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Low duty-cycle pulsed irradiation reduces magnetization transfer and increases the inhomogeneous magnetization transfer effect

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ABSTRACT

Intense off-resonant RF irradiation can lead to saturation of the macromolecular pool magnetization and enhance bound pool dipolar order responsible for the inhomogeneous magnetization transfer (ihMT) effect, but the intensity of RF power in human imaging studies is limited by safety constraints on RF heating. High RF intensities can still be achieved if applied in short pulses with low duty-cycle. Here we investigate the benefits of low duty-cycle irradiation for MT and ihMT studies with both theoretical and experimental methods.

Solutions for *pulsed* irradiation of a two-pool model including dipolar order effects were implemented. Experiments were conducted at 3 T in the brain and through the calf of healthy human subjects. 2D echo planar images were acquired following a preparation of RF irradiation with a 2 s train of 5 ms pulses repeated from between 10 to 100 ms for duty-cycles (DCs) of 50% to 5%, and at varying offset frequencies, and time averaged RF powers. MT and ihMT data were measured in regions of interest within gray matter, white matter and muscle, and fit to the model.

RF irradiation effects on signal intensity were reduced at 5% relative to 50% DCs. This reduced RF effect was much larger for single than dual frequency irradiation. 5% DC irradiation reduced single and dual frequency MT ratios but increased ihMT ratios up to 3 fold in brain tissues. Muscle ihMT increased by an even larger factor, depending on the frequency and applied power. The model predicted these changes with duty-cycle. The model fit the data well and constrained model parameters.

Low duty-cycle pulsed irradiation reduces MT effects and markedly increases dipolar order effects. This approach is an attractive method to enhance ihMT signal-to-noise ratio and demonstrates a measurable ihMT effect in muscle tissue at 3 T under acceptable specific absorption rates. The effects of duty-cycle changes demonstrated in a separate MT/ihMT preparation provide a route for new applications in magnetization-prepared MRI sequences.

1. Introduction

Magnetization transfer (MT) and inhomogeneous magnetization transfer (ihMT) MRI can be used to produce images reflecting macromolecular content and biophysical properties of tissues [1,2]. Both techniques are sensitive to myelin content and this has led, particularly in the case of MT MRI, to their application in studies of neurological disorders [3–9]. Both techniques have also been applied in the study of other substances/tissues, e.g. muscle [10–12]. Applications of MT in MRI have been widely explored and documented [10,13–15]. IhMT is a much newer method that highlights dipolar order relaxation mechanisms in macromolecules by subtracting a minimum of two MT images obtained with different parameters.

Both MT and ihMT are achieved by applying RF irradiation relatively far from resonance to preferentially attenuate the magnetization of short T_2 protons in macromolecules. Reduction of the magnetization in such components is detected through exchange with the bulk magnetization of free protons, which provides the main measurable signal during MRI [1,10]. The term 'saturation' has been loosely used to describe the effect of off-resonance irradiation on the macromolecular pool, but this pool is usually far from being selectively saturated [16], i.e. magnetization greatly reduced relative to the thermal equilibrium magnetization, at powers achievable within RF safety limits in humans. This power restriction prevents the observation of selective saturation phenomena

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that can help to measure exchange rates, which are otherwise poorly constrained by experiments [16]. It also limits the magnitude of the transfer effect and consequently the sensitivity of any measurements.

One potential strategy for achieving transient selective saturation of the macromolecular pool is to apply short pulses of higher power, but with large gaps between pulses such that the time averaged power is acceptable [17,18]. Pulses are already widely used for MT studies because long continuous wave irradiation is not compatible with the high power RF amplifiers used for most clinical MRI scanners, and because they permit interleaving of irradiation and image acquisition [17–21]. When the fraction of time spent on RF irradiation, or duty-cycle (DC), is not too small, studies have indicated the MT effects are similar to continuous wave irradiation with the same time averaged power [22]. However, this approximation to a continuous wave saturation becomes less accurate for small DCs, and some studies have examined the impact of low DC, higher power irradiation to MT [23,24]. The effect of low DC pulsing on ihMT experiments has not been extensively studied. Off-resonance saturation with pulses as short as 1–10 ms have been employed to create dipolar order for measurement of the dipolar relaxation time, T_{1D} [25,26]. We have reported preliminary results with low DC pulses for ihMT both as a magnetization prepared sequence [27], and as part of a signal-to-noise optimized 3D steady state gradient-echo ihMT acquisition [28].

Here we use magnetization prepared echo-planar imaging (EPI) in human subjects at 3 T to systematically compare MT and ihMT signal differences as a function of DC for fixed time averaged power. A numerical model is also used to compare the low DC results with a physical model for MT and ihMT.

2. Theory

MT and ihMT effects can be well approximated using a two-pool model including dipolar order effects in the bound pool [11,29]. The two-pool MT model considers the exchange of (longitudinal) magnetization, M_z between a measurable, free pool of protons, A, assumed to be most of the water in tissue, and a more restricted (semi-solid) pool, B associated with bound protons within macromolecules that have very short T_2. Dipolar order effects arise when the RF irradiation is strong enough to attenuate one side within the bound pool line faster than the characteristic time, the dipolar relaxation time T_{1D}, for equilibrating magnetization across the line [30,31]. This non-uniform, or inhomogeneous, saturation of the line is described as the source of the ihMT signal [11,26,32,33]. Dipolar order effects can be modeled by adding a third, dipolar order component, β, which corresponds to the inverse spin temperature of the dipolar order and is coupled to the bound pool magnetization by RF irradiation. For ihMT, β is a measure of the saturation of one side of the macromolecular pool line relative to the other side. The differential equations (assuming zero contribution from transverse components due to relaxation and spoiling) for this model are given by:

$$
\begin{aligned}
\frac{dM_z^A}{dt} &= R_{1A}(M_0^A - M_z^A) - R_{rfA}M_z^A - R(M_0^B M_z^A - M_0^A M_z^B) \\
\frac{dM_z^B}{dt} &= R_{1B}(M_0^B - M_z^B) - W(M_z^B - 2\pi\Delta\beta) + R(M_0^B M_z^A - M_0^A M_z^B) \\
\frac{d\beta}{dt} &= \left(\frac{2\pi\Delta}{D^2}\right) W(M_z^B - 2\pi\Delta\beta) - \frac{1}{T_{1D}}\beta
\end{aligned}
\tag{1}
$$

These equations describe the change of magnetization with time in both the free pool, A, and the macromolecular pool, B. The third equation describes the variation of dipolar order in the macromolecular pool. The rate constant R describes the exchange of magnetization between the free pool and the macromolecular pool. $M_0{}^A$ and $M_0{}^B$ represent the thermal equilibrium longitudinal magnetization and R_{1A} and R_{1B} represent the longitudinal relaxation rate of pools A and B respectively. R_{rfA} is the rate of longitudinal magnetization loss from pool A due to the RF irradiation. The frequency dependence of this RF loss rate corresponds to the lineshape, which is assumed to be Lorentzian, and is approximated by $(\omega_1^2/(2\pi\Delta)^2)/T_{2A}$, where ω_1^2 is the power of the RF pulse and Δ is the offset frequency in Hz. The transition probability W (also referred to as R_{rfB}) is equal to $\pi\omega_1^2 g(2\pi\Delta)$, where $g(2\pi\Delta)$ is the normalized lineshape of the system, which is assumed to be super-Lorentzian for the bound spin system [11,29]. D represents the local field, which is determined by the assumed lineshape of the bound pool. T_{1D} is the relaxation time of dipolar order.

IhMT compares the effects of single frequency irradiation to those when the irradiation power is equally divided between positive and negative versions of the offset frequency. For such dual frequency irradiation, the coupling between the dipolar order and bound magnetization is effectively nulled [11,34]. This relates to the simpler two-pool model described by the following differential equations for the longitudinal magnetization of pools A and B:

$$
\begin{aligned}
\frac{dM_z^A}{dt} &= R_{1A}(M_0^A - M_z^A) - R_{rfA}M_z^A - R(M_0^B M_z^A - M_0^A M_z^B) \\
\frac{dM_z^B}{dt} &= R_{1B}(M_0^B - M_z^B) - WM_z^B + R(M_0^B M_z^A - M_0^A M_z^B)
\end{aligned}
\tag{2}
$$

As opposed to the regular, single frequency RF irradiation MT experiments for which this model was initially developed, the above differential equations are appropriate for dual offset frequency irradiation or uniform saturation experiments centered on-resonance [11,35].

The differential equations in Eqs. (1) and (2) are solved to provide values for $M_{z,\text{single}}$ and $M_{z,\text{dual}}$ respectively [11]. Solutions to Eqs. (1) and (2) for repeated square pulse irradiation can be performed either analytically [36,37], or numerically. Numerical methods using eigen decomposition have been introduced by Sled and Pike [36] and others [38], and are fast and accurate. These methods are employed in this work for fitting of experimental data to the model.

MT and ihMT effects are usually quantified as difference ratios. The MT and ihMT ratios are conventionally defined as:

$$
\text{MTR} = 1 - \frac{M_z^A}{M_0^A} \quad \text{and} \quad \text{ihMTR} = 2(\text{MTR}_{\text{dual}} - \text{MTR}_{\text{single}}) \tag{3}
$$

Alternative ratios based on inverse differences have been used because theory provides a simpler relation to parameter(s) of interest [39]. This is the case for MT and ihMT effects, for which inverse ratios suggest a more linear dependence with RF power within a range and under certain conditions [40–42]. We can replace the conventional magnetization transfer ratio, MTR, with the inverse MT ratio, MTR_{inv} [39], and analogously an inverse ihMT ratio, $\text{ihMTR}_{\text{inv}}$:

$$
\text{MTR}_{\text{inv}} = \frac{M_0^A}{M_z^A} - 1 = \frac{\text{MTR}}{1 - \text{MTR}} \tag{4}
$$

$$
\begin{aligned}
\text{ihMTR}_{\text{inv}} &= 2(\text{MTR}_{\text{inv,dual}} - \text{MTR}_{\text{inv,single}}) \\
&= \frac{(M_0^A)^2}{M_{z,\text{single}} M_{z,\text{dual}}} \text{ihMTR}
\end{aligned}
\tag{5}
$$

The subscripts single or dual refer to the magnetization (signal) ratios following RF saturation preparation applied at a single offset frequency or both positive and negative versions of the offset frequency respectively.