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Modeling the porous and viscous responses of human brain tissue behavior

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Abstract

The biomechanical characterization of human brain tissue and the development of appropriate mechanical models is crucial to provide realistic computational predictions that can assist personalized treatment of neurological disorders with a strong biomechanical component. Here, we present a novel material model that combines finite viscoelasticity with a nonlinear biphasic poroelastic formulation, developed within the context of the Theory of Porous Media. Embedded in a finite element framework, our model is capable of predicting the brain tissue response under multiple loading conditions. We show that our model can capture both experimentally observed fluid flow and conditioning aspects of brain tissue behavior in addition to its well-established nonlinear and compression-tension asymmetric characteristics. Our results support the notion that porous and viscous effects are highly interrelated and that additional experimental data are required to reliably identify the model parameters. The modular and object-oriented design with automatic differentiation makes our open-source code easily amendable to future extensions. We provide a solid foundation towards the development of a reliable and comprehensive biomechanical model for brain tissue, which will be a versatile and useful tool in elucidating the rheology of brain tissue behavior to help the biomedical and clinical communities in the future study, prevention and treatment of brain injury and disease.

Keywords: theory of porous media, finite viscoelasticity, finite element method, material modeling, brain mechanics, mechanical testing

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1. Introduction

Computational modeling has the potential to provide meaningful insights into the underlying mechanisms of neurological disorders that exhibit significant biomechanical factors such as traumatic brain injury, stroke, encephalitis, tumors and certain congenital brain defects. Personalized predictive and preventive approaches to aid in the treatment of such disorders will only be possible when we provide realistic models of human brain tissue behavior, based on a more thorough understanding of the underlying mechanobiological aspects involved in brain structure, function and response. In this sense, characterizing the biomechanical response of brain tissue is essential to develop reliable models to elucidate the role mechanics plays in brain function [1–4].

Characterizing brain tissue response to loading is complicated due to its extreme softness and heterogeneous microstructure [5]. Despite the large variation in the published experimental data, the response of brain tissue is undoubtedly time-dependent, and its highly nonlinear, conditioning, hysteretic, and tension-compression asymmetric behavior is widely recognized by researchers in the field [1, 4, 6–10].

A variety of models based on the field equations of continuum mechanics have been proposed to computationally reproduce brain tissue response, yet a general consensus has not been reached regarding their adequacy in different applications. In general, most models developed to date have been tailored to reproduce particular loading scenarios or predict specific applications, but are not transferable to other arbitrary loading cases. Based on the distinct aspect of the material response being modeled, these can be roughly classified into time-independent and time-dependent contributions [11].

Finite strain hyperelasticity is the preferred approach to model the nonlinear time-independent response. Although the simple neo-Hookean model is extensively used, it cannot capture key features such as the tension-compression asymmetry or the nonlinear response beyond the small strain regime. Several studies indicate that only the Ogden model can appropriately capture these characteristics [3, 12–14].

Viscoelastic models are typically chosen to reproduce the time-dependent preconditioning and hysteresis, as well as the stress relaxation observed in experiments [11]. The popular Prony series approach to describe the evolution of the response over time is limited to linear elasticity, and computationally expensive [7]. Past works published by our group [7, 13, 15] use a family of finite viscoelastic Ogden model [16] to predict the essential features of brain tissue: nonlinearity, preconditioning, hysteresis, and tension-compression asymmetry. Yet, our monophasic viscoelastic model can only implicitly capture the effects of extracellular fluid flow within the network of cells and extracellular matrix. Our findings support the hypothesis that brain tissue rheology is characterized by at least two different timescales, which we attribute to viscous and porous effects, respectively [1]. The viscous response can be related to the intracellular interactions within the network of cells forming the solid phase of the tissue, while the porous behavior is associated with the interaction between the solid and fluid phases.

To explicitly model the fluid flow within the tissue, a poroelastic framework must be used. A handful of experimental studies have identified porous effects in brain tissue through consolidation tests [17–20], supporting this modeling approach. Based on mixture theory, poroelasticity has been used extensively to model hydrated biological tissues such as cartilage [21–26] and, more recently, brain [27–35]. The tissue is generally treated as a biphasic material consisting of a fluid-saturated porous deformable nonlinear elastic solid [21, 22, 27, 28, 33–35]. Extensions to multiphasic mixtures have also been developed, for example, to separately account for the blood and extracellular fluid within the fluid phase [30, 31], or to incorporate electrochemical reactions in the tissue via a triphasic model [23–25, 29].

In view of all these previous studies and experimental findings, we propose a novel constitutive model for brain tissue, which combines finite viscoelasticity [16] to capture the time-dependent response of the solid matrix with a biphasic poroelastic material formulation developed within the context of the Theory of Porous Media [36]. Embedded in a finite element framework, it allows us to predict the behavior of brain tissue under a wide range of loading conditions. The use of poro-viscoelasticity to reproduce brain tissue behavior has already been investigated in recent years [37–39], but these studies focus on the role of the cerebrospinal fluid circulation and are based on important simplifications that critically limit the scope of applications.

To the best of our knowledge, ours is the first study to develop a computational model of brain tissue
response with the aim of capturing and exploring the fluid flow effects of consolidation tests as well as the nonlinearity, tension-compression asymmetry and conditioning observed in cyclic loading experiments.

2. Kinematics and balance relations

2.1. Preliminaries

Brain tissue is composed of a solid network of cells embedded within an extracellular matrix (ECM) and bathed by interstitial fluid (ISF). The porous behavior is attributed to the free-flowing ISF, while the viscoelastic response is associated with the deforming proteins and glycans forming the ECM as well as the intracellular interactions between membrane, nucleus, and cytoplasm during cellular deformation [7]. Within the framework of the Theory of Porous Media [40], this material is treated as an immiscible aggregate of a nonlinear viscoelastic solid skeleton \( S \) saturated with pore fluid \( F \), as shown in Figure 1.

ISF bathes and surrounds the brain capillaries and neural cells and, together with the ECM, it completely occupies the extracellular space [41]. Therefore, we consider the biphasic material is fully-saturated and

\[
 n_S + n_F = 1, \tag{1}
\]

where \( n_S \) and \( n_F \) are the current volume fractions of the solid and fluid, respectively.

In addition, we assume individual material incompressibility, i.e. the real or effective densities of the solid and fluid constituents, \( \rho^{SR} \) and \( \rho^{FR} \), respectively, are constant. Pore fluid incompressibility is justified by the high water content of ISF. The solid component represents the ECM, cells and capillaries and, as a whole, is also assumed to be incompressible. This hypothesis is based on the fact that ECM consists in a dense network of proteins and glycans [42], and that the water trapped within cells amount to over 70% of their total mass [43], rendering this aggregate virtually incompressible.

Finally, we will assume quasi-static processes, a constant temperature and no mass exchange between the solid and fluid components, i.e. no phase transition, for all our derivations.

2.2. Kinematics

The solid and fluid constituents of the biphasic material occupy simultaneously the same spatial position \( x \) in the current configuration at a given time \( t \), but the material particles of each component proceed from different reference positions at time \( t_0 \), see Figure 2. Then, the constituent deformation map is \( x = \chi_S(X_S, t) = \chi_F(X_F, t) \), and the displacement of the solid component is \( u_S = x - X_S \). The seepage velocity \( w_F \), which describes the motion of the fluid with respect to the deforming solid, is

\[
 w_F = v_F - v_S = \frac{\partial x_F}{\partial t} - \frac{\partial x_S}{\partial t}. \tag{2}
\]

The material deformation gradient and right Cauchy-Green tensors of the solid component are, respectively,

\[
 F_S = \frac{\partial x}{\partial X_S} = \nabla_S x \quad \text{and} \quad C_S = F_S^T \cdot F_S. \tag{3}
\]

Therein, the operator \( \nabla_S(\bullet) \) indicates the partial derivative of (\( \bullet \)) with respect to the reference position \( X_S \) of the solid component.
2.3. Mass balance relations

Material incompressibility of the individual components allows factoring out the real densities from the mass continuity equations to obtain the volume fraction balance equations,

\[ \frac{\partial n^\alpha}{\partial t} + \nabla n^\alpha \cdot \mathbf{v}_\alpha + n^\alpha \nabla \cdot \mathbf{v}_\alpha = 0, \quad \alpha = \{S, F\}, \] (4)

where \( \alpha = \{S, F\} \) correspond to the solid and the fluid components, respectively. The volume balance of the solid skeleton can be integrated towards

\[ n^S = \frac{n_0^S}{J_S} \quad \text{with} \quad J_S = \det(F_S) > 0. \] (5)

Here, \( n_0^S \) is the volume fraction of the solid component referring to the solid reference configuration at time \( t_0 \). It is a fixed value directly related to the initial porosity of the biphasic material \( n_0^S \) through the saturation condition, i.e. \( n_0^S = 1 - n_0^F \).

The volume balance of the fluid component can be rewritten in terms of the seepage velocity (2), which, considering the material time derivative of the saturation condition and the volume balance of the solid, leads to

\[ \nabla \cdot (n^F \mathbf{w}_F) + \dot{\ln}(J_S) = 0. \] (6)

This is the strong form of the mass balance equation for the biphasic material in the current configuration. Here, the well-known relation \( \nabla \cdot \mathbf{v}_S = \frac{J_S}{J_S} = \ln(J_S) \) has been introduced. The first term in (6) is a measure of the outflow of fluid from the deforming solid skeleton, while the second term is an indication of how fast the solid skeleton changes its volume.

2.4. Linear momentum balance relations

The linear momentum balance equation for each constituent reads [36]

\[ \nabla \cdot \mathbf{\sigma}^\alpha + \rho^\alpha \mathbf{b}_t^\alpha + \mathbf{p}^\alpha = \mathbf{0}, \] (7)

where \( \alpha = \{S, F\} \) correspond to the solid and the fluid components, respectively. Here, \( \mathbf{\sigma}^\alpha \) is the Cauchy stress tensor, \( \rho^\alpha = n^\alpha \rho^\alpha_R \) is the partial density, \( \mathbf{b}_t^\alpha \) is the vector of body forces per unit mass, and \( \mathbf{p}^\alpha \) is the momentum exchange between fluid and solid phases. That is, \( \mathbf{p}^S \) corresponds to the loads the fluid exerts on the solid, and \( \mathbf{p}^F \) is due to the loads the solid exerts on the fluid. Hence, by virtue of the action-reaction law, \( \mathbf{p}^S + \mathbf{p}^F = \mathbf{0} \) is satisfied. Adding both momentum equations leads to the overall momentum balance,

\[ \nabla \cdot \mathbf{\sigma} + \rho \mathbf{g} = \mathbf{0}, \] (8)
which is the strong form of the linear momentum balance equation for the biphasic material in the current configuration. Here, the overall Cauchy stress tensor \( \sigma = \sigma^S + \sigma^F \) has been introduced, and we assume the only body force acting on the material is gravity such that \( b^S = b^F = \rho g \) and

\[
\rho \equiv \rho^{SR} \frac{n^S_{0S}}{J_S} + \rho^{FR} \left[ 1 - \frac{n^S_{0S}}{J_S} \right],
\]

is the deformation-dependent homogenized density of the biphasic material.

### 2.5. Weak form of the governing equations

The strong form of the governing equations (6) and (8) transferred to the reference configuration read

\[
\nabla_S \cdot W + J_S = 0 \quad \text{and} \quad \nabla_S \cdot P + \rho_0 \, g = 0,
\]

respectively, where \( W := w \cdot \text{cof} (F_S) \) and the volume-weighted seepage velocity \( w := n^F w_F \) have been introduced. The first Piola-Kirchhoff stress tensor is introduced. The first Piola-Kirchhoff stress tensor is

\[
\sigma^S \quad \text{of the "extra" terms (9).}
\]

Here, \( D \) is a measure of the internal dissipation, \( d(\bullet) \) is the rate of deformation tensor of the corresponding constituent velocity, \( d(\bullet) = \nabla^\text{sym} \psi(\bullet) \), and \( \psi(\bullet) \) is the strain-energy function of each constituent.

Proceeding from standard arguments of rational thermodynamics, the entropy inequality for a biphasic material in the current configuration is

\[
\mathcal{D} = \sigma^S : d_S - \tilde{\psi}_S + \sigma^F : d_F - \tilde{\psi}_F - \tilde{p}^F \cdot w_F \geq 0.
\]

Here, \( \mathcal{D} \) is a measure of the internal dissipation, \( d(\bullet) \) is the rate of deformation tensor of the corresponding constituent velocity, \( d(\bullet) = \nabla^\text{sym} \psi(\bullet) \), and \( \psi(\bullet) \) is the strain-energy function of each constituent.

The Cauchy stress tensors and the momentum exchange vectors of each constituent are defined in terms of the “extra” terms (9) and the unspecified pore (excess) pressure \( p \) as follows:

\[
\sigma^S = \sigma^S_E - n^S p 1, \quad \sigma^F = \sigma^F_E - n^F p 1 \equiv -n^F p 1,
\]

### 3. Thermodynamic basis and constitutive equations

#### 3.1. Clausius-Duhem inequality

The weak form of the linear momentum balance equation in the solid reference configuration is

\[
\int_{B_0} \nabla(\delta u) : \tau \, dV_{0S} - \int_{B_0} \delta u \cdot \rho_0 \, g \, dV_{0S} - \int_{\partial B_0^S} \delta u \cdot T^* \, dA_{0S} = 0 \quad \forall \delta u,
\]

where \( \delta u \) is the test function corresponding to the solid displacement and \( T^* \) is the prescribed traction vector on the boundary \( \partial B_0^S \). For convenience, we have introduced the Kirchhoff stress tensor \( \tau = J_S \sigma \) by replacing the energetically conjugate pair \((P, \delta F_S)\) given in the reference configuration, with the pair \((\sigma, \nabla (\delta u))\) given in the current one.

The weak form of the mass balance equation in the solid reference configuration is

\[
\int_{B_0} \delta p \, J_S \, dV_{0S} - \int_{B_0} \nabla(\delta p) \cdot w_J \, dV_{0S} + \int_{\partial B_0^S} \delta p \, Q^* \, dA_{0S} = 0 \quad \forall \delta p,
\]

where \( \delta p \) is the test function corresponding to the pore pressure \( p \), and \( Q^* \) is the prescribed fluid flow across the boundary \( \partial B_0^S \). Similarly to the linear momentum balance equation, we have replaced the product in the second integral to introduce the Kirchhoff-type volume-weighted seepage velocity \( w_J \).

The constitutive equations for the solid and fluid components in the current configuration, \( \tau \) and \( w \), respectively, must now be defined to complete the governing equations.
\[
\rho F p^F = -\rho S S = \hat{p}_F^E + p\nabla n^F.  \tag{16}
\]

Here, a perfect fluid is assumed such that no shear stresses are generated, and the viscous or frictional part of the fluid stress tensor can be neglected, \( \sigma_E^F \approx 0 \). Note, however, that the fluid viscosity is included via the production term \( \hat{p}_F^E \), also known as the effective drag force.

Considering the definitions above, the saturation condition, and introducing a Lagrangean multiplier that can be assimilated to the pore pressure \( p \), reduces the entropy inequality to

\[
D = S_S^E \cdot \frac{1}{2} \dot{C}_S - \dot{\Psi}_S - \dot{\Psi}_F - \hat{p}_F^E \cdot w_F \geq 0.  \tag{17}
\]

Here, the energetically conjugate pair \( (\sigma_S^E, d_S) \) has been replaced with the equivalent \( (S_S^E, \frac{1}{2} \dot{C}_S) \), where \( S_S^E \) is the second Piola-Kirchhoff stress tensor of the solid component. This substitution will prove useful in posterior derivations. Henceforth, we assume that the strain-energy function \( \Psi(\bullet) \) of a given constituent only depends on the variables included into the process by the constituent itself.

### 3.2. Constitutive equation for the pore fluid

We consider the strain-energy function \( \Psi_F = \rho_F \psi_F(n^F) \) for the pore fluid, where \( \psi_F(n^F) \) is the free-energy function of the constituent. Introducing the additional constitutive assumption that the energy potential of a fluid constituent does not recognize the domain where the fluid exists on further reduces \( \psi_F = \psi_F(-) \) since the volume fraction \( n^F \) is the local domain variable of the fluid constituent. Therefore, the time derivative of the fluid strain-energy function in (17) is null \( (\dot{\Psi}_F = 0) \).

The effective drag force \( \hat{p}_F^E \) is defined in terms of the general permeability tensor \( S \), which is related to experimental data through the intrinsic permeability tensor \( K_S^t \) via

\[
\hat{p}_F^E = -S \cdot w_F  \quad \text{with} \quad S = (n^F)^2 \mu_{FR}^{-1}(K_S^t)^{-1}.  \tag{18}
\]

Here, \( \mu_{FR} \) is the effective shear viscosity of the pore fluid. The intrinsic permeability tensor is deformation-dependent [45], and reads

\[
K_S^t = \left(\frac{J_S - n_{GS}^S}{1 - n_{GS}^S}\right)^\kappa K_0^S,  \tag{19}
\]

which allows accounting for the fact that, under excess compression values, the pores lock close and reduce the permeability of the material. Here, \( K_0^S \) is the initial intrinsic permeability tensor and the control parameter \( \kappa \geq 0 \) defines the nonlinearity of this deformation dependency.

Inserting the definitions of \( \sigma_F^E \) (15) and of \( \hat{p}_F^E \) (16) into the fluid momentum balance equation (7), and considering (18) results eventually in

\[
w = -\frac{1}{\mu_{FR}} K_S^t \cdot [\nabla p - \rho_{FR} \mathbf{g}],  \tag{20}
\]

which is the Darcy-like filter law defining the constitutive behavior for the fluid component.

### 3.3. Constitutive equation for the viscoelastic solid

We model viscoelasticity via the multiplicative decomposition of the deformation gradient tensor into elastic and viscous parts [16], i.e.

\[
F = F_S^e \cdot F_S^v  \tag{21}
\]

and the split of the strain-energy function of the solid component into an equilibrium part \( \Psi^{eq} \) and a non-equilibrium part \( \Psi^{neq} \),

\[
\Psi_S = \Psi^{eq}(C_S) + \Psi^{neq}(C_S^v).  \tag{22}
\]
The total and the elastic right Cauchy-Green tensors $C_S$ and $C^e_S$, respectively, are related through the viscous part of the deformation gradient tensor by

$$C^e_S = (F^e_S)^{-T} \cdot C_S \cdot (F^e_S)^{-1}. \quad (23)$$

Introducing the time derivative $\dot{\Psi}_S$ into the Clausius-Duhem inequality (17), considering $\dot{\Psi}_F = 0$, and rearranging the terms results in

$$D = \left[ S^E_S - 2 \frac{\partial \Psi_{eq}}{\partial C_S} - 2 \left( (F^e_S)^{-1} \cdot \frac{\partial \Psi_{neq}}{\partial C_S} \cdot (F^e_S)^{-T} \right) \right] : \frac{1}{2} C_S - \frac{\partial \Psi_{neq}}{\partial C^e_S} : \frac{\partial C^e_S}{\partial F^e_S} : \dot{F}^e_S - \dot{p}^e_F \cdot w_F \geq 0. \quad (24)$$

This expression must hold for any arbitrary deformation process and, thus, the first term in the brackets must be null, such that the inequality is reduced to

$$D = D_v + D_p \geq 0, \quad (25)$$

where the dissipation due to internal processes occurring within the viscous solid component is

$$D_v = - \frac{\partial \Psi_{neq}}{\partial C^e_S} : \frac{\partial C^e_S}{\partial F^e_S} : \dot{F}^e_S, \quad (26)$$

and the dissipation due to the seepage process related to the material porosity is

$$D_p = \mu^{FR} \left[ \left( K^S_i \right)^{-1} \cdot w \right] \cdot w \geq 0. \quad (27)$$

Here, (18) has been introduced. The intrinsic permeability is defined in (19), and the volume-weighted seepage velocity is given in (20). This expression is always non-negative, given that $\mu^{FR}$ and the components of $K^S_i$ are necessarily positive.

Addition of the constituent stresses defined in (14) and (15), and considering $\tau = J_S \sigma$, yields the Kirchhoff stress tensor as

$$\tau = \tau^S + \tau^F = \tau^S_E - p J_S \mathbf{1}, \quad (28)$$

where the saturation condition has been considered and the extra stress $\tau^E_E$ is obtained via the pushforward operation on $S^E_S$, i.e.

$$\tau^E_E = \tau^E_{eq} + \tau^E_{neq} = 2 F^e_S \cdot \frac{\partial \Psi_{eq}}{\partial C_S} \cdot F^e_S + 2 F^e_S \cdot \frac{\partial \Psi_{neq}}{\partial C^e_S} \cdot (F^e_S)^T. \quad (29)$$

Previous work in our group [1] has shown that a modified one-term Ogden model fits best the experimental data characterizing brain tissue response to mechanical loading. Yet, a recent study [46] argued that only an Ogden hyperelastic model with both negative and positive nonlinearity constants can predict the mechanical behavior of the brain tissue in three-dimensional non-homogeneous tension and compression loading scenarios. Hence, for the sake of generality, we will base both the equilibrium and non-equilibrium parts of the strain-energy function on the three-term Ogden material model. Then, the equilibrium part is split into an isochoric and a volumetric part according to

$$\Psi^{eq} = \Psi^{Ogd, eq} + U (J_S), \quad (30)$$

where the extension function

$$U (J_S) = \lambda \left( 1 - \frac{n^S_S}{n^O_S} \right)^2 \left[ J_S \left( J_S - 1 \right) - \ln \left( \frac{J_S}{1 - \frac{n^O_S}{n^O_S}} \right) \right] \quad (31)$$

describes the compressibility effects of the poro-viscoelastic material, including the concept of compactation point [36]. Here, $\lambda$ is the second Lamé parameter of the solid component.
isochoric elastic principal stretches \( \tilde{\lambda}_n \).

The corresponding isochoric equilibrium part of the Kirchhoff extra stress tensor is

\[
\mathbf{\tau}^\text{vol}_E = \lambda \left( 1 - n_{0S}^S \right)^2 \left[ \frac{J_S}{1 - n_{0S}^S} - \frac{J_S}{J_S - n_{0S}^S} \right] \mathbf{1},
\]

(32)

The three-term Ogden strain-energy function for the isochoric equilibrium part is

\[
\Psi_{\text{Ogd,eq}} = \sum_{i=1}^{3} \frac{\mu_\infty, i}{\alpha_\infty, i} \left[ \tilde{\lambda}_{S,1}^{\alpha_\infty, i} + \tilde{\lambda}_{S,2}^{\alpha_\infty, i} + \tilde{\lambda}_{S,3}^{\alpha_\infty, i} - 3 \right],
\]

(33)

where \( \alpha_\infty, i \) and \( \mu_\infty, i \) are equilibrium constitutive parameters and \( \tilde{\lambda}_{S,a} \), for \( a \in \{1, 2, 3\} \), are the isochoric principal stretches. These are related to the principal stretches \( \lambda_{S,a} \) through the Jacobian \( \lambda_{S,a} = J_S^{-1/3} \tilde{\lambda}_{S,a} \).

The corresponding isochoric equilibrium part of the Kirchhoff extra stress tensor is

\[
\mathbf{\tau}^\text{Ogd,eq}_E = \sum_{A=1}^{3} \beta_{\infty, A} \mathbf{n}_{S,A} \otimes \mathbf{n}_{S,A} \quad \text{with} \quad \beta_{\infty, A} = \sum_{i=1}^{3} \mu_\infty, i \left[ \tilde{\lambda}_{S,A}^{\alpha_\infty, i} - 1 \right] \left[ \tilde{\lambda}_{S,1}^{\alpha_\infty, i} + \tilde{\lambda}_{S,2}^{\alpha_\infty, i} + \tilde{\lambda}_{S,3}^{\alpha_\infty, i} \right],
\]

(34)

where \( \mathbf{n}_{S,A} \) are the eigenvectors of the left Cauchy-Green tensor \( \mathbf{b}_S = \mathbf{F}_S \cdot \mathbf{F}_S^T \), such that \( \mathbf{b}_S = \sum_{A=1}^{3} \tilde{\lambda}_{S,A}^2 \mathbf{n}_{S,A} \otimes \mathbf{n}_{S,A} \).

The non-equilibrium part of the strain-energy function is entirely isochoric and defined in terms of the isochoric elastic principal stretches \( \tilde{\lambda}_{S,a}^{\text{neq}} = (J_S)^{-1/3} \tilde{\lambda}_{S,a}^{\text{eq}} \), for \( a \in \{1, 2, 3\} \), as

\[
\Psi^{\text{neq}} = \Psi_{\text{Ogd,neq}} = \sum_{i=1}^{3} \frac{\mu_i}{\alpha_i} \left[ \left( \tilde{\lambda}_{S,1}^{\alpha_i} \right)^{\alpha_i} + \left( \tilde{\lambda}_{S,2}^{\alpha_i} \right)^{\alpha_i} + \left( \tilde{\lambda}_{S,3}^{\alpha_i} \right)^{\alpha_i} - 3 \right],
\]

(35)

where \( \alpha_i \) and \( \mu_i \) are the non-equilibrium constitutive parameters. The corresponding isochoric non-equilibrium part \( \mathbf{\tau}^\text{Ogd,neq}_E \) of the Kirchhoff extra stress tensor is

\[
\mathbf{\tau}^\text{Ogd,neq}_E = \sum_{A=1}^{3} \beta_A \mathbf{n}^e_{S,A} \otimes \mathbf{n}^e_{S,A} \quad \text{with} \quad \beta_A = \sum_{i=1}^{3} \mu_i \left[ \left( \tilde{\lambda}_{S,A}^{\alpha_i} \right)^{\alpha_i} - 1 \right] \left( \tilde{\lambda}_{S,1}^{\alpha_i} \right)^{\alpha_i} + \left( \tilde{\lambda}_{S,2}^{\alpha_i} \right)^{\alpha_i} + \left( \tilde{\lambda}_{S,3}^{\alpha_i} \right)^{\alpha_i} = \sum_{i=1}^{3} \mu_i \left[ \tilde{\lambda}_{S,A}^{\alpha_i} - 1 \right] \left[ \tilde{\lambda}_{S,1}^{\alpha_i} + \tilde{\lambda}_{S,2}^{\alpha_i} + \tilde{\lambda}_{S,3}^{\alpha_i} \right],
\]

(36)

where \( \mathbf{n}^e_{S,A} \) are the eigenvectors of the elastic part of the left Cauchy-Green tensor, \( \mathbf{b}_S^e = \mathbf{F}_S^e \cdot (\mathbf{F}_S^e)^T \), such that \( \mathbf{b}_S^e = \sum_{A=1}^{3} (\lambda_{S,A}^e)^2 \mathbf{n}^e_{S,A} \otimes \mathbf{n}^e_{S,A} \).

To a priori satisfy \( \mathcal{D}_v \geq 0 \), and with the assumption of isotropy, we choose the evolution equation [15] for the internal variable \( \mathbf{C}^S \), which is directly related to \( \mathbf{b}_S^e \), as

\[
- \mathcal{L}_v \mathbf{b}_S^e \cdot (\mathbf{b}_S^e)^{-1} \frac{1}{\eta} \mathbf{\tau}^{\text{neq}},
\]

(37)

where the additional parameter introduced, \( \eta > 0 \), is the viscosity of the solid component. Then, the viscous dissipation (26) is reduced to

\[
\mathcal{D}_v = \frac{1}{2\eta} \mathbf{\tau}^{\text{neq}} : \mathbf{\tau}^{\text{neq}} \geq 0,
\]

(38)

which is necessarily non-negative.

### 3.4. Reduction to nonlinear poroelasticity

The methods used to deduce the constitutive model of the solid component outlined above hold in the deduction of a nonlinear poroelastic formulation using Ogden hyperelasticity. In this case, the strain-energy function of the solid constituent (22) is replaced by

\[
\Psi = \Psi_{\text{Ogd}} + U(J_S),
\]

(39)
where the extension function has been given in (31) and the Ogden strain-energy function $\Psi_{\text{Ogd},\text{eq}}$ defined for the nonlinear viscoelastic model (33),

$$
\Psi_{\text{Ogd}} = \sum_{i=1}^{3} \frac{\mu_i}{\alpha_i} \left[ \tilde{\lambda}_{1i}^\alpha + \tilde{\lambda}_{2i}^\alpha + \tilde{\lambda}_{3i}^\alpha - 3 \right].
$$

Then,

$$
\tau_{\text{Ogd}}^E = \sum_{A=1}^{3} \beta_A \mathbf{n}_A \otimes \mathbf{n}_A
$$

with

$$
\beta_A = \sum_{i=1}^{3} \mu_i \left[ \tilde{\lambda}_{1i}^\alpha - \frac{1}{3} \sum_{j=1}^{3} \tilde{\lambda}_{ji}^\alpha + \tilde{\lambda}_{3i}^\alpha \right] \quad \text{is the corresponding isochoric part of the Kirchhoff extra stress tensor of the solid component.}
$$

The volumetric part is given in (32) as it remains the same as for the nonlinear poro-viscoelastic model. A detailed derivation of the formulation outlined here as well as the verification of the nonlinear poro-viscous reduction of our formulation with computational results published in the literature [36] are available in the supplementary material.

4. Numerical implementation

4.1. Time discretization of the governing equations

To rewrite the weak form of the mass balance equation (12) at time $t_{n+1}$, we consider the relationships

$$
\left( J_S \right)_{n+\beta} = \frac{\left( J_S \right)_{n+1} - \left( J_S \right)_n}{\Delta t} \quad \text{with} \quad \Delta t = t_{n+1} - t_n,
$$

where $t_n$ indicates the previous time step. The time-integration parameter $\beta \in [0, 1]$ regulates

$$
(\bullet)_{n+\beta} = (\bullet)_n + \beta \left[ (\bullet)_{n+1} - (\bullet)_n \right],
$$

and should be set to $\beta \geq 1/2$ based on a linearized analysis of accuracy and stability [47]. We will use $\beta = 1$ to recover a stable implicit one-step backward differentiation time integration. Then, the temporally discretized mass balance equation is

$$
\int_{B_0} \delta p \left[ \left( J_S \right)_{n+1} - \left( J_S \right)_n \right] dV_0 + \int_{B_0} \left( \nabla (\delta p) : J_S \mathbf{w} \right)_{n+1} dV_0 + \int_{\partial B_0^e} \delta p (\mathbf{Q}^*)_{n+1} dA_{0S} = 0 \quad \forall \delta \mathbf{p}. \quad (44)
$$

The linear momentum balance equation (11) is time independent and, hence, written directly at time $t_{n+1}$,

$$
\int_{B_0} \left( \nabla (\delta \mathbf{u}) : \tau \right)_{n+1} dV_0 - \int_{B_0} \delta \mathbf{u} \cdot (\rho_0)_{n+1} g dV_0 + \int_{\partial B_0^e} \delta \mathbf{u} \cdot (T^*)_{n+1} dA_{0S} = 0 \quad \forall \delta \mathbf{u}. \quad (45)
$$

4.2. Finite element implementation

These temporally discretized governing equations have been implemented in a finite element (FE) framework using the open source FE library deal.II [48]. We choose to linearize the governing equations using the automatic differentiation tools offered by the Sacado library available from the Trilinos software package. Then, only the components of the vector of residuals given below must be implemented. We also use the parallel functionality of Trilinos, which is built on top of the Message Passing Interface (MPI). The governing equations are linearized using forward automatic differentiation. The displacement residual is computed in terms of the temporally and spatially discretized linear momentum balance equation as

$$
R_u := \sum_{c=1}^{n_{\text{max}}} \int_{B_0} \mathbf{N}^u \cdot \rho_0 \ g dV_0 + \sum_{f=1}^{n_{\text{max}}} \int_{\partial B_0^e} \mathbf{N}^u \cdot T^* dA_{0S} - \sum_{c=1}^{n_{\text{max}}} \int_{B_0} \nabla \mathbf{N}^u : \tau dV_0 = 0, \quad (46)
$$
where the first two terms correspond to the external forces and the last term to the internal ones. The subscript \(n+1\) is dropped for clarity and the deal.II notation is followed, i.e. each of the three displacement shape functions correspond to a vector \(N^u\), and its gradient with respect to the spatial configuration is a second-order tensor \(\nabla N^u\). The operator \(\frac{A}{C}\) indicates summation over the \(n_{\text{max}}\) elements that form the spatially discretized domain. To advance the viscoelastic constitutive equation in time, we adopt the implicit exponential time integration scheme outlined in [7] with the same time step \(\Delta t\) as above.

The pressure residual derives from the temporally and spatially discretized mass balance equation and is

\[
R_p := - \Delta t \sum_{c=1}^{n_{\text{max}}} \int_{B_0} N^p \cdot Q^{*} \ dA_{0S} - \sum_{c=1}^{n_{\text{max}}} \int_{B_0} N^p \cdot [(J_S)_{n+1} - (J_S)_n] \ dV_{0S} + \Delta t \sum_{c=1}^{n_{\text{max}}} \int_{B_0} \nabla N^p \cdot (J_S)_{n+1} \ w \ dV_{0S} = 0.
\]

(47)

Here, the first term corresponds to the external fluxes, while the last two are due to the internal ones. The subscript \(n+1\) is dropped from terms other than \(J_S\) for clarity.

We use a direct method to solve monolithically for the unknown solid displacements and fluid (excess) pore pressure values. In all our examples quadratic shape functions are used to approximate the solid displacements, linear shape functions are used to approximate the pore pressure, and a quadrature of order 3 is considered. The complete code is provided in the supplementary material and available in the deal.II code gallery website.

5. Results

5.1. Consolidation experiments

We reproduced the geometry, boundary conditions and loading scenario described in [17], see Figure 3, where a human brain tissue sample was subjected to uniaxial confined compression under free drainage at the top and bottom faces of the specimen. We used the coarsest mesh possible which allowed us to reproduce the experimental set-up without locking or over-constraining the degrees of freedom.

Regarding the material model, we used the reduction to nonlinear poroelasticity described in Section 3.4. The mean values of the two-term Ogden model identified in the corresponding experimental study [17] were used for the solid component in our model: \(\mu_1 = 1.044\ \text{kPa}, \mu_2 = 4.309\ \text{kPa}, \alpha_1 = 4.305, \) and \(\alpha_2 = 7.736\). The second Lamé parameter required in the extension function was computed as

\[
\lambda = \frac{2\mu\nu}{1-2\nu} \text{ with } \mu = \frac{1}{2} \sum_i \mu_i \alpha_i,
\]

(48)

where a Poisson’s ratio \(\nu = 0.49\) was considered, resulting in \(\lambda = 334\ \text{kPa}\). As to the poroelastic parameters, we considered the effective shear viscosity of the fluid component to be that of water at room temperature, \(\mu^{FR} = 0.89\ \text{mPa} \cdot \text{s}\). As a simplifying hypothesis, the initial intrinsic permeability tensor was assumed to be isotropic, i.e. \(K_S^0 = K_S^0 \mathbf{1}\). In addition, the initial solid volume fraction was fixed at \(n_{0S}^S = 0.8\), following [30]. We adjusted the remaining values \((\kappa \text{ and } K_S^S)\) to obtain a reasonable fit to the experimental curve. Finally, the effect of gravity was included in the simulation, and the density of water at room temperature was assumed for both the solid and fluid effective densities, \(\rho^{SR} = \rho^{FR} = 0.997\ \text{mg/mm}^3\). The input file used is provided in the supplementary material.

Figure 4 shows that nonlinear poroelasticity with a purely hyperelastic solid component, i.e. neglecting viscous effects, is sufficient to accurately predict the consolidation response of brain tissue subjected to an oedometric test. Figure 5 illustrates how changing each of the porous parameters affects the consolidation response. With increasing initial solid volume fraction \(n_{0S}^S\), the consolidation rate decreases and fluid takes slightly longer to flow out of the loaded sample. We observe a similar trend for the deformation-dependency.
Figure 3: Details of the geometry, boundary conditions and loading used to numerically reproduce the consolidation response of human brain tissue measured in [17]. The computational model is comprised of 320 elements and 9544 degrees of freedom. Time steps of 2 s were considered, with residual and error tolerances of $10^{-6}$.

Figure 4: Nonlinear poroelasticity is sufficient to reproduce the experimental results from [17] for an uniaxial consolidation case on human brain tissue. A dead load was applied on the top surface, and both top and bottom surfaces had drained boundaries. The consolidation ratio is defined as the current value of the vertical shortening in the sample divided by its final shortening at the end of the consolidation process.
control parameter $\kappa$, which slows down the consolidation process with increasing values of $\kappa$. Conversely, an increase of the initial intrinsic permeability of the solid $K_S^0$ reduces the total consolidation time. The effective shear viscosity of the fluid $\mu^{FR}$ has the exact inverse effect to $K_S^0$, which is an expected outcome given in (20). An increase in $\mu^{FR}$ results in a slower consolidation rate, especially at the beginning of the process.

5.2. Cyclic experiments under multiple loading modes

We simulated the cyclic loading experiments detailed in previous publications by our group [7, 13] using both the reduced poroelastic material model and the full poro-viscoelastic model. The geometry, boundary conditions and loading patterns used in our simulations are described in Figure 6. Again, we used the coarsest mesh possible to still guarantee reasonable and consistent results. We used the same material parameters as in the previous subsection for the poroelastic examples. For the poro-viscoelastic examples, we considered the one-term Ogden hyperelastic and viscous parameters identified in [7]. The effects of gravity were neglected in all simulations. The input files used are provided in the supplementary material.

Figure 7 shows that nonlinear poroelasticity alone cannot capture the conditioning behavior of human brain tissue subjected to cyclic loading under shear, compression or tension. Viscosity must be introduced in the solid component to reproduce the preconditioning and hysteretic response observed in experiments. The nominal and shear stresses corresponding to our simulations are the $z$ and $x$ components, respectively, of the vector

$$T = \int \sigma \cdot n \, dA / A_0,$$

where $\sigma$ is the Cauchy stress tensor, $n$ is the outward unit vector of the loaded surface and $A_0$ is the original cross-section of the sample. The stretch corresponds to an averaged vertical stretch, $\lambda_z = 1 + \Delta u / H$, where $H$ is the initial height of the sample and $\Delta u$ is the imposed displacement, while the amount of shear is $\gamma = \Delta u / H$.

The poroelastic response does not show significant conditioning effects in the stress versus stretch plots of Figure 7. However, hysteresis and preconditioning are observed when computing seepage velocity versus pressure equivalent plots. Figure 8 shows the porous characteristics corresponding to the poroelastic compression example. The volume of fluid accumulated outside the sample is the sum of the fluid flow across the drained boundaries over time, which is computed as

$$Q^{total} = \int \int w \cdot n \, dA \, dt,$$

where $w$ is the volume-weighted seepage velocity and $n$ is the outward unit vector of the drained surface. The fluid reaction pressure is

$$R_p = \int -p \, dA / A_0,$$

where $p$ is the pore pressure of the fluid. The porous dissipation is computed as

$$D_p^{total} = \int \int D_p \, dV \, dt,$$

where the porous dissipation density rate $D_p$ is given in (27). We observe a delay in the porous response to loading, and more fluid flow across the boundary in the outward direction during compressive loading than back in during unloading. In addition, the porous dissipation increases over time and is directly related to the fluid flow, as predicted by (27).

Finally, Figures 9-11 illustrate the inhomogeneous response to loading for the poro-viscoelastic simulations. The maximum displacement of the loaded surface in all three loading modes (point B) result in the largest stress values throughout the simulation, as expected. Yet, for shear and compressive loading cases, fluid flow is barely present at this time step. Under tensile loading, however, a considerable amount of outward fluid flow is observed close to the bottom and top surfaces of the sample. Larger seepage velocity
Figure 5: Effect of each porous parameter on the consolidation response: initial solid volume fraction $n_{0S}^S$ (top left), deformation-dependency control parameter for the specific permeability $\kappa$ (top right), initial intrinsic permeability of the solid $K_0^S$ (bottom left), and effective shear viscosity of the fluid $\mu^{FR}$ (bottom right). The baseline response (dashed curve) in all cases corresponds to the model used to obtain the results presented in Figure 4 with a coarser mesh (40 elements, 1410 degrees of freedom), a lower load value (1 kPa) and neglecting gravitational effects to reduce computation times.
(a) For shear testing, displacement-driven loading was imposed on the bottom surface in the \(x\)-direction, with displacements in the \(y\)- and \(z\)-directions fixed.

(b) For compressive and tensile testing, displacement-driven loading was imposed on the top surface in the vertical direction, with displacements in the \(x\)- and \(y\)-directions fixed.

Figure 6: Geometry, boundary conditions, and loading patterns of the computational model to reproduce the biomechanical experiments on human brain tissue under multiple loading modes [7]. A total of 512 elements and 15468 degrees of freedom were used. Time steps of 0.1 s were considered, with residual and error tolerances of \(10^{-8}\).
Figure 7: Shear, compressive and tensile tests from [7] (top row) showing the representative pre-conditioning and hysteretic behavior for a specimen of human brain tissue subjected to three consecutive cycles of loading. Nonlinear poroelasticity alone is unable to predict the preconditioning and barely captures the hysteretic effects (center row). The complete poro-viscoelastic formulation can capture these features (bottom row) and reproduces the experimental results.
values consistently correspond with the faster loading rates (e.g., point A for shear; point C for compression; and point A for tension). However, the loading and unloading within a same cycle of a same loading mode is not symmetric. As an example, the peak seepage velocity values during loading are larger than during unloading (points A and C) for both the shear and compressive loading cases. Conversely, for the tensile loading case, we observe larger peak seepage velocity values during loading. The shear loading case also produces asymmetric results between the positive and negative loading directions of the same cycle (points A and D). Moreover, the first cycle shows different values of the mapped properties with respect to the subsequent ones for an equivalent loading value in all loading modes. For example, the second cycle under compressive loading has larger pressure, compressive stress and seepage velocity values than the first one (points A and D), but the first cycle under tensile loading has larger seepage velocity values at the point of maximum displacement than the corresponding point in the second one (points B and D).

6. Discussion

We have combined nonlinear poroelasticity with finite viscoelasticity following the Theory of Porous Media to reproduce mechanical behavior of brain tissue in response to multiple loading modes. The formulation, implemented using the finite element library deal.ii, has been made available to the community via the code gallery on the deal.ii website (https://www.dealii.org/code-gallery.html).

As far as we know, it is the first open-source poro-viscoelastic finite element formulation that is fully nonlinear and developed in a finite strain framework. Its modular and object-oriented design, as well as the automatic differentiation feature, will allow for easy extension of the formulation to include alternative constitutive models for the fluid and solid components, as well as additional features such as continuum growth of the solid part. Additional fields to account for swelling via osmolarity, and growth proportional to cell density or morphogen concentrations, to name a few, should be straightforward to add. All in all, the numerical framework presented in this study has the potential to become a versatile and useful tool in elucidating the rheology of brain tissue behavior.

The porous part of the formulation has been verified using previously published computational results [36]. We have computationally reproduced testing set-ups characterizing different aspects of human brain tissue responses described in [17] and [13]. We have identified the porous properties in our model via the uniaxial deformation at free drainage [17], which characterizes its consolidation behavior. To determine...
Figure 9: FE results for the poro-viscoelastic simulation reproducing the biomechanical experiments on human brain tissue under cyclic shear loading.
Figure 10: FE results for the poro-viscoelastic simulation reproducing the biomechanical experiments on human brain tissue under cyclic compressive loading.
Figure 11: FE results for the poro-viscoelastic simulation reproducing the biomechanical experiments on human brain tissue under tensile shear loading.
the viscous parameters, tests that provide the conditioning and hysteretic response of the tissue [13] were used. Our computational predictions qualitatively agreed with the experimental results, allowing us to study individual viscous and porous effects in different loading scenarios.

6.1. Nonlinear poroelasticity reproduces consolidation experiments

The nonlinear poroelastic formulation alone can reproduce the consolidation tests described in [17], as shown in Figure 4. Unlike the poroelastic analytical modeling approach used in the original study, we were able to predict the experimental results without need of a viscous phase by adjusting the porous parameters in our finite element model, see Figure 5.

A handful of computational studies have used different poroelastic modeling approaches to capture fluid effects in brain tissue behavior, especially in cerebral oedema [32, 33], tumor growth [35] and drug-delivery applications [30, 31]. In this study we confirmed that brain tissue should be modeled as a fluid-saturated porous material to adequately predict its response to oedometric deformations. In addition, we showed that there seems to be no significant viscous contribution under such loading conditions and nonlinear poroelasticity is sufficient to fully capture the consolidation process in brain tissue.

6.2. Poroelasticity alone is not sufficient to capture stress conditioning due to cyclic loading

The nonlinear poroelastic formulation cannot capture the stress conditioning effects due to biomechanical cyclic loading on brain tissue [13] unless the solid component is modeled as viscoelastic. Figure 7 shows that the poroelastic model calibrated with the consolidation tests are unable to predict the preconditioning and hysteretic response. However, the poro-viscoelastic formulation closely matches the computational predictions of the viscoelastic model our group published in previous studies [7, 15].

Our results support the notion that brain tissue modeling must include both porous and viscous contributions to adequately capture its response to a wide range of loading scenarios under a single modeling framework. We have begun to explore the separate effects of the porous and viscous phases, but further studies, both computational and experimental, are needed to disentangle their specific contributions to the overall tissue response.

6.3. Poroelastic response exhibits preconditioning and hysteresis in fluid flow space

Despite the fact that the results obtained with the nonlinear poroelastic model in Figure 7 do not seem to capture the preconditioning and hysteresis in the stress versus stretch curves, the model does present conditioning characteristics. While exploring the effect of the porous parameters on these responses, we realized that conditioning in the stress space is mostly a manifestation of the viscous dissipation. The constitutive law governing the viscoelastic solid component (28) defines the Kirchhoff stress tensor \( \mathbf{\tau} \) in terms of the displacement variables \( \mathbf{u} \), with a hydrostatic contribution associated with the fluid pore pressure \( p \). The behavior of the fluid component (20) is defined by the volume-weighted seepage velocity \( \mathbf{w} \), which is proportional to the gradient of the pressure variable \( p \), and to the deformation-dependent intrinsic permeability tensor. Thus, these two constitutive models are weakly coupled, which could explain the slight hysteresis observed in the stress space for the poroelastic response to compressive and tensile loading.

However, our formulation predicts a larger amount of porous dissipation (27), which should produce conditioning effects elsewhere. We determined that the variable space related to the fluid flow and pressure was where the effects of such dissipation should appear. Indeed, Figure 8 (left) shows a marked hysteresis and preconditioning when plotting an equivalent to the nominal stress versus average stretch on the loading surface, but for the quantities associated with the fluid material model, i.e. seepage velocity across drained boundaries versus averaged pressure on the loading surface. The plots over time given in the same figure (right) confirm that there is a preconditioning effect. We observe that the first loading cycle differs from the subsequent ones, with a larger amount of fluid leaving the sample in the former.

In conclusion, we have identified a clear conditioning effect of the porous contribution in brain tissue response using a nonlinear poroelastic formulation without any viscous component. Past studies have used poroelastic formulations to predict brain tissue behavior on the basis of the observed biphasic nature of the tissue structure. It is generally agreed upon that free flowing fluid within the tissue and its effects on the
observed macroscopic response to loading under different drainage conditions can potentially be captured through poroelasticity. Yet, how porous behavior exactly contributes to conditioning in the response has been barely examined. Our group discussed in previous publications [1, 15] the need to identify the timescale and extent of porous effects, and differentiate them from the viscous contribution. The computational framework presented here sets the basis for future modeling studies to help elucidate the porous effects in brain tissue response, and how these are related to behaviors like conditioning and hysteresis, that have up to now mostly been attributed to viscous effects.

6.4. Porous and viscous effects are highly interrelated

We examined the response of the poro-viscoelastic model to the different loading modes and observed some differences in the global trends with respect to the poroelastic equivalents. Namely, the amount and the direction of the fluid flow across the drained boundaries of the sample changes significantly between the poroelastic model and its poro-viscoelastic counterpart (e.g., see videos provided in the supplementary material). This, in turn, affects the outgoing fluid flow pattern shown in Figure 8 that is associated with the porous dissipation. We have seen that the relation between the porous and viscous parameters can totally reverse the final average direction of fluid flow, which is counter-intuitive to the physical interpretation of the experimental set-up.

It is important to note that the parameters of the solid component used in the poroelastic model have been adjusted using separate experiments to the ones in the poro-viscoelastic model. Thus, we cannot extract any conclusions regarding porous and viscous effects in brain tissue behavior from the insights gained about the interrelations between the viscous, porous and elastic parts of our formulation, beyond the fact that their effects are decidedly coupled. This had already been suggested in the literature [5, 38] and, albeit we are unable to shed light on the nature of brain tissue response, our numerical formulation confirms that porous and viscous contributions are interconnected.

In addition, our computational observations, see Figures 9-11, agree with recent studies [1, 46] on the importance of the loading and boundary conditions selected in modeling approaches. The inhomogeneous stretch and pressure distributions in the modeled tissue directly dictate the viscous and porous behavior of the sample. Again, we would need to conduct a thorough parameter identification and sensitivity study to be able to extract meaningful relations between the separate model components.

6.5. Additional experiments are required to test viscous versus porous effects

Current experiments do not allow us to satisfactorily distinguish between the porous and viscous parts of brain tissue response to loading. Exhaustive experiments to characterize human brain tissue to date have used set-ups conceived for the characterization of solid materials. A few studies attempted to measure the porous behavior of different brain tissues, but a comprehensive and systematic characterization of the biphasic nature of human brain tissue is lacking. New testing set-ups must be designed, with the poro-viscoelastic modeling framework in mind, that will allow us to isolate the different responses and unequivocally identify the corresponding parameters in the model.

In addition, testing set-ups should be carefully optimized to ensure controllable boundary conditions that are computationally reproducible. For example, in Figure 7, our poro-viscoelastic model predicts lower shear stresses for the initial segment of the first shear loading cycle than for the first segment in subsequent cycles, while the experimental results show the opposite trend. This might be related to initial effects of the fluid being put into motion, given that the experimental protocol started with simple shear experiments while the other loading modes were performed consecutively. Therefore, new tests must be ideated, based on insights from computational simulations, to ensure the computational reproducibility of experimental set-ups as well as the identification and isolation of porous effects.

Through this approach we will be able to reliably elucidate the porous versus viscous contributions in brain tissue response and, potentially, obtain a computational model capable of predicting brain tissue behavior in a wide range of experimental set-ups or loading conditions. In this study we have focused on oedometric tests and cyclic tests under multiple loading modes, but such a calibrated model should be able to predict other types of experimental results, like those obtained from nanoindentation or rotational rheometry testing set-ups.
A single model that can account for multiple loading scenarios across different spatial and temporal scales will help us to identify and associate specific aspects of the observed tissue response to the underlying tissue structure, a first step to advance towards microstructurally-motivated material laws. These are key for future modeling approaches to inform personalized computational models to aid in the study, prevention and treatment of neurological disorders known to have a strong biomechanical component.

7. Conclusions

*In silico* medicine and patient-specific simulations can aid in the prevention and treatment of certain neurological disorders, reducing in this way the societal burden as well as the economic and personal impact of these injuries and diseases. To provide feasible approaches within this context, it is essential that we develop a realistic model of human brain tissue behavior that can capture the main characteristics of brain tissue response to multiple loading scenarios. We present a unified model to capture both fluid flow and conditioning aspects of brain tissue behavior in addition to its well-established nonlinear and compression-tension asymmetric characteristics. The proposed finite element formulation brings together a nonlinear biphasic poroelastic formulation developed within the context of the Theory of Porous Media with a finite viscoelastic model. Our computational model can predict the consolidation behavior of human brain tissue under oedometric testing as well as the nonlinearity, tension-compression asymmetry, preconditioning and hysteresis of human brain tissue subjected to cyclic loading under multiple loading modes. The results obtained in this study support the idea that porous and viscous effects are interconnected. However, additional experiments and novel testing set-ups are needed to be able to reliably identify the parameters governing the porous and viscous components in our model. Only then, we will be able to understand the role of the porous and viscous contributions to human brain tissue behavior and, ultimately, relate them to its microstructure and mechanobiological functions. The full open-source code is available online and its modular, object-oriented design using automatic differentiation provides a solid foundation for future extensions of the material models as well as code functionality. Our contribution is a first step towards the development of a reliable and comprehensive biomechanical model for brain tissue, which could ultimately serve as the cornerstone of personalized computational simulations to help the biomedical and clinical communities in the study, prediction and treatment of brain injury and disease.

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