Model Based Non-invasive Estimation of PV Loop from Echocardiography

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Abstract— **We introduce a model-based approach for the non-invasive estimation of patient specific, left ventricular PV loops. A lumped parameter circulation model is used, composed of the pulmonary venous circulation, left atrium, left ventricle and the systemic circulation. A fully automated parameter estimation framework is introduced for model personalization, composed of two sequential steps: first, a series of parameters are computed directly, and, next, a fully automatic optimization-based calibration method is employed to iteratively estimate the values of the remaining parameters. The proposed methodology is first evaluated for three healthy volunteers: a perfect agreement is obtained between the computed quantities and the clinical measurements. Additionally, for an initial validation of the methodology, we computed the PV loop for a patient with mild aortic valve regurgitation and compared the results against the invasively determined quantities: there is a close agreement between the time-varying LV and aortic pressures, time-varying LV volumes, and PV loops.**

I. Introduction

The left ventricular pressure-volume (PV) loop represents an efficient tool for understanding and characterizing cardiac function. It contains information regarding stroke volume, cardiac output, ejection fraction, myocardial contractility, cardiac oxygen consumption, and other important measures of the heart and the systemic circulation. For example, the extent of ventricular remodeling, the degree of ventricular-arterial mismatching [1], and the left ventricular end-diastolic pressure-volume relationship [2] represent strong predictors of congestive heart failure. Pathologies such as left ventricular hypertrophy, dilated cardiomyopathy, aortic and mitral valve stenosis, and regurgitation [3] are manifested in the PV-loop. Hence, a method for an efficient estimation of the PV loop would represent a powerful diagnostic tool for clinicians. Medical imaging modalities such as MRI, CT, and echocardiography can be used to estimate the time-varying LV volume through the heart cycle in a non-invasive manner, which can then be combined with an invasive measurement of LV pressure to obtain the PV loop [4].

In this paper, we introduce a model-based approach for the non-invasive estimation of left ventricular, patient-specific PV loops: a lumped parameter circulation model is personalized using a two step parameter estimation framework. The input data required for the model personalization are acquired through routine non-invasive clinical measurements and echocardiography.

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In a clinical scenario, the values of the cardiovascular model parameters are not available on a per-patient basis, and different optimization-based approaches were proposed to estimate these parameters, focused mainly on the arterial systemic circulation. A fully automatic calibration method for Windkessel models was suggested [5], where the input was specified by non-invasively acquired systolic/diastolic pressures and, in some cases, additional flow data. In a different approach, Windkessel parameters were estimated using a state-space approach and a least squares method from time-varying pressure and flow rate profiles [6].

II. Methods

A. Lumped Parameter Model

The lumped parameter circulation model employed for the current study is displayed in fig. 1. It comprises three main components: venous pulmonary circulation, the left heart and the systemic circulation. For the venous part of the pulmonary circulation, we use a model composed of a resistance (R_{pulVen}) and compliance (C_{pulVen}):

$$C_{pulVen}\ \frac{dP_{LA}}{\mathrm{dt}} = Q_{C-pulVen}\ , \tag{1}$$

$$Q_{pulVen}\ = Q_{C-pulVen}\ + Q_{LA-in}\ . \tag{2}$$

where the venous pulmonary flow rate (Q_{pulVen}) is considered to be constant in time.

The left heart model has four components: left atrium (LA), mitral valve, left ventricle (LV) and aortic valve. We use a time-varying elastance model for the LA and the LV [7]:

$$P(t) = E(t)\cdot(V(t)-V_0) - R_sQ(t) \tag{3}$$

where E is the time-varying elastance, V is the cavity volume, V_0 is the dead volume of the cavity, and R_s is a source resistance which accounts for the dependence between the flow and the cavity pressure [8] ($R_s = K_sE(t)(V(t)-V_0(t))$, K_s - constant). The cavity volume is equal to:

$$dV/\mathrm{dt} = Q_{in} - Q_{out}\ , \tag{4}$$

where Q_{in} represents the inlet flow rate into the cavity and Q_{out} represents the outlet flow rate from the cavity. The mitral valve and the aortic valve are modeled using a resistance, an inertance and a diode to simulate the closure and the opening of the valve [9]. When the valve is open, the following relationship holds:

$$P_{in} - P_{out} = R_{valve}\cdot Q + L_{valve}\cdot dQ/\mathrm{dt}\ , \tag{5}$$

where P_{in} and P_{out} represent the pressures at the inlet and respectively the outlet of the valve. When the valve is closed, the flow rate through the valve is set to zero. Each valve opens when P_{in} becomes greater than P_{out}, and closes when the flow rate becomes negative. A three-element Windkessel model is used for the systemic circulation, represented by the following relationship between instantaneous flow and pressure:

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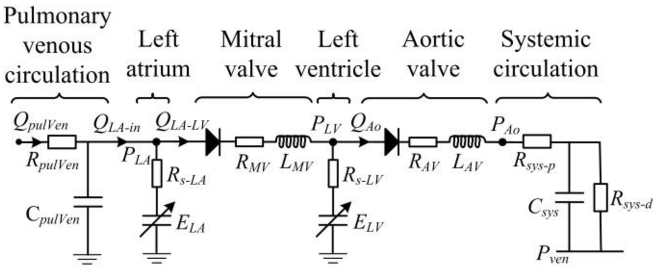

Figure 1. Lumped parameter model representing the venous pulmonary circulation, the left heart and the systemic circulation.

$$\frac{dP_{Ao}}{\mathrm{dt}} = R_{sys-p}\frac{dQ_{Ao}}{\mathrm{dt}} - \frac{P_{Ao} - P_{ven}}{R_{sys-d}\cdot C_{sys}} + \frac{Q_{Ao}\left(R_{sys-p} + R_{sys-d}\right)}{R_{sys-d}\cdot C_{sys}}, \quad (6)$$

where $R_{sys\text{-}p}$ and $R_{sys\text{-}d}$ are the proximal and distal resistances respectively, C_{sys} is the compliance, and P_{ven} is the venous pressure. A total of nine equations are obtained, which are solved implicitly using the forward Euler time integration scheme.

B. Parameter Estimation Framework

To compute patient-specific left ventricular PV loops using the lumped parameter model, the parameters of the model are personalized. The model personalization framework consists of two sequential steps. First, a series of parameters are computed directly, and next, a fully automatic optimization-based calibration method is employed to estimate the values of the remaining parameters, ensuring that the personalized computations match the measurements. Table I lists the patient-specific input parameters used in the current study, together with their source. Figure 2 displays an image acquired through echocardiography, illustrating the steps required for extracting the last two quantities from table I.

During the first step of the parameter estimation framework, the mean arterial pressure (MAP) is determined:

$$MAP = DBP + \left[1/3 + \left(HR \cdot 0.0012\right)\right]\cdot\left(SBP - DBP\right) \quad (7)$$

Then, the end-systolic volume is computed:

$$ESV = EDV \cdot \left(1 - EF\right)/100 \ . \quad (8)$$

Next, the stroke volume is determined:

$$SV = EDV - ESV \ , \quad (9)$$

and the average aortic flow rate is computed:

$$\overline{Q_{Ao}} = SV \cdot 60/HR \ . \quad (10)$$

Finally, the total systemic resistance, as well as the proximal and distal components, are determined:

$$R_{sys-t} = \left(MAP - P_v\right)/\overline{Q_{Ao}}\,, \qquad R_{sys-p} = \rho\cdot R_{sys-t};\quad R_{sys-d} = \left(1-\rho\right)\cdot R_{sys-t}\,, \quad (11)$$

where ρ is the proximal resistance fraction. Since the lumped model is used for a pulsatile steady-state computation, the average inlet flow rate (Q_{pulVen}) is equal to the average outlet flow rate, given by (10). Hence:

$$Q_{pulVen} = \overline{Q_{Ao}} \ . \quad (12)$$

TABLE I. LIST OF PATIENT-SPECIFIC INPUT PARAMETERS.

Input	**Source**
Systolic blood pressure (*SBP*)	Cuff measurement (arms)
Diastolic blood pressure (*DBP*)	Cuff measurement (arms)
Heart Rate (*HR*)	Routine measurement
Ejection fraction (*EF*)	Echocardiography
End-diastolic volume (*EDV*)	Echocardiography

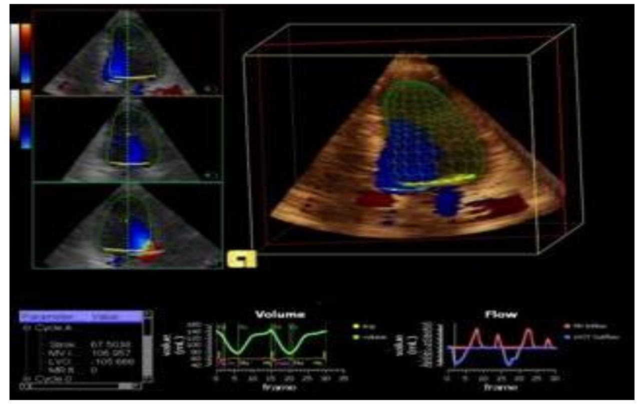

Figure 2. Image acquired through echocardiography illustrating the steps required to extract the end-diastolic volume and the ejection fraction.

The normalized elastance curve is used for the left ventricle model [7], which is denormalized using the minimum and maximum elastance values, and the time at which the maximum elastance is reached. The minimum elastance value is set to 0.08 mmHg/ml, and the time at which the maximum elastance of the left ventricle is reached is computed using $t_{max} = 0.16\cdot T + 0.17$, where T is the period. The maximum elastance value is estimated as described further down. A two-hill function is used to determine the elastance curve for the left atrium, whereas the minimum elastance is set to 0.08 mmHg/ml, the maximum elastance is set to 0.17 mmHg/ml, and the onset of the contraction is set at $0.85T$ [9].

During the second step of the parameter estimation framework, an optimization-based calibration method is employed to estimate the maximum elastance of the left ventricle model, $E_{max\text{-}LV}$, the dead volume of the left ventricle, $V_{0\text{-}LV}$, and the compliance of the systemic Windkessel model, C_{sys}.

The parameter estimation problem is formulated as a numerical optimization problem, the goal of which is to find a set of parameter values for which a set of objectives are met. Since the number of parameters to be estimated is set equal to the number of objectives, the parameter estimation problem becomes a problem of finding the root for a system of nonlinear equations. To solve the system of equations, we use the dogleg trust region method [10]. The objectives of the parameter estimation method are formulated based on the systolic and diastolic pressures, and the ejection fraction, leading to the system of nonlinear equations:

$$\boldsymbol{r}\begin{pmatrix} E_{max-LV} \\ V_{0-LV} \\ C_{sys} \end{pmatrix} = \begin{Bmatrix} \left(SBP\right)_{comp} - \left(SBP\right)_{ref} \\ \left(DBP\right)_{comp} - \left(DBP\right)_{ref} \\ \left(EF\right)_{comp} - \left(EF\right)_{ref} \end{Bmatrix} = \begin{Bmatrix} 0 \\ 0 \\ 0 \end{Bmatrix}, \quad (13)$$

where, $\boldsymbol{r}(\boldsymbol{x})$ is a vector function, called in the following objective function, and $\boldsymbol{x}$ is the vector of the unknowns, i.e. the parameters to be estimated. Each component of the objective function is formulated as the difference between the computed value of a quantity – $(\bullet)_{comp}$ (determined using the lumped parameter model) and its reference value – $(\bullet)_{ref}$ (determined through measurement). To evaluate the objective function for a given set of parameter values, the lumped parameter model is run exactly once.

An outline of the parameter estimation method is illustrated in fig. 3. First, a grid of physiological parameter value sets is considered, and the initial solution, $\boldsymbol{x}_0$, is chosen as the parameter value set leading to the smallest L_2 norm for the objective function $\boldsymbol{r}(\boldsymbol{x})$. Since the lumped parameter model has a small computational time, the Jacobian matrix required to compute the step size at each iteration of the optimization method is estimated using finite differences. The finite differences of the parameters, to be used for

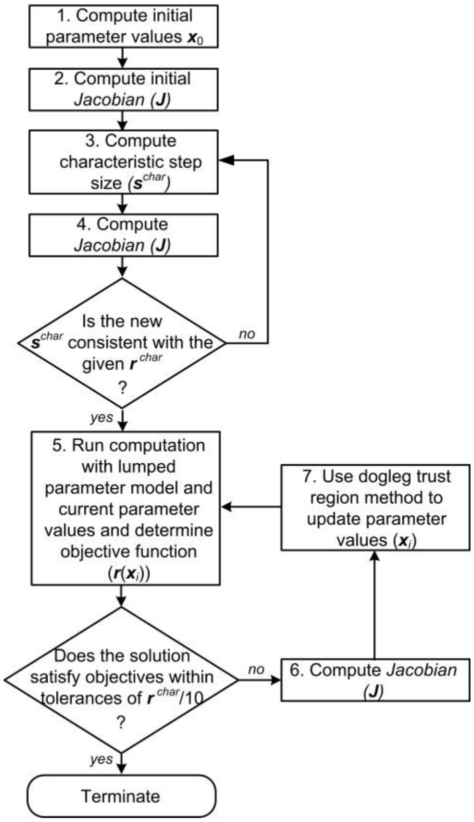

Figure 3. Parameter calibration method.

the computation of the Jacobian, are called in the following characteristic step sizes, s_j^{char} . To determine the characteristic step sizes, we choose a set of characteristic values for the objective function, r_i^{char} , and apply a fixed point iteration method. The fixed point iteration method consists of two sequential steps. First, the characteristic step size values are computed:

$$s_j^{char} = 1 \Big/ \sqrt{\sum_{i=1}^{n_{eq}} \left(J_{ij} \Big/ r_i^{char} \right)} . \tag{14}$$

Next, the Jacobian matrix is computed:

$$J_{ij} = \frac{1}{s_j^{char}} \left[\boldsymbol{r}\left(\boldsymbol{x}_0 + \frac{1}{2} s_j^{char} \boldsymbol{d}_j \right) - \boldsymbol{r}\left(\boldsymbol{x}_0 - \frac{1}{2} s_j^{char} \boldsymbol{d}_j \right) \right] \cdot \boldsymbol{d}_i \,, \tag{15}$$

where $\boldsymbol{d}_i$ and $\boldsymbol{d}_j$ represent the unit vectors in the ith and jth direction. These two steps are iterated until the characteristic step size is consistent with the chosen characteristic objective function. Next, the lumped parameter model is run using the current parameter value set and the objective function is evaluated. Each computation, with a given set of parameter values, is run until the L_2 norms of the normalized differences between the aortic pressure and flow rate profiles at the current and the previous cardiac cycle are smaller than 10^{-5}. If all objective function values are smaller than the tolerance limit ($r_i^{char}/10$), the calibration method is terminated. Otherwise, the Jacobian matrix is recomputed and the parameter values are updated. The characteristic values for the pressure and ejection fraction objectives were set to 1 mmHg and 0.005 respectively. When applying the dogleg trust region method, the parameters and the objective function components are scaled using the previously determined characteristic values. Although the patient-specific values of the end-diastolic and end-systolic volumes are neither used directly as parameters of the lumped model nor tuned, they are automatically matched. This can be motivated as follows: the outlet flow rate of the model is imposed through the inlet pulmonary venous flow rate (equation (12)), and since HR is imposed for the left atrium and ventricle models, the patient-specific stroke volume SV is matched (equation (10)). In the system of equations composed of (8) and (9), SV is matched, and EF is matched as a result of running the calibration method. Hence, only two unknowns are remaining (EDV and ESV), leading to a unique solution of the system.

III. RESULTS

To evaluate the performance of the proposed methodology for the non-invasive estimation of left ventricular PV loops, next we present results for three healthy volunteers. Systolic and diastolic pressure values were acquired using cuff-based measurements and the ejection fraction and end diastolic volumes were estimated from the echocardiography performed at rest state in a horizontal position using the Siemens ACUSON SC 2000 ultrasound system. The values of the parameters which are not estimated through the methodology described in the previous section were set as follows, based on literature data [9], [11]: R_{AV} = 25.0 g/(cm^4·s), L_{AV} = 0.5 cm^2/s, R_{MV} = 20.0 g/(cm^4·s), L_{MV} = 0.5 cm2/s, R_{pulVen} = 30.0 g/(cm^4·s), C_{pulVen} = 0.5 (cm^4·s^2)/g, ρ = 0.09, P_{ven} = 5.0 mmHg, $V_{0\text{-}LA}$ = 3 ml, $K_{s\text{-}LA}$ = 10·10-9 s/ml, and $K_{s\text{-}LV}$ = 4·10-9 s/ml.

Table II lists the input parameters for the three healthy volunteers, and the output parameters obtained after applying the parameter estimation framework. The output parameter values are in the physiological range reported in literature [3]. The computed time-varying pressure profiles and PV loops are displayed in fig. 4: left - aortic systolic and diastolic pressures, as well as the heart rate are matched exactly, right – end-diastolic volume and the ejection fraction, from table II, are exactly matched.

Additionally, to perform an initial validation of the methodology, we computed the PV loop for a patient with mild aortic valve regurgitation and compared the results against the invasively determined quantities. Fig. 5 displays a comparison between model-based computed results and invasively performed measurements. The input data used for the parameter estimation framework were extracted from the invasive measurements as follows: SBP was the maximum aortic pressure (181.5 mmHg), DBP was the minimum aortic pressure (89.7 mmHg), EDV was the maximum LV volume (196.68 ml), EF (53.1 %) was computed from EDV and ESV, determined as minimum LV volume (92.26 ml), and HR was determined from the period of the time-varying pressure (47 bpm). All these values are matched exactly for the output parameter values: $E_{max\text{-}LV}$ = 0.968 mmHg/ml, $V_{0\text{-}LV}$ = -88.71 ml, C_{sys} = 1.065·10^{-3} cm^4·s^2/g. There is a close agreement between the time-varying LV and aortic pressures, time-varying LV volumes, and PV loops. Moreover, the four phases of the cardiac cycle can be clearly identified in the computed results (fig. 5a and fig. 5b): 1: isovolumetric contraction phase, 2: ventricular ejection phase, 3: isovolumetric relaxation phase, and 4: ventricular filling phase. The mild aortic valve regurgitation can be observed in the PV loop in fig. 5c, where the line corresponding to the isovolumetric relaxation has a slight curvature, and in fig. 5b,

TABLE II. INPUT AND OUTPUT PARAMETER VALUES FOR THREE HEALTHY VOLUNTEERS.

Parameter	Volunt. 1	Volunt. 2	Volunt. 3
SBP [mmHg]	120	117	117
DBP [mmHg]	70	65	67
HR [bpm]	86	61	90
EF	70 %	69 %	61 %
EDV [ml]	108	108	78
$E_{max\text{-}LV}$ [mmHg/ml]	3.30	2.40	1.52
$V_{0\text{-}LV}$ [ml]	2.18	4.33	-43.41
C_{sys} [cm^4·s^2/g]	1.383·10^{-3}	1.930·10^{-3}	0.749·10^{-3}

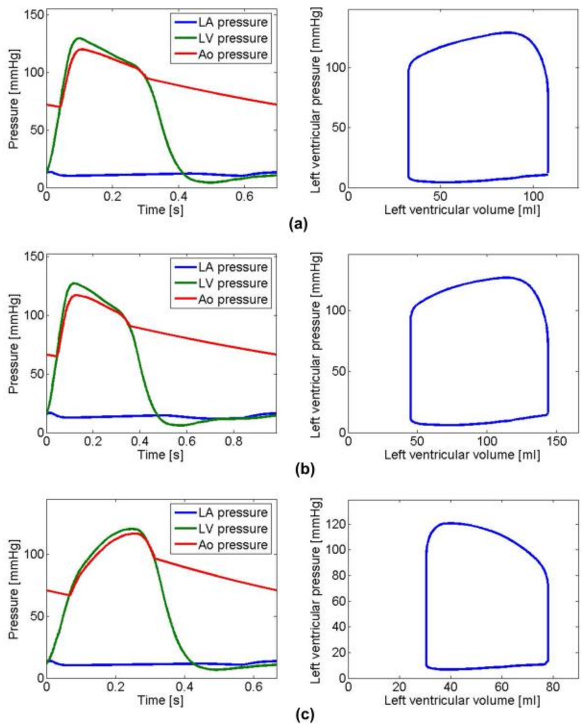

Figure 4. Computed time-varying LA pressure, LV pressure and aortic pressure (left side) and PV loops for (a) volunteer 1, (b) volunteer 2, and (c) volunteer 3.

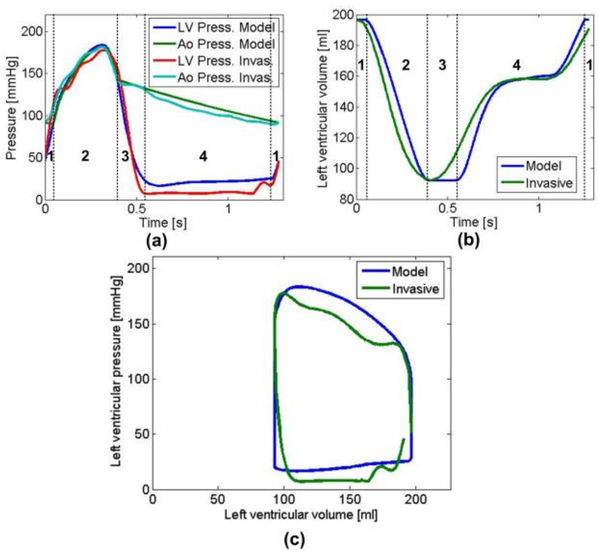

Figure 5. Comparison of model-based computation against invasive measurements, for (a) time-varying left ventricular and aortic pressures, (b) time-varying left ventricular volume, and (c) PV loop.

during the second part of phase 3, where the LV volume increases slightly. The average execution time for the four volunteers/patients was of 28.9 seconds on a standard Intel i7 CPU core with 3.4 GHz.

IV. Discussion and Conclusions

We have introduced a fully automated, non-invasive model-based method for the estimation of patient-specific left ventricular PV loops. Initial results demonstrate that the proposed parameter estimation framework ensures a perfect agreement between the computed quantities and the clinical measurements. The lumped parameter model used in the current study has been designed specifically for the estimation of the left ventricular PV loop: it leads to fast computation times, and it enables the accurate computation of the main quantities required for the PV loop (time-varying LV pressure and volume). Although the current study used LV volume information acquired through echocardiography, the proposed method can be applied, without any restriction, along with other medical imaging techniques which can provide similar data: magnetic resonance, computer tomography.

The current study has a series of limitations. First, *SBP* and *DBP* for the three volunteers were acquired through cuff-based measurements, which do not exactly represent the aortic systolic and diastolic values. Secondly, the lumped parameter model in fig. 1 is designed for the estimation of the PV loop of healthy subjects. Future work will focus in the implementation of different mitral/aortic valve models, capable of modeling valve stenosis/regurgitation.

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