Title: Mathematical Modelling Of The Blood Pressure Signal

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Mathematical Modelling Of The Blood Pressure Signal

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Parameter estimation

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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 maintain 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**.
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 continuous 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 pressure of 135/60 mmHg.
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 $\tau$.

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.
Table 2.1: Meaning and nominal values of the parameters

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

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

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 $\tau$ plays a role.

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

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

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

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:

\[
f(P_a(t), P_a(t-\tau)) = \frac{\alpha T_s}{1 + \gamma T_p} - \beta T_p \tag{2.4}
\]

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
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_H$</td>
<td>0.84</td>
<td>s$^{-2}$</td>
</tr>
<tr>
<td>$\beta_H$</td>
<td>1.17</td>
<td>s$^{-2}$</td>
</tr>
<tr>
<td>$\gamma_H$</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>$\alpha_s$</td>
<td>93</td>
<td>mmHg</td>
</tr>
<tr>
<td>$\beta_s$</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>$\alpha_p$</td>
<td>93</td>
<td>mmHg</td>
</tr>
<tr>
<td>$\beta_p$</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

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 compartment 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:

\[
Q_{in} = Q_{stored} + Q_{out}
\]  

(2.7)

The distensibility, also named compliance, is defined as

\[
C = \frac{dV}{dP_{in}}
\]  

(2.8)

And so \(Q_{stored}\) is

\[
Q_{stored} = \frac{dV}{dt} = \frac{dV}{dP_{in}} \frac{dP_{in}}{dt} = C \frac{dP_{in}}{dt}
\]  

(2.9)

The resistance is related to how easily the blood flows.

\[
Q_{out} = \frac{P_{in}}{R}
\]  

(2.10)

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

\[
Q_{in} = C \frac{dP_{in}}{dt} + \frac{P_{in}}{C}
\]  

(2.11)
Figure 2.2: Windkessel model as a circuit

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C )</td>
<td>1.55</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>( R )</td>
<td>1.05</td>
<td>s·mmHg/ml</td>
</tr>
<tr>
<td>( V_s )</td>
<td>67.9</td>
<td>ml</td>
</tr>
<tr>
<td>( H )</td>
<td>1.24</td>
<td>beat/s</td>
</tr>
<tr>
<td>( T )</td>
<td>( 1/H )</td>
<td>s</td>
</tr>
<tr>
<td>( T_{sys} )</td>
<td>( T/3 )</td>
<td>s</td>
</tr>
<tr>
<td>( P_0 )</td>
<td>100</td>
<td>mmHg</td>
</tr>
</tbody>
</table>

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:

\[
\frac{dP}{dt} + \frac{P}{RC} = \frac{Q}{C} \quad (2.12)
\]

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

\[
\frac{dP}{dt} + \frac{P}{RC} = \frac{Q}{C} \quad (2.13)
\]

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.

\[
\int_{t_0}^{t_0+T} Q(t) \, dt = V_s \quad (2.14)
\]
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 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

\[
Q(\bar{t}) = \begin{cases} 
Q_M & \bar{t} \leq \frac{1}{3} \\
0 & \text{otherwise}
\end{cases} \tag{2.18}
\]
We impose the volume in a beat equals to $V_s$.

$$\int_{t_0}^{t_0+T} Q(t) \, dt = \frac{T}{3} Q_M = V_s$$  \hspace{1cm} (2.19)

Then,

$$Q_M = \frac{3V_s}{T} = 3V_sH = 3 \cdot 67.9 \cdot 1.24 = 252.588 \text{ ml/s}$$  \hspace{1cm} (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

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

Imposing also that the volume ejected each beat is $V_s$,

$$\int_{t_0}^{t_0+T} Q(t) \, dt = \frac{T}{2} Q_M = V_s$$  \hspace{1cm} (2.22)
Figure 2.5: Pressure computed with pulse train \( Q(t) \)

and so

\[
Q_M = 2 \frac{V_s}{T} = 2 V_s H = 2 \cdot 67.9 \cdot 1.24 = 168.392 \text{ ml/s} \tag{2.23}
\]

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 asymmetry, but the waveform is too spiky to be realistic.

So we need something as smooth as the sine but asymmetric 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 $Q(t)$
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 asymmetry 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:

\[
\dot{V}_a = Q_+ - Q_c \tag{2.27}
\]
\[
\dot{V}_v = Q_c - Q_- \tag{2.28}
\]
\[
\dot{V}_{LV} = Q_- - Q_+ \tag{2.29}
\]

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

\[
Q_c = \frac{p_a - p_v}{R_c} \tag{2.30}
\]
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:

\[
Q_+ = \frac{[p_{LV} - p_a]_+}{R_a} \quad (2.31)
\]
\[
Q_- = \frac{[p_v - p_{LV}]_+}{R_v} \quad (2.32)
\]

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

\[
V_a = V_{a0} - C_a p_a \quad (2.33)
\]
\[
V_v = V_{v0} - C_v p_v \quad (2.34)
\]
\[
V_{LV} = V_{LV0} - C_{LV} p_{LV} \quad (2.35)
\]

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

Table 2.4: Meaning and nominal values of the parameters

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

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

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

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:

\[ \rho \frac{\partial u}{\partial t} + \frac{\partial p}{\partial x} = \mu \frac{\partial}{\partial r} \left( r \frac{\partial u}{\partial t} \right) \]

where \( u(t, r) \) is the longitudinal velocity, \( \rho \) is the blood’s density, \( \mu \) 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 arrhythmia).

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 Description 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:
\[ \dot{V}_e = Q_{LV} - Q_e \] (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)

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,

\[ C_e \dot{p}_e = Q_{LV} - Q_e \] (3.5)
\[ C_a \dot{p}_a = Q_e - Q_a \] (3.6)
\[ C_v \dot{p}_v = Q_a - Q_v \] (3.7)

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

\[
\left( \frac{p_{LV}}{E_{LV}} \right) = Q_v - Q_{LV}
\] (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, instead 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:

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

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 \( R_{e0} = R_e \). 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
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<tbody>
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<td>ml/mmHg</td>
</tr>
<tr>
<td>$C_a$</td>
<td>1.5</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>$C_v$</td>
<td>50</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>$R_{e0}$</td>
<td>0.016</td>
<td>s·mmHg/ml</td>
</tr>
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<td>$R_a$</td>
<td>0.06</td>
<td>s·mmHg/ml</td>
</tr>
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<td>$R_c$</td>
<td>1.2</td>
<td>s·mmHg/ml</td>
</tr>
<tr>
<td>$R_v$</td>
<td>0.016</td>
<td>s·mmHg/ml</td>
</tr>
</tbody>
</table>

Table 3.1: Nominal values of the parameters
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:

$$E_{LV}(\tilde{t}) = \begin{cases} E_d + (E_s - E_d) \sin^2(\omega \tilde{t}) & \tilde{t} \leq \phi \\ E_d & \text{otherwise} \end{cases}$$  \hspace{1cm} (3.13)

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

If we plot this function for constant values $E_d = 0.06\text{mmHg/ml}$, $E_s = 3.0\text{mmHg/ml}$ and $T = 0.9s$ (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 $\varepsilon$ 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,

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

(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 resistance as described before.

3.2.4 Respiratory sinus arrhythmia

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

We can model this variation as

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

(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
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 \( \omega \) does. This affects, mainly, the systolic pressure. So, instead of a constant, elastance height is

\[
E_s(t) = E_{s0} + c_1 \sin \left( \frac{E_{s0} t}{c_2} \right)
\]  

(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 subtract 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

\[
C_c \dot{p}_c = \frac{p_{LV} - p_e}{R_c} - \frac{p_e - p_a}{R_a} + f(t, t_1, \Delta t) \tag{3.17}
\]

\[
C_a \dot{p}_a = \frac{p_e - p_a}{R_a} - \frac{p_a - p_v}{R_v} \tag{3.18}
\]

\[
C_v \dot{p}_v = \frac{p_a - p_v}{R_c} - \frac{p_v - p_{LV}}{R_v} H(p_v - p_{LV}) \tag{3.19}
\]

\[
\left( \frac{p_{LV}}{E_{LV}} \right) = \frac{p_v - p_{LV}}{R_v} H(p_v - p_{LV}) - \frac{p_{LV} - p_e}{R_c} - f(t, t_1, \Delta t) \tag{3.20}
\]

We take an impulse of the form:

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

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 \(\Delta t\) 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 \(c_4 = 500\), \(c_5 = 4 \log(100)\).
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 $h = 0.01s$. We integrate between $t_0 = 0s$ and $t_F = 60s$ 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:

\begin{align*}
p_{eo} &= 35 \text{ mmHg} \\
p_{ao} &= 35 \text{ mmHg} \\
p_{vo} &= 5 \text{ mmHg} \\
p_{LV0} &= 35 \text{ mmHg}
\end{align*}

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 appropriate 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 \( \theta \), with nominal value \( \theta_0 \), 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 \( p_a((1-q)\theta_0) \) and \( p_a((1+q)\theta_0) \) be the output arterial pressures for a perturbed parameter \( \theta \) (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 $R_c$

\[
\delta_2 = \left( \int_0^{20T} \left( p_a((1 + q)\theta_0) - p_a((1 - q)\theta_0) \right)^2 \right)^{\frac{1}{2}}
\]  
(4.1)

\[
\delta_\mu = \left| \mu\left(p_a((1 + q)\theta_0)\right) - \mu\left(p_a((1 - q)\theta_0)\right) \right|
\]  
(4.2)

\[
\delta_\sigma = \left| \sigma\left(p_a((1 + q)\theta_0)\right) - \sigma\left(p_a((1 - q)\theta_0)\right) \right|
\]  
(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, $p_a((1 - q)\theta_0)$ and $p_a((1 + q)\theta_0)$, 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 influential 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 $p_{a0} = p_{e0} = p_{LV0}$. 

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Figure 4.2: Signals for a perturbation 0.5 of $E_d$

Figure 4.3: Signals for a perturbation 0.01 of $C_e$
Table 4.1: $L_2$ distance between signals for each parameter and perturbation

<table>
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</tr>
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<td>$\Delta t_0$</td>
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<td>$\Delta t_0$</td>
</tr>
</tbody>
</table>

4.3 Results

4.3.1 Influence on $L_2$ distance

Table 4.1 shows the resulting $L_2$ distance between $p_a((1 - q)\theta_0)$ and $p_a((1 + q)\theta_0)$ for each parameter and perturbationation. 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 measurement 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 conditions. 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 $\Delta t_0$ has no influence at all on the result. This is because it has only influence in the first beat, and from the second the $\Delta t$ is computed from the previous beat.
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. $\phi$  
5. $\omega_0$  
6. $R_c$  
7. $A$  
8. $R_{e0}$  
9. $R_a$  
10. $c_4$  
11. $c_6$  
12. $c_2$  
13. $c_5$  
14. $c_3$  
15. $\varepsilon$  
16. $\Delta t_0$

4.3.2 Influence on absolute difference of mean values

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

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
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, $\Delta t_0$ has no influence in the result.

So, if we use the sensitivity function $\delta_\mu$ instead of $\delta_2$, the obtained results are not exactly the same (since $\delta_2$ sums all the differences in signals and $\delta_\mu$ only measures the difference between their mean values). However, both measures rank, approximately, the same parameters to be influential, and the others to be not so influential.

From the $\delta_\mu$ 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. $\omega_0$
7. $R_v, R_{v0}$
8. $\phi$
9. $p_{v0}$
10. $R_a$
11. $c_4$
12. $c_6$
13. $c_5$
14. $\epsilon$
15. $Re_M$
16. $c_2$
17. $c_3$
18. $c_1$
19. $\Delta t_0$

### 4.3.3 Influence on absolute difference of standard deviations

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

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 ($\omega_0$ and $\phi$) 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 $\delta_\mu$. And, again, $\Delta t_0$ has no influence in the result.

From the $\delta_\sigma$ distances seen in table 4.3, the following classification was made:

1. $\omega_0$
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. $R_v, R_{v0}$
8. $\phi$
9. $R_a$
10. $c_4$
11. $c_5$
12. $Re_M$
13. $c_6$
14. $\epsilon$
15. $p_{v0}$
16. $c_3$
17. $c_2$
18. $c_1$
19. $\Delta t_0$

### 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 classification 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.
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<td>0.000</td>
<td>$\Delta t_0$</td>
</tr>
</tbody>
</table>

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 feasible, 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, $\omega_0$, 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. $p_{s0}$
4. $A$
5. $R_c$
6. $\omega_0$
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:

\[
\delta_\mu = |\mu(p_a) - \mu(\hat{p}_a)| \tag{5.1}
\]

\[
\delta_\sigma = |\sigma(p_a) - \sigma(\hat{p}_a)| \tag{5.2}
\]

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 \( \theta \) near its nominal value \( \theta_0 \), we will use the results of perturbing \( \theta \) a certain value \( q \). Then, the derivative is computed this way:

\[
\frac{\partial \mu}{\partial \theta} \approx \frac{\mu(p_a((1 + q)\theta_0)) - \mu(p_a((1 - q)\theta_0))}{(1 + q)\theta_0 - (1 - q)\theta_0} \tag{5.4}
\]

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 \( \omega_0 \) 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 \( \mu \) respect to \( C_v \). Remember that the nominal value of \( C_v \) was 50 ml/mmHg.

\[
\frac{\partial \mu}{\partial C_v} \approx \mu \left( p_a \left( (1 + 0.1) \cdot 50 \right) \right) - \mu \left( p_a \left( (1 - 0.1) \cdot 50 \right) \right) \frac{(1 + 0.1) \cdot 50 - (1 - 0.1) \cdot 50}{(1 + 0.1) \cdot 50 - (1 - 0.1) \cdot 50} \tag{5.5}
\]

Repeating this operation for each significant parameter and for \( \mu \) and \( \sigma \), 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 \( \omega_0 \) and \( c_2 \) from the patient’s signal.

- While there is not chaos or iteration number is less than 100,
  - Compute \( \delta_\mu \) and \( \delta_\sigma \).
    * If \( \frac{\delta_\mu}{\mu(p_a)} > \frac{\delta_\sigma}{\sigma(p_a)} \), then do \( \Theta_{n+1} = \Theta_n - \alpha \nabla \mu \).
    * Else, do \( \Theta_{n+1} = \Theta_n - \alpha \nabla \sigma \).
  - Compute parameters depending on \( \Theta_{n+1} \).
  - Plot together \( p_a(\Theta) \) and \( \hat{p}_a \).

- Save resulting \( \Theta \).

In each iteration, the \( \delta_\mu \) \( \delta_\sigma \) 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 \( \frac{\delta_\mu}{\mu(p_a)} \) to \( \frac{\delta_\sigma}{\sigma(p_a)} \). Both distances are normalized because, if they were not, \( \delta_\mu \) 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
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,

\[
\delta_2 = \left( \int (p_a - \hat{p}_a)^2 \right)^{\frac{1}{2}}
\]  

(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
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 output 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 $\omega$ respect to respiration, fine-tuning of the calculated $\omega$, 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
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 automatic 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 specific 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, $\phi$. Since the elastance function depends on $\phi$ very much (it has a sine shape the first $\phi$ part of the beat and is flat the rest), a
very small increase of $\phi$ 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.
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Table 5.1: Parameter values for patient 1

Figure 5.8: Result of patient 1
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<td>$A$</td>
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Table 5.2: Parameter values for patient 2

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</table>

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
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<thead>
<tr>
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Table 5.4: Parameter values for patient 4

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</table>

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 norepinephrine.

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 5 mmHg 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
<table>
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<td>$c_6$</td>
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</table>

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 5 mmHg 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 5 mmHg). 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 5 mmHg). The patient’s pathology was tagged under the category “transplantation”. The patient was also given norepinephrine.

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
<table>
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<td>0.0016665</td>
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<td>( p_{a0} )</td>
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Table 5.7: Parameter values for patient 8

Figure 5.15: Result of patient 8
<table>
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<td>0.42314</td>
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Table 5.8: Parameter values for patient 9

![Figure 5.16: Result of patient 9](image-url)
5.4 Discussion

From the previous nine patients, we can see that our 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.

Further 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.
Bibliography


