AAPM 2004 - Continuing Education Course - MRI Physics and Technology - 3

Advanced MRI - An Overview of Techniques and Applications

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Introduction

Image contrast in MRI depends on an extensive list of *intrinsic* and *extrinsic* parameters.

– Intrinsic parameters include:

- *proton density*
- *spin-lattice relaxation time (T_1)*
- *spin-spin relaxation time (T_2)*
- *chemical environment*
- *velocity*
- *diffusion*
- *perfusion*
- *temperature*

– Extrinsic parameters include:

- *echo time (TE)*
- *repetition time (TR)*
- *flip angle (α)*
- *contrast agents*
- *saturation pulses*
- *inversion pulses*
- *flow compensation pulses (GMN)*
- *diffusion sensitization pulses*

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Introduction

Four "advanced" MR applications to be discussed in this course:

– Assessing the microvascular environment
  - Use of dynamic contrast enhanced (DCE) or dynamic susceptibility change (DSC) MRI to assess changes in the microvascular environment (capillaries and venules).

– Assessing changes in ^{1}H diffusion
  - Use of diffusion imaging techniques to determine the rate and principle direction of thermal (Brownian) motion of protons.

– Assessing areas of neuronal activation
  - Use of blood oxygen level dependent (BOLD) MRI to determine regions of neuronal activation based on hemodynamic response.

– Assessing biochemical changes non-invasively
  - Use of MR spectroscopy (MRS).

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Assessing the microvascular environment

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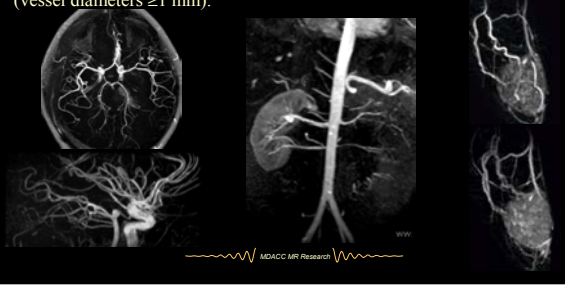
Assessing microvascular changes

MR angiographic techniques can assess macroscopic vascular morphology (vessel diameters ≥1 mm).



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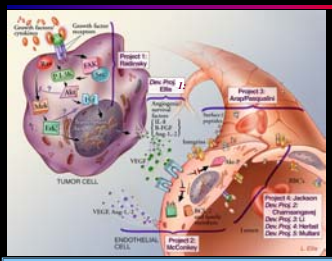
Assessing microvascular changes



To grow beyond ~ 2mm in diameter, and to metastasize, tumors must induce changes in the local vasculature. Early detection of such changes would allow assessment of the therapeutic efficacy of anti-angiogenic or anti-vascular agents and aid in differential diagnosis of lesions.

To assess microvascular changes (capillaries/venules), high speed imaging techniques are required.

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Assessing microvascular changes

- The most common MR techniques for assessing microvascular changes:
  - Dynamic contrast agent enhanced MRI (DCE-MRI)
  - Dynamic susceptibility change MRI (DSC-MRI)
- Both require rapid temporal sampling, with preferred sampling rates on the order of
  - 5 - 10 sec per image set for DCE-MRI
  - 1 - 2 sec per image set for DSC-MRI
- Both require the infusion of exogenous contrast agents.

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Common MRI contrast agents

Paramagnetic Contrast Agents

- Gadolinium is the most common paramagnetic atom used in MR agents
- Gd is toxic - must be tightly chelated
- Three common Gd agents:
  - Magnevist (gadopentetate dimeglumine) ionic
  - Omniscan (gadodiamide) non-ionic
  - Prohance (gadoteridol) non-ionic
- Osmotic loads of all three are *significantly* less than iodinated agents
- Affect both T_1 and T_2 relaxation times, with the dominant effect being shortening of the T_1 relaxation time (at routine clinical doses).

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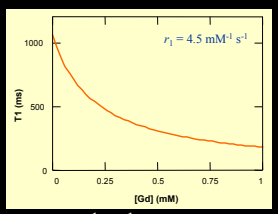
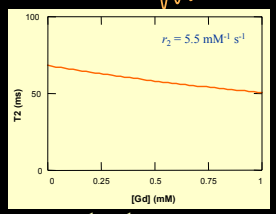
Paramagnetic contrast agent effects





$$\frac{1}{T_1} = \frac{1}{T_{1,0}} + r_1[Gd] \qquad \frac{1}{T_2} = \frac{1}{T_{2,0}} + r_1[Gd]$$

Effects of increasing Gd-DTPA concentration on T_1 (left) and T_2 (right) relaxation times in gray matter ($T_{1,0}$ = 1055 ms, $T_{2,0}$ = 68 ms). Note the dominant effect on T_1 relaxation times.

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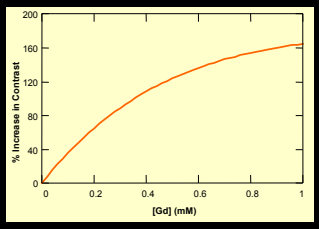
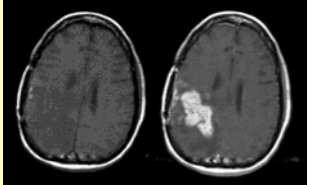
Paramagnetic contrast agent effects





Percent increase in contrast for gray matter as a function of Gd-DTPA concentration for a SE sequence with TR/TE = 400ms/18ms.

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DCE-MRI

- DCE-MRI acquisitions typically are based on fast spoiled gradient-echo sequences (FSPGR, FLASH):
  - Spoiling maintains T_1-weighting even with very short TRs
  - Trade-off between need for good temporal resolution and adequate spatial coverage
  - Both 2D and 3D acquisition modes are commonly used
- More recently, fast spoiled gradient echo sequences with echo train readout (with, typically, ET=2) have been used to improve temporal resolution or anatomic coverage.

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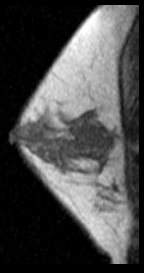
DCE-MRI



Fast Spoiled Gradient-Echo Sequence

$\alpha = 25^o$

TE / TR = 4.2 / 15 ms

22 x 18 cm FOV

256 x 128 matrix

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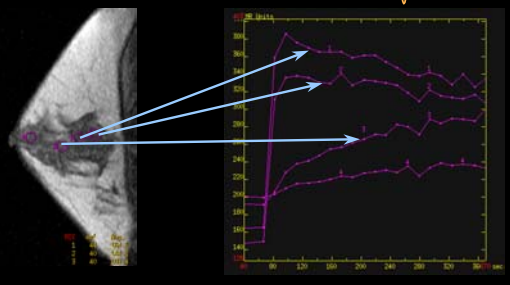
DCE-MRI



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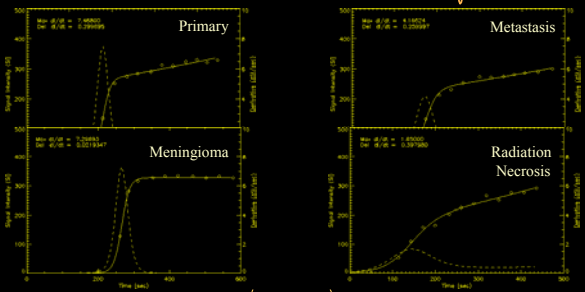
DCE-MRI



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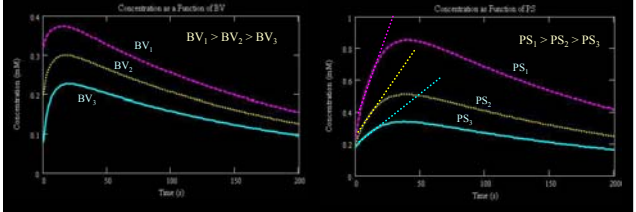
DCE-MRI



Two-Compartment Pharmacokinetic Model (Blood Volume Effects)

Two-Compartment Pharmacokinetic Model (Permeability or Extraction Flow Effects)

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DCE-MRI analysis issues

Qualitative, Semi-quantitative, or Quantitative

- Qualitative
  - Visual examination of uptake curves
- Semi-quantitative
  - Time to peak enhancement
  - Maximum uptake (maximum signal difference)
  - Maximum rate of uptake (maximum slope)
  - Area under the curve (AUC) and initial AUC
- Quantitative
  - Pharmacokinetic modeling

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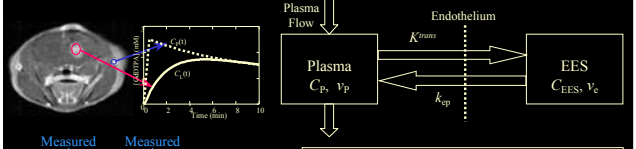
Two Compartment Pharmacokinetic Model



Measured Measured

$$C_L(t) = v_P C_P(t) + C_{EES}(t)$$

$$C_{EES}(t) = K^{trans} \int_0^t C_P(t') \; e^{-k_{ep}(t-t')} \; dt'$$

C_p = [Gd] in plasma (mM) = C_b / (1-Hct)

C_{EES} = [Gd] in extravascular, extracellular space (mM)

K^{trans} = endothelial transfer coefficient (min^{-1})

k_{ep} = reflux rate (min^{-1})

v_p = fractional plasma volume, v_e = fractional EES volume

Standardized parameters as proposed by Tofts *et al.*, *J Magn Reson Imaging*, 10:223-232, 1999.

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Quantitative methods

Quantitative DCE-MRI data analysis

- Primary model: two-compartment pharmacokinetic model
- Regimes:
  - Flow-limited (Kety model) - high permeability
  - Permeability surface area-limited - low permeability
  - Mixed model
- Measures:
  - K^{trans} - endothelial transfer coefficient (min^{-1})
  - v_p - fractional plasma volume
  - k_{ep} - reflux rate (min^{-1})

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Quantitative methods

- Flow-limited case:
  - K^{trans} => EF --- the "extraction flow product"
    - $E = (1 - e^{-PS/F})$
    - Most generally true for current FDA-approved small MW agents!
- Permeability-limited case:
  - K^{trans} => EF => PS
    - Since E => PS / F
    - Typically true for contrast agents with MW > ~50 kD

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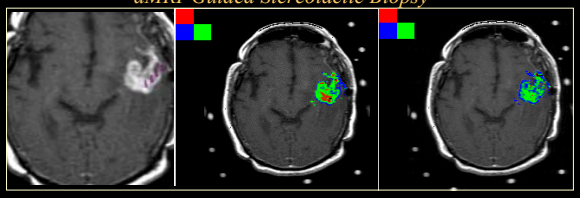
DCE-MRI - Parametric mapping

dMRI-Guided Stereotactic Biopsy



DCE-MRI T1W Image | Plasma Volume Fraction Map | K^{trans} Map

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DSC-MRI principles

Bolus infusion of paramagnetic contrast agent

- Principle: Bolus of paramagnetic substance passing through the microvasculature causes localized T_2* signal loss in areas of increased local blood flow/volume. This results in transient areas of hypointensity on T_2- and T_2*-weighted (*e.g.*, gradient-echo) images. The area under the signal intensity "washout" curve is proportional to rCBV.
- Advantages: 1) ~30% change in signal at 1.5T, 2) rapid study (<2 min).
- Disadvantages: 1) Requires IV bolus infusion, 2) assumes intravascular contrast agent, *i.e.*, rCBV and rCBF may be underestimated in brain lesions associated with a highly fenestrated BBB, such as many GBMs, or in any organ system with a large first pass extraction fraction, *e.g.*, liver.

Reference: Aronen *et al.*, Radiology 191(1):41-51, 1994.

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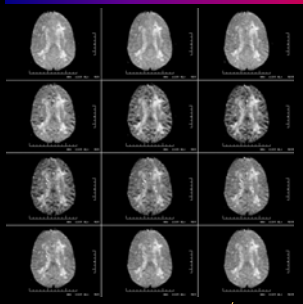
DSC-MRI principles



0.2 mmol/kg gadodiamide bolus infusion at 5 cc/sec

SE-EPI
TE/TR = 80/1700 ms
30 cm FOV, 128x128 matrix
125 kHz, 5 mm slice, 1.5 mm gap
65 phases, 1:52 min

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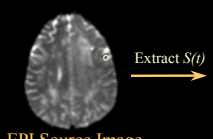
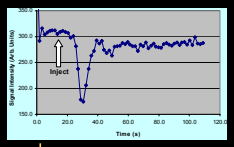
DSC-MRI

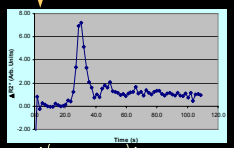


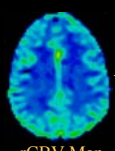
EPI Source Image

Extract $S(t)$



$\Delta R_2^* = -1/TE \ ln[S(t)/S(0)]$





rCBV Map

$$rCBV = \int_0^{\tau} \Delta R_2^*(t)\,dt$$

$$rMTT = \frac{\int_0^{\tau} \tau\,\Delta R_2^*(t)\,dt}{\int_0^{\tau} \Delta R_2^*(t)\,dt}$$

$$rCBF = \frac{rCBV}{rMTT}$$

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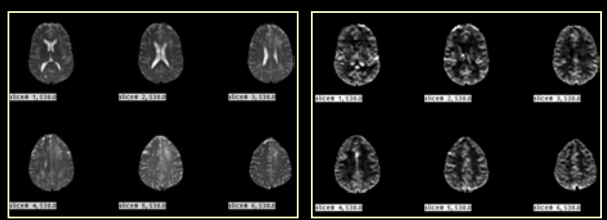
DSC-MRI



SE-EPI Source Images | rCBV Maps

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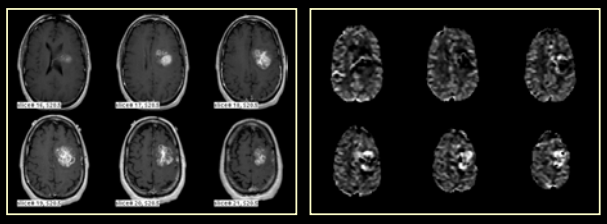
DSC-MRI



T_1-weighted Post-Gd | Computed rCBV Maps

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Assessing changes in ^1H diffusion

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Diffusion imaging

With the appropriate modification of a SE sequence, the image contrast can be made to depend on the rate of random, Brownian, motion of the water protons, *i.e.,* diffusion-weighted image contrast is obtained.

As the range of motion in diffusion processes is quite small compared to physiologic and gross patient motion, image acquisition rates need to be quite rapid. Therefore, successful diffusion imaging typically requires EPI class scanners capable of acquiring images in 50 - 100 ms per image.

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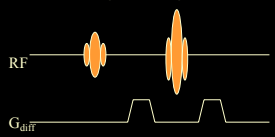
Diffusion imaging

The addition of two "diffusion-sensitizing" gradients to an EPI SE sequence provides a means of generating diffusion-weighted images.



The degree of diffusion-weighting depends on properties of the diffusion-sensitizing gradient pulses, which are taken into account in the "*b*-value" (s/mm^2). In the presence of these gradients, the signal is attenuated according to $S/S_0 = e^{-bD}$, where D is the diffusion coefficient (mm^2/s).

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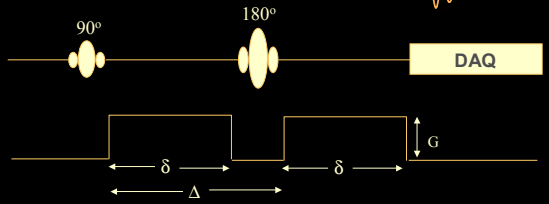
Diffusion imaging



$$b = \gamma^2 G^2 \delta^2 \left(\Delta - \frac{\delta}{3} \right)$$

Stejskal, Tanner, J Chem Physics , 1965

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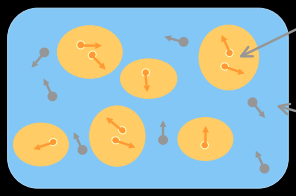
Diffusion imaging



$$D_{measured} = \frac{D_{intra} V_{intra} + D_{extra} V_{extra}}{V_{intra} + V_{extra}}$$

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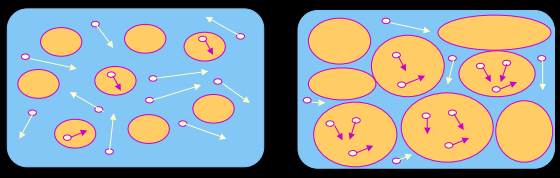
Diffusion imaging

Tissue Sample A

Tissue Sample B



Freely Diffusing Water = Dark

Restricted Diffusion = Bright

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Diffusion imaging

- Diffusion is described by a tensor.
- In materials with isotropic diffusion, the off-diagonal elements of the tensor are zero.
- In non-isotropic diffusing materials, the off-diagonal elements are non-zero, but (ideally) are symmetric.
- By applying the diffusion sensitizing gradient directions appropriately, the tensor elements can be completely defined.

$$\bar{\bar{D}} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

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Diffusion imaging

Diffusion Anisotropy

It should be noted that in many tissues, *e.g.*, white matter tracts, the diffusion rates are anisotropic since water diffuses along the tracts more freely than transverse to the tracts.

The effects of anisotropy can be removed by acquiring images with *x*-, *y*-, and *z*-diffusion-weighted images and computing the trace of the diffusion tensor, $D_{ave} = \sqrt[3]{D_{xx} D_{yy} D_{zz}}$.

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Diffusion imaging

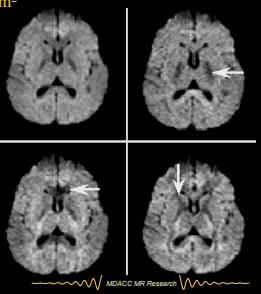
b-value = 800 s/mm^2

Isotropic DWI

S/I DWI

R/L DWI

A/P DWI



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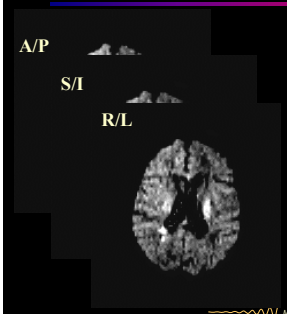
Diffusion imaging

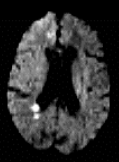
A/P

S/I

R/L



Isotropic Diffusion Image



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Diffusion imaging

Image Display

There are two ways of displaying images with diffusion-based contrast:

Diffusion-weighted imaging (DWI) - areas of unrestricted diffusion appear *hypo*intense and areas of restricted diffusion appear *hyper*intense.

Advantage: Very fast, no extra post-processing steps.

Disadvantage: T_2 "shine through" can be problematic. (Due to T_2 weighting of the sequence, *i.e.*, long TE intervals, necessary in order to obtain adequate *b*-values. This problem is decreased with high performance gradient subsystems.)

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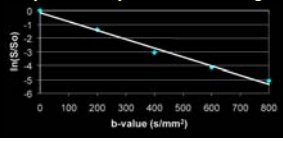
Diffusion imaging

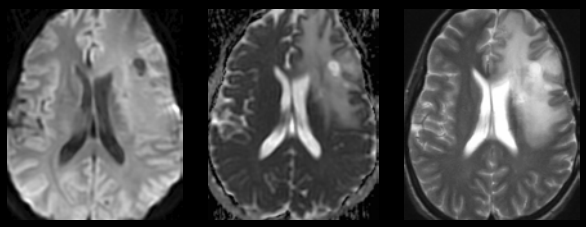
Apparent diffusion coefficient (ADC) imaging - areas of unrestricted diffusion appear *hyper*intense and areas of restricted diffusion appear *hypo*intense. Requires the acquisition of multiple sets of DWIs with varying *b*-values to allow computation of ADC values on a pixel-by-pixel basis by linear regression analysis of the signal attenuation equation, $ln(S/S_0) = -b * ADC$.

Advantage: T_2 "shine-through" is eliminated.

Disadvantage: Requires multiple *b*-values for regression => extra time.



ADC vs DWI



DWI | ADC (2 point) | T_2-weighted

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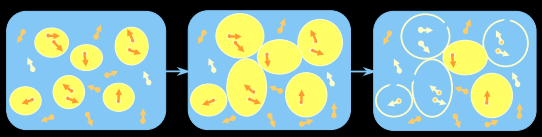
Diffusion imaging - Ischemic injury



normal tissue | cells swell | membranes break

D_{normal} | $D < D_{normal}$ | $D > D_{normal}$

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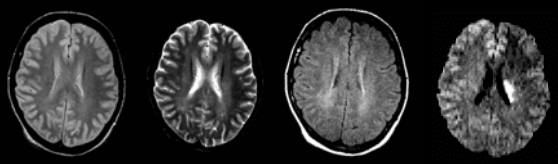
Diffusion imaging in acute stroke



PDW | T2W | FLAIR | Diffusion

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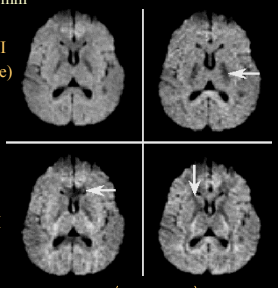
Diffusion weighted imaging

b-value = 800 s/mm²

Isotropic DWI ("Trace" image)



S/I DWI

R/L DWI

A/P DWI

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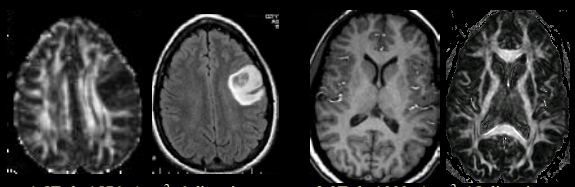
Diffusion tensor imaging (DTI)

Using multiple diffusion encoding directions to determine the diffusion tensor terms, eigenvalue/eigenvector analysis can be used to determine the *principle diffusion direction*. This is the basis of "tractography".



1.5T, *b*=1576 s/mm², 6 directions | 3.0T, *b*=1000 s/mm², 15 directions

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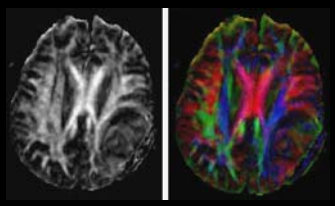
Diffusion tensor imaging (DTI)

Furthermore, fractional (or relative) anisotropy indices can be computed to more fully characterize the white matter tract directions.



Red:
Right/left

Green:
Anterior/posterior

Blue:
Superior/inferior

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Image from X. Joe Zhou, Ph.D.

Assessing areas of neuronal activation

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BOLD functional MRI - Principles

*Blood oxygen level dependent **(BOLD)** contrast*

- Principle: Uses the difference in the magnetic state of oxyhemoglobin (diamagnetic) *vs* deoxyhemoglobin (paramagnetic) to provide image contrast.
- Advantage: Totally noninvasive. Requires no infusion.
- Disadvantage: Much smaller change in signal intensity compared to bolus injection technique (~1-5% changes at 1.5T).

References: Ogawa *et al.*, Magn Reson Med 14:68, 1990; Kwong *et al.*, Proc Natl Acad Sci USA 89:5675, 1992.

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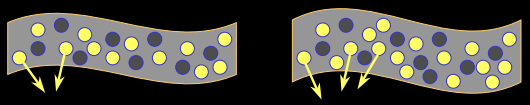
Functional MRI - BOLD Principles

*Blood oxygen level dependent **(BOLD)** contrast*



Normal State
- ~ 60% oxyHb
- Normal oxygen extraction rate
- Relatively large susceptibility effect
- Baseline MR signal intensity

Neuronal Activation State
- ~ 75% oxyHb (↑ Flow & volume)
- ~ 5% ↑ in oxygen extraction rate
- Decreased susceptibility effect
- Increased MR signal intensity

References: Ogawa *et al.*, Magn Reson Med 14:68, 1990; Kwong *et al.*, Proc Natl Acad Sci USA 89:5675, 1992.

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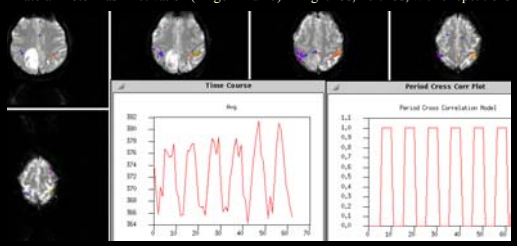
Functional MRI

Bilateral Motor Task Activation (Finger-Thumb) -- Right 15s, Left 15s, with 6 repetitions



Cross-correlation analysis: Orange/Red - Right Hand / Blue/Purple - Left Hand

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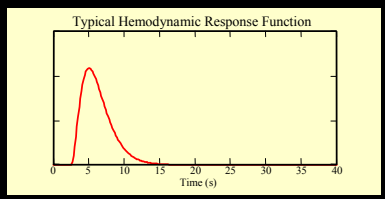
Hemodynamic Response Function



Approximate hemodynamic response function for delta function stimulus

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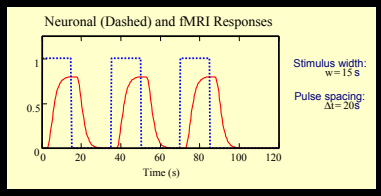
Latency in fMRI Response



~2 sec delay from time of activation until start of fMRI signal response
~6-8 sec delay from time of activation until peak of fMRI signal response

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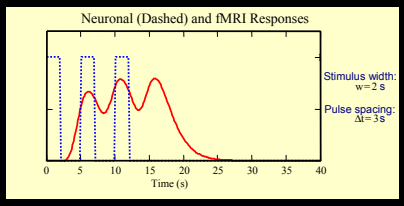
Latency in fMRI Response



~2 sec delay from time of activation until start of fMRI signal response
~6-8 sec delay from time of activation until peak of fMRI signal response

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fMRI Stimulation Devices

MR-Compatible Video Goggles

MR-Compatible Audio Headphones

MR-Compatible Response Pads

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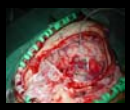
fMRI Applications in Oncology

Initial Clinical Application

Neurosurgical planning

- Goal: Maximize resection volume (for best prognosis) while preserving "eloquent centers" (for quality of life).
- Benefits:
  - Pre-surgical planning
  - Decreased OR time
    - Replace evoked potential mapping (sensorimotor)
    - Minimize need for awake craniotomy / direct cortical stimulation (speech / memory)
  - Replace pre-surgical Wada procedure (speech / memory)



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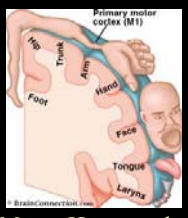
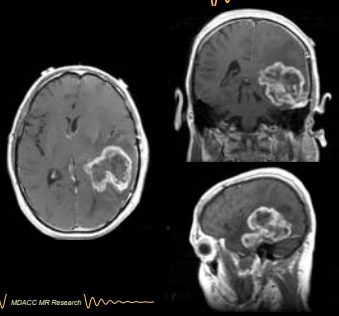
Locations of "Eloquent Centers"



Motor Homunculus

Ref: BrainConnection.com



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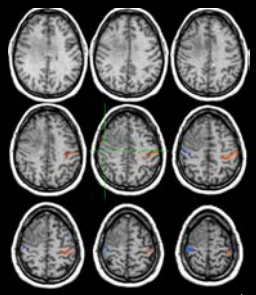
Functional MRI - Motor



Bilateral Hand Mapping for Presurgical Planning

Paradigm:
Bilateral finger-thumb tapping
15s off, (15 s right, 15 s left) x 5

Sequence:
Single-shot GR-EPI
60° flip, TE/TR = 60/3000ms
BW = 121 kHz, 1 NEX
128 x 128 matrix, 32 x 32 cm FOV
6 sections, 55 phases, 2:45 min

Analysis:
Cross-correlation analysis, p=0.001, r=0.443.

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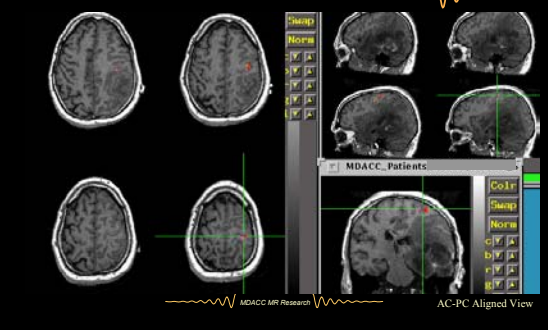
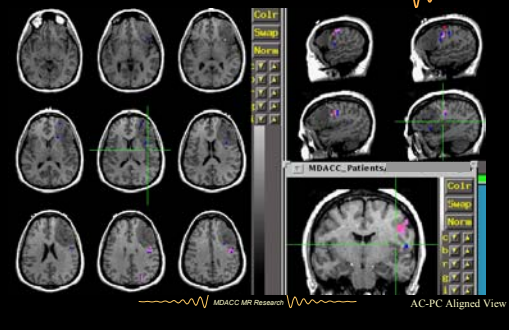
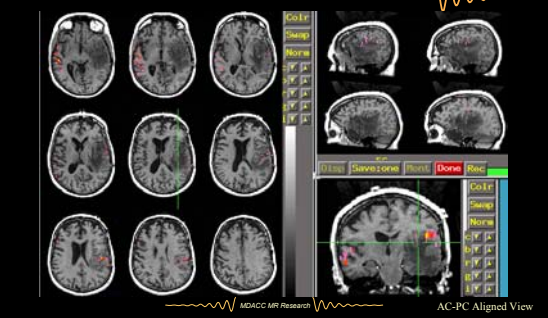
Functional MRI - Motor



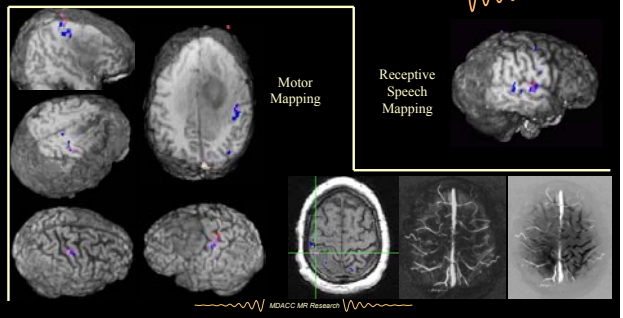
Functional MRI - Expressive speech



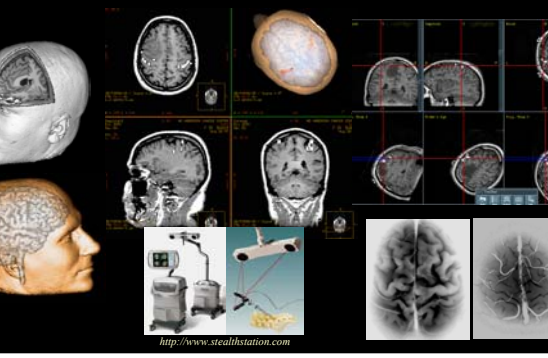
Functional MRI - Receptive speech



3D Display and Surface Vascular Mapping (3T Data)



fMRI and surgical planning



Assessing biochemical changes

Introduction to spectroscopy

- Recall the Larmor relation that relates resonant frequency to magnetic field strength:

$$\nu = \gamma \ B_{nucleus}$$

where ν is the resonant frequency (MHz), γ is the gyromagnetic ratio ($\gamma/(2\pi)$=42.57 MHz/T for protons), and $B_{nucleus}$ is the applied magnetic field strength (T) *at a given nucleus*.

- However, the value of $B_{nucleus}$ depends on the local electronic environment, *i.e.*, it is the value of the applied field, B_o, modified by the magnetic field due to the chemical environment.

Introduction to spectroscopy

- Therefore, nuclei in different chemical (electronic) environments will have slightly different resonance frequencies depending on the amount of local nuclear shielding, σ:

$$\nu = \gamma B_o (1 - \sigma)$$

- It is this local shielding effect that results in spectra with multiple peaks for a given nuclear species, where the peak positions depend on the local chemical environment.

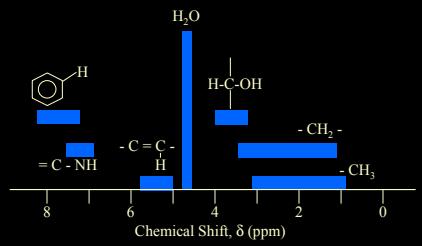
Introduction to spectroscopy

- The position of a given spectral peak is usually given in terms of *chemical shift* with respect to some reference,

$$\delta_x = [(\nu_x - \nu_{ref}) / \nu_{ref}] \times 10^6$$

- It is given in *parts per million* (ppm) to make the separations between the peaks independent of applied field strength.
- Note, however, that the separation of the peaks (in Hz) *does* depend on field strength. Therefore, the spectral resolution improves as field strength increases. (So does the SNR of the spectral peaks.)
- For ^{1}H MRS applications, the reference is usually water.

Introduction to spectroscopy



Requirements

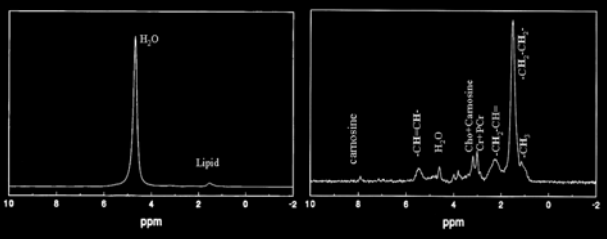
The success of an MRS examination depends upon the following:

- High quality localization
  The volume from which the chemical information (spectrum) is obtained must be accurately known.
- Highly homogeneous magnetic field
  Linewidths of peaks are inversely proportional to T_2*, so improved homogeneity results in narrower peaks (improved spectral resolution).
- Efficient water suppression (^{1}H MRS)
  This is aided by improved homogeneity as well.
- Spectral quantitation

Water suppression (^{1}H MRS)

- In ^{1}H MRS studies, water is seldom the molecule of interest. While the fact that we're about 80% water is good news for MRI, it is very bad news for MRS.
- The metabolites of interest are usually about a factor of 8,000 less in concentration than water. Therefore, we must have a very efficient means of suppressing the water resonance in order to readily detect the metabolite resonances.

^1H MRS - Gastrocnemius muscle



Without H_2O Suppression

With H_2O Suppression

Water suppression (^1H MRS)

- The most commonly utilized method for water suppression is based on the same principle as "fat sat". (For MRS sequences, the suppression pulses are commonly referred to as CHESS pulses - *chem*ically *s*elective *s*aturation.)
- Typically, multiple (often 3), narrow bandwidth (~50 Hz) pulses are applied at the water resonance frequency preceding the localization sequence.
- Multiple pulses are used to improve the degree of water suppression.

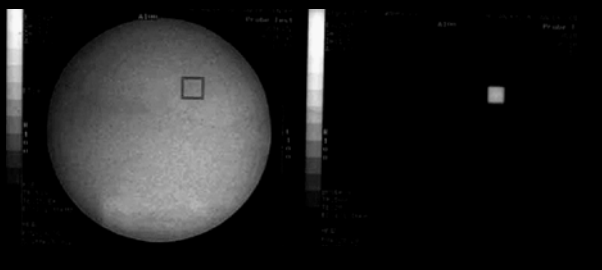
Water suppression (^1H MRS)

Localization

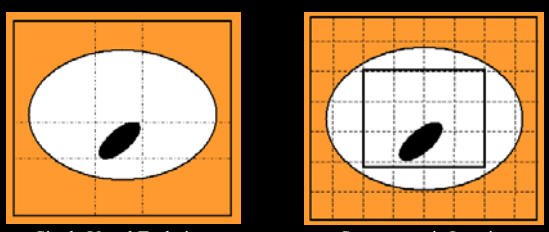
For a spectrum to have any significance, the region from which it is obtained must be accurately known. The most commonly used localization techniques are:

- Single voxel volume localization: The VOI is the intersection of three slice selective gradient/RF pulses. Each slice thickness can be individually varied to define VOI.
- Spectroscopic imaging: Uses phase-encoding for localization.
- Hybrids: Usually a combination of SVL and SI techniques.

Localization



Localization techniques



Single Voxel Technique

Spectroscopic Imaging Technique

Single voxel localization

- The most common single volume localization techniques are those based on the *st*imulated *e*cho *a*cquisition *m*ode (STEAM) and *p*oint *res*olved *s*pectroscopy (PRESS) sequences.
  - STEAM: 90^o-90^o-90^o-acquire
  - PRESS: 90^o-180^o-180^o-acquire
- Advantage of STEAM: shorter minimum echo times
- Advantage of PRESS: 2x SNR incrase compared to STEAM (for peaks with no *J*-coupling)

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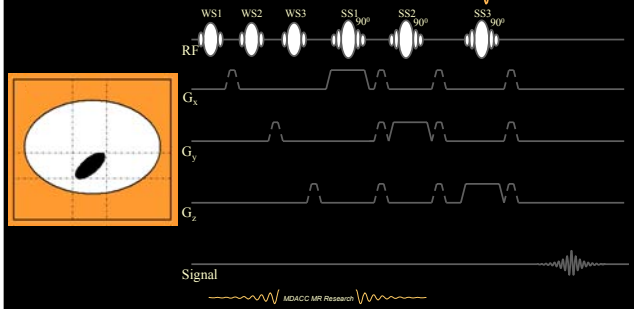
STEAM



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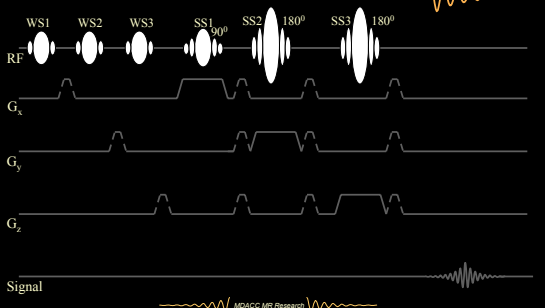
PRESS



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Spectroscopic imaging techniques

Instead of relying on the intersection of three planes to define a single VOI, SI techniques use phase-encoding for part or all of the localization to yield multiple VOIs.

- 2DSI: Uses one slice selection gradient/RF pair to define a slice, and then phase-encodes the remaining two dimensions. (Most commonly used SI method.)
- 3DSI: Uses three phase-encoding gradients to define a 3D volume of voxels.

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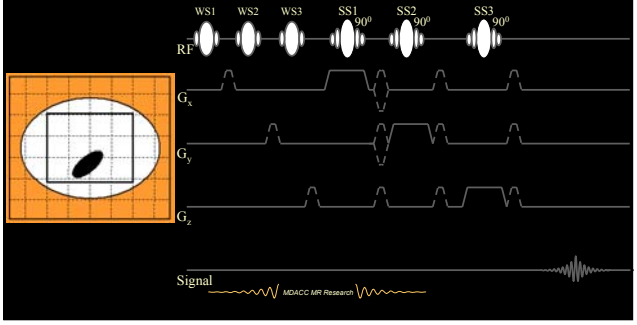
Spectroscopic imaging (SI)



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Spectroscopic imaging techniques

While SVL techniques are faster for obtaining a single localized spectrum, SI techniques have the following advantages:

- Spectra from multiple VOIs can be obtained for comparison.
  Useful for comparing suspected pathological tissue with normal-appearing contralateral region, or for better assessment of lesion heterogeneity.
- Spectra from smaller VOIs can be obtained as compared to SVL techniques.
  Less partial volume averaging, better assessment of heterogeneity.
- "Metabolite maps", in which pixel intensity is proportional to chemical concentration, can be generated.

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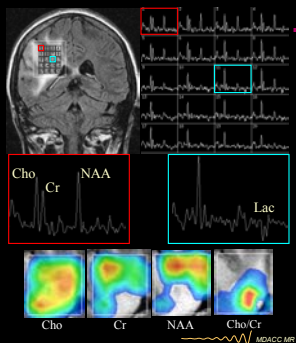
SI "Met Maps"



^{1}H MR Spectroscopic Imaging Applications

NAA:	*N*-acetylaspartate
Cho:	Choline compounds
Cr:	Creatine/ phosphocreatine
Lac:	Lactate

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Spectroscopic imaging techniques

Disadvantages of SI techniques include:

- rather long acquisition times:
  2DSI: $T_{scan} = N_{x\_phase} \times N_{y\_phase} \times N_{averages}$
- spatially-dependent water suppression efficiency & spectral quality
  much larger volume over which field homogeneity must be optimized -- more difficult to accomplish than with SVL.
- "spectral-bleed" from one voxel to another is possible due to phase-encoding point spread function. (Can be minimized by increasing N_{phases}, but this costs time.)

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What can be seen?

In ^{1}H MRS of the brain, the primary peaks are:

- NAA: *N*-acetylaspartate (viable neurons only) 2.0 ppm
- Cr: total creatine (creatine + phosphocreatine) 3.0 ppm
- Cho: choline (phosphotidylcholine, *etc*.) 3.2 ppm
- Lac: lactate 1.4 ppm

(All of the above can be detected at short *and* relatively long TE acquisitions.)

- GABA: γ-aminobutyric acid
- Simple amino acids, *e.g.,* alanine, glutamate, glutamine
- NAAG: *N*-acetylaspartylglutamate
- Asp: aspartate

(The above are in the 2.2-2.6 ppm range and typically require short TE acquisitions.)

- Lipids: range of chemical shifts, but dominant is methyl at 1.3 ppm
- Ins: *myo*-inositol 3.6 ppm
- Glucose (at ~ 3.5 ppm)

(The above require relatively short TE acquisitions.)

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Choice of echo times

- Note that the choice of echo times in MRS exams is critical. As you increase TE, of course, the signal from all metabolites decreases due to spin dephasing.
- Short TE: more spectral peaks means improved chances for lesion characterization or evaluation of therapy. *However*, the examinations are more difficult to obtain reproducibly, mainly due to decreased water suppression efficiency.

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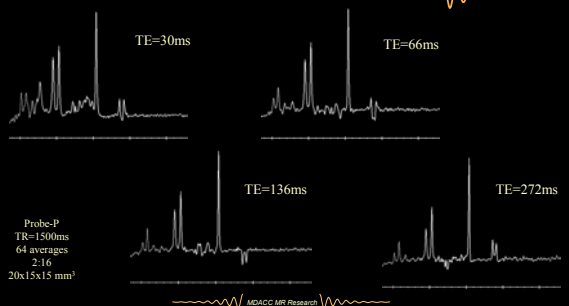
Effect of echo time



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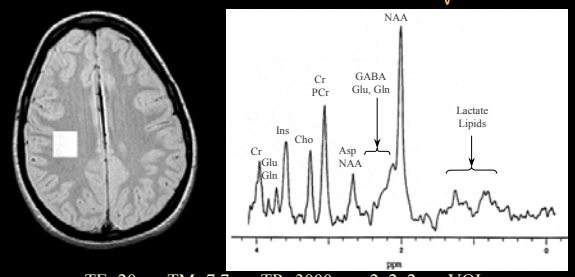
Short TE ^{1}H MRS



TE=20ms, TM=7.7ms, TR=3000ms - 2x2x2 cm VOI

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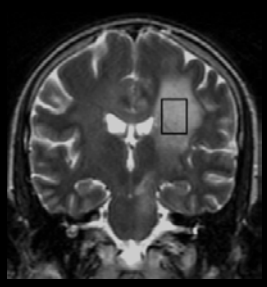
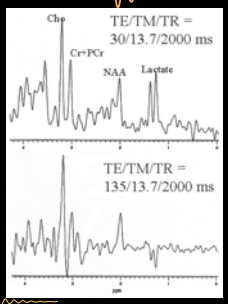
^1H MRS - Glioma





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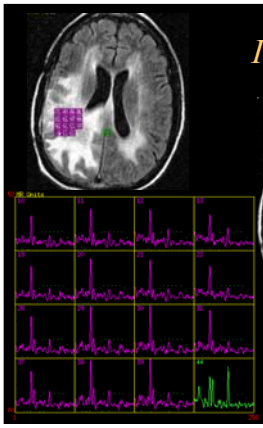
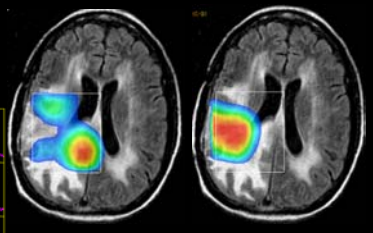
In vivo MR spectroscopy

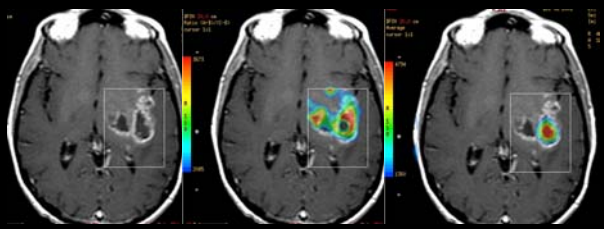




NAA Cho/Cr

Glioblastoma Multiforme

Tumor and necrosis



T1+C Cho/Cr Map Lipids

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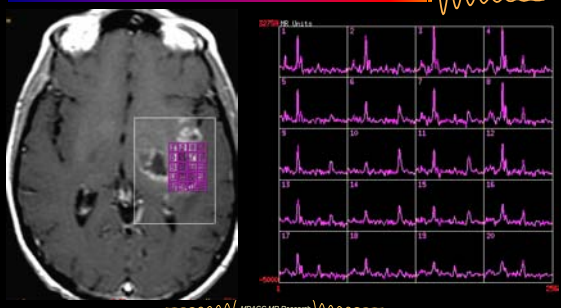
Tumor and necrosis



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Spectral quantitation

Quantitative analysis comes in two forms:

- Relative concentrations
  - Most commonly involves taking the ratio of peak areas, *e.g.*, NAA/Cr and Cho/Cr in brain.
  - Problem: Changes in ratios can be due to changes in, for example, NAA *or* Cr.
- Absolute concentrations
  - Much more difficult and requires some form of "standard".
  - External standard: small container of known concentration of reference sample from which reference spectrum is obtained.
  - Internal standard: most commonly taken as water.

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Very important

- When comparing MRS data, be sure you take the TE and TR times into account.
- Each metabolite has its own T_1 and T_2 relaxation times. Therefore, as you change TE and/or TR, the relative peak areas and heights change.
- If you must compare data acquired at different TE and TR values, you can approximately normalize the data using the equations for T_2-decay and T_1-recovery appropriate for the particular localization sequence, and reported *in vivo* T_1 and T_2 relaxation times for each metabolite of interest.

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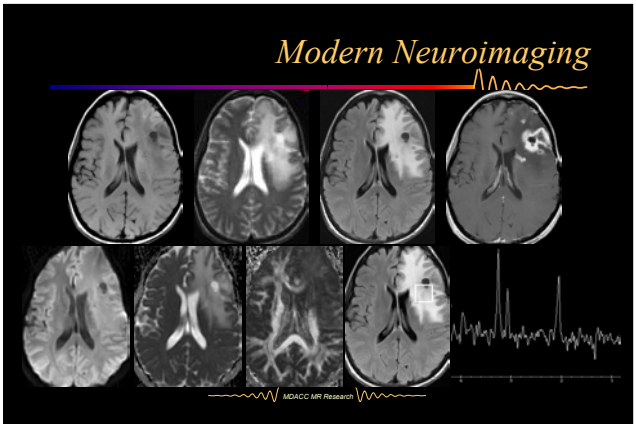
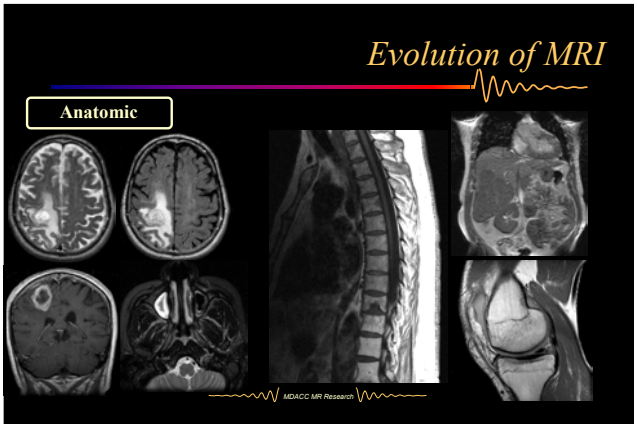
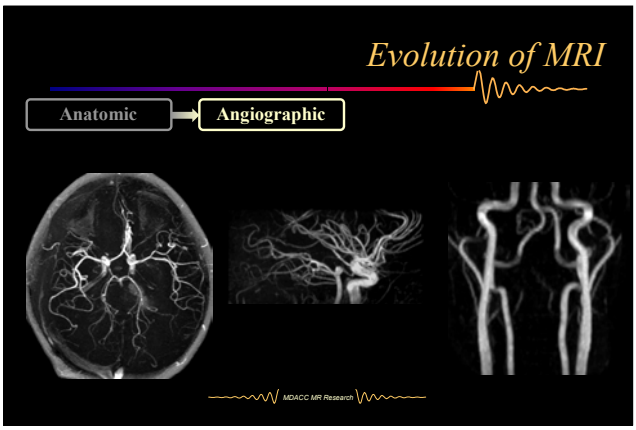
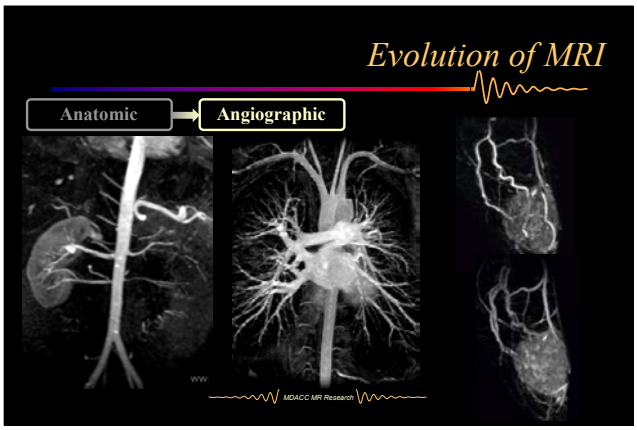
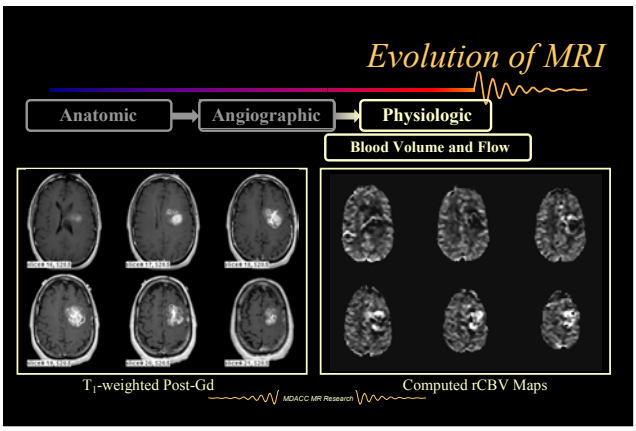
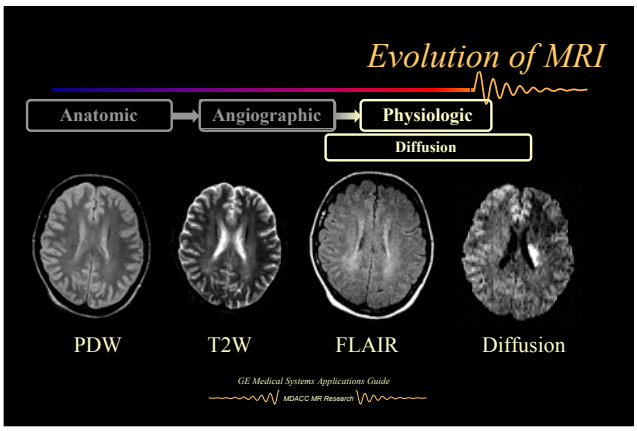

Modern Neuroimaging
MDACC MR Research


Evolution of MRI
Anatomic
MDACC MR Research


Evolution of MRI
Anatomic
Angiographic
MDACC MR Research


Evolution of MRI
Anatomic
Angiographic
MDACC MR Research

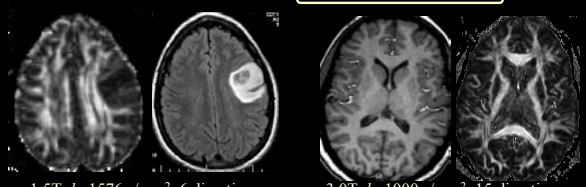

Evolution of MRI
Anatomic
Angiographic
Physiologic
Blood Volume and Flow
T1-weighted Post-Gd
Computed rCBV Maps
MDACC MR Research


Evolution of MRI
Anatomic
Angiographic
Physiologic
Diffusion
PDW
T2W
FLAIR
Diffusion
GE Medical Systems Applications Guide
MDACC MR Research

Evolution of MRI

Anatomic → Angiographic → **Physiologic**

Diffusion Tractography



1.5T, b=1576 s/mm^2, 6 directions

3.0T, b=1000 s/mm^2, 15 directions

MR Diffusion Tensor Imaging

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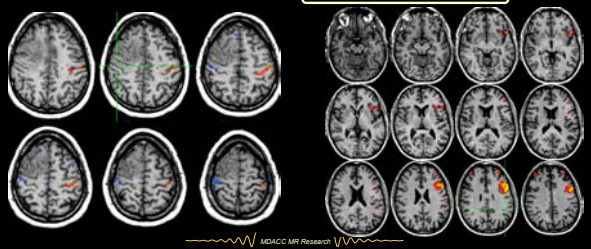
Evolution of MRI

Anatomic → Angiographic → **Physiologic**

Neuronal Activation



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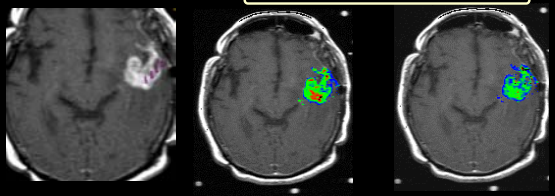
Evolution of MRI

Anatomic → Angiographic → **Physiologic**

Plasma Volume & Vascular Permeability



T1W Image | Plasma Volume Fraction Map | K^{trans} Map

Two-Compartment Pharmacokinetic Modeling of Contrast Uptake Kinetics

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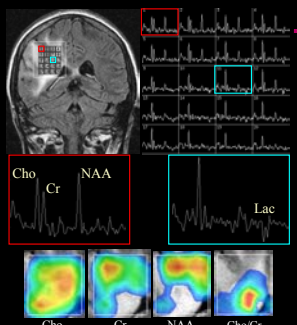
Evolution of MRI



Cho Cr NAA Cho/Cr

^{1}H MR Spectroscopic Imaging Applications

NAA:	*N*-acetylaspartate
Cho:	Choline compounds
Cr:	Creatine/ phosphocreatine
Lac:	Lactate

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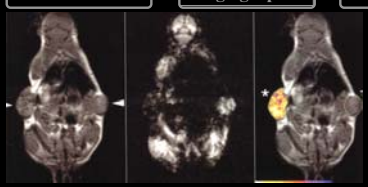
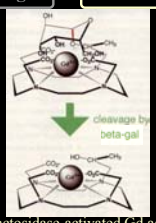
Evolution of MRI

Anatomic → Angiographic → Physiologic → **Molecular**



Transferrin receptor-targeted monocrystalline iron-oxide nanoparticles (MIONS)
Basilion *et al.* - MGH
Nature Medicine, March 2000



β-galactosidase-activated Gd agent
Meade *et al.* - Northwestern
Nature Biotechnology, March 2000

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