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Study of Cerebral Blood Volume and Blood Flow Using Integral Equation Theory

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Abstract. The aim of this work is to explore the relation between hemodynamic responses measured by NIRS (near infrared spectroscopy) and the input stimulus. An input-output nonlinear system consisting of a neural model and the Windkessel/Balloon model is used in the simulations. In this investigation, the input-output state model is used to explore hemodynamic responses to short (2 second) and long (20 second) stimuli. The simulated results are compared to published data to demonstrate the validity of the simulated results.

1 Introduction

This paper presents a series of simulation studies to explore the effects of blood vessel compliance and length of input stimulus on the temporal hemodynamic output response functions. The model used in the input-output state system is a combination of the neural response model [1] and the Windkessel/Balloon model [2]. The neural response model specifies the relationship between input stimulus and the synaptic activity while the Windkessel model shows the relationship between neural activity and hemodynamic changes.

In the present work, we used the hemodynamic input-output state model to explore the dependence of NIRS response estimates on various system parameters especially the temporal dynamics of the input signal and the flow-volume coupling coefficient, γ. The input-output state model consists of a linear part (linking the stimulus to the synaptic activity) and a nonlinear part (relating the synaptic activity to the blood flow and volume) [3].

2 Hemodynamic Model

Consider the hemodynamic model system described by the differential equations:

$$\dot{x} = A(t)x(t) + B(t)u(t) \tag{2.1}$$

$$y(t) = x_3(t) \tag{2.2}$$

where $x(t)$ is a 3×1 vector, $u(t)$ and $y(t)$ are scalars and

$$A(t) = \begin{bmatrix} -\frac{1}{\tau_s} & -\frac{1}{\tau_f} & 0 \\ 1 & 0 & 0 \\ 0 & \frac{1}{\tau_0} & 0 \end{bmatrix} \tag{2.3}$$

$$B(t) = \begin{bmatrix} \epsilon u(t) + \frac{1}{\tau_f} \\ 0 \\ \frac{-x_3^{\gamma}(t)}{\tau_0} \end{bmatrix} \tag{2.4}$$

where $x(t) = \begin{bmatrix} s(t) \\ f_{in}(t) \\ v(t) \end{bmatrix}$, $x(0) = \begin{bmatrix} 0 \\ 1 \\ 1 \end{bmatrix}$

A is a constant matrix with respect to time and the matrix B describes the relationship with the input signal and the relation of flow and volume. It should be noted that the nonlinearity arises from the flow and volume relationship, given by the term x_3^{γ} where γ is the compliance coefficient that describes the nonlinearity of the system. The problem is set up using the variation of parameters approach [4]. Each element of A and B describes a physical parameter that models the link between blood flow and volume in the human brain.

A linear model is assumed to link synaptic activity, u(t), the input signal to the hemodynamic system, to the neural response, $x_1(t) = s(t)$, which represents a flow inducing signal. The input signal, $u(t)$, is a step function over time and describes an activity that creates changes in brain response. This activity can be as simple as motor response caused by finger tapping to a more complex cognitive task, such as a verbal fluency examination. The blood flow is defined as the input flow to the brain region under consideration, $x_2(t) = f_{in}(t)$. The efficacy of synaptic activity, ϵ, represents the degree of increase in neural response that is caused by the input stimulus and in turn also determines the increase in blood flow. The parameter, τ_s, represents the signal decay constant for the neural signal which determines the time the system takes to return to baseline or equilibrium state. The time-constant for autoregulatory feedback, τ_f, is related to the blood flow and creates the oscillatory dynamics that are characteristic of the hemodynamic system. The mean transit time of the blood, τ_0, represents the time taken for blood to traverse through the region of interest in the brain modeled by the Windkessel compartment[3]. The most important parameter examined in this paper is the stiffness parameter, γ, which determines the nonlinear relationship between flow and volume, when laminar flow is assumed [5]. This parameter describes the compliance of the Windkessel compartment and determines the stiffness of the blood capillaries and thus determines changes in the blood volume in the system. In previously published literature, this value has been estimated at between 2.5 and 3.03 [1, 7]. In this paper we conduct simulations for different values of γ between 1 and 5 and present the value that gives us a steady state flow-volume exponent that has been observed through empirical studies.

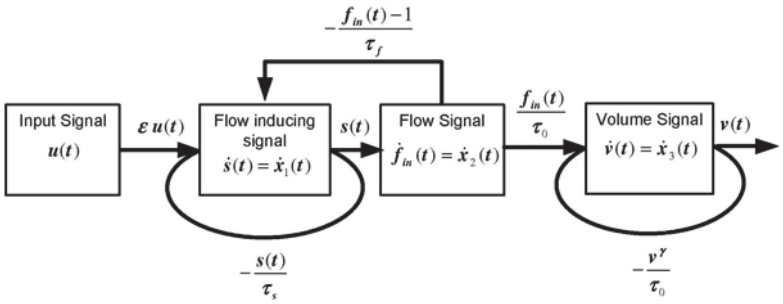

Figure 1: Block diagram of system [1]

2.1 Analytic Solution

We integrate the system equations using the variation of parameters method.

$$x(t) = e^{tA}x(0) + \int_0^t e^{(t-s)A}B(s)ds \tag{2.5}$$

Using the power series expansion for $e^{tA} = I + tA + \frac{t^2A^2}{2!} + \dots$ and substituting A from Equation (2.3) we get

$$e^{tA} \approx \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} + \begin{bmatrix} -\frac{1}{\tau_s} & -\frac{1}{\tau_f} & 0 \\ 1 & 0 & 0 \\ 0 & \frac{1}{\tau_0} & 0 \end{bmatrix} t + \begin{bmatrix} -\frac{1}{\tau_s} & -\frac{1}{\tau_f} & 0 \\ 1 & 0 & 0 \\ 0 & \frac{1}{\tau_0} & 0 \end{bmatrix}^2 \frac{t^2}{2} \tag{2.6}$$

$$e^{tA} \approx \begin{bmatrix} 1 - \frac{t}{\tau_s} + \frac{t^2}{2}\left(\frac{1}{\tau_s^2} - \frac{1}{\tau_f}\right) & -\frac{t}{\tau_f} + \frac{t^2}{2\tau_f\tau_s} & 0 \\ t - \frac{t^2}{2\tau_s} & 1 - \frac{t^2}{2\tau_f} & 0 \\ \frac{t^2}{2\tau_0} & \frac{t}{\tau_0} & 1 \end{bmatrix} \tag{2.7}$$

Substituting in Equation (2.5)

$$x_1(t) \approx -\frac{t}{\tau_f} + \frac{t^2}{2\tau_f\tau_s} + \int_0^t \left\{ \left[\epsilon u(s) + \frac{1}{\tau_f} \right] \left[1 - \frac{(t-s)}{\tau_s} + \frac{(t-s)^2}{2} \left(\frac{1}{\tau_s^2} - \frac{1}{\tau_f} \right) \right] \right\} ds \tag{2.8}$$

$$x_2(t) \approx 1 - \frac{t^2}{2\tau_f} + \int_0^t \left\{ \left[\epsilon u(s) + \frac{1}{\tau_f} \right] \left[(t-s) - \frac{(t-s)^2}{2\tau_s} \right] \right\} ds \tag{2.9}$$

$$x_3(t) \approx 1 + \frac{t}{\tau_0} + \int_0^t \left\{ \left[\epsilon u(s) + \frac{1}{\tau_f} \right] \left[\frac{(t-s)^2}{2\tau_0} \right] - \frac{x_3^\gamma}{\tau_0} \right\} ds \tag{2.10}$$

These equations can be integrated and solved simultaneously using a numerical integration technique. The technique adopted in this paper is an adaptive step Runge-Kutta (4,5) method. Details are discussed in the next section.

2.2 Numerical Solution

The system examined in this paper is a canonical initial value problem where the behavior of the system is described by a set of ordinary differential equations of the form $dx/dt = g(x,t)$ where g is a known function, x is the state of the system, and dx/dt is the time derivative of x. The variables x and dx/dt are vectors. As the name suggests, in an initial value problem x at time=0 is known and we wish to follow x over time thereafter [6]. Equivalently, the system of differential equations can be represented by a set of integral equations as follows [2].

$$x_1(t) = e^{\frac{-t}{\tau_s}} \int_0^t \left(-\frac{x_1(s)}{\tau_s} - \frac{x_2(s)-1}{\tau_f} + \epsilon u(s) \right) ds \tag{2.11}$$

$$x_2(t) = 1 + \int_0^t x_1(s) ds \tag{2.12}$$

$$x_3(t) = 1 + \int_0^t \left(\frac{x_2(s)}{\tau_0} - \frac{x_3^{\gamma}(s)}{\tau_0} \right) ds \tag{2.13}$$

where

$$\begin{array}{ll} u(t) = 1; & 0 \le t \le t_0 \\ u(t) = 0; & \text{otherwise} \end{array} \tag{2.14}$$

where t_0 marks the end of the input stimulus.

The standard differential equation solver used in this paper is the fourth-order Runge-Kutta method. This method has more precision than the Euler's algorithm from which it is derived and offers several attractive features such as ease of programming and mathematical simplicity. Adaptive step size control is used to give better accuracy to a solution while minimizing computational effort. With the addition of an adaptive step size, the fourth-order Runge-Kutta method is both robust and capable of providing solutions to complex problems.

3 Results

We simulated blood flow and blood volume time traces for an input stimulus of 2 seconds and 20 seconds. The simulated results are compared to published results for stimulus of 2 second and 20 second finger tapping exercise. Both the simulated and the published results show changes relative to baseline (initial conditions).

3.1 Simulations for varied compliance

The objective of the paper is to demonstrate the effect that varying compliance has on the flow and volume relationship. To achieve this end, we present graphs of blood flow and blood volume with a constant stimulus input of 2 seconds. We use the following typical values for our simulation: $\epsilon = 0.54$, $\tau_s = 0.86$ seconds, $\tau_f = 0.41$ seconds and $\tau_0 = 1$ second [1]. Next, the time traces for blood volume and blood flow for γ=1, 2, 3, 4 and 5 are plotted to compare the change induced in the hemodynamic responses by varying compliance.

As seen in Figure 2, changing compliance does not change the flow graph to a large extent and the curves almost overlap each other. This is to be expected since blood flow depends only on the neural activity and the input stimulus. Blood volume exhibits large changes with varying compliance. This also follows the predicted physical behavior of a Windkessel chamber which can be imagined as an expandable tube. As the tube becomes more compliant ($1/\gamma$ increases), the blood volume shows larger increases due to decreased resistance that the flow faces.

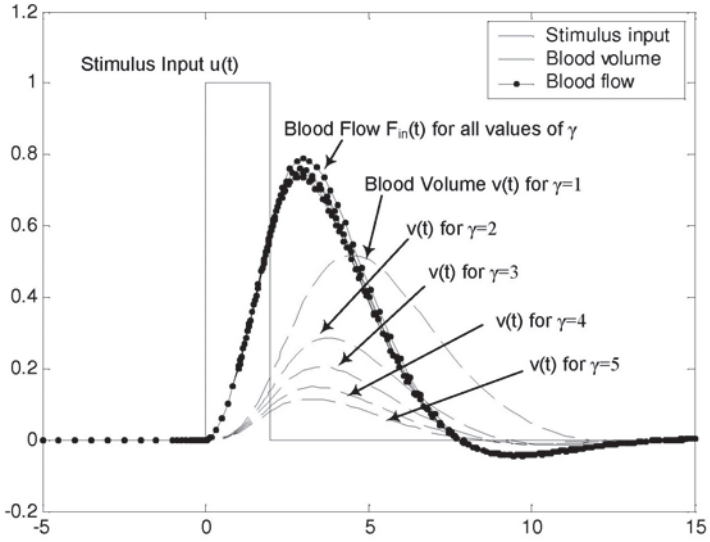

Figure 2: Simulated results for different compliance: Stimulus=2 seconds

To further quantify our results, we calculate the ratio of maximum flow to maximum volume for each value of γ. The results are presented in Table 1. We compare these results to previously published data, which predict a flow to volume ratio of ≈3.5. Thus we conclude that for the human brain, a stiffness coefficient $\gamma \approx 3$ is appropriate [7]. These results concur with previously published results [5, 7] which predict γ ≈3.03.

To validate the model for longer duration input, we repeat calculations of blood flow and blood volume using the same system with a constant stimulus input of 20 seconds. We use the following typical values for our simulation: ϵ=0.3, τ_s=0.86 seconds, τ_f=0.41 seconds and τ_0=1 second. Next the time traces for γ=1, 2, 3, 4 and 5 are plotted to compare the change induced in the system by varying compliance (Refer Figure 3). Similar to the results obtained with a 2 second input we observe that changing compliance does not change the flow graph significantly while blood volume exhibits large changes with varying compliance.

We repeat calculations of the flow to volume ratio for each value of γ. The results

Table 1: Simulation results compared to Published results: Stimulus=2 seconds

Stiffness coefficient(γ)	Flow to volume ratio
1	1.439562
2	2.577324
3	3.851490
4	5.111237
5	6.398648

are presented in Table 2. Since there is very little data published with simultaneous measurements of blood flow and blood volume, we surmise that the flow-volume ratio should remain the same with varying input. This is a reasonable assumption, since flow-volume ratio depends only the changes in the compliance parameter of the system and should therefore not be affected by the change in duration of the input stimulus. We again observe that a stiffness coefficient, $\gamma \approx 3$ is appropriate which gives a flow to volume ratio of 3.68.

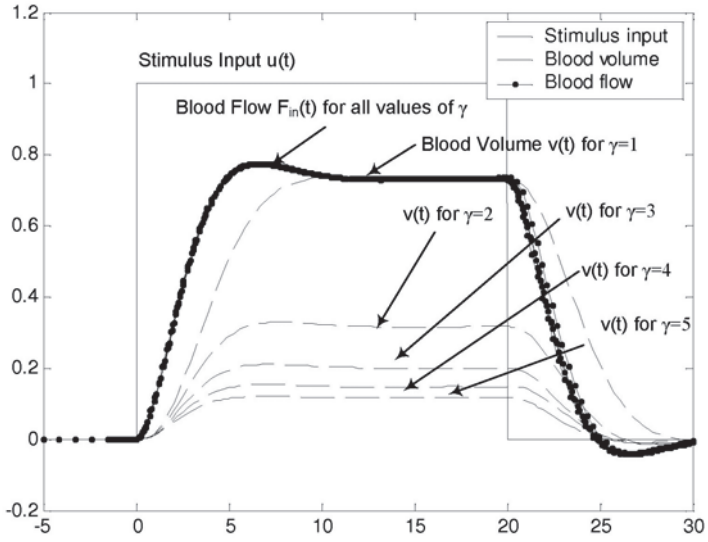

Figure 3: Simulated results for different compliance: Stimulus=20 seconds

Table 2: Simulation results compared to Published results: Stimulus=20 seconds

Stiffness coefficient(γ)	Flow to volume ratio
1	1.052535
2	2.351108
3	3.685428
4	5.025735
5	6.362376

3.2 Comparison to published results

In this section we compare our simulated results to published results. Figure 4 shows results simulated with a 2 second input stimulus. These results are compared to previously published results measured during a 2 second finger tapping task using near infrared spectroscopy to image the motor cortex of human subjects. The stimulus is started at time=0 second in the published results. In the measured data, the stiffness parameter, γ , is optimized to 3.6 which gives a flow to volume ratio of 4.5 [5]. We simulate flow and volume curves using the same stiffness parameter of 3.6 and our results yield a flow to volume ratio of 4.6 which is comparable to the published data.

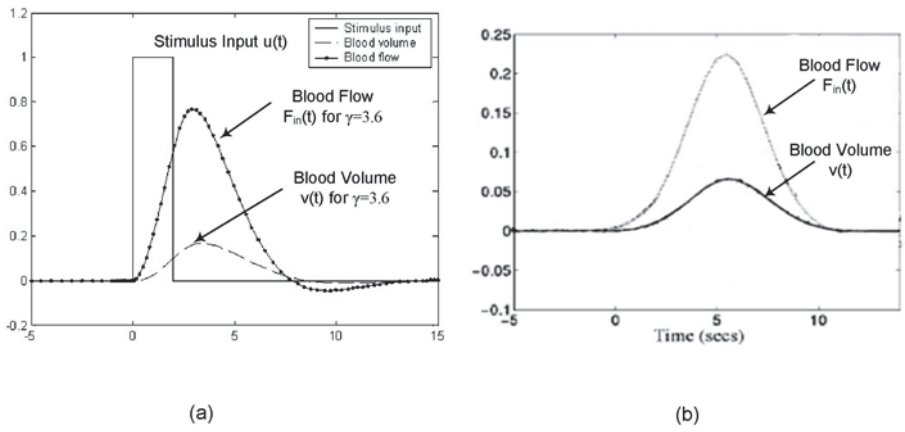

Figure 4: Stimulus=2 seconds (a) Simulation results (b)Published results [5]

Next, we compare our simulated results for longer duration stimuli to previously published data. Figure 5 shows results simulated with a 20 second input stimulus. The data was collected from the motor cortex of human subjects using near infrared spectroscopy during a 20 second finger tapping task. The stimulus is started at time=0

second in the published results. The published results contain a comparison on younger and older subjects and the blood volume changes induced by the same task across the two age groups [9]. This is an interesting result to compare our simulations, since arteries and capillaries harden and lose compliance with advanced age [8]. Thus the paper compares the changes of varying compliance on blood volume changes keeping all other parameters that relate to stimulus constant. We present a qualitative comparison of our simulated results with the published results in Figure 5. We assume γ=3.8 for young subjects which yields a flow-volume ratio of 4.5 and a γ=7.6 for elderly subjects which yields a flow-volume ratio of 9. We see that the volume graphs obtained using these values concur with published results.

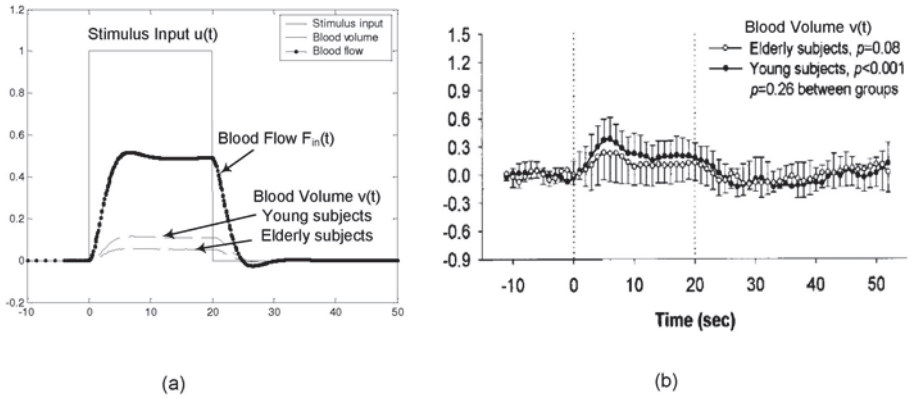

Figure 5: Stimulus=20 seconds (a) Simulation results (b) Published results [9]

4 Conclusions

We have demonstrated the use of variation of parameters integration with a numerical Runge-Kutta method to solve blood flow and blood volume states during activation in the human brain. We primarily examine the effects of changing compliance on the relationship between blood flow and blood volume and also compare our results to published data. Our work can be extended by inclusion of multimodality data, such as NIRS and functional magnetic resonance imaging, that includes simultaneous measurement of blood flow, volume and oxygenation for more accurate estimation of system parameters.

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