AN ANALYSIS OF BLOOD-OXYGEN-LEVEL-DEPENDENT SIGNAL PARAMETER ESTIMATION USING PARTICLE FILTERS

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ABSTRACT

The Blood-Oxygen-Level-Dependent (BOLD) signal that is measured by functional magnetic resonance imaging (fMRI) has been the subject of extensive research since the first development of the balloon model. While there are definite benefits to moving from the Canonical Hemodynamic Response function to a physiologically inspired BOLD model, significant barriers remain. Optimizing even the simplest balloon model requires searching within 7 dimensions, and even more complex models exist. Whereas traditional methods of analyzing fMRI aims to determine where activation occurs, BOLD models seek a parametric representation of the signal. Unfortunately, the nonlinear nature of these models makes it difficult to analyze, therefore this work demonstrates the use of a particle filter to regresses the simplest form of the BOLD model. The results show that the system of equations are not observable, leading to a large range of parameters that are consistent with the measurements.

Index Terms— BOLD Response, Functional MRI, Nonlinear Systems, Particle Filter, Bayesian Statistics, System Identification

1. INTRODUCTION

Traditional methods of analyzing Functional Magnetic Resonance Imaging (fMRI) images perform regression using the linear combination of explanatory variables. Though moving to a state space model with more more degrees of freedom requires additional computation, in this paper Particle Filters will be used to estimate the governing parameters of the Blood-Oxygen-Level-Dependent (BOLD) model at a computation cost that would still allow real time calculations for multiple voxels. The parameters guiding the BOLD model could provide insight into functional differences between patients and brain regions. More practically, this algorithm is an alternative to the General Linear Model for activation detection. Though computation intensive, this method is capable of modeling nonlinear effects and provides more detailed output.

This work focuses on the observability of the BOLD state equations from Friston et al. [1]. Because of the nonlinearities in the state equations, no analytical method exists to determine observability. Therefore Particle Filters are used to build a joint mixture Probability Density Function (PDF) of the model parameters. This work will show that this method is sufficient for predicting the BOLD signal, without requiring excessive computation. Because particle filters estimate a full posterior distribution, it was possible to calculate correlation of model parameters, an indicator of observability.

1.1. BOLD Model

It is well known that the two types of Hemoglobin (Hb) act as contrast agents in Echo Planar Imaging (EPI) imaging [2, 3, 4]. Despite this, the connection between Deoxygenated Hemoglobin (dHb)/Oxygenated Hemoglobin (O2Hb) and neural activity is non-trivial. Intuitively, increased metabolism will increase dHb, however blood vessels are quick to compensate by permitting increased local blood flow. Increased inflow, accomplished by loosening capillary beds, precedes a matching outflow, driving increased blood volume. Since the local Magnetic Resonance (MR) signal depends on the ratio of dHb to O2Hb, increased blood volume also affects this ratio. This was the impetus for the ground breaking balloon model [2] and windkessel model [5]. These works derive the changes in dHb ratio and volume of capillaries given Cerebral Blood Flow (CBF) and Cerebral Metabolic Rate of Oxygen (CMRO2) waveforms.

Although Buxton et al. demonstrated that a well chosen flow waveform could explain most features of the BOLD signal, it stopped short of proposing a deterministic waveform for the CBF and CMRO2 [2]. Friston et al. gave a simple expression for CBF input based on a flow inducing signal, and proposed that metabolic rate should be a linear function of the CBF [1]. By combining these equations with the balloon model from Buxton et al., it is possible to predict the BOLD signal from a stimulus function:

$$\dot{s} = \epsilon u(t) - \frac{s}{\tau_s} - \frac{f-1}{\tau_f} \quad (1)$$

$$\dot{f} = s \quad (2)$$

$$\dot{v} = \frac{1}{\tau_0}(f - v^{\alpha}) \quad (3)$$

$$\dot{q} = \frac{1}{\tau_0}\left(\frac{f(1-(1-E_0)^f)}{E_0} - \frac{q}{v^{1-1/\alpha}}\right) \quad (4)$$

where s is a flow inducing signal, f is the input CBF, v is normalized Cerebral Blood Volume (CBV), and q is the normalized local dHb content. The parameters controlling blood flow are ϵ, which is a neuronal efficiency term, $u(t)$ which is the stimulus, and τ_f, τ_s which are time constants. The parameters for the evolution of blood volume are E_0 which is the resting metabolic rate and α which is Grubb's parameter controlling the balloon model. τ_0 is a single time constant controlling the speed of v and q.

Obata refined the readout equation of the BOLD signal based on the dHb content (q) and local blood volume (v), resulting in the final BOLD measurement Equation 5 [6].

$$
\begin{aligned}
y &= V_0((k_1+k_2)(1-q)-(k_2+k_3)(1-v)) \quad (5)\\
k_1 &= 4.3 \times \nu_0 \times E_0 \times TE = 2.8\\
k_2 &= \epsilon_0 \times r_0 \times E_0 \times TE = .57\\
k_3 &= \epsilon_0 - 1 = .43
\end{aligned}
$$

Where $\nu_0 = 40.3s^{-1}$ is the frequency offset in Hz for fully de-oxygenated blood (at 1.5T), $r_0 = 25s^{-1}$ is the slope relating change in relaxation rate with change in blood oxygenation, TE is the echo time used by the EPI sequence and $\epsilon_0 = 1.43$ is the ratio of signal MR from intravascular to extravascular regions at rest. In Deneux et al. [7] it was found that the parameters are far from perpendicular, and that very different parameters could give nearly identical BOLD output; this work builds on that by calculating a joint distribution for the model parameters of this version of the model.

There have been many previous attempts to learn the parameters of the balloon model, although none enjoy the ubiquity of the General Linear Model (GLM). Friston et al. proposed a novel combination of linear and nonlinear modeling to generate parameter estimates [8]. Thus Friston et al. approximated the Jacobian, $\frac{\partial Y}{\partial \theta}$, by approximating the response using a low-order Volterra Kernel [8]. Unfortunately, estimating a Volterra kernel takes longer than simply integrating the state variables. Thus, this method was simplified to a generic nonlinear-least squares algorithm.

In Johnston et al. [9], a hybrid particle filter/gradient descent algorithm was used to simultaneously derive the static and dynamic parameters, (more generally known as parameters and state variables, respectively). A particle filter was used to calculate the time course of the state variables. The estimated distribution of the state variables was then used in a Maximum Likelihood fashion to find the most likely set of parameters. This process was repeated until the parameters converged. This method is more complex than using the particle filter to calculate the parameters, takes longer to run and does not account for uncertainty in parameters.

Hu et al. used an Unscented Kalman Filter to simultaneously calculate the model parameters and state variables [10]. However, because the Kalman Filter assumes a multivariate Gaussian for the state variables, $X(t-1)$, the posterior distribution is limited. Additionally, a nonlinear transformation of a Gaussian, such as the state transition function of the Balloon Model, can be significantly non-Gaussian.

In Vakorin et al., a combination of Genetic Algorithms and Simulated Annealing was used to estimate not only the parameters, but the true stimuli driving the BOLD signal [11]. This addresses the inherent uncertainty of exactly when stimuli get applied. Unfortunately this algorithm took more than 16 hours per voxel to run.

In his PhD thesis, Murray [12] used a particle filter based approach to integrate the BOLD equations. The method used in that work focused primarily on estimating the BOLD output and state equations as a nonlinear stochastic differential equation. The primary difference between that work and this is that Murray [12] took the parameters as a given. Thus, differences in the BOLD output were assumed to be driven by noise in the underlying state equations. Because the parameters were held constant, the BOLD estimate was poor. However, the primary purpose of that work was to advance understanding of filtering techniques; and the filtering framework created in Murray [12], dysii, forms the basis for the particle filter used in this work.

2. METHODS

2.1. Particle Filter

Particle filters, a type of Sequential Monte Carlo (SMC) method, are a powerful method for on line estimation of the posterior probability distribution of parameters given a timeseries and a model. The concept of particle filters is similar to that of the Unscented Kalman Filter; however, distributions are stored as an empirical distribution rather than as the first two moments of a Gaussian. Thus, particle filters are preferred when the model is nonlinear, and non-Gaussian. The particle filters are a well established technique and are described in great detail in Arulampalam et al., Thrun et al. and Murray [13, 14, 12]. The particle filter was set with each particle representing one possible system realization: $\{\tau_0, \alpha, E_0, V_0, \tau_s, \tau_f, \epsilon, s, f, v, q\}$. Initially 16,000 particles were drawn from the prior, however after resampling the number was dropped to 1000. This gave the prior sufficient density to cover parameter space, but saved computation time once the solution space became more compact. The parameters were drawn independently from the gamma distribution:

	τ_0	α	E_0	V_0	τ_s	τ_f
α	0.880					
E_0	-0.766	-0.523				
V_0	0.624	0.424	-0.796			
τ_s	0.620	0.295	-0.748	0.344		
τ_f	0.000	-0.397	-0.431	0.196	0.699	
ϵ	0.616	0.656	-0.641	0.285	0.446	-0.097

Table 1. Correlation Matrix of Posterior Distribution for 40 minute simulated BOLD signal.

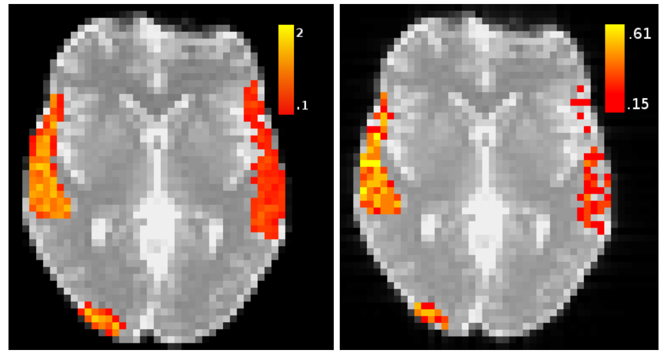
$\tau_0 \sim \Gamma(.98, .25)$, $\alpha \sim \Gamma(.33, .045)$, $E_0 \sim \Gamma(.34, .03)$, $V_0 \sim \Gamma(.04, .03)$, $\tau_s \sim \Gamma(1.54, .25)$, $\tau_f \sim \Gamma(2.46, .25)$, $\epsilon \sim \Gamma(.7, .6)$. To reduce the size of the search space from 11 to 7, $\{s, f, v, q\}$ were assumed to start at resting state, $\{0, 1, 1, 1\}$. Although it is common to add noise to the state during integration (to emulate noise in the state updates), this was not performed because regularization during resampling tended to expand the distribution. Additionally the cloud of particles is able to account for some amount of stationary randomness. Initially each particle is weighted equally, however as new measurements arrive, they alter the probability of particles being a solution. New measurements are incorporated into the weights by Equation 6:

$$w_k^i \propto w_{k-1}^i P(y_k|x_k^i) \tag{6}$$

where i is the particle index, and k is the time index. $P(y_k|x_k^i)$ is the probability of the observed measurement coming from the i^{th} particle and depends on the measurement noise and the observation function, Equation 5. x_k^i is calculated from x_{k-1}^i using the balloon model, Equation 1 through Equation 4. For all the analysis in this work, 1400 Euler integration points per TR (2.1 s) were used. When the number of particles with significant (non-zero) weights dropped below 50, regularized resampling was applied. Thus, a new set of particles was drawn from the smoothed version of the mixture PDF.

Because fMRI drift can add structure to the noise, a spline with 1 knot every 20 measurements was fitted to and then subtracted from the timeseries [15, 16]. The level was then converted to % difference from the original mean. Since the BOLD signal is predominantly positive, a constant (the Gaussian normed Median Absolute Deviation of the % difference signal) was added to each point.

Given the state-space equations for the BOLD signal, simulating a single time series is straightforward. After generating a true signal, identically and independently distributed (I.I.D.) Gaussian noise and a Wiener process with Gaussian I.I.D. steps were added to the true signal. Finally a carrier level was added, since BOLD is measured as a % difference from the baseline. For single voxel analysis, the noise was kept relatively low ($\sigma = 0.001$ for I.I.D. Gaussian Noise, and $\sigma = .0005$ for Wiener Steps) to explore the properties of the model. This noise was added to the the BOLD signal typically peaks at $0.01 - 0.03$ (1-3%). To simulate a slice



(a) SNR (b) Mutual Information

Fig. 1. Results of POSSUM simulated data. $a)$ SNR of POSSUM additive noise. $b)$ Mutual Information between the signal predicted by the particle filter and the actual signal.

	Sim Value	Prior		Posterior	
		μ	σ	μ	σ
τ_0	1.45	.98	.25	1.07319	0.297749
α	0.3	.33	.045	0.317955	0.07311
E_0	0.47	.34	.03	0.364195	0.0457019
V_0	0.044	.04	.03	0.110542	0.0500039
τ_s	1.94	1.54	.25	1.86785	0.390455
τ_f	1.99	2.46	.25	2.50166	0.348326
ϵ	1.8	.7	.6	1.58716	1.14536

Table 2. Comparison of the true value (left), the initial (prior) distribution (center two columns) and the mean/variance of the estimates across simulated voxels (Right two Columns).

with Physics-Oriented Simulated Scanner for Understanding MRI (POSSUM) [17], it's code was modified to output activation levels based on sets of parameters rather than activation levels. For the POSSUM simulated data, SNR was significantly lower although the noise did not include drift ($< 6dB$).

3. RESULTS

A primary advantage of the particle filter is that it estimates a complete joint distribution of the parameters and states. This allows for more detailed analyses not available to many other methods. In particular it is possible to calculate the correlation of the parameters in the posterior distribution. The correlation matrix for the single 40 minute simulation is shown in Table 1. For POSSUM simulations, Figure 1 shows the the mutual information between the estimated timeseries and the preprocessed signal. Note that in order to remove all false positives a threshold of 0.15 bits was applied, the regions of significant SNR are visible despite this. Each estimate was generated from the mean of the particles' parameters at the end of the run. Additionally the mean and variance of the parameter estimates (mean) across the spatial regions of Figure 1 are given in Table 2.

4. DISCUSSION

The data shows substantial correlation present in the parameter estimates for the 40 minute simulated data. Correlation of constants is a definite sign of the model being underdetermined and thus not observable. This is in spite of low noise, and the particle filter's solution converging to a Root-Mean-Squared error of less than 0.002.

On a larger scale, the particle filter also performed well, clearly locating regions of activation in spite of Signal-to-Noise Ratio well below 6dB. However, the final parameter estimates varied more than the initial (prior) distribution (Table 2). This effect is slightly deceiving because the distributions were far from Gaussian, and many were bimodal. It is significant, however, that such a wide range of solutions could give good estimates for the true BOLD signal.

From the results, it is clear that the BOLD model as presented by Friston et al. is not observable, and thus parameter estimates suffer from very large variance [1]. Therefore any work attempting to estimate these parameters from the BOLD signal alone is likely measuring the variance due the model rather than the variance due to try physiological differences. There are two ways to deal with this problem. First, as specified in Deneux et al., certain parameters could be held constant [7]. This solution is relatively easy, and would also reduce computation time. A better way of dealing with this problem is simultaneously measuring fMRI and CBF. This additional measurement, which is closer to original stimulus, could make the Balloon Model observable.

Despite the lack of observability, the BOLD estimates generated by the particle filter stayed near the noise level. Thus, for the purpose of estimating BOLD levels between measurements, the particle filter is sufficient. The on-line nature of the particle filter could also be utilized, along with BOLD estimates, for adaptive control. Thus the stimulus could be adapted during the fMRI scan based on BOLD estimates within a small neural region. The particle filter also has the distinct benefit of estimating a full posterior distribution. A joint distribution of parameters allows for more advanced analysis; such as non-parametric hypothesis testing. While the particle filter took a day of processing for full brain calculations, its speed was sufficient on a quad core machine to perform real time calculations of small regions (approximate run time .27 seconds per voxel-measurement).

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