In vivo Fourier Shifted Two-Dimensional Zero-Quantum Coherence ^{1}H NMR Spectroscopy of Glutamate and Glutamine

S. R. Snyder[1], S. Schmitter[1], A. Nagel[1], and P. Bachert[1]

[1]Dept. of Medical Physics in Radiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

Introduction: In the past unequivocal detection of glutamate (Glu) at clinical MRI field strengths has been associated with the difficulty of separating it not only from glutamine (Gln), but also from other metabolites, such as glucose and GABA, which are found in the same ppm ranges as that of Glu. In the STEZQC-2D (Stimulated Echo Zero-Quantum Coherence (ZQC) – Two Dimensional) method developed by Sotak [1], the Mixing Time (TM, the delay time between the second and third 90° pulses in the Stimulated Echo Acquisition Mode (STEAM) sequence) is linearly increased over a series of spectra. A Fourier transformation along the ΔTM axis provides a measurement parameter, the ZQC modulation frequency, which is unique for each scalar-coupled metabolite. It is equal to the difference of the one-dimensional resonating frequencies of the coupled nuclei within the molecule. When this frequency is plotted over the chemical shift to form a two-dimensional spectrum, two identification parameters for scalar-coupled metabolites are provided.
Previously, it has been shown that using this method, Glu can be differentiated from Gln (know together as Glx) as well as all other metabolites in the 3.70 to 3.80 ppm range (that of the α-triplet) [2]. However, due to the only slight difference in the ZQC modulation frequency between Glu and Gln (210 and 200 Hz (Glu) and 202 and 200 Hz (Gln)), acquisition times exceeded four and a half hours. Now we demonstrate, that using this technique along with a Fourier shift, acquisition times can be achieved that are acceptable for *in vivo* measurements.

Materials and Methods: Series of ^{1}H NMR spectra with increasing TM were obtained from single voxels in Glu (40 mmol/L), Gln (40 mmol/L), and Glx (20 mmol/L each) model solutions on a whole-body MR tomograph (3T, Magnetom TRIO, Siemens Medical Solutions, Erlangen, Germany). Since the ZQC modulation frequency of Glu is 210 Hz, a ΔTM of 2 ms was used, so as not to violate the Nyquist sampling theorem. Choosing all parameters to obtain a minimal acquisition time (TA), one finds for TE = 72 ms, TR = 1000 ms, NEX = 128, BW = 2000 Hz, VS = 512, ΔTM = 2 ms, and 128 steps, a TA of over four and a half hours. The 128 steps are necessary to achieve significant resolution to distinguish the Glu with a ZQC modulation frequency of 210 Hz from Glx with ZQC modulation frequencies of 202 and 200 Hz, since the resolution along the ZQC modulation axis $\Delta\nu = 1/(\Delta TM \times N)$, where N is the number of steps in the series.
In order to decrease this acquisition time, we undersample along the ZQC modulation axis, measuring with a ΔTM greater than the maximal ΔTM = 2.38 ms as provided by the Nyquist sampling theorem. This allows a smaller number of steps to be recorded, which translates to a shorter TA, with no resolution loss. To convert the measured undersampled data into observable frequencies, a Fourier shift is applied. Each individual spectrum is multiplied with a phase, the amount of which linearly increases with the number of the step in the series. For each 360° of phase which are acquired over the series, the data is shifted one line in frequency-space.

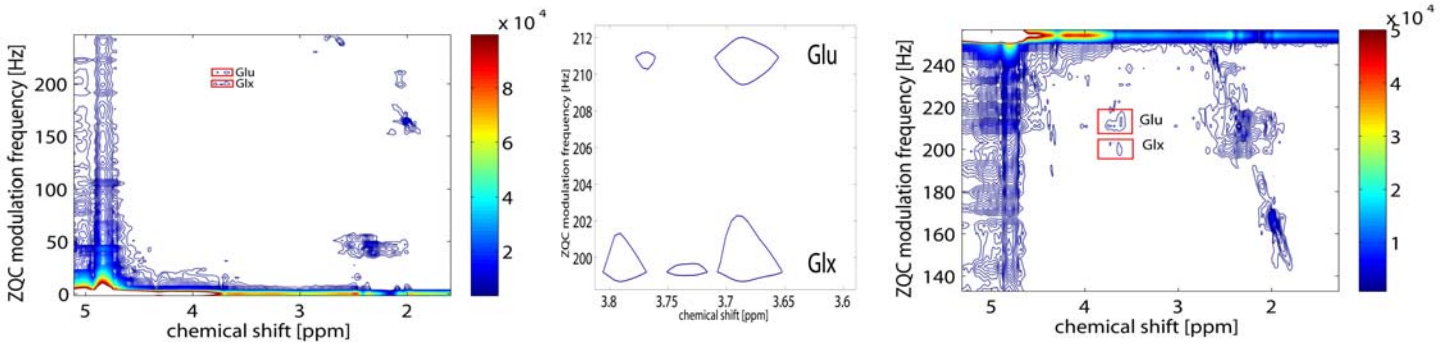

Figure 1: Glx model solution (left) non-undersampled 2-D spectrum recorded with ΔTM = 2 ms, 128 steps, TA = 4 h 33 min, (middle) enlarged area of Glu and Glx peaks from the non-undersampled 2-D spectrum, (right) undersampled 2-D spectrum recorded with ΔTM = 4 ms, 64 steps, TA = 2 h 16 min.

Results: Fig. 1 provides a comparison of the Glx model solution sampled with ΔTM = 2 ms (left) and ΔTM = 4 ms (right). Using the undersampling technique, the measurement time with ΔTM = 4 ms is only half of that with ΔTM = 2 ms.
Fig. 2 shows a 2D spectrum from a 3x3x3 cm^3 voxel of the temporal lobe of a healthy volunteer, recorded with TR = 980 ms, TE = 72 ms, ΔTM = 8 ms, BW = 2000 Hz, VS = 512, NEX = 128, 24 steps, and TA = 50 min. The peaks resulting from the α-triplet of Glu at 208.3-213.5 ± 2.6 Hz are separated from those of the α-triplets of Glu and Gln 198.0 ± 2.6 Hz.

Discussion: Applying the Fourier shift theory to undersampled STEZQC-2D data of Glx in model solutions or *in vivo* measurements, it is possible to distinguish the Glu with a ZQC modulation frequency of 210 Hz from Glu and Gln with ZQC modulation frequencies of 202 and 200 Hz in 50 min, with no loss in resolution along the ZQC modulation axis. The acquisition time can theoretically be further decreased by using an even greater ΔTM, however, we have found that the signal then decays too quickly. Additionally, care must be taken when performing the Fourier Shift, that the desired Glx ZQC modulation frequencies are not shifted to the frequencies where strong signals from non-coupled metabolites are located.

[1] C.H. Sotak. "A volume-localized, two-dimensional NMR method for the determination of lactate using zero-quantum coherence created in a stimulated echo pulse sequence." Magn Reson Med **7** (1988) 364-70.
[2] S. R. Snyder, S. Kirsch, K. Kraus, and P. Bachert, In ''Proceedings, 16th Annual Meeting, ISMRM, Toronto'', **16** : (2008) 1564.

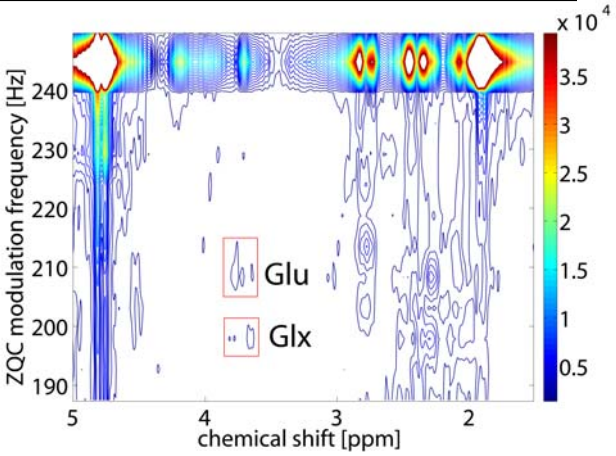

Figure 2: ***In vivo* measurement of Glu**: 3x3x3 cm^3 voxel of the temporal lobe of a healthy volunteer, recorded with ΔTM = 8 ms, 24 steps, and TA = 50 min.