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Real-time imaging of human brain function by near-infrared spectroscopy using an adaptive general linear model

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Abstract

Near-infrared spectroscopy is a non-invasive neuroimaging method which uses light to measure changes in cerebral blood oxygenation associated with brain activity. In this work, we demonstrate the ability to record and analyze images of brain activity in real-time using a 16-channel continuous wave optical NIRS system. We propose a novel real-time analysis framework using an adaptive Kalman filter and a state-space model based on a canonical general linear model of brain activity. We show that our adaptive model has the ability to estimate single-trial brain activity events as we apply this method to track and classify experimental data acquired during an alternating bilateral self-paced finger tapping task.

Keywords

NIRS; General linear model; Kalman filtering; Data classification

Introduction

Over the last few decades, functional near-infrared spectroscopy (NIRS) has been attracting interest from the psychology and medical imaging communities for its ability to non-invasively measure the cerebral hemodynamic changes associated with functional brain activity (Jobsis, 1977; Cope et al., 1988; Delpy et al., 1987; Villringer and Chance, 1997). NIRS is an optical spectroscopy technique which uses time-resolved, multi-wavelength measurements to infer changes in the optical absorption of tissue and thereby to report changes in oxy- and deoxy-hemoglobin, the two primary absorbing chromophores in biological tissue that vary dynamically with a functional task. Similar to functional magnetic resonance imaging (fMRI), NIRS-based brain studies can be used to record changes in cerebral blood oxygenation during the performance of a specific activation task. This technique has been applied to the study of numerous brain systems and several clinical conditions (see Obrig and Villringer, 2003 for review).

Traditionally, brain imaging studies have generally been performed in two-stages; collection of the experimental data followed by an offline analysis of the signals and interpretation of brain activity. In recent years, however, the combination of more powerful and faster computers, improved data analysis schemes, and a desire to develop experimental designs using biofeedback given to the test subject, has motivated attempts by several groups to develop real-time data analysis schemes to assess brain activation at the same time as data collection. To date, real-time brain imaging has been performed with NIRS (Coyle et al., 2007; Sitaram et

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al., 2007), EEG (Mason et al., 2004; Funase et al., 2006; Muller et al., 2008), and fMRI modalities (LaConte et al., 2007; Weiskopf et al., 2007; Christopher Decharms, 2008). The ability to provide real-time estimates of brain activity has become increasingly attractive to researchers — offering the potential to apply these methods towards applications in the development of brain–computer interfaces (Weiskopf et al., 2004), the study of complex subject–interaction tasks such as the field of neuroeconomics (Sanfey et al., 2003; Singer, 2007; Walter et al., 2005), and potential clinical assessment tools capable of providing immediate feedback to guide medical and behavioral therapies (Chute, 2002; Hintz et al., 2001; Shingu et al., 2003). It is believed that these new neuroimaging tools may one day have the possibility to offer cerebral-based diagnostics in a variety of clinical examinations to enhance existing qualitative, observational, or behavioral assessments (Chute, 2002; Christopher Decharms, 2008; Weiskopf et al., 2007).

Over the last several years, real-time functional MRI, in particular, has been used for a growing number of applications (reviewed in Weiskopf et al., 2007; Christopher Decharms, 2008). However, some of the drawbacks of fMRI-based approaches are the cost and restrictions of the fMRI scanner, which limit its usability to lab facilities. In comparison to fMRI, generally, NIRS instrumentation is smaller, more portable, and less expensive to purchase and maintain. For these reasons, NIRS techniques are ideally suited for the development of portable and potentially clinical real-time systems.

In comparison to the more standardized and traditional off-line analysis approaches for characterizing evoked hemodynamic signals (for example, see Friston, 2007), real-time brain imaging requires several modifications which have been discussed in (Coyle et al., 2004a,b; Matthews et al., 2008; Weiskopf et al., 2007). In particular, not only do these computations need to occur quickly and efficiently, which in general is now fairly straightforward with moderate-grade computers, but more importantly many of the quality assurance tests performed on data need to be automated, including detection, rejection, and correction of motion artifacts, removal of systemic physiological signals, and automated thresholding for visualization and secondary analysis of activation images. In this regard, real-time NIRS brain imaging methods pose several additional and unique challenges in comparison to fMRI, as was recently discussed in Matthews et al. (2008). One of the challenges in the analysis of optical signals is its sensitivity to superficial and global physiological changes. Linear time-series methods, such as bandpass filtering, can be used to remove high-frequency cardiac signals and low-frequency drifts in the optical signal (e.g. Boas et al., 2004) and can be implemented as analog or digital real-time filters. However, bandpass filters are not effective at removing several specific physiological noise signals such as respiratory and blood pressure (e.g. Mayer wave) fluctuations (Franceschini et al., 2006; Toronov et al., 2000) since these fluctuations are difficult to distinguish from typical brain activations by frequency signatures alone. Additionally, bandpass filters cannot remove motion artifacts (e.g. sudden, large, non-physiological changes in the signal due to probe movement relative to the head). As reviewed in Boas et al. (2004), many of the existing sophisticated analysis methods that have been proposed for removing this systemic physiological noise, are based on retrospective correction of signal using partial linear regression of independently measured physiology either from an external monitor or from local recordings of superficial responses by additional short-distance NIRS measurements (e.g. (Diamond et al., 2005, 2006; Saager and Berger, 2005); also see RETROICOR methods developed for fMRI (Deckers et al., 2006; Glover et al., 2000)). Alternatively, methods to filter systemic effects by reducing spatial covariance due to the physiology using principal or independent component analysis have been proposed (Franceschini et al., 2006). While principal component analysis has been used to remove these additional sources of physiological noise (Zhang et al., 2005a; Franceschini et al., 2006), as well as for removal of motion artifacts (Wilcox et al., 2005), these algorithms are based on the projection of the spatial covariance structures from resting-state signals and, thus, require

training data, for example using a separate baseline data file to determine the physiological components. Principal component methods also have the limitation of not being able to attribute each component to a specific physiological signal prior to the start of the study since the relative contributions of the major physiological signals (blood pressure, respiration, and cardiac) may vary such that it is difficult to know how many and which principal components need to be removed. Thus, these methods are difficult to implement in a real-time analysis scheme. More recently, Zhang et al. (2007a,b) described the potential to use adaptive filters to remove physiology from NIRS signals. Although in their paper adaptive filtering was used as a post-processing step in analysis of their functional signals, they expressly point out that an advantage of this approach is the potential of its application to real-time analysis.

In our current paper, we present an online data processing scheme using a similar adaptive filter for the purpose of estimating the cerebral brain activity in real time from NIRS. Our approach is based on a time-variant (or adaptive) version of the canonical general linear model (GLM) of brain activity. The canonical general linear model was introduced by Friston et al. (1994) and has extensively been used in analysis of functional MRI (e.g. in the software SPM; statistical parametric mapping (Friston, 2007); and AFNI, analysis of functional neuroimages (Cox, 1996) among others). Recently, several optical studies have also begun to adapt this approach (Cohen-Adad et al., 2007; Diamond et al., 2005; Zhang et al., 2005a; Schroeter et al., 2004). Unlike the conventional linear time-invariant regression analysis used in these earlier works, in our model we propose an adaptive algorithm based on the Kalman filter (Welch and Bishop, 1995) to estimate the coefficients of this general linear model for each individual time-point. In this way, our adaptive modeling approach provides a real-time estimate of brain activation on a single-trial basis and allows us to take advantage of several features of the Kalman filter that are beneficial to analysis of optical signals. In particular, a Kalman filter weighs the current estimation of brain response between a prediction of the model based on the history of evoked responses from all previous trials and new information from the current data point. After each new data point is made available, this weight is reevaluated. This provides an optimal estimate of brain activity and a means of tracking inter-trial changes in the evoked response. In comparison to the fixed window averaging methods, which evaluate real-time signals by averaging data from a sliding window covering the last several trials, approaches which have been used in the majority of real-time imaging applications to date (e.g. Nakai et al., 2006), we believe that our adaptive filtering method provides a more flexible means to perform real-time imaging by incorporating prior knowledge about the expected reproducibility of the evoked response within the prior estimates of the processes noise of the Kalman filter. In comparison to the initial adaptive model proposed in Zhang et al. (2007a,b), which used an auto-regressive model as the basis of the state prediction, we use a framework similar to the canonical general linear model which allows us to introduce both knowledge of the timing of stimulus events and a prior expectation of the shape of the evoked response. Note also that our adaptive version of the standard general linear model allows for more flexibility in the temporal dynamics of the hemodynamic response of oxy- and deoxy-hemoglobin in comparison to the static canonical temporal model, since the coefficients multiplying this canonical function (typically denoted β) can also vary in time. In this way, the canonical hemodynamic response is used as a prior on the shape of the evoked response, rather than a strict canonical assumption.

To account for the physiological noise specific to the optical data, we have introduced additional regressors into our adaptive model based on the time-varying physiological model developed by Prince et al. (2003). In addition to modeling the canonical functional response, we include a trigonometric series with adaptive amplitude and phase components in order to model the specific physiological noise contributions from the respiratory, cardiac, and blood pressure (Mayer) wave signals. This model allows a tunable bandwidth to remove these systemic physiological signals.

In this paper, we described the real-time implementation of our adaptive model using an extended Kalman filtering algorithm. In order to demonstrate the application of our model, we show data from a self-paced motor activation in which a NIRS probe was placed over the left and right motor areas. During this study, the subject tapped the fingers of one of their two hands and our real-time NIRS system was used to estimate and display the brain activation signal, as well as to classify the handedness of the tapping per trial and to feedback the results to the individual.

Theory

Near-infrared brain imaging

The NIRS technique is a non-invasive method used to measure functional brain signals (Jobsis, 1977; Wray et al., 1988; Delpy et al., 1988). NIRS instruments use low levels of light (typically between 5–10 mW) within the wavelength region of 650–850 nm light to record changes in the optical absorption of tissues over time. During functional brain activation, increases in blood flow, volume and oxygenation result in changes in absorption due to underlying changes in the concentration of oxy- and deoxy-hemoglobin, HbO_2 and HbR respectively. These absorption changes are measured by a spatially distributed array of light source and detector pairs placed on the surface of the head of the subject. Due to the low optical absorption of biological tissue in the near-infrared region of the light spectrum, often referred to as the “near-infrared window”, light can penetrate up to several centimeters of tissue. This optical window allows light to penetrate deep enough to sample through the outer 1.5–2 cm of skin and skull and reach the outer approximately 5–10 mm of brain tissue (Wang et al., 1995; Fukui et al., 2003), which provides sensitivity to hemoglobin changes in the outermost cortex of the brain.

In functional NIRS studies, optical absorption changes ΔOD (optical density), are assumed to be small, and can be modeled as a linear combination of changes in oxy- and deoxy-hemoglobin as given by the modified Beer–Lambert law (MBLL) (Cope et al., 1988; Kocsis et al., 2006). An absorption change at a given wavelength λ is expressed as a linear combination from the contributions of each hemoglobin species and is given by

$$\Delta\text{OD}_{i,j}^{\lambda} = L_{i,j}^{\lambda} \cdot \text{DPF}^{\lambda} \left(\varepsilon_{\text{HbR}}^{\lambda} \Delta[\text{HbR}] + \varepsilon_{\text{HbO}_2}^{\lambda} \Delta[\text{HbO}_2] \right), \quad (1)$$

where ε is the extinction coefficient for a given wavelength for each hemoglobin species, $L_{i,j}$ is the effective path length covered by photons from a source i to a detector j . DPF is the differential length factor (Cope et al., 1988). $\Delta[\text{HbO}_2]$ and $\Delta[\text{HbR}]$ are respectively the changes in oxy- and deoxy-hemoglobin.

Description of general linear model

In general, most standard analysis of functional hemodynamic changes in neuroimaging techniques such as NIRS or fMRI is based on an assumption of the linear addition of hemodynamic changes. In this standard linear model, the contributions of individual hemodynamic changes for each trial are summed along with any residual activation from previous trials plus an additional noise term. This assumption of linearity is generally true provided that the time interval between stimulus events is sufficiently long (e.g. 4–6 s; Cannestra et al., 1998). In general, the observations of hemodynamic changes may be expressed as a system of linear equations given in matrix form by the expression (for further discussion, see Friston, 2007)

$$Y = G\beta + e, \quad (2)$$

where Y is the observed times-series of a hemodynamic variable, G is known as the design convolution matrix and describes the experimental paradigm (e.g. the stimulus timing), and β is the set of coefficients for the functional response which we seek to estimate. The final term e is the measurement error, which is often assumed to be independent zero-mean Gaussian distributed random variables. It is often conventional in fMRI analysis to assume that the hemodynamic response is relatively smooth temporal function and can be modeled using a limited temporal support vector. This hemodynamic response is frequently assigned a canonical *a priori* shape. For example, the evoked response may be modeled as a linear combination of modified gamma-variant functions (Glover, 1999). With this simplification, the problem of determining brain function then reduces to one of estimating only a single or in some cases a limited number of coefficients, β , which scale the contributions from each temporal support. This assumption reduces the number of degrees-of-freedom of this model and thus improves statistical significance in comparison to a traditional deconvolution (Friston, 2007; Cox, 1996). Following this approach, in our model, the evoked functional response $y_k^{\text{Functional}}$ is modeled as a linear combination of N_s gamma-variant functions, where N_s is the number of stimuli presented in the experiment. The gamma-variant function Γ_n is given by

$$\Gamma_n(t) = \frac{1}{n! \tau_h^n} \left(\frac{t - t_0}{\tau_h} \right)^n e^{-(t-t_0)/\tau_h} u(t - t_0), \quad (3)$$

where $u(\cdot)$ is the unit step function given by

$$u(t - t_0) = \begin{cases} 1 & \text{if } t - t_0 \geq 0 \\ 0 & \text{otherwise} \end{cases}. \quad (4)$$

In this model, τ_h and t_0 define the response width and onset time. These were set at 1.1 s and 0.0 s, respectively, and n was 5 following the nominative values reported in (Glover, 1999).

The observable evoked hemodynamic signal $y_k^{\text{Functional}}$ is thus described by the summed contribution of each functional stimulus and given by

$$y_k^{\text{Functional}} = \sum_i \Gamma_n(t - S_i) \beta_k, \quad (5)$$

where S_i is the i th stimulus. Note that this is simply a convolution of the stimulus and the canonical hemodynamic impulse response to predict the expected brain imaging data. For example, in our case of 20 s task durations, the functional model was obtained by a convolution of Γ_n with a repeated 20 s boxcar function.

In comparison to fMRI, it is well known that the sensitivity of NIRS measurements are greatest towards the surface of the head. Thus, background signals from systemic physiology are often a confounding additional signal to the functional response. To model these effects in our model, these fluctuations can be expressed as a linear combination of sinusoids at the specific physiological frequencies (e.g. the cardiac, ~1 Hz; respiratory, ~0.25 Hz; and Mayer wave

frequencies, ~ 0.10 Hz). This model was introduced by Prince et al. (2003) to remove this physiology from optical signals. Similarly, our model of systemic physiology is given by

$$y_k^{\text{Physiology}} = \sum_i a_{i,k} \sin(2\pi f_i t + \theta_{i,k}), f_i \in \{0.1\text{Hz}, 0.25\text{Hz}, 1\text{Hz}\}. \quad (6)$$

Assuming that the evoked functional response, physiological artifacts and measurement noise v_k are additive, the overall model of the measurable hemodynamic signal is given by

$$y_k = y_k^{\text{Functional}} + y_k^{\text{Physiology}} + \text{DC}_k + v_k \quad (7)$$

where the term DC_k has been added in order to account for constant (DC) offsets in the signal. The parameters of the model that will be eventually estimated can be presented in a single state vector x_k as follows:

$$x_k = [\beta_k \ a_k \ \theta_k \ \text{DC}_k]^T \quad (8)$$

where T is the transpose operator. Thus, the observable signal y_k is finally given by a non-linear observation function $h(\cdot)$ operating on a state vector x_k , and subject to additive noise v_k :

$$y_k = h(x_k, v_k). \quad (9)$$

In our model, our state vector x_k is assumed to be time-variant and thus, we will estimate the value of these states using the extended Kalman filter, which will be detailed in the next section. Throughout the description of our model above, we have introduced the subscript k to indicate the temporal dependance of the model, which will now be elaborated in the following section.

Kalman estimator

The Kalman filter method is an adaptive tracking scheme that estimates the state of a process using a recursively updated regularized linear inversion routine. The recent technical report by Welch and Bishop (1995) provides a clear and readable tutorial on the subject, which will only be briefly covered here. For non-linear state-space models, the extended Kalman filter (Welch and Bishop, 1995) approach uses a local linearization of the model to perform the state estimation.

The extended Kalman estimator begins with an update of the state vector (x_k ; Eq. (8)) based on its value at the previous time-point, x_{k-1} , and the error covariance of this vector ($\mathbf{P}_k$), such that:

$$\begin{aligned} \hat{x}_{k|k-1} &= f(x_{k-1}, w_{k-1}), \\ \mathbf{P}_{k|k-1} &= \mathbf{A}_k \mathbf{P}_{k-1} \mathbf{A}_k^T + \mathbf{W}_k \mathbf{Q}_{k-1} \mathbf{W}_k^T, \end{aligned} \quad (10)$$

where $\hat{x}_{k|k-1}$ is an estimate of x_k as obtained from the stochastic operator $f(\cdot)$ given the process noise w_k , and $\mathbf{P}_{k|k-1}$ is the new projected error covariance based on the prior data collected up until the current time-point. $\mathbf{Q}_k$ is the noise covariance matrix which is injected at time step k . In a practical sense, the $\mathbf{Q}_k$ controls the size of the step that each of the states can take from

its current value. If this value is small, the model will approach a time-invariant (static) set of states and if it is large, the state may be highly variable over time. $\mathbf{A}_k$ and $\mathbf{W}_k$ are the Jacobians of the state update model (f) evaluated at the time point k as given by:

$$\mathbf{A}_k(i, j) = \frac{\partial f_i}{\partial x_j}(\widehat{x}_{k-1}), \quad (11)$$

$$\mathbf{W}_k(i, j) = \frac{\partial f_i}{\partial w_j}(\widehat{x}_{k-1}). \quad (12)$$

In our model, we assume that the states follow a Wiener process, such that both $\mathbf{A}_k$ and $\mathbf{W}_k$ equal identity matrices. This is equivalent to a one-dimensional random-walk of the state vector over time. Based on this prediction of the new state vector at the current time point, the expected observations at time-point k would thus be estimated as

$$\tilde{y}_k = h(\widehat{x}_{k|k-1}) \quad (13)$$

Once a prediction for the observation is obtained based on the previous time-points, the extended Kalman filter corrects the estimate of the state vector based on the error between this prediction of the observations and the new data using the definitions:

$$\mathbf{G}_k = \mathbf{P}_{k|k-1} \mathbf{H}_k^T (\mathbf{H}_k \mathbf{P}_{k|k-1} \mathbf{H}_k^T + \mathbf{V}_k \mathbf{R}_k \mathbf{V}_k^T)^{-1}, \quad (14)$$

$$\widehat{x}_k = \widehat{x}_{k|k-1} + \mathbf{G}_k (y_k - \tilde{y}_k), \quad (15)$$

$$\mathbf{P}_k = (\mathbf{I} - \mathbf{G}_k \mathbf{H}_k) \mathbf{P}_{k|k-1}, \quad (16)$$

where $\mathbf{G}_k$ is the Kalman gain at step k , $\widehat{x}_k$ is the updated state estimate given measurement y_k , and $\mathbf{P}_k$ is the updated error covariance matrix. $\mathbf{R}_k$ is the measurement noise covariance matrix at time step k . $\mathbf{H}_k$ and $\mathbf{V}_k$ are the Jacobians of the observation model described in Eq. (9) with respect to the state vector and measurement noise evaluated at the (i, j) th element and time step k :

$$\mathbf{H}_k(i, j) = \frac{\partial h_i}{\partial x_j}(\widehat{x}_{k|k-1}), \quad (17)$$

$$\mathbf{V}_k(i, j) = \frac{\partial h_i}{\partial w_j}(\widehat{x}_{k|k-1}). \quad (18)$$

In this work, the state vector was initialized to zero ($\hat{x}_0=0$). The *a priori* estimates of the process and measurement noise covariances ($\mathbf{Q}$ and $\mathbf{R}$ respectively) were set at $(50\%/s)^2$ and $(0.5 \mu M/s)^2$. These values were empirically determined at the initial development of this experiment and chosen to give an appropriate tracking of evoked signals. Normalized units were used for the state vector since this vector contains mixed units (e.g. amplitude and phase of the sinusoids modeling the systemic physiology). It is important to scale the state vector to avoid large discrepancies in the magnitude of these terms of the model. In the Kalman filter these two covariance matrices allow tuning of the filter behavior. As aforementioned, if the process noise is assumed low and/or the measurement noise is assumed high, then the Kalman tracker approaches a static solution similar to the standard general linear model. In the other extreme, the Kalman estimator will tend to overly track the observations and will not effectively remove noise from the data. Tuning the Kalman filter has been discussed in previous work (Diamond et al., 2005) and was done empirically in our current project. We used the same parameters for all subjects and we noted that over a reasonable range of 2–3 orders of magnitude in each of these estimates, our results did not notably change.

Methods

Experimental design and subject characteristics

In order to demonstrate the effectiveness of our adaptive linear model and real-time system, optical studies were performed on three healthy individuals. All subjects gave voluntary consent and this study was approved by a local institutional review board at the University of Pittsburgh Medical Center. The subjects' ages ranged from 26 to 43 years old and all three were male. Two subjects were right-handed, while one subject is left-handed (self-reported, see Table 1). During the study, subjects were seated in a chair viewing a computer screen on which the real-time display of their activation state was shown. The subjects were given an auditory cue to begin and end the task during which they were instructed to sequentially tap each of their fingers to their thumb on either their right or left hands. Tapping was self-paced. Each stimulus block lasted for 20 s with a 20 s rest period between trials. The handedness for each block was logged by the researcher for input into the post-processing. Each experimental run lasted 6 min and four to five functional runs were repeated for each subject. An additional single 6 min run was recorded at the start of the experiment, which was used to train the linear classifier model.

Description of instrumentation

We used a commercial Cw6 instrument manufactured by TechEn Inc (Milford, MA). Our current system is a variation of the continuous wave instrument described in Joseph et al. (2006). Our instrument has capacity for up to 16 avalanche photodiode detectors (Hamamatsu C5460-01) and 16 lasers (8 positions each with 2 wavelength colors; 690 nm and 830 nm) (Hitachi HL6738MG and Hitachi HL8325G). Each of these lasers is square-wave amplitude-modulated at unique carrier frequencies between 6.4 and 9.4 kHz (200 Hz steps), which is used to identify the light from this laser. The analog signals from each of the 16 photon detectors are digitalized at 54 kHz. Two onboard digital signal processing chips perform the real-time demodulation of each of the up to 256 source-detector combinations. These signals are down-sampled to a software-selectable rate of up to 50 Hz and are sent as digital signals (32-bit) over a USB-2 interface to the controlling computer. The final data rate of this instrument is determined by the limits of the USB-2 interface and depends on the actual number of measurement source-detector pairs demodulated as dictated by the layout of the head probe and optode spacings. For this study, we used a data rate of 4 Hz, which was additionally limited by our real-time Kalman filtering program (described in Section 1 Introduction) and data transfer rates to the real-time classifier and subject display modules (Fig. 1).

Real-time acquisition and analysis software

We developed a custom analysis software to perform both the data collection and real-time implementation of our functional estimator. This software consisted of both a C++ written driver and back-end application interface that managed all instrument interfacing and data storage via USB-2 serial communication and a Matlab (Version 7.0.1) written front-end graphical interface for visualization and real-time signal processing. This front-end Matlab interface was developed from our existing software HOMER, which has been described in (Huppert et al., 2005). This software was designed and tested to handle up to 256 possible NIRS source-detector combinations at a sample rate of up to 10 Hz. The data management was handled by three independent Windows timing threads to avoid potential data loss due to computational overhead. The data acquisition was run on a 2.4 GHz quad-core processor under Windows XP (SP3).

A second computer was networked to the primary data acquisition computer and used for further real-time processing of the brain activation signals. This computer managed the classification of the brain activation signals (e.g. determination of left versus right hand self-paced finger tapping) based on the estimated single-trial estimates of the brain activation states from the dynamic linear model (see Section 2 Theory). Finally, a third dedicated computer was used to present the stimulus and biofeedback to the subject using the E-prime software (Psychology Software Tools Inc., Pittsburgh PA). This program was also used to indicate the onset times of the stimulus blocks to both the subject and to the Cw6 instrument via an analog voltage signal. This channel was used to trigger events for the real-time averaging algorithm. Thus, no prior knowledge of stimulus timing was required by our software to run the real-time analysis. A schematic diagram of our instrument, interface, and computer arrangements is shown in Fig. 1.

The real-time implementation of our Kalman filter as described in the previous section was done in Matlab as a custom plugin to our data acquisition software. This was run on the data acquisition computer. Conversion of the raw data signals (voltage signals) to optical density changes and subsequently to oxy- and deoxy-hemoglobin via the modified Beer–Lambert law was done in real-time as a preprocessing step before feeding our Kalman filter-based general linear model. Although, in theory, the Beer–Lambert equation can be integrated into the general linear model as described in Diamond et al. (2006), this still requires estimation of optical density, which as defined in Eq. (1) requires normalization by the mean signal intensity. To solve for this mean signal intensity, we use a second Kalman filter, which acted on the raw data signal per channel. This state model was given by the expressions:

$$Io_k = Io_{k-1} + w_k, \quad (19)$$

$$yk = Io_k + v_k. \quad (20)$$

Optical density changes are thus given by:

$$\Delta OD_k = \text{Log}_{10} \frac{I(t)}{Io_k}. \quad (21)$$

The state processes noise covariance Q of the MBLL filter was optimized to provide slowly updated estimate of the mean intensity for each source-detector pair. In initial studies, this was verified to closely match the standard methods to estimate optical density by normalization by

the mean signal. Optical signals were subsequently normalized to the estimated I_0 signal and converted to changes in optical density. The Beer–Lambert law was implemented using a linear inverse. A partial volume of 60 and differential pathlength of 6 was used for both wavelengths ($L=3$ cm). The calculation of optical density and the Beer–Lambert law were implemented in a second plugin to our data acquisition software. By performing the Beer–Lambert as a preprocessing step to our adaptive general linear model, thus avoiding off-diagonal terms in the measurement forward model (c.f. Diamond et al., 2006), we were able to more efficiently implement our model by taking advantage of sparse matrix representations of the model.

Classification of motor activation

In this project, we have used a simple linear classifier to estimate the handedness of the activation based on the estimates of the evoked functional state variables (β_k) from each optical channel. After each update of the Kalman filter model, the current value of β was passed to the classifier program. Since the state β multiplies the canonical linear model (GLM), β is only updated during stimuli periods. Our algorithm used a linear discriminant, which fits a multivariate normal density to each group, with a pooled estimate of covariance as described in Krzanowski (1988) and Seber (1984). The covariance for the two groups (left and right tapping) was determined from a single experimental run (6 min; 8 tapping blocks) at the start of the study. For all three subjects, no additional filtering or manual removal of stimulus epochs was done on this training data. The training data was not included in the further analysis of the performance of our model. The values for the state variables (β_k) for all optical source-detector pairs (channels) and both oxy- and deoxy-hemoglobin signals were used in the model. Each time-point of the data was analyzed independently and thus a classification label of left or right tapping was estimated for each point and updated to a computer screen in front of the subject every 500 ms (described in Section 2 Theory).

Results

Using the Cw6 optical imaging system with our customized control and analysis software, we were able to detect and visualize brain activation in real-time using NIRS at data rates of 4 Hz for the full compliment of up to 256 source-detector combinations. A total of 56 combinations were used in the probe for this study. This approach allows spatially resolved imaging of the brain signals. In order to demonstrate this system, we recorded NIRS signals from the bilateral motor cortex regions during an alternating left/right hand self-paced finger tapping task. Specifically, this task was chosen as a means to test our adaptive real-time brain estimation algorithm by providing two distinct, experimentally-controllable, activation states (namely, left and right hemisphere activation).

One experiment subject is left-handed, which is revealed in the bilateral activation to both right and left hemispheres. Thus, this task allowed us to examine the ability of our model to provide single-trial estimates of brain activity.

Fig. 2 shows our experimental setup. On the left is shown the optical probe geometry used to measure the motor activation from both hemispheres. These signals were collected by our Cw6 system and processed through the scheme as was presented in Fig. 1. An analog voltage signal indicating the onset and duration of the stimulus was recorded by one of the auxiliary analog channels of the Cw6 system. This analog signal was converted to a binary representation indicating the stimulus blocks and used to convolve the gamma-variant canonical response via Eq. (5). In this way, the experimental timing does not need to be defined in the analysis prior to data collection, which allows us to perform experiments with subject-paced timing. The Kalman estimator was updated in real-time (4 Hz in this study) and the results are displayed on a separate window. In Fig. 2 (right panel), we show an image from the visualization of this real-time Kalman filter module. Here, we display both the time-courses of the hemoglobin

signals for user-selectable channels on the probe and also images reconstructed of the data from the current trial. This data shows an example of the real-time display for four sessions of tapping (namely, right/left/right/left) from subject B. The channels displayed are from the right hemisphere and are seen to respond primarily to the left-handed tapping. The image at the bottom of this figure shows the spatial map from the last trial in the time-course (left tapping). These topographic images showing the location of the activation patterns were calculated using a back-projection algorithm based on the optical forward model calculated from a semi-infinite homogenous slab approximation ($\mu_a = 0.1 \text{ cm}^{-1}$, $\mu'_s = 10 \text{ cm}^{-1}$) and the Matlab PMI toolbox from Massachusetts General Hospital.

Performance of adaptive model of brain activation

The Kalman filter and adaptive general linear model provide real-time estimates of the magnitude of the brain activation signals given in the state variable containing β , the coefficient multiplying the canonical functional response. This approach provides a means to track single trial variability in the evoked response. In this study, we have introduced this variability by alternating between left and right handed self-paced finger tapping. In Fig. 3, we compare our Kalman estimator against the raw data signals recorded by our instrument. The top and bottom panels of this figure show time-courses from a region-of-interest taken from the left and right hemispheres respectively. In this figure, the estimate of the filtered observation ($\hat{y}$) of the evoked functional signal from the Kalman tracker is shown along with the unfiltered data. The averaged response (static estimate) for the left and right handed tapping trials is also shown for reference as calculated by taking into account the proper left/right labels of each trial. Note that the Kalman filter algorithm makes no use of whether the subject is tapping the right or left hand. The results shown in Fig. 3 demonstrate the ability of this algorithm to switch between the two states, and thus to assess dynamic variability in the evoked functional response.

Real-time classification of motor activity

Our real-time classifier algorithm estimated the most probable classification of left versus right hemisphere activation and displayed the results to the subject. This result was presented to the subject as a graphic which placed a mark on the top (if left-hand tapping) or bottom of the screen (if right-hand tapping) as shown in Fig. 4. In this figure, the true labels for each trial have been added for comparison. Obviously, the true labels were not known to the algorithm at the time of collection. Our simple linear classifier correctly classified 79% of the finger-tapping events overall for the 3 subjects. The results for the individual subjects is presented in Tables 1 and 2. Note that this initial linear classifier algorithm was very simple in comparison to other available approaches that have been described for post-processing analysis (e.g. LaConte et al., 2007; Sitaram et al., 2007). This initial approach was used in this study to assess the effectiveness of our adaptive general linear model and we believe that classification efficiency could be improved using more sophisticated models in future work.

In Fig. 4, we show an example of our classifier performance and the display as seen by the subject. The correctly classified time-points have been identified by circles, while the incorrect points are shown as crosses. An estimate of the handedness is calculated for every time point during which the stimulus was on. We scored an overall correct label if the classification was correct for more than half of the time-points in a single trial epoch.

Because the Kalman filter uses the history of the states to predict the current value, a short lag of about 2–3 s is observed before the classifier is seen to switch handedness. This is limited by the slow nature of the hemodynamic response, which also persists several seconds after the tapping exercise has ended for each trial.

We anecdotally noted that during the experiment, the evoked hemodynamic response was sensitive to subject attention. During trials where the subject self-reported not being fully attentive to the task, the brain responses tended to be smaller and more classification errors were observed. The role of subject attentiveness on the magnitudes of single-trial hemodynamic events remains to be explored and offers a potential future application for our adaptive filtering methodology.

Comparison of adaptive and static models

In order to further validate our Kalman estimation approach, we compared our adaptive model to the results obtained via a more conventional static estimation of the left and right-handed evoked response obtained by block averaging. In post-processing, we calculated the average hemodynamic response across all the left and right trials from the original data and the output of our Kalman filter based on the recorded handedness for each stimulus block. In Fig. 5, we show spatial images of the maps obtained during left and right handed tapping in each of the three subjects from the average of all the trials. The top row, which displays the results from a standard block average of the raw (unfiltered) signals shows a large systemic change over most of the probe due to contamination from background physiology. This is particularly observed in subjects B and C, who both had demonstrated a large Mayer wave component in the raw data signals. Without filtering, this background physiology interferes with the detection of localized brain activation and no channels show significant activation. For this reason, a vast majority of previous NIRS studies have utilized filtering to remove these background signals as discussed in the introduction and reviewed in Boas et al. (2004). The data shown in the unfiltered case is particularly unremarkable without these steps. In the middle row of Fig. 5, we show the averaged response of the data processed using our adaptive Kalman filter. Since this approach is able to remove much of the systemic physiological trends from the inclusion of the sinusoidal regressors at 1 Hz, 0.25 Hz, and 0.1 Hz and constant (DC) term, which also removes very low frequency drift in the adaptive model, a more focal activation is observed with a primarily activation observed in the contralateral motor region during the task. The ipsilateral activation was smaller or negligible with the exception of the subject A who was left-handed, which showed slightly more bilateral activation compared to the other two subjects. These findings are consistent with the expectations of activation associated with this motor task. To further confirm the findings of our adaptive model, we applied an alternative physiological filtering method using a principal component-based filter (PCA) as described by Zhang et al. (2005b). This principal component filtering method removes spatial structures that match the covariance of baseline data and has been used to remove global effects in functional signals (Franceschini et al., 2006). These tools are included in the data analysis program HOMER (Massachusetts General Hospital; www.nmr.mgh.harvard.edu/DOT). Using this PCA filtering (Fig. 5, bottom), the contralateral activation patterns are more clearly visible than seen in the unfiltered data. In this analysis, 3, 4, and 2 principal components were removed from subjects A, B, and C respectively according to the procedure outlined in (Franceschini et al., 2006) based on removal of the first N -eigenvector components that accounted for up to 80% of spatial covariance of the data. The PCA results were qualitatively consistent with the results from our adaptive filter. Both approaches produced primarily contralateral activation patterns and the largest activations were seen in approximately the same regions of the probe. There were, however, some discrepancies between these images which are most likely due to a combination of incomplete removal of systemic effects by the adaptive model and/or over-filtering by PCA filter produced since brain activation is not necessarily orthogonal to spatial components calculated from the background physiological signals (see Franceschini et al., 2006 for discussion). The color scales in Fig. 5 were consistent between the three levels of filtering within a subject but vary between subjects. In Fig. 5, optical channels that were statistically significant ($p \leq 0.05$, uncorrected) are indicated by a dotted line between the

corresponding source and detector pair. The Kalman and PCA filtered images give similar results and localization of the activity to similar regions of the probe.

Finally, in Fig. 6, we show the average time-courses for the left and right finger tapping for regions-of-interest selected in the left and right hemispheres using the output of our adaptive filter. The contralateral activation patterns exhibited the expected hyperemic evoked response of increases in oxy- and total-hemoglobin and a decrease in deoxy-hemoglobin. The ipsilateral activation patterns were smaller and in most cases were a bit more contaminated with systemic physiological noise. The regions shown are the same for the ipsilateral and contralateral activations. The evoked responses for subject A were larger than the other two subjects, which is probably due to partial volume errors and probe placement relative to subject anatomy.

Discussion

We have described an adaptive version of the general linear model, which can be used for real-time assessment of brain function. To demonstrate this model, we have performed a motor-task activation study, consisting of an alternately left and right handed self-paced finger tapping tasks. This study allows us to highlight several important features of our model. First, the adaptive model provides a means to perform single-trial estimation of the evoked brain response. We have chosen this specific bilateral motor task as this represents an extreme case of inter-trial variability. Since we do not incorporate the number of stimulus conditions or labels of the conditions into our Kalman tracking algorithm, this allows us to test how our method performs. A further advantage of the Kalman filter is the explicit separation of priors for the process and measurement noise terms ($\mathbf{Q}$ and $\mathbf{R}$ respectively). In particular, the process noise term, which can be thought of as a prior on the amount of randomness added to the states at each additional time point allows tuning of the fluctuations in the state (in our case the coefficients of our general linear model). In the limit of small $\mathbf{Q}$, the states remain constant, thus approaching the conventional static solution of the standard general linear model (Friston, 2007). Annealing methods can be introduced to force this convergence. In our case, however, $\mathbf{Q}$ was set to be higher than expected for a single condition repeated measurement, which allowed inter-trial variability in the states such that the changes between left and right hand tapping could be tracked. The addition of process noise to the states also allows deviations from the canonical hemodynamic shape. For example, here, we have assumed a gamma-variant canonical response and convolved this with the stimulus presentation (boxcar) function. As demonstrated in Fig. 6, because of the allowed temporal-variability in the coefficients multiplying this function (β) within the Kalman framework, this assumption does not place a strict restriction on the shape of the response. Instead, the gamma-variant shape is used as a prior where, again, the magnitude of the expected processes noise $\mathbf{Q}$ allows adjustment of the strength of this prior. In the earlier work by Diamond et al. (2006), a similar Kalman filter approach was used to estimate the coefficients on a set of Gaussian based temporal supports. Similar to the general linear model used here, the evoked hemodynamic response was expressed as a linear combination of these canonical basis functions. By using multiple overlapping Gaussian functions, more temporal variability could be modeled compared to the single canonical response (e.g. a single gamma-variant function). However, more model parameters were required using the Gaussian basis set. Recent work on comparing optical and fMRI responses has suggested that these responses are similar (Huppert et al., 2006) and has justified the assumption of a reduced dimensional (gamma-variant) canonical function based on standard fMRI analysis. Because the additional temporal structure contained in the states β allows variations from the strict canonical prior, we believe that this reduced basis set is sufficient. Note, however, that our model can also be extended with additional terms if needed, for example, an undershoot of the evoked response can be explicitly included in the model by adding the first derivative of the gamma-variant (dispersion term) as an additional regressor.

A further advantage of our model is its real-time applicability. The Kalman filter algorithm has fairly low computational overhead, which allowed us to implement this method at a high sample rate (4 Hz in this study). We believe that this approach can also be applied to other imaging modalities as well, in particular functional MRI. To date, the majority of real-time analysis approaches, which have been used in fMRI and optical studies, have used fixed interval averaging techniques. For example, brain responses may be reported from the average of the last n -seconds or trials, where n is defined *a priori* ($n=0$ represents examination of only the current time-point). In contrast, within the Kalman filtering scheme, the estimate of the brain signal at each time instant is a weighted combination of the prior history and current new data. In our model, where the states are assumed to undergo a random walk process, our prediction of the current brain activity is that it will be the same as it was in the last trial unless the new data informs otherwise. Even in the case that inter-trial variability is high, as we have purposefully introduced using our left/right self-paced finger tapping task, the Kalman filter can effectively track the brain activity in real-time. Note that this approach is not limited to blocked or slow event-related designed experiments and can be used even in the case of rapid event-related experiments which require deconvolution due to overlap in the evoked responses.

Finally, the Kalman filtering approach allows for removal of background physiological signals from cardiac, respiratory, and Mayer wave fluctuations. This use of the Kalman filter has recently been demonstrated in several other similar works. Our model followed the description introduced by Prince et al. (2003) and incorporated sinusoids with time-varying amplitude and phase which operated around specific frequencies to model the physiological fluctuations. The Kalman filter allows adjustment of the effective bandwidth of these filters through the introduction of the process noise, which models variations about the central frequency. Inclusion of these non-linear regressors reduces the physiological noise in the estimate of the evoked response. In a work by Zhang et al. (2007a,b), systemic interference is removed using adaptive autoregressive filtering model within a similar Kalman filtering framework. This could offer a further option to be explored in future work by extension of our current model.

Limitations of adaptive model

While our adaptive GLM approach offers these several advantages, adaptive filtering, in general, is not without some limitations. In the Kalman filtering model, prior distributions must be assumed for both the process and observation noise (Q and R respectively). These two distributions determine the behavior of the Kalman tracker and, in particular, how closely the model will follow data and how sensitive the model is to noise. This tuning is done prior to the experiment and requires some expectation of the inter-trial variability in the response. In the case for this study, we had prior knowledge that the process noise would be large, since we knew that switching between the left and right handed movement would give different responses. However, this information may not be always known. In the case of a repeated task that is more reproducible between trials, setting the process noise large might reduce the statistical power of the GLM model, since the model will be more sensitive to fluctuations. On the other hand, if the process noise is estimated too low, then the filter will be slow to adjust to sudden changes. If, for example, the data shows a series of strong hemodynamic responses, then there will be a bias to estimate a similar response on the next trial. This can lead to over estimation of the response for that epoch. To correct for these errors, adaptive filters are often followed by backward smoothing step such as a fixed-interval smoother (Welch and Bishop, 1995). This filter moves backwards in time over the data to correct for the phase introduced by the Kalman filter. However, this filtering cannot be done in real-time. Furthermore, since this model assumes that both sources of noise have normal distributions, regressors must be included to remove systemic physiology and whiten the residual error of the model. Our approach using sinusoidal regressors is an approximation to account for this structured noise, however, experimentally measured regressors, such as from multi-distance NIRS

measurements or external monitors, might provide a more accurate model of this physiology. In future work, these may be included in the model in a similar way allowing the scaling of these regressors to be the new state variable. The use of the canonical general linear model may also pose some limitations. Although these methods have been used in previous work (Cohen-Adad et al., 2007; Diamond et al., 2005; Zhang et al., 2005a; Schroeter et al., 2004), the canonical general linear model has not been fully quantified for NIRS data with respect to potential differences between oxy- and deoxy-hemoglobin. In particular, in this model, we used the canonical gamma-variant function derived from fMRI literature to model both the hemoglobin components of the signal. Previous work by Huppert et al. (2006) showed that the deoxy-hemoglobin signal closely matched this fMRI response, but that the oxy-hemoglobin signal was slightly different and peaked earlier. Since this study used a longer duration stimulus (20 s), the shape of this canonical function is less important than with short duration stimuli. However, more work is needed to define the proper form of a specifically oxy-hemoglobin canonical response. Since our approach allows additional temporal variation of the coefficient multiplying this canonical, the shape of this function is used as a prior within our model, rather than a strict constraint as with the conventional static general linear model approach. Nevertheless, improving the canonical prior should improve the model of the data and provide better estimates of brain activation.

Future extensions

The focus of this paper was the development of the adaptive general linear model capable of providing real-time estimates of brain activity through tracking of the states beta, which multiplied the canonical functional response profiles. In this current work, the states were input into a simple linear classifier to determine left versus right-handed self-paced finger tapping. While this classifier scheme performed well for this simple task and for demonstrating the adaptive linear more, more sophisticated approaches have been described for pattern-based classification. Recently, Sitaram et al. (2007) have used pattern classification for the purpose of identifying left hand or right hand activity from NIRS using two approaches, support vector machines and hidden Markov model. In both cases of that work, the classification was performed off-line. Real-time implementations of these methods would be possible and perhaps required in adapting this approach to more complex functional tasks.

Currently, our scheme does not explicitly address motion-related artifacts. In this study, all subjects were highly cooperative and no motion artifacts were detected in post-processing examinations of the data. However, in general, motion artifacts will need to be addressed in generalizing this method to future work. It is likely that the Kalman filter, as implemented in this work, will be less sensitive to large motion errors, since a prior is used to describe the expected level of physiological variation and observation noise. Generally, motion artifacts are represented by large, abrupt changes in signal intensity as the optical probe moves relative to the subjects head and therefore are detected as outliers beyond the range of statistically likely fluctuations set by the observation and process noise matrices in the Kalman filter. Furthermore, the Kalman filter is based on a model prediction of the current measurement based on the history of the data. In this sense, a Kalman filter can be used to perform interpolation of missing data. If external measurements of motion were available, for example by using accelerometers to measure probe displacements or by defining a prior criterion for flagging large signal changes, these data points can in theory be excluded in real-time; allowing the Kalman filter to interpolate over short bad patches of data containing the motion artifact. These approaches will be examined in future work.

Conclusions

NIRS is a neuroimaging modality with appealing properties as a relatively cheap and compact fashion of obtaining functional brain images at a high temporal resolution. In this work, we have introduced and demonstrated a real-time algorithm for tracking functional brain signals using a multi-channel NIRS system. Our algorithm is based on an adaptive version of the general linear model. This model allows both single-trial and real-time tracking of brain signals and used extended Kalman filter. As a demonstration of this Kalman filtering approach, we have recorded NIRS signals during a left hand and right self-paced finger tapping and shown that our method is capable of tracking and classifying activation from the two tasks. In addition, we have incorporated methods to remove physiological artifacts due to cardiac, respiratory, and blood pressure changes. This approach has several advantages over previously described real-time analysis methods.

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Fig. 1. Schematic of real-time analysis process stream. Real-time data collection, analysis, and biofeedback were handled by three separate computers which networked via network communications. Each of the major components of this process is discussed in separate sections of this text.

Fig. 2.

Experimental setup and graphical interface for real-time studies. On the left of this figure is shown the optical probe geometry and subject orientation for the motor task study. The bilateral fiber optic probe was placed on the subject's head, while seated viewing the biofeedback monitor. In the panel on the right is shown our real-time display with data collected from subject B. Labels for the tapping epochs have been added for clarity. The time-course of oxy- (solid lines) and deoxy-hemoglobin (dotted lines) are shown for four optical source-detector pairs from the right motor cortex (upper right panel). The real-time interface displays the back-projection image of oxy- and deoxy-hemoglobin for the most current trial (in this case, a left-hand tapping trial is shown).

Fig. 3.

Region-of-interest time-courses of raw and Kalman filtered signals. In this figure is shown region-of-interest signals from the left and right motor cortices and the response to the two hand tapping conditions. In each plot, an entire 6 min data run is shown. The red line shows the raw (unfiltered) data as recorded by our system. The blue line shows the results of our Kalman filter. Finally, the black line shows the idealized result from a static estimate of the general linear model accounting for the different conditions. Labels for the right and left handed tapping are added for clarity.

Fig. 4.

Real-time classification of handedness. The linear classifier was used to estimate left versus right-handed tapping. In this figure, the results for a single data run is shown (subject B; same as Fig. 3). Correct (circle) and incorrect (cross) labeled data points are shown. Data points classified as right-handed are displayed on the bottom and left-handed are displayed on the top. During the experiment, the subject viewed an image similar to this figure (of course, without the correct/incorrect labels and marked “truth”) as shown in Fig. 1.

Fig. 5.

Spatial images of left and right motor activity. In this figure, we show back-projection images constructed from the post-hoc average of all left and right activations for the three subjects. In the top row, we show images reconstructed from the raw data prior to any filtering. The middle row shows that results from our adaptive estimator, which includes regressors to remove systemic fluctuations. The expected contralateral activations are seen for each subject. Finally, in the bottom row, the raw signals were processed using principal component analysis (Franceschini et al., 2006) to remove systemic effects to produce activation patterns closer to those observed using our Kalman estimator.

Fig. 6. Time courses of motor activation. In this figure, we show the region-of-interest time courses from the left (dotted line) and right (solid line) hemispheres. Oxy- (red), deoxy- (blue) and total- (green) hemoglobin traces are shown for each hemisphere, condition, and subject.

Table 1

Summary of results obtained from three subjects

	Subject A	Subject B	Subject C
Handedness	Left-handed	Right-handed	Right-handed
Trial 1	75%	100%	88%
Trial 2	88%	100%	75%
Trial 3	100%	88%	50%
Trial 4	63%	100%	75%
Trial 5	63%	—	—
Total	31 of 40 (77%)	30 of 32 (93.8%)	22 of 32 (68.8%)

Real-time classification of handedness. In this table is shown the percent-correct scores for our linear classifier in each run for each subject.

Table 2

Summary of error rates from the three subjects in Table 1

Detection error	Subject A	Subject B	Subject C
True/left	75%	87%	63%
False/left	20%	0%	25%
True/right	80%	100%	75%
False/right	25%	13%	37%

Classification errors. Summary of classification of handedness error rates from the three subjects in Table 1. True/left is indicated as the correct classification of a left-tapping episode. False/left is defined as an incorrect (right-hand) label predicted during left-hand tapping.