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Research paper

A tissue-level anisotropic criterion for brain injury based on microstructural axonal deformation

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ARTICLE INFO

Article history:
Received 20 June 2011
Received in revised form
16 September 2011
Accepted 23 September 2011
Published online 1 October 2011

Keywords:
Traumatic brain injury (TBI)
Diffuse axonal injury (DAI)
Brain injury criterion
Axons
Neurons
Finite element method

ABSTRACT

Different length scales from micrometers to several decimeters play an important role in diffuse axonal injury. The kinematics at the head level result in local impairments at the cellular level. Finite element methods can be used for predicting brain injury caused by a mechanical loading of the head. Because of its oriented microstructure, the sensitivity of brain tissue to a mechanical load can be expected to be orientation dependent. However, the criteria for injury that are currently used at the tissue level in finite element head models are isotropic and therefore do not consider this orientation dependence, which might inhibit a reliable assessment of injury. In this study, an anisotropic brain injury criterion is developed that is able to describe the effects of the oriented microstructure based on micromechanical simulations. The effects of both the main axonal direction and of local deviations from this direction are accounted for. With the anisotropic criterion for brain injury, computational head models will be able to account for aspects of diffuse axonal injury at the cellular level and can therefore more reliably predict injury.

1. Introduction

Traumatic brain injury (TBI) can be caused by a mechanical action on the head, for instance as a result of a sports or road traffic accident. More than 1.5 million cases were reported in the United States in 2003 (Rutland-Brown et al., 2006). One of the most frequently occurring types of TBI is diffuse axonal injury (DAI) (Gennarelli et al., 1982). For an improvement of the prevention or diagnosis of TBI, it is necessary to better understand the relation between the mechanical insult on the head and the resulting injury. Brain injury criteria are used to assess an injury level resulting from mechanical loading. The brain injury criterion most commonly used nowadays is the head injury criterion (HIC) (NHTSA, 1972). However, it has a number of drawbacks, among which is the fact that it is based on the translational accelerations of the head only. Although injury occurs as a result of a mechanical load on the head, the actual injury happens at the cellular level within the brain (Ommaya et al., 1994; Povlishock, 1993). Therefore, more sophisticated brain injury criteria that take this cellular level into account may be able to better predict brain injury.

More detailed mechanical effects can be included in the relation between a mechanical load and the resulting brain injury by using computational models. Three-dimensional finite element (FE) models of the head and brain have been developed to describe brain tissue strains and stresses caused by a mechanical insult (e.g., Takhounts et al. (2003), Zhang et al. (2004), Kleiven (2007), Marjoux et al. (2008) and Chatelin et al. (in press)). The outcome of these head models can be interpreted by means of tissue-level injury criteria that can be

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doi:10.1016/j.jmbbm.2011.09.012

obtained from experiments in which mechanically deformed brain tissue is related to cell damage or electrophysiological impairments of the neurons (e.g., Bain and Meaney (2000), Bain et al. (2001), Morrison III et al. (2003), Morrison III et al. (2006), Geddes-Klein (2006), LaPlaca et al. (2005), Cater et al. (2006) and LaPlaca and Prado (2010)). Some of the tissue-level criteria are based on strains, strain rates, or the product of strain and strain rate, but it is difficult to obtain a threshold for injury for any of the currently used injury criteria. Besides numerical head modeling for injury prediction, also several modeling studies have focused on the relation between the tissue-level mechanical behavior and the cellular-level structures (Arbogast and Margulies, 1999; Khoshgoftar et al., 2007; Abolfathi et al., 2009; Karami et al., 2009). In a previous study, the FE method was used to investigate the cellular-level effect of brain injury (Cloots et al., 2011). Even though research on TBI is being conducted at different length scales, current numerical head models do not include the effects of the cellular structure.

To understand how the global head load and cellular injury are connected, it is important to make a distinction between the different length scales that play a role (see Fig. 1). The mechanical load on the head results in a head acceleration, which causes tissue stress and strain concentrations due to the geometrical heterogeneities at the tissue level. This again leads to cellular-level stress and strain concentrations, which are affected by the cellular microstructure. At the latter length scale, individual cells can be distinguished. Neurons and glial cells consist of a cell body from which processes extend (Marieb, 1998; Nolte, 2002). The typical diameter of these cell bodies is about 5 μm for glial cells, whereas for neurons it is less than 10 μm or up to 20 μm for non-pyramidal neurons and other cortical and hippocampal neurons, respectively (Rajkowska and Goldman-Rakic, 1995; Rajkowska et al., 1998; Pierri et al., 2001; Cotter et al., 2002; Highley et al., 2003; Hutsler, 2003). Most neuronal cell bodies are in the cortex, but their axons can be many centimeters long with a uniform diameter extending into the other parts of the brain, whereas dendrites taper away from the soma and rarely exceed 500 μm in length (Alberts et al., 1994). The vast majority of brain tissue consists of axons, and even in the cerebral cortex, which is relatively rich in cell bodies and blood vessels in comparison with other parts of the brain, 60–70% of the volume consists of neuronal axons and dendrites, 5–10% of glial processes, 10–20% of cell bodies and blood vessels, and the remaining part is extracellular space (Fenstermacher et al., 1970; Braitenberg and Schüz, 1998; Ventura and Harris, 1999; Chklovskii et al., 2002).

An important aspect of DAI is that it is associated with discrete local impairments of axons at locations where these have to deviate because of the presence of an inclusion (e.g., a blood vessel or a soma) (Povlishock, 1993; Sahuquillo et al., 2001; Gaetz, 2004). It has been shown in a previous study that there might be a mechanical cause for this, as concentrations of axonal stretch can occur more easily there, depending on the local material properties, axonal orientations, and loading directions (Cloots et al., 2011). From experiments with tissue deformations, the results indicate that axons are mostly sensitive to injury for stretch in the axial direction of the axon (LaPlaca et al., 2005). This could indicate that the micromechanics at an axonal level should be accounted for in head-level FE simulations. However, the typical resolution of existing head models is much larger than the axonal length scale, which means that these micromechanical effects cannot be incorporated in the numerical head model in a conventional manner. To overcome this problem, a multi-scale approach can be adopted, in which two computational models of different length scales are coupled (e.g., Kouznetsova et al. (2001) and Cloots et al. (2010, submitted for publication)). However, drawbacks of this approach are the complexity of modeling as well as the high computational demands, since, for each integration point of the head model for which the micromechanical effects need to be accounted for, a micromechanical problem must be solved. For practical applications, FE head models should be able to predict axonal injury based on axonal orientation without the need for a nested multi-scale coupling. Therefore, the aim of this study is to develop an anisotropic injury criterion that accounts for the micromechanical effects that are important for DAI and that can be directly applied at the tissue level of a numerical head model.

2. Methods

In this study, a critical volume element (CVE) is modeled that represents a critical region of the brain tissue for axonal injury at the micrometer length scale. As opposed to a representative volume element, which represents a microstructure that is continuously repeated throughout the material and thereby describes the macroscopic material behavior, the CVE represents only regions that are relatively sparsely present in the microstructure, and thereby the mechanical heterogeneities of the CVE do not influence the macroscopic material behavior. Two different configurations of a CVE are developed that can predict the strain concentrations at an axonal level caused by a deformation that is applied at the level of the homogenized tissue. One configuration represents a geometry with a cell body as an inclusion and the other configuration represents a geometry with a blood vessel as an inclusion. Within those CVEs, the mechanical response of the tissue anisotropically depends on local axonal orientations. Furthermore, an anisotropic brain injury criterion is developed that can capture the concentrated axonal stretch within the CVE, which is considered to be critical for brain injury, as a function of the applied homogenized tissue strain.

2.1. *Critical volume element*

In a previous study, a CVE was developed that describes DAI at an axonal level (Cloots et al., 2011). It was modeled with a plane strain assumption and was based on the pathological observation of discrete local impairments of axons near an obstruction, such as a blood vessel or soma (Povlishock, 1993). For the model, it was assumed that this typical critical geometry may be one of the causes for injury due to mechanical strain concentrations in the axons surrounding the obstruction (Cloots et al., 2011). Furthermore, it was