Lecture #16
NMR Relaxation in Cartilage

• Topics
  • Normal cartilage structure and function
  • Osteoarthritis

• References
Articular Cartilage Function

Principal Functions

• Provide a smooth, lubricated surface for low friction articulation
• Facilitate the transmission of loads
Structure and Composition

- **Structure**
  - Multiple Zones with Varying collagen fiber ultrastructure, ECM, and chondrocytes
  - 2-4 mm Thick
  - No Vessels or Nerves

- **Composition**
  - Water (65-80%)
  - Collagen (10-20%)
    - 90-95% Type II Collagen
  - Proteoglycan (10-15%)

Articular Cartilage

- Connective tissue providing synovial joint lubrication and absorption of mechanical shock.
- Consists of chondrocytes within a large extracellular matrix (ECM)
- ECM components: water: 65-85%, collagen: 15-20%, proteoglycans: 3-10% mostly glycosaminoglycan (GAG)
Cartilage Collagen

- The orientation and alignment of collagen matrix varies according to the depth from the articular surface as well as regionally within the joint.
Osteoarthritis

- Early changes: hydration, loss of PG, disruption of collagen
- Late changes: dehydration, further loss of PG and collagen, thinning

Li, et al., JMRI, 38:991–1008 (2013)
MRI of Morphologic Changes

T2w FSE w/ Fat Sat

- Cartilage Loss
- Fibrillation
- Bone Marrow Lesions
- Osteophyte Formation
T2 Relaxation Time Mapping

- Reflects ability of free water protons to move and exchange energy inside cartilaginous matrix
- Indirect assessment of collagen structure and orientation
- Widely Available

T₂ and Collagen

- T₂ relaxivity strongly influences by anisotropy of cartilage collagen fiber orientation (magic angle effect).
- Produces a laminar appearance on T₂-weighted images, with signal intensity depending both on depth and...
Magic Angle Effects

Orientation effects

Age dependence

Figure 6. SE image of an adult human knee joint, showing the dependence of the MRI visualization of the cartilage on the orientation to the static magnetic field. If the normal axis of the cartilage surface is parallel to the static field, the femoral cartilage appears bilaminar with a small superficial zone of high intensity and a broad deep zone of low intensity. The zone of high intensity increases up to a maximum (of the whole uncalcified cartilage thickness) at an angle of about 54° ('magic angle') between normal axis and $B_0$.

Figure 5. A schematic illustration of the development of the cartilage network structure with age without consideration of varying cartilage thickness (indicated right on the inserted microimages). The scheme based on data derived from parallel μMRI and PLM measurements of sheep femoral and tibial condyle (weight-bearing region, medial condyle). PLM and MR images of femoral condyle at some stages of cartilage development are shown. In reference to the femoral condyle, a faster structural development was observed in case of tibia plateau. Blue, yellow and red colors correspond to predominantly tangential, radial and isotropic zones, respectively.

Magic Angle Effects

- Dipolar Interactions of water associated with collagen fibers reduce $T_2$ and are orientation dependent
  - Maximal at angle of 0°
  - Minimal at an angle of 55°.

Challenges

Magic Angle Effects
- Dipolar Interactions of water associated with collagen fibers reduce $T_2$ and are orientation dependent

Proteoglycan changes may precede changes to collagen content

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<tr>
<th>Technique</th>
<th>$T_2$ Relaxation Time Mapping</th>
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<td>Magic Angle Effects, Less Specific, May not capture initial biochemical changes</td>
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Cartilage Proteoglycans

- GAG units on the proteoglycans provide a strong negative charge density within the cartilage.
- Exchangeable –OH and –NH protons
- Negative charge attracts positive counter-ions and water molecules
  - strong electrostatic repulsive force between the proteoglycans
  - swelling of the proteoglycans is constrained by the surrounding collagen meshwork, which produces an interstitial fluid pressure
$T_{1\rho}$ Relaxation Time Mapping

- Probes the slow motion interactions between motion-restricted water molecules and their local macromolecular environment
- Sensitive to changes in ECM, such as PG loss
- Provides a larger dynamic range and a more sensitive detection of PG loss at early stages of cartilage degeneration

During spin-locking, the magnetization (signal) decays with time constant $T_{1\rho}$

$$S(t_{SL}) = S_0 e^{-\left(\frac{t_{SL}}{T_{1\rho}}\right)}$$

Cartilage and $T_{1\rho}$

Which of the following statements are true (all from review articles)?

1. “In $T_{1\rho}$ …the magnetization undergoes relaxation in the presence of the applied $B_1$ field…”
2. “The measurements of $T_{1\rho}$ probe molecular fluctuations in the kHz range because of the dependence on the RF-generated magnetic field ($B_1$), whereas $T_2$ probes fluctuations in the MHz range because of the dependence on the static magnetic field ($B_0$).”
3. “The $B_1$ field attenuates the effect of dipolar relaxation, static dipolar coupling, chemical exchange and background gradients on the signal.”
4. “…probes the slow motion interactions between motion-restricted water molecules and their local macromolecular environment. The macromolecules in articular cartilage ECM restrict the motion of water molecules. Changes to the ECM, such as PG loss, therefore, can be reflected in measurements of $T_{1\rho}$.”
5. “$T_{1\rho}$ reflects interaction of collagen with water.”
6. “$T_{1\rho}$ is sensitive to low-frequency exchange interactions between water molecules and the large, slow tumbling macromolecules.”
7. “$T_{1\rho}$ may be more sensitive to the initial changes in the cartilage ECM associated with PG depletion, whereas $T_2$ is sensitive only to later changes in the collagen network.”
8. “$T_{1\rho}$ values appear to be unaffected by the laminar structure of cartilage.”
9. “$T_{1\rho}$ relaxation phenomena are sensitive to physicochemical processes with inverse correlation times on the order of the nutation frequency of the spin-lock pulse.”
\( T_{1\rho} \)

- \( T_{1\rho} \) differs from \( T_2 \) in that:
  - probes density function at \( J(\gamma B_1) \) or \( J(2\gamma B_1) \) rather than \( J(0) \).
  - User selects \( \omega_1 = \gamma B_1 \), typically 0.1-3 KHz.

Random fields model:

\[
\frac{1}{T_{1\rho}} = \langle \hat{I}_z | \hat{I}^\prime | \hat{I}_z \rangle = \gamma^2 \langle B^2 \rangle (J(\omega_1) + J(\omega_0))
\]

Dipolar coupling:

\[
\frac{1}{T_{1\rho,DD}} = \left( \frac{\mu_0}{4\pi} \right)^2 \frac{3\gamma^4 \hbar^2}{10\pi^2 r^6} \left( \frac{3}{2} J(2\omega_1) + \frac{5}{2} J(\omega_0) + J(2\omega_0) \right)
\]

- Key idea: \( T_{1\rho} \) is maximally sensitive to physical processes with time variations at frequency \( \omega_1 \) (2\( \omega_1 \) for dipolar interactions).

- For cartilage, we want to be sensitive to chemical exchange of water with –OH and -NH groups on the GAG molecules.

- Typically studies conducted with \( \gamma B_1 = \sim 500 \text{ Hz} \)

- May be sensitive to earliest OA changes (GAG loss)
Cartilage $T_{1\rho}$ Examples

- In general, $T_{1\rho}$ has been shown to correlate with loss of GAG, but often similar to $T_2$ mapping, although $T_{1\rho}$ dynamic range is larger.

Li, et al., JMRI, 38:991–1008 (2013)

Additional $T_{1\rho}$ Considerations

- Reduces magic angle effects
- Age effects
- Exercise effects


Li, et al., JMRI, 38:991–1008 (2013)
"$T_{1\rho}$ imaging is often performed with a relatively high locking field e.g. 500 Hz. If the $R_{1\rho}$ dispersion that we report is largely the result of chemical exchange, it follows that protocols that use locking fields of 500 Hz are selectively removing the contribution of exchange, and thus their sensitivity to proteoglycans. It is the difference between low and high locking fields that reflects the specific contributions of exchanging protons, not the absolute values of $T_2$ ($\approx$ the low field value of $T_{1\rho}$) or the value at high field. This interpretation differs from some previous conclusions about the origins of $T_{1\rho}$ effects."
**$T_{1\rho}$ Dispersion**

- The dependence of the relaxation rate on $\omega_1$ is the dispersion
  - The effect of increasing $\omega_1$ is to gradually overcome the effect of very low or zero frequency relaxation mechanisms and simultaneously increase the specificity to higher frequency relaxation mechanisms.

$v_1 = 0 \text{ Hz} \quad \quad \quad \quad \quad v_1 = 2 \text{ kHz}$

- Field Artifacts
- Proton Dipole-Dipole Coupling
- Chemical Exchange Amide and Hydroxyl
- Molecular Rotation of Water Protons
T₁ρ Relaxation Time Mapping - Challenges

- Spin-lock pulse is often limited by SAR restrictions
  - May not adequately decouple the residual dipolar interactions from the collagen network
  - Longer Scan Times to decrease average amounts of energy deposited
- T₁ρ is not as specific to GAG content as other MR methods

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Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC):

- Negatively charged contrast agent Gd(DTPA)$_{2}^{-}$ will distribute in cartilage in inverse relation to the negatively charged GAG concentration
- T1 relaxation time can be used to quantify GAG concentration
- Highly specific to GAG

Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC):

**Challenges**
- Diffusion of Gd(DTPA)$^{2-}$ into the cartilage may be dependent on collagen content and diffusion direction
- Long Scan Times
- Invasive
- May pose health risks for individuals with renal impairment
- Expensive

**Technique**
- **dGEMRIC**

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<td>GAG Content</td>
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<td>Challenges</td>
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**Injection of** Gd(DTPA)$^{2-}$, **Exercise** (10–20 min), **Delay Time** (60-80 min), **Imaging** \([T_1\) Mapping] (90-180 min post injection)
Diffusion Imaging

- Diffusion is the primary transport mechanism into cartilage.
- Diffusion is affected by the structure and composition of the collagen matrix and can be measured by the apparent diffusion coefficient (ADC).
- ADC can be a marker of early cartilage degeneration.

Raya et al. Radiology. 2012, 262, 550-559
Diffusion Imaging - Challenges

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<th>Diffusion Imaging</th>
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<tr>
<td>Biochemical Correlate</td>
<td>Collagen Network, PG Concentration</td>
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<tr>
<td>Challenges</td>
<td>Low SNR, Poor visualization of Deep layers</td>
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Low SNR
- Due to long echo times and short T2 of Cartilage
- Particularly deep layers of Cartilage

Sensitivity to Motion

Long Scan Times
GagCEST

- Exchange of hydroxyl (-OH) protons on GAG and bulk water protons can be exploited to measure GAG distribution

- High specificity to GAG without the need for special hardware or intravenous contrast

Schmitt B et al.. Radiology 2011;260(1).
Chemical Exchange Saturation Transfer (CEST)

Solute Pool ($P_s$) (GAGs)

Water Pool ($P_w$)

$P_s \ll P_w$

RF $\Delta \omega = 1$ ppm

$K_{sw} \quad K_{ws}$

$S_0$

MT + Spillover

$\text{CEST}_{\text{sym}}$

$\text{CEST}_{\text{sym}} = \frac{M_{\text{sat}}(-\Delta \omega) - M_{\text{sat}}(\Delta \omega)}{M_{\text{ctrl}}}$

Exchange Rate dependence

- CEST requires a discrete chemical shift difference between water and the exchangeable proton on the CEST agent is preserved

- Chemical shift difference ($\Delta\omega$) is directly related to the magnetic field strength

Chemical Exchange & pH Dependence

- Chemical Exchange rate plays a critical role in optimal saturation parameters

- \( B_1 \) and Duration can be used to control saturation

- Slow Exchange \( \rightarrow \) Low amplitude, long duration

- Fast Exchange \( \rightarrow \) High Amplitude, short duration

\[ B_0 = 300 \, \text{MHz}, \, \Delta \omega = 3 \, \text{ppm (900 Hz)}, \, T_{1w} = 2.4s, \, T_{2w} = 100 \, \text{ms}, \, M_{0w} = 110, \, M_{0s} = 0.30 \]
Understanding CEST Contrast

Components of CEST

- CEST Effects
- Direct Water Saturation
- Magnetization Transfer (MT)
- NOE
- CEST effects from other Exchangeable protons

\[ CEST_{\text{asym}} = \frac{M_{\text{sat}}(-\Delta \omega) - M_{\text{sat}}(\Delta \omega)}{M_{\text{ctrl}}} \]
GagCEST

- Hydroxyl protons (-OH) attached to GAGs have a resonance frequency 1 ppm down field from the water resonance

- Fast exchange Rates (500-1500 s\(^{-1}\))

GagCEST - Challenges

- Difficult at 3T
  - High exchange rate
  - Proximity of resonance frequencies between GAG hydroxyl protons and bulk water protons

- Precise $B_0$ field maps and advanced post-processing tools are also required

Quantitative MT imaging is sensitive to MM bound protons

- Uses Rf saturation pulses ranging from 2.5 – 20 kHz off-resonance.
- Calculate bound proton fraction, exchange rate, $T_2$ of bound protons.
Ultrashort Echo Time (UTE) Imaging

Areas with short T2 (<10 ms) have limited signal on traditional MRI

UTE sequences allow for echo times as short as 8μs

Allows for visualization of the deep layers of cartilage

Bae W et al. Osteoarthritis Cartilage. 2013 Jan;21(1):77-85
**T2* Mapping of Articular Cartilage**

*Current Status of Research and First Clinical Applications*

*Gustav Andreisek, MD, MBA* and *Markus Weiger, PhD*

- UTE-based T₂* mapping with typical TEs from 0.5-40 ms
- Depthwise T₂* gradient
- Potential to quantitatively reflect loss of collagen fiber integrity and changes in bound water.

**FIGURE 2.** Magnified T2* map of the retropatellar cartilage of the right knee in a 45-year-old female patient, which was calculated from a multiecho 2D FLASH GRE MR sequence (3.0 T; TR, 625 milliseconds; TEs, 4.4, 11.9, 19.4, 27.0, 34.5 milliseconds; in-plane resolution, 0.4 mm). Full thickness of the retropatellar cartilage was preserved without signs of focal loss; however, in the central portion, areas with increased T2* values (ROI position 1) are seen within the cartilage with an otherwise normal zonal behavior (ROI position 2).
Sodium ($^{23}\text{Na}^+$) Imaging

- Positively charged sodium ions exist in association with the negatively charged GAG side-chains
- Direct measure of GAG content
- Low sodium content (<50 mmol/L) of surrounding structures enables very high cartilage tissue contrast

Madelin et al. Radiology 2013 Aug;268(2):481-91
# Sodium (\(^{23}\text{Na}\)) MRI

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Name</th>
<th>Spin</th>
<th>Frequency at 1.5T (MHz)</th>
<th>Relative sensitivity</th>
<th>Natural abundance (%)</th>
<th>In vivo concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^1\text{H})</td>
<td>hydrogen (protons)</td>
<td>1/2</td>
<td>63.87</td>
<td>1</td>
<td>100</td>
<td>100 (MRI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02 (MRS)</td>
</tr>
<tr>
<td>(^{23}\text{Na})</td>
<td>sodium</td>
<td>3/2</td>
<td>16.89</td>
<td>0.0925</td>
<td>100</td>
<td>0.05</td>
</tr>
</tbody>
</table>

- Low sensitivity (although \(T_1 = 30-40\) ms allows short TRs)
- Sodium ion homeostasis is a vital cellular function.

![Cell membrane diagram]

<table>
<thead>
<tr>
<th>K(^+)</th>
<th>ATP</th>
<th>Pump</th>
<th>Intracellular 10 mM</th>
<th>Extracellular 150 mM</th>
</tr>
</thead>
</table>

- Spin 3/2 ?!?
\[ ^{23}\text{Na, a Spin 3/2 Nuclei} \]

- Nuclei with spin > 1/2 posses an electric quadrupole moment since the charge distribution is no longer spherically symmetric.

- Four energy levels
  - Three single quantum transitions.
    - Time-dependent perturbation theory yields 3:4:3 relative intensities.
  - Double and triple quantum transitions also possible.
  - If electric field seen by nucleus is spatially homogeneous, all three transitions have the same \( \omega_0 \).

\[ \text{Single peak} \]
$^{23}\text{Na}, \text{ a Spin 3/2 Nuclei}$

- In the presence of non-zero spatial electric field gradients:

New term in Hamiltonian: $\hat{H} = \hat{H}_{\text{Zeeman}} + \hat{H}_{\text{dipole}} + \hat{H}_J + \hat{H}_Q$
Static Quadrupolar Effects

- Static E-field gradients results in shifts of the resonance frequencies of the two outer transitions (to first order, inner transition insensitive to E-field gradient)

- Splitting depends on strength of E-field gradient and molecular orientation (ranges from kHz to MHz).

- In vivo, range of splittings results in very broad outer lines
  - In practice, typically results in only 40% NMR visibility.
  - Effect called “heterogeneous broadening”.
Dynamic Quadrupolar Effects

• Dynamic (time-varying) E-field gradients are also present.

• Time-depended quadrupolar splittings average out to zero, but fluctuations induce relaxation.

• When $T_2$ of the outer lines are much shorter than the inner line (typically the case), the outer lines are very broad.
  
  – Effect called “homogeneous broadening”.
  
  – In practice, both static and dynamic quadrupolar effects are present in vivo.

  – Typically results in only 40% NMR visibility. More specifically, an observed bi-exponential decay with one very short component.
Quadrupolar Relaxation

• Summary
  – The electrical quadrupole moment interacts with local electric field gradients.
  – Quadrupolar effects dominate \textit{in vivo} $^{23}\text{Na}$ relaxation

• Under the limit of extreme narrowing, outer lines disappear and inner line decays as …

\[
\frac{1}{T_1} = \frac{1}{T_2} = \frac{3}{10} \left( \frac{2I + 3}{I^2(I + 1)} \right) \left( 1 + \frac{\eta^2}{3} \right) \left( \frac{e^2 Q q}{2 \hbar} \right)^2 \tau_c
\]
Intracellular vs. Extracellular $^{23}\text{Na}$

- **Extracellular environment**
  - In aqueous solution (extreme narrowing condition) $^{23}\text{Na}$ $T_2$ decay is monoexponential of 30-40 ms.
  - Sodium in the fast isotropic tumbling regime exhibits only single quantum coherence

- **Intracellular environment**
  - Rapid exchange between free $^{23}\text{Na}$ and $^{23}\text{Na}$ bound to slowly tumbling macromolecular sites contribute to biexponential $T_2$ decay with a short component of 1-3 ms.
  - Sodium ions in this motionally-restricted tumbling regime exhibit both double and triple-quantum coherence
Intracellular vs. Extracellular $^{23}$Na

- Typically, intracellular $^{23}$Na concentration is of greater interest.

- Two main approaches to separate large extracellular from smaller intracellular $^{23}$Na signal.
  - Shift reagents (toxicity restrict these mainly to use with in vitro cell systems and perfused organs).
  - Double and triple-quantum coherence filtering
$^{23}$Na Imaging of Cerebral Ischemia

$^{23}$Na MRI performed with ultrashort-TE 3D PR with twisted projections…i.e. interleaved spirals (Stanford is not the only place that uses spiral MRI!).
TR/TE=80/0.4 ms, 16 slices, 10 min, 0.22 cm$^3$ isotropic voxels


\( \text{\(^{23}\)Na Imaging of Cartilage} \)

- For cartilage, the \(^{23}\)Na of interest is all extracellular.

- Negatively charged proteoglycans (PG) that attract cations (mainly sodium) which draw in water by osmosis to provide cushioning
  - Cartilage sodium \(~300\ \text{mM}\)
  - Synovial fluid \(~150\ \text{mM}\)

- Loss of PG = early sign of cartilage degeneration.
Double and Triple Quantum Imaging

- $^{23}$Na ions interacting with the PG exhibit restricted tumbling and are most clinically interesting.

“Our while single quantum images can be used to determine PG content, TQF images are more specific because they show sodium in slow motion regime primarily associated with the presence of macromolecules. The images may potentially be sensitive to structural changes in macromolecule arrangement in the extracellular matrix. Furthermore, TQF imaging can be used to suppress unwanted fluid signals.”
## Summary

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<th>Diffusion Imaging</th>
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Ultra High Field (7T)

Advantages

- Higher SNR!!
  - Increases linearly with $B_0$
- Increased $\Delta \omega$
  - Increases linearly with $B_0$
- Increased $T_1$

Challenges

- Field Inhomogeneity
  - $B_0$ & $B_1$ Inhomogeneities increase
- SAR
  - Power Deposition increases quadratically with $B_0$
- Availability
Figure 8.
Sodium MRI is sensitive to cartilage glycosaminoglycan. Advances in coil design and high field have made this a potential clinical tool. Here a patient with a prior anterior cruciate ligament tear shows areas of focal cartilage glycosaminoglycan loss (left) despite a normal proton MRI (right).

Choi and Gold, Magn Reson Imaging Clin N Am. Author manuscript; available in PMC May 2012 May 1.
Pulse sequences, parameters and analysis methods vary across vendors, sites, and studies

Must be considered when comparing results across studies