Mathematical Modelling of the Cardiovascular System Haemodynamics

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Abstract. In this paper we propose a model of the cardiovascular system, where stressed blood volume is a model parameter instead of an initial condition. Stressed blood volume (SBV) is an important indicator of fluid responsiveness, i.e., this term can help to classify patients between responders and non-responders to fluid therapy. We study a six compartment model, then using the conservation of total blood volume, one differential equation of the original model is omitted and a new model is obtained. Comparing the haemodynamic signals of the previous model and the new version, we show that the simulations are qualitatively similar. One important difference with the original model is that the initial conditions for solving the proposed model are arbitrary. This allows us to perform a sensitivity analysis using automatic differentiation of the reduced model for all model parameters without excluding any parameter a priori, unlike the authors of the original formulation have done. This analysis showed that two parameters, the heart period and the stressed blood volume, have a major effect on the performance of the model.

Keywords: Cardiovascular System, Mathematical Model, Sensitivity Analysis.

1 Introduction

In this study, a cardiovascular model of five differential equations is presented, which is a reduced proposal based on the closed-loop model of Pironet *et al.* Due to the complex circulatory interactions, the model-based method and the mathematical descriptions of the system has been used for monitoring and analyzing haemodynamic signals. Some applications of this kind of models are teaching quantitative physiology [8], simulating cardiovascular adaptation to orthostatic stress [7] and computing stressed blood volume [12].

The model proposed by Defares *et al.* is one of the first models that introduce the electrical circuit components representation of the heart haemodynamic. The cardiovascular system in the model consists of the two ventricles connected by the systemic and pulmonary circulations. From the electrical representation of the model, the authors developed an electrical circuit analogue computer for simulating haemodynamics in real-time [2]. Furthermore, the development of cardiovascular simulators like CVSim software has been based on this model [8].

Smith *et al.* developed a minimal model of the cardiovascular system, which includes the direct ventricular interaction through modelling of the septum and the pericardium [14]. This model-based method has been validated against animal data and the subject-specific parameters can be identified by using data obtained from measurements typically available in the intensive care unit [13]. The sixteen model parameters are stressed volume, six resistances, six elastances, the cardiac period and two values for the width of the Gaussian functions which appear in the definition of the ventricles.

Considering the above model without the direct ventricular interaction and using data of pigs, Pironet *et al.* have computed the stressed blood volume, which is an important determiner of "fluid responsiveness", i.e., this term can help to classify patients between responders and non-responders to fluid therapy [12]. In fact, Maas *et al.* have proved that in humans the capacity to improve cardiac output in response to infuse fluids and the stressed blood volume are inversely proportional under the assumption of circulatory arrest on the forearm [10].

Unlike this experimental work, Pironet et al. have solved a parameter identification problem for eleven of the sixteen parameters because the cardiac period, the elastance of the two ventricles and the two parameters of the width have been excluded. This problem consists in determining the parameters for which the measure of error between the model output and a corresponding set of observations is minimized. The solution of it relies on the following three steps procedure. First, are nominal values assigned to the model parameters. Second, are some parameters selected by performing a sensitive analysis on the error vector, which is associated to the parameter vector. Third, are the most sensitive parameters identified by solving a minimum norm problem with an iterative algorithm. Based on this procedure, the authors have found that stressed volume is one of the parameters to which the error vector is the most sensitive and have assigned an optimized value to it.

The aim of this study was to propose a model of the entire circulation assuming supine position based on the model of Pironet *et al.* to evaluate the relative importance of the model parameters on the performance of the model without excluding any parameter. The method used was carrying out a first order sensitivity analysis around a nominal point of the parameters, which implies to differentiate the set of state equations with respect to the vector of parameters, and to assume that the vector of input variables does not depend on the parameters. This assumption it is not accomplished by the original formulation of Pironet *et al.*, in order to avoid this, it is proposed reducing the number of differential equations by one using that there is a conserved quantity of stressed blood volume.

The paper is organized as follows: In section 2 a basic framework to the physics of cardiovascular circulation is presented. Section 3 contains a brief summary of the basic concepts for developing lumped models and the demonstration that the model of Defares *et al.* and Pironet *et al.* are equivalent. In section 4 the proposed reduction of the model of Pironet *et al.* and the sensitivity analysis of this model is presented.

2 Physics of the Cardiovascular System

The cardiovascular system is defined as a set composed of the heart, blood vessels (arteries, veins and capillaries) and blood. The set of structural and functional relations, which are established between these components, are integrated to the system to accomplish the blood circulation [6].

From a mechanical point of view, each half of the heart is composed of an atrium and a ventricle acting like a pulsatile pump coupled to the another one: the “right heart” which drives desoxygenated blood to the lungs and the “left heart” that propels oxygenated blood to all tissues of the body. In this sense, two circulations are distinguished: the *systemic circulation* and the *pulmonary circulation*. There are four heart valves which open and close to ensure a one-way flow through the heart. When the difference of pressure is positive, the valves are opened to allow the flux of blood. However, when the difference of pressure is negative, they are closed to avoid flux of blood from leaking backwards.

In haemodynamics, two important issues are the definition of the compliance chamber and the resistance vessel. The compliance chamber is considered a compartment with elastic walls, in which no opposition to blood flow is found. On the other hand, the resistance vessel compartment determines the resistance of blood flow through the “tube” . Both concepts can be defined as follows.

Definition 1. *The compliance (C) of an elastic chamber, inverse term of elastance (E), is the relation between the volume of the compartment (V) with respect to the pressure in it (P), given by the equation:*

$$V = CP + V_u = E^{-1}P + V_u, \tag{1}$$

where V_u is the unstressed volume of the chamber.

Definition 2. *The vascular resistance (R) against blood flow is defined as a relation between the pressure gradient (ΔP) and the total flux of a fluid (Q), given by the equation:*

$$Q = \frac{\Delta P}{R}, \tag{2}$$

where ΔP denotes the pressure difference of the adjacent compartments.

There are two blood volumes in which the total volume within the blood vessels can be divided. Up to 75% of the blood can be considered as unstressed volume (V_u). V_u denotes the blood which is contained in the vasculature at zero transmural pressure, i.e., the blood which does not create stress across the vessel walls because it is only filling out its natural shape. Due to the elastic properties of the blood vessels, it is possible to add more volume, this extra volume is referred as stressed volume (V_s) since it is responsible of stretching the walls and creating a distending pressure. Using the fact, that the total blood volume in a compliance vessel is the same as the sum of unstressed volume and stressed volume in it, i.e., $V_S = V - V_U$, it is possible to re-write (1) in terms of stressed volume as it follows

$$P = \frac{1}{C} V_s = E V_s. \tag{3}$$

3 Mathematical Models of the Cardiovascular System

In this section, it is given the derivation of the equations governing the closed lumped models of Defares *et al.* and Pironet *et al.* Based on the analogies between hydraulic parameters and electrical parameters that associate pressure with voltage, volume with charge, flow with current, compliance with capacitance and vascular resistance with resistance. It is possible to represent both models as the circuit with six capacitors, six resistors and four diodes. A schematic diagram of these models is given in Figure 1. The capacitors denote the properties of compliance of systemic arteries (C_{sa}), systemic veins (C_{sv}), pulmonary arteries (C_{pa}), pulmonary veins (C_{pv}), left ventricle (C_{lv}) and right ventricle (C_{rv}). The resistors R_s and R_p are associated to the flow resistance in the systemic capillaries and pulmonary capillaries, respectively. For mimicking the heart valves, four combinations of diode-resistor are considered. Then, $R_{ao} - D_{ao}$, $R_{mi} - D_{mi}$, $R_{pu} - D_{pu}$ and $R_{tr} - D_{tr}$ represent the aortic valve, mitral valve, pulmonary valve and tricuspid valve, respectively.

For simplicity, it is assume that compliance of arteries and veins of both circulations and all the vascular resistances are constants throughout their respective compartment. On the other hand, both ventricles are considered as time-varying capacitors [16], which means that the elastance of the left ventricle, $E_{lv} : [0, \infty) \to \mathbb{R}$, and the elastance of the right ventricle, $E_{rv} : [0, \infty) \to \mathbb{R}$, are invertible functions of class C^1, which mimic the ratio of intra-ventricular pressure and intra-ventricular volume in the respective compartment.

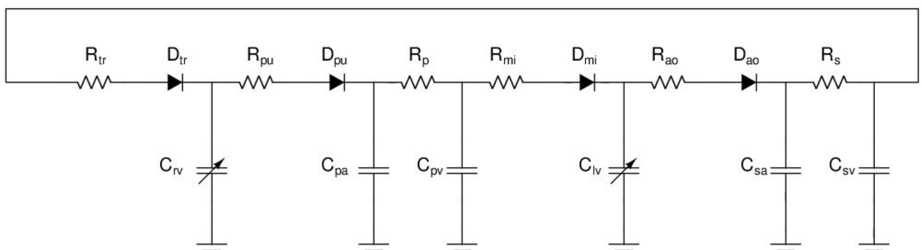

Fig. 1. Electrical analog for the cardiovascular system. Notice that $C_{lv} = E_{lv}^{-1}$ and $C_{rv} = E_{rv}^{-1}$

A first approach in studying the volume and the pressure in different compartments of the cardiovascular system considers models without control mechanisms, which means that the regulation of human blood pressure is neglected [12, 4, 14, 11, 15]. These kind of models usually assume that the function of elastance used to model ventricle muscle activation is a $T-$periodic function, where T denotes the heart period . In particular, the elastance functions (E_k, $k = \{lv, rv\}$) given by Smith *et al.* are considered for this work [14]. E_k is defined as:

$$E_k(t) = E_{max,k} \exp\left[-W_k \left(t \bmod T - \frac{T}{2}\right)^2\right]$$

$E_{max,lv}$ and $E_{max,rv}$ denote the end-systolic elastance of the left and right ventricle, respectively.

In order to get the model of Defares *et al.*, which is originally given for the state vector $\mathtt{p} = [P_{lv}, P_{sa}, P_{sv}, P_{rv}, P_{pa}, P_{pv}]$. It is necessary to apply the Kirchhoff's laws to the circuit shown in Figure 1. Then, substituting the following equations.

$$\begin{aligned}
Q_i &= R_i^{-1} \Delta P_i,\ i = \{mi, ao, s, tr, pu, p\} \\
Q_j &= C_j \dot{P}_j,\ j \in \{sa, sv, pa, pv\} \\
Q_k &= E_k^{-1}(\dot{P}_k - \dot{E}_k V_{s,k}),\ k \in \{lv, rv\} \\
P_k &= E_k(t) V_{s,k},\ k \in \{lv, rv\}.
\end{aligned}$$

It is gotten that the state equations for the model of Defares *et al.* are

$$\begin{aligned}
\dot{P}_{lv} &= E_{lv}\left(\frac{P_{pv} - P_{lv}}{R_{mi}} H(Q_{mi}) - \frac{P_{lv} - P_{sa}}{R_{ao}} H(Q_{ao})\right) + \frac{\dot{E}_{lv}}{E_{lv}} P_{lv}, \\
\dot{P}_{sa} &= \frac{1}{C_{sa}}\left(\frac{P_{lv} - P_{sa}}{R_{ao}} H(Q_{ao}) - \frac{P_{sa} - P_{sv}}{R_s}\right), \\
\dot{P}_{sv} &= \frac{1}{C_{sv}}\left(\frac{P_{sa} - P_{sv}}{R_s} - \frac{P_{sv} - P_{rv}}{R_{tr}} H(Q_{tr})\right), \\
\dot{P}_{rv} &= E_{rv}\left(\frac{P_{sv} - P_{rv}}{R_{tr}} H(Q_{tr}) - \frac{P_{rv} - P_{pa}}{R_{pu}} H(Q_{pu})\right) + \frac{\dot{E}_{rv}}{E_{rv}} P_{rv}, \\
\dot{P}_{pa} &= \frac{1}{C_{pa}}\left(\frac{P_{rv} - P_{pa}}{R_{pu}} H(Q_{pu}) - \frac{P_{pa} - P_{pv}}{R_p}\right), \\
\dot{P}_{pv} &= \frac{1}{C_{pv}}\left(\frac{P_{pa} - P_{pv}}{R_p} - \frac{P_{pv} - P_{lv}}{R_{mi}} H(Q_{mi})\right).
\end{aligned}$$

$H(t)$ is the standard Heaviside step function defined by $H(t) = 0$ for $t \leq 0$ and $H(t) = 1$ for $t > 0$, which reflects the fact that if a diode D_i is in the OFF state then the resistance in the respective compartment R_i is infinite, with $i \in \{ao, mi, pu, tr\}$. Therefore, the blood flow in the compartment is zero, i.e., $Q_i = 0$ and $H(Q_i) = 0$. Also, the fact that if a diode D_i is in the ON state then blood flow in the compartment is positive and $H(Q_i) = 1$.

Since E_{lv} and E_{rv} depends only of the time. Then, the model of Defares *et al.* can be written as the following linear system

$$\dot{\mathtt{p}} = A_D(t)\mathtt{p} \tag{4}$$

where A_D is the coefficient matrix. There is a theorem of Liapunov [1892] which affirms that the equation $\mathtt{p} = M(t)\mathtt{y}$, where M is an invertible matrix of functions of class C^1, transforms the system (4) to $\dot{\mathtt{y}} = B(t)\mathtt{y}$, where B is a periodic coefficient matrix whose characteristic multipliers coincide with those of (4). The proof of this theorem is given in [3], Th. 2.2.7. According to the above remark, the transformation $\mathtt{p} = M(t)\mathtt{v}$, where $\mathtt{v}$ are the state variables $\mathtt{v} = [V_{s,lv}\ V_{s,sa}\ V_{s,sv}\ V_{s,rv}\ V_{s,pa}\ V_{s,pv}]$ and the matrix M is defined as $M = diag(E_{lv},\ E_{sa}, E_{sv}, E_{rv}, E_{pa}, E_{pv})$, carries the model of Defares *et al.* into the model considered by Pironet *et al.*, which is given by

$$\dot{\mathtt{v}} = A_P(t)\mathtt{v}, \tag{5}$$

where A_P is equal to $M_P^{-1}(A_D M_P - \dot{M}_P)$. Since the elastance functions E_{lv} and E_{rv} are T-periodic functions. Then both systems have the same characteristic multipliers. It is worth pointing out that the set of characteristic multipliers determine the behavior of the solutions, the existence of a periodic solution and the stability of the system.

4 Reduced Cardiovascular Model

Pironet *et al.* note that the vector of initial conditions for solving (5) must satisfy that the sum of its entries is equal to the total stressed blood volume, denoted by SBV. Then, the complete model of Pironet *et al.* is given by

$$\begin{aligned}
\dot{V}_{s,lv} =& - E_{lv}V_{s,lv}\left(\frac{H(Q_{mi})}{R_{mi}} + \frac{H(Q_{ao})}{R_{ao}}\right) + V_{s,sa}\frac{H(Q_{ao})}{R_{ao}C_{sa}} + V_{s,pv}\frac{H(Q_{mi})}{R_{mi}C_{pv}},\\
\dot{V}_{s,sa} =& E_{lv}V_{s,lv}\frac{H(Q_{ao})}{R_{ao}} - \frac{V_{s,sa}}{C_{sa}}\left(\frac{H(Q_{ao})}{R_{ao}} + \frac{1}{R_s}\right) + \frac{V_{s,sv}}{C_{sv}R_s},\\
\dot{V}_{s,sv} =& \frac{V_{s,sa}}{C_{sa}R_s} - \frac{V_{s,sv}}{C_{sv}}\left(\frac{1}{R_s} + \frac{H(Q_{tr})}{R_{tr}}\right) + E_{rv}V_{s,rv}\frac{H(Q_{tr})}{R_{tr}},\\
V_{s,rv} =& V_{s,sv}\frac{H(Q_{tr})}{R_{tr}C_{sv}} - E_{rv}V_{s,rv}\left(\frac{H(Q_{tr})}{R_{tr}} + \frac{H(Q_{pu})}{R_{pu}}\right) + V_{s,pa}\frac{H(Q_{pu})}{R_{pu}C_{pa}},\\
\dot{V}_{s,pa} =& E_{rv}V_{s,rv}\frac{H(Q_{pu})}{R_{pu}} - \frac{V_{s,pa}}{C_{pa}}\left(\frac{H(Q_{pu})}{R_{pu}} + \frac{1}{R_p}\right) + \frac{V_{s,pv}}{C_{pv}R_p},\\
\dot{V}_{s,pv} =& E_{lv}V_{s,lv}\frac{H(Q_{mi})}{R_{mi}} + \frac{V_{s,pa}}{C_{pa}R_p} - \frac{V_{s,pv}}{C_{pv}}\left(\frac{1}{R_p} + \frac{H(Q_{mi})}{R_{mi}}\right),\\
SBV =& V_{s,lv}(0) + V_{s,sa}(0) + V_{s,sv}(0) + V_{s,rv}(0) + V_{s,pa}(0) + V_{s,pv}(0).
\end{aligned}$$

So the initial conditions of this model depend on the stressed blood volume. In order to get a formulation of this model in which initial conditions are arbitrary and stressed blood volume appears in the differential equations, it is important to notice that in normal conditions a constant quantity of blood (V_T) is contained in the human circulatory system. Then, assuming that V_T is known, it is feasible to compute the stressed blood volume in the systemic venous circulation $V_{s,sv}$ in terms of the other state variables. Hence,

$$V_{s,sv} = V_T - V_u - V_{s,lv} - V_{s,rv} - V_{s,sa} - V_{s,pa} - V_{s,pv} \tag{6}$$

where $V_u = V_{u,sa} + V_{u,sv} + V_{u,pa} + V_{u,pv} + V_{u,lv} + V_{u,rv}$. Finally, omitting the differential equation of $V_{s,sv}$ and substituting (6) in the remaining equations of complete model of Pironet *et al.* it is gotten the simplification of this model,

$$\begin{aligned}
\dot{V}_{s,lv} =& - E_{lv} V_{s,lv} \left(\frac{H(Q_{mi})}{R_{mi}} + \frac{H(Q_{ao})}{R_{ao}} \right) + V_{s,sa} \frac{H(Q_{ao})}{R_{ao} C_{sa}} + V_{s,pv} \frac{H(Q_{mi})}{R_{mi} C_{pv}}, \\
\dot{V}_{s,sa} =& V_{s,lv} \left(E_{lv} \frac{H(Q_{ao})}{R_{ao}} - \frac{1}{C_{sv} R_s} \right) - V_{s,sa} \left(\frac{H(Q_{ao})}{C_{sa} R_{ao}} + \frac{1}{C_{sa} R_s} + \frac{1}{C_{sv} R_s} \right), \\
& + \frac{1}{C_{sv} R_s} \left(SBV - V_{s,rv} - V_{s,pa} - V_{s,pv} \right), \\
\dot{V}_{s,rv} =& - V_{s,rv} \left(\frac{E_{rv} H(Q_{tr})}{R_{tr}} + \frac{E_{rv} H(Q_{pu})}{R_{pu}} + \frac{H(Q_{tr})}{R_{tr} C_{sv}} \right) + V_{s,pa} \left(\frac{H(Q_{pu})}{R_{pu} C_{pa}} \right. \\
& \left. - \frac{H(Q_{tr})}{R_{tr} C_{sv}} \right) + \frac{H(Q_{tr})}{R_{tr} C_{sv}} \left(SBV - V_{s,lv} - V_{s,sa} - V_{s,pv} \right), \\
\dot{V}_{s,pa} =& E_{rv} V_{s,rv} \frac{H(Q_{pu})}{R_{pu}} - \frac{V_{s,pa}}{C_{pa}} \left(\frac{H(Q_{pu})}{R_{pu}} + \frac{1}{R_p} \right) + \frac{V_{s,pv}}{C_{pv} R_p}, \\
\dot{V}_{s,pv} =& E_{lv} V_{s,lv} \frac{H(Q_{mi})}{R_{mi}} + \frac{V_{s,pa}}{C_{pa} R_p} - \frac{V_{s,pv}}{C_{pv}} \left(\frac{1}{R_p} + \frac{H(Q_{mi})}{R_{mi}} \right).
\end{aligned}$$

4.1 Sensitivity Analysis

The sensitivity functions let to study the influence of a model parameter onto the model output. However, these functions are not dimensionless quantities, reason why it is difficult to compare the sensitivity for different parameters. To avoid this, relative sensitivity is considered.

The reduced mathematical model can be re-written as

$$\frac{dx(t)}{dt} = f(t, x(t, \mathbf{p}), \mathbf{p})$$

where $x = [V_{s,lv}, V_{s,sa}, V_{s,rv}, V_{s,pa}, V_{s,pv}]$ is the state variables vector and $\mathbf{p} = [W_{lv}, W_{rv}, T, SBV, E_{max,lv}, E_{max,rv}, E_{sa}, E_{sv}, E_{pa}, E_{pv}, R_s, R_p, R_{mt}, R_{av}, R_{tc}, R_{pv}]$ is the parameter vector.

Let $\mathbf{p}^0$ be the parameter vector with nominal values. The relative sensitivity functions are calculated with the equation

$$S_{ij}(t) = \frac{p_j^0}{x_i(t, p^0)} \frac{\partial x_i(t, p^0)}{\partial p_j}, \tag{7}$$

where $i \in \{1, \ldots, 5\}$ $j \in \{1, \ldots, 16\}$.

Using Automatic Differentiation this sensitivity functions are exactly computed. In order to determine the parameters that most greatly affect the model dynamics and since the sensitivities are time-variant functions, the integral of the absolute value of relative sensitivities in the period $[0, t_f]$

$$I_{ij} = \int_0^{t_f} |S_{ij}| dt \tag{8}$$

is calculated, where t_f is the final time points, respectively. In practice, the integral is approximated with a trapezoidal method.

5 Results

Due to the numerical instability that the terms $\dot{E}_{lv} E_{lv}^{-1}$ and $\dot{E}_{rv} E_{rv}^{-1}$, which appear in the (4) model [4]. Only the models of Pironet *et al.* and the reduction of this model are simulated. There are sixteen model parameters in these models. In this work all simulations were conducted assuming pig number 2 with 31.0 kg and stressed blood volume of 990 ml, which model parameters are reported and computed by [12], details about the assigning of these nominal values are found in the original reference. The parameters related with the elastance functions are the heart period, the width of each function, the end-systolic elastance of the left and right ventricle with the following values $T = 0.474$ (s), $W_{lv} = 68.9$, $W_{rv} = 239$ (s^2), $E_{max,lv} = 1.3$ and $E_{max,rv} = 1.84$ (mm Hg/ml), respectively. The resistance in the systemic capillaries, pulmonary capillaries, aortic valve, pulmonary valve, mitral valve and tricuspid valve are $R_s = 1.69$, $R_p = 0.256$, $R_{av} = 0.04$, $R_{pv} = 0.03$, $R_{mt} = 0.05$ and $R_{tc} = 0.04$ (mm Hg s/ml). Finally, the elastance in the compartments related with the arteries and veins of both circulations are $E_{sa} = 1.03$, $E_{sv} = 0.00710$, $E_{pa} = 0.699$, $E_{pv} = 0.433$ (mm Hg/ml).

The code was entirely developed and written in Octave and makes use of Martin Fink's myAD package [5], which provides a full framework for performing automatic differentiation in the Octave-environment.

Fig. 2 shows the validation of the reduced model against the original formulation by simulation. In particular, Fig. 2a shows the pressures waveforms of the systemic circulation using the complete model of Pironet *et al.* and Fig. 2b shows the same waveforms using the reduced version of this model. A mean arterial systemic pressure of 60 mm Hg or greater indicates an adequate tissue perfusion. Derived from the minimum and maximum values of the aortic pressure waveform (dashed line), it is gotten that for the above simulations this value is 102 mm Hg. The pressure-volume loops of both ventricles using the model of Pironet *et al.* (Fig. 2c) and the reduced version of this model (Fig. 2d) are also presented. The intra-ventricular pressure in both simulations is in the range of 0-50 and 0-120 (mm Hg) for the right and left ventricle, respectively.Since the reduced model has five state variables and sixteen model parameters. There are eighty relative sensitive functions S_{ij}, $i \in \{1, \ldots, 5\}$ $j \in \{1, \ldots, 16\}$. Due to the extension of this paper, in Table 1 is summarized the values for the integral of the absolute value of relative sensitivities computed using (8). The first order relative sensitivity analysis around the nominal parameter vector p=[68.9,239,0.474,990,1.3,1.84,1.03,0.0710,0.699,0.433,1.69,0.256,0.05,0.04,0.04, 0.03] of the reduced version of the model of Pironet *et al.* showed that heart period parameter (T) is the most sensitive parameter for all the state variables (Notice that the values of I_{13}, I_{23}, I_{33}, I_{43} and I_{53} are the greatest for each column in Table 1). In second or third place appears the values of the I_{ij} related with the relative sensitivity of the state $i \in \{1, \ldots, 5\}$ and the elastance of the compartment i, i.e., a very sensitive parameter for each compartment is that related with the properties of elasticity of the respective compartment. Also the stressed blood volume appears in second or third place.

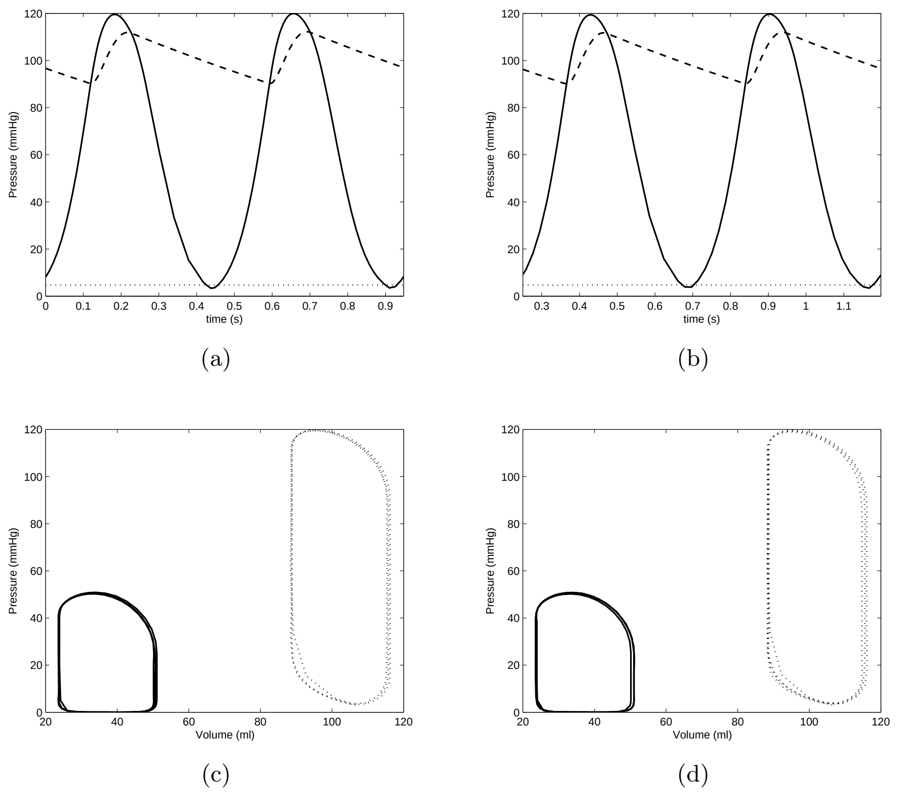

Fig. 2. Simulations of the pressures waveforms of the systemic circulation using model of Pironet *et al.* (2a) and the reduced form of this model (2b). *Solid line:* left ventricular pressure (P_{lv}), *dashed line:* aortic pressure (P_{sa}), *dotted line:* systemic vein pressure (P_{sv}). Pressure-volume loops of both ventricles using model of Pironet *et al.* (2c) and the reduced form (2d). *Solid line:* right ventricle, *dotted line:* left ventricle.

Table 1. Values for the integral of the absolute value of relative sensitivities

I_{ij}	i	1	2	3	4	5
j		V_{sa}	V_{pa}	V_{pv}	V_{lv}	V_{rv}
1	W_{lv}	3.2823	14.7651	**27.5285**	4.4656	7.6817
2	W_{rv}	5.1989	6.5559	6.1118	5.3763	9.0972
3	T	**293.5285**	**576.0204**	**606.0967**	**349.3209**	**981.7219**
4	SBV	**19.3250**	**22.8469**	21.6789	**19.6447**	**24.1578**
5	E_{lv}	2.4921	3.1688	3.6778	**20.7309**	2.9383
6	E_{rv}	0.4076	0.8474	0.4478	0.4043	**20.2093**
7	E_{sa}	**22.5017**	2.9541	3.2713	4.0641	2.8110
8	E_{sv}	11.9153	14.2128	13.4559	12.1294	15.0483
9	E_{pa}	1.0760	**24.7842**	0.9760	1.0859	3.6289
10	E_{pv}	1.0555	1.8552	**22.9095**	1.1959	1.3454
11	R_s	18.1934	0.7841	3.2550	13.7335	2.7022
12	R_p	1.1640	9.4063	1.3112	1.1849	5.2503
13	R_{mi}	1.3771	5.9197	11.1448	1.4349	3.0740
14	R_{ao}	0.2073	0.0968	0.2933	0.9907	0.0439
15	R_{tr}	9.7370	12.3486	11.5693	10.0734	13.0519
16	R_{pu}	0.1743	0.3028	0.2266	0.1796	1.8917

Figure 3 shows the waveform of V_{sa} using the nominal values, augmenting ten percent of the nominal value for T and augmenting ten percent of the nominal value for R_p. It is important to highlight that T is the most sensitive parameter and R_p is an insensitive parameter for V_{sa}.

6 Conclusions

It has been shown that under certain conditions the Defares *et al.* and Pironet *et al.* models are equivalent. In the sense that there is a transformation that carries system (4) into (5) and makes the set of characteristic multipliers associated to each model coincide. Moreover, it is given a reduced version of the model of Pironet *et al.*, instead of a system of six differential equations, this reduced version has five differential equations. Some differences between these models are that the first one is a linear homogeneous system of differential equations and the second one is a linear non-homogeneous system of differential equations with constant forcing terms. The initial conditions of the reduced model do not depend of any parameter, unlike the original model which depends of the stressed blood volume.

Comparing the simulations of the complete model of Pironet *et al.* and the reduced version of this model allows one to conclude that the simulations are qualitatively similar. The sensitivity analysis of the reduced model is explored. This analysis showed that two parameters, the heart period and the stressed blood volume, have a major effect on the performance of the model since the normalized ranking of the five state variables associated with these parameters have some of the highest values. Other authors have shown that beat durations

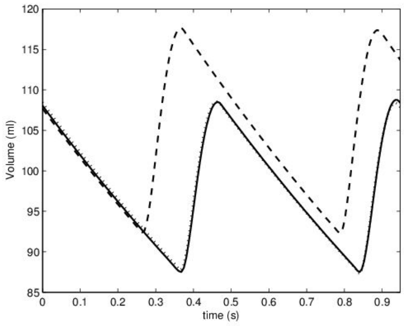

Fig. 3. Waveform for V_{sa} using *Solid line:* nominal parameters, *dashed line:* $T = 0.5214$, *dotted line:* $R_p = 0.2816$

are variable even under sinusoidal conditions causing pressure variability between beats [1, 9], the above fact seems to corroborate that heart period is a very sensitive parameter. Because the heart period is not greatly altered by the parameter identification problem according to Pironet *et al.*[12], this parameter was not considered for the sensitivity analysis of the work of Pironet *et al.* The results suggest that the reduced version can be validated. However, a rigorous proof of this fact exceeds the scope of this paper and must be addressed in a future investigation. Also as future work, the reduced model is going to be coupled with a baroreflex model, with the main objective of solving a control problem associated with the fluid therapy.

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