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A combined experimental, modeling, and computational approach to interpret the viscoelastic response of the white matter brain tissue during indentation

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ABSTRACT

Viscoelastic properties of the white matter brain tissue are systematically studied in this paper utilizing indentation experiments, mathematical modeling, and finite element simulation. It is first demonstrated that the internal stiffness of the instrument needs to be thoroughly obtained and incorporated in the analysis as its contribution to the recorded mechanical response is significant for experiments on very compliant materials. The flat-punch monotonic indentation is then performed indirectly on sagittal plane slices with pushing a large rigid coverslip into the sample surface. The recorded load and displacement data are used for calibrating different viscoelastic models and presenting numerical values for the model elements. Consequently, the accuracy of the findings based on the theoretical models is investigated by performing finite element simulations which suggest a considerable substrate effect that causes violation of the semi-infinite half-space assumption in modeling of the material behavior. Accordingly, correction factors for adjusting the viscoelastic constants are obtained and presented. Since the Maxwell model shows a superior capability in rendering the mechanical response of the brain, an extension of this model to Multimode Maxwell viscoelastic solid is proposed for modeling the tissue behavior under a more complex load-hold-unload indentation cycle that shows acceptable agreement with experimental observations.

1. Introduction

Mechanical aspects of the brain tissue, which is regarded as an extremely vulnerable organ during impact and blast loading conditions, have recently attracted researchers in the field of biomechanics (Kuhl, 2016; Prevost et al., 2011). Besides externally imposed traumatic situations, mechanics has been shown to have a consequential role during growth and folding (Bayly et al., 2014; Budday et al., 2014; Tallinen et al., 2016), and also some pathological conditions of the brain tissue (Murphy et al., 2011; Stewart et al., 2017; Streitberger et al., 2012, 2011). While the timescale of these phenomena ranges from milliseconds to years, studying the rate dependent mechanical characteristics of the brain is of essential importance in modeling and simulations that seek enhancing design criteria for protective devices like helmets, or understanding the mechanisms involved in pathobiological conditions of the brain.

Brain tissue exhibits a strong rate dependent behavior which can be satisfactorily expressed in terms of viscoelastic models in the realm of small deformation. Accordingly, the viscoelastic characterization of the brain has received considerable attention during recent years. In the direct mechanical testing scheme, viscoelastic characterization can be performed via two different procedures. The first approach is applying cyclic loads (or displacements) at different amplitudes and frequencies which might be termed as the frequency domain viscoelastic characterization. Many researchers have used this approach for examining the frequency and regional dependent viscoelastic properties of the brain tissue. For example, Bilston et al. (1997) reported storage and loss moduli of the bovine brain samples via shear rheometery; Arbogast and Margulies (1998) investigated the effect of the orientation of the axonal bundles of the brainstem on its viscoelastic response during oscillatory shear tests; Nicolle et al. (2004) measured the interregional variation of the linear viscoelastic shear modulus of porcine and human brain tissues and also proposed a visco-hyperelastic model for the brain; Hrapko et al. (2008) scrutinized the anisotropy, temperature, and precompression dependence of the dynamic shear response of the brain; and Samadi-Dooki et al. (2017) explored the anisotropy, inhomogeneity, and postmortem time dependence of the viscoelastic moduli through indirect oscillatory flat-punch indentation.

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Nevertheless, numerical interpretation of the rate dependence of the viscoelastic properties from frequency dependent results is not easy in general. In addition, performing numerical simulation for model calibration and further developments based on frequency dependent parameters is complicated and costly in terms of the required computational resources.

Another approach for viscoelastic characterization of the materials is studying the temporal variation of the mechanical resistance for parametric modeling of the material behavior which is termed as time domain viscoelastic characterization in here. For the brain tissue, use of this method has mostly been limited to investigation of the relaxation behavior of the tissue. For example, Takhounts et al. (2003) examined different linear and nonlinear viscoelastic models to interpret the relaxation behavior of bovine and human brain tissues; Elkin et al. (2011) utilized microindentation experiments to investigate interregional variation of the relaxation modulus of porcine brains using Prony series fitting scheme; Chen et al. (2015) incorporated the same technique to evaluate the inhomogeneity of the porcine white matter brain tissues using a 5 *mm* flat circular probe; and Budday et al. (2015) compared the stress relaxation properties of the bovine brain white and gray matters. The results of the relaxation studies can be conveniently used in commercial finite element simulation packages, however, the values obtained for viscoelastic constants based on relaxation may not accurately reflect the rate dependent behavior in other loading conditions (load ramp, creep, etc.).

According to the aforementioned limitations of the available information on the viscoelastic characteristics of the brain tissue, physical and numerical parametrization of the viscoelastic response of the brain yet require thorough and in depth investigation to better reflect the overall rate dependent behavior of this tissue. In addition, the extremely soft nature of the brain tissue necessitates considering the effect of the internal response of the testing instrument on the recorded overall load and/or displacement. In fact, the scatteredness of the reported mechanical properties of the brain tissue from different studies (up to 2 orders of magnitude (Chatelin et al., 2010)) implicitly suggests a considerable effect of the testing machine on the obtained results which have been poorly incorporated in the post-test analyses. Moreover, some boundary conditions which are "assumed" for post-test analyses of the experimental information are generally developed for stiff solids and might require to be revisited for soft materials. For example, in instrumented indentation experiments, the effect of the substrate is generally neglected if the total indentation depth is below a certain portion of the total sample thickness, regardless of the impression expansion size. This assumption is valid for indentation of stiff solids which is usually accomplished using a sharp tip. However, for the case of soft materials where a bigger probe size is used, substrate effect might not be negligible, even for shallow indentations (Finan et al., 2014).

This paper is aimed at studying different basic viscoelastic models for the white matter brain tissue through presenting an analytical-numerical procedure that can give physical insight into the nature of the rate dependent deformation behavior. Indentation technique is used in this study as a powerful method for mechanical characterization of biological materials with requiring minimal amount of tissue and sample preparation, and providing fast data acquisition within short postmortem time (Budday et al., 2015; Feng et al., 2017a, 2017b, 2013; Gefen and Margulies, 2004). Accordingly, experimental observations of the indirect flat-punch indentation during which the indentation load is transferred from a flat end probe to the tissue indirectly via a large circular coverslip, are theoretically and numerically analyzed. In this way, contribution of the internal stiffness of the instrument to the overall load-displacement curves, which is shown here to be significant, is first obtained. Next, different viscoelastic models are parametrized with curve fitting the indentation load and displacement information. While it is demonstrated that the Maxwell and Standard Maxwell models can appropriately interpolate the experimental curves, the accuracy of the numerical values based on the curve fitting process is then investigated with using them as input parameters for a set of dynamic finite element simulations. Since the simulation results show a considerable discrepancy with the experimental values suggesting a violation from the assumptions of the theoretical modeling during experiments, correction factors for adjusting the viscoelastic constants are obtained and presented in this work. Despite the previous trial and error optimization based methods for evaluating the mechanical properties of soft materials (Liu et al., 2009), the correction method presented in this work requires only one set of readjustment of the numerical model parameters which saves considerable amount of time and computing resources. Finally, the appropriateness of the Maxwell model is further investigated and developed with proposing a general Multimode Maxwell model for the brain and comparing the load-hold-unload indentation cycles based on experiments and numerical simulations. Accordingly, the closed-form mathematical solution for the flat-punch indentation force due to the applied piecewise linear displacement field is derived and presented. The model parameters including springs and dampers, and their associated time constants are analytically obtained and numerically confirmed.

2. Materials and methods

2.1. Sample preparation

Seven brains from adult dogs (3–4 years of age) were obtained as byproducts of an IACUC approved study from the School of Veterinary Medicine of LSU. Following the humane euthanasia via overdose of pentobarbital (Beuthanasia-D Special, Merck & Co. Inc., Madison, NJ) at 90 mg/kg intravenously, brains were removed immediately and placed in physiological saline solution. They were then transported to the testing location in an ice-cooled box within 15 min. At the testing location, brains were maintained at 4 °C in a refrigerator; and prior to testing, they were allowed to warm to the room temperature for 10 min. For indentation experiments, sagittal slices of ~10 mm thickness were made using a sharp knife since cuts in this direction expose the maximum apparent white matter area compared to other directions. In addition, the sagittal direction has shown to minimally benefit from the axonal tracts reinforcing effect during indentation tests (Samadi-Dooki et al., 2017), hence, testing this direction reveals a more homogeneous response of the cellular matrix within the white matter. All of the samples were tested within 5 h postmortem to reduce tissue degradation due to factors such as protein decay and necrosis (Ferrer et al., 2007).

2.2. Indentation apparatus

Indentation tests were carried out using an Agilent T-150 UTM instrument (Fig. 1-a) with the theoretical displacement and load resolutions of less than 0.01 nm and 50 nN, respectively. Indirect monotonic indentation scheme is used in this study during which the indentation load is transferred from the indenter's tip to the tissue surface via a round coverslip (Samadi-Dooki et al., 2017). To ensure the homogenous behavior of the tissue under the indentation loading, a relatively large coverslip (5 mm radius and 0.15 mm thick) is used. This size of the loading part also increases the load range on the sample for a certain displacement, which increases the accuracy of the measurement by significantly surpassing the load resolution of the instrument. Moreover, the bigger coverslip size ensures that the tissue response is greater than that of the internal resistance of the testing machine, hence, it is the dominant term in the overall recorded load. Since the stiffness of the glass coverslip is orders of magnitude larger than that of the brain tissue, it can be assumed as a rigid disk during the analysis. To further assure no localization of the load, the sharp probe of the indenter is also replaced by a 1 mm radius cylindrical one (Fig. 1-c).

In Fig. 1-b, the internal configuration of the indentation apparatus,