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MODELING OF THE HUMAN CARDIOVASCULAR SYSTEM: ANALYSIS OF THE BLOOD FLOW RATE

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Abstract. *This work presents a model for the human cardiovascular system, applying the lumped parameter model, taking into account the concept of hybrid systems (discrete event systems combined with systems of continuous variables) for a detailed characterization of the cardiovascular system functioning, and an analysis using Matlab®/Simulink. The numerical simulations presented consistent results, when compared with medical data, regarding physiological variables, such as blood pressure and blood flow rate, indicating the validity of the model.*

Keywords: *Cardiovascular system, Lumped parameter model, Blood flow rate, Hemodynamic, Hybrid systems.*

Nomenclature		AT	Atherosclerosis or Thrombosis
		AV	Aortic Valve
C	Capacitance	LA	Left Atrium
$\mathcal{C}$	Complacency of the vessel wall	LV	Left Ventricle
D	Diode (Valve)	MAX	Maximum Value
E	Elastance	MIN	Minimum Value
HR	Heart Rate	MV	Mitral Valve
I	Electrical current	PA	Pulmonary Artery
K	Coefficient	PAR	Pulmonary Arterioles
L	Inductance	PAS	Pulmonary Arteries
$\mathcal{L}$	Blood inertia	PAV	Pulmonary Vein
P	Blood pressure	PC	Pulmonary Capillaries
Q	Blood flow rate	PV	Pulmonary Valve
q	Charge	PVS	Pulmonary Veins
R	Electrical resistance	RA	Right Atrium
$\mathcal{R}$	Viscous flow resistance	RS	Repeating Sequence
t	Time	RV	Right Ventricle
V	Volume	SA	Systemic Arteries
v	Voltage	SAR	Systemic Arterioles
		SC	Systemic Capillaries
Subscripts		SV	Systemic Veins
		TV	Tricuspid Valve
0	Initial Value; Offset Value	VC	Vena Cava
A	Aorta	Z	Zener

1. INTRODUCTION

According to the World Health Organization (2017), cardiovascular diseases (CVDs) are the number one cause of death globally; more people die annually from CVDs than from any other cause. Thus, many studies related to identifying problems in the human cardiovascular system and ways for solving them, totally or partially, have increased over the years (Jorge et al., 2018).

The laws of blood fluid dynamics, called hemodynamic, govern the cardiovascular system. Hemodynamic may be described by three parameters: blood flow (cardiac output), blood pressure and vascular resistance. The measurement of these hemodynamic parameters is the foundation for diagnosing different CVDs (Westerhof et al., 2005).

Since there is a growing demand for restrictions on *in vivo* testing for the medical equipment industry, including the case of animal testing (Watanabe et al., 2014), new strategies and platforms for *in vitro* tests and tools for evaluating implantable medical devices, such as Ventricular Assist Devices (VADs), must be considered (Jorge et al., 2018).

Knowing that any closed fluid system has analogy with electrical circuits (Westerhof et al., 2005), the cardiovascular system is considered analogous to electrical circuits. Thus, lumped parameter models, known as 0D model or electrical circuits, of the cardiovascular system are an appropriate method to obtain several hemodynamic parameters of the blood circulation (Formaggia et al., 2009; Rahman and Haque, 2012; Gul, 2016).

Based on data surveys in Jorge et al. (2018), although there are studies on blood flow modeling under specific flow conditions and vessel sizes (continuous system) (Yobing, 2013), there are not many studies dealing with the discrete nature of the elements of the cardiovascular system, such as the coupling of the different types of blood vessels and heart valves performance, considering variations in the positions of the human body and the health states of a person (discrete event system) (Jorge et al., 2018). Thus, the analysis of these documents show the importance of considering the combination of the system of continuous variables with discrete event systems (hybrid systems) to integrate a more appropriate and effective way to describe the cardiovascular system (Jorge et al., 2018).

Hybrid systems are defined as systems in which state variables of a continuous and discrete nature are simultaneously found. The evolution of the system may occur partially as a function of time and/or as a function of the discrete event occurrence. This means that, in a hybrid system, subsystems belonging to the two classes presented coexist simultaneously (Villani et al., 2007).

In general, the approaches to the modeling of hybrid systems consist in extensions of continuous models, such as ordinary differential equations in which variables whose value may be modified in a discontinuous way in time are included. Other approaches consist in modifying modeling techniques applied to discrete event systems, whereby new elements are introduced to represent the continuous dynamics of the system, such as in the models based on Hybrid Petri net. In addition, there are also intermediate approaches that combine models of continuous systems, described by differential equations, and discrete systems, described by finite automata or Petri net, in which an interface is established for the communication between the two types of models (Jorge et al., 2019).

This work proposes a model for the human cardiovascular system, applying the lumped parameter model, taking into account the concept of hybrid systems and simulating it in Matlab®/Simulink. The focus lies on the analysis and comparison of the blood flow rate from medical data with simulated data of the model for the cardiovascular system, besides considering the simulations under normal and abnormal conditions, derived from the occurrence of discrete events.

2. METHODOLOGY

Based on the survey of publications analyzed in Jorge et al. (2018), a specific technique, known as Computational Fluid Dynamics (CFD), has been applied to model the cardiovascular system. The CFD models from the studied cases may be classified as: 0D Model, 1D Model, 2D Model and 3D Model.

In this work, the 0D Model or the lumped parameter model was applied to model the cardiovascular system, since this technique represents physiological variables, such as blood pressure, blood flow rate, viscous flow resistance and others, of the blood circulation system, presenting an immediate solution, when compared with the other CFD models. Moreover, the lumped parameter model has no spatial dimension and physiological variables are assumed spatially uniform within the model, varying only as a function of time (t).

According to Formaggia, Quarteroni and Veneziani (2009) and Rahman and Haque (2012), each segment of a blood vessel may be represented by a resistor-inductor-capacitor (RLC) electrical circuits (0D model). As shown in Tab. 1, electrical voltage ($\mathcal{v}$) corresponds to the pressure (P) in the blood vessel segment, electrical current (I) corresponds to the blood flow rate (Q), electrical charge (q) corresponds to blood volume (V), electrical resistance (R) corresponds to the resistance to viscous blood flow ($\mathcal{R}$), inductance (L) corresponds to the blood inertia ($\mathcal{L}$) and, capacitance (C) corresponds to the complacency of the vessel wall ($\mathcal{C}$) (Jorge et al., 2019; Gul, 2016).

Table 1. Analogy among elements of the fluid dynamics, physiological variables and electrical system.

Fluid Dynamics	Physiologyical Variables	Electrical System
Pressure	Blood pressure (P)	Voltage ($\mathcal{v}$)
Flow rate	Blood flow rate (Q)	Current (I)
Volume	Blood volume (V)	Charge (q)
Viscosity	Viscous flow resistance ($\mathcal{R}$)	Resistance (R)
Inertance	Blood inertia ($\mathcal{L}$)	Inductance (L)
Elastic coefficient	Complacency ($\mathcal{C}$)	Capacitance (C)

This model considers the blood leaves the left ventricle, flows through the systemic circulation (body except lungs) into the right part of the heart (atrium and ventricle) and from there through the vessels of the pulmonary circulation (lungs) back into the left atrium and ventricle (Guyton and Hall, 2011) and (Tortora and Derrickson, 2014).

The parameters in the lumped parameter model are derived from the blood flow data, measured in a selected human body state under normal or abnormal conditions, according to Fig. 1. However, several difficulties make parameter setting a challenging task, such as: the invasive nature of many of the measurements, restricted access to the required measurement sites due to anatomical configuration, practical difficulties in the orientation of flow probes (particularly invasive ones), difficulties in synchronizing pressure and flow data (particularly when they are not measured simultaneously), limited precision in the pressure/flow sensors, all of which contribute to the accuracy of the model parameters (Shi, Lawford and Hose, 2011). Perhaps more important, the data available of the pressure measurement provides only part of the information needed to estimate the model parameters. Thus, it is necessary to develop more accurate and efficient techniques to optimize the parameter setting in lumped parameter models (Jorge et al., 2019).

2.1 Cardiovascular Model

The model of pulsatile human blood circulation consists of a pumping heart coupled to lumped descriptions of the systemic and the pulmonary circulation. The ventricles are guided by a pair of time-varying elastance functions, whereas the two atria are purely passive chambers. In addition, there are four heart valves (mitral, aortic, tricuspid and pulmonary) in these chambers, as shown in Fig. 1. The valves allow a small amount of volume to flow back into the left and right atria and ventricles before closure is completed. When the left atrial pressure exceeds the left ventricular pressure, the mitral valve (*MV*) opens and the left ventricle is filled with blood. After that, when left ventricular pressure exceeds root aortic pressure, the aortic valve (*AV*) opens and blood flows through the systemic circulation, consisting of aorta (*A*), systemic arteries (*SA*), systemic arterioles (*SAR*), systemic capillaries (*SC*), systemic veins (*SV*) and vena cava (*VC*). The veins return the blood to the passive right atria. Next, when the right atrial pressure exceeds the right ventricular pressure, the tricuspid valve (*TV*) opens and the right ventricle is filled with blood. Then, when right ventricular pressure exceeds the root pulmonary artery pressure, the pulmonary valve (*PV*) opens and blood flows through the pulmonary circulation, consisting of pulmonary artery (*PA*), pulmonary arteries (*PAS*), pulmonary arterioles (*PAR*), pulmonary capillaries (*PC*), pulmonary veins (*PVS*) and pulmonary vein (*PAV*).

In addition, a variable resistor (R_{AT}) is included in this model to represent the formation of fat plaques or thrombus accumulation (atherosclerosis or thrombosis) in the aorta, which is derived from the occurrence of a discrete event.

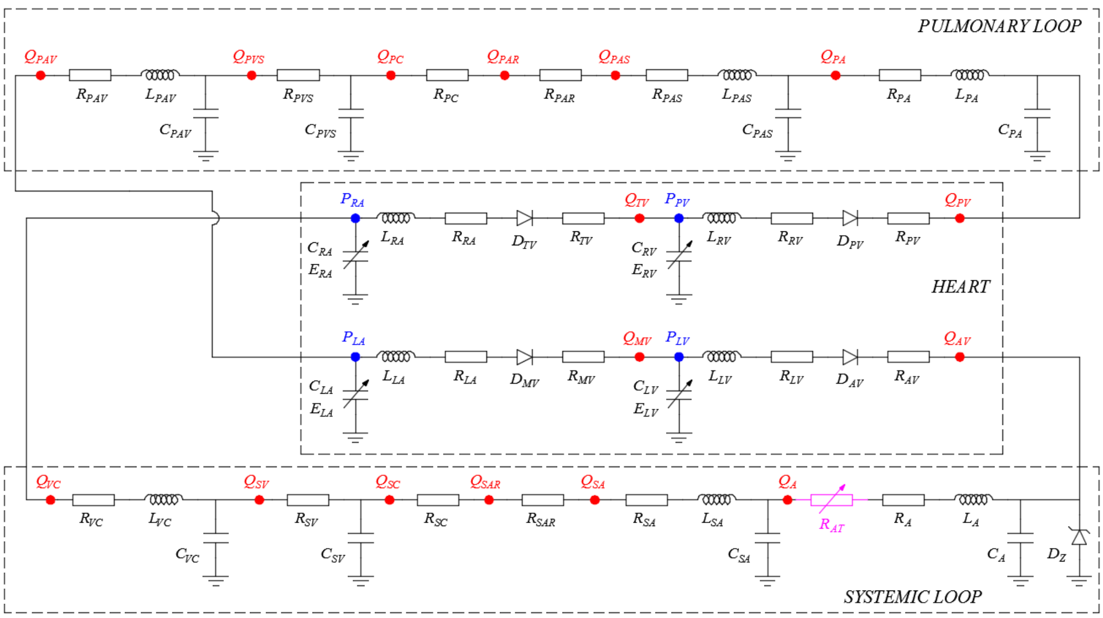

Figure 1. Main components of the cardiovascular system model.

2.1.1 Heart

The cardiac contractile properties of the atria and ventricles are assumed to be defined by time-varying elastance functions. The relation between left ventricular cavity pressure (P_{LV}) and ventricular volume (V_{LV}) is described by (Ferreira et al., 2005):

$$P_{LV} = E_{LV}(t)\left(V_{LV} - V_{LV\_0}\right), \tag{1}$$

where V_{LV_0} represents the left ventricular volume at zero pressure. The elastance function $E(t)$ is given by (Ferreira et al., 2005):

$$E(t) = (E_{max} - E_{min})E_n(t_n) + E_{min}, \quad (2)$$

where $E_n(t_n)$ is called *double hill function* and it is given by (Ferreira et al., 2005):

$$E_n(t_n) = 1.55\left[\frac{\left(\frac{t_n}{0.7}\right)^{1.9}}{1+\left(\frac{t_n}{0.7}\right)^{1.9}}\right]\left[\frac{1}{1+\left(\frac{t_n}{1.17}\right)^{21.9}}\right]. \quad (3)$$

In Equation (3), $E_n(t_n)$ is the normalized time-varying elastance, $t_n = t/T_{max}$, $T_{max} = 0.2 + 0.15.t_c$ and t_c is the cardiac cycle interval, i.e, $t_c = 60/HR$, where HR is the heart-rate. Notice that E(t) is a re-scaled version of $E_n(t_n)$ and the constants E_{max} and E_{min} are related to the end-systolic pressure volume relationship (ESPVR) and the end-diastolic pressure volume relationship (EDPVR), respectively (Ferreira et al., 2005).

The behavior of the left and right atria and the right ventricle is modeled by a similar description.

2.1.2 Equations for the Cardiovascular Model

The notation used in the electrical analogy of the cardiovascular system is represented in Fig. 2 (Formaggia, Quarteroni and Veneziani, 2009).

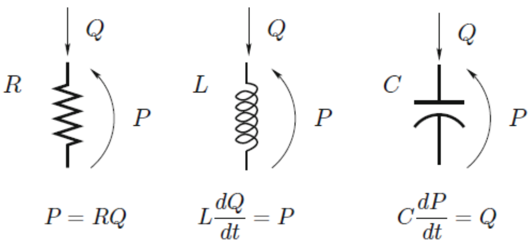

Figure 2. Electrical analogy of the cardiovascular system.
Available from: Formaggia, Quarteroni and Veneziani (2009).

The cardiovascular model is comprised of a system of differential equations (Korakianitis and Shi, 2005), as follows:

- **Heart**

- Left Heart Chamber

$$\begin{cases}\frac{dQ_{MV}}{dt} = \frac{P_{LA} - P_{LV} - (R_{LA} + R_{MV})Q_{MV}}{L_{LA}} & , \textit{ mitral valve is open} \\ Q_{MV} = 0 & , \textit{ mitral valve is closed}\end{cases}, \quad (4)$$

$$P_{LA} = E_{LA}(t)(V_{LA} - V_{LA\_0}), \quad (5)$$

$$\begin{cases}\frac{dQ_{AV}}{dt} = \frac{P_{LV} - P_{A} - (R_{LV} + R_{AV})Q_{AV}}{L_{LV}} & , \textit{ aortic valve is open} \\ Q_{AV} = 0 & , \textit{ aortic valve is closed}\end{cases}, \quad (6)$$

- Right Heart Chamber

$$\begin{cases}\frac{dQ_{TV}}{dt} = \frac{P_{RA} - P_{RV} - (R_{RA} + R_{TV})Q_{TV}}{L_{RA}} & , \textit{ tricuspid valve is open} \\ Q_{TV} = 0 & , \textit{ tricuspid valve is closed}\end{cases}, \quad (7)$$

$$P_{RA} = E_{RA}(t)(V_{RA} - V_{RA\_0}), \quad (8)$$

$$\begin{cases}\frac{dQ_{PV}}{dt} = \frac{P_{RV} - P_{PA} - (R_{RV} + R_{PV})Q_{PV}}{L_{RV}} & , \textit{ pulmonary valve is open} \\ Q_{PV} = 0 & , \textit{ pulmonary valve is closed}\end{cases}, \quad (9)$$

$$P_{RV} = E_{RV}(t)(V_{RV} - V_{RV\_0}). \quad (10)$$

• Blood Systemic Circulation

- Aorta

$$\frac{dQ_A}{dt} = \frac{P_A - P_{SA} - (R_A + R_{AT})Q_A}{L_A}, \tag{11}$$

- Systemic Arteries

$$\frac{dQ_{SA}}{dt} = \frac{P_A - P_{SV} - (R_{SA} + R_{SAR} + R_{SC})Q_{SA}}{L_{SA}}, \tag{12}$$

- Systemic Arterioles and Capillaries

Systemic arteries and capillaries are considered pure resistances. Since the electrical current is the same in series-connected resistors (Nilsson and Riedel, 2015), by analogy, the systemic arteries, arterioles, and capillaries have the same flow rate.

$$Q_{SAR} = Q_{SC} = Q_{SA}, \tag{13}$$

- Systemic Veins

$$Q_{SV} = \frac{P_{SV} - P_{VC}}{R_{SV}}, \tag{14}$$

- Vena Cava

$$\frac{dQ_{VC}}{dt} = \frac{P_{VC} - P_{RA} - R_{VC}Q_{VC}}{L_{VC}}. \tag{15}$$

• Blood Pulmonary Circulation

- Pulmonary Artery

$$\frac{dQ_{PA}}{dt} = \frac{P_{PA} - P_{PAS} - R_{PA}Q_{PA}}{L_{PA}}, \tag{16}$$

- Pulmonary Arteries

$$\frac{dQ_{PAS}}{dt} = \frac{P_{PA} - P_{PVS} - (R_{PAS} + R_{PAR} + R_{PC})Q_{PAS}}{L_{PAS}}, \tag{17}$$

- Pulmonary Arterioles and Capillaries

Pulmonary arterioles and capillaries are considered as pure resistances. Since the electrical current is the same in series-connected resistors (Nilsson and Riedel, 2015), by analogy, the pulmonary arteries, arterioles and capillaries have the same flow rate.

$$Q_{PAR} = Q_{PC} = Q_{PAS}, \tag{18}$$

- Pulmonary Veins

$$Q_{PVS} = \frac{P_{PVS} - P_{PAV}}{R_{PVS}}, \tag{19}$$

- Pulmonary Vein

$$\frac{dQ_{PAV}}{dt} = \frac{P_{PAV} - P_{LA} - R_{PAV}Q_{PAV}}{L_{PAV}}. \tag{20}$$

2.1.3 System Parameter Values

The parameter values for this human cardiovascular model is guided by data available in the literature (Korakianitis and Shi, 2005; Blanco and Feijóo, 2010; Fresiello et al., 2015), and are given in Tab. 2, 3 and 4. The goal is to obtain realistic average pressure and flow levels in the system.

Table 2. Parameters for the heart.

Part	Parameter	Value	Unit
Left Heart	E_{LA_max} *(Systole)*	0.35	mmHg/ml
	E_{LA_min} *(Diastole)*	0.15	mmHg/ml
	E_{LV_max}	2.50	mmHg/ml
	E_{LV_min}	0.10	mmHg/ml
	L_{LA}	0.00001	mmHg.s/ml
	L_{LV}	0.00001	mmHg.s/ml
	R_{AV}	0.001	mmHg.s²/ml
	R_{LA}	0.02	mmHg.s²/ml
	R_{LV}	0.0001	mmHg.s²/ml
	R_{MV}	0.007	mmHg.s²/ml
	V_{LA_0}	4	ml
	$V_{LA,0}$	190	ml
	V_{LV_0}	6	ml
	$V_{LV,0}$	290	ml
Right Heart	E_{RA_max}	0.40	mmHg/ml
	E_{RA_min}	0.15	mmHg/ml
	E_{RV_max}	1.15	mmHg/ml
	E_{RV_min}	0.10	mmHg/ml
	L_{RA}	0.00001	mmHg.s/ml
	L_{RV}	0.00001	mmHg.s/ml
	R_{PV}	0.001	mmHg.s²/ml
	R_{RA}	0.02	mmHg.s²/ml
	R_{RV}	0.0001	mmHg.s²/ml
	R_{TV}	0.007	mmHg.s²/ml
	V_{RA_0}	8	ml
	$V_{RA,0}$	190	ml
	V_{RV_0}	15	ml
	$V_{RV,0}$	290	ml

The parameter values of elastance functions $E(t)$ are chosen to obtain systolic and diastolic time periods in close agreement with standard human pressure and flow profiles found in (Noordergraaf, 1978; Nichols, O'Rourke and Vlachopoulos, 2011; Guyton and Hall, 2011). Minimal elastance (E_{min}) provides ventricular filling, maximal elastance (E_{max}) and inductance (L) are chosen to obtain proper pressure and flow curves.

$V_{LA,0}$, $V_{LV,0}$, $V_{RA,0}$ and $V_{RV,0}$ represent the initial values for the left and right volume of the atria and ventricles.

Table 3. Additional parameters.

Parameter	Value	Unit
HR	70	bpm
K_{RS}	0.89	-
t	10	s
t_{delay}	0.59	s

According to Tab. 3, the HR is 70 beats per minute (bpm), the coefficients for repeating sequence (K_{RS}) of elastance functions are 0.86, the simulation time (t) is 10 seconds and the time delay (t_{delay}) between contractions of atria and ventricles is 0.59 seconds.

Table 4. Parameters for the blood vessels.

Branch	Parameter	Value	Unit
Systemic Circulation	C_A	0.06	ml/mmHg
	L_A	0.0001	mmHg.s/ml
	R_A	0.05	mmHg.s²/ml
	R_{AT}	0 (min) or 10,000 (max)	mmHg.s²/ml
	C_{SA}	1.40	ml/mmHg
	L_{SA}	0.002	mmHg.s/ml
	R_{SA}	0.35	mmHg.s²/ml
	R_{SAR}	0.40	mmHg.s²/ml
	R_{SC}	0.45	mmHg.s²/ml
	C_{SV}	20	ml/mmHg
	R_{SV}	0.01	mmHg.s²/ml
	C_{VC}	9	ml/mmHg
	L_{VC}	0.01	mmHg.s/ml
	R_{VC}	0.009	mmHg.s²/ml
Pulmonary Circulation	C_{PA}	0.18	ml/mmHg
	L_{PA}	0.00012	mmHg.s/ml
	R_{PA}	0.025	mmHg.s²/ml
	C_{PAS}	3.5	ml/mmHg
	L_{PAS}	0.0017	mmHg.s/ml
	R_{PAS}	0.044	mmHg.s²/ml
	R_{PAR}	0.07	mmHg.s²/ml
	R_{PC}	0.11	mmHg.s²/ml
	C_{PVS}	20	ml/mmHg
	R_{PVS}	0.004	mmHg.s²/ml
	C_{PAV}	10	ml/mmHg
	L_{PAV}	0.01	mmHg.s/ml
	R_{PAV}	0.002	mmHg.s²/ml

3. RESULTS AND DISCUSSION

In order to evaluate the capability of the proposed model to emulate the cardiovascular system hemodynamics, tests are performed by simulation using Matlab®/Simulink. These numerical simulations ignore the effects of gravity; one may hence assume that blood flows solely in response to pressure gradients. In addition, the four heart valves were simulated with the traditional on–off valve model. Thus, the normal reverse flow in the heart valves, following valve closure, is not presented in the results.

Figure 3 shows the left cardiac cycle from medical data (Guyton and Hall, 2011).

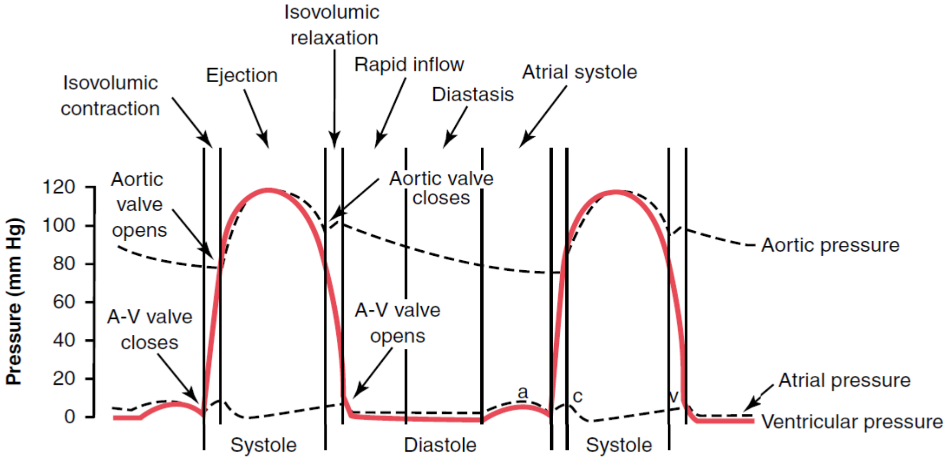

Figure 3. Left cardiac cycle from medical data.
Available from: Guyton and Hall (2011).

Figure 4 shows simulated hemodynamic waveforms throughout the cardiovascular system model under normal conditions. The comparison of the numerical simulation for the left cardiac cycle (Fig. 4 (a)) with medical data (Fig. 3) shows good agreement. Moreover, the results for the right cardiac cycle and flow rate into the heart and the systemic and pulmonary circulation are in agreement with corresponding human data found in the literature (Noordergraaf, 1978; Korakianitis and Shi, 2005; Ferreira et al., 2005; Blanco and Feijóo, 2010; Nichols, O'Rourke and Vlachopoulos, 2011; Guyton and Hall, 2011; Bakir et al., 2018).

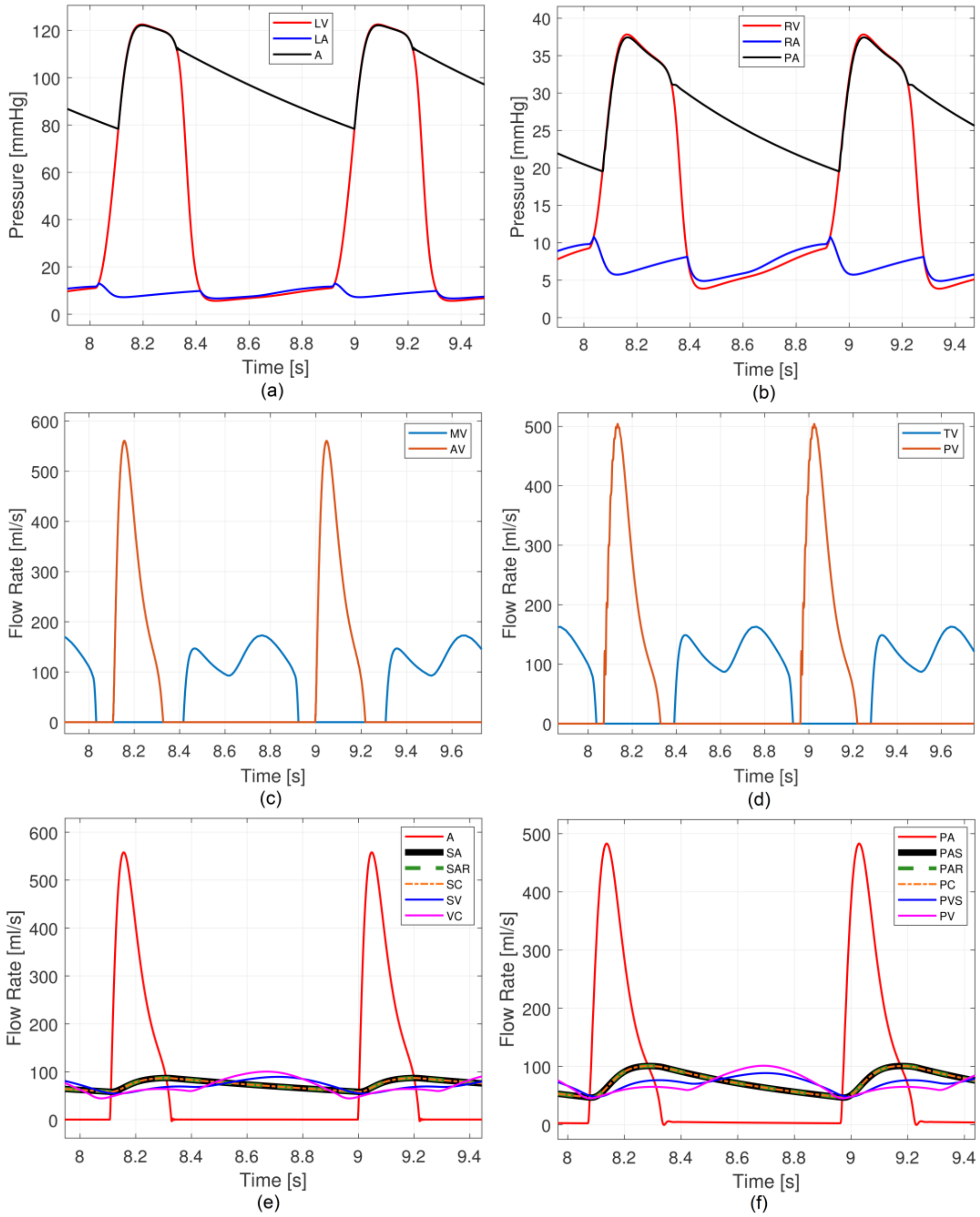

Figure 4. Numerical simulations of the cardiovascular system model under normal conditions. (a) Left cardiac cycle. (b) Right cardiac cycle. (c) Flow rate in the mitral and aortic valves (left heart). (d) Flow rate in the tricuspid and pulmonary valves (right heart). (e) Flow rate in the systemic circulation. (f) Flow rate in the pulmonary circulation.

During the normal functioning of the cardiovascular system, events, such as cardiovascular diseases, may occur and change the behavior of this system. Figure 5 shows simulated hemodynamic waveforms throughout the cardiovascular system model in response to the total aortic blockage generated by atherosclerosis or thrombosis.

The results in Fig. 5 show that, before total aortic blockage, the blood pressure and flow increases over time, while the blood pressure decreases over time after the total aortic blockage, as expected.

Therefore, all the results are consistent, since there is good agreement with medical data and related papers, and indicate the validity of the proposed model for the cardiovascular system.

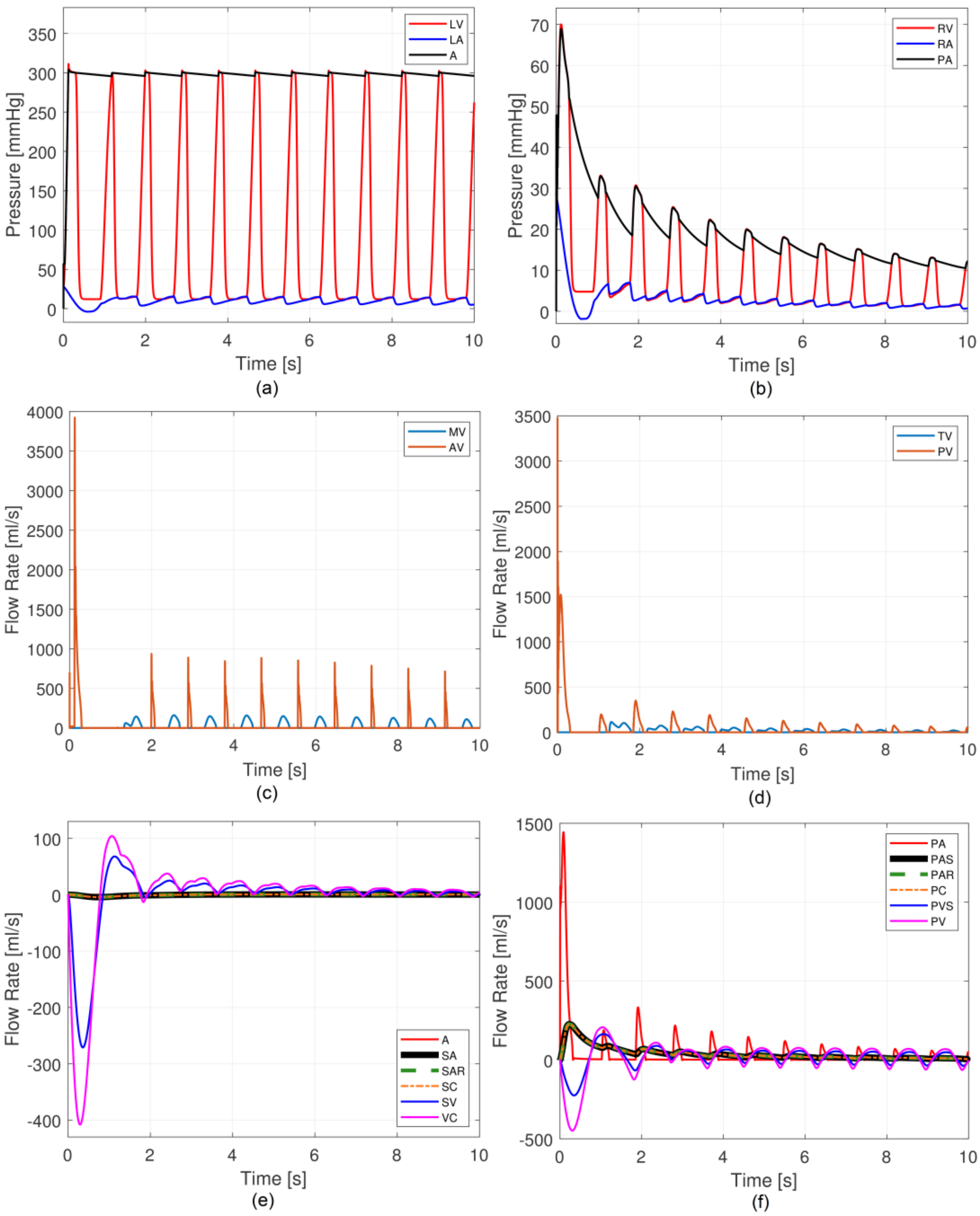

Figure 5. Numerical simulations of the cardiovascular system model considering a total aortic blockage. (a) Left cardiac cycle. (b) Right cardiac cycle. (c) Flow rate in the mitral and aortic valves (left heart). (d) Flow rate in the tricuspid and pulmonary valves (right heart). (e) Flow rate in the systemic circulation. (f) Flow rate in the pulmonary circulation.

4. CONCLUSION

This work proposed a model for the cardiovascular system, applying the lumped parameter model and taking into account the concept of hybrid systems for a more detailed characterization of the cardiovascular system functioning. This model was implemented in Matlab®/Simulink.

The numerical simulations show simulated hemodynamic waveforms throughout the cardiovascular system model under normal conditions and in response to the occurrence of a discrete event, such as total aortic blockage generated by atherosclerosis or thrombosis. The results presented a good agreement with medical data and related papers, indicating the validity of the proposed model for the cardiovascular system.

Future works will consider increasing the blood vessels network into the proposed model, replacing the traditional on–off valve model by dynamic valves and include other events, such as variations in the body positions and the cardiovascular diseases, to analyze the hemodynamic throughout in the cardiovascular system model.

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6. REFERENCES

Bakir, A. A., Abed, A. A., Stevens, M. C., Lovell, N. H. and Dokos, S., 2018. *A Multiphysics Biventricular Cardiac Model: Simulations with a Left-Ventricular Assist Device*. Frontiers in Physiology, vol. 9, n° 1259.

Blanco, P. J. and Feijóo, R. A., 2010. “A 3D-1D-0D Computational Model for the Entire Cardiovascular System”. *In Asociación Argentina de Mecánica Computacional*, vol. 29, pp. 5887-5911.

Ferreira, A., Chen, S., Simaan, M. A., Boston, F. J. and Antali, J. F, 2005. “A Nonlinear State-Space Model a Combined Cardiovascular System and a Rotary Pump”. *In 44th IEEE Conference on Decision and Control*, Seville, Spain, pp. 897-902.

Fresiello, L., Ferrari, G., Di Molfetta, A., Zielinski, K., Tzallas, A., Jacobs, S., Darowski, M., Kozarski, M., Meyns, B., Katertsidis, N. S., Karvounis, E. C., Tsipouras, M. G. and Trivella, M. G., 2015. “A cardiovascular simulator tailored for training and clinical uses”. *In Journal of Biomedical Informatics - Elsevier*, vol. 57, pp. 100-112.

Formaggia, L., Quarteroni, A. and Veneziani, A., 2009. *Cardiovascular mathematics - modeling and simulation of the circulatory system*. Milan: Springer.

Gul, R., 2016. *Mathematical modeling and sensitivity analysis of lumped-parameter model of the human cardiovascular system*. Ph.D. thesis, University of Berlin, Berlin, Germany.

Guyton, A. C. and Hall, J. E., 2011. *Textbook of Medical Physiology*. 12th ed., Elsevier Health Sciences.

Jorge, A. A., Riascos, L. A. M., Junqueira, F., Santos Filho, D. J. and Miyagi, P. E., 2019. “Model of the Human Cardiovascular System based on Hybrid Systems*”. In 6th IEEE/SMC International Conference on Control, Decision and Information Technologies - CODIT*, Paris, France.

Jorge, A. A., Ribeiro, S. A., Junqueira, F., Santos Filho, D. J. and Miyagi, P. E., 2018. “Human blood circulatory system modeling based on hybrid systems”. *In 13th IEEE/IAS International Conference on Industry Applications - INDUSCON*, São Paulo, Brazil.

Korakianitis, T. and Shi, Y., 2005. “Numerical simulation of cardiovascular dynamics with healthy and diseased heart valves”. *In Journal of Biomechanics - Elsevier*, vol. 39, pp. 1964-1982.

Nichols, W., O’Rourke, M. F. and Vlachopoulos, C., 2011. *McDonals’s Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. 6th ed., Hodder Arnold.

Nilsson, J. W. and Riedel, S. A., 2015. *Electric Circuits*. 10th ed., Pearson Education Limited.

Noordergraaf, A., 1978. *Circulatory System Dynamics*. Academic Press, San Diego, California.

Rahman, S. and Haque, A., 2012. “Mathematical modeling of blood flow*”. In International Conference on Informatics, Electronics & Vision - ICIEV*, pp. 672-676.

Shi, Y., Lawford, P. and Hose, R., 2011. “Review of zero-D and 1-D models of blood flow in the cardiovascular system”. *In Biomedical Engineering*, vol. 10, n° 33.

Tortora, G. J. and Derrickson, B., 2014. *Principles of Anatomy and Physiology*. 14th ed., Wiley.

Villani, E., Miyagi, P. E. and Valette, R., 2007. *Modelling and analysis of hybrid supervisory systems: a Petri net approach*. Springer Science & Business Media, London, England.

Watanabe, M., Fonseca, C. D. and Vattimo, M. F. F., 2014. “Instrumental and Ethical aspects of experimental research with animal models”. *In Journal of School of Nursing - University of Sao Paulo*, vol. 48, pp. 173-183.

Westerhof, N., Stergiopulos, N. and Noble, M. I. M., 2005. *Snapshots of Hemodynamics*. Basic Science for the Cardiologist.

World Health Organization (WHO), 2017. “Cardiovascular diseases”. 04 Feb. 2019 <https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)>.

Yobing, S., 2013. *Lumped parameter modeling of cardiovascular system dynamics under different healthy and diseased conditions*. Ph.D. thesis, University of Sheffield, South Yorkshire, England.

7. RESPONSIBILITY NOTICE

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