Predictive modeling of secondary pulmonary hypertension in left ventricular diastolic dysfunction

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Abstract

Diastolic dysfunction is a common pathology occurring in about one third of patients affected by heart failure. This condition is not associated with a marked decrease in cardiac output or systemic pressure and therefore is more difficult to diagnose then its systolic counterpart. Compromised relaxation or increased stiffness of the left ventricle with or without mitral valve stenosis induces an increase in the upstream pulmonary pressures, and classified as secondary or group II (2018 Nice classification) pulmonary hypertension. This may result in an increase in the right ventricular afterload leading to right ventricular failure. Elevated pulmonary pressures are therefore an important clinical indicator of diastolic heart failure (sometimes referred to as heart failure with preserved ejection fraction), showing significant correlation with associated mortality. Accurate measurements of this quantity, however, are typically obtained through invasive catheterization, and after the onset of symptoms. In this study, we use the hemodynamic consistency of a differential-algebraic circulation model to predict pulmonary pressures in adult patients from other, possibly non-invasive, clinical data. We investigate several aspects of the problem, including the well posedness of a modeling approach for this type of disease, identifiability of its parameters, to the accuracy of the predicted pulmonary pressures. We also find that a classifier using the assimilated model parameters as features is free from the problem of missing data and is able to detect pulmonary hypertension with sufficiently high accuracy. For a cohort of 82 patients suffering from various degrees of heart failure severity we show that systolic, diastolic and wedge pulmonary pressures can be estimated on average within 8, 6 and 6 mmHg, respectively. We also show that, in general, increased data availability leads to improved predictions.

1 Introduction

Diastolic heart failure (sometimes referred to as heart failure with preserved ejection fraction or HFpEF) is a serious, often fatal, cardiovascular pathology. It is characterized by a dysfunctional relaxation or excessive stiffness of the left ventricle, and is not accompanied by significant alterations in systemic circulatory indicators, e.g., left ventricular ejection fraction, cardiac output or the mean arterial pressure [1]. In 2013, heart failure was mentioned in 1 of every 9 death certificates in the United States, and was the underlying condition in roughly 20\% of these cases. The number of deaths attributable to heart failure was approximately as high in 1995 as it was in 2013, with hospital discharges remaining stable from 2000 to 2010 [2]. It is also estimated that about one-third of the patients with CHF have a normal LVEF [3].

It has been observed that PH is highly prevalent and often severe in HFpEF and that both pulmonary venous and arterial hypertension contribute to the severity of HFpEF with a marked correlation between systolic pulmonary arterial pressure (SPAP) and mortality [4]. Due to the limited accuracy of non invasive techniques to detect PH [5], early diagnosis of HFpEF relies on invasive pressure acquisitions through right heart catheterization [6]. Methods allowing an accurate indirect estimation of pulmonary pressures using minimally invasive measurement practices would therefore be extremely beneficial for early diagnosis of this silent but deadly disease.
In this study, we investigate how the physics-based consistency of a lumped parameter hemodynamic model containing three compartments, i.e., a four-chamber heart, systemic and pulmonary circulation compartments, may be used to monitor PH in patients from non-invasive and uncertain clinical measurements. The development of computer models to study hemodynamics in humans started in the 1960s and was first applied to investigate mechanisms of venous return and physiologic response to uncommon acceleration [7]. It continued in the 1980s with improved models of the human ventricle [8], simulation of autonomous, closed-loop cardiovascular systems [9] and inclusion of short-term arterial pressure control by the carotid baroreceptors [10]. Application of these models to investigate the hemodynamics of the superior vena cava and the blood distribution into the lungs in the context of the bidirectional cavopulmonary anastomosis in single-ventricle children is discussed in [11] with a detailed analysis of the Norwood circulation reported in [12], studying the effects of shunt diameter, systemic and pulmonary vascular resistance, and heart rate on hemodynamics and oxygenation. In addition, a review on modeling practices for the systemic to pulmonary artery shunt is provided in [13].

Due to the typically large number of parameters in these models and the difficulty associated with manual tuning, estimation approaches were also developed since the late 1970s. Estimation of changes in left ventricular resistance-capacitance (RC) or resistance-inductance-capacitance (RLC) parameters due to injection of various drugs from instantaneous aortic pressures and mean aortic flow is discussed in [14, 15]. Two-stage Prony-Marquardt optimization is applied in [16] to characterize patient-specific hemodynamic properties of the left ventricle and its systemic load. Computer-based adaptive control systems for left ventricular bypass assist devices are discussed in [17, 18], with an extended Kalman filter approach proposed in [19, 20]. A modified recursive least squares algorithm for estimating systemic arterial parameters with application to a total artificial heart control system is discussed in [21]. Identification of patient-specific model parameters using an iterative, proportional gain-based identification method and a minimal number of clinical measurements is presented in [22], while a study on seven patients undergoing coronary artery bypass grafting is discussed in [23]. Other studies include automatic parameter estimation of three-element Windkessel open-loop boundary conditions [24] and left ventricular viscoelastic model identification and comparison [25, 26]. More recently, examples of automatic parameter tuning in lumped circulatory models have included the physiology of children with congenital heart disease undergoing the first stage (i.e., Norwood) of single ventricle palliation surgery [27], construction of optimally trained patient-specific models for coronary artery disease [28] and predicting time evolution of ventricular dilation and thickening [29]. A study using lumped parameter models in diastolic heart failure is finally discussed in [30].

Circuit models in hemodynamics typically contain tens of parameters which need to be trained from clinical records collected at multiple visits, which include a variable but typically sparse number of clinical measurements. This aggravates the ill-conditioning of the inverse problem, where model outputs do not change in response to perturbations along a number of unidentifiable linear combinations of parameters. In these circumstances, optimization may not be successful in identifying global optima and sequential Monte Carlo techniques [31] may underperform in practice, as data typically represent extremes (maxima/minima) or mean values of clinical indicators over one heart cycle.

Two technological trends make the present contribution particularly timely. On one hand, there is increasing importance attributed to the availability of large training datasets which is at the base of the current revolution in AI and deep learning [32]. This includes anonymous electronic health record (EHRs) for specific sub-populations affected by a common clinical condition. On the other hand, there is increasing availability of computational resources on the cloud which create a perfect infrastructure for distributed computing with lightweight models. For these reasons, we envision an increased adoption of numerical models as regularizers to determine physics-informed predictive distributions for missing data in EHRs, going beyond currently adopted, physics-agnostic multiple imputation methods [33]. This study aims to be a first step in this direction, and provides the following new contributions:

• We propose a systematic approach to train patient-specific circulatory models with clinical data uncertainty, and demonstrate the results obtainable on a modest cohort of 82 patients.

• Explore optimal parameter training as a possible approach to increase the feature space in order to
facilitate classification of cardiovascular anomalies.

In Section 2.1, we discuss the differential formulations of a compartmental circulation model for human adults, including circuit elements, a generic heart model, systemic and pulmonary compartments. This is followed by an analysis of two datasets in Section 2.2, the first used for validation, while the second containing EHRs for 82 patients. Our numerical investigation is articulated through answers to the questions formulated in Section 2.3, using the numerical algorithms and tools briefly introduced in Section 2.4 and 2.5. Results are highlighted in Section 3 and related to physiological admissibility of the selected model, ability to capture dysfunction mechanisms, sensitivity and identifiability of input parameters, predictive performance for pulmonary pressures, non-pulmonary target ranking and viability of model-based PH classifiers. Conclusions are discussed in Section 4. Finally, for convenience, a list of acronyms is provided in Table 1.

### Table 1: List of acronyms.

| Acronym | Description                        | Acronym | Description                        |
|---------|------------------------------------|---------|------------------------------------|
| CHF     | Congestive heart failure           | LVEF    | Left ventricular ejection fraction  |
| HFpEF   | Heart failure with preserved ejection fraction | PH      | Pulmonary hypertension             |
| SPAP    | Systolic pulmonary arterial pressure | DPAP    | Diastolic pulmonary arterial pressure |
| MPAP    | Mean pulmonary arterial pressure    | PCW     | Pulmonary capillary wedge pressure  |
| PVR     | Pulmonary vascular resistance       | SVR     | Systemic vascular resistance        |
| RAP     | Mean right atrial pressure          | CVP     | Central venous pressure             |
| LVEF    | Left ventricular ejection fraction  | RVEF    | Right ventricular ejection fraction |
| RVEDP   | Right ventricular end diastolic pressure | LVEDV   | Left ventricular end diastolic volume |
| SBP     | Systolic blood pressure             | DBP     | Diastolic blood pressure            |
| HR      | Heart rate                          | CO      | Cardiac output                      |
| LPN     | Lumper parameter network            | MAP     | Maximum a posteriori                |
| OOP     | Object oriented programming         | MCMC    | Markov chain Monte Carlo            |

2 Materials and Methods

**Compliance with Ethical Standards** - The study was classified as *research not involving human subjects* and approved on June 13th, 2019 by the Office of Research Compliance and Institutional Review Board at the University of Notre Dame under IRB #19-05-5371. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this retrospective study formal consent is not required.

2.1 Modeling Approach

Blood circulation in adults can be simulated through a *lumped parameter model* (sometimes also referred to as *zero-dimensional* or *0D* model). The foundation beneath a lumped parameter model lies in the equations that govern the voltage and current in an electrical circuit. Utilizing the hydrodynamic analogy [34], the equations for voltage transition into equations for pressure, and the equations for current transition into the equations for flow.

In this study, we consider patient-specific 0D representations containing seven compartments: the four chambers in a bi-ventricular heart, a compliant aortic arch, and the pulmonary and systemic circulations. The pulmonary compartment is represented through an RC circuit as shown in Figure 1.

2.1.1 Generic Heart Model Compartment

The four heart chambers are represented by a series arrangement of a pressure-volume generator, an inductor, an ideal unidirectional valve and a resistor, following prior work. The atrial and ventricular pressure-
Figure 1: Lumped parameter hemodynamic model with RC pulmonary circuit.

Volume generators are formulated through a combination of an activation function and active/passive pressure curves [8, 12]

\[ P_{i,\text{act}} = E_{i,\text{act}}(V_i - V_{i,0}), \quad P_{i,\text{pas}} = K_{i,\text{pas},1} \left[ e^{K_{i,\text{pas},2}(V_i - V_{i,0})} - 1 \right], \quad P_i = P_{i,\text{pas}} + A_i P_{i,\text{act}}, \] (1)

where the index \( i \) refers to either the right-left or atrial-ventricular chamber, \( i \in \{ra, rv, la, lv\} \). The active pressure curve is assumed linear and characterized by an active elastance \( E_{i,\text{act}} \) and unstressed chamber volume \( V_{i,0} \). Additionally, passive volumes and pressures are related through an exponential relation, characterized by two elastance coefficients \( K_{i,\text{pas},1} \) and \( K_{i,\text{pas},2} \), respectively [8, 12]. The pressure-volume generator is completed by an activation function \( A_i \) of the form

\[ A_i = \begin{cases} \frac{1 - \cos \left(2\pi t_{c,r}\right)}{2}, & \text{if } t_{c,r} < 1 \\ 0, & \text{otherwise,} \end{cases} \] (2)

where \( t_{c,r} \) is the relative chamber activation time, ranging from 0 (beginning of systole) to 1 (end of systole). The chamber volume is also determined through the equations

\[ \begin{align*}
\frac{dV_{ra}}{dt} &= Q_{\text{sys,v}} - Q_{ra,rv} \cdot \phi_T, \\
\frac{dV_{rv}}{dt} &= Q_{ra,rv} \cdot \phi_T - Q_{rv,pa} \cdot \phi_P, \\
\frac{dV_{la}}{dt} &= Q_{pul} - Q_{la,lv} \cdot \phi_M, \\
\frac{dV_{lv}}{dt} &= Q_{la,lv} \cdot \phi_M - Q_{lv,ao} \cdot \phi_A,
\end{align*} \] (3)

where \( \phi_i, i \in \{T, P, M, A\} \) are valve activation functions for the tricuspid (T), pulmonary (P), mitral (M) and aortic (A) valve respectively. These are equal to one for a negative pressure gradient through the valve and zero otherwise. Moreover, valves are modeled as perfect, without accounting for possible leakage or regurgitation. For models including valve prolapse and consequent regurgitation the reader is referred to, e.g., [35]. An inductance element located downstream with respect to the pressure-volume generator simulates the inertia of the blood in the chamber, according to the differential equation

\[ \begin{cases} 
\frac{dQ_i}{dt} = (P_i - P_{dn} - R_i Q_i)/L_i, & \text{if } P_i \geq P_{dn} \\
0, & \text{otherwise,}
\end{cases} \] (4)
where $Q_i$ is the volumetric blood flow going through the $i$-th chamber, $P_i$ and $P_{dn}$ the pressure in the $i$-th and downstream chamber, respectively, $R_i$ the viscous resistance located between chamber $i$ and chamber $dn$, and $L_i$ an inductance parameter.

Additionally, the selected model is fully capable of representing the physiologic consequences of a stenotic valve, as an increase in the resistance of the associated compartment would accentuate the pressure drop across the valve and lead to an increase of the upstream pressure. Finally, we remark that systolic and diastolic functions are separately represented in this model, using three parameters for each chamber, i.e., $K_{i,\text{act}}$, $K_{i,\text{pas},1}$ and $E_{i,\text{pas},2}$. Identification of these parameters from clinical health records would therefore be informative of systolic and diastolic chamber function.

We note that the RL parameters of each cardiac chamber are kept fixed in this study (see Table A1) or, in other words, we assume that valve stenosis has been excluded as a possible cause of pulmonary hypertension, for example through a non-invasive echocardiographic assessment.

### 2.1.2 Aortic and Systemic Compartment

An aortic compartment consisting of an isolated capacitor is positioned downstream of the left ventricular outflow, modeled through an equation of the form

$$\frac{dP_{ao}}{dt} = \frac{Q_{up} - Q_{dn}}{C_{ao}},$$  \hspace{1cm} (5)

where $Q_{up}$ and $Q_{dn}$ are the volumetric flow rate from the left ventricle and abdominal aorta, respectively, $P_{ao}$ is the aortic pressure and $C_{ao}$ the aortic compliance. We compare the value of $P_{ao}$ computed by this model with the clinically acquired brachial pressure.

An RCR circuit simulates the systemic circulation, with $C_{sys}$ used to represent the overall systemic compliance, while two resistors simulate the viscous resistance in arteries and veins $R_{sys,a}$ and $R_{sys,v}$, respectively. The algebraic-differential equations for the systemic compartments are therefore:

$$Q_{sys,a} = \frac{P_{ao} - P_{sys}}{R_{sys,a}}, \hspace{0.5cm} Q_{sys,v} = \frac{P_{sys} - P_{ra}}{R_{sys,v}}, \hspace{0.5cm} \frac{dP_{sys}}{dt} = \frac{Q_{sys,a} - Q_{sys,v}}{C_{sys}}.$$  \hspace{1cm} (6)

### 2.1.3 Pulmonary Compartment

The pulmonary circulation is represented through a RC circuit with equations

$$Q_{pa} = \frac{P_{pa} - P_{la}}{R_{pa}}, \hspace{0.5cm} \frac{dP_{pa}}{dt} = \frac{Q_{rv,pa} \cdot \phi_P - Q_{pa}}{C_{pa}},$$  \hspace{1cm} (7)

where the pulmonary, left atrial and right ventricular pressures are denoted by $P_{pa}$, $P_{la}$ and $P_{rv}$, and pulmonary capacitance and resistance are $C_{pa}$ and $R_{pa}$, respectively. The pulmonary flow rate is denoted as $Q_{pa}$, while $Q_{rv,pa}$ denotes the flow across the pulmonary valve, having activation equal to

$$\phi_P = \begin{cases} 0 & \text{if } P_{pa} \geq P_{rv} \\ 1 & \text{otherwise} \end{cases}$$  \hspace{1cm} (8)

### 2.2 Available Data Sets

Two data sets are used throughout this study. Synthetic patient-agnostic clinical measurements representing increasing severity of diastolic left ventricular dysfunction are used initially, while anonymized patient-specific electronic health records (EHR) for a cohort of 82 patients are utilized in the second part of the study.
2.2.1 Validation Data Set

The validation data set (Table 2) contains the mean and standard deviation of thirteen different clinical targets for three different heart failure groups: healthy patients, mild heart failure patients, and patients with severe heart failure. Normal physiologic parameters were determined from the literature [36], while parameters associated with severe left ventricular diastolic dysfunction were assigned with the supervision of a clinician. The values for mild heart failure patients were obtained through a linear interpolation between severe dysfunction and healthy conditions.

Table 2: Validation data set containing the mean and standard deviation of clinical targets for three levels of increasing diastolic heart failure severity.

| Qty         | Description                        | Units       | Severe HF | Moderate HF | Healthy | σ  |
|-------------|------------------------------------|-------------|-----------|-------------|---------|----|
| HR          | Heart Rate                         | bpm         | 80        | 80          | 80      | 3  |
| RAP         | Right Atrial Pressure              | mmHg        | 15        | 9           | 4       | 0.5|
| sPAP        | Systolic Pulmonary Artery Pressure | mmHg        | 50        | 35          | 20      | 1  |
| dPAP        | Diastolic Pulmonary Artery Pressure| mmHg        | 25        | 19          | 12      | 1  |
| PCW         | Pulmonary Capillary Wedge Pressure | mmHg        | 25        | 17          | 9       | 1  |
| SBP         | Systolic Blood Pressure            | mmHg        | 120       | 120         | 120     | 1.5|
| DBP         | Diastolic Blood Pressure           | mmHg        | 80        | 80          | 80      | 1.5|
| SVR         | Systemic Vascular Resistance       | dynes·s·cm⁻⁵| 1800      | 1375        | 1350    | 50 |
| CO          | Cardiac Output                     | L/min       | 3.5       | 4.375       | 5.25    | 0.2|
| sRV         | Systolic Right Ventricular Pressure| mmHg        | 50        | 35          | 20      | 1  |
| RVEDP       | Right Ventricular End Diastolic Pressure| mmHg          | 15        | 9           | 4       | 1  |
| sLV         | Systolic Left Ventricular pressure | mmHg        | 120       | 120         | 120     | 1.5|
| LVEDP       | Left Ventricular End Diastolic Pressure| mmHg        | 25        | 16          | 6       | 2  |

2.2.2 EHR Data Set

Completely anonymized patient-specific clinical measurements for 82 adult patients were provided in the context of a research project funded by Google through its ATAP initiative, focusing on *Modeling Noninvasive Measurements of Cardiovascular Dynamics*. There are 26 clinical data targets, which are listed below in Table 3. Missing data were present with the pattern highlighted in Figure 2, with patients having zero to nineteen of the clinical targets. Two of the 84 patients in the dataset did not have any of the relevant clinical targets and were therefore excluded from the study (see the patient with zero available targets in Figure 2a). The remaining 82 patients had between one and nineteen clinical targets. While there is not a single patient that has all 26 measurements, at least three clinical targets (heart rate, diastolic blood pressure, and systolic blood pressure) are available for all but one patient. Additionally, only a single patient in the dataset contains the central venous pressure target. Finally, the standard deviations for each clinical target are also shown in Table 3, which were determined through a preliminary literature review [37, 38, 39].

A histogram of clinical data occurrences is illustrated in Figure 2a, and displays three main modes: the majority of patients have either four, eight, or seventeen available clinical measurements, likely due to the data aggregation produced by certain screening procedures. Additionally, a heat map of the EHRs is illustrated in Figure 2b, where each row of the heat map was normalized to a zero to one range, to highlight the relative magnitude of the clinical target.

2.3 Methodological Approach

This study is articulated through a number of logically consequential questions driving our numerical experiments. These questions are:
Table 3: Patient-specific EHR data set containing 26 clinical measurements and associated units.

| n. | REDCap Token | Description                  | Units       | Measurement type                      | σ     |
|----|--------------|------------------------------|-------------|---------------------------------------|-------|
| 1  | heart_rate   | Heart rate                   | bpm         | NI                                    | 3.0   |
| 2  | systolic_bp  | Systolic blood pressure      | mmHg        | NI                                    | 1.5   |
| 3  | diastolic_bp | Diastolic blood pressure     | mmHg        | NI                                    | 1.5   |
| 4  | cardiac_output | Cardiac output           | L/min       | Invasive TD or NI echo                | 0.2   |
| 5  | systemic_vascular_resistance | Systemic vascular resistance          | dynes·s·cm⁻⁵ | from RAP, SBP and CO                  | 50.0  |
| 6  | pulmonary_vascular_resistance | Pulmonary vascular resistance          | dynes·s·cm⁻⁵ | from PAP, PCW and CO                  | 5.0   |
| 7  | cvp          | Central venous pressure      | mmHg        | NI (CVP=RAP) or JVP/IVC CI            | 0.5   |
| 8  | right_ventricle_diastolic | Right ventricle diastolic pressure       | mmHg        | Invasive catheter                     | 1.0   |
| 9  | right_ventricle_systolic | Right ventricle systolic pressure       | mmHg        | NI echo and invasive catheter        | 1.0   |
| 10 | rvdp         | Right ventricle EDP          | mmHg        | NI same as RAP with no TS             | 1.0   |
| 11 | aov_mean_pg  | Average PG across aortic valve | mmHg        | NI echo                              | 0.5   |
| 12 | aov_peak_pg  | Peak PG across aortic valve  | mmHg        | NI echo                              | 0.5   |
| 13 | mv_decel_time | Mitral valve deceleration time | ms          | NI echo                              | 6.0   |
| 14 | mv_e_a_ratio | Mitral valve E/A ratio       | -           | NI echo                              | 0.2   |
| 15 | pv_at        | Pulmonary valve acceleration time | ms        | NI echo                              | 6.0   |
| 16 | pv_max_pg    | Peak PG across pulmonary valve | mmHg        | NI echo                              | 0.5   |
| 17 | ra_pressure  | Mean right atrial pressure   | mmHg        | NI (CVP≈RAP) or JVP/IVC CI          | 0.5   |
| 18 | ra_vol_a4c   | Right atrial volume          | mL          | NI echo                              | 3.0   |
| 19 | la_vol_a4c   | Left atrial volume           | mL          | NI echo                              | 3.0   |
| 20 | lv_e一秒     | Left ventricular end systolic volume | mL      | NI echo                              | 10.0  |
| 21 | lv_vol_a4c   | Left ventricular volume      | mL          | NI echo                              | 20.0  |
| 22 | lvef         | Left ventricular ejection fraction | -       | NI echo                              | 2.0   |
| 23 | lvot_max_flow | Peak flow velocity across LVOT | cm/s       | NI echo                              | -     |
| 24 | pap_diastolic | Diastolic PAP                | mmHg        | Invasive catheter                     | 1.0   |
| 25 | pap_systolic | Systolic PAP                 | mmHg        | Invasive catheter                     | 1.0   |
| 26 | wedge_pressure | Pulmonary wedge pressure    | mmHg        | Invasive catheter                     | 1.0   |

NI: Non-invasive. echo: Doppler echocardiography. PAP: Pulmonary arterial pressure. JVP: jugular vein pressure. IVC CI: Inferior vena cava collapsibility index. RAP: Right atrial pressure. TD: thermo dilution. PG: pressure gradient. EDP: end diastolic pressure. LVOT left ventricular out flow tract. TS: tricuspid stenosis.

1. **Physiological admissibility of 0D representations under normal and heart failure conditions** - Are model outputs able to reproduce sets of clinical targets ranging from healthy to pathological conditions? In other words, is the identification problem well-posed, in the sense that model outputs are able to represent a wide spectrum of conditions from health to disease?

2. **Ability to model distinct diastolic/systolic dysfunction mechanisms** - Is the selected model formulation able to separately represent the systolic and diastolic functions of the heart muscle? And does the alteration of these properties produce expected modifications in the physiology represented through model outputs?

3. **Parameter sensitivity and identifiability** - Once a set of quantities whose prediction is of interest (e.g., pulmonary arterial pressure) has been identified, do they show non-negligible sensitivity with respect to changes in the parameters associated with physiologic relevant mechanisms affecting these quantities? Moreover, are these parameters identifiable so that it is possible to uniquely estimate their distribution from the available clinical data? Is this estimate robust (i.e., characterized by a limited uncertainty)?

4. **Relative importance of non-pulmonary clinical targets** - Which minimal set of clinical targets should be collected to guarantee accurate model predictions for systolic, diastolic pulmonary pressure and pulmonary venous wedge pressure? In other words, we would like to rank the non-pulmonary targets, starting with those producing maximally accurate predictions on the pulmonary arterial pressure. This allows for identification of a minimal set of maximally informative clinical quantities for predicting specific model outputs.

5. **Detecting pulmonary arterial hypertension from assimilated circulation models** - Group II pulmonary arterial hypertension is typically detected by a mean pulmonary pressure higher than 25 mmHg or a systolic pulmonary pressure higher than 35 mmHg [40]. Instead of direct characterization
Based on clinical data, would it be possible to detect pulmonary arterial hypertension by classification from the parameters of a model trained with non-invasive measurements? Once assimilated, a model can be used to generate a large number of features, leading to a higher dimensional space with possibly improved separability [41].

2.4 Inference

Consider a set of $m$ measured clinical targets represented through the random vector $\mathbf{d} \in \mathbb{R}^m$ with each component $d_i \sim \rho_i(d_i), i = 1, \ldots, m$ and joint density $\mathbf{d} \sim \rho(\mathbf{d}) = \rho_1(d_1) \rho_2(d_2) \cdots \rho_m(d_m)$. We design a physiologic 0D circuit model with $n$ parameters $\mathbf{y} \in \mathbb{R}^n$, so its outputs match the observed targets or, in other words, we introduce a statistical model of the form

$$d_i = G_i(\mathbf{y}) + \epsilon_i = o_i + \epsilon_i, \quad i = 1, \ldots, m,$$

and assume each noise component $\epsilon_i \sim \mathcal{N}(0, \sigma^2_i)$ to follow a zero-mean Gaussian distribution. Note that the $i$-th realization from the parameter vector $\mathbf{y}$ is denoted by $\mathbf{y}^{(i)}$ and that the $i$-th model output is denoted by $o_i = G_i(\mathbf{y})$, while the vector $\mathbf{o} \in \mathbb{R}^m$ contains the complete set of model outputs.

Each model is trained using two different approaches, i.e., by determining a maximum a posteriori estimate of the parameters $\mathbf{y}$ using repeated Nelder-Mead optimization [42], and by solving an inverse problem through adaptive Markov chain Monte Carlo sampling, specifically, through the differential evolution adaptive Metropolis algorithm [43, 44] and assessing convergence through the Gelman-Rubin diagnostic [45]. In both cases, the posterior distribution $P(\mathbf{y}|\mathbf{d})$ is obtained by combining a uniform prior $P(\mathbf{y})$ (see the admissible parameter ranges in Table A1) with a Gaussian likelihood

$$P(\mathbf{y}|\mathbf{d}) \propto P(\mathbf{d}|\mathbf{y}) \cdot P(\mathbf{y}), \quad P(\mathbf{d}|\mathbf{y}) = \frac{1}{\sqrt{(2\pi)^m \prod_{i=1}^m \sigma^2_i}} \exp \left( -\frac{1}{2} \sum_{i=1}^m \frac{(d_i - G_i(\mathbf{y}))^2}{\sigma_i^2} \right).$$

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**Figure 2:** Histogram of data availability among the 82 patients (left) and missing data pattern (right).
2.5 Computational tools

The tulip (Tools for Uncertainty quantification, Lumped modeling and Identification of Parameters) software framework was developed to answer the above research questions. Tulip is a OOP C++ code designed to simplify the task of estimating parameters of lumped models for human circulation and contains abstractions for computational models, operations performed on these models (e.g., optimization, Bayesian estimation, local and global sensitivity analysis, etc.) and data sources used to store the available clinical targets. For an overview of the procedures for statistical data assimilation used in this study, the interested reader is referred to [46, 47].

3 Results

3.1 Physiological admissibility

The circulation model discussed in Section 2.1 was first trained on the validation dataset in Section 2.2.1. We then generated a collection of model outputs using a subset $y^{(i)}$, $i = 1, \ldots, 5000$ parameter realizations from the converged MCMC samples, and compared the resulting distributions (after post-processing with Gaussian kernel density estimation) with the distributions assumed for the targets $d$. Specifically, we assumed that each clinical target follows a normal distribution with the mean and standard deviations listed in Table 2. The Kullback–Leibler (KL) divergence [48] was used to determine the agreement between the model-based predictions and measurements. The KL divergence measures how much information is lost when one uses the predicted, instead of the assumed, target distribution and a small KL divergence suggests physiological admissibility.

As shown in Figure 3, the KL divergence is negligible for all targets except SVR for severe cases of pulmonary hypertension, which is due to the specific RCR circuit layout selected for the systemic compartment and therefore a consequence of the lumped parameter model formulation. Furthermore, this difference was found to be independent of the selection of prior ranges for the systemic compliance and arterial/venous resistance. The maximum difference in SVR is however equal to $\approx 21.3\%$, which is considered acceptable, since this occurs only under severe pulmonary hypertension, a condition at the end of the pathologic spectrum, which represents a small fraction of the total number of hypertensive patients.

### Table 4: Validation data set. Model outputs for MAP parameter realization and clinical target set for severe heart failure conditions.

| Severe HF | Measured | Computed | Rel. diff. [%] | Severe HF | Measured | Computed | Rel. diff. [%] |
|----------|----------|----------|----------------|----------|----------|----------|----------------|
| HR       | 80       | 77.922   | -2.598         | CO       | 3.5      | 3.597    | 2.771         |
| SBP      | 120      | 117.880  | -1.767         | SVR      | 1800     | 1415.456  | -21.364       |
| DBP      | 80       | 75.798   | -5.253         | sRV      | 50       | 51.239   | 2.478         |
| RAP      | 15       | 14.412   | -3.920         | dRV      | 15       | 14.194   | -5.373        |
| sPAP     | 50       | 49.037   | -1.926         | sLV      | 120      | 120.320  | 0.267         |
| dPAP     | 25       | 23.838   | -4.648         | dLV      | 25       | 21.451   | -14.196       |
| PCW      | 25       | 26.201   | 4.804          |          |          |          |                |

3.2 Inverse assessment of dysfunction mechanisms

We now focus on the ability of our model to distinguish between diastolic and systolic dysfunction mechanisms. Specifically, we aim to determine whether the selected model parameterization is able to separately represent the relaxation or contraction (i.e. diastolic or systolic) function of the heart muscle. Recall that diastolic function, and therefore left ventricular stiffness, during relaxation relate to the linear and
Figure 3: KL divergence between predicted and assumed clinical targets for varying heart failure severity (top). Agreement between the target and predicted SVR distributions (bottom).

exponential passive curve parameters $K_{i,pas,1}$ and $K_{i,pas,2}$ in equation (1). These two parameters directly relate to the condition that we aim to assess.

Figure 4 shows the mean diastolic and systolic chamber function parameters and associated 10%-90% confidence intervals, grouped by anatomical relevance (i.e., left ventricle, right ventricle) and plotted for healthy patients and patients with mild and severe heart failure, respectively. Comparison between heart failure conditions allows one to assess how model parameters change as a result of disease progression. This change is shown in Figure 4, where many of the parameters that related to pulmonary hypertension do in fact change as patients progress from healthy to mild, and mild to severe diastolic dysfunction. The results show how the passive left ventricular curve slope $K_{lv,pas,1}$ increases when going from healthy to mild and mild to severe, while the pulmonary resistance increases, as expected. Additionally, the left ventricular active elastance parameter $E_{max,lv}$ remains nearly constant; the model correctly predicts no reduction in systolic function. This confirms that the physiological model used for this study can in fact distinguish between systolic/diastolic dysfunction mechanisms.

3.3 Sensitivity and identifiability of circulation model parameters

Results from the above sections confirm the well-posedness of the selected model formulation for the full spectrum of diastolic dysfunction, from mild to severe. We now focus on determining the most relevant model parameters that significantly alters the main quantities of interest, particularly the systolic, diastolic and pulmonary wedge pressures. In addition, we study both the structural and practical identifiability in an effort to determine unimportant parameters and their non-identifiable combinations.
Figure 4: Variation of mean parameter values and associated confidence intervals under increasing heart failure severity. Right and left ventricular model parameters shown in the Figure are the ventricular passive curve slope $K_{\text{pas},i,1}$, exponent factor $K_{\text{pas},i,2}$, active curve slope $E_{\text{max},i}$ and unstressed ventricular volume $V_{i,0}$ (where $i \in \{rv,lv\}$). It also shows the following resistance parameters: $R_{pa}$ (pulmonary resistance), $R_{sys,a}$ (arterial systemic resistance), $R_{sys,v}$ (venous systemic resistance).

3.3.1 Average local sensitivities

Nondimensional local sensitivities are computed for all outputs as

$$\frac{\Delta o_i}{\Delta y_i} \cdot \frac{y_{i,\text{map}}}{o_{i,\text{map}}}$$

where $\frac{\Delta y_i}{y_{i,\text{map}}} = 0.01$, (11)

so that we consider the relative change in model outputs that correspond to a 1% variation in each parameter. The maximum a posteriori parameter vector $\mathbf{y}_{\text{map}}$ and the corresponding model outputs $\mathbf{o}_{\text{map}} = \mathbf{G}(\mathbf{y}_{\text{map}})$ are computed from MCMC for each of the 82 patients in the cohort, and used to compute the sensitivities in equation (11). The resulting sensitivities are then averaged across all patients.

Figure 5a illustrates the average sensitivities obtained by training our model with the complete list of clinical targets, including systolic, diastolic and venous wedge pulmonary pressures and pulmonary vascular resistance. We note that large sensitivities are apparent for the heart rate across all outputs while at the same time, accurate measurements of heart rate are easy to obtain non-invasively. Additionally, to check how the sensitivities were affected by the availability of pulmonary pressure targets (i.e., the very same quantities we would like to predict), we re-computed sensitivities using parameter estimates $\mathbf{y}_{\text{map}}$ obtained by excluding the pulmonary pressure targets during training. The average sensitivities appear to be minimally affected by the selective inclusion of pulmonary pressure targets.

Figure 5b suggests the following important parameters. Changes in the heart rate or $t_{\text{sys}}$ directly affect the amount of blood flow ejected by the ventricles, altering the mean pulmonary pressures under a constant PVR and initial value (i.e., $P_{pa,ini}$). As already discussed in the above sections, the left ventricular diastolic pressure/volume ratio $K_{lv,pas,1}$ and the associated exponential factor $K_{lv,pas,2}$ govern the diastolic properties of the left ventricle, while the $E_{\text{max},lv}$ is instead responsible for the systolic function. The left atrioventricular and aortic valve resistance $R_{la,lv}$ and $R_{lv,ao}$, respectively, govern the pressure drop from the left atrium to the left ventricle and from the left ventricle to the aorta. These two parameters therefore affect the left atrial and ventricular pressures and, in turn, the upstream pulmonary pressures. Mitral or aortic valve stenosis are typical examples of this mechanism (see, e.g., [49]). The pulmonary resistance and capacitance parameters $R_{pa}$ and $C_{pa}$ clearly affect the mean pulmonary pressures and their range, while
changes in systemic vascular resistance $R_{sys,a}$ or $R_{sys,v}$ affect the left ventricular afterload and, in turn the pulmonary pressures.

Figure 5: Average local sensitivities using a perturbation factor of 1%. (a) Average local sensitivity table for all parameters and model outputs. (b) Average local sensitivities table for all parameters and pulmonary outputs only. The values in each row are scaled to make their sum equal to 100.0 and a two cutoffs are used equal to 25 and 12.5 for (a) and (b), respectively.
3.3.2 Structural identifiability

Structural identifiability analysis is performed to gain understanding of our ability to recover a given set of model parameters, through the solution of an inverse problem from idealized noiseless clinical targets that belong to the model range. This is in contrast with the analysis in the next section of the practical identifiability where real clinical data is used instead. We solve the model for the default parameter combination in Table A1 and regard the outputs as data, from which a MAP estimate of the default parameter values is re-computed by MCMC followed by NM optimization. Additionally, histograms are generated using 5000 samples from the MCMC parameter traces and compared to the default (true) parameter set. The results for right, left ventricular and resistor parameters can be seen in Figures 7, 8, and 9, respectively. The true parameters are always found within the parameter distributions from MCMC and often correspond to the mode of the histogram.

The coefficients of variation for the model parameters marginal posteriors and associated learning factors are shown in Figure 6. While parameters with higher coefficient of variation have a greater spread relative to their mean, the learning factor quantifies how much the marginal variance is reduced by conditioning the model output to the available observations or in other words how much the marginal variance is reduced from the prior to the posterior [46]. Figure 6 shows that the parameters with the largest coefficient of variation are also the parameters with the smallest learning factor, as expected. Heart timing parameters, systemic and pulmonary resistance and compliance, aortic compliance and active ventricular parameters are generally well learned.

![Figure 6: Bar plot of the coefficient of variation (CV) alongside the learning factor (θ) for each parameter. a and b represent the minimum and maximum bound of each parameter uniform marginal prior.](image-url)

The analysis is completed by a comparison between the true and optimal physiology, calculated using 5000 parameter combinations from the MCMC traces, and analyzed over a single heart cycle. The results for the aortic, pulmonary, and left ventricular pressures and flows, as well as the left and right ventricular pressure-volume loop are reported in Figure 10. Pressures, flows and volumes agree well with those generated from the default parameter set.
3.3.3 Practical identifiability

We also perform local identifiability analysis through the Fisher information matrix rank [50] to determine the presence of non-identifiable parameter combinations and unimportant parameters. To do so, we compute the matrix \( \frac{\partial G(y_{\text{map}})}{\partial y} \) of local derivatives for our output quantities \( o_{\text{map}} = G(y_{\text{map}}) \) with respect to the parameters \( y \). The Fisher Information matrix \( I(y_{\text{map}}) \) can be computed as

\[
I(y_{\text{map}}) = \left[ \frac{\partial G(y_{\text{map}})}{\partial y} \right] B \left[ \frac{\partial G(y_{\text{map}})}{\partial y} \right]^T,
\]

where \( B \) is the inverse covariance matrix of the output quantities.
where the precision matrix $B$ contains the inverse target variances, i.e., $B_{i,i} = 1/\sigma_i^2$ and $B_{i,j} = 0$ for $i \neq j$. Rank deficiency in $I(y_{\text{map}})$ reveals the presence of non identifiable parameter combinations as illustrated in Figure 11a by plotting the FIM eigenvalues ordered by magnitude for all patients. Small eigenvalues are observed across all analyzed patients, confirming a lack of local identifiability.

Eigenvectors for all patients whose corresponding eigenvalues were less than a selected cut-off were superimposed on the same radar plot, to search for situations characterized by dominant components, representative of unimportant parameters. This process is visualized in Figure 11a, illustrating that all eigenvalues colored by patient and Figure 11b, showing the effect of changing the cut off value on the number of selected patients. Specifically, it shows that no significant changes result by adopting cut-offs in the range $[1 \times 10^{-12}, 1 \times 10^{-16}]$.

Figure 12 shows an example of two of the 17 radar plots generated for this study. The plot on the left shows an example of unimportant parameter with dominant eigenvalue associated with the parameter $V_{la,ini}$, i.e., the initial left atrial volume. Instead, the radar plot on the right does not show any clear pattern involving parameter combinations that significantly change across patients. This local identifiability analysis confirms how initial conditions for pressures, flows and volumes (except $P_{pa,ini}$, $P_{ao,ini}$ and $P_{sys,ini}$ as per the results of the previous sensitivity analysis) are generally unimportant.

### 3.4 Prediction of pulmonary pressures

We now focus on the problem of using the physiological consistency of our compartmental model to predict pulmonary pressures from other possibly non-invasive clinical targets. To do so, we have trained our models without including the pulmonary pressures (i.e., systolic, diastolic, wedge pressures and pulmonary...
Figure 11: (a) Scatter plot of eigenvalues vs. eigenvectors for all patients. Red horizontal line represents selected cut-off value. FIM eigenvalues at identified parameters plotted in increasing order. (b) Plot of number of patients selected (eigenvalues less than cut-off) for each eigenvector.

Figure 12: Selection of two of the 17 total radar plots of all parameters whose eigenvalues are less than the selected cut-off. (a) Example of unimportant initial condition, i.e. whose perturbation has no effect on the model results. (b) Example of non-identifiable parameter combinations where no dominant parameter can be identified and where the combination significantly changes across patients.

vascular resistance) as targets, and propagated forward the estimated parameters to quantify the marginal distributions for the predicted pulmonary pressures. We then evaluated the error between predicted and true pulmonary pressures together with their variability.
Figure 13: Predictive performance for pulmonary pressure. Absence of PAP targets in average prediction errors is represented using dashed lines. The shaded region represents the area bounded by the 5th and 95th percentile of the 5000 simulations that were generated for the computation of the average error.

We first represented each patient in a plot showing mean pulmonary arterial pressure versus pulmonary vascular resistance. This representation allows for an easy identification of hypertensive patients, even though other quantities (e.g., systolic pulmonary pressure other than just the mean value) may be also be relevant to classify group II pulmonary arterial hypertension due to left heart disease. Figure 13a contains the clinical values, together with the predicted pressures for $\gamma_{\text{map}}$, both for the case where the model is trained with (green squares) and without (red diamonds) PAPs and PVR. Even training without pulmonary targets, the pressure and resistance range is still covered rather well, instead of collapsing around baseline healthy conditions. This suggests a certain degree of correlation between the information provided by PAPs and PVR and the other clinical targets, confirming that indirect estimation of pulmonary pressures from these targets is indeed possible.

In Figure 13b we also plotted the average absolute pressure error across 31 patients (those for which the pulmonary pressure were available and characterized by having more than 6 REDCap entries) versus the minimum number of prescribed clinical targets. For patients with at least 11 REDCap entries, the average errors on the predicted pressures is around 8 mmHg for systolic PAP, and 6 mmHg for Diastolic PAP and PCW.

3.5 Relative importance of non-pulmonary targets

In this section, we investigate which clinical targets are the most important to include during training, in order to minimize errors in pulmonary pressure predictions. In other words, we rank clinical targets starting from those having a more beneficial impact on the accuracy in predicting pulmonary hypertension. We achieve this goal through a sequence of optimization steps. We start by performing training using optimization with a single target at a time. The target found to minimize the average combined prediction error for pulmonary pressures is ranked first and permanently added to the list of targets to be included in
all successive optimization steps. The percent error was computed for each clinical pulmonary target that was available for each patient. Percentage error expresses the percentage difference between the model output and the clinical target, while a cumulative percentage error was calculated by taking the sum of the percentage errors for each pulmonary target that was clinically available for each patient. To avoid bias towards patients with fewer available pulmonary targets, the cumulative percentage error is transformed to an average combined prediction error through division by the number of available pulmonary targets. Let \( p \in \{1, 2, 3, 4\} \) be the number of pulmonary targets that is available in the data of a certain patient. The percent error of clinical target \( s_{i,target}, i = 1, \ldots, p \) is computed as \( e_i = 100 \cdot |s_{i,target} - s_{i,output}|/s_{i,target}, i = 1, \ldots, p \), while the average combined prediction error is \( \sum_{i=1}^{p} e_i/p \).

All remaining targets are iteratively tested and those producing the minimum average combined PAP errors are progressively ranked, until all targets have been considered. The process above is repeated for each patient. Figures 14 and 15 show the resulting average ranking and associated occurrences, the number of patients where a specific target was collected.

The list of targets ordered by average rank and filtered by occurrence is also shown in Table 5. Most of the quantities (except MPAP, PCW, PVR and SVR) can be estimated non-invasively. From RAP (or CVP, RVEDP), SBP-DBP, HR and SVR it is possible to estimate the cardiac output. From CO, HR and LVEF it is possible to estimate LVEDV which is correlated with PCW. This might explain why PCW is always estimated better than SPAP and DPAP. The mitral valve deceleration time and velocity E/A ratio are indicators of diastolic LV function and therefore correlated with PAP. If PVR, CO and PCW are known, then it is possible to estimate MPAP which is correlated to SPAP and DPAP. Finally the parameter ranking is summarized for all patients in Figure 16.

![Error vs Ranks Graph](https://example.com/figure14)

**Figure 14:** Target ranking and minimum error.

### 3.6 PH classifiers from assimilated circulation models

In this section, we explore the use of trained lumped parameter models for automatic detection of abnormal pulmonary pressures from minimally invasive clinical measurements. We employ a naïve Bayes classifiers [51] to detect pulmonary hypertension from our dataset. Specifically, we use each clinical target as a separate classification feature, and have labeled 22 hypertensive patients based on the mean pulmonary pressure being greater than or equal to 25 mmHg or a systolic pulmonary pressure of at least 35 mmHg.

Our dataset contains a non-negligible ratio of missing data, with 1 to 19 out of a total of 24 available targets in the selected cohort of 82 patients. To overcome this issue and to verify how classification
results depend on the strategy selected for missing data imputation, five different missing data imputation approaches were tested. The first method tested was complete-case analysis, considering only the 4 variables that were available for all patients, i.e., heart rate, systolic blood pressure, diastolic blood pressure, and cardiac output. The remaining four missing data methods consisted of replacing the missing values with (1) zeros, (2) the max value of the data set, (3) a value far outside the range of the data set (10 times the max), or (4) the median. In addition to the training of four separate classifiers using four different missing data methods, a fifth naïve Bayes classifier was trained on the MAP parameters of the model. The data for the MAP parameters from the model is a complete set, so no missing data method is required. Figure 17 shows how the above imputation approaches affect classification accuracy. At first sight, the high accuracy produced by a multiple imputation strategy using the maximum inter-patient clinical value (or 10 times its value) may seem surprising. This can be explained by observing how, in such a case, the probability of the feature associated with the missing data is essentially zero, thus essentially reducing the number of features and increasing the resulting accuracy.
Figure 16: (a) Ranks of clinical targets for each patient in order of importance (i.e., green more importance, red less important). (b) Minimum combined prediction error associated with the introduction of each clinical target for all the patients included in the study. Note how blank entries correspond to missing clinical targets.

We then grouped patients according to a training and a testing set, consisting of 4/5 and 1/5 of the available data, respectively. Training and testing is performed either using the raw clinical data or model parameters assimilated through optimization and MCMC, resulting in approximately 88% accuracy for the classifier trained with the 24 raw clinical datapoints and about 76.4% accuracy for the classifier trained with the 45 assimilated parameter values. Of the 82 patients, 65 contained enough information for ground truth classification of whether or not the patient should be identified as hypertensive. Based on these data we were able to classify 22 of the 65 patients, or about one third of the patients, as being affected by pulmonary hypertension and the remaining two thirds with normal PAP pressures. This imbalance is known to introduce bias [52], with the classifier more likely to label patients as non-hypertensive (as 2/3 of the training data are non-hypertensive). As a remedy, six different approaches were applied to deal with this imbalance, which represents a mixture of over-sampling methods, under-sampling methods, and a combination of both. Figure 18 show the principal component decomposition and contingency table for the unbalanced data and the data balanced with the centroid clustering approach, whereas Figure 19
Table 6: Training accuracy improvements using the original dataset and following pre-processing to balance the relatively small number of hypertensive positives.

| Pre-processing Data for Classification | Training data type for classifier | Complete Data | Missing Data Imputed | Balanced Data |
|---------------------------------------|----------------------------------|---------------|----------------------|--------------|
| Clinical Data                         | 0.8082                           | 0.8801        | 1.0                  |
| Parameters                            | 0.7640                           | N.A.          | 1.0                  |

shows the resulting effect of each unbalanced data method on the overall area under the receiver operating characteristic curve (ROC) for the classifier trained on the model parameters. For such a classifier, centroid clustering [53] increases accuracy from 76.4% up to 100%. In addition, data balance using Synthetic Minority Oversampling TEchnique (SMOTE) [54] increases the accuracy of the model trained on the data from 88% to 100%.

We again remark that the number of patients in this study is small and future studies will investigate generalization of this approach to larger datasets.

Figure 17: Accuracy of a naïve Bayes classifiers for pulmonary hypertension using different approaches for multiple imputation.

4 Conclusion

This study demonstrates that a relatively simple lumped parameter compartmental model can represent a wide range of physiologies, spanning healthy patients to patients affected by severe diastolic left ventricular dysfunction. In this context, an activation formulation for the heart chambers has proven important to separately account for systolic and diastolic pressure-volume behavior. When trained using ideal clinical data from subjects with diastolic left ventricular dysfunction, the parameters associated with the governing
**Figure 18:** Principal component decomposition (left) along with the contingency table (right) for the unbalanced data and balanced through centroid clustering.

**Figure 19:** Accuracy of a Naive Bayes classifier for pulmonary hypertension, using identified lumped parameters as features, and various methods to handle unbalanced data. The methods used were Random Over-sampling (ros), Random Under-sampling (rus), an over-sampling method: SMOTE (Synthetic Minority Oversampling TEchnique) (sm), two under-sampling methods: Tomek Links (tl) and Cluster Centroids (cc), and a combination method that performs over-sampling followed by under-sampling through applying SMOTE followed by Tomek Links (smt). Physiological mechanisms (i.e., diastolic ventricle relaxation) change in a way that is consistent with the underlying physiology of the dysfunction. The average parameter sensitivities are determined after training with real data from 82 patients, confirming intuition for the most important parameters. Pulmonary pressures were found to be mostly sensitive to heart rate and contraction timing parameters, diastolic and systolic pressure/volume ratio parameters ($K_{pas,1,lv}$, $K_{pas,2,lv}$ and $E_{max,lv}$), left atrioventricular and aortic...
valve resistance \((R_{lv,la}, R_{lv,lv}, R_{lv,ao})\), pulmonary resistance and capacitance \((R_{pa}, C_{pa})\) and systemic resistance \((R_{sys})\). Additionally, the model was found to be locally unidentifiable, with initial conditions generally unimportant. The structural identifiability analysis showed that inference of model parameters is feasible under perfect, noiseless conditions and with a sufficiently large number of available clinical targets. Target ranking based on sequential optimization reveals the most important non-invasively acquired clinical targets to be the heart rate, systemic pressures, pulmonary valve acceleration time, mitral valve deceleration time and mitral valve E/A peak ratio. Clinical targets requiring invasive measurement practices that positively affect the prediction of pulmonary pressures are instead central venous pressure, right ventricular systolic and diastolic pressure, systemic vascular resistance, cardiac output and mean right atrial pressure. After investigating parameter identifiability/sensitivity, pulmonary pressures in 82 patients with various heart failure severities were predicted from a lumped hemodynamic model, trained based on the remaining clinical targets. The average absolute pressure error on the 11 patients characterized by at least 11 distinct clinical entries was found approximately equal to 8 and 6 mmHg for systolic and diastolic/wedge pulmonary pressures, respectively. Finally, we have shown that MAP estimates of circulation model parameters can be used to detect elevated pulmonary pressures, and that a simple classifier provide high accuracy on balanced data, even when these parameters are identified without measuring systolic, diastolic, wedge pulmonary pressures and pulmonary vascular resistance. Future work will be devoted to the systematic demonstration of the proposed approach on larger patient dataset, opening new avenues for translational applications of model-based diagnostics, improving model formulations targeting specific diseases and for the development of improved and more efficient estimation approaches.

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Appendices

Appendix A  Uniform priors and default parameter set

Table A1 shows the maximum and minimum ranges for each lumped parameter. The default parameter values used for the structural identifiability analysis in Section 3.3.2 are also reported.

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Table A1: Maximum and minimum values defining the priors for the model parameters.

| Parameter                                      | Symbol | Default(*) | Min(*) | Max(*) |
|------------------------------------------------|--------|------------|--------|--------|
| Heart Rate                                     | HR     | 78.0       | 40.0   | 100.0  |
| Atrial relative activation duration            | $t_{as}$ | 0.2       | 0.05   | 0.4    |
| Atrial relative activation time shift          | $t_{pws}$ | 9.5       | 5.0    | 10.0   |
| Ventricular relative activation duration       | $t_{svs}$ | 0.4       | 0.1    | 0.5    |
| Atrial passive curve slope, right atrium       | $K_{pas,ra,1}$ | 5.0       | 0.1    | 10.0   |
| Atrial passive curve exponent factor, right atrium | $K_{pas,ra,2}$ | 0.006   | 0.0001 | 0.06   |
| Atrial active curve slope, right atrium        | $E_{max,ra}$ | 0.1       | 0.05   | 5.0    |
| Unstressed right atrial volume                 | $V_{ra,0}$ | 0.0       | 0.0    | 50.0   |
| Atrial passive curve slope, left atrium        | $K_{pas,la,1}$ | 5.0       | 0.1    | 10.0   |
| Atrial passive curve exponent factor, left atrium | $K_{pas,la,2}$ | 0.0065  | 0.0001 | 0.06   |
| Atrial active curve slope, left atrium         | $E_{max,la}$ | 0.2       | 0.05   | 5.0    |
| Unstressed left atrial volume                  | $V_{la,0}$ | 0.0       | 0.0    | 50.0   |
| Ventricular passive curve slope, right ventricle | $K_{pas,rv,1}$ | 5.0       | 0.1    | 20.0   |
| Ventricular passive curve exponent factor, right ventricle | $K_{pas,rv,2}$ | 0.03   | 0.0001 | 0.01   |
| Ventricular active curve slope, right ventricle | $E_{max,rv}$ | 0.5       | 0.1    | 5.0    |
| Unstressed right ventricular volume            | $V_{rv,0}$ | 0.0       | 0.0    | 50.0   |
| Ventricular passive curve slope, left ventricle | $K_{pas,lv,1}$ | 2.0       | 0.1    | 20.0   |
| Ventricular passive curve exponent factor, left ventricle | $K_{pas,lv,2}$ | 0.003  | 0.0001 | 0.01   |
| Ventricular active curve slope, left ventricle | $E_{max,lv}$ | 4.0       | 1.0    | 5.0    |
| Unstressed left ventricular volume             | $V_{lv,0}$ | 20.0      | 0.0    | 50.0   |
| Inductance of right atrium                    | $L_{ra,rv}$ | 0.1       | 0.1    | 0.1    |
| Resistance of right atrium                    | $R_{ra,rv}$ | 10.0      | 10.0   | 10.0   |
| Inductance of right ventricle                 | $L_{rv,pa}$ | 0.1       | 0.1    | 0.1    |
| Resistance of right ventricle                 | $R_{rv,pa}$ | 15.0      | 15.0   | 15.0   |
| Inductance of left atrium                     | $L_{la,lv}$ | 0.1       | 0.1    | 0.1    |
| Resistance of left atrium                     | $R_{la,lv}$ | 8.0       | 8.0    | 8.0    |
| Inductance of left ventricle                  | $L_{lv,ao}$ | 0.1       | 0.1    | 0.1    |
| Resistance of left ventricle                  | $R_{lv,ao}$ | 25.0      | 25.0   | 25.0   |
| Aortic capacitance                            | $C_{ao}$ | 1.0e-3     | 1.0e-5 | 0.001  |
| Pulmonary capacitance                         | $C_{pa}$ | 4.0e-3     | 100.0e-6 | 0.01   |
| Pulmonary resistance                          | $R_{pa}$ | 130.0      | 1.0    | 500.0  |
| Systemic capacitance                          | $C_{sys}$ | 400.0e-6   | 100.0e-6 | 0.05   |
| Systemic Resistance - Arteries                | $R_{sys,a}$ | 400.0   | 100.0  | 800.0  |
| Systemic Resistance - Veins                   | $R_{sys,v}$ | 1200.0 | 500.0  | 2500.0 |

(*) All units are in the CGS system.

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