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Practical identifiability and uncertainty quantification of a pulsatile cardiovascular model

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ABSTRACT

Mathematical models are essential tools to study how the cardiovascular system maintains homeostasis. The utility of such models is limited by the accuracy of their predictions, which can be determined by uncertainty quantification (UQ). A challenge associated with the use of UQ is that many published methods assume that the underlying model is identifiable (e.g. that a one-to-one mapping exists from the parameter space to the model output). In this study we present a novel workflow to calibrate a lumped-parameter model to left ventricular pressure and volume time series data. Key steps include using (1) literature and available data to determine nominal parameter values; (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) frequentist and Bayesian UQ calculations to assess the predictive capability of the model. Our results show that it is possible to determine 5 identifiable model parameters that can be estimated to our experimental data from three rats, and that computed UQ intervals capture the measurement and model error.

1. Introduction

Precision medicine is a growing model of healthcare that proposes to customize of care, medical decisions, practices, and products to each individual patient. This approach is important, as pathologies such as cancer, autoimmune disorders, and cardiovascular diseases are unique to a given individual making it challenging to develop diagnostic and treatment protocols. One approach, to studying patient-specific complexities, is to use mathematical modeling to estimate function and predict features that are difficult to measure, thus providing a more comprehensive set of information to distinguish between individual patients.

A rich history of cardiovascular modeling exists in the literature, typically presented either from a fluid dynamics perspective (resulting in systems of PDEs) [1–3] to study local flow properties, or from a compartment perspective (resulting in systems ODEs) to study systems level dynamics [4,5]. The model type used depends on the questions investigated. Fluid dynamics models (1D-3D) are excellent for examining flow properties, e.g. how local flow is impacted by geometric structure, such as flow past a stent, flow changes following bypass surgery, flows in aneurysms, valves function, or flow and wave propagation changes in hypertension or diabetes [6–11]. However, due to computational complexity, 1D-3D models are typically not used in studies aiming to understand how the CV system interacts with other systems, e.g. autonomic control by neuro-humoral mechanisms, the immune system, or physiologically-based pharmacokinetics [12–14]. The main obstacle is that models used in this setting often need to be solved over long time-scales. For these types of applications compartment ODE models are more appropriate. One disadvantage to ODE models is that they are difficult to parameterize and fit to data. To illustrate the steps associated with this process we have chosen to analyze a simple 5-compartment (0D) model inspired by models used to predict changes during head-up tilt [15]. In ODE models, compartments represent groups of vessels (e.g. large or small arteries or veins, capillaries, or vessels supplying specific tissues or organs) coupled to a heart compartment that act as a pump to drive the system. Some models include both pulmonary and systemic circulations [16], while others analyze one of the two systems [17]. ODE models of this type can be used to extract vascular properties such as vascular resistance, cardiac contractility, or compliance by fitting models to pressure and flow data

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from noninvasive imaging studies [15,18,19] and/or from invasive catheterization [20–22] studies.

One of the biggest challenges in calibrating compartment models to data is obtaining accurate parameter estimates. Even in its basic form, where the model is formulated using systems of linear differential equations, forced by a contracting heart, it is typically not possible to uniquely estimate all model parameters. To overcome this, we use sensitivity analysis and subset selection for *a-priori* study of the model structure followed by parameter estimation and uncertainty quantification. In general, parameters that are unidentifiable as a result of model structure are referred to as *structurally unidentifiable* [23], whereas parameters that are unidentifiable as a result of practical restrictions, such as availability and quality of data, are referred to as *practically unidentifiable* [24]. Theoretically, structural identifiability is a prerequisite for practical identifiability. However, in practice it can be difficult to establish the former, since analysis is restricted to models for which it is possible to define a unique input-output relation [23].

Only a few studies have addressed structural identifiability in cardiovascular models. Kirk et al. [25], studying Windkessel models, showed that three of four parameters are identifiable, and Pironet et al. [26] demonstrated that every parameter in a linear six-compartment model including a left and right heart, systemic and pulmonary arteries and veins are structurally identifiable if outputs contain both pressure (in all arteries and veins) and left/right ventricular stroke volume, while models relying on either pressure or volume alone are structurally unidentifiable. Other studies have employed sensitivity and practical, opposed to structural, identifiability analysis to predict arterial blood pressure and cardiac output [15,19,27,28]. Several recent studies have addressed uncertainty quantification, mostly for analysis of 1D fluid dynamics models. To our knowledge, these methodologies have not previously been applied to analysis of compartment models. The study by Eck et al. [29] developed a guide to uncertainty quantification in cardiovascular models presenting a number of methodologies. Several studies have predicted uncertainties in specific one-dimensional fluid mechanics models [30–35]. Of these, three studies accounted for uncertainty using Kalman filtering [30–32], two used polynomial chaos expansion, and one [35] used an MCMC approach based on the Delayed Rejection Adaptation Metropolis (DRAM) algorithm [36]. To our knowledge, none of these studies combined these techniques into an organized workflow for the determination of model parameters in compartmental CV models given a specific data set.

In this study, we present a general multi-stage workflow applied to analysis of a five compartment model for the systemic circulation with left ventricular volume and blood pressure data from three Sprague Dawley rats. The key steps in our workflow include: (1) the use of literature and available data to compute nominal parameter values specific to each rat; (2) sensitivity analysis and subset selection to determine a set of identifiable parameters; (3) optimization to compute point estimates for the identifiable parameters; and (4) statistical techniques to quantify uncertainty of the model output.

2. Methods

2.1. Experimental data

Data analyzed here are extracted from experiments performed on 3 Sprague-Dawley (SD) rats (2 male, 1 female). The average weight of these animals was 358.0 ± 19.6 g. The rats were anesthetized with sodium pentobarbital (50 mg/kg, ip), and catheters were placed in a femoral vein and artery for administration of anesthetics and monitoring of systemic blood pressure, respectively. A pressure-volume conductance catheter (Millar SPR-869, 2F tip with four electrodes and 6 mm spacing) was inserted through the right carotid artery into the left ventricle. For each rat basic physiological measures (sex, weight, heart rate, average stroke volume and cardiac output, Table 1) were recorded along with continuous measurements of left ventricular volume and pressure. For this study, approximately 20-second time-series data, measured at rest, were selected for model identification and the final 0.5 s of each data set was used to calibrate the model, shown in Fig. 1.

Table 1
Rat average data.

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

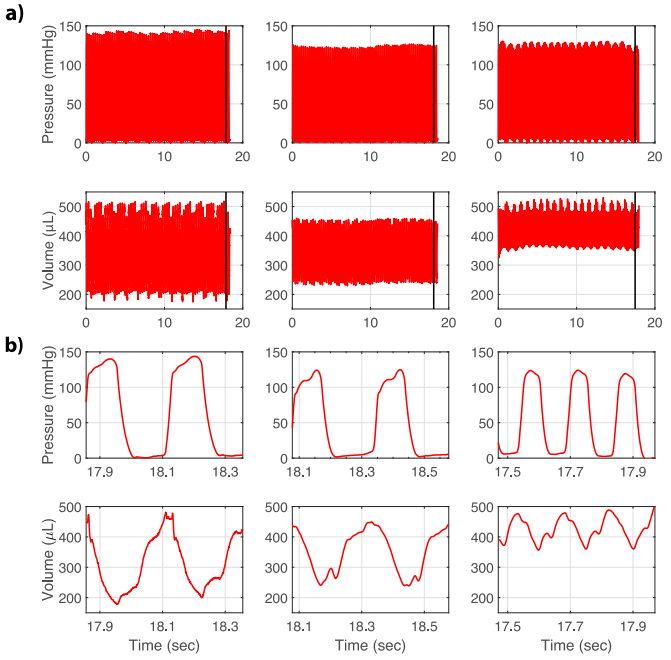

Fig. 1. Left ventricle pressure and volume data from three rats. Each column corresponds to a different rat. **(a)** shows the 20-second raw time-series data and **(b)** shows a zoomed-in view of the final 0.5 s used to calibrate the model output (marked by vertical black lines on the top two rows.).

Volume-conductance calibration

One of the most common methods for translating conductance measurements to volume is using Baan's equation

$$V(t) = \frac{L^2}{\alpha\sigma}[G(t) - G^p],$$

where $V(t)$ is the left ventricular volume, L is the spacing between electrodes on the catheter, σ is the specific conductivity of the blood, $G(t)$ is the measured total conductance (measured as a voltage directly proportional to the conductance), G^p is the parallel conductance through the myocardium, and α is a stroke volume scaling factor determined from cuvette calibration, obtained by infusing a known hypertonic saline bolus before the experiment and extracting known volumes after the experiment. This allows subtraction of parallel conductance through the myocardium from the total measured conductance.

In this study, the baseline left ventricular pressure and volume time-course analyzed is extracted from a longer experimental time-course involving sequential blood withdrawals. This experimental manipulation (blood withdrawal) violates the assumption of constant σ, G^p (and possibly α) in Baan's equation. It has previously been found that the volume-voltage relationships determined using cuvette calibration measures is highly sensitive to changes in hematocrit and hence conductivity of blood [21,37]. Furthermore, sufficient loss of blood