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Title: Mathematical Modelling Of The Blood Pressure Signal

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Introduction

Mathematical modelling is getting more and more important in plenty of fields. A good model helps us understand deeply how a system works. Furthermore, it can be used to make simulations of the system under certain conditions and, from them, predictions of its behaviour.

In particular, mathematical modelling is important in biomedical engineering. A deep understanding of the physiology and all the components taking part in a certain process may lead to a better control of this process through drugs, devices, etc.

One of the fields of interest in medical engineering is the management of the blood pressure. It is well known that the arterial pressure gives an idea of the cardiovascular system's performance. A high level of blood pressure may indicate that there is a risk of more severe cardiovascular diseases - even heart attack. On the other hand, in a hospital context with very ill patients, low pressure values might indicate blood loss and other critical situations. In very critical patients, the blood pressure is measured with an arterial catheter.

The objective of this work is to develop a model of the continuous arterial pressure signal provided by the arterial catheter, and to validate it against real data to evaluate it.

The mathematical model that we present was partially developed in a workshop held at CRM in December, 2010, in collaboration with Sabirmedical SL. The company's objective was to develop a system to measure the blood pressure continuously and non-invasively using expert systems. To do so, it was necessary to have a good model to understand in detail the physiology of the cardiovascular system and which factors affect the blood pressure. This company provided the real data used in this work. The main objective was to develop a model which included certain characteristics of the signal but keeping it as simple as possible, so it would be easy to understand and interpret. In consequence, the model presented here comes from a very applied framework and has been useful in a product's development. It may be considered a good example of mathematical models in engineering.

This thesis consists of five chapters. The first one is a very brief review of the circulatory system and the blood pressure signal, emphasizing the particular characteristics we want to model. In the second chapter, some of the existing models of the blood pressure are presented, and their utility in our particular problem is discussed. The third chapter presents the model we have developed with all its components, and integrates it for a theoretical set of parameters. Since one of the objectives of the work is fitting the model into real arterial signals, the model's parameters must be estimated for each patient. The first part of the parameter estimation is explained in chapter four - a sensitivity analysis, to determine which parameters have the greatest influence on the solution. In the fifth chapter we can see the second part of the parameter estimation method, and the result for each patient - their real blood pressure signal compared to the one obtained with the model.

To sum up, we can say that this work presents a model and a method to adjust it to given data, and a comparison of the model with real signals.

Chapter 1

Review of the cardiovascular system and the blood pressure signal

The cardiovascular system, also named the circulatory system, is a very complex organ system. It is necessary to feed oxygen and nutrients to the rest of the body organs and tissues, to mantain the body's temperature, etc. This is achieved by means of a fluid: the blood. It is constantly pumped by the heart, and circulates through a very complex network composed of arteries, capillaries and veins.

We can first divide the circulation in two systems:

- The **pulmonary circulation** goes from the heart to the lungs and carries de-oxygenated blood through pulmonary arteries. Once in the lungs, the red cells get the oxygen. The oxygenated blood then goes to the heart again through pulmonary veins.

- The **systemic circulation** carries oxygenated blood coming from the pulmonary system to the rest of the body. This is the system we will study in this work.

How does the systemic circulation work? The blood leaves the heart's left ventricle through the aortic valve and the aorta (a wide artery). The aorta divides into smaller arteries, and then into arterioles and, after them, the smallest branches of the system, the capillaries. They have a very small diameter, but are responsible for feeding all the organs and tissues with the glucose, nutrients, and oxygen that the blood carries. The de-oxygenated blood continues to find the venules, small unions of capillaries, and they join into veins, and finally all together join into a wide vein, the vena cavae, which brings the blood to the heart. This is constantly happening in our body, more than once each second!

To accurately model this network of blood vessels we could use a very complex fractal model of the geometry. There are kilometers of blood vessels inside a human body, branching like trees and then joining again. In consequence, in this work a simpler model of the systemic circulation will be used. The cardiovascular system will be simplified into a heart, which ejects blood to the arteries. The blood goes into the capillary network and then to the veins, to go to the heart again through the mitral valve.

More particularly, each section (arteries, capillaries and veins) will be treated as a single vessel, and we will only take into consideration their average pressures and flows. The same with the heart - instead of modelling it with two ventricles and two atriums, we will only model the left ventricle, which ejects the blood to the arteries.

A diagram of this simplification of the cardiovascular system is shown in figure 1.1.

Each heart beat consists in a contraction, named **systole**, and a relaxation, named **diastole**.

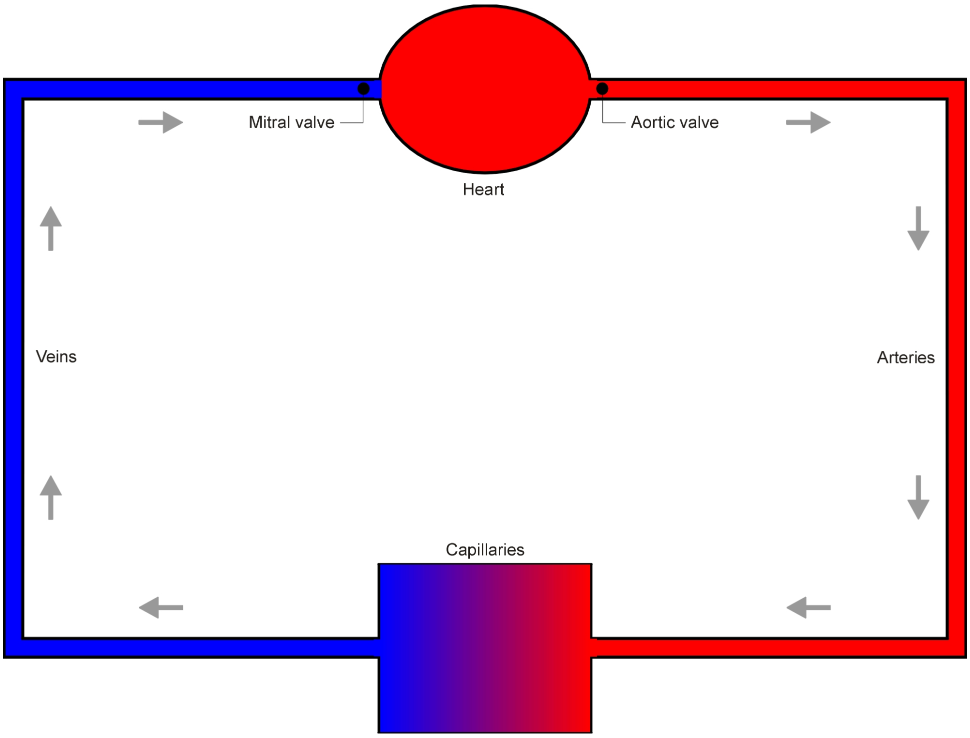

Figure 1.1: The cardiovascular system

All the vessels have their own resistance to the blood flow, which depends on their radius, the viscosity of the blood, etc. ([1]). They are not rigid - their elasticity is called the compliance, and is very different in each kind of vessel. While the aorta is almost rigid, the arteries are a little bit compliant. But, most important of all, the veins have a much higher compliance than the other vessels. This is because they have an additional function - they store blood.

We call blood pressure the pressure exerted by circulating blood upon the walls of blood vessels. In the aorta, the pressure is very high; it decreases in the arteries; when it gets into the veins, the pressure is much lower; and when it gets into the heart again, the blood pressure is almost 0.

The most important measure of the blood pressure is the arterial one.

The blood pressure is usually measured in millimeters of mercury, mmHg. The most common tool to measure it is the sphygmomanometer - the cuff placed around the arm which inflates for about a minute. However, this gives a measure at a single point in time. When a continuous arterial pressure measure is needed, an arterial catheter is placed in the radial or femoral artery. This happens mainly in ICUs with very critical patients.

In figure 1.2 we can see an example of the countinuous signal that the arterial catheter provides.

From this signal, we may observe some things:

- It is an oscillating signal. Each oscillation corresponds to one heart beat, one ejection of blood.

- In the example, the higher value of the oscillations is near 135 mmHg. This is called the **systolic pressure**. The lower value of the oscillations (here 60) is the **diastolic pressure**. When the pressure is measured with a cuff, it provides two numbers, corresponding to the previous two pressures. In this case, we would say that the patient has an arterial

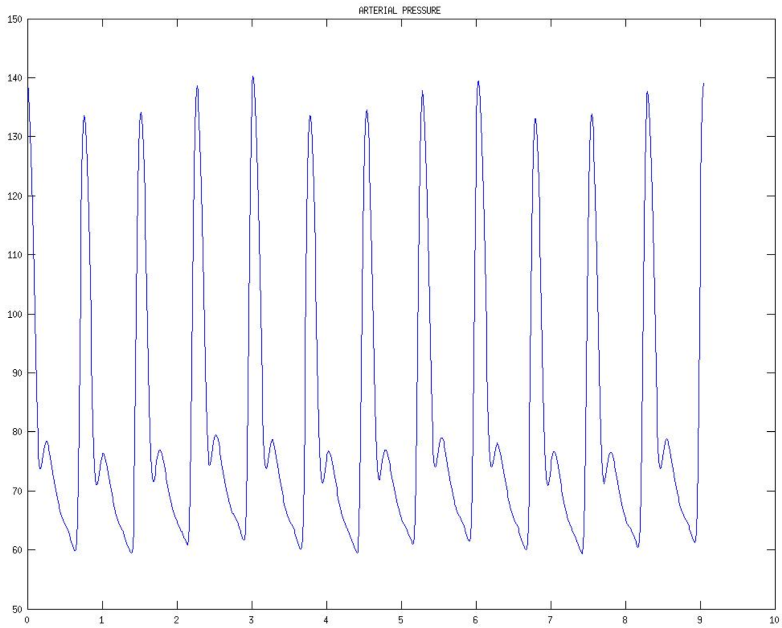

Figure 1.2: An arterial catheter signal

pressure of 135/60.

- We can also see that the systolic pressure (and, less visible, the diastolic pressure and the heart rate) also oscillates. The frequency for this particular subject is more or less a cycle every five beats. This oscillation is caused by the patient's respiration. During the inspiration, there is a cardiac acceleration and an increase in pressure. When the lungs eject the air, the heart rhythm and the blood pressure decrease again. This motion is called **respiratory sinus arrhythmia**.

- The last thing we should observe is a small peak at the end of every beat. This is the **dicrotic notch**. This does not always look like a clear peak but sometimes may be a flat part or a change in slope. The dicrotic notch appears due to the aortic valve closing. Just before it happens, the pressure inside the heart is lower than in the aorta, and this makes the valve close. But sometimes there is a little backflow due to this pressure difference, which makes this small peak appear in the wave.

With the knowledge of all these elements of the circulatory system, we can now start thinking of a way of modelling the arterial pressure signal.

Chapter 2

Review of mathematical models for blood pressure

2.1 Introduction

In this section we summarize some popular models for the circulatory system. We also compute solutions for two of the simple and discuss their applicability to the actual blood pressure signal.

2.2 The Ottesen model

2.2.1 Description

The first example of a blood pressure model we will see is the baroreflex-feedback, published by Johnny T. Ottesen in [2, 3].

This model does not model the pulsatile blood pressure signal, but the variations in blood pressure due to the baroreflex mechanism. The baroreflex is the part of the autonomic nervous system which regulates the heart rate and the blood pressure. It consists of sensors placed in the heart and the aortic arch, connected to the posterior part of the brain.

Two nervous systems carry the brain's decision to increase or decrease the blood pressure to the corresponding destination. They are:

- The **sympathetic** nervous system: when it is activated, it produces an increase in heart rate (and so in cardiac output), and vasoconstriction (increase in vessel's resistance). The consequence is that the blood pressure increases. The effects of the sympathetic system are almost instantaneous.

- The **parasympathetic** nervous system: it has the opposite effect. It decreases the heart rate to decrease the blood pressure. The parasympathetic acts with a small time delay, which we will call τ.

In this mathematical model, resistances and compliances are assumed to be constant during a short period of time in which the model is integrated, and the baroreflex acts only on the heart rate. The stroke volume (volume of blood ejected in each heart beat) is also taken as constant.

The model takes into account the variations in two different types of vessels, arteries and veins. In each of them, the pressure is assumed to be homogeneous. Let $P_a(t)$ be the arterial pressure, $P_v(t)$ the venous one, and $H(t)$ the heart rate. These three are the dependent variables

Parameter	Meaning	Value	Units
c_a	Arterial compliance	1.55	ml/mmHg
c_v	Venous compliance	519	ml/mmHg
R	Peripheral resistance	1.05	mmHg·s/ml
r	Venous outflow resistance	0.068	mmHg·s/ml
V_s	Stroke volume	67.9	ml
H_0	Typical mean heart rate	1.24	1/s
P_{a0}	Typical mean arterial pressure	100	mmHg
P_{v0}	Typical mean venous pressure	7	mmHg

Table 2.1: Meaning and nominal values of the parameters

in Ottesen's model. Every time, the change in arterial pressure depends on the two pressures and the volume of blood ejected; the change in venous pressure depends on both pressures, including a resistance of the heart's valve. The variation in heart rate is modelled as a function which will reflect the baroreflex feedback, and here is where the time delay τ plays a role.

$$\dot{P}_a(t) = -\frac{1}{c_a R} P_a(t) + \frac{1}{c_a R} P_v(t) + \frac{1}{c_a} V_s H(t) \tag{2.1}$$

$$\dot{P}_v(t) = -\frac{1}{c_v R} P_a(t) - \left(\frac{1}{c_v R} + \frac{1}{c_v r}\right) P_v(t) \tag{2.2}$$

$$\dot{H}(t) = f\big(P_a(t), P_a(t-\tau)\big) \tag{2.3}$$

The meaning of each parameter and its nominal value can be found in table 2.1.

What is the function that regulates the heart rate? In [2] some physiologically realistic assumptions are made, such as differentiability or sign. Based on these assumptions, the following ad-hoc function is suggested:

$$f\big(P_a(t), P_a(t-\tau)\big) = \frac{\alpha_H T_s}{1 + \gamma_H T_p} - \beta_H T_p \tag{2.4}$$

where T_s and T_p are the sympathetic and the parasympathetic tone respectively, and are modelled as the following sigmoidals:

$$T_s(t,\tau) = \frac{1}{1 + \left(\frac{P_a(t-\tau)}{\alpha_s}\right)^{\beta_s}} \tag{2.5}$$

$$T_p(t) = \frac{1}{1 + \left(\frac{P_a(t)}{\alpha_p}\right)^{\beta_p}} \tag{2.6}$$

The values suggested in [2] of the heart rate function are shown in table 2.2.

2.2.2 Integration

If we integrate numerically the equations 2.1, 2.2 and 2.3, with the suggested sigmoidals for the baroreflex feedback mechanism, and the suggested parameters, the arterial pressure signal we obtain is the one shown in figure 2.1. As we can see, the resulting signal oscillates near the

Parameter	Value	Units
α_H	0.84	s^{-2}
β_H	1.17	s^{-2}
γ_H	0	
α_s	93	mmHg
β_s	7	
α_p	93	mmHg
β_p	7	

Table 2.2: Suggested values of the parameters

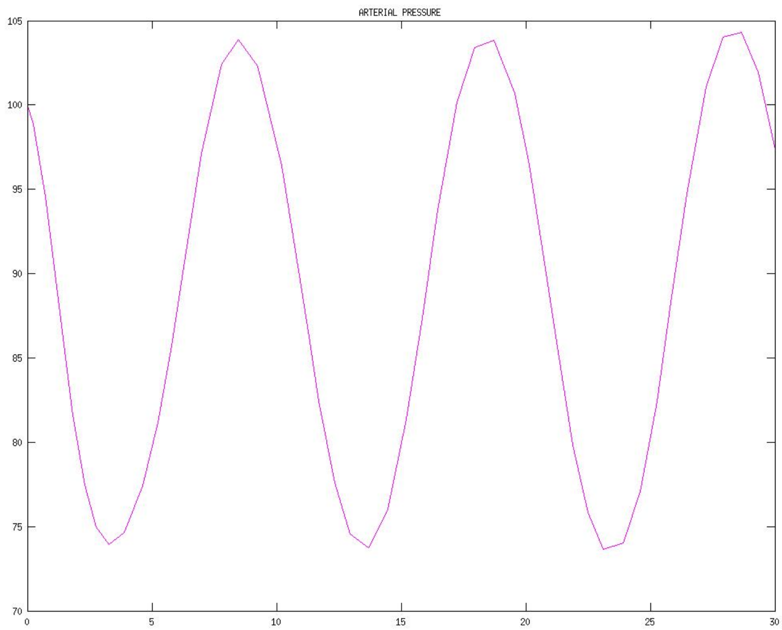

Figure 2.1: Arterial pressure

typical mean arterial pressure (between 75 and 105 mmHg), in very slow oscillations (near 10 seconds each full cycle).

This baroreflex-feedback model is good to predict the behaviour of the mean arterial pressure during a certain period of time in steady patients. Moreover, the author claims that it has been tested against real data and it has given good results. However, it does not reflect the pulsatile component of the blood pressure signal, which we want to model. Nevertheless, it is a good example of a mathematical model, in the sense that it is reasonably accurate enough, but also very simple and easy to interpret.

In [4], Fowler and McGuiness rescale the model and simplify it to investigate the roles played by gain and delay, and the effects of ageing.

2.3 The windkessel model

2.3.1 Description

Compartment models are a particular type of lumped parameters model. They consist in splitting the system into sections, named compartments. The main assumption is that each comparment is homogeneous - in this case, each compartment has got the same blood pressure. The windkessel model is a simple example of a compartment model. We will focus a little on the understanding, integration and result of this model, since our model is also a compartment model.

The first description of the cardiovascular system as a compartment model was published in 1733 by the physiologist Stephen Hales, who compared the dampening blood pressure due to compliance of blood vessels with an air chamber from some 18th century machines. He named this a *windkessel* model (german translation of *air chamber*). Nevertheless, that description was very qualitative. It became a mathematical model in 1899 thanks to another physiologist, Otto Frank. He quantified the concept in the basis of conservation of mass. [5].

The windkessel model consists of two compartments: the heart (which induces pulsatility) and the systemic arteries (which have a vascular resistance and some distensibility). The flow into the arteries (Q_{in}) can be split into flow stored and flow outgoing, this way:

$$Q_{in} = Q_{stored} + Q_{out} \tag{2.7}$$

The distensibility, also named compliance, is defined as

$$C = \frac{dV}{dP_{in}} \tag{2.8}$$

And so Q_{stored} is

$$Q_{stored} = \frac{dV}{dt} = \frac{dV}{dP_{in}}\frac{dP_{in}}{dt} = C\frac{dP_{in}}{dt} \tag{2.9}$$

The resistance is related to how easily the blood flows.

$$Q_{out} = \frac{P_{in}}{R} \tag{2.10}$$

If we substitute Q_{out} and Q_{stored} in equation 2.3.1, we obtain the following:

$$Q_{in} = C\frac{dP_{in}}{dt} + \frac{P_{in}}{C} \tag{2.11}$$

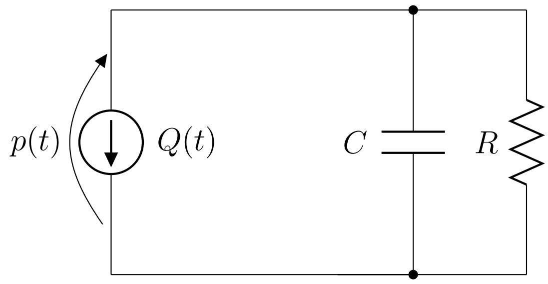

Figure 2.2: Windkessel model as a circuit

Parameter	Value	Units
C	1.55	ml/mmHg
R	1.05	s·mmHg/ml
V_s	67.9	ml
H	1.24	beat/s
T	$1/H$	s
T_{sys}	$T/3$	s
P_0	100	mmHg

Table 2.3: Nominal values of the parameters

Dividing by the compliance and renaming Q_{in} and P_{in} to Q and P, we have the governing differential equation of the windkessel model:

$$\frac{dP}{dt} + \frac{P}{RC} = \frac{Q}{C} \tag{2.12}$$

A very common representation of the windkessel system is an analogy with an electric circuit, with the heart as the current source Q, a resistance and a capacitance (equivalent to arterial compliance). The equivalent to the voltage would be the blood pressure, P. This formulation fulfills Ohm's and Kirchoff's laws of the electric circuits. Figure 2.2 shows the two-compartment windkessel model drawn as an electric circuit.

After that, models with more compartments (more *windkessels*) have been built, to introduce the heart valve's own resistance and the inertia of the blood flow ([6], [7]).

2.3.2 Integration

We are now going to focus on the two-compartment windkessel model. The equation of the model is

$$\frac{dP}{dt} + \frac{P}{RC} = \frac{Q}{C} \tag{2.13}$$

Nominal parameters of the resistance, the compliance, the stroke volume, the heart rate, the systolic fraction of each beat and the initial mean pressure, taken from the previous model [2], are shown in table 2.3.

We have to choose a flow, $Q(t)$, such as the volume in a whole beat corresponds to the stroke volume, i.e.

$$\int_{t_0}^{t_0+T} Q(t)\, dt = V_s \tag{2.14}$$

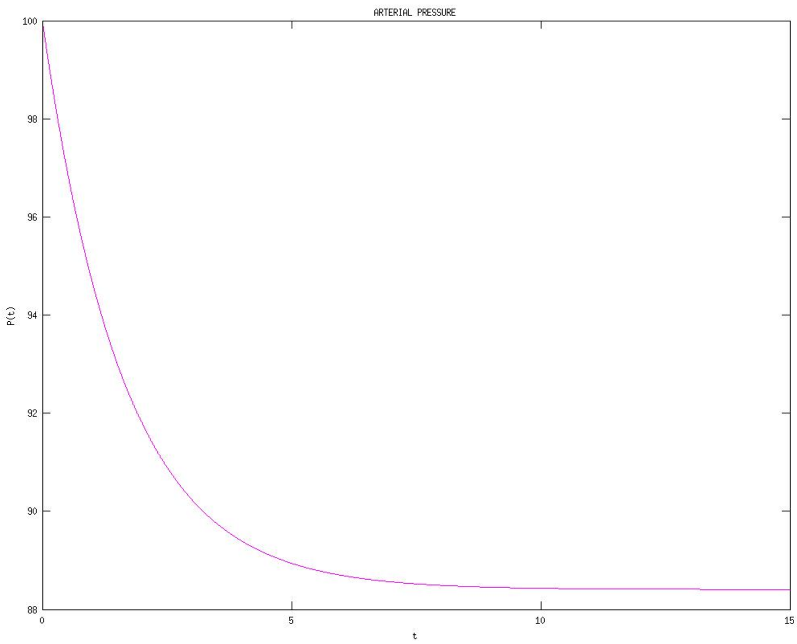

Figure 2.3: Pressure computed with constant $Q(t)$

2.3.2.1 Constant flow

If we take the flow to be a constant, $Q(t) = Q_0$, it must satisfy

$$\int_{t_0}^{t_0+T} Q_0 \, dt = Q_0 T = V_s \tag{2.15}$$

Then,

$$Q_0 = \frac{V_s}{T} = V_s H = 67.9 \cdot 1.24 = 84.196 \,\text{ml/s} \tag{2.16}$$

Immediately, equation 2.13 becomes linear, with constant coefficients, and can be solved analytically, giving as a result

$$P(t) = Q_0 R + (P_0 - QR) e^{-\frac{t}{RC}} \tag{2.17}$$

We can see how the pressure looks like in figure 2.3.

2.3.2.2 Train of pulses flow

From the previous subsection it is clear that we need to induce pulsatility in the flow. We can do so with a pulse train which has value $Q_m = 0$ during diastole diastole and Q_M during the systole, and whose integral during a whole beat is V_s. If $\bar{t}$ is the time modulo the cardiac period, $\bar{t} \in [0, T]$, then the flow will be

$$Q(\bar{t}) = \begin{cases} Q_M & \bar{t} \leq \frac{1}{3} \\ 0 & \text{otherwise} \end{cases} \tag{2.18}$$

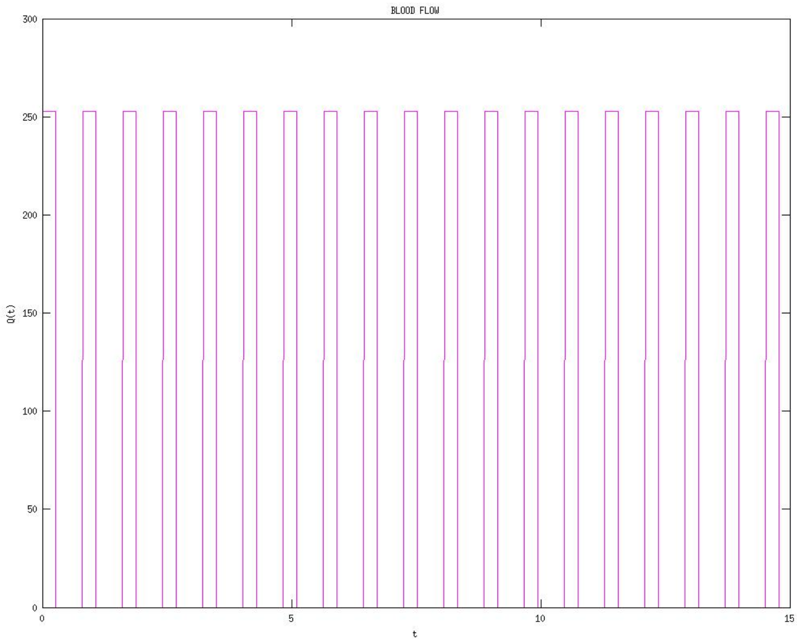

Figure 2.4: $Q(t)$ as a pulse train

We impose the volume in a beat equals to V_s.

$$\int_{t_0}^{t_0+T} Q(t)\,dt = \frac{T}{3}Q_M = V_s \tag{2.19}$$

Then,

$$Q_M = 3\frac{V_s}{T} = 3V_sH = 3 \cdot 67.9 \cdot 1.24 = 252.588\,\text{ml/s} \tag{2.20}$$

We can see the flow as a pulse train in figure 2.4, and the pressure obtained from this flow in figure 2.5.

As we can see, the pressure obtained is pulsatile but too sharp. We can also note that the pressure values are not realistic (the amplitude of oscillation is too small). In order to solve this problem, a proper set of parameters should be found.

2.3.2.3 Sine flow

We can try with a smoother pulsatile flow, such as a sine wave. Imposing that $Q(t)$ oscillates between 0 and Q_M, it must be

$$Q(t) = \frac{Q_M}{2}\left(1 + sin\left(\frac{2\pi t}{T} - \frac{\pi}{2}\right)\right) \tag{2.21}$$

Imposing also that the volume ejected each beat is V_s,

$$\int_{t_0}^{t_0+T} Q(t)\,dt = \frac{T}{2}Q_M = V_s \tag{2.22}$$

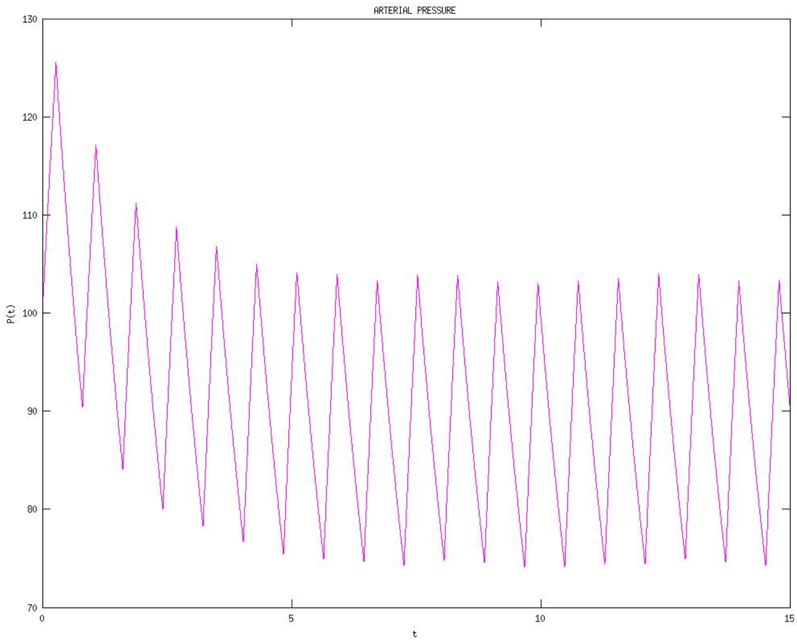

Figure 2.5: Pressure computed with pulse train $Q(t)$

and so

$$Q_M = 2\frac{V_s}{T} = 2V_sH = 2 \cdot 67.9 \cdot 1.24 = 168.392\,\text{ml/s} \tag{2.23}$$

Figure 2.6 shows the smooth sine flow, and figure 2.7 the pressure obtained from this flow.

2.3.2.4 Sine squared flow

As we can see, the pressures obtained in subsections 2.3.2.1, 2.3.2.2 and 2.3.2.3 follow the same baseline, but oscillate in a different way, depending on the imposed flow.

While in the constant flow case the pressure does not oscillate, in the sine case it does, but the resulting pressure waveform is too much similar to a sine. Actual pressure waves are not so symmetric (beat to beat), i.e., the slope in the systole (pressure going up) is much greater, in absolute value, than the slope of the diastole. The pressure obtained with a pulse train flow does fulfill this asymetry, but the waveform is too spiky to be realistic.

So we need something as smooth as the sine but asymetric as the pulse train. We can take a pulse which is a sine squared in the systole and zero in the diastole.

$$Q(\bar{t}) = \begin{cases} Q_M \sin^2\left(\frac{\pi\bar{t}}{T_sT}\right) & \bar{t} \leq \frac{1}{3} \\ 0 & \text{otherwise} \end{cases} \tag{2.24}$$

We calculate the value of Q_M as in previous cases.

$$\int_{t_0}^{t_0+T} Q(t)\,dt = \frac{(3\sqrt{3}+8\pi)T}{48\pi}Q_M = V_s \tag{2.25}$$

Then,

$$Q_M = \frac{48\pi}{3\sqrt{3}+8\pi}\frac{V_s}{T} = \frac{48\pi}{3\sqrt{3}+8\pi} \cdot 67.9 \cdot 1.24 = 418.626\,\text{ml/s} \tag{2.26}$$

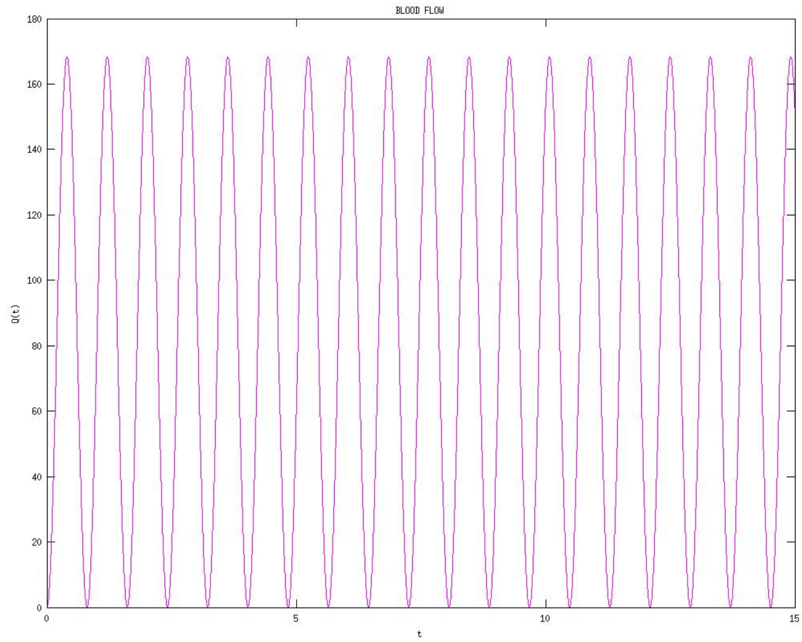

Figure 2.6: $Q(t)$ as sine wave

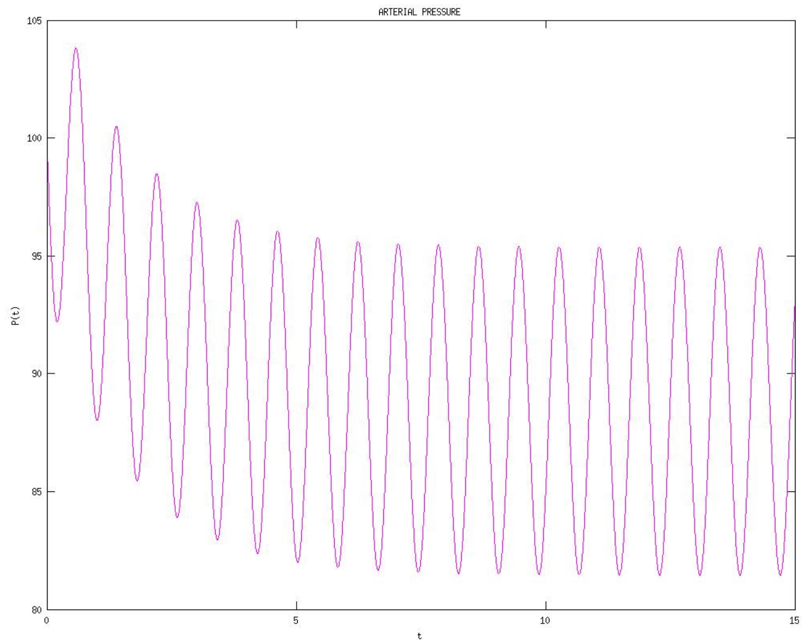

Figure 2.7: Pressure computed with sine $Q(t)$

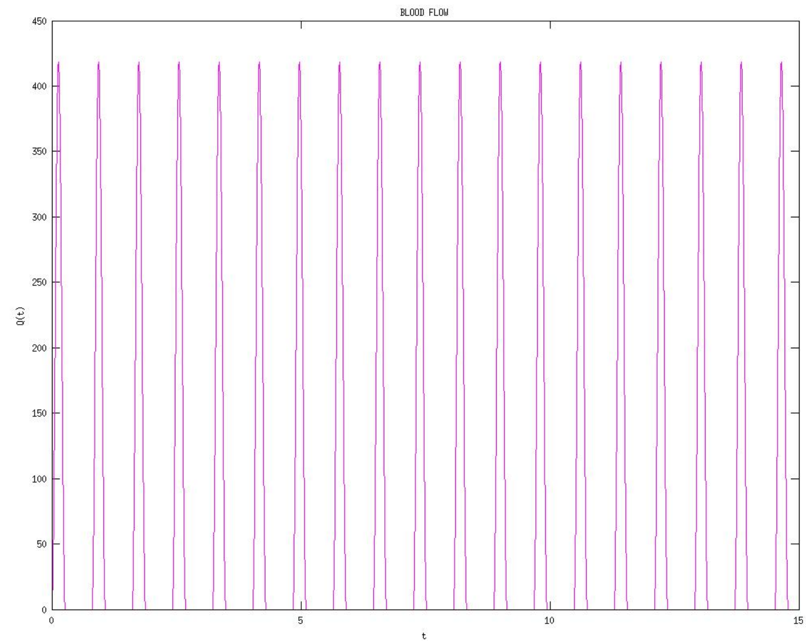

Figure 2.8: $Q(t)$ as a sine squared

We can see the flow as a sine squared in figure 2.8, and the pressure obtained from this flow in figure 2.9.

The obtained pressure shows the desired asymetry but is still too spiky, and the downslope part of the beat too linear. The type of flow we induce affects the solution but it is never good enough.

Therefore, we can claim that the windkessel model itself is too poor to provide a good representation of the pressure.

2.4 The Chapman-Fowler-Hinch model

2.4.1 Description

In the book [8], the authors suggest a more refined compartment model.

Three compartments are used: arteries (suffix a), veins (v), and the heart's left ventricle (LV). Each chamber has volume V and pressure p. Both flow rates to and from the left ventricle are denoted by Q_- and Q_+, respectively, and the blood flow through the capillaries is denoted by Q_c. Conservation of blood volume is then expressed by the following equations:

$$\begin{aligned} \dot{V}_a &= Q_+ - Q_c && (2.27) \\ \dot{V}_v &= Q_c - Q_- && (2.28) \\ \dot{V}_{LV} &= Q_- - Q_+ && (2.29) \end{aligned}$$

Let R_c be the capillary resistance. Then, the capillary blood flow is

$$Q_c = \frac{p_a - p_v}{R_c} \tag{2.30}$$

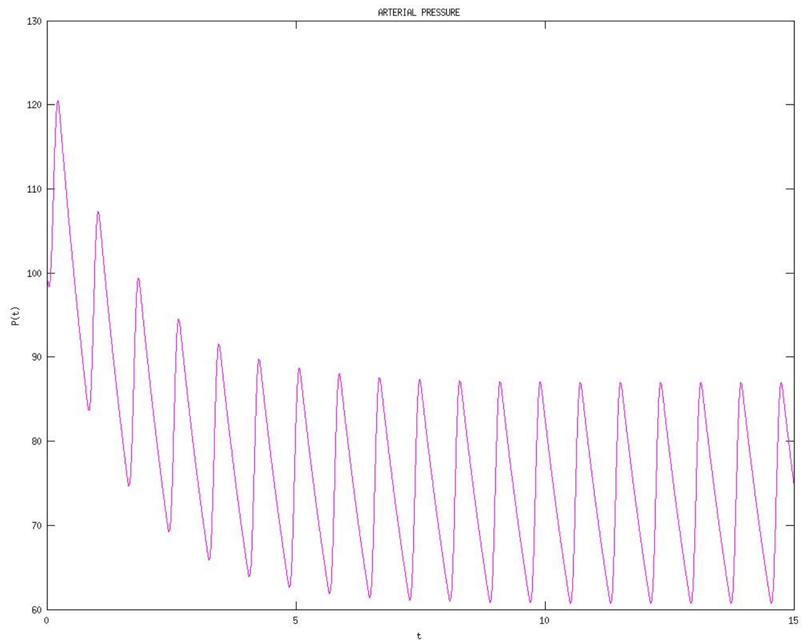

Figure 2.9: Pressure computed with sine squared $Q(t)$

The resistances associated with the flow to and from the left ventricle are R_v and R_a. To represent the effect of the heart valves, which do not allow backflow, heaviside functions are used. They represent them as $[x]_+ = \max\{x, 0\}$. Then, the flows are the following:

$$Q_+ = \frac{[p_{LV} - p_a]_+}{R_a} \tag{2.31}$$

$$Q_- = \frac{[p_v - p_{LV}]_+}{R_v} \tag{2.32}$$

In order for incompressible blood to circulate, compartment models must be able to change. The simplest assumption is linear dependence through compliances, C.

$$V_a = V_{a0} - C_a p_a \tag{2.33}$$

$$V_v = V_{v0} - C_v p_v \tag{2.34}$$

$$V_{LV} = V_{LV0} - C_{LV} p_{LV} \tag{2.35}$$

The inverses of the compliances are called elastances, E. In particular, the left ventricle's elastance varies between the values E_d and E_s (diastolic and systolic elastance) to represent the heart's cycles of contraction and relaxation. The elastance function is modelled with function valued E_s during the first time of the cardicac cycle, t_s, and E_d during the diastole, t_d. The other two compliances are assumed to be constant.

Substituting the flows and the volumes in equations 2.27 to 2.29, we obtain the model's system of equations, which is the following:

Parameter	Meaning	Value	Units
V_{a0}	Initial arterial blood volume	0	ml
V_{v0}	Initial venous blood volume	4500	ml
V_{LV0}	Initial heart blood volume	17	ml
R_a	Arterial resistance	0.06	mmHg·s/ml
R_v	Venous resistance	0.016	mmHg·s/ml
R_c	Capillary resistance	1.2	mmHg·s/ml
C_a	Arterial compliance	1.5	ml/mmHg
C_v	Venous compliance	50	ml/mmHg
E_s	Systolic elastance	3.0	mmHg/ml
E_d	Diastolic elastance	0.06	mmHg/ml
T_s	Systolic time	0.3	s
T_d	Diastolic time	0.6	s

Table 2.4: Meaning and nominal values of the parameters

$$R_c C_a \dot{p}_a = -(p_a - p_v) - \frac{R_c}{R_a}[p_{LV} - p_a]_+ \tag{2.36}$$

$$R_c C_v \dot{p}_v = (p_a - p_v) - \frac{R_c}{R_v}[p_v - p_{LV}]_+ \tag{2.37}$$

$$\dot{\left(\frac{p_{LV}}{E_{LV}}\right)} = \frac{[p_v - p_{LV}]_+}{R_v} - \frac{[p_{LV} - p_a]_+}{R_a} \tag{2.38}$$

Suggested values from the parameters, which the authors have adapted from [9], can be found in Table 2.4.

This model is more refined than the windkessel model, despite being also a compartment model. However, it does not model certain features such as respiratory variations in frequency and pressure or the dicrotic notch (although it does have two valves opening and closing).

As we will see in chapter 3, the model we suggest can be thought as a more complex version of this one, adding one additional compartment and some refinements to model some additional features.

2.5 The Seidel-Herzel model

In [10], a much more complex model of the cardiovascular system is presented. It takes into account the baroreflex-feedback loop but also includes the pulsatility of the blood flow. Although it is very complete, in the sense that it takes into account a lot of factors, and so it is very accurate, the fact that it consists in a set of 14 differential equations, including delays, variables calculated in each heart cycle, etc. makes it very difficult to deal with.

Since our goal is to develop a model which we can easily interpret and understand, we will neglect Seidel-Herzel's model, which is far from simple and definitely lacks interpretability.

2.6 Ursino

If the previous model is difficult to understand, Ursino's [9] is even more so. It combines the concept of compartment model, a pulsatile heart, and the baroreflex mechanism, to create a 42-equation system, with a great amount of parameters.

Although it has been an influence to the subsequent models of blood pressure, it is clearly far from our objective, which is developing a model that is as simple as possible.

2.7 Fluid dynamics

The blood is a fluid which flows inside a system of tubes of different sizes. So why not model it using classical fluid dynamics?

To model the blood flow using Navier-Stokes equations, we should have a very accurate model of the cardiovascular system's geometry: how vessels bifurcate, lengths and diameters of every one of them, etc.

In [11], they assume that the blood flow in arteries can be modelled as a one-dimensional axisymmetric flow of an incompressible and Newtonian fluid through a rigid vessel, and so they simplify the N-S equations to the following:

$$\rho \frac{\partial u}{\partial t} + \frac{\partial p}{\partial x} = \frac{\mu}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u}{\partial t} \right) \tag{2.39}$$

where $u(t, r)$ is the longitudinal velocity, ρ is the blood's density, μ is the viscosity, and the pressure $p(x, t)$ is assumed to be constant over the cross-sectional area, and so independent of the radius r. They use this model to study in detail the pressure and velocity in a large vessel, and combine it with a windkessel model. They suggest that applications of this approach may be the development of anesthesia simulators or the study of the blood flow in dynamic changes, such as posture changes.

A similar model is used in [12] to study in detail the blood flow in large vessels. They carry out two different simulations: the first one, in the aorta; the second one, the iliac bifurcation including part of the femoral arteries.

In [13], the author model in an extremely detailed manner the geometry of curved tubes, and study the radial changes in blood velocity inside a vessel. A very precise geometry of a cardiovascular system from a particular subject is obtained by means of magnetic resonance imaging which is then used in the model.

To sum up, the fluid dynamics approach may be useful to model very precisely pressure and velocity in a certain vessel when the geometry is well known. However, with the current computational power a fluid dynamics model of the whole cardiovascular system is not possible.

Note that this model can also be coupled with elasticity of blood vessels.

Chapter 3

Four compartment model of the cardiovascular system

3.1 Introduction

Some models seen in chapter 2 only take into account the main blood pressure and its variations, but do not model the pulsatile component. Others, such as [8], model the blood pressure wave including the pulsatile component but miss some additional details. The goal of this project is to provide a simple mathematical model capable of reproducing a blood pressure signal and so use this model to aid in the automatic interpretation of certain medical conditions. For this purpose we require a model that includes details of the aortic valve and its closing time, the dicrotic notch (due to the valve closing) and the variation in pulse pressure and heart rate as a consequence of respiration (respiratory sinus arrhytmia).

Our model is derived from the three compartment model of [8] but introduces various changes to more accurately predict the blood pressure curve.

3.2 Desription of the model

3.2.1 Compartments

First of all, we define the compartments needed. We model the systemic circulation with two compartments, one for the arteries and the other for the veins (since venous return is important for heart performance). These compartments will be denoted by subscripts a and v, respectively. The heart is the region between veins and arteries. A human heart actually has four different sections - two atria and two ventricles. However, for simplicity, we will only model the left ventricle, which is the part that pumps blood into the arteries. We will denote it by LV. Finally, to model properly the aortic valve closure (that will take place when the pressure outside the heart is greater than the left ventricle pressure) we need to introduce another compartment, denoted e, which accounts for the aortic arch (the region between the heart, after the aortic valve, and the arteries).

Since the volume variation in a compartment is the difference between the incoming and the outgoing flux, we can state the following conservation of mass equations:

$$
\begin{aligned}
\dot{V}_e &= Q_{LV} - Q_e && (3.1)\\
\dot{V}_a &= Q_e - Q_a && (3.2)\\
\dot{V}_v &= Q_a - Q_v && (3.3)\\
\dot{V}_{LV} &= Q_v - Q_{LV} && (3.4)
\end{aligned}
$$

Compliance of a vessel is defined as change in volume for unit change in pressure [1, 14, 15]. Using this, we can write $\dot{V}_* = C_*\dot{p}_*$ (replacing the asterisk with each vessel's name). Then,

$$
\begin{aligned}
C_e\dot{p}_e &= Q_{LV} - Q_e && (3.5)\\
C_a\dot{p}_a &= Q_e - Q_a && (3.6)\\
C_v\dot{p}_v &= Q_a - Q_v && (3.7)
\end{aligned}
$$

The heart is not a compliant vessel like the others. It pumps due to a stimulation from the nervous system, so we have to prescribe this also. We will write an elastance (inverse of the compliance) function which oscillates between two values, E_s and E_d (systolic and diastolic elastances). So the fourth equation will be

$$
\dot{\left(\frac{p_{LV}}{E_{LV}}\right)} = Q_v - Q_{LV} \tag{3.8}
$$

Now we apply Poiseuille's law to replace the fluxes, which are proportional to the pressure difference between the vessel's ends. This constant of proportionality is denoted R_* and named resistance. In consequence, we can write $Q_* = \frac{\Delta p_*}{R_*}$.

We will use the resistance in the e compartment to model the aortic valve, so R_e will be a variable function, depending on the pressure difference, insted of a constant. The valve will be open when the pressure is lower in the exit region than in the heart, and closed otherwise. The mitral valve (between the veins and the heart) also needs to be modelled, but no closing time is needed (this valve does not affect the dicrotic notch). Hence we can model it as a Heaviside function.

At the end, our system of equations will be:

$$
\begin{aligned}
C_e\dot{p}_e &= \frac{p_{LV} - p_e}{R_e} - \frac{p_e - p_a}{R_a} && (3.9)\\
C_a\dot{p}_a &= \frac{p_e - p_a}{R_a} - \frac{p_a - p_v}{R_c} && (3.10)\\
C_v\dot{p}_v &= \frac{p_a - p_v}{R_c} - \frac{p_v - p_{LV}}{R_v} H(p_v - p_{LV}) && (3.11)\\
\dot{\left(\frac{p_{LV}}{E_{LV}}\right)} &= \frac{p_v - p_{LV}}{R_v} H(p_v - p_{LV}) - \frac{p_{LV} - p_e}{R_e} && (3.12)
\end{aligned}
$$

A diagram of the compartments of the model including pressures, compliances and resistances is shown in figure 3.1.

Canonical values of the compliances and resistances are provided in [8]. The aorta is taken to be as compliant as the arteries, but since it is wider, its resistance is set $R_{e0} = R_v$. The values of the parameters are shown in 3.1.

A more detailed description of each function of the model is provided below.

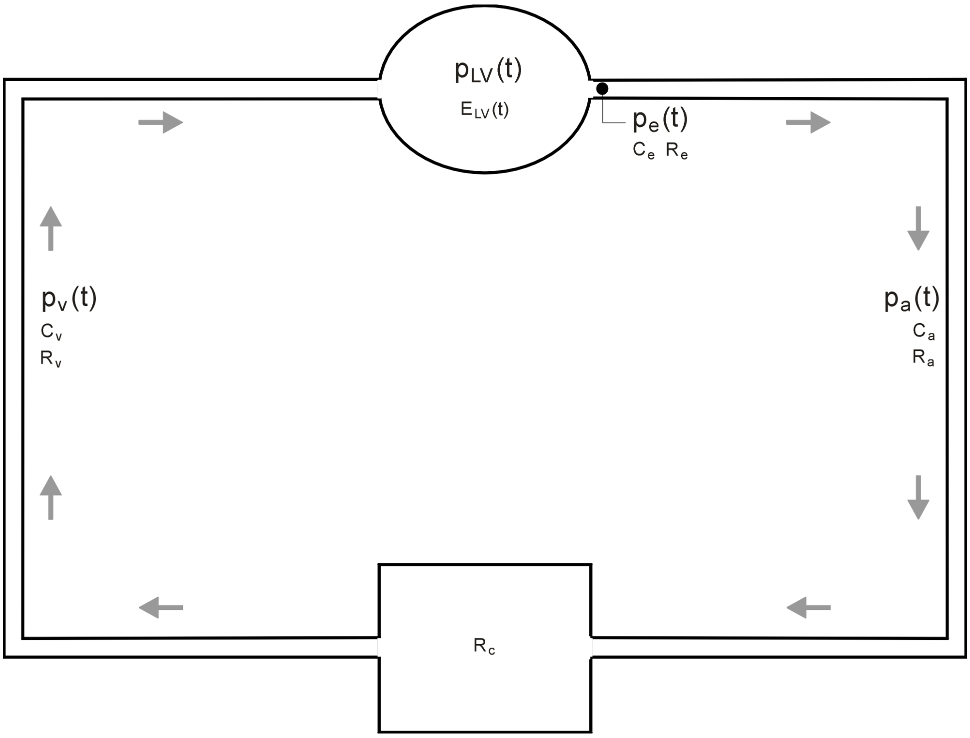

Figure 3.1: Compartments of the model

Parameter	Value	Units
C_e	1.5	ml/mmHg
C_a	1.5	ml/mmHg
C_v	50	ml/mmHg
R_{e0}	0.016	s·mmHg/ml
R_a	0.06	s·mmHg/ml
R_c	1.2	s·mmHg/ml
R_v	0.016	s·mmHg/ml

Table 3.1: Nominal values of the parameters

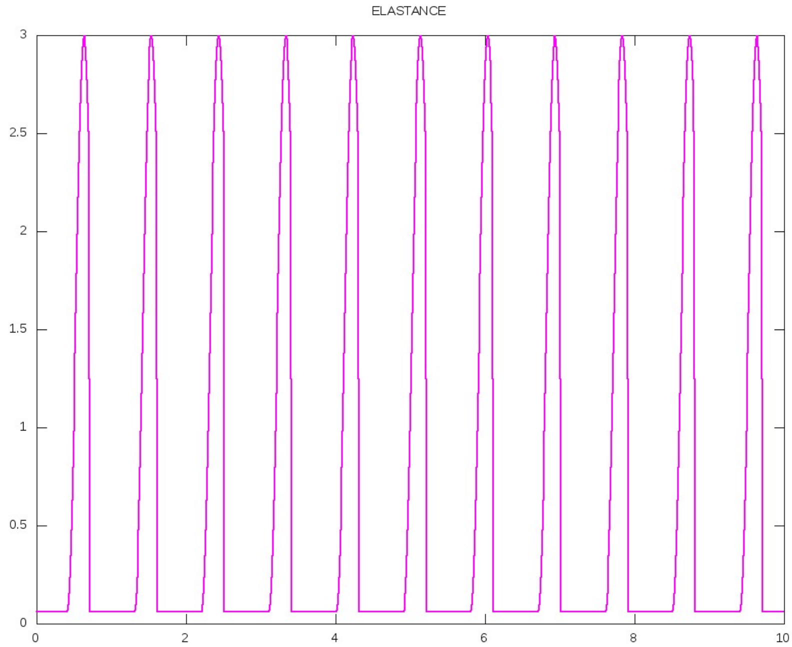

Figure 3.2: Elastance

3.2.2 Elastance function

The elastance is a function that simulates the heart contraction. In [1, 8] it is mentioned that the systole lasts about $\phi = \frac{1}{3}$ of a heart period, and the diastole the other $\frac{2}{3}$. Moreover, in [8] the elastance is described as an oscillating function which is a constant value, E_d, during the diastole, and increases to reach a value E_s and decreases again during the systole.

A function that fits this description is the following:

$$E_{LV}(\bar{t}) = \begin{cases} E_d + (E_s - E_d)\sin^2(\omega \bar{t}) & \bar{t} \leq \phi \\ E_d & \text{otherwise} \end{cases} \tag{3.13}$$

Here ω is the heart angular frequency, and $\bar{t}$ the time modulo the cardiac period: $\bar{t} \in [0, T]$, where $T = \frac{2\pi}{\omega}$, so total time is $t = nT + \bar{t}$ for some $n \in \mathbb{Z}$.

If we plot this function for constant values $E_d = 0.06$mmHg/ml, $E_s = 3.0$mmHg/ml and $T = 0.9$s (values taken from[8]), we obtain figure 3.2.

3.2.3 Aortic valve

In equations (3.9) and (3.12) there appears R_e, which is not a constant but a variable function that represents the aortic valve opening and closing in each cardiac cycle. Since we need a closure time to model the dicrotic notch, it has to be a continuous function instead of a Heaviside, but tending to a step function (closure is fast). We choose an exponential function which increases from R_{e0} (the aortic resistance when valve is open) and saturates when it reaches R_{eM} (large enough to consider the valve completely closed at this resistance). The parameters ε and A model the velocity at which the valve closes, and depend on the subject's health (the healthier the valve, the faster it closes). The valve starts closing when the pressure

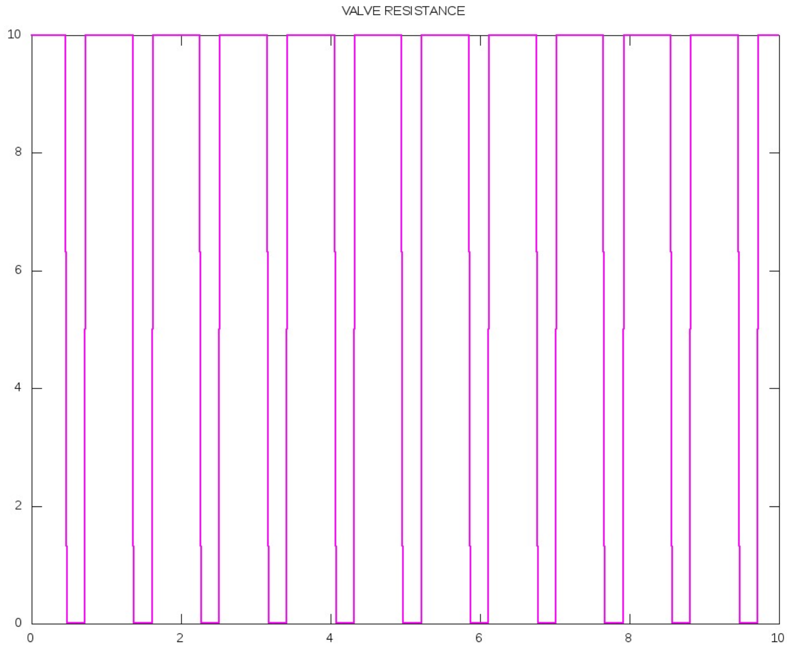

Figure 3.3: Valve resistance

is greater in the aortic arch than in the left ventricle, to prevent influx. Then,

$$Re(p_{LV} - p_e) = \min\left\{R_{e0}\left(1 + \varepsilon e^{-A(p_{LV}-p_e)}\right), R_{eM}\right\} \tag{3.14}$$

Figure 3.3 is a plot of the valve resistance function, if we put $\varepsilon = 10^{-5}$, $A = 0.5$ and maximum resistance $R_{eM} = 10$.

Figure 3.4 shows how the arterial pressure looks like with elastance and resitance as described before.

3.2.4 Respiratory sinus arrhytmia

Respiration makes heart frequency change, although the subject stays still. This motion, named respiratory sinus arrhytmia, produces a cardiac acceleration during inspiration and the inverse effect during exhalation [16].

We can model this variation as

$$\omega(t) = \omega_0 + c_3 \sin\left(\frac{\omega_0 t}{c_2}\right) \tag{3.15}$$

where c_3 is the amplitude of the oscillation and c_2 the respiratory frequency with respect to the heart rate, i.e., how many times the heat beats in a breath.

In figure 3.5 we can see how the heart frequency (in beats per minute, $F = \frac{60\omega}{2\pi}$) changes, if $c_3 = 0.01$ and $c_2 = 6$.

Frequency change in time causes sine-shaped oscillations of the systolic and diastolic pressures. However, the amplitude of oscillation of the diastolic pressure is much greater than this amplitude for the systolic. In figure 3.6 we can see this effect (this may be compared to figure 3.4 where the maximum and minimum values are constant).

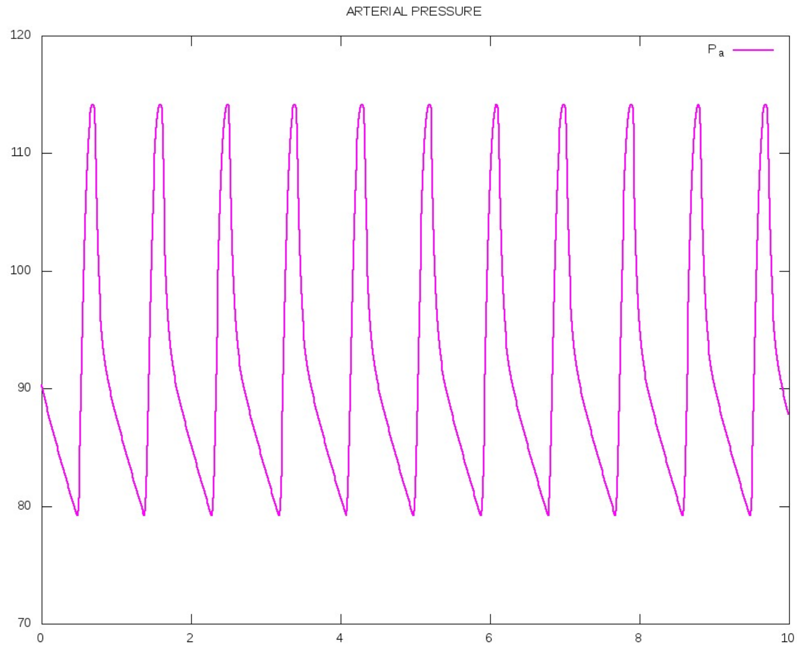

Figure 3.4: Arterial pressure

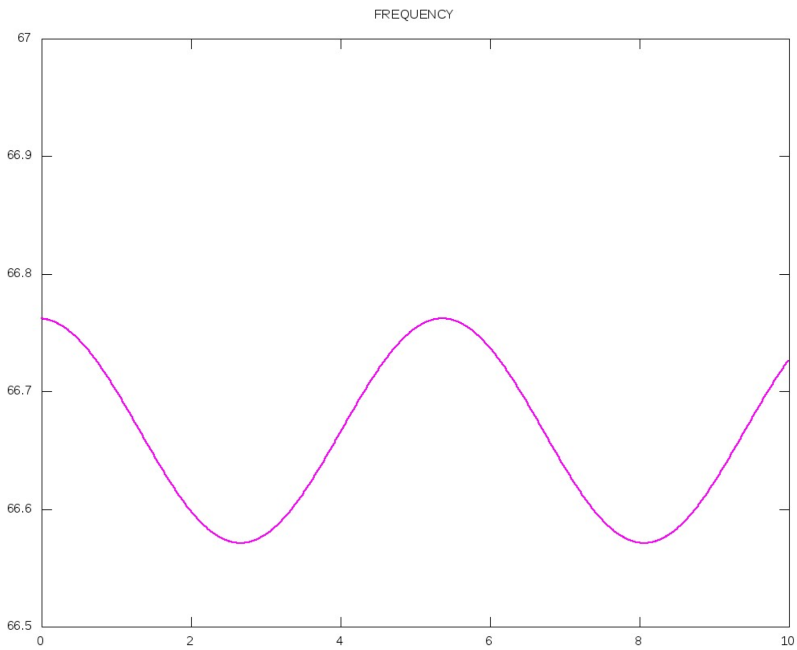

Figure 3.5: Heart frequency

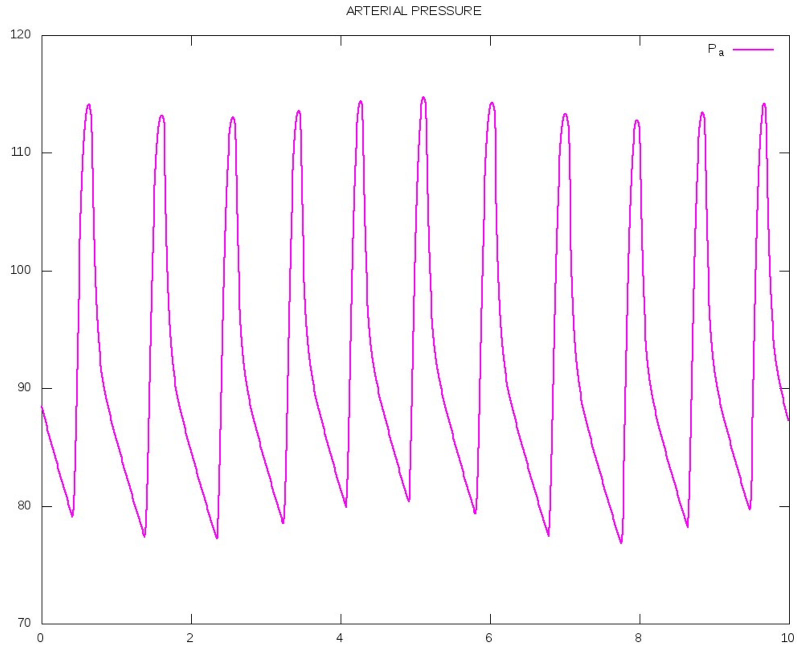

Figure 3.6: Arterial pressure

Nevertheless, experimental data shows that systolic pressure actually oscillates more than the diastolic. In order to adjust the model to this fact, we make the elastance height, E_s, oscillate at the same rhythm as ω does. This affects, mainly, the systolic pressure. So, instead of a constant, elastance height is

$$E_s(t) = E_{s0} + c_1 \sin\left(\frac{E_{s0} t}{c_2}\right) \tag{3.16}$$

Notice that the parameter c_2 is the same in equations (3.15) and (3.16), so both have the same oscillation frequency.

Figure 3.7 is how the elastance looks like with this new E_s.

Figure 3.8 shows the arterial pressure with varying elastance height if $c_1 = 0.1$, and c_3, c_2 remain the same as before.

3.2.5 Dicrotic notch

Now that we have the four compartment model, including the aortic valve and respiration, we want a dicrotic notch to appear when the arterial pressure has negative slope, given that the dicrotic notch appears when the valve closes, due to an increase in pressure in the e region and a decrease inside the heart. Hence, we add a Gaussian impulse to the $\dot{p}_e$ equation and we substract it from $\dot{p}_{LV}$'s: this ensures conservation of mass. It is like a wave propagation in a very small scale. The system becomes the following:

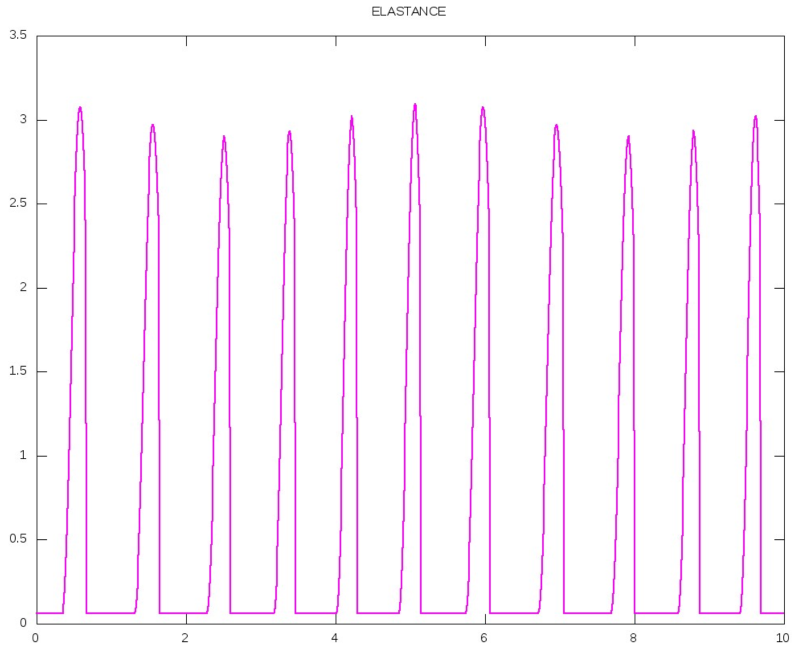

Figure 3.7: Elastance

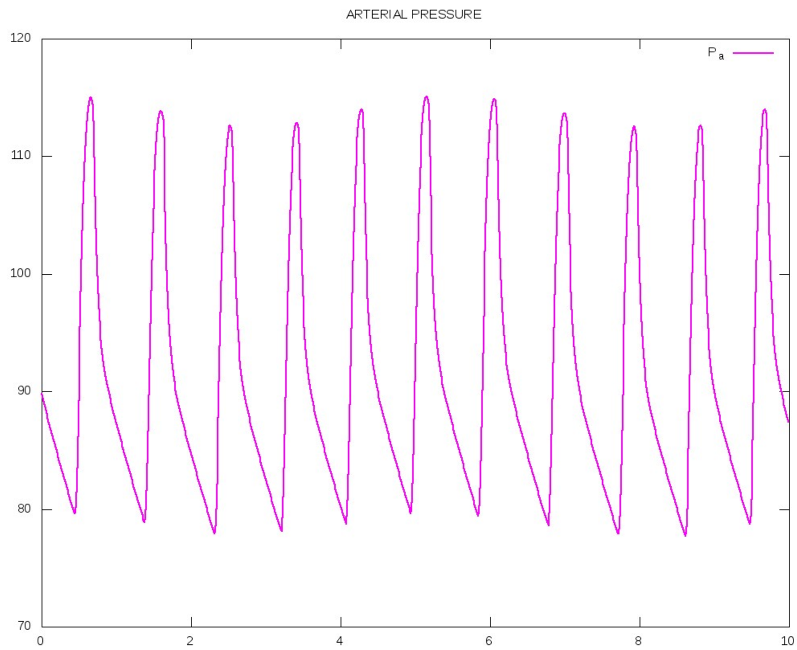

Figure 3.8: Arterial pressure

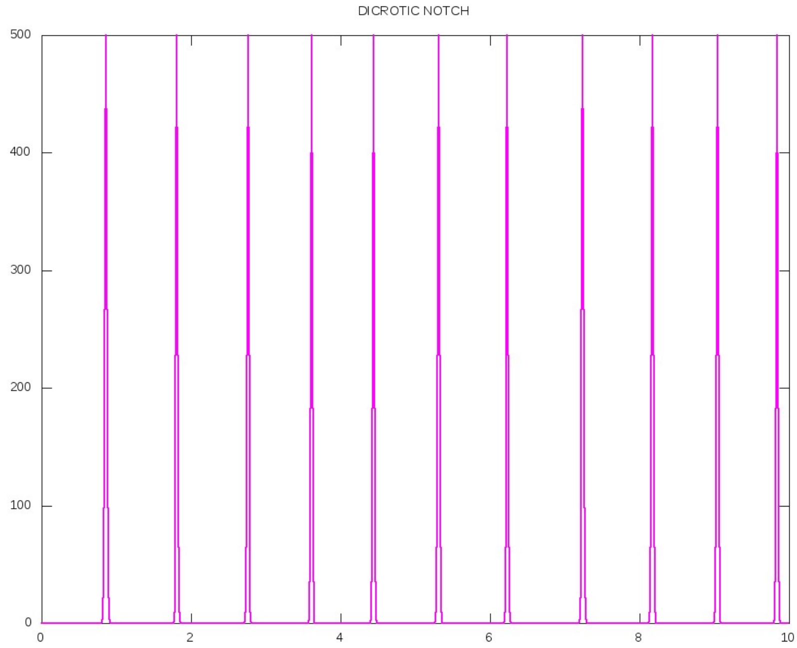

Figure 3.9: Dicrotic notch

$$
\begin{aligned}
C_e \dot{p}_e &= \frac{p_{LV} - p_e}{R_e} - \frac{p_e - p_a}{R_a} + f(t, t_1, \Delta t) && (3.17)\\
C_a \dot{p}_a &= \frac{p_e - p_a}{R_a} - \frac{p_a - p_v}{R_c} && (3.18)\\
C_v \dot{p}_v &= \frac{p_a - p_v}{R_c} - \frac{p_v - p_{LV}}{R_v} H(p_v - p_{LV}) && (3.19)\\
\dot{\left(\frac{p_{LV}}{E_{LV}}\right)} &= \frac{p_v - p_{LV}}{R_v} H(p_v - p_{LV}) - \frac{p_{LV} - p_e}{R_e} - f(t, t_1, \Delta t) && (3.20)
\end{aligned}
$$

We take an impulse of the form:

$$f(t, t_1, \Delta t) = c_4 e^{-\frac{c_5}{\Delta t^2}(t - t_1 - c_6 \Delta t)^2} \tag{3.21}$$

This has three parameters: c_4 determines the notch's height; c_5 its width and sharpness; and c_6 the notch position in the downslope (time delay since the valve starts closing).

It also has three variables: t refers to the time, as usual; t_1 is the particular time when the valve has started closing, so the time when $p_e(t_1) - p_{LV}(t_1) = 0^-$; and Δt is the total closure time of the valve (it must be computed each time in the previous cardiac cycle, since we start adding the notch when the valve is not closed yet).

Notice that the Gaussian impulse is only added when the blood pressure goes downslope and the valve starts closing; otherwise, it is equal to zero. Figure 3.9 shows how these impulses look like if $c_4 = 500$, $c_5 = 4\log(100)$.

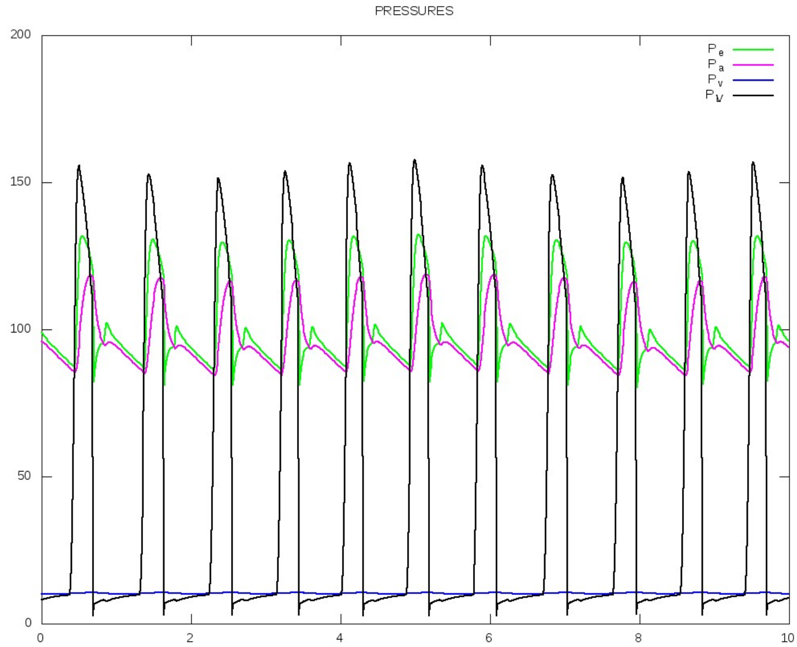

Figure 3.10: All pressures

3.3 Integration

We now apply all the model refinements and integrate the system of equations. The chosen method is a fourth order Runge-Kutta with time step $h = 0.01$s. We integrate between $t_0 = 0$s and $t_F = 60$s and, once we have got the solution, we only pick the last 10 seconds of it (to ensure it has reached its stationary state). Initial conditions are chosen to make the arterial pressure give realistic values:

$$p_{e0} = 35 \text{ mmHg} \tag{3.22}$$
$$p_{a0} = 35 \text{ mmHg} \tag{3.23}$$
$$p_{v0} = 5 \text{ mmHg} \tag{3.24}$$
$$p_{LV0} = 35 \text{ mmHg} \tag{3.25}$$

Then, the stationary solution we obtain for all the pressures is shown in figure 3.10
Our main interest is arterial pressure, which can be seen in figure 3.11.

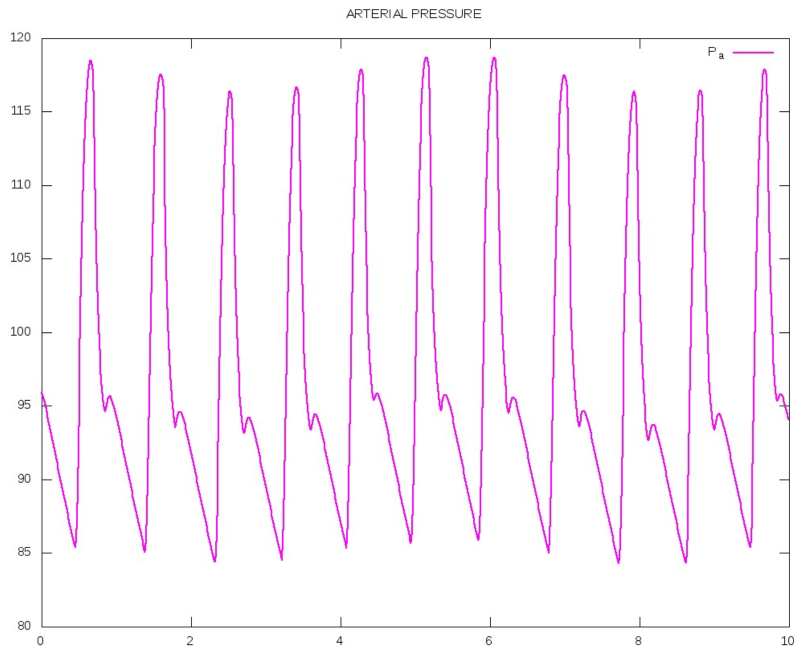

Figure 3.11: Arterial pressure

Chapter 4

Parameter sensitivity analysis

4.1 Introduction

In the next chapters we will try to adjust the model's parameters to fit the blood pressure signal of particular patients. This will be done step by step.

In our model there are 21 parameters and 4 initial conditions. To simplify, we can say that the model has 25 parameters in total. Therefore, choosing the appropiate set of parameters to make the result fit a particular patient signal can be difficult. Do we need to optimise all the parameters at the same time? If not, in which order? Or maybe only some of them? Which is the best estimation method?

In [17] a sensitivity analysis is suggested to determine which parameters are more important, and after that a parameter estimation based on the results of such analysis. Although the mathematical model they use is not the same, we will use a procedure based on theirs.

The only pressure data we have is arterial so this is the only one taken into account in the analysis and parameter estimation.

The sensitivity analysis consisted in perturbing each parameter of the model and integrating the system of equations to see how the resulting arterial pressure changes with such perturbations.

4.2 Methods

For each parameter θ, with nominal value θ_0, and for given perturbations q, the system was integrated for $\theta = (1-q)\theta_0$ and $\theta = (1+q)\theta_0$, while all the other parameters were set to their respective nominal values.

Let $p_a\big((1-q)\theta_0\big)$ and $p_a\big((1+q)\theta_0\big)$ be the output arterial pressures for a perturbed parameter θ (and the remaining 24 parameters set to their nominal value). Five values of the perturbation q were used: 0.01, 0.05, 0.1, 0.2 and 0.5. As we will see, the perturbation $q = 0.01$ led to very small changes in the output signal. The perturbation $q = 0.5$ led to chaotic behaviour for some of the parameters. In consequence, these two values of q were dismissed and only the other three were used for the analysis.

Three different measurements of the influence of parameters were used. They were the L_2 distance between both signals, equation 4.1, the absolute difference of each signal's mean value, equation 4.2, and the absolute difference of each signal's standard deviation, equation 4.3.

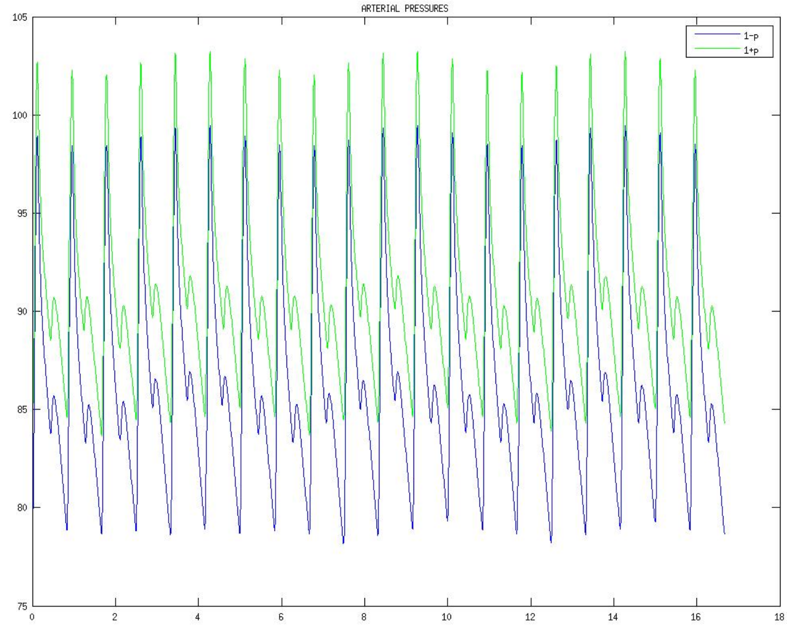

Figure 4.1: Signals for a perturbation 0.1 of R_c

$$\delta_2 = \left(\int_0^{20T} \Big(p_a\big((1+q)\theta_0\big) - p_a\big((1-q)\theta_0\big) \Big)^2 \right)^{\frac{1}{2}} \tag{4.1}$$

$$\delta_\mu = \left| \mu\Big(p_a\big((1+q)\theta_0\big)\Big) - \mu\Big(p_a\big((1-q)\theta_0\big)\Big) \right| \tag{4.2}$$

$$\delta_\sigma = \left| \sigma\Big(p_a\big((1+q)\theta_0\big)\Big) - \sigma\Big(p_a\big((1-q)\theta_0\big)\Big) \right| \tag{4.3}$$

These three measures were taken over a signal window of 20 beats of length in the stationary part of the solution. For instance, figure 4.1 shows the two signals, $p_a\big((1-q)\theta_0\big)$ and $p_a\big((1+q)\theta_0\big)$, where the perturbed parameter was $\theta = R_c$ and the perturbation value was $q = 0.1$, while figure 4.2 shows them for $\theta = E_d$ (the large perturbation value causes the large difference in results), and $q = 0.5$ and figure 4.3 shows them for $\theta = C_e$ and $q = 0.01$.

For each of the three measures, a ranking of the parameters (ordered by influence) was made. This classification was made dismissing the two extreme values of perturbations, as said before. The other three values led to very coherent results, so parameters were easy to classify.

Since our objective was reducing the number of parameters to estimate as much as possible, some physiologically relevant relationships between parameters were kept when classifying the parameters. For instance, in the previous chapter we defined the diastolic elastance as the inverse of the venous compliance (the heart, when it relaxes, is as stiff as a vein). Then in the rankings both C_v and E_d will appear in the same position (the highest of the two). This is also coherent because, for each set of related parameters, when one of them showed to be influent on the result, the others also did. Particularly, the fixed relationships between parameters were: $C_v = E_d$, $C_a = C_e = E_{s0}$, $R_{e0} = R_v$ and $p_{a0} = p_{e0} = p_{LV0}$.

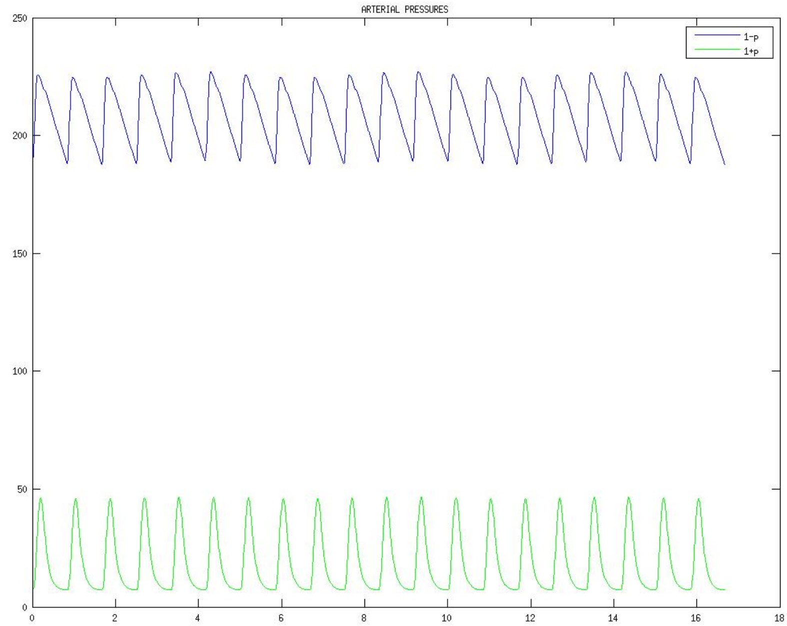

Figure 4.2: Signals for a perturbation 0.5 of E_d

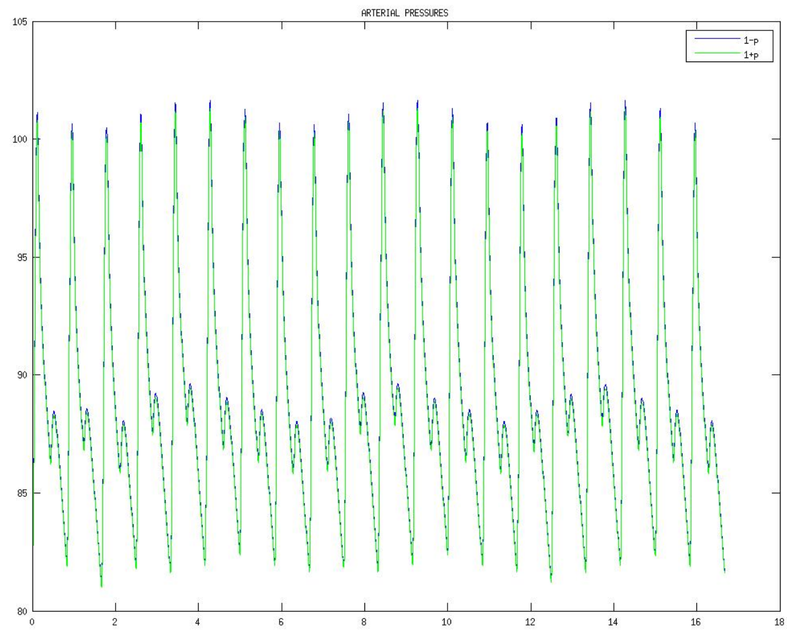

Figure 4.3: Signals for a perturbation 0.01 of C_e

$q = 0.01$		$q = 0.05$		$q = 0.1$		$q = 0.2$		$q = 0.5$	
ϕ	17.87	E_d	22.66	E_d	32.26	E_d	39.52	E_d	88.13
ω_0	16.52	p_{a0}	20.27	p_{a0}	28.73	p_{a0}	34.90	p_{a0}	70.73
E_d	10.17	ϕ	19.75	ϕ	20.35	E_{s0}	28.41	A	53.03
p_{a0}	9.10	ω_0	10.10	E_{s0}	20.01	C_v	23.99	E_{s0}	47.59
E_{s0}	6.38	E_{s0}	14.17	ω_0	17.75	A	20.23	C_v	38.49
c_2	5.69	C_v	12.01	C_v	16.96	ω_0	20.10	R_c	33.29
C_v	5.41	R_c	9.92	R_c	14.04	R_c	20.04	ω_0	32.31
A	4.52	A	9.69	A	13.81	ϕ	19.66	R_{e0}	25.44
R_c	4.49	C_a	7.79	C_a	10.96	C_a	15.48	C_a	24.49
C_a	3.65	R_{e0}	7.09	R_{e0}	9.93	R_{e0}	14.11	ϕ	22.83
R_{e0}	3.55	C_e	6.34	C_e	8.89	C_e	12.53	C_e	19.85
C_e	2.81	c_2	6.19	R_v	8.56	R_v	12.07	R_v	18.82
R_v	2.71	R_v	6.08	p_{v0}	7.23	p_{v0}	10.20	p_{v0}	16.10
p_{v0}	2.28	p_{v0}	5.15	c_6	6.51	R_a	9.16	R_a	14.31
c_6	2.17	c_6	4.78	R_a	6.49	c_6	8.60	c_4	11.82
R_a	2.05	R_a	4.62	c_4	5.88	c_4	8.35	c_6	11.69
c_4	1.86	c_4	4.16	c_2	5.37	c_2	6.81	c_5	10.17
c_5	1.31	c_3	3.18	c_5	4.16	c_5	5.94	ε	9.43
ε	1.26	ε	3.17	ε	4.13	ε	5.76	R_{eM}	8.29
R_{eM}	0.99	c_5	2.94	c_3	3.64	R_{eM}	4.70	c_2	5.94
c_1	0.57	R_{eM}	2.23	R_{eM}	3.51	c_3	4.32	c_3	4.74
c_3	0.55	c_1	1.28	c_1	1.81	c_1	2.56	c_1	4.28
Δt_0	0	Δt_0	0	Δt_0	0	Δt_0	0	Δt_0	0

Table 4.1: L_2 distance between signals for each parameter and perturbation

4.3 Results

4.3.1 Influence on L_2 distance

Table 4.1 shows the resulting L_2 distance between $p_a\big((1-q)\theta_0\big)$ and $p_a\big((1+q)\theta_0\big)$ for each parameter and perturbartion. Each column is already ordered from greatest to smallest L_2 distance.

The first fact we can see is that the bigger the perturbation q is, the bigger the effect on the result is (in terms of L_2 distance, but later we will see that the other two measure functions behave the same way). This may seem obvious but it is good to see that results are the expected. We can also see that, as it was said before, perturbations 0.05, 0.1 and 0.2 give pretty coherent results, whilst 0.01 and 0.5 sometimes don't. This will happen again with the other measurement functions.

The parameters which seem to have a greater influence on the result are the compliances and elastances, the resistances, the initial frequency, the systolic fraction of the beat, the valve parameter A, and the initial conditons. The parameters related to details, such as height and shape of the dicrotic notch, or rate of change in frequency and pressure due to respiration, appear in the final positions.

Note that Δt_0 has no influence at all on the result. This is because it has only influence in the first beat, and from the second the Δt is computed from the previous beat.

$q = 0.01$		$q = 0.05$		$q = 0.1$		$q = 0.2$		$q = 0.5$	
E_d	2.516	E_d	12.52	E_d	25.40	E_d	52.42	E_d	190.04
p_{a0}	2.019	p_{a0}	10.01	p_{a0}	20.16	p_{a0}	40.68	p_{a0}	122.24
ϕ	1.928	E_{s0}	4.86	E_{s0}	9.77	E_{s0}	19.72	A	65.83
E_{s0}	0.975	C_v	3.518	C_v	7.01	C_v	14.04	E_{s0}	55.05
C_v	0.698	R_c	2.381	R_c	4.777	R_c	9.703	C_v	36.183
R_c	0.466	A	2.123	A	4.466	A	9.623	ω_0	28.540
A	0.434	ω_0	2.042	ω_0	3.963	ω_0	8.262	R_c	26.914
ω_0	0.293	ϕ	1.754	C_a	2.837	C_a	5.659	R_{e0}	15.122
C_a	0.276	C_a	1.430	R_{e0}	2.164	R_{e0}	4.555	C_a	14.152
R_{e0}	0.215	R_{e0}	1.101	ϕ	1.894	C_e	3.584	ϕ	10.642
C_e	0.181	C_e	0.913	C_e	1.802	R_v	3.553	C_e	8.975
R_v	0.179	R_v	0.888	R_v	1.782	p_{v0}	2.533	R_v	8.627
p_{v0}	0.128	p_{v0}	0.629	p_{v0}	1.267	ϕ	2.191	p_{v0}	6.316
R_a	0.092	R_a	0.445	R_a	0.892	R_a	1.795	R_a	4.573
c_4	0.074	c_4	0.369	c_4	0.731	c_4	1.481	c_4	3.743
c_2	0.055	c_6	0.244	c_6	0.487	c_6	0.975	c_6	2.492
c_6	0.049	c_5	0.185	ε	0.375	c_5	0.758	c_5	2.211
ε	0.038	ε	0.182	c_5	0.372	ε	0.758	ε	2.055
c_5	0.037	R_{eM}	0.112	R_{eM}	0.235	R_{eM}	0.475	R_{eM}	1.522
R_{eM}	0.022	c_2	0.019	c_2	0.038	c_3	0.030	c_2	0.040
c_1	0.001	c_3	0.008	c_1	0.005	c_2	0.020	c_3	0.031
c_3	0.000	c_1	0.003	c_3	0.005	c_1	0.010	c_1	0.005
Δt_0	0.000	Δt_0	0.000	Δt_0	0.000	Δt_0	0.000	Δt_0	0.000

Table 4.2: Difference of means between signals for each parameter and perturbation

From the L_2 distances seen in table 4.1, dismissing perturbations 0.01 and 0.5, and grouping parameters if they were related in the model (such as E_d to C_v), the following rating of the influence of the parameters was made:

1. E_d, C_v
2. p_{a0}, p_{e0}, p_{LV0}
3. E_{s0}, C_a, C_e
4. ϕ
5. ω_0
6. R_c
7. A
8. R_v, R_{e0}
9. p_{v0}
10. c_6
11. R_a
12. c_2
13. c_4
14. c_5
15. ε
16. c_3
17. R_{eM}
18. c_1
19. Δt_0

4.3.2 Influence on absolute difference of mean values

Table 4.2 shows the resulting absolute difference of means between $p_a\big((1-q)\theta_0\big)$ and $p_a\big((1+q)\theta_0\big)$ for each parameter and perturbartion. Each column is already ordered from greatest to smallest δ_μ.

As said before, larger perturbations q lead to larger differences of the mean of the signals. Again, the three central perturbations classify the parameters in a similar order, while the two others don't.

The parameters with greater influence on the results are similar to those with greatest influence in the L_2 distance, although they are not exactly in the same order in all cases. And, again, Δt_0 has no influence in the result.

So, if we use the sensitivity function δ_μ instead of δ_2, the obtained results are not exactly the same (since δ_2 sums all the differences in signals and δ_μ only measures the difference between their mean values). However, both measures rank, approximately, the same parameters to be influent, and the others to be not so influent.

From the δ_μ distances seen in table 4.2, dismissing extreme perturbations, and grouping parameters, the following ranking of the influence of the parameters was made:

1. E_d, C_v
2. p_{a0}, p_{e0}, p_{LV0}
3. E_{s0}, C_a, C_e
4. R_c
5. A
6. ω_0
7. R_v, R_{e0}
8. ϕ
9. p_{v0}
10. R_a
11. c_4
12. c_6
13. c_5
14. ε
15. R_{eM}
16. c_2
17. c_3
18. c_1
19. Δt_0

4.3.3 Influence on absolute difference of standard deviations

Table 4.3 shows the resulting absolute difference of standard deviations between $p_a\big((1-q)\theta_0\big)$ and $p_a\big((1+q)\theta_0\big)$ for each parameter and perturbartion. Each column is already ordered from greatest to smallest δ_σ.

Once more, larger perturbations q lead to larger differences of the standard deviation of the signals. And again, the three central perturbations classify the parameters in a similar order, but now parameters related to time (ω_0 and ϕ) appear in higher positions, and we can see that compliances tend to influence more than resistances in the variability of the signal, while resistances influenced more than compliances in the mean value. Anyway, the classification is very similar to that for δ_μ. And, again, Δt_0 has no influence in the result.

From the δ_σ distances seen in table 4.3, the following classification was made:

1. ω_0
2. E_d, C_v
3. E_{s0}, C_a, C_e
4. p_{a0}, p_{e0}, p_{LV0}
5. A
6. R_c
7. R_v, R_{e0}
8. ϕ
9. R_a
10. c_4
11. c_5
12. R_{eM}
13. c_6
14. ε
15. p_{v0}
16. c_3
17. c_2
18. c_1
19. Δt_0

4.4 Discussion

If we look at the three previous rankings, we can see a clear similarity between them. This coherence from a sensitivity function to another is very good news.

If we pick any of the coherence functions and we look at the classifiacion for each perturbation value in the range $q = 0.05$ to $q = 0.2$, we can see also a similarity. This similarity of ranking for different values of the perturbation applied is another good news.

$q = 0.01$		$q = 0.05$		$q = 0.1$		$q = 0.2$		$q = 0.5$	
ϕ	1.950	ω_0	0.564	ϕ	1.310	ω_0	2.606	A	19.050
ω_0	0.123	E_d	0.465	ω_0	1.250	E_d	1.852	ω_0	9.569
E_d	0.078	p_{a0}	0.366	E_d	0.809	A	1.466	p_{a0}	5.342
C_a	0.074	C_a	0.334	C_a	0.684	C_a	1.407	ϕ	3.943
C_e	0.065	C_e	0.320	C_e	0.656	C_e	1.329	C_a	3.809
p_{a0}	0.056	R_c	0.284	p_{a0}	0.612	R_c	1.164	C_e	3.469
$0\ A$	0.056	A	0.234	A	0.602	p_{a0}	1.161	R_{e0}	3.291
R_c	0.049	R_{e0}	0.184	R_c	0.570	E_{s0}	0.711	R_c	3.190
E_{s0}	0.034	E_{s0}	0.173	E_{s0}	0.351	R_{e0}	0.707	R_a	1.552
R_{e0}	0.032	R_a	0.155	R_{e0}	0.311	R_a	0.617	E_d	1.409
R_a	0.029	c_4	0.131	R_a	0.309	c_4	0.522	c_4	1.309
c_4	0.026	C_v	0.099	c_4	0.254	C_v	0.490	C_v	1.137
C_v	0.024	c_5	0.066	C_v	0.232	c_5	0.267	c_5	0.745
c_5	0.013	ϕ	0.049	c_5	0.132	R_{eM}	0.167	R_{eM}	0.541
c_2	0.012	R_{eM}	0.038	R_{eM}	0.084	ϕ	0.144	E_{s0}	0.525
R_{eM}	0.008	R_v	0.035	c_6	0.069	c_6	0.134	R_v	0.347
c_6	0.007	c_6	0.034	R_v	0.063	R_v	0.127	c_6	0.330
ε	0.006	p_{v0}	0.023	ε	0.052	ε	0.106	ε	0.281
R_v	0.006	ε	0.022	p_{v0}	0.038	p_{v0}	0.076	p_{v0}	0.199
p_{v0}	0.003	c_3	0.008	c_3	0.008	c_2	0.016	c_1	0.014
c_1	0.001	c_1	0.003	c_1	0.006	c_3	0.016	c_3	0.014
c_3	0	c_2	0.001	c_2	0.002	c_1	0.012	c_1	0.003
Δt_0	0.000	Δt_0	0.000	Δt_0	0.000	Δt_0	0.000	Δt_0	0.000

Table 4.3: Difference of standard deviations between signals for each parameter and perturbation

The objective of this analysis was to determine which parameters are the most important and the ones to be estimated, or the ones to be estimated first, when fitting the model's signal to a real one. At some point, it is necessary to decide how many parameters it is worth estimating. A good number may be 5. It is small enough to make the estimation feasable, and large enough to contain the most important parameters (if we look at the sensitivity tables, we can see that the first parameters show a much higher sensitivity than the middle or bottom ones).

When ranking them, one of these five appeared to be the initial frequency, ω_0, which will not be estimated but calculated directly from the signal (number of peaks divided by time, and a change of units). Therefore, a sixth parameter was included in the list of the significant ones, so the estimation was still made with five parameters.

Putting together the three different sensitivity functions and the three chosen perturbation values, we can conclude that the significant parameters, in order of influence, are the following:

1. E_d, C_v
2. E_{s0}, C_a, C_e
3. p_{a0}
4. A
5. R_c
6. ω_0

Chapter 5

Parameter estimation

5.1 Introduction

In chapter 4 we have seen which parameters of the model have the greatest influence on the result. Now it's time to apply this knowledge to find sets of parameters which make the model's arterial pressure signal fit a real one.

We have recorded signals from nine real patients who where in the hospital's ICU. Additionally, we have some information about their pathology, drug administration, etc. The main purpose was to automate the parameter estimation. As we will see, it has not been completely possible.

The first approach was to estimate the 21 parameters and 4 initial conditions at the same time, using one of the Matlab's built-in optimization functions. Although the algorithm was set to achieve a huge number of iterations, it did not seem to converge in a long time period (more than 48 hours of computation). It was clear that all the parameters at the same time could not be estimated, and we decided to run a sensitivity analysis to decide which parameters should be estimated first.

After that, we could apply the sensitivity analysis' results. A four stage algorithm was chosen. The first and second stages consisted in estimating only the parameters tagged as important in the sensitivity analysis, using two different automatic methods. The third stage was estimating the rest of the parameters, also automatically. The last step was adjusting manually some of them, mainly the ones related to the signal's shape (dicrotic notch, variability due to respiration, etc.). This had to be done manually since the objective function did not capture properly those kind of shape details.

For each patient, the parameter estimation was made over a time window of three respiratory cycles of length (so the respiratory variations were visible although the length was different from one patient to another). We will see that, although the final parameters do not always have a clear physiological sense, the results look good and the model can be adapted to fit a wide range of signal's values and shapes.

As a convention, in all plots in this chapter, the blue line will represent the patient's recorded arterial signal, and the magenta one will be the model's output arterial pressure.

5.2 Methods

5.2.1 Stage 1: Approximate gradient method for the five significant parameters

Each patient had their own values of systolic, diastolic and mean pressure. The first goal was to get a signal which oscillated with the same amplitude as the patient's, and near the same average value.

Which objective function reflects mean value and amplitude of oscillations? It can be a double objective function: the mean of the signal and the standard deviation.

Let $p_a = p_a(t)$ be the arterial pressure signal obtained by integration of the model with a certain set of parameters, and let $\hat{p}_a = \hat{p}_a(t)$ be the arterial pressure signal recorded from a patient. Then we define the two objective functions, in a very similar way as in the sensitivity analysis, as following:

$$\delta_\mu = \big|\mu(p_a) - \mu(\hat{p_a})\big| \tag{5.1}$$

$$\delta_\sigma = \big|\sigma(p_a) - \sigma(\hat{p_a})\big| \tag{5.2}$$

It was tried first to do this stage directly with a Matlab optimization function. However, with a very large number if iterations it did not converge in most cases, since the result of the model with nominal values of parameters can be very different from the recorded signal.

Therefore, a simpler method was necessary. The most popular optimization method is the so-called Gradient Descent. If we want to minimize an objective function $F(x)$, we start with an initial value x_0 and iterate in the following way:

$$x_{n+1} = x_n - \alpha \nabla F(x_n) \tag{5.3}$$

Unluckily, an explicit, analytic expression of the objective functions (and their gradients) is not available. Can we approximate this gradient somehow? In the previous chapter, we have seen how the mean and standard deviation of p_a change for small perturbations near the nominal value of the parameters. In consequence, we have seen an approximation of the gradient near one point. Calculating the gradient for a lot of points would be very expensive computationally, so we will use the gradient near the origin as a very coarse approximation of the gradient everywhere.

To calculate the derivative of an objective function with respect to a certain parameter θ near its nominal value θ_0, we will use the results of perturbing θ a certain value q. Then, the derivative is computed this way:

$$\frac{\partial \mu}{\partial \theta} \approx \frac{\mu\Big(p_a\big((1+q)\theta_0\big)\Big) - \mu\Big(p_a\big((1-q)\theta_0\big)\Big)}{(1+q)\theta_0 - (1-q)\theta_0} \tag{5.4}$$

The same can be done for the standard deviation instead of the mean, and we will have an approximation of the gradient of each objective function.

More particularly, we only need to know the derivative of the mean and deviation respect to the five parameters tagged as important in chapter 4, which were C_v, p_{a0}, C_a, R_c and A (and their associates). Remember that ω_0 does not need to be estimated, it can be calculated from the patient's signal. To calculate the derivatives, the perturbation $q = 0.1$ was picked.

For instance, let's calculate the derivative of μ respect to C_v. Remember that the nominal value of C_v was 50 ml/mmHg.

$$\frac{\partial \mu}{\partial C_v} \approx \frac{\mu\Big(p_a\big((1+0.1)\cdot 50\big)\Big) - \mu\Big(p_a\big((1-0.1)\cdot 50\big)\Big)}{(1+0.1)\cdot 50 - (1-0.1)\cdot 50} \tag{5.5}$$

Repeating this operation for each significant parameter and for μ and σ, we obtain the following approximations to their gradients:

$$\nabla\mu \approx (-0.700, 6.671, -9.457, 19.902, 44.661) \tag{5.6}$$

$$\nabla\sigma \approx (-0.023, 0.204, -2.28, -2.375, -6.020) \tag{5.7}$$

After that, an iterative process was built. Let $\Theta = (C_v, p_{a0}, C_a, R_c, A)$ be the vector of parameters to estimate, and $\Theta_0 = (50, 35, 15, 1.2, 0.5)$ the vector of their nominal values. A step of $\alpha = 0.0005$ was chosen. In case no chaos was reached, the maximum number of iterations was set to 100. The heart frequency and the respiratory frequency were computed from the signal (with additional information from the patient's monitor). The algorithm, then, was the following:

- Set $\Theta = \Theta_0$ and compute ω_0 and c_2 from the patient's signal.
- While there is not chaos or iteration number is less than 100,
  - Compute δ_μ and δ_σ.
    - If $\frac{\delta_\mu}{\mu(\hat{p}_a)} > \frac{\delta_\sigma}{\sigma(\hat{p}_a)}$, then do $\Theta_{n+1} = \Theta_n - \alpha\nabla\mu$.
    - Else, do $\Theta_{n+1} = \Theta_n - \alpha\nabla\sigma$.
  - Compute parameters depending on Θ_{n+1}.
  - Plot together $p_a(\Theta)$ and $\hat{p}_a$.
- Save resulting Θ.

In each iteration, the δ_μ δ_σ distances between the model and the recorded signal are computed. Then, the algorithm decides if it is more important to change the mean or the standard deviation of the model's output. To do so, it compares $\frac{\delta_\mu}{\mu(\hat{p}_a)}$ to $\frac{\delta_\sigma}{\sigma(\hat{p}_a)}$. Both distances are normalized because, if they were not, δ_μ would always be bigger, since the average of the signal is greater than the amplitude of the oscillations.

Once it was decided which is the function to optimize, it applies the gradient method to it. The parameters depending on the estimated ones, such as the elastances (which depend on the compliances), were calculated from the new ones. So, while the dimensionality of the method is 5, we are estimating many more parameters at the same time.

The process usually stopped after less than 25 iterations, when the system reached chaos (the signal from the model suddenly reached extremely high values or infinity). This meant that some of the parameters had passed their maximum or minimum acceptable value. We can see an example of this chaotic behaviour in figure 5.1.

We can also see the performance of this coarse approximation to the gradient method for a particular patient in figures 5.2 (first iteration) and 5.3, from the second iteration to the best one, showing only the result of one of every two iterations.

Figure 5.4 shows the result of this method on this patient.

The parameters obtained in this first stage were used in the second stage as initial parameters, so we forget about their nominal values from now on and go to the second stage of the parameter estimation.

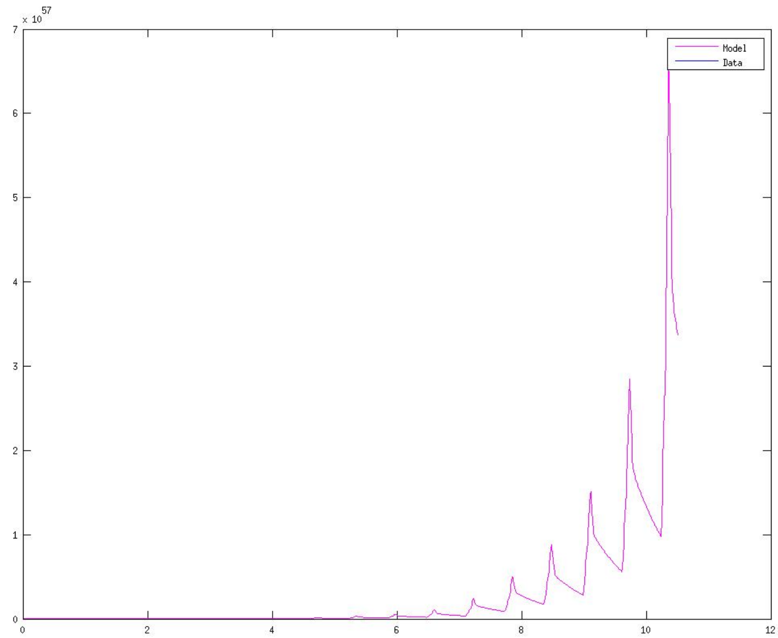

Figure 5.1: Beginning of chaotic behaviour

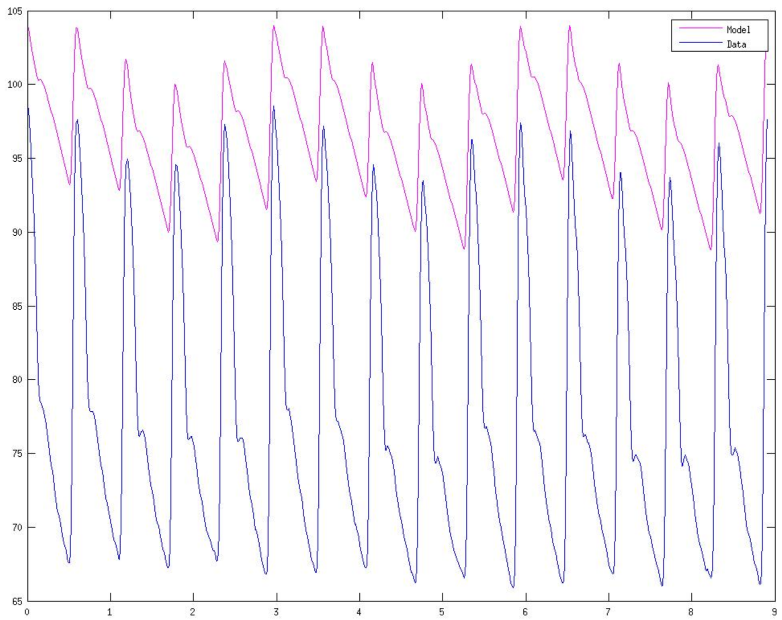

Figure 5.2: Initial iteration

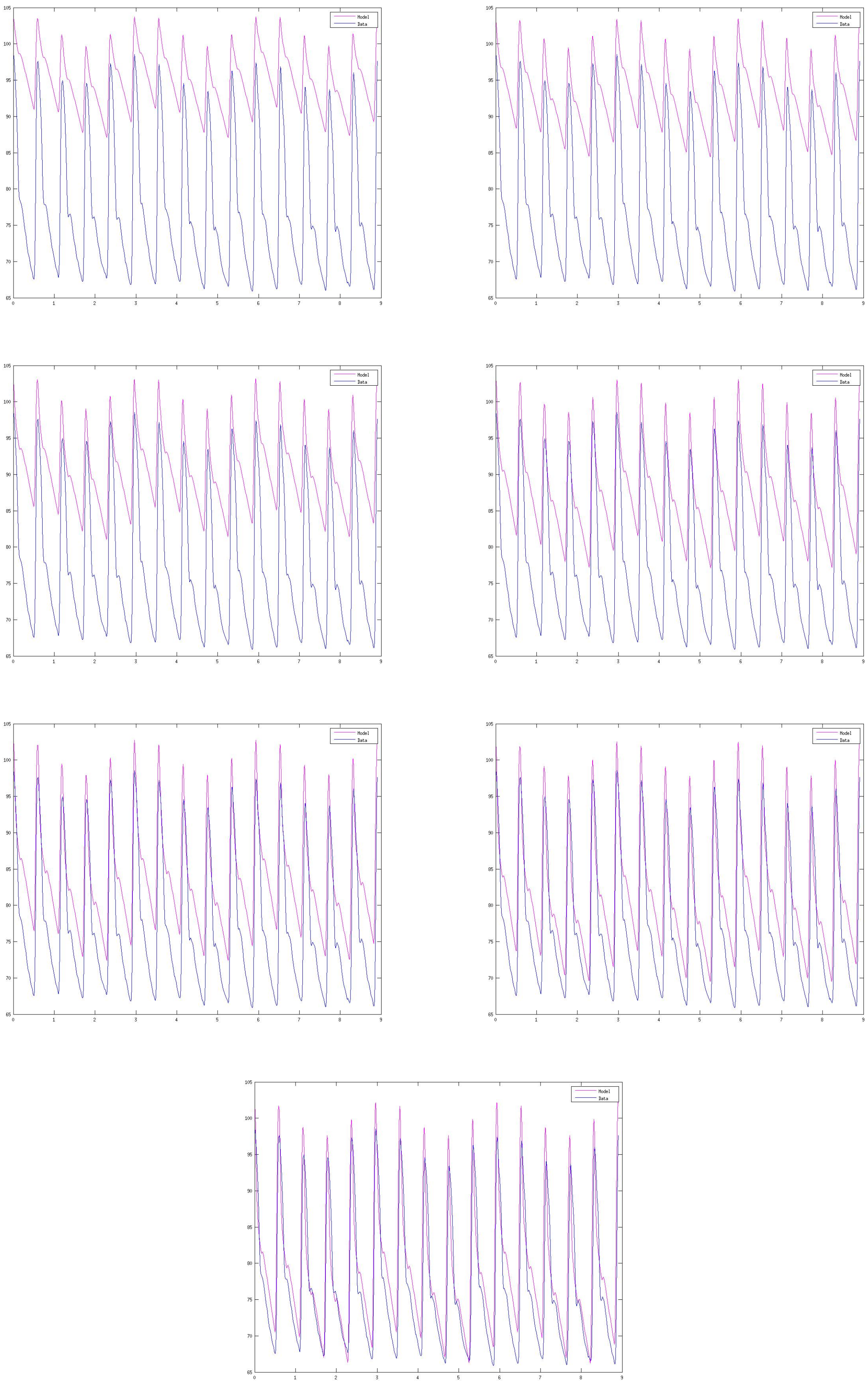

Figure 5.3: How the method works

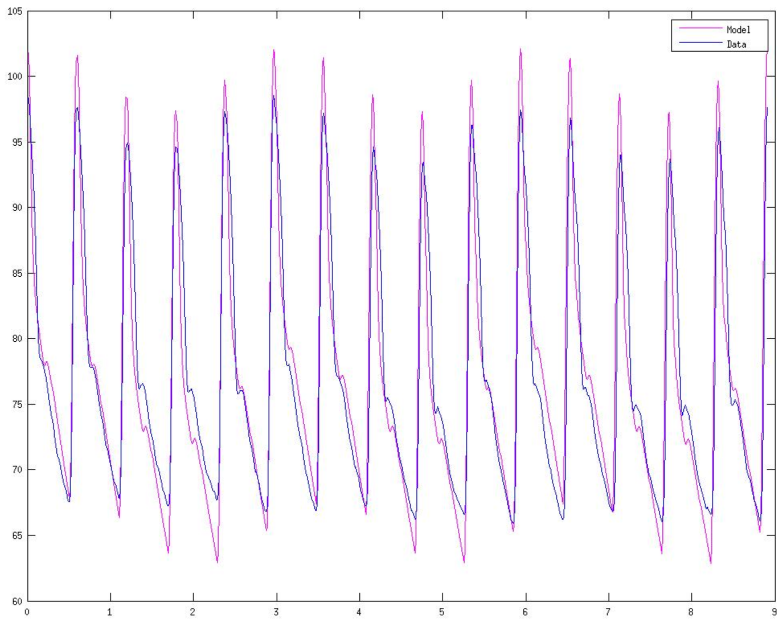

Figure 5.4: Result of stage 1

5.2.2 Stage 2: Nelder-Mead method for the five significant parameters

The previous stage was an approximate way to obtain a signal oscillating near the same values than the desired one. Now we want to refine the result, but still using the five significant parameters.

From the multiple possibilities in optimization methods in which it is not necessary an explicit expression of the objective function, the Nelder-Mead method was chosen. It is the algorithm used in Matlab's built-in function *fminsearch*, whose use is quite simple.

The method uses the idea of a simplex (a polytope of $n+1$ vertices in a n-dimensional space) to find a local minima of the function to be minimized. Instead of trying in random points, the algorithm uses the information it has of the objective function in a simplex's vertices and changes one point every time. The result is that it returns the point where the function reaches a local minimum with a relatively low computational cost.

In this case, the function's parameter corresponding to the maximum number of iterations was set to 2000. In this 5-dimensional problem, this corresponds to a maximum of 10000 evaluations of the function, i.e. 10000 integrations of the model.

The objective function to minimize was the L_2 distance between the model's output and the recorded arterial pressure,

$$\delta_2 = \left(\int (p_a - \hat{p}_a)^2 \right)^{\frac{1}{2}} \tag{5.8}$$

As in the previous two objective functions, this was evaluated over a time period of three respiratory cycles.

The initial value of the parameters to be estimated fed to the algorithm was the result of the first stage's estimation, and still the parameters which depend on others were calculated in

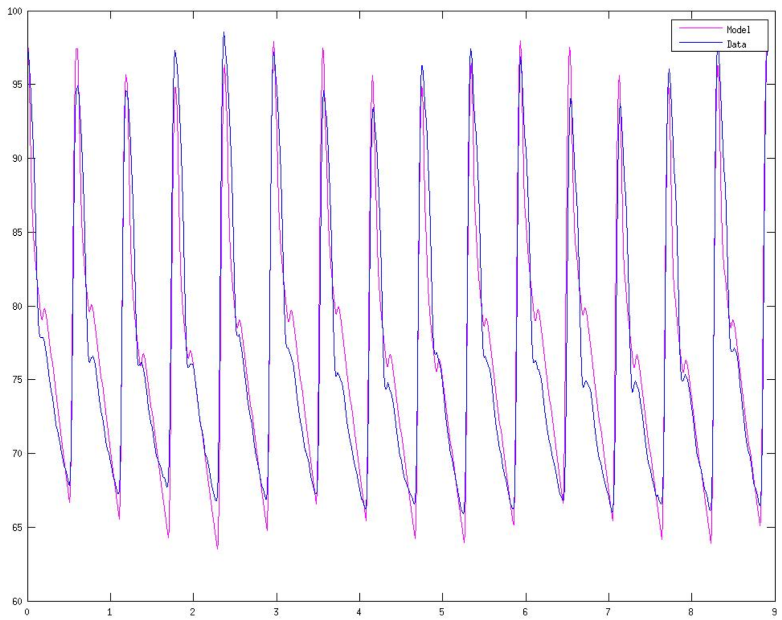

Figure 5.5: Result of stage 2

each iteration.

In figure 5.5 we can see the result of this stage in the same patient as before. If we compare it to figure 5.4, we can easily see that there is an improvement of the result, which is still far from perfect, but the signals look closer than before. Their oscillation amplitude and average is more similar now than before.

5.2.3 Stage 3: Nelder-Mead method for all the parameters

In this stage, the previous step was repeated, but now all the parameters are estimated at the same time. Now that both signals are closer than they were at the beginning, the method is more likely to converge, and it effectively did.

The objective function was again the L_2 distance between model's oputput and patient's signal, and the initial parameters were the ones obtained in the previous stage.

Now the relationships between the parameters were ignored. It has physiological meaning to think in E_d as the inverse of C_v, i.e., when the heart is relaxed is as stiff as a vein, but it could be that for a particular patient it is not exactly the same stiffness but slightly different. At this point, the dimensionality of the optimization problem becomes 25, and all parameters are independent from all the others.

Again, the maximum number of iterations was set to 2000, but now the dimensionality is higher, so there were a maximum of $25 \cdot 2000 = 50000$ evaluations of the function.

In figure 5.6 we can see the result of this stage in the same patient as the previous examples.

This part of the process gave a very good result in estimating the parameters related to time-domain: variability of ω respect to respiration, fine-tuning of the calculated ω, etc. As we can see in the plot, the respiratory variations of the systolic and diastolic pressures are very well synchronized. Also the position of the dicrotic notch seems to improve, and each beat is

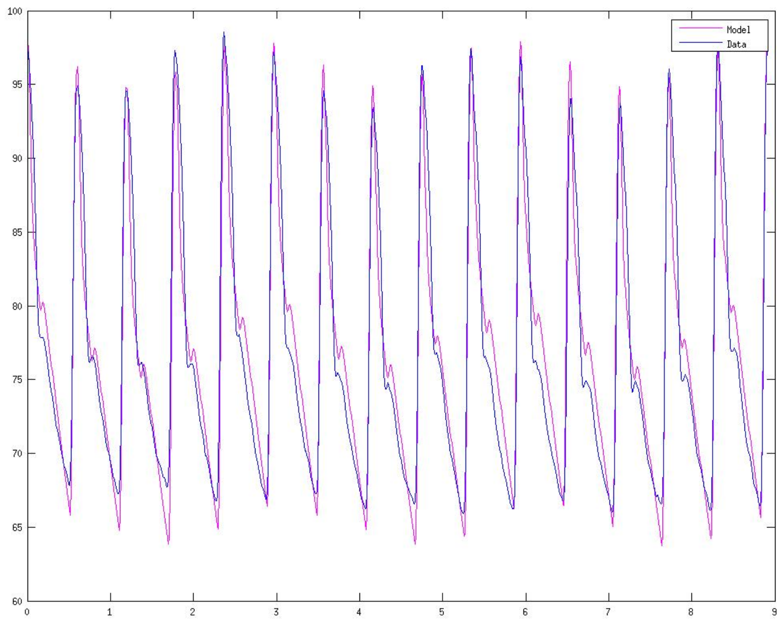

Figure 5.6: Result of stage 3

perfectly aligned with its corresponding beat from the patient's signal.

Nevertheless, this stage still failed at capturing properly some features such as the dicrotic notch's height or sharpness, the exact position, etc. This justified a last fine-tuning of the parameters obtained, which is the next stage.

5.2.4 Stage 4: Manual refinement

As it was said, the automathic three-stage method of estimation was not enough for some patients since it missed some details related mainly to the shape of the signal.

A possible solution could be building objective functions which reflected each detail, such as the difference in heights of the dicrotic notches. But this would have meant repeating the method again for each feature we wanted to represent, which would have been very long, and also dangerous in a specfic sense. Let's explain.

During the automatic parameter estimation, the model showed a strong interdependence of the parameters. This is, for instance, that although the main parameters related to the amplitude of oscillation were the resistances and compliances, a small change in another parameter, such as the notch's height, c_4, could also lead to a notorious change in the amplitude, in combination with some other parameter's certain values, whilst with other values it lead to no significant changes.

This interdependence caused, sometimes, unexpected behaviours of the model due to a particular combination of parameters.

Other times, a small change in a parameter led to a chaotic behaviour, as we have seen before. A parameter, different from the five significant ones, that usually led to unexpected results was the fraction of the beat corresponding to the systole, ϕ. Since the elastance function depends on ϕ very much (it has a sine shape the first ϕ part of the beat and is flat the rest), a

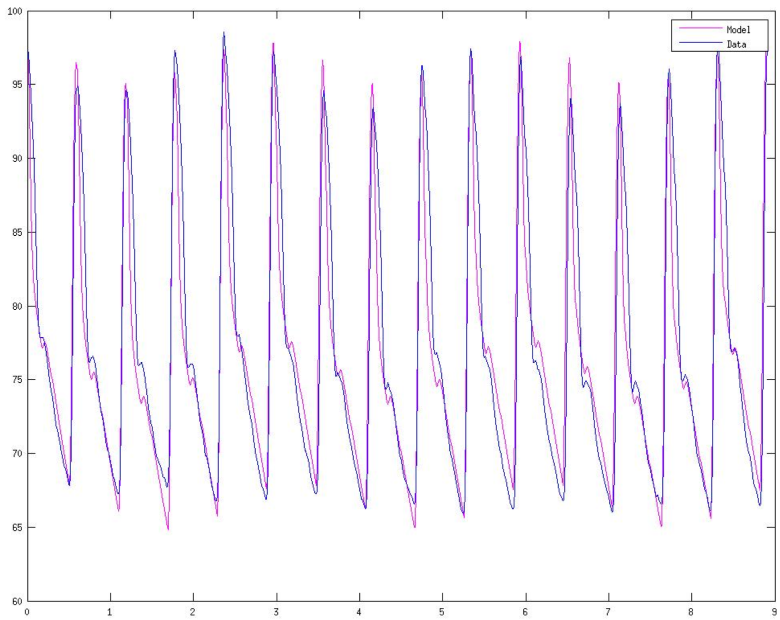

Figure 5.7: Result of stage 4

very small increase of ϕ led to 'double peaks', like two heart beats where it should be one.

This odd behaviour of the model made dangerous to keep on automatically varying the parameter's values once the result was so close to the desired one. In consequence, the fine-tuning of the parameters to better adjust to the patient's signal shape was made manually, varying only one parameter a very small quantity at the same time, in a careful way.

In figure 5.7 there is the result of this manual refinement in the same patient as previous figures.

In this patient we can see, for instance, a small improvement in the dicrotic notch's position, closer in general to the original. In other patients it was also necessary to adjust parameters such as systolic variation due to respiration. This one was delicate, because it cannot be controlled independently from diastolic variation, and in most of the cases the first was too low while the second was too big.

The manual refinement of the parameters concluded the four-stage method to estimate the parameters for each patient, and now we will see the result for all the available patients.

5.3 Results

5.3.1 Patient 1

This patient shows normal values of blood pressure (120/70 mmHg) and heart rate (79 bpm). The signal shows a tiny dicrotic notch, but not explicitly a peak in the notch. Respiratory variations are very little. The patient's pathology was tagged under the category "transplantation".

The final parameters obtained are shown in table 5.1, and the comparison between patient's signal and model output in figure 5.8.

Parameter	Value	Parameter	Value	Parameter	Value
R_{e0}	0.0055222	p_{a0}	55.0000	E_{s0}	0.57000
R_a	0.020797	p_{v0}	16.628	ϕ	0.33334
R_c	0.41279	p_{LV0}	49.714	R_{eM}	10.009
R_v	0.0055259	ω_0	8.3706	ε	0.00001
C_e	1.6946	c_3	0.00049874	A	0.40341
C_a	2.0000	c_2	4.0153	Δt_0	0.75786
C_v	15.0000	c_1	0.01000	c_4	150.00
p_{e0}	49.896	E_d	0.065511	c_5	18.445
				c_6	1.0000

Table 5.1: Parameter values for patient 1

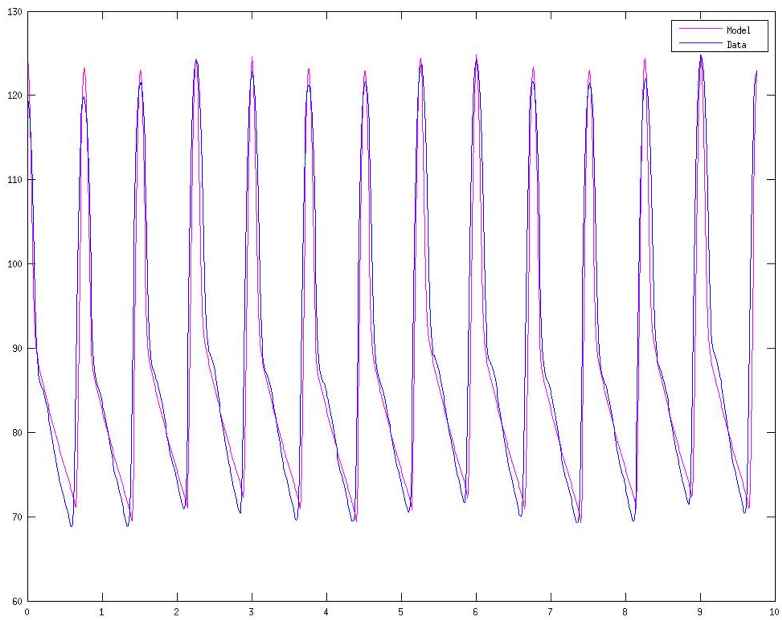

Figure 5.8: Result of patient 1

Parameter	Value	Parameter	Value	Parameter	Value
R_{e0}	0.0062786	p_{a0}	19.442	E_{s0}	0.3555
R_a	0.023572	p_{v0}	5.9987	ϕ	0.33337
R_c	0.42	p_{LV0}	19.977	R_{eM}	10.199
R_v	0.0062338	ω_0	7.3437	ε	0.00001
C_e	2.8126	c_3	0.00088425	A	0.45123
C_a	2.8126	c_2	4.0152	Δt_0	0.8586
C_v	56.639	c_1	0.02775	c_4	0.000006
p_{e0}	19.387	E_d	0.0177	c_5	18.435
				c_6	4.5189

Table 5.2: Parameter values for patient 2

Parameter	Value	Parameter	Value	Parameter	Value
R_{e0}	0.0038808	p_{a0}	17.355	E_{s0}	0.34
R_a	0.0154	p_{v0}	5.7844	ϕ	0.33273
R_c	0.29025	p_{LV0}	17.355	R_{eM}	10.116
R_v	0.0038895	ω_0	10.578	ε	0.00001
C_e	2.9196	c_3	0.0001	A	0.4515
C_a	2.9193	c_2	7.003	Δt_0	0.59617
C_v	55.456	c_1	0.006	c_4	0.000001
p_{e0}	17.355	E_d	0.0181	c_5	18.436
				c_6	4.5053

Table 5.3: Parameter values for patient 3

5.3.2 Patient 2

This patient shows normal-low values of blood pressure (100/60 mmHg) and normal heart rate (69 bpm). The signal does not show a dicrotic notch, only a change in slope. Respiratory variations are in the order of 5mmHg in systolic pressure. The patient's pathology was tagged under the category "transplantation".

We can see the patient's estimated parameters in table 5.2 and the graphic result in figure 5.9.

5.3.3 Patient 3

This patient's pathology was tagged under the category "haemorrhagic". The loss of blood led to low values of blood pressure (85/45 mmHg). Due to this fact, the patient was administrated norepirephrine (vasoconstrictor drug). The heart rate was high (100 bpm), as a natural reaction to the low blood pressure. Absence of dicrotic notch and little respiratory variation in systolic pressure may be observed.

Patient's parameters are shown in table 5.3 and pressure signal in figure 5.10.

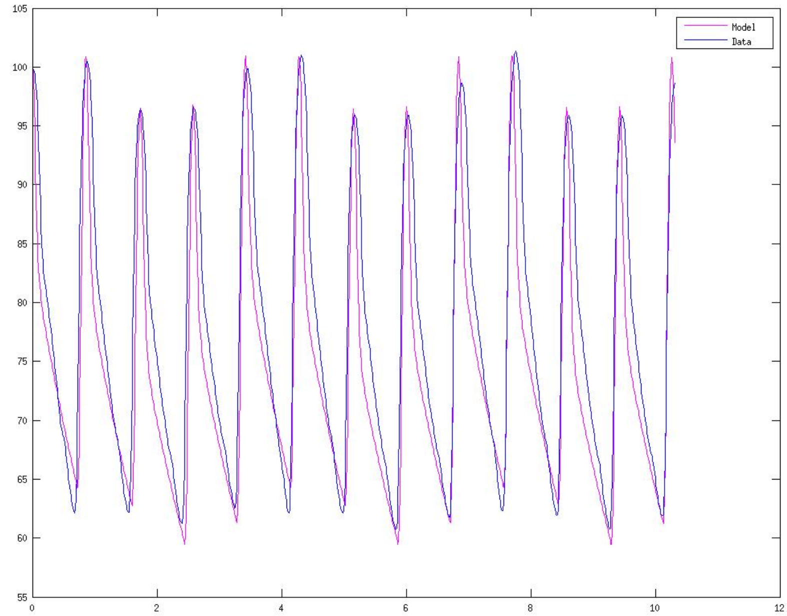

Figure 5.9: Result of patient 2

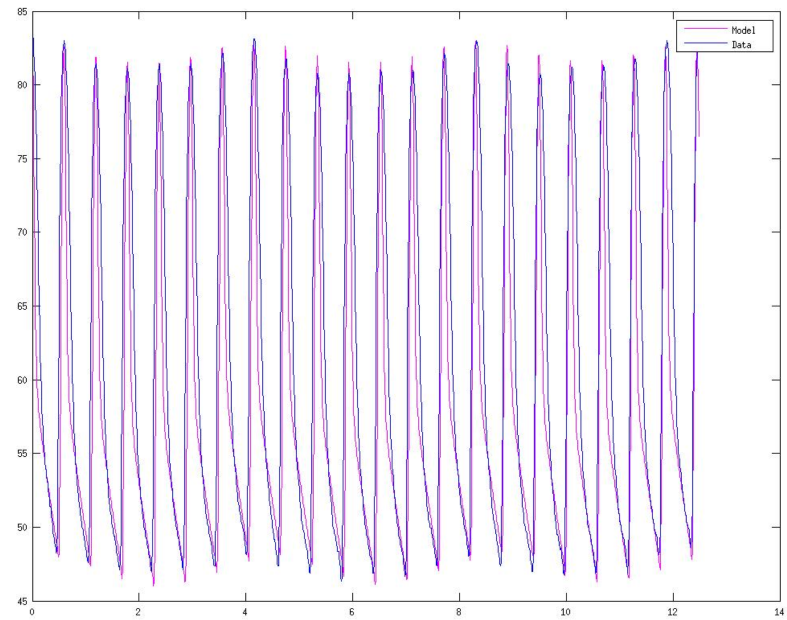

Figure 5.10: Result of patient 3

Parameter	Value	Parameter	Value	Parameter	Value
R_{e0}	0.007786	p_{a0}	27.497	E_{s0}	0.76205
R_a	0.029788	p_{v0}	10.719	ϕ	0.33189
R_c	0.536	p_{LV0}	31.007	R_{eM}	10.009
R_v	0.0078384	ω_0	8.7974	ε	0.00001
C_e	0.9048	c_3	0.001002	A	0.53013
C_a	0.9028	c_2	6.0683	Δt_0	0.71476
C_v	38.997	c_1	0.088016	c_4	0.000002
p_{e0}	27.124	E_d	0.056655	c_5	18.644
				c_6	4.5229

Table 5.4: Parameter values for patient 4

Parameter	Value	Parameter	Value	Parameter	Value
R_{e0}	0.0037297	p_{a0}	18.004	E_{s0}	0.39861
R_a	0.014031	p_{v0}	6.0008	ϕ	0.33335
R_c	0.37623	p_{LV0}	18.012	R_{eM}	10.001
R_v	0.0037171	ω_0	10.581	ε	0.00001
C_e	2.5096	c_3	0.000125	A	0.49395
C_a	2.5087	c_2	5.0652	Δt_0	0.59383
C_v	60.775	c_1	0.014987	c_4	500.00
p_{e0}	17.993	E_d	0.019723	c_5	18.417
				c_6	3.0758

Table 5.5: Parameter values for patient 5

5.3.4 Patient 4

This patient shows normal-low values of blood pressure (115/55 mmHg) and normal heart rate (83 bpm). The signal does not show a dicrotic notch. Respiratory variations are very high (more than 10 mmHg in systolic pressure). The patient's pathology was tagged under the category "respiratory" and he/she was also given norepirephrine.

The final parameters obtained are shown in table 5.4, and the comparison between patient's signal and model output in figure 5.11.

5.3.5 Patient 5

This patient shows low values of blood pressure (95/65 mmHg) and high heart rate (100 bpm). The signal presents a small dicrotic notch. Respiratory variations are less than 5mmHg in systolic pressure. The patient's pathology was tagged under the category "transplantation".

The patient's estimated parameters can be seen in table 5.5 and the graphic result in figure 5.12.

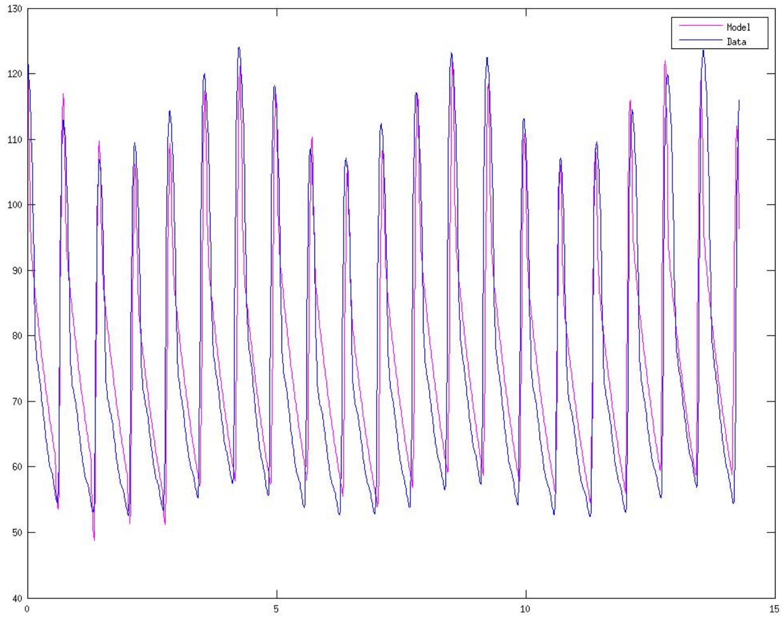

Figure 5.11: Result of patient 4

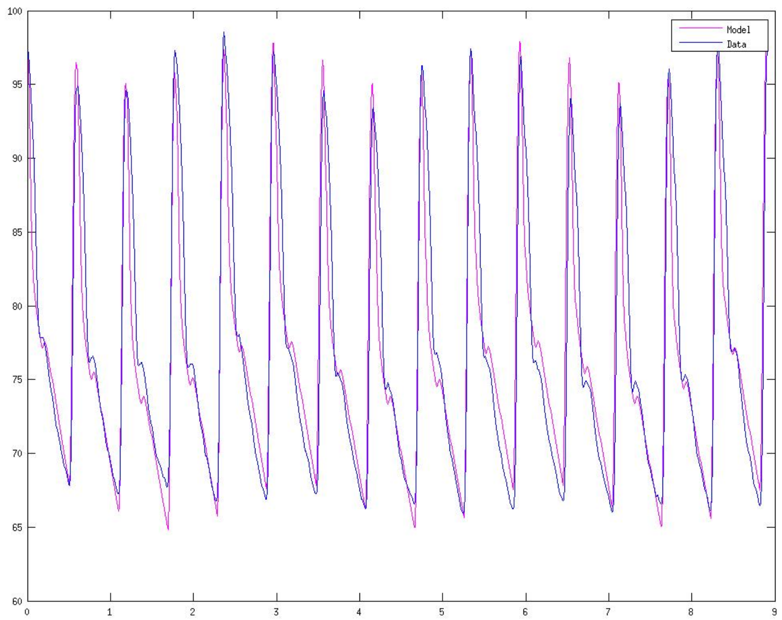

Figure 5.12: Result of patient 5

Parameter	Value
R_{e0}	0.0049252
R_a	0.018469
R_c	0.40001
R_v	0.0049253
C_e	1.5402
C_a	1.0459
C_v	49.9978
p_{e0}	21.783

Parameter	Value
p_{a0}	21.781
p_{v0}	7.2597
p_{LV0}	21.761
ω_0	8.3339
c_3	0.000125
c_2	4.0001
c_1	0.015
E_d	0.029022

Parameter	Value
E_{s0}	0.64627
ϕ	0.33338
R_{eM}	10.004
ε	0.00001
A	0.43995
Δt_0	0.75182
c_4	400.00
c_5	1.0009
c_6	3.4889

Table 5.6: Parameter values for patient 6

5.3.6 Patient 6

This patient shows normal values of blood pressure (135/60 mmHg) and normal heart rate (80 bpm). The signal shows a large dicrotic notch. Respiratory variations are in the order of 5mmHg in systolic pressure. The patient's pathology was tagged under the category "neurologic". There is also a small dose of vasoconstrictor drugs.

Patient's parameters are shown in table 5.6 and pressure signal in figure 5.13.

5.3.7 Patient 7

Patient with extremely high blood pressure values (220/85 mmHg) and high heart rate (104 bpm). It was not possible to find a set of parameters for the model to fit this patient's arterial pressure signal. When any parameter was adjusted to increase the blood pressure values in the resulting signal, the model went chaotic and the output went unstable.

Anyway, the patient's recorded signal can be seen in figure 5.14. Notice the extremely high values of the systolic pressure, near 220, and the high diastolic, higher than 80.

5.3.8 Patient 8

This patient shows normal values of blood pressure (140/60 mmHg) and high heart rate (95 bpm). The signal shows a small dicrotic notch at the end of the downslope part of the beat (later than usual). Respiratory variations are normal (in the order of 5mmHg). The patient's pathology was tagged under the category "post-surgery".

We can see the patient's estimated parameters in table 5.7 and the graphic result in figure 5.15. We can see that the patient's blood pressure shows an ascending tendency, which the model is not able to capture.

5.3.9 Patient 9

This patient shows normal values of blood pressure (125/65 mmHg) and normal-high heart rate (88 bpm). The signal shows a very high dicrotic notch. Respiratory variations are normal (in the order of 5mmHg). The patient's pathology was tagged under the category "transplantation". The patient was also given norepirephrine.

Patient's parameters are shown in table 5.8 and pressure signal in figure 5.16.

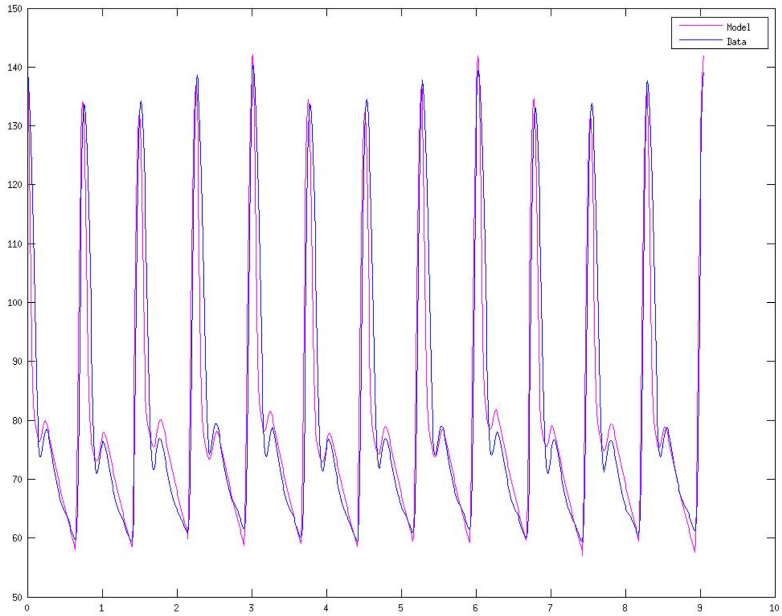

Figure 5.13: Result of patient 6

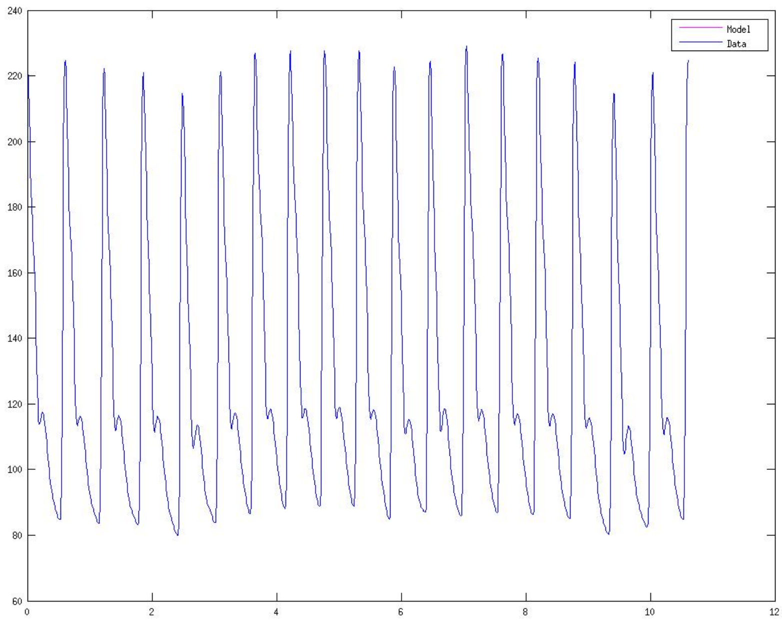

Figure 5.14: Signal of patient 7

Parameter	Value	Parameter	Value	Parameter	Value
R_{e0}	0.0054166	p_{a0}	21.03	E_{s0}	0.72163
R_a	0.021146	p_{v0}	7.0892	ϕ	0.33322
R_c	0.36564	p_{LV0}	24.265	R_{eM}	10.002
R_v	0.0054171	ω_0	10.134	ε	0.00001
C_e	1.3858	c_3	0.0001	A	0.52291
C_a	1.0786	c_2	5.0002	Δt_0	0.62655
C_v	27.171	c_1	0.0016665	c_4	150.00
p_{e0}	21.03	E_d	0.038919	c_5	1.9999
				c_6	3.0001

Table 5.7: Parameter values for patient 8

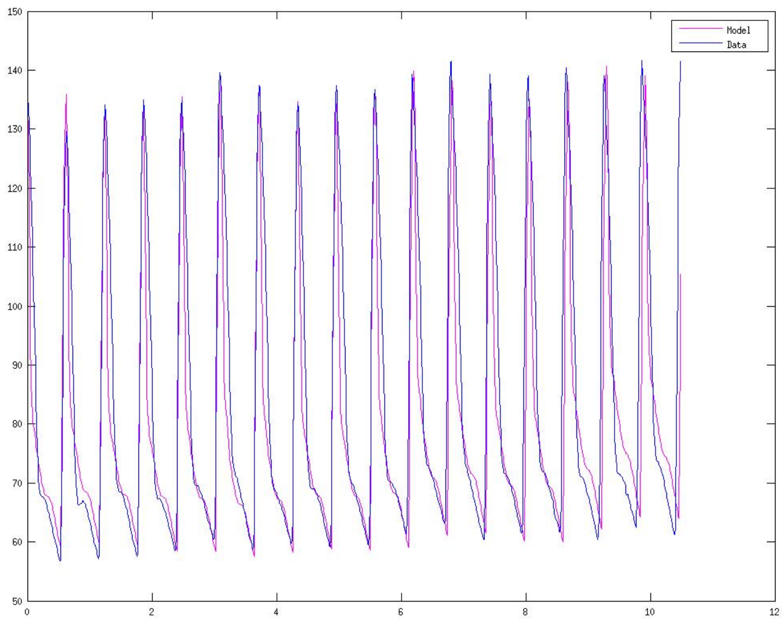

Figure 5.15: Result of patient 8

Parameter	Value	Parameter	Value	Parameter	Value
R_{e0}	0.0056467	p_{a0}	26.146	E_{s0}	0.7129
R_a	0.017145	p_{v0}	5.8856	ϕ	0.33333
R_c	0.42314	p_{LV0}	21.146	R_{eM}	10.058
R_v	0.005707	ω_0	9.2249	ε	0.000099
C_e	1.3753	c_3	0.0001447	A	0.37178
C_a	1.335	c_2	5.9999	Δt_0	0.67807
C_v	30.492	c_1	0.017459	c_4	450.00
p_{e0}	26.146	E_d	0.031455	c_5	1.5898
				c_6	3.534

Table 5.8: Parameter values for patient 9

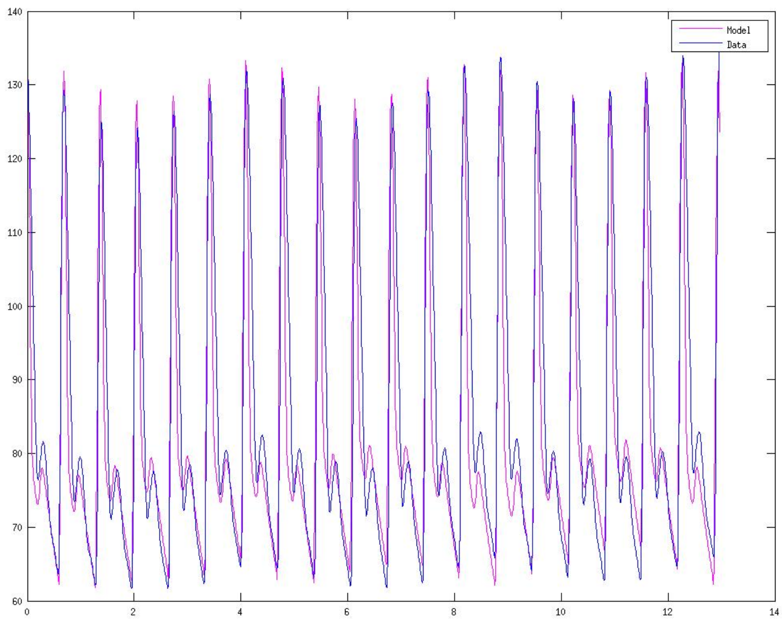

Figure 5.16: Result of patient 9

5.4 Discussion

From the previous nine patients, we can see that out mathematical model is able to reproduce the blood pressure signal of a wide range of patients.

Proper sets of parameters were found for patients with average values of blood pressure, such as 1, 2, 4, 6, 8 and 9. It was also possible for patients with low or very low blood pressure, like 3 and 5. However, it was not possible to adjust the model to fit a very high blood pressure signal (and with a high amplitude of oscillation), which was the case for patient 7. This was due to the chaotic behaviour of the model at extreme values of the parameters.

The two main novel features included in the model were the variations of pressure and heart rate due to respiration and the dicrotic notch. We can see that the model can perfectly deal with small respiratory variations, like in patients 1, 3 and 5, regular variations, such as patients 2, 6, 8 and 9, and very high, like in patient 4. Moreover, the model can reflect the absence of a dicrotic notch, or just a change in the slope (patients 1, 2, 3 and 4), notches with a small peak (such as patient 5), big dicrotic notches (like in 6 and 9) and even notches placed in an uncommon place of the wave (8). Nevertheless, the position of the notch is controlled by one parameter, and is related to its position in the downslope part of the wave. During the parameter estimation, it was found that the model lacks a way to control the slope itself, and more important than this, a way to control the variability of the position of the notch. We can see in all the signals with regular or big notches that their height, sharpness and position varies in a very different manner than they do in the patient's signal to be reproduced.

Another fact that was noticed during the parameter estimation was that it is not possible to control the respiratory variations in systolic and diastolic pressures independently. In all the cases, the variability of the systolic pressure was less than the desired one (the patient's), and the variability of diastolic was too high. The solution was finding a balance between them. This fact can be seen in patient 4, the one with highest respiratory variation.

A minor detail that the model does not reflect is that the respiratory variation, now modelled as a sinusoidal change in elastance height, does not always look like a sine in real signals. In most of them, the decrease in systolic pressure is faster than the increase. See, for instance, patient number 2: in the three respiratory cycles plotted, the lowest peak is the first after the highest, and the next two are progressively higher.

Another feature not present in the model is the ascending or descending tendency in blood pressure, which happens in patient 8. The model is thought to vary pressure due to respiration, but not in a long-term. This may be solved with non-constant values of parameters (compliances and resistances, mainly).

It has already been mentioned that there was some chaotic behaviours in the model due to certain changes in parameters or, more specifically, certain combinations of parameters.

At the end of the estimation process, we can see that not all the parameters we have obtained have a physiological meaning. For instance, patients who were given vasoconstrictor drugs should have very low values of compliances and high resistances, and this is not always the case (look at patient 6, for instance).

In any case, the parameter estimation has shown that the model can reproduce a wide variety of real blood pressure signals.

Conclusions

The objective of this work was to present a new mathematical model of the arterial pressure signal and test it against real data.

As we have seen, the model provided here includes some features which had not been present in any of the previous models. These are the respiratory variations of frequency and pressure, the aortic valve closing and the dicrotic notch.

We have also seen that there are a few parameters which have a great influence on the resulting signal, and should be the first to be estimated and the more important ones. Moreover, we have also seen that some other parameters do not seem to make a big influence on the result in terms of the distance between signals, but they can change the signal's shape: respiratory variation, dicrotic notch, etc.

The goal was not to develop a very efficient or accurate method for parameter estimation, but only one that worked. The method presented here is not 100% automatic and consists of many parts, but we can say that it worked as expected.

At the end, we have seen the model's performance compared to recorded signals and it reproduces very different kinds of arterial signals, with different values of pressure, shape, etc.

In consequence, we can claim that the model performs as expected in terms of accuracy. Furthermore, each component has a clear meaning, so the parameters and results are interpretable.

However, we can also seen some limitations. The main one may be the lack of simplicity, although it was one of the objectives. The existence of a large number of parameters, the interdependence between them and the chaotic behaviour of the model under certain values are factors that add a difficulty in the interpretation of the results.

Additionally, the model failed to reproduce the more extreme example of signal available, with very high values of blood pressure and a wide amplitude of oscillation of the signal. All these and more technical limitations of the model, such as the dependence between systolic and diastolic respiratory variations, or the lack of control of the position of the notch, are explained in detail at the end of the fifth chapter.

Futher work would be a formal stability analysis, although the presence of variables computed in each beat (in the valve close and the dicrotic notch) make it impossible to do using classical methods (linearization, etc.). This might help us avoid chaos or unexpected results under certain conditions. In addition, solving the technical limitations would be another interesting progress. For instance, adding a way to control the variability of height and size of the dicrotic notch, or making it possible to control variation of the systolic and diastolic pressures independently.

Nevertheless, we have seen that the model is able to simulate a wide range of signals accurately and so it can be used to understand how the cardiovascular system works, which was the main goal.

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