Investigating patient-specific cerebroventricular fluid complexity in dementia

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1. Introduction

Dementia is a general term for a range of progressive, organic brain diseases that are characterized by problems of short-term memory, disturbances in language, psychological changes, psychiatric changes and lifestyle impairments [1-3].

On a global scale, 46 million people currently live with dementia [4], whilst by 2050, this number is expected to rise to 132 million [5]. The estimated cost of Dementia will increase from $818 billion in 2015 to over $1,000 billion by 2018 [5].

Mild cognitive impairment (MCI) is defined as a state between normal aging and dementia. It is defined as objective cognitive impairment relative to the person's age, with concern about the cognitive symptoms, in a person with essentially normal functional activities who does not have dementia [8-9,12]. It affects 19% of people age 65 and over [10]. Around 46% of people with MCI develop dementia within 3 years, compared with 3% of the age-matched population [11].

It is postulated that reduced CSF production, and hence a lower turnover of CSF (up to a threefold decrease during AD [13]), may lead to a decrease in the clearance of toxic molecules such as Aβ [14] from the ISF space. AQP4 can also be considered as a major component in altering the disturbance of Aβ clearance [15]. Furthermore, it is possible that advanced AD may be connected to either lower or elevated CSF pressure [16-17].

In this brief manuscript, the methodology behind the investigation of CSF dynamics in the cerebroventricular system is outlined. This involves the novel coupling of a finite-volume flow solver and a multiporoelastic model for perfused brain tissue. This link forms part of the designated biomechanistic theme within the VPH-DARE@IT research platform,

2. Materials and Methods

Flow through the multidimensional ventricles (obtained via T1-weighted acquisition) is solved using the Multiphysics software CFD-ACE+ (ESI Group, Paris, France) which is based on the finite volume approach, along with central spatial differencing, algebraic multigrid scheme and the SIMPLEC pressure–velocity coupling. The coupling between the poroelastic solver and the flow solver is achieved through appropriate CFD-ACE+ user-defined subroutines.

Mesh generation for the cerebroventricular volumes was achieved via the use of CFD-VisCART (ESI Group, Paris, France), which is an unstructured adaptive Cartesian grid generation system.

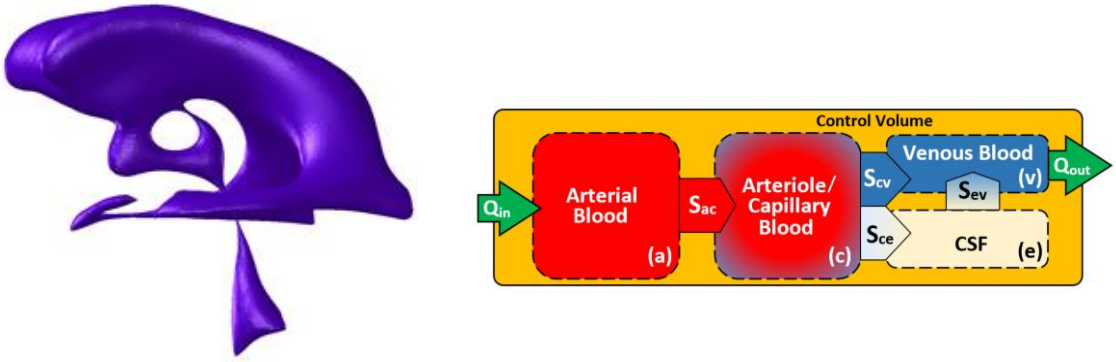

Figure 1: (Left) Ventricular geometry of an MCI patient used for the computational fluid dynamics simulations (Right) The four-compartment MPET model. Flow is prohibited between the CSF and the arterial network, whilst directional transfer exists between (a) and (c), (c) and (v), (c) and (e) and finally (e) and (v).

The current state of knowledge about dementia, and more broadly integrative cerebral dynamics and its associated constitutive requirements, advocates that poroelastic theory provides a suitable framework to better understand the disease. In this work, Multiple-network poroelastic Theory (MPET) is used as a novel spatio-temporal model of fluid regulation and tissue displacement in various scales within the cerebral environment, and is directly used to provide the boundary conditions that are used in the finite-volume based flow solver.

Biologically, the quadruple MPET system [19] is derived by accommodating a high pressure arterial network (*a*), lower pressure arteriole/capillary network (*c*), extracellular/CSF network (*e*) and finally a venous network (*v*), and is discussed further in the next section. The 3D MPET model is discretised with the finite element method (using linear tetrahedral elements). In order to solve the 3D FEM based MPET system, the Portable, Extensible Toolkit for Scientific Computation (PETSc) was utilised, as it is suitable for large-scale scientific application codes written in Fortran (amongst others).

Subject-specific models for circadian blood flow variability incorporating the effect of modifiable lifestyle factors being developed within VPH-DARE@IT as a means of personalising the boundary conditions of the arterial compartment within the four-compartment (arterial, capillary, CSF/ISF and venous) MPET model. This subject-specific approach segregates the feeding territories of the surface of the outer parenchyma with waveform profiles arising from internal carotid and vertebral artery respectively. The parenchymal tissue and cerebroventricular system used for each simulation are also subject-specific, and are currently used as the inner and outer surfaces of the discretized domain used in the MPET simulations, in addition to the surfaces where the boundary conditions are prescribed.

3. Results

Currently, the solution fields borne out of the MPET simulations are complete, and a depiction of the scalar pressures for the CSF/ISF compartment are shown below for one control (Fig. 2, Left) and MCI (Fig. 2, Centre) patient. In addition, the waveforms corresponding to the left and right internal carotid artery (vertebral artery profiles are not shown here) flow rates that are used to feed the arterial compartment of the same control case are also shown in (Fig. 2, Right).

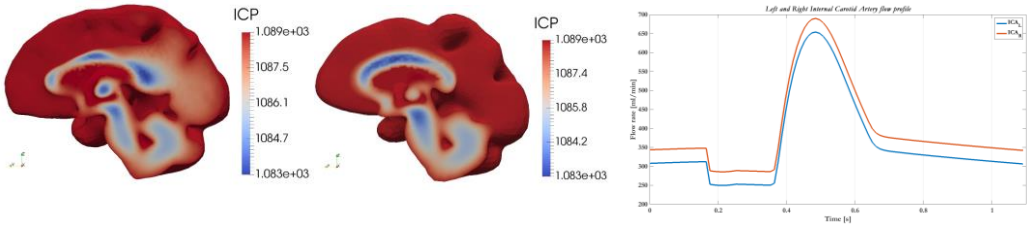

Figure 2: (Left): Solution field for intracranial pressure (in Pa) in a control case. (Centre) Solution field for intraranial pressure (in Pa) in an MCI patient. (Right) Typical continuous waveforms of flow rate for the left and right internal carotid artery used to feed the arterial compartment of the MPET system.

4. Discussion and Conclusions

In this work, the overarching clinical question that is necessary to be answered is if there are any indicators in the solution fields computed through the coupled finite-volume flow solver and MPET system (such as ICP, CSF flow, perfusion through parenchymal tissue) that correlate with clinical findings. For instance, it has been shown that sleep drives metabolic clearance from the brain [18]. In order to be able to better understand how the complicated nature of the flow within the cerebroventricular system could drive the nature of these developments (especially in the case of ICP), it is necessary to compare the flow profiles of both control and MCI patients. This not only requires the use of patient-specific cerebroventricular volumes, but also patient specific flow rate levels during high activity and rest/sleep. In the VPH-DARE@IT project, numerous control and MCI cases are at our disposal, and in this work the focus is on a couple of data sets involving: a male control and MCI patient (both 66 years of age) and a female control and MCI patient (both 82 years of age).

For the aforementioned cases, the 3D MPET model is solved, and the scalar pressure outputs are used to feed the finite-volume based flow solver, which gives rise to computational fluid dynamics (CFD) simulations depicting the complicated nature of CSF dynamics in the cerebral ventricles of the two control and two MCI patients. Important anatomical considerations pertaining to the cerebroventricular geometry will be examined, such as the effects of the interthalamic adhesion on the overall velocity profiles within the ventricles, and in particular, the Sylvian aqueduct. The fourth ventricle possesses the most complex flow found in the cerebroventricular system. Vortices have been observed in previous studies on acute hydrocephalus [19], and develop from the complicated partition of CSF flow arising from the aqueduct of Sylvius (which largely determines the nature of the CSF flow in the fourth ventricle). The other portion of CSF generally travels along the floor of the fourth ventricle and leaves via the three foramina. Flow exits through the foramen of Magendie and a comparatively lower amount through the central canal. CSF flow is generally slow in the lateral ventricles and it will be investigated whether this conforms to the centrifugal based classification outlined in Stadlbauer et al. [20].

The ability of the model to partition flow characteristics allied to control or MCI patients (under different levels of activity) is being examined. In addition, the ability to simulate the complicated nature of flow in the ventricles also allows for investigations of obstruction or atresia of the foramen of Magendie, bilateral foramina of Luschka and central canal. This extends the capabilities of the methodology to capture any associated effects of fourth ventricle outlet obstruction, in addition to being able to predict if any symptoms can be alleviated via the use (simulated) of endoscopic third or fourth ventriculostomy.

The novelty of being able to link the CFD focused study conducted here with the 3D MPET results can also allow for novel observations of cerebral fluid flow and its interaction with the surrounding parenchyma (for instance, observing swelling and/or draining in the periventricular region).

5. References

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