JOINT ESTIMATION FOR NONLINEAR DYNAMIC SYSTEM FROM FMRI TIME SERIES

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ABSTRACT

There is an increasing interest in the interactions of factors more directly related to the neutral activity in hemodynamic response (HR) with respect to different experimental conditions. In this work, we present a state-space approach, based on the Balloon Model for blood oxygenation level dependent (BOLD) responses, which allows the estimation of the hidden state variables and parameters of the hemodynamic response at the same time. It offers an alternative strategy for understanding the interactions of indirectly observed factors and exploring the changes of biophysical model parameters in variant experimental conditions.

***Index Terms*—** hemodynamic response, joint estimation, Unscented Kalman filter

1. INTRODUCTION

A major issue in the interpretation of the fMRI BOLD signal is that the measurements are only indirectly related to the neural activity and interregional interactions from which they derive. Hence, it is important to derive a quantitative understanding of those factors more directly related to the neutral activity, such as changes in flow, oxygen extraction, blood volumes and their combined effects. Such information is required to clarify the relationship between neutral activation and experimental paradigm, and the significance of the observed transients in the BOLD signal.

The Balloon Model has been developed as a comprehensive biophysical model of hemodynamic modulation for describing the changes in physiological variables during brain activation [1]. It combines the coupling mechanism of manifold physiological variables, and has successfully simulated pronounced transients in BOLD signal, including initial dips, overshoots and a prolonged post-stimulus undershoot.

This model then has been extended to include the relationship of evoked neutral activity and blood flow [2], where the model parameters are estimated in activated voxels using a Volterra kernel expansion. An alternative approach to characterize the model dynamics is apply maximum likelihood [3] or state-space strategy. [4, 5]

In this paper, we investigate the sensitivity of Balloon model, i.e. how does the change of one parameter effect the system output. This simple approach can reasonably decrease the number of estimated variables, with no expenses to the estimation accuracy. Subsequently, we present a novel, unscented kalman filter (UKF) approach for joint parameter and state estimation of the nonlinear dynamics system.

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2. METHODOLOGY

2.1. Balloon Model

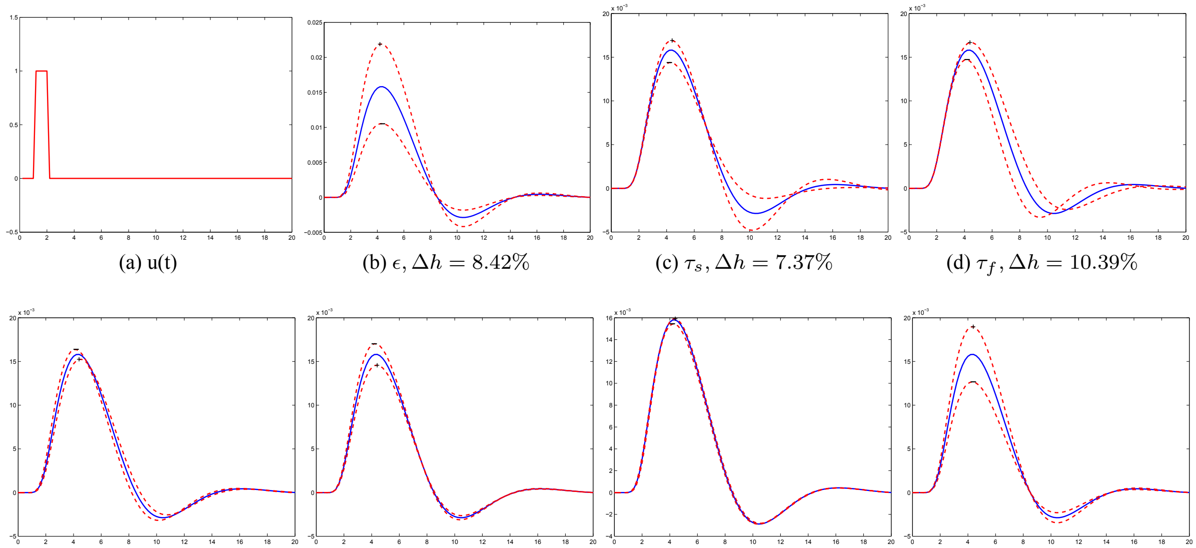
The Balloon model describes the dynamics intertwinement between the blood flow f, the blood venous volume v and the veins deoxyhemoglobin content q. It consists of three subsystem linkings: (1) neural activity to changes in flow; (2) changes in flow to changes in blood volume and venous outflow; (3) changes in flow, volume and oxygen extraction fraction to changes in deoxyhemoglobin. Quantitatively:

$$\begin{cases} \ddot{f} = \epsilon u(t) - \frac{\dot{f}}{\tau_s} - \frac{f-1}{\tau_f} \\ \dot{v} = \frac{1}{\tau_0}(f - v^{1/\alpha}) \\ \dot{q} = \frac{1}{\tau_0}(f\frac{1-(1-E_0)^{1/f}}{E_0} - v^{1/\alpha}\frac{q}{v}) \end{cases} \tag{1}$$

where ϵ is the neuronal efficacy; $u(t)$ is the neuronal inputs; τ_s reflects signal decay; τ_f is the feedback autoregulation time constant; τ_0 is the transit time; α is the stiffness parameter; and E_0 represent the resting oxygen extraction fraction. All variables are expressed in normalized form, relative to the resting values. Eq. 1 has a second-order time derivative, and we can transform it into the standard form by introducing a new variable $\dot{f} = s$, so that the time behavior of the system can be tracked by following the motion of a point in a four-dimensional $\mathbf{x}(t) = [\dot{f}, f, v, q]^T$ state space.

Furthermore, the BOLD signal can be expressed as:

$$\begin{cases} y(t) = V_0(k_1(1-q) + k_2(1-\frac{q}{v}) + k_3(1-v)), \\ k_1 = 7E_0, \quad k_2 = 2, \quad k_3 = 2E_0 - 0.2, \end{cases} \tag{2}$$



(a) u(t) (b) $\epsilon, \Delta h = 8.42\%$ (c) $\tau_s, \Delta h = 7.37\%$ (d) $\tau_f, \Delta h = 10.39\%$

(e) $\tau_0, \Delta h = 4.53\%$ (f) $\alpha, \Delta h = 3.91\%$ (g) $E_0, \Delta h = 1.33\%$ (h) $V_0, \Delta h = 10.10\%$

Fig. 1: The predicted response to 1s stimulation for typical parameter values ($\epsilon = 0.54; \tau_s = 1.54; \tau_f = 2.46; \tau_0 = 0.98; \alpha = 0.33; E_0 = 0.34; V_0 = 0.02.$). The estimated response for θ_0^{i+} and θ_0^{i-} show as red, while the response for the reference θ_0 show as blue. The corresponding output variations be also given in minipage caption. Δh represents mean response change.

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appropriate for a 1.5 Tesla magnet [1], where V_0 is the resting blood volume fraction.

Statistical models usually can be explained as the fixed effects, which capture the underline pattern, plus the random error term. Thus, we rewrite Eqns. (1) and (2) as:

$$\dot{\mathbf{x}} = f(\mathbf{x}, \boldsymbol{\theta}, \mathbf{u}, \mathbf{v}), \qquad v \sim N(0, \mathbf{Q}) \tag{3}$$

$$\mathbf{y} = h(\mathbf{x}, \boldsymbol{\theta}, \mathbf{w}) \qquad w \sim N(0, \mathbf{R}) \tag{4}$$

where f and h are nonlinear equations, $\mathbf{x}(t) = [\dot{f}, f, v, q]^T$ is the state of the system, $\boldsymbol{\theta} = \{\epsilon, \tau_s, \tau_f, \tau_0, \alpha, E_0, V_0\} \in \mathbb{R}^l$ is system parameters, the neuronal inputs $\mathbf{u}$ represents system input, $\mathbf{v}$ is the process noise, $\mathbf{y}$ is the observation vector, and $\mathbf{w}$ is measurement noise.

Equations (3) and (4) constitute a so-called state-space representation of the fMRI BOLD responses to a given stimulation, and the goal now is to estimate a set of hidden state variables $\mathbf{x}$ and parameter variables $\boldsymbol{\theta}$ based on the observations vector $\mathbf{y}$.

2.2. Sensitivity Analysis

The balloon model possesses strong nonlinear characteristics, in which the effects of model parameters on the output strongly interweave together. Since only a few measures per trial are recorded, it is difficulty to estimate complex models with many parameters. There are problems arising from such identification of complex nonlinear system, that is, if $\mathbb{R}^l \rightarrow \mathbb{R} : \mathbf{x} \mapsto \mathbf{h}(\mathbf{x})$ is an bijection, in other words, if it one-to-one maps one distinct domain $\mathbb{R}^l$ to other distinct set $\mathbb{R}$.

Friston et al. [2] reported typical values of the six parameters. Furthermore, we assume a plausible value of the resting blood volume fraction $V_0 = 0.02$. Thus we have a typical parameters set $\theta_0 = \{0.54, 1.54, 2.46, 0.98, 0.33, 0.34, 0.02\}$. Given an neuronal input $u(t)$, we aim to investigate how much the system output is sensitive to changes in one parameter.

For each of the seven parameters $\theta_0^i \in [0.8\theta_0^i, 1.2\theta_0^i]$, we vary it by increasing (+) or decreasing (-) 20%, compute the change of the system output, and plot the resulting time course. Denoted θ_0^{i+} the supremum limit set for parameter θ_0^i, and θ_0^{i-} the infimum limit set for parameter θ_0^i, we then have (*the triangle inequality*): $||h(\theta_0^{i+}) - h(\theta_0^i)|| \leq ||h(\theta_0^{i+})|| + ||h(\theta_0^i)||$, where $||.||$ denotes the L^2-norm of a vector. Thus, for the supremum limit set for parameter θ_0^i, the corresponding change of the system output can be defined as:

$$\triangle h^+ = \frac{||h(\theta_0^{i+}) - h(\theta_0^i)||}{||h(\theta_0^{i+})|| + ||h(\theta_0^i)||} \leq 1 \tag{5}$$

$\triangle h^-$ can be defined similarly for the infimum limit of parameter θ_0^i. We can now define the mean change of the system output $\Delta h := (\Delta h^+ + \Delta h^-)/2$, for changes of θ_0^i.

Figure 1 shows how do one parameter change the system output by comparing responses to given 1s stimulation for a set of typical parameter values. The estimated responses for θ_0^{i+} and θ_0^{i-} are shown in red, while the responses for the reference θ_0 are shown as blue. The corresponding output

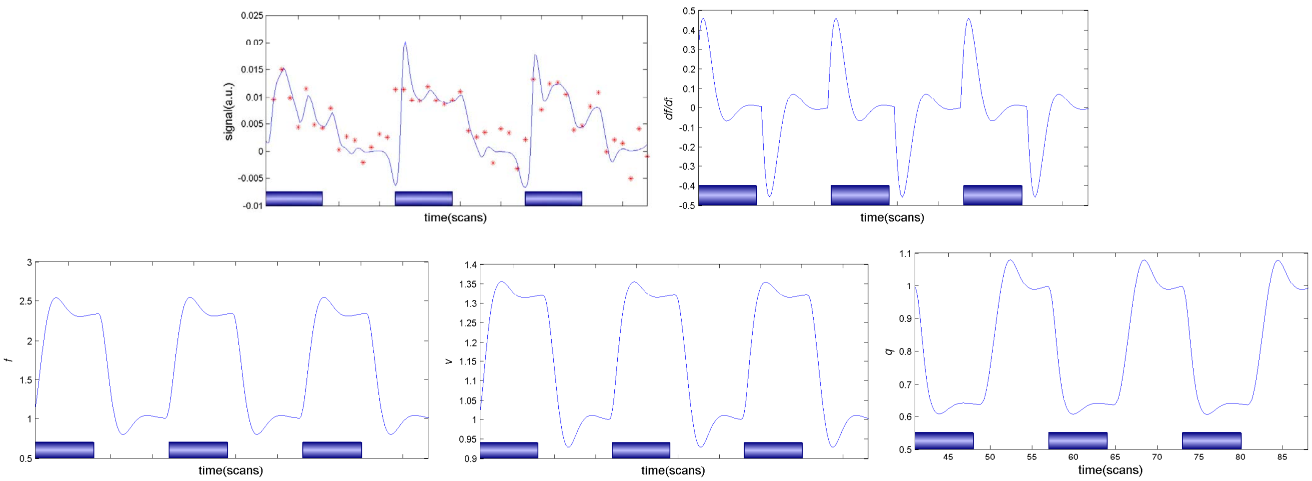

Fig. 2: Time series of the estimated hidden states of hemodynamic response to auditory stimulation of emotional words. From top to bottom: the fitted BOLD signal y, the first derivative of the blood flow $\dot{f}$, the blood flow f, the blood venous volume v and the veins deoxyhemoglobin content q. Stimulus duration is shown as bar in blue.

variations are also given in minipage caption.

Our goal is to reasonably decrease the number of variables needed to be estimated, in order to relieve the coupling between the different parameters, with no expenses to the estimation accuracy. As shown in Fig. 1, the system output has less dependence on the changes of parameters τ_0, α, and E_0. Thus, these parameters are assumed to be known, i.e. $\tau_0 = 0.98$, $\alpha = 0.33$, and $E_0 = 0.34$, in the following parameter estimation efforts.

2.3. UKF Estimations of States and Parameters

A standard solution to state-space models with Gaussian noise is through the Kalman filter and its variants. It propagates mean and covariance, of the state distribution to estimate the state of a linear system, where a linear operator can be applied to yield accurate estimate of the mean and covariance of the state. Unscented Kalman filter [6] is a extension of the Kalman paradigm to nonlinear system that propagates the first two moments through the unscented transformation.

The unscented transform (UT) deterministically chooses a set of weighted sigma points that match the prior distribution, and propagates them through the actual nonlinear function. Then, the first two moments can be recalculated from these propagated points. It can capture the posterior mean and covariance accurately to the 3rd order (Taylor series expansion) for Gaussian noise process. The standard UKF implementation is briefly described in Algorithm 1 for state estimation [7]. For joint filtering problem (state estimate and parameter identification), the system state and parameters are concatenated into a single higher-dimensional joint vector, and then a standard UKF is run on the joint state space to produce simultaneous estimates of the states $\mathbf{x}$ and the parameters $\boldsymbol{\theta}$.

Since the differential equations in Eqn. (3) are not soluble analytically, we employ a fourth order Runge-Kutta method to investigate the information about the trajectory, where step length h is set to $0.2s$ to make the truncation error involved sufficiently small. Furthermore, the vector $\mathbf{x}(0) = \{\dot{f}, f, v, q, \epsilon, \tau_s, \tau_f, V_0\}^T = (0, 1, 1, 1, 0.54, 1.54, 2.46, 0.02)^T$ represents the initial condition for the filtering approach [3].

2.4. Experiment

Total 128 acquisitions were made (RT=2s), in blocks of 8, giving 16 16-second blocks. The condition for successive blocks alternated between rest and auditory stimulation, starting with rest. Auditory stimulation was emotionally neutral words presented at a rate of 60 per minute.

We chose the largest activation blob as region of interest, using routine fMRI analysis of SPM2, and defined the seed cluster based on faces and edges but not corners so that this voxel had 18 neighbors. The final seed time series were extracted by averaging the time series of the 19 voxels.

3. RESULTS AND DISCUSSION

Figure 2 shows the estimated time course of the hidden states of hemodynamic response to auditory stimulation of emotional words. The estimated flow signal indicates an approximately 100% increase, following a post-stimulus undershoot. The blood venous volume signal has a similar response, but with much less increase than flow signal to stimulus. The total deoxyhemoglobin response q is qualitatively the inverse of the blood flow f and the blood venous volume v. An initial transient decrease in deoxyhemoglobin can be observed. Then, an increases in blood flow will cause the increase of the amount of deoxyhemoglobin. All these predictions of the Balloon model concur with the known physiological effects in fMRI BOLD signal.

Furthermore, the obtained system parameters are $\boldsymbol{\theta} = \{\epsilon, \tau_s, \tau_f, V_0\}^T = \{0.5415, 1.534, 2.467, 0.01\}^T$. The values of these parameters are all between the ranges reported in the literature [2]. These physiological plausible parameters estimated in voxel may provide valuable information to evaluate activation. However, the interference between parameters offer too much flexibility, and parameters in balloon model are poorly identifiability. The accuracy of each parameter is still questionable. The fMRI signal alone may not allow in general to estimate all parameters, and further studies are needed in elaborated experimental paradigm for the decorrelation of parameters effects, other measurement modalities for some physiological parameters and mathematical methods for global optimization of multimodal function.

In conclusion, we presented a state space framework which allows the estimation of the states and parameters of the hemodynamic approach from BOLD responses. It makes possible quantitative assessment of brain physiology.

4. REFERENCES

[1] R. B. Buxton, E. C. Wong, and L. R. Frank, "Dynamics of blood flow and oxygenation changes during brain activation: The balloon model," *Magn. Reson. Med*, vol. 39, pp. 855–864, 1998.

[2] K. J. Friston, A. Mechelli, R. Turner, and C. J. Price, "Nonlinear responses in fmri: The balloon model, volterra kernels, and other hemodynamics.," *NeuroImage*, vol. 12, pp. 466–477, 2000.

[3] T. Deneux and O. Faugeras, "Using nonlinear models in fmri data analysis: model selection and activation detection.," *Neuroimage*, vol. 32, pp. 1669–1689, 2006.

[4] L. A. Johnston, E. Duff, and G. F. Egan, "Partical filtering for nonlinear bold signal analysis," *MICCAI'06*, pp. 292–299, 2006.

[5] J. J. Riera, J. Watanabe, I. Kazuki, M. Naoki, E. Aubert, T. Ozaki, and R. Kawashima, "A state-space model of the hemodynamic approach: nonlinear filtering of bold signals," *NeuroImage*, vol. 21, pp. 547–567, 2004.

[6] S. J. Julier and J. K. Uhlmann, "Unscented filtering and nonlinear estimation," *Proceeding of The IEEE*, vol. 92, no. 3, pp. 401–422, 2004.

[7] V. Merwe and E.A. Wan, "The square-root unscented kalman filter for state andparameter-estimation.," *ICASSP'01*, vol. 6, pp. 3461–3464, 2001.

Algorithm 1: The Unscented Kalman filter (UKF)

• *Initialization*:

$$\hat{\mathbf{x}_0} = \mathbb{E}[\mathbf{x}_0] \quad \mathbf{P}_0 = \mathbb{E}[(\mathbf{x}_0 - \hat{\mathbf{x}_0})(\mathbf{x}_0 - \hat{\mathbf{x}_0})^T]$$

For $k \in \{1, \ldots, \infty\}$,

• *Calculate sigma points*:

$$\mathcal{X}_{k-1} = [\hat{\mathbf{x}}_{k-1} \quad \hat{\mathbf{x}}_{k-1} + \eta\sqrt{\mathbf{P}_{k-1}} \quad \hat{\mathbf{x}}_{k-1} - \eta\sqrt{\mathbf{P}_{k-1}}]$$

• *Time-update equations*:

$$\mathcal{X}_{k|k-1} = F[\mathcal{X}_{k-1}, \mathbf{u}_{k-1}]$$

$$\hat{\mathbf{x}}_k^- = \sum_{i=0}^{2L} W_i^{(m)} \mathcal{X}_{i,k|k-1}$$

$$\mathbf{P}_k^- = \sum_{i=0}^{2L} W_i^{(c)} [\mathcal{X}_{i,k|k-1} - \hat{\mathbf{x}}_k^-][\mathcal{X}_{i,k|k-1} + \hat{\mathbf{x}}_k^-]^T + \mathbf{R}^{\mathbf{v}}$$

• *Measurement-update equations*:

$$\mathcal{Y}_{k|k-1} = \mathbf{H}[\mathcal{X}_{k|k-1}]$$

$$\hat{\mathbf{y}}_k^- = \sum_{i=0}^{2L} W_i^{(m)} \mathcal{Y}_{i,k|k-1}$$

$$\mathbf{P}_{\tilde{\mathbf{y}}_k\tilde{\mathbf{y}}_k} = \sum_{i=0}^{2L} W_i^{(c)} [\mathcal{Y}_{i,k|k-1} - \hat{\mathbf{y}}_k^-][\mathcal{Y}_{i,k|k-1} - \hat{\mathbf{y}}_k^-]^T + \mathbf{R}^{\mathbf{n}}$$

$$\mathbf{P}_{\mathbf{x}_k\mathbf{y}_k} = \sum_{i=0}^{2L} W_i^{(c)} [\mathcal{X}_{i,k|k-1} - \hat{\mathbf{x}}_k^-][\mathcal{Y}_{i,k|k-1} - \hat{\mathbf{y}}_k^-]^T$$

$$\mathcal{K}_k = \mathbf{P}_{\mathbf{x}_k\mathbf{y}_k}\mathbf{P}_{\tilde{\mathbf{y}}_k\tilde{\mathbf{y}}_k}^{-1}$$

$$\hat{\mathbf{x}}_k = \hat{\mathbf{x}}_k^- + \mathcal{K}_k(\mathbf{y}_k - \hat{\mathbf{y}}_k^-)$$

$$\mathbf{P}_k = \mathbf{P}_k^- - \mathcal{K}_k \mathbf{P}_{\tilde{\mathbf{y}}_k\tilde{\mathbf{y}}_k} \mathcal{K}_k^T$$

• *Parameters*: α determines the size of the sigma-point distribution, and is usually set to $1e - 4 \leq \alpha \leq 1$, β is constant, equal to 2 for a Gaussian distribution, L is the states dimension, $\lambda = L(\alpha^2 - 1)$ and $\eta = \sqrt{(L+\lambda)}$ is scaling parameter,$\{W_i\}$ is a set of scalar weights ($W_0^{(m)} = \lambda/(L+\lambda)$, $W_0^{(c)} = \lambda/(L+\lambda) + (1 - \alpha^2 + \beta)$, $W_i^{(m)} = W_i^{(c)} = 1/\{2(L+\lambda)\}$, $i = 1,\ldots,2L$). $\mathbf{R_v}$ is the process-noise covariance, $\mathbf{R_n}$ is the observation-noise covariance.