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Dual-scan acquisition for accelerated continuous-wave EPR oximetry

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Abstract

Statistical analysis reveals that, given a fixed acquisition time, linewidth (and thus pO_2) can be more precisely determined from multiple scans with different modulation amplitudes and sweep widths than from a single scan. For a Lorentzian lineshape and an unknown but spatially uniform modulation amplitude, the analysis suggests the use of two scans, each occupying half of the total acquisition time. We term this mode of scanning as dual-scan acquisition. For unknown linewidths in a range $[\Gamma_{\min}, \Gamma_{\max}]$, practical guidelines are provided for selecting the modulation amplitude and sweep width for each dual-scan component. Following these guidelines can allow for a 3–4 times reduction in spectroscopic acquisition time versus an optimized single-scan, without requiring hardware modifications. Findings are experimentally verified using L-band spectroscopy with an oxygen-sensitive particulate probe.

Keywords

EPR; Spectroscopy; Oximetry; Overmodulation; Cramér-Rao lower bound; LiNc-BuO

1. Introduction

Electron paramagnetic resonance (EPR) is a spectroscopic method for the detection of species with unpaired electrons. Long data acquisition times have limited the scope of EPR for biological studies, such as *in vivo* measurements of pO_2 and pH.

For continuous-wave (CW) EPR, the data are collected by measuring the absorption of electromagnetic radiation, usually in the microwave range, by paramagnetic species in the presence of an external magnetic field. For imaging applications, an additional magnetic field in the form of a linear magnetic field gradient is applied to provide spatial encoding. Recent efforts to accelerate EPR data collection include both hardware and algorithm developments. For example, overmodulation [1], fast scan [2], rapid scan [3, 4], pulsed EPR [5, 6], parametric modeling [7], adaptive and uniform data sampling [8], digital detection [9],

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10, 11], and multisite oximetry [12, 13] have shown potential to accelerate the acquisition process.

To improve signal-to-noise ratio (SNR), magnetic field modulation is universally employed in CW EPR [14]. To increase signal strength, the magnetic field modulation amplitude (B_m) is often set to three or four times the half-width half-maximum (HWHM) linewidth (Γ) expected to be measured in the experiment. In previous work, we have demonstrated how to set B_m and the sweep width (ΔB) for increased sensitivity when performing a single-scan [15].

In this study we ask the following question: can a fixed scan time be split into multiple scans with various modulation amplitudes and sweep widths to provide more informative measurements than a single-scan? By way of analogy, what can we gain by examining this spectral object from multiple perspectives? Our primary investigative tool is the Cramér-Rao lower bound (CRLB). Given a candidate number of scans R , the time for each scan, and the settings for each scan, the CRLB allows us to determine how well the linewidth, Γ , can be estimated. The provided bound is on the standard deviation (std.) of the estimation error: no unbiased estimator can perform better than this.

The remainder of the paper is organized as follows: Section 2 presents the signal model and the statistical sensitivity analysis used to optimize acquisition parameters; Section 3 briefly describes the construction of the phantom as well as the protocols used to collect data on an L-band spectrometer; Section 4 presents results from both simulation and L-band oximetry experiment; Section 5 includes discussion; and Section 6 summarizes the conclusions.

2. Theory

2.1. Signal model

Our analysis relies on the following assumptions: (i) the value of Γ is unknown, but resides in a known range $[\Gamma_{\min}, \Gamma_{\max}]$; (ii) signal intensity d is unknown; (iii) the n th scan's modulation amplitude ($B_{m,n}$) is unknown, but constant over the extent of the sample; (iv) the center field of the lineshape is known; (v) the sweep rate is low enough to avoid the rapid-scan regime [3]; (vi) measurement noise is additive white Gaussian [7]; and (vii) the lineshape is a modulation-distorted Lorentzian, as detailed below.

Note that each modulation amplitude, B_m , though nominally set by the experimenter, is considered unknown. This is because the actual B_m values vary slightly but unpredictably from the set value. Also note that we have assumed the center field of the lineshape is known. In many situations, the center field may vary slightly between scans or not be properly calibrated; numerical study as well as lab experiments (not shown) indicate that small center field offsets do not significantly affect our results.

Our signal model for the modulation-distorted Lorentzian lineshape is adapted from Robinson et al. [16] and has previously proven effective in EPR oximetry [1, 15]. Because the linewidths encountered in EPR oximetry are large compared to the ratio of the modulation frequency to the gyromagnetic constant, distortion due to the modulation frequency is ignored, yielding the following model for the modulation-distorted lineshape, f :

$$f(B; d, \Gamma, B_m) = \text{Im} \left(\frac{dB_m}{\alpha} \right), \quad (1)$$

where

$$\alpha = \frac{a^2}{2} \left(1 + \sqrt{1 - \left(\frac{B_m}{2a} \right)^2} \right) - \frac{B_m^2}{8} \quad (2)$$

and

$$a = B + j\Gamma. \quad (3)$$

Here, B is the applied magnetic field, j is the imaginary unit, and $\text{Im}(\cdot)$ represents the imaginary part of its argument.

Each scan is composed of M_n successive samples taken at uniform intervals across the field scan. The measured data for scan $n \in \{1, \dots, R\}$ is then given by

$$Y_{i,n} = f(B_{i,n}; d, \Gamma, B_{m,n}) + \frac{N}{\sqrt{T_n/M_n}} \equiv f_{i,n} + \frac{N}{\sqrt{T_n/M_n}}, \quad (4)$$

where

$$B_{i,n} = \frac{i\Delta_{B,n}}{M_n - 1} - \frac{\Delta_{B,n}}{2}, i \in \{0, \dots, M_n - 1\}, \quad (5)$$

and N is additive white Gaussian noise with standard deviation σ_N . T_n is the time spent on scan n : $T_1 + \dots + T_R$ must equal T , the total time of the experiment. The penalty for spending less time on a given scan is to either increase the noise in each sample of the scan or to decrease the number of samples in the scan. Figure 1 shows an example of two simulated equal-time scans with different modulation amplitudes and sweep widths.

Let $\vec{\theta} = [d, \Gamma, B_{m,1}, \dots, B_{m,R}]$ denote a list of $R + 2$ unknown parameters. Once the scan parameters are selected, noisy measurements $Y_n = [Y_{0,n}, \dots, Y_{M_n-1,n}]$ are collected (either by simulation or by experiment), and the unknown linewidth is estimated by a weighted least-squares curve fit:

$$\hat{\vec{\theta}} = \underset{\vec{\theta}}{\text{argmin}} \sum_{i,n} \frac{T_n}{M_n} (f_{i,n} - Y_{i,n})^2. \quad (6)$$

Here $\hat{\vec{\theta}}$ is the estimated value of $\vec{\theta}$.

2.2. Statistical analysis

The CRLB provides a lower bound on the standard deviation of an unbiased parameter estimator. Intuitively, if small changes in presumed parameter values cause a *small* change in the fit error of Equation 6, then the estimation is easily corrupted by noise. Conversely, if small changes in presumed parameter values cause a *large* change in the fit error, then the estimation is more robust to noise. This intuition is formalized by the CRLB, which can be used as a tool for experiment design.

The CRLB is computed from the inverse of the Fisher information matrix, $\mathcal{Q}$ (see [17], page 378). Each scan is described by a separate information matrix, $\mathcal{Q}_n$. For the n th scan, let $p(Y_n | \vec{\theta})$ be the probability density function of the data Y_n conditioned on parameters $\vec{\theta}$. Then the elements of the corresponding information matrix according to Equation 4 are as follows:

$$(\mathcal{J}_n)_{k,l} = -\mathbb{E}_{\vec{Y}_n} \left[\frac{\partial^2}{\partial \theta_k \partial \theta_l} \log \left(p(\vec{Y}_n | \vec{\theta}) \right) \right] = \frac{T_n}{2M_n \sigma_N^2} \mathbb{E}_{\vec{Y}_n} \left[\sum_i \frac{\partial}{\partial \theta_k} \frac{\partial}{\partial \theta_l} (Y_{i,n} - f_{i,n})^2 \right] = \frac{T_n}{M_n \sigma_N^2} \sum_i \left(\frac{\partial}{\partial \theta_k} f_{i,n} \right) \left(\frac{\partial}{\partial \theta_l} f_{i,n} \right).$$

Here $\mathbb{E}_{\vec{Y}_n} [\cdot]$ denotes the expectation over $\vec{Y}_n$. The size of the information matrix, $\mathcal{Q}_n$, is $(R+2) \times (R+2)$.

Fisher information from independent experiments is additive. When multiple scans are performed, the total information is the sum of the information from each scan:

$$\mathcal{J} = \sum_n \mathcal{J}_n. \quad (8)$$

The CRLB on the standard deviation of the estimated linewidth $\hat{\Gamma}$ is obtained from the Fisher information as follows:

$$\text{CRLB}_{\hat{\Gamma}}(\vec{\theta}; \Delta_{B,1}, \dots, \Delta_{B,R}, T_1, \dots, T_R, \sigma_N) = \sqrt{(\mathcal{J}^{-1})_{2,2}}. \quad (9)$$

Given a range $[\Gamma_{\min}, \Gamma_{\max}]$, the goal is to determine the number of scans, R , and the corresponding parameters $B_{m,1}, \dots, B_{m,R}, \Delta_{B,1}, \dots, \Delta_{B,R}, T_1, \dots, T_R$ that minimize the average $\text{CRLB}_{\hat{\Gamma}}$ across $[\Gamma_{\min}, \Gamma_{\max}]$. To this end, for a candidate number of scans, R , and a fixed range $[\Gamma_{\min}, \Gamma_{\max}]$, we exhaustively numerically search for the R modulation amplitudes, R sweep widths, and R scan times to minimize the average $\text{CRLB}_{\hat{\Gamma}}$. For the sake of comparison, parameters for single-scan acquisition (i.e., $R = 1$) were also optimized to minimize the average $\text{CRLB}_{\hat{\Gamma}}$.

3. Material and Methods

In this section, we describe the construction of oxygen-sensitive phantoms. We also outline the data acquisition protocols used for L-band oximetry.

The first step in computing the optimized parameters for either a single-scan or a dual-scan experiment is to assume a range of oxygen values that we expect from a given oximetry application. Here, we assume an oxygen range of 0–15 mmHg. Such low oxygen levels are often encountered in cancer oximetry [18]. The second step is to select an oxygen-sensitive probe and compute $[\Gamma_{\min}, \Gamma_{\max}]$ based on the oxygen range. Here, we have used lithium octa-*n*-butoxy naphthalocyanine (LiNc-BuO) [19], a commonly used oxygen-sensitive particulate probe. The anoxic linewidth and oxygen sensitivity of LiNc-BuO, as measured on an L-band CW spectrometer, were 0.356 G and 6.93 mG/mmHg, respectively, yielding a Γ range of 0.356–0.460 G.

A total of ten samples were prepared, each consisting of a 1 mm i.d. capillary tube filled with 50–80 μg of LiNc-BuO. The pO_2 values for the capillary tubes were varied by adding small quantities of sodium hydrosulfite [13] and flame sealing the tubes. The true linewidth values of all ten samples were measured individually under high SNR conditions. Two out of ten samples, named as S_1 and S_2 , had linewidths in the intended Γ range and were thus selected for oximetry measurements. The measured linewidths of S_1 and S_2 were 0.383 G (3.9 mmHg) and 0.436 G (11.5 mmHg), respectively.

The data were collected on an L-band (1.26 GHz) CW spectrometer [20] using a volume reentrant resonator with a 12 mm diameter. Three datasets were collected for both S_1 and S_2 , using a traditional single-scan approach, an optimized single-scan approach, and an optimized dual-scan approach. Here we define the traditional scan as one in which the modulation amplitude and sweep width are set to 2–4 times $\Gamma_{\max}$ and 10–15 times $\Gamma_{\max}$, respectively. For the single-scan approaches, each dataset contained 24 scans. For the dual-scan approach, each dataset contained 24 pairs of scans. Acquisition parameters were as follows: $T = 200$ ms; for single-scan, $M_n = 2048$; for dual-scan, $M_n = 1024$. A delay of 10 ms was allowed between two adjacent scans in each dataset to allow for the spectrometer to stabilize to the correct values of Δ_B and B_m before the next scan. Values of Δ_B and B_m used for each approach are given in Table 4.

4. Results

4.1. Simulated results

Figure 2 shows bounds on the precision when estimating Γ , as a function of the true Γ , when using a variety of approaches. These CRLB results are shown for linewidths from 0.356 to 0.564 G, corresponding to the range 0–30 mmHg pO₂ when using a LiNc-BuO probe [19]. The settings used in each approach are listed in Table 1. Other scan settings are $d = 10$, $M_n = 256$ for single-scan, $M_n = 128$ for dual-scan, $\sigma_N = 1$, and $T = 1$. Based on these and other results from exhaustive searching, we conclude that the best approach is to perform two scans with $T_1 = T_2$. For example, when we tried three scans, initialized with $T_1 = T_2 = T_3$, and allowed the times to vary, the results for minimum CRLB converged to $T_1 = T_2 = T/2$ and $T_3 = 0$, which is the dual-scan approach.

Figure 3 shows the predicted linewidth estimation error for three Γ ranges: 0.356–0.460 G (0–15 mmHg pO₂), 0.356–0.564 G (0–30 mmHg pO₂), and 0.356–1.465 G (0–160 mmHg pO₂). These ranges were selected to represent a tumor oximetry experiment, a tissue oximetry experiment, and a broad-range oximetry experiment, respectively. The figure shows both theoretical results (based on the CRLB) and the results of numerical simulations. The simulated results for each experiment were calculated from 200 ideal scans with artificial noise added, fit according to Equation 6. In each case, the scan settings (see Table 2) were selected to minimize the average CRLB $\hat{\Gamma}$ across the given linewidth range. Again in each case $d = 10$, $M_n = 256$ for single-scan, $M_n = 128$ for dual-scan, $\sigma_N = 1$, and $T = 1$.

4.2. Scan parameter selection

The modulation amplitudes and sweep widths that provide the best results depend on $\Gamma_{\min}$ and $\Gamma_{\max}$. For a given range $[\Gamma_{\min}, \Gamma_{\max}]$, our analysis does not provide a simple closed-form description of the optimized scan parameters. Because it may be impractical to perform an extensive computer search to discover the optimized parameters prior to every experiment, simple guidelines were determined as follows. In Figure 4, we have assumed $\Gamma_{\min} = 0$ and derived the dual-scan ($T_1 = T_2$) parameters as a function of $\Gamma_{\max}$. From linear regression of these curves we arrive at approximate guidelines applicable when $\Gamma_{\min}$ is much less than $\Gamma_{\max}$. The guidelines, given in Table 3, provide recommended modulation amplitudes and sweep widths merely in terms of $\Gamma_{\max}$. Although the guidelines were devised for $\Gamma_{\max} \gg \Gamma_{\min}$, predicted results show only a minimal drop in performance when $\Gamma_{\min}$ is not significantly smaller than $\Gamma_{\max}$. Figure 5 demonstrates how well the simple guidelines perform in a variety of experimental scenarios. In the worst case considered, following the guidelines results in a 4% increase in $\hat{\Gamma}$ standard deviation versus the more thoroughly optimized approach. A similar approach was used to produce simple guidelines for single-scan acquisition, yielding the following guidelines: $B_{m,1} = 2.91\Gamma_{\max}$ and $\Delta_{B,1} = 6.01\Gamma_{\max}$.

4.3. Experimental results

Figure 6A shows the experimentally determined estimation results for a traditional single-scan approach, an optimized single-scan approach, and an optimized dual-scan approach. Because our instrument does not allow for fine tuning of the modulation amplitude or sweep width, we were not able to precisely follow our guidelines for optimized performance. We selected the nearest available values of the parameters, which are listed in Table 4.

5. Discussion

It may be instructive to visualize the approaches recommended in this paper. Figure 7 depicts three sample results from our experiment: a traditional scan, an optimized single-scan, and an optimized dual-scan.

So far, our objective has been to minimize the mean standard deviation of $\hat{\Gamma}$ across $[\Gamma_{\min}, \Gamma_{\max}]$ for a fixed acquisition time. Equivalently, we can specify our objective in terms of acquisition time: given a desired precision, perform the necessary measurements in as little time as possible. The standard deviation of $\hat{\Gamma}$ is proportional to $1/\sqrt{T}$, where T is the total acquisition time. Based on our predicted, simulated, and experimental results, we conclude that following the dual-scan guidelines from Table 3 can result in a 6–10 times speedup versus a traditional single-scan and a 3–4 times speedup versus an optimized single-scan. Figure 6B shows how we could trade the improved precision we found experimentally for shorter acquisition times.

Our instrument did not allow us to precisely follow the guidelines for the optimized dual-scan approach. Despite this, the dual-scan results still outperformed the single-scan results as predicted. This is because both the optimized single-scan approach and the optimized dual-scan approach are robust; that is, a small deviation from the optimized scan parameters only leads to a small drop in performance.

While calibrating the instrument's modulation amplitude (data not shown), we observed a spectral distortion and unexplained attenuation for $B_m > 3$ G. This distortion and attenuation could be due to nonlinear behavior of the modulation amplifier or excessive eddy currents generated in the body of the resonator. Caution should be observed when applying high modulation amplitudes.

Drift in RF circuitry may cause a gradual change in the value of d . Since the signal model assumes that the value of d does not change between the two components of dual-scan acquisition, it is important to collect the two components in close succession to minimize drift in d .

As noted in Section 2, the actual value of the modulation amplitude, in general, is not exactly known and varies slightly and unpredictably from the value set by the user. In some situations the modulation amplitude may be known exactly; the analysis presented here does not apply directly to this case. However, similar analysis (not shown) indicates that a dual-scan approach still outperforms a single-scan approach in this scenario.

Our approach can be extended to spectral-spatial imaging, using either particulate or diffuse probes. In the imaging case, we would not expect to be able to find the *optimal* set of scan parameters, due to the increased computational complexity of the optimization problems involved and the unknown distribution of spin density; the amount of improvement possible remains to be seen. In addition, fully realizing improvements suggested by our CRLB analysis may require the use of a complicated imaging algorithm rather than traditional

tomographic techniques [7], possibly increasing the post-processing time for an imaging experiment significantly.

6. Conclusion

For CW EPR oximetry, a dual-scan approach provides more precise linewidth measurements than a single-scan. The improved precision can lead to a 3–4 times decrease in acquisition time versus a single-scan approach. The dual-scan approach presented provides scan parameters in terms of $\Gamma_{\max}$ only, making it simple to use.

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- A new data acquisition method for EPR-based oximetry is presented.
- The method replaces a traditional single-scan with two different, faster scans.
- Statistical analysis yields the optimal scan parameters for the two scans.
- The proposed method offers reduction in acquisition time by a factor of 3–4.

Figure 1. Two equal-time ($T_1 = T_2$) scans may be more informative than a single-scan. A HWHM linewidth of 0.4 G is depicted here, with $d = 10$, $\sigma_N = 1$, and $M_n = 1024$.

Figure 2.
Comparison of predicted estimation performance for a variety of scan approaches.

Figure 3. Predicted and simulated results for an optimized dual-scan experiment, compared to the same for an optimized single-scan experiment.

Figure 4.
Optimized parameters as a function of $\Gamma_{\max}$, assuming $\Gamma_{\min} = 0$.

Figure 5. Predicted linewidth estimation performance when following the simple dual-scan guidelines in Table 3, compared to performance using more thoroughly optimized settings.

Figure 6.

(A): Comparison of estimation results using two single-scan approaches and a dual-scan approach. Bottom: S_1 ; top: S_2 . The vertical bars represent ± 3 standard deviations of the estimates; smaller bars indicate more reliable measurements. (B): Given a desired precision, how long will each experimental approach take? The dual-scan time shown includes an extra 10% penalty to allow the instrument to stabilize between scans.

Figure 7.

Sample experimental scans. (A): Single-scan with traditional scan parameters. (B): Optimized single-scan. (C): Optimized dual-scan. The settings used for each approach are given in Table 4. For (A) and (B), $M_n = 2048$; for (C), $M_n = 1024$.

Table 1

Optimized scan settings for the predictions shown in Figure 2. Modulation amplitudes and sweep widths are in Gauss.

	A	B	C	D
$B_{m,1}$	1.83	1.90	0.74	0.78
$\Delta_{B,1}$	8.46	3.84	1.65	1.62
T_1	1.00	1.00	0.50	0.33
$B_{m,2}$	—	—	3.96	4.43
$\Delta_{B,2}$	—	—	5.56	6.27
T_2	—	—	0.50	0.33
$B_{m,3}$	—	—	—	9.66
$\Delta_{B,3}$	—	—	—	16.50
T_3	—	—	—	0.33

Table 2

Optimized scan settings to achieve the results shown in Figure 3.

	Single-scan				Dual-scan			
	pO ₂ (mmHg)	0–15	0–30	0–160	0–15	0–30	0–160	0–160
$B_{m,1}$ (G)		1.61	1.90	4.36	0.65	0.74	1.78	1.78
$\Delta_{B,1}$ (G)		3.24	3.84	8.95	1.38	1.65	4.14	4.14
$B_{m,2}$ (G)		—	—	—	3.17	3.96	9.50	9.50
$\Delta_{B,2}$ (G)		—	—	—	4.68	5.56	13.36	13.36

Table 3

Simple guidelines for dual-scan parameter selection based solely on $\Gamma_{\max}$.

Dual-scan acquisition	
$B_{m,1} = 1.22\Gamma_{\max}$	$B_{m,2} = 6.46\Gamma_{\max}$
$\Delta_{B,1} = 2.74\Gamma_{\max}$	$\Delta_{B,2} = 8.99\Gamma_{\max}$

Table 4

Experimental results from Figure 6A, and the scan settings used to achieve them. All values are in Gauss.

	Single-scan, traditional	Single-scan, optimized	Dual-scan, optimized
$B_{m,1}$	1.03 =2.24 $\Gamma_{\max}$	1.46 =3.17 $\Gamma_{\max}$	0.61 =1.33 $\Gamma_{\max}$
$\Delta_{B,1}$	6.00 =13.04 $\Gamma_{\max}$	2.76 =6.00 $\Gamma_{\max}$	1.26 =2.74 $\Gamma_{\max}$
$B_{m,2}$	—	—	2.63 =5.72 $\Gamma_{\max}$
$\Delta_{B,2}$	—	—	4.13 =8.98 $\Gamma_{\max}$
Mean $\hat{\Gamma}$ std.	0.0026	0.0014	0.0007