Contemporary MR: Pushing the Limits

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MR Contrast: Mechanisms, Agents, and Experiments

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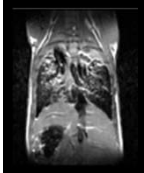
Human MR Images

Heart

Brain

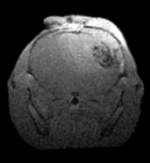
Cervical Spine

Murine MR Images

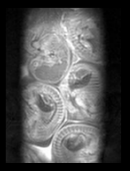


Fibrotic Lung

Cervix



Brain Tumor



Embryos

Magnetic Resonance Imaging

- The focus is on water with its ~110 M equivalent protons.
- Water has a wide variety of biophysical magnetic signatures in tissues and organs.
  - Properties are sensitive to local environment
  - Provide detailed structural information
  - Enhance contrast
- Pathological tissue has different relaxation characteristics than healthy tissue.

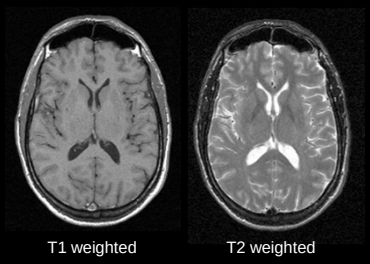
Why We Need Contrast

- How do you find a lake in the middle of the ocean?
  - Contrast/Noise Ratio (CNR) vs. Signal/Noise Ratio (SNR)
- How to distinguish organs & soft tissues in an MRI image?
  - Normal vs. Abnormal
  - Healthy vs. Damaged
  - Viable vs. Pathologic
- Encode physical properties of tissue in the MR image (development of tissue contrast).
- Which physical property do we encode?
  - What are we trying to measure?
  - What property generates the best contrast?

Sources of Contrast in MRI

- T1 (Longitudinal relaxation)
- T2 (Transverse relaxation)
  - Exogenous contrast agents (shorten T1, T2)
- Diffusion
- Velocity: Perfusion & Flow
- Magnetization Transfer
- Blood Oxygenation Level Dependence (BOLD), [functional MRI]

MRI of Normal Human Brain



T1 weighted T2 weighted

- Water in gray matter has different T1 and T2 relaxation times than water in white matter or CSF.

Image of, and courtesy of, Professor Jeffrey Neil, Washington University in St. Louis

Relaxation

- Relaxation is a return to equilibrium from a non-equilibrium (perturbed) state
  - Temperature
  - Concentration
  - Pressure
  - Mechanical stress/strain
  - Magnetization in an MR magnet

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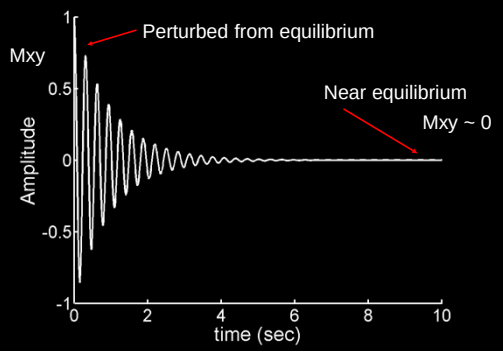
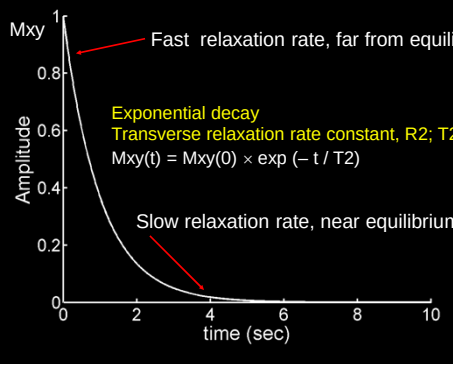
MR Relaxation

- At thermal equilibrium:
- There is no detectable water magnetization in the xy plane.
- The water 1H magnetization is stored, polarized, aligned fully along the magnetic field axis (z-axis).

MR Relaxation



MR: Transverse Relaxation



MR: Longitudinal Relaxation

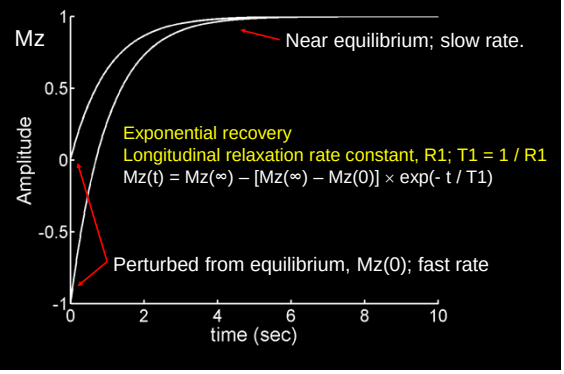
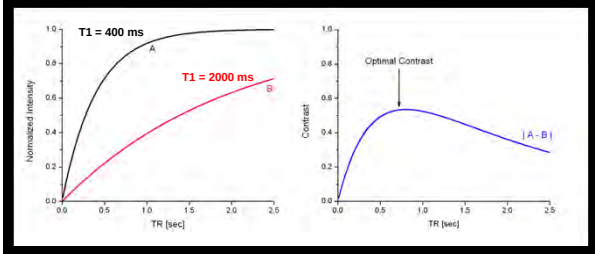
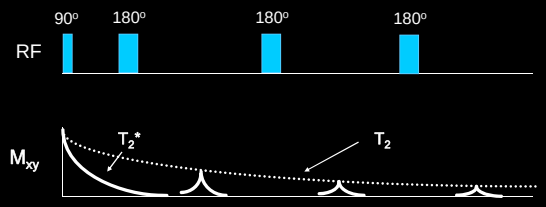


Image Contrast



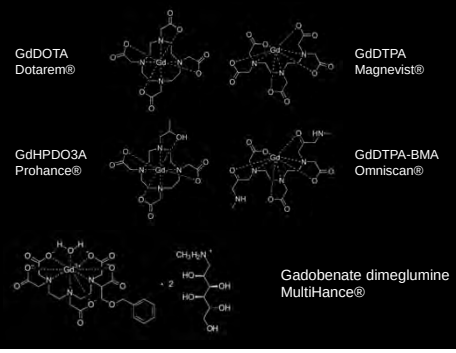
T_2* vs. T_2



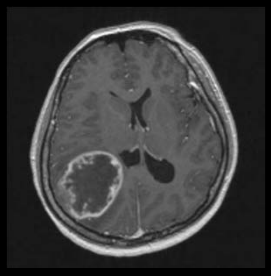
Contrast Agents

- Contrast agents are compounds, built around paramagnetic centers (e.g., Gd, Fe), that shorten the relaxation time of water.
- Water in tissue accessible to the contrast agent may appear brighter (T1 agent) or darker (T2 agent) than surrounding water.
- Unlike PET tracers or optical probes, MR contrast agents are never observed directly in imaging experiments.

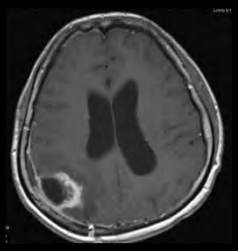
Gadolinium-based Clinical Contrast Agents



Gd-Enhanced, T1-Weighted Imaging



Brain Tumor (GBM)



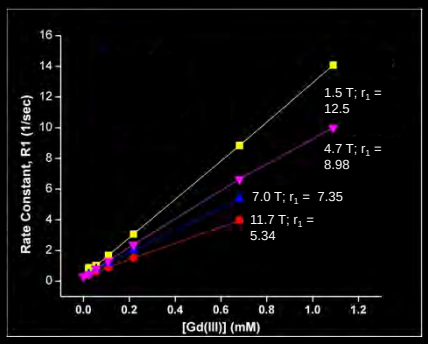
Radiation Necrosis

Dr. Sarah Jost, Swedish Hospital, Seattle, WA

MR Water Relaxivity – What is it, How do we Measure it?

- Relaxivity "r_1" (mM^{-1} sec^{-1}) is a quantitative measure of how effective an agent is at relaxing water (at increasing R1).
- $R1 = R1_0 + r_1 * [contrast\ agent, (CA, mM)]$
  - R1 is the measured water R1 (sec^{-1})
  - $R1_0$ is the water R1 in the absence of agent;
    - For pure water $R1_0$ ~ 0.25 sec^{-1} (T1 ~ 4 sec);
    - For tissue water, $R1_0$ ~ 1 sec^{-1} (T1 ~ 1 sec),
- Measure R1 at a series of low mM agent concentrations and plot against [CA]; slope of straight-line fit is r_1.
- Clinical agents (DTPA, DOTA) have r_1 ~ 4 mM^{-1} sec^{-1}; at 1mM, water R1 ~ 4.25 sec^{-1} (T1 ~ 0.24 sec).

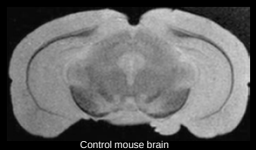
MR water relaxivity – How do we measure it?



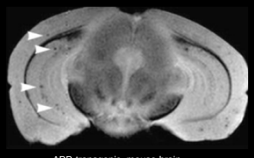
T2 (Negative) Contrast Agents

- Superparamagnetic Iron Oxide Nanoparticles
- Mechanism of Relaxivity is Magnetic Susceptibility
  - Shorten T2 of water molecules by perturbing local magnetic field surrounding particle
  - Effects extend well beyond the size of the particles
- Nanoparticles are categorized by their diameters
  - Superparamagnetic Iron Oxide (SPIO, 50 – 500 nm)
  - Ultrasmall Superparamagnetic Iron Oxide (USPIO, <50 nm)
  - Very Small Paramagnetic Iron Oxide (VSPIO, <10 nm)
- Nanoparticles have been developed with iron oxide cores and a wide variety of different surface coatings
  - Dextran, Starch
  - Albumin
  - Polyethenlene glycol (PEG)
  - Dendrimers

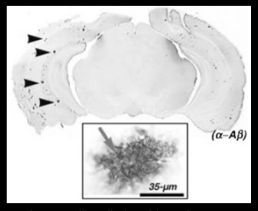
Monocrystalline Iron Oxide (MION) Particles Image Alzheimer's Plaques



Control mouse brain



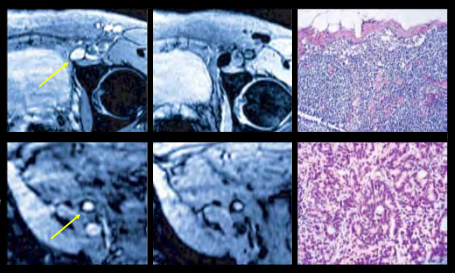
APP-transgenic mouse brain



Plaque Specific Antibody Staining and MION

Y Wadghiri, et al., *Magn Reson Med*, **50**, 293 (2003)

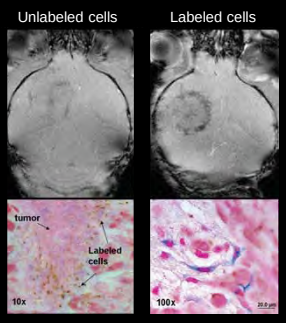
USPIOs Detect Metastatic Lymph Node (LN) Disease in Patients with Prostate Cancer



Harisinghani et al., *New England J Medicine*, 348, 2491 (2003)

Iron-Labeled Endothelial Precursor Cell Imaging

Murine glioma-Sca 1 model; Implant stem cells

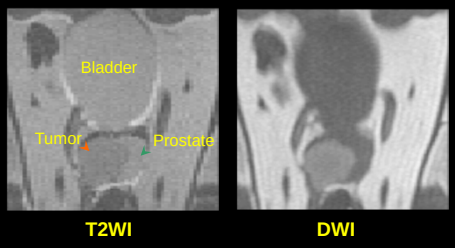


S Anderson and JA Frank in T Barrett, et al., *J Magn Reson Imaging*, **26**, 235 (2007)

Diffusion MRI

- MRI intensity is made sensitive to water displacement motion.
- Water displacement (apparent diffusion) can be an important source of image contrast.
- Water displacement motion reveals microstructure at a scale (~ 1 μm) much finer than achievable image resolution (~100 μm).
- Intensities in DWI experiments are sensitive to the magnitude of diffusion in one or more directions; create parametric maps of the apparent diffusion constant, ADC.

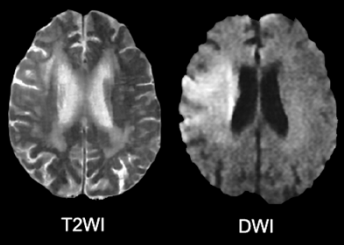
Spontaneous Prostate Cancer Transgenic Mouse Model



S.-K. (Victor) Song, et al., *Cancer Research*, **62**, 1555 (2002)

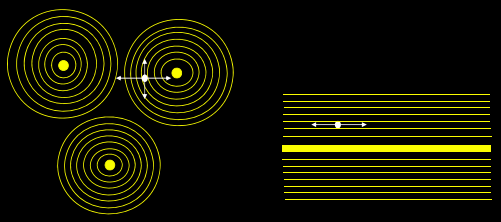
Diffusion MR Imaging of Stroke

Four hours after onset of left hemiparesis



Courtesy of Dr. Katie Vo, Washington University in St. Louis

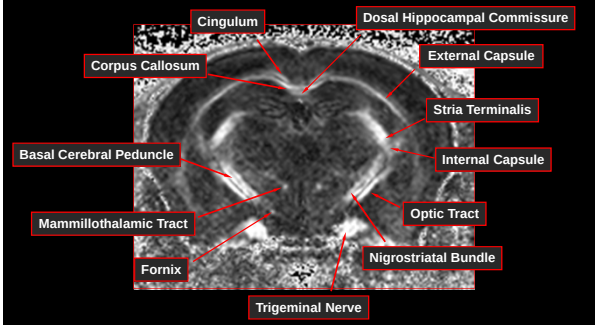
Water Motion in White Matter



Perpendicular to axons

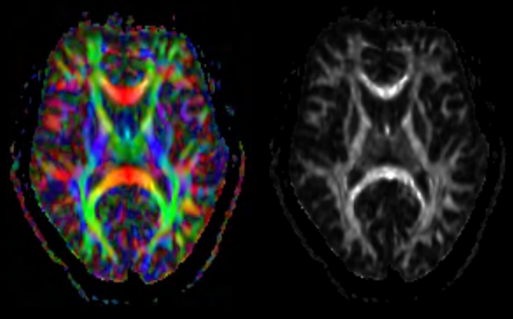
Parallel to axons

In Vivo RA Map of a Mouse Brain



Courtesy of S.-K. (Victor) Song, Washington University in St. Louis

Anisotropy: Color and BW



Courtesy of Dr. Joshua Shimony, Washington University in St. Louis

Dynamic contrast enhanced (DCE) MRI

- Inject a bolus of contrast agent; monitor MRI signal enhancement as a function of time in T1-weighted images.
- Contrast agents diffuse from blood pool to extracellular (interstitial) space at a rate determined by the permeability of the microvessels, their surface area, and blood flow.
- Quantitatively assess physiologic properties of tissue such as capillary permeability (K^{trans}), extracellular volume fraction (v_e), blood volume and flow.
- Clinically, "small" molecule DCE results have been shown to correlate with changes in these physiological parameters in response to therapy (e.g., angiogenesis).

Angiogenesis

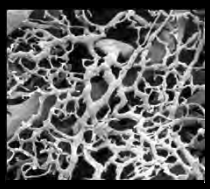
- Process by which new blood vessels grow toward and into tissues.
- Occurs in growth & development and in some normal processes requiring repair, remodeling and regeneration of tissues (e.g., wound healing).
- Critical for the development, growth, and metastasis of solid tumors.
- High level of vascularization is associated with higher tumor aggressiveness and increased potential for metastasis.

Tumor microcirculation - abnormal

– flow and blood volume
– microvascular permeability
– increased fractional volume of EES

Normal

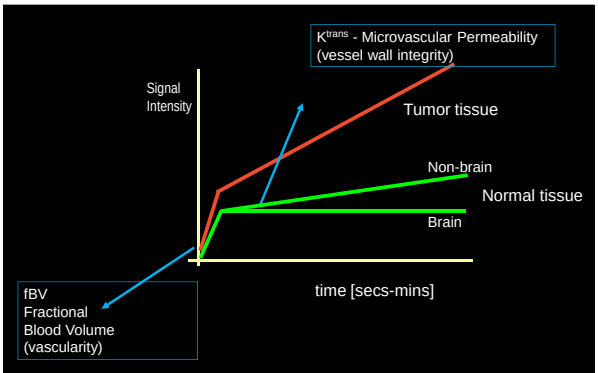
Tumor



McDonald and Choyke, *Nature Medicine*, **9**, 713 (2003)

Relating DCE signal to underlying physiology

- Convert Δ signal to Δ concentration of CA ([CA])
- Use model to relate [CA] over time to parameters that describe the exchange of contrast agent between plasma and interstitial water in a tissue:
  - Blood flow and volume
  - Microvascular permeability
  - Surface Area
  - Volume of extravascular, extracellular space



- Blood volume can be measured by first pass of a bolus of contrast agent through the microcirculation
- Progressive enhancement reflects permeability

**courtesy Professor Tim Roberts, University of Pennsylvania*

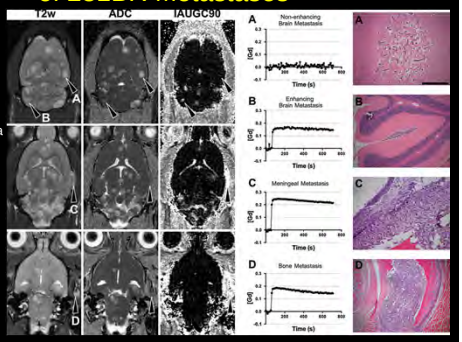
Metastatic Site Determines Characteristics of 231BR Metastases

A = Brain parenchyma

B = Ventricles or sulci

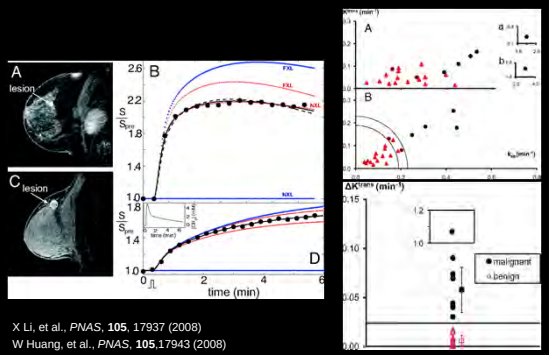
C = Meninges

D = Bone



M Budde, et. al., *Clin Exp Metastasis*, **29**, 51 (2012)

DCE – Human Breast Cancer



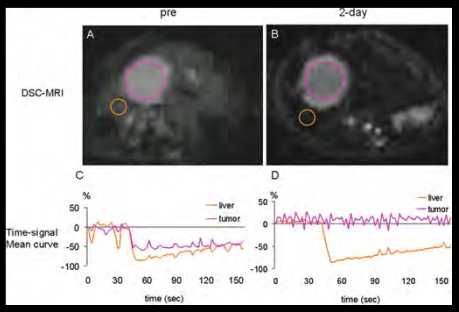
X Li, et al., *PNAS*, **105**, 17937 (2008)
W Huang, et al., *PNAS*, **105**,17943 (2008)

Dynamic susceptibility contrast (DSC) MRI

- Inject a bolus of contrast agent; monitor MRI signal change, with high temporal resolution, in T2*-weighted images.
- First-pass of bolus through the vascular results in signal loss in surrounding tissue due to magnetic susceptibility effects, arising from the paramagnetic contrast agent.
- Quantitatively assess perfusion properties of tissue such as blood volume, blood flow, and mean transit time.
- *Absolute* blood volume and flow are difficult to measure. Results are often reported as relative blood volume (rBV) and relative blood flow (rBF), normalized to contralateral (healthy) tissue.

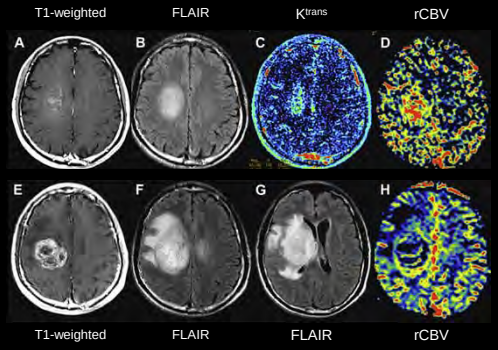
DSC – Vascular Disrupting Agent

Rhabdomyosarcoma in a Wag/Rij rat; Treat with CA-4P



F Chen, et al., *Methods in Mol Biol*, **771**, 489 (2011)

Glioma Progression



S Lacera and M Law, *Neuroimag Clin N Am*, **19**, 527 (2009)