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Clinical High-resolution Mapping of the Proteoglycan-bound Water Fraction in Articular Cartilage of the Human Knee Joint

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Abstract

Purpose—we applied a recently introduced method to achieve clinically-feasible *in-vivo* mapping of the proteoglycan water fraction (PgWF) of human knee cartilage with improved spatial resolution and stability as compared to existing methods.

Material and Methods—Multicomponent driven equilibrium single-pulse observation of T_1 and T_2 (mcDESPOT) datasets were acquired from the knees of two healthy young subjects and one older subject with previous knee injury. Each dataset was processed using Bayesian Monte Carlo (BMC) analysis incorporating a two-component tissue model. We assessed the performance and reproducibility of BMC and of the conventional analysis of stochastic region contraction (SRC) in the estimation of PgWF. Stability of the BMC analysis of PgWF was tested in two independent high-resolution (HR) datasets from each of the two young subjects.

Results—Unlike SRC, the BMC-derived maps from the two HR datasets were essentially identical. Furthermore, SRC maps showed substantial random variation in estimated PgWF, and mean values that differed from those obtained using BMC. In addition, PgWF maps derived from conventional low-resolution (LR) datasets exhibited partial volume and magnetic susceptibility effects. These artifacts were absent in HR PgWF images. Finally, our analysis showed regional variation in PgWF estimates, and substantially higher values in the younger subjects as compared to the older subject.

Conclusions—BMC-mcDESPOT permits HR *in-vivo* mapping of PgWF in human knee cartilage in a clinically-feasible acquisition time. HR mapping reduces the impact of partial volume and magnetic susceptibility artifacts compared to LR mapping. Finally, BMC-mcDESPOT demonstrated excellent reproducibility in the determination of PgWF.

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Keywords

Magnetic resonance imaging; Proteoglycan water fraction; Knee cartilage

1. INTRODUCTION

There remains an outstanding need for accurate high-resolution (HR) mapping of the macromolecular components of cartilage. Previous pre-clinical and clinical magnetic resonance imaging (MRI) studies have sought to define proteoglycan water fraction (PgWF) as an indicator of cartilage degeneration [1–7]. It has been shown that PgWF performs better as a clinical diagnostic marker for distinguishing between normal and degenerative cartilage as compared to conventional transverse relaxation time, T_2 [5]. In recent studies [4, 5], Liu *et al.* have demonstrated the feasibility of *in-vivo* whole human knee mapping of PgWF through use of the multicomponent driven equilibrium single pulse observation of T_1 and T_2 (mcDESPOT) protocol; initially developed to map myelin water fraction (MWF) in human brain [8, 9]. This represents an important step toward *in-vivo* mapping of PgWF, given the limitations of classical multi-spin-echo (MSE) MRI sequences, such as CPMG or GRASE [10], for this purpose. MSE-based sequences require long repetition times to mitigate T_1 dependence, and long echo times (TE) for HR imaging due to gradient strength limitations. The use of steady-state imaging sequences, such as mcDESPOT, overcomes these problems and permits whole knee coverage within clinically-feasible acquisition times, and with sufficiently short TE to improve the detection of the PgWF signal, with its relatively short T_2 .

In Liu *et al.* [4, 5], the voxel size was $0.625 \text{ mm} \times 0.625 \text{ mm} \times 3 \text{ mm}$. This provides excellent in-plane resolution, but relatively poor resolution in the slice direction. As a result, given the high degree of curvature and thinness of knee articular cartilage, low thru-plane resolution is prone to partial volume effects that may lead to inaccurate maps and bias in the estimation of PgWF in several cartilage regions. The desirability of imaging at the highest possible resolution is particularly important for better characterization of depth-dependent changes in cartilage tissue composition. While increasing the spatial resolution of the acquired images can attenuate the negative impact of partial volume effects, this comes at the expense of decreased signal-to-noise ratio (SNR), directly reducing the reliability of parameter determination from mcDESPOT [11–13].

In a recent studies [12, 14], it has been shown that both accuracy and precision in quantitative parameter estimates from mcDESPOT were greatly enhanced through use of a new Bayesian Monte Carlo (BMC) analysis as compared to estimates obtained using stochastic region contraction (SRC), a nonlinear least squares-based algorithm conventionally used for parameter estimation from mcDESPOT data [4, 5, 11, 12, 15]. Our principal aim in this study is to demonstrate the potential of the BMC analysis of mcDESPOT data (BMC-mcDESPOT) to provide HR maps of PgWF in human knee cartilage. We show that reliable results may be obtained using BMC-mcDESPOT with a voxel size of only $0.4 \text{ mm} \times 0.4 \text{ mm} \times 1.5 \text{ mm}$, corresponding to a voxel volume of 0.24 mm^3 , which is ~5 times smaller than the volume used in the aforementioned analyses [4, 5].

We demonstrate the reproducibility of the BMC analysis for the estimation of PgWF from HR mcDESPOT datasets, and compare that with the reproducibility of the SRC analysis. We then compare HR and low resolution (LR) PgWF maps obtained from BMC-mcDESPOT. Analyses were performed on two healthy young men, and one older man who had sustained a traumatic knee injury.

2. Material and METHODS

2.1. Data Acquisition

All experiments were performed on a 3T whole body Philips MRI system (Achieva, Best, The Netherlands) using the internal quadrature body coil for transmission and an eight-channel phased-array knee coil for reception. Data were collected from the knees of 22- and 23-year-old healthy males with no history of knee surgery or pain, and from the knee of an 86-year old-man who sustained a skiing injury 20 years prior to the present study, followed 7 years later by arthroscopic surgery. This latter subject reported chronic knee pain exacerbated by flexion. For each subject, LR and HR datasets were acquired in the sagittal plane. Two independent HR datasets were obtained from the knees of the young subjects to evaluate the reproducibility of the BMC and SCR analyses in PgWF determination.

The LR mcDESPOT imaging datasets consisted of 3D SPGR images acquired with FAs $\alpha_{SPGR} = [4\ 6\ 8\ 10\ 12\ 14\ 16\ 20]^\circ$, $TE_{SPGR} = 1.24$ ms and $TR_{SPGR} = 4.8$ ms, and 3D bSSFP images acquired with FAs $\beta_{bSSFP} = [2\ 7\ 11\ 16\ 24\ 32\ 40\ 60]^\circ$, $TE_{bSSFP} = 3.1$ ms and $TR_{bSSFP} = 6.3$ ms. The bSSFP images were acquired with two different radio-frequency (RF) pulse phase increments, of 0 or π . All images were obtained with field of view (FoV) = $160 \times 140 \times 120$ mm³, matrix size = $256 \times 224 \times 40$, and SENSE factor = 2. The total acquisition time for a full dataset was ~11 min.

The HR mcDESPOT imaging datasets consisted of 3D SPGR images acquired with FAs $\alpha_{SPGR} = [4\ 6\ 8\ 10\ 12\ 14\ 16\ 20]^\circ$, $TE_{SPGR} = 1.7$ ms and $TR_{SPGR} = 5.2$ ms, and 3D bSSFP images acquired with FAs $\beta_{bSSFP} = [2\ 7\ 11\ 16\ 24\ 32\ 40\ 60]^\circ$, $TE_{bSSFP} = 3.9$ ms and $TR_{bSSFP} = 7.7$ ms. The bSSFP images were again acquired with two different RF phase-pulse increment of 0 or π . All images were obtained with FoV = $160 \times 140 \times 90$ mm³, matrix size = $400 \times 350 \times 60$, and SENSE factor = 2. The total acquisition time for a full dataset was ~28 min.

The nature of the experimental procedures was fully explained to the subjects, from whom written informed consent was obtained prior to participation. All examinations were performed in compliance with the standards established by our local Institutional Review Board.

2.2. Data Analysis

Images from each of the mcDESPOT datasets were analyzed on a voxel-wise basis. To account for the off-resonance effects seen with the bSSFP images, off-resonance maps were generated according to the DESPOT₂-FM method [16], and combined with the SPGR and bSSFP datasets to generate PgWF maps [4, 5, 12, 15]. Analysis was performed explicitly accounting for nonzero TE, as incorporated into the TE-corrected-mcDESPOT (TEC-

mcDESPOT) signal model [11, 17], using an underlying two-component non-exchanging model [11, 12]. Manual segmentation was performed to delineate the cartilage regions over which PgWF maps were generated. Of note, careful visual inspection indicated that registration of images obtained at different FA values was not required. Indeed, such registration is problematic in bSSFP imaging due to the presence of off-resonance bands. All numerical calculations were performed with MATLAB (MathWorks, Natick, MA, USA).

2.2.1. Reproducibility of BMC and SRC Analyses—The reproducibility of the BMC- and SRC-mcDESPOT analyses for HR mapping of PgWF was assessed by analyzing, for both of the two healthy young subjects, two independent datasets acquired in immediate succession. Wide limits for the initial parameter bounds were used to avoid an over-constrained parameter space [12, 15]. These limits were $0 \leq f_s \leq 0.5$, $1 \text{ ms} \leq T_{2,s} \leq 50 \text{ ms}$, $30 \text{ ms} \leq T_{2,l} \leq 200 \text{ ms}$, $100 \text{ ms} \leq T_{l,s} \leq 2000 \text{ ms}$ and $100 \text{ ms} \leq T_{l,l} \leq 3000 \text{ ms}$. For each of these datasets, representative PgWF maps were compared, and the mean and standard deviation (SD) of PgWF values were calculated over all cartilage regions of several slices.

2.2.2. High- vs. Low-resolution PgWF Mapping—HR and LR PgWF maps derived using BMC-mcDESPOT were compared for each of the three subjects, with the mean and SD of PgWF values calculated in five different regions of interest (ROIs). The first ROI lay within the trochlea, the second ROI lay within the central medial femoral condyle (CMFC), the third ROI lay within the posterior medial femoral condyle (PMFC), the fourth ROI lay within the medial tibial plateau (MTP), and the fifth ROI enclosed all cartilage regions. ROI segmentation was performed manually, following a procedure outlined previously [4]. The purpose of the ROI analysis was to evaluate differences between HR and LR mapping in regions that may differ in Pg or collagen content and magic angle effect.

3. RESULTS

Figure 1 shows examples of HR PgWF maps from the knee cartilage of the two young healthy subjects derived using BMC- (Fig. 1a) or SRC- (Fig. 1b) mcDESPOT. For each subject, results from two HR datasets acquired in immediate succession with the same experimental parameters are shown. Visual inspection of the BMC-mcDESPOT images shows that the details of the voxel-by-voxel variation in PgWF is remarkably consistent between the two datasets, indicating the relative lack of sensitivity of the BMC analysis to experimental noise (Fig. 1a). More quantitatively, the mean and SD of the estimates of PgWF were essentially identical between the two datasets (first line of Table 1). Results for SRC are shown in Figure 1b and the second line of Table 1. Clearly, the variation of voxel intensities is much greater than in the BMC-mcDESPOT analysis, as is also reflected in the greater difference in values between the two SRC-mcDESPOT acquisitions. In addition, unlike BMC, SRC results exhibit derived PgWF estimates clustered preferentially towards the upper search space limit, in spite of the use of wide search space limits. In addition, in regions that did not display such clustering, there is substantial variation between the two independent acquisitions. Consistent with this, the mean and SD values of the estimates of PgWF (second line of Table 1) were substantially higher than those calculated using BMC. Overall, these results strongly indicate the much greater accuracy and stability to noise of

BMC as compared to SRC for PgWF determination from mcDESPOT imaging data. Stability with respect to noise is a central issue in higher-dimensional parameter estimation.

Figure 2 shows examples of PgWF maps derived from LR or HR *in-vivo* articular cartilage mcDESPOT images using the BMC analysis. The HR images were acquired with a voxel volume of 0.24 mm^3 , which is ~ 5 times smaller than the voxel volume of the LR images. Moving to HR increases the resolution through the depth of the cartilage from ~ 4 to ~ 7 voxels. Representative PgWF maps are displayed for each of the three participants. Visual inspection of PgWF maps and corresponding quantitative analyses (Table 2) show that for each participant, LR and HR parameter maps were similar in most, but not all, cartilage regions. The red arrows show regions with low PgWF values derived from the LR images. Corresponding zoomed regions from the LR SPGR images show that overall signal intensity in these regions was also very low, indicating magnetic susceptibility effects. In fact, this artifact was not visible on the HR SPGR images due to the relatively low magnetic field variation within a voxel. In addition, the yellow arrows indicate regions with derived PgWF that differed between the LR and HR maps, especially in the interface between the bone and cartilage, attributable to partial volume effects. Further, the mean and SD of the estimates of PgWF were calculated in five different ROIs from each LR and HR dataset of each subject (Table 2). The mean and SD of PgWF derived from LR and HR datasets were similar in several cartilage regions. However, SD values of PgWF derived from LR datasets were, overall, higher as compared to those derived from HR despite the higher SNR in LR datasets. We attribute this to the fact that partial volume and susceptibility artifacts, clearly seen in PgWF maps derived from LR datasets, led to local over- or under-estimates of PgWF values and therefore to higher dispersion. Table 2 also shows regional variation in derived PgWF estimates, with higher mean values seen in the MTP and lower mean values seen in the trochlea, for both healthy young subjects. Finally, mean PgWF values from the knee of the older subject were, overall, lower compared to the healthy young subjects in all cartilage regions (Fig. 2 and Table 2).

4. DISCUSSION

Multicomponent T_2 studies of cartilage have opened a new avenue for noninvasive macromolecular analysis of cartilage with clear applications in the investigation of the progression of osteoarthritis and potential therapies [1–7]. In this study, we have demonstrated the feasibility of *in-vivo* HR mapping of PgWF in human knee cartilage. Our work is based on the use of the BMC-mcDESPOT protocol previously described for HR mapping of MWF in the brain, in which data collected according to the mcDESPOT protocol is analyzed using Bayesian methods and a corrected signal model [14, 17]. We note that while the basic methodology for BMC-mcDESPOT has been presented previously [12, 14], there are significant challenges involved in applying this approach to cartilage, with its much shorter T_2 values, higher noise due to HR imaging and strong susceptibility effects as compared to brain. Our work builds on previously published use of mcDESPOT for PgWF determination in human cartilage at substantially lower spatial resolution [4, 5]. Indeed, it is the greater stability with respect to noise of the BMC approach as compared to SRC that permits the implementation of a HR protocol. A set of full simulations indicating the improved performance of BMC- as compared to SRC-mcDESPOT was presented in Refs.

[11, 12, 14] for a wide range of tissue parameters and SNRs, including input values encompassing typical and plausible parameters for cartilage analysis. Thus, while precision may be evaluated from the reproducibility of our human cartilage results, accuracy can be determined by the results of these simulation analyses performed with known input parameters.

Our results indicate the advantages of using HR as compared to LR mapping. As expected, HR mapping allows greater depiction of details of the variation of PgWF distribution (Figs. 1–2). This permits improved assessment of incipient cartilage degradation. Furthermore, HR imaging results in a substantial reduction of the partial volume effects seen in several cartilage regions (Fig. 2). Indeed, the substantially greater derived PgWF values from LR datasets as compared to HR datasets at bone-cartilage interfaces is likely due to corruption of cartilage signal by bone. Further, additional focal regions of low apparent PgWF seen in the LR PgWF maps are absent in the HR maps; we attribute these to susceptibility artifacts for several reasons. First, they correspond to very low intensity regions in the LR SPGR images (Fig. 2). In addition, this signal abnormality is not visible in either the HR or LR bSSFP images, in which T_2^* refocusing occurs at the time of signal acquisition [18]. Finally, these features are not present in the HR SPGR images, in which there is relatively low magnetic field variation within a voxel. Therefore, the use of small voxel volume, that is, HR imaging, avoids the introduction of potentially substantial bias in estimated values of PgWF. Finally, the BMC-mcDESPOT analysis demonstrated much greater reproducibility in the estimation of PgWF from HR imaging datasets as compared to SRC-mcDESPOT (Fig. 1). This clearly indicates the high degree of stability of BMC-mcDESPOT to noise.

Our results showed, overall, similar mean PgWF values in all analyzed cartilage regions between the two healthy young subjects (Tables 1–2), while lower mean PgWF values were calculated from both the LR and HR imaging datasets from the older subject (Table 2). While these values for PgWF are entirely consistent with previous studies [1–5, 22–23], with this small number of subjects, no statistical conclusions can be drawn regarding age or disease status. However, the goal of these analyses is to indicate the reproducibility and utility of the BMC-mcDESPOT analysis of cartilage in human subjects, and to establish consistency with previous findings.

In this study, we compared the performance of the BMC analysis with that of the SRC, conventionally used for parameter estimation with mcDESPOT [4, 5, 15]. We found substantially improved performance in the estimation of PgWF using BMC (Figs. 1–2, Tables 1–2), in full agreement with previous numerical and *in-vivo* results for MWF mapping in human brain [12]. These were attributed to several factors, including the implicit incorporation of noise SD into the model and the marginalization over nuisance parameters in BMC analysis [12]. We also found that derived PgWF values were in good agreement with those reported in the literature using the mcDESPOT signal model and SRC analysis [4, 5]. However, in the present work, we based our analysis on SPGR and bSSFP signal models that account for nonzero TE, that is, the TEC-mcDESPOT signal model [17]. It has been shown that the neglect of the transverse signal decay that occurs during TE may introduce large biases in parameter estimates from mcDESPOT [17]. Finally, we did not incorporate exchange into the mcDESPOT signal model for several reasons. First, even the

most basic form of mcDESPOT requires a fit of five unknown parameters using SRC or, with Bayesian analysis, marginalization over four nuisance parameters [12, 14]. Further, we have found through simulation analysis (data not shown) that the inclusion of exchange as an additional unknown parameter requires further constraints on the initial parameter bounds of the SRC algorithm for reliable parameter estimates, even at infinite SNR. This is likely due to the increased complexity of the local minimum structure in the nonlinear least squares parameter fits and the further flattening of the parameter energy surfaces [11–14, 19]. A related issue is that there is limited literature on expected values for exchange parameters, while the results are highly dependent upon initial estimates. However, the formalism for the extension of the BMC-mcDESPOT analysis to incorporate exchange is straightforward.

Further advances will permit even more reliable PgWF determination using mcDESPOT. In particular, analyses of factors that result in signal deviation from the ideal SPGR and bSSFP models are needed. These factors include diffusion [20, 21], magnetization transfer [22], signal modeling [23], magnetization spoiling [24, 25], magic angle effects [26], internal gradients [27, 28] and noise distribution [29, 30]. Nevertheless, the present work stands to indicate the feasibility of high quality *in-vivo* HR mapping of PgWF in articular cartilage of the human knee joint in an acceptable clinical acquisition time through use of BMC-mcDESPOT.

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Figure 1a.

Cartilage PgWF maps derived from in-vivo articular cartilage mcDESPOT datasets using the BMC analysis. For each of the two healthy young subjects, PgWF maps were derived from two HR datasets acquired in immediate succession and with the same experimental parameters. Visual inspection of the PgWF maps shows that, for each subject, derived parameter maps from the two HR datasets are very similar. This indicates the high reproducibility and stability of the BMC analysis to noise for HR PgWF determination.

Figure 1b.

Cartilage PgWF maps derived from in-vivo articular cartilage mcDESPOT datasets using the SRC analysis. For each of the two healthy young subjects, PgWF maps were derived from two HR datasets acquired in immediate succession and with the same experimental parameters. Visual inspection of the PgWF maps shows that, for each subject, derived parameter maps from the two HR datasets are different in detail to a much greater extent than in the BMC analysis (Fig. 1a). This indicates the instability of the SRC analysis to noise for HR PgWF determination.

Figure 2. Cartilage PgWF maps derived from low-resolution (LR) and high-resolution (HR) in-vivo articular cartilage mcDESPOT images using the BMC analysis. Representative maps are displayed for each of the three subjects. Red arrows indicate regions with prominent magnetic susceptibility artifacts, with zoomed inserts indicating the corresponding region within the SPGR image. Yellow arrows indicate regions with prominent partial volume effects.

Table 1

Means and standard deviation (SD) values of cartilage proteoglycan water fraction (PgWF) estimates calculated over all cartilage regions in several slices using the Bayesian Monte Carlo (BMC) or stochastic region contraction (SRC) analysis. Results are shown for the two healthy young subjects and for both of the high-resolution (HR) mcDESPOT datasets.

	Healthy young subject 1		Healthy young subject 2	
	HR dataset 1	HR dataset 2	HR dataset 1	HR dataset 2
BMC	0.280 ± 0.062	0.279 ± 0.058	0.278 ± 0.064	0.281 ± 0.062
SRC	0.357 ± 0.167	0.376 ± 0.158	0.344 ± 0.165	0.366 ± 0.151

Table 2

Mean and standard deviation (SD) values of cartilage proteoglycan water fraction (PgWF) values calculated in five different regions of interest (ROIs) from both low-resolution (LR) and high-resolution (HR) datasets for each of the three subjects using the Bayesian Monte Carlo (BMC) analysis. The first ROI lay within the trochlea, the second ROI lay within the central medial femoral condyle (CMFC), the third ROI lay within the posterior medial femoral condyle (PMFC), the fourth ROI lay within the medial tibial plateau (MTP), and the fifth ROI enclosed all cartilage regions.

	Healthy young subject 1		Healthy young subject 2		Injured old subject	
	HR dataset	LR dataset	HR dataset	LR dataset	HR dataset	LR dataset
Trochlea	0.256 ± 0.049	0.256 ± 0.076	0.264 ± 0.058	0.257 ± 0.063	0.252 ± 0.054	0.245 ± 0.044
CMFC	0.274 ± 0.053	0.269 ± 0.065	0.278 ± 0.049	0.272 ± 0.052	0.261 ± 0.054	0.248 ± 0.060
PMFC	0.285 ± 0.069	0.276 ± 0.057	0.272 ± 0.055	0.271 ± 0.061	0.247 ± 0.047	0.239 ± 0.032
MTP	0.297 ± 0.067	0.318 ± 0.087	0.291 ± 0.071	0.307 ± 0.073	0.224 ± 0.054	0.204 ± 0.068
All regions	0.280 ± 0.062	0.284 ± 0.079	0.278 ± 0.064	0.281 ± 0.067	0.233 ± 0.056	0.223 ± 0.061