Supporting Information for Myelin Water Fraction Estimation Using Small-Tip Fast Recovery MRI

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This Supporting Information presents additional results and discussion for experiments not included in the main body of the manuscript.

S1 Estimator RMSE for White and Gray Matter Tissue Values

We compared MWF estimates from scan designs A and B. We simulated test data using the two-compartment non-exchanging STFR signal model using tissue values typical of white matter and gray matter (see Table 1), and we estimated MWF using STFR2-PERK. We plotted RMSE of MWF estimates from both scan designs versus the additional myelin water off-resonance $\Delta\omega_\mathrm{f}$. Supporting Information Figure S1 shows the results.

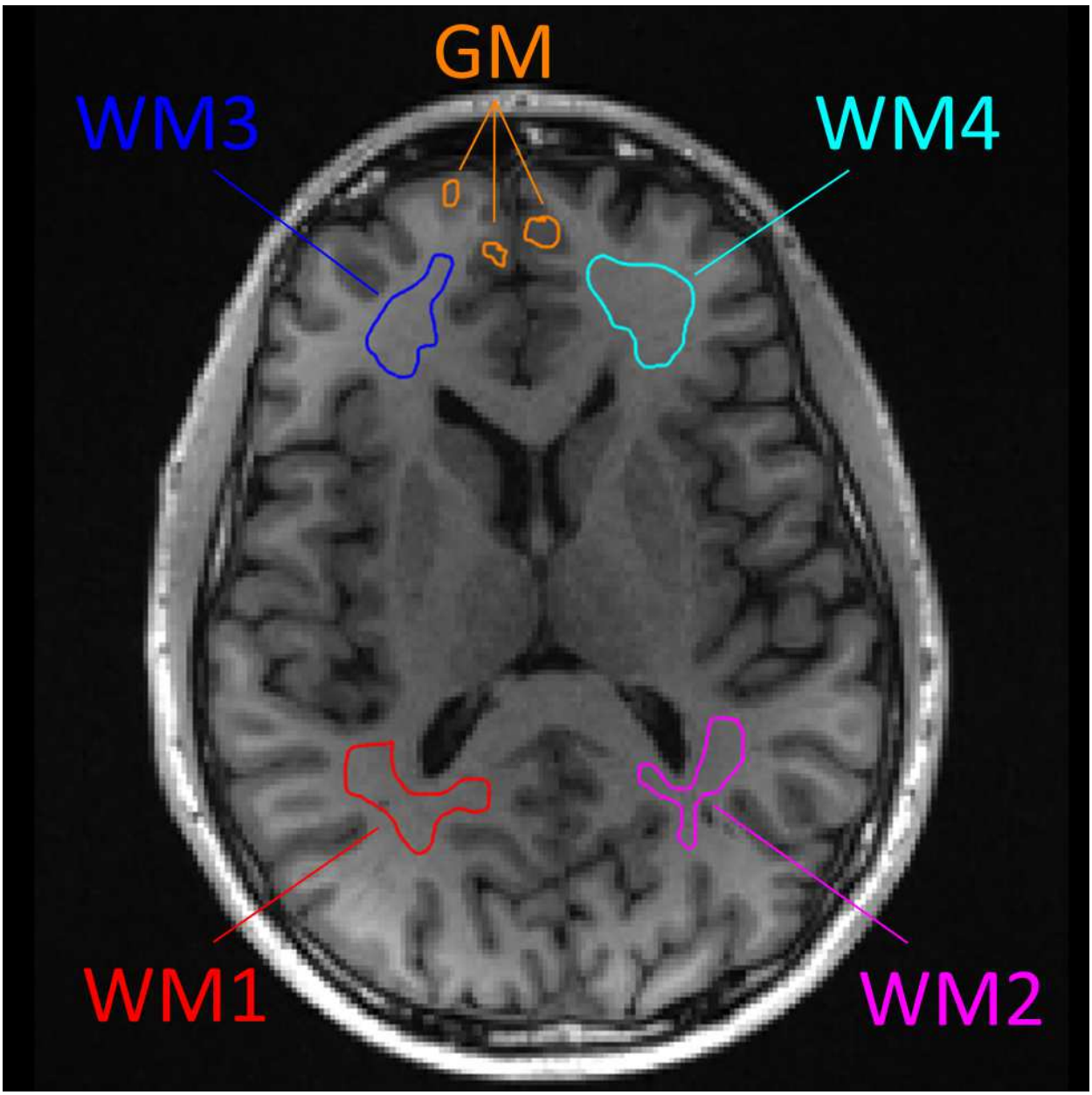
Supporting Information Figure S1 indicates that scan design A gives better MWF estimates in white matter over values of $\Delta\omega_\mathrm{f}$ we expect to see, but scan design B performs better in gray matter. However, the values of $T_{1,\mathrm{f}}$ and $T_{1,\mathrm{s}}$ for gray matter are (slightly) outside of the range of values used for the scan designs and for training our estimator. When quantifying MWF in gray matter is of interest, one probably should use a wider range of values for scan design and training.

S2 Estimator Performance with Model Mismatch

We compared MWF estimates from STFR2-PERK, STFR3-PERK, MESE-NNLS, MESE-PERK, and STFR3-PERK-JE for different ground truth models. First, we generated test data for white matter and gray matter tissue values using a four-compartment exchanging model. The four compartments were myelin water, axonal water (i.e., water in myelinated axons), all other water, and macromolecules. Myelin water was in exchange with the macromolecular pool, myelin water and axonal water exchanged with each other, and myelin water and all other water exchanged with each other. Supporting Information Figure S2 shows the results, and Supporting Information Table S1 reports numerical values. STFR3-PERK still provides good MWF estimates despite the model mismatch between the test data and the training data.

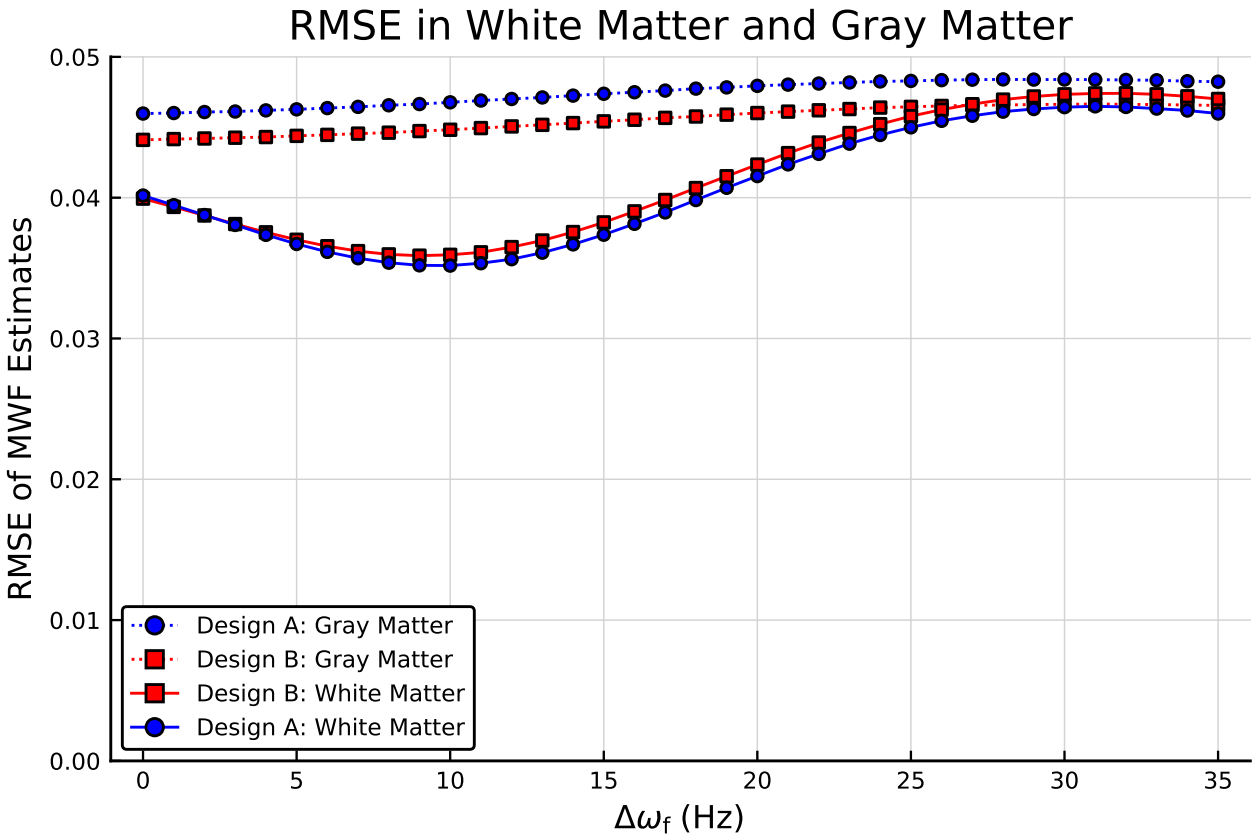
We then generated test data for white matter and gray matter tissue values using a three-compartment non-exchanging model. The three compartments were the same as in the three-compartment exchanging model that STFR3-PERK was trained with, except no exchange occurred (i.e., the exchange rates were set to 0). Supporting Information Figure S3 shows the results, and Supporting Information Table S2 reports numerical values. Without exchange, the three-compartment model becomes essentially a two-compartment model because the T_2 of the macromolecular pool is so small. Thus it makes sense that STFR2-PERK gives good MWF estimates. The overestimation of MWF could be because the macromolecular pool has a nonzero f_m, but since it contributes no signal the estimator assumes that the smaller signal is due to a larger MWF. MESE-NNLS does better without exchange, though it still underestimates gray matter MWF, while STFR3-PERK does poorly. It is possible, though, that if the training ranges for the residence times

Supporting Information Figure S1: White matter (WM) and gray matter (GM) regions of interest (ROIs). The underlying image is from a standard MP-RAGE acquisition, acquired in the same scan session and registered to the other scans. The ROIs are labeled to correspond to Table 4 in the paper.

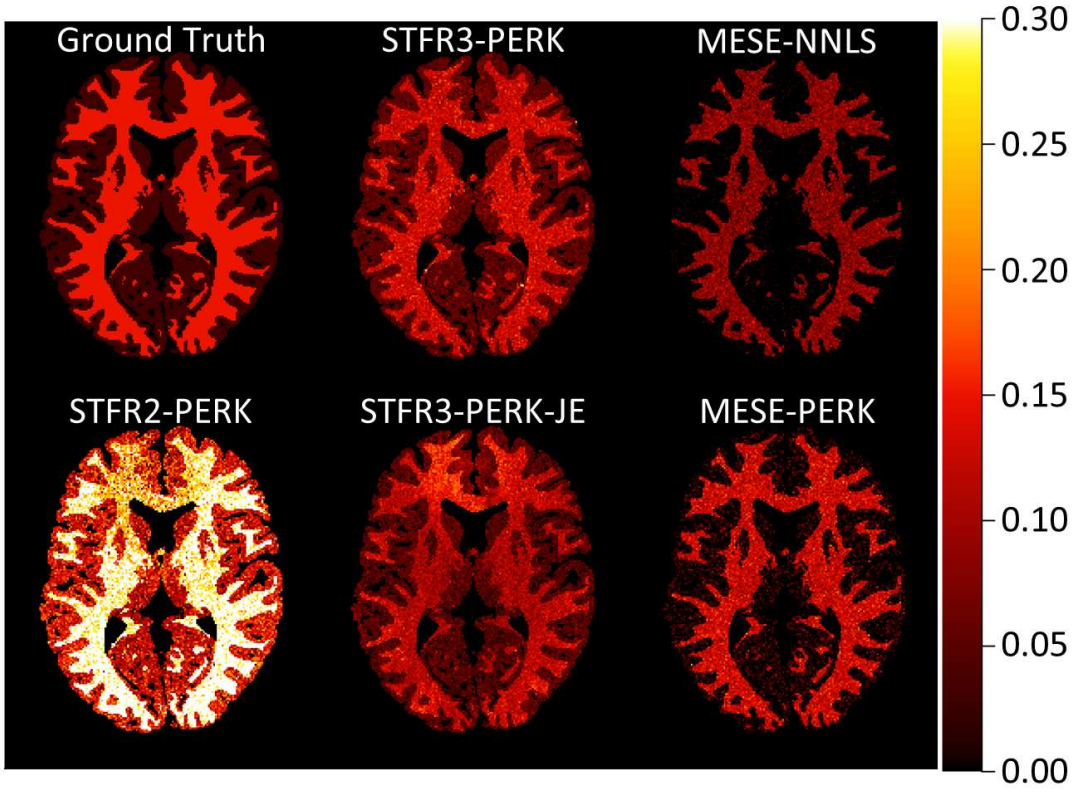


Supporting Information Table S1: Numerical results for Supporting Information Figure S2.

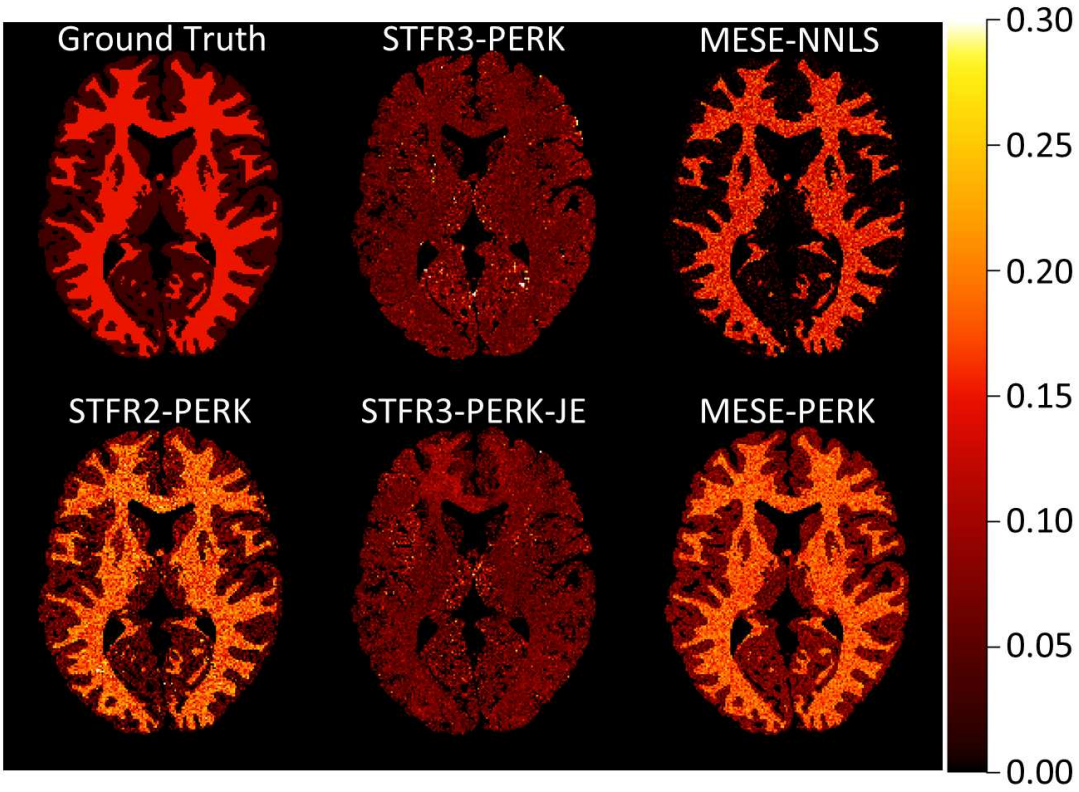
	White Matter (MWF = 0.15)			Gray Matter (MWF = 0.03)			
	RMSE	Mean	St. Dev.	RMSE	Mean	St. Dev.	Time (s)
STFR2-PERK	0.170	0.308	0.062	0.112	0.133	0.044	**14.7**
STFR3-PERK	**0.028**	**0.130**	**0.020**	**0.028**	0.052	0.017	42.1
STFR3-PERK-JE	0.040	0.120	0.026	**0.028**	**0.046**	0.022	42.2
MESE-NNLS	0.071	0.084	0.024	0.029	0.001	**0.004**	1623.6
MESE-PERK	0.033	0.127	0.023	0.056	-0.005	0.043	167.3



Supporting Information Figure S2: RMSE of MWF estimates for white matter and gray matter simulated test data. Scan design A has better RMSE in white matter for values of $\Delta\omega_{\mathrm{f}}$ we expect to see in white matter. This better RMSE in white matter is at the cost of worse RMSE in gray matter. Note that the values of $T_{1,\mathrm{f}}$ and $T_{1,\mathrm{s}}$ for gray matter were outside of the range of values used for the scan designs and for training our estimator.



Supporting Information Figure S3: MWF maps from five methods using simulated test data for a four-compartment tissue model with exchange. The four compartments considered were myelin water, axonal water (i.e., water in myelinated axons), all other water, and macromolecules. The results are similar to those using the three-compartment model with exchange. Supporting Information Table S1 shows numerical results.



Supporting Information Figure S4: MWF maps from five methods using simulated test data for a three-compartment tissue model without exchange. Without exchange, the three-compartment model becomes essentially a two-compartment model because the T_2 of the macromolecular pool is so small. Thus it makes sense that STFR2-PERK performs well. Surprisingly, MESE-PERK still produces good MWF estimates, even though it is trained with the three-compartment exchanging model (like STFR3-PERK). This could be because the T_R of the MESE scan is long compared to the residence times governing exchange. Furthermore, it is possible that if the training ranges for the residence times were adjusted appropriately (increased) then STFR3-PERK would also do well. Supporting Information Table S2 shows numerical results.

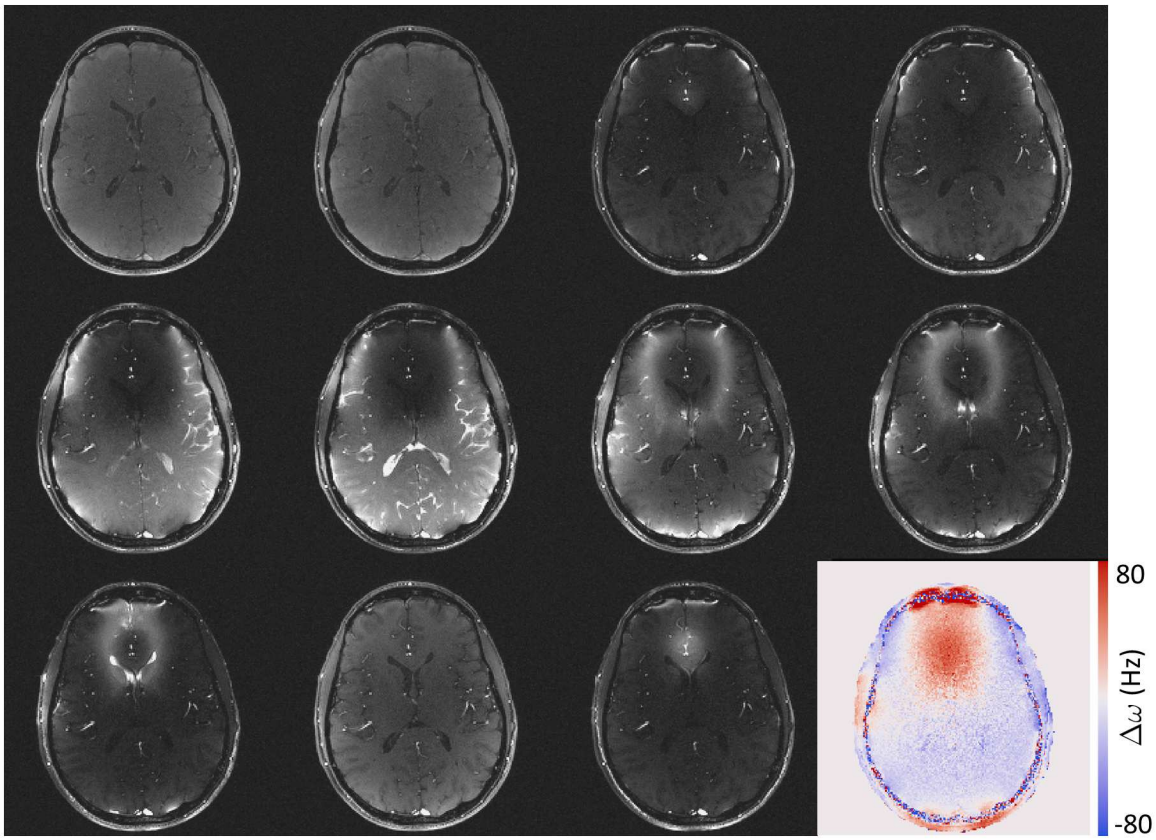
were adjusted appropriately (increased, to allow for less exchange) then STFR3-PERK would also do well, although doing so might cause greater estimator bias. It is somewhat surprising that MESE-PERK still gives good MWF estimates, despite being trained with the three-compartment exchanging model. This could be because the T_R of the MESE scan is long compared to the residence times (more than 10× longer).

S3 Estimator Bias

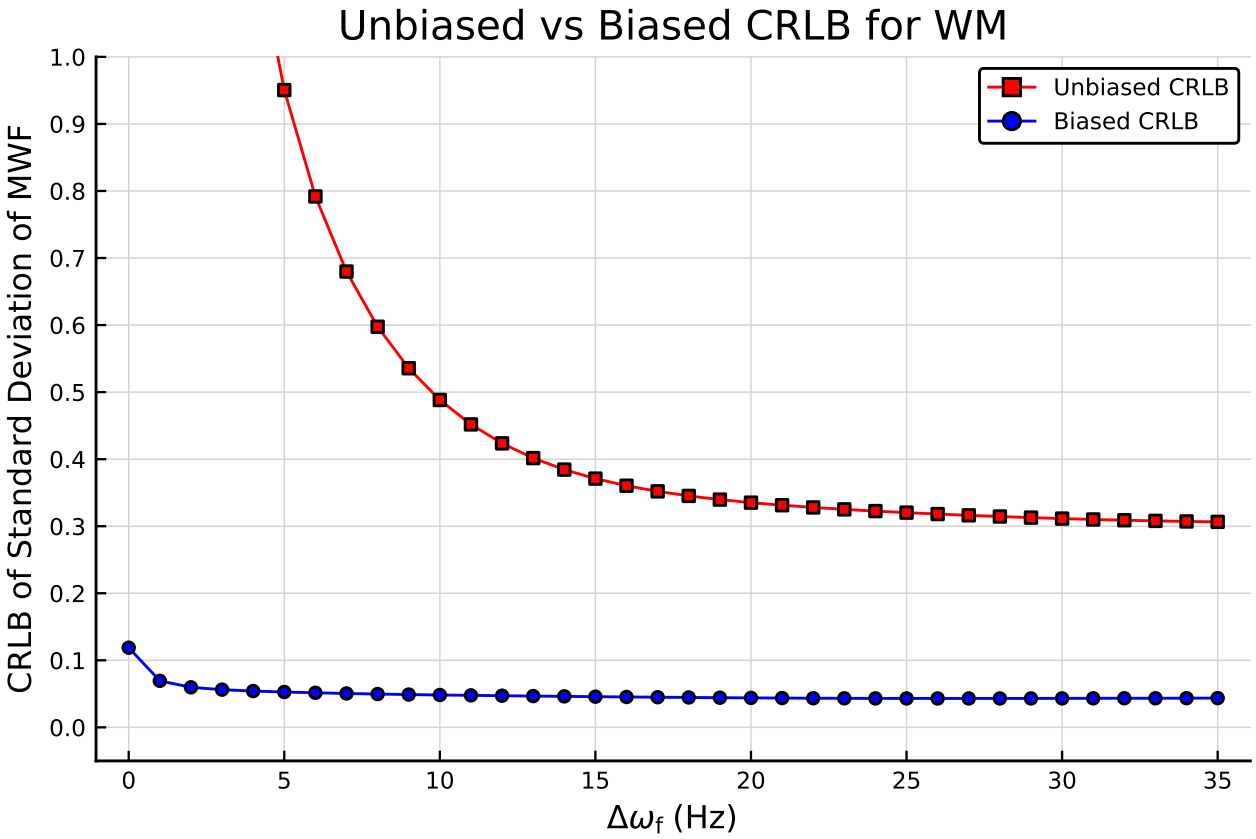
To assess the effect of MWF estimator bias, we computed the biased CRLB [10] of scan design A for fixed white matter tissue values (for the two-compartment non-exchanging model). (This is unlike what we did in Figure 2, where we calculated an expected CRLB over distributions of the parameters.) The biased CRLB indeed was smaller than the unbiased CRLB (see Supporting Information Figure S5), suggesting that estimator bias is why our estimates had low variance. We investigated the bias of our STFR3-PERK estimator for test data using the three-compartment exchanging model with fixed white matter tissue values. We found that even with (mild) estimator bias, our proposed MWF estimation technique is still sensitive to changes in MWF (see Supporting Information Figure S6). Furthermore, our estimator bias decreases as SNR

Supporting Information Table S2: Numerical results for Supporting Information Figure S3.

	White Matter (MWF = 0.15)			Gray Matter (MWF = 0.03)			
	RMSE	Mean	St. Dev.	RMSE	Mean	St. Dev.	Time (s)
STFR2-PERK	0.048	0.181	0.037	0.047	**0.045**	0.044	**14.8**
STFR3-PERK	0.097	0.055	**0.020**	0.051	0.058	0.043	41.9
STFR3-PERK-JE	0.092	0.061	0.024	0.047	**0.045**	0.045	41.9
MESE-NNLS	**0.031**	**0.148**	0.031	**0.027**	0.007	**0.013**	1606.2
MESE-PERK	0.038	0.178	0.025	0.046	0.066	0.029	142.1

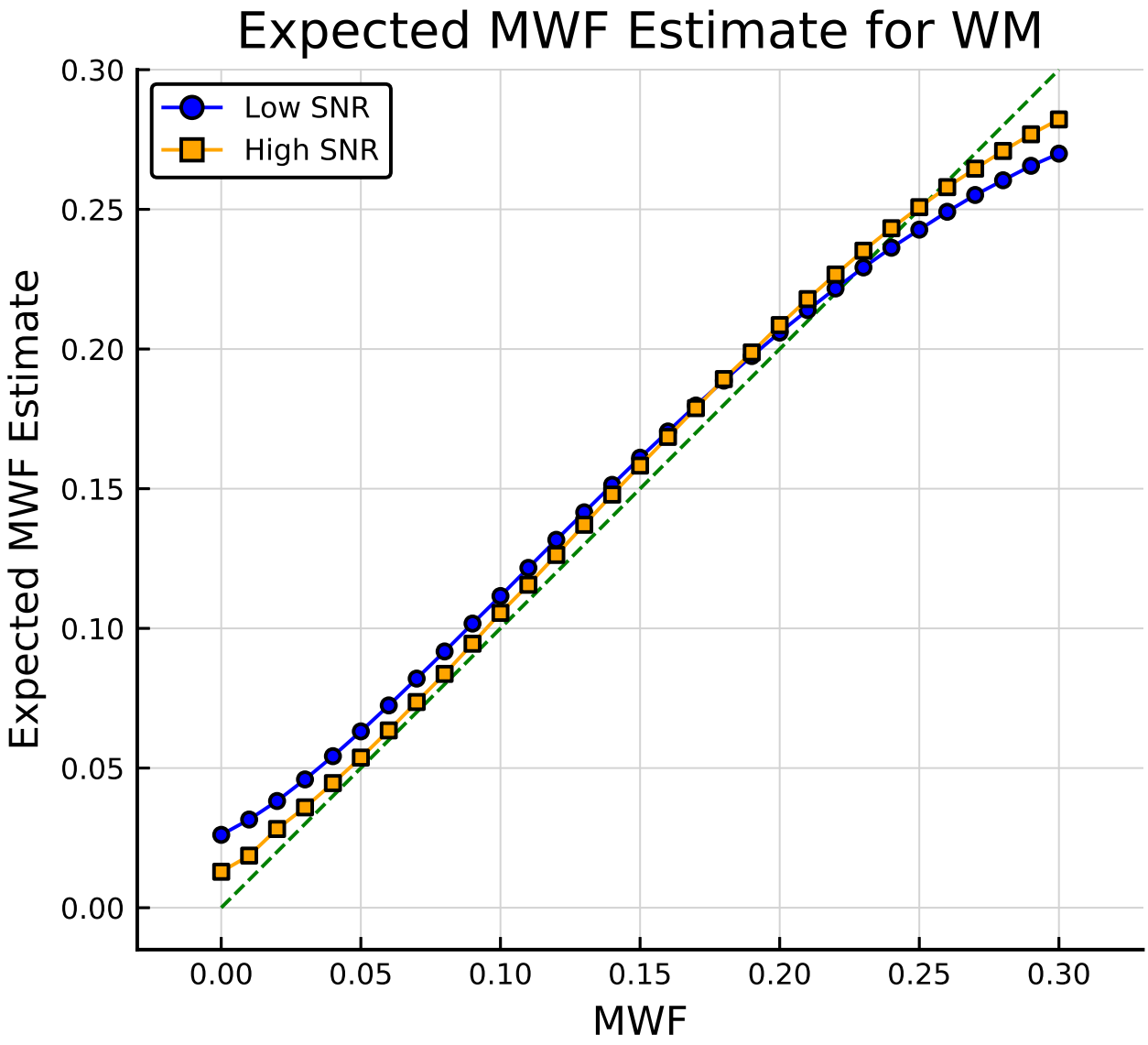


Supporting Information Figure S5: In vivo images for two SPGR and nine STFR scans using scan design A. Each image is the square root sum of squares combination of the individual coil data. STFR produces contrast similar to balanced SSFP, including a similar off-resonance profile that induces the characteristic banding artifact of balanced SSFP. Different points of this profile are sampled as the phase ϕ of the STFR tip-up excitation varies. The nine STFR images are sorted by increasing ϕ, so this off-resonance profile is easily visualized. In the lower right is the field map estimated from the two SPGR scans.



Supporting Information Figure S6: Comparison of biased and unbiased CRLBs for white matter tissue values using the two-compartment non-exchanging model. The biased CRLB is much lower than the unbiased CRLB, suggesting that bias is the reason why our STFR-based MWF estimation results in estimates with low variance. However, our proposed method still shows sensitivity to changes in MWF (see Supporting Information Figure S6).

increases (e.g., by using larger voxels). Thus, while the proposed method is biased, it still shows promise for detecting changes in MWF.



Supporting Information Figure S7: Expected MWF estimates from the proposed STFR3-PERK MWF estimation technique for fixed white matter tissue values from a three-compartment exchanging model. The proposed method is (mildly) biased, yet it is still very sensitive to changes in true MWF value. Furthermore, bias decreases as SNR increases. (An unbiased estimator would have estimates along the line of identity, i.e., along the dashed line.)