



## A sensitivity analysis of a personalized pulse wave propagation model for arteriovenous fistula surgery. Part B: Identification of possible generic model parameters

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### ABSTRACT

Decision-making in vascular access surgery for hemodialysis can be supported by a pulse wave propagation model that is able to simulate pressure and flow changes induced by the creation of a vascular access. To personalize such a model, patient-specific input parameters should be chosen. However, the number of input parameters that can be measured in clinical routine is limited. Besides, patient data are compromised with uncertainty. Incomplete and uncertain input data will result in uncertainties in model predictions. In part A, we analyzed how the measurement uncertainty in the input propagates to the model output by means of a sensitivity analysis. Of all 73 input parameters, 16 parameters were identified to be worthwhile to measure more accurately and 51 could be fixed within their measurement uncertainty range, but these latter parameters still needed to be measured. Here, we present a methodology for assessing the model input parameters that can be taken constant and therefore do not need to be measured. In addition, a method to determine the value of this parameter is presented. For the pulse wave propagation model applied to vascular access surgery, six patient-specific datasets were analyzed and it was found that 47 out of 73 parameters can be fixed on a generic value. These model parameters are not important for personalization of the wave propagation model. Furthermore, we were able to determine a generic value for 37 of the 47 fixable model parameters.

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### 1. Introduction

A vascular access (VA) is required for end-stage renal disease (ESRD) patients undergoing hemodialysis therapy. The vascular access is the site at the body where blood is withdrawn to the dialyzer and returned after filtration. Preferably, a vascular access is created surgically by connecting an artery and vein in the arm, i.e. an arteriovenous fistula (AVF).

Planning the optimal location for AVF surgery by the surgeon could be improved if a quantitative measure of the postoperative vascular access flow (brachial artery inflow) and of the postoperative systolic pressure distal to the anastomosis were available

before surgery [1–3]. Therefore, we developed a distributed lumped parameter pulse wave propagation model that can make an individualized prediction of the postoperative mean brachial flow and the systolic pressure distal to the anastomosis [4].

To use distributed wave propagation models in individualized treatment planning, model input parameters should be adapted to patient-specific conditions and therefore measurements on patients are needed. However, in clinical practice, measurements are associated with relatively large measurement uncertainties compared to in vitro measurements resulting from restrictions in measurement time, limited facilities and available modalities. These inaccurate and incomplete datasets will result in output uncertainties and, therefore, insight into the propagation of measurement uncertainties to output uncertainty is needed. To this end, a global sensitivity analysis can be applied [5–7]. The insight obtained by such a global sensitivity analysis can be used to determine the model parameters that are most rewarding to measure more accurately, as accurate measurements of these parameters

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will result in the largest reduction in the uncertainty of the predicted mean brachial flow and distal systolic pressure (parameter prioritization). Moreover, the global sensitivity analysis can be used to determine model parameters that can be fixed onto a constant value (parameter fixing), because they do not significantly influence the output uncertainty. Therefore in part A [8], we set-up a framework and used this to execute a variance-based sensitivity analysis on our wave propagation model. Parameters were varied within their measurement uncertainty and in this way we determined which model parameters should be measured more accurately to reduce the uncertainty in the prediction of mean brachial flow and distal systolic pressure (parameter prioritization), and which parameters could be fixed within their measurement uncertainty domain. We found that improving measurements was only rewarding for 16 out of 73 model parameters, whereas 51 parameters could be fixed within their measurement uncertainty domain. Improving measurements of these 51 model parameters are therefore not beneficial in order to obtain a reduction in output uncertainty and, moreover, fixing these 51 parameters within their measurement uncertainty domain still means that these parameters need to be measured or estimated for each patient. In this paper (part B), we will present a methodology to identify model input parameters, for which a constant generic value can be taken. As a result, the number of required patient-specific measurements will be reduced. Parameter fixing used to reduce the number of model parameters is amongst others described by Saltelli et al. [5,6].

An intuitive strategy to determine which model parameters can be fixed is to first define model parameters for an average patient and, thereafter, perform a sensitivity analysis, comparable to the analysis in part A, but now while each model parameter is varied within its population uncertainty domain. However, defining parameters for an average patient is not trivial, because, to compute reliable mean values for the model parameters, a large number of patients is required. In addition, model parameters might be grouped within the complete input space, for example as a result of gender differences or because of a relation between the parameter and age or body-mass-index (BMI). Since in a sensitivity analysis all model parameters are varied within the complete population uncertainty domain, a sensitivity analysis for parameter fixing should be performed within each (sub)group to avoid non-physiological combinations of input parameters. For non-physiological parameter combinations, the model will not converge which will hamper the sensitivity analysis. Therefore, in this study we performed a sensitivity analysis by segmenting the input parameter space. For this we selected patient-specific datasets and applied the population uncertainty on each individual set. This approach reduces the chance of non-physiological input, while the relevant part of the input space is still covered.

The outline of this paper is as follows. First, we describe our distributed wave propagation model and the global sensitivity method that is used in this study. Thereafter, we describe the input parameters that are selected as possible candidates for parameter fixing and we define their uncertainty domains based on the variation within the patient population. Furthermore, the Monte Carlo experiments executed for the global sensitivity analysis are described. Finally, the parameters are discussed that can be fixed and generically chosen.

## 2. Materials and methods

### 2.1. The wave propagation model

The wave propagation model used in this study has demonstrated to have potential in supporting AVF surgery planning [4].

In this study we use two different model topologies (computational domains) that are shown in Fig. 1 (mid panels). The first topology represents a lower arm AVF configuration and consists of the main arteries of the right arm, a truncated part of the aorta, the vertebral artery and the right and left common carotid arteries. To model the AVF, this topology is further extended with an anastomosis segment and a venous outflow tract of upper and lower arm veins. The second topology represents an upper arm AVF, for which the outflow tract consists of the upper arm veins.

Each vessel of the computational domain is divided in segments. In each segment the relation between local pressure and flow is described. All arterial and venous segments are modeled with a lumped parameter approach (Fig. 1, right panel) derived from local mass and momentum equations. To determine the resistance  $R$ , the inertance  $L$  and the compliance  $C$  geometrical (vessel length, radius, wall thickness) and mechanical (Young's modulus) vessel properties are required. The anastomosis segment is modeled with a nonlinear resistor amongst other dependent on anastomosis angle and blood flow. Parts of the cardiovascular system for which information on local pressure and flow is not needed are terminated with three-element windkessels consisting of a characteristic impedance  $Z_{wk}$ , a peripheral resistance  $R_{wk}$  and a peripheral compliance  $C_{wk}$ . On the first node a measured aortic flow is prescribed, whereas the vessel at venous outflow is closed with a fixed intravenous pressure. For more details about the model we refer to Huberts et al. [4] and part A.

### 2.2. Global sensitivity analysis

#### 2.2.1. Variance-based method

The variance-based method will only be described briefly because this was extensively described in part A and, previously, by Saltelli et al. [5–7]. The variance-based method is a method in which the total variance  $V(Y)$  of the output  $Y$  is apportioned to the input parameters. Sobol [9] showed that for  $k$  independent input parameters  $X_i$  with  $i = 1, \dots, k$ , the normalized output variance can be decomposed to

$$\sum_i S_i + \sum_i \sum_{i>j} S_{ij} + \sum_i \sum_{i>j} \sum_{l>j} S_{ijl} + \dots + S_{12\dots k} = 1, \quad (1)$$

in which  $S_i \in [0, 1]$  represents the fraction of the total output variance resulting from parameter  $X_i$ , whereas the higher order indices  $S_{ij}$ ,  $S_{ijl}$  and  $S_{12\dots k}$  describe the fractions of the total variance resulting from interactions between parameters. The main sensitivity index is defined as  $S_i = V(E(Y|X_i))/V(Y)$  in which  $(E|Y=X_i)$  represents the conditional expected value of the output  $Y$  given  $X_i$  and  $V(E(Y|X_i))$  the variance of this conditional expected value. For an exact definition of the integrals used to calculate the expected value  $E$  and the variance  $V$ , the reader is referred to the appendix of part A [8]. This sensitivity index can be interpreted as the expected reduction of output variance if the true value of parameter  $X_i$  was known and is used in parameter prioritization.

In the case of additive models the total output variance only consists of main effects ( $\sum_i S_i = 1$ ). When interactions between the model parameters are present, the main sensitivity index is not sufficient to determine which parameters can be fixed within their uncertainty ranges, because contributions via interactions with other parameters can be large. Therefore, in parameter fixing, higher order effects should be taken into account. However, calculating all higher order effects is computationally expensive unless (1) converges to one quickly. Therefore, Homma et al. [10] derived a total sensitivity index for parameter fixing.

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