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A Baroreflex Control Model Using Head-Up Tilt Test

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Abstract

The searching for mathematical models to resemble the baroreflex mechanism is an active field of research because all knowledge as not yet been acquired. The researchers have been trying to decompose and analyse each effector in the whole pathway and insight has been slowly gained. 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 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 shows 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 new possibilities could be opened, such as drug testing and the etiology of some pathologies.

The baroreflex is a negative feedback control system that controls the blood pressure values, meaning that it can be thought as a closed-loop system with multiple blocks representing the major physiological variables. Control theory and effectors separation through blocks have been studied in the latest years with the development of some models to assess several observed characteristics (Ringwood & Malpas, 2001; Kawada, et al., 2002). In this thesis, a model for the baroreflex was built using control theory 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 is an incremental model, meaning that only signal variations are accounted (variation of sympathetic and parasympathetic innervation, for example). The tests were carried out by introducing in the mean arterial pressure the head-up tilt table test as the disturbance signal and by checking out how the system answers to this disturbance and following 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 previous existing models.

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

Keywords: Autonomic nervous system, model, baroreflex, baroreceptors, mean arterial pressure, heart rate.

Resumo

A procura de modelos matemáticos cujo comportamento se assemelhe ao do baroreflexo é um campo activo na pesquisa actual especialmente porque ainda existem mecanismos cujo comportamento é desconhecido. A decomposição do circuito em várias partes e a análise em separado dos órgãos efectores tem sido um método de adquirirem conhecimento de maneira mais consistente. Um dos grandes problemas desde o início prendeu-se com o facto de ser impossível efectuar testes em indivíduos, sendo por isso utilizados animais, o que levou ao incremento da pesquisa de modelos que simulassem o baroreflexo e outros que lhe estão associados. A inexistência de um modelo matemático que apresente um comportamento semelhante e que dê uma explicação válida para alguns dos fenómenos observados é um hiato no conhecimento e seria o método ideal para executar testes em medicina. O avanço no conhecimento e a abertura de novas possibilidades, tais como testes de medicamentos e a pesquisa mais aprofundada da etiologia de algumas patologias, são também possíveis com um modelo.

O baroreflexo é um mecanismo de controlo da pressão arterial com realimentação negativa, que pode ser visto como um circuito fechado com vários blocos a representar as principais variáveis fisiológicas. A teoria de controlo e a separação dos órgãos efectores tem sido bastante estudada nos últimos anos com o desenvolvimento de alguns modelos para estimar características observadas (Ringwood & Malpas, 2001; Kawada, et al., 2002). Nesta dissertação foi desenvolvido um modelo para o baroreflexo usando a teoria de controlo e simulações foram feitas para avaliar o seu funcionamento face a perturbações de sinal. A intenção foi modelar a influência do sistema nervoso autónomo na pressão arterial e ritmo cardíaco com vista a obter um sistema estável e com um sinal de saída coerente. O modelo descrito é um modelo incremental que conta apenas com variações de sinal (variações de enervação do simpático e parasimpático, por exemplo). Os testes foram feitos ao se introduzir um sinal da mesa de *tilt* como perturbação da pressão arterial média e pela verificação das alterações e recuperações da pressão arterial média e ritmo cardíaco. O modelo baseia-se em pressupostos fisiológicos e introduz algum conteúdo inovador relativamente aos modelos já existentes.

Os resultados mostram que o modelo tem o comportamento esperado quando os baroreceptores sentem uma queda da pressão arterial. Os valores da pressão arterial média recuperam o seu valor inicial na janela de tempo esperada enquanto o ritmo cardíaco não recupera totalmente devido ao aumento do diferencial de pressão nas várias partes do corpo. O mesmo acontece para o débito cardíaco devido à influência do ritmo cardíaco. A alteração de parâmetros altera o comportamento do modelo pelo que diferentes testes podem ser executados e dar resultados diferentes de acordo com as mudanças introduzidas.

Palavras-chave: Sistema nervoso autónomo, modelo, baroreflexo, baroreceptores, pressão arterial média, ritmo cardíaco.

Acknowledgements

This master thesis is the result of an intense labour for the past six to seven months. During that time, on a daily basis, the search and review of previous works and papers was hard and enlightened me with some of the past ideas of other researchers. While this research provided useful tools to help focus this work, it also helped me to gain insight on this small but truly important physiological mechanism in our body, one among many others. The basic understanding laid the foundations of the model and then sustained its growing while the time was running. During all the time, I had several people who supported me in many ways.

I would like to thank to my IST tutor, Prof. João Sanches, for all the team efforts, time spent, resources, availability, interest and commitment to this thesis and the work side by side, and to *Institute for Systems and Robotics* for providing resources and a place to work.

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Abbreviations List

ANS – Autonomic Nervous System
AOP – Aortic Pressure
AV - Atrioventricular
BP – Blood Pressure
CTR – Control Period
CO – Cardiac Output
CSP – Carotid Sinus Pressure
CVLM – Caudal Ventrolateral Medulla
CVS – Cardiovascular System
ECG - Electrocardiogram
HR – Heart Rate
HUT – Head-up Tilt
IML – Intermediolateral
IMM – Intermediomedial
MAP – Mean Arterial Pressure
NTS – Nucleus of Tractus Solitarius
PD – Proportional and Derivative
PI – Proportional and Integrative
PID – Proportional, Integrative and Derivative
RVLM – Rostral Ventrolateral Medulla
SA - Sinoatrial
SV – Stroke Volume
SBP – Systolic Blood Pressure
T1-L5 – Thoracic 1 to Lumbar 5 vertebrae
T1-L2 – Thoracic 1 to Lumbar 2 vertebrae
TT – Tilting Table
TA1 – Tilt Adaptation 1

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1. Introduction

The searching for mathematical models to resemble the baroreflex circuit is an active field of research. The discovery of baroreceptors and chemoreceptors (Heymans & Neil, 1958) in monkeys opened new doors to gain insight in the control of arterial pressure by the baroreflex, an important mechanism in maintaining homeostasis. By setting new and improved ways to identify the mechanisms in the baroreflex, the researchers tried to decompose and analyse each effector in the whole pathway. A major problem present since the beginning was the impossibility in carrying tests in human subjects, which lead to the usage of animal subjects like mice, dogs and rabbits. Other simulation models were also built and tested to help further the researchers.

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. Control theory and separation of effectors through blocks have been studied in the latest years in models applied to this research field. The baroreflex is a control system of the blood pressure with a negative feedback loop, meaning that it can be seen as a closed-loop system with multiple blocks representing the major physiological variables. To identify some characteristics of the system, it is necessary to open the loop to gain insight on it. This is easier when looking on simple systems with linear components but it turns out a great problem when non-linear systems and equations are introduced.

The impossibility and complexity of the baroreflex turned its modelling into a challenge. 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 that influence this mechanism make it truly difficult to mathematically describe the whole baroreflex.

1.1. Objectives and Motivation

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 model would be useful in providing further knowledge and in executing some tests on its constituents to know where a provided stimulus or disturbance would affect more the mechanism. It would be a good and practical way of providing more insight into some of the causes and etiology for hypertension or related diseases.

In this thesis, a model for the baroreflex was built and simulations were run in order to show its proper functioning when a disturbance affects the signal. The most important features were included but, for the sake of simplicity, some less important mechanisms were left aside although their missing doesn't affect the essential functioning of the model. The intention was to modulate the autonomic nervous system influence in the baroreflex and to check how this influence is felt and changes the heart rate and arterial pressure.

1.2. State of the Art

In the last years, several models have been created to further advance in our physiological knowledge. By using electrical stimulation (Kawada, et al., 2000), 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 the reverse, to compare it with the estimated open-loop transfer functions. After introducing a carotid sinus pressure (CSP) perturbation, data analysis fitted a second order system whose parameters did not diverge significantly between open and closed-loop analysis for the transfer function from the autonomic nervous system (ANS) to AOP (peripheral component). It was fitted a high-pass filter from the AOP to ANS (neural component), working on the frequency domain. With a very different approach, the peripheral component was also modelled with a second order system (Kawada, et al., 2002) and the neural component was simulated as a derivative filter followed by a sigmoidal non-linearity or the opposite, as seen in Figure 1. The objective was to test which was the best approximation to the physiological behaviour and reasonable results have been 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 (Sato, et al., 1999). They found a good agreement between open-loop operational curves and closed-loop functioning of the system when submitted to several perturbations.

It was proposed a mathematical model that includes the main features of the baroreceptors for a different part of the baroreflex. This model described several equations with different firing frequencies assigned to each specific physiological property (Itani & Koushanpour, 1989).

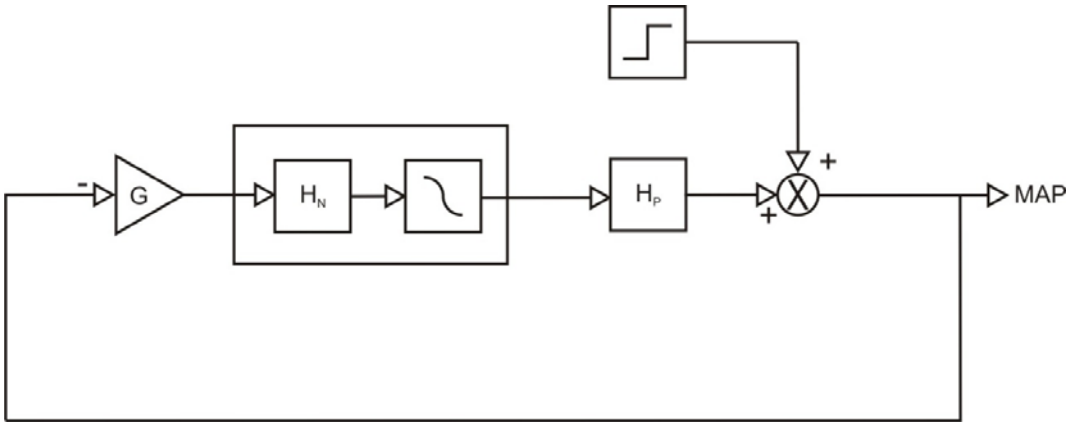


Figure 1: Model used to simulate the baroreflex system (Kawada, et al., 2002). A step disturbance was introduced and the system response was observed. The neural arc of the baroreflex is followed by a non-linear element, specifically a sigmoidal nonlinearity. The G block represents a constant gain, H_N represents the transfer function of the neural arc and H_P stands for the transfer function of the peripheral arc.

The study of two different models (one with the open loop and one with closed-loop) and the characterisation (Chapuis, Vidal-Petiot, Oréa, Barrès, & Julien, 2004) 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 system was fitted in the peripheral mechanisms (from the sympathetic nerve activity to arterial pressure). On the other hand, a combination of a derivative filter with a time delay and a second order system was fitted in the central mechanism of the baroreflex (from the arterial pressure to sympathetic nerve activity, including the baroreceptors). The parameters were found on an animal by animal basis due to the predicted instability of the negative feedback loop.

On the other hand, a first order system was modelled with a delay to resemble vasculature, to estimate open-loop gain and to test dynamics (Burattini, Borgdorff, & Westerhof, 2004). Still, better results seemed to be achieved with second order models (Burgess, Hundley, Li, Randall, & Brown, 1997). 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 (Burgess, Hundley, Li, Randall, & Brown, 1997) and by introducing small changes like sigmoidal characteristics and both afferent and efferent delays (Ringwood & Malpas, 2001), 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 (Figure 2). A common methodology to all models is the exclusive use of sympathetic enervation system.

The baroreceptors have also been studied and mathematical models have been developed based on its characteristics. No attempt was made do distinguish between carotid and aortic baroreceptors. The input is the pressure sensed by the baroreceptors and the output is the resulting firing frequency of the baroreceptors.

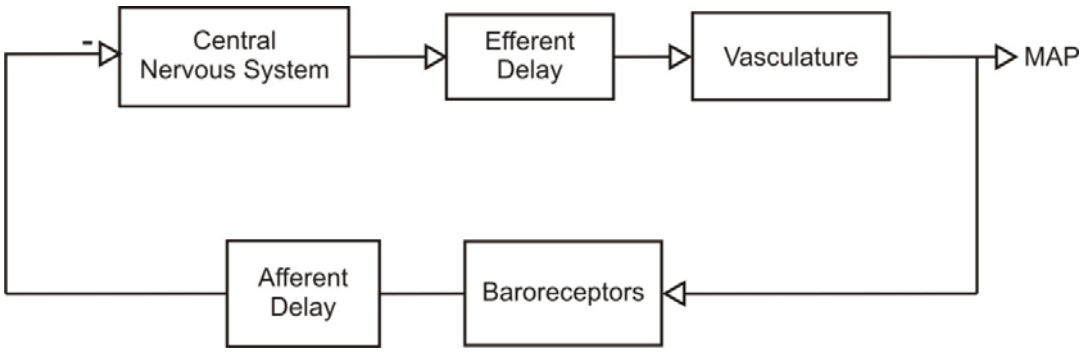


Figure 2: Simulation model used to test non-linear components in the baroreflex (Ringwood & Malpas, 2001). Two possible sources were tested: the central nervous system block and the vasculature block.

Further models and descriptions are presented (Ursino & Magosso, 2002 and Ursino, 1998) where the baroreflex is modelled to influence the heart rate. This models account with the volume stretch receptors presented in the lungs that also influence blood pressure regulation and heart rate. The approximated model was made through a hydraulic analogue of cardiovascular system with several compartments. The objective was to analyse the relationships between pulsatile heart and the carotid baroreflex. Some simplifications to the

more complex model (Ursino, 1998) were introduced without significant changes in the regulatory response (Ursino & Magosso, 2002; Figure 3). On the other hand, dynamic characteristics and the transfer function of the carotid sinus baroreflex system in dogs where determined (Kawada, Fujiki, & Hosomi, 1992) using three different methodologies: single sinusoidal input, Gaussian white-noise input and a sum-of-sinusoidal input.

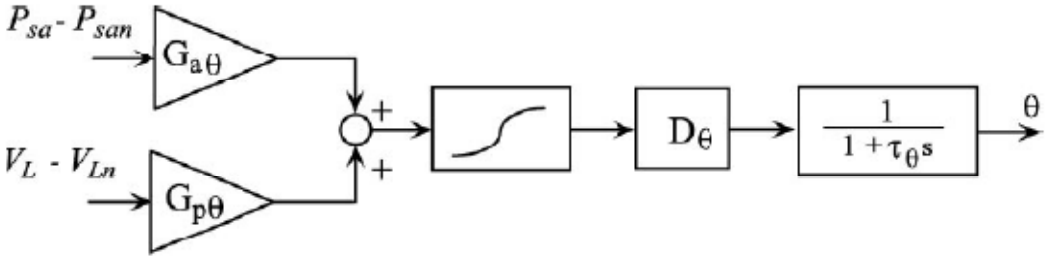


Figure 3: Example of a sympathetic regulation system (Ursino & Magosso, 2002). A general effector is under autonomic nervous system influence with a pure delay, a first-order system and a sigmoidal relationship. Before the summation, arterial baroreceptors and pulmonary stretch receptors input information is received.

1.3. Original Contributions

This approach will introduce some physiological concepts that the previous models have not used. The physiology of the baroreflex is still not fully understood and some simplifications are introduced to this complex mechanism in the explanation. A global model for the baroreflex mechanism is presented where all the major elements are modeled. This model introduces two simultaneous negative feedback loops in the baroreflex, both reflecting the total autonomic innervation: the sympathetic innervation branch and the parasympathetic innervation branch. No mentions to parasympathetic modulation or both sympathetic and parasympathetic were found in the literature. The definition of the parasympathetic autonomic system is also new, just like the usage of an incremental model to the baroreflex.

The division on the peripheral arc of the baroreflex into two blocks is an innovation. Instead of using a block to resemble all the vasculature, two distinct blocks are presented: the one that simulates the heart and the other that simulates the cardiovascular system. Also new is the sympathetic innervation of the heart block to excite or inhibit the myocardium and trigger systolic volume variations, besides the changes caused in the heart rate, triggered by parasympathetic innervation. The same happens in the cardiovascular system but for the vessels' lumen radius variations, which is also an important contribute in the baroreflex to maintain a stable blood pressure. This model has the possibility of withdrawing the autonomic innervation variations in both the systolic volume and the vessel's radius, making them constant through all simulations. The goal was to obtain a simple but accurate model of the physiological processes involved in the baroreflex.

1.4. Thesis Organisation

This thesis is organized as followed: first the physiological basis of the baroreflex and its underlying principles are described and explained with all important details in chapter 2. There, the baroreceptors, the autonomic nervous system, the heart and the cardiovascular system are mentioned. In chapter 3, a mathematical formulation of the blocks and model is done and some mathematical considerations are presented to explain the relevant choices. Further ahead, in chapter 4, the results are shown and its discussion is done side by side with it. Finally in chapters 5 and 6 respectively, the conclusions and farther works are introduced. Literature revision and important background work are in the bibliography at chapter 7.

2. Physiological Background

In this section it will be provided a full description of the physiological mechanisms underlying the baroreflex way of functioning, coupled with the physiological fundaments required to understand the underlying principles of the control system.

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 (Sanders, Ferguson, & Mark, 1988; Shepherd & Shepherd, 2001).

2.1. Blood Pressure

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. Its peak is located in the aorta and pressure is continuously dropping until it reaches the right atrium, where it becomes null. This blood pressure drop is what allows the blood to flow through pressure differences (the bigger the difference, the bigger the blood flow). During a cardiac cycle and in the aorta, 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 (Tortora & Grabowski, 2001). Other variable of interest is the mean arterial pressure, calculated using the systolic and diastolic pressures.

There are several factors that influence blood pressure. The cardiac output is one major factor and is primarily affected by the heart rate and the stroke volume. It acts on blood volume. The increase of heart rate will pump more blood to the blood vessels in a constant window of tim, thus increasing the blood pressure (assuming a constant stroke volume for all cardiac cycles). The same happens with the increase of stroke volume, with a direct increase of the pumped blood. The other major influence in the blood pressure is given by vascular resistance. The vascular resistance is the opposition to the blood flow by the walls of the blood vessels. It is affected by the size of the lumen of the blood vessels, the blood viscosity and the total blood vessels length. An increase in the viscosity of the blood (and thus its thickness) will increase blood pressure by increasing the attrition in the walls of blood vessels, with a slight decrease of flow velocity. The opposing effect occurs with the lumen, with an increase of it decreasing the blood pressure and allowing a bigger flow. A small decrease of a vessel's radius greatly increases the blood pressure. Blood viscosity is also an important factor as it increases the

attrition in the vessels walls, causing the blood flow to be slower and the increase of the blood pressure. The vessels' length also contributes to the vascular resistance. If the length increases, the afterload of the heart (the resistance heart encounters when is pumping the blood) also increases and so does the blood pressure. 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. The adjustments are made to the blood volume, heart rate (HR), stroke volume (SV) and vascular resistance by these systems (Sircar, 2008; Tortora & Grabowski, 2001). These systems, specially the baroreflex system, will be discussed below.

2.2. Baroreceptors

From all baroreceptors spread through the human body, the most important ones are those that give rise to the carotid and aortic baroreflexes (Figure 4). They exert an important part of the total control of the blood pressure (Thrasher, 2004). These two baroreceptors were the ones considered in this model to provide local input to the *autonomic nervous system* (ANS). The carotid sinus is a small dilation located above the bifurcation of the common carotid and inside the internal carotid artery. On the other hand, the aortic sinus is located in the transverse part of the aortic arch, near to the beginning of the left subclavian artery.

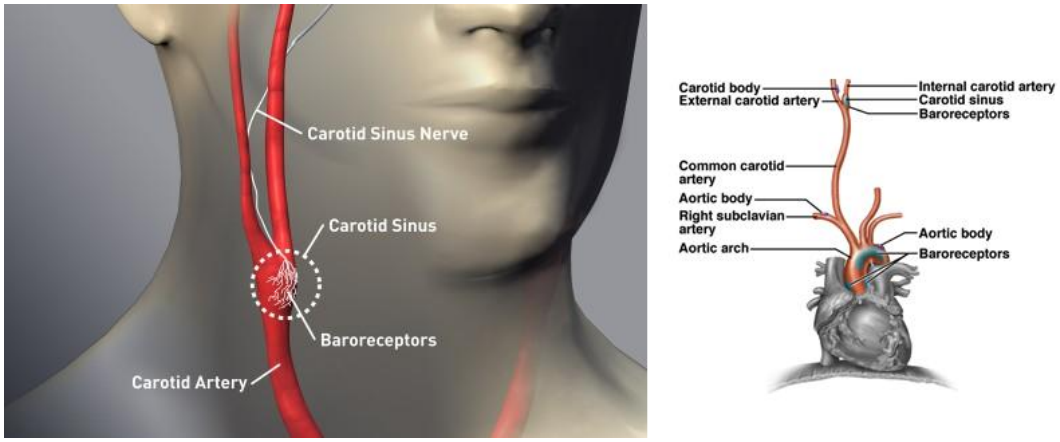


Figure 4: Location of the two most important baroreceptors in the human body within the blood vessels. In here it is shown the neural ending of the carotid baroreceptor that carries the information to be processed in the cardiovascular center.

The 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 (Itani & Koushanpour, 1989). The mechanical deformation according to blood pressure changes is reflected on its output and later those changes are reflected in many physiological variables such as the heart

rate, the heart contractility, the stroke volume, the total systemic resistance and the venous capacitance by the action of the autonomic nervous system, through sympathetic and vagal innervation (Figure 5). The active baroreceptors fire action potentials ("spikes") and the mechanical deformation changes the firing rate of those action potentials (Figure 5). The firing rate (or frequency) increases as the stretching deformation is bigger and decreases if it is lower than the initial set point. The baroreceptors exhibit resetting properties of the set point which were not included in this model (Thrasher, 2004). Other important regulatory mechanisms were not considered in this model, namely the renin-angiotensin-aldosterone system, other hormonal regulation systems (Tortora & Grabowski, 2001) and the respiratory center mechanisms that also introduces changes percepted in the lungs. Used as a pressure sensor by the autonomic nervous system, the baroreceptors are subjected to noisy events introduced by themselves and by the other parts of the baroreflex (Karemaker & Wesseling, 2008).

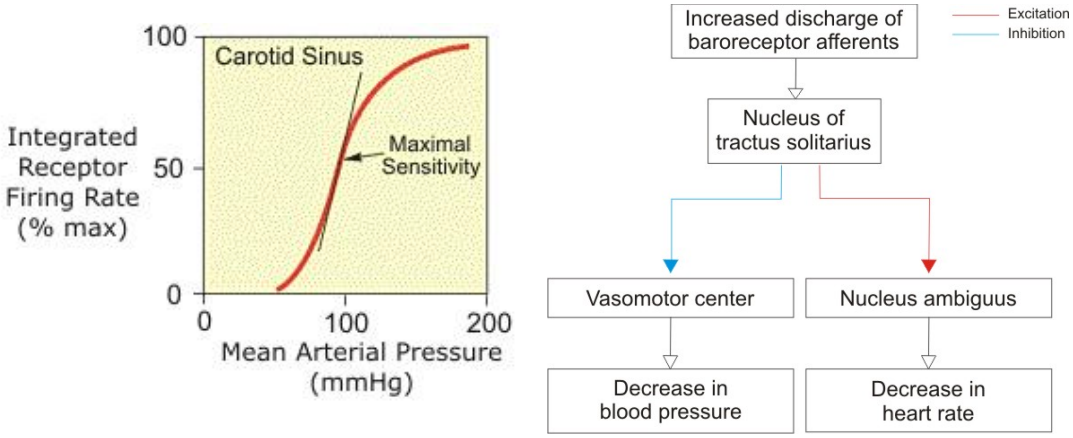


Figure 5: Typical response curve of the baroreceptors to a mean arterial pressure input, in this case the carotid sinus baroreceptor (Klabunde, Arterial Baroreceptors, 2007). This curve exhibits a sigmoidal non-linearity and the maximal sensitivity is achieved around 100 mmHg. The baroreceptors will trigger blood pressure changes by increasing the rate of discharge on the nucleus of tractus solitarius (NTS).

2.3. Autonomic Nervous System

The action potentials generated in the baroreceptors are relayed to the *nucleus of tractus solitarius* (NTS), located in the *medulla oblongata* and where the cardiovascular center and the medullary rhythmicity center (respiratory center) are located (Spyer, 1981). The frequency of this action potentials input determines the response and actions triggered in the NTS. The *medulla oblongata* is part of the brain stem and is located inferior to the brain, being a continuation of the spinal cord (Tortora & Grabowski, 2001). It also receives controlling input from higher brain areas including the limbic system and the cerebral cortex. The signals from the baroreceptors are carried through two cranial pair of nerves, the glossopharyngeal (IX) and the vagus (X) (this last one included in the parasympathetic branch of the autonomic nervous system) to stimulate the cardiovascular center. On the other hand, generated action potentials

will trigger the inhibition of a different pathway, the thoracolumbar or sympathetic branch. The two pathways are somewhat different, both on its constituents and on the kind of fibers used. 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. There are several cardiovascular centers in the autonomic nervous system (Sircar, 2008). The hypothalamic autonomic center controls medullary sympathetic (also vasomotor) and parasympathetic (also nucleus ambiguus) centers through the pressor area (located in the ventral hypothalamus, also called the rostral ventrolateral medulla - RVLM) and the depressor area (located in the anterior hypothalamus, also called caudal ventrolateral medulla - CVLM) (Spyer, 1981). There are also sympathetic control centers, namely the intermediolateral cells (IML) and intermediomedial cells (IMM). IML cells control sympathetic fibers pathways and are inhibited by the IMM cells. The nucleus ambiguus controls the vagal fibers pathways (Figure 6).

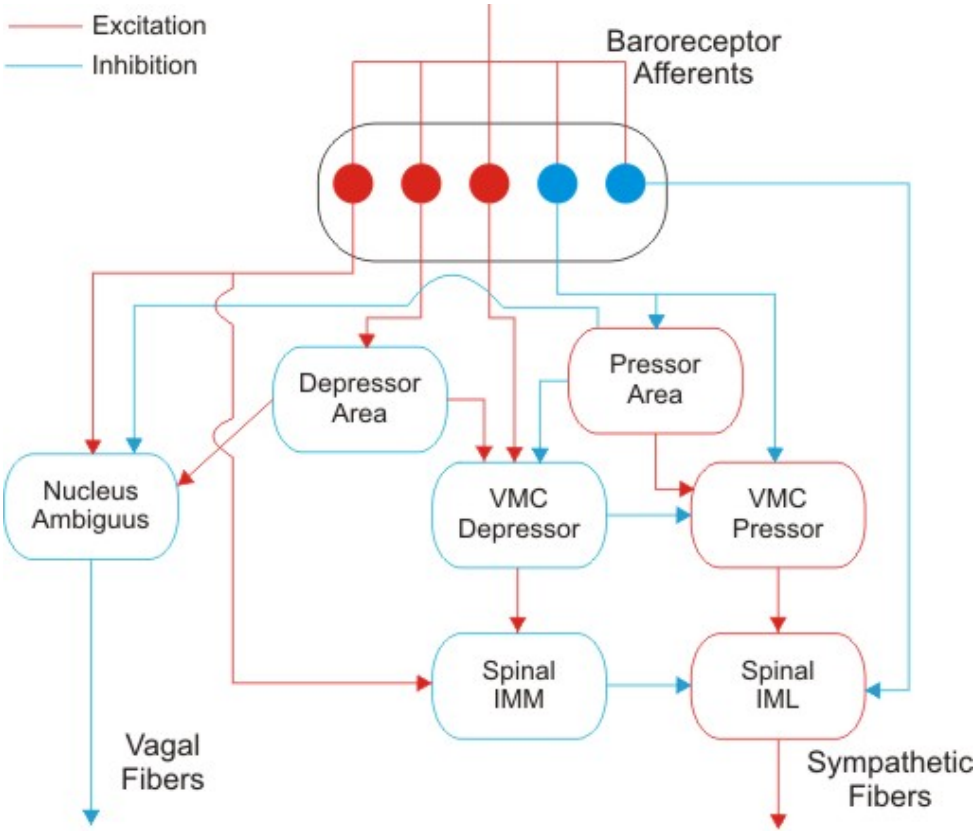


Figure 6: Schematics of the central connections of the baroreceptors afferents and its interconnections (Sircar, 2008). Inhibition and excitation occur at several levels to maximize the effects of the baroreflex.

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), with the synapse between them being made in an autonomic ganglion, which is a set of neuronal cell bodies outside the central nervous system. The preganglionic neurons are completely myelinated, increasing the signal transmission speed, while the postganglionic are

unmyelinated, which decreases the speed of transmission. The postganglionic neuron reaches the effector (an organ or even a small portion of an organ) and either carries an excitatory or inhibitory signal (Figure 7).

The parasympathetic branch is the fastest between the two branches with its cell bodies being located in the glossopharyngeal (IX) and the vagus (X) cranial nerve pairs concerning the blood pressure (additionally they are located also in pair III and pair VII for different homeostatic mechanisms), as referred before. The reason for being faster is because the parasympathetic postganglionic neurons are shorter than the sympathetic postganglionic neurons. Additionally, the parasympathetic ganglia, the terminal ganglia, are also located closer to the effector organs when compared to the sympathetic ganglia, thus boosting the parasympathetic signal. The sympathetic ganglia are located closer to the spinal cord, causing the preganglionic neurons to be short (this concerning the sympathetic trunk ganglia, the only one of interest for blood pressure). A particular characteristic of the sympathetic branch is the possible four paths that can be taken by a signal in the sympathetic trunk ganglia. This subject will not be discussed nor accounted during the whole model. The sympathetic branch of the autonomic nervous system uses the thoracic and lumbar segments of the spinal cord while the parasympathetic branch uses the craniosacral segments (Figure 8). Heart sympathetic innervation fibers originate in spinal segments T1-L5 and blood vessels innervating fibers originate from T1-L2 and are responsible for the continuous discharge that preserves the tonic vasoconstriction (Spyer, 1981). Parasympathetic heart innervation originates in the nucleus ambiguus (location of departure of preganglionic parasympathetic neurons, posterior to the inferior olivary nucleus in the lateral portion of the rostral medulla) and has two main effectors: the sinoatrial node for right vagus and the atrioventricular node for the left vagus (Sircar, 2008).

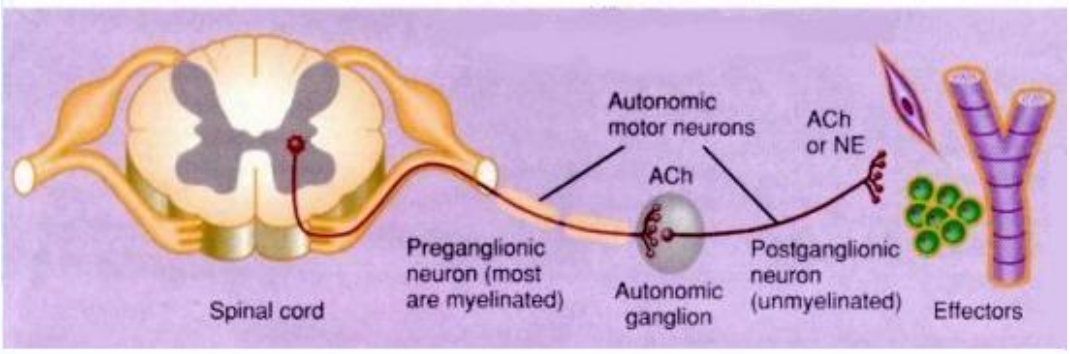


Figure 7: Structure of an autonomic motor neuron and its pathway until it reaches a general effector. It can be seen that the preganglionic neuron is myelinated (in general) while the postganglionic neuron is unmyelinated (Tortora & Grabowski, 2001).

Another difference between both branches concerns the different neurotransmitters used. The parasympathetic branch has cholinergic neurons (the neurotransmitter is acetylcholine) in both preganglionic and postganglionic neurons, causing the effects to be short-lived and very precise. The same happens with sympathetic preganglionic neurons. However,

most sympathetic postganglionic neurons are adrenergic (the neurotransmitter is norepinephrine), which results in a slower activation (as explained above) but also causes the effect to last longer because norepinephrine inactivation is a slow process within the human body.

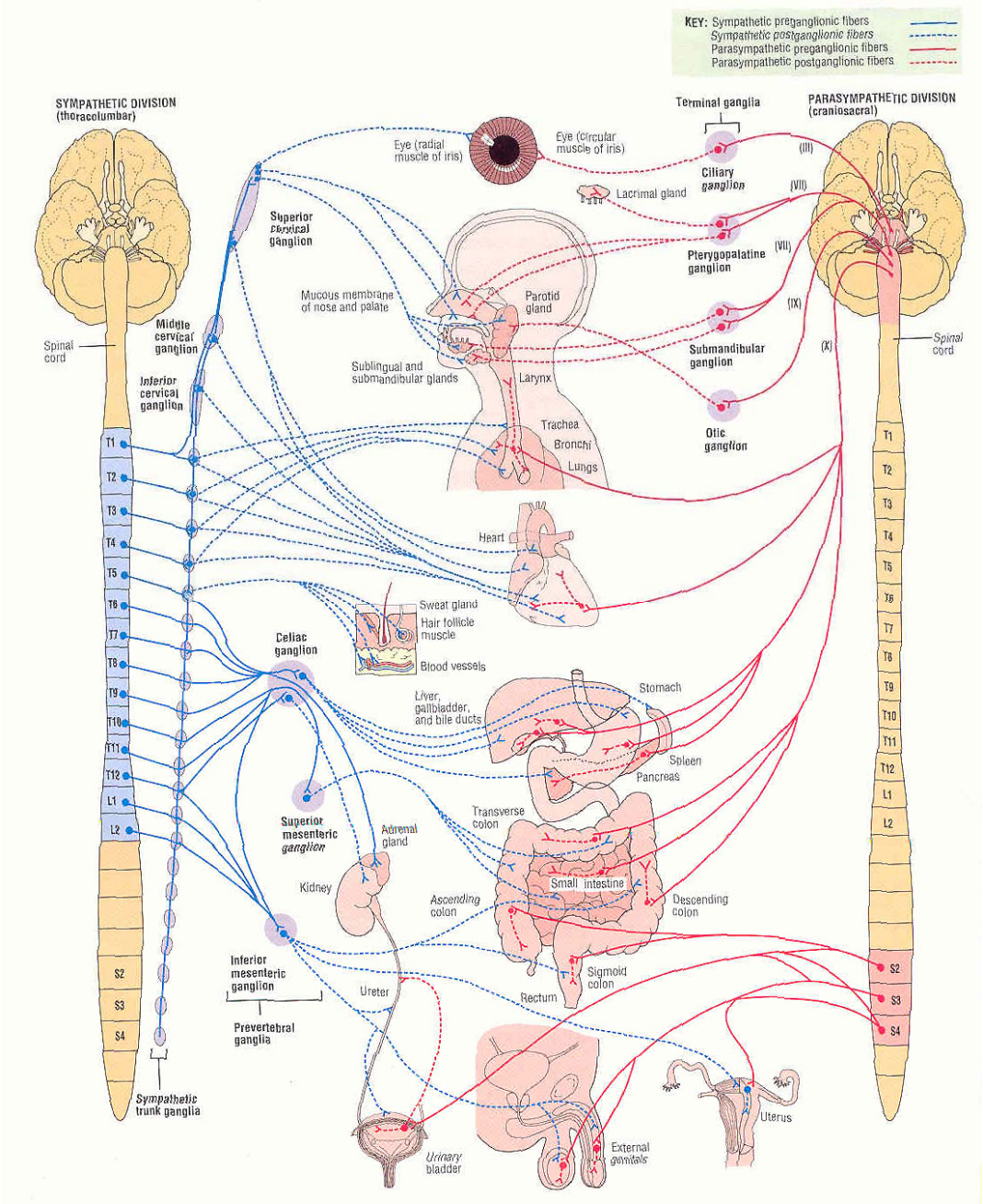


Figure 8: Autonomic nervous system schematics from sympathetic and parasympathetic branches (Tortora & Grabowski, 2001). It can be seen the dual innervation for the majority of organs and the longer sympathetic postganglionic neurons when compared with the parasympathetic branch.

The increased activation of the NTS triggers a vagal stimulation and a vasomotor inhibition, decreasing the sympathetic branch output. A blood pressure increase therefore

produces 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 resulting physiological changes can be stated by monitoring the blood pressure and watch it to start decreasing little after the baroreceptors were activated. 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 that will not be accounted and discussed because they will not take part in this model.

2.4. Heart

The heart is a muscular organ responsible for pumping the blood through the blood vessels by repeated contractions. 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. The fibers connect themselves through *intercalated discs* that make them hold together. These discs also allow the action potentials to quickly spread through all muscle fibers. In a physiological condition, the contraction signal starts in the sinoatrial node (SA) and propagates through the atriums (causing them to contract) until it reaches a slower pacemaker, the atrioventricular node (AV). The AV node slows down the conduction in order to allow the atriums to empty themselves and to complete the filling of the ventricles. After passing the atrioventricular node, the action potentials enter the atrioventricular bundle (or bundle of His) and trigger ventricles contraction.

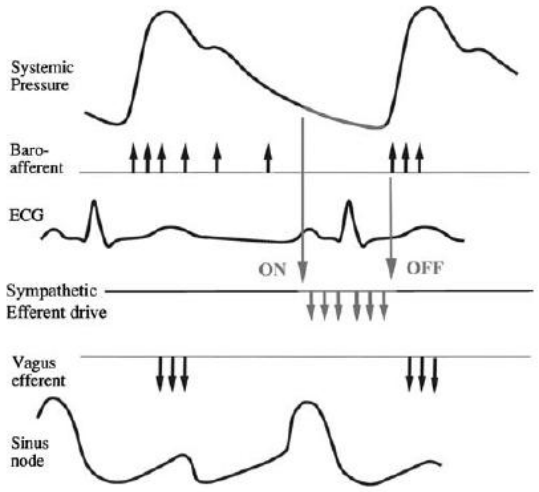


Figure 9: Functional overview of the baroreflex during a cardiac cycle (Karemaker & Wesseling, 2008). With the increase of the systemic pressure, the sympathetic branch is silenced by the stimulation of the parasympathetic branch and the pressure drops. The opposite effect also occurs with the sympathetic stimulation alongside with the pressure drop.

Although the sinoatrial node sets a constant heart rate of about 90 to 100 beats/min, both parasympathetic and sympathetic branches can influence this rate 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. 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) (Klabunde, Regulation of Pacemaker Activity, 2007; André Ng, Brack, & Coote, 2001). 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. This action increases the force of muscle contraction by releasing certain substances, such as epinephrine and norepinephrine. The coupling of both branches and all its effects quickly directs the blood pressure values to homeostasis (Figure 10). 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 (Klabunde, Frank-Starling Mechanism, 2007).

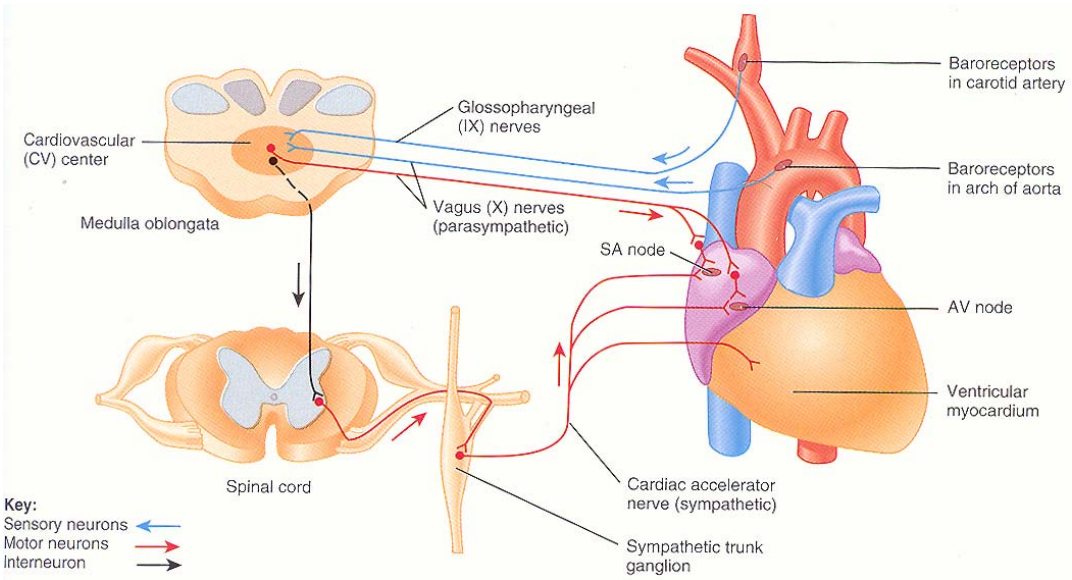


Figure 10: Schematics of heart innervation by the autonomic nervous system (Tortora & Grabowski, 2001) showing also some parts of the baroreflex. The preganglionic and postganglionic fibers can be seen both in parasympathetic and sympathetic innervation of the heart. The interneurons come from the cardiovascular center through the spinal cord until it reaches an effector, inhibiting or exciting the sympathetic preganglionic neurons. Parasympathetic ganglia are not shown because of the proximity to the effector organ.

2.5. Blood vessels

There are five main different types of vessels: arteries, arterioles, capillaries, venules and veins. The wall of arteries has three different layers, called tunicas: the intima, the media and adventitia. 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 from it (Sircar, 2008). The tunica media includes an important layer of smooth muscle tissue (Figure 11). With the increasing distance to the heart, the elastic layer gets short and the muscle fibers increase. Arterioles are the resistance vessels, having almost no elastic fibers. To have an almost continuous blood flow thought the capillaries, the biggest pressure drop occurs in these vessels, eliminating the pulsatile component. Capillaries have small walls so diffusion of O_2 and nutrients can occur easily to the underlying cells. Venules are small vessels and their structure is similar to the capillaries structure. Veins are important blood reservoirs, easily distensible and with an excellent capacitance. Their structure is very similar to the structure of arteries and they are mainly constituted by smooth muscle. They also contain important inward valves that prevent blood backflow in orthostatic stress situations.

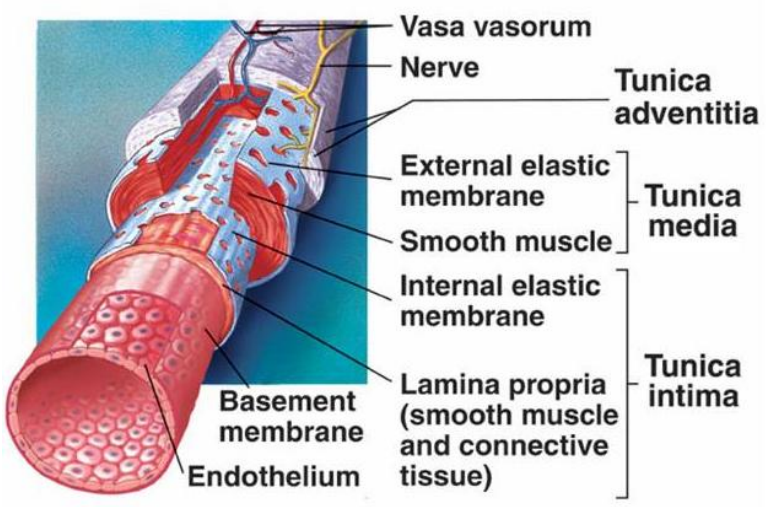


Figure 11: Structure of a general blood vessel, in this case an artery. Both the external and internal elastic membranes become shorter as the vessels get away from the aorta and closer of the vena cava.

The walls of arteries are constituted mainly 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. 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. The expansion that occurs when the blood flows through a vessel gives rise to hysteresis with different expansion and deformation curves, causing the blood vessels

not to obey Hooke's law (Fung, 1993). The blood flow is pulsatile in the arteries and becomes almost continuous in arterioles due to the increasing resistance and the need to supply the destination cells. However, the viscoelasticity of the walls turns the pulsatile flow into one that is almost continuous. The veins have an important property that causes them to present lower resistance to the blood flow: they do not have a circular shape when the transmural pressure (pressure across the wall of a cardiac chamber or a blood vessel) is low. Instead, they have an ellipsoidal shape, which causes them to increase the resistance to the blood flow. The transmural pressure is the primary way of controlling the blood pressure in these capacitance vessels.

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. Myelinated and unmyelinated nerves are contained in tunica adventitia. Parasympathetic action is restricted to some specific vessels, generally located near or in the cerebral cortex. The total peripheral resistance is generally affected by two main variables in the blood vessels. The lumen variation (vasoconstriction) is one of those variables and is directly affected sympathetic activity, that causes vasodilatation or vasoconstriction whether the blood pressure increases or decreases, respectively. The venous return (affected directly by the cardiac output) is the second physiological variable to change and it 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 (Klabunde, Venous Return, 2007). The gravity also strongly affects it by decreasing the right atrium pressure and arterial pressure. This decrease on venous return is counteracted by venous valves and by muscular rhythmical contraction of lower limbs that pumps the blood to the vena cavas. Other mechanisms such as respiration also influence the venous return but such an approach is not the objective of this work. The entire cardiac output depends on the stroke volume (influenced by the heart contractility as explained in **2.4**) and the heart rate. Because of the pulsatile variation of the cardiac output alongside with the cardiac cycle, the cardiac output is generally given as the mean blood volume pumped by the ventricle in a minute.

2.6. Head-up tilt test

The human cardiovascular system is well adapted to orthostatic stress when changing from a resting supine position to elevated position (Enishi, Tajima, Akimoto, & Mita, 2004). 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, decreasing venous return and accordingly 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. These mechanisms cause the blood pressure to rise and help to restore homeostasis and venous return alongside with the baroreflex mechanisms.

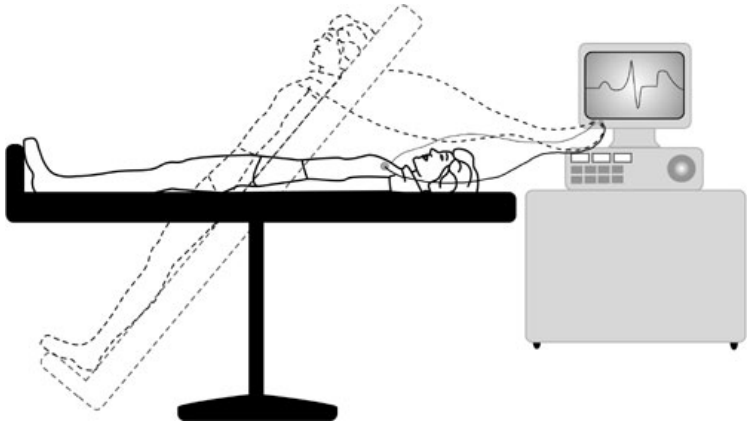


Figure 12: Schematics of a head-up tilt (HUT) test. The subject lies down in a bed with footrest and the table is continuously tilted until it reaches an angle of about 60-80 degree vertical angle. Electrocardiogram (ECG) and blood pressure are continuously monitored.

The Tilt Table Test is used to determine a cause of syncope (loss of consciousness). For some people it is related to an abnormal nervous system reflex causing the heart to slow and the blood vessels to dilate, lowering the blood pressure. When this happens there is a reduced amount of blood to the brain after introducing the orthostatic stress, causing one to faint. This type of syncope is called vasovagal, neurocardiogenic or abnormal vasoregulatory syncope and is considered benign (not dangerous or life-threatening). This is performed while the subject is being closely monitored (Tilt Table Test, Online).

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 (Figure 12). They are also asked to describe any symptoms experienced during the test. If a faint occurs, the table will be returned to a horizontal position and monitoring continues until full recovery, which is usually immediate (Barón-Esquivias & Martínez-Rubio, 2003).

Tilting table test results are relatively well known and intensively used for some clinical diagnosis (usually to assess vagal syncope). After monitoring the blood pressure (both diastolic and systolic), heart rate, stroke volume and cardiac output, their variation is quite common to all subjects (Barón-Esquivias & Martínez-Rubio, 2003; Youde, Panerai, Gillies, & Potter, 2003). 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 as the blood starts to flow and accumulate more in the legs with the increase of gravity, reducing venous return. One would expect that the drop of pressure in atriums combined with

the increased pressure in the legs would increase blood flow. However, 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 of systolic pressure). The stroke volume is reduced according to the reduction of the venous return because of the Frank-Starling law (Saks, Dzeja, Schlattner, Vendelin, Terzic, & Wallimann, 2006). Therefore, in fact, there is a decrease of systemic blood pressure in a more pronounced way than the increase caused by gravity which explains the poorer venous return. 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 (Figure 13). After a few minutes, blood pressure and cardiac output values return to the levels of supine position, with a small maintained increase of heart rate (caused by the delayed sympathetic stimulation) and of the vascular resistance (Petersen, Williams, Gordon, Chamberlain-Webber, & Sutton, 2000).

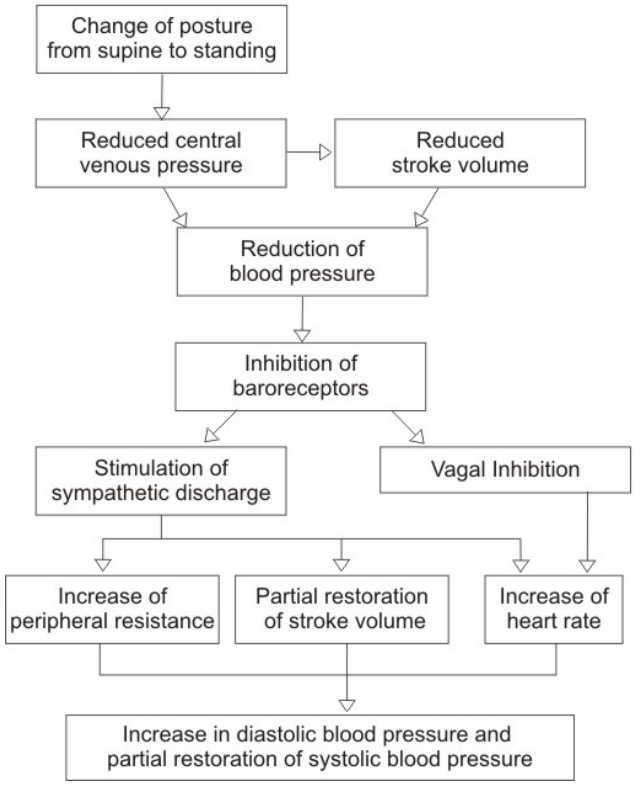


Figure 13: Diagram showing changing conditions while performing the head-up tilt test and elevation from supine position (Sircar, 2008). The position changing from supine to standing elicits an autonomic nervous system response to restore homeostasis.

3. Model Description

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 (Figure 15). The baroreceptors sense the instantaneous blood pressure and provide their information to the autonomic nervous system that acts on the heart and blood vessels (Figure 14).

In this chapter, a mathematical model implemented using MATLAB© *Simulink* Toolbox is described. The dynamics of the mean arterial pressure (MAP) is obtained by interconnecting the main components involved in the baroreflex. This model is incremental, meaning that only physiological parameters variations are modelled (variations to the standard value). In its first versions, the model had simple concepts and some innervation fibers were absent. Then, some complexity has been slowly introduced, 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 was to build a model that accurately reproduced the most important behaviour aspects of the autonomic nervous system in order to predict and explain some of the most important pathologies, like hypertension.

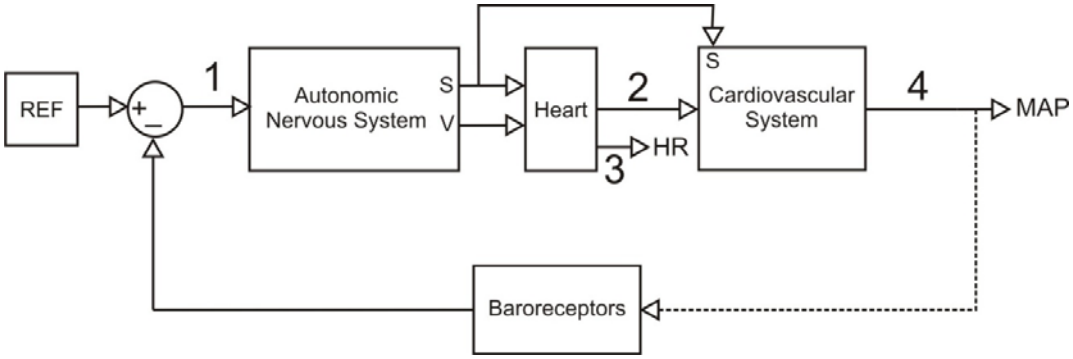


Figure 14: Schematics of the model built to simulate the baroreflex mechanisms. The main blocks were considered and dimensioned according with the physiological principles previously described. **S-** Sympathetic innervation; **V-** Vagal innervation; **1-** Baroreceptors input; **2-** Cardiac output (CO); **3-** Heart rate (HR); **4-** Mean Arterial Pressure (MAP); **REF-** Reference pressure for the incremental model.

The baroreflex is a feedback closed-loop circuit because of the peripheral information of the baroreceptors to the autonomic nervous system. As explained in **2.2** and **2.3**, this input signal will trigger changes in sympathetic and parasympathetic innervation (this last mainly through the vagus pair of cranial nerves) that will modify the functioning of the heart and the mechanical properties of the cardiovascular 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. Parasympathetic influence in the cardiovascular system is narrowed to certain vessels and its importance is not comparable with sympathetic innervation, hence sympathetic

one is the only considered. 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. In Figure 15, a general control system is presented. The output signal is measured by the sensors that trigger changes on the plant by activating the controller that changes it to approximate it with the input signal. This scheme is the basic form of any control model and was the basis for the baroreflex model described here.

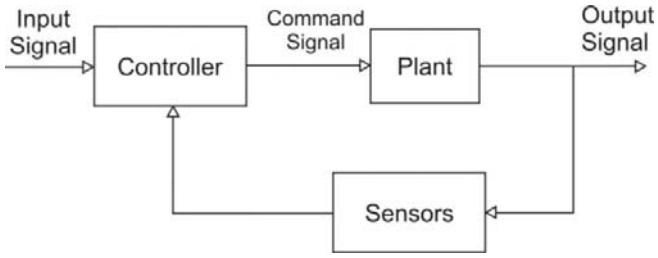


Figure 15: Schematics of a general control system with a feedback loop to the controller providing the necessary information to make both the input and output signals the same.

3.1. Mathematical and Signal considerations

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 of elemental components have shown to be enough to capture the characteristics of the process involved in the baroreflex. Gaining insight on the blocks and also on a PID (proportional, integrative and derivate) control block is needed to successfully understand the model.

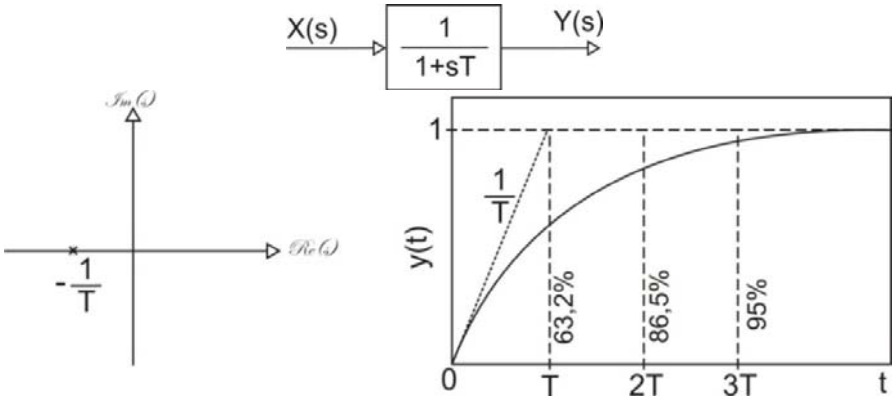


Figure 16: Schematics of a general first order system, with the input signal X(s) and the output signal Y(s) (Lourtie, 2002). The poles/zeros map is also presented to show the location of the pole and zeros (in this case there is only a pole for s=-1/T) in the real axis (s-plane). At last, the block response to a step is shown with a delay given by the location of the pole.

A first order system can be described by the transfer function in Figure 16 (in the Laplace form), where the inverse of T is the cutting frequency of the system. It can also be seen the kind of response and the delay time of the block in terms of the location its pole (Figure 16). Slower systems have poles located near the imaginary axis while in faster systems they are located farther. The step response of this kind of systems reaches 95% of the final value in a time that is 3 times the location of the pole in the real axis. It is important to have all the poles on the left-hand side of the s-plane to have a causal and stable system (Lourtie, 2002; Oppenheim, Willsky, & Nawab, 1997).

On the other hand, a second order system has a more complex transfer function (Figure 17). The poles localization is given by the natural frequency of oscillation (ω_n) and the damping coefficient (ξ). Depending on the value taken by the damping coefficient, the system has different behaviours:

- $\xi<1$: under-damped system (complex conjugated poles);
- $\xi=1$: critically damped system (double real pole);
- $\xi>1$: over-damped system (two distinct real poles);

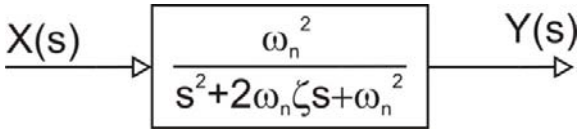
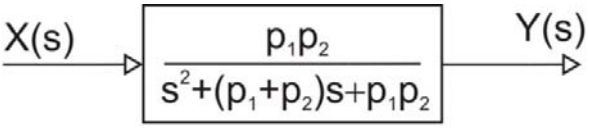


Figure 17: Typical impulse response of a second order system (two poles and without zeros). ω_n stands for the natural frequency and ξ for the damping coefficient (Lourtie, 2002; Oppenheim, Willsky, & Nawab, 1997).



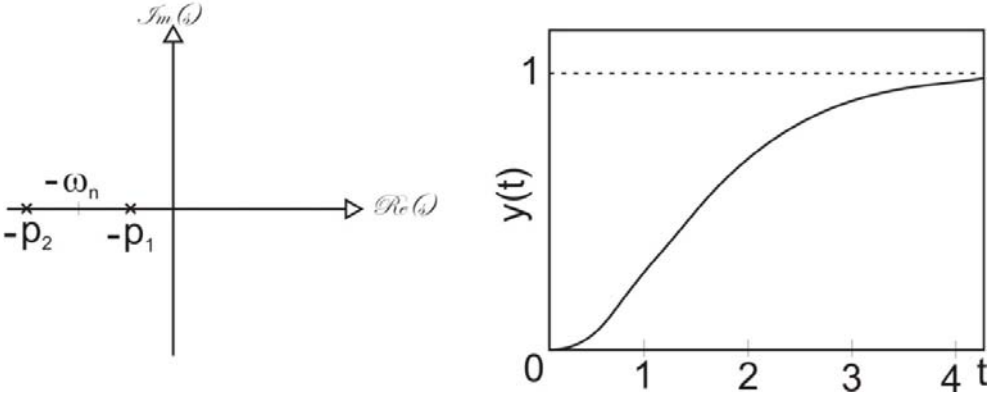


Figure 18: Second order over-damped system. The poles/zeros map is presented to show the location of the pole and zeros (in this case there two poles for $s=-p_1$ and $s=-p_2$) in the real axis. On the right side, the block response to a step input signal is shown (Lourtie, 2002), with its quickness depending on the poles location on the poles/zeros map.

Despite the fact of the different behaviours, the two distinct real poles system was the one used in the several blocks that constitute the model. The two poles are located near - ω_n, one on the left side and the other on the right side (Figure 18) and they do not introduce oscillation in the response to an input signal because the poles are both real. 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 (Oppenheim, Willsky, & Nawab, 1997).

The PID block produces a command signal based on an error signal. It consists of a proportional term (P), an integrative term and a derivative term (Figure 19). The proportional term amplifies or reduces the error signal in order to maximize it and accelerate the convergence to the desired value. The integrative and derivative terms each have unique properties that make them suitable to be used in this baroreflex model. The integrative term introduces a pole in the origin (for s=0) which improves the accuracy of the system 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. On the other hand, the derivative term is a compensating system that improves the relative stability and increases the speed of the system by introducing a zero in the origin (for s=0) without affecting the accuracy. The biggest problem is the increase of high frequency noise in the system. 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). The variation over the time analysis also speeds up the system to reach the final value. The adjustment of the several parameters is needed to obtain a better accuracy and relative stability (Morgado, 1995).

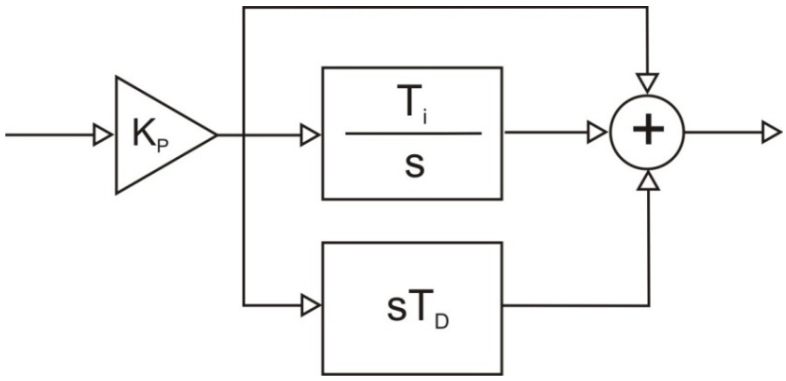


Figure 19: Diagram of the blocks that constitute the PID controller. The gain K_P stands for the proportional gain while T_i stands for the integrative controller and T_D for the derivative one. The three signals are summed at the end of the block.

The developed model is very complex and has some non-linear blocks. 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. After it, the whole system simulations will be seen with small tests being carried out, in chapter **4**.

3.2. Baroreceptors Block

The baroreceptors block constitutes the first part of the neural pathway of the baroreflex. The signal input is the mean arterial pressure and this signal will suffer the action of a first order system preceded by a gain (Figure 20). This system represents the conversion of the pressure in spike rates performed by the baroreceptors, depending on the intensity of the mean arterial pressure. The value of T chosen for the system was based on values found on literature for baroreceptors latency (Eckberg, 1976; Seagard, Brederode, Dean, Hopp, Gallenberg, & Kampine, 1990).

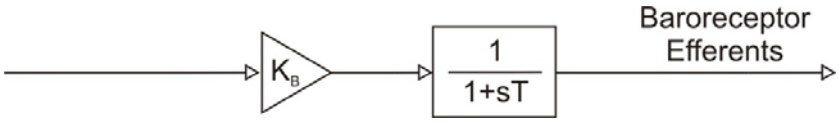


Figure 20: Schematics of the baroreceptors block in the baroreflex model. The mean arterial pressure will enter the first order system with slightly changes cause by the gain K_B. This gain can be changed directly. The value of T is 0.25 seconds.

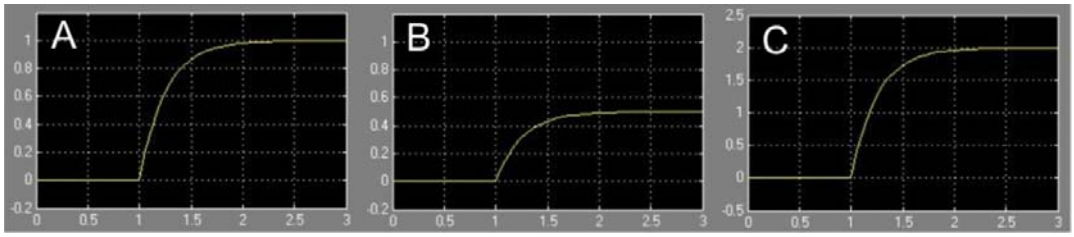


Figure 21: Results obtained from the baroreceptors block when a step signal is used as baroreceptors afferent signal. T=0.25 s; **A-** K_B=1; **B-** K_B=0.5; **C-** K_B=2.

In order to show its functioning, some simulations were run by introducing a step signal as baroreceptors afferent and by checking the baroreceptors efferent signal (Figure 21). It can be seen that the results are similar to the ones presented before (Figure 16), in this case with the gain K_B varying among the three represented signals. There is a quick recovery by the baroreceptors when the step is introduced, which is in agreement with the first order system that is used and the expected latency time.

3.3. Autonomic Nervous System (ANS) Block

The ANS block constitutes the second and last block of the neural pathway in the model of the baroreflex (Figure 22). The 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).

The sympathetic branch is inhibited by an increase of the baroreceptors activity, meaning that the negative inversion of the baroreceptors signal fits well. This behavior is

obtained by defining a positive value for the gain K_S in Figure 22. The parasympathetic branch activity is increased with the increase of the baroreceptors activity, making it a positive feedback loop. Therefore, the signal was inversed 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. This signal modification will be shown in chapter **3.4** with the discussion of the peripheral arc blocks.

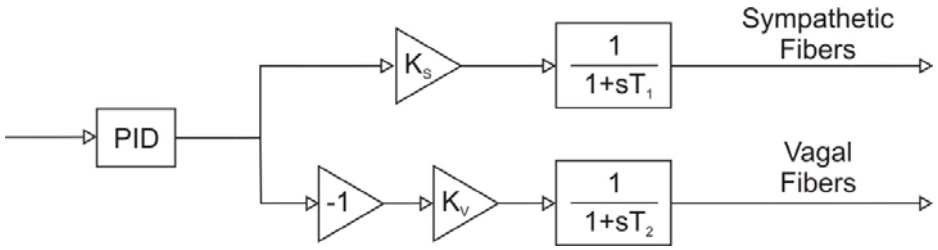


Figure 22: Schematics of the autonomic nervous system block. The PID controls both the sympathetic and the parasympathetic innervation fibers for the peripheral arc. Both systems are considered here like first order systems with different time constants but similar absolute gains K_S and K_V.

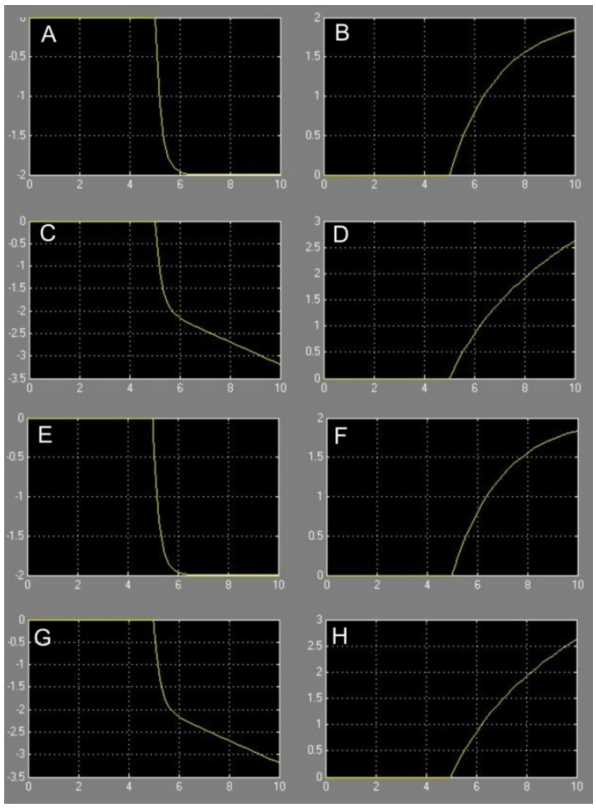


Figure 23: Simulations run with a step as input signal in the autonomic nervous system block. Here sympathetic and parasympathetic fibers innervation is shown. The used values are: K_S=K_V=1, T_1=2 s, T_2=0.25 s, $K_{Proportional}$=2, $K_{Integrative}$=0.25, $K_{Derivative}$=1. Left side shows parasympathetic fibers and right side shows sympathetic fibers. **A & B –** Only proportional part is considered; **C & D –** Proportional and Integrative parts are considered. **E & F –** Proportional and Derivative parts are considered; **G & H –** All are considered.

To show the functioning of the autonomic nervous system block, several simulations were run (Figure 23). 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). It is clearly visible the proportional and integrative influences on the output signal and slight differences caused by the derivative part. The derivative part concerns the differential pressure response on the changes sensed in the mean arterial pressure while the integrative part, in a closed loop, causes the system to return to its starting point. The proportional part acts like a direct gain from the baroreceptors output signals to the autonomic nervous system.

3.4. Heart Block

The heart block is innervated by sympathetic and parasympathetic fibers coming from the autonomic nervous system. The heart rate and the cardiac output are the physiological parameters measured in the output signal (Figure 24). As stated in chapter **2.4**, 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. In that way, it was necessary to obtain this signal according to the following equation (Tortora & Grabowski, 2001):

$$CO = SV \times HR \quad \textbf{(1)}$$

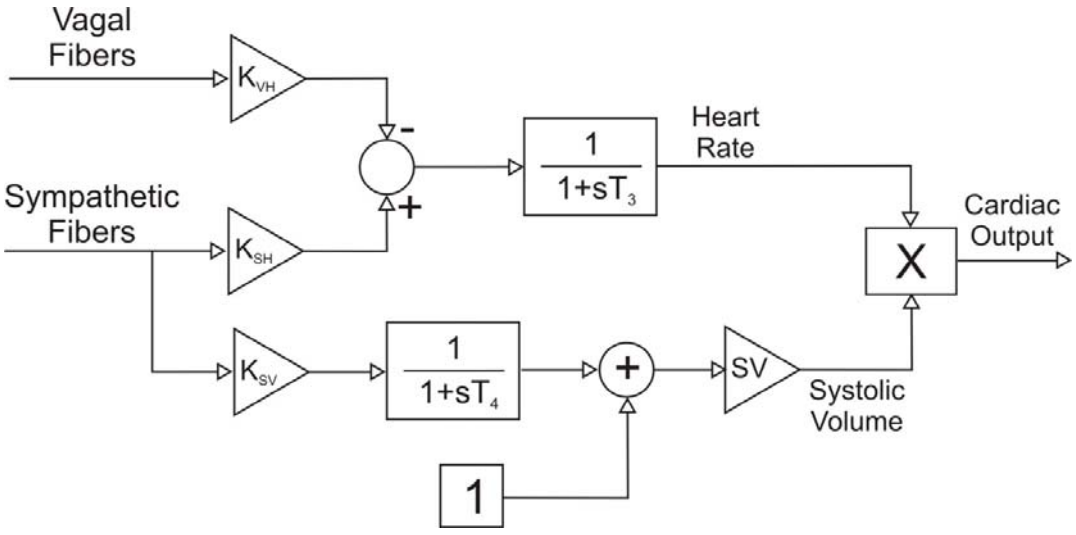


Figure 24: Schematics of the heart block on the baroreflex model. The parasympathetic influence has the opposite signal of the sympathetic influence, mediated by the gains K_{VH} and K_{SH}, respectively. The heart rate signal is then multiplied by the systolic volume to give the cardiac output. The 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 constituted by the block with time constant T_4.

The multiplication of the systolic volume by the heart rate was implemented in order to obtain the cardiac output (Figure 24). Although the heart rate that accounts for the cardiac output is seen as a mean value of the number of heart beats for minute, the model was implemented with instantaneous values, meaning that fast variations in the heart rate will also affect with the same speed the cardiac output.

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. To show the functioning and once again, steps were used to simulate the sympathetic and parasympathetic innervating fibers. The results are shown below (Figure 25).

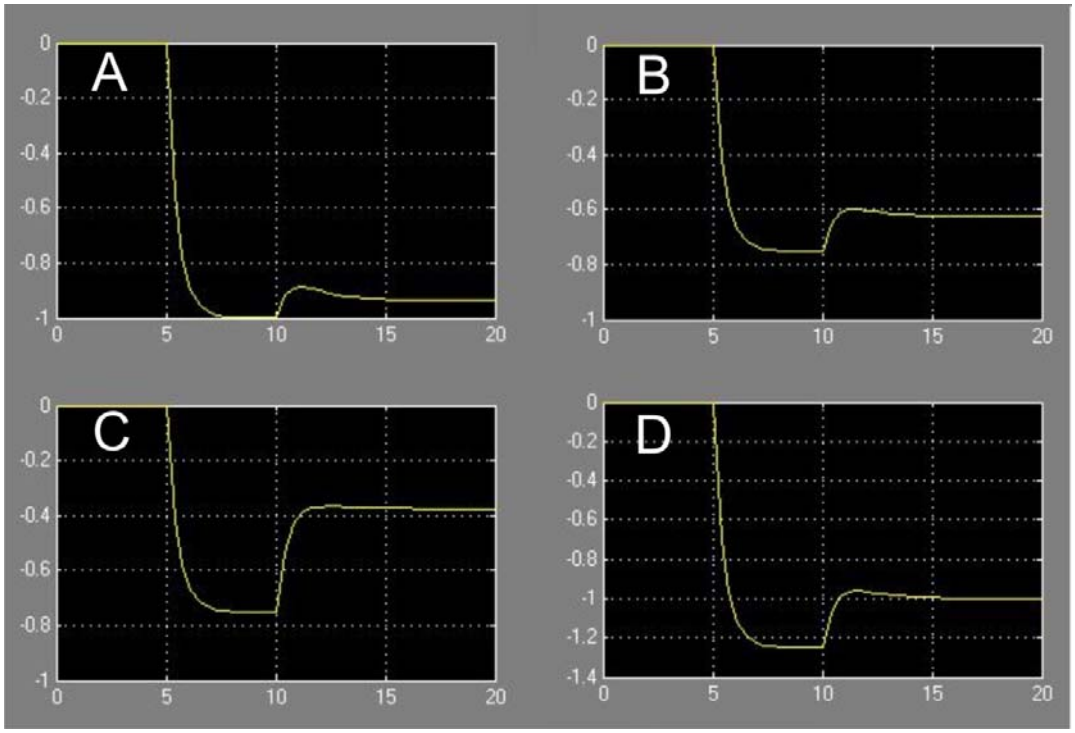


Figure 25: Tests showing the heart block functioning when stimulating signals come from the innervating sympathetic and parasympathetic fibers. Parasympathetic innervation has a more pronounced effect on the heart thus its gain was considered bigger than the sympathetic innervation gain. Values used: T_3=0.5 seconds; T_4=1 second; SV=0.1; K_{SV}=0.005; **A –** Testing values used: K_{VH}=0.2 and K_{SH}=0.05; **B -** K_{VH} value decreased; **C –** K_{SH} value increased with decreased K_{VH} value; **D –** K_{VH} increased with increased K_{SH} value.

Parasympathetic influence reduces the heart rate (thus also reduces the cardiac output) while sympathetic influence does the opposite. This was achieved by the negative signal to the parasympathetic effect and the positive signal for sympathetic effect (Figure 24). The weighting of both influences is physiologically different thus the different gains were introduced to account for those differences, with the parasympathetic influence being bigger than the sympathetic

influence. Changing the gains introduces expected changes in the functioning of the block when comparing with the physiological behaviour.

3.5. Cardiovascular System Block

The second block of the peripheral arc is the cardiovascular system block that only suffers the influence of the sympathetic system (see Figure 14), the only one that is accounted because parasympathetic innervation is restricted to small vessels and vessels in the head. Physiologically, in a simple manner, this system can be characterised by an elastic component and a viscous component of the blood vessels' walls. Accounting this, the cardiovascular system was modelled as a second order system with two real poles in an open-loop situation (in a closed loop situation they can be complex conjugated with natural frequency ω_n and damping coefficient ξ). 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. Without sympathetic innervation, the tonus would be constant and given by a reference radius, a parameter defined to each simulation.

The vascular resistance has been described by the Hagen-Poiseuille law (Aletti, Lanzarone, Constantino, & Baselli, 2006):

$$R = \frac{8.\mu.l}{\pi.r^4} \quad \textbf{(2)}$$

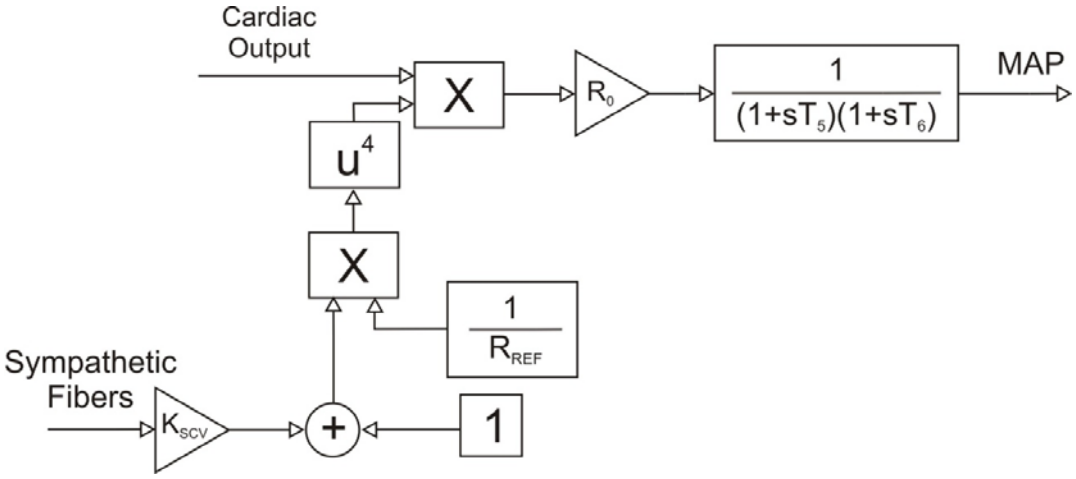


Figure 26: Diagram of the cardiovascular block of the baroreflex model. Sympathetic fibers change the radius of the vessels with an intensity that is changed by the gain K_{SCV}. The parameters of the elastic and viscous properties of the cardiovascular system are modelled by the second order system controlled by a gain R_0 that completes the Hagen-Poiseuille law description by this block. In here, **s** represents the sympathetic fibers signal coming from the autonomic nervous system block that used in expression **(3)**.

where **μ** 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 law was implemented in the cardiovascular system block to

simulate the vascular resistance in an approximated way **(3)**, where r_{REF} is the defined radius of reference for a blood vessel. The viscosity of the blood and the length of the blood vessel were assumed to be invariant **(3)** and were incorporated in the gains (Figure 26). By adjusting the time parameters T_5 and T_6 it is possible to adjust the speed of the system and the kind of system desired (in this case over-damped).

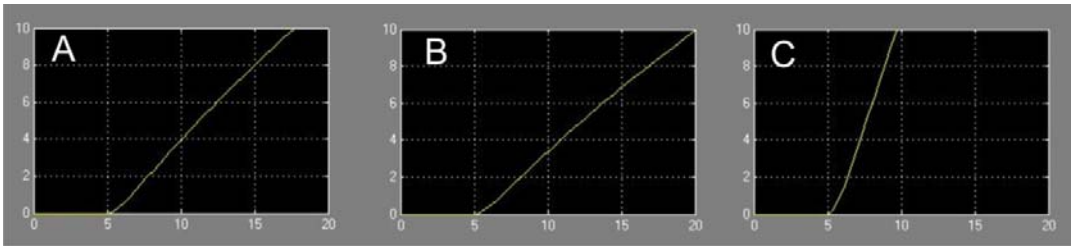


Figure 27: Graphics showing the output of the cardiovascular system block represented in Figure 25. Values used: R_0=40; R_{REF}=1; K_{SCV}=0.1; T_5=1.5 seconds; T_6=30 seconds. **A –** Test with the values stated before; **B –** Increase of sympathetic influence by increasing the final value of the step input signal; **C –** Decrease of R_{REF} to a value of 0.75.

This block has also a non-linear behaviour caused by the sympathetic innervation of the vessels and the changes it causes in the radius. Tests were performed like in all the previous blocks (Figure 27). A small radius variation has a quite pronounced variation in MAP as expected by **(2)**. Both sympathetic innervation and cardiac output signals were considered as step signals. 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.

3.6. Tilt Block

Besides the four main blocks of the baroreflex model, a disturbance block is used. This block simulates the tilt test and triggers the changes that are compensated through the baroreflex (Figure 28). A saturated ramp causes the default signal to change in any direction because of the inverting block (see Figure 29). The start time and the slope are default parameters defined inside the ramp block. This signal will be summed with the default signal to give the disturbed signal, in this case directly in the MAP signal.

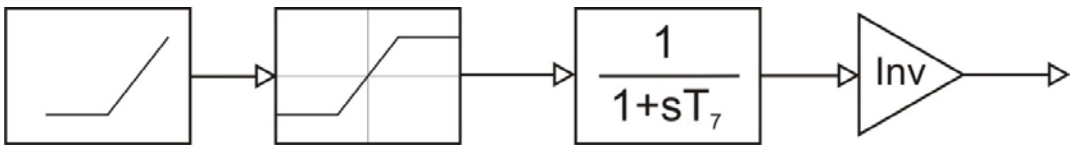


Figure 28: Schematics of the disturbance block used. The **Inv** block is a constant value block that inverts the signal if needed. The first order system was used to smooth the corners caused by the previous saturation block.

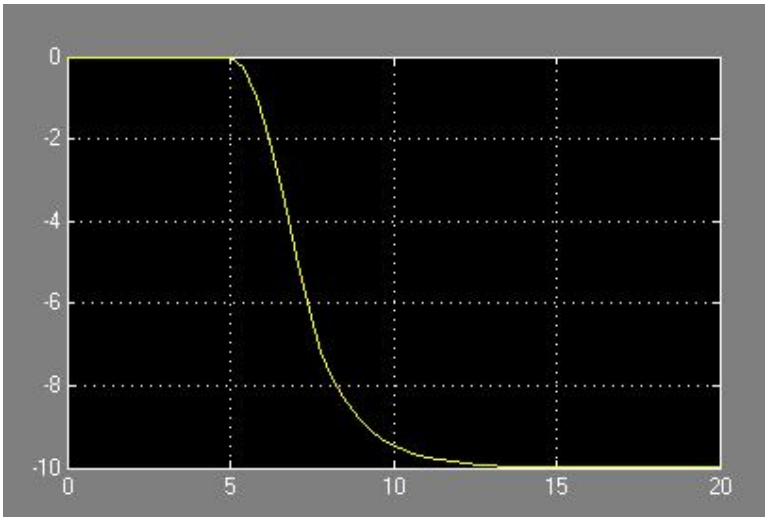


Figure 29: Visualization of the filtered ramp signal of the head-up tilt test. The ramp had a slope of 10 and started at time 5, finishing at time 15 because the saturation was -10/10.

In Figure 29 it is shown an example of the kind of disturbance introduced in to model to test mean arterial pressure control. To smooth the signal and its variations, a first order system was also used to modulate this signal (Figure 28). The parameters of this block can be changed to better suit a desirable disturbance. This one was chosen because the variation is not immediate and because the drop time can be regulated.

4. Results & Discussion

In this section the overall model will be tested and subjected to some parameter changes to show it is 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 (heart rate for example). The same kind of noise was also introduced in the baroreceptors output signal because they are sensors, thus they introduce some noise. The values used can be seen in Table 1.

Block	Parameters		Values
Baroreceptors	K_B		0.2
	T		0.25 seconds
ANS	PID	K_P	5
		T_i	0.15
		T_D	1
	K_S		1
	K_V		1
	T_1		2 seconds
	T_2		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
Cardiovascular System	R_{REF}		1
	R_0		75
	K_{SCV}		0.01
	T_5		40 seconds
	T_6		0.8 seconds
Disturbance	T_7		2 seconds
	Slope		4
	Ramp Limit		-60

Table 1: Typical simulation values for the baroreflex model.

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_i) was kept low. The value of T in the baroreceptors block was chosen from the literature (Eckberg, 1976; Seagard, Brederode, Dean, Hopp, Gallenberg, & Kampine, 1990). Tilting starts at 15 seconds and lasts another 15 seconds.

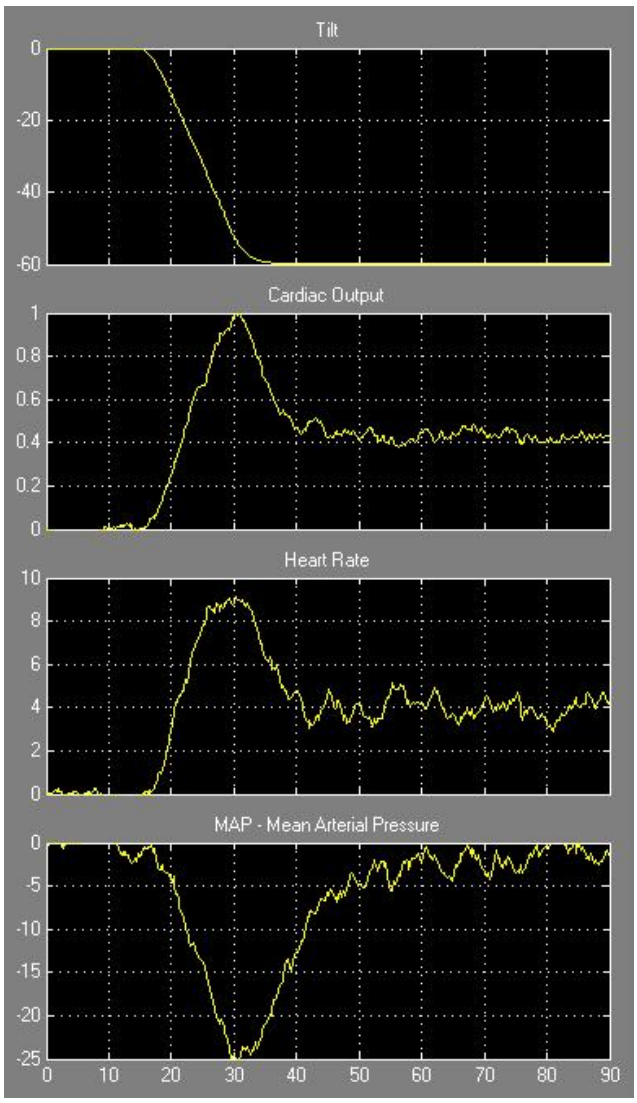


Figure 30: Simulation run with the baroreflex model using the parameters stated in Table 1. The introduced disturbance can be seen (Tilt) as well as cardiac output, heart rate and MAP.

A simulation with these parameters was run in the model (Figure 30). Changes in the heart rate and cardiac output can be seen clearly 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. Changes in systolic volume and heart contractility are hidden in the cardiac output signal. 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 or sympathetic variations in the innervation, removing systolic volume changes (constant systolic volume), 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.

4.1. Reference radius (R_{REF}) reduction (from 1 to 0.9)

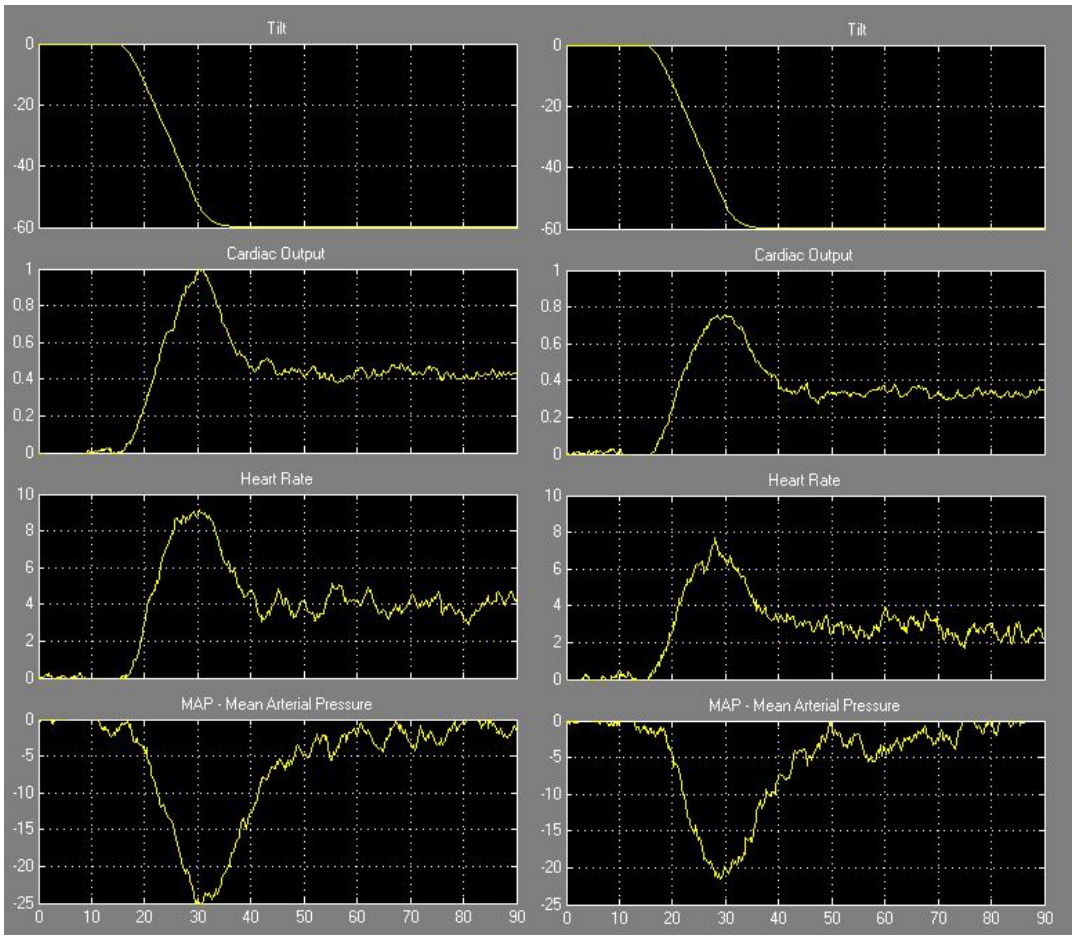


Figure 31: Result differences between radius 1 and radius 0.9. Changes can be perceived in all variables according to what was physiologically expected. The tilt disturbance remains the same for both cases. **Left:** case of Figure 30 with radius 1. **Right:** Radius chosen to be 0.9.

A reduction of the reference radius should increase the pressure. In Figure 31, 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.

4.2. Sympathetic influence on the radius eliminated or greatly reduced

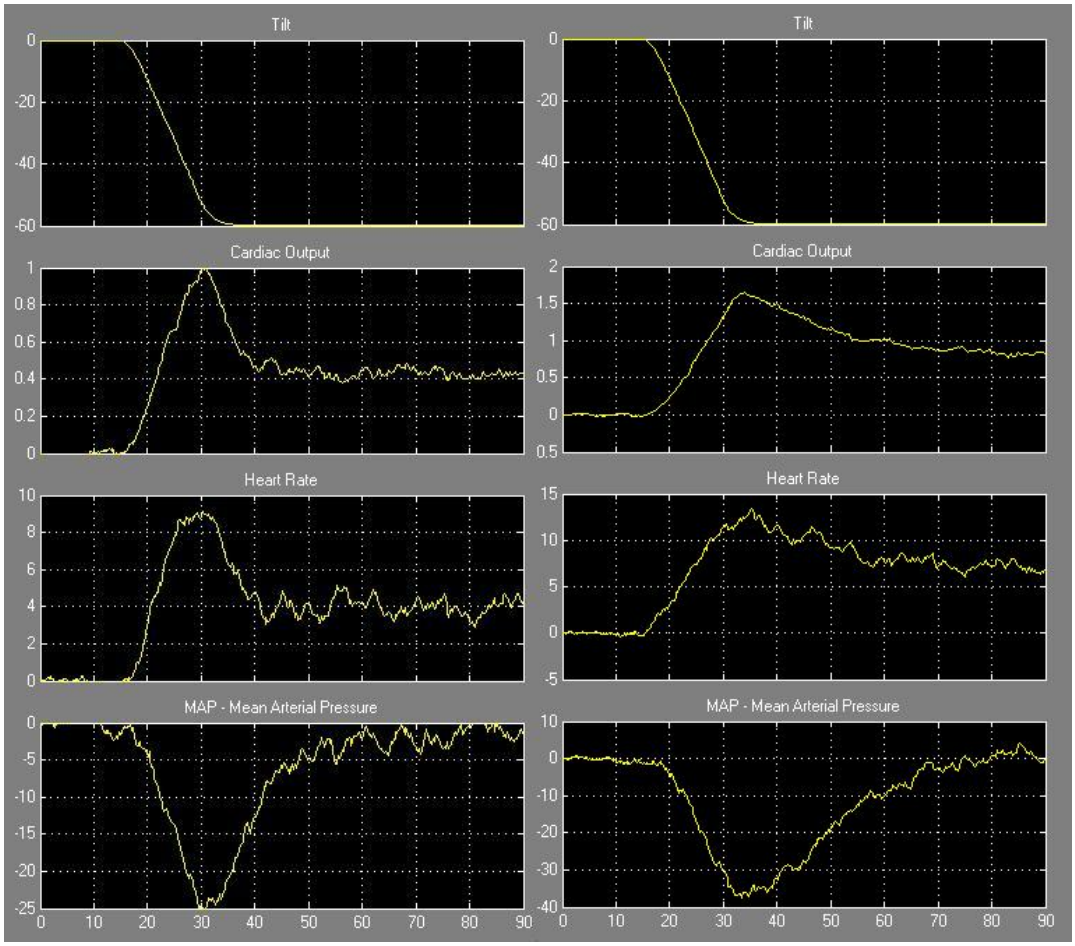


Figure 32: Results of changing the sympathetic influence on the radius. The increase of sympathetic influence provides a similar curve but very different results to the decrease of the reference radius. On the other hand, a great reduction of its influence increases the drop of blood pressure felt by the baroreceptors. Tilt disturbance signal is the same.

Sympathetic influence greatly enhances mean arterial pressure changes (Figure 32). The inexistence of such innervation or a great reduction of it is observed in some pathologies. The sympathetic influence increases not only the speed of recovery but also does not allow the drop to be so significant. The lack of it has to be compensated by other mechanisms, especially the ones involving the heart like cardiac output and the heart rate. It can be seen in Figure 32 that a bigger drop of the mean arterial pressure is overcompensated by a bigger increase in the heart rate, thus also of the cardiac output (when compared with an innervated cardiovascular

system simulation of the model) The sympathetic innervation is inexistent, meaning that the vessels have a constant radius and tonicity.

The aging process is one of some of the processes that introduce changes like this, especially a degradation of the elastic properties of the walls and the reduction of the tonicity of the smooth muscle tissue that surrounds the lumen of the vessels.

4.3. Sympathetic influence on the SV eliminated or greatly reduced

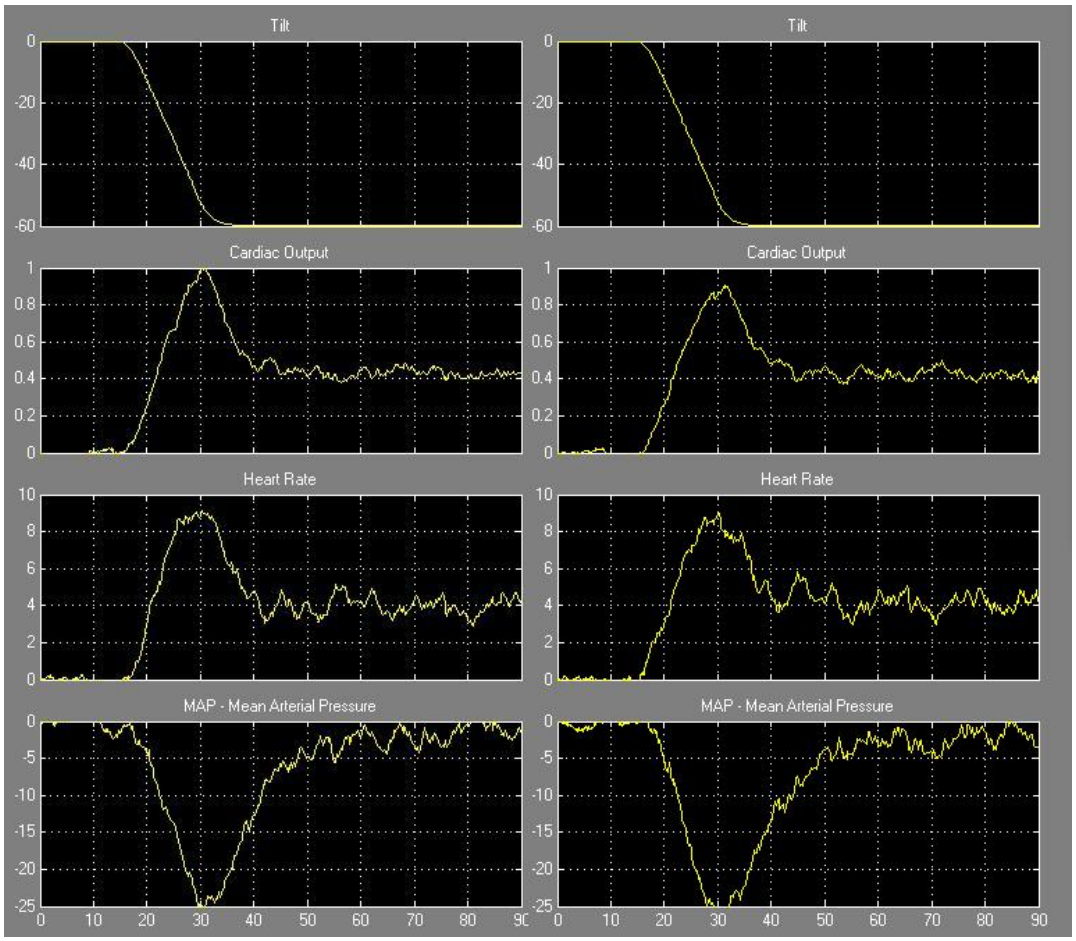


Figure 33: Results of changing the sympathetic influence on the systolic volume. The withdrawal of sympathetic influence (constant systolic volume - **right**) provides very similar results to the model with the changing systolic volume (**left**). The biggest differences appear in the cardiac output, which was expected by **(1)**. Tilt disturbance signal is the same.

Applying a constant systolic volume in the model can be achieved by removing sympathetic innervation from the heart. When this is done, small changes are expected to happen to the mean arterial pressure signal (which is not directly affected) and to the heart rate. However, changes in cardiac output are expected to be more visible since it is directly affected by changes affecting the systolic volume **(1)**. That can also be seen in Figure 33. The mean

arterial pressure drop has no significant differences in the two cases and a very small decrease of the heart rate can also be seen. The biggest difference is noted in the cardiac output, with a decrease of about 10%. With the drop of mean arterial pressure comes the increase of the heart rate and cardiac output. Because the sympathetic is being excited in this situation, a variable systolic volume allows the increase of the systolic fibers by increasing the contractility of myocardium fibers. A bigger contractility leads to a bigger systolic volume and a bigger cardiac output. The cardiac output then does not increase so much.

4.4. Constant sympathetic innervation of the heart

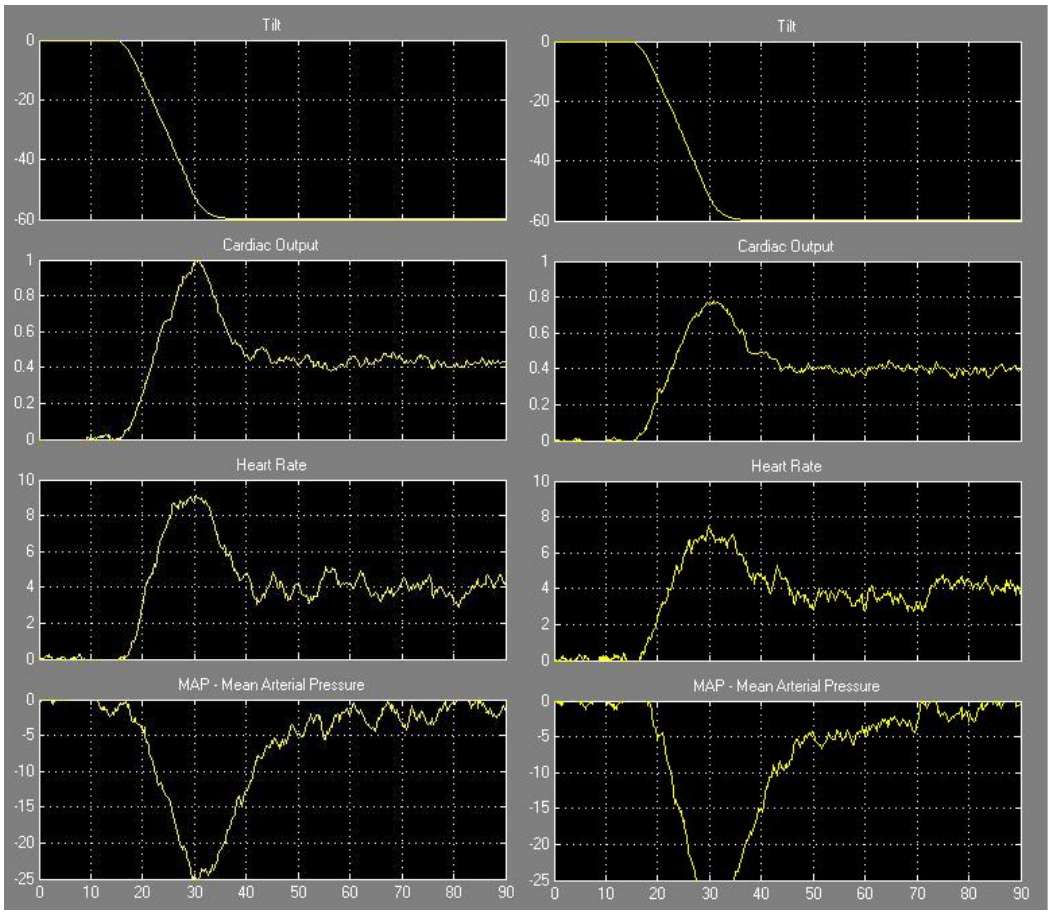


Figure 34: Results of eliminating changes of the sympathetic influence on the heart. The removal of sympathetic changes keeps the systolic volume constant (**right)**. Changes can be seen in both the heart rate and the cardiac output, with their signals being reduced by about 20% when compared to a variable innervated heart block. Tilt disturbance signal is the same. **Left:** signals from Figure 30.

By eliminating changes of the sympathetic influence on the heart, changes are expected in all output signals, especially on the cardiac output and the heart rate, although these two directly influence the mean arterial pressure. Sympathetic lack of innervation changes of the

heart causes no changes to happen in the systolic volume (previous explained situation) and also the cardiac output not to increase so much. The lack of innervation changes of the sinoatrial node also lowers the heart rate signal (Figure 34). Sympathetic innervation excites the SA node and increases the heart rate. By comparison it can be easily seen that the heart rate does not increase as it should in a normal innervation case. As a result, mean arterial pressure is not compensated so well and the initial drop is deeper than the normal case. The return to the original value is also slower. An important point to be noted is that changes in the mean arterial pressure are not very significant because sympathetic innervation in the heart has 4 times less influence on the heart rate than parasympathetic influence, thus the elimination of the variation of sympathetic innervation is easily compensated by a small increase of parasympathetic innervation.

4.5. Constant parasympathetic innervation of the heart

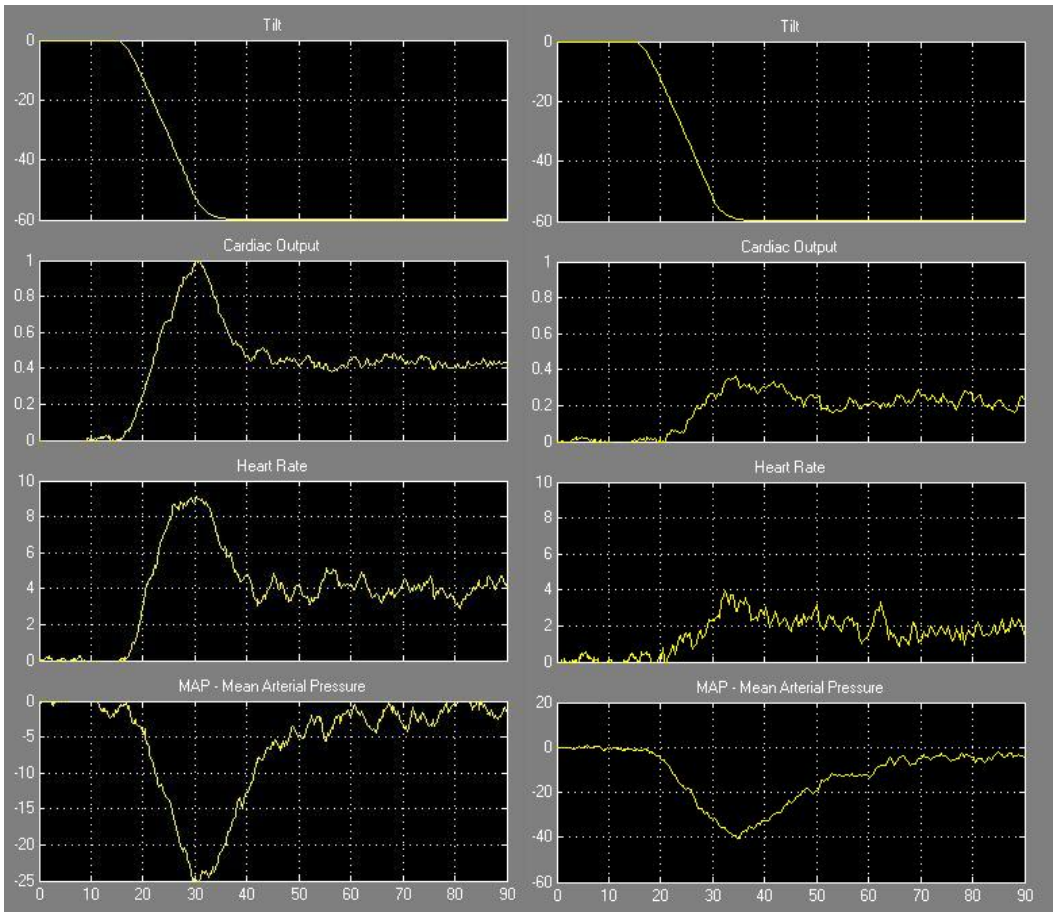


Figure 35: Results of eliminating changes of the parasympathetic influence on the heart. The removal of parasympathetic variations introduces profound changes in all signals (**right)**. Changes of about 60% can be seen in the heart rate and the cardiac output when compared to a variable innervated heart block. Tilt disturbance signal is the same. **Left:** signals taken from Figure 30.

On the other hand, eliminating variations of parasympathetic innervation of the heart has profound consequences 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 (Figure 35).

4.6. Decrease of baroreceptors afferent signal (K_B=0.1)

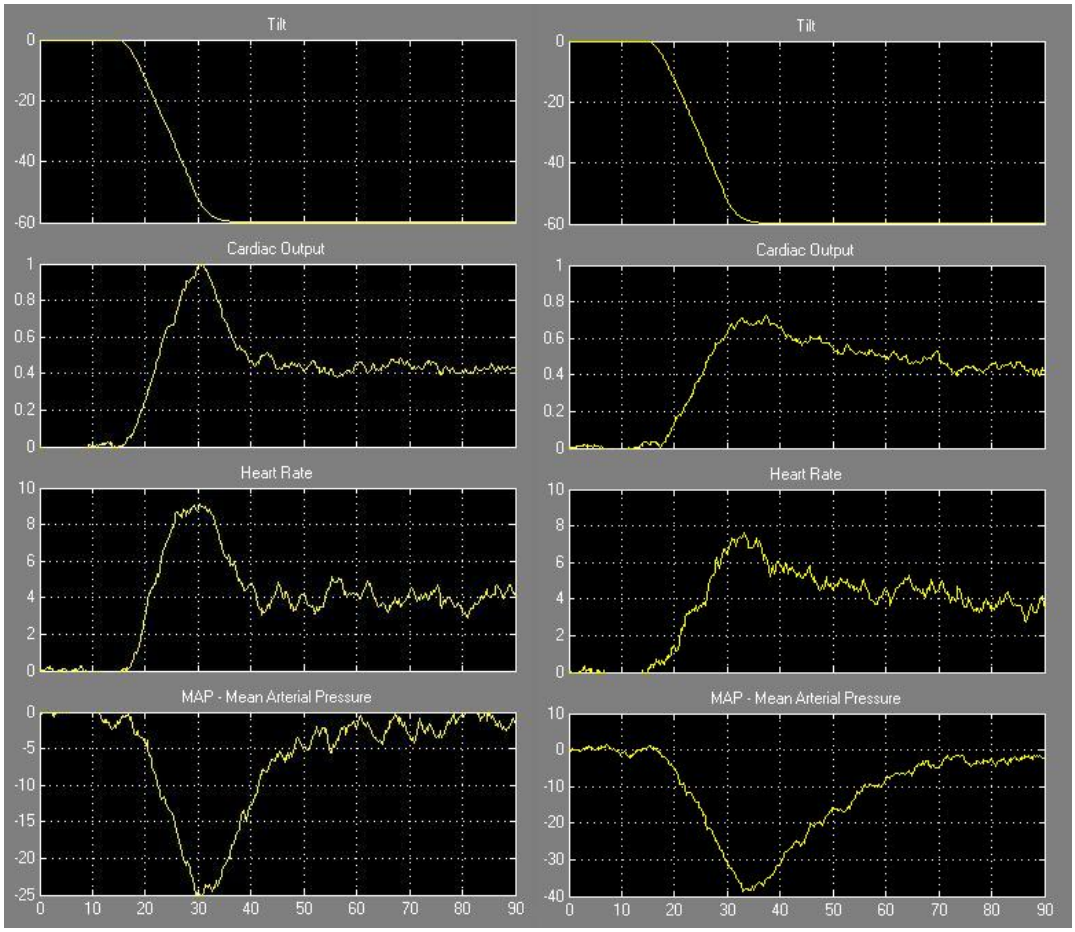


Figure 36: Results of decreasing the baroreceptors afferent signal. Changes are evident at all levels, especially in the mean arterial pressure signal with the increase of the drop (**right)**. The cardiac output and the heart rate also do not increase as much as the normal test carried before (**left)**. Tilt disturbance signal is the same.

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 (Figure 36).

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. This simulation tried to achieve the raw results obtained and show in Figure 37. As shown there, the performed tilt test caused the systolic blood pressure to drop and also caused the excitation of the sinoatrial node to increase the heart rate (Ducla-Soares, et al., 2007). The monitoring was done during 90 seconds, the same time of the simulations carried out with this model.

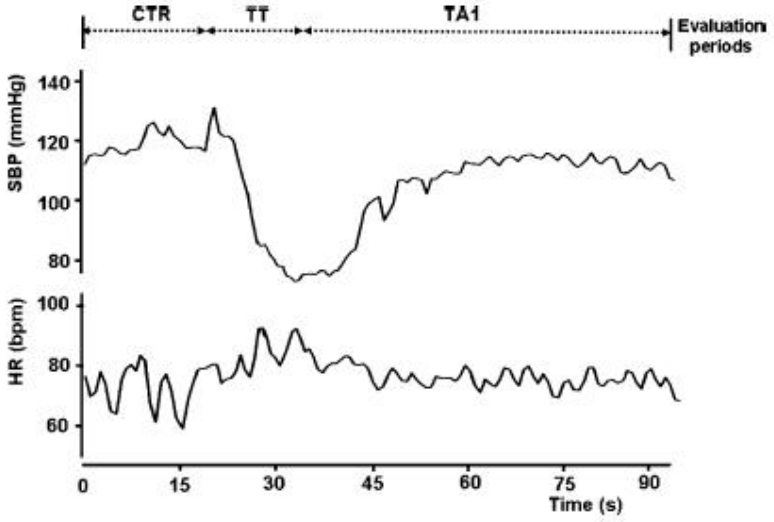


Figure 37: Raw data from systolic blood pressure and heart rate obtained from HUT test (Ducla-Soares, et al., 2007). CTR - Control Period; TT - Tilting Table; TA1 - Tilt Adaptation, which corresponds to the first minute after tilt is over.

5. 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 (Ducla-Soares, et al., 2007). The model introduced new concepts like the division of the peripheral arc into two distinct blocks: the heart block and the cardiovascular block. Though physiologically feasible, this allows a better stabilisation and a better understanding of the model functioning while permitting a better control of the physiological parameters of interest: the mean arterial pressure and the heart rate. These two variables are under control of the parasympathetic and sympathetic innervation with different weightings controlled by the gains of the system.

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. In order to better understand its functioning, each block was explained and tests were shown with small variations in the block parameters, 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 same happens to the myocardium fibers concerning the systolic volume in the heart block, allowing small changes in the value if needed to compensate mean arterial pressure alterations. 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.

6. Future Developments

Although the system behaviour is closer to the raw data presented, some approximations and simplifications were used in the proposed model. In the baroreceptors, a first order system was used as a first approximation and for the sake of simplicity. A second order over-damped system can be more suitable to be used instead. The same happens for the myocardium fibers innervated by the sympathetic autonomic system in the heart block and also the sinoatrial node with the innervation by the both the sympathetic and parasympathetic autonomic system. 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. Concerning the sympathetic and parasympathetic fibers, first order systems were used for both branches in the autonomic nervous system block. Like the heart and baroreceptors block, a second order over-damped system could be more proper to resemble the fibers activation. The PID block is the most used block in the control theory and seems to manage and control perfectly the negative feedback loop mechanism.

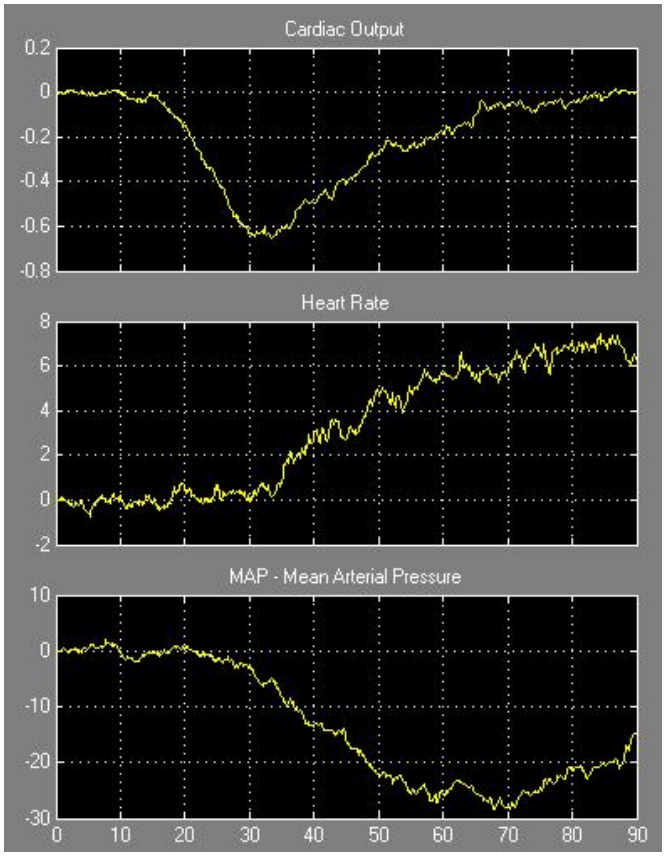


Figure 38: Graphics showing the results when the disturbance is applied to the cardiac output. The cardiac output returns to the original values while the mean arterial pressure recovery is very slow and the heart rate remains increased.

The disturbance signal was introduced directly in the mean arterial pressure system, causing it to change in time. Different disturbances can be applied (Figure 38) to further improve the system and help further in assessing the functioning of the baroreflex mechanism. To help, the development of a tilt table was started. This tilt could be particularly useful to obtain experimental results especially because of its application to mice. Animal experimental results are not biased by the conscious perception, which makes them more trustworthy than human experimental results most of the times.

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8. Appendices

8.1. RecPad 2008 and CFD 2008 Papers

Autonomic Nervous System Control Model

José Santos[1,2], João Sanches[1,2] and Luis Silva Carvalho[3,4] (MD)

I. Introduction

The discovery of baroreceptors and chemoreceptors [1] in monkeys provided insight in the control of arterial pressure by baroreceptors and baroreflex. The arterial pressure changes in a glimpse of an eye or even during a whole cardiac cycle [2], [3]. However, the dynamic of this variation and its control is not yet fully understood. The non-linear behaviour and the great number of variables makes it truly difficult to mathematically describe the baroreflex.

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 [4], [5]. Here, a model using control theory was built for the baroreflex and simulations were run in order to show how it works when a disturbance affects the signal [6], [7], [8]. The intention was to modulate the autonomic nervous system (ANS) influence in the baroreflex and how this influence is felt and changes the heart rate (HR) and the mean arterial pressure (MAP). The objective was to achieve a model that could account some of the known variations and to further increase the knowledge of baroreflex, motivated by one of the most common pathologies of the western world, the hypertension. Increasing knowledge could provide a more accurate and earlier prevention. The model described is an incremental model which means that only signal variations are accounted. The tests were carried out by introducing the head-up tilt table test (HUT) as the disturbance signal in MAP and by checking out how the system answers to this disturbance.

The results show the expected behaviour when a blood pressure drop is felt by the baroreceptors caused by the HUT [9]. MAP values recover to the initial values in the expected time window while the HR does not perform a full recovery because of the differential pressure increase in the whole body. The same happens with the cardiac output (CO) because it is influenced primarily by the HR. By changing parameters, one can adjust the model to perform in a different way.

II. Model Representation

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 two most important ones are the aortic and the carotid. They sense MAP and provide information to the ANS that acts on the heart and blood vessels. The mathematical model was implemented using MATLAB© Simulink Toolbox.

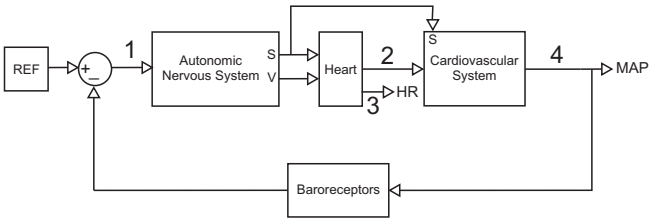

Fig. 1. Schematics of the model built to simulate the baroreflex mechanisms. The main blocks were considered and dimensioned according with physiological principles. **S**- Sympathetic innervation; **V**- Vagal innervation; **1**- Baroreceptors input; **2**- CO; **3**- HR; **4**- MAP; **REF**- Reference pressure.

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 MAP values from a reference pressure (in this case zero), shown in Fig. 1.

The baroreceptors block and the ANS block constitute the neural arc blocks of the model. All the blocks considered in the baroreflex model are described by differential equations, besides the non-linear aspects. Only first and second order systems are used. Their speed is given by the location of the poles given by the transfer function. The non-linear behaviour is achieved by simple product and summation operations.

This model introduces the feedback to the autonomic nervous system that influences the sympathetic and parasympathetic innervation of the heart (causing changes in the HR and the CO) and sympathetic innervation of the cardiovascular system (causing the blood vessels’ radius to change).

III. Results & Discussion

The model was tested and subjected to some parameter changes to show if it is in agreement with the expected physiological behaviour. Gaussian noise with null mean and small variance was introduced to simulate the noise of the devices measuring the physiological parameters. A small variation in one parameter can trigger profound changes while some others change only slightly the overall result. Tilting starts at 15 seconds and lasts another 15 seconds.

Changes in the HR and the CO can be seen clearly in Fig. 2 A when a disturbance is introduced in the model in

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a way that reduces the MAP. A blood pressure reduction triggers compensation mechanisms that increase HR and CO 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. HR remains a little increased because of the tilting. 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) in order to better judge the behaviour of the model.

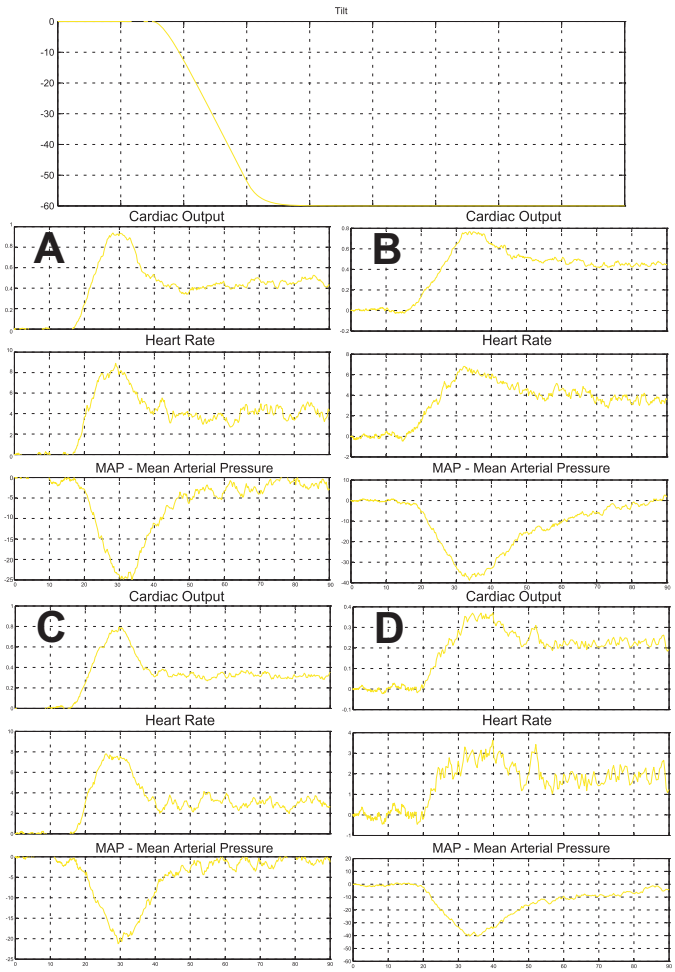

Fig. 2. Results obtained with the model. The tilt disturbance remains the same for all cases. **A** - Simulation run with the baroreflex model where the disturbance can be seen (Tilt) as well as the CO, the HR and the MAP; **B** - Decreasing of the baroreceptors afferent signal. Changes are evident at all levels, especially in the MAP signal with the drop increase. CO and HR also do not increase as much as in **A**. **C** - Results from eliminating changes of the parasympathetic influence on the heart. Changes of about 60% can be seen in the HR and the CO when compared to a variable innervated heart block; **D** - Result differences between a radius of 1 and a radius of 0.9. Changes can be perceived in all variables according to what was physiologically expected.

The decrease of baroreceptors afferent signal decreases the intensity of the signal transmitted to the ANS block, triggering slower changes. This decreases the negative feedback loop mechanism signal and reduces the efficiency of the baroreflex. Parasympathetic and sympathetic innervation variations are not so acute thus HR and CO signals will not increase as much as they were supposed to compensate the MAP drop. MAP values are slower in returning to the initial point as shown in Fig. 2 B.

On the other hand, eliminating variations on parasympathetic innervation of the heart has profound consequences. Both HR and CO are severely affected by the lack of parasympathetic inhibition when a sudden MAP drop occurs. Sympathetic innervation cannot quickly compensate the fall (the system recovers slowly) making it more abrupt. HR and CO do not increase so much causing the system to drop more the MAP signal and to recover more slowly (Fig. 2 C).

A reduction of the reference radius should increase the pressure. In Fig. 2 D, it can be seen a considerable difference in the MAP signal, with a not so abrupt fall. A lower radius causes the pressure not to drop so much but also affects HR and CO curves. Both HR and CO 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 CO and HR is also lower when the radius is decreased.

IV. Conclusions

The proposed model had a similar behaviour to the baroreflex mechanism and to the raw data used as basis for the results [10]. It introduced new concepts like the division of the peripheral arc into two distinct blocks: the heart block and the cardiovascular block. Radius variations and innervating changes were introduced and the results were fairly expected. The changes carried out in all tests trigger variations that are consistent to what is physiologically expected, making this model a progress in the modulation of the baroreflex circuit.

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Autonomic Nervous System Control Model of the Blood Pressure and Heart Rate Physiological Variables

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The *autonomic nervous system* (ANS) is a control center of major physiological variables. Among those, the ANS stabilizes and maintains in an acceptable level the values of blood pressure across the body. The ANS receives input information from several pressure sensors, the *baroreceptors*, and outputs signals that will influence the heart (to control the heart rate) and the vascular system (to control the peripheral resistance among the vessels). The ANS aims to regulate the *mean arterial pressure* (MAP) to keep it as constant as possible when suffering the influence of external or internal disturbances. Several mechanisms involved in this complex closed loop control process are known but there are still some unknown details. In this work a simplified model of this complex control system is described where the main mechanisms involved are modeled by using physiological knowledge. The goal is to obtain an accurate model and use it to help in the study of several vascular disorders such as hypertension.

1 Introduction

The systemic arterial pressure is one of the widest measured physiological variables and has been studied intensively during the last century. With the increasing knowledge, new questions arose and also the need to find new answers. Modeling the systemic activity using computational models has become a powerful tool in increasing the knowledge and in predicting the behavior of several variables or systems of interest.
Blood pressure is related to several known pathologies and several tests can assess its variability. The control and the provoked changes are exerted by the ANS through the sympathetic and vagal limbs. To exert that control, input information is required from the baroreceptors spread through the body (plus the volume receptors in some particular cases), specially the carotid sinus and the one that exists in the aortic arch [1]. The impulses originated in the baroreceptors and carried to a portion of ANS, the *nucleus tractus solitarius* (NTS) and *medulla oblongata* (where the cardiovascular center is located) represents one feedback loop control system of the blood pressure [2, 3]. This feedback control loop, called *baroreflex*, commands the ANS response and output, whether excitatory or inhibitory [4, 5, 6]. The signals then go through the sympathetic trunk and ganglia and also through the vagal fibers until they reach the effectors. Influences of both limbs are reflected in the heart (contractility of the heart muscle and also the heart rate), the arteriolar radius, veins tonus and also breathing, which exerts a mechanical influence in the whole system. However, the influences of each limb differs in the strength and type according to the effector. It is well known that vagal fibers do not influence vascular resistance (with few exceptions), although they influence in a more pronounced way the heart rate when compared to the sympathetic fibers. The heart rate will influence MAP by acting on the cardiac output and the vascular resistance influences the heart afterload and MAP [7].
We will present a simplified mathematical model in the next section, comprising some of these physiological variables and features. Our aim is to achieve a model with similar behavior regarding the blood pressure and

heart rate changes during the *head-up tilt* (HUT) test and try to extrapolate some conclusions by introducing disturbances on it by checking what kind of changes are observed after it. The HUT test is performed with a subject lying in a tilting bed. The test starts with the bed in the supine position and proceeds to a standing position at constant speed during 15 seconds, until the bed reaches 60 degrees. After an evaluation period of blood pressure and heart rate, the bed returns to the supine position.

2 Model

In this section we present the model used to resemble the blood pressure negative feedback loop control system. It consists of four major connected blocks as shown in figure 1. The simulations are conducted using the MATLAB Simulink Toolbox. MAP is compared with a reference pressure (here 0 mmHg - incremental model) and this model allows to track changes relative to that reference pressure.

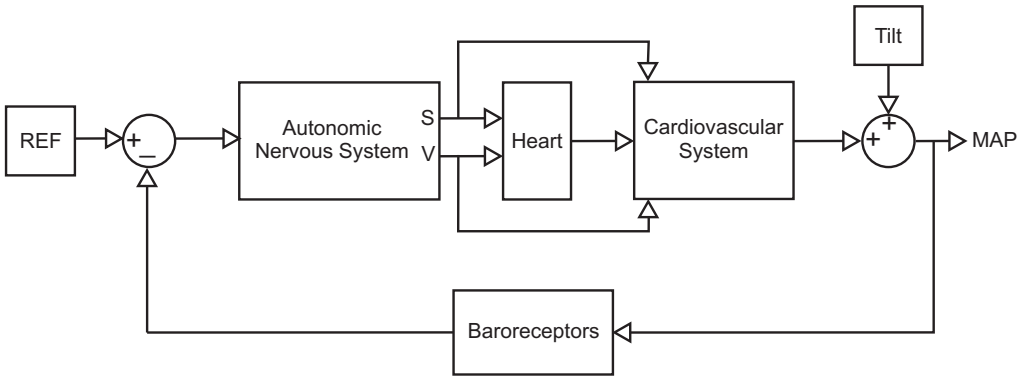

Figure 1: Mathematical model used to track blood pressure changes and resemble its variation in the baroreflex negative feedback loop. In the ANS block, S refers to sympathetic output and V to vagal output.

The autonomic nervous system is the control block. It consists of a proportional controller that commands the sympathetic and vagal outputs of the ANS. Each of these limbs is composed by a constant gain and a first order low pass filter. The sympathetic limb low pass filter system is slower than the vagal one and each has its own exit from the ANS block. The opposing effects of both limbs are reflected on the different gains and its signs, with the vagal being negative and the sympathetic being positive.
The sympathetic and vagal limbs exiting from the control block will innervate the heart and cardiovascular system (shown in figure 1). Both influences are felt at the same time, which results in a summation of both signals inside the heart block. The increased effect of the vagal output in the heart is simulated by applying a constant gain to this output before the summation with the sympathetic output. The heart itself is represented also by a constant gain to amplify the resulting signal of the total innervation. The cardiac output signal will enter the cardiovascular system block alongside with the ANS outputs.
Inside the cardiovascular block, ANS outputs will influence the total peripheral resistance by changing blood vessels' radius. However, this simplified model still does not include that influence, mostly coming from the sympathetic output. The heart block output will be multiplied by a constant gain and after a second order low pass filter with one zero is applied. The final result, which is also the output signal of that block, is the MAP. The tilt disturbance will be added to this output signal and the summation can be visualized. Changes will also be perceived in the baroreceptors block (consisted by a first order low pass filter affected

by a constant gain), whose output will be compared with the reference pressure before entering the ANS block.
The tilt block introduces the blood pressure drop characteristic of the head-up tilt test by changing positions between supine one and standing position of 60 degrees [8]. It is expected that blood pressure begins to recover after a few seconds of starting the HUT test.

3 Experimental results

The experimental results used as background for this simplified model were the ones obtained by Rocha *et al* [8]. Blood pressure and heart rate are monitored during the whole test (see figure 2).

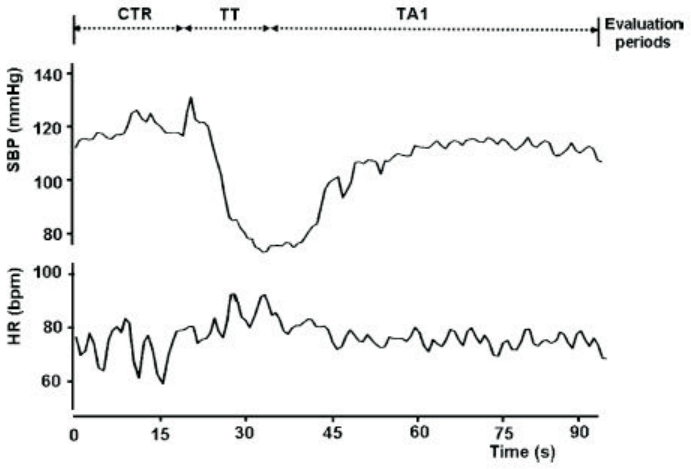

Figure 2: Raw data from systolic blood pressure and heart rate obtained from HUT test by Rocha *et al* [8]. CTR - Control Period; TT - Tilting Table; TA1 - Tilt Adaptation, corresponding to the first minute after tilt is over.

For this model, some of the values used in the blocks were extrapolated from the physiological knowledge while others were tested and found to be acceptable. The HUT test was simulated 15 seconds after the beginning of the simulation and lasted another 15 seconds. Total simulation time was 90 seconds. Tilt signal disturbance output is not shown. The results of the model can be checked in figure 3. It can be seen that the system's response to the HUT test disturbance (with a small delay, around 1 second) follows the outcome presented in figure 2 for both blood pressure and heart rate variations. It can be observed the characteristic drop of blood pressure during HUT test plus the expected increase of heart rate, one of the physiological responses to compensate the blood pressure drop.

4 Conclusions

Based on physiological insights, we successfully managed to build a simplified model that resembles blood pressure and heart rate variations. This models also stabilizes blood pressure and heart rate values by a negative feedback control system. Similar behavior was found between the experimental data in figure 2 and

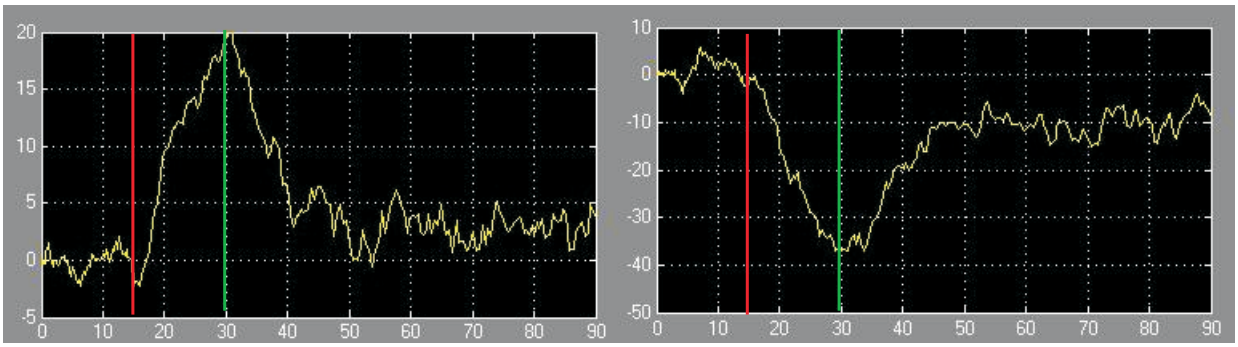

Figure 3: Outputs from the simplified model. Left graphic output shows the variation of heart rate during the HUT test induced by the tilt block while right graphic output shows the MAP variation during the HUT test. Red line shows the beginning of tilt and green line the end.

data obtained by this model (figure 3). This model may allow a better understanding of the whole control system and contribute to new insights.
It is important to notice that there are other major influences in the control of blood pressure and heart rate that we did not account in this model, specifically the sympathetic innervation of blood vessels and the breathing influence. The model is currently being improved to include such features.

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