Optimization of a Mathematical Model of Cerebral Autoregulation Using Patient Data

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Abstract: This study presents an analysis of a cerebral autoregulation (CA) model developed by Ursino and Lodi (1997). We have used this model to analyze non-invasive measurements of cerebral blood flow velocity (CBFV) and arterial blood pressure obtained during postural change from sitting to standing for a healthy young subject. This paper includes a sensitivity analysis, ranking model parameters from the most to the least sensitive, and an analysis (using a methodology called subset selection) that allows identification of correlations among model parameters. Finally, we estimated patient specific parameters using the Levenberg-Marquardt optimization method minimizing the least square errors between computed and measured values of CBFV.

Keywords: Cerebrovascular Autoregulation, Modeling, Parameter Estimation, Nonlinear least squares optimization, Subset Selection.

1. INTRODUCTION

Cerebral autoregulation (CA) is a homeostatic mechanism characterized by the maintenance of cerebral blood flow (CBF) in spite of changes in cerebral perfusion pressure. It has been shown that alterations in CA are associated with the presence of vascular disease such as hypertension and stroke (Hu et al., 2008a) as well as cardiovascular risk factors such as diabetes (Hu et al., 2008b). The examination of CA alterations with respect to disease, aging, vasoactive drugs and other factors that effect vascular function is often difficult due to the inherently complexity of CA dynamics for which many aspects display pronounced nonlinearities; (Giller and Mueller, 2003). In order to gain insight into the ways that CA may change in response to disease, we employed a mathematical model originally developed by Ursino and Lodi (1997).

This model was developed to characterize the nonlinear time pattern of intracranial pressure (ICP) dynamics in interaction with arterial pressure, cerebrospinal fluid circulation, and autoregulatory action.

We chose this model because we believe that it sufficiently accounts for the physics of the cerebrovasculature to quantify the variations in CBF, while remaining relatively simple compared to other models. In spite of this simplicity, however, the model has more parameters than can be accurately estimated from noninvasive measurements of cerebral blood flow velocity (CBFV) and arterial blood pressure. In the following sections we will discuss the derivation of this model, a procedure for selecting identifiable parameters, and a numerical technique for estimating model parameters using patient-specific data.

We have used similar techniques for previous studies (Ellwein et al., 2009; Pope et al., 2009), however, both of these studies were developed to study dynamics in closed-circuit lumped parameter models that only aimed at predicting beat-to-beat values of cerebral blood flow and pressure, without any attempt to model the dynamics of CA. The latter aspect introduces additional nonlinearities into the model, which makes it more difficult to estimate reliable model parameters.

2. HEMODYNAMIC MODEL OF CA

The hemodynamic properties of the cerebral vasculature were approximated with a lumped parameter model. The model is schematically illustrated in Fig. 1.

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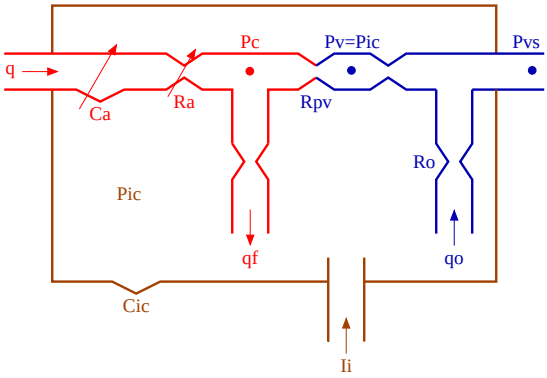

Fig. 1. Schematic of the hemodynamic model of cerebral blood flow.

Using terminology derived from electrical RC-circuits, flow (q, ml/sec) is analogous to current, pressure (p, mmHg) is analogous to voltage, stressed volume (V ml) is analogous to charge, compliance (C, ml/mmHg) is analogous to capacitance, and resistance (R, mmHg sec/ml) is the same in both formulations. Using this analogy, we can describe the volume compliance of the cerebral arteries by

$$V_a = C_a(p_a - p_{ic}), \tag{1}$$

where V_a, C_a, and p_a are the stressed arterial volume, compliance, and pressure, respectively, and p_{ic} is the intracranial pressure. We assume that the arterial compliance is altered by smooth muscle tension, making this a time-varying quantity, regulated by CA. Therefore, differentiating (1) with respect to time gives

$$\frac{dV_a}{dt} = C_a\left(\frac{dp_a}{dt} - \frac{dp_{ic}}{dt}\right) + \frac{dC_a}{dt}(p_a - p_{ic}).$$

The regulation of vessel tone is achieved by defining arterial compliance by

$$\frac{dC_a}{dt} = \frac{1}{\tau}\left[-C_a + \sigma(G \cdot x)\right], \tag{2}$$

where σ is a sigmoid control function,

$$\sigma(Gx) = \frac{(C_{an} + \Delta C_a/2) + (C_{an} - \Delta C_a/2)e^{Gx/k_\sigma}}{1 + e^{Gx/k_\sigma}},$$

with

$$x = \frac{q - q_n}{q_n} \tag{3}$$

and

$$k_\sigma = \Delta C_a/4.$$

The subscript n denotes the basal value of a parameter for a specific individual. The feedback control σ is designed to be a saturable function in which ΔC_a is a parameter describing the limits of CA. Assymetry in the CA capacity with respect to basal conditions motivates the alteration in ΔC_a, depending on the sign of x,

$$\Delta C_a = \begin{cases} \Delta C_{a1}, \text{ if } & x > 0 \\ \Delta C_{a2}, \text{ if } & x \leq 0, \end{cases}$$

and G is the autoregulatory gain.

The cerebral arterial blood flow, q, used in (3), is calculated in analogy to Ohm's law by

$$q = \frac{p_a - p_c}{R_a}, \tag{4}$$

where R_a is the lumped arterial vessel resistance to flow given by

$$R_a = \frac{k_R C_{an}^2}{V_a^2}.$$

In this equation, k_R is a model parameter, and C_{an} denote the basal value of the arterial compliance.

For the capillary pressure, p_c in (4) it is assumed that the outflow pressure acting on the cerebral capillaries is equal to the intracranial pressure p_{ic}. Furthermore, it is assumed that flow leaking from the capillaries is negligible. Therefore,

$$p_c = \frac{p_a R_{pv} + p_{ic} R_a}{R_{pv} + R_a}. \tag{5}$$

Equations (1-5) comprise a system of two ordinary differential equations (ODE's) given by (2) and

$$\frac{dp_{ic}}{dt} = \frac{k_E \cdot p_{ic}}{1 + C_a \cdot k_E \cdot p_{ic}}\left[C_a\frac{dp_a}{dt} + \frac{dC_a}{dt}(p_a - p_{ic}) + \frac{p_c - p_{ic}}{R_f} - \frac{p_{ic} - p_{vs}}{R_0}\right]. \tag{6}$$

Patient-specific simulation of CA dynamics was achieved by using continuous arterial pressure (p_a) as well as the change in arterial pressure with respect to time (dp_a/dt) as inputs to the model. The state variables of the system of ODE's are p_{ic} and C_a. However, these are not quantities that are easily available from measurement. Therefore, the model output is CBFV ($\hat{v}$) computed as

$$\hat{v}(t_i) = \frac{q(t_i)}{A_c}, \tag{7}$$

where $q(t_i)$ is computed from (1-5), and A_c is the cross sectional area of the middle cerebral artery (MCA).

3. EXPERIMENTAL METHODS

Data analyzed in this study were recorded in Dr. Novak's Syncope and Falls in the Elderly (SAFE) laboratory at Beth Israel Deaconess Medical Center, Boston, MA. Data obtained from a healthy young subject include continuous measurements of blood pressure from the index finger, obtained using the Finometer device (Finapres, Ohmeda Monitoring Systems, Englewood CO, FMS (2008)), and CBFV measured by transcranial Doppler (TCD) ultrasonography (MultiDop X4, DWL Neuroscan Inc, Sterling, VA) in both middle cerebral arteries (MCA). For this analysis, only one of the TCD recordings was used. Arterial pressure and CBFV were recorded during a postural change from sitting to standing at 500 Hz and stored on a custom Labview system. We assumed that cerebral blood flow (CBF) is proportional to CBFV by a factor representing a constant cross sectional area of the insonated artery.

3.1 Experimental Procedure

After instrumentation, the subject is asked to sit quietly with the legs elevated at 90° for several minutes until pressure and heart rate were stable. The patient was then instructed to stand while recording of pressure and CBFV continued. Measurements during standing were continued until a new steady state was obtained, judged by a trained technician. One hundred seconds of data were used for the analysis presented in this study.

3.2 Pre-Processing

The raw data were too noisy to directly be used as an input to the mathematical model. Recall that both the measured arterial pressure (p_a) and the numerically calculated pressure gradient (dp_a/dt), which is sensitive to measurement noise, are required as inputs. Furthermore, the model developed by Ursino and Lodi (1997) was not intended to quantify the pulsitile hemodynamics of the cerebral vasculature, but only the mean physiological responses. Thus we smoothed both pressure and CBFV using filtering. Filtering was achived by assuming that, given a continuous data signal, $x(t)$, the mean signal could be represented by

$$\overline{x}(t) = \alpha \int_{-\infty}^{t} x(t) e^{-\alpha(t-s)} ds, \tag{8}$$

where α is a relaxation time. While we do not have data from before 0 seconds, we assume that the effect of the data at $t < 0$ is negligibly small. Therefore, differentiating (8) with respect to time, we can express the smoothing function as the ordinary differential equation

$$\frac{d\overline{x}}{dt} = \alpha \left[-\overline{x}(t_i) + x_i^d \right]$$

with $\overline{x}(0)$ (the initial condition) set equal to the overall mean of the data where the patient is resting in sitting position. In the above expression, long relaxation times ($\alpha \ll 1$) give rise to a phase-shift of the data, while very large values of α (short relaxation) lead to integration errors. For this analysis we used $\alpha = 2$ seconds.

Data were sampled at 500 Hz. Using this high resolution of data for calculations gave rise to very long computation times, thus, we down sampled the results to 50 Hz. We found that there were no appreciable errors due to down-sampling, though when estimating standard errors (not done for this study) of the parameters, we we anticipate that it may be beneficial to use a higher sampling rate. Fig. 2 shows the down-sampled and filtered data ($\overline{x}$) together with the original signals.

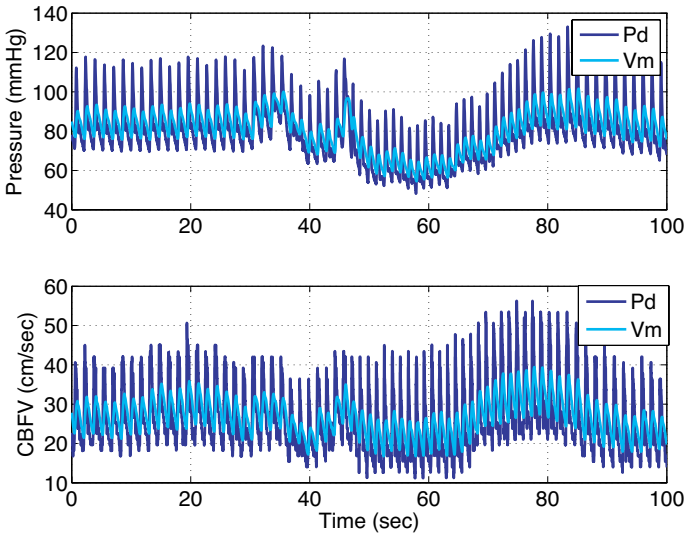

Fig. 2. Smoothed pressure (top) and flow velocity (bottom) data (blue) compared with the raw data (green)

3.3 Nominal Parameter Values

A set of nominal parameter values θ_p and initial conditions θ_i for the differential equations (1-6) can be derived using insight from the physiology combined with knowledge of the subject studied.

The orginal manuscript by Ursino and Lodi (1997) discusses aspects of this procedure, however, their model lists no method for calculating the parameter values for a specific individual. Furthermore, we have introduced an additional parameter A_c. We use *a priori* values (from the original study by Ursino and Lodi (1997)) for parameters p_{an}, p_{cn}, p_{icn}, q_n, p_{vs}, V_{an}, q_{fn}, G, and τ , but predict p_{an} and q_n using average values from data recorded at baseline (during sitting), where we assume that the system is in steady-state. The remaining parameter values were calculated from functional relations implicitly derived using the assumption that the system is in steady state. All parameter values are given in Table 1.

Table 1. Parameters of the hemodynamic model of CA. Superscript * indicates that the value of the parameter was determined by the suggested value in Ursino and Lodi (1997). Subscript n indicates that the parameter represents a basal value.

Parameter	Description	Initial Value
p_{cn} $(mmHg)$	Capillary pressure	25*
p_{icn} $(mmHg)$	ICP	9.5*
q_n (ml/s)	Art. l flow	estimated
p_{vs} $(mmHg)$	Venous pressure	6*
V_{an} (ml)	Art. volume	13.5*
q_{fn} (ml/s)	CSF formation	2/300*
k_E (ml^{-1})	Cranial elastance	.11*
τ (s)	CA relaxation	20*
G $(unitless)$	CA gain	1.5*
$p_{an}(mmHg)$	Art. pressure	estimated
R_0 $(mmHg \cdot s/ml)$	CSF outflow resist.	$(p_{icn} - p_{vsn})/q_{fn}$
R_f $(mmHg \cdot s/ml)$	CSF inflow resist.	$(p_{cn} - p_{icn})/q_{fn}$
C_{an} $(ml/mmHg)$	Art. compliance	$V_{an}/(p_{an} - p_{icn})$
$C_{a,mx}$ $(ml/mmHg)$	Max C_a	$6\,C_{an}$
$C_{a,mn}$ $(ml/mmHg)$	Min C_a	$.5\,C_{an}$
ΔC_{a1} $(ml/mmHg)$	σ amplitude 1	$2(C_{a,mx} - C_{an})$
ΔC_{a2} $(ml/mmHg)$	σ amplitude 2	$2(C_{an} - C_{a,mn})$
R_{an} $(mmHg \cdot s/ml)$	Art. resist.	$(p_{an} - p_{cn})/q_n$
R_{pv} $(mmHg \cdot s/ml)$	Pial vein resist.	$R_{an}\frac{p_{icn}-p_{cn}}{p_{cn}-p_{an}}$
k_R $(mmHg^3 \cdot s/ml)$	Resist. coeff.	$V_{an}^2\frac{p_{an}-p_{cn}}{C_{an}^2 q_n}$
A_c (cm^2)	Area of MCA	estimated
C_{a0} $(ml/mmHg)$	Initial C_a	C_{an}
P_{ic0} $(mmHg)$	Initial ICP	p_{icn}

We note that p_{cn}, V_{an}, q_{fn}, $C_{a,mx}$, $C_{a,mn}$, and p_{an} are only used in the calculation of initial parameter values and are not themselves model parameters. C_{an} is used in calculation of initial parameter values and is used as the approximation of the initial condition C_{a0}. Therefore, parameter estimation did not include these quantities. An additional parameter A_c is also fixed for identifiability purposes discussed in the next section. Thus model parameters analyzed include $\theta = \{p_{icn}, q_n, p_{vs}, k_E, \tau, G, R_0, R_f, C_{an}, \Delta C_{a1}, \Delta C_{a2}, R_{an}, R_{pv}, k_R, C_{a0}, p_{ic0}\}$.

4. ESTIMATION OF MODEL PARAMETERS

The model described in Section 1 has thirteen parameters (excluding p_{cn}, V_{an}, q_{fn}, $C_{a,mx}$, $C_{a,mn}$, p_{an}, and A_c), θ_p

and two initial conditions θ_i, giving a total of fifteen candidate parameters. Several of these have clinical interest. In particular, with respect to disease and aging, we are interested in distinguishing between those alterations in the cerebrovascular response to arterial pressure changes that can be attributed to CA mechanisms, characterized by τ and G, and those that can be attributed to hemodynamic characteristics, such as those that are summarized by R_0, k_E, and q_n. However, since several parameters are correlated, reliable prediction of these parameters will not be feasible without first reducing the parameter space. For instance, A_c is correlated with k_R due to the functional relation given by (4) in which

$$\hat{v} = \frac{q}{A_c} = \frac{V_a^2(p_a - p_c)}{A_c k_R C_{an}^2}. \tag{9}$$

Therefore, A_c was held fixed in this analysis. The reduced parameter vector θ_p and θ_i can then be estimated together as $\theta = [\hat{\theta}_p^T, \theta_i^T]^T$.

To estimate model parameters we used a nonlinear least-squares technique minimizing the least squares error between computed and measured values of cerebral blood flow velocity. To this end we define the residual r and the least squares cost J as

$$r(t_i;\hat{\theta}) = \frac{\hat{v}(t_i;\hat{\theta}) - v_i}{v_i\sqrt{N}} \quad \text{and} \tag{10}$$
$$J(\hat{\theta}) = r^T r,$$

where N is the total number of data points, $\hat{v}(t_i;\theta)$ are the (θ-dependent) model estimates of the CBFV at time t_i and v_i are the corresponding TCD estimates of CBFV. Before applying nonlinear least squares optimization to estimate model parameters, we use sensitivity analysis and subset selection to determine the set of parameters that we can reasonably estimate given numerical constraints.

4.1 Sensitivity Analysis

The goal of this analysis is to find a parameter set $\hat{\theta}^*$ that minimizes the least-squares cost defined by (10). However, applying the optimization procedure using all parameters can be comuptationally cumbersome if not naive. We conducted sensitivity analysis in order to determine if the model is insensitive to some parameters, allowing us to exclude them from the optimization procedure.

In order to determine which of the parameters the model was insensitive to, we computed normed relative sensitivities. The j^{th} sensitivity function ($j = 1 \ldots n$, where n is the total number of model parameters) is given by

$$S_j(t_i) = \frac{\partial y}{\partial \theta_j} \tag{11}$$

where $y(t)$ is the model output (CBFV) and θ_j is the j^{th} parameter. Many applications, (e.g. our previous study (Ellwein et al., 2009)) include several outputs of different order, thus it is often necessary to make sensitivities relative to compare sensitivities across outputs. In our application, we only have one output quantity CBFV, thus this is not a requirement. However, for comparison with previous studies, we predict the parameter ranking using relative sensitivities. Relative sensitivity functions (non dimensional) can be obtained by scaling sensitivities relative to the model parameter and the output as

$$S_j(t_i)^R = \frac{\partial y}{\partial \theta_j}\frac{\theta_j}{y}. \tag{12}$$

We used a forward difference approximation to compute the j^{th} partial derivative of the model output by

$$\frac{\partial y}{\partial \theta_j} \approx \frac{y(t_i;\theta + he_j) - y(t_i;\theta)}{h} \tag{13}$$

where e_j is the unit vector in the direction of the j^{th} parameter. We used $h = 10^{-2}$. We then computed the norm of (12) by

$$S_{j,(norm)} = \left(\frac{1}{N}\sum_{i=1}^{N} S_j(t_i)^{R^2}\right)^{1/2}. \tag{14}$$

In order to obtain an over-all scaling of the sensitivity of the model output to each of the parameters. The results can be seen in Fig. 3.

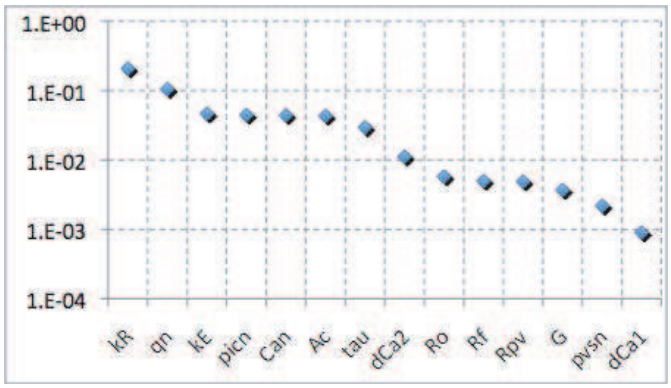

Fig. 3. Log_{10}-scaled relative sensitivities of the model parameters (of θ_p).

For this analysis, no parameters had a sufficiently small $S_{j,(norm)}$ to warrent exclusion, however, since initial parameter values are, in part, computed from patient-specific values, this may not be the case for all individuals. Consequently, for this subject subset selection was performed on all 15 model parameters to determine which of them were numerically estimable.

4.2 Subset Selection

We can see from equations (1-6) that some of the parameters are not linearly independent with respect to the model output, e.g. we showed in (9) that A_c is correlated with k_R. Other correlations may exist but are not so obvious. To tease out these correlations we use a subset selection method originally proposed by Golub and Loan (1983) and used in some of our previous studies (Ellwein et al., 2009; Pope et al., 2009).

This method predicts correlations by analyzing the numerical rank of the Jacobian, which can be computed from the residual vector (10) as $r' = \partial r/\partial\theta$. The numerical rank is assessed using singular value decomposition

$$r' = U\Sigma V^T,$$

where Σ is the diagonal matrix of singular values of r' in decreasing order, V is the matrix of right singular vectors,

and the superscript T denotes the matrix transpose. We form a partition $V = [V_\rho, V_{n-\rho}]$ in which ρ is the numerical rank of r'. Using ρ we find a permutation matrix P such that

$$V_\rho^T P = Q\hat{R},$$

where Q is full rank and the first ρ columns of $\hat{R}$ form an upper triangular matrix with diagonal elements in decreasing order. P is then used to reorder θ according to $\hat{\theta} = P^T\theta$. We find that $\hat{\theta} = [\hat{\theta}_\rho, \hat{\theta}_{n-\rho}]$, in which $\hat{\theta}_\rho$ is a vector containing the ρ estimable parameters.

Using this procedure, we determined a set of identifiable parameters ($\hat{\theta}$), listed in Table 2. It should further be noted that all of these parameters are sensitive (see Fig. 3). The remaining parameters $\hat{\theta}_{n-\rho}$ are held fixed at their nominal parameter values.

5. NUMERICAL OPTIMIZATION

The parameter vector $\hat{\theta}_\rho$ was estimated from data using the Levenberg-Marquardt (L-M) method (Kelley, 1999). L-M is an iterative method that uses the gradient of the cost with respect to the parameters to determine an appropriate alteration in the parameter values.

5.1 Verification of Convergence

We verified the convergence of the L-M method by analysing the cost J, defined in (10) and the gradient norm for each iteration. The results can be seen in Fig. 4. For each iteration, we expect that both the gradient norm and the cost will decrease. Results of our computations (see Fig. 4) showed that both the gradient norm and the cost are dramatically reduced, with only modest reductions over the last few iterations. From these observations we concluded that the algorithm has reached a local minimum and considered the final value of $\hat{\theta}_\rho$ to be the optimal value.

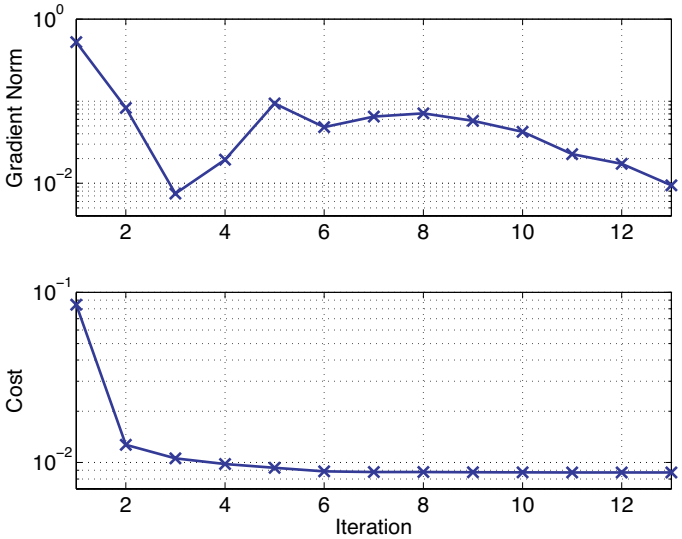

Fig. 4. Gradient norm and least squares cost at each iteration

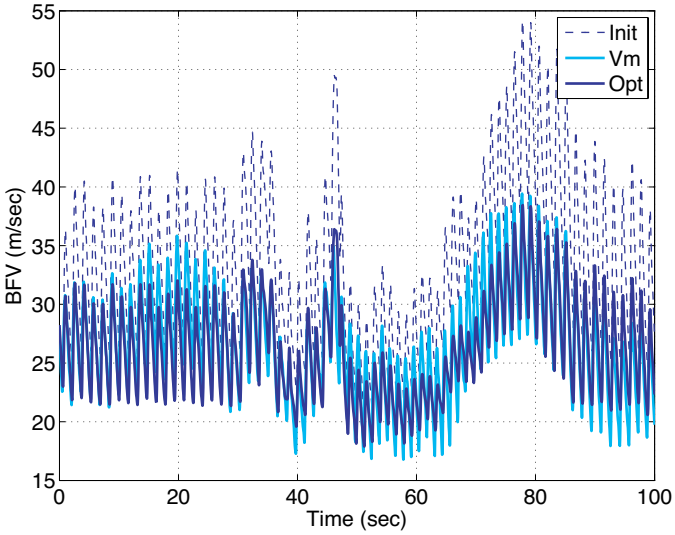

Fig. 5. Comparison of the model, computed with starting (–) and optimized (-) values of parameters, with data.

6. RESULTS AND DISCUSSION

In this study, we analyzed the model developed by Ursino and Lodi (1997) using sensitivity analysis and subset selection to identify a set of parameters that can be estimated using noninvasive measurements of arterial blood pressure and cerebral blood flow velocity. We found that out of fifteen model parameters eight could be estimated reliably using the data. We estimated this subset of parameters by means of the L-M method.

The final, optimized values of the parameters, and their starting values, are listed in Table 2. We found that all parameters are within a physiologically relevant range and the cost is reduced by over one order of magnitude.

Table 2. Comparison of nominal and optimized parameters. The initial cost was 0.52439, which was reduced to 0.00941 over 13 iterations of the G-N routine.

Parameter	Starting Value	Optimal Value
p_{ic0}	9.500	6.712
q_n	6.968	5.741
tau	20.00	14.16
R_{pv}	2.224	5.307
ΔC_{a1}	1.791	2.021
ΔC_{a2}	0.1791	0.2352
C_{an}	0.1791	0.2300
C_{a0}	0.1791	0.2706

We can qualitatively compare the optimized parameters with the starting values of parameters by examining Fig. 5. We see that the optimal parameters do a better job of matching the cerebrovascular response than the starting parameters.

These results depend on the relaxation factor α that was chosen to smooth the data. We found that larger values of α provided a greater numerical rank of the Jacobian matrix described in Section 4.2, resulting in a greater number of identifiable parameters predicted by subset selection. We must also consider that both sensitivity analysis and subset selection are local methods, that predict results depending on initial parameter values. Since the model

is nonlinear, the results (i.e., the sensitivity rankings, the final subset chosen, and their respective optimal values) may not be the same if a different set of initial values are chosen. We used initial parameter values defined by Ursino and Lodi (1997), but did not conduct a further analysis investigating the behavior of this model away from these values. One way to investigate the is to recompute sensitivities and apply subset selection using the optimized parameter values.

7. CONCLUSIONS

We found that the model proposed by Ursino and Lodi (1997) is able to predict CA dynamics observed during postural change from sitting to standing for a single subject using measured arterial pressure and MCA flow velocity. The results of this study show that it is feasible to use this model to analyze dynamics of individual subjects and may be suitable to study variations in CA between populations. Ultimately, this technique can be used to determine how these parameters vary with respect to disease and aging while taking into account the highly nonlinear nature of blood pressure-cerebral blood flow variations. Thus, future work should consist of estimating standard errors of paramter estimates and formulation of a hypothesis testing procedure to determine if differences in the fitted parameters exist between groups while taking into account intra-subect parameter uncertainty.

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