Exploring obstructive hydrocephalus through a multiscale modelling approach

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1 Introduction

Hydrocephalus can be succinctly described as the abnormal accumulation (imbalance between production and circulation) of cerebrospinal fluid (CSF) within the brain. Using hydrocephalus as a test bed, one is able to account for the necessary mechanisms involved in the interaction between cerebral fluid production, transport and drainage.

The current state of knowledge about hydrocephalus, and more broadly integrative cerebral dynamics and its associated constitutive requirements, advocates that poroelastic theory provides a suitable framework to better understand the disease. Multiple-network Poroelastic Theory (MPET) is used to develop a novel spatio-temporal model of fluid regulation and tissue displacement in varying scales. This template is used to represent perfused brain tissue.

We have used this platform to conduct 1D MPET, coupled 1D MPET - 3D flow (within the cerebroventricular system) and 3D MPET simulations. These are used to investigate aqueductal stenosis (1D MPET), the role of endoscopic fourth ventriculostomy (EFV) in alleviating edema formation due to fourth ventricle outlet obstruction (1D MPET-3D flow) in addition to observing the capability of a newly developed 3D MPET model in capturing important characteristics allied to clearance of CSF/ISF and blood perfusion between healthy subjects and patients with mild cognitive impairment (MCI). The 3D MPET model is currently employed within the VPH-DARE@IT project (which focuses on dementia), which is described in the last section.

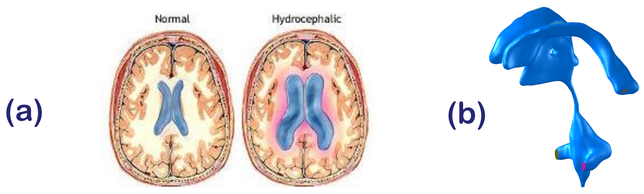


Figure 1. (a) A depiction of the enlarged lateral ventricles when under hydrocephalic conditions (b) A subject specific depiction of the cerebral ventricles.

2 Methods

Human brain tissue is well described by a poroelastic medium. Poroelastic behaviour is best described by two phenomena, namely solid-to-fluid coupling and vice-versa.

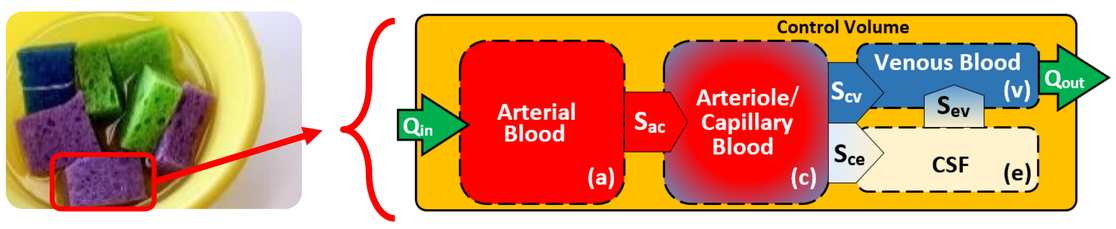


Figure 2. (Left) We can think of parenchymal tissue as a porous sponge. (Right) A schematic representation of our model representing parenchymal tissue. There are four fluid networks that can communicate with each other.

Multiple-Network Poroelastic Theory (MPET)

- In this work, the solid porous matrix represents brain parenchyma, whilst the communicating fluid phases that will be taken into account are: arterial blood (a), arteriole/capillary blood (c), venous blood (v) and the CSF/ISF (e) space, i.e. four networks [1].
- The transfer of fluid between four fluid networks is also required to obey the law of continuity for the entire system, and so directionality between fluid compartments must be accurately specified. These directional constraints can be seen in Figure 2 (S_{ac}, S_{cv}, S_{ce}, S_{ev}).
- The system of PDEs that represent the quadruple-MPET medium are given by one equation for the displacement, and four equations for pressure (one for each fluid compartment).
- The system of equations are complete with the addition of relevant initial and boundary conditions.

Solving the MPET system

Geometry

- Brain anatomy acquired through MRI
- We segment the ventricles and periphery of the parenchyma and skull
- External smoothing, to preserve key anatomical features

The coupled system of equations, along with the relevant initial and boundary conditions, are solved using our own in-house finite difference (FDM) and finite element (FEM) based templates. In addition, we are also coupling these with established finite-volume (FV) based flow solvers (CFD-ACE+).

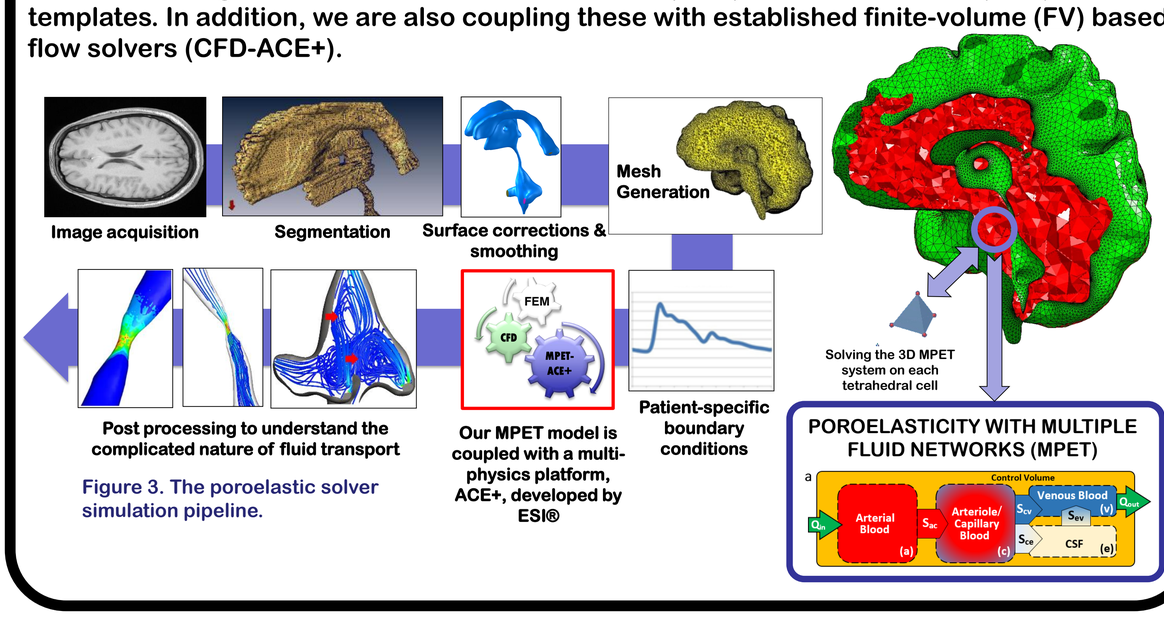
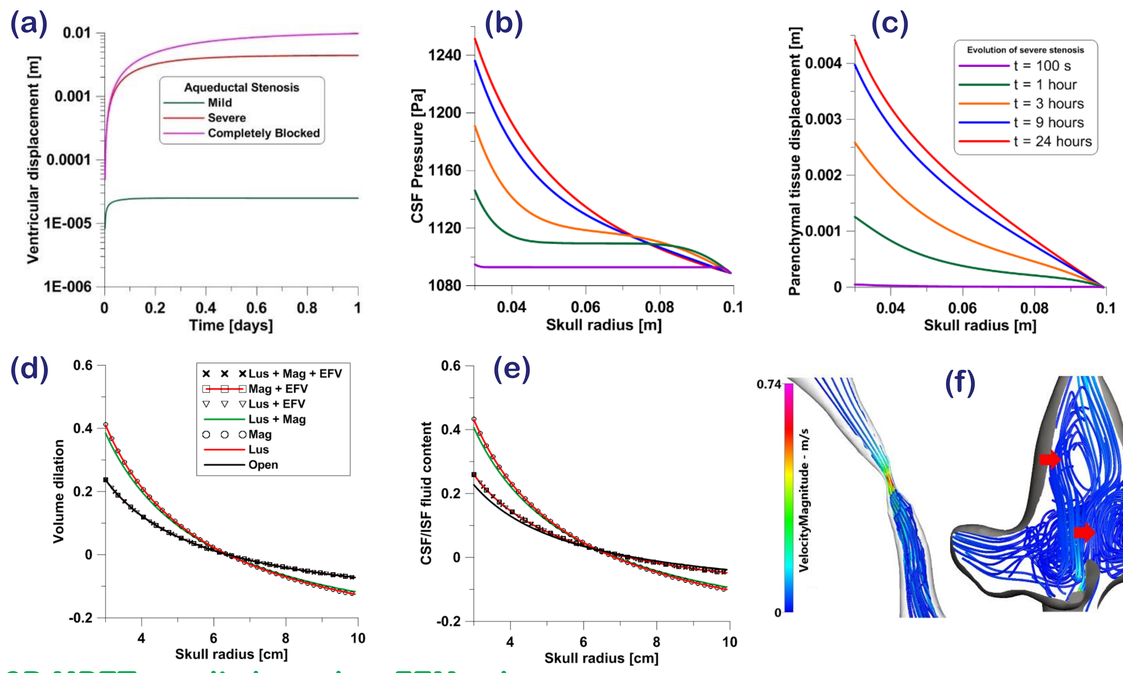


Figure 3. The poroelastic solver simulation pipeline.

3 Results

1D MPET results based on FDM and FDM-FV solvers



3D MPET results based on FEM solver

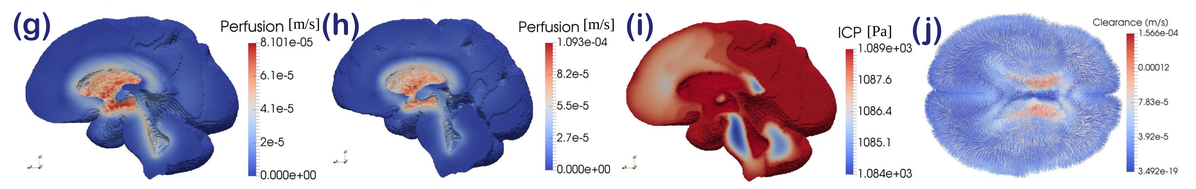


Figure 4. (a) Ventricular displacement is tracked with time for two degrees of aqueductal stenosis severity (mild, severe) and atresia (completely blocked). (b) Transient evolution of CSF/ISF pore pressure within parenchymal tissue. (c) Transient evolution of parenchymal tissue displacement between the ventricles and skull. (d) Variation of volume dilation within the parenchymal tissue from the ventricles (3cm radius) to the skull (10cm radius). (e) Variation of CSF/ISF fluid content (edema) within parenchymal tissue. (f) Velocity streamlines of the severely stenosed aqueduct and velocity streamlines of the aqueduct and fourth ventricle in a healthy subject in the sagittal plane. Two vortices are identified via the red arrows. (g) Perfusion for a control subject (female, 82 years old) during a period of high activity. (h) Perfusion for an MCI patient (female, 82 years old) during a period of high activity. (i) ICP during a period of high activity for the control subject. (j) Clearance of CSF/ISF within the parenchymal tissue of the MCI patient.

4 Discussion

- To date, we have used our coupled 1D MPET models to investigate a variety of scenarios allied to obstructive and communicating hydrocephalus
- As shown in the results (Figure 4a-f), we can attempt to simulate the effects of aqueductal stenosis and obstructing the outlets of the cerebral ventricles in addition to observing the alleviation of these symptoms (higher ventricular dilatation and fluid accumulation is observed when using the coupled 1D MPET model with realistic cerebroventricular geometries) via surgical techniques (EFV).
- The increasing ventricular pressure (complemented with ventriculomegaly) during severe stenosis is causing the trans-parenchymal tissue region to respond, and this coping mechanism is most attenuated at the regions closest to the skull and the ventricles. After 9 hours, the parenchymal tissue shows to be coping well with the additional pressure burden, since both ventriculomegaly and ventricular CSF pressure show small increases between 9 and 24 hours.

Under the guidance of the VPH-DARE@IT project (see next section), some of the expected advantages of using such a framework are outlined below:

- We have also successfully implemented our 3D MPET model based on a tetrahedral element based FEM discretization. Imposing boundary conditions that mimic a state of MCI, like increased ICP, can allow intricate investigation of underlying features that form this complex pathophysiology.
- Lifestyle-related circadian profiles have been incorporated. Subject/patient-specific boundary conditions (24h Holter recordings of blood pressure and heart rate) inform the 3D MPET model.
- 24-hour Holter BP and clinical ultrasound measurements in 52 MCIs (16 processed) and 52 age-matched normal controls (39 processed)
- Lumped parameter circulation model used to translate the Holter BP measurements into continuous blood pressure waveforms. Model parameters are initialised from literature and further calibrated at each time point using surrogate models and nonlinear optimisation. A cerebral autoregulation model is used to translate arterial BP waveforms into cerebral blood flow predictions leading to a prediction of MCA-L and MCA-R flow rates over a 24-hour period
- Currently, we are in the process of embedding the 3D MPET model in the ESI environment, which will allow us to understand the more intricate systems that dictate the evolution of dementia symptoms
- Predisposition to cognitive loss may therefore be linked to modifiable risk factors, such as those witnessed relating to ICP, perfusion and clearance (or further down the line, atherosclerosis/arteriosclerosis)
- Linking the glymphatic system [2] within the above argument. Currently, clearance of CSF/ISF is incorporated to capture such effects (Figure 4j)

5 VPH-DARE@IT Project

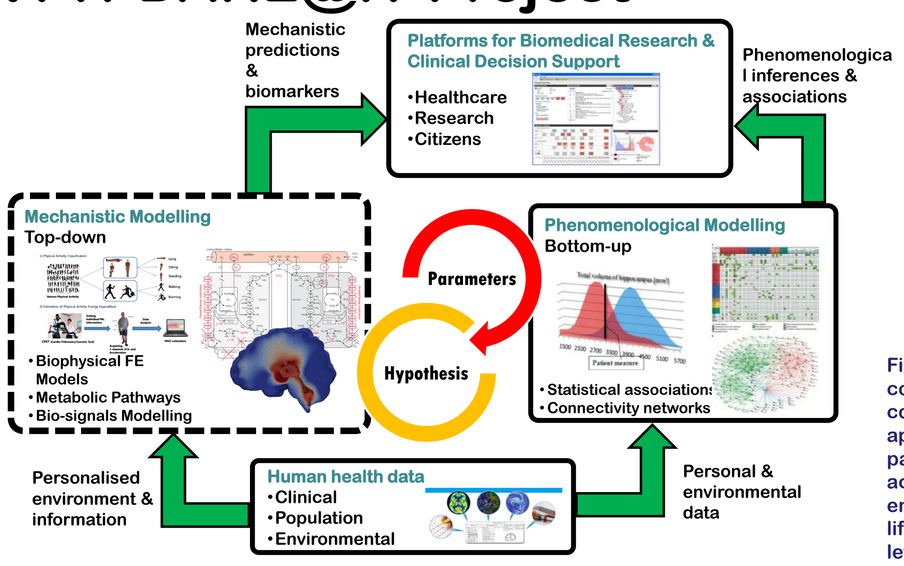


Figure 5. VPH-DARE@IT concept in a nutshell: combining the appropriate modelling paradigm and accounting for environmental and lifestyle factors at each level.

References

[1] J. C. Vardakis, B. J. Tully, Y. Ventikos, "Exploring the Efficacy of Endoscopic Ventriculostomy for Hydrocephalus Treatment via a Multicompartmental Poroelastic Model of CSF Transport: A Computational Perspective", PLoS ONE, vol. 8, 2013.

[2] J. J. Iliff and M. Nedergaard, "Is there a cerebral lymphatic system?", *Stroke*, vol. 44, pp. 93-95, 2013.

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