# A Baroreflex Control Model Using Head-Up Tilt Test

José Manuel Monteiro Grilo Lema Santos

***Abstract*— The searching for mathematical models to resemble the baroreflex mechanism is an active field of research because not all knowledge as been acquired yet. A major problem present since the beginning was the impossibility in carrying tests in human subjects, which lead to the usage of animal subjects. This impossibility has led to an increase search of models that simulate not only this mechanism but also several others that are correlated with the baroreflex. The inexistence of a mathematical model that provides a valid explanation and a reasonable behaviour when compared to the baroreflex is a major gap. Such a mechanism would fit perfectly in carrying several tests that are unavailable in the current medical practice. Further insight could also be acquired and open new possibilities such as drug testing and finding out more about the etiology of some pathologies.**

**The baroreflex is a control system with a negative feedback that exists to control the blood pressure values. Control theory and separation of effectors through blocks have been studied in the latest years with the development of some models to assess several observed characteristics [1], [2]. In this thesis, a model using control theory was built for the baroreflex and simulations were run in order to show its proper functioning when a disturbance affects the signal. The intention was to modulate the autonomic nervous system influence in the baroreflex and how this influence is felt and changes the heart rate and arterial pressure. For this, it was necessary to modulate each part of this system to try to achieve a stable and reasonable output signal. The model described is an incremental model which means that only signal variations are accounted (variation of sympathetic and parasympathetic innervation, for example). The tests were carried out by introducing the head-up tilt table test as the disturbance signal in the mean arterial pressure and by checking out how the system answers to this disturbance and watching carefully the evolution of mean arterial pressure (MAP) and heart rate (HR). The model was based in physiological knowledge and introduces some new features to the existing models.**

**The results show the expected behaviour when a blood pressure drop is felt by the baroreceptors and caused by the tilting table. Mean arterial pressure values recover to the initial values in the expected time window while the heart rate does not perform a full recovery because of the increase of the differential pressure in the whole body. The same happens with the cardiac output because it is influenced primarily by the heart rate. By changing parameters one can adjust the model to perform in a different way. The tests carried out all gave results that were the expected ones according to the changes introduced.**

***Index Terms*— Autonomic nervous system, model, baroreflex, baroreceptors, mean arterial pressure, heart rate.**

Correspondent author: José Santos (jlemasantos@ist.utl.pt).

My thanks to Prof. João Sanches, Prof. Luis Silva Carvalho, Prof[a] Adélia Sequeira, Prof[a] Fátima Vaz, to Ana Rita Xavier and Joana Coelho.

Affiliation: Instituto de Sistemas e Robótica and Instituto Superior Técnico, Lisbon, Portugal

## I. Introduction

The discovery of the baroreceptors and chemoreceptors [3], [4] in monkeys opened new doors to gain insight in the control of arterial pressure by the baroreceptors and baroreflex, an important mechanism in maintaining homeostasis. The arterial pressure is not a static variable in the human body. It changes in a glimpse of an eye or even during a whole cardiac cycle. However, the dynamic of this variation and its control is not yet fully understood. The impossibility and complexity of the baroreflex turned into a challenge its modelling. The further understanding and the new discoveries in this field always add knowledge to previous findings. However, the non-linear behaviour and the great number of variables influenced and that influence this mechanism makes it truly difficult to mathematically describe the whole baroreflex. In the last years, several models have been created to further advance in our physiological knowledge.

### *A. Physiology*

The baroreflex is an important homeostatic short-term mechanism to adjust arterial pressure and maintain it in acceptable values, by executing rapid adjustments around a mean arterial pressure (MAP). Although there is evidence of other kind of receptors (such as volume receptors and chemoreceptors) and reflexes (such as cardiopulmonary reflexes and ergoreflexes), the arterial baroreceptors play the major role in the control of blood pressure [5], [6].

Blood pressure (BP) is the pressure exerted in the blood vessels' walls by the blood when pumped by the heart and is considered one of the vital signs. In the aorta and during a cardiac cycle, the pressure has a typical variation between the blood pressure peak when the left ventricle is pumping the blood (systole, with values around 120 mmHg for a typical young adult) and the resting period of the heart (diastole, with blood pressure around 80 mmHg). This pulsatile nature is due to the cardiac output cycles. Small changes happen all the time due to internal or external stimuli [7]. There are several factors that influence blood pressure. The heart rate and the stroke volume have a profound effect on the pressure by acting on blood volume. The other major influence in the blood pressure is given by vascular resistance and blood viscosity. Each of these may in turn be influenced by physiological factors, such as exercise, disease, diet, obesity and excess weight, just to mention a few. Several mechanisms control blood pressure through negative feedback loop systems and make adjustments to the blood volume, heart rate (HR), stroke volume (SV) and vascular resistance [7], [8].

The baroreflex system is one of the most important control systems. From all baroreceptors spread through the human body, the most important are the ones that give rise to the carotid and aortic baroreflexes as shown in Fig. 1, which exert an important part of the total control of the blood pressure [9]. The baroreceptors are specialized autonomic coiled sensory neurons (mechanoreceptors or stretch receptors) that continuously monitor blood pressure, both the steady (or mean) arterial pressure and the rate of pressure change [10]. The active baroreceptors fire action potentials (”spikes”) and the mechanical deformation changes the firing rate of those action potentials. The firing rate, or frequency, increases as the stretching deformation is bigger and decreases if it is lower than the initial set point [11]. All these pathways are a set of motor neurons, constituted by the preganglionic neurons (in the central nervous system) and the postganglionic neurons (in the peripheral nervous system). The preganglionic neuron is completely myelinated, increasing the signal transmission speed, while the postganglionic is unmyelinated, which decreases the speed of transmission. The signal is either excitatory or inhibitory, depending on the cardiovascular center command. The parasympathetic branch is the fastest because parasympathetic postganglionic neurons are shorter than the sympathetic postganglionic neurons and because the terminal ganglia are also located closer to the effector organs. There are also differences between both branches concerning the different neurotransmitters used in both branches.

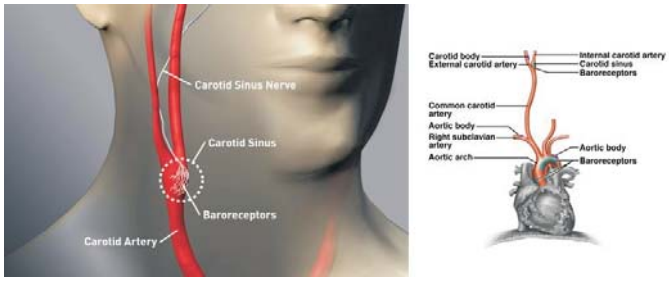


Fig. 1. Location of the two most important baroreceptors in the human body within the blood vessels. In here it is shown the neural ending of the carotid baroreceptor that carries the information to be processed in the cardiovascular center.

The action potentials generated in the baroreceptors are relayed to the nucleus of tractus solitarius (NTS), located in the medulla oblongata, where the cardiovascular center and the medullary rhythmicity center (respiratory center) are located [12]. The frequency of this input action potentials determine the response and actions triggered in the NTS with the signals being carried through two cranial pair of nerves, the glossopharyngeal (IX) and the vagus (X), carrying the parasympathetic innervation signals. Generated action potentials will trigger the inhibition of a different pathway, the thoracolumbar or sympathetic innervation system. The majority of the effectors are under a dual influence although there are cases of innervation by only one of the branches, with the influences being opposite. The increased activation of the NTS triggers a vagal stimulation and a vasomotor inhibition, decreasing the sympathetic branch output. An increased blood pressure then has an active response by the parasympathetic branch and an inactivation of the sympathetic branch, meaning that the response is amplified and maximized by the baroreflex. The mechanisms of regulation for the blood pressure will act mainly on two effectors: the heart and the blood vessels. There are other compensation mechanisms though less important in the control of the blood pressure.

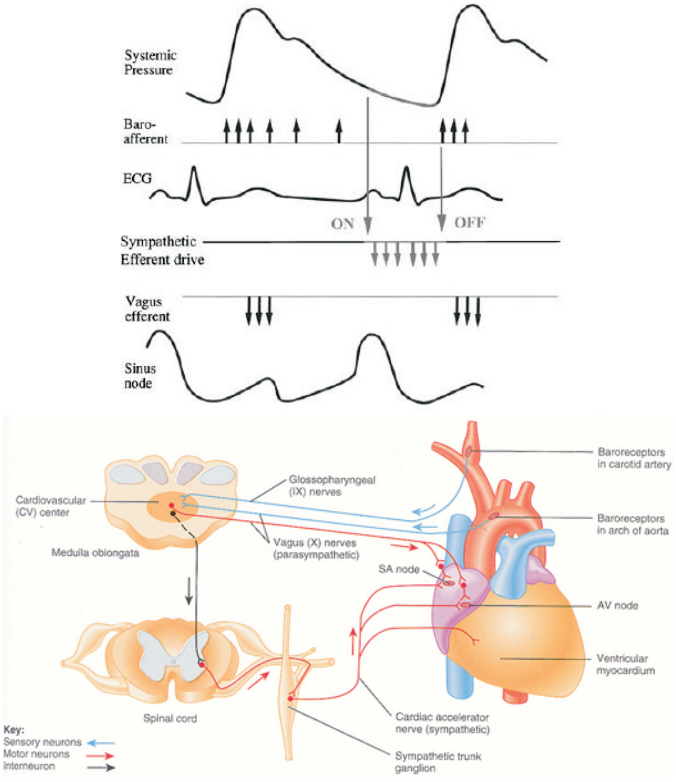


Fig. 2. On the top, functional overview of the baroreflex during a cardiac cycle [13]. With the increase of the systemic pressure, the sympathetic branch is silenced by the stimulation of the parasympathetic branch and the pressure drops. The opposite effect also occurs with the sympathetic stimulation alongside with the pressure drop. Below, schematics of heart innervation by the autonomic nervous system showing also some parts of the baroreflex [7].

The myocardium is composed by specialized muscle cells and pumping is achieved by the spread of action potentials generated by specific cardiac fibers that act as pacemakers. In a physiological condition, the contraction of the heart starts in the sinoatrial node (SA) and propagates by the atriums (causing them to contract) until it reaches a slower pacemakers, the atrioventricular node (AV). Although the sinoatrial node sets a constant heart rate, both parasympathetic and sympathetic branches can influence this in order to make corrections to blood pressure values. While the sympathetic branch accelerates the heart by stimulating the sinoatrial node and the atrioventricular node, the parasympathetic branch does the opposite by slowing the rate of fire in the sinoatrial node (Fig. 2). However and besides the different speed of signal transmission in the neurons, changes introduced by the

parasympathetic branch are more abrupt and stronger than the ones caused by the sympathetic branch (in fact, a strong parasympathetic stimulus can cause bradycardia or even stop the heart) [14]. Still in the heart, sympathetic innervations of myocardial fibers help to regulate and act on stroke volume by increasing or decreasing the heart contractility, respectively. Heart contractility is also influenced by the quantity of blood inside heart chambers, a phenomenon known as the Frank-Starling mechanism. One states that an increase of the volume of blood filling the heart will increase heart contractility by distending more the contracting fibers therefore increasing ventricular preload, in an independent manner regarding neural and hormonal control [15].

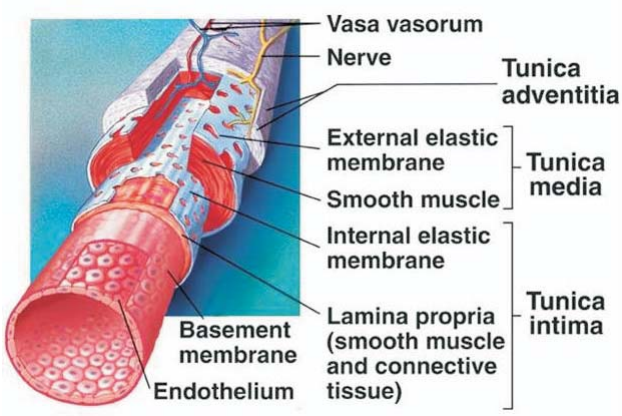


Fig. 3. Structure of a general blood vessel, in this case an artery. Both the external and internal elastic membranes become shorter as the vessels get away from the aorta and closer of the vena cava.

The wall of arteries has three different layers, called tunicas. All the tunicas have elastic layers between each other because arteries receive the major impact of cardiac output and there is the need to accommodate that impact in the blood pressure, preventing a sudden rise [8]. They are consisted by by elastin, collagen and smooth muscle. Elastin and collagen are predominant in vessels near the heart, with the smooth muscle becoming more present as the blood go away through arterioles, capillaries, venules and veins (Fig. 3). Elastin and collagen provide the vessels with elastic properties (especially elastin, which is much more elastic than collagen) while the smooth muscle introduces a viscous component. Mixing all these properties makes the blood vessels a viscoelastic material, with both elastic and viscous properties [16]. The regulatory action exerted on the blood vessels is mostly done by sympathetic innervation of the smooth muscle of the media tunica, which contracts with sympathetic stimuli and reduces the lumen size of the vessels. Parasympathetic action is restricted to some specific vessels, generally located near or in the cerebral cortex. The blood pressure is generally affected by two main variables in the blood vessels: the total peripheral resistance and the venous return. The total peripheral resistance is directly affected by lumen size variation induced by sympathetic activity, that causes vasodilatation or vasoconstriction. The venous return (affected directly by the cardiac output) concerns the blood volume returning to the heart. It is affected by sympathetic innervation of veins which causes the venous return to change by promoting changes on cardiac output according to Frank-Starling law [17].

### *B. Baroreflex modulation*

By using electrical stimulation [18], it was tried the exploration of this closed-loop system in the rabbits, specially the transfer functions from the autonomic nervous system (in this case the sympathetic limb) to the aortic pressure (AOP) and otherwise, to compare it with the estimated open-loop transfer functions. After introducing a carotid sinus pressure (CSP) perturbation, data analysis fitted a second order low pass filter whose parameters did not diverge significantly between open and close-loop analysis. With a very different approach, it was also modelled the peripheral component with a second order low-pass filter [2], even with the modulation of the neural component with a derivative filter followed by a sigmoidal non-linearity or the opposite (Fig. 4). The objective was to test which was the best approximation to the physiological behaviour and reasonable results were achieved. It has also been promoted a different approach (in spite of the same schematics) by analytically determining the functioning point of the baroreflex negative feedback loop to be the intersection of two operational curves [19].

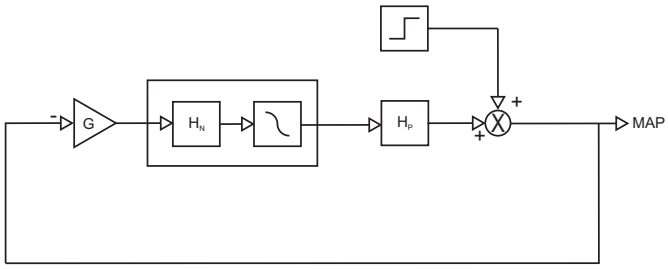


Fig. 4. Model used to simulate the baroreflex system [2]. A step disturbance was introduced and the system response was observed. The neural arc of the baroreflex is followed by a non-linear element, specifically a sigmoidal nonlinearity. The G block represents a constant gain, $H_N$ represents the transfer function of the neural arc and $H_P$ stands for the transfer function of the peripheral arc.

For a different part of the baroreflex, a mathematical model that includes the main features of the baroreceptors was proposed. This model described several equations with different firing frequencies assigned to each specific physiological property [10]. The study of two different models (one with the open loop and one with closed-loop) and the characterisation [20] of the transfer functions from the central and peripheral limbs of the baroreflex was tested when the system suffered a pressure perturbation. A second order low-pass filter was fitted in the peripheral mechanisms (from the sympathetic nerve activity to arterial pressure). On the other hand, a first order low-pass filter with a delay to resemble vasculature, to estimate open-loop gain and to test dynamics [21]. Still, better results seemed to be achieved

with second order models [22]. In the second order model, baroreceptors where represented as a time delay and the central nervous system as proportional and derivative (PD) control system. Based on the model proposed [22] and by introducing small changes like sigmoidal characteristics and both afferent and efferent delays [1], it was concluded that the existence of a non-linearity, within the central nervous system and/or vasculature, was likely to present little better results in the overall model when the comparison with a linear model is made. Further models and descriptions are presented [23], [24] where the baroreflex is modelled to influence the heart rate. Some simplifications to the more complex model were introduced without significant changes in the regulatory response. On the other hand, dynamic characteristics and the transfer function of the carotid sinus baroreflex system in dogs where determined [25] using three different methodologies: single sinusoidal input, Gaussian white-noise input and a sum-of-sinusoidal input.

### *C. Tilt table test*

The human cardiovascular system is well adapted to orthostatic stress when changing from a resting supine position to elevated position [26]. The venous return is extremely affected by the gravity in this situation and normal blood pressure is barely enough to make the blood return to the heart. Blood is shifted to the legs with a decrease of the venous return and accordingly of the stroke volume, which causes a reduction of cardiac output and blood pressure. To account this and besides the inward valves, orthostatic stress is compensated by pumping mechanisms, such as the skeletal muscle pump and respiratory pump.

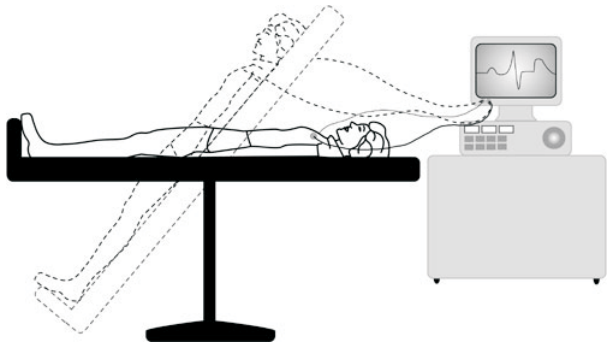

Fig. 5. Schematics of a head-up tilt (HUT) test. The subject lies down in a bed with footrest and the table is continuously tilted until it reaches an angle of about 60-80 degree vertical angle. Electrocardiogram (ECG) and blood pressure are continuously monitored.

The Tilt Table Test is used to determine a cause of syncope (loss of consciousness) [27]. The subject is asked to lie down on a special examining table with safety belts and a footrest. A blood pressure cuff (or similar device) is attached to one of the arms to monitor the blood pressure during the test and an ECG is recorded to monitor the heart rate. After an initial resting period, the table is tilted upright to a 60-80 degree vertical angle for approximately 45 minutes (tilting lasts about 15 seconds). The subjects are instructed to limit leg movements and not to shift their weight during the test in order to perform accurate measures of the blood pressure [28]. After monitoring the blood pressure (both diastolic and systolic), heart rate, stroke volume and cardiac output, their variation is quite common to all subjects [28], [29]. There are some differences, however, related to the perception and anticipation of the movement of the table. With the tilting, there is a marked reduction of the right atrium pressure. The pressure reduction in the right atrium combined with the reduction of venous return significantly reduces stroke volume (thus cardiac output) and blood pressure (especially on systolic pressure). The stroke volume is reduced according to the reduction of the venous return because of the Frank-Starling law [30]. As a result, baroreflex inhibition by the silencing of baroreceptors will result in sympathetic activation and vagal inhibition, which increases the heart rate, the contractility of the heart (thus the stroke volume) and the vascular resistance by vasoconstriction.

## II. Modulation

The baroreflex processes may be described by a canonical feedback control system where the heart and blood vessels are the so called ”plant”, the autonomic nervous system is the controller and the baroreceptores are the sensors. The baroreceptors sense the instantaneous blood pressure and provide their information to the autonomic nervous system that acts on the heart and blood vessels. In this chapter, a mathematical model implemented using MATLAB© Simulink Toolbox is described. This model is incremental, meaning that only physiological parameters variations are modelled (variations to the standard value). Some levels of complexity has been slowly introduced during the time, accomplishing the present model. This means that this model is prepared to answer to variations in the mean arterial pressure and that all the signals and outputs are the result of these variations. The main goal is to build a model that accurately reproduces the most important behaviour aspects of the autonomic nervous system.

The baroreflex is a feedback closed-loop circuit because of the peripheral information of the baroreceptors to the autonomic nervous system. The objective is to prevent great deviations of mean arterial pressure values from a reference pressure (in this case zero because it is an incremental model). A negative feedback loop was considered in order to achieve such functioning. Blocks will be explained one at each time and insight will be gained upon its characteristics. However some mathematical, signal and control considerations must be explained before gaining the insight on all the blocks of the model shown in Fig. 6.

### *A. Mathematical Formulation*

All the blocks considered in the baroreflex model are described by differential equations, besides the non-linear aspects. In order to fully understand the complex functioning of the model, mathematical and signal insight is needed. Only first and second order systems are used in the blocks that constitute the model. The non-linear behavior is achieved by simple product and summation operations. These three types

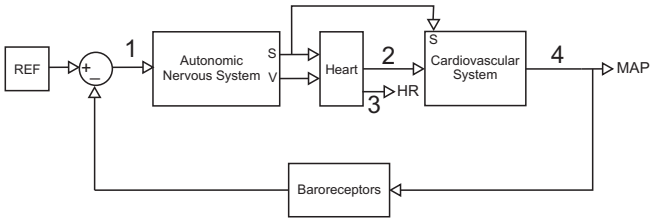


Fig. 6. Schematics of the model built to simulate the baroreflex mechanisms. The main blocks were considered and dimensioned according with the physiological principles previously described. **S-** Sympathetic innervation; **V-** Vagal innervation; **1-** Baroreceptors input; **2-** Cardiac output (CO); **3-** Heart rate (HR); **4-** Mean Arterial Pressure (MAP); **REF-** Reference pressure for the incremental model.

of elemental components have shown to be enough to capture the characteristics of the process involved in the baroreflex. A first order system can be described by the transfer function in the upper part of Fig. 7 (in the Laplace form), where the inverse of T is the cutting frequency of the system. It can be seen the kind of response and the delay time of the block in terms of the location its pole [31], [32]. Slower systems have poles located near the imaginary axis while in faster systems they are located farther. On the other hand, a second order system has a more complex transfer function (lower part of Fig. 7). The poles localization is given by the natural frequency of oscillation $\omega_n$ and the damping coefficient $\xi$. The two distinct real poles system were the one used in the several blocks that constitute the model (over-damped system for $\xi > 1$). Its behaviour is well described in the lower part of Fig. 7. Once again, the closest pole to the imaginary axis is the dominant pole, with the establishing time depending on the distance between the two poles, which means that for a constant $p_1$, the increase of $p_2$ also increases the speed of the system.

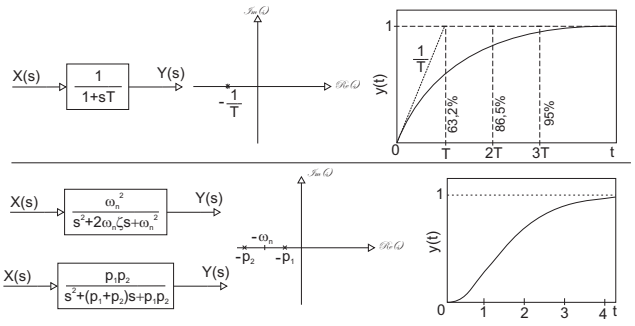


Fig. 7. Schematics of a general first order system (upper transfer function), of the impulse response of a second order system (mid transfer function) and of a second order over-damped system (lower transfer function) [31], [32]. The behaviours of the first order system and the second order system are also described.

The PID block produces a command signal based on an error signal. It consists of a proportional term (P), an integrative term (I) and a derivative term (D). The proportional term maximizes the error and accelerates the convergence of the system to the desired value. The integrative term improves but also increases the instability, especially for higher gains. The system also becomes slower because the establishing time increases (time to reach the final value) and there is a reduction in the sensibility of the system to signal variations. The derivative term is a compensating system that improves the relative stability and increases the speed of the system without affecting the accuracy. This term also anticipates the behaviour of the system by checking not only the error value but also its variation over the time (prediction properties) [33].

The total transfer function would be the ideal way of analysis however the non-linear blocks makes impossible to deal with such analysis. Instead, each block was tested in order to carefully explain and show their functioning even though it is not in a closed loop situation.

### *B. Neural Arc Blocks*

The baroreceptors block and the autonomic nervous system block constitute the neural arc blocks of the model (Fig. 8). The value of T in the baroreceptors was chosen for the system was based on values found on literature for baroreceptors latency [34], [35]. The ANS block input is the inverse baroreceptors efferent signal (negative feedback loop) that enters the PID control block. This block then controls both sympathetic and parasympathetic (vagal) innervation of the peripheral arc (constituted by the heart block and the cardiovascular system block).

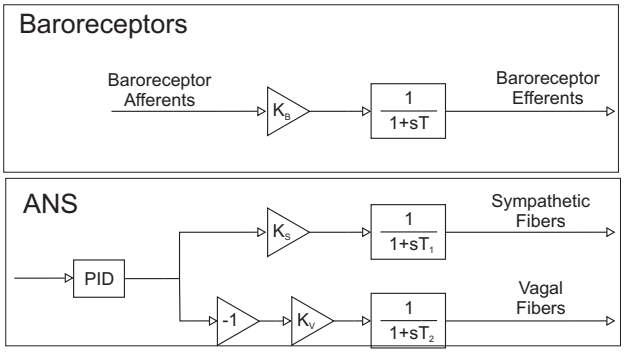


Fig. 8. **Up:** Schematics of the baroreceptors block in the baroreflex model. The mean arterial pressure will enter the first order system with slightly changes cause by the gain KB. This gain can be changed directly. The value of T is 0.25 seconds. **Down:** Schematics of the autonomic nervous system block. The PID controls both the sympathetic and the parasympathetic innervation fibers for the peripheral arc. Both systems are considered here like first order systems with different time constants but similar absolute gains $K_S$ and $K_V$.

The sympathetic branch is inhibited by an increase of the baroreceptors activity, meaning that the negative inversion of the baroreceptors signal fits well (Fig. 6). This behavior is obtained by defining a positive value for the gain $K_S$. The parasympathetic branch activity is increased with the increase of the baroreceptors activity, making it a positive feedback loop. Therefore, the signal was inverted to correspond to a positive loop (the same could be achieved with a negative value for the gain $K_V$). Despite this positive effect, parasympathetic effect in its effectors tends to be negative (slows down the heart rate for example), which turns it into a negative loop also. The time constant $T_1$ for the

sympathetic fibers is considerably bigger than $T_2$ to account for the differences on the conductivity speed by the fibers (myelinated in parasympathetic case and unmyelinated in the sympathetic case, both postganglionic neurons). Tests can be observed in Fig. 8 for both blocks. The parameters where changed in the baroreceptors block. In the ANS block only one test is shown.

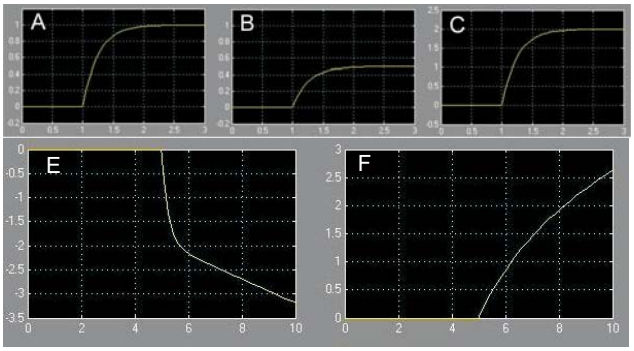


Fig. 9. **Up:** Results obtained from the baroreceptors block when a step signal is used as baroreceptors afferent signal. T=0.25 s; A- $K_B$=1; B- $K_B$=0.5; C- $K_B$=2. **Down:** Simulations run with a step as input signal in the autonomic nervous system block. Here sympathetic and parasympathetic fibers innervation is shown. The used values are: $K_S$=$K_V$=1, $T_1$=2 s, $T_2$=0.25 s, $K_{Proportional}$=2, $K_{Integrative}$=0.25, $K_{Derivative}$=1. E- Parasympathetic fibers; F- Sympathetic fibers.

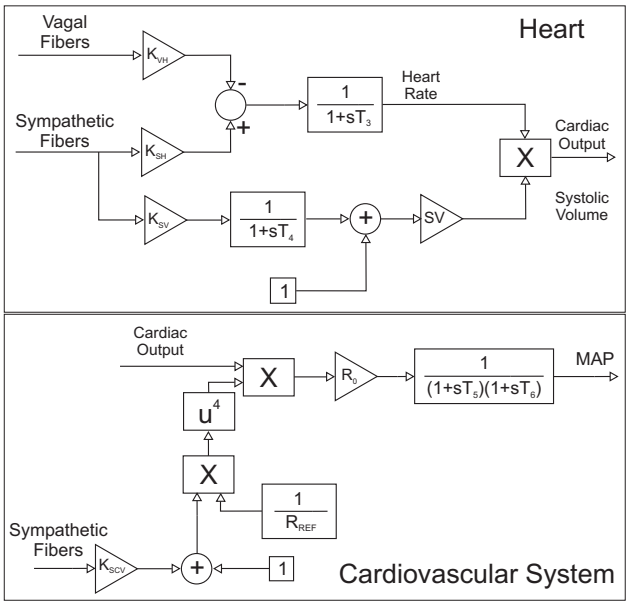


Fig. 10. **Up:** Schematics of the heart block. The parasympathetic influence has the opposite signal of the sympathetic influence, mediated by the gains $K_{VH}$ and $K_{SH}$, respectively. The constant block exhibits the property of a constant systolic volume in the absence of sympathetic innervation. The $K_{SV}$ gain is part of the myocardium fibers mechanism. **Down:** Diagram of the cardiovascular block. Sympathetic fibers change the radius of the vessels with an intensity that is changed by the gain $K_{SCV}$. The parameters of the elastic and viscous properties of the cardiovascular system are modelled by the second order system.

### *C. Peripheral Arc Blocks*

The heart block and the cardiovascular block constitute the peripheral arc of the baroreflex. Sympathetic and parasympathetic fibers coming from the autonomic nervous system innervate the heart. The heart rate and the cardiac output are the physiological parameters measured in the output signal. Parasympathetic innervation affects the heart rate while sympathetic innervation affects both the heart rate (HR) and the systolic volume (CV). The heart block was implemented to give the cardiac output (CO) as the signal output of the block according to equation **1** [7]. The multiplication of the systolic volume by the heart rate was implemented in order to obtain the cardiac output.

$$CO = SV \times HR \tag{1}$$

The block with time constant $T_3$ concerns the sinoatrial node. On the other side, the block with time constant $T_4$ concerns the myocardium fibers (the heart contractility). In the absence of sympathetic innervation, the myocardium exhibits constant properties of contractility thus causing the systolic volume to remain the same. The values for $T_3$ and $T_4$ have to be chosen according with the time of response for both the sinoatrial node and the myocardium fibers.

The cardiovascular system block only suffers the influence of the sympathetic system. This system can be characterised by an elastic component and a viscous component of the blood vessels' walls. The input signal depends on the cardiac output (CO) signal that comes from the heart block. The sympathetic innervation modulates primarily the total peripheral resistance by changing the vascular tonus and the vessels' radius, according to the Hagen-Poiseuille expression **2**.

$$R = \frac{8\mu l}{\pi r^4} \tag{2}$$

In there, $\mu$ is the viscosity of the blood, **l** is the length of the blood vessel, **r** is the vessels' radius and **R** is the resistance. This expression is modelled in Fig. 10 after the sympathetic innervation and according to expression **3**.

$$x = CO \times (\frac{K_{SCV} \times s + 1}{r_{REF}})^4 \approx CO \times R \tag{3}$$

In here, **x** is the block output (so the mean arterial pressure), **s** is the sympathetic signal and $\mathbf{r}_{REF}$ is the reference radius for a defined vessel. The viscosity of the blood and the length of the blood vessel were assumed to be invariant and were incorporated in the gains of the block.

This block has also a non-linear behaviour caused by the sympathetic innervation of the vessels and the changes it causes in the radius. A small radius variation has a quite pronounced variation in MAP as expected. The second order system has a quick response but has also a slow adaptation (viscous part) because two poles were used, with one being quite fast (s=1.5) and one being very slow (s=0.025) to resemble some accommodation that exists in the blood vessels. Again several tests were performed and results are shown in Fig. 11. In the heart, he weighting of both autonomic influences is physiologically different thus the different gains were introduced to account for those differences, with the parasympathetic influence being bigger than the sympathetic

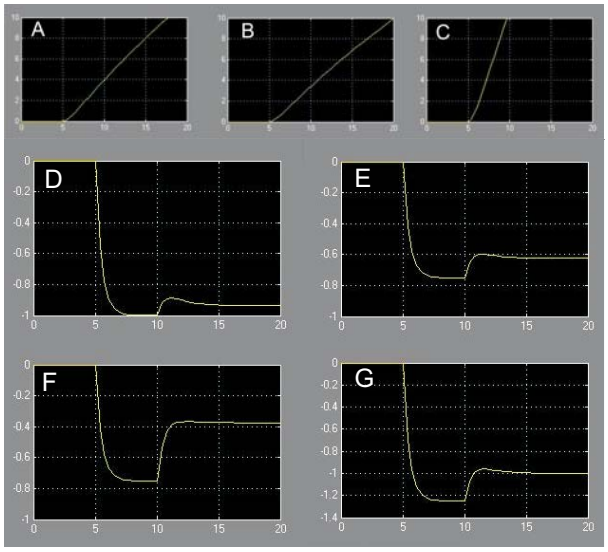


Fig. 11. **Up:** Graphics showing the output of the cardiovascular system block. Values used: $R_0$=40; $R_{REF}$=1; $K_{SCV}$=0.1; $T_5$=1.5 seconds; $T_6$=30 seconds. A - Test with the values stated before; B - Increase of sympathetic influence by increasing the final value of the step input signal; C - Decrease of $R_{REF}$ to a value of 0.75. **Down:** Tests showing the heart block functioning when stimulating signals come from the innervating sympathetic and parasympathetic fibers. Parasympathetic innervation has a more pronounced effect on the heart thus its gain was considered bigger than the sympathetic innervation gain. Values used: $T_3$=0.5 seconds; $T_4$=1 second; SV=0.1; $K_{SV}$=0.005; D - Testing values used: $K_{VH}$=0.2 and $K_{SH}$=0.05; E - $K_{VH}$ value decreased; F - $K_{SH}$ value increased with decreased $K_{VH}$ value; G - $K_{VH}$ increased with increased $K_{SH}$ value.

influence. All the results shown are simulated in an open-loop circuit. The disturbance block that introduces the tilt signal is shown in Fig. 12. To smooth the signal and its variations, a first order system was also used to modulate this signal.

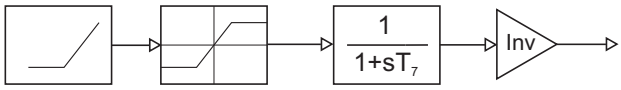


Fig. 12. Schematics of the disturbance block used. The **Inv** block is a constant value block that inverts the signal if needed. The first order system was used to smooth the corners caused by the previous saturation block.

## III. Results & Discussion

In this section the overall model will be tested and subjected to some parameter changes to show it is in agreement with the expected physiological behaviour. Gaussian noise with null mean and small variance will be introduced to simulate the noise of the devices measuring the physiological parameters of interest. A small variation in one parameter can trigger profound changes in the model while some others change only slightly the overall result. The faster conductivity by the parasympathetic fibers when compared with sympathetic fibers is included in $T_1$ and $T_2$, with $T_1$ being significantly bigger than $T_2$. The same happens with the parasympathetic innervation of the heart when compared to sympathetic one, accounted in a bigger value of $K_VH$ when compared with $K_{SH}$. To achieve a stable system, the integrative gain of the PID ($T_{Integrative}$) was kept low. Tilting starts at 15 seconds and lasts another 15 seconds.

Changes in the heart rate and cardiac output can be seen clearly in Fig. 13 when a disturbance is introduced in the mean arterial pressure in a way that reduced MAP. By the baroreflex, a blood pressure reduction triggers compensating mechanisms that increase the heart rate and the cardiac output in order to restore the fall felt by the baroreceptors. A fast recovery of MAP occurs in the first seconds after the initial fall and is followed by a slower recovery until it achieves the initial value of the simulation. The heart rate remains a little increased because of the tilting (an elevated person always have a bigger heart rate when compared to the supine position). This simulation showed the basic functioning of the model. Other simulations can be carried out to test some specific physiological situations, such as removing parasympathetic variations in the innervation, changing the radius of the vessels or introduce small disturbances in some signals (lowering baroreceptors afferents for example) in order to better judge the behaviour of the model.

The decrease of baroreceptors afferent signal decreases the intensity of the signal transmitted to the commanding block (the ANS block), triggering slower changes when compared to a normal signal because the error to the reference is lower. This decreases the negative feedback loop mechanism and reduces the efficiency of the baroreflex. By doing this, parasympathetic and sympathetic innervation variations are not so acute thus the heart rate and the cardiac output signals will not increase as much as they were supposed to compensate the mean arterial pressure drop caused by the tilt. The mean arterial pressure values are also slower in returning to the initial point as shown in Fig. 13 B.

On the other hand, eliminating variations of parasympathetic innervation of the heart has profound consequences

TABLE I
Typical simulation values for the baroreflex model

| Block | Parameters | Values |
|---|---|---|
| Baroreceptors | $K_B$ | 0.2 |
| | T | 0.25 seconds |
| ANS | $K_{Proportional}$ | 5 |
| | $T_{Integrative}$ | 0.15 |
| | $T_{Derivative}$ | 1 |
| | $K_V$ | 1 |
| | $T_1$ | 2 seconds |
| | $T_2$ | 0.25 seconds |
| | T | 0.25 seconds |
| Heart | $K_{VH}$ | 0.2 |
| | $K_{SH}$ | 0.05 |
| | $K_{SV}$ | 0.005 |
| | SV | 0.1 |
| | $T_3$ | 0.5 seconds |
| | $T_4$ | 2.5 seconds |
| CVS System | $R_{REF}$ | 1 |
| | $R_0$ | 75 |
| | $K_{SCV}$ | 0.01 |
| | $T_5$ | 40 seconds |
| | $T_6$ | 0.8 seconds |
| Tilt | $T_7$ | 2 seconds |
| | Slope | 4 |
| | Ramp Limit | -60 |

on its functioning. Both the heart rate and the cardiac output are severely affected by the lack of parasympathetic inhibition when a sudden mean arterial pressure occurs. Sympathetic innervation changes cannot quickly compensate the fall (the system recovers very slowly) and the drop is more abrupt. The heart rate and the cardiac output increase much less when compared to the normal case of variations in parasympathetic innervation, causing the system to drop more the mean arterial pressure signal and to recover more slowly until it reaches the initial values (Fig. 13 C).

A reduction of the reference radius should increase the pressure. In Fig. 13 D, it can be seen a considerable difference in the mean arterial pressure signal, with a not so abrupt fall. A lower radius causes the pressure not to drop so much but also affects the heart rate and cardiac output curves. Both the heart rate and the cardiac output increase with the tilt disturbance but this increase does not reach the previous values, meaning that the radius reduction also helped to compensate the blood pressure drop. The plateau reached by cardiac output and heart rate is also lower when the radius is decreased.

These are just some of the tests that can be carried out. Dozens of different simulations can be run to test the model and by changing the parameters, providing different results.

## IV. Conclusions

The incremental model proposed in this master thesis had a similar behaviour to the baroreflex mechanism and to the raw data used as the basis for the results [36]. The model introduced new concepts like the division of the peripheral arc into two distinct blocks: the heart block and the cardiovascular block. In order to fully characterise the system, the transfer function of the whole system was desirable. However, such an approach was not possible due to the high non-linearity of some of the approximations in the cardiovascular block and in the heart block. Each block was then explained and tests were carried to achieve some insight on how it works, although in an open-loop system (meaning that each block was tested as if it was alone and neither of the others existed). The *Hagen-Poiseuille* law (2) allows the introduction of a radius of interest to any vessel and also the testing of the radius variation. Blood viscosity and the vessel length are changeable in the model parameters of the cardiovascular block. All this factors are directly affected by sympathetic variations in the efferent innervating fibers. The changes carried out in all tests trigger system variations that are consistent to what is physiologically expected, making this model a progress in the modulation of the baroreflex circuit.

### A. Future Work

Although the system behaviour is closer to the raw data presented, some approximations and simplifications were used in the proposed model. In the baroreceptors, heart and ANS, first order systems were used as a first approximation and for the sake of simplicity. A second order over-damped system could be more suitable in both cases. Regarding the cardiovascular system, the second order system is also an approximation. A higher level system could fit in more properly.

The disturbance signal was introduced directly in the mean arterial pressure system, causing it to change in time. Different disturbances can be applied to further improve the system. The development of a tilting table for mice was also started.

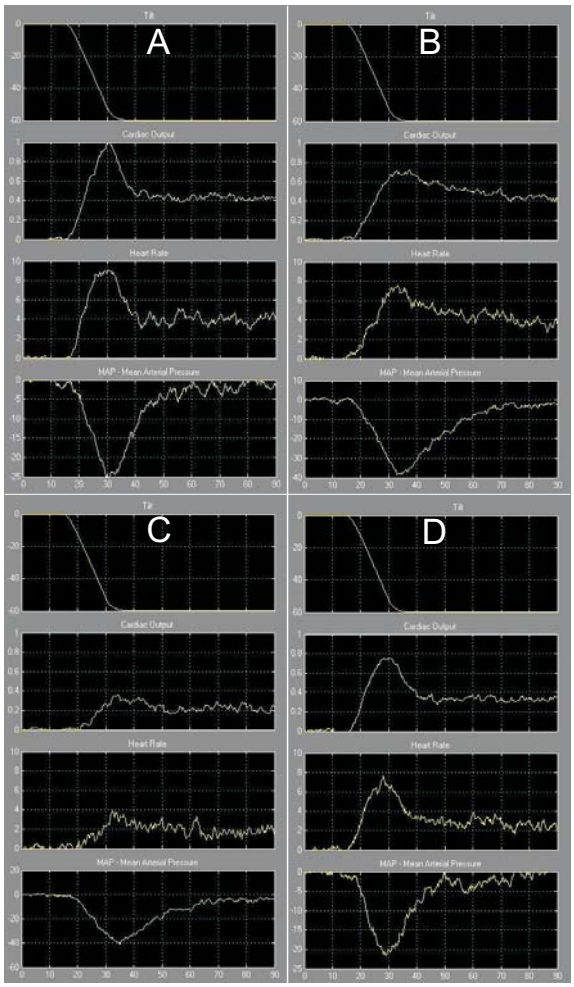


Fig. 13. Results obtained with the model. Gaussian white noise is perfectly observed in all the graphics above. The tilt disturbance remains the same for all cases. **A** - Simulation run with the baroreflex model using the parameters stated in Table I. The introduced disturbance can be seen (Tilt) as well as cardiac output, heart rate and MAP; **B** - Results of decreasing the baroreceptors afferent signal. Changes are evident at all levels, especially in the mean arterial pressure signal with the increase of the drop. The cardiac output and the heart rate also do not increase as much as in **A**. **C** - Results of eliminating changes of the parasympathetic influence on the heart. The removal of parasympathetic variations introduces profound changes in all signals. Changes of about 60% can be seen in the heart rate and the cardiac output when compared to a variable innervated heart block; **D** - Result differences between radius 1 and radius 0.9. Changes can be perceived in all variables according to what was physiologically expected;

## References

[1] J. Ringwood and S. Malpas, "Slow oscillations in blood pressure via a nonlinear feedback model," *American Journal of Physiology*, vol. 280, pp. 1105–1115, 2001.

[2] T. Kawada, Y. Yanagiya, K. Uemura, T. Miyamoto, C. Zheng, M. Li, M. Sugimachi, and K. Sunagawa, "Input-size dependence of the baroreflex neural arc transfer characteristics," *American Journal of Physiology*, vol. 282, pp. 404–415, 2002.

[3] C. Heymans, "Baroceptor and chemoceptor reflexes in monkeys," *Circulation Research*, vol. 6, pp. 567–569, 1958.

[4] C. Heymans and E. Neil, "Reflexogenic areas of the cardiovascular system," 1958.

[5] J. Sanders, D. Ferguson, and A. Mark, "Arterial baroreflex control of sympathetic nerve activity during elevation of blood pressure in normal man: dominance of aortic baroreflexes," *Circulation*, vol. 77, pp. 279–288, 1988.

[6] R. F. J. Shepherd and J. T. Shepherd, "Control of blood pressure and the circulation in man," in *Autonomic Failure*, C. Bannister, Roger; Mathias, Ed. Oxford, UK: Oxford University Press, 2001, pp. 72–75.

[7] G. Tortora and S. R. Grabowski, *Introduction to the human body*. John Wiley, 2001.

[8] S. Sircar, *Principles of Medical Physiology*. Thieme, 2008.

[9] T. Thrasher, "Baroreceptors and the long-term control of blood pressure," *Experimental Physiology*, vol. 89, pp. 331–341, 2004.

[10] T. Itani and E. Koushanpour, "A mathematical model of the arterial baroreceptors." IEEE Engineering in Medicine & Biology Society 11th Annual International Conference, 1989.

[11] "Arterial baroreceptors." [Online]. Available: http://www.cvphysiology.com/Blood%20Pressure/BP012.htm

[12] K. M. Spyer, "Neural organisation and control of the baroreceptor reflex," *Reviews of Physiology, Biochemistry and Pharmacology*, vol. 88, pp. 24–104, 1981.

[13] J. Karemaker and K. Wesseling, "Variability in cardiovascular control: the baroreflex reconsidered," *Cardiovascular Engineering*, vol. 8, pp. 23–29, 2008.

[14] "Regulation of pacemaker activity." [Online]. Available: http://www.cvphysiology.com/Arrhythmias/A005.htm

[15] "Frank-starling mechanism." [Online]. Available: http://www.cvphysiology.com/Cardiac%20Function/CF003.htm

[16] Y. Fung, *Biomechanics - Mechanical properties of living tissues*, 2nd ed. New York, USA: Springer, 1993.

[17] "Venous return." [Online]. Available: http://www.cvphysiology.com/Cardiac%20Function/CF016.htm

[18] T. Kawada, T. Sato, M. Inagaki, T. Shishido, T. Tatewaki, Y. Yanagiya, C. Zheng, M. Sugimachi, and K. Sunagawa, "Closed-loop identification of carotid sinus baroreflex transfer-characteristics using electrical stimulation," *Japanese Journal of Physiology*, vol. 50, pp. 371–380, 2000.

[19] T. Sato, T. Kawada, M. Inagaki, T. Shishido, H. Takaki, M. Sugimachi, and K. Sunagawa, "New analytic framework for understanding sympathetic baroreflex control of arterial pressure," *American Journal of Physiology*, vol. 276, pp. 2251–2261, 1999.

[20] B. Chapuis, E. Vidal-Petiot, V. Oréa, C. Barrès, and C. Julien, "Linear modelling analysis of baroreflex control of arterial pressure variability in rats," *Journal of Physiology*, vol. 559, pp. 639–649, 2004.

[21] R. Burattini, P. Borgdorff, and N. Westerhof, "The baroreflex is counteracted by autoregulation, thereby preventing circulatory instability," *Indian Pacing and Electrophysiology Journal*, vol. 89, pp. 397–405, 2004.

[22] D. Burgess, J. Hundley, S. Li, D. Randall, and D. Brown, "First-order differential-delay equation for the baroreflex predicts the 0.4-hz blood pressure rhythm in rats," *American Journal of Physiology*, vol. 273, pp. 1878–1884, 1997.

[23] M. Ursino and E. Magosso, "Role of short-term cardiovascular regulation in heart period variability: a modeling study," *American Journal of Physiology*, vol. 284, pp. 1479–1493, 2002.

[24] M. Ursino, "Interaction between carotid baroregulation and the pulsating heart: a mathematical model," *Heart and Circulatory Physiology*, vol. 275, pp. 1733–1747, 1998.

[25] T. Kawada, N. Fujiki, and H. Hosomi, "Systems analysis of the carotid sinus baroreflex system using a sum-of-sinusoidal input," *Japanese Journal of Physiology*, vol. 42, pp. 15–34, 1992.

[26] K. Enishi, F. Tajima, H. Akimoto, and R. Mita, "Initial drop of blood pressure during head-up tilt in patients with cerebrovascular accidents," *Environmental Health and Preventive Medicine*, vol. 9, pp. 228–233, 2004.

[27] "Tilt table test." [Online]. Available: http://www.hrspatients.org/patients/heart_tests/tilt_table.asp

[28] G. Barón-Esquivias and A. Martínez-Rubio, "Tilt table test: State of the art," *Indian Pacing and Electrophysiology Journal*, vol. 3, pp. 239–252, 2003.

[29] J. Youde, R. Panerai, C. Gillies, and J. Potter, "Reproducibility of circulatory changes to head-up tilt in healthy elderly subjects," *Age and Ageing*, vol. 32, pp. 375–381, 2003.

[30] V. Saks, P. Dzeja, U. Schlattner, M. Vendelin, A. Terzic, and T. Wallimann, "Cardiac system bioenergetics: metabolic basis of the frank-starling law," *Journal of Physiology*, vol. 571, pp. 253–273, 2006.

[31] A. V. Oppenheim, A. S. Willsky, and S. H. Nawab, *Signals & Systems*, 2nd ed. New Jersey, USA: Prentice Hall, 1997.

[32] I. Lourtie, *Sinais e Sistemas*, 1st ed. Lisboa, Portugal: Escolar Editora, 2002.

[33] E. J. R. Morgado, *Controlo: Texto de apoio*. Lisboa, Portugal: Associação dos Estudantes do Instituto Superior Técnico, 1995.

[34] D. L. Eckberg, "Temporal response patterns of the human sinus," *Journal of Physiology*, vol. 258, pp. 769–782, 1976.

[35] J. Seagard, J. F. M. van Brederode, C. Dean, F. A. Hopp, L. A. Gallenberg, and J. P. Kampine, "Firing characteristics of single-fiber carotid sinus baroreceptors," *Circulation Research*, vol. 66, pp. 1499–1509, 1990.

[36] J. L. Ducla-Soares, M. Santos-Bento, S. Laranjo, A. Andrade, E. Ducla-Soares, J. P. Boto, L. Silva-Carvalho, and I. Rocha, "Wavelet analysis of autonomic outflow of normal subjects on head-up tilt, cold pressor test, valsalva manoeuvre and deep breathing," *Experimental Physiology*, vol. 92, pp. 677–686, 2007.