Abstract: Physiological control mechanisms are receiving an increasing amount of attention due to their primary role in homeostasis, while systems theory is becoming an indispensable tool for understanding the dynamic behaviors that emerge. In this context, a topic that has been intensively studied is the nervous control of the cardiovascular system on short term. This paper tries to develop a common framework for future efforts in modeling the nervous control of the cardiovascular system in orthostatic stress, through a systemic analyze of the roles and interactions of the regulatory mechanisms identified in the literature.

1. INTRODUCTION

The idea that physiological systems possess some kind of control mechanisms that make homeostasis possible has been put forward by scientists several decades ago (Grodins (1963), Houk (1988)). It is now generally accepted that the human body has many physiological control mechanisms that make sure that the organism is maintained under certain physiological limits, which ensure a stable behavior, around a certain equilibrium point or on a stable limit cycle. Of course all these control mechanisms interact with each other, but because the entire human organism is very hard to grasp as a single complex model, most mechanisms are studied independently, usually being studied only for certain well defined scenarios (Kovács (2008)). That means an implicit separability based approach that is not generally true.

One of the most studied systems of the human body is the cardiovascular system (CVS), as it plays a crucial role in complex living organisms, explaining also the high mortality rate encountered in cardiovascular diseases. Global control mechanisms of the CVS act on short-term (Monti et al. (2004)) or long-term (Raffai et al. (2010)) on the entire system / human body to maintain appropriate blood flow, while these mechanisms are supplemented by local mechanisms in each vascular region. Hence, the overall control process which stabilizes the system is quite complicated.

Beside the conclusions drawn from the literature (e.g. Batzel et al. (2005), Monti et al. (2004)), which pointed the difficulty of modeling the CVS from a systemic point of view, we should take into account other three issues. i) The CVS, which is a distributed parameter system, is usually characterized through lumped parameter models. ii) Despite the existing continuous time and discrete time processes, the developed models are of continuous type. iii) The rigorous integration of different sub-models built on experimental data taken from different types of animals and even humans.

An often used clinical scenario for studying nervous control mechanisms that influence the CVS is that of orthostatic stress (Heldt (2004)). It acts like a disturbance especially on the Vascular System (VS). In this context, so far, mainly four mechanisms have been identified in the literature: the baroreflex (Ursino (1998)), the cardiopulmonary reflex (Magosso et al. (2001)), a local-cardiac reflex (Vadigepalli et al. (2001)) and the vestibular sympathetic reflex (Radtke et al. (2003)). All these mechanisms involve a specific type of receptors (measurements), certain nervous regions of the Central Nervous System (processing) – more specifically the Medulla Oblongata (MO), and the Peripheral Autonomic Nervous System (PANS) that embeds the sympathetic and parasympathetic systems (distribution of nervous control signals to the CVS) - (Berne et al. (2003)). Fig. 1 structures the above mentioned aspects in a block diagram, designed from a systemic point of view. This embeds in a unitary manner both known subsystems with existing mathematical models, as well as subsystems with little information and without quantitative models.

Fig. 1. Block diagram of the nervous control system and the CVS (Codrean (2010)).
Regarding Fig. 1 it should be mentioned that the cardiac receptors are representative for the cardiopulmonary reflex and for the cardiac-local reflex. In accordance with what was suggested in Houk (1988), the diagram underlines three control strategies: feedback (baroreflex, cardiopulmonary-reflex, local-cardiac reflex), feedforward (vestibular-sympathetic reflex), and adaptive control (thorough the influence of the Higher Nervous Centers (HNC) on the MO).

Consequently, given the fact that the role of each subsystem from Fig. 1 in our orthostatic stress scenario has been attested in the literature thorough experiments, this global system represents a full description of the nervous control of the CVS in orthostatic stress. However, this global system does not have a complete and unitary model yet, and instead, different subsystems or group of subsystems have been modeled qualitatively or quantitatively by different groups of scientists, for certain scenarios. In this context, the aim of this paper is to develop a common framework for future efforts in modeling the nervous control of the CVS in orthostatic stress ("knowledge map"), and to rigorously analyze the roles and interactions between all mentioned regulatory mechanisms from systems theory and control theory point of view.

2. THE CARDIOVASCULAR SYSTEM AS A CONTROLLED PROCESS

2.1 The Heart System

Due to a chain reaction of electrical, chemical and mechanical phenomenon, the heart represents the most complex subsystem of Fig. 1. The informational flow between its subsystems (SAN (sino-atrial node), LV (left ventricle), RV (right ventricle), RA (right atrium), LA (left atrium)) is captured in Fig. 2 (bold lines for blood flow and thin lines for nervous signals). The coupling between the RV and LV subsystems is achieved through a flexible common wall between the ventricles (the septum). The atrial septum is usually assumed to be rigid, so the atria are uncoupled and have no direct mechanical influence on each other (Lu et al. (2001)). The atrium compartments contract before the ventricular compartments, due to the time delay \( \tau \) applied to the signal \( u \) generated by the SAN subsystem.

The inputs which influence the Heart’s dynamic behavior are: the nervous sympathetic signal which affects the heart rate \( n_{HR}^s \), the nervous parasympathetic signal which affects the heart rate \( n_{HR}^p \), the nervous vector signal that contains the sympathetic and parasympathetic components and affects the contractility force of the heart \( n_C^s \). The outputs ventricle pressures \( P_v \) and atrium blood pressures \( P_a \) of the Heart are feed back through receptors to the Nervous Control System (NCS). The Heart and the VS are interconnected like in Fig. 1 through the cardiac output (CO) and the venous return (VR), which are both vector signals, corresponding to the left and right side of the heart.

It’s important to make two remarks regarding Fig. 2 involving atrial contraction and the parasympathetic activity influence on contraction. Although in most models atrial contraction is neglected, it should be noted that for small values of the Heart Rate (HR) atrial contraction accounts only about 10% of left ventricular filling, but for higher values of HR (ex. exercise) the atrial contraction contribution can reach 40% (Klabunde (2004)). Regarding the parasympathetic influence on contractility, many authors consider only the sympathetic influence over the contractility of the ventricle (the parasympathetic influence is neglected). However, regarding the nervous influence over the atrium \( n_{C}^{PA} \) it is stated that there is a stronger, more obvious parasympathetic influence over its contractility (Berne et al. 2003).

The SAN subsystem dictates the moment of contraction of the atrium and ventricles, while the VR and the sympathetic activity \( n_C^s \) determine the force of contraction. Moreover, the SAN is the main device for controlling the HR.

Most lumped models of the SAN can be embedded in a common structure like the one from Fig. 3. The first part of the model brings a dynamic component that takes into account the chemical reactions that take place and the interactions between the sympathetic and parasympathetic signals. Under the assumption that the chemical reactions that take place are mutually independent, in Olufsen et al. (2006) the change of concentration of two neurotransmitters – norepinephrine \( C_{nor} \) and acetylcholine \( C_{ach} \) – is described through simple linear state equations - (1) and (2) (Appendix A). Many authors include such equations that behave like low-pass filters in their models, but most of them do not distinguish that the dynamics refers to chemical reactions. The interaction between the sympathetic and parasympathetic signals has been modeled with different types of functions, some being linear and some nonlinear. Some representative examples are the linear function (3) used in Olufsen et al. (2006) and the nonlinear function (4) used in Lu et al. (2001).
The second part of the model, the Impulse Frequency Modulator (IPFM), is a quasi-periodic (pulsatile) process. It transforms the prescribed heart rate HR into an actual sawtooth periodic signal u(t) that has the frequency equal to HR, and generates a train of impulses of the same frequency. The signal u(t) is then used as a timer, to coordinate ventricle and atrial contractions. I(t) represents action potentials that travel thorough the heart and eventually lead to ventricle and atrial contraction. The transformation from Fig. 3 is considered by most authors as an “integrate and fire model” - (Olufsen et al. (2006), Ursino (1998), Vadigepalli et al. (2001)).

Onwards, for the LV, RV, LA and RA subsystems we will use the generic term cardiac chamber. Fig. 4 highlights the elastic part of a chamber (with a passive pressure \( P_{i,p} \)) and its muscular part (which generates an active pressure \( P_{i,a} \)). \( P_{i,t} \) is the pressure from the downstream chamber/compartment, while \( P_i \) the total pressure of the current compartment \((P_i = P_{i,t} + P_{i,a}, i = LV,...)\) which will influence the upstream chamber /compartment. Also, one can observe that the chamber’s muscular part is represented by a force generator block \( G_F \). It is influenced by the HR through the signal \( u(t) \), by nervous activity that prescribes the force of muscular contraction (the signal \( n_{e,C} \) represents a combination of a sympathetic and parasympathetic activity specific to each chamber), and by the corresponding compartment outflow - \( q_{i,out} \). Each subsystem \( i \) contains, besides a structure like the one in Fig. 4, a valve that restricts the flow to a unidirectional path. The valves make it possible that at each time moment the cardiac chamber’s volume is increasing due to an input flow, is decreasing due to an output flow, or remains constant.

Fig. 4. The cardiac chamber subsystem (\( i= LV, RV, RA, LA \))

Generally, the pressure \( P_i \) in a chamber \( i \) can be written as a function of the contraction force – expressed through the active pressure \( P_{i,a} \) – and chamber volume \((V_i)\): \( P_i = f_a(V_i, P_{i,a}) \). It depends on modeling objectives, chosen in such a way to reproduce more accurately the experimental results. Taking into consideration only the ventricular contraction (contraction of the atriums is neglected), the input-output dependence \((5)\) and the activation function \((6)\), adopted as a squared half-sine wave, were used in Ursino (1998). The influence of the HR on the pressure generated appears via \( T = 1/HR \), and is negligible. In Ottesen et al. (2003) the ventricular pressure \( P_i \) is expressed as function of time \( t \), heart rate HR, volume \( V_c \), outflow \( q_{i,c} \), and the ventricle’s contractile state (parameter \( c \)) – \((7)\), while the activation function \((8)\) incorporates the changes in ventricle pressure due to HR observed in experiments. Thus, the HR influences the pressure through two sigmoidal functions: \( \beta(\text{HR}) \), which denotes end of contraction, and \( p_c(\text{HR}) \), which represents peak ventricular pressure. Other attempts are presented in Heldt (2004) where atrium contraction was included, or Deserranno et al. (2007) where the contraction mechanism is based on what happens at the sub-cellular level.

Regarding the Heart System, it should also be noted that for the change in volume \( V \), most authors use expressions drawn from Kirchhoff’s laws for electrical analog circuits, where the flow \( q_i \) is equivalent with an electrical current, and the pressure \( P_i \) with electrical potential. Hence, \((9)\) is a simple example of this, and was used in Ellwein (2007).

2.2 The Vascular System

The VS contains two blood pathways: the systemic circulation \((5)\) and the pulmonary circulation \((P)\). Each pathway can be divided into large arterial vessels, small vessels, and large venous vessels (Fig. 5). There are 6 subsystems: LSA (large systemic arteries), SSV (small systemic vessels), LSV (large systemic veins), LPA (large pulmonary veins), SPV (small pulmonary vessels), and LPV (large pulmonary veins). Consequently, each of these 6 subsystems contains one or more compartments, according to the modeling objectives. Fig. 5 illustrates only the blood flow pathways (thick lines), and the nervous control signals exercised by the nervous control system (thin lines).

A common approach for lumped models of the VS is based on compartmental modeling. Each part or subsystem of the VS is considered as a separate compartment (or a series of several compartments) with certain interconnections with the adjacent compartments. Fig. 6 shows, according to systems theory, how a subsystem \( i \) (model of a vascular compartment), is connected to upstream and downstream subsystems. The considered model has only one input and output flows, with output impedance, easily extendable for multiple inputs and outputs models (that converge or diverge at the level of the \( i \) subsystem). The variables \( P_i \) denote the influence of external pressures and the parameter \( \alpha \) (tilt angle) gives the influence of orthostatic stress. Parameter changes influence differently the compartment dynamics depending on the vessel type. In the literature, a change in the peripheral resistance (parameter R) is proved to have a high impact in arterioles and small arteries compartments, the influence coming from the sympathetic system - \( n_{HR} \) (Fig. 5).

Volume \( V \) is important considering the veins – which act as blood reservoirs – with a large amount of unstressed volume \((V_u)\). Nervous influence on vasoconstriction \((n_V)\) changes \( V_u \) heavily in the veins, leading to an increase in VR.

Fig. 5. The Vascular System
3. THE NERVOUS CONTROL SYSTEM

3.1 The Receptors

There are mainly three types of receptors in Fig. 1, each of them representing the afferent part of specific feedback loops. The baroreceptors are high-pressure receptors, placed in the walls of arteries, detecting changes in arterial pressure and altering their firing rate. Ursino (1998) considered that the firing rate is related to the mean pressure and also to the rate of change in pressure. Based on this assumption, the model developed in Ursino (1998) consists in a series connection between a high-pass filter (17) and a static sigmoid characteristic (18). Starting from the experimental observations that the baroreceptors exhibit several nonlinearities (like threshold and saturation, adaptation, asymmetry), Olufsen et al. (2006) present a model consisted mainly of a system of three first order coupled ordinary differential equations - (19), where the input \( P_{bas} \) represents mean blood pressure obtained through (20). The output signal \( n_{ba} \) is obtained using (21), where \( N \) is the baseline firing rate.

The cardiac receptors are low pressure receptors located mainly in the veins, aorta, ventricles, and pulmonary arteries (Berne et al. 2003, Eckberg 2004). Contradictory results and hypothesis on this topic can be found in literature, so the nervous control implications of these receptors is still under debate. Although, some consider that nearly all cardiac receptors converge in the MO, there is an increasing evidence that a part of the atrial receptors have afferent pathways leading to the autonomic ganglia, and that the ganglia is capable of complex neural processing (Vadigepalli et al. 2001). This pathway, also called the local cardiac reflex, is believed to be actually the Bainbridge reflex reported in the literature. Regarding the mathematical models that describe the cardiac receptors, mainly all authors model only some of the receptors that take part in the cardiopulmonary reflex. Because of the sparse experimental data available, these models are presented in a very simplistic manner (e.g. (22)-Magosso et al. 2001)). The only attempt to model the atrial receptors responsible for the Bainbridge reflex as second order linear filters was found in Vadigepalli et al. 2001).

Considering orthostatic stress as a modeling scenario, the contribution of the vestibular receptors in the vestibular-sympathetic reflex is also important. Various reports in the literature confirm the presence of a vestibulo-sympathetic reflex that contributes to the nervous control of the CVS (e.g. Radtke et al. 2003). The vestibular receptors consist of the Otolith organs and the Semicircular Canals, but the first are considered to play the most important role in the vestibulo-sympathetic reflex in orthostatic stress (Balaban et al. 2004). An interesting approach of modeling the Otolith Organ is in Fernandez et al. 1976, as fractional order system – (23). The vestibular receptors are modeled in most cases as purely resistant parts. By representing the compartments as state space models the focus is shifted from different forms and levels of detail of the models by different authors to the dynamic behavior analysis (the equations can be congregate by making simple adjustments like in case of parameter \( a \)).

3.2 The Central Nervous System

Despite the efforts to identify the specific areas that form the pathways from the afferent receptor inputs to the sympathetic and parasympathetic outflows in the PANS, there are still regions in the MO for which little or no information is available. Based on available information in literature, we developed a generally accepted pathway of information processing for neural cardiovascular regulation (Fig 7).

The signals coming from the baroreceptors and cardiac receptors (\( n_{ba} \) and \( n_{ba} \)) converge in the Nucleus Tractus Solitarius (NTS). This is the primary processing region that receives information from the receptors of the CVS. Although the idea of a pressure reference set-point is highly speculative, some consider that NTS may receive a certain reference signal \( n_{ref} \) from HNC. The Nucleus Ambiguous / Dorsal Motor Nucleus of the Vagus (NA/DMNX) subsystem communicates with the Parasympathetic subsystem of the
PANS (Fig. 7). The Ventral Lateral Medulla (VLM) subsystem receives input signals from the NTS and the Vestibular Nucleus (VN), and communicates with the Sympathetic subsystem of the PANS. The VN receives afferent information from the Vestibular Receptors. It is also believed that HNC can alter the gain or sensitivity of the NA/DMNX and VLM subsystems.

Most experiments focused on studying the behavior of neurons from the NTS region, while scarcely information can be found about the VLM and NA/DMNX regions. Based on experimental data, some authors developed cellular models of the neurons in the NTS, based on the Hodgkin-Huxley formalism or its different extensions, while others used artificial neural networks. At a physiological level, one representative attempt is that of Ursino (1998), where simple exponential and sigmoid functions were used – (25), (26) – to approximate the information processing that takes place. Furthermore, in order to develop a quantitative model for the vestibular-sympathetic reflex, recent efforts have focused on obtaining a model for the VN from experimental frequency characteristics of individual neurons (Ceregan et al. (2010)).

3.3 The Peripheral Autonomic Nervous System

The PANS has two major divisions: the Sympathetic System (SS) and the Parasympathetic System (PS). The SS has an excitatory effect on the CVS, while the PS has an inhibitory effect. Although in some approaches the SS and PS are treated as independent systems, the systems are not separable because interactions may appear at different levels. The interactions are complex, because the coupling between the SS and the PS may vary in time, exhibiting a certain excitatory effect on the CVS, while the PS has an inhibitory effect. A logical model for the vestibular-sympathetic reflex, recent efforts have focused on obtaining a model for the VN from experimental frequency characteristics of individual neurons (Ceregan et al. (2010)).

As a further exemplification, we will focus only on the effect of the PANS on the HR through the signals \( n^p_{HR} \) and \( n^s_{HR} \). Two important attempts are presented in Ursino (1998) and Olufsen et al. (2006). In Olufsen et al. (2006) the observed inhibitory effect of the PS over the SS was considered, and the effect of the vestibular-sympathetic reflex was introduced through a generated impulse function \( u \) – (27). In Ursino (1998) the activity of the SS and PS are considered to be independent. The SS activity was modeled through a logarithmic function with time delay - (28), while for the PS a simple gain and time delay were used - (29).

Regarding the local cardiac reflex, which influences the SS through signal \( n_{lr} \) (Fig. 8), Vadigepalli et al. (2001) provided the only modeling attempt. Because the model was conceived at a sub cellular level it is inappropriate to integrate it into the global system from Fig. 1, and it will not be further detailed.

4. CONCLUSIONS

After decades of research on the nervous control of the CVS, the topic is far from being fully understood, even for simple scenarios like the movement from sitting to standing. For reaching a deeper understanding, a complete homogeneous model of the nervous control of the CVS should be developed, which would embed four regulatory mechanisms. Therefore, models for the vestibular-sympathetic reflex and cardiac local reflex should be developed, the neural processing of information at the level of the CNS should be carefully assessed and included in the models, and also the interaction of the regulatory mechanisms at the level of the PANS should be identified.

REFERENCES


Appendix A

\[
\begin{align*}
T_{nuc} \cdot C_{nuc}(t) + C_{nuc}(t) &= n_{nuc}(t) \\
T_{arch} \cdot C_{arch}(t) + C_{arch}(t) &= n_{arch}(t)
\end{align*}
\]

\[
\begin{align*}
f_{HR}(n_{HR}, n_{HR}, HR_0) &= \frac{1}{\tau_{HR}} (C_{nuc} \cdot C_{arch} \cdot HR_0) = \\
&= K_{nuc} \cdot C_{nuc} - K_{arch} \cdot C_{arch} \cdot HR_0 + HR_0
\end{align*}
\]

\[
f_{HR}(n_{HR}, n_{HR}, HR_0) = \frac{1}{\tau_{HR}} (n_{HR} - n_{HR}^0, HR_0) = HR_0 + K_{HR}n_{HR} - \\
- K_{HR}n_{HR}^2 - K_{HR}n_{HR} + K_{HR}n_{HR}^0 - K_{HR}n_{HR}^0
\]

\[
P_I(t) = \frac{1}{f_0} \left\{ \left[ \frac{E_{I, max}(n_{H}, C]}(V(t-V(n_{H}, C]))P_0 \right. \left( e^{E_{I, max}(n_{H}, C]}(V(t-V(n_{H}, C])) - 1 \right) + \\
P_{0, HR}(E_{I, max}(n_{H}, C]) \left( \frac{1}{f_0} \left( 1 - K_{HR} \cdot q_{HR}(t) \right) \right) \right\} \right.
\]

\[
f(t, HR) = \frac{p_0(HR) \cdot \left \{ (n_{HR} + 1) - \beta \cdot (HR) \right \}^2}{\left( [n_{HR} + 1] \cdot (1 - \beta \cdot (HR)) \right)_{\geq 0} \leq \beta \cdot (HR) \leq 1}
\]