

# Coupling the Guyton Model to Pulsatile Ventricles using a Multiresolution Modelling Environment

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## Abstract

In this paper, we propose the substitution of the original, non-pulsatile cardiac sub-model of the Guyton model by an elastance-based pulsatile model of the heart, including interventricular interaction through the septum. Parameters of this cardiac model were identified by comparing the simulations obtained from the original Guyton model with those obtained from the proposed integrated, pulsatile model, during the 5 minutes simulation of a sudden severe muscle exercise. A close match is observed between the simulations obtained with the original and the pulsatile new model.

## 1. Introduction

Hypertension is a multifactorial pathology that may be caused by a number of genetic and environmental factors. In order to analyze this complex pathology, Guyton, Coleman, and Granger proposed a pioneering integrated, multi-organ, lumped-parameter model of the global cardiovascular system and its regulation [1]. However, this model, as well as their more recent versions [2] does not include a pulsatile representation of the cardiac function and, as a consequence, they are unable to represent short-term regulatory loops, such as the autonomic baroreflex control [3]. The advantage of coupling a pulsatile heart to the Guyton circulatory model have been already shown in [4] in the context of cardiac electrotherapy.

In this paper, we propose the substitution of the original, non-pulsatile cardiac sub-model of the G72 model with an elastance-based pulsatile model of the heart, including interventricular interaction through the septum. The simulations obtained with the pulsatile model are compared with one of the Guyton original benchmark experiments. This substitution process is not simple, as it requires the identification of the pulsatile model parameters that will preserve the stability and physiological properties of the G72 model, as well as and the appropriate handling of the heterogeneous time-scales that will be involved within the new model. The Guyton

model implementation is first presented. Then, the integration of pulsatile ventricles and the parameter identification are described. Finally, the pulsatile model outputs are confronted to the original model outputs during the simulation of a short period of sudden vigorous exercise, which is an original benchmark test of Guyton and colleagues.

## 2. Guyton model implementation

Within the framework of the SAPHIR project, the G72 model has been re-implemented by using an object-oriented multiresolution modeling tool, developed in our laboratory (M2SL) [5]. The use of M2SL allowed us to create the corresponding modules of the Guyton model as different physiological and functional blocks, each with specified inputs and outputs, and without manually specifying integration step-sizes. This was a mandatory step, preliminary to the replacement of original modules by updated or more detailed versions. In fact, M2SL allows straightforward representation of the hierarchical modularity of these models and automatically deals with the different time scales, whereas other simulation environments presented limitations related to lack of modular representation (eg. Berkely-Madona), slow execution time, difficulties with multi-resolution models, and, especially, impossibility of using multiple formalisms (eg. Simulink).

In order to implement the G72 model using M2SL, atomic model classes were created for each one of the 'blocks' described in the original paper. In addition, a coupled model class was defined to create instances of all other classes, as sub-model components, and to perform input-output couplings between these components [6]. Accuracy of the M2SL implementation of the G72 models was verified against simulation results from the original models (benchmarks provided by Ronald J. White, who worked in Guyton's laboratory during the 70s and 80s) and compared with other simulation environments [7].

### 3. Multiresolution integration of pulsatile ventricles

#### 3.1. Model description

In order to implement a pulsatile heart, the Guyton left and right heart models were replaced by a coupled model including four valves two pulsatile ventricles and the interventricular septum (figure 1). The heart valves are represented as non-ideal diodes, that correspond to modulated resistances. The pulsatile left ventricle and the valves were connected to the hemodynamic block of G72 by connecting PLA (left atrial pressure) and PA (arterial pressure) as inputs and the mitral and aortic flows (QMI and QLO) as outputs. Likewise, implementation of the pulsatile right ventricle was performed, by using the right atrial pressure (PRA) and pulmonary arterial pressure (PPA) as inputs and flows through the tricuspid and pulmonary valves (QTR and QRO) as outputs.

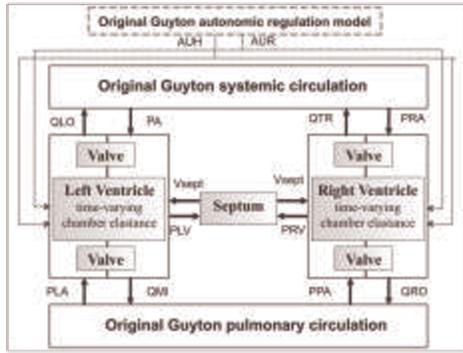


Figure 1: Integration of pulsatile ventricles in the original Guyton circulatory model.

Each ventricle is modeled as a single time-varying elastance. The main advantages of this approach are related to their low computational costs and the fact that they can be easily integrated into a model of the circulation. Time-varying elastances have shown a satisfying behavior in response to physiological variations (change of position, temperature, physical activity, etc.) [8]. The ventricular model of Smith [9] was chosen, since it integrates a representation of the septum dynamics. The myocardial contraction is represented by a time-varying chamber elastance. The driving function is defined as

$$e(t) = \sum_{i=1}^N A_i e^{B_i(t-C_i)^2}$$

Smith [9] proposes parameter values to define the function's profile:  $N = 1$ ;  $A = 1$ ;  $B = 250s^{-2}$  and  $C = 0.27s$ .

During the cardiac cycle, the ventricular elastance varies between minimum and maximum values defined respectively by the End Systolic Pressure-Volume Relationship (ESPVR) and the End Diastolic Pressure-Volume Relationship (EDPVR).

$$P_{es}(V) = E_{es}(V - V_d)$$

$$P_{ed}(V) = P_0(e^{\lambda(V-V_0)} - 1)$$

$P_{es}$  and  $E_{es}$  are respectively the end systolic pressure and elastance;  $V_d$  is the volume at zero pressure;  $P_{ed}$  is the end-diastolic pressure;  $P_0$ ,  $\lambda$ , and  $V_0$  are the parameters defining the EDPVR. The pressure-volume relationship can be defined as:

$$P(V) = e(t)P_{es}(V) + (1 - e(t))P_{ed}(V)$$

The ventricle elastance is also connected to the autonomic control in order to take into account the regulation of heart rate (chronotropic effect) and ventricular contractility (inotropic effect). In the original Guyton model, the output signal of the heart rate regulation module is continuous. To obtain pulsatile blood pressure, an Integral Pulse Frequency Modulation (IPFM) model was integrated [10]. The input of the IPFM model is the Guyton variable for autonomic regulation of heart rate (AUR) and each emitted pulse of the IPFM generates a variation of the ventricular elastance, which depends on the inotropic control (AUH) and AUR as follows:

$$E_{es} = AUH \cdot E_{es0}$$

where  $E_{es0}$  is the basal value for the end-systolic elastance.  $E_{es}$  is modulated by AUH, as it is an indicator of ventricular contractility

$$e(t) = A e^{B(t \cdot AUR - C)^2}$$

where  $t$  is the time elapsed since the last activation pulse.

The direct ventricular interaction is described by an interventricular septum model, which is represented as a flexible common wall between the left and right ventricles. The left ventricle free wall volume ( $V_{lvf}$ ) and the right ventricle free wall volume ( $V_{rvf}$ ) are defined as:

$$V_{lvf} = V_{lv} - V_{spt}$$

$$V_{rvf} = V_{rv} + V_{spt}$$

where  $V_{spt}$  is the septum volume and  $V_{lv}$  and  $V_{rv}$  are respectively the left and right ventricle volumes. The computation of the septum volume is the solution of the equation linking the septum pressure to the difference of left and right ventricle pressures.

$$P_{sept} = P_{lv} - P_{rv}$$

$$P_{sept} = e(t)E_{es\_sept}(V_{sept} - V_{d\_sept}) + (1 - e(t))P_{0sept}(e^{\lambda(V_{sept} - V_0)} - 1)$$

The ventricular model contains a minimal number of parameters in order to improve identifiability. The integration of the pulsatile model in the original Guyton circulation requires the adaptation of some ventricular parameters.

### 3.1. Parameter identification

Parameters of this cardiac model were identified by comparing the simulations obtained from the original G72 model with those obtained from the proposed integrated, pulsatile model, during the 5 minutes simulation of a sudden severe muscle exercise (Figure 2). An Evolutionary Algorithm was used to minimize the fitness function  $\varepsilon$ , which was computed as the sum of eight error functions that correspond to the eight variables presented in the original Guyton experience: VUD (urinary output), PVO (muscle venous oxygen pressure), PMO (muscle cell oxygen pressure), PA (mean arterial pressure), AUP (sympathetic stimulation), QLO (cardiac output), BFM (muscle blood flow), and MMO (rate of oxygen usage by muscle cells). In order to obtain the same order of magnitude for each error function, signals were first detrended and scaled. Then, an error function is associated with each of these signals:

$$\varepsilon_X = \frac{1}{N} \sum_{t=0}^{5 \min} \left| \hat{X}_{pulsatile}(t) - \hat{X}_{original}(t) \right|$$

where the variable  $X_{original}$  corresponds to the original Guyton output variables and  $X \in \{VUD, PVO, PMO, PA, AUP, QLO, BFM \text{ or } MMO\}$ . The variables  $X_{pulsatile}$  stand for the output of the Guyton model including pulsatile ventricles. The global error function is computed as the sum of all the error functions.

$$\varepsilon = \varepsilon_{VUD} + \varepsilon_{PVO} + \varepsilon_{PMO} + \varepsilon_{PA} + \varepsilon_{AUP} + \varepsilon_{QLO} + \varepsilon_{BFM} + \varepsilon_{MMO}$$

The set of specific parameters  $P$ , that needed to be identified, were thus  $P = [B, C, P_0, V_d, V_0, \lambda, E_{es}]$  where  $B$  and  $C$  are the elastance parameters,  $P_0$ ,  $\lambda$ ,  $V_d$  and  $V_0$  are the parameters defining the ESPVR and the EDPVR. They are supposed to be equal for the left and right ventricles.  $E_{es}$  is the end-systolic elastance of the right ventricle. The left ventricle end-systolic elastance is supposed to be equal to  $E_{esLV} = E_{es} \cdot (E_{esLV0}/E_{es0})$  where  $E_{esLV0}$  and  $E_{es0}$  are respectively the original values of left and right ventricular systolic elastance defined in Smith [7].

The error function  $\varepsilon$  had to be minimized in order to determine the optimal set of parameters  $P^*$ . Evolutionary Algorithms were chosen because they are particularly adapted to complex nonlinear problems characterized by a poorly-known state-space. Evolutionary algorithms are stochastic search methods inspired from the natural selection process. In these algorithms, the set of parameters  $P$  (or "chromosomes") characterizes each "individual" of a "population", which will evolve to get close to the optima [11].

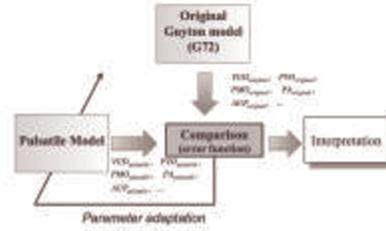


Figure 2: Parameters adaptation process.

First, a set of random "chromosomes" was used to create the initial population. The parameters corresponding to each individual were generated using a uniform distribution bounded by feasibility intervals: [50 1500] for  $B$ , [0.1 3] for  $C$ , [1 10] for  $P_0$ , [1 40] for  $V_d$ , [1 40] for  $V_0$ , [0.1 15] for  $\lambda$ , [50 500] for  $E_{es}$ . These intervals were defined to be large enough to allow a satisfying exploration of the parameter space.

Once the initial population was created, an iterative process was performed. The error function  $\varepsilon$  was computed at each iteration in order to evaluate the performance of each individual. Solutions with low error values were recombined with other solutions (cross-over) and small, random modifications of a chromosome were also introduced (mutation).

## 4. Results

Figure 3 shows the comparison between the pulsatile and the original model during the simulation of sudden severe muscle exercise, which is a benchmark test of original Guyton publication [5]. Thirty seconds after the beginning of simulation, the exercise parameter of the G72 model was changed to 60 times its normal value ( $EXC=60.0$ ), corresponding to an approximately 15-fold increase in the whole-body metabolic rate, the time constant for the local vascular response to metabolic activity was reduced by 1/40 ( $A4K=0.025$ ). Then, two minutes after the beginning of simulation, the exercise parameter value was reset to normal ( $EXC=1.0$ ).

Within seconds of the onset of exercise, cardiac output and muscle blood flow rose considerably to values respectively equal to 20 l/min and 16.6 l/min. The urinary output fell to its minimum level while arterial pressure increased moderately, while the muscle cell and venous  $PO_2$  decrease rapidly. The muscle metabolic activity showed an instantaneous increase, but then decreased considerably owing to the development of a metabolic loss in the muscles. After completing the exercise, the muscle metabolic activity fell below normal, but cardiac output, muscle blood flow and arterial pressure remained elevated for a while as the person was repaying his/her oxygen debt.

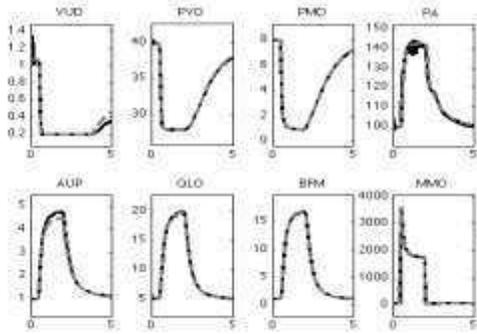


Figure 3: Comparison of the pulsatile model (black curves) with the original Guyton model (blue dashed curves) during a 5 minutes simulation of sudden severe muscle exercise. The black lines were obtained by a moving average mean filter, applied to each pulsatile variable, with a temporal support of 1 min. See the text for abbreviations.

The identified parameters are equal to:  $B=1223.5s$ ,  $C=1.0$ ,  $Vd=10.7$  ml,  $V0=33.6$  ml,  $\lambda=12.1$ ,  $P0=9$ mmHg and  $Ees=2.6122$  mmHg/ml. It can be noticed that all the identified values are higher than the original values. For example, the identified  $Ees$  is equal to 2.6122 mmHg/ml whereas the original value is 0.6525 mmHg/ml. It means that the global cardiac performance (contractility, ...) should be increased to reproduce an elevation of the arterial pressure and cardiac output, during severe exercise, similar to the original signal obtained by Guyton.

## 5. Conclusion

This paper presents an example of multiresolution integration in which the non-pulsatile ventricles of the original G72 model are replaced by a pulsatile, elastance-based model. The results show that a close match was obtained between the simulations performed with the original Guyton model and the new model, integrating a pulsatile heart. The main advantage of the integration of pulsatile ventricles is to keep the original Guyton short and long term regulatory loops, while simulating realistic profiles for the left and right ventricles pressure.

The good agreements between the simulations obtained with the pulsatile and the original model illustrates that the general response of the model is preserved. However, it could be interesting to estimate the overall model behavior by using sensitivity analysis methods in order to evaluate the Input/Output relationship of each Guyton module [12]. The global pulsatile model could then be used to simulate both short-term and long-term responses to pharmacological or device therapy in heart failure patients. The same methodology will be applied to improve the definition of boundary conditions

in of more detailed models of the ventricular dynamics [13].

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