Virtual laboratory for simulation and learning of cardiovascular system function in BME studies

Laboratorio virtual para la simulación y el aprendizaje del sistema cardiovascular en estudios de ingeniería biomédica

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Abstract

The application of engineering system analysis is a very important field in biomedical engineering (BME) studies: modeling, simulation and control of the most important physiological systems. A virtual laboratory for the analysis and the study of human circulatory system is presented in this paper. This laboratory is based on the compilation of several mathematical models described in the literature. In addition, some model parameters have been tuned by means of experimental data under caffeine stimulus. The computational tool has been built using MATLAB/SIMULINK and EJS, so it combines good computation capabilities with interactivity. The virtual laboratory has been designed in order to understand the operation of the circulatory system under normal conditions, and to predict circulatory variables at different types and levels of stimuli and conditions.

----- *Keywords:* Biomedical engineering, interactivity, circulatory system, EJS

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Resumen

La aplicación de la ingeniería al análisis de sistemas es un campo muy importante en los estudios ingeniería Biomédica (BME, por sus siglas en inglés): modelado, simulación y control de los sistemas fisiológicos más importantes. En este documento se presenta un laboratorio virtual para el análisis y el estudio del sistema circulatorio humano. Este laboratorio se basa en la compilación de varios modelos matemáticos descritos en la literatura. Además, algunos parámetros del modelo han sido mejorados por medio de datos experimentales del estímulo de cafeína. Esta herramienta computacional se ha construido utilizando MATLAB / Simulink y EJS, por lo que combina buena capacidad de cálculo con interactividad. El laboratorio virtual ha sido diseñado con el fin de comprender el funcionamiento del sistema circulatorio en condiciones normales, y para predecir variables circulatorias en diferentes tipos y niveles de estímulos y condiciones.

----- *Palabras clave:* Ingeniería biomédica, interactividad, sistema circulatorio, EJS

Introduction

Biomedical Engineering (BME) is different to other engineering areas in the sense of obtaining results from experimental procedures and reproducing real physiological situations. It is very difficult and expensive to interact with the human being body (collaboration of volunteers or patients to be analyzed, instrumentation with specials safety conditions, ethic and legal requirements for the protocols, etc) and even dangerous in certain situations. The use of virtual labs is proposed in order to overcome this drawback and allow students and researchers to interact with the human body. These labs can be built in a complete interactive way, so the students can qualitatively understand the behavior behind the complex models used to represent the human body [1].

The field of BME includes many areas; one of them is the application of engineering principles (modeling, simulation, and control) to biologic problems [2]. In this work the computer modeling of a physiologic system in order to understand its operation under normal situations and to predict physiological variables at different levels of stimuli and conditions is addressed.

The cardiovascular system is composed mainly of the blood, heart, and blood vessels. Blood circulates through out the body to provide individual cells with oxygen and nutrients and helps dispose of metabolic wastes. Arterial pressure control is carried out by a sophisticated non-linear multi-input, multifeedback system termed the baroreflex [3]. The Autonomic Nervous System (*ANS*) interacts with the cardiovascular system. This interaction and stimuli from the former is critical to understand the function of the later and can provide significant prognostic information. The ANS is predominantly an efferent system transmitting impulses from the Central Nervous System (*CNS*) to peripheral organs. Its effects include control of Heart Rate (*HR*), heart contraction, constriction and dilatation of blood vessels, contraction and relaxation of smooth muscle in various organs, and glandular secretions [4].

The virtual laboratory presented in this paper is a useful tool for understanding the cardiovascular system operation, for identifying the stimuli from the ANS and for predicting different situations in a visually attractive and interactive way for the student and researcher on BME.

Methodology

Cardiovascular system model

Empirical and functional models have been proposed in the literature to describe various aspects of the cardiovascular system. Some of them also include the respiratory system interaction through an autonomic neural controller [5]. The cardiovascular system is structured in different intermediate processes (see figure 1). Components in the system include a nonlinear carotid sinus compartment stimulated by the Arterial Blood Pressure (*ABP*), a sino-atrial node component that regulates the *HR* with both parasympathetic and sympathetic controls, a peripheral resistance component controlled by the α-sympathetic activity, a hemodynamic sub-model based on a simple two-element Windkessel model, and a component that controls changes in stroke volume via changes in the venous return and cardiac contractility [3].

The central autonomic control determines the total α-sympathetic, f_{tas}, β-sympathetic, f_{tbs}, and parasympathetic, f_{tp}, influences on *HR* and peripheral resistance from the baroreflexes, chemoreflexes and lung stretch receptors reflexes. Autonomic control afferent signals, f_{tas}, f_{tbs} and f_{tp} allow simulation of different stimuli related with the sympathetic and parasympathetic systems [7].
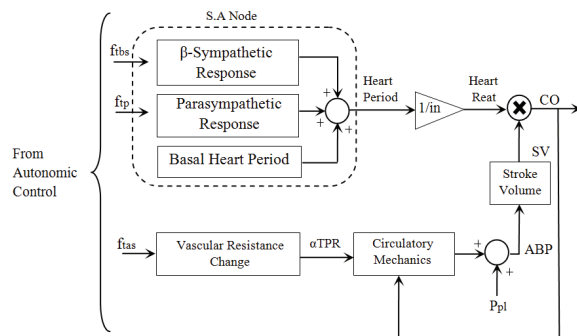

Figure 1 Block diagram of the cardiovascular system described by Ursino [3] and Cavalcanti and Belardinelli [6]

Sino Auricular Node: Ursino [3] describes the Sino Auricular Node (SA) as a subsystem that translates changes in β-sympathetic and parasympathetic efferent activity into changes in Heart Period, HP (reciprocal of instantaneous HR) which is obtained by assuming a linear interaction between the sympathetic and parasympathetic responses (Equation 1).

$$HP = \Delta HP_{bs} + \Delta HP_p + HP_{basal} \qquad (1)$$

Being ΔHP_{bs} and ΔHP_p the changes in *HP* modulated by β-sympathetic and parasympathetic responses respectively, and HP_{basal} denotes *HP* in the absence of cardiac innervations, that is 0.58s in one 70-kg body weight subject. β-Sympathetic response is modeled assuming first-order dynamics (Equation 2):

$$\frac{d}{dt}\Delta HP_{bs} = \frac{1}{\tau_{bs}}\left[-\Delta HP_{bs}(t) + \sigma_{bs}(t)\right] \qquad (2)$$

Being τ_{bs} the β-sympathetic time-constant, and σ_{bs} a function related to β-sympathetic firing frequency, f_{tbs}, which can be considered zero when the firing frequency is too low. Delay associated with the β-sympathetic effect on the *HP*, is longer than that of the parasympathetic response. The parasympathetic or vagal response is also modeled assuming first-order dynamics (Equation 3):

$$\frac{d}{dt}\Delta HP_p = \frac{1}{\tau_p}\left[-\Delta HP_p(t) + \sigma_p(t)\right] \qquad (3)$$

Similarly, in this case τ_p is the parasympathetic time constant and σ_p is proportional to parasympathetic firing frequency, f_{tp}.

Total Peripheral Resistance (TPR): The α-sympathetic nerves control the peripheral vascular activities. During hypotension/hypertension, vasoconstriction/vasodilatation occurs to prevent further decreasing/increasing in the blood pressure. This subsystem is modeled

using a first-order dynamic system (Equation 4 and Equation 5) as in the case of the β-sympathetic component:

$$\alpha_{TPR} = \alpha_{PR} + \alpha_{TPR,0} \qquad (4)$$

$$\frac{d}{dt}\alpha_{PR} = \frac{1}{\tau_{tas}}\left[-\alpha_{PR}(t) + \sigma_{PR}(t)\right] \qquad (5)$$

Being α_{TPR} the change factor of the total peripheral resistance. $\alpha_{TPR,0}$ the base *TPR* change value, τ_{tas} the α-sympathetic time constant and σ_{PR} one function associated with α-sympathetic firing frequency, f_{tas}, that can be considered negligible when the firing frequency is too low.

Stroke Volume (SV) and Circulation: The stroke volume and the HP determine the cardiac output, *CO* (see Figure 1). Inputs for this subsystem are the *HP*, the scaling factor for the *TPR*, α_{TPR} and the pleural pressure, P_{pl}. An intermediate variable is the *ABP* and the resulting output variable in *CO*. This join with the vasculature modulate ABP. The α-sympathetic nerves control resistance and compliance in the circulation. In the model proposed by Cavalcanti and Belardinelli [6], the circulation subsystem used a two-element Windkessel model where the inputs were the *CO* and scaling factor for the *TPR*, α_{TPR} such that the model determines the *ABP* by means of the following expression (Equation 6):

$$\frac{d}{dt}ABP(t) = \frac{1}{C_{art}(\alpha_{TPR}R_{TPR})}\left[\alpha_{TPR}R_{TPR}CO(t) + ABP(t)\right] \quad (6)$$

Where C_{art} represents the arterial compliance and R_{TPR} the total peripheral resistance.

The *SV* is determined by the venous return, V_n, the HP and the heart contractility, C_n (Equation 7) [8]:

$$SV = HP \cdot V_n + C_n \qquad (7)$$

Venous return and contractility are first order transfer functions with *ABP* as input variable and with their respective delays [9].

Autonomic nervous system stimuli

Almost every process that affects the autonomic control system also affects the cardiovascular system through the vagal and sympathetic activity. The *ANS* plays an important role in the regulation of cardiac adaptation during dynamic exercise and during the exposition to certain substances in humans and conscious animals. Five stimuli can be simulated in the virtual laboratory.

Exercise. HR and SV increase during rhythmic or dynamic exercise, which produces an increase in *CO*. Recent works stated that cardiac sympathetic nerve discharge, f_{tbs}, increases during exercise in proportion to the running speed, and also stated that cardiac sympathetic outflow is stimulated during dynamic exercise although the intensity of exercise is moderate and even low, in concert with cardiac parasympathetic withdrawal [10].

Cholinergic intoxication. It produces increases of parasympathetic system activity, cardiac period (bradycardia) and also hypotension [11]. It is known that this kind of intoxication can be produced by the contact of the respiratory way, digestive or physically with anticholinesterases present in pesticides used in the prevention of plagues that affect the crops or in insecticides. These anticholinesterases inhibit the regulatory function of the acetyl-cholinesterase enzyme, which is responsible of metabolizing the acetylcholine (*ACh*), what derives in an excess of the mentioned neurotransmitter which implies an over excitation of the parasympathetic receptors, and an increase of the frequency of spikes generated by the above mentioned receptors, f_{tp}.

Caffeine. It is found in coffee, tea, chocolate, and many soft drinks and it keeps us awake by counteracting the effects of inhibitory neurotransmitters. Xanthines such as caffeine and theophylline block adenosine receptors [12]. This effect implies an increase in α-sympathetic and β-sympathetic activity that produces vasoconstriction, higher blood pressure and increased *HP* and contraction force. This activity is thought to be responsible for the stimulant effects of these agents [13].

Hemorrhage. It is defined as an acute blood volume loss (10% of total or more) and it modifies directly cardiovascular variables like: systemic arterial pressure, *CO* and total systemic resistance. In addition, it also affects the HR because the system has a baroreceptors feedback that also affects the *HR* [3].

Scare. Panic disorder is a situation with acute autonomic symptoms such as palpitations, difficulty to breathe, heart pounding, tremulousness and fear of dying because of a heart attack. Thus, the investigation of abnormal cardiovascular function in panic disorder is of specially interest [14]. In healthy people the scare could produce a panic crisis or only a light fear, but in all cases the autonomic system switched to an alert situation characterized by higher α and β sympathetic activity. In addition in patients with panic disorder there is a decrease in cardiac vagal function proportional to the increase in sympathetic function [14].

Identification of caffeine response

In order to simulate each stimulus it is necessary to determine the relationship between the stimulus level and the change of model parameters for the ANS. These parameters were tuned by means of experimental data in the case of caffeine stimulus and were configured according with scientific literature in the remainder ones [10, 11, 14].

Experiment description

Thirteen healthy volunteers (10 women and 3 men, age 23.2 ± 3.5 yr, 164 ± 8 cm, 60.3 ± 9.4 kg), who have not been taking medication, participated in the study. After 2h from their last food intake and 48h of caffeine abstinence they were comfortably installed in a temperature-controlled laboratory. Using a vital signs monitor (CSI model Poet Plus 8100), blood pressure, HR, and oxygen saturation were recorded. In a double-blind, placebo-controlled (descafeined coffee), crossover trial, each subject received a cup of black coffee without sugar (9g diluted in 100ml of water, 153 ± 25 mg/kg) each 20 min, during 1 h.

Parameter estimation

Collected mean values of blood pressure and HR during the trial from 0 to 4 cups were used to estimate the change rate of four ANS parameters related with xanthines: gain and baseline of f_{tas} and f_{tbs} via Nelder-Mead Simplex optimization technique [15] with MATLAB. Curves of f_{tas} and f_{tbs} versus coffee cups are included in CardioLab in order to simulate the effect of caffeine in the cardiovascular system. Table 1 shows the obtained parameter values in five different stages of the trial and systolic blood pressure and HR variation in experimental data. Prediction error was lower than 15% in all cases. Similar procedures have been implemented in the case of the other stimuli.

Table 1 Parameter estimation

Cup of Coffee	0	1	2	3	4
Heart Rate(bpm)	82.63	77.64	73.72	73.27	72.36
Systolic Blood Pressure (mmHg)	121.5	123.5	122.6	124.9	125.3
α-sympathetic gain	6.26	19.93	13.24	19.62	19.08
β-sympathetic Gain	1.03	1.82	1.55	1.60	1.94
Baseline α-sympathetic gain	5.01	9.20	8.60	5.57	7.28
Baseline β-sympathetic gain	5.72	16.95	27.78	15.17	17.27

Prediction error lower than 15% in all cases

Results and discussion

Tool development

Presented software application is based on Easy Java Simulation (EJS) [16], an open source java-based tool that allows creating interactive dynamic simulations.

The circulatory model is quite complex, for that reason the simulation model has been implemented in MATLAB/SIMULINK in order to profit from computation capabilities of this tool. The view and the interactivity have been completely designed and implemented in EJS linked to MATLAB/SIMULINK [17].

Interactive elements

The interactive module of the interface of the Virtual Laboratory is shown in figure 2. Most relevant parameters can be changed by means of sliders and tabs in order to simulate different cardiovascular conditions.
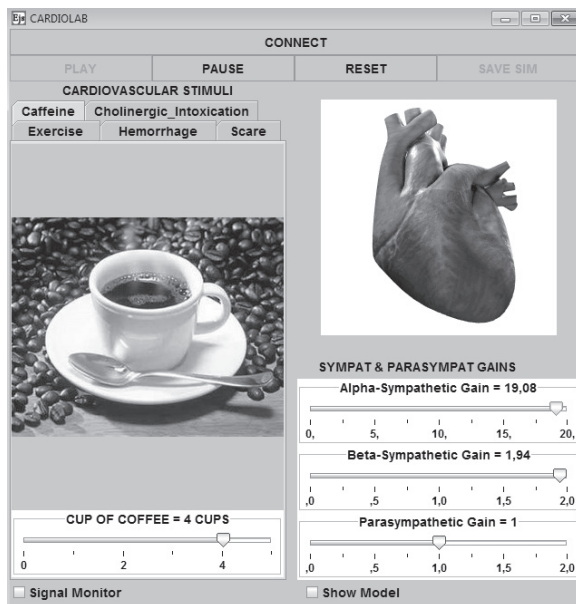

Figure 2 Virtual Laboratory Interface: The alpha and beta sympathetic gains increase at high caffeine concentrations

A multisignal scope can be seen in the right side of the interface when the user selects this option (figure 3). Two important types of simulations compose the interactive module:

•   Cardiovascular stimuli such as exercise, hemorrhage, scare, caffeine and cholinergic intoxication.

•   Sympathetic and Parasympathetic gains: α-sympathetic gain, β-sympathetic gain and parasympathetic gain.
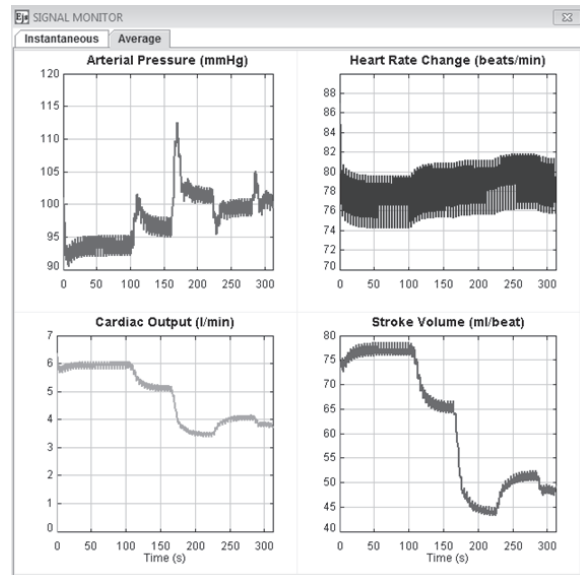

Figure 3 Average mode of the Signals Monitor, where the onset instants of stimuli are evident

In the first one, user can select the kind of stimulus clicking one of the five tabs available. A representative picture is shown in each tab: a kid with his leg bleeding because of a hemorrhage, a man fumigating without proper protection for cholinergic intoxication, a victim of a terrible scare during a panic attack, a runner when exercise is simulated and a cup of coffee for caffeine as it can be seen in figure 2. User can change the level of stimulus modifying the value of the cardiovascular parameter by means of a slider.

Regarding Sympathetic and Parasympathetic panels, the user can stimulate the cardiovascular

system with pharmacological products that produce blockade or hyperactivation of sympathetic or parasympathetic nervous systems. In this panel, user can configure its own stimulation profile. Additionally when the user sets the stimulus level in the five tabs mentioned above the sympathetic and parasympathetic sliders change their value in agreement with the stimulus.

A big animated picture of the heart is shown in the middle of the virtual laboratory and its HP and force of contraction change according to the simulation results. Finally, standard options in virtual laboratories are provided such as to "play", to "pause", to "reset", and to "save" the simulation results ("save-sim"). The last option allows saving the average value of all the variables shown in the "Signal Monitor" in one MATLAB file. It permits further analysis of simulation results or its comparison with experimental data. Furthermore, external windows appear when the user clicks the options "Show Model" (the MATLAB/SIMULINK model is shown) and/or "Signal Monitor".

Signal monitor

The user can choose between to different display modes, the instantaneous and the average one. In the former, following variables are shown during the cardiac cycles corresponding to the last 30 seconds: *ABP*, *HR*, *CO* and *SV*. In the Average mode, the variables are shown from the beginning of the simulation (see figure 3). One illustrative example is used in order to show the capabilities of the tool.

Firstly, a cup of coffee is drunk by the subject (9g diluted in 100ml of water) at 100 seconds. Average signals can be seen in figure 3, where changes in all variables occur in that moment. The ABP increases due to the increased α and β-Sympathetic gains, which develop vasoconstriction as a result of the stimulant effect of xanthines. The HR decreases (HP increases) thanks to the compensation generated by barorreceptors. The cardiac output (CO) increases because of the augmented heart

contractility. Sometime after the coffee ingestion, blood pressure and cardiac output remain in a lightly higher value (see figure 3).

Subsequent stimuli applied at intervals of 60 seconds (2, 3 and 4 cups of coffee) increase the effect over ABP and HR.

Conclusions

In this paper a virtual laboratory designed to analyze the human circulatory control system has been introduced. This laboratory is completely graphic and interactive, so it can be used to illustrate the behavior of human circulatory control system under certain circumstances and the influence of relevant parameters in the system. This virtual lab allows obtaining sensations and experiences that would be very difficult otherwise because of the difficulties in performing experimental human studies. The use of virtual laboratories and interactivity in BME has proved to be an efficient way to shortcut the learning process and improve the students capabilities. The tool has been built combining MATLAB/SIMULINK and EJS. While the former allows implementing complex models in straightforward manner, the latter allows designing attractive views and introducing interactivity easily. This combination is quite suitable for virtual laboratory development.

Acknowledgements

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