Introduction: what do we mean by Quantitative MRI?

Paul S Tofts PhD
Chair of Imaging Physics, Brighton and Sussex Medical School, UK

1. *Quantify* means to measure. *Quantitative Analysis* was first used in a chemical context, meaning 'analysis designed to determine the amounts or proportions of the components of a substance' [1]. The notion of quantitative MRI first surfaced in the 1980's, as physicists measured the NMR properties of tissue (PD T_1 and T_2), attempting to use these to characterise biological tissue, in order to differentiate different tissues on the basis of these parameters. Since then various strands have emerged, creating a new and evolving paradigm called 'quantitative MR'. The scope of this has at least in part been defined by the book on the subject[1], and also by courses on the subject run by ISMRM.

2. The *paradigmatic shift* in quantitative MR is that the MRI scanner is no longer seen as a camera, but a scientific measuring instrument. Thus notions of accuracy (closeness to the truth, characterised by systematic error) and precision (repeatability, or random error) become relevant, and indeed these are all familiar from the context of school science experiments. A more contemporary task is weighing ourselves on the bathroom scales: we expect the value to be true (in order to make comparisons with other machines, or to estimate whether we are obese according to some consensus viewpoint). We also expect the value to be repeatable, in order that we can measure small day-to-day changes. There is a biological component to the day-to day variation (e.g. through hydration status); we expect the instrumental variation to be much less than this, and we can characterise the short-term variation by repeated sequential weighing operations. These concepts are all readily applicable to quantitative MRI, where we could expect the same reliability as a blood test gives.

3. There are *three principle themes* which are important in the context of carrying out better clinical MRI studies: *sensitivity, specificity and accuracy*. To understand nonideal sensitivity and accuracy, and to improve their values, requires a detailed understanding of the *process of measurement*. This has two major components: data acquisition and data analysis. These can both be characterised in some detail in order to locate the major sources of nonideal behaviour; often improvements to the measurement process can then be made. For example, incorrect flip angles often result from a nonuniform B_1 field; these give poor accuracy, which can be improved by measuring B_1 or by using improved acquisition sequences. Subjective analysis of images can give poor reproducibility; this can be improved by defining analysis rules, or by automating the procedure using computer programmes.

4. *Sensitivity needs reproducibility.* In many contexts, the ability to measure reliably small changes in a tissue parameter value is sought; thus the instrumental variance becomes important. In a cross sectional study the instrumental variation should be much less than the within-group (between individual) variation, in order not to degrade the statistical power of the study. In a serial study, where changes within an individual over time are measured, then the instrumental variation should be much less than the within-individual variation, which is much more demanding. An example will be shown of how attention to machine instability has reduced instrumental variation and hence the sample size needed to power a clinical cross-sectional study. Reproducibility is usually measured using the Bland Altmann approach, where pairs of repeated measurements on subjects are made. Often these can be in healthy volunteers. From these, the instrumental variation (standard deviation) can be found.

5. *Sensitivity to biological changes.* A technique could be perfectly reproducible, yet completely insensitive to biological change (caused by for example disease). Thus after good reproducibility has been shown (often in healthy volunteers), sensitivity to biological change

should be demonstrated. This could be done by measuring patients in which a particular change was already known (e.g. reduction in renal function), or possibly in healthy volunteers where a particular change can ethically be brought about (e.g. increase in lactic acid concentration in muscle after application of a tourniquet).

6. *Specificity to biological changes*. There are now several independent ways (often >10) of characterising a given piece of tissue, and these often correspond to different aspects of the biology or physiology. 'Gold standard' measurements of biology can come from histology or biochemical analysis of post-mortem samples. Thus in Multiple Sclerosis, there have been extensive studies of how quantitative MRI measurements (e.g. MT) correlate with histological parameters (e.g. myelin concentration). Once these relationships are established, the interpretation of changes in quantitative parameters becomes more certain, and inferences about disease process and its modification by treatment can in turn sometimes be made.

7. The *principle tissue parameters* that have become candidates for quantitative biomarkers are Proton Density (PD) which largely corresponds to water content, the longitudinal relaxation time T_1, the transverse relaxation time T_2, diffusion and its tensor, magnetisation transfer ratio (and so called 'quantitative MT'), spectroscopy (which enables metabolite concentrations to be measured), dynamic T_1-weighted MRI (used to measure uptake of contrast agents and the transfer constant K^{trans} particularly in tumours), dynamic $T_2^{(*)}$-weighted MRI (for blood flow and volume), and blood flow using Arterial Spin Labelling (ASL). Image analysis techniques include volume, histograms and texture.

8. *Accuracy*. For a measurement to be plausible it should be reasonably close to the truth. If it is to be used in a multi-centre study of any kind, then its accuracy needs to be good. Accuracy can be measured using test objects (phantoms) with known characteristics (e.g. volume or T_1 value), and there is a whole science of phantom design and use for each MR quantity.

9. An *imaging biomarker* has similar characteristics to a quantitative measure, and it is instructive to look at the characteristics of good biomarkers and how this can improve our approach to quantification.

10. *More information*: this syllabus (an updated version) is on http://www.paul-tofts-phd.org.uk/talks/ismrm2010_qmri.pdf, ; the oral presentation is on http://www.paul-tofts-phd.org.uk/talks/ . The qMRI site http:/www.qmri.org has a variety of information and is growing. The book [1] gives a comprehensive tour of the issues, and surveys the principle qMR tissue parameters, although the clinical applications are now a little dated.

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1. Tofts PS. Quantitative MRI of the brain: measuring changes caused by disease. John Wiley, 2003.