A Nonlinear BOLD Model Based on the Bipolar Gamma Variate Function Incorporated with Refractory Effect and Neural Adaptation

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A short title: Nonlinear BOLD Model

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ABSTRACT

A mathematical model to regress the nonlinear BOLD fMRI signal is developed by incorporating the refractory effect and neural adaptation into the linear BOLD model of the bipolar Gamma variate function. The refractory effect was accounted for as a relaxation of the BOLD capacities corresponding to the bipolar components of the BOLD signal. The neural adaptation was modeled by allowing the stimulus intensity to vary in time. When tested with the published fMRI data of finger tapping, the proposed model improved regression relative to the linear BOLD model. Specifically, the nonlinear BOLD model reliably reproduced nonlinear BOLD effects such as the reduced post-stimulus undershoot and the saddle pattern of the prolonged stimulation, in addition to the reduced BOLD signal for the repetitive stimulation.

Key words

Gamma variate function
Nonlinear BOLD model
Refractory effect
Neural adaptation
INTRODUCTION

A mathematical model of the temporal characteristics of the blood-oxygen-level-dependent (BOLD) fMRI signal (1) has been developed (2) to study neurophysiology (3, 4) and to analyze brain activation through the correlation (5) and deconvolution (6) of the BOLD time course. The Gamma variate function (GVF) has been used as the basis function of the BOLD model for both linear (5-8) and nonlinear (9-11) analysis of the BOLD signal. Specifically, the bipolar GVF can model the biphasic temporal characteristics of the BOLD signal with the observed post-stimulus undershoot (9, 12, 13). However, the bipolar GVF needs to be revised to account for the nonlinear characteristics of the BOLD signal. The most prominent nonlinear characteristic is the reduced BOLD signal for successive stimuli in a series of stimuli (5, 14-16). In addition, there have been observations of additional nonlinear characteristics such as the reduced post-stimulus undershoot (12) and a saddle pattern formed by the initial and post-stimulus overshoot (11, 17) for a prolonged stimulus.

The nonlinearity of the BOLD signal has been attributed to the refractory effect (18, 19) and neural adaptation (5, 10, 15, 20). These two potential sources of nonlinearity can be incorporated into the bipolar GVF for an improved regression of the nonlinear BOLD signal (21).

THEORY

A BOLD vector model will be introduced to incorporate the refractory effect and the neural adaptation into the linear BOLD model. Then, the BOLD vector will be separately defined for positive and negative BOLD components. The overall block diagram for the nonlinear BOLD model is shown in Fig. 1.
The BOLD vector and relaxation

When a pair of stimuli are applied with an inter-stimulus interval shorter than the refractory period, the amplitude of the BOLD signal from the second stimulus is smaller than that from the first stimulus (18,19). Furthermore, the BOLD signal from the second stimulus is progressively reduced as the inter-stimulus interval shortens. In the Nuclear Magnetic Resonance (NMR) field, such a saturation effect has been observed on the NMR spin and has been formulated as the longitudinal or $T_1$ relaxation (22). Analogous to the NMR formulation, a BOLD relaxation can be introduced to represent the recovery of the BOLD capacity from a saturated or stimulated state to an equilibrium or resting state.

Therefore, the nonlinearity of the BOLD signal due to the refractory effect can be modeled by incorporating the magnetization vector and the $T_1$ relaxation concept of NMR into the BOLD model by defining a BOLD vector, a BOLD capacity, and BOLD relaxation. When a resting state of the BOLD capacity, $M_0$, is excited by an impulse stimulus with an intensity $\theta$ at $t = 0$, i.e., $x(0)=\theta$ in Fig. 1, the BOLD capacity after the stimulus, $M_z(0^+)$, can be described as the longitudinal component along the $z$ axis of a BOLD vector analogous to the magnetization vector in NMR as shown in Fig. 2:

$$M_z(0^+) = M_0 \cos \theta, \quad 0 \leq \theta \leq 90^\circ,$$

where the superscript $+$ on the time variable denotes the time point immediately after the impulse stimulus is applied at $t = 0$ (23). By adopting the NMR formulation again, the BOLD activity can be represented by the $x$ component of the BOLD vector which is rotated from the $z$ axis onto the $x$ axis in the $xz$ plane:
\[ M_z(0^+) = M_0 \sin \theta. \] (2)

The BOLD capacity \( M_z(t) \) then recovers exponentially from \( M_z(0^+) \) to a resting state \( M_0 \) as illustrated in Fig. 3 (23):

\[ M_z(t) = M_z(0^+) \exp \left( -\frac{t}{T_1} \right) + M_0 \left[ 1 - \exp \left( -\frac{t}{T_1} \right) \right], \quad t \geq 0, \] (3)

where \( T_1 \) is the BOLD relaxation time accounting for the refractory effect.

**Refractory effect in a repetitive stimulation**

If a series of \( N_t \) impulse stimuli are applied repetitively with a constant stimulus intensity \( \theta \) at an interval \( T_S \), i.e.,

\[ x(t) = \sum_{k=0}^{N_t-1} \theta \delta(t - kT_S), \] (4)

for a delta function \( \delta(t) \), then the BOLD capacity \( M_z(kT_S) \) before and after each stimulus applied at \( t = kT_S \) can be denoted as \( M_z(kT_S^-) \) and \( M_z(kT_S^+) \), respectively. From the generalization of Eq. (3) for the steady state of \( M_z(t) \), the BOLD capacity before the \( k \)th stimulus is obtained as (23)

\[ M_z(kT_S^-) = M_z((k-1)T_S^-) \cos \theta E_i + M_0 (1 - E_i), \] (5)

where

\[ E_i = \exp \left( -\frac{T_S}{T_1} \right). \] (6)

The time course of \( M_z(t) \) for a series of impulse stimuli with constant intensity \( \theta \) is shown in Fig. 7 for two different \( T_1 \) times representing the positive and negative BOLD components.
BOLD capacity with the longer $T_i$ saturates more rapidly to a lower amplitude than that with the shorter $T_i$. The BOLD activity is obtained from Eqs. (2) and (5) as

$$M_z(kT_S^{-}) = M_z(kT_S^{-}) \sin \theta. \quad (7)$$

**Neural adaptation modeled by a decaying stimulus intensity**

It is well established that the neural response to stimulation can decrease during repetitive stimuli such as finger tapping or a visual checker board due to neural adaptation (10,11). The neural adaptation was recognized previously by recording the local field potentials in parallel with fMRI (20,24).

Neural adaptation can be modeled by allowing the stimulation intensity to vary with time during the repetitive stimuli. A simple and reasonable function to represent the time varying stimulus is an exponentially decaying curve from its initial intensity $\theta_0$ to a final intensity $\theta_f$ with a time constant $T_\theta$ as (15)

$$\theta(t) = \theta_f + \left(\theta_0 - \theta_f\right) \exp\left(\frac{-t}{T_\theta}\right), \quad 0 \leq \theta_f \leq \theta_0 \leq 90^\circ. \quad (8)$$

The time-varying stimulus intensity in Eq. (8) can be incorporated into Eqs. (5) and (7) as

$$M_z(kT_S^{-}) = M_z((k-1)T_S^{-}) \cos \theta((k-1)T_S^{-}) E_1 + M_0(1-E_1) \quad (9)$$

and

$$M_z(kT_S^{-}) = M_z(kT_S^{-}) \sin \theta(kT_S^{-}), \quad (10)$$

respectively.
**Bipolar GVF**

The BOLD signal is often biphasic with a post-stimulus undershoot following the positive activation (25). As confirmed by optical imaging (18,26,27) and fMRI (25,28-31), the BOLD signal can be decomposed into positive and negative components. From these studies, it has been noted that the positive and negative components may be attributed to an increase of the cerebral blood flow and to an increase of the cerebral blood volume, respectively (25,28,32).

To model the biphasic BOLD signal with a post-stimulus undershoot, the BOLD impulse response function, \( h(t) \), needs to be modeled as a superposition of two BOLD impulse response functions with opposite polarity. One of the more common BOLD model functions is the normalized GVF, which can be expressed as (33)

\[
g(t) = \frac{1}{g_{\text{max}}} t^a \exp\left(-\frac{t}{b}\right), \quad t \geq 0, \quad a > 0, \quad b > 0,
\]

where \( g_{\text{max}} \) is the maximum of \( g(t) \) at \( t = ab \) (34). The superposition of the two GVFs with opposite polarity may be expressed as one function referred to as a bipolar GVF (Fig. 5):

\[
h(t) = g_p(t) - \lambda g_n(t), \quad \lambda \geq 0
\]

or

\[
h(t) = h_p(t) + h_n(t).
\]

Subscripts \( p \) and \( n \) denote the positive and negative components, respectively, and \( \lambda \) denotes the relative contribution of the negative component. The parameters of Eq. (13) can be estimated from a BOLD signal resulting from an impulse stimulus such as the 1-second stimulus.
A Nonlinear BOLD signal of the proposed model

Each component of the bipolar GVF can be assumed to recover from a stimulated state to a resting state with an independent BOLD relaxation time. In other words, there will be two BOLD vectors representing the positive and negative BOLD signals with respective BOLD relaxation times $T_{1p}$ and $T_{1n}$. Corresponding to the two BOLD vectors, the bipolar BOLD capacities and activities can be written as $M_{zi}$ and $M_{xi}$ respectively where the subscript $i$ can be $p$ or $n$ for the positive or negative component. In the same context, the resting BOLD vector can be represented for each bipolar component as $M_{0i}$.

Equation (9) can be reformulated for these two components as

$$M_{zi}(kT_S^-) = M_{zi}((k-1)T_S^-)\cos\theta((k-1)T_S^-)E_{ui} + M_{0i}(1-E_{ui}),$$

where

$$E_{ui} = \exp\left(-\frac{T_S}{T_{ui}}\right).$$

From Eq. (10), the BOLD activity $M_{zi}(kT_S^+)$ can be expressed as

$$M_{zi}(kT_S^+) = M_{zi}(kT_S^-)\sin\theta(kT_S).$$

$M_{zi}(kT_S^+)$ will determine the amplitude of the each component of the bipolar BOLD signals. Therefore, the BOLD signal $y(t-kT_S)$ can be obtained by being convolved with the corresponding BOLD impulse response functions in Eq. (13) as

$$y(t-kT_S) = M_{zi}(kT_S^+)h_i(t-kT_S) + M_{zi}(kT_S^+)h_i(t-kT_S).$$

The BOLD signal $y(t)$ from a stimulus block can be described by a convolution operator $*$ as
\[ y(t) = M_{sp}(t) * h_p(t) + M_{na}(t) * h_n(t). \]  

(18)

The parameters for the BOLD impulse response function of Eq. (13) can be estimated from a BOLD signal acquired from an impulse stimulus. The BOLD relaxation times and the neural adaptation parameters can then be estimated from the BOLD signal acquired during a prolonged stimulus or a pair of stimuli with variable inter-stimulus intervals.

**METHODS**

The experimental data set was borrowed from published data which consisted of finger tapping at 3 Hz for durations of 1, 2, 4, 8, and 16 s with the permission from the author (Fig. 3E for 1 s and 3A for other durations in (12)). The time start point of the data set has been set to start from zero second instead of 1 second. The function, lsqcurvefit, in the Matlab optimization tool box (The MathWorks, Inc.) was used for the regression analysis.

The impulse response function of Eq. (13) was estimated from the BOLD signal with a stimulus duration of 1 second. The impulse response function was then used to regress the BOLD signal of the 16-second stimulus for the linear and different kinds of nonlinear BOLD models. Four kinds of nonlinear models were analyzed: only the refractory effect, only the neural adaptation, both the refractory and neural adaptation, and the neural adaptation with the refractory parameters determined from the refractory effect only. The estimated BOLD models were used to produce the BOLD responses of different stimulus durations and they were compared with the BOLD signals.
RESULTS and DISCUSSIONS

The fitting to the 1-second response shown in Fig. 4 resulted in parameters for the impulse response function as \( a_p = 2.5, b_p = 2.4, a_n = 7.6, b_n = 1.2, \) and \( \lambda_n = 0.82. \) The bipolar GVFs and the BOLD impulse response are shown in Fig. 5. The positive component increases faster than the negative component, which results in the initial positive signal followed by the post-stimulus undershoot on the combined signal.

The linear model responses were constructed and shown in Fig. 6. Compared to the BOLD signals, there are discrepancies in the amplitudes, the time delay to the peak, the post-stimulus undershoot, and the saddle pattern for 16-second stimulus.

From the regression of the refractory model to the 16-second BOLD signal, the BOLD relaxation parameters were estimated as \( T_{1p} = 2.6 \) s, \( T_{1n} = 4.0 \) s, and \( \theta = 81.9^\circ. \) By use of the relaxation parameters, the BOLD capacities of bipolar components for the 16-second stimulus are shown in Fig. 7. The positive BOLD capacity reduces to 0.43 by the 1st stimulus and then saturates at 0.35 at the 4th stimulus. The negative BOLD capacity reduces to 0.35 by the 1st stimulus and saturates to 0.25 at the 3rd stimulus. The saturation of the BOLD capacities can contribute to the nonlinear increase of the BOLD response amplitudes at longer stimulus durations. In addition, the negative component saturates faster to the lower level than the positive one, which can contribute to the suppression of the post-stimulus undershoot at the longer stimulus. The BOLD responses of various stimulus durations are constructed and shown in Fig. 8. The saddle pattern at the 16-second stimulus is reproduced. The saddle pattern can also be found in BOLD signals reported in the literature: figures 10 and 11 in (5); figure 4 in (9); figure 8 in (35); figure 2 in (36); figure 1 in (11).
The modeling only with the neural adaptation failed to obtain the decay of the stimulus amplitude and hence could not improve the fitting than the linear model as shown in Fig. 9. This could be due to the limitation of the fitting procedure for too many parameters. Therefore, the regression was attempted by use of the relaxation parameters which were determined previously only by use of the refractory effect in Fig. 8.

Considering that the nonlinear properties of the BOLD signal can be constructed, the refractory effect can be the major contributor to the nonlinear BOLD signal.

The slower relaxation for the negative component compared to that of the positive one may suggest that the cerebral blood volume recovers more slower than the cerebral blood flow during the inter-stimulus duration (18,28). Therefore, the negative component saturates faster than the positive component when the inter-stimulus interval becomes shorter. Then, the summed BOLD signal in Eq. (13) can be enhanced because of the reduced canceling term of the negative component. This possibility may influence the design of fMRI protocols and the analysis of the BOLD signal, in particular for event-related fMRI. Furthermore, the proposed BOLD model may contribute to new insights in understanding the neurophysiology underlying the temporal characteristics of the BOLD fMRI signal.
CONCLUSIONS

The proposed BOLD model reliably reproduced nonlinear BOLD effects such as the reduced post-stimulus undershoot and the saddle pattern of the prolonged stimulation, in addition to the reduced BOLD signal for the repetitive stimulation. The newly introduced concepts such as the BOLD vector, the BOLD capacity, and the BOLD relaxation were effective in incorporating both the refractory effect and neural adaptation into the linear BOLD model. The separation of the BOLD signal into two bipolar components and their characteristic BOLD relaxation times were essential to the modeling of the nonlinear BOLD signal in particular with the post-stimulus undershoot. This result suggests that the refractory effect and neural adaptation may be major sources of the nonlinear BOLD signal.
ACKNOWLEDGMENTS

The author greatly appreciates the generosity and guidance of Dr. Gary Glover. The author discussed the idea with Dr. Glover by email and later at the 2004 Conference of the International Society of Magnetic Resonance in Medicine, where Dr. Glover advised that the author use the data published in his paper so the two models could be compared more directly.
REFERENCES

**FIGURE LEGENDS**

Fig. 1. A block diagram of a nonlinear BOLD model with the neural adaptation and the BOLD relaxation for the refractory effect. The BOLD impulse response functions for the positive and negative BOLD signals are represented as $h_p(t)$ and $h_n(t)$, respectively.

Fig. 2. A BOLD vector model to represent the BOLD capacity $M_z$ and activity $M_x$ when a stimulation $\theta$ is applied to the resting BOLD capacity $M_0$. 
Fig. 3. A time course of the BOLD capacity $M_z(t)$ when a pair of impulse stimuli are applied at an inter-stimulus interval $T_s$.

Fig. 4. A BOLD impulse response function overlaid with the BOLD signal.
Fig. 5. A BOLD impulse response function constructed as a superposition of two GVF\'s with opposite polarity. The parameters for Eq. (13) were $a_p = 2.5$, $b_p = 2.4$, $a_n = 7.6$, $b_n = 1.2$, and $\lambda_n = 0.82$.

Fig. 6. BOLD responses of the linear model. The amplitudes of signal and model were normalized in reference to the maximum values of the 16-second stimuli for each set.
Fig. 7. BOLD capacity of the refractory effect. A total of 16 stimuli with a constant stimulation intensity of $\theta = 81.9^\circ$ are applied repetitively at every $T_s = 1$ s as indicated by the down arrows at the top of the graph. $\tau_p = 2.6$ s (solid line) and $\tau_{re} = 4.0$ s (dashed line).
Fig. 8. BOLD responses of the nonlinear model with refractory. $\tau_p = 2.6\ s$, and $\tau_x = 4.0\ s$. The amplitudes of signal and model were normalized in reference to the maximum values of the 16-second stimuli for each set.

Fig. 9. BOLD model only with the neural adaptation. $\theta_0 = 8.02^\circ$, $\theta_f = 26.9^\circ$, and $\tau_\theta = 100\ s$. The amplitudes of signal and model were normalized in reference to the maximum values of the 16-second stimuli for each set.
Fig. 10. Nonlinear model by use of the refractory values of $\tau_{rp} = 2.6$ s, and $\tau_{rs} = 4.0$ s. $\theta_0 = 75^\circ$, $\theta_f = 14^\circ$, and $\tau_\theta = 2.0$ s. The amplitudes of signal and model were normalized in reference to the maximum values of the 16-second stimuli for each set.
Fig. 11. Nonlinear model with both refractory and neural adaptation. $T_p = 1.6 \, \text{s}$, and $T_s = 11 \, \text{s}$. $\theta_0 = 83^\circ$, $\theta_r = 14^\circ$, and $\theta_T = 1.7 \, \text{s}$. The amplitudes of signal and model were normalized in reference to the maximum values of the 16-second stimuli for each set.