A method for quantifying average metabolite concentrations in anatomically-defined brain regions

Ryan J. Larsen[1], Michael Newman[1,2], Chao Ma[3,4], and Bradley Sutton[1,5]

[1]Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, IL, United States, [2]Department of Computer Science, University of Illinois at Urbana-Champaign, Urbana, IL, United States, [3]Beckman Institute, Urbana, IL, United States, [4]Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, United States, [5]Department of Biomedical Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, United States

Introduction. Magnetic Resonance Spectroscopy (MRS) measurements are sufficiently sensitive to characterize changes in the brain due to interventions in exercise or diet.(1) However, these effects can be limited to specific brain regions. It is therefore important to develop methods that provide quantitative measurements of average metabolite concentration within various regions of the brain that are functionally and metabolically distinct. This requires the integration of spectroscopic information with high-resolution MRI images. A variety of methods have been proposed for using anatomical data as prior knowledge for improving maps of metabolite distribution.(2-5) Typically, these methods are used to map the distribution of the metabolite signal. However, proper normalization of the signal is required for the maps to be quantitatively accurate. Here we propose a method for quantifying metabolite concentrations in brain regions of complex shape, using water as an internal reference. This method builds upon established methods of quantification, including the use of LCModel, and the use of segmentation to accurately perform water-scaling. The quantified signal is used to create an anatomical reconstruction by exploiting prior knowledge that metabolites are not detectable within Cerebral Spinal Fluid (CSF). This is done using a Projection On the Convex Set (POCS) algorithm on the measured distribution of metabolites.(*6*)

Methods. We performed Magnetic Resonance Spectroscopy Imaging (MRSI) scans on 72 subjects on a 3T Trio (Siemens Instruments) after obtaining informed consent. We performed a 2D spin echo double phase-encoded MRSI scan of the region centered on the cortical regions immediately superior to the lateral ventricles (TR: 1800 ms, TE 135 ms, 16 x16 matrix size, thickness: 13 mm, weak water suppression, see Fig. 1(a)). Fat bands were applied to regions of fat near the brain. An identical scan without water suppression was also obtained. Following the scan we performed a T_2-weighted scan with the same center and slice orientation so that the scan could be registered to a high resolution whole-brain MPRAGE scan (TR: 1900 msm TE: 2.32 ms, TI: 900 ms, 0.9 x 0.9 x 0.9 mm), which was segmented using SPM8 software. Voxels for which the sum of the Gray Matter (GM), White Matter (WM), and Cerebral Spinal Fluid (CSF), was less than 99% of the voxel volume were discarded.

Results. LCModel was used to calculate the concentration of N-acetyl aspartic acid (NAA), in units of *m*mol/L within each voxel (Fig 1(b)). The water-scaling factors were corrected using volume fractions of GM, WM, and CSF within each voxel, literature values of T_1 and T_2 of NAA, T_1 and T_2 of water, and volume fraction of NMR-visible water within GM, WM, and CSF.(*7, 8*) Voxels with for which the Cramer-Rao error estimate was > 20% were discarded (see Fig. 1(b)). The calculated concentration values depend on both the number of NAA molecules and the volume of NMR-visible water within the voxel. Because the distribution of water is well-characterized by the MRI scan, we only apply the POCS algorithm to a map of the number distribution of NAA molecules. The number of NAA molecules within each voxel is calculated by multiplying the concentration of NAA (*m*mol/L) in that voxel by the volume of NMR-visible water within the voxel. Significantly, for most subjects, the calculated number of NAA molecules within a given voxel does not correlate with the NAA signal from that voxel, which was calculated from the original spectrum, using LCModel with no water-scaling (see Fig. 1(c)). This difference reflects inhomogeneity due to non-uniform transmission and reception of RF signal, and underscores the importance of signal normalization.

We perform a FFT on the low-resolution map of NAA distribution, and zero-fill the resulting matrix to match the high resolution of the MPRAGE scan. We then apply the POCS algorithm to the resulting distribution. This is an iterative method that introduces non-zero values at high spatial frequencies to account for the fact that no metabolite is present within the CSF, while maintaining consistency within the original data at low spatial frequencies. The operation is performed for each of the high-resolution slices within the thickness of the MRSI scan. The resulting maps are then integrated over specific brain regions that were previously defined within an MNI template and transformed to the subject space by SPM8. The integrated NAA value for a given brain region is then divided by the amount of NMR-visible water within each region to obtain a representative value of NAA concentration for each brain region.

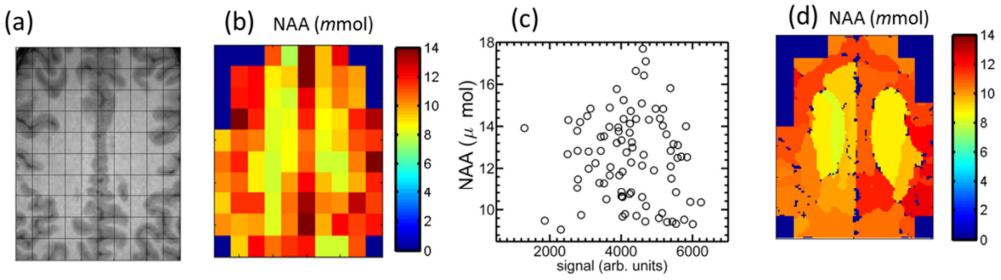

Fig. 1 *Representative MRSI data from a single subject for which* FOV: 160 mm x 208mm, ROI: 100 mm x 130 mm,. *(a) Placement of center 10 x 10 voxels relative to the MPRAGE scan. (b) Calculated distribution of NAA concentration, calculated for each voxel. (c) Calculated values of number of moles of NAA in the voxels do not correlate with NAA signal. (d) Average NAA concentration within various brain regions. Brain regions are based on maps obtained from WFU PickAtlas and JHU white matter atlas.*

Conclusion. We have demonstrated the use of a POCS algorithm to calculate concentration of NAA for multiple brain regions. We applied the algorithm only to the metabolite distribution, which was properly quantified beforehand. Unlike the distribution of metabolite signal, this distribution is not subject to inhomogeneity from RF transmission and reception, and is likely to be more suitable for use with algorithms that use prior knowledge from MRI scans to correct MRSI data. Further validation of this approach will be performed by using metabolite concentrations from all of the brain regions of irregular shape to measure values of global GM and WM that are consistent with those measured using metabolite concentrations from only the voxels.(*7*)

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