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Bayesian Modeling of NMR Data: Quantifying Longitudinal Relaxation *in Vivo*, and *in Vitro* with a Tissue-Water-Relaxation Mimic (Crosslinked Bovine Serum Albumin)

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Abstract

Recently, a number of MRI protocols have been reported that seek to exploit the effect of dissolved oxygen (O₂, paramagnetic) on the longitudinal ¹H relaxation of tissue water, thus providing image contrast related to tissue oxygen content. However, tissue water relaxation is dependent on a number of mechanisms, and this raises the issue of how best to model the relaxation data. This problem, the model selection problem, occurs in many branches of science and is optimally addressed by Bayesian probability theory.

High signal-to-noise, densely sampled, longitudinal ¹H relaxation data were acquired from rat brain *in vivo* and from a cross-linked bovine serum albumin (xBSA) phantom, a sample that recapitulates the relaxation characteristics of tissue water *in vivo*. Bayesian-based model selection was applied to a cohort of five competing relaxation models: (i) monoexponential, (ii) stretched-exponential, (iii) biexponential, (iv) Gaussian (normal) R₁-distribution, and (v) gamma R₁-distribution. Bayesian joint analysis of multiple replicate datasets revealed that water relaxation of both the xBSA phantom and *in vivo* rat brain was best described by a biexponential model, while xBSA relaxation datasets truncated to remove evidence of the fast relaxation component were best modeled as a stretched exponential. In all cases, estimated model parameters were compared to the commonly used monoexponential model. Reducing the sampling density of the relaxation data and adding Gaussian-distributed noise served to simulate cases in which the data are acquisition-time or signal-to-noise restricted, respectively. As expected, reducing either the number of data points or the signal-to-noise increases the uncertainty in estimated parameters and, ultimately, reduces support for more complex relaxation models.

1. Introduction

Essentially all data analysis employs a data model (or data representation), either explicitly or implicitly. Generally, the data are considered to be the sum of the signal plus noise and it is the estimated signal model parameters that are of primary interest. In the ideal case, the underlying principles governing the measurement protocol and the signal response are known and form the basis of the signal model. Often, however, this is not the case and there exists a cohort of competing signal models from which to choose. This may be because the underlying principles are not fully known or because the underlying principles dictate a signal model that is too complex for meaningful comparison to data that are insufficiently informative and, thus, simplified models based on the full complex model must be considered. In either case, the analyst is faced with the model selection problem, specifically, choosing which of a cohort of competing signal models best represents the data, without “over fitting” (i.e., fitting the noise).

Bayesian probability theory based model selection provides the optimal answer to this challenge. Bayesian analysis is “optimal” in the sense that other methods can approach, but not surpass, the Bayesian result. To determine the optimal model amongst a cohort of competing models, it is necessary to balance the degree of accuracy to which the model recapitulates the data (the goodness of fit, characterized by the residuals) against the number of free parameters in each model (the complexity). Conceptually, the law of parsimony, or Occam's razor, achieves such balance, to wit, “Plurality must not be posited without necessity”, i.e., amongst competing hypotheses, the simplest is best. Occam's razor is implicit in Bayesian probability theory. Indeed, Cox's theorem [1] and its further elaboration by Jaynes [2, 3] states that Bayesian probability theory is the optimal method for making quantitative inference about data (i.e., optimally balancing model goodness of fit against model complexity).

In brief, Bayesian probability theory quantifies the probability for a model/hypothesis, described by a posterior probability distribution, given the evidence (data) and all prior information about the system. In a qualitative sense, the posterior probability for a model is inversely related to the aggregate calculated uncertainty over all parameter estimates in a given model. (A more quantitative description of posterior probabilities is provided in Methods.) This qualitative description is useful, in that it highlights the intrinsic penalties associated with: (i) the evidence – uncertainty in the evidence, in the form of noisy and/or sparse data, propagates into calculated posterior probability distributions, and (ii) the model/hypothesis – increased parameterization/complexity must result in substantially reduced aggregate uncertainty for a more complex model to be favored (satisfaction of Occam's razor).

MRI pulse sequences that leverage relaxation properties (e.g., T_1 , T_2 , T_2^*) of the tissue water ^1H magnetization, i.e., that yield a relaxation-dependent signal-intensity (relaxation-dependent “contrast”), form the foundation of a wide range of important research and clinical MRI protocols. Recently, a number of MRI protocols have been reported that seek to exploit the effect of dissolved oxygen (O_2 , paramagnetic) on the longitudinal relaxation of tissue water, thereby providing image contrast related to tissue oxygen content [4-7].

However, water relaxation in tissue is complicated by competing mechanisms (e.g., magnetization transfer) [8-11] and confounds (e.g., blood flow) [4] and, while the MRI literature is dominated by monoexponential relaxation modeling, such an approach is oversimplified.

Our interest in quantifying tissue water longitudinal relaxation stems from the possibility of creating images in which voxel intensities reflect the dissolved O_2 content. Molecular oxygen, O_2 , is slightly paramagnetic and, thus, acts as a relaxation agent, albeit with a small relaxivity ($\text{mM}^{-1}\text{sec}^{-1}$). The underlying question is then, “Can we make tissue water longitudinal relaxation measurements of sufficient accuracy and precision so as to quantify the content of dissolved O_2 ”? The two principal tissue water relaxation mechanisms that compete with dissolved paramagnetic O_2 are: (i) magnetization transfer (through-space and chemical exchange) with the tissue’s “macromolecular matrix” and (ii) blood flow, which can bring equilibrium magnetization into the selected image slice. The “apparent” relaxation effects of blood flow can be largely mitigated by appropriate choice of pulse-sequence and are not dealt with here. However, to explore the effects of magnetization transfer on tissue water relaxation data and modeling thereof, we have employed cross-linked BSA (x-BSA) as a tissue mimic, one that exhibits strong magnetization transfer effects but, of course, none of the confounds introduced by blood flow. Given this tissue mimic, the question is then how to best model the relaxation data, the model selection challenge.

Biophysical modeling of tissue water longitudinal relaxation has been a topic of investigation for decades. A monoexponential function is the simplest and most commonly used relaxation model [4, 12, 13]. Use of this model assumes that there effectively exists a single, uniform population of water molecules (extreme narrowing) that can be characterized by a single longitudinal relaxation rate constant. Some have modeled tissue water longitudinal relaxation as a biexponential function, with two distinct (“slow” and “fast”) relaxation populations [8, 10]. However, the assumption of two relaxation populations is undoubtedly a simplification and the heterogeneity of tissue microstructure has led others to model relaxation based on a pseudo-continuous distribution of relaxation populations, each with a unique relaxation rate constant [14]. The stretched exponential characterizes such a system with a single relaxation rate constant and a “stretching” parameter, α , which describes, empirically, the unknown distribution of relaxation populations. Alternatively, the distribution can be explicitly assumed in the model, with Gaussian [15] and gamma [15] functions serving as the most common distributions.

Bayesian model selection is broadly applicable to a wide range of NMR data-analysis problems when a selection from amongst a cohort of competing signal models must be made. In the present paper, we illustrate the use of Bayesian probability theory for data-driven model selection using longitudinal relaxation data obtained *in vivo* (mouse brain white matter) and *in vitro* with a tissue surrogate (xBSA). Water ^1H magnetization relaxation data were acquired with a high signal-to-noise ratio (SNR) and high sampling density (regarding post inversion delay times, TIs) to compare amongst a cohort of competing, semi-empirical relaxation models under near ideal circumstances. SNR and sampling density were degraded in these same datasets to examine the impact of data quality on “optimal” (most probable) relaxation model selection and derived parameter estimates. As the data quality

decreases, becoming less informative, complex models become less probable and simpler models are preferred, a quantitative, statistical (probabilistic) manifestation of Occam's razor.

2. Methods

2.1 Phantom Preparation and Data Acquisition

Samples of cross-linked 15% (by weight) bovine serum albumin (xBSA) were prepared by diluting a 30% BSA solution (Sigma Aldrich, St. Louis, MO, USA) using phosphate buffered saline (PBS, pH 7.4). Samples were cross-linked using a 2.5% (by volume) solution of 50% glutaraldehyde (Electron Microscopy Sciences, Hatfield, PA, USA). Samples were stirred with a spatula for one minute and then placed in the refrigerator ($\sim 4^{\circ}\text{C}$) for two days. Four cylindrical pieces of xBSA were then extruded and each was placed into a 5 mm, susceptibility-matched, symmetrical NMR microtube (Shigemi Inc, Allison Park, PA, USA) and maintained at 37°C for ~ 24 hours prior to data acquisition.

^1H NMR relaxation experiments were performed on a 500-MHz (11.74 T) Agilent/Varian high-resolution NMR spectrometer. Most longitudinal relaxation data were collected using a Modified Fast Inversion Recovery (MFIR) pulse sequence [16], as shown in Figure 1A. Acquisition parameters were: 10,000 Hz bandwidth, 2,500 complex data points, water ^1H linewidth ~ 60 Hz, 96 exponentially spaced inversion delay times (TI) ranging from 5 ms to 7.5 s, and 96 exponentially spaced wait times (W) ranging from 8.495 s to 1 s. Values of TI and W were chosen such that the total repetition time ($\text{TR} = \text{W} + \text{TI}$) was a constant value of 8.5 s. Four phase-cycled transients were collected for each TI; short, square, RF pulses were employed for inversion ($\theta_1 \sim 22 \mu\text{s}$; 180 degrees) and readout ($\theta_2 \sim 1.5 \mu\text{s}$; 10 degrees); and two steady-state ('dummy scan') acquisitions were utilized. A 1-ms crusher gradient was applied following the inversion pulse to suppress any residual transverse magnetization arising from imperfect inversion. Relaxation data for each of the four samples were acquired in triplicate, resulting in twelve total datasets.

A separate set of experiments was performed to compare data acquired with the MFIR pulse sequence to data acquired with the standard Inversion Recovery (IR) pulse sequence under two different conditions. Acquisition parameters for the MFIR experiment were: 10,000 Hz bandwidth, 2,500 complex data points, water ^1H linewidth ~ 150 Hz, 64 exponentially spaced inversion delay times (TI) ranging from 5 ms to 7.5 s, and 64 exponentially spaced wait times (W) ranging from 8.495 s to 1 s. Values of TI and W were chosen such that the total repetition time ($\text{TR} = \text{W} + \text{TI}$) was a constant value of 8.5 s. Four phase-cycled transients were collected for each TI; square, RF pulses were employed for inversion and readout; and five steady-state ('dummy scan') acquisitions were utilized. Acquisition parameters for the IR experiment were: 64 exponentially spaced inversion delay times (TI) ranging from 5 ms to 7.5 s, and a relaxation delay time (time following the θ_2 readout pulse) of 10 s. All other parameters were the same as the MFIR experiment.

For these comparative experiments, two sets of square, RF pulse widths were utilized, designated as either "short" (broad excitation bandwidth) or "long" (narrow excitation bandwidth). For the short pulse width condition, the inversion pulse $\theta_1 \sim 22 \mu\text{s}$ (180 degrees)

and the observation pulse $\theta_2 \sim 11 \mu\text{s}$ (90 degrees). For the long pulse width condition, the inversion pulse $\theta_1 \sim 1.3 \text{ ms}$ (180 degrees) and the observation pulse $\theta_2 \sim 650 \mu\text{s}$ (90 degrees). All relaxation data (MFIR vs. IR; short vs. long pulses) were acquired in interleaved fashion in triplicate on a single sample, resulting in three replicate datasets for each of the four protocols.

2.2 In Vivo Subject Preparation and Data Acquisition

All animal experiments were approved by the Washington University Institutional Animal Care and Use Committee. *In vivo* ^1H relaxation data were collected on a 4.7-T small-animal MRI system (Agilent Technologies, Santa Clara, CA, USA) using a laboratory-built, actively decoupled, volume-transmit/surface-receive coil pair. One 200 g female Sprague Dawley Rat was anesthetized with 1% isoflurane in 100% O_2 , and body temperature was monitored with a rectal thermometer and maintained at 37°C *via* the combination of circulating warm water and warm air. An Inversion Recovery Point RESolved Spectroscopy (IR-PRESS) sequence selecting a $1.6 \times 1.6 \times 1.6 \text{ mm}^3$ voxel was modified to minimize apparent relaxation contributions from blood flow, as shown in Figure 1B. Specifically, the sequence employed: (i) a non-slice-selective inversion pulse, followed by 8-gauss/cm crusher gradients applied along all three axes to destroy any transverse magnetization created by an imperfect inversion pulse, and (ii) weak, diffusion-sensitizing gradients applied along all three axes (total $b = 100 \text{ s/mm}^2$) to destroy any transverse coherence of blood-water ^1H magnetization flowing into the PRESS voxel *via* the vasculature. Acquisition parameters were: 4006 Hz bandwidth, 2048 complex data points, water ^1H linewidth $\sim 11 \text{ Hz}$, 128 exponentially spaced inversion delay times (TI), ranging from 0.0075 sec to 4.25 sec, effective echo time (TE) of 20 ms and a repetition time (TR) of 5 sec. Relaxation data were collected in triplicate from the corpus callosum (white matter).

2.3 Mathematical Models

The monoexponential relaxation model is given by:

$$M_z(t) = A * \exp(-t * R_1) + C, \quad [1]$$

in which $M_z(t)$ is the net longitudinal magnetization, A is a constant amplitude, t is time (corresponding to the inversion delay time, TI, in our experiments), R_1 is the longitudinal relaxation decay rate constant, and C is a constant offset. Similarly, the biexponential model can be written as:

$$M_z(t) = A * [f * \exp(-t * R_{1,fast}) + (1 - f) * \exp(-t * R_{1,slow})] + C, \quad [2]$$

in which F is the fraction of the total amplitude of the “fast” relaxation component and $(1-F)$ is the fraction of the “slow” relaxation component. The stretched monoexponential relaxation model is described by inserting a fractional power law into the monoexponential function:

$$M_z(t) = A * \exp(-t^\alpha * R_1) + C, \quad [3]$$

in which α is the stretching exponent.

Two additional models were considered: A Gaussian-type (normal) distribution function for R_1 [15] and an R_1 distribution function based on the gamma distribution [15]. The Gaussian-type function is given by:

$$P(R_1) = \begin{cases} A * \exp\left(-\frac{(R_1 - R_{1,max})^2}{2\sigma^2}\right) + C, & R_1 > 0 \\ 0, & R_1 < 0 \end{cases}, \quad [4]$$

in which A is a normalization constant:

$$A^{-1} = \sigma \sqrt{\frac{\pi}{2}} \left[1 + \Phi\left(\frac{R_{1,max}}{\sigma\sqrt{2}}\right) \right]. \quad [5]$$

$R_{1,max}$ corresponds to the peak of the distribution, σ is the standard deviation of the distribution (σ^2 is the variance), Φ the error function, and C is constant offset. The modified gamma-type distribution is of the form:

$$M_z(t) = (t=0) * \left(\frac{a}{a + t * R_{1,max}} \right)^{(a+1)} + C, \quad [6]$$

in which $M_z(t=0)$ is the initial net longitudinal magnetization, a is a shape parameter, and C is a constant offset.

2.4 Bayesian-Based Model Selection

The posterior probability for each of the relaxation models was calculated using Bayes' theorem [2, 3]:

$$P(M|DI) = \frac{P_{(M|I)} P(D|MI)}{P(D|I)}, \quad [7]$$

in which $P(M|DI)$ is the posterior probability for a model M, given data D, and prior information I; $P(M|I)$ is the prior probability for a model given the prior information; $P(D|I)$

$M|I$) is the probability for the data, given the model and the prior information; and $P(D|I)$ is the direct probability for the data, given the prior information. To calculate the posterior probability for a model given the data and the prior information, the direct probability for the data, given the model and the prior information, must first be calculated. As an example, the stretched exponential model has two calculated parameters, α and R_1 , such that the expansion of $P(D|M|I)$ is of the form:

$$P(D|M|I) = \int d\alpha dR_1 P(\alpha R_1|M|I) P(D|\alpha R_1 M|I), \quad [8]$$

in which $P(\alpha R_1|M|I)$ is the joint prior probability for α and R_1 , given the model and the prior information, and $P(D|\alpha R_1 M|I)$ is the direct probability, given the parameters, model, and prior information.

In Bayesian probability theory, the entire multidimensional integral or “hypervolume” covering the full range of possible parameter values must be computed and contributes directly to $P(M|D|I)$. Every hypervolume is computed by integrating the joint prior probability for the parameters weighted by the direct probability of the data, given the parameters. Using in-house developed Bayesian analysis software (available for free download at bayer.wustl.edu) that utilizes Markov-chain Monte Carlo simulations to approximate the high-dimensional integrals, the posterior probabilities for each of the models, and their associated parameters, were calculated.

In each case, the results shown are from the joint analysis of either three (*in vivo*) or twelve (xBSA) replicate datasets. Generally, in a joint analysis, some of the model parameters are assigned as common (common valued) to all members of the full set of replicate datasets and some are assigned as unique (uniquely valued) to each member of the full set of replicate datasets. In the joint analysis employed herein, the reported model parameters (e.g., relaxation rate constants) were taken as common to all members of the full set of replicate datasets. The values of each of the model's common parameters that best represented the full set of replicate datasets were taken as optimal (most probable). We note that Bayesian joint analysis is distinct from averaging either the datasets or the parameters estimated from each dataset. In Bayesian joint analysis, the probability distributions weight the parameter estimates toward those favored by the more informative (e.g., higher signal-to-noise, fewer artifacts) members of the full set of replicate datasets. Herein, data quality was relatively uniform (equally informative) across all replicate datasets.

Within the Markov-chain Monte Carlo simulation, 50 parallel simulations were performed to sample the posterior probabilities for the model and its parameters. Simulated annealing brought the 50 simulations into steady-state equilibrium, at which time 50 samples from each of the 50 simulations were drawn. Thus, in total, 2,500 parameter samples were used to characterize the posterior probability density distributions for the models and their parameters.

Herein, the peak (maximum) of the relevant posterior probability density distributions are taken as the optimal (most probable) parameter estimates. Alternatively, one could choose the mean of the distribution. For symmetrical distributions, these choices are, obviously, equivalent. Uncertainty in a given parameter estimate is taken as $\pm$ the standard deviation (square root of the variance) of the distribution. More precise parameter estimates are characterized by narrower posterior probability density distributions.

2.5 Data Truncation, Sampling Density Reduction, and Noise Addition

As will be described, Bayesian model selection heavily favored the biexponential model for the xBSA longitudinal relaxation data (*vide infra*). In this case, the fast relaxation component is characterized by a rate constant that is two orders of magnitude greater than that of the slow relaxation component, but has an amplitude that is only 2% that of the slow component. As a consequence, the available dynamic range and sampling density is limited, until the slow component dominates the signal. In practice, accurate characterization of this small-amplitude fast component will often be impractical due to time constraints and/or insufficient SNR and further, might be uninteresting for some experiments (e.g., contrast agent quantification, when it is expected that the relaxation modulating effects of the agent will only be observable on the slow rate constant). To simulate a potential time saving inversion recovery experiment, we truncated our datasets to include only data points associated with the slow component. Based on estimation of the relaxation rate constant for the fast relaxation component ($R_{1,\text{fast}} = 1/T_{1,\text{fast}}$) from the joint analysis of twelve full, 96-TI-value datasets, the first 45 TIs were removed, obviating information on relaxation occurring during the period of $5 \times T_{1,\text{fast}}$, and the smallest TI was then approximately 160 ms.

To more accurately mimic the *in vivo* case, in which both acquisition time and SNR may be limited, these twelve truncated xBSA relaxation datasets (i.e., minimum TI ~ 160 ms, data reflecting only the slow relaxation component) were further modified. (i) To simulate the acquisition-time-limited case, the sampling density was made increasingly sparse by iteratively removing every other data point, until only seven TIs remained. Bayesian joint analysis was then performed on the full datasets (51 TIs), intermediate-size datasets (26 TIs), and small-size datasets (7 TIs). (ii) To explore the effect of limited SNR, Gaussian-distributed noise (zero mean, standard deviation of one) was added to each of the twelve full (51 TI values) datasets. Prior to the addition of noise, these *in vitro* xBSA samples exhibit very high SNR (SNR = 600), defined throughout as the signal amplitude at the longest TI value divided by the root mean square noise value. Added Gaussian-distributed noise reduced the SNR to an intermediate value (SNR = 100) and a lower value (SNR = 25) typical of *in vivo* relaxation datasets. Bayesian joint analysis was then performed on the full datasets (51 TIs) at each of the three SNRs. (iii) To determine the combined effects of limited data sampling density and limited SNR on parameter estimation, Gaussian-distributed noise was added to reduce the SNR to an intermediate value (SNR = 100) followed by the reduction of the sampling density to achieve the full datasets (51 TIs), intermediate-size datasets (26 TIs), and small-size datasets (7 TIs). Bayesian joint analysis was then performed on the twelve, intermediate SNR valued datasets at each of the three sampling densities.

3. Results

As shown in Figure 2, Bayesian joint analysis of the twelve full (96 TIs) relaxation datasets, collected using the xBSA sample, selected the biexponential as the heavily favored model. However, residuals from both biexponential and monoexponential models display clear, smooth oscillations, characteristic of under-parameterization, suggesting that the biexponential model does not fully represent xBSA relaxation data characterized by both high signal-to-noise, SNR = 600, and high sampling density, 96 TIs (Fig. 2B). The root mean squared (RMS) of the residuals of the biexponential model (0.002) was substantially less than that of the monoexponential model (0.011). The resulting parameter estimates from this model are $R_{1,\text{slow}} = 0.4164 \pm 0.0003 \text{ s}^{-1}$ and $R_{1,\text{fast}} = 34 \pm 1 \text{ s}^{-1}$ (Fig. 2C). The fractions of the total amplitude corresponding to the slow and fast relaxation components are 0.9801 ± 0.0003 and 0.0199 ± 0.0003 , respectively. (Note, the amplitude and the rate constant of the fast relaxation component will depend upon the extent of magnetization transfer produced by the relaxation measurement protocol (*vide infra*.) When the monoexponential model is used, R_1 is calculated to be $0.4290 \pm 0.0008 \text{ s}^{-1}$. For comparison, parameter estimates from both the favored biexponential model and the monoexponential model can be found in Table 1.

The biexponential model was also heavily favored by Bayesian joint analysis of three full (128 TIs) *in vivo* datasets collected within the corpus callosum (white matter) of rat brain. The residuals from both the favored biexponential fit and the monoexponential fit show oscillations (Fig. 3B) that are similar to those seen with the xBSA sample. Similar to the xBSA sample, the RMS of the residuals of the biexponential model (0.007) was less than that of the monoexponential model (0.008), a difference of ~15%, and the resulting parameter estimates for the favored model are $R_{1,\text{slow}} = 0.681 \pm 0.003 \text{ s}^{-1}$ and $R_{1,\text{fast}} = 29 \pm 3 \text{ s}^{-1}$ (Fig. 3C). The fractions of the total amplitude associated with the slow and fast relaxation components are 0.973 ± 0.001 and 0.027 ± 0.001 , respectively. By comparison, when the monoexponential model is used, the derived rate constant is $R_1 = 0.708 \pm 0.003 \text{ s}^{-1}$. Parameter estimates from both models can be found in Table 1.

Following truncation of the xBSA datasets as described in Methods, twelve datasets, corresponding to the slow relaxation component (51 TIs; Figure 4), were analyzed jointly and the stretched exponential model was found to be heavily favored. Residuals from the stretched exponential model and the monoexponential model (Fig. 4B) show similar oscillatory patterns as in the full xBSA relaxation dataset, suggesting that neither model is able to characterize fully the longitudinal relaxation of the sample. However, it is evident from the RMS residuals that the stretched exponential model (0.0007) achieves a better goodness of fit than the monoexponential model (0.0021). The resulting parameter estimates from this model are $R_1 = 0.4197 \text{ s}^{-1} \pm 0.0002 \text{ s}^{-1}$ (Fig. 4C) with $\alpha = 0.9759 \pm 0.0004$. When the monoexponential model is used, the derived rate constant R_1 is found to be $0.4157 \pm 0.0003 \text{ s}^{-1}$. Parameter estimates from both models can be found in Table 1.

Modification of the truncated (slow relaxation component only) xBSA datasets to more closely approach the *in vivo* case with respect to either limited sampling density, SNR, or the combination thereof, leads to Bayesian-estimated posterior probability densities for the

stretched exponential with respect to the number of TIs (Figure 5A), the SNR (Figure 6), and the number of TIs at decreased SNR (Figure 5B). In the case of high SNR with decreasing sampling density, the resulting parameter estimates are (Figure 5A, Table 2) $R_1 = 0.4197 \pm 0.0002 \text{ s}^{-1}$ and $\alpha = 0.9760 \pm 0.0004$ for 51 TIs; $R_1 = 0.4197 \pm 0.0002 \text{ s}^{-1}$ and $\alpha = 0.9759 \pm 0.0006$ for 26 TIs; and $R_1 = 0.4195 \pm 0.0004 \text{ s}^{-1}$ and $\alpha = 0.977 \pm 0.001$ for 7 TIs. The stretched exponential is favored in all cases. The resulting parameter estimates in the case of high sampling density, 51 TIs, with decreasing SNR (Figure 6, Table 3) are $R_1 = 0.4197 \pm 0.0002 \text{ s}^{-1}$ and $\alpha = 0.9759 \pm 0.0004$ for SNR = 600; $R_1 = 0.419 \pm 0.001 \text{ s}^{-1}$ and $\alpha = 0.975 \pm 0.004$ for SNR = 100; and $R_1 = 0.423 \pm 0.004 \text{ s}^{-1}$ with $\alpha = 0.97 \pm 0.01$ for SNR = 25. The stretched exponential model is heavily favored for the SNR = 600 and SNR = 100 datasets, as denoted by the asterisk (*) in the figure. For the monoexponential model (Fig. 6C) the resulting parameter estimates are $R_1 = 0.4157 \pm 0.0003 \text{ s}^{-1}$ for SNR = 600; $R_1 = 0.415 \pm 0.001 \text{ s}^{-1}$ for SNR = 100; and $R_1 = 0.419 \pm 0.004 \text{ s}^{-1}$ for SNR = 25 (for which the monoexponential model was favored). In the case of intermediate signal (SNR = 100) with decreasing sampling density, the resulting parameter estimates are (Figure 5B, Table 2) $R_1 = 0.419 \pm 0.001 \text{ s}^{-1}$ and $\alpha = 0.975 \pm 0.004$ for 51 TIs; $R_1 = 0.418 \pm 0.001 \text{ s}^{-1}$ and $\alpha = 0.970 \pm 0.004$ for 26 TIs; and $R_1 = 0.418 \pm 0.002 \text{ s}^{-1}$ and $\alpha = 0.963 \pm 0.005$ for 7 TIs. The stretched exponential is favored in all cases.

To validate methodology employed herein for quantifying relaxation, data acquired with the MFIR protocol were compared to data acquired with the standard inversion recovery (IR) protocol under two conditions: (i) short 90 and 180 degree RF-pulses (θ_2 and θ_1 , respectively), as are commonly employed with high resolution (analytical) NMR spectrometers, herein ~ 10 and $20 \mu\text{s}$, respectively; and (ii) long 90 and 180 degree RF-pulses as are commonly employed with MRI scanners, herein ~ 650 and $1,300 \mu\text{s}$, respectively. Data were acquired in triplicate on a single xBSA sample, interleaving the MFIR and IR protocols. When short pulses yielding broad excitation bandwidths were employed, the MFIR and IR protocols resulted in essentially identical parameter estimates for the most probable model, biexponential. When long pulses yielding narrow excitation bandwidths were employed, the MFIR and IR protocols again resulted in essentially identical parameter estimates for the most probable model, biexponential. Of particular note, however, the estimated fractional amplitude of the fast relaxation component (F) increased markedly from $\sim 3\%$ with short (broadband) pulses to $\sim 20\%$ with long (narrow band) pulses. Consistent with the signal-to-noise increase for the fast relaxation component, and corresponding decrease for the slow component, the uncertainty in the estimated $R_{1,\text{fast}}$ decreased and that for the estimated $R_{1,\text{slow}}$ increased [17]. These results are summarized in Table 4.

4. Discussion

The biexponential model is heavily favored for the high SNR, high sampling density, relaxation datasets from both the xBSA phantom and mouse brain (white matter) *in vivo*, supporting the conclusion that the xBSA phantom is a good *in vitro* longitudinal relaxation surrogate for tissue [8, 10]. In addition, both samples (xBSA, *in vivo* brain) yield derived model parameters that have similar characteristics: (i) the relaxation rate constants associated with the fast and slow relaxation components are well-resolved, separated by two orders of magnitude, and (ii) the fractions of the total amplitude attributable to the fast and

slow relaxation components from the xBSA phantom and the *in vivo* results are comparable. Though the *in vivo* and *in vitro* data were collected at different magnetic field strengths – 200 MHz and 500 MHz, respectively – and, thus, the R_1 values cannot be directly compared, as expected, relaxation of the dominant component ($R_{1,\text{slow}}$) at 11.74 T vs. 4.7 T is less efficient due to reduced spectral density at the higher resonance frequency. Finally, the residuals from the biexponential modeling of both the xBSA and *in vivo* datasets show the same systematic oscillatory feature, indicating that, while the model captures well the principal features of the signal, it does not fully characterize the data. However, when tested against a triexponential function, Bayesian model selection still heavily favored the biexponential model in both the *in vitro* and *in vivo* cases (data not shown). In Bayesian analysis, each additional parameter added to a model naturally incurs a penalty related to the posterior probability distribution of that parameter, so that more complex models (models with more parameters) must markedly improve the goodness of fit (e.g., chi squared) or be rejected, a manifestation of Occam's razor.

The failure of a triexponential function to improve the modeling indicates that the penalty associated with adding two additional parameters (a third rate constant and associated fractional amplitude) more than offsets any resulting improvement in the goodness of fit. The failure of the triexponential model, of course, does not preclude the use of other models that might better describe the system. Having demonstrated that the xBSA phantom mimics *in vivo* tissue longitudinal relaxation will allow us to utilize this phantom in future experiments as a tissue surrogate to further probe the R_1 measurement as regards modifiers of interest, e.g., pH, protein content, pO_2 .

As the monoexponential model is used frequently to fit longitudinal relaxation data, the residuals and the Bayesian-estimated posterior probability distributions from the favored model were compared with those from the monoexponential model for the full, 96 TIs, and truncated, 51 TIs, xBSA relaxation datasets, and the *in vivo* datasets, 128 TIs. In all cases, we observe a clear shift in the location of the peak (maximum probability) of the posterior probability distribution for the slow decay-rate constant derived with the favored model vs. the rate constant posterior probability distribution derived from a monoexponential fit. The monoexponential model is a relatively poor representation of the system, lacking sufficient parameters to accurately characterize the longitudinal relaxation, especially for the early time points (short TI values). For both the full xBSA and *in vivo* datasets, the monoexponential model attempts to characterize both the fast and slow components with a single rate constant, resulting in a skewed parameter estimation. Attempting to fit a dataset with a model that lacks sufficient complexity may yield a precise parameter estimate(s) that is not accurate, as seen in Figures 2C (full xBSA dataset), 3C (*in vivo* dataset), and 4C (truncated xBSA dataset). In each case, however, the change in the uncertainty of the estimated rate constant from the preferred rate-constant model is insignificant compared to that derived from the less probable, simple monoexponential model.

As noted, given its rapid decay and small fractional amplitude, it is difficult to characterize accurately the fast relaxation component. This will be especially true in relaxation experiments *in vivo*, in which acquisition time and SNR are limiting. Consequently, it is worth considering how to collect data corresponding only to the slow component, and to

consider how doing so may affect the derived parameters. Using the resulting $T_{1,\text{fast}}$ from the joint analysis of twelve full xBSA datasets with 96 TIs, the time $t = 5 \times T_{1,\text{fast}}$ was calculated and the data points collected at shorter TI values were dropped (truncated) from the dataset. In principle, at $\text{TI} = 5 \times T_{1,\text{fast}}$, >99% of the fast relaxation component will have returned (decayed) to thermal equilibrium polarization so that, in effect, all of the relaxation signal derives from the slow relaxation component. Therefore, it would seem logical that the favored (most probable) relaxation model describing the truncated data would be monoexponential. Instead, however, these data were best described by the stretched exponential model. As illustrated by the estimated parameter values shown in Results, the stretching parameter (α) is very close to 1 and, therefore, the stretched model is not far removed from a pure monoexponential. However, as shown in Figure 4B, even a small change in α is enough to produce significant changes in the resulting residuals. The RMS residual from the monoexponential fit is three times greater than that of the stretched exponential, illustrating that the added complexity results in significantly improved modeling of the data. In addition, the peak in the posterior probability density for the R_1 relaxation rate constant (Fig. 4C) for the monoexponential ($R_1 = 0.4157 \text{ s}^{-1}$) is shifted with respect to the peak of the distribution corresponding to the stretched exponential ($R_1 = 0.4197 \text{ s}^{-1}$). This shift is significant enough that the distributions are well resolved, demonstrating that the choice of model does affect the accuracy of parameter estimation. (If only the relative differences in parameter values between tissue types, and not their true values, are important, this introduction of bias into parameter estimation may not matter.) Thus, when attempting to quantify R_1 accurately and precisely, model selection is necessary. When applied to a cohort of competing signal models, Bayesian model selection can provide: (i) an avenue to make quantitative biophysical inferences and (ii) a check against over-interpretation/over-parameterization of data. Of the five models we tested, the biexponential and stretched exponential models best represent the full TI datasets and the truncated datasets, respectively. However, systematic smooth oscillations in the residuals demonstrate that these functions do not fully model the data.

The existence of these systemic oscillations, even from the favored choice among our cohort of five signal models, is not a limitation of Bayesian-based model selection but, instead, is a limitation in the ability of the models used to represent the data. As described previously, even when a more complex exponential model --a triexponential model - was included, the biexponential model was still favored. This means the increase in parameterization did not result in a sufficiently decreased residual so as to favor the more complex model. To further reduce or eliminate those systemic oscillations, other signal models will have to be explored. A model that accounts for exchange between water-relaxation-populations, such as the Bloch-McConnell exchange model [18] or perhaps a multi-modal R_1 distribution model, such as those based on the work of Brownstein and Tarr [19, 20] may result in a substantially improved data representation.

To select the “best” (most probable) model, M_{opt} , from the cohort of competing models, $M = \{M_i\}$, the Bayesian-based algorithm seeks the highest valued posterior probability $P(M|D)$, Eq. [7]. Assuming relatively uninformative model prior probabilities, $P(M)$, as employed herein, $P(M|D)$ is principally determined by the marginal direct probability for the data, $P(D|M)$, given model M , which is inversely proportional to the aggregate calculated

uncertainty over all parameters (more formally, integration over all probability distributions); see Eq. [8] for an example. A more complex model must result in a significant decrease in the aggregate uncertainty to be favored over a model with fewer free parameters, a manifestation of Occam's razor. Examples of this are given by the modeling residuals described in Results, as well as the RMS residual values for the favored and monoexponential models shown in Table 1.

Often, experiments are acquisition-time- or signal-to-noise-limited. To better understand the effect of such limitations, the data corresponding to the xBSA slow relaxation component were modified. To mimic time constraints, the xBSA datasets with 51 TIs were truncated to reduce the sampling density within each dataset. Collecting data with all 51 TI values, which requires 20 or more minutes, represents the case of no significant time constraints, as in, for example, the study of *ex vivo* tissue samples. 26 TIs, requiring perhaps 10 minutes of data collection, represents a typical small-animal scan. Finally, the relaxation experiment employing only 7 TIs, represents a short data-collection period, as might be required for a clinical scan. For each of these cases, Bayesian-based model selection was performed jointly on twelve datasets and, in each case, the stretched exponential model was heavily favored.

The effect of decreasing sampling density, mimicking increasingly limited data-acquisition time, on the Bayesian-estimated posterior probability distribution for the decay-rate constant is illustrated in Figure 5A. As the number of TIs decreases, the posterior probability distribution becomes broader, demonstrating that certainty in the parameter estimation decreases with decreasing sampling density. We note that as the original xBSA datasets were acquired under very high SNR conditions and the preferred model, the stretched exponential, has only four parameters, the Bayesian-estimated posterior probability distributions are narrow, even for the case of 7 TIs.

To see this effect more clearly, Gaussian-distributed noise was added to the twelve xBSA datasets with 51 TIs to reduce the SNR to the intermediate case of $\text{SNR} = 100$, which can be achieved in a single voxel *in vivo* MR spectroscopy (MRS) relaxation experiment, and subsequently truncated to reduce the sampling density to 26 TIs and further 7 TIs. For each of these cases, Bayesian-based model selection was performed jointly on twelve datasets and, in each case, the stretched exponential model was heavily favored. The resulting posterior probability distributions for the rate constants are shown in Figure 5B. We see the same general trend as that of the high SNR case (Fig. 5A), broadening of the distributions as the sampling density decreases. Here, the effect is exacerbated by the decreased SNR ($\text{SNR} = 600$ vs. 100).

To simulate the case in which signal-to-noise is the limiting factor, Gaussian-distributed noise was added to the 51 TI datasets so that the SNR decreased from its original value of 600, to an intermediate value of 100, and further down to 25, typical of an *in vivo* MR imaging relaxation experiment. For the $\text{SNR} = 25$ case, the monoexponential model was heavily favored, whereas the stretched exponential model was heavily favored for both the cases of $\text{SNR} = 600$ and $\text{SNR} = 100$. The resulting Bayesian-estimated posterior probability distributions for the decay-rate constant and alpha parameters from the stretched exponential

model are shown in Figures 6A and 6B, respectively. Figure 6C shows the resulting parameter estimates when the monoexponential model is used.

As the SNR decreased, the resulting posterior probability distributions become much broader, with the standard deviation for the R_1 estimation increasing by a factor of approximately 5. It is important to note that in this case, the standard deviation is not a measure of the spread of measured rate constants within our population. Here, the standard deviation is a Bayesian-derived measure of the uncertainty in the calculated parameter estimate. The added noise can be thought of as uncertainty within the data, which is propagated through, and reflected in, the increased uncertainty of the parameter estimates. This means that with increased noise, the precision of the parameter estimation decreases.

There is also a shift in the peak of the posterior probability distribution for the case of SNR = 25 with respect to the high and intermediate SNR cases (Figs. 6A & 6B, Table 3). This can be explained by the change in the favored model, as the result of fitting the data with a different model introduces bias into the parameter estimation. While the variations in the parameter estimates (shifts in positions of the peaks of the posterior probability distributions) and uncertainties therein (changes in widths of the posterior probability distributions) are modest as SNR and sampling density are degraded, the trends are informative and consistent with what would be observed under more severe degradation of data quality.

An important consideration regarding this result is that, while a SNR = 25 can be considered low, the joint analysis of three (*in vivo*) and twelve (xBSA) replicate datasets, each with different additive noise elements but the same noise power, greatly increases the statistical power of Bayesian inference. From a frequentist point of view, assuming all dataset members are of equal quality (i.e., equally informative), the full dataset SNR is proportional to the square root of the number of replicate members in the dataset. Thus, while each of the twelve replicate members of the xBSA dataset had SNR = 25, the full dataset can be considered to have a SNR = $25 \times (12)^{1/2} = 87$. Thus, even under conditions in which each xBSA dataset member had SNR = 25, the joint analysis of twelve replicate members yielded quite precise parameter estimates.

The tissue-mimicking xBSA phantom possesses both a narrow water ^1H resonance, characteristic of a small, highly mobile, randomly reorienting molecule and a very broad crosslinked-protein ^1H resonance feature, characteristic of semi-solid macromolecules. A short, 180-degree pulse will invert magnetization over a broad range of resonance frequencies (e.g., $20\ \mu\text{s} \rightarrow \sim 5,000\ \text{Hz}$), thus, to first approximation, inverting both the water and the crosslinked protein ^1H magnetization. In this case, ^1H magnetization transfer between water and protein pools does not act as an efficient longitudinal relaxation mechanism for water. A long, 180-degree pulse will invert magnetization over a narrow range of resonance frequencies (e.g., $1.6\ \text{ms} \rightarrow \sim 600\ \text{Hz}$), thus, to first approximation, inverting the water ^1H magnetization while leaving the majority of the protein ^1H magnetization in the thermally equilibrated (Boltzmann) polarized state. In this case, ^1H magnetization transfer between water and protein pools acts as an efficient longitudinal relaxation mechanism for water. The data summarized in Table 4 bear this out. In the case of

short (broadband) RF pulses, the fractional amplitude of the fast relaxation component, which reflects the population of water molecules that relax via magnetization transfer with the crosslinked protein pool, is near zero (~3%), but increases markedly to 20% in the case of long (narrowband) RF pulses. Long RF pulses (1 - 4 ms) are typical of *in vivo* MRI protocols and, thus, magnetization transfer effects will manifest significantly in longitudinal relaxation experiments *in vivo* [10].

In conclusion, we have shown that xBSA displays similar longitudinal relaxation characteristics to that of *in vivo* brain tissue, allowing for future characterization of the effects of likely important endogenous modifiers of R_1 in tissue, such as pO_2 , pH, and protein content. We have also shown that the MFIR pulse sequence yields very similar results to the standard IR pulse sequence but that, in the presence 1H magnetization transfer between water and cross-linked protein, pulse widths can have a substantial effect upon relaxation characteristics and, thus, parameter estimates. Finally, we have shown the utility of Bayesian-based model selection (and related parameter estimation) for selecting amongst a cohort of competing signal models. As data become less informative (e.g., sparser, lower SNR), simpler models (e.g., those with fewer parameters) are preferred, in the Bayesian sense of being more probable, given the data and the prior information.

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Fig. 1.

(A) Schematic illustration of the Modified Fast Inversion Recovery (MFIR) pulse sequence [16]. RF refers to the radio frequency output and signal acquisition: θ_1 is a 180 degree (π) inversion pulse, θ_2 is a 10 degree magnetization sampling pulse. G_{crush} represents the magnetic field gradient pulse applied to destroy (crush) any transverse magnetization coherence produced following a non-ideal θ_1 inversion pulse. TI is the variable time from the inversion pulse to the magnetization sampling pulse, W is the waiting time, and TR is the time to repetition. TR is the sum of TI and W and is a constant value. (B) Schematic illustration of the Inversion Recovery Point Resolved Spectroscopy (IR-PRESS) pulse sequence. A non-slice-selective inversion pulse is followed by a PRESS readout sequence, employing weak diffusion sensitizing gradients to destroy transverse magnetization coherence within the vasculature (i.e., to suppress signal from flowing blood).

Fig. 2.

(A) Representative full, 96 TI relaxation dataset (black diamonds: signal intensity vs. TI) from the xBSA phantom, fit with the heavily favored biexponential model (gray line). (B) The resulting residuals from both the biexponential model (solid black line) and the monoexponential model (dashed black line) are plotted against the “inversion number” (i.e., the 96 TI increments arranged linearly by increment number). The biexponential fit has a resulting root mean square (RMS) residual of 0.002, whereas the monoexponential fit has an RMS residual of 0.011. (C) Bayesian-estimated posterior probability densities from joint analysis of all twelve xBSA relaxation datasets for (i) the rate constant for the slow component from the biexponential fit (solid black line), peaking at $R_{1,slow} = 0.4164 \pm 0.0003 \text{ s}^{-1}$ and (ii) the rate constant from the monoexponential fit (dashed black line), peaking at $R_{1,mono} = 0.4290 \pm 0.0008 \text{ s}^{-1}$; inlaid is the rate constant for the fast component from the biexponential fit (dotted black line), peaking at $R_{1,fast} = 33 \pm 1 \text{ s}^{-1}$.

Fig. 3.

(A) Representative full, 128 TI dataset (black diamonds) from *in vivo* corpus callosum in rat brain, fit with the heavily favored biexponential model (gray line), plotted against the time from the inversion pulse. (B) Resulting residuals from the favored biexponential fit (solid black line) and the monoexponential model (dashed black line) are plotted against the “inversion number” (i.e., the 128 TI increments arranged linearly by increment number). The biexponential fit achieves an RMS residual value of 0.007, whereas the monoexponential fit achieves a value of 0.008. (C) Bayesian-estimated posterior probability densities from joint analysis of all three *in vivo* corpus callosum relaxation datasets for (i) the rate constant corresponding to the “slow” relaxation component from the favored biexponential fit (solid black line), peaking at $R_{1,slow} = 0.681 \pm 0.003 \text{ s}^{-1}$ and (ii) the rate constant from the monoexponential model (dashed black line), peaking at $R_{1,mono} = 0.708 \pm 0.003 \text{ s}^{-1}$; inlaid is the rate constant corresponding to the “fast” component from the favored biexponential model (dotted black line), peaking at $R_{1,fast} = 29 \pm 3 \text{ s}^{-1}$.

Fig. 4.

(A) Representative truncated dataset from xBSA phantom illustrating the “slow” relaxation component (black diamonds), fit with the heavily favored stretched exponential model (gray line), plotted against the time from the inversion pulse. (B) The resulting residuals from the heavily favored stretched exponential model (solid black line) and the monoexponential model (dashed black line) are shown against the “inversion number” (i.e., the 51 TI increments arranged linearly by increment number). The stretched exponential fit achieves an RMS residual value of 0.0007, whereas the monoexponential fit achieves an RMS residual value of 0.0021. (C) Bayesian-estimated posterior probability densities from joint analysis of all twelve truncated datasets for the rate constants from (i) the favored stretched exponential (solid black line), peaking at $R_1 = 0.4197 \pm 0.0002 \text{ s}^{-1}$ and (ii) the monoexponential model (dashed black line), peaking at $R_1 = 0.4157 \pm 0.0003 \text{ s}^{-1}$.

Fig. 5.

Bayesian-estimated posterior probability density of the heavily favored, stretched exponential model's decay-rate constant, R_1 , (A) for the case of 51 TIs (solid black line) peaking at $R_1 = 0.4197 \pm 0.0002 s^{-1}$, 26 TIs (solid gray line) peaking at $R_1 = 0.4197 \pm 0.0002 s^{-1}$, and 7 TIs (dotted black line) peaking at $R_1 = 0.4195 \pm 0.0004 s^{-1}$ following truncation of the original 96 TI datasets. (B) The same culled datasets as in (A) following the addition of Gaussian-distributed noise to reduce the SNR to approximately 100. For each case, the heavily favored model is the stretched exponential and the R_1 is found to be $0.419 \pm 0.001 s^{-1}$ for 51 TIs, $0.418 \pm 0.001 s^{-1}$ for 26 TIs, and $0.418 \pm 0.002 s^{-1}$ for 7 TIs. Each posterior probability density curve is the result of twelve jointly analyzed xBSA relaxation datasets.

Fig. 6.

Bayesian-estimated posterior probability densities for the cases of SNR = 600 (solid black line), SNR = 100 (solid gray line), and SNR = 25 (dotted black line) for the “slow” relaxation component (51 TIs) following the addition of Gaussian-distributed noise. (A) The posterior probability densities for the R_1 determination, using the stretched exponential model. The case of SNR = 600 peaks at $R_1 = 0.4197 \pm 0.0002 \text{ s}^{-1}$, SNR = 100 peaks at $R_1 = 0.419 \pm 0.001 \text{ s}^{-1}$, and SNR = 25 peaks at $R_1 = 0.423 \pm 0.004 \text{ s}^{-1}$. (B) The corresponding posterior probability densities for α in each of the three cases. When SNR = 600, α peaks at 0.9759 ± 0.0004 ; for SNR = 100, α peaks at 0.975 ± 0.004 ; for SNR = 25, α peaks at 0.97 ± 0.01 . (C) The posterior probability densities for the R_1 determination using the monoexponential model. The case of SNR = 600 peaks at $R_1 = 0.4157 \pm 0.0003 \text{ s}^{-1}$, SNR = 100 peaks at $R_1 = 0.415 \pm 0.001 \text{ s}^{-1}$, and SNR = 25 peaks at $R_1 = 0.419 \pm 0.004 \text{ s}^{-1}$. In each case, if the model used was the favored model, an asterisk (*) accompanies the label. The heavily favored model for the SNR = 600 and SNR = 100 was found to be the stretched exponential and for the case of SNR = 25 the heavily favored model was found to be the monoexponential.

Table 1
Rate Constants and RMS Residuals from xBSA Phantom and *in Vivo* Joint Analyses

	Monoexponential Model		Stretched Exponential Model		Biexponential Model		
	R_1 (s ⁻¹)	RMS Residual	R_1 (s ⁻¹)	RMS Residual	$R_{1,slow}$ (s ⁻¹)	$R_{1,fast}$ (s ⁻¹)	RMS Residual
xBSA, 96 TIs	0.4290 ± 0.0008	0.011			0.4164 ± 0.0003	34 ± 1	0.002
xBSA, truncated, 51 TIs	0.4157 ± 0.0003	0.0021	0.4197 ± 0.0002	0.0007			
<i>In vivo</i> rat brain, 128 TIs	0.708 ± 0.003	0.008			0.681 ± 0.003	29 ± 3	0.007

Table 2
Sparsity & SNR Reduction Effects Upon Parameter Estimates in xBSA Phantom

TI > 5*$T_{1,fast}$ (160 ms–7.5 s)	SNR = 600		SNR = 100	
	R_1 (s⁻¹)	α	R_1 (s⁻¹)	α
51 TIs	0.4197 ± 0.0002	0.9760 ± 0.0004	0.419 ± 0.001	0.975 ± 0.004
26 TIs	0.4197 ± 0.0002	0.9759 ± 0.0006	0.418 ± 0.001	0.970 ± 0.004
7 TIs	0.4195 ± 0.0004	0.977 ± 0.001	0.418 ± 0.002	0.963 ± 0.005

Table 3
Parameter Estimates for xBSA Phantom Following SNR Reduction

51 TIs (160 ms – 7.5 s)	Stretched Exponential Model		Monoexponential Model
	R_1 (s ⁻¹)	α	R_1 (S ⁻¹)
SNR = 600	$0.4197 \pm 0.0002^*$	$0.9759 \pm 0.0004^*$	0.4157 ± 0.0003
SNR = 100	$0.419 \pm 0.001^*$	$0.975 \pm 0.004^*$	0.415 ± 0.001
SNR = 25	0.423 ± 0.004	0.97 ± 0.01	$0.419 \pm 0.004^*$

* denotes favored model.

Table 4
Summary of Parameter Estimates for xBSA Phantom Comparing MFIR & IR vs. Pulse Width

	MFIR			IR		
	$R_{1,slow}$ (s^{-1})	$R_{1,fast}$ (s^{-1})	(1-F)	$R_{1,slow}$ (s^{-1})	$R_{1,fast}$ (s^{-1})	(1-F)
Short Pulse Widths	0.5071 ± 0.0003	54 ± 1	0.9750 ± 0.0003	0.5071 ± 0.0003	52 ± 1	0.9769 ± 0.0003
Long Pulse Widths	0.539 ± 0.001	52.3 ± 0.6	0.8197 ± 0.0009	0.539 ± 0.001	51.5 ± 0.7	0.8319 ± 0.0009