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Sensitivity analysis of a model of the cardiovascular system

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***Abstract*— In this paper we consider the sensitivity analysis of a model of the cardiovascular system (CVS) simulating the transition to aerobic exercise and where the control for the system is implemented via an optimal control. Classical and generalized sensitivity analysis are discussed and compared and their application to the CVS model is analyzed.**

I. INTRODUCTION

The cardiovascular system (CVS) includes a significant number of interacting control loops that serve to stabilize or appropriately adjust the CVS under a variety of conditions. Quantitative modeling of the CVS has been carried out to understand these interactions over the last several decades. At two modeling poles we could consider the early and comprehensive model of A. C. Guyton et al. [4] in comparison to the simpler model presented by F. S. Grodins [3]. On the one hand, the Guyton model exhibits multiple aspects of cardiovascular control interaction but is so complex as to be essentially unusable for application to individuals especially in the clinical setting. On the other hand, the Grodins model template has been adapted to model particular aspects of cardiovascular control and used to fit individual data [5]. However, these models are not generally speaking, complex enough to capture significant interactions of the various cardiovascular control loops.

To devise models of sufficient complexity that are at the same time applicable to clinical settings it s necessary to address several issues:

- Models of sufficient complexity involve a significant number of parameters which thus renders the inverse problem of parameter identification difficult.
- The restricted number of non-invasively measurable CVS quantities (such as blood pressure and heart rate) further complicates the parameter estimation problem.
- Individuals vary widely in the relative responses of available control mechanisms, rendering an appeal to general tendencies difficult. For example, cardiac output can be varied either by changes in heart rate or contractility or both and individuals vary with respect to the relative activation of these elements.

The appearance of new techniques and methods are contributing to making the above listed issues more easily addressed. Biomedical measurements are continuously being devised to expand the accessibility and quality of measurements of physiological values and expanding computational power and numerical algorithm efficiency allow for more complex problems. Generalized sensitivity analysis (GSA) represents a method for discerning which data (and what time intervals) will have the greatest influence on the process of parameter identification for a model.

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Sensitivity analysis

a) Classical sensitivities: Let the variable $y = y(x)$ for $x \in D$, where D is some open interval and y is differentiable on D. Let $x_0 \in D$ be given and assume that $x_0 \neq 0$, $y_0 = y(x_0) \neq 0$. Corresponding to Δx with $x_0 + \Delta x \in D$ we define $\Delta y = y(x_0 + \Delta x) - y(x_0)$ and consider the relative errors $\Delta x/x_0$ and $\Delta y/y_0$. The *sensitivity* $\sigma_{y,x}(x_0)$ of y with respect to x at x_0 is defined as:

$$\sigma_{y,x}(x_0) = \lim_{\Delta x \to 0} \frac{\Delta y/y_0}{\Delta x/x_0} = \frac{x_0}{y_0}\, y'(x_0). \tag{1}$$

From the definition of $\sigma_{y,x}$ it easily follows that $\sigma_{y,x}$ is invariant under change of units in x or y.

In order to decide how a model's parameters should be determined via parameter estimation, sensitivities of model outputs can be studied with respect to changes in the parameters. It is important to base such decisions on relative sensitivities as defined above and not on the derivatives of the measured outputs with respect to the parameters as the latter may lead to wrong conclusions regarding the degree of dependence on the various parameters.

b) Generalized sensitivities: Generalize sensitivity functions (GSF) as introduced in [7] provide information on the relevance of measurements of output variables of a system for the identification of certain parameters. That is to say, using GSF one can describe the sensitivity of parameter estimates with respect to measurements. For a single output system where the output of the model is given by

$$y(t) = f(t, \theta), \quad 0 \leq t \leq T, \tag{2}$$

where $\theta = \mathrm{col}(\theta_1, \ldots, \theta_p)$ is the vector of model parameters and f is a sufficiently smooth function. At times $0 \leq t_1 < \cdots < t_M \leq T$ we have measurements ξ_k corresponding to the model outputs $y(t_k)$, $k = 1, \ldots, M$. We assume that the measurements have the form

$$\xi_k = z(t_k) + e_k, \quad k = 1, \ldots, M,$$

where $z(t)$, $0 \leq t \leq T$, is the 'true' output of the system and e_k is the measurement noise for the measurement ξ_k. We impose the following conditions on the e_k's:

(i) e_k has zero mean, $k = 1, \ldots, M$.
(ii) The e_k's are identically distributed.
(iii) The variance σ_k^2 of e_k is not dependent on θ.

A *generalized sensitivity function* $g_i(t_{k_0})$ with respect to the parameter θ_i at the time instant t_{k_0} for θ in a neighborhood of θ_0 is given by (see [7])

$$g_i(t_{k_0}) = \sum_{k=1}^{k_0} \frac{1}{\sigma_k^2} \Big(\Big(\sum_{j=1}^{M} \frac{1}{\sigma_j^2} \big(\nabla_\theta f(t_j,\theta)\big)^{\mathsf{T}} \nabla_\theta f(t_j,\theta) \Big)^{-1} \times \big(\nabla_\theta f(t_k,\theta)\big)^{\mathsf{T}} \Big)_i \big(\nabla_\theta f(t_k,\theta)\big)_i. \tag{3}$$

Generalized sensitivities (GS) can provide at least two useful types of information in regards to the dependence of parameter estimates on the measurements of an output variable:

i) Information on the correlation between parameters with respect to measurements for a specific output variable of the system. Oscillatory and non-monotonic behavior of the generalized sensitivities indicates a strong correlation between the parameters, while a more or less monotonic increase of the GSF from 0 to 1 indicates little correlation between the parameters.
ii) If the GSF for a parameter is monotonically increasing, then those measurements taken in that time interval where the GSF essentially increases from 0 to 1 provide all the information on the parameter.

II. MODEL

The CVS model we will consider is depicted in the block diagram of Figure 1. The cardiovascular model is divided into pulmonary and systemic vascular circuits each of which is further subdivided into an arterial and a venous part resulting in four compartments for the model. Each compartment is considered to be a vessel with compliant walls, exhibiting no resistance to blood flow and characterized by the pressure in the vessel, which then determines the blood volume for that vessel. Resistance vessels representing muscle tissue and other organs in case of the systemic circuit and the alveolar region in case of the pulmonary circuit connect the arterial and venous compartments. The systemic venous compartment is connected to the pulmonary arterial compartments via the right ventricle, while the pulmonary venous and systemic arterial compartments are connected by the left ventricle. For simplicity, the atria are viewed as part of the related venous compartments. Pulsatile flow is not included given the time frame for transition to exercise. Thus mean values of quantities over one heart cycle are presented.

A. Basic model equations

The following notation is employed: The subscripts 'a', 'v', refer to 'arterial' and 'venous',respectively, while the subscripts 's' and 'p' stand for 'systemic' and 'pulmonary', respectively. The subscripts 'ℓ' and 'r' indicate left and the right hearts, respectively.

We associate a pressure P and a volume V of blood for each compartment. The pressure-volume relation of each compartment vessel is assumed to be linear (unstressed volume is not considered). Hence the compliance values will be compromise values (see [3]).

The cardiac output Q_{co} generated by a ventricle, is given by

$$Q_{\text{co}} = HV_{\text{str}}, \tag{4}$$

where H denotes the heart rate and V_{str} the stroke volume.

The systemic blood flow F_{s} through the peripheral resistance region of the systemic circuit R_{s} and the pulmonary flow F_{p} through the pulmonary circuit resistance R_{p} are determined by a form of Ohm's law:

$$F_{\text{s}} = \frac{1}{R_{\text{s}}}(P_{\text{as}} - P_{\text{vs}}) \quad \text{and} \quad F_{\text{p}} = \frac{1}{R_{\text{p}}}(P_{\text{ap}} - P_{\text{vp}}). \tag{5}$$

The rate of change $\dot{V}$ for the volume V in a compartment is the difference between the flow into and the flow out of the compartment. We obtain the following equations for the four compartments ([3],see also [1]):

$$\begin{aligned} c_{\text{as}}\dot{P}_{\text{as}} &= Q_\ell - F_{\text{s}}, & c_{\text{vs}}\dot{P}_{\text{vs}} &= F_{\text{s}} - Q_{\text{r}}, \\ c_{\text{ap}}\dot{P}_{\text{ap}} &= Q_{\text{r}} - F_{\text{p}}, & c_{\text{vp}}\dot{P}_{\text{vp}} &= F_{\text{p}} - Q_\ell. \end{aligned} \tag{6}$$

Assuming constant total blood volume V_{tot} over the transition times we consider, the above equations imply

$$c_{\text{as}}P_{\text{as}} + c_{\text{vs}}P_{\text{vs}} + c_{\text{ap}}P_{\text{ap}} + c_{\text{vp}}P_{\text{vp}} \equiv V_{\text{tot}}. \tag{7}$$

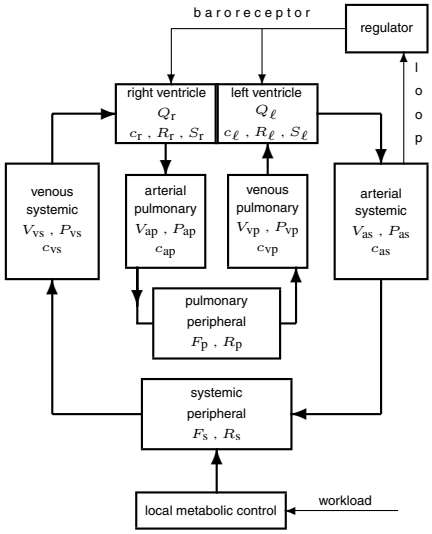

Fig. 1. Block-diagram of the basic cardiovascular model.

For derivation of the expressions for the left and right ventricular outputs, the reader is referred to the in depth discussion given in [5] (see also [1]). Ventricular output is determined by the product of stroke volume V_{str} and H, as expressed in (4). The formula for $V_{\text{str},\ell}$ is given as

$$V_{\text{str},\ell} = \frac{c_\ell P_{\text{vp}} a_\ell(H) f(S_\ell, P_{\text{as}})}{a_\ell(H) P_{\text{as}} + k_\ell(H) f(S_\ell, P_{\text{as}})}, \tag{8}$$

where

$$\begin{aligned} k(H) = e^{-(cR)^{-1} t_d(H)} \quad &\text{and} \quad a(H) = 1 - k(H), \\ f(S,P) := \min\Big(S, P\Big), &\, S \geq 0, \\ t_d(H) = \frac{1}{H^{1/2}}\Big(\frac{1}{H^{1/2}} - \kappa\Big), & \end{aligned} \tag{9}$$

where κ is in the range of 0.04 – 0.05, and $f(S,P)$ assures that ventricular stroke volume cannot exceed end-diastolic volume (see [5] or [1]). $V_{\text{str,r}}$ is formed by replacing P_{as} with P_{ap}, P_{vp} with P_{vs}, and 'ℓ' with 'r'.

Equations (6), together with the auxiliary equations described above, determine a nonlinear system of four ordinary differential equations, reflecting the essential features of the Grodins' formulation of the mechanical part of the cardiovascular system. The constraint imposed by (7), defines for a given V_{tot}, c_{as}, c_{vs}, c_{ap} and c_{vp} a hyperplane in $\mathbb{R}^4$, which is invariant for the above described differential equations (6). We can use equation (7) to express one of the pressures in terms of the other pressures.

B. Control features of the model

We must include control features to respond to perturbations or stresses. These controls include the regulation of H, the contractilities of the ventricles, and aspects of control of vascular resistances. We will describe the construction of a feedback control, which regulates H in response to arterial systemic pressure (baroreflex). We will also assume that the ventricular contractilities vary according to variations in the heart rate. In the ergometric stress context, contractilities of the ventricles are increased or decreased in the same direction as heart rate by at least by sympathetic activity and perhaps other mechanisms such as the Bowditch effect. Since in the basic model we do not model sympathetic and parasympathetic activities directly, we model the variations of the contractilities by the following system of differential equations (see [5] or [1]):

$$\begin{aligned} \dot{S}_\ell &= \sigma_\ell, \quad \dot{\sigma}_\ell = -\alpha_\ell S_\ell - \gamma_\ell \sigma_\ell + \beta_\ell H, \\ \dot{S}_{\text{r}} &= \sigma_{\text{r}}, \quad \dot{\sigma}_{\text{r}} = -\alpha_{\text{r}} S_{\text{r}} - \gamma_{\text{r}} \sigma_{\text{r}} + \beta_{\text{r}} H, \end{aligned} \tag{10}$$

where α_ℓ, β_ℓ, γ_ℓ, α_{r}, β_{r} and γ_{r} are positive constants.

Systemic resistance is also changed by global autonomic and local effects. For the purpose of ergometric exercise, we consider the local metabolic control on resistance to dominate. This local control acts to increase blood flow to a tissue region when increased O_2 demand. We can express this following [6]:

$$R_{\text{s}} = A_{\text{pesk}} C_{\text{v,O}_2}, \tag{11}$$

where A_{pesk} is a positive constant and $C_{\text{v,O}_2}$ is the concentration of O_2 in the venous blood in the capillary region.

Let M_{T} be the metabolic rate for the tissue region, which is partially satisfied by the O_2 supply provided by the blood flow in the tissue region and partially by anaerobic biochemical reactions providing an energy flow M_b, which we assume to be dependent on the rate of change of $C_{\text{v,O}_2}$,

$$M_{\text{T}} = F_{\text{s}}(C_{\text{a,O}_2} - C_{\text{v,O}_2}) + M_b, \quad M_b = -K \frac{d}{dt} C_{\text{v,O}_2}, \tag{12}$$

where $C_{\text{a,O}_2}$ is the concentration of O_2 in the arterial blood, which is assumed to be constant, and $K > 0$ is some constant. Differentiating (11) and using equations (8) and (12) we obtain the following differential equation for R_{s}:

$$\dot{R}_{\text{s}} = \frac{1}{K}\Big(A_{\text{pesk}}\Big(\frac{P_{\text{as}} - P_{\text{vs}}}{R_{\text{s}}} C_{\text{a,O}_2} - M_{\text{T}}\Big) - (P_{\text{as}} - P_{\text{vs}})\Big). \tag{13}$$

In order to model the response of the cardiovascular system to a constant ergometric workload W imposed on a test person on a bicycle ergometer starting at time $t = 0$ we use an empirical formula for the resulting metabolic rate M_{T}, $M_{\text{T}} = M_0 + \rho W$, where M_0 is the metabolic rate in the systemic tissue region corresponding to zero workload and ρ is a positive constant.

As already stated above we assume that the baroreceptor loop is modeled by designing a feedback law which controls the heart rate. Thus we add the equation

$$\dot{H} = u(t). \tag{14}$$

Thus our model for the cardiovascular system consists of Grodins' model system equations (6), together with equations (10) for the contractilities, equation (13) modeling the local metabolic control process and equation (14) describing the control influence. This gives a system of ordinary differential equations in $\mathbb{R}^{10}$ which leaves the hyperplane given by (7) invariant.

The control $u(t)$ in equation (14) represents the arterial baroreceptor loop which measures and responds to P_{as}. In particular, we consider a situation where the cardiovascular system transitions from the equilibrium state x^{rest} corresponding to zero workload, $M_{\text{T}} = M_{\text{T}}^{\text{rest}} = M_0$, to the equilibrium state x^{exer} corresponding to the imposed constant workload W^{exer}, $M_{\text{T}} = M_{\text{T}}^{\text{exer}} = M_0 + \rho W^{\text{exer}}$. The control $u(t)$ is chosen such that the quadratic cost functional

$$J(u(\cdot), x^{\text{rest}}) = \int_0^\infty \big(q_{\text{as}}^2 (P_{\text{as}}(t) - P_{\text{as}}^{\text{exer}})^2 + u(t)^2\big)\, dt \tag{15}$$

is minimized, where $P_{\text{as}}(t)$ is the first component of the solution $x(t)$ of the model system with initial condition $x(0) = x^{\text{rest}}$ and $W = W^{\text{exer}}$. The positive constant q_{as}^2 is a weighting factor. The cost functional penalizes deviations of the arterial systemic pressure from the equilibrium value and large values of the control function, i.e., of $\dot{H}(t)$. That only the first component P_{as} of the state vector enters the cost functional reflects the assumption that only this component is sensed in the system.

Considering the linearized system about the equilibrium state x^{exer}, the control that stabilizes the system is given by a linear feedback law:

$$u^*(t) = K(x^*(t) - x^{\text{exer}}), \quad t \geq 0, \tag{16}$$

where K is obtained via the Riccati matrix equation. This feedback law provides the optimal control for the linearized system $\dot{x}(t) = A(x(t) - x^{\text{exer}}) + Bu(t)$ minimizing the cost functional (15) among all $u \in L^2(0,\infty;\mathbb{R})$. For the nonlinear system, $u^*(t)$ given by (16) (now $x^*(t)$ being the solution of the closed loop system $\dot{x} = \mathcal{F}(x(t), p, W^{\text{exer}}, K(x^* - x^{\text{exer}}))$, $x(0) = x^{\text{rest}}$) is also a stabilizing control provided that $\|x^*(t) - x^{\text{exer}}\|$ and $|u^*(t)|$ are small enough.

III. The Bicycle Ergometer Test

The goal of the modeling process described above is to simulate the response of the CVS to a constant ergometric workload especially in regards to the role played by the

baroreceptor loop. In the following we present some results of the sensitivity analysis we performed using data which were obtained from bicycle ergometer tests with test persons in upright sitting position. In these tests, data recordings began 10 minutes before the exercise phase started. The workload W^{exer} for the exercise phase, lasting also for 10 minutes, was constant. In order to meet the assumptions of the modeling process, a rather low workload was chosen of 75 Watts. Measurements for H and P_{as} were made with an Ohmeda 2300 Finapress Continuous N.I.B.P. At a later stage of the study we also obtained measurements for the cardiac output Q_ℓ of the left ventricle using Doppler-echocardiography. With the echocardiographic system Vingmed CFM 800 we obtained measurements every 30 seconds on the average.

IV. RESULTS

In this section we present a few of the numerous sensitivity investigations. Figures 2 and 3 show that one has to consider sensitivities and not just derivatives in order to determine which parameters have more influence on the dynamics of the system than others. According to the sensitivities of P_{as} with respect to the compliances of the four compartments, it is c_{vs} which has the strongest influence on P_{as} and not c_{as} as could be concluded from the derivatives.

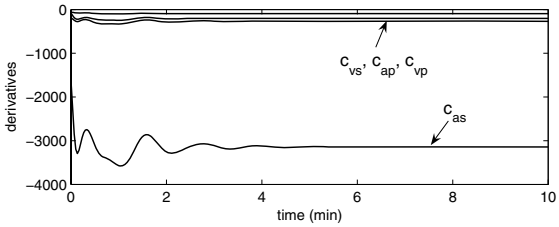

Fig. 2. Derivatives of P_{as} with respect to c_{as}, c_{vs}, c_{ap} and c_{vp}.

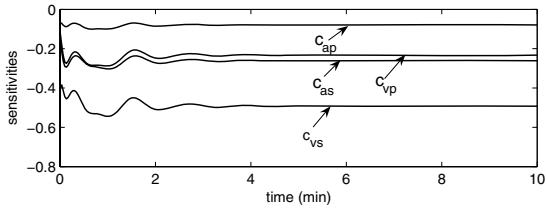

Fig. 3. Sensitivities of P_{as} with respect to c_{as}, c_{vs}, c_{ap} and c_{vp}.

From Figure 4 we see that the dependence of the parameters γ_ℓ, γ_{r} and K (compare equations (10) respectively (13)) on the measurements for P_{as} are rather uncorrelated. Furthermore, we see that for K only measurements for P_{as} up to approximately $1\,\frac{1}{2}$ minutes are of relevance, whereas for γ_ℓ and γ_{r} measurements up to 5 minutes are relevant.

Figure 5 show that information for γ_ℓ and γ_{r} contained in the measurements for H are rather strongly correlated, whereas the information for K is independent from the information on γ_ℓ and γ_{r}. It follows also that measurements for H beyond 3 minutes carry not much information for all of these parameters.

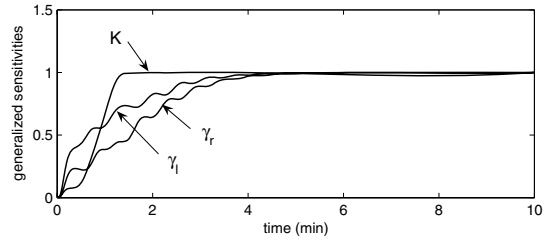

Fig. 4. Generalized sensitivities for γ_ℓ, γ_{r} and K with respect to measurements for P_{as}.

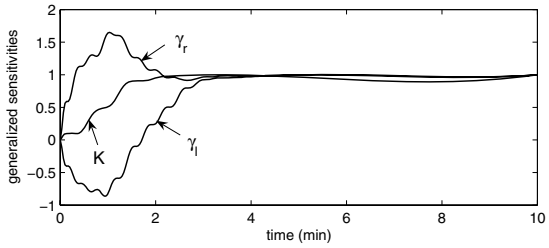

Fig. 5. Generalized sensitivities for γ_ℓ, γ_{r} and K with respect to measurements for H.

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