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Multisite EPR oximetry from multiple quadrature harmonics

R. Ahmad [a,*], S. Som [b], D.H. Johnson [a], J.L. Zweier [a], P. Kuppusamy [a], L.C. Potter [c]

[a] Davis Heart and Lung Research Institute, Department of Internal Medicine, The Ohio State University, Columbus, OH 43210, USA
[b] School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA 30308, USA
[c] Department of Electrical and Computer Engineering, The Ohio State University, Columbus, OH 43210, USA

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ABSTRACT

Multisite continuous wave (CW) electron paramagnetic resonance (EPR) oximetry using multiple quadrature field modulation harmonics is presented. First, a recently developed digital receiver is used to extract multiple harmonics of field modulated projection data. Second, a forward model is presented that relates the projection data to unknown parameters, including linewidth at each site. Third, a maximum likelihood estimator of unknown parameters is reported using an iterative algorithm capable of jointly processing multiple quadrature harmonics. The data modeling and processing are applicable for parametric lineshapes under nonsaturating conditions. Joint processing of multiple harmonics leads to 2–3-fold acceleration of EPR data acquisition. For demonstration in two spatial dimensions, both simulations and phantom studies on an L-band system are reported.

1. Introduction

Any imbalance in tissue oxygen levels may affect metabolic homeostasis and lead to pathophysiological conditions [1]. For instance, the role of hypoxia in cancer treatment [2] and wound healing [3] has been well documented. Hence, a precise knowledge of the levels of oxygen in the tissue of interest is of great importance in our ability to understand the mechanism of pathogenesis and to develop strategies to correct the imbalance.

Electron paramagnetic resonance (EPR) is a branch of spectroscopy in which electrons with unpaired spins, when placed in a magnetic field, absorb electromagnetic radiation to transition from a low energy level to a high energy level. Environment-dependent spectral changes of paramagnetic materials have led to widespread biological application of EPR, including measurement of pO_2 [4], pH [5], perfusion [6], redox [7], and detection of short-lived radicals [8].

The measurement of oxygen concentration or pO_2 by EPR involves the use of an exogenous probe consisting of paramagnetic material in either particulate (solid) or soluble form. The reversible changes in the EPR linewidth of the probe caused by the interaction [9] of two paramagnetic species – molecular oxygen and the probe – have been used to quantify pO_2. Despite the unique advantages of EPR oximetry [4], its transition to broad in vivo application has been slow. Some of the technical problems encountered in EPR oximetry include: requirement of nontoxic exogenous probes, nonresonant absorption resulting in unwanted heating of aqueous samples and small penetration depth at higher frequencies, and poor signal-to-noise ratio (SNR) resulting in long acquisition times at lower frequencies.

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 [10], fast scan [11], rapid scan [12], pulsed EPR [13], parametric modeling [14], adaptive and uniform data sampling [15], digital detection [16–18], and multisite oximetry [19,20] have shown potential to accelerate the acquisition process.

Digital detection, employing a digital heterodyne reception, simultaneously collects absorption and dispersion spectra across multiple harmonics. Digital detection offers significant advantages over the traditional homodyne phase-sensitive detection (PSD), which enables the collection of only one harmonic component. While digital detection increases the amount of EPR data collected in a given time and allows for the flexibility of retrospective signal processing, multisite EPR oximetry, under spatially sparse probe distributions, reformulates an otherwise large problem to a smaller problem with lesser unknowns. Independently, both digital detection and multisite oximetry have been shown to reduce the acquisition time for EPR oximetry. In this work, we present a framework

* Corresponding author. Address: 420 W 12th Ave., Suite 126A, Columbus, OH 43210, USA. Fax: +1 614 292 8454.
E-mail address: Rizwan.Ahmad@osumc.edu (R. Ahmad).

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to take advantage of both these developments simultaneously. Multiharmonic projection data from digital detection are jointly processed to estimate linewidth information at multiple locations. Simulations and experimental data suggest that acquisition and processing of multiple harmonics further accelerates multisite oximetry by a factor of 2–3.

The remainder of the paper is organized as follows: Section 2 provides a brief overview of digital detection and multisite oximetry and describes the proposed data modeling that connects digital detection data to multisite oximetry; Section 3 presents results from both simulation and L-band multisite oximetry using a phantom; Section 4 includes discussion; Section 5 summarizes the conclusions; and Appendices A and B provide derivations of applicable data models.

2. Methodology

2.1. Receiver overview

The details of the digital receiver used to collect multiharmonic projection data have been described before [17] and only a brief synopsis is provided here. The microwave signal reflected from the resonator is amplified and bandpass filtered before it is sampled in channel 1, C_1, of the analog-to-digital converter (ADC). By sampling at a rate, ω_s, below the carrier frequency, ω_c, aliases of the bandpass signal are replicated periodically. An appropriate selection of ω_s ensures that the replicas of the signal are disjoint in frequency, and hence that aliasing artifacts are avoided. For example, with $\omega_c = 2\pi \times 1.28 \times 10^9$ rad/s and $\omega_s = 2\pi \times 400 \times 10^6$ rad/s, an alias of the original bandpass microwave signal is centered at $2\pi \times 80 \times 10^6$ rad/s (i.e., $\omega_c - k\omega_s$ for $k = 3$). Thus, sampling effectively provides demodulation to a digital intermediate frequency (IF) signal.

The microwave source signal is likewise bandpass filtered and is sampled in channel 2 of the ADC, thereby providing a reference for digital demodulation from IF to baseband. Specifically, the contents of C_1 are digitally multiplied with the contents of C_2 and its Hilbert transform to generate in-phase (Y_I) and out-of-phase (Y_Q) baseband channels, respectively. While the two channels of the ADC are time-locked by virtue of a common sampling clock, the sampling clock is not time-locked to the microwave source in this architecture. Both Y_I and Y_Q are then digitally cross-correlated with sinusoidal waveforms at the modulation frequency ω_m and its multiples to extract quadrature harmonics $y_{I,1}, y_{I,2}, y_{I,3} \ldots$, and $y_{Q,1}, y_{Q,2}, y_{Q,3} \ldots$, respectively. The sampled data streams from C_1 and C_2 are decomposed into small blocks, and all the postprocessing is carried out on a block-by-block basis. We use the notations C_1 and C_2 to describe the physical channels of the dual-channel ADC, while the notations I and Q are reserved for the channels that describe quadrature baseband data or extracted EPR quadrature harmonics.

Although the ADC was capable of sampling at a rate up to 500 MHz, we used a lower sampling frequency of 100 MHz. A disadvantage of low sampling rate is the decrease in effective vertical resolution of the ADC [21]. A limited (8 GB) on-board ADC memory was not adequate for higher sampling rates for the long scans required at high magnetic gradient projections. Traditional automatic frequency control (AFC) circuitry [22], employing a PSD, was used to lock the ω_c to the resonance frequency of the resonator. The time-constant of the AFC was kept large enough to ensure that there was no AFC response to ω_m or any of its multiples. A Bruker field controller (ER 032M) was used to sweep the magnetic field.

2.2. Multisite oximetry overview

Multisite oximetry is an EPR-based method that allows measuring oxygen from multiple sites simultaneously, without performing the time consuming spectral-spatial imaging. In 1993, Smirnov et al. [23] proposed an EPR-based multisite oximetry method. Later, Grinberg et al. [19] suggested a similar but improved method. By collecting two projections along a single magnetic gradient orientation, each projection with a different gradient strength, the pO_2 values at multiple sites are estimated using a convolution-based fitting method. This approach has been applied to study cerebral ischemia in rats [24]. The method relies on identifying and collecting projections for which signals from various sites minimally overlap and can be visually separated. Also, its application is strictly limited to the Lorentzian lineshape.

Subsequently, Som et al. [20] suggested a more comprehensive framework for multisite oximetry. The key assumptions made are: (i) the EPR spectrum belongs to a known parametric function family; (ii) the probe distribution is spatially sparse, i.e., the localized spin pockets, called sites, constitute only a small fraction of the field-of-view (FOV); and (iii) each site exhibits a single pO_2 value. Under these assumptions, each spatial voxel is characterized by an unknown spin density and linewidth, and the proposed forward model relates the collected projection data to these unknowns. These parameters are then estimated jointly from a small set of projections. This method not only provides an estimate of linewidth (pO_2) at each site but also reconstructs the spatial distribution of the sites. This approach does not impose any restrictions on the geometry or number of sites. It also does not require a priori knowledge of site locations or a suitable gradient orientation for a given geometry of sites. This approach is a supplement and not a direct alternative to the previous multisite methods which are more restrictive but, when applicable, can offer larger acquisition time savings.

The method proposed in this paper is an extension of our previous work [20]. Unlike the previous version, which solves the multisite problem using undermodulated first harmonic absorption data, this method is capable of jointly processing overmodulated projection data across multiple harmonics for accelerated multisite oximetry.

2.3. Forward modeling

Although it is possible to extend the previous forward model [20] from undermodulated first harmonic absorption data to overmodulated multiharmonic data, here we have adopted a different strategy to avoid the lengthy derivations and extensive computational burden associated with the previous model, which requires computing integrals of the lineshape over the 4D spectral-spatial domain. In the case of overmodulation, the mathematical expressions that describe lineshape become increasingly complex as we move to higher harmonics, making the derivation of analytical expressions extremely tedious and the related coding prone to errors.

Consider a spectral-spatial object with one spectral and three spatial dimensions. The object contains $U \geqslant 2$ spatially nonoverlapping EPR active sites, each occupying a small fraction of the spatial FOV. The voxels that do not belong to any of the sites have zero intensity. Each site may possess a different lineshape and microwave phase α which are assumed to be uniform across the spatial extent of a single site. The parametric expression of the lineshape is known but the actual lineshape parameters, such as linewidth, are unknown.

We can decompose the object into U unique spectral-spatial subobjects, each with the same FOV as the original object but containing only one EPR active site. An EPR projection of a subobject is equivalent to the spatial profile of the subobject convolved with the lineshape of the site in that subobject. The spatial profile for a particular gradient orientation is computed by the Radon transform of the spatial component of the subobject. Both the spatial