Poromechanical Modelling for Living Tissue: Theoretical Development

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Abstract

This document outlines the theoretical framework developed in Thomas Lavigne's PhD research, structured in two parts. The first part introduces a monophasic interstitium, presenting both single- and two-compartment poromechanical models. In the second part, a more complex bi-phasic interstitium is explored through three progressively advanced sections. It begins with a single-compartment biphasic model, advances to a two-compartment biphasic model that includes vascularization, and culminates with the integration of oxygen biochemistry into the model. This work builds on the foundational theories established by Sciumè [2], Urcun [4], Lavigne et al. [1].

Keywords: Poro-elasticity, Multi-compartment, Mono-phasic, Bi-phasic, Oxygen biochemistry

Part I

Mono-phasic Interstitium

1. Monophasic single-compartment porous medium

This section provides the theoretical foundation for a poroelastic model consisting of a solid scaffold filled with a single fluid phase within a single compartment. The considered species and distribution as part of the problem as recalled in Table 1.

Phase \ Species	ECM	Other structures (glands, hair, etc.)	Cells in the interstitium	Water	Oxygen	Other Species
Solid (s)	✓	✓	✓	✓		
Liquid (l)				✓	✓	✓

Table 1: Description of the phases. ECM stands for Extra-Cellular Matrix.

Remark

The solid scaffold is here considered to be the connective tissue composed of the ECM and all the cells.

The primary variables of the problem are the solid displacement $\mathbf{u}^s$, and the fluid pressure p^l.

Each of the species occupies part of the volume of a well defined Representative Elementary Volume. Such volume fractions are defined according to Equation 1 and respect the constrain Equation 2.

$$\varepsilon^\alpha = \frac{\text{Volume}^\alpha}{\sum_{\text{phases}} \text{Volume}^{\text{phases}}} \tag{1}$$

$$\varepsilon^s + \varepsilon^l = 1 \tag{2}$$

One can define the porosity ε Equation 3 and re-define the solid fraction with respect to the porosity Equation 4.

$$\varepsilon = \varepsilon^l \tag{3}$$

$$\varepsilon^s = 1 - \varepsilon \tag{4}$$

For later computation, we further introduce the state law:

$$\frac{1}{\rho^\alpha}\frac{\mathrm{D}^s\rho^\alpha}{\mathrm{D}t} = \frac{1}{K^\alpha}\frac{\mathrm{D}^s p^\alpha}{\mathrm{D}t} \tag{5}$$

where K^α is the bulk modulus of the phase α.

Storativity coefficient

This expression is used if the densities are not assumed constant. This leads to the apparition of the storativity coefficient:

$$S = \frac{\varepsilon}{K^l} + \frac{1-\varepsilon}{K^s}$$

1.1. *Strong form*

The porous medium reads the classical conservation laws of mechanics. The momentum conservation reads:

$$\nabla \cdot \mathbf{t}^{\text{tot}} = 0 \tag{6}$$

where $\mathbf{t}^{\text{tot}}$ is the total stress tensor defined as:

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$$\mathbf{t}^{\text{tot}} = \sum_{\alpha=s,c,l} \varepsilon^\alpha \mathbf{t}^\alpha = \underbrace{\varepsilon^s \tau^s}_{\mathbf{t}^{\text{eff}}(\mathbf{u}^s)} - \varepsilon^s p^s \mathbf{1} - \varepsilon p^l \mathbf{1} \tag{7}$$

where $\varepsilon^s \tau^s$ is the effective stress tensor, p^s is the solid pressure empirically defined such that:

$$p^s = \beta p^l \tag{8}$$

where β is the Biot coefficient $\beta = 1 - \frac{K^s}{K^m}$, K^s being the bulk modulus of the porous skeleton and K^m being the bulk modulus of the solid material composing the porous skeleton

As a result, introducing Equations 4 and 8 in Equation 81:

$$\mathbf{t}^{\text{tot}} = \mathbf{t}^{\text{eff}} - [\beta + \varepsilon(1-\beta)]\, p^l \mathbf{1} \tag{9}$$

Biot Coefficient

In case of assumed incompressibility, the Biot coefficient is

$$\beta = 1$$

As a result, the bulk's modulus of each phase is infinite and the previous equation becomes

$$\mathbf{t}^{\text{tot}} = \mathbf{t}^{\text{eff}} - p^l \mathbf{1}$$

The mass conservation equations are introduced for each phase of the medium, considering that the phases densities are constant, and assuming incompressibility of the phases. To get the final forms of the continuity equations, we further introduce the material derivative:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(f) = \frac{\partial}{\partial t}(f) + \nabla(f) \cdot \mathbf{v}^s \tag{10}$$

The divergence of the product between a scalar a and a vector $\mathbf{u}$ respects:

$$\nabla \cdot (a\mathbf{u}) = a\,\nabla \cdot (\mathbf{u}) + \nabla a \cdot \mathbf{u} \tag{11}$$

- Solid phase:

$$\frac{\partial}{\partial t}(\rho^s \varepsilon^s) + \nabla \cdot (\rho^s \varepsilon^s \mathbf{v}^s) = 0 \tag{12}$$

$$\underset{(10)}{\Longrightarrow} \frac{\mathrm{D}^s}{\mathrm{D}t}(\rho^s \varepsilon^s) - \nabla(\rho^s \varepsilon^s) \cdot \mathbf{v}^s + \nabla \cdot (\rho^s \varepsilon^s \mathbf{v}^s) = 0 \tag{13}$$

$$\underset{(10)+(11)}{\Longrightarrow} \frac{\mathrm{D}^s}{\mathrm{D}t}(\rho^s \varepsilon^s) + \rho^s \varepsilon^s \nabla \cdot \mathbf{v}^s = 0 \tag{14}$$

$$\underset{(4)+(14)*\frac{1}{\rho^s}}{\Longrightarrow} -\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) + (1-\varepsilon)\nabla \cdot \mathbf{v}^s = 0 \tag{15}$$

Introducing the density variation

Using the storativity coefficient remark, Eq. 14 becomes:

$$\rho^s \frac{\mathrm{D}^s}{\mathrm{D}t}((1-\varepsilon)) + (1-\varepsilon)\frac{\mathrm{D}^s}{\mathrm{D}t}(\rho^s) + \rho^s \varepsilon^s \nabla \cdot \mathbf{v}^s = 0$$

Introducing Eq. 5:

$$\rho^s \frac{\mathrm{D}^s}{\mathrm{D}t}((1-\varepsilon)) + (1-\varepsilon)\frac{\rho^s}{K^s}\frac{\mathrm{D}^s p^s}{\mathrm{D}t} + \rho^s \varepsilon^s \nabla \cdot \mathbf{v}^s = 0$$

Dividing by ρ^s, and introducing Eq. 8 it becomes:

$$-\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) + \frac{(1-\varepsilon)\beta}{K^s}\frac{\mathrm{D}^s p^l}{\mathrm{D}t} + (1-\varepsilon)\nabla \cdot \mathbf{v}^s = 0$$

Equation 15 further gives:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) = (1-\varepsilon)\nabla \cdot \mathbf{v}^s \tag{16}$$

Update of the porosity induced by the solid displacement

Equation 16 allows to update the internal variable according to the current displacement.

A first order approximation in time allows to assess the porosity at the new time-step implicitly such that:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon(t)) = (1-\varepsilon(t))\nabla \cdot \mathbf{v}^s(t) \tag{17}$$

$$\Longrightarrow \varepsilon(t) = \varepsilon(t-\mathrm{d}t) + (1-\varepsilon(t))\nabla \cdot (\mathbf{u}^s(t) - \mathbf{u}^s(t-dt)) \tag{18}$$

$$\varepsilon(t) = \frac{\varepsilon(t-\mathrm{d}t) + \nabla \cdot (\mathbf{u}^s(t) - \mathbf{u}^s(t-dt))}{1 + \nabla \cdot (\mathbf{u}^s(t) - \mathbf{u}^s(t-dt))} \tag{19}$$

Introducing the density variation

According to the previous blocks, with $\mathrm{d}\mathbf{u}^s = \mathbf{u}^s(t) - \mathbf{u}^s(t-\mathrm{d}t)$:

$$-\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) + \frac{(1-\varepsilon)\beta}{K^s}\frac{\mathrm{D}^s p^l}{\mathrm{D}t} + (1-\varepsilon)\nabla \cdot \mathbf{v}^s = 0$$

Gives:

$$\varepsilon(t) = \frac{\varepsilon(t-\mathrm{d}t) + + \frac{(1-\varepsilon)\beta}{K^s}\mathrm{d}p^l + \nabla \cdot \mathrm{d}\mathbf{u}^s}{1 + \nabla \cdot \mathrm{d}\mathbf{u}^s}$$

- IF phase:

Starting from Eq. 10 and introducing the local form of the mass conservation we have:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\rho^l\varepsilon^l) - \frac{\partial}{\partial t}(\rho^l\varepsilon^l) - \nabla(\rho^l\varepsilon^l)\cdot\mathbf{v}^s = 0 \tag{20}$$

$$\frac{\partial}{\partial t}(\rho^l\varepsilon^l) + \nabla\cdot(\rho^l\varepsilon^l\mathbf{v}^l) = 0 \tag{21}$$

$$\Longrightarrow \frac{\mathrm{D}^s}{\mathrm{D}t}(\rho^l\varepsilon^l) + \nabla\cdot(\rho^l\varepsilon^l\mathbf{v}^l) - \nabla(\rho^l\varepsilon^l)\cdot\mathbf{v}^s = 0 \tag{22}$$

$$\underset{(11)}{\Longrightarrow} \frac{\mathrm{D}^s}{\mathrm{D}t}(\rho^l\varepsilon^l) + \nabla\cdot(\rho^l\varepsilon^l\mathbf{v}^l) - \nabla\cdot(\rho^l\varepsilon^l\mathbf{v}^s) + \rho^l\varepsilon^l\nabla\cdot\mathbf{v}^s = 0 \tag{23}$$

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\rho^l\varepsilon^l) + \nabla\cdot(\rho^l\varepsilon^l(\mathbf{v}^l - \mathbf{v}^s)) + \rho^l\varepsilon^l\nabla\cdot\mathbf{v}^s = 0 \tag{24}$$

$$\underset{*\frac{1}{\rho^l}}{\Longrightarrow} \frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) + \nabla\cdot(\varepsilon(\mathbf{v}^l - \mathbf{v}^s)) + \varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{25}$$

We further introduce the Darcy's law for the fluids:

$$\varepsilon(\mathbf{v}^l - \mathbf{v}^s) = -\frac{k^l}{\mu^l}(\nabla p^l - \rho^l\mathbf{g}) \tag{26}$$

where k^α is the permeability of the phase α and μ_α is the dynamic viscosity of the phase α.

The fluid velocities can therefore be replaced by the fluid pressure such that (by neglecting the inertial terms):

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) - \nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + \varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{27}$$

Introducing the density variation

Using the storativity coefficient remark, Eq. 14 becomes:

$$\rho^l\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) + \varepsilon\frac{\mathrm{D}^s}{\mathrm{D}t}(\rho^l) - \nabla\cdot\left(\rho^l\frac{k^l}{\mu^l}\nabla p^l\right) + \rho^l\varepsilon\nabla\cdot\mathbf{v}^s = 0$$

Introducing Eq. 5:

$$\rho^l\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) + \varepsilon\frac{\rho^l}{K^l}\frac{\mathrm{D}^s p^l}{\mathrm{D}t} - \nabla\cdot\left(\rho^l\frac{k^l}{\mu^l}\nabla p^l\right) + \rho^l\varepsilon\nabla\cdot\mathbf{v}^s = 0$$

Dividing by ρ^l, it becomes:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) + \varepsilon\frac{1}{K^l}\frac{\mathrm{D}^s p^l}{\mathrm{D}t} - \nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + \varepsilon\nabla\cdot\mathbf{v}^s = 0$$

Transforming Equation 27 by summing Equation 15, we get:

$$-\nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + \nabla\cdot\mathbf{v}^s = 0 \tag{28}$$

Introducing the density variation

The sum of the mass conservation equations becomes:

$$\underbrace{\left(\frac{(1-\varepsilon)\beta}{K^s} + \frac{\varepsilon}{K^l}\right)}_{=S}\frac{\mathrm{D}^s p^l}{\mathrm{D}t} - \nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + \nabla\cdot\mathbf{v}^s = 0$$

1.2. Variational Formulation

Let one consider $(q^l, \mathbf{w})$ the test functions defined in the mixed space $L_0^2(\Omega)\times[H^1(\Omega)]^3$. The solutions of the problem are the fluid pressure, and the displacement of the solid: $(p^l, \mathbf{u}^s)$.

Starting from Equations 6, 28, the problem to be solved reads:

$$\mathbf{u}^s = \mathbf{u}_{\text{imposed}} \text{ on } \partial\Omega_u \tag{29}$$

$$p^\alpha = p_{\text{imposed}} \text{ on } \partial\Omega_p^\alpha \tag{30}$$

$$\int_\Omega \frac{k^l}{\mu^l}\nabla p^l \nabla q^l \mathrm{d}\Omega + \int_\Omega \nabla\cdot\left(\frac{\mathrm{D}^s\mathbf{u}^s}{\mathrm{D}t}\right) q^l \mathrm{d}\Omega = 0,\ \forall\ q^l \in L_0^2(\Omega) \tag{31}$$

$$\int_\Omega \mathbf{t}^{\text{eff}}(\mathbf{u}^s) : \nabla\mathbf{w}\mathrm{d}\Omega - \int_\Omega (\beta + \varepsilon(1-\beta))\, p^l\nabla\cdot\mathbf{w}\mathrm{d}\Omega - \int_{\Gamma_s} \mathbf{t}^{\text{imposed}}\cdot\mathbf{w}\mathrm{d}\Gamma_s = 0, \forall\ \mathbf{w} \in [H^1(\Omega)]^3 \tag{32}$$

Introducing the density variation

The variational form reads for the mass conservation equations:

$$\int_\Omega S\frac{\mathrm{D}^s p^l}{\mathrm{D}t} q^l\mathrm{d}\Omega + \int_\Omega \frac{k^l}{\mu^l}\nabla p^l\nabla q^l\mathrm{d}\Omega + \int_\Omega \nabla\cdot\left(\frac{\mathrm{D}^s\mathbf{u}^s}{\mathrm{D}t}\right) q^l\mathrm{d}\Omega = 0,\ \forall\ q^l \in L_0^2(\Omega)$$

1.3. Matrix Form

The problem could be re-written as a matrix system:

$$\mathbf{C}_B\cdot\begin{bmatrix}\frac{\mathrm{D}^s p^l}{\mathrm{D}t}\\ \frac{\mathrm{D}^s\mathbf{u}^s}{\mathrm{D}t}\end{bmatrix} + \mathbf{K}_B\cdot\begin{bmatrix}p^l\\ \mathbf{u}^s\end{bmatrix} = \begin{bmatrix}\mathbf{f}_l\\ \mathbf{f}_s\end{bmatrix} \tag{33}$$

An example is provided in Sciumè et al. [3].

1.4. Terzaghi Analytical solution

The Terzaghi consolidation problem is often used for benchmarking porous media mechanics. The Terzaghi problem consist in an uni-directional confined compression experiment of a column. Assuming small and uni-directional strains, incompressible homogeneous phases and constant mechanical properties, the analytical expression of the pore pressure is given in terms of a series Equation 34

$$p^l = \frac{4p_0}{\pi} \sum_{k=1}^{+\infty} \frac{(-1)^{k-1}}{2k-1} \cos\left[(2k-1)\frac{\pi}{2}\frac{y}{h}\right] \exp\left[-(2k-1)^2 \frac{\pi^2}{4}\frac{c_v t}{h^2}\right] \tag{34}$$

$$c_v = \frac{k^\varepsilon}{\mu^l (S_\beta + \frac{\beta^2}{M})} \tag{35}$$

$$M = \frac{3K^s(1-\nu)}{(1+\nu)} \tag{36}$$

$$S_\beta = \frac{\beta - \varepsilon_0^l}{K^s} + \frac{\varepsilon_0^l}{K^l} \tag{37}$$

Where $p_0 = \mathbf{t}^{\text{imposed}} \cdot \mathbf{n}$ is the full applied load, y is the altitude, h is the initial height of the sample , c_v is the consolidation coefficient defined by (Equation 35), M the longitudinal modulus (Equation 36), S_β the inverse of the Biot Modulus (Equation 37) and ε_0^l is the initial porosity.

2. Monophasic two-compartment porous medium

Remark

This example allows a direct comparison to the "Mouse Experiment" and consolidation in G. Sciumè article. It allows to ensure a good implementing of the permeability matrix as well as the evaluation of the blood Flux and the LDF.

Starting from the previous example, we now add to the REV a second compartment corresponding to the vascular system. The system is now described in Table 3.

A further species has been introduced and the volume fraction constrain has been updated accordingly in Equation

$$\varepsilon^s + \varepsilon + \varepsilon^b = 1 \tag{38}$$

Similarly to the previous example, we introduce the extra-vascular porosity ε and the vascular porosity ε^b such that:

$$\varepsilon^s = 1 - \varepsilon - \varepsilon^b \tag{39}$$

2.1. Hypotheses

To develop this formulation, several hypotheses have been introduced.

Hypothesis 1

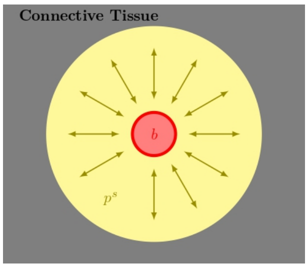
The blood vessels are mostly surrounded by extra-vascular fluids, hence they have no relevant mechanical interaction with the "structural" ECM fibbers.
Alternatively: The water absorbed by the constituents of the ECM impose a pressure being in equilibrium locally with the IF one. Vessels are compressed with this same pressure of the IF.Thus, solid scaffold = ECM + CELLS + absorbed fluid.

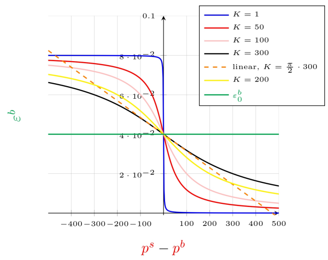
Hypothesis 2

The solid pressure, p^s, is assumed being related with pressures of extra-vascular space only and respects Eq. 8.

Hypothesis 3

Consistently with hypothesis 3 we suppose that ε^b depends on $(p^b - p^s)$.





How does it work?

The solid scaffold interacts with the blood vessels via the extra-vascular fluids.
This is a reasonable assumption for the considered system and significantly simplifies the mathematical formulation.

Based on these hypotheses, we can introduce a state equation for the vascular volume fraction (called here vascular porosity) (which will drive ischaemia). The following image provides a graphical interpretation of Hypothesis 3 and of the introduced state law:

An alternative for the vascular porosity computation is here introduced.

$$\varepsilon^b = \varepsilon_0^b \cdot \left(1 - \frac{p^s - p^b}{K}\right) \tag{40}$$

where ε_0^b stands for the initial blood volume fraction and K is the vessels compressibility. The atan formulation allows to prevent negative values.

The expression of the derivative of the blood porosity with respect to time is required to settle the mechanical system. For the ease of reading, its computation is proposed here-after.

According to the state law defined defined for the vascular porosity Equation 123, its derivative can be expressed as:

$$\frac{\mathrm{D}^s \varepsilon^b}{\mathrm{D}t} = \frac{\mathrm{D}^s \varepsilon^b}{\mathrm{D}p^s}\frac{\mathrm{D}^s p^s}{\mathrm{D}t} + \frac{\mathrm{D}^s \varepsilon^b}{\mathrm{D}p^b}\frac{\mathrm{D}^s p^b}{\mathrm{D}t} \tag{41}$$

Furthermore, using Equation 8 with $\beta = 1$, we get:

$$\frac{\mathrm{D}^s p^s}{\mathrm{D}t} = \frac{\mathrm{D}^s p^l}{\mathrm{D}t} \tag{42}$$

Furthermore, we can compute $\tilde{C}_{e,p} = \frac{\mathrm{D}^s \varepsilon^b}{\mathrm{D}p^s}$ such that:

$$\tilde{C}_{e,p} = \frac{\mathrm{D}^s \varepsilon^b}{\mathrm{D}p^s} = -\frac{\varepsilon_0^b}{K} \tag{43}$$

Immediately, we also have:

$$\frac{\mathrm{D}^s \varepsilon^b}{\mathrm{D}p^b} = -\tilde{C}_{e,p} \tag{44}$$

Finally, the derivative of the state function reads:

$$\frac{\mathrm{D}^s \varepsilon^b}{\mathrm{D}t} = \tilde{C}_{e,p}\left(\frac{\mathrm{D}^s p^l}{\mathrm{D}t} - \frac{\mathrm{D}^s p^b}{\mathrm{D}t}\right) \tag{45}$$

Similarly we can introduce the change in vascular permeability such that:

$$k^b = k_0^b \left(\frac{\varepsilon^b}{\varepsilon_0^b}\right)^{\alpha_b}, \ \alpha_b \geq 2 \tag{46}$$

Anisotropic vascular permeability

In the case were the blood permeability is not isotropic and is described as a matrix with a preferential direction, for example x, we would have:

$$\mathbf{k_0^b} = \begin{bmatrix} k_x & 0 & 0 \\ 0 & \frac{k_x}{100} & c \\ 0 & 0 & \frac{k_x}{100} \end{bmatrix} \tag{47}$$

2.1.1. Strong Form

As for the single-compartment theory, the porous medium reads the classical conservation laws of mechanics. The momentum conservation reads:

$$\nabla \cdot \mathbf{t}^{\text{tot}} = 0 \tag{48}$$

where $\mathbf{t}^{\text{tot}}$ is the total stress tensor defined as (adapted from Equation 9):

$$\mathbf{t}^{\text{tot}} = \sum_{\alpha=s,c,l,b} \varepsilon^\alpha \mathbf{t}^\alpha \tag{49}$$

$$= \underbrace{\varepsilon^s \tau^s}_{\mathbf{t}^{\text{eff}}(\mathbf{u}^s)} - \varepsilon^s p^s \mathbf{1} - \varepsilon p^l \mathbf{1} - \varepsilon^b p^b \mathbf{1} \tag{50}$$

where $\varepsilon^s \tau^s$ is the effective stress tensor, p^s is the solid pressure empirically defined Equation 8 with $\beta = 1$.

As a result, introducing Equations 39 and 8 in Equation 50:

$$\mathbf{t}^{\text{tot}} = \mathbf{t}^{\text{eff}} - \underbrace{(1-\varepsilon^b)}_{=\varepsilon^s+\varepsilon} p^l \mathbf{1} - \varepsilon^b p^b \mathbf{1} \tag{51}$$

We then introduce the mass conservation to each phase with the same intermediate operations as before.

- Solid phase:

$$-\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon + \varepsilon^b) + (1 - \varepsilon - \varepsilon^b)\nabla \cdot \mathbf{v}^s = 0 \tag{52}$$

$$\implies \frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) = -\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^b) + (1 - \varepsilon - \varepsilon^b)\nabla \cdot \mathbf{v}^s \tag{53}$$

- Vascular phase:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^b) + \nabla \cdot (\varepsilon^b(\mathbf{v}^b - \mathbf{v}^s)) + \varepsilon^b \nabla \cdot \mathbf{v}^s = 0 \tag{54}$$

For the blood, the Darcy's law reads:

$$\varepsilon^b(\mathbf{v}^b - \mathbf{v}^s) = -\frac{k^b}{\mu^b}(\nabla p^b - \rho^b \mathbf{g}) \tag{55}$$

Therefore, the blood mass conservation gives:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^b) - \nabla \cdot \left(\frac{k^b}{\mu^b}\nabla p^b\right) + \varepsilon^b \nabla \cdot \mathbf{v}^s = 0 \tag{56}$$

Finally, with Equation 45, Equation 56 becomes:

$$\tilde{C}_{e,p}\left(\frac{\mathrm{D}^s p^l}{\mathrm{D}t} - \frac{\mathrm{D}^s p^b}{\mathrm{D}t}\right) - \nabla \cdot \left(\frac{k^b}{\mu^b}\nabla p^b\right) + \varepsilon^b \nabla \cdot \mathbf{v}^s = 0 \tag{57}$$

Update of the porosity induced by the solid displacement

Equation 53 allows to update the internal variable according to the current displacement.

To have the evolution of the extra-vascular porosity, we inject Equation 56 in 53:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) = -\nabla \cdot \left(\frac{k^b}{\mu^b}\nabla p^b\right) + (1-\varepsilon)\nabla \cdot \mathbf{v}^s \tag{58}$$

A first order approximation in time allows to assess the porosity at the new time-step implicitly such that (with $\mathbf{du}^s(t) = (\mathbf{u}^s(t) - \mathbf{u}^s(t-dt))$):

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon(t)) = (1-\varepsilon(t))\nabla \cdot \mathbf{v}^s(t) - \nabla \cdot \left(\frac{k^b}{\mu^b}\nabla p^b(t)\right)\mathrm{d}t \tag{59}$$

$$\implies \varepsilon(t) = \varepsilon(t-\mathrm{d}t) + (1-\varepsilon(t))\nabla \cdot \mathbf{du}^s(t) - \nabla \cdot \left(\frac{k^b}{\mu^b}\nabla p^b(t)\right)\mathrm{d}t \tag{60}$$

$$\implies \varepsilon(t) = \frac{\varepsilon(t-\mathrm{d}t) + \nabla \cdot \mathbf{du}^s(t) - \nabla \cdot \left(\frac{k^b}{\mu^b}\nabla p^b(t)\right)\mathrm{d}t}{1 + \nabla \cdot \mathbf{du}^s(t)} \tag{61}$$

Alternative form for the update of the porosity induced by the solid displacement

An alternative to compute the porosity would be to replace the derivative of the vascular porosity by its expression:

$$\varepsilon(t) = \frac{\varepsilon(t-\mathrm{d}t)+C_{e,p}\left[\mathrm{d}p^b-\mathrm{d}p^l\right]+(1-\varepsilon^b)\nabla\cdot\mathrm{d}\mathbf{u}^s(t)}{1+\nabla\cdot\mathrm{d}\mathbf{u}^s(t)} \tag{62}$$

(with $\mathrm{d}\mathbf{u}^s(t) = (\mathbf{u}^s(t)-\mathbf{u}^s(t-dt))$, $\mathrm{d}p^b(t) = (p^b(t)-p^b(t-dt))$, $\mathrm{d}p^l(t) = (p^l(t)-p^l(t-dt)))$
Another alternative is:

$$\varepsilon(t) = \frac{\varepsilon(t-\mathrm{d}t)+\varepsilon^b(t-\mathrm{d}t)-\varepsilon^b(t)(1+\nabla\cdot\mathrm{d}\mathbf{u}^s(t))+\nabla\cdot\mathrm{d}\mathbf{u}^s(t)}{1+\nabla\cdot\mathrm{d}\mathbf{u}^s(t)} \tag{63}$$

- IF phase:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) - \nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + \varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{64}$$

Finally, summing Equations 64 and 58, we obtain for the mass conservation of the IF phase:

$$-\nabla\cdot\left(\frac{k^b}{\mu^b}\nabla p^b\right) - \nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + \nabla\cdot\mathbf{v}^s = 0 \tag{65}$$

2.2. Variational Form

Let one consider (q^c,q^l, q^b,$\mathbf{w}$) the test functions defined in the mixed space $L^2_0(\Omega)\times L^2_0(\Omega)\times[H^1(\Omega)]^3$. The solutions of the problem are the capillary pressure, the cell pressure, the blood pressure, and displacement of the solid: (p^l, p^b, $\mathbf{u}^s$).

Using Equations 48, 57, 65, the problem to be solved reads:

$$\mathbf{u}^s = \mathbf{u}_{\text{imposed}} \text{ on } \partial\Omega_u \tag{66}$$

$$p^\alpha = p_{\text{imposed}} \text{ on } \partial\Omega_p^\alpha \tag{67}$$

$$\begin{aligned}&\int_\Omega \frac{k^b}{\mu^b}\nabla p^b\nabla q^l\mathrm{d}\Omega\\ &+\int_\Omega \frac{k^l}{\mu^l}\nabla p^l\nabla q^l\mathrm{d}\Omega\\ &+\int_\Omega \nabla\cdot\left(\frac{\mathrm{D}^s\mathbf{u}^s}{\mathrm{D}t}\right)q^l\mathrm{d}\Omega = 0,\ \forall\ q^l\in L^2_0(\Omega)\end{aligned} \tag{68}$$

$$\begin{aligned}&\int_\Omega \tilde{C}_{e,p}\frac{\mathrm{D}^s p^l}{\mathrm{D}t}q^b\mathrm{d}\Omega\\ &-\int_\Omega \tilde{C}_{e,p}\frac{\mathrm{D}^s p^b}{\mathrm{D}t}q^b\mathrm{d}\Omega\\ &+\int_\Omega \frac{k^b}{\mu^b}\nabla p^b\nabla q^b\mathrm{d}\Omega\\ &+\int_\Omega \varepsilon^b\nabla\cdot\left(\frac{\mathrm{D}^s\mathbf{u}^s}{\mathrm{D}t}\right)q^b\mathrm{d}\Omega = 0,\ \forall\ q^b\in L^2_0(\Omega)\end{aligned} \tag{69}$$

$$\begin{aligned}&\int_\Omega \mathbf{t}^{\text{eff}}(\mathbf{u}^s):\nabla\mathbf{w}\mathrm{d}\Omega\\ &-\int_\Omega\left(1-\varepsilon^b\right)p^l\nabla\cdot\mathbf{w}\mathrm{d}\Omega\\ &-\int_\Omega \varepsilon^b p^b\nabla\cdot\mathbf{w}\mathrm{d}\Omega\\ &-\int_{\Gamma_s}\mathbf{t}^{\text{imposed}}\cdot\mathbf{w}\mathrm{d}\Gamma_s = 0,\ \forall\ \mathbf{w}\in[H^1(\Omega)]^3\end{aligned} \tag{70}$$

2.3. Matrix form

The problem could be re-written as a matrix system:

$$\tilde{\mathbf{C}}_C\cdot\begin{bmatrix}\frac{\mathrm{D}^s p^l}{\mathrm{D}t}\\ \frac{\mathrm{D}^s p^b}{\mathrm{D}t}\\ \frac{\mathrm{D}^s\mathbf{u}^s}{\mathrm{D}t}\end{bmatrix}+\tilde{\mathbf{K}}_C\cdot\begin{bmatrix}p^l\\ p^b\\ \mathbf{u}^s\end{bmatrix}=\begin{bmatrix}\mathbf{f}_l\\ \mathbf{f}_b\\ \mathbf{f}_s\end{bmatrix} \tag{71}$$

An example is provided in Sciumè et al. [3].

Part II
Bi-phasic Interstitium

3. Single-compartment biphasic poro-elastic model

This section provides the theoretical foundation for a poroelastic model consisting of a solid scaffold filled with two fluid phases within a single compartment. The considered species and distribution as part of the problem as recalled in Table 2.

Phase \ Species	ECM	Other structures (glands, hair, etc.)	Cells in the interstitium	Water	Oxygen	Other Species
Solid (s)	✓	✓				
Liquid (l)				✓	✓	✓
Cell (c)			✓	✓	✓	✓

Table 2: Description of the phases. ECM stands for Extra-Cellular Matrix.

Remark

The solid scaffold is here considered to be the connective tissue composed of the ECM and stroma cells.

The primary variables of the problem are the solid displacement $\mathbf{u}^s$, the capillary pressure, and the IF (non-wetting phase) pressure p^{lc}, p^l.

Choosing the primary variables

When using the classical laws of poro-elasticity (introducing a multi-phase fluid), it is common to consider the the non-wetting phase and the capillary pressures. This provides simplifications in the definition of the forms.

Each of the species occupies part of the volume of a well defined Representative Elementary Volume. Such volume fractions are defined according to Equation 72 and respect the constrain Equation 73.

$$\varepsilon^\alpha = \frac{\text{Volume}^\alpha}{\sum_{\text{phases}} \text{Volume}^{\text{phases}}} \tag{72}$$

$$\varepsilon^s + \varepsilon^c + \varepsilon^l = 1 \tag{73}$$

One can define the porosity ε Equation 74 and re-define the solid fraction with respect to the porosity Equation 75.

$$\varepsilon = \varepsilon^c + \varepsilon^l \tag{74}$$

$$\varepsilon^s = 1 - \varepsilon \tag{75}$$

We further introduce the saturation S^α of the wetting and non-wetting non-miscible phases in the fluid space and their constrain Equation 76.

$$\frac{\varepsilon^c}{\varepsilon} + \frac{\varepsilon^l}{\varepsilon} = S^c + S^l = 1 \tag{76}$$

Wetting and Non-Wetting phases

In poromechanics, the terms ”wetting” and ”non-wetting” phases are commonly used, though they may seem unconventional when applied to living tissues. The concept is as follows: within a pore, the two fluid phases coexist, but typically one phase is more closely bound to the solid scaffold, while the other occupies the central region of the pore. These are referred to as the wetting and non-wetting phases, respectively. The capillary pressure is then defined as the difference between the pressures of the non-wetting and wetting phases, and it is closely linked to the saturation of each phase.
For example, consider water and air coexisting in a porous concrete medium. The water adheres to the edges of the solid, while the air fills the central part of the pore. In this case, the pressure in the air (the non-wetting phase) is higher than in the water (the wetting phase).
In our system, a reasonable approximation would be to consider the cells as the wetting phase and the interstitial fluid (IF) as the non-wetting phase.

The capillary pressure in the phase is defined Equation 77.

$$p^{lc} = p^l - p^c \tag{77}$$

where $p^c = p^l - p^{lc}$ is the wetting phase pressure, *e.g.* the cell pressure in the present case.

The state law for the saturation-capillary pressure relationship (according to the wetting / non-wetting description) is defined Equations 78, 79.

$$S^c = 1 - \left[\frac{2}{\pi}\arctan\left(\frac{p^{lc}}{a}\right)\right] \tag{78}$$

where a is a constant parameter depending on the connective tissue microstructure.

Remark

It is not necessary to define S^c_0, the initial saturation in cell. It will result from a good choice of the initial value of p^{lc} leading to a saturation of the cells approximating an initial value of our choice.
This then requires **an initial period with no load** to let the model reach its initial equilibrium.

$$S^l = 1 - S^c \tag{79}$$

3.1. *Strong form*

The porous medium reads the classical conservation laws of mechanics. The momentum conservation reads:

$$\nabla \cdot \mathbf{t}^{\text{tot}} = 0 \tag{80}$$

where $\mathbf{t}^{\text{tot}}$ is the total stress tensor defined as:

$$\mathbf{t}^{\text{tot}} = \sum_{\alpha=s,c,l} \varepsilon^\alpha \mathbf{t}^\alpha = \underbrace{\varepsilon^s\tau^s}_{\mathbf{t}^{\text{eff}}(\mathbf{u}^s)} - \varepsilon^s p^s \mathbf{1} - \varepsilon(S^c p^c + S^l p^l)\mathbf{1} \tag{81}$$

$$\xRightarrow[(77)+(79)]{} \mathbf{t}^{\text{tot}} = \underbrace{\varepsilon^s\tau^s}_{\mathbf{t}^{\text{eff}}(\mathbf{u}^s)} - \varepsilon^s p^s \mathbf{1} - \varepsilon(S^c(p^l - p^{lc}) + (1 - S^c)p^l)\mathbf{1} \tag{82}$$

$$\Longrightarrow \mathbf{t}^{\text{tot}} = \underbrace{\varepsilon^s\tau^s}_{\mathbf{t}^{\text{eff}}(\mathbf{u}^s)} - \varepsilon^s p^s \mathbf{1} - \varepsilon(p^l - S^c p^{lc})\mathbf{1} \tag{83}$$

where $\varepsilon^s\tau^s$ is the effective stress tensor, p^s is the solid pressure empirically defined such that:

$$p^s = S^c p^c + S^l p^l \tag{84}$$

$$\xRightarrow[(77)+(79)]{} p^s = p^l - S^c p^{lc} \tag{85}$$

As a result, introducing Equations 75 and 85 in Equation 81:

$$\mathbf{t}^{\text{tot}} = \mathbf{t}^{\text{eff}} - (p^l - S^c p^{lc})\mathbf{1} \tag{86}$$

The mass conservation equations are introduced for each phase of the medium, considering that the phases densities are constant, and assuming incompressibility of the phases. To get the final forms of the continuity equations, we further introduce the material derivative:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(f) = \frac{\partial}{\partial t}(f) + \nabla(f) \cdot \mathbf{v}^s \tag{87}$$

The divergence of the product between a scalar a and a vector $\mathbf{u}$ respects:

$$\nabla \cdot (a\mathbf{u}) = a\nabla \cdot (\mathbf{u}) + \nabla a \cdot \mathbf{u} \tag{88}$$

• Solid phase:

$$\frac{\partial}{\partial t}(\rho^s\varepsilon^s) + \nabla\cdot(\rho^s\varepsilon^s\mathbf{v}^s) = 0 \tag{89}$$

$$\underset{(87)+(88)}{\Longrightarrow} \frac{\mathrm{D}^s}{\mathrm{D}t}(\rho^s\varepsilon^s) + \rho^s\varepsilon^s\nabla\cdot\mathbf{v}^s = 0 \tag{90}$$

$$\underset{(75)+(90)*\frac{1}{\rho^s}}{\Longrightarrow} -\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) + (1-\varepsilon)\nabla\cdot\mathbf{v}^s = 0 \tag{91}$$

Equation 91 further gives:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) = (1-\varepsilon)\nabla\cdot\mathbf{v}^s \tag{92}$$

Update of the porosity induced by the solid displacement

Equation 92 allows to update the internal variable according to the current displacement.

A first order approximation in time allows to assess the porosity at the new time-step implicitly such that:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon(t)) = (1-\varepsilon(t))\nabla\cdot\mathbf{v}^s(t) \tag{93}$$

$$\Longrightarrow \varepsilon(t) = \varepsilon(t-\mathrm{d}t) + (1-\varepsilon(t))\nabla\cdot(\mathbf{u}^s(t) - \mathbf{u}^s(t-dt)) \tag{94}$$

$$\varepsilon(t) = \frac{\varepsilon(t-\mathrm{d}t) + \nabla\cdot(\mathbf{u}^s(t) - \mathbf{u}^s(t-dt))}{1+\nabla\cdot(\mathbf{u}^s(t) - \mathbf{u}^s(t-dt))} \tag{95}$$

• Cell phase:

$$\frac{\partial}{\partial t}(\rho^c\varepsilon^c) + \nabla\cdot(\rho^c\varepsilon^c\mathbf{v}^c) = 0 \tag{96}$$

$$\underset{\text{split}+(88)+(96)*\frac{1}{\rho^c}}{\Longrightarrow} \frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^c) + \nabla\cdot(\varepsilon^c(\mathbf{v}^c - \mathbf{v}^s)) + \varepsilon^c\nabla\cdot\mathbf{v}^s = 0 \tag{97}$$

$$\underset{(76)}{\Longrightarrow} \frac{\mathrm{D}^s}{\mathrm{D}t}(S^c\varepsilon) + \nabla\cdot(S^c\varepsilon(\mathbf{v}^c - \mathbf{v}^s)) + S^c\varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{98}$$

• IF phase:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^l) + \nabla\cdot(\varepsilon^l(\mathbf{v}^l - \mathbf{v}^s)) + \varepsilon^l\nabla\cdot\mathbf{v}^s = 0 \tag{99}$$

$$\underset{(76)}{\Longrightarrow} \frac{\mathrm{D}^s}{\mathrm{D}t}(S^l\varepsilon) + \nabla\cdot(S^l\varepsilon(\mathbf{v}^l - \mathbf{v}^s)) + S^l\varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{100}$$

$$\begin{aligned}\underset{(79)}{\Longrightarrow} \frac{\mathrm{D}^s}{\mathrm{D}t}((1-S^c)\varepsilon) + \nabla\cdot((1-S^c)\varepsilon(\mathbf{v}^l - \mathbf{v}^s)) \\ +(1-S^c)\varepsilon\nabla\cdot\mathbf{v}^s = 0\end{aligned} \tag{101}$$

$$\begin{aligned}\Longrightarrow \frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) - \frac{\mathrm{D}^s}{\mathrm{D}t}(S^c\varepsilon) + \nabla\cdot((1-S^c)\varepsilon(\mathbf{v}^l - \mathbf{v}^s)) \\ +(1-S^c)\varepsilon\nabla\cdot\mathbf{v}^s = 0\end{aligned} \tag{102}$$

$$\begin{aligned}\underset{(92)}{\Longrightarrow} -\frac{\mathrm{D}^s}{\mathrm{D}t}(S^c\varepsilon) + \nabla\cdot((1-S^c)\varepsilon(\mathbf{v}^l - \mathbf{v}^s)) \\ +(1-S^c\varepsilon)\nabla\cdot\mathbf{v}^s = 0\end{aligned} \tag{103}$$

We further introduce the Darcy's law for the fluids:

$$\varepsilon^l(\mathbf{v}^l - \mathbf{v}^s) = -\frac{k^l}{\mu^l}(\nabla p^l - \rho^l\mathbf{g}) \tag{104}$$

$$\varepsilon^c(\mathbf{v}^c - \mathbf{v}^s) = -\frac{k^c}{\mu^c}(\nabla p^c - \rho^c\mathbf{g}) \tag{105}$$

where k^α is the permeability of the phase α and μ_α is the dynamic viscosity of the phase α.

The fluid velocities can therefore be replaced by the fluid pressures such that (by neglecting the inertial terms):

• Cell phase:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(S^c\varepsilon) - \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^c\right) + S^c\varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{106}$$

Developing the time derivative and considering Equation 77, we obtain:

$$\begin{aligned}&\left(S^c\frac{\mathrm{D}^s\varepsilon}{\mathrm{D}t} + \varepsilon\frac{\mathrm{D}^s S^c}{\mathrm{D}t}\right) \\ &-\nabla\cdot\left(\frac{k^c}{\mu^c}\nabla(p^l - p^{lc})\right) + S^c\varepsilon\nabla\cdot\mathbf{v}^s = 0\end{aligned} \tag{107}$$

$$\begin{aligned}\underset{(92)}{\Longrightarrow} &\left(S^c(1-\varepsilon)\nabla\cdot\mathbf{v}^s + \varepsilon\frac{\mathrm{D}^s S^c}{\mathrm{D}p^{lc}}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t}\right) \\ &-\nabla\cdot\left(\frac{k^c}{\mu^c}\nabla(p^l - p^{lc})\right) + S^c\varepsilon\nabla\cdot\mathbf{v}^s = 0\end{aligned} \tag{108}$$

$$\begin{aligned}\Longrightarrow &\ \varepsilon\frac{\mathrm{D}^s S^c}{\mathrm{D}p^{lc}}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} \\ &-\nabla\cdot\left(\frac{k^c}{\mu^c}\nabla(p^l - p^{lc})\right) + S^c\nabla\cdot\mathbf{v}^s = 0\end{aligned} \tag{109}$$

Considering Equations 78 and 79, one can compute the coefficient $\frac{\mathrm{D}^s S^c}{\mathrm{D}p^{lc}}$ such that:

$$\frac{\mathrm{D}^s S^c}{\mathrm{D}p^{lc}} = -\frac{2}{a\pi}\frac{1}{1+\left(\frac{p^{lc}}{a}\right)^2} \tag{110}$$

Let one consider the coefficient $C_{m,c} = \varepsilon\frac{\mathrm{D}^s S^c}{\mathrm{D}p^{lc}}$ such that:

$$\Longrightarrow C_{m,c}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} - \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^l\right) + \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + S^c\nabla\cdot\mathbf{v}^s = 0 \tag{111}$$

• IF phase:
Using Equation 104, we get:

$$-\frac{\mathrm{D}^s}{\mathrm{D}t}(S^c\varepsilon) - \nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + (1-S^c\varepsilon)\nabla\cdot\mathbf{v}^s = 0 \tag{112}$$

Transforming Equation 112 by summing Equation 106, we get:

$$-\nabla\cdot\left(\left[\frac{k^c}{\mu^c} + \frac{k^l}{\mu^l}\right]\nabla p^l\right) + \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + \nabla\cdot\mathbf{v}^s = 0 \tag{113}$$

3.2. Variational Formulation

Let one consider (q^c,q^l,$\mathbf{w}$) the test functions defined in the mixed space $L^2_0(\Omega)\times L^2_0(\Omega)\times[H^1(\Omega)]^3$. The solutions of the problem are the capillary pressure, the cell pressure, and the displacement of the solid: (p^l, p^{lc}, $\mathbf{u}^s$).

Starting from Equations 80, 111, 113, the problem to be solved reads:

$$\mathbf{u}^s = \mathbf{u}_{\text{imposed}} \text{ on } \partial\Omega_u \tag{114}$$

$$p^\alpha = p_{\text{imposed}} \text{ on } \partial\Omega_p^\alpha \tag{115}$$

$$\begin{aligned} \int_\Omega C_{m,c} \frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} q^c \mathrm{d}\Omega + \int_\Omega \frac{k^c}{\mu^c} \nabla p^l \nabla q^c \mathrm{d}\Omega \\ - \int_\Omega \frac{k^c}{\mu^c} \nabla p^{lc} \nabla q^c \mathrm{d}\Omega \end{aligned} \tag{116}$$

$$+ \int_\Omega S^c \nabla \cdot \left(\frac{\mathrm{D}^s \mathbf{u}^s}{\mathrm{D}t} \right) q^c \mathrm{d}\Omega = 0, \ \forall\ q^c \in L_0^2(\Omega)$$

$$\begin{aligned} \int_\Omega \left[\frac{k^c}{\mu^c} + \frac{k^l}{\mu^l} \right] \nabla p^l \nabla q^l \mathrm{d}\Omega - \int_\Omega \frac{k^c}{\mu^c} \nabla p^{lc} \nabla q^l \mathrm{d}\Omega \\ + \int_\Omega \nabla \cdot \left(\frac{\mathrm{D}^s \mathbf{u}^s}{\mathrm{D}t} \right) q^l \mathrm{d}\Omega = 0, \ \forall\ q^l \in L_0^2(\Omega) \end{aligned} \tag{117}$$

$$\begin{aligned} \int_\Omega \mathbf{t}^{\text{eff}}(\mathbf{u}^s) : \nabla \mathbf{w} \mathrm{d}\Omega - \int_\Omega \left(p^l - S^c p^{lc} \right) \nabla \cdot \mathbf{w} \mathrm{d}\Omega \\ - \int_{\Gamma_s} \mathbf{t}^{\text{imposed}} \cdot \mathbf{w} \mathrm{d}\Gamma_s = 0, \forall\ \mathbf{w} \in [H^1(\Omega)]^3 \end{aligned} \tag{118}$$

3.3. Matrix Form

The problem could be re-written as a matrix system:

$$\mathbf{C} \cdot \begin{bmatrix} \frac{\mathrm{D}^s p^l}{\mathrm{D}t} \\ \frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} \\ \frac{\mathrm{D}^s \mathbf{u}^s}{\mathrm{D}t} \end{bmatrix} + \mathbf{K} \cdot \begin{bmatrix} p^l \\ p^{lc} \\ \mathbf{u}^s \end{bmatrix} = \begin{bmatrix} \mathbf{f}_l \\ \mathbf{f}_{lc} \\ \mathbf{f}_s \end{bmatrix} \tag{119}$$

An example is provided in Sciumè et al. [3].

4. Two-compartments biphasic vascularised model

Starting from the previous example, we now add to the REV a second compartment corresponding to the vascular system. The system is now described in Table 3.

Phase \ Species	ECM	Other structures (glands, hair, etc.)	Cells in the interstitium	Water	Oxygen	Other Species
Solid (s)	✓	✓				
Liquid (l)				✓	✓	✓
Cell (c)			✓	✓	✓	✓
Vascular (blood) (b)				✓	✓	✓

Table 3: Description of the phases. ECM stands for Extra-Cellular Matrix.

A further species has been introduced and the volume fraction constrain has been updated accordingly in Equation

$$\varepsilon^s + \varepsilon^c + \varepsilon^l + \varepsilon^b = 1 \tag{120}$$

Similarly to the previous example, we introduce the extra-vascular porosity ε and the vascular porosity ε^b such that:

$$\varepsilon = \varepsilon^c + \varepsilon^l \tag{121}$$

$$\varepsilon^s = 1 - \varepsilon - \varepsilon^b \tag{122}$$

The saturation in the extra-vascular space still read Equation 76, keeping the same description of the wetting and non-wetting phases. As a result, the state laws introduced previously for the saturation have been kept too (Equations 78, 79).

4.1. Hypotheses

To develop this formulation, several hypotheses have been introduced.

Hypothesis 1

The blood vessels are mostly surrounded by extra-vascular fluids, hence they have no relevant mechanical interaction with the "structural" ECM fibbers.

Hypothesis 2

The solid pressure, p^s, is assumed being related with pressures of extra-vascular space only and respects Equation 85.

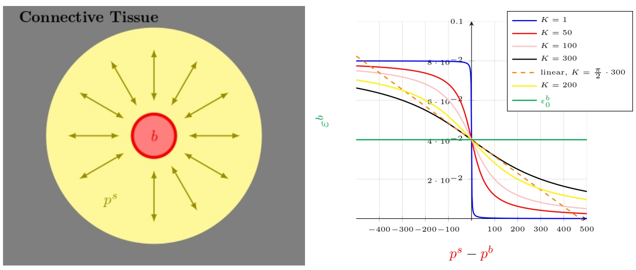
Hypothesis 3

Consistently with hypothesis 3 we suppose that ε^b depends on $(p^b - p^s)$.

How does it work?

The solid scaffold interacts with the blood vessels via the extra-vascular fluids.
This is a reasonable assumption for the considered system and significantly simplifies the mathematical formulation.

Based on these hypotheses, we can introduce a state equation for the vascular volume fraction (called here vascular porosity) (which will drive ischaemia). The following image provides a graphical interpretation of Hypothesis 3 and of the introduced state law:



$$\varepsilon^b = \varepsilon_0^b \cdot \left(1 - \frac{2}{\pi} \arctan \left(\frac{p^s - p^b}{K} \right) \right) \tag{123}$$

where ε_0^b stands for the initial blood volume fraction and K is the vessels compressibility. The atan formulation allows to prevent negative values.

The expression of the derivative of the blood porosity with respect to time is required to settle the mechanical system. For the ease of reading, its computation is proposed here-after.

According to the state law defined defined for the vascular porosity Equation 123, its derivative can be expressed as:

$$\frac{\mathrm{D}^s\varepsilon^b}{\mathrm{D}t} = \frac{\mathrm{D}^s\varepsilon^b}{\mathrm{D}p^s}\frac{\mathrm{D}^s p^s}{\mathrm{D}t} + \frac{\mathrm{D}^s\varepsilon^b}{\mathrm{D}p^b}\frac{\mathrm{D}^s p^b}{\mathrm{D}t} \tag{124}$$

Furthermore, using Equations 85, 110, we get:

$$\begin{aligned}\frac{\mathrm{D}^s p^s}{\mathrm{D}t} &= \frac{\mathrm{D}^s p^l}{\mathrm{D}t} - \frac{\mathrm{D}^s S^c p^{lc}}{\mathrm{D}t} &(125)\\ &= \frac{\mathrm{D}^s p^l}{\mathrm{D}t} - S^c\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} - p^{lc}\frac{\mathrm{D}^s S^c}{\mathrm{D}p^{lc}}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} &(126)\\ &= \frac{\mathrm{D}^s p^l}{\mathrm{D}t} - \underbrace{\left(S^c + p^{lc}\frac{\mathrm{D}^s S^c}{\mathrm{D}p^{lc}}\right)}_{=C_{state}}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} &(127)\end{aligned}$$

where C_{state} is a constant defined for the ease of reading.

Furthermore, we can compute $C_{e,p} = \frac{\mathrm{D}^s\varepsilon^b}{\mathrm{D}p^s}$ such that:

$$C_{e,p} = \frac{\mathrm{D}^s\varepsilon^b}{\mathrm{D}p^s} = -\frac{2\varepsilon^b_0}{\pi K}\frac{1}{1+\left(\frac{p^l - S^c p^{lc} - p^b}{K}\right)^2} \tag{128}$$

Immediately, we also have:

$$\frac{\mathrm{D}^s\varepsilon^b}{\mathrm{D}p^b} = -C_{e,p} \tag{129}$$

Finally, the derivative of the state function reads:

$$\frac{\mathrm{D}^s\varepsilon^b}{\mathrm{D}t} = C_{e,p}\left(\frac{\mathrm{D}^s p^l}{\mathrm{D}t} - C_{state}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} - \frac{\mathrm{D}^s p^b}{\mathrm{D}t}\right) \tag{130}$$

Similarly we can introduce the change in vascular permeability such that:

$$k^b = k^b_0\left(\frac{\varepsilon^b}{\varepsilon^b_0}\right)^{\alpha_b}, \ \alpha_b \geq 2 \tag{131}$$

Anisotropic vascular permeability

In the case were the blood permeability is not isotropic and is described as a matrix with a preferential direction, for example x, we would have:

$$\mathbf{k_0^b} = \begin{bmatrix} k_x & 0 & 0 \\ 0 & \frac{k_x}{100} & c \\ 0 & 0 & \frac{k_x}{100} \end{bmatrix} \tag{132}$$

4.1.1. Strong Form

As for the single-compartment theory, the porous medium reads the classical conservation laws of mechanics. The momentum conservation reads:

$$\nabla \cdot \mathbf{t}^{\text{tot}} = 0 \tag{133}$$

where $\mathbf{t}^{\text{tot}}$ is the total stress tensor defined as (adapted from Equation 86):

$$\begin{aligned}\mathbf{t}^{\text{tot}} &= \sum_{\alpha=s,c,l,b}\varepsilon^\alpha\mathbf{t}^\alpha &(134)\\ &= \underbrace{\varepsilon^s\tau^s}_{\mathbf{t}^{\text{eff}}(\mathbf{u}^s)} - \varepsilon^s p^s\mathbf{1} - \varepsilon(p^l - S^c p^{lc})\mathbf{1} - \varepsilon^b p^b\mathbf{1} &(135)\end{aligned}$$

where $\varepsilon^s\tau^s$ is the effective stress tensor, p^s is the solid pressure empirically defined Equation 85.

As a result, introducing Equations 122 and 85 in Equation 135:

$$\mathbf{t}^{\text{tot}} = \mathbf{t}^{\text{eff}} - \underbrace{(1-\varepsilon^b)}_{=\varepsilon^s+\varepsilon}(p^l - S^c p^{lc})\mathbf{1} - \varepsilon^b p^b\mathbf{1} \tag{136}$$

We then introduce the mass conservation to each phase with the same intermediate operations as before.

- Solid phase:

$$\begin{aligned}&-\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon+\varepsilon^b) + (1-\varepsilon-\varepsilon^b)\nabla\cdot\mathbf{v}^s = 0 &(137)\\ \Longrightarrow\ &\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) = -\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^b) + (1-\varepsilon-\varepsilon^b)\nabla\cdot\mathbf{v}^s &(138)\end{aligned}$$

- Vascular phase:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^b) + \nabla\cdot(\varepsilon^b(\mathbf{v}^b - \mathbf{v}^s)) + \varepsilon^b\nabla\cdot\mathbf{v}^s = 0 \tag{139}$$

For the blood, the Darcy's law reads:

$$\varepsilon^b(\mathbf{v}^b - \mathbf{v}^s) = -\frac{k^b}{\mu^b}(\nabla p^b - \rho^b\mathbf{g}) \tag{140}$$

Therefore, the blood mass conservation gives:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^b) - \nabla\cdot\left(\frac{k^b}{\mu^b}\nabla p^b\right) + \varepsilon^b\nabla\cdot\mathbf{v}^s = 0 \tag{141}$$

Finally, with Equation 130, Equation 141 becomes:

$$\begin{aligned}C_{e,p}\left(\frac{\mathrm{D}^s p^l}{\mathrm{D}t} - C_{state}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} - \frac{\mathrm{D}^s p^b}{\mathrm{D}t}\right) - \nabla\cdot\left(\frac{k^b}{\mu^b}\nabla p^b\right)\\ +\varepsilon^b\nabla\cdot\mathbf{v}^s = 0\end{aligned} \tag{142}$$

To have the evolution of the extra-vascular porosity, we inject Equation 141 in 138:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) = -\nabla\cdot\left(\frac{k^b}{\mu^b}\nabla p^b\right) + (1-\varepsilon)\nabla\cdot\mathbf{v}^s \tag{143}$$

A first order approximation in time allows to assess the porosity at the new time-step implicitly such that (with $\mathbf{du}^s(t) =$

$(\mathbf{u}^s(t) - \mathbf{u}^s(t-dt))$):

$$\frac{D^s}{Dt}(\varepsilon(t)) = (1-\varepsilon(t))\nabla\cdot\mathbf{v}^s(t) - \nabla\cdot\left(\frac{k^b}{\mu^b}\nabla p^b(t)\right)dt \tag{144}$$

$$\implies \varepsilon(t) = \varepsilon(t-dt) + (1-\varepsilon(t))\nabla\cdot d\mathbf{u}^s(t) - \nabla\cdot\left(\frac{k^b}{\mu^b}\nabla p^b(t)\right)dt \tag{145}$$

$$\implies \varepsilon(t) = \frac{\varepsilon(t-dt) + \nabla\cdot d\mathbf{u}^s(t) - \nabla\cdot\left(\frac{k^b}{\mu^b}\nabla p^b(t)\right)dt}{1+\nabla\cdot d\mathbf{u}^s(t)} \tag{146}$$

Alternative form for the update of the porosity induced by the solid displacement

An alternative to compute the porosity would be to replace the derivative of the vascular porosity by its expression:

$$\varepsilon(t) = \frac{\varepsilon(t-dt)+C_{\varepsilon,p}\left[dp^b + C_{state}dp^{lc} - dp^l\right] + (1-\varepsilon^b)\nabla\cdot d\mathbf{u}^s(t)}{1+\nabla\cdot d\mathbf{u}^s(t)} \tag{147}$$

(with $d\mathbf{u}^s(t) = (\mathbf{u}^s(t)-\mathbf{u}^s(t-dt))$, $dp^b(t) = (p^b(t)-p^b(t-dt))$, $dp^l(t) = (p^l(t)-p^l(t-dt))$, $dp^{lc}(t) = (p^{lc}(t)-p^{lc}(t-dt))$)

Another alternative is:

$$\varepsilon(t) = \frac{\varepsilon(t-dt)+\varepsilon^b(t-dt)-\varepsilon^b(t)(1+\nabla\cdot d\mathbf{u}^s(t))+\nabla\cdot d\mathbf{u}^s(t)}{1+\nabla\cdot d\mathbf{u}^s(t)} \tag{148}$$

- Cell phase:

$$\frac{D^s}{Dt}(S^c\varepsilon) - \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^c\right) + S^c\varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{149}$$

$$\implies \left(S^c\frac{D^s}{Dt}(\varepsilon) + \varepsilon\frac{D^s}{Dt}(S^c)\right) - \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla(p^l - p^{lc})\right) + S^c\varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{150}$$

$$\underset{(138)}{\implies} \left(S^c\left[-\frac{D^s}{Dt}(\varepsilon^b) + (1-\varepsilon-\varepsilon^b)\nabla\cdot\mathbf{v}^s\right] + \varepsilon\frac{D^s}{Dt}(S^c)\right) - \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^l\right) + \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + S^c\varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{151}$$

$$\underset{(111)}{\implies} -S^c\frac{D^s\varepsilon^b}{Dt} + C_{m,c}\frac{D^s p^{lc}}{Dt} - \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^l\right) + \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + S^c(1-\varepsilon^b)\nabla\cdot\mathbf{v}^s = 0 \tag{152}$$

Introducing Equation 141 in Equation 152, we get:

$$S^c\left(-\nabla\cdot\left(\frac{k^b}{\mu^b}\nabla p^b\right) + \varepsilon^b\nabla\cdot\mathbf{v}^s\right) + C_{m,c}\frac{D^s p^{lc}}{Dt} - \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^l\right) + \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + S^c(1-\varepsilon^b)\nabla\cdot\mathbf{v}^s = 0 \tag{153}$$

Finally the mass conservation of the cell phase reads:

$$C_{m,c}\frac{D^s p^{lc}}{Dt} - S^c\nabla\cdot\left(\frac{k^b}{\mu^b}\nabla p^b\right) - \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^l\right) + \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + S^c\nabla\cdot\mathbf{v}^s = 0 \tag{154}$$

- IF phase:

$$\frac{D^s}{Dt}(S^l\varepsilon) - \nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + S^l\varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{155}$$

$$\underset{(77)+(79)}{\implies} \frac{D^s}{Dt}(\varepsilon) - \frac{D^s}{Dt}(S^c\varepsilon) - \nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + (1-S^c)\varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{156}$$

$$\underset{(149)+(143)}{\implies} -\nabla\cdot\left(\frac{k^b}{\mu^b}\nabla p^b\right) + (1-\varepsilon)\nabla\cdot\mathbf{v}^s - \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla\underbrace{(p^l - p^{lc})}_{=p^c}\right) + S^c\varepsilon\nabla\cdot\mathbf{v}^s - \nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + (1-S^c)\varepsilon\nabla\cdot\mathbf{v}^s = 0 \tag{157}$$

Finally, we obtain for the mass conservation of the IF phase:

$$-\nabla\cdot\left(\frac{k^b}{\mu^b}\nabla p^b\right) - \nabla\cdot\left(\left[\frac{k^c}{\mu^c} + \frac{k^l}{\mu^l}\right]\nabla p^l\right) + \nabla\cdot\left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + \nabla\cdot\mathbf{v}^s = 0 \tag{158}$$

4.2. Variational Form

Let one consider $(q^c, q^l, q^b, \mathbf{w})$ the test functions defined in the mixed space $L_0^2(\Omega)\times L_0^2(\Omega)\times[H^1(\Omega)]^3$. The solutions of the problem are the capillary pressure, the cell pressure, the blood pressure, and displacement of the solid: $(p^l, p^{lc}, p^b, \mathbf{u}^s)$.

Using Equations 133, 142, 154, 158, the problem to be solved reads:

$$\mathbf{u}^s = \mathbf{u}_{\text{imposed}} \text{ on } \partial\Omega_u \tag{159}$$

$$p^\alpha = p_{\text{imposed}} \text{ on } \partial\Omega_p^\alpha \tag{160}$$

$$\begin{aligned}&\int_\Omega C_{m,c}\frac{D^s p^{lc}}{Dt}q^c d\Omega \\ &+ \int_\Omega S^c\frac{k^b}{\mu^b}\nabla p^b\nabla q^c d\Omega \\ &+ \int_\Omega \frac{k^c}{\mu^c}\nabla p^l\nabla q^c d\Omega \\ &- \int_\Omega \frac{k^c}{\mu^c}\nabla p^{lc}\nabla q^c d\Omega \\ &+ \int_\Omega S^c\nabla\cdot\left(\frac{D^s\mathbf{u}^s}{Dt}\right)q^c d\Omega = 0, \ \forall\, q^c \in L_0^2(\Omega)\end{aligned} \tag{161}$$

$$
\begin{aligned}
&\int_\Omega \frac{k^b}{\mu^b}\nabla p^b \nabla q^l \mathrm{d}\Omega \\
&+\int_\Omega \left[\frac{k^c}{\mu^c}+\frac{k^l}{\mu^l}\right]\nabla p^l \nabla q^l \mathrm{d}\Omega \\
&-\int_\Omega \frac{k^c}{\mu^c}\nabla p^{lc}\nabla q^l \mathrm{d}\Omega \\
&+\int_\Omega \nabla\cdot\left(\frac{\mathrm{D}^s \mathbf{u}^s}{\mathrm{D}t}\right) q^l \mathrm{d}\Omega = 0,\ \forall\ q^l \in L_0^2(\Omega)
\end{aligned}
\tag{162}
$$

$$
\begin{aligned}
&\int_\Omega C_{e,p}\frac{\mathrm{D}^s p^l}{\mathrm{D}t} q^b \mathrm{d}\Omega \\
&-\int_\Omega C_{e,p} C_{state}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} q^b \mathrm{d}\Omega \\
&-\int_\Omega C_{e,p}\frac{\mathrm{D}^s p^b}{\mathrm{D}t} q^b \mathrm{d}\Omega \\
&+\int_\Omega \frac{k^b}{\mu^b}\nabla p^b \nabla q^b \mathrm{d}\Omega \\
&+\int_\Omega \varepsilon^b \nabla\cdot\left(\frac{\mathrm{D}^s \mathbf{u}^s}{\mathrm{D}t}\right) q^b \mathrm{d}\Omega = 0,\ \forall\ q^b \in L_0^2(\Omega)
\end{aligned}
\tag{163}
$$

$$
\begin{aligned}
&\int_\Omega \mathbf{t}^{\mathrm{eff}}(\mathbf{u}^s) : \nabla \mathbf{w} \mathrm{d}\Omega \\
&-\int_\Omega \left(1-\varepsilon^b\right)\left(p^l - S^c p^{lc}\right)\nabla\cdot \mathbf{w} \mathrm{d}\Omega \\
&-\int_\Omega \varepsilon^b p^b \nabla\cdot \mathbf{w} \mathrm{d}\Omega \\
&-\int_{\Gamma_s} \mathbf{t}^{\mathrm{imposed}}\cdot \mathbf{w} \mathrm{d}\Gamma_s = 0, \forall\ \mathbf{w} \in [H^1(\Omega)]^3
\end{aligned}
\tag{164}
$$

4.3. Matrix form

The problem could be re-written as a matrix system:

$$
\tilde{\mathbf{C}}\cdot\begin{bmatrix} \frac{\mathrm{D}^s p^l}{\mathrm{D}t} \\ \frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} \\ \frac{\mathrm{D}^s p^b}{\mathrm{D}t} \\ \frac{\mathrm{D}^s \mathbf{u}^s}{\mathrm{D}t} \end{bmatrix} + \tilde{\mathbf{K}}\cdot\begin{bmatrix} p^l \\ p^{lc} \\ p^b \\ \mathbf{u}^s \end{bmatrix} = \begin{bmatrix} \mathbf{f}_l \\ \mathbf{f}_{lc} \\ \mathbf{f}_b \\ \mathbf{f}_s \end{bmatrix}
\tag{165}
$$

An example is provided in Sciumè et al. [3].

5. Oxygen Biochemistry

Let consider the exchange of oxygen between the blood compartment and the cells in the extra-vascular space through the IF. The idea is to set the mass conservation equation of the blood with a mass exchange between the blood and the IF and a consumption law by the cells.

5.1. Strong form

Let $\omega^{O2,l}$ be the mass fraction of oxygen in the IF and $\omega^{O2,b}$ the mass fraction of oxygen in the blood. $\omega^{O2,l}$ is a new unknown in the problem to be computed. According to the formulas in Sciumè et al. 2021, the mass conservation of the species reads:

$$
\begin{aligned}
&\underbrace{\frac{\partial}{\partial t}(S^l\varepsilon\rho^l\omega^{O2,l})}_{\text{Accumulation rate}} + \underbrace{\nabla\cdot(S^l\varepsilon\rho^l\omega^{O2,l}\mathbf{v}^l)}_{\text{Outward of species advective transport}} \\
&+ \underbrace{\nabla\cdot(S^l\varepsilon\rho^l\omega^{O2,l}\mathbf{u}^{O2,l})}_{\text{Outward of species diffusive transport}} - \underbrace{S^l\varepsilon r^{O2,l}\mathbf{u}^{O2,l})}_{\text{Intraphase reactive exchange of mass}} \\
&+ \underbrace{\Sigma_\kappa \overset{O2,l\to O2,\kappa}{M}}_{\text{Intraphase mass transport of the species}} + \underbrace{\omega^{O2,l}\Sigma_\kappa \overset{\kappa\to IF}{M}}_{\text{Interphase mass transport}} = 0
\end{aligned}
\tag{166}
$$

In our case, this equation can be re-written:

$$
\begin{aligned}
&\underbrace{\frac{\mathrm{D}^s}{\mathrm{D}t}(S^l\varepsilon\rho^l\omega^{O2,l})}_{\text{Accumulation rate}} + \underbrace{\nabla\cdot(S^l\varepsilon\rho^l\omega^{O2,l}(\mathbf{v}^l-\mathbf{v}^s))}_{\text{Infiltration}} \\
&+ \underbrace{\nabla\cdot(S^l\varepsilon\rho^l\omega^{O2,l}\mathbf{u}^{O2,l})}_{Diffusion} + \underbrace{S^l\varepsilon\rho^l\omega^{O2,l}\nabla\cdot\mathbf{v}^s}_{\text{ECM deformation}} \\
&= \underbrace{\overset{O2,b\to O2,l}{M}}_{\text{Blood to IF transport}} - \underbrace{\overset{O2,l\to O2,c}{M}}_{\text{O2 consumption from the cells}}
\end{aligned}
\tag{167}
$$

where the increase of oxygen from blood is driven by (exchange proportional to the vessel wall area):

$$
\overset{O2,b\to O2,l}{M} = h_v\varepsilon^b(\omega^{O2,b}-\omega^{O2,l})
\tag{168}
$$

where $\omega^{O2,b}$ is the mass fraction of oxygen within the blood and is assumed constant. The coefficient h_v is representative of the vessel wall permeability.

The consumption of oxygen from the cells is proportional to the fluid saturation in cells and is given by (ω_{crit} is the hypoxia threshold obtained from Henry's law and γ_0 relates to the cell metabolism):

- if $\omega^{O2,l} \geq \omega_{crit}$:

$$
\overset{O2,l\to O2,c}{M} = \gamma_0 S^c\varepsilon
\tag{169}
$$

- if $\omega^{O2,l} \leq \omega_{crit}$:

$$
\overset{O2,l\to O2,c}{M} = \gamma_0 S^c\varepsilon\left[\frac{1}{2}\left(1-\cos\pi\frac{\omega^{O2,l}}{\omega_{crit}}\right)\right]
\tag{170}
$$

Introducing the Fick's law, the diffusive flux of oxygen reads:

$$
\omega^{O2,l}\mathbf{u}^{O2,l} = -D_{eff}^{O2,l}\nabla\omega^{O2,l}
\tag{171}
$$

where $D_{eff}^{O2,l}$ is the effective diffusion coefficient of oxygen:

$$D_{eff}^{O2,l} = D_0^{O2,l}(\varepsilon^l)^\delta = D_0^{O2,l}(S^l\varepsilon)^\delta \tag{172}$$

where $D_0^{O2,IF}$ is the diffusion coefficient of oxygen in the bulk interstitial fluid and δ is a coefficient related to the tortuosity of the medium.

Considering a constant density ρ^l, the mass conservation becomes:

$$\begin{aligned}
&S^l\varepsilon\frac{\mathrm{D}^s}{\mathrm{D}t}(\omega^{O2,l}) + S^l\omega^{O2,l}\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) + \varepsilon\omega^{O2,l}\frac{\mathrm{D}^s}{\mathrm{D}t}(S^l)\\
&-\nabla\cdot(\frac{k^l}{\mu^l}\omega^{O2,l}\nabla p^l) - \nabla\cdot(S^l\varepsilon D_{eff}^{O2,l}\nabla\omega^{O2,l})\\
&+S^l\varepsilon\omega^{O2,l}\nabla\cdot\mathbf{v}^s = \frac{1}{\rho^l}\left(\overset{O2,b\rightarrow O2,l}{M} - \overset{O2,l\rightarrow O2,c}{M}\right)
\end{aligned} \tag{173}$$

Using Equation 88, we get:

$$\nabla\cdot(\frac{k^l}{\mu^l}\omega^{O2,l}\nabla p^l) = \omega^{O2,l}\nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + \frac{k^l}{\mu^l}\nabla\omega^{O2,l}\nabla p^l \tag{174}$$

Then, Equation 173 becomes:

$$\begin{aligned}
&(1-S^c)\varepsilon\frac{\mathrm{D}^s}{\mathrm{D}t}(\omega^{O2,l})\\
&+\omega^{O2,l}\left(\underbrace{\frac{\mathrm{D}^s}{\mathrm{D}t}((1-S^c)\varepsilon) - \nabla\cdot\left(\frac{k^l}{\mu^l}\nabla p^l\right) + (1-S^c)\varepsilon\nabla\cdot\mathbf{v}^s}_{(156)\implies=0}\right)\\
&-\frac{k^l}{\mu^l}\nabla\omega^{O2,l}\nabla p^l - \nabla\cdot((1-S^c)\varepsilon D_{eff}^{O2,l}\nabla\omega^{O2,l})\\
&=\frac{1}{\rho^l}\left(\overset{O2,b\rightarrow O2,l}{M} - \overset{O2,l\rightarrow O2,c}{M}\right)
\end{aligned} \tag{175}$$

$$\begin{aligned}
&(1-S^c)\varepsilon\frac{\mathrm{D}^s}{\mathrm{D}t}(\omega^{O2,l})\\
&-\frac{k^l}{\mu^l}\nabla\omega^{O2,l}\nabla p^l - \nabla\cdot((1-S^c)\varepsilon D_{eff}^{O2,l}\nabla\omega^{O2,l})\\
&=\frac{1}{\rho^l}\left(\overset{O2,b\rightarrow O2,l}{M} - \overset{O2,l\rightarrow O2,c}{M}\right)
\end{aligned} \tag{176}$$

5.2. *Variational form*

Let one consider (w_o) the test function defined in the space $L_0^2(\Omega)$. The following system of equation completes the system of equation of the previous section.

Let one consider $(q^c, q^l, q^b, \mathbf{w}, w_o)$ the test functions defined in the mixed space $L_0^2(\Omega)\times L_0^2(\Omega)\times[H^1(\Omega)]^3\times L_0^2(\Omega)$. The solutions of the problem are the capillary pressure, the cell pressure, the blood pressure, the displacement of the solid and the oxygen mass fraction: $(p^l,\ p^{lc},\ p^b,\ \mathbf{u}^s,\ \omega^{O2,l})$.

Using Equations 133, 142, 154, 158, and 176, the problem to be solved reads:

$$\mathbf{u}^s = \mathbf{u}_{\text{imposed}} \text{ on } \partial\Omega_u \tag{177}$$

$$p^\alpha = p_{\text{imposed}} \text{ on } \partial\Omega_p^\alpha \tag{178}$$

$$\begin{aligned}
&\int_\Omega C_{m,c}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t}q^c\mathrm{d}\Omega\\
&+\int_\Omega S^c\frac{k^b}{\mu^b}\nabla p^b\nabla q^c\mathrm{d}\Omega\\
&+\int_\Omega \frac{k^c}{\mu^c}\nabla p^l\nabla q^c\mathrm{d}\Omega\\
&-\int_\Omega \frac{k^c}{\mu^c}\nabla p^{lc}\nabla q^c\mathrm{d}\Omega\\
&+\int_\Omega S^c\nabla\cdot\left(\frac{\mathrm{D}^s\mathbf{u}^s}{\mathrm{D}t}\right)q^c\mathrm{d}\Omega = 0,\ \forall\ q^c\in L_0^2(\Omega)
\end{aligned} \tag{179}$$

$$\begin{aligned}
&\int_\Omega \frac{k^b}{\mu^b}\nabla p^b\nabla q^l\mathrm{d}\Omega\\
&+\int_\Omega\left[\frac{k^c}{\mu^c}+\frac{k^l}{\mu^l}\right]\nabla p^l\nabla q^l\mathrm{d}\Omega\\
&-\int_\Omega \frac{k^c}{\mu^c}\nabla p^{lc}\nabla q^l\mathrm{d}\Omega\\
&+\int_\Omega \nabla\cdot\left(\frac{\mathrm{D}^s\mathbf{u}^s}{\mathrm{D}t}\right)q^l\mathrm{d}\Omega = 0,\ \forall\ q^l\in L_0^2(\Omega)
\end{aligned} \tag{180}$$

$$\begin{aligned}
&\int_\Omega C_{e,p}\frac{\mathrm{D}^s p^l}{\mathrm{D}t}q^b\mathrm{d}\Omega\\
&-\int_\Omega C_{e,p}C_{state}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t}q^b\mathrm{d}\Omega\\
&-\int_\Omega C_{e,p}\frac{\mathrm{D}^s p^b}{\mathrm{D}t}q^b\mathrm{d}\Omega\\
&+\int_\Omega \frac{k^b}{\mu^b}\nabla p^b\nabla q^b\mathrm{d}\Omega\\
&+\int_\Omega \varepsilon^b\nabla\cdot\left(\frac{\mathrm{D}^s\mathbf{u}^s}{\mathrm{D}t}\right)q^b\mathrm{d}\Omega = 0,\ \forall\ q^b\in L_0^2(\Omega)
\end{aligned} \tag{181}$$

$$\begin{aligned}
&\int_\Omega \mathbf{t}^{\text{eff}}(\mathbf{u}^s):\nabla\mathbf{w}\mathrm{d}\Omega\\
&-\int_\Omega\left(1-\varepsilon^b\right)\left(p^l - S^c p^{lc}\right)\nabla\cdot\mathbf{w}\mathrm{d}\Omega\\
&-\int_\Omega \varepsilon^b p^b\nabla\cdot\mathbf{w}\mathrm{d}\Omega\\
&-\int_{\Gamma_s}\mathbf{t}^{\text{imposed}}\cdot\mathbf{w}\mathrm{d}\Gamma_s = 0, \forall\ \mathbf{w}\in[H^1(\Omega)]^3
\end{aligned} \tag{182}$$

$$\begin{aligned}
&\int_\Omega (1-S^c)\varepsilon\frac{\mathrm{D}^s}{\mathrm{D}t}(\omega^{O2,l})w_o\mathrm{d}\Omega\\
&-\int_\Omega \frac{k^l}{\mu^l}\nabla\omega^{O2,l}\nabla p^l w_o\mathrm{d}\Omega\\
&+\int_\Omega (1-S^c)\varepsilon D_{eff}^{O2,l}\nabla\omega^{O2,l}\nabla w_o\mathrm{d}\Omega\\
&=\int_\Omega\frac{1}{\rho^l}\left(\overset{O2,b\rightarrow O2,l}{M} - \overset{O2,l\rightarrow O2,c}{M}\right)w_o\mathrm{d}\Omega,\ \forall\ w_o\in L_0^2(\Omega)
\end{aligned} \tag{183}$$

5.3. Matrix form

The problem could be re-written as a matrix system:

$$\bar{\mathbf{C}} \cdot \begin{bmatrix} \frac{D^s p^l}{Dt} \\ \frac{D^s p^{lc}}{Dt} \\ \frac{D^s p^b}{Dt} \\ \frac{D^s \mathbf{u}^s}{Dt} \\ \frac{D^s \omega^{O2,l}}{Dt} \end{bmatrix} + \bar{\mathbf{K}} \cdot \begin{bmatrix} p^l \\ p^{lc} \\ p^b \\ \mathbf{u}^s \\ \omega^{O2,l} \end{bmatrix} = \begin{bmatrix} \mathbf{f}_l \\ \mathbf{f}_{lc} \\ \mathbf{f}_b \\ \mathbf{f}_s \\ \mathbf{f}_{O2,l} \end{bmatrix} \tag{184}$$

An example is provided in Sciumè et al. [3].

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Appendix A. What does the system become when the unknown is not the capillary pressure?

For the biphasic extra-vascular domain, one could think about having the two phases' pressures as the unknown. It has not been considered here due to the hypothesis carried out in the capillary pressure - saturation relationship. The hypothesis behind this relationship is $p^{nw} \geq p^w$, nw and w referring to the non-wetting and wetting phase. Otherwise, the saturation are not physical anymore.

Considering the capillary pressure allows to reduce the strong coupling by removing an unknown dependency within the saturation definition. A precise work would be needed to allow an exchange between the non-wetting and wetting phase which is not allowed by the atan form.

Appendix B. Alternative for the bi-phasic two-compartment porous medium

Remark

This extension requires special attention to the boundary conditions for the blood flow induced by the gradient in pressure.

The system is now described in Table 3. Conversely to the previous case we consider the primary variables being p^c, p^{lc}, p^{sb}, and $\mathbf{u}^s$, introducing the pressure gap between the solid and the blood compartments p^{sb} such that:

$$p^{sb} = p^s - p^b \tag{B.1}$$

$$p^b = p^s - p^{sb} \tag{B.2}$$

$$\underset{(85)}{\Longrightarrow} \quad p^b = p^c + (1 - S^c)p^{lc} - p^{sb} \tag{B.3}$$

The state law for the vascular porosity becomes:

$$\varepsilon^b = \varepsilon_0^b \cdot \left(1 - \frac{2}{\pi} \arctan\left(\frac{p^{sb}}{K}\right)\right) \tag{B.4}$$

where ε_0^b stands for the initial blood volume fraction and K is the vessels compressibility. The atan formulation allows to prevent negative values.

The expression of the derivative of the blood porosity with respect to time is required to settle the mechanical system. For the ease of reading, its computation is proposed here-after.

According to the state law defined defined for the vascular porosity Equation B.4, its derivative can be expressed as:

$$\frac{D^s \varepsilon^b}{Dt} = \frac{D^s \varepsilon^b}{D p^{sb}} \frac{D^s p^{sb}}{Dt} \tag{B.5}$$

Furthermore, we can compute $C_{e,p} = \frac{D^s \varepsilon^b}{D p^{sb}}$ such that:

$$\bar{C}_{e,p} = \frac{D^s \varepsilon^b}{D p^{sb}} = -\frac{2\varepsilon_0^b}{\pi K} \frac{1}{1 + \left(\frac{p^{sb}}{K}\right)^2} \tag{B.6}$$

Finally, the derivative of the state function reads:

$$\frac{D^s \varepsilon^b}{Dt} = \bar{C}_{e,p} \frac{D^s p^{sb}}{Dt} \tag{B.7}$$

Similarly we can introduce the change in vascular permeability such that:

$$k^b = k_0^b \left(\frac{\varepsilon^b}{\varepsilon_0^b}\right)^{\alpha_b}, \ \alpha_b \geq 2 \tag{B.8}$$

Anisotropic vascular permeability

In the case were the blood permeability is not isotropic and is described as a matrix with a preferential direction, for example x, we would have:

$$\mathbf{k_0^b} = \begin{bmatrix} k_x & 0 & 0 \\ 0 & \frac{k_x}{100} & c \\ 0 & 0 & \frac{k_x}{100} \end{bmatrix} \tag{B.9}$$

Appendix B.1. Strong Form

As for the single-compartment theory, the porous medium reads the classical conservation laws of mechanics. The momentum conservation reads:

$$\nabla \cdot \mathbf{t}^{\text{tot}} = 0 \tag{B.10}$$

where $\mathbf{t}^{\text{tot}}$ is the total stress tensor defined as (adapted from Equation 86):

$$\mathbf{t}^{\text{tot}} = \sum_{\alpha=s,c,l,b} \varepsilon^\alpha \mathbf{t}^\alpha \tag{B.11}$$

$$= \underbrace{\varepsilon^s \tau^s}_{\mathbf{t}^{\text{eff}}(\mathbf{u}^s)} - \varepsilon^s p^s \mathbf{1} - \varepsilon(p^l - S^c p^{lc})\mathbf{1} - \varepsilon^b p^b \mathbf{1} \tag{B.12}$$

where $\varepsilon^s \tau^s$ is the effective stress tensor, p^s is the solid pressure empirically defined Equation 85.

As a result, introducing Equations 122 and 85 in Equation B.12:

$$\mathbf{t}^{\text{tot}} = \mathbf{t}^{\text{eff}} - \underbrace{(1 - \varepsilon^b)}_{=\varepsilon^s + \varepsilon}(p^l - S^c p^{lc})\mathbf{1} - \varepsilon^b p^b \mathbf{1} \tag{B.13}$$

$$\mathbf{t}^{\text{tot}} = \mathbf{t}^{\text{eff}} - (p^l - S^c p^{lc})\mathbf{1} + \varepsilon^b p^{sb} \mathbf{1} \tag{B.14}$$

We then introduce the mass conservation to each phase with the same intermediate operations as before.

- Solid phase:

$$-\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon + \varepsilon^b) + (1 - \varepsilon - \varepsilon^b)\nabla \cdot \mathbf{v}^s = 0 \tag{B.15}$$

$$\implies \frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) = -\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^b) + (1 - \varepsilon - \varepsilon^b)\nabla \cdot \mathbf{v}^s \tag{B.16}$$

- Vascular phase:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^b) + \nabla \cdot (\varepsilon^b(\mathbf{v}^b - \mathbf{v}^s)) + \varepsilon^b \nabla \cdot \mathbf{v}^s = 0 \tag{B.17}$$

For the blood, the Darcy's law reads:

$$\varepsilon^b(\mathbf{v}^b - \mathbf{v}^s) = -\frac{k^b}{\mu^b}(\nabla p^b - \rho^b \mathbf{g}) \tag{B.18}$$

Therefore, the blood mass conservation gives:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^b) - \nabla \cdot \left(\frac{k^b}{\mu^b}\nabla p^b\right) + \varepsilon^b \nabla \cdot \mathbf{v}^s = 0 \tag{B.19}$$

Finally, with Equation B.7, Equation B.19 becomes:

$$\bar{C}_{e,p}\frac{\mathrm{D}^s p^{sb}}{\mathrm{D}t} - \nabla \cdot \left(\frac{k^b}{\mu^b}\nabla(p^l - S^c p^{lc} - p^{sb})\right) + \varepsilon^b \nabla \cdot \mathbf{v}^s = 0 \tag{B.20}$$

Update of the porosity induced by the solid displacement

Equation B.16 allows to update the internal variable according to the current displacement.

To have the evolution of the extra-vascular porosity, we inject Equation B.19 in B.16:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) = -\bar{C}_{e,p}\frac{\mathrm{D}^s p^{sb}}{\mathrm{D}t} + (1 - \varepsilon - \varepsilon^b)\nabla \cdot \mathbf{v}^s \tag{B.21}$$

A first order approximation in time allows to assess the porosity at the new time-step implicitly such that (with $\mathbf{du}^s(t) = (\mathbf{u}^s(t) - \mathbf{u}^s(t - dt))$):

$$\varepsilon(t) = \frac{\varepsilon(t - \mathrm{d}t) + (1 - \varepsilon^b)\nabla \cdot \mathbf{du}^s(t) - \bar{C}_{e,p}(p^{sb}(t) - p^{sb}(t - dt))}{1 + \nabla \cdot \mathbf{du}^s(t)} \tag{B.22}$$

- Cell phase:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(S^c \varepsilon) - \nabla \cdot \left(\frac{k^c}{\mu^c}\nabla p^c\right) + S^c \varepsilon \nabla \cdot \mathbf{v}^s = 0 \tag{B.23}$$

$$\implies \left(S^c \frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) + \varepsilon \frac{\mathrm{D}^s}{\mathrm{D}t}(S^c)\right) - \nabla \cdot \left(\frac{k^c}{\mu^c}\nabla(p^l - p^{lc})\right) + S^c \varepsilon \nabla \cdot \mathbf{v}^s = 0 \tag{B.24}$$

$$\underset{(B.16)}{\implies} \left(S^c \left[-\frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon^b) + (1 - \varepsilon - \varepsilon^b)\nabla \cdot \mathbf{v}^s\right] + \varepsilon \frac{\mathrm{D}^s}{\mathrm{D}t}(S^c)\right) - \nabla \cdot \left(\frac{k^c}{\mu^c}\nabla p^l\right) + \nabla \cdot \left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + S^c \varepsilon \nabla \cdot \mathbf{v}^s = 0 \tag{B.25}$$

$$\underset{(111)}{\implies} -S^c \frac{\mathrm{D}^s \varepsilon^b}{\mathrm{D}t} + C_{m,c}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} - \nabla \cdot \left(\frac{k^c}{\mu^c}\nabla p^l\right) + \nabla \cdot \left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + S^c(1 - \varepsilon^b)\nabla \cdot \mathbf{v}^s = 0 \tag{B.26}$$

Difference with the previous formulation

The difference is here. Because of the simple expression of the derivative of the vascular porosity, we do not use the mass conservation of the vascular compartment but its formal expression.

Introducing Equation B.7 in Equation B.26, we get:

$$-S^c \bar{C}_{e,p}\frac{\mathrm{D}^s p^{sb}}{\mathrm{D}t} + C_{m,c}\frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} - \nabla \cdot \left(\frac{k^c}{\mu^c}\nabla p^l\right) + \nabla \cdot \left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + S^c(1 - \varepsilon^b)\nabla \cdot \mathbf{v}^s = 0 \tag{B.27}$$

- IF phase:

$$\frac{\mathrm{D}^s}{\mathrm{D}t}(S^l \varepsilon) - \nabla \cdot \left(\frac{k^l}{\mu^l}\nabla p^l\right) + S^l \varepsilon \nabla \cdot \mathbf{v}^s = 0 \tag{B.28}$$

$$\underset{(77)+(79)}{\implies} \frac{\mathrm{D}^s}{\mathrm{D}t}(\varepsilon) - \frac{\mathrm{D}^s}{\mathrm{D}t}(S^c \varepsilon) - \nabla \cdot \left(\frac{k^l}{\mu^l}\nabla p^l\right) + (1 - S^c)\varepsilon \nabla \cdot \mathbf{v}^s = 0 \tag{B.29}$$

$$\underset{(B.7)+(B.16)+(B.24)}{\implies} -\bar{C}_{e,p}\frac{\mathrm{D}^s p^{sb}}{\mathrm{D}t} + (1 - \varepsilon - \varepsilon^b)\nabla \cdot \mathbf{v}^s - \nabla \cdot \left(\frac{k^c}{\mu^c}\nabla p^l\right) + \nabla \cdot \left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + S^c \varepsilon \nabla \cdot \mathbf{v}^s - \nabla \cdot \left(\frac{k^l}{\mu^l}\nabla p^l\right) + (1 - S^c)\varepsilon \nabla \cdot \mathbf{v}^s = 0 \tag{B.30}$$

Finally, we obtain for the mass conservation of the IF phase:

$$\implies -\bar{C}_{e,p}\frac{\mathrm{D}^s p^{sb}}{\mathrm{D}t} - \nabla \cdot \left(\left[\frac{k^c}{\mu^c} + \frac{k^l}{\mu^l}\right]\nabla p^l\right) + \nabla \cdot \left(\frac{k^c}{\mu^c}\nabla p^{lc}\right) + (1 - \varepsilon^b)\nabla \cdot \mathbf{v}^s = 0 \tag{B.31}$$

Appendix B.2. Variational Form

Let one consider (q^c,q^l, q^b,$\mathbf{w}$) the test functions defined in the mixed space $L^2_0(\Omega) \times L^2_0(\Omega) \times [H^1(\Omega)]^3$. The solutions of the problem are the capillary pressure, the cell pressure, the gap pressure between the solid and vascular compartments, and displacement of the solid: (p^c, p^{lc}, p^{sb}, $\mathbf{u}^s$).

Using Equations B.10, B.20, B.27, B.31, the problem to be solved reads:

$$\mathbf{u}^s = \mathbf{u}_{\text{imposed}} \text{ on } \partial\Omega_u \tag{B.32}$$

$$p^\alpha = p_{\text{imposed}} \text{ on } \partial\Omega_p^\alpha \tag{B.33}$$

$$\begin{aligned}
&-\int_\Omega S^c \bar{C}_{e,p} \frac{\mathrm{D}^s p^{sb}}{\mathrm{D}t} q^c \mathrm{d}\Omega \\
&+\int_\Omega C_{m,c} \frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} q^c \mathrm{d}\Omega \\
&+\int_\Omega \frac{k^c}{\mu^c} \nabla p^l \nabla q^c \mathrm{d}\Omega \\
&-\int_\Omega \frac{k^c}{\mu^c} \nabla p^{lc} \nabla q^c \mathrm{d}\Omega \\
&+\int_\Omega S^c (1-\varepsilon^b) \nabla \cdot \left(\frac{\mathrm{D}^s \mathbf{u}^s}{\mathrm{D}t}\right) q^c \mathrm{d}\Omega = 0, \; \forall \; q^c \in L^2_0(\Omega)
\end{aligned} \tag{B.34}$$

$$\begin{aligned}
&-\int_\Omega \bar{C}_{e,p} \frac{\mathrm{D}^s p^{sb}}{\mathrm{D}t} q^l \mathrm{d}\Omega \\
&+\int_\Omega \left[\frac{k^c}{\mu^c} + \frac{k^l}{\mu^l}\right] \nabla p^l \nabla q^l \mathrm{d}\Omega \\
&-\int_\Omega \frac{k^c}{\mu^c} \nabla p^{lc} \nabla q^l \mathrm{d}\Omega \\
&+\int_\Omega (1-\varepsilon^b) \nabla \cdot \left(\frac{\mathrm{D}^s \mathbf{u}^s}{\mathrm{D}t}\right) q^l \mathrm{d}\Omega = 0, \; \forall \; q^l \in L^2_0(\Omega)
\end{aligned} \tag{B.35}$$

$$\begin{aligned}
&\int_\Omega \bar{C}_{e,p} \frac{\mathrm{D}^s p^{sb}}{\mathrm{D}t} q^b \mathrm{d}\Omega \\
&+\int_\Omega \frac{k^b}{\mu^b} \nabla p^l \nabla q^b \mathrm{d}\Omega \\
&-\int_\Omega \frac{k^b}{\mu^b} \nabla (S^c p^{lc}) \nabla q^b \mathrm{d}\Omega \\
&-\int_\Omega \frac{k^b}{\mu^b} \nabla p^{sb} \nabla q^b \mathrm{d}\Omega \\
&+\int_\Omega \varepsilon^b \nabla \cdot \left(\frac{\mathrm{D}^s \mathbf{u}^s}{\mathrm{D}t}\right) q^b \mathrm{d}\Omega = 0, \; \forall \; q^b \in L^2_0(\Omega)
\end{aligned} \tag{B.36}$$

$$\begin{aligned}
&\int_\Omega \mathbf{t}^{\text{eff}}(\mathbf{u}^s) : \nabla \mathbf{w} \mathrm{d}\Omega \\
&-\int_\Omega \left(p^l - S^c p^{lc}\right) \nabla \cdot \mathbf{w} \mathrm{d}\Omega \\
&+\int_\Omega \varepsilon^b p^{sb} \nabla \cdot \mathbf{w} \mathrm{d}\Omega \\
&-\int_{\Gamma_s} \mathbf{t}^{\text{imposed}} \cdot \mathbf{w} \mathrm{d}\Gamma_s = 0, \forall \; \mathbf{w} \in [H^1(\Omega)]^3
\end{aligned} \tag{B.37}$$

Appendix B.3. Matrix form

The problem could be re-written as a matrix system:

$$\tilde{\mathbf{C}} \cdot \begin{bmatrix} \frac{\mathrm{D}^s p^l}{\mathrm{D}t} \\ \frac{\mathrm{D}^s p^{lc}}{\mathrm{D}t} \\ \frac{\mathrm{D}^s p^b}{\mathrm{D}t} \\ \frac{\mathrm{D}^s \mathbf{u}^s}{\mathrm{D}t} \end{bmatrix} + \tilde{\mathbf{K}} \cdot \begin{bmatrix} p^l \\ p^{lc} \\ p^{sb} \\ \mathbf{u}^s \end{bmatrix} = \begin{bmatrix} \mathbf{f}_l \\ \mathbf{f}_{lc} \\ \mathbf{f}_{sb} \\ \mathbf{f}_s \end{bmatrix} \tag{B.38}$$

An example is provided in Sciumè et al. [3].

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