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Book Review

Review of Quantitative MRI of the Brain, edited by Paul Tofts. John Wiley and Sons, Chichester 2003, £175.00.

As the field of MRI matures it is building its muscles in the area of quantitative imaging. This addition to the technical repertoire of MR application texts is a most welcome foray into the realm of quantitative imaging. Professor Tofts has brought together experienced researchers in the field to address issues related to MR parametric measurements, diffusion, flow, statistics and a variety of other important considerations when quantifying data. This text offers the reader an opportunity to delve into the methodology and analysis of quantitative MRI in detail.

The book begins with a somewhat historical overview of MR imaging in Chapter 1 of Section A. Right away, however, the focus is on the main thrust of the book when he states: 'Procedures have to be found which are insensitive to operator influence.' Chapter 2 tackles the measurement process. It is a fine review for the seasoned researcher who will have experienced many of the problems described herein, and a warning to those interested in trying it. Problems coming from RF effects and the need for a careful statistical analysis are thoughtfully described. Many important points from image uniformity to the reciprocity principle are covered here. The chapter closes with some statistical discussion including the important issue of receiver operator characteristics. Chapter 3 continues with an excellent overview of quality assurance issues. Many important details are discussed from Cramer–Rao bounds, to the fact that long T_2 can cause transverse magnetization coherences, to RF penetration effects. Other subtle but important issues such as phantom testing and using a fungicide to prevent deterioration of the gel are also discussed.

Section B begins with a discussion of measuring proton density. As simple as this would seem to be, there are many issues to deal with to obtain accurate and precise results. Again RF uniformity issues arise as does the simple question, 'Does free spin density equal water content?' Bound vs unbound water is discussed, as are the practical methods for measuring the two. This chapter begins a continuing thread of linking the technical measurements with clinical applications. For example, evidence is given that myelin lesions have 7.7% higher water content than normal appearing white matter. Chapter 5 discusses T_1 measurements and their value. The basics of measurement are presented, and problems with partial volume and the issues of fast and slow exchange addressed. Important methods such as inversion recovery, Look–Locker and TOMROP are reviewed. Clinically, for example, it is noted that quantification of T_1 changes has been shown to be important in detecting hemorrhage at certain stages. Chapter 6 continues with an in-depth discussion of T_2. The only out of order but important material that appears here is the first overview of the basics of MRI. The discussion on this topic, however, is excellent. Artifacts in T_2 images from partial volume effects, slice profile and a variety of other causes are reviewed. Changes in T_2 are known to have many important implications for detecting disease. Numerous examples are presented at the end of this chapter covering epilepsy, stroke, hippocampal disease, multiple sclerosis and neuro-degenerative diseases.

The next seven chapters cover other quantifiable parameters. Chapter 7 presents an excellent review of diffusion-weighted and diffusion tensor imaging. Current terminology is carefully introduced as well as difficulties in tracking fibers due to multiple contributions coming from a single voxel. Issues of resolution, signal-to-noise, cardiac gating, eddy current effects and other factors are covered. On the clinical side, a careful discussion of stroke is given, as well as hints as to cellular disruption in trauma. At the end of the chapter it is recognized that, 'because of the possible age dependence of DTI parameters, it is crucial to have groups of patients and controls that are age and gender matched.' In Chapter 8, magnetization transfer (MT) is carefully introduced. This is a nice technical review of the basics of magnetization transfer. The clinical discussion section focuses heavily on its use in multiple sclerosis patients. Here, the results from many papers on the topic are reviewed and they conclude that: 'in human studies evidence has built up to support the hypothesis that MTR values reflect histology.' MTR refers to the magnetization transfer ratio, which is the fractional change in signal induced by the MT process (usually in white matter) relative to the value without any MT pulses. They continue to point out that this method is able to visualize effects in normal appearing white matter in trauma as well. Chapter 9 goes on to a different concept, that of spectroscopy. This is a difficult topic to do justice to in a single chapter, but the basic concepts and normalization concerns are well covered here. They point out that errors in absolute measurements of NAA, Cho or Cre are approaching the 5% level with current systems and software. There are many factors affecting normalization such as T_1 and T_2 of the tissues of interest, water references, temperature, RF non-uniformities, etc. These effects are coherently presented. Proper quantitation may allow detection of metabolites as a function of time in longitudinal studies of patients. They discuss clinical uses of MR spectroscopy with the following goal in mind: to gain insight into the pathophysiology of the disease that augments what is currently available in morphological imaging. Here they again warn of the need for normative data as there are age changes over time of

the metabolites. Throughout this book there are many important technical insights. Here is another one: there has been a concern that doing spectroscopy after contrast agent injection would not be possible. The authors point out that any line broadening effect appears to be small and that it is now generally accepted that spectroscopic results can be confidently interpreted under these circumstances. They go on to discuss clinical implications of reduced NAA or other changes in Cho and Cre in a variety of diseases.

Chapters 10 and 11 cover dynamic contrast enhanced imaging using T_1 or T_2 methods, respectively. The kinetics of low molecular weight extracellular contrast agents is nicely reviewed in Chapter 10, as are the tracer kinetic concepts in Chapter 11. They note that the T_1 relaxation is dominated by the contrast agent presence in the interstitial space and then state: 'In the absence of the blood–brain barrier, contrast medium immediately begins to extravasate into tissue compartments, with well vascularized pathology exhibiting the earliest signal increase, followed by areas of gliosis and necrosis.' A multi-compartment exchange process is discussed, as are the concentration–time relationships expected from various models. Sensitivities to various technical parameters are reviewed with a special emphasis on the arterial input function as a necessary pre-requisite for an accurate quantification of kinetic modelling. The use of histograms for permeability and transfer constant is introduced. Mechanisms of T_2 losses and magnetic field effects are presented for T_2* signal behavior in Chapter 11. Clinical applications are presented for tumor evaluation and vascular disease in both chapters.

Chapter 12 introduces the reader to fMRI and its basic connections with physiology. Within this material, the multiple sources that contribute to changes in oxygen saturation in the vascular system are revealed. A brief overview of current models of flow and its effects on the fMRI signal response is presented. The roles of intravascular and extravascular sources of signal change are drawn to the reader's attention. Many artifacts related to magnetic field effects with EPI and head motion raise their ugly heads again. The authors mention that fMRI responses can be 3–5% at 1.5 T, but do not mention at which resolutions this occurs. A further amplification of the functional response as a function of method would have been nice. Many analysis programs exist, but only a few are mentioned herein. Their strengths and weaknesses are not discussed. Paradigms and their sensitivities are put forward with warnings about consistency of studies from site to site. This chapter, as with a number of other chapters, also points out that multi-center trials would be invaluable for a better understanding of inter-subject variation and reproducibility. It is noted here that fMRI often shows more activated regions than other methods such as electrical stimulation. Thus, as the quantification of excitatory response is different, so must the interpretation be different. For example, in language studies the authors note: 'that fMRI at this time cannot replace stimulation . . . but can serve to shorten the stimulation procedure because it reliably predicted the absence of critical language function where no fMRI activity was found.'

The focus on the importance of cerebral perfusion continues in Chapter 13 with an overview of arterial spin labeling (ASL) methods. The authors distinguish between two general categories of ASL, continuous and pulsed, and the advantages and difficulties of both. Two critical points are brought to the fore, the need for proper balancing of magnetization transfer effects and the fact that although echo-planar imaging is used there is no need to have long echo times (so image quality improves compared to the T_2* dynamic contrast enhanced methods). Sadly, there is a lack of quantitative data reported here, presumably due to the fact that absolute measurements are hard to obtain for many reasons. In order to test large numbers with this approach one needs a consistent model and as they close their chapter they note that this is so 'due to the large inter-subject perfusion variations.'

Throughout the technical chapters there has been a focus on multiple sclerosis, dementia, tumors and other neurodegenerative diseases. Section C contains only a single chapter on the biology of multiple sclerosis. However, this is a welcome discussion of what it is that MR is trying to understand, often indirectly. Many pathological references and correlations are reviewed. Some important conclusions are drawn. For example in the detection and visualization of MS lesions they note that: 'T_2-weighted lesions are very sensitive but have poor specificity and cannot reflect the amount of myelin and axonal loss.' They also state that: 'Gd enhancement is a consistent finding of new MS lesions.' They go on to note that the state of MS lesions is very hard to correlate with MTR or DWI as they can change their patho-physiology in a short period of time. What they can say quantitatively is that both can show local demyelination through a reduced MTR or increased apparent diffusion coefficient because of the increase in local water content (i.e. edema and inflammation lead to an increase in water content). The role of spectroscopy and cellular imaging are discussed, with the latter being an exciting new direction for better detection of inflammatory lesions with macrophage activity with the uptake of iron particulate agents.

Section D covers technical approaches for analyzing images. Chapter 15 covers the important topic of image registration. It introduces the reader to the necessary language of the mathematics of a matrix and optimization formulation of the problem. It discusses a number of approaches, from shearing methods for rotations to mutual information. The main weakness is that there is no summary of the accuracy or precision associated with any of the methods. This makes it hard to make any choices between methods. This concern is partly alleviated by a nice summary of available software to deal with registration. Chapter 16 continues with volumetric analysis of data. Again methodology is reviewed (but without

specific mathematical detail as in the previous chapter), as well as a discussion of the errors inherent in any method used. These errors include partial volume effects and RF variation, which make segmentation difficult. They comment that full brain gray/white matter segmentation is still unreliable but that progress is being made. Three-dimensional methods are very important here, but are only briefly discussed. A main point regarding consistency across sites is missed with respect to three-dimensional methods and that is that they are much more forgiving to system variations than other methods. Two-dimensional methods using T_2 and spin density can be used in multi-spectral approaches. The authors warn that manual segmentation should be avoided when possible (probably due to personal bias and training errors), although it is used for hippocampal or other single object studies, as are semi-automated as well as automated approaches. They also warn that system scaling issues with gradients may warrant the need for daily calibration of systems to ensure minimization of systematic errors. Finally, they show two very strong and encouraging applications of volume measurements. First, in Alzheimer's disease, they state that one paper was able to predict using volume measurements those patients: 'who would convert with a sensitivity of 95% and a specificity of 90% based predominantly upon measures of the entorhinal cortex and superior temporal sulcus.' For the study of surgical patients with epilepsy, volume measurements may help to determine who will respond to surgery. Specifically they state that one study showed 'that those with atrophy of the amygdala-hippocampal formation responded better to the surgery than those who did not.' What is missing in this chapter is a summary of what the current capabilities actually are from a quantitative perspective. Chapter 17 opens the door to two new directions, shape and texture analysis. The former has found uses in schizophrenia and the hippocampus, while the latter is still finding its applications, with epilepsy and tumor evaluation being two key candidates. In the former case, it will be critical to determine what constitutes normality. The question then will be 'Can a departure from normality be captured by shape analysis?' This section closes with a new direction in quantification in Chapter 18, the use of histograms. Histograms of signal response can be obtained either globally or locally. Although this leads to a loss of spatial information, it does give a perspective of the general distribution of signal, whether from T_1 weighted images or T_1 maps or any other image or map. The peak values, or bimodal shape, or other special characteristics may well correlate with the state of a disease, as in multiple sclerosis. The authors point out that this is the case when viewing MTR plots: 'Some studies have shown a significant relationship between histogram metrics and physical disability.' One goal could be to show differences between MS sub-groups, for example, and to be able to predict future outcomes for patients. The authors give a good technical description of how to produce robust histograms.

The final chapter on the 'Future of Quantitative MR Imaging' expresses an important goal that is in some cases already met with MR spectroscopy and with methods like MR angiography but has a long way to go for many diseases. That is, 'With improved technique, we can expect to pass from group comparisons to treatments customized to the individual patient.'

SUMMARY

Globally, this text focuses on quantitative methods for neuro-imaging. Its clinical focus is dominated by an interest in multiple sclerosis of many of the authors, but also covers other diseases. The one major difficulty is the large number of acronyms used. This makes it hard to read individual parts of the chapters. In a number of chapters, there is, disappointingly, not a single table of expected quantitative numbers but rather a review of methodologies. This is perhaps less a fault of the authors than it is of the state-of-the-art in the field itself today. As such, this book is a careful reminder that we need to be looking into more multi-center trials and a less parochial view of individual research efforts. For example, it took nearly 10 years for MR angiography to make it into the clinical realm as an accepted (and payable) standard, due to lack of large numbers in clinical trials. The same has happened for perfusion measurements, whether using dynamic contrast enhanced imaging or arterial spin labeling. Quantifying the results of these new methods earlier on may well lead to their more rapid acceptance. For this reason alone, this text offers the reader insights into attacking certain areas in MR today that are sorely in need of global quantification. This text will serve as an excellent summary of the above methods for those interested in technical details and analysis for magnetic resonance imaging.

E. MARK HAACKE, Ph.D
The MRI Institute for Biomedical Research
440 E Ferry Street
Unit 2, Detroit
MI 48202 USA
e-mail: nmrimaging@aol.com
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