

An order parameter without magic angle effect (OPTIMA) derived from $R_{1\rho}$ dispersion in ordered tissue

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Purpose: MR R_2 imaging of ordered tissue exhibits the magic angle effect, potentially masking subtle pathological changes in cartilage. This work aimed to develop an orientation-independent order parameter (S) exclusively sensitive to collagen degeneration.

Methods: A theory was developed based on $R_{1\rho}$ dispersion coupled with a simplified molecular motion model in which anisotropic $R_2^a(\theta)$ became directly proportional to correlation time $\tau_b(\theta)$ and S could be derived. This new parameter was validated with ex vivo $R_{1\rho}$ dispersion reported on orientated ($n = 4$), enzymatically depleted bovine cartilage ($n = 6$), and osteoarthritic human knee specimens ($n = 14$) at 9.4 Tesla, which was further demonstrated on 1 healthy human knee in vivo at 3 Tesla.

Results: $\tau_b(\theta)$ from orientation-dependent $R_{1\rho}$ dispersion revealed a significantly high average correlation ($r = 0.89 \pm 0.05$, $P < 0.05$) with $R_2^a(\theta)$ on cartilage samples and a moderate correlation ($r = 0.48$, $P < 0.001$) for the human knee in vivo. The derived S (10^{-3}) significantly decreased in advanced osteoarthritis (1.64 ± 0.03 vs. 2.30 ± 0.11 , $P < 0.001$) and collagen-depleted samples (1.30 ± 0.11 vs. 2.12 ± 0.12 , $P < 0.001$) when compared with early osteoarthritis and the control, respectively.

Conclusion: The proposed order parameter could be a potentially useful orientation-independent MR biomarker for collagen alterations in cartilage and other highly structured tissues.

KEYWORDS

anisotropic R_2 , collagen, correlation time, magic angle effect, order parameter, $R_{1\rho}$ dispersion

1 | INTRODUCTION

The properties of water in nature are not uniform, which is particularly true in living systems.¹ Many highly structured tissues, such as peripheral nerves, white matter, skeletal and myocardial muscles, and tendons and articular cartilage, can be found in the human body.^{2,3} MR imaging, particularly that characterizing water proton transverse R_2 relaxation and longitudinal $R_{1\rho}$ relaxation in a rotating frame of these specialized tissues, often exhibits an orientation-dependent phenomenon

referred to as the magic angle (MA) effect, which could be completely eliminated in a particular $R_{1\rho}$ measurement if the spin-lock (SL) RF power is strong enough.⁴⁻⁷

The MA effect in cartilage stems exclusively from anisotropic R_2 (i.e., $R_2^a(\theta)$) relaxation that is induced by the restricting reorientation of some water molecules bound to collagen⁸⁻¹¹; thus, a knowledge of $R_2^a(\theta)$ could be indicative of collagen degenerative alterations. As pointed out,⁷ $R_2^a(\theta)$ could be isolated from a $R_{1\rho}$ dispersion map, which will be computed from images obtained as a function of SL RF

power at a constant time of SL (TSL). By contrast, a typical $R_{1\rho}$ relaxation rate map is derived from images measured as a function of TSL at a constant SL power.¹²

The recently proposed composite relaxation metric ($R_2-R_{1\rho}$) for evaluation of cartilage degeneration can be regarded as a simple 2-point $R_{1\rho}$ dispersion.¹³ Similarly, an efficient alternative to $R_2-R_{1\rho}$, anisotropic R_2 of collagen degeneration (ARCADE) mapping,¹⁴ could be viewed as a 1-point $R_{1\rho}$ dispersion. Although it could be measured efficiently,¹⁴ $R_2^a(\theta)$ is still only useful for longitudinal studies in which the MA effect could be automatically accounted for if cartilage is considered at the same location and the same imaging protocol is followed. In a recent study,¹⁵ the pressing need for the MA effect removal was well demonstrated; the changes in $R_2^a(\theta)$ triggered by cartilage degeneration were several times smaller than those by the MA effect. Because of this confounding effect, an editorial was also published; it called for a multidisciplinary effort to eliminate this MA effect for the better evaluation of cartilage degeneration.¹⁶

In the past decade, several techniques have been proposed in which either anisotropic R_2 relaxation was completely suppressed by increasing a TE or R_1 relaxation was utilized that had no specific information on collagen integrity.^{2,6,17} Currently, it is still an unmet need for developing a novel method to separate the MA effect and yet maintain the intrinsic sensitivity of anisotropic R_2 to collagen alterations. Therefore, the aim of this work was to develop a theoretical framework in which an Order Parameter wITHout (reverse IT) MA effect (OPTIMA) could be derived from $R_{1\rho}$ dispersion of motion-restricted water in collagen. The proposed order parameter was validated on publicly available ex vivo $R_{1\rho}$ dispersion measured at 9.4 Tesla (T) and then demonstrated on 1 human knee in vivo at 3T.

2 | THEORY

The intramolecular dipolar relaxation rates R_2^{DD} and $R_{1\rho}^{DD}$ of proton pairs in liquid water undergoing isotropic tumbling are usually given by Equations 1 and 2,^{18,19} where d , τ_c , ω_0 , and ω_1 denote, respectively, a constant of $1.028 * 10^5$ (s^{-1}) for an internuclear distance of 1.59 (Å), a molecular rotational correlation time, an angular Larmor frequency, and a SL RF strength.

$$R_2^{DD} = d^2 \left\{ \frac{3\tau_c}{2} + \frac{2.5\tau_c}{1 + \omega_0^2\tau_c^2} + \frac{\tau_c}{1 + 4\omega_0^2\tau_c^2} \right\} \quad (1)$$

$$R_{1\rho}^{DD} = d^2 \left\{ \frac{1.5\tau_c}{1 + 4\omega_1^2\tau_c^2} + \frac{2.5\tau_c}{1 + \omega_0^2\tau_c^2} + \frac{\tau_c}{1 + 4\omega_0^2\tau_c^2} \right\}. \quad (2)$$

In biological tissues, water molecules are typically interfacing with many types of macromolecules such that their otherwise unhampered molecular reorientations are markedly hindered and/or slowed down.²⁰

For MR relaxation studies on these biological tissues,²¹ it is convenient to categorize water molecular motions into 3 distinct timescales: picosecond (ps), nanosecond (ns), and micro- to millisecond (μs - ms). The commonly accessible static magnetic fields (B_0) for ex vivo and clinical studies are 9.4T or 7.0T and 3.0T; correspondingly, $\omega_1/2\pi$ is usually limited to 2 and 0.5 kHz to prevent any potential RF heating hazards.¹² As a result, $R_{1\rho}^{DD}$ will become R_2^{DD} when τ_c is on the ps (i.e., $\omega_0^2\tau_c^2 \ll 1$) or ns (i.e., $\omega_1^2\tau_c^2 \ll 1$) timescale.²¹ On the other hand, $R_{1\rho}^{DD}$ approximates to $R_2^{DD} / (1 + 4\omega_1^2\tau_c^2)$ when τ_c is on the μs - ms (i.e., $\omega_0^2\tau_c^2 \gg 1$) timescale because the first terms in Equations 1 and 2 are the dominant relaxation contributors.¹⁴

In addition to the aforementioned dominant intramolecular dipolar relaxation mechanism, an intermolecular dipolar interaction or a translational diffusion process could also contribute a constant amount ($\sim 30\%$) of the total R_2 or $R_{1\rho}$ on the ps and ns timescales, as previously reported.^{7,21} Moreover, R_2 and $R_{1\rho}$ relaxation can be further enhanced by a different relaxation mechanism named as the *chemical exchange* (CHEX) effect,^{22,23} often taking place on the μs - ms timescale. An increase in R_2 due to this mechanism is usually quantified as $R_2^{ex} = p_{A/B} \Delta\omega^2 (2\tau_{ex})$,²⁴ where $p_{A/B}$, $\Delta\omega$, and τ_{ex}^{-1} denote, respectively, molecular fractions, angular chemical shift difference, and exchange rate between 2 biological water states (A and B). Note that τ_{ex}^{-1} is redefined here as an average, instead of a sum, of the rate constants of the forward (k_{AB}) and reverse (k_{BA}) reactions. As predicted,²⁴ the CHEX effect on $R_{1\rho}$ would be quenched to $R_2^{ex} / (1 + 4\omega_1^2\tau_{ex}^2)$, depending directly on ω_1 . It is worthwhile to mention that R_2^{ex} can comprise some contributions from water diffusion in the susceptibility-induced field inhomogeneities that only might be relevant at higher B_0 .²⁵

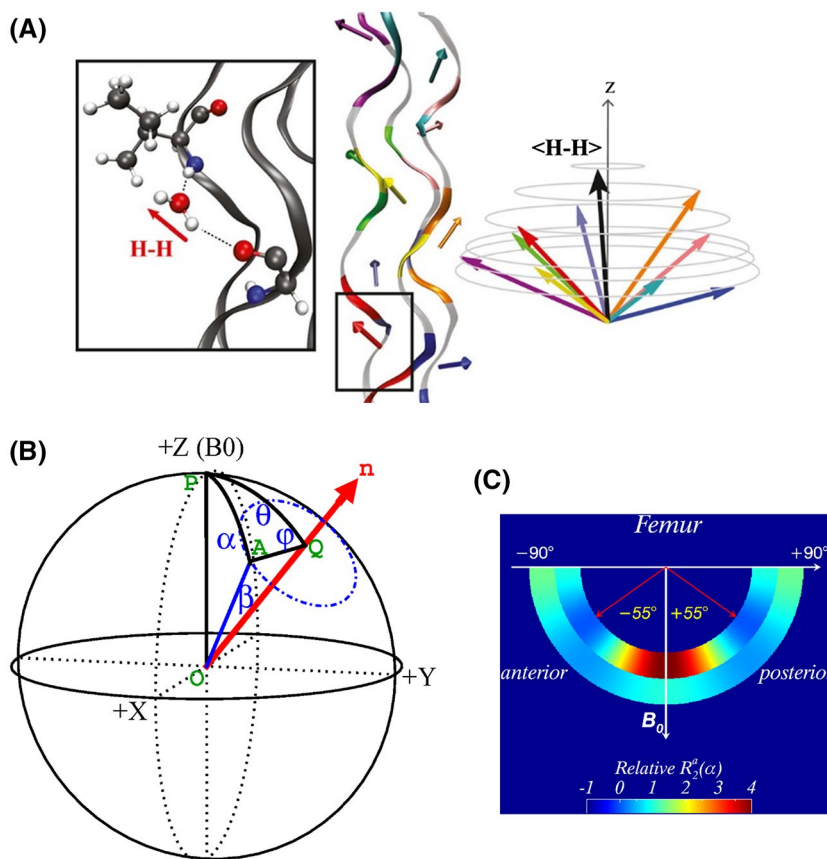
For the highly ordered tissues such as articular cartilage, the observed R_2 and $R_{1\rho}$ might be summarized using Equations 3 and 4,^{14,21,26}

$$R_2 = R_2^i + R_2^{ex} + R_2^a(\theta) \quad (3)$$

$$R_{1\rho} = R_2^i + \frac{R_2^{ex}}{1 + 4\omega_1^2\tau_{ex}^2} + \frac{R_2^a(\theta)}{1 + 4\omega_1^2\tau_b^2}, \quad (4)$$

where R_2^i , R_2^{ex} , and $R_2^a(\theta)$, respectively, stand for a *nonspecific isotropic* relaxation component including both inter- and intramolecular dipolar interactions (e.g., molecular rotational and translational diffusions) on the ps and ns timescales²⁶; a *specific isotropic* relaxation contribution by

FIGURE 1 An illustrative intramolecular dipolar interaction vector H-H (red) in bridged water and an ensemble-averaged (black) vector $\langle\text{H-H}\rangle$ along a triple-helix model peptide (A) as simulated by a molecular dynamics study (Reprinted with permission from Reference 11. Copyright © 2016, American Chemical Society). The average $\langle\text{H-H}\rangle$ vector (\overline{OA}), with an angle of α to B_0 (+Z) as shown in Figure 1B, rotates at an angle of β around an axially symmetric axis in collagen fibers (\vec{n}), which in turn forms an angle of θ to B_0 (+Z). The time-dependent angles are α and φ . The orientation-dependence of the normalized anisotropic $R_2^a(\theta)$ were simulated in Figure 1C for the superficial and deep halves of model femoral cartilage



the CHEX between hydroxyl ($-\text{OH}$) protons in bulk water and in proteoglycans (mostly glycosaminoglycan [GAG]),²² and a *specific anisotropic* relaxation enhanced by some motion-restricted water undergoing slow ($\tau_b \sim \mu\text{s-ms}$) molecular reorientations within a triple-helix microstructure in collagen.^{9,14,27} Apparently, $R_{1\rho}$ will turn respectively into R_2 or R_2^i when ω_1 is absent or sufficiently strong (i.e., $\omega_1 \gg \tau_b^{-1}$ and τ_{ex}^{-1}).

According to the previous findings,^{14,27} R_2^{ex} in general hardly contributes more than a few percent of R_2 or $R_{1\rho}$ at 3.0T, which could be attributed primarily to a small chemical shift difference (i.e., $\Delta\omega \approx 1$ ppm) and a slow CHEX rate (i.e., $\tau_{ex}^{-1} \approx 1$ kHz). Although it is largely insignificant at 3T, R_2^{ex} might need to be reconsidered when $R_2^a(\theta)$ is close to 0 at the particular cartilage locations, such as in the transitional zone or near the MA orientations.¹⁴ Moreover, R_2^{ex} exhibits a quadratic increase with B_0 and thus has the potential to play a significant role at higher B_0 .²⁷ When indeed becoming appreciable, R_2^{ex} could be isolated from the dipolar relaxation by performing either orientation-dependent $R_{1\rho}$ dispersion studies or B_0 -dependent R_2 comparisons.^{27,28}

$R_2^a(\theta)$ in cartilage originates from those preferentially orientated water in collagen,^{8,10} where a motion-restricted water molecule is “fixed” by 2 hydrogen bonds connecting with neighboring polypeptide chains in triple-helix interstices.^{10,11}

As a result, an effective $\langle\text{H-H}\rangle$ dipolar interaction vector, as depicted in Figure 1A, tends to align along the principal axis of collagen fibers as simulated by a recent molecular dynamics study on a hydrated collagen model peptide.¹¹ It is customary to quantify $R_2^a(\theta)$ as $R_2^a \langle 3 \cos^2 \theta - 1 \rangle^2 / 4$, where θ is an angle between the collagen fiber direction (\vec{n}) and B_0 (+Z) and R_2^a is the maximum of $R_2^a(\theta)$.⁹ In this static picture, an effective $\langle\text{H-H}\rangle$ vector is assumed parallel to \vec{n} , and the normalized $R_2^a(\theta)$ attains the maximum of 4 or the minimum of 0 when θ becomes 0° or the MA of $\pm 54.7^\circ$, as simulated in Figure 1C for collagen fibers in the deep half of cartilage.⁸ Note that an additional ensemble averaging is required to derive $R_2^a(\theta)$ for those collagen fibers in the superficial half of a femoral cartilage model, resulting in not only less but also different relaxation anisotropy.^{8,29}

It can be more revealing to depict an illustrative dipolar interaction vector \overline{OA} in a dynamic picture, assuming an axially symmetric reorientation model, as shown in Figure 1B. In this scenario, \overline{OA} (with an angle of α to B_0) rapidly rotates about a symmetric axis \vec{n} in collagen fibers at a fixed angle of β , where \vec{n} makes an angle of θ with respect to B_0 . Accordingly, a time or an ensemble average $R_2^a(\alpha)$ in Equation 5 could be mathematically transformed into $R_2^a(\theta)$ in Equation 6 by invoking an equality of $\langle 3 \cos^2 \alpha - 1 \rangle = \langle 3 \cos^2 \beta - 1 \rangle \langle 3 \cos^2 \theta - 1 \rangle / 2$.³⁰⁻³² During this mathematic

transformation, the spherical law of cosines (i.e., $\cos\alpha = \cos\beta \cos\theta + \sin\beta \sin\theta \cos\varphi$) was employed and both $\langle\cos\varphi\rangle$ and $\langle\cos 2\varphi\rangle$ became 0.³⁰ Note that a time or ensemble average is indicated by angle brackets, and τ_{\perp} in Equations 5 and 6 is an effective correlation time for molecular motion around an axis perpendicular to \vec{n} . Consequently, $R_2^a(\theta)$ could be characterized by 2 terms grouped in 2 pairs of curly brackets in Equation 6, with the first signifying a residual dipolar interaction constant and the second an orientation-dependent correlation time.

$$R_2^a(\alpha) = \frac{3}{2} \left\{ d \frac{3\langle\cos^2\alpha - 1\rangle}{2} \right\}^2 \tau_{\perp} \quad (5)$$

$$R_2^a(\theta) = \left\{ \frac{3}{2} \left(d \frac{3\langle\cos^2\beta - 1\rangle}{2} \right)^2 \right\} \left\{ \left(\frac{1 - 3\cos^2\theta}{2} \right)^2 \tau_{\perp} \right\}. \quad (6)$$

A scaling factor S within the first term in Equation 6, defined as $\langle 3\cos^2\beta - 1 \rangle / 2$, was called an *order parameter* in the literature,³³ which is an intrinsic measure of water molecular reorientation restriction or anisotropy.³⁴ The second term in Equation 6 is directly related to the well-known MA effect in which τ_b , an alternative to $(1 - 3\cos^2\theta)^2 \tau_{\perp} / 4$, becomes orientation-dependent, which is a characteristic of anisotropic molecular motion.³⁵ It was argued that τ_b could have been associated with different processes of breaking and reforming the new hydrogen bonds mediated by the bridged water in collagen triple-helix interstices.³² On the other hand, τ_b could be considered as characterizing a much slower (i.e., $\tau_{\perp} \gg \tau_{\parallel}$) molecular reorientation about an axis perpendicular to \vec{n} .¹⁴ For this special case, only 1 correlation time is adequate to characterize the very anisotropic molecular motion; otherwise, at least 2 terms are required.³⁶

Given that $R_2^a(\theta)$ and $\tau_b(\theta)$ could be derived from $R_{1\rho}$ dispersion profile, an order parameter S can be calculated with Equation 7, and the corresponding uncertainty in S can also be determined if the measurement errors in $R_2^a(\theta)$ and $\tau_b(\theta)$ are available. It is worth underlining that a rotational axis (\vec{n}) relative to B_0 could be manipulated arbitrarily by an experimenter in an orientation-dependent relaxation study; however, an intrinsic water bonding property in collagen, rooted in S , should be intact. In other words, $R_2^a(\theta)$ should be directly proportional to $\tau_b(\theta)$ in the orientation-dependent $R_{1\rho}$ dispersion measurements, regardless of collagen fiber orientations.

$$S = \sqrt{\frac{2 R_2^a(\theta)}{3d^2 \tau_b(\theta)}}. \quad (7)$$

3 | METHODS

3.1 | $R_{1\rho}$ dispersion acquisitions

3.1.1 | Orientated bovine cartilage specimens

Publicly available $R_2(\theta)$ relaxation and $R_{1\rho}(\theta, \omega_1)$ dispersion datasets were collected by Hänninen et al of the University of Eastern Finland⁶ on bovine patellar cartilage samples ($n = 4$) at 9.4T. These samples were identified as *BIS1*, *BIS2*, *BIS3*, and *B2S3* according to the experiment log files found in the public deposit site (<https://doi.org/10.5281/zenodo.519752>). Seven orientations ($\theta \approx n * 15^\circ$, $n = 0-6$) and 4 continuous wave (CW) $\omega_1/2\pi$ (0.25, 0.5, 1.0, 2.0 kHz) were employed for the measurements. The pertinent relaxation depth profiles were extracted, and the corresponding angle and depth profile maps were reprocessed using an included MatLab script (MathWorks, Natick, MA) with a linear interpolation replaced with a spline. Current data analyses were limited to the deep cartilage, defined as an average between 40% and 80% depth. These datasets were intended to validate the predicted correlation between $R_2^a(\theta)$ and $\tau_b(\theta)$.

3.1.2 | Osteoarthritic human knee specimens

These $R_{1\rho}$ dispersion profiles were measured at 9.4T by Rautiainen et al. of the University of Oulu in Finland.³⁷ The average dispersed $R_{1\rho}$ relaxation rates were listed in Table 3 of the original publication for the superficial (SZ) and radial zones on early ($n = 5$) and advanced ($n = 9$) osteoarthritic (OA) samples obtained from the tibial plateaus of patients undergoing total knee replacements. Four CW $\omega_1/2\pi$ values (0.125, 0.25, 0.5, 1 kHz) were used in $R_{1\rho}$ dispersion studies, and a spin-echo R_2 was treated as a specific $R_{1\rho}$ with $\omega_1/2\pi$ of 0. The normal to cartilage surface was set approximately parallel to B_0 ($\theta \cong 0^\circ$). These datasets were intended for a sensitivity test for S .

3.1.3 | Enzymatically degraded bovine cartilage

These $R_{1\rho}$ dispersion studies were conducted at 9.4T by Hanni et al of the University of Oulu in Finland³⁸ on 3 adjacent subsections in cartilage with and without enzymatic degradations: control, glycosaminoglycan-digested (GAG-), and collagen-depleted (CA-). Three subsections were taken from the same region in each of the intact bovine patellae ($n = 6$). Four CW $\omega_1/2\pi$ values (0.125, 0.25, 0.5, 1 kHz) were used in $R_{1\rho}$ dispersion measurements. Specimens were orientated with articular surfaces perpendicular to B_0 . These datasets were used for a specificity test for S .

3.1.4 | Healthy human knee in vivo

One human knee was studied with $R_{1\rho}$ dispersion in the sagittal plane using a 16-channel transmit/receive knee coil (with the maximum possible $B_1 \sim 27 \mu\text{T}$, equivalent to $\omega_1/2\pi \sim 1.15 \text{ kHz}$) on a 3T MR scanner. Twenty-five $T_{1\rho}$ -weighted 3D images were acquired using a SL-prepared T_1 -enhanced 3D transient field echo pulse sequence, with varying TSLs (1, 10, 20, 30, and 40 ms) and $\omega_1/2\pi$ (0.125, 0.25, 0.5, 0.75, and 1.0 kHz). The SL was self-compensated using the rotary echo scheme.³⁹ The specific absorption rate of $R_{1\rho}$ pulse sequence with the longest TSL and the highest ω_1 was about 45% less than the allowed maximum local extremities value (20 W/Kg) in the normal operating mode.

Each $T_{1\rho}$ -weighted 3D image dataset was collected in an interleaved segmented elliptical centric encoding scheme in k-space.⁴⁰ There were 52 shots in total, with each collecting 64 profiles, and a shot interval was 2000 ms. Each profile was collected with TR/TE of 8.5/4.3 ms and RF flip angle of 10° . An acquisition bandwidth was 382 Hz, and fat signal was suppressed with binomial 1-2-1 pulses.

The FOV was $130 \times 130 \times 96 \text{ mm}^3$ with an acquired voxel size of $0.4 \times 0.4 \times 3.0 \text{ mm}^3$. With a compressed SENSE⁴¹ reduction factor of 3, each dataset took 1.75 minutes, leading to the total scan duration of about 45 minutes. This in vivo study aimed at a feasibility test in a clinical setting.

3.2 | $R_{1\rho}$ dispersion modeling

3.2.1 | Orientated bovine cartilage specimens

S was derived after R_2^{ex} had been removed from $R_{1\rho}(\theta, \omega_1)$, as shown in a workflow chart in Figure 2C. Specifically, the

minimum of $R_2(\theta)$ expressed by $R_2^a(3 \cos^2(\theta + \delta) - 1)^2/4$ was first determined using Equation 3, identifying a measured MA θ_{MA} and a sum of R_2^i and R_2^{ex} . In this step, the orientation-dependence curve was allowed to float an angle δ within a limited range to account for any potential errors in positioning samples or an intrinsic deviation of deep collagen fibers from an assumed perpendicular orientation to articular surface.⁶

Then, a specific $R_{1\rho}(\theta_{MA}, \omega_1)$ dispersion was modeled using Equation 4, excluding $R_2^a(\theta)$, separating R_2^{ex} from R_2^i . Next, $R_{1\rho}(\theta, \omega_1)$ dispersion was fitted using Equation 4 without R_2^{ex} for each orientation θ except those near θ_{MA} ; accordingly, an individual $S(\theta)$ was computed with Equation 7 for each pair of the fitted $R_2^a(\theta)$ and $\tau_b(\theta)$. Last, an average S and its SD were calculated for each of 4 samples from those $S(\theta)$ derived from different sample orientations.

3.2.2 | OA human knee specimens

With a simplified $R_{1\rho}$ dispersion model, $R_2^a(\theta \cong 0)$ and $\tau_b(\theta \cong 0)$, with the uncertainties of ΔR_2^a and $\Delta \tau_b$, were determined using Equation 4 without R_2^{ex} . S was then calculated based on Equation 7, and the relative uncertainty in S (i.e., $\Delta S/S$) was estimated as $0.5 * \sqrt{(\Delta R_2^a/R_2^a)^2 + (\Delta \tau_b/\tau_b)^2}$.

3.2.3 | Enzymatically degraded bovine cartilage samples

The modeled $\tau_b(\theta \cong 0)$ and $R_2^a(\theta \cong 0)$, respectively, were listed and shown in Table 1 and Figure 1 for the superficial (5% depth) and full (100% depth) cartilage zones from the original publication.³⁸ The precise R_2^a values and their

FIGURE 2 Two representative orientation-dependent depth-profile maps of T_2 (A) relaxation times (ms) and $T_{1\rho}$ relaxation times (ms) with a spin-lock RF strength ($\omega_1/2\pi$) of 2 kHz (B) measured on the bovine cartilage sample B1S2 (Reproduced from the publicly available data in Ref. 6). A horizontal depth-profile starts from the articular surface (0%) to the bone interface (100%), and the deep zone was defined as reported between 40% and 80% in depth, highlighted with 2 vertical dashed lines (B). A workflow chart (C) is included to guide the perspective readers better following the data analysis

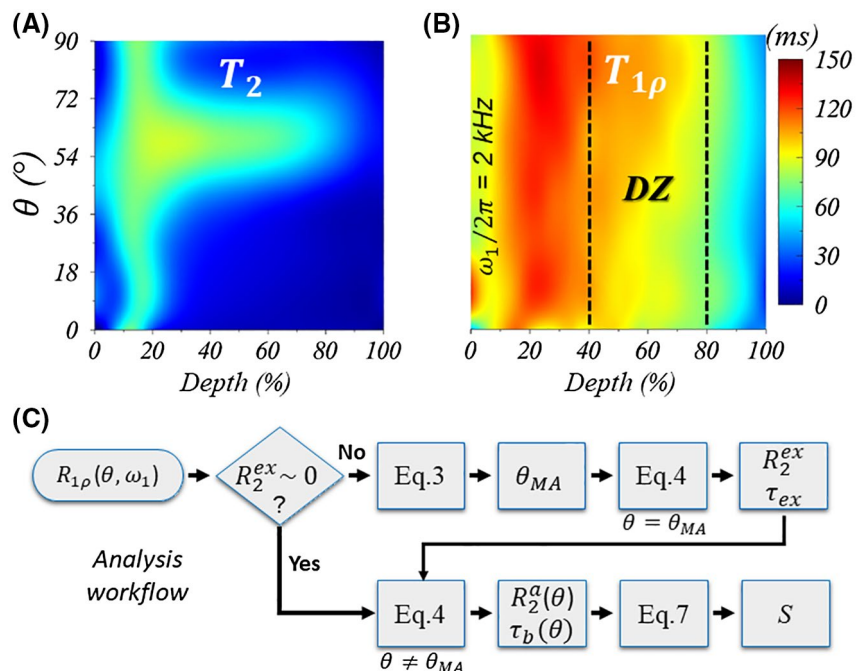


TABLE 1 $R_{1\rho}$ dispersion model parameters in the deep zone of 4 bovine patellar cartilage specimens at 9.4T

	R_2^a	R_2^i	θ_{MA}	R_2^{ex}	τ_{ex}	$\langle \tau_b(\theta) \rangle$	$\langle R_2^a(\theta) \rangle$	$S (10^{-3})$
B1S1	98.3 ± 1.7 (88%)	10.1 ± 0.3 (9%)	77.6 ± 0.3	3.8 ± 0.4 (3%)	192.4 ± 42.5	251.1 ± 65.7	67.6 ± 23.2	4.09 ± 0.28
B1S2	147.5 ± 2.4 (90%)	10.4 ± 0.2 (6%)	59.6 ± 0.3	5.6 ± 0.2 (3%)	161.7 ± 12.9	523.8 ± 27.3	83.5 ± 18.2	3.15 ± 0.28
B1S3	185.1 ± 2.0 (93%)	11.1 ± 1.2 (6%)	58.5 ± 0.1	3.4 ± 1.3 (2%)	115.4 ± 85.4	355.2 ± 28.3	146.0 ± 20.5	5.08 ± 0.24
B2S3	103.1 ± 0.6 (88%)	10.0 ± 0.5 (9%)	61.8 ± 0.1	3.7 ± 0.8 (3%)	293.4 ± 120.1	367.8 ± 18.5	65.7 ± 23.1	3.29 ± 0.57
AVE	133.5 ± 35.4 (90%)	10.4 ± 0.4 (7%)	64.4 ± 8.9	4.1 ± 0.9 (3%)	190.7 ± 65.3	374.5 ± 112.5	90.7 ± 37.7	3.90 ± 0.89

The absolute (1/s) and relative (%) rates are for the maximum anisotropic R_2^a , isotropic R_2^i , and chemical exchange contribution R_2^{ex} . Others include the measured MAs θ_{MA} (°), chemical exchange correlation times τ_{ex} (μ s), average residual dipolar interaction correlation times $\langle \tau_b(\theta) \rangle$ (μ s), average anisotropic $\langle R_2^a(\theta) \rangle$ (1/s) and average order parameters S . All data are reported as mean ± SD.

MA, magic angle; μ s, microsecond; T, Tesla.

uncertainties were kindly provided (email communication in March 2019 with Dr. Matti Hanni of the University of Oulu). Therefore, S and its uncertainty could be computed as aforementioned.

3.2.4 | Healthy human knee in vivo

$R_{1\rho}$ -weighted 3D images were first coregistered following an established protocol, and $R_{1\rho}$ pixel maps were then generated by fitting the aligned images to a 2-parameter exponential decay model using different ω_1 .¹⁴ Next, different cartilaginous tissues were angularly and radially segmented,⁴² and an ROI-based $R_{1\rho}$ dispersion profile in the deep zone was modeled with Equation 4 without R_2^{ex} . Last, an average S and its descriptive statistics were calculated for each cartilage compartment.

3.3 | Nonlinear least-squares curve fitting

The curve fittings for R_2 orientation-dependence and $R_{1\rho}$ dispersion in Equations 3 and 4 were carried out using a publicly available IDL (Harris Geospatial Solutions, Inc., Broomfield, CO) script that relies on the Levenberg-Marquardt technique (<http://purl.com/net/mpfit>).⁴³ Because the fits were unweighted, the output formal 1-sigma fitting errors had been scaled such that the obtained reduced chi-squared χ^2 values were close to unity. The searching ranges were constrained for the model parameters: $\delta = [-30^\circ, 30^\circ]$; $R_2^{ex} = [0, 30]$ (1/s); τ_{ex} and $\tau_b = [10^1, 10^4]$ (μ s); $R_2^i = [0, 30]$ (1/s); and $R_2^a = [0, 300]$ or $[0, 30]$ (1/s) for ex vivo or in vivo data, respectively. If the fitted parameters were equal to the boundary values or their relative uncertainties were larger than 300%, the fits were deemed to be failed and thus were excluded from further analysis.

3.4 | Statistical analysis

The differences and correlations between any 2 relaxation metrics were quantified using the Student t test (a 2-tailed distribution) and the Pearson correlation coefficient (r), with the statistical significance considered at $P < 0.05$.

Intergroup comparisons were visualized using box-and-whisker and bar plots, and the correlations were presented in scatterplots overlaid with 95% confidence level data ellipses for an enhanced visualization.⁴⁴ All measurements are shown as mean ± SD unless stated otherwise, and all image and data analysis were conducted with an in-house software developed in IDL 8.5.

4 | RESULTS

4.1 | Orientated bovine cartilage specimens

Two orientation-dependent relaxation depth-profile maps are reproduced in Figure 2 for T_2 (A) and $T_{1\rho}$ (B) with $\omega_1/2\pi$ of 2 kHz from the sample B1S2.⁶ The MA effect can be recognized in the deep cartilage when orientated near 60° relative to B_0 (A). However, this R_2 ($1/T_2$) anisotropy was largely quenched in $R_{1\rho}$ ($1/T_{1\rho}$) with a larger ω_1 (B), as previously reported.⁵

The logic of the following data analysis is provided in a workflow chart (Figure 2C). As shown in Figure 3A, 3 orientation-dependent $R_{1\rho}$ were modeled (solid lines) for the measured averages (dashed lines) with $\omega_1/2\pi$ (kHz) of 0 (red), 0.25 (green), and 2.0 (blue). An example of separating R_2^{ex} (Figure 3B) and an example of modeling $R_{1\rho}$ dispersion (Figure 3C) are also included.

An apparent MA θ_{MA} of $59.6 \pm 0.3^\circ$ was fitted with Equation 3 when R_2 ($\omega_1/2\pi = 0$) at the minimum (Figure 3A). $R_{1\rho}$ dispersion at θ_{MA} was then modeled using Equation 4 (Figure 3B), resulting in a dispersed R_2^{ex} of 5.6 ± 0.2 (1/s), a constant isotropic R_2^i of 10.4 ± 0.2 (1/s), and τ_{ex} of 161.7 ± 12.9 (μ s). After eliminating R_2^{ex} , a typical ($\theta = 20^\circ$) $R_{1\rho}$ dispersion was best characterized using Equation 4 with a dominant R_2^a of 86.3 ± 5.3 (1/s), a minor constant R_2^i of 11.3 ± 3.3 (1/s), and τ_b of 459.0 ± 28.7 (μ s) (Figure 3C).

Table 1 summarizes the partitioned R_2 absolute (1/s) and relative (%) relaxation rates, θ_{MA} , τ_{ex} (μ s), $\langle R_2^a(\theta) \rangle$ and $\langle \tau_b(\theta) \rangle$ denoting data ellipse centroids, as well as an average S for each of 4 samples. The largest and smallest average S values as seen in Figure 4B were related, respectively, to the

FIGURE 3 Three orientation-dependent $R_{1\rho}$ (1/s) relaxation profiles with $\omega_1/2\pi$ of 0 (red), 0.25 (green), and 2 kHz (blue) for the same sample B1S2 (A), with solid lines standing for best fits to $R_2^a (3 \cos^2 \theta - 1)^2 / 4$ for the averages measured in the deep cartilage indicated by the dashed lines in the middle of shaded areas (i.e., \pm SDs). Two specific $R_{1\rho}$ (1/s) dispersion profiles induced by chemical exchange effect ($\theta = 60^\circ$) and by residual dipolar interaction ($\theta = 20^\circ$) are respectively demonstrated in Figure 3B,C

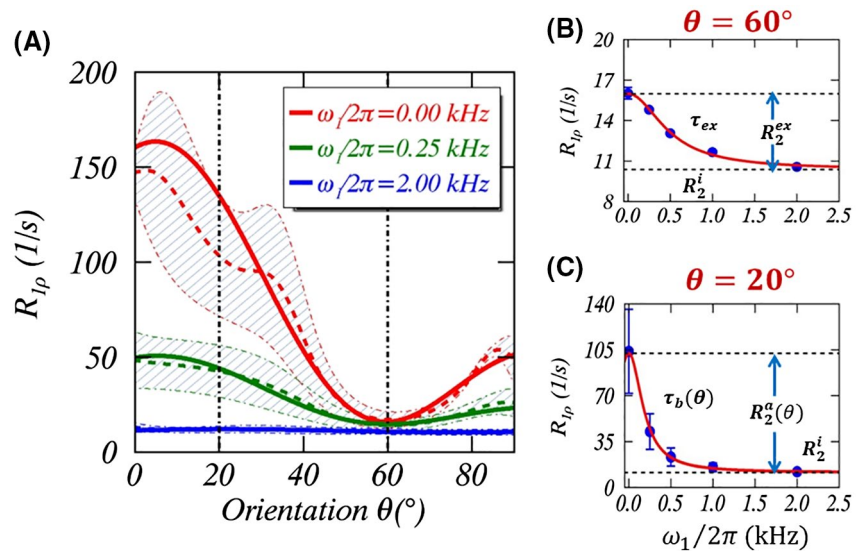
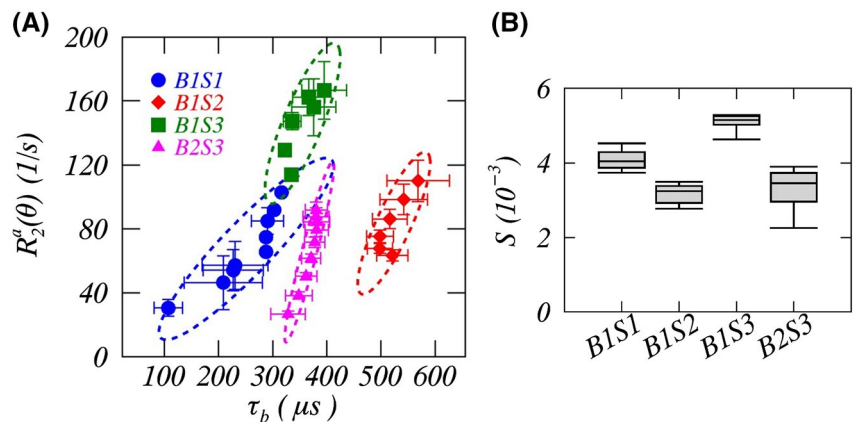


FIGURE 4 A scatterplot showing the positive correlations between $R_2^a(\theta)$ (1/s) and τ_b (μ s) from the orientation-dependent $R_{1\rho}$ dispersion measurements (A), and the box-and-whisker plot comparing the derived order parameter S (10^{-3}) among 4 bovine cartilage samples (B). μ s, microsecond



largest and smallest ratios of $\langle R_2^a(\theta) \rangle$ and $\langle \tau_b(\theta) \rangle$ for B1S3 and B1S2. As noted,⁶ θ_{MA} was not exactly equal to the theoretical value of 54.7° but differed on average by about 10° . Accordingly, an average S was determined only from those sample orientations in which $R_{1\rho}$ relaxation underwent substantial dispersion: $\theta < 50^\circ$ (B1S1 and B2S3) or 35° (B1S2 and B1S3).

An anisotropic R_2^a and an isotropic R_2^{ex} generally contributed the most ($\sim 90\%$) and the least ($\sim 3\%$) to the total R_2 , which was in good agreement with the literature.^{7,27} More importantly, $\tau_b(\theta)$ demonstrated on average a significantly high correlation ($r = 0.89 \pm 0.05$, $P < 0.05$) with $R_2^a(\theta)$ as demonstrated in Figure 4A, in accordance with the predicted from this work. An average S was then compared for each sample in Figure 4B, revealing a smaller intrasample variation compared to an intersample variation, that is, 9.5% versus 22.8%.

4.2 | OA human knee specimens

Figure 5A presents the observed (symbols) and the modeled (lines) contrasting $R_{1\rho}$ dispersion profiles³⁷ in the superficial

(SZ, solid lines) and radial (dashed lines) zones for early (blue) and advanced (red) OA specimens. The differences in $R_{1\rho}$ between 2 OA grades tend to decrease as ω_1 increases, indicating that the cartilage degenerative changes are best characterized by an anisotropic R_2^a rather than an isotropic R_2^i . It is worthwhile to mention that R_2^a in radial zones (empty symbols) was much larger than those in SZ (filled symbols), as previously documented.^{4,6}

Table 2 summarizes the $R_{1\rho}$ dispersion-modeling results (R_2^i , R_2^a , τ_b and S) for different cartilage compartments with 2 OA grades. As shown in Figure 5B, S (10^{-3}) from early OA was significantly larger than that from advanced OA, particularly in SZ (i.e., 1.89 ± 0.05 vs. 1.01 ± 0.04 , $P < 0.001$). This observation indicated that the integrity of collagen microstructure had been further compromised in advanced OA.

4.3 | Enzymatically degraded bovine cartilage samples

The $R_{1\rho}$ dispersion modeling results for the selectively modified cartilage samples are also tabulated in Table 2.

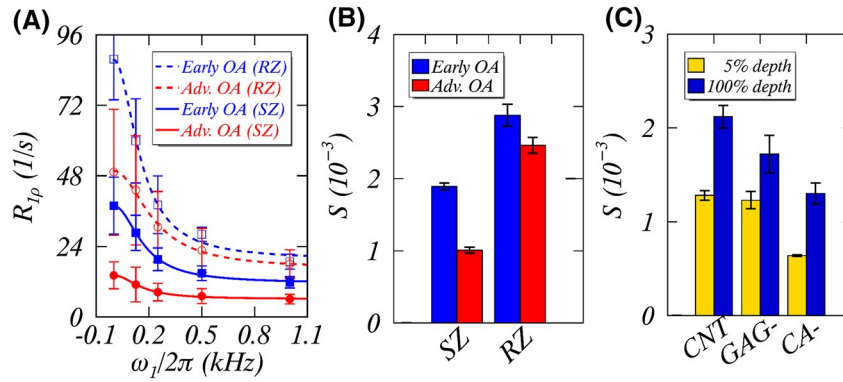


FIGURE 5 For early (blue) and advanced (red) OA in human knee specimens (A-B), the measured (symbols) and modeled (lines) $R_{1\rho}$ dispersion profiles at 9.4T are shown for the superficial (solid lines) and radial (dashed lines) cartilage zones (A). The derived order parameters S (10^{-3}) are compared in B. For enzymatically depleted bovine patellae samples (C), the derived S (10^{-3}) are compared among the CNT, GAG-, and CA- within 5% (yellow) and 100% (blue) cartilage zonal depth at 9.4T. CA-, collagen-depleted; CNT, control; GAG-, glycosaminoglycan-depleted; OA, osteoarthritis; RZ, radial zone; SZ, superficial zone; T, Tesla

The observed S alterations after enzymatic depletions in 2 cartilage zones are compared in Figure 5C. With regard to control, the water ordering/bonding capacity in SZ (5% depth, yellow) was more disrupted when comparing collagen-depleted to glycosaminoglycan-depleted samples.

Specifically, S exhibited no difference between glycosaminoglycan-depleted and control (1.23 ± 0.09 vs. 1.28 ± 0.05 , $P = 0.262$); however, it clearly revealed a significant difference between collagen-depleted and control (0.64 ± 0.01 vs. 1.28 ± 0.05 , $P < 0.001$). A similar trend was observed when $R_{1\rho}$ dispersion was measured on the whole cartilage (100% depth, blue). Note that the $R_{1\rho}$ dispersion model used in the original work³⁸ was the same as Equation 4 without R_2^{ex} .

4.4 | Healthy human knee in vivo

Figure 6B shows 3 ROI-based $R_{1\rho}$ dispersion profiles (colored lines) from the femoral (red), tibial (green), and patellar (blue) cartilage deep zones, highlighted by colored arrows on one $R_{1\rho}$ -weighted ($\omega_1/2\pi = 1$ kHz, TSL = 1 ms) image slice (Figure 6A). The maximum and minimum of R_2 , that is, $R_{1\rho}$ with $\omega_1/2\pi$ of 0, were respectively found in the tibial and femoral cartilage compartments, consistent with the theoretical prediction because the collagen fibers from these 2 ROIs were nearly parallel or at the MA to B_0 .^{8,9}

Noticeably, $R_{1\rho}$ dispersion modeling was only successful for the highlighted ROIs in the tibial or the patellar but not in the femoral compartment; specifically, the fitted R_2^i (1/s), R_2^a (1/s), and τ_b (μ s) values were 12.9 ± 0.3 , 11.0 ± 0.2 , and 148 ± 6.1 in the tibial and 6.7 ± 9.1 , 14.2 ± 8.0 , and 134.4 ± 132.7 in the patellar cartilage. The overall qualities of $R_{1\rho}$ dispersion data from this particular image slice could be appreciated in Figure 6C-E for all segmented ROIs in the femoral (6C), tibial (6D), and patellar (6E) locations, showing some

unexpected $R_{1\rho}$ dispersion profiles particularly when using a weak ω_1 .

The total numbers of the segmented ROIs in the femoral, tibial, and patellar cartilage from all image slices were 466, 55, and 50; however, only 52%, 61%, and 76% of those were successfully modeled. The descriptive statistics for $R_{1\rho}$ dispersion profiles (measured and modeled) and the derived S are summarized in Table 3. As ω_1 increased, the average $R_{1\rho}$ and its variation would decrease, indicating that $R_2^a(\theta)$ had been progressively quenched, as previously reported.^{5,6}

Compared with the derived R_2^a , R_2^i became more clustered indicated by a relatively smaller SD, for example, 11.7 ± 2.9 versus 11.3 ± 4.9 (1/s) in the femoral cartilage, and the same trend could also be found in Figure 5A. More importantly, $\tau_b(\theta)$ were positively correlated ($r = 0.48$, $P < 0.001$) with $R_2^a(\theta)$ for all cartilage compartments as demonstrated in Figure 7A. Subsequently, the derived S (10^{-3}) statistics from each cartilage location were compared in Figure 7B, showing no significant differences between the tibial (1.82 ± 0.64) and the femoral (1.74 ± 0.53 , $P = 0.49$) or the patellar (1.97 ± 0.33 , $P = 0.21$) cartilage. However, a significant ($P < 0.01$) difference was observed between the femoral and the patellar cartilage.

5 | DISCUSSION

5.1 | General comments

A theoretical framework has been formulated in this work to derive an orientation-independent MR metric in ordered tissue, which was verified and demonstrated for its sensitivity, specificity, and feasibility. The preliminary results show that the introduced order parameter could be a potentially useful MR biomarker for collagen alterations in cartilage and other

TABLE 2 $R_{1\rho}$ dispersion model parameters from different cartilage zones in OA human knee samples (early vs. advanced OA) and enzymatically depleted bovine cartilage specimens at 9.4T

	Human Knee Tibial Cartilage Samples				Bovine Patellar Cartilage Specimens					
	Early OA		Advanced OA		CNT		GAG-		CA-	
	SZ	RZ	SZ	RZ	SZ	FZ	SZ	FZ	SZ	FZ
$R_2^i(1/s)$	11.5 ± 0.5	19.5 ± 2.2	6.1 ± 0.2	16.4 ± 1.2	8.7 ± 0.2	12.9 ± 0.5	6.5 ± 0.2	10.4 ± 0.8	2.7 ± 0.1*	13.1 ± 0.8
$R_2^s(1/s)$	26.4 ± 0.7	68.0 ± 3.2	8.0 ± 0.3	33.2 ± 1.4	9.9 ± 0.6	22.1 ± 2.0	12.3 ± 1.1	17.7 ± 1.5	1.64 ± 0.1*	9.6 ± 0.7
$\tau_b(\mu s)$	467 ± 24	516 ± 46	495 ± 34	347 ± 29	383 ± 30	310 ± 31	516 ± 73	376 ± 83	251 ± 9	357 ± 56
$S(10^{-3})$	1.89 ± 0.05	2.88 ± 0.15	1.01 ± 0.04	2.46 ± 0.11	1.28 ± 0.05	2.12 ± 0.12	1.23 ± 0.09	1.72 ± 0.20	0.64 ± 0.01	1.30 ± 0.11

All data are reported as mean ± SD.

*SDs are less than 0.1 (1/s).

CA-, collagen-depleted; CNT, control; FZ, full cartilage zone; GAG-, glycosaminoglycan-depleted; μs , microsecond; OA, osteoarthritis; RZ, radial cartilage zone; SZ, superficial cartilage zone; T, Tesla.

TABLE 3 The measured and modeled average $R_{1\rho}$ dispersion parameters in the femoral, tibial, and patellar compartments from 1 healthy human knee in vivo at 3T

	$R_{1\rho}(1/s)$ with $\omega_1/2\pi$ (kHz)						Fitted Parameters		
	0.125	0.25	0.5	0.75	1.0	1.0	$R_2^i(1/s)$	$R_2^s(1/s)$	$\tau_b(\mu s)$
Femoral	19.2 ± 5.4	18.2 ± 4.1	15.2 ± 3.2	14.1 ± 2.7	13.9 ± 3.2	11.7 ± 2.9	11.3 ± 4.9	272.7 ± 146.3	1.74 ± 0.53
Tibial	19.4 ± 3.4	19.7 ± 2.5	17.5 ± 2.8	15.8 ± 2.0	15.0 ± 1.5	12.7 ± 1.7	8.7 ± 4.1	198.8 ± 152.8	1.82 ± 0.64
Patellar	16.7 ± 4.0	18.7 ± 3.7	12.4 ± 1.6	12.2 ± 1.9	11.4 ± 1.9	9.4 ± 2.1	10.8 ± 4.1	171.7 ± 49.1	1.97 ± 0.33

All data are reported as mean ± SD.

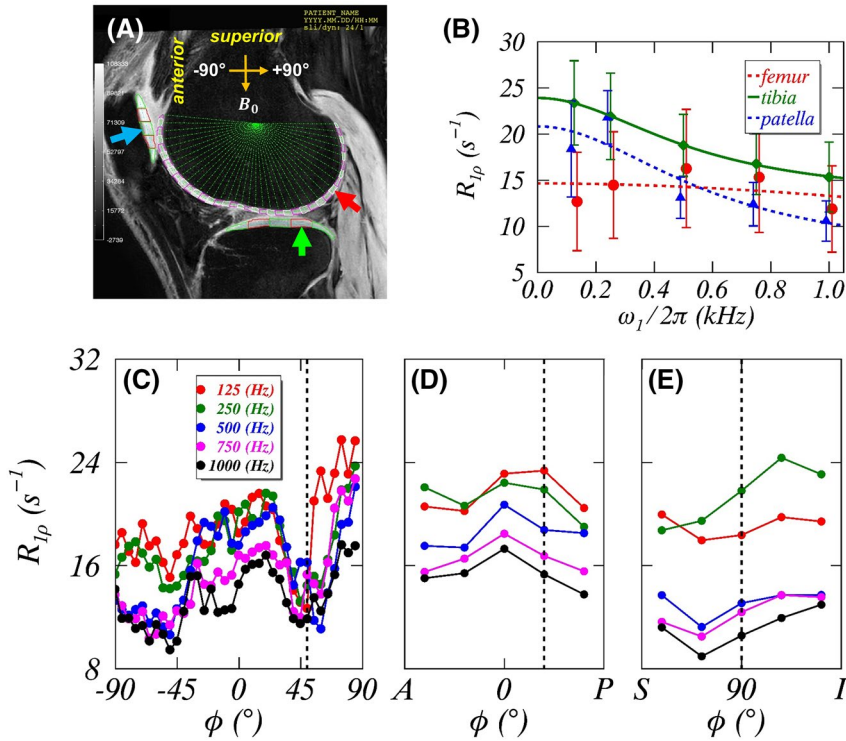


FIGURE 6 A representative $R_{1\rho}$ -weighted image slice ($\omega_1/2\pi = 1$ kHz, TSL = 1 ms) with angularly and radially segmented ROIs overlaid (A). Three ROIs are highlighted by colored arrows in the femoral (red), tibial (green), and patellar (blue) compartments; the corresponding $R_{1\rho}$ dispersion profile (filled symbols) and modeling (solid and dashed lines) are plotted (B). The orientation-dependent $R_{1\rho}$ dispersion profiles of all segmented ROIs are presented for the femoral (C), tibial (D), and patellar (E) cartilage. Note that the orientation angles for the tibial ($\theta = 0^\circ$) and patellar ($\theta = 90^\circ$) compartments are just for an annotation purpose, and the dashed-lines indicate the specific $R_{1\rho}$ dispersion profiles shown in B. ROI, region of interest; TSL, time of spin-lock

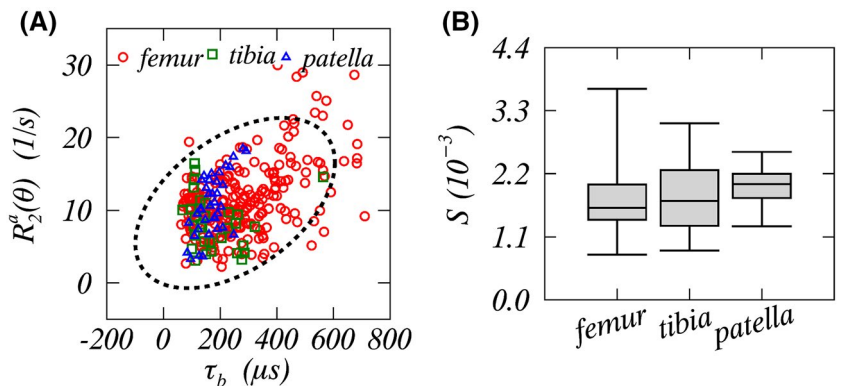


FIGURE 7 A scatterplot (A) of anisotropic $R_2^a(\theta)$ (1/s) and correlation time τ_b (μs), and a box-and-whisker diagram (B) of the order parameters S (10⁻³) derived from the femoral (red circles), tibial (green squares), and patellar (blue triangles) compartments in an asymptomatic adult knee at 3T

highly organized tissues. To the best of our knowledge, this is the first effort to separate the MA effect from MR relaxation without loss of intrinsic water ordering information in cartilage.

5.2 | An order parameter for restricted molecular reorientation

Water proton relaxation in biological tissues had been thoroughly studied in the past^{20,21}; however, an additional anisotropic dipolar relaxation contribution has to be included to better characterize R_2 in highly ordered tissues such as articular cartilage, and this particular contribution could be quenched as expressed in Equations 3 and 4.¹⁴

It is not straightforward to comprehend the biophysical relaxation mechanism for an anisotropic relaxation.⁷ As previously reported,^{7,27} $R_{1\rho}$ dispersion was predominantly induced

by the anisotropic dipolar interaction of water molecules associated with collagen, and the CHEX effect would only contribute appreciably at higher B_0 . The measured relaxation contributions to R_2 , as reported in Table 1, are in line with previous findings.²⁷

When deriving S , we have drawn an analogy between the MA spinning (MAS) in solid NMR and water preferential alignments in collagen.³⁰ As a result, the related theoretical backgrounds used for developing the MAS technique can be equally applied to the anisotropic molecular reorientations in collagen, resulting in the separated MA effect from a residual dipolar coupling constant.

5.3 | A theory validation on orientated cartilage

Because of diminishing $R_{1\rho}$ dispersion near MA orientations, an average S was only derived from limited sample

orientations, which could be partially responsible for the reported varying SD in S and the observed non-zero x-intercepts inferred from the data ellipse orientations. It is interesting to note that the sample B1S1 presented almost no x-intercept in Figure 4A, and it happened to have more data points for calculating S because of the unusual sample orientations with θ_{MA} close to 80° (see Table 1). On the other hand, the average S values were substantially different among 4 samples, possibly due to the varied internal (e.g., cartilage location, animal age) or external factors (e.g., hydration, temperature).

It was somewhat unexpected that the estimated R_2^{ex} hardly ($\sim 3\%$) contributed to R_2 in bovine cartilage at 9.4T given that $\sim 15\%$ to 20% R_2 increase was reported at 7T compared to 3T for human knee cartilage. Whereas the reported R_2^{ex} estimates were derived from R_2 measurements at 3T and 7T, our estimates were based on $R_{1\rho}$ dispersion at θ_{MA} that might be compromised by some systematic errors.

Had both the collagen fibers and B_0 been perpendicular to the cartilage surface, the minimum R_2 should have been detected around θ_{MA} of 54.7° . Yet, an average apparent θ_{MA} measured in this study was offset by about 10° ,⁶ implying that either B_0 and/or collagen fibers in the deep zone were not exactly perpendicular to the cartilage surface.

5.4 | Evaluating sensitivity and specificity ex vivo

The most sensitive relaxation parameter was reportedly that with the highest orientation anisotropy,⁶ which was clearly supported by the experimental data in Figure 5A when comparing an anisotropic R_2^a ($\omega_1 = 0$) with an isotropic R_2^i ($\omega_1 \rightarrow \infty$) for early and advanced OA samples. Recently, τ_b was proposed as a promising novel biomarker for the evaluation of cartilage degeneration.³⁸ The final outcome of these evaluations using either R_2^a or τ_b would have been different had the samples been orientated otherwise. In this regard, the proposed new metric could be advantageous and had been validated not only sensitive to the OA grades but also specific to collagen degradation.

5.5 | Measuring an order parameter in vivo

Due to the lengthy in vivo imaging protocol, it was likely that the observed $R_{1\rho}$ dispersion had been compromised by the motion or blurring artifacts.¹⁴ Furthermore, the quantitative accuracy of $R_{1\rho}$ dispersion could be further compounded by an inconsistent spin-locking and an imperfect imaging pulse sequence.⁴⁰ In this work, a smaller RF flip angle of 10° and a shorter TR of 8.3 ms, relative to R_1 of 1240 ms in cartilage at 3T,⁴⁵ were used to partially mitigate these potential systematic errors.

Not all segmented ROIs could be optimally modeled in this work. Had the stricter criterion been used to define a

successful fit, the overall successful rates would have been reduced, suggesting that $R_{1\rho}$ dispersion data had possibly been impaired by imaging artifacts. To some extent, an imperfect imaging protocol could account for why some curve fittings were not successful. However, a diminishing $R_{1\rho}$ dispersion near the MA locations was probably the primary reason contributing to a lower successful rate in the femoral (35%) cartilage compared to in the tibial (49%) cartilage.

Relatively large S variations in human knee cartilage in vivo were observed, which might be induced by intrinsically different biomechanical properties at various cartilage locations such as weight-bearing and non-weight-bearing areas. Preferentially oriented water in collagen plays a crucial and yet not fully understood role in biomechanics of cartilage⁴⁶; hence, S might be served as an indicator for varying biomechanical functions among different cartilaginous joint tissues. For instance, $S(10^{-3})$ was about 2 for human knee cartilage in vivo (Figure 7B) compared with that of around 4 for bovine patellar cartilage (Figure 4B) and about 35 for the cartilage in hydrated ($\sim 25\%$) bovine Achilles tendon.³³

5.6 | Limitations and future work

Several limitations to this work must be acknowledged. First, only a limited number of cartilage samples and human knee in vivo were examined; thus, the reported statistical analysis might be biased. Second, the proposed method might become less reliable for some femoral cartilage near the MA locations. Third, the $R_{1\rho}$ dispersion acquisition strategy for human knee in vivo was by no means the best of choice, and the lengthy scan duration could have contributed to the considerable variations to the reported order parameters. Last, there was no gold standard to which the derived order parameter could be compared in vivo; therefore, a direct association between the measured and the physical reality could not be confirmed.

Before undertaking in vivo validations on a large cohort of subjects, a few technical challenges must be overcome in designing an efficient and reliable $R_{1\rho}$ dispersion acquisition strategy. To date, none of the existing spin-locking pulses are suitable for quantitative $R_{1\rho}$ dispersion investigations due to their sensitivities to B_1 and B_0 field artifacts when using a larger range of ω_1 .^{47,48} Neither was the reported phase cycling strategy⁴⁰ optimal for improving $R_{1\rho}$ quantitative accuracy; it would have doubled the scan time if this method had been implemented in our imaging pulse sequence. Further work is underway to develop an efficient $R_{1\rho}$ dispersion imaging protocol suitable for clinical studies. Hopefully, it will facilitate a thorough validation of the proposed novel MR metric on human knee in vivo and expand to other highly organized tissues.

6 | CONCLUSION

We have developed a theoretical framework and applied it to both ex vivo and in vivo studies on articular cartilage. The preliminary results from these studies demonstrate that an orientation-independent order parameter could be derived from $R_{1\rho}$ dispersion that is both sensitive and specific to the integrity of microstructure in collagen. It is foreseen that the developed method will probably broaden the current spectrum of the compositional MR imaging applications on articular cartilage and other highly ordered tissues.

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CONFLICT OF INTEREST

An invention disclosure (OTT # 2019-280) was reported to the University of Michigan.

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