

BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
Department of Control Engineering and Information Technology



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TDK research

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Neural ODE based cardiovascular model identification for
personalized fluid resuscitation

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Abstract

Acute circulatory failure (ACF) is a clinical syndrome when the heart and circulatory circulation cannot provide adequate blood supply to meet the metabolic needs of the organs. ACF affects 30% of intensive care unit (ICU) patients. Fluid resuscitation is the primary treatment of ACF. However, it fails in a significant proportion (up to 50%) of cases due to lack of clinically feasible non-invasive perfusion markers to assess the efficacy of the fluid therapy. Unfortunately, unsuccessful fluid therapy negatively affects the outcome of the patient's treatment, increasing the length of stay in the intensive care unit and, in parallel, increasing the costs of the treatment. Based on recently published studies, it is possible that the identification of the Stress Blood Volume parameter of the cardiovascular system can be used to assess the efficacy of the fluid therapy. The development of the diagnostic method requires the identification of the central arterial pressure curve based on the femoral arterial pressure, which is frequently available in intensive treatment; then, the central arterial pressure curve can be used to identify the cardiovascular system parameters. The present TDK research aims to develop a parameter-identification method for the Tube-load model-based transfer function connecting the femoral and central arterial pressure curve by using the so-called Physics-informed Neural Network methodology, namely the Neural ODE method. The TDK study presents the adaptation of the Neural ODE method to the given parameter identification problem and the validation of the developed identification method. The developed identification method was used on a series of measurement data recorded in animal experiments, modeling a wide range of possible physiological states of the human circulatory system.

Keywords: personalized model-based medical therapy methods, cardiovascular system, physiological system modeling, parameter identification, transfer function, Neural ODE, intensive care

Kivonat

Betegek kórházi kezelése során akut keringési elégtelenségről (Acute Circulatory Failure – ACF), ill. keringéses sokkról akkor beszélünk, amikor a szív és a keringési rendszer nem tudja biztosítani a megfelelő vérellátást a szervek anyagcsere szükségleteinek kielégítéséhez. Ez a kórkép az intenzív osztályon (intensive care unit - ICU) ápolott betegek kb. 30%-át érinti. A sokkos állapot kezelésére folyadék terápia a leggyakrabban alkalmazott kezelési eljárás, azonban az esetek jelentős részében (kb. 50%-ában) ez sikertelen. Jelenleg nincs klinikailag széleskörűen alkalmazható, nem invazív perfúziós marker a folyadékterápia eredményességének értékelésére, mely lehetővé tenné a terápia keringésre gyakorolt hatásának közvetlen mérését. A sikertelen folyadékterápia következményei sajnos negatívan befolyásolják a beteg kezelésének kimenetelét, megnövelik az intenzív osztályon történő kezelés időtartamát és ezzel párhuzamosan a kezelés költségeit.

A közelmúltban publikált kutatások alapján valószínűsíthető, hogy a keringési rendszert jellemző ún. Stressed Blood Volume paraméter meghatározása lehetőséget adhat a folyadékterápia hatásosságának vizsgálatára. A diagnosztikai módszer kidolgozásához szükség van a klinikai gyakorlatban gyakran mért femorális artériás nyomás alapján meghatározni a centrális artériás nyomásgörbét, mely ezután felhasználható a kardiovaszkuláris rendszert leíró modellek paramétereinek identifikációjára.

A TDK dolgozat célja, hogy az ún. Tube-load modell alapján származtatott, a femorális és centrális artériás nyomás között felírható átviteli függvény paraméterei identifikációjának módszerét kidolgozza az ún. Physics-informed Neural Network, egész pontosan a Neural ODE módszer alapján. A dolgozat bemutatja a Neural ODE módszer adaptálását az adott paraméter identifikációs problémára, ill. a kidolgozott módszer validációját. A módszer segítségével lehetőség nyílt az identifikációs módszert olyan, állatkísérletek során rögzített mérési adatsoron alkalmazni, mely modellállatok segítségével a lehetséges élet-tani állapotok széles körét lefedte.

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1 Introduction

In the case of Acute Circulatory Failure (ACF), fluid therapy is a widely used intervention to stabilize heart function [9]. However, the effectiveness of fluid therapy is not directly predictable, and the therapy can also be harmful. Physiological models are able to predict fluid responsiveness - describing the effectiveness of fluid therapy for the patient -, but aortic (central arterial) blood pressure must be used to identify their parameters. The measurement of central arterial blood pressure is highly invasive and so not common in clinical practice. However, the aortic pressure can be approximated using femoral arterial pressure measurements. The Tube-load model [3] describes the relationship between the femoral and central arterial blood pressure if the correct parameters of the model are known for the current patient.

The main goal of this research is to develop a parameter identification method for the transfer function, which will allow us to determine the central arterial pressure based on the femoral arterial pressure in a given clinical case. Using the aortic pressure, fluid responsiveness can be estimated, which will help to improve the effectiveness of fluid therapy in clinical practice.

1.1 Objectives

The TDK research investigates the identification of the parameters of the transfer function derived from the Tube-load model with the NeuralODE method [6]. The NeuralODE method combines classical ordinary differential equations with modern neural networks.

The aims of the research are twofold. The first objective includes the examination of the applicability and robustness of the NeuralODE method for the given parameter identification problem. The second objective is the examination of the identified parameters. A valuable research outcome will be the variability of the parameters using a physiological experiment's data set and the clinical interpretation of the parameter changes. By identifying the possible parameter sets of the examined transfer function, the parameter space can be reduced, supporting further research aiming at the development of an Artificial Intelligence-based semi-automated fluid responsiveness assessment method.

2 Data and Methods

2.1 Data

The experimental data set was collected from a series of animal experiments performed at the Centre Hospitalier Universitaire de Liège in a joint project with the University of Canterbury. The details of the animal experiments are described in detail in the PhD thesis of Rachel Genevieve Rose Smith, titled 'Model-based hemodynamic management of critically ill patients' [1]. This section provides a brief summary of the procedures. Thus, the following sections are written with extensive use of the above-cited PhD thesis.

In the experiments, a cohort of 7 pure Piétrain pigs, weighing 18.5 kg to 29.0 kg, were used. The subjects were initially sedated and anaesthetized. Sedation and anaesthesia were maintained via a continuous infusion of pharmaceutical drugs, namely sufentanil, Thiobarbital and Nimbex, delivered via a superior vena cava catheter. Pigs were mechanically ventilated. High-fidelity pressure catheters were used in the proximal aorta (P_{ao}), femoral artery (P_{abd}), and vena cava (P_{cv}) to measure blood pressure. Left ventricular pressures (P_{LV}) and volumes (V_{LV}) were also measured. Flow into the aorta (Q_{ao}) was measured using an aortic flow probe positioned on the proximal aorta near the aortic valve. Once the probe was located, the thorax was held closed using clamps. All data was measured with a sampling rate of 250 Hz and recorded as a single Notocord data file.

The pigs underwent different haemodynamic interventions during the measurements:

- **Recruitment Manoeuvres (RM):** A number of respiratory recruitment manoeuvres in which positive end-expiratory pressure (PEEP) is increased in steps of 5 cmH₂O. Increasing positive end-expiratory pressure reduces systemic venous return to the right heart and increases pulmonary resistance. The reduction in flow in and out of the right ventricle leads to a corresponding drop in flow into the left ventricle and a drop in stroke volume (SV). The effect of PEEP changes may be reduced due to the opening and then clamping of the chest for placement of the aortic flow probe. Pigs 2, 4, 5 and 7 underwent five recruitment manoeuvres. Pigs 1, 3, and 6 died before completion of the experimental protocol and underwent two recruitment manoeuvres.
- **Fluid Infusion:** Intravenous infusions of saline solution, delivered at a rate of 500mL over 30 min. This intervention aims to increase circulatory volume and ventricular preload, thus SV. Pigs 2, 4, 5 and 7 underwent three fluid infusions. Pigs 1, 3, and 6 died before completion of the experimental protocol and underwent one infusion.
- **Endotoxin:** An infusion of endotoxin (E. Coli lipopolysaccharide) at a rate of 0.5mgkg⁻¹ over 30 minutes to produce a septic shock-like response: inflammation, capillary leakage, decreased afterload, hypovolemia, tissue hypoxia and eventual

cardiac failure. Pigs 2, 4, 5 and 7 completed the full endotoxin infusion. Pigs 1, 3, and 6 died from circulatory failure before completion of the infusion.

The schedule of the interventions is shown in Figure 2.1.

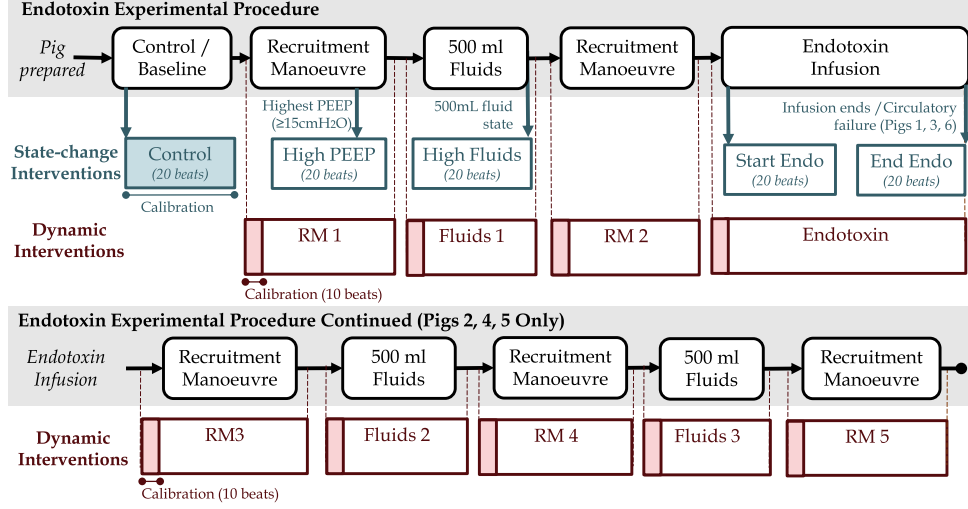


Figure 2.1: The schedule of interventions performed on the examined pigs [1]

2.2 Methods

This chapter summarizes the models used in this research.

2.2.1 Three-Chambered Model

The Three-Chambered Model (TCM) is a lumped parameter model of the cardiovascular system [2]. It consists of three elastic chambers, representing the left ventricle (lv), the aorta (ao) and one vena cava (vc). The first is an active chamber, while the others are passive chambers. The two passive chambers are described by the following equations:

$$P_{ao} = E_{ao}V_{S,ao}(t) \quad (2.1)$$

$$P_{vc} = E_{ao}V_{S,vc}(t), \quad (2.2)$$

where P is pressure, E is elastance, and V_S is stressed blood volume, each at the anatomical location indicated by the indexes. The left ventricle is the active chamber, represented by the following equation [10]:

$$P_{lv} = E_{lv}e(t)V_{S,lv}(t), \quad (2.3)$$

where E_{lv} is the maximum elastance, and $e(t)$ is the normalised pressure-volume ratio, which is a T-periodic function - T being the duration of a heartbeat - ranging from nearly 0 - during filling - to 1 - at end-systole [2]. The product of $e(t)$ and E_{lv} represents

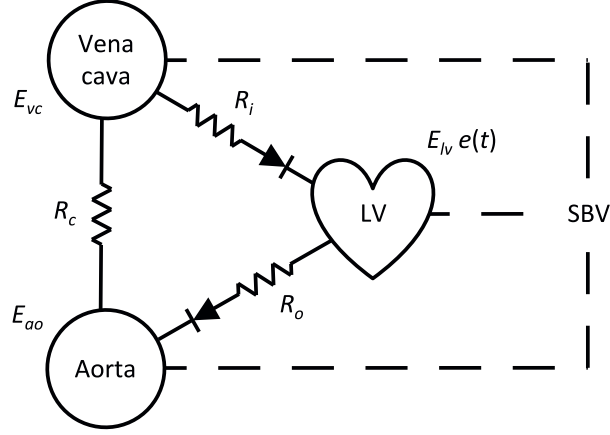


Figure 2.2: The Three-Chambered Model [2]

the time-varying elastance of the left ventricle, which makes it an active chamber. The representation of the TCM is shown in Figure 2.2.

The chambers are connected through resistances. R_o represents the resistance of the aortic valve, R_c corresponds to the resistance of the systemic circulation, while R_i incorporates all resistances from the tricuspid valve to the mitral valve, including the whole pulmonary circulation. Flow is described by Ohm's law, with the addition of two one-way valves:

$$Q_c(t) = \frac{P_{ao}(t) - P_{vc}(t)}{R_c} \quad (2.4)$$

$$Q_i(t) = \begin{cases} \frac{P_{vc}(t) - P_{lv}(t)}{R_i}, & \text{if } P_{vc} > P_{lv} \\ 0, & \text{otherwise.} \end{cases} \quad (2.5)$$

$$Q_o(t) = \begin{cases} \frac{P_{lv}(t) - P_{ao}(t)}{R_o}, & \text{if } P_{lv} > P_{ao} \\ 0, & \text{otherwise.} \end{cases} \quad (2.6)$$

The rate at which the volumes change is given by the continuity equations:

$$\dot{V}_{S,lv} = Q_i(t) - Q_o(t) \quad (2.7)$$

$$\dot{V}_{S,ao} = Q_o(t) - Q_c(t) \quad (2.8)$$

$$\dot{V}_{S,vc} = Q_c(t) - Q_i(t). \quad (2.9)$$

The summation of the three continuity equations yields

$$\dot{V}_{S,lv} + \dot{V}_{S,ao} + \dot{V}_{S,vc} = 0. \quad (2.10)$$

By integrating Equation 2.10, the sum of stressed volumes is a constant and a model parameter:

$$V_{S,lv} + V_{S,ao} + V_{S,vc} = \text{SBV}. \quad (2.11)$$

The TCM has eight parameters: the three resistances (R_o , R_c , R_i), three elastances (E_{lv} , E_{ao} , E_{vc}), the sum of the stressed volumes of the chambers (stressed blood volume (SBV)) and the cardiac period (T).

Stressed blood volume is shown to be a potential index of fluid responsiveness. SBV can be estimated using the Three Chambered Model, avoiding highly invasive measurement methods, and so stressed blood volume can be used in clinical practice to indicate fluid responsiveness [11].

2.2.2 Tube-load model

The Tube-load model describes the arterial system as an arbitrary number of parallel uniform lossless tubes, representing the large conduit arteries, in series with loads, that stand for peripheral blood vessels, as shown in Figure 2.3.

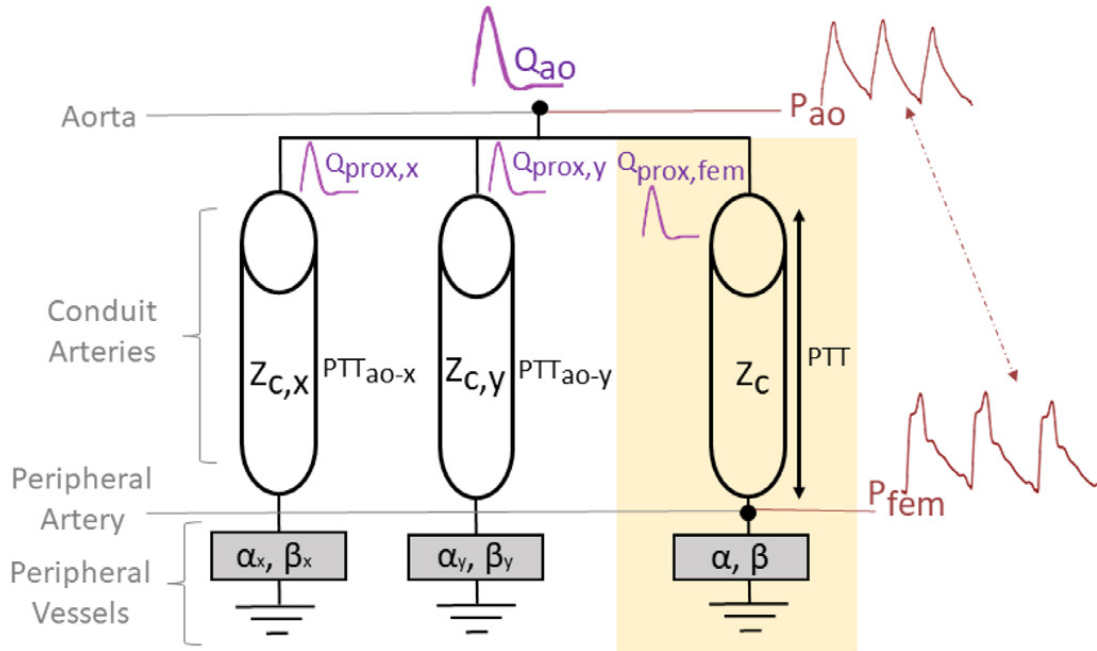


Figure 2.3: The schematic figure of the Tube-load model [3]

The time it takes for pressure waves generated by the heart (the left ventricle) to travel through the large arteries to the periphery is called pulse transit time (PTT). These waves are reflected to some extent, which leads to differences between Q_{ao} and P_{ao} waveform shapes, as the reflected wave increases pressure but decreases flow. The Tube-load model captures this effect by modelling forward- and backward-travelling waves along the uniform tubes. Each tube and load represents a pathway to a different peripheral vascular bed. In the model, the pressure of each tube at the proximal end is the aortic pressure (P_{ao}). The aortic flow (Q_{ao}) equals the sum of the proximal flows of all tubes. The femoral pressure (P_{fem}) is the distal pressure of a tube, and this parameter, together with PTT is used to estimate central flows and pressures ($Q_{ao,est}$, $P_{ao,est}$), assuming changes in the proximal femoral arteries are representative of the changes in the aorta. The character-

istic impedance of the tube (Z_c), representing the resistance of the conduit arteries, is assumed constant. The impedance of distal arterial beds (Z_{load}) is modelled in the frequency domain as a single pole and zero, characterized by parameters A , B , with a gain factor Z_c :

$$Z_{load}(\omega) = Z_c \frac{j\omega + B}{j\omega + A}, \quad (2.12)$$

where ($0 < A < B$) and Z_c is the impedance of the corresponding tube, ensuring pressure wave reflections are positive, stable, and become negligible at high frequencies. As the frequency becomes very large, the peripheral load tends to Z_c , and the tube and load are impedance matched, so there are no reflections. The model can be used to create transfer functions between central and peripheral pressures and flows in the frequency domain. Thus, $P_{ao,est}$, and $Q_{ao,est}$ are calculated using measured P_{fem} and PTT [3]:

$$\frac{P_{ao,est}(\omega)}{P_{fem}(\omega)} = \frac{\left(\frac{B+A}{2} + j\omega\right) e^{j\omega PTT} + \left(\frac{B-A}{2}\right) e^{-j\omega PTT}}{j\omega + B} \quad (2.13)$$

Using the Laplace transform, the transfer function can be represented in the continuous time domain:

$$\dot{P}_{ao,est}(t) + BP_{ao,est} = \dot{P}_{fem}(t + PTT) + \frac{B+A}{2}P_{fem}(t + PTT) + \frac{B-A}{2}P_{fem}(t - PTT) \quad (2.14)$$

Equation 2.14 describes the transfer function with parameters A , B and PTT , that we have identified in this work.

2.2.3 Alternative methods to estimate central blood pressure from peripheral pressure waves

Identifying the parameters of Equation 2.14 gives a solution to model the cardiovascular system and estimate the central blood pressure wave. However, the parameters may vary between subjects, and the identification process depends on measurement data. Due to the possible unavailability or poor quality of clinical measurement data, alternative methods were also developed to estimate central blood pressure. Murphy [4] implemented a linearised estimation of the central blood pressure wave based on specified landmark points of a single peripheral blood pressure wave. Figure 2.4 shows the landmark points and the construction of the linearised approximation.

The two components of the pressure waves are the forward- and backward-travelling, or forward-travelling and reflected waves (P_f and P_r). The information regarding P_f and P_r is contained in the second derivative of the peripheral (femoral) pressure wave. Based on the second derivative, the femoral pressure waves are categorized into three groups and the method is defined for each group.

Six landmark points are used to define the estimated central pressure: the two diastolic feet of the measured femoral pressure wave, a primary and secondary systolic shoulder,

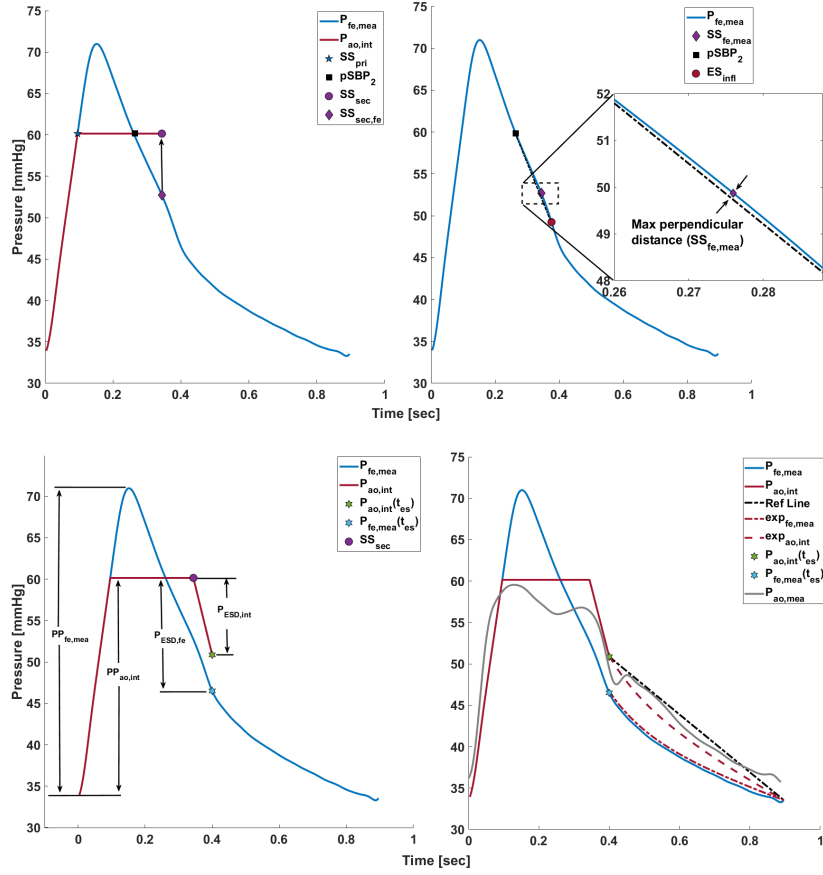


Figure 2.4: The construction steps of the linearised approximation method [4]

the systolic pressure reference value ($pSBP_2$), and an estimate for central end-systolic pressure. The exact definition of these points will not be discussed in this work.

In the first section of the wave, until the primary systolic shoulder, the reflected wave can be neglected, and the aortic pressure is estimated with the femoral pressure. Then, between the first and second systolic shoulders, the aortic pressure is estimated constant, with the value of $pSBP_2$. The late systolic pressure drop is estimated to be proportional to the same drop of the femoral pressure until the estimated end-systolic pressure. Finally, the diastolic component of the aortic pressure wave is estimated by fitting an exponential to the diastolic part of the femoral pressure wave and then rotating the exponential so that it connects the estimated end-systolic aortic pressure and the end-diastolic femoral pressure.

Figure 2.5 shows the measured aortic and femoral pressures, together with the estimated aortic pressure waves using the pulse wave analysis method, approximating the aortic pressure with a linearised model. The measurements were taken in an animal experiment, where the aortic and femoral blood pressures, together with other physiological signals, were measured invasively in pigs during different interventions, namely 'Baseline', 'After Fluids', 'High PEEP' and 'End Endo' sections. It is clear that the estimation approximates the aortic pressure wave well in some cases, but it is not robust and does not reflect certain characteristics of the pressure wave. However, the only measurement needed

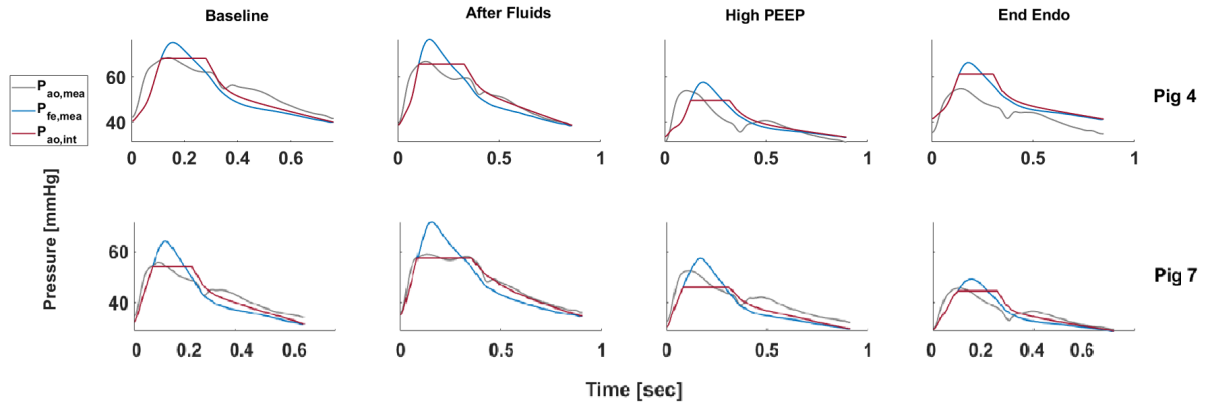


Figure 2.5: The linearised approximation method used for physiological measurements [4]

is the femoral pressure, which makes the method easily applicable in clinical settings.

2.2.4 Physics-informed machine learning

In the past 50 years, there has been tremendous progress in understanding multiscale physics in diverse applications, from geophysics to biophysics, by numerically solving **partial differential equations** (PDEs) using finite differences, finite elements, spectral and even meshless methods. However, solving real-life physical problems with missing, gappy or noisy boundary conditions through traditional approaches is currently impossible [5].

Current advances in machine learning models lead to refined neural networks able to fit observations precisely in a data-driven manner. However, the ability to create and collect data has outpaced understanding it [5]. Since ANN models have no physical constraints, they can produce physically inconsistent solutions, and while they are performing well in many cases, the physical inconsistencies can lead to a lack of robustness and poor generalization. Integration of physical laws into machine learning models is a promising way of creating powerful data-driven models that are consistent with the physical rules. Physics-informed learning is defined as the process by which prior knowledge stemming from our observational, empirical, physical or mathematical understanding of the world can be leveraged to improve the performance of a learning algorithm. A recent example reflecting this new learning philosophy is the family of ‘physics-informed neural networks’ (PINNs) [5]. This is a class of deep neural networks that integrates data and mathematical formulas, including PDEs. The use of data versus mathematical formulas depends on the use case. As Figure 2.6 shows, when small amount of data is available, it is used to set boundary and initial conditions of the physical models, therefore, the solution is mostly based on physical formulas. As more and more data is used, the pattern is found in the data itself, so there is no need for physical formulas. Physics-informed neural networks work in the middle of the spectrum. They integrate some physics with some data, thus leveraging the availability of real-life data and also keeping the solution consistent with the physical laws. There are several ways to embed physics in machine learning models. These are acquiring enough and appropriate data so that it represents the physical laws (observational bias), creating neural networks that implicitly embed physics in their structure (e.g. convolutional neural networks)(inductive bias), enforcing physical laws using appropriately selected loss functions (learning bias), or a hybrid of these biases.

2.2.5 NeuralODE

Neural Ordinary Differential Equations (NeuralODEs) are a new family of deep neural networks that combine the fields of differential equations with artificial neural networks [6]. The combination of the two fields seems natural since both differential equations and neural networks aim to specify an arbitrary nonlinear transform. In the case of neural networks, this is done using linear weights and a non-linear activation function for each layer. Ordinary differential equations define a non-linear transform by defining the

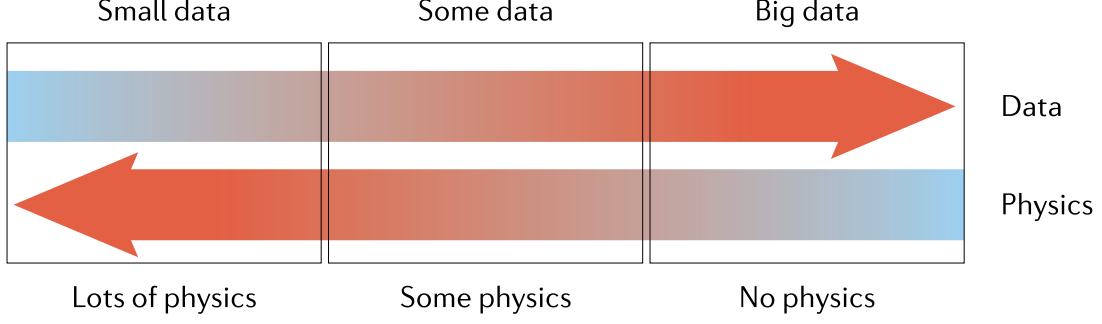


Figure 2.6: The dependency of models on data and physics [5]

derivative of the examined variable and thus leverage a priori knowledge of the structure of the problem.

As our machine learning models grow and are hungry for larger and larger amounts of data, differential equations have become an attractive option for specifying nonlinearities in a learnable (via the parameters) but constrained form [12]. Neural Ordinary Differential Equations are one of the ways ODEs and ANNs can be combined. The starting point is the Residual Neural Network (ResNet). ResNets are neural networks that are characterized by skip connections with identity mappings, as can be seen in Figure 2.7.

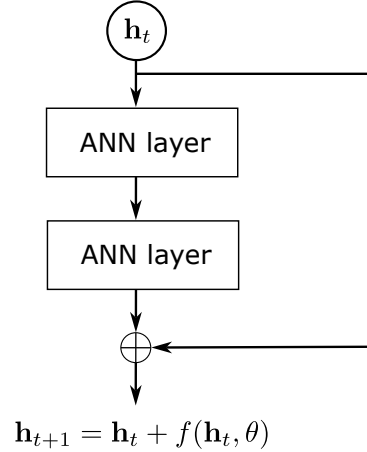


Figure 2.7: Model of the residual neural network

The output is the sum of the layer output and input/hidden state:

$$\mathbf{h}_{t+1} = \mathbf{h}_t + f(\mathbf{h}_t, \theta) \quad (2.15)$$

where $t \in 0 \dots T$, h_t is the state variable vector of the t^{th} layer of the neural network ($\mathbf{h}_t \in \mathbb{R}^D$) and θ represents the weights of the network. Equation 2.2.5 can be seen as an Euler discretisation of a continuous transformation. If so, we can produce the original differential equation by adding more layers to the ResNet and taking smaller steps. In the limit, the neural network can be defined by an ODE:

$$\frac{d\mathbf{h}(t)}{d(t)} = f(\mathbf{h}(t), t, \theta) \quad (2.16)$$

Starting from the input layer $h(0)$, we can define the output layer $h(T)$ to be the solution to this ODE initial value problem at some time T . This value can be computed by a black-box differential equation solver, which evaluates the hidden unit dynamics f wherever necessary to determine the solution with the desired accuracy. Figure 2.8 contrasts these two approaches [6].

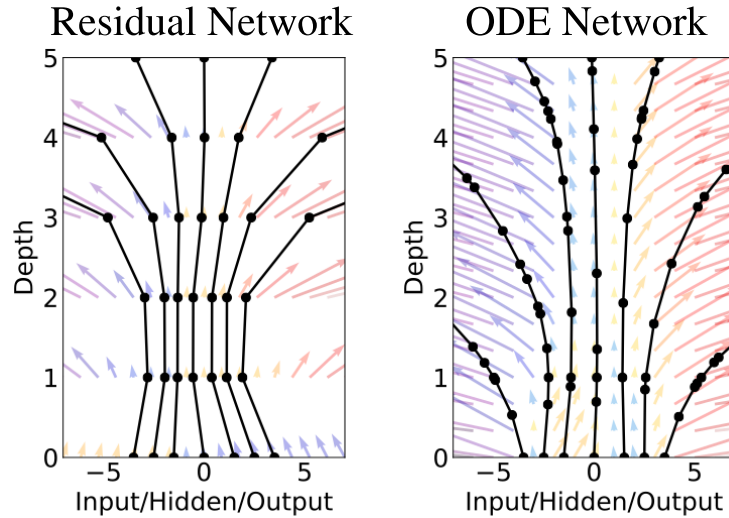


Figure 2.8: The difference and similarity between ResNets and NeuralODEs [6].

The main difficulty in training continuous-depth networks is performing backpropagation, which is the method to calculate the derivative of the loss function with respect to each parameter. The authors of the NeuralODE method treat the ODE solver as a black box, and compute gradients using the adjoint sensitivity method, which is applicable to all ODE solvers. The adjoint sensitivity method calculates gradients by solving a second, augmented ODE backwards in time. The approach scales linearly with problem size, has low memory cost, and explicitly controls numerical error [6].

Using neural network models with ODE solvers has numerous benefits, such as:

Memory efficiency: The adjoint sensitivity method provides a way to compute gradients of a scalar-valued loss with respect to all inputs of any ODE solver without backpropagating through all the operations of the solver. Not storing any intermediate quantities of the forward pass allows for training the models with constant memory cost as a function of depth, a major bottleneck of training deep models.

Adaptive computation: Modern ODE solvers provide guarantees about the growth of approximation error, monitor the level of error, and adapt their evaluation strategy on the fly to achieve the requested level of accuracy. This allows the cost of evaluating a model to scale with problem complexity. After training, accuracy can be reduced for real-time or low-power applications.

Continuous time-series models: Unlike recurrent neural networks, which require discretising observation and emission intervals, continuously-defined dynamics can naturally incorporate data which arrives at arbitrary times [6].

3 Results and Discussion

Solving Equation 2.14 for the derivative of aortic pressure yields a differential equation that enables the calculation of the aortic pressure based on an initial value and femoral pressure data.

$$\dot{P}_{ao,est}(t) = -BP_{ao,est} + \dot{P}_{fem}(t + PTT) + \frac{B + A}{2}P_{fem}(t + PTT) + \frac{B - A}{2}P_{fem}(t - PTT) \quad (3.1)$$

The goal of the presented research was to develop a NeuralODE-based parameter identification method defining A and B parameters of the Equation 3.1.

The transfer function takes the femoral arterial pressure wave as an input and outputs the aortic pressure wave's derivative. The questions regarding the identification problem were the following:

- (a) the optimal time window width to use for training the NeuralODE model,
- (b) the robustness of the NeuralODE method in terms of the parameter identification of the physiological experiment,
- (c) the variability of the parameters during the physiological experiment.

To develop the identification method, first, the optimal time window width was determined to use for learning, then a benchmark test was designed and performed to assess the robustness of the method, and finally, the experimental pig data was used to identify the parameters through time and examine the variability of them.

3.1 Calculating pulse transit time for each pulse

Pulse transit time (*PTT*) is a parameter of the used transfer function (Equation 3.1). It is the time it takes the pulse to propagate from the aorta to the femoral artery. It can be calculated from the measured waves, as it is the delay between the foot of P_{ao} and P_{fem} (see Figure 3.1). The localization of the foot of P_{ao} and P_{fem} is done using the `findminima()` function of the Peak.jl package¹. After filtering based on the prominence of the found minima, false values can be deleted. Filtering is most important in the case of the aortic waves since the dicrotic notch² produces a local minimum that needs to be ignored. In some extreme cases, the dicrotic notch can create a global minimum for the wave of one beat, in these cases, a more sophisticated method was used, which resulted in robust foot detection [13].

¹<https://github.com/halleysfifthinc/Peaks.jl>

²The dicrotic notch is a pressure drop caused by the closing of the aortic semilunar valve. More details can be found in the Appendix.

After localizing the minima of the aortic and femoral pressure waves, PTT is calculated as the delay between the respective feet. In the case of an anomaly, such as severe arrhythmia, it is possible that either the femoral or the aortic waves are distorted, so the minima cannot be found. To solve these anomalous situations, when the PTT rises above 0.25 seconds, the previous valid PTT value is used instead.

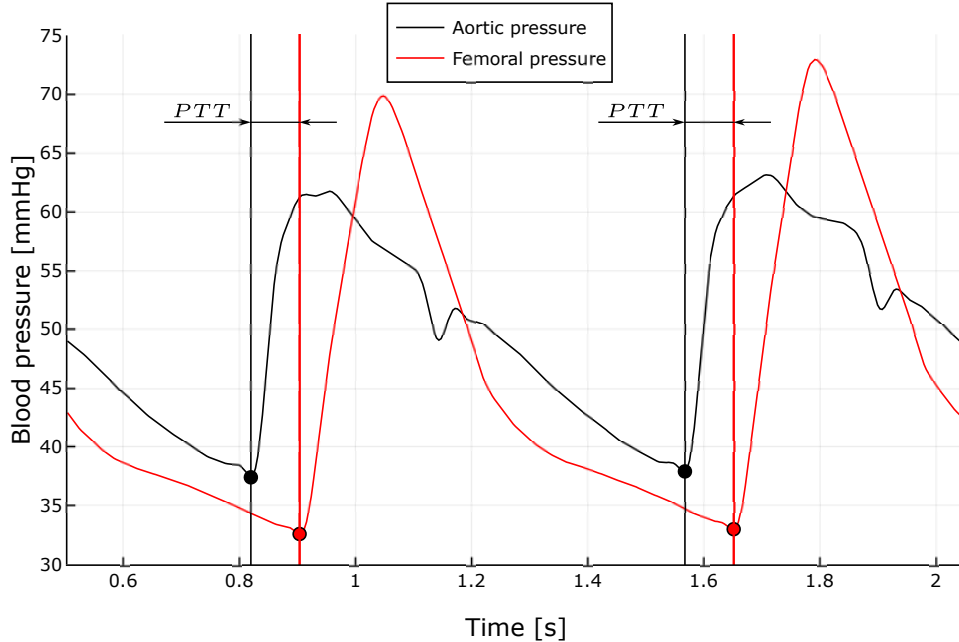


Figure 3.1: The pulse transit time parameter

3.2 Defining the optimal time window width for learning

The parameter identification is achieved by using the NeuralODE machine learning model. The training of the model is based on measurements of femoral and aortic pressure waves in pigs (the data is described in Section 2.1). Using the NeuralODE method, the parameter set is iteratively updated so that the solution of the differential equation in Equation 3.1 approximates the actual aortic pressure with the maximum accuracy.

We aim to identify the parameters of the model as frequently as possible. To this end, the measurement data is divided into small slices, and the parameters are learned on these subsets. When choosing the appropriate time window width for the learning, there is a trade-off between computational time and accuracy, which is a characteristic property of every learning task. An interesting question regarding the transfer function is how long transient effects the parameters have on the output. If these effects last only one period, then it would be enough to train the model on one period of femoral and aortic pressure waves.

To test the assumption that learning on longer data yields more accurate results, the learning was performed with 1-second, 3-second, 5-second and 10-second long time window widths (for this test, the 'Control/Baseline' part of the data set of pig #7 was used). For

the first sequence, the parameters were initialized with previously identified values and optimized with a NeuralODE layer, minimizing the mean squared error of the output and the measured aortic pressure waves. Then, the time window was shifted 1 second forward, and the optimization was performed with the parameters initialized with the optimal values of the previous period. Figure 3.2 shows the first, second and third time windows using a 3-second time window width.

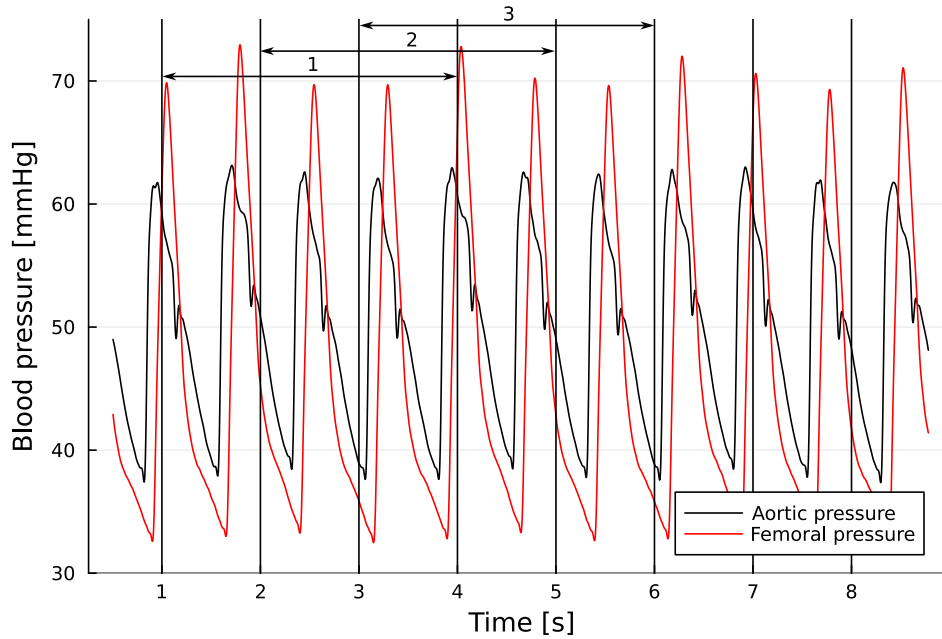


Figure 3.2: The time windows used with a 3-second time window width.

Figure 3.3 shows the result of the experiment, where an interesting periodicity is visible in the identified value of the A parameter.

As the time windows are selected based on time elapsed and not on the cardiac cycles, and we did not know any physiological explanation for a periodicity, we assumed that a possible cause of the periodicity is the phase shift of the cardiac cycle at the beginning of the time window that is used during each optimization. To visualize the phase at each second, the minima of the femoral arterial pressure waves found when calculating the PTT were used. We were able to calculate the phase of the femoral pressure waves at the start of each period used for training the model. The phase is plotted next to the ' A ' parameters in Figure 3.4. It can be seen that the same kind of periodicity is present in the phase of the waves at the start of the time windows, so this has caused the experienced artefact during training.

To compensate this periodic inaccuracy in the subsequent phases of the research, time windows were selected based on the start and the end of a cardiac cycle. With this modification, each training data starts at the same phase of a cardiac cycle.

A significant difference in identified parameters was present between the training with 1-second and 3-second time window widths. When the transfer function is used to calculate the aortic waves, an initial condition has to be set. The phase of the wave at the beginning

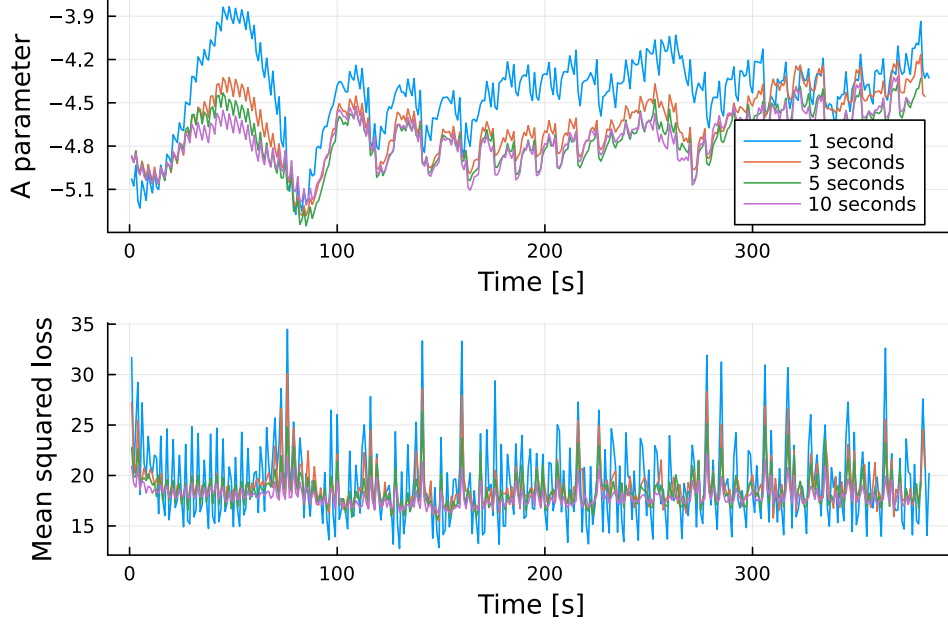


Figure 3.3: The periodic change in learned 'A' parameters

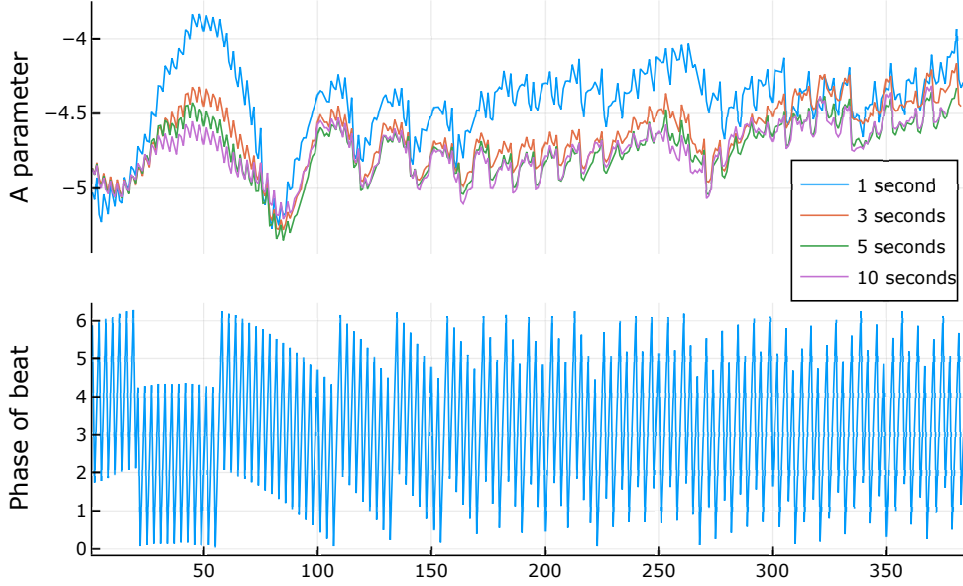


Figure 3.4: The phase at the start of each time window corresponds to periodicity

of the time window influences the initial value of the calculated aortic pressure, and so the solution depends on the phase. Figure 3.5 shows the dependency of the solution on the initial phase (for the parameters: $A = 7.98$, $B = 21.99$, $PTT = 0.084$). In the figure, it is also visible that the dependency on the initial condition vanishes by the time of the start of the second wave. This means that if the time window width used for learning is 3 seconds, then the effect of the phase at the start of the time window is much less than in the 1-second case. A solution to the problem is to use longer time window widths but to even lower the effects, the phase that minimizes the error of the initial condition has

to be used.

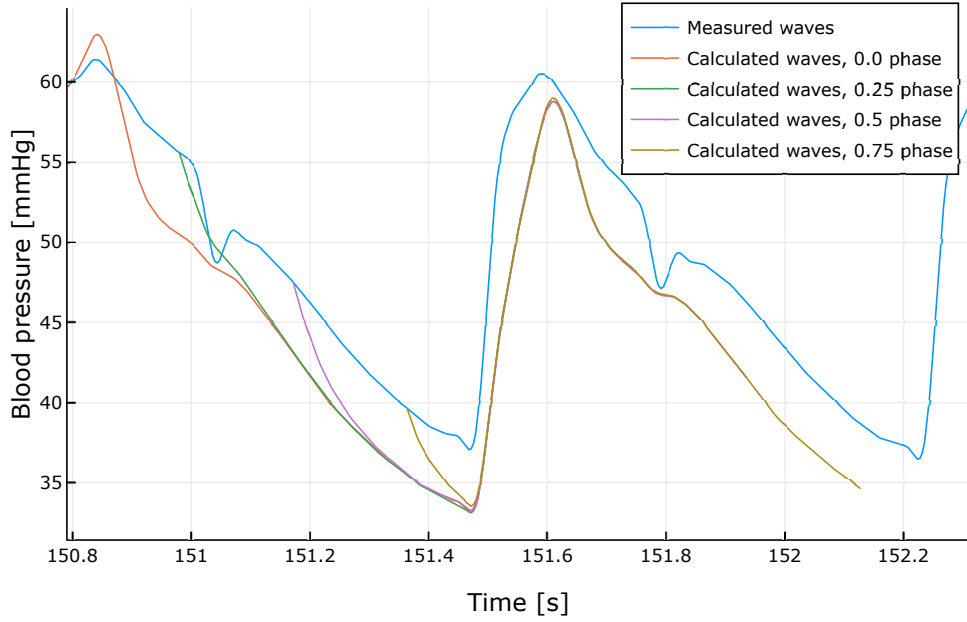


Figure 3.5: The effect of phase on initial condition

Using the optimal phase to start the learning results in similar waves for the first beat as the second and third ones. The error is visualized between the 1st and 2nd, 1st and 3rd and 2nd and 3rd beats respectively. Figure 3.6 shows one beat of measured femoral and aortic pressure waves, and one beat of calculated aortic pressure waves. Below the plot are the errors between the different beats of the solution of the ODE as the function of the starting phase of the learning. The trends of the error curves were similar in different beats of the measurement data. Based on this result, if the learning starts at 75% of the beat, the initial condition has little effect on the solution. Thus, in further simulations, the learning was always started at 75% of each beat.

We have found that the length of the time window is optimal at 3 seconds. In Figure 3.3, it is visible that for 3, 5 and 10 seconds, the results are similar, but running times are higher for longer time window widths. The difference in the 1-second length case is caused by the described phase properties. By setting the starting phase at 75%, the 1-beat period length should yield accurate results, however, using a 3-beat length for the learning period results in more robust parameter identification.

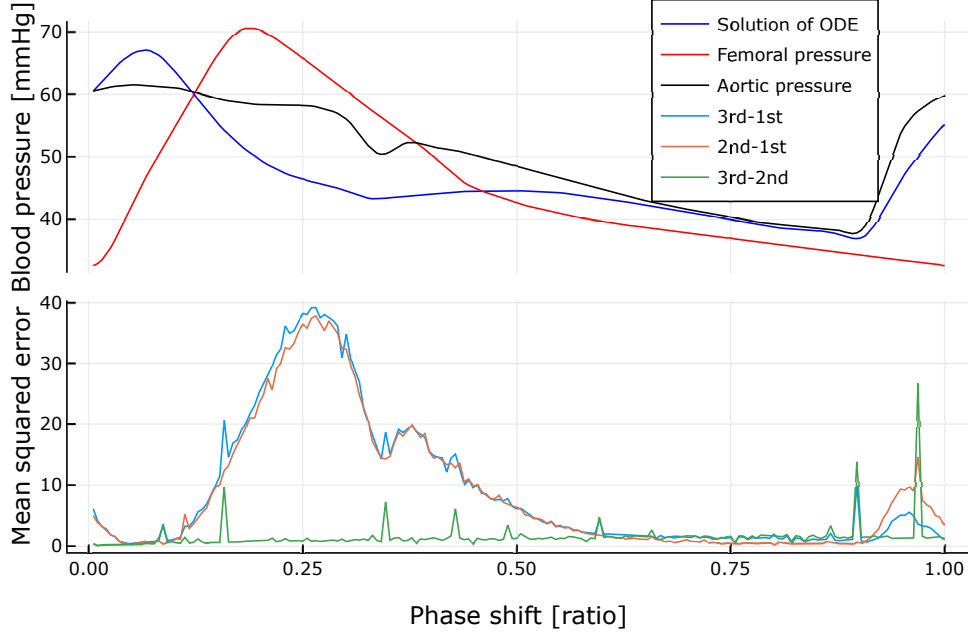


Figure 3.6: The effect of phase on mean squared error

3.3 Estimating the robustness of the used method

To assess the robustness of the NeuralODE method regarding the identification of model parameters, a benchmark test was designed. During parameter identification, the error between the measured aortic pressure and the solution of the ODE (Equation 3.1) with the actual parameter set is minimized. However, if the model does not fit the measurements with any possible parameter set, the error will remain large even after training. To examine the effects of only the identification method, simulated aortic pressures (the solution of the ODE with one specific parameter set) were used instead of the measurements. If the method does not find the parameter set used during the simulation, then it is not robust and realistic parameter estimation cannot be expected using the measurements.

From earlier simulations, the parameter set: $A = 6.923$, $B = 32.008$, $PTT = 0.084$ was found to approximate the measured data well, so these parameters were used to solve the differential equation of Equation 3.1 for the period of the 'Control/Baseline' data of the experimental pigs data (pig #7), using the measured aortic pressure as the initial value. Figure 3.7 shows a clip from the simulated data.

During the benchmark test, the learning process was started from different initial parameters, semi-randomly sampled from the parameter space. From parameters close to the simulation parameters, values were sampled with higher density and from farther with lower density. Figure 3.8 shows the sampling of the parameter space. The red cross indicates the A and B parameters used for the simulation, and the blue dots indicate the different initialization points used during the benchmark test.

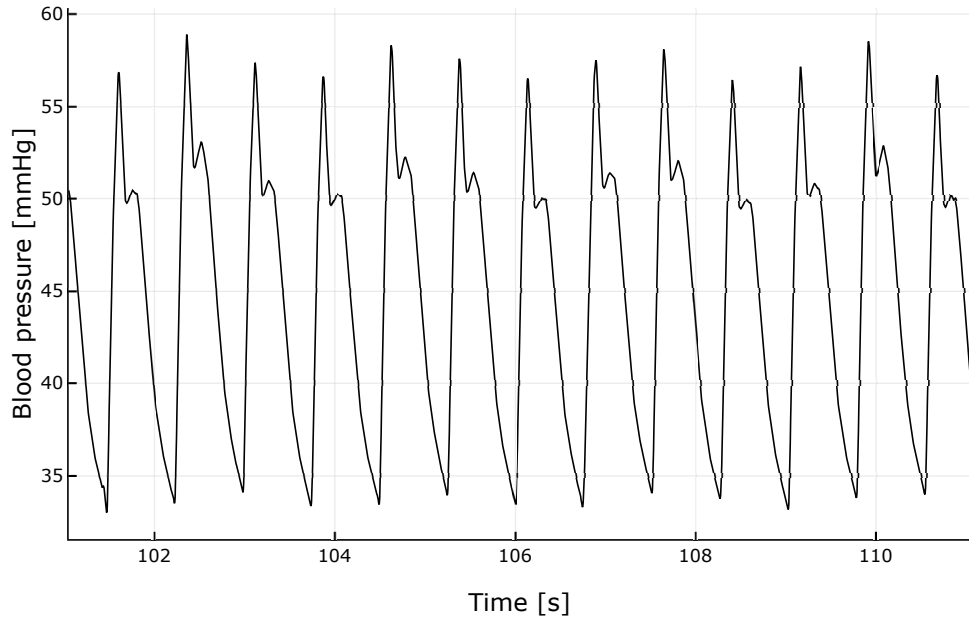


Figure 3.7: Section of the simulated blood pressure signal used for the benchmark test

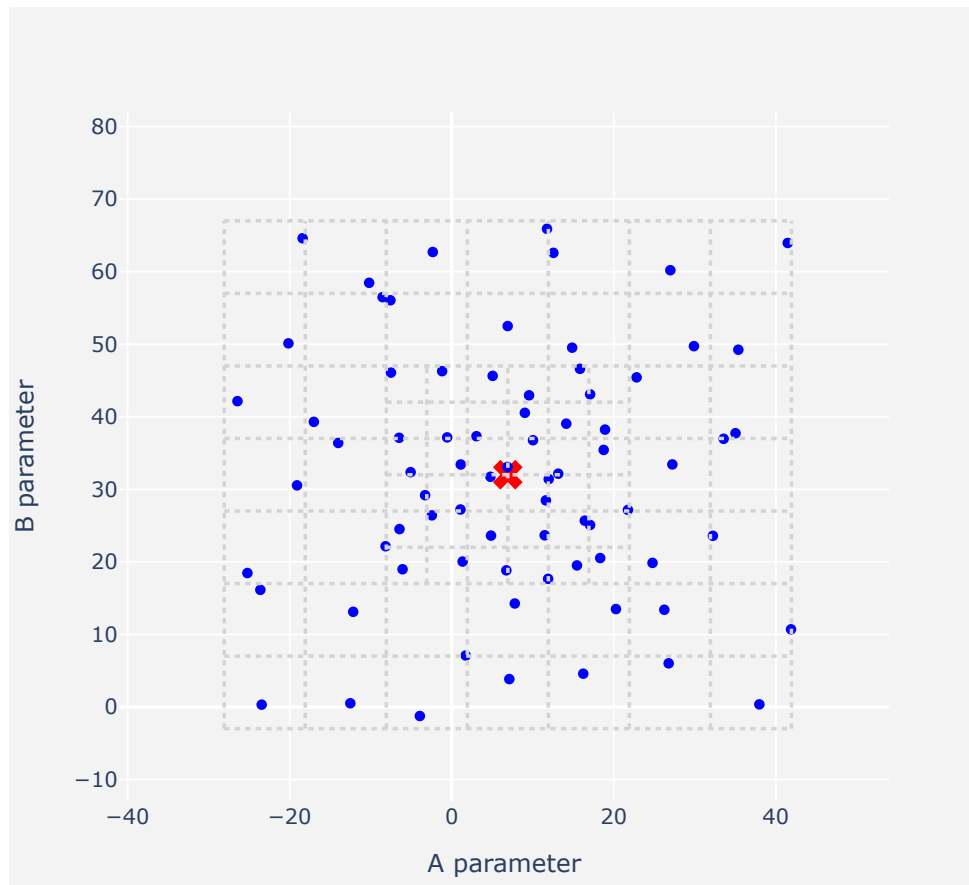


Figure 3.8: The sampling of the parameter set

During the simulation, the trajectory of the parameters could be visualized starting from different initialization points during the different epochs of learning. The parameters

during learning are shown in Figure 3.9. It is obvious, looking at the plots, that there is a correlation between the A and B parameters, as the majority of the points are gradually moving to a straight line during the learning process. It is likely that there are local minima of the loss function, as there are 4 points that do not converge to the simulated parameters, but they get stuck at different locations in the parameter space. However, most of the points do converge to the simulation parameters, so if the initialization is appropriate - which means that the initial parameter values are close enough to the actual parameters - then the method is robust, and the parameters converge to the optimum.

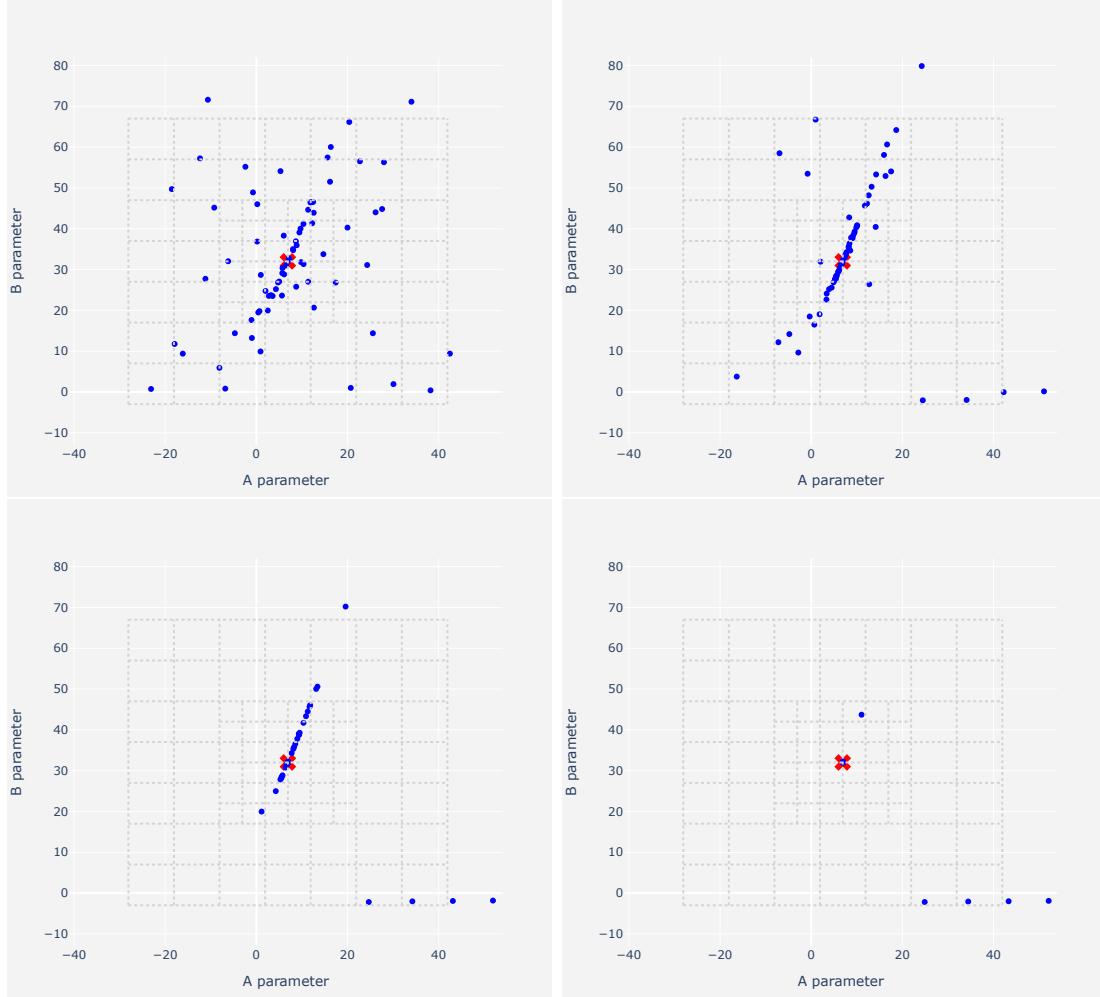


Figure 3.9: The resulting parameters values after 4 (top left), 10 (top right), 20 (bottom left) and 40 (bottom right) training cycles.

3.4 Identified parameters during the physiological experiment

In the previous sections, the optimal time window width to use during the learning of parameters was determined, and the method was proven robust assuming that the parameters are initialized at physiologically reasonable values. In this section, the results of parameter identification for the whole experimental pig data set of pigs #4 and #7 are presented.

3.4.1 Identified parameters for pig #7

During the parameter identification, 3-beat sequences were used in each time window with a 75% phase offset. The other parameters of the learning were: 0.01 learning rate, minimum 1000, and maximum 2000 epochs (the stopping condition was the reduction of the change in the loss function below a value). The parameters were initialized at $A = 7.0, B = 20.0$ for the first time window and later with the identified values of the previous period.

Figure 3.10 shows the result of the parameter identification for pig #7.

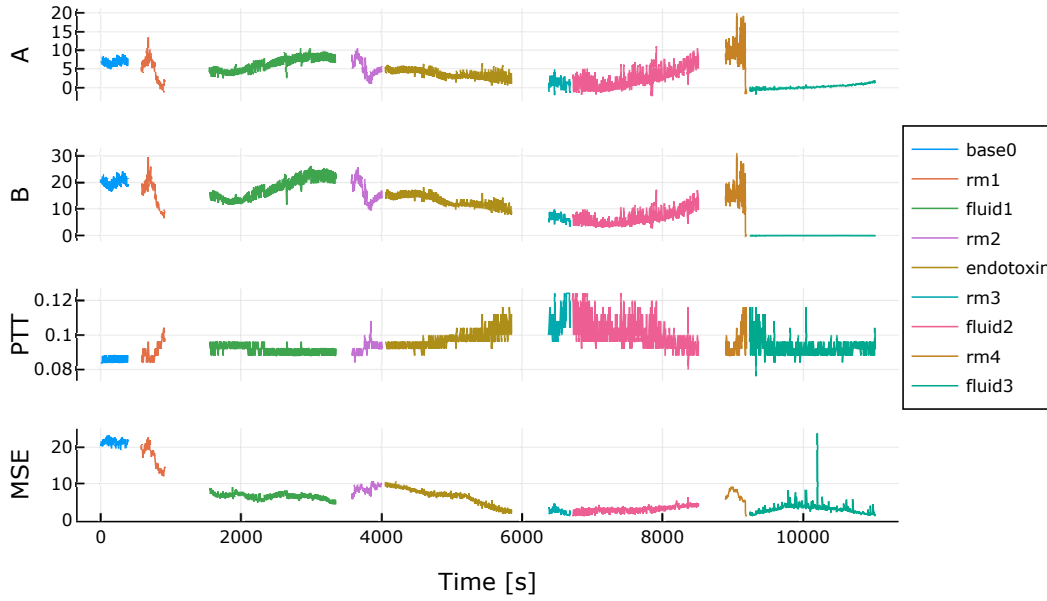


Figure 3.10: The parameter identification in the different phases of the animal experiment of pig #7

The PTT values are calculated as described in Section 3.1. Since the sampling time was 0.004 [s], PTT values are not continuous, and the other parameters are influenced by the variability of the pulse transit time, so their values are also noisy. To make up for this, a 15-sample (0.06 [s]) window moving average was used, and this resulted in smoother parameter curves - shown in Figure 3.11.

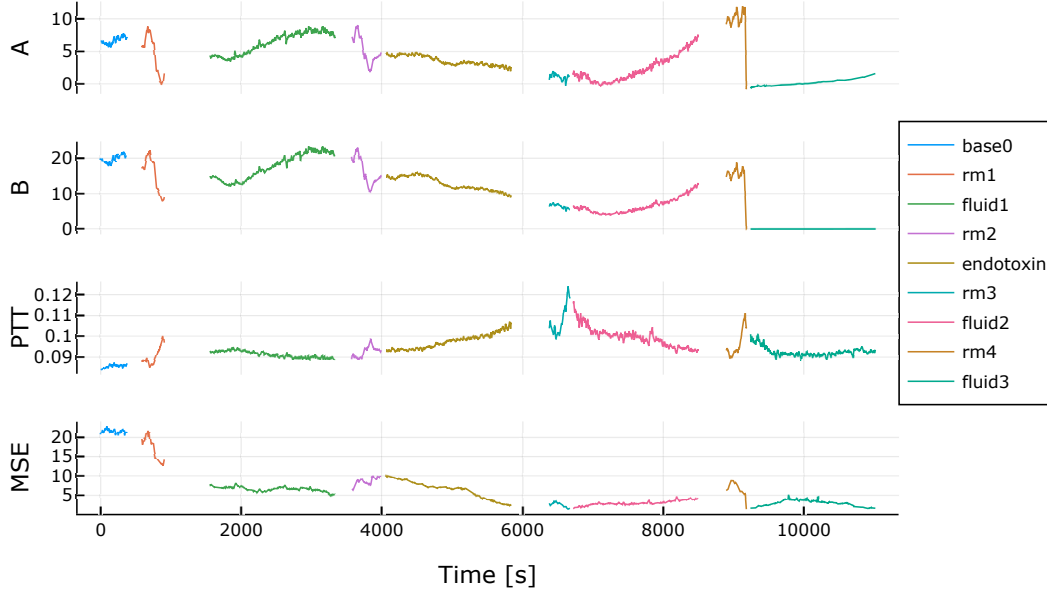


Figure 3.11: The identified transfer function parameters in different phases of the experiment after smoothing for pig #7

To analyse the learned parameters in different sections of the data, normal distributions were fitted to each parameter's distribution. Figure 3.12 shows the empirical distribution functions of the data and Figure 3.13 shows the cumulative distribution functions of the fitted normal distributions of each section. The means of these distributions can be found in Table 3.1 and the standard deviations in Table 3.2.

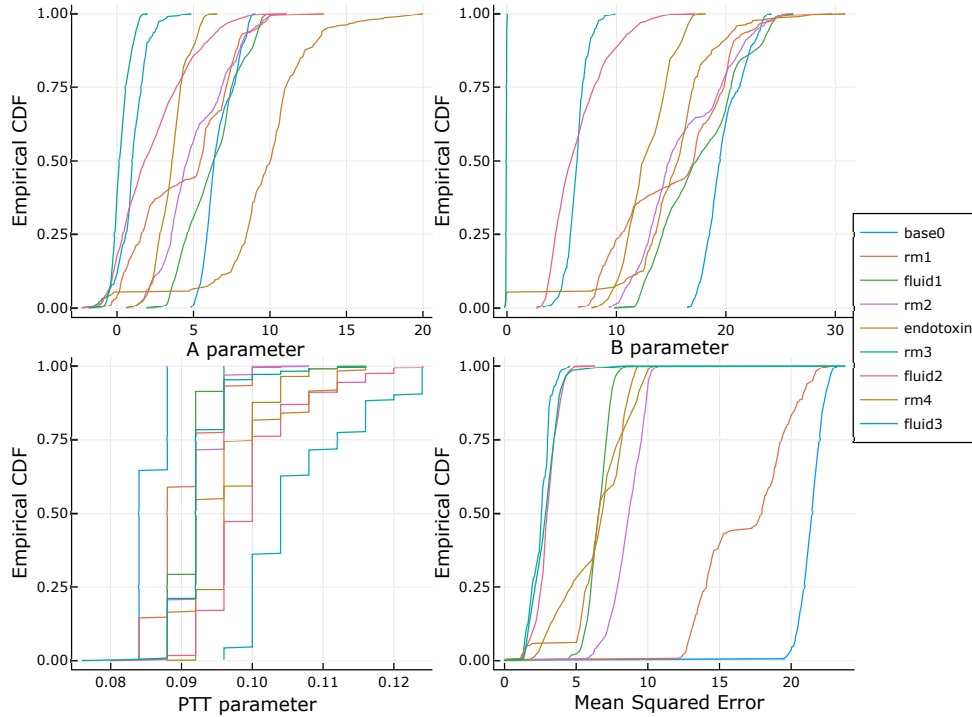


Figure 3.12: The empirical cumulative distribution functions of the parameters and the Mean Squared Error in the nine phases of the experiment for pig #7.

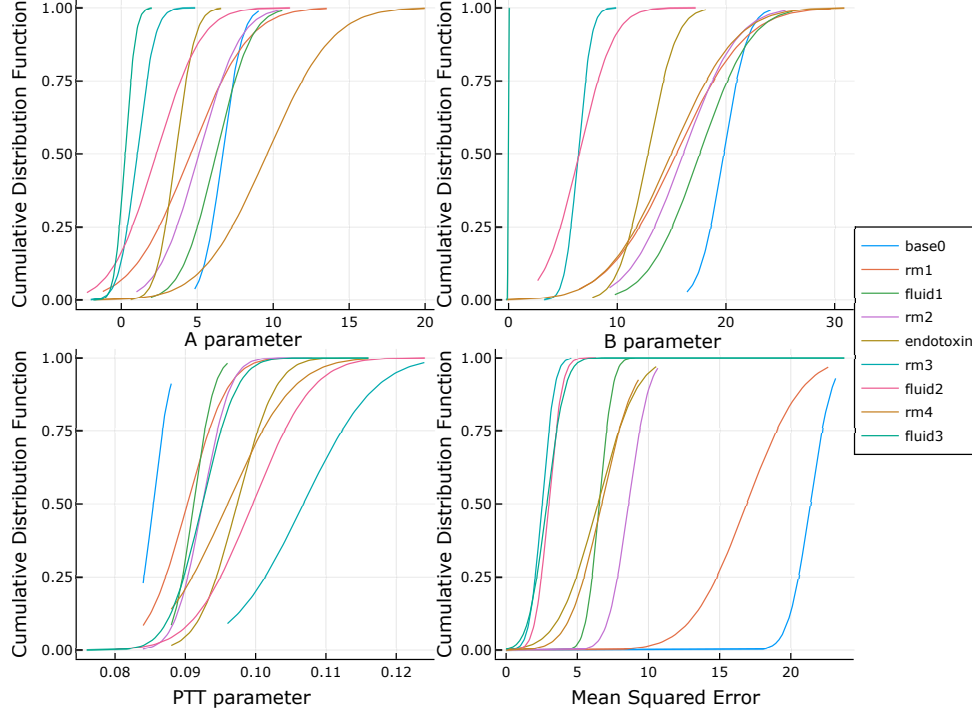


Figure 3.13: The fitted cumulative distribution functions of the parameters and the Mean Squared Error in the nine phases of the experiment for pig #7.

	base0	rm1	fluid1	rm2	endotoxin	rm3	fluid2	rm4	fluid3
A	6.665	4.548	6.241	5.112	3.583	1.031	2.308	9.59	0.246
B	19.783	15.421	17.579	16.069	12.776	6.401	6.491	14.964	-0.055
PTT	0.085	0.09	0.091	0.092	0.097	0.107	0.1	0.096	0.092
MSE	21.365	16.896	6.544	8.6	6.423	2.521	2.987	6.698	2.849

Table 3.1: The mean values of each fitted normal distribution for pig #7.

	base0	rm1	fluid1	rm2	endotoxin	rm3	fluid2	rm4	fluid3
A	1.033	3.058	1.824	2.16	1.002	0.932	2.351	3.403	0.544
B	1.761	5.022	3.75	3.931	2.113	0.967	2.541	4.735	0.025
PTT	0.002	0.005	0.002	0.003	0.004	0.008	0.007	0.007	0.004
MSE	1.214	3.099	0.743	1.142	2.203	0.697	0.75	1.812	1.024

Table 3.2: The standard deviation of each fitted normal distribution for pig #7.

Looking at the data, it is clear that there is an anomaly with the last section's parameters. This can be due to the poor state of the pig by the time of the last section. The health status of the examined pig worsens after the endotoxin infusion. Therefore, the most important are the base0, rm1, fluid1 and rm2 sections. During the 'base0' section, no intervention is carried out on the pig. This results in a small standard deviation and stable parameters. During sections 'rm1', 'rm2', 'rm3' and 'rm4', recruitment manoeuvres are performed on the pig. The parameters are changing similarly during these periods, so

it is probable that the high standard deviation is due to this intervention. During sections 'fluid1' and 'fluid2', a fluid bolus is given to the pig. The slow but continuous change in parameters possibly represents the effect of the fluid bolus - which is a part of fluid therapy.

In summary, the change in parameters corresponds to the changes in the interventions carried out on the pig. Therefore, the identified parameters reflect the health status or haemodynamic changes of the pig, and the identification method is successful.

3.4.2 Identified parameters for pig #4

During the parameter identification of pig #4, most of the details of the learning were the same as for pig #7. The parameters were initialized at $A = 15.0, B = 30.0$ for the first time window and later with the identified values of the previous period. One difference compared to the method used for pig #7 was that the optimizer and the parameters were re-initialized after each section of the data. This had to be done because negative parameter values were identified in the recruitment manoeuvre section and got stuck at a local minimum for the fluid section, as Figure 3.14 shows. This problem is due to the small gap between the two sections, which has caused the parameters to get stuck.

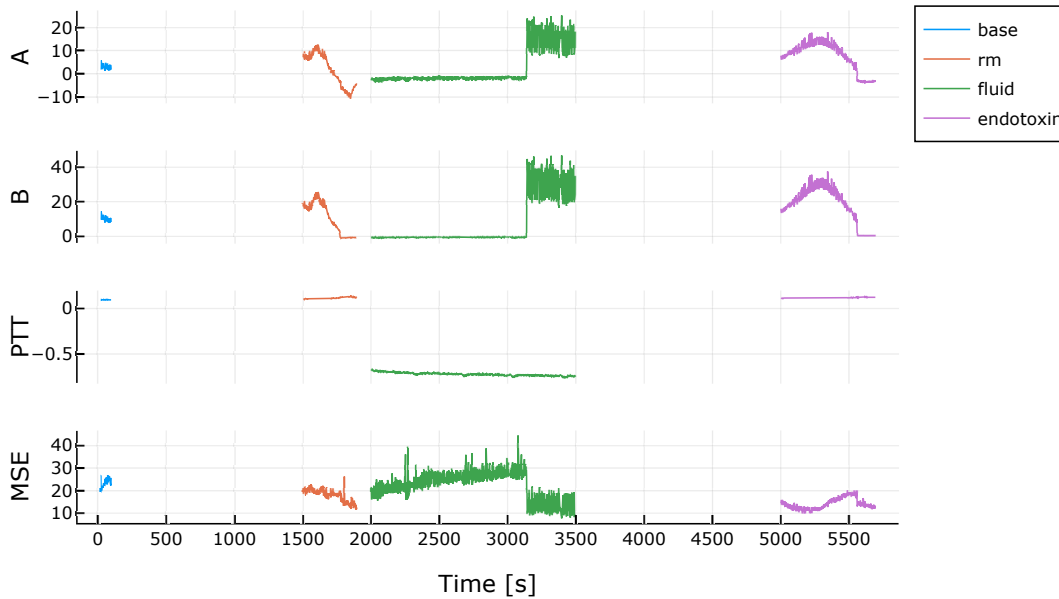


Figure 3.14: The parameters got stuck at a local minimum of the loss function without re-initializing the optimizer.

Figure 3.15 shows the result of the parameter identification for pig #4.

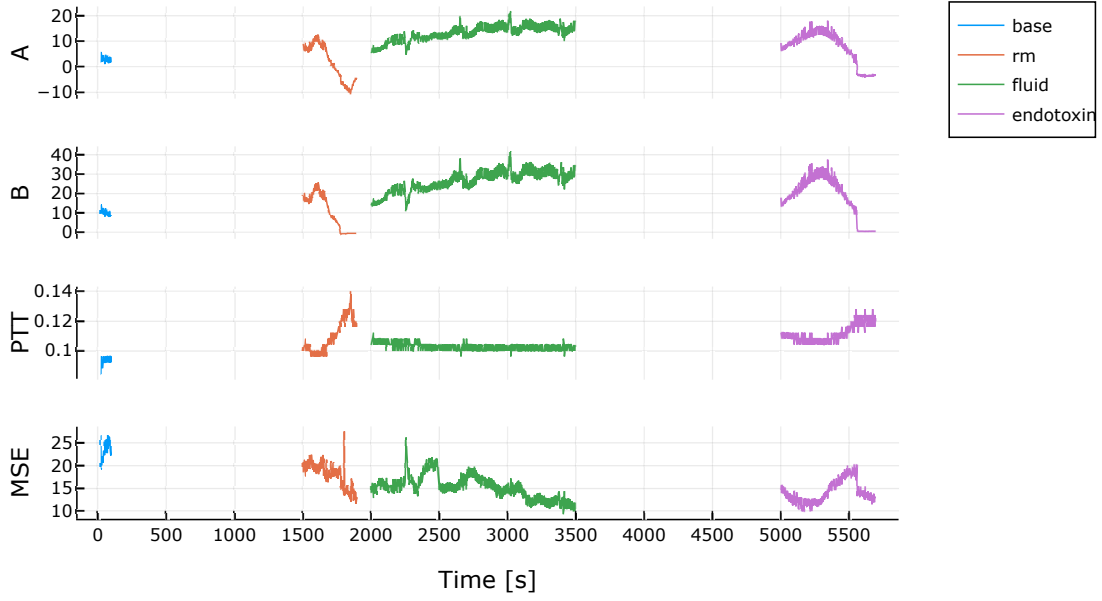


Figure 3.15: The parameter identification in the different phases of the animal experiment of pig #4

As for the identification of pig #7, a 15-sample (0.06 [s]) window moving average was used, and this resulted in smoother parameter curves shown in Figure 3.16.

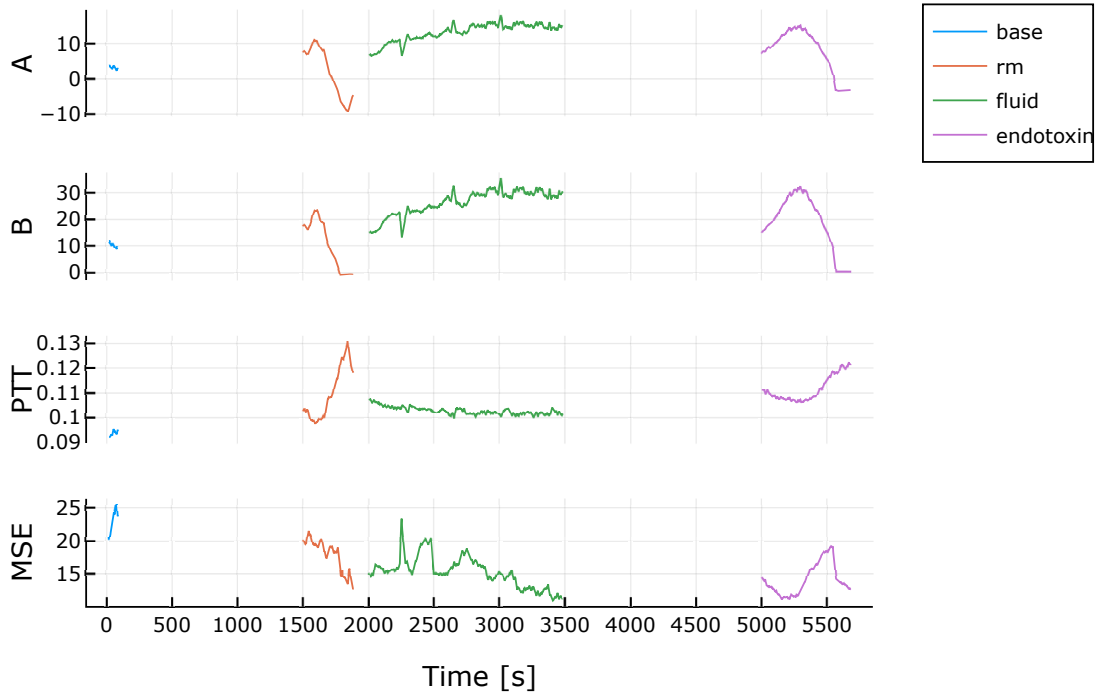


Figure 3.16: The identified transfer function parameters in different phases of the experiment after smoothing for pig #4

The same plots and tables were generated for the identified parameters of pig #4 as for pig #7, and the results are shown in Figures 3.17 and 3.18, and in Tables 3.3 and 3.4.

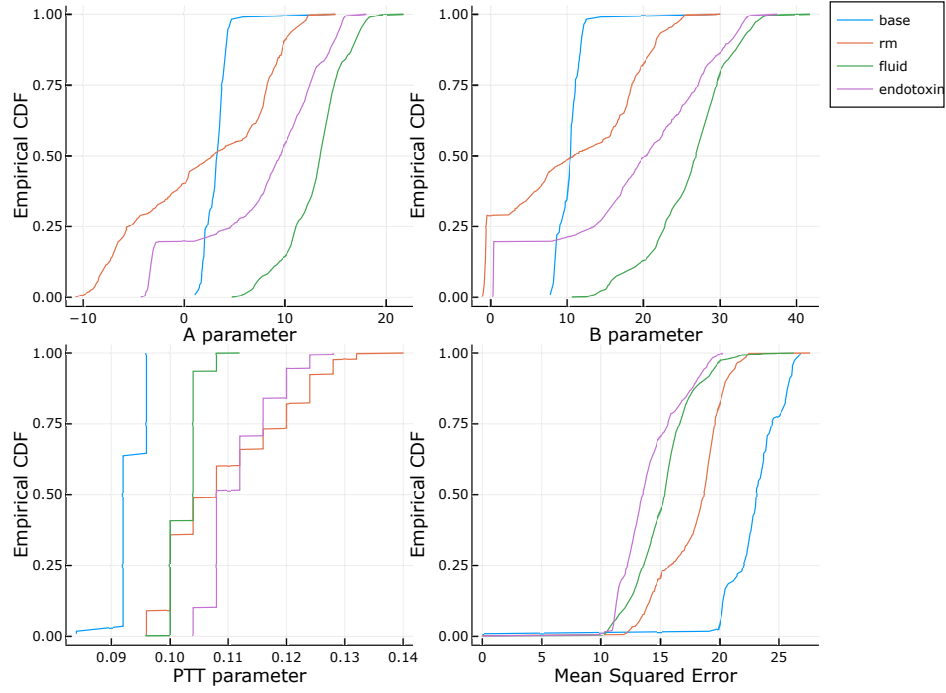


Figure 3.17: The empirical cumulative distribution functions of the parameters and the Mean Squared Error in the four phases of the experiment for pig #4.

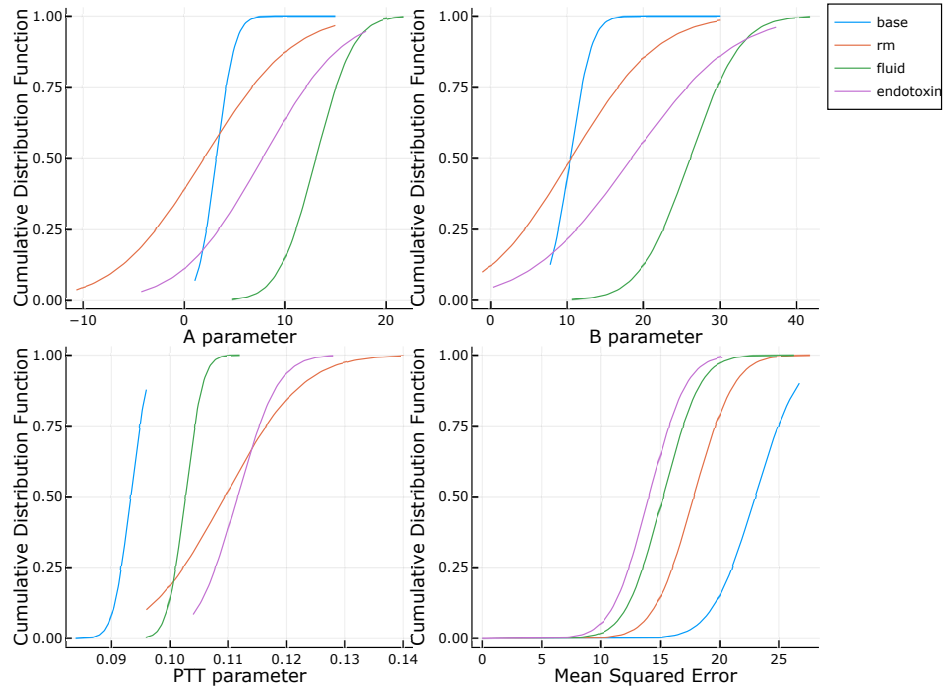


Figure 3.18: The fitted cumulative distribution functions of the parameters and the Mean Squared Error in the four phases of the experiment for pig #4.

The experiment conducted on pig #4 was shorter than on pig #7, so fewer conclusions can be derived from the results. However, it is clear that it is physiologically inconsistent

	base	rm	fluid	endotoxin
A	3.218	1.983	13.072	7.758
B	10.426	10.586	26.106	18.491
PTT	0.093	0.109	0.103	0.112
MSE	22.995	17.83	15.235	14.043

Table 3.3: The mean values of each fitted normal distribution for pig #4.

	base	rm	fluid	endotoxin
A	1.44	7.01	2.942	6.331
B	2.254	8.991	5.217	10.654
PTT	0.002	0.011	0.002	0.006
MSE	2.898	2.683	2.492	2.489

Table 3.4: The standard deviation of each fitted normal distribution for pig #4.

that the parameters take on negative values - in section 2.2.2 we stated that for the parameters: $0 > A > B$. Visualizing the aortic pressure and flow waves for a few beats can help understand the anomaly. Figure 3.19 shows these waveforms. The location of the dicrotic notch is indicated by the red dots. The dicrotic notch is caused by the closing of the aortic semilunar valve, resulting in a pressure drop. However, it is not normally the global minimum of the aortic pressure for the full cardiac cycle. On the flow waveforms, blood regurgitation is visible (indicated by negative flow values), which is also not physiological. These explain the resulting negative parameter values. It is worth mentioning that at the end of the "endotoxin" section, the parameters also take on negative values, however, in the last section of the experiment, the pig was probably dying, which explains the anomaly.

3.4.3 Comparison of the identified parameters for the two subjects

The first three sections of pig #4 are comparable to the similar sections of pig #7.

In the Control/Baseline sections, it is similar that the loss function takes on higher values than in other sections. This is probably because the waveforms that the transfer function can produce are not able to fit perfectly to the healthy pig aortic pressure waveforms. In the recruitment manoeuvre sections, the change in the parameters is similar in the two pigs, first an increase and then a big decrease followed by an increase at the end. The most important difference is the appearance of negative values in the identified parameters in a limited section of the experiment on pig #4. In the "fluid" sections, which are the most important for our research, a steady increase in parameter values is visible for both pigs' parameters.

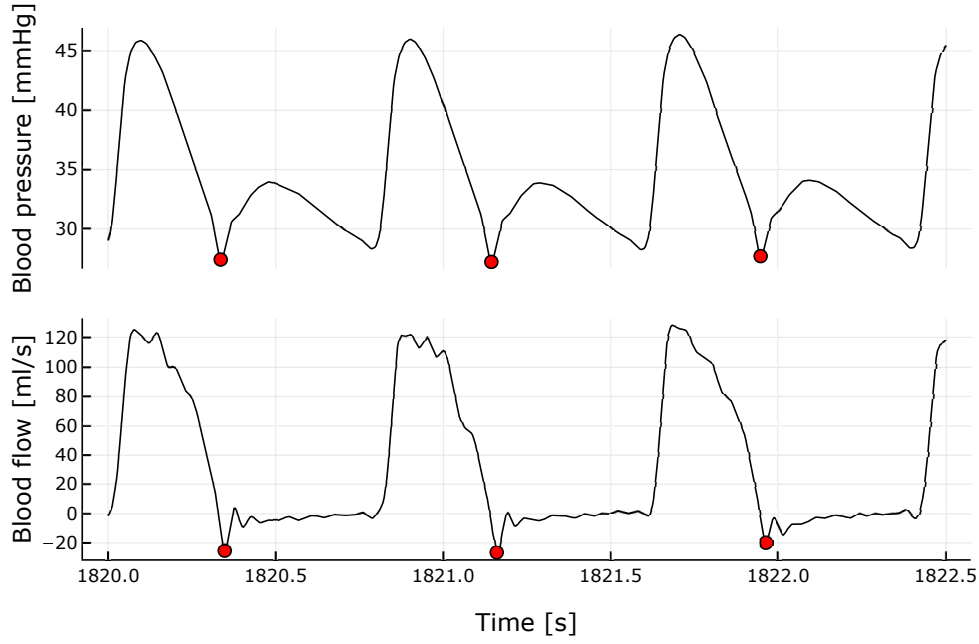


Figure 3.19: The central arterial pressure and flow waves at the second half of the recruitment manoeuvre for pig #4.

3.5 Conclusion

The aims of the research were the examination of the applicability of the NeuralODE method for the given parameter identification problem and the assessment of the variability of the identified model parameters.

As it has been presented in Section 3 , the NeuralODE method was successfully adapted for the parameter identification of a transfer function derived from the Tube-load model.

First, the optimal time window width was determined, allowing parameter identification with clinically acceptable accuracy. Using fixed window widths based on length in seconds turned out to cause an artefact since the phase of the cardiac cycle was shifted at the start of each window. A solution to this problem was to define the time windows that are synchronous with the cardiac cycles. The calculated output depends heavily on the location of the start of the window since the initial condition is set at that location. We found that starting the time windows at the beginning of the cardiac cycle causes larger errors than starting them at 75% of the cycle, as the effect of the error caused by the initial condition setting is the smallest in this case. To sum up, the correct time window is defined by the cardiac cycles, and at the start of the window, the cardiac cycle should be at 75% to yield the optimal time window used for learning the parameters.

Next, the robustness of the method regarding the identification of model parameters was assessed using a benchmark test. A set of aortic pressure waves was simulated using femoral arterial pressure measurements and a chosen parameter set. The parameters were learned using the simulated central arterial pressure, so the correct parameters were given - the simulation parameters - and the robustness of the method - i.e. its dependency on

the initial value settings - could be tested. Based on the results of the benchmark test, the method is robust if the parameters are initialized according to the physiologically valid parameter domain.

Finally, the physiological experiment's data set was used to identify the model parameters over all the phases of the clinical experiment, covering a wide range of physiological and pathological states of the subjects. The parameters were identified for two subjects, providing a way to estimate the physiologically valid parameter space of the transfer function derived from the Tube-load model.

3.5.1 Limitations and future work

The developed parameter identification method was tested on a data set from measurements of an animal experiment. The data set consists of measurements in different physiological states of the subjects, which makes the data set diverse, and suitable for the research. However, the aim of the project that the current research is a part of is to develop an Artificial Intelligence-based semi-automated fluid responsiveness assessment method that is used in Intensive Care Units. To validate the developed method, further research is necessary using human data.

Future work includes the validation of the method on further data and the development of a method that is capable of identifying the parameters of the examined transfer function using only femoral arterial pressure waves.

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4 Appendix

The appendix contains chapters that are not included in the research documentation, but may be useful for the understanding of the preceding chapters.

Physiological background

This section reviews the main physiological principles needed to derive the later described physiological models which are used in this work. The main ideas covered are the cardiac cycle and fluid therapy.

The cardiac cycle

The sequential contraction and relaxation of the atria and ventricles produced by electrical changes, pressures, and mechanical actions constitute the cardiac cycle [7]. The contraction is called systole, while relaxation is diastole. During one cardiac cycle both the atria and the ventricles go through a systole and a diastole phase, shifted in time. During the analysis of the cardiac cycle, more attention is paid to the left atrium (LA) and ventricle (LV) than the right side of the heart, as the left ventricle supplies the oxygenated blood to the organs of the body.

Figure 4.1 shows the pressure, volume and ECG curves during one cardiac cycle. On the pressure axis, the left atrial pressure (LAP), left ventricular pressure (LVP) and the aortic pressure are shown, and on the volume axis the volume of the left ventricle is graphed. In the following, the physiological background of the different characteristics of the curves will be described.

The left atrium contracts before the ventricular systole. This contraction, also called the "atrial kick" is represented by the 'a' wave on Figure 4.1. The systole of the atrium results in a small increase of venous pressure and the ventricular diastole as the contraction forces blood flow to the ventricle. Interestingly, the contraction accounts for only one-tenth of the ventricular filling, as most of the blood flows to the ventricle from the pulmonary veins passively through the left atrium. When enough blood flows into the ventricle, so that the pressure of the atrium is lower than of the ventricle, the mitral valve (separating the LA and LV) closes. At this point, the ventricular volume is at its maximum and is referred to as left ventricle end-diastolic volume (LVEDV). This represents the preload of the LV [7].

Ventricular systole consists of isovolumetric contraction, rapid- and reduced ventricular ejection. Isovolumetric contraction happens at the start of ventricular systole. Following the closure of the mitral valve and before the opening of the semilunar valve (separating the ventricle and the aorta), the ventricular pressure rapidly increases without any change in ventricular volume. This is called the isovolumetric contraction, and causes the 'c' wave

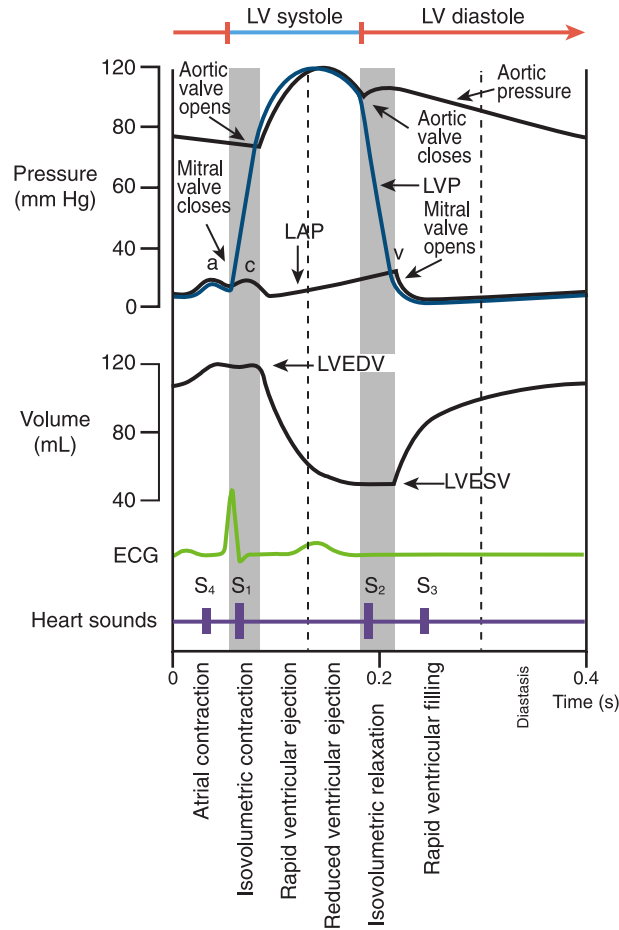


Figure 4.1: Blood pressure, volume and ECG during one cardiac cycle [7]

on Figure 4.1, as the atrial pressure increases when the mitral valve is pushed into the atrium by the increasing pressure of the ventricle. When the pressure of the ventricle exceeds the aortic pressure, the semilunar valve opens and blood begins to flow to the aorta, starting the ejection phase of the systole. The ejection can be divided to a rapid and a reduced ejection phase. Rapid ejection is taking place until the peak of ventricular and aortic pressures and is characterized by greater flow to the aorta and a large rate of rise in pressures. After the rapid ejection, reduced ejection follows, during which aortic pressure is higher than ventricular pressure, but the potential energy stored in the stretched arterial walls allows blood to flow in the direction of higher pressure. At the end of ejection and before the start of isovolumetric relaxation, the ventricular volume is at its minimum, referred to as left ventricle end-systolic volume (LVESV). The difference between LVEDV and LVESV is the stroke volume (SV).

Ventricular diastole begins with isovolumetric relaxation of the ventricle. During this period both the mitral and the semilunar valves are closed, meaning the volume of the ventricle is constant, however, the pressure decreases. Isovolumetric relaxation begins when the semilunar valve closes. During the closure aortic pressure drops, which can be seen on Figure 4.1. The drop is called the dicrotic notch. After the closure of the valve, the aortic pressure increases before decreasing gradually. The increase after the dicrotic

notch is called dicrotic wave. During isovolumetric relaxation of the ventricle, the atrium is filled with blood passively. When the mitral valve opens, the pressure of the atrium is at the maximum, which is signed by 'v' on Figure 4.1. With the opening of the mitral valve, blood flows into the ventricle, referred to as rapid filling. After the rapid filling, blood still flows passively to the ventricle from the atrium at a lower rate, referred to as diastasis.

During the cardiac cycle, the pressure-volume relationship of the left ventricle can be described with the P-V loop shown on Figure 4.2. The loop consists of four phases: LV filling, isovolumetric contraction, LV ejection and isovolumetric relaxation. At the end of LV filling, the mitral valve closes and the left ventricle is at the end of its diastole, the pressure and volume are called left ventricle end-diastolic pressure (LVEDP) and left ventricle end-diastolic volume. At the end of LV ejection, the aortic valve closes and the ventricle reaches the end of its systole. The pressure and volume of this point are called left ventricle end-systolic pressure (LVESP) and left ventricle end-systolic volume (LVESV). The width of the loop - the difference between LVEDV and LVESV - is the stroke volume. The slope of the curve at the end of diastole represents the reciprocal of the LV compliance - also called the end-diastolic pressure-volume relationship (EDPVR). The slope of the curve at the end of systole is the end-systolic pressure-volume relationship and represents the contractility of the LV. The ejection fraction (EF) is the ratio of stroke volume to end-diastolic volume (EDV).

The concepts of elastance and compliance are important to describe the changes in P-V loops when preload, afterload, or contractility of the heart is altered. Elastance is the change in pressure per unit change in volume. Compliance is the change in volume per unit change in pressure (reciprocal of elastance). For a given LVEDV, the LVEDP will depend on the compliance of the ventricle. Thus, for a given LVEDV, cardiac abnormalities such as hypertrophy, ischemia, infarction, or structural anomalies may decrease ventricular compliance and therefore increase the LVEDP [7].

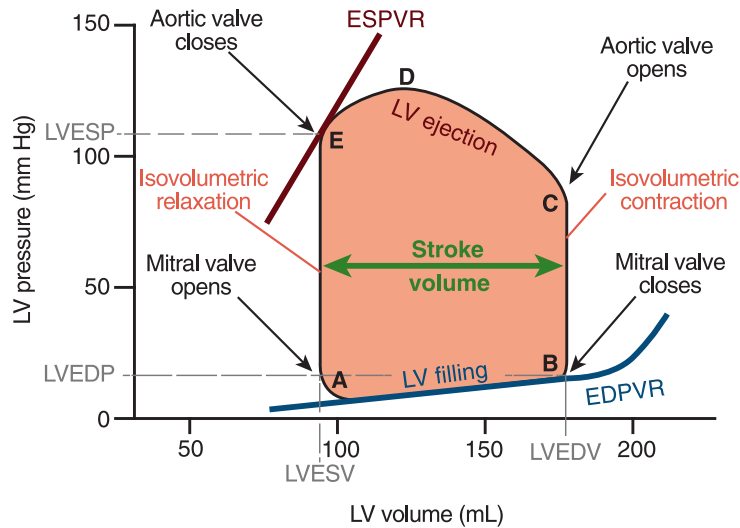


Figure 4.2: The pressure-volume loop [7]

Cardiac output

Cardiac output (CO) is the volume of blood flowing through the heart in one minute. It is determined by two factors, the heart rate and the stroke volume: $CO = HR \cdot SV$. The equation is intuitive, given that heart rate is the frequency, and stroke volume is the volume of blood flowing through the heart in one period. However, the relationship between the two factors is complex, thus there is no linear connection between CO and HR, or CO and SV.

Heart rate is determined mainly by the pace of impulses coming from the SA node. The rate is heavily influenced by the autonomous nervous system. Sympathetic effects result in a faster heart rate, while parasympathetic ones slow the heart rate. However, changes in heart rate affect stroke volume, so the relationship between heart rate and cardiac output is not linear.

Stroke volume is the volume of blood ejected from the heart with each heartbeat. It can be defined as the difference of end diastolic and end systolic volume ($SV = ESV - EDV$). It has three main determinants, preload, contractility and afterload. An increase in ventricular filling (preload) will result in an increase in the EDV and a larger SV. A larger systemic arterial pressure (afterload) will increase the ESV, thereby resulting in a smaller SV. Finally, release of norepinephrine from the sympathetic nervous system (resulting in increased myocardial contractility - contractility) will decrease the ESV and result in a larger SV [7].

Figure 4.3 shows the effects of volume infusion, and changing ventricular contractility and afterload. On the left, the changes in the Starling curve can be seen, while the right columns shows the effects on the pressure-volume loop and on stroke volume. Volume infusion (fluid therapy) increases preload, thus we move on the Starling curve and stroke volume increases. Increased contractility leads to increased filling, so increased SV. Decreased afterload alters the Starling curve resulting in decreased end systolic volume and increased stroke volume.

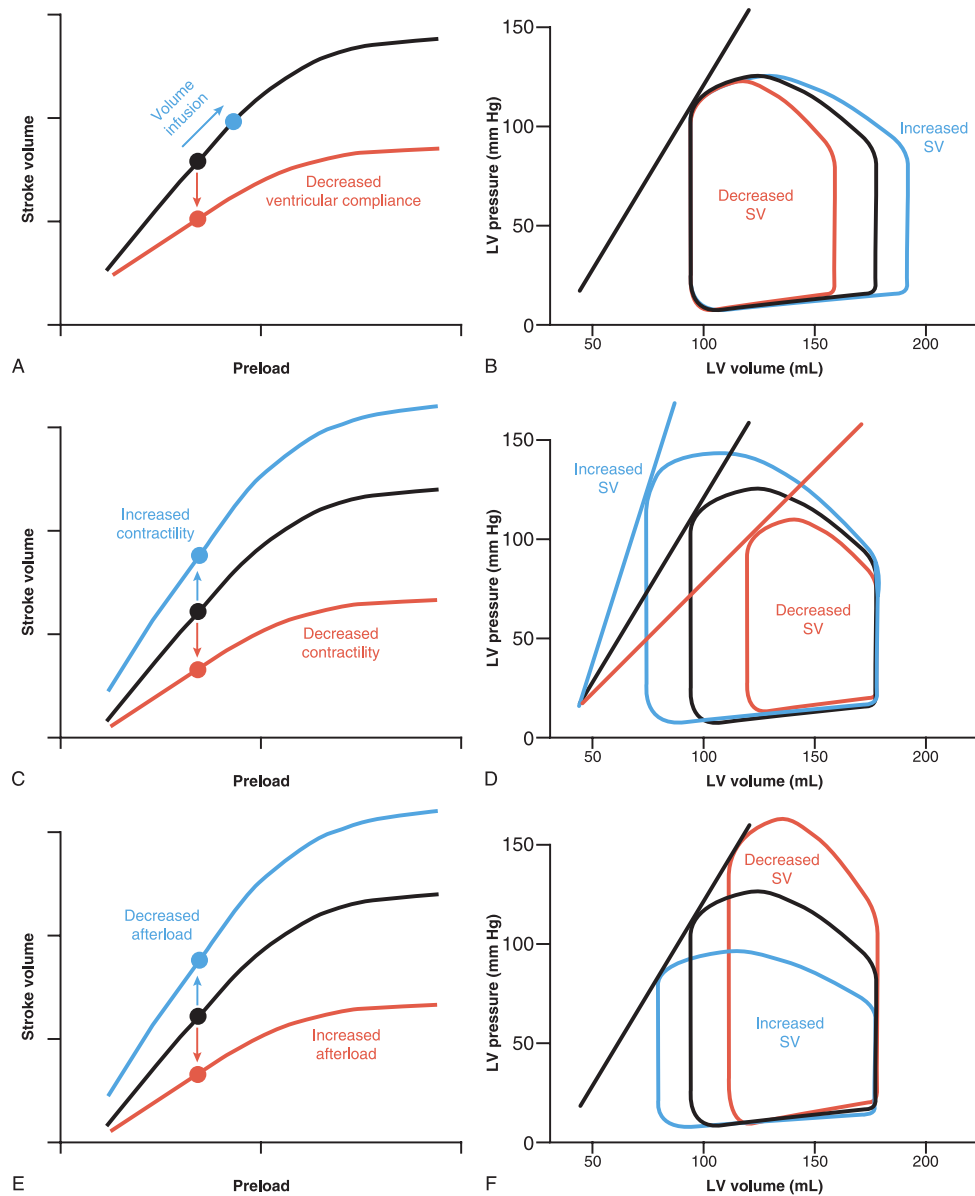


Figure 4.3: The stroke volume changing with parameters [7]

Fluid therapy

This section includes chapters of the book 'Fluid Resuscitation' by Wallace HA and Regunath H. [14]

The primary role of fluid resuscitation is to maintain organ perfusion (hemodynamics) and substrate (oxygen, electrolytes, among others) delivery through the administration of fluid and electrolytes. An enteral route can be used; however, when oral intake is not possible, clinicians can replace fluid losses by intravenous (IV) administration.

Body fluids are distributed into intracellular and extracellular compartments. Intracellular compartment contributes to most total body water. Extracellular fluids are within the interstitial, intravascular, and trans-cellular spaces.

Sepsis is a leading cause of morbidity and mortality in critically ill patients with mortality ranging between 20% to 45%. Uncontrolled inflammation, tissue hypoperfusion, microvascular and micro-cellular level abnormalities, and dysfunction are critical determinants in the progression toward multiple organ failure, which predict poor outcomes. Septic shock is defined as refractory hypotension that results from a systemic inflammatory response syndrome (SIRS) caused by or suspected to be from an infection.

The key characteristic of septic shock is systemic vasodilation which results in hypovolemia, decreased tissue perfusion and decreased oxygen delivery. The main aim of fluid resuscitation is to restore hemodynamics to optimize tissue perfusion and ultimately the tissue oxygen delivery.

Large amounts of intravenous fluids can cause hypervolemia and potentially electrolyte imbalance. In septic shock, overzealous use of intravenous fluids for a prolonged period can cumulatively increase the total body water, especially in patients with compromised renal, cardiac or hepatic function. This excess free water often accumulates in the extravascular lung (pulmonary edema) and subcutaneous tissues (pedal or sacral edema) and poses problems during recovery, for example, failure to wean from the ventilator and muscle weakness, both of which will cause prolongation of hospital stay and increase the associated risk of nosocomial complications. A 0.9% saline causes hyperchloremic acidosis following excess use and is associated with nephrotoxicity.

To avoid these complications, fluid responsiveness has to be determined. Fluid responsiveness shows whether the continued fluid therapy will result in better heart function. Physiological models can be used to determine fluid responsiveness.

Total Stressed Blood Volume (SBV_T) has been shown to be a potential index of fluid responsiveness [2]. SBV_T is defined as 'the total pressure generating blood volume in the circulation' [15]. SBV_T is the difference between the total volume in the circulation and the minimum volume required to fill blood vessels to the point a force is applied to the vessel wall. It thus influences venous return and is a direct potential measure of tissue perfusion, two metrics of importance in treating sepsis. SBV_T has a negative correlation with fluid responsiveness [2]. However, direct measurement of SBV_T requires multiple cardiac arrests and fluid boluses. These procedures make it unethical to measure directly, creating a need for a real-time model based analogue. [2] first introduced a lumped three chambered cardiovascular system model which outputs a set of parameters, one of which is SBV_T [11].

Physiological models of the cardiovascular system

The cardiovascular system is composed of the heart, the systemic- and the pulmonary circulatory systems. The fluid dynamics and the describing characteristics are highly complex. The existing models either aim to capture the full complexity of the system or to minimize complexity while still maintaining the most important features of the system's dynamics.

Lumped parameter models describe the whole arterial system, in terms of a pressure-flow relation at its entrance, by a small number of parameters that have a physiological meaning. One cannot study phenomena that take place inside the arterial tree such as wave travel and reflections of waves, etc [8]. The Windkessel is a lumped model. There are multiple types of the Windkessel, based on the element number - the haemodynamic and electrical presentations of the different types of Windkessel models are shown on the left of Figure 4.4. The two element Windkessel consists of a resistance and a capacity element. In the arterial system these correspond to the flow resistance of the arteries and the compliance caused by the elasticity of arteries. The three-element Windkessel model is extended with an impedance element. The impedance can modify the frequency response, which is crucial to deal with the effect of reflecting waves. The right side of Figure 4.4 shows the value and phase of the impedance modulus as the function of frequency. It is clear that the two-element Windkessel is not suitable to model the phase response, however, adding an impedance results in better performance. The four element Windkessel is further extended, with an inertance element, which aims to increase the accuracy in low-frequency range. Overall, the Windkessel models are used for their simplicity and clinical relevance. While keeping the number of model parameters low, the models are closely related to actual physiological phenomena - arterial resistance, compliance and the frequency response to wave reflections.

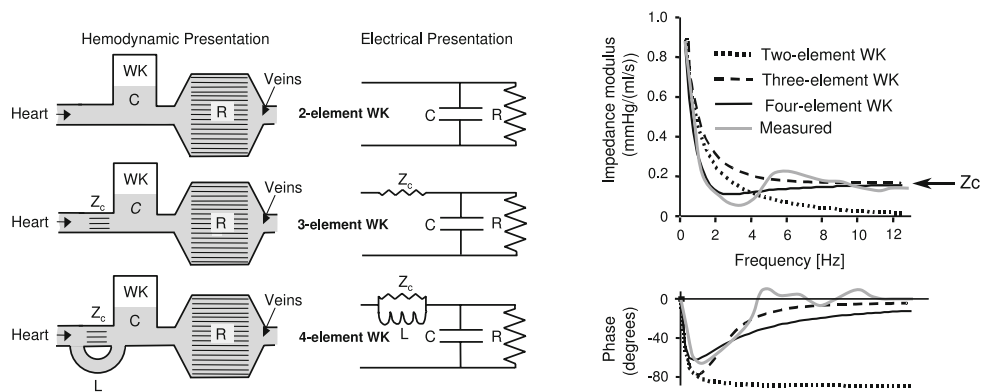


Figure 4.4: The Windkessel model with different element numbers [8]

Computational fluid dynamics models can be performed in a one- or three-dimensional way. These models use the advances in computational fluid dynamics (CFD) and in medical imaging.

For incompressible flows, almost all CFD analyses solve the Navier-Stokes and continuity

equations which govern fluid motion. These equations are non-linear, partial differential equations based upon the principle of conservation of mass and momentum. Simplification of these equations yields familiar formulae, but for complex geometries analytical solutions are not possible, so specialised software applications (CFD solvers) calculate approximate numerical solutions. Non-linearity, due to convective fluid acceleration, makes this challenging, especially in three dimensional (3D) models; so CFD analyses require significant computational power and time [16].

One-dimensional simulations only account for change of flow parameters along one axis, and time, while three-dimensional analyses calculate parameters along all three dimensions and time. While in three-dimensions the model represents the whole physical space, it requires much greater computational power and time, as well as more boundary conditions.

The CFD model construction and solution has seven phases [16]: clinical imaging, segmentation and reconstruction, discretisation, boundary conditions, simulation, post-processing and validation. During clinical imaging multiple modalities can be used to gain a high resolution, three-dimensional image of the vascular system. Segmentation and reconstruction converts the medical image to in-silico geometries, that define the physical boundaries of the simulation - also of the vascular system. If the imaging contains a full cardiac cycle, anatomical motion can be tracked over segmented regions. CFD works with discrete volumetric elements, thus the so called "meshing" - or discretisation - needs to be performed. The resolution of the mesh needs to be modified so that the simulation is able to capture important hemodynamic behaviours, but the simulation's power and time need increases with the number of elements. For the simulations, the inlet, outlet and wall boundaries must be defined. This can be done using clinical data, or patient specific data. After boundary conditions are defined, the simulation can be constructed. A fluid model must be defined - that contains fluid viscosity and density - and then the simulation is performed. After the post processing of the simulation's output data, the results have to be validated against an acceptable standard.

The advantages of CFD analyses of the cardiovascular system are the spatial and temporal resolution. However, their complexity and time requirement make them unsuitable for clinical use.

The **combination of lumped parameter models and CFD simulations** is also a researched area [17][18]. Here, the lumped parameter model is used to define the boundary conditions for the computational fluid dynamics model, which then simulates the more precise model dynamics.

Finally, with advances in machine learning and **data-driven technologies**, there are more and more data-driven approaches in modelling the cardiovascular system. With sensor fusion and machine learning tools, blood pressure can be predicted [19], which is useful for trauma prevention. Artificial neural networks are also suitable to predict future values from acquired data, and they are used to predict blood pressure [20].