Research Article

A computational model for microcirculation including Fahraeus-Lindqvuist effect, palsma skimming and fluid exchange with the tissue interstitium

Luca Possenti,[1] Simone di Gregorio,[1] Giorgio Raimondi,[2] Giustina Casagrande,[1] Maria Laura Costantino,[1] and Paolo Zunino*[2]

[1] *LaBS, Dipartimento di Chimica, Materiali e Ingegneria Chimica "Giulio Natta", Politecnico di Milano, Italy*
[2] *MOX, Department of Mathematics, Politecnico di Milano, Itlay*

Correspondence: *Paolo Zunino, MOX, Department of Mathematics, Politecnico di Milano Email: paolo.zunino@polimi.it

Received tbd; Revised tbd; Accepted tbd

Summary

We present a two phase model for microcirculation that describes the interaction of plasma with red blood cells. The model takes into account of fundamantal effects characterizing the microcirculation, such as the Fahraeus-Lindqvuist effect and palsma skimming. Besides these features, the model describes the interaction of capillaries with the surrounding tissue, and in particular the interaction of capillary transmural flow with the surrounding interstitial pressure. Furthermore, the capillaries are represented as one-dimensional channels with arbitrary, possibly curved configuration. The latter two features rely on the unique ability of the model to account for variations of flow rate and velocity along the axis of the capillary, according to a local (differential) formulation of mass and momentum conservation. Indeed, the model stands on a solid mathematical foundation, which is also addressed in this work. In particular, we present the model derivation, variational formulation and approximation using the finite element method. Finally, we conclude the work with a comparative computational study of the importance of the Fahraeus-Lindqvuist, plasma skimming and capillary leakage effect on the distribution of flow in a microvascular network.

Keywords: microcirculation, Fahraeus-Lindqvuist, palsma skimming, capilary leakage

1 Introduction

ec:intro⟩?

To be added...

2 A two phase model for microcirculation coupled with the interstitial flow

sec:flow⟩?

We define a mathematical model for fluid transport in a permeable biological tissue perfused by a capillary network. We consider a domain Ω that is composed by two parts, Ω_v and Ω_t, the capillary bed and the tissue interstitium, respectively. Assuming that the capillaries can be described as cylindrical vessels, we denote with Γ the outer surface of Ω_v, with R its radius and with Λ the centerline of the capillary network. Any physical quantity of interest, such as the blood pressure p and the blood velocity $\boldsymbol{u}$, is a function of space (being $\boldsymbol{x} \in \Omega$ the spatial coordinates). We consider steady-state flow conditions, as a result all variables are independent of time. The flow model in the vascular domain Ω_v reads as follows:

$$\begin{cases} \nabla \cdot \boldsymbol{u}_t = 0 & \text{in } \Omega_t \\ \boldsymbol{u}_t + \dfrac{\mathrm{K}}{\mu_t} \nabla p_t = 0 & \text{in } \Omega_t \\ \rho \dfrac{\partial \boldsymbol{u}_v}{\partial t} + \rho(\boldsymbol{u}_v \cdot \nabla)\boldsymbol{u}_v = \nabla \cdot \boldsymbol{\sigma} & \text{in } \Omega_v \\ \nabla \cdot \boldsymbol{u}_v = 0 & \text{in } \Omega_v \end{cases} \tag{1}$$

eq:3D3D

where μ_t and K denote the dynamic blood viscosity and the hydraulic permeability of the interstitial tissue, respectively, and ρ is the blood density. We assume that the fluid in the interstitial space is equivalent to blood plasma, such that the viscosity μ_t is set equivalent to the plasma one at body temperature, which will be later denoted by μ_{ref}. At the interface $\Gamma = \partial\Omega_v \cap \partial\Omega_t$ we impose continuity of the flow:

$$\boldsymbol{u}_v \cdot \boldsymbol{n} = \boldsymbol{u}_t \cdot \boldsymbol{n} = f(p_t, p_v) \text{ with } f(p_t, p_v) = L_p((p_v - p_t) - \sigma R_g T(c_v - c_t)), \quad \boldsymbol{u}_t \cdot \boldsymbol{\tau} = 0, \quad \text{on } \Gamma \tag{2}$$

eq:KK

where $\boldsymbol{n}$ is the outward unit vector normal to the capillary surface. The fluid flux across the capillary wall can be obtained on the basis of linear non-equilibrium thermodynamic arguments, originally developed by Kedem and Katchalsky. In particular L_p is the hydraulic conductivity of the vessel wall, R_g is the universal gas constant and T is the absolute temperature. In (2) c_v and c_t represent the effect of proteins, mostly albumin, on the osmotic (or oncotic) pressure gradient. Namely, $-\sigma R_g T(c_v - c_t)$ is the net osmotic pressure gradient across the capillary wall. Because of osmosis, the pressure drop across the capillary wall is affected by the difference in the concentration

of chemicals, namely $c_v - c_t$, where c_v and c_t denote the concentration in the capillaries and in the interstitium, respectively. The osmotic pressure is modulated by the reflection coefficient σ that quantifies the departure of a semi-permeable membrane from the ideal permeability (where any molecule is able to travel across the membrane without resistance). We assume that c_v and c_t are given and are independent of r, s, θ.

2.1 Derivation of the governing flow equations a capillary with arbitrary geometry

The one dimensional model that governs the bulk flow in each branch of a generic microcirculation network is obtained as follows. Let us define a local cylindrical coordinate system (r, θ, s) at each point of the centerline of the capillaries. We denote with $\boldsymbol{e}_r, \boldsymbol{e}_\theta, \boldsymbol{e}_s$ the radial, circumferential and axial unit vectors. The model is based on the following, geometric, kinematic and dynamic assumptions:

Circular section For each value of the arc length s along a network branch, the intersection between the orthogonal plan to $\boldsymbol{e}_s$ and the vessel is circular.

Dominance of axial velocity The radial and circumferential velocity components are negligible compared to the axial component, namely $\boldsymbol{u}_v = [0, 0, u_v(r, \theta, s)]^T$.

Body forces We neglect the effect of gravity and other possible types of body forces (inertia, Coriolis).

Steady flow We neglect transient phenomena. Microcirculation is characterized by negligible fluctuations of the blood pressure due to the heartbeat, namely the Womersley numbers at the level of capillary circulation are negligible. For this reasons, we just aim to determine the steady flow conditions.

Dominance of viscous forces Microcirculation is also characterized by the dominance of viscous forces over inertial forces acting on infinitesimal fluid particles, namely the Reynolds number characterizing the flow is low.

Viscosity We assume that the apparent viscosity of blood, μ_v is independent of the local deformation rate conditions. However, the viscosity is not a constant parameter but it depends on the hematocrit.

Under these assumptions the mass balance and momentum equations governing an incompressible flow, such as blood reduce to the following form,

$$u_r = u_\theta = 0, \partial_r p_v = 0,\ \partial_\theta p_v = 0,\ \partial_s u_v = 0,\ -\mu_v \Delta u_v + \partial_s p = 0, \tag{3}$$ eq:flow1

for any $(r,\theta,s) \in \Omega_v$ where Δ denotes the Laplace operator with respect to cylindrical coordinates $\Delta u = 1/r\partial_r(r\partial_r u)+1/r^2\partial^2_\theta u+\partial^2_s u$. We now aim to transform this equation into a simpler one that is defined on the center-line of the capillary, solely. To this purpose, we need to introduce first a parametrization of each curvilinear branch. Let $\mathbf{\Psi} : \mathrm{R} \to \mathrm{R}^3$ be the parametric arg length, such that $\mathbf{\Psi} \in C^3(\mathrm{R})$ and $\|d_z\mathbf{\Psi}(z)\| = 1$ for any $z \in [0, L]$ being L the length of a generic branch of the capillary network. Note that $s = \int_0^z \|d_\zeta \mathbf{\Psi}(\zeta)\| d\zeta = z$. The curvature of the arc at a specific location, is $\kappa = \|d_{zz}\mathbf{\Psi}(z)\|$; the centripetal unitary direction is $\boldsymbol{N} = d_{zz}\mathbf{\Psi}(z)/\kappa$ and the center C_0 of the osculating circle is the point in the direction $\boldsymbol{N}(z)$ with distance $1/\kappa$ from $\mathbf{\Psi}(z)$.

In order to proceed with the one-dimensional model derivation, we set the following ansatz: the axial velocity profile can be decomposed as $u_v(r,\theta,s) = \overline{u}_v(s)\Phi(r,\theta)$ where $\overline{u}_v$ represents the mean or bulk velocity of the blood stream on the cross section identified by the arc length s, denoted by $\Sigma(s)$. More precisely, in what follows we will use the notation

$$\overline{u}_v(s) = \frac{1}{\pi R^2}\int\limits_{\Sigma(s)} u_v \, d\sigma\,, \quad \overline{p}_v(s) = \frac{1}{\pi R^2}\int\limits_{\Sigma(s)} p_v \, d\sigma\,, \quad \overline{\overline{p}}_t(s) = \frac{1}{2\pi R}\int\limits_{\partial\Sigma(s)} p_t \, d\sigma\,,$$

where $\overline{\overline{p}}_t$ is the mean interstitial pressure on the boundary of a section Σ. The function $\phi(r,\theta)$ is a shape factor that is represented as

$$\Phi(r,\theta) = \phi(r/R)(1 + ar\cos\theta + br\sin\theta + cr^2\cos\theta\sin\theta + dr^2\cos^2\theta + er^2\sin^2\theta). \tag{4}$$?eq:profile

The radially symmetric part of the profile, namely $\phi(r/R)$ is usually modeled as,

$$\phi(\rho) = \frac{\gamma+2}{\gamma}\left(1-\rho^\gamma\right),$$

which coincides with the classic Poiseuille parabolic flow profile (observed in straight cylindrical channels) for $\gamma = 2$.

We aim to find a suitable expression for the parameters a, b, c, d, e in terms of the geometry of the arc, namely $\mathbf{\Psi}$, such that the shape factor coincides with the classic parabolic Poiseuille profile when the arc is rectilinear, while it deviates from this pattern when the arc is curved. To this purpose, we set the following additional assumptions:

Choice of θ We assume that on each cross section the axis $\theta = 0$ is colinear with the vector $\mathbf{N}$.

Symmetry of the profile We require that the velocity profile in each section is such that $\Phi(r,\theta,\psi) = \Phi(r,-\theta,\psi) \quad \forall r,\theta,\psi$. As a result of that the coefficient b, c must vanish, namely $b = c = 0$.

Linear dependence We assume that the correction factor to the velocity profile at any point s, namely $(1 + ar\cos\theta + br\sin\theta + cr^2\cos\theta\sin\theta + dr^2\cos^2\theta + er^2\sin^2\theta)$ is linearly dependent of the distance from the center of the osculating circle relative to this point.

We are now able to determine the coefficients a, d, e which satisfy these assumptions. For the linear dependence of the velocity with the distance from the center of the osculating circle, our profile must be zero in $C_0 = (r = 1/\kappa, \theta = 0, \psi)$, that is $(1 + a/\kappa + d/\kappa^2) = 0 \rightarrow d = -a\kappa - \kappa^2$. Furthermore, since the velocity profile is linear dependent to the distance from the center of the osculating circle we have that all the points with distance $1/\kappa$ from it must have the same velocity. The set of points of each cross section with distance $1/\kappa$ from the point C_0 are:

$$\varphi = \{(r, \theta) : \quad r = \frac{2\cos\theta}{\kappa}, \quad \theta \in [-\frac{\pi}{2}; +\frac{\pi}{2}]\}.$$

Moreover we have that $\Phi(r = 0, \theta, \psi) = \phi(0)$ and so $\forall(r, \theta) \in \phi$ then $\Phi(r, \theta, \psi) = \phi(r/R)$. It follows that $\forall(r, \theta) \in \varphi$:

$$0 = ar\cos\theta + dr^2\cos^2\theta + er^2\sin^2\theta = 2\frac{a}{\kappa}\cos^2\theta + 4\frac{d}{\kappa^2}\cos^4\theta + 4\frac{e}{\kappa^2}\cos^2\theta\sin^2\theta.$$

Now for $\theta = \pm\frac{\pi}{2}$ the equation is verified. In the other cases we can divide all by $2\cos^2\theta/\kappa^2$, to obtain:

$$0 = a\kappa + 2d\cos^2\theta + 2e\sin^2\theta \qquad \forall\theta \in (-\frac{\pi}{2}; +\frac{\pi}{2}).$$

To find the value of the parameters we need two more equations. Thus, we test it on two particular cases: $\theta = \pi/4, \theta = \pi/3$. For $\theta = \pi/4$, using $d = -a\kappa - \kappa^2$ we obtain:

$$0 = a\kappa + 2d(\frac{1}{2}) + 2e(\frac{1}{2}) = a\kappa + d + e = a\kappa - \kappa^2 - a\kappa + e = e - \kappa^2.$$

For that $e = \kappa^2$. Finally for $\theta = \pi/3$, using the previous result we have:

$$0 = a\kappa + 2d(\frac{1}{4}) + 2e(\frac{3}{4}) = a\kappa + \frac{d}{2} + \frac{3e}{2} = a\kappa - \frac{\kappa^2}{2} - \frac{a\kappa}{2} + \frac{3\kappa^2}{2} = \frac{a\kappa}{2} + \kappa^2$$

So we obtain $a = -2\kappa$ and $d = \kappa^2$. In a general configuration the curvature is dependent on the arc length $\kappa = \kappa(s)$. In conclusion, the velocity profile is of the form:

$$\Phi(r, \theta, \psi) = \phi(rR^{-1})(1 + r^2\kappa^2(\psi) - 2\kappa(\psi)r\cos\theta). \tag{5}$$ eq:profil

Now we derive the reduced model for flow in curved vessels by replacing the velocity profile (5) into the mass and momentum balance equations (3) and we integrate these equations on a portion of vessel, P delimited by two cross sections $\Sigma(s_1), \Sigma(s_2),\ s_2 > s_1$. In this way, we obtain simplified equations that depend only on the arc length s. We start first from the continuity equation, using the fact that $\boldsymbol{n} = \boldsymbol{e}_s$ on $\Sigma(s_1)$ and $\Sigma(s_2)$ we obtain:

$$
\begin{aligned}
0 = \int_P \nabla \cdot \boldsymbol{u}_v d\Omega = \int_{\partial P} \boldsymbol{u}_v \cdot \mathbf{n}\, d\sigma = \int_{\Sigma(s_1)} \boldsymbol{u}_v \cdot \boldsymbol{n} d\sigma + \int_{\Sigma(s_2)} \boldsymbol{u}_v \cdot \boldsymbol{n}\, d\sigma + \int_\Gamma \boldsymbol{u}_v \cdot \boldsymbol{n}\, d\sigma \\
= -\int_{\Sigma(s_1)} u_v\, d\sigma + \int_{\Sigma(s_2)} u_v\, d\sigma + \int_\Gamma f(p_t, p_v)\, d\sigma \simeq -\overline{u}_v(s_1)\pi R^2(s_1) + \overline{u}_v(s_2)\pi R^2(s_2) + \int_{s_1}^{s_2} f(\overline{p}_t, p_v) dz \\
= \int_{s_1}^{s_2} [f(\overline{\overline{p}}_t, \overline{p}_v) + \partial_s(\pi R^2 \overline{u}_v)] dz\,.
\end{aligned}
\tag{6}
$$

eq:interf_a

According to (3), in particular $\partial_r p_v = \partial_\theta p_v = 0$, we notice that $p_v(r, s, \theta) = \overline{p}_v(s)$. Furthermore, in equation (6) we have adopted the assumption that the radius of the capillary is small if compared to the domain Ω. More precisely, we have set that

$$
\int_\Gamma f(p_t, p_v)\, d\sigma = \int_{s_1}^{s_2}\int_0^{2\pi} f(p_t, p_v) R(s) d\theta\, ds = \int_{s_1}^{s_2}\int_0^{2\pi} f(p_t, \overline{p}_v) R(s) d\theta\, ds \simeq \int_{s_1}^{s_2} 2\pi R(s) f(\overline{\overline{p}}_t, \overline{p}_v)\, ds\,,
$$

where the last approximation becomes exact when $R \to 0$ because,

$$
\lim_{R\to 0} \int_0^{2\pi} f(p_t(R(s), s, \theta), \overline{p}_v) d\theta = \lim_{R\to 0} f(\overline{\overline{p}}_t(s), \overline{p}_v)\,.
$$

Since the cross sections $\Sigma(s_1)$, $\Sigma(s_2)$ are arbitrarily chosen, we conclude that the equation holds pointwise, namely

$$
\partial_s(\pi R^2 \overline{u}_v) + 2\pi R(s) f(\overline{\overline{p}}_t, \overline{p}_v) = 0. \tag{7}
$$

{?}

Let us now apply the averaging technique to the momentum balance equation, that is the last of (3). We have:

$$
\begin{aligned}
\int_P \Delta u_v\, d\Omega = \int_{\partial P} \nabla u_v \cdot \boldsymbol{n}\, d\sigma = -\int_{\Sigma(s_1)} [\partial_s u_v\, d\sigma + \int_{\Sigma(s_2)} \partial_s u_v\, d\sigma + \int_\Gamma \nabla u_v \cdot \boldsymbol{n}\, d\sigma = \int_\Gamma \nabla u_v \cdot \boldsymbol{e}_r\, d\sigma. \\
= \int_\Gamma \partial_r u_v d\sigma = \int_\Gamma \overline{u}_v(s) \partial_r \Phi(r, \theta) d\sigma = \int_\Gamma \overline{u}_v(s) R^{-1} \phi'(rR^{-1})(1 - 2\kappa r\cos\theta + \kappa^2 r^2) + \phi(rR^{-1})(2\kappa^2 r - 2\kappa\cos\theta)\, d\sigma \\
= \int_{s_1}^{s_2}\int_0^{2\pi} \overline{u}_v(s) R\big(R^{-1}\phi'(1)(1 - \kappa\cos\theta + \kappa^2 R^2) + \phi(1)(2\kappa^2 R - 2\kappa\cos\theta)\big) d\theta ds.
\end{aligned}
\tag{8}
$$

{?}

Now using the fact that $s(1) = 0$, the periodicity of $\cos\theta$ we obtain:

$$\int_P \Delta u_v \, d\Omega = \int_{s_1}^{s_2} 2\pi\phi'(1)(1+\kappa^2 R^2)\overline{u}_v(s)\, ds, \tag{9}$$ {?}

such that the averaged/one-dimensional form of the momentum equation becomes

$$-2\pi\mu_v(s)\phi'(1)\big(1+\kappa^2(s)R^2\big)\overline{u}_v(s) + \pi R^2 \partial_s \overline{p}_v(s) = 0. \tag{10}$$ {?}

2.2 Extension to a network of capillaries

Now that we have derived the 1D model equations we need to generalize them to a more complex topology. To this purpose, we decompose the network in Λ_i branches, $i = 1, ..., N$. The branches are parametrized by the arc length s_i; a tangent unit vector $\boldsymbol{\lambda}_i$ is also defined over each branch, accounting for an arbitrary branch orientation. Differentiation over the branches is defined using the tangent unit vector, namely $\partial_{s_i} := \nabla \cdot \boldsymbol{\lambda}_i$ on Λ_i, i.e. ∂_{s_i} represents the projection of ∇ along λ_i. So far, the equations that govern the flow in each branch of the network are uncoupled. in order to make the flow problem fully coupled we need to enforce constraints at the junctions of the branches. Junctions are defined as the points $\boldsymbol{y}$ such that

$$\boldsymbol{y}_j = \boldsymbol{\Psi}_i(s_i^*) = \boldsymbol{\Psi}_{\hat{i}}(s_{\hat{i}}^*), \;\; s_i^* \in \{0, L_i\} \;\; \forall i, \hat{i} = 1, \ldots, N$$

Let us count the junctions with the index $j = 1, 2, \ldots, M$ and let us denote with $\mathcal{K}_j$ the set of indices i such that $\boldsymbol{\Psi}_i(s_i^*) = \boldsymbol{y}_j$. These are the branches that join at the j-th junction. There may be branches that end inside or at the boundary of the domain Ω. The former are said dead ends and are denoted with $\boldsymbol{z}$. The indices of branches featuring a dead end are $i \in \mathcal{E}$. The latter points are called boundary ends and are identified by the symbol $\boldsymbol{x}$. The set of branches intersecting the outer boundary is $i \in \mathcal{B}$.

The branches that merge at the j-th junction can be subdivided according to different criteria. We present here two options, both useful later on. Let $\boldsymbol{\lambda}_i$ be the orientation of a given branch of the network and let $\boldsymbol{e}_s$ be the outgoing tangential unit vector at the each of the two endpoints of the branch, identified respectively by the arc length coordinates $s = 0$ and $s = L$.

The ingoing endpoints are identified by the following conditions: $\boldsymbol{\lambda}_i \cdot \boldsymbol{e}_s(s) < 0$ for $s = 0$ and $s = L$. The outgoing points are obviously the ones such that $\boldsymbol{\lambda}_i \cdot \boldsymbol{e}_s(s) > 0$. The indices i that correspond to ingoing branches at the j-th junction are denoted with $\mathcal{K}_j^-$, while the indices of the outgoing branches at the junction are collected in $\mathcal{K}_j^+$.

If we add the orientation of the flow to this classification we obtain that the inflow endpoints are identified by the following conditions that involves the orientation of the flow: $\overline{u}_v(s)\boldsymbol{\lambda}_i \cdot \boldsymbol{e}_s(s) < 0$ for $s = 0$ and $s = L$. The outflow points are obviously the ones such that $\overline{u}_v(s)\boldsymbol{\lambda}_i \cdot \boldsymbol{e}_s(s) > 0$. The corresponding indices are collected in the sets $\mathcal{K}_j^{in}$, $\mathcal{K}_j^{out}$, respectively. We classify similarly the boundary ends, subdividing the points $\boldsymbol{x}$ into ingoing or outgoing, namely $\boldsymbol{x}^-, \boldsymbol{x}^+$, or into inflow and outflow $\boldsymbol{x}^{in}, \boldsymbol{x}^{out}$. At these points, we set the vascular pressure equal to a prescribed value $\overline{p}_v(\boldsymbol{x}_i) = g_v,\ i \in \mathcal{B}$, while the value of hematocrit will be enforced at the inflow points solely, $\boldsymbol{x}^{in}$. We finally notice that ingoing/outgoing or inflow/outflow refer to the role of the junction with respect to the neighboring branches.

We enforce balance of flow rates and continuity of pressure at each junction, namely,

$$\sum_{i \in \mathcal{K}_j} \pi R_k^2 \overline{u}_{v,i} = 0,\ j = 1, 2, \dots, M\,, \quad \overline{p}_{v,i} = \overline{p}_{v,\hat{\imath}},\ i, \hat{\imath} \in \mathcal{K}_j,\ j = 1, 2, \dots, M\,.$$

At dead ends of the network we set no-flow conditions $\pi R^2 \overline{u}_v|_{\boldsymbol{z}_i} = 0,\ i \in \mathcal{E}$, where $|_{\boldsymbol{z}_i}$ is a shorthand notation for the evaluation of a function (or better the whole term) in the point $\boldsymbol{z}_i$. For simplicity, we assume that all dead ends take place at the endpoint of the branch, namely they satisfy $\boldsymbol{\lambda}_i \cdot \boldsymbol{e}_s(s = L) > 0$.

In conclusion, the coupled model that describes the bulk velocity of blood flow in the network is the following,

$$\begin{cases} \partial_s\big(\pi R_i^2(s)\overline{u}_{v,i}(s)\big) + 2\pi R_i(s) f(\overline{\overline{p}}_t(s), \overline{p}_v(s)) = 0 & \text{on } \Lambda_i,\ i = 1, \dots, N\,, \\ -2\pi\mu_{v,i}(s)\phi'(1)\big(1 + \kappa_i^2(s)R_i^2(s)\big)\overline{u}_{v,i}(s) + \partial_s \overline{p}_{v,i}(s) = 0 & \text{on } \Lambda_i,\ i = 1, \dots, N\,, \\ \sum_{i \in \mathcal{K}_j} \pi R_k^2 \overline{u}_{v,i}|_{\boldsymbol{y}_j} = 0, & j = 1, 2, \dots, M\,, \\ \overline{p}_{v,i}|_{\boldsymbol{y}_j} = \overline{p}_{v,\hat{\imath}}|_{\boldsymbol{y}_j} & i, \hat{\imath} \in \mathcal{K}_j,\ j = 1, 2, \dots, M\,. \end{cases} \tag{11}$$ eq:flow_red

We notice that in the case of a straight, cylindrical, impermeable pipe, i.e. $\gamma = 2$, the coefficient $\phi'(1) = -4$ and $f(\overline{\overline{p}}_t, \overline{p}_v) = 0$, such that these equations coincide with the standard Poiseuille flow.

Finally, we address the coupling of the reduced model (11) with the porous media equation in the surrounding environment, as described in (1). We follow the approach proposed in (2), where the interaction of the manifold Λ with the bulk domain Ω is represented my means of the distribution of a concentrated sources on Λ. Owing to these assumptions, we identify Ω_t with Ω and we introduce a new term on the left hand side to the first equation of (1). To guarantee mass conservation, this new term must be opposite to $f(\overline{\overline{p}}_t(s), \overline{p}_v(s))$ and be multiplied by δ_{Λ_i} that is

a distribution of Dirac masses along the manifold Λ_i. As a result of that, the flow model that describes capillaries as one-dimensional channels coupled with a porous interstitial tissue reads as follows:

$$\begin{cases} \nabla \cdot \boldsymbol{u}_t - 2\pi R(s) f(\overline{\overline{p}}_t(s), \overline{p}_v(s))\delta_\Lambda = 0 & \text{in } \Omega \\ \boldsymbol{u}_t + \frac{\mathrm{K}}{\mu_t}\nabla p_t = 0 & \text{in } \Omega \\ \partial_s\big(\pi R_i^2(s)\overline{u}_{v,i}(s)\big) + 2\pi R_i(s) f(\overline{\overline{p}}_t(s), \overline{p}_v(s)) = 0 & \text{on } \Lambda_i,\ i = 1, \dots, N\,, \\ -2\pi\mu_{v,i}(s)\phi'(1)\big(1 + \kappa_i^2(s)R_i^2(s)\big)\overline{u}_{v,i}(s) + \partial_s\overline{p}_{v,i}(s) = 0 & \text{on } \Lambda_i,\ i = 1, \dots, N\,, \\ \sum_{i\in\mathcal{K}_j} \pi R_k^2 \overline{u}_{v,i}|_{\boldsymbol{y}_j} = 0, & j = 1, 2, \dots, M\,, \\ \overline{p}_{v,i}|_{\boldsymbol{y}_j} = \overline{p}_{v,\hat{\imath}}|_{\boldsymbol{y}_j} & i, \hat{\imath} \in \mathcal{K}_j,\ j = 1, 2, \dots, M\,. \end{cases} \tag{12}$$

eq:flow_r

2.3 Modeling the Fahraeus-Lindqvuist and the palsma skimming effects

As previously mentioned, the viscosity of blood flowing through very small channels can not be considered to be constant. The main factor that affects the apparent (or effective) viscosity of blood is the volumetric concentration of red blood cells, namely the hematocrit. Several phenomenological models are available to quantify this dependence, we refer here to a widely used one, proposed in (7):

$$\frac{\mu_v}{\mu_{ref}} = \left[1 + \left(\frac{\mu_{0.45}}{\mu_{ref}} - 1\right) \cdot \frac{(1-H)^C - 1}{(1-0.45)^C - 1} \cdot \left(\frac{D}{D-1.1}\right)^2\right] \cdot \left(\frac{D}{D-1.1}\right)^2 \tag{13}$$

eq:Pries_

where H is the discharge hematocrit, defined such that $(\pi R^2(s))\overline{u}_v(s)H(s)$ is the total flow of red blood cells that crosses a section $\Sigma(s)$ of a capillary. In the expression (13), C is a parameter depending on the diameter $D = 2R$ of the capillary and on the hematocrit H:

$$C = (0.8 + e^{-0.075D}) \cdot \left(-1 + \frac{1}{1 + 10^{-11}D^{12}}\right) + \frac{1}{1 + 10^{-11}D^{12}} \tag{14}$$

?eq:Pries_

and $\mu_{0.45}$ is a nominal value viscosity, related to the value at 45% hematocrit,

$$\frac{\mu_{0.45}}{\mu_{ref}} = 6 \cdot e^{-0.085D} + 3.2 - 2.44 \cdot e^{-0.06D^{0.645}}. \tag{15}$$

?eq:Pries_

The reference viscosity μ_{ref} is obtained from the dynamic viscosity of water (H_2O) as follows

$$\mu_{ref} = 1.8\mu_{H_2O} = 1.8\frac{\mu_0}{1 + 0.0337T + 0.00022T^2}. \tag{16}$$?eq:mu_plasm

where T is the temperature (measured in Celsius) and $\mu_0 = 1.808$ centi-Poise (cP) is the viscosity of water at 0 C^o.

The model (13) entails the need to model the dynamics of hematocrit in the microvascular network. To this purpose we propose a one-dimensional model for transport of hematocrit that will be coupled to (12). This model is set on the following assumptions.

Steady flow conditions As we did for the bulk flow model, we study the hematocrit transport in steady conditions.

Transport dominated regime Let us analyze the Péclét number that characterizes the hematocrit transport,

$$Pe = \frac{L\overline{v}}{D} \tag{17}$$?eq:Peclet?

where $L \simeq 10^{-5}m$ is the RBC characteristic scale (also comparable with the capillary diameter), $\overline{v} \simeq 10^{-4}m/s$ is the average velocity of RBC in the capillaries and $D \simeq 10^{-12}m^2/s$ is the diffusivity parameter of RBC in water (1, 3, 5). As a result we obtain $Pe \simeq 10^3$ that justifies the assumption.

Reactions and leak off We assume that the RBC do not leak off from the capillaries and we neglect any effects involving production or sequestration of RBC from the blood stream.

Absence of trifurcations at network junctions We assume that all the inner junctions of the network can be classified either as anastomoses or bifurcations.

On the basis of these hypotheses, the dynamics of hematocrit in a capillary network, where each capillary branch is modeled as a one-dimensional channel, is described by the mass balance equation. Denoting the flow rate of hematocrit across a single channel as Q_H, owing to the definition of discharge hematocrit we directly have $Q_H = \pi R^2 \overline{u}_v H$ and the mass balance equation for hematocrit becomes,

$$\partial_s\left(\pi R_i^2 \overline{u}_{v,i} H_i\right) = 0 \text{ on } \Lambda_i,\ i = 1, 2, \dots . \tag{18}$$ eq:trasport

Equation (18) will be taken as the governing equation for hematocrit in each branch of the capillary network. We observe that this equation can be easily combined with the first of (12) to obtain

$$\pi R_i^2 \overline{u}_{v,i} \partial_s H - 2\pi R_i f(\overline{\overline{p}}_t, \overline{p}_v) H_i(s) = 0 \text{ on } \Lambda_i,\ i = 1, 2, \dots . \tag{19}$$ {?}

It shows that hematocrit is not constant along the axis of the branch, despite we neglect RBC reactions and leak off. However, hematocrit varies because the plasma can leak off and consequently the volumetric concentration of RBC may increase.

Equation (18) is not sufficient to uniquely determine the value of hematocrit in the network. It must be combined with suitable conditions for conservation of hematocrit at the junctions and at the boundary of the network. As (18) is a pure transport equation, it is well known that we have to prescribe a condition of the value of hematocrit at each inflow endpoint of the network branches. Let us denote by $\partial\Lambda_{in}$ the inflow points at the boundary of the network. On all these points we enforce a given value of hematocrit, namely $H = H_0$ on $\partial\Lambda_{in}$. For the internal junctions we exploit mass conservation of hematocrit. Let us consider a generic junction with multiple branches joining at a single node. Given the orientation of the flow, we can subdivide the branches into $K_{out} = \text{card}(\mathcal{K}_j^{out})$ outgoing ones and $K_{in} = \text{card}(\mathcal{K}_j^{in})$ inflow branches. We need to prescribe as many constraints as the number of inflow branches, namely N_{in}. Mass conservation always provides one constraint that is,

$$\sum_{i \in \mathcal{K}_j^{out}} \pi R_i^2 \overline{u}_{v,i} H_i = \sum_{i \in \mathcal{K}_j^{in}} \pi R_i^2 \overline{u}_{v,i} H_i \,. \tag{20}$$?eq:mass_c

The previous equation is not in general sufficient to close the problem in the case $K_{in} > 1$. The simple case $K_{in} = 1$ identifies anastomoses, where one, two or multiple outflow branches merge into a sigle inflow. In this case, since all the terms on the left hand side are known, hematocrit value on the right is uniquely determined. In case of bifurcations, namely $K_{in} = 2$, the problem can be solved by means of the flow split model proposed in (6). Since we exclude the presence of trifurcations or more complex configurations, this approach will be entirely sufficient to determine the distribution of hematocrit in the network. Without loss of generality, let us consider the classic Y-shaped configuration, where one parent vessel divides into two branches. We denote by the subscript f the quantities related to the parent vessel and with α, β the daughter branches. Given $Q_* = \pi R_*^2 \overline{u}_{v,*}$ with $* = f, \alpha, \beta$ and H_f, we aim to determine H_α and H_β, which provide hematocrit values at the inflow of the outgoing bifurcation branches. Using the approach of (6) we define,

$$F_{QB\alpha} = \frac{Q_\alpha}{Q_f} \quad F_{QE\alpha} = \frac{Q_\alpha H_\alpha}{Q_f H_f},$$

and we calculate these fractions using the following model

$$\begin{cases} F_{QE\alpha} = 0 & if\ F_{QB\alpha} \le X_0 \\ \text{logit}(F_{QE\alpha}) = A + B\text{logit}(\frac{F_{QB\alpha}-X_0}{1-2X_0}) & if\ X_0 < F_{QB\alpha} < 1 - X_0 \\ F_{QE\alpha} = 1 & if\ F_{QB\alpha} \ge 1 - X_0 \end{cases} \quad (21)$$?eq:Pries_s

where $\text{logit}(x) = \ln[x/(1-x)]$, X_0 is the fractional blood flow rate under which any RBC will flow into the daughter branch α and $D_*, , f, \alpha, \beta$ are the vessel diameters. Finally, the desired hematocrit levels are determined as

$$H_\alpha = F_{QE\alpha} H_f Q_f / Q_\alpha\,, \quad H_\beta = (1 - F_{QE\alpha}) H_f Q_f / Q_\beta\,. \quad (22)$$?eq:Pries_s

3 Mathematical formulation and numerical approximation

3.1 Weak formulation of the two phase flow problem

For the variational formulation of the coupled flow problem (12), we proceed as previously described in (4) for a similar case. Let's multiply the Darcy equations of (12) by test functions $q_t \in Q_t = L^2(\Omega)$, $\boldsymbol{v}_t \in \boldsymbol{V}_t = H_{div}(\Omega)$. Owing to Green's formula we have

$$\big(\nabla p_t\,,\, \boldsymbol{v}_t\big)_\Omega = -\big(p_t\,,\, \nabla\cdot\boldsymbol{v}_t\big)_\Omega + \big(p_t\,,\, \boldsymbol{v}_t\cdot\boldsymbol{n}_t\big)_\Omega = -\big(p_t\,,\, \nabla\cdot\boldsymbol{v}_t\big)_\Omega + \big(g_t\,,\, \boldsymbol{v}_t\cdot\boldsymbol{n}_t\big)_{\partial\Omega}$$

where g_t is a prescribed value of the interstitial pressure at the artificial boundaries of the tissue slab, namely $\partial\Omega$. For the network, we multiply the third equation of (12) by a test function $q_v \in Q_v$. In general, it is sufficient that $Q_v \subset L^2(\Lambda)$, but we require that the pressure is continuous at the junctions, according to the last equation of (12). Let $q_v|_{\boldsymbol{y}_j}$ be the uniquely defined value of q_v at the location of the j-th junction. We weakly enforce the flow rate compatibility constraints at the junctions, by multiplying the fifth equation of (12) by $q_v|_{\boldsymbol{y}_j}$ and we add it to the third equation. In this way, we obtain the third equation of (23). To derive the last equation of (23), we multiply the fourth equation of (12) by a test function $v_{v,i} \in V_{v,i} \in H^1(\Lambda_i)$ and by πR_i^2. Then, we sum the contribution of each branch of the network. Moreover, using again Green's formula, we transfer the spatial derivative from the pressure to the test function, as follows,

$$\sum_i \big(\partial_s \overline{p}_{v,i}\,,\, \pi R_i^2 v_{v,i}\big)_{\Lambda_i} = -\sum_i \big(\overline{p}_{v,i}\,,\, \partial_s(\pi R_i^2 v_{v,i})\big)_{\Lambda_i} + \sum_i \big[\overline{p}_{v,i}\pi R_i^2 v_{v,i}|_{s=L} - \overline{p}_{v,i}\pi R_i^2 v_{v,i}|_{s=0}\big].$$

Using the continuity of the pressure at junction points, the last term in the previous expression can be arranged junction by junction as follows,

$$\sum_i \left[\overline{p}_{v,i}\pi R_i^2 v_{v,i}|_{s=L} - \overline{p}_{v,i}\pi R_i^2 v_{v,i}|_{s=0}\right]$$
$$= \sum_j \overline{p}_v|_{\boldsymbol{y}_j}\left[\sum_{i\in\mathcal{K}_j^+}\pi R_i^2 v_{v,i}|_{\boldsymbol{y}_j} - \sum_{i\in\mathcal{K}_j^-}\pi R_i^2 v_{v,i}|_{\boldsymbol{y}_j}\right] + \sum_{i\in\mathcal{B}}\left[\overline{p}_v\,\pi R_i^2 v_v|_{\boldsymbol{x}_i^+} - \overline{p}_v\,\pi R_i^2 v_v|_{\boldsymbol{x}_i^-}\right] + \sum_{i\in\mathcal{E}}\overline{p}_v\,\pi R_i^2 v_v|_{\boldsymbol{z}_i^+}.$$

We finally use the last term of the previous expression to enforce pressure boundary conditions at the boundary points of the network, namely $\overline{p}_v|_{\boldsymbol{x}_i^+} = g_v^+$ and $\overline{p}_v|_{\boldsymbol{x}_i^-} = g_v^-$ for any $i \in \mathcal{B}$. Combining all these equations, the weak formulation of problem (12) reads as follows:

$$\begin{cases} \left(\nabla\cdot\mathbf{u}_t\,,\,q_t\right)_\Omega - \left(2\pi R f(\overline{\overline{p}}_t,\overline{p}_v)\delta_\Lambda\,,\,q_t\right)_\Omega = 0 & \forall q_t\in Q_t,\\[2ex] \frac{\mu_t}{K}\left(\mathbf{u}_t\,,\,\boldsymbol{v}_t\right)_\Omega - \left(p_t\,,\,\nabla\cdot\boldsymbol{v}_t\right)_\Omega = -\left(g_t\,,\,\boldsymbol{v}_t\cdot\boldsymbol{n}_t\right)_{\partial\Omega} & \forall \boldsymbol{v}_t\in\boldsymbol{V}_t,\\[2ex] \sum_i\left(\partial_s(\pi R_i^2\overline{u}_{v,i}\,,\,q_v\right)_{\Lambda_i} + \sum_i\left(2\pi R f(\overline{\overline{p}}_t,\overline{p}_v)\,,\,q_v\right)_{\Lambda_i} - \sum_{i\in\mathcal{E}} q_v\pi R_i^2\overline{u}_{v,i}|_{\boldsymbol{z}_i^+} & \\ \quad - \sum_j q_v|_{\boldsymbol{y}_j}\left[\sum_{i\in\mathcal{K}_j^+}\pi R_i^2\overline{u}_{v,i}|_{\boldsymbol{y}_j} - \sum_{i\in\mathcal{K}_j^-}\pi R_i^2\overline{u}_{v,i}|_{\boldsymbol{y}_j}\right] = 0 & \forall q_v\in Q_v,\\[2ex] \sum_i\left(-2\pi\mu_{v,i}\phi'(1)\left(1+\kappa_i^2R_i^2\right)\pi R_i^2\overline{u}_{v,i}\,,\,v_{v,i}\right)_{\Lambda_i} - \sum_i\left(\overline{p}_v\,,\,\partial_s(\pi R_i^2 v_{v,i})\right)_{\Lambda_i} & \\ \quad + \sum_j\overline{p}_v|_{\boldsymbol{y}_j}\left[\sum_{i\in\mathcal{K}_j^+}\pi R_i^2 v_{v,i}|_{\boldsymbol{y}_j} - \sum_{i\in\mathcal{K}_j^-}\pi R_i^2 v_{v,i}|_{\boldsymbol{y}_j}\right] + \sum_{i\in\mathcal{E}}\overline{p}_v\,\pi R_i^2 v_v|_{\boldsymbol{z}_i^+} & \\ \quad = -\sum_{i\in\mathcal{B}}\left[g_v^+\,\pi R_i^2 v_v|_{\boldsymbol{x}_i^+} - g_v^-\,\pi R_i^2 v_v|_{\boldsymbol{x}_i^-}\right] & \forall v_v\in V_v. \end{cases} \tag{23}$$ eq:weak_f

For hematocrit, we multiply the governing equation (18) by a test function $w_i \in H^1(\Lambda_i)$. Then, we use Green's formula to transfer the derivative from H_i to w_i and we sum over the branches. In this way we obtain the following expression,

$$\sum_i\left(\partial_s(\pi R_i^2\overline{u}_{v,i}H_i)\,,\,w_i\right)_{\Lambda_i} = -\sum_i\left(\pi R_i^2\overline{u}_{v,i}H_i\,,\,\partial_s w_i\right)_{\Lambda_i} + \sum_i\left[\pi R_i^2\overline{u}_{v,i}H_i w_i|_{s=L} - \pi R_i^2\overline{u}_{v,i}H_i w_i|_{s=0}\right].$$

Then, we rearrange the last term of the previous equation junction by junction, as well as we isolate the terms on the boundary and on the dead ends,

$$+\sum_i \left[\pi R_i^2 \overline{u}_{v,i} H_i w_i|_{s=L} - \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{s=0}\right] = \sum_j \left[\sum_{i\in\mathcal{K}_j^{out}} \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{y}_j} - \sum_{i\in\mathcal{K}_j^{in}} \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{y}_j}\right]$$
$$+\sum_{i\in\mathcal{B}} \left[\pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{x}_i^{out}} - \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{x}_i^{in}}\right] + \sum_{i\in\mathcal{E}} \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{z}_i^+} \quad (24)$$ eq:hematocr

Using the previous expression, we enforce the mass balance of hematocrit at the network junctions and the boundary conditions. For this purpose we define the following quantities for the j-th junction. The blood flow split relative to all the inflow branches is,

$$F_{QB,j,i} = \frac{\pi R_i^2 \overline{u}_{v,i}|_{\boldsymbol{y}_j}}{\sum_{i\in\mathcal{K}_j^{out}} \pi R_i^2 \overline{u}_{v,i}|_{\boldsymbol{y}_j}}\,, \quad \forall\, i \in \mathcal{K}_j^{in}\,,$$

and let $F_{QE,j,i}$ be the corresponding split of discharge hematocrit,

$$\begin{cases} F_{QE,j,i} = 1 & if\ \text{card}(\mathcal{K}_j^{in}) = 1; \\ F_{QE,j,i} = 0 & if\ \text{card}(\mathcal{K}_j^{in}) = 2 \wedge F_{QB,j,i} \le X_0; \\ logit(F_{QE,j,i}) = A + Blogit(\frac{F_{QB,j,i}-X_0}{1-2X_0}) & if\ \text{card}(\mathcal{K}_j^{in}) = 2 \wedge X_0 < F_{QB,j,i} < 1 - X_0; \\ F_{QE,j,i} = 1 & if\ \text{card}(\mathcal{K}_j^{in}) = 2 \wedge F_{QB,j,i} \ge 1 - X_0. \end{cases} \quad (25)$$ eq:FQE

As a consequence of these definitions, the discharge hematocrit entering each branch downstream the j-th junction is,

$$\pi R_i^2 \overline{u}_{v,i} H_i|_{\boldsymbol{y}_j} = F_{QE,j,i} \sum_{i\in\mathcal{K}_j^{out}} \pi R_i^2 \overline{u}_{v,i} H_i|_{\boldsymbol{y}_j}.$$

We weakly enforce the hematocrit split conditions in the variational formulation as follows,

$$\sum_{i\in\mathcal{K}_j^{in}} \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{y}_j} = \sum_{i\in\mathcal{K}_j^{in}} F_{QE,j,i} w_i|_{\boldsymbol{y}_j} \left(\sum_{i\in\mathcal{K}_j^{out}} \pi R_i^2 \overline{u}_{v,i} H_i|_{\boldsymbol{y}_j}\right).$$

We also enforce the boundary conditions for hematocrit at the boundary of the network,

$$\pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{x}_i^{in}} = \pi R_i^2 \overline{u}_{v,i} H_0 w_i|_{\boldsymbol{x}_i^{in}}\,.$$

Substituting, for clarity, these terms into (24), we obtain,

$$
\begin{aligned}
&+\sum_i \left[\pi R_i^2 \overline{u}_{v,i} H_i w_i|_{s=L} - \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{s=0}\right] \\
&\qquad = \sum_j \sum_{i\in\mathcal{K}^{out}} \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{y}_j} + \sum_{i\in\mathcal{B}} \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{x}_i^{out}} + \sum_{i\in\mathcal{E}} \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{z}_i^+} \\
&\qquad\qquad - \sum_j \sum_{i\in\mathcal{K}_j^{in}} F_{QE,j,i} w_i|_{\boldsymbol{y}_j} \left(\sum_{i\in\mathcal{K}_j^{out}} \pi R_i^2 \overline{u}_{v,i} H_i|_{\boldsymbol{y}_j} \right) - \sum_j \sum_{i\in\mathcal{B}} \pi R_i^2 \overline{u}_{v,i} H_0 w_i|_{\boldsymbol{x}_i^{in}} \,.
\end{aligned}
$$

Consequently, the variational formulation of the hematocrit governing equation reads as follows,

$$
\begin{aligned}
&-\sum_i \left(\pi R_i^2 \overline{u}_{v,i} H_i \,,\, \partial_s w_i \right)_{\Lambda_i} \\
&\qquad + \sum_j \sum_{i\in\mathcal{K}^{out}} \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{y}_j} + \sum_{i\in\mathcal{B}} \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{x}_i^{out}} + \sum_{i\in\mathcal{E}} \pi R_i^2 \overline{u}_{v,i} H_i w_i|_{\boldsymbol{z}_i^+} \\
&\qquad - \sum_j \sum_{i\in\mathcal{K}_j^{in}} F_{QE,j,i} w_i|_{\boldsymbol{y}_j} \left(\sum_{i\in\mathcal{K}_j^{out}} \pi R_i^2 \overline{u}_{v,i} H_i|_{\boldsymbol{y}_j} \right) = \sum_j \sum_{i\in\mathcal{B}} \pi R_i^2 \overline{u}_{v,i} H_0 w_i|_{\boldsymbol{x}_i^{in}} \quad \forall w_i \in H^1(\Lambda_i) \,. \quad (26)
\end{aligned}
$$

eq:hemato

3.2 Numerical approximation and solution strategy

3.2.1 Finite element approximation

The discretization of problem (23) is achieved by means of the finite element method. One of the main advantages of our formulation is that the partitions of Ω and Λ are completely independent. For this reason we address the two approximations separately.

We denote with $\mathcal{T}_t^h$ an admissible family of partitions of $\bar{\Omega}$ into tetrahedrons K

$$
\bar{\Omega} = \bigcup_{K\in\mathcal{T}_t^h} K,
$$

that satisfies the usual conditions of a conforming triangulation of Ω. Here, h denotes the mesh characteristic size, i.e. $h = \max_{K\in\mathcal{T}_t^h} k_K$, being h_K the diameter of simplex K. Moreover, we are implicitly assuming that Ω is a *polygonal* domain. The solutions of (23) are approximated using discontinuous piecewise-polynomial finite elements for pressure

and $\mathbf{H}^{div}$-conforming *Raviart-Thomas* finite elements (?MR1115205) for velocity, namely

$$Y_k^h := \{v_h \in L^2(\Omega),\ v_h|_K \in P_k(K) \quad \forall K \in \mathcal{T}_t^h\}, \tag{27}$$?def:Pdisc?

$$RT_k^h := \{\mathbf{w}_h \in H_{div}(\Omega),\ \mathbf{w}_h|_K \in P_k(K;\mathbb{R}^d) \oplus \mathbf{x}\, P_k(K) \quad \forall K \in \mathcal{T}_t^h\}, \tag{28}$$?def:RT?

for every integer $k \geq 0$, where $\mathcal{P}_k$ indicates the standard space of polynomials of degree $\leq k$ in the variables $\mathbf{x} = (x_1, \ldots, x_d)$. For the simulations presented later on, the lowest order *Raviart-Thomas* approximation has been adopted, corresponding to $k = 0$ above.

Concerning the capillary network, we adopt the same approach used at the continuous level, namely we split the network branches in separate sub-domains. Furthermore, each curved branch Λ_i is approximated by a piecewise linear 1D line, denoted with Λ_i^h. More precisely the latter is a partition of the i-th network branch made by a sufficiently large number of segments. In this way, we obtain the following discrete domain:

$$\Lambda_h = \bigcup_{i=1}^{N} \Lambda_i^h\,.$$

The solution of (23) over a given branch Λ_i^h is approximated using continuous piecewise-polynomial finite element spaces for both pressure and velocity. Since we want the vessel velocity to be discontinuous at multiple junctions, we define the related finite element space over the whole network as the collection of the local spaces of the single branches. Conversely the pressure has been assumed to be continuous over the network, therefore its finite element approximation is standard. We will use the following families of finite element spaces for pressure and velocity, respectively:

$$X_{k+1}^h(\Lambda) := \{w_h \in C^0(\bar{\Lambda}) w_h|_S \in P_{k+1}(S) \quad \forall S \in \Lambda^h\}, \tag{29}$$?def:Xh?

$$W_{k+2}^h(\Lambda) := \bigcup_{i=1}^{N} X_h^{k+2}\left(\Lambda_i^h\right), \tag{30}$$?def:Wh?

for every integer $k \geq 0$. As a result, we use generalized Taylor-Hood elements on each network branch, satisfying in this way the local stability of the mixed finite element pair for the network. At the same time, we guarantee that the pressure approximation is continuous over the entire network Λ^h. In particular, for the numerical experiments shown later on we have used the lowest order, that is $k = 0$.

For hematocrit we proceed as for the velocity approximation. In particular, we approximate equation (26) with the finite element space W^h_{k+2} defined on Λ^h_i. For the sake of generality, let us define the families of discrete subspaces of the functional spaces for $k \geq 0$:

$$\boldsymbol{V}^h_t = RT^h_k(\Omega) \quad \text{and} \quad Q^h_t = Y^h_k(\Omega)\ ,$$
$$V^h_v = W^h_{k+2}(\Lambda^h) \quad \text{and} \quad Q^h_v = X^h_{k+1}(\Lambda^h) \quad \text{and} \quad W^h_v = W^h_{k+2}(\Lambda^h)\,.$$

Then, the finite element approximation of equations (23) and (26) reads as follows: find $\boldsymbol{u}^h_t \in \mathbf{V}^h_t\ ,\ p^h_t \in Q^h_t\ ,\ u^h_v \in V^h_v\ ,\ p^h_v \in Q^h_v\ , H^h \in W^h_v$ such that

$$\begin{cases}
\big(\nabla\cdot\boldsymbol{u}^h_t\ ,\ q^h_t\big)_\Omega - \big(2\pi R f(\overline{\overline{p}}^h_t, \overline{p}^h_v)\delta_\Lambda\ ,\ q^h_t\big)_\Omega = 0 & \forall q^h_t \in Q^h_t,\\[2ex]
\frac{\mu_t}{K}\big(\boldsymbol{u}^h_t\ ,\ \boldsymbol{v}^h_t\big)_\Omega - \big(p_t\ ,\ \nabla\cdot\boldsymbol{v}^h_t\big)_\Omega = -\big(g_t\ ,\ \boldsymbol{v}^h_t\cdot\boldsymbol{n}_t\big)_{\partial\Omega} & \forall \boldsymbol{v}^h_t \in \boldsymbol{V}^h_t,\\[2ex]
\sum_i \big(\partial_s(\pi R_i^2\overline{u}^h_{v,i}\ ,\ q^h_v\big)_{\Lambda^h_i} + \sum_i \big(2\pi R f(\overline{\overline{p}}^h_t, \overline{p}^h_v)\ ,\ q^h_v\big)_{\Lambda^h_i} - \sum_{i\in\mathcal{E}} q^h_v \pi R_i^2 \overline{u}^h_{v,i}|_{\boldsymbol{z}^+_i}\\
\qquad - \sum_j q^h_v|_{\boldsymbol{y}_j}\Big[\sum_{i\in\mathcal{K}^+_j}\pi R_i^2\overline{u}^h_{v,i}|_{\boldsymbol{y}_j} - \sum_{i\in\mathcal{K}^-_j}\pi R_i^2\overline{u}^h_{v,i}|_{\boldsymbol{y}_j}\Big] = 0 & \forall q^h_v \in Q^h_v,\\[2ex]
\sum_i\big(\ -2\pi\mu_{v,i}\phi'(1)\big(1+\kappa_i^2R_i^2\big)\pi R_i^2\overline{u}^h_{v,i}\ ,\ v^h_{v,i}\big)_{\Lambda_i} - \sum_i\big(\ \overline{p}^h_v\ ,\ \partial_s(\pi R_i^2 v^h_{v,i})\ \big)_{\Lambda^h_i}\\
\qquad + \sum_j \overline{p}^h_v|_{\boldsymbol{y}_j}\Big[\sum_{i\in\mathcal{K}^+_j}\pi R_i^2 v^h_{v,i}|_{\boldsymbol{y}_j} - \sum_{i\in\mathcal{K}^-_j}\pi R_i^2 v^h_{v,i}|_{\boldsymbol{y}_j}\Big] + \sum_{i\in\mathcal{E}}\overline{p}^h_v\,\pi R_i^2 v^h_v|_{\boldsymbol{z}^+_i}\\
\qquad = -\sum_{i\in\mathcal{B}}\Big[\,g^+_v\,\pi R_i^2 v^h_v|_{\boldsymbol{x}^+_i} - \,g^-_v\,\pi R_i^2 v^h_v|_{\boldsymbol{x}^-_i}\,\Big] & \forall v^h_v \in V^h_v\ ,\\[2ex]
-\sum_i\big(\pi R_i^2\overline{u}^h_{v,i}H^h_i\ ,\ \partial_s w_i\big)_{\Lambda^h_i}\\
\qquad + \sum_j\sum_{i\in\mathcal{K}^{out}}\pi R_i^2\overline{u}^h_{v,i}H^h_i w^h_i|_{\boldsymbol{y}_j} + \sum_{i\in\mathcal{B}}\pi R_i^2\overline{u}^h_{v,i}H^h_i w^h_i|_{\boldsymbol{x}^{out}_i} + \sum_{i\in\mathcal{E}}\pi R_i^2\overline{u}^h_{v,i}H^h_i w^h_i|_{\boldsymbol{z}^+_i}\\
\qquad - \sum_j\sum_{i\in\mathcal{K}^{in}_j} F_{QE,j,i} w^h_i|_{\boldsymbol{y}_j}\Big(\sum_{i\in\mathcal{K}^{out}_j}\pi R_i^2\overline{u}^h_{v,i}H^h_i|_{\boldsymbol{y}_j}\Big) = \sum_j\sum_{i\in\mathcal{B}}\pi R_i^2\overline{u}^h_{v,i}H_0 w^h_i|_{\boldsymbol{x}^{in}_i} & \forall w^h_i \in W^h_v\,.
\end{cases} \tag{31}$$

eq:disc_w

We notice that problem (31) is a fully coupled nonlinear problem. Indeed, velocities and pressures on Ω and Λ are coupled through the linear term $f(\overline{\overline{p}}_t, \overline{p}_v)$, while the velocity field on Λ is affected by hematocrit through the nonlinear viscosity model. More precisely we have $\mu_{v,i} = \mu_{v,i}(H_i)$ as prescribed in equation (13). Finally, hematocrit is heavily affected by the flow field in the network, through transport and also by the flow split at network branches, defined in (25). In order to solve such complex problem, we will adopt an iterative splitting strategy, addressed in the next section.

3.2.2 Iterative strategy for the solution of the nonlinear problem

To describe the iterative splitting strategy used to decouple (31) we define a shorthand notation. More precisely, let us group the first four equations of (31) into the fluid mechanics operator $\mathcal{F}^h$. Given Ω, Λ^h, the external data g_t, g_v and the parameters for the porous medium K, μ_t the operator $\mathcal{F}^h$ takes as input the viscosity of the fluid μ_v as a function defined on Λ^h and gives back the solution of the fluid mechanics problem, namely $[\boldsymbol{u}_t^h, u_v^h, p_t^h, p_v^h] = \mathcal{F}^h(\mu_v)$. Similarly, the last equation of (31) can be represented as the operator $\mathcal{H}^h$ such that, given the velocity field in the network u_v^h it gives back the hematocrit level at each point of Λ^h, precisely $H^h = \mathcal{H}^h(u_v^h)$. Using these operators and given an initial guess of the hematocrit distribution $H^{h,0}$, the iterative method to solve (31) consists of performing the following steps for any $k > 0$ until convergence:

1. calculate the apparent viscosity of blood, $\mu_{v,i}^k = \mu_{v,i}(H_i^{h,k-1})$;
2. solve the fluid mechanics problem $[\boldsymbol{u}_t^{h,*}, u_v^{h,*}, p_t^{h,k}, p_v^{h,k}] = \mathcal{F}^h(\mu_v^k)$;
3. apply relaxation of the velocity fields to enhance convergence,

$$\boldsymbol{u}_t^{h,k} = \alpha \boldsymbol{u}_t^{h,*} + (1-\alpha)\boldsymbol{u}_t^{h,k-1} \text{ and } \boldsymbol{u}_v^{h,k} = \alpha \boldsymbol{u}_v^{h,*} + (1-\alpha)\boldsymbol{u}_v^{h,k-1},\ \alpha \in (0,1];$$

4. solve the hematocrit problem $H^{h,*} = \mathcal{H}^h(u_v^{h,k})$;
5. apply relaxation $H^{h,k} = \beta H^{h,*} + (1-\beta)H^{h,k-1}$ with $\beta \in (0,1]$;
6. test convergence by means of the following indicators,

$$\frac{\left\|\mathbf{U}_v^{k+1} - \mathbf{U}_v^k\right\|}{\|\mathbf{U}_v^k\|} + \frac{\left\|\mathbf{p}_v^{k+1} - \mathbf{p}_v^k\right\|}{\|\mathbf{p}_v^k\|} + \frac{\left\|\mathbf{U}_t^{k+1} - \mathbf{U}_t^k\right\|}{\left\|\mathbf{U}_t^k\right\|} + \frac{\left\|\mathbf{p}_t^{k+1} - \mathbf{p}_t^k\right\|}{\left\|\mathbf{p}_t^k\right\|} < \epsilon_{\mathcal{F}}\,,$$

$$\frac{\left\|\mathbf{H}^{k+1} - \mathbf{H}^k\right\|}{\|\mathbf{H}^k\|} < \epsilon_{\mathcal{H}}$$

where $\epsilon_{\mathcal{F}}$, $\epsilon_{\mathcal{H}}$ is a fixed tolerance and $\mathbf{U}_t$, $\mathbf{U}_v$, $\mathbf{p}_t$, $\mathbf{p}_v$, $\mathbf{H}$ are the degrees of freedom that characterize the finite element functions $\boldsymbol{u}_t^h$, u_v^h, p_t^h, , $p_v^{h,k}$, H^h respectively.

4 Numerical simulations

4.1 Verification and validation of the computational model

4.1.1 Single capillary branch case

4.1.2 Y-shaped bifurcations and anastomoses

4.2 Comparative studies on a microvascular network

5 Conclusions

References

1. Carr Russell T, Xiao Jewen. Plasma Skimming in Vascular Trees: Numerical Estimates of Symmetry Recovery Lengths. *Microcirculation.* 1995jan;2(4):345–353.

2. Cattaneo L., Zunino P. Computational models for fluid exchange between microcirculation and tissue interstitium. *Networks and Heterogeneous Media.* 2014;9(1):135–159.

3. Higgins John M., Eddington David T., Bhatia Sangeeta N., Mahadevan L. Statistical dynamics of flowing red blood cells by morphological image processing. *PLoS Computational Biology.* 2009;5(2).

4. Notaro Domenico, Cattaneo Laura, Formaggia Luca, Scotti Anna, Zunino Paolo. A mixed finite element method for modeling the fluid exchange between microcirculation and tissue interstitium,In Ventura Giulio, Benvenuti Elena (eds.) 2016 (pp. 3–25)., Advances in discretization methods: Discontinuities, virtual elements, fictitious domain methods Cham: Springer International Publishing.

5. Pinho D., Lima R., Pereira A. I., Gayubo F. Tracking Red Blood Cells in Microchannels: A Comparative Study Between an Automatic and a Manual Method 2013 (pp. 165–180).

6. Pries A R, Secomb T W. Microvascular blood viscosity in vivo and the endothelial surface layer. *American journal of physiology. Heart and circulatory physiology.* 2005;289(6):H2657–H2664.

7. Pries A R, Secomb T W, Gessner T., Sperandio M B, Gross J F, Gaehtgens P. Resistance to blood flow in microvessels in vivo. *Circulation Research.* 1994nov;75(5):904–915.

□