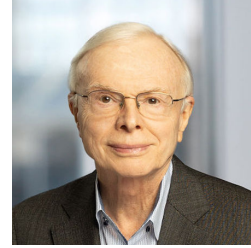


2020-2021 Grand Challenge Award Final Report

Awardee: **Thomas J.R. Hughes, Professor
Aerospace Engineering & Engineering Mechanics**

Research Award Title: **Uncovering the Secrets of the
Glymphatic System and Implications for Neuro-
degenerative Disease: A Computational Medicine
Approach**



Research Summary

An estimated 6.5 million Americans suffer from neurodegenerative diseases such as Alzheimer's Disease (AD) that result in progressive degeneration and death of nerve cells (neurons) impairing movement and/or mental functioning. In spite of monumental research efforts and numerous clinical trials, no successful treatment has emerged that can cure or retard the course of the disease; suggesting that there are major gaps in our understanding of underlying disease processes and the progression of key AD biomarkers. Delayed clearance of aberrant proteins such as amyloid beta from the brain leading to excessive deposition has been suggested as a possible mechanism for triggering the cascade to AD and other neurodegenerative diseases. To date, however, there is little to no quantitative and mechanistic understanding of the transport and clearance of small molecules, agglomerates, and debris from the brain. Such clearance is thought to occur through a brain-wide perivascular pathway for cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange, known as the glymphatic system. A well-validated 3D computational model of the glymphatic system could enable quantification of transport and clearance of key AD biomarkers throughout the brain and elucidate their role in neurodegenerative disease onset and progression.

Currently, there exists no comprehensive subject-specific modeling framework geared toward providing a macro level understanding of glymphatic transport of molecules, proteins and nanoparticles. The paucity of research in this area may be attributed in part to the challenges associated with creating geometrically authentic models of the complex cerebrovasculature network necessary for delineating CSF flow pathways, and then functionally coupling them to glymphatic transport processes in the brain parenchyma. There is also a dearth of relevant modeling of transport mechanisms with existing quantitative published data that can be used to verify simulation results and model assumptions.

The purpose of this research was to begin to mathematically model and characterize the glymphatic system in rodent models through imaging, and to simulate CSF flow-coupled transport of molecules throughout the brain. Figure 1 presents the mathematical model, consisting of an advection-diffusion-reaction (ADR) partial differential equation incorporating an amyloid plaque accumulation law. The model was discretized using a Galerkin Isogeometric finite element formulation.

Transport Model

Advection-Diffusion-Reaction Equation

$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) - \nabla \cdot (\mathbf{u} c) + S^+ - S^-(\mathbf{u}, c) - \frac{\partial P}{\partial t} \quad \text{on } \Omega$$

Neumann Boundary Condition

$$\frac{\partial c}{\partial n} = 0 \quad \text{on } \partial \Omega$$

Initial Condition

$$c(t_0) = c_0 \quad \text{on } \Omega$$

c := A β concentration, nM

D := A β diffusivity, mm²/min

\mathbf{u} := CSF velocity, mm/s

S^+ := A β production, nM/min

S^- := A β clearance, nM/min

:= $|\mathbf{u}|c/\alpha$

α := clearance length scale, mm

P := Fibrilized A β density, nM

Plaque Accumulation Model

Plaque Accumulation Law

$$P = \theta G(r) \quad \text{on } \Omega$$

$$r = \max_{\xi} \tau$$

Constitutive Law

$$\tau = \tau(c) = ac \quad \text{on } \Omega$$

Initial Condition

$$P(t_0) = P_0 = 0 \quad \text{on } \Omega$$

θ := carrying capacity for Fibrilized A β , nM

G := Plaque Accumulation function

r := Plaque Accumulation parameter, nM

r_i := Plaque inception threshold, nM

r_s := Plaque saturation threshold, nM

τ := Constitutive Law, nM

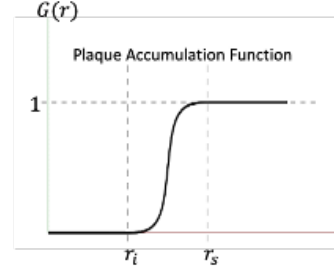


Fig. 1: Glymphatic Transport Model. Amyloid beta (A β) transport, elimination, and deposition are modeled using an advection-diffusion-reaction equation coupled with an irreversible plaque accumulation (damage) model. Elimination of A β from the brain is accounted for by the homogeneous boundary condition in the transport model. Plaque (fibrilized A β) formation begins when the accumulation parameter, τ , exceeds a critical threshold, r_i . Initially, we will assume that plaque formation depends only on the A β concentration through a constitutive model, $\tau = c$. Additionally, we assume that the plaque accumulation function is a smooth step function parameterized in terms of an inception threshold, r_i and saturation threshold, r_s .

Simulation results are reported in Figure 2, showing plaque accumulation as a function of CSF flow. The diffusion coefficient is obtained from mouse imaging data and the CSF flow velocity is determined from a Darcy flow calculation and utilized in the ADR equation. As can be seen, reducing CSF flow velocity increases plaque accumulation. Work is continuing and we hope to extend the model to full 3D simulations of a mouse brain in future work.

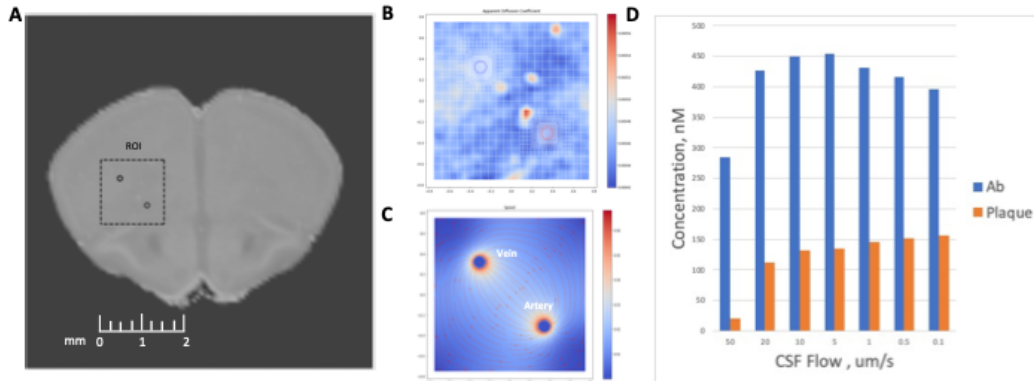


Fig. 2: Preliminary Simulation Results. Plaque formation increases with low cerebrospinal fluid (CSF) flow velocity in a 2D model of perivascular transport. (A) Model geometry in 2D derived from a region of interest (ROI) drawn from diffusion weighted imaging (DWI) of a control C57BL/6 mouse. (B) Apparent

diffusion coefficient distribution and C) CSF streamlines within the ROI. D) Amyloid beta ($A\beta$) and plaque formation after 12 months of age with decreasing CSF flow signifying glymphatic dysfunction.

Key Personnel: The research team collaborating on this work consisted of Shaolie Hosain, Associate Research Professor of Computational Science and Engineering at the Oden Institute and Assistant Investigator at the Texas Heart Institute; Ananth Annapragada, Professor of Radiology, Baylor College of Medicine; David Paydarfar, Professor of Neurology, Dell Medical School; Michael Abdelmalik, Assistant Professor of Mechanical Engineering, Technical University of Eindhoven; and Michael Johnson and Frimpong Baidoo, Oden Institute PhD students.

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