Solid-State MRI for the Study of Calcified Tissues[#]

Felix W Wehrli
Department of Radiology
Perelman School of Medicine
University of Pennsylvania

Bone is a hierarchically organized composite biomaterial evolved so as to optimally fulfill its multiple functions ranging from weight-bearing and locomotion to serving as a store for calcium and phosphorus. Bone's major chemical constituents are an organic fraction, consisting predominantly of type-I collagen (~50% by volume), an inorganic or mineral fraction (~35%), made up of poorly mineralized nonstoichiometric calcium hydroxyl apatite, with the mineral crystals interspersed in the gaps between successive collagen fibrils (1). The balance is water, with its majority bound to collagen, and a smaller fraction occupying the bone's pore structure. The bone's compressive strength is largely conferred by the material's inorganic component whereas collagen that is responsible for the material's tensile strength. On a macrostructural level bone is about 80% compact (or cortical) and 20% trabecular. Cortical bone forms the shell encasing bone marrow and blood vessels, dominating the shaft of the extremities and femoral neck whereas trabecular bone, consisting of a meshwork on interconnected plates and rods, is dominant in the vertebrae, ribs and near the joints where stresses are multidirectional and tensile and torsional loading occurs.

Bone is a living tissue with its own blood supply and ability for self-repair through a process called 'remodeling', referring to the interplay of two types of cells: osteoblasts, the bone-forming, and osteoclasts, the bone-resorbing cells. A third type of cells, the osteocytes occupying small cavities on the order of 30 μm in diameter, act as pressure transducers providing signals to osteoblast to induce bone formation. Osteocytes are interconnected with each other through a system of channels, called canaliculi, about 100 nm in diameter. Cortical bone further is permeated by a network of much larger channels of 50-100μm diameter, carrying blood vessels, in contrast to the blood supply to trabecular bone, which is effected through the marrow's microvascular system.

The structural and physiologic organization of cortical bone substantially differs from its trabecular counterpart. With a porosity on the order of 5-20% it is far denser than trabecular bone, which typically has a pore volume fraction of 80% or greater. Water is the dominant chemical constituent present in the bone's pore space. However, a significant, typically larger, fraction of cortical bone water is collagen bound. Both fractions possess short T_2 and are thus *not detectable with conventional spin-echo or gradient-echo methods*. However, the emergence of what is now termed "ultra-short echo time (UTE)" MRI during the past decade has made detection (2) and quantification (3) of bone water possible. UTE MRI has generally proven useful to make heavily collagenated connective tissues such as articular cartilage, tendon, ligaments, and bone "visible" (4).

It was recognized early that the most common spatial encoding techniques based of phase encoding in the second dimension as in Cartesian sampling are generally not suited for imaging spins with very short transverse relaxation, as the delay imparted by the phase-encoding period entails prohibitive signal losses. Radial acquisition techniques generally meet the requirement for minimizing the delay δ between the end of the RF pulse and beginning of sampling to satisfy $\delta << T_2^*$. The second requirement is for the RF pulse duration to be short enough so as to minimize coherence losses during the pulse ($\tau_{RF} < T_2^*$) (5). Third, the sampling frequency bandwidth (BW) must be large enough so that for the total sampling time, $T_s \cong T_2^*$, as a means to minimize point-spread function (PSF) blurring.

For imaging calcified connective tissues a family of radial 2D and 3D k-space mapping techniques have emerged as favorites (2,6-8) even though other methods, such as SWIFT (9) have shown some merit as well.

[#] This syllabus material is drawn from a recent review article by the author (J Magn Reson 229: 35-48; 2013)

Pulse design, pulse sequences and reconstruction for UTE MRI have recently been reviewed (10), as have methods and applications specific to bone (11,12). 2D UTE, a radial encoding technique based on half-pulses not requiring slice gradient rephasing, was first described over two decades ago (13), but not re-examined until 10 years later, by researchers at Oxford University and the University of California in San Diego, in part spurred by advances in scanner hardware (2). This group of researchers (who coined the acronym UTE) recognized the method's potential for visualizing sub-millisecond T_2 tissues, in particular in conjunction with soft-tissue suppression techniques such as echo subtraction or inversion nulling (see, for instance, (4)). Notable in 2D UTE is the requirement for two acquisitions of each radial line with opposite polarity of the slice-selection gradients. In this manner, the imaginary signal components cancel upon summing of the two signals (14). 3D implementations are also being practiced, both a hybrid version with Cartesian sampling in the third dimension (7), as well as full 3D radial sampling (8). Lastly, rather than using ramp sampling, one can excite the spins in the presence of a constant encoding gradient (also referred to as 3D zero echo-time (ZTE) imaging (15,16)). Since this encoding scheme fails to capture the lowest spatial-frequency signals, alternative means are required to collect the missing samples, such as resampling that portion of k-space at much lower gradient amplitude (17) or via single-point mapping as in PETRA (pointwise encoding time reduction with radial acquisition) (18). Recent data suggest ZTE to provide significantly better SNR than does UTE (19). Nevertheless, a problem inherent to all 3D radial methods is the very large number of projections that are required, resulting in prohibitively long scan times unless significant undersampling is used, for example, in conjunction with compressed sensing.

Detection of calcified tissues, most typically cortical and trabecular bone, calcified cartilage, teeth or extra-osseous calcifications, studied with the techniques outlined above, is hampered by the signals of the surrounding soft tissues. Not only are the latters' spin densities far greater, their transverse relaxation times are one to two orders of magnitude longer. The need to selectively suppress the undesired signals has been recognized early and a variety of strategies have been offered. Most exploit the differential life times of the two proton species. In the simplest approach a second echo collected at $TE>>T_{2,short}$ is subtracted from the UTE signal (6) but this method may be sensitive to gradient-induced eddy currents and, of course, sacrifices SNR as all subtraction methods do. More effective approaches use saturation pulses that are long relative to T_2 of the fast-decaying spins of interest, leaving the short-T_2 protons largely unaffected (5). Various embodiments of the method are now in widespread use, including water and fat saturation consisting of successively applied frequency-selective saturation pulses (WASPI (17)) or dual-band saturation pulses (20). Single and double-inversion nulling have also been practiced. In order to simultaneously suppress soft tissue signals arising from fat and water Du et al applied adiabatic inversion pulses in succession, first on resonance with water and subsequently with the methylene proton chemical shift of triacyl glyceride (fat) in such a manner as to time the pulses so that the longitudinal magnetization of both components is nulled immediately prior to playing out the excitation half-pulse (21). In contrast, the short-T_2 protons of the bone water are saturated only by the inversion pulses. In a recent comparison of the various suppression techniques Li et al concluded that combination of dual-band saturation UTE with echo subtraction to provide good short-$\boldsymbol{T_2}$ SNR and CNR, albeit at the expense of greater sensitivity to B1 homogeneity. In distinction, IR-UTE was found to yield lower short-T_2 SNR efficiency while providing highly uniform short- T_2 contrast (20).

While mere visualization of protons that ordinarily elude detection by Cartesian imaging strategies is important in its own right as illustrated in the previous section, quantification of the water residing in the pore spaces of bone tissue versus that bound to the organic matrix, can provide new insight into the structural and molecular organization of the tissue (3,7,22-24). One approach is based on calibration of the signal with a reference sample of known proton concentration and similar T_2 relaxation characteristics (3,22). The authors in (22) validated their method in specimens of human cortical bone by means of deuterium exchange techniques by measuring the native water expelled from the bone after prolonged immersion in D_2O in comparison to measurements by UTE.

One complication that affects the clinical value of bulk bone water measurements is that it comprises both pore and bound water. Loss of osteoid as in osteoporosis, reduces bound water (which scales with matrix density), while pore water increases. Even though the gain of pore water is greater than the loss of bound

water, bulk bone water is an imperfect surrogate of pore water. Non-image based measurements based on T_2 relaxometry (25) and deuterium NMR (26) support the notion that a greater fraction of bone water is collagen bound as opposed to pore-resident, calling for methods allowing separation of the two water pools. In (27) the authors hypothesized that pore water, by virtue of its greater mobility, should have longer T_2*. The authors showed in bovine cortical bone that the T_2* decay fits a bicomponent model yielding fractions on the order of 80 and 20% with T_2* time constants of 300μs and 2ms, respectively, which they attributed to bound and free (i.e. pore) water. One potential flaw of the T_2* relaxometric approach is the wide distribution of pore water T_2*, as well as its shortening with increasing field strength. The latter is due to inhomogeneous broadening of the resonance caused by the bone's internal field (28). Therefore, methods based on T_2 selective RF pulses may be preferable (29). One such approach is based on measurement of the signal with and without long-T_2 suppression. The resulting suppression ratio (fraction of unsuppressed to suppressed signal) has been shown to be a strong predictor of porosity (30). The underlying rationale is that with an increase in pore size T_2 increases as well, resulting in enhanced suppression.

Lastly, solid-state MRI may also have potential to gain detailed insight into the bone's mineral properties. Bone mineral density (BMD) is commonly assessed by X-ray based modalities, either dual-energy X-ray absorptiometry or quantitative computed tomography, which provide a density measure expressed in g/cm^2 or g/cm^3, respectively. Both methods use ionizing radiation even though the former's dose is minimal. The density measurements are non-specific and are apparent in the sense that the resolution is such that reduced tissue mineralization (as in osteomalacia) could not be distinguished from bone of greater microporosity. This ambiguity, it has been argued (31), precludes distinction of osteoporosis in which bone becomes porous but is generally normally mineralized, from osteomalacia, a disorder in which the bone is hypomineralized, typically due to vitamin D deficiency. The same group of authors reasoned that true mineralization density (variably also denoted 'degree of mineralization of bone', DMB (32) or 'extent of bone mineralization' (33)) could be obtained by quantifying matrix volume (i.e. the fractional volume of bone occupied by bone tissue).

While the path delineated above toward noninvasive quantification of DMB is plausible, the method is fraught with difficulties. Chief among these are the extremely unfavorable relaxation properties of ^{31}P in bone mineral with T_2/T_1 ratios on the order of 10^{-5} - 10^{-6} depending on field strength (34) (compared to about 0.02 for protons in soft tissue). Nevertheless, 3D radial ^{31}P imaging in animal models has yielded unique information on mineralization in model systems of osteomalacia (35) and response to antiresorptive treatment (36). The very short T_2 of ^{31}P in bone mineral and its further shortening with field strength (reaching 120μs at 7T) is likely a consequence of the significant chemical shift anisotropy of hydroxyl apatite (~40ppm) (37). In spite of these adversities, recent work in human cortical bone *ex vivo* suggests that noninvasive quantification of DMB in vivo by ^{31}P ZTE methods may be feasible. Lastly, Wu et al (38) recently have been able to acquire ^{31}P images of the human wrist in vivo at 3T field strength on a clinical scanner with a custom-built birdcage transmit-receive coil.

In summary, solid-state MRI methods have already demonstrated their potential for the study of mineralized tissues in humans and translation of both ^{1}H and ^{31}P UTE and ZTE to studies in patients appears feasible.

1. Ritchie R, Buehler M, Hansma P. Plasticity and toughness of bone. Phys Today 2009:41-47.
2. Robson MD, Gatehouse PD, Bydder M, Bydder GM. Magnetic resonance: an introduction to ultrashort TE (UTE) imaging. J Comput Assist Tomogr 2003;27(6):825-846.
3. Techawiboonwong A, Song HK, Wehrli FW. In vivo MRI of submillisecond T(2) species with two-dimensional and three-dimensional radial sequences and applications to the measurement of cortical bone water. NMR Biomed 2007;21(1):59-70.
4. Robson MD, Bydder GM. Clinical ultrashort echo time imaging of bone and other connective tissues. NMR Biomed 2006;19(7):765-780.
5. Sussman MS, Pauly JM, Wright GA. Design of practical T2-selective RF excitation (TELEX) pulses. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 1998;40(6):890-899.

6. Reichert IL, Robson MD, Gatehouse PD, He T, Chappell KE, Holmes J, Girgis S, Bydder GM. Magnetic resonance imaging of cortical bone with ultrashort TE pulse sequences. Magnetic resonance imaging 2005;23(5):611-618.
7. Rad HS, Lam SC, Magland JF, Ong H, Li C, Song HK, Love J, Wehrli FW. Quantifying cortical bone water in vivo by three-dimensional ultra-short echo-time MRI. NMR in Biomedicine 2011;24(7):855-864.
8. Du J, Bydder M, Takahashi AM, Carl M, Chung CB, Bydder GM. Short T2 contrast with three-dimensional ultrashort echo time imaging. Magnetic resonance imaging 2011;29(4):470-482.
9. Idiyatullin D, Corum C, Park JY, Garwood M. Fast and quiet MRI using a swept radiofrequency. J Magn Reson 2006;181(2):342-349.
10. Pauly JM. Selective Excitation for Ultrashort Echo Time Imaging. Encyclopedia of Magnetic Resonance: John Wiley & Sons, Ltd; 2012.
11. Wehrli FW. Image-based Assessment of Cortical Bone. Encyclopedia of Magnetic Resonance: John Wiley & Sons, Ltd; 2012.
12. Wehrli FW. Magnetic resonance of calcified tissues. Journal of magnetic resonance 2013;229:35-48.
13. Bergin CJ, Pauly JM, Macovski A. Lung parenchyma: projection reconstruction MR imaging. Radiology 1991;179(3):777-781.
14. Pauly J, Conolly C, Macovski A. Supression of long-T2 components for short T2 imaging. 1992; New York. p 145.
15. Weiger M, Pruessmann KP, Bracher AK, Kohler S, Lehmann V, Wolfram U, Hennel F, Rasche V. High-resolution ZTE imaging of human teeth. NMR Biomed 2012;25(10):1144-1151.
16. Weiger M, Pruessmann KP, Hennel F. MRI with zero echo time: hard versus sweep pulse excitation. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2011;66(2):379-389.
17. Wu Y, Dai G, Ackerman JL, Hrovat MI, Glimcher MJ, Snyder BD, Nazarian A, Chesler DA. Water- and fat-suppressed proton projection MRI (WASPI) of rat femur bone. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2007;57(3):554-567.
18. Grodzki DM, Jakob PM, Heismann B. Ultrashort echo time imaging using pointwise encoding time reduction with radial acquisition (PETRA). Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2012;67(2):510-518.
19. Seifert AC, Li C, Rajapakse CS, Bashoor-Zadeh M, Bhagat YA, Wright AC, Zemel BS, Zavaliangos A, Wehrli FW. Bone mineral 31P and matrix-bound water densities measured by solid-state 31P and 1H MRI. NMR in Biomedicine 2014;27(7):739-748.
20. Li C, Magland JF, Rad HS, Song HK, Wehrli FW. Comparison of optimized soft-tissue suppression schemes for ultrashort echo time MRI. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2011;68(3):680-689.
21. Du J, Takahashi AM, Bae WC, Chung CB, Bydder GM. Dual inversion recovery, ultrashort echo time (DIR UTE) imaging: creating high contrast for short-T(2) species. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2010;63(2):447-455.
22. Techawiboonwong A, Song HK, Leonard MB, Wehrli FW. Cortical bone water: in vivo quantification with ultrashort echo-time MR imaging. Radiology 2008;248(3):824-833.
23. Biswas R, Bae W, Diaz E, Masuda K, Chung CB, Bydder GM, Du J. Ultrashort echo time (UTE) imaging with bi-component analysis: bound and free water evaluation of bovine cortical bone subject to sequential drying. Bone 2012;50(3):749-755.
24. Du J, Hermida JC, Diaz E, Corbeil J, Znamirowski R, D'Lima DD, Bydder GM. Assessment of cortical bone with clinical and ultrashort echo time sequences. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2012.
25. Horch RA, Nyman JS, Gochberg DF, Dortch RD, Does MD. Characterization of 1H NMR signal in human cortical bone for magnetic resonance imaging. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2010;64(3):680-687.
26. Ong HH, Wright AC, Wehrli FW. Deuterium nuclear magnetic resonance unambiguously quantifies pore and collagen-bound water in cortical bone. J Bone Miner Res 2012;27(12):2573-2581.
27. Diaz E, Chung CB, Bae WC, Statum S, Znamirowski R, Bydder GM, Du J. Ultrashort echo time spectroscopic imaging (UTESI): an efficient method for quantifying bound and free water. NMR Biomed 2012;25(1):161-168.
28. Horch RA, Gochberg DF, Nyman JS, Does MD. Clinically compatible MRI strategies for discriminating bound and pore water in cortical bone. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2012.
29. Manhard MK, Horch RA, Harkins KD, Gochberg DF, Nyman JS, Does MD. Validation of quantitative bound- and pore-water imaging in cortical bone. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2014;71(6):2166-2171.

30. Li C, Seifert AC, Rad HS, Bhagat YA, Rajapakse CS, Sun W, Lam SC, Wehrli FW. Cortical bone water concentration: dependence of MR imaging measures on age and pore volume fraction. Radiology 2014;272(3):796-806.
31. Wu Y, Ackerman JL, Chesler DA, Graham L, Wang Y, Glimcher MJ. Density of organic matrix of native mineralized bone measured by water- and fat-suppressed proton projection MRI. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2003;50(1):59-68.
32. Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. Bone 2000;27(5):687-694.
33. Cao H, Ackerman JL, Hrovat MI, Graham L, Glimcher MJ, Wu Y. Quantitative bone matrix density measurement by water- and fat-suppressed proton projection MRI (WASPI) with polymer calibration phantoms. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2008;60(6):1433-1443.
34. Seifert AC, Wright AC, Wehrli SL, Ong HH, Li C, Wehrli FW. 31P NMR Relaxation of Cortical Bone Mineral at Multiple Magnetic Field Strengths and Levels of Demineralization. NMR in Biomedicine 2013;26(9):1158-1166.
35. Anumula S, Magland J, Wehrli SL, Zhang H, Ong H, Song HK, Wehrli FW. Measurement of phosphorus content in normal and osteomalacic rabbit bone by solid-state 3D radial imaging. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2006;56(5):946-952.
36. Anumula S, Wehrli SL, Magland J, Wright AC, Wehrli FW. Ultra-short echo-time MRI detects changes in bone mineralization and water content in OVX rat bone in response to alendronate treatment. Bone 2010;46(5):1391-1399.
37. Wu Y, Glimcher MJ, Rey C, Ackerman JL. A unique protonated phosphate group in bone mineral not present in synthetic calcium phosphates. Identification by phosphorus-31 solid state NMR spectroscopy. J Mol Biol 1994;244:423-435.
38. Wu Y, Reese TG, Cao H, Hrovat MI, Toddes SP, Lemdiasov RA, Ackerman JL. Bone mineral imaged in vivo by (31) P solid state MRI of human wrists. Journal of magnetic resonance imaging : JMRI 2011;34(3):623-633.