How reliable are current practices in reconstructing relaxation spectra for detecting the T2 myelin water signal when applied to real in vivo T2 decays?

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**Purpose** To assess the reliability of current practices of reconstructing relaxation spectra from T2 decays in detecting the T2 myelin water signal in vivo.

**Background** The most often cited reports as the first reliable detection of the T2 myelin water signal in vitro [1] and in vivo [2-3] used the Whittall and MacKay version of nonnegative least square (WMNNLS) [4] to reconstruct the relaxation spectrum for the T2 decay. The T2 myelin signal is usually assumed to be any signal with a time constant below about 50ms. While other groups have reported detections by fitting T2 decays to a few monoexponential decays, it was argued [1-4] that these detections were "biased", and thus unreliable, because they introduced prior information, other than the assumption that the relaxation spectrum was nonnegative. Data conserving reconstruction matrices (DCRM) were introduced as a more reliable detection method [6-8] but requires several times the signal to noise ratio (SNR). DCRM has a solid theoretical basis for the claim that it uses no prior information, is unbiased and reliable [6-8].

**Method** A T2 decay, that was acquired in vivo from white matter in a human brain with SNR of 650 on a 1.5T MRI scanner [6-7], was degraded to SNR of 100 by adding idea noise (Gaussian, additive, uncorrelated, stationary, mean of zero). The decay had been sampled at 32 echoes spaced at 10ms. The decay was then reconstructed with DCRM, WMNNLS and fitted to a few monoexponentials [5]. A spectrum was also reconstructed with a variation of WMNNLS where, instead of constraining the time constant to zero below 20ms as required by WMNNLS, it was constrained to zero below 63ms (RNNLS). To further test the algorithms' reliability, a simulated T2 decay was generated from the RNNLS reconstructed spectrum. Twenty different versions of the simulated decay were then generated by adding ideal noise to each decay so the SNR of each was 100. The 20 simulated decays were then reconstructed with WMNNLS and fitted to a few monoexponentials. (DCRM matrices are available at www.kscover.ca for download).

**Results and Discussion** For DCRM the large error bar compared to the size of the T2 myelin water signal indicated the SNR of 100 was too low for a reliable T2 myelin water signal measurement (Fig 1). WMNNLS, RNNLS and fitting a few monoexponentials all reconstructed spectra consistent with the decays. However, the first and last showed a solid myelin signal while RNNLS did not, confirming in vivo decays with 100 SNR are consistent with both the existence and nonexistence of a T2 myelin water signal. Spectra reconstructed from the 20 simulated decays showed a highly reproducible, but false positive, T2 myelin water signal. The total myelin signal below 50ms was 0.12 ± 0.07 and 0.11 ± 0.03 respectively, consistent with the values in the literature. Thus, in reconstructing relaxation spectra, both fitting a few monoexponentials and WMNNLS showed a bias that yielded a highly reproducible myelin signal when there was no signal below 63ms in the original spectrum. Reducing the regularization of WMNNLS would do little to alter its reliability as it will behave more like fitting a few monoexponentials which seems to be even less reliable.

**Conclusions** It has been demonstrated that both of the commonly used practises of reconstructing a relaxation spectrum for a T2 decay are unreliable. While DCRM has been used to reliably detect the myelin signal in vivo [6-7] it requires several times the SNR. As the multiecho sequences to acquire big voxels, which are needed for the higher SNR required by DCRM, are many times faster than the sequences for typical voxel volumes [7], it is recommended that big voxel sequences be acquired for a variety of structures and pathologies in vivo. The reliability of all reconstruction algorithms for T2 decays can then be re-evaluated, for a range of SNR's, based on these decays.

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