Translational Methods for Retrospective Long Term Evaluation of Cancer with MRS

D. H. Wu[1], L. Garrett[1], J. Modi[1], B. Han[1], and H. Cao[1]
[1]Radiological Center, University of Oklahoma Health Sciences Center, Edmond, Oklahoma, United States

Introduction: Cancer patients often require long term monitoring of their disease for progressive changes. For example, this is of particular significance for individuals who have been afflicted with childhood cancers. Serial imaging of patients over time (often over many years) can involve a variety of types of scanners as well as multiple institutions. MR spectroscopy (MRS) data can provide critical differential information pertaining to tumor type/grade, location for biopsy/resection, and evaluation of treatment success/failure[1]. However, data collected by different machine types and processed from different institutions may not be comparable. This discrepancy can compromise the assessment of disease progression or remission. It is desirable to make data from different technological generations compatible and even comparable.

The objective of the present work was to create and evaluate a method that offers efficient, accurate, and objective data analysis as required in these cases of long-term, serial imaging of a disease. The process proposed in this work included the extraction and analysis of MRS records from both old film and digital images so that an entire patient's record could be examined.

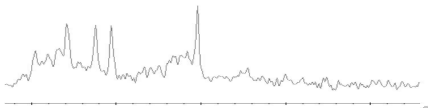

Figure 1: Example of a digitized original MRS distribution. Note that often these spectral contain noise contamination and significant peak overlap. This requires substantial image segmentation processing to extract proper spectral curves.

Additionally, as part of the procedure, we impose a minimal requirement that the analysis algorithms of the data permit the user to bracket two frequencies for the peaks of interest. This requirement is due to common peak overlapping that result from both subject-to-subject and environment-to-environment variations. Thus, our technique improves the practicality of training technologists for efficiency, but still meets minimal requirements. To further evaluate the procedure's utility, the new software was subjected to 'tolerance' testing under a variety of common physics confounds including: 1) relaxation differences, 2) baseline drift, and 3) signal to noise differences found commonly in clinical MRS.

Method: We evaluated twenty four MRS cases across a wide variety of disease populations on a GE 1.5 T scanner in accordance with institutional IRB requirements. This was performed across a wide variety of disease populations including radiation necrosis, neurodegenerative disease, primary brain tumor, developmental delay, and seizure disorder. The heterogeneity of these subjects allowed us to evaluate the tolerance of the algorithms in a varied patient population common to a clinical setting.

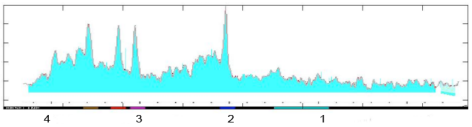

Figure 2: This figure illustrates image processed (region growing with morphological filtering) extraction of data the original. Note, we also show that occasionally several points 'leak' but points are easily manually corrected.

$$Area = f * \int_{x_{min}}^{x} \left[\frac{A}{\sigma\sqrt{2\pi}} \exp[\frac{-(t-t_c)^2}{2\sigma^2}] \right] dt + (1-f) * \int_{x_{min}}^{x} \left[\frac{A}{(t-t_c)^2 + (\Gamma/2)^2} \right] dt \quad (1)$$

Initially, older data was digitized. Then image extraction was performed in customized software (see figure 2). The resultant spectral data was curve fit to equation 1 by a nonlinear optimization Marquart Levenberg routine. This equations reflects combination of Gaussian and Lorentzian terms where A=amplitude, σ=standard deviation, f=fraction of Gaussian/Lorentzian Mixture, Γ=FWHM of Lorentzian. In order to increase accuracy and speed convergence of the optimization procedure, we have primed the system with a deterministic estimation for A, σ, f, Γ by a newly introduced method to retrieve first pass estimates from a 'moment' based computation. As shown in figure 3, this method first included a peak determination step followed by folding the left side of the peak and averaging the result with the right side of the peak. Then the first-moment was calculated from the resulting averaged solution and compared to expected first moment of a pure Gaussian distribution for estimating σ and Γ. Following the steps of image and spectral data analysis, equivalence statistical testing was then performed in JMP (Cary, NC).

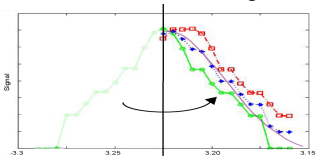

Figure 3: The moment generating method is demonstrated in this figure. After the peak detection, the left side of the distribution (green with circles) is flipped across the peak axis (reversed in frequency). The right side of the distribution (red with squares) is averaged with the flipped sequence as shown by the dotted blue line. The first moment is calculated and compared to the expected Gaussian distribution.

Results: The twenty four cases were evaluated under tolerance to baseline drift, additive noise level, and broadening to achieve estimate comparisons between our procedure and standardized results. The mean locations for the bracketing frequency with standard deviations were calculated to be. Cho=3.11-3.30ppm / σ=0.060; NAA=1.98-2.19, σ=0.055; Cr=2.94-3.12, σ=0.038. A comparison to 'expert' evaluation was compared against the method by two-sided equivalence testing (TOST) in JMP/SAS (Cary, NC)[2]. Despite, the population variation, the method achieved a equivalence (which limits at 0.8) for both NAA and Cho.

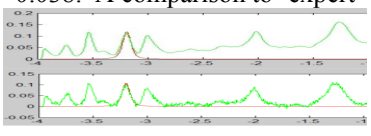

Figure 4: a) Simulated baseline drift across the spectra.b) Additive Gaussian noise & Curve Fit

Discussion: We have demonstrated the ability to retrieve a retrospective review of digitized images (from both film and image data) that permits fundamental baseline removal and frequency bracketing with the target of creating a user-friendly tool that most technologists are able to operate. This newly created clinical workflow will improve long term care for patients that may require important decisions pertaining to whether the status of a tumor has changed (such as tumor reoccurrence). A central concept is that we have also conducted tolerance testing in which common confounds to artifacts that arise from shimming, electronic noise, field inhomogenity, coil sensitivities, relaxation which cause variation in base line drift, line broadening and SNR degradation common to clinical environments. Portability and the ability of MRS to maintain stable and reproducible measurements has been one of the fundamental threats for MRS in achieving future clinical reimbursement. Our results illustrate that is possible to improve MRS standards for retrospective review. MRS has been steadily growing but this will require faster throughput and consistency in the analysis over long periods of time.

[1].***Nelson, S.J.***,. *Mol Cancer Ther, 2003. 2(5):497;* [2] ***Kutner****, Applied Linear Statistical Model, McGraw Hill 2004;*