A Fractional-Order Model for T_2 Relaxation in Normal and Degraded Cartilage

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Introduction: MRI is increasingly used as a sensitive, noninvasive diagnostic modality for OA, but suffers from lack of specificity for matrix degradation. The initial phases of OA are characterized by disruption and loss of collagen and proteoglycan, the two major matrix components of cartilage. While changes in monoexponential relaxation times (e.g. T1, T2, and T1rho) have been observed to accompany cartilage degradation (1,2), these parameters exhibit limited sensitivity to cartilage pathology and limited specificity for particular cartilage matrix components. Non-negative least squares (NNLS) fits have previously been used to quantify and characterize underlying relaxation components in cartilage (3,4) in an attempt to improve sensitivity and specificity, but require high SNR. Recently, we derived a fractional-order relaxation model through imposing a memory kernel in the integral form of the Bloch equations. This leads to a stretched-exponential (Str-Exp) function for transverse magnetization decay (5). This physically-motivated model captures important features of the relaxation through the fractional-order parameter α, which reflects matrix microstructure. We previously observed a correspondence between α and the concentration of pure cartilage matrix components in solution, suggesting its sensitivity to matrix composition. Here, we extend this analysis by applying Str-Exp fits to normal and enzymatically degraded cartilage, showing the sensitivity of the fractional-order parameter α to loss of matrix proteoglycan. We also compare the T_2 distributions derived from the fractional-order model with T_2 distributions derived using NNLS, which makes no a prior assumption regarding the number of underlying relaxation components; these comparisons demonstrate the ability of the fractional-order approach to capture features of the relaxation distribution through adjustment of a single parameter, α. In addition, we find that our Str-Exp analysis is more stable in the presence of noise as compared to NNLS analysis, supporting its potential for clinical MRI applications.

Materials and Methods: *Cartilage Sample Preparation.* Bovine nasal cartilage (BNC) disks (diameter = 8 mm) were excised from the nasal septa of 5-6 month-old calves (Green Village Packing, Green Village, NJ). Samples were randomly assigned to control or treatment categories. Treated samples were incubated for 24 hrs in 0.1 units/ml Chondroitinase AC (ChAC, Seikagaku Corp., Tokyo, Japan) at 37 ºC. *T_2 Measurement.* NMR measurements were performed using a 9.4 T Bruker DMX spectrometer with a spectroscopic CPMG pulse sequence with sampling of each echo maximum. Acquisition parameters included: TE/TR = 600μs/10s, 2048 echoes, and NEX = 64. *T_2 fits.* Data were fit using monoexponential (Exp) and stretched-exponential (Str-Exp) functions (Eqs. 1&2). For comparison, T_2 distributions were resolved using a NNLS method similar to that described in (3) (Eq. 3). All fits were preformed in MATLAB (The MathWorks, Natick, MA).

Table 1. Fits to relaxation models and biochemical results for control and enzymatically degraded cartilage.

	Exp	Str-Exp		NNLS								sGAG	H_2O
Treatment	T_2	$T_{2,str}$	α	$T_{2,1}$	$T_{2,2}$	$T_{2,3}$	$T_{2,4}$	w_1	w_2	w_3	w_4	mg/mg	%
Control	82.8	75.1	0.879	0.8	10.7	31.5	86.5	0.025	0.034	0.108	0.833	0.161	77.77
	(5.0)	(4.9)	(0.005)	(0.2)	(0.5)	(1.4)	(6.7)	(0.004)	(0.002)	(0.013)	(0.012)	(0.012)	(0.68)
ChAC	125.0	118.7	0.935	1.4	10.2	38.9	129.0	0.024	0.008	0.035	0.933	0.097	80.36
	(12.2)*	(13.0)*	(0.015)*	(1.3)	(0.6)	(6.5)	(11.8)*	(0.016)	(0.001)*	(0.020)*	(0.037)*	(0.012)*	(0.89)*

Relaxation results are mean (SD) with T_2 in msec. $T_{2,i}$ and w_i represent NNLS-derived T_2 components and magnetization fractions. * indicates $p<0.05$.

$$M_{xy}(TE\cdot n) = b + M_{xy}(0)\cdot\exp\{-(TE\cdot n/T_2)\} \quad \textbf{Eq.1}$$

$$M_{xy}(TE\cdot n) = b + M_{xy}(0)\cdot\exp\{-(TE\cdot n/T_{2,se})^{\alpha}\} \quad \textbf{Eq.2}$$

$$M_{xy}(TE\cdot n) = b + \sum_{i=1}^{M-1} w_i\cdot\exp\{-(TE\cdot n/T_{2,i})\} \quad \textbf{Eq.3}$$

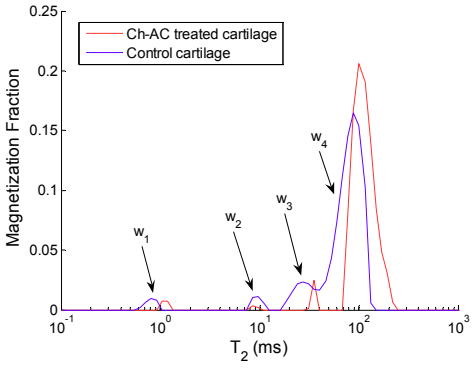

Fig 1. Example NNLS-derived T_2 distributions of Ch-AC treated and control cartilage.

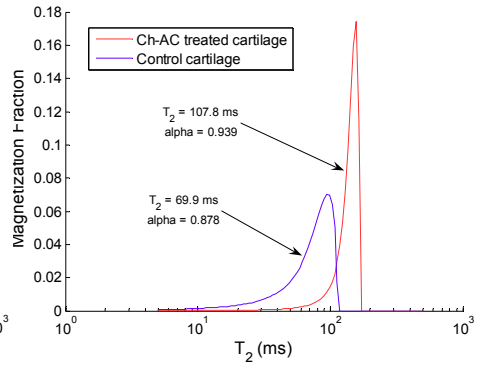

Fig 2. Example Str-Exp T_2 distributions of Ch-AC treated and control cartilage samples from Fig 1.

Results and Discussion: Biochemical results (Table 1) show a 39% loss of sGAG and a 3% increase in water content from Ch-AC treatment. As expected, Exp T_2 significantly increased, consistent with a loss of sGAG and an increase in hydration. We have previously shown a correspondence between specific NNLS-derived T_2 components and sGAG content in normal and degraded cartilage (4). Consistent with this, the current study shows a reduction of the magnetization fractions w_2 and w_3 and an increase in $T_{2,4}$ with sGAG loss (Table 1, Fig. 1). Str-Exp fits show both an increase in $T_{2,str}$ and α with degradation (Table 1), reflecting a reduction in microstructural tissue complexity; graphically, the distribution narrows and shifts to longer values of T_2 (Fig. 2), similar to the envelope of the NNLS-derived T_2 distribution (Fig. 1). F-test comparisons between Exp and Str-Exp fits show a statistically significant improvement in χ^2 with the addition of α. Fig. 3 shows the influence of α on the T_2 distribution, demonstrating a broad distribution for low values of α with a progressively narrower distribution with increasing α; the distribution converges to a single exponential for α = 1, representing the Exp limit. Numerical simulations of Str-Exp relaxation data in the presence of noise show accuracy and precision of $T_{2,se}$ and α to within 0.7% at SNRs of 100 (data not shown).

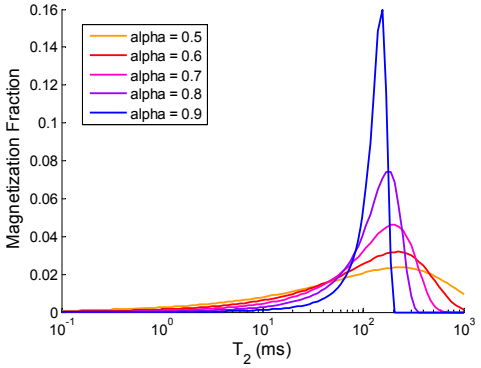

Fig 3. Example Str-Exp T_2 distributions for a fixed $T_{2,str}$ = 116ms and over a range of α.

Conclusions: As previously shown, NNLS is useful in providing a distribution of physically discrete water compartments which correspond to cartilage matrix components. The fractional-order model, derived from the Bloch equations, provides an alternative and physically plausible model of T_2 relaxation in cartilage, in which the fractional-order parameter, α, reflects the microstructural complexity of the underlying matrix. It has the additional advantage of exhibiting a single parameter to describe the degree of degradation and may be especially useful in cases for which the SNR is limited.

References: 1.) Menezes, N.M., et al. Magn. Reson. Med. 2004; 2.) Lin, P-C., et al. Magn. Reson. Med. 2009; 3.) Reiter, D.A., et al. Magn. Reson. Med. 2009; 4.) Reiter, D.A., et al. ISMRM 2009 p72; 5.) Magin R.L., et al. *submitted*.