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Diffusion Sensitive MR in Biological Systems: Insights, Puzzles, Pitfalls.

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1. The Good: the Great Promise of Diffusion MR *in Vivo.*

Diffusion ^{1}H magnetic resonance (MR) monitoring of the incoherent displacement motion of water can typically be made sensitive to rms displacements over a range of 1-10 microns. It follows that diffusion ^{1}H MR of water reports on displacement barriers (hindrances and restrictions) of similar length scales and, thus, holds great promise for quantifying the microstructural architecture of living systems and changes therein in the face of physiologic and pathologic challenge. Indeed, diffusion sensitive MR has become a valued component of many research and clinical protocols at hospitals and institutions world-wide.

2. The Bad: the MR Diffusion Signal *in Vivo* is Relatively Uninformative.

Nevertheless, except in systems of relatively simple geometries, the MR "diffusion signal" is generally uninformative, characterized by a monotonic decay in q-space or b-value. While the MR diffusion signal is often of empirical value, for example, in detecting regions of brain injury (stroke), extracting quantitative microstructural information and changes therein is challenging.

3. The Ugly: Quantification *via* Biophysical Models of the MR Diffusion Signal.

An approach employed by our laboratory, and others, has been to reduce the nearly intractable geometric complexities of tissue microstructure to a few salient features and then to model the MR diffusion signal as a function of parameters characterizing these features [1-4]. Validation of such modeling can take a variety of forms, for example: (i) constructing *in silico* systems where "ground truth" is known, (ii) using cell cultures where light microscopy can measure relevant barrier distances and geometries, (iii) employing genetically engineered or otherwise physiologically challenged laboratory animal models where specific hypothesized effectors of water diffusion are modulated, and (iv) tracking exogenous or endogenous molecules and ions as compartment-specific/selective secondary (inferential) reporters of water diffusion.

4. *Caveat Emptor*: MR Diffusion Data and Biophysical Models.

This presentation will discuss diffusion MR in the context of applications to intact biological systems and will examine strategies to develop a more quantitative interpretation of the biophysical determinants that govern the MR diffusion signal in living systems. While advances in quantitative interpretation of the MR diffusion signal *in vivo* have been made, seemingly simple questions – such as why the diffusion coefficient decreases rapidly and markedly in brain injury – remain to be answered. Further, the longevity of conceptually appealing but generally incorrect biophysical models of MR diffusion phenomena *in vivo* provides a textbook lesson regarding the manner in which simple, easily understood ideas can dominate the intellectual landscape long after the introduction of strong contradictory evidence.

5. References.

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[3]. J.J.H. Ackerman and J.J. Neil, Biophysics of Diffusion in Cells, in *Diffusion MRI: Theory, Methods and Applications* (D Jones, ed.), Chapter 8, Pages 110-124, Oxford University Press, Oxford, 2010.

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