Combining multi gradient echo acquisitions with inversion recovery: Estimating the residence time of myelin water from transient MT effects.

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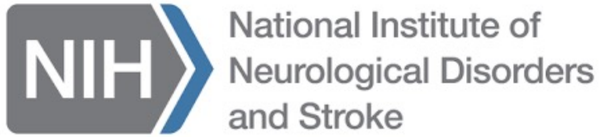
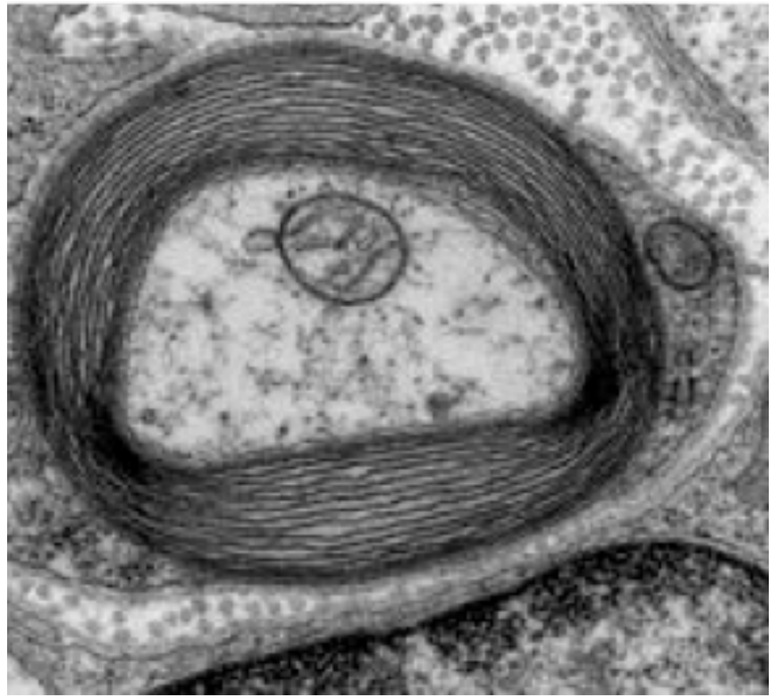


Summary

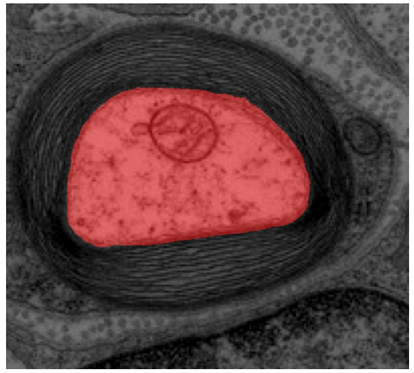
In this study, we combine MGRE based myelin water imaging with MT and inversion preparation pulses to measure the evolution of the magnetization in myelin water and axonal/interstitial water as function of delay time after the MT/inversion pulse (an MT pulse is aimed at selectively saturating the semi-solids in the tissue). A model was fitted to this data including relaxation and the exchange processes between semi-solids and water (MT effects) and between myelin water and axonal/interstitial water, resulting in an in-vivo measure of permeability of myelin lipid layers in human brain.

Water in White Matter

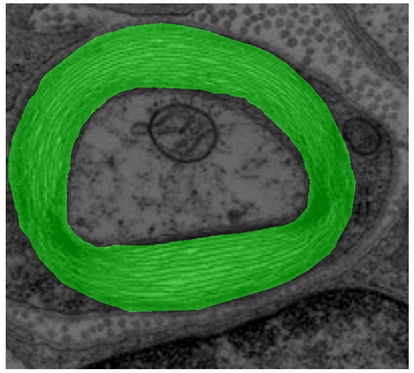
Water in white matter (WM) can be divided in three compartments: Axonal, Myelin, and Interstitial compartments.



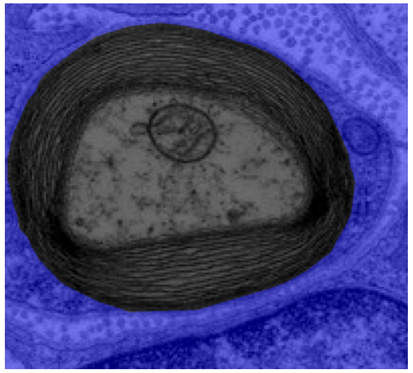
Electron micrograph of an axon
Trinity College, Hartford, CT



Axonal compart-ment



Myelin compart-ment



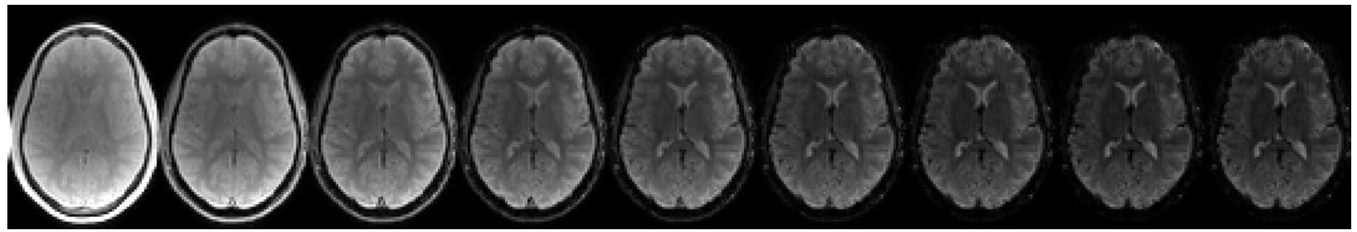
Interstitial compart-ment

Three Compartment Model

The signal from the three water compartments can be separated in an multi-gradient echo (MGRE) acquisition, based on their differences in offset frequency (ω) and T^*_2 decay rate (R^*_2, Sati et.al., NeuroImage 77:268).

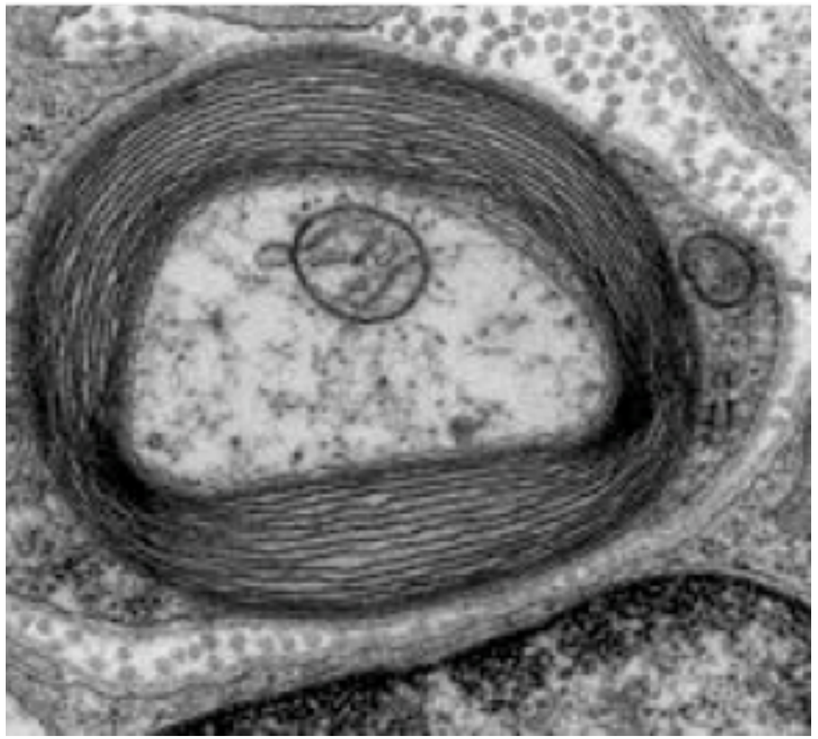
$$S = (a_a e^{-R^*_{2,a} t + i\omega_a t} + a_m e^{-R^*_{2,m} t + i\omega_m t} + a_i e^{-R^*_{2,i} t + i\omega_i t}) e^{i\phi}$$

MGRE Image series



Semi-Solids in White Matter

WM tissue has 30% non-water semi-solids, mostly proteins and lipids. The majority of these are in the myelin sheath.



Electron micrograph of an axon
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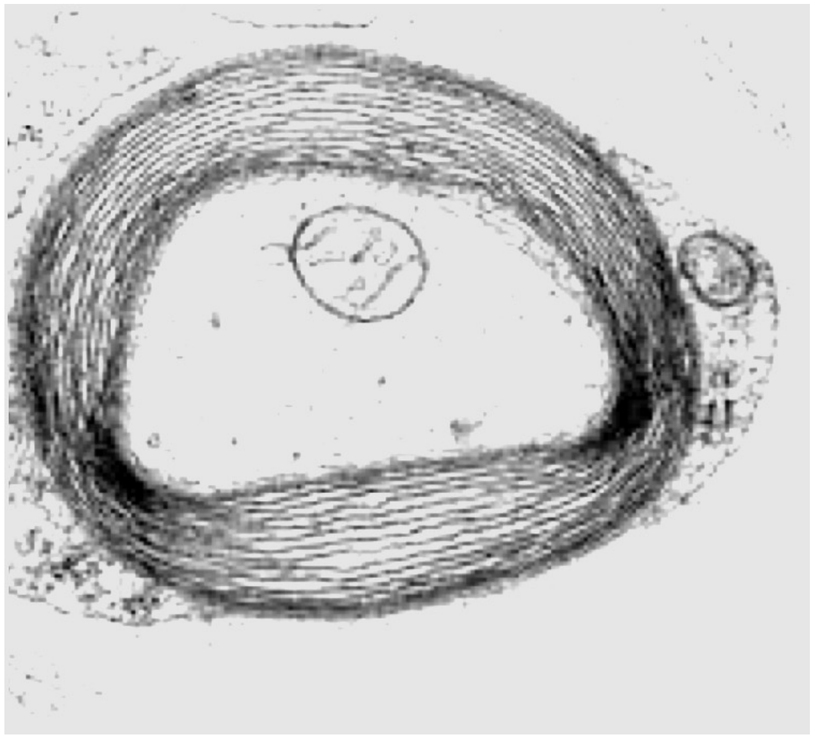
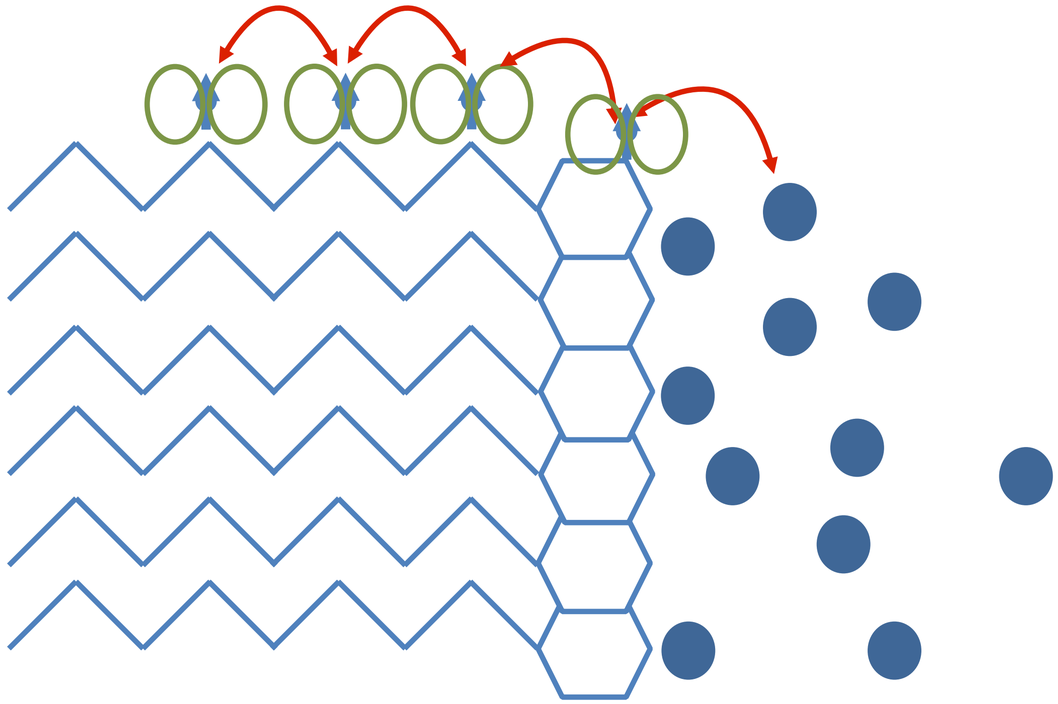


Same image, manipulated to highlight the myelin semi-solids

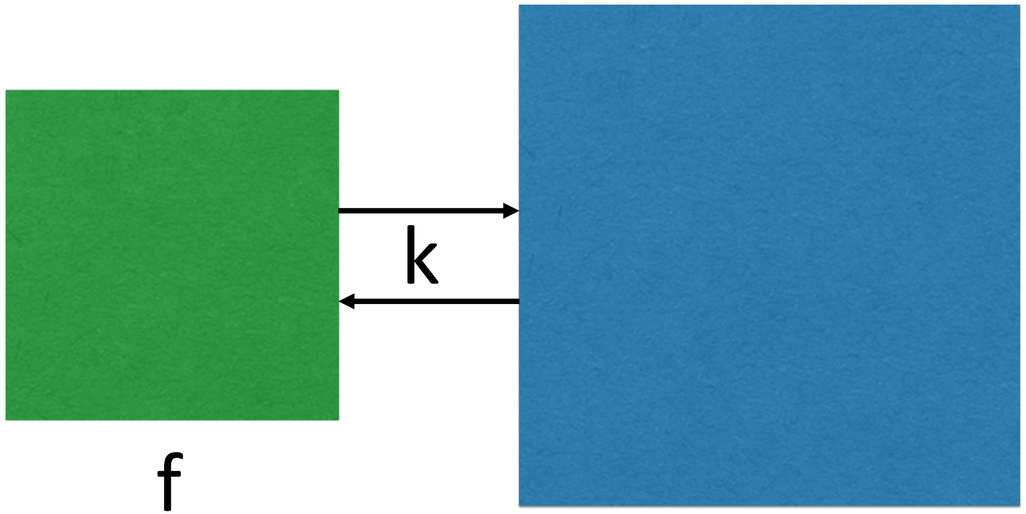
Magnetization Transfer

Although the lipid ^{1}H-protons are not visible in normal MRI because of their short (<100µs) T_2, they can indirectly influence the water signal through exchange, which can be either through chemical exchange or magnetic interaction. Even though this only happens at the solid/water interface, most lipid protons participate as they are strongly coupled to each other and effectively form one pool. This exchange is called magnetization transfer (MT).



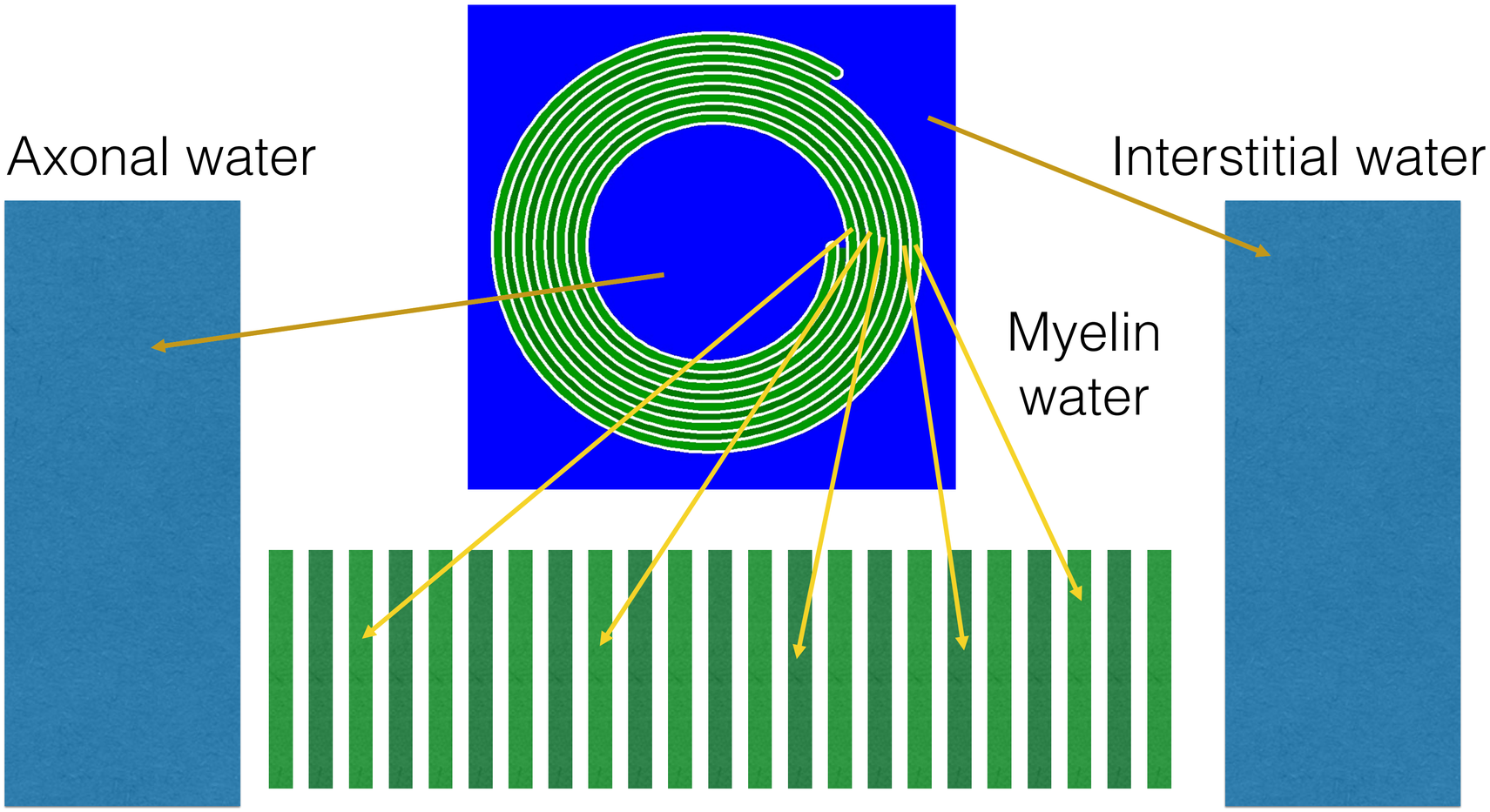
MT model

The classic model to analyze MT is a two pool model: one pool of semi-solids, one pool for water. This model does not explicitly include myelin water, often not visible in MRI due to its short T_2* (~6ms @ 7T).



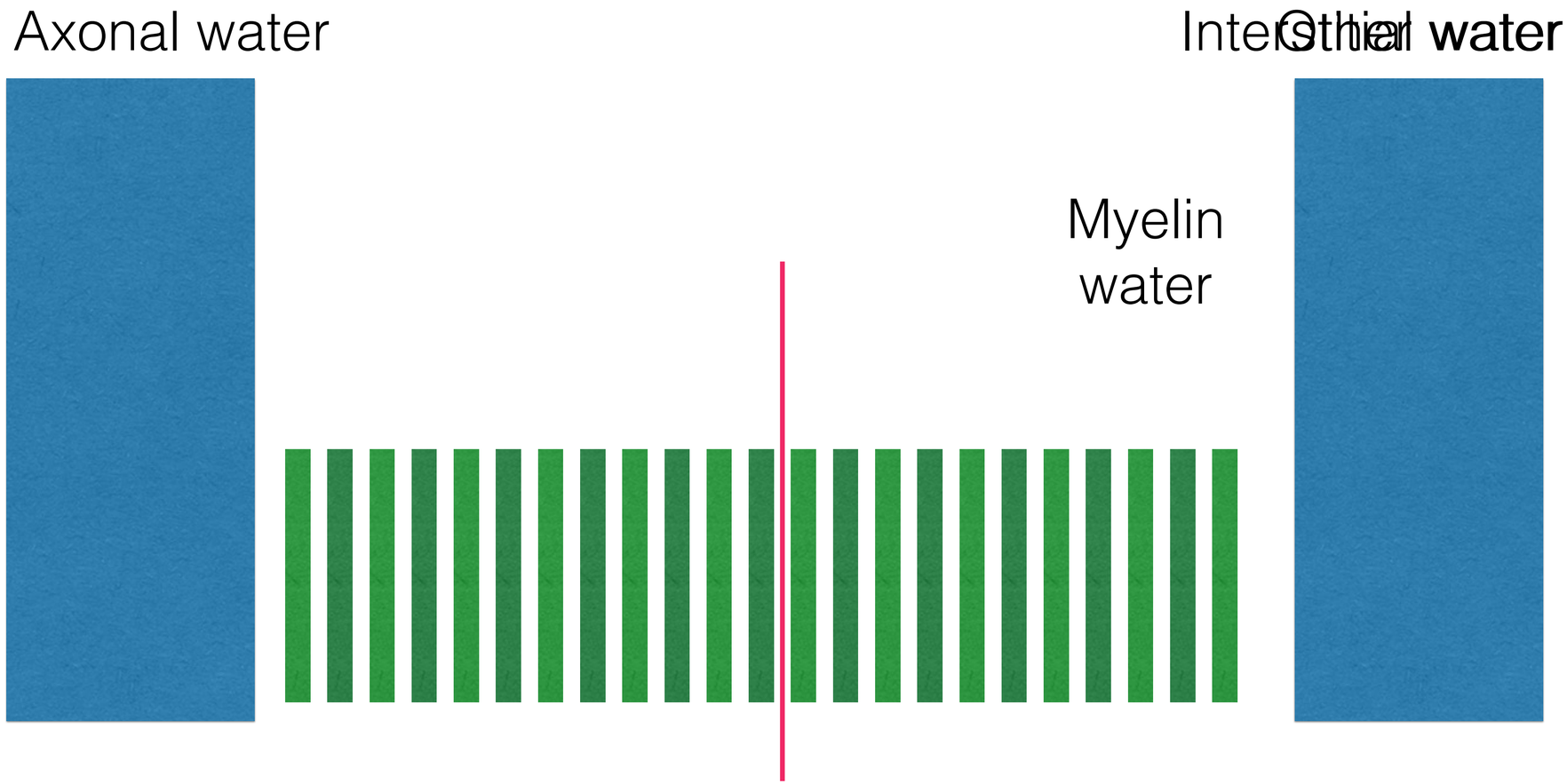
Multi-Layer Model

A multi-layer (ML) model was developed to include the layers of semi-solids and water in myelin and the exchange between these layers, as well as exchange with the neighboring axonal and interstitial water.



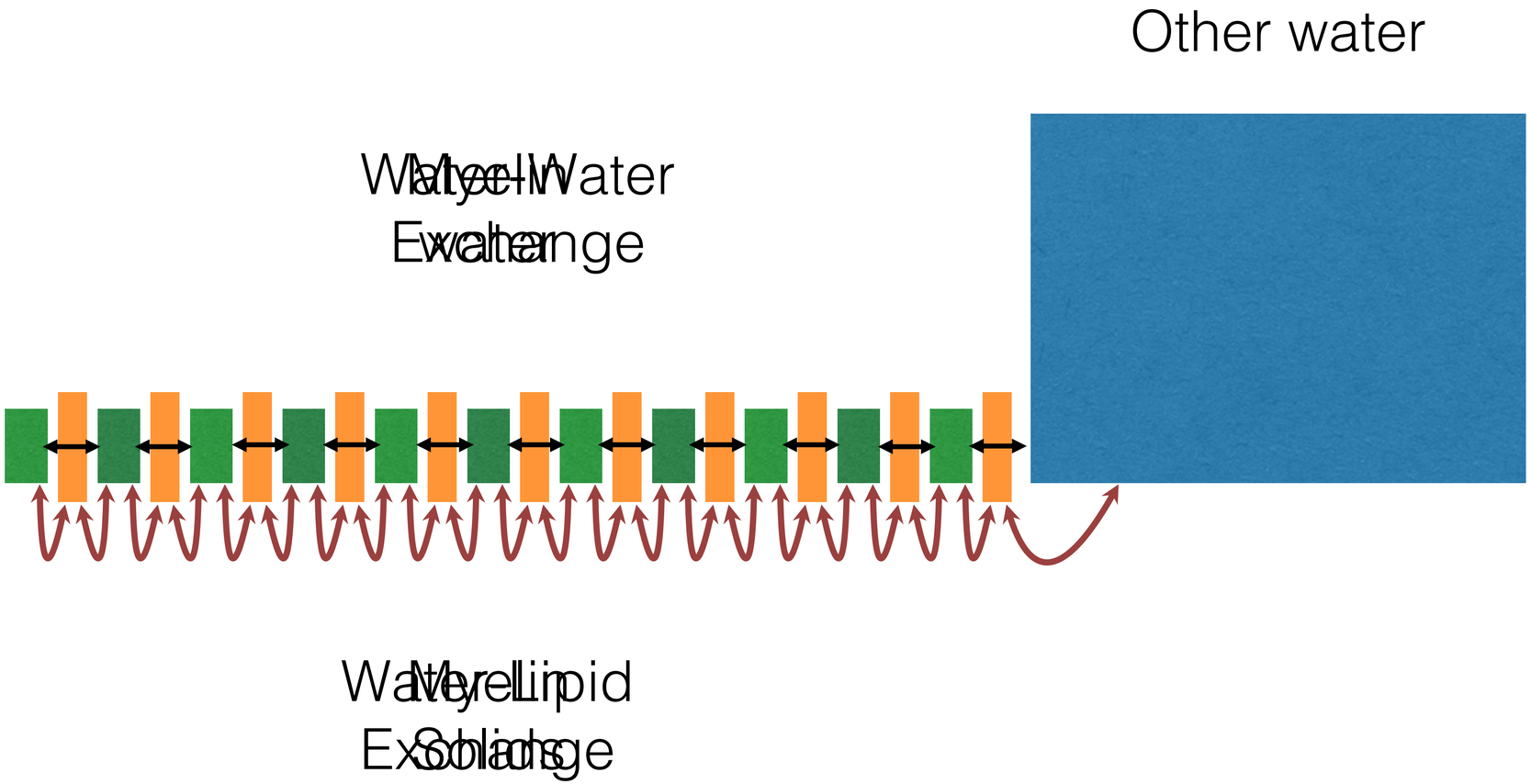
Multi-Layer Model

To simplify to model and reduce to number of parameters to be estimated, it is assumed axonal and interstitial water have similar properties. The resulting symmetry can then be used to reduce to model to half of the number of layers.



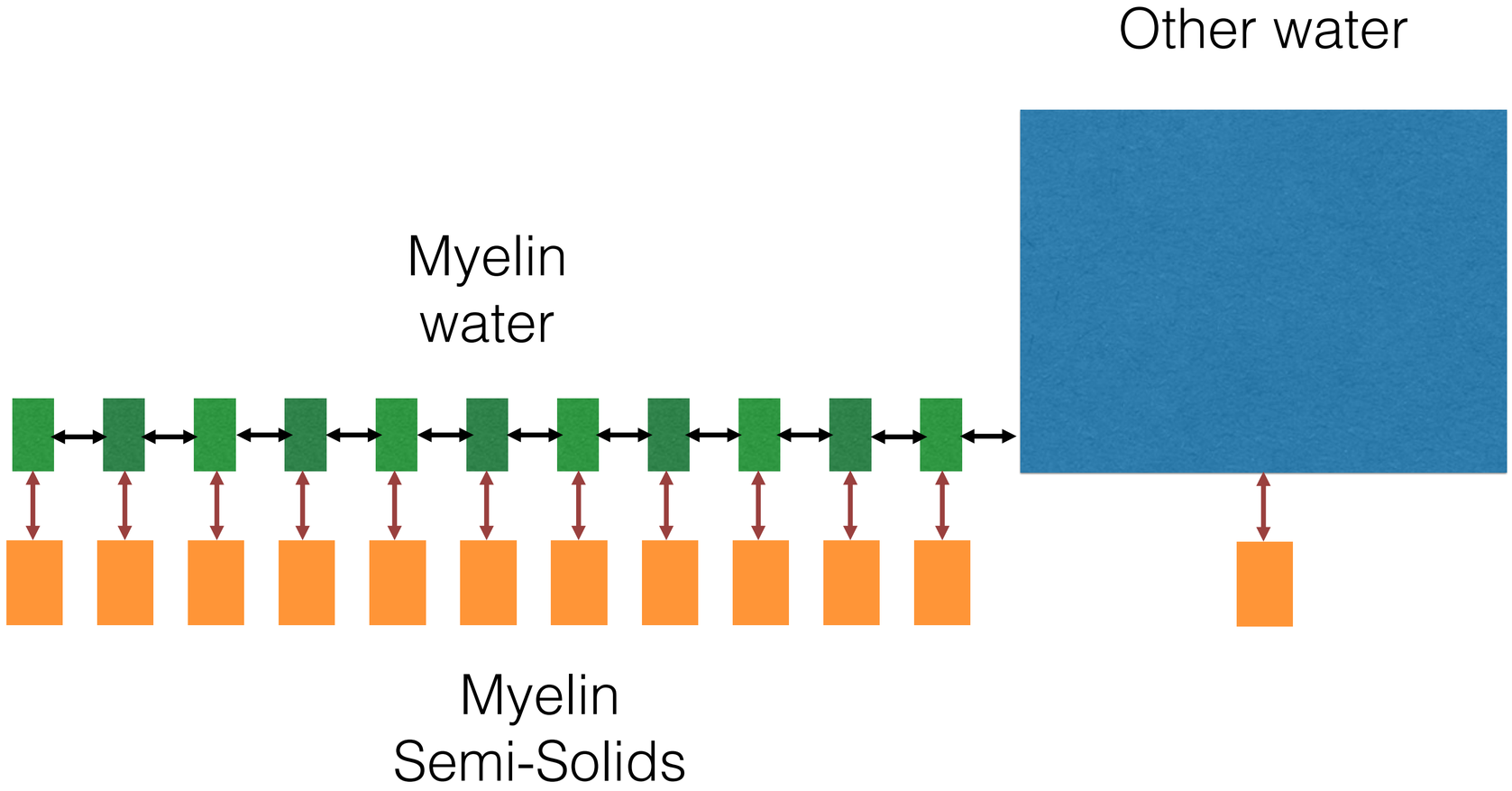
Multi-Layer Model

Next, we add the myelin solids and the two exchange processes: water-water exchange across a lipid layer and the solids-water MT effect.



Multi-Layer Model

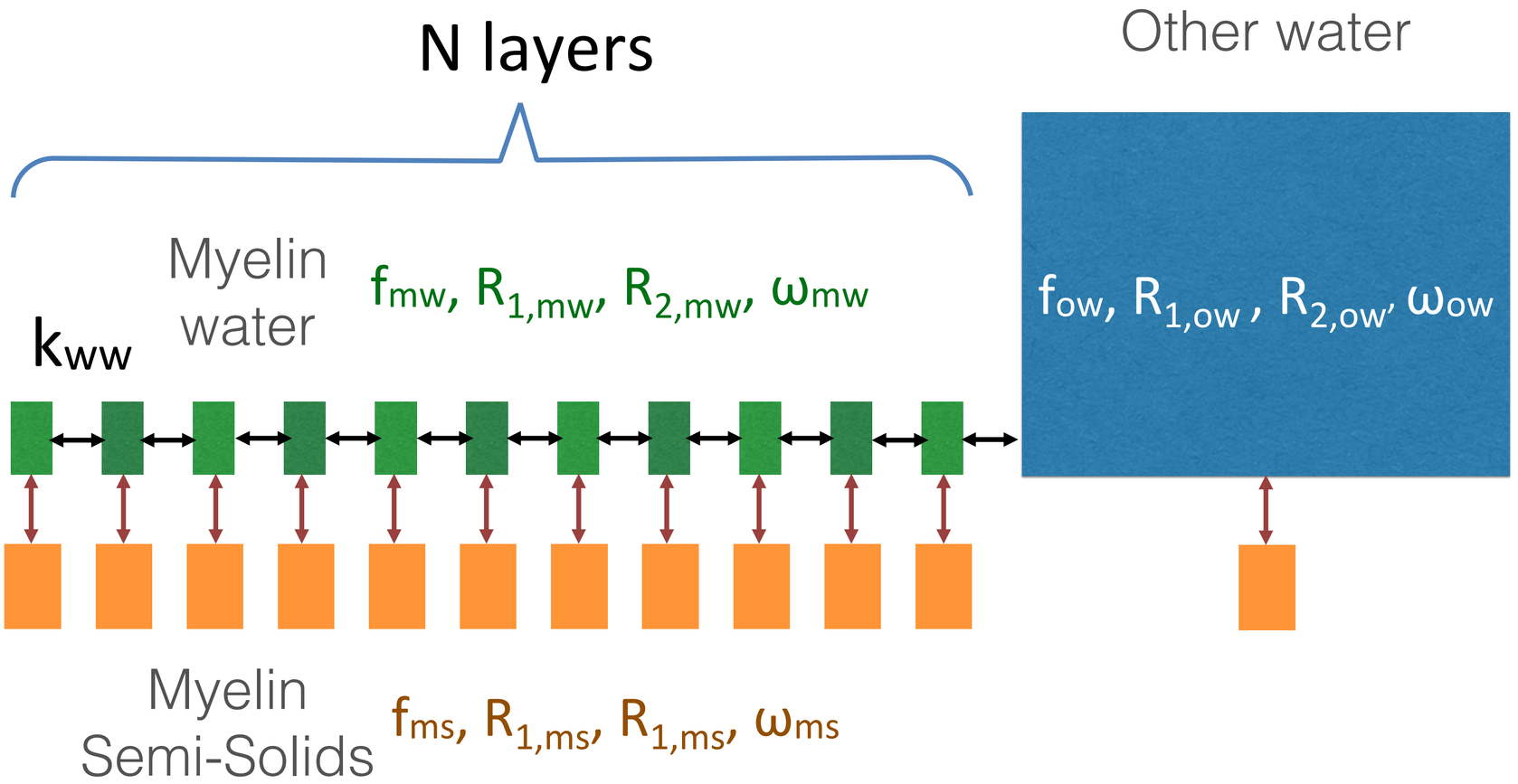
The myelin semi-solids can be regarded as separate compartments, each exchanging with its own water layer, without affecting the equations of the model.



Parameters

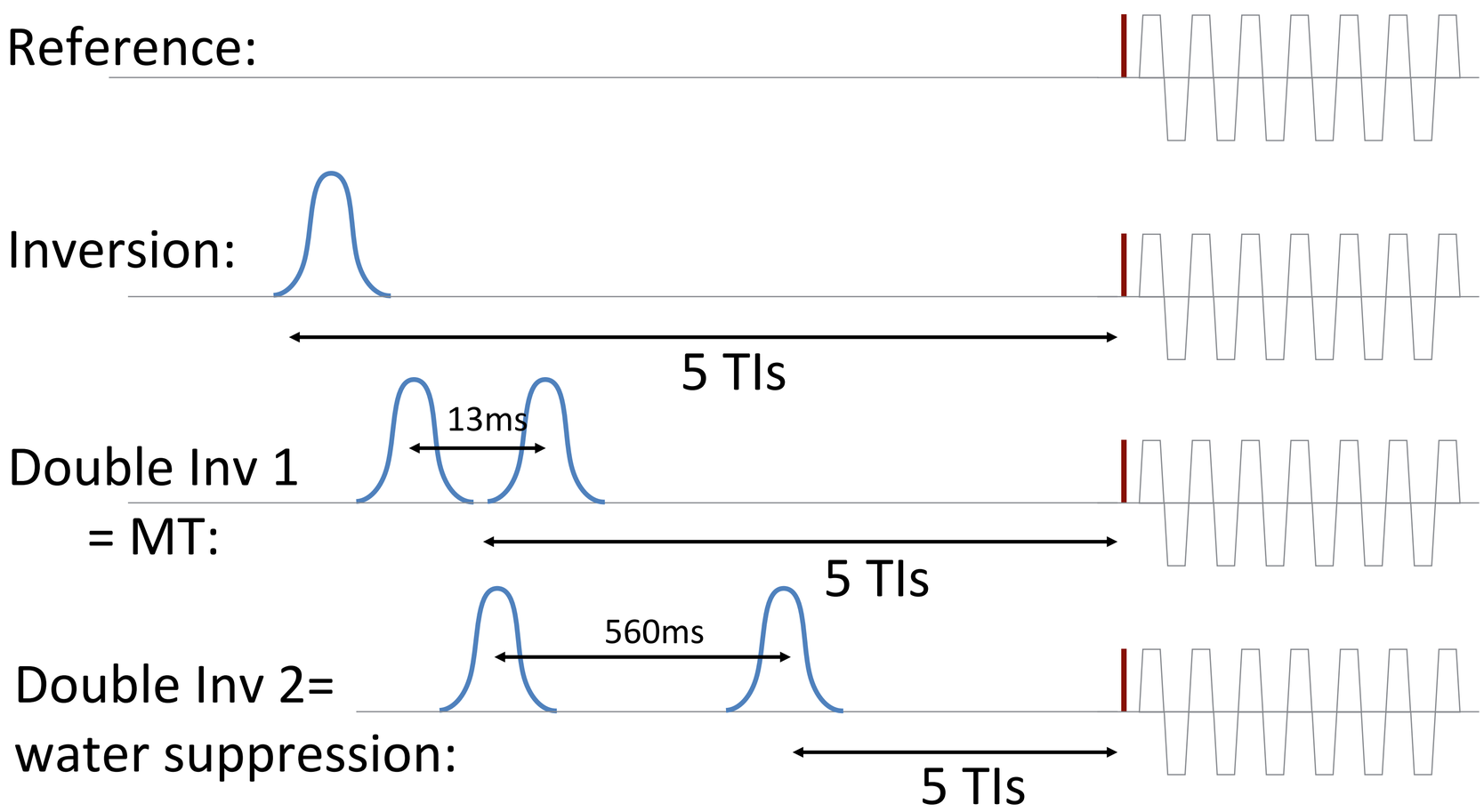
The model has 15 parameters:

- Number of layers: N
- Exchange rates: k_{ww}, k_{ws}
- Three each of:
  - Relative size: f
  - M_z relaxation rate: R_1
  - Transverse rel. rate: R_2
  - Offset freq.: ω



MGRE Experiments

One reference and three M_z prepared scan types were used, each with a MGRE acquisition. The different inversion pulse preparations alter the relative M_z levels in the various pools, so that exchange and relaxation can be observed. The evolution of the magnetization is sampled at five delay times (TI).



MGRE Experiments

The purpose of the four scan types was to measure the amplitude and evolution of the two water pools with different starting conditions:

- Reference: all pools relaxed (all M_z= 1)
- Inversion: the OW (other water) inverted, partial saturation for semi-solids
- MT: saturated semi-solids, the water at M_z=1 (double inversion= 360° rotation).
- Water suppression: M_z=0 for OW by adjusting the timing of the two inversions (and the TR) as in ViSTa (Oh et.al., NeuroImage 83:485).

The inversion pulses have different effects on the three types of spins due to the different T_2^* values. The pulses are expected to invert the spins in the the OW pool, (partly) saturate the semi-solids, and have an intermediate effect on the myelin water.

Analysis

Data from 10 subjects, acquired at 7T, were averaged in the splenium of the corpus callosum.

Analysis was done in two steps:

1) individual fitting of triple exponential model to MGRE data
2) fitting of the multilayer exchange model to averages over subjects

In step 1, first the reference data was fitted with the full model. Then for all other data, the non-linear parameters were fixed, and fitted amplitudes were normalized by the results of reference fitting. This resulted in 5x3 (TIs, scan types) amplitudes per subject, from which the averages and standard errors over subjects were derived.

Fixing Parameters

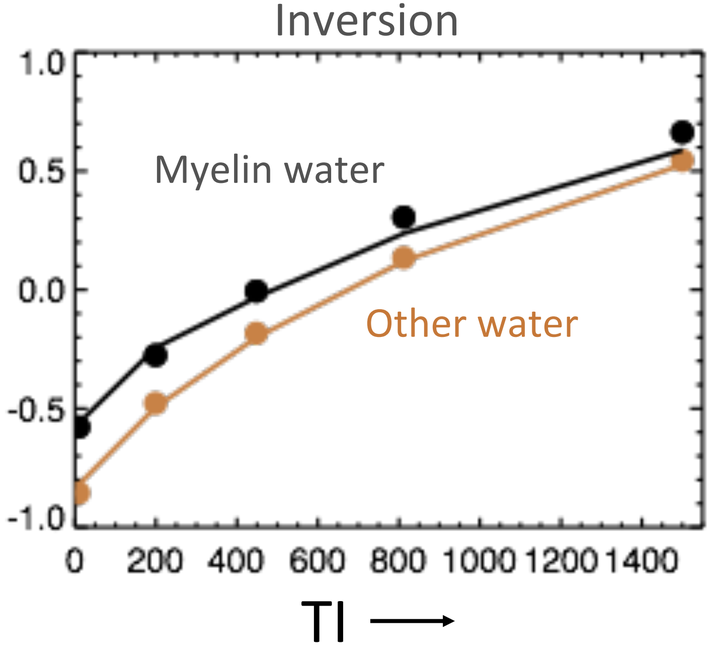
To reduce the number of parameters to be fitted, the following were fixed in the multiplayer model:

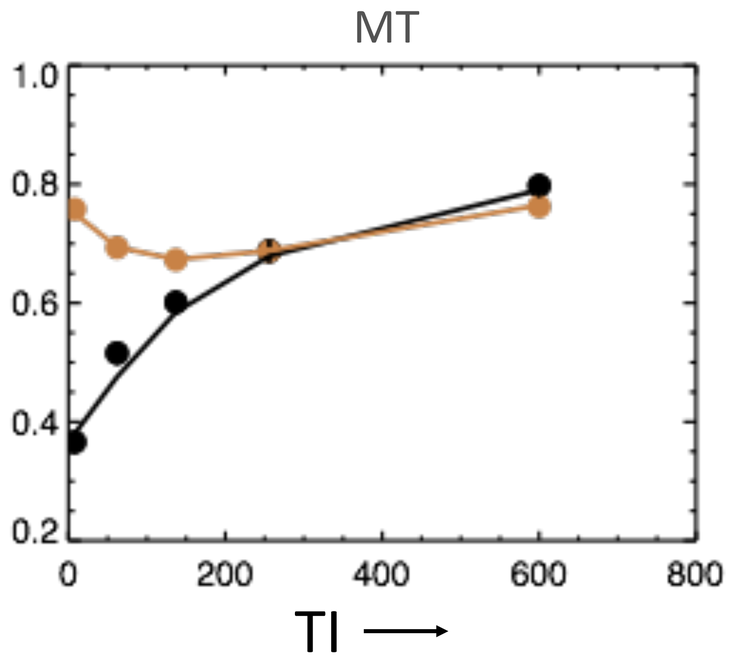
- N (number of layers) = 5, 9, 12, 15 (the model was fitted four times)
- $R_{2,mw}$, R_{2ow}= 0.136, 0.032 /ms, and ω_{mw} = 0.236 /ms from MGRE reference (ω_{ow} =0)
- $R_{2,ms}$ = 16 /ms and ω_{ms} = 4.4 /ms from MT spectrum data (MRM 2017, doi: 10.1002/mrm.26594)
- f_{mw}/f_{ow}= 0.12/0.88 from MGRE reference
- $f_{ms} + f_{mw} + f_{ow}$= 1 by definition

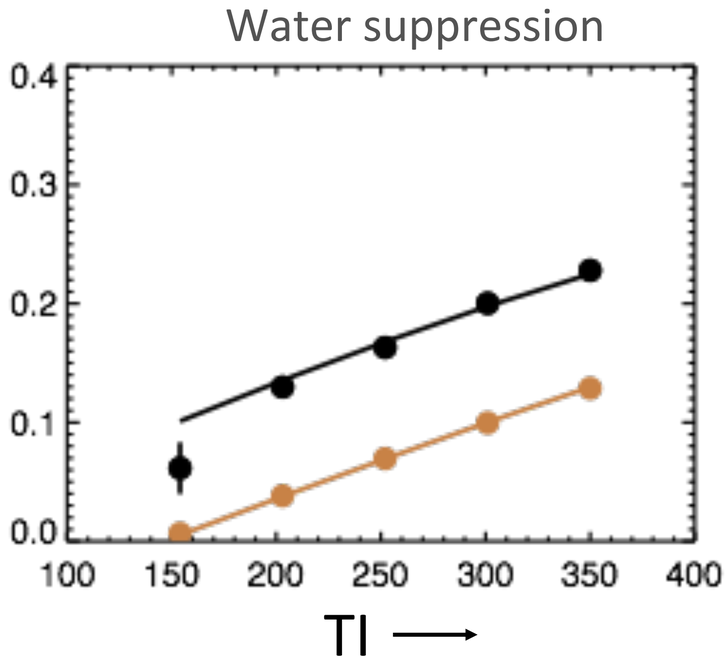
Free parameters remaining to be fitted:

- $R_{1,ow}$
- $R_{1,ms}$= $R_{1,mw}$ (these were set equal, as they showed too much correlation to separate)
- k_{ww}
- k_{ws}
- f_{ms}

Results: MGRE and ML fit







Normalized and subject averaged data for the three different scans with pre-pulses plotted as dots, the fitted model (for N=9) as lines. The other water is the sum of the axonal and interstitial components of the MGRE analysis; for the model results, the myelin water is the sum of all layers.

Results: Fitted Parameters

Solids fraction: f_{ms}= 25 %

Combined solids and myelin water relaxation rate: $R_{1,ms}$ $R_{1,mw}$ = 1.8 /s

Other water rel. rate: $R_{1,ow}$ = 0.36 /s

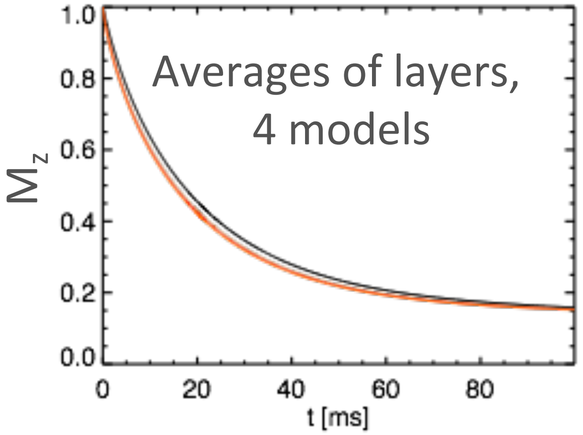
Total water-solid exchange, (N+1)k_{ws}= 3.1 /s

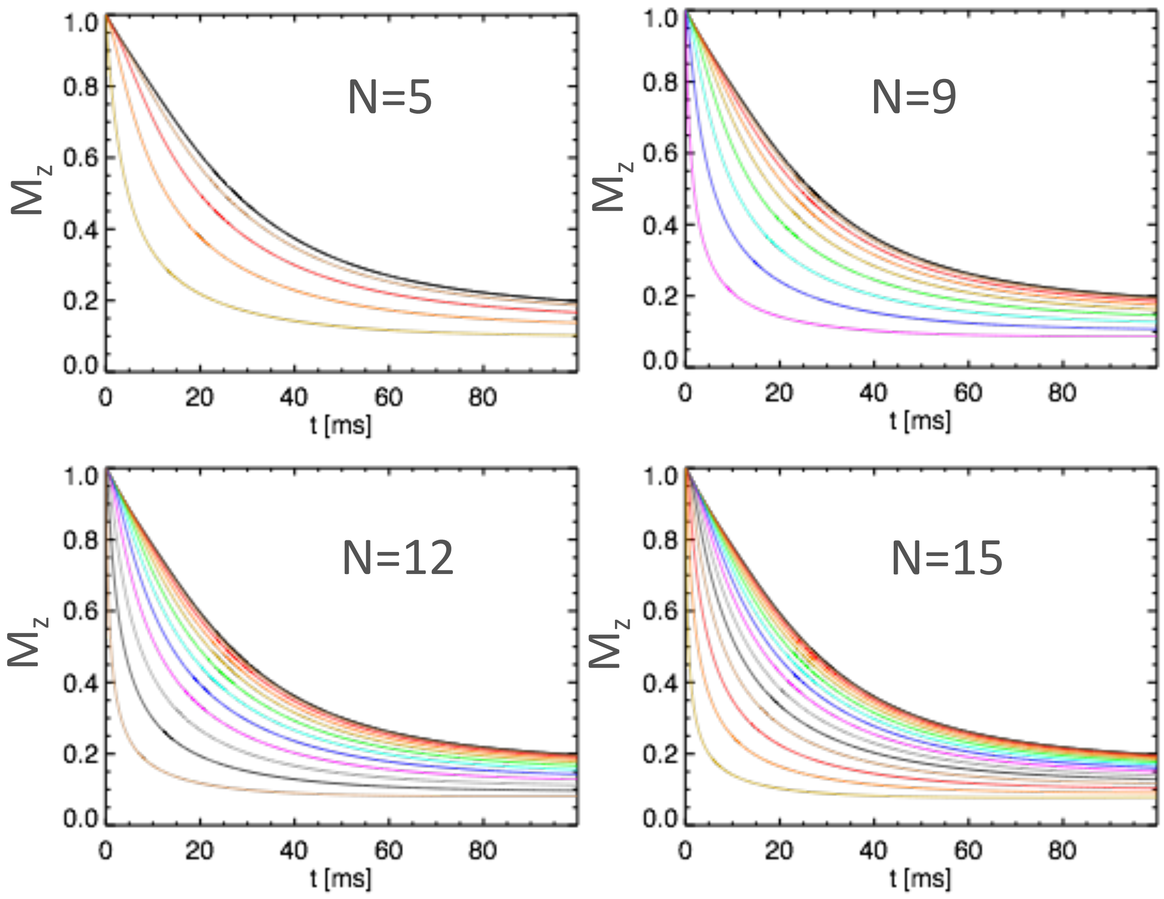
Water-water exchange: k_{ww}= 8.1 /s (rates relative to total volume)

The R_1 and f_{ms} results are consistent with previous results (van Gelderen et.al. NeuroImage 128:85), the exchange rates do not directly compare to the two-pool model used in that analysis.

Effect of Number of Layers

For the four choices of N, the model was fitted to the MGRE data and the resulting parameter sets were used to simulate the decay of the the magnetization from a starting condition of M_z=1 for myelin water, and M_z=0 for the other pools, while ignoring relaxation. While the individual layers, plotted on the right, decay at very different rates, the average of the layers, plotted below, decays at the same rate for all for models (decay time 15ms).





Result: Exchange and Decay Times

Single compartment exchange times (calculated as τ=f/k) and decay times of average M_z (see previous slide), both in ms.

N		*5*	*9*	*12*	*15*
τ	*Semi-solids*	*84*	*80*	*78*	*77*
	Myelin water	*1.83*	*0.61*	*0.34*	*0.22*
	Other water	*178*	*78*	*60*	*50*
Decay Time of average	*Semi- solids*	*96*	*97*	*98*	*98*
	Myelin water	*17*	*15*	*14*	*14*
	Other water	*112*	*112*	*112*	*112*

Discussion

- Semi-solids fraction: f_{ms}= 25% (in splenium of corpus callosum)
- Exchange across myelin layers is fast:
  - single layer 200-500µs (exchange time τ=f/k, for N=9-15)
  - decay time aggregate of myelin water layers: 15ms
- MT exchange time is dominated by exchange between semi-solids and water, which may include an effect of the rate of spin-diffusion within the semi-solids. The exchange between myelin water and the main water pools adds a minor delay
- T_1 dominated by exchange and relaxation in semi-solids fraction ($R_{1,ms} >> R_{1,ow}$): therefore T_1 and MT both reflect f_{ms}

Discussion

It was not possible to determine the number of myelin lipid layers from the data, the model fitted equally well to the data with different values of N. As only the average of the myelin water layers is available as input data, the combined effect of the number of layers and the layer permeability is given by the data, as reflected in the average decay time and plots for the four values of N used. Using the average axon size in the splenium of the corpus callosum ROI from electron microscopy: 1 µm (Aboitiz et.al. Brain Res 598:143), the number of myelin lipid layers can be estimated to be about 20, or N=10 in the ML-model, which results in a permeability of about 3 µm/s, consistent with previous findings (Dortch et.al. MRM 70:1450).