Challenges and perspectives in brain tissue testing and modeling

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While long underestimated, more and more evidence confirms that mechanics play a critical role for brain function and dysfunction. Therefore, computational simulations based on the field equations of nonlinear continuum mechanics can provide important insights into the underlying mechanisms of brain injury and disease. Realistic numerical predictions, however, require models capable of capturing the complex and unique mechanical behavior of this ultrasoft, highly heterogeneous and adaptive tissue. In recent years, contradictory experimental results have retarded progress in this field. Here, we summarize the key characteristics of brain tissue behavior on different length and time scales and propose application-specific modeling approaches, which are as complex as necessary but as simple as possible. The presented considerations will, on the one hand, facilitate well-designed future experiments and, on the other hand, help to choose the appropriate constitutive law for a specific application.

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1 Introduction

Computational mechanics is a valuable tool to mechanistically understand pathological conditions associated with the human brain. To date, brain tissue remains one of the least understood tissues in the human body. Due to its ultrasoft, gel-like, and biphasic nature, its mechanical response is highly sensitive to the length and time scales during loading. In addition, brain tissue displays a high degree of microstructural heterogeneity. Therefore, the mechanical characterization of brain tissue has been challenging, both from an experimental and a modeling perspective.

In the following, we propose mechanical modeling approaches to capture the different aspects of brain tissue behavior and discuss open challenges. We further demonstrate why constitutive models have to be carefully chosen according to the application of interest.

2 Experimental characterization of brain tissue

Depending on the testing techniques, different aspects of the complex mechanics of brain tissue control the recorded response, as illustrated in Figure 1. Despite some inconsistencies regarding previous results in the literature, there are certain well-established characteristics that have been observed independent of the testing method. The response of brain tissue is

• nonlinear and compression-tension asymmetric with significantly higher stresses in compression than in tension [3].
• strain-rate-dependent, where stresses increase with increasing loading rate [2, 15].
• highly hysteretic and conditioning with higher stresses and larger hysteresis during the first loading cycle than during subsequent cycles. Importantly, conditioning effects are recoverable [3].
• mechanically not notably anisotropic [3], while diffusion properties may indeed show certain direction-dependencies.
• region-dependent, wherein regional trends highly depend on the time and length scales during loading [3].

Other experimental observations remain equivocal, for instance the influence of age, death, and post mortem time.

3 Mechanical characterization of brain tissue

The value of a computational simulation critically depends on the adequate choice of constitutive models. Those need to capture the various experimentally observed aspects of brain tissue behavior, as summarized in Section 2. In the following, we propose mathematical formulations to model the specific time-independent and time-dependent response of brain tissue.

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Fig. 1: a) Mechanical testing techniques and their range of application. AFM atomic force microscopy; IND indentation; MMT multiaxial mechanical testing; OST oscillatory shear testing; MRE magnetic resonance elastography; NDG neurodegeneration; NRG neuroregeneration; DAI diffuse axonal injury; TG tumor growth; NPH normal pressure hydrocephalus; NDV neurodevelopment; NS neurosurgery; TBI traumatic brain injury. b) Sensitivity of the evolving surface morphology during brain development towards the material parameters used in finite element simulations. With increasing material nonlinearity from top to bottom, the wavelength increases. Adapted from [6].

Fig. 2: Effects of inhomogeneous deformation. a) Analytically determined material parameters for brain tissue from the cortex lead to an overestimation of compressive and tensile stresses and an underestimation of shear stresses when used in finite element simulations. b) Finite element simulations reveal the inhomogeneous deformation and stress states during simple shear as well as uniaxial compression and tension loadings, which can be observed during experiments. Adapted from [6].

3.1 Finite hyperelastic constitutive model for brain tissue

For extremely slow loadings, time-dependent effects such as hysteresis and conditioning are negligible, and we may limit ourselves to time-independent effects, the nonlinearity and compression-tension asymmetry. To model the hyperelastic response of brain tissue, we postulate the existence of a strain-energy function \( \psi(F) \), which is defined per unit reference volume and only depends on the deformation gradient \( F \). Previous studies have shown that the one-term Ogden model, i.e. \( \psi = 2 \mu [\lambda_1^\alpha + \lambda_2^\alpha + \lambda_3^\alpha - 3] / \alpha^2 \), best represents the hyperelastic response of brain tissue under multiple loading conditions [3].

Depending on the loading conditions, it may be appropriate to model brain tissue as an incompressible or compressible solid [10]: If movement of free flowing cerebrospinal fluid into the ventricles and the subarachnoid space is possible, for instance during slow processes such as brain development, brain tissue effectively changes its local volume. Therefore a slight compressibility with a Poisson’s ratio of 0.45 to 0.49 seems appropriate [1]. In this case, we may add a volumetric contribution to the modified one-term Ogden model [8, 13] \( \psi = \psi_{\text{iso}} + \psi_{\text{vol}} = 2 \mu [\lambda_1^\alpha + \lambda_2^\alpha + \lambda_3^\alpha - 3] + \frac{\kappa}{4} [J^2 - 1 - 2 \ln J] \), where \( \psi_{\text{iso}} \) describes the isochoric response, \( \psi_{\text{vol}} \) describes the purely volumetric response, \( \lambda_a = J^{-1/3} \lambda_a \) with \( a = \{1, 2, 3\} \) are the volume-preserving parts of the principal stretches, and \( \kappa \) denotes the bulk modulus.
Figure 2a illustrates that the one-term Ogden model is capable of inherently capturing the main characteristics of the time-independent response of brain tissue from the cortex [3], the nonlinearity and the compression-tension asymmetry. It is capable of representing multiple loading modes simultaneously. The analytical model fit in Figure 2a (dashed curves) is based on the assumption that brain tissue deforms homogeneously during loading. When used in finite element simulations, however, the corresponding material parameters tend to overestimate compressive and tensile stresses, and underestimate shear stresses (Figure 2a, solid curves) as the actual deformation displays certain inhomogeneities (Figure 2b). To address these limitations, we recommend calibrating the material parameters with inverse identification schemes in the future.

3.2 Finite viscoelastic constitutive model for brain tissue

The hyperelastic constitutive model presented in Section 3.1 cannot capture the characteristic time-dependent effects, the highly hysteretic behavior, the significant strain-rate-dependence, and the characteristic conditioning, as pointed out in Section 2. To additionally model these viscoelastic effects of brain tissue behavior, we decompose the deformation gradient into elastic and viscous parts \( F = F^e \cdot F^v \), where \( i = 1, \ldots, m \) denotes the parallel arrangement of \( n \) viscoelastic elements. Motivated by our previous experimental findings [3], we assume an isotropic, incompressible material response for both the elastic and the viscoelastic behavior. We thus introduce the viscoelastic free-energy function \( \psi \) as the sum of three terms, an equilibrium part \( \psi^{eq} \), a non-equilibrium part \( \psi^{neq} = \sum_{i=1}^{m} \psi_i \), and a term \( p [ J - 1 ] \) that enforces the incompressibility constraint \( J - 1 = 0 \) via the Lagrange multiplier \( p \). We adopt a modified one-term Ogden model, which best represents the hyperelastic response of brain tissue [3], parameterized in terms of the total stretches \( \lambda_i \) for the equilibrium energy, \( \psi^{eq} = \frac{2\mu_u}{\alpha^2} [ \lambda_1^{\alpha_1} + \lambda_2^{\alpha_2} + \lambda_3^{\alpha_3} - 3 ] \), and the deviatoric elastic principal stretches \( \tilde{\lambda}^{(e)}_{ia} = (\tilde{\lambda}^{(e)}_i)^{-1/3} \lambda^{(e)}_{ia} \) for the non-equilibrium energy, \( \psi_i(\tilde{\lambda}^{(e)}_{ia}) = \frac{2\mu_u}{\alpha^2} [ \tilde{\lambda}^{(e)}_{i1} + (\tilde{\lambda}^{(e)}_{i2})^{\alpha_1} + (\tilde{\lambda}^{(e)}_{i3})^{\alpha_2} - 3 ] \). The equilibrium and non-equilibrium Kirchhoff stress tensors are then calculated as \( \tau^{eq} = \sum_{a=1}^{3} \sum_{n=1}^{\infty} \lambda_i n_a \otimes n_a \) and \( \tau^{neq} = \sum_{a=1}^{3} \tau_i \), with \( \tau_i = \sum_{a=1}^{3} \frac{\partial \psi_i}{\partial \lambda_i} \lambda_i n_a \otimes n_a \), respectively. To conform to the reduced dissipation inequalities for each individual mode \( i \), \( D^{reduced} = -\tau_i \cdot \frac{1}{\eta_i} [ \mathcal{L}_i b_i \cdot (b_i')^{-1} ] \geq 0 \), we prescribe evolution laws for the viscous dampers as \( -\mathcal{L}_i b_i \cdot (b_i')^{-1} = \frac{1}{\eta_i} \tau_i \), with \( b_i = \sum_{a=1}^{3} (\lambda_i^{(e)} a) n_a \otimes n_a \) to specify the temporal evolution of the viscoelastic kinematics [4,11]. Finally, for comparison with the experimental measurements in [3], we calculate the Piola stress tensor \( P \) as the partial pull back of the Kirchhoff stress tensor, i.e., \( P = \tau \cdot F^{-1} = [ \tau^{eq} + \tau^{neq} - p I ] \cdot F^{-1} \).

The proposed finite viscoelastic model, which combines the hyperelastic one-term Ogden model with two viscoelastic elements, can, in addition to the experimentally observed compression-tension asymmetry and nonlinearity, capture time-dependent effects including hysteresis and the successive softening for stepwise loading [4]. A single set of material parameters is sufficient to simultaneously fit cyclic loadings and the early and late relaxation behavior of brain tissue from the cortex, as illustrated in Figure 3 [4].

While the simultaneous analysis of multiple loading conditions has significantly improved the parameterization compared to previous viscoelastic models based on a single loading mode [9,14], the asymmetry predicted by the model in Figure 3 is still less pronounced than observed in experiments. Furthermore, the parameters are based on the assumption of a homogeneous deformation state. To improve the fit of the model, an inverse parameter identification scheme could be used in the future to potentially address the issues discussed in Figure 2.

4 Application-specific choice of constitutive models

The complexity of the brain tissue response highly depends on the loading conditions and so does the appropriate modeling approach. Depending on the time and length-scales during a certain application, a different constitutive structure may be expedient. To save computational cost, it is advisable to choose a model that is as complex as necessary, but as simple as possible. Slow processes such as brain surgery may be modeled using finite hyperelasticity, moderately fast processes such as brain development may be modeled with visco- and poro-elastic effects, and extremely fast processes such as brain injury are dominated by stiffening effects at very high rates due to the incompressible fluid trapped inside the tissue. Besides the model structure, it is essential to choose appropriate material parameters with regard to the loading conditions of interest. Figure 1b impressively demonstrates that while the hyperelastic Ogden model with material nonlinearity on the order of \( \alpha \approx -20 \) well represented multiple loading modes in Figure 2a, it leads to unrealistic results when used for simulations of cortical folding during brain development [1]. This can be attributed to the fact that strains in the valleys of the developing cortical folds are much higher than those during the experiments; the model predicts unphysiologically high stresses for larger strains. We may therefore conclude that material parameters should always be calibrated from loading conditions, strains, strain rates, and loading modes, which are comparable to those relevant for the application of interest. For extreme loading rates, very fast and slow loadings, the hysteresis closes and the response follows the same path during loading and unloading. In both cases, we may use the hyperelastic formulation as a first approximation, but, importantly, with different sets of material parameters. During slow loadings, the fluid inside brain tissue is free to escape and doesn’t contribute to tissue stiffness; during fast loadings, the fluid offers resistance yielding a significantly higher stiffness. In general,
the nonlinearity, quantified by the parameter $\alpha$, decreases with increasing strain rate, while the shear modulus $\mu$ increases. As brain tissue is a biphasic material, for certain applications it will be inevitable to explicitly model the biphasic nature of brain tissue, e.g., through the theory of porous media [7]. Importantly, poro-elasticity alone is not sufficient to capture the highly hysteretic response of brain tissue [10] so that a poro-viscoelastic model should be used. One drawback is that the data available in the literature are to date not sufficient to adequately calibrate poro-viscoelastic constitutive models.

If we succeed in resolving the remaining challenges in the mechanical testing, modeling, and simulation of the brain, computational mechanics may valuably advance daily clinical practice by assisting diagnosis and treatment of neurological diseases.

Acknowledgements  The financial support by the German Research Foundation grants STE 544/50 and BU 3728/1-1 as well as the Emerging Talents and Emerging Fields Initiative by the FAU to PS and SB, and by the National Science Foundation grant CMMI 1727268 as well as the Stanford Bio-X IIP seed grant and the Humboldt Research Awards to EK is gratefully acknowledged.

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