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# Biomechanics of brain tissue

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ABSTRACT

The dynamic behavior of porcine brain tissue, obtained from a series of in vitro observations and experiments, is analyzed and described here with the aid of a large strain, nonlinear, viscoelastic constitutive model. Mixed gray and white matter samples excised from the superior cortex were tested in unconfined uniaxial compression within 15 h post mortem. The test sequence consisted of three successive load–unload segments at strain rates of 1, 0.1 and 0.01 $s^{-1}$, followed by stress relaxation ($n = 25$). The volumetric compliance of the tissue was assessed for a subset of specimens ($n = 7$) using video extensometry techniques. The tissue response exhibited moderate compressibility, substantial nonlinearity, hysteresis, conditioning and rate dependence. A large strain kinematics nonlinear viscoelastic model was developed to account for the essential features of the tissue response over the entire deformation history. The corresponding material parameters were obtained by fitting the model to the measured conditioned response (axial and volumetric) via a numerical optimization scheme. The model successfully captures the observed complexities of the material response in loading, unloading and relaxation over the entire range of strain rates. The accuracy of the model was further verified by comparing model predictions with the tissue response in unconfined compression at higher strain rate (10 $s^{-1}$) and with literature data in uniaxial tension. The proposed constitutive framework was also found to be adequate to model the loading response of brain tissue in uniaxial compression over a wider range of strain rates (0.01–3000 $s^{-1}$), thereby providing a valuable tool for simulations of dynamic transients (impact, blast/shock wave propagation) leading to traumatic brain injury.



## 1. Introduction

The study of the mechanical properties of brain matter – at the tissue continuum level – has been the focus of numerous investigations in the past four decades (see for example [1–7]). Many investigators have concentrated their effort on characterizing the coupled time and strain/stress dependencies inherent in the response of the tissue to externally applied mechanical transients, e.g. frontal or lateral impact on the head by a rigid mass [8–10], linear or angular acceleration pulses applied to the skull [11,12] or indentation of the cortex surface [13]. Understanding how these loading/kinematic conditions applied to the organ boundary translate into local stress–strain states within the tissue continuum is challenging, because the brain is, from a biomechanical perspective, a highly complex organ housing multiple "substructures", e.g. brainstem, cerebellum, thalamus, cerebral cortex, corpus callosum, associated with somewhat distinct mechanical properties [14–16]. Most biomechanical studies have been conducted in vitro, although a few measurements have also been reported in vivo [17–21]. The results of different studies are at times difficult to reconcile, due to the wide range of variation in experimental protocols, including the species/age of the subjects (human, porcine, bovine or murine), the loading configurations (compression, shear, tension or indentation), the loading histories (cyclic, stress relaxation or creep) and test regime (small/large strains or low/high strain rates). The collected data have facilitated the development of a large variety of constitutive models, some of which have been shown to account for essential features of the tissue response [22–24] under selected test conditions. Nonetheless, the integration of all the characteristic features of the large strain tissue response (hysteretic behavior, rate dependence, nonlinearity, shear and volumetric behavior) into one single constitutive framework has not been achieved thus far.

This study is a component of a multidisciplinary effort aimed at elucidating some key effects of primary blast on the central nervous system [25] and represents a first step towards the development of a predictive model for the response of brain tissue over an extensive range of strains and strain rates. A parallel effort is underway to assess differences between tissue properties under in vivo and in vitro conditions, where the proposed constitutive formulation is employed to analyze the results of indentation tests

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performed with a custom dynamic tool [26]. The first section of this paper describes the experimental component of the study (test protocols and main results gathered on porcine cortical samples), while the second section addresses the modeling effort (constitutive laws, numerical implementation, model validation and predictions). Both are preceded by a brief literature review. Some of the limitations inherent in the current model formulation are discussed in the last section, guiding the effort for future model refinements. This paper constitutes a preliminary step in the development of a comprehensive experimental database and enhanced computational tools to be employed in support of a variety of clinical applications, as well as to elucidate mechanically mediated pathways leading to traumatic brain injury.

## 2. Experiments

### 2.1. Literature review

Mechanical tests on brain samples have been conducted mainly in the linear regime via small oscillatory deformations imposed on the tissue, in pure shear or in torsion, over a wide spectrum of frequencies [27–30]. In assessing the time/frequency dependence of the linear viscoelastic properties of the tissue (i.e. storage and loss moduli), these studies have uncovered some important aspects of the tissue dynamics. The thrust of the results reported, nonetheless, suffers from a few limitations. First, most of the data so gathered lack consistency, in that the magnitude of the measured scalar moduli varied at times by more than 10-fold in relative terms from one study to another [31]. This lack of consistency may be attributed to multiple factors, including: inter-species/intra-species variations (e.g. animal breed, age, sex and inherent biological variability); differences in (1) post mortem testing time, (2) tissue storage and hydration conditions, (3) tissue preparation/excision methods, (4) specimen neuroanatomical orientation, (5) temperature conditions, (6) interfacial testing conditions (degree of tissue friction/adherence/slipping on the test fixtures) and (7) pre-conditioning effects prior to actual testing. Further, the scope of these investigations was limited per se to small deformations, as the tissue had been shown to deviate from linearity at strains greater than 1% [32,33]. More recently, the nonlinear features of the tissue response have been partly characterized in compression [34,35], tension [36] and shear [23,37]. While some of these studies measured the tissue response over more than two orders of strain rate magnitude, they were mostly focused on a limited set of test histories (e.g. single load ramp and stress relaxation tests or sinusoidal load–unload cyclic tests at low to medium strains), excluding any direct assessment of the tissue volumetric behavior. Some attempts have been made to retrieve quantitative information on the tissue volumetric compliance [38,39], but these attempts remain scarce and limited in scope, most investigators relying on incompressibility assumptions or speculative arguments [34,40,41]. The experimental part of this study aimed to address some of the limitations noted in previous investigations via the systematic collection of experimental data on porcine cortical specimens in unconfined uniaxial compression comprising the following measurements: (1) nonlinear strain and strain rate dependencies in load and unload over three orders of strain rate magnitude (0.01–1 $s^{-1}$) in the large deformation regime (up to 50% nominal strain); (2) long-term time dependencies in relaxation; (3) lateral tissue deformation to assess volumetric compliance. A porcine model was preferred to other animal models because its gyrencephalic brain, architecturally close to the human brain, has been proven to share with the latter some similarities in terms of pre- and postnatal cerebral development relative to tissue growth, myelination and composition [42–46]. Swine models constitute, moreover, an affordable alternative to more costly, ethically sensitive primate models.

### 2.2. Test protocol – unconfined uniaxial compression in vitro

#### 2.2.1. Specimen preparation

Sixteen 6- to 18-month-old swine brains (female, Yorkshire breed) were obtained from a local vendor (Research 87 Inc., Boylston, MA), following a protocol approved by the Committee on Animal Care at the Massachusetts Institute of Technology. Pigs having reached at least six months of age may be considered cerebrally mature [42] and were therefore selected to minimize age-related variability (neonatal pigs have been shown to have significantly softer brains [31]). The brains were sectioned along the mid-sagittal plane and transferred on ice to the laboratory within 3 h post mortem. Each hemisphere was rinsed upon delivery in phosphate-buffered saline (PBS, 10 mM phosphate buffer) and kept refrigerated in solution to limit tissue degradation. Shortly before testing mixed gray and white matter samples were excised from the superior cortical region (frontal and parietal lobes) and maintained hydrated in PBS during all subsequent steps. No notable differences were observed in mechanical properties between the two cortical regions. This observation complements findings previously reported by Coats and Margulies [47] on local cortical gray matter homogeneities at the subcentimetric/millimetric tissue level. Preliminary investigations of the optimal sample size for uniaxial compression tests [48] showed that large samples, in the cubic centimeter range, yielded the most consistent results. All the data collected for this study were therefore obtained from samples that were approximately, 25.4 × 25.4 mm in cross-section and 9 mm in thickness (Fig. 1A). The mechanical properties obtained shall be viewed as "homogenized" properties of the superior cortex (gray and white matter combined), although the samples tested were composed predominantly of gray matter, accounting typically for ~70% of the sample mass. The experimental protocols were primarily designed so as to reduce the sources of experimental variability arising from tissue handling, which are many, given the delicate nature of the brain parenchyma. Separating intermingled gray and white matter of the superior cortex was ill-suited to this study because the separation/cutting process implied further alterations in the tissue virgin state (via shearing or stretching) which were deemed too costly relative to the potential benefits.

#### 2.2.2. Axial and lateral measurements

The samples ($n$ = 25 from $N$ = 16 Yorkshire sows) were tested in unconfined uniaxial compression on commercial testing machines equipped with 20 N load cells (ElectroForce 3200, Bose Corp., Framingham, MN ($n$ = 11); Zwick Z2.5/TS1S, Ulm, Germany ($n$ = 14)). Prior to testing the platens were humidified with PBS to minimize friction at the tissue–platen interface. All tests were conducted at room temperature ($T$ = 21 °C). Samples were tested between 4 and 15 h post mortem, with no significant variations in tissue response being noted in relation to post mortem test time differences. The responses measured were also found to be comparable with those reported by Tamura et al. [35], who conducted similar tests within a shorter time frame post mortem (see Section 3). A preload of 0.02 N (corresponding to a compressive stress of ~30 Pa) was imposed on each sample prior to testing in order to accurately determine the sample thickness. Each sample was subjected to a sequence of three loading segments, at nominal strain rates of 1, 0.1 and 0.01 $s^{-1}$, respectively, each comprising five load–unload cycles to 50% nominal strain, followed by a ramp relaxation segment to 50% nominal strain held for 300 s with a ramp rate of 1 $s^{-1}$. Fig. 1 illustrates the imposed strain history (Fig. 1C) and the resulting stress history (Fig. 1D) for one representative tissue specimen. The transverse displacements were captured