Published in final edited form as:

J Magn Reson. 2016 December ; 273: 105–112. doi:10.1016/j.jmr.2016.10.001.

Accelerated Dynamic EPR Imaging using Fast Acquisition and Compressive Recovery

Rizwan Ahmad, Ph.D., Alexandre Samouilov, PhD, and Jay L. Zweier, MD

Abstract

Electron paramagnetic resonance (EPR) allows quantitative imaging of tissue redox status, which provides important information about ischemic syndromes, cancer and other pathologies. For continuous wave EPR imaging, however, poor signal-to-noise ratio and low acquisition efficiency limit its ability to image dynamic processes in vivo including tissue redox, where conditions can change rapidly. Here, we present a data acquisition and processing framework that couples fast acquisition with compressive sensing-inspired image recovery to enable EPR-based redox imaging with high spatial and temporal resolutions. The fast acquisition (FA) allows collecting more, albeit noisier, projections in a given scan time. The composite regularization based processing method, called spatio-temporal adaptive recovery (STAR), not only exploits sparsity in multiple representations of the spatio-temporal image but also adaptively adjusts the regularization strength for each representation based on its inherent level of the sparsity. As a result, STAR adjusts to the disparity in the level of sparsity across multiple representations, without introducing any tuning parameter. Our simulation and phantom imaging studies indicate that a combination of fast acquisition and STAR (FASTAR) enables high-fidelity recovery of volumetric image series, with each volumetric image employing less than 10 s of scan. In addition to image fidelity, the time constants derived from FASTAR also match closely to the ground truth even when a small number of projections are used for recovery. This development will enhance the capability of EPR to study fast dynamic processes that cannot be investigated using existing EPR imaging techniques.

Graphical abstract

Corresponding Author: Dr. Rizwan Ahmad, Ph.D. The Ohio State University, ahmad.46@osu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

EPR; redox; dynamic imaging; compressive sensing

2 Introduction

Methods allowing in vivo mapping of physiologically important tissue parameters such as oxygen content, redox status, and acidosis are of critical importance for diagnostics and optimization of treatment strategies of various pathological states, including cancer and ischemic heart disease. Electron paramagnetic resonance (EPR) is magnetic resonance based technique that has been extensively used to measure tissue oxygen [1], redox [2,3], and acidosis [4,5] in small animals. More recently, EPR oximetry has been used for evaluation of topical tumors in human subjects [6,7]. EPR can characterize the tissue redox status in vivo by measuring the rate of the paramagnetic probe decay, which in biological systems is attributed to the tissue reducing capacity [8,9] or (in case of oxidizable probes) to the processes related to generation of oxidative reactive species in various pathological conditions [10]. Kinetics of these processes is reflected in the redox status of the tissue.

Current EPR technology, when used in the spectroscopic mode, is adequate to investigate both slow and rapid kinetics. However, interpretation of EPR spectroscopy data is confounded by the redistribution of the paramagnetic probe in the body and by the variations in the redox properties of different organs and tissues. Therefore, there is a need to obtain the spatially resolved redox status of the tissue. Several modalities of the EPRI can be utilized for kinetic experiments including pulsed [11], continuous wave (CW) [12], and rapid scan [13,14]. In general, pulsed EPRI is the most efficient modality for imaging; however, its application is limited to the probes with long relaxation time thus not allowing the use of common nitroxides or triarylmethyl probes at normoxic conditions. Acquisition of EPR imaging in both rapid scan and CW modalities are lengthy processes requiring minutes or tens of minutes of acquisition, depending on the dimensions of the acquisition space. For example, EPR imaging, when performed in three spatial dimensions, may require hundreds of projections with reasonable signal-to-noise ratio (SNR) to reconstruct high-fidelity images. Even if each projection acquisition takes only one second to acquire, the entire 3D images can take several minutes to acquire.

Fast acquisition (FA) in CW mode enables collecting a larger number of projections in a given scan time [15,16]. Compared to a small number of high-SNR projections, collecting a larger number of projections with relatively low SNR improves information content of the data by reducing redundancies. Although increasing the scan speed and uniformly distributing the projections [17,18] lead to a more efficient acquisition, SNR may become the limiting factor for in vivo application. Therefore, for realistic SNR values, FA and uniform sampling of the projection data may not be adequate to achieve high-fidelity imaging of rapid dynamic processes. In addition to improving the data acquisition, several data processing methods have also been proposed. Ahn et al. in 2007 demonstrated that projection interpolation can reduce streak artifacts associated with filtered backprojection [19]. Iterative reconstruction methods have also been shown to improve image quality [20,21]. More recently, compressive sensing-inspired iterative techniques have been proposed, enabling EPR imaging from a small number of projections [22,23]. In this study, we propose a new data processing method, called spatio-temporal adaptive recovery (STAR), which exploits sparsity in multiple representations to allow robust recovery from noisy data. Collectively, FA and STAR (FASTAR) lead to a more efficient data acquisition and utilization of priori information, enabling quantitative dynamic imaging in three spatial dimensions.

3 Theory

For CW EPR imaging, data are collected in the form of projections. For a spatio-temporal object, $f(x, y, z, t)$, the spatial projection $p(r, \alpha, \beta, t)$ can be expressed as:

$$\tilde{p}(r; \alpha, \beta, t) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(x, y, z, t) \delta(x \cos \alpha \sin \beta + y \sin \alpha \sin \beta + z \cos \beta - r) dx dy dz, \quad (1)$$

where t represents time and spherical coordinates defined by α, β and r represent the orientation of the projection. For applications where EPR spectrum is spatially invariant, the acquired projection data can be represented by a convolution of the spatial projection data in Eq. 1 and the EPR spectrum, $g(r)$, yielding

$$p(r; \alpha, \beta, t) = \tilde{p}(r; \alpha, \beta, t) * g(r) + \omega, \quad (2)$$

where ‘*’ represents 1D convolution with respect to r , and ω is white Gaussian noise with standard deviation σ . For discretized x, y, z and r , the projection acquisition can be written in matrix form, yielding

$$P_k = A_k F_k + N_k, \quad (3)$$

where P_k, A_k, F_k and represent the projection data, the linear operator that combines Radon transform (Eq. 1) and 1D convolution (Eq. 2), and the spatio-temporal object, respectively,

for the k^{th} projection. In Eq. 3, we assume the acquisition of one projection is considerably faster compared to the dynamics that need to be investigated; therefore, we ignore the change that the spatio-temporal object experiences during the acquisition of a projection. Instead of recovering F for every k , we rearrange the projection data into T frames and aim to perform recovery at a lower temporal resolution of $M\tau$, where M is the number of the projections in each frame and τ is the scan time for each projection. For brevity, we express this forward model in Eq. 3 as

$$P \approx AF + N, \quad (4)$$

where P is a vector that contains measured data from all projections, N is a vector that represents noise in the projection data, A is the measurement matrix, and F is the spatio-temporal object, with T frames at a temporal resolution of $M\tau$. Although it is possible to solve Eq. 4 for $M = 1$, but such a fine temporal resolution would make the problem computationally intractable, especially when a large number of projections are used.

To estimate F , the traditional strategy is to apply filtered backprojection (FBP) independently on each temporal frame. The dynamic information, e.g., redox status, is then extracted using voxel-by-voxel fitting of the reconstructed image series.

Most recent efforts in the area of compressive sensing have been focused on solving a regularized least squares problem with an ℓ_1 -norm penalty enforced on a sparse representation of the signal to be recovered [24]. This formulation can be written as

$$\hat{F} = \arg \min_F \|AF - P\|_2^2 + \lambda \|\Psi F\|_1, \quad (5)$$

where the first term is the data fidelity term, and ΨF is a sparse representation of F under a linear transform Ψ . Common choices of Ψ include wavelet transform and finite differences [25]. The value of λ in Eq. 5 is often tuned manually. The unconstrained formulation [26] in Eq. 5 can be equivalently written in a constrained form:

$$\hat{F} = \arg \min_F \|\Psi F\|_1 \text{ such that } \|AF - P\|_2^2 \leq MT\sigma^2, \quad (6)$$

where σ^2 is the variance of additive white Gaussian noise.

The extensions of Eq. 5 and Eq. 6, where multiple regularization terms are used to better exploit the data structure, have been proposed. However, the resulting compound regularization introduces D tuning parameters, where D is the number of regularization terms. The manual tuning can easily become intractable when $D \geq 2$. For STAR, we extend the problem in Eq. 6 from a single regularization to composite regularization ($D > 1$), yielding,

$$\hat{F} = \arg \min_F \sum_{d=1}^D \lambda_d \|\Psi_d F\|_1 \text{ such that } \|AF - P\|_2^2 \leq MT\sigma^2, \quad (7)$$

where $\Psi_d F$ is the d^{th} sparse representation of F under a linear transformation Ψ_d and λ_d is the regularization strength for the d^{th} representation. In contrast to traditional compressive sensing methods, where λ_d values are tuned manually, we auto-tune λ_d parameters in a data-driven fashion. The STAR algorithm, adapted from a recently published method by Ahmad et al., is summarized in Table 1 [27].

In Table 1, L_d indicates the number of rows in Ψ_d . The primary computational step of STAR is the constrained minimization in line 4 of the algorithm given in Table 1. This is a convex optimization problem and can be readily solved by existing techniques (e.g., Douglas-Rachford splitting [28], ADMM [29], NESTA-UP [26], and MFISTA [30]). In addition, the positivity constraint was enforced on the estimate of F because EPR images are real-valued and positive in general. Note, STAR requires the user to set a small regularization term $\varepsilon > 0$ whose role is to prevent the denominator in line 5 from reaching zero. For typical choices of the analysis operators Ψ_d and σ^2 , the vector $\Psi_d \hat{F}^{(j)}$ will almost never be exactly zero, in which case it suffices to set $\varepsilon = 0$. For implementation of STAR, the convex optimization problem (line 4) was solved by employing 12 iterations of Douglas-Rachford splitting [28], and the process was repeated after updating the values of λ_d (line 5). A fixed value of $J = 16$ was used for all the data processed in this paper; however, the j -indexed iterations were terminated when $\|\hat{F}^{(j)} - \hat{F}^{(j-1)}\|_2 / \|\hat{F}^{(j)}\|_2 < 1 \times 10^{-6}$.

A distinguishing feature of STAR is that it enforces sparsity simultaneously across multiple representations. It has been shown that multiple representations provide a more comprehensive expression of the underlying structure, and the image recovery that exploits sparsity in multiple or redundant representations tend to outperform methods that exploit sparsity under a single, orthogonal transform [31]. Also, the level of sparsity across different representations can vary widely. For example, for most medical imaging applications, the wavelet approximation coefficients, compared to detail coefficients, are rarely sparse. Likewise, for dynamic imaging applications, the finite difference operation applied along temporal dimension may exhibit different level of sparsity than when applied in the spatial dimensions. Since sparsity level for each representation is not known in advance, the user is left to either treat all representations identically or manually tune the regularization strengths for each representation, which can easily become intractable for $D > 2$. In contrast, STAR adapts, in a data-driven manner, to the inherent level of sparsity in each representation and selects λ_d based on the update rule given in the line 6 of the algorithm summarized in Table 1. Intuitively, STAR selects smaller λ_d values for representations that have larger ℓ_1 norm, which implies that STAR preferentially encourages sparsity in the representations that are sparse. Moreover, the proposed adaptation does not require the use of any additional tuning parameters. In fact, STAR uses no tuning parameters beyond the measurement noise power, which, for EPR, can be easily measured.

4 Material and Methods

4.1 Hardware setup

Magnet and Magnet Power Supply—The magnetic field B_0 is generated by a water-cooled spherical solenoid resistive magnet, with an axial opening of 29 cm in diameter, capable of generating magnetic field up to 0.117 T. The design was originally reported by Hoult et al. [32] and later adapted for EPR experiments [33]. The magnet is constructed on two aluminum cast hemispherical formers. The magnet provides homogeneity of better than 3 ppm over a spherical volume of 10 cm. Inductance of serially connected hemispherical coils is 328 mH with active resistance $\sim 8.5 \Omega$. Its magnetic field is horizontally oriented. The magnet was powered by a Copley power supply Model 262NH capable of providing current up to ~ 35 A with existing coils. The magnetic field is current-controlled and its stability relies on the high-precision adjustable reference voltage. The magnet is water cooled and thermo-stabilized through heat exchanger.

Gradient Coils and Gradient Power Supplies—The gradient coil set (BFG-U-140-25) used for EPRI was constructed by Resonance Research Inc. It is a water-cooled set of 3D field cylindrical fast gradients that is interfaced to the gradient power supply amplifiers. The X and Y gradient is a multilayer 2×16 coil set formed from 1.5 mm thick copper plate formed around 1050 mm long fiberglass tube and inner diameter of 138 mm. Z gradient is 66 turn symmetrically distributed solenoid. The gradient coils have low inductance and low resistance (X coil: 1320 μH /143 m Ω ; Y coil: 1550 μH /166 m Ω Z coil: 760 μH /266 m Ω). The gradient coil set is capable of generating a sustained gradient of 250 mT/m along the X, Y, and Z and 500 mT / m at 25 % duty cycle with linearity of about ± 1 % in a spherical volume of 80 mm and ± 5 % in a spherical volume of 140 mm. Rise time 10-90 % is 1 msec. The gradients are powered by a three modified Copley 261P switching amplifiers capable of 62 A per channel, controlled by the computer console with our EPRI data acquisition system through “Data Translation” communication board, model DT-2823. Cooling of the gradient coils (resistive power dissipation = 2.7 kW) is provided by a water circuit heat exchanger (Varian, USA) that also shares the water circuit with the main magnet and sweep coil. Gradient coils are equipped with 8 thermocouple temperature detectors connected to an external scanner interfaced with a safety interlock system that also monitors cooling water pressure.

Sweep Coil and Sweep Power Supply—Sweep of the main magnetic field was provided by a water cooled cylindrical coil (BFM-235-25) constructed by Resonance Research Inc. It is a solenoid resistive magnet formed on the plastic tube with 230 mm inner diameter and placed concentrically over gradient setup. The coil is capable of providing field sweep of ± 3 mT with rise time of 1 msec. The sweep coil has 396 μH inductance and 84 m Ω resistance. Inhomogeneity of the field in 50 mm diameter spherical volume is less than 0.01 %. Sweep coil is equipped with 4 thermocouple temperature detectors.

EPR Resonator—A 8-gap loop-gap L-band resonator (1.24 GHz, ID = 43 mm, length = 48 mm) was similar to the one described in [34] and positioned orthogonally to the magnet bore. The 8-gap design with gaps oriented radially from the center enabled a larger-diameter

resonator to be built for this frequency than would be possible with a lower number of similar gaps, provided good homogeneity of the B_1 magnetic field and good modulation field penetration. This design was previously demonstrated to provide good spatial separation of E and B_1 fields. The dimensions of the resonator were chosen to accommodate and obtain EPR images of the whole body of a living mouse. Resonator was designed with an EPR/NMR coimaging application in mind, therefore the ID of the resonator was increased to accommodate sample holder and fiducials. All elements are enclosed in a nylon mechanical rigid silver plated housing and attached to the resonator holder for easy positioning it in isocenter of the magnet. The resonator is inductively coupled. The quality factor Q of the empty resonator measured using a RF network analyzer was 240, and it dropped to 120 with a resonant frequency of 1.24 GHz when loaded with a the phantom. Helmholtz pair used for field modulation (15 turns of 0.8 mm transformer wire) with diameter 130 mm is connected in serial. Modulation coils are powered through a Haffler FG-P3000D amplifier in non-resonance mode, typically at 100 kHz.

4.2 Simulation studies

A $32 \times 32 \times 32$ dynamic digital phantom with 24 temporal frames was created in Matlab (Mathworks, Natick, MA). The non-zeros voxels in the phantom had three different time constants. Within each region belonging to a specific time constant, spatial intensity gradient was created to avoid piece-wise constant construction, which favors compressive sensing methods. The signal dynamics were modeled by a single exponential decay, with the time constants (in minutes) listed in Figure 1, which shows three orthogonal slices passing through the center of the phantom. The projection data were simulated using these parameters: sweepwidth of 1.6×10^{-3} T, field-of-view $64 \times 64 \times 64$ mm³, number of samples per projection of 128, and golden angle radial sampling [17,35]. The lineshape was assumed to be the first derivative of the Lorentzian function. Ten datasets were simulated at high SNR

($\frac{P_{\max}}{\sigma} = 1000$, with $P_{\max}$ being the maximum absolute value of the vector, P , and σ being noise standard deviation) and narrow peak-to-peak linewidth (2.4×10^{-5} T), and another ten

datasets were simulated at relatively low SNR ($\frac{P_{\max}}{\sigma} = 100$) and broad peak-to-peak linewidth (14×10^{-5} T). The high SNR, narrow linewidth (HS-N) setting mimicked the use of trityl radicals, while low SNR, broad linewidth (LS-B) setting mimicked the use of nitroxide radicals, albeit only a single resonance peak was simulated. The ten datasets, for each combination of SNR and linewidth, differed in terms of the number of projections per frames (N_{pf}). We used the following ten values for $N_{pf} = 8, 16, 24, 32, 48, 64, 80, 96, 128$, and 256. For reconstruction, both FBP and STAR were used for all twenty datasets. For FBP, each temporal frame was reconstructed independently using N_{pf} projections. For STAR, all the frames were reconstructed jointly using $N_{pf} \times 24$ projections. Four dimensional, undecimated wavelet transform (UWT) was used to sparsify the spatio-temporal images, and each of the 16 subbands of UWT was treated as a separate sparse representation, i.e., $D = 16$.

4.3 Phantom studies

Before performing the phantom imaging experiment, we conducted a small study to demonstrate that the hardware setup reported above is capable of performing fast scan. We collected two EPR spectra from a 2 mM 3-Carbamoyl-2,2,5,5-tetramethyl-1-pyrrolidinyl-N-oxyl (3-Carbamoyl-PROXYL from Sigma-Aldrich) sample (6 ml): one using a slow scan (500 ms with no averaging) and the other using fast scan (5 ms with 100 averages). The SNR of the two spectra—defined as the ratio of peak amplitude and noise standard deviation—were compared to establish equivalence between slow and fast scans.

For dynamic imaging, a phantom was constructed of three 55 mm long plastic tubes with 11.5 mm ID. Tubes were filled with 2, 2 and 4 mM concentration of 3-Carbamoyl-2,2,5,5-tetramethyl-1-pyrrolidinyl-N-oxyl nitroxide solution with the linewidth (peak-to-peak) of 14.2×10^{-5} T. Immediately before measurements, solution of ascorbic acid (from Sigma-Aldrich) was added to each tube in amount to obtain final concentration of 10, 20 and 20 mM in each tube correspondently. Tubes were sealed, arranged, and placed in the resonator. Time between initial addition of ascorbic acid and start of image acquisition was less than one minute. To perform 3D imaging, three tubes with three different combinations of nitroxide and ascorbic acid concentrations were taped together and placed inside the resonator. The projection data were collected nonstop for approximately 20 minutes. In addition, spectroscopic data were collected from each individual tube. The sample preparation and the acquisition protocol used for imaging and spectroscopy were identical except for the field gradients, which were turned off for the spectroscopy. Some of the parameters values used for data acquisition include: system frequency 1.18 GHz, field-of-view $65 \times 65 \times 65$ mm³, number of projections 2304, radial sampling with golden mean, sweepwidth 1.7×10^{-3} T, spatial gradient 26×10^{-3} T/m (only applied for imaging data), field modulation amplitude 1.0×10^{-4} T, time per sweep 0.5 s, and reconstruction matrix $32 \times 32 \times 32$. For imaging, the data was divided into 36 uniformly spaced temporal bins, with $N_{pf} = 64$. To mimic high acceleration rates, the image reconstruction process was repeated by retrospectively discarding some of the projections in each of the 36 bins. In total, we used the following six values for N_{pf} : 12, 16, 24, 32, 48, and 64. Four dimensional UWT was used to sparsify the spatio-temporal images, and each of the 16 subbands of UWT was treated as a separate sparse representation, i.e., $D = 16$. To establish ground truth, the time constant were estimated from the spectroscopic data.

4.4 Quality Assessment

For simulation, the reconstructed images were analyzed in terms of visual assessment, recovery SNR ($20 \log (\|F\|_2 / \|F - \hat{F}\|_2)$), and time constants, which were estimated by fitting a single exponential function to the reconstructed simages on voxel-by-voxel basis. The time constant values were individually calculated for each of the three regions identified in Figure 1, with the mean and standard deviation calculated from the voxels within each region. For the experimental data, only visual assessment and time constants were used for quality assessment. Again, the time constant values were individually calculated for each of the three tubes and compared against the ground truth established from the spectroscopic data. For time constant calculation, the voxels belonging to each of the three tubes were identified by performing a single FBP reconstruction from all 2304 projections. Such reconstruction

generated a 3D image with high spatial fidelity—adequate to identify the three-tubes—but no temporal dimension.

5 Results

Figure 2 shows the spectra collected under two different scan rates. The SNR from the slow and fast scans were 102 and 99, respectively. Also, no appreciable spectral distortion was observed for the fast scan, indicating that the hardware setup is capable of sweeping 1.6 mT in just 5 ms. The simulation results are summarized in Figures 3-6. Figure 3 shows representative results when only 16 projections are used per 3D frame, i.e., $N_{pf}=16$, with a total of 16×24 projections for the entire image series. The projection simulation process is repeated for two different setups: (i) LS-B and (ii) HS-N. The reconstruction is performed using both STAR and FBP, resulting in four reconstructed image series: LS-B with FBP, HS-N with FBP, LS-B with STAR, and HS-N with STAR. Figure 4 is similar to Figure 3 except for the number of projections. For the results shown in Figure 4, 256 projections are used per 3D frame, i.e., $N_{pf}=256$. Figure 5 shows recovery SNR as a function of N_{pf} for FBP and STAR. The results are shown for both LS-B and HS-N. Figure 6 displays the estimated time constants as a function of N_{pf} . The time constant values from the proposed FASTAR approach at $N_{pf}=8$ compare favorably to the FBP values at $N_{pf}=256$.

Figures 7 and 8 show results from the experimental data. Figure 7 shows a 2D plane extracted from a 3D reconstructed image, with the cross-sections of all three tubes visible. The same plane is shown at three different time points (frames). The STAR with $N_{pf}=16$ with is compared against FBP $N_{pf}=16$ and FBP with $N_{pf}=64$. Figure 8 shows time constant values calculated from FBP and STAR-based reconstructions for different N_{pf} values. The time constant values from the proposed FASTAR approach at $N_{pf}=12$ compare favorably to the FBP values at $N_{pf}=64$. All the processing was done in Matlab using ordinary CPU-based computing resources. Among all the datasets processed in this work, the worst (longest) computation time was less than 50 minutes.

6 Discussion

In this work, we have implemented a new processing method for dynamic EPR. The method, FASTAR, is based on fast acquisition and iterative, regularized reconstruction. The features that distinguish FASTAR from previously proposed compressive sensing methods [22,23] include: (i) a rapid golden angle radial sampling that allows a retrospective tradeoff between spatial and temporal resolutions, (ii) a composite regularization-based compressive recovery that allows exploiting sparsity in multiple sparse representations to achieve high acceleration, and (iii) data-driven auto-tuning of free parameters, eliminating the need to hand-adjust regularization strength. We have demonstrated the application for FASTAR using realistic simulation and experimental data.

Simulation studies were conducted under conditions of LS-B and HS-N. These two conditions encompass the possible diversity encountered in vivo. For example, the HS-N condition may represent the use of relatively high concentration of EPR spin probes with narrow linewidth (e.g., trityls), and the LS-B condition may represent the use of relatively

low concentration of EPR spin probe with broad linewidth (e.g., nitroxides). Figure 3 shows that FASTAR provides high fidelity images from a very small number of projections. The FASTAR images are free of streak artifacts that are visible in FBP reconstruction. Although FASTAR images capture all the main features of the phantom shown in Figure 1, moderate blurring of the edges is visible in the images. The performance of FASTAR improves, albeit slightly, when the HS-N dataset is used. Figure 4 shows the results when 256 projections are used for each 3D frames. As expected, the quality of FBP reconstruction is improved (compared to Figure 3), with significant reduction in streak artifacts. However, FBP reconstructions still exhibit artifacts, appearing as intensity inhomogeneities. In comparison, FASTAR images are free of visible artifacts and have more defined edges. In the case of HS-N, FASTAR images are visually indistinguishable from the input shown in Figure 1. The recovery SNR for FASTAR and FBP is provided in Figure 5. For both LS-B and HS-N conditions, FASTAR consistently outperforms FBP by 8 dB or more for a wide range of N_{pf} values. As expected, the recovery SNR of HS-N is higher than that of LS-B, but the difference is more pronounced at high values of N_{pf} . The calculated values of the time constants are shown in Figure 6. FASTAR-based images yield more accurate quantification of time constant values even when N_{pf} is small. For example, the quantification based on FASTAR at $N_{pf}=8$ compares favorably to the quantification based on FBP at $N_{pf}=256$, highlighting more than an order of magnitude savings in scan time. For LS-B case, FBP fails to yield accurate estimation of time constants even at $N_{pf}=256$, which is suggestive of the errors introduced by the explicit deconvolution step, which employs low-pass filtering. For FASTAR, the deconvolution is embedded into the forward model and thus no systematic errors are introduced during the reconstruction.

The experimental results shown in Figures 7 and 8 closely follow the simulation results. The results shown in Figure 7 indicate that FASTAR can create high fidelity dynamic images from a small number of projections. At $N_{pf}=16$ (temporal resolution of 8 s), FASTAR is able to resolve the three tubes and is free of artifacts. For FBP, the artifacts mask most of the image details. If the content of the image is not known in advance, it would be challenging to visualize the underlying object for FBP images with $N_{pf}=16$. Even at $N_{pf}=64$, FBP images still exhibit blurred edges and visible artifacts. Figure 8 shows the quantification of time constant values. For FASTAR, the time constant quantification is accurate even at small N_{pf} values. For FBP, on the other hand, the time constant quantification exhibits significantly high bias and variance. Even at $N_{pf}=64$, the time constant values extracted from FBP images are not accurate, in particular for the tube with the highest value of time constant. A high value of time constant leads to a more rapid loss in signal, making the quantification susceptible to artifacts from the tubes with strong signal. We have demonstrated that the hardware setup is capable of scanning at least 1.6 mT in 5 ms without introducing any artifacts or losing SNR. For the phantom imaging, we chose a more modest scan rate (500 ms per projection) to keep the computation tractable by lowering number of projections. For imaging that involves rapidly changing conditions, e.g., a beating rat heart, existing set up can be used to collect projections at a faster rate to suppress the effects of cardiac motion. In cases where fast scan results in a large corpus of data, parallel computing can be used to solve the optimization problem in STAR.

In future, we will validate FASTAR in vivo using small animal models. We recognize that the spatio-temporal content of in vivo redox maps is expected to be more complex compared to the digital and physical phantoms used in this work. However, by employing multiple sparsifying transforms, STAR is well-equipped—compared to other more traditional compressive sensing methods—to exploit complex structure of in vivo data. Therefore, we anticipate that FASTAR will facilitate quantitative redox imaging in vivo.

7 Conclusions

We have proposed and validated a new method to process dynamic CW EPR data. The preliminary results suggest that the method, called FASTAR, yields an accurate image recovery from a small number of noisy projections. In addition to creating artifact-free images, FASTAR is also able to accurately quantify kinetics at high temporal resolution. The acceleration afforded by the combination of fast scan and compressive recovery provides a new opportunity to investigate rapid dynamic processes that cannot be studied using existing acquisition and processing protocols. Also, lack of tuning parameters makes FASTAR attractive for in vivo applications where manual adjustment, without access to the ground truth, can be challenging.

Acknowledgments

This research was supported by NIH grants R01EB014542 and R01EB016096

References

1. Ahmad R, Kuppusamy P. Theory, instrumentation, and applications of electron paramagnetic resonance oximetry. *Chem Rev*. 2010; 110:3212–3236. [PubMed: 20218670]
2. Fujii H, Sato-Akaba H, Kawanishi K, Hirata H. Mapping of redox status in a brain-disease mouse model by three-dimensional EPR imaging. *Magn Reson Med*. 2011; 65:295–303. DOI: 10.1002/mrm.22598 [PubMed: 20860000]
3. Cook JA, Gius D, Wink DA, Krishna MC, Russo A, Mitchell JB. Oxidative stress, redox, and the tumor microenvironment. *Semin Radiat Oncol*. 2004; 14:259–66. DOI: 10.1016/j.semradonc.2004.04.001 [PubMed: 15254869]
4. Khramtsov VV, Grigor'ev IA, Foster MA, Lurie DJ. In vitro and in vivo measurement of pH and thiols by EPR-based techniques. *Antioxid Redox Signal*. 2004; 6:667–76. DOI: 10.1089/152308604773934431 [PubMed: 15130294]
5. Gallez B, Mäder K, Swartz HM. Noninvasive measurement of the pH inside the gut by using pH-sensitive nitroxides. An in vivo EPR study. *Magn Reson Med*. 1996; 36:694–7. [PubMed: 8916019]
6. Williams BB, Khan N, Zaki B, Hartford A, Ernstoff MS, Swartz HM. Clinical electron paramagnetic resonance (EPR) oximetry using India ink. *Adv Exp Med Biol*. 2010; 662:149–56. DOI: 10.1007/978-1-4419-1241-1_21 [PubMed: 20204785]
7. Swartz HM, Williams BB, Zaki BI, Hartford AC, Jarvis LA, Chen EY, Comi RJ, Ernstoff MS, Hou H, Khan N, Swartz SG, Flood AB, Kuppusamy P. Clinical EPR: unique opportunities and some challenges. *Acad Radiol*. 2014; 21:197–206. DOI: 10.1016/j.acra.2013.10.011 [PubMed: 24439333]
8. Hyodo F, Matsumoto Ki, Matsumoto A, Mitchell JB, Krishna MC. Probing the Intracellular Redox Status of Tumors with Magnetic Resonance Imaging and Redox-Sensitive Contrast Agents. *Cancer Res*. 2006; 66:9921–9928. DOI: 10.1158/0008-5472.CAN-06-0879 [PubMed: 17047054]
9. Kuppusamy P, Li H, Ilangovan G, Cardounel AJ, Zweier JL, Yamada K, Krishna MC, Mitchell JB. Noninvasive imaging of tumor redox status and its modification by tissue glutathione levels. *Cancer Res*. 2002; 62:307–12. [PubMed: 11782393]

10. Utsumi H, Yamada K. In vivo electron spin resonance-computed tomography/nitroxyl probe technique for non-invasive analysis of oxidative injuries. *Arch Biochem Biophys*. 2003; 416:1–8. [PubMed: 12859975]
11. Hyodo F, Matsumoto S, Devasahayam N, Dharmaraj C, Subramanian S, Mitchell JB, Krishna MC. Pulsed EPR imaging of nitroxides in mice. *J Magn Reson*. 2009; 197:181–5. DOI: 10.1016/j.jmr.2008.12.018 [PubMed: 19157932]
12. Matsumoto KI, Hyodo F, Matsumoto A, Koretsky AP, Sowers AL, Mitchell JB, Krishna MC. High-resolution mapping of tumor redox status by magnetic resonance imaging using nitroxides as redox-sensitive contrast agents. *Clin Cancer Res*. 2006; 12:2455–62. DOI: 10.1158/1078-0432.CCR-05-2747 [PubMed: 16638852]
13. Mitchell DG, Rosen GM, Tseitlin M, Symmes B, Eaton SS, Eaton GR. Use of Rapid-Scan EPR to Improve Detection Sensitivity for Spin-Trapped Radicals. *Biophys J*. 2013; 105:338–342. DOI: 10.1016/j.bpj.2013.06.005 [PubMed: 23870255]
14. Mitchell DG, Quine RW, Tseitlin M, Meyer V, Eaton SS, Eaton GR. Comparison of continuous wave, spin echo, and rapid scan EPR of irradiated fused quartz. *Radiat Meas*. 2011; 46:993–996. DOI: 10.1016/j.radmeas.2011.03.035 [PubMed: 22003310]
15. Sato-Akaba H, Fujii H, Hirata H. Improvement of temporal resolution for three-dimensional continuous-wave electron paramagnetic resonance imaging. *Rev Sci Instrum*. 2008; 79:123701.doi: 10.1063/1.3033161 [PubMed: 19123563]
16. Chen Z, Reyes LA, Johnson DH, Velayutham M, Yang C, Samouilov A, Zweier JL. Fast gated EPR imaging of the beating heart: spatiotemporally resolved 3D imaging of free-radical distribution during the cardiac cycle. *Magn Reson Med*. 2013; 69:594–601. DOI: 10.1002/mrm.24250 [PubMed: 22473660]
17. Johnson DH, Ahmad R, Liu Y, Chen Z, Samouilov A, Zweier JL. Uniform spinning sampling gradient electron paramagnetic resonance imaging. *Magn Reson Med*. 2014; 71:893–900. DOI: 10.1002/mrm.24712 [PubMed: 23475830]
18. Redler G, Epel B, Halpern HJ. Maximally spaced projection sequencing in electron paramagnetic resonance imaging. *Concepts Magn Reson Part B Magn Reson Eng*. 2015; 45:33–45. DOI: 10.1002/cmr.b.21280 [PubMed: 26185490]
19. Ahn KH, Halpern HJ. Comparison of local and global angular interpolation applied to spectral-spatial EPR image reconstruction. *Med Phys*. 2007; 34:1047–52. DOI: 10.1118/1.2514090 [PubMed: 17441251]
20. Spitzbarth M, Drescher M. Simultaneous iterative reconstruction technique software for spectral-spatial EPR imaging. *J Magn Reson*. 2015; 257:79–88. DOI: 10.1016/j.jmr.2015.06.001 [PubMed: 26102454]
21. Johnson CA, McGarry D, Cook JA, Devasahayam N, Mitchell JB, Subramanian S, Krishna MC. Maximum Entropy Reconstruction Methods in Electron Paramagnetic Resonance Imaging. *Ann Oper Res*. 2003; 119:101–118. DOI: 10.1023/A:1022978322046
22. Johnson DH, Ahmad R, He G, Samouilov A, Zweier JL. Compressed sensing of spatial electron paramagnetic resonance imaging. *Magn Reson Med*. 2014; 72:893–901. DOI: 10.1002/mrm.24966 [PubMed: 24123102]
23. Qiao Z, Redler G, Epel B, Qian Y, Halpern H. 3D pulse EPR imaging from sparse-view projections via constrained, total variation minimization. *J Magn Reson*. 2015; 258:49–57. DOI: 10.1016/j.jmr.2015.06.009 [PubMed: 26225440]
24. Candes EJ, Wakin MB. An Introduction To Compressive Sampling. *IEEE Signal Process Mag*. 2008; 25:21–30. DOI: 10.1109/MSP.2007.914731
25. Lustig M, Donoho D, Pauly JM. Sparse MRI: The application of compressed sensing for rapid MR imaging. *Magn Reson Med*. 2007; 58:1182–1195. [PubMed: 17969013]
26. Becker S, Bobin J, Candes E. NESTA: A Fast and Accurate First-order Method for Sparse Recovery. *SIAM J Imaging Sci*. 2011; 4:1–39. DOI: 10.1137/090756855
27. Ahmad R, Schniter P. Iteratively Reweighted L1 Approaches to Sparse Composite Regularization. *IEEE Trans Comput Imaging*. 2015; 1:220–235. DOI: 10.1109/TCI.2015.2485078
28. Combettes PL, Pesquet JC. Image Restoration Subject to a Total Variation Constraint. *IEEE Trans Image Process*. 2004; 13:1213–1222. DOI: 10.1109/TIP.2004.832922 [PubMed: 15449583]

29. Boyd S. Distributed Optimization and Statistical Learning via the Alternating Direction Method of Multipliers. *Found Trends® Mach Learn*. 2010; 3:1–122. DOI: 10.1561/22000000016
30. Tan, Zhao; Eldar, YC.; Beck, A.; Nehorai, A. Smoothing and Decomposition for Analysis Sparse Recovery. *IEEE Trans Signal Process*. 2014; 62:1762–1774. DOI: 10.1109/TSP.2014.2304932
31. Carrillo RE, McEwen JD, Van De Ville D, Thiran JP, Wiaux Y. Sparsity averaging for compressive imaging. *IEEE Signal Process Lett*. 2013; 20:591–594. DOI: 10.1109/LSP.2013.2259813
32. Hoult DI. Electromagnet for nuclear magnetic resonance imaging. *Rev Sci Instrum*. 1981; 52:1342.doi: 10.1063/1.1136769
33. Deng Y, He G, Petryakov S, Kuppusamy P, Zweier JL. Fast EPR imaging at 300 MHz using spinning magnetic field gradients. *J Magn Reson*. 2004; 168:220–7. DOI: 10.1016/j.jmr.2004.02.012 [PubMed: 15140431]
34. Petryakov S, Samouilov A, Kesselring E, Wasowicz T, Caia GL, Zweier JL. Single loop multi-gap resonator for whole body EPR imaging of mice at 1.2 GHz. *J Magn Reson*. 2007; 188:68–73. DOI: 10.1016/j.jmr.2007.05.021 [PubMed: 17625940]
35. Feng L, Axel L, Chandarana H, Block KT, Sodickson DK, Otazo R. XD-GRASP: Golden-angle radial MRI with reconstruction of extra motion-state dimensions using compressed sensing. *Magn Reson Med*. 2016; 75:775–788. DOI: 10.1002/mrm.25665 [PubMed: 25809847]

Highlights

For EPR imaging, long scan times limit its ability to image dynamic processes.

We present a data acquisition and processing framework to accelerate EPR imaging.

The method couples fast acquisition with compressive sensing-inspired image recovery.

The method enables EPR-based redox imaging with high spatial and temporal resolution.

Figure 1.

A $32 \times 32 \times 32$ 3D digital phantom used for simulation studies. (a) Intensity maps for three orthogonal planes passing through the center. (b) Corresponding time constant maps. The phantom has three “materials” with time constants of 5, 10, and 15 minutes.

Figure 2.

EPR spectra of the low-field peak of 2 mM 3CP collected under two different scan rates. For a total scan time of 500 ms, slow scan (blue line on the top) employed a single field sweep while fast scan (red line on the bottom) averaged 100 fast sweeps. Both slow and fast acquisitions exhibit similar SNR values of 102 and 99, respectively.

Figure 3.

Reconstruction results when $N_{pf} = 16$. (a) Intensity maps. (b) Corresponding time-constant maps. First row: Filtered backprojection (FBP) from projections with low SNR and broad linewidth (LS-B). Second row: FBP from projections with high SNR and narrow linewidth (HS-N). Third row: STAR from projections with LS-B. Fourth row: STAR from projections with HS-N. Three orthogonal planes from the first temporal frame are shown.

Figure 4.

Reconstruction results when $N_{pf} = 256$. (a) Intensity maps. (b) Corresponding time-constant maps. First row: Filtered backprojection (FBP) from projections with low SNR and broad linewidth (LS-B). Second row: FBP from projections with high SNR and narrow linewidth (HS-N). Third row: STAR from projections with LS-B. Fourth row: STAR from projections with HS-N. Three orthogonal planes from the first temporal frame are shown.

Figure 5. Recovery SNR for the digital phantom. (a) Results from the data with high SNR and narrow linewidth (HS-N). (b) Results from the data with low SNR and broad linewidth (LS-B). Npf indicates the number of projections/frame.

Figure 6.

Time constants estimated from the reconstructed digital phantom image series. Each time constant corresponds to one of the three materials identified in Figure 2. (a) Results from the data with high SNR and narrow linewidth (HS-N). (b) Results from the data with low SNR and broad linewidth (LS-B). Npf indicates the number of projections/frame. The true values of the time constants are indicated by horizontal dashed lines in gray. The error bars indicate the $\pm 2 \times$ standard deviation among the voxels that belong to the region of same time constant.

Figure 7.

Images reconstructed with filtered backprojection (FBP) and the proposed STAR approach.

(a) Representative intensity maps from one slice at three time points (frames) are shown.

The true values of the time constants for the tubes marked with 1, 2, and 3 were 27.1 min,

18.8 min, and 16.9 min, respectively. (b) Corresponding time constant maps.

Figure 8.

The estimated time constants from the three tubes shown in Figure 8. Dash lines present the time constants calculated from the EPR spectral measurements of the decay of the individual tubes. The error bars indicate the $\pm$ standard deviation among the voxels that belong to the same physical tube.

Table 1**STAR algorithm**

1:	input: $\{\psi_d\}_{d=1}^D, A, P, \sigma^2, \varepsilon$
2:	initialization: $\lambda_d = 1 \forall d$
3:	for $j = 1, 2, 3, \dots, J$
4:	$F^{(j)} \leftarrow \arg \min_F \sum_{d=1}^D \lambda_d^{(j)} \ \psi_d F\ _1 \text{ s.t. } \ AF - P\ _2^2 \leq \text{MT}\sigma^2, F \geq 0$
5:	$\lambda_d^{(j+1)} \leftarrow \frac{L_d}{\varepsilon + \ \psi_d F^{(j)}\ _1}, d=1, 2, \dots, D$
6:	End
7:	output: $\hat{F} \leftarrow F^{(J)}$