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A Sensitivity Based Improvement Method of a Cardiovascular Model in Exercise Scenario

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Abstract: The sensitivity analysis is usually used for two purposes: to determine the effect of the deviation of a certain parameter on the response of a system regarding a nominal situation and to rank the parameters of a system from the most to the least sensitive with respect to the output signal. The present paper extends the sensitivity analysis approach on time-variable parameters (parametric functions) and develops as a case study the transition regime of the cardiovascular system (CVS) in exercise scenario. The proposed extension is used to identify the proper variations of three parameter functions determined by the exercise level. The final results show that the performances of the CVS model are improved by following a three step correction method.

Keywords: sensitivity analysis, time-varying parameter, cardiovascular system, exercise scenario, parameter optimization.

1. INTRODUCTION

There are many changes in a human body when subjecting it to physical effort. These changes can involve different regulatory mechanisms. A major role in adapting the human body to physical exercise conditions is played by the CVS.

The behavior of the CVS in the case of physical exercise is described in different papers using mathematical models of closed loop systems with the intensity of the exercise as the reference signal (Ursino and Magosso, 2002; Ursino and Magosso, 2006; Abbass et al., 2012; Batzel et al., 2007; Kappel and Peer, 1993). The complexity of these models depends on the detail level of the CVS structure and of the physiological mechanisms that act in and between the CVS and the nervous control system.

In particular, the mathematical model proposed in (Ursino and Magosso, 2002; Ursino and Magosso, 2006) consists of 13 subsystems describing the heart, the systemic and the pulmonary circulations of the CVS and a complex control system including the metabolic regulation, baroreflex mechanism and ventilation response. Due to its complexity, this model is only of qualitative importance. The model used in (Abbass et al., 2012) does not take into account the above subsystems of CVS and provides only correlation equations between heart rate and arterial blood pressure. The control loop is based on describing the brain activity in response to physical workload. The influences of the respiratory system and thermoregulation are also included. Thus, the regulatory mechanisms are detailed, but only two signals of the CVS are provided.

In order to improve its performance, the model used in this paper, is the lumped parameters model presented in (Batzel et al., 2007; Timischl, 1998). Compared with the previous mentioned CVS models, this one provides: the blood pressures of the arterial/venous pulmonary and systemic compartments, the systemic resistance and the heart rate as state variables. The local metabolic regulation process is included in the model equations and the nervous control signal, based on the baroreflex mechanism, is synthesized using control theory instruments. Therefore, this model allows the analysis of the effect of physical exercise on the main characteristic signals of the CVS, but maintains an average degree of complexity. The restricted level of detail regarding the control mechanisms is partially compensated by the three parameters that take different values in the rest and exercise regimes: M_T (metabolic rate), A_{pesk} (Peskin constant) and R_p (pulmonary resistance). Although the steady state values for these parameters can be found using estimation methods, their transient variations are unknown.

The purpose of this paper is to determine these parameters as functions of time, called parametric functions, suitable in describing the change from rest to exercise state. For this, a three step method based on the sensitivity theory is proposed.

The sensitivity theory is usually used to determine the effect of the deviation of one or more parameters on the behavior of a system with respect to a nominal regime. For the model used in this paper, a sensitivity analysis is performed to determine which parameter has the major influence over the measurable signals of the CVS (Kappel and Batzel, 2006). Subsequently, the generalized sensitivity function is used for parameter ranking and selection (Banks et al., 2010). In the present paper the sensitivity analysis is used to determine the parameters influence, in this particular pattern of dynamic system response. Usually, the modelling of physiological systems is based on the grey-box methods, including two stages: mathematical description of the physiological phenomena and parameter identification using data measurements. Therefore, the sensitivity analysis becomes a tool in the evaluation and improvement of the physiological models (Batzel et al., 2009).

The next section presents the methodology used in the study. The class of dynamic systems with regime changing input signal and the sensitivity functions with respect to the parametric functions are introduced. Sections 3 and 4 are focused on applying the methodology on the CVS with baroreflex control loop in rest-exercise regime. Step, exponential and sigmoid type candidate variations for the three parametric functions are used. Based on these candidate variations, in section 5, the effects of the parametric function deviations on the system response of two measurable signals are evaluated. The proposed correction method of parametric functions is used and validated based on the improvement of the system response.

2. METHODOLOGY

Let

$$\dot{x}(t) = \tilde{F}(x, p_f, p, r), \qquad x(0) = x_0 \tag{1}$$

be a dynamical nonlinear lumped parameter system with $t \in \Im \subset \Re$, $\Im$ - time horizon, $x \in \Re^n$, state variable, $p_f \in \Re^{n_{pf}}$ time variable parameters, restricted by r, $p \in \Re^{n_p}$ constant parameters, $r \in \Re$, input variable designed for changing the operating regime.

Regarding model (1), the following assumption is made:

Model (1) expresses the dependences of a physical system. The model's behavior with respect to a step variation $r(t)$ reveals the transition between two steady-state operating regimes. This model is characterized by a set of constant parameters p (for the entire temporal horizon) and a set of variable parameters p_f that take different values in the steady state regimes, installed before and after the change of *r*. The unknown time variable functions $p_f(t)$, called further parametric functions, are generated by the system depending on $r(t)$. The dependences are included in the model (1).

The present study analyses the possibility of finding appropriate approximations for $p_f(t)$ based on some state variable measurements for system (5) and using the sensitivity theory.

The sensitivity theory of the dynamic systems develops models that generate sensitivity functions which can be used in estimating the effect with respect to the parameters deviations on the output signals (Frank, 1976). Consider the state signal $x(t)$ of (1) and the sensitivity function $S_{x,p_0}(t)$ regarding parameter p, computed for a nominal value p_0. The response of (1) for $p = p_0 + \Delta p$, Δp being a constant deviation, can be approximated to:

$$x(t) = x_0(t) + S_{x,p_0}(t)\Delta p\,, \; \Delta p = const\,, \tag{2}$$

where $x_0(t)$ is the solution of (1) when $p = p_0$.

In this paper the sensitivity theory is extended to the parametric functions $p_f(t)$ as follows: Considering the nominal parametric functions $p_{f0}(t)$, additional deviations $\Delta p_f(t)$ cause a modification of the state trajectory $x_0(t)$ that can be approximated using specific sensitivity functions defined with respect to $p_f(t)$ and computed for $p_{f0}(t)$. Hence, for $p_f(t) = p_{f0}(t) + \Delta p_f(t)$, $x(t)$ can be approximated by:

$$x(t) = x_0(t) + S_{x,p_{f0(t)}}(t)\Delta p_f(t) \tag{3}$$

Further, the sensitivity functions $S_{x,p_{f0(t)}}(t)$ will be used to obtain the parametric functions $p_f(t)$, $n_f = 3$, of a CVS model with baroreflex loop. The model reproduces a constant effort scenario. This will be determined by using the sensitivity functions for evaluating the effect of some deviations regarding the parametric functions from nominal synchronous step parametric functions on two measurable signals of the system.

3. THE MATHEMATICAL MODEL OF CLOSED LOOP SYSTEM FOR THE REST-EXERCISE REGIME

The exercise scenario, used in this study, consists in subjecting the CVS in rest regime, at a moment t_{exer}, to a constant effort, via a step variation of the workload W (exercise input):

$$W(t) = \begin{cases} 0 & t \in [t_0, t_{exer}) = \Im^{rest} \\ W^{exer} & t \in [t_{exer}, t_f] = \Im^{exer} \end{cases}. \tag{4}$$

Here $\Im^{rest}$ is the rest regime temporal horizon and $\Im^{exer}$ is the exercise regime temporal horizon.

The mathematical model of the CVS used for this scenario, together with the modelling hypotheses and structural assessments (detailed in (Batzel *et al.*, 2007)) is the 9th order continuous-time nonlinear system:

$$\dot{x}(t) = F(x, p, W, u), \;\; x(t_0) = x^{rest}, \; t \in \Im^{rest} \cup \Im^{exer}. \tag{5}$$

where $x = \left[p_{as}, p_{vs}, p_{ap}, S_l, \sigma_l, S_r, \sigma_r, R_s, H\right]^T$ is the state vector of the system, p is the parameter vector:

$$p = [c_{as}, c_{vs}, c_{ap}, c_{vp}, c_l, c_r, V_{tot}, R_l, R_r, k, C_{aO_2}, K, M_0, \rho_M, \alpha_l, \beta_l, \gamma_l, \alpha_r, \beta_r, \gamma_r, R_p, A_{pesk}]^T.$$

$u(t)$ represents the control signal of the CVS, provided by the baroreflex mechanism, leading the system from the stationary rest regime (x^{rest}) to the stationary exercise regime (x^{exer}). The components of the vector operator F are

$$F_1(t) = \frac{1}{c_{as}}\left(Q_l(t) - \frac{p_{as}(t) - p_{vs}(t)}{R_s(t)}\right)$$

$$F_2(t) = \frac{1}{c_{vs}}\left(\frac{p_{as}(t) - p_{vs}(t)}{R_s(t)} - Q_r(t)\right)$$

$$F_3(t) = \frac{1}{c_{ap}}\left(Q_r(t) - \frac{p_{ap}(t) - p_{vp}(p_{as}(t), p_{vs}(t), p_{ap}(t))}{R_p}\right)$$
$$F_4(t) = \sigma_l(t)$$
$$F_5(t) = -\alpha_l S_l(t) - \gamma_l \sigma_l(t) + \beta_l H(t)$$
$$F_6(t) = \sigma_r(t)$$
$$F_7(t) = -\alpha_r S_r(t) - \gamma_r \sigma_r(t) + \beta_r H(t)$$
$$F_8(t) = \frac{A_{pesk}}{K}\left(C_{aO_2}\frac{p_{as}(t) - p_{vs}(t)}{R_s(t)} - M_T\right) - \frac{p_{as}(t) - p_{vs}(t)}{K}$$

The rest of variables have the meaning:

$$Q_l(t) = H\frac{c_l p_{vp}(p_{as}, p_{vs}, p_{ap}) a_l(H) S_l}{a_l(H) p_{as} + k_l(H) S_l}$$
$$Q_r(t) = H\frac{c_r p_{vs} a_r(H) S_r}{a_r(H) p_{ap} + k_r(H) S_r}$$
$$k_\bullet(H) = e^{-\frac{t_d(H)}{c_\bullet R_\bullet}},\ a_\bullet(H) = 1 - k_\bullet(H), \text{ with } \bullet \in \{l, r\}$$
$$t_d = t_d(H) = \frac{1}{H^{\frac{1}{2}}}\left(\frac{1}{H^{\frac{1}{2}}} - k_b\right)$$
$$p_{vp}(p_{as}(t), p_{vs}(t), p_{ap}(t)) = \frac{V_{tot} - c_{as}p_{as}(t) - c_{vs}p_{vs}(t) - c_{ap}p_{ap}(t)}{c_{vp}}.$$

The last state equation of (5) is $H'(t) = u(t)$. Consequently, the control signal $u(t)$ imposes the variation of the heart rate during physical exercise and is responsible for the proper transition of the heart rate from the rest regime to the exercise regime. According to (Batzel et al., 2007), the shape of the control signal is:

$$u(t) = K_u(x(t) - x^{exer}),\ t \geq t_{exer}.$$

x^{exer} represents the stationary level of x in the exercise regime. K_u is the control gain, obtained as the solution of a linear quadratic optimization criterion, using the cost function (6).

$$J(u, x^{rest}) = \int_0^\infty (q_{as}^2(p_{as}(t) - p_{as}^{exer})^2 + u(t)^2)dt \tag{6}$$

The cost functional $J(\cdot,\cdot)$ penalizes the deviation of the arterial systemic pressure from the steady exercise value and the intensity of the control $u(t)$ and synthesizes the baroreflex mechanism.

Since for the stationary rest regime $u(t) = 0$, the control signal becomes:

$$u(t) = K_u(x(t) - x^{exer}),\ K_u = \begin{cases} 0, & t \in \Im^{rest} \\ const \neq 0, & t \in \Im^{exer} \end{cases} \tag{7}$$

Thus, the closed loop model used in this study is (5) complemented with (7). Obviously, the parameter vector is supplemented with the weighting factor q_{as} used in the linear quadratic optimization problem.

Under input W the values of three components from p: M_T (metabolic rate), A_{pesk} (Peskin constant) and R_p (pulmonary resistance), know substantial changes (Batzel et al., 2007). The first 2 parameters appear in the 8th state equation of (5) that describes the metabolic local regulation of blood vessels in active muscles. The chemical process that takes place in the active muscles, resulting in a decrease of the systemic resistance R_s during exercise, depends on the value of the metabolic rate M_T. According to (Batzel et al., 2007), regarding the metabolic rate the empirical dependence $M_T = M_0 + \rho_M W^{exer}$ is adopted. M_0 is the metabolic rate in the rest regime and ρ_M is a positive constant. Literature states that the coefficient A_{pesk} is variable, without an agreement on how it changes. The pulmonary resistance R_p decreases during exercise, following the increase of the lung blood volume (Flamm et al., 1990). In this way the blood pressures of the pulmonary region are maintained at normal limits.

Based on the above considerations, M_T, A_{pesk} and R_p are further considered as parametric functions $p_f(t)$ correlated, through t_{exer}, with the effort $W(t)$ and having the general shape:

$$\begin{cases} p_f(t) = p_f^{rest}, & t \in \Im^{rest} \\ p_f(t) \in (p_f^{rest}, p_f^{exer}], & t \in [t_{exer}, t_f) \\ p_f(t) = p_f^{exer}, & t = t_f \end{cases} \tag{8}$$

Specifically, $p_f(t)$ can be a step function as in (Batzel et al., 2007) and (Kappel and Peer, 1993), included in (1):

$$p_{f,T}(t) = \begin{cases} p_f^{rest}, & t \in \Im^{rest} \\ p_f^{exer}, & t \in \Im^{exer} \end{cases}, \tag{9}$$

or an exponential function as in (Timischl, 1998):

$$p_{f,E}(t) = \begin{cases} p_f^{rest}, & t \in \Im^{rest} \\ p_f^{rest} + (p_f^{exer} - p_f^{rest})(1 - e^{-\frac{t - t_{exer}}{T}}), & t \in \Im^{exer} \end{cases} \tag{10}$$

Also, it is important to consider that parametric functions of the sigmoid type, are frequently used in describing transient processes in biological systems, i.e.:

$$p_{f,S}(t) = \begin{cases} p_f^{rest}, & t \in \Im^{rest} \\ p_f^{rest} + \dfrac{(p_f^{exer} - p_f^{rest})}{1 + e^{-a(t - (t_{exer} + b))}}, & t \in \Im^{exer} \end{cases} \tag{11}$$

Finally, by substituting (7) in (5), and considering (9)-(11), for the CVS with the baroreflex feedback loop, a model of type (1) is obtained:

$$\dot{x}(t) = \tilde{F}(x, p, p_f, W),\ x(t_0) = x^{rest},\ t \in \Im^{rest} \cup \Im^{exer}. \tag{12}$$

Here: W represents the input variable r in (1),

$$p = [c_{as}, c_{vs}, c_{ap}, c_{vp}, c_l, c_r, V_{tot}, R_l, R_r, k_b, C_{a.O_2}, K, M_0, \rho_M, \alpha_l, \beta_l, \gamma_l, \alpha_r, \beta_r, \gamma_r, q_{as}]^T$$

is the constant parameter vector, and $p_f = [R_p, A_{pesk}, M_T]^T$

represents the parametric function vector. The result (12) will be used further for computing the sensitivity models with respect to the parametric functions in order to approximate them.

4. SENSITIVITY FUNCTION GENERATOR

Let $p_{f_i}(t)$ be one of the parametric function vector p_f of (12). Then, the sensitivity generator of the state vector x with respect to $p_{f_i}(t)$ is:

$$\dot{S}_{x,p_{f_i,0}(t)}(t,p,p_{f0}(t),W) = \underbrace{\left.\frac{\partial\tilde{F}}{\partial x}\right|_{(12)^0} S_{x,p_{f_i,0}(t)}(t,p,p_{f0}(t),W) + \left.\frac{\partial\tilde{F}}{\partial p_{f_i,0}(t)}\right|_{(12)^0}}_{\tilde{G}},$$

$$S_{x,p_{f_i,0}(t)}(t_0,p,p_{f0}(t_0),W) = 0,\ t \in \Im^{rest} \cup \Im^{exer} \qquad (13).$$

$p_{f0}(t)$ is the vector of nominal parametric functions $p_f(t)$ and $S_{x,p_{f_i,0}(t)}(t,p,p_{f0}(t),W)$ is the sensitivity function of x with respect to $p_{f_i}(t)$. According to (3) the effect of a deviation $\Delta p_{f_i}(t)$ from the nominal variation $p_{f_i,0}(t)$ on the state $x(t)$ can be approximated as:

$$x(t) = x_0(t) + S_{x,p_{f_i}(t)}(t,p_0,p_{f0}(t),W)\Delta p_{f_i}(t)\ . \qquad (14)$$

$x_0(t)$ is the solution of (12) in the nominal regime $(12)^o$.

Due to the uncertainties on the temporal variation of p_f, the deviation $S_{x,p_{f_i}(t)}(t,p_0,p_{f0}(t),W)\Delta p_{f_i}(t)$ is hard to evaluate and manipulate. This step down can be overcome by splitting the evaluation problem of the deviation effect in two problems corresponding to the rest regime, and the exercise regime. Consequently, the system (12) can be seen as a switching-regime system (Fig. 1) for witch $W(t)$ given by (4) is the switching signal.

For $t \in \Im^{rest}$, $W(t)$ imposes the rest regime characterized by:

$$\dot{x}(t) = \tilde{F}^{rest}(x,p,p_f^{rest},0),\ x(t_0) = x^{rest},\ t \in \Im^{rest}, \qquad (15)$$

where $\tilde{F}^{rest}$ is $\tilde{F}$ from (12) for $K_u = 0$, and $p_f^{rest} = [R_p^{rest}, A_{pesk}^{rest}, M_0]^T$. For $t \in \Im^{exer}$, $W(t)$ imposes the exercise regime characterized by:

$$\dot{x}(t) = \tilde{F}^{exer}(x,p,p_f^{exer}(t),W^{exer}),\ x(t_{exer}) = x^{rest},\ t \in \Im^{exer}, \qquad (16)$$

where $\tilde{F}^{exer}$ is $\tilde{F}$ from (12) for $K_u \neq 0$, and $p_f^{exer}(t) = [R_p(t), A_{pesk}(t), M_T(t)]^T$ is the parametric functions vector for which

$p_f^{exer}(t_f) = [R_p^{exer}, A_{pesk}^{exer}, M_0 + \rho_M W^{exer}]^T$ holds.

For the parametric functions of the switching-regime system the nominal step variation (17) is considered.

$$p_{f0}(t) = p_f^{rest}[U(t-t_0) - U(t-t_{exer})] + p_f^{exer}[U(t-t_{exer}) - U(t-t_f)] \qquad (17)$$

where

$p_f^{rest} = [R_p^{rest}, A_{pesk}^{rest}, M_0]^T$,

$p_f^{exer} = [R_p^{exer}, A_{pesk}^{exer}, M_0 + \rho_M W^{exer}]^T$

and $U(t)$ is the unit step input.

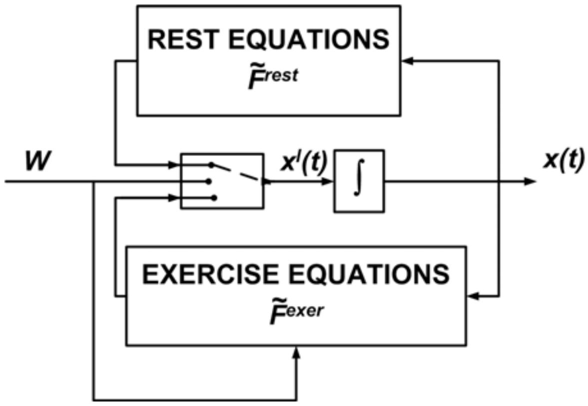


Fig. 1. The representation of the close loop model as switching-regime system.

Consequently, the sensitivity generator (13) can be represented also as a switching-regime sensitivity generator (Fig. 2).

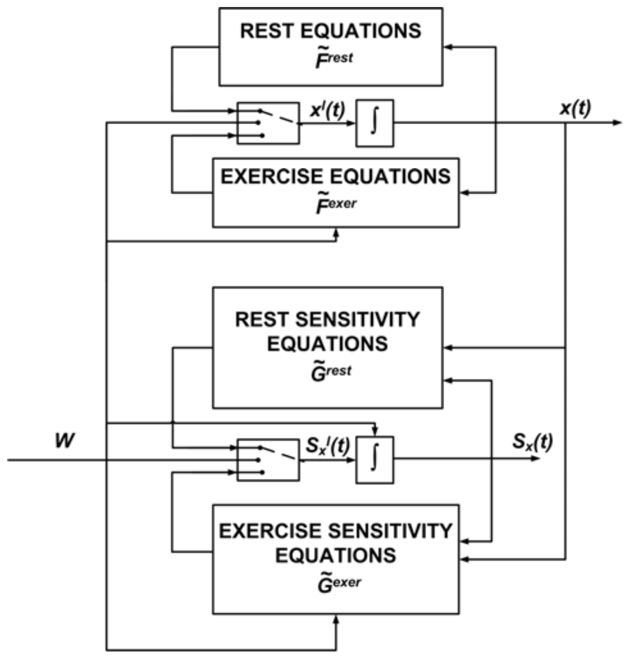


Fig. 2. Structure of the sensitivity generator.

The rest sensitivity generator equations $\tilde{G}^{rest}$ are obtained using (18):

$$\dot{S}^{rest}_{x,p_{f_i}^{rest}}(t,p_0,p_{f_i}^{rest},0) = \underbrace{\left.\frac{\partial\tilde{F}^{rest}}{\partial x}\right|_{(15)^0} S_{x,p_{f_i}^{rest}}(t,p_0,p_{f_i}^{rest},0) + \left.\frac{\partial\tilde{F}^{rest}}{\partial p_{f_i}}\right|_{(15)^0}}_{\tilde{G}^{rest}},$$

$$S^{rest}_{x,p_{f_i}^{rest}}(t_0,p_0,p_{f_i}^{rest},0) = 0,\ t \in \Im^{rest}, \qquad (18)$$

The exercise sensitivity equations $\tilde{G}^{exer}$ are obtained using (19):

$$\dot{S}^{exer}_{x,p^{exer}_{f_i}}(t,p_0,p^{exer}_{f_i},W^{exer}) = \underbrace{\left.\frac{\partial\tilde{F}^{exer}}{\partial x}\right|_{(16)^0} S_{x,p^{exer}_{f_i}}(t,p_0,p^{exer}_{f_i},W^{exer}) + \left.\frac{\partial\tilde{F}^{exer}}{\partial p_{f_i}}\right|_{(16)^0}}_{\tilde{G}^{exer}} ,$$

$$S^{exer}_{x,p^{exer}_{f_i}}(t_{exer},p_0,p^{exer}_{f_i},W^{exer}) = 0,\ t \in \Im^{exer} \tag{19}$$

In the top of Fig. 2, instead of (12), the nominal closed loop models (15), for the rest regime, respectively (16), for exercise regime, are used. The exercise input W has the role of switching regime signal, but it also resets the sensitivity generator at $t = t_{exer}$.

5. RESULTS AND SIMULATION

5.1 Parameter assignment of nominal models. The candidate parametric functions

The parameters of the nominal models (15) and (16) have the values shown in the table from the Appendix. The values marked with $^{(*)}$ have been taken from (Batzel et al., 2007; Kappel and Peer, 1993). The values of the other parameters have been estimated based on the arterial systemic pressure $p_{as}(t)$ and heart rate $H(t)$ measured samples from (Kappel and Peer, 1993) and the methodology described in (Batzel *et al.*, 2007). Using these parameters and considering for H the steady state values $H^{rest} = 67.11$ beats/min and $H^{exer} = 95.08$ beats/min, all steady rest states x^{rest} and exercise states x^{exer} values have been computed. The simulation results of the nominal closed loop model, together with the measured variations for $p_{as}(t)$ and $H(t)$ are shown in comparison in Fig. 3. The transient simulated response of $H(t)$ is adequate, but the simulated variation of $p_{as}(t)$ has greater values than the measured samples.

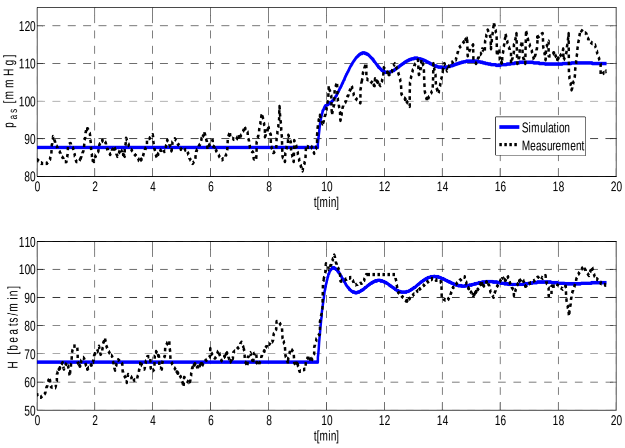


Fig. 3. The variations of $p_{as}(t)$ and $H(t)$ on the rest interval $\Im^{rest} = [0,\ \ 9.7]$ min and exercise interval $\Im^{exer} = [9.7,\ \ 19.67]$ min ($t_{exer} = 9.7$ min).

Three types of candidate parametric functions $p_f(t)$ are considered: the step variation (9), adopted as nominal variation, the exponential variation (10), with $T = 30$ sec, and the sigmoid variation (11) with $a = 0.0693$ sec^{-1} and $b = 30$ sec (Fig. 4). As mentioned, the parametric functions and their parameters were chosen to model the transition from the steady rest regime to the steady exercise regime, taking into account the system response time.

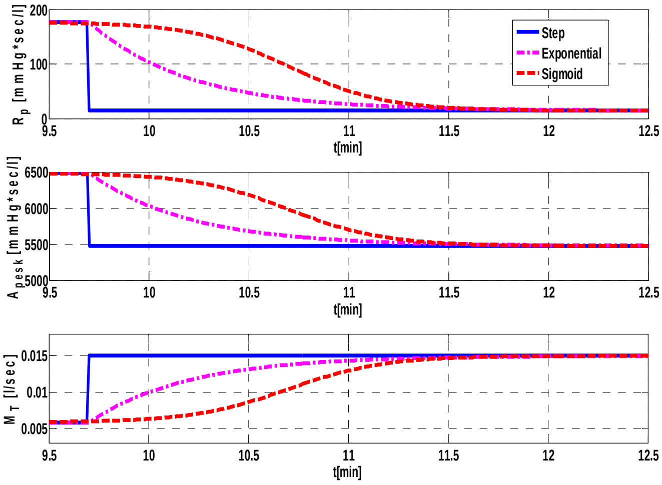


Fig. 4. The candidate parametric functions variations.

5.2 The effect of the of the candidate parametric functions on the $H(t)$ and $p_{as}(t)$

The following sensitivity analysis looks toward the exercise regime when the transient response occurs. For this purpose, the sensitivity exercise generators (19) of $p_{as}(t)$ and $H(t)$ with respect to R_p, A_{pesk} and M_T corresponding to the nominal values $p^{exer}_f(t_f)$ have been computed. With their help the effects of a candidate parametric function over $p_{as}(t)$ and $H(t)$ can be estimated using (14) as:

$$\Delta x(t) = x(t) - x_0(t) \cong S^{exer}_{x,p_{f_{i,0}}}(t,p_0,p^{exer}_{f_{i,0}}(t),W^{exer})\Delta p^{exer}_{f_i}(t),\ t \in \Im^{exer} \tag{20}$$

where $\Delta p^{exer}_{f_i}(t)$ is the deviation of the chosen candidate function from the nominal parametric function. Using (20) the effects illustrated in Fig. 5 were obtained.

The main observations provided by Fig. 5 are:

i) For both types of deviations $\Delta p^{exer}_{f_i}(t)$ the effect on $p_{as}(t)$ is more intense than the effect on $H(t)$. The deviations $\Delta R^{exer}_p(t)$ and $\Delta M^{exer}_T(t)$ can cause alterations up to 16.44 mmHg in $p_{as}(t)$ (Fig. 5a). This can be considered a large deviation since during the transient regime $p_{as}(t) \in [87.56,\ \ 110.05]$ mmHg. Instead, the maximum deviation in $H(t)$, of 8.67 beats/min, is small comparatively to range $H(t) \in [67.11,\ \ 105]$ beats/min of the transient regime (Fig. 5b).

ii) $\Delta A^{exer}_{pesk}(t)$ has the least influence on $p_{as}(t)$ and $H(t)$, both for exponential and sigmoid parametric function deviations. Indeed, in the case of $p_{as}(t)$ the hierarchy of effects of the deviations is:

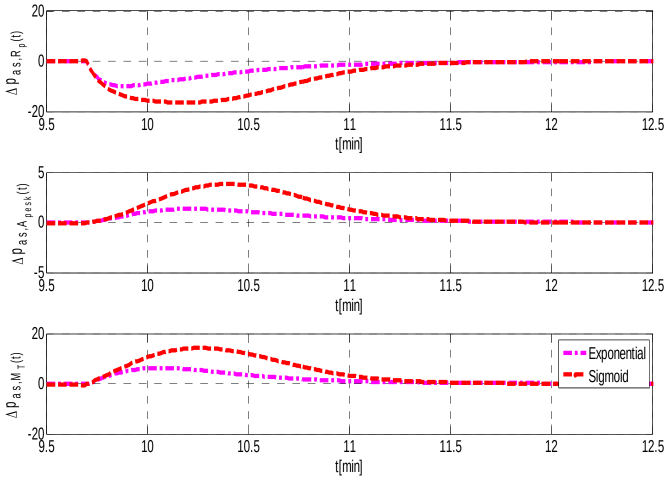
effect of $\Delta R_p^{exer}(t) \geq$ *effect of* $\Delta M_T^{exer}(t) >>$ *effect of* $\Delta A_{pesk}^{exer}(t)$,

and for $H(t)$:

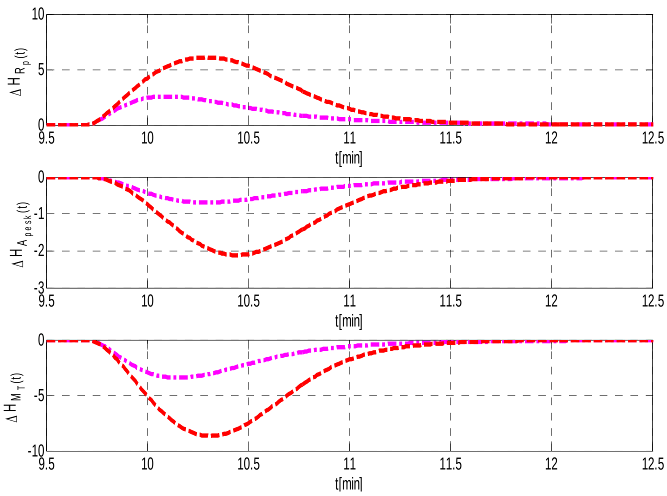
effect of $\Delta M_T^{exer}(t) \geq$ *effect of* $\Delta R_p^{exer}(t) >>$ *effect of* $\Delta A_{pesk}^{exer}(t)$.

However, it is observed that the effects of $\Delta R_p^{exer}(t)$ and $\Delta M_T^{exer}(t)$ are of opposite sign.

iii) The effect of $\Delta p_{f_i,S}^{exer}(t)$ is almost double than the effect of $\Delta p_{f_i,E}^{exer}(t)$.



-a-



-b-

Fig. 5. The variations $\Delta p_{as,p_{f_i}^{exer}(t)}(t)$ -a- and $\Delta H_{p_{f_i}^{exer}(t)}(t)$ -b- as effect of the variations $\Delta p_{f_i,E}^{exer}(t)$ and $\Delta p_{f_i,S}^{exer}(t)$ due to modification of the candidate functions.

These observations can be noted also in the variations of $p_{as}(t)$ and $H(t)$ obtained by using (14) independently for every parametric function deviation. E.g., Fig. 6 presents the effect in $p_{as}(t)$ and $H(t)$ of $\Delta R_{p,E}^{exer}(t)$, $\Delta R_{p,S}^{exer}(t)$. The strong effect of $\Delta R_p^{exer}(t)$ over $p_{as}(t)$, consisting in the decrease of $p_{as}(t)$ below the rest steady value, can be observed. The effect of $\Delta R_p^{exer}(t)$ on $H(t)$ is moderate.

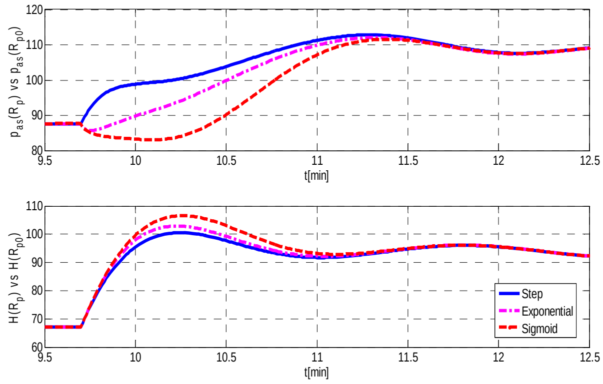


Fig. 6. The variations $p_{as,0}$ versus p_{as} and H_0 versus H for $\Delta R_{p,E}^{exer}(t)$ and $\Delta R_{p,S}^{exer}(t)$.

Fig. 7 shows the weak effect of $\Delta A_{pesk,E}^{exer}(t)$ and $\Delta A_{pesk,S}^{exer}(t)$ over $p_{as}(t)$ and $H(t)$. Therefore, it implies that for $A_{pesk}(t)$ it is sufficient to consider the nominal step variation (9).

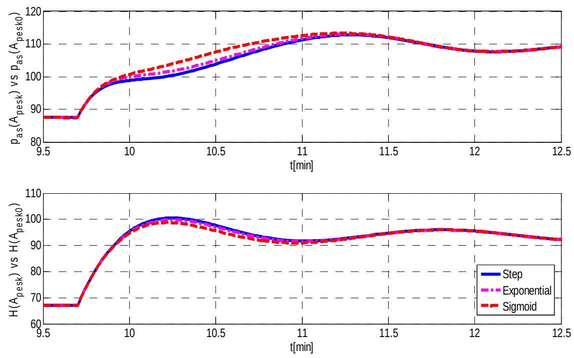


Fig. 7. The variations $p_{as,0}$ versus p_{as} and H_0 versus H for $\Delta A_{pesk,E}^{exer}(t)$ and $\Delta A_{pesk,S}^{exer}(t)$.

Fig. 8 demonstrates that the effect of $\Delta M_T^{exer}(t)$ is opposite to the effect of $\Delta R_p^{exer}(t)$ over $p_{as}(t)$ and $H(t)$. It can be seen also that the effect of $\Delta M_T^{exer}(t)$ over $H(t)$ is greater than that of $\Delta R_p^{exer}(t)$.

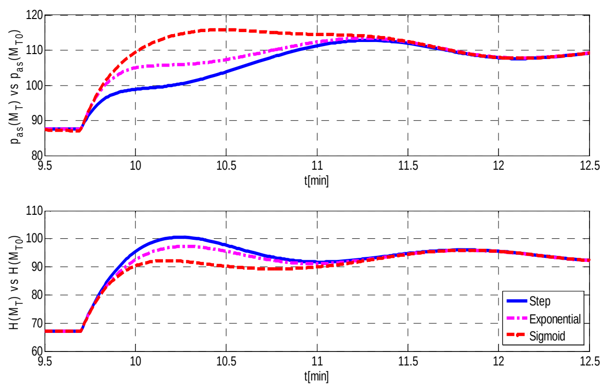


Fig. 8. The variations $p_{as,0}$ versus p_{as} and H_0 versus H for $\Delta M_{T,E}^{exer}(t)$ and $\Delta M_{T,S}^{exer}(t)$.

Using the results obtained so far, more accurate models for the three parametric functions $R_p(t)$, $A_{pesk}(t)$ and $M_T(t)$ are developed in the next section.

5.3 Nominal parametric functions improving

To improve the parametric functions the following three step correction method is applied:

i) Determination of the temporal intervals for which the adjustment of the state variables simulated variations is desired, in order to fit the measurable samples;

By comparing the simulated variations of $p_{as}(t)$ and $H(t)$ with the measurable samples (Fig.3), it can be stated that $H(t)$ is satisfactory approximated by using the nominal parametric functions. $p_{as}(t)$ has between $[10.5,\ \ 12]$ min an overshoot of about 5 mmHg that it is not found in the measurements.

ii) The deviations $\Delta p_{f_i}^{exer}(t)$ necessary to make the adjustments identified in the previous step are chosen;

It is already stated that the deviation of $A_{pesk}(t)$ from the nominal step variation has little effect over $p_{as}(t)$ and $H(t)$. So, it remains to determine the proper deviations for $R_p(t)$ and $M_T(t)$. The previous analysis is synthesized in Fig. 9 and Fig. 10.

Figure 9 shows that using a sigmoid deviation $\Delta R_{p,S}^{exer}(t)$ and an exponential deviation $\Delta M_{T,E}^{exer}(t)$ the desired effect on $p_{as}(t)$ can be obtained for $t \in [10.5,\ \ 11.4]$ min. The result is the best for the candidate parametric functions taken into account. However, it does not completely solve the problem. Indeed, the cumulative effect of the mentioned deviations determines also a decrease of $p_{as}(t)$ for $t \in [9.7,\ \ 10.5]$ min and is negligible for $t \in [11.4,\ \ 12]$ min.

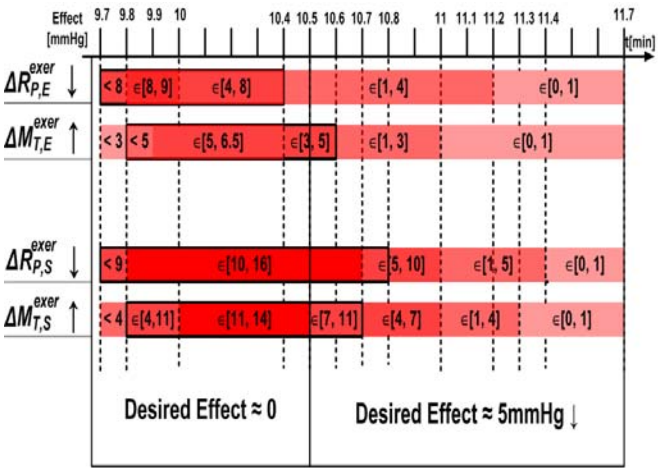


Fig. 9. The effect of $\Delta R_p^{exer}(t)$ and $\Delta M_T^{exer}(t)$ on $p_{as}(t)$.

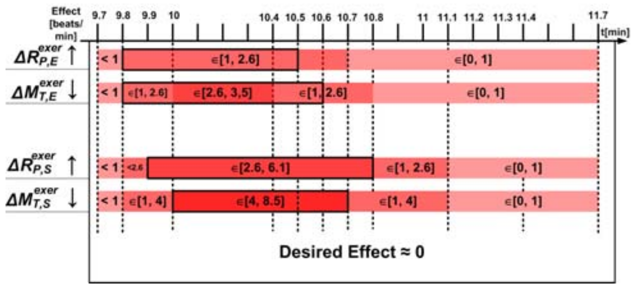


Fig. 10. The effect of $\Delta R_p^{exer}(t)$ and $\Delta M_T^{exer}(t)$ on $H(t)$.

Note that Fig. 10 shows that the chosen deviations for $R_p(t)$ and $M_T(t)$ do not have a significant effect on $H(t)$.

iii) The nominal parametric functions $p_{f_i0}^{exer}(t) = p_{f_i}^{exer}$ are corrected using the deviations $\Delta p_{f_i}^{exer}(t)$ chosen at ii) with:

$$p_{f_i}^{exer}(t) = p_{f_i}^{exer} + \Delta p_{f_i}^{exer}(t),\ t \in \Im^{exer}. \tag{21}$$

The final shapes of parametric functions are obtained using (21) for $R_p(t)$ and $M_T(t)$, respectively retaining the form (9) for $A_{pesk}(t)$.

They are given in equations (22) and should be attached to the model (5):

$$R_p(t) = \begin{cases} R_p^{exer}, & t \in \Im^{rest} \\ R_p^{rest} + \dfrac{(R_p^{exer} - R_p^{rest})}{1 + e^{-0.0693(t-(t_{exer}+30))}}, & t \in \Im^{exer} \end{cases} \tag{22.1}$$

$$A_{pesk}(t) = \begin{cases} A_{pesk}^{rest}, & t \in \Im^{rest} \\ A_{pesk}^{exer}, & t \in \Im^{exer} \end{cases} \tag{22.2}$$

$$M_T(t) = \begin{cases} M_0, & t \in \Im^{rest} \\ M_0 + \rho_M W^{exer}(1 - e^{-\frac{t-t_{exer}}{30}}), & t \in \Im^{exer} \end{cases} \tag{22.3}$$

The variations of the parametric functions (22) are presented in Fig.11.

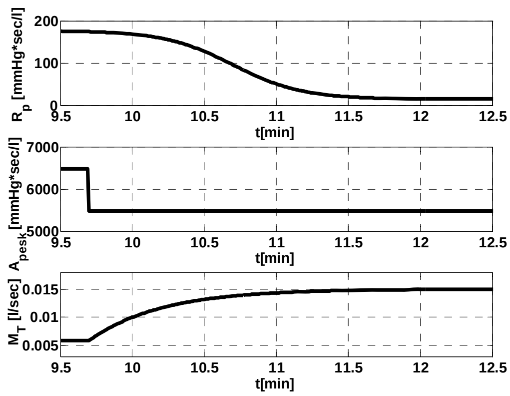


Fig. 11. The final parametric functions $R_{p,S}(t)$, $A_{pesk,T}(t)$ and $M_{T,E}(t)$.

Figure 12 shows the simulated variations of $p_{as}(t)$ and $H(t)$, using the corrected parametric functions $R_{p,S}(t)$, $A_{pesk,T}(t)$ and $M_{T,E}(t)$.

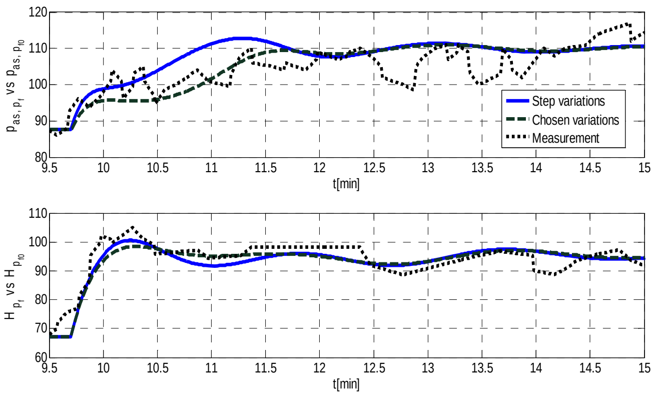


Fig. 12. The variations of $p_{as}(t)$ and $H(t)$ for $R_{p,S}(t)$, $A_{pesk,T}(t)$ and $M_{T,E}(t)$.

To evaluate the improvement of the close loop system response when the three corrected parametric functions (22) are used, the average absolute deviation for $p_{as}(t)$ and $H(t)$ was computed on $\Im^{exer}$. The results are inserted in Table 1.

It is noted that the use of corrected parametric functions brings an improvement of about 8% in the average absolute deviation of $p_{as}(t)$. However, the average deviation of $H(t)$ increases with 0.77%, but this effect can be considered negligible.

Table 1. The average absolute deviations:

$$\Delta x_{med} = \frac{1}{N}\sum_{i=1}^{N}\left|x^{mas}(i) - x^{sim}(i)\right|$$

Parametric functions			$\Delta p_{as,med}$ [mmHg]	ΔH_{med} [beats/min]
$R_p(t)$	$A_{pesk}(t)$	$M_T(t)$		
$R_{p,T}(t)$	$A_{pesk,T}(t)$	$M_{T,T}(t)$	4.3010	2.4556
$R_{p,E}(t)$	$A_{pesk,E}(t)$	$M_{T,E}(t)$	4.3599	2.8104
$R_{p,S}(t)$	$A_{pesk,S}(t)$	$M_{T,S}(t)$	4.6091	3.3526
$R_{p,S}(t)$	$A_{pesk,T}(t)$	$M_{T,E}(t)$	3.9581	2.4745

6. CONCLUSION

The model of the CVS can be improved by introducing the concept of parametric function as an attribute of the time-variant systems. The step-type parametric functions, currently considered, could be corrected by the development of sensitivity generators through extension of the sensitivity theory with respect to dynamic systems. In this paper the theoretical approach is explained via a case-study that considers three parameters of the CVS. For these parameters, by following a three step method, and using parametric functions composed from step- exponential- and sigmoidal functions, temporal restrictions are synthesized. The result was evaluated and proved to be satisfactory for the case study.

The method proposed can be used to improve the transient response of the CVS with baroreflex loop without adding new equations or parameters. Once the parametric functions have been chosen, they are integrated in the CVS model as nominal parametric functions. Thus, the degree of complexity of the model and the control loop is maintained allowing an easy analysis of its properties.

Based on this method, searching algorithms of the appropriate parametric functions of the CVS can be designed. Their variations can provide useful information for local physiological processes that take place in the exercise scenario.

REFERENCES

Abbass, M.A., ElSamahy, E. and Genedy, A. (2012). Modeling and Simulation of the Cardiovascular System for Healthy Subjects under Physical Stress, *2012 Cairo International Biomedical Engineering Conference (CIBEC)*, Cairo, Egypt, Dec. 20-21, pp.179-182.

Banks, H.T., Cintron-Arias, A. and Kappel, F. (2010). *Parameter selection methods in inverse problem formulation*, CRSC Tech. Report CRSC-TR10-03, NCSU, Raleigh, In Batzel, J.J., Bachar, M. and Kappel, F. (eds). (2013). Mathematical Modeling and Validation in Physiology: Application to the Cardiovascular and Respiratory Systems, *Lecture Notes in Mathematics* Vol. 2064, pp. 43-73, Springer, Berlin.

Batzel, J.J., Kappel, F., Schneditz, D. and Tran H.T. (2007). *Cardiovascular and Respiratory Systems – Modeling, Analysis and Control*, SIAM.

Batzel, J., Baselli, G., Mukkamala, R. and Chon, K.H. (2009). Modelling and disentangling physiological mechanisms: linear and nonlinear identification techniques for analysis of cardiovascular regulation, *Philosophical Transactions of the Royal Society A*, Vol. 367, pp. 1377–1391.

Flamm, S.D., Taki, J., R. Moore, R., Lewis, S.F., Maltais, F., Ahmad, M., Callahan, R., Dragotekes, S. and Alpert, N. (1990). Redistribution of regional and organ blood volume and effect on cardiac function in relation to upright exercise intensity in healthy human subjects, *Circulation*, Vol. 81, pp. 1550-1559.

Frank, P.M., (1976). *Empfindlichkeitsanalyse dynamischer Systeme: eine einführende Darstellung*, Oldenbourg, München, 1976

Kappel, F. and Batzel, J. (2006). Sensitivity Analysis of a model of cardiovascular system, *Conf Proc IEEE Eng Med Biol Soc*,. Vol.1, pp: 359-62.

Kappel, F. and Peer, R.O. (1993). A mathematical model for fundamental regulation processes in the cardiovascular system, *Journal of Mathematical Biology*, Vol. 31, pp. 611-631.

Ursino, M. and Magosso, E. (2002). Cardiovascular response to dynamic aerobic exercise: a mathematical model, *Med. Biol. Eng. Comput.*, Vol. 40, pp. 660–674.

Ursino, M. and Magosso, E. (2006). Short-term autonomic control of the cardio-respiratory system: a summary with the help of a comprehensive mathematical model, *Proceedings of the 28th IEEE EMBS Annual International Conference*, New York City, USA, Aug 30-Sept 3.

Timischl, S. (1998). *A Global Model of the Cardiovascular and Respiratory system*, Ph.D. diss., Graz University.

Appendix PARAMETERS FOR THE NOMINAL MODELS OF THE CLOSED LOOP MODEL

Parameter	Value	Unit
c_{as} (*)	0.001	[l mmHg^{-1}]
c_{vs} (*)	0.5	[l mmHg^{-1}]
c_{ap} (*)	0.003	[l mmHg^{-1}]
c_{vp} (*)	0.1	[l mmHg^{-1}]
c_l (*)	0.02	[l mmHg^{-1}]
c_r (*)	0.05	[l mmHg^{-1}]
V_{tot} (*)	6.1	[l]
R_l (*)	18	[mmHg sec l^{-1}]
R_r (*)	7	[mmHg sec l^{-1}]
k_B (*)	0.4	[sec$^{1/2}$]
C_{aO_2} (*)	0.1977	[1]
K	3.98196	[1]
ρ_M (*)	1.83e-004	[l sec^{-1} Watt^{-1}]
α_l	0.000650	[l sec^{-2}]
α_r	0.002459	[l sec^{-2}]
β_l	0.011746	[mmHg sec^{-1}]
β_r	0.016849	[mmHg sec^{-1}]
γ_l	0.022404	[l sec^{-1}]
γ_r	0.0120671	[l sec^{-1}]
q_{as}	0.001731	[1 sec^{-2}mmHg]
A_{pesk}^{rest}	6485.402	[mmHg sec l^{-1}]
A_{pesk}^{exer}	5478.241	[mmHg sec l^{-1}]
R_p^{rest}	176.849	[mmHg sec l^{-1}]
R_p^{exer}	14.3924	[mmHg sec l^{-1}]
M_0	0.0058	[l sec^{-1}]