Wavelets, Nuclear Magnetic Resonance Spectroscopy, and the Chemical Composition of Tumors

PANAGIOTACOPULOS NICK D., Ph.D.,
LERTSUNTIVIT SUKIT, M.Sc., SAVIDGE LEE ANN, M.Sc.
Electrical Engineering Dept., California State University, Long Beach, CA 90840, USA
and
LIN ALEXANDER B.Sc., SHIC FREDERICK B.Sc., ROSS BRIAN D., M.D., Ph.D.
Huntington Medical Research Institutes, Pasadena, CA 91105, USA

Abstract: - In this paper we report a method based on the continuous wavelet transform that is used for the analysis of nuclear magnetic resonance spectroscopic (MRS) signals. MRS is a safe, non-invasive, and accurate method of obtaining in-vivo biochemical information. It has been utilized in diagnosing human brain tumors in a clinical setting. Wavelet transforms can extract more information from the original MRS signals than that obtained from the Fourier transform methods. By comparing results from data obtained from tumor and healthy patients, we can observe frequency differences for various MRS signals consistent with the results obtained from existing methods.

Key-Words: wavelets, tumor, nuclear magnetic resonance spectroscopy

1 Introduction

Nuclear Magnetic Resonance Spectroscopy (MRS) is a non-invasive assay, much like magnetic resonance imaging (MRI), which allows clinicians to determine concentrations of chemicals or metabolites in regions of interest. Widely available on clinical MR scanners, it is fast becoming an important clinical tool in the diagnosis of various pathologies in different parts of the body. It has been shown to be of great diagnostic value in the evaluation of lesions as tumors or non-tumor especially in the brain [1-4].

Prior to MRS, the standards for diagnosing brain tumor were medical imaging and stereotactic biopsy. The disadvantage to imaging tests such as x-ray, PET, and MRI were that although they were proficient at recognizing large lesions in the brain, smaller lesions were often much more difficult to ascertain whether they were tumor or not [5]. Even in cases of well-defined lesions, the non-quantifiable observations could lead to an inaccurate diagnosis (i.e. stroke vs. tumor). When imaging alone could not determine malignancy, patients could only turn to biopsies in the form of surgical removal or fine needle aspirates. Surgeries obviously carry risk of neurological deficit due to post-surgical hemoraging and are restricted to areas of the brain that are relatively easy to access. Fine needle or stereotactic biopsies induced less trauma in the brain but since it only removes a small part of tissue, has been demonstrated to sometimes be inaccurate such as when the sample is removed from the wrong area [6-7]. Biopsies also suffer from the same qualitative issues as imaging.

MRS resolves these issues by providing a safe (completely non-invasive), quantitative, and accurate measurement. This is done by obtaining a spectra, which represents a fast-Fourier transform (FFT) of the free-induction decay (FID) of the MR signal after water suppression and optimization of acquisition. The frequency or parts per million in the spectra identifies the chemical or metabolite and the amplitude indicates the concentration of that brain chemical. The major metabolites measured by proton MRS are: n-acetyl aspartate (NAA): a marker of neurons, creatine (Cr): an energy marker, choline (Cho): a membrane marker, myo-inositol (mI): a glial cell marker, and lacate/lipid (Lac/Lip): markers of cell death. The biochemistry of a region of interest can thus be determined. The differences in the biochemistry of diseased brain and normal brain can then be used as a diagnostic tool to screen for pathologies such as brain tumors. In brain tumors, NAA is decreased due to a loss of neurons in the area of the lesion, Cho is increased dramatically due to the proliferation of tissue in cell death, and Lac/Lip is often increased due to this cell death. This biochemical "signature" is a very sensitive and specific test to determine if lesion within the region of interest is a tumor [5].

Traditionally, the spectral analysis of MRS signal is done using Fourier methods. This method represents the data in frequency domain. Wavelet transforms can utilize both time and frequency domain to provide detailed analysis, which may lead to the discovery of other important markers that may be of clinical importance. Using the wavelet transform as a "mathematical microscope", issues such as degree of malignancy and tumor typing, which are not well addressed by current Fourier transform results, may be resolved.

2 Problems in Tumor Characterization Current Diagnostic Methods

There are two basic questions that must be answered once a tumor is found: (1) is the tumor benign or malignant? and (2) can it be categorized? An accurate and timely answer to

human body, its diagnosis is easier. However, for interior

step is a radiographic appearance examination. Such examination is based on the shape and gray level intensity -ray, CAT or MRI images. If the

radiologist can draw some useful conclusions. However, if the tumors are small and not clearly shown, then a reliable conclusion is not easy. Furthermore, most of these images are corrupted by noise a
psychophysical perception problems
difficult. Clearly, no biochemical analysis can be obtained such an examination. In addition, techniques based on oved to be
unreliable [8]. For a more reliable diagnosis, at the end, all

invasive technique, which can provide the biochemical composition of the tumor. There are two kinds of biopsies. is surgical and the second is known as needle (aspiration) biopsy. Both kinds will create trauma and

could be risky, in the sense that it may propagate cancerous cells in other parts of the bod -cautionary -up the creation of blood

the samples are usually large and provide adequate data for an accurate biochemical analysis, this is unt
needle biopsy where the samples are smaller, and in many cases inadequate, or they may be taken from the wrong

manipulating the needle) It is thus not unusual that an accurate and re
need for a better diagnostic method is clear.

MRS [9] is a tool that has been used by chemists for many

compound consists of molecules, and molecules are

nucleus and a cloud of electrons. The nucleus is made up of two types of subatomic particles, the protons (p), and the anics these
subatomic particles are intrinsically spinning. If a number of

their respective spins will add and the nucleus will have a net nuclear spin. The net nuclear spin is zero for all th
except those with an odd number of protons and an even number of neutrons (and vice versa). These are the nuclei of

have north and south magnetic poles, have no preferred orientation in
magnetic field, **H**
(favorable state). The next thing we do is to change the orientation of the nuclei (perturb the nuclei) in the field (turn e other way). To achieve
this (less favorable) state we have to apply energy into the

a precisely tuned pulsed radio frequency (RF) field orthogonal to the static field , that is generated from a radio of the

nucleus then we achieve resonance and the RF at which resonance occurs is known as resonance or Larmor frequency $\boldsymbol{\omega}$. The equation: $\boldsymbol{\omega} = -\gamma\mathbf{H}$, where **H** is the magnetic field strength, and γ is the gyromagnetic ratio (which is associated with each nucleus), is the key equation in nuclear magnetic resonance (NMR) and MRS. It is the connection to particular nuclei that gives MRS and NMR its ability to look at a specific atomic species in a complex system. Clearly, one can select which nuclei to observe by using the appropriate frequency $\boldsymbol{\omega}$. The resonant response signal of the nuclei is known as free induction decay (FID). It occurs exactly when resonance is achieved, the RF field is removed and the nuclei are coming back to their initial favorable state. The signal is detected by a receiver coil placed around the chemical substance under study. If we Fourier transform the FID signal we obtain its frequency spectrum, which gives a convenient representation of the resonant frequency content of the FID signal. For example, phossphorus-31 (^{31}P) spectroscopy provides information such as the cellular energy-state and intracellular pH, as well as phospholipid metabolism, whereas water-suppressed proton spectroscopy can quantify the concentrations of various intermediary metabolites including amino acids and lactate. Most of the spectroscopy techniques critically depend upon the quality of the spectral resolution that can be obtained. Good resolution can be achieved by optimizing the magnetic field homogeneity over the sample volume under investigation. One way to achieve good homogeneity is by limiting the volume of interest by some form of volume selection mechanism (localization). Along this line a number of volume selection methods are used such as: SPARS (spatially resolved spectroscopy) and STEAM (stimulated echo acquisition mode).

4 Problem Solution Using Wavelets

In the effort to understand and analyze digital signals, Fourier transforms (FT), and short time Fourier transforms (STFT) have been used. Although, they decompose a signal to its frequency components and determine the relative energy of each component, they do not tell when the signal exhibited a particular frequency. For instance, if the frequency content varies drastically from interval to interval, the FT sweeps over the entire time axis and washes out any local characteristics in the signal (i.e. high frequency bursts, spikes, discontinuities and transients). In other words, the FT has problems in resolving a signal in both the time and frequency domain. On the other hand, the STFT positions a time window at any point on the time axis and calculates the FT of the signal within the spread of that window. The basic problem with STFT is that once the time-window resolution is fixed, the corresponding frequency resolution is also fixed (Heisenberg's uncertainty principle). This has the following implications. If the signal has transient components, which have duration smaller than the time window used, it is difficult to locate it with precision better than the time

window spread. In addition, if the signal has important features of different sizes, we cannot find easily an optimum time window for its analysis. If the window is too wide, it takes samples from too many components, and if the window is too narrow, it takes too few samples. Therefore, STFT is suitable only for the analysis of signals where all the features in the signal are approximately of the same scale.

A recently developed signal analysis mathematical technique [10] known as the wavelet transform (WT), has been successfully applied in analyzing complex non-stationary signals. This technique is particularly useful in time-frequency evaluations requiring the highest possible resolution in both time and frequency domains.

As it is known, Fourier theory deals with the representation of a signal with a finite sum of simple terms (referred to as frequency components) involving orthogonal functions (sines and cosine), called basis functions, multiplied by appropriately chosen coefficients. These coefficients depend on the signal itself and on the basis functions chosen. In the case of wavelets we may think of replacing the sines and cosines with special basis functions, formed by the scaling and translation of a special function subsequently referred to as the mother wavelet. These functions must be simultaneously oscillatory and have amplitudes, which decay quickly to zero in both negative and positive directions. They are better suited for representing short bursts of high frequency signals or long duration of slowly varying signals. The mother wavelet expands or contrasts in time depending on the scaling parameter, which causes a corresponding contraction or expansion in the frequency domain. We may think of the WT as a "mathematical microscope", with the compressed mother wavelet used to detect singularities or abrupt changes in the signal and the expanded mother wavelet used to detect other low frequency features. These characteristics make the WT a more powerful tool than the FT, and provide a better time-frequency signal analysis.

4.1 Continuous Wavelet Transform (CWT)

Given a non-stationary signal S(t) (i.e. the mean, the variance, and the first-order pdf for S(t) is different for every t_1 and t_2), the WT of this signal is defined as the inner product of S(t) with the two-parameter (**a**,**b**)-family of basis functions:

$$\psi_{\mathbf{a},\mathbf{b}}(t) = \frac{1}{\sqrt{\mathbf{a}}}\psi\left(\frac{t-\mathbf{b}}{\mathbf{a}}\right), \qquad \mathbf{a}>0$$

where: **a** is a scale parameter (dilation), **b** is a time delay parameter (translation), $\psi(t)$ is known as the mother wavelet, and $\psi_{\mathbf{a},\mathbf{b}}(t)$ as the wavelet In mathematical terms the WT of the signal S(t) is defined by:

$$W[S(\mathbf{a},\mathbf{b})] = \langle S(t), \psi_{\mathbf{a},\mathbf{b}}(t)\rangle = \int_{-\infty}^{\infty} S(t)\psi_{\mathbf{a},\mathbf{b}}(t)dt$$

where: S(t) and $\psi(t)$ are square integrable functions $L^2([R])$. In wavelet analysis, the basis functions $\psi_{\mathbf{a},\mathbf{b}}(t)$ (waves) are oscillating functions just as sines and cosines are in Fourier analysis. More specifically, the basis functions (sines, and cosines) in the Fourier analysis oscillate forever; while the basis functions $\psi_{\mathbf{a},\mathbf{b}}(t)$ in wavelet analysis are localized in time, last only for a few cycles, and like the FT, the WT is invertible. The basis functions, $\psi_{\mathbf{a},\mathbf{b}}(t)$, constitute the building blocks of wavelet analysis. According to the first equation given above, the wavelets are scaled and translated versions of the mother wavelet $\psi(t)$, while the delay parameter **b** gives the position of the wavelet $\psi_{\mathbf{a},\mathbf{b}}(t)$, and the scale **a** governs its frequency content. If $\mathbf{a} << 1$, then $\psi_{\mathbf{a},\mathbf{b}}(t)$ is highly contracted and corresponds to high frequencies, while if $\mathbf{a} >> 1$, then $\psi_{\mathbf{a},\mathbf{b}}(t)$ is spread out and corresponds to low frequencies.

In STFT analysis the goal is to measure the local frequency content of the signal. On the other hand, in wavelet analysis, the W(S(**a,b**))'s, which are known as wavelet coefficients, represent how well the signal S(t) and the wavelet $\psi_{\mathbf{a},\mathbf{b}}(t)$ match for all **a** and **b** parameters. If the signal S(t) is similar to $\psi_{\mathbf{a},\mathbf{b}}(t)$, then the coefficients will have large magnitude. Actually, the coefficients represent the degree of correlation between the two functions at the particular scale and translation. The set of all wavelet coefficients W(S(**a,b**)) is representing the signal S(t) in the wavelet domain with respect to the wavelet $\psi_{\mathbf{a},\mathbf{b}}(t)$. The quantity $|W(S(\mathbf{a},\mathbf{b}))|^2$ is known as *scalogram* of S(t), and represents the distribution of the signal's energy in the time-scale plane. However, many times |W(S(**a,b**))| is also used. In our analysis, the $\psi_{\mathbf{a},\mathbf{b}}(t)$ used was a Morlet type wavelet.

5 Approach

Although several brain tumor and control MRS signals were analyzed, only two cases are presented in this paper. Both cases were obtained from the same patient and correspond to the left and right portions of the brain as indicated by square voxels in Fig. 1.

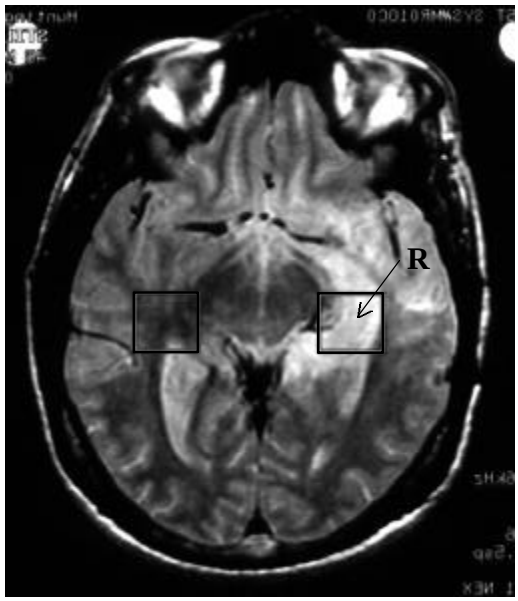

Fig 1. MRI image of the cross-section of a head.

The case associated with the healthy individual will be referred to as the control case and the case associated with tumor will be referred to as tumor case. The regions of interest (ROI) are indicated by small squares on the right and left portions of the MRI head image and are denoted by R-ROI and L-ROI respectively. The L-ROI is the control case while the R-ROI corresponds to the tumor case.

Since the purpose of the study was to identify the chemical difference between control and tumor cases, it was necessary to acquire and analyze MRS signals, subsequently referred to as free induction decay (FID). The FIDs were obtained from a 1.5 Tesla GE SIGNA 5x series clinical magnet using a 30 ms short-echo STEAM with a repetition time of 1.5s and 30 ms short-echo PRESS with a repetition time of 2s [9]. Time-scale and time-frequency analysis were also performed using the continuous wavelet transform with a Morlet wavelet as the analyzing function.

6 Results

Figures 2-9 summarize the results of our studies.

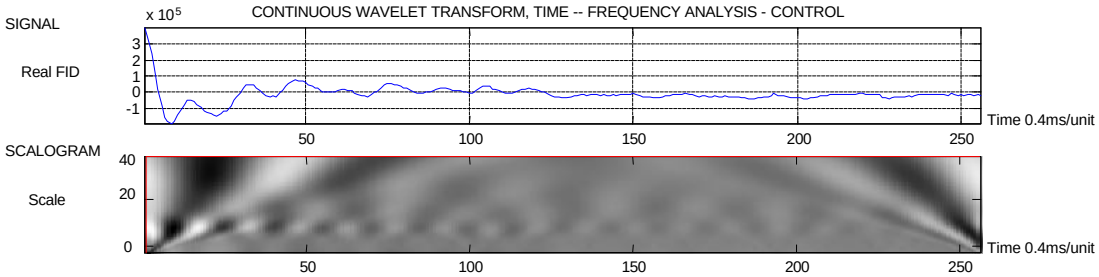

Fig 2 FID and Scalogram of the control case.

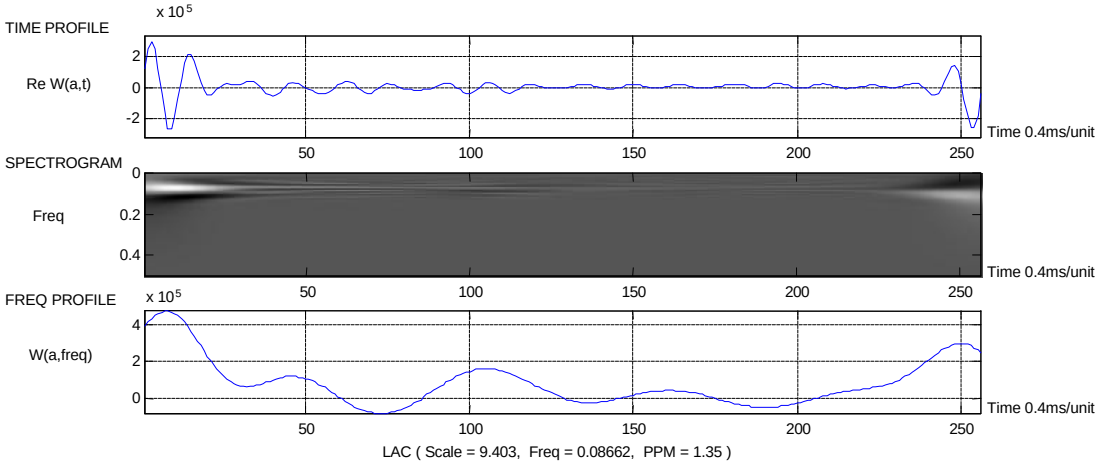

Fig 3 Time-frequency analysis diagram corresponding to Lactate (LAC)

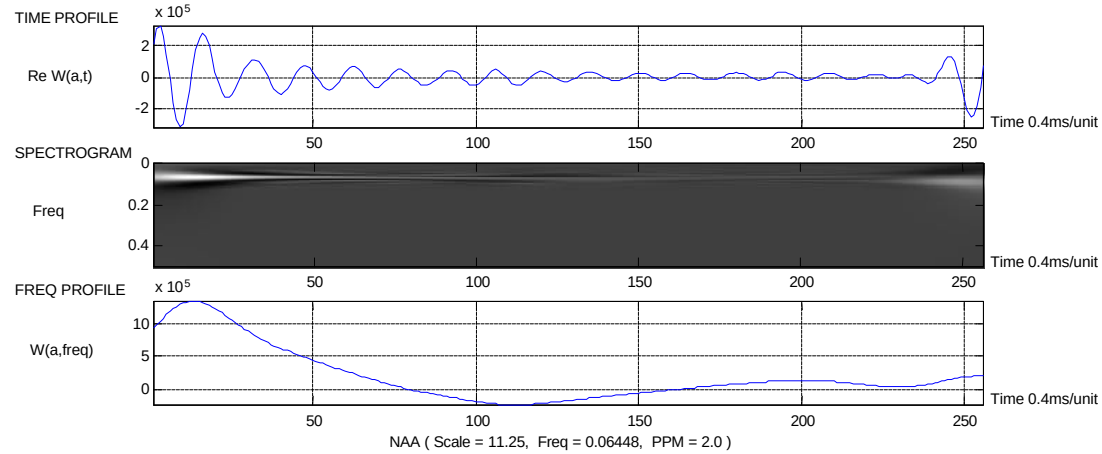

Fig 4 Time-frequency analysis diagram corresponding to N-Acetyl-Aspartate (NAA)

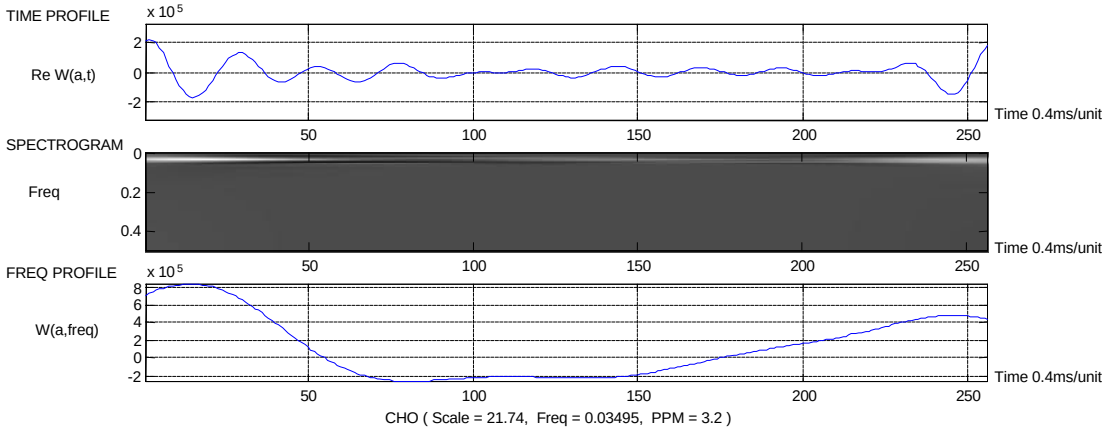

Fig 5 Time-frequency analysis diagram corresponding to Choline (CHO)

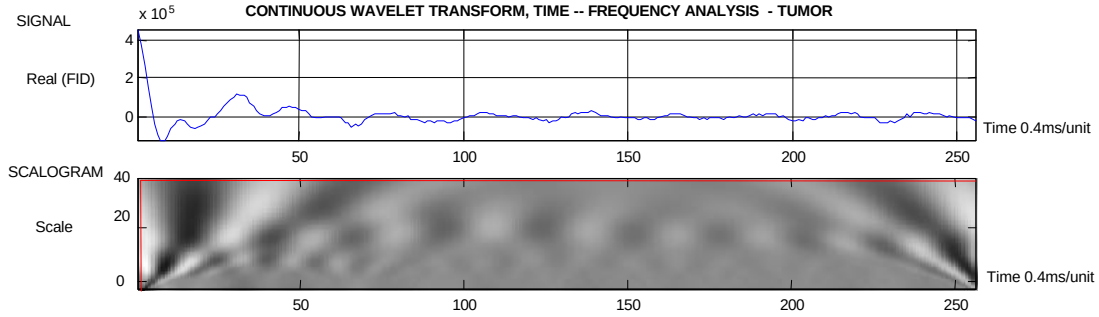

Fig 6 FID and Scalogram of the tumor case.

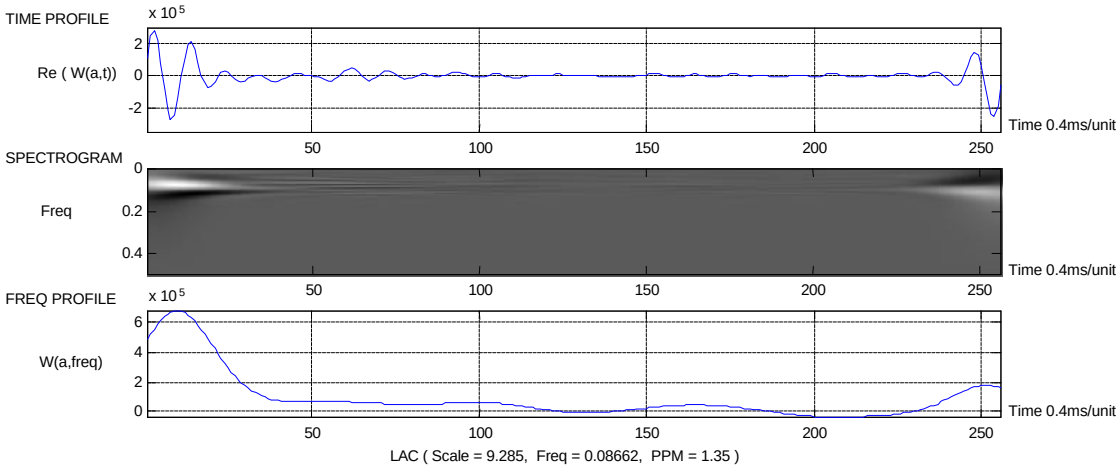

Fig 7 Time-frequency analysis diagram corresponding to Lactate (LAC)

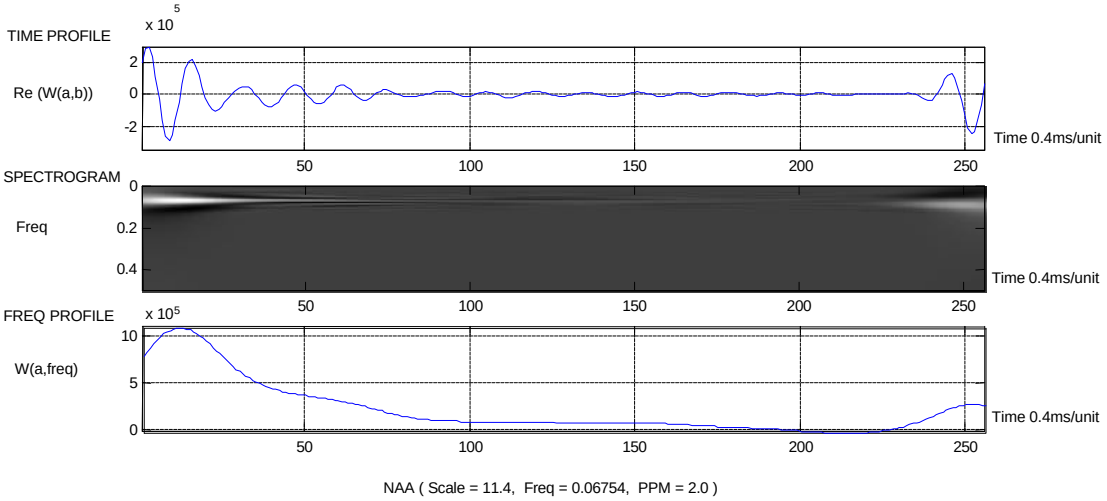

Fig 8 Time-frequency analysis diagram corresponding to N-Acetyl-Aspartate (NAA)

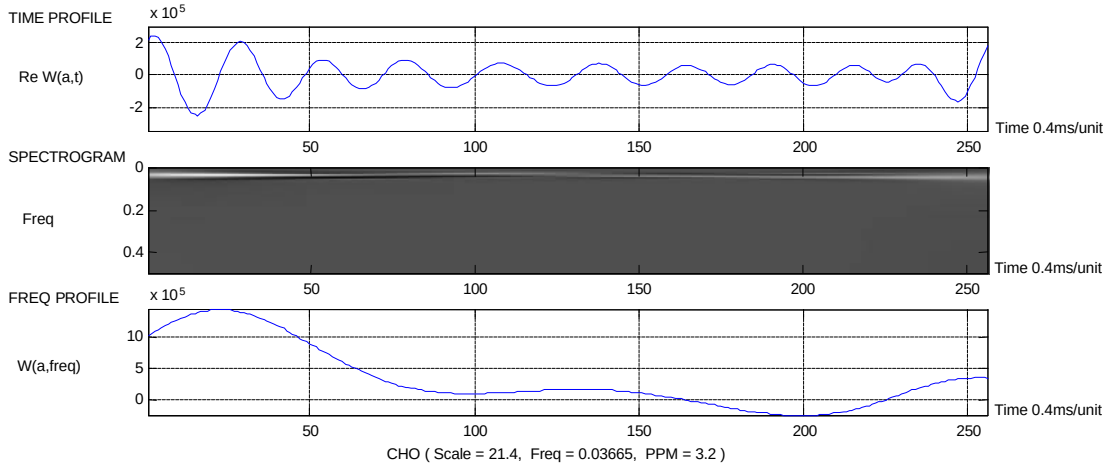

Fig 9 Time-frequency analysis diagram corresponding to Choline (CHO)

7 Conclusion

In Figures 2 and 6, we can visually observe differences between the FIDs and scalograms of the control and tumor cases. However, these differences are too subjective to be used as a basis for biochemical analysis. On the other hand, wavelet-based time-frequency analysis enables us to determine the existence and concentration of a wide range of metabolites such as lactate, N-acetyl-aspartate, and choline in the L-ROI and R-ROI.

In Figures 3 and 7, a comparison of the maximum amplitude of the time-scaled frequency profile between the L-ROI and R-ROI revealed that lactate was larger in the tumor case than the corresponding control case. Similar comparisons in Figures 4, 8 and Figures 5, 9 indicated that, in tumors, NAA decreased while CHO increased. These findings are consistent with the results obtained from the conventional Fourier method.

Although only three metabolites are discussed in this paper, the wavelet-based technique shown has been extended to other metabolites, and has provided a complete chemical profile for both the L-ROI and the R-ROI.

References:

[1] ER Danielsen and BD Ross, *Magnetic Resonance Spectroscopy Diagnosis of Neurological Diseases*. Marcel Dekker, 1999

[2] H Bruhn, J Frahm, ML Gynell, et al. *Non-invasive differentiation of tumors with use of localized H-1 MR spectroscopy in-vivo. Initial experience its with cerebral tumors*. Radiology, 1989, 172:541-54

[3] D Ott, J Hennig, T Ernst, *Human Brain Tumors: Assessment with in Vivo Proton MR Spectroscopy*, Radiology, 1993; 186:745-752

[4] Castillo et al, *Proton MR Spectroscopy of Brain Tumors, Neuroimaging Clinics of North America*, 1998; 8

[5] A. Lin, S Bluml, A Mamelak. .*Efficacy of Proton Magnetic Resonance Spectroscopy In Clinical Decision Making for Patients with Suspected Malignant Brain Tumors*. Journal of Neuro-Oncology. 45(1): 69-81, 1999

[6] Bernstien et al, *Complications of CT-Guided Stereotactic Biopsy of Intra-axial Brain Lesions*, J Neurosurg 81(2):165-8, 1994

[7] Soo et. Al, *Failed Stereotactic Biopsy in a Series of 518 case*. Stereotact Funct Neurosurg 64(4): 183-96, 1995

[8] Partain, Leon C., et. al., *Nuclear Magnetic Resonance Imaging*, W.B. Saunders Company, 1983.

[9] Cho, Z.H., Jones, J.P. and Singh, M., *Foundations of Medical Imaging*, Wiley Interscience, New York, 1993.

[10] Vetterli, M. and Kovacevic, J., *Wavelets and Subband Coding*, Englewood Cliffs, Prentice Hall,1995..