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Efficient and robust estimation of blood oxygenation levels in single cerebral veins

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Abstract

Blood oxygenation level is an important measure that can be used alongside functional magnetic resonance imaging data in order to obtain closer correlates of neuronal activation. A robust estimate of this measure has thus far not been demonstrated. This is mainly due to the lack of knowledge of the underlying parameters which influence the numerical estimates of blood oxygenation. In this paper, we present a systematic analysis of the estimation performance of venous hemoglobin oxygen saturation (Y_v) as a function of noise, physiologic and geometric parameters. Furthermore, we present a novel algorithm for estimating Y_v from the temporal decay of an MR signal. The proposed algorithm incorporates prior information about the functional dependence between Y_v and relaxation rates. We compare our algorithm to an existing method in the literature and analyze the estimation performance. We show that our proposed algorithm is more efficient, achieving gains in performance as high as 92 %. We also show how our estimation algorithm takes advantage of signal features that are specific to the underlying physiology and geometry. We argue that optimal acquisition sequences, and corresponding estimation methods, should take into account such features in order to obtain robust estimates of blood oxygenation.

Keywords

Blood oxygenation; Single vessel; BOLD; Numerical modeling; Estimation; Venous blood; Quantitative fMRI

1 Introduction

Blood oxygenation level dependent (BOLD) fMRI is the leading technique for measuring local intravascular response to neuronal activation. This hemodynamic response essentially alters the ratio of oxygenated (oxy-) to deoxygenated (deoxy-) hemoglobin and thus inherently modifies the underlying paramagnetic properties of total hemoglobin [11]. T_2^* -weighted MRI sequences, the basis of BOLD fMRI, detect these paramagnetic changes. The resulting measurements, however, are only an indirect consequence of neuronal stimulation: any process that affects the neurovascular coupling (oxy/deoxy-hemoglobin ratio) can systematically confound the BOLD fMRI signal. For example, BOLD signal is influenced

by the subject's respiration, resulting in a lower response during hypo-capnia than during hyper-capnia [4, 11, 17]. Therefore, the same subject might show a different BOLD signal when they are slightly hyperventilating (e.g., more anxious) compared to a relaxed state with baseline respiration. Other confounding factors inducing similar effect include, drugs, substances, age, attention/fatigue level, excitation/inhibition processes, cerebrovascular disease, location of the scan site [7, 17], etc. This can make comparison across different fMRI sessions, subjects, groups and/or studies prone to errors. Furthermore, because of regional differences in neurovascular coupling [1, 10] this indirect measure can impede comparison of BOLD responses among different parts of the brain, even during the same session. fMRI is thus not well suited to quantify neuronal activation in absolute terms. One prevalent approach to get over this limitation is to measure relative signal fluctuations between an "active" task (e.g., viewing a face) versus a "baseline" condition (e.g., viewing a tree) [11]. This approach is suboptimal for two important reasons. First, it is not always possible to design experiments where active and baseline conditions are completely decoupled. That is, baseline tasks may affect the response to the active task of interest. Second, the inherent assumption in such an experimental paradigm is that the task of interest simply adds on a pre-existing brain baseline activation. This does not account for nonlinear neuronal response [6, 8]. Therefore, the detection and quantification of more direct neuronal activity measures is of critical importance in fMRI. One such quantity is the venous hemoglobin oxygen saturation ratio (Y_v) which quantifies the regional balance between global oxygen delivery and cerebral oxygen consumption [11]. Y_v can be looked at as the metabolic activity response to neuronal stimulation, and is thus closely related to neuronal activity. Alongside methods which estimate oxygen extraction fraction (OEF), cerebral blood flow (CBF) and cerebral blood volume (CBV) [2, 9], knowledge of Y_v would enable us to better interpret the origin of the underlying hemodynamic response. It is therefore important to measure Y_v accurately. One such measurement method involves the insertion of a catheter into the internal jugular vein [5]. Other techniques, such as the use of micro-electrodes, near-infrared spectroscopy and, positron emission tomography (PET), are either invasive, inaccurate, and/or impractical to use in fMRI studies. Recently, it has been demonstrated that estimates of cerebral blood oxygenation levels can in fact be extracted from the temporal decay of an MR signal. The theory behind this effect was first introduced by Yablonskiy and Haacke [18] where the authors showed that the transverse magnetization of a single vein induces local magnetic field inhomogeneity both inside and outside the vessel. This induced field inhomogeneity is a direct function of vessel blood properties, such as Y_v . It is thus theoretically possible to extract Y_v from the measured signal in/around a vessel. However, in order for this quantity to be a closer correlate of neuronal activation, Y_v needs to be measured in sites in close proximity to activation areas. This task consists of extracting features from signals generated around a network of small randomly oriented capillaries [9, 15]. This difficult estimation problem would require careful performance analysis and validation. Unfortunately, a closed-form relationship between Y_v and the MR temporal signal evolution does not exist for rectangular image voxels [18]. Furthermore, in the common case of a multi-compartment voxel, wherein the voxel includes the vessel as well as surrounding tissue, the model for this functional relationship becomes even more complicated [20]. Therefore, numerical models will be critical in order to extract estimates of Y_v from MR data. Thus we argue that it is necessary to first validate these numerical methods in simple and tractable geometries. One such method reported in the literature [13, 14] uses a numerical model for temporal signal decay in a single voxel traversed by single venous vessels. The authors illustrated the ability of their model, and corresponding estimation method, to quantify Y_v during changing physiologic conditions induced by carbogen and caffeine intake. However, the proposed numerical-based technique has not been validated for robustness. This is difficult to perform in-vivo or with phantoms. In this paper, we use numerical simulations to conduct systematic analysis of the estimation performance of Y_v as a function of the geometric properties of the vessel, signal-to-noise

ratio (SNR), and physiologic conditions. We perform the simulations using the methods proposed in [13] and show that the resulting estimates are in fact not robust. We then propose another estimation algorithm which incorporates prior-knowledge about the functional relationship between $T2/T2^*$ of venous blood and Y_v . This closed-form relationship was reported by Silvennoinen et al. [16 and Zhao et al. 19] as a second-order polynomial. The authors in [16, 19] suggest using this relationship in order to extract estimates of Y_v from $T2/T2^*$ values estimated from the magnitude decay of a voxel. In this paradigm, the robustness of the estimate of Y_v therefore depends directly on the robustness of $T2/T2^*$ estimates. The latter is complicated by the fact that measurement of $T2/T2^*$ values in blood depends on hemoglobin concentration and Y_v [16, 19]. The second contribution of our paper is an estimation method which incorporates this prior knowledge about the underlying physiologic relationship between $T2/T2^*$ and Y_v . We then propose a numerical model and corresponding estimation routine which we show to outperform methods attempting to extract these parameters separately. Our numerical model takes into account complex signal decay profiles, modulated by various levels of noise, vessel geometry and physiologic conditions.

2 Methods

2.1 Signal from a vein

In the static dephasing regime¹, the NMR signal obtained from a relaxation voxel V can be written as the weighted sum over all spins emitting transverse magnetization in that volume [18], namely,

$$S(t) = \int_V d^3\mathbf{r} \rho(\mathbf{r}) e^{-t/T2^*(\mathbf{r})} e^{i\omega(\mathbf{r})t} \quad (1)$$

where $\mathbf{r}$ denotes the spatial location, $\rho(\mathbf{r})$ is the spin density, $T2^*(\mathbf{r})$ is the transverse relaxation time as measured with a gradient echo sequence and $\omega(\mathbf{r})$ is the resonance frequency given by $\omega(\mathbf{r}) = \gamma B(\mathbf{r})$, where γ is the gyromagnetic ratio, and $B(\mathbf{r})$ is the magnetic field inhomogeneity. Of interest to us is a voxel V containing a single vessel surrounded by tissue. Approximating the vessel as an infinitely long homogeneously magnetized cylinder of radius a and using sphere of Lorentz concepts, it can be shown [18] that this inhomogeneous magnetic field induced by the magnetic susceptibility difference between the vein and its surrounding tissue is given by

$$B(\mathbf{r}) = \begin{cases} \frac{\Delta\chi}{2} \sin^2\theta a^2 \frac{\cos 2\varphi}{r^2} B_0 & \text{if } |\mathbf{r}| > a \\ \frac{\Delta\chi}{6} (3 \cos^2\theta - 1) B_0 & \text{if } |\mathbf{r}| \leq a \end{cases} \quad (2)$$

where θ is the vessel tilt angle with respect to the main magnetic field B_0 , (r, φ) represent the position in cylindrical coordinates in the z -plane of $\mathbf{r}$ and $\Delta\chi$ is the magnetic susceptibility difference between the vein and tissue $\Delta\chi = \chi_{\text{vein}} - \chi_{\text{tissue}}$. If the cylinder is filled with venous blood, we can write this susceptibility difference as a function of the blood oxygenation level Y_v and blood's hematocrit (Hct)

$$\Delta\chi = \Delta\chi_0 \text{Hct} (1 - Y_v) \quad (3)$$

¹It is widely assumed that the MR signal decay due to magnetic dephasing resulting from susceptibility differences occurs faster than the diffusion phenomena.

where $\Delta\chi_0$ is the magnetic susceptibility difference between fully oxygenated and deoxygenated red blood cells [13]. In the case of a homogeneous volume V containing only venous blood, it is clear from (1)–(3) that we can readily extract the underlying quantities ρ , $T2^*$ and Y_v from the temporal profile of $S(t)$. However, this seemingly simple task is complicated by the fact that measurement of $T2^*$ values in blood depends on hemoglobin concentration (and thus Hct) and Y_v [16, 19]. We will discuss the implications of this fact in Sect. 2.2. In the case of a heterogeneous volume V , such as one containing parenchyma, veins and/or arteries, the temporal decay possesses a more complex profile which depends on the interference between the spatially varying phase and magnitude terms in (1). In such cases, the task of decoupling the phase (e.g., Y_v) and magnitude (e.g., ρ , $T2^*$) variables of various compartments becomes difficult. In fact, even in the case of a two-compartment voxel model, a closed-form solution is only available for a cylindrical voxel. Thus, a numerical approach needs to be adopted in order to extract the value of Y_v from $S(t)$. Before presenting the numerical methods, we summarize next one key finding in the literature which we will take advantage of in order to obtain a robust and efficient estimate of Y_v .

2.2 Functional relationship between $T2^*$ and Y_v

Equations (1) and (2) suggest that $T2^*$ and Y_v influence the temporal evolution of the signal $S(t)$ independently. In fact, $T2^*$ and Y_v are optimized as two independent variables in the numerical model of [13]. However, in recent work [16, 19], the authors showed that these two parameters are in fact not independent but rather possess a given functional relationship. The authors offer exchange-based and diffusion-based perspectives to argue that the transverse relaxation rates vary quadratically with any chemical shift difference, and consequently magnetic susceptibility difference, between hydrogen protons in the erythrocyte and the plasma compartments. Any such difference will be due to the concentration of deoxyhemoglobin, i.e. $(1 - Y_v)$. Namely,

$$\frac{1}{T2^*} = A(\text{Hct}) + C(\text{Hct})(1 - Y_v)^2 \quad (4)$$

where the A and C terms have been calibrated to Hct values. In order to estimate Y_v , the authors in [16] suggest measuring $T2^*$ first by fitting the magnitude of the measurement to a sum of decaying exponentials, with contributions from parenchyma, arteries and veins. Then, Y_v is extracted from $T2^*$ according to (4). In our paper, instead of deducing Y_v from $T2^*$, we advocate the use of an algorithm that jointly estimates $T2^*$ and Y_v , while using prior information about the functional relationship (4).

2.3 Numerical problem formulation

The signal presented in (1) is a simplified representation of what is actually measured in reality. In a two-dimensional (2D) slice-selective imaging experiment, the temporal evolution of the encoding gradients defines a discrete grid in spatial frequency domain over which the measurements are made. This grid is then inverse Fourier transformed to yield a 2D array of measurements. Namely, we can write the measurement at pixel location (p, q) in the image domain as follows:

$$G_{p,q}(t) = \mathcal{D}\mathcal{F}\mathcal{J}_{p,q}^{-1} \times \left\{ \int_V d^3\mathbf{r} \rho(\mathbf{r}) e^{-t/T2^*(\mathbf{r})} e^{i\omega(\mathbf{r})t} e^{i2\pi(m\Delta k_x x + n\Delta k_y y)} \right\} + W_{p,q}(t) \quad (5)$$

where $m\Delta k_x$ and $n\Delta k_y$ represent the $(N_x \times N_y)$ spatial frequency grid traversed by the gradients, $m = 0, 1, \dots, N_x$, $n = 0, 1, \dots, N_y$, $\mathcal{D}\mathcal{F}\mathcal{J}_{p,q}^{-1}$ is the inverse discrete Fourier transform (DFT) operator which transforms the measurements to the image domain at

location (p, q) , and W is the additive noise component. The original object distribution is obviously defined by $\rho(\mathbf{r})$, $T_2^*(\mathbf{r})$ and $B(\mathbf{r})$ on a continuous grid, spanned by $\mathbf{r}$. For obvious practical reasons, we chose in our simulations to represent the original object on an artificial oversampled grid of size $1,024 \times 1,024$. Figure 1 illustrates one example spatial distribution at $t = 0$ around a single venous vessel. This example assumes a physiological condition given by the following vessel parameters²: spin density $\rho_v = 1$, $Y_v = 0.9$, transverse relaxation $T_{2v}^* = 50$ ms, Hct = 0.42. Note that, hereafter, T_{2v}^* and Y_v are jointly chosen so as to satisfy (4). The background tissue is assumed to have a spin density $\rho_t = 1$, and transverse relaxation $T_{2t}^* = 1$ s. The vessel simulated here has an inner diameter of $750 \mu\text{m}$ assumed to be perfectly centered in the middle of the grid. Note that, in this paper, we use $\Delta\chi_0 = 4\pi 0.18$ ppm (SI).

In order to simulate the measurements, a multi-echo gradient echo (MEGE) sequence was modeled in (5). This is accomplished by replacing the appropriate form of t as a function of the sampling grid (m, n) . The imaging parameters were the following: the range of TE was from 5 ms to 1 s with a step size of $\Delta\text{TE} = 10$ ms, the bandwidth was set to 243.75 Hz per pixel, and the number of repetitions is 1. The acquisition matrix size is $N_x = 128$, $N_y = 128$, with a field-of-view (FOV) varying in the range of 110–190 mm. This span of FOV values simulates a range of relative vein area of 0.2–0.6 times the image voxel area. This factor is also referred to as the partial volume fraction, λ , and is given by,

$$\lambda = \frac{\pi a^2}{\Delta x^2} \quad (6)$$

where a is the radius of the vessel and Δx is the size of the square voxel. Figure 2 shows the magnitude and phase of the simulated image obtained at the first echo time with the sequence described above, for the example vessel geometry of Fig. 1. Note that the center voxel contains contributions from both, the background tissue and the signal from the vessel, since here $\lambda = 0.5$. Also note the “ringing” artifacts, due to finite sampling, which causes signal from a given voxel to propagate onto other voxels. Our task here is to extract an estimate of Y_v from the temporal profile of $G_{p_0, q_0}(t)$, where the location (p_0, q_0) corresponds to the voxel centered on the vessel, in our case $\{p_0 = 64, q_0 = 64\}$. As expected, $G_{64, 64}(t)$ will not only be affected by vessel tilt θ , vessel radius a , blood hematocrit level (Hct), spin density in blood ρ_v and blood's relaxation constant T_{2v}^* but, it will also be affected by the spin density and relaxation constant of tissue surrounding the vessel. We will illustrate in Sect. 3 how $G_{64, 64}(t)$ changes with these parameters.

First, similar to Sedlacik et al. [13], we propose fitting the measured data $m_{p_0, q_0}(t)$ against the modeled measurement $G_{p_0, q_0}(t)$. The corresponding algorithm, denoted by $\mathcal{A}_1$, consists of solving the following equation numerically:

$$\left[\widehat{Y}_v, \widehat{T_{2v}^*}, \widehat{\rho}_v, \widehat{a} \right] = \underset{Y, T_{2v}^*, \rho, a}{\operatorname{argmin}} \left\| G_{p_0, q_0}(t) - m_{p_0, q_0}(t) \right\|^2 \quad (7)$$

The choice of the numerical routine, or search method, which solves this least squares (LS) problem is arbitrary here. It is unclear what optimization method the authors in [13] have adopted. Furthermore, their numerical method was not validated in a controlled setting, which is a critical step needed to quantify the efficiency and robustness of the technique. Thus, we choose to solve problem (7) using a variety of optimization methods, including

² For comparison purposes, the values chosen hereafter are in agreement with the simulations of [13].

gradient-descent methods, line-search methods and simulated annealing (SA) [12]. For each of those methods, we evaluate the estimation performance of algorithm $\mathcal{A}_1$ as a function of key parameters such as SNR, vessel geometry and physiological parameters.

Motivated by the model of [16] introduced in Sect. 2.2, we also propose the following algorithm, denoted by $\mathcal{A}_2$, whereby we impose our prior knowledge about the functional relationship between $T2_v^*$ and Y_v . Namely, we solve the following:

$$\left[\widehat{Y}_v, \widehat{T2_v^*}, \widehat{\rho}_v, \widehat{a} \right] = \underset{Y_v, a}{\operatorname{argmin}} \left\| G_{p_0, q_0}(t) - m_{p_0, q_0}(t) \right\|^2 \quad \text{s.t.} \quad \frac{1}{T2_v^*} = A(Hct) + C(Hct)(1 - Y_v)^2 \quad (8)$$

This algorithm can be looked at as a constrained version of algorithm $\mathcal{A}_1$. Given the prior information incorporated in the problem formulation, we expect algorithm $\mathcal{A}_2$ to yield more accurate estimates that are also more robust. One question we answer is the following: is this gain in performance significant enough to warrant the careful modeling of the inter-dependence between Y_v and $T2_v^*$? If so, can we constrain the optimization methods to search for such an underlying model? We answer the former question in Sect. 3, while the latter is discussed in Sect. 4.

3 Results

3.1 Temporal decay profiles

As indicated in Sect. 2.3, the estimation method fits the temporal evolution of the measurement $m(t)$ at pixel location (p_0, q_0) to the numerical model. The efficiency of the estimate depends on the functional relationship between the model $G_{p_0, q_0}(t)$ and the parameter to be estimated. For example, if $G_{p_0, q_0}(t)$ does not vary with Y_v , or if the variation is masked by a given level of noise, then it becomes difficult to get an efficient estimate of Y_v .

We empirically explore such relationships in Fig. 3 where we plot the profile of the magnitude of $G_{64, 64}(t)$ as a function of TE for various values of Y_v and geometry parameters. In order to show the full variation with echo time, the range of TE chosen for this figure was from 5 to 2,000 ms. For clarity, we use a logarithmic scale for the horizontal axis. We illustrate here the case of measurements with no noise. Figure 3a–c show the variation of $|G_{64, 64}(t)|$ with Y_v , for $\lambda = 0.5$ and $\theta = 0^\circ, 50^\circ$ and 90° , respectively. As a reference, we include the exponential decay in a voxel containing only background tissue (blue curve). The green, red and magenta curves represent the temporal evolution of the signal from a voxel centered around the vessel, for decreasing levels of Y_v . Note that, for $\theta = 50^\circ$ and 90° , the signature of the decay for each Y_v consists of sharp oscillations that have distinct peak locations and amplitudes. On the other hand, for $\theta = 0^\circ$, $|G_{64, 64}(t)|$ changes smoothly with Y_v , and only for TE $\gg 15$ ms. This is expected. Recall that, inside the vessel, Y_v is modulated by the amplitude of the signal (due to $T2^*$ dependence) as well as its phase (due to susceptibility-induced field inhomogeneity). Outside of the vessel, Y_v is only modulated by the phase. Due to signal interference, the resulting beating (oscillations) is therefore expected to carry very distinct features that depend on Y_v . For $\theta = 0^\circ$, the phase outside the vessel is zero, hence Y_v 's contribution to $|G_{64, 64}(t)|$ comes entirely from the signal inside of the vessel, which decays quite rapidly compared to the tissue. As the angle increases, the phase terms outside the vessel increase, and so do the oscillations. The amplitude of these oscillations increases if the signal contributions from both compartments increase. For example, if λ decreases, the signal from inside of the vessel decreases and the magnitude of the oscillations decreases. This is shown in Fig. 3d where we plot the decay for $\lambda = 0.18$ and $\theta = 90^\circ$. The characteristic oscillations have clearly decreased in magnitude

as compared to Fig. 3c. We expect estimation algorithms to better discriminate between different Y_v s in vessels whose decay profiles possess strong “distinctive” features that are a function of Y_v . The strength of these Y_v -dependent features should be compared to the noise level. Robust estimation methods would take advantage of these strong Y_v -dependent features. Obviously, as we have seen here, these features are a function of vessel geometries as well. We expect the performance of the estimation methods to depend on these features, their location, strength and functional dependence on Y_v . We validate these expectations in the next section. In Sect. 4, we discuss the implications of this observation on designing pulse sequences for improved Y_v estimation.

3.2 Estimation performance

We report the estimation performance of the optimization algorithms presented in Sect. 2.3. Hereafter, we use the root mean squared error (RMSE) as a quality metric of the estimate. All simulations below were repeated 5000 times for each SNR of interest. Formally, the RMSE of an estimate $\hat{x}$ of a variable x is defined as:

$$\text{RMSE}\{\hat{x}\} = \sqrt{\langle \|x - \hat{x}\|^2 \rangle} \quad (9)$$

where $\langle . \rangle$ denotes the sample mean. We chose the RMSE here as it is an indication of both, the bias in the estimate and its variance. Clearly, the goodness metric (RMSE) of the estimate is a function of the underlying noise level in the measurements. We quantify this noise level using the SNR (ratio of the standard deviation of the signal to that of the noise). A typical SNR range that will be considered here is 70–150. First, we study the estimation performance for a specific geometry characterized by $(\theta = 0^\circ, \lambda = 0.2)$ and a given physiologic condition defined by $(Y_v = 0.9, \text{Hct} = 0.42, \rho_v = 0.9, T2_v^* = 45.2 \text{ ms})$. As pointed out in Sect. 2.3, the parameters we want to estimate are $Y_v, T2_v^*, \rho_v$ and λ : all being vessel properties. The background tissue properties, $T2_t^*$ and ρ_t , are easily extracted from voxels containing tissue only easily located in proximity of the vessel. This step is straight-forward and precedes estimation algorithms (7) and (8). Table 1 lists the RMSE of the estimate of $\hat{Y}_v, \hat{T2}_v^*, \hat{\rho}_v$ and $\hat{\lambda}$, obtained using algorithms (7) (first and third rows) and (8) (second and fourth rows). The noise regimes here correspond to an SNR of 150 (first and second rows) and 100 (third and fourth rows). All the RMSEs are unitless, except that of $\hat{T2}_v^*$ which is in the units of seconds. We note the following: first, we can see that, as expected, the constrained estimation algorithm $\mathcal{A}_2$ outperforms the unconstrained algorithm $\mathcal{A}_1$ in estimating the value of all parameters of interest. In particular, it improves the RMSE of $\hat{T2}_v^*$ from 24 to 0.24 ms, an impressive two orders of magnitude of improvement in the efficiency of the estimate. The improvement in the estimate of $\hat{Y}_v$ is 92 %. Second, the RMSE increases as SNR increases, as expected. For a realistic SNR of 100, we see that our proposed algorithm $\mathcal{A}_2$ achieves an estimate $\hat{Y}_v$ within an accuracy of 0.01, a factor of 10 improvement over the literature’s algorithm $\mathcal{A}_1$. Finally, note that the RMSE of $\hat{\rho}_v$ and $\hat{\lambda}$ are relatively large for both algorithms. The reason for this is the following. In the typical two-compartment voxel under consideration, the vessel is completely included in the volume V . Thus, the signal from voxel V at time $t = 0$, $S_0 \triangleq S(t = 0)$, is influenced by the proton density distribution inside the voxel V and the size of that voxel (1). Specifically, in our model, we can write, $S_0 \propto \pi a^2 \rho_v + (\Delta x^2 - \pi a^2) \rho_t = \text{const}$, where Δx is the size of the voxel and a is the radius of the vessel. It is clear that estimating ρ_v and a (i.e., λ) from S_0 is an under-determined problem. This is in contradiction with the estimation performance suggested in [13], where the authors’ simulations show ability to almost perfectly estimate ρ_v and λ . In fact, we observed that, unless the optimizer is initialized close to the true values of ρ_v and λ

(which is not realistic), the resulting RMSEs are as reported in Table 1. Instead, we claim that what could be estimated efficiently is the weighted proton density (ρ_{wpd}) defined as:

$$\rho_{\text{wpd}} \triangleq \frac{S_0}{\Delta x^2} = \lambda \rho_v + (1-\lambda) \rho_t = \text{const.} \quad 0 < \lambda < 1 \quad (10)$$

We see from Table 1 that the error in the estimate $\hat{\rho}_{\text{wpd}}$ is drastically less than that of $\hat{\rho}_v$. Hereafter, we report the RMSE in $\hat{\rho}_{\text{wpd}}$.

The results presented so far are for a specific physiological condition, as indicated in Table 1. Next, we present results averaged over various physiological conditions of interest. Specifically, we allow Y_v to take on any value in the range of [0.4–0.9], $T2_v^*$ will change correspondingly from [12–45] ms and ρ_v in the range of [0.7–1.2]. The values are chosen uniformly from within their range. Table 2 presents the results from a low noise regime (SNR = 150) to a high noise regime (SNR = 70). We note the following. First, we note that algorithm $\mathcal{A}_2$ consistently performs better than $\mathcal{A}_1$. Similar to above, the improvement in estimation performance is as high as 90 %. This is an important conclusion: including prior information about the functional relationship between blood hemoglobin oxygenation levels and blood's relaxation rates substantially improves the estimation performance. Second, we note that the performance quickly degrades with noise. For example, at an SNR of 70, the error in the estimate of Y_v is ten times larger than that at an SNR of 100, with a corresponding RMSE of 0.15 (recall $0 < Y_v < 1$).

Finally, we analyze the impact of the vessel geometry on the RMSE of the estimates. Specifically, we ask the following question: will λ and θ affect the accuracy of the estimate? We answer this in Fig. 4a, b where we plot the RMSE in the estimate $\hat{Y}_v$ obtained using algorithm $\mathcal{A}_2$ (8) as a function of λ and θ , respectively. We see that, RMSE $\{\hat{Y}_v\}$ decreases as θ increases. This is expected. As pointed out in Sect. 3.1 and Fig. 3, Y_v possesses a stronger signature, in the form of more distinctive oscillations, at larger values of θ . Our simulations suggest that the RMSE of $\hat{Y}_v$ is expected to be 10 times larger at $\theta = 0^\circ$ as compared to that at $\theta = 90^\circ$. Nevertheless, RMSE $\{\hat{Y}_v\}$ at $\theta = 0^\circ$ is 0.05, still a good estimation performance at an SNR of 100. Similarly, we also note that, as λ increases from 0.3 to 0.55, the accuracy in $\hat{Y}_v$ increases by 35 %. This is again due to λ s in the mid-range generating more distinct features. As λ increases, the larger signal contribution from the exterior of the vessel will decrease, and thus the external field inhomogeneity will be modulated by an increasingly weaker signal. This reduces the amplitude of the oscillations and the robustness of the resulting estimate.

4 Discussion

We have presented two algorithms for estimating venous hemoglobin oxygen saturation (Y_v) from the temporal decay of an MR signal. The first method, denoted by $\mathcal{A}_1$ (7), was proposed earlier in the literature [13], albeit without rigorous analysis of estimation performance. We proposed a second algorithm, $\mathcal{A}_2$ (8), which incorporates prior information about the functional dependence between Y_v and $T2_v^*$ in blood [16, 19]. We have performed a rigorous analysis of the estimation performance of both algorithms as a function of the vessel's geometric property (θ, λ) and the underlying physiologic condition (Y_v). The observed reduction in the RMSE of the estimate of Y_v as obtained with our proposed algorithm was as high as 92 %. In fact, in all our simulations, irrespective of the parameters of the pulse sequence, we observed a systematic and considerable improvement in the estimation accuracy of algorithm $\mathcal{A}_2$ over that of $\mathcal{A}_1$. Furthermore, it was observed that the estimates returned by $\mathcal{A}_1$ were not robust. In fact, we should note that we were unable to

replicate the estimation performance reported in [13], unless the optimizer in $\mathcal{A}_1$ was initialized in the vicinity of the optimal solution. This was the case even when we used global search methods, such as Simulated Annealing. This is because the local minima correspond to solutions that, in the presence of noise, closely fit the magnitude decay profile, $|G_{64,64}(t)|$. We also should note that the choice of the optimizer utilized had an impact on the performance of algorithm $\mathcal{A}_2$ as well. We illustrate this in Table 3 where we report the average estimation performance (RMSE) using algorithm $\mathcal{A}_2$ using 2 different optimization methods. The first row reports results obtained using a direct search method (Nelder–Mead) [3] while the second row uses the global stochastic search method SA. We also explored in this table the influence of retaining phase information. The first column reports results obtained by fitting only the magnitude of the decay $|m_{64,64}(t)|$ to $|G_{64,64}(t)|$, while the second column fits both the magnitude and phase. It is clear from this table that SA outperforms the simplex search method, and that retaining phase information with SA yields the best estimate of Y_v , yielding an improvement in RMSE by up to a factor of 95 % over the other methods. Note that this important non-trivial fact has not been mentioned so far in literature attempting to extract Y_v using numerical models. We note that the SA algorithm we used here had an inner loop of 1,000 iterations and an outer loop of 100 iterations. The annealing was chosen to have an adaptive cooling schedule.

Another important contribution in this work is the rigorous performance analysis of the estimation algorithm $\mathcal{A}_2$. This is key to understanding the conditions under which the estimate of Y_v is reliable. Specifically, we have studied the performance of the algorithm under different noise, physiologic and geometric conditions:

- Considering different levels of noise, we have shown that $\hat{Y}_v$ is within ± 0.014 of Y_v for SNRs higher than 100. However, at mid-to-low levels of SNR (< 70), this RMSE increases to 0.15. Given that Y_v is between 0 and 1, in most cases between 0.45 and 0.9, this error constitutes around 33 % of the range. Therefore, the estimates at mid-to-low SNR are not robust.
- We also investigated this robustness for different physiological conditions. For example, we observed that, at large values of Y_v , the RMSE of the estimate $\hat{Y}_v$ increases slightly. This is because of the value of the phase term being proportional to $(1 - Y_v)$. At SNR levels of 100, when Y_v increased from 0.45 to 0.9, the RMSE of the estimate increased from 0.014 to 0.098. However acceptable, this is a 60 % increase. This observation is important in order to understand the confidence level for various oxygenation states.
- We also reported the performance as a function of geometric properties of the vessel. For example, we observed that the RMSE for vessels parallel to the main magnetic field are a factor of 10 higher as compared to vessels perpendicular to it. This was predicted empirically in Sect. 3.1 and that is precisely what our simulations verified.

It is important to note that, in all three bullets above, the estimation performance is mostly improved in the case when the decay profiles possess a large degree of Y_v -dependent features, as compared to the noise level. This concept of “feature-to-noise” ratio is critical for both, designing efficient pulse sequences and corresponding Y_v estimation methods. Specifically, one can readily design a pulse sequence that mainly probes the temporal region (TE ranges) that is highly sensitive to Y_v , rather than the regions that only smoothly vary with Y_v . More interestingly, using the framework introduced here, we can optimize the pulse sequence parameters so as to maximize the features’ strengths and in turn the efficiency/robustness of the resulting Y_v estimates. In fact, this optimization routine can simultaneously search for optimal post-processing and estimation parameters. This yields a

joint acquisition-processing optimization framework for efficient estimation of Y_v . We illustrate such an optimization framework with the following formulation:

$$\left[\widehat{Y}_v, \widehat{T2}_v^*, \widehat{\rho}_{\text{wpd}}, \{\text{TE}\}_{1:M} \right] = \underset{T2^*, \{\text{TE}\}_{1:M}, \rho_{\text{wpd}}}{\text{argmin}} \left\| G_{p,q}(t) - m_{p,q}(t) \right\|^2 \quad \text{s.t.} \quad \frac{1}{T2_v^*} = A(\text{Hct}) + C(\text{Hct})(1 - Y_v)^2 \quad (11)$$

One way to look at this formulation is the following: for a given $T2_v^*$, tuning the values of the echo time train $\{\text{TE}\}_{1:M}$ modifies the performance of the $T2_v^*$ fitting algorithm, which in turn modifies the estimate of Y_v . This tuning can then be repeated until a value of $\{\text{TE}\}_{1:M}$ is found which best explains (in the RMSE sense) the measurements.

We discuss next the underlying assumption about the prior-knowledge of the Hct value. It is often assumed that Hct is known. This is reasonable in general, as prior physiological information can be collected. It was reported however that Hct often changes with location in the brain, age, sex and psychological condition [19]. Estimating Hct however numerically is not straight-forward. This is because Hct multiplies the term $(1 - Y_v)$ in (2). This implies that the estimation algorithm $\mathcal{A}_1$ will only be able to estimate the product, and not decouple the individual values. We claim that we can use a slightly modified version of our algorithm $\mathcal{A}_2$ to estimate Hct. We skip the details here but report that our simulations show that this formulation can achieve an improvement in RMSE of the Hct estimate of 60 %.

Finally, we note that the prior knowledge of the fitted $T2_v^*/Y_v$ model parameters A and C is not necessary for applying our method. The authors in [16] derived the parameters that best fit a quadratic model. However, we argue that we can in fact optimize for the A and C parameters that best explain (in the RMSE sense) the underlying functional relationship between Y_v and $T2_v^*$ which is present in the current measurement. This is done simply by solving the following problem:

$$\left[\widehat{Y}_v, \widehat{T2}_v^*, \widehat{\rho}_{\text{wpd}}, \widehat{A}, \widehat{C} \right] = \underset{T2^*, \widehat{A}, \widehat{C}, \rho_{\text{wpd}}}{\text{argmin}} \left\| G_{p,q}(t) - m_{p,q}(t) \right\|^2 \quad \text{s.t.} \quad Y = 1 - \sqrt{\frac{1}{C} \left(\frac{1}{T2^*} - A \right)} \quad (12)$$

Other parametric models could also be solved for as well. This could be a valuable tool for validating functional relationships between Y_v and $T2_v^*$.

To conclude, we presented here an algorithm and framework for estimating venous blood oxygenation levels which incorporates prior information about the functional dependence between Y_v and relaxation rates. The corresponding numerical method can be used to validate the performance of various acquisition sequences and corresponding estimation routines. In their validation, the authors in [14] chose to compute Y_v in the *V. centralis* (parallel to $\mathbf{B}_0$) and the *V. thalamostriata* (perpendicular to $\mathbf{B}_0$). Due to lack of the knowledge of the ground truth in-vivo, the authors were not able to quantify the quality of the estimate in each vein. Our simulations, however, will enable us to quantify the quality of the estimate for various physiologic conditions, vessel geometries and noise levels.

Future work includes validating the observed features in the temporal decay as a function of Y_v and utilizing pulse sequences that are optimized to detecting such features. Together with proposed algorithms 8, 11 and 12, we expect such pulse sequences to yield more accurate estimates of venous oxygenation. We also will be demonstrating the utility of the proposed numerical tools in vivo.

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Fig. 1.

The 2D grid showing the **a** magnitude and **b** phase of the original spatial distribution inside/outside a vessel. The parameters here assume a vessel oriented at 50° to the main field ($B_0 = 3\text{ T}$), and containing oxygenated blood with $\rho_v = 1$, $T2_v^* = 50\text{ ms}$, $Y_v = 0.9$, and $\text{Hct} = 0.42$

Fig. 2.

The simulated measurement obtained by the hypothetical acquisition of the pulse sequence. The partial volume fraction is $\lambda = 0.5$. We can see that **a** the magnitude and **b** the phase are undersampled/smoothed versions of Fig. 1a, b, respectively, with apparent ringing artifacts. We only show here the center portion of the image, for clarity

Fig. 3.

A profile of the temporal decay of the magnitude of $G_{64,64}(t)$ for various values of hemoglobin oxygen saturation Y_v , with a geometry given by $\lambda = 0.5$ and **a** $\theta = 0^\circ$, **b** $\theta = 50^\circ$, and **c** $\theta = 90^\circ$. Also included is the temporal decay in the surrounding tissue (*blue curve*). We compare **c** to **d** the profile of the decay for $\theta = 90^\circ$ and $\lambda = 0.18$. Background parameters are chosen to be $\rho_t = 1$, $T2_t^* = 1\text{s}$ (color figure online)

Fig. 4. **a** RMSE of $\hat{Y}_v$ as a function of θ for SNR of 100. λ is fixed at 0.3. **b** RMSE of $\hat{Y}_v$ as a function of λ for SNR of 100. θ is fixed at 90°

Table 1

RMSE of $\hat{Y}_V$, $\hat{T}_{2V}$, $\hat{\rho}_V$, $\hat{\lambda}$ and $\hat{\rho}_{\text{vpd}}$ obtained using optimization algorithms (7) and (8)

	RMSE $\{\hat{\rho}_V\}$	RMSE $\{\hat{T}_{2V}^*\}$	RMSE $\{\hat{\rho}_V\}$	RMSE $\{\hat{\lambda}\}$	RMSE $\{\hat{\rho}_{\text{vpd}}\}$
$\mathcal{A}_1$, SNR = 150	0.0487	0.0246	0.1	0.04	0.009
$\mathcal{A}_2$, SNR = 150	0.0035	0.00024	0.1	0.04	0.008
$\mathcal{A}_1$, SNR = 100	0.1097	0.048	0.18	0.12	0.07
$\mathcal{A}_2$, SNR = 100	0.01	0.0065	0.18	0.1	0.06

Geometric parameters: ($\theta = 0^\circ$, $\lambda = 0.3$), Physiologic parameters ($Y_V = 0.9$, Hct = 0.42, $\rho_V = 1.1$, $T_{2V} = 45.2$ ms)

Table 2

RMSE of $\hat{Y}_v$, $\hat{T}_{2v}$ and $\hat{\rho}_{\text{wpd}}$ obtained with $\mathcal{A}_1$ and $\mathcal{A}_2$ for physiologic parameters chosen uniformly from within a predefined range

	RMSE $\{\hat{Y}_v\}$	RMSE $\{\hat{T}_{2v}^*\}$	RMSE $\{\hat{\rho}_{\text{wpd}}\}$
$\mathcal{A}_1$, SNR = 150	0.0622	0.0297	0.0109
$\mathcal{A}_2$, SNR = 150	0.0045	0.0003	0.0084
$\mathcal{A}_1$, SNR = 100	0.1327	0.052	0.076
$\mathcal{A}_2$, SNR = 100	0.014	0.0074	0.0602
$\mathcal{A}_1$, SNR = 70	0.36	0.102	0.027
$\mathcal{A}_2$, SNR = 70	0.15	0.025	0.023

The geometric parameters are ($\theta = 0^\circ$, $\lambda = 0.3$)

Table 3

RMSE of $\hat{Y}_V$ using two different optimization methods which implement $\mathcal{A}_2$, obtained with/without retaining phase information

RMSE { $\hat{Y}_V$ }	Magnitude-only	Magnitude and Phase
Nelder Mead	0.0587	0.0517
Simulated annealing	0.0189	0.0035

Geometric parameters: ($\theta = 0^\circ$, $\lambda = 0.3$), Physiologic parameters ($Y_V = 0.9$, Hct = 0.42, $\rho_V = 1.1$, $T2_V^* = 45.2$ ms), SNR = 100