

MAGNETIC RESONANCE SPECTROSCOPY

BioE-594- Advanced MRI

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Topics to be Discussed:

- What is Spectroscopy.
- Basic spectroscopic techniques.
- What is Magnetic resonance spectroscopy.
- Methodology of MRS.
- Prognosis.

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➤ What is spectroscopy:

- Spectroscopy deals with interactions between electromagnetic radiation and matter.
- It is the study of spectra that is the dependence of physical quantities on frequency.
- It is often used in physical and analytical chemistry for the identification of substances through the spectrum emitted or absorbed.

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• NMR spectrum:

- Observation of chemical shift differences provides the basis for the use of NMR as a method for spectroscopic chemical analysis for identifying chemical and molecular structure.
- Resonance frequency (chemical shifts) are plotted as a function of their intensities.

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Basic spectroscopic techniques

- Continuous wave method spectroscopy.
- Fourier transform spectroscopy.
- Proton NMR Spectroscopy.
- Carbon-13 NMR Spectroscopy.
- Correlation spectroscopy.

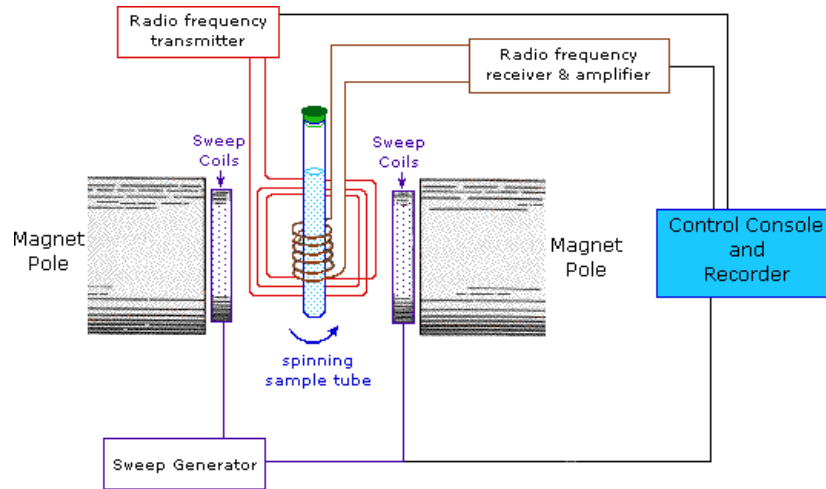
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➤ Continuous wave method spectroscopy

- Throughout its first two decades, nuclear magnetic resonance practice utilized a technique known as continuous-wave (CW).
- In this technique the excitation of spins is carried out by RF magnetic field of slowly changing frequency, which is present during the entire period of spectrum recording field interacts continuously with the spin system, hence the name CW.

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CW-spectrometer



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Main parts of CW Spectrometers

1. Magnetic field stability and field homogeneity
 - The magnetic field stability is accomplished by superconducting electromagnets.
 - Line broadening occurs due to field inhomogeneity, the inhomogeneity can be reduced by reducing the volume of sample and the pole caps should have maximum area.
2. The RF transmitter, the detector and the phase correction.
 - RF transmitter is a radiation source for creating an excitation field B_1 .
 - For the detection of resonance absorption the method used
 - Bloch method, the probe is placed inside the transmitter which is oriented perpendicularly to B_0 and creates the Rf field and the receiver coil is oriented perpendicularly to both transmitter coil and B_0 around the probe, the voltage is induced in the receiver and recorded.

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3. Sensitivity, spectrum accumulation.

- The smaller the number of nuclei to be detected the more sensitive is the spectrometer which is determined by the noise level. The noise level can be lowered by the elimination of possible sources of noise, a careful design of amplifiers, oscillators and power supplies, lowering the temperature of receiver coil.
- A significant increase in signal to noise ratio is possible by spectrum accumulation techniques, in which the spectra are recorded in series frequency and intensity data are added and stored in the computer connected to the spectrometer.

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4. Spectrum integration, signal intensity measurement.

- The spectrum is integrated with the help of built in integrators.
- By measuring the step heights the intensity of the signal is measured.

5. Double resonance method.

- Exciting two or more sets of nuclei with different chemical shifts by application of two or more RF oscillators (to solve various technical problems of recording spectra).

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6. NMR solvents and reference substances.

- For high resolution spectra, it is advisable to measure dilute solution.
- Chloroform-d (CDCl_3) is the most common solvent for nmr measurements, due to its good solubilizing character.
- Other deuterium labeled compounds, such as deuterium oxide (D_2O), benzene-d₆ (C_6D_6), acetone-d₆ (CD_3COCD_3) are also available for use as nmr solvents.

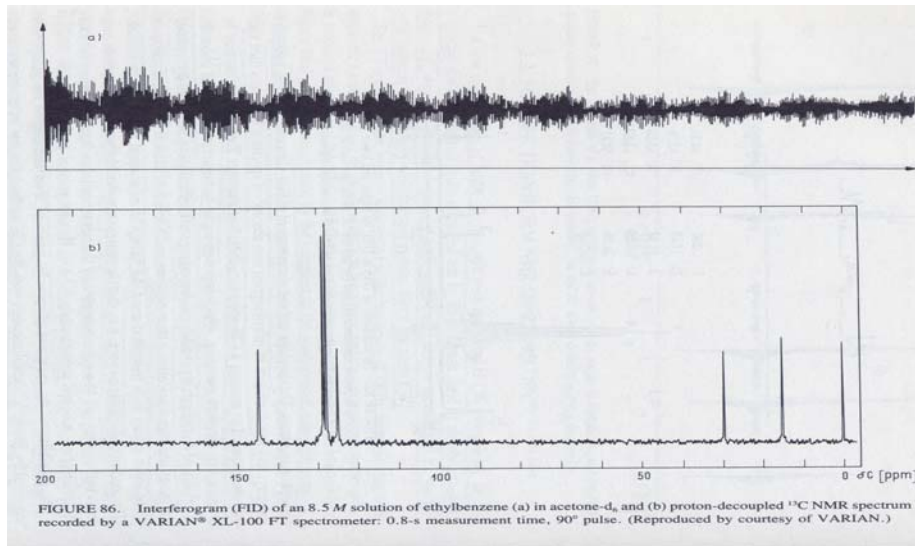
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Fourier Transform NMR Spectroscopy

- The FT spectrometers became widespread at the beginning of 1970's.
- The magnetic nuclei are excited by short RF pulses of discrete frequency, and the spectroscopic information is recorded after switching off the RF field.
- An interferogram is obtained (figure) which is transformed by the computer of the spectrometer, using the principle of Fourier analysis, into the usual frequency-dependent absorption spectrum.
- The interferogram is produced by the difference between the frequency of the RF field and the larmor frequencies of the magnetic moment components induced by RF field.

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- Figure of interferogram



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- Advantage of Fourier transform spectroscopy over CW is requires much less time than to measure a spectrum of the same quality.
- It is done by averaging the interferograms produced by repeated RF pulses and than transforming them.

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Proton MR Spectroscopy

- An imaging method of detecting and measuring activity at the cellular level. It provides chemical information and is used in conjunction with magnetic resonance imaging (MRI), which gives spatial (3-dimensional) information.
- Proton NMR spectra are characterized by chemical shifts in the range +12 to -4 ppm.

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Carbon-13 NMR Spectroscopy

- Carbon-13 NMR is the application of nuclear magnetic resonance in spectroscopy with respect to carbon. It is the carbon pendant of proton NMR and it allows the identification of carbon atoms in an organic molecule just as proton NMR identifies hydrogen atoms.
- The typical range of chemical shifts of ^{13}C signals is larger than for ^1H .

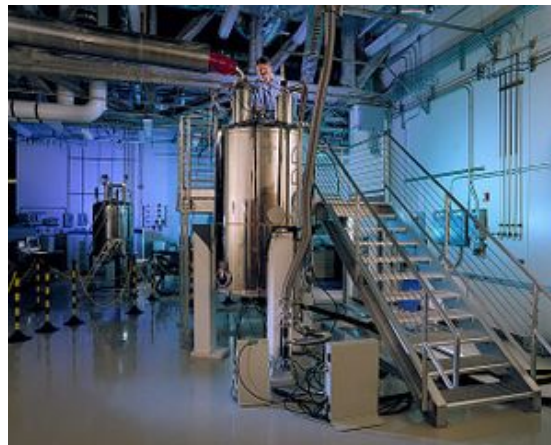
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Correlation spectroscopy

- Correlation spectroscopy is one of several types of two-dimensional nuclear magnetic resonance (NMR) spectroscopy.
- Two-dimensional NMR spectra provide more information about a molecule than one-dimensional NMR spectra and are especially useful in determining the structure of a molecule, particularly for molecules that are too complicated to work with using one-dimensional NMR.

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Pacific Northwest National Laboratory's high magnetic field (800 MHz) NMR spectrometer being loaded with a sample.



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➤ What is magnetic resonance spectroscopy (MRS):

- MRS is the medical name for NMR spectroscopy as it applies to medicine.
- Magnetic resonance spectroscopy is the use of the NMR phenomenon to study underlying pathology.
- Magnetic Resonance Spectroscopy (MRS) evaluates the human metabolism in clinics and research.
- It analyzes using certain atomic nuclei to determine different local environments of hydrogen, carbon or other atoms in the molecule of an organic compound.

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Basics of MRS

- The physical foundations of spectroscopy are the same as for MRI.
- Both studies in vivo and in vitro can be performed with MRS.
- The primary difference is that in MRI magnetic gradients are used to perform the readouts of the magnetization signal; in spectroscopy all such gradients are avoided.
- Another important difference is that in MRI we can tolerate a quite spatially inhomogeneous applied external field (B_0), and still create good images.
- In spectroscopy, on the other hand, the B_0 field over the region studied has to be extremely homogeneous.
- Surface coils are used for selecting the region of interest.

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- **Nuclei:**
 - Not all nuclei possess magnetic moments. Of those that do, the spin quantum number may be greater than 1/2.
- **Signals:**
 - The factors that determine the strength of a MRS signal depend primarily on the number of nuclei present under the coil and on the energy between the ground and excited states (the higher the better). This energy is related to the strength of the applied field B_0 and the magnetic moment of the nucleus.

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- **Chemical shift**
 - The chemical shift is frequency dependent and it is expressed as a dimensionless number given by
$$\delta = [(F_{\text{nuc}} - F_{\text{ref}}) / F_{\text{ref}}] \times 10^6$$
where
 F_{nuc} is the resonance frequency of the sample and F_{ref} is the resonance frequency of a reference sample. The chemical shift δ is expressed in ppm (parts per million) and is independent of the frequency of the magnet used.

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- Spin-spin coupling:
 - Spin–spin coupling is the exchange of spin between nuclei that is not propagated through space but is mediated by the binding electrons that connect the nuclei.
 - Two identical spin 1/2 nuclei can exist in the following states with respect to B_0 . $\downarrow\downarrow\uparrow\uparrow\uparrow\downarrow\downarrow\uparrow$
 - The last two are degenerate (i.e. identical) so that a triplet of states is created each of which can produce a unique spectrum (=triplet peak). Similarly, three such nuclei can produce a quadruplet spectrum. This coupling is independent of the applied B_0 field and is measured directly in frequency units (Hz).

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MRS Machine



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Methodology of MRS

- What techniques can be used.
- What Parameters can be measured by MRS.
- What types of samples can be used.
- What techniques are available for automated classification of spectra .
- Clinical Applications.
- Prognosis.

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1. What techniques can be used:

- ^1H MRS was the first one to be applied to the medicine. Major application is In vivo examination of brain, examination of the prostate that allows distinction of benign hyperplasia from malignant tissue.
- ^{31}P MRS is mostly used because of its greater chemical shift dispersion. ^{31}P MRS is used for examinations of myopathies and other muscle diseases and diagnosing metabolic disorders.
- ^{13}C MRS is used in vivo to diagnose the normal and heperplastic prostrate.
- ^{19}F MRS in vivo detection of fluorinated drugs which are antipsychotic.

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2. What Parameters can be measured by MRS

- Chemical shift, peak heights, peak areas, or ratios of peaks are measured.
- The presence of metabolic (anabolic and/or catabolic) products of a drug, such as the anti-neoplastic drug, 5-fluorouracil, can be seen.
- Depending on the pharmacological time course and the spectral time resolution, rates of appearance and disappearance of peaks attributed to drugs (often tagged with NMR sensitive isotopes) can be measured.

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3. What types of samples can be used

- From extracts to cell suspensions to biopsies to in vivo .
- Chemical extracts, generally provide higher resolution spectra than those from cells, biopsies or tissue.

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4. What techniques are available for automated classification of spectra

- Techniques such as pattern recognition and multivariate analysis have been developed for automatic classification of ^1H spectra. They go under such names as linear discriminant analysis, artificial neural networks (ANN), genetic algorithm, among others.

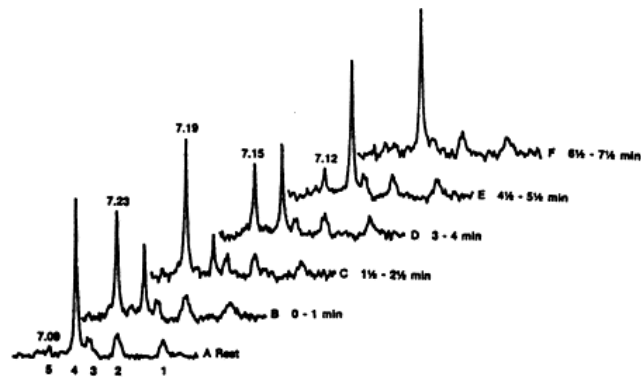
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5. Clinical Applications of MRS

- Skeletal muscle:
 - ^{31}P MRS provides quantitative assessment of muscle energetics, including Creatine phosphate (CrP) and ATP, as well as intercellular pH.
 - Diseases of skeletal muscle are studied by ^{31}P MRS. A dramatic example of the potential of the technique is the confirmation of **McArdle's syndrome**, an inherited disease in which patients have difficulty making use of their muscles.
 - The spectrum is obtained from resting muscle and from an exercising muscle.
 - And the changes in energetics can be seen.

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Figure: ^{31}P MR spectra at 1.9T of skeletal muscle from a patient with McArdle's Syndrome



The first spectrum acquired at rest shows normal energetics and intercellular pH, spectra acquired during ischemic exercise shows a decrease in CrP(4) with concomitant increase in inorganic phosphate, Pi(5) but little change in intercellular pH(3).

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- Cardiac muscle:

- Normal and infarcted tissue can be differentiated using ^1H MRS.

- Bottomley and Weiss measured total creatine in spectra obtained from patients with histories of myocardial infarction using spatially localized, water-suppressed ^1H MRS.
 - Creatine levels were significantly lower in regions of infarction relative to non-infarcted regions.
 - The technique was validated by comparing creatine levels determined by MRS with those determined in biopsy assays in an animal model of infarction. Using this technique, it may be possible to distinguish healthy from infarcted non-viable myocardium, a valuable adjunct in assessment of damaged heart.

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- Other Techniques used are:
 - Hollander and coworkers used a combination of volume selection and 2D gradient phase encoding to suppress intense lipid signals from subcutaneous adipose and epicardial lipids, but allow signal from myocardial lipid to be observed in the human heart.

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- Liver

- ^{31}P MRS and ^{13}C MRS of liver extracts provide information on changes in high energy phosphate and lipid metabolism in response to disease or cancer

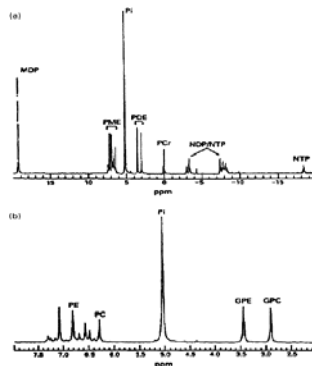


Figure: In vitro ^{31}P MR spectrum, 11.7 T, of a perchloric acid extract from a normal liver. (A) full spectrum and (B) phosphomonoester(26%) which has phosphocholine, phosphoethanolamine and nucleoside monophosphate and phosphodiester(20%) region which has glycerophosphorylcholine and glycerophosphorylethanolamine.

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Persistent problem to visualize Liver is the spectral contamination from the adjacent skeletal muscle which is visible as phosphocreatine peak in the below spectrum

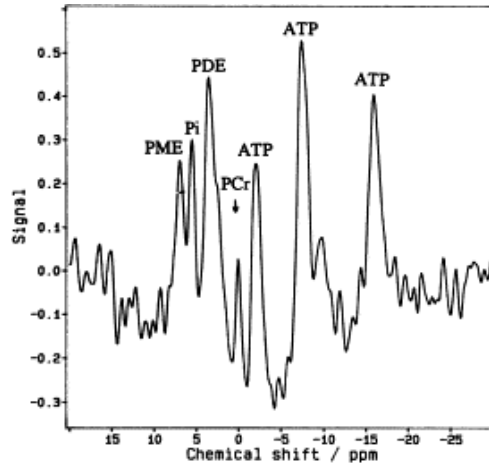


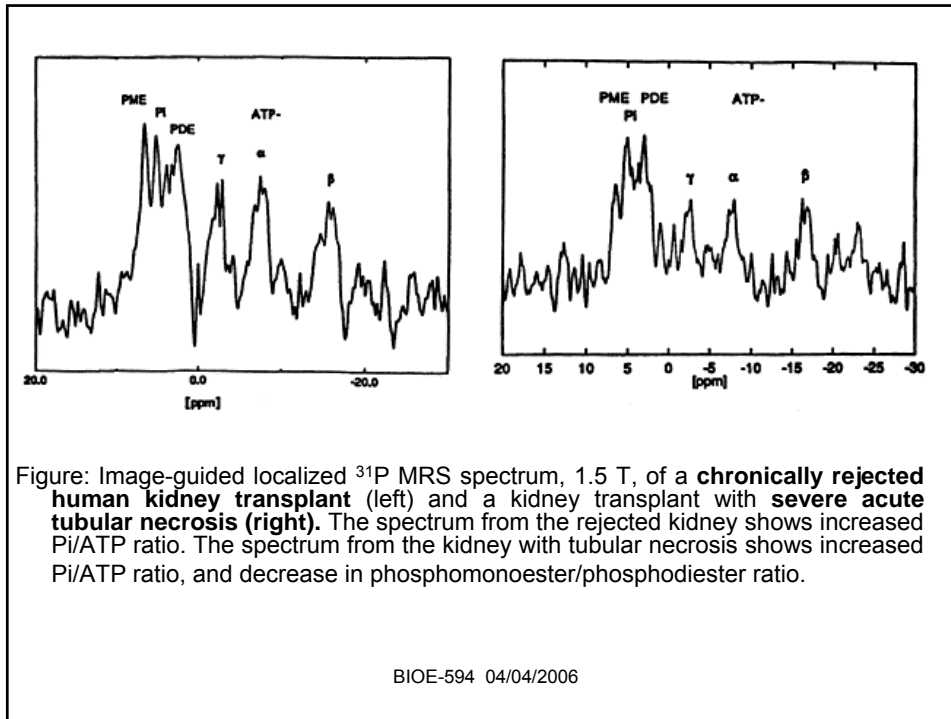
Figure: In vivo ^{31}P MRS at 2 T of localized liver spectrum of healthy subject.

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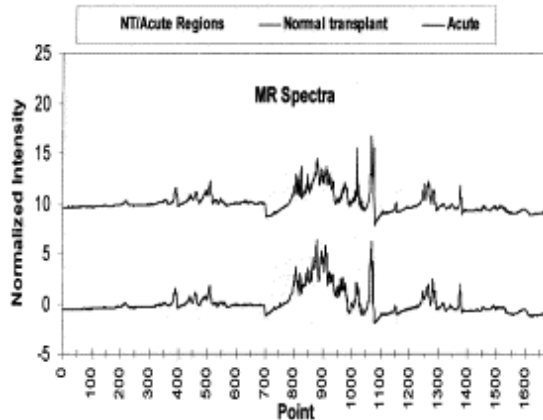
- Kidney

- ^{31}P MRS is used for differentiate the healthy transplanted human kidney and early stages of rejection.
- Heindel and coworkers have reported on ^{31}P MRS of transplanted human kidney.
- Transplanted kidneys undergoing rejection (both acute and chronic) and will be found to have elevated Pi to ATP ratios and reduced pH, in comparison with kidneys from patients with no evidence of transplant dysfunction as shown in the figure:

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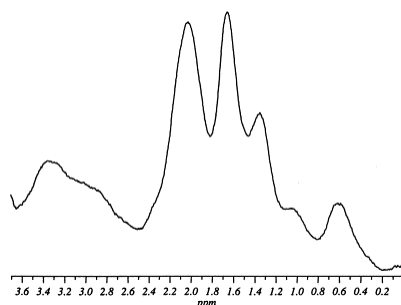
- ^1H MRS which is In vitro is able to differentiate between healthy transplants and kidneys undergoing rejection following transplantation.



^1H MR spectra at 360 MHz of urine samples obtained from patients with normal (upper spectrum) and rejecting (lower spectrum) kidneys.

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- Cancer of thyroid:
 - The method used is ^1H MRS and is done in vivo.
 - to examine thyroid glands in vivo requires a multi ring surface coil to deal with the particular location of the gland in the body.



- Fig. shows the spectrum from a voxel located within a thyroid nodule, diagnosed clinically as goitre.

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- Breast Cancer
 - Single voxel ^1H MRS spectra of breast tumours are recorded using two-turn breast coil, Gribbested identified a peak at 3.3ppm choline containing, present in varying intensity in the ^1H MR spectra of patients with ductal carcinoma. Cho/Cre ratios can be measured.

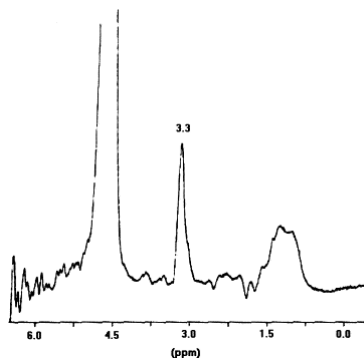


Figure: Localized ^1H MR spectrum, 1.5 T, from a large ductal carcinoma, showing an intense signal at 3.3 ppm

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- Brain:

- ^1H and ^{31}P MRS has been used for the identification and non-invasive assay of energetics, osmolytes, biochemical markers, and neurotransmitters associated with disorders of the brain

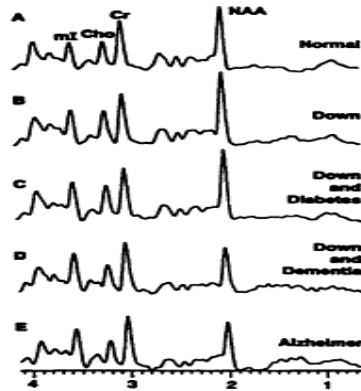
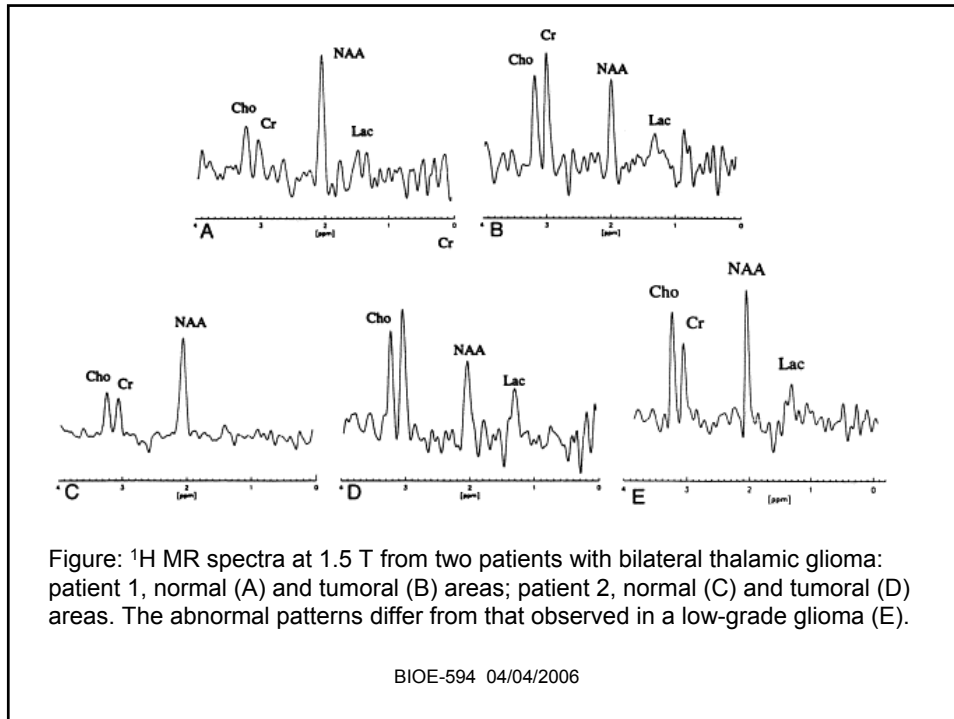


Figure: ^1H MRS, 1.5 T, of adults with Down's Syndrome showing elevated myo-inositol and choline. N-acetylaspartate (acetylated form of amino acid) levels remain normal until dementia develops, at which time spectra are indistinguishable from those due to AD.

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- Bilateral thalamic gliomas, in which a large tumour appears symmetrically in both thalami, is considered to be anatomically different from other gliomas.
- Estève and coworkers studied two patients with this condition using in vivo ^1H and ^{31}P MRS. The ^1H spectra indicated increased creatine/phosphocreatine peaks in these tumours relative to normal brain tissue in the same subject, as shown in Figure

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Prognosis

- MRS is a versatile technique to look at biochemical changes in organs in response to a variety of disease states.
- MRS has a major impact on both the science and the diagnosis and therapeutic monitoring of the brain.

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