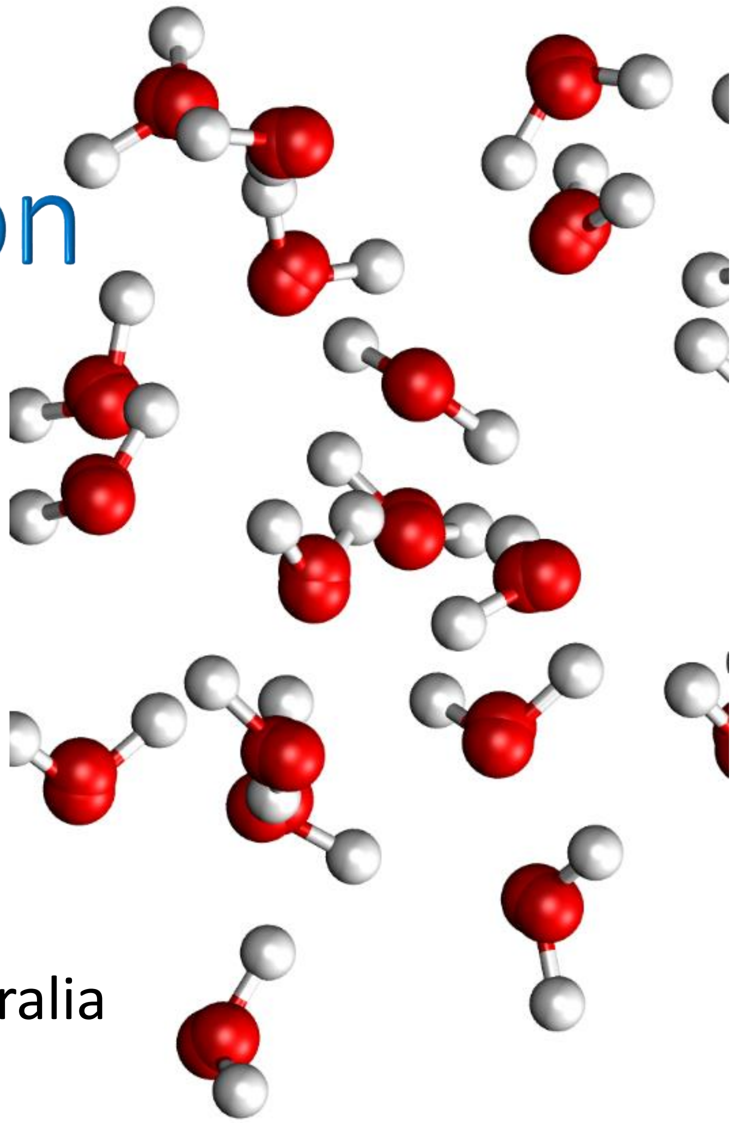
1H Nuclear Spin Relaxation Rates of Water near a Collagen Molecule

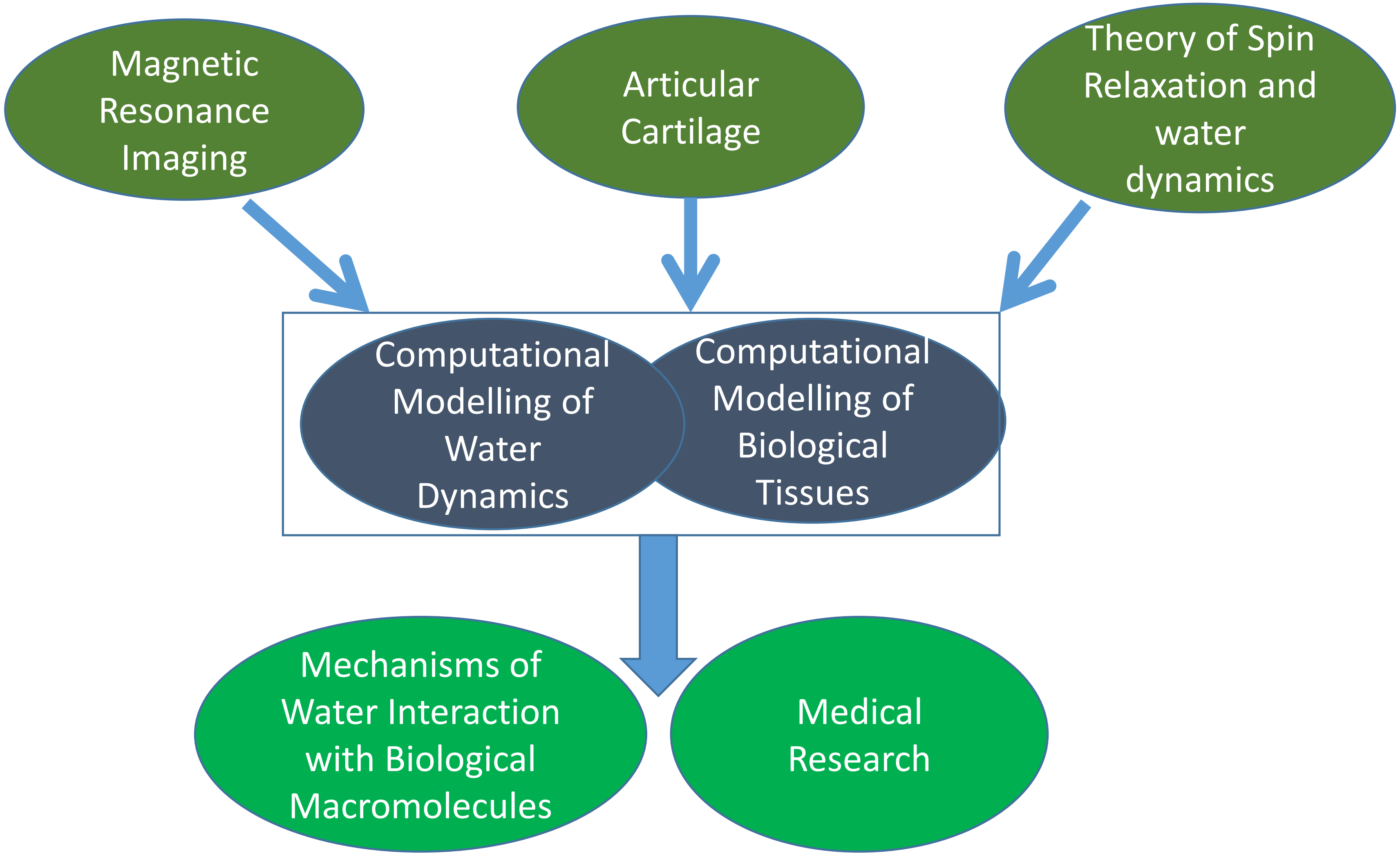


Monika Madhavi

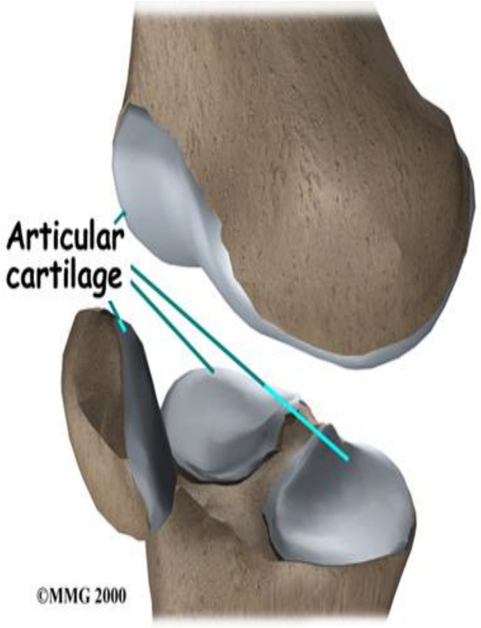
University of Colombo, Sri Lanka

Queensland University of Technology, Australia

Research Context

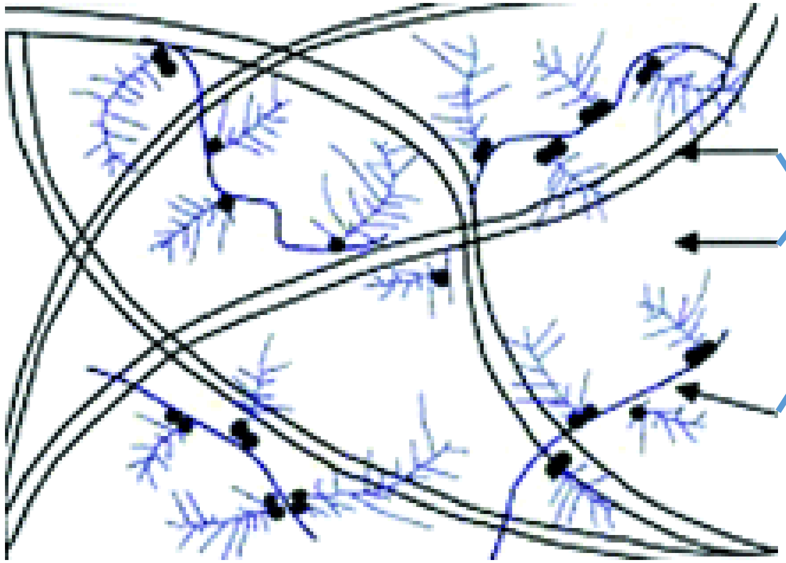


Articular Cartilage



http://www.houstonmethodist.org/orthopedics/where-does-it-hurt/knee/articular-cartilage-problems/

Structure



Fox, A.J.S., Bedi, A. and Rodeo, S.A., The basic science of articular cartilage: structure, composition, and function. *Sports Health: A Multidisciplinary Approach*, *1*(6), pp.461-468, 2009

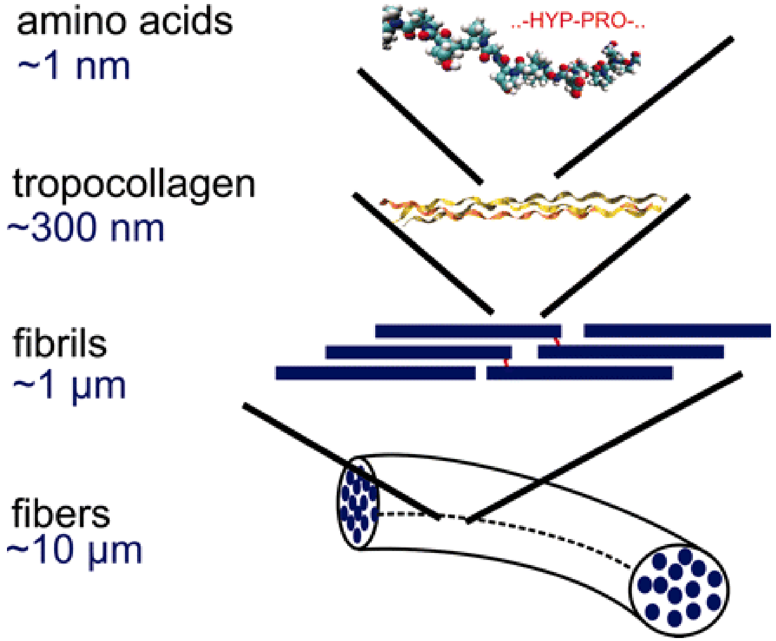
Composition

Water 65 – 80%
Collagen 15 – 20%
Proteoglycan 5 – 10%

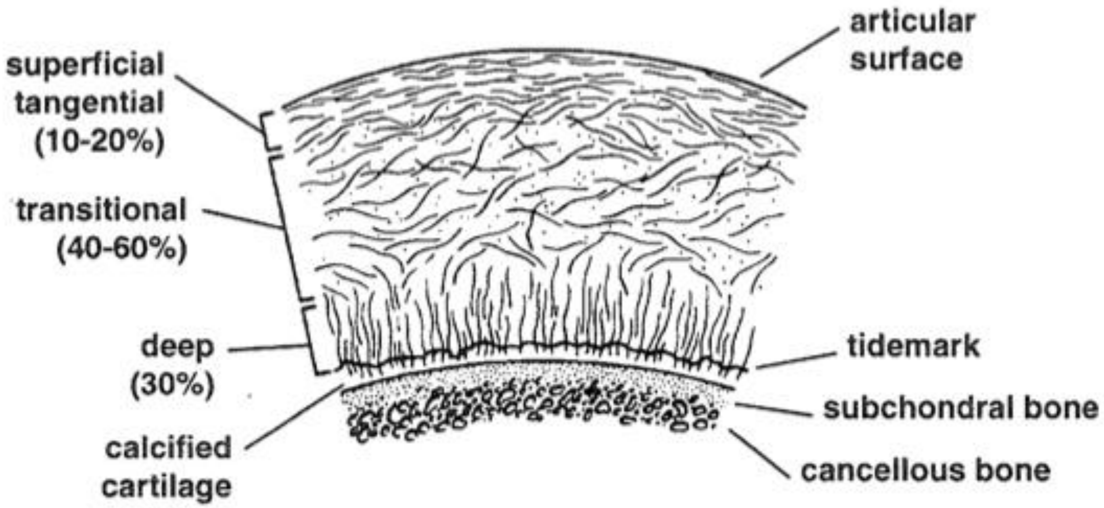
Function

- Distribute loads

Cartilage Microstructure - Collagen



Buehler, M.J., Nature designs tough collagen: explaining the nanostructure of collagen fibrils. *Proceedings of the National Academy of Sciences*, *103*(33), pp.12285-12290, 2006.



https://www.studyblue.com/notes/note/n/articular-cartilage/deck/8636007

Magnetic Resonance Imaging

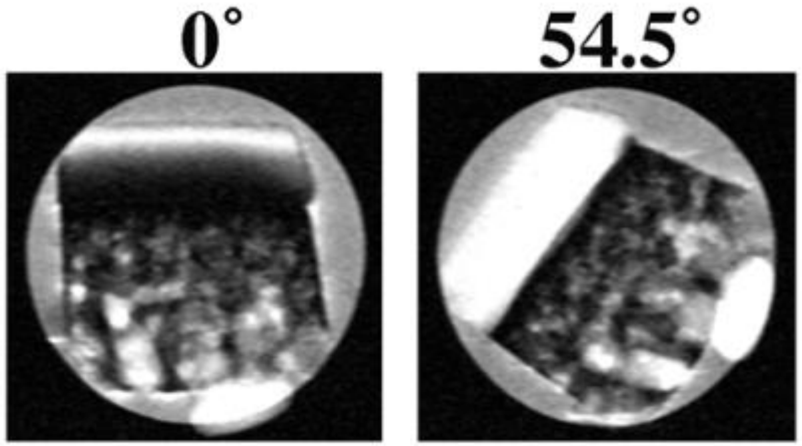
Capable of probing
cartilage morphology
cartilage physiology → Early diagnose of OA

Important MRI parameters

Sensitive to:

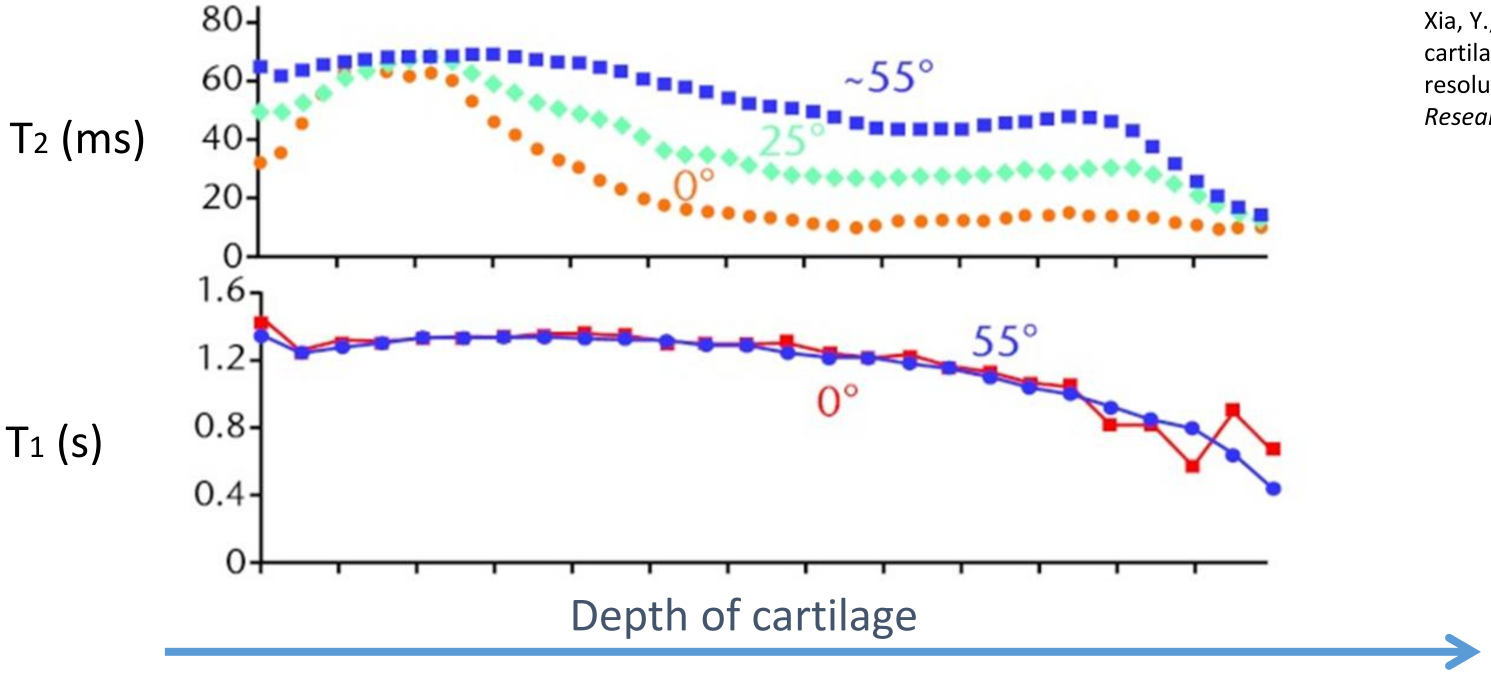
Important MRI parameters	Sensitive to
Spin-lattice relaxation time (T_1)	highest frequencies of motion
Spin-spin relaxation time (T_2)	lower frequencies of motion
Spin-lattice relaxation time in the rotating frame ($T_{1\rho}$)	intermediate frequencies

MRI of cartilage



Orientation with magnetic field

Y. Xia, J. B. Moody, and H. Alhadlaq, "Orientational dependence of T2 relaxation in articular cartilage: A microscopic MRI (uMRI) study," *Magn. Reson. Med.*, vol. 48, no. 3, pp. 460–469, 2002.

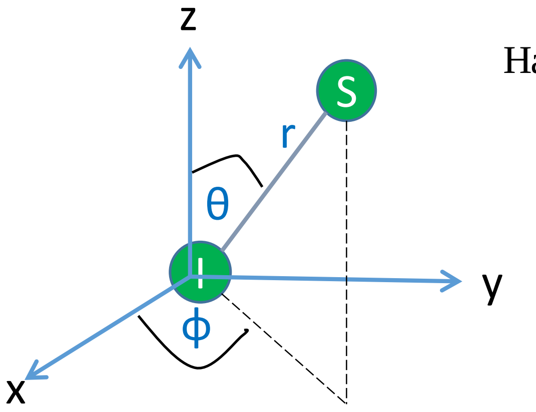


Xia, Y., 2013. MRI of articular cartilage at microscopic resolution. *Bone and Joint Research*, *2*(1), pp.9-17.

Anisotropy of spin relaxation

- Is a biomarker of the microstructure of cartilage
- Arises due to:
  - Dipolar interaction between water and macromolecules
  - Exchange of water between bound and free states

Theory of spin relaxation



$$\text{Hamiltonian } H_D = -\frac{\mu_0}{4\pi}\gamma_I\gamma_S\left(\frac{I.S}{\vec{r}^{\,3}} - \frac{3(I.\vec{r})(S.\vec{r})}{\vec{r}^{\,5}}\right)$$

$$\hbar \mathrm{H} = \sum_q F^{(q)} A^{(q)}$$

$$A^{(0)} = \alpha\left\{-\frac{3}{2}I_z S_z + \frac{1}{6}\left(I_+ S_- + I_- S_+\right)\right\}$$

$$A^{(1)} = \alpha\left\{I_z S_+ + I_+ S_z\right\}$$

$$A^{(2)} = \frac{1}{2}\alpha I_+ S_+$$

$$\alpha = -\frac{3}{2}\gamma_I\gamma_S\hbar$$

$$F^{(0)} = \frac{1-3\cos^2\theta}{r^3}$$

$$F^{(1)} = \frac{\sin\theta\cos\theta e^{-i\phi}}{r^3}$$

$$F^{(2)} = \frac{\sin^2\theta e^{-2i\phi}}{r^3}$$

Random functions of the relative positions of two spins

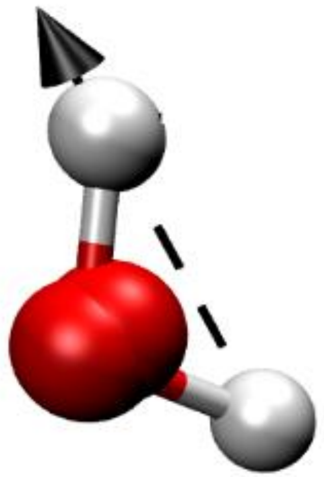
Theory of spin relaxation

Autocorrelation function

$$G^{(q)}(\tau) = \left\langle F^{(q)}(t) F^{(q)*}(t+\tau) \right\rangle$$

Spectral density of motion

$$J^{(q)}(\omega) = \int_{-\infty}^{\infty} G^{(q)}(\tau) e^{-i\omega\tau} d\tau$$



For a water molecule both spins are protons having $I = S = \frac{1}{2}$

$$\frac{1}{T_1} = \frac{3}{2}\gamma^4 \hbar^2 I(I+1)\left\{J^{(1)}(\omega_I) + J^{(2)}(2\omega_I)\right\}$$

$$\frac{1}{T_2} = \gamma^4 \hbar^2 I(I+1)\left\{\frac{3}{8}J^{(2)}(2\omega_I) + \frac{15}{4}J^{(1)}(\omega_I) + \frac{3}{8}J^{(0)}(0)\right\}$$

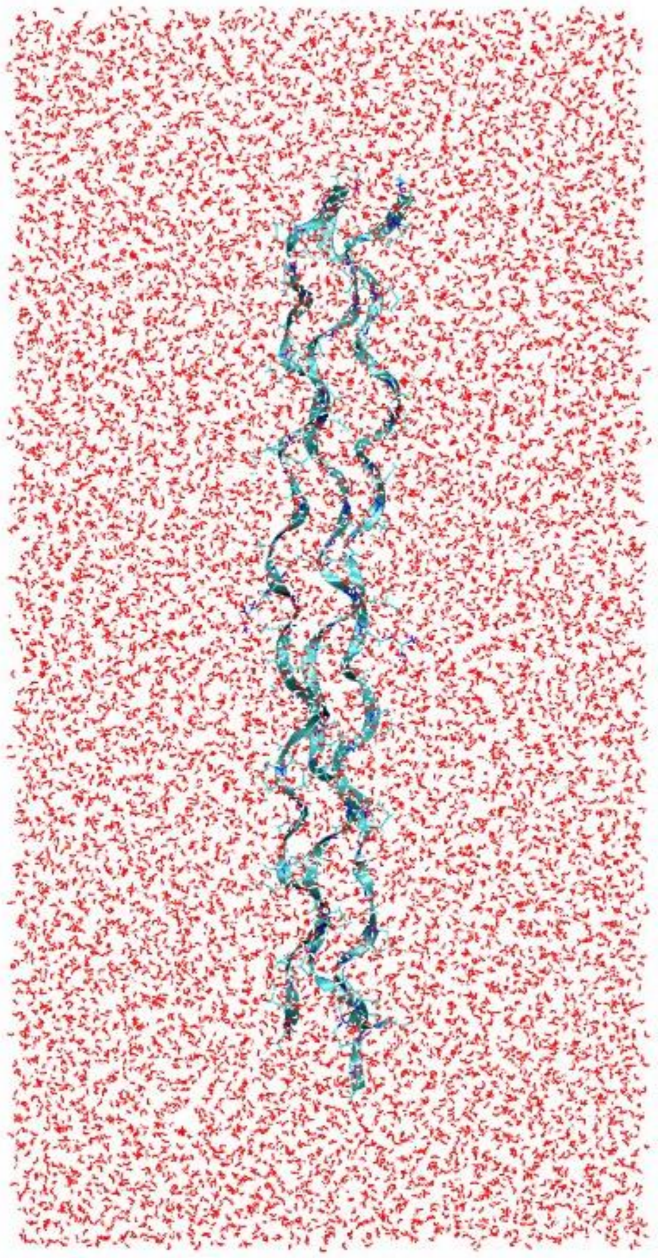
In the limit of very short correlation time $\tau_C << \frac{2\pi}{\omega_0}$ which is always true for MRI,

$$J^{(q)}(\omega) \approx J^{(q)}(0)$$

$$J^{(0)} : J^{(1)} : J^{(2)} = \left\langle \left|F^{(0)}\right| \right\rangle^2 : \left\langle \left|F^{(1)}\right| \right\rangle^2 : \left\langle \left|F^{(2)}\right| \right\rangle^2 = 6:1:4$$

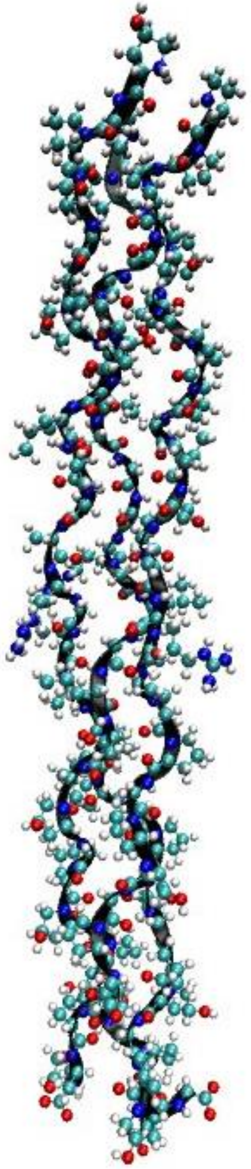
MD Simulation Setup

- Collagen is the fundamental building block of cartilage extracellular matrix.
- Collagen type III – PDB ID 1BKV
- Water – TIP4P/2005
- Force field - CHARMM all-atom force field param22
- Added additional parameters for hydroxyproline
- Simulated with NAMD



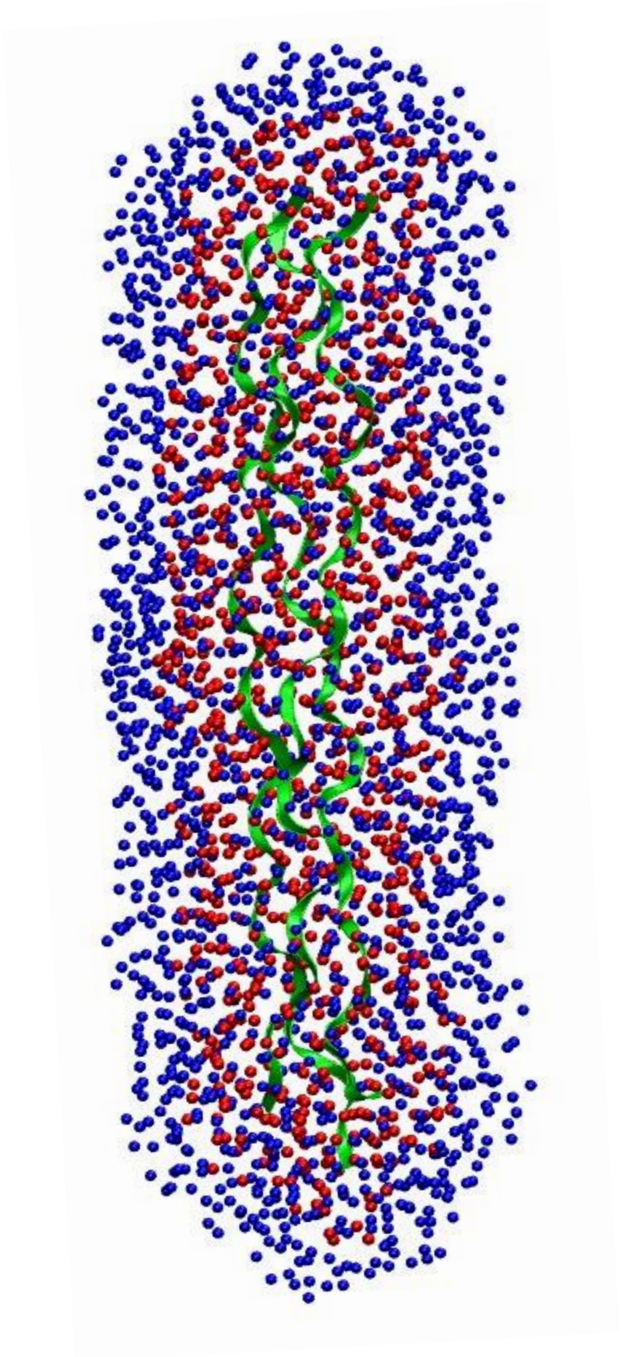
MD Simulation Setup

- Minimization
  - Protein backbone fixed until bad contacts are removed
  - Fixed atoms removed and minimized further
  - Heated the system with harmonic constraints on backbone C atoms
- Equilibration
  - Turned on constant pressure and alpha carbons were restrained
  - CA atoms released and equilibrated further



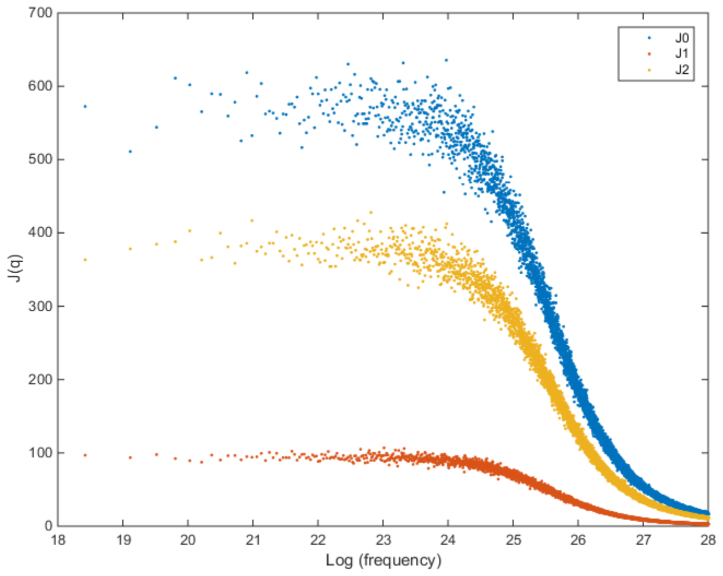
MD Simulations – Analysis

- Backbone C fixed
- 10 ns simulation with 1 fs time step
- Coordinates saved at 0.1 ps
- Spin relaxation rates of different hydration shells were calculated



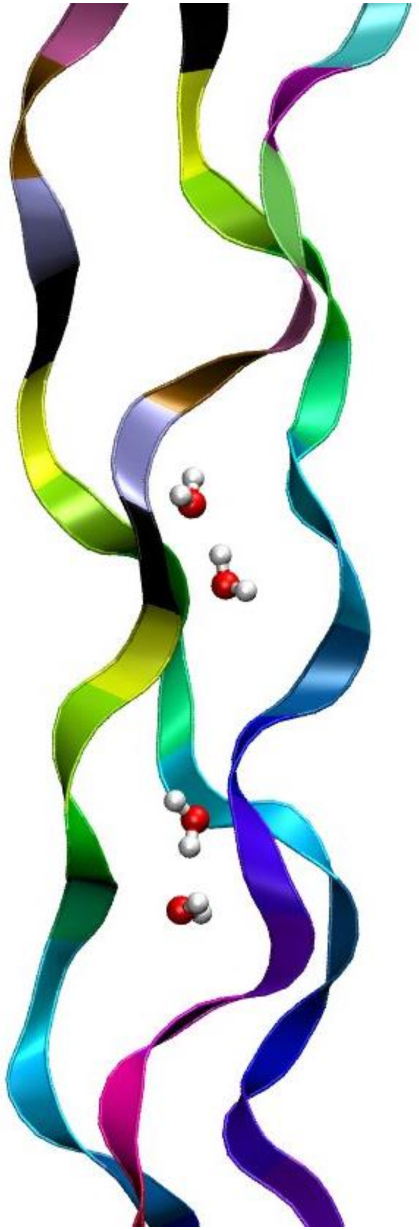
Results

Hydration shell	5 A shell	5 – 10 A shell	Bulk water
Relaxation Time T_1 (s)	0.41 s	0.45 s	3.2 s



Conclusions

- Spin relaxation time (T_1) is reduced in the 5A shell than bulk water
- Water molecules make bridges between collagen helixes
- Bridged water molecules show highly restricted rotational diffusive motion



Future Studies

- Extend the analysis of spin relaxation rates to thinner water shells
- Rotational diffusion propagator of collagen bound water
- Spin relaxation anisotropy of collagen bound water

Acknowledgements

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Thank you