Estimating Mean and Pulsatile Cerebral Blood Flow During Orthostatic Stress

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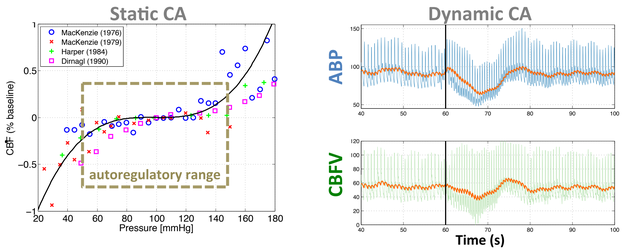
Introduction

Cerebral autoregulation (CA) is a local process modulating vessel properties to maintain cerebral blood flow (CBF) despite fluctuations in arterial blood pressure (ABP). Four mechanisms contribute to regulate flow. The myogenic response describes the influence of circumferential mechanical stresses and strains on vascular smooth muscle cell tone. During the neurogenic response, astrocytes sense neural activity and regulate CBF via end feet. The metabolic response corrects the mismatch between neurogenic flow increase and CBF demand. The shear-dependent response is characterized by the production of nitric oxide by the endothelium. Previous models aim to describe either static CA (steady-state ABP/CBF relationship) or dynamic CA (transient CBF response). This work proposes a simple patient-specific model predicting transient CBF velocity (CBFV) that describes both static and dynamic CA responses.



Experimental Data

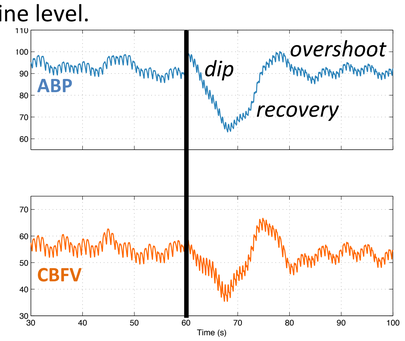
Pulsatile ABP (via Finapress) and CBFV (via Transcranial Doppler ultrasound) data collected during postural change from sitting to standing. To account for oscillations reflected in the data, the filtered signals are computed as moving averages according to equation

$$\bar{x}(t) = \alpha \int_{-\infty}^{t} x(s) e^{-\alpha(t-s)}\, ds \quad \text{where} \quad x = \left[p_a, V_{mca}^d\right]$$

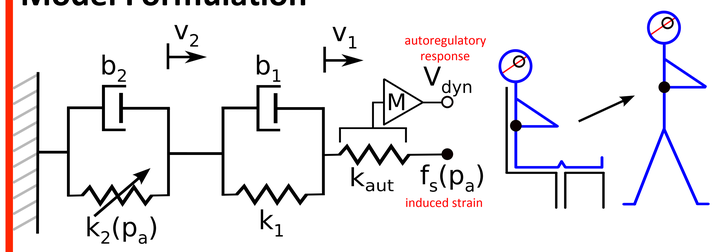
To incorporate the averaged ABP and CBFV into the model, we differentiate to obtain

$$\frac{d\bar{x}}{dt} = \alpha(x - \bar{x})$$

When looking at the filtered signals, there are *dip*, *recovery*, and *overshoot* dynamics in both ABP and CBFV that resemble viscoelastic stress relaxation. These trends are similar to the baroreflex [6]. Upon standing, denoted by the vertical line, blood is pooled in the legs and the ABP drops in the upper body. In response to the imposed stress, the CA mechanisms are triggered and the pial arteries and penetrating arterioles exhibit viscoelastic deformation, causing CBFV to adapt to its metabolic demand and return to its baseline level.



Model Formulation



$$\text{Stresses:}\quad \varepsilon_0 = f_s(p_a) - v_1,\quad \varepsilon_1 = v_1 - v_2,\quad \varepsilon_2 = v_2 \qquad \text{Strains:}\quad \sigma_0 = k_{aut}(f_s(p_a) - v_1),\quad \sigma_1 = k_1(v_1 - v_2) + b_1\left(\frac{dv_1}{dt} - \frac{dv_2}{dt}\right),\quad \sigma_2 = k_2(p_a)v_2 + b_2\frac{dv_2}{dt}$$

The simple nonlinear ODE model aims to predict transient CBFV as a function of ABP on a patient-specific basis. The autoregulatory response is described using the mechanical analog, consisting of a Kelvin-Voigt element (spring and dashpot in parallel) in series with a Maxwell element. The input is the total strain induced by the ABP stimulus $f_s(p_a)$, and the dynamic CA response V_{dyn} is represented by the strain sensed by the spring k_{aut}. Apply the constraint that $\sigma_0 = \sigma_1$ and $\sigma_0 = \sigma_2$ and rearrange terms to arrive at the ODE system describing the autoregulatory response, where a, b, and c are nonnegative parameters dependent on viscoelastic elements. Static CA results from a polynomial fit to normalized experimental data from animals [1,3,5] to capture impaired autoregulation below 50 mmHg and above 150 mmHg. By defining the function a priori, the curve does not result from model dynamics and therefore no additional parameters are introduced to the model. The predicted velocity profile of the blood flow in the MCA is the combination of the subject's steady-state behavior and the dynamic autoregulatory response.

$$\frac{dv_1}{dt} = -(a+b+c)v_1 + (c - R_{aut}(p_a))v_2 + (a+b)f_s(p_a)$$

$$\frac{dv_2}{dt} = -bv_1 - R_{aut}(p_a)v_2 + bf_s(p_a)$$

$$a = \frac{k_{aut}}{b_1},\quad b = \frac{k_{aut}}{b_2},\quad c = \frac{k_1}{b_1},\quad R_{aut}^*(p_a) = \frac{k_2(p_a)}{b_2}$$

$$f_{aut}(p_a) = (2.03\cdot10^{-6})p_a^3 - (6.02\cdot10^{-4})p_a^2 + (5.94\cdot10^{-2})p_a - 1.95 \qquad \text{Static CA}$$

$$R_{aut}(p_a) = \frac{bcf_{aut}(p_a)}{cf_s(p_a) - (a+c)f_{aut}(p_a)} \qquad \text{Computed so that } f_{aut}(p_a) \text{ is steady-state of system}$$

$$V_{dyn} = M(f_s(p_a) - v_1) \qquad \text{Dynamic CA}$$

$$V_{mca} = V_{bas} + V_{dyn} \qquad \text{Model output}$$

Model Stability

In response to a step change pressure, the steady-state of the system is

$$v_1^* = \frac{\bar{f}_s(bc + aR_{aut})}{bc + (a+c)R_{aut}} \xrightarrow[(R_{aut} = 0)]{\text{within autoregulatory range}} v_1^* = \bar{f}_s$$

$$v_2^* = \frac{bc\bar{f}_s}{bc + (a+c)R_{aut}} \qquad\qquad v_2^* = \bar{f}_s$$

For simulations, initial conditions were computed assuming the system is in steady-state. The input pressure p_a is set to be the average over the baseline portions of the experiment. The system has two negative real eigenvalues, resulting in two distinct time constants that represent both the fast and slow autoregulation mechanisms.

Parameter Estimation

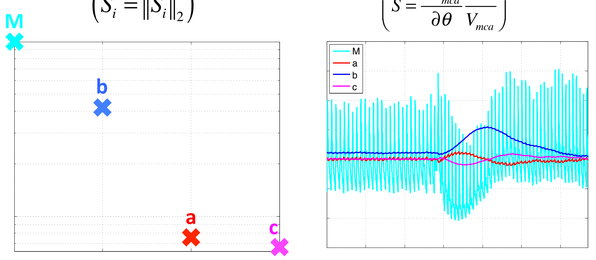
Ideal fits were obtained by minimizing the least squares error between model output and data. Three parameters (a,b,c) were estimated using the gradient-based Levenberg-Marquardt method [2].

Parameter	Description	Nominal Values	Value (Y)	Value (E)
a	Dynamic element	0.25	0.466	2.50
b	Dynamic element	0.1	0.0100	0.280
c	Dynamic element	0.9	0.290	2.71
M	Mathematical amplifier	1.0	1.2	1.0
V_{bas} (cm/s)	Patient-specific CBFV	-----	57.4	37.7

Model Analysis

Sensitivities S_i describe how sensitive the model output is to a given value of the i^{th} parameter, given by $S = \frac{\partial V_{mca}}{\partial \theta}$.

Ranked Sensitivities $\left(\bar{S}_i = \|S_i\|_2\right)$ | Relative Sensitivities $\left(\tilde{S} = \frac{\partial V_{mca}}{\partial \theta}\frac{\theta}{V_{mca}}\right)$



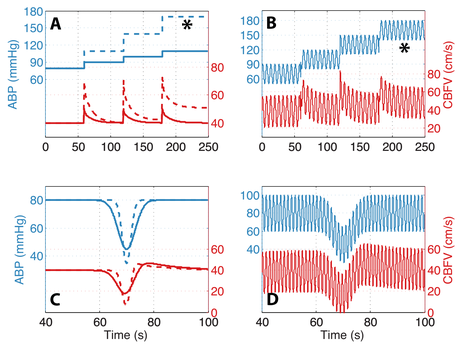
Relative sensitivities are useful since output and parameters may have different units, and ranked sensitivities provide a comparison of parameter sensitivites (*M* most sensitive). Correlation analysis [7] can be used to explore possible pairwise correlations amongst parameters. There are no correlated parameters in our model, thus the parameters may be uniquely identified.

Model Identifiability

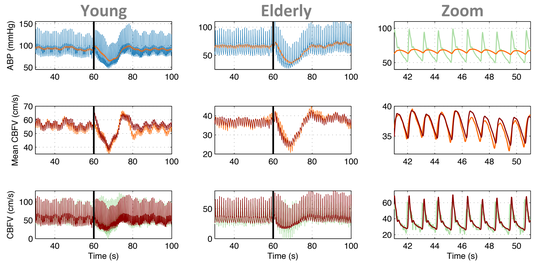
Analysis addresses question of which parameters can be inferred uniquely from given input/output data [6]. When ABP is within the autoregulatory range, the system reduces to linear ODEs. Coefficient map is one-to-one, thus the model is structurally identifiable in a, b, c, and M.

Qualitative Response

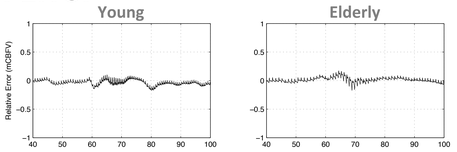
Model response to various pressure stimuli, including step increases (A), oscillating step increases (B), ABP drop and recovery (C), and oscillating ABP drop and recovery (D). For step increases outside of the autoregulatory range, denoted by an asterisk, the CBFV response settles to a higher value than the original steady-state.



Quantitative Results



Model Error



Conclusion

Unlike previous attempts to model CA, this approach consists of two ODEs, four algebraic expressions, and only five parameters. Despite its simplicity, our model is able to effectively predict both averaged and pulsatile CBFV. Future work will be focused on characterizing the effects of age and hypertension in humans.

References

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Acknowledgements

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