Statistical Simulation of MR Spectroscopy of Brain Lesions by Neural Network
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Citation

Abstract
PURPOSE- To generate or simulate an artificial or virtual MR spectroscopic effect of normal state of brain or any pathology from the signal intensity or the image shades to give some idea to the radiologists about the various chemical components of brain lesion and its chemical or physical environment. By this radiologist can suggest the neurosurgeon or physician about management and treatment when a facility of MR spectroscopy is not available.

OBSERVATION- It has been observed that there is a relationship between the T2 value of cerebral tissue, signal intensity and gray shade value of pixel with the specific pattern and amplitude of the peak of metabolites of MR Spectroscopy (MRS) of normal or pathological brain. The T2 value of brain tissue, log of spectral plot of signal of the image and signal intensity level (all as independent Numeric Variables) are consistent with the various amplitude of peaks of metabolites like lipid, lactate, N acetyl aspartate (NAA), choline, creatine (as dependendent variables) as MR spectroscopic graph. A data set of position of the metabolites and amplitude of the peaks and valleys is found to be unique of a particular T2 value, signal intensity or gray shade value of tissue in normal and disease state (independent Category Variables).

MATERIALS AND METHODS: MRI and MRS are done in patients of normal and pathological cases. T2 mapping is done and gray shade was generated from the mapping. The T2 value of tissue and corresponding gray shade value(GSV) of pixel of a T2 MR image and the amplitude of the peaks of various metabolites like lipid, lactate, N- Acetyl Aspartate (NAA),choline, creatine of corresponding MRS etc are measured (quantified). Data sets of both normal and disease state were prepared. The datasets are examined by a Neural Net work (mathematical) program. Live prediction of the amplitude of the metabolite peak (NAA or Choline etc) can be generated as dependent numeric variable against the signal intensity (independent category variable) and other known independent numeric variables.

RESULTS: The various values obtained are put into an Excel data sheet and are analyzed. A neural Net work program live predicts the unknown variables. Ultimately a graph of spectrum of peaks of the metabolites can be generated in the excel dataset of the values of the amplitude in the Y axis, plotting against the location of the metabolites in the X axis.

DISCUSSION-: This graph resembles the MRS graph of the peaks of the normal or abnormal brain tissue.

INTRODUCTION
Magnetic Resonance Spectroscopy (MRS) detects magnetic resonance signals produced by atomic nuclei located within molecules in living tissue. 1H MR Spectroscopy (H MRS) states about the chemical environment of cerebral tissue both in normal and pathological state.

There are numerous metabolites found in the human brain, only several of them occur in significant quantities and are useful in proton spectroscopic studies. Positively charged moving proton in the nucleus has its own magnetic field which is very much influenced by the electrons moving in the orbits( having their own magnetic field). This is called magnetic shield which has influence on the precision of frequency of hydrogen(H) proton in different chemicals. The difference of frequency precision of H proton of water in a 1Tesla magnet (42,576100Hz) and that of H proton in a lipid (42.575.955 Hz) is the Chemical Shift ( here it is 145Hz(1,2,3)( Figure1A) This chemical shift expresses frequency of precision in Hz multiplied by million is the part per million (PPM). A spectrum of the metabolites is plotted on a two dimensional graph. The horizontal axis(X) represents the frequencies (chemical shifts) in PPM as independent
variable and the vertical (Y) axis represents the amplitude of the concentration of the metabolites peak as dependant numeric variables. Quantification of the MRS signal amplitude can provide a means of estimating the tissue concentration of the signal generating molecules. The molecules that produce readily detected MRS signals tend to have relatively low molecular weight and are able to move freely within the fluid compartments of biological tissues. Many such molecules are components of metabolic pathways and MRS is thereby sensitive to certain aspects of tissue metabolism. Major metabolites are NAA, Choline, Creatine, Lactate, Glutamine, glutamate, Lipid, Myo-Inositol (4) (Figure 1B). Their properties are tabulated in the Table 1. The overall level of total creatine in normal and pathological brain is fairly constant. Change in the amplitude can be regarded as trends in normal and disease state which gives a Specific Graph Pattern (5).

**Figure 1a**
Chemical Shift

**Figure 1b**
Normal MRI of brain in T2 sequence with voxel and C MRS

<table>
<thead>
<tr>
<th>ppm</th>
<th>Metabolite</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9-</td>
<td>Lipids</td>
<td>Products of brain destruction</td>
</tr>
<tr>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3</td>
<td>Lactate</td>
<td>Product of anaerobic glycolysis</td>
</tr>
<tr>
<td>2</td>
<td>NAA</td>
<td>Neuronal marker</td>
</tr>
<tr>
<td>2.2-</td>
<td>Glutamine, glutamate</td>
<td>Neurotransmitter</td>
</tr>
<tr>
<td>2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Creatine/GABA</td>
<td>Energy metabolism</td>
</tr>
<tr>
<td>3.2</td>
<td>Choline</td>
<td>Cell membrane marker</td>
</tr>
<tr>
<td>3.5</td>
<td>Myo-Inositol</td>
<td>Glial cell marker, osmolite</td>
</tr>
</tbody>
</table>

Table 1

Each pixel has a numerical value, called a digital number (DN) that records the intensity of electromagnetic energy measured for the ground resolution cell represented by that pixel (6,7,8,9,10). Digital numbers range from zero to 255 on a gray scale (out of 256 shades) in a DICOM image. The image may be described in strictly numerical terms on a three-coordinate system with x and y locating each pixel and z giving the DN, which is displayed as a gray-scale shade (intensity) value (GSV) (11,12,13,14,15,16). Other than GSV these peaks vary in their amplitude against other factors like: i) a tissue T2 value derived from brain mapping ii) intensity of signal in image pixel, iii) logarithmic value of the image signal spectrum. The dynamic range of an image can be compressed by replacing each pixel value with its logarithm.

If the graph of the peak amplitude of the metabolites are analyzed, a typical pattern is noted of normal brain against a T2 value of 75ms with a GSV of 85 (out of 256) (Figure 2). In this graph amplitude of peak of creatine was taken as the reference value or 1, the peaks can be expressed as aspect ratio as the peak amplitude of NAA is 2, Choline -1.8, Lipid and lactate -0.8, Myo-Inositol -1.5, Glutamine and glutamate-0.45 respectively (17,18,19) (Figure 2A).
Figure 2a
MRS of normal brain

If peak amplitude of the metabolite (choline, NAA, lipid etc) is determined against the corresponding tissue T2 value of brain and brain lesions, signal intensity, log of image signal spectrum and a particular GSV of image pixel in normal and disease state (independent numeric variables) then a data set can be tabulated in an excel spread sheet and a pattern graph of the peaks can be generated (20,21). The amplitude of the metabolites of peaks and valleys (maximum and minimum values) are plotted in the Y axis as dependent variables (21,22) which respond to independent numerical variables mentioned above and show change or trend in different disease state. Live prediction of the peak of the metabolites (dependent numeric variable) of an unknown lesion in an image is possible by Neural Network when the independent numeric variables are already known. The trend of the amplitude (or peaks) of graph against corresponding T2 value of tissue, GSV, signal intensity or logarithmic value gives a particular pattern (Figure 3A and B). The pattern graph supports the study’s hypothesis mostly (23). A graph can be generated in the excel data sheet resembling original MRS.

Figure 2b
voxel showing GSV and measurement of amplitude of various metabolite peaks

Figure 3a and b
T2 image, region of interest( XY coordinates, GSV, MRS like; Graph generated in excel spread sheet

MATERIALS AND METHODS
We examined 110 cases after taking proper ethical permission (Table2). Both MRI and MRS were done in each case.

Table 2

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLIOMA</td>
<td>25</td>
</tr>
<tr>
<td>Low grade glioma</td>
<td>6</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>14</td>
</tr>
<tr>
<td>Oligodendroglioma-</td>
<td>2</td>
</tr>
<tr>
<td>Pilocytic Astoyctoma--</td>
<td>1</td>
</tr>
<tr>
<td>Medulloblastoma----</td>
<td>2</td>
</tr>
<tr>
<td>INFLAMMATORY-</td>
<td>5</td>
</tr>
<tr>
<td>Tumefactive MS</td>
<td>2</td>
</tr>
<tr>
<td>Solid brain abscess</td>
<td>1</td>
</tr>
<tr>
<td>OTHERS</td>
<td>2</td>
</tr>
<tr>
<td>Metastass</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoma-----------</td>
<td>2</td>
</tr>
<tr>
<td>Normal Cases-------</td>
<td>78</td>
</tr>
</tbody>
</table>

MR SPECTROSCOPY AND MRI scan was performed on the 3 Tesla magnet using a quadrature head coil. 1H MRS data were acquired for the suspected pathological cases. The
MR imaging sequences of these studies included axial T1 weighted (TR/TE:450/15), T2 weighted (4500/120), FLAIR (8500/120), sagittal FLAIR, and coronal T2 weighted, with a matrix size of $256 \times 256 \times 48$ and a pixel size of $1 \times 1 \times 3$ mm. For identifying regions of active tumor or disease the sensitivity and specificity of these images may not be optimal as the invading margin may remain invisible. Patients underwent single voxel point-resolved MR spectroscopy [PRESS] at short TE (30ms) and long TE (135ms) (PRESS) before operation to identify region of abnormal metabolism (24,25,26,27,28,29,30,31) that corresponds pathology of the tumor/mass anatomy of MR image. For MRS the region of tissue studied was chosen to include most of the pathology, surrounding normal tissue avoiding bone and subcutaneous fat, and contra lateral tissue.

Following methods were done to determine the independent numerical variables of gray and white matter and various brain lesions like:-

i) Gray scale value (GSV) of image,

ii) Signal intensity of the image,

iii) T2 value of tissue

iv) Logarithm of signal spectrum of the region of interest of the image.

DETERMINATION OF GRAY SCALE VALUE AND SIGNAL INTENSITY

DICOM images of T2 sequence were loaded in a DICOM editor (Sante DICOM Editor, Sante Soft, Greece). A voxel or rectangular box ($1 \times 1$cm) is selected as region of interest (Figure 4A). Signal intensity and GSV of normal tissue and various brain lesions were determined and tabulated in an Excel Spreadsheet (32). Their relationship is shown in Figure 4B.

DETERMINATION OF LOGARITHMIC VALUE OF SIGNAL SPECTRUM OF THE IMAGE

A raw data containing the signal of region of interest (ROI) of the T2 image of various brain lesions and normal tissue was generated by the DICOM editor. This raw data was then processed in a special mathematical software DADiSP (DSP Development Corporation, MA, USA) as a Binary data type with signed integer. Signal were processed in different windows of the program like Fast Fourier Transform, Spectral plot of the image signal and Logarithm of the image spectrum by a method to specify logarithmic axis using the SETXLOG and SETYLOG functions (32,33,34). The maximum peak value of the logarithm were determined in dB and tabulated serially (Figure 5A,B,C).
Figure 5a
DADiSP program shows signal of the image (in Binary) of normal brain loaded in window 1, Fast Fourier Transform in window 2, spectral image in window 3 and Logarithmic value of maximum peak (in dB) of image spectrum in the window 4.

Figure 5b
DADiSP showing various windows of signal processing of a glioma and logarithmic value in window 4

Figure 5c
DADiSP showing various windows of signal processing of central portion of degenerated tumor and logarithmic value in window 4

Figure 5d
Relationship between signal intensity and spectral logarithmic value.

T2 MAP GENERATION:
Quadrature head coil was used and a T2 weighted scan was performed in 3T Siemens (Germany) Magnetom Trio Tim syngo MR B15 scanner to note effect of T2 decay and its relationship with pixel gray scale value. In order to obtain T2 map, 5 images of different echo times (TE) eg. 30, 60, 90, 120, 150, 180ms were applied in a 3.0T magnet (35, 36, 37, 38). The selected parameters were: slice thickness - 8mm at the ventricular levels with a matrix 256 X 256 (FOV 220mm). To measure the mean T2 intensity (S) regions of interests (ROI) 5mm square were placed in the body and frontal horns of the lateral ventricle for CSF, cortex of parietal lobe for gray matter and centrum semiovale for the white matter. A T2 map was generated (Figure 4 B and C) using dedicated software installed within the magnet by fitting the image signal intensities (S) acquired at different echo times to a single exponential decay, $S = S_0 e^{-TE/T2}$ on a pixel by pixel basis (24).

To avoid fitting noise, pixels having intensity values below a global threshold in the TE=30ms for image and those for which the fit failed, were assigned a T2 value of zero. T2 values of tissue of normal brain and pathological lesions were determined from the T2 map directly (Figure 6 A and B). A T2 shade (out of 256 shade and 8 bit) was also prepared to get the tissue value easily (Figure 6C). In the T2 map T2 values of various tissues and masses were easily obtained and tabulated (39) (Table 3). In excel data sheet the T2 value and corresponding gray shades were tabulated (Table3).
**Figure 6a, b, & c**
A. T2 MAP in a 3 Tesla and B. 0.3 Tesla magnet C. T2 shade generation from the T2 map

**NEURAL NETWORK**
A data set manager was prepared in a Neural network program (Palisade Neural Tool 6.1.2) as Independent Category Variables of tissue like gray and white matters, various tumors and infarction, fatty degeneration etc. Dependent Numerical variables are the maximum peak (amplitude) of the NAA, Choline, Creatine, Lipid, lactate, myoinositol, glutamine and glutamate which are to be predicted one after another against independent numerical variables like T2 value of brain and brain lesions, GSV (as pixel gray value signature), signal intensity and logarithmic value of the image signal spectrum (in dB) in a region of interest of the image. Once a statistical characterization or pattern was achieved for each information class, the image was then classified by examining the amplitude of metabolite peak for each pixel and making a decision about which of the signatures it resembles most. The missing peak (or unknown maximum value) against a particular pixel value of corresponding data set of independent numeric variables as signature data set was live predicted by the network. Figure 6 shows the schematic diagram of relationship of a particular region of interest with independent numeric variable and dependent numeric variable as metabolites’ peak and the specific graph pattern (of MRS).

**Figure 7**
Schematic diagram showing relationship of Image Data Set, Pixel Gray value(GSV) signature, metabolite peak (amplitude) signature and specific graph patterns- i) above-origin MRs, ii)below- simulation of MRs in excel spread sheet

**RESULTS AND OBSERVATION**
From the table 3 it was evident that T2 value of CSF and edema fluid were high due to high velocity of the proton taking excess time to exchange energy (hn) to the surrounding lattice for relaxation unlike the relatively low velocity of the proton of solid component of tissue.

<table>
<thead>
<tr>
<th>TISSUE</th>
<th>T2 VALUE (ms)</th>
<th>GRAY SHADE VALUE (GSV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>400</td>
<td>255</td>
</tr>
<tr>
<td>CSF</td>
<td>360</td>
<td>250</td>
</tr>
<tr>
<td>EDEMA</td>
<td>300</td>
<td>230</td>
</tr>
<tr>
<td>TUMOR</td>
<td>21</td>
<td>180</td>
</tr>
<tr>
<td>TUMOR</td>
<td>34</td>
<td>168</td>
</tr>
<tr>
<td>TUMOR</td>
<td>51</td>
<td>145</td>
</tr>
<tr>
<td>TUMOR</td>
<td>55</td>
<td>125</td>
</tr>
<tr>
<td>White matter</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>Gray matter</td>
<td>75</td>
<td>81</td>
</tr>
</tbody>
</table>

Relationship of T2 value and gray shade was determined from the graph 7A and B:

\[ y = 0.256x + 154.3 \]

where, Y is the GSV and X is the T2 value of fluid/liquid component – (1) (Figure 5A)
y = -1.884x + 226.8 where, Y is the GSV and X is the T2 value of solid component of tissue – (2) (Figure5B)

**Figure 7a and b**

A. T2 value vs gray shade value of liquid component of tissue. B. Solid component of tissue.

DICOM image is superior to JPG, TIFF, BMP images as no loss of data occur when the images are converted into this extension, and proper gray shade value (GSV) can be determined accurately. A particular image of the brain pathology (normal, Astrocytoma or brain tumor, metastasis, abscess, infarction etc) will have a particular pattern of MRS (metabolite amplitude signature) depending on the maximum peak against a pixel GSV, T2 value, signal intensity, log of image signal spectrum (Figure 7). This pixel GSV may be designated as “pixel gray value signature”. Neural network live predicts the amplitude of the metabolites (maximum peak) against the above mentioned independent variables (Table 4A,B,C). Table 5 depicts the summary of training and testing of neural net work.

**Table 4a**

Neural net work shows a portion of the data set undergone training and testing to predict the choline peak.

**Table 4b**

Live prediction of peak values of choline (in violet color) in an image of unknown lesion when all the independent variables are known.

**Table 4c**

Live prediction of peak values of NAA (violet color) in an image of unknown lesion when all the independent variables are known.
A MRS like graph could be generated in the excel data sheet for a particular brain pathology or of a normal study from the predicted data of the metabolite peaks. Following observation was noticed:

1) Normal MRS pattern was seen from gray shades value (GSV) 72 (of a selected voxel in the DICOM image) through GSV 127 shades with a declining NAA peak heights (amplitude) and increasing Choline (Cho) peak height. Peak height of Creatine (Cr) does not change much (except in Metastasis). So Cr was chosen as the reference peak to compare with the other peak heights (Figure 4).

2) From GSV 128 up to 186 peak height of Cho remains high in comparison to peak height of Cr. In GSV 160 shade Cho is maximum and 4 times that of Cr (Cho/Cr ratio=4) height and NAA peak becomes very much less and NAA/Cr ratio is almost 1. MI (myoinositol) to Cr ratio is also approximately 1 (in patients of Astrocytoma Gr-I to Gr-II). In comparison lipid, lactate peak heights remain less.

3) In high grade Astrocytoma Gr III and IV (GSV 205 to 235) due to fatty degeneration and anaerobic metabolism lipid and lactate peaks are tall. Lipid to Cr ratio is almost 2.88 and lactate to Cr ratio about 1.1.
4) In Infarction lactate is high (GSV 238 to 246 according to the age of infarction) and lactate to Cr ratio is almost 1.5, NAA to Cr or Cho to Cr ratio is 1. Lipid peak is much less.

5) In the centre of the abscess shade GSV190 to 203 lipid level is very much high (Lipid to Cr ratio7:1) and lactate to Cr ratio is 5:1. NAA, Cr and Cho amplitudes are very much less.

6) To establish a relationship of Gray shade Value and amplitude of MRS metabolite peaks raw data files were used by Auto correlation of the peaks of a particular spectrum and then Cross correlation of other MRS spectrum. Particular emphasize on the amplitude of major peaks like NAA, Cr, Cho, Lactate ,Lipid and MI, Cr2 were done ignoring the other weaker peaks(valleys) but keeping their locations in the base points (X axis-as S1,S2 S3….S10)

MRS LIKE CURVE GENERATION- Data of the Gray shade values (pixel gray value signature) and amplitude of the peaks (signature of metabolites peaks) are put into an Excel spread sheet as columns against rows #78 through 255 GSV . The steps of live prediction of neural network is recapitulated below :

1. A DICOM image of T2 sequence is loaded in a DICOM editor.
2. A box resembling a voxel is selected in the pathological part of the image. GSV out of 256 and signal intensity can be read from the region of interest (ROI) (Figure9A).
3. A Dataset manager was created of the data of independent numeric variables (Signal intensity, GSV, T2 value of tissue and Log of signal spectrum) already we know to train and Test the values (Table 4A). Live prediction of signature amplitude of MRS peaks corresponding to of independent numeric variables of a region of interest of a gray shade value of an unknown image can be done almost accurately from the previous test values of the metabolites(4B,C) So metabolites like, NAA, Choline, creatine, lipid and lactate can be predicted one after another.
4. A matrix of two rows was created in the excel spread sheet to generate the graph simulating MRS (Figure 9B ). First row is the base points location (like 0,0.5,0.8,1.3,2.2,3.3,2.3,3.7,4,5 etc as if the PPM locations. No emphasis was given to the weaker signals of metabolites (valleys) but their locations in the X axis as PPM were denoted as Signal V1,V2,V3 V4,…V10) and are placed sequentially along with the position of the metabolites.

Figure 9a

Figure 9b

Upper row indicates the base point location PPM of the peak and valleys of metabolites. Lower row denotes the predicted value of the metabolite peaks of determined by neural network.

MRS SIMULATION

1) MRS GRAPH OF A NORMAL BRAIN

A DICOM image of T2 sequence of normal brain is loaded in the DICOM editor (Figure10A) with original MRS generated in a 3T scanner. Region of interest (ROI) as voxel (white box) is shown in left para ventricular white matter. GSV shown is 86 and signal intensity -98, tissue T2 value derived from T2 map -73ms and Log of signal spectrum-85.4. Neural network live predicts the peak of the various metabolites one by one which are already determined and tabulated in the Table 10B in the column of base points. To simulate a MRS like effect values of the valleys are also placed in between the peaks including the doublet effect of lactate. When these values are put into the y axis below the base points of X axis of the Matrix (Figure10C) a normal MRS like graph is generated (Figure10D)
Figure 10a
DICOM image and original MRS generated in 3T scanner.

Figure 10b
Predicted all the metabolites tabulated sequentially as per position in the base point of a normal tissue against T2 value, log of spectrum, GSV

Figure 10c
Placing the values of predicted metabolite peaks in the Y axis below the corresponding base points in the Matrix

Figure 10d
MRS like Graph generated in the excel spread sheet

2) MRS GRAPH GENERATION OF GLIOBLASTOMA

A DICOM image of T2 sequence of a Glioblastoma is loaded in the DICOM editor (Figure 11A) with original MRS generated in a 3T scanner. Region of interest (ROI) as voxel (white box) is shown within the tumor. GSV shown is 172 and signal intensity 345, tissue T2 value 80ms, Log of signal spectrum 84. Neural network live predicts the peak of the various metabolites one by one which are already determined and tabulated in the Table 11B in the column of base points . To simulate a MRS like effect values of the valleys are also placed in between the peaks including the doublet effect of lactate. When these values are put into the y axis below the base points of X axis of the Matrix (Figure 11C) a normal MRS like graph is generated (Figure 11D)

Figure 11a
DICOM image of a Glioblastoma and original MRS generated in 3T scanner.

3) MRS GRAPH GENERATION OF THE DEGENERATED COMPONENT OF GLIOBLASTOMA

A DICOM image of T2 sequence of a Glioblastoma is loaded in the DICOM editor (Figure 12A) with original MRS generated in a 3T scanner. Region of interest (ROI) as voxel (white box) is shown within the solid component of tumor as well as in the peripheral degenerated portion. In the peripheral part GSV-213, signal intensity-462, T2 value- 255 and log of signal spectrum 78 dB.

Neural network live predicts the peak of the various metabolites one by one which are already determined and tabulated in the Table 10B in the column of base points . To simulate a MRS like effect values of the valleys are also placed in between the peaks including the doublet effect of lactate. When these values are put into the y axis below the
base points of X axis of the Matrix (Figure12C) a normal MRS like graph is generated (Figure12D)

4) MRS GRAPH EFFECT OF A BRAIN ABSCESS

Figure 13 B shows brain abscess with simulated MRS resembling original MRS having high peak of lipid and lactate. GSV 252 signal intensity 675, log value of signal -69, selected. The graph is generated in the spread sheet after getting the predicted value of the metabolite peaks and placing in the y axis of the matrix below the corresponding base points.

In this way MRS like graphs of infarction, glioblastoma, low grade glioma, metastasis and brain abscess were generated from the predicted peaks values of metabolites determined by Neural Network and independent numeric variables (Figure 14,15,16,17,18)

CONCLUSION

T2 value is derived from a T2 map and a gray shade is generated from the T2 value. Signal intensity was determined from the DICOM editor and logarithmic value of the signal spectrum was deduced from the DADiSP program. A correlation of Pixel gray shade value signature and metabolite peak signature (Particular pattern) was determined. Maximum value of the peak along with the minimum values (valleys) of metabolites were placed in the Y axis and location of the metabolite peak were placed in the X axis as the base points resembling PPM (part per million) in an Excel data sheet. When these two data sets were selected a MRS like graph of a region of interest of a lesion of an image could be generated simulating an original MRS generated from the 3T magnet.

References

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