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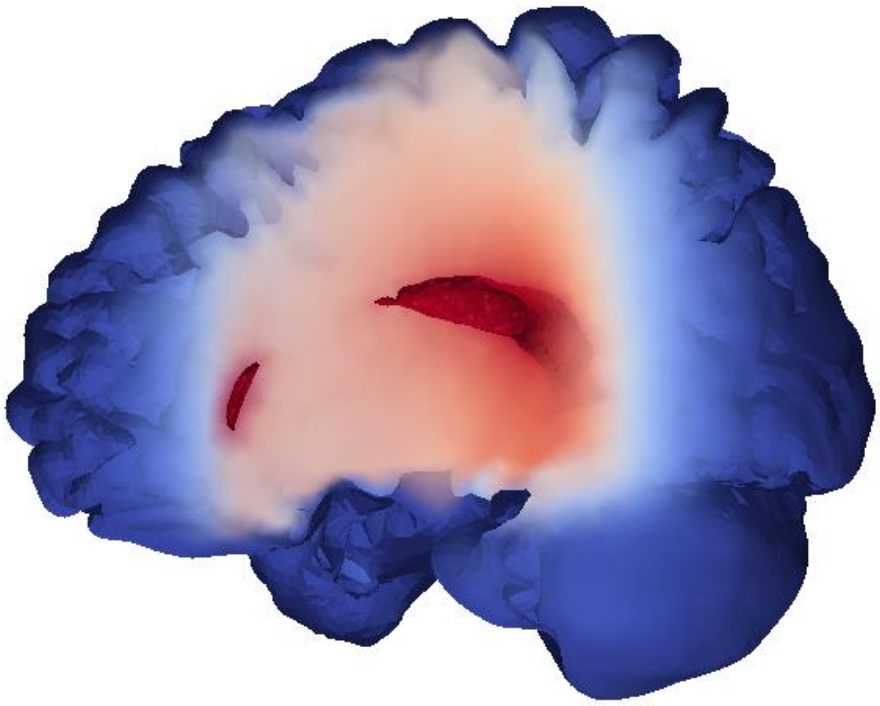

Uncertainty Quantification through multilevel Monte Carlo simulation in FEniCS

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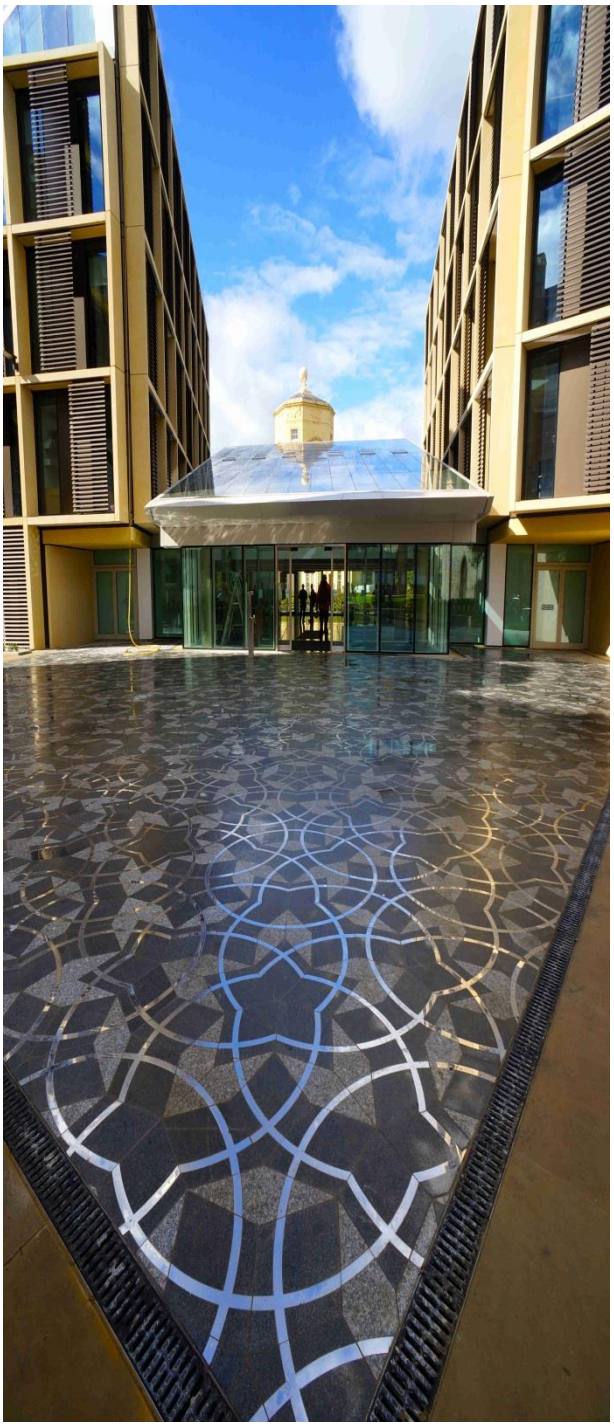
simula



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1. Introduction

The Project Motivation: Brain Disease

Simula Biomedical Computing department (BioComp) is a multi-disciplinary research department that focuses on the simulation of physiological processes that affect human health. BioComp expertise ranges from medical research and bioengineering to mathematical modelling and scientific computing. One of BioComp's current interests is the simulation of the fluid dynamics within the brain, which we refer to as the brain '**waterscape**'. Anomalies in the brain waterscape are believed to be related to common diseases such as **dementia** and **hydrocephalus**.

The most famous type of dementia is Alzheimer's disease, which affects over 44 million people worldwide.

Dementia is a generic term that describes a wide range of diseases which have the common denominator of creating a disorder in a person's mental processes. Examples include memory loss, personality changes, impaired reasoning and thinking, and deterioration of social behaviour. Worldwide, about 47 million people suffer from dementia and every year 7.7 millions more cases are diagnosed, with an expected 75.6 million people being affected by 2030. This leads to an enormous health care cost : $604 billion per year in the US alone. 'More research is needed to develop new and more effective treatments and to better understand the causes of dementia' (World Health Organization).

Hydrocephalus is an abnormal accumulation of a brain fluid, called cerebrospinal fluid, in cavities within the brain called **ventricles**. The occurrence of such a disease is quite high: over a million people are affected in the US alone. This can cause symptoms such as abnormal head enlargement and vomiting in children and chronic headaches, cognitive challenges and mild dementia in adults.

All of these diseases are related to anomalies in fluid flow in or around the brain. This makes the brain waterscape interesting. However, studying these anomalies *in vivo* is difficult. Invasive experiments are performed on mice, but they are not necessarily representative of what goes on in the human brain and they cannot be performed on people. Non-invasive experiments, instead, do not give us enough information. For this reason, computer simulations of mathematical models describing these phenomena are gaining popularity as they represent an alternative avenue of investigation.

It has been claimed that some of the procedures that are used to measure the intracranial pressure might affect the pressure value itself.

Computer simulations are based on mathematical models, which rely on physiological information which is obtained through *in vivo* measurements. Modern techniques allow the measurement of most physical parameters with a reasonable degree of accuracy. Nevertheless, measurement errors are still present, and, in some cases, the measurement itself can affect the quantity which is being measured. Overall, some of the physiological aspects of the fluid dynamics of the brain are still not well understood.

An additional source of uncertainty comes from a lack of knowledge in the medical and biological fields about the brain waterscape physiology and pathology. Models for fluid flow in the brain are therefore inherently uncertain. This uncertainty might increase further in the case of patient-specific simulations, where only partial data are available. The focus of our project is to estimate the expected behaviour of the fluid dynamics of the brain under this uncertainty. This is extremely important for medical applications. In this project, we formulate the simulation of the fluid flow as an **Uncertainty Quantification** problem, which we solve through the use of **multilevel Monte Carlo** (MLMC) simulations and the **finite element method** (FEM).

Biological Background

The human brain is influenced by three different types of flow networks: the **blood vasculature**, the **cerebrospinal fluid** (CSF) and the **interstitial fluid** (ISF). These networks are separated by semi-permeable membranes, which only allow exchange of certain substances and liquids.

The vascular network carries the nutrients to the brain cells within the **parenchyma** (the cerebral matter) and it is strongly related to the production of CSF, which is believed to be produced from blood plasma in the brain ventricles. From the ventricles, the CSF flows in the spinal canal and in the **subarachnoid space**, the space between the arachnoid and pia meninges (see Figure 1).

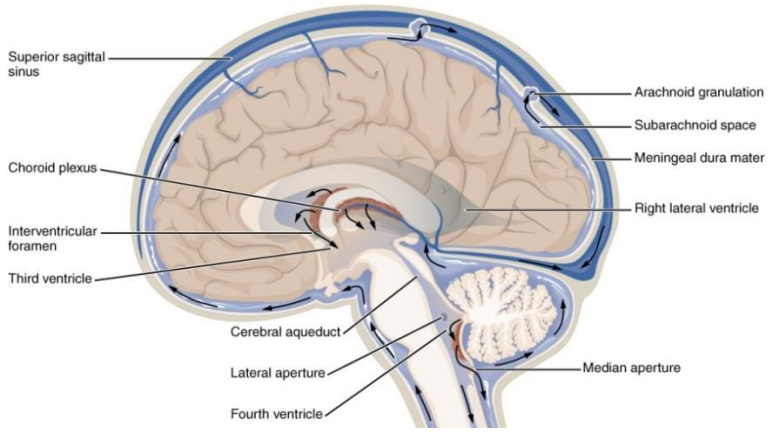

Figure 1: A schematic of the brain CSF flow. CSF is produced within the ventricles and flows around the brain before being reabsorbed in the subarachnoid space. The parenchyma is made of brain cells and it is coloured in grey in the picture. Picture taken from http://www.wikiwand.com/en/Cerebrospinal_fluid.

Brain cells absorb their nutrients from the vascular system and release metabolic waste into the interstitial space, the space between the cells. Here, the waste is absorbed and collected by the ISF, which permeates the brain tissue. The interstitial space and the ISF make the parenchyma a sponge-like solid permeated by liquid.

Although flow exchange is possible between the different networks, there is still a lot of uncertainty in the academic community about this physiological process. Another topic on which the debate is still open is the presence of a strong **intracranial pressure**, whose baseline has been reported to have significantly different values.

2. Mathematical Model

Modelling Interstitial Fluid Flow

In this project, we focus on the analysis of a single fluid: the ISF. In particular, we want to simulate the pressure of the fluid within the brain parenchyma. If the pressure is high, it can "push" on the brain ventricles, causing their enlargement. In hydrocephalus, this is what happens: an accumulation of liquid in the ventricles causes them to dilate. It is interesting to study the extent of this enlargement. For this reason, we compute the deformation of the brain tissue as well.

We consider the brain tissue as a sponge permeated by liquid. A sponge-like material is called **porous**. Fluid in a deformable porous medium is obstructed by the solid structure and it moves more slowly than it would, say, in a river. The extent to which this happens can be quantified by a variable called the **permeability**. Because of this resistance, two things happen: the liquid pushes the solid medium, which deforms and, *vice-versa*, the solid pushes the liquid with it as it deforms. The mathematical model we consider is given by the **Biot equations** and it accounts for this behaviour.

In the case of pathologies such as hydrocephalus, the time for disease development is extremely long (years). We therefore consider a **steady-state** approximation, which means that we simulate the long-term stable behaviour of the fluid. We assume that the brain tissue is fixed (it does not deform) at the arachnoid interface and that all the forces that act

on the ventricle walls are in equilibrium (the ventricles are still). Lastly, we apply a sensible value of the intracranial pressure, taken from the literature.

Quantifying the Model Uncertainty

The win at a lottery, the value of a playing card drawn from a deck, whether it will be sunny next week... All of these can be modelled as random variables.

Many parameters are uncertain in our model. In this project, we focus on two physical quantities: the intracranial pressure and the permeability, and we model them as **random variables**. A random variable is a variable whose value depends on an aleatory (or **stochastic**) event. For example, the outcome of a die roll is a random variable that can have values between 1 and 6 according to how the die is cast. The way the die positions on the table is random and it affects the value of the die roll.

Simulating a stochastic event allows us to compute the related value attained by the random variable. This operation is called **sampling**. Consider a game in which we win a pound if a coin flip is heads and we lose a pound otherwise. How much are we expecting to win on average if we play many times? To compute the expected win, or better, the **expected value** of the coin toss, we can flip the coin a lot of times and take the average of the win and losses. For this game, we have equal probability (50%-50%) to win or lose a pound so the expected win of this game is 0 pounds. The win here is a random variable and this method of computing the expected value is called the **Monte Carlo method**.

In our model, the fact that permeability and intracranial pressure are taken to be random variables causes the fluid pressure and displacement to be uncertain as well. Similarly as for the coin toss, we want to be able to draw samples from the distribution of fluid pressure and of brain tissue displacement so as to compute their expected values (the expected behaviour of the brain system). By using the FEM to solve the mathematical model, we can compute pressure and displacement for a given permeability and intracranial pressure.

Sampling the intracranial pressure value is much easier to do than sampling the permeability. This is because the intracranial pressure has one value, while the permeability varies with position. The model we use is a modification of the Biot model, which describes the behaviour of a porous media (the brain matter) saturated by a fluid. The intracranial pressure sampling can be simplified by exploiting a property of the Biot model called linearity. Sampling the permeability, instead, requires the specification of its **probability distribution** and a sampling method. A distribution is a measure of the probability of a random variable to attain a given value. For example, the distribution of a coin toss is 50% probability of flipping heads and 50% probability of flipping tails.

The distribution of the permeability is itself unknown, but we can provide a model for this distribution, which means that we can assume that the distribution behaves in a certain way according to some physical principles and constraints. In particular, we prescribe a different permeability value for each direction so as to model the fact that the brain tissue is not homogeneous and it is more or less porous (it obstructs flow more or less) according to the flow direction. This property is called **anisotropy**. In particular, we will have, as an approximation, a higher permeability in the vertical direction.

Once we have a model for the distribution, we also need to formulate a sampling method or strategy. Our sampling strategy requires the solution of a (modified Helmholtz) equation, which can be solved by using the FEM.

Monte Carlo methods are perfectly suited for parallelization. This means that we can considerably improve efficiency by dividing the workload across different processors.

We now have all the ingredients needed for the Monte Carlo method to compute the expected behaviour of the fluid flow in the brain system. However, this method is computationally costly, to the extent that a single simulation would take roughly a week to run on a common laptop. For this reason, we use instead a more advanced method, called **multilevel Monte Carlo** (MLMC). MLMC uses a hierarchy of approximation **levels**. Each level is characterised by an accuracy degree and computational cost. On the **coarse** levels, we make a rough, but cheap approximation of the samples, while on the **fine** levels, the accuracy is high at a high cost price. MLMC draws many (cheap) samples from the coarse levels and corrects them with samples taken from the fine levels (expensive, but we only need a small amount of them). This procedure allows a fine level approximation quality at

(roughly) a coarse level cost. From a week, the computational time goes down to four hours on a common laptop and less than an hour on a more powerful computer.

3. Numerical Results

We simulate the ISF flow under hydrocephalus conditions. In Figure 2, we show the expected value of the fluid pressure (red = high pressure, blue = low pressure). We note that this is higher in the middle portion of the parenchyma as the permeability is, on average, higher in this region. The pressure is highest on the ventricular wall, causing it to dilate; see displacement plot in Figure 3.

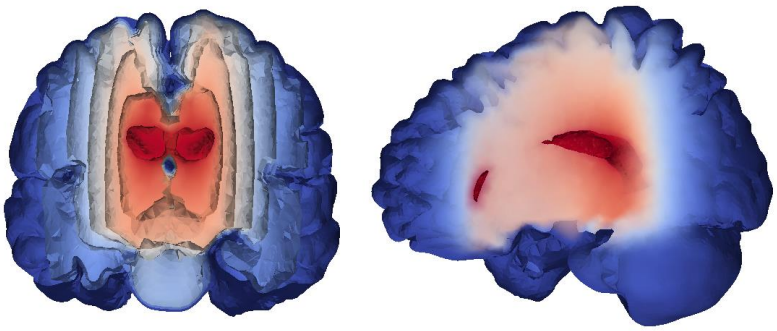

Figure 2: Expected value of the ISF pressure. Pressure is higher in the regions coloured in red and lower in those coloured in blue. The highest pressure values are around the ventricles and in the middle of the brain parenchyma.

In Figure 3, we see that the displacement is higher near the ventricles, especially on the lower bit of the ventricle horns ("tips"). This causes the ventricles to enlarge, a phenomenon which is one of the typical symptoms of hydrocephalus. Our numerical simulation agrees with the expected physiological behaviour of the brain.

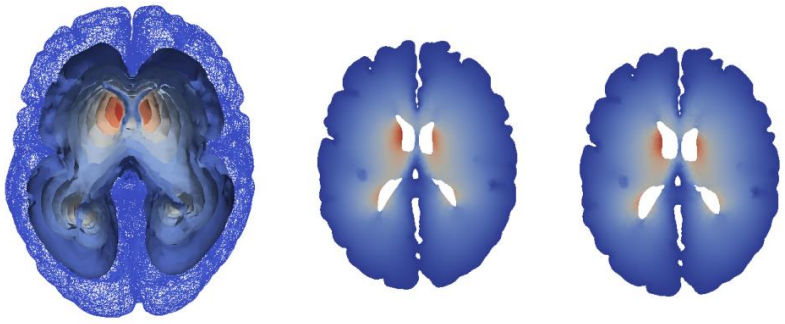

Figure 3: Expected value of the brain displacement (red = large displacement, blue = small displacement). We show the normal ventricle size in the brain slice in the middle and the dilated ventricles in the slice on the right.

Finally, we can simulate the long term propagation of the concentration of an injected medicine, and we show the results are shown in Figure 4. We see that, if we wait long enough, the medicine (dissolved in the ISF) reaches the whole parenchyma. Although this is a simple test case, simulations of this kind can be very useful for studying the dynamics of drug delivery.

It is also possible to simulate the behaviour of an injected tracer. Tracers are used to highlight the presence of fluid in MRI scans.

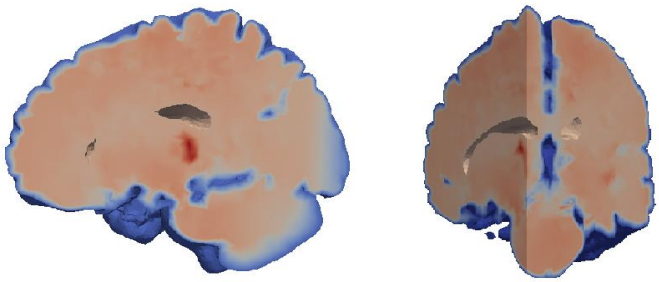

Figure 4: Expected value of the medicine concentration. We coloured in pink and red the regions reached by the injected medicine. The red regions represent a higher medicine concentration, while the blue regions indicate a lower concentration.

4. Discussion, Conclusions and Recommendations

Simulating the fluid dynamics of the brain is important for medical applications, such as disease investigation and treatment. However, these simulations are hard to set-up since some of the physiological aspects of the brain are still not well understood. This leads to uncertainty in the formulation of mathematical models and in the related parameters. To simulate the physics of the fluids within the brain under this uncertainty, we chose a stochastic version of the Biot model.

The equations related to this model were solved by using finite elements and multilevel Monte Carlo simulation. The solutions obtained are comparable with other results presented in the literature and behave as mathematically expected. The computational improvement in comparison to standard Monte Carlo methods is quite significant (about 85 times faster).

In this study, we chose a simple model as a starting point. For more accurate simulations, it would be useful to investigate models of higher complexity. If permeability data was available, it would also be possible to compute its probability distribution and have a realistic measure of how far the actual fluid behaviour is from the computed expected value. Further research will be focused on the development of more advanced mathematical techniques (for Monte Carlo simulation and equation solving), which are currently not available in the literature. These techniques could be applied widely, for example in mathematical finance, vehicle manufacturing, oil reservoir simulation, engineering.

5. Potential Impact

Marie E. Rognes, Head of the Biomedical Computing Department at Simula, commented:

"*Simula Research Laboratory is a limited company owned by the Norwegian Ministry of Education and Research. Our main objective is to create knowledge about fundamental scientific challenges that are of genuine value for society. In the Simula Biomedical Computing Department and the associated Centre for Biomedical Computing (CoE) we aim to develop and apply novel simulation technologies to reach new understanding of complex physical processes affecting human health. We target selected medical problems where insight from mathematical modeling can contribute to changing clinical practice.*

One of our current fundamental research goals is to use modelling and simulation to better understand and predict the flow of fluid and solutes through brain tissue. These physiological mechanisms are crucial for the well-being of the brain. In spite of their importance, we understand them but little. Mathematics and numerics could play a crucial role in gaining new insight, and medical doctors express an urgent need for

modelling and simulation to overcome limitations in traditional techniques. Indeed, a new avenue of investigation to understand these physiological prosesses has tremendous long-term clinical impact in association with neurological diseases such as dementia and oedema.

Matteo's project is a ground-breaking first step in this direction. By applying advanced numerical techniques, he has quantified the propagation of uncertainty in material parameters through a model for the fluid flow in brain tissue. This allows us to rigorously examine the validity of the model results and lays the ground for reliable in silico studies of the brain's waterscape. Indeed, the possibility of analyzing and quantifying uncertainty in our model results is essential for the longer term clinical impact of our research."