Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

***A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.

Biomedical Imaging

(Orvosbiológiai képalkotás)

CLINICAL MRI METHODS

(MRI a diagnosztikában)

LAJOS R. KOZÁK

Basics of MR Spectroscopy (MRS)

MRS or nuclear magnetic resonance (NMR) spectroscopy is one of the earliest MR-based method.

It operates on the magnetic resonance principle:

- Nuclei in the tissues of the body can become radio transmitters and receivers if they are in an external magnetic field.
- The resonance frequency depends on the strength of the magnetic field B and a constant called gyromagnetic ratio (γ)
- The γ is unique for each specific isotope. The values of γ are sufficiently different that isotopes can be separated easily with tuning the frequency of excitation.
- Variations of the magnetic field strength result in variations of resonance frequency ν

$$\nu = \frac{\gamma}{2\pi} B$$

Basics of MR Spectroscopy (MRS)

The gyromagnetic ratio (γ) is the constant term of the equation; it depends only on the isotope to be measured:

- stable isotopes that contain an odd numer of protons and/or neutrons have an intrinsic magnetic moment and thus susceptible to RF excitation

Nuclei	Unpaired p^+	Unpaired n^0	Net spin	γ [MHz/T]
^{1}H	1	0	1/2	42.58
^{13}C	0	1	1/2	10.71
^{19}F	0	1	1/2	40.08
^{23}Na	2	1	3/2	11.27
^{31}P	0	1	1/2	17.25

$$\nu = \frac{\gamma}{2\pi} B$$

Basics of MR Spectroscopy (MRS)

The magnetic field (B) is the technical term of the equation:

- the main field (B_0) is used to introduce the basic alignment
- gradients (G_X, G_Y, G_Z) are used for spatial encoding (MRI, localized MR spectroscopy)
- **B is affected by the chemical environment:**
    - the distribution of electrons in the chemical bonds introduce local field inhomogeneities, and thus **local differences in resonance frequency**

B_0

G_X, G_Y, G_Z

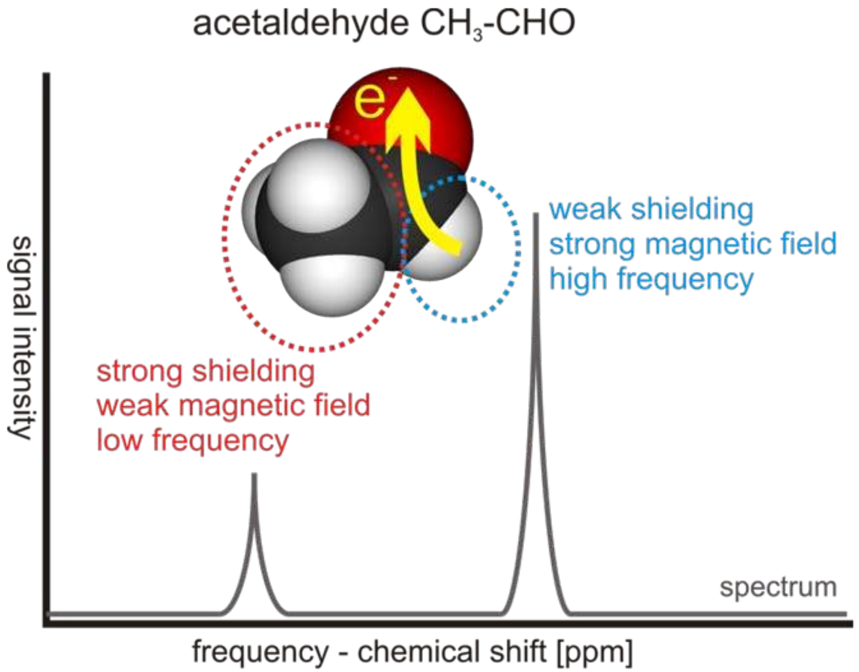
$$\nu = \frac{\gamma}{2\pi} B$$

chemical composition

Basics of MR Spectroscopy (MRS)

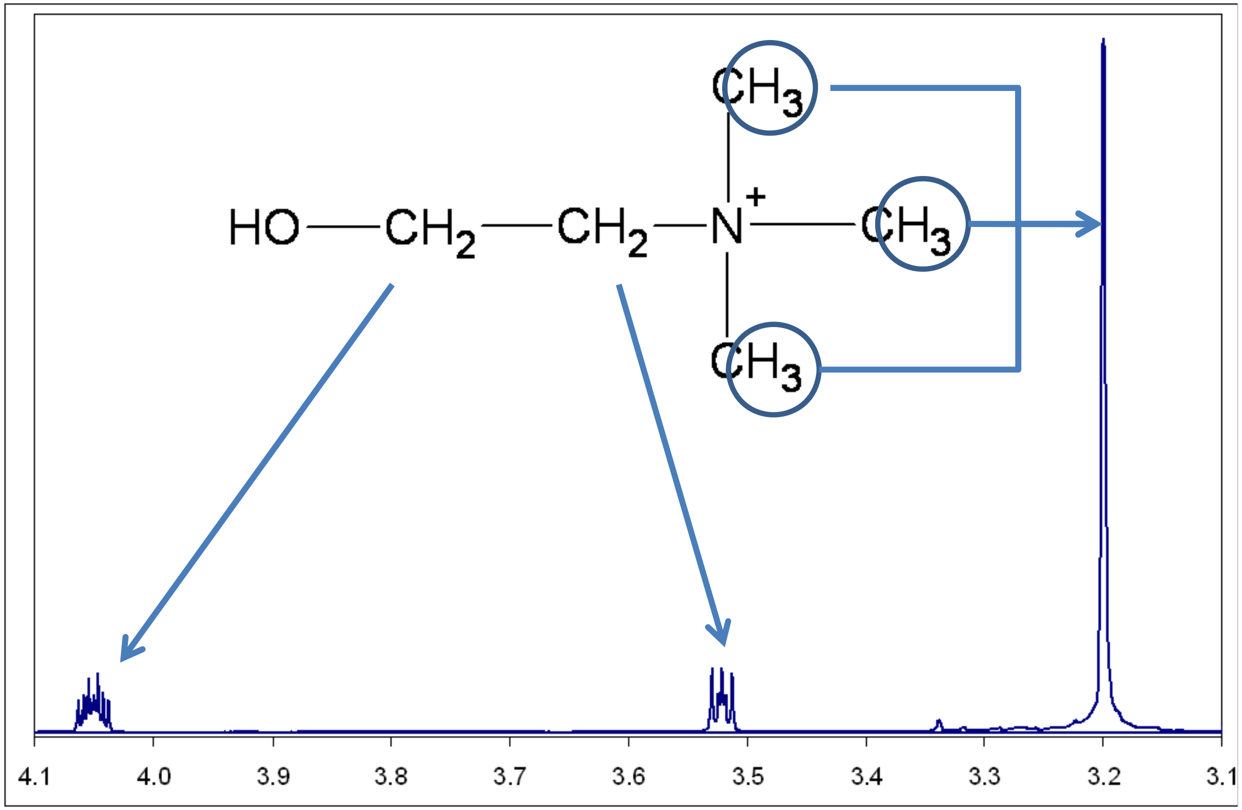
The distribution of electrons in the chemical bonds lead to various shielding effects

- Weak shielding is present when a nucleus draws the e^- from the proton:
    - Strong magnetic field
    - Higher resonance frequency
- Where the shielding remains stronger:
    - Weak magnetic field
    - Lower resonance frequency



^{1}H MR Spectrum of cholin

The peaks corresponding to protons are shifted according to the chemical environment



MRS acquisition

MRS sequences are spin echo sequences, TE strongly influences the resulting spectrum.

Single voxel techniques:

- PRESS (Point RESolved Spectroscopy)
  - Higher SNR
  - Less precisely defined voxels
- STEAM (Stimulated Echo Acquisition Mode)
  - About half the SNR of PRESS
  - More precise voxels
  - Less demanding technologically

Multi voxel technique:

- CSI (Chemical Shift Imaging)

The spectrum depends on:

- Magnetic field
- TE : echo time
- TR : repetition time
- the region of the brain
- the patient’s age, etc.

MRS quality criteria

- Volume
  - as big as possible, at least: 1 cm^3
- Max 20% partial volume
- No contact with
  - CSF
  - bone marrow fat
  - air in sinuses
- No patient movement
- Magnetic field inhomogeneities < 10 Hz FWHM
- MRS measurement before contrast material (CM) administration
  - about 10% choline decrease after CM administration

The concentration of H_2O is about 10000 times higher than that of metabolites, this is reflected in the MRS signal.

To have equal SNR for the metabolites 10000 times bigger voxels are needed.

Moreover, water signal has to be suppressed.

Normal compounds

with [1]H MRS

Large signals at long TE

- N-acetyl aspartate (NAA)
- Creatine (Cr) and phosphocreatine (PCr)
- Cholines (Cho)
- Glycerophosphocholine (GPC)
- Phosphocholine (PC), free choline (Cho)

Large signals at short TE

- Glutamate (Glu)
- Glutamine (Gln)
- Myo-inositol (mI)

Small signals (short or long TE)

- N-Acetyl aspartylglutamate (NAAG), aspartate
- Taurine, betaine, scyllo-inositol, ethanolamine
- Threonine
- Glucose, glycogen, purine nucleotides
- Histidine

Pathological compounds

with [1]H MRS

Long TE

- Lactate (Lac)
- Hydroxy-butyrate, acetone
- Succinate, pyruvate
- Alanine
- Glycine

Short TE

- Galactitol, Lipids
- Macromolecules
- Phenylalanine

Exogenous compounds (short or long TE)

- Propan-1,2-diol
- Mannitol
- Ethanol
- Methyl sulfonylmethane (MSM)

Clinical significance of specific compounds

N-acetyl aspartate (NAA)
~ 2.00 pmm

- neuron specific amino acid derivative
- reflects the health of neurons (**neuronal marker**)
- decreased in neurodegenerative processes
- decreased in large necrotic tumors
- elevated in Canavan disease

Creatine/ Phosphocreatine (Cr, PCr)
~ 3.00 ppm

- a reservoir for high energy phosphate for generation of adenosine triphosphate [ATP] ➔ **energy metabolite**
- the most stable metabolite in the brain usually used as a reference peak to generate NAA/Cr and Cho/Cr ratios for quantification

Choline (Cho)
~ 3.25 ppm

- membrane phospholipid metabolite
- associated with glial cell membrane integrity (**cell membrane marker**)
- elevated in malignant tumors
- elevated in ischemia
- elevated in inflammations
  - can be used to monitor multiple sclerosis

Clinical significance of specific compounds

Lactate (Lac)
~1.33 ppm

- indicates **hypoxia** and/ or **glycolysis**
- elevated in infarcts
- elevated in abscesses
- elevated in mitochondrial disorders
- elevated in malignant tumors
- elevated in multiple sclerosis plaques

Lipids
~0.9-1.4 ppm

- indicate **tissue necrosis**
- elevated in e.g. metabolic disturbances

Glutamate/ Glutamine (Glu/ Gln)
~2.1-2.5 ppm

- **excitatory neurotransmitter**
- elevated in stroke
- elevated in lymphoma
- elevated in hypoxia

Myo-inositol (mI)
~3.56 ppm

- cell membrane marker (**shows cell destruction**) / intracellular transmitter
- elevated in Alzheimer's
- elevated in diabetes
- elevated in recovered hypoxia

Specific metabolites

- metabolic diseases
- can be very specific, e.g. in nonketotic hyperglycinemia

Clinical indications of MRS

Oncology

- Neuro-oncology
- Haemato-oncology

Inflammations

- Meningo-encephalitis
- ADEM
- MS
- Abscess
- Differential diagnosis: stroke

Metabolic diseases

Neonatology

Oncology is the main indication for MRS

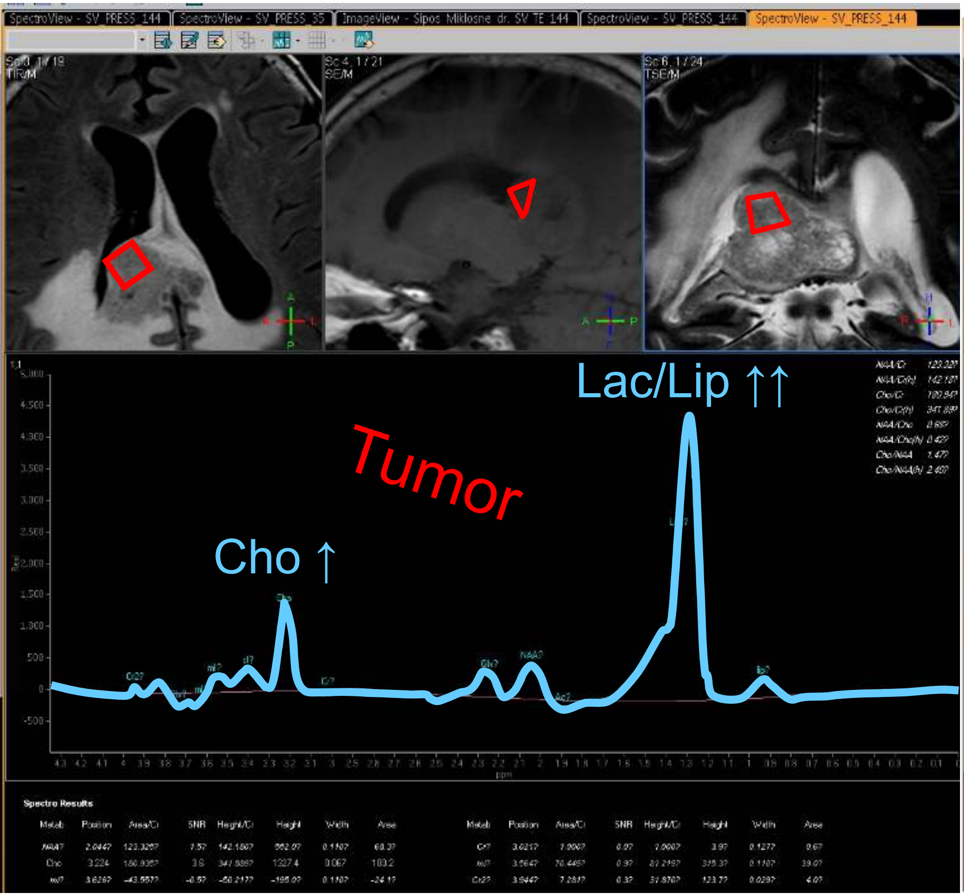
- differential diagnosis: tumor vs. inflammation
- tumor dignity assessment
- tumor inhomogeneity assessment
- assessing residual / recidive tumors
  - choline at least 40-60% higher than in the norm. side
- Post radiation masses
  - all of the typical metabolites strongly decreased, but still present
- Postoperative gliosis
  - all of the typical metabolites are absent

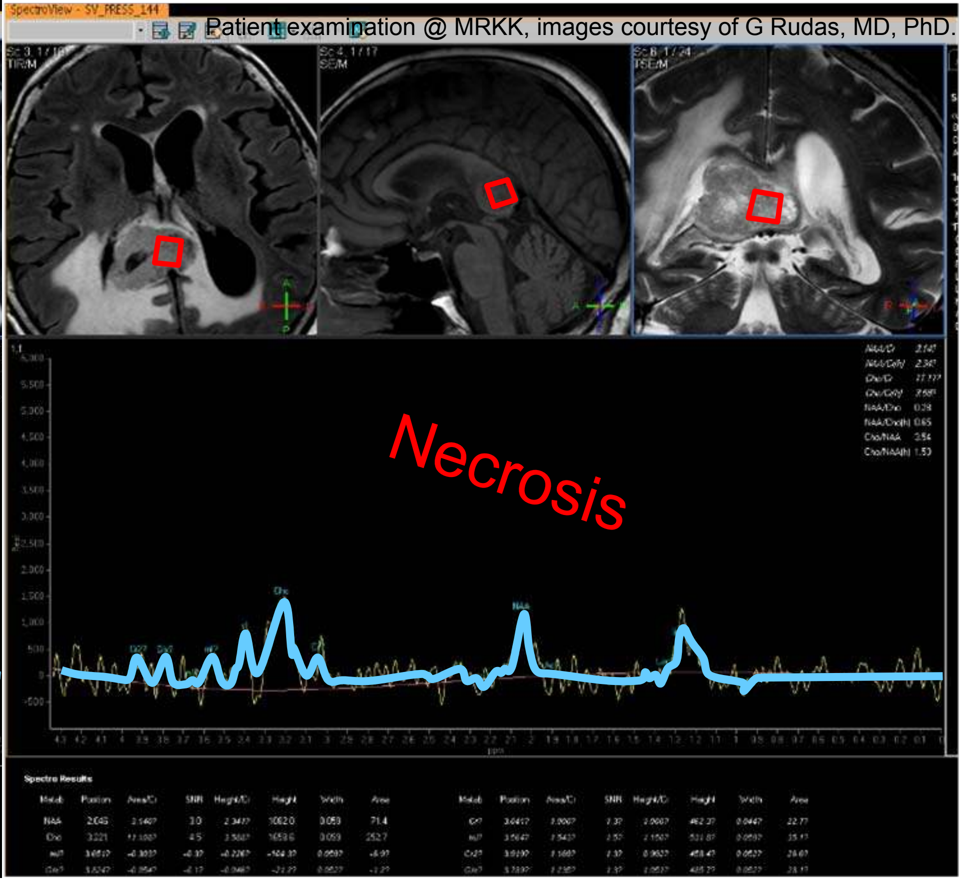
MRS is a non invasive in vivo „biopsy”

Differentiating viable and necrotic parts of tumor metastasis

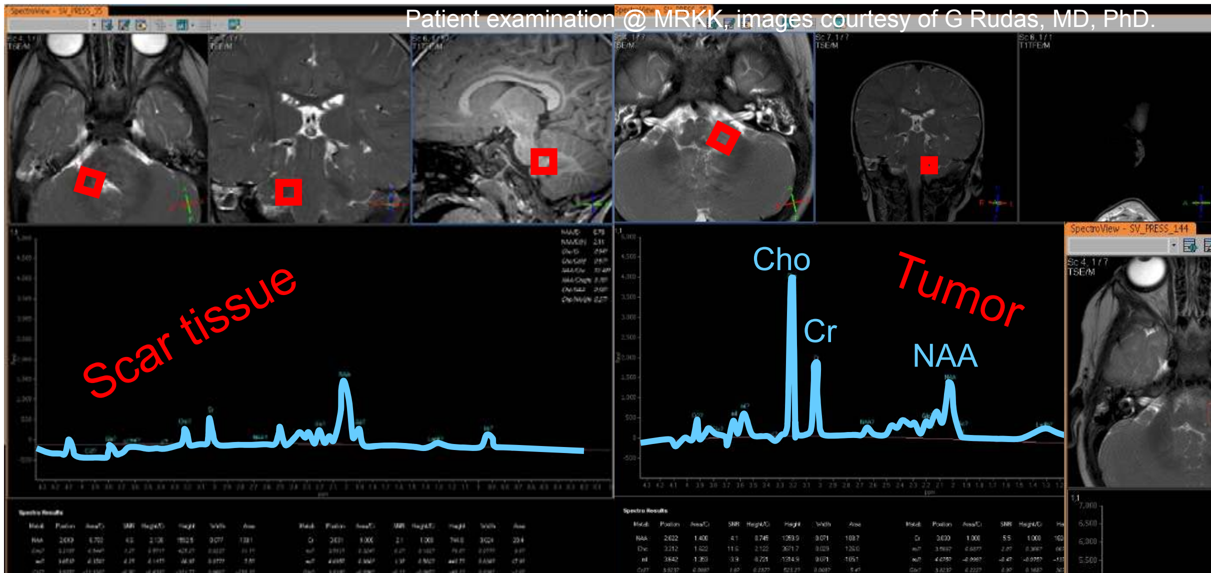
Metastasis of pulmonary origin

Patient examination @ MRKK, images courtesy of G Rudas, MD, PhD.

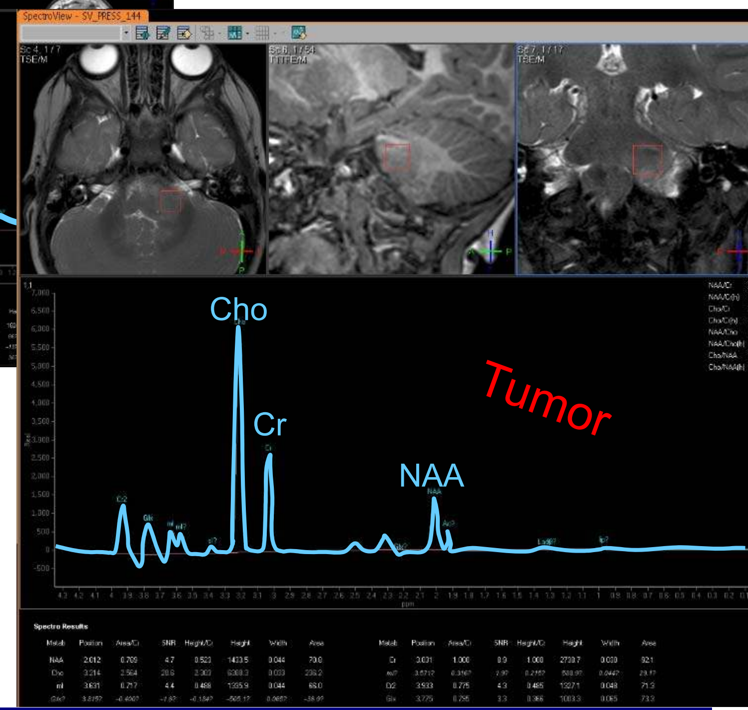




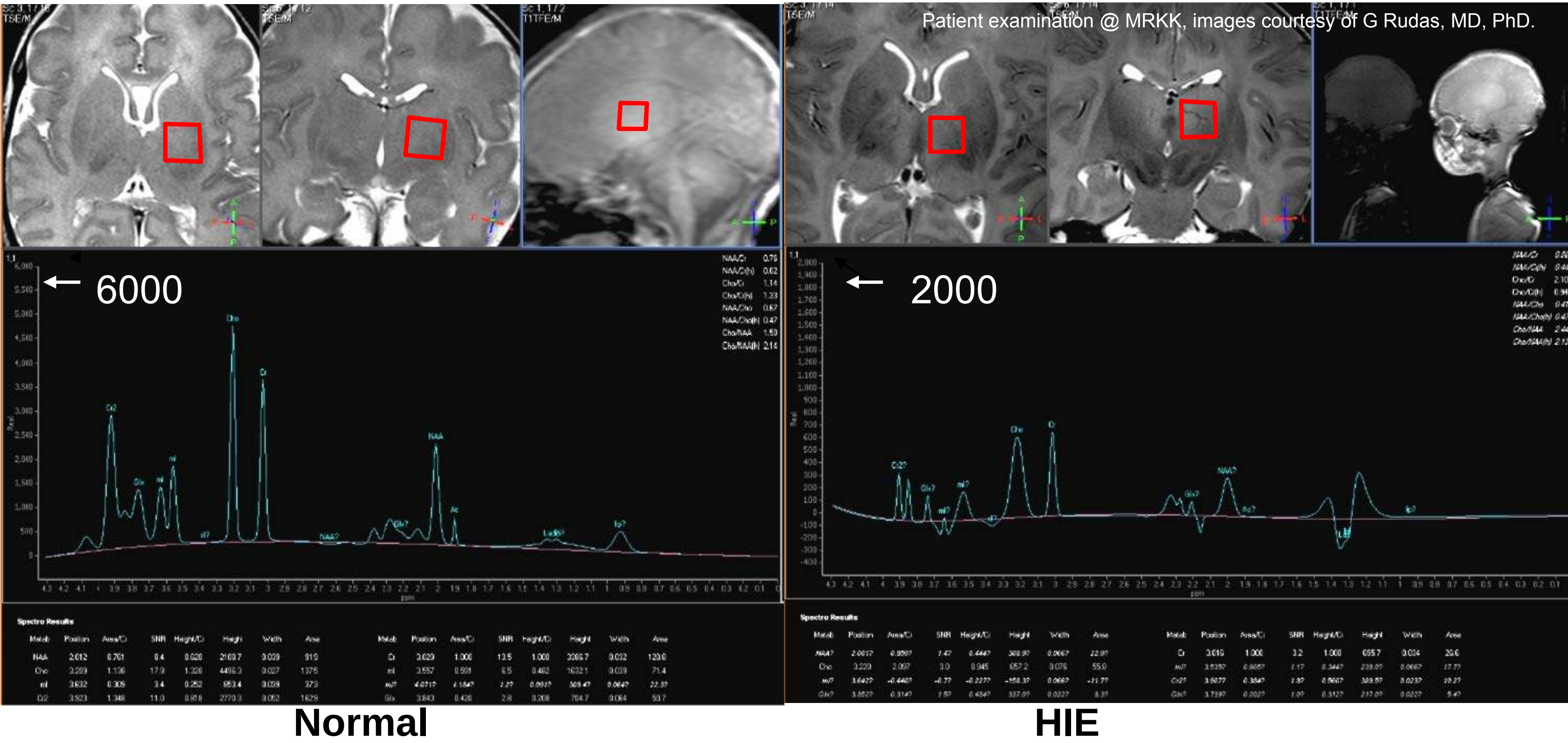
Glioma in the brainstem



3 mo follow-up



Neonatology example: diagnosis of hypoxic ischemic encephalopa



SENSE Spectro CSI provides spectra in multiple voxels. The lacta is indicative of metastasis in this case.

Future of MRS / research applications

Quantitative MRS *e.g. Marliani et al., AJNR, 2010*

MR spectroscopy is done after calibration with either

- internal endogenous marker
- external reference
- LC-model software

Multinuclear MRS e.g. Lyoo et al., Psychiatry Res, 2003

Specific hardware for simultaneous ^{1}H, ^{13}C, ^{19}F, ^{31}P, MRS spectroscopy measurements

- ^{31}P: measuring ATP, i.e. energy accessibility and consumption
- ^{19}F: not present in the human body, but numerous drugs contain F
    - information on drug distribution / kinetics
    - monitoring cytostatic therapy

MRS thermometry *e.g. Zhu et al., MRM, 2008*

Linear relationship between the ^{1}H MR resonance frequency of tissue water and the tissue's temperature.

MRI contrast agents

MRI contrast agents alter T1, T2, or T2* of various tissues, resulting in changes of image contrast.

Contrast agents are useful for the detection of tumors, infection, inflammation, infarction and lesions.

MRI contrast materials are called contrast “agents” since it is the effect that the magnetic properties of the contrast agent has on the relaxation of tissues that is imaged, and not the contrast material itself.

X-ray contrast media

Barium and iodine compounds are used to enhance contrast in x-ray procedures.

These compounds are referred to as contrast “media” since their presence appears directly on the images.

MRI contrast agents

Endogenous

- e.g. hemoglobin
  - BOLD contrast, see fMRI chapter
    - dexyhemoglobin is diamagnetic
    - deoxyhemoglobin is paramagnetic

Exogenous

- **Paramagnetic agents**
  have positive magnetic susceptibility due to the presence of one or more unpaired electrons
  - Gd^{3+}
  - Dy^{3+}
  - Fe^{2+}
  - Mn^{3+}

Exogenous cont'd

- **Ferromagnetic agents**
  are solids with crystalline structures that develop small magnetic domains. When placed in an external magnetic field (B0), the multitude of magnetic domains will align with the field and retain magnetism when removed from B0
  - Fe
  - Ni
  - Co

- **Superparamagnetic agents**
  are smaller solid particles each of which develop a "single domain". The domains align with B0; but do not retain the alignment after being removed from B0
  - Magnetite (Fe_3O_4)

MRI contrast agents

Positive contrast agents

(relaxation agents)

- cause hyperintensity on T1 weighted images
- the presence of a positive agent stimulates an increase in spin flip transitions resulting in reduced T1 values and increased brightness on T1 weighted images
- cause hypointensity on T2 weighted images because of susceptibility effects

The most common positive contrast agent is the paramagnetic gadolinium (Gd).

Negative contrast agents

(shift agents, chemical shift agents or frequency agents)

- cause hypointensity on T2 weighted images
- produce substantial magnetic inhomogeneity due to magnetic susceptibility
- magnetic inhomogeneity perturbs the Larmor frequency of protons, resulting in a loss of phase coherence and reduced T2 values

Dysprosium (Dy) is also paramagnetic but acts to reduce T2 or T2* without affecting T1.

MRI contrast agents

Safety considerations

Most of the agents appropriate for contrast enhanced MRI are toxic metals, therefore they are usually used in a chelated form.

Gadolinium

- in its pure form can bind to membranes, transport proteins, enzymes, etc. in the lungs, liver, bones and spleen.
- small amount of pure metallic Gd can cause liver necrosis
- chelation shields the toxic metal ion from direct interaction with the tissues
- chelation may also change susceptibility effects

Chelates are cleared from the body via glomerular filtration.

If the glomerular filtration rate is decreased, e.g. due to kidney disease, toxic metals can slowly be released from the chelates and cause toxicity.

Nephrogenic systemic fibrosis is a possible complication which is highly correlated with the use of Gd contrast agents in patients with kidney disease.

MRI contrast agents

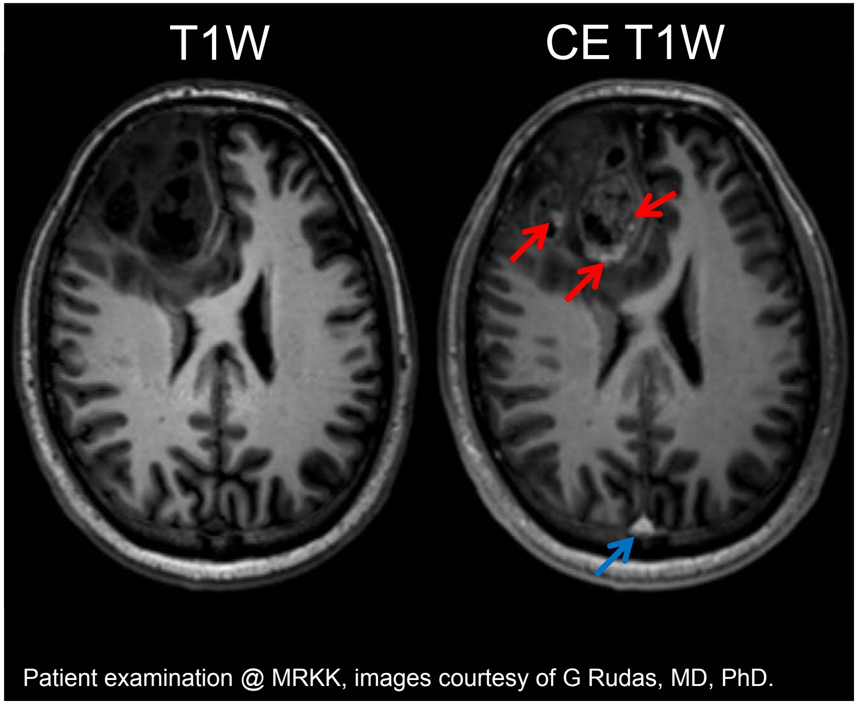
Clinical applications

Mostly Gd-chelates are used, chelation differs between pharmaceuticals.

Some brands are: Magnevist (Bayer-Schering), Ultravist (Bayer-Schering), Optimark (Covidien), ProHance (Bracco), etc.

Contrast enhanced MRI

- Central nervous system tumors (diagnosis, differential diagnosis)
  - Gd-chelates do not pass the blood-brain barrier ➔ if the barrier is distrupted the contrast agent accumulates in the tissue
- Angiography
- MR perfusion (see later)
- etc.



Contrast enhancement in case of a malignant brain tumor (glioblastoma multiforme). Red arrows represent CA enhancement in the lesion, while the blue arrow represent a physiological enhancement in the venous sinus.

MR Perfusion
(Perfusion Weighted Imaging, PWI)

Perfusion

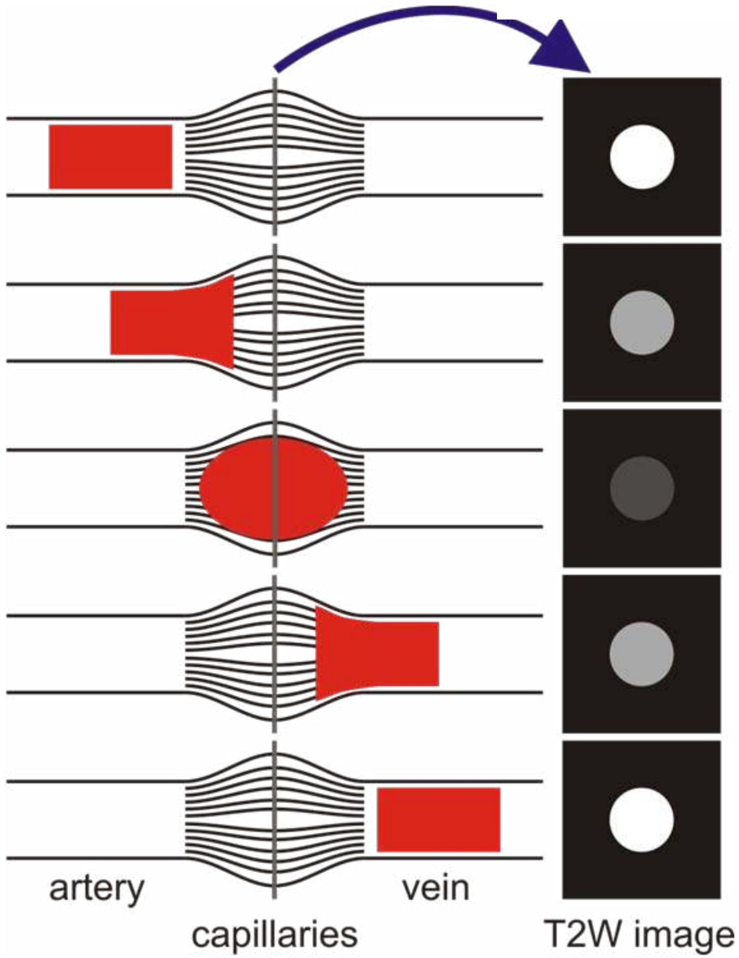
- the delivery of oxygen and nutrients to the cells via capillaries
- Identified with blood flow
- measured in milliliters per minute per 100 g of tissue

Measuring perfusion

- Dynamic susceptibility contrast (DSC) imaging in the brain
  - GD-chelate contrast agent
- Arterial spin labeling
  - See ASL chapter

DSC imaging in the brain

- injection of a bolus of Gd-chelate contrast agent
  - Gd-chelates do not cross the healthy blood-brain barrier
- the paramagnetic Gd causes signal drop at in the vicinity of the bolus on T2W images
- the labeled bolus spreads trough the circulation
- the intensity change during the first pass represents perfusion

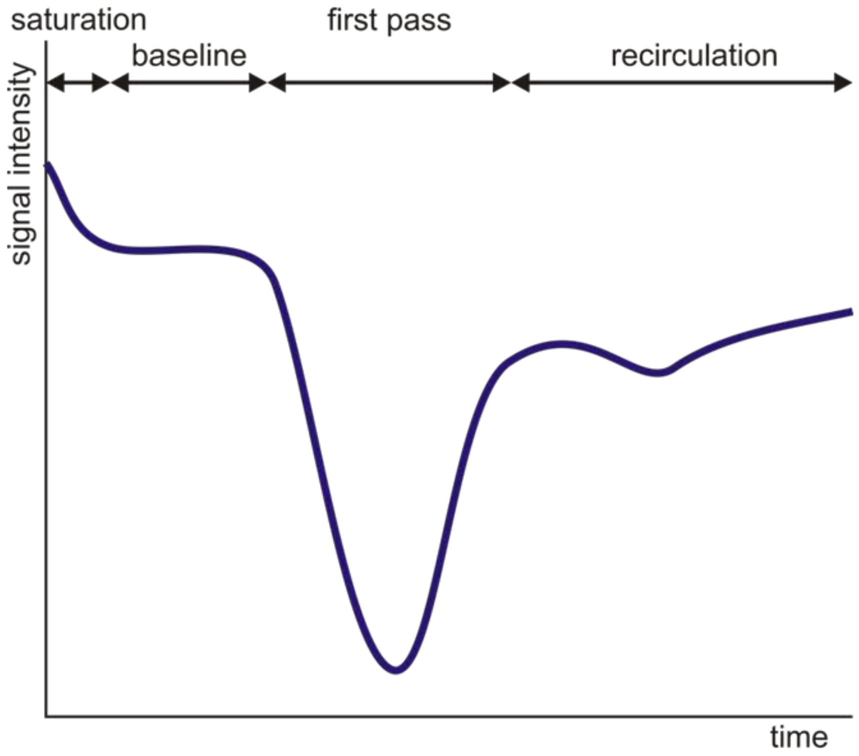


Based on a figure from P Barsi, MD, PhD

DSC imaging

Sequences

- Gradient-Echo EPI (GRE-EPI)
  - High signal drop
  - Sensitive to capillaries & larger vessels
- Spin-Echo EPI (SE-EPI)
  - Signal drop only 25% of GRE-EPI
  - Sensitive mainly to capillaries



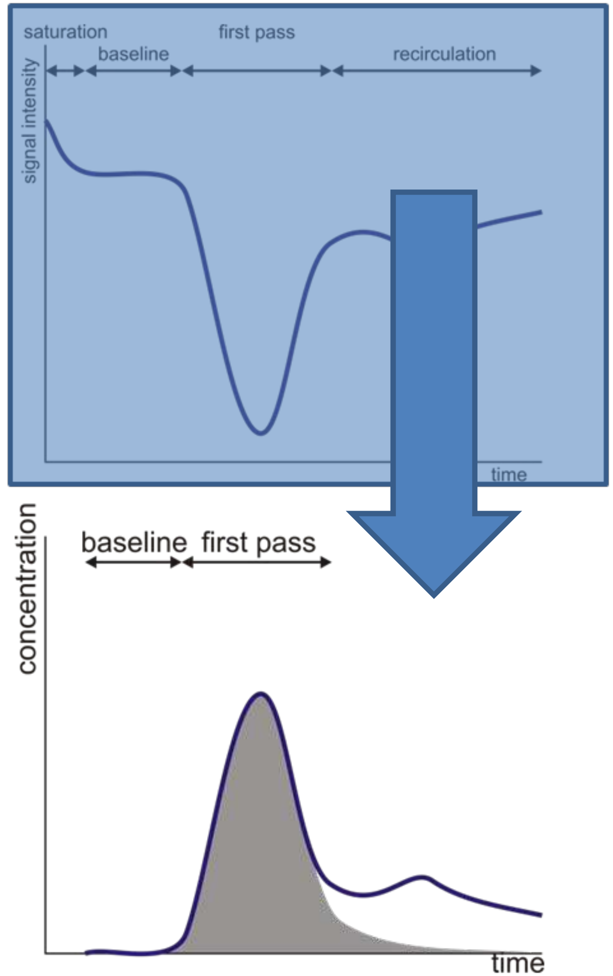
For a detailed account on technical aspects, see Wu et al., Neuroimag Clin N Am, 2005

Perfusion calulation

- Baseline determination
  - starting point
  - endpoint
- Concentration-time curve calculation

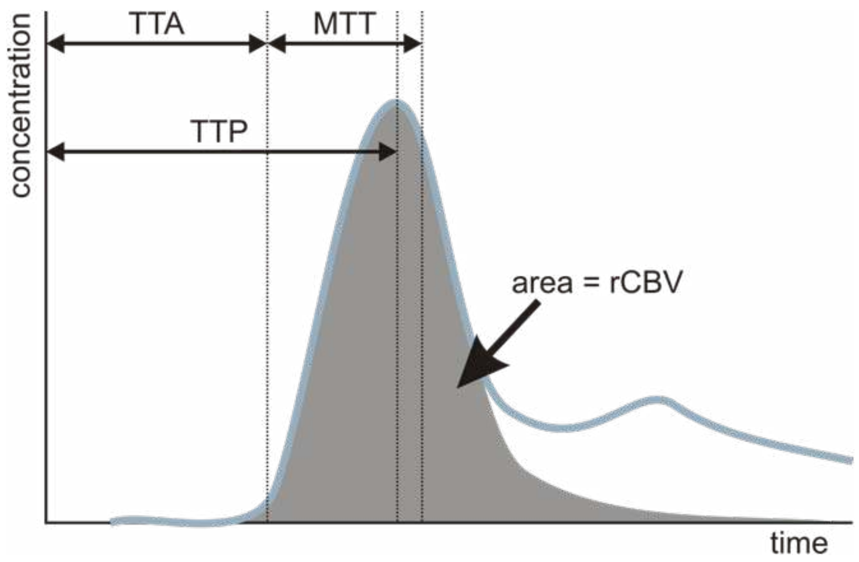
$$c(t) = -\frac{k}{TE}\ln\frac{S(t)}{S_0}$$

- Curve fitting



Perfusion parameters

- Time to arrival (**TTA**, [s])
  - time when the contrast agent reaches the tissue
- Time to peak (**TTP**, [s])
  - time of peak concentration
- Mean transit time (**MTT**, [s])
  - the average time required for any given particle to pass through the tissue, following an idealised input function
- Relative cerebral blood volume (**rCBV**, [ml/100g, %/100g])
  - the volume of distribution of the Gd-chelate during its first passage through the brain



Clinical applications of MR Perfusion

Cerebrocascular diseases

- acute stroke
- stenosis (decrease in vessel diameter)

Tumors

- differential diagnosis
- grading

Other indications

- Trauma
- Dementia
- Epilepsy, etc

PWI in stroke

- Changes seen almost immediately after the ischemic event
  - more sensitive than conventional MRI
- Perfusion findings often more extensive than those on DWI in **early stroke**
  - PWI more accurately reflects the amount of tissue under ischemic conditions in the hyperacute period than DWI
  - abnormal PWI results correlate with an increased risk of stroke
- PWI - DWI = **tissue at risk**

PWI and tumors

- many tumors have high rCBV
- regions of increased rCBV correlate with areas of active tumor
- heterogeneous patterns of perfusion suggest high grade
- radiation necrosis typically demonstrates low rCBV

- Lesion characterization may be possible
  - meningeomas have very high CBV in contrast to Schwannomas

PWI in other diseases

Dementias

- Perfusion parameters correlate well with PET and SPECT findings in Alzheimer's disease

Traumatic brain injury

- focal rCBV deficits correlate with cognitive impairment

Schizophrenia

- decreased frontal lobe rCBV

PWI future applications

Perfusion weighted MRI using the dynamic susceptibility imaging principle poses a risk due to the contrast agents used.

Arterial spin labeling (see the ASL chapter) can eliminate this risk and opens the possibility to serial perfusion measurements for the

- follow-up of therapy, e.g. in stroke, traumatic brain injury, etc.
- follow-up of disease-related perfusion changes, e.g. in dementias