Adaptive Spectral Registration Method for Glutathione Measurement using J-difference Editing

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Introduction: A J-difference editing technique MEGA-PRESS [1] has been widely used to measure metabolites of small concentration, such as GABA, glutamate, NAAG, and glutathione (GSH) [2]. In order to reduce subtraction errors in the J-difference spectrum, it is necessary to correct for frequency and phase changes in each individual acquisition, which are caused by subject motion and system instabilities. The reported frequency and phase correction methods [3,4] for J-difference editing use a Lorenzian and/or Gaussian curve to fit a singlet peak such as the NAA or creatine peak in order to find the relative frequency and phase for each acquisition. In this work, we present a fully automated spectral registration method for frequency, phase, and linear baseline corrections. Instead of using a Lorenzian and/or Gaussian curve, target spectra for spectral registrations are generated from the data by a fitting and selection process. Spectral registrations are performed using broader ranges of spectral data instead of just one peak in the spectrum. A linear baseline correction is also done in the spectral registration process, which is important for GSH measurement where residual water baseline is a bigger problem than for other J-difference editing experiments.

Method and Results: For GSH measurement, we implemented a MEGA-PRESS pulse sequence [5] on a 3 T Philips scanner. The pulse sequence has a TR of 2 s, a TE of 131 ms, and 256 acquisitions. There are two types of acquisitions in the pulse sequence. Half of the acquisitions are "on" acquisitions and the other half are "off" acquisitions [2]. A simple way of generating the J-difference spectrum is to subtract the averaged "off" spectra from the averaged "on" spectra. However, the frequency, phase, and water baseline fluctuate for each individual acquisition because of subject motion and system instabilities. These variations will result in subtraction errors if they are not properly corrected for. In order to perform spectral registration, raw data from all acquisitions are saved and then processed offline. In each acquisition, 2048 data points are collected with a spectral bandwidth of 2 kHz, which is zero padded to 16384 data points, multiplied by a 1 Hz exponential decay function, and Fourier transformed to the frequency domain. This interpolated frequency domain data has a spectral resolution of 0.12 Hz. In the spectral registration process, frequency shift by a fraction of a data point (0.12 Hz) is realized by cubic spline interpolation.

The first step of spectral registration is zeroth-order phase adjustment for the spectra. The NAA, creatine, and choline singlet peaks in the averaged "on" spectrum are fitted with three Voigt curves [6]. The zeroth-order phase is obtained from the fit and removed from each "on" and "off" spectrum. A Levenberg-Marquardt optimization subroutine programmed in IDL is used in this and hereafter fitting processes.

The goal of the second step is to generate one target spectrum for the "on" acquisitions and another target spectrum for the "off" acquisitions. These two target spectra will be used later to register each "on" and "off" spectra, respectively. First, the 128 "on" spectra are grouped into 64 pairs. The two spectra in each pair are aligned to each other by shifting one of them. The complex spectral data from 1.9 to 3.3 ppm are used in this fitting process. The root mean square (rms) error between each pair of spectra is recorded. After this frequency alignment, each pair of spectra is averaged into one spectrum. Thus 64 averaged spectra are created, whose rms errors are then sorted into ascending order. Half of the spectra (32 spectra) with highest rms errors are discarded from this process. The remaining spectra (32 spectra) are grouped into 16 pairs, and then get aligned and averaged by the same process. This process repeats until there is only one averaged spectrum left, which will be used as the target spectrum for the "on" acquisitions. The target spectrum for the "on" acquisitions is an average of 16 individual "on" spectra. A target spectrum for the 128 "off" spectra is similarly generated.

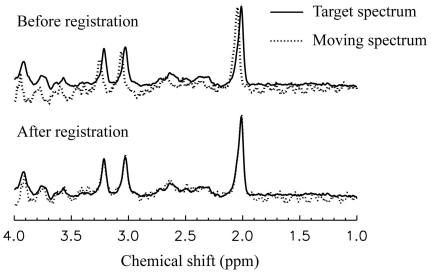

Fig. 1. *Spectral registration: registering each spectrum to the corresponding target*

In the third step, each "on" and "off" spectrum is registered to the "on" and "off" target, respectively. Spectral data from 1.9 to 3.3 ppm are used in the optimization process. The difference between the target and moving spectrum which is minimized in the optimization process can be expressed as:

$$\mathrm{diff}(n) = \mathrm{real}[\mathrm{spect}(n-\Delta n)\exp(i\varphi_0)] + b_0 + b_1 n - \mathrm{real}[\mathrm{target}(n)]$$

where n counts data points in each spectrum; diff(n) is the difference term being minimized; real[·] denotes the real part of a complex number; spect(n-Δn) represents the n^{th} data point of an individual "on" or "off" spectrum shifted by Δn points where Δn is a real number; i is the imaginary unit; ϕ_0 is the zeroth-order phase; b0 and b1 represent the zeroth and first order baseline; target(n) represents the n^{th} data point of the corresponding "on" or "off" target spectrum. After registering each "on" spectrum to the "on" target, the registration rms errors are sorted into ascending order. Several spectra, e.g. 5, with largest rms errors are discarded. The remaining "on" spectra are averaged to give the "averaged on" spectrum. The "averaged off" spectrum is computed similarly. Fig. 1 shows an individual "on" spectrum (dotted line) and the "on" target (solid line) before and after registration in an in vivo experiment.

In the fourth step of spectral registration, the "averaged on" and "averaged off" spectra are first line broadened by a 3 Hz Lorenzian function. Then the "averaged off" spectrum is registered to the "averaged on" spectrum by frequency, phase, and baseline adjustment similar to the previous step except that this registration is performed on a different range of spectral data. Two segments of data are used here in the optimization process, one from 1.92 to 2.12 ppm surrounding the NAA singlet peak, and the other from 3.08 to 3.19 ppm in between the creatine and choline peaks. Finally, the registered "averaged off" spectrum is subtracted from the "averaged on" spectrum to give the difference spectrum.

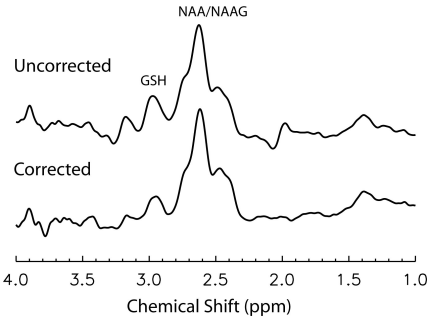

Fig. 2. *J-difference spectra of a stroke patient*

Over forty scans from ten normal volunteers and four stroke patients have been performed in accordance with procedures approved by our institutional review board. Good quality GSH peak is observed from all scans. Difference spectra of a stroke patient are shown in Fig. 2. The spectrum on the top was processed without spectral registration. The spectrum on the bottom was processed using this spectral registration method.

Conclusion and Discussion: Subject motion has always been a challenge for J-difference spectroscopy and in vivo spectroscopy in general. It is especially challenging to scan stroke patients because it is hard to keep a stroke patient motionless during a long scan. This spectral registration method appears to be robust in processing data from normal volunteers and stroke patients in the presence of small patient movements.

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