Magnetization Transfer Basics

Greg J. Stanisz

Physical Sciences, Sunnybrook Research Institute; Department of Medical Biophysics, University of Toronto, ON, Canada

stanisz@sri.utoronto.ca

Magnetization transfer (MT) in a magnetic resonance imaging (MRI) context was first discovered by Drs Wolff & Balaban [1] who were attempting to perform a spin transfer experiment by selective saturation of urea looking for small signal suppression in water. Instead, they found a significant loss of image intensity from the proton signal in tissue. This generalized signal suppression, now known as MT, has become accepted as an additional way to generate unique contrast in MRI that can be used to advantage in a variety of clinical applications such as: multiple sclerosis [2], osteoarthritis [3], cancer [4, 5], angiography [6] and cardiovascular disease [7, 8]. The detailed underlying biophysics of MT is quantitatively understood [9], enabling MT to be optimally exploited in MRI. Standard MRI detects signal only from mobile protons (water) with sufficiently long T_2 relaxation times (i.e. greater than 10 ms) so that spatial encoding gradients can be played out between excitation and acquisition before the signal has completely decayed. The T_2 of the less mobile protons associated with macromolecules and membranes in biological tissues are too short (i.e. less than 100 μs) to be detected directly in MRI. However, coupling between the macromolecular protons and the mobile or 'liquid' protons allows the spin state of the macromolecular (semisolid) protons to influence the spin state of the liquid protons through exchange processes. As shown in Fig. 1, it is possible to saturate the macromolecular spins preferentially using an off-resonance radio frequency pulse. The macromolecular spins have a much broader absorption lineshape than the liquid spins, making them as much as 10^6 times more sensitive to an appropriately placed off-resonance irradiation. This preferential saturation of the macromolecular spins can be transferred to the liquid spins, depending on the rate of exchange between the two spin populations, and hence can be detected with MRI.

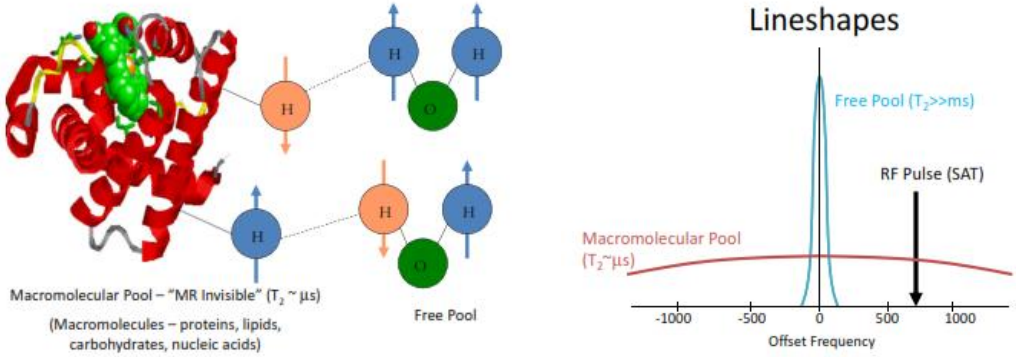

Figure 1. *Magnetization Transfer exchange between macromolecules and water protons –a) the macromolecular spins, exhibiting much broader absorption lineshape than liquid protons, can be preferentially saturated using RF off-resonance pulse.*

Magnetization Transfer experiment is typically performed using off-resonance RF saturation pulse followed by imaging read-out (Fig.2a) and the MT results are typically plotted in the form of "Z-spectrum" [10]:

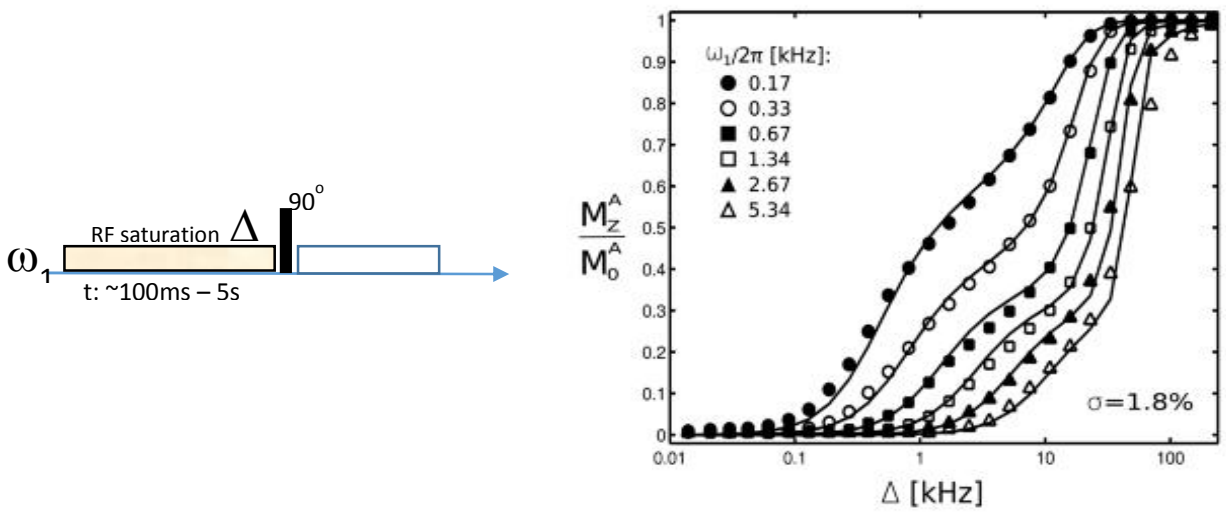

Figure 2. *MT sequence – left. Long RF saturation pulse with amplitude* μ_1 *and off-resonance frequency,* α *is followed by 90° pulse and imaging read-out. "Z-spectrum" for mouse spinal cord [11]– right. Magnetization is plotted as a function of offset-frequency for seven RF power amplitudes.*

Collection of the full Z-spectrum, as presented in Fig. 2a is often impractical due to time considerations and limitations of system hardware (such as upper level of RF amplitude and duration of the saturation pulse). Therefore, it is often customary use a train of shorter RF pulses and to express MT contrast in terms of "so called" magnetization transfer ratio, MTR:

$$MTR = \frac{M_z(0) - M_z(\Delta)}{M_z(0)}$$

Where $M_z(0)$ denotes magnetization (signal) in the absence of RF saturation pulse and $M_z(\Delta)$ is a signal as measured at given offset frequency (typically few kHz). It has to be noted however, that the MTR is not a pure measure of the MT effect since it also contains the effects of RF saturation on the liquid pool (direct effect). This is illustrated in Fig.3 which describes that contributions of direct effect and MT to the Z-spectrum.

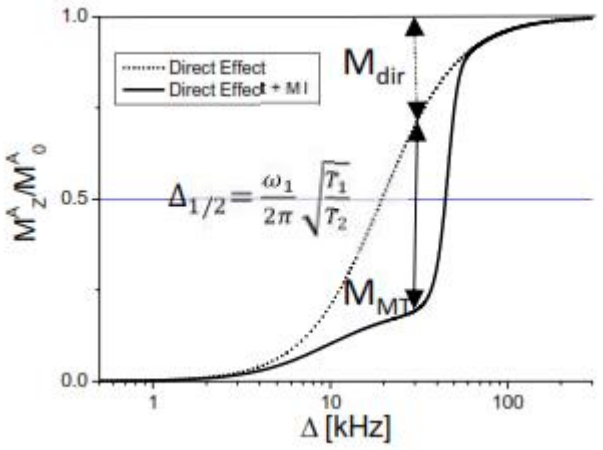

Figure 3. *Longitudinal magnetization of the liquid pool as a function of saturation pulse frequency,* α*. Dotted line represents directed effect of the RF saturation on the liquid pool. Magnetization decrease, also called "direct effect",* M_{dir} *is a direct consequence of RF saturation on the liquid pool. The MT effect causes additional magnetization decrease (solid line –* M_{MT}*). The magnetization transfer ratio, MTR is a sum of* M_{dir} *and* M_{MT} *contributions. The position of direct effect is related to the amplitude of the saturation pulse and longitudinal and transverse relaxation of the liquid pool: the offset frequency at the half maximum saturation,* $\alpha_{1/2}$ *increases linearly with* μ_1*.*

More advanced MT data analysis is usually based on the MT model of water exchange between liquid and semisolid pool, first developed by Henkelman *et al* [12] for agar and later modified by Sled and Pike [13] for more realistic imaging sequences that instead of using continuous wave (CW) irradiation apply a train of shorter RF saturation pulses (pulsed MT).

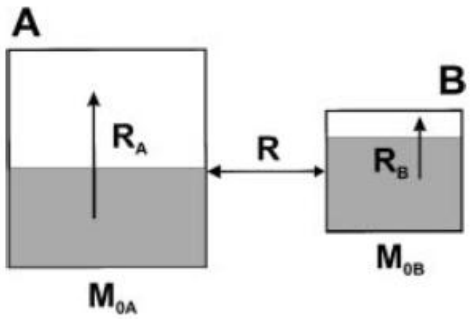

Figure 4. *A two-pool model of MT exchange. The shaded region of each pool represents saturated spins in liquid (A) and semisolid pool (B). R_A and R_B represent longitudinal relaxation of each pool, whereas R denotes magnetization transfer exchange.*

A mathematical formalism of a two-pool MT model or its extensions has been discussed by many groups and will be described in the next presentation. Figure 4 serves as a reminder that it is not possible to fully saturate macromolecular pool without also irradiating the liquid pool. Moreover, the effects of longitudinal relaxation (especially of the liquid pool, R_A) have a profound effect on the magnitude of the MT effect (Fig.5).

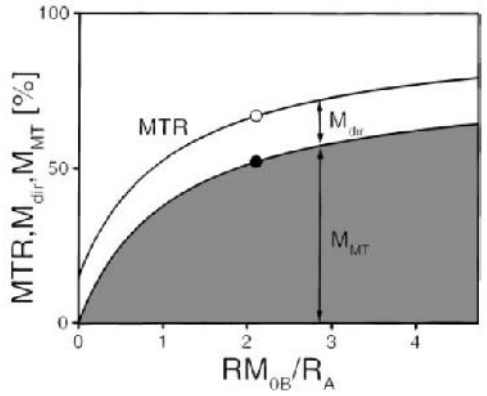

Figure 5. *Calculated values of magnetization transfer ratio, MTR; direct effect, M_{dir} and contribution of the MT effect, M_{MT} as a function of parameter RM_{0B}/R_A for saturation pulse amplitude μ_1=0.67kHz and offset frequency, a=8kHz. Experimental values of MTR and M_{MT} for white matter are shown as data points.*

Essentially, every tissue exhibits magnetization transfer effect (Table 1). The magnitude of the MT depends on type of macromolecules contributing to the MT exchange. MT is the largest for collagen (cartilage, tendon) or myelin (white matter) rich tissues. Blood with negligible macromolecular content exhibits very small MT effect.

Tissue	This paper measured at 3 T			
	M_{0D} [%]	R [s^{-1}]	T_{2D} [μs]	MTR [%]
Liver	6.9 ± 0.7	51 ± 10	7.7 ± 0.2	77 ± 5
Skeletal muscle	7.4 ± 1.3	66 ± 6	8.7 ± 0.1	88 ± 2
Heart	9.7 ± 0.2	52 ± 7	8.1 ± 0.1	89 ± 1
Kidney	7.1 ± 1.0	46 ± 7	8.1 ± 0.3	82 ± 1
Cartilage 0°	17.1 ± 2.4	57 ± 3	8.3 ± 0.1	85 ± 1
Cartilage 55°	18.2 ± 0.4	60 ± 5	8.3 ± 0.1	86 ± 1
White matter	13.9 ± 2.8	23 ± 4	10.0 ± 1.0	85 ± 1
Gray matter	5.0 ± 0.5	40 ± 1	9.1 ± 0.2	84 ± 1
Optic nerve	15.8 ± 1.1	23 ± 2	10.0 ± 0.6	86 ± 2
Spinal cord	12.6 ± 1.8	26 ± 5	10.5 ± 0.6	83 ± 1
Blood	2.8 ± 0.7	35 ± 7	280 ± 50	11 ± 4

Table 1. *Magnetization transfer parameters for wide range of tissue: macromolecular pool fraction, M_{0B}, MT exchange rate, R and transverse relaxation time of the semi-solid pool, T_{2B} along with magnetization transfer ratio, MTR measured at saturation pulse amplitude μ_1=0.67kHz and offset frequency, a=5kHz. Adapted from [14].*

Since the onset of the MT applications in clinical and basic research MRI there has been a debate in the literature regarding the symmetry of the MT effect in respect to central frequence of water (Δ=0). Early MT works indicate symmetrical lineshape of semi-solid pool and its super-lorentzian shape [15] whereas recent papers [16] strongly indicate its assymetric behaviour. This slight controversy arrises from the fact that large macromolecules contributing to the MT effect are not the only source of magnetization exchange with water. In recent years there is a growing interest in yet another MR contrast mechanism that focuses on magnetization exchange between water (liquid pool) and small molecules and their amine, amide and aliphatic groups [16]. The mechanism of this exchange is chemical in nature hence the name of this effect – chemical exchange saturation transfer (CEST). Experimentally, both MT and CEST are inseparable since they are based on similar saturation scheme. The difference between CEST and MT are mainly based on the nature of the exchange and the characteristics of molecules contributing to the effect (Table 2).

Table 2. *Major differences between MT and CEST*

	MT	**CEST**
Source of exchanging spins	Macromolecules (mostly long chain lipids)	Small molecules (mostly proteins)
T2 relaxation of molecular pool	~10μs	~1ms
Central frequency	0	Few ppm, ~kHz
Nature of exchange	Physical (mostly) Chemical	Chemical
Lineshape	Super-lorentzian or gaussian	Lorentzian
Optimal RF saturation power	0.5 – 1 μT	10 – 15 μT

In summary, MT is a unique contrast mechanism which basic underlying NMR physics is well understood. Although mainly used in context of white matter or cartilage diseases it can be easily extended to many other pathologies offering complimentary information to more standard relaxation based imaging techniques.

REFERENCES

1. Wolff, S. and R. Balaban, *Magnetization Transfer Contrast (MTC) and Tissue Water Proton Relaxation In Vivo.* Magn Reson Imag, 1989. **10**: p. 135-144.
2. Dousset, V., et al., *Experimental Allergic Encephalomyelitis And Multiple-Sclerosis - Lesion Characterization With Magnetization Transfer Imaging.* Radiology, 1992. **182**(2): p. 483-491.
3. Kim, D.K., et al., *Analysis of water-macromolecule proton magnetization transfer in articular cartilage.* Magnetic Resonance in Medicine, 1993. **29**(2): p. 211-215.
4. Arima, K., et al., *The progress in diagnostic imaging for staging of bladder and prostate cancer: Endorectal magnetic resonance imaging and magnetization transfer contrast.* Acta Urologica Japonica, 1999. **45**(8): p. 553-557.
5. Arnold, J.F.T., et al., *Potential of Magnetization Transfer MRI for Target Volume Definition Patients With Non-Small-Cell Lung Cancer.* Journal of Magnetic Resonance Imaging, 2008. **28**(6): p. 1417-1424.
6. Goodrich, K.C., et al., *A quantitative study of ramped radio frequency, magnetization transfer, and slab thickness in three-dimensional time-of-flight magnetic resonance angiography in a patient population.* Investigative Radiology, 1996. **31**(6): p. 323-332.

7. Kusuoka, H., V.P. Chacko, and E. Marban, *MYOCARDIAL ENERGETICS DURING VENTRICULAR-FIBRILLATION INVESTIGATED BY MAGNETIZATION TRANSFER NUCLEAR-MAGNETIC-RESONANCE SPECTROSCOPY.* Circulation Research, 1992. **71**(5): p. 1111-1122.
8. Semple, S.I.K., et al., *Comparison of four magnetization preparation schemes to improve blood-wall contrast in cine short-axis cardiac imaging.* Magnetic Resonance in Medicine, 1998. **39**(2): p. 291-299.
9. Henkelman RM, Stanisz GJ, and Graham JS, *Magnetization transfer in MRI: a review.* NMR in Biomed, 2001. **14**: p. 57-64.
10. Grad, J. and R. Bryant, *Nuclear magnetic cross-relaxation spectroscopy.* J Magn Reson, 1990. **90**: p. 1-8.
11. Portnoy, S. and G. Stanisz, *Modeling Pulsed Magnetization Transfer.* Mag Res Med, 2007. **58**: p.144-155.
12. Henkelman, R.M., et al., *Quantitative interpretation of magnetization transfer.* Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine, 1993. **29**(6): p. 759-766.
13. Sled JG and Pike GB, *Quantitative imaging of magnetization transfer exchange and relaxation properties in vivo using MRI.* Magn Reson Med, 2001. **46**: p. 923-932.
14. Greg J. Stanisz, E.E.O., Joseph Pun, Michael Escaravage, Simon J. Graham, Michael J. Bronskill, R. Mark Henkelman, *T1, T2 relaxation and magnetization transfer in tissue at 3T.* Magnetic Resonance in Medicine, 2005. **9999**(9999): p. NA.
15. Morrison C, Stanisz GJ, and R. Henkelman, *Modeling magnetization transfer for biological-like systems using a semi-solid pool with a super-Lorentzian lineshape and dipolar reservoir.* J Magn Reson B, 1995. **108**: p. 103-113.
16. van Zijl, P.C.M. and N.N. Yadav, *Chemical Exchange Saturation Transfer (CEST): What is in a Name and What Isn't?* Magnetic Resonance In Medicine, 2011. **65**(4): p. 927-948.