MODELING OF THE CARDIOVASCULAR SYSTEM AND ITS CONTROL MECHANISMS FOR THE EXERCISE SCENARIO

– PhD Thesis Summary –

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The objective of the PhD thesis is designing a model that mimics the Cardiovascular System (CVS) when it transitions from the rest regime to the exercise regime. The exercise scenario consists in a constant effort test. The model validation is based on two case studies (ergometric bicycle tests) taken from references. The model is accompanied by a parametrization procedure that uses the temporal variations of the heart rate *H* and the arterial systemic pressure *Pas* measured during an effort test.

For reaching this objective, several steps have been taken:

1. Describing the physiological CVS processes and identifying them using mathematical models.
2. Finding the formulas and the value ranges for the CVS model parameters.
3. Obtaining the methods that determine the temporal variation of the parameters that describe the local regulatory mechanisms.
4. Determining the CVS command function that drive the system from the rest regime to the exercise regime.

By using this model, the temporal variations of the CVS signals (the cardiac output, the pulmonary pressures and the systemic resistance), specific to the transition from the rest regime to the exercise regime, are obtained throughout simulation. These variations offer additional information regarding the health status of a certain person and can be used for diagnosis in medical centers using computer applications.

The thesis has six chapters. (Fig.1)

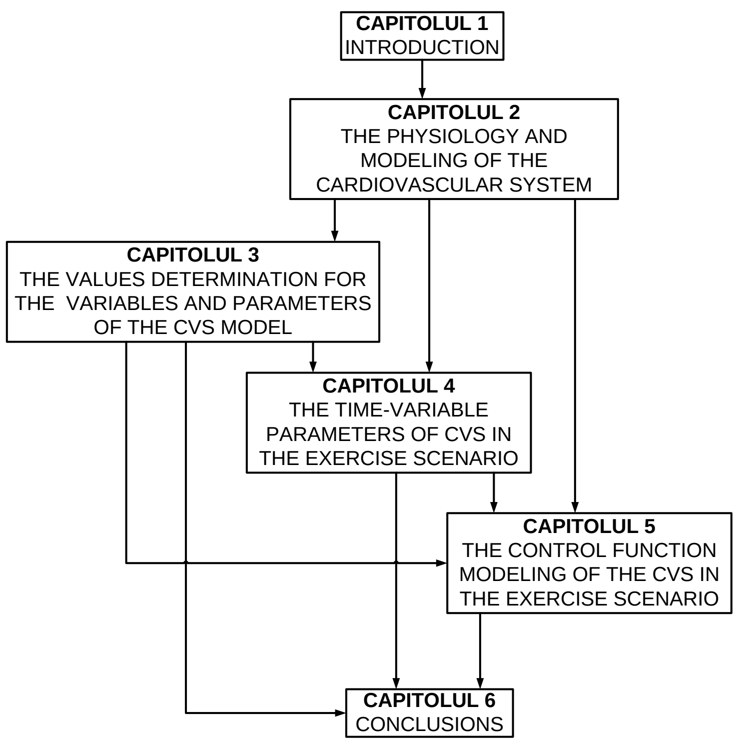

Fig. 1 The PhD thesis structure

The first chapter of the thesis presents the research domain, the objective and the manner in which this objective was reached throughout the chapters. The steps presented above are detailed in the chapters 2-5. The thesis ends with the conclusions chapter.

For proper understanding of the physiological phenomena that take place in the CVS and the regulatory mechanisms, first of all, it was necessary to enumerate them and to provide a systemic description based on informational models. This is done in *the second chapter* of the thesis. Also, cardiovascular signals and the parameters of the CVS are defined and a classification of the local and global regulatory mechanisms is presented. The emphasis is on the exercise scenario and on the main regulatory mechanisms that drive the CVS model from the rest regime to the exercise regime. At the end of the second chapter, the model (2.33) proposed by [1] and the modeling hypothesis are presented. The model disregards the pulsatile behavior of the cardiovascular signals and is a lumped parameters model. Its structure contains the heart's ventricles, the blood vessels of the two circulations lumped together in four compartments (arterial systemic, venous systemic, arterial pulmonary, venous pulmonary) and the blood vessels situated in the active muscles and lungs lumped together in two peripheral regions. The local regulatory mechanisms are included in the system by considering the systemic resistance as a state variable and assuming that the three parameters change their values from the rest to the exercise regime. The control function, given by the nervous system and describing the global regulatory mechanisms, is obtained as a solution for an optimal control problem. It is a nonlinear 9^{th} order model and the parameters vector has 23 components.

The second chapter contributes by assembling a systemized and structured presentation using a system engineering specific language, based on medical science knowledge [2,3]. The second chapter can be used by all interested in the CVS modelling both from the medical and engineering fields. Identifying the physiological processes doesn't relate exclusively to the exercise scenario and the presented subsystem models can be adapted and used to determine the models for different operating scenarios of the CVS.

The use of the model (2.33) from [1] has been leading to the following problems:

1. Determining the values of the parameters and the initial conditions for the mathematical model,
2. The parameters variability from the rest regime to the exercise regime and the manner of integrating their temporal variation in the model,
3. The synthesis of a command function that can drive the system from the rest regime to the exercise regime, in accordance to the experimental variations of the arterial systemic pressure P_{as} and the heart rate H.

The chapters 3-5 present the solutions to these problems, which don't increase the complexity of the model. The solutions are based on the CVS physiology and the regulatory mechanisms and use only the variations of the cardiovascular signals that are usually obtained by measurements or from medical references.

The problem of the CVS model parametrization is resolved in *the 3^{rd} chapter*. It is a difficult problem because of certain aspects:

- Lack of unity regarding the domain values of the parameters and also the lack of specifications regarding the initial conditions values,
- The need to utilize a reduced number of measured variations of cardiac activities for determining the parameters and the initial conditions: *Pas*, *H*
- The parametrization based on the *Pas* and *H* variations must provide normal values for all the cardiovascular signals, both for the rest regime and for the exercise regime.

Also, the parameter values for the CVS model are hard to obtain mostly because they are related to the person for which the CVS is modelled. Also, some of the parameters lose their physiological meaning due to the approximations and simplifications that take place in the modelling process. In the 3rd chapter, formulas are given for the model parameters (2.33). They are determined using the steady state equations of the CVS and by imposing conditions on the local processes dynamics. The rest and exercise steady values of the blood pressure in the four compartments, the heart rate and the ventricles ejection fraction need to be known for obtaining the parameters using the proposed formulas. The values for these signals are obtained from measurements (arterial systemic pressure and heart rate) and from tables with normal physiological values for the rest and exercise regimes. Table 3.1 (with the normal ranges for the CVS variables in rest regime) and Table A3.5.5 (with the percentage changes of CVS signals in exercise regime) are obtained by an analysis of the medical references (Appendixes A3.2, A3.3). The study was challenging because the values and domains presented in literature are different due to the measuring methods utilized, to the particularities of each tested person (age, sex, health state) and to the imposed exercise scenario (the intensity of the exercise, the body position). Using the values and the domains established for the cardiovascular signals and also the (3.1), (3.5), (3.6), (3.9), (3.14-3.16) formulas, the parameters of the CVS model can be determined.

Chapter three shows an analysis of the influences on the cardiovascular signals of the parameter rest values in exercise regime. This analysis showed that if only some parameters change their values from the rest to exercise regime, some of the cardiovascular signals will not have the appropriate variations in the exercise scenario. Thus, for the final model (5.44) all the parameters of the CVS have different values in the two operating regimes. Their values are computed using the tables and formulas presented above.

The 3rd chapter contributions are the parameter formulas: (3.1), (3.5), (3.6), (3.9), (3.14-3.16), the tables 3.1 and 3.2 with the normal ranges for the CVS variables in rest regime and the table A3.3.5 with the percentage changes of CVS signals in exercise regime. These results can be used in the parametrization of various cardiovascular system models. They are established using physiological reasoning and they are valid for the CVS functioning.

The second problem, that refers to the parameter variability, is solved in *the 4th chapter*. Three parameters (the pulmonary resistance R_p, the metabolic rate M_T and the coefficient A_{pesk}) change their values from the rest to exercise regime in [1]. Their variations represent the action of the local control mechanisms in the active muscles and lungs that influence the systemic and pulmonary resistances.

The notion of parametric function is introduced in order to integrate these parameters temporal variations in the model. Also, the cardiovascular model is included in the class of dynamical nonlinear lumped parameter regime-switching systems. Thus, the cardiovascular model is changing the operating regime due to a switching input signal (the intensity of the exercise) which changes its value from zero, in rest regime, to a constant value, in the exercise regime.

The parametric functions are obtained using the sensitivity functions of the heart rate and the arterial systemic pressure. The sensitivity theory was extended by introducing the sensitivity functions of the parametric functions and the sensitivity generators as regime-switching systems. Two methods were established:

- The method of obtaining the parametric functions using candidate parametric function variations [4],
- The method of determining the parametric functions based on the correction of the nominal variation with the deviations of the parametric functions obtained based on the desired adjustments in the output signals [5].

The first method uses temporal variations, chosen on physiological reasoning, as candidate functions and analyses the effect on the heart rate and arterial systemic pressure of the parametric function deviations from the nominal step variation. The result of the method is the combination of the candidate parametric functions that provides the best improvement on the cardiovascular signals transient variations. The method has a degree of restriction due to the few types of evaluated candidate functions. The method was used in a case study. The obtained parametric functions for the three parameters improve the response of the model (2.33). These variations can be used also in establishing dynamical models for systemic and pulmonary resistance in exercise scenario.

The second method uses a searching algorithm for determining the adjusted deviations of nominal parametric functions based on minimizing the difference between the simulated response and the measured data for the arterial systemic pressure and heart rate. The algorithm steps are: i) Computing the maximal deviation of the heart rate and arterial systemic pressure due to the parametric functions deviations from the nominal variations (the calculus uses the sensitivity functions); ii) determining the temporal periods in which the cardiovascular signals are desired to be improved (the difference between the simulated responses and the measured data for the arterial systemic pressure and heart rate are greater than a threshold); iii) Computing the parametric functions deviations by considering as reference data the signals differences mentioned in the previous step; iv) Obtaining the final variations of the parametric functions by adding the determined deviations to the nominal variations.

This method is used in the parametrization of the final model (5.44). The resulted variations of the parametric functions have similar forms as the variations obtained with the first method. A cardiovascular model which uses exogenous models for the systemic and the pulmonary resistances is established, based on this conclusion. The model (4.31) provides the estimating temporal variations of the cardiac output and of other cardiovascular signals in exercise regime [6]. The main characteristics of the model (4.31) are: i) the input signal is the measured variation of the heart rate; ii) the structure of the model is composed of the two ventricles, the four compartments and the two regions (same as the model (2.33)); iii) the parameter values of the circulations models and the heart ventricles have constant, but different values in the rest and the exercise regimes (computed with the formulas presented in the chapter 3); iv) the local regulatory mechanisms are integrated in the model by linear standard models; v) the parameters of these models are obtained using an estimating algorithm that minimizes the difference between the simulated and measured values of the arterial system pressure. This model provides the temporal variations of the cardiovascular signal that are difficult to be obtained by measurements, using the arterial systemic and heart rate variations measured during an exercise scenario.

The contributions of the chapter 4 are: presenting the CVS model as a regime-switching system, introducing the concept of parametric function as an attribute of the time-variant systems, extending the sensitivity theory to the parametric functions, establishing two methods of determining the parametric functions variations and obtaining a CVS model for estimating the cardiac output temporal variation in exercise scenario. The two methods of determining the parametric function apply to every situation in which a parameter of a model changes its value, but its variation is not fully known. The parametric functions obtained using these methods can be correlated with standard variations or standard model responses. The variations of the cardiovascular signals estimated with the model (4.31) provide additional information in evaluating the health state of a person in test effort.

The third problem regarding the synthesis of the control function for the CVS is resolved in *the 5th chapter*. The global regulatory mechanisms of the CVS, activated by the nervous system, are difficult to model based on the physiological processes. The control function had to be synthesized so that the main regulatory mechanisms are taken into consideration. Also, the control function must be easy to use and to operate only with the measured signals: the arterial systemic pressure and the heart rate.

In chapter 5 are presented two control function synthesis methods:

- The synthesis of the control function using a “pole-by-pole” allocation method [7];
- The synthesis of the control function based on physiological reasoning [8].

Both synthesis methods use the linearized model of the CVS in the vicinity of the exercise steady state. The control function is obtained using a state compensator. The manner of obtaining the control function based on the state compensator is taken from [1], but the determination of the compensator vector is changed. The control function in [1] is determined as the solution of a linear quadratic control problem corresponding to the minimization of the quadratic cost function (2.31). The cost function penalizes only the deviation of systemic blood pressure from the steady exercise value. Throughout it, the baroreflex mechanism is considered. The influence of the weighting factor of the cost function (2.31) on the poles and zeroes of the Laplace transforms of the heart rate and the arterial systemic pressure was investigated. The conclusion is that the model of the CVS provides an optimum in the case of the arterial systemic pressure variation, but not so much in the case of the heart rate variation.

In order to improve the heart rate simulated variation, only the pole with the zero value of the open loop model has to be relocated. The first method of synthesis the control function is based on this observation and uses the algorithm presented in [9]. Using this algorithm, it was established that a different cost function which penalizes the heart rate from the exercise value can be used instead of (2.31). The new control function was applied in two case studies with good results.

However, this synthesis method is difficult to be used. It implies the root locus analysis of the transfer function (5.28)

The second method for obtaining the state compensator is based on the integration of the most important regulatory mechanisms which activates at exercise: the nervous command that determines the rising of the heart rate and the baroreflex stabilization mechanism of the arterial systemic pressure. the linearized system mathematical model was considered as two systems connected in series by the heart rate. This allows the control function synthesis by a successive addition of components that represent the regulatory mechanisms. The two mentioned mechanisms are integrated in the command function by using a component that is dependent of the heart rate deviation from the exercise value (representing the CVS nervous control) and a second component depending on arterial systemic pressure (representing the baroreflex mechanism). The second component was imagined in two manners: the first by using the velocity of the arterial systemic pressure and the second by using the difference of the arterial systemic pressure from its exercise value. By applying the first solution in the two case studies, it was showed that the value of the weighting factor of this component can have either positive or negative values. The second control function form, (5.39), leads to better results. It is easier to be parameterized and to be used in obtaining the closed loop CVS model.

Thus, the response of the model (2.33) completed with the control function (5.39) is better than the response of the model presented in [1]. The methods of determining the parametric functions presented in the chapter 4 were used for the CVS model (2.33) where the command function is obtained with (5.39). The simulation conclusion was that, by modifying the parametric functions from the nominal case, the model's response in the transitory regime doesn't substantially improve. This underlines the fact that the command function (5.39) is adequate for obtaining the suitable transitory response for the CVS model in the exercise scenario.

The 5.4 paragraph presents the new CVS model that includes the command function for the exercise scenario. This 4^{th} order model has a more reduced complexity compared to the one in [1] and faithfully reproduces the CVS signals variations in the exercise scenario. The model integrates the global regulatory mechanisms by using the control function (5.39) and the local regulatory mechanisms by using the parametric functions for systemic and pulmonary resistances determined with the second method presented in chapter 4. Eliminating certain state signals from the model in [1] is compensated by considering that the parameters of the sanguine circulations and the ventricles have different values for the two operating regimes. The model (5.44) is provided with a complete methodology for utilization and parametrization. Therefore, the model can be widely applied and it can be used in modeling a specific exercise scenario and also, by modifying it, in modeling other operating scenarios of the CVS.

The contributions of the chapter 5 are the two synthesis methods of the control function and de new mathematical model of the CVS and its control mechanisms (5.44). The control function (5.39) operates only with signals that can be obtained by measurements (*Pas* and *H*). The model (5.44) is an alternative to the existing models presented in references. It provides appropriated temporal variations for all of the state variables. It can be used for the study of different physiological processes, in training courses of medical students and in application for the cardiac rehabilitation.

The obtained results in this PhD thesis are meant to be used by all the researchers that study the modeling of the CVS and its regulatory mechanisms. The bibliographic references from the engineering field offer mostly mathematical models that can be used only for some particular cases and the references from the medical field offer statistical studies that provide theoretical correlations between different CVS signals. The main contribution of this thesis is that the proposed models and formulas, presented above, are determined by combining the knowledge of the two fields. This can lead to other related research used for:

- CVS modeling for other types of efforts, including the ones for the current activities;
- The results integration in computer applications for medical centers.

The thesis has 135 pages, 43 tables, 101 figures and 87 references.

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