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# A Model of the Dynamic Relationship between Blood Flow and Volume Changes During Brain Activation

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**A Model of the Dynamic Relationship between Blood Flow and Volume Changes  
During Brain Activation**

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**Abstract:**

The temporal relationship between changes in cerebral blood flow (CBF) and cerebral blood volume (CBV) is still poorly understood. Grubb et al. (Grubb et al. 1974) measured the steady state relationship between changes in CBV and CBF following hypercapnic challenge which has been used extensively in the modelling of haemodynamic response to activation particularly in the context of magnetic resonance imaging and the blood oxygen level dependent (BOLD) signal. More recently the 'Balloon model' (Buxton et al. 1998) and 'Windkessel model' (Mandeville et al. 1999) have been proposed to describe the temporal dynamics of changes in CBV and CBF. In the study reported here a model based on the windkessel model incorporating delayed compliance is presented and compared with the original Windkessel model. The modified model is better able to capture the dynamics of CBF and CBV changes, particularly in the later stages.

**Keywords:** Dynamic modelling, cerebral blood flow, cerebral blood volume, Balloon, Windkessel, delayed compliance.

**Running title:** A model of changes in blood flow and volume



## **1. Introduction**

Roy and Sherrington (1890) proposed that increases in neural activity, metabolism, and blood flow were tightly coupled. However, the precise nature of the temporal relationship between the changes in cerebral blood volume (CBV) and cerebral blood flow (CBF), an elemental aspect of neurovascular physiology, is still poorly understood. With the developments of functional magnetic resonance imaging (fMRI), and particularly in the increasing use of brief duration transient stimuli in event related studies it is becoming increasingly important to clarify the temporal dynamics of the relationship. The blood oxygen level dependent (BOLD) signal is the image contrast commonly used in human fMRI studies resulting from a complex interplay of blood volume, flow, and increases in oxygen consumption (Jones et al 2001). In our study, changes in CBV are measured by optical imaging spectroscopy (OIS) and changes in CBF are measured using laser Doppler flowmetry (LDF).

The relationship between changes in blood flow (volume flux per unit time through a tissue volume element) and volume was first established by Grubb et al. (1974). It was found that volume changes followed flow changes raised to an exponent and the power

law relationship  $CBV = CBF^{0.38}$  has been used extensively in the modeling of the haemodynamic response to activation (Buxton et al., 1998; Mandeville et al., 1999). However the relationship was based on 'steady state' measurements, and its generalisation to activation paradigms involving transient changes is not established.

A biomechanical model (the Balloon model) was introduced by Buxton et al. (1998). This model assumes that the volume changes occur primarily in the venous compartment, and the rate of change is proportional to the difference between the inflow and outflow of the compartment with a time constant. Mandeville et al., (1999) modelled the dynamics of the relationship in terms of the resistance and capacitance of the venous and capillary microvasculature (Windkessel theory). Both the Balloon and the Windkessel model fail to capture the dynamics of the relationship between flow and volume during the return to baseline phase of the response. In this study a model with delayed compliance is presented which is better able to describe these aspects of the dynamics of CBF and CBV.

## **2. Methods**

### ***2.1 Experimental data***

Two data sets were used in this study: The first was intensity data obtained with electrical stimulation (20s) of different intensities (0.8, 1.2, 1.6 mA at 5Hz); the second

was frequency data obtained with brief (2s) electrical stimulation applied at different frequencies (1-5Hz at an intensity of 1.2mA). The two data sets presented here are adapted from Jones et al. (2001) and Martindale et al. (2003).

In our study, OIS has been used to measure changes in oxygenated haemoglobin ( $HbO_2$ ) and deoxygenated hemoglobin ( $Hbr$ ), where the total haemoglobin is given by  $Hbt = HbO_2 + Hbr$ . Under the assumption that hematocrit (the percentage by volume of red blood cells in blood) remains constant and normalised changes to baseline are used, the changes in CBV are proportional to the changes in Hbt (Mayhew et al. 2001), i.e.,  $\frac{V}{V_0} = \frac{Hbt}{Hbt_0}$ . The spectroscopy data collection and analysis procedure were described in detail in Mayhew et al. (2000).

All the data were captured at 7.5Hz, and are presented in normalised changes from the baseline value, i.e.,  $v = \frac{V}{V_0}$  and  $f = \frac{F}{F_0}$  represent normalised CBV and CBF respectively.

The experimental procedure for concurrent measurement of volume and flow changes is described in greater detail in (Jones et al 2001). The first stage is to locate a whisker barrel using single wavelength illumination, then the slit spectrograph mounted on the camera is appropriately sited over the center of the barrel region. After placement of the spectrograph, an LDF probe is placed over the barrel region to measure flow changes.

The stimulation of somatosensory cortex using electrical stimulation of the whisker pad was given for two sets of stimulus. The first set consisted of three levels of electrical stimulation with intensities 0.8, 1.2 and 1.6 mA under a pulse of 5Hz. Each trial lasted 50s with the stimulus onset at 10s with a 20s duration. The set of second stimulus consisted of five levels of pulse frequency of 1, 2, 3, 4, 5Hz with pulse intensity of 1.2mA. Each trial lasted 23s with stimulus onset at 8s with a 2s duration. LDF time series were then collected concurrently with spectrographic data. The flow data were averaged over 30 trials. Figure 1a and Figure 1b show the normalised blood flow time series.

The same stimulus and data collection procedures were used for the OIS response data. Figure 2a and Figure 2b show the normalised blood volume time series. Clearly the stimulation intensity and pulse frequency within the ranges shown here do not change the shape of the dynamics of CBF and CBV.

## ***2.2 Balloon Model and Windkessel Model***

Figure 3 shows the comparison of the time series of CBF and CBV. All the data were normalised to within the range of 0 to 1 with respect to the baseline and peak values. The initial stages of the time series are very similar in shape, onset time and time to peak. After the onset of the stimulus, the flow increase has roughly the same time constant as that of volume. However flow returns to the baseline much faster than



volume. The time constants for flow and volume during the stimulus onset period and the return to baseline period are different. This temporal mismatch between flow and volume changes has been previously reported by Buxton et al. (1998) and used to explain the BOLD post-stimulus undershoot, a common phenomenon in fMRI activation studies. Therefore it is pivotal to construct a proper dynamic relationship between flow and volume to describe the temporal mismatch.

The relationship between normalised changes of blood flow (CBF) and volume (CBV), first established by Grubb et al. (1974) is

$$v = f^{\Phi} \quad (1)$$

where  $\Phi = 0.38$ .

This relationship was based on steady state measurements. It was found that the values of  $\Phi$  can vary between 0.18 and 0.35 during brief stimulation (Jones et al. 2001, Jones et al. 2002, Mandeville et al. 1998, 1999). This suggests that Grubb's relationship cannot completely capture the complexity of the dynamic flow-volume relationship.

A biomechanical model called the 'Balloon model' (Buxton et al. 1998) relates the changes in volume ( $v$ ) in a compliant compartment to the difference between inflow  $f_{in}$  and outflow  $f_{out}$  of that compartment with a time constant  $\tau$  (average venous transit time):

$$\tau \dot{v} = f_{in} - f_{out}(v) \quad (2)$$

where  $f_{out}(v)$  is related to  $v$  by the Grubb's relationship. This model is a nonlinear first order system. Implementation shows that it cannot model the slow return to baseline behaviour of the blood volume. In fact Buxton et al. (1998) modelled  $f_{out}(v)$  as the sum of a linear component and a power law, although the explicit functional form of  $f_{out}(v)$  was not given.

Mandeville et al. (1999) formulated the dynamic response using resistance and capacitance (windkessel theory) and the model can be written in terms of the normalised changes as,

$$\tau \dot{v} = f_{in} - f_{out}(v) = f_{in} - \frac{v^{\alpha+\beta}}{A(t)} = f_{in} - \frac{v^\gamma}{A(t)} \quad (3)$$

where  $\gamma = \alpha + \beta$  (c.f. Eqn. 3 in Friston et al. 2000). The variable  $A(t)$  was given as slow exponential curve to model the delayed compliance. At steady state  $f = v^\gamma$ , this agrees with the empirical results from Grubb's law. During the dynamic phases of stimulus onset and offset, Mandeville et al. (1999) found it was necessary to use two very different time constants to model the fast dynamics during the onset period and the slow dynamics during the return to baseline period.

It is well known that the walls of large arteries and veins expand and contract with changes in transmural pressure. This is known as vessel compliance. Moreover, due to the viscous properties of the blood vessels, the initial increase or decrease in pressure is much larger than the delayed stretch or relaxation of the vessel walls allowing the pressure to reach its steady state. This is known as the delayed compliance. Ideally, a

model including this delayed compliance would describe the temporal mismatch between blood flow and volume. In the following section, we will try to relate blood volume to flow, taking into account explicitly the delayed compliance phenomena.

### ***2.3 Modified Windkessel Model with Compliance (MWMC)***

The compliance (C) relates the pressure change ( $\Delta P$ ) to the change in volume ( $\Delta V$ ) as:

$$C = \frac{\Delta V}{\Delta P}, \quad \text{or} \quad \Delta P = \frac{\Delta V}{C} \quad (4)$$

However, introducing the pressure change explicitly into the equation for compliance would introduce more parameters and complexity. Instead we model the compliance by introducing a normalised state variable  $c$  as:

$$\tau_c \dot{c} = v^\beta - c \quad (5a)$$

where at baseline condition,  $c(0) = 1$ . Furthermore Eqn. 4 suggests that the flow and volume relationship could be modified to include the compliance variable in the denominator as

$$f_{out} = \frac{v^{\alpha+\beta}}{c} \quad (5b)$$

Thus Eqn. 2 becomes

$$\tau_0 \dot{v} = f_{in} - f_{out} = f_{in} - \frac{v^{\alpha+\beta}}{c} \quad (5c)$$

The model defined by Eqns. 5(a), (b) and (c) is now a second order nonlinear system.

The additional state variable  $c$  takes care of the delayed compliance in CBV (possibly

due to stress relaxation during stimulus cessation). There is no longer the need for two time constants to model the different dynamics during the different phases of the blood volume changes.

Immediately after the onset of the stimulus, if  $\tau_c \gg \tau_0$ ,  $c$  will increase very slowly from its initial condition of unity, thus having little effect on the system. Hence the behavior of the system is very similar to that of the Windkessel model,  $f_{out}$  and  $v$  are mainly related by the power law. At steady state, if the stimulus duration is longer than the time constant  $\tau_c$ ,  $c$  reaches its steady state value  $v^\beta$ , and  $f_{out}$  will have a steady state value  $\frac{v^{\alpha+\beta}}{v^\beta} = v^\alpha$ , which is the equivalent to the Grubb's relationship. When the stimulation is withdrawn, it will take considerable time for  $c$  to return to its baseline ( $\tau_c \gg \tau_0$ ). As  $f_{out} = \frac{v^{\alpha+\beta}}{c}$  is governed by the first order system (5c) with faster time constant  $\tau_0$ ,  $f_{out}$  has to follow  $f_{in}$  accordingly. Now we have the situation that  $f_{out}$  is close to its baseline value of unity, but  $c$  is still considerably away from its baseline value. Hence the system forces  $v$  to return to its baseline at a speed closer to that of  $c$ , much slower than that of  $f_{in}$ .

The results in the next section will demonstrate the effectiveness of the model in capturing the mismatch between CBF and CBV during stimulus cessation.

### 3. Results

The experiments described in section 2 comprised two sets of data. Each set was modeled using Mandeville's version of the Windkessel model (Eqn. 3) and our modified model with added compliance (Eqn. 5). The measured normalised flow ( $f$ ) was used as input to the system, and the predicted normalised volume ( $v$ ) as output was compared to the measured volume. The parameters of the two models were estimated using a nonlinear least squares algorithm (Levenberg-Marquardt algorithm, using the MATLAB function '*lsqnonlin*').

#### *Comparison of the two models*

Results from the simulations are shown in Figures 4-5. In each figure the solid line represents the original data, the dashed line represents the prediction of the Windkessel model, and the dotted line represents the prediction of the modified Windkessel model with compliance (MWMC).

It can be seen from Figures 4-5 that although the Windkessel model fits the early stages of the experimental data reasonably well, the predicted time series returns to baseline much faster than the data over the latter stages of the response. In contrast, the MWMC gives excellent predictions over the whole duration of the time series and over all data sets and particularly over the return to baseline stage.

Tables 1 and 2 show the optimised values for the parameter  $\gamma$  used in the Windkessel model for both the intensity (long duration) and frequency (short duration) data using a value of  $\tau_0 = 0.3$  throughout (Zheng et al. 2002). For both stimulation data sets there is little difference in the range of values of  $\gamma$  which lies between 3.6 and 4.6. This is larger than the values of 2.63 ( $=1/0.38$ ) expected from Grubb's relationship.

Tables 3 and 4 show the optimised values for the parameters  $\alpha$ ,  $\beta$  and  $\tau_c$ . The parameter  $\alpha$  *at steady state* would be expected to correspond to the value of the parameter  $\gamma$  in the Windkessel model. For the intensity data with long stimulus duration, the values of  $\alpha$  are very similar to the values of  $\gamma$  found for the Mandeville model, as can be seen in Table 3. For the frequency data with short stimulus duration, the data did not have sufficient time to reach a steady state. Instead the dynamics of the system are largely determined by the sum of the parameters  $\alpha + \beta$  if the time constant  $\tau_c$  is much larger than the time constant  $\tau_0 = 0.3s$ . From Table 4, we see that  $\tau_c$  is indeed much larger than 0.3s, and the sum  $(\alpha + \beta)$  ranges between 4.2 and 5, which is similar to the range of the parameter values for  $\gamma$ .

#### **4. Discussion**

In this study, the dynamic relationship between changes in CBF and CBV has been explored. Both the Balloon and original Windkessel models cannot adequately describe the transient relationship of CBV and CBF.

A modified Windkessel model with compliance (MWMC) was presented. This improved model gives good predictions both in the transient regime and at steady state. The main characteristic of this model is the introduction of an additional state variable  $c$  which models the delayed compliance in the system. The model was applied to the LDF and OIS data assuming that the blood volume changes occur primarily in the venous compartment. However the model is not restricted by this assumption. If there are data available supporting the partitioning of the variables to specific compartments of the microvascular structure, the model can then be applied to the individual compartments.

Figure 6 shows the normalised CBF, CBV, the predicted volume and the compliance variable  $c$  (5Hz data as an example). It can be seen that the dynamics of  $c$  is much slower.  $\alpha$ ,  $\beta$  and  $\tau_c$  are three independent parameters each having a different role in determining the system dynamics which will be discussed below.

*Time constant  $\tau_c$*

The time constant  $\tau_c$  determines the rate of change of the compliance variable  $c$ . After the onset of the stimulus, because  $\tau_c \gg \tau_0$ ,  $c$  increases more slowly than does the flow, and when stimulation stops, it will take longer for  $c$  to return to its baseline value. As

$f_{out} = \frac{v^{\alpha+\beta}}{c}$ , the normalised blood flow can return to unity (baseline) only if the term

$v^{\alpha+\beta}$  is very similar to the term  $c$ . This effectively forces blood volume to return to baseline at a similar rate to that of  $c$ , and much slower than blood flow.

It can be seen (Figure 3a) that under conditions of long stimulus duration the time to return to baseline is much greater than for the brief stimulation data (Figure 3b) and from Tables 3-4, it can be seen that the values of  $\tau_c$  for long stimulation data sets are greater than for the brief stimulation condition. This implies that the value of the parameter  $\tau_c$  is physiologically coupled to the duration of the stimulation although the mechanism is not understood.

#### *Values of the parameters $\alpha$ and $\beta$*

In the Windkessel model and MWMC, the values of the exponent of  $v$  are  $\gamma$  and  $(\alpha + \beta)$  respectively. For long stimulation data set, the blood flow and volume have sufficient time to reach their new steady states, and they are related in MWMC by  $f_{out} = v^\alpha$ . Hence the values of  $\alpha$  are similar to those for  $\gamma$ , as can be seen in Tables 1 and 3. For brief stimulation, blood flow and volume do not have sufficient time to reach a steady state. Instead the values of  $(\alpha + \beta)$  are similar to those for  $\gamma$  because during



the dynamic phase of stimulus onset, the compliance variable  $c$  has little impact on the system (as  $\tau_c \gg \tau_0$ ), therefore the system is mainly governed by  $\tau_0 \dot{v} \approx f_{in} - v^{\alpha+\beta}$ , which is similar to the original Windkessel model with  $\gamma$  in place of  $\alpha + \beta$ . The parameter  $\beta$  also determines the steady state value of the compliance variable  $c$ .

In summary, it was found that the relationship between changes in CBF and CBV under different stimulation conditions can be described by a model incorporating delayed compliance with a time constant dependent on stimulus duration.

In all the models evaluated it was assumed that the blood volume changes occur predominantly in the venous compartment, and the arteriolar dilation contributed little to the volume changes. This assumption is not fundamental to the MWMC model and future work may need to extend it to different compartments of the microvasculature.

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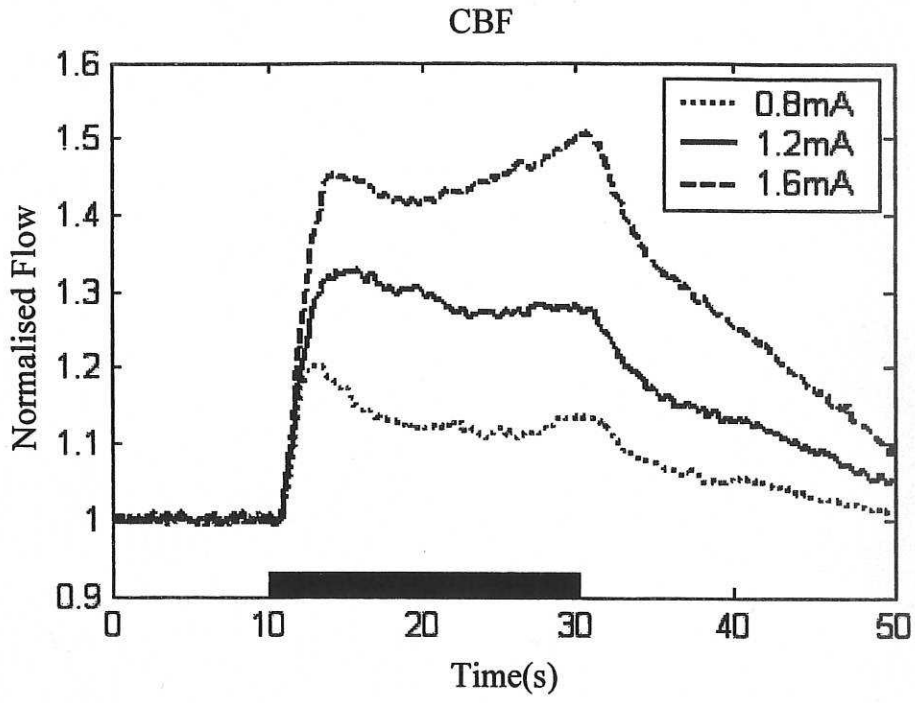
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Figure 1 ---Y Kong et al

(a)



(b)

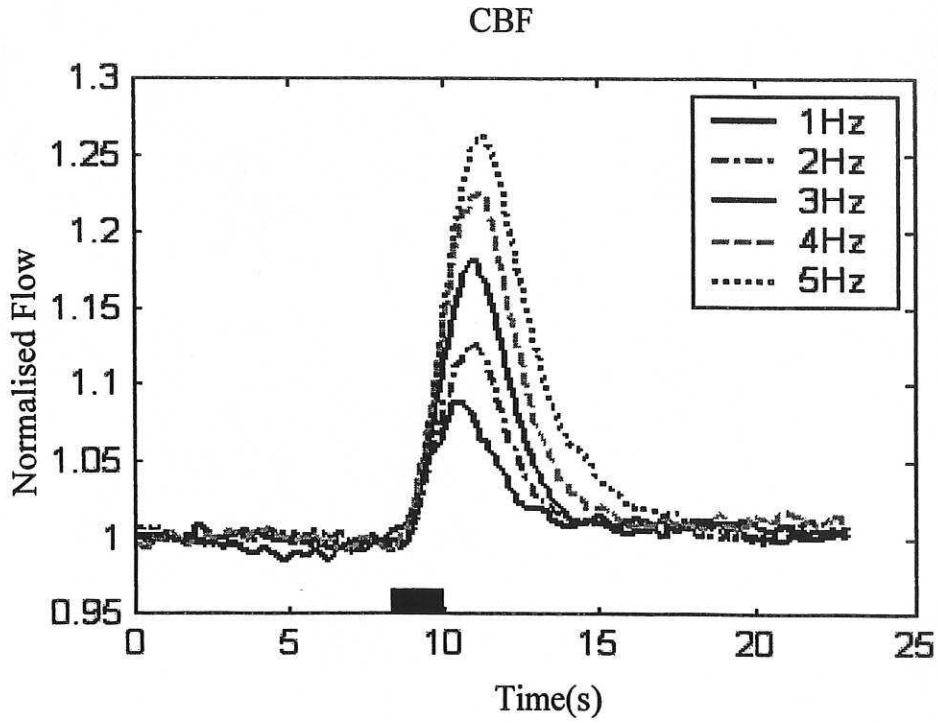
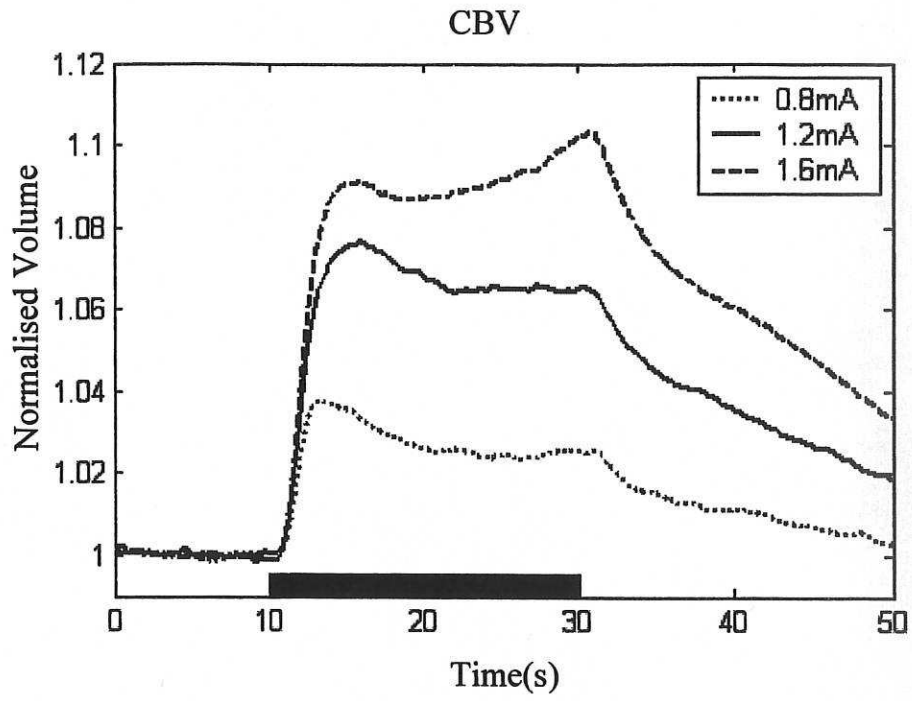


Figure 2 ---Y Kong et al

(a)



(b)

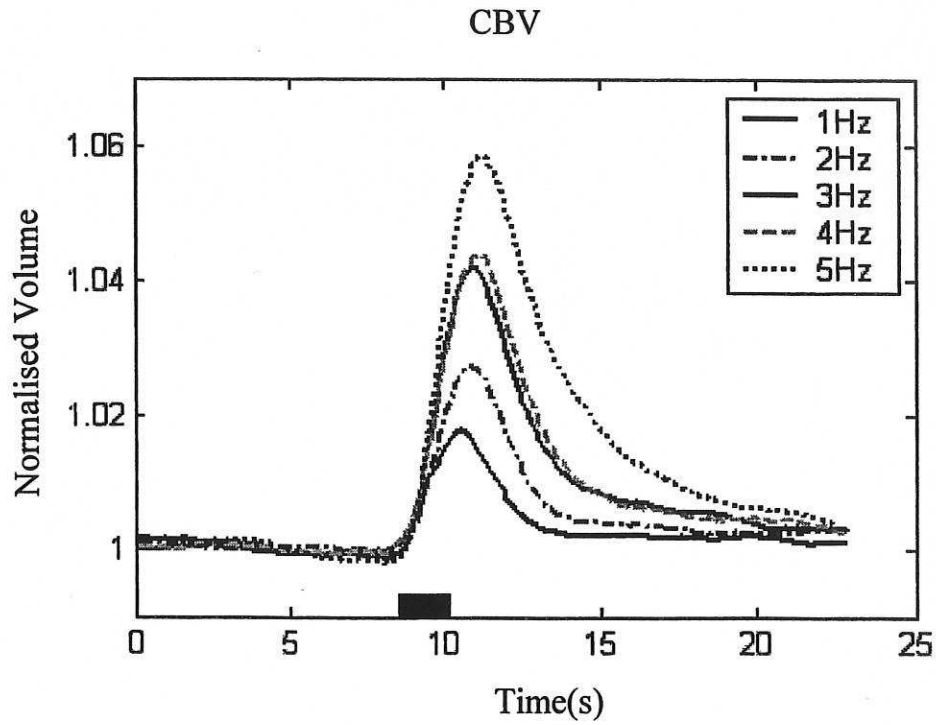
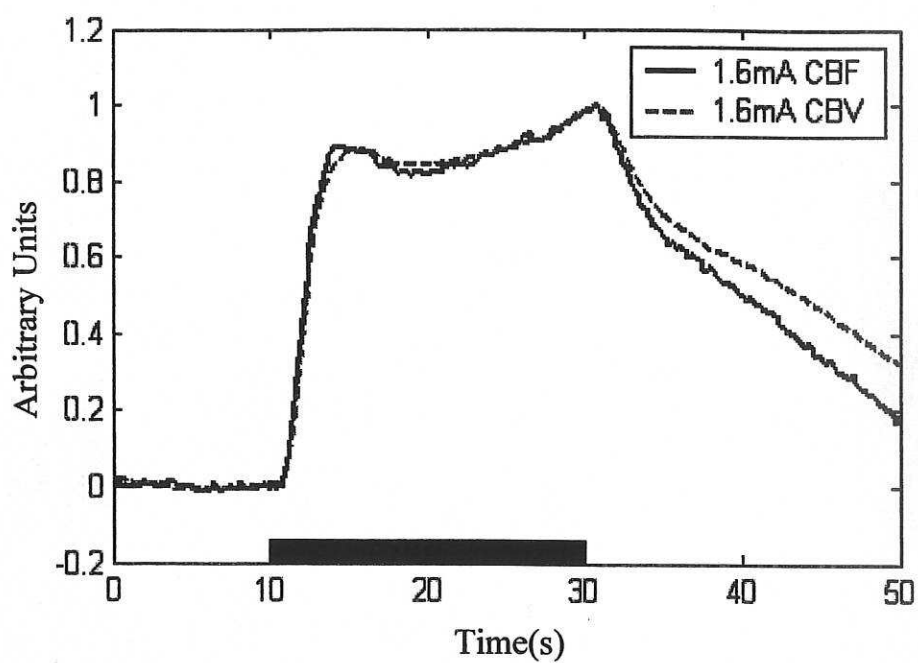


Figure 3 ---Y Kong et al

(a)



(b)

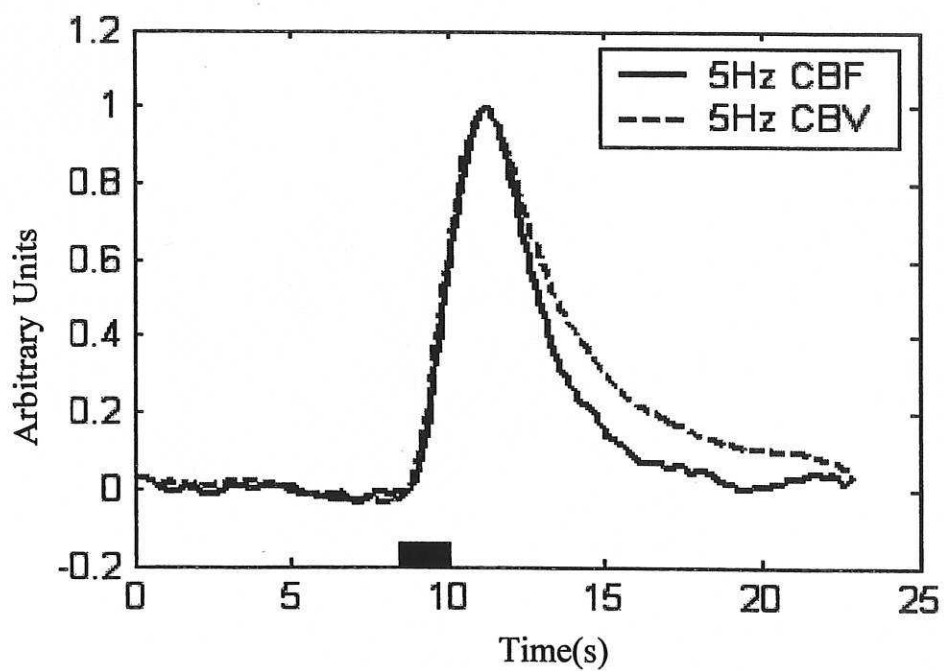


Figure 4 ---Y Kong et al

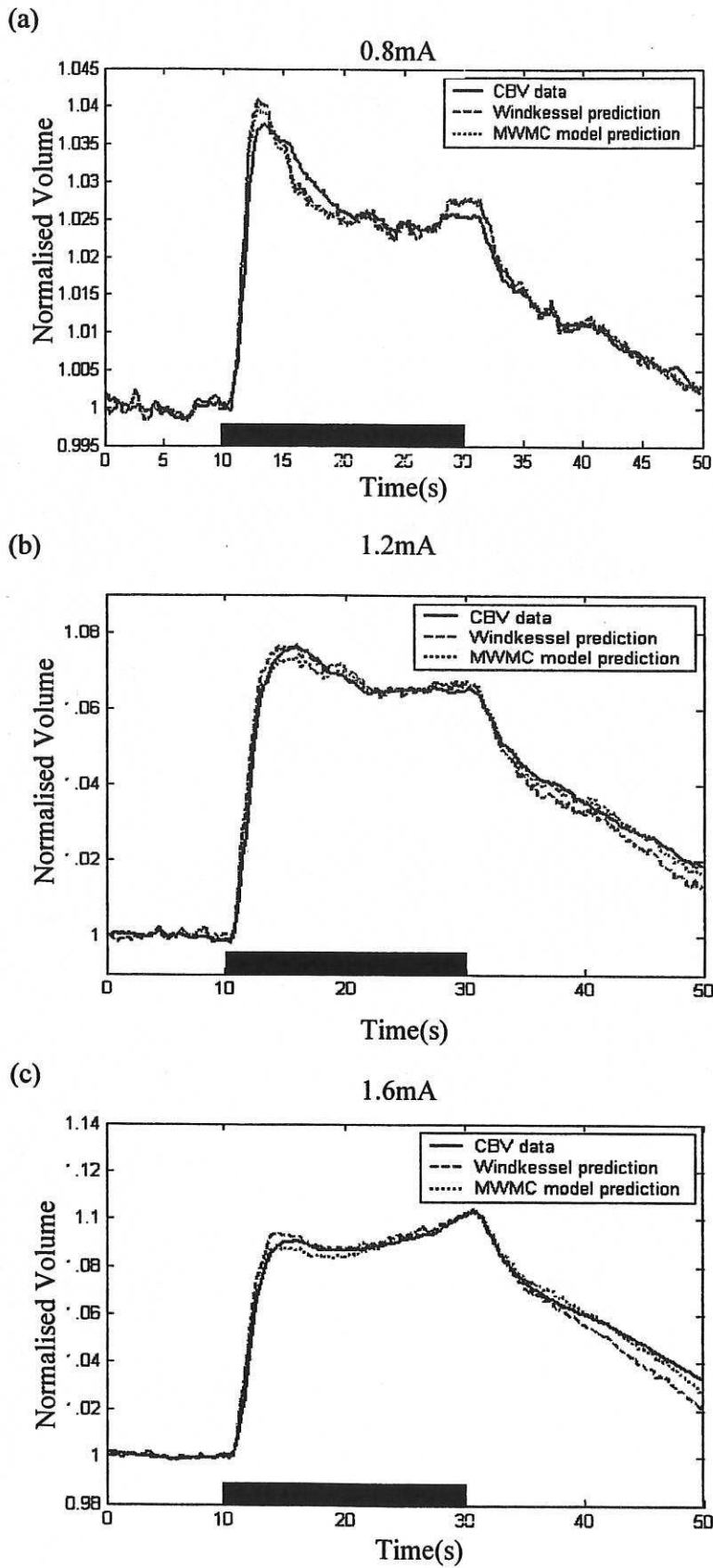




Figure 5 ---Y Kong et al

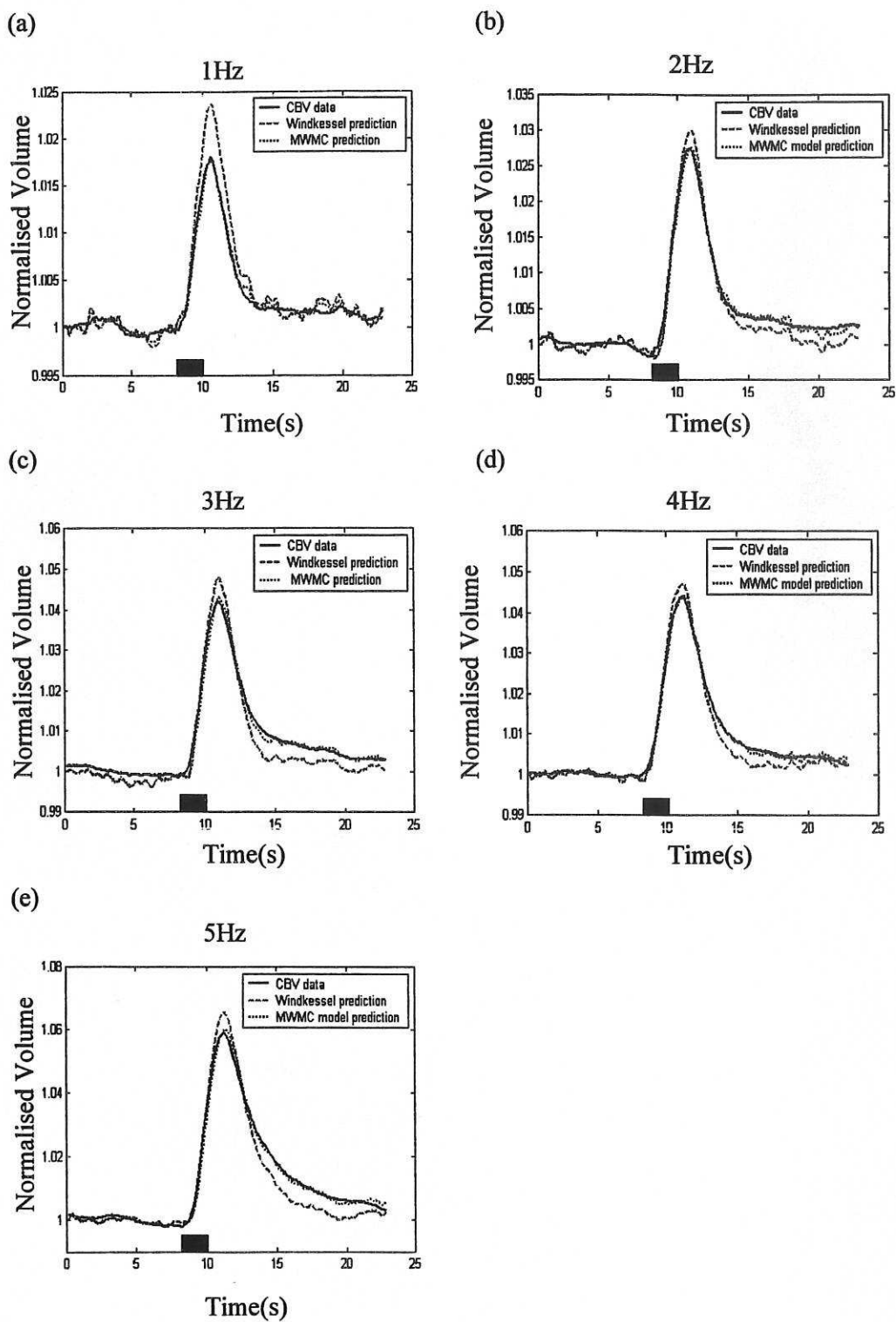
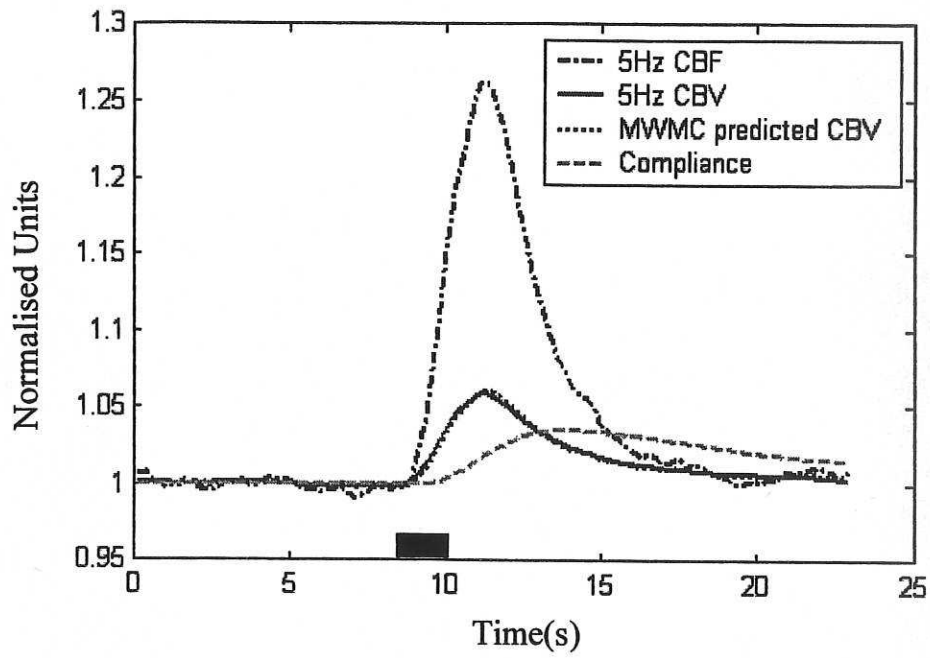


Figure 6 ---Y Kong et al



intensity parameter	0.8mA	1.2mA	1.6mA
$\gamma$	4.6	3.8	4.2

Table 1. Estimated values of  $\gamma$  for different intensity data set, stimulus duration is 20s.

Frequency parameter	1Hz	2Hz	3Hz	4Hz	5Hz
$\gamma$	3.6	4.0	3.6	4.4	3.7

Table 2. Estimated values of  $\gamma$  for different frequency data set, stimulus duration is 2s.

Intensity parameter	0.8mA	1.2mA	1.6mA
$\alpha$	4.6	3.5	3.7
$\beta$	0.2	0.6	0.8
$\tau_c$ (s)	22.6	29.6	29.9
$\alpha + \beta$	4.8	4.1	4.5

Table 3. Estimated values of  $\alpha$ ,  $\beta$  and  $\tau_c$  for different intensity data set, stimulus duration is 20s. The values of  $\alpha + \beta$  are also shown.

Frequency parameter	1Hz	2Hz	3Hz	4Hz	5Hz
$\alpha$	4.2	2.5	2.7	3.8	2.9
$\beta$	0.7	2.0	1.5	1.2	1.4
$\tau_c$ (s)	26.7	14.5	5.1	4.0	5.0
$\alpha + \beta$	4.9	4.5	4.2	5.0	4.3

Table 4. Estimated values of  $\alpha$ ,  $\beta$  and  $\tau_c$  for different frequency data set, stimulus duration is 2s. The values of  $\alpha + \beta$  are also shown.

