

# Optimizing relaxation-exchange magnetic resonance imaging for parameter mapping in white matter

**Primary:** Acquisition & Reconstruction - Quantitative Imaging: head and neck   **Secondary:** Neuro - White Matter   **Presentation:** Digital Poster, Traditional Poster, PowerPitch Oral, Oral   **Keywords:** PULSE SEQUENCE DESIGN WHITE MATTER MAGNETIC RESONANCE FINGERPRINTING QUANTITATIVE MAGNETIC RESONANCE IMAGING

**Cyrus Najarian**<sup>1</sup>, **Navid Seraji-Bozorgzad**<sup>2,3</sup>, **Scott D Swanson**<sup>4,5</sup>, **Nicole Seiberlich**<sup>1,2,4</sup>, **Jon-Fredrik Nielsen**<sup>1,2,4,6,7</sup>, **Jeffrey A Fessler**<sup>1,4,7,8,9</sup>

<sup>1</sup>Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, United States of America

<sup>2</sup>University of Michigan, Ann Arbor, MI, United States of America

<sup>3</sup>Department of Neurology, University of Michigan, Ann Arbor, MI, United States of America

<sup>4</sup>Department of Radiology, University of Michigan, Ann Arbor, MI, United States of America

<sup>5</sup>Department of Biophysics, University of Michigan, Ann Arbor, MI, United States of America

<sup>6</sup>Functional MRI Laboratory, Department of Radiology, University of Michigan, Ann Arbor, MI, United States of America

<sup>7</sup>Electrical Engineering and Computer Science, University of Michigan, Ann Arbor, MI, United States of America

<sup>8</sup>ECE, University of Michigan, Ann Arbor, MI, United States of America

<sup>9</sup>Department of Electrical and Computer Engineering, University of Michigan, Ann Arbor, MI, United States of America

 **Presenting Author:** Cyrus Najarian (najarian@umich.edu)

## Impact

Our optimized REXI sequence significantly improves quantitative estimation of relaxation and exchange parameters while accounting for  $B_0/B_1$  inhomogeneity. This framework enhances scan efficiency and precision, laying the groundwork for clinical translation of REXI in evaluating myelin integrity and white-matter pathology.

## Synopsis

**Motivation:** Quantifying white matter exchange in vivo is important, but challenging due to long scan times and limited parameter specificity.

**Goals:** We developed an optimized relaxation-exchange imaging sequence to jointly estimate relaxation, exchange, and field inhomogeneity parameters efficiently.

**Approach:** Using Cramér–Rao Lower Bound optimization, we systematically vary flip angles and RF phases to enhance encoding efficiency and reduce scan time while preserving precision.

**Results:** Simulations in urea and BrainWeb phantoms show improved precision, reduced uncertainty, and noise robustness. A hybrid PERK + L-BFGS framework further refines  $T_1$ ,  $T_2$ , and exchange-rate maps, enabling rapid, accurate characterization of white matter microstructure.

## Introduction

Quantitative MRI techniques—especially those sensitive to water compartmentalization and exchange—offer more specific insight into tissue microstructure than conventional MRI<sup>1</sup>. Relaxation-exchange imaging (REXI), shown in [Figure 1](#), captures signal contributions from distinct water pools (e.g., myelin and intra/extracellular) with different  $T_1$  and  $T_2$  values using a series of multi-echo spin-echo (MESE) acquisitions with varying mixing times<sup>2</sup>. However, robust estimation of exchange from standard REXI can be challenging since  $B_0$  and  $B_1$  inhomogeneities,  $T_1$  decay, and chemical shift effects are not modeled. By optimizing the REXI scan design while incorporating these effects into the signal model, we can improve the ability to estimate exchange and jointly estimate these other tissue and scan parameters in a fingerprinting-like methodology.

## Methods

We used the Cramér–Rao Lower Bound (CRLB) to optimize a REXI-inspired sequence for jointly estimating  $T_1$ ,  $T_2$ , exchange rate ( $K_x$ ), proton density ( $M_0$ ), myelin water fraction (MWF), chemical shift ( $\Delta f_{\text{shift}}$ ),  $B_0$  inhomogeneity ( $\Delta f_{\text{bulk}}$ ), and  $B_1$  inhomogeneity ( $\kappa$ ) based on the Bloch-McConnell equations. Previous work<sup>3</sup> has optimized  $TE_1$ ,  $TE_2$ , and mixing times ( $t_m$ ), whereas here we also optimized the flip angles and RF phases during the detection block, designing a fingerprinting-like sequence that better encodes exchange dynamics<sup>4</sup>. We used Bloch simulations to generate a single isochromat signal model from the previously described REXI sequence for a urea phantom study and compared the CRLB to our optimized scan design<sup>2,3</sup>.

Given the high dimensionality of the parameter space, we employed a Parametric Estimation via Regression Kernel (PERK) method for parameter estimation trained on synthetic Bloch-McConnell data corrupted with Gaussian noise ( $\text{SNR} = 35 \text{ dB}$ )<sup>5</sup>. PERK outputs initialized a final refinement step using L-BFGS optimization for nonlinear least squares fitting. We evaluated this framework using simulated data ( $\text{SNR} = 47 \text{ dB}$ ) from a BrainWeb phantom, sampling realistic parameter distributions for each gray and white matter voxel<sup>6</sup>.

## Results

The optimized REXI sequence substantially improved the precision of parameter estimation compared with the standard design. As shown in [Figure 2](#), CRLB analysis revealed a marked reduction in parameter variance by roughly 30–45% across  $T_1$ ,  $T_2$ , MWF, and  $K_x$  indicating stronger sensitivity to exchange-driven signal evolution. This improvement was achieved while shortening the overall scan time by nearly 25%.

Optimization of the flip angles and phases yielded more distinctive signal trajectories, visualized in [Figure 3](#). Despite short  $T_2$  values, the new detection scheme maintained measurable signal amplitudes beyond 400 ms, demonstrating its ability to capture both fast and slow exchange components. Noise-robustness was further confirmed in [Figure 4](#), where voxelwise CRLB maps remained stable at an SNR of 47 dB. Regions of lowest CRLB aligned with simulated white-matter areas, as the scan design was optimized with respect to this tissue type.

Finally, [Figure 5](#) compares the ground-truth and reconstructed parameter maps. Although PERK alone produced biased estimates in regions of high parameter coupling, combining PERK initialization with L-BFGS refinement yielded sharp, spatially consistent reconstructions. Across white-matter voxels, relative errors largely remained below 15%, even in voxels with  $B_0$  and  $B_1$  inhomogeneity.

## Discussion

These results highlight how the optimized REXI sequence strengthens both the encoding and estimation of relaxation-exchange dynamics. By integrating variable flip angles and phase modulation into the detection block, the sequence encodes multicomponent relaxation pathways more efficiently than traditional fixed-angle schemes. The hybrid PERK + L-BFGS estimation pipeline leverages PERK’s rapid global approximation while refining with gradient-based optimization, balancing computational speed with quantitative accuracy.

The ability to jointly recover T1 decay and chemical-shift, while also accounting for B<sub>0</sub>/B<sub>1</sub> inhomogeneity marks an advancement over conventional REXI fitting that typically neglects such effects. Although exchange-rate estimates exhibited the largest residual error, their spatial distribution mirrored known myelin-rich regions, suggesting physiological validity. A patch-based approach, leveraging assumptions of local parameter consistency, might allow for improved estimation.

### Conclusions

By merging a fingerprinting-style pulse design with a novel estimation strategy, this work demonstrates a robust framework for quantifying relaxation and exchange parameters in realistic brain tissue simulations. The results show that the optimized REXI sequence not only accelerates acquisition but also enhances parameter precision, resilience to noise, and correction for B<sub>0</sub>/B<sub>1</sub> inhomogeneity. These advances work towards quantitative exchange estimation in pre-clinical and clinical settings, where improved modeling of myelin and water-exchange dynamics could provide new biomarkers for demyelinating and neurodegenerative disease.

### References

1. Van Der Weijden, C. W. J., Biondetti, E., Gutmann, I. W., Dijkstra, H., Mckerchar, R., De Paula Faria, D., De Vries, E. F. J., Meilof, J. F., Dierckx, R. A. J. O., Prevost, V. H., & Rauscher, A. (2023). Quantitative myelin imaging with MRI and PET: an overview of techniques and their validation status. *Brain*, 146(4), 1243-1266. <https://doi.org/10.1093/brain/awac436>

2. Wu, X., He, Q., Yin, Y., Tan, S., Zhang, B., Li, W., Hsu, Y.-C., Xue, R., & Bai, R. (2024 Nov 26). Relaxation-exchange magnetic resonance imaging (REXI): a non-invasive imaging method for evaluating trans-barrier water exchange in the choroid plexus. *Fluids and Barriers of the CNS*, 21(1). <https://doi.org/10.1186/s12987-024-00589-7>

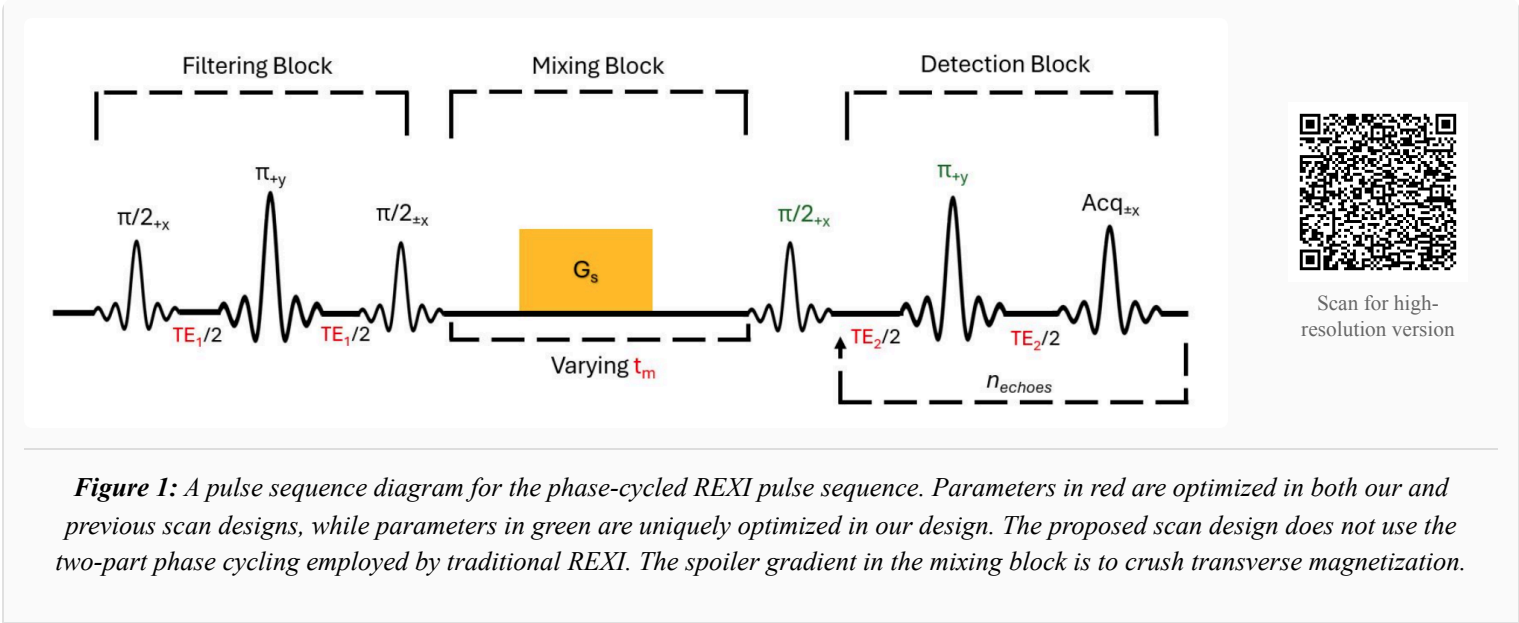
3. Wu X, Tan S, Zhang Y, et al. Feasibility of relaxation-exchange magnetic resonance imaging (REXI) for measuring water exchange across the blood–CSF barrier in the human choroid plexus. *Journal of Cerebral Blood Flow & Metabolism*. 2025;0(0). <https://doi.org/10.1177/0271678x251369218>

4. Ma, D., Gulani, V., Seiberlich, N., Liu, K., Sunshine, J. L., Duerk, J. L., & Griswold, M. A. (2013-03-13). Magnetic resonance fingerprinting. *Nature* 2013 495:7440, 495(7440). <https://doi.org/10.1038/nature11971>

5. Nataraj, G., Nielsen, J.F., Scott, C. and Fessler, J.A., 2018. Dictionary-free MRI PERK: Parameter estimation via regression with kernels. *IEEE transactions on medical imaging*, 37(9), pp.2103-2114. <https://doi.org/10.1109/TMI.2018.2817547>

6. Collins, D.L., Zijdenbos, A.P., Kollokian, V., Sled, J.G., Kabani, N.J., Holmes, C.J. and Evans, A.C., 1998. Design and construction of a realistic digital brain phantom. *IEEE transactions on medical imaging*, 17(3), pp.463-468. <https://doi.org/10.1109/42.712135>

### Figures and Tables

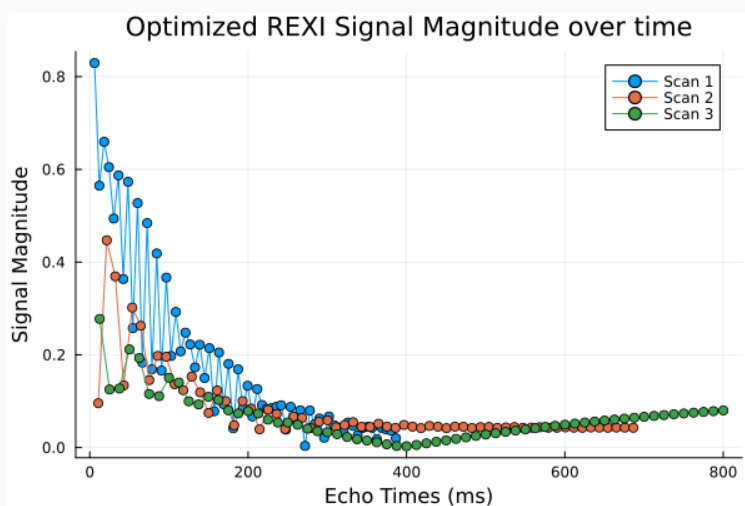


| Coefficient of Variations at SNR of 40dB | REXI<br>(jointly estimating parameters)<br>Time per line of k-space = 19.35 seconds | REXI<br>(estimating selected parameters)<br>Time per line of k-space = 19.35 seconds | Optimized REXI<br>Time per line of k-space = 15.47 seconds |
|------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------|
| R1 <sub>a</sub> (ms)                     | 104.40%                                                                             | -                                                                                    | 7.05%                                                      |
| R1 <sub>b</sub> (ms)                     | 19.47%                                                                              | -                                                                                    | 1.97%                                                      |
| R2 <sub>a</sub> (ms)                     | 10.23%                                                                              | 5.61%                                                                                | 2.53%                                                      |
| R2 <sub>b</sub> (ms)                     | 6.33%                                                                               | 2.24%                                                                                | 1.00%                                                      |
| k <sub>x</sub> (ms <sup>-1</sup> )       | 46.11%                                                                              | 13.2%                                                                                | 5.52%                                                      |
| F <sub>a</sub>                           | 64.68%                                                                              | 5.08%                                                                                | 1.20%                                                      |
| Δf (Hz)                                  | 512.43%                                                                             | -                                                                                    | 0.01%                                                      |



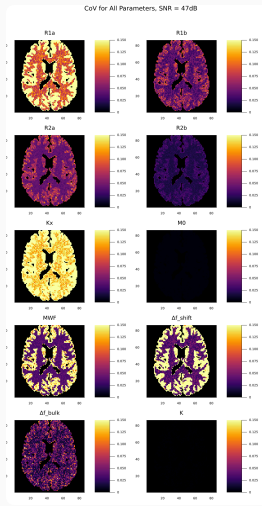
Scan for high-resolution version

**Figure 2:** Comparisons of the coefficient of variation for 7 different urea phantom MR parameters. Our optimized REXI jointly estimates all 7 tissue parameters, has a lower coefficient of variation, and takes less time per line of k-space



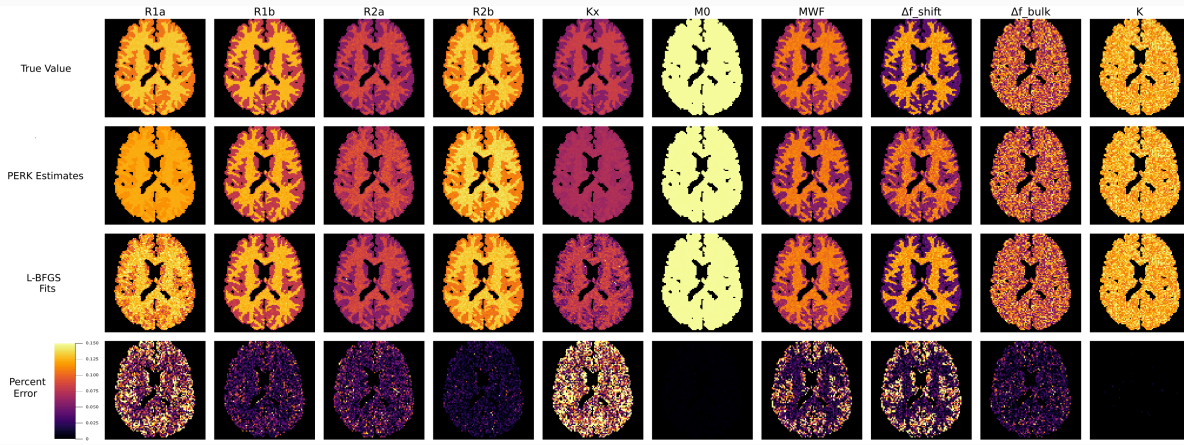
Scan for high-resolution version

**Figure 3:** Plotted signal magnitude over time for our REXI scan optimized for the precision of white matter myelin water exchange.



Scan for high-resolution version

**Figure 4:** Coefficients of variations (at 47dB SNR) are primarily under 15% for white matter. Grey matter, for some parameters, is still able to be estimated despite the sequence not being optimized with respect to those tissue parameter ranges.



Scan for high-resolution version

**Figure 5:** True values, PERK estimates, fits, and percent error for each parameter. After fine tuning with a quasi-Newton optimization, our proposed framework shows good estimation of all white matter parameters from simulated noisy optimized REXI data.