Practical Identifiability and Uncertainty Quantification of a Pulsatile Cardiovascular Model

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Abstract

Mathematical models of the circulation continue to be an essential tool to study how the cardiovascular (CV) system maintains homeostasis. The utility of these models is ultimately limited by how much we can trust the accuracy of their predictions. The predictive capability of a model can be measured by uncertainty quantification (UQ). A challenge in implementing UQ procedures is that many published methods require that the model be identifiable. An identifiable model is one with a one-to-one mapping from the parameter space to the model output. In this paper we use a novel and reproducible methodology to calibrate a lumped-parameter CV model to left ventricular pressure and volume time series data from rats. Key steps in our methodology include using (1) literature and available data to define a set of nominal parameter values specific to each rat; (2) sensitivity analysis and subset selection to determine a set of identifiable parameters; (3) optimization to find a point estimate for identifiable parameters; and (4) both frequentist and Bayesian UQ methods to assess the predictive capability of the model.

Keywords: Cardiovascular dynamics; modeling; parameter estimation; uncertainty quantification; patient-specific modeling.

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1. Introduction

Precision medicine is a growing model of healthcare that proposes to customize of care, medical decisions, practices, and products to the individual patient. This approach is particularly important, as pathologies such as cancer, autoimmune disorders, and cardiovascular diseases are unique to a given individual and are thus challenging to develop diagnostic and treatment tools. One of the many approaches to studying patient-specific complexities is to use mathematical modeling, which for the circulatory system can provide critical insight into how the body maintains homeostasis.

A rich history of cardiovascular modeling exists in the literature; see, e.g., [1, 2, 3, 4, 5]. One way to use mathematics to study cardiovascular dynamics is via compartment models. Compartments are used to represent the various blood vessels and the heart, often formulated analogously to electrical circuits, with capacitors, resistors, and inductors [6, 7, 8]. The compartments are interpreted as entities containing volume (analogous to charge) that have pressure (voltage) and flow (current) both in and out of each compartment. Typical models comprise compartments representing groups of vessels (e.g. large arteries or veins, small arteries or veins, capillaries, or arteries leading to specific organs) as well as a heart acting as a pump driving the system. Some models include both pulmonary and systemic circulations [9], while others focus on the flow in only one of the two systems [10]. For pulsatile models, the contraction and relaxation of the heart is often modeled using empirical expressions, e.g. [11, 12, 13, 14, 15, 16]. Compartmental cardiovascular models have been validated using a range of data, including noninvasive arterial pressure and cerebral blood flow velocity data [17, 13, 18], while other studies have compared model predictions against invasively obtained data, e.g. [19, 20, 21].

One of the biggest challenges in calibrating compartment models to data is obtaining accurate parameter estimates. Compartments representing blood vessels are typically represented by systems of linear differential equations, yet
the elastic and resistive properties of the vessels, cardiac pumping, and valve dynamics are often nonlinearly related to the model states \[8\]. Furthermore, fixed parameters appear in nonlinear combinations, and the presence of pulsatility makes it difficult to uniquely estimate all model parameters. Identifiability analysis is therefore a critical step in the parameter estimation process. It addresses if it is possible to uniquely recover the model parameters from a given set of data. For ordinary differential equation (ODE) models, this problem is typically broken into broad and often overlapping categories: structural identifiability \[22\], which considers the best-case scenario when the data are assumed to be known (smooth and noise free), and practical identifiability, which incorporates practical estimation issues that come with real data (noise and bias) \[23\].

Only a few studies have addressed structural identifiability in cardiovascular models. Kirk et al. \[24\] studying Windkessel models showed that three of the four parameters are identifiable \[22\]. A more general analysis can be found in the recent study by Pironet et al. \[25\] who demonstrated that every parameter in a closed-loop six-compartment cardiovascular model including a left and right heart, systemic and pulmonary arteries and veins is structurally identifiable for clinical output data including arterial and venous pressures along with stroke volume, while models relying on either pressure or volume alone are structurally unidentifiable. Sensitivities and identifiability were analyzed in a number of previous studies predicting arterial blood pressure \[26, 13, 18\]. Sensitivity analysis was also addressed by Gul \[27\] in a more complex cardiovascular model. One study includes a general review on how to account for uncertainties \[28\], and a few studies have considered uncertainties in one-dimensional models \[29, 30, 31\]. Hellevik et al. has use sensitivity analysis based on generalized polynomial chaos expansion to analyze a stochastic model of pressure waves in the arterial circulation \[32\], and developed a practical guide to use polynomial chaos in both sensitivity analysis and uncertainty quantification \[33\].

In this study, we present a multi-stage process of parameter estimation and uncertainty quantification for an individual-specific lumped-parameter cardio-
vascular dynamics model. Model output is fitted to left ventricular volume and blood pressure data experimentally obtained from Sprague Dawley rats. The key steps in our methodology include: (1) the use of literature and available data to define a set of nominal parameter values specific to each rat; (2) sensitivity analysis and subset selection to determine a set of identifiable parameters; (3) optimization to find a point estimate for identifiable parameters; and (4) statistical techniques to quantify uncertainty in parameter estimates, including both frequentist and Bayesian methods. We outline these steps in the following sections, accompanied by numerical results.

2. Methods

2.1. Experimental Data

Experiments performed on 3 Sprague-Dawley (SD) rats (2 male, 1 female) studied basal CV function. The average weight of these animals was $358.0 \pm 19.6$ g. In each experiment, the animal was anesthetized with sodium phenobarbital, and catheters were placed in the femoral artery and vein for administration of anesthetics. A pressure-volume conduction catheter (Millar SPR-869, 2F tip with four electrodes and 6mm spacing) was inserted through the right carotid artery into the left ventricle to simultaneously obtain pressure and volume measurements. 20-second-long, pressure-volume measurements were selected for model identification and are shown in Figure 1. The final 0.5 seconds of each data set is used to calibrate the model and is shown in Figure 2.

Volume measurements from the conduction catheter were calibrated at baseline, based on the observation that end diastolic and end systolic volumes of the left ventricle scaled with animal weight based on values taken from the literature. Left ventricular volumes at end systole and end diastole for control rats used in 20 published studies were represented as a function of body weight shown in Figure 3. The rats used in these studies were SD, Wister-Kyoto and Lewis strains and represented a total of 191 control animals. A variety of measurement techniques were used including conduction catheter, ultrasound and
magnetic resonance imaging (MRI). MRI based volume measurement techniques have been adopted as the gold standard for ventricular volume studies, so trends for the left ventricular end diastolic and stroke volumes as a function of body weight were determined from the 13 MRI-based studies (see Figure 3 for the data and exponential fit to the data used in the volume catheter calibration for animals at baseline). Left ventricular end systolic volume was used to calibrate the average end systolic voltage measurement from the catheter and was determined by subtracting the functional fit of left ventricular stroke volume from the functional fit of left ventricular end diastolic volume.

2.2. Model

This study uses a five-compartment model to predict pressure, flow, and volume in the left ventricle and systemic circulation. Compartments represent the left ventricle, the large and small arteries and veins; see Figure 4 for a schematic...
diagram. Following the electrical circuit analogy, blood flow ($q$) is analogous to current, pressure ($p$) to voltage, volume ($V$) to charge, vessel resistance ($R$) to electric resistance, and vessel elastance ($E$) to the reciprocal of capacitance. The flow in and out of each compartment is governed by Poiseuille’s law, relating flow and pressure as

$$q = \frac{p_{\text{in}} - p_{\text{out}}}{R}. \quad (1)$$

The elastance of each compartment gives the pressure-volume relation

$$p - p_{\text{ext}} = E(V - V_{\text{un}}), \quad (2)$$

where $p_{\text{ext}}$ is the external tissue pressure and $V_{\text{un}}$ is the unstressed blood volume (both assumed constant). Finally, conservation of volume gives

$$\frac{dV}{dt} = q_{\text{in}} - q_{\text{out}}. \quad (3)$$
For the circuit shown in Figure 4, we derive a system of five differential equations in the form of (3), detailed in the Appendix.

The beating of the heart is modeled by a periodic time-varying elastance function \( [26] \) defined over one cardiac cycle of length \( T \) as

\[
E_{lv}(t) = \begin{cases} 
  E_{\text{min}} + \frac{E_{\text{Max}} - E_{\text{min}}}{2} (1 - \cos(\pi t/T_S)) & 0 < t < T_S \\
  E_{\text{min}} + \frac{E_{\text{Max}} - E_{\text{min}}}{2} \cos(\pi(t - T_S)/(T_R - T_S)) & T_S < t < T_R \\
  E_{\text{min}} & T_R < t < T 
\end{cases} 
\]

(4)

where \( E_{\text{min}} \) and \( E_{\text{Max}} \) denote the minimum and maximum elastance, respectively, of the left ventricle. \( T_S \) denotes time for end systole and \( T_R \) the time...
Figure 4: Systemic circulation represented using five compartments, including the left heart (lh) (i.e., the left ventricle), the large (la) and small (sa) systemic arteries, and the large (lv) and small (sv) systemic veins. The model is analogous to an RC circuit with capacitors denoting vessel elastance and resistors separating each compartment. Pumping of the heart is ensured by a time-varying elastance function \( E_{lv}(t) \) over one cardiac cycle.

Heart valves are included to control the flow into and out of the left ventricles. This effect has been previously modeled using a number of methodologies accounting for inertia \[8, 34\], using pressure dependent resistances \[18\], or using simple diodes to create an on-off switch \[25\]. While the diodes approach is easier to formulate, it introduces a discontinuity in the system of equations not characteristic of the pressure-dependent resistances or valves accounting for inertia. Even when accounting for inertia, the system of ODEs arising in pulsatile cardiovascular models is stiff and requires careful attention when solving numerically; for more details on solving stiff differential equations, see, e.g., \[35, 36\].
Figure 5: The time-varying elastance is modeled using a smooth piecewise trigonometric function defined over the length of one cardiac cycle $T$ (given by equation (4)). Maximum elastance is achieved at $t = T_S$ (at the end of systole) and the end contraction is marked by $t = T_R$. Note that $T_S < T_R$.

In this study, we model the two heart valves using simple diodes given by

$$q_{\text{valve}} = \begin{cases} \frac{p_{\text{in}} - p_{\text{out}}}{R_{\text{valve}}} & \text{if } p_{\text{in}} > p_{\text{out}} \text{ (i.e., if valve is open)} \\ 0 & \text{otherwise (i.e., if valve is closed)} \end{cases}$$

where $\text{valve} = \text{av}$ or $\text{mv}$, representing the aortic (av) and mitral (mv) valves, respectively.

In summary, the vectors of model states $x$ and parameters $\theta$ are given by

$$x = \{V_{la}, V_{sa}, V_{lh}, V_{sv}, V_{lh}\}$$

$$\theta = \{R_A, R_S, R_V, E_{la}, E_{sa}, E_{av}, E_{lv}, T_S, T_R, E_{min}, E_{Max}\}$$

where the resistance parameters ($R$) represent the arterial, systemic, and venous vascular resistance; the elastance parameters ($E$) represent the ability of the arteries and veins to stretch; the timing ($T_S, T_R$) and elastance ($E_{min}, E_{Max}$) parameters define the elastance function [4]. We assume that the external pressures of the the model compartments are at a reference pressure of zero.
2.3. Nominal parameters and initial values

Nominal parameters and initial values can be obtained from analysis of data and known physiological features extracted from literature. As noted above, parameters in this study include resistance, elastance, and timing of the cardiac cycle, which can be determined as a function of resting blood volumes, pressures, cardiac output, and heart rate. Below we discuss how to calculate a priori values for all model parameters; Table 2 gives specific relations for each parameter, while Table 3 lists the nominal parameter values. Figure 6 shows the characteristics from the data that were used to extract these parameter values.

2.3.1. Blood volume

Total blood volume for healthy adult Wistar rats is assumed to be 57µl/g body weight [37]. Measurements analyzed in this study are from 2 male and 1 female healthy Sprague Dawley rats (Charles River Laboratories, USA). Nominal parameter values for blood volume are computed using the body weight for the rat studied, summarized in Table 1. Following suggestions by Young [38]...
Table 1: Rat average data.

| Rat   | Weight (g) | Heart rate (beats/min) | Stroke volume (µl) | Cardiac output (ml/min) |
|-------|------------|------------------------|-------------------|------------------------|
| Rat 1 | 339        | 240±3                  | 308±1             | 74±0.2                 |
| Rat 2 | 350        | 240±3                  | 216±1             | 52±0.2                 |
| Rat 3 | 342        | 420±3                  | 143±1             | 60±0.2                 |

and Gelman [39], venous volume is approximately 77.5% assuming that capillaries are lumped with the venous compartment and arterioles with the arterial compartments have about 22.5% of the total volume. The model includes two arterial and two venous compartments, separating the large and small systemic and arteries and veins. This study assumes that the large arteries contain about 2.5% of the total blood volume, while the large veins contain about 7.5% of the total blood volume, the small arteries 20%, and the small veins 70% of the total volume, respectively. For each compartment, the volume is given by

\[ V_i = d_i V_{\text{total}} \]  

where \( V_{\text{total}} \) is the total volume of blood, \( V_i \) refers to the \( i \)th compartment, and \( d_i \) is the corresponding percentage. Values for \( d_i \) are given in Table 2.

Within any cardiac cycle, only a small percentage of the volume (i.e., the stressed volume) is pumped out. Literature estimates for the total unstressed volume vary significantly, from about 60% to 90% [40, 37, 39, 38, 41]. For this study we assume that each compartment has the same 70% unstressed volume, which can be expressed as

\[ V_{i,\text{un}} = 0.7 V_i. \]

2.3.2. Cardiac output

For each rat, the average stroke volume (given in Table 1) can be extracted from measurements of maximum and minimum left ventricular volume. Cardiac output can subsequently be calculated as the product of stroke volume and heart rate (i.e., \( \text{CO} = \text{HR}_d \cdot V_{\text{str,d}} \)).
2.3.3. Vascular resistance

Using the baseline cardiac output and pressures, the vascular resistances can be computed from Ohm’s law \( \frac{\pi}{\rho} \). For vasculature the resistance is best calculated from analysis of mean pressure values. For example, arterial resistance is predicted by

\[ R_A = \frac{\bar{P}_{la} - \bar{P}_{sa}}{CO}, \quad (8) \]

where the mean pressure is set to \( \bar{P}_{la} = P_{la,\text{dia}} + \frac{1}{3} P_{la,\text{pulse}} \) \[42\]. This formula uses diastolic pressure, which is predicted from the maximum left ventricular pressure \( \max(p_{lh,s}) \) assuming a pulse pressure of 30 mmHg.

The exceptions to mean considerations are for the valve resistances, which operate around the maximum and minimum ventricular pressure, computed as

\[ R_{av} = \frac{\max(p_{lh,d}) - P_{la,M}}{CO} \quad \text{and} \quad R_{mv} = \frac{P_{lh} - \min(p_{lh,d})}{CO} \quad (9) \]

where \( R_{av} \) is the aortic valve resistance and \( R_{mv} \) is the mitral valve resistance. Since the venous pressure does not vary significantly, the average pressure of the large veins is used to predict \( R_{mv} \). We do not have data for the large arteries for this study, so the average large artery pressure is approximated from the max left ventricular pressure. Table 2 gives the equations used to set the remaining resistance parameters.

2.3.4. Vascular compliance

Each vascular compartment is associated with a compliance, which in this study is assumed constant. Assuming that the tissue pressure is negligible (i.e., \( p_{ext} = 0 \)), large artery elastance is estimated as

\[ E_{la} = \frac{P_{la,M}}{V_{la} - V_{la,un}}, \quad (10) \]

following the pressure-volume relation \( 2 \). Table 2 gives the equations used to set the remaining elastance parameters.

2.3.5. Heart parameters

The elastance function \( 4 \) has four parameters, including the timing parameters denoting the length of the cardiac contraction \( T_S \) and relaxation \( T_R \),
as well as the minimum ($E_{\text{min}}$) and maximum ($E_{\text{Max}}$) elastance, respectively. Unstressed ventricular volume has been estimated for rats at 37µl \[43\]. For each rat, the timing parameters $T_S$ and $T_R$ can be extracted from data, as shown in Figure 6. $T_S$ denotes the time at which the left ventricular volume reaches its maximum (at $\max(p_{lh,d})$), and $T_R$ is the time at which $p_{lh}$ reaches its baseline after contraction. The minimum elastance $E_{\text{min}}$ is associated with end-diastole, where the left ventricular pressure is minimal and ventricular volume is maximal. On the other hand, the maximum elastance $E_{\text{Max}}$ is associated with systole, where the ventricular pressure is maximal and ventricular volume is minimal. These considerations let us set

$$E_{\text{min}} = \frac{\min(p_{lh,d})}{\max(V_{lh,d}) - V_{lh,un}} \quad \text{and} \quad E_{\text{Max}} = \frac{\max(p_{lh,d})}{\min(V_{lh,d}) - V_{lh,un}} \quad (11)$$

### 2.3.6. Initial conditions

Assuming that the model simulation begins at the end of contraction, we set the initial value of the volume in each compartment so that each compartment is fully stressed. This implies that

$$V_{0,i} = V_i - V_{i,\text{un}} \quad (12)$$

where $V_{0,i}$ is the initial volume of the $i$th compartment.

### 3. Model Analysis

The model described in Section 2.2 is linear with respect to the states but nonlinear with respect to the parameters. This gives rise to multiple parameter interactions that inevitably complicate the parameter estimation process. While a model with many nonlinear parameter interactions can be structurally identifiable, unidentifiable parameter relationships often result in an ill-conditioned optimization problem (i.e., the optimization algorithm fails to converge). With respect to the model in this work, substituting equations (1) and (2) into equation (3) results in the division of an elastance ($E$) by a resistance ($R$) parameter. Additionally, the timing ($T_S$, $T_R$) and heart elastance ($E_{\text{min}}$, $E_{\text{Max}}$) parameters
Table 2: Quantities used to determine nominal parameter estimates.

| Quantity | Equation | Reference |
|----------|----------|-----------|
| $V_{la}$ | $0.025 V_{total}$ | [38] [39] |
| $V_{sa}$ | $0.2 V_{total}$ | [38] [39] |
| $V_{lv}$ | $0.075 V_{total}$ | [38] [39] |
| $V_{sv}$ | $0.7 V_{total}$ | [38] [39] |

| Quantity | Equation | Reference |
|----------|----------|-----------|
| $R_{av}$ | $\max(p_{lh,d}) - p_{la,M}$ | CO (9) |
| $R_{mv}$ | $p_{lv} - \min(p_{lh,d})$ | CO (9) |
| $R_{A}$ | $\frac{p_{la} - p_{sa}}{V_{la} - V_{la,un}}$ | CO (10) |
| $R_{S}$ | $\frac{p_{sa} - p_{sv}}{V_{sv} - V_{sv,un}}$ | CO (10) |
| $R_{V}$ | $\frac{p_{sv} - p_{lv}}{V_{sv} - V_{sv,un}}$ | CO (10) |

| Quantity | Equation | Reference |
|----------|----------|-----------|
| $T_{S}$ | $t_{\max(V_{lh,d})}$ | | |
| $T_{R}$ | $t_{\min(p_{lh,d})}$ | | |

are added/subtracted to/from each other in the elastance function [4]. Determining whether or not a specific parameter interaction is identifiable is a nontrivial process that intuitively motivates some form structural identifiability analysis. Pironet et al. [25] illustrated that the division of elastance and resistance parameters is an identifiable relationship for a similarly formulated cardiovascular model; however the model that they analyzed uses a simplified elastance driving function that contains no parameters. Mahdi et al. [22] provided some guidelines for constructing arbitrarily complex structurally identifiable spring-dashpot networks, however their results are constrained to linear viscoelastic formulations. Our methodology is motivated by analyzing the practically identifiable components of cardiovascular models to make predictive inference through the use of uncertainty quantification.

In this section, we outline a systematic methodology for parameter estima-
tion in lumped cardiovascular models, comprising the following steps:

1. **Local sensitivity analysis** is used to study how the model parameters influences model output.
2. **Structured correlation analysis** is used to construct a subset of parameters with minimal parameter interactions.
3. **Levenberg-Marquardt nonlinear least squares optimization** is used to estimate the parameter subset.
4. **Frequentist prediction and confidence intervals** are used to quantify uncertainty in model solutions.
5. **The DRAM (Delayed Rejection Adaptive Metropolis) algorithm** is used to determine parameter distributions and credible intervals.

While the analysis is devised for a relatively simple model with specific output data (left ventricular pressure and volume), the approach introduced is applicable to any differential equations model.

### 3.1. Local Sensitivity Analysis

Sensitivity analysis quantifies how the model output changes in response to changes in parameter values [26]. In this study we use derivative-based (local) sensitivities to quantify the local influence of model output on each parameter. This is computed using the partial derivatives of the model output with respect to each model parameter. Derivative-based sensitivity methods are local in that they are evaluated at a specific parameter configuration, as opposed to global sensitivities (e.g., Sobol indices or Morris elementary effects [44]), which explore the entirety of the parameter space.

Local sensitivities are computed by differentiating the model residual \( r(t, \theta) \) (difference between data and model) with respect to the parameter vector \( \theta \). We define the sensitivity matrix \( S \) as

\[
S_{i,j} = \frac{\partial r(t_i, \theta)}{\partial \theta_j},
\]

where \( \theta_j \) is the \( j \)th parameter and \( t_i \) is the \( i \)th time step. The matrix \( S \) can be calculated analytically for simple models; however, numerical approximation
of $S$ is more practical for complex models. Here we employ finite differences to approximate $S$ by

$$S_{i,j} = \frac{r(t_i, \theta_j + h e_i) - r(t_i, \theta_j)}{h},$$

where $h$ is chosen to reflect the precision of the model output and $e_i$ is the unit vector in the $i$th component direction. If the error in the model evaluation (ODE solver error tolerance) is on the order of $\varepsilon$, the step should be $h = \sqrt{\varepsilon}$ to get an error of same magnitude in the sensitivities [13]. We tested the stability of our finite difference approximation by reducing the ODE solver tolerance and observing that the results of the sensitivity analysis converged the same values (results not included). We note that other finite difference approximation schemes could be employed here. For $p$ parameters, a more stable approximation such as central differences requires $2p$ model evaluations, whereas the forward differences only requires $p + 1$. We recommend the use of analytical sensitivities or central differences if numerical accuracy is of more concern than computational cost.

### 3.2. Subset Selection: Structured Correlation Analysis

The nonlinearly parameterized model considered in this work has inherent parameter interactions that necessitate the need for selecting parameter subsets with minimal unidentifiable parameter interactions. While various subset selection algorithms exist (e.g. [45]), we employ the structured correlation method by Ottesen et al. [46] to construct a set of model parameters that we are able to estimate. The structured correlation method is based on a linearization of the model output, which can be obtained without significant computational cost. For completeness, we summarize this method as follows.

Using the sensitivity matrix $S$ in (13), we compute the Fisher Information Matrix (FIM) $F$ by

$$F = \sigma^2 S^T S,$$

where $\sigma^2$ is the model variance. The covariance matrix $\Gamma$ is given by the inverse of the FIM,

$$\Gamma = F^{-1}.$$
Note that $\mathbf{F}$ can only be inverted if $\mathbf{S}$ is full rank. Linearly dependent columns of $\mathbf{S}$ are a result of parameters being perfectly correlated, meaning that a parameter can be algebraically expressed in terms of other parameters. The entries of $\mathbf{\Gamma}$ are used to compute the correlation matrix $\mathbf{C}$ with entries given by

$$C_{i,j} = \frac{\Gamma_{i,j}}{\sqrt{\Gamma_{i,i}\Gamma_{j,j}}}.$$ 

Correlations between parameters show how the parameter values depend on each other when fitting experimental data from the same system. According to the structural correlation method, a pair of parameters with a large correlation (and strongly coupled uncertainty) cannot both be uniquely estimated. Therefore this method systematically removes parameters that are correlated and relatively insensitive from the parameter set until an identifiable set remains.

We note that before correlation analysis is performed, it should be checked that the parameters are indeed sensitive. Parameters that are very insensitive (below $h$ or have marginal influence on model output) should not be included in the construction of $\mathbf{S}$, as it can lead to inaccurate estimations of parameter correlations.

### 3.3. Nonlinear Least Squares Optimization: Levenberg-Marquardt

The goal of nonlinear least squares is to find the set of parameters $\hat{\theta}$ that minimizes the difference between the model output $x(t, \theta)$ and the data $y$, assumed to be some function of the model output corrupted with additive noise; i.e.,

$$y_i = g(x(t_i, \theta)) + \epsilon_i,$$

where $y_i$ denotes the $i$th data point, $x(t_i, \theta)$ the model response at the $i$th time point, $g(\cdot)$ the observation function mapping the model variables to the measured states, and $\epsilon_i$ the normally distributed observation error. In this study, we assume linear observations of left ventricular volume blood pressure, so $g(x(t_i, \theta)) = P x(t_i, \theta)$ where $P$ is the projection matrix picking out these measured components.
To fit our model to the data, we use a generalized nonlinear least squares procedure to determine a parameter set \( \hat{\theta} \) which minimizes the sum of squares cost function \( J(\theta) \),

\[
\hat{\theta} = \arg \min_{\theta} J(\theta),
\]

where

\[
J(\theta) = \sum_{k=1}^{2} J_k(\theta),
\]

(17)

\[
J_k(\theta) = r_k^T r_k.
\]

(18)

The residual vectors \( r_k \) are defined as

\[
r_1 = p_{lv}^m - p_{lv}^d \quad \text{and} \quad r_2 = \frac{V_{lv}^m - V_{lv}^d}{\max(V_{lv}^d) - \min(V_{lv}^d)}.
\]

(19)

The superscripts “m” and “d” denote the model and data, respectively. Dividing the residuals by the amplitude of the data ensures that the optimization procedure gives equal weight to both model states.

To estimate \( \hat{\theta} \) we employ the Levenberg-Marquardt optimization routine in the style of [47], where the goal is to find parameter configurations where the gradient \( \nabla J(\theta) \) equals zero. Since the Levenberg-Marquardt algorithm is gradient based the choice of the initial parameter vector \( \theta_0 \) is important, as the cost function may have multiple minima and can lead the algorithm to an unrealistic local minimum. Using the physiologically-justified nominal parameter values described in Section 2.3 helps to avoid this issue, by placing the starting point nearby a realistic minimum.

3.4. Uncertainty Quantification

Uncertainty quantification (UQ) is the process of determining uncertainties in estimated model parameters given uncertainties in model formulation and experimental measurements (the inverse problem) as well as establishing how uncertainties in model inputs (such as parameters) affect the model output (forward propagation of uncertainty). In this work, we utilize UQ procedures from both frequentist and Bayesian statistical frameworks. We calculate confidence
intervals and Bayesian credible intervals to measure the precision of the model in predicting the mean response. These approaches are outlined below; for more details, see, e.g. [44].

3.4.1. Frequentist Approach

Frequentist uncertainty propagation methods are computationally inexpensive compared their Bayesian analog. Most frequentist statistics are derived from asymptotic assumptions such that their uncertainty distributions take a Gaussian shape, whereas Bayesian methods make no assumption about shape of their uncertainty distributions. One of the main benefits of the asymptotic assumptions is that uncertainty distributions can be expressed as explicit formulas in the frequentist perspective. Frequentist confidence intervals can be calculated from

\[ \hat{y}_i \pm t_{N-p}^{\alpha/2} s (g_i^T S^T S)^{-1} g_i)^{1/2}, \] (20)

where \( t_{N-p}^{\alpha/2} \) is the student t-distribution with \( N - p \) degrees of freedom (\( N \) is the number of data points and \( p \) is the number of parameters), \( s \) is the estimate of the model standard deviation \( \sigma \), \( S \) is the sensitivity matrix, and \( g_i \) is the \( i \)th row of \( S \) stacked as a column vector. Frequentist prediction intervals can be calculated in a similar manner by

\[ \hat{y}_i \pm t_{N-p}^{\alpha/2} s (1 + g_i^T S^T S)^{-1} g_i)^{1/2}. \] (21)

3.4.2. Bayesian Approach: Delayed Rejection Adaptive Metropolis (DRAM)

While frequentist methodology is fundamentally rooted in quantifying uncertainty in terms of repeating the data generating procedure, Bayesian inference is conditioned on a single data set; this allows for uncertainty about parameters to be expressed by probability distributions. In the Bayesian framework, \( \theta \) represents a vector of random variables. Given observations \( y = \{y_1, \ldots, y_n\} \), Bayes’ formula

\[ \pi(\theta \mid y) = \frac{\pi(y \mid \theta)\pi(\theta)}{\pi(y)} \] (22)

describes how the posterior density \( \pi(\theta \mid y) \) relates to the prior density \( \pi(\theta) \), encompassing any a priori information known about the parameters, and the
likelihood $\pi(y \mid \theta)$ of observing the data $y$ for the model given $\theta$. The marginal density $\pi(y)$ of the data typically functions as a normalization factor and can be determined by

$$\pi(y) = \int \pi(y \mid \theta) \pi(\theta) d\theta.$$  \hspace{1cm} (23)

Under the hypothesis [16], the likelihood function is given by

$$\pi_k(y \mid \theta) = e^{-J_k(\theta)/2\sigma^2}/(2\pi \sigma^2)^{n/2},$$ \hspace{1cm} (24)

where $J_k(\theta)$ denotes the least square cost defined by (18) and (19). With a known likelihood and prior density $\pi_k(\theta)$, it is possible to estimate the posterior density $\pi(\theta \mid y)$ if the integral (23) in the normalizing constant can be estimated. While this route is theoretically possible, the evaluation of high-dimensional integrals is a difficult and expensive, and is currently an active area of research; see, e.g., sparse grid methods [48, 49] and quasi-Monte Carlo methods [50, 51].

An alternative is to use Monte Carlo integration to randomly sample from the density $\pi(y \mid \theta)\pi(\theta)$. Many suitable Markov chain Monte Carlo (MCMC) methods exist in the literature (see [52] for an overview). This study uses the DRAM algorithm [53]. DRAM combines two methods for improving efficiency of Metropolis-Hastings type MCMC algorithms: delayed rejection (DR) [54] and adaptive Metropolis (AM) [55]. These Metropolis-type methods are acceptance-rejection algorithms that accept new parameter samples only if the likelihood of the new candidate is higher than the current sample. DR allows for additional proposals per step if the initially proposed step is not accepted, thereby increasing the acceptance ratio and well-mixing of the sample. AM allows for updating of the covariance matrix based on the history of the sample, thereby helping the algorithm to make better proposals and move toward the correct posterior distribution faster, reducing the burn-in period.

We use samples taken from the DRAM-estimated parameter probability distributions to compute Bayesian credible and prediction intervals; for more details, see [53, 44]. In this study, we utilize the MCMC toolbox provided by Haario et al. (2006) at http://helios.fmi.fi/~lainema/mcmc/, which in-
4. Results

In this section, we use the step-by-step procedure described in Section 3 to systematically estimate an identifiable subset of the parameters for the cardiovascular compartment model derived in Section 2.2 that best fit the left ventricular volume and blood pressure data described in Section 2.1. To align the phase of the model with the phase of the data, we shift the starting point of the data so that both model and data begin at the same point of the cardiac cycle, as shown in Figure 7 and described in Section 2. This shift serves as a proxy for estimating initial conditions.

Next, we use local sensitivity analysis and the structured correlation method, along with physiological knowledge, to construct a subset of identifiable model parameters. Using the nominal parameters listed in Table 3, we optimize the subset parameters using a Levenberg-Marquardt optimization scheme; we test the convergence of the optimizer by varying the initial guess around the nominal
values. Once we arrive at a converged set of optimized parameters, we use both frequentist and Bayesian methods to perform UQ, constructing confidence and credibility intervals along with prediction intervals for the model output predictions.

To demonstrate our methodology is reproducible across data sets we fit this model to the three data sets shown in Figure 2. Detailed results from Rat 1 are presented here as a representative example. Frequentist and Bayesian UQ results for Rats 2 and 3 are given in the Appendix.

4.1. Sensitivity Analysis and Subset Selection

Figure 8 depicts normalized ranked parameter sensitivities and the subset of identifiable parameters (25) for all three animals. Ranking the parameters by sensitivity provides initial insight into what parameters are most influential in determining model behavior. Note that the ranked sensitivities of parameters $R_a$ and $E_{ao}$ are orders of magnitude smaller than the other parameters, thus these parameters were removed \textit{a priori} from the set of parameters analyzed. Subsequently we used the structured correlation algorithm from Section 3.2 to obtain an identifiable parameter set. Using a correlation threshold $\gamma = 0.85$ as an upper bound on the pairwise correlations between parameters we found the identifiable subset

$$\theta = \{ R_s, T_S, T_R, E_{\text{min}}, E_{\text{Max}} \}.$$ \hspace{1cm} (25)

4.2. Optimization

Using the Levenberg-Marquardt nonlinear least squares routine with the cost function (17), we estimated the parameter subset (25). Results were verified by randomly perturbing the nominal values by 10% and optimizing these perturbed parameters. For ten unique perturbations, all of the parameters converged to the same values (results not included). Table 3 lists the nominal and optimized values of the parameters for Rat 1. Figure 10 shows the model fit using the optimized parameter values in Table 3 compared to the data.
To determine the optimal shift of the data, we optimized the subset (25) at many distinct data shifts. Figure 9 shows the cost (17) and gradient plotted as a function of relative data shifts for Rat 1. Note that there are multiple parabolic minimums for the cost as this reflects the pulsatile nature of cardiovascular mechanics. We ultimately chose the data shift that gave us the smallest value of the cost function as the optimal data shift.

4.3. Uncertainty Quantification

To perform UQ on the optimized parameter values, we consider both the frequentist formulas stated in Section 3.4.1 and the Bayesian inference using DRAM as described in Section 3.4.2. Using the optimized values, we can apply equations (20) and (21) to compute frequentist confidence and prediction intervals, respectively. We use the Levenberg-Marquardt optimized parameters as means for the diffuse prior distribution of the DRAM algorithm. Chains of 100,000 sample points were generated using DRAM. Figure 11 shows the resulting DRAM-estimated parameter chains, parameter densities, and pairwise correlations between the parameters. Figure 12 compares the resulting frequen-
Figure 9: Determining the optimal data shift for Rat 1. The top plot shows the value of the gradient and the bottom plot shows the value of the cost function (17) as a function of relative data shifts. The red “x” in the bottom plot denotes the smallest value of the cost function and our optimal data shift. Results for Rat 2 and 3 show a similar pattern.

Figure 10: Model fit for Rat 1 using Levenberg-Marquardt optimized parameter values listed in Table 3. The top panel show pressure fit, and the bottom panel shows the volume fit. Results for Rat 2 and 3 are not included but have a comparable quality of fit.
tist and Bayesian UQ.

5. Discussion

In this work we present a step-by-step, systematic approach for parameter estimation in a cardiovascular compartment model where model parameters contain nonlinear interactions. We show that by removing parameter interactions by means of local sensitivity analysis and structured correlation methodology, we can obtain a subset of model parameters that are structurally identifiable. We use nonlinear least squares optimization to estimate this subset of parameters to provide a high quality fit to the data. Furthermore, both frequentist and Bayesian UQ methods allow us to obtain confidence, credibility and prediction intervals around the model output.

It is well appreciated that blood vessels dilate and constrict in order to maintain homeostatic levels of blood flow and pressure. With the exception of heart rate and arterial pulse pressure, acquiring other cardiovascular measures such as flows or ventricular pressures are experimentally difficult and often invasive. Thus it is incredibly challenging to quantify the functionality of the heart and vasculature. The parameters in the model presented here represent physiological characteristics of cardiovascular functionality that can provide insight into mechanics but are incredibly difficult to measure in vivo. These simple cardiovascular models derived from an electrical circuit analogy can provide experimental biologists a framework to estimate quantities such as vessel stiffness (compliance) and resistance [38, 39]. However, the uncertainty associated with these estimates are non-negligible and necessitates a mathematical approach to explore the nuances of the parameter interactions.

While there are many parameter estimation methodologies that one can consider, not all methods are appropriate for a given application. The art lies in choosing an appropriate method (or systematic combination of methods, as done in this work) that works well for the application at hand. In situations where good nominal parameter estimates are not available, global sensitivity methods
(e.g., Sobol indices, Morris screening) can be used to explore the entirety of the parameter space to provide insight into which parameters are the most influential in defining model behavior.

The parameters $E_{\text{min}}$ and $E_{\text{Max}}$ are subtracted from one another in the elasticity function \([4]\). One might expect $(E_{\text{Max}} - E_{\text{min}})$ to be an unidentifiable parameter interaction, however this quantity is referred to as cardiac contractility. Physiologically it is well understood that contractility of the heart is indicative of its overall functionality and acts a diagnostic measurement for physicians. By not removing both $E_{\text{min}}$ and $E_{\text{Max}}$ from the set of parameters we are considering, the structured correlation analysis algorithm produces the identifiable subset \([25]\).

The structured correlation analysis algorithm we employ is local in nature: distinct parameterizations are likely to produce different results. However, the largest limitation to using this algorithm is that it only provides a first order approximation of the parameter correlations, so it does not capture all of the nonlinear parameter interactions. We leverage this limitation by using DRAM to estimate the parameters in a Bayesian framework. By representing the parameters as random variables, we can trace out the exact shape of their joint densities and can visualize the parameter interactions, as shown in Figure \([11]\). Unidentifiable parameter subsets typically take more MCMC iterations to converge and have often have more correlation in their pair-wise density plots. This demonstrates the power of using Bayesian parameter estimation techniques together with asymptotic subset selection methods in an iterative process to refine ones understanding of different model parameterizations and potentially find a practically identifiable subset of parameters.

We note that in the pairwise densities of Figure \([11]\) there is a degree of correlation between $E_{\text{Max}}$, $E_{\text{min}}$, $T_S$ and $T_R$ despite the subset \([25]\) being identifiable. Intuitively one would expect large parameter interactions to hinder the identifiability of a model, however it is crucial to understand that while intimately related, correlation and identifiability are distinct concepts. Correlation refers to the precise structure and relationship between interacting parameters,
whereas identifiability refers to the mapping between the parameter space and model output being one-to-one. So while minimizing parameter interactions and correlations can be an effective strategy to find an identifiable subset of parameters, it is not an exhaustive or universally applicable strategy to an arbitrary model. We found that approaching the parameter estimation problem from a Bayesian perspective was particularly useful in this regard. It should also be noted that the ideal subset of parameters to estimate is highly dependent on the type of data available (i.e. pressure in large systemic arteries rather than the left ventricle, or only pressure or volume time series without the other.)

Representing parameters as probability distributions is very intuitive and can provide information about the identifiability of a multi-dimensional parameter distribution. Plots of parameter chains and densities such as those seen in Figures 11 are the fundamental diagnostic tools to assess if the MCMC parameter optimizer has converged. The posterior parameter chain plot should ideally be white noise of the distribution, and the posterior parameter density should have a single clearly defined mean. Unidentifiable parameter distributions often have multi-modal distributions that can be observed from plots of the parameter chain and the density. One can interpret a multi-modal distribution as a parameter chain that has not converged, or an unidentifiable parameter. Should the first scenario be the case be, one can run the MCMC algorithm for more iterations until the distribution converges to the true posterior. However, if the converged parameter distribution is still multi-modal, it indicates that multiple values of a parameter can be used to produce the same model output. By definition, this means that the parameter is unidentifiable. We used DRAM to estimate the parameters in (25) along with $E_{sa}$ to provide an example of parameter densities from an unidentifiable subset in the Appendix.

Parameter identifiability is important to consider beyond the mathematical needs of having a well-posed optimization problem. Parameters represent meaningful uncertainties about a system of interest and many modeling studies seek to compare parameter values between individuals or populations to investigate functional differences. Moving forward, we would like to use the methodology
presented in this paper to compare parameter values between control and pre-hypertensive rats to determine if there are distinguishing characteristics that may be useful in predicting hypertension in a clinical setting. Unidentifiable parameterizations would make this future study doomed to fail, as comparing differences between multi-modal distributions is very difficult to do in the context of what our model parameters represent. However, comparing uni-modal distributions of the systemic resistance ($R_S$) parameter could plausibly make for a compelling study in investigating the pathogenesis of primary hypertension. Identifiable model parameterizations ensure that our models are physiologically interpretable and mathematically tractable.

Having a high-quality model fit is rarely the end of one’s modeling efforts. Mathematical models are often constructed to make predictions about what they represent. Thus it is critical that one quantifies the limitations of a model’s predictive power. The field of uncertainty quantification has grown tremendously in the past few years, as the reliability of mathematical models are necessarily subject to scrutiny and the difficulty in propagating uncertainty through a model is an interesting and challenging problem. One such difficulty in performing UQ is that many published methods require that the parameters be identifiable. Our emphasis on having an identifiable subset of parameters has allowed us to use both frequentist and Bayesian uncertainty propagation methods to achieve interpretable and tight uncertainty bounds around our model solutions.

Due to its intuitive flexibility in representing parameters as random variables, an advantage of the Bayesian framework is that UQ is an intrinsic feature. Assuming one has an identifiable parameterization and converged parameter chains, one simply has to the evaluate the model over the parameter chains to obtain credible and prediction intervals. These uncertainty bounds are not subject to any potentially limiting assumption about their distribution, as their frequentist analogs are. However, the largest limitation to MCMC-type Bayesian approaches is the sheer computational cost. MCMC methods are incredibly robust, often requiring thousands of model evaluations to construct a converged posterior parameter distribution. For sufficiently complex models,
MCMC may be an impractical route. As an alternative, sequential Bayesian methods such as particle filtering \cite{56, 57, 58, 59} or ensemble Kalman filtering \cite{60, 61, 62, 63} may reduce computational time by evaluating the model from one data point to the next, as opposed to integrating over the entire data set at once. For the cardiovascular model presented here, we can see in Figure 12 that there is very little appreciable difference between the employed statistical approaches. Thus for future studies using this model and corresponding data sets, frequentist UQ alone may be sufficient.

Appendix

Model Equations

The complete system of differential equations describing the rates of change of the compartments of the model analyzed in this work are given as follows:

\[
\frac{dV_{lv}}{dt} = q_{mv} - q_{av}
\]

\[
\frac{dV_{ao}}{dt} = q_{av} - \frac{E_{ao}V_{ao} - E_{as}V_{as}}{R_A}
\]

\[
\frac{dV_{sa}}{dt} = \frac{E_{ao}V_{ao} - E_{sa}V_{sa}}{R_A} - \frac{E_{sa}V_{sa} - E_{sv}V_{sv}}{R_S}
\]

\[
\frac{dV_{sv}}{dt} = \frac{E_{sa}V_{sa} - E_{sv}V_{sv}}{R_S} - \frac{E_{sv}V_{sv} - E_{vc}V_{vc}}{R_V}
\]

\[
\frac{dV_{vc}}{dt} = \frac{E_{sv}p_{sv} - E_{vc}V_{vc}}{R_V} - q_{mv}
\]

where

\[
q_{av} = \begin{cases} p_{lv} - \frac{E_{ao}V_{ao}}{R_{av}} & \text{if valve open, i.e. } p_{lv} > p_{ao} \\ 0 & \text{otherwise (valve closed)} \end{cases}
\]

\[
q_{mv} = \begin{cases} E_{vc}V_{vc} - p_{lv} & \text{if valve open, i.e. } p_{vc} > p_{lv} \\ 0 & \text{otherwise (valve closed)} \end{cases}
\]

and

\[ p_{lv} = E_{lv}(t)V_{lv}, \]
\[
E_{IV}(t) = \begin{cases} 
E_{\text{min}} + \frac{E_{\text{Max}} - E_{\text{min}}}{2} (1 - \cos(\pi t / T_S)) & 0 < t < T_S \\
E_{\text{min}} + \frac{E_{\text{Max}} - E_{\text{min}}}{2} \cos(\pi (t - T_S)/(T_R - T_S)) & T_S < t < T_R, \\
E_{\text{int}} & T_R < t < T
\end{cases}
\]

Model Fit for Rat 2 and 3

Using the methodology presented in this paper we fit our simple cardiovascular model to time series data sets of left ventricular pressure and volume from three individual rats. In Section 4 we present in detail the results of fitting the model to the data from Rat 1. We found that subset 25 was identifiable across data sets. In Figure 13 we can see our computed frequentist and Bayesian uncertainty intervals for the rat 2 and 3 data sets.

Unidentifiable subset

To illustrate how an unidentifiable subset of parameters can result in multimodal posterior parameter distribution we re-ran DRAM using subset 25 and \(E_{sa}\). We can see in Figure 14 that including \(E_{sa}\) in the subset makes \(T_S\)’s posterior distribution bimodal. Additionally, \(E_{sa}\)’s posterior distribution is somewhat bimodal. We note that while the modality of posterior parameter distributions can be used to assess the identifiability of a subset of parameters, an individual parameter exhibiting multi-modal behavior is not itself unidentifiable. The posterior parameter density is a joint-distribution of all the parameters, so any multi-modal behavior has to be considered in the context of the other parameters in the distribution.

References

References

[1] J. T. Ottesen, M. S. Olufsen, J. K. Larsen, Applied Mathematical Models in Human Physiology, SIAM, 2004.
[2] L. Formaggia, A. M. Quarteroni, A. Veneziani (Eds.), Cardiovascular mathematics: modeling and simulation of the circulatory system, Springer, 2009.

[3] J. T. Ottesen, V. Novak, M. S. Olufsen, Development of patient specific cardiovascular models predicting dynamics in response to orthostatic stress challenges, in: Mathematical Modeling and Validation in Physiology, Springer, 2013, pp. 177–213.

[4] A. M. Quarteroni (Ed.), Modeling the Heart and the Circulatory System, Springer, 2015.

[5] F. N. Van de Vosse, N. Stergiopulos, Pulse wave propagation in the arterial tree, Annual Review of Fluid Mechanics 43 (2011) 467–499.

[6] P. Blanco, F. RA, A 3d-1d-0d computational model for the entire cardiovascular system, Mecánica Computacional 24 (2010) 5887–5911.

[7] I. Kokalari, T. Karaja, M. Guerrisi, Review on lumped parameter method for modeling the blood flow in systemic arteries, J Biomed Sci Eng 6 (2013) 92–99.

[8] S. Yubing, P. Lawford, R. Hose, Review of zero-d and 1-d models of blood flow in the cardiovascular system, Biomedical Eng Online 10 (33).

[9] M. L. Neal, J. B. Bassingthwaighte, Subject-specific model estimation of cardiac output and blood volume during hemorrhage, Cardiovascular engineering 7 (3) (2007) 97–120.

[10] D. Zinemanas, R. Beyar, S. Sideman, Relating mechanics, blood flow and mass transport in the cardiac muscle, International journal of heat and mass transfer 37 (1994) 191–205.

[11] J. Ottesen, M. Danielsen, Modeling ventricular contraction with heart rate changes, J Theor Biol 222 (2003) 337–346.
[12] P. Segers, N. Stergiopulos, N. Weterhof, P. Wouters, P. Kohl, P. Verdonck, Systemic and pulmonary hemodynamics assessed with a lumped-parameter heart-arterial interaction model, J Eng Math 47 (2003) 185–199.

[13] S. Pope, L. Ellwein, C. Zapata, V. Novak, C. Kelley, M. Olufsen, Estimation and identification of parameters in a lumped cerebrovascular model, Math Biosci Eng 6 (2009) 93–115.

[14] J. Lumens, T. Delhaas, B. Kirn, T. Arts, Three-wall segment (triseg) model describing mechanics and hemodynamics of ventricular interaction, Ann Biomed Eng 37 (2009) 2234–2255.

[15] J. Lumens, T. Delhaas, B. Kirn, T. Arts, Three-wall segment (triseg) model describing mechanics and hemodynamics of ventricular interaction, Annals of biomedical engineering 37 (11) (2009) 2234–2255.

[16] B. W. Smith, J. G. Chase, R. I. Nokes, G. M. Shaw, G. Wake, Minimal haemodynamic system model including ventricular interaction and valve dynamics, Medical engineering & physics 26 (2) (2004) 131–139.

[17] M. Olufsen, J. Ottesen, H. Tran, L. Ellwein, L. Lipsitz, N. V, Blood pressure and blood flow variation during postural change from sitting to standing: model development and validation, J Appl Physiol 99 (2005) 1523–1537.

[18] N. D. Williams, Mathematical modeling of cardiovascular dynamics during head-up tilt, North Carolina State University, 2014.

[19] J. Revie, D. Stevenson, J. Chase, C. Hann, B. Lambermont, A. Ghysen, P. Kolh, G. Shaw, S. Heldmann, T. Desaive, Validation of subject-specific cardiovascular system models from porcine measurements, Comp Meth Prog Biomed 109 (2013) 197–210.

[20] P. Pacher, T. Nagayama, P. Mukhopadhyay, S. Bátkai, D. A. Kass, Measurement of cardiac function using pressure–volume conductance catheter technique in mice and rats, Nature protocols 3 (9) (2008) 1422.
[21] E. T. Mackenzie, J. K. Farrar, W. Fitch, D. I. Graham, P. C. Gregory, A. M. Harper, Effects of hemorrhagic hypotension on the cerebral circulation. i. cerebral blood flow and pial arteriolar caliber., Stroke 10 (6) (1979) 711–718.

[22] A. Mahdi, N. Meshkat, S. Sullivant, Structural identifiability of viscoelastic mechanical systems, PloS one 9 (2) (2014) e86411.

[23] H. Miao, X. Xia, A. S. Perelson, H. Wu, On identifiability of nonlinear ode models and applications in viral dynamics, SIAM review 53 (1) (2011) 3–39.

[24] J. Kirk, M. Saccomani, S. Shroff, A priori identifiability analysis of cardiovascular models, Cardiovasc Eng Technol 4 (2013) 500–512.

[25] A. Pironet, P. Dauby, J. Chase, P. Docherty, J. Revie, T. Desaive, Structural identifiability analysis of a cardiovascular system model, Med Eng Physics 38 (2016) 433–441.

[26] L. Ellwein, H. Tran, C. Zapata, V. Novak, M. Olufsen, Sensitivity analysis and model assessment: mathematical models for arterial blood flow and blood pressure, Cardiovasc Eng 8 (2008) 94–108.

[27] R. Gul, Mathematical modeling and sensitivity analysis of lumped-parameter model of the human cardiovascular system, Ph.D. thesis, The Free University, Berlin, Germany (2016).

[28] V. Eck, W. Donders, J. Sturdy, J. Feinberg, T. Delhaas, L. Hellevik, W. Huberts, A guide to uncertainty quantification and sensitivity analysis for cardiovascular applications, Num Meth biomed Eng doi: 10.1002/cnm.2755.

[29] P. Chen, A. Quarteroni, G. Rozza, Simulation-based uncertainty quantification of human arterial network hemodynamics, Int J Numer Meth Biomed Eng 29 (2013) 698–721.
[30] A. Arnold, C. Battista, D. Bia, Y. Zocalo, R. Armentano, H. Tran, M. Olufsen, Uncertainty quantification in a patient-specific one-dimensional arterial network model: EnKF-based inflow estimator, ASME J Ver Val Uncer Quant 2 (1) (2017) 011002.

[31] V. Eck, J. Feinberg, H. Langtangen, L. Hellevik, Stochastic sensitivity analysis for timing and amplitude of pressure waves in the arterial system, Int J Numer Meth Biomed Eng DOI: 10.1002/cnm.2711.

[32] V. Eck, J. Feinberg, H. Langtangen, L. Hellevik, Stochastic sensitivity analysis for timing and amplitude of pressure waves in the arterial system, International journal for numerical methods in biomedical engineering 31 (4).

[33] V. G. Eck, W. P. Donders, J. Sturdy, J. Feinberg, T. Delhaas, L. R. Hellevik, W. Huberts, A guide to uncertainty quantification and sensitivity analysis for cardiovascular applications, International journal for numerical methods in biomedical engineering 32 (8).

[34] J. Mynard, M. Davidson, D. Penny, J. Smolich, A simple, versatile valve model for use in lumped parameter and one-dimensional cardiovascular models, Int J Numer Meth Biomed Eng 28 (2012) 626–641.

[35] R. J. LeVeque, Finite Difference Methods for Ordinary and Partial Differential Equations: Steady-State and Time-Dependent Problems, SIAM, 2007.

[36] A. Iserles, A First Course in the Numerical Analysis of Differential Equations, Cambridge University Press, 2008.

[37] N. Trippodo, Total circulatory capacity in the rat. effects of epinephrine and vasopressin on compliance and unstressed volume., Circulation research 49 (4) (1981) 923–931.

[38] D. B. Young, Control of cardiac output, Integrated Systems Physiology: From Molecule to Function 2 (1) (2010) 1–97.
[39] S. Gelman, Venous function and central venous pressurea physiologic story, The Journal of the American Society of Anesthesiologists 108 (4) (2008) 735–748.

[40] J. Beneken, B. DeWit, A physical approach to hemodynamic aspects of the human cardiovascular system, Physical bases of circulatory transport: Regulation and exchange (1967) 1–45.

[41] R. J. Gotwals. Cardiovascular physiology: The windkessel model [online] (2000-2003).

[42] R. Klabunde. Cardiovascular physiology concepts [online] (2014).

[43] G. London, A. C. Simon, Y. Weiss, M. E. Safar, Arterial and venous systems in essential hypertension, Vol. 63, Springer Science & Business Media, 2012.

[44] R. C. Smith, Uncertainty quantification: theory, implementation, and applications, Vol. 12, SIAM, 2013.

[45] H. Miao, X. Xia, A. Perelson, H. Wu, On identifiability of nonlinear ode models and applications in viral dynamics, SIAM Rev 53 (2011) 3–39.

[46] J. T. Ottesen, J. Mehlsen, M. S. Olufsen, Structural correlation method for model reduction and practical estimation of patient specific parameters illustrated on heart rate regulation, Mathematical biosciences 257 (2014) 50–59.

[47] C. T. Kelley, Iterative methods for optimization, Vol. 18, Siam, 1999.

[48] S. Smolyak, Quadrature and interpolation formulas for tensor products of certain classes of functions, Sov Phys Dokl 148 (1963) 1042–1045.

[49] H.-J. Bungartz, M. Griebel, Sparse grids, Acta Numerica 13 (2004) 147–269.

[50] J. Halton, On the efficiency of certain quasi-random sequences of points in evaluating multi-dimensional integrals, Numerische Mathematik 2 (1960) 84–90.
[51] S. Joe, F. Kuo, Remark on algorithm 659: Implementing sobol’s quasirandom sequence generator, ACM Trans Mathe Software (TOMS) 29 (2003) 49–57.

[52] C. Andrieu, J. Thoms, A tutorial on adaptive mcmc, Statistics and Computing 18 (4) (2008) 343–373.

[53] H. Haario, M. Laine, A. Mira, E. Saksman, Dram: efficient adaptive mcmc, Statistics and Computing 16 (4) (2006) 339–354.

[54] A. Mira, On metropolis-hastings algorithm with delayed rejection, Metron LIX (3-4) (2001) 231–241.

[55] H. Haario, E. Saksman, J. Tamminen, An adaptive metropolis algorithm, Bernoulli 7 (2001) 223–242.

[56] J. P. Kaipio, E. Somersalo, Statistical and Computational Inverse Problems, Springer, New York, 2005.

[57] J. Liu, M. West, Combined parameter and state estimation in simulation-based filtering, in: A. Doucet, N. de Freitas, N. Gordon (Eds.), Sequential Monte Carlo Methods in Practice, Springer, New York, 2001, pp. 197–223.

[58] M. Pitt, N. Shephard, Filtering via simulation: auxiliary particle filters, J Amer Statist Assoc 94 (1999) 590–599.

[59] A. Arnold, D. Calvetti, E. Somersalo, Linear multistep methods, particle filtering and sequential Monte Carlo, Inverse Problems 29 (8) (2013) 085007.

[60] G. Evensen, Sequential data assimilation with a nonlinear quasi-geostrophic model using Monte Carlo methods to forecast error statistics, J Geophys Res 99 (C5) (1994) 10143–10162.

[61] G. Burgers, P. J. Leeuwen, G. Evensen, Analysis scheme in the ensemble Kalman filter, Mon Weather Rev 126 (6) (1998) 1719–1724.
[62] G. Evensen, The ensemble Kalman filter for combined state and parameter estimation, IEEE Control Syst Mag 29 (3) (2009) 83–104.

[63] A. Arnold, D. Calvetti, E. Somersalo, Parameter estimation for stiff deterministic dynamical systems via ensemble Kalman filter, Inverse Problems 30 (10) (2014) 105008.
Figure 11: (Top) Parameter chains of subset (25) using DRAM with 100,000 sample points. The first 10,000 samples are considered as the burn-in period and are not used in computing the resulting parameter densities or Bayesian UQ. (Middle) Parameter densities of subset (25). (Bottom) Pairwise correlations of the resulting parameter densities from DRAM. Each plot can be interpreted as a marginal density by integrating over all of the other parameters not contained in the respective plot.
Figure 12: Uncertainty propagation of pressure in the left ventricle. The red curve is the data, the blue dotted lines show the frequentist confidence interval (20), and the green dashed lines show the frequentist prediction interval (21). The black line is the model evaluated with the means of the DRAM estimated parameter densities, the dark grey band (too narrow to be seen in this figure) is the Bayesian credible interval, and the light grey band is the Bayesian prediction interval.
Table 3: Model parameter values for Rat 1 data. Parameters denoted with an * are included in subset 25 and estimated using Levenberg-Marquardt optimization and DRAM. Reported DRAM values are the means of the resulting parameter sample chains with the 10,000 sample burn-in removed.

| Parameter | Units            | Nominal Values | Optimized Values | DRAM Mean Values |
|-----------|------------------|----------------|------------------|------------------|
| $R_a$     | sec*mmHg/µl      | 0.0011         | -                | -                |
| $R_v$*    | sec*mmHg/µl      | 0.0942         | 0.1600           | 0.1588           |
| $R_v$     | sec*mmHg/µl      | 0.0002         | -                | -                |
| $E_{ao}$  | µl/mmHg          | 0.9641         | -                | -                |
| $E_{sa}$  | µl/mmHg          | 0.1193         | -                | -                |
| $E_{sv}$  | µl/mmHg          | 0.0006         | -                | -                |
| $E_{vc}$  | µl/mmHg          | 0.0050         | -                | -                |
| $T_s$*    | sec              | 0.2500         | 0.4544           | 0.4518           |
| $T_R$*    | sec              | 0.6000         | 0.7309           | 0.7403           |
| $E_m$*    | mmHg/µl          | 0.0043         | 0.0050           | 0.0049           |
| $E_M$*    | mmHg/µl          | 0.5476         | 0.5965           | 0.5904           |
Figure 13: Frequentist Uncertainty Quantification for Rat 2 (Top) and 3 (Bottom). The top plot is the pressure time series, and the bottom plot is the volume time series. The red curve denotes the data, the blue dashed lines show the frequentist confidence interval \cite{20}, and the green dashed lines show the frequentist prediction interval \cite{21}. The black line is the model evaluated with the means of the DRAM estimated parameter densities, the dark grey band (too narrow to be seen in this figure) is the Bayesian credible interval, and the light grey band is the Bayesian prediction interval.
Figure 14: Parameter densities of an unidentifiable subset. Posterior parameter chains were computed using 100,000 iterations of DRAM, with the first 10,000 iterations removed as burn-in.