Published in final edited form as:
Osteoarthritis Cartilage. 2007 April ; 15(4): 363–365.

Resolution 'Scaling Law' in MRI of Articular Cartilage

Yang Xia
Department of Physics and Center for Biomedical Research, Oakland University, Rochester, MI 48309, USA

Keywords

cartilage; MRI; imaging; resolution; microscopy

A recent editorial review in this journal [1] discussed whether MRI was fulfilling its promise for molecular imaging of cartilage in osteoarthritis (OA) and related joint diseases. Many issues in the implementation of three MRI techniques (T2, T1rho, and dGEMRIC) were discussed in both clinical and high resolution environments. Although the theoretical bases of these MRI techniques are reasonably comprehensible, quantitative correlations between the values of these MRI parameters and the healthy states of the cartilage tissue have not yet been proved to be reliable and consistent in clinical trials of OA. The authors [1] concluded accurately that "the factors associated with cartilage degeneration may have differential and competing effects" on the values of these parameters. In this short note, we would like to participate in this discussion by exploring the influence of an *additional* factor, the image resolution, in MRI of cartilage, based on our limited experience in microscopic imaging of cartilage using T2 relaxation and in quantitative correlation among several microscopic imaging techniques.

Fundamental Issues in Cartilage Imaging by MRI

Before we try to elaborate on the influence of image resolution in MRI of cartilage, a seemingly trivial factor, let's first outline some fundamental issues in our quest for better management of arthritis using the molecular imaging methods of MRI.

1. Even though articular cartilage is quite thin, its morphological structure has a distinct depth-dependent heterogeneity across its (thin) thickness. In the simplest sense, cartilage has three sub-tissue zones from the articular surface to the bone: the superficial zone, the transitional zone, and the radial zone. Each of these three zones is distinctly characterized by a different orientation of collagen fibers [2–4]. As a result, a bulk MRI measurement is unlikely to be useful in ***molecular*** imaging of cartilage because of the averaging of different structures. (It should be noted that MRI ***is*** an effect tool in ***morphological*** imaging of cartilage, which relates the volume / area / thickness of cartilage tissue to the clinical grade of tissue lesion [5, 6].)
2. Articular cartilage curves as a two-dimensional surface at the ends of bones in synovial joint. The biomechanical, physical, morphological, and molecular properties of the tissue from different locations in a single joint surface can have noticeable topographic variations [7–14]. Therefore, identifying the precise sampling site where

Corresponding Address: Yang Xia, Ph. D., Department of Physics, Oakland University, Rochester, Michigan 48309, USA, Phone: (248) 370-3420, Fax: (248) 370-3408, Email: xia@oakland.edu.

the measurement is done can become an important factor, especially when multiple specimens/subjects are involved in the study.

3. The earliest clinically detectable lesion tends to be localized and small (e.g., occurring near the articular surface at certain topographical locations) [15–17]. Therefore, any method for early detection likely needs a *wide* field of view to survey the surface in order to identify any localized lesion.

4. Because MRI requires a specimen to be placed in a strong magnetic field, the physical orientation of some macromolecules (eg, collagen fibers, muscle fibers) can cause the tissue to behave differently in MRI when the same tissue is oriented differently in the magnet [18–21]. For that reason, the physical orientation of the specimen (including human) in the magnet can become important in MRI experiments.

5. The degradation of articular cartilage leading to OA and other diseases is an insidious and continuing process, characterized at different degradation stages by different types of structural and molecular changes [17, 22]. The mechanisms of these changes exist at multiple levels, including biochemically, molecularly, ultra-structurally, and histologically. Some of these mechanisms may co-exist 'intrinsically' while others co-exist because of multiple molecular environments, consequently nulling and voiding any significant outcome.

The Importance of Imaging Resolution

As one can see, these fundamental issues are intricate and convoluted; the solution for one issue could be undesirable for another issue. Except for the issue of competing mechanisms, however, the influence of all other issues towards the outcome of our measurement can be minimized if we can 'tailor' the molecular environment ***within*** any single voxel (individual volume elements of an image). By improving the image resolution, a smaller voxel can better resolve individual sub-tissue zones, better differentiate topographical variations, better identify local tissue degradations, and better map tissue curvatures. Perhaps more importantly, a smaller voxel could simplify the molecular populations in the volume element, hence reducing the averaging effect of competing mechanisms.

In addition to several of our μMRI studies that used healthy cartilage [14, 23], one recent μMRI study in our lab found a number of detectable changes in an animal model of early OA [24]. An important feature of these significant OA cartilage findings is their strong topographical dependency on the tibial surface, since they were ***not*** significant in the central locations of the tibias where there was no meniscus (i.e., the site/load dependency). To obtain these meaningful results, the transverse pixel sizes of 13.7 μm to 23.1 μm had been used in μMRI. If the resolutions of this tibial OA study were not that high, these significant findings of early lesion would likely be missed.

The 'Scaling Law' in Cartilage Imaging

Let's set aside, for the moment, the immediate sighs of "How can we get a 13.7 μm resolution in clinical MRI?", and answer a simple question: "Is this microscopic resolution a necessity in human MRI?" In these μMRI experiments of canine cartilage [23], the total thickness of the non-calcified tissue was about 650μm. At that resolution, one has about 50 pixels across the entire depth of non-calcified tissue; in other words, each pixel represents approximately 2% of the total thickness of the tissue. So, the question can be rephrased as, "How fast does the morphological structure (hence, molecular environment) change in articular cartilage along its depth?" Since the same pieces of tissue in these studies were also imaged by polarized light microscopy (PLM) at a much higher resolution [23], the thicknesses of the sub-tissue zones were known: 49.7±23.8μm for the superficial zone, 100.8±14.4μm for the transitional zone,

and 472.8±31.5μm for the radial zone. One can easily see that the thinnest zone in the tissue only had about three pixels across its thickness - this 13.7 μm resolution was therefore not a luxury, but a necessity.

However, this 13.7 μm resolution was a necessity only for a *thin* piece of cartilage 650μm thick. If we keep the same relative dimensionality (2% thickness per image pixel) in the structural variation of articular cartilage and in cartilage imaging, since the clinically important human cartilage (from knees and hips) is much thicker, we could scale up the resolution requirement and still obtain results comparable to the microscopic studies. We would need a pixel resolution of 27.4 μm for tissue 1.3 mm thick or 41μm for tissue 2 mm thick. A pixel size of 41μm, though it is still a challenge in clinical environments, could conceivably be reachable! (It should be noted that this recommendation for clinical resolution is made purely based on the need to resolve tissue structures in imaging. A discussion of various experimental and technical consequences of this recommendation is beyond the scope of this short note.)

The Importance of Voxel Orientation when the Voxel Size is Not Isotropic

Before we rush to fine-tune our instruments, we need to understand the importance of one more parameter in MRI experiments: the size and direction of the image slice. An ideal MRI protocol for cartilage imaging should use a 3D **k**-space sampling with an isotropic resolution, which offers several distinct advantages over the 2D slice selection protocol [6, 25–28]. However, 3D imaging at high resolution is extremely time and computationally consuming; many MRI experiments are done in a 2D (coronal, sagittal, axial) format using the slice selection. The use of slice selection essentially tailors the shape of the individual image voxels from a ‘cube’ to a ‘pencil’. In the 13.7-μm μMRI experiments [23], a 1-mm slice thickness was used. So the next question is, what is the best way of orienting this pencil-shaped voxel?

For experiments that characterize the depth-dependent variations in cartilage, one can orient the short dimension of this elongated voxel to be parallel with the tissue thickness, to resolve different histological zones in high resolution. By placing the long dimension of this elongated voxel orthogonal to the radial direction, one can reduce the experimental time and improve SNR. Of course, the topographical variations over the 2D joint surface will cause some structural averaging over this long dimension, and for that one has to consider the ratio of the slice thickness over the joint size. For experiments that study other features of the tissue/tissue degradation, one might want to orient the elongated voxel in some other direction. In essence, if one can tailor the imaging voxel in such a way that the molecular environment inside this volume is the simplest and most homogenous possible, any effect due to partial volume averaging and competing mechanisms would be minimized.

Conclusion Remarks

In summary, in imaging articular cartilage using MRI, the parameter of imaging resolution can have some non-trivial effects on the outcomes of the experiment. By reducing the size of the imaging voxel, one can improve the homogeneity of the molecular environment, consequently reducing any artifacts due to partial volume averaging and/or competing mechanisms. By placing the imaging dimensions carefully, one can optimize the experiments by utilizing the symmetry of the tissue structures. By managing the relative orientation between the specimen (tissue block as well as human) and the direction of the magnetic field, one can manipulate the magic angle effect in cartilage MRI. The goal here is to simplify the molecular environment within each voxel so that the desired mechanisms become dominant.

Based on our limited experience in μMRI of cartilage using T2 relaxation, it seems that a transverse resolution of approximately 2% relative tissue depth per image pixel is a necessity, which, at the present time, poses challenges to the whole-body scanners. However, one needs

to recognize that most of the clinical MRI scanners are designed as the generic version of the MRI system, with a primary target in neurological applications and body scans. Valuable information at higher resolutions and the social importance of managing joint diseases are sufficient motivations for all of us to work together to ***design*** effective MRI systems ***around*** our problem (musculoskeletal conditions) and to develop novel MRI protocols that are exquisitely sensitive to a small set of relevant events in the tissue degradation.

Finally, having a fine spatial resolution in MRI is not going to solve all issues in molecular MRI of cartilage. The competing mechanisms [1] intrinsically co-existing at the molecular level will pose the ultimate limit to the potential of the technology. In view of the complex molecular and ultrastructural changes due to early diseases and the interdependent relationships among concentration-structure-property-function in articular cartilage, applying multidisciplinary techniques together can discriminate among the various factors/changes and their influence on the functional integrity of cartilage as a load-bearing biological tissue, thus providing critical information towards the development of novel methods for early detection and effective monitoring of the etiology of cartilage diseases at both clinical and molecular levels.

Acknowledgements

R01 grant from NIH (AR 45172).

References

1. Burstein D, Gray ML. Is MRI fulfilling its promise for molecular imaging of cartilage in arthritis? Osteoarthritis and Cartilage 2006;14:1087–1090. [PubMed: 16901724]
2. Benninghoff A. Form und Bau der Gelenkknorpel in ihren Beziehungen zur Funktion. Erste Mitteilung Zeitschrift für Anatomie und Entwicklungsgeschichte 1925;76:43–63.
3. Buckwalter, JA.; Rosenberg, LC.; Hunziker, EB. Articular cartilage: composition, structure, response to injury, and methods of facilitation repair. In Articular cartilage and knee joint function. In: Ewing, JW., editor. Basic science and arthroscopy, Bristol-Myers/Zimmer Orthopaedic Symposium. New York: Raven Press; 1990. p. 19-56.
4. Huber M, Trattnig S, Lintner F. Anatomy, Biochemistry and Physiology of Articular Cartilage. Investigative Radiology 2000;35(10):573–80. [PubMed: 11041151]
5. Eckstein F, Heudorfer L, Faber SC, Burgkart R, Englmeier KH, Reiser M. Long-term and resegmentation precision of quantitative cartilage MR imaging (qMRI). Osteoarthritis and Cartilage 2002;10(12):922–8. [PubMed: 12464552]
6. Xia Y. The total volume and the complete thickness of articular cartilage determined by MRI. Osteoarthritis and Cartilage 2003;11(7):473–4. [PubMed: 12814609]
7. Meachim G. Effect of age on the thickness of adult articular cartilage at the shoulder joint. Annals of the Rheumatic Diseases 1971;30(1):43–6. [PubMed: 5548442]
8. Zimny ML, Redler I. Morphological Variations within a Given Area of Articular Surface of Cartilage. Z Zellforsch 1974;147:163–167. [PubMed: 4824490]
9. Kincaid SA, Van Sickle DC. Regional histochemical and thickness variations of adult canine articular cartilage. American Journal of Veterinary Research 1981;42(3):428–32. [PubMed: 7271007]
10. Kiviranta I, Tammi M, Jurvelin J, Helminen HJ. Topographical variation of glycosaminoglycan content and cartilage thickness in canine knee (stifle) joint cartilage. Application of the microspectrophotometric method. Journal of Anatomy 1987;150:265–76. [PubMed: 3654339]
11. Korvick D, Athanasiou K. Variations in the mechanical properties of cartilage from the canine scapulohumeral joint. American Journal of Veterinary Research 1997;58(9):949–53. [PubMed: 9284997]
12. Gomez S, Toffanin R, Bernstorff S, Romanello M, Amenitsch H, Rappolt M, et al. Collagen fibrils are differently organized in weight-bearing and not-weight-bearing regions of pig articular cartilage. The Journal of Experimental Zoology 2000;287(5):346–52. [PubMed: 10980493]

13. Xia Y, Moody J, Alhadlaq H, Burton-Wurster N, Lust G. Characteristics of Topographical Heterogeneity of Articular Cartilage over the Joint Surface of a Humeral Head. Osteoarthritis and Cartilage 2002;10(5):370–380. [PubMed: 12027538]

14. Xia Y, Moody J, Alhadlaq H, Hu JN. Imaging the Physical and Morphological Properties of a Multi-Zone Young Articular Cartilage at Microscopic Resolution. Journal of Magnetic Resonance Imaging 2003;17(3):365–374. [PubMed: 12594728]

15. Hwang WS, Li B, Jin LH, Ngo K, Schachar NS, Hughes GN. Collagen fibril structure of normal, aging, and osteoarthritic cartilage. The Journal of Pathology 1992;167(4):425–33. [PubMed: 1403362]

16. Squires GR, Okouneff S, Ionescu M, Poole AR. The pathobiology of focal lesion development in aging human articular cartilage and molecular matrix changes characteristic of osteoarthritis. Arthritis and Rheumatism 2003;48(5):1261–70. [PubMed: 12746899]

17. Pritzker KP, Gay S, Jimenez SA, Ostergaard K, Pelletier JP, Revell PA, et al. Osteoarthritis cartilage histopathology: grading and staging. Osteoarthritis and Cartilage 2006;14(1):13–29. [PubMed: 16242352]

18. Hayes CW, Parellada JA. The magic angle effect in musculoskeletal MR imaging. Topics in Magnetic Resonance Imaging 1996;8(1):51–56. [PubMed: 8820094]

19. Xia Y, Farquhar T, Burton-Wurster N, Lust G. Origin of cartilage laminae in MRI. Journal of Magnetic Resonance Imaging 1997;7(5):887–894. [PubMed: 9307916]

20. Xia Y. Magic Angle Effect in MRI of Articular Cartilage - A Review. Investigative Radiology 2000;35 (10):602–621. [PubMed: 11041155]

21. Mosher TJ, Smith H, Dardzinski BJ, Schmithorst VJ, Smith MB. MR Imaging and T2 Mapping of Femoral Cartilage: In Vivo Determination of the Magic Angle Effect. American Journal of Roentgenology 2001;177:665–669. [PubMed: 11517068]

22. Poole AR, Rizkalla G, Ionescu M, Reiner A, Brooks E, Rorabeck C, et al. Osteoarthritis in the human knee: a dynamic process of cartilage matrix degradation, synthesis and reorganization. Agents Actions Suppl 1993;39:3–13. [PubMed: 8456642]

23. Xia Y, Moody J, Burton-Wurster N, Lust G. Quantitative In Situ Correlation Between Microscopic MRI and Polarized Light Microscopy Studies of Articular Cartilage. Osteoarthritis and Cartilage 2001;9(5):393–406. [PubMed: 11467887]

24. Alhadlaq H, Xia Y, Moody JB, Matyas J. Detecting Structural Changes in Early Experimental Osteoarthritis of Tibial Cartilage by Microscopic MRI and Polarized Light Microscopy. Annals of Rheumatic Diseases 2004;63(6):709–717.

25. Glaser C, Faber S, Eckstein F, Fischer H, Springer V, Heudorfer L, et al. Optimization and validation of a rapid high-resolution T1-w 3D FLASH water excitation MRI sequence for the quantitative assessment of articular cartilage volume and thickness. Magnetic Resonance Imaging 2001;19(2): 177–85. [PubMed: 11358655]

26. Nakanishi K, Tanaka H, Sugano N, Sato Y, Ueguchi T, Kubota T, et al. MR-based three-dimensional presentation of cartilage thickness in the femoral head. European Radiology 2001;11(11):2178–83. [PubMed: 11702157]

27. Hargreaves BA, Gold GE, Beaulieu CF, Vasanawala SS, Nishimura DG, Pauly JM. Comparison of new sequences for high-resolution cartilage imaging. Magnetic Resonance in Medicine 2003;49(4): 700–9. [PubMed: 12652541]

28. Gold GE, Hargreaves BA, Reeder SB, Vasanawala SS, Beaulieu CF. Controversies in protocol selection in the imaging of articular cartilage. Seminars in Musculoskeletal Radiology 2005;9(2): 161–72. [PubMed: 16044384]