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Laurea Magistrale In Ingegneria Aerospaziale

Cardiovascular System Modeling and Simulation in Microgravity Conditions

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Abstract

The cardiovascular system is one of the most important in the human body. Thanks to the blood circulation, it allows the exchange of Oxygen and Carbon Dioxide to the cells and the distribution of nutrients, hormones, and much more. My work at the Jet Propulsion Laboratory was focused on developing a mathematical model capable of simulating the human cardiovascular system and its adaptability to space conditions. In particular, I studied the influence of gravity on the system. Finally, the model has been implemented using Python language.

Acknowledgements

I would like to thank my supervisors from Politecnico di Torino: Prof. Paolo Maggiore and Dott. Matteo Davide Lorenzo Dalla Vedova for their patience and constant support. I want to thank my mentor from JPL, Dott. Marco Bruno Quadrelli, for giving me this amazing opportunity and for his guidance throughout my entire work. Moreover, I can't spare to thank all the wonderful people I met at JPL, from my office colleagues to my roommates, I will miss you so much. Finally, I wish to thank my family for always being so close to me, even at ten thousand kilometers of distance.

Contents

List of Figures

List of Tables

Introduction

The human body has evolved for millions of years adapting to the earth's gravity, developing control mechanisms to face every possible condition. With the starting of the space era, humans started to explore and study space conditions and, in particular, micro-gravity. Astronauts on the space station, who live for several months in these conditions due to the artificial zero-gravity environment, experience several problems. "The human body can be considered a fluid-filled hydraulic system, responding to changes in acceleration fields and whose physiological response limits human tolerance" [7]. The main effect of the absence of hydrostatic pressure is the fluid shift through the body. Without Gravity pushing downward, blood finds a new distribution, shifting from lower organs, especially legs, towards the head and upper organs. This immediately causes facial puffiness, nasal congestion, headache, and nasal voice, along with the reduction of calves diameter up to 30%. These symptoms are usually referred to as space sickness and often pass after a couple of days. After this period the built-in control system of the cardiovascular system (Baroreflex) adapts to the new condition becoming less sensible [8]. Since the arterial baroreflex receptors are located in the upper part of the body, the cardiovascular system senses too much of blood and starts to eliminate the excess, bringing to anemia within four days. Thus, the system manifests a higher kidneys activity and filtration rate, causing frequent urination and an increase of the risk of kidney stones [7]. Together with the loss of plasma and blood, astronauts experience Jugular venous distension, changes in the heart rate and blood pressure, and finally heart size and mass reduction. When astronauts come back from their flights, their atrophied and less sensitive cardiovascular system has to withstand the hydrostatic load generated by gravity, causing complete opposite problems [8]. The purpose of this thesis is to create a model of the cardiovascular system capable of simulating these changes in order to have a better understanding of these processes, develop a way to limit negative effects in order to extend human tolerance of micro-gravity conditions, and help the recovery of astronauts re-entering on earth. The problem consists of creating a model for a functioning cardiovascular system in nominal conditions, designing the built-in control systems of the human body (arterial baroreflex and cardiopulmonary reflex), and finally modeling and analyzing what happens to the model if it is put in micro-gravity conditions. In order to get familiar with the problem, the first model developed only included six compartments. Once that the problem was clear and studied, the number of

compartments has been incremented simply subdividing certain compartments and adding atria to the system. The system was developed using the electrical analogy and comparing pressure and voltage, flow and current. This way of using a simple mechanical or electrical model to simulate cardiovascular phenomena dates back to the work of Moens and Kortweg, who modeled arterial pulse propagation in 1878 and the work of Otto Frank and his "Windkessel" (air chamber in German) model [9]. Another milestone in this field was the model developed from the experiment of Dr. A. Guyton and has been largely used to teach physiology, using circuital components to simulate the physical system. Finally, an important assumption done in the model is neglecting the blood inertia. Its contribution does not affect excessively the system dynamics and thus has been decided to not consider it at the moment yet not excluding the possibility of implementing this feature in the future.

Chapter 1

Model Definition

The cardiovascular system is composed of several organs. It is possible to divide the entire system into a subset of compartments, each one representing one or more organs. This model considers organs as compartments in a zero-dimensional lumped parameter model. A model consisting of enough zero-dimensional compartments can be assimilated to a 1-dimensional system. Milisic and Quarteroni have given a mathematical proof that zero-dimensional models for the vessel network can be regarded as first-order discretization of a one-dimensional linear system [10]. It is particularly convenient to model the the system using a lumped parameter electrical circuit since it can be analyzed using Kirchhoff's current and voltage laws. Thus, each compartment is considered as a set of electrical components linked together in a circuit, following the electrical analogy: blood circulating through the different cavities and vessels behaves similarly to the current flowing through a circuit. Analogously, blood pressure can be compared to the voltage, driving blood from areas with high pressure towards lower pressure zones. Elastic properties of the different tissues are modeled as capacitors since they can provide blood flow when the heart pressure drops. Each chamber in the heart has been modeled as a variable capacitor, function of the systole time, systolic elastance, and diastolic elastance. Heart valves are modeled as diodes, preventing the reverse flow during the diastole. Finally, fluid resistance has been modeled as electrical resistance.

1.1 Six Compartment Model

The problem has been approached by taking into account only 6 compartments. This way, it was possible to get familiar with it and the several dynamics involved. This model is composed of the following parts:

- Right Heart
- Left Heart
- Pulmonary Arteries
- Arteries
- Pulmonary Veins
- Veins

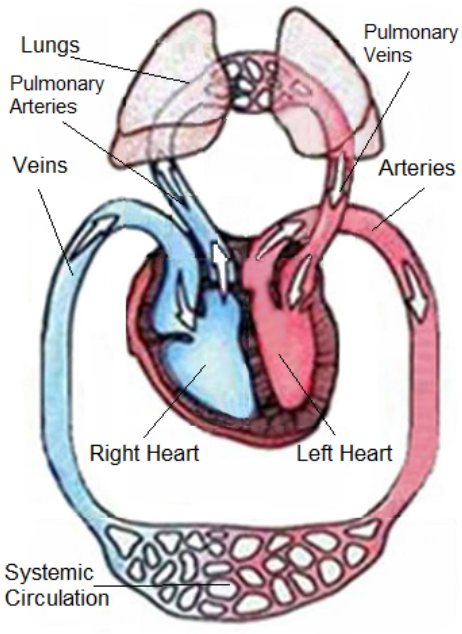

Figure 1.1: Cardiovascular System model [1]

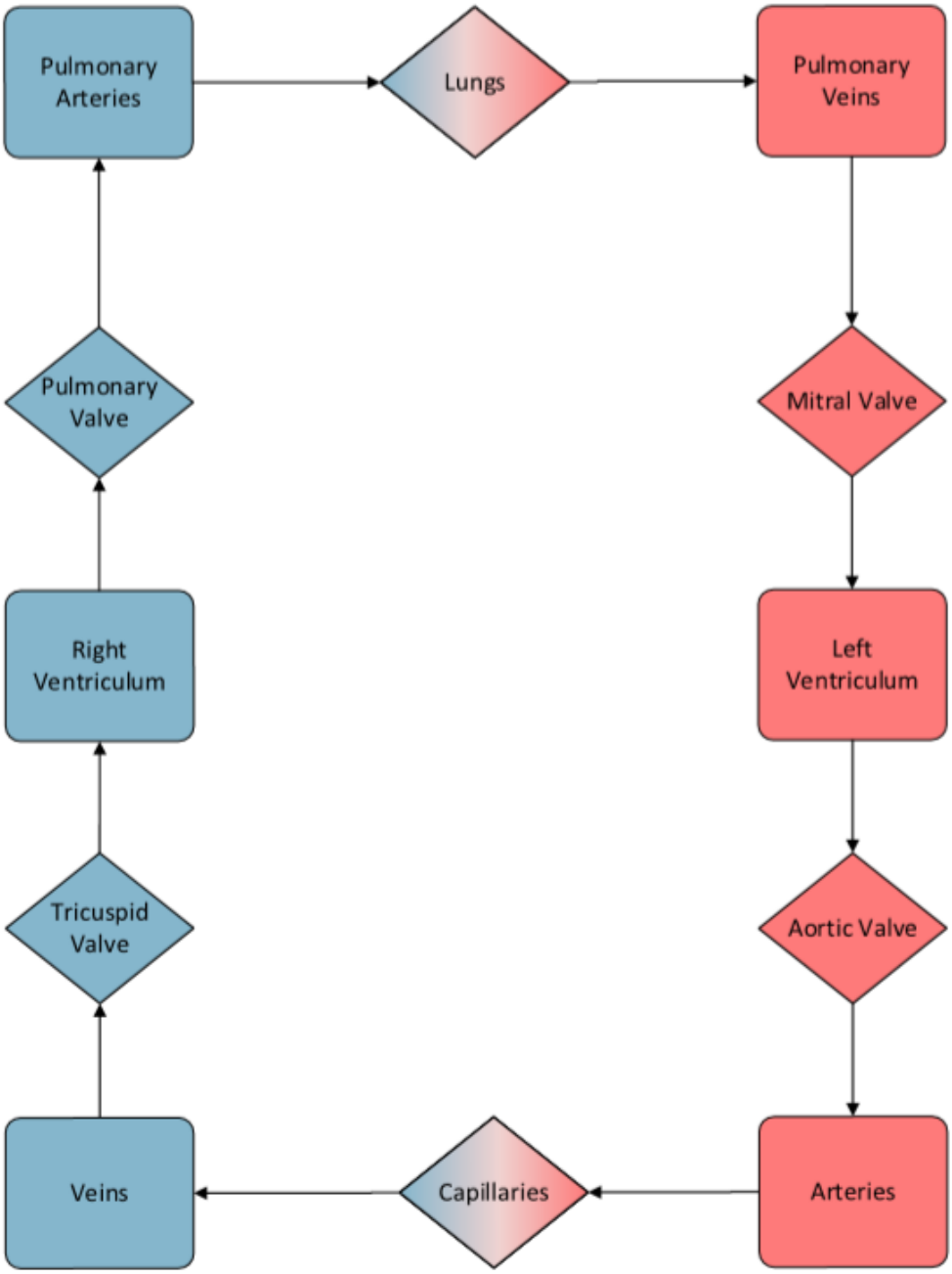

Figure 1.2: Six Compartment Model

1.1.1 Right Heart

The right heart pumps blood into the pulmonary circulation, which is responsible for the exchange of carbon dioxide with oxygen in the lungs. In this model the right ventricle is directly connected to the venous system through the tricuspid valve, disregarding the presence of the right atrium. Since atria have not been modeled, their functions have been absorbed by other compartments. A time-varying elastance equation (inverse of capacitance) has been proposed by [11] based on the empirical data gathered by [12]. All the parameters, including $E_{RH_{dias}}$ and $E_{RH_{sys}}$, are reported in the Appendix (A).

$$E_{RH}(t) = \begin{cases} E_{RH_{dias}} + \frac{E_{RH_{sys}} - E_{RH_{dias}}}{2}\left[1 - \cos\left(\frac{\pi t}{0.3\sqrt{T_{n-1}}}\right)\right] & 0 \leq t \leq T_s, \\ E_{RH_{dias}} + \frac{RH_{E_{sys}} - E_{RH_{dias}}}{2}\left[1 + \cos\left(\frac{2\pi(t - 0.3\sqrt{T_{n-1}}}{0.3\sqrt{T_{n-1}}}\right)\right] & T_s < t \leq \frac{3}{2}T_s, \\ E_{RH_{dias}} & \frac{3}{2}T_s < t \leq T_n \end{cases} \tag{1.1}$$

Where T_n is the duration of the cardiac cycle at the nth step, T_{n-1} is the duration of the cardiac cycle at the previous one and T_s is Systolic Time of the nth beat, calculated through the Bazett formula [13]:

$$T_s = \frac{K}{\sqrt{T_{n-1}}} \tag{1.2}$$

K is called Bazett constant and actually depends on the heart rate and sex. In the same article we can also find an equation for the systole length:

$$L_s = \frac{60}{(k\sqrt{R})} \tag{1.3}$$

The variable k slightly varies according to the posture. Mean values for K and k are reported respectively in Table A.2 and Table A.3.

$$C_{RH}(t) = \frac{1}{E_{RH}(t)} \tag{1.4}$$

Ventricles pumping action is modeled as a variable capacitor (C_{RH}).

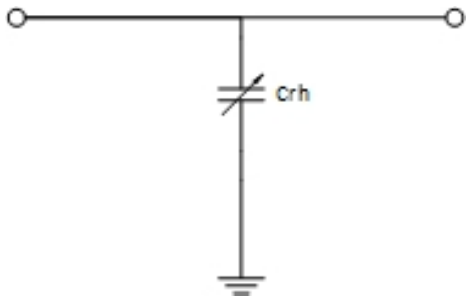

Figure 1.3: Right Heart electrical equivalent circuit

1.1.2 Left Heart

The left heart receives oxygen-rich blood from the lungs and drives it into systemic circulation. The pumping action of the ventricles is represented, just like in the right heart as a variable capacitor (C_{LH}) through Heldt's formula. [11]

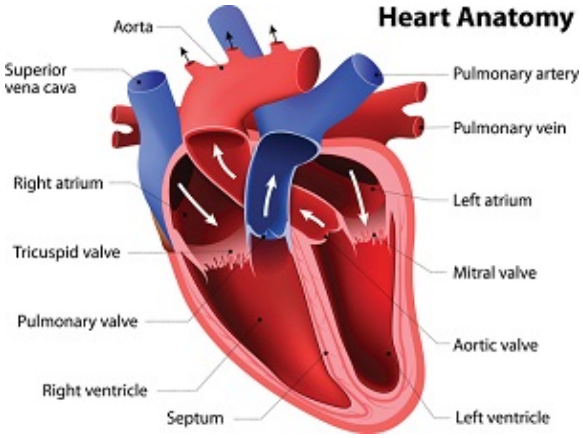

Figure 1.4: Heart Anatomy [2]

$$E_{LH}(t) = \begin{cases} E_{LH_{dias}} + \frac{E_{LH_{sys}} - E_{LH_{dias}}}{2} \left[1 - \cos\left(\frac{\pi t}{0.3\sqrt{T_{n-1}}}\right)\right] & 0 \leq t \leq T_s, \\ E_{LH_{dias}} + \frac{LH_{E_{sys}} - E_{LH_{dias}}}{2} \left[1 + \cos\left(\frac{2\pi(t - 0.3\sqrt{T_{n-1}}}{0.3\sqrt{T_{n-1}}}\right)\right] & T_s < t \leq \frac{3}{2}T_s, \\ E_{LH_{dias}} & \frac{3}{2}T_s < t \leq T_n \end{cases} \quad (1.5)$$

$$C_{LH}(t) = \frac{1}{E_{LH}(t)} \tag{1.6}$$

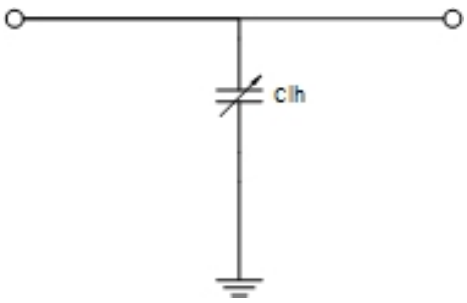

Figure 1.5: Left Heart electrical equivalent circuit

1.1.3 Valves

All the valves have been considered as on-off diodes, representing the impossibility of reverse flow. In fact, when the pressure upstream is greater than the one downstream, the valve is opened and so the diode is in a conduction state. On the other way around, the valve is closed and doesn't let the blood flow through, so the diode is considered in a non-conduction state. The aortic valve connects the left heart to the Aorta, the largest of all the arteries. It is essential for a healthy cardiovascular system since it prevents the blood to flow back into the ventricle when its pressure drops during diastole. Since we are not considering atria in this model, the Mitral valve connects directly pulmonary veins to the left ventricle and the Tricuspid valve links the venous System to the right heart. Finally, we find the pulmonary valve connecting the right ventricle to the pulmonary arteries.

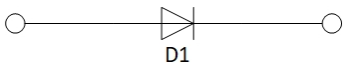

Figure 1.6: Pulmonary Valve electrical equivalent circuit

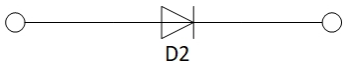

Figure 1.7: Mitral Valve electrical equivalent circuit

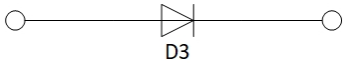

Figure 1.8: Aortic Valve electrical equivalent circuit

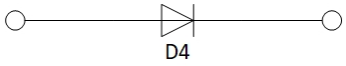

Figure 1.9: Tricuspid Valve electrical equivalent circuit

1.1.4 Arteries

All the vessels carrying blood away from the heart are called arteries. When the blood exits the left ventricle, passing through the aortic valve, it enters the largest artery of the entire human body: the Aorta. From the Aorta a series of systemic arteries branch out. These arteries then divide into arterioles which finally end in capillaries. In this compartment have been included the contributes of Aorta, arteries and arterioles. When the heart pushes blood through the arteries during the systole, thanks to their elastic properties, they accumulate elastic energy by expanding their width. Then, during the diastole, the heart stops providing the pressure and arteries shrink back to their original size, releasing the elastic energy accumulated. This mechanism manages to maintain the arterial pressure to a level high enough to allow the blood to flow until the following heartbeat. The entire arterial system but the pulmonary arteries has been represented as a single capacitor, using the value provided by T. A. Parlikar in [14]. Fluid-Dynamic resistance has been modeled as electrical resistance.

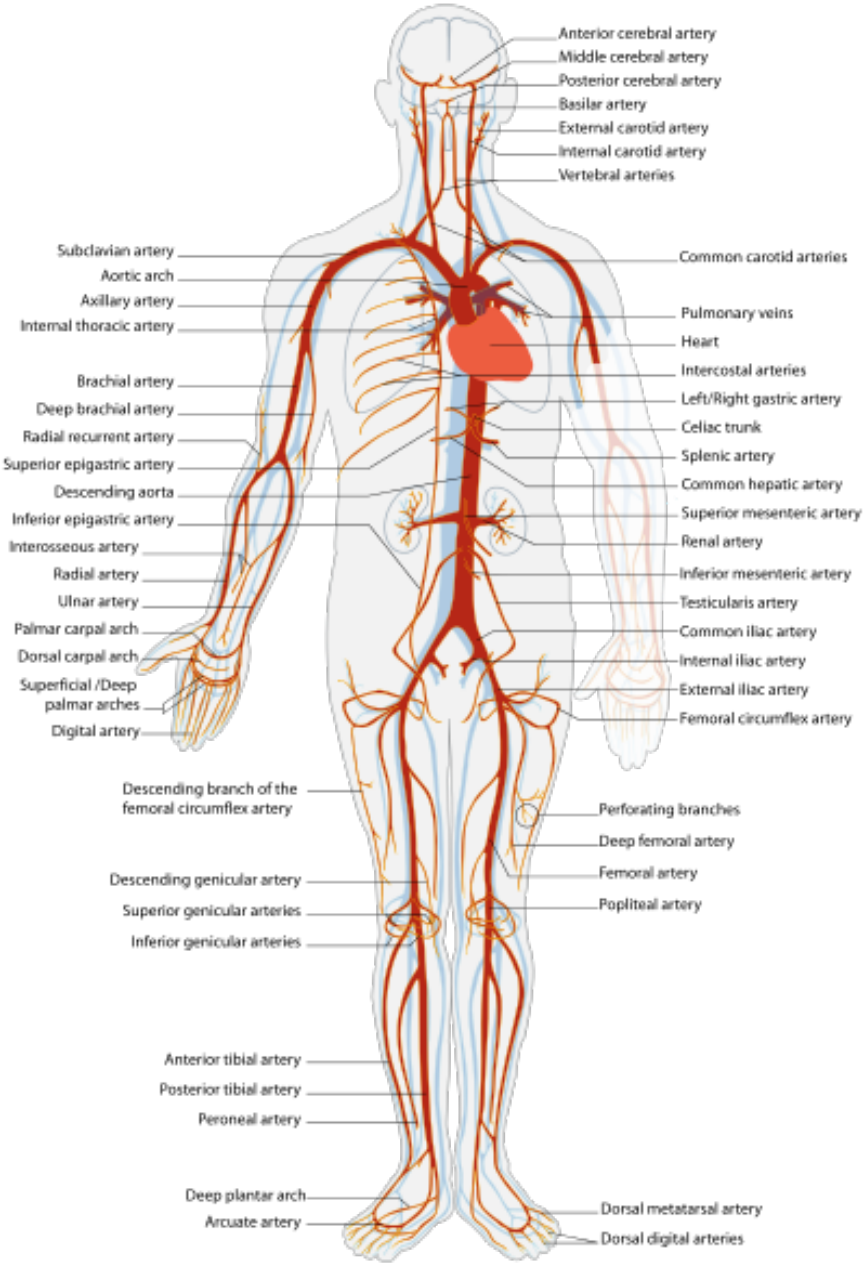

Figure 1.10: Arteries of the human circulatory system [3]

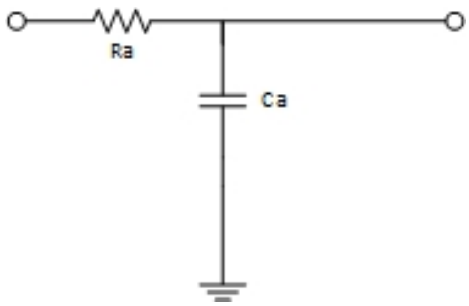

Figure 1.11: Arteries electrical equivalent circuit

1.1.5 Veins

All the vessels carrying blood towards the heart are called veins. They carry carbon dioxide-rich blood away from cells starting as capillaries, becoming venules, and finally veins. As already done with the arteries, all the veins but the pulmonary veins have been represented as a single capacitor, once again using the value provided by T. A. Parlikar in [14].

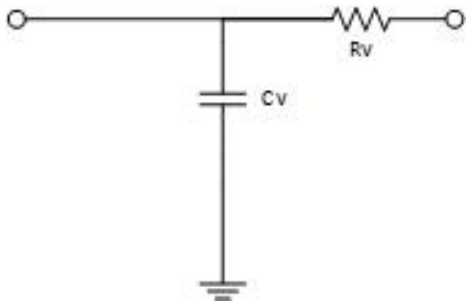

Figure 1.12: Veins electrical equivalent circuit

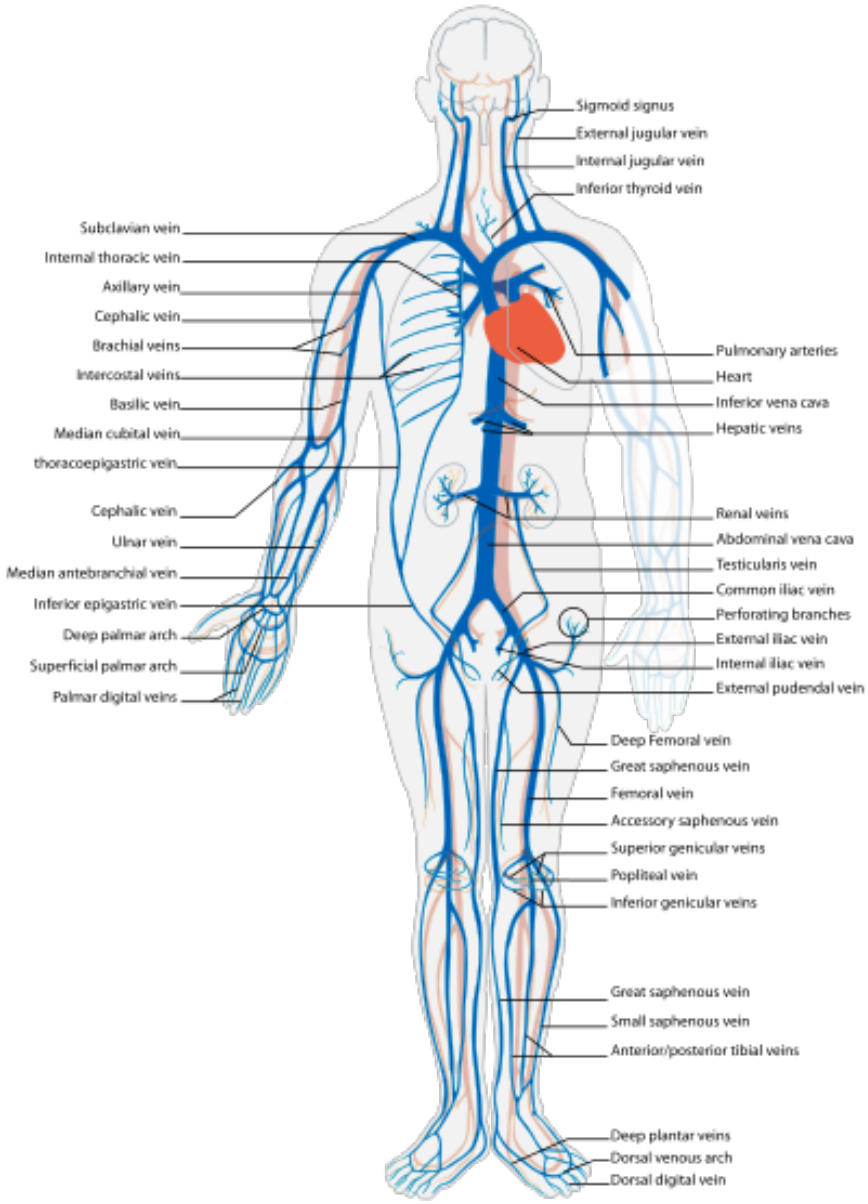

Figure 1.13: Veins of the human circulatory system[4]

1.1.6 Pulmonary Arteries

Pulmonary arteries are the sole type of artery carrying carbon dioxide-rich blood. They originate from the right heart and end into the lungs. They have been modeled once again as a capacitor and a resistance. Lung vessels present higher blood capacitance compared to the systemic circulation.

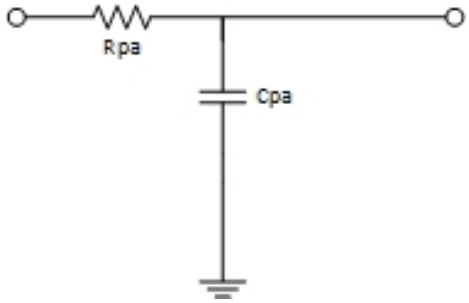

Figure 1.14: Pulmonary Arteries electrical equivalent circuit

1.1.7 Pulmonary Veins

Pulmonary Veins are the only kind of vein carrying oxygen-rich blood. They originate from the lungs and terminate into the left heart. They have been modeled as a capacitor, just like every other blood vessel, and their fluid-dynamic resistance has been modeled a resistance.

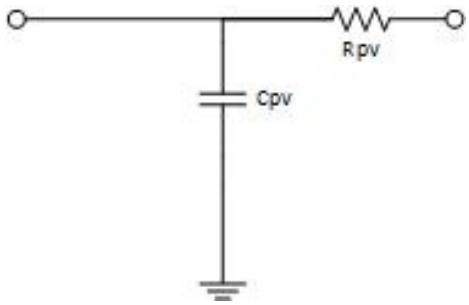

Figure 1.15: Pulmonary Veins electrical equivalent circuit

1.1.8 Lungs

The entire pulmonary circulation is characterized by lower pressure than systemic circulations, allowing a better diffusion of the oxygen into the blood. "Local pulmonary blood flow

and volume are therefore exquisitely sensitive to even a small variation in perfusion or transmural pressure that naturally occur with changes in hydrostatic pressure components" [15]. A static value of resistance (R_1) has been used to develop this first model flow dissipation, even though this assumption will be overcome later.

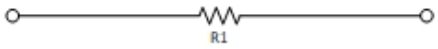

Figure 1.16: Lungs electrical equivalent circuit

1.1.9 Systemic Circulation

Finally, we assembled the fluid-dynamic resistance from all capillaries in one single component. Unfortunately, this simplification does not permit to distinguish between the several blood flows in the head, legs, arms and torso and thus will be overcome later.

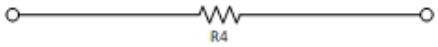

Figure 1.17: Systemic circulation electrical equivalent circuit

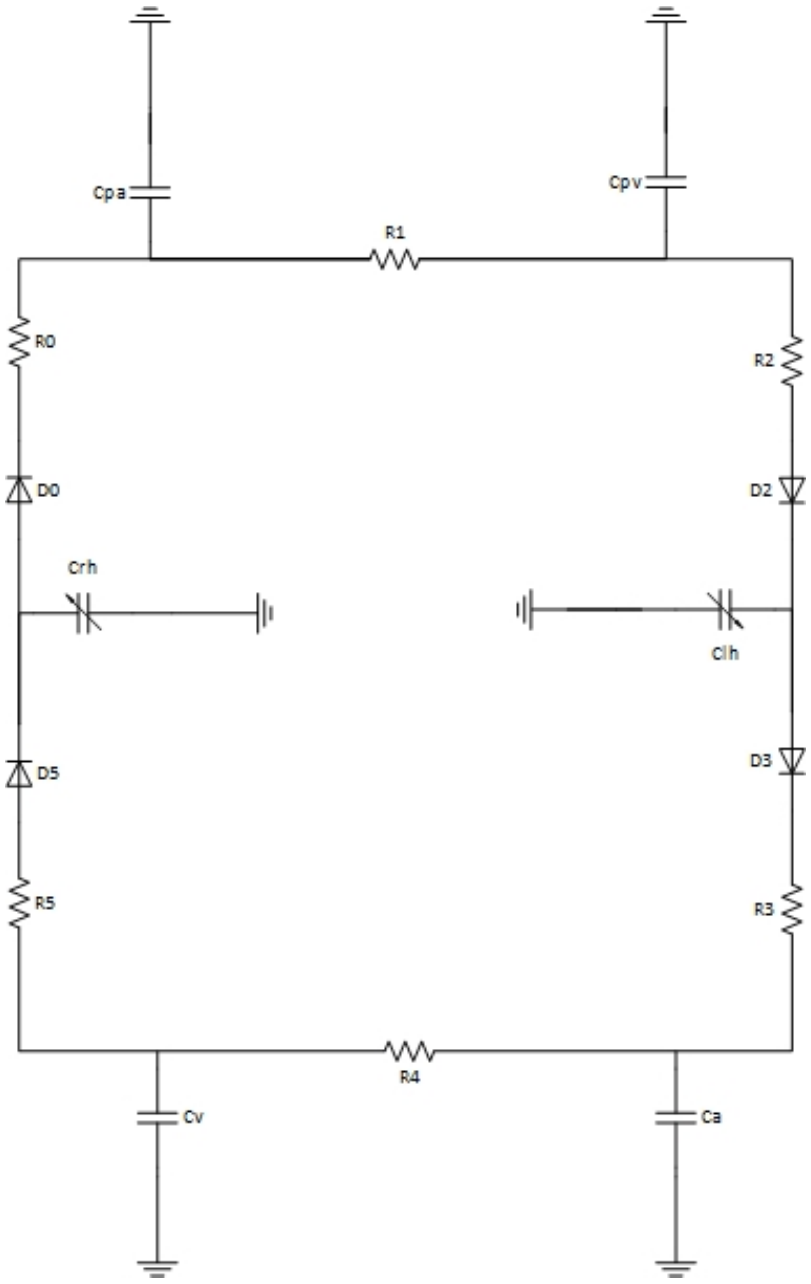

Figure 1.18: Six compartment model electrical equivalent circuit

1.1.10 Equations

In order to describe the behavior of the several organs, modeled as compartments, a set of mathematical equations has been employed. Supposing to know the initial pressure in each compartment it is possible to calculate the flow using Ohm's law (1.7). Ohm's law has been adapted via the electric analogy to bind pressure and flows through a resistance that has been considered fixed, non-dependent by the physical quantities aforementioned. In a few parts of the circuit, the flow has to pass through a valve (in this case there are 4 valves, as previously described). Valves have been modeled as ideal diodes. When pressure upstream is higher than the pressure downstream the diode lets the blood flow. Conversely, the valve closes, preventing reverse flow (1.1.10). In order to proceed, incoming and outgoing blood flows in each node have to be determined. This is carried out thanks to Kirchhoff's law for junctions (1.9). At this point, it is possible to use the constitutive equations of capacitors, which binds flow, pressure, and capacitance through a derivative relation (1.10) to propagate pressure to the next time-step. This equation can be solved with a numerical method. Volume in each compartment is computed as a zero-pressure filling volume V_0 plus pressure times capacitance. Thus, even if it not evident in equations, blood flow from one compartment to another makes the pressure and consequently the volume of the organ change, following the equation (1.11).

$$\Delta P_i = R_i q_i \tag{1.7}$$

$$q_d = \begin{cases} q_d & P_{us} > P_{ds}, \\ 0 & P_{ds} \leq P_{us} \end{cases} \tag{1.8}$$

$$\sum q_i = 0 \tag{1.9}$$

$$q_i = P_i \frac{dC_i}{dt} + C_i \frac{dP_i}{dt} \tag{1.10}$$

$$V = V_0 + PC \tag{1.11}$$

Finally, the generation of heartbeats has been done through an Integral Pulse Frequency Modulation (IPFM) [16]. This model allows for calculating the value of Transmembrane

Potential $M(t)$ every step. This value changes due to neural control through sympathetic or parasympathetic activity.

$$\int_{t_{k-1}}^{t_k} m(t)\,dt = \int_{t_{k-1}}^{t_k} (m0 + mr(t))\,dt \tag{1.12}$$

Where $m0$ is the inverse of the mean heart rate in resting condition and it is supposed constant, while $m_r(t)$ is the control action exerted by the arterial baroreflex and in this first model has a null value. The function $m(t)$ is defined as the inverse of the instantaneous heart rate variability (R-R interval) and equals:

$$m(t) = \frac{1}{I(t)} = \frac{1}{I_0 + \Delta I_{AB}(t)} \tag{1.13}$$

Where I_0 is the nominal heart rate of 67 beats per minute and $\Delta I_{AB}(t)$ is the control action. A new heartbeat occurs when the value of the integral exceeds a threshold potential $\Gamma = 1$ and the time passed since the previous beat is at least 0.2 times the preceding cardiac cycle length. This last constraint represents the refractory interval of time for cardiac pulse generating cells. Thus the heart beats in t_k when:

$$\begin{cases} \int_{t_{k-1}}^{t_k} m(t)\,dt \geq \Gamma \\ t_k - t_{k-1} \geq 0.2(t_{k-1} - t_{k-2}) \end{cases} \tag{1.14}$$

1.2 Twenty-one Compartment Model

The first model manages to describe the cardiovascular system dynamics but still lacks some important features, like the atrium-ventricular dynamic and it is not suitable to describe the effect of gravity since all the several arteries and veins are grouped in just two compartments with the same height difference from the heart. The Twenty-one Compartment Model overcomes these limits introducing the left and right atrium and subdividing the several vessel branches in different compartments. This new model includes the following:

- Ascending Aorta
- Brachiocephalic Arteries
- Head and Arms Arteries
- Head and Arms Veins
- Superior Vena Cava
- Thoracic Aorta
- Abdominal Aorta
- Renal Arteries
- Renal Veins
- Splanchnic Arteries
- Splanchnic Veins
- Legs Arteries
- Legs Veins
- Abdominal Veins
- Thoracic Inferior Vena Cava
- Right Atrium
- Right Ventricle
- Pulmonary Arteries
- Pulmonary Veins
- Left Atrium
- Left Ventricle

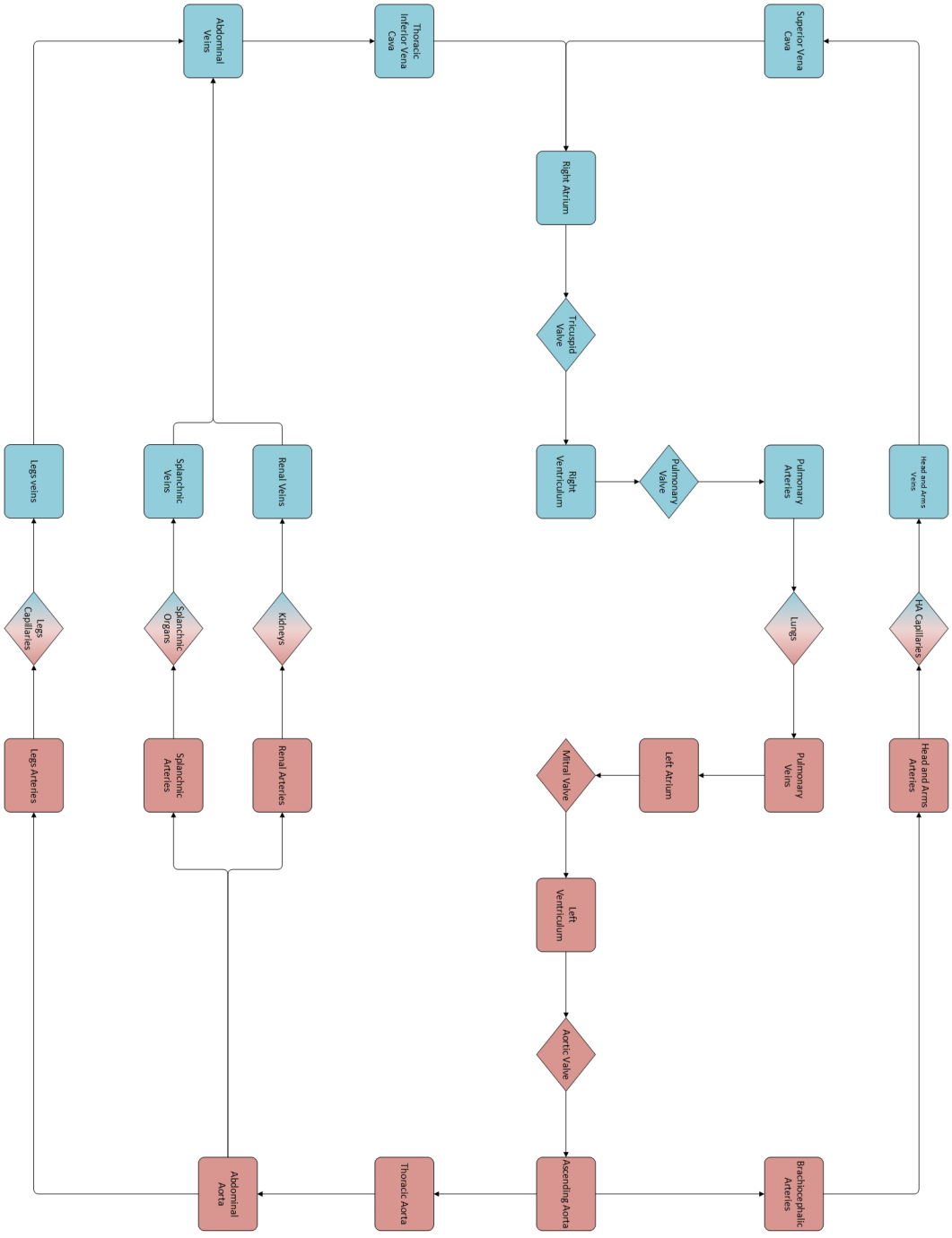

Figure 1.19: Six Compartment Model

This new model is very similar to the previous one, each type of compartment is modeled in the same way. Atria are modeled just like the ventricles 1.1, yet their beat comes 0.2 seconds before in a regular beat. There is one valve more, the eustachian valve, linking veins to the Right Atrium, preventing reverse flow during atrial contraction. This valve does not find an analog between the pulmonary veins and the left atrium since the pressure exerted by the heart is strong enough to keep the blood flowing in one direction. The arterial compartment has been divided into several branches, starting from brachiocephalic arteries and thoracic aorta branching out of the ascending aorta and then again parting the abdominal aorta into renal, splanchnic and legs arteries. The same considerations can be done for veins, merging several times before ending into the venae cavae. The equations used in the model are the same as the previous one, the only difference is the dimension of the system. For this reason, this model is computationally heavier than the previous one but still reasonably fast. Although all these changes make the model more complicated and slower than the previous one, there is a significant advantage as concerns accuracy. As already said, operating and properly modifying this model, it is possible to catch the effect of gravity in a clear way. Moreover, it is now possible to model the Cardiopulmonary Reflex since it works comparing the pressure sensed in the right atrium with a reference, providing a control action consequently. Together with Arterial Baroreflex, the Cardiopulmonary Reflex represents the built-in control system of the cardiovascular system, making possible facing all the different external loads, such as gravity, and condition the body could be in, like a sudden need of more oxygen to cells during movements.

Finally, the effect of intrathoracic pressure has been added to the model, taking into account the pressure induced by respiration by the compression and expansion of the thoracic cage. In this model, this pressure only modules the value of the lungs' resistance, yet affecting the dynamic of the entire system. Again all the parameters of the model are reported in Appendix A and they come from [15].

$$R_{lungs} = R_{0lungs}\frac{Pth}{max(|Pth|)} \tag{1.15}$$

The intrathoracic pressure has been modeled as a sinusoidal function that varies between -4 and -6 mmHg with a frequency of 12 breaths per minute [11].

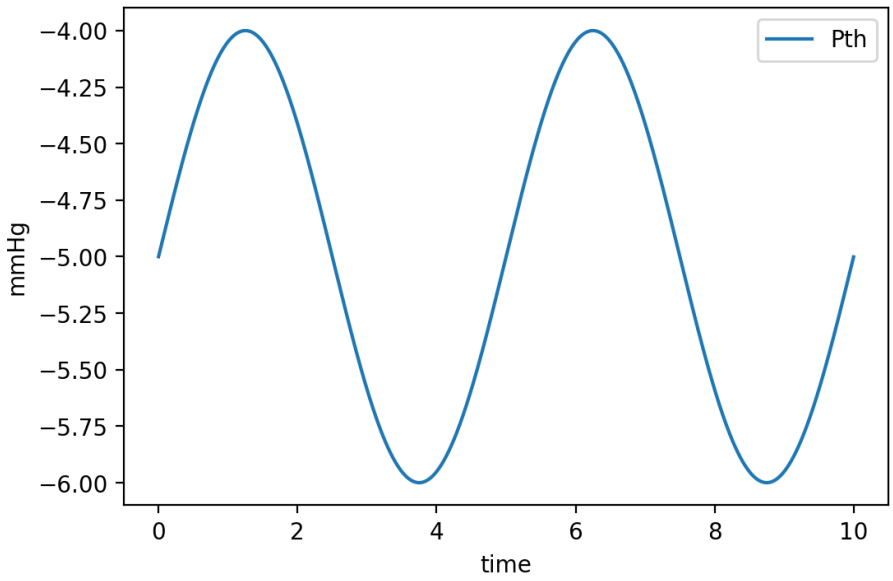

Figure 1.20: Thoracic Pressure curve

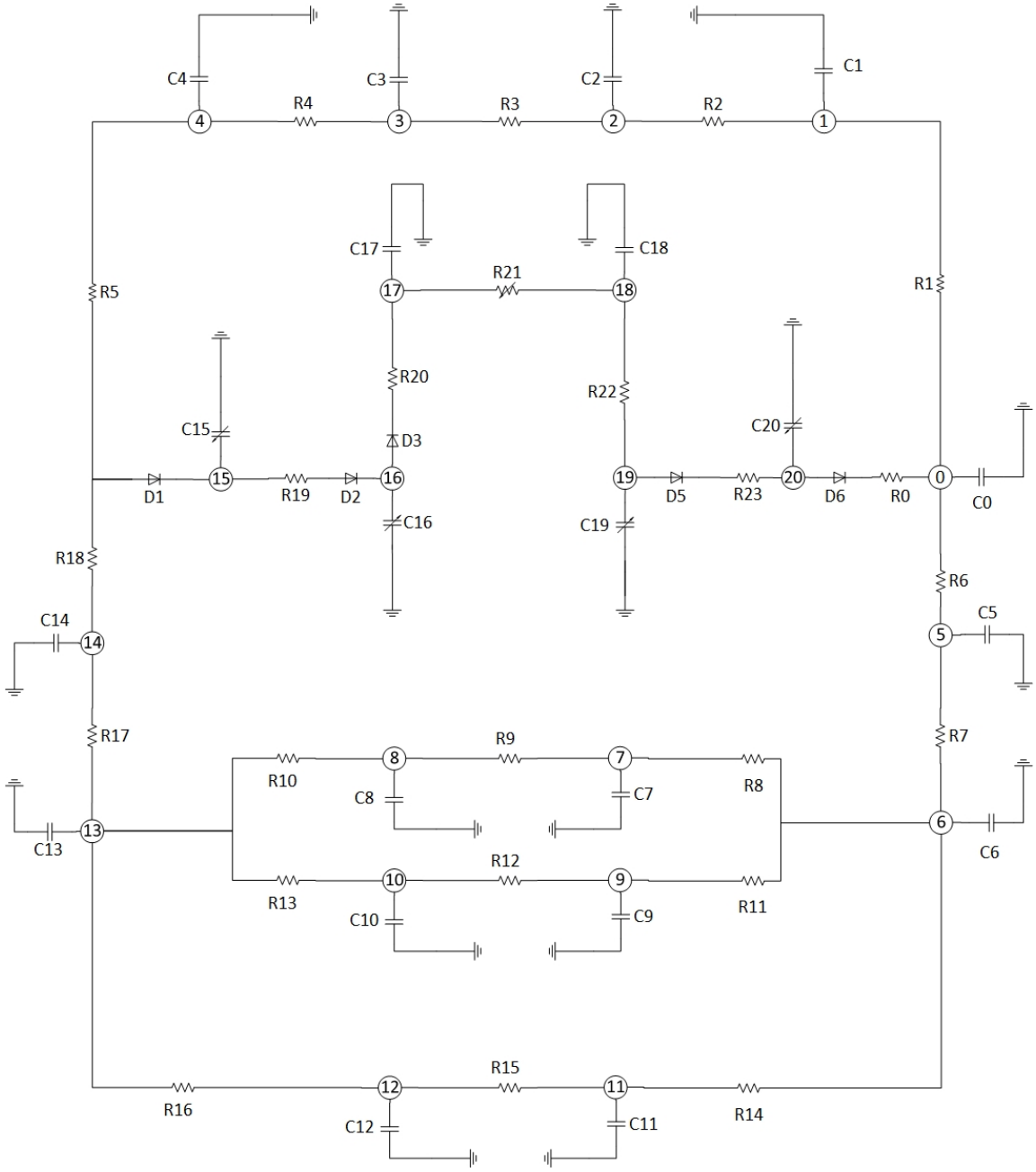

Figure 1.21: Twentyone Compartment Electrical Model

1.2.1 Gravity Effect

The cardiovascular system is subjected to gravitational loads since, depending on the posture, the compartments are located in different heights compared to the pump of this hydraulic system: the heart. This height difference between the several compartments generates a hydrostatic load according to Bernoulli's principle. For a standing position, the values adopted are reported in Table 1.1.

Compartment	**Height [m]**
Ascending Aorta	0
Brachiocephalic Arteries	+0.1
Head and Arms Arteries	+0.3
Head and Arms Veins	+0.3
Superior Vena Cava	+0.1
Thoracic Aorta	−0.1
Abdominal Aorta	−0.3
Renal Arteries	−0.3
Renal Veins	−0.3
Splanchnic Arteries	−0.3
Splanchnic Veins	−0.3
Legs Arteries	−1
Legs Veins	−1
Abdominal Veins	−0.3
Thoracic Inferior Vena Cava	−0.1
Right Atrium	0
Right Ventricle	0
Pulmonary Arteries	+0.05
Pulmonary Veins	+0.05
Left Atrium	0
Left Ventricle	0

Table 1.1: Compartment Height

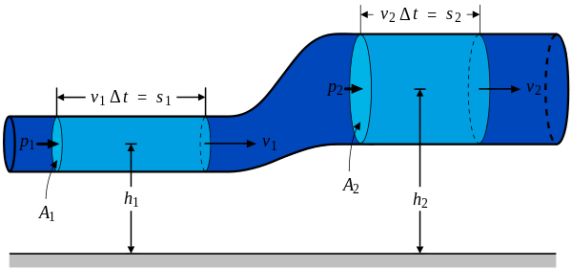

Figure 1.22: Bernoulli's principle graphic representation 1.16

$$P + \rho g z + \frac{1}{2}\rho V^2 = constant \tag{1.16}$$

Where ρ is the blood density and it is considered a constant with a mean value of $1060\frac{Kg}{m^3}$ and V is the blood speed in the vessels. In regular conditions, the value of V can be considered constant and thus the equation 1.17 simplifies to:

$$P + \rho g z = constant \tag{1.17}$$

On the other hand in some clinical conditions, like arteriosclerosis, the accumulation of lipid material into the arteries reduces the actual conduit section, determines an increasing speed, and thus a pressure drop. This makes the vessel shrink even more, decreasing once again the blood flow through the conduit. A similar effect can be found in upper body veins space conditions. Due to the absence of gravity, pressure increases, causing blood speed to drop and thus increasing the risk of stagnant flow. In fact, as demonstrated by [17], in veins like the jugulars pressure drops and phenomena of flow stasis occur, causing thrombosis.

$$P_n + \rho g z_n = P_{n-1} + \rho g z_{n-1} \tag{1.18}$$

$$\Delta P = \rho g (z_n - z_{n-1}) \tag{1.19}$$

This pressure differential is added between two compartments with a different value of height and it is represented as a Voltage generator in the equivalent circuital scheme.

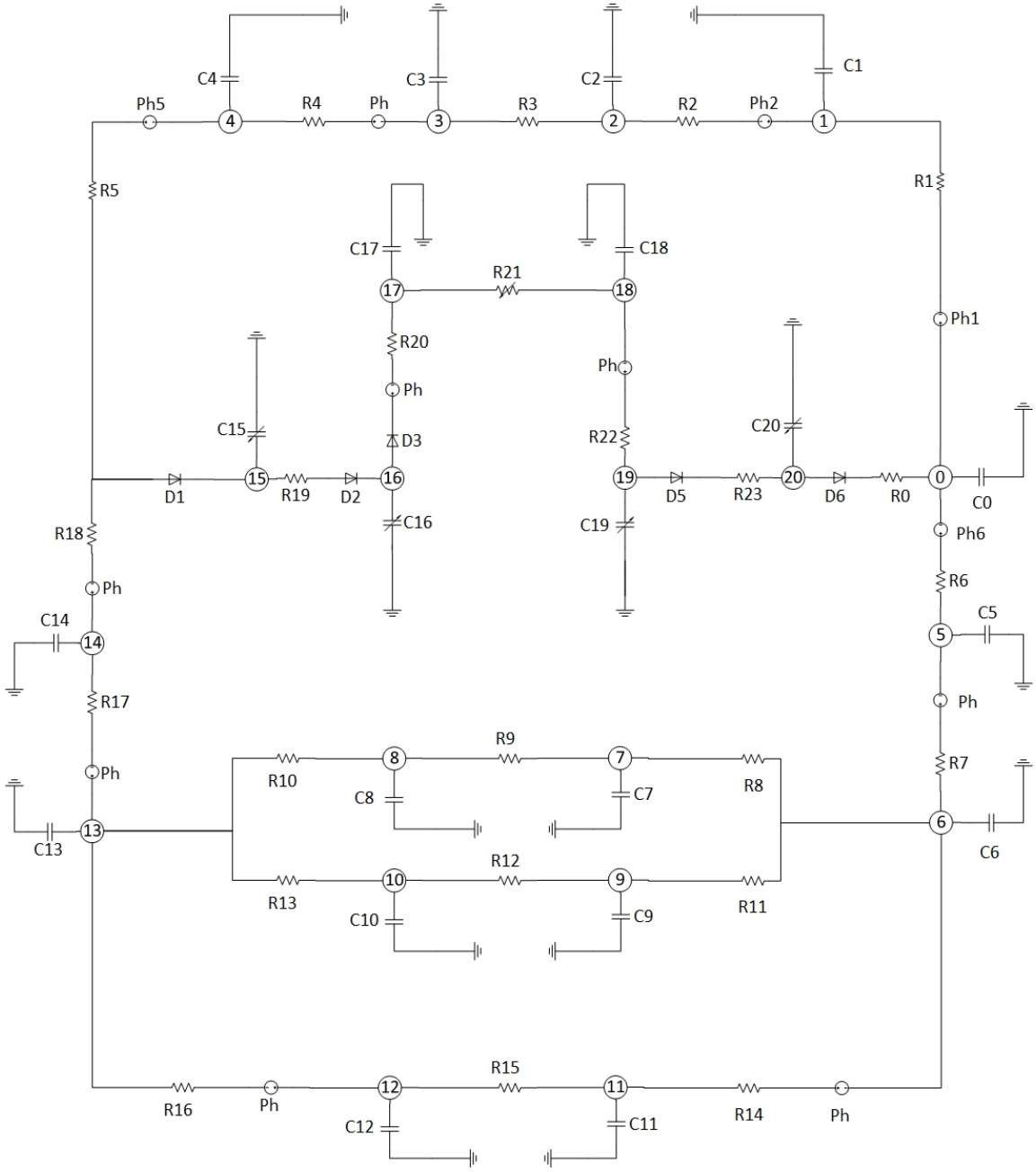

Figure 1.23: Twentyone Compartment Electrical Model

1.2.2 Arterial Baroflex

The Arterial Baroflex controls the high-pressure side of the system. It is capable of rapid and decisive response to sudden hemodynamic stresses [15]. It consists of pressure receptors in the arterial walls of the aortic arch and the carotid sinuses, linked to the nervous system by neural pathways. The reflex then compares these pressures with a reference one and enacts a control on heart rate, arterial resistance, venous zero-pressure filling volume, and cardiac contractility. In this work, the Arterial Baroreflex is modeled as a set-point controller aiming at minimizing the error signal. The arterial baroreflex operates through both two nervous systems. The Sympathetic nervous system releases Norepinephrine with the effects of increasing the heart rate, cardiac contractility, arterial resistance and decreases venous zero pressure filling volume. The Parasympathetic releases acetylcholine, with opposite effects. An equal gain for the heart rate control has been used for both the sympathetic and parasympathetic system, following the data used by Heldt in his thesis.

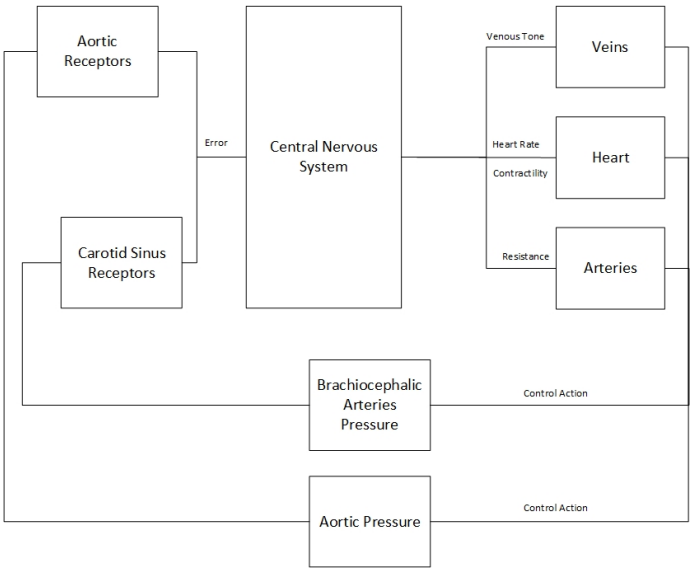

Figure 1.24: Arterial Baroreflex Schematic Representation

Mathematically, the reflex takes samples of pressure from the aortic arch and the carotid sinus every time step. These values are averaged in order to get two mean values (Aortic and Brachiocephalic Pressure) every 0.1 seconds. At this point, the two values found are arithmetically averaged and compared to a reference value of $95mmHg$. The error created then gets saturated through the equation 1.20.

$$\overline{P_{CS}} = \frac{\int P_{CS}(t)\ dt}{T}$$

$$\overline{P_{AA}} = \frac{\int P_{AA}(t)\ dt}{T}$$

$$\overline{P_A} = \frac{\overline{P_{CS}} + \overline{P_{AA}}}{2}$$

$$e_{AB} = \overline{P_A} - P_{Ref}$$

$$E_{AB} = 18 \arctan \frac{e_{AB}}{18} \tag{1.20}$$

The control action is determined from the error E_{AB} times a Gains, specific for each one of the involved variables, as displayed in Table A.10 in Appendix A. Gain values employed in this model come from Heldt PhD thesis [15].

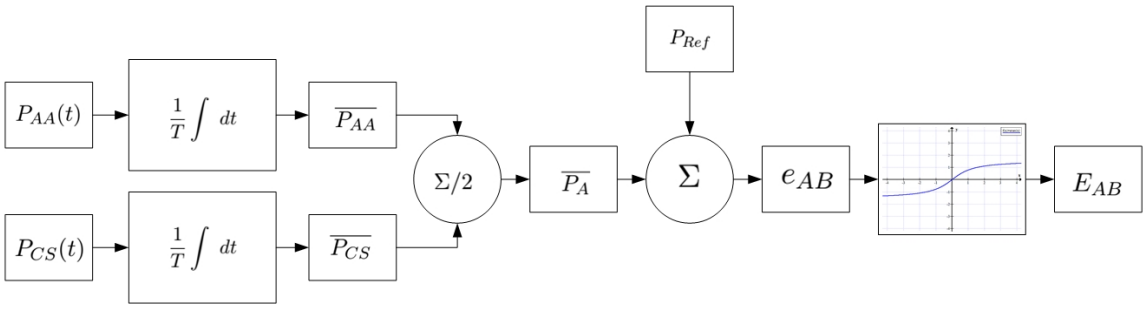

Figure 1.25: Arterial Baroreflex Flowchart

1.2.3 Cardiopulmonary Reflex

The Cardiopulmonary Reflex is the low-pressure side equivalent of the Arterial Baroreflex. Their architecture is very similar except for the fact that Cardiopulmonary receptors are located in the right atrium.
"While its role in long term neurohumoral control and renal fluid-electrolyte balance is hardly questioned, the effects of this reflex are still on debate" [15]. In fact, it is known that it influences the dynamic of vasopressin, antidiuretic hormone, atrial natriuretic peptide, and ADH. Moreover, "cardiopulmonar mediated vagal outflow has long been thought to contribute to vaso-vagal syncope during prolonged orthostatic stress or hemorrhage. It is also associated with a triad of cardiopulmonary responses (bradycardia, hypotension, and apnea) commonly referred to as Bezold-Jarisch reflex" [15].
Cardiopulmonary control of heart rate, known as Bainbridge reflex, has been largely documented in canines experiments but its significance or even its existence in humans has been questioned. For this reason, it won't be considered in the model, together with the influence on cardiac contractility. Thus, the control effects of the cardiopulmonary reflex manage arterial resistance and venous unstressed volume. The gains used to model this control system are displayed in Table A.11 in Appendix A and come from Heldt PhD thesis [15].

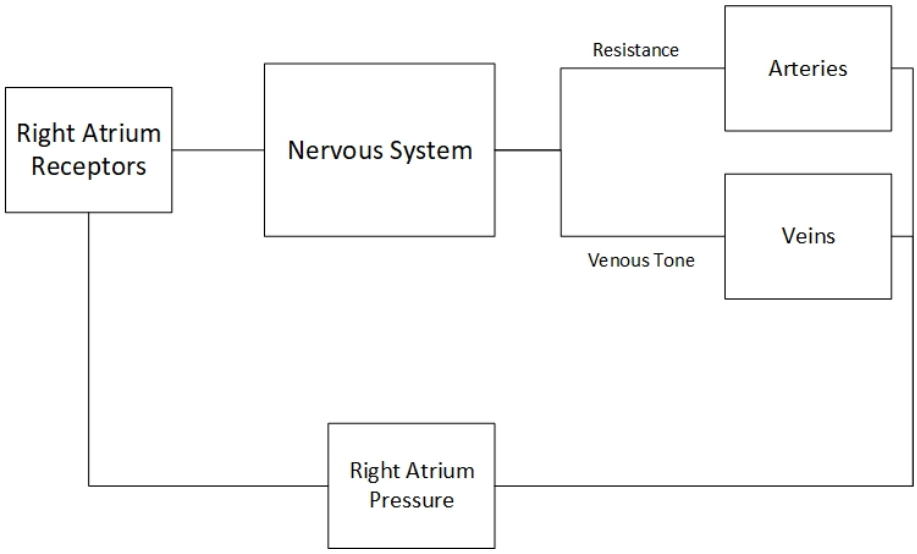

Figure 1.26: Cardiopulmonary Reflex Schematic Representation

The model takes samples of pressure from the right atrium every time step averaging the values in order to get a single mean value every 0.1 seconds. This value is then compared to a reference of $5mmHg$. The error created then gets saturated through an equation slightly different than before 1.21.

$$\overline{P_{CP}} = \frac{\int P_{CP}(t)\ dt}{T}$$

$$e_{CP} = \overline{P_{CP}} - P_{Ref}$$

$$E_{CP} = 5 \arctan \frac{e_{CP}}{5} \tag{1.21}$$

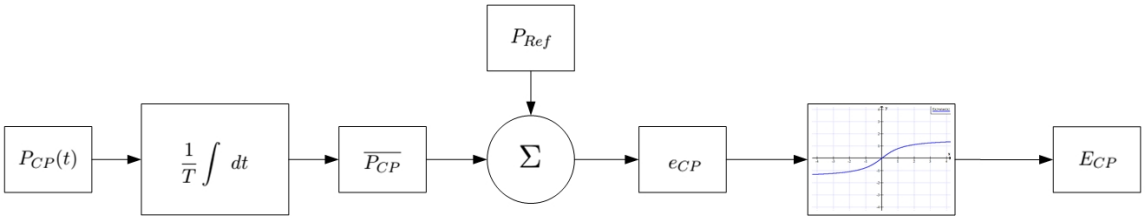

Figure 1.27: Cardiopulmonary Reflex Flowchart

Chapter 2

Software Implementation

The Entire software has been written in python 3.8 and it is divided into several files:

`data.py`
`Heart_class.py`
`functions.py`
`main.py`

The first file contains all the data the program needs, like gains, initial conditions for variables, and values of the several electrical components (B.1).

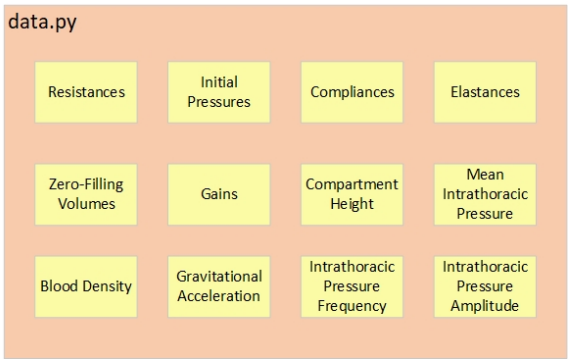

Figure 2.1: data.py schematic content

The second file is where the Heart class is located. This class gathers all the data needed to build the model of the heart and contains two important attributes. The first class function is called ”senoatrialpacemaker” and it is responsible for determining when the heart will beat again in the model thanks to the equation 1.14. The second one is

called ”beat” and computes the Compliance and Compliance derivative in every step of the beat.

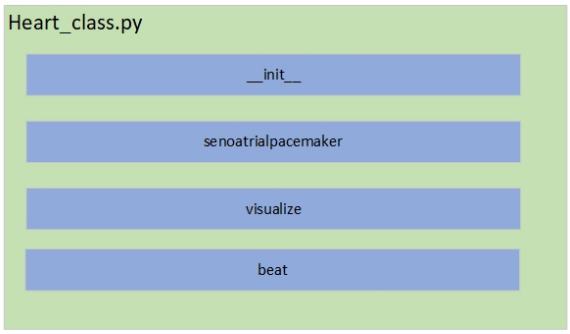

Figure 2.2: Heart class.py schematic content

The third file, as one could imagine from its name, contains all the different functions used in the main, in order to guarantee a well ordered, understandable, and reusable code.

Figure 2.3: functions.py schematic content

Name	**Description**
Initialization	This function takes data from the data.py file and prepares all the variables that will be used in the simulation
Heart append	Takes the compliances and derivatives for each part of the heart and stores the values in a list
sys ode	Defines the pressure differential equation to be solved to propagate pressure to the next time step
intrathoracic	Takes inputs from the data file and computes the intrathoracic pressure in every time step
flowcalculator	Starting from the compartments pressure, this function determines the blood flow between the compartments
compliance ass	This function assembles the Compliance and Compliance Derivative vectors (C and DC) to be used in the differential equation system
gravity	Computes gravitational effect on the compartments based on their height difference from the heart.
feedAB	This function contains the control actions of the Arterial Baroreflex
feedCP	This function contains the control actions of the Cardiopulmonary Reflex

Table 2.1: Function Description

Finally, the script main.py simply calls the other functions in the right order. It contains two main loops. The first one, the external loop, runs once per heartbeat and defines the heart compliances and its derivative before entering into the internal loop. The internal loop runs n times, where n depends on the heart cycle length and the time step. The time step used in the simulations is 10^{-4}. Every thousand steps the script activates the control action (10 Hz frequency). At the beginning of the internal loop, all the effects of the control action, gravity, and intrathoracic pressure are added to the proper value. At this point, the compliance C and its derivative DC are assembled. Then the flow between, in and out of the several compartments is computed starting from the pressure. The value of pressure is propagated in the next time step through the python routine solve_ivp with a Runge-Kutta method of order 4 and 5 ($RK45$). Finally, all the variables are saved in lists. The entire code has been reported in Appendix B

The diagram 2.4 has been created thanks to the python routine cProfile. It shows the hierarchy of the program together with the percentage of time spent inside a function out of the whole execution time and the number of function calls. The color code evidences the most computationally heavy functions. As expected, the program spends the majority of the time solving the 21 equation differential system.

The diagram 2.5 shows the relations between the variables and how they are computed. The yellow rectangles represent variables, the blue one functions, and the green ones class functions. Finally, the Red arrows indicate the control action.

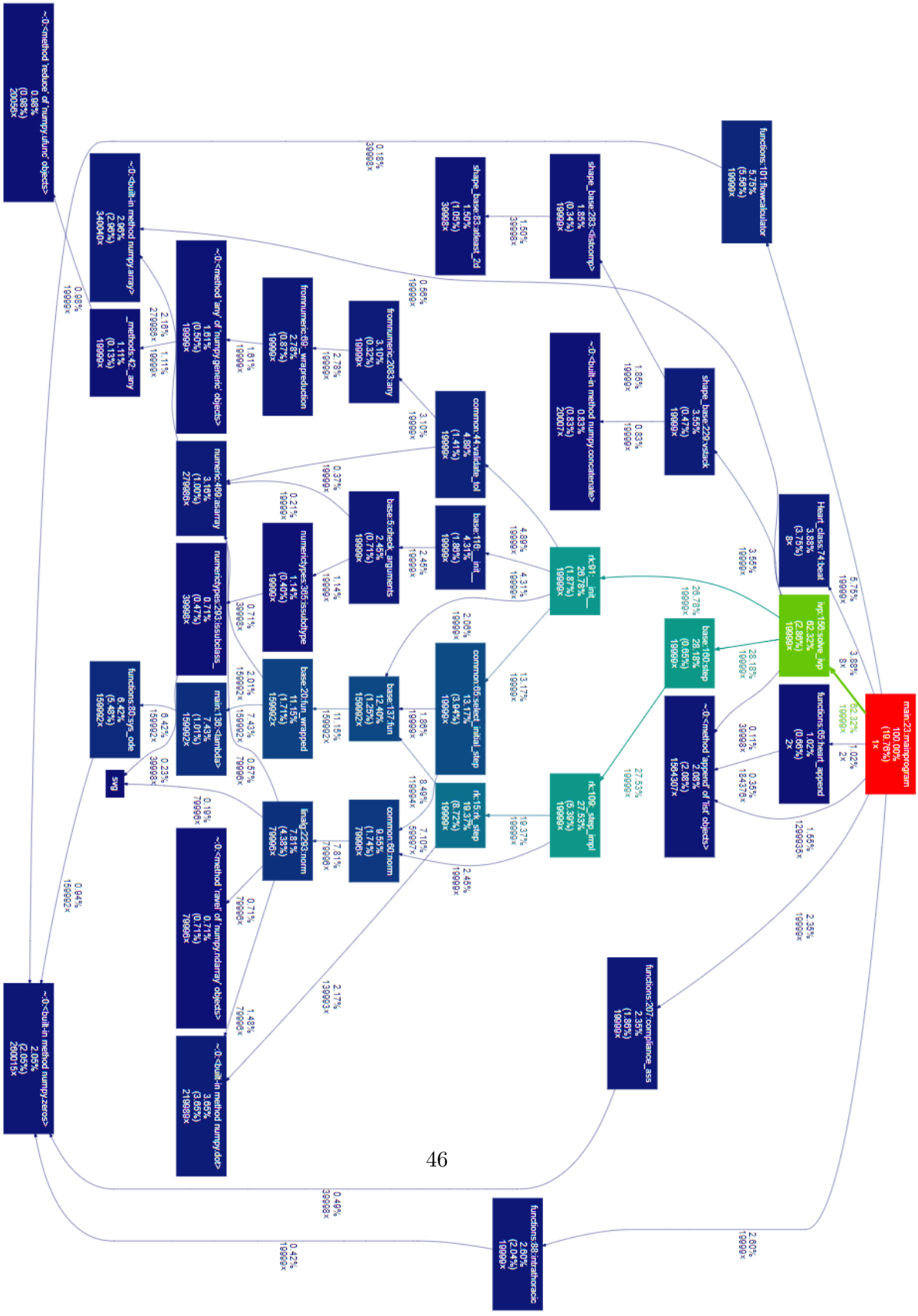

Figure 2.4: Program profiling

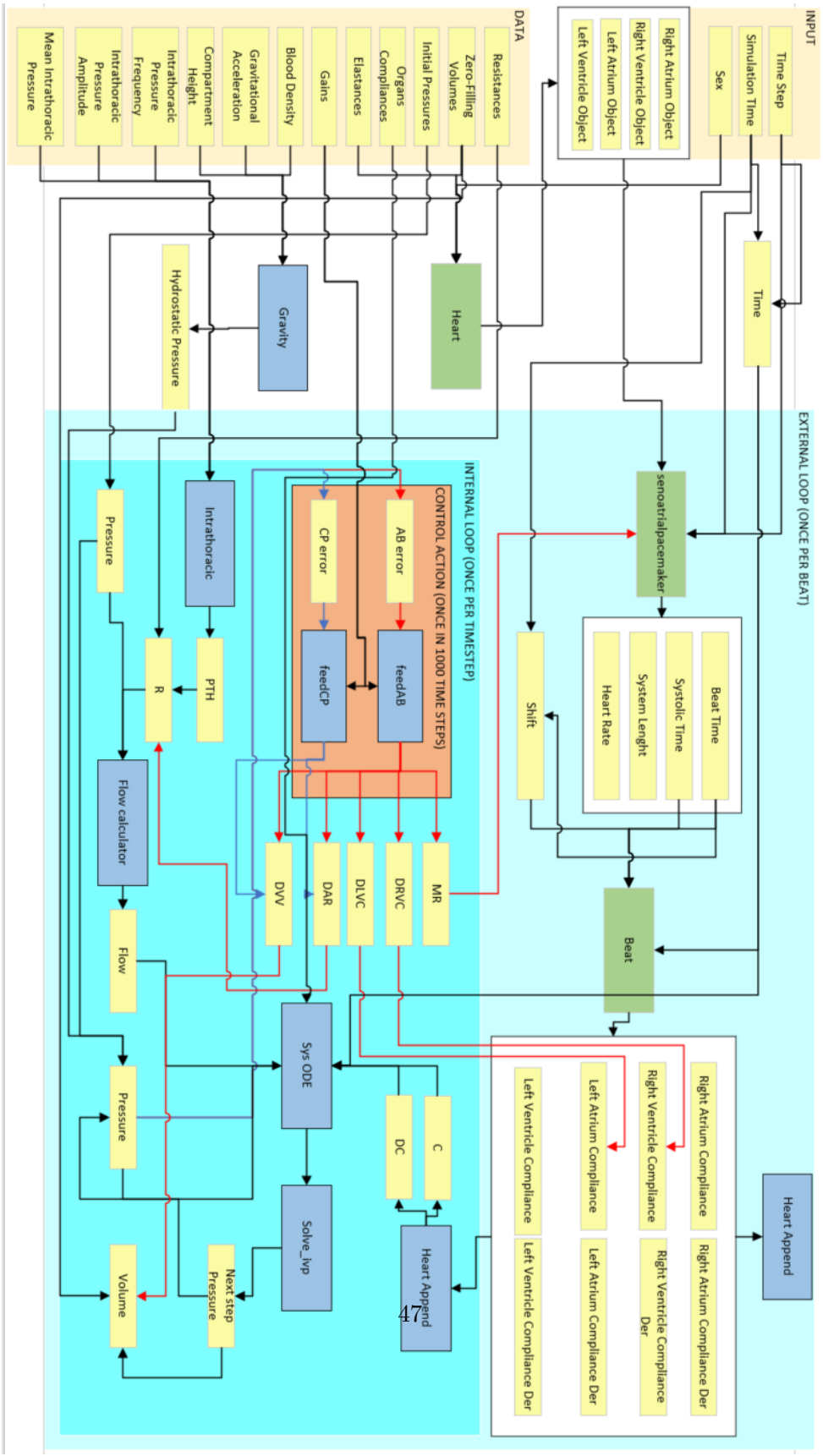

Figure 2.5: Program scheme

Chapter 3

Simulations

This chapter will present the results obtained by running simulation with the program described in the previous chapters. They will be compared with experimental data and with the simulation from the program CVSIM from physionet.org [18] in order to validate the model.

3.1 Base Model

Before starting analyzing the several variables curves, like pressure, compliance, and heart cycle, it is appropriate to recognize the presence of a transitory phenomenon that manifests itself at the beginning of the simulation. This is a numerical effect and it does not represent the behavior of the system. Unfortunately, it could not be eliminated due to the fact that it depends on the value of the equivalent resistance and compliance of the system which have been found in scientific literature and thus were not modifiable. The two following charts describe the pressure dynamics in the left and right heart, showing the relation between atrial (in green), ventricular (in blue), and arterial pressure (in red).

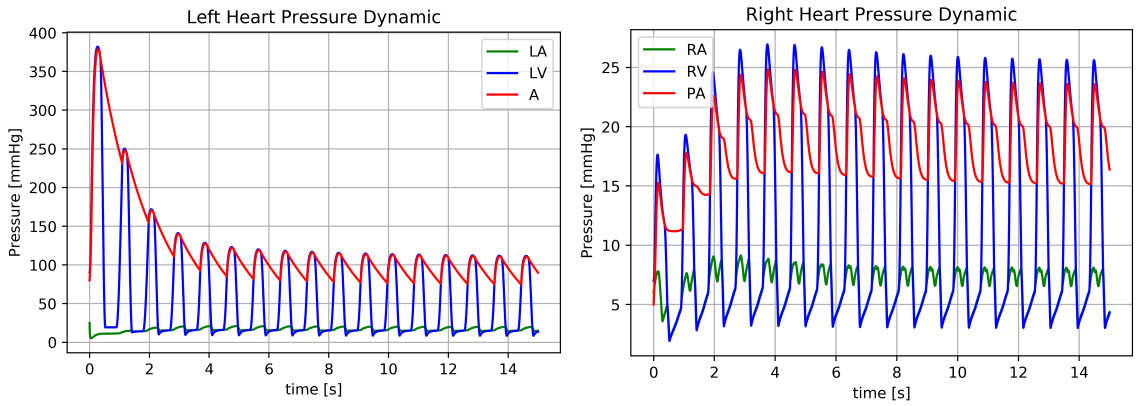

Figure 3.1: System Transitory

The heart chambers compliance, modeled thank to the equation 1.1, is reported in figure 3.2. Since compliance is the inverse of elastance, lower values of compliance imply a high elasticity and thus the contraction. It is also possible to notice the time shift between atrial and ventricular contractions. In the following pictures, 'RA' indicates the right atrium, 'LA' the left atrium, 'RV' the right ventricle, 'LV' the left ventricle.

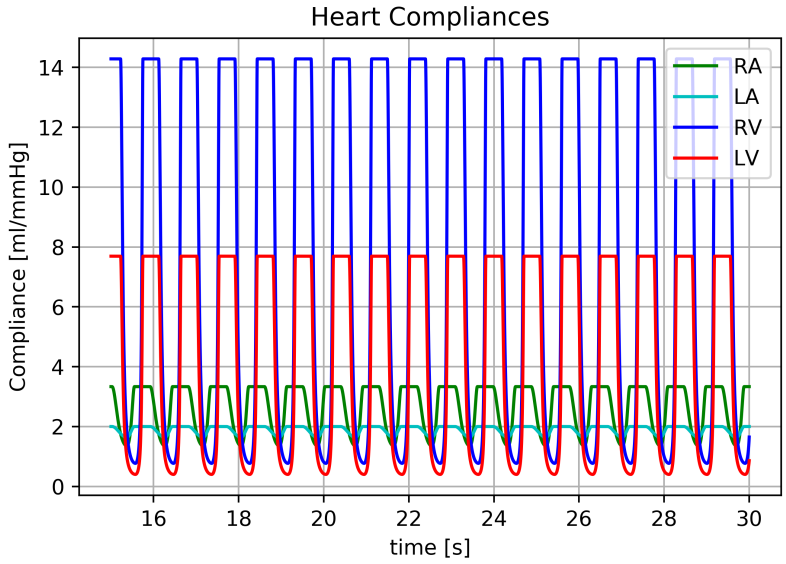

Figure 3.2: Heart chambers compliance

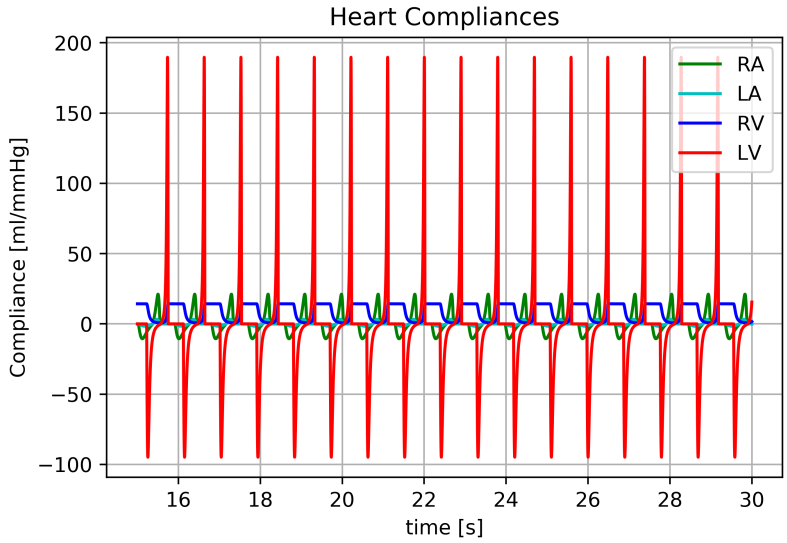

Figure 3.3: Heart chambers compliance derivative

The Left heart pressure dynamic is reported in picture 3.5. It is possible to notice how the arterial pressure decreases before the systole since blood is pushed only by the elastic action of arteries. As soon as the left ventricular pressure becomes greater than the aortic pressure, the aortic valve opens and allows the blood flow, increasing aortic pressure almost to the ventricular level. At the same time, the left atrium starts filling up due to the action of the right ventricle, thus its pressure rises. When the ventricle pressure starts dropping the valve closes and a new cycle begins. Similar behavior can be encountered in the right heart, with the sole difference of being on a lower pressure since, as already said, in order to correctly oxygenate the blood, the pressure has to be lower than $25 mmHg$.

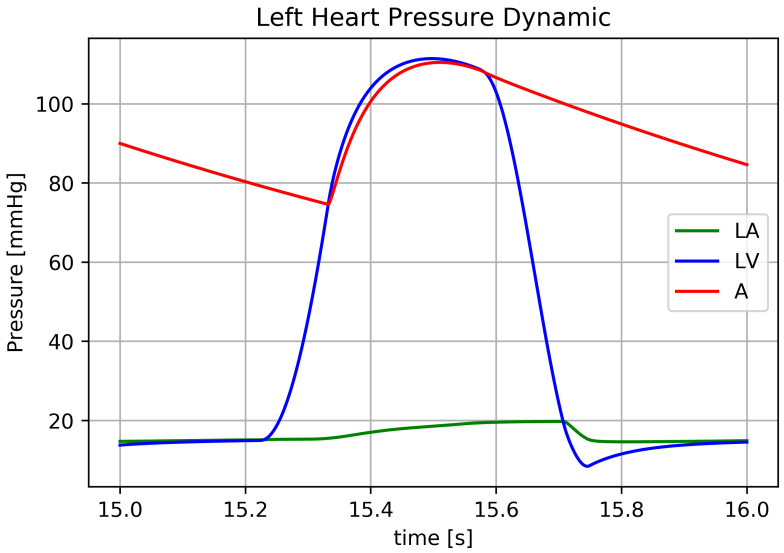

Figure 3.4: Left heart pressure dynamic closeup

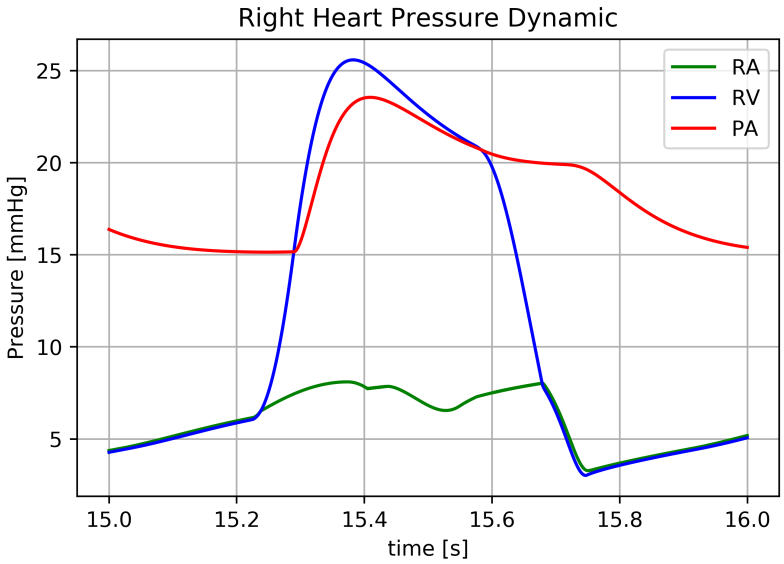

Figure 3.5: Right heart pressure dynamic closeup

Right and left atrium, as already said, differs anatomically for the absence of the Eustachian valve in the left one. The left atrium operates at higher pressures than the right one. In fact, the maximum pressure is around $20mmHg$ and a minimum of about $5 - 10mmHg$. On the other hand, being in the low-pressure part of the system, the right atrium operates between $2mmHg$ and $8mmHg$. At the beginning of the left atrium chart (3.6), pressure starts to increase slightly due to atrial systole, only to sharply rise during the ventricle systole due to the fact that the ventricular pressure is still very high and the Mitral valve remains closed. The right atrium pressure dynamic is portrayed in 3.7 and compared by the experimental data in 3.8. The rise at the beginning of the curve in the right atrial pressure is caused by atrial systole. Then the ventricular contraction causes the tricuspid valve to bulge upwards into the right atrium, thus increasing pressure [5]. After the contraction, the tricuspid valve moves away, decreasing atrial pressure. The subsequent peak is caused by blood flowing through the system and ending in the atrium with the tricuspid valve still closed. Finally, when the ventricular pressure drops under the atrial, the tricuspid valve opens and lets the blood flow into the ventricle letting a new cycle begin. All these events can be found in the ECG as ripples.

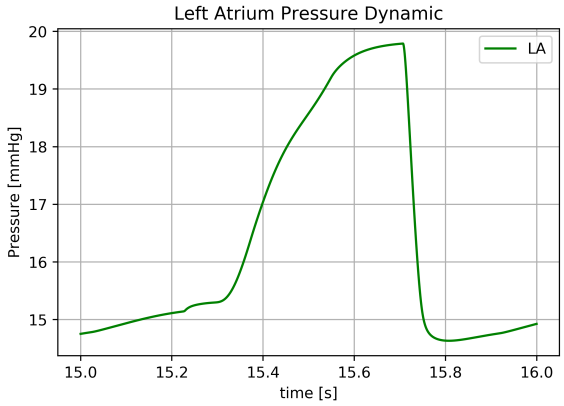

Figure 3.6: Left atrium pressure dynamic closeup

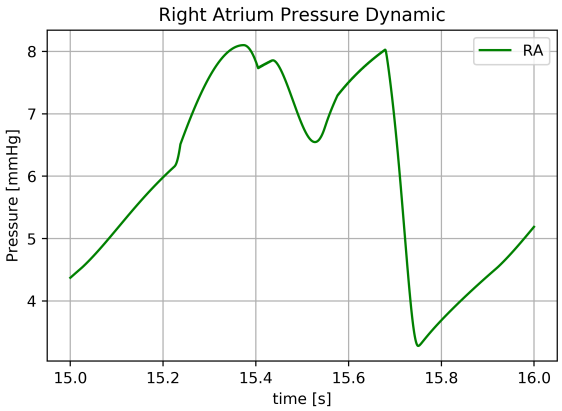

Figure 3.7: Right atrium pressure dynamic closeup

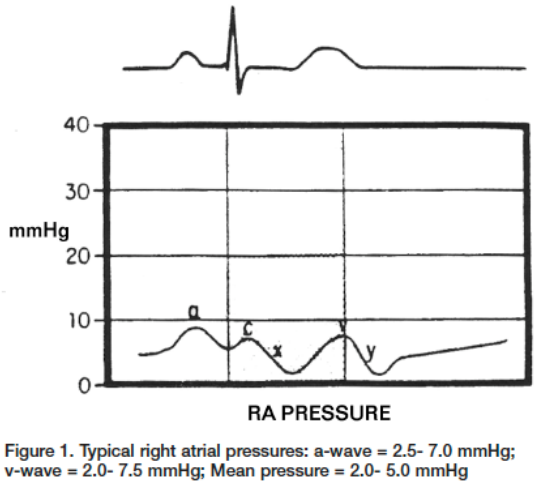

Figure 3.8: Right atrium pressure from experimental data [5]

In figure 3.9 and 3.10 is shown how the pressure varies in the left atrium (in green), ventricle (in blue), and the aorta (in red). The results have been compared to the program CVSIM, obtaining an excellent similarity.

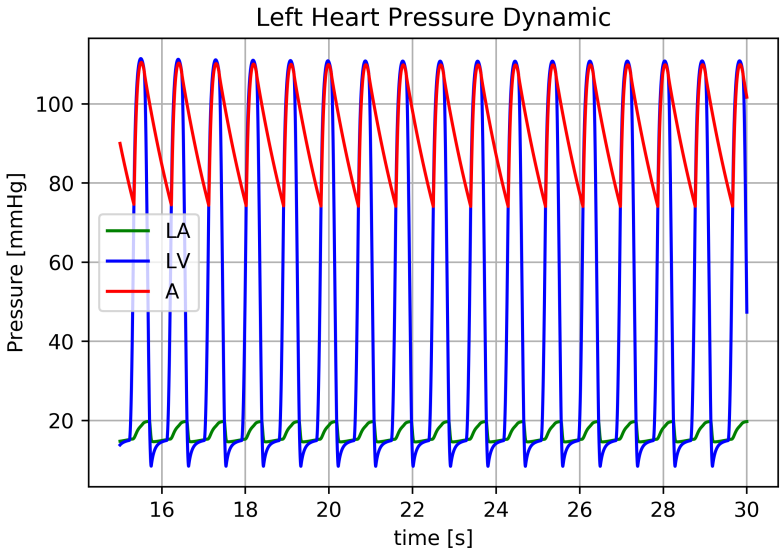

Figure 3.9: Left heart pressure dynamic

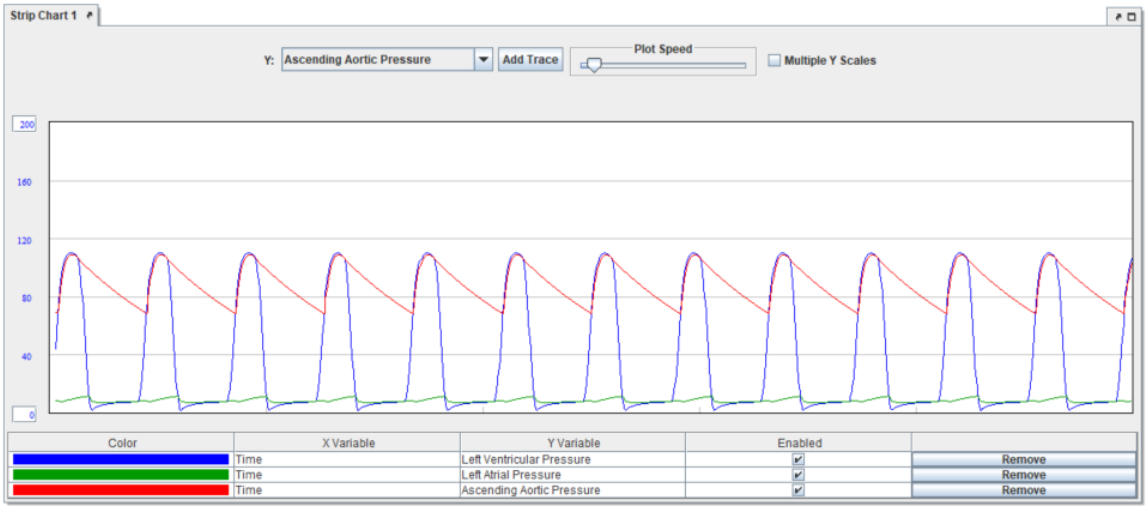

Figure 3.10: Left heart pressure dynamic from CVSIM

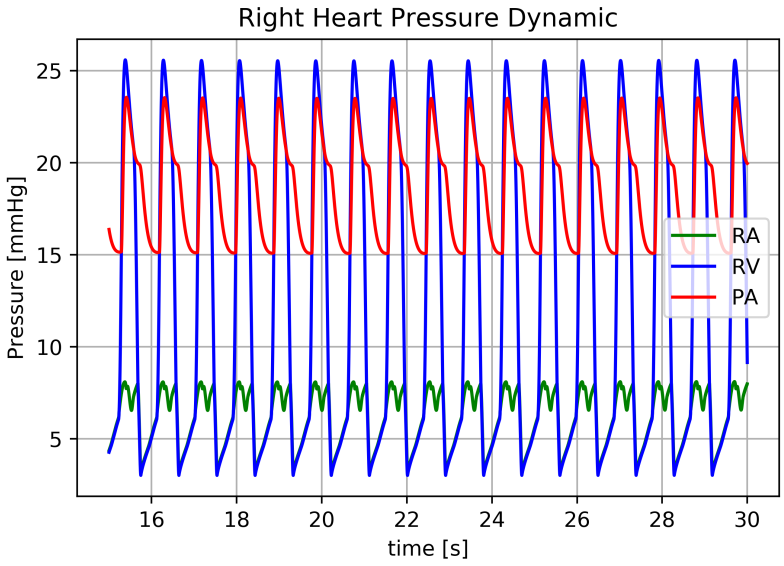

Figure 3.11: Right heart pressure dynamic

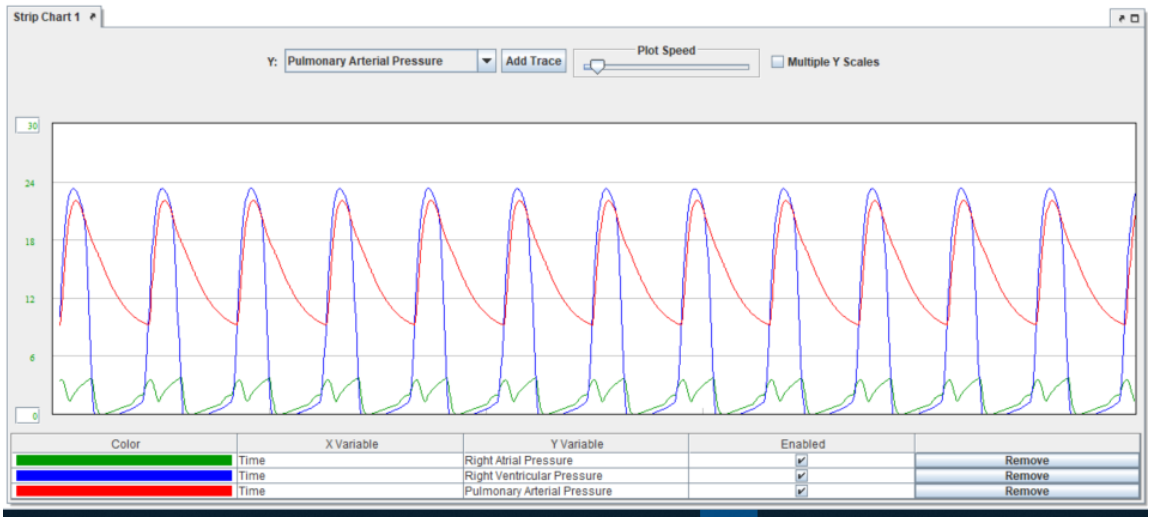

Figure 3.12: Right heart pressure dynamic from CVSIM

Another important curve to analyze is the Pressure-Volume cycle curve of the ventricles. It describes very well the pumping function of the heart as the area inside the cycle represents the work done by the single heart chamber. It is also possible to distinguish between the several cardiac phases. Starting from the top left part of the curve and proceeding anticlockwise it is possible to notice the isovolumic relaxation, where the cardiac valves are closed and the cardiac muscle relaxes, causing a reduction of the ventricle pressure with a constant value of volume. When the ventricular pressure drops under the atrial, the valve between atria and ventricles opens allowing blood inflow (descending part of the curve). The ascending part that follows is caused by the atrial systole, increasing the value of pressure in the ventricles since the valve is still opened. During the atrial diastole and when the ventricular systole starts, all the valves are again closed and the ventricles contract, increasing the value of pressure against a constant value of volume (isovolumic contraction). Finally, when the ventricular pressure goes over the aortic one, ejection occurs, pumping blood through the systemic circulation as concerns the left ventricle and through the pulmonary circulation for the right ventricle.

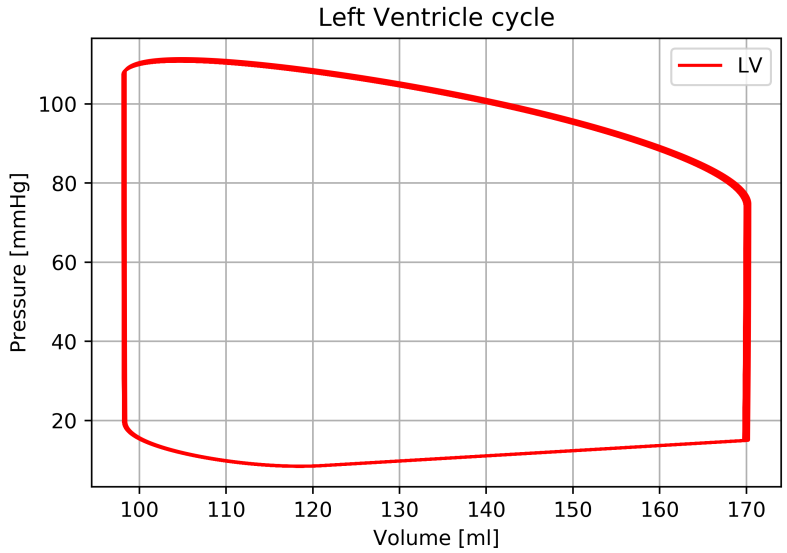

Figure 3.13: Left heart pressure volume curve

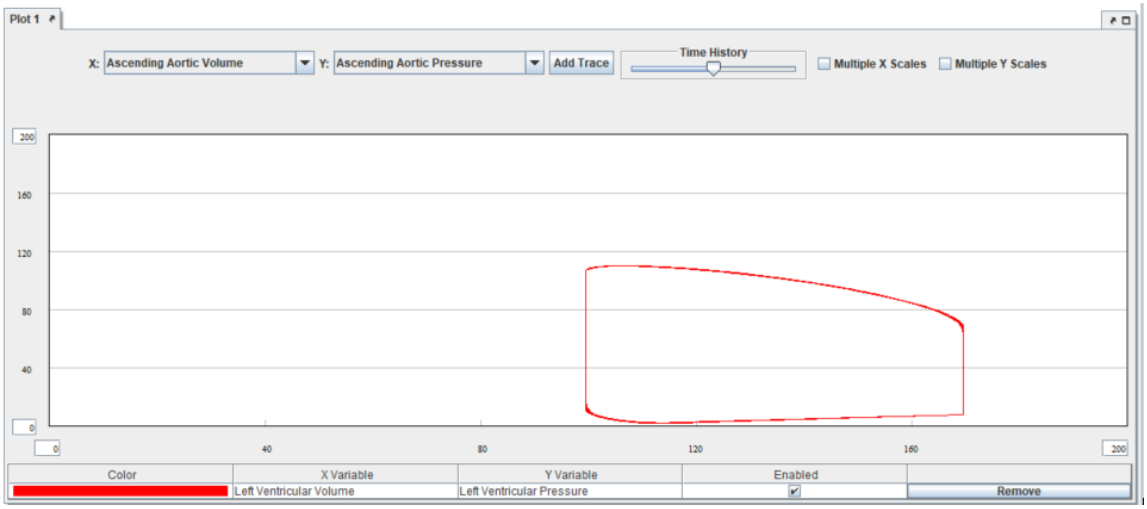

Figure 3.14: Left heart pressure volume curve from CVSIM

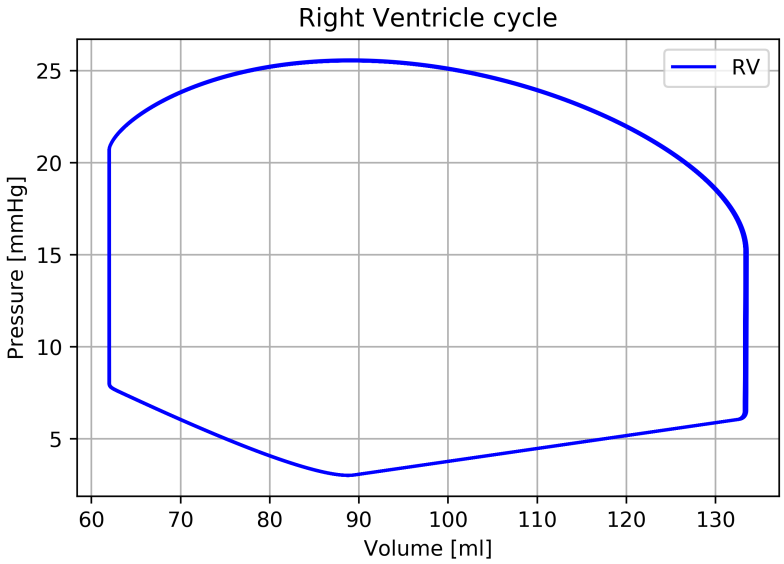

Figure 3.15: Right heart pressure volume curve

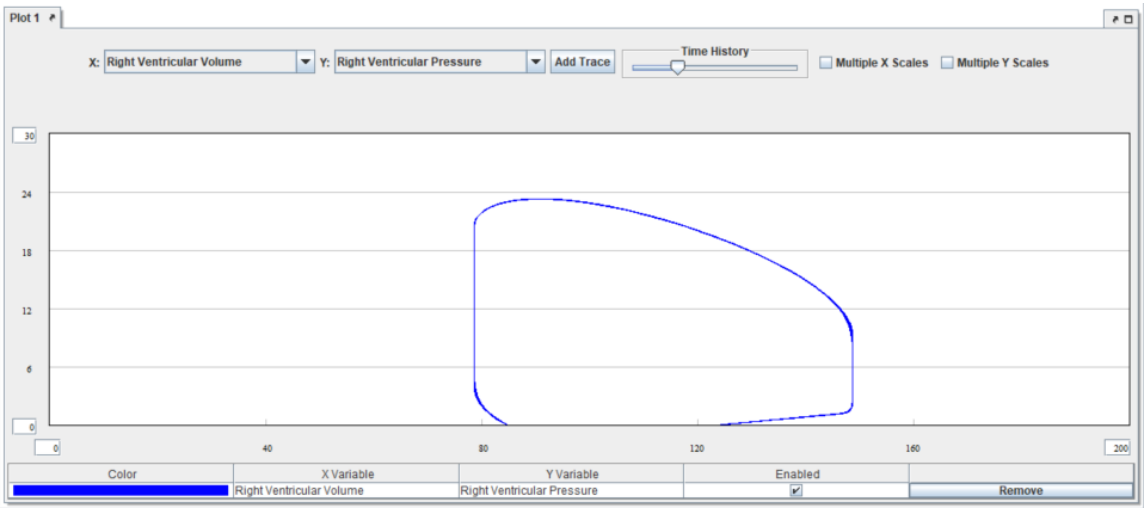

Figure 3.16: Right heart pressure volume curve from CVSIM

Finally, comparing the volume curves between the program and CVSIM, it can be noted how there is a slight difference in the Left Heart Volume curve. This is because the coefficient used in CVSIM differs from the one found in Heldt PhD thesis used in this program and for the presence of the Eustachian valve in this model.

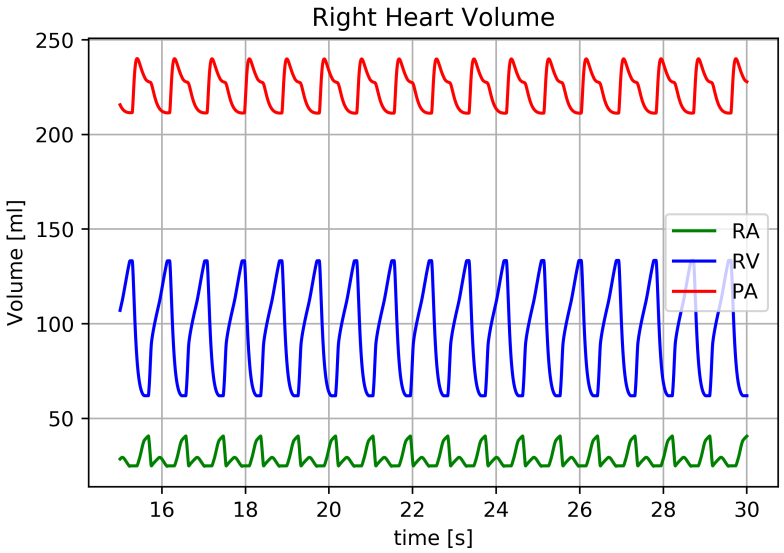

Figure 3.17: Right heart chambers volume

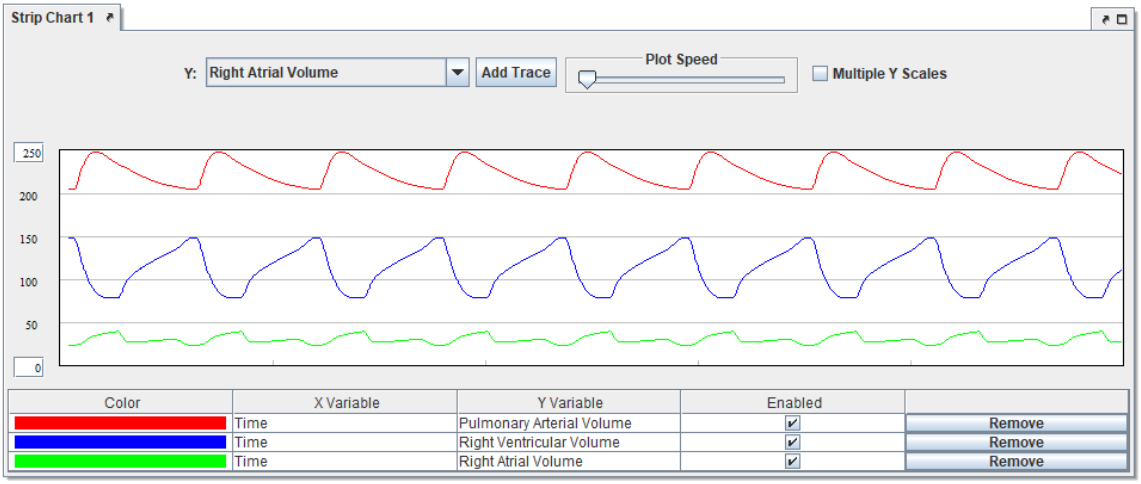

Figure 3.18: Right heart chamber volume from CVSIM

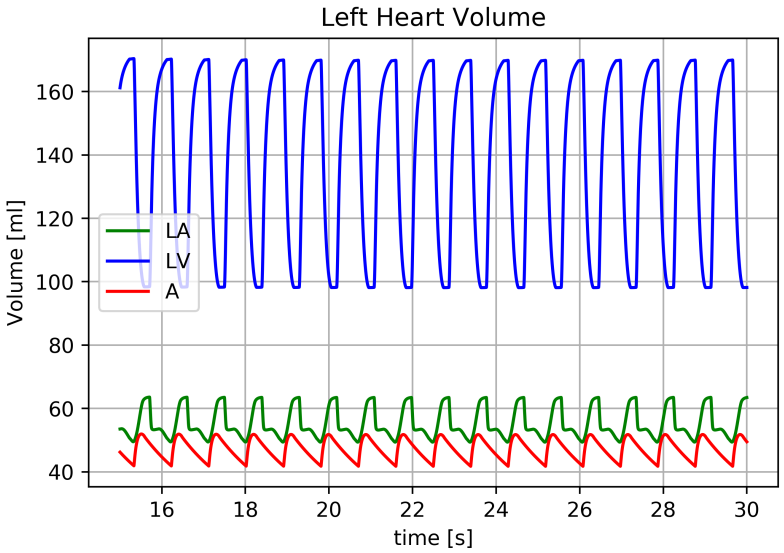

Figure 3.19: Left heart chambers volume

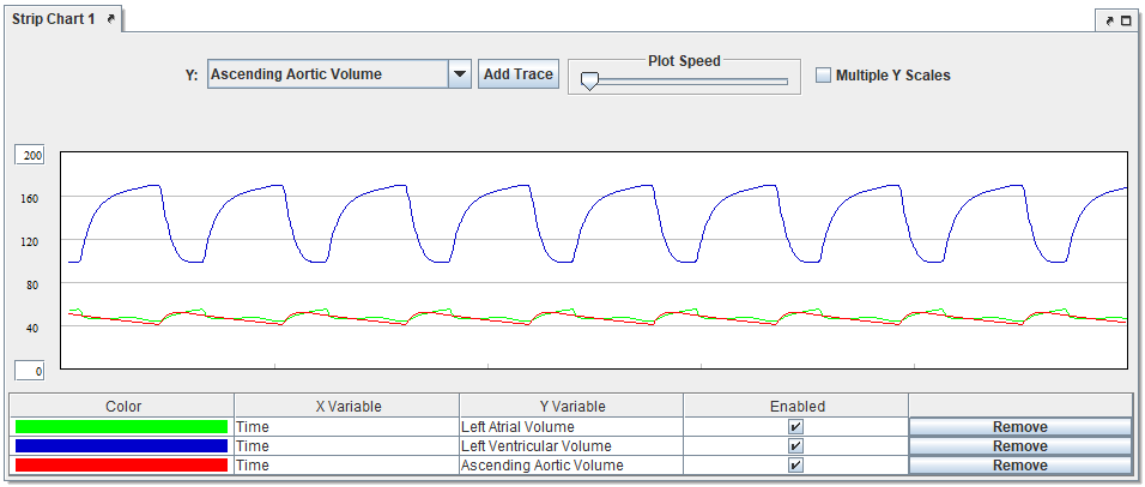

Figure 3.20: Right heart chamber volume from CVSIM

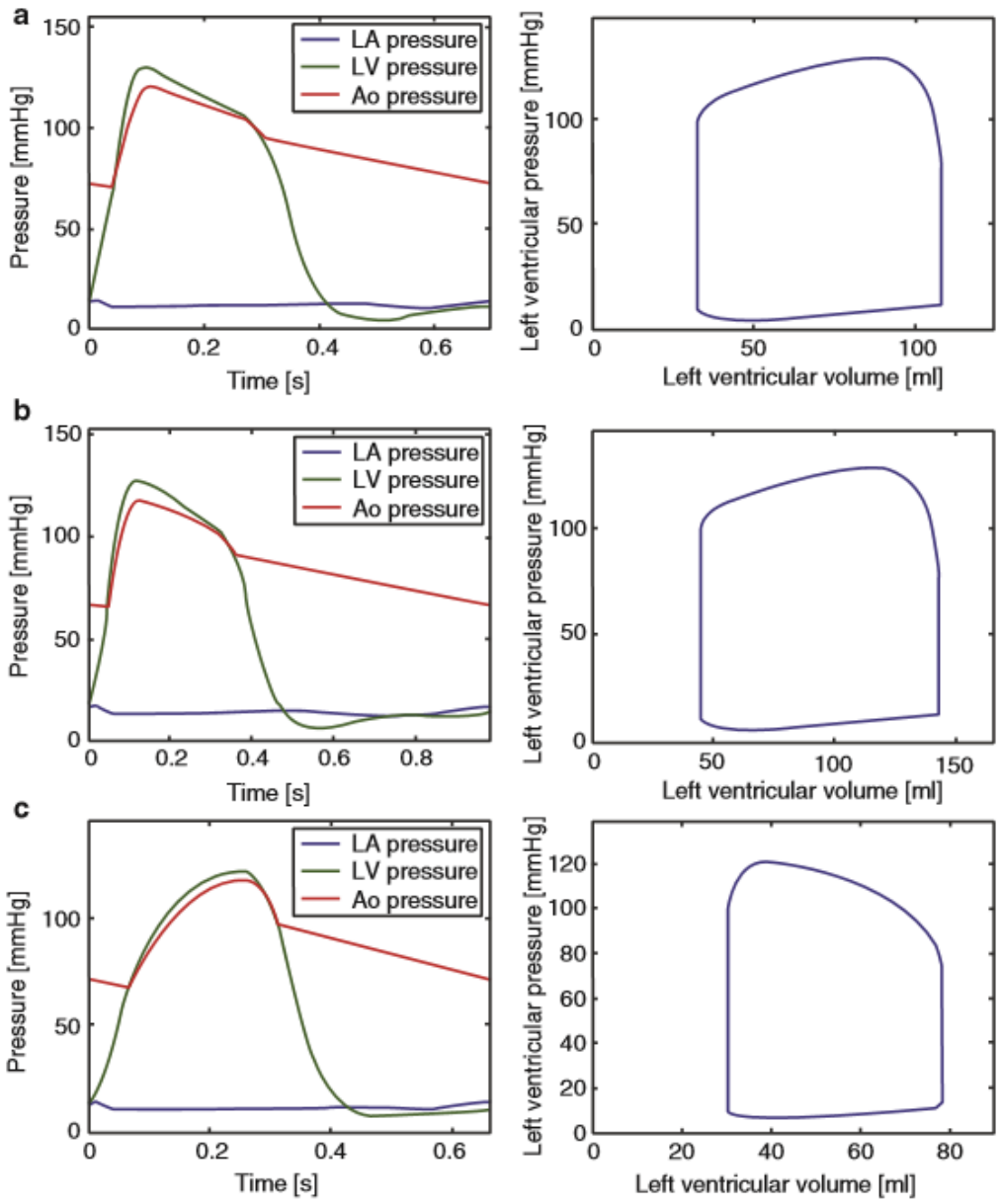

Fig. 5.5 Computed time-varying LA pressure, LV pressure and aortic pressure (*left side*) and PV loops for (**a**) volunteer 1, (**b**) volunteer 2, and (**c**) volunteer 3 (Itu et al. 2014)

Figure 3.21: Experimental data from [6]

3.2 Effect of respiration

Respiration causes the lungs to expand and contract in a cyclical fashion. For this reason, the opposing pressure in the alveoli can be described as a sinusoidal wave. The effect on the cardiovascular system is a periodic oscillation in both pulmonary circulation and systemic. However, this effect is much more evident in the first one since the pressure variation is almost negligible in the latter as it' s only visible in the left atrium pressure curve.

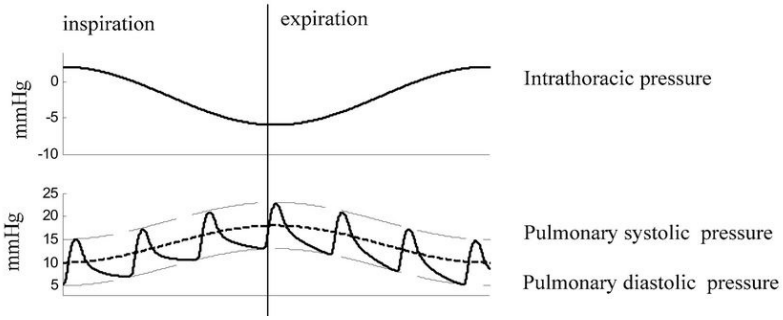

Figure 3.22: Respiration Effect

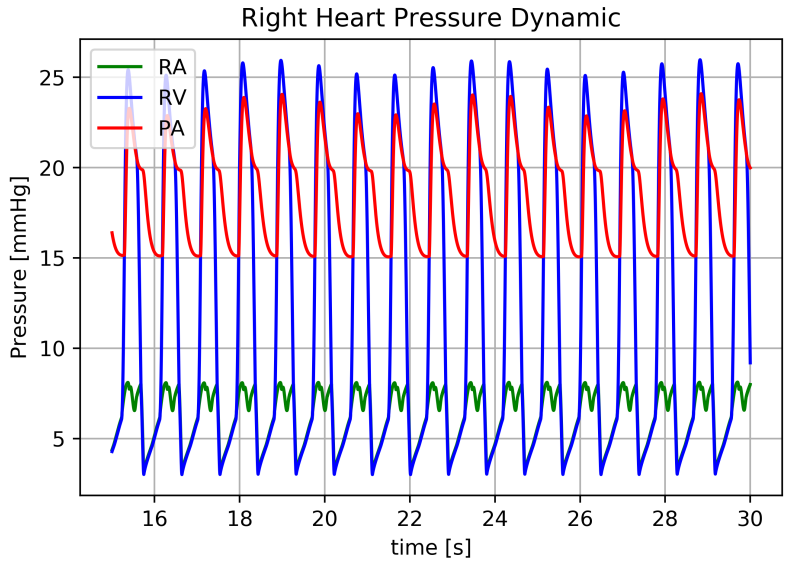

Figure 3.23: Right Heart Dynamics with Respiration Effect

3.3 Arterial Baroreflex and Cardiopulmonary Reflex

Adding the control loop to the model, it is possible to catch the variation in all the influenced variables. Since the system is not subjected to any load yet, these variations are only evident in the initial transitory, settling when the transitory ends. However, there are some residual oscillations caused by respiration as the cardiopulmonary reflex senses the pressure from the right atrium, just like it happens in reality. The heart rate, after a brief transitory, stabilizes itself on 65 bpm, a value that falls well within the normal heart rate in rest conditions. Also, the results obtained in the simulations have been compared by the experimental data gathered by Lucian Mihai Itu, Puneet Sharma, and Constantin Suciu in the book "Patient-Specific Hemodynamic Computations: Application to Personalized Diagnosis of Cardiovascular Pathologies" [6], resulting compliant.

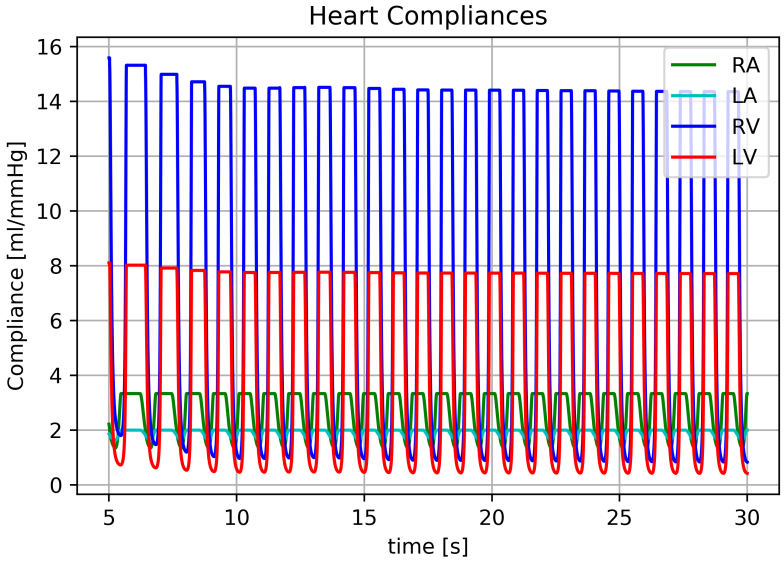

Figure 3.24: Reflex Effect on Heart Chamber Compliance

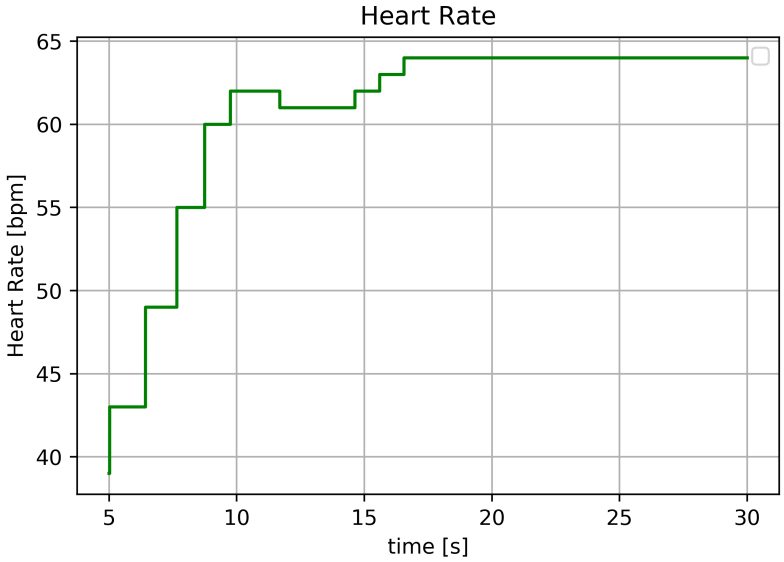

Figure 3.25: Heart Rate Curve

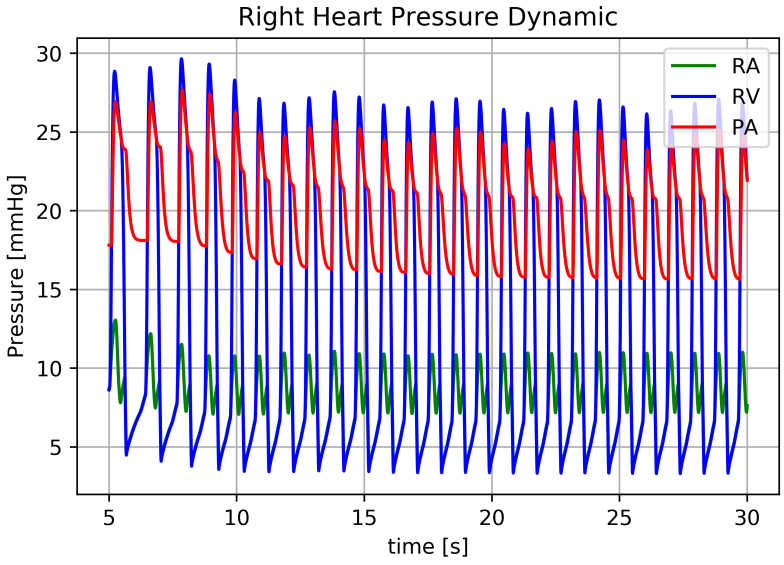

Figure 3.26: Control Loops effect on Right Heart Dynamic

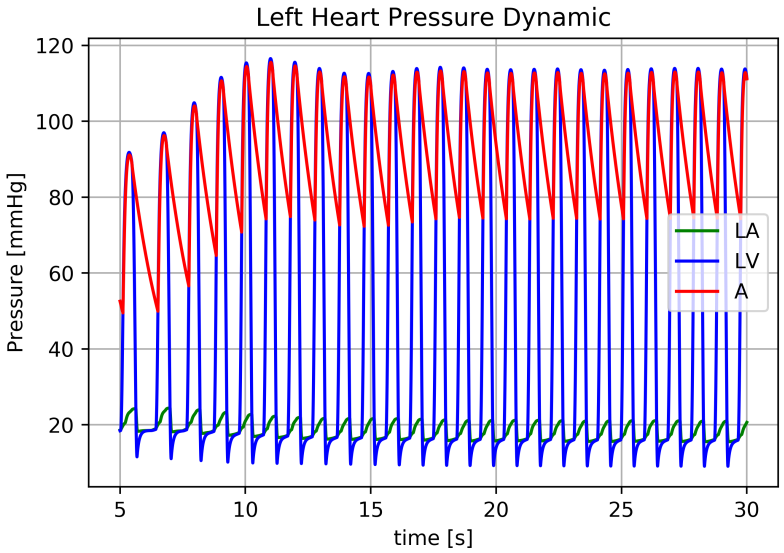

Figure 3.27: Control Loops effect on Left Heart Dynamic

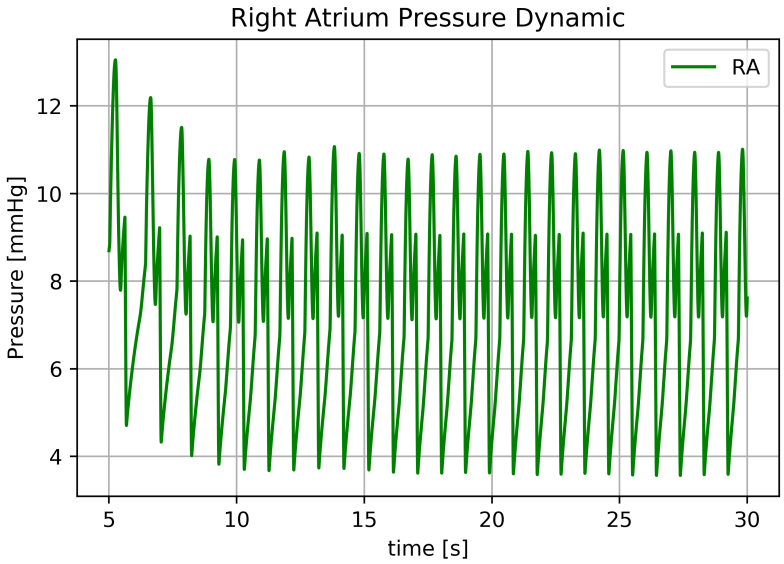

Figure 3.28: Control Loops effect on Right Atrium Closeup

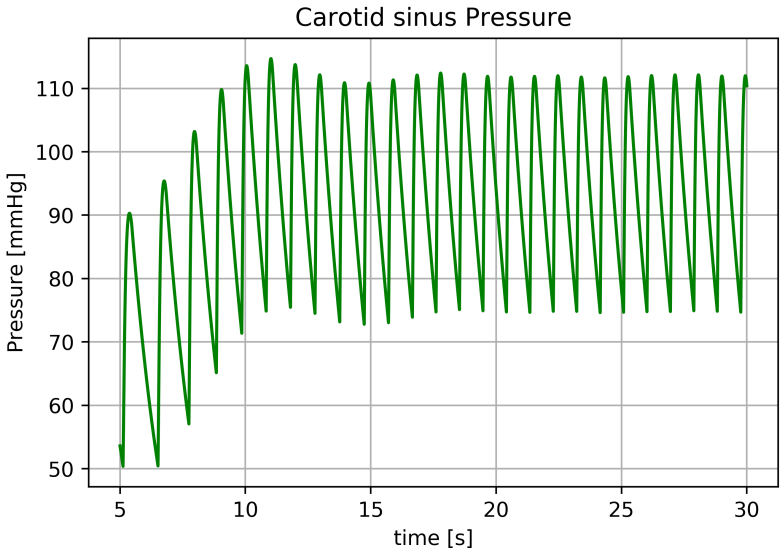

Figure 3.29: Control Loops effect on Carotidal Sinus

3.4 Gravity Effect

The human body on earth is always subject to the effect of gravity. When lying horizontally its effect can be neglected, since all the several organs are on the same level. This changes in a standing position. In this case, the hydrostatic pressure has to be taken into account. This additional pressure pushes the body fluids downwards resulting in pressure and blood volume drop in the organs above the heart and increasing them in the compartment below. The human body has developed several control mechanisms to fight these sudden changes. The principal is the Arterial Baroreflex, sensing the pressure variation and providing an appropriate control action. The problem of high pressure in the legs arteries is balanced by the fact that all the capillaries leak. As the pressure increases, capillaries leak more, draining part of the excess blood through the lymphatic system. Another mechanism is the presence of valves in the veins, preventing reverse flow in organs where pressure could drop too much. Finally, there is the muscular pumping action, helping the blood to climb from legs to the heart. The model manages to simulate correctly these effects of gravity. In fact, all these behavior taken into account and their consequences are observed in the simulations.

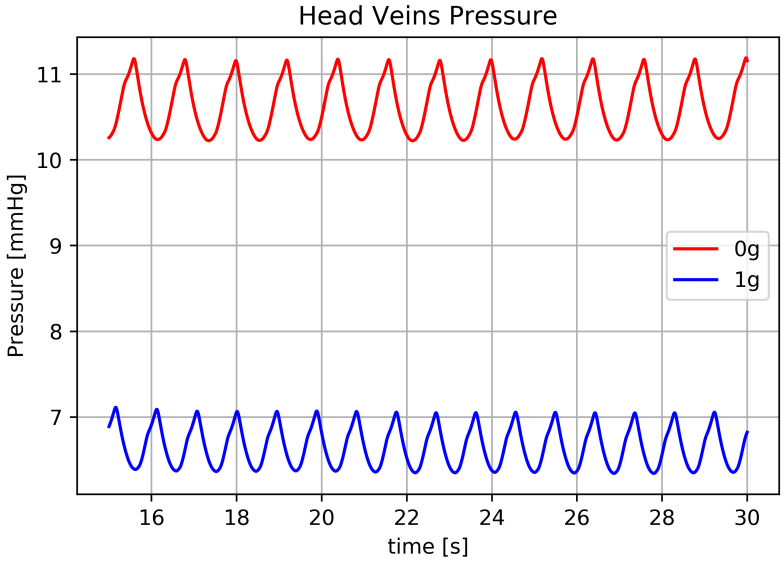

Figure 3.30: Head Veins Pressure change with gravity

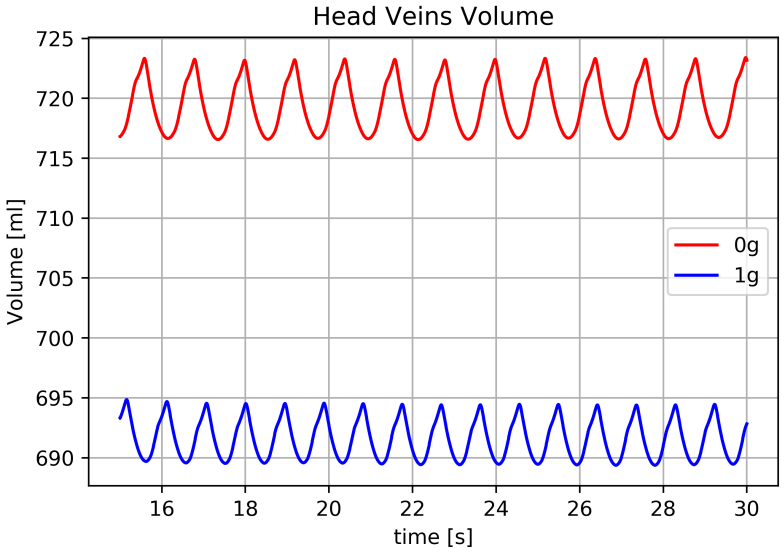

Figure 3.31: Head Veins Volume change with gravity

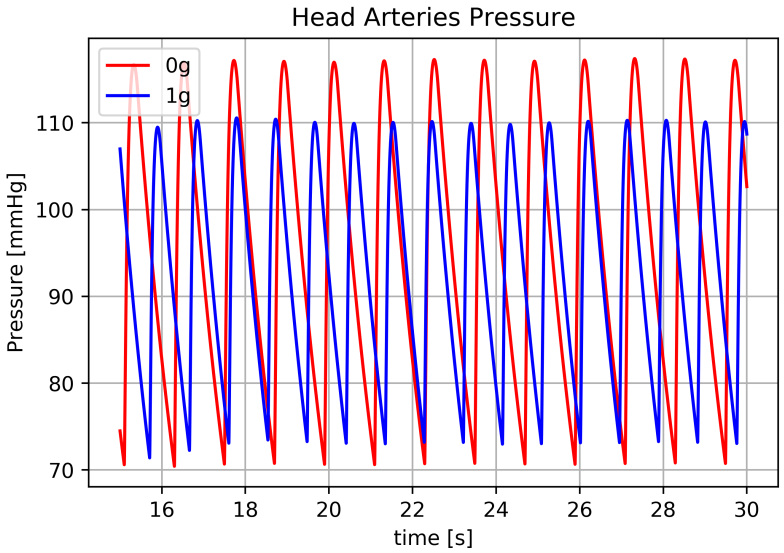

Figure 3.32: Head Arteries Pressure change with gravity

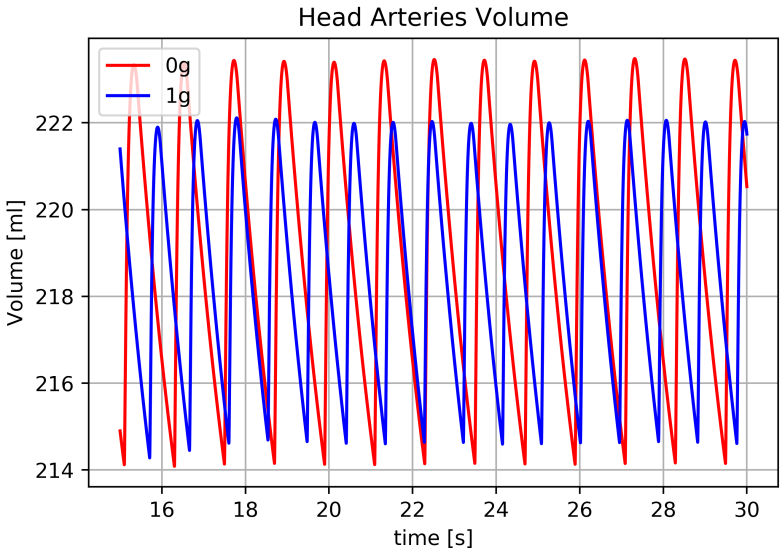

Figure 3.33: Head Arteries Volume change with gravity

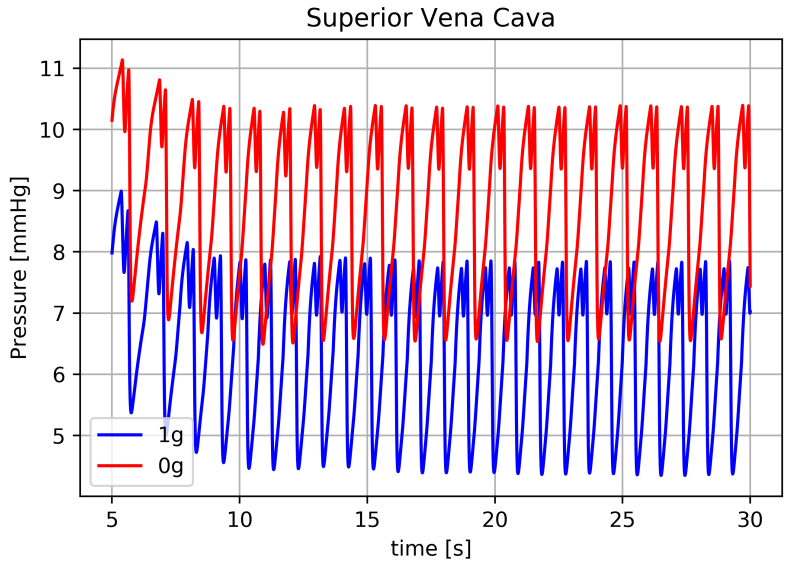

Figure 3.34: Superior Vena Cava Pressure change with gravity

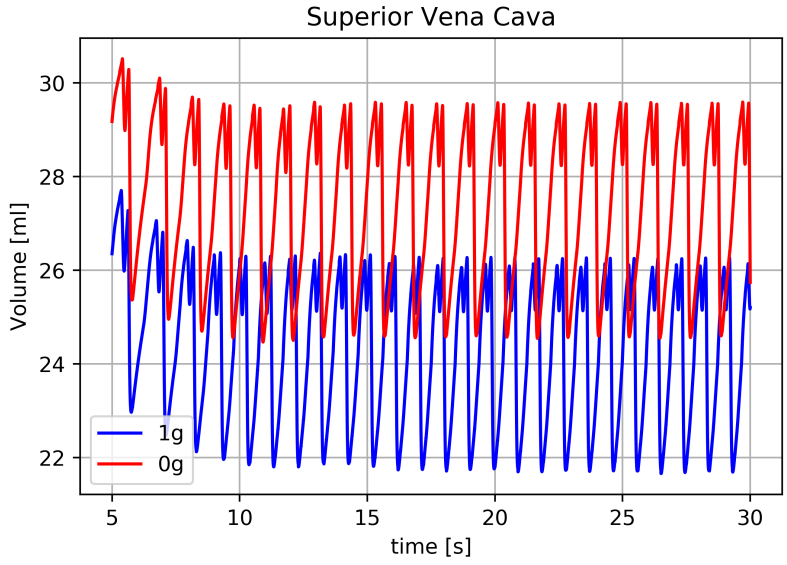

Figure 3.35: Superior Vena Cava Volume change with gravity

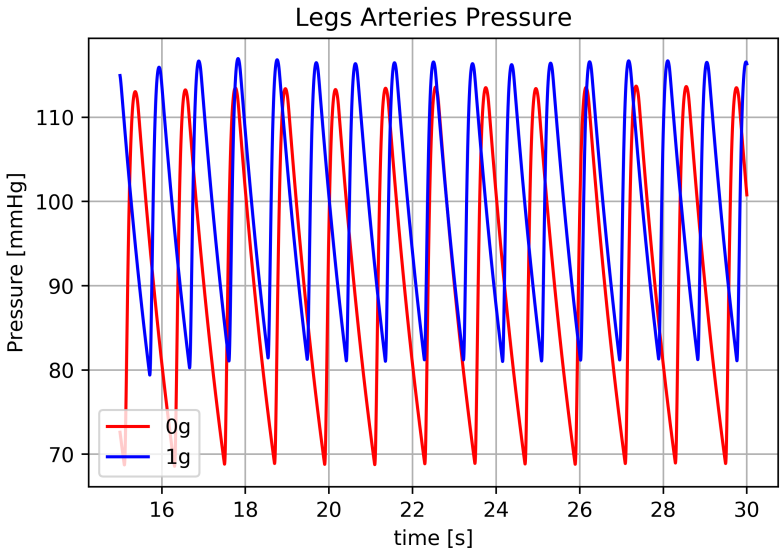

Figure 3.36: Legs arteries pressure change with gravity

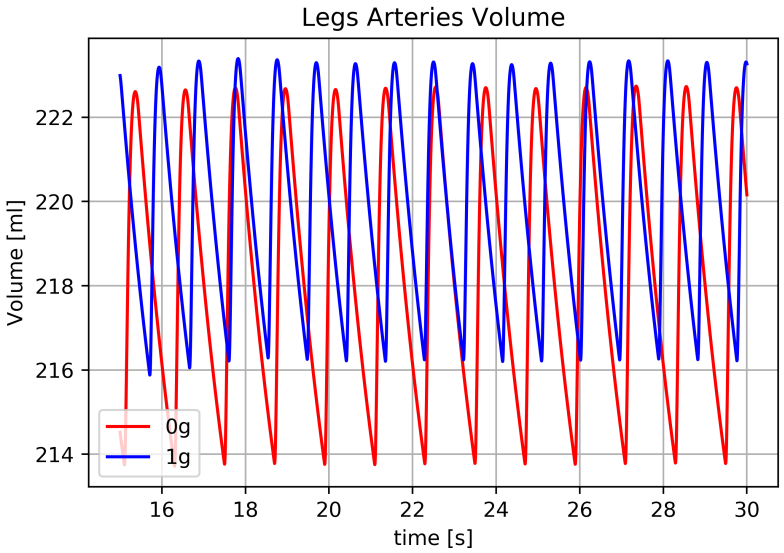

Figure 3.37: Legs arteries volume change with gravity

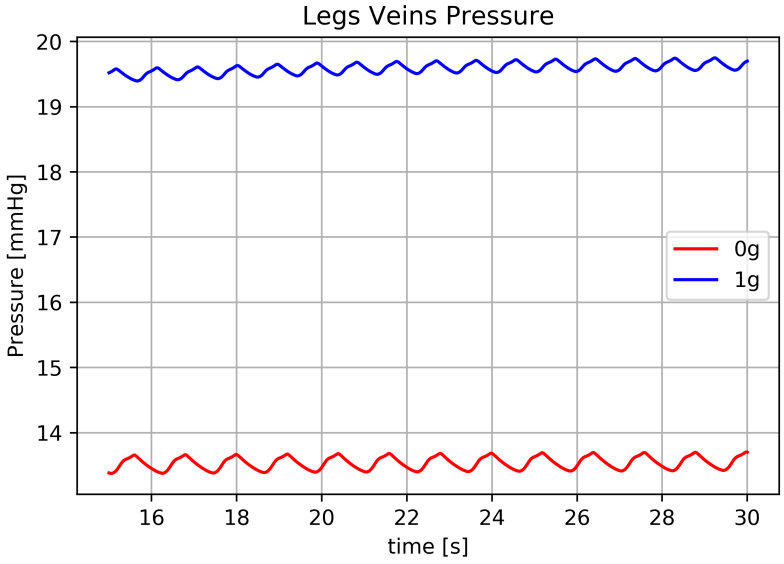

Figure 3.38: Legs veins pressure change with gravity

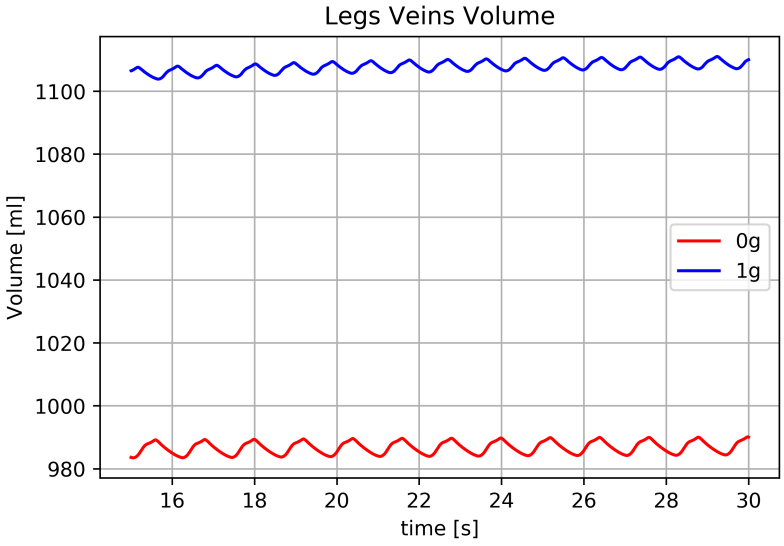

Figure 3.39: Legs veins volume change with gravity

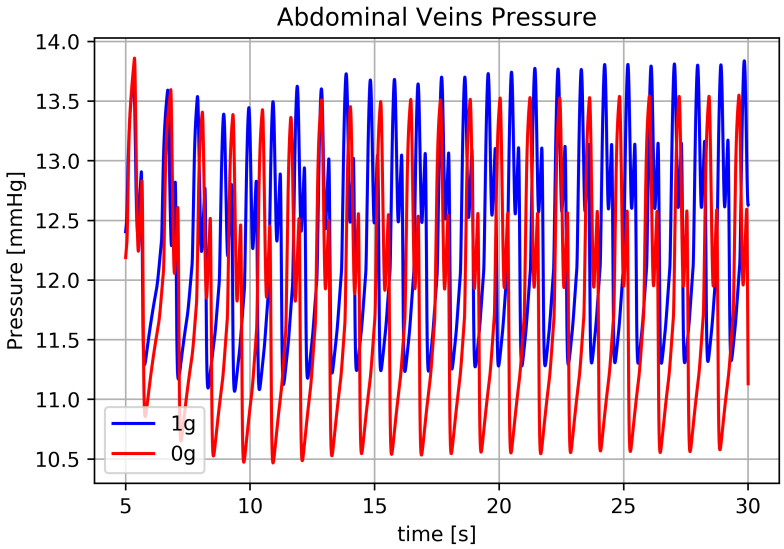

Figure 3.40: Abdominal veins pressure change with gravity

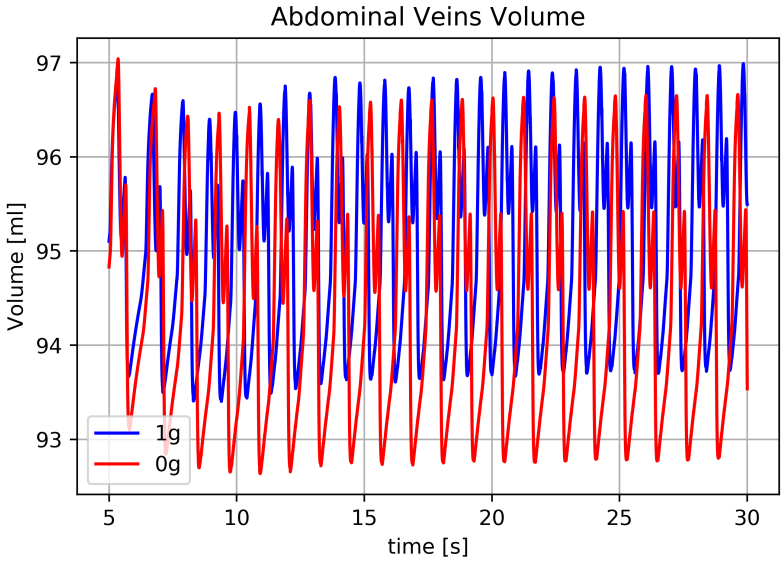

Figure 3.41: Abdominal veins volume change with gravity

The figures above show the effect of gravity, comparing results from two different simulations with different values of g. It is evident how the fluid shift to the upper compartments, increasing both pressure and volume of both veins and arteries. Legs arteries present a slight decrease in both pressure and volume since gravity does not push the blood downwards anymore. However, a greater difference would have been found if there was no Arterial Baroreflex. A more complicated explanation lies behind the behavior of legs and abdominal veins compartments. Leg veins pressure in microgravity condition is lower than the one in simulation with gravity. This appears to be wrong, since it's easier for the blood to climb without the gravity pushing it back. However, the gravitational load is been applied only after that node, between Leg Veins and Abdominal veins, and not between Leg arteries and veins. However, this effect is not evident since it is balanced by the increased flow coming from the Kidneys and Splanchnic Organs.

The model has been subjected to a step variation of the value of gravity. This has been done by changing the angle *theta* from a value of $\frac{\pi}{2}$ to 0.

$$Ph = \rho g h \sin(\theta)$$

It is possible to notice the reaction of the system while responding to the variation. As already discussed, when the gravity drops to zero the body fluids shift to the upper part of the system, thus increasing the pressure. This is evident in figure 3.48 and 3.49, where there is a firm increase in volume. This causes the receptors to sense more pressure than it should normally be, so the control system acts by decreasing the heart rate (figure 3.43).

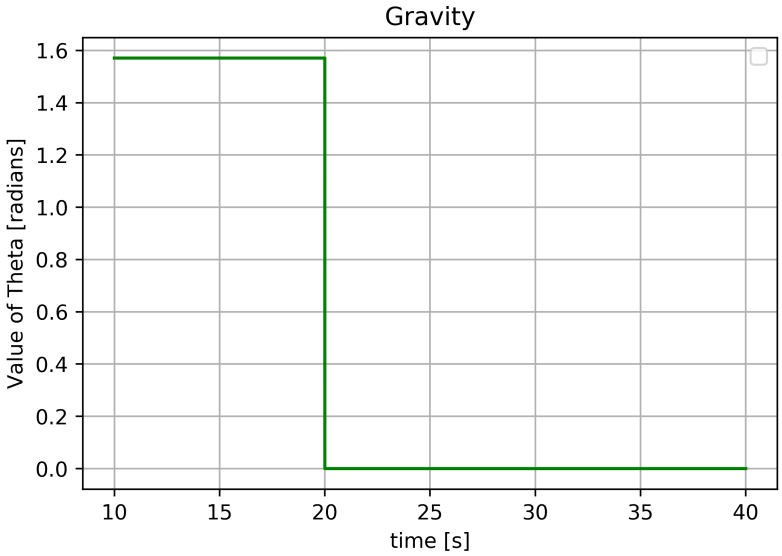

Figure 3.42: Gravity Variation through the angle theta

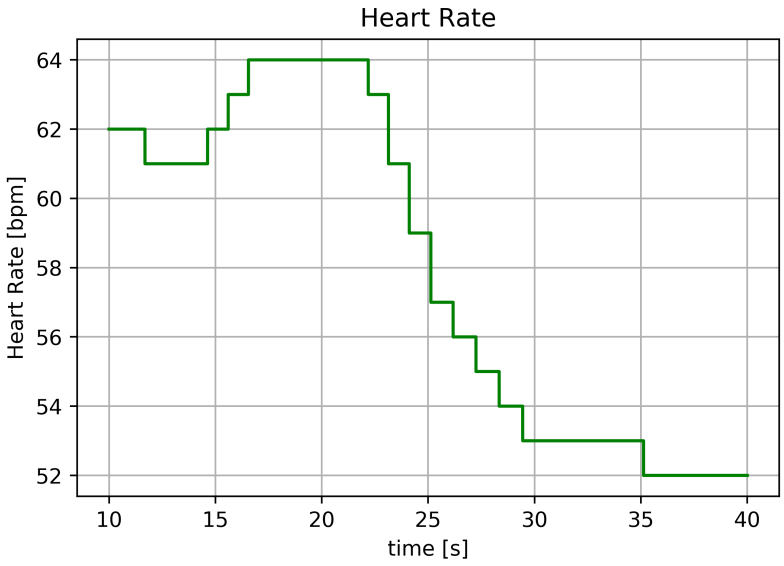

Figure 3.43: Heart Rate in the step simulation

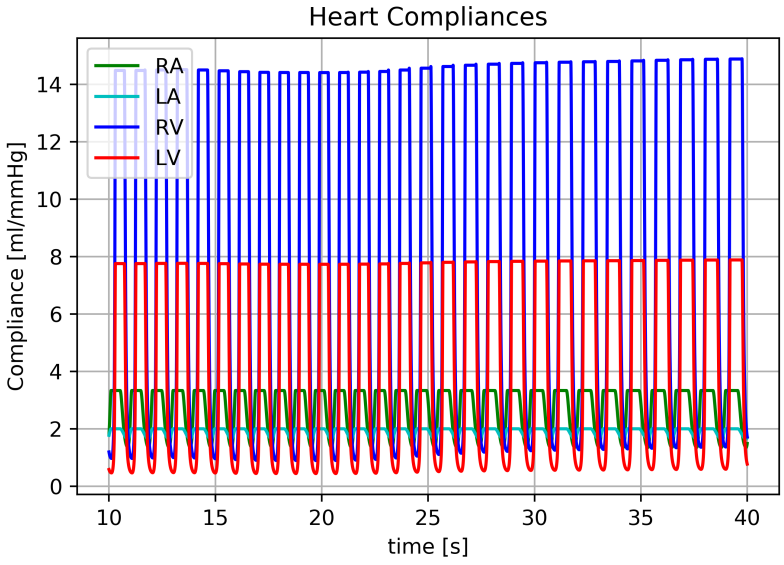

Figure 3.44: Heart compliance in the step simulation

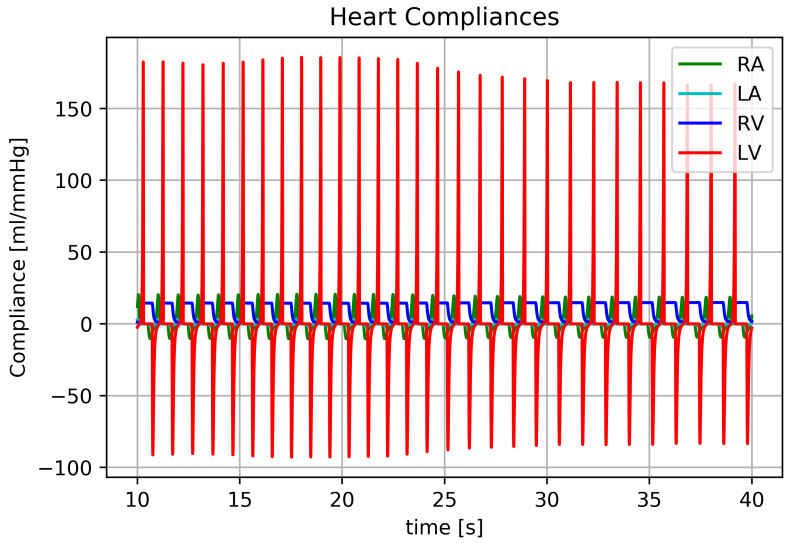

Figure 3.45: Heart compliance derivative in the step simulation

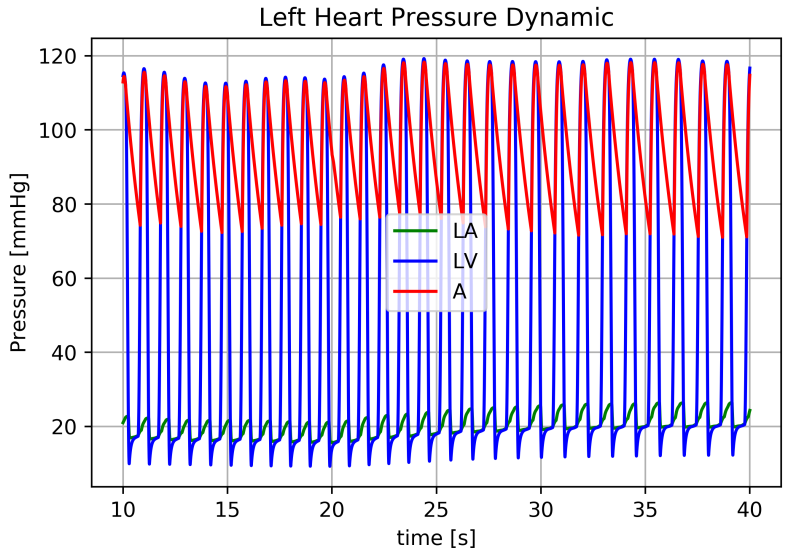

Figure 3.46: Left heart pressure dynamic in the step simulation

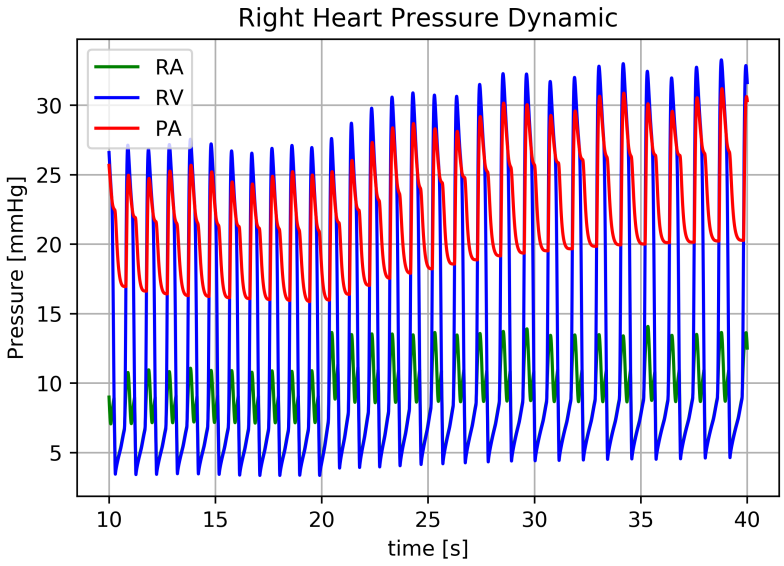

Figure 3.47: Right heart pressure dynamic in the step simulation

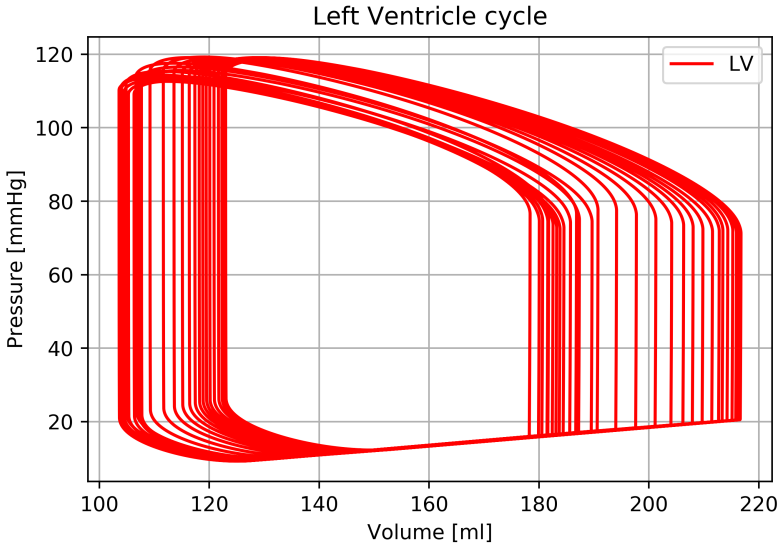

Figure 3.48: Left ventricle cycle in the step simulation

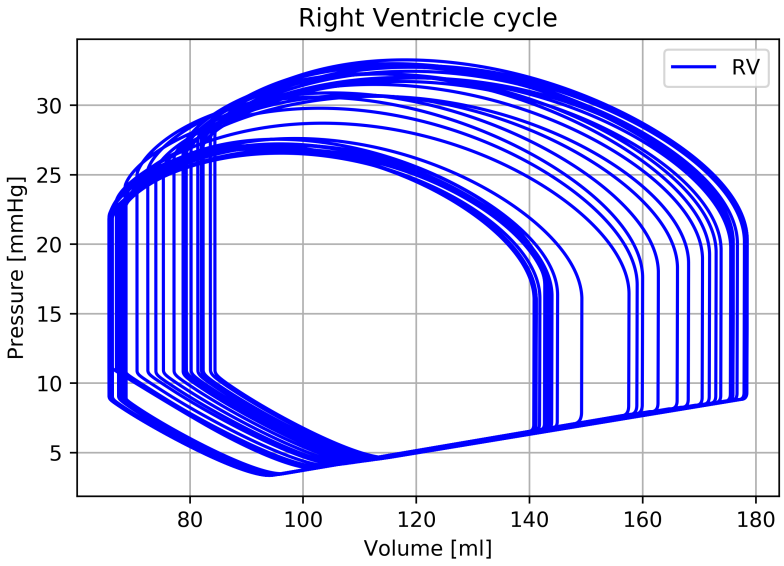

Figure 3.49: Right ventricle cycle in the step simulation

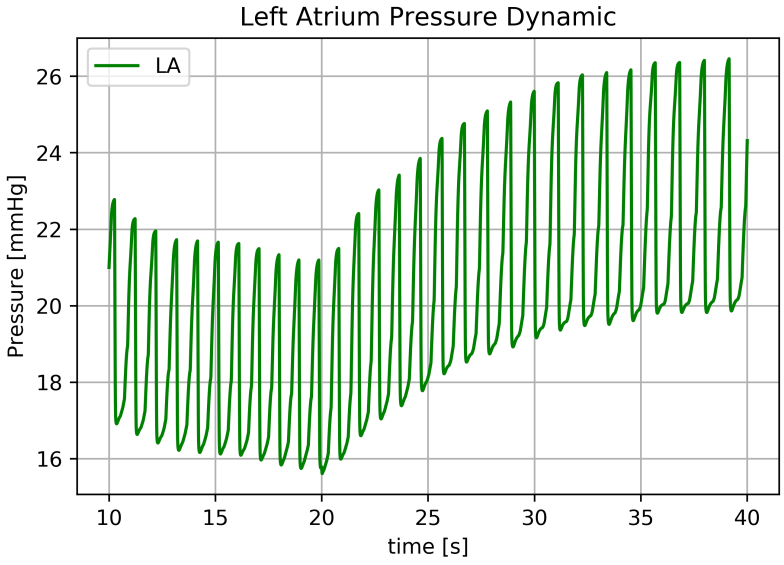

Figure 3.50: Left atrium pressure dynamic in the step simulation

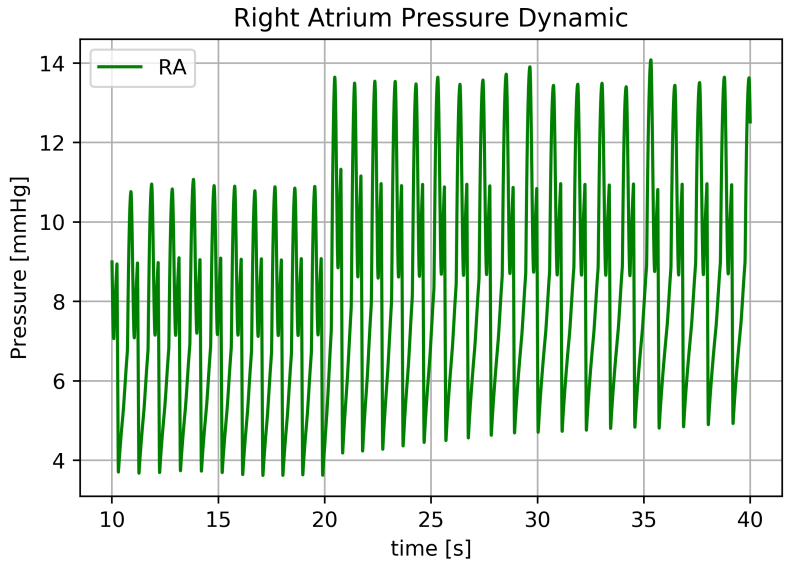

Figure 3.51: Right atrium pressure dynamic in the step simulation

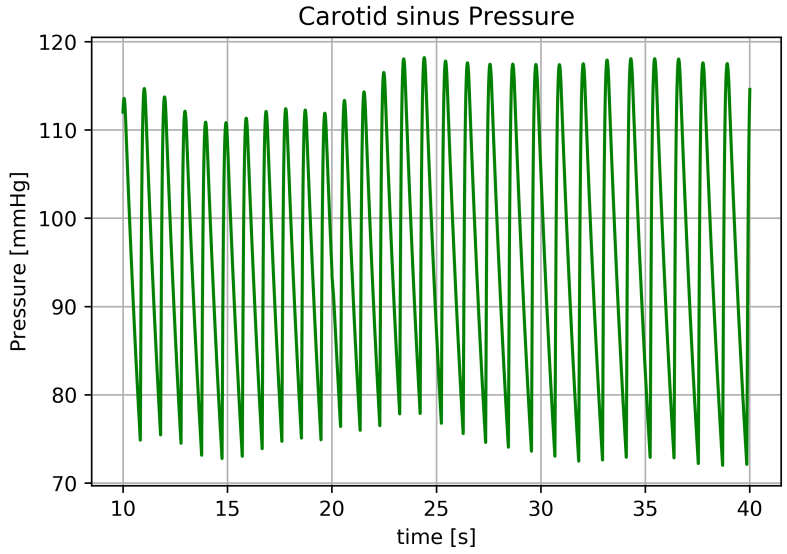

Figure 3.52: Brachiocephalic arteries (Carotid Sinus) pressure dynamic in the step simulation

Finally, the reaction of the system to a ramp variation of the previously mentioned angle θ has been studied (Figure 3.54). Instead of the sudden variation of the previous case, the system undergoes a linear variation of the angle, determining a gradual decrease in gravity action. This is reflected in the following figures, not presenting anymore an abrupt variation but a blunt transition between the two regimes.

$$\theta(t) = \begin{cases} \frac{\pi}{2} & t < 20, \\ \frac{3\pi}{2} - \frac{\pi}{20}t & 20 \leq t \leq 30, \\ 0 & t > 30, \end{cases} \tag{3.1}$$

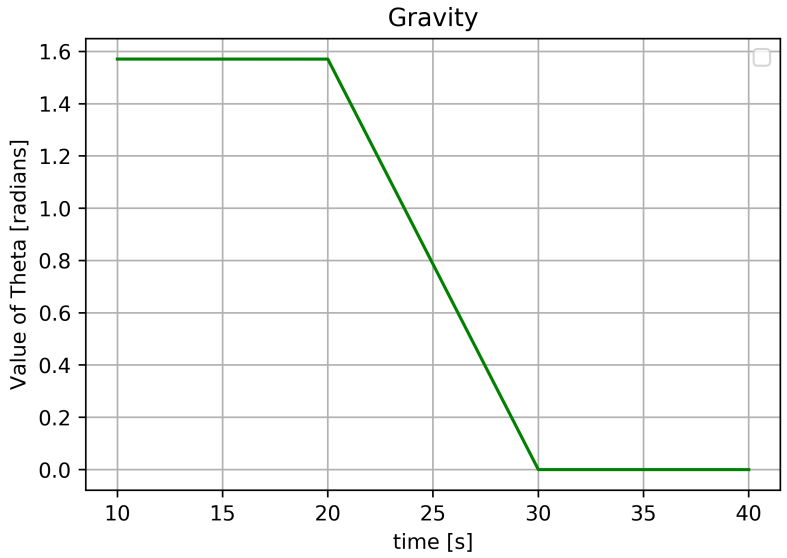

Figure 3.53: Gravity Variation through the angle theta

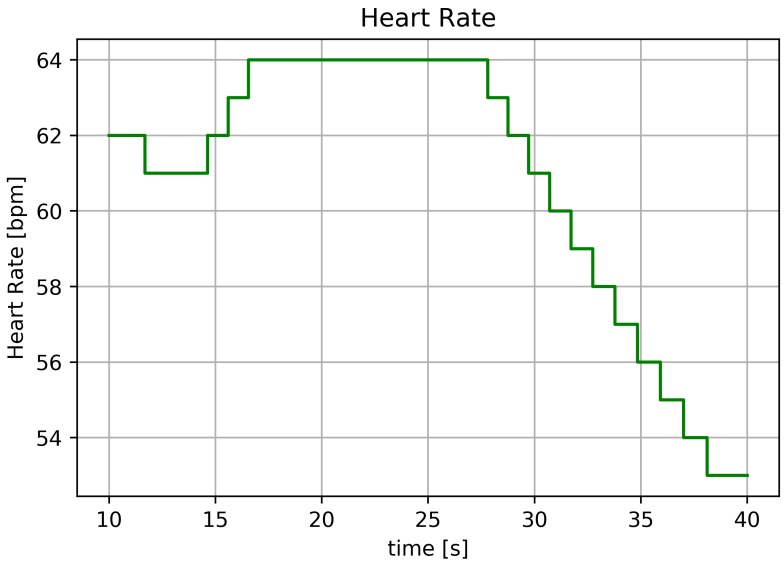

Figure 3.54: Heart Rate in the Ramp simulation

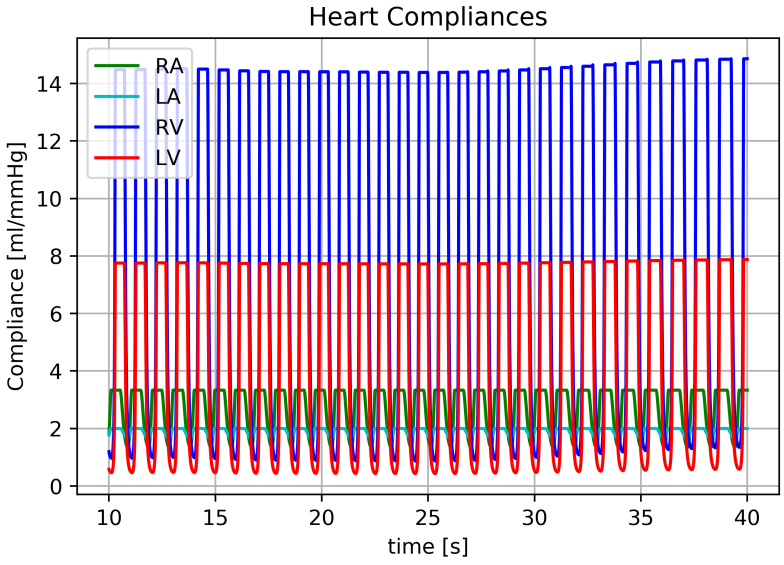

Figure 3.55: Heart compliance in the ramp simulation

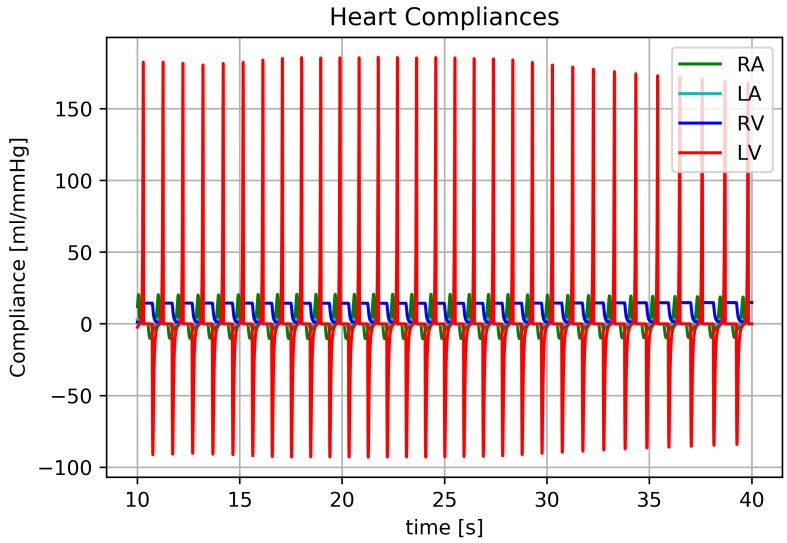

Figure 3.56: Heart compliance derivative in the ramp simulation

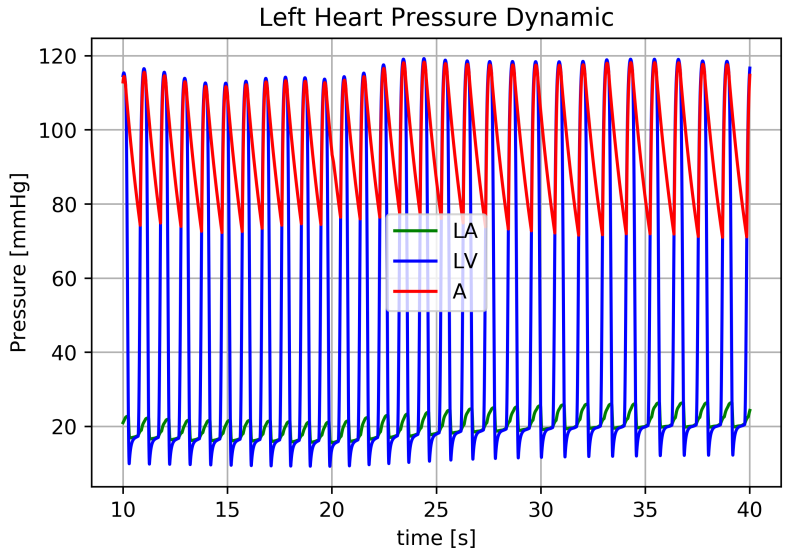

Figure 3.57: Left heart pressure dynamic in the ramp simulation

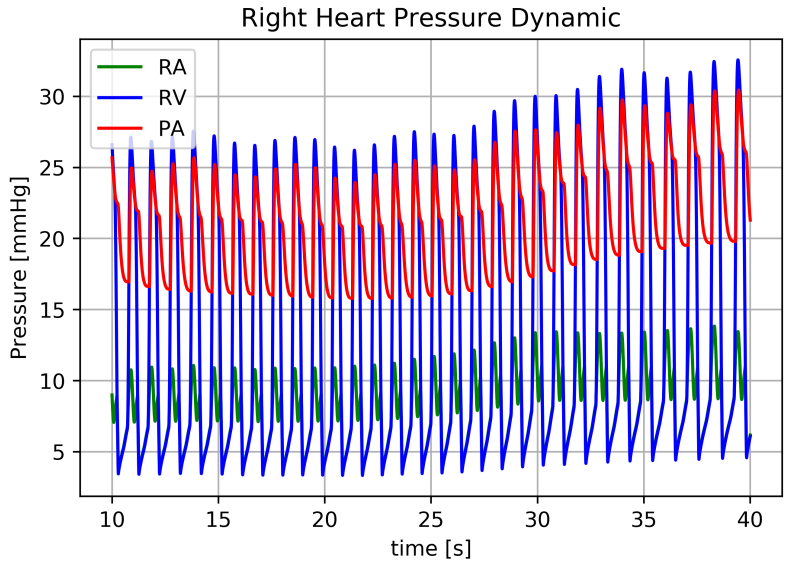

Figure 3.58: Right heart pressure dynamic in the ramp simulation

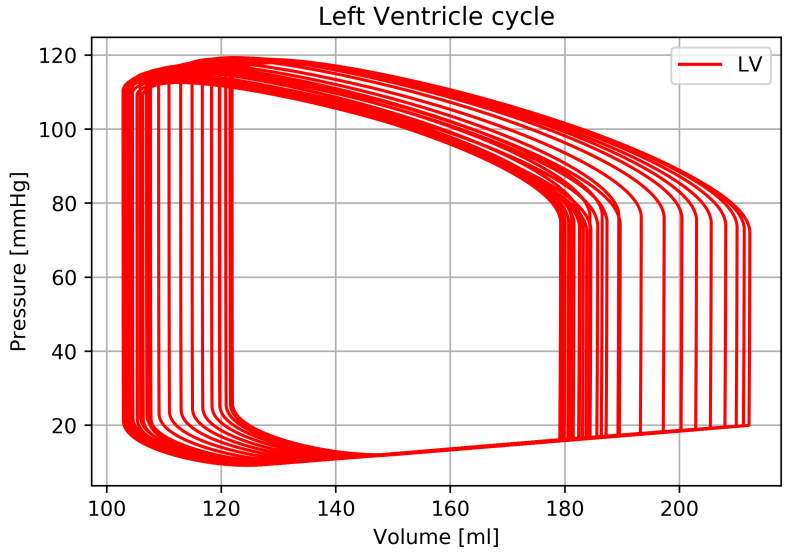

Figure 3.59: Left ventricle cycle in the Ramp simulation

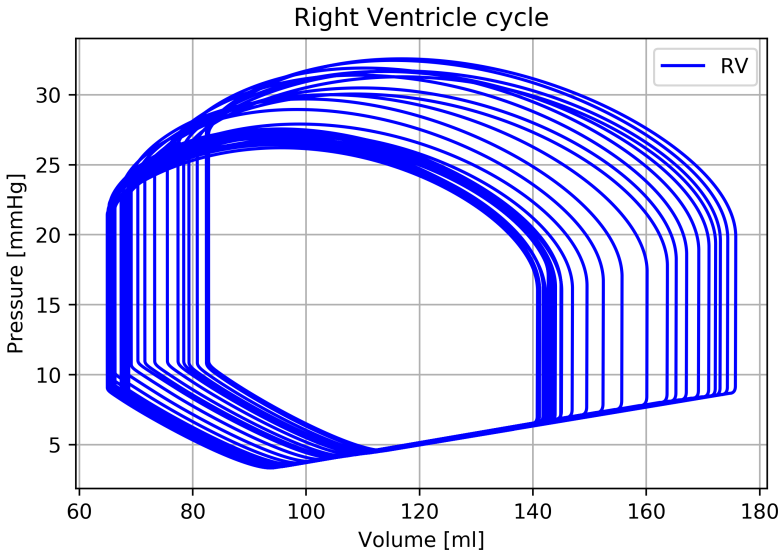

Figure 3.60: Right ventricle cycle in the ramp simulation

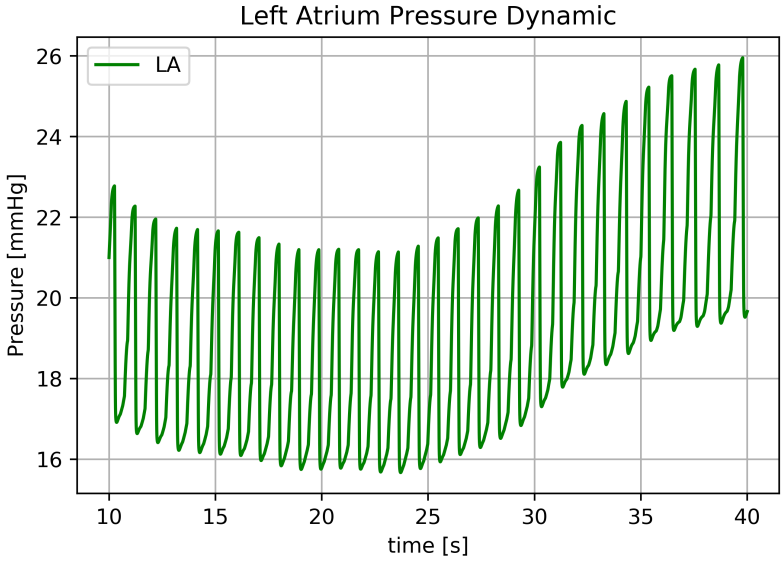

Figure 3.61: Left atrium pressure dynamic in the ramp simulation

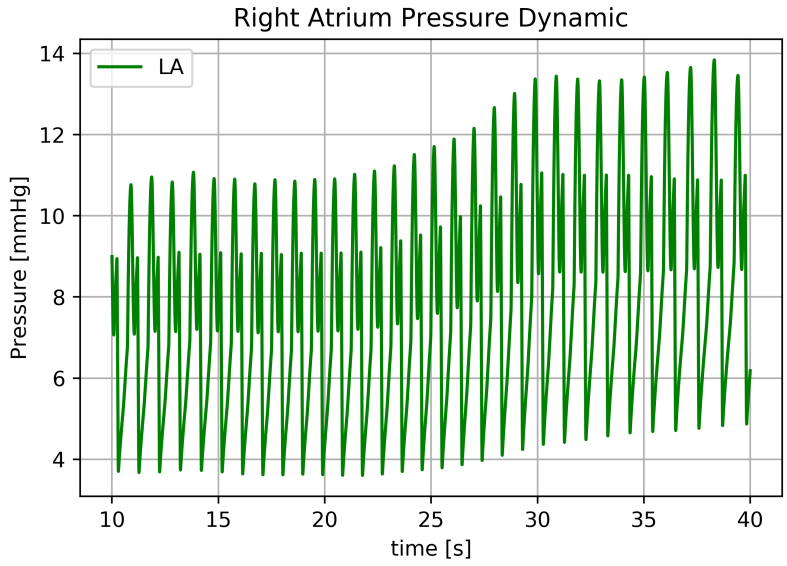

Figure 3.62: Right atrium pressure dynamic in the ramp simulation

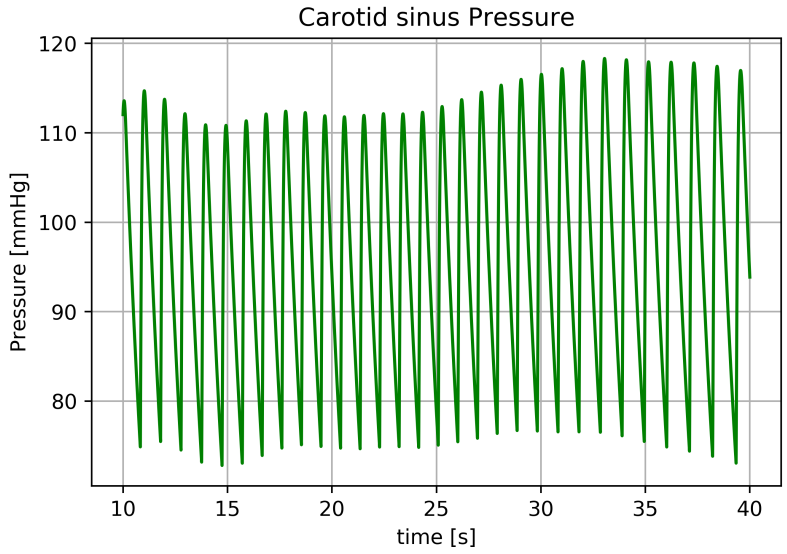

Figure 3.63: Brachiocephalic arteries (Carotid Sinus) pressure dynamic in the ramp simulation

Chapter 4

Conclusion and Future Work

The purpose of this thesis was to develop a model of the cardiovascular system, complete with the control loop, capable of simulating microgravity conditions that the astronauts have to face during their time spent on orbit. The model has been implemented in Python 3.8 and divided in four files (data.py, Heart class.py, function.py and main.py). The complete version of the model simulated at nominal condition on earth has been compared with both the software CVSIM developed by Dr. Heldt in his PhD thesis "Computational Models of Cardio vascular Response to Orthostatic Stress" [15] and experimental data gathered by Lucian Mihai Itu, Puneet Sharma and Constantin Suciu in the book "Patient-Specific Hemodynamic Computations: Application to Personalized Diagnosis of Cardio vascular Pathologies" [6]. The model also has been designed in order to be able to compare different postures, through the variation of the parameter k as reported in Table A.3, and the influence of sex, through the parameter K (Table A.2). Finally, the program developed during the course of this thesis has proved to be consistent with the phenomena found in data gathered in microgravity conditions. In fact, it correctly represents the fluid shift, the heartbeat drop, and the pressure changes in every compartment. However, this is just a first step in the development of a whole-body model, putting the basis for a better understanding and modeling of the dynamic of consequent effects, like the anemia, bone weight loss, and hormonal changes. This would develop an instrument capable of performing both predictive and direct real-time analysis of the health and performances of astronauts [19]. For this reason, in the future this program could be expanded including the dynamic of the hypothalamic-pituitary-adrenal (HPA) axis [20] and neural control, using a variable value of gain, dependent from hormones concentration, for the reflexes action instead of a fixed scalar value. In turn, the concentration of hormones would be a function of the neural firing dynamics [21]. It also would be interesting to perform a sensitivity analysis to understand the impact of the initial pressure and in general of all the parameters of the model on the evolution of the simulation. Finally, a graphic user interface (GUI) for the six compartment program was implemented thanks to the library

"Tkinter" on python, in order to make the program easier to interact with. This feature will be developed in the future also for the 21 compartment model.

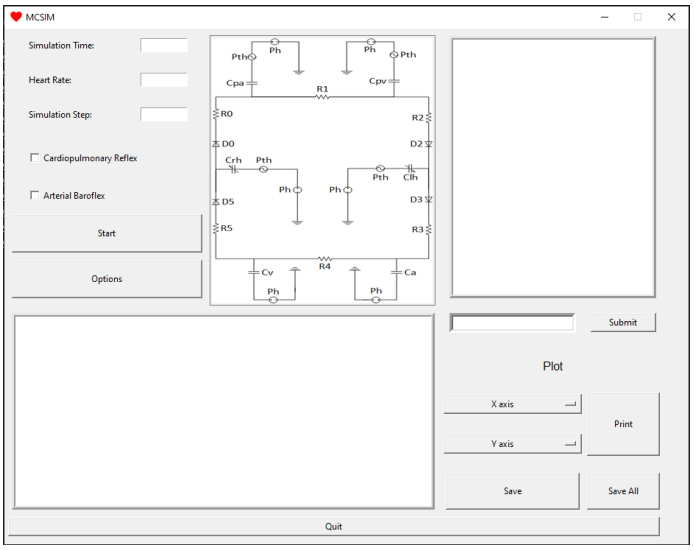

Figure 4.1: Graphic User Interface of the program

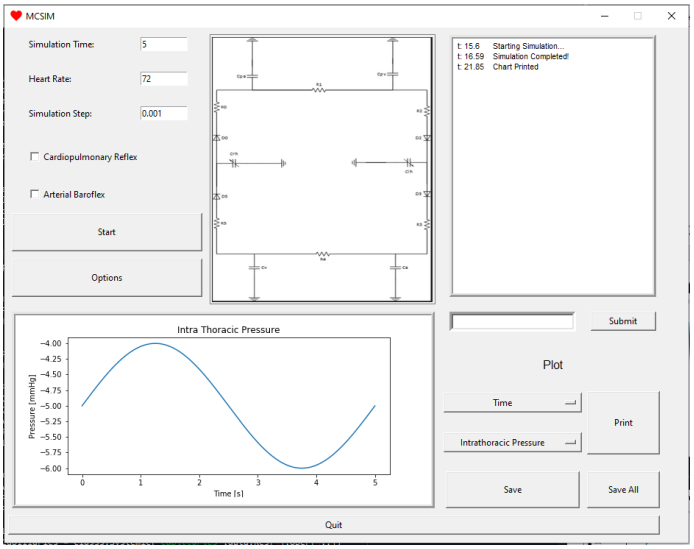

Figure 4.2: Example of simulation

Appendix A

Parameter Values

Physical Quantity	**Unit**
Time	s
Resistance	PRU($\frac{mmHg}{\frac{ml}{s}}$)
Capacitance	$\frac{ml}{mmHg}$
Volume	ml
Elastance	$\frac{mmHg}{ml}$

Table A.1: Measurement Unit

Sex	**K**
Male	0.37
Female	0.4

Table A.2: Mean values of K

Posture	**k**
Standing	28.25
Sitting	26
Standing	25

Table A.3: Mean values of k

A.1 Six Parameters Model

Compartment	**R (PRU)**	**C** ($\frac{ml}{mmHg}$)
Veins	0.01	100
Arteries	0.006	1.6
Pulmonary Arteries	0.003	4.3
Pulmonary Veins	0.01	8.3
Lungs	0.08	-
Systemic Circulation	1	-

Table A.4: Six compartment model Resistances and Compliances

Compartment	E_d ($\frac{mmHg}{ml}$)	E_s ($\frac{ml}{mmHg}$)
Left Heart	0.1	2.5
Right Heart	0.1	0.83

Table A.5: Heart end-systolic and end-diastolic elastance value in 6 compartment model

Compartment	$P0$ $(mmHg)$	$V0$ (ml)
Left Ventricle	8	15
Right Ventricle	12	15
Systemic arteries	8	715
Systemic Veins	5	2500
Pulmonary Arteries	90	90
Pulmonary veins	15	400

Table A.6: Zero-pressure filling volume in 6 compartment model

A.2 Twenty-one Compartment Model

Compartment	E_d $(\frac{mmHg}{ml})$	E_s $(\frac{ml}{mmHg})$
Right Atrium	0.3	0.74
Right Ventricle	0.07	1.3
Left Atrium	0.5	0.61
Left Ventricle	0.13	2.5

Table A.7: Heart end-systolic and end-diastolic elastance value in 21 compartment model

Compartment	**R (PRU)**	**C ($\frac{ml}{mmHg}$)**
Ascending Aorta	0.007	0.28
Brachiocephalic arteries	0.003	0.13
Head and arms arteries	0.014	0.2
Head and arms capillaries	4.9	-
Head and arms veins	0.11	7
Superior Vena Cava	0.028	1.3
Thoracic Aorta	0.011	0.21
Abdominal Aorta	0.010	0.10
Renal arteries	0.010	0.21
Kidneys	4.1	-
Renal veins	0.11	5
Splanchnic arteries	0.07	0.2
Splanchnic organs	3	-
Splanchnic veins	0.07	60
Legs arteries	0.09	0.2
Legs capillaries	4.5	-
Legs veins	0.10	20
Abdominal veins	0.019	1.3
Thoracic inferior vena cava	0.028	0.5
Tricuspid Valve	0.001	-
Pulmonary Arteries	0.006	3.4
Lungs	0.021	-
Pulmonary Veins	0.006	9
Mitral Valve	0.010	-

Table A.8: Twentyone compartment model Resistances and Compliances

Compartment	**P0 (mmHg)**	**V0 (ml)**
Ascending Aorta	80	21
Brachiocephalic arteries	65	5
Head and arms arteries	60	200
Head and arms veins	3	645
Superior Vena Cava	1	16
Thoracic Aorta	75	16
Abdominal Aorta	70	10
Renal arteries	60	20
Renal veins	11	30
Splanchnic arteries	60	300
Splanchnic veins	11	11
Legs arteries	60	200
Legs veins	11	716
Abdominal veins	7	79
Thoracic inferior vena cava	6	33
Right Atrium	6	14
Right Ventricle	7	46
Pulmonary Arteries	5	160
Pulmonary Veins	1	430
Left Atrium	25	24
Left Ventricle	90	55

Table A.9: Twenty-one compartment model Initial pressure and zero-pressure filling volume

Effect	**Gain**
R-R wave interval	11 $\frac{ms}{mmHg}$
Left Ventricle Contractility	0.007 $\frac{ml}{mmHg^2}$
Right Ventricle Contractility	0.022 $\frac{ml}{mmHg^2}$
Arterial Resistance	-0.05 $\frac{PRU}{mmHg}$
Venous Unstressed Volume	31 $\frac{ml}{mmHg}$

Table A.10: Static Gains values of the Arterial Baroreflex model

Effect	**Gain**
Arterial Resistance	0.05 $\frac{PRU}{mmHg}$
Venous Unstressed Volume	100 $\frac{ml}{mmHg}$

Table A.11: Static Gains values of the arterial Cardiopulmonary Reflex model

Appendix B

Code

Here it is reported the code produced and used for the simulations.

B.1 data.py

```
import numpy as np
import math


#COMPLIANCE
#Values in  ml/mmHg
C = np.array(np.zeros([21]))

C[0] = 0.28 #Ascending Aorta
C[1] = 0.13 #brachiocephalic Arteries
C[2] = 0.2#0.42 #Head and Arms Arteries
C[3] = 7    #HA Veins
C[4] = 1.3  #Superior Vena Cava (SVC)
C[5] = 0.21 #Thoracic Aorta
C[6] = 0.10 #Abdominal Aorta
C[7] = 0.21 #Renal Arteries
C[8] = 5    #Renal Veins
C[9] = 0.2#0.42 #Splanchnic Arteries
C[10] = 60#50  #Splanchnic Veins
C[11] = 0.2#0.42#Legs Arteries
C[12] = 20#27  #Legs Veins
C[13] = 1.3 #Abdominal Veins
```

```
C[14] = 0.5 #Thoracic Inferior Vena Cava
#15 16 19 20 heart
C[17] = 3.4 #Pul Art
C[18] = 9 #Pul Vein

#Initial Pressure
P0 = np.zeros([21])
#Values in mmHg
P0[0] = 80 #Ascending Aorta
P0[1] = 65 #Brachiocephalic Arteries
P0[2] = 60  #Head and Arms Arteries
P0[3] = 3   #HA Veins
P0[4] = 1 #Superior Vena Cava (SVC)
P0[5] = 75 #Thoracic Aorta
P0[6] = 70 #Abdominal Aorta
P0[7] = 60  #Renal Arteries
P0[8] = 7+5  #Renal Veins
P0[9] = 60   #Splanchnic Arteries
P0[10] = 7+4 #Splanchnic Veins
P0[11] = 60  #Legs Arteries
P0[12] = 7+4   #Legs Veins
P0[13] = 3+4   #Abdominal Veins
P0[14] = 1+5   #Thoracic Inferior Vena Cava
P0[15] = 6 #Right Atrium
P0[16] = 7 #Right Ventricle
P0[17] = 5 #Pulmonary Arteries
P0[18] = 1 #Pulmonary Veins
P0[19] = 25 #Left Atrium
P0[20] = 90 #Left Ventricle



#Heart Parameters

Es = np.zeros([4])
Ed = np.zeros([4])
V0 = np.zeros([4])

#Heart Rate
HR0 = 67
shift0 = 0.633299999998058
```

```
#Heart Resistances
Rrh = 0.005/5 #PRU
Rlh = 0.010 #PRU

#Right Atrium
Es[0] = 0.74 #mmHg/ml
Ed[0] = 0.3 #mmHg/ml
V0[0] = 14 #ml

#Right Ventricle
Es[1] = 1.3 #mmHg/ml
Ed[1] = 0.07 #mmHg/ml
V0[1] = 46 #ml

#Left Atrium
Es[2] = 0.61 #mmHg/ml
Ed[2] = 0.5 #mmHg/ml
V0[2] = 24 #ml

#Left Ventricle
Es[3] = 2.5 #mmHg/ml
Ed[3] = 0.13 #mmHg/ml
V0[3] = 55 #ml

#Hormon concentration
CC0 = 2

#Organs Zero Volume
ZV = np.array(np.zeros([21]))
#Values in PRU (PRU = mmHG/(ml/s))
ZV[0] = 21   #Ascending Aorta
ZV[1] = 5    #brachiocephalic Arteries
ZV[2] = 200  #Head and Arms Arteries
ZV[3] = 645  #HA Veins
ZV[4] = 16   #Superior Vena Cava (SVC)
ZV[5] = 16   #Thoracic Aorta
ZV[6] = 10   #Abdominal Aorta
ZV[7] = 20   #Renal Arteries
ZV[8] = 30   #Renal Veins
ZV[9] = 300  #Splanchnic Arteries
```

```
ZV[10] = 11  #Splanchnic Veins
ZV[11] = 200 #Legs Arteries
ZV[12] = 716 #Legs Veins
ZV[13] = 79  #Abdominal Veins
ZV[14] = 33  #Thoracic Inferior Vena Cava
ZV[15] = V0[0] #RA
ZV[16] = V0[1] #RV
ZV[19] = V0[2] #LA
ZV[20] = V0[3] #LV
ZV[17] = 160 #Pulmonary Arteries
ZV[18] = 430 #Pulmonary Veins

#Organs Resistance
Res = np.array(np.zeros([24]))
#Values in PRU (PRU = mmHG/(ml/s))
Res[0] = 0.007 #20-0
Res[1] = 0.003 #0-1
Res[2] = 0.014 #1-2
Res[3] = 4.9#3.3 #2-3
Res[4] = 0.11  #3-4
Res[5] = 0.028 #4-15
Res[6] = 0.011 #0-5
Res[7] = 0.010 #5-6
Res[8] = 0.010  #6-7
Res[9] = 4.1 #7-8
Res[10] = 0.11  #8-13
Res[11] = 0.07  #6-9
Res[12] = 3#2.4 #9-10
Res[13] = 0.07 # 10-13
Res[14] = 0.09 #6-11
Res[15] = 4.5 #3.9 #11-12
Res[16] = 0.10  #12-13
Res[17] = 0.019 #13-14
Res[18] = 0.028#0.008 #14-15
Res[19] = Rrh #15-16
Res[20] = 0.006 #16-17
Res[21] = 0.3*0.07 #17-18
Res[22] = 0.006 #18-19
Res[23] = Rlh # 19-20
```

```
#Intrathoracic Pressure
Ptor = 5 #mmHg
amplitude = 1 #mmHg
frequency = 2*math.pi*(12/60) #breath per second


#Hydrostatic Pressure

rho = 1060 #Kg/m^3 Blood Density
g = 9.81 #m/s^2 Gravity Acceleration
#Conversion Factor
conv = 0.00075

hh = np.zeros([7])

# Meters [m]
hh[0] = +0.3
hh[1] = +0.1
hh[2] = +0.05
hh[3] = 0
hh[4] = -0.1
hh[5] = -0.3
hh[6] = -1

Ph = np.zeros(7)

Ph = rho*g*hh*conv


#Static Gain (Heldt)
GABs = np.zeros(5)
GCPs = np.zeros(2)

GABs[0] = 11 #HR
GABs[1] = 0.007 #LV contr
GABs[2] = 0.022 #RV contr
GABs[3] = -0.05 #Art res
GABs[4] = 31 #Venous 0-Volume
GABp = 11 #HR
GCPs[0] = -0.05 #Art res
GCPs[1] = 100 ##Venous 0-Volume
```

B.2 Heart Class.py

```
import numpy as np
import math

class Heart():

    def __init__(self,name,Es,Ed,V0,sex = None,K = None,k = None):
         self.name = name #Organ Name
         self.Es = Es     #Systolic Elastance
         self.Ed = Ed     #Diastolic Elastance
         self.V0 = V0     #Zero-Pressure Volume
         self.sex = sex   #Patient sex
         self.K = K       #Bazett constant
         self.k = k       #Systolic Constant

         if self.sex == 'M':
             self.K = 0.37
             self.k = 28.25
         elif self.sex == 'F':
             self.K = 0.4
             self.k = 28.25
         else:
             self.K = (0.4 + 0.37)/2
             self.k = 28.25


    def senoatrialpacemaker(self,t_start,int_step,HR,mr):

        #compute next beat

        K = self.K
        k = self.k
        I0 = 60/HR #beat_length [seconds]
        G = 1 #threshold
        M = 0 #initializing membrane potential
```

```
        t = t_start
        m = 1/(I0+mr) #mr in seconds



        while True:
            t = t+int_step
            M = M + m*(int_step)
            if (M>=G) and (t) >= 0.2*(I0):
                M=0
                t_end = t

                time = np.arange(t_start,t_end,int_step)
                t_sys = K*np.sqrt(t_end-t_start)
                l_sys = 60/(k*np.sqrt(HR))
                HR = round((60/int_step)/np.size(time))
                return time, t_sys, l_sys, HR

    def visualize(self):


        print(f'''
        Name: \t \t \t {self.name}
        Systolic Elastance: \t {self.Es}
        Diastolic Elastance: \t {self.Ed}
        Zero-Pressure Volume: \t {self.V0}
        Bazett Constant: \t {self.K}
        Systolic Constant: \t {self.k}
        Sex: \t \t \t {self.sex}
        ''')


    def beat(self,time,T_sys,int_step,shift):

        shift = int(shift/int_step)
        lt = len(time)

        heart_elastance = np.zeros(len(time))    #Heart Elastance
        C = np.zeros(len(time))                  #Compliance
        DC = np.zeros(len(time))                 #Compliance Derivative
```

```
for step in range(len(time)):

    t = time[step]-time[0]

    if t >= 0 and t < T_sys:

        heart_elastance[step] = 0.5*(self.Es-self.Ed)*(1-math.cos ...
        ... (math.pi*t/T_sys))+self.Ed

    elif t >= T_sys and t <= 3*T_sys/2:

        heart_elastance[step] = 0.5*(self.Es-self.Ed)*(1+math.cos ...
        ... (2*math.pi*(t-T_sys)/T_sys))+self.Ed

    else:

        heart_elastance[step] = self.Ed



    C[step] = 1/ heart_elastance[step]
    if step == 0:
        DC[step] == 0
    else:
        DC[step] = (C[step]-C[step-1])/int_step


if shift!=0:
    tempvar1 = C[:(lt-shift)]
    tempvar2 = C[(lt-shift):]
    tempvar3 = DC[:(lt-shift)]
    tempvar4 = DC[(lt-shift):]

    C = np.concatenate((tempvar2,tempvar1),axis = 0)
    DC = np.concatenate((tempvar4,tempvar3),axis = 0)

return C, DC
```

B.3 function.py

```
import data
import numpy as np
import math


def inizialization():

    HR = [data.HR0]

    CRA = []
    CRV = []
    CLA = []
    CLV = []
    DCRA = []
    DCRV = []
    DCLA = []
    DCLV = []


    PORG0 = PORG1 = PORG2 = PORG3 = PORG4 = PORG5 = PORG6 = PORG7 = PORG8 ...
    ... = PORG9 = PORG10 = PORG11 = PORG12 = PORG13 = PORG14 = PORG15 = PORG16 = ...
    ... PORG17 = PORG18 = PORG19 = PORG20 = []
    QORG0 = QORG1 = QORG2 = QORG3 = QORG4 = QORG5 = QORG6 = QORG7 = QORG8 ...
    ... = QORG9 = QORG10 = QORG11 = QORG12 = QORG13 = QORG14 = QORG15 = QORG16 = ...
    ... QORG17 = QORG18 = QORG19 = QORG20 = []
    VV0 = VV1 = VV2  = VV3 = VV4 = VV5 = VV6 = VV7 = VV8 = VV9 = VV10 = VV11 ...
    ...  = VV12 = VV13 = VV14 = VV15 = VV16 = VV17 = VV18 = VV19 = VV20 = []


    PPs = [PORG0,PORG1,PORG2,PORG3,PORG4,PORG5,PORG6,PORG7,PORG8, ...
    ... PORG9,PORG10,PORG11,PORG12,PORG13,PORG14,PORG15,PORG16 ...
    ... ,PORG17,PORG18,PORG19,PORG20]
    QQs = [QORG0,QORG1,QORG2,QORG3,QORG4,QORG5,QORG6,QORG7,QORG8, ...
    ... QORG9,QORG10,QORG11,QORG12,QORG13,QORG14,QORG15,QORG16, ...
    ... QORG17,QORG18,QORG19,QORG20]
    VVs = [VV0, VV1, VV2,VV3, VV4, VV5,VV6, VV7, VV8,VV9, VV10, ...
    ... VV11, VV12, VV13, VV14,VV15, VV16, VV17,VV18, VV19, VV20]

    for num in range(len(VVs)):
```

```
        VVs[num] = [data.ZV[num]]

    for num in range(len(PPs)):
        PPs[num] = [data.P0[num]]

    T=0

    R = data.Res
    Porg = np.zeros(21)
    Vorg = np.zeros(21)
    #Control initialization
    mr = 0
    shift = data.shift0

    PrefAB = 95
    PrefCP = 5

    DXcontrol_LVCAB =0
    DXcontrol_RVCAB =0
    DXcontrol_ARAB =0
    DXcontrol_VVAB =0
    DXcontrol_ARCP = 0
    DXcontrol_VVCP = 0
    DX =  [DXcontrol_LVCAB, DXcontrol_RVCAB, DXcontrol_ARAB, ...
    ... DXcontrol_VVAB, DXcontrol_ARCP, DXcontrol_VVCP]

    return  HR, CRA, CRV, CLA, CLV,DCRA, DCRV, DCLA, DCLV, ...
    ... Porg, PPs, QQs, VVs, T, R, mr, PrefAB, PrefCP, DX ,shift,Vorg


def heart_append(CRA, CRV, CLA, CLV, DCRA, DCRV, DCLA, ...
... DCLV, cRA, cRV, cLA, cLV, dcRA, dcRV, dcLA, dcLV):

    for n in range(len(cRA)):

            CRA.append(cRA[n])
            DCRA.append(dcRA[n])
            CRV.append(cRV[n])
            DCRV.append(dcRV[n])
            CLA.append(cLA[n])
            DCLA.append(dcLA[n])
```

```
            CLV.append(cLV[n])
            DCLV.append(dcLV[n])

    return CRA, CRV, CLA, CLV, DCRA, DCRV, DCLA, DCLV

def sys_ode(t,Pc,Qc,C,DC,Ph):

    dp = np.zeros([21])
    dp = (Qc-(Pc)*DC)/C

    return dp


def intrathoracic(Amplitude,instant, frequency, Ptor):

    Pth = np.zeros(21)

    Pth[[0,1,4,5,15,16,17,18,19,20]] = Amplitude*math.sin(instant*frequency) - Ptor

    return Pth




def flowcalculator(P,R,Ph):


    Qtrans = np.zeros([24])
    Q = np.zeros([21])

    #Eustachian Valve
    if P[14]>(P[15]  - (Ph[15]-Ph[4])) or P[4]>(P[15] - (Ph[15]-Ph[14])) :

        Qraiup = (P[4]-P[15] - (Ph[15]-Ph[4]))/(R[5])
        if Qraiup < 0: Qraiup = 0

        Qraidw = (P[14]-P[15] - (Ph[15]-Ph[14]))/R[18]
        if Qraidw < 0: Qraidw = 0
    else:
```

```
    Qraiup = 0
    Qraidw = 0



Qlai =  (P[18]-P[19] - (Ph[19]-Ph[18]))/R[22]
if Qlai < 0: Qlai = 0

#Tricuspid Valve

if P[15]>(P[16] - (Ph[16]-Ph[15])):
    Qrvi = (P[15]-P[16]  - (Ph[16]-Ph[15]))/R[19]
    if Qrvi < 0: Qrvi = 0

else:
    Qrvi = 0

#Mitral Valve
if  P[19]>(P[20] - (Ph[20]-Ph[19])):
    Qlvi = (P[19]-P[20] - (Ph[20]-Ph[19]))/R[23]
    if Qlvi < 0: Qlvi = 0

else:
    Qlvi = 0


#Pulmonary Valve
if P[16]>(P[17] - (Ph[17]-Ph[16])):
    Qrvo = (P[16]-P[17])/R[20]
    if Qrvo < 0: Qrvo = 0

else:
    Qrvo = 0

# Aortic Valve
if P[20]>(P[0] - (Ph[0]-Ph[20])) :
    Qlvo = (P[20]-P[0] - (Ph[0]-Ph[20]))/R[0]
    if Qlvo < 0: Qlvo = 0
else:
    Qlvo = 0
```

```
#flows determination
Qup = (P[0]-P[1] - (Ph[1]-Ph[0]))/R[1]
if Qup < 0: Qup = 0
Qhaa = (P[1]-P[2] - (Ph[2]-Ph[1]))/R[2]
if Qhaa < 0: Qhaa = 0
Qhac = (P[2]-P[3] - (Ph[3]-Ph[2]))/R[3]
if Qhac < 0: Qhac = 0
Qhav = (P[3]-P[4] - (Ph[4]-Ph[3]))/R[4]
if Qhav < 0: Qhav = 0
Qdw = (P[0]-P[5] - (Ph[5]-Ph[0]))/R[6]
if Qdw < 0: Qdw = 0
Qaba = (P[5]-P[6] - (Ph[6]-Ph[5]))/R[7]
if Qaba < 0: Qaba = 0

Qka = (P[6]-P[7] - (Ph[7]-Ph[5]))/R[8]
if Qka < 0: Qka = 0
Qkc = (P[7]-P[8] - (Ph[8]-Ph[7]))/R[9]
if Qkc < 0: Qkc = 0
Qkv = (P[8]-P[13] - (Ph[13]-Ph[8]))/(R[10])
if Qkv < 0: Qkv = 0

Qsa = (P[6]-P[9] - (Ph[9]-Ph[6]))/R[11]
if Qsa < 0: Qsa = 0
Qsc = (P[9]-P[10] - (Ph[10]-Ph[9]))/R[12]
if Qsc < 0: Qsc = 0
Qsv = (P[10]-P[13] - (Ph[13]-Ph[10]))/(R[13])
if Qsv < 0: Qsv = 0

Qla = (P[6]-P[11] - (Ph[11]-Ph[6]))/R[14]
if Qla < 0: Qla = 0
Qlc = (P[11]-P[12] - (Ph[12]-Ph[11]))/R[15]
if Qlc < 0: Qlc = 0
Qlv = (P[12]-P[13] - (Ph[13]-Ph[12]))/(R[16])
if Qlv < 0: Qlv = 0
Qabv = (P[13]-P[14] - (Ph[14]-Ph[13]))/R[17]
if Qabv < 0: Qabv = 0

Qp = (P[17]-P[18] - (Ph[18]-Ph[17]))/R[21]
if Qp < 0: Qp = 0
```

```
    Qtrans = [Qup,Qhaa,Qhac,Qhav,Qraiup,Qrvi,Qrvo,Qp,Qlai,Qlvi,Qlvo, ...
    ... Qdw,Qaba,Qka,Qkc,Qkv,Qsa,Qsc,Qsv,Qla,Qlc,Qlv,Qabv,Qraidw]


    Q[0] = Qlvo - (Qup+Qdw)
    Q[1] = Qup - Qhaa
    Q[2] = Qhaa-Qhac
    Q[3] = Qhac-Qhav
    Q[4] = Qhav-Qraiup
    Q[5] = Qdw - Qaba
    Q[6] = Qaba - (Qka+Qsa+Qla)
    Q[7] = Qka - Qkc
    Q[8] = Qkc-Qkv
    Q[9] = Qsa-Qsc
    Q[10] = Qsc-Qsv
    Q[11] = Qla-Qlc
    Q[12] = Qlc-Qlv
    Q[13] = (Qkv+Qsv+Qlv)-Qabv
    Q[14] = Qabv - Qraidw
    Q[15] = (Qraiup+Qraidw)-Qrvi
    Q[16] = Qrvi-Qrvo
    Q[17] = Qrvo-Qp
    Q[18] = Qp-Qlai
    Q[19] = Qlai-Qlvi
    Q[20] = Qlvi-Qlvo


    return Qtrans,Q


def compliance_ass(compliance,cRA,cRV,cLA,cLV,dcRA,dcRV,dcLA,dcLV):

    C = np.zeros(21)
    DC = np.zeros(21)

    C[:15] = compliance[:15]
    C[15:17] = [cRA,cRV]
    C[17:19] = compliance[17:19]
    C[19:21] = [cLA,cLV]
```

```
    DC[15:17] = [dcRA,dcRV]
    DC[19:21] = [dcLA,dcLV]

    return C,DC

def gravity(rho,g,hh,conv,theta):

    Ph = np.zeros(21)

    g = g*math.sin(theta)

    Ph[0] = rho*g*(hh[3])*conv
    Ph[1] = rho*g*(hh[1])*conv
    Ph[2] = rho*g*(hh[0])*conv
    Ph[3] = rho*g*(hh[0])*conv
    Ph[4] = rho*g*(hh[1])*conv

    Ph[5] = rho*g*(hh[4])*conv
    Ph[6] = rho*g*(hh[5])*conv

    Ph[7] = rho*g*(hh[5])*conv
    Ph[8] = rho*g*(hh[5])*conv
    Ph[9] = rho*g*(hh[5])*conv
    Ph[10] = rho*g*(hh[5])*conv
    Ph[11] = rho*g*(hh[6])*conv
    Ph[12] = rho*g*(hh[6])*conv
    Ph[13] = rho*g*(hh[5])*conv

    Ph[14] = rho*g*(hh[4])*conv
    Ph[15] = rho*g*(hh[3])*conv

    Ph[16] = rho*g*(hh[3])*conv
    Ph[17] = rho*g*(hh[2])*conv
    Ph[18] = rho*g*(hh[2])*conv
    Ph[19] = rho*g*(hh[3])*conv

    Ph[20] = rho*g*(hh[3])*conv

    return Ph
```

```
def feedAB(Gp,Gs,e):



    G1A = Gp
    G1B = Gs[0]
    G2 = Gs[1]
    G3 = Gs[2]
    G4 = Gs[3]
    G5 = Gs[4]


    E1A = G1A*e
    E1B = G1B*e
    E2 = G2*e
    E3 = G3*e
    E4 = G4*e
    E5 = G5*e

    DX = [E1A,E1B,E2,E3,E4,E5]

    return DX

def feedCP(G,e):



    GA = G[0]
    GB = G[1]



    EA = GA*e
    EB = GB*e


    DX = [EA,EB]

    return DX
```

B.4 main.py

```
import numpy as np
from matplotlib import pyplot as plt
from scipy.integrate import  solve_ivp
import math

import data
import functions
import Heart_class


N = 10
int_step = 0.0001 #seconds
time = np.arange(0,30+N,int_step)
S = 'M'


counter = 0
eAB = 0
eCP = 0

theta = math.pi/2

MR = 0
dlvc = 0
drvc = 0
DLVC = 0
DRVC = 0
DAR = 0
DVV = 0


R = np.zeros(24)

#Variable initialization
HR, CRA, CRV, CLA, CLV,DCRA, DCRV, DCLA, DCLV, Porg, PPs, QQs, VVs, T, R0, mr, ...
... PrefAB, PrefCP, DX, shift,Vorg = functions.inizialization()

#Class Definition
```

```
RA = Heart_class.Heart('Right Atrium',data.Es[0],data.Ed[0],data.V0[0],S)
RV = Heart_class.Heart('Right Ventricle',data.Es[1],data.Ed[1],data.V0[1],S)
LA = Heart_class.Heart('Left Atrium',data.Es[2],data.Ed[2],data.V0[2],S)
LV = Heart_class.Heart('Left Ventricle',data.Es[3],data.Ed[3],data.V0[3],S)

THETA = []
PTH = []


#External loop: once per beat
while T < time[-1]:

    print(T)
    beat_time, T_sys, L_sys, hr = RA.senoatrialpacemaker(T,int_step,HR[-1],MR)
    MR = 0

    if hr>=200: hr=200
    shift = 60/hr - 0.2

    print(f'shift = {shift}')
    #Compliances and Derivatives, already shifted
    cRA,dcRA = RA.beat(beat_time,T_sys,int_step,shift)
    cRV,dcRV = RV.beat(beat_time,T_sys,int_step,0)
    cLA,dcLA = LA.beat(beat_time,T_sys,int_step,shift)
    cLV,dcLV = LV.beat(beat_time,T_sys,int_step,0)

    #Compliance control variation
    cRV += DRVC
    cLV += DLVC

    #appending function
    CRA, CRV, CLA, CLV, DCRA, DCRV, DCLA, DCLV = functions.heart_append(CRA, CRV, ...
    ... CLA, CLV, DCRA, DCRV, DCLA, DCLV, cRA, cRV, cLA, cLV, dcRA, dcRV, dcLA, dcLV)

    print(hr)
    #Internal loop, once per integration step
    for steps in range(len(beat_time)-1):

        #control on time vector length
        if counter+1 >= np.size(time):
            break
```

```
        for num in range(len(PPs)):
            Porg[num] = PPs[num][-1]

        for num in range(len(VVs)):
            Vorg[num] = VVs[num][-1]


#         if time[counter] > 20 and time[counter]<30:
#             theta = (3*math.pi/2)-(math.pi/2)*(time[counter]/10)
#         elif time[counter]>=30:
#             theta = 0

        if time[counter]>=20:
            theta = 0
        THETA.append(theta)
        Ph = functions.gravity(data.rho,data.g,data.hh,data.conv,theta)

        #control loop
        if counter%1000 == 0 and counter != 0:
            eAB = 18*math.atan(((np.mean(PPs[0][counter-1000:counter]) ...
            ... +np.mean(PPs[1][counter-1000:counter]))/2-95)/18)
            eCP = 5*math.atan((np.mean(PPs[15][counter-1000:counter])-5)/5)

            DXAB = functions.feedAB(data.GABp,data.GABs,eAB)
            DXCP = functions.feedCP(data.GCPs,eCP)

            mr = (DXAB[0])/1000
            dlvc = (DXAB[2])
            drvc = DXAB[3]
            DAR = DXAB[4]+DXCP[0]
            DVV = DXAB[5]+DXCP[1]




        #HR control
        MR += mr/len(beat_time)

        #Compliance control variation
```

```
        DRVC += drvc/len(beat_time)
        DLVC += dlvc/len(beat_time)




        Pth =    functions.intrathoracic(data.amplitude, ...
        ... time[counter], data.frequency, data.Ptor)
        PTH.append(Pth[0])
#
        R[:21] = R0[:21]
        R[21] = R0[21]*PTH[-1]/-5
        R[22:25] = R0[22:25]
#
#        #R control
        R[[0,1,2,6,7,8,11,14,21]] += DAR/len(beat_time)

        #Compliance and derivative determination
        C,DC = functions.compliance_ass(data.C,cRA[steps],cRV[steps],cLA[steps], ...
        ... cLV[steps],dcRA[steps],dcRV[steps],dcLA[steps],dcLV[steps])
        Qtrans,Qorg = functions.flowcalculator(Porg,R,Ph)




        sol = solve_ivp(lambda t, y: functions.sys_ode(t,y,Qorg,C,DC,Ph), ...
        ... [beat_time[steps],beat_time[steps+1]], Porg, method='RK45')

        Porg = sol.y[:,1]


        Vorg = data.ZV + Porg*C

        #V control
        Vorg[[3,4,8,10,12,13,14,18]] += DVV/len(beat_time)

        counter += 1
```

```
        #Saving Porg
        for num in range(len(PPs)):
            PPs[num].append(Porg[num])

        #Saving Volume, flow, heart rate
        HR.append(hr)
        for num in range(len(VVs)):
            VVs[num].append(Vorg[num])

        for num in range(len(QQs)):
           QQs[num].append(Qorg[num])




    T = beat_time[-1]
    if counter+1 >= np.size(time):
        break


print('out of cycle')




n=int(N/int_step)

s = counter



#funzione di plotting
compliance_figure = plt.figure(0)
plt.plot(time[n:s],CRA[n:s],'g',label = 'RA')
plt.plot(time[n:s],CLA[n:s],'c',label = 'LA')
plt.plot(time[n:s],CRV[n:s],'b',label = 'RV')
plt.plot(time[n:s],CLV[n:s],'r',label = 'LV')
plt.legend()
plt.title('Heart Compliances')
plt.xlabel('time [s]')
```

```
plt.ylabel('Compliance [ml/mmHg]')
plt.grid()
compliance_figure.savefig(f'img/Heart Compliances 21p ...
... time {int(T)}.png', bbox_inches = 'tight', dpi = 500)
plt.show()

compliance_derfigure = plt.figure(0)
plt.plot(time[n:s],DCRA[n:s],'g',label = 'RA')
plt.plot(time[n:s],DCLA[n:s],'c',label = 'LA')
plt.plot(time[n:s],CRV[n:s],'b',label = 'RV')
plt.plot(time[n:s],DCLV[n:s],'r',label = 'LV')
plt.legend()
plt.title('Heart Compliances')
plt.xlabel('time [s]')
plt.ylabel('Compliance [ml/mmHg]')
plt.grid()
compliance_derfigure.savefig(f'img/Heart Compliances derivative 21p ...
... time {int(T)}.png', bbox_inches = 'tight', dpi = 500)
plt.show()

frhp = plt.figure(1)
ra = plt.plot(time[n:s],PPs[15][n:s],'g', label ='RA')
plt.plot(time[n:s],PPs[16][n:s],'b', label ='RV')
plt.plot(time[n:s],PPs[17][n:s],'r', label ='PA')
plt.title('Right Heart Pressure Dynamic')
plt.xlabel('time [s]')
plt.ylabel('Pressure [mmHg]')
plt.grid()
plt.legend()
frhp.savefig(f'img/Right Heart Pressure Dynamic 21p ...
... time {int(T)}.png', bbox_inches = 'tight', dpi = 500)
plt.show()


flhp = plt.figure(2)
plt.plot(time[n:s],PPs[19][n:s],'g', label ='LA')
plt.plot(time[n:s],PPs[20][n:s],'b', label ='LV')
plt.plot(time[n:s],PPs[0][n:s],'r', label ='A')
plt.legend()
plt.title('Left Heart Pressure Dynamic')
plt.xlabel('time [s]')
```

```
plt.ylabel('Pressure [mmHg]')
plt.grid()
flhp.savefig(f'img/Left Heart Pressure Dynamic 21p ...
... time {int(T)}.png', bbox_inches = 'tight', dpi = 500)
plt.show()

flh = plt.figure(2)
plt.plot(VVs[20][n:s],PPs[20][n:s],'r', label ='LV')
plt.legend()
plt.title('Left Ventricle cycle')
plt.xlabel('Volume [ml]')
plt.ylabel('Pressure [mmHg]')
plt.grid()
flh.savefig(f'img/Left Ventricle cycle 21p ...
... time {int(T)}.png', bbox_inches = 'tight', dpi = 500)
plt.show()

frh = plt.figure(2)
plt.plot(VVs[16][n:s],PPs[16][n:s],'b', label ='RV')
plt.legend()
plt.title('Right Ventricle cycle')
plt.xlabel('Volume [ml]')
plt.ylabel('Pressure [mmHg]')

plt.grid()
frh.savefig(f'img/Right Ventricle cycle 21p ...
... time {int(T)}.png', bbox_inches = 'tight', dpi = 500)
plt.show()


fr3 = plt.figure(1)
plt.plot(time[n:s],PPs[15][n:s],'g', label ='RA')
plt.title('Right Atrium Pressure Dynamic')
plt.xlabel('time [s]')
plt.ylabel('Pressure [mmHg]')
plt.grid()
plt.legend()
fr3.savefig(f'img/Right Atrium Pressure Dynamic 21p ...
... time {int(T)}.png', bbox_inches = 'tight', dpi = 500)
plt.show()
```

```
fhr = plt.figure()
plt.plot(time[n:s],HR[n:s],'g')
plt.title('Heart Rate')
plt.xlabel('time [s]')
plt.ylabel('Heart Rate [bpm]')
plt.grid()
fhr.savefig(f'img/Heart Rate 21p ...
... time {int(T)}.png', bbox_inches = 'tight', dpi = 500)
plt.show()


fhre = plt.figure()
plt.plot(time[n:s],PPs[1][n:s],'g')
plt.title('Carotid sinus Pressure')
plt.xlabel('time [s]')
plt.ylabel('Pressure [mmHg]')
plt.grid()
fhre.savefig(f'img/Carotid Sinus Pressure 21p ...
... time {int(T)}.png', bbox_inches = 'tight', dpi = 500)
plt.show()
fr32 = plt.figure(1)
plt.plot(time[n:s],PPs[19][n:s],'g', label ='LA')

plt.title('Left Atrium Pressure Dynamic')
plt.xlabel('time [s]')
plt.ylabel('Pressure [mmHg]')
plt.grid()
plt.legend()
fr32.savefig(f'img/Left Atrium Pressure Dynamic 21p ...
... time {int(T)}.png', bbox_inches = 'tight', dpi = 500)
plt.show()


fr33 = plt.figure(1)
plt.plot(time[n:s],THETA[n:s],'g')
plt.title('Gravity')
plt.xlabel('time [s]')
plt.ylabel('Value of Theta [radians]')
plt.grid()
plt.legend()
```

```
fr33.savefig(f'img/Gravity theta 21p ...
... time {int(T)}.png', bbox_inches = 'tight', dpi = 500)
plt.show()
```

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