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Modeling cerebral blood flow and regulation

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Abstract— **Cerebral autoregulation is a homeostatic mechanism which maintains blood flow despite changes in blood pressure in order to meet local metabolic demands. Several mechanisms play a role in cerebral autoregulation in order to adjust vascular tone and caliber of the cerebral vessels, but the exact etiology of the dynamics of these mechanism is not well understood. In this study, we discuss two patient specific models predicting cerebral blood flow velocity during postural change from sitting to standing. One model characterises cerebral autoregulation, the other describes the beat-to-beat distribution of blood flow to the major regions of the brain. Both models have been validated against experimental data from a healthy young subject.**

I. INTRODUCTION

Cerebral autoregulation (CA) maintains blood flow despite changes in blood pressure. Typically, CA is assessed by analyzing relations between arterial blood pressure (ABP) and middle cerebral arterial (MCA) blood flow velocity (BFV). Analysis of CA based only on these measurements is far from ideal, but more detailed experimental interrogation of the cerebrovascular physiology involves measurements that are either invasive or that cannot quantify dynamics over all relavent time scales. Since CA dynamics are difficult to characterize directly, a number of methods have been proposed to assess the health of the CA system using only ABP and BFV measurements (examples include the autoregulatory index (ARI) [1] and multi-modal pressure-flow (MMPF) method [2]). Most of these methods are based on signal processing techniques, which cannot examine the individual physiological components of this system such as the mechanical properties of the vessels, the cerebrospinal fluid circulation and vasoreactivity. One way to examine these components within the context of the whole system is to use a mathematical model. This approach can be used to determine several characteristic quantities, such as vessel stiffness, cerebrospinal fluid (CSF) outflow, vascular resistance, and the active time scales involved with CA. A model could be used to assess regional vasoreactivity as well. A recent review by David et al [3] discusses this important topic, but to our knowledge, no existing patient specific models have attempted to assess changes in CA in the different regions of the brain.

In this study we analyze a model proposed by Ursino and Lodi [4]. In addition, we show how regional blood flow can be predicted using a 1D fluid dynamic model. Both models are open loop models that use blood pressure and BFV measurements as inputs to predict cerebral BFV dynamics during a postural change from sitting to standing. We show how these models are validated against experimental data, and we discuss how the two models can be coupled to assess regional CA.

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II. METHODS

This work aims at understanding CA during postural change from sitting to standing. We will analyze two models that relate transcranial Doppler BFV measurements from the middle cerebral artery (MCA) and Finapres (Finapres, Ohmeda Monitoring Systems, Englewood CO) measurements of arterial blood pressure. The first is a compartmental model that uses arterial blood pressure as an input to predict changes in cerebrovascular tone and intracranial pressure during a change in arterial pressure (such as during a postural change from sitting to standing). The second is a 1D fluid dynamic model which uses measurements of carotid and basilar BFV to predict regional cerebrovascular resistance and compliance at rest. For both models the output quantities will be predicted using nonlinear optimization techniques minimizing the sum of squared errors between computed and measured values of cerebral BFV.

A. Cerebral autoregulation

1) Hemodynamic model: The Ursino and Lodi (U-L) model can be formulated to use mean arterial blood pressure as an input to predict mean cerebral BFV. This model lumps all cerebral arteries into one unit and describes how cerebral blood flow can be predicted, accounting for changes in cerebral vascular tone and intercranial pressure. A diagram of this model is shown in Figure II-A.1. This model uses an electrical analogy, where cerebral BFV v_c can be given by

$$v_c = \frac{q}{A_a} = \frac{p_a - p_c}{R_a A_a}, \tag{1}$$

where q is the cerebral blood flow rate to the MCA territory, A_a is the cross-sectional area of the MCA, p_a is the input arterial pressure, p_c is the arterial capillary pressure, and R_a is the cerebrovascular resistance.

We apply volume balance at the level of the capillaries where the venous pressure just distal to the cerebral capillaries p_v is equal to the intracranial pressure p_{ic}. Furthermore,

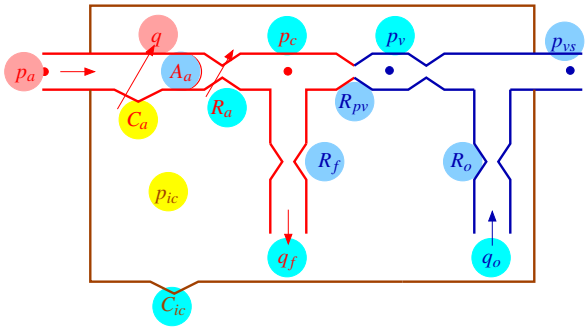

Fig. 1. Schematic of the hemodynamic model. Quantities on the model are marked with three colors. yellow variables are found as solutions to ODE's, pink denote variables for which we have data, light blue are constant parameters, and turquise quantities are auxiliary functions.

we assume that the volume of CSF flow out of the capillaries is negligible compared to the blood volume. Therefore, setting $p_v = p_{ic}$ the capillary pressure can be found as

$$p_c = \frac{p_a R_{pv} + p_{ic} R_a}{R_{pv} + R_a}, \tag{2}$$

where R_{pv} is the constant venous resistance to flow.

The intracranial pressure p_{ic} is found as a solution to the differential equation

$$\frac{dp_{ic}}{dt} = \frac{k_E p_{ic}}{1 + C_a k_E p_{ic}} \left[C_a \frac{dp_a}{dt} + \frac{dC_a}{dt}(p_a - p_{ic}) + \frac{p_c - p_{ic}}{R_f} - \frac{p_{ic} - p_{vs}}{R_0} \right], \tag{3}$$

where k_E, R_f, R_0, and p_{vs} are constant parameters, arterial pressure p_a and dp_a/dt are input from measurements, the capillary pressure p_c is given by (2), and vascular compliance C_a is found from the solution of a ODE describing CA and is discussed in the next section.

Finally, the resistance to flow, defined as $R_a \equiv \Delta p/q$ can be derived from the Poiseuille's equation and is given by

$$R_a = \frac{k_R}{V_a^2}, \quad \text{where} \quad V_a = C_a(p_a - p_{ic}), \tag{4}$$

where k_R is a constant parameter and V_a is the stressed arterial volume.

2) Autoregulation model: Cerebral blood flow is regulated by many factors. In this model we assume that cerebral blood flow q, is maintained about a set point q_n by regulating cerebral vascular tone. We can thus view the deviation in cerebral blood flow from this set point by the scaling $\xi = (q - q_n)/q_n$.

The regulation of vascular tone is achieved by control of C_a by the equation

$$\frac{dC_a}{dt} = \frac{1}{\tau}(-C_a + \sigma), \tag{5}$$

where σ is the autoregulatory control function and τ is a relaxation constant which determines the time scale of the effects of σ.

The control function σ is a function of ξ, but is limited in its capacity to act on the arterial vessels. For this CA system, the control is modeled as

$$\sigma(G\xi) = \frac{(C_{a,n} + \Delta C_a/2) + (C_{a,n} - \Delta C_a/2)e^{G\xi/k_\sigma}}{1 + e^{G\xi/k_\sigma}}, \tag{6}$$

where ΔC_a is a function that describes the saturation limits of σ, G is the autoregulatory gain, and $k_\sigma = \Delta C_a/4$. Finally, $C_{a,n}$ denotes the basal (or set-point) value for C_a.

In summary, the U-L model can be formulated as a system of two ODE's, (3) and (6), for which the state variables are p_{ic} and C_a. Patient-specific simulation of CA dynamics was achieved 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, with the model output v_c computed from p_a, C_a, and p_ic as in (1).

B. Alternative CA Description

The CA model described above only permits first order dynamics. It is well known that CA is complex, and it is likely that the simplified model with only one time-scale τ is not adequate for predicting observed cerebral BFV responses. Furthermore, CA may display hysteresis, showing more pronounced changes in cerebrovascular tone (faster and with bigger amplitude) in response to a decrease in blood pressure than during an increase in blood pressure.

Ursino and coworkers have developed a CA model with multiple time-scales exploiting the segmented nature of the the cerebral arteries [5], but to our knowledge nobody has derived a CA model that can predict hysteresis effects. In this study we show preliminary results using an open loop control model that predicts cerebrovascular tone (compliance and resistance). Similar to previous work [7] we describe the open loop control by defining cerebral compliance C_a using a piecewise linear function of the form

$$C_a(t) = \sum_{i=1}^{n+1} \gamma_i H_i(t) \tag{7}$$

where $H_i(t)$ are n hat functions defined by

$$H_i(t) = \begin{cases} \frac{t - t_{i-1}}{t_i - t_{i-1}}, & t_{i-1} \le t \le t_i \\ \frac{t_{i+1} - t}{t_{i+1} - t_i}, & t_i \le t \le t_{i+1} \\ 0, & \text{otherwise} \end{cases} \tag{8}$$

The coefficients γ_i of this function may be estimated along with the model parameters and the time-course of C_a variations are used to predict changes in cerebrovascular resistance through the functional relation given in equation (4).

C. Regional Cerebral Blood Flow

To obtain information about regional cerebral blood flow velocity, it is necesary to present major vessels in the cerebral vasculature. This can be done using a 1D fluid dynamic model using vessel geometries obtained from MRA measurements of the radii and length of the vessels of the circle of Willis (coW). This model is described in detail in [6]. Regional blood flow velocity is then predicted by solving

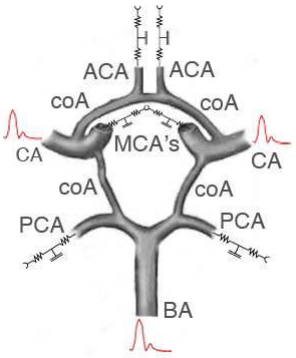

Fig. 2. 1D model of the coW including inflow vessels (the carotid CA and basilar BA arteries as well as the anterior (ACA), middle (MCA), posterior (PCA), communicating (coA). Inflow to the model is denoted by a wave and outflows are marked with a Windkessel element.

the 1D Navier Stokes equations for each vessel of the coW. The vessels included in this model are shown in Fig. 2. For each vessel, flow $q(x,t)$, pressure $p(x,t)$, and vessel area $A(x,t)$ are computed as solutions to the following 1D Navier Stokes equations,

$$\frac{\partial A}{\partial t}+\frac{\partial q}{\partial x}=0 \tag{9}$$

$$\frac{\partial q}{\partial t}+\frac{1}{2}\frac{\partial}{\partial x}\left(\frac{q^2}{A}\right)+\frac{A}{\rho}\frac{\partial p}{\partial x}=\frac{4\mu q}{A}, \tag{10}$$

where μ is the viscosity of blood (constant) and ρ is the blood density. This model is obtained assuming a parabolic velocity profile across the vessel wall. The first equation ensures conservation of mass and the second conservation of momentum. These equations are combined with a Kelvin viscoelastic model that relates vessel area and arterial pressure as

$$p-p_0+\tau_\sigma\frac{\partial p}{\partial t}=\frac{Eh}{r_0}\left(s+\tau_\varepsilon\frac{\partial s}{\partial t}\right),\quad s(t)=1-\sqrt{\frac{A}{A_0}}.$$

In this equation E is Young's modulus, h is the wall thickness, and r_0 is the radius at $p=p_0$.

At the internal boundaries (i.e., at the junctions between vessels) we applied two conditions. For a junction with N_J vessels, we assume that flow is conserved, $\sum_{i=1}^{N_J} q_i=0$, where flow into the junction is considered positive, and flow out is considered negative. We also assume that the pressure of each vessel at the junction is equal, $p_1=p_2=\cdots=p_{N_J}$.

The external boundary condition for each of the outflow vessels is described by the three-element windkessel model

$$R^s+\frac{\partial q}{\partial t}+\frac{R^s+R^p}{R^pC}q=\frac{\partial p}{\partial t}+\frac{1}{R^pC}p \tag{11}$$

where $q(L_i,t)$ is flow and $p(L_i,t)$ is pressure at the boundary of vessel i having length L, C is the vessel compliance, and R^s and R^p are resistances to flow. At the inflow vessels, we prescribe time varying BFV obtained from measurements of the internal carotid arteries and the basilar artery.

D. Patient-Specific Parameter Identification

1) Autoregulation Model: Nominal values for the parameters of the U-L model were determined from literature, by estimation from data, and functional relations, assuming that the system is at steady state. To determine if the model could predict the observed data, we used sensitivity analysis and subset selection as described in [8] to identify a set of parameters that can be reliably estimated given blood flow velocity data. We then estimated these parameters using the Levenberg-Marquart method [9] minimizing the least squares error between computed and measured values for cerebral BFV, i.e., we minimized the cost

$$J=\sum_{i=1}^{N}|v_c^c(t_i)-v_c^m(t_i)|^2,$$

where superscript c denotes computed values, and superscript m denotes measured values. All quantities are evaluated at times t_i where measurements were taken.

To validate the 1D model of the coW, we used ensemble Kalman filtering to estimate all resistors and capacitors for all outflows. We used an ensemble size of $n=100$ to estimate all 12 parameters over an 8 second period.

2) Distributed Model: In order to accurately determine the parameters of the windkessel boundary conditions of the fluid dynamic model, an initial guess for the outflow resistances can be made by approximating the coW in 0D. By electrical analogy, the resistance to flow of each vessel (given in Fig. 2) can be approximated by Ohm's law, and the resistances can be determined using the vessel geometries and the Poiseuille equation. Applying a flow conservation law at each of the nodes in Fig. 2, and setting the flow at each of the boundaries to volumetric flow measurements from arterial spin labeled MRI, we can derive a system of linear algebraic equations for which we can find a unique solution, which includes the total outflow resistance $R_{i,Tot}$ of each of the i outflow vessels of the arterial network. However, there are two resistors at each boundary.

As suggested in [10] and [11], in order to minimize non-physiological reflected waves, the first of these resistors, R^p should be equal to the characteristic impedance of the corresponding outflow vessel. This is given by

$$R_i^p=Z_0=\rho c_0/A_0, \tag{12}$$

where R_i^p is the first boundary condition resistance of the i^{th} outflow vessel, ρ is the density of blood, c_0 is the Moens-Korteweg characteristic wave speed of the vessel, calculated $c_0=\sqrt{\frac{Eh}{2\rho r_0}}$, and A_0 and r_0 are the characteristic area and radius of the vessel, respectively. Since the resistors are in series, the combined resistance is given by the sum of the resistances. Therefore, if we know the total resistance $R_{i,Tot}$ for the i^{th} outflow vessel, we may calculate the value of the second resistor R_i^s by taking

$$R_i^s=R_{i,Tot}-R_i^p \tag{13}$$

for vessel i.

III. RESULTS

Results of simulations are shown in Fig. 3. We can see that the U-L CA model can predict BFV changes during standing, but not the BFV level before and after standing. It was, however, able to predict BFV accurately during the standing phase (compare red and turqouise traces on Fig.3 bottom left graph). Note how cerebral vascular tone (top right) predicted with U-L model shows approximately the same dynamics during the activation phase, while the baseline value is too low before the sit-to-stand and too high after the sit-to-stand when compared to using the modified U-L (MU-L) model using (7).

The results of the 1D model (shown for the right MCA in the bottom right panel of Fig.3) showed that during steady state (sitting) the 1D model was able to predict observed MCA BFV dynamics. In particular, note that the 1D model is able to predict the BFV waveform.

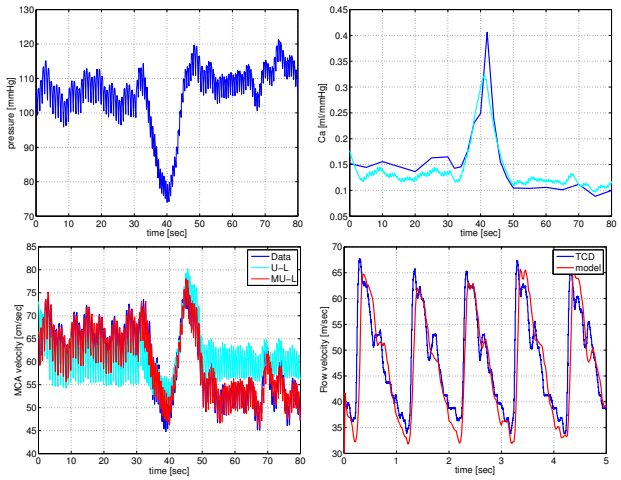

Fig. 3. A representative comparison of models to data from a healthy young subject. The top left panel shows input pressure for the CA model, which dips at the point when the patient stands. The top right panel shows the resulting cerebrovascular tone computed with the autoregulation (turqoise) and piecewise (blue) linear models., and the bottom row shows the fit to MCA BFV with the autoregulation model (left) and the 1D model (right). The 1D model is able to reproduce the BFV waveform while the autoregulation model is able to reproduce the observed BFV dynamics in response to a postural transition.

The results shown above are from a representative subject. We have analyzed MCA BFV using the U-L CA model for 16 heatlhy young subjects, and for 9/16 subjects the U-L model by itself was able to predict observed dynamics.

IV. DISCUSSION

In this paper we have shown that we can predict beat-to-beat regional blood flow of a subject at rest. We have further shown that the U-L model can predict BFV dynamics during standing for some subjects, but for some subjects the CA model fails to predict the level of C_a before and after standing. Rather than describing C_a as in (5), we propose to model CA as an arbitrary open-loop control implemented by predicting C_a using a piecewise linear function. This allows us to examine a realistic time course for C_a without the constraints of (5) and may permit us to determine a more appropriate control function. Results ofthe 1D model show that the model can predict regional BFV, but much work is needed to couple this model with the CA model.

In future work we propose to use the CA model to predict regional regulation of cerebral blood flow, one way to do so would be to use measured blood pressure as an input to the 1D fluid model and regulate the resistors and capacitors in the windkessel models using the U-L model with piecewise linear control. Finally, the 1D model should be modified to account for changes in intracranial pressure.

V. ACKNOWLEDGMENTS

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