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Optimization Strategies for Evaluation of Brain Hemodynamic Parameters with qBOLD Technique

Xiaoqi Wang¹, Alexander L. Sukstanskii², and Dmitriy A. Yablonskiy^{2,1}

¹Department of Physics, Washington University in St Louis, One Brookings Drive, Saint Louis, MO 63130, USA

²Department of Radiology, Washington University in St Louis, One Brookings Drive, Saint Louis, MO 63130, USA

Abstract

qBOLD (quantitative Blood Oxygenation Level Depend) technique provides an MRI-based method to measure tissue hemodynamic parameters such as oxygen extraction fraction (OEF) and deoxyhemoglobin-containing (veins and pre-venous part of capillaries) cerebral blood volume fraction (dCBV). It is based on a theory of MR signal dephasing in the presence of blood vessel network and experimental method – Gradient Echo Sampling of Spin Echo (GESSE) previously proposed and validated on phantoms and animals. In vivo human studies also demonstrated feasibility of this approach but also recognized that obtaining reliable results requires high SNR in the data. In the present paper, we analyze in detail the uncertainties of the qBOLD parameter estimates in the framework of the Bayesian probability theory, namely, we examine how the estimated parameters OEF and dCBV depend on their “true values”, signal-to-noise ratio, and data sampling strategies. Based on this analysis we develop strategies for optimization of the qBOLD technique for dCBV and OEF evaluation. In particular, it is demonstrated that the use of GESSE sequence allows substantial decrease of measurement errors as the data are acquired on both sides of spin echo. We test our theory on phantom mimicking the structure of blood vessel network. A 3D GESSE pulse sequence is used for the acquisition of the MRI signal that was subsequently analyzed by Bayesian Application Software. The experimental results demonstrated a good agreement with theoretical predictions.

1. Introduction

Quantitative evaluation of brain hemodynamics, particularly the relationship between brain function and oxygen utilization, is important for understanding normal human brain operation (1) as well as understanding the pathophysiology of disorders such as stroke (2), Alzheimer’s disease (3,4), Huntington’s disease, Parkinson’s disease (5,6) and other neurological disorders. It can also be of great importance for evaluation of hypoxia within tumors of the brain and other organs (7,8). Currently, clinically accepted methods for measuring oxygen extraction fraction (OEF) – one of the main parameters characterizing brain hemodynamics – rely on PET techniques (e.g., (9)). However, the presence of ionizing radiation, low spatial resolution, and rather restricted availability inhibit broad application of PET-based methods in human research and clinical practice.

A fundamental discovery by Ogawa and co-workers (10) of the BOLD (Blood Oxygenation Level Dependent) contrast opened a possibility to use this effect to study brain

hemodynamic properties by means of MRI measurements. The most widely used application of BOLD contrast is based on studying dynamic properties of brain during functional stimulation, i.e. fMRI (functional MRI) (11–14). However, BOLD effect can also be used to studying brain hemodynamic in a resting (baseline) state because, despite variable blood flow and activity amongst brain regions, a long-standing observation is that in healthy human subjects OEF, on average, is remarkably constant across the brain in the resting state (15) and can be used as the primary index of brain function (15,16).

Quantitative BOLD (qBOLD) approach, that we have previously proposed and validated on phantoms (17) and in vivo rodent studies (18), is based on a mathematical model of BOLD contrast (19) and allows mapping of hemodynamic parameters, such as OEF and deoxygenated cerebral blood volume (dCBV). In vivo human studies (20–24) also demonstrated feasibility of this approach. At the same time experiments demonstrated that obtaining reliable results requires relatively high SNR in the data (17,21,23,25). In the present paper, we analyze in detail the uncertainties of the qBOLD parameter estimates in the framework of the Bayesian probability theory (e.g., (26,27)), namely, we examine how the estimated parameters OEF and dCBV depend on their “true values”, signal-to-noise ratio (*SNR*), and data sampling strategies. Based on this analysis we provide recommendations on optimization of the qBOLD technique for dCBV and OEF evaluation. We further validate our theoretical conclusions on experimental phantom studies.

2. Theoretical model of BOLD signal

First we briefly outline theoretical background behind the qBOLD technique. According to the model proposed in (19), the extravascular FID signal in the presence of mesoscopic magnetic field inhomogeneities induced by blood vessel network can be presented in the form:

$$S(t) = S_0 \cdot \exp[-\zeta \cdot f(t/t_c) - R_2 t] \quad [1]$$

where zero time t corresponds to the position of RF excitation pulse, S_0 is the initial signal amplitude, $R_2 = 1/T_2$ describes a T_2 -relaxation, $\zeta = \text{dCBV}$ is the deoxyhemoglobin-containing part of blood vessels (veins and pre-venous part of capillaries) cerebral blood volume fraction which should be distinct from the total cerebral blood volume (CBV) defined by other modalities, like PET. The characteristic dephasing time t_c is (19)

$$t_c^{-1} = \gamma \cdot \frac{4\pi}{3} \cdot \chi \cdot B_0 \quad [2]$$

where B_0 is the external magnetic field, γ is gyromagnetic ratio, and χ represents susceptibility difference between deoxygenated blood and surrounding tissue. This parameter can be related to the blood oxygenation level Y ($Y=1$ for fully oxygenated blood and $Y=0$ for fully deoxygenated blood), blood hematocrit, H_{cb} and susceptibility difference between completely deoxygenated and completely oxygenated red blood cells, $\Delta\chi_0 = 0.264$ ppm (28) according to equation

$$\chi = \Delta\chi_0 \cdot H_{cb}(1-Y) \quad [3]$$

Hence, measuring χ we can estimate blood oxygenation level and finally *OEF*:

$$OEF = 1 - Y/Y_a \quad [4]$$

where Y_a is oxygenation level of arterial blood (under normal condition Y_a is very close to unity). The function $f(t/t_c)$ in Eq. [1] depends on an orientation distribution of blood vessels in the brain tissue; for uniformly distributed and randomly oriented vessels, this function is given by (19)

$$f(t/t_c) = \int_0^1 du \frac{(2+u)\sqrt{1-u}}{3u^2} \left[1 - J_0\left(\frac{3u}{2} \cdot \frac{t}{t_c}\right) \right] \quad [5]$$

where J_0 is a Bessel function. The function $f(t/t_c)$ can also be represented using a generalized hypergeometric function ${}_1F_2$ (29):

$$f(t/t_c) = {}_1F_2\left(\left\{-\frac{1}{2}\right\}; \left\{\frac{3}{4}, \frac{5}{4}\right\}; -\frac{9}{16} \cdot \left(\frac{t}{t_c}\right)^2\right) - 1 \quad [6]$$

In the short-time and long-time regimes, the function $f(t/t_c)$ depends on its argument quadratically and linear, respectively:

$$f(t/t_c) = \begin{cases} 0.3 \cdot (t/t_c)^2, & t/t_c \ll 1 \\ |t|/t_c - 1, & |t|/t_c \gg 1 \end{cases} \quad [7]$$

The linear behavior of the function $f(t/t_c)$ at large argument leads to a mono-exponential time dependence of the signal:

$$S(t) = S_0 \cdot \exp(\zeta) \cdot \exp(-R_2^* t), \quad t \gg t_c; \quad [8]$$

$$R_2^* = R_2 + R_2', \quad R_2' = \frac{4\pi}{3} \cdot \gamma \cdot \zeta \cdot \chi \cdot B_0.$$

Importantly, the volume fraction ζ and the susceptibility difference χ appear in Eq. [8] only as a product, hence to resolve these two parameters, measurement interval should include short time regime $t < t_c$ (17) where parameters ζ and χ decouple because the function $f(t/t_c)$ exhibits a quadratic time dependence, Eq. [7].

Since the short time interval is important for decoupling of parameters ζ and χ , it was proposed in (17) to use GESSE (gradient echo sampling of spin echo) approach when MR signal is sampled around Spin Echo (SE) which practically doubles the short time interval as compared to the Free Induction Decay (FID) experiment. The expression for MR signal around SE is similar to the Eq. [1] with S_0 being MR signal amplitude at SE and time t counting from SE, being negative before SE. For our theoretical analysis we will use the following equation for MR signal:

$$S(t) = S_0 \cdot \exp\left[-\zeta \cdot (f(t/t_c) - t/t_c) - R_2^* \cdot t\right] \quad [9]$$

where parameter R_2^* is defined by Eq. [8] and parameter t_c by Eq. [2]. The measurements for sufficiently long time $t \gg t_c$ result in a very accurate estimate of the parameter R_2^* . That is why it is more convenient to modify the expression for the signal in Eq. [1] by introducing R_2^* instead of R_2 as in Eq. [9].

3. Bayesian approach

The basic quantity in Bayesian approach to parameters estimates is the joint posterior probability, $P(\{p_j\}|D\sigma I)$, for the model parameters $\{p_j\}$ given all of the data D , the prior information I and the standard deviation of the prior probability of the noise, σ . The model parameters that we will consider are

$$\{p_j\} = \{S_0, \zeta, \chi, R_2^*\} \quad [10]$$

as defined by Eq.[9] (we use parameter χ as independent parameter instead of t_c as they are directly related by Eq. [2]). In a high signal-to-noise approximation, the joint posterior probability can be represented in the form (26,30):

$$P(\{p_j\}|D\sigma I) \propto \exp\left(-\frac{Q}{2\sigma^2}\right) \quad [11]$$

where

$$Q = \sum_{n=0}^{N-1} [D(t_n) - \hat{S}(t_n)]^2 \quad [12]$$

Here the function $\hat{S}(t_n)$ represents our model in Eq. [9] with true parameters $\{\hat{p}_j\}$ (the values that would correspond to the “noiseless” signal) and the signal is described in terms of Eq. [9]: $D(t_n) = S(t_n, \{p_j\})$ with parameters $\{p_j\}$ that differ from the true parameters $\{\hat{p}_j\}$ due to the presence of the noise in the acquired signal: $p_j = \hat{p}_j + \delta p_j$. The sum in Eq. [12] is over the N evenly spaced time points $t_n = T_0 + n \cdot \delta t$, $n = 0, 1, \dots, N-1$, where T_0 is initial sampling point. Generally speaking, our analysis can be performed for an arbitrary spacing between time points (e.g., irregularly spaced, repeated values, etc.) however, in what follows, we restrict ourselves to the evenly spaced set only.

The marginal posterior probability, represented symbolically as $P(p_j|D\sigma I)$, for each of the parameter p_j can be obtained by integrating the joint posterior probability distribution $P(\{p_j\}|D\sigma I)$ over all other parameters:

$$P(p_j|D\sigma I) \propto \iint \left(\prod_{i \neq j} dp_i \right) P(\{p_j\}|D\sigma I) \propto \iint \left(\prod_{i \neq j} dp_i \right) \exp\left(-\frac{Q}{2\sigma^2}\right). \quad [13]$$

Generally, the probability distributions $P(p_j|D\sigma I)$ may have a rather complicated structure, however, in the case of high signal-to-noise ratio, the problem can be substantially simplified because the integrand in Eq. [13] has a sharp maximum with respect to all the arguments and the integrations in Eq. [13] can therefore be carried over in the Laplace approximation. Expanding the signal $D(t)$ as a function of the parameters $\{p_j\}$ about their true values $\{\hat{p}_j\}$,

$$D(t_n) = \hat{S}(t_n) + \sum_{j=1}^M S_{j(t_n)} \cdot \delta p_j + O((\delta p_j)^2), \quad S_{j(t_n)} = \left(\frac{\partial S}{\partial p_j} \right)_{p_j = \hat{p}_j} \quad [14]$$

(M is a number of model parameters; in our case, $M = 4$), the function Q can be written as a symmetric and positively defined quadratic form with respect to δp_j :

$$Q = \sum_{i,j=1}^M C_{ij} \delta p_i \delta p_j \quad [15]$$

where the coefficients C_{ij} are elements of the variance-covariance matrix $\mathbf{C}$,

$$C_{ij} = \sum_{n=0}^{N-1} S_i(t_n) S_j(t_n) \quad [16]$$

As the function Q in Eq. [15] has the quadratic form, the integration in Eq. [13] can be readily achieved resulting in the marginal posterior probability distribution for the parameters p_j in the Gaussian form:

$$P(p_j | D, \sigma, I) \propto \exp \left(-\frac{(p_j - \widehat{p}_j)^2}{2\sigma_j^2} \right) \quad [17]$$

where

$$\sigma_j = \sigma \cdot \left(\frac{\Delta_{jj}}{\Delta} \right)^{1/2} \quad [18]$$

Here Δ is the determinant of the variance-covariance matrix $\mathbf{C}$, and Δ_{jj} are the minors of this matrix corresponding to the diagonal elements jj . The quantity σ_j being the width of the distribution corresponding to the parameter p_j determines the uncertainty of this parameter, and the estimated values of p_j take the form

$$(p_j)_{est} = \widehat{p}_j \pm \sigma_j = \widehat{p}_j \cdot (1 \pm \varepsilon_j), \quad \varepsilon_j = \sigma_j / \widehat{p}_j \quad [19]$$

In what follows, we will analyze how the uncertainties $\{\sigma_j\} = \{\sigma_{s_0}, \sigma_\zeta, \sigma_\chi, \sigma_{R_2^*}\}$, Eq. [18] (or the relative errors ε_j , Eq. [19]) depend on the acquisition parameters δt , N , T_0 and true values of the model parameters $\hat{S}_0$, $\hat{\zeta}$, $\hat{\chi}$, $\hat{R}_2^*$. Analytical calculation of these dependencies is not possible due to complicated structure of underlying equations. Herein we will derive some general scaling relationships and provide numerical calculations for typical parameters.

It is easy to verify that the uncertainties σ_j are inversely proportional to $SNR = \hat{S}_0 / \sigma$. It is also important to note that the dimensionless errors ε_j can depend only on the dimensionless ratios of time variables, not on time variables themselves. There are 5 time parameters in our problem: the time interval between measurements δt (sampling interval), the characteristic dephasing time $\hat{t}_c$, the relaxation time $\hat{T}_2 = 1/\hat{R}_2$, the starting measurement time T_0 (with respect to SE position), and the final measurement time after SE T (the parameter $\hat{R}_2^*$ entering the matrix $\mathbf{C}$ is determined as $\hat{R}_2 + \hat{\zeta}/\hat{t}_c$). We will choose the following set of four independent dimensionless time parameters:

$$\widehat{R}_2 \widehat{t}_c = \widehat{t}_c / T_2, \quad T_0 / \widehat{t}_c, \quad T / \widehat{t}_c, \quad \delta t / \widehat{t}_c \quad [20]$$

Thus, the relative errors ε_j in Eq. [19] can be presented as functions of these four dimensionless parameters and SNR :

$$\varepsilon_j = \frac{1}{SNR} \cdot U_j \left(\zeta, R_2 t_c; \frac{T_0}{t_c}, \frac{T}{t_c}, \frac{\delta t}{t_c} \right) \quad [21]$$

For brevity, the caps marking true values of the parameters in the arguments of the functions U_j are omitted hereafter.

It should be noted that the noise intensity in the signal, σ , is known to be proportional to the square root of signal acquisition bandwidth, hence inversely proportional to δt .

Consequently, the prior probability of the noise $\sigma \propto 1/\sqrt{\delta t}$, and $SNR \propto \sqrt{\delta t}$. Thus, it is convenient to present the relative errors ε_j in a standardized form:

$$\varepsilon_j = \frac{1}{SNR_0} \cdot \left(\frac{t_c}{\delta t} \right)^{1/2} \cdot U_j \left(\zeta, R_2 t_c; \frac{T_0}{t_c}, \frac{T}{t_c}, \frac{\delta t}{t_c} \right), \quad [22]$$

where SNR_0 is a hypothetical SNR that would correspond to SNR of the MR signal at SE time TE with a sampling time interval $\delta t = t_c$.

4. Theoretical Results

Equations [18]–[22] derived above allow analyzing the dependences of relative errors on the parameters of GESSE sequence (T_0 , T , δt), system/tissue (ζ , t_c , R_2) and SNR .

4.1. Dependence on the sampling time interval δt

Figure 1 shows that the relative errors ε_ζ and ε_χ depend on δt non-monotonically. The relative error for the parameter R_2^* is much smaller than for the two other parameters and is practically independent of δt . Such a behavior of the relative errors is due to the specific structure of the signal in Eq. [9]. For short values of δt , the ratios Δ_{jj}/Δ in the right-hand side of Eq. [18] increase slower than δt , and therefore the errors in Eq. [22] decrease therefore as δt increasing. If, however, $\delta t > 1.5 t_c$, the second time point (at $t = \delta t$) is located within the time interval where the signal is mono-exponential with time (recall that $1.5 t_c$ represents a time when signal behavior changes from quadratic to linear regime (19)) and the volume fraction ζ and the susceptibility difference χ enter the signal only as a product and cannot be resolved separately. That is why the corresponding errors substantially increase with δt increases. Hence, the relative errors as functions of δt have minima at certain intermediate values of δt , as illustrated in Figure 1.

The position of the minima of two curves, shown in Figure 1 for $T = 10 t_c$, are around $\delta t/t_c \sim 1$; for longer total time T , these positions are shifted towards $\delta t/t_c \sim 1.5$. These positions provide the optimal choice of time step for determining the parameters ζ and χ in the framework of the qBOLD method. The minima are rather shallow, therefore in what follows, we will calculate all the errors for $\delta t = t_c$.

4.2. Dependence on the volume fraction ζ

The volume fraction ζ enters the elements of the variance-covariance matrix $\mathbf{C}$ in two ways: (i) in exponents (as in Eq. [9]) and (ii) as a factor. An analysis of the minors Δ_{jj} and determinant Δ entering the right-hand-side of Eq. [18] demonstrates that for the model under consideration, Eq. [9], the uncertainties $\delta\zeta$ and δR_2^* depend on ζ only in exponents. As a result, for small values of ζ , these uncertainties only weakly depend on ζ whereas the

uncertainty of susceptibility difference $\delta\chi$ contains $1/\zeta$ as a factor and, consequently, strongly depends on this parameter. Thus, the relative errors ε_ζ and ε_χ are proportional to $1/\zeta$, while $\varepsilon_{R_2^*}$ is practically independent of ζ . This feature is illustrated in Figure 2, where the relative errors are plotted as functions of $1/\zeta$ (note that the parameter R_2^* can be measured extremely accurately by sampling data at the mono-exponential part of the signal ($t > 1.5t_c$, see Eq. [8]). Hence the relative error for this parameter ($\varepsilon_{R_2^*} \sim 0.004$ in Figure 2) is much smaller than for two other parameters.

Thus, the volume fraction can be excluded from the arguments of the functions U_j in the right-hand side of Eq. [21], and the relative errors of the parameters can be presented in the form:

$$\varepsilon_\zeta = \frac{1}{\text{SNR}_0} \cdot \left(\frac{t_c}{\delta t}\right)^{1/2} \cdot \frac{1}{\zeta} \cdot F_\zeta\left(R_2 t_c; \frac{T_0}{t_c}, \frac{T}{t_c}, \frac{\delta t}{t_c}\right), \quad \zeta \ll 1 \quad [23]$$

$$\varepsilon_\chi = \frac{1}{\text{SNR}_0} \cdot \left(\frac{t_c}{\delta t}\right)^{1/2} \cdot \frac{1}{\zeta} \cdot F_\chi\left(R_2 t_c; \frac{T_0}{t_c}, \frac{T}{t_c}, \frac{\delta t}{t_c}\right), \quad \zeta \ll 1 \quad [24]$$

$$\varepsilon_{R_2^*} = \frac{1}{\text{SNR}_0} \cdot \left(\frac{t_c}{\delta t}\right)^{1/2} \cdot F_{R_2^*}\left(R_2 t_c; \frac{T_0}{t_c}, \frac{T}{t_c}, \frac{\delta t}{t_c}\right), \quad \zeta \ll 1 \quad [25]$$

where the functions F_ζ , F_χ and $F_{R_2^*}$ are practically independent of ζ .

Note a similarity between our result for the uncertainty of the volume fraction, σ_ζ obtained here in the framework of the Bayesian analysis, and the approximate expression for σ_ζ obtained in (17) in the framework of the error propagation law,

$$\delta\zeta = \frac{1}{\text{SNR}} \cdot \left[1 + R_2^* \delta t \cdot E(R_2^* T)\right]^{1/2} \quad [26]$$

$$E(x) = \frac{1}{x^4} \left[(2x^2 - 6x + 9)\exp(2x) - (8x^2 + 12x + 9)\right]$$

Both the expressions provide rather close estimates for the uncertainty σ_ζ and demonstrate only a marginal dependence on the parameter ζ itself.

4.3. Dependence on R_2

Figure 3a demonstrates the dependences of the relative errors ε_ζ and ε_χ on the parameter R_2 (solid lines). It should be noted that the parameter R_2 is not related to the mesoscopic magnetic field inhomogeneities we are targeting in the present study, and can be found from independent studies. In this case, R_2 can be considered as a fixed number, and the number of fitting parameters reduces to 3. One should expect that this would lead to decreased uncertainties, as demonstrated in Figure 3a by the dashed lines. Note that the corresponding line for the relative error ε_ζ practically coincides with the solid line, whereas the relative error ε_χ , calculated for the case when R_2 is considered as a fixed number, is significantly smaller than in the case when R_2 (or R_2^*) is a fitting parameter. Hence, accuracy in determining parameter χ can be substantially improved by independent measurement of tissue relaxation time T_2 .

4.4. Dependence on the total measurement time T and initial sampling time T_0

Figure 3b illustrates the dependences of the relative errors on the final measurement time T . All the relative errors sharply decrease with the measurement time increases up to $T \sim 5-$

$10t_c$, and then the slopes of the curves become much smaller. It means that too long measurement time is not required for accurate measurement of the parameters: accuracy does not substantially improve for time T exceeding $10t_c$.

However, the accuracy of the parameter estimates can be improved by exploring negative (with respect to TE) initial time T_0 , i.e. starting the measurements prior to echo time TE as it is always done in GESSE experiment (17,18,21) (recall that in the case of spin echo measurements, time t is counted from SE echo). Figure 3c demonstrates the dependences of the relative errors on T_0 . As we can see, at $T_0 < 0$, the relative error of the volume fraction ϵ_ζ remains practically the same as for $T_0 = 0$ and rapidly increases when the measurements start after echo time TE . The relative error of the susceptibility difference ϵ_χ smoothly decreases with starting the measurements prior to echo time TE and reaches a plateau approximately at $T_0 = -t_c$.

This important result can be explained as follows. To discriminate two model parameters, χ and ζ , it is important to get data in the interval where the function f depends on time quadratically, Eq. [7]. If the measurements start before the spin echo, the “length” of such an interval is practically doubled. That is why the errors decrease when $T_0 < 0$. If T_0 is positive, the quadratic regime can be lost, and the parameters χ and ζ , appearing in the signal only as a product, Eq. [8], cannot be separated. As a result, the errors go up.

Generally speaking, the measurements can be started immediately after 180° pulse at time $TE/2$; in our notation, it corresponds to $T_0 = -TE/2$. It is interesting to analyze how the relative errors ϵ_j depend on the echo time TE . For this purpose, the signal amplitude $S(t)$ should be modified to incorporate an explicit dependence on T_2 -relaxation at echo time TE , namely,

$$S(t) \rightarrow S(t) \cdot \exp(-R_2 \cdot TE) = S_0 \cdot \exp \left[-\zeta \cdot f(t/t_c) - (R_2^* - \zeta/t_c) \cdot (t + TE) \right] \quad [27]$$

Figure 4 demonstrates the dependences of the relative errors ϵ_j on the echo time TE when the measurements start at $T_0 = -TE/2$. The relative errors ϵ_ζ and $\epsilon_{R_2^*}$ monotonically increase with TE increases, whereas the relative error ϵ_χ has a minimum at $TE \sim 3t_c$; thus, this value of spin echo time TE is optimal for measuring the susceptibility difference.

5. Phantom Study

We tested our theory on a phantom consisting of 0.5-mm diameter polyethylene filament strands (fish lines), threaded in parallel along a 75 mm length to form a matrix of 17×17 filaments. The average volume fraction (ζ) occupied by the filaments is about 7%. The filament matrix was placed horizontally and immersed in a spherical container (fish ball) filled with a solution of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ (3.75mg/ml) and NaCl (5mg/ml) in water.

3D GESSE (17) images ($32 \times 32 \times 32$ matrix with resolution of $4 \times 4 \times 4 \text{ mm}^3$) were acquired on a 3T whole body scanner Trio (SIEMENS, Erlanger, Germany) with a single channel knee coil. Other GESSE sequence parameters were: $TR=300 \text{ ms}$, SE time = 68 ms, $\delta t=1.77 \text{ ms}$, 90 gradient echoes with SE at 15th gradient echo, total measurement time 5 min, the signal was sampled only in unipolar readout gradients.

Raw data from Siemens scanner was imported into MATLAB (MathWorks Inc., Natick, MA, USA) running on a PC with Dual Six Core Intel® Xeon® Processor E5645 and 12 GB memory for image reconstruction and processing. A 3D Hanning filter was applied to reduce Gibbs ringing artifacts and to increase SNR. The resultant SNR was about 800.

A mesoscopic inhomogeneous magnetic field is induced due to the susceptibility difference between the filaments and water solution, and the MR signal can be described by equation similar to Eq. [1]. Note, however, that for parallel filaments, the function f appearing in Eq. [1] differs from that given in Eq. [5] (the latter corresponds to randomly oriented cylinders). For the system of parallel cylinders, the function f (to differentiate this case from that discussed above, we denote it f_p) can be presented in the form (19,29):

$$f_p(t/t_p) = \int_0^1 du \frac{1 - J_0\left(u \cdot \frac{t}{t_p}\right)}{3u^2} = {}_1F_2\left(\left\{-\frac{1}{2}\right\}; \left\{\frac{1}{2}, 1\right\}; -\frac{1}{4} \cdot \left(\frac{t}{t_p}\right)^2\right) - 1 \quad [28]$$

where the characteristic time $t_p^{-1} = R_p = 2\pi\gamma\chi B_0$ is also slightly different (by a numerical coefficient) from the characteristic time t_c used in the previous sections. However, the general behavior of the function f_p is very similar to that of the function f in Eq. [6]. Macroscopic magnetic field inhomogeneities are described by additional function $F(t)$ that is calculated based on phase information (details will be published elsewhere). Hence the model for GESSE signal $S_p(t)$ is:

$$S_p(t) = S_0 \cdot \exp\left[-\zeta \cdot f_p(t/t_p) - R_2(TE+t)\right] \cdot F(t) \quad [29]$$

with four fitting parameters (S_0 , ζ , χ , R_2). This model was fitted to the experimentally measured GESSE signal on a pixel-by-pixel basis by the nonlinear least-square curve fitting function (χ^2 -minimization) from MATLAB Optimization Toolbox. Also, MATLAB Parallel Toolbox was used to boost calculation speed.

A representative signal evolution profile from a pixel in the filament region and the fitting curve are illustrated in Figure 5 (symbols and solid line, respectively). Note the excellent fit of the function [29] to the experimental data.

The maps of the model parameters are shown in Figure 6 for several values of the initial measurement time T_0 to compare with theoretical predictions discussed in the previous section (to analyze experimental data with a given T_0 , we just ignored all data points prior to T_0).

The R_2^* maps show practically no dependence on time T_0 . The ζ and especially χ maps however substantially depend on T_0 . Results obtained with the earliest initial measurement time $T_0/\delta t = -14$ (data are acquired starting *before* spin echo time TE) are rather homogeneous within the fish line region; some artifacts appear on the maps when data are acquired starting from the spin echo time ($T_0/\delta t = 0$), whereas the maps obtained when starting point of data acquisition is *after* spin echo ($T_0/\delta t = +3$) are substantially contaminated with artifacts.

The signal was also analyzed by means of Bayesian Application Software (G. Larry Bretthorst, Washington University in St. Louis). The latter makes it possible to obtain the probability distributions of the model parameters $P(p_j|D\sigma I)$. The standard deviations σ_j of these distributions determine the uncertainties of parameters estimates. The typical distributions of the estimated parameters for a single pixel are presented in Figure 7. Due to high SNR, all the distributions are close to Gaussian; the mean and peak values of the distributions are practically identical and coincide with the values obtained by means of the χ^2 -minimization routine. The width of the distributions determines the uncertainties of the estimated parameters, σ_j , which can be compared with our theoretical predictions (the mean values of the distributions are used as “true” values $\hat{p}_j$ of the parameters).

It should be noted that the model parameters found from experimental data depend on the initial measurement time T_0 . This dependence is illustrated in Figure 8; each symbol corresponds to the signal analyzed starting from different T_0 (from $T_0 = -14\delta t$ to $T_0 = +3\delta t$). As we see, the fitting parameters are practically independent from T_0 when data acquisition starts *before* the spin echo time, $T_0 < 0$.

In Figure 9 the uncertainties in the model parameters, σ_j , obtained experimentally (width of the probability distributions) are compared with the theoretical predictions. Figure 9 demonstrates a good agreement between the experimental and theoretical values of the uncertainties in the model parameters. It should be emphasized that the uncertainties for dCBV, ζ , and susceptibility, χ , sharply increase when data acquisition starts *after* the spin echo time ($T_0 > 0$), despite the total number of acquired echos changes insignificantly (from 90 to 75).

6. Conclusion

The Bayesian analysis approach is used herein for analyzing the uncertainties in the parameter estimates in the model of the MR signal in the presence of mesoscopic magnetic field inhomogeneities induced by blood vessel network. The uncertainties for the model parameters (the volume fraction ζ , susceptibility difference χ , and R_2^* relaxation rate constant) are analyzed as functions of the “true” values of the parameters, the signal-to noise ratio, the initial measurement time (with respect to the spin echo position), and the total number of echoes used in GESSE pulse sequence experiment. The expressions obtained for the uncertainties make it possible to predict a necessary SNR required for obtaining a desired accuracy of the model parameters. The theoretical predictions for the parameter estimates are shown to be in a good agreement with experimental data obtained with the phantom of a known structure. It is demonstrated that the parameter uncertainties can be substantially decreased if the measurements start before the spin echo time, as in GESSE approach. It is also shown that an optimal time interval between the gradient echoes in GESSE sequence δt is about t_c - the characteristic dephasing time.

Our paper is devoted to optimizing GESSE sequence parameters for qBOLD technique. It is not about improving and/or testing theoretical models of BOLD effect. Yet, we would like to make a few comments on factors other than discussed above that can influence the accuracy of the qBOLD approach. First we note that the version of the qBOLD technique developed in (21) takes into account the multicomponent structure of the brain tissue – intracellular, ISF/CSF (interstitial and cerebrospinal fluids) and blood components. The above analysis was conducted under the assumption that both extravascular compartments – intracellular and extracellular -have similar MR properties. The effect of their differentiating is discussed below in the Appendix. Another issue is related to the model assumption of the static dephasing regime (19). The effect of water diffusion and validity criteria of the static dephasing regime were discussed in a number of publications, e.g., (17,19,24,31–35). The detail analysis of the effects of water diffusion on qBOLD parameters estimates was provided in (22,24). Another important issue – macroscopic field inhomogeneities and their effect on qBOLD parameter estimates – was addressed in (17).

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Appendix

Generalized models

Our consideration in the main text was devoted to the signal from a single compartment (parenchyma tissue). A general qBOLD model (18) includes also contributions from ISF/CSF (interstitial and cerebrospinal fluids) and intravascular venous blood. The normalized GESSE signal from the ISF/CSF compartment (denoted hereafter as s_e) can be described similarly to that from the tissue compartment s_t , Eq. [1] or Eq. [27]:

$$s_e(t) = \exp[-\zeta \cdot f(t/t_c) - R_{2e} \cdot (t + TE)] \quad [30]$$

where R_{2e} is the transverse relaxation rate constant of ISF/CSF (here we ignore the frequency and phase shifts from the cellular tissue component). The normalized signal from the venous blood vessels network can be presented in the form (29) (see also (18)):

$$s_b(t) = \exp(i \frac{t}{2t_c}) \frac{[C(\eta) - i \operatorname{sgn}(t) S(\eta)]}{\eta} \cdot \exp[-R_{2b} \cdot (t + TE)], \quad \eta = \left(\frac{3|t|}{\pi t_c}\right)^{1/2} \quad [31]$$

where $C(\cdot)$ and $S(\cdot)$ are the Fresnel functions (note that we use here the definition of the Fresnel functions as in (36) which is different by the factor $\pi/2$ in the argument from that used in (37) and adopted in (18)). The relaxation rate constant R_{2b} describing T_2 -relaxation of blood, is related to the blood oxygenation level Y by the following empirical relationship ($B_0 = 3T$ and $H_{cr} = 0.34$ are assumed) (18):

$$R_{2b} = 5 + 173 \cdot (1 - Y)^2 \quad [s^{-1}] \quad [32]$$

Using Eqs. [2]–[3], this parameter can be expressed via the characteristic time t_c (in ms):

$$R_{2b} = 0.005 + 1.37 \cdot t_c^{-2} \quad [ms^{-1}] \quad [33]$$

The expression for the total signal in the qBOLD model can be written as (18):

$$S_{total}(t) = S_0 \cdot \left\{ [(1 - \lambda - \zeta) \cdot \exp(-R_2 \cdot (t + TE)) + \lambda \cdot \exp(-R_{2e} \cdot (t + TE))] \cdot \exp[-\zeta \cdot f(t/t_c)] + \zeta \cdot \exp(i \frac{t}{2t_c}) \frac{[C(\eta) - i \operatorname{sgn}(t) S(\eta)]}{\eta} \cdot \exp[-R_{2b} \cdot (t + TE)] \right\}$$

where λ is a fraction of the ISF/CSF signal.

Depending on GESSE pulse sequence parameters and different preparation strategies, contributions from ISF/CSF and/or blood signals in Eq. [34] can be suppressed. Therefore below we analyze models accounting for (i) tissue and ISF/CSF signals, (ii) tissue and blood signals, and (iii) all the contributions. As the relaxation rate constant R_2^b is expressed in Eq. [33] in terms of the parameter t_c in the model (i) (tissue and blood), the signal contains the same fitting parameters as in Eq. [27]. Whereas the models (ii) and (iii) have two additional fitting parameters: R_{2e} and λ . Results are presented in Figure 10 for an experiment when the measurement starts at $T_0 = -TE/2$.

The two-compartment model (i) comprising of tissue and ISF/CSF contains additional fitting parameters; as a result, the relative errors in this model (dashed lines) are substantially higher than in the one-compartment (tissue-only) model (solid lines). However, adding blood vessel network system which doesn't have additional fitting parameters (models (ii) and (iii)) decreases the errors. Note also a substantially non-monotonic behavior of the errors in the models (i) – (iii). The presence of an additional minimum at $T_e \sim 10t_c$ may be useful for pulse sequence optimization. Note also that the lines corresponding to the model (ii) and (iii) are very close.

Figure 1.

The relative errors as functions of $\delta t/t_c$ calculated based on Eqs. 18–22 and the model described in Eqs. 6 and 9; $t_c=8$ ms, $\zeta=0.03$, $R_2=13$ s⁻¹, $SNR_0=500$, $T_0=0$ (FID experiment), $T=10t_c$.

Figure 2.

The relative errors as functions of $1/\zeta$. $t_c=8$ ms; $R_2=13$ s $^{-1}$, $SNR_0=500$, $\delta t = t_c$, $T_0=0$, $T=10t_c$.

Figure 3.

The relative errors as functions of R_2 (A), T (B), and T_0 (C); $t_c=8$ ms, $\zeta=0.03$, $SNR_0=500$; $T=10t_c$ (in (A, C); $R_2=13$ s⁻¹ (in (B, C); $T_0=0$ (in (A, B)). Solid lines in (A) correspond to the case when R_2 is a fitting parameter; dashed lines correspond to the case when R_2 is considered as a constant known from an independent experiment (the corresponding line for the relative error ϵ_ζ is not shown because it practically coincides with the solid line). The relative error $\epsilon_{R_2^*}$ in (C) is much smaller than for two other parameters (~ 0.004) and is not shown.

Figure 4. The relative errors as functions of the echo time TE when the measurement starts immediately after 180° pulse (at $T_0 = -TE/2$); $t_c=8$ ms, $R_2=13$ s $^{-1}$, $SNR_0=500$, $\zeta=0.03$, $T_0=10$ t_c .

Figure 5.

A representative signal evolution profile (normalized by its value at the spin echo time) from a pixel in the filament region and the fitting curve (solid line). The fitting parameters are: $\zeta = 0.075$, $t = 3.49\text{ms}$, $R_2 = 11.9\text{s}^{-1}$. Time t is counting from the spin echo time TE (marked by the vertical dotted line). Due to T_2 relaxation, the maximum of the signal is shifted from the spin echo time TE ($t=0$).

Figure 6.

Maps of the volume fraction ζ (first row), susceptibility difference χ (second row), and relaxation constant R_2^* (third row) for different initial measurement time T_0 : first column - $T_0/\delta t = -14$, second column - $T_0/\delta t = 0$, third column - $T_0/\delta t = +3$. The value of χ for fish lines is found to be 0.056 ± 0.003 ppm, the value of R_2 is homogeneous across the whole phantom and is equal to 11.9 ± 0.2 s⁻¹.

Figure 7.

Typical distributions of the model parameters for the initial measurement time $T_0 = -14\delta t$.

$$(\zeta)_{est} = (7.58 \pm 0.07) \cdot 10^{-2}, (\chi)_{est} = (5.64 \pm 0.05) \cdot 10^{-2} \text{ ppm}, (R_2^*)_{est} = (33.5 \pm 0.03) \text{ s}^{-1}$$

Figure 8. Dependence of the model parameters found from experimental data (for a single pixel) on the initial measurement time T_0 .

Figure 9.

The dependencies on the initial measurement time T_0 of the uncertainties in the model parameters, σ_j , obtained experimentally (symbols) and their theoretical predictions (solid lines).

Figure 10.

The comparison of the relative errors ϵ_ζ (a) and ϵ_χ (b) as functions of TE (when the measurement starts at $T_0 = -TE/2$). Solid lines - one-compartment model discussed in the main text; dashed lines - two-compartment model (i) - tissue & ISF/CSF; dotted lines - two-compartment model (ii) - tissue & blood; dash-dotted lines - three-compartment model (iii) - tissue & CSI/CSF & blood. $t_c = 8$ ms, $R_2 = 13$ s $^{-1}$, $SNR_0 = 500$, $\zeta = 0.03$, $T = 10$ t_c , $\lambda = 0.1$, $R_{2e} = 8$ s $^{-1}$.