

Magnet-Resonance-Spectroscopy

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10.11.2017

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General Remarks:

Within this lecture, it is only possible to briefly touch the topic!

→ for detailed descriptions, please check the literature (or lectures in www)

„Interactive“ examples:

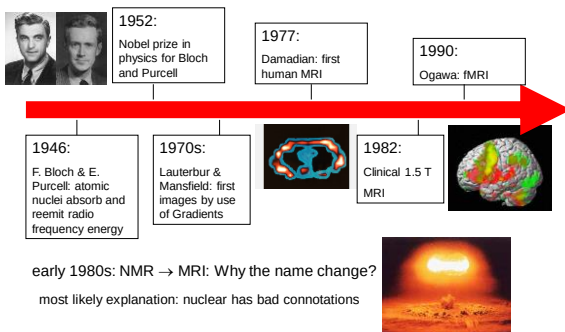
- Understanding NMR Spectroscopy by Keeler on YouTube
- Basics of NMR by J.P. Hornak at Rochester Institute of Technology

Literature examples:

- Understanding NMR Spectroscopy, Keeler 2002
- NMR Spectroscopy Explained, Jacobson 2007
- In vivo MRS, R.d.Graaf 2007
- Advanced:
 - Magnetic Resonance Imaging, Haacke, Wiley

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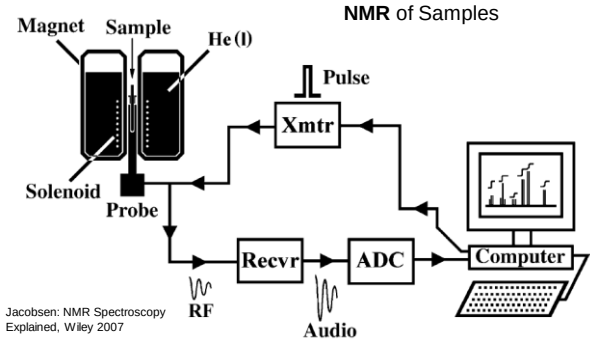
History of NMR



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Necessary Hardware

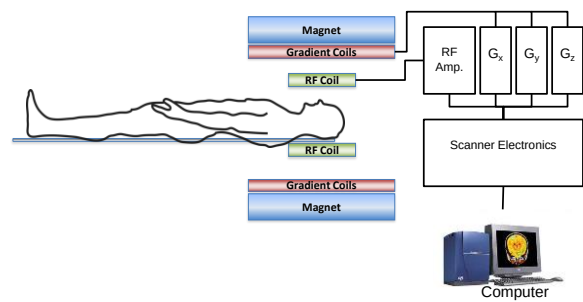
NMR of Samples



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Necessary Hardware

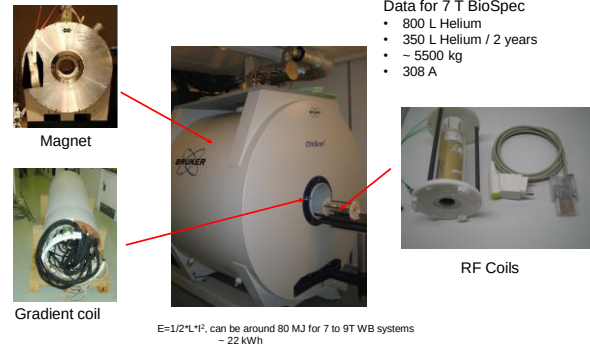
In vivo MRI



Necessary Hardware

Data for 7 T BioSpec

- 800 L Helium
- 350 L Helium / 2 years
- ~ 5500 kg
- 308 A



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Safety

The enormous strength of the magnet makes safety **essential!**

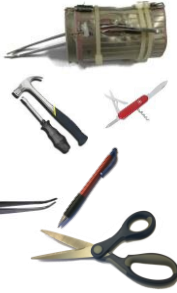
Things fly ~ even big things!



Source: Simplyphysics

Make sure you are aware of the hazards.

Screen yourself every time before entering the scanner room for metallic objects.



Magnetic field is ALWAYS on!

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MR Physics

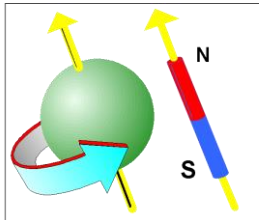
- Can measure only certain nuclei:
 ^1H , ^{13}C , ^{19}F , ^{23}Na , ^{31}P (and others)

- ^1H (proton)
 - abundant: high concentration in human body or in animals (water!)
 - high sensitivity: yields large signals

- Hydrogen ion is positively charged

Spin:

- A particle rotating upon its own axis
- Electrons, protons and neutrons spin
- Spinning, charged particles are magnetic

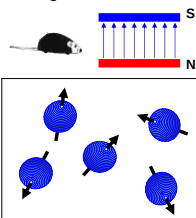


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MR Physics

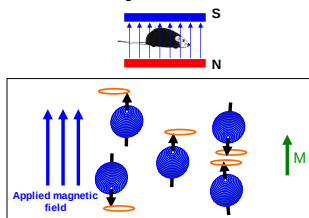
Animal + Magnet:

Without magnetic field:



No net magnetization
Spins randomly oriented

With magnetic field:

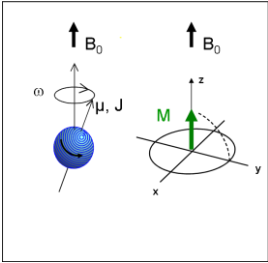


Low net magnetization
only $\Delta N \sim 0.00064\%$ of protons at 7 T
Boltzmann $\frac{N^\downarrow}{N^\uparrow} = e^{-\frac{\Delta E}{k_B T}}$

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Resonance Principle



Angular momentum from spinning (J)
+ Magnetic moment (μ)
+ External magnetic field (B)

= Precession (ω)

Precession (Larmor) Frequency

$$\omega = \gamma \cdot B$$

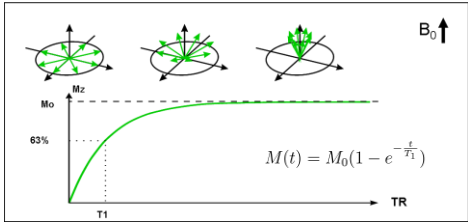
γ = Gyromagnetic Ratio
(depends on nuclei,
e.g. protons: 42 MHz/T)

B = Magnetic Field Strength

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Longitudinal Relaxation Time T1 and TR

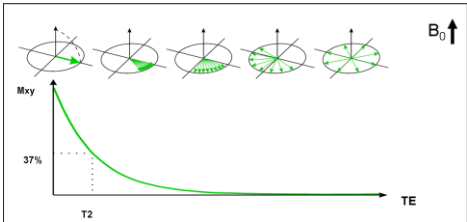


Longitudinal Relaxation = Energy transfer between excited spins and Tissue (Spin-Lattice-Relaxation)
✓ Reestablishing of longitudinal (B0) magnetization with time constant T1
TR (repetition time) = time to wait after excitation before sampling T1

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MR Physics

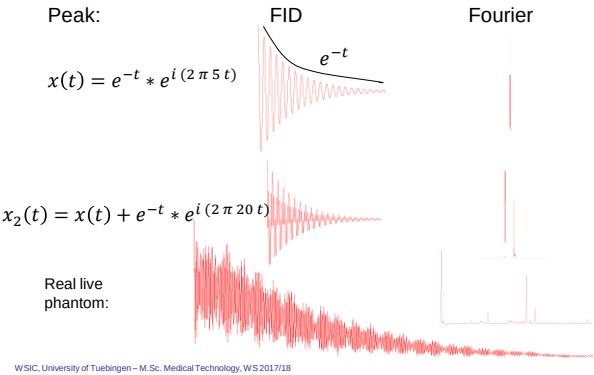
Transverse Relaxation Time T2 and TE



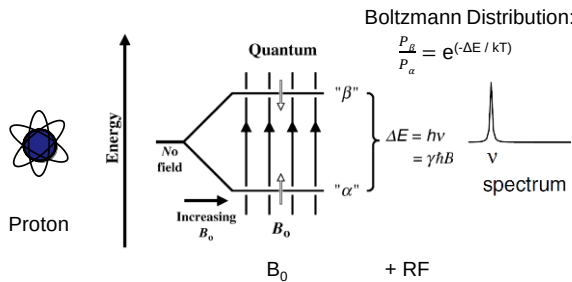
Transverse Relaxation = Decay of magnetization by interaction between nuclei (Spin-Spin-Relaxation)
TE (time to echo) = time to wait to measure T2 or T2* (after refocusing with spin echo or gradient echo)

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Convolved Signals and Fourier Transformation



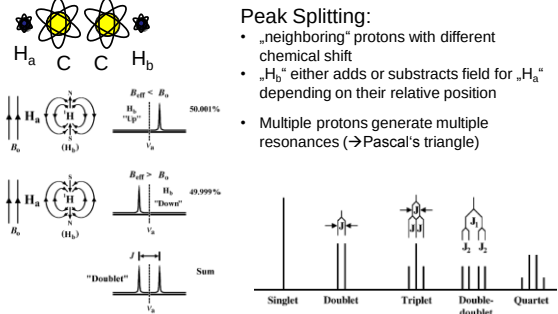
MRI Signal and where does it come from:



Jacobson: NMR Spectroscopy Explained, Wiley 2007 & Keeler: Understanding NMR Spectroscopy, Wiley 2002

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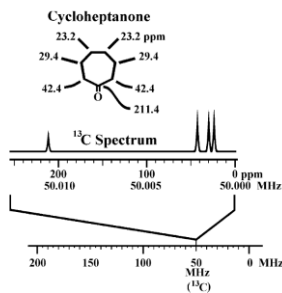
MRI Signal and where does it come from (III):



Jacobson: NMR Spectroscopy Explained, Wiley 2007 & Keeler: Understanding NMR Spectroscopy, Wiley 2002

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MRI Signal and where does it come from (II):



- Multiple Peaks from 1 compound:
- Resonance frequency depends on entire structure
 - Symmetry is reflected in spectrum intensity („equivalent peaks“)

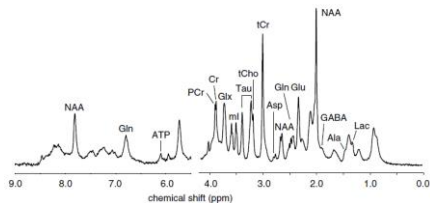
Example:
50.000 MHz * 1.0000232
(= 23.2 ppm) = 50.00116 MHz

Peak frequency ν scales with B_0 , but remains at fixed ppm!

Jacobsen: NMR Spectroscopy Explained, Wiley 2007 & Keeler: Understanding NMR Spectroscopy, Wiley 2002

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Example Spectrum

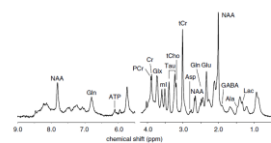


In reality: many resonances overlap
→ identification of specific metabolites not always possible
(esp. Quantification!)

d. Graaf: In vivo NMRS, Wiley 2007

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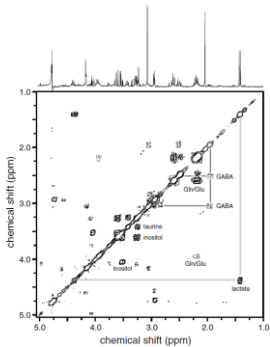
Resonance in 2D



d. Graaf: In vivo NMRS, Wiley 2007

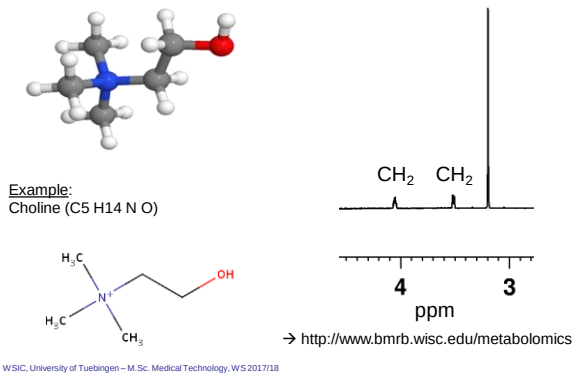
Example:
COrelation SpectroscopY (COSY)

Additional excitation pulses and delay times separate spins by introducing additional phase shifts.

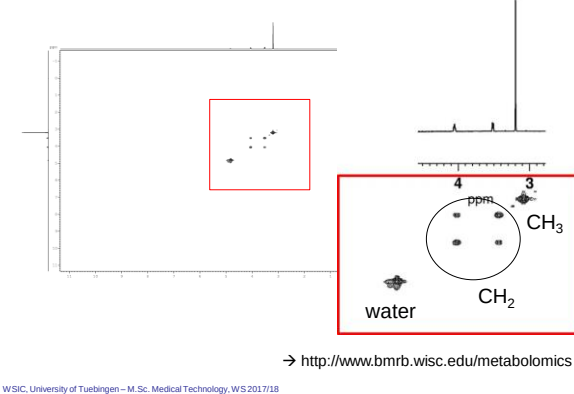


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Example COSY



Example COSY



Applications of Magnetic Resonance Spectroscopy

- Ex vivo: Structure Analysis
- Ex vivo: Metabonomics
- In vivo: Fatty Liver Disease
- Hyperpolarized MRI



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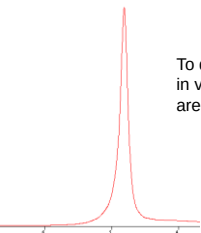
Ex vivo: Metabonomics

- Metabolomics:
- Studies small molecules (< 1500 Da) of living systems
 - > 42000 metabolites and variants listed (e.g. in HMDB)
 - Only small fraction of metabolites and pathways currently known
 - NMR allows:
 - Determining structures
 - Investigate metabolite pathways and dynamics (by doping with stable isotopes)

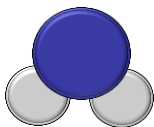
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Some important metabolites

Water
Peak at 4.7 ppm.
Most abundant compound, > 2/3 of the body.
Concentration so high – unsuppressed, only water detectable (in vivo)!



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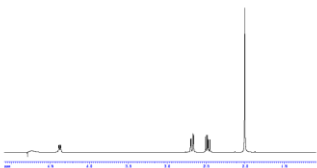
To detect any other metabolite in vivo, suppression techniques are necessary!

Sources and more:
R. d. Graaf, In vivo MRS, Wiley
<http://www.bmr.b.wisc.edu/metabolomics>

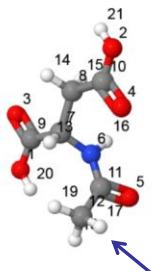
Some important metabolites

N-Acetyl Aspartate (NAA)
Peaks at 2.02, 2.49, 2.67 & 4.39 ppm

- Present in nervous systems, with different concentrations during development and origin.
- Marker for neuronal density/function, details unclear.



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N-Acetyl Aspartic Acid

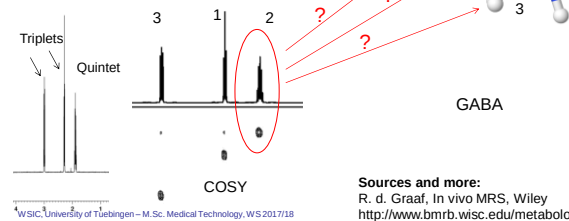
Sources and more:
R. d. Graaf, In vivo MRS, Wiley
<http://www.bmr.b.wisc.edu/metabolomics>

Some important metabolites

γ-Aminobutyric Acid (GABA)

Peaks at 1.89, 2.28 & 3.01 ppm

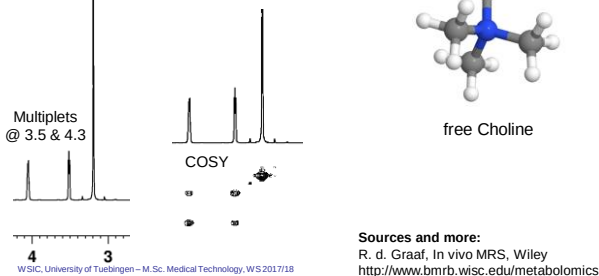
- Inhibitory neurotransmitter
- Changes with substance abuse, neurological/psychiatric disorders
- Target for anti-epileptic drugs (↑GABA)



Some important metabolites

Choline-containing Compounds (tCho)

Include: free choline, phsphorylcholine, glycerphosphocholine,.....
Most prominent peak ~3.2 ppm from the three methyl-groups

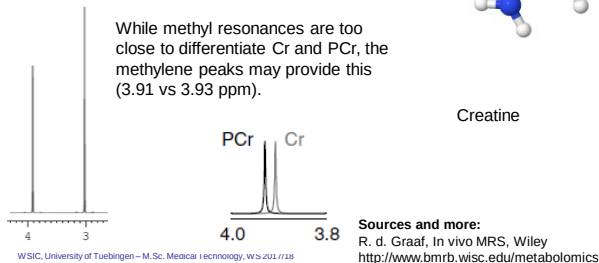


Some important metabolites

Total Creatine (tCr)

Includes: Creatine and Phosphocreatine
Peaks at 3.0 and 3.93 ppm

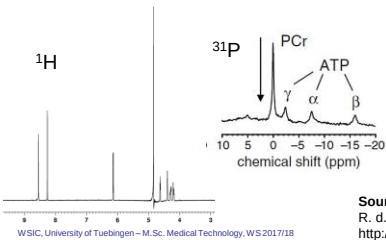
- Energy metabolism (buffers ATP-levels)
- Energy transport (production→consumption)



Some important metabolites

Adenosine Triphosphate (ATP)
Detection with ³¹P as ¹H signals show complex coupling pattern close to water.

- THE energy donor!



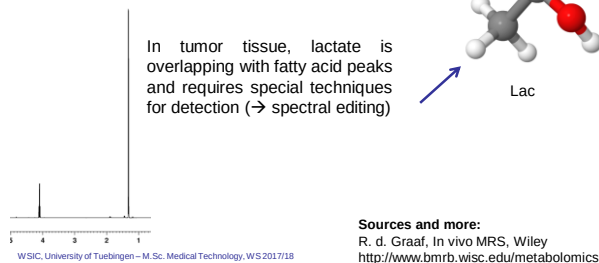
Some important metabolites

Taurine (2-aminoethanesulfonic acid)
Peaks at 3.25 and 3.42 ppm, significant overlap with choline!
Function is unknown, suggested as osmoregulator and modulator of neurotransmitters.
Decreasing concentrations over time, uptake via food, but nonessential amino-acid



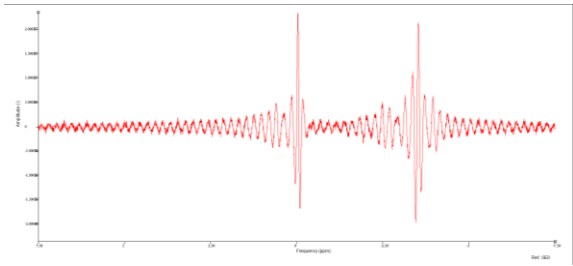
Some important metabolites

Lactate
Peaks at 1.31 & 4.1 ppm.
End-product of anaerobic glycolysis, always present in low concentrations. Increased in restricted oxygen supply (e.g. stroke, hypoxia and tumors)



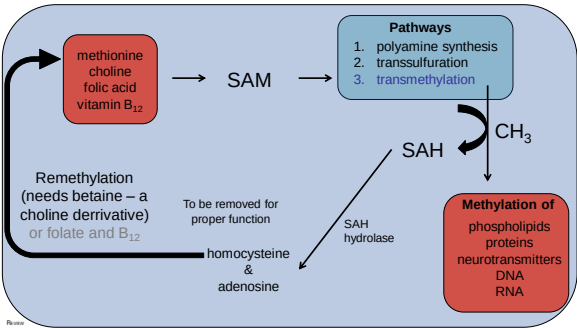
In vivo Fatty Liver Disease

how to make sense out of this:



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One-carbon metabolism



Review
Molecular alterations in hepatocarcinogenesis induced by dietary methyl deficiency

Igor P. Pogribny¹, S. Jill James² and Frederick A. Beland¹

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Further impact

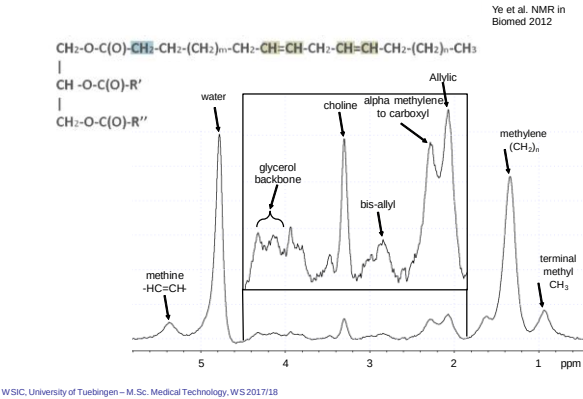
- 1. Altered Lipid Metabolism
- 2. Induction of oxidative stress
- 3. DNA damage
- 4. Epigenetic alterations
 - 1. DNA methylation changes
 - 2. Histone modification changes
 - 3. MircoRNA alterations

Review
Molecular alterations in hepatocarcinogenesis induced by dietary methyl deficiency

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Window to lipid metabolism



Data analysis

~ 30 publications with in vivo MRS in rodents
~ 20 different imaging protocols of different groups

1. $\%Lipid = \frac{\int Fat}{\int H_2O}$

2. $\%Lipid = \frac{\int Fat}{\int Fat + \int H_2O}$

3. $\%Lipid = \frac{\int Fat}{\int Fat + \int H_2O / 0.7}$

4. $\%Lipid = \frac{\int Fat}{\int all}$

1. Methylene

2. Methylene + Methyl

3. All from 3.0 – 0.0 ppm

Comparison of results quite difficult.

Further analysis:

Magn Reson Mater Phys
DOI 10.1007/s10334-012-0310-2

RESEARCH ARTICLE

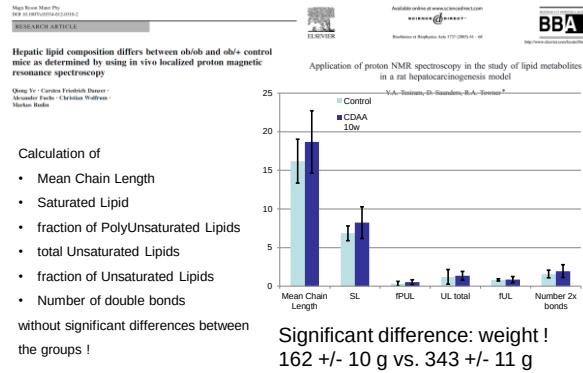
Hepatic lipid composition differs between ob/ob and ob/+ control mice as determined by using in vivo localized proton magnetic resonance spectroscopy

Qiong Ye · Carsten Friedrich Danzer · Alexander Fuchs · Christian Wulfrum · Markon Rudin

$$MCL = \frac{1}{3} \times Lip09 + \frac{1}{3} \times (Lip13 + Lip16 + Lip21 + Lip23 + Lip28) + Lip52k53 + \frac{1}{3} \times Lip09$$
$$Lipid\ mass = \frac{1}{2} \times (Lip13 + Lip16 + Lip21 + Lip23 + Lip28 + Lip41 + Lip43) \times 14 + (Lip52k53) \times 13 + \frac{1}{3} \times (Lip09) \times 15 + \frac{1}{3} \times (Lip09) \times 12 + \frac{2}{3} \times (Lip09) \times 16$$
$$SL = \frac{3}{2} \cdot \frac{Lip13}{Lip09}$$
$$fPUL = \frac{3}{2} \cdot \frac{Lip28}{Lip09}$$
$$UL_{total} = \frac{3}{2} \cdot \frac{Lip52k53}{Lip09}$$
$$fUL = \frac{3}{4} \cdot \frac{Lip21}{Lip09}$$
$$fLM = \frac{lipid\ mass}{lipid\ mass + \frac{1}{2} \cdot J_{water} \cdot 18}$$
$$fSL = 1 - fUL$$
$$fMUL = fUL - fPUL$$

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Results

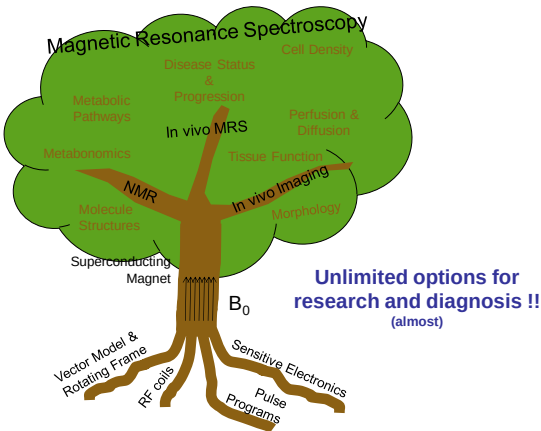


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Changes in the model ?



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