NeuroImage xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

A biophysical model of brain deformation to simulate and analyze longitudinal MRIs of patients with Alzheimer's disease

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ARTICLE INFO

Article history:
Received 14 September 2015
Accepted 23 March 2016
Available online xxxx

Keywords:
Biophysical model
Alzheimer's disease
Simulation of atrophy
Longitudinal MRIs simulation
Longitudinal modeling

ABSTRACT

We propose a framework for developing a comprehensive biophysical model that could predict and simulate realistic longitudinal MRIs of patients with Alzheimer's disease (AD). The framework includes three major building blocks: i) atrophy generation, ii) brain deformation, and iii) realistic MRI generation. Within this framework, this paper focuses on a detailed implementation of the brain deformation block with a carefully designed biomechanics-based tissue loss model. For a given baseline brain MRI, the model yields a deformation field imposing the desired atrophy at each voxel of the brain parenchyma while allowing the CSF to expand as required to globally compensate for the locally prescribed volume loss. Our approach is inspired by biomechanical principles and involves a system of equations similar to Stokes equations in fluid mechanics but with the presence of a non-zero mass source term. We use this model to simulate longitudinal MRIs by prescribing complex patterns of atrophy. We present experiments that provide an insight into the role of different biomechanical parameters in the model. The model allows simulating images with exactly the same tissue atrophy but with different underlying deformation fields in the image. We explore the influence of different spatial distributions of atrophy on the image appearance and on the measurements of atrophy reported by various global and local atrophy estimation algorithms. We also present a pipeline that allows evaluating atrophy estimation algorithms by simulating longitudinal MRIs from large number of real subject MRIs with complex subject-specific atrophy patterns. The proposed framework could help understand the implications of different model assumptions, regularization choices, and spatial priors for the detection and measurement of brain atrophy from longitudinal brain MRIs.

Introduction

Alzheimer's disease (AD) is one of the most common types of dementia. It is a neurodegenerative disease that progresses gradually over several years with the accumulation of neurofibrillary tangles (NFTs) and amyloid-β (A-β) plaques (Braak and Braak, 1991). These microscopic neurobiological changes are followed by the progressive neuronal damage that leads to the atrophy of the brain tissue. The atrophy or the volume changes of brain tissue is a macroscopic change that structural magnetic resonance imaging (MRI) can estimate in different brain regions (Frisoni et al., 2010).

There is no treatment of AD so far, partly because the exact mechanisms of the disease are not well known. Nevertheless, there has been several clinical trials and disease-modifying drug development efforts in the past three decades (Schneider et al., 2014). Since the external symptoms appear several years after the changes seen in imaging (Frisoni et al., 2010), longitudinal images can play an important role in the development of disease-modifying drugs. So far, structural MRIs have primarily been used for estimating local volume changes in individual AD patients; these measurements have been used to formulate hypotheses on the temporal dynamics of AD.

An interesting alternative avenue consists in modeling the tissue loss process in order to compare (in a *forward modeling* setting) different hypotheses for the prediction of patient-specific time series MRIs. The ability of developing realistic individual models of brain shape changes to predict patient-specific longitudinal MRIs can have far reaching consequences. For instance, the patient-specific AD trajectories predicted by the model could be useful in monitoring drug effects in AD patients by comparing them against the observed brain changes.

It is nevertheless very challenging to develop a comprehensive model that can predict realistic synthetic time series of MRIs following AD patient's trajectory. Modeling neurodegeneration is a complex task requiring a hierarchy of models accounting, respectively, i) for how and where neuronal death occurs, ii) for its effects on brain shape changes and iii) for the subsequent brain appearance in longitudinal MRI. In Fig. 1, we show a breakdown of this complex process in three major modeling blocks which represents, at a very high level, the comprehensive modeling and simulation of realistic longitudinal MRIs in AD. The first block abstracts the multi-scale models of neuronal death at the cellular level into a macroscopic map of how the atrophy spreads spatially and evolves temporally at each voxel of the brain MRI.

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http://dx.doi.org/10.1016/j.neuroimage.2016.03.061
1053-8119/

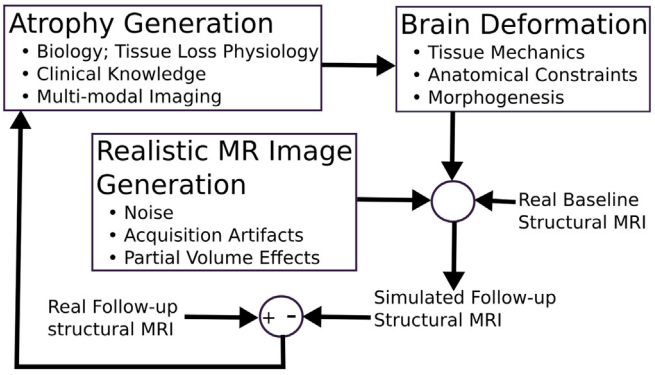

Fig. 1. High level systems diagram for modeling and simulation of longitudinal MRIs in AD patients. Spatial and temporal distribution of neuronal deaths is represented in atrophy generation block which causes the brain shape changes represented in brain deformation block. This deformation along with the MRI acquisition conditions variability result intensity change in time series structural MRI of AD patients. The error in predicted follow-up from the actual observed follow-up MRI could also be used to optimize for the parameters of the developed models using a feedback system as shown above.

Knowing the patterns of local neuronal deaths and local volume loss is just one aspect of the problem; we also need to model the consequences of neuronal loss on brain shape changes. This is represented by the block *Brain Deformation* in Fig. 1. We believe that biomechanics of brain tissue does play an important role in the way brain's shape change as a result of local volume loss, and this topic is going to be one of the main subjects of this paper.

Finally, time-series of structural MRIs capture the brain shape changes but also contain additional noise, partial volume effects, and image acquisition artifacts. This is also an important aspect to consider when modeling and simulating the appearance of change in longitudinal MRIs for AD patients. This part is shown in *Realistic MRI generation*. Furthermore, a proper optimization framework might also be necessary to estimate the patient-specific parameters of the models if we are to perform model personalization. This is represented by a feedback loop in Fig. 1.

A number of atrophy simulators (Smith et al., 2003; Camara et al., 2006; Karaçali and Davatzikos, 2006; Pieperhoff et al., 2008; Sharma et al., 2010) have been proposed in the literature. These simulators address either just the *Brain Deformation* or both the *Brain Deformation* and *Realistic MRI generation* blocks in Fig. 1. They propose different methods to simulate time-series images with a desired volume change. All of these simulators were developed with the objective of evaluating atrophy estimation algorithms. We can broadly distinguish two major approaches used in such simulators: Jacobian based, and biomechanical models.

In Jacobian-based methods (Karaçali and Davatzikos, 2006; Pieperhoff et al., 2008; Sharma et al., 2010), the desired level of atrophy is set at each voxel, and the deformation that best approximates the prescribed level of atrophy is found. Optimization of the deformation involves regularization to enforce the smoothness of the transformation and topology preservation. These simulation approaches have a number of limitations, which prevent their use and generalization in modeling oriented applications. The main issues that we identified are the following:

Plausibility and interpretation

The modeling assumptions and the regularization parameters of the energy minimization cannot be easily linked to the biophysical and mechanical process of tissue deformation. The choice of certain regularizations such as topology preservation can also have some undesirable side effects such as making it difficult to simulate the opening up of sulci.

Spatially varying tissue properties

Brain tissue and CSF are considered to respond to the volume change with the same law which is not the case in reality. Indeed, while neuronal loss in brain tissue is a gradual process, the CSF is replaced three to four times with the production of about 500–600 ml per day (Damkier et al., 2013). Jacobian-based approaches with uniform tissue properties are thus limited to explore questions such as: do different brain regions such as brain stem, cerebellum, cortex, etc., respond with physical deformation in the same way to the neuronal deaths and local volume loss? Can we have parameters with a physical meaning for different brain tissue types that change the deformation we get even for exactly the same atrophy pattern? If tissues respond differently to the same amount of volume loss in brain, these models cannot accurately model the resulting shape changes and on the appearance of time-series MRIs unless the regularization is made spatially varying.

Skull invariance

In AD, the brain deforms but the skull is rigid and hence the deformation model should not allow skull to move. The skull invariance is not imposed in (Karaçali and Davatzikos, 2006); In Sharma et al. (2010), as the authors show, imposing skull invariance results in larger error in the obtained Jacobian near the skull. Since the cortical surface lying near the skull is an important area for AD, it is desirable not to have error in the obtained Jacobian in these areas. Finally, when only volume loss is prescribed, as seems to be the case in the evaluation experiments of (Sharma et al., 2010, 2013), it is not clear which regions of the brain expand to compensate for the volume loss since the volume within the skull must be constant when skull invariance is imposed. The spatial distribution of the resulting non-zero error in the desired vs. obtained Jacobian map is not easy to control in this case.

Biomechanical models generate tissue deformation based on biomechanical principles. As far as we know, the only model proposed so far for AD application other than the one we present here was a thermoelastic one (Smith et al., 2003; Camara et al., 2006). In this thermoelastic model, one defines the volume changes in particular structures and tissues of a meshed brain by assigning different thermal coefficients. Thermoelastic model of tissue deformation is solved using finite element method (FEM) to obtain a deformation field. To simulate time series of images, the deformation field interpolated from the mesh to input baseline image is used. An important limitation of this method is that it requires estimating regional thermal coefficients based on the desired volume changes which makes it difficult to prescribe complex voxel-wise atrophy patterns accurately. Although different tissue types can be differently modeled by considering tissue-specific values of thermo-elastic constants, the meaning of these parameters is difficult to link to the AD process. Furthermore, the variability of the resulting brain deformation depending on the choice of the tissue-specific parameters has not been investigated. Finally, FEM involves moving back and forth from voxels of patients MRI to reference labeled 3D mesh which creates numerical difficulties and inaccuracies in the model personalization.

In Khanal et al. (2014), we proposed a proof of concept for a new biomechanics-based tissue loss model that addresses the limitations of the previous simulators discussed above. This biophysically plausible model of brain deformation due to atrophy is constrained to fit a prescribed atrophy rate at each voxel of the parenchyma. In this work, after analyzing in detail the modeling assumptions, we provide a thorough derivation of the mathematical formulation and of the numerical implementation. There is evidence that endogenous mechanical forces at the cellular level influence brain structure and function. Although the detailed mechanisms of these interaction still deserve further investigation (Tyler, 2012; Mueller and Tyler, 2015), it is clear that they play a role at the macroscopic level which is the scale where we observe changes in the structural MRIs.

Please cite this article as: Khanal, B., et al., A biophysical model of brain deformation to simulate and analyze longitudinal MRIs of patients with Alzheimer's disease, NeuroImage (2016), http://dx.doi.org/10.1016/j.neuroimage.2016.03.061