Macro-scale models for fluid flow in tumour tissues: impact of microstructure properties

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Abstract
Understanding the dynamics underlying fluid transport in tumour tissues is of fundamental importance to assess processes of drug delivery. Here, we analyse the impact of the tumour microscopic properties on the macroscopic dynamics of vascular and interstitial fluid flow. More precisely, we investigate the impact of the capillary wall permeability and the hydraulic conductivity of the interstitium on the macroscopic model arising from formal asymptotic 2-scale techniques. The homogenization technique allows us to derive two macroscale tissue models of fluid flow that take into account the microscopic structure of the vessels and the interstitial tissue. Different regimes were derived according to the magnitude of the vessel wall permeability and the interstitial hydraulic conductivity. Importantly, we provide an analysis of the properties of the models and show the link between them. Numerical simulations were eventually performed to test the models and to investigate the impact of the microstructure on the fluid transport. Future applications of our models include their calibration with real imaging data to investigate the impact of the tumour microenvironment on drug delivery.

Keywords Two-scale homogenisation · Fluid flow in tumours · Interstitial fluid pressure · Tumour microscopic structure

Mathematics Subject Classification 92B05 · 35B27 · 78M35

1 Introduction

Interstitial and capillary fluids are strongly connected in malignant tissues and are mainly involved in the transport of molecules in tumours. When drugs are intra-
venously injected, they have to overcome several barriers, including vascular transport, transvascular transfer, interstitial transport and finally cellular uptake (Jain 1994). The biological and physicochemical properties of the tumour microenvironment play a significant role in the drug delivery process (Baxter and Jain 1989). The geometrical microstructure of the tumour also has an important impact on the fluid flow (Baish et al. 1996).

Neoplastic tissues are highly heterogeneous. They are generally characterized by Chauhan et al. (2011) accumulated solid stress (Helmlinger et al. 1997), abnormal blood vessels network (Sevick and Jain 1989), elevated interstitial fluid pressure (IFP) (Boucher and Jain 1992), that almost equals the microvessel pressure (MVP) and dense interstitial structure (Netti et al. 2000). These traits, that distinguish tumour tissues from normal ones, cause barriers to drug delivery (Jain 1994). The heterogeneous spatial distribution of tumour vessels and poor lymphatic drainage impair a uniform delivery of therapeutic agents in tumours. Blood vessels are unevenly distributed, leaving avascular spaces. Moreover, their walls are leaky and hyperpermeable in some places while not in other (Dvorak et al. 1995; Hilmas and Gillette 1974; Vogel 1965).

Blood flow velocity is also compromised by the elevated viscous and geometrical resistance offered by the tumour vasculature (Baish et al. 1996). Finally, the lack of an efficient lymphatic network inside the tumour coupled with leaky tumour vessels leads to a high IFP (Young et al. 1950) almost equal to the microvascular pressure (Boucher and Jain 1992). Due to elevated IFP, the tumour interstitium is characterized by no pressure gradient (Boucher et al. 1990; Jain and Baxter 1988).

Several mathematical models have been developed during the last decades to investigate the features of fluid transport in the tumour microenvironment. The porous medium theory has been employed to model interstitial fluid flow (IFF) relying on Darcy’s law and using average field variables defined over the whole tissue (Jain 1987; Netti et al. 1995). Fluid transport through the blood vessels has been exploited in both discrete and continuous manners, including spatial and temporal variations. In either discrete and continuous models, the IFF and microvascular fluid (MVF) are usually coupled by Starling’s law (Starling 1896), that describes the fluid filtration through the highly permeable vessels walls. Microscopic models of the flow patterns around an individual capillary and a network of blood vessels have been introduced relying on the Krogh cylinder model (Krogh 1922; Apelblat et al. 1974; Blake and Gross 1982). Poiseuille’s law can be considered to describe the blood flow in a cylindrical domain (Baish et al. 1997; Pozrikidis and Farrow 2003; Solta and Chen 2011). Furthermore, Navier-Stokes equations have been adopted to model the spatio-temporal variations in blood flow (Blake and Gross 1982; Netti et al. 1995). More detailed biophysical models have been developed to take into account the more realistic heterogeneity of the tumour vasculature (Bartha and Rieger 2006). Welter and Rieger (2013) introduced an exhaustive biophysical model the incorporates tumour growth, vascular network (including arteries and veins), angiogenesis, vascular remodeling, porous medium description for the extracellular matrix (ECM) and interstitial fluid, interstitial fluid pressure and velocity and chemical entities (such as oxygen, nutrients, drugs). On the other hand, continuous models based on mixture theory have been exploited to describe interstitial and vascular fluid flow, assuming that the two phases are present at each point of the tumour (Schuff et al. 2013). Multiscale models have
further been employed to investigate the coupling between tumor growth, angiogenesis, vascular remodelling and fluid transport (Owen et al. 2009) and the impact of collagen microstructure on interstitial fluid flow (Wijeratne et al. 2017). Imaging data have been integrated to both continuum and discrete models to quantify the effect of the heterogeneity on the fluid transport (Zhao et al. 2007; Sweeney et al. 2019).

The increasing amount of imaging data makes it possible to recover vascular networks in details. However, solving discrete models on the entire vessel tree might be computationally expensive. The formal 2-scale homogenization technique allows to take into account microscopic features on the macroscopic dynamic of fluid flow. 2-scale asymptotic expansion has been previously applied to fluid and drug transport in tumours. A system of Darcy’s equations has been derived in Shipley and Chapman (2010) to couple interstitial and vascular fluid flows in malignant tissues assuming a periodic medium. A higher complexity has been taken into account in Penta et al. (2015), with the introduction of rheological effects in the blood flow and of local heterogeneity. A generalization of homogenized modelling for vascularized poroelastic materials has also been presented (Penta et al. 2014; Penta and Merodio 2017). More recently, higher complexity has been added to the homogenized models (Shipley et al. 2020) considering three length scales for the vessel network (i.e., arteriole, venule and capillary scales).

Roughly speaking, 2 type of models have been proposed be used to describe fluid flow in tumors. Baxter and Jain suggested that simple Darcy’s law can describe the experimental observations (Baxter and Jain 1989). The tumor is considered as a one-phase medium at a pressure which satisfies a static diffusive equation, whose tensor reflected the global effect of the microstructure. More recently, Shipley and Chapman derived a biphasic model by 2-scale expansion techniques (Shipley and Chapman 2010). In their work, which was also obtained later on by Penta et al., the tumour is composed of a capillary phase and an interstitium phase. Each phase is at a specific pressure and the pressures are coupled through an elliptic system which makes appear the difference between the 2 pressures. Thanks to the 2-scale expansion under periodic assumptions, the authors provide a link between the homogenised tensors and the microstructure.

The present work aims to clarify the links between the monophasic and the biphasic models. Interestingly, we enlighten about the assumptions on the microstructure that lead to the monophasic instead of the biphasic homogenised model. In particular we show that the model derived by Shipley and Chapman is the distinguished model from which the other uncouled and monophasic models might be derived under specific assumptions. In addition, our results show also that the biphasic model exhibits an exponential decay from the tumour boundary that might be difficult to capture numerically, justifying the use of monophasic model. However the appropriate boundary condition has then to be chosen, as performed in Sect. 3.5.

More precisely, we compare different asymptotic regimes of the global fluid dynamics, depending on the microscopic rheological properties of the tumours. We first derive a microscopic model composed of Darcy’s law for the interstitium phase and Stokes equation for the capillary phase, with a Starling’s law at the interface vessel wall/interstitium. This derivation is performed thanks to an asymptotic analysis as the thickness of the capillary walls tends to zero similarly to previous works in electromag-
netic studies (Amar et al. 2006; Perrussel and Poignard 2013). This microscopic model provides us the starting point of a formal 2-scale analysis under periodic assumption (Allaire 1992) to derive effective macroscale tissue models.

We provide then the asymptotic model for any order of magnitude of two parameters the permeability of the vessel wall and of the interstitial hydraulic conductivity. In particular we show that if the interstitial hydraulic conductivity is at least as small as the wall permeability, then the model is monophasic. If the wall permeability is smaller that the interstitial hydraulic conductivity by one order of magnitude, then the two phases are coupled. In this case, the coupling is tight if the magnitude of the wall permeability is of the same order as the microstructure periodicity, and weak if it is smaller.

The characterization of the different limit models of great interest from the modelling point of view, because a cancer tissue might be composed of regions exhibiting different rheological behaviours. It is therefore important to determine how to pass from a model to another one in accordance with the microstructure properties. Eventually, numerical simulations on the macroscopic models are performed and the results are compared to the literature.

Based on the results presented in this paper, the knowledge of the tissue microstructure determines the choice of the macroscopic model, which is crucial to study the impact of the tumour microscopic characteristics on drug delivery. It is worth noting that imaging data can provide the tissue microstructure that can be integrated in the homogenised model. This modelling technique prevents the resolution of the original micro-scale model that might be unfeasible as it requires the discretisation of the entire vessel network and porous medium. Moreover, the heterogeneities of malignant tissues can be taken into account by considering the spatial variability of the micro-vessel features at the macroscopic scale.

The papers is outlined as follows. In Sect. 2, we present the general microscopic model that accounts for most of the phenomena encountered in living tissue. In particular thanks to an asymptotic analysis with respect to the thickness of the capillary wall, we derive a Starling’s law as a transmission condition linking the interstitium and the inner capillary. This microscale model is the starting point of our formal 2-scale expansion. In Sect. 3, we present the formal 2-scale expansion and give the asymptotic models that are derived under different smallness assumptions on the parameters of the microscale model. We also present geometrical assumptions on the two phases—in particular in terms of connectivity— to ensure the positiveness of the resulting homogenised tensors. Numerical simulations are given in Sect. 4. The influence of the geometry of the microstructure on the hydraulic tensor properties is first studied. In particular, tensor anisotropy is shown when the microstructure is oriented. Then the exponential decay\(^1\) from the tumour boundary of the difference of the interstitium and the capillary phases is evaluated in terms of the parameters and shown numerically. The conclusion Sect. 5 puts the results in perspectives with biological applications of the results.

\(^1\) The details of the proof of this behaviour is out of the scope and given in Vaghi et al. (2022).
2 Microscopic model of fluid transport in tumours

At the microscale, the domain $\Omega \in \mathbb{R}^N$ (with $N = 2, 3$) is the medium that consists of the interstitium $\Omega_t$, the vessel wall $\Omega_m$ and the capillary region $\Omega_c$. The interfaces between the inner capillary and the vessel wall on one side and between the interstitium and the vessel wall on the other side are denoted respectively by $\Gamma = \partial \Omega_c \cap \partial \Omega_m$ and $\Gamma_\delta = \partial \Omega_t \cap \partial \Omega_m$. Figure 1(Left) shows the section of a capillary in the surrounding interstitium. In the three regions, the fluid flow is assumed to be incompressible.

The interstitium—composed by the cells and the extracellular matrix and collagen—is modeled as an isotropic porous medium, where the velocity $u_t$ and pressure $p_t$ follow the Darcy’s law:

$$\nabla \cdot u_t = 0, \quad u_t = -k_t \nabla p_t \quad \text{in } \Omega_t, \quad (1a)$$

where $k_t$ is the hydraulic conductivity in the interstitium. In the capillaries, we assume that the fluid is Newtonian with a constant viscosity $\mu$. Neglecting the inertial effects and under the assumption of a laminar flow, the Stokes equation enables to describe the vessel velocity $u_c$ and pressure $p_c$:

$$\nabla \cdot u_c = 0, \quad \mu \nabla^2 u_c = \nabla p_c \quad \text{in } \Omega_c. \quad (1b)$$

Similarly to the interstitium, the capillary wall $\Omega_m$—of thickness $\delta$—is considered as a porous medium with hydraulic conductivity $k_m$, leading to

$$\nabla \cdot u_m = 0, \quad u_m = -k_m \nabla p_m \quad \text{in } \Omega_m. \quad (1c)$$

Fig. 1 *Left:* schematic of the domain considered to compute the interface conditions between the capillaries and the interstitium. $\Omega_m$ denotes the vessel wall region, $\Gamma_\delta$ is the interface between the vessel wall and the interstitium. The transmission conditions are derived as $\delta \to 0$ using asymptotic expansion. *Right:* schematic representation of the domain of the microscopic model: section of the capillary in the surrounding tissue.
2.1 Interface conditions

At the two boundaries \( \Gamma \) and \( \Gamma_\delta \), we have to consider interface conditions in order to couple the different equations. We make the following choices, similarly to Discacciati and Quarteroni (2009):

1. Continuity of the normal velocity on both \( \Gamma \) and \( \Gamma_\delta \):

\[
\begin{align*}
\mathbf{u}_c \cdot \mathbf{n} &= \mathbf{u}_m \cdot \mathbf{n} \quad \text{on } \Gamma, \\
\mathbf{u}_t \cdot \mathbf{n} &= \mathbf{u}_m \cdot \mathbf{n} \quad \text{on } \Gamma_\delta.
\end{align*}
\]

This condition guarantees the continuity of mass through the two interfaces and it is a natural choice since the fluid is assumed to be incompressible in the three regions.

2. Balance of the normal forces at the interfaces \( \Gamma, \Gamma_\delta \):

\[
\begin{align*}
p_c - \mu [(\mathbf{n} \cdot \nabla) \mathbf{u}_c] \cdot \mathbf{n} &= p_m \quad \text{on } \Gamma, \\
p_t &= p_m \quad \text{on } \Gamma_\delta.
\end{align*}
\]

Condition (2) is due to the fact that the blood force in \( \Omega_c \) acting on \( \Gamma \) is equal to the normal component of the Cauchy stress vector (Layton et al. 2002), while the only force in \( \Omega_m \) acting on the interface is the Darcy pressure \( p_m \). Analogously, equation (3) is motivated by the fact that the only forces acting on the interface \( \Gamma_\delta \) are the Darcy’s pressures \( p_m \) and \( p_t \) in the respective regions \( \Omega_m \) and \( \Omega_t \).

3. Beavers-Joseph-Saffmann condition on the tangential component of the capillary velocity at the boundary with a porous medium \( \Gamma \):

\[
\mathbf{u}_c \cdot \mathbf{\tau} = -\frac{\sqrt{k_m \mu}}{\alpha_{BJ}} [(\mathbf{n} \cdot \nabla) \mathbf{u}_c] \cdot \mathbf{\tau} \quad \text{on } \Gamma,
\]

where \( \alpha_{BJ} \) is a constant depending on the properties of the interface. This condition comes from the experimental evidence shown by Beavers and Joseph (1967) who observed that the slip velocity along \( \Gamma \) was proportional to the shear stress along \( \Gamma \). Equation of the form (4) was derived by Saffmann using a statistical approach and the Brinkman approximation for non-homogeneous porous medium (Saffman 1971).

Non-dimensionalization

In order to identify the small parameters in the above partial differential equations, it is crucial to perform a dimensional analysis. This analysis enables us to quantify the relative amplitude of the different parameters involved. We rescale our fields as follows:

\[
x = Lx', \quad \mathbf{u} = U\mathbf{u}', \quad p = \frac{\mu LU}{d^2} p' + p_0.
\]
where $L$ is the characteristic domain length, $d$ is the mean intercapillary distance and $U$ is a characteristic velocity. The non-dimensional fluid transport problem reads (neglecting the primes for the sake of simplicity) then as

$$
\nu \nabla^2 \mathbf{u}_c = \nabla p_c, \quad \nabla \cdot \mathbf{u}_c = 0, \quad \text{in } \Omega_c, \quad (6a)
$$

$$
\mathbf{u}_t = -\kappa \nabla p_c, \quad \nabla \cdot \mathbf{u}_t = 0, \quad \text{in } \Omega_t, \quad (6b)
$$

$$
\mathbf{u}_m = -\kappa_m \nabla p_m, \quad \nabla \cdot \mathbf{u}_m = 0, \quad \text{in } \Omega_m, \quad (6c)
$$

with the interface conditions on $\Gamma$

$$
\mathbf{u}_c \cdot \mathbf{n} = \mathbf{u}_m \cdot \mathbf{n} \quad \text{on } \Gamma, \quad (6d)
$$

$$
p_c - \nu (\mathbf{n} \cdot \nabla) \mathbf{u}_c \cdot \mathbf{n} = p_m \quad \text{on } \Gamma, \quad (6e)
$$

$$
\mathbf{u}_c \cdot \mathbf{\tau} = -R_\tau [(\mathbf{n} \cdot \nabla) \mathbf{u}_c \cdot \mathbf{\tau}] \quad \text{on } \Gamma. \quad (6f)
$$

and on on $\Gamma_\delta$

$$
\mathbf{u}_t \cdot \mathbf{n} = \mathbf{u}_m \cdot \mathbf{n} \quad \text{on } \Gamma_\delta, \quad (6g)
$$

$$
p_t = p_m \quad \text{on } \Gamma_\delta, \quad (6h)
$$

where

$$
\nu = \frac{d^2}{L^2}, \quad \kappa = \frac{k_t \mu}{d^2}, \quad \kappa_m = \frac{k_m \mu}{d^2}, \quad R_\tau = \frac{\sqrt{k_m \mu}}{\alpha_B L},
$$

are dimensionless quantities.

### 2.2 Effective Starling law to replace the thin wall of the capillary

Let us now perform the asymptotic analysis as the thickness of the capillary wall $\delta$ tends to 0, assuming that $\kappa_m$ is proportional to $\delta$ with a proportionality coefficient $R_n$ that will be defined later on:

$$
\kappa_m = \delta R_n.
$$

We assume that the capillary is tubular along the direction $z \in (0, Z_0)$, where $Z_0$ is the characteristic length of the capillary along $z$. We neglect the bending along this axis. Let us denote by $\eta$ the normal variable to the vessel membrane and by $\theta$ the tangential variable to the vessel wall. With these coordinates, the Laplacian is defined by

$$
\nabla^2 : \frac{1}{\delta^2} \frac{\partial^2}{\partial \eta^2} + \frac{1}{\delta(1 + \delta \xi \eta)} \frac{\partial}{\partial \eta} + \frac{1}{(1 + \delta \xi \eta)^2} \frac{\partial^2}{\partial \theta^2} + \frac{\partial^2}{\partial z^2},
$$

where $\xi$ is the curvature of the section. Identifying $\Omega_m$ and the set $\{(\eta, \theta, z) \in (0, 1) \times \Gamma \times (0, Z_0)\}$, therefore, the fluid transport equations (6) in the capillary wall and the
interface conditions are rewritten as

\[
\left( \frac{\partial^2}{\partial \eta^2} + \frac{\delta}{1 + \delta \zeta \eta} \frac{\partial}{\partial \eta} + \frac{\delta^2}{(1 + \delta \zeta \eta)^2} \frac{\partial^2}{\partial \zeta^2} \right) p_m = 0 \quad \text{in } \Omega_m, \tag{7a}
\]

\[
uuc \cdot n = -R_n \partial_\eta p_m \quad \text{on } \Gamma \tag{7b}
\]

\[
\partial_\eta p_m = \frac{\kappa}{R_n} \nabla p_t \cdot n \quad \text{on } \Gamma_\delta \tag{7c}
\]

\[
\nuc - \nu[(n \cdot \nabla) \nuuc] \cdot n = p_m \quad \text{on } \Gamma \tag{7d}
\]

\[
P_t = p_m \quad \text{on } \Gamma_\delta \tag{7e}
\]

\[
uuc \cdot \tau = -R_\tau [(n \cdot \nabla) \nuuc] \cdot \tau \quad \text{on } \Gamma \tag{7f}
\]

The limit fluid flow problem at the microscale is obtained thanks to an asymptotic analysis. The formal expansion of the variables \(p_m\), \(p_t\), \(p_c\) and \(\nuuc\) in powers of \(\delta\)

\[
p_m = p_m^{(0)} + \delta p_m^{(1)} + \delta^2 p_m^{(2)} + \cdots
\]

\[
P_t = p_t^{(0)} + \delta p_t^{(1)} + \delta^2 p_t^{(2)} + \cdots
\]

\[
\nuuc = \nuuc^{(0)} + \delta \nuuc^{(1)} + \delta^2 \nuuc^{(2)} + \cdots
\]

is injected in the equations. Equating coefficients of order 1\(=\delta^0\) in (7a)--(7f), we obtain the following system of equations

\[
\partial_\eta^2 p_m^{(0)} = 0 \quad \text{in } \Omega_m \tag{8a}
\]

\[
\nuuc^{(0)} \cdot n = -R_n \partial_\eta p_m^{(0)} \quad \text{on } \Gamma \tag{8b}
\]

\[
\partial_\eta p_m^{(0)} = \frac{\kappa}{R_n} \nabla p_t^{(0)} \cdot n \quad \text{on } \Gamma_\delta \tag{8c}
\]

\[
\nuuc^{(0)} - \nu[(n \cdot \nabla) \nuuc^{(0)}] \cdot n = p_m^{(0)} \quad \text{on } \Gamma \tag{8d}
\]

\[
P_m^{(0)} = p_t^{(0)} \quad \text{on } \Gamma_\delta \tag{8e}
\]

\[
\nuuc^{(0)} \cdot \tau = -R_\tau [(n \cdot \nabla) \nuuc^{(0)}] \cdot \tau \quad \text{on } \Gamma \tag{8f}
\]

From (8a) and (8c) we infer

\[
\partial_\eta p_m^{(0)} = \frac{\kappa}{R_n} \nabla p_t^{(0)} \cdot n \quad \text{in } \Omega_m \tag{9}
\]
Equations (9) and (8d) then lead to

\[ p_m^{(0)} = \left( \frac{\kappa}{R_n} \nabla p_t^{(0)} \cdot \mathbf{n} \right) \eta + p_c^{(0)} - \nu [\mathbf{n} \cdot \nabla u_c^{(0)}] \cdot \mathbf{n} \quad \text{in} \ \Omega_m. \]  

(10)

from which we infer thanks to (8e) the expression of \( p_t^{(0)} \):

\[ p_t^{(0)} = p_m^{(0)}(\eta = 1) = \frac{\kappa}{R_n} \nabla p_t^{(0)} \cdot \mathbf{n} + p_c^{(0)} - \nu [\mathbf{n} \cdot \nabla u_c^{(0)}] \cdot \mathbf{n} \quad \text{on} \ \Gamma_\delta. \]  

(11)

From equations (11), (8b) and (8c) we derive formally the boundary conditions for small \( \delta \):

\[ \kappa \nabla p_t^{(0)} \cdot \mathbf{n} = R_n \left( p_t^{(0)} - p_c^{(0)} + \nu [\mathbf{n} \cdot \nabla u_c^{(0)}] \cdot \mathbf{n} \right) \quad \text{on} \ \Gamma, \]  

(12a)

\[ u_c^{(0)} \cdot \mathbf{n} = -\kappa \nabla p_t^{(0)} \cdot \mathbf{n} \quad \text{on} \ \Gamma, \]  

(12b)

\[ u_c^{(0)} \cdot \tau = -R_\tau [(\mathbf{n} \cdot \nabla)u_c^{(0)}] \cdot \tau \quad \text{on} \ \Gamma. \]  

(12c)

Transmission conditions (12a)–(12b) can be rewritten as

\[ u_t \cdot \mathbf{n} = u_c \cdot \mathbf{n} = R_n (p_c - p_t - \nu [(\mathbf{n} \cdot \nabla)u_c] \cdot \mathbf{n}) \quad \text{on} \ \Gamma, \]  

(13)

which is similar to Starling’s law, that is the most widely used equation in literature to model flux transport across the vessel wall (Jain and Baxter 1988; Baish et al. 1997) and reads

\[ u_c \cdot \mathbf{n} = L_p (p_c - p_t - \sigma (\pi_c - \pi_t)), \]

where \( L_p \) is the vascular permeability, \( \sigma \) is the osmotic reflection coefficient (\( \sigma \in (0, 1) \)) that expresses the glycosyl filter function through the endothelial wall and \( (\pi_c - \pi_t) \) is the oncotic pressure difference between the capillaries and the interstitium. However, the latter can be considered negligible compared to the interstitial fluid pressure difference in tumors (Jain 1987; Voutour and Stylianopoulos 2014). Moreover, the viscous term in equation (13) is usually neglected but it is necessary to guarantee the well-posedness of the problem and does not change the physical meaning since it is based on the balance of the normal forces (Penta et al. 2015).

The parameters \( R_n \) and \( L_p \) are linked by \( R_n = \frac{L_p L_\mu}{d^2} \). Therefore, the limit microscopic model reads as

\[ \nu \nabla^2 u_c = \nabla p_c, \]

\[ \nabla \cdot u_c = 0, \quad \text{in} \ \Omega_c, \quad (14a) \]

\[ u_t = -\kappa \nabla p_c, \quad \nabla \cdot u_t = 0, \quad \text{in} \ \Omega_t, \quad (14b) \]

\[ u_c \cdot \mathbf{n} = u_t \cdot \mathbf{n} \quad \text{on} \ \Gamma, \quad (14c) \]

\[ u_c \cdot \mathbf{n} = R_n (p_c - p_t - \nu [\mathbf{n} \cdot \nabla u_c] \cdot \mathbf{n}) \quad \text{on} \ \Gamma_t, \quad (14d) \]

\[ u_c \cdot \tau = -R_\tau [(\mathbf{n} \cdot \nabla)u_c] \cdot \tau, \quad \text{on} \ \Gamma. \quad (14e) \]
where

\[ \nu = \frac{d^2}{L^2}, \quad \kappa = \frac{k_t \mu}{d^2}, \quad R_n = \frac{L_p L \mu}{d^2}, \quad R_T = \frac{\sqrt{k_n \mu}}{\alpha BJ L}, \]

are dimensionless quantities depending on the microscopic properties of the tissue.

### 3 Formal derivation of continuum macroscale models for different regimes

This section is devoted to the derivation of a continuum macro-scale models from the microscopic model (14) using the 2-scale asymptotic expansion method (Arbogast and Lehr 2006; Conca 1985; Allaire 1992) and under different asymptotic regimes depending on the capillary wall permeability and the hydraulic conductivity of the interstitium.

#### 3.1 Geometrical setting

Let us first present the geometrical setting. We assume that \( d \) is the mean inter-capillary distance and \( L \) is the tissue characteristic length such that \( \varepsilon = \frac{d}{L} \ll 1 \). We denote by \( Y \) the reference periodic unit cell that \( [0, 1]^N \). It is composed by the interstitium \( Y_t \) and the capillaries \( Y_c \). The interface between \( Y_t \) and \( Y_c \) is denoted \( \Gamma_1 \). The normal vector \( n \) to the interface \( \Gamma_1 \) is directed outwardly from the vascular domain \( Y_c \) towards \( Y_t \).

The total domain \( \Omega \) is divided periodically in each direction in squares \( Y_n^\varepsilon \) such that

\[ Y_n^\varepsilon = \varepsilon n + \varepsilon Y, \quad Y_{i,n}^\varepsilon = \varepsilon n + \varepsilon Y_t, \quad Y_{c,n}^\varepsilon = \varepsilon n + \varepsilon Y_c, \quad \Gamma_n^\varepsilon = \varepsilon n + \varepsilon \Gamma_1, \quad \forall n \in \mathbb{Z}^N. \]

The difficult problem of the boundary conditions and their influence on the expansion is out of the scope of the paper. The reader may consider \( \Omega \) as a manifold without boundary, for instance the unit cube with periodic condition.

The domain \( \Omega \) is thus composed of two subdomains \( \Omega_n^\varepsilon = \bigcup_n Y_{i,n}^\varepsilon \) and \( \Omega_c^\varepsilon = \bigcup_n Y_{c,n}^\varepsilon \) that depend on \( \varepsilon \) and are connected when \( N = 3 \). The interface between the two subdomains is \( \Gamma^\varepsilon = \bigcup_n \Gamma_n^\varepsilon \). Figure 2 shows a schematic illustration of the periodic domain and of the unitary cell \( Y \).

#### 3.2 The fluid flow model and the 3 asymptotic regimes

The fluid flow model reads in the oscillating domain \( \Omega = \Omega_c^\varepsilon \cup \Omega_t^\varepsilon \cup \Gamma^\varepsilon \) as:

\[
\begin{align*}
\nu \nabla^2 u_c^\varepsilon &= \nabla p_c^\varepsilon + f_c, & & \nabla \cdot u_c^\varepsilon = 0, \quad \text{in } \Omega_c^\varepsilon, \\
\nabla \cdot u_t^\varepsilon &= 0, \quad \text{in } \Omega_t^\varepsilon, \\

\end{align*}
\]

\[
\begin{align*}
\nabla \cdot u_c^\varepsilon &= 0, \quad \text{on } \Gamma^\varepsilon, \\
\end{align*}
\]

\[
\begin{align*}
\nabla \cdot u_c^\varepsilon &= 0, \quad \text{in } \Omega_t^\varepsilon, \\

\nabla \cdot u_c^\varepsilon &= 0, \quad \text{on } \Gamma^\varepsilon, \\
\end{align*}
\]

\[
\begin{align*}
\nabla \cdot u_c^\varepsilon &= 0, \quad \text{on } \Gamma^\varepsilon, \\
\end{align*}
\]
As mention previously, no boundary conditions are considered in this section to avoid the emergence of boundary layers that prevent the following derivation. Since these boundary layers are exponentially decaying, their influence is restricted to the vicinity of the boundary. The source term $f_c$ is supposed infinitely smooth in $\Omega_c^\epsilon$. While it is natural to consider the scaling $\nu = O(\epsilon^2)$ on the viscosity to avoid trivial limit, the parameters $R_n$, and $\kappa$ are then taken as

$$
\nu = \epsilon^2 \bar{\nu}, \quad R_n = \epsilon^\gamma \bar{R}_n, \quad \kappa = \epsilon^\eta \bar{\kappa}
$$

so that $\bar{\nu}$, $\bar{R}_n$ and $\bar{\kappa}$ are of order 1. Shipley et al. and Penta et al. have considered previously the cases $\gamma = 1$, $\eta = 0$ (Shipley and Chapman 2010), while we consider here the cases $(\gamma, \eta) \in \mathbb{N}^2$.

### 3.3 Heuristics of the formal 2-scale expansion

According to the multiple scales theory, it is natural to introduce the fast variable $y = x/\epsilon$. The idea of the 2-scale expansion consists in assuming that any field $g^\epsilon$ appearing in the problem (15) – $g^\epsilon$ stands for $u^\epsilon_c$, $u^\epsilon_t$, $p^\epsilon_c$ and $p^\epsilon_t$ – has an expansion under the form

$$
g^\epsilon(x) = \sum_{\ell=0}^{\infty} \epsilon^\ell g^{(\ell)}(x, x/\epsilon), \quad \forall x \in \Omega,
$$

where $g^{(\ell)}(x, x/\epsilon)$ represents the $\ell$th order correction term.
where the fields \( (x, y) \mapsto g^{(\ell)}(x, y) \) are \( Y \)-periodic at any order \( \ell \geq 0 \). In order to identify the problem satisfied by each field \( g^{(\ell)} \), it is crucial to rewrite the differential operators as

\[
\nabla = \nabla_x + \frac{1}{\varepsilon} \nabla_y, \quad \nabla \cdot = \nabla_x \cdot + \frac{1}{\varepsilon} \nabla_y \cdot, \quad \nabla^2 = \nabla_x^2 + \frac{2}{\varepsilon} \nabla_x \cdot \nabla_y + \frac{1}{\varepsilon^2} \nabla_y^2.
\]

Problem (15) is then rewritten in the variables \((x, y)\), making appear the asymptotic parameter \( \varepsilon \) and the parameters \((\gamma, \eta)\):

\[
\tilde{v} \left( \nabla_y^2 u^{\varepsilon}_{c} + 2\varepsilon \nabla_y \cdot \nabla_x u^{\varepsilon}_{c} + \varepsilon^2 \nabla_x^2 u^{\varepsilon}_{c} \right) = \frac{1}{\varepsilon} \nabla_y p^{\varepsilon}_{c} + \nabla_x p^{\varepsilon}_{c} + f_c \quad \text{in} \ \Omega^{\varepsilon}_c \times Y_c, \quad (17a)
\]

\[
\frac{1}{\varepsilon} \nabla_y \cdot u^{\varepsilon}_{c} + \nabla_x \cdot u^{\varepsilon}_{c} = 0 \quad \text{in} \ \Omega^{\varepsilon}_c \times Y_c, \quad (17b)
\]

\[
\frac{1}{\varepsilon^2} \nabla_y^2 p^{\varepsilon}_{c} + \frac{2}{\varepsilon} \nabla_x \cdot \nabla_y p^{\varepsilon}_{c} + \nabla_x^2 p^{\varepsilon}_{c} = 0 \quad \text{in} \ \Omega^{\varepsilon}_f \times Y_f. \quad (17c)
\]

The interface conditions on \( \Gamma^{\varepsilon} \times \Gamma_Y \), vary according to the value of \( \gamma \) and \( \eta \):

\[
\frac{1}{\varepsilon^\gamma} R_n \upsilon^{\varepsilon}_{c} \cdot n + (p^{\varepsilon}_{f} - p^{\varepsilon}_{c}) + \varepsilon \tilde{v} [(n \cdot \nabla_y)u^{\varepsilon}_{c}] \cdot n + \varepsilon^2 \tilde{v} [(n \cdot \nabla_x)u^{\varepsilon}_{c}] \cdot n = 0, \quad (17d)
\]

\[
\frac{1}{\varepsilon} [(n \cdot \nabla_y)u^{\varepsilon}_{c}] \cdot \tau + [(n \cdot \nabla_x)u^{\varepsilon}_{c}] \cdot \tau + \frac{1}{R_f} u^{\varepsilon}_{c} = 0. \quad (17e)
\]

\[
\varepsilon^\eta \bar{\kappa} \nabla_y p^{\varepsilon}_{f} \cdot n + \varepsilon u^{\varepsilon}_{c} \cdot n + \varepsilon^{1+\eta} \bar{\kappa} \nabla_x p^{\varepsilon}_{f} \cdot n = 0. \quad (17f)
\]

### 3.3.1 Formal cascade of equalities

Injecting the expansions in power of \( \varepsilon \), we infer the following cascade of equations linking formally the coefficients \( (u^{\varepsilon}_{k, c}, u^{\varepsilon}_{k, f}, p^{\varepsilon}_{k, c}, p^{\varepsilon}_{k, f}) \), with the usual convention that \( (u^{\varepsilon}_{c, f}, u^{\varepsilon}_{f, f}, p^{\varepsilon}_{c, f}, p^{\varepsilon}_{f, f}) = (0, 0, 0, 0) \) for any index \( \ell \) strictly negative:

\[
- \nabla_y p^{k-1}_{c} + \tilde{v} \nabla^2 u^{k-1}_{c} - \nabla_y p^{k-1}_{c} + 2 \nabla_y \cdot \nabla_x u^{k-2}_{c} + \nabla^2_x u^{k-3}_{c} = \delta_1 f_c, \quad \text{in} \ \Omega^{\varepsilon}_c \times Y_c, \quad (18a)
\]

\[
\nabla_y \cdot u^{k-1}_{c} + \nabla_x \cdot u^{k-2}_{c} = 0 \quad \text{in} \ \Omega^{\varepsilon}_c \times Y_c, \quad (18b)
\]

\[
\nabla^2_y p^{k}_{f} + 2 \nabla_y \cdot \nabla_x p^{k-1}_{f} + \nabla^2_x p^{k-2}_{f} = 0 \quad \text{in} \ \Omega^{\varepsilon}_f \times Y_f. \quad (18c)
\]

The interface conditions on \( \Gamma^{\varepsilon} \times \Gamma_Y \), vary according to the value of \( \gamma \) and \( \eta \):

\[
\frac{1}{R_n} u^{k-1}_{c} \cdot n + (p^{k-1-\gamma}_{f} - p^{k-1-\gamma}_{c}) + \varepsilon \tilde{v} [(n \cdot \nabla_y)u^{k-2-\gamma}_{c}] \cdot n
\]

\[
+ \varepsilon \tilde{v} [(n \cdot \nabla_x)u^{k-3-\gamma}_{c}] \cdot n = 0, \quad (18d)
\]
\[(n \cdot \nabla_y)u^{k-1}_c \cdot \tau + [(n \cdot \nabla_x)u^{k-2}_c] \cdot \tau + \frac{1}{R_t} u^{k-2}_c \cdot \tau = 0, \quad (18e)\]

\[u^{k+\eta-1}_c \cdot n + \tilde{\kappa} \nabla_y p^k_t \cdot n + \tilde{\kappa} \nabla_x p^{k-1}_t \cdot n = 0. \quad (18f)\]

### 3.3.2 Derivation of the leading term

The above equalities (26) enables us to derive successively—and formally—the coefficients \((u^c_k, u^t_k, p^c_k, p^t_k)\). Our main interest here is to derive the leading term for different value of \((\gamma, \eta) \in \mathbb{N}^2\).

- First, taking \(k = 0\) in (18a), we infer that \(\nabla_y p^0_c = 0\), hence \(p^0_c\) depends only on \(x\):

\[p^0_c = p^0_c(x).\]

Then consider the problem satisfied by \(p^0_t\). If \(\gamma - \eta \geq 0\), it reads:

\[\nabla^2_y p^0_t = 0, \quad \text{in } Y_t\]

\[\tilde{\kappa} \nabla_y p^0_t \cdot n = -u^{\eta-1}_c \cdot n = \tilde{\kappa} \nabla_x (p^{\eta-1-\gamma}_t - p^{\eta-1-\gamma}_c), \quad \text{on } \Gamma_Y\]

hence \(\nabla_y p^0_t \cdot n = 0\) since \(\eta - 1 - \gamma \leq -1\), and thus similarly to \(p^0_c\), the pressure \(p^0_t\) depends only on \(x\). If \(\gamma - \eta \leq -1\), the problem satisfied by \(p^0_t\) reads:

\[\nabla^2_y p^0_t = 0, \quad \text{in } Y_t\]

\[\tilde{\kappa} (p_t^0 - p^0_c) = -u^\gamma_c \cdot n = -\tilde{\kappa} \nabla_y p_t^{1+\gamma-\eta} \cdot n, \quad \text{on } \Gamma_Y.\]

We then infer that if \(\gamma - \eta \leq -1\), the only solution of the above equation is

\[p^0_t = p^0_t(x) = p^0_c(x).\]

We thus have shown that whatever the couple \((\gamma, \eta) \in \mathbb{N}^2\), \(p^0_c\) and \(p^0_t\) depends only on \(x\), and even \(p^0_t(x) = p^0_c(x)\) if \(\gamma - \eta - 1 \leq 0\).

- Then, taking \(k = 1\), we infer that \((u^0_c, p^1_t)\) satisfies the following problem set in \(Y_c\):

\[-\nabla_y p^1_c + \bar{u} \nabla^2_y u^0_c = \nabla_x p^0_c + \bar{f}_c, \quad (19a)\]

\[\nabla_y \cdot u^0_c = 0 \quad (19b)\]

\[\frac{1}{\tilde{R}_n} u^0_c \cdot n = -(p^\gamma_t - p^\gamma_c), \quad (19c)\]

\[[(n \cdot \nabla_y)u^0_c] \cdot \tau = 0. \quad (19d)\]

Using the compatibility condition on the divergence, we infer that whatever \(\gamma \in \mathbb{N}\):

\[\tilde{R}_n \int_{\Gamma_Y} (p^\gamma_t - p^\gamma_c) dy = \int_{Y_c} \nabla_y \cdot u^0_c dy = 0.\]
Note that this result is compatible with the convention if $\gamma \geq 1$, and it says that if $\gamma = 0$, then

$$p_0^c(x) = p_0^0(x).$$

Thanks to the following corrector $(W_j, P_j)_{j=1,\ldots,N}$ where $N$ is the dimension (equal to 2 or 3 here):

\begin{align}
\bar{\nu} \nabla^2 y W_j + e_j &= \nabla y P_j & \text{in } Y_c, \\
\nabla y \cdot W_j &= 0 & \text{in } Y_c, \\
W_j \cdot n &= 0 & \text{on } \Gamma_Y, \\
[(n \cdot \nabla y) W_j] \cdot \tau &= 0 & \text{on } \Gamma_Y, 
\end{align}

the coefficients $(u_0^c, p_1^c)$ reads as

\begin{align}
\left. u_0^c(x, y) \right| &= - \sum_{j=1}^N W_j \left( (\nabla x p_0^c + f_c) \cdot e_j \right) := -\mathcal{V}(y) \left( \nabla x p_0^0(x) + f_c \right), \\
\left. p_1^c(x, y) \right| &= - \sum_{j=1}^N P_j \left( (\nabla x p_0^c + f_c) \cdot e_j \right) + \bar{p}_c^{(1)}(x) \\
&:= -\mathcal{P}(y) \cdot \left( \nabla x p_0^0(x) + f_c \right) + \bar{p}_c^{(1)}(x),
\end{align}

Consider now $p_1^t$. It satisfies

\begin{align}
\nabla^2 y p_1^t &= 0, & \text{in } Y_t, \\
\bar{\kappa} \nabla_y p_1^t \cdot n &= -\bar{\kappa} \nabla_x p_0^0 \cdot n - u_0^0 \cdot n, & \text{on } \Gamma_Y.
\end{align}

If $\gamma - \eta \geq 0$, we have

$$\bar{\kappa} \nabla_y p_1^t \cdot n = -\bar{\kappa} \nabla_x p_0^0 \cdot n + \bar{R}_n(p_1^{\eta-\gamma} - p_0^{\eta-\gamma}) = -\bar{\kappa} \nabla_x p_0^0 \cdot n + \delta_0^{\eta-\gamma} \bar{R}_n(p_1^0 - p_0^0),$$

on $\Gamma_Y$.

Using the compatibility condition we infer that if $\eta = \gamma$ then necessarily $p_1^0 = p_0^0$. Moreover defining $G'$, such that:
\[ \nabla_y G^j = 0 \quad \text{in } Y_t \] (24a)
\[ \nabla_y G^j \cdot n = n \cdot e_j \quad \text{on } \Gamma_Y, \] (24b)

then if \( \gamma - \eta \geq 0 \) we infer that \( p_t^1 \) reads as

\[
p_t^1(x, y) = -\sum_{j=1}^{N} G^j \left( \nabla_x p_t^0 \cdot e_j \right) + \tilde{p}_t^1(x) := -G(y) \cdot \nabla_x p_t^0(x) + \tilde{p}_t^1(x). \] (25)

• Now, taking \( k = 2 \), we infer that \((u_t^1, p_t^2)\) satisfies the following problem set in \( Y_c \):

\[ -\nabla_y p_c^2 + \tilde{\nu} \nabla_y^2 u_t^1 = \nabla_x p_c^1 - 2\tilde{\nu} \nabla_y \cdot \nabla_x u_t^0, \] (26a)
\[ \nabla_y \cdot u_t^1 = -\nabla_x \cdot u_t^0 \] (26b)
\[ \frac{1}{R_n} u_t^1 \cdot n = -\left( p_t^{1-\gamma} - p_c^{1-\gamma} \right) - \left[ (n \cdot \nabla_y) u_t^{\gamma} \right] \cdot n, \] (26c)
\[ \left[ (n \cdot \nabla_y) u_t^0 \right] \cdot \tau = -\left[ (n \cdot \nabla_y) u_t^0 \right] \cdot \tau - \frac{1}{R} u_t^0 \cdot \tau. \] (26d)

Using the compatibility condition on the divergence, we infer that for any \( \gamma \geq 1 \):

\[ \nabla \cdot \left( \frac{1}{Y_c} \int_{Y_c} \nabla\left( \nabla_x p_c^0 + f_c \right) \right) + \delta^\gamma_1 \tilde{R}_n \frac{|\Gamma|}{|Y_c|} (p_t^0 - p_c^0) = 0, \]

where \( \delta^\gamma_1 \) is the Kronecker symbol equal to 1 if \( \gamma = 1 \) and 0 elsewhere.

If \( \gamma - \eta \geq 1 \), the coefficient \( p_t^2 \) satisfies:

\[ \nabla_y p_t^2 = -2\nabla_y \cdot \nabla_y p_t^1 - \nabla_y^2 p_t^0, \quad \text{in } Y_t \]
\[ \tilde{k} \nabla_y p_t^2 \cdot n = -\tilde{k} \nabla_x p_t^1 \cdot n - u_t^{1+\eta} \cdot n = -\tilde{k} \nabla_x p_t^1 \cdot n + \tilde{R}_n (p_t^{1+\eta-\gamma} - p_c^{1+\eta-\gamma}). \]

Integrating over \( Y_t \), one infers the problem satisfied by \( p_t^0 \) if \( \gamma - \eta \geq 1 \):

\[ \nabla \cdot \left( \kappa \left( I - \frac{1}{Y_t} \int_{Y_t} G(y) \nabla_x p_t^0 \right) \right) - \delta^\gamma_1 \tilde{R}_n \frac{|\Gamma|}{|Y_t|} (p_t^0 - p_c^0) = 0, \]

It remains to consider the case \( \gamma = 0 \). Suppose first \( \gamma = 0, \eta = 0 \). The pressure \( p_t^2 \) satisfies

\[ \nabla_y p_t^2 = -2\nabla_y \cdot \nabla_y p_t^1 - \nabla_y^2 p_t^0, \quad \text{in } Y_t \]
\[ \tilde{k} \nabla_y p_t^2 \cdot n = -\tilde{k} \nabla_x p_t^1 \cdot n - u_t^1 \cdot n. \]

We already know that

\[ p_t^1 = -G \cdot \nabla p_t^0(x), \quad u_t^0 = \nabla\left( \nabla_x p_t^0 + f_c \right) \]
and
\[ \int_{\Gamma_Y} \mathbf{u}_c^1 \cdot \mathbf{n} \, dy = \int_{Y_c} \nabla_y \cdot \mathbf{u}_c^1 \, dy = -\nabla_x \cdot \int_{Y_c} \mathbf{u}_c^0 \, dy, \]

Then integrating over \( Y_t \) implies that
\[ \nabla_x \cdot \left( \kappa \left( \frac{\mathbb{I} - \frac{1}{|Y_t|} \int_{Y_t} G \, dy}{\int_{Y_t} G \, dy} \right) \nabla_x p_t^0 \right) = -\nabla_x \cdot \left( \frac{1}{|Y_t|} \int_{Y_c} \nabla_y \left( \nabla_x p_c^0 + f_c \right) \right). \]

Consider now \( \gamma = 0, \eta = 1 \). Using (23), we infer the compatibility condition:
\[ 0 = \int_{\Gamma_Y} \mathbf{u}_c^1 \cdot \mathbf{n} \, dy = -\nabla_x \cdot \int_{Y_c} \mathbf{u}_c^0 \, dy. \]

If \( \eta \geq 2 \), we have successively
\[ -\nabla_x \cdot \int_{Y_c} \mathbf{u}_c^0 \, dy = \int_{Y_c} \nabla_y \cdot \mathbf{u}_c^1 \, dy = \int_{\Gamma_Y} \mathbf{u}_c^1 \cdot \mathbf{n} \, dy = -\nabla_y \nabla_x p_t^{2-\eta} - \int_{\Gamma_Y} \nabla x p_t^{1-\eta} = 0. \]

Hence for any \( \eta \geq 1 \) and \( \gamma = 0 \), \( p_c^0 = p_t^0 \) satisfies
\[ \nabla \cdot \left( \frac{1}{|Y_c|} \int_{Y_c} \nabla_y \left( \nabla_x p_c^0 + f_c \right) \right) = 0. \]

To summarize, the following proposition has been shown.

**Proposition 3.1** Denoting by \( z \mapsto \chi_H(z) \) the Heaviside function equal to 1 if \( z \geq 0 \) and 0 elsewhere, we have shown formally that the leading order terms \( p_c^0, p_t^0 \) of the expansion satisfies, for any \((\gamma, \eta) \in \mathbb{N}^2\):

\[ \nabla \cdot \left( E \nabla_x p_c^0 \right) + \delta_0^{\gamma+\eta} \nabla_x \cdot \left( \frac{|Y_c|}{|Y_t|} \kappa K \nabla x p_t^0 \right) + \delta_0^\gamma \bar{R}_n \frac{|\Gamma|}{|Y_c|} (p_t^0 - p_c^0) = F_c, \tag{27a} \]

\[ \chi_H(\gamma - \eta - 1) \nabla \cdot \left( \kappa K \nabla_x p_t^0 \right) - \chi_H(1 - \gamma + \eta) \bar{R}_n \frac{|\Gamma|}{|Y_t|} (p_t^0 - p_c^0) = 0, \tag{27b} \]

where the tensors \( K \) and \( E \) are defined by:

\[ [K]_{ij} = \delta_{ij} - \frac{1}{|Y_t|} \int_{Y_t} \nabla_y G^j \cdot e_i \, dy, \quad [E]_{ij} = \frac{1}{|Y_c|} \int_{Y_c} \nabla W_j \cdot e_i \, dy, \tag{28} \]

and

\[ F_c = -\nabla \cdot (E f_c). \]
The velocity $u^e_c$ and $u^e_t$ are then approached by

$$
\begin{align}
    u^e_c(x) & \sim \chi_{\Omega^e}(x) \left( E + \nabla_y (x/\varepsilon) \right) \nabla_x p^0_c(x), \\
    u^e_t(x) & \sim \chi_{\Omega^e}(x) e^\eta K \left( K + \nabla_y G(x/\varepsilon) \right) \nabla_x p^0_t(x).
\end{align}
$$

(29a)

(29b)

### 3.4 Tensors properties

In order to ensure the well-posedness of the models that we have derived, the permeability tensors $K$ and $E$ need to be positive definite. This section is devoted to the analysis of the tensor properties with respect to the periodic cell $Y$.

**Lemma 3.2** The tensor $K$ is symmetric and positive definite.

**Proof** Thanks to the Lax-Milgram theorem, problem (24) has a unique solution in $H^1(Y_t)/\mathbb{R}$. The variational formulation associated to (24) reads

$$
\int_{Y_t} \nabla_y G^j \cdot \nabla_y \varphi \, dy - \int_{\Gamma_t} e_j \cdot n_{\text{out}} \varphi \, ds = 0,
$$

for any periodic $\varphi \in H^1(Y_t)$ such that $\langle \varphi \rangle_{Y_t} = 0$. Considering $\varphi = G^i$ on $Y_t$, the following equations hold thanks to the divergence theorem

$$
0 = \int_{Y_t} \nabla_y G^j \cdot \nabla_y G^i \, dy - \int_{\Gamma_t} e_j \cdot n_{\text{out}} G^i \, ds
= \int_{Y_t} \nabla_y G^j \cdot \nabla_y G^i \, dy - \int_{Y_t} \nabla_y \left( G^i e_j \right) \, dy
= \int_{Y_t} \nabla_y G^j \cdot \nabla_y G^i \, dy - \int_{Y_t} \nabla_y G^i \cdot e_j \, dy.
$$

Therefore, the tensor $K$ can be rewritten as

$$
[K]_{ij} = \delta_{ij} - \frac{1}{|Y_t|} \int_{Y_t} \nabla_y G^j \cdot e_i \, dy,
= \delta_{ij} - \frac{1}{|Y_t|} \int_{Y_t} \nabla_y G^j \cdot \nabla_y G^i \, dy,
= \frac{1}{Y_t} \int_{Y_t} \nabla_y (G^i - y_i) \nabla_y (G^j - y_j) \, dy.
$$

It follows that the tensor $K$ is symmetric. To prove that the tensor is positive definite, we consider any $\lambda \in \mathbb{R}^N$ and define

$$
\phi = \sum_{i=1}^N \lambda_i G^i.
$$
The function $\phi$ is periodic and belongs to the space $H^1(Y_t)$. We prove that $K$ is semi-positive definite:

$$|Y_t|\lambda^T K\lambda = \int_{Y_t} |\nabla_y (\phi - y \cdot \lambda)|^2 \, dy \geq 0,$$

that is true for any $\nabla_y (\phi - y \cdot \lambda)$. The equality holds if and only if

$$\nabla_y \phi = \lambda.$$

However, under the assumption of periodicity in a connected domain, $\nabla_y \phi = \lambda$ if and only if $\nabla_y \phi = \lambda = 0$. Therefore, $K$ is positive definite.

**Remark 3.3** The interstitial domain $Y_t$ has to be connected to guarantee the positive definiteness of the tensor $K$ (otherwise, it is semi-positive definite).

**Lemma 3.4** If the capillary domain $Y_c$ is connected, then the tensor $E$ is symmetric and positive definite.

**Proof** We proceed analogously as Arbogast and Lehr (2006). Thanks to the Lax-Milgram lemma, there exist a unique weak solution to problem (20), which variational formulation reads as

$$\int_{Y_c} v \nabla_y W^i : \nabla_y v \, dy - \int_{Y_c} e^j \cdot v \, dy = 0,$$

for any periodic $v \in H^1(Y_c)$ such that $\nabla_y \cdot v = 0$ and $v \cdot n = 0$ on $\Gamma_Y$. Taking $v = W^i$ the following identity holds:

$$|Y_c|[E]_{ij} = \int_{Y_c} W^j \cdot e_i \, dy,$$

$$= \int_{Y_c} v \nabla_y W^j : \nabla_y W^i \, dy.$$

Therefore the tensor is symmetric. To prove that it is positive definite, we take any $\lambda \in \mathbb{R}^N$ and define

$$\psi = \sum_{i=1}^N \lambda_i W^i.$$

We first prove that $\lambda^T E \lambda$ is non-negative. Indeed,

$$|Y_c|\lambda^T E \lambda = \int_{Y_c} v \nabla_y \psi : \nabla_y \psi \, dy \geq 0.$$
The equality holds if and only if \( \nabla_y \psi = 0 \). Then, the following equation must be satisfied

\[
\forall v \in H^1(Y_c) : \nabla_y \cdot v = 0,
\]

\[
0 = \int_{Y_c} v \nabla_y \psi : \nabla_y v \, dy - \int_{\Gamma_Y} \left( \left[ (n \cdot \nabla_y \psi) \cdot n \right] (v \cdot n) \right) \, ds = \int_{Y_c} \lambda \cdot v \, dy. \tag{30}
\]

Since (30) holds for any \( v \) in the appropriate space defined above, it is valid also for \( v = \lambda \). Therefore, we conclude that (30) is true if and only if \( \lambda = 0 \) and state that \( E \) is positive definite.

\[\square\]

**Remark 3.5** When the domain \( Y_c \) is not connected, then the unique solution to problem (20) is \( W^j = 0 \) and \( P^j = y_j \). In this case the tensor \( E \) is zero. If \( Y_t \) is not connected, then the unique solution to problem (24) is \( G^j = y_j \). In this case the tensor \( K \) is zero.

The fact that the effective tensor \( E \) or \( K \) are zero if the corresponding phase \( Y_c \) or \( Y_t \) is not connected means that there is no long-range coupling of the pressure in the phase \( Y_c \) or \( Y_t \). Since it is disconnected, the homogenised pressure does not satisfy an elliptic equation.

**Remark 3.6** The tensor \( \bar{\kappa} K + \frac{|Y_c|}{|Y_t|} E \) is symmetric and positive definite since it is the sum of two symmetric and positive definite tensors.

**Remark 3.7** If one of the two domains (\( \Omega_c^\varepsilon \) or \( \Omega_t^\varepsilon \)) is not connected, and if \( \gamma - \eta \geq 1 \) then \( p_c = p_t \), which means that the pressure of the disconnected phase is determined locally by the pressure of the connected phase (which satisfies an elliptic equation).

### 3.5 Links between the different limit problems

We have shown that for any \( (\gamma, \eta) \in \mathbb{N}^2 \), the limit problems of (15) as \( \varepsilon \) goes to zero is given by (27). As shown in this section, the case \( (\gamma = 1, \eta = 0) \) is the distinguished model from which the other models are derived. For large capillary permeability \( \tilde{R}_n \), the tissue behaves as a monophasic material, and the question of appropriate boundary condition is adressed at the end of the section.

In this section, we show the link between the different models. We assume that both instertitium and capillary phases are connected so that both \( E \) and \( K \) are postive definite and the problem (27) complemented with Dirichlet, Neumann or Robin-Fourier conditions is well-posed.

**Passing from the case \( (\gamma = 1, \eta = 0) \) to \( (\gamma \geq 2, \gamma - \eta \geq 1) \)**

Consider the limit model in the case \( (\gamma = 1, \eta = 0) \). According to (27), it reads

\[
\nabla \cdot (\bar{\kappa} K \nabla p_t) = \frac{\tilde{R}_n |\Gamma_Y|}{|Y_t|} (p_t - p_c) \quad \text{in } \Omega, \tag{31a}
\]

\[
\nabla \cdot (E \nabla p_c) = \frac{\tilde{R}_n |\Gamma_Y|}{|Y_c|} (p_c - p_t) \quad \text{in } \Omega, \tag{31b}
\]
Consider now that \( \bar{\kappa} = \varepsilon^{a} \kappa \) and \( \bar{R}_{n} = \varepsilon^{b} R_{n} \), with \( b - a \geq 0 \) and \( b > 0 \). It is clear that (31b) is not a singular perturbation of the operator \( \nabla \cdot (E \nabla \cdot ) \) in the sense of Kato (1995) and thus the solution to problem (31) tends to the solution to the following problem, which is nothing that model \( \gamma - \eta = 1 + a - b \geq 1 \) with \( \gamma > 1 \):

\[
\nabla \cdot (\bar{\kappa} K \nabla p_t) = \delta_{0}^{b-a} \frac{\bar{R}_{n}|\Gamma_{Y}|}{|Y_{t}|} (p_t - p_c) \quad \text{in } \Omega,
\]

\[
\nabla \cdot (E \nabla p_c) = 0 \quad \text{in } \Omega,
\]

\[
p_t|_{\partial \Omega} = p_{t,\infty}, \quad p_c|_{\partial \Omega} = p_{c,\infty}, \quad \text{on } \partial \Omega.
\]

**Passing from the case \( (CR = 1, DC_1 = 0) \) to \( (CR = 0, DC_1 = 0) \)**

Considering \( \bar{R}_{n} \) of the order of \( \varepsilon^{-1} \) and \( \bar{\kappa} \) of the order of 1, model \( (\gamma = 1, \eta = 0) \) reads then

\[
\varepsilon \nabla \cdot (\bar{\kappa} K \nabla p_t) = \frac{\bar{R}_{n}|\Gamma_{Y}|}{|Y_{t}|} (p_t - p_c) \quad \text{in } \Omega, \tag{32a}
\]

\[
\varepsilon \nabla \cdot (E \nabla p_c) = \frac{\bar{R}_{n}|\Gamma_{Y}|}{|Y_{c}|} (p_c - p_t) \quad \text{in } \Omega \tag{32b}
\]

\[
p_t|_{\partial \Omega} = p_{t,\infty}, \quad p_c|_{\partial \Omega} = p_{c,\infty}, \quad \text{on } \partial \Omega. \tag{32c}
\]

Here the asymptotic analysis is much trickier since both equations (32a)–(32b) are singular perturbation of the div-grad operator. In particular, a delicate asymptotic analysis makes appear a exponential decay of the \( p_t - p_c \) from the boundary, showing that out of the vicinity of the tumor boundary, both pressures are equal. The details of this results are given in Vaghi et al. (2022), however we expose here the main arguments in the simple case where \( \bar{\kappa} K \) and \( E \) are colinear to the identity, that is for a \( \lambda \neq 0 \):

\[
\bar{\kappa} K = \lambda E
\]

Then simple calculation shows that

\[
\nabla \cdot (E \nabla (p_t - p_c)) = \frac{\bar{R}_{n}}{\varepsilon} \left( \frac{|\Gamma_{Y}|}{\lambda |Y_{t}|} + \frac{|\Gamma_{Y}|}{|Y_{c}|} \right) (p_t - p_c) \quad \text{in } \Omega \tag{33}
\]

It is well-known, especially in conduction theory (Balanis 2012; Haddar et al. 2005) that problem (33) makes appear a so-called skin depth effect: the pressure difference \( p_t - p_c \) decays exponentially fast from the boundary. More precisely, denoting by \( \alpha \) the factor given by

\[
\alpha = \sqrt{\bar{R}_{n} \left( \frac{|\Gamma_{Y}|}{\lambda |Y_{t}|} + \frac{|\Gamma_{Y}|}{|Y_{c}|} \right)}
\]
hence in the local coordinates near the boundary

$$p_t - p_c = (p_t,\infty - p_c,\infty)e^{-\frac{\alpha}{\sqrt{\epsilon}}x_n} + o(\epsilon),$$

where $x_n$ is the normal variable with respect to the tumor boundary.

Interestingly, we thus obtain that in this asymptotic regime, the solution to model ($\gamma = 1$, $\eta = 0$) with Dirichlet boundary conditions can be approached by the solution to model ($\gamma = 0$, $\eta = 0$) with the following appropriate boundary condition

$$\nabla \cdot \left( (\lambda + 1)E \nabla p \right) = 0, \quad \text{in } \Omega$$

$$p|_{\partial \Omega} = \frac{1}{2} \left( (p_t,\infty + p_c,\infty) - \frac{|Y_c| - \lambda|Y_t|}{|Y_c| + \lambda|Y_t|} \left( p_t,\infty - p_c,\infty \right) \right), \quad \text{on } \partial \Omega.$$ 

The rigorous proof is provided in Vaghi et al. (2022). The result involves Riemannian geometry results which are far from the scope of this paper, however the general idea of the exponential decay of the pressure difference remains.

## 4 Numerical simulations

The Galerkin Finite Elements Method was used to discretize the equations in order to test the homogenized models. The 3 following cases are considered: ($\gamma = 0$, $\eta = 0$), ($\gamma = 1$, $\eta = 0$), ($\gamma = 2$, $\eta = 1$). 3D simulations were run in order to analyse the impact of the micro-scale geometry on the homogenized solutions and the influence of the vessel permeability $R_n$ on the fluid transport. The following strategy has been adopted:

- The periodic cell was considered as the unit cube $(0,1)^3$ in $\mathbb{R}^3$. The domain was divided in two regions ($Y_t$ and $Y_c$) and the software Gmsh was used to perform the triangulation $T_h$. Problem (20) was discretized with the Galerkin Finite Elements Method. Piecewise linear polynomials ($P_1$) were used for the variable $P_j$. For the variable $W_j$, we used piecewise linear polynomials with bubbles ($P_{1b} = \{ v \in H^1(\Omega) : \forall K \in T_h \ v|_K \in P_1 \oplus \text{Span}\{\lambda^K_0, \lambda^K_1, \lambda^K_2, \lambda^K_3\} \}$, where $\lambda^K_j$, $j = 0,\ldots,N$ are the 4 barycentric coordinate functions of the element $K$). Problem (24) was solved on the domain $Y_t$ using piecewise linear polynomials ($P_1$) for the variable $G^j$.
- The tensors $K$ and $E$ were computed according to (28).
- The homogenized model (27) for the three cases ($\gamma = 0$, $\eta = 0$), ($\gamma = 1$, $\eta = 0$), ($\gamma = 2$, $\eta = 1$) was simulated on the normalized sphere of radius 0.5 using the Galerkin Finite Elements Method. Quadratic piecewise elements ($P_2$) were used for both $p_t$ and $p_c$.

### 4.1 Cell problems: tensor properties varying the microstructure

The tensors $K$ and $E$ defined in (28) have different properties according to the microstructure. To analyse them, we solved equations (24) and (20) in the unitary
Fig. 3 Different structures of the unit periodic cell with the respective volume and surface fractions. The mesh represents the capillary domain $Y_c$, while the difference between the box and the mesh is the interstitial compartment $Y_t$.

cell, i.e. the cube $(0, 1)^3 \subset \mathbb{R}^3$. Different geometric configurations for the domains $Y_t$ and $Y_c$ were tested (Fig. 3).

Table 1 provides the values of the elements in the two tensors $K$ and $E$. These results confirm the analysis done in Sect. 3.4. Indeed, the tensors $K$ and $E$ are symmetric and positive definite when the two domains are connected (Fig. 3a–c). When the capillaries are not connected in all the directions (Fig. 3d, e), the tensor $E$ is semi-positive definite as the solution to the cell problems (24) is trivial: $W^j = 0$ and $P^j = e_j, j = 1, 2, 3$. Figure 3 provides the values of the interstitial and capillary volume fractions ($|Y_t|$ and $|Y_c|$, respectively) and of the vascular surface $\Gamma_Y$.

4.2 Macroscopic dynamic of fluid transport in tumours

We eventually considered realistic parameters to test model (2). The homogenized model was tested with a tumor considered as a sphere of normalized radius 0.5. Table 2 provides the values of the parameters of the model. Regarding the interstitial hydraulic conductivity $k_t$, the vascular permeability $L_p$ and the tumour characteristic length $L$, we considered values relative to different tissues, as summarized in Tables 3, 4 and 5, respectively. Simulations were run considering different microstructures, namely the ones shown in Fig. 3a–c. Dirichlet boundary conditions were considered for the interstitial and capillary pressure, specifically $p_t, \infty = 0$ and $p_c, \infty = 1$ (normalized values).

Parameter influence

First, we looked at the behaviour of the solution varying the parameters $k_t, L_p$ and $L$. Examples of solutions as a function of the radius are shown in Fig. 4. In this case, we considered the microstructure of Fig. 3c. Results relative to the interstitial pressure and velocity were in agreement with the ones found in Baxter and Jain (1989), where the authors considered the following model:

$$\nabla \cdot (K \nabla p_t) = \frac{R_n S}{k V} (p_t - p_c),$$  (34)
### Table 1  Values of the tensors $K$ and $E$ for the different microstructures depicted in Fig. 3

|       | $K_{11}$ | $K_{12}$ | $K_{13}$ | $K_{21}$ | $K_{22}$ | $K_{23}$ | $K_{31}$ | $K_{32}$ | $K_{33}$ |
|-------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| Figure 3a | 0.808    | 7.5e-5   | 7.89e-6  | 7.5e-5   | 0.808    | 5.49e-5  | 7.89e-6  | 5.49e-5  | 0.808    |
| Figure 3b | 0.877    | -1.76e-3 | 3.91e-3  | -1.76e-3 | 0.814    | 2.29e-3  | 3.91e-3  | 2.29e-3  | 0.933    |
| Figure 3c | 0.72     | -1.09e-4 | 1.03e-4  | -1.09e-4 | 0.72     | 3.98e-5  | 1.03e-4  | 3.98e-5  | 0.72     |
| Figure 3d | 1        | -3.19e-8 | -9.81e-8 | -3.19e-8 | 0.895    | 1.01e-4  | -9.81e-8 | 1.01e-4  | 0.895    |
| Figure 3e | 0.954    | -4.69e-5 | 5.2e-5   | -4.69e-5 | 0.954    | 8.14e-5  | 5.2e-5   | 8.14e-5  | 0.954    |

|       | $E_{11}$ | $E_{12}$ | $E_{13}$ | $E_{21}$ | $E_{22}$ | $E_{23}$ | $E_{31}$ | $E_{32}$ | $E_{33}$ |
|-------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| Figure 3a | 2.2e-3   | 8e-6     | -1.1e-6  | 8e-6     | 2.2e-3   | -1.3e-5  | -1.1e-6  | -1.3e-5  | 2.2e-3   |
| Figure 3b | 9.5e-4   | 8.1e-7   | 2.3e-5   | 8.1e-7   | 1.8e-4   | 7.7e-6   | 2.3e-5   | 7.7e-6   | 2.9e-3   |
| Figure 3c | 4.0e-4   | -8.7e-7  | -7.4e-7  | -8.7e-7  | 4.0e-4   | -2.7e-6  | -7.4e-7  | -2.7e-6  | 4.0e-4   |
| Figure 3d | 4.7e-3   | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 0        |
| Figure 3e | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 0        |
| Parameter | Description                           | Value     | Unit           | References            |
|-----------|---------------------------------------|-----------|----------------|-----------------------|
| \( \mu \) | Blood viscosity                       | \( 4 \cdot 10^{-3} \) | kg m\(^{-1}\) s\(^{-1}\) | Rand et al. (1964)    |
| \( d \)   | Mean intercapillary distance         | \( 50 \cdot 10^{-6} \) | m              | Less et al. (1991)    |
| \( \alpha_{BJ} \) | BJS constant                      | 1         | --             | --                    |
| \( p_{I,\infty} \) | Surrounding interstitial pressure   | 0         | mmHg           | --                    |
| \( p_{C,\infty} \) | Surrounding capillary pressure       | [15,80]   | mmHg           | Boucher and Jain (1992) |
Table 3  Values of the interstitial hydraulic conductivity $k_t$ of different tissues

| Tissue                        | $k_t$ \( [m^3 s kg^{-1}] \) | References                  |
|-------------------------------|-------------------------------|-----------------------------|
| Dog squamous cell tissue      | $1.8 \cdot 10^{-12}$         | Guyton et al. (1971)        |
| Mouse mammary carcinoma       | $1.88 \cdot 10^{-13}$        | Jain et al. (2007)          |
| Hepatoma 5123 in vivo         | $2.9 \cdot 10^{-15}$         | Swabb et al. (1974)         |

Table 4  Values of the vessel permeability $L_p$ of different tissues

| Tissue                          | $L_p$ \( [m^2 s kg^{-1}] \) | References                  |
|---------------------------------|------------------------------|-----------------------------|
| Mouse mammary carcinoma         | $1.86 \cdot 10^{-10}$        | Jain et al. (2007)          |
| R3230 mammary adenocarcinoma    | $4.5 \cdot 10^{-11}$         | Sevick and Jain (1991)      |
| Healthy rat hindquarter tissue  | $2.3 \cdot 10^{-12}$         | Rippe et al. (1978)         |

Table 5  Characteristic length (diameter) of the tumour and corresponding tumour volume and value of $\varepsilon$

| Characteristic length $L$ \( [mm] \) | Tumor volume \( [mm^3] \) | $\varepsilon = d/L$ |
|---------------------------------------|---------------------------|---------------------|
| 5                                     | 4.2                       | 0.05                |
| 10                                    | 523.6                     | 0.01                |
| 15                                    | 4200                      | 0.005               |

where the vascular pressure $p_c$ is assumed to be constant and $S/V$ is the vascular area per unit volume of the tumour. Therefore, we considered this value to be equal to $|\Gamma_Y|$. The slight differences between the results obtained from the homogenized model and Baxter and Jain model (34) (Fig. 4A) are due to the different rescaling of the equation, since we considered $S/V$ to be the vascular area per unit volume of the interstitial compartment ($|\Gamma_Y|/|\Gamma_t|$).

The interstitial fluid pressure is large and almost constant in the centre of the tumour and has a sharp drop at the periphery for increasing values of $\tilde{R}_n$ and decreasing values of $\tilde{k}$. As a consequence, the interstitial fluid velocity is almost zero in the centre of the tumour (since the pressure gradient is close to zero) and large at the periphery. The microvessel fluid pressure is almost constant and close to the value at the boundary. For large values of the parameter $\tilde{R}_n$, the capillary pressure decreases and gets closer to the interstitial fluid pressure. As a consequence, also the microvessel fluid velocity is close to zero in the centre of the tumour.

Eventually, we observed the skin depth effect of $p_c - p_t$ when the permeability of the vessel walls increases (Fig. 4B). Indeed, the pressure difference is almost zero at the centre of the tumour and increases exponentially in correspondence of the boundary.

**Microstructure**

We fixed the parameter values $k_t = 1.8 \cdot 10^{-12}$ m$^3$ s kg$^{-1}$, $L_p = 1.86 \cdot 10^{-10}$ m$^2$ s kg$^{-1}$ and $L = 5$ mm and looked at the behaviour of the solutions relative to the different
Fig. 4  A Normalized values (n.v.) of interstitial fluid pressure and flow (IFP and IFF), of microvascular pressure (MVP) and of blood velocity as functions of the normalized radius ñ varying the parameter $\bar{R}_n/\kappa$. The microstructure considered in this case corresponds to Fig 3c. The blue lines are the simulations of the homogenized model (2) and the red lines are the results of Baxter and Jain model Baxter and Jain (1989). B Difference between $\hat{p}_{pc}$ and $\hat{p}_{pt}$ in normalized values (n.v.) as functions of the normalized radius $\hat{r}$ varying the parameter $\bar{R}_n$ and with $\bar{\kappa}$ fixed.

microstructures. Figure 5 shows the results relative to the unitary cells of Fig. 3A–C. In all cases, the IFP shows a sharp drop at the periphery and it equates the capillary pressure in the centre of the tumour, while the capillary pressure is approximately constant in the whole tumour. The interstitial fluid velocity $u_t$ is directed outward from the domain, while the blood velocity is directed inward. The two velocities are radially homogeneous in cases Fig. 5A, C, while they show asymmetries in case Fig. 5B due to the asymmetric microscopic structure of Fig. 3B.

We noticed that only when the capillary subdomain is smaller than the interstitial region, the blood velocity is larger than the interstitial fluid flow (data not shown). This is biologically relevant as the capillary volume fraction is usually within the range [16%, 50%] (Forster et al. 2017) and the average blood velocity is larger than the interstitial fluid velocity (Walker-Samuel et al. 2018; Kamoun et al. 2010).

**Boundary conditions**

Eventually, we tested model (2) with different boundary conditions. In particular, Neumann boundary conditions were considered for the capillary pressure, in order to ensure the continuity of the normal velocity in the vessels at the tumour periphery:

$$-\nabla p_c \cdot n = u_{c, \infty} \cdot n,$$

where $u_{c, \infty}$ is the blood velocity in the surrounding tissue. Dirichlet boundary conditions were imposed to the interstitial pressure. Well-posedness of model (2) is guaranteed with this set of boundary conditions for $(p_t, p_c) \in H^1_0(\Omega) \times H^1(\Omega)$.

We ran experiments with different boundary conditions for the capillary pressure $p_c$ as summarized in Table 6. Homogeneous Dirichlet boundary conditions were considered for the interstitial fluid pressure $p_t$. Figure S1 shows the results at the centre
Fig. 5 3D slices at the centre of the sphere with the interstitial pressure (first column), the capillary pressure (second column), interstitial velocity (third column) and capillary velocity (fourth column). Results were computed using the microstructure of Fig. 3a (A), of Fig. 3b (B) and of Fig. 3c (C) and setting $k_t = 1.8 \cdot 10^{-12}$ m$^3$ kg$^{-1}$, $L_p = 1.86 \cdot 10^{-10}$ m$^2$ kg$^{-1}$ and $L = 5$ mm. IFP, interstitial fluid pressure; MVP, microvascular pressure; IFF, interstitial fluid flow.

Table 6 Different boundary conditions considered for the microvessel pressure $p_c$

| Experiment     | Boundary condition (on $\partial \Omega$)                        | Parameter value (normalized)                      |
|----------------|-----------------------------------------------------------------|--------------------------------------------------|
| Dirichlet      | $p_c = p_{c, \infty}$                                           | $p_{c, \infty} = 1$                               |
| Neumann 1      | $-\nabla p_c \cdot \mathbf{n} = u_{c, \infty} \cdot \mathbf{n}$ | $u_{c, \infty} = -1 \cdot 10^{-3} \mathbf{n}$    |
| Neumann 2      | $-\nabla p_c \cdot \mathbf{n} = u_{c, \infty} \cdot \mathbf{n}$ | $u_{c, \infty} = [-1 \cdot 10^{-5}, 0, 0]^T$     |

of the sphere as function of the normalized radius. The interstitial pressure increases at the centre of the tumour and equates the blood pressure in the three cases. When considering the case “Neumann 2”, the blood velocity is constantly high inside the domain and the capillary pressure profile is therefore due to the gradient along the $x$-axis.
5 Discussion

We have provided an analysis of the impact of microstructure properties of the tumour employing the homogenisation theory.

First, we have described a model at the microscopic scale that couples vascular, transvascular and interstitial fluids, adopting an asymptotic expansion technique. Then, we have derived three macro-scale models according to the vessel wall permeability and the interstitial hydraulic conductivity. After having analysed the well-posedness of the problems, we performed numerical simulations to assess some properties according to the microstructure.

Well-posedness is guaranteed when the two subdomains $Y_t$ and $Y_c$ are connected. When one region is not connected with respect to one axis, the fluid is not transported along this direction. For example, in Fig. 3e the capillary microstructure is a closed sphere, therefore there is no fluid transport in the blood vessels; in Fig. 3d, the vessel geometry is connected only along the $x$-axis that is the only direction for the capillary fluid flow. This represents a limit for the 2D simulations, as the subdomains $Y_t$ and $Y_c$ cannot be both connected. In this case, one among the interstitial or the vessel flow is always zero. However, tensors $K$ and $E$ can be determined by calibrating directly the homogenized models to medical imaging data.

Furthermore, we motivated the links between the various regimes and shown that model (2) covers a wide range of cases, confirming previous results (Shipley and Chapman 2010). In particular, we have shown that model (1) is equivalent to model (2) under certain conditions and that model (2) can be approximated to model (3) under certain assumptions on the parameters.

Eventually, we calibrated model (2) with parameters taken from the literature and analysed their influence on the solutions. We observed that different microstructures and different sets of boundary conditions strongly impact the macroscopic dynamics of the fluids. The geometric shape of the unitary cell influences the isotropy of the capillary fluid velocity, while the vascular volume fraction affects the blood velocity. Indeed, when the capillary volume fraction $|Y_c|$ is large, the blood velocity $u_c$ is equal or lower than the interstitial fluid velocity $u_t$. This might not be biologically relevant. On the other hand, when the capillary volume fraction is smaller the blood velocity is of higher magnitude and gets closer to the average values (around 1.62 mm ·s$^{-1}$ Stamatelos et al. 2014). This confirms that the homogenized models are consistent with biological observations. Indeed, the vascular volume fraction lies within the values of 16 Possible improvements of our computations might be achieved by considering the correctors and by adding boundary layers, to take into account the Dirichlet boundary conditions that are imposed to the true solution $(p^e_t, p^e_c)$ of the micro-scale model, but are not satisfied by the periodic solutions to the homogenized ones.

The current work focuses on the analysis of asymptotic models that describe fluid transport in tumour tissues. Fluid velocities are necessary to develop convection-diffusion models for the description of drug transport in tumour tissues. This motivated our choice of a steady-state model, as in reality, the time variation of the fluid transport is negligible with respect to the evolution of drug distribution inside the tumour. However, spatial tumour growth might be included in the model.
Further extensions might include a relaxation of the periodicity hypothesis, that might not be realistic in a biological context, as tumours are highly heterogeneous. This question is complex and few results have been obtained in these directions. Actually, the current results on stochastic homogenisation are proven under an ergodic assumption which states that the domain is somehow almost invariant under a specific translation. This assumption enables to define properly a representative volume element, which the stochastic equivalent to the periodic unit cell. The homogenisation correctors $\mathcal{W}$, $\mathcal{P}$, $\mathcal{G}$ can then be computed in this representative volume, enabling the computation of the effective tensors $\mathbf{E}$ and $\mathbf{K}$ (Kanit et al. 2003).

Moreover, rheological effects of blood should be included to model blood transport in capillaries (Pries et al. 1994).

Applications of the models include the incorporation of 3D imaging data. Images provide the microstructure of the vessel network, that is necessary to compute the correctors.

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