

# MULTIVOXEL MR SPECTROSCOPY TOOL FOR BRAIN CANCER DETECTION IN NEURONAVIGATION

## *Performance*

Juan José Fuertes<sup>1</sup>, Valery Naranjo<sup>1</sup>, Pablo González<sup>1</sup>, Ángela Bernabeu<sup>2</sup>, Mariano Alcañiz<sup>1,3</sup> and Javier Sanchez<sup>4</sup>

<sup>1</sup>*Instituto Interuniversitario de Investigación en Bioingeniería y Tecnología Orientada al Ser Humano (I3BH), Universitat Politècnica de València, I3BH/LabHuman, Camino de Vera s/n, 46022, Valencia, Spain*

<sup>2</sup>*Inscanner S.L., Unidad de Resonancia Magnética, Alicante, Spain*

<sup>3</sup>*Ciber, Fisiopatología de Obesidad y Nutrición, CB06/03 Instituto de Salud Carlos III, Madrid, Spain*

<sup>4</sup>*Philips Healthcare España, María de Portugal 1, 28050, Madrid, Spain*

**Keywords:** Magnetic Resonance Spectroscopy, Brain Cancer Detection, Multivoxel, Magnetic Resonance Imaging, Neuronavigator.

**Abstract:** This work presents a simple and interactive spectroscopic tool to help clinicians for brain cancer detection. Firstly, Magnetic Resonance Spectroscopy (MRS) and Magnetic Resonance Imaging (MRI) are registered to perform brain analysis. After processing the spectroscopic signals with HLSVD method for water suppression, zero-filling and phase-correction algorithms, and apodization functions to improve the signal-to-noise ratio (SNR), the metabolite brain maps are generated in order to analyze brain composition. A 3D-spatial distribution of the anatomical and spectroscopic images and how they are registered are presented to facilitate surgery planning. The goal is to generate metabolite brain maps which can be merged with anatomical images in the neuronavigator to provide the surgeon with the exact point where performing the biopsy.

## 1 INTRODUCTION

Many spectroscopic tools have been developed to solve the problem of quantifying signals in <sup>1</sup>H MRS data in the last 20 years (Castillo et al., 1996; Stoyanova et al., 1995). The most popular tools are the jMRUI software package (Stefan et al., 2009), the LCModel<sup>TM</sup> (Gruber et al., 2004) and the AQSES software (Simonetti et al., 2006) among a large series of software applications. All of them incorporate the main algorithms to process the spectroscopic signals in order to correct distortions and imperfections, perform water suppression and generate metabolite maps (Poulet et al., 2007).

They offer black box quantitation algorithms based on singular value decomposition (SVD) such as HSVD (De Beer and Van Ormondt, 1992), HLSVD (Pijnappel et al., 1992) and HTLS (Van Huffel et al., 1994), which are efficient to quantify signals with good signal-to-noise ratio (SNR); in addition, they

are used to suppress the dominant signals, for example the water coin. Moreover, these tools also offer quantitation algorithms with available prior knowledge such as AMARES (Vanhamme and Van Huffel, 1997) or QUEST (Ratiney et al., 2005), which let us impose conditions on the model-function parameters. There are much more methods for spectroscopic analysis, but in summary, the main steps included in most of software tools (Poulet et al., 2007) in order to quantify the signals and generate the metabolite maps are:

1. Phase correction.
2. Dominant signals removal.
3. Signal enhancement with noise reduction.
4. Estimation of spectral parameters.
5. Quantitation with model functions or signal basis sets.

There are many frameworks which already exist, therefore there are no need to re-invent the wheel but understand processes, appreciate limitations and

provide clinicians with the needs they have. The software we present incorporates the main algorithms to process the data, performs the registration between spectroscopic data and MR images, and generates the metabolite maps. Additionally, it introduces a 3D view to merge the 3D anatomical information reconstructed from the MR images with the metabolite information from the spectroscopic signals in order to satisfy clinicians. It combines the effect of molecular structure on the magnetic field experienced by an atomic nucleus, the *Chemical Shift*, with the effects of the magnetic field gradients used in MRI. In addition, the MRS has enormous potential because it allows direct observation of the chemical basis of disease.

In this work we are focusing on multivoxel spectroscopy analysis instead of single voxel spectroscopy in order to study the features of multiple voxels at the same time. This is significant when the area to study is not well defined, such as tumour monitoring or biopsy surgery, where the spatial distribution has notable importance. It provides the clinicians with information about the physical constitution of each disease.

In short, the aim of this work is to provide the surgeon with a 3D view about the area where the patient has the tumour and to generate a DICOM metabolite image which will be used in the neuronavigator when the surgeon will perform the biopsy. In this way, it will be able to detect clearly the tumour area.

This paper is set up as follows: section 2 shows the software structure, explaining briefly each of the four blocks of the tool: multivoxel selection, signal processing, metabolite brain maps and 3D image reconstruction view. In section 3 the features of the algorithms to process the signals are detailed and section 4 shows the image registration to provide the 3D brain view; in section 5, an acceptability test of the software is shown. Finally, a brief conclusion is given in section 6 and the future work is introduced in section 7.

## 2 TOOL WINDOW STRUCTURE

This section explains how the application for brain cancer detection is organized. It allows the surgeon to see “the inside” of the anatomical patient’s brain together with the metabolite maps after the signals are analyzed. The tool is divided into four blocks (Figure 1). In the first block, anatomical images are shown in order to select the voxels of the signals which will be processed. In the second block, the

spectroscopic signals are processed in order to generate the metabolite maps which are presented with the MR images in the third block. Finally, the fourth block shows a 3D-view of the anatomical structure of the patient’s brain and the field of view (FOV) of the spectroscopy imaging (also the VOI that stands for the volume of interest excited inside the FOV) which let the surgeon see the surgery planning to perform the biopsy.

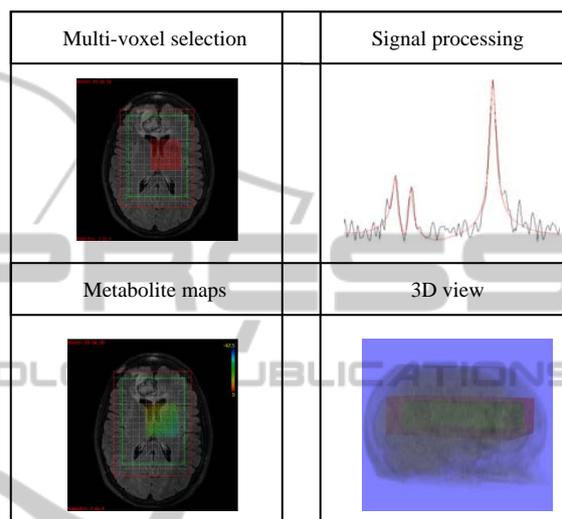


Figure 1: Block diagram of the software tool.

### 2.1 Anatomical Images and Multivoxel Selection

The first step once the application is running is to load the anatomical images of the patient, providing the user with the axial, coronal and sagittal images so as to select those slices which are going to be analyzed with spectroscopy imaging. Next, the spectroscopic data are loaded and we are able to select those voxels which belong to the tumour area.

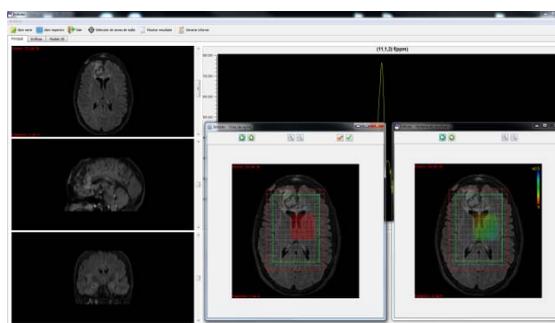


Figure 2: Main window of the tool.

The spectroscopy imaging has a size of  $H*W*P$  millimetres, where  $H$  stands for height,  $W$  stands for width and  $P$  stands for depth. In this way, the size of each voxel can be calculated. Figure 2 shows the main window where we can see the anatomical images with the spectroscopic voxels. The red box is the field of view of the spectroscopy imaging and the red box belongs to the area of those voxels which are excited. Both boxes are registered with the anatomical images as we will show in section 4.

## 2.2 Signal Processing

After the voxels of spectroscopic images have been selected, the signals are processed to quantify and generate the metabolite maps. In Figure 3 it is possible to see the processing block interface, where water suppression, signal to noise improvement and quantifying algorithms are applied.

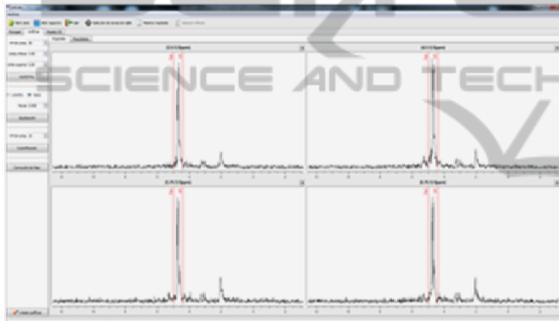


Figure 3: Signal processing window.

This block is divided into two windows: in the first one, the original signals in time and frequency domain are shown. In x-axis, milliseconds, hertz, parts per million (ppm) and points are the existing options; real, imaginary and module options are available in y-axis. In the second block, the result after processing the signals is given, calculating the metabolite amplitudes to create the colour maps.

There are much more tools such as zoom, inverse illustration, etc. and it is also possible to analyze each signal independently clicking on it.

## 2.3 Metabolite Brain Maps

Once the original signals are processed and quantified, the metabolite maps are shown as a blue-red scale in order to emphasize the areas where there is carcinogenic tissue. In Figure 4 the multivoxel selection window and the result-window are shown where the metabolite maps are registered with anatomical images. There is also the option to generate a medical report automatically in *pdf*

format with the patient information, the disease features, the anatomical images, the metabolite maps, and the information that the clinicians wish.

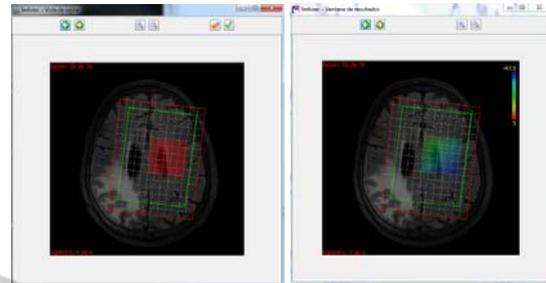


Figure 4: Creation of metabolite maps.

## 2.4 3D Anatomical View - Surgery Planning

In order to know the planning of the MR spectroscopy, the 3D model of patient's head (Figure 5) has been reconstructed and the registration with the volume of spectroscopy imaging (FOV and VOI) performed. In this way, the surgeon knows exactly the area to study with spectroscopic technique and where the tumour is located.

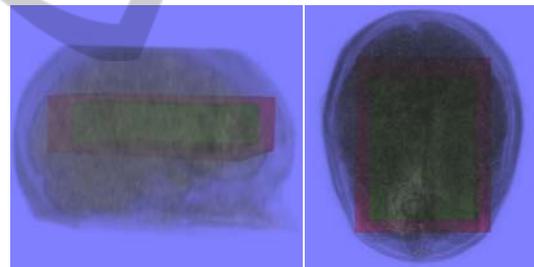


Figure 5: 3D brain reconstruction with spectroscopic volume.

In addition, once the signals are processed and the colour maps generated, it is also possible to recover the 3D colour maps to see the dangerous regions together with anatomical information (see Figure 6).

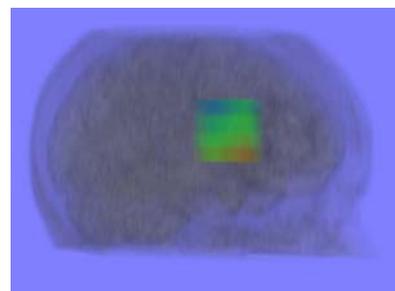


Figure 6: 3D metabolite map reconstruction.

If all metabolite maps corresponding to anatomical images are generated, the 3D colour reconstruction of the full spectroscopic imaging is performed. In this way the surgeon knows as a colour scale the aggressiveness of the tumour.

### 3 SIGNAL PROCESSING METHODS

The purposes of signal processing methods incorporated in this application are water removal, baseline and phased correction, signal to noise improvement and signal quantitation. With this aim, many algorithms have been proposed since 1990 in the time and frequency domain (Vanhamme et al., (2011), but nowadays only some of them are really used in multivoxel spectroscopy imaging. Ideally, the FID signal obtained with the MRS machine is noiseless and results exactly from the addition of  $K$  exponentially damped sinusoids which are characterized by frequencies  $f_k$ , amplitudes  $A_k$ , phases  $\varphi_k$ , damping factors  $\alpha_k$ , length of the FID  $N$ ,  $i$  the square root of  $-1$  and  $\Delta t$  the sampling interval, as:

$$X_n = \sum_{k=1}^K A_k e^{i\varphi_k} e^{(-\alpha_k + 2\pi i f_k)n\Delta t} \quad n = 0, \dots, N-1. \quad (1)$$

Before applying the water removal algorithm, it is also possible to correct the phase of each signal in order to know the sign of the peaks; moreover, it has to take into account because phase is the main factor that affects resolution. In order to remove the water signal, the exponentially damped sinusoids whose frequencies appear in the water region are selected and subtracted from the original FID through the Hankel Lanczos Singular Value Decomposition (HLSVD-PRO) algorithm (Laudadio et al., 2002), which estimates the whole set of model parameters making full use of mathematical model functions. Optimal values of number of sinusoids ( $K$ ) and Hankel size ( $N$  and  $M$ ) must be determined; therefore, values obtained by computer simulations are established by default ( $K=25$ ,  $N=1024$  and  $M=512$ ), allowing the clinicians to change these values for each signal (Cabanes et al., 2001). The user can select the water region with two cursors as well.

After the water signal is suppressed, Lorentzian and Gaussian functions to improve the signal to noise ratio are applied. The exponentially function implemented to improve de SNR is:

$$f(t) = e^{-\text{sign}(\text{factor}) \cdot \text{factor} \cdot t} \quad (2)$$

where *factor* is the apodization coefficient, *sign* is the sign of the factor, and *t* is the time which is  $t^2$

when the function is Gaussian.

At this time, the quantitation method is performed in order to know the concentration of the metabolites in each voxel. AMARES and HLSVD are the algorithms which can be used in our application. In Figure 7 the signal fitting with HLSVD method is shown. As the concentration of each metabolite is known, it is possible to determine the relationship among them. In this way, the colour maps of Naa/Cr, Cho/Cr, Cho/Naa, etc. are calculated (N-acetylaspartate (Naa), creatine (Cr), cholina (Cho)).

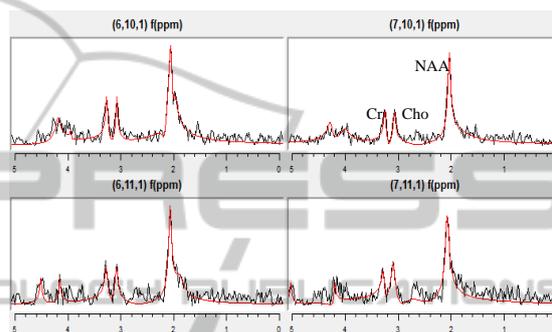


Figure 7: Signal quantitation with HLSVD method.

The new metabolite maps are saved in DICOM format images to be used in the neuronavigator. In this way, the red areas where the tumour is aggressive will be highlight to let the surgeon perform the biopsy accurately.

### 4 IMAGE REGISTRATION

The 3D anatomical view was introduced in section 2.4 to show the new functionality included in this software tool. in this manner, the surgeon is able to see the sagittal, coronal and axial views and the 3D view of the spectroscopic planning (Figure 8).

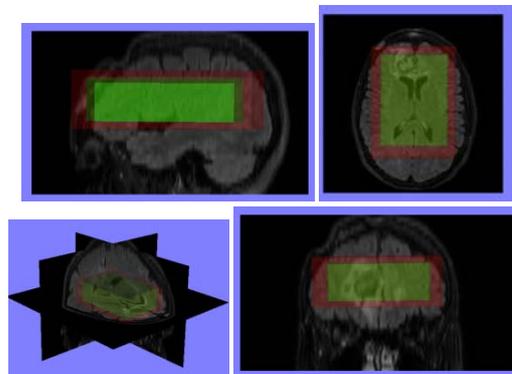


Figure 8: Sagittal, axial, coronal and 3D view.

The first step for image registration is to locate both anatomical and spectroscopic images in the 3D space with their own rotation matrix. At this point, it is possible to know which anatomical images belong to each spectroscopic slice, through the expression:

$$e(x, y, z) = c(x, y, z) + t * M' \quad (3)$$

where the absolute position of the each spectroscopic slice is calculated.  $e(x,y,z)$  is the absolute position of the edges of the spectrum,  $c(x,y,z)$  is the center of the FOV,  $t$  is the thickness of each slice and  $M$  is the rotation matrix. Thus, the surgeon knows exactly the anatomical areas which have been analyzed with MR spectroscopy.

## 5 ACCEPTABILITY TEST

One of the most important features when we deal with medical software is the clinicians' acceptability besides the required accuracy. In order to make easier the use of this application, we have been working in the design of a user-friendly interface, asking doctors for *ease of use (green)*, *noticed usability (blue)*, *human-machine interaction (yellow)* and *satisfaction level (orange)*. After creating the first version of the software, the obtained results in a 10 point scale after asking 5 radiologists and medical engineers are:

Table 1: Results of the acceptability test.

Clarity when using methods	8
Software learning (easy)	9.4
Methodology to process data	9
Direct methods route	10
Signal processing methods (number and suitable)	8.4
Image processing methods (number and suitable)	9
Generate a PDF report	10
Time-work relation	8.6
Human-machine interaction	10
User friendly interface	10
I would like to use this tool in my work	9
Graphical results	9.4
Easy	9
Intuitive	8.6
Useful	9
Handy	9

The table 1 shows the evaluation results of the software in terms of acceptability: the user satisfaction and the human interaction prove the good performance of the tool. We have to improve the noticed usability in order to make the tool more suitable.

## 6 CONCLUSIONS

In this paper, a software tool to help surgeons detect brain cancer through the use of magnetic resonance spectroscopy has been presented.

Many applications and algorithms have been proposed in the last years, but only some of them are really used. The application presented in this paper integrates whose algorithms that are daily used providing the clinician with a user-friendly tool. Furthermore, our goal is not to re-invent the algorithms but understand processes and provide the clinicians with the needs they have. This is the reason why a novel 3D planning view which shows the area analyzed with MRS is incorporated. It consists of anatomical and spectroscopic images, and the 3D reconstruction of patient's brain.

Another significant feature of the tool is the creation of metabolite brain maps. They must be compatible with neuronavigator, so the surgeon knows exactly the point where pointing with a needle when it is performing the surgery. For this reason the images are saved in DICOM format.

## 7 FUTURE WORK

Coming soon experiments are focused on making a comparison with other software to verify the functionality of the algorithms in order to generate reliable metabolite maps. As far as new tool methods are concerned, the fusion with functional images such as Positron Emission Tomography (PET) is being studied. The goal is to perform a 3D PET reconstruction and register anatomical, metabolite and functional images.

Another area of study is the creation of DICOM images which are compatible with neuronavigator. In this way, we are working on the enhancement of the tumour areas to provide the surgeon with a friendly interface to perform the biopsy accurately. Once the DICOM images are generated, the surgeon will perform the biopsy in the operation theatre, taking samples of the emphasized brain tissue and corroborating if the patient has or not tumour. PET

will be also fused with the rest of images in the neuronavigator.

New quantification and water removal methods based on non-linear filters (1D mathematical morphology) are also being studied for its application to MR spectroscopy.

## ACKNOWLEDGEMENTS

This work has been supported by Centro para el Desarrollo Tecnológico Industrial (CDTI) under the project ONCOTIC (IDI-20101153), and partially by projects Consolider-C (SEJ2006-14301/PSIC), “CIBER of Physiopathology of Obesity and Nutrition, an initiative of ISCIII” and Excellence Research Program PROMETEO (Generalitat Valenciana. Conselleria de Educaci3n, 2008-157). We would like to express our deep gratitude to the Hospital Cl3nica Benidorm for its participation in this project. The work of Juan Jos3 Fuertes has been supported by a FPI grant from “Programa de Ayudas de Investigaci3n y Desarrollo (PAID)” of UPV.

## REFERENCES

- Cabanes, E., Confort-Gouny, S., Le Fur, Y., Simond, G. and Cozzone, P.J. (2001). Optimization of Residual Water Signal Removal by HLSVD on Simulated Short Echo Time Proton MR Spectra of the Human Brain. *Journal of Magnetic Resonance*. 150:116-125.
- Castillo, M., Kwock, L., and Mukherji, S. (1996). Clinical application of proton MR spectroscopy. *American Journal of Neuroradiology*. 17:1-15.
- De Beer, R. and Van Ormondt, D. (1992). Analysis of NMR data using time domain fitting procedures. *NMR Basic Principles and Progress*. 26:202-48.
- Gruber, S., Stadibauer, A., Mlynarik, V., Ganslandt, O., and Moser, E. (2004). An LCModel-based automatic software tool for the reconstruction of anatomically- and pathologically-matched voxels using high-resolution 3D-spectroscopic imaging: Applications in tumour patients. In *Proc. ISMRM*, volume 11.
- Laudadio, T., Mastronardi, N., Vanhamme, L., Van Hecke, P. and Van Huffel, S. (2002). Improved Lanczos algorithms for blackbox MRS data quantitation. *Journal of Magnetic Resonance*. 157:292-297.
- Pijnappel, W. W. F., Van den Boogaart, A., De Beer, R., and Van Ormondt, D. (1992). SVD-based quantification of magnetic resonance signals. *Journal of Magnetic Resonance*. 97(1):122-134.
- Poulet, J., Sima, D. M., Van Huffel, S., and Van Hecke, P. (2007). Frequency-selective quantitation of short-echo time 1H magnetic resonance spectra. *Journal of Magnetic Resonance*. 186(2):293-304.
- Ratiney, H., Sdika, M., Coenradie, Y., Cavassila, S., Van Ormondt, D., and Graveron-Demilly, D. (2005). Time domain semi-parametric estimation based on a metabolite basis set. *NMR in Biomedicine*. 18(1):1-13.
- Simonetti, A. W., Poulet, J-B., Sima, D. M., De Neuter, B., Vanhamme, L., Lemmerling, P., and Van Huffel S. (2006). An open source short echo time MR quantitation software solution: AQSES.
- Stefan, D., Di Cesare, F., Andrasescu, A., Popa, E., Lazariiev, A., Vescovo, E., Strbak, O., Williams, S., Starcuk, Z., Cabanas, M., Van Ormondt, D., and Graveron-Demilly, D. (2009). Quantitation of magnetic resonance spectroscopy signals: the jMRUI software package. *Measurement Science and Technology*, volume 20.
- Stoyanova, R., Kuesel, A., and Brown, T. (1995) Application of principal-component analysis for spectral Quantitation. *Journal of Magnetic Resonance*. 115:265-269.
- Van Huffel, S., Chen, H., Decanniere, C., and Van Hecke, P. (1994) Algorithm for time-domain NMR data fitting based on total least squares. *Journal of Magnetic Resonance*. 110:228-237.
- Vanhamme, L., and Van Huffel, S. (1997). Improved method for accurate and efficient quantification of MRS data with use of prior-knowledge. *Journal of Magnetic Resonance*. 129(1):35-43.
- Vanhamme, L., Sundin, T., Hecke, P. V., and Huffel, S. V. (2001). MR Spectroscopic Quantitation: a Review of Time-Domain Methods. *NMR in Biomedicine*. 14:233-246.