Using Real MEG and fMRI Data for Parameter Estimation of the Integrated Model

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Abstract: *An integrated model for magnetoencephalography (MEG) and functional Magnetic Resonance Imaging (fMRI) is proposed in this paper. In the model, the neural activity is related to the post synaptic potentials (PSPs) which are the common link between MEG and fMRI. Each PSP is modeled by the direction and strength of its current flow which are treated as random variables. The overall neural activity in each voxel is used for equivalent current dipole in MEG and as input of the extended Balloon model in fMRI. The parameters of the proposed integrated model are estimated using the real data. Good fitness of the real data with our model suggests that the proposed model is capable to generate simulation data similar to the real data.*

Keywords: MEG; fMRI; Integrated Model; Real Data

1 Introduction

For illustrating the relationship between magnetoencephalography (MEG) and functional Magnetic Resonance Imaging (fMRI), an integrated model is required. If this model is based on physiological facts, different experimental conditions can be simulated by changing parameters of this model. In addition, it can be used for evaluating proposed methods for integrated MEG and fMRI analysis. We introduce a model based on the physiological principles (Fig. 1). Post synaptic potentials (PSPs) and action potentials are two main indices for showing neural activities. It is assumed that both of MEG and fMRI are only related to the PSPs [1,2]. In the proposed model, PSPs are the main link between the MEG and fMRI signals. In a given external stimulus, a simple first order linear model represents the number of active PSPs at each time. Several parameters are introduced for each PSP whose variations in different neurons are modeled using random variables. Different aspects of excitatory post synaptic potentials (EPSPs) and inhibitory post synaptic potentials (IPSPs) (like their directions and strengths) are used for producing MEG and blood oxygen level dependent (BOLD) signals.

In the fMRI part of the model, we introduce a relationship between the strength of the PSPs with neural activity which is used as input of the extended Balloon model (EBM) [3] for producing the BOLD output. In the MEG part of the model, different spatial distributions and directions are considered for the EPSP and IPSP and equivalent current dipole (ECD) is calculated for each voxel using the vector sum of all active PSPs. A static Gaussian kernel is introduced for modeling the crosstalk from neural activities of the adjacent voxels in BOLD.

The parameters of the proposed model are estimated using real data. Both fMRI and MEG signals are acquired for the same auditory stimulus. After registration of the MEG and the fMRI to the 3D anatomical MRI data and several preprocessing on both signals, the parameters of the model are estimated by minimizing of the mean square error between the real and simulated data. Real data is properly fitted by our model, suggesting the ability of the proposed model for generating the real integrated fMRI/MEG data sets.

2 Proposed Integrated Model

The proposed model relates the MEG and fMRI signals in an active voxel of the brain (Fig. 1). The model is constructed based on the fact that PSPs are the main link between the two techniques. Since each voxel of the cortex contains a huge number of neurons and synapses whose activities are not deterministically known, we consider a stochastic model for PSPs so that each parameter (like direction and strength of PSP) has a probability density function (pdf). The MEG signal is produced according to both direction and strength of the PSPs. The BOLD only depends on

the overall strengths of PSPs, which is the input of the EBM for producing the BOLD signal. An overview of the physiological principles that lead to the proposed integrated model is presented in our previous work [4] which can be used for details of the following subsections.

2.1 PSP Production Mechanism

Block 1 in Fig. 1 implements the relationship between the external stimulus and the number of active PSPs. The number of active PSPs at each time point is considered as the output of a linear system whose input is the external stimulus:

$$\sum_{k=0}^{r} a_k \frac{d^k N(t)}{dt^k} = N_{ss}\, Stm(t - t_{af}) \quad (1)$$

where t_{af} is the delay due to different relay processes in the long afferent pathways. We use the first order linear model as the simplest linear model in our integrated model.

2.2 Constructing BOLD from PSPs

The first block of fMRI in the proposed model is "Crosstalk from Neural Activities of Adjacent Voxels" (see Fig. 1). Neural activities in a voxel change its blood flow and that of the neighboring voxels that we refer to it as spatial crosstalk in fMRI. The Gaussian spatial smoothing kernel is used for modeling the spatial crosstalk of BOLD signal in the proposed model. We consider the effective synaptic activities as:

$$u_e(r;t) = G(r;0,\sigma) *** u(r;t);\ \sigma = (\sigma_x, \sigma_y, \sigma_z) \quad (2)$$

where $u(r;t)$ is the synaptic activities in a voxel located at $r = (x,y,z)$, $G(r\ ;\ 0\ ,\ \sigma)$ is a 3D Gaussian kernel with zero mean and standard deviation σ and "$***$" shows 3D convolution.

In the proposed model, EBM is used as the main mechanism for relating PSPs (as the neural activity) to the BOLD. In the EBM, there is a set of nonlinear state space equations which relate the neural activity $u(t)$ to the BOLD. We will link PSPs to the EBM by introducing a relationship between PSPs and neural activity. The input to the EBM is the overall synaptic activity which is linearly related to regional cerebral blood flow. We eventually find a relationship between synaptic activity and PSPs.

Each PSP consumes a little energy and causes a small change in the blood flow. So it is logical to consider synaptic activity as the input of the EBM and proportional to the total consumed energy by the PSPs. The PSP voltage is modeled by multiplying a constant peak value ΔV and a normalized waveform $\varphi(t)$:

$$\varphi(t) = \frac{t}{\tau_{PSP}} e^{-\frac{(t-\tau_{PSP})}{\tau_{PSP}}} \quad (3)$$

$$V(t) = \Delta V \varphi(t) \quad (4)$$

where τ_{PSP} is time constant of $\varphi(t)$ and is considered as a random variable with truncated Gaussian distribution $\tau_{PSP} \sim TN(2,1;0,\infty)$ ms. The truncated Gaussian variable denoted by $x \sim TN(\mu,\sigma;a,b)$ is a variable whose probability for $x<a$ or $x>b$ is zero and its pdf is like the Gaussian distribution (except a scalar normalization) in the interval $x \in [a,b]$ with mean μ and standard deviation σ.

The consumed energy by PSP is found by:

$$E = \int_0^\infty V(t).I(t)dt \quad (5)$$

where $I(t)$ is post synaptic current. For simplicity, we use a constant value for $I(t)$ and according to (3)-(5) get:

$$E = I\tau_{PSP}\Delta V \quad (6)$$

If $N(t)$ PSPs fire at time t, the consumed energy for each of them is represented by (6). The neural activity should be proportional to the sum of the consumed energy. Therefore, the following equation relates the synaptic activity (or neural activity) $u(t)$ to the parameters of the PSPs:

$$\begin{cases} E = \sum_{k=1}^{N(t)} E_k = \sum_{k=1}^{N(t)} I\tau_{PSP}^k \Delta V_k \propto \sum_{k=1}^{N(t)} \tau_{PSP}^k \Delta V_k \\ u(t) \propto \sum_{k=1}^{N(t)} \tau_{PSP}^k \Delta V_k \end{cases} \quad (7)$$

2.3 Constructing MEG Signal from PSPs

From a distance, the PSP looks like a current dipole oriented along the dendrite. Approximately, the current dipole due to PSP is [1]:

$$\vec{q} = \frac{\pi}{4} d^2 \sigma_{in} \Delta V \cdot \vec{n} \quad (8)$$

$$\vec{q} = \beta \Delta V \cdot \vec{n} \quad , \quad \beta = \frac{\pi}{4} d^2 \sigma_{in} \quad (9)$$

where d is the diameter of the dendrite, σ_{in} is the intracellular conductivity per unit length, ΔV is change of voltage during PSP and $\vec{n}$ is the unit vector which shows current dipole orientation along the dendrite. We consider the direction of current dipoles (of PSP) as a random variable for modeling the different kinds of dendrite tree structures.

We define "reference vector" as a vector that is perpendicular to the cortical surface in each voxel. For the sake of simplicity, we assume cylindrical symmetry around the direction of the reference

vector and consider only one parameter for modeling the angle between the reference vector and direction of each current dipole in our model. This angle in our model is θ which is considered as a truncated Gaussian random variable whose pdf is $f_\Theta(\theta)$.

$$\begin{cases} f_\Theta(\theta) = \dfrac{e^{\frac{-\theta^2}{2\sigma^2}}}{k} \\ k = \sqrt{2\pi}\,\sigma\, erf(\dfrac{\pi}{\sqrt{2}\sigma}) \\ \sigma_T^2 = \sigma^2(1 - \dfrac{2\pi\sigma^2}{k} e^{\frac{-\pi^2}{2\sigma^2}}) \end{cases} ; -\pi < \theta \le \pi \quad (10)$$

where *erf*(.) is the error function and σ is the standard deviation of θ whose pdf is considered as a Gaussian. σ_T is the standard deviation of the truncated θ whose pdf, $f_\Theta(\theta)$, is a truncated Gaussian. σ can get any positive value.

If N PSPs of the pyramidal cells fire at time t, then the ECD from the sum of their activities is:

$$\vec{q}(t) = \sum_{k=1}^{N} w_k \beta_k \Delta V_k \varphi_k(t) \cdot \vec{n}_k \quad (11)$$

where w_k is +1 for EPSP and -1 for IPSP, ΔV_k shows peak of kth PSP, β_k is a coefficient according to (9) that models parameters of the kth synapse and its neighboring dendrite and $\varphi_k(t)$ is unitary peak waveform for the kth PSP at time t according to (3). The number of pyramidal PSPs in a voxel that start to fire at time t is considered as $N(t)$. Due to the sample rate of 508.63 Hz in MEG data, we consider sampling time of 1.97 ms for $N(t)$. The ECD in a voxel is derived from (11):

$$\vec{Q}(t) = \sum_{d=0}^{D} \sum_{k=1}^{N(t-d)} w_k \beta_k \Delta V_k \varphi_k(t+d) \cdot \vec{n}_k \quad (12)$$

where $\varphi_k(t+d)$ is the waveform of the kth PSP whose activation started at previous d sample time and D is the maximum duration of PSP which we set as approximately D=30 ms according to the maximum value of τ_{PSP} in (3). The projections of $\vec{Q}(t)$ onto two normal vectors can be found as:

$$\begin{cases} \vec{Q}(t) = Q_p(t)\vec{n}_p + Q_n(t)\vec{n}_n \\ Q_p(t) = \sum_{d=0}^{D} \sum_{k=1}^{N(t-d)} w_k \beta_k \Delta V_k \varphi_k(t+d) \cos(\theta_k) \\ Q_n(t) = \sum_{d=0}^{D} \sum_{k=1}^{N(t-d)} w_k \beta_k \Delta V_k \varphi_k(t+d) \sin(\theta_k) \end{cases} \quad (13)$$

where n_p is the unit vector parallel to the reference vector and n_n is the unit vector orthogonal to it.

The "Lead Field from Forward Problem" is the final part of the MEG modeling in Fig. 1. After choosing a head model (spherical approximation or realistic head model), following matrix equation relates the measured magnetic field and ECDs in voxels of the brain:

$$B(t) = L(\vec{r}_Q)\,\vec{Q}(t) \quad (14)$$

where $\vec{Q}(t)$ is ECDs in region of interest in the brain, L is lead field matrix and $B(t)$ is measured field by sensors.

2.4 Relationship between MEG and fMRI

If all random variables in (13) are considered independent, the mean value of ECD is:

$$\begin{cases} \bar{\vec{Q}}(t) = \{\sum_{d=0}^{D} \sum_{k=1}^{N(t)} E[w_k] E[\beta_k] E[\Delta V_k] E[\varphi_k(d)] E[\cos(\theta_k)]\} \cdot \vec{n}_p \\ \bar{\vec{Q}}(t) = \bar{Q}(t).\vec{n}_p \end{cases} \quad (15)$$

$$\bar{Q}(t) = \bar{\varphi}\,\bar{V}\,\bar{\beta}\,[\,(1-r)\,g(\sigma_T^E) - r\,g(\sigma_T^I)\,]N(t) = K_M N(t) \quad (16)$$

where E[.] is "expected value", r is the mean value of IPSP ratio, $\bar{V}$ is mean amplitude of PSP, $\bar{\beta}$ is mean of β according to (9), $\bar{\varphi} = \sum_{d=0}^{D} E[\varphi_k(d)]$ according to $\varphi(t)$ in (3), $g(\sigma_T^E)$ and $g(\sigma_T^I)$ show the average effects of the projected ECD onto the reference vector for EPSP and IPSP respectively. The second term of (13) vanishes in averaging because of the odd property of sine function and even property of the pdf of θ. The function $g(\sigma_T)$ is the expected value of $cos(\theta)$ with respect to the truncated θ and is defined by:

$$\begin{cases} g(\sigma_T) = \int_{-\pi}^{\pi} \cos(\theta) f_\Theta(\theta) d\theta \\ \sigma_T^2 = \sigma^2(1 - \dfrac{2\pi\sigma^2}{k} e^{\frac{-\pi^2}{2\sigma^2}}) \end{cases} \quad (17)$$

where σ_T is standard deviation of the truncated θ and $f_\Theta(\theta)$ is the truncated Gaussian distribution defined in (10). The K_M in (16) is only related to the physiological parameters in a voxel that are independent of the external stimulus and we'll estimate it by using the real MEG data.

According to the relationship between the synaptic activities as the input of EBM and the PSPs in (7):

$$\begin{cases} \bar{u}(t) \propto E[\sum_{k=1}^{N(t)} \Delta V_k] \\ \bar{u}(t) \propto N(t)\bar{\tau}_{PSP}\bar{V}k_{pyramidal} \;\Rightarrow\; \bar{u}(t) \propto N(t) \end{cases} \quad (18)$$

where $N(t)$ represents the number of active pyramidal cells and $k_{pyramidal}$ shows the effect of non-pyramidal cells (which is silent for MEG) in

the synaptic activity, which is approximately constant for each voxel [4]. Instead of the proportionality (18), we consider its equality form, considering the proportional gain in the "neuronal efficacy ε" in the EBM. Considering (16) and (18), we get:

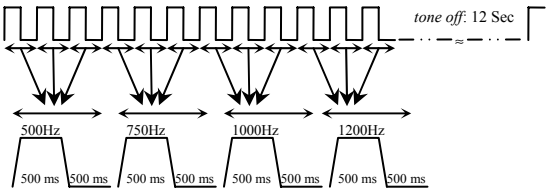
$$\begin{cases} \overline{Q}(t) = K_M N(t) \\ \text{BOLD}(t) = \text{Extende Balloon Model}\big(N(t)\big) \end{cases} \quad (19)$$

According to (19), the nonlinear relationship between ECD and BOLD segregates into two parts: a linear relation between ECD and $N(t)$ and a nonlinear relation between BOLD and $N(t)$ as a result of the nonlinearity of the EBM.

3 Model Parameter Estimation

3.1 Auditory Task Data

Parameters of the proposed model are estimated with real data of auditory block design in a healthy male subject. Each block consists 12 seconds of *tones on* followed by 12 seconds of *tones off*. During the *tones on* period, 3 tone bursts presented with a 15 ms rise/fall time at a rate of one per second for each of 4 tone frequencies 500Hz, 750 Hz, 1000 Hz and 1200 Hz:



The MEG data was measured by the 148 channel whole head Neuromagnetometer (4D Neuroimaging). 50 blocks (epochs) of MEG data were acquired and sampled at 508.63 Hz and initially band-pass filtered 0.1-100 Hz before disk storage. The heart artifact was removed and data were further band-pass filtered 0.5 to 50 Hz before analysis. The 78th sensor has most significant signal between all sensors. The average signal of this sensor is illustrated in Fig. 2-a. We use ICA on raw data as the next preprocessing stage after removing the nuisance channels, and then the ICA components were averaged over time for all blocks. The stimulus correlated component of ICA after time averaging is illustrated in Fig. 2-b. The contour map of this component in all sensors is illustrated in Fig. 3.

The resolution of the 3-D anatomical MRI data is 256x256x66 voxels where the voxel size is 0.9375x0.9375x2.5 mm. The head digitization points are used to ensure a precise registration, when the points lay on the scalp surface of the MRI scan. For fMRI studies, we used the GE product echo planner imaging (EPI) sequence with 64 by 64 data acquisition matrix, TE of 30 ms, TR of 2 s, field of view 240 mm and slice thickness of 5 mm. Each volume contains 16 slices. After discarding initial time-series, 16 block sequences of the fMRI data were acquired using the same stimulus block paradigm as employed in acquiring the MEG data. The motion correction is done by using the SPM and then the linear drift was removed from the data. We use the t-test for activation detection and assume a simple linear model for hemodynamic response function. The SPM is used for registration of the detected activation in the fMRI slices to the 3D anatomical MRI data.

3.2 MEG Parameters Estimation

After registration of the MEG coordinate with the 3D anatomical MRI data, the cortical model is constructed which consists 2734 cortical location in the subject gray matter. We use only the main component of ICA for activation detection in MEG, thus the waveforms of all sensors are similar to this component and difference between them is restricted to different scalar gains. The common waveform of all sensors and the spatial distribution of the scalar gains are illustrated in Figs. 2-b and 3 respectively.

The Multi-Resolution FOCUSS (MR-FOCUSS) [5] is used for solving the inverse problem for activation detection in MEG. Whereas the relationship between the dipoles and the measured field in the sensors is linear in the MR-FOCUSS, thus the waveforms of the activation in all cortical voxels are similar to the waveform of the main component of ICA and difference between them are the magnitude and the direction of the current dipole in each voxel. According to (16), the spatial and temporal parts of ECD in each voxel can be separated to the two parts: K_M and $N(t)$. $N(t)$ can be assumed proportional to the waveform of the main component of ICA. Moreover, K_M in each voxel is the magnitude of the dipole which is calculated by the inverse solution of the scalar map in Fig. 3. Fig. 4 illustrates map of K_M in different cortical voxels.

We estimate the parameters of the linear filter in (1) by using the stimulus profile in Fig. 2-c and assuming $N(t)$ as the main component of ICA. The first order approximation of the linear filter is used in our proposed model whose parameters are t_{af} and an exponential decay $\tau = a_1/a_0$. For estimating

these parameters, we use the *fminsearch* function of the MATLAB which is an iterative method for finding the local minimum of the error between $N(t)$ and its estimation. The estimated values are τ=395 ms and t_{af}=0 ms. The $N(t)$ and its estimation are illustrated in Fig. 2-d.

3.3 fMRI Parameters Estimation

The parameters of the proposed model which is related to fMRI are two sets: parameters related to the spatial crosstalk in (2) and parameters of the EBM in (19). At First, we estimate the parameters which are related to the spatial crosstalk. Fig. 5 illustrates the detected activation from the fMRI time series after removing the single active voxels and Fig. 6 illustrates the registration of the Fig. 5 to the 3D anatomical data. For estimating $\sigma = (\sigma_x, \sigma_y, \sigma_z)$ in (2), the Gaussian kernel is fitted to the detected activation in a region with maximum activation in 6th, 7th and 8th slice of the fMRI volume in Fig. 5. The hotspot of the active region is assumed as the center of the Gaussian kernel. All voxels neighboring the central voxels in a sphere with diameter of 25 mm are considered for curve fitting. The standard deviation of the estimated Gaussian kernel is $(\sigma_x, \sigma_y, \sigma_z) = (7.5, 7.5, 5.5)$ mm.

For estimating the parameters of the EBM, we select 14 voxels which contain maximum activation in both hemispheres. As we imply in the above paragraph, these voxels lay in 6th, 7th and 8th slice of the fMRI volume in Fig. 5. For each voxel, the average of its time series over 16 blocks is calculated and used for estimating the parameters of the EBM in the voxel. The parameters of the EBM are: $\varepsilon, \tau_s, \tau_f, \tau_0, \alpha, E_0$.

According to (19), we use the estimated $N(t)$ as synaptic activity input of the EBM which is illustrated in Fig. 7-a. For estimating the 6 unknown parameters of the EBM in each voxel, we start with a proper initial estimation of the parameters, and then we use the *fminsearch* function of MTLAB for finding the local minimum of the mean square error (MSE) between estimated and real BOLD signal in the voxel. For calculating the MSE in each iterations of the *fminsearch* function, the values of 6 parameters in previous iteration are used for solving the nonlinear differential equations of the EBM by using the SIMULINK toolbox of MATLAB. Figs. 7-b, 7-c and 7-d illustrate the real and the estimated BOLD signals of the three active slices where for each slice the average BOLD responses of all active voxels in the slice are considered. We estimate the parameters of the EBM in all 14 active voxels whose histograms are illustrated in Fig. 8.

4 Conclusion

The purpose of this paper is to present an integrated MEG and fMRI model (Fig. 1) and estimate its parameters using real data. In the model, the neural activity is related to the PSPs which is common link between MEG and fMRI. Each PSP is modeled by the direction and strength of its current flow which are treated as random variables. The overall neural activity in each voxel is used for equivalent current dipole in MEG and as input of extended Balloon model in fMRI. The parameters of the proposed model are estimated by using real data. Both fMRI and MEG signals are acquired for same auditory stimulus. After registration of the MEG and the fMRI to the 3D anatomical MRI data and several preprocessing on both signals, the parameters of the model are estimated by minimizing of the mean square error between real and generated data. Good fitness of the real data with our model suggests the ability of the proposed model for simulating the real integrated fMRI/MEG data sets.

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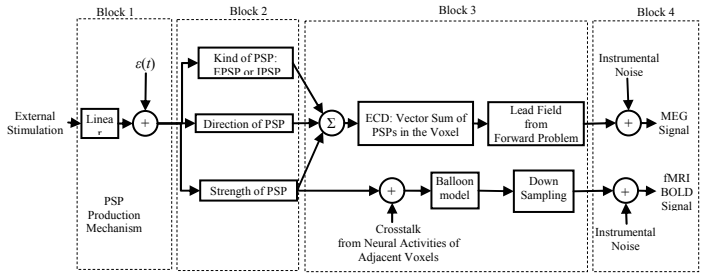

Fig. 1. Schematic Diagram for the proposed integrated MEG and fMRI model.

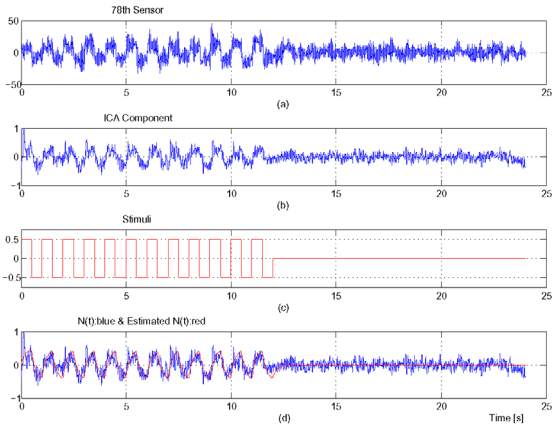

Fig. 2. Illustration of the averaged MEG data and estimation of the number of the active PSPs ($N(t)$). (a) Average MEG data over 50 blocks in 78th sensor. (b) The main component of ICA. (c) Stimulus profile. (d) The $N(t)$ (blue plot) and its estimation (red plot).

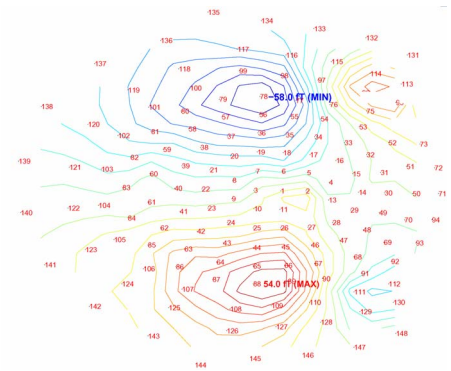

Fig. 3. Contour map of the main component of ICA.

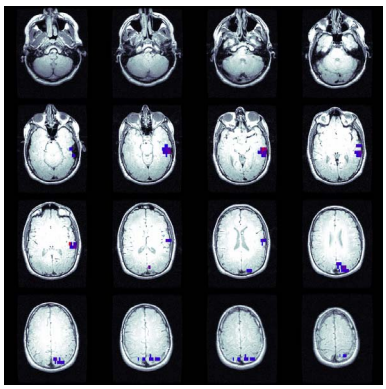

Fig. 4. Illustration of the detected activation of the MEG data after registration to the 3D anatomical MRI data.

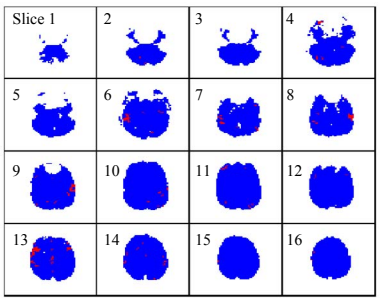

Fig. 5. Illustration of the detected activation from the fMRI time series.

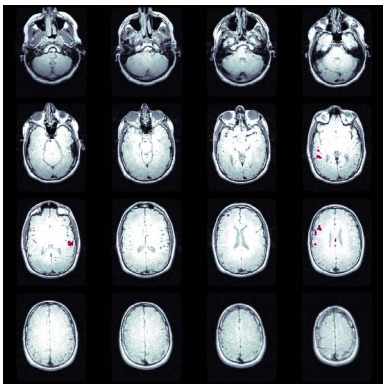

Fig. 6. Illustration of the detected activation from the fMRI time series after registration of the detected activation in Fig. 5 to the 3D anatomical data.

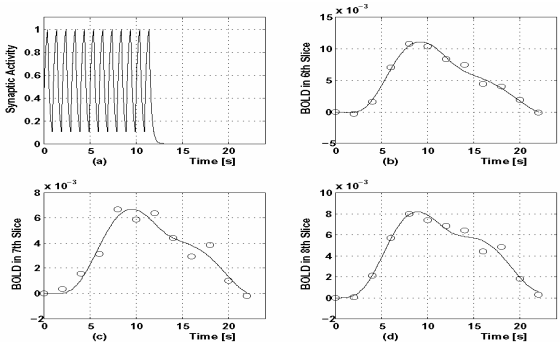

Fig.7. Illustration of the number of active PSPs ($N(t)$), real and estimated BOLD responses. (a) Estimated $N(t)$ as input of the EBM. (b) Illustration of the real (-o- plot) and the estimated BOLD signals of the 6th slice of Fig. 5 where the average BOLD responses of all active voxels in this slice are considered. (c) Same as (b) for 7th slice of Fig. 5. (d) Same as (b) for 8th slice of Fig. 5.

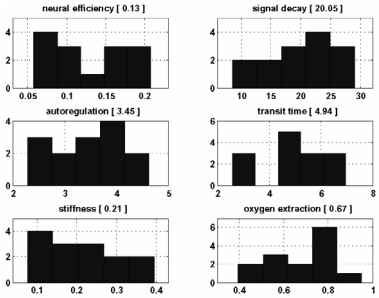

Fig. 8. Illustration of the histogram of the estimated EBM parameters in 14 active voxels.