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An Inverse Problem Approach for Parameter Estimation of Cardiovascular System Models

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Abstract— **Left ventricular assist devices (LVADs) are mechanical pumps that help patients with chronic heart failure waiting for a heart transplant. Mathematical models of these devices can be used along cardiovascular system (CVS) models to evaluate the assistance performance under different operating modes. The estimation of the CVS model parameters for a particular patient and numerical simulations allow the implementation of adequate LVAD operation mode. This work presents a method to estimate the parameters of a CVS model using only one hemodynamic variable: the systemic arterial pressure (P_s). Synthetic signals of P_s are used to solve this ill-posed inverse problem partially, and the results show the high accuracy of the proposed method, which achieves 0.5%.**

Clinical relevance— **The measurements of hemodynamic variables using noninvasive techniques avoid many clinical problems arising from invasive measures such as infections.**

I. Introduction

Cardiovascular diseases have remained the leading causes of death globally in the last 15 years. Ischaemic heart disease and stroke were the leading causes of cardiac death, with 15.2 million deaths in 2016 [1]. Only in the USA, more than 250,000 patients suffer from advanced systolic Heart Failure (HF), and there exists a population of 500,000 patients in the European Union [2]. Although classical treatments such as advanced pacemakers or implantable defibrillators have changed the prognosis in HF patients, heart transplantation remains the optimal treatment for HF. As an alternative treatment, ventricular assist devices (VAD's) have been used as a bridge to transplant or even as destination therapy because of the lack of donors.

The use of numerical models from cardiovascular systems (CVS) and VADs can support several clinical and experimental strategies. For example, coupled CVS-VAD models can be brought to analyze the cardiovascular response under VAD assistance with physiological control systems [3]. In these cases, although it is possible to change all controller parameters during the tuning process, the performance is evaluated against a CVS model with generic parameters that do not represent a particular patient.

The parameter estimation of a specific CVS model is not a simple task because it has to be done from hemodynamic variables. Pironet *et al.* [4] consider a seven-parameter model of the CVS and investigated which of these parameters could be uniquely determined using indices derived from measurements of experimental animal data such as arterial and venous pressures and stroke volume. Yu *et al.* [5] make use of an extended Kalman filter estimator for the parameter identification of a lumped element circuit with a time-varying capacitor used to represent the systemic circulation and the left ventricle. This study shows that flow measurements are necessary to estimate the individual model parameters. However, these variables are impossible to obtain in some clinical settings and difficult under any conditions.

Faragallah *et al.* [6], developed a feedback control system to automatically adjust the pump motor current to provide blood flow in response to the level of activity of the patient, which is determined following an inverse problem approach. The results were simulated using a CVS model to reproduce the left ventricle and systemic circulation behavior correctly. The authors used pump flow as the data and estimated the systemic vascular resistance, R_s.

This work presents a method based on inverse problem theory to estimate the parameters of a CVS model using only one hemodynamic variable is used: the systemic arterial pressure (P_s). It is due to the ease of accessing its measure in clinical settings by noninvasive methods. Sensitivity analysis is done to determine the effect of all CVS model parameters on the behavior of $P_s(t)$ and then discard those irrelevant to the parameter estimation problem.

II. Cardiovascular System Model

The CVS model used in this work is based on the one developed by Simaan *et al.* [7]. It consists of a 5th order nonlinear electric circuit (lumped parameter model) capable of reproducing the left atrial pressure, left ventricular pressure, aortic pressure, total flow, and systemic arterial pressure (Fig. 1).

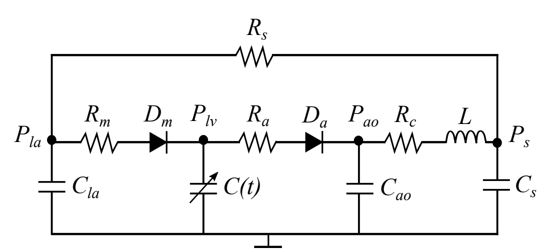

Fig. 1. 5th order nonlinear electric circuit (lumped parameter model) of the CVS.

In this model, the left atrium is represented by the capacitor C_{la}; the mitral valve is represented by both resistor R_m

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and diode D_m; the aortic valve is represented by both resistor R_a and diode D_a; the left ventricle is modeled by the time-varying capacitor $C(t)$; the aortic compliance is represented by the capacitor C_{ao} and the systemic arterial circulation comprising the elements R_c, L, C_s and R_s is modeled using a four-element Windkessel model. All parameters of the CVS model and their associated values are listed in Table I.

TABLE I
PARAMETERS OF THE CVS MODEL.

Resistances (mmHg s/ml)		
R_s	1.0000	Systemic vascular resistance
R_c	0.0398	Characteristic resistance
R_m	0.0050	Mitral valve resistance
R_a	0.0010	Aortic valve resistance
Compliances (ml/mmHg)		
$C(t)$	Time varying	Left ventricular Compliance
C_{ae}	4.4000	Left atrial compliance
C_s	1.3300	Systemic compliance
C_{ao}	0.0800	Aortic compliance
Inertances (mmHg s^2/ml)		
L	0.0005	Inertance of blood in aorta

Simaan *et al.* [7] uses a time-varying elastance function, $E(t)$, for modeling the behavior of the left ventricle. It is calculated as follows:

$$E(t) = (E_{max} - E_{min})E_n(t_n) + E_{min} \tag{1}$$

where the constants E_{max} and E_{min} are related to the ventricular condition. The term $E_n(t_n)$ is a normalized elastance defined as follows:

$$E_n(t_n) = 1.55 \left[\frac{\left(\frac{t_n}{0.7}\right)^{1.9}}{1 + \left(\frac{t_n}{0.7}\right)^{1.9}} \right] \left[\frac{1}{1 + \left(\frac{t_n}{1.17}\right)^{21.9}} \right] \tag{2}$$

where $t_n = t/T_{max}$ is the normalized time, $T_{max} = 0.2 + 0.15t_c$ and t_c is the cardiac cycle, i.e., $t_c = \mathrm{HR}/60$, where HR is the heart rate.

The function $E(t)$ describes the relationship between the ventricular pressure and the ventricular volume and can be defined according to the following expression [8]:

$$E(t) = \frac{P_{lv}(t)}{V_{lv}(t) - V_o} \tag{3}$$

where V_o is an empirical constant over a wide range of intraventricular volume. By using equation (3), and assuming $V_{lv}(t)$ is an available state variable that can be obtained from the state vector, $P_{lv}(t)$ might be calculated as $P_{lv}(t) = E(t)\left[V_{lv}(t) - V_o\right]$ and the use of the derivative of the time-varying capacitor $C(t)$ is avoided. It was made because this term may cause numerical instabilities [9]. The variable $V_{lv}(t)$ is calculated as:

$$\begin{aligned} \dot{V}_{lv}(t) =& Q_m(t) - Q_{ao}(t) \\ =& \frac{D_a}{R_a}P_{ao}(t) - \left[\frac{D_m}{R_m} + \frac{D_a}{R_a}\right]E(t)V_{lv}(t) \\ &+ \frac{D_m}{R_m}P_{lv}(t) + \left[\frac{D_m}{R_m} + \frac{D_a}{R_a}\right]E(t)V_o \end{aligned} \tag{4}$$

where Q_m is the flow from left atrium to left ventricle during the filling phase and $Q_{ao}(t)$ is the flow from left ventricle to aorta during the ejection phase. The new state vector is defined as

$$x(t) = \left[P_{ao}(t), Q_{ao}(t), V_{lv}(t), P_{as}(t), P_{la}(t)\right]^T \tag{5}$$

where $P_{ao}(t)$ is the aortic pressure, $Q_{ao}(t)$ is the total flow through inductance L, $V_{lv}(t)$ is the left ventricular volume, $P_{as}(t)$ is the systemic arterial pressure and $P_{la}(t)$ is the left atrial pressure.

We also adapted the implementation of the heart valve's behavior. Now, the ideal diodes D_a and D_m take values of either 1 if the valve is open; or 0 if the valve is closed. Using basic circuit analysis methods, it is possible to derive five differential equations to describe this CVS model. The matrix equation of the CVS system is given by

$$\dot{x}(t) = A(t)x(t) + B(t) \tag{6}$$

where the matrices $A(t)$ and $B(t)$ are given by

$$A(t) = \begin{bmatrix} \frac{-D_a}{R_a C_{ao}} & \frac{-1}{C_{ao}} & \frac{D_a}{R_a C_{ao}}E(t) & 0 & 0 \\ \frac{1}{L_s} & \frac{-R_c}{L_s} & 0 & \frac{-1}{L_s} & 0 \\ \frac{D_a}{R_a} & 0 & a_{33} & 0 & \frac{D_m}{R_m} \\ 0 & \frac{1}{C_s} & 0 & \frac{-1}{R_s C_s} & \frac{1}{R_s C_s} \\ 0 & 0 & \frac{D_m}{R_m C_{la}}E(t) & \frac{1}{R_s C_{la}} & a_{55} \end{bmatrix} \tag{7}$$

with $a_{33} = -\left[\frac{D_m}{R_m} + \frac{D_a}{R_a}\right]E(t)$, $a_{55} = \frac{-1}{C_{la}}\left[\frac{1}{R_s} + \frac{D_m}{R_m}\right]$ and:

$$B(t) = \begin{bmatrix} \frac{-D_a}{R_a C_{ao}}E(t)V_0 \\ 0 \\ \left[\frac{D_m}{R_m} + \frac{D_a}{R_a}\right]E(t) \\ 0 \\ \frac{-D_a}{R_a C_{ao}}E(t)V_0 \end{bmatrix} \tag{8}$$

III. SENSITIVITY ANALYSIS

For the estimation problem described in this work, the parameters that are regarded as unknown quantities are in vector $\theta = [R_s, R_c, R_m, R_a, C_{la}, C_s, C_{ao}, L_s, E_{max}, E_{min}]$. To evaluate the influence of deviations in all parameters of θ on the $P_s(t)$, the normalized sensitivity was calculated as:

$$S_{\theta_i}^{P_{as}}(t) = \frac{\theta_i}{P_s}\frac{\partial P_s}{\partial \theta_i},\ (i = 1 \ldots, N) \tag{9}$$

where $S_{\theta_i}^{P_{as}}$ is the normalized sensitivity, θ_i is the i-th parameter of θ and N is the order of θ [10]. In this paper, only $P_s(t)$ was analyzed it can be obtained from non-invasive measurements.

The sensitivity analysis was done changing the values of θ in 5% and examining the sensitivity curves corresponding to each parameter of θ during a cardiac cycle of 1 second (Fig. 2). The curves in Fig. 2.(a), $S_{E_{max}}^{P_{as}}$ and $S_{R_s}^{P_{as}}$, are the two higher; and the curves in Fig. 2.(b), $S_{R_m}^{P_{as}}$ and $S_{R_a}^{P_{as}}$, are the two lower, which are referent to the mitral valve and aortic valve resistances respectively. Only these four curves were shown to facilitate this analysis once maximum and minimum values of the other curves are between them.

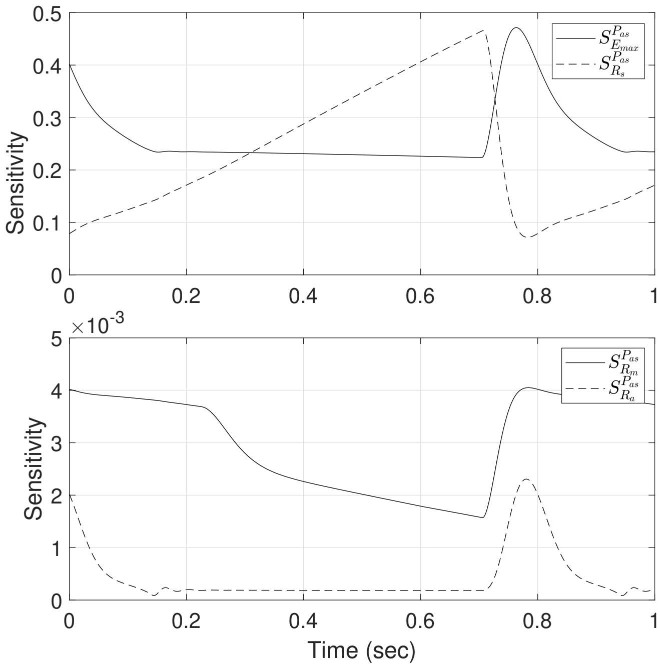

Fig. 2. Sensitivity curves of P_s with respect to variations in the parameters E_{max}, R_s, R_m and R_a.

These results indicate that P_s has a very low sensitivity to the parameter R_a, which means that a little ability to determine this parameter is expected. So, this parameter will not be estimated and its value will be maintained as in the original model [7].

IV. Inverse problem

Different methods have been successfully used in the past to estimate parameters in linear and non-linear inverse problems. For definitions, techniques and algorithms of inverse problems, see [11] and references therein.

As explained in the previous section, the parameter R_a were not included in the estimation process. Therefore, the new vector of parameters is defined as $\theta = [R_s, R_c, R_m, C_{la}, C_s, C_{ao}, L_s, E_{max}, E_{min}]$, where $P_s(\theta)$ is the systemic arterial pressure depending on the values of θ. Thus, the inverse problem here is to determine θ for a specific patient only from his P_s^* in such a way the resulting $\mathcal{F}(\theta)$ is very close to the data of the patient P_s^*. It is a minimization problem that can be formulated as follow:

$$\theta = \min_{\theta} \|P_s^* - \mathcal{F}(\theta)\| \tag{10}$$

subject to:

$$\mathrm{LB}_i \leq \theta_i \leq \mathrm{UP}_i, \text{ for } i = 1, 2, \ldots, N. \tag{11}$$

where $\|\cdot\|$ is a norm, $\mathcal{F}$ is the operator that maps θ to $P_s(\theta)$ using Equation (6) and LB_i and UB_i are the lower and upper bounds for the parameters.

V. Results and Discussions

This section presents an example using synthetic signals to illustrate the model developed in this paper. Firstly, it is supposed the ground truth of parameters is given in Table II. It is important to emphasize that these values are used in this work only as a proof of concept.

TABLE II
The ground truth, initial points, estimated values and relative errors of the parameter estimation

	ground truth	initial points	estimated values	relative errors
R_s	1.20000	1.55313	1.19560	0.00366
R_m	0.00550	0.00593	0.00553	0.00688
R_c	0.03990	0.04905	0.03986	0.00089
C_{la}	4.80000	3.25727	4.85713	0.01190
C_s	1.50000	1.05328	1.50454	0.00302
C_{ao}	0.08500	0.13831	0.08635	0.01596
L_s	0.00055	0.00064	0.00055	0.00626
$E_{\max}$	1.54000	1.16660	1.54456	0.00296
$E_{\min}$	0.06000	0.04573	0.05976	0.00392

The P_s is calculated from Equation (6) by using the 4th order Runge-Kutta method in a fine mesh with a step size equal to 0.00005. Then, Gaussian noise is added, that is:

$$P_s^{\epsilon} = P_s \times (1 + \delta\mathcal{N}(0, 1)) \tag{12}$$

where $\delta = 0.005$ represents some error when the blood pressure is measured.

In order to avoid the inverse crime [12], P_s^{ϵ} is interpolated to a coarser mesh with step size equal to 0.0001. Finally, the inverse problem is solved to estimate the parameters in the coarser mesh using the MATLAB function lsqnonlin with the default 'trust-region-reflective' algorithm [13]. The initial value of each θ_i is randomly chosen between LP_i and UP_i values, as stated in Equation (12). The initial points and the estimated values also can be seen in Table II, as well as the relative errors (RE) that are calculated using the ground truth value, θ_i, and the estimated value, $\hat{\theta}_i$, as follow:

$$\mathrm{RE}_{\theta_i} = \frac{\sqrt{(\theta_i - \hat{\theta}_i)^2}}{\theta_i} \tag{13}$$

The evolution of every parameter during the optimization steps can be seen in Figure 3, showing that all the parameters converge very fast. The evolution of the estimated values of E_{max} and R_s, which are the parameters with the two high sensitivities curves, can be seen in Figures 3.(a) and 3.(b). Although the parameter R_m has the second lower sensitivity curve, it has not the most significant RE, as can be seen in Figure 3.(c). In Figure 3.(d) it is shown the evolution of the parameter C_{ao}, which has the most significant RE.

With the estimated values of all parameters, P_s can be recovered and compared with P_s^{ϵ} that was generated with ground truth values and after polluted with Gaussian noise (Fig. 4). It can be seen that these two arterial pressures are very close with the residual equal to 0.5%.

VI. Conclusion

In this work, an inverse problem approach is applied to estimate the parameters of the CVS model developed by Simaan *et al.* [7] only from data of systemic arterial pressure.

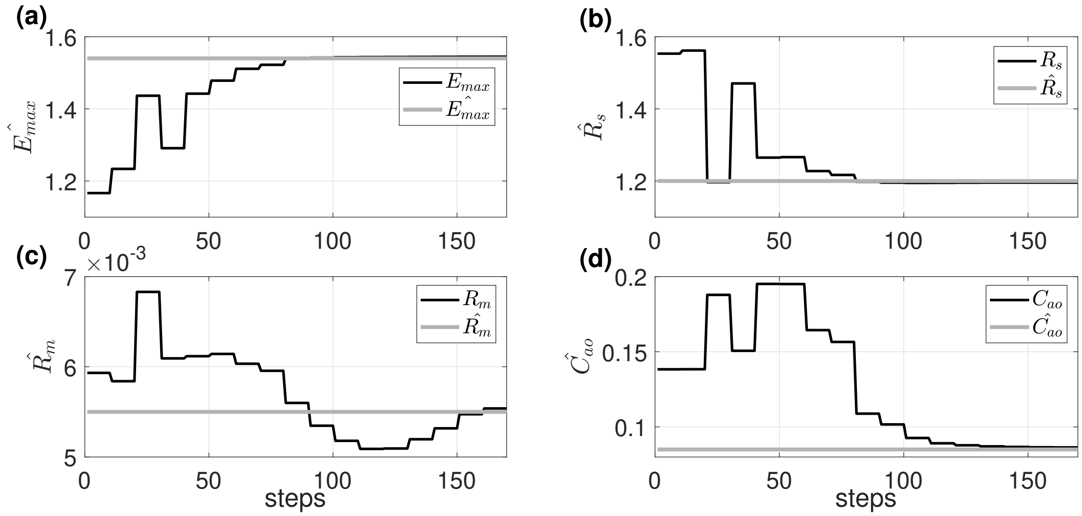

Fig. 3. The estimated (blue) and the ground true (red) values for the parameter C_s.

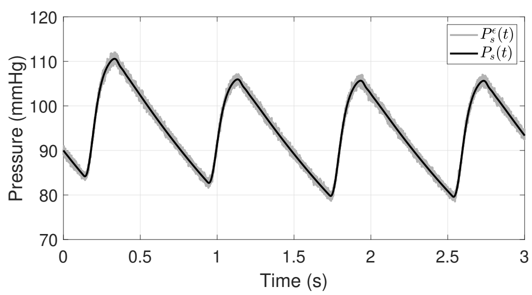

Fig. 4. Comparison between P_s^ϵ, generated with ground truth values, P_s, generated with estimated parameters and polluted with Gaussian noise.

The importance of this approach is to provide a patient-specific cardiovascular model to improve the performance of treatments, such as the tuning of the controllers applied to ventricular assist devices [3].

By solving the optimization problem, nine of ten parameters are estimated and can be used to recover the arterial pressure with a minimum relative error. Although sensitivity analysis has shown that the curve of P_s is little sensitive to parameters R_a and R_m, the RE of C_{ao} was more significant than all others. Thus, other sensitivity analyses must be done to investigate this fact better.

In the optimization problem stated in (11), the search space of each θ_i is reduced by LB_i and UB_i. The values of these bounds are empirically defined, which can generate a stability problem. So, the general stability of the CVS model must be deeply considered to avoid numerical instabilities and non-physiological values for the parameters of vector θ.

In future work, real ECG signals will be used in place of synthetic data as input of this estimation method. Besides, additional hemodynamic variables obtained by non-invasive techniques, such as R-wave amplitude and estimates of cardiac output, will be considered.

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