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Ph.D. DISSERTATION DEFENSE

Candidate:	Shima Jalalian Sedaghati
Degree:	Doctor of Philosophy
School/Department:	Charles V. Schaefer, Jr. School of Engineering and Science
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Title:	Multiphysics Modeling of Alzheimer's Disease
Chairperson:	Dr. Johannes Weickenmeier, Department of Mechanical Engineering, SES
Committee Members:	Dr. Robert Chang, Mechanical Engineering, SES Dr. Yong Shi, Mechanical Engineering, SES Dr. Mehmet Kurt, Mechanical Engineering, University of Washington

ABSTRACT

Early and reliable diagnosis of Alzheimer's disease is challenging due to the complex interactions between protein pathology and structural neurodegeneration. The aim of the research is to develop a multiphysics framework that predicts the effect of Alzheimer's disease on brain shape changes to distinguish between healthy and accelerated aging. As a result, we developed a framework that couples the progression of neurotoxic proteins and local tissue volume loss to capture essential hallmark features of dementia.

We use diffusion tensor imaging data from the Human Connectome Project to construct anatomically informed brain networks and couple them with finite element simulations to track disease progression. We introduce five mechanomarkers to characterize regional tissue deterioration: displacement, area stretch, curvature change, cortical thickness, and sulcal depth.

We calibrated the model by optimizing region-specific white and gray matter shrinkage rates using longitudinal data from Alzheimer's Disease Neuroimaging Initiative. Validation was performed by aligning simulated ventricular volume trajectories and cortical thickness change profiles with clinical observations across cognitively normal, mild cognitive impairment, and Alzheimer's disease cohorts.

Our framework reveals that Aβ-driven atrophy precedes tau-mediated degeneration by up to 12.5 years. Our model predicts that AD accelerates normal brain aging by 12 years and identifies distinct regional vulnerabilities, with early structural changes in temporal and occipital regions progressing to parietal and frontal areas, consistent with established disease staging.

This integrated approach provides three key advances: (i) it explains how network architecture influences protein accumulation patterns and subsequent atrophy; (ii) it captures the temporal sequence of accelerated structural changes across disease stages; and (iii) it identifies region-specific vulnerabilities by considering protein-spreading patterns and mechanical tissue properties. By bridging microscopic protein dynamics with macroscopic tissue-level changes, our framework enhances the mechanistic understanding of neurodegeneration and identifies potential early markers for tracking disease progression before significant cognitive decline.