

## Modeling Pulsatility in the Human Cardiovascular System

*Aurelio de los Reyes V and Franz Kappel*

In this study we investigated, modified and combined two existing mathematical cardiovascular models, a non-pulsatile global model and a simplified pulsatile left heart model. The first goal of the study was to integrate these models. The main objective is to have a global lumped parameter pulsatile model that predicts the pressures in the systemic and pulmonary circulation, and specifically the pulsatile pressures in the the finger arteries where real-time measurements can be obtained. Modifications were made in the ventricular elastance to model the stiffness of heart muscles under stress or exercise state. The systemic aorta compartment is added to the combined model. A finger artery compartment is included to reflect measurements of pulsatile pressures. Parameters were estimated to simulate an average normal blood pressures. Preliminary simulation results are presented.

*AMS Subj. Classification:* 92C30

*Key Words:* mathematical cardiovascular model, pulsatility, contractility, left ventricular elastance

### Introduction

Cardiovascular modeling has a longstanding desire to understand the behavior of the blood pressures in the peripheral and systemic compartments, cardiac outputs, ventricular elastance and contractility in the human circulatory system. In Kappel and Peer (1993) [4] and Timischl (1998) [12], efforts have been done to model non-pulsatile blood flow simulating values of quantities taken over one heart beat respectively over one breath. These models are considered to be global in the sense of considering all essential subsystems such as systemic and pulmonary circulation, left and right ventricles, baroreceptor loop, etc. These are used to describe the overall reaction of the cardiovascular-respiratory system under a constant ergometric workload imposed on a test person on a bicycle-ergometer. The basic control autoregulatory mechanisms were constructed assuming that the regulation is optimal with respect to a cost criterion. The model was extended and used to describe the response of the

cardiovascular-respiratory system under orthostatic stress condition, see for example Fink et al. (2004) [5] and Kappel et al. (2007) [3]. In the study done by Olufsen et al. (2009) [9], a simple lumped parameter cardiovascular model was developed to analyze cerebral blood flow velocity and finger blood pressure measurements during orthostatic stress (sit-to-stand).

## 1. Cardiovascular Modeling

The cardiovascular model presented here is the combination of two existing cardiovascular models: a non-pulsatile global model adapted from the earlier work of Kappel and Peer (1993) [4] and a simplified pulsatile left heart model by Olufsen et al. (2009) [9]. The non-pulsatile global model is based on Grodin's mechanical part of the cardiovascular system. It incorporates all the essential subsystems such as systemic and pulmonary circulation, left and right ventricles, baroreceptor loop, etc. This model considered the mean values over one heart cycle instead of the instantaneous values. On the other hand, the pulsatile left heart model utilizes a minimal cardiovascular structure to close the circulatory loop. The model consists of two arterial compartments and two venous compartments combining vessels in the body and the brain, and a heart compartment representing the left ventricle.

The combined cardiovascular model includes arterial and venous pulmonary, left and right ventricles, systemic aorta, finger arteries, and arterial and venous systemic compartments as shown in Figure 1. The pressures and the compliances in the compartments are denoted by  $P$  and  $c$ , respectively, while resistances are denoted by  $R$ . In the right ventricle,  $Q$  is the cardiac output and  $S$  is the contractility. The subscripts mainly stand for the name of the compartments. That is,  $ap$ ,  $vp$ ,  $lv$ ,  $sa$ ,  $fa$ ,  $as$ ,  $vs$ , and  $rv$  correspond to arterial pulmonary, venous pulmonary, left ventricle, systemic aorta, finger arteries, arterial systemic, venous systemic and right ventricle compartments, respectively. In addition, subscripts  $mv$  and  $av$  denote the mitral valve, respectively aortic valve. Also,  $sa_1$  and  $sa_2$  as subscripts for  $R$  (i.e.,  $R_{sa_1}$  and  $R_{sa_2}$ ) correspond to two different resistances connecting the systemic aorta to finger arteries and systemic aorta to arterial systemic compartment, respectively.

The current model is mathematically formulated in terms of an electric circuit analog. The blood pressure difference plays the role of voltage, the blood flow plays the role of current, the stressed volume plays the role of an electric charge, the compliances of the blood vessels play the role of capacitors, and the resistors are the same in both analogies. The stressed volume in a compartment is the difference between total and unstressed volume (i.e., the volume in a compartment at zero transmural pressure). Thus, stressed volume is

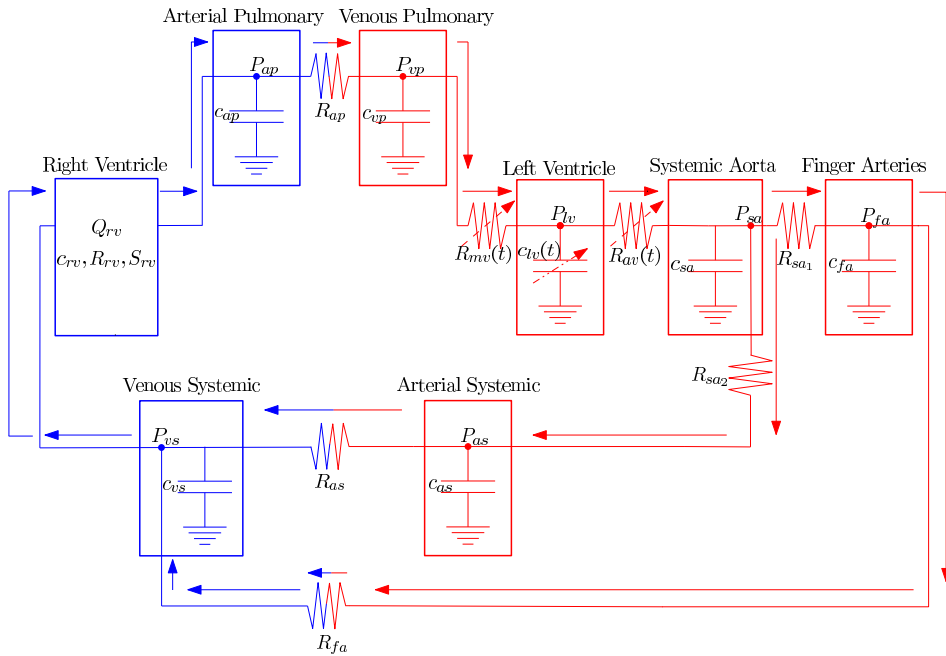


FIGURE 1. The electric analog of the global pulsatile model depicting the blood flow in the pulmonary and systemic circuit including the systemic aorta and finger arteries compartment.

the additional volume added to the unstressed volume when positive transmural pressure causes a stretching of the vascular walls.

The following are the basic assumptions of the modeling process:

- The vessels in the arterial and venous parts of the systemic or pulmonary circuits are lumped together as a single compartment for each of these parts. Each compartment is considered as a vessel with compliant walls in which its volume is characterized by the pressure in the vessel. Thus, these vessels are called *compliance vessels*.
- The systemic peripheral or pulmonary peripheral region is composed of capillaries, arterioles, and venules which are lumped together into a single vessel. These vessels are considered to be pure resistances to blood flow and characterized only by flow through the vessel. Therefore these vessels are called *resistance vessels*.
- The atria are not represented in the model. It is assumed that the right atrium is part of the venous systemic compartment and the left atrium is part of the venous pulmonary compartment.

**1.1. Blood Volume in the Compartment.** For each compartment, we associate the pressure  $P(t)$  and the volume  $V(t)$  of the blood. Assuming linear relationship between the transmural pressure and the total volume, we have

$$(1) \quad V(t) = cP(t),$$

where  $c$  represents the compliance of the compartment which is assumed to be constant. In this case, the unstressed volume is zero and the stressed volume equals the total volume in the compartment. Generally, the total volume in the compartment can be expressed as

$$(2) \quad V(t) = cP(t) + V_u,$$

where  $V_u$  denotes the unstressed volume. A more physiologically realistic approach is to consider that the relation between pressure and total volume is  $V = f(P)$ , which is nonlinear. In this case, the unstressed volume is given by  $V_u = f(0)$  and the compliance,  $c(P)$  at pressure  $P$  is  $f'(P)$  assuming smoothness on  $f$ .

For simplicity, we used (2) assuming  $V_u = 0$  in most of the compartments except in the left ventricle. This is mainly to avoid introduction of additional parameters which cannot be observed directly. This however introduces a modeling error that needs to be considered for further investigations.

**1.2. Blood Flow and Mass Balance Equations.** The blood flow is described in terms of the mass balance equations, that is, the rate of change for the blood volume  $V(t)$  in a compartment is the difference between the flow into and out of the compartment. For a generic compartment, we have

$$(3) \quad \frac{d}{dt}(cP(t)) = F_{in} - F_{out},$$

where  $c$  denotes the compliance,  $P(t)$  the blood pressure in the compartment and  $F_{in}$  and  $F_{out}$  are the blood flows into and out of the compartment, respectively. The loss term in the compartment is the gain term in the adjacent compartment. Also, the flow  $F$  between two compartments can be described by Ohm's law. That is, it depends on the pressure difference between adjacent compartments and on the resistances  $R$  against blood flow. Thus we have the relation

$$(4) \quad F = \frac{1}{R}(P_1 - P_2),$$

where  $P_1$  and  $P_2$  are pressures from adjacent generic compartments 1 and 2, respectively.

The blood flow out of the venous systemic compartment is the cardiac output  $Q_{rv}(t)$  which is the blood flow into the arterial pulmonary. The cardiac

output generated by the right ventricle is

$$(5) \quad Q_{rv}(t) = HV_{str}(t),$$

where  $H$  is the heart rate and  $V_{str}(t)$  is the stroke volume, that is the blood volume ejected by one beat of the ventricle. Following the discussions given in Batzel et. al (2007) [1], the cardiac output of the right ventricle can be expressed as

$$(6) \quad Q_{rv}(t) = H \frac{c_{rv}P_{vp}(t)a_{rv}(H)f(S_{rv}(t), P_{ap}(t))}{a_{rv}(H)P_{ap}(t) + k_{rv}(H)f(S_{rv}(t), P_{ap}(t))},$$

where we have chosen that the function  $f(S_{rv}(t), P_{ap}(t))$ , according to Timischl (1998) [12] is given by

$$(7) \quad f(S_{rv}(t), P_{ap}(t)) = 0.5(S_r(t) + P_{ap}(t)) - 0.5((P_{ap}(t) - S_r(t)) + 0.01)^{1/2}.$$

This function chooses the minimum value between  $S_{rv}$  and  $P_{ap}$  at a specific time point  $t$ . Also,

$$(8) \quad k_{rv}(H) = e^{-(c_{rv}R_{rv})^{-1}t_d(H)} \quad \text{and} \quad a_{rv}(H) = 1 - k_{rv}(H),$$

and

$$(9) \quad t_d(H) = \frac{1}{H^{1/2}} \left( \frac{1}{H^{1/2}} - \kappa \right),$$

where  $\kappa$  is in the range of  $0.3 - 0.4$  when time is measured in seconds and in the range of  $0.0387 - 0.0516$  when time is measured in minutes.

Moreover, the change in the volume in the left ventricle  $dV_{\ell v}(t)/dt$  as modeled in [9] is

$$(10) \quad \frac{dV_{\ell v}(t)}{dt} = \frac{P_{vp}(t) - P_{\ell v}(t)}{R_{mv}(t)} - \frac{P_{\ell v}(t) - P_{sa}(t)}{R_{av}(t)}$$

where  $P_{vp}(t)$ ,  $P_{\ell v}(t)$  and  $P_{sa}(t)$  are respectively, the blood pressures in the venous pulmonary, left ventricle and systemic aorta compartments and the time-varying elastances  $R_{mv}(t)$  and  $R_{av}(t)$  in the mitral valve and aortic valve, respectively.

**1.3. Opening and Closing of the Heart Valves.** In order to model the left ventricle as a pump, the opening and closing of the mitral and aortic valves must be included. During the diastole, the mitral valve opens allowing the blood to flow to the ventricle while the aortic valve is closed. Then the heart muscles start to contract, increasing the pressure in the ventricle. When the left ventricular pressure exceeds the aortic pressure, the aortic valve opens, propelling the pulse wave through the vascular system [6].

Rideout (1991) [10] originally proposed a model of the succession of opening and closing of these heart valves. A piecewise continuous function was later

developed by Olufsen et al., see for example [6] and [9]. This function represents the vessel resistance which characterized the *open* valve state using a small baseline resistance and the *closed* state using a value of larger magnitudes. The time-varying resistance is given as

$$(11) \quad \begin{aligned} R_{mv}(t) &= \min \left( R_{mv,open} + e^{(-2(P_{vp}(t) - P_{lv}(t)))}, 10 \right) , \\ R_{av}(t) &= \min \left( R_{av,open} + e^{(-2(P_{lv}(t) - P_{sa}(t)))}, 10 \right) , \end{aligned}$$

where  $R_{mv}(t)$  and  $R_{av}(t)$  are the time varying mitral valve and aortic valve resistances, respectively. The first equation suggests that when  $P_{lv}(t) < P_{vp}(t)$ , the mitral valve opens and the blood enters the left ventricle. As  $P_{lv}(t)$  increases and becomes greater than  $P_{vp}(t)$ , the resistance exponentially grows to a large value. A similar remark can be deduced from the second equation. The value 10 is chosen to ensure that there is no flow when the valve is closed and remains there for the duration of the closed valve phase. The open and closed transition is not discrete. An exponential function is used for the partially opened valve, with the amount of *openness* [9].

**1.4. Time-Varying Elastance Function.** The slope of a pressure-volume curve which has pressure on the  $y$ -axis and volume on the  $x$ -axis is called the *ventricular elastance* or simply the *elastance*. It is a measure of stiffness of the ventricles. Elastance and compliance are inverse of each other.

According to Ottesen et al. (2004) [7], the relationship between the left ventricular pressure  $P_{lv}$  and the stressed left ventricular volume  $V_{lv}(t)$  is described by

$$(12) \quad P_{lv}(t) = E_{lv}(t) (V_{lv}(t) - V_d) ,$$

where  $E_{lv}(t)$  is the time-varying ventricular elastance and  $V_d$  (constant) is the ventricular volume at zero diastolic pressure.

In [9], the time-varying elastance function  $E_{lv}(t)$  is given by

$$(13) \quad E_{lv}(t) = \begin{cases} E_m + \frac{E_M - E_m}{2} \left[ 1 - \cos \left( \frac{\pi t}{T_M} \right) \right] , & 0 \leq t \leq T_M \\ E_m + \frac{E_M - E_m}{2} \left[ \cos \left( \frac{\pi}{T_r} (t - T_M) \right) + 1 \right] , & T_M \leq t \leq T_M + T_r \\ E_m , & T_M + T_r \leq t < T . \end{cases}$$

This is a modification of a model developed by Heldt et al. (2002) [2]. Here,  $T_M$  denotes the time of peak elastance, and  $T_r$  is the time for the start of diastolic relaxation. These are both functions of the length of the cardiac cycle  $T$ . These parameters are set up as fractions where  $T_{M,frac} = T_M/T$  and  $T_{r,frac} = T_r/T$ .

Moreover,  $E_m$  and  $E_M$  are the minimum and maximum elastance values, respectively. The above elastance function (13) is sufficiently smooth. Its derivative can be easily computed as follows

$$(14) \quad \frac{dE_{\ell v}(t)}{dt} = \begin{cases} \frac{E_M - E_m}{2} \left[ \frac{\pi}{T_M} \sin \left( \frac{\pi t}{T_M} \right) \right], & 0 \leq t \leq T_M \\ \frac{E_M - E_m}{2} \left[ -\frac{\pi}{T_r} \sin \left( \frac{\pi}{T_r} (t - T_M) \right) \right], & T_M \leq t \leq T_M + T_r \\ 0, & T_M + T_r \leq t < T. \end{cases}$$

In our model, further modifications of the elastance function in (13) has been done. The maximum elastance  $E_M$  can be interpreted as a measure of the contractile state of the ventricle, see [8] and [11]. For normal resting heart,  $E_M$  can be a parameter constant. However, during exercise state, the contractility of the heart muscles may vary and could depend on the heart rate. That is, an increase in heart rate may result to an increase ventricular elastance. Thus we considered  $E_M$  as a function dependent on the heart rate  $H$ . Such function must be positive-valued, bounded and continuous. We chose the Gompertz function for  $E_M(H)$ , a sigmoidal function given by

$$(15) \quad E_M(H) = a \exp(-b \exp(-cH)) ,$$

where  $a, b, c$  are positive constants. The constant  $a$  determines the upper bound of the function,  $b$  shifts the graph horizontally and  $c$  is the measure of the steepness of the curve.

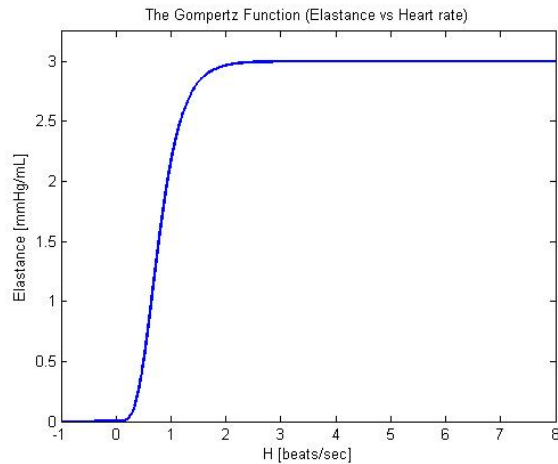
In Ottesen (2004) [7] and Olufsen et al. (2009) [9],  $E_M = 2.49$  [mmHg/mL]. Figure 2(a) depicts the maximum elastance curve where constants  $a, b$  and  $c$  were estimated obtaining  $E_M = 2.4906$  [mmHg/mL] at  $H = 70/60$  beats per second.

Since,  $E_M$  is now  $H$ -dependent,  $T_M$  which is the time of peak elastance should be  $H$ -dependent as well. We considered  $T_M$  as the time for systolic duration which is defined by the Bazett's formula given by

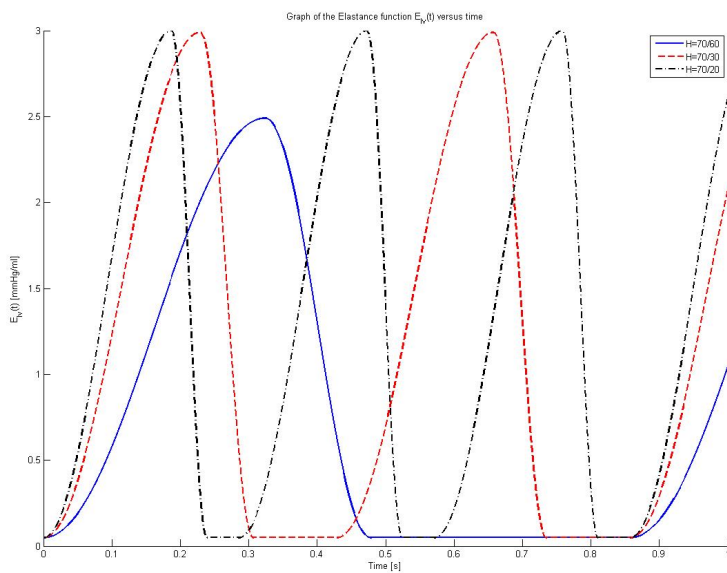
$$(16) \quad T_M = \frac{\kappa}{H^{1/2}} .$$

Figure 2(b) depicts the elastance function with varying heart rates. As the heart rate increases, the maximum elastance value increases as well. Notice also the decrease in the time for peak elastance and the smaller support of the elastance curve.

**1.5. Filling Process in the Right Heart.** The filling process in the right ventricle depends on the pressure difference between the filling pressure and the pressure in the right ventricle when the inflow valve (tricuspid valve) is open. Following Batzel et al. (2007) [1], the blood inflow into the right ventricle is



(a)



(b)

FIGURE 2. (a) The maximum elastance  $E_M$  expressed as a sigmoidal function dependent on the heart rate  $H$ . (b) The elastance function with varying heart rates.



given by

$$(17) \quad \frac{dV_{rv}(t)}{dt} = \frac{1}{R_{rv}} (P_v(t) - P_{rv}(t)),$$

where  $V_{rv}(t)$  is the volume in the right ventricle at time  $t$  after the filling process has started,  $P_v(t)$  is the venous filling pressure,  $P_{rv}(t)$  is the pressure in the right ventricle, and  $R_{rv}$  is the total resistance to the inflow into the right ventricle.

As in [1], it is assumed that  $P_v(t)$  is constant during the diastole,  $P_v(t) \equiv P_v$ , the end-systolic volume at the end of a heart beat equals the end-systolic volume of the previous heart beat and the compliance  $c_{rv}$  of the relaxed ventricle remains constant during the diastole.

**1.6. The Contractility of the Right Ventricle.** There is a heart mechanism called the *Bowditch effect*. It roughly states that changing the heart rate causes a concordant change in the ventricular contractilities. In this study, we adapted the model presented in Batzel et al. (2007) [1] (see also [4]), where sympathetic and parasympathetic activities were not considered directly. Thus, the variations of the contractilities can be described by the following second order differential equation

$$(18) \quad \ddot{S}_r + \gamma_r \dot{S}_r + \alpha_r S_r = \beta_r H,$$

where  $\alpha_r, \beta_r$  and  $\gamma_r$  are constants. This set-up guarantees that the contractility  $S_r$  varies in the same direction as the heart rate  $H$ . Introducing the state variable  $\sigma_r = \dot{S}_r$  and transforming (18) into systems of first order differential equations, we have

$$(19) \quad \begin{aligned} \dot{S}_r &= \sigma_r, \\ \dot{\sigma}_r &= -\alpha_r S_r - \gamma_r \sigma_r + \beta_r H. \end{aligned}$$

**1.7. The Combined Model Equations.** The model can be described as a system of coupled first order of ordinary differential equations with state variables  $x(t) = (P_{sa}, P_{fa}, P_{as}, P_{vs}, P_{ap}, P_{vp}, P_{lv}, S_r, \sigma_r)^T \in \mathbb{R}^9$ , representing pressures in the systemic aorta, finger arteries, arterial systemic, venous systemic, arterial pulmonary and left ventricle compartments, right ventricular contractility and

its derivative, respectively. These are given by

$$\begin{aligned}
 \frac{dP_{sa}}{dt} &= \frac{1}{c_{sa}} \left( \frac{P_{lv} - P_{sa}}{R_{av}(t)} - \frac{P_{sa} - P_{fa}}{R_{sa_1}} - \frac{P_{sa} - P_{as}}{R_{sa_2}} \right), \\
 \frac{dP_{fa}}{dt} &= \frac{1}{c_{fa}} \left( \frac{P_{sa} - P_{fa}}{R_{sa_1}} - \frac{P_{fa} - P_{vs}}{R_{fa}} \right), \\
 \frac{dP_{as}}{dt} &= \frac{1}{c_{as}} \left( \frac{P_{sa} - P_{as}}{R_{sa_2}} - \frac{P_{as} - P_{vs}}{R_{as}} \right), \\
 \frac{dP_{vs}}{dt} &= \frac{1}{c_{vs}} \left( \frac{P_{as} - P_{vs}}{R_{as}} + \frac{P_{fa} - P_{vs}}{R_{fa}} - Q_r \right), \\
 \frac{dP_{ap}}{dt} &= \frac{1}{c_{ap}} \left( Q_r - \frac{P_{ap} - P_{vp}}{R_{ap}} \right), \\
 \frac{dP_{vp}}{dt} &= \frac{1}{c_{vp}} \left( \frac{P_{ap} - P_{vp}}{R_{ap}} - \frac{P_{vp} - P_{lv}}{R_{mv}(t)} \right), \\
 \frac{dP_{lv}}{dt} &= E_{lv} \left( \frac{\frac{dE_{lv}}{dt} P_{lv}}{E_{lv}^2} + \frac{P_{vp} - P_{lv}}{R_{mv}(t)} - \frac{P_{lv} - P_{sa}}{R_{av}(t)} \right), \\
 \frac{dS_r}{dt} &= \sigma_r, \\
 \frac{d\sigma_r}{dt} &= -\alpha_r S_r - \gamma_r \sigma_r + \beta_r H,
 \end{aligned}
 \tag{20}$$

where the time-varying resistances  $R_{av}(t)$  and  $R_{mv}(t)$  are given in equation (11), the cardiac output of the right ventricle  $Q_{rv}$  is given in equation (6) and other auxiliary equations such as for  $k_{rv}$  and  $a_{rv}$  are given in (8), the duration for diastole  $t_d$  is given in (9) and the right ventricular contractility  $S_r$  is given in (19).

## 2. Simulation Results and Discussions

Figure 3 shows the preliminary simulation results of the combined cardiovascular model (1.7) using the values of the parameters given in Table 1. The parameters are estimated to produce an average normal pulsatile pressures in the finger arteries which is 120/90 mmHg. Less pulsatility is observed in the arterial systemic compartment. In the venous pulmonary and arterial pulmonary compartments, the pulsatility is very small which is observed physiologically. Here, the contractility of the right ventricle is assumed to be constant considering a rest normal condition. Furthermore, it is also observed numerically that when the heart rate is increased, pulsatility is increased. The blood pressures in most of the compartments except the venous systemic compartment increased.

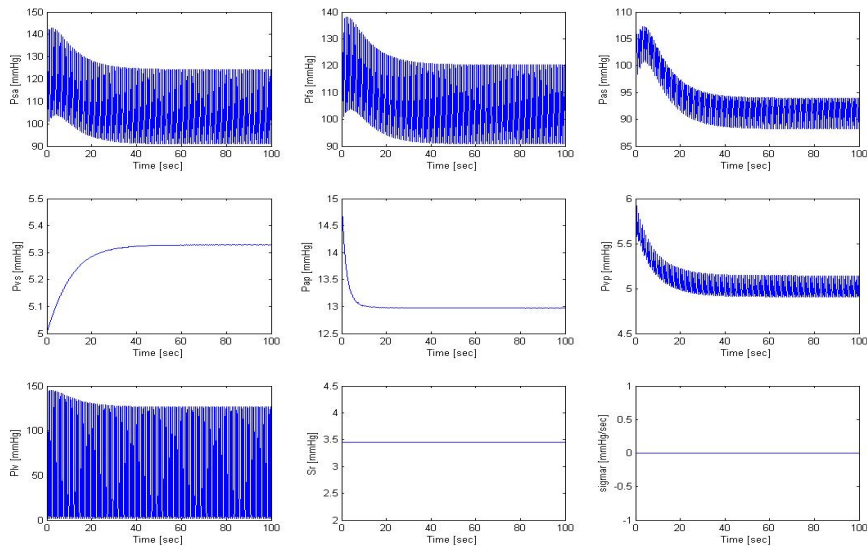
This is due to the Frank- Starling mechanism assumed in the filling process of the right ventricle as assumed in [1]. On the other hand, decreasing the heart rate produces the opposite result.

Parameter	Meaning	Value	Units
$c_{sa}$	Compliance of the systemic aorta compartment	1.15	mL/mmHg
$c_{fa}$	Compliance of the finger arteries compartment	0.105	mL/mmHg
$c_{as}$	Compliance of the arterial systemic compartment	3.75	mL/mmHg
$c_{vs}$	Compliance of the venous systemic compartment	750.95	mL/mmHg
$c_{rv}$	Compliance of the relaxed right ventricle	44.131	mL/mmHg
$c_{ap}$	Compliance of the arterial pulmonary compartment	25.15	mL/mmHg
$c_{vp}$	Compliance of the venous pulmonary compartment	175.75	mL/mmHg
$R_{mv,open}$	Resistance when the mitral valve is open	0.001	mmHg s/mL
$R_{av,open}$	Resistance when the aortic valve is open	0.001	mmHg s/mL
$R_{sa1}$	Resistance between systemic aorta and finger arteries	0.4745	mmHg s/mL
$R_{sa2}$	Resistance between systemic aorta and arterial systemic	0.1834	mmHg s/mL
$R_{fa}$	Resistance between finger and venous systemic compartment	44.9980	mmHg s/mL
$R_{as}$	Resistance in the peripheral region of the systemic circuit	1.2229	mmHg s/mL
$R_{rv}$	Inflow resistance of the right ventricle	0.002502	mmHg s/mL
$R_{ap}$	Resistance in the peripheral region of the pulmonary circuit	0.1097	mmHg s/mL
$E_m$	Minimum elastance value of the left heart	0.029	mmHg/mL
$V_d$	Unstressed left heart volume	10	mL
$\kappa$	Constant in the Bazett's formula	0.35	s
$\alpha_r$	Coefficient of $S_r$ in the differential equation for $S_r$	0.00797	$s^{-2}$
$\beta_r$	Coefficient of $H$ in the differential equation for $S_r$	0.02355	mmHg/s
$\gamma_r$	Coefficient of $\dot{S}_r$ in the differential equation for $S_r$	0.03102	$s^{-1}$
$a$	Constant in the Gompertz function	3	mmHg/mL
$b$	Constant in the Gompertz function	10	
$c$	Constant in the Gompertz function	3.415	$s^{-1}$

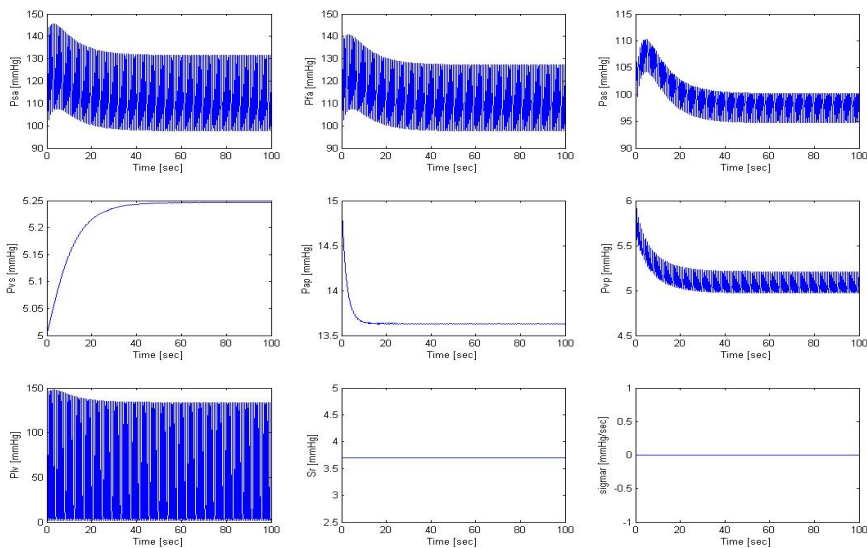
TABLE 1. The table of parameters.

### 3. Ongoing and Future Work

This modeling effort is a work in progress. A lot of considerations can be accounted to have a more holistic view of the overall behavior of the human cardiovascular system under specific conditions. The following are ongoing and future work on this area:



(a)



(b)

FIGURE 3. Simulations depicting the plots of the state variables at the heart rates (a)  $H = 70/60$  beats per second and (b)  $H = 75/60$  beats per second.

- to look closer into the relationship between the right ventricle contractility  $S_r$  and the left ventricle elastance  $E_M$  with regard to its physiological relevance,
- to investigate the behavior of the pulsatile model under a constant workload,
- to design a feedback law mechanism which controls the heart rate,
- to estimate and identify sensitive parameters,
- to investigate further the role of the unstressed volumes in the modeling process, and
- to include the respiratory system in the global pulsatile model.

Moreover, the model can be extended to describe the response of the cardiovascular system under a constant workload as in [4] and [12], its behavior under orthostatic stress as in [5] and [3], and to study blood loss due to haemorrhage.

**Acknowledgment.** The authors are grateful to the Austrian Academic Exchange Service (ÖAD) for granting scholarship to Mr. de los Reyes under Technologiestipendien Südostasien (Doktorat) program to work on this project.

## References

- [1] J.J. Batzel, F. Kappel, D. Schneditz, and H.T. Tran, *Cardiovascular and respiratory systems: Modeling, analysis and control*, SIAM, Philadelphia, PA, 2007.
- [2] T. Heldt, E.B. Shim, R.D. Kamm, and R.G. Mark, Computational modeling of cardiovascular response to orthostatic stress, *Journal of Applied Physiology* **92**, 2002, 1239–1254.
- [3] F. Kappel, M. Fink, and J.J. Batzel, Aspects of control of the cardiovascular-respiratory system during orthostatic stress induced by lower body negative pressure, *Mathematical Biosciences*, **206**(2), 2007, 273–308.
- [4] F. Kappel and R.O. Peer, A mathematical model for fundamental regulation processes in the cardiovascular system, *Journal of Mathematical Biology*, **31**(6), 1993, 611–631.
- [5] M. Fink, J.J. Batzel, and F. Kappel, An optimal control approach to modeling the cardiovascular-respiratory system: An application to orthostatic stress, *Cardiovascular Engineering*, **4**(1), 2004, 27–38.
- [6] M.S. Olufsen, J.T. Ottesen, H.T. Tran, L.M. Ellwein, L.A. Lipsitz, and V. Novak, Blood pressure and blood flow variation during postural change from sitting to standing: Model development and validation, *Journal of Applied Physiology*, **99**, 2005, 1523–1537.

- [7] J.T. Ottesen, M.S. Olufsen, and J.K. Larsen, *Applied mathematical models in human physiology*, SIAM, Philadelphia, PA, 2004.
- [8] J.L. Palladino and A. Noordergraaf, A paradigm for quantifying ventricular contraction, *Cellular and Molecular Biology Letters*, **7** (2), 2002, 331–335.
- [9] S.R. Pope, L. Ellwein, C. Zapata, V. Novak, C.T. Kelley, and M.S. Olufsen, Estimation and identification of parameters in a lumped cerebrovascular model, *Mathematical Biosciences and Engineering*, **6**(1), 2009, 93–115.
- [10] V. Rideout, *Mathematical and computer modeling of physiological systems*, Prentice Hall, Englewood Cliffs, NJ, 1991.
- [11] K. Sunagawa and K. Sagawa, Models of ventricular contraction based on time-varying elastance, *Critical Reviews in Biomedical Engineering*, **7**(3), 1982, 193–228.
- [12] S. Timischl, *A global model of the cardiovascular and respiratory system*, Ph.D. thesis, University of Graz, Institute for Mathematics and Scientific Computing, 1998.

Institute for Mathematics  
and Scientific Computing,  
University of Graz,  
Heinrichstraße 36,  
8010 Graz, AUSTRIA

E-Mail: 06delosr@edu.uni-graz.at