CURRICULUM VITÆ

Professor **Paul Tofts** DPhil FIPEM

updated October 1st 2005 extracted from full CV

Appendix 5 - Research Activity

1. **Ionising radiation SPECT and CT RPMS 1975-8 and UCL 1978-80**
   At the Royal Postgraduate Medical School, Hammersmith Hospital, with the MRC cyclotron unit, I used radioisotope images to measure lung function, and to tomographically image the liver. Radioactive gases from the MRC Cyclotron Unit were imaged using a gamma camera. I designed a CT machine[1,2] to image the heart. At UCL Medical physics I used one of the first CT machines (EMI 5005 whole body scanner) to measure muscle size[3] and composition in muscular dystrophy, and bone mineral content in osteoporosis.

2. **In-vivo NMR spectroscopy of neonates at UCL 1978-85**
   The first NMR spectrometer capable of studying humans (neonatal brains and adult limb muscles) was installed at UCL medical physics by Oxford Instruments. I constructed the surface coil[4] for the first human brain spectra, collected from premature babies at University College Hospital[5]. I made the first measurements of metabolite concentration[6,7] *in vivo*, in rat brain and muscle. In the first issue of the new journal NMR in Biomedicine, my review on measuring metabolite concentrations was the opening article[8].

3. **MS and permeability from Gd MRI contrast agent at IoN Queen Square 1985-99**
   In 1985 I joined the new MS NMR Research Unit at Queen Square, where Multiple Sclerosis lesions could be visualised using the new NMR imaging technique. The total volume of MS lesion could be measured[9] and used as an indicator of disease severity and progression. The new contrast agent Gd-DTPA was being used to detect leakage in the blood-brain barrier (BBB) in MS lesions. I used dynamic MRI of Gd to measure BBB (capillary) permeability[10,11]. This consists of repeated imaging using a T_1-weighted sequence, and measuring the time course of the uptake of Gd. A mathematical compartmental model is then fitted to give estimates of the permeability and extracellular space. Aspects of the model were refined[12,13]. This model was reconciled with others[14,15] and an international agreement was reached on interpretation and nomenclature[16]. The model has since been applied extensively in cancer[17-19], to quantify tumour vascularity, and is now sometimes known as the 'Tofts model'. This measurement can be combined with blood volume[20]

4. **Magnetisation Transfer (MT), diffusion and other new MR parameters 1995-2005**
   The phenomenon of MT enables measurements to be made on normally invisible restricted protons located in cell structures. These are often more specific for biological change than conventional MRI. Initial measurements were with the Magnetisation Transfer Ratio, which at first showed large inter-centre variation[21]. The causes of differences between measurements made on different MRI scanners have now been analysed and largely removed, enabling multi-centre studies to be made[22]. A more fundamental way of measuring the properties of tissue (Quantitative MT) has been developed more recently[23,24], where the fraction of restricted protons is obtained explicitly, and this shows promise in being more specific for biological change[25]. A 3D volume acquisition gives improved signal-to-noise ratio and spatial resolution[26].

   The diffusion of water is very sensitive to the presence or absence of biological barriers at the cellular level, and measurements of the apparent diffusion coefficient enable microscopic

biological changes to be detected[27,28] even though the spatial resolution of the MRI machine is about 1mm.

Blood flow can be measured accurately using arterial spin labelling[29], and normal intra-subject variation can be observed[30]. In MS, acute lesions show increased blood flow[31].
There are a number of structural parameters which can be extracted from MRI images. These include the obvious ones such as size and volume, and the more subtle ones such as texture[32]. Histograms of large volumes of tissue are exquisitely sensitive to subtle changes in normal-appearing tissue[33 34] (after a common artefact in their generation had been solved[35]), and multi-centre performance can be good[36] .

5. Quantification - a new paradigm in MRI 1978-2005

After the initial successes in measuring metabolite concentration and capillary permeability, it was clear that a paradigm change in the way that MR machines are used was appropriate. A move from the *MRI-camera* to the *MR-scientific-instrument* would allow a whole range of quantities to be measured in the living body. There was increasing interest from clinicians (both in academia and pharmaceutical companies) in measuring the effects of disease and its progression, and the effects of drug treatments in clinical trials. The first book on the subject was designed, a range of international authors agreed to contribute, and in 2003 *Quantitative MRI: measuring changes caused by disease* was published by Wiley[37]. The reviews were excellent, it won the BMA Radiology book prize, and went paperback. ISMRM (the International Society for Magnetic Resonance in Medicine) asked for a course on the subject. A new topic in medicine had been born.

Individual patient treatment (for example in cancer) could include quantitative imaging to assess what type of treatment would be effective (e.g. chemotherapy, radiotherapy, surgery etc), and ongoing imaging to measure response to treatment (not only has the tumour decreased in size?, but also has it lost its ability to grow?) and whether an alternative was likely to be more suitable.

Many aspects of the physical MR instrument were understood and characterised. Phantoms (test objects) were developed[38 39 40], and programs of Quality Assurance set up[41,42]. Image intensity nonuniformity was understood[43,44] and corrected[45,46]. Small objects can sometimes be characterised without partial volume error[47]. The factors which must be controlled in order to carry out multi-centre studies were identified[22,48,49]. Accurate ways of measuring MR parameters in the presence of the inevitable imperfections were developed[50].

6. Quantitative applications in AD, epilepsy, gliomas, SLE and retina 1995-2005

With the success of the quantitative techniques, it became easier to interest clinicians outside MS in collaborating. The optimised techniques, with established reliability and normative data, could easily be used in other neurological diseases. On the new epilepsy imager, MT and the T_2 relaxation time were found to be abnormal[51,52]. In Neuropsychiatric SLE subtle changes in the MT properties of normal-appearing brain were seen[53]. Retinal disease could be characterised by the leakage of Gd from capillaries[54] and retinal oxygenation can also be measured noninvasively[55,56]. Recent work has shown that in gliomas the tumour type and prognosis can be predicted from the MRI Gd and diffusion behaviour. In Alzheimer's Disease the hippocampal restricted proton concentration decreases in line with cognitive function. Post-mortem studies of MS tissue[57] enable the relationship between MR and biological changes to be clarified.

Reference List

1. Gore JC, Tofts PS. Statistical limitation in computed tomography. Phys Med Biol 1978; 23(6):1176-1182.
2. Gore JC, Tofts PS. Absolute values of attenuation coefficient in computed tomography. Phys Med Biol 1979;

24:828-830.
3. Grindrod S, Tofts P, Edwards R. Investigation of human skeletal muscle structure and composition by X-ray computerised tomography. Eur J Clin Invest 1983; 13(6):465-468.
4. Tofts PS, Cady EB, Delpy DT, Costello AM, Hope PL, Reynolds EO, Wilkie DR, Gould SJ, Edwards D. Surface coil NMR spectroscopy of brain. Lancet 1984; 323(8374):459.
5. Cady EB, Costello AM, Dawson MJ, Delpy DT, Hope PL, Reynolds EO, Tofts PS, Wilkie DR. Non-invasive investigation of cerebral metabolism in newborn infants by phosphorus nuclear magnetic resonance spectroscopy. Lancet 1983; 1(8333):1059-1062.
6. Wray S, Tofts PS. Direct in vivo measurement of absolute metabolite concentrations using 31P nuclear magnetic resonance spectroscopy. Biochim Biophys Acta 1986; 886(3):399-405.
7. Tofts PS, Wray S. Noninvasive measurement of molar concentrations of 31P metabolites in vivo, using surface coil NMR spectroscopy. Magn Reson Med 1988; 6(1):84-86.
8. Tofts PS, Wray S. A critical assessment of methods of measuring metabolite concentrations by NMR spectroscopy. NMR Biomed 1988; 1(1):1-10.
9. Wicks DA, Tofts PS, Miller DH, du Boulay GH, Feinstein A, Sacares RP, Harvey I, Brenner R, McDonald WI. Volume measurement of multiple sclerosis lesions with magnetic resonance images. A preliminary study. Neuroradiology 1992; 34(6):475-479.
10. Tofts PS, Kermode AG. Blood brain barrier permeability in multiple sclerosis using labelled DTPA with PET, CT and MRI. J Neurol Neurosurg Psychiatry 1989; 52(8):1019-1020.
11. Tofts PS, Kermode AG. Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts. Magn Reson Med 1991; 17(2):357-367.
12. Tofts PS, Berkowitz BA. Rapid measurement of capillary permeability using the early part of the dynamic Gd-DTPA MRI enhancement curve. J Magn Reson series B 1993; 102:129-136.
13. Tofts PS, Berkowitz BA. Measurement of capillary permeability from the Gd enhancement curve: a comparison of bolus and constant infusion injection methods. Magn Reson Imaging 1994; 12(1):81-91.
14. Larsson HB, Tofts PS. Measurement of blood-brain barrier permeability using dynamic Gd-DTPA scanning--a comparison of methods. Magn Reson Med 1992; 24(1):174-176.
15. Tofts PS. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. J Magn Reson Imaging 1997; 7(1):91-101.
16. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, Larsson HB, Lee TY, Mayr NA, Parker GJ, Port RE, Taylor J, Weisskoff RM. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. J Magn Reson Imaging 1999; 10(3):223-232.
17. Tofts PS, Berkowitz B, Schnall MD. Quantitative analysis of dynamic Gd-DTPA enhancement in breast tumors using a permeability model. Magn Reson Med 1995; 33(4):564-568.
18. Leach MO, Brindle KM, Evelhoch JL, Griffiths JR, Horsman MR, Jackson A, Jayson GC, Judson IR, Knopp MV, Maxwell RJ, McIntyre D, Padhani AR, Price P, Rathbone R, Rustin GJ, Tofts PS, Tozer GM, Vennart W, Waterton JC, Williams SR, Workman P. The assessment of antiangiogenic and antivascular therapies in early-stage clinical trials using magnetic resonance imaging: issues and recommendations. Br J Cancer 2005; 92(9):1599-1610.
19. Dyke JP, Panicek DM, Healey JH, Meyers PA, Huvos AG, Schwartz LH, Thaler HT, Tofts PS, Gorlick R, Koutcher JA, Ballon D. Osteogenic and Ewing sarcomas: estimation of necrotic fraction during induction chemotherapy with dynamic contrast-enhanced MR imaging. Radiology 2003; 228(1):271-278.
20. Johnson G, Wetzel SG, Cha S, Babb J, Tofts PS. Measuring blood volume and vascular transfer constant from dynamic, T(2)*-weighted contrast-enhanced MRI. Magn Reson Med 2004; 51(5):961-968.
21. Berry I, Barker GJ, Barkhof F, Campi A, Dousset V, Franconi JM, Gass A, Schreiber W, Miller DH, Tofts PS. A multicenter measurement of magnetization transfer ratio in normal white matter. J Magn Reson Imaging 1999; 9(3):441-446.
22. Barker GJ, Schreiber W, Gass A, Ranjeva JP, Campi A, van Waesberghe JH, Franconi JM, Watt HC, Tofts PS. A standardised method for measuring Magnetisation Transfer Ratio on MR imagers from different manufacturers - the EuroMT sequence. MAGMA 2005; in press.
23. Ramani A, Dalton C, Miller DH, Tofts PS, Barker GJ. Precise estimate of fundamental in-vivo MT parameters in human brain in clinically feasible times. Magn Reson Imaging 2002; 20(10):721-731.
24. Tozer D, Ramani A, Barker GJ, Davies GR, Miller DH, Tofts PS. Quantitative magnetization transfer mapping of bound protons in multiple sclerosis. Magn Reson Med 2003; 50(1):83-91.
25. Davies GR, Ramani A, Dalton CM, Tozer DJ, Wheeler-Kingshott CA, Barker GJ, Thompson AJ, Miller DH, Tofts PS. Preliminary magnetic resonance study of the macromolecular proton fraction in white matter: a potential marker of myelin? Mult Scler 2003; 9(3):246-249.
26. Cercignani M, Symms MR, Schmierer K, Boulby PA, Tozer DJ, Ron M, Tofts PS, Barker GJ. Three-dimensional quantitative magnetisation transfer imaging of the human brain. Neuroimage 2005; 27(2):436-441.
27. Clark CA, Barker GJ, Tofts PS. Magnetic resonance diffusion imaging of the human cervical spinal cord in vivo. Magn Reson Med 1999; 41(6):1269-1273.

28. Horsfield MA, Lai M, Webb SL, Barker GJ, Tofts PS, Turner R, Rudge P, Miller DH. Apparent diffusion coefficients in benign and secondary progressive multiple sclerosis by nuclear magnetic resonance. Magn Reson Med 1996; 36(3):393-400.
29. Parkes LM, Tofts PS. Improved accuracy of human cerebral blood perfusion measurements using arterial spin labeling: accounting for capillary water permeability. Magn Reson Med 2002; 48(1):27-41.
30. Parkes LM, Rashid W, Chard D, Tofts PS. Normal cerebral perfusion measurements using arterial spin labelling; reproducibility, stability, age and gender effects. submitted 2003.
31. Rashid W, Parkes LM, Ingle GT, Chard DT, Toosy AT, Altmann DR, Symms MR, Tofts PS, Thompson AJ, Miller DH. Abnormalities of cerebral perfusion in multiple sclerosis. J Neurol Neurosurg Psychiatry 2004; 75(9):1288-1293.
32. Mathias JM, Tofts PS, Losseff NA. Texture analysis of spinal cord pathology in multiple sclerosis. Magn Reson Med 1999; 42(5):929-935.
33. Dehmeshki J, Ruto AC, Arridge S, Silver NC, Miller DH, Tofts PS. Analysis of MTR histograms in multiple sclerosis using principal components and multiple discriminant analysis. Magn Reson Med 2001; 46(3):600-609.
34. Dehmeshki J, Barker GJ, Tofts PS. Classification of disease subgroup and correlation with disease severity using magnetic resonance imaging whole-brain histograms: application to magnetization transfer ratios and multiple sclerosis. IEEE Trans Med Imaging 2002; 21(4):320-331.
35. Tozer DJ, Tofts PS. Removing spikes caused by quantization noise from high-resolution histograms. Magn Reson Med 2003; 50(3):649-653.
36. Steens SC, dmiraal-Behloul F, Schaap JA, Hoogenraad FG, Wheeler-Kingshott CA, Le CS, Tofts PS, van Buchem MA. Reproducibility of brain ADC histograms. Eur Radiol 2004; 14(3):425-430.
37. Tofts PS. Quantitative MRI of the brain: measuring changes caused by disease. John Wiley, 2003.
38. Tofts PS, Shuter B, Pope JM. Ni-DTPA doped agarose gel--a phantom material for Gd-DTPA enhancement measurements. Magn Reson Imaging 1993; 11(1):125-133.
39. Tofts PS, Barker GJ, Dean TL, Gallagher H, Gregory AP, Clarke RN. A low dielectric constant customized phantom design to measure RF coil nonuniformity. Magn Reson Imaging 1997; 15(1):69-75.
40. Tofts PS, Lloyd D, Clark CA, Barker GJ, Parker GJ, McConville P, Baldock C, Pope JM. Test liquids for quantitative MRI measurements of self-diffusion coefficient in vivo. Magn Reson Med 2000; 43(3):368-374.
41. Tofts PS, Barker GJ, Filippi M, Gawne-Cain M, Lai M. An oblique cylinder contrast-adjusted (OCCA) phantom to measure the accuracy of MRI brain lesion volume estimation schemes in multiple sclerosis. Magn Reson Imaging 1997; 15(2):183-192.
42. Barker GJ, Tofts PS. Semiautomated quality assurance for quantitative magnetic resonance imaging. Magn Reson Imaging 1992; 10(4):585-595.
43. Tofts PS. Standing waves in uniform water phantoms. J Magn Reson series B 1994; 104:143-147.
44. Barker GJ, Simmons A, Arridge SR, Tofts PS. A simple method for investigating the effects of non-uniformity of radiofrequency transmission and radiofrequency reception in MRI. Br J Radiol 1998; 71(841):59-67.
45. Wicks DA, Barker GJ, Tofts PS. Correction of intensity nonuniformity in MR images of any orientation. Magn Reson Imaging 1993; 11(2):183-196.
46. Tofts PS, Barker GJ, Simmons A, MacManus DG, Thorpe J, Gass A, Miller DH. Correction of nonuniformity in images of the spine and optic nerve from fixed receive-only surface coils at 1.5 T. J Comput Assist Tomogr 1994; 18(6):997-1003.
47. Tofts PS, Silver NC, Barker GJ, Gass A. Object strength--an accurate measure for small objects that is insensitive to partial volume effects. MAGMA 2005; 18(3):162-169.
48. Tofts PS. Standardisation and optimisation of magnetic resonance techniques for multicentre studies. J Neurol Neurosurg Psychiatry 1998; 64 Suppl 1:S37-S43.
49. Filippi M, Horsfield MA, Ader HJ, Barkhof F, Bruzzi P, Evans A, Frank JA, Grossman RI, McFarland HF, Molyneux P, Paty DW, Simon J, Tofts PS, Wolinsky JS, Miller DH. Guidelines for using quantitative measures of brain magnetic resonance imaging abnormalities in monitoring the treatment of multiple sclerosis. Ann Neurol 1998; 43(4):499-506.
50. Parker GJ, Barker GJ, Tofts PS. Accurate multislice gradient echo T(1) measurement in the presence of non-ideal RF pulse shape and RF field nonuniformity. Magn Reson Med 2001; 45(5):838-845.
51. Tofts PS. Novel MR image contrast mechanisms in epilepsy. Magn Reson Imaging 1995; 13(8):1099-1106.
52. Tofts PS, Sisodiya S, Barker GJ, Webb S, MacManus D, Fish F, Shorvon S. MR magnetization transfer measurements in temporal lobe epilepsy: a preliminary study. AJNR Am J Neuroradiol 1995; 16(9):1862-1863.
53. Dehmeshki J, van Buchem MA, Bosma GP, Huizinga TW, Tofts PS. Systemic lupus erythematosus: diagnostic application of magnetization transfer ratio histograms in patients with neuropsychiatric symptoms--initial results. Radiology 2002; 222(3):722-728.
54. Berkowitz BA, Tofts PS, Sen HA, Ando N, de Juan E Jr. Accurate and precise measurement of blood-retinal barrier breakdown using dynamic Gd-DTPA MRI. Invest Ophthalmol Vis Sci 1992; 33(13):3500-3506.
55. Berkowitz BA, McDonald C, Ito Y, Tofts PS, Latif Z, Gross J. Measuring the human retinal oxygenation response to a hyperoxic challenge using MRI: eliminating blinking artifacts and demonstrating proof of

concept. Magn Reson Med 2001; 46(2):412-416.
56. Trick GL, Liggett J, Levy J, Adamsons I, Edwards P, Desai U, Tofts PS, Berkowitz BA. Dynamic contrast enhanced MRI in patients with diabetic macular edema: initial results. Exp Eye Res 2005; 81(1):97-102.
57. Mottershead JP, Schmierer K, Clemence M, Thornton JS, Scaravilli F, Barker GJ, Tofts PS, Newcombe J, Cuzner ML, Ordidge RJ, McDonald WI, Miller DH. High field MRI correlates of myelin content and axonal density in multiple sclerosis--a post-mortem study of the spinal cord. J Neurol 2003; 250(11):1293-1301.