Quantitative Medical Imaging

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Abstract

The field of medical imaging is undergoing a radical shift, from subjective interpretation to quantitative analysis and measurement. This transformation is well established in the clinical trials arena, and is beginning to enter the diagnostic field as well. This paper will consider the implications of this change in terms of instrumentation, procedure, and analysis. It will include a brief review of the principal imaging modalities (CT, MRI, PET, Ultrasound), and will examine in detail the acquisition and analysis techniques that will be required to successfully complete the transition from qualitative to quantitative imaging.

Introduction

In the past three decades, medical science has made great strides toward the understanding of cellular biochemistry and the mechanisms of disease. In concert with this change, the technologies available for medical imaging have proliferated. In particular, cross-sectional imaging techniques, which allow the precise reconstruction of three dimensional structures within the body, and functional imaging techniques, which allow the assessment of biological function as well as form, have become widely available. These imaging techniques potentially provide a tremendous amount of information about disease state and response to treatment. However, the means to interpret that information has badly lagged behind the ability to acquire it.

A good example of this phenomenon is given by the RECIST (Response Evaluation Criteria In Solid Tumors) standard, which is the primary imaging endpoint for assessing disease progression or response to treatment in many types of cancer. This technique reduces the assessment of structural changes in tumors to a simple summation of longest diameters, limited to the axial imaging plane. This technique was originally developed with plane film x-ray imaging in mind, and fails to take advantage of the far richer three dimensional information set available in a spiral CT scan. In some cases, the assessment gleaned from RECIST will correlate well with the changes seen in "true" tumor volume. In others, however, it will not. An example of this is given in Figure 1 below.

The continued use of RECIST as a standard evaluation in cancer is not due to any strong argument that single diameters are better than, or even equivalent to, a full volumetric assessment. Rather, it is due to the lack of availability of convenient and reliable tools for producing volumetric measurements. Several groups, including VirtualScopics, are now in the process of producing, validating, and commercializing tools in this and other areas which will allow the use of precise, quantitative measurement in medical imaging, first in the clinical trials arena, and later in the clinic itself.
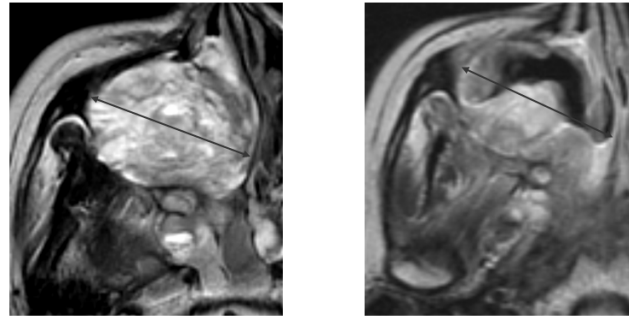

Figure 1: (l) Baseline scan showing a large tumor filling much of the subject's right sinus cavity. Standard RECIST measurement is shown by black arrows. (r) Follow-up scan showing the same tumor, which has cavitated, losing approximately 70% of its bulk. However, the standard RECIST measure is roughly unchanged.

Quantitative Medical Imaging in Clinical Trials

Recent scientific advances have brought about massive changes in the business of drug discovery and development. Large companies that once had relatively few compounds in development now juggle hundreds of potential candidate compounds. For the industry to sustain itself, companies must devise ways to quickly identify promising compounds and cull ineffective ones. Various estimates place the cost of developing a single compound from discovery to the pharmacy shelf at between $800 million and $1.7 billion. The Tufts Center for the Study of Drug Development in its Impact Report, Volume 4, Number 5, September/October 2002 estimated that it costs $808 million, on average, to develop and win market approval for a new drug in the United States. This study stated that better pre-clinical screens, to increase success rates from the current 21.5% to one in three, could reduce capitalized total cost per approved drug by $242 million.

Quantitative imaging can reduce late-stage attrition dramatically by offering more accurate information much earlier in the drug development process. As an example, dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is able to provide information about blood flow and vascular permeability in tumors. This information allows a relatively small trial to quickly determine whether an anti-angiogenic or vascular disruptive agent is having the desired effect [1,2]. Whereas Phase I clinical trials normally focus on dosage and safety, studies that incorporate quantitative imaging can also test for drug efficacy, offering information that can save millions of dollars by allowing companies to better prioritize their drug pipelines and make go/no-go decisions much earlier. In pre-clinical research, scientists can test method of action and lay the foundation for a more streamlined clinical trial process from Phase I through Phase III by obtaining critical information about efficacy.

The value of medical image analysis stems from quantification and automation. While the primary shortcoming of standard endpoints, such as pain or functionality scoring, is that they are largely subjective and difficult to reproduce, quantitative imaging allows the replacement of a subjective evaluation — knee pain ranked on a scale of 1 to 10 — with an objective quantification — cartilage volume in cubic millimeters. Automation in the image analysis process — using a computer algorithm to measure lesion size rather than a clinician with a ruler — provides a degree of accuracy and reproducibility that cannot be duplicated by manual techniques. A good example of this phenomenon is provided by the measurement, using MRI, of lesion burden in multiple sclerosis (MS) patients. MS lesions generally are irregularly shaped, and tend to have fuzzy, indistinct boundaries (see Figure 2). As a result, several studies have estimated the inter-operator coefficient of variability (CV) in white matter lesion burden measurement at 20% or more [3,4] and the intra-operator CV at ~7%. Introducing automation into this process can reduce this variation to 2% or less [3], allowing statistically significant efficacy findings to be obtained far earlier in the development process.
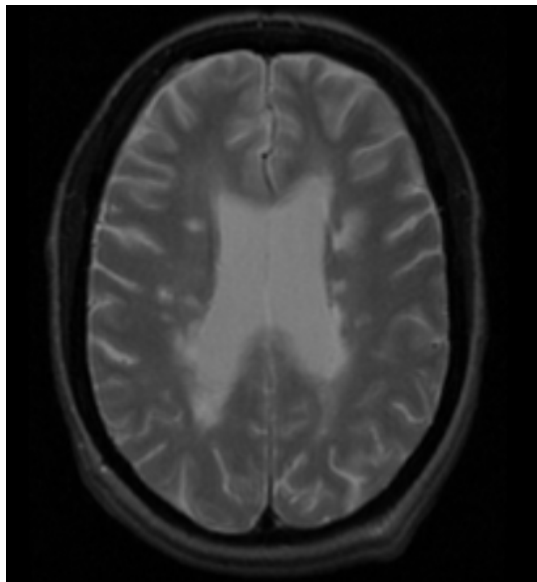

Figure 2: A T2 weighted MRI scan of the brain of a multiple sclerosis patient. The irregular bright areas surrounding the ventricles are white matter lesions. The small size and indistinct boundaries of these lesions make them very difficult to quantify manually.

Precise, automated measurement brings another critical benefit: it enables the detection of small changes in structure and function over time. In evaluation of osteoarthritis, for example, MRI of the cartilage in the knee coupled with automated measurement of volume and chemical composition shows disease changes in months; these changes would not be apparent using standard x-ray evaluation for years. With this quality of information, researchers can more confidently make the go/no-go decision for a compound early in the evaluation process, allowing scarce resources to be allocated to the most promising candidates.

Reproducible medical image analysis is driven by algorithms that enable quantitative, volumetric measurement of structures and metabolic functions. Guided by the information present in the images, as well as embedded anatomical knowledge, the algorithms enable segmentation of different tissue types such as bone, muscle, fat and fluid. From an MRI knee scan, for instance, it is possible to produce a three-dimensional reconstruction that graphically distinguishes cartilage from underlying bone, as well as from ligaments, fluid, degenerated menisci or inflamed synovium (see Figure 3). This capability provides a valuable assessment tool for clinical research in osteoarthritis — a disease with multiple endpoints — because it allows the very sensitive and specific measurement of all the components of the knee joint and the detection of small changes in any of those components over time.
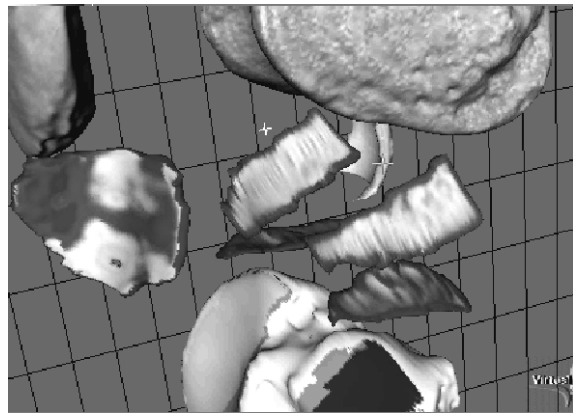

Figure 3: Three dimensional rendering of the knee joint of an osteoarthritis subject, showing tibial, femoral and patellar cartilage components.

Functional Imaging Techniques

In addition to structural measurements such as size, thickness or shape, properly utilized medical imaging can allow the assessment of functional parameters. Functional imaging encompasses a wide variety of imaging techniques, including functional MRI (fMRI), DCE-MRI, dynamic contrast-enhanced computed tomography (DCE-CT) and positron emission tomography (PET). These methods allow the assessment of the metabolic activity of an organ or lesion through the measurement of markers such as tissue blood volume, blood flow, oxygen utilization or glucose metabolism.

In the clinic, functional imaging makes it possible to distinguish between scar tissue and viable tumor, and in some cases between benign lesions and malignant ones. In drug development, functional imaging allows the direct measurement of drug effects that otherwise would only be observable indirectly, through their influence on patient survival or well-being. Several functional imaging modalities, including DCE-MRI, DCE-CT, and dynamic PET, allow the direct measurement of parameters such as blood flow, blood volume, and vessel permeability. These methods work by measuring the concentration of an injected tracer in the blood and in the target tumor every few seconds for several minutes. The form and magnitude of the resulting time-

concentration curves are then fit to a model which produces the measured parameters [5].

Functional imaging imposes an additional burden on the radiologist. Obtaining a measurement of tissue blood flow from a DCE-MRI scan requires the application of a complex mathematical model, and currently there is no standardized commercial software available to accomplish this. Various academic groups have shown coefficients of variation for DCE-MRI measurements ranging from 6% to 45%. Clearly, it is vital for researchers and clinicians interested in these modalities to partner with individuals or companies with experience and expertise in both image acquisition and data modeling and measurement.

Applications in Neurology and Cardiology

In evaluating diseases of the brain, automated medical image analysis is particularly useful. Because the brain has no moving parts and has a fairly consistent structure from person to person, it is possible to generate a generalized map, or anatomic atlas, of the location and shape of many of its important structures. Under the supervision of a neuroradiologist, this map can then be applied to a series of patient scans to provide a consistent measurement of neural structures that frequently have unclear or even arbitrary boundaries.

A good example of an important but difficult to measure neural structure is the hippocampus, a gray matter structure of the brain that is involved in a number of functions, including the formation of long-term memory. Changes in the hippocampus are implicated in a number of diseases, including intractable temporal lobe epilepsy and Alzheimer's disease. The hippocampus is adjacent to and difficult to separate from other gray matter structures, including the amygdala and the caudate nucleus (see Figure 4). Manual measurements of the hippocampus are difficult to reproduce because there is no clearly visible boundary with these structures. An automated measurement technique using an anatomical atlas might not always agree with any particular radiologist. However, experiments have shown that any given radiologist is unlikely to precisely agree even with himself if asked to measure the same scan a week or two later [3,6]. When tracking changes over time the key factor is reproducibility, and in that area automated methods provide a significant advantage.
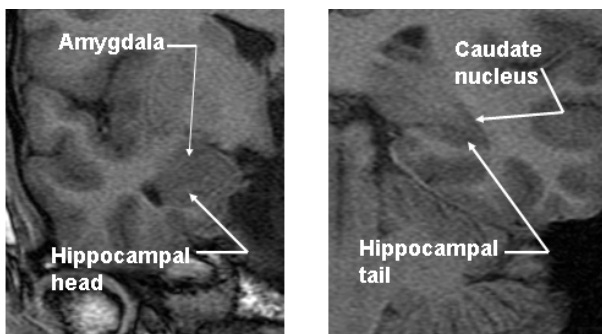

Figure 4: The hippocampus, as seen in T1-weighted MRI brain scans. (l) The boundary between the hippocampal head and the amygdala. (r) The boundary between the hippocampal tail and the caudate nucleus.

Medical image analytics also have shown great promise in cardiology and angiography. It was long thought that the key danger sign in the assessment of arterial disease was vascular occlusion — the narrowing or blockage of the coronary or carotid arteries. However, it is now known that large vascular plaques can form in key arteries without narrowing the lumen at all, by pushing the outer wall of the vessel outward rather than pushing the inner wall inward. Such plaques either can be relatively harmless or deadly, depending on what is inside them and how likely they are to break open, spilling their contents into the blood stream. The most dangerous plaques have thin walls and large liquid cores filled with lipids and other substances. When these plaques burst, the contents quickly form clots, which can then lodge in the brain, heart or lungs.

With the proper acquisition parameters, MRI can allow the identification and measurement of vascular plaques. More importantly, it also can allow a determination of plaque composition. This makes it possible for surgeons to distinguish between a relatively benign plaque that can be left for future observation, and a potentially deadly one that requires immediate surgery.

Practical Considerations

Although the potential benefits of the techniques discussed here are many and varied, it is important to bear in mind that there are several obstacles that must be overcome before these methods can be fully exploited in either the clinical trial or diagnostic arenas. Primary among these is that the personnel and systems presently deployed at radiology sites have been trained and designed around qualitative rather than quantitative imaging. This means that many of the imaging techniques necessary for quantitative imaging are not routine for these sites, and must be learned.

Equally important, the equipment maintenance standards currently in place at most imaging sites are not sufficient to support precise quantitative measurement. Figure 5 shows two MRI scans of the same linearity and volume phantom. This phantom is a device, roughly the size of a small suitcase, which contains a regular grid of known geometry. A scan of this phantom can be compared to the expected results in order to highlight problems with the field homogeneity, coil function, etc., of the scanner under examination. The scan on the right was obtained from a clinical scanner that was in routine use at the imaging center at the time of acquisition.

The distortion which is apparent in the phantom scan was present in all clinical scans obtained using this machine, and had been for some time prior to this quality check. It seems fairly obvious to ask why this problem was not noted by the site technicians or radiologists. The answer is simple: This sort of distortion can be backed out by the human visual system as long as it is consistent over time, and is therefore not a major impediment to qualitative interpretation of the images generated by the system. The requirements for quantitative imaging are fundamentally different, and in fact significantly more stringent. Failure to take this into account can result in measurements that are meaningless or misleading.
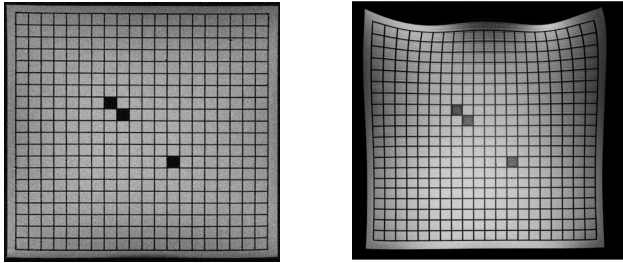
Figure 5: (l) MRI scan of a volume and linearity phantom obtained using a well-maintained system. (r) MRI scan of the same phantom obtained using a clinical scanner that was in routine use at the site. This scanner eventually required RF coil replacement.

Conclusions

Quantitative medical imaging promises immense benefits for both diagnostic and clinical trial applications. In the clinical trials arena, quantitative imaging allows precise direct measurement of the biological activity of a compound. This replaces inference of drug effect through observation of secondary effects such as changes in reported pain. Because the error bar placed on quantitative measurement is much smaller than that placed on more subjective measures, statistically significant results relating to compound efficacy can be obtained in smaller, earlier phase clinical trials. This allows the decision point on further compound development to be pushed back from late phase II or even phase III to phase I trials, where failure is far less costly. In the diagnostic arena, precise quantitative measures may help facilitate the personalization of medicine, by assessing quickly and accurately whether a particular subject is responding favorably to a given targeted compound. A great deal of development and validation work is still required to bring all of these potentialities to full fruition, but the next ten years should see many of these techniques making their way into routine clinical use.

References

[1] Glenn Liu, Hope S. Rugo, *et al.,* ”Dynamic Contrast-Enhanced Magnetic Resonance Imaging As a Pharmacodynamic Measure of Response After Acute Dosing of AG-013736, an Oral Angiogenesis Inhibitor, in Patients With Advanced Solid Tumors: Results From a Phase I Study”, J Clin Oncol 23, 24, pp. 5464 – 5473 (2005).

[2] Edward Ashton, Teresa McShane, and Jeffrey Evelhoch, "Inter-Operator Variability in Perfusion Assessment of Tumors in MRI Using Automated AIF Detection", LNCS 3749, pp. 451 – 458 (2005).

[3] Edward Ashton, Chihiro Takahashi, Michel J. Berg, *et al.,* "Accuracy and Reproducibility of Manual and Semiautomated Quantification of MS Lesions by MRI", J Magn Reson Imag 17, pp. 300 – 308 (2003).

[4] K. Van Leemput, F. Maes, D. Vandermeulin, *et al.,* ”Automated segmentation of multiple sclerosis lesions by model outlier detection”, IEEE Trans Med Imaging 20, pp. 677 – 688 (2001).

[5] Paul Tofts, "Modeling tracer kinetics in dynamic Gd-DTPA MR Imaging", J Magn Reson Imag 7, pp. 91 – 101 (1997).

[6] Edward Ashton, Kevin J. Parker, Michel J. Berg, and Chang Wen Chen, "A Novel Volumetric Feature Extraction Technique, with Applications to MR Images", IEEE Trans Med Imaging 16, pp. 365 – 371 (1997).