A Biomechanics-Informed Mathematical Framework for Early Tau Pathology Accumulation Following Traumatic Brain Injury

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I. INTRODUCTION

Traumatic brain injury (TBI) is increasingly recognised as a risk factor for long-term neurodegeneration, particularly in disorders associated with abnormal tau accumulation, such as chronic traumatic encephalopathy (CTE) [1-2]. Histopathological studies indicate that repetitive or severe head trauma may be followed by progressive tau deposition in characteristic brain regions, yet the mechanistic link between the initial mechanical insult and the later biochemical response remains insufficiently understood [3-4].

Experimental studies have also demonstrated that TBI can induce tau aggregation and spreading over time [5]. Computational biomechanics has shown that head impacts generate heterogeneous strain fields within the brain, highlighting mechanically vulnerable regions such as sulcal depths and gray–white matter interfaces [6-7]. However, these two lines of evidence are usually treated separately: FE models describe deformation; biological studies describe pathological progression.

This short communication presents an initial computational framework that combines experimentally informed tau progression with FE-derived mechanical fields to estimate how local tissue deformation may shape the spatiotemporal emergence of tau-related pathology after TBI.

II. METHODS

A preliminary workflow was developed in three steps. First, published measurements from tau-transgenic mice subjected to TBI were used to define the global temporal trend of tau progression [5]. Second, a three-dimensional FE head model, including cerebral gray and white matter, cerebellum, brainstem, corpus callosum, cerebrospinal fluid, and cortical and trabecular bone, was used to simulate a frontal impact scenario in Abaqus and compute the spatial distribution of maximum principal strain (MPS), adopted here as a surrogate of local mechanical vulnerability [6-7]. Third, the experimentally informed temporal evolution was implemented in Python and combined with the FE-derived strain field to generate regional tau estimates over time.

In the proposed mathematical formulation, the biological data constrain the global temporal progression, whereas the normalised mechanical field modulates the local magnitude of the response. The simplified form of the equation used to estimate the local tau fraction is: $\tau_i(t) = 0.35\left(1-e^{-w_i^4 Y_e(t)}\right)$, where $\tau_i(t)$ is the local tau fraction at node i and time t; w_i is the normalised mechanical field obtained from the FE-derived maximum principal strain, with values between 0 and 1; and $Y_e(t)$ is the homogeneous extended volume obtained from the 3D Avrami nucleation–growth model, which governs the global tau-aggregation kinetics. The constant 0.35 represents the upper saturation level adopted from the calibrated experimental tau burden. Therefore, the biological model controls the temporal evolution of tau accumulation, while the mechanical field determines where tau preferentially develops within the brain mesh.

III. INITIAL FINDINGS

The first result of the framework is that the temporal progression inferred from the biological dataset can be reproduced while preserving spatial heterogeneity imposed by the mechanical field. The calibrated time course shows a very limited increase in tau burden during the acute and early subacute phases, followed by a more pronounced rise at later post-injury times, in agreement with experimental observations [5].

When this temporal evolution is projected onto the FE mesh, the predicted pathology is not uniformly distributed. Instead, early elevated values emerge preferentially in regions exposed to higher MPS during impact. In the present frontal-impact simulation, this led to a concentration of the response in frontal cortical zones and

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nearby mechanically loaded regions. As time progresses, these initially localised areas enlarge and become more spatially continuous, while the global average remains constrained by the calibrated biological trajectory.

Figure 1 presents an example of this behaviour, showing the FE-derived strain field and representative predicted tau maps at selected post-injury times.

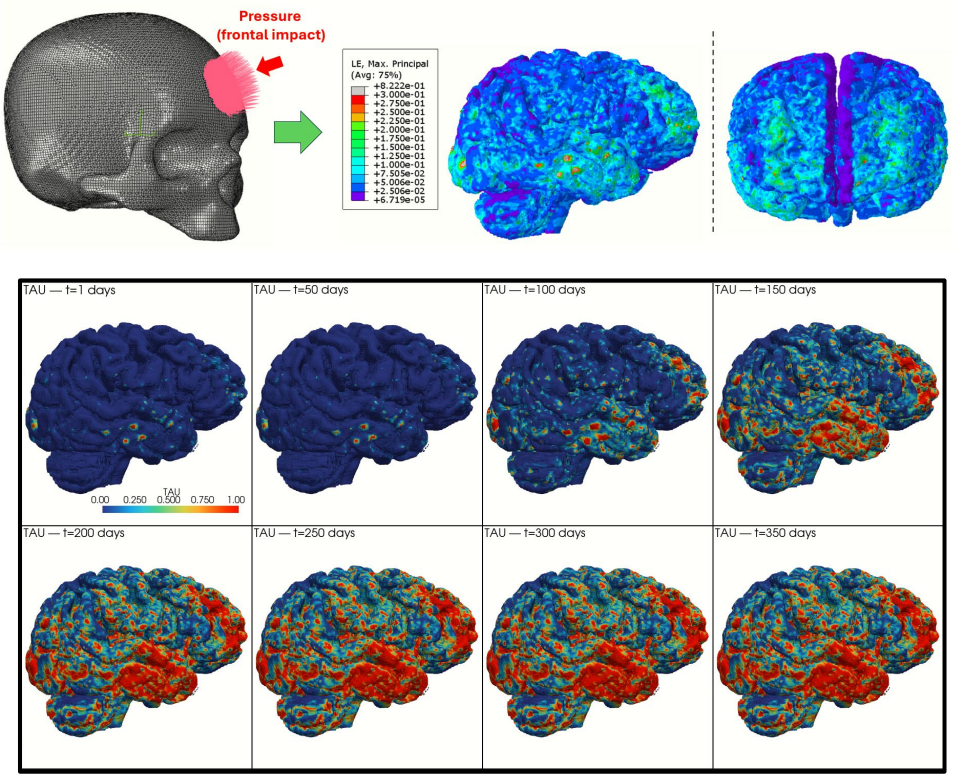

Fig. 1. Example of FE-derived maximum principal strain field and corresponding predicted regional tau distribution at representative post-injury times.

IV. DISCUSSION

These preliminary results suggest that coupling experimental tau kinetics with FE-derived mechanical fields is a promising strategy for studying mechanobiological pathways after TBI. In contrast to approaches that focus only on pathological spreading, the present framework introduces tissue mechanics as an initiating spatial factor, which is relevant for CTE-like pathology characterised by region-specific deposition patterns [3-4].

A key strength of the approach is that it provides a coherent link between two domains that are often studied separately: injury biomechanics and subsequent pathological evolution. In this framework, biological data define the overall temporal progression, whereas biomechanics helps identify where pathology may preferentially emerge. This structure makes the model mechanistically interpretable and suitable for future extensions, such as repeated impacts, subject-specific anatomies, or tractography-informed propagation.

The study remains a proof of concept. The biological calibration is limited, the spatial response is based on a single impact scenario, and no connectivity-mediated spreading or inflammatory processes are yet included. Even so, the results support the idea that biomechanics may contribute to modelling downstream neurodegenerative processes after TBI.

V. REFERENCES

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