**What Is Tissue Microstructure & Why Might We Want to Measure It?**
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MR images in practice portray the average “macroscopic” NMR properties of (mainly) mobile water from within individual voxels whose linear dimensions are typically of order hundreds - thousands of microns, determined (mainly) by the available signal to noise ratio of image acquisition. Each voxel thus contains thousands to millions (or more) of cells, and each cell may contain about $10^{10}$ (or more) protein, sugar and lipid molecules, as well as the water that produces the signal for MR images. Clearly, therefore, conventional MRI (without high-resolution MR spectroscopy) is not well suited to provide detailed, specific information about tissue composition, or to be able to identify subtle, specific molecular changes, and at first glance only relatively crude estimates can be derived of tissue structure. However, a variety of approaches have been developed that allow information to be obtained from proton MRI about the heterogeneity of tissue proton properties and their micro-anatomic features and arrangements on scales much below voxel dimensions, permitting the derivation of parameters that can be used for quantitative tissue characterization. Decreasing the voxel size in conventional MR imaging introduces contrast based on resolving the spatial heterogeneity of NMR properties across a region, whereas sub-voxel tissue characterization assumes there are water populations and interactions that occur on much finer scales that defy precise localization but whose statistical properties can be accurately derived from within a defined sample volume. Examples of such approaches include quantitative magnetization transfer and multi-component relaxation measurements, from which the sizes of sub-populations of protons and their exchange properties may be derived; techniques that are sensitized to the self-diffusion of tissue water, which can reveal information on the scales of restrictions or hindrances to free diffusion and their anisotropy even below the scale of single cells; and hybrid methods that combine these or which incorporate other descriptors such as chemical shift and exchange rates without the need for spectral resolution. Appropriate measurements and models for their interpretation can be used to obtain novel insights into variations between tissues and their changes with pathological and other processes. These methods have found applications in several tissues including nerve, tumor, muscle and bone.