k(g_{ij}^{\mathbf{r}(0)})\mathbf{w}^l - \frac{1}{2} \mathbf{u}^T B_0^l(g_{ij}^{\mathbf{r}(0)})\mathbf{w}^k.$$

Additionally, we define the vector ξ ,

$$(3.25) \quad \xi^l = \sum_{k=1}^3 \mathbf{u}^T B_0^k(g_{ij}^{\mathbf{r}(0)}) \frac{\partial \mathbf{w}^l}{\partial x^k} + \mathbf{u}^T A_1(g_{ij}^{\mathbf{r}(0)})\mathbf{w}^l + \mathbf{u}^T B_1^l(g_{ij}^{\mathbf{r}(0)})\mathbf{u}.$$

Then, (3.22) can be written as

$$(3.26) \quad \mathcal{K}^{kl} \frac{\partial^2 p}{\partial x^k \partial x^l} + \xi^l \frac{\partial p}{\partial x^l} = 0,$$

where the terms $\Omega^{kl} \frac{\partial^2 p}{\partial x^k \partial x^l}$ vanish since Ω is an antisymmetric tensor.

Identities. We can simplify the terms that appear in (3.23) and (3.25) as follows (see Appendix C for details):

$$(3.27a) \quad \mathbf{u}^T A_1(g_{ij}^{\mathbf{r}(0)})\mathbf{w}^l = \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{s=1}^3 r^s L^s w_j^l \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s};$$

$$(3.27b) \quad \mathbf{u}^T B_1^l(g_{ij}^{\mathbf{r}(0)}) \mathbf{u} = \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{s=1}^3 [r^l L^l r^s L^s + 2x_j^l r^s L^s] \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s};$$

$$(3.27c) \quad \mathbf{u}^T C_0^{kl}(g_{ij}^{\mathbf{r}(0)}) \mathbf{u} = \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N [r^k L^k r^l L^l + r^l L^l x_j^k + r^k L^k x_j^l] g_{ij}^{\mathbf{r}(0)};$$

$$(3.27d) \quad \mathbf{u}^T B_0^k(g_{ij}^{\mathbf{r}(0)}) \mathbf{w}^l = \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^k L^k w_j^l g_{ij}^{\mathbf{r}(0)};$$

$$(3.27e) \quad \mathbf{u}^T B_0^k(g_{ij}^{\mathbf{r}(0)}) \frac{\partial \mathbf{w}^l}{\partial x^k} = \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{k=1}^3 r^k L^k \frac{\partial w_j^l}{\partial x^k} g_{ij}^{\mathbf{r}(0)}.$$

Substituting from the identities in (3.27c) and (3.27d) into (3.23) we have

$$(3.28) \quad \mathcal{K}^{kl} = \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N [r^k L^k r^l L^l + r^l L^l x_j^k + r^k L^k x_j^l + r^k L^k w_j^l + r^l L^l w_j^k] g_{ij}^{\mathbf{r}(0)}.$$

Following [7], we choose

$$(3.29) \quad \mathbf{w}^l = -L^l \mathbf{v}^l - \mathbf{X}^l,$$

where $\mathbf{X}^l = (x_1^l, \dots, x_N^l)^T$ such that, from (3.20), we have

$$(3.30) \quad L^l A_0(g_{ij}^{\mathbf{r}(0)}) \mathbf{v}^l = -A_0(g_{ij}^{\mathbf{r}(0)}) \mathbf{X}^l + B_0^l(g_{ij}^{\mathbf{r}(0)}) \mathbf{u} = \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N r^l L^l g_{ij}^{\mathbf{r}(0)}.$$

Substituting from (3.29) into (3.28) we have

$$(3.31) \quad \mathcal{K}^{kl} = \frac{L^k L^l}{2L^1 L^2 L^3} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N [r^k r^l + r^k v_i^l + r^l v_i^k] g_{ij}^{\mathbf{r}(0)},$$

where we have relabelled $i \leftrightarrow j$ and $\mathbf{r} \leftrightarrow -\mathbf{r}$ and then used the identity in (3.7). We have also divided (3.22) by $L^1 L^2 L^3$ in order that \mathcal{K}^{kl} will represent the permeability tensor [see (3.37) et seq.].

It has been shown in [7] that

$$(3.32) \quad \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^k v_i^l g_{ij}^{\mathbf{r}(0)} = \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^l v_i^k g_{ij}^{\mathbf{r}(0)}.$$

Therefore, we can also write \mathcal{K}^{kl} as

$$(3.33) \quad \mathcal{K}^{kl} = \frac{L^k L^l}{2L^1 L^2 L^3} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N [r^k r^l + 2r^k v_i^l] g_{ij}^{\mathbf{r}(0)}.$$

Substituting from (3.27a), (3.27b), and (3.27e) into (3.25) we have

$$(3.34) \quad \xi^l = \frac{L^l}{L^1 L^2 L^3} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{s=1}^3 r^s L^s \left[\left(\frac{1}{2} r^l + v_i^l \right) \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s} + \frac{\partial v_i^l}{\partial x^s} g_{ij}^{\mathbf{r}(0)} \right].$$

Taking the divergence of (3.33) we have

$$(3.35) \quad \frac{\partial \mathcal{K}^{kl}}{\partial x^k} = \frac{L^l}{L^1 L^2 L^3} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{k=1}^3 r^k L^k \left[\left(\frac{1}{2} r^l + v_i^l \right) \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^k} + \frac{\partial v_i^l}{\partial x^k} g_{ij}^{\mathbf{r}(0)} \right] = \xi^l.$$

Therefore, (3.26) can be written as the Darcy equation,

$$(3.36) \quad \nabla \cdot (\mathcal{K} \cdot \nabla p) = 0.$$

3.2. Macroscopic fluid velocity. Following [7], the macroscopic Darcy velocity in the k direction, U^k , is given by

$$(3.37) \quad U^k = \frac{L^k}{2L^1 L^2 L^3} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^k q_{ij}^{\mathbf{r}}.$$

Using the scaling introduced in section 2, (3.37) defines the scale of the Darcy velocity as

$$\mathbf{U}^* = \frac{\pi}{128} \frac{d_0^{*4} \Delta p_0^*}{l_0^{*2} \Lambda_0^* \mu_0^*} \mathbf{U},$$

which is equivalent to the characteristic scale of the flow in a vessel divided by the scale of the cross-sectional area of the unit cell. Substituting from (2.5) into (3.37), expanding \mathbf{P} and $g_{ij}^{\mathbf{r}}$ as in (3.10) and (3.11), and substituting from (3.14) and (3.19), we obtain

$$(3.38) \quad \begin{aligned} U^k &= -\frac{L^k}{2L^1 L^2 L^3 \epsilon} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^k \left(g_{ij}^{\mathbf{r}} + \frac{1}{2} \epsilon \sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}}}{\partial x^s} + O(\epsilon^2) \right) \\ &\quad \times \left[p_j + \epsilon \sum_{l=1}^3 (x_j^l + r^l L^l) \frac{\partial p_j}{\partial x^l} - p_i - \epsilon \sum_{l=1}^3 x_i^l \frac{\partial p_i}{\partial x^l} + O(\epsilon^2) \right] \\ &= -\frac{L^k}{2L^1 L^2 L^3} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^k g_{ij}^{\mathbf{r}(0)} \\ &\quad \times \left[p_j^{(1)} + \sum_{l=1}^3 (x_j^l + r^l L^l) \frac{\partial p_j^{(0)}}{\partial x^l} - p_i^{(1)} - \sum_{l=1}^3 x_i^l \frac{\partial p_i^{(0)}}{\partial x^l} \right] + O(\epsilon) \\ &= -\frac{L^k}{2L^1 L^2 L^3} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{l=1}^3 r^k g_{ij}^{\mathbf{r}(0)} [w_j^l + x_j^l + r^l L^l - w_i^l - x_i^l] \frac{\partial p}{\partial x^l} + O(\epsilon) \\ &= -\frac{L^k L^l}{2L^1 L^2 L^3} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{l=1}^3 r^k g_{ij}^{\mathbf{r}(0)} [v_i^l - v_j^l + r^l] \frac{\partial p}{\partial x^l} + O(\epsilon) \\ &= -\frac{L^k L^l}{2L^1 L^2 L^3} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{l=1}^3 g_{ij}^{\mathbf{r}(0)} [2r^k v_i^l + r^k r^l] \frac{\partial p}{\partial x^l} + O(\epsilon). \end{aligned}$$

In the fourth line we substituted \mathbf{w}^l from (3.29) and in the fifth line we relabeled $j \rightarrow i$ and $\mathbf{r} \leftrightarrow -\mathbf{r}$ in the v_j^l term, and then used the identity in (3.7). Combining (3.33) and (3.38), the Darcy velocity can be written as

$$(3.39) \quad \mathbf{U} = -\mathcal{K} \cdot \nabla p.$$

Transforming back to dimensional variables, we have that the dimensional Darcy velocity is given by

$$(3.40) \quad \mathbf{U}^* = -\frac{\mathcal{K}_0^*}{\mu_0^*} \mathcal{K} \cdot \nabla^* p^*,$$

where

$$\mathcal{K}_0^* = \frac{\pi}{128} \frac{d_0^{*4}}{l_0^{*2}}.$$

Therefore, we verify that the macroscopic permeability has the appropriate dimensions of length squared.

We see from (3.36) and (3.39) that the blood pressure and velocity at the macroscale can be solved if the macroscopic permeability tensor, \mathcal{K} , is known. According to (3.33), \mathcal{K} depends on the leading-order vessel conductance,

$$(3.41) \quad g_{ij}^{\mathbf{r}(0)} = \frac{d_{ij}^4}{l_{ij} \mu(h_{ij}^{\mathbf{r}(0)}, \tilde{d}_{ij})},$$

which is a function of the leading order of the vessel haematocrit, $h_{ij}^{\mathbf{r}(0)}$. Consequently, we now turn to evaluate $h_{ij}^{\mathbf{r}(0)}$.

4. Homogenization of the haematocrit propagation. Under steady flow conditions, the haematocrit is uniform along a vessel [see (2.2)], although it changes between vessels due to the nonlinear effect of phase separation occurring at flow bifurcations. In what follows, we consider three different types of vessels that may exist within each unit cell (see illustration in Figure 2): (i) vessels that originate from bifurcating flow junctions; (ii) vessels that originate from converging flow junctions; (iii) vessels that originate from nodes in neighboring unit cells and terminate inside the unit cell (henceforth we will refer to these vessels as “inlet vessels”). Our goal is to determine a relation of the type in (2.8) between the haematocrit in a given vessel and the haematocrit and flow in its parent vessel(s). In what follows we explicitly evaluate the functional form of this relation for the three aforementioned types of vessels.

4.1. Bifurcating flow junctions. It was observed experimentally (e.g., [5, 11, 23, 33]) that, at flow bifurcations, the RBC component of blood does not generally split in proportion to the flow splitting; instead, RBC splitting appears to be a nonlinear function of the ratio of the flow rates at the junction, the local geometry of the vessels (specifically the diameters), and the haematocrit entering the bifurcating junction. The model of Pries et al. [33] is a popular nonlinear empirical relation for representing haematocrit splitting at flow bifurcations. We will use the aforementioned model with the later refinement of coefficients that was carried out in Pries and Secomb [35]. Henceforth, we will denote this model as the Pries model for brevity. Using the Pries model, we have that the ratio of the haematocrit flux, $h_J q_J$, entering a vessel J to the haematocrit flux in its parent vessel, $h_{J_p} q_{J_p}$, satisfies

$$(4.1) \quad \frac{h_J}{h_{J_p}} \psi_{J/J_p} = \frac{\exp [a_{J_p} D (d_J/d_{J'})] (\psi_{J/J_p} - c_{J_p})^{1+b_{J_p}}}{\exp [a_{J_p} D (d_J/d_{J'})] (\psi_{J/J_p} - c_{J_p})^{1+b_{J_p}} + (1 - \psi_{J/J_p} - c_{J_p})^{1+b_{J_p}}}.$$

Here, $\psi_{J/J_p} = q_J/q_{J_p} \in [0, 1]$, where q_J and q_{J_p} represent the (absolute) magnitudes of the flows in vessels J and J_p , respectively. The subscript J' represents the sister

branch of vessel J , while the known function $D(\cdot)$ has the property that $D(d_J/d_{J'}) = -D(d_{J'}/d_J)$ [33, 35]. The haematocrit and flow in (4.1) are evaluated at specific vessel locations (either \mathbf{x}_J or \mathbf{x}_{J_p}). Additionally, a_{J_p} , b_{J_p} and c_{J_p} are functions of the haematocrit and diameter of the parent vessel

$$\frac{a_{J_p}}{a} = \frac{b_{J_p}}{b} = \frac{c_{J_p}}{c} = \frac{1 - h_{J_p}}{\tilde{d}_{J_p}},$$

where a , b and c are $O(1)$ constants and we use the micron-unit-scaled diameter, \tilde{d}_{J_p} , for consistency with the functional form of the Pries model (similar to the viscosity model by [34]; see (2.3)). Most vessels have diameters much larger than one micron, so that $\tilde{d}_{J_p} \gg 1$. Therefore, we may introduce the small parameter, $\alpha\epsilon$, to the definition of \tilde{d}_{J_p} as follows:

$$(4.2) \quad \tilde{d}_{J_p} = \frac{d_{J_p}^* d_0^*}{d_\mu^* d_0^*} = \frac{1}{\alpha\epsilon} d_{J_p},$$

where d_0^* is the reference diameter of the vessels in the network ($\gg 1\mu\text{m}$) and the nondimensional, $O(1)$, vessel diameter is

$$d_{J_p} = \frac{d_{J_p}^*}{d_0^*}.$$

The small parameter is defined by

$$\alpha\epsilon = \frac{d_\mu^*}{d_0^*} \ll 1.$$

Therefore, using the definition of ϵ in (2.4), we have that

$$\alpha = \frac{(d_\mu^*/d_0^*)}{(l_0^*/\Lambda_0^*)},$$

representing the ratio of the two small parameters in the asymptotic expansion.

Introducing the rescaling in (4.2) into (4.1) we have

$$(4.3) \quad \begin{aligned} \frac{h_J}{h_{J_p}} \psi_{J/J_p} &= \exp[\alpha\epsilon a_{J_p} D(d_J/d_{J'})] (\psi_{J/J_p} - \alpha\epsilon c_{J_p})^{1+\alpha\epsilon b_{J_p}} \\ &\times \left[\exp[\alpha\epsilon a_{J_p} D(d_J/d_{J'})] (\psi_{J/J_p} - \alpha\epsilon c_{J_p})^{1+\alpha\epsilon b_{J_p}} \right. \\ &\left. + (1 - \psi_{J/J_p} - \alpha\epsilon c_{J_p})^{1+\alpha\epsilon b_{J_p}} \right]^{-1}. \end{aligned}$$

Expanding (4.3) in powers of ϵ and dividing by ψ_{J/J_p} we have

$$(4.4) \quad \begin{aligned} \frac{h_J}{h_{J_p}} &= 1 + \alpha\epsilon \left(\frac{1 - h_{J_p}}{d_{J_p}} \right) \left[b(1 - \psi_{J/J_p}) \ln \left(\frac{\psi_{J/J_p}}{1 - \psi_{J/J_p}} \right) \right. \\ &\left. + c \left(2 - \frac{1}{\psi_{J/J_p}} \right) + a(1 - \psi_{J/J_p}) D(d_J/d_{J'}) \right] + O(\epsilon^2). \end{aligned}$$

We note that this expansion holds provided that $D(d_J/d_{J'}) \lesssim O(1)$ and that ψ_{J/J_p} is not in the neighborhood of $\alpha\epsilon c_{J_p}$ or $1 - \alpha\epsilon c_{J_p}$, namely $|\ln(\psi_{J/J_p}/(1 - \psi_{J/J_p}))| \lesssim O(1)$.

From (4.4) we note that, at leading order, the haematocrit in the daughter branches equals the haematocrit in the parent branch. Consequently, the leading-order haematocrit is uniform across the unit cell. Accordingly, we now expand the haematocrit around the reference state in which the haematocrit is equal to $h(\mathbf{x})$ for all vessels in the unit cell,

$$(4.5) \quad h_J = h + \epsilon h_J^{(1)} + O(\epsilon^2).$$

Similarly, we expand the flow around its leading order value

$$(4.6) \quad q_J = q_J^{(0)} + \epsilon q_J^{(1)} + O(\epsilon^2).$$

The absolute magnitude of the flow associated with the reference state, $q_J^{(0)}$, can be derived from the leading order flow problem. Expanding (2.5) in a manner similar to that used to expand (3.38) we have

$$(4.7) \quad q_J^{(0)} \equiv |q_{j_0 j_1}^{\mathbf{r}(0)}| = g_J(h) \left| \sum_{l=1}^3 L^l [v_{j_0}^l - v_{j_1}^l + r_J^l] \frac{\partial p}{\partial x^l} \right|,$$

where j_0 and j_1 are the end nodes of vessel J , and \mathbf{r}_J is the cell-neighbor indicator associated with vessel J . In (4.7), we have used the fact that the leading order vessel conductance is a function of the leading order haematocrit, $g_{j_0 j_1}^{\mathbf{r}(0)} \equiv g_J(h)$.

We note here that if j_0 and j_1 are the edge nodes of vessel J , we define \mathbf{x}_J as

$$(4.8) \quad \mathbf{x}_J = \frac{1}{2}(\mathbf{x}_{j_0} + \mathbf{x}_{j_1} + \mathbf{r}_J \circ \mathbf{L}) \equiv \bar{\mathbf{x}}_{j_0 j_1}^{\mathbf{r}_J},$$

in accordance with the definition in (3.2). We now expand the haematocrit in vessel J located at \mathbf{x}_J around the cell origin, \mathbf{x} :

$$(4.9) \quad h_J(\mathbf{x} + \epsilon \mathbf{x}_J) = h_J(\mathbf{x}) + \epsilon \sum_{s=1}^3 x_J^s \frac{\partial h_J}{\partial x^s} \Big|_{\mathbf{x}} + O(\epsilon^2).$$

The $O(\epsilon)$ haematocrit in the daughter branches is then determined by substituting (4.5)–(4.7) and (4.9) into (4.4)

$$(4.10) \quad \begin{aligned} q_J^{(0)} \left(h_{J_p}^{(1)} - h_J^{(1)} \right) &= q_J^{(0)} \sum_{s=1}^3 (x_J^s - x_{J_p}^s) \frac{\partial h}{\partial x^s} \\ &\quad - \alpha h \left(\frac{1-h}{d_{J_p}} \right) q_J^{(0)} \left[b(1 - \psi_{J/J_p}^{(0)}) \ln \left(\frac{\psi_{J/J_p}^{(0)}}{1 - \psi_{J/J_p}^{(0)}} \right) \right. \\ &\quad \left. + c \left(2 - \frac{1}{\psi_{J/J_p}^{(0)}} \right) + a(1 - \psi_{J/J_p}^{(0)}) D(d_J/d_{J'}) \right]. \end{aligned}$$

For brevity we write (4.10) as

$$(4.11) \quad q_J^{(0)} \left(h_{J_p}^{(1)} - h_J^{(1)} \right) = q_J^{(0)} \sum_{s=1}^3 (x_J^s - x_{J_p}^s) \frac{\partial h}{\partial x^s} - \alpha h(1-h) f_J^{(0)},$$

where

$$(4.12) \quad f_J^{(0)} = \frac{q_J^{(0)}}{d_{J_p}} \left[b(1 - \psi_{J/J_p}^{(0)}) \ln \left(\frac{\psi_{J/J_p}^{(0)}}{1 - \psi_{J/J_p}^{(0)}} \right) + c \left(2 - \frac{1}{\psi_{J/J_p}^{(0)}} \right) + a(1 - \psi_{J/J_p}^{(0)}) D(d_J/d_{J'}) \right]$$

is a function containing details of the splitting rule at leading order.

LEMMA 4.1. $f_J^{(0)} = -f_{J'}^{(0)}$

Proof. Starting from (4.12) and replacing $\psi_{J/J_p}^{(0)} = 1 - \psi_{J'/J_p}^{(0)}$ in the first and third terms of the equation, and using $\psi_{J/J_p}^{(0)} = q_J^{(0)}/q_{J_p}^{(0)}$ in the second term, we have

$$(4.13) \quad f_J^{(0)} = \frac{1}{d_{J_p}} \left[-bq_J^{(0)} \psi_{J'/J_p}^{(0)} \ln \left(\frac{\psi_{J'/J_p}^{(0)}}{1 - \psi_{J'/J_p}^{(0)}} \right) + c \left(2q_J^{(0)} - q_{J_p}^{(0)} \right) + aD(d_J/d_{J'}) q_J^{(0)} \psi_{J'/J_p}^{(0)} \right].$$

Using $q_J^{(0)} = q_{J_p}^{(0)} - q_{J'}^{(0)}$ we have

$$(4.14) \quad f_J^{(0)} = \frac{1}{d_{J_p}} \left[-b(q_{J_p}^{(0)} - q_{J'}^{(0)}) \psi_{J'/J_p}^{(0)} \ln \left(\frac{\psi_{J'/J_p}^{(0)}}{1 - \psi_{J'/J_p}^{(0)}} \right) - c \left(2q_{J'}^{(0)} - q_{J_p}^{(0)} \right) + aD(d_J/d_{J'}) q_{J'}^{(0)} (1 - \psi_{J'/J_p}^{(0)}) \right].$$

Using $\psi_{J'/J_p}^{(0)} = q_{J'}^{(0)}/q_{J_p}^{(0)}$ in the first and second terms, and $D(d_J/d_{J'}) = -D(d_{J'}/d_J)$ [35] in the third term, we have

$$(4.15) \quad f_J^{(0)} = -\frac{q_{J'}^{(0)}}{d_{J_p}} \left[b(1 - \psi_{J'/J_p}^{(0)}) \ln \left(\frac{\psi_{J'/J_p}^{(0)}}{1 - \psi_{J'/J_p}^{(0)}} \right) + c \left(2 - \frac{1}{\psi_{J'/J_p}^{(0)}} \right) + aD(d_{J'}/d_J) (1 - \psi_{J'/J_p}^{(0)}) \right].$$

On the other hand, replacing $J \rightarrow J'$ in (4.12) we have

$$(4.16) \quad f_{J'}^{(0)} = \frac{q_{J'}^{(0)}}{d_{J_p}} \left[b(1 - \psi_{J'/J_p}^{(0)}) \ln \left(\frac{\psi_{J'/J_p}^{(0)}}{1 - \psi_{J'/J_p}^{(0)}} \right) + c \left(2 - \frac{1}{\psi_{J'/J_p}^{(0)}} \right) + a(1 - \psi_{J'/J_p}^{(0)}) D(d_{J'}/d_J) \right].$$

Comparing (4.15) and (4.16) we have that $f_J^{(0)} = -f_{J'}^{(0)}$ as required. \square

4.2. Converging flow junctions. At nodes where the flow in two vessels converge into one, we have the following haematocrit flow balance:

$$(4.17) \quad q_J h_J|_{\mathbf{x}+\epsilon\mathbf{x}_J} = \sum_{J_p} q_{J_p} h_{J_p}|_{\mathbf{x}+\epsilon\mathbf{x}_{J_p}},$$

where the summation is over the two parent vessels of vessel J . We expand h_J and q_J around their reference state and expand $h_J(\mathbf{x} + \epsilon\mathbf{x}_J)$ around \mathbf{x} , as for (4.5)–(4.7) and (4.9). We note that in (4.7), $q_J^{(0)}$ is already given in $\mathbf{x} + \epsilon\mathbf{x}_J$ as a function of the leading order pressure and haematocrit, hence, it is not necessary to expand it around the cell origin. Accordingly, we obtain

$$(4.18) \quad \sum_{J_p} q_{J_p}^{(0)} h_{J_p}^{(1)} - q_J^{(0)} h_J^{(1)} = \sum_{s=1}^3 \left(x_J^s q_J^{(0)} - \sum_{J_p} x_{J_p}^s q_{J_p}^{(0)} \right) \frac{\partial h}{\partial x^s},$$

where we have used the fact that the net flow balance at each node is zero, i.e., $\sum_{J_p} q_{J_p} - q_J = 0$.

4.3. Inlet vessels. Recalling the sidebar discussion in section 3 regarding the periodicity of the network, we assume

$$(4.19) \quad h_{ij}^{\mathbf{r}}(\mathbf{x}) = h_{ji}^{-\mathbf{r}}(\mathbf{x}),$$

in accordance with (3.7). Transforming from node to vessel notations, (4.19) states that if J is an inlet vessel having corresponding periodic outlet vessel \hat{J} , then we have

$$(4.20) \quad h_J(\mathbf{x}) = h_{\hat{J}}(\mathbf{x}).$$

Taking the $O(\epsilon)$ terms from (4.20) and multiplying by $q_J^{(0)}$ we have

$$(4.21) \quad q_J^{(0)} \left(h_{\hat{J}}^{(1)} - h_J^{(1)} \right) = 0.$$

4.4. Asymptotic solution for the haematocrit. Combining all types of vessels, (4.11), (4.18) and (4.21), into a single relation we have

$$(4.22) \quad Y_J^{\text{sp}} q_J^{(0)} \left(h_{J_p}^{(1)} - h_J^{(1)} \right) + Y_J^{\text{co}} \left(\sum_{J_p} q_{J_p}^{(0)} h_{J_p}^{(1)} - q_J^{(0)} h_J^{(1)} \right) + Y_J^{\text{in}} q_J^{(0)} \left(h_{\hat{J}}^{(1)} - h_J^{(1)} \right) \\ = Y_J^{\text{sp}} \left(q_J^{(0)} \sum_{s=1}^3 (x_J^s - x_{J_p}^s) \frac{\partial h}{\partial x^s} - \alpha h(1-h) f_J^{(0)} \right) \\ + Y_J^{\text{co}} \sum_{s=1}^3 \left(x_J^s q_J^{(0)} - \sum_{J_p} x_{J_p}^s q_{J_p}^{(0)} \right) \frac{\partial h}{\partial x^s}, \quad \text{for } J = 1, \dots, M.$$

Here, $Y_J^{\text{sp}} = 1$ if vessel J originates from a splitting bifurcation and $Y_J^{\text{sp}} = 0$ otherwise; $Y_J^{\text{co}} = 1$ if vessel J originates from a converging bifurcation and $Y_J^{\text{co}} = 0$, otherwise; $Y_J^{\text{in}} = 1$ if vessel J is an inlet vessel and $Y_J^{\text{in}} = 0$, otherwise. If we write the first-order vessel haematocrit as a vector, $\mathbf{h}^{(1)} = (h_1^{(1)}, \dots, h_M^{(1)})^T$, then we obtain a system of M equations for $h_J^{(1)}$ ($J = 1, \dots, M$), which can be written in a matrix form as follows:

$$(4.23) \quad \mathbf{Q} \mathbf{h}^{(1)} = \sum_{s=1}^3 \boldsymbol{\eta}^s \frac{\partial h}{\partial x^s} - \alpha h(1-h) \boldsymbol{\varpi},$$

where the matrix \mathbf{Q} is given by

$$(4.24) \quad Q_{JK} = \begin{cases} -q_J^{(0)} & \text{if } J = K, \\ q_J^{(0)} & \text{if } K \text{ is the parent vessel of } J \text{ at a splitting junction} \\ & \text{or } K \text{ is the periodic outlet vessel of inlet } J, \\ q_K^{(0)} & \text{if } K \text{ is the parent vessel of } J \text{ at a converging junction.} \end{cases}$$

The vectors $\boldsymbol{\eta}^s$ and $\boldsymbol{\varpi}$ read

$$(4.25) \quad \begin{aligned} \eta_J^s &= Y_J^{\text{sp}} q_J^{(0)} (x_J^s - x_{J_p}^s) + Y_J^{\text{co}} \left(q_J^{(0)} x_J^s - \sum_{J_p} q_{J_p}^{(0)} x_{J_p}^s \right) \text{ and} \\ \varpi_J &= Y_J^{\text{sp}} f_J^{(0)}. \end{aligned}$$

It is straightforward to show that each column K of Q_{JK} has either two or three nonzero entries according to how many daughter vessels it has: (i) $(-q_K^{(0)}, q_K^{(0)})$ if K is either an outlet vessel or one of the parent vessels in a converging-flow junction; (ii) $(-q_K^{(0)}, q_{K_{d_1}}^{(0)}, q_{K_{d_2}}^{(0)})$ if K is a parent vessel at a splitting junction where K_{d_1} and K_{d_2} are the indices of the daughter vessels. Therefore, due to conservation of flow at bifurcations, we have

$$(4.26) \quad \mathbf{Q}^T \mathbf{u} = \mathbf{0},$$

where we have used the $[M \times 1]$ vector $\mathbf{u} = (1, \dots, 1)^T$. Accordingly, we can use the Fredholm alternative to write the solvability condition of (4.23) as a partial differential equation for the propagation of the leading-order haematocrit at the macroscale,

$$(4.27) \quad \mathbf{u}^T \left(\sum_{s=1}^3 \boldsymbol{\eta}^s \frac{\partial h}{\partial x^s} - \alpha h (1-h) \boldsymbol{\varpi} \right) = 0.$$

Finally, (4.27) can be simplified to obtain

$$(4.28) \quad \mathcal{C} \cdot \nabla h = \alpha h (1-h) \mathcal{S},$$

where

$$(4.29) \quad \mathcal{C}^s = \mathbf{u}^T \boldsymbol{\eta}^s \text{ and } \mathcal{S} = \mathbf{u}^T \boldsymbol{\varpi}.$$

LEMMA 4.2. $\mathcal{S} = 0$.

Proof. Combining (4.25) and (4.29) we have

$$(4.30) \quad \mathcal{S} = \mathbf{u}^T \boldsymbol{\varpi} = \sum_{J=1}^M Y_J^{\text{sp}} f_J^{(0)}.$$

From Lemma 4.1 we have that daughter vessels have equal and opposite values of $f_J^{(0)}$, such that they cancel each other when all splitting vessels are summed together. Consequently, we have $\mathcal{S} = 0$. \square

LEMMA 4.3. $\mathcal{C}/(L^1 L^2 L^3) = \mathbf{U}$.

Proof. Dividing \mathcal{C}^s by $(L^1L^2L^3)$ and using (4.25), we have

$$(4.31) \quad \frac{\mathcal{C}^s}{L^1L^2L^3} = \frac{\mathbf{u}^T \boldsymbol{\eta}^s}{L^1L^2L^3} = \frac{1}{L^1L^2L^3} \sum_{J=1}^M \left[Y_J^{\text{sp}} q_J^{(0)} (x_J^s - x_{J_p}^s) + Y_J^{\text{co}} \left(q_J^{(0)} x_J^s - \sum_{J_p} q_{J_p}^{(0)} x_{J_p}^s \right) \right].$$

We note that internal vessels do not contribute to this sum because they are both daughter and parent vessels such that their contributions, appearing with both positive and negative signs, are cancelled out. Therefore, (4.31) can be written as

$$(4.32) \quad \frac{\mathcal{C}^s}{L^1L^2L^3} = \frac{1}{L^1L^2L^3} \sum_{J=1}^M Y_J^{\text{in}} q_J^{(0)} (x_J^s - x_{\hat{J}}^s) = \frac{L^s}{2L^1L^2L^3} \sum_{\mathbf{r}} \sum_{i=1}^N \sum_{j=1}^N r^s q_{ij}^{\mathbf{r}(0)} = U^s,$$

where \hat{J} is the periodic outlet vessel corresponding to inlet vessel J , and we have used the definition of U^s from (3.37). We have also used that, at leading order, $q_J^{(0)} = q_{\hat{J}}^{(0)}$ [see (4.7)]. Thus, we have proved that the Darcy velocity, \mathbf{U} , is equal to the haematocrit advection vector. \square

Finally, we apply Lemmas 4.2 and 4.3 to (4.28) to obtain the final form of the homogenized equation for haematocrit propagation

$$(4.33) \quad \mathbf{U} \cdot \nabla h = 0.$$

5. Summary of the homogenized model. The following is the final homogenized model for macroscopic blood flow and haematocrit propagation developed in this manuscript:

$$(5.1a) \quad \nabla \cdot (\mathcal{K}(h) \cdot \nabla p) = 0,$$

$$(5.1b) \quad \mathbf{U} = -\mathcal{K}(h) \cdot \nabla p,$$

and

$$(5.1c) \quad \mathbf{U} \cdot \nabla h = 0.$$

Here, $p(\mathbf{x})$, $\mathbf{U}(\mathbf{x})$, and $h(\mathbf{x})$ are the pressure, flow velocity, and haematocrit, respectively, at the macroscale; $\mathcal{K}(h)$ is the macroscopic permeability tensor given by

$$(5.2) \quad \mathcal{K}^{kl} = \frac{L^k L^l}{2L^1L^2L^3} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \frac{d_{ij}^A (r^k r^l + 2r^k v_i^l)}{l_{ij} \mu(h, \tilde{d}_{ij})},$$

where \mathbf{v}^l is a solution to the linear system of equations:

$$(5.3) \quad A_0(g_{ij}^{\mathbf{r}(0)}) \mathbf{v}^l = \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N r^l g_{ij}^{\mathbf{r}(0)}.$$

Here,

$$A_0(g_{ij}^{\mathbf{r}(0)}) = \sum_{\mathbf{r} \in \mathcal{N}} \left[g_{ij}^{\mathbf{r}(0)} - \delta_{ij} \sum_{m=1}^N g_{im}^{\mathbf{r}(0)} \right]$$

and

$$g_{ij}^{\mathbf{r}(0)} = \frac{d_{ij}^A}{l_{ij} \mu(h, \tilde{d}_{ij})}.$$

6. Validation of the homogenized model. In order to validate the convergence of the network model to the homogenized model as the network size increases, we considered a simple uni-directional flow for which the homogenized model admits an analytical solution. To facilitate a uni-directional flow in response to a uni-directional pressure gradient, we considered a network in which the periodic unit cell is symmetric with respect to the direction of the pressure gradient (such that the off-diagonal terms of the permeability tensor vanish). To this end, we generated a periodic tessellation of a single-hexagon-unit-cell, forming a honeycomb network consisting of N_{row} rows of hexagons (each row comprises N_{row} or $N_{\text{row}} - 1$ hexagons, alternately) in the plane $(x^{1*}, x^{2*}) = (x^*, y^*) \in ([0, x_{\text{max}}^*], [-y_{\text{max}}^*, y_{\text{max}}^*])$. We used uniform vessel length, l_0^* , and a diameter distribution as illustrated in Figure 3, which is symmetric with respect to the x -axis. We applied pressure boundary conditions at x_{min}^* and x_{max}^* , no flow conditions at y_{min}^* and y_{max}^* , and a y -dependent inlet haematocrit profile:

$$(6.1) \quad \begin{aligned} p^*(0, y^*) &= \Delta p_0^*, \quad p^*(x_{\text{max}}^*, y^*) = 0, \\ q^*(x^*, -y_{\text{max}}^*) &= 0, \quad q^*(x^*, y_{\text{max}}^*) = 0, \quad \text{and} \\ h(0, y^*) &= 0.45 \exp \left[- \left(\frac{y^*}{0.6 y_{\text{max}}^*} \right)^2 \right]. \end{aligned}$$

We solved numerically the blood flow model described in section 2 for the given honeycomb network, with a large number of unit cells, $N_{\text{row}} \gg 1$, and using the boundary conditions in (6.1). After solving the network model, we subdivided the domain into N_{grid} grid cells and evaluated the average haematocrit, h_n , and the x -component of the Darcy velocity, u_n , at every grid cell n based on the vessel values of haematocrit and flux:

$$(6.2a) \quad u_n = \frac{128}{\pi} \frac{l_0^* \mu_0^*}{d_0^{4*}} \frac{2y_{\text{max}}^*}{\Delta p_0^*} \frac{1}{2Ly^*} \sum_{J \in \mathcal{S}_n} r_J^x q_J^*,$$

$$(6.2b) \quad h_n = \frac{\sum_{J \in \mathcal{S}_n^{\text{in}}} h_J q_J^*}{\sum_{J \in \mathcal{S}_n^{\text{in}}} q_J^*}.$$

Here, u_n and h_n are given in nondimensional forms, with the characteristic macroscopic length scale chosen as $2y_{\text{max}}^*$ and the reference diameter chosen as $d_0^* = 20 \mu\text{m}$. In (6.2a), \mathcal{S}_n denotes all the vessels that cross the boundaries of grid cell n ; in (6.2b), $\mathcal{S}_n^{\text{in}}$ denotes all the *inlet* vessels of grid cell n .

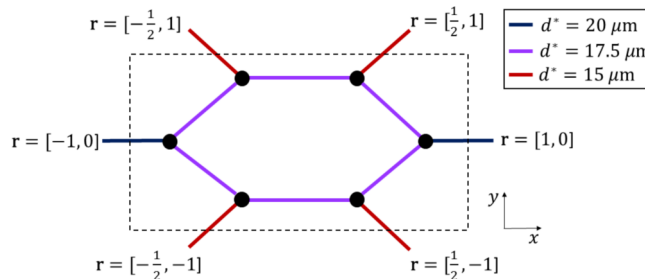


FIG. 3. Schematic of the single-hexagon periodic unit cell used to construct a honeycomb network and to validate the homogenized model. The unit cell comprises six nodes, six internal vessels, and six boundary vessels. The boundary vessels connect to neighboring unit cells, and the associated \mathbf{r} vectors of the neighboring cells are indicated. Edge colors are used to indicate vessel diameters.

The spatially averaged results of the network model were compared to the solution of the homogenized model. The boundary conditions in (6.1), together with the symmetry of the unit cell with respect to the direction of pressure gradient, led to a simple analytic solution of the (nondimensional) homogenized model in (5.1):

$$(6.3) \quad \begin{aligned} p(x) &= 1 - \bar{L}x, \\ h(y) &= 0.45 \exp \left[- \left(\frac{y}{0.3} \right)^2 \right], \\ u(h) &= \bar{L} \mathcal{K}^{xx}(h). \end{aligned}$$

Here, the characteristic length scale was chosen as $2y_{\max}^*$, thus the factor $\bar{L} = 2y_{\max}^*/x_{\max}^* \approx 1.1258$ accounts for the length scale ratio of the honeycomb network. The permeability, \mathcal{K}^{xx} , is obtained from (5.2), whereas $\mathcal{K}^{xy} = 0$ due to the structural symmetry of the honeycomb network.

In Figure 4 we present the average haematocrit and velocity for two network sizes (Figures 4(a), (b): $N_{\text{row}} = 25$, Figure 4(c), (d): $N_{\text{row}} = 97$). In the homogenized model, there are no “diffusive” effects and haematocrit only travels in the direction of the flow velocity, which is in the x -direction in the present case. However, the results for the network model reveal subdominant “diffusive” effects which manifest as haematocrit flow in the opposite direction to the direction of the haematocrit gradient, leading to reductions in $\partial h / \partial y$ as x increases. Nevertheless, this effect becomes less pronounced as the system size increases, which is consistent with the purely advective form of the homogenized model at leading order. To further emphasize the convergence of the average network model to the homogenized model as the system size increases, Figures 4(e), (f) compare the y -profiles of haematocrit and velocity at $x = 0.5$ (middle of the domain) generated from networks of increasing sizes with those for the homogenized model (6.3). We see that as the network size increases the profiles converge to those of the homogenized model.

7. Probability distribution of the macroscopic permeability. The macroscopic permeability tensor, given by (5.2), is a function of the macroscopic haematocrit, h , the distribution of vessel diameters and lengths, and the topology of the unit cell. In this section we illustrate how these features affect the components of the permeability tensor. We consider two different network topologies: 2D honeycomb networks (subsection 7.1) and three-dimensional (3D) networks having vessels oriented in random directions (subsection 7.2). For each network topology, we assume that the distribution of vessel diameters is log-normal,

$$\tilde{d} \sim \text{Lognormal}(\eta_{LN}, \sigma_{LN}^2),$$

where $\tilde{d} = d^*/d_{\mu}^*$ and $d_{\mu}^* = 1 \mu\text{m}$. For all results presented in this section, we fix $\sigma_{LN} = 0.3$, and $\langle \tilde{d} \rangle = 20$ (here, and henceforth, angular brackets denote mean values), such that $\ln(\eta_{LN}) = \langle \tilde{d} \rangle e^{-\sigma_{LN}^2/2} \approx 19.12$. Using these parameters, the probability of obtaining $\tilde{d} < 10$ is very small ($\approx 1.5\%$), and most vessels satisfy $\tilde{d} \gg 1$, as required for the validity of the asymptotic expansion [see (4.2) et seq.]. We note that, in practice, many capillaries are expected to have diameters in the range $6 - 10 \mu\text{m}$ [8]. In future work we intend to extend the current model to account for smaller vessel diameters by developing a fully nonlinear homogenized model. This, in turn, would enable us to use diameter distributions that more closely resemble those associated with physiological networks.

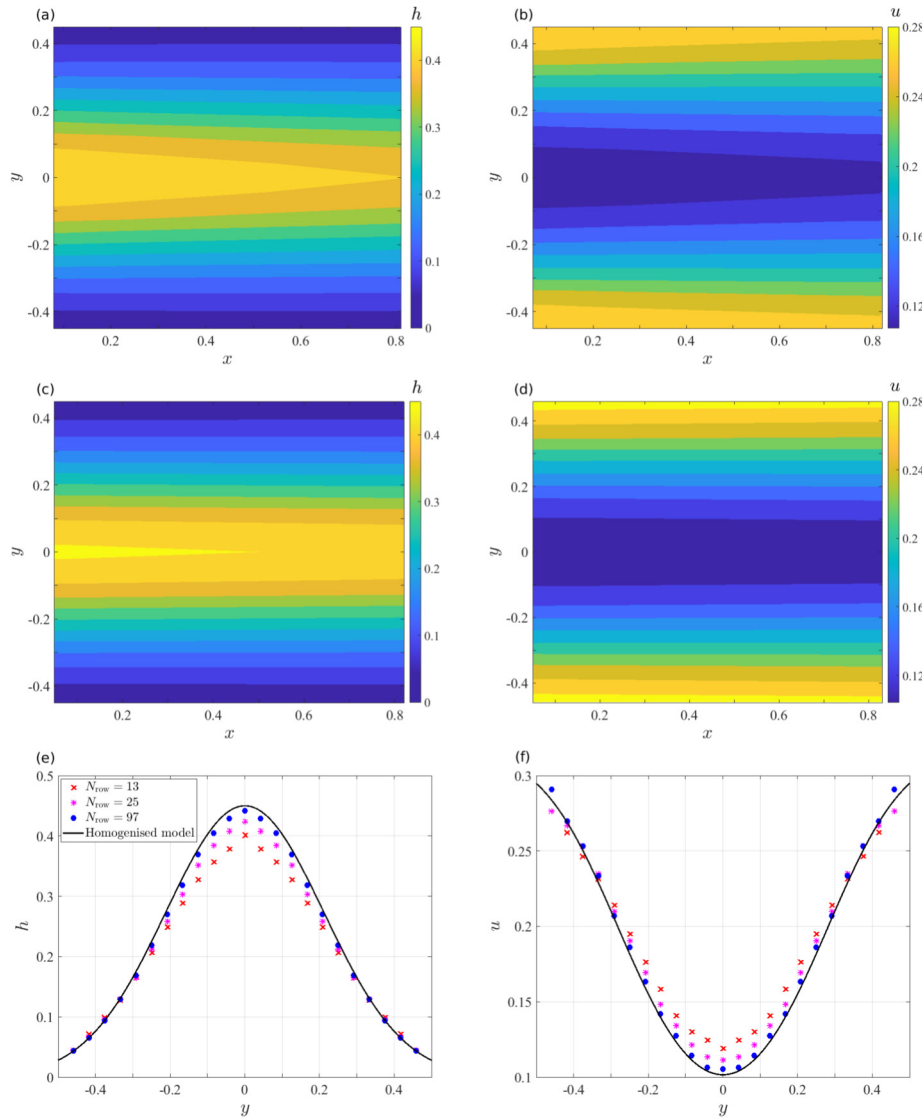


FIG. 4. Convergence of the spatially averaged haematocrit (a), (c) and velocity (b), (d) to the homogenized model with increasing size of the honeycomb network. Contours of spatially averaged haematocrit values and velocity in honeycomb networks of size (a), (b) $N_{\text{row}} = 25$, (c), (d) $N_{\text{row}} = 97$. Panels (e) and (f) present the haematocrit and velocity y -profiles at $x = 0.5$ for different network sizes (symbols), obtained from spatially averaging the network-model results. The results converge to the homogenized model (black lines) as the network size increases.

7.1. Two-dimensional honeycomb networks. We generated periodic unit cells of honeycomb networks having N_{row} rows of hexagons as illustrated in Figure 5 for the case of $N_{\text{row}} = 5$. We used uniform vessel lengths ($l = 1$ in nondimensional units) and a diameter distribution as described above.

We ran 10^6 realizations, in each of which we evaluated the macroscopic permeability (using (5.2)) of a honeycomb network ($N_{\text{row}} = 9$) with vessel diameters chosen at random using the log-normal distribution described above; each realization had a fixed haematocrit in all vessels in the range $h \in [0, 0.7]$. We note that we calculated the

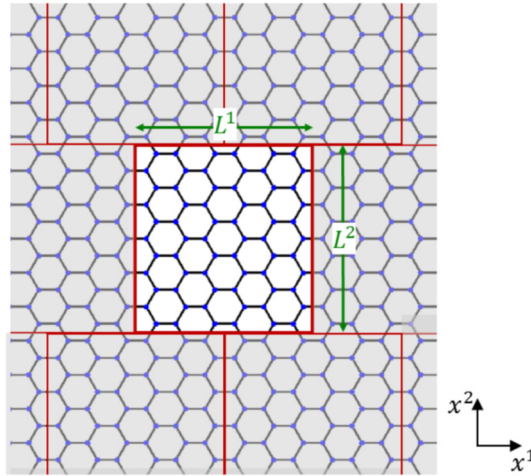


FIG. 5. Schematic of a 2D honeycomb network in the (x^1, x^2) plane composed of unit cells having $N_{\text{row}} = 5$ rows of hexagons. Each unit cell has six neighboring cells corresponding to (clockwise from the top-left cell) $\mathbf{r} = (-\frac{1}{2}, 1), (\frac{1}{2}, 1), (1, 0), (\frac{1}{2}, -1), (-\frac{1}{2}, -1), (-1, 0)$.

permeability based on a uniform haematocrit value across the unit cell. In section 4, we showed that the leading-order haematocrit value at the unit cell is uniform. Therefore, for a given cell architecture, the permeability depends only on this leading order (uniform) haematocrit value. The results presented in Figure 6 show how the diagonal and off-diagonal entries of the permeability tensor are distributed. Due to the intrinsic symmetries of the honeycomb network, the distribution of the diagonal components is identical. Therefore, Figure 6(a) presents the distribution of \mathcal{K}^{11} and \mathcal{K}^{22} , which we denote as \mathcal{K}^{nn} . Also, due to the symmetries of the honeycomb-network, the mean value of the off-diagonal components (denoted \mathcal{K}^{nt} , where $\mathcal{K}^{nt} = \mathcal{K}^{tn}$ due to the symmetry of the permeability tensor) is zero. This is readily apparent in Figure 6(b).

Curves presenting the permeability tensor components as a function of h for the case of uniform vessel diameters are presented in Figure 6. Due to the symmetry of the honeycomb network, the uniform vessel diameter results in $\langle \mathcal{K}^{nt} \rangle = 0$. For the diagonal terms, Figure 6(a) shows that a uniform diameter which equals the mean of the distribution ($\tilde{d} = 20$) produced a larger permeability than the mean of the distribution. This is due to the nonlinear dependence of the vessel conductance on the vessel diameter, which leads to vessels smaller than the mean value producing a greater reduction in the permeability than increases caused by vessels that are larger than the mean value. Even so, it is possible to obtain a good approximation for the mean value by using a uniform value for the vessel diameters which is smaller than the mean of the distribution.

When evaluating the macroscopic permeability (per unit length) of a honeycomb unit-cell having uniform vessel diameters, we can take the conductance out of the summation in (5.2) to obtain

$$(7.1) \quad \mathcal{K}^{kl} = \frac{L^k L^l}{2L^1 L^2} \frac{(\tilde{d}/\tilde{d}_0)^4}{\mu(h, \tilde{d})} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N (r^k r^l + 2r^k v_i^l).$$

Here we choose the reference diameter to be the mean diameter so that the nondimensional parameter, $\tilde{d}_0 = 20$, represents the reference network diameter scaled by

the reference viscosity-function diameter. The vessel length is absent from (7.1) because it is uniform in honeycomb networks. For an equal-vessel-diameter honeycomb network, the summation in (7.1) yields

$$(7.2) \quad \mathcal{K}^{nn} \approx 0.577 \frac{(\tilde{d}/\tilde{d}_0)^4}{\mu(h, \tilde{d})} \quad \text{and} \quad \mathcal{K}^{nt} = 0.$$

On the other hand, if we wish to approximate the mean of the distribution of \mathcal{K}^{nn} using a representative uniform diameter, we expect that

$$(7.3) \quad \langle \mathcal{K}^{nn} \rangle \propto [\mu(h, \tilde{d} = \text{const})]^{-1}.$$

Using the explicit expression for μ (see Appendix A), we fitted the following functional form for $\langle \mathcal{K}^{nn}(h) \rangle$ to the random-diameter data in Figure 6:

$$(7.4) \quad \langle \mathcal{K}^{nn}(h) \rangle = \frac{c_1}{1 + c_2 [(1-h)^{c_3} - 1]},$$

and obtained $c_1 \approx 0.345$, $c_2 \approx 2.359$, and $c_3 \approx -1.059$. Then, the representative uniform diameter of the random distribution is obtained by substituting the explicit form for $\mu(h, \tilde{d})$ from (A.1) into (7.2) and equating to (7.4) for the case of $h = 0$. The resulting equation is

$$(7.5) \quad \tilde{d}^2(\tilde{d} - 1.1)^2 = \frac{0.345\tilde{d}_0^4}{0.577}.$$

Solving (7.5) numerically we obtained $\tilde{d} \approx 18.142$. The solid black line in Figure 6(a) shows \mathcal{K}^{nn} for a uniform diameter, $\tilde{d} = 18.142$, while the dashed-black line presents the mean, $\langle \mathcal{K}^{nn} \rangle$, of the random vessel diameter distribution. The two curves are almost indistinguishable, showing that this uniform diameter provides an excellent approximation to the mean of the distribution.

It is noticeable in Figure 6 that the standard deviation of the permeability decreases as the haematocrit value increases. To better illustrate this trend,

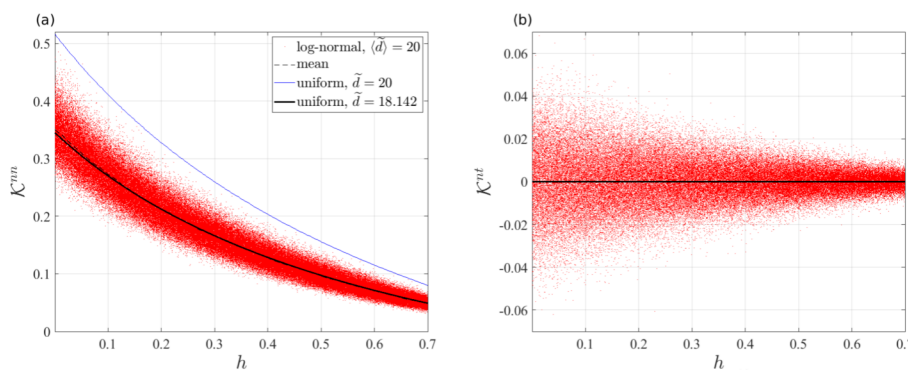


FIG. 6. Scatter plots showing how the diagonal and off-diagonal component elements of the permeability tensor, (a) \mathcal{K}^{nn} and (b) \mathcal{K}^{nt} , respectively, depend on the macroscopic haematocrit, h . The results were generated from 10^6 realizations of a honeycomb network in which the unit cell had $N_{\text{row}} = 9$ rows (190 nodes, 304 vessels) and where the vessel diameters were distributed according to a log-normal distribution with mean diameter, $\langle \tilde{d} \rangle = 20$, and $\sigma_{LN} = 0.3$. The solid lines show the permeability for cases in which uniform vessel diameters were used; the mean of the distribution of the permeability is given by the dashed-black line (coincides with the uniform-vessel-diameter line in Figure 6(b)).

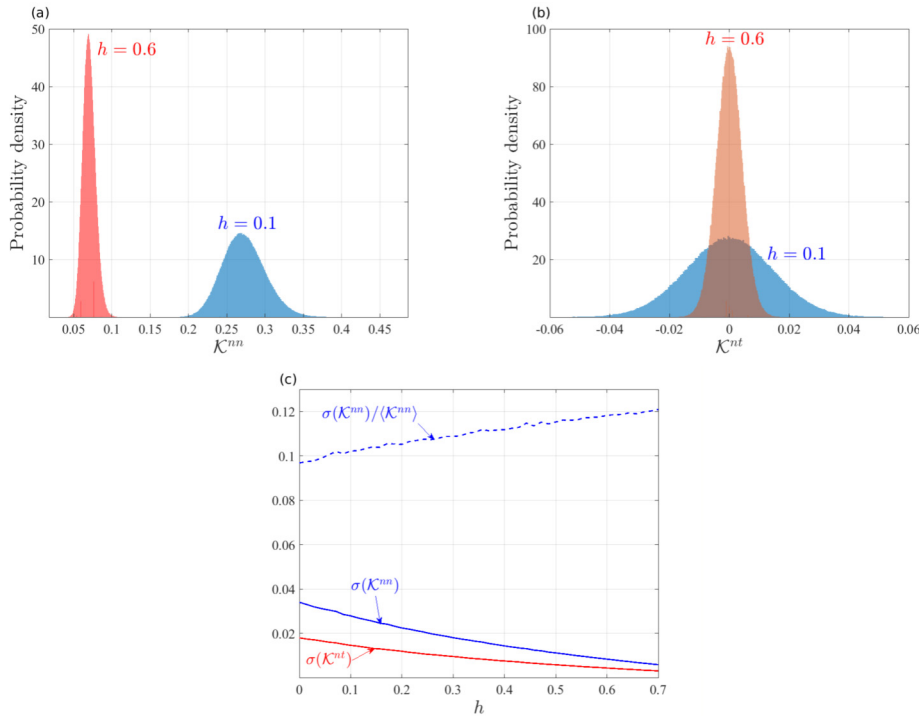


FIG. 7. The probability density distribution of (a) \mathcal{K}^{nn} and (b) \mathcal{K}^{nt} for haematocrit values of $h = 0.1$ (blue bars) and $h = 0.6$ (red bars). The results were generated from 10^6 realizations of a honeycomb network in which a periodic unit cell had $N_{\text{row}} = 9$ rows (190 nodes, 304 vessels) and where the vessel diameters are distributed according to a log-normal distribution with mean diameter, $\langle d \rangle = 20$, and $\sigma_{LN} = 0.3$. In (c) the standard deviation of the distributions, $\sigma(\mathcal{K}^{nn})$ (solid-blue line) and $\sigma(\mathcal{K}^{nt})$ (solid-red line), are plotted against the haematocrit value; the coefficient of variation of \mathcal{K}^{nn} is shown by the dashed-blue line. (Figure in color online.)

Figures 7(a), (b) show the probability density distribution of the permeability tensor components for two values of haematocrit, $h = 0.1, 0.6$, while Figure 7(c) presents the standard deviation and the coefficient of variation of the permeability tensor components as a function of the haematocrit value. We notice in Figures 7(a), (b) the wider distribution of the permeability components for the smaller value of haematocrit. This is also manifested in Figure 7(c) by the decrease in the standard deviation of the distributions as the haematocrit increases. However, the coefficient of variation of \mathcal{K}^{nn} increases as the haematocrit increases, meaning that we expect to observe larger relative deviations from the mean value for larger haematocrit values. This is because the gradients of the blood viscosity with respect to the vessel diameter increase when the haematocrit increases (see, for example, Figure 1.12 in [36]). This, in turn, leads to greater relative variability in vessel conductance for larger values of haematocrit.

7.2. Three-dimensional networks with random vessel orientations. We used the following algorithm to generate (3D) unit cells containing periodic networks with random vessel orientations:

- (I) We defined a cubical cell, with an edge length, \tilde{L}_0 , that contains the unit-cell nodes (as usual, tildes denote scaling with $1 \mu\text{m}$).
- (II) We generated N_{tree} realizations of tree-type networks where each tree had N_{gen} generations. For each tree we positioned the first node at a random

location within the unit cell and then randomly chose the positions of the two daughter nodes such that the distance of each node from the parent node (i.e., the vessel length) was sampled according to a given vessel length distribution [see item (III) below]. The position of each node was sampled from a uniform distribution over the surface of a sphere where its origin was the parent node and its radius was the sampled vessel length. We repeated the process for the daughter nodes (now viewing them as the parent nodes of the next generation) until the required number of generations, N_{gen} , was reached.

- (III) The distribution of the vessel length-to-diameter ratio, R , was chosen from a log-normal distribution with a mean $\langle R \rangle$. Assigning the random log-normally distributed vessel diameter, \tilde{d} , the vessel length, \tilde{l} , was given by $\tilde{l} = R\tilde{d}$.
- (IV) In order to impose periodicity, if the position $\tilde{\mathbf{x}}_0$ of a node fell outside the cell box, it was shifted according to the transformation

$$\tilde{x}_0^k \rightarrow \begin{cases} \tilde{x}_0^k + \tilde{L}_0, & \tilde{x}_0^k < -\tilde{L}_0/2, \\ \tilde{x}_0^k - \tilde{L}_0, & \tilde{x}_0^k > \tilde{L}_0/2. \end{cases}$$

- (V) We randomly connected the open ends in the first and last generations of each tree between the different trees or within the same tree such that each node in the network had a coordination number of 3.
- (VI) The nondimensional components of the permeability tensor were calculated via

$$(7.6) \quad \mathcal{K}^{kl} = \frac{\langle \tilde{l} \rangle^2}{2\langle \tilde{d} \rangle^4 \tilde{L}_0} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \frac{\tilde{d}_{ij}^4 (r^k r^l + 2r^k v_i^l)}{\tilde{l}_{ij} \mu(h, \tilde{d}_{ij})}.$$

An example of a periodic unit cell generated using the aforementioned algorithm is presented in Figure 8.

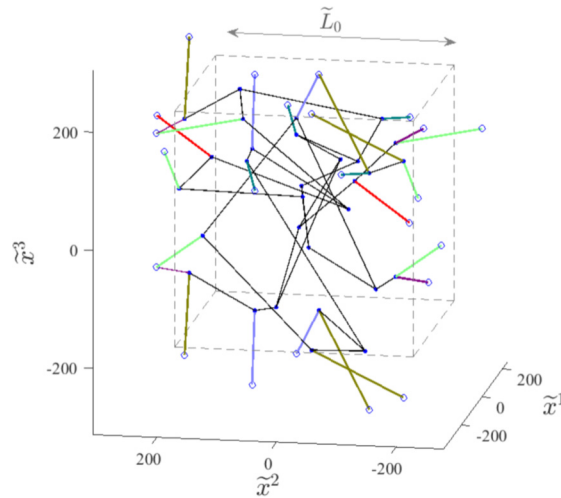


FIG. 8. Illustration of a periodic unit cell of a 3D random network composed of $N_{\text{tree}} = 2$ trees, each having $N_{\text{gen}} = 3$ generations. Vessels connected to neighboring unit cells are marked in color, where vessels connected to the same or opposite neighbor (having identical $|\mathbf{r}|$) share the same color. The cell box is illustrated by the dashed-grey lines; nodes outside of the cell box belonging to neighboring unit cells are indicated by open circles. (Figure in color online.)

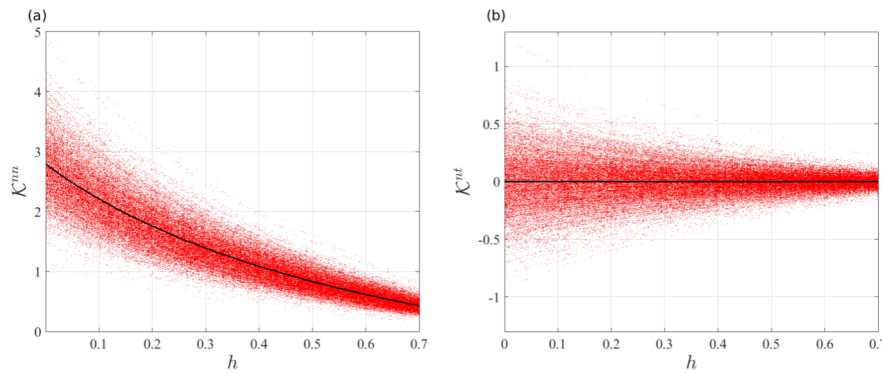


FIG. 9. Scatter plots showing how the diagonal and off-diagonal component elements of the permeability tensor, (a) \mathcal{K}^{nn} and (b) \mathcal{K}^{nt} , respectively, depend on the haematocrit, h . The results were generated from 10^6 realizations of a 3D random network in which a periodic unit cell had $N_{\text{tree}} = 6$ trees, each composed of $N_{\text{gen}} = 5$ generations (378 nodes, 567 vessels), in a cubical box with edge length $\tilde{L}_0 = 400$. The vessel diameters are distributed according to a log-normal distribution with mean diameter, $\langle \tilde{d} \rangle = 20$, and $\sigma_{LN} = 0.3$; the length-to-diameter ratio of the vessels is log-normally distributed with mean, $\langle R \rangle = 6$, and $\sigma_{LN} = 0.3$. The means of the distributions are given by the black lines.

We ran 10^6 realizations of 3D periodic unit cells (as described above) each with uniform haematocrit values in the range $h \in [0, 0.7]$. Figure 9 shows the scatter in the components of the resulting permeability tensor. Due to the average anisotropy induced by the randomly oriented vessels in the network, the distributions of all diagonal components are similar, as are the distributions of all off-diagonal components. Therefore, we present the distribution of all diagonal terms together and denote them by \mathcal{K}^{nn} [Figure 9(a)]; the off-diagonal terms are denoted by \mathcal{K}^{nt} [Figure 9(b)]. Here, because the network is anisotropic on average, the mean of the off-diagonal terms, $\langle \mathcal{K}^{nt} \rangle = 0$, which is readily apparent in Figure 9(b). Comparing the order-of-magnitude of the permeabilities of the 3D random network and the 2D honeycomb network (subsection 7.1), we notice that the former is approximately ten times larger. This means that a 3D network consisting of 2D honeycomb unit cells lying in the (x^1, x^2) plane stacked in the x^3 direction, with a density $\sim 10/l_0^*$ (where l_0^* is the dimensional vessel length in the honeycomb unit cell) will have a permeability similar in magnitude to that of the 3D network presented in Figure 9.

To illustrate how the statistical features of the 3D random networks change as the haematocrit value varies, in Figures 10(a), (b) we plot the probability density distribution of the permeability tensor components for two values of haematocrit, $h = 0.1, 0.6$; Figure 10(c) presents the results for the standard deviation and coefficient of variation of the permeability tensor components as a function of the haematocrit value. As in Figure 7, the standard deviation of the distributions decreases as the haematocrit increases, while the coefficient of variation of \mathcal{K}^{nn} increases as the haematocrit increases. However, the relative increase in the coefficient of variation is smaller in the 3D random network than in the honeycomb network ($\approx 10\%$ increase in the former compared to $\approx 20\%$ increase in the latter between $h = 0$ to $h = 0.7$). This is because the 3D random network allows for a change in the vessel length, such that vessels with larger diameter are more likely to be longer. Due to the opposing effects of vessel diameter and length on the conductance (see (5.2)), this leads to smaller relative variability in the vessel conductances as the haematocrit increases compared to the case in which the vessel lengths are fixed.

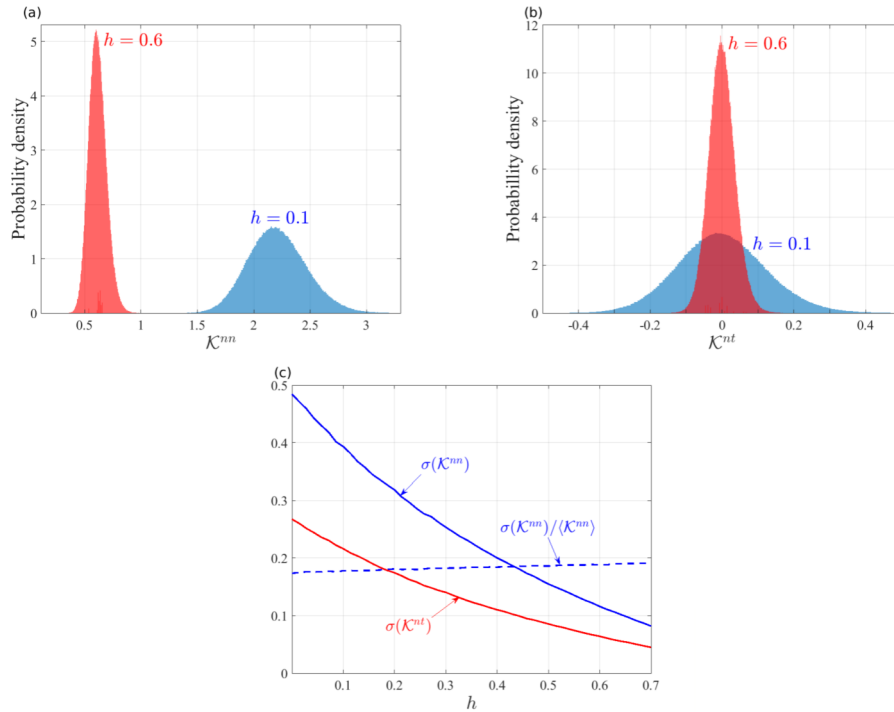


FIG. 10. The probability density distribution of (a) \mathcal{K}^{nn} and (b) \mathcal{K}^{nt} for haematocrit values of $h = 0.1$ (blue bars) and $h = 0.6$ (red bars) generated from 10^6 realizations of a 3D random network in which a periodic unit cell had $N_{\text{tree}} = 6$ trees, each composed of $N_{\text{gen}} = 5$ generations (378 nodes, 567 vessels), in a cubical box with edge length $\tilde{L}_0 = 400$. The vessel diameters are distributed according to a log-normal distribution with mean diameter, $\langle \tilde{d} \rangle = 20$, and $\sigma_{LN} = 0.3$; the length-to-diameter ratio of the vessels is log-normally distributed with mean, $\langle R \rangle = 6$, and $\sigma_{LN} = 0.3$. In (c) the standard deviation of the distributions, $\sigma(\mathcal{K}^{nn})$ (solid-blue line) and $\sigma(\mathcal{K}^{nt})$ (solid-red line), are plotted against the haematocrit value; the coefficient of variation of \mathcal{K}^{nn} is shown by the dashed-blue line. (Figure in color online.)

8. Conclusion. The goal of the present work was to formulate a macroscopic, coarse-grained description for blood flow in the microcirculation. We adopted a standard description of blood as a continuous mixture of plasma and haematocrit, which is formulated as a nonlinear system of algebraic equations for the nodal pressures, flow, and haematocrit in the network edges (vessels). Here, two factors drive the nonlinearities: the dependence of blood viscosity on the haematocrit [34], and the coupling of haematocrit and flow at network bifurcations due to the nonlinear splitting phenomenon [33]. In contrast to previous studies of flow in networks [7] and blood flow homogenization (e.g., [6, 9, 37]), which assumed a single-phase, linear Stokes flow, in this work we accounted for the two-phase nature of blood and the associated nonlinearities. Consequently, we have developed a coupled set of equations describing the flow and haematocrit propagation at the macroscale.

In order to account for the nonlinearity of blood flow and to facilitate the homogenization procedure, we focused on the limit of small haematocrit heterogeneity. This scenario prevails when the diameter of the vessels in the network are sufficiently large (typically much larger than the diameter of a single RBC), and when the diameters of daughter vessels at bifurcations are not markedly different. Under these conditions we were able to study the asymptotic limit at which the vessel haematocrits deviate

slightly from the average haematocrit in the periodic unit cell and, thus, to formulate a coarse-grained equation for the average-haematocrit propagation. Interestingly, but perhaps not surprisingly, this resulted in a purely advective equation for the propagation of haematocrit at the macroscale, where the effect of haematocrit splitting has been averaged out. Considering the homogenization of the flow, in this limit, the slow change of the leading order haematocrit enabled us to follow the homogenization methodology developed by Chapman and Wilmott [7] and to derive a Darcy model with a haematocrit-dependent permeability tensor, due to the effect that the haematocrit fraction has on the effective blood viscosity. The resulting homogenized model can be used to evaluate the way in which structural features of the vascular network affect blood flow and the haematocrit distribution at the macroscale.

We calculated the components of the permeability tensor for two different network topologies: (i) 2D honeycomb networks and (ii) 3D networks with randomly oriented vessels. For both types of networks a distribution of vessel diameters was considered. As expected, the mean permeability decreases as the haematocrit value increases due to the increase in flow resistance. However, it was observed that the coefficient of variation of the permeability increases with the haematocrit. This was rationalized in terms of the increase in the blood viscosity gradient with respect to the vessel diameter as the haematocrit level increases.

The homogenization methodology we used in this paper is based on the assumption that the network is homogeneous at the microscale such that it can be approximated using a representative periodic unit cell (or at least a statistical distribution of this unit cell). As observed by [25], this assumption is reasonable for the more distal parts of the microcirculation, whereas the fractal nature of the more proximal regions of the microcirculation cannot be accounted for within the homogenization methodology. Peyrounette et al. [31], and later on Shipley, Sweeney, and co-workers [38, 39], derived hybrid discrete-continuum models for blood flow where a homogenized model is used in the capillary region and the larger vessels, that feed the capillaries, are solved discretely. While in the models of [31, 38, 39] the haematocrit value was fixed, these models can now be extended to account for spatially varying haematocrit using the homogenized model developed in this paper. Therefore, we view the homogenized model developed here as part of a more general hybrid vascular-network model that includes both a homogenized-continuum description of the capillary bed and a discrete model for flow in the larger vessels.

The limit of small haematocrit heterogeneity studied in this work is likely to prevail in regions of the microcirculation where vessel diameters are sufficiently large and when vessel bifurcations are mostly regular (bifurcations of vessels with similar diameters). However, tumor vascular networks are known to be highly abnormal and, thus, to promote irregular blood flow and haematocrit distributions [20, 29]. Understanding this irregular flow is of great biological significance as it is hypothesized to give rise to the phenomenon of cycling hypoxia in tumors [13, 28] where some regions of the tumor experience cycles of hypoxia and reoxygenation. In turn, cycling hypoxia is associated with poor prognosis, such as selective advantage for malignant growth [2, 18], and chemo- and radio-therapy resistance [15, 16, 19]. In order to homogenize the blood flow and haematocrit transport in tumors, the small haematocrit heterogeneity assumption must be relaxed and the full nonlinearity of blood-flow at the microscale taken into account. Additionally, to account for the phenomenon of cycling hypoxia, a methodology to homogenize unsteady blood-flow must be developed. While this may not be analytically tractable, a data-driven approach where the unit-cell problem is solved numerically to generate data for the coarse-graining process [40] may prove useful. This suggests an avenue for future research.

Since RBCs are the blood component that is responsible for transporting and delivering oxygen to biological tissues, it is important to better understand their distribution in the microcirculation. Having formulated equations that describe the transport of haematocrit at the macroscale, it is now possible to derive a coarse-grained description for the oxygen distributions at the tissue-level. This is especially important in order to understand how large-scale regions of (sustained) hypoxia form in tumors and, thus, constitutes a natural topic for future work.

Other possible extensions of the current blood flow model could account for interactions between the blood vessels and the surrounding tissue, for example via plasma leakage into the interstitial space which leads to increased interstitial pressure. This phenomenon is especially important in tumors because of the high leakiness of their blood vessels and the corresponding large interstitial pressures, which has been associated with an increased risk of metastasis [12, 17]. In the context of homogenization of *linear* (constant haematocrit) blood flow, the coupled system of blood and interstitial flows results in a coupled system of linear Darcy equations for the two flow domains [37]. We expect that under the assumption of small leakiness rate (i.e., slight haematocrit changes along a vessel due to leakiness), the current haematocrit-dependent homogenized model could be extended to account for vessel leakiness, and that it would manifest as a source term in the haematocrit propagation equation. An additional fluid-tissue interaction that is important in the context of tumor blood flow is the compressive pressure applied by tumor cells on the blood vessels which can cause their diameters to decrease. This, in turn, can reduce the supply of oxygen to cells in the vicinity of compressed blood vessels and to consequent cell death or migration away from the vessels, relieving the pressure that the vessels experience. In this way, coupled nonlinear interactions between blood flow and cell densities arise. The homogenization of coupled tissue and vascular-network domains constitutes an interesting avenue for future research.

Appendix A. The blood viscosity model. Here we detail the functional form of the empirical model for the *apparent* blood viscosity due to Pries et al. [34]. For a vessel having a diameter, d (in micron units), and haematocrit fraction, h , the relative viscosity (blood apparent viscosity divided by plasma viscosity) is given by

$$(A.1) \quad \mu(h, d) = \left[1 + (\mu^\circ - 1) \frac{(1-h)^C - 1}{(1-0.45)^C - 1} \left(\frac{d}{d-1.1} \right)^2 \right] \times \left(\frac{d}{d-1.1} \right)^2.$$

The following expression for the blood viscosity is fit to data collected in vivo [34]. Here, the reference viscosity, μ° , and the exponent, C , are given by the following empirical expressions:

$$(A.2) \quad \mu^\circ(d) = 6 \exp(-0.085d) - 2.44 \exp(-0.06d^{0.645}) + 3.2$$

and

$$(A.3) \quad C(d) = [0.8 + \exp(-0.075d)] \left\{ \left[1 + 10 \left(\frac{d}{10} \right)^{12} \right]^{-1} - 1 \right\} + \left[1 + 10 \left(\frac{d}{10} \right)^{12} \right]^{-1}.$$

Appendix B. Proofs for the identities in (3.12). We have

$$\begin{aligned}
 \text{(B.1)} \quad A_0^T &= \sum_{\mathbf{r} \in \mathcal{N}} \left[g_{ji}^{\mathbf{r}} - \delta_{ji} \sum_{m=1}^N g_{jm}^{\mathbf{r}} \right] = \sum_{\mathbf{r} \in \mathcal{N}} \left[g_{ji}^{-\mathbf{r}} - \delta_{ji} \sum_{m=1}^N g_{jm}^{\mathbf{r}} \right] \\
 &= \sum_{\mathbf{r} \in \mathcal{N}} \left[g_{ij}^{\mathbf{r}} - \delta_{ji} \sum_{m=1}^N g_{jm}^{\mathbf{r}} \right] = A_0,
 \end{aligned}$$

where we have relabeled $\mathbf{r} \leftrightarrow -\mathbf{r}$ in the first sum and then used relation (3.7). Also,

$$\text{(B.2)} \quad (A_0 \mathbf{u})_i = \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N \left[g_{ij}^{\mathbf{r}} - \delta_{ij} \sum_{m=1}^N g_{im}^{\mathbf{r}} \right] = \sum_{\mathbf{r} \in \mathcal{N}} \left[\sum_{j=1}^N g_{ij}^{\mathbf{r}} - \sum_{m=1}^N g_{im}^{\mathbf{r}} \right] = \mathbf{0}, \text{ for } i = 1, \dots, N.$$

In a similar manner we can show that $A_1 \mathbf{u} = \mathbf{0}$.

We have

$$\begin{aligned}
 \text{(B.3)} \quad (\mathbf{u}^T A_0)_j &= \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \left[g_{ij}^{\mathbf{r}} - \delta_{ij} \sum_{m=1}^N g_{im}^{\mathbf{r}} \right] = \sum_{\mathbf{r} \in \mathcal{N}} \left[\sum_{i=1}^N g_{ij}^{\mathbf{r}} - \sum_{m=1}^N g_{jm}^{\mathbf{r}} \right] \\
 &= \sum_{\mathbf{r} \in \mathcal{N}} \left[\sum_{i=1}^N g_{ij}^{\mathbf{r}} - \sum_{m=1}^N g_{jm}^{-\mathbf{r}} \right] \\
 &= \sum_{\mathbf{r} \in \mathcal{N}} \left[\sum_{i=1}^N g_{ij}^{\mathbf{r}} - \sum_{m=1}^N g_{mj}^{\mathbf{r}} \right] = \mathbf{0}, \text{ for } j = 1, \dots, N,
 \end{aligned}$$

where we have relabeled $\mathbf{r} \leftrightarrow -\mathbf{r}$ in the second sum and then used relation (3.7).

We have

$$\begin{aligned}
 \text{(B.4)} \quad \mathbf{u}^T B_0^l \mathbf{u} &= \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \left[(x_j^l + r^l L^l) g_{ij}^{\mathbf{r}} - \delta_{ij} x_i^l \sum_{m=1}^N g_{im}^{\mathbf{r}} \right] \\
 &= \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \left[(x_i^l + r^l L^l) g_{ji}^{\mathbf{r}} - \delta_{ij} x_i^l \sum_{m=1}^N g_{im}^{\mathbf{r}} \right] \\
 &= \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \left[(x_i^l - r^l L^l) g_{ji}^{-\mathbf{r}} - \delta_{ij} x_i^l \sum_{m=1}^N g_{im}^{\mathbf{r}} \right] \\
 &= \sum_{\mathbf{r} \in \mathcal{N}} \left[\sum_{i=1}^N (x_i^l - r^l L^l) \sum_{j=1}^N g_{ij}^{\mathbf{r}} - \sum_{i=1}^N x_i^l \sum_{m=1}^N g_{im}^{\mathbf{r}} \right] \\
 &= -L^l \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^l g_{ij}^{\mathbf{r}} = L^l \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^l g_{ji}^{-\mathbf{r}} = L^l \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^l g_{ij}^{\mathbf{r}} = 0,
 \end{aligned}$$

where we have relabeled $i \leftrightarrow j$ and $\mathbf{r} \leftrightarrow -\mathbf{r}$ in the first sum, and then used (3.7). We followed the same procedure in the last line.

Appendix C. Proofs for the identities in (3.27). We have

$$\begin{aligned}
 \text{(C.1)} \quad & \mathbf{u}^T A_1(g_{ij}^{\mathbf{r}(0)}) \mathbf{w}^l \\
 &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N w_j^l \left[\sum_{i=1}^N \sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s} - \sum_{m=1}^N \sum_{s=1}^3 (x_j^s + x_m^s + r^s L^s) \frac{\partial g_{jm}^{\mathbf{r}(0)}}{\partial x^s} \right] \\
 &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N w_j^l \left[\sum_{i=1}^N \sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s} - \sum_{m=1}^N \sum_{s=1}^3 (x_j^s + x_m^s - r^s L^s) \frac{\partial g_{jm}^{-\mathbf{r}(0)}}{\partial x^s} \right] \\
 &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N w_j^l \left[\sum_{i=1}^N \sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s} - \sum_{m=1}^N \sum_{s=1}^3 (x_j^s + x_m^s - r^s L^s) \frac{\partial g_{mj}^{\mathbf{r}(0)}}{\partial x^s} \right] \\
 &= \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{s=1}^3 r^s L^s w_j^l \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s},
 \end{aligned}$$

where we have relabeled $\mathbf{r} \leftrightarrow -\mathbf{r}$ in the second sum and then used (3.7) in the first sum.

We have

$$\begin{aligned}
 \text{(C.2)} \quad & \mathbf{u}^T B_1^l(g_{ij}^{\mathbf{r}(0)}) \mathbf{u} = \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N \left[(x_j^l + r^l L^l) \sum_{i=1}^N \sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s} \right. \\
 & \quad \left. - x_j^l \sum_{m=1}^N \sum_{s=1}^3 (x_j^s + x_m^s + r^s L^s) \frac{\partial g_{jm}^{\mathbf{r}(0)}}{\partial x^s} \right] \\
 &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N \left[(x_j^l + r^l L^l) \sum_{i=1}^N \sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s} \right. \\
 & \quad \left. - x_j^l \sum_{m=1}^N \sum_{s=1}^3 (x_j^s + x_m^s - r^s L^s) \frac{\partial g_{jm}^{-\mathbf{r}(0)}}{\partial x^s} \right] \\
 &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N \left[(x_j^l + r^l L^l) \sum_{i=1}^N \sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s} \right. \\
 & \quad \left. - x_j^l \sum_{m=1}^N \sum_{s=1}^3 (x_j^s + x_m^s - r^s L^s) \frac{\partial g_{mj}^{\mathbf{r}(0)}}{\partial x^s} \right] \\
 &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N \left[2x_j^l \sum_{i=1}^N \sum_{s=1}^3 (r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s} \right. \\
 & \quad \left. + r^l L^l \sum_{i=1}^N \sum_{s=1}^3 (x_i^s + x_j^s + r^s L^s) \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s} \right] \\
 &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{s=1}^3 [r^l L^l r^s L^s + 2x_j^l r^s L^s + r^l L^l (x_i^s + x_j^s)] \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s} \\
 &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{s=1}^3 [r^l L^l r^s L^s + 2x_j^l r^s L^s] \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s},
 \end{aligned}$$

where we have relabeled $\mathbf{r} \leftrightarrow -\mathbf{r}$ and then used (3.7) in the second sum. In the last line we made use of

$$\sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^l L^l x_i^s \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s} = - \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^l L^l x_j^s \frac{\partial g_{ij}^{\mathbf{r}(0)}}{\partial x^s}.$$

We have

(C.3)

$$\begin{aligned} \mathbf{u}^T C_0^{kl}(g_{ij}^{\mathbf{r}(0)}) \mathbf{u} &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \left[(x_j^k + r^k L^k)(x_j^l + r^l L^l) g_{ij}^{\mathbf{r}(0)} - \delta_{ij} x_i^k x_i^l \sum_{m=1}^N g_{im}^{\mathbf{r}(0)} \right] \\ &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N \left[(x_j^k + r^k L^k)(x_j^l + r^l L^l) \sum_{i=1}^N g_{ij}^{\mathbf{r}(0)} - x_j^k x_j^l \sum_{m=1}^N g_{jm}^{\mathbf{r}(0)} \right] \\ &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N \left[(x_j^k + r^k L^k)(x_j^l + r^l L^l) \sum_{i=1}^N g_{ij}^{\mathbf{r}(0)} - x_j^k x_j^l \sum_{m=1}^N g_{jm}^{-\mathbf{r}(0)} \right] \\ &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{j=1}^N \left[(x_j^k + r^k L^k)(x_j^l + r^l L^l) \sum_{i=1}^N g_{ij}^{\mathbf{r}(0)} - x_j^k x_j^l \sum_{m=1}^N g_{mj}^{\mathbf{r}(0)} \right] \\ &= \frac{1}{2} \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N [r^k L^k r^l L^l + r^l L^l x_j^k + r^k L^k x_j^l] g_{ij}^{\mathbf{r}(0)}, \end{aligned}$$

where we have went through the same steps as in (C.2).

We have

$$\begin{aligned} \text{(C.4)} \quad \mathbf{u}^T B_0^k(g_{ij}^{\mathbf{r}(0)}) \mathbf{w}^l &= \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \left[(x_j^k + r^k L^k) g_{ij}^{\mathbf{r}(0)} - \delta_{ij} x_i^k \sum_{m=1}^N g_{im}^{\mathbf{r}(0)} \right] w_j^l \\ &= \sum_{\mathbf{r} \in \mathcal{N}} \left[\sum_{i=1}^N \sum_{j=1}^N w_j^l (x_j^k + r^k L^k) g_{ij}^{\mathbf{r}(0)} - \sum_{m=1}^N \sum_{j=1}^N w_j^l x_j^k g_{jm}^{\mathbf{r}(0)} \right] \\ &= \sum_{\mathbf{r} \in \mathcal{N}} \left[\sum_{i=1}^N \sum_{j=1}^N w_j^l (x_j^k + r^k L^k) g_{ij}^{\mathbf{r}(0)} - \sum_{m=1}^N \sum_{j=1}^N w_j^l x_j^k g_{jm}^{-\mathbf{r}(0)} \right] \\ &= \sum_{\mathbf{r} \in \mathcal{N}} \left[\sum_{i=1}^N \sum_{j=1}^N w_j^l (x_j^k + r^k L^k) g_{ij}^{\mathbf{r}(0)} - \sum_{m=1}^N \sum_{j=1}^N w_j^l x_j^k g_{mj}^{\mathbf{r}(0)} \right] \\ &= \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N r^k L^k w_j^l g_{ij}^{\mathbf{r}(0)}, \end{aligned}$$

where we have relabeled $\mathbf{r} \leftrightarrow -\mathbf{r}$ and then used (3.7) in the second sum. In a similar manner we have

$$\text{(C.5)} \quad \mathbf{u}^T B_0^k(g_{ij}^{\mathbf{r}(0)}) \frac{\partial \mathbf{w}^l}{\partial x^k} = \sum_{\mathbf{r} \in \mathcal{N}} \sum_{i=1}^N \sum_{j=1}^N \sum_{k=1}^3 r^k L^k \frac{\partial w_j^l}{\partial x^k} g_{ij}^{\mathbf{r}(0)}.$$

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