Uncertainty Quantification of Coupled 1D Arterial Blood Flow and 3D Tissue Perfusion Models Using the INSIST Framework

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Abstract. We perform uncertainty quantification on a one-dimensional arterial blood flow model and investigate the resulting uncertainty in a coupled tissue perfusion model of the brain. The application of interest for this study is acute ischemic stroke. The outcome of interest is infarct volume, estimated using the change in perfusion between the healthy and occluded state (assuming no treatment). Secondary outcomes are the uncertainty in blood flow at the outlets of the network, which provide the boundary conditions to the pial surface of the brain in the tissue perfusion model. Uncertainty in heart stroke volume, heart rate, blood density, and blood viscosity are considered. Results show uncertainty in blood flow at the network outlets is similar to the uncertainty included in the inputs, however the resulting uncertainty in infarct volume is significantly smaller. These results provide evidence when assessing the credibility of the coupled models for use in *in silico* clinical trials.

Keywords: uncertainty quantification · blood flow modelling · tissue perfusion modelling · *in silico* clinical trials · acute ischemic stroke.

1 Introduction

The development of *in silico* clinical trials and physics-based models for personalised medicine is a growing field due to an increased accessibility to compute resources, models, and data. However, such models require a large number of parameters, many of which are expensive, time consuming, or even impossible, to measure within a clinical setting. Consequently, we turn to uncertainty quantification (UQ) to determine how unmeasured parameters impact the results from these models, and which parameters account for any significant variation in the results. A UQ analysis is likely to be critical to prove that these models are sufficiently credible to provide evidence of efficacy of new treatments, according to the current standards on simulation of medical devices [1].

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DOI: 10.1007/978-3-030-77980-1_52

Though uncertainty quantification of physics-based models is a well established field, less work has been done on uncertainty quantification of multi-scale and multi-physics models. An approach taken in [14]—a semi-intrusive Monte Carlo method—is to replace the computationally-heavy model in a coupled multi-scale system with a surrogate model. This reduces the number of samples required of the expensive model, hence allowing for a Monte Carlo analysis to be performed in a reasonable computational time.

For the models used in this paper, a non-intrusive uncertainty quantification method is appropriate given the models' complexity. Two well-established non-intrusive methods are quasi-Monte Carlo (QMC) and polynomial chaos [4, 13]. In this paper we use a QMC method for its robustness and flexibility.

The intention of the INSIST project is *in silico* clinical trials for acute ischemic stroke [10]. The first elements to these trials are modelling blood flow through the arteries and the resulting perfusion throughout the brain, both with and without an occlusion. We are interested in applying UQ methods to a 1D blood flow model coupled to a 3D model of perfusion [15]. Uncertainty analysis of blood flow through the arterial network has been studied in several models previously [2, 3, 18]. This study intends to understand how the uncertainty in blood flow impacts the results of the perfusion model in a stroke scenario.

2 Methods

We investigate the uncertainty propagation in a one-way coupled 1D arterial blood flow and 3D tissue perfusion model [15]. We are primarily interested in the uncertainty in the change in perfusion between the healthy state of the system (pre-stroke) and the occluded state (after stroke).

The outcome metric of interest is the volume of tissue that has a 70% decrease in perfusion between the healthy and occluded state, as an estimate of infarct volume without treatment [8]. The secondary outcomes of interest are the variation in blood flow through the occluded vessel in the healthy state; and the uncertainty in the change in flow rates between the healthy and occluded states in the artery outlets, which form the boundary conditions for the tissue perfusion model.

2.1 The INSIST Framework

The blood flow and tissue perfusion models are run as part of the INSIST framework [10]. The framework links a patient-generation model to physics-based models for blood flow, blood perfusion in the brain, thrombolysis, and thrombectomy. The intention of INSIST is to run large cohorts of patients, however for the purposes of this UQ investigation, we instead generate multiple copies of a single patient. The patient has an associated set of parameters generated using a statistical model built on clinical data from the MR CLEAN Registry [5]. The parameters generated by this model are therefore considered to be known parameters, and not investigated in the study.

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DOI: 10.1007/978-3-030-77980-1_52

2.2 The Blood Flow and Tissue Perfusion Models

The two models we are using in this study are an arterial blood flow model, and a tissue perfusion model. The blood flow model is a 1D steady state blood flow model for the artery network from the heart to the pial surface of the brain [15]. The tissue perfusion model uses a 3D finite-element Darcy flow model with three compartments: arteriole, capillary, and venules [8]. The blood flow model provides the boundary conditions for the tissue perfusion model.

2.3 Uncertainty Quantification

In order to efficiently undertake uncertainty quantification (UQ) activities, the INSIST framework is linked to the open-source library EasyVVUQ [16]. We use a quasi-Monte Carlo approach for UQ, and Sobol indices to determine the parameter contributions to output uncertainty, calculated using the Saltelli and Jansen/Saltelli methods for the first and total order indices respectively [6, 17]. A total of 3,000 samples were run using Sobol quasi-random sequences to generate the sampling matrices required for the Sobol indices [17] using EasyVVUQ [16].

This paper shows the effect of uncertainty in the arterial blood flow on the estimated infarct volume, calculated using the change in perfusion in the tissue perfusion model. We focus here on aleatoric uncertainty—parameter uncertainty due to inherent variation in the population. The parameters we consider are given in Table 1. Distribution parameters and shapes are based off population studies found in the literature (sources shown in table).

For the purposes of this study, we only consider one occlusion location: the M1 segment in the middle cerebral artery (MCA), as it was the most commonly occluded segment in the MR CLEAN Registry (58% of patients) [5]. We also assume that the clot is impermeable. We intend to use this same method to investigate uncertainty in artery morphology parameters and tissue perfusion model parameters, however these are not included in the results below.

3 Results

3.1 Effect of Uncertainty on Infarct Volume

The primary outcome of interest for the study is the estimate of infarct volume without treatment. This estimate is determined using a threshold on the change in tissue perfusion between the healthy and occluded states (70% reduction) [8]. Figure 1a shows the resulting uncertainty in infarct volume given the uncertainty in the blood flow model parameters given in Table 1. The mean infarct volume is $\mu_{\text{iv}} = 268.3$ mL and the standard deviation is $\sigma_{\text{iv}} = 0.5$ mL. This gives a coefficient of variation of $\text{CV}_{\text{iv}} = 0.002$, which is 2 orders of magnitude lower than the variation in the input parameters. We note the right tail of the distribution is associated with low pre-stroke pressures in the occluded vessel, which occur when the product of viscosity, heart rate, and heart stroke volume is very high.

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DOI: 10.1007/978-3-030-77980-1_52

Table 1: The parameters with aleatoric uncertainty in the 1D arterial blood flow model; their distributions and source; and their determined Sobol indices. CV: Coefficient of variation. Heart stroke volume is the volume of blood pumped out the left ventricle per heart beat.

Parameter	Distribution	CV	Source	Sobol first	Sobol total
Blood density (kg.m^{-3})	U(1040, 1055)		[9]	0.00	0.00
Blood viscosity (mPa.s)	N(4.2, 0.9)	0.21	[7]	0.07	0.10
Heart stroke volume (mL)	N(95, 14)	0.15	[11]	0.36	0.40
Heart rate (bpm)	N(73,12.2)	0.17	[12]	0.42	0.50

3.2 Effect of Uncertainty on Blood Flow Model Outputs

Though the primary outcome of interest is the infarct volume, it is useful to investigate the uncertainty in the outputs of the blood flow model, which provides the input to the tissue perfusion model. The main artery of interest for this study is the occluded vessel: the right MCA. The resulting distribution of flow rates in this vessel is shown in Fig. 1b. For the 3,000 samples, the mean flow rate through the right MCA vessel is $\mu_{\text{ov}} = 2.47$ mL/s, with a standard deviation of $\sigma_{\text{ov}} = 0.45$ mL/s, and hence a coefficient of variation of $\text{CV}_{\text{ov}} = 0.18$. This is of the same order of magnitude as the uncertainty in the inputs, given in Table 1.

Also relevant are the arteries providing flow to the pial surface of the brain and hence providing the boundary conditions for the coupled perfusion model. On average, the boundary vessels in the brain, excluding the occluded vessel, have a 7% change in their flow rate between the healthy and occluded state. The uncertainty in blood flow for each of these boundary outlets is shown in Fig. 2, for the healthy state. The mean coefficient of variation for the boundary vessels of the brain in the healthy state is $\overline{\text{CV}}_{\text{bv}} = 0.19$, similar to the occluded vessel. For the change in flow between healthy and occluded state it is $\overline{\text{CV}}_{\delta\text{bv}} = 0.22$.

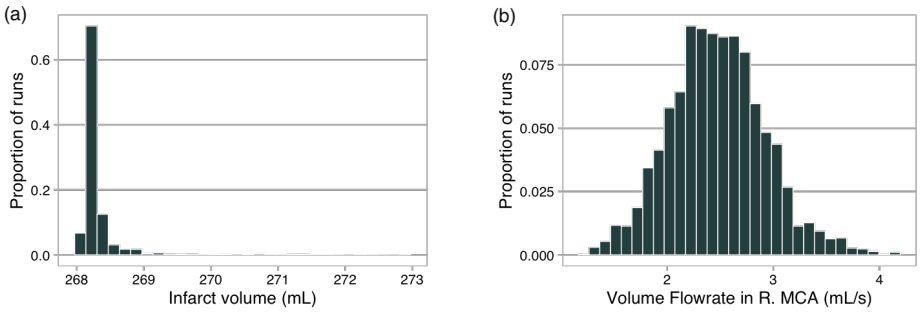

Fig. 1: Effect of uncertainty in arterial blood flow parameters on (a) infarct volume, estimated using a change in perfusion threshold, and (b) healthy state volume flow rate through the occluded vessel: right middle cerebral artery (MCA).

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DOI: 10.1007/978-3-030-77980-1_52

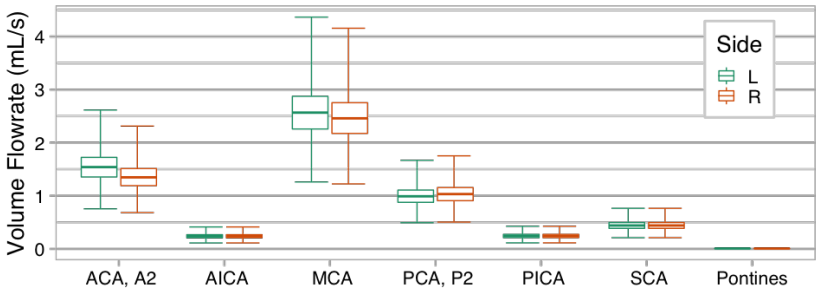

Fig. 2: Quantiles (box) and range (error bars) for blood flow in vessels providing the boundary conditions for the perfusion model. ACA: anterior cerebral artery, AICA: anterior inferior cerebellar artery, MCA: middle cerebral artery, PCA: posterior cerebral artery, PICA: posterior inferior cerebellar artery, SCA: superior cerebellar artery.

3.3 Sensitivity Analysis

The sensitivity of blood flow in the occluded vessel to each of the parameters considered is given in Table 1. The table shows the first order and total effect for each parameter. It can be seen that almost all the uncertainty in the blood flow is due to uncertainty in the heart rate and heart stroke volume. The product of heart rate and stroke volume determine the flowrate at the input boundary of the artery network (the ascending aorta), explaining their large impact on the output sensitivity.

There is also a small sensitivity to blood viscosity. We would expect flowrate to be inversely proportional to viscosity for laminar flow in a pipe, which explains viscosity's effect. Based on the Hagen-Poiseuille law density and viscosity should have the same weight, so the lack of sensitivity to density is due to the low variation in the parameter. Given this result, when further uncertainties from the blood flow and tissue perfusion models are added, it would be possible to exclude blood density in order to minimise the number of simulations required in an extended UQ.

4 Discussion

The results showed that, although the uncertainty in the arterial blood flow output is on the same order of magnitude as the input uncertainties, the uncertainty in the final determined infarct volume is two orders of magnitude lower. This is likely due to several assumptions and simplifications in the models. This includes the assumption that infarct volume can be estimated well using the relative change in perfusion; the use of an impermeable clot; and no modelling of collateral flow in the brain. Given the brain mesh is the same between patients,

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DOI: 10.1007/978-3-030-77980-1_52

this means the same region of the brain is always blocked and becomes infarct. The small differences in infarct volume likely come solely from small differences in blood flow in the regions of the brain bounding the infarct region.

Additionally, we determined that the change in flow rate in the other boundary vessels is only 7% of the healthy flow, and consequently the impact of the uncertainty in the change in flow rate ($\overline{\mathrm{CV}}_{\delta \mathrm{bv}} = 0.22$) becomes much less significant when considered relative to the baseline flowrate. This would then also significantly decrease the uncertainty in the final infarct volume, given its definition as a reduction in flow of 70%.

Our results show that, though there may be a high level of uncertainty in the outcomes of one model in a framework such as INSIST, this is not indicative of the uncertainty in the whole system. This can help prove increased credibility of the whole workflow for *in silico* clinical trials, as opposed to assessing credibility based off the uncertainty results for each of the models individually.

In future work, we intend to continue to investigate UQ of each model independently and compare this to a UQ of the coupled system. This will involve incorporating uncertainty in further parameters in the arterial blood flow model, as well as parameters in the tissue perfusion model. Additionally, we intend to incorporate a tissue death model, which will likely increase the uncertainty in the infarct volume compared to the current perfusion threshold estimate.

As more parameters are added to the system, computational times will likely become infeasible using the proposed approach. To deal with this increased computational load, we consider two options. Firstly, not including parameters whose uncertainty is not determined to have a significant effect, such as blood density (Table 1). Secondly, exploiting the independence of the models using a semi-intrusive approach. In such an approach, the UQ analysis of tissue perfusion, and any further coupled models, builds on top of the results from the UQ of the blood flow model, as opposed to treating the coupled model as a black box.

INSIST has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 777072.

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DOI: 10.1007/978-3-030-77980-1_52

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