

MRI began as a method of imaging soft tissue, with the goal of using the relaxation properties and proton concentrations to generate tissue and cancer contrast.^{1; 8; 12; 14; 15}

This talk will give an introduction to some of the physiology and biochemistry discussed in the talks. Studies of energy metabolism including ^{31}P ^{6; 10} and ^1H (for lactate)⁷ were among the first uses of in vivo spectroscopy. However much more is possible. Many additional applications have grown for spectroscopy as multinuclear and contrast agent research develops. More metabolic processes including aspects of lipid metabolism and ionic regulation are now studied

I will introduce glycolysis, lactate metabolism and mitochondrial energy metabolism, some lipid biochemistry and ion channel regulation. I will include the Pasteur effect (whereby lactate production decreases in the presence of oxygen) and the Warburg effect (where lactate production is high in the presence of oxygen). The relationship between intracellular and extracellular pH will be discussed, especially in the context of tumor metabolism. This is relevant given the interesting developments in pH sensitive MR for cancer studies.²²

The regulation of pH is a good transition into the regulation of cerebral blood flow, perfusion and neurovascular coupling. These are all inter-linked when it comes to the interpretation of fMRI. I will discuss regulation of cerebral blood flow and the potential link to neuronal functional activation. In brain, unlike in other organs, blood flow increases with activation such that brain oxygen levels increase¹⁶ and deoxyhemoglobin is reduced.^{9; 11}

It can be argued that mapping of brain function with MRI began in 1990 with the description of the BOLD effect and examples in animal models^{17; 18}. This was rapidly followed in 1991 and 1992 with MRI's of human brain function.^{35; 13} The principles using the bold effect relied on earlier studies showing the changes that deoxyhemoglobin has on susceptibility and blood relaxation times including work by Pauling²⁰ and Thulborn.²¹

Perfusion, based on the Oxford English Dictionary, is the passage of a liquid, especially blood, through an organ or tissue. Wikipedia notes that in physiology, "perfusion is the process of a body delivering blood to a capillary bed in its biological tissue". A central theme is that the fluid is within the organ. We commonly refer to perfusion imaging as that imaging the flow of fluid through the microvasculature of the capillary bed. This is in contrast to whole organ blood delivery, usually measured in a large vessel, and usually termed "flow" imaging. I will introduce the concepts of large vessel flow and microvascular perfusion and introduce aspects of blood flow regulation in brain. One of the interesting historical arguments links perivascular pH with flow regulation² which relates to the high sensitivity of cerebral blood flow to changes in CO_2 ¹⁹

The aim of this talk is to introduce physiological and biochemical concepts that will help understand and put into perspective the MR applications discussed in this session.

REFERENCES

1. Andrew, E. R. (1980) N.m.r. imaging of intact biological systems. Philos Trans R Soc Lond B Biol Sci **289**(1037): 471-81.
2. Apkon, M. and W. F. Boron (1995) Extracellular and intracellular alkalinization and the constriction of rat cerebral arterioles.[erratum appears in J Physiol (Lond) 1995 Aug 1;486(Pt 3):795]. J. Physiol. **484**(Pt 3): 743-53.

3. Bandettini, P. A., E. C. Wong, R. S. Hinks, R. S. Tikofsky and J. S. Hyde (1992) Time course EPI of human brain function during task activation. Magn Reson Med **25**(2): 390-7.
4. Belliveau, J. W., D. N. Kennedy, R. C. McKinstry, B. R. Buchbinder, R. M. Weisskoff, M. S. Cohen, J. M. Vevea, T. J. Brady and B. R. Rosen (1991) Functional mapping of the human visual cortex by magnetic resonance imaging. Science **254**: 716-717.
5. Blamire, A. M., S. Ogawa, K. Ugurbil, D. Rothman, G. McCarthy, J. M. Ellermann, F. Hyder, Z. Rattner and R. G. Shulman (1992) Dynamic mapping of the human visual cortex by high-speed magnetic resonance imaging. Proc Natl Acad Sci U S A **89**(22): 11069-73.
6. Bottomley, P. A., K. Kogure, R. Namon and O. F. Alonso (1982) Cerebral energy metabolism in rats studied by phosphorus nuclear magnetic resonance using surface coils. Magn Reson Imaging **1**(2): 81-5.
7. Cox, I. J. (1996) Development and applications of in vivo clinical magnetic resonance spectroscopy. Prog Biophys Mol Biol **65**(1-2): 45-81.
8. Damadian, R. (1971) Tumor detection by nuclear magnetic resonance. Science. **171**(976): 1151-3.
9. Dunn, A. K., A. Devor, H. Bolay, M. L. Andermann, M. A. Moskowitz, A. M. Dale and D. A. Boas (2003) Simultaneous imaging of total cerebral hemoglobin concentration, oxygenation, and blood flow during functional activation. Optics Letters. **28**(1): 28-30.
10. Hoult, D. I., S. J. W. Busby and D. G. Gadian (1974) Observation of tissue metabolites using ³¹P NMR. Nature **252**: 285-287.
11. Kleinschmidt, A., H. Obrig, M. Requardt, K. D. Merboldt, U. Dirnagl, A. Villringer and J. Frahm (1996) Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. J Cereb Blood Flow Metab **16**(5): 817-26.
12. Kramer, D. M., J. S. Schneider, A. M. Rudin and P. C. Lauterbur (1981) True three-dimensional nuclear magnetic resonance zeugmatographic images of a human brain. Neuroradiology. **21**(5): 239-44.
13. Kwong, K. K., J. W. Belliveau, D. A. Chesler, I. E. Goldberg, R. M. Weisskoff, B. P. Poncelet, D. N. Kennedy, B. E. Hoppel, M. S. Cohen, R. Turner, H.-M. Cheng, T. J. Brady and B. R. Rosen (1992) Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci U S A **89**(12): 5675-5679.
14. Lauterbur, P. C. (1973) Image formation by induced local interactions: examples employing nuclear magnetic resonance. Nature Lond. **242**: 190-191.
15. Lauterbur, P. C. (1980) Progress in n.m.r. zeugmatography imaging. Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences. **289**(1037): 483-7.
16. Leniger-Follert, E. and D. W. Lübbers (1976) Behavior of microflow and local PO₂ of the brain cortex during and after direct electrical stimulation. A contribution to the problem of metabolic regulation of microcirculation in the brain. Pflugers Arch. **366**(1): 39-44.
17. Moonen, C. T., C. M. van Zijl, J. A. Frank, D. Le Bihan and E. C. Becker (1990) Functional magnetic resonance imaging in medicine and physiology. Science **250**: 53-61.
18. Ogawa, S., T. M. Lee, A. R. Kay and D. W. Tank (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A **87**(24): 9868-72.
19. Pandit, J. J., R. M. Mohan, N. D. Paterson and M. J. Poulin (2003) Cerebral blood flow sensitivity to CO₂ measured with steady-state and Read's rebreathing methods. Respir Physiol Neurobiol **137**(1): 1-10.
20. Pauling, L. and C. Coryell (1936) The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. Proc Natl Acad Sci **22**: 210.
21. Thulborn, K. R., J. C. Waterton, P. M. Mathews and G. K. Radda (1982) Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. Biochim Biophys Acta **714**: 265-270.

22. Zhang, X., Y. Lin and R. J. Gillies (2010) Tumor pH and its measurement. J Nucl Med **51**(8): 1167-70.