Towards a Deeper Understanding of Axonal Injury Mechanisms Using a Novel Biomechanical Model of Normal Pressure Hydrocephalus

Vahid Darvishi[1], Martina Del Giovane[2, 3], Michael C. B. David[2, 3], Magdalena A. Kolanko[2, 3], David Sharp[2, 3], Paresh A. Malhotra[2, 3, 4], Chris Carswell[2, 4], Mazdak Ghajari[1]

[1]HEAD Lab, Dyson School of Design Engineering, Imperial College London, London, SW7 2AZ, UK
[2]Department of Brain Sciences, Imperial College London, London, UK
[3]UK Dementia Research Institute Care Research and Technology Centre, Imperial College London and the University of Surrey, London, UK
[4]Department of Neurology, Imperial College Healthcare NHS Trust, London, United Kingdom

ABSTRACT

Mechanical loading of axons can damage them, but studying this relationship in human is difficult. Normal pressure hydrocephalus (NPH) is a neurological condition marked by the enlargement of brain ventricles, which can provide an opportunity for investigating the relationship between brain deformation and axonal injury. In this study, we introduce a high-resolution, anatomically precise finite element model of the brain that includes critical structures like the sulci, falx cerebri, septum pellucidum, and pia mater. We developed an age-specific brain template using MRI data from 30 healthy adults aged 62 to 82, capturing key anatomical features often neglected in earlier models. Additionally, we propose a novel simulation method based on displacement data from MRI scans of 22 NPH patients to model ventricular enlargement, offering greater precision than conventional pressure-based techniques. The model's outputs closely matched clinical observations, replicating changes such as a 75.6% reduction in posterior interhemispheric distance (compared to 70.8%), and a 26.5% thinning of the septum pellucidum (versus 26.3%). This consistency acts as a strong validation of the model. Furthermore, areas of high biomechanical strain identified by the model suggest potential sites for future axonal injury investigations. Incorporating axonal anatomy into the model in future work will enhance our ability to understand how biomechanical forces contribute to axonal damage in the brain.

INTRODUCTION

NPH first described by Hakim and Adams in 1964, is a neurological condition seen mostly in older adults. It is marked by enlarged brain ventricles and symptoms including gait disturbance, urinary incontinence, and cognitive decline—collectively known as Hakim's triad (Bräutigam et

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al., 2019; Wang et al., 2020; Adams et al., 1965; Relkin et al., 2005), While past studies estimated low prevalence, recent data suggest NPH is more common, affecting up to 2.5% of those over 65 (Sundström et al., 2022). Often misdiagnosed as Alzheimer's due to similar symptoms, NPH is notable for its potential reversibility, particularly through cerebrospinal fluid (CSF) shunting (Schwamb et al., 2014). However, outcomes of shunting are inconsistent, likely due to an incomplete understanding of the disease's biomechanical basis (Bräutigam et al., 2019; Wang et al., 2020).

Recent modeling efforts have used realistic 3D brain geometries to study NPH, but many focus mainly on fluid flow and overlook structural strain and tissue damage (Chen et al., 2013; Cheng & Bilston, 2010; Clatz et al., 2007; Dutta-Roy et al., 2008; Lefever et al., 2013). Limitations in prior models include simplified anatomy, 2D geometry, or reliance on data from young brains. Additionally, most models apply artificial pressure gradients to simulate ventricular expansion—an approach inconsistent with NPH's normal CSF pressure (Dutta-Roy et al., 2008).

To overcome these gaps, we developed a highly detailed, anatomically accurate finite element model of the aging brain and introduced a novel loading method based on actual displacement data. This model aims to better replicate NPH-related changes and improve understanding of the biomechanical factors contributing to the disease.

METHODS

MRI data from 30 healthy controls (HC, aged 62–82) and 22 NPH patients were used to create two brain templates using Advanced Normalization Tools (ANTs). A finite element (FE) model was developed from the HC template via an in-house pipeline (Duckworth et al., 2022), focusing on anatomically accurate ventricles. These were then registered to the NPH template using multiple tools, generating displacement fields for simulating ventricular expansion. Strain distribution was analyzed in various brain regions. The overall process of the FE model creation has been illustrated in Figure 1, but the modelling part has been divided into several subsections, each discussed individually below in more detail.

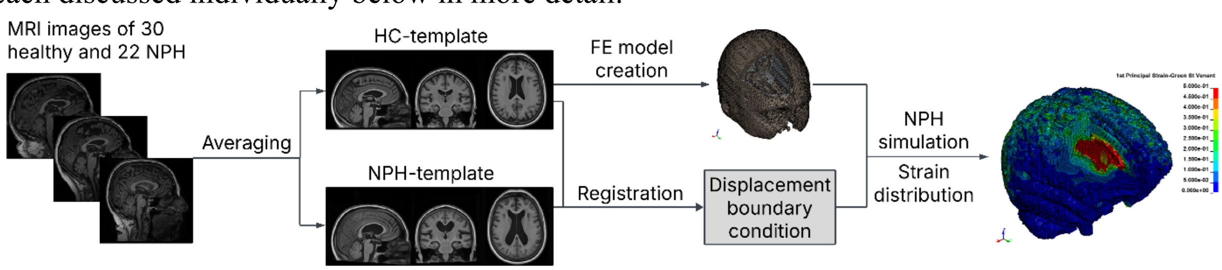

Figure 1: The overall process of FE model development.

Model Components and Geometry Refinements

Brain Geometry and Mesh Quality. The HC brain template was segmented (FMRIB, Freesurfer) and meshed into 844,580 elements with size ranging from 0.299 to 2.704 mm. Mesh quality was validated using multiple criteria Figure 2.

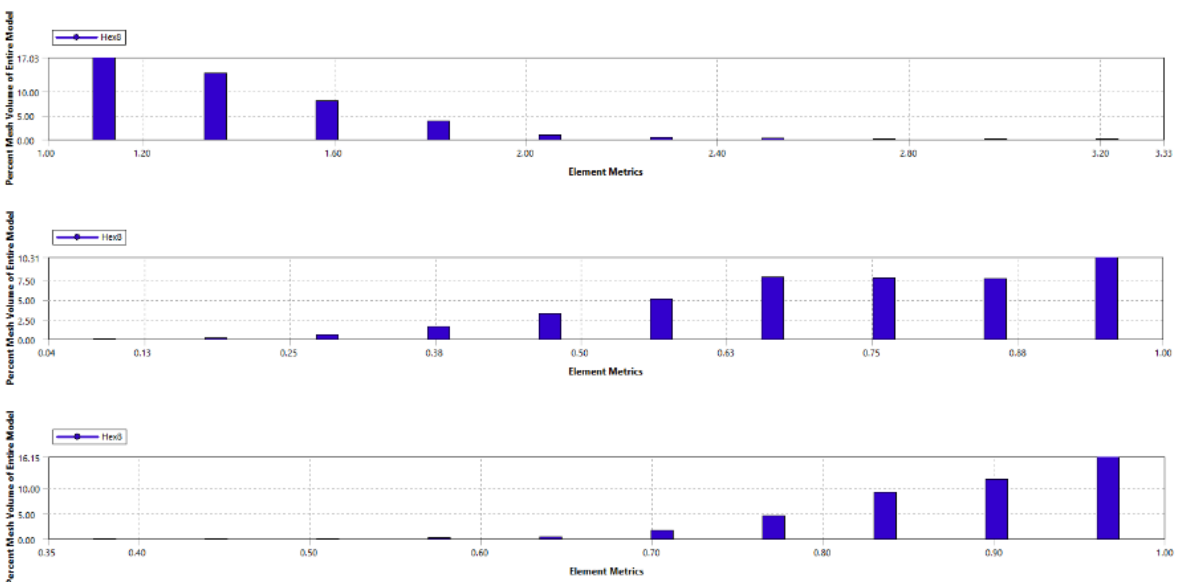

Figure 2: Mesh quality metrics for the FE model. From top to bottom aspect ratio, Jacobian ratio and element quality respectively.

Ventricular System. All four ventricles, particularly the lateral ventricles, were manually segmented using 3D Slicer to ensure anatomical fidelity, especially in the lower regions often omitted in prior models.

Septum Pellucidum (SP). A thin layer (avg. 2.42 mm) was added to represent the SP, marking the first time this structure was modeled in 3D for NPH simulations.

Falx Cerebri. Modeled as a 0.91 mm hyperelastic shell using the Ogden model. Contacts with adjacent brain regions were defined to capture realistic interactions.

Sulci. Included in the model geometry for the first time in 3D NPH simulations, improving anatomical realism and biomechanical accuracy Figure 3.

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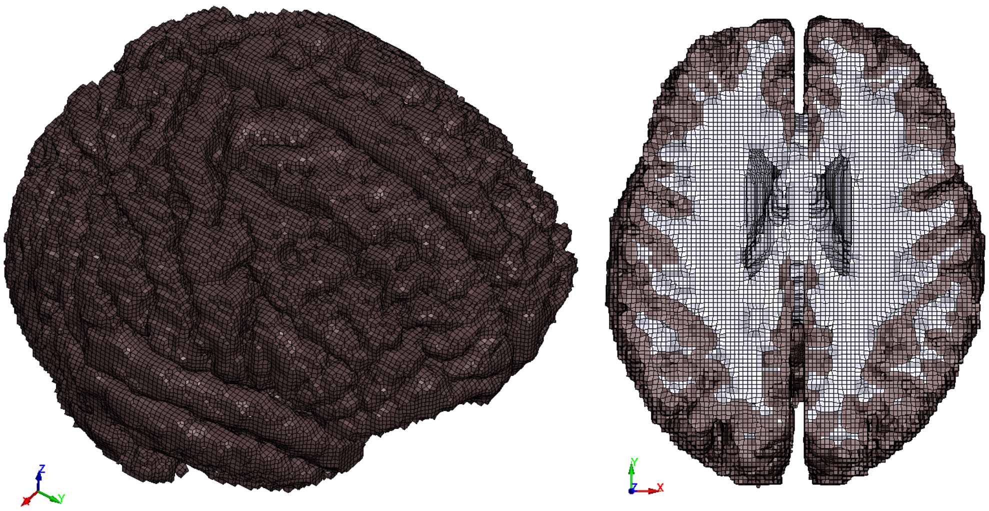

Figure 3: Consideration of Sulci anatomy in FE model of NPH in this study

Pia Mater. The Pia mater, a thin membrane surrounding the brain, was modeled as a shell with a thickness of 0.2 mm.

Material Models

A quasi-static, two-term isotropic Ogden hyperelastic model was used as mentioned in equation 1 (Ogden, 1997), omitting viscous effects due to the slow progression of NPH for brain tissue. Viscous properties were retained for pia matter to support stable brain contact interactions during simulation.

$$W = \sum_{i=1}^{3} \sum_{j=1}^{n} \frac{\mu_j}{\alpha_j} \left(\lambda_i^{\alpha_j} - 1 \right) + K(J - 1 - \ln J) \qquad (1)$$

Loading and Boundary Conditions

Unlike previous pressure-based models, this study introduced a displacement-based loading method using registration-derived deformations from ANTs, ICP, and other tools. This allowed for non-uniform, anatomically accurate ventricle expansion aligned with MRI observations.

Simulation Control and Stability

Time Scaling. To simulate a long-term disease in a feasible runtime, expansion durations of 10–5000 ms were tested. A duration of 500 ms provided a reliable quasi-static simulation.

Hourglass Energy Control. To ensure numerical stability, hourglass energy was maintained below 6% of internal energy. Tuning the hourglass coefficient improved element performance and prevented simulation failure.

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RESULTS

Manual segmentation of MRI scans from healthy individuals produced a more anatomically accurate representation of the ventricular system, including lower regions often omitted in past models. However, since the lower parts expand less in NPH, the focus was placed on the upper lateral ventricles for registration and simulation. Over 30 variations of each ventricle were generated using multiple registration methods and compared to NPH MRI images. The best alignment—achieving 79% accuracy—was obtained through a combined approach.

With detailed ventricular anatomy and added structures such as sulci, falx, and the SP, the FE model successfully simulated NPH-related anatomical changes.

Septum Pellucidum

The model predicted a 26.5% reduction in SP thickness during ventricular expansion, closely matching the 26.3% observed in MRI scans. Thinning was more pronounced in posterior regions (Figure 4).

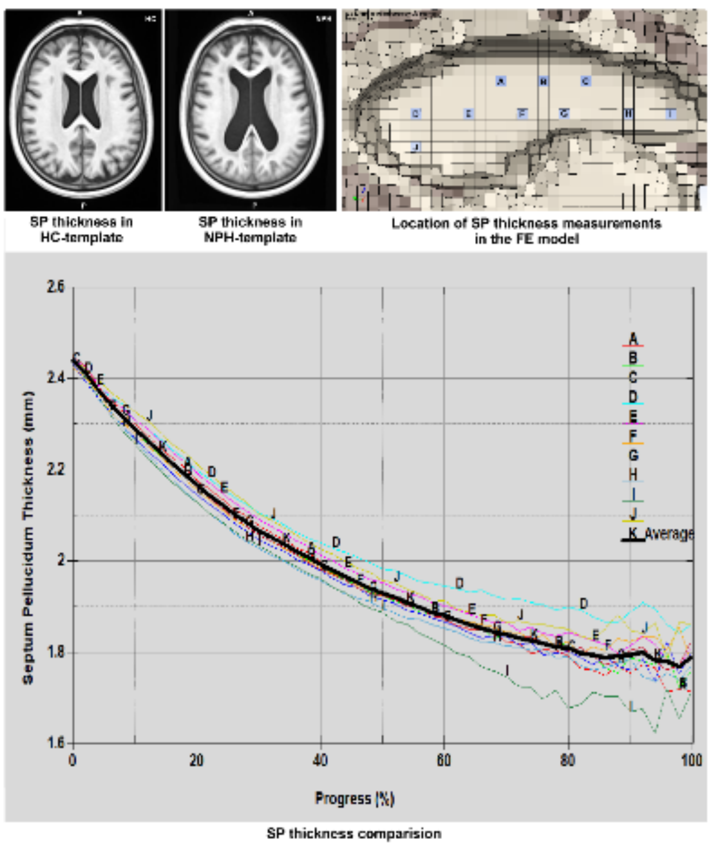

Figure 4: SP thickness comparison between MRI images and the FE model. Top left shows SP thickness in HC and NPH MRI templates, Top right shows location of thickness measurements in the FE model, and bottom shows SP thickness measurements at each time step during the NPH process

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Interhemispheric Distance

MRI data showed the brain hemispheres moving closer together in posterior regions in NPH. The model replicated this pattern accurately (Figure 5).

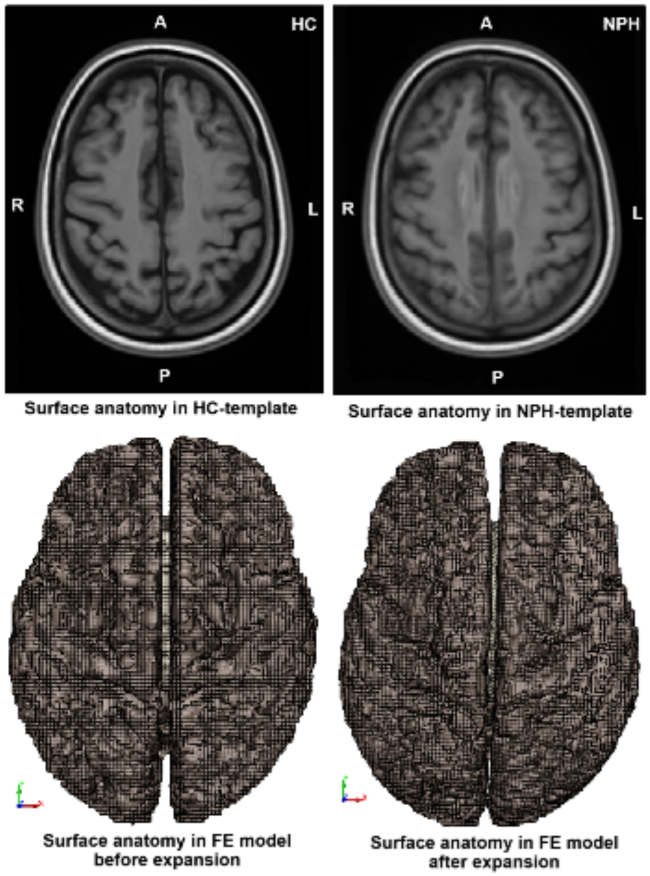

Figure 5: Gradual decrease in the distance between the left and right hemispheres as a result of NPH. Top shows reduction in inter-hemispheric distance observed in MRI images of HC (left) and NPH (right) templates and bottom shows FE model at time 0 ms (left) representing HC and 500 ms (right) representing NPH.

Brain Strain Predictions

Strain analysis revealed high levels (up to 0.5) in specific regions of the brain (Figure 6).

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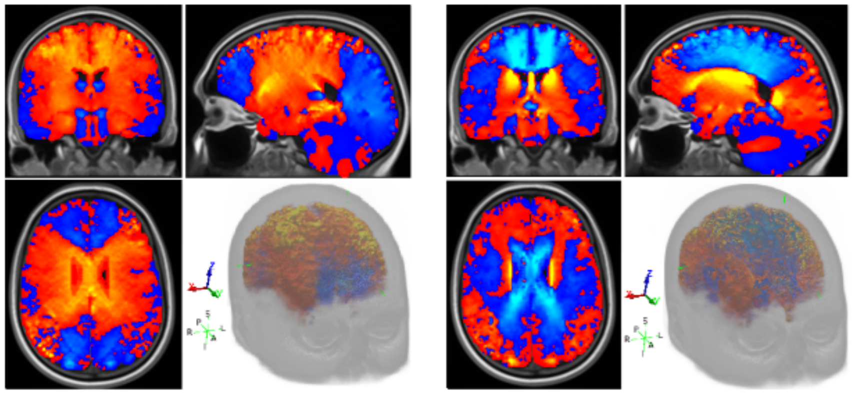

Figure 6: Strain distribution calculated by the FE model of NPH.

DISCUSSION

The development of a highly precise and biofidelic FE model of NPH has been successfully achieved through the integration of detailed anatomical features essential for capturing the complex mechanical interactions within the cranial cavity. Several critical parameters were systematically optimized to enhance model fidelity, including the selection of age-matched control templates, implementation of realistic contact algorithms between brain structures, and tuning of kinetic and hourglass energy thresholds. Furthermore, the overall simulation duration was adjusted to maintain quasi-static conditions, and a novel displacement-based boundary condition was formulated using a registration matrix derived from MRI-based image alignment. These technical advancements collectively enabled the accurate biomechanical representation of NPH-associated deformations.

A significant advancement of this study lies in its incorporation of intricate anatomical features previously neglected or oversimplified in earlier FE models. Specifically, the inclusion of sulci, falx cerebri, SP, and pia mater provided a more faithful representation of cerebral anatomy. These structures play crucial roles in modulating the brain's mechanical response; for instance, the sulci alter local stress distributions, while the falx cerebri and SP contribute to constraining deformation during ventricular expansion. The ventricular system, with particular attention to the lower segments of the lateral ventricles—commonly omitted in past studies—was also accurately reconstructed. These anatomical refinements markedly enhance the model's biofidelity and ability to simulate real-world deformation patterns in NPH.

Beyond anatomical detail, the study introduces a novel displacement-driven loading strategy for simulating ventricular expansion. This approach enables spatially non-uniform expansion, closely mimicking the heterogeneous deformation observed in clinical MRI of NPH patients. In contrast, previous studies typically relied on pressure-based loading conditions, which assumed uniform ventricular expansion and depended on arbitrarily selected pressure gradients.

These simplifications often failed to replicate the spatial variability and true mechanics of ventricular enlargement, limiting their accuracy and predictive value.

The model's predictive capabilities were validated through comparison with MRI-derived anatomical markers. The posterior inter-hemispheric distance was reduced by 70.8% in the model, consistent with the observed 75.6% reduction in patients. Additionally, the thickness of the SP was predicted to decrease by 26.5%, in excellent agreement with the 26.3% reduction measured in MRI. These results confirm the model's accuracy in capturing key structural changes associated with NPH.

Future work is needed to simulate the NPH process using a model that incorporates axonal anatomy, as illustrated in Figure 7, in order to account for strain along the direction of axons. With this enhancement, it will be possible to more accurately predict axonal strain and compare it with DTI markers. This comparison could provide valuable insights into the relationship between biomechanical forces exerted on brain tissue and resulting axonal damage.

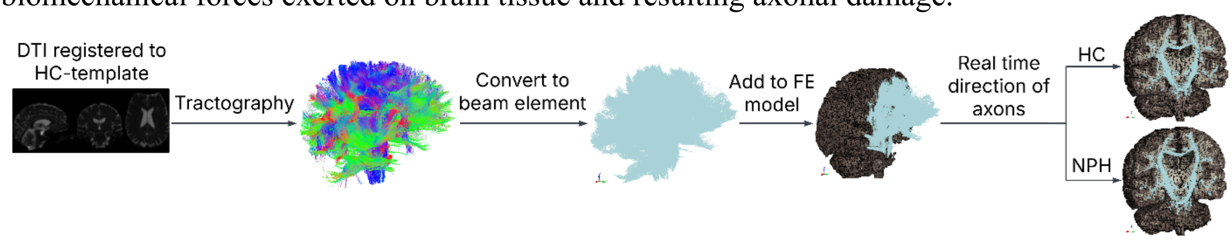

Figure 7: Flowchart of axonal map generation and its implementation in the FE model.

Despite its strengths, the model presents areas for improvement. The image registration process, while effective overall, remains a limiting factor in certain regions. Future work should aim to improve registration fidelity and reduce reliance on manual corrections, thereby streamlining the process of generating displacement fields. Additionally, although the Ogden hyperelastic model used here is widely regarded as suitable for brain tissue, exploring alternative constitutive models could provide insight into the influence of material assumptions, especially as displacement-based loading is known to reduce sensitivity to material parameters. Lastly, the current model is based on averaged imaging data, which may not fully capture the variability among individual NPH patients. Future studies should focus on developing patient-specific models to support personalized diagnostics and treatment planning.

CONCLUSIONS

This study presents a novel FE model of NPH that incorporates detailed brain anatomy and introduces a displacement-based loading paradigm to simulate ventricular expansion with high anatomical and mechanical fidelity. The model accurately replicates key neuroimaging features of NPH, including ventricular enlargement and morphological deformations, demonstrating strong agreement with MRI-derived metrics. This consistency provides validation for the model's predictive capabilities.

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Furthermore, the model highlights regions of elevated mechanical strain. These predictions of concentration of strain in certain regions of the brain, enabling future comparison with MRI imaging. In future work, this model will be used to analyze patterns of axonal injury observed in diffusion imaging, providing a new opportunity for studying biomechanics of axonal injury in humans.

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