

## Contrast Agents for MRI: Gadolinium

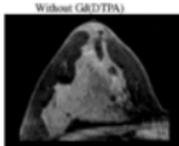
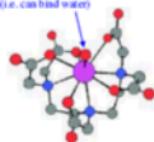
**Gd(DTPA)** DTPA is a highly flexible chelate that forms a rigid and exceedingly stable complex with  $Gd^{3+}$  ions.

A single exchangeable water molecule is coordinated to the metal ion (i.e. Gd(DTPA) has one coordination site).

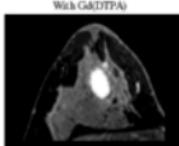
The larger the number of coordination sites, the stronger the influence gadolinium has on the relaxation time of the surrounding water, but the less stable the complex.

Gd(DTPA) has nine coordination sites in all but eight are occupied by the chelate.

Free coordination site  
(i.e. can bind water)



Without Gd(DTPA)



With Gd(DTPA)

The image shows a fibrosarcoma that was not visible on x-ray mammography

The DTPA chelate is ionic and highly hydrophilic and does not bind to protein in the blood, ensuring rapid distribution in the bloodstream and fast clearance through the kidneys.

Pharmacology and toxicology studies have confirmed that some demetallation occurs in vivo in situations where Gd(DTPA) has a long residence time (e.g. severe renal failure).

## Contrast Agents for MRI: Gadolinium

**Low Osmolality Chelates** Gd-DTPA has an osmolality approximately seven times higher than plasma osmolality since the three positive charges of gadolinium do not balance the charges of the five carboxyl groups.

The excess negative charges results in the need for cations (e.g. meglumine).

In one variant of the DTPA structure there are only three negative groups, the other two have been replaced by non-ionizing methylamide groups (Gd-DTPA-BMA)



In the structure Gd-DTPA-BMA the metal ion is coordinated by three amino nitrogens, the three carboxylic oxygen atoms, and the two amide carbonyl atoms.

As with Gd-DTPA, this leaves the way open for a single water molecule.

Gd-DTPA-BMA also has similar stability as Gd-DTPA.

NOTE: Although Gd(DTPA) is just as hypertonic as X-ray agents, the dose typically used is significantly less.

## Contrast Agents for MRI: Gadolinium

**Pharmacokinetics of Gd-Chelates** The ionic and non-ionic gadolinium chelates have essentially the same pharmacokinetics.

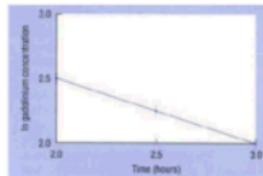
Gd-chelates are extracellular fluid space markers that pass rapidly between the plasma and interstitial spaces.

The Gd-chelates are eliminated rapidly by the kidneys by glomerular filtration with no significant tubular excretion or reabsorption.

- They can be used as tracers for glomerular filtration.

Gd-chelates cannot cross the intact blood-brain barrier, but can cross an injured barrier.

The pharmacokinetics of the gadolinium chelates can be approximated by the same two-compartment model used for iodinated contrast agents.



The slope of the line (i.e. glomerular filtration rate per unit volume)  $\lambda_2 = 0.009 \text{ min}^{-1}$ .

## Gadolinium Chelates: Clinical Applications

**Gd-Chelates Clinical Applications** Approximately 80% of Gd usage is for central nervous system diseases.

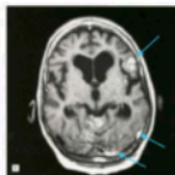
All gadolinium chelates in clinical use today are non-specific contrast agents.

Usually, contrast enhanced studies are performed as static examinations, however, dynamic studies have been introduced to assess organ function.

**Imaging the brain:** Pathological breakdown or absence of the  brain barrier allows paramagnetic contrast agents to cross into the extracellular space.

Following a bolus injection, uptake and enhancement can occur in less than 5 minutes for meningiomas (tumor that develops from the membrane that surrounds the brain).

Other lesions (e.g. low malignancy tumors, demyelination) may be reached only after 15 - 30 minutes.



## Gadolinium Chelates: Clinical Applications

### Gd-Chelates Clinical Applications

#### Imaging the brain:

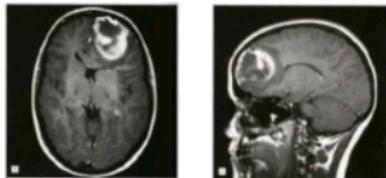
The extent of brain tumor enhancement indicates the degree of blood-brain-barrier breakdown and the degree of malignancy.

Low grade primary tumors usually display little contrast enhancement.

Gd-contrast agents are also very useful in highlighting brain infection and inflammatory disease.

- Early (i.e. small) abscesses (localized collection of pus surrounded by inflamed tissue) reveal focal enhancement
- Bigger abscesses reveal ring enhancement.

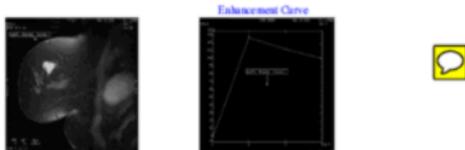
Ring enhancement can also be seen with large acute multiple sclerosis plaques and metastatic tumors.



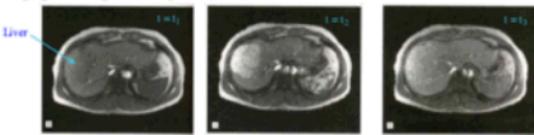
### Gadolinium Chelates: Clinical Applications

**Breast Lesions:** The uptake of contrast agent in breast tissue is associated with angiogenesis and therefore tissue metabolism.

Static or dynamic imaging can be performed; however, whether the rate of uptake can allow for the differentiation between malignant and benign lesions is debatable.



**Liver Lesions:** In the liver, highly vascularized pathologies can be best differentiated from equilibrium with the interstitial compartment is reached (similar to x-ray, i.e. by dynamic imaging following a bolus injection).



## Gadolinium Chelates: Clinical Applications

**Dynamic Imaging of the Heart:** The acquisition of one image per heart beat while a bolus of contrast agent is injected allows for the construction of a time-intensity curve.

Time-intensity curves can be used to calculate perfusion and other dynamic parameters.

The first pass of contrast agent through the heart can be used to delineate the cardiac chambers and myocardium. This can help reveal ischemic tissue.

2.5 seconds post injection: No enhancement

10 seconds post injection: Enhancement of right ventricular lumen.

15 seconds post injection: Enhancement of left ventricular lumen.

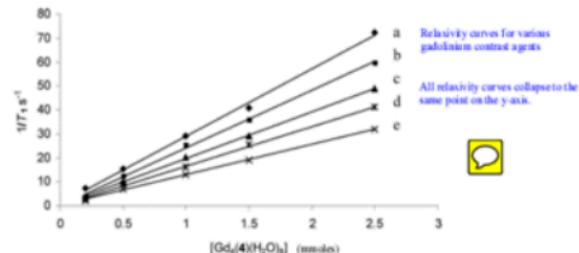


**Other Applications:** Following intravenous administration of paramagnetic contrast agent, many spinal cord diseases can more easily be imaged, as well as bone infections, and joint diseases.

### Characterization of MR Contrast Agents

**Relaxivity** Relaxivity is the ability of an MR contrast agent to shorten relaxation times.

Relaxivities in the longitudinal ( $R_1$ ) and transverse ( $R_2$ ) direction are calculated as the slope of the curve  $1/T_1$  versus concentration of contrast agent and  $1/T_2$  versus concentration of contrast agent, respectively.



The higher the relaxivity (i.e. steeper slope) of the contrast agent the larger the effect on the surrounding water protons - higher contrast.

## Macromolecular Gadolinium Agents

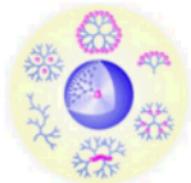
**Macromolecular Gd Agents** To date only low molecular weight (~500 Da) molecules with chelated gadolinium ions have been approved for clinical use.

Macromolecular agents can be defined as those contrast agents of a substantially higher molecular weight (>20 kDa) and which remain largely in the intravascular space (i.e. blood pool agents).

Macromolecular agents can provide progressive enhancement of tissues with abnormally increased capillary permeability (e.g. tumors or myocardial infarcts).

Various macromolecular formulations have been investigated in clinical trials. Agents include macromolecules such as albumin, dextran, and polylysine.

Entry into the clinical arena has been hampered by poor renal clearance, toxicity, and immunogenicity.



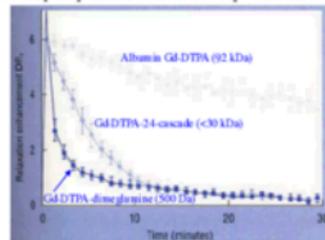
## Macromolecular Gadolinium Agents

### Examples of Macromolecular Gd Agents

Agent	Molecular weight (Da)	Plasma half-life (in the rat)	Ultimate excretion	Rapid excretion in normal tissues	MRI potency compared with gadolinium (at 10-20MHz)	Comments
Gd-DTPA	500 approximately	30 minutes	Yes	Yes	1	Extracellular fluid agent; clinically available
Albumin-Gd-DTPA <sub>20</sub>	92,000	3 hours	No	No	3-4	Not completely eliminated; immunogenic
Dextran-Gd-DTPA	75-400,000	>1.5 hours	No	No	3	Hepatic clearance
Gd-DTPA-24-cascade polymer	<30,000	0.5-1.5 hours	Yes	Yes	2	Relatively short plasma half-life
Polylysine-Gd-DTPA	30-480,000	1-2 hours	Yes	<50 kDa: yes >50 kDa: no	3-4	Polydisperse
MPEG-polylysine-Gd-DTPA	430,000	14 hours	Yes	No	4	Not completely eliminated (17% retained after 12 days)

## Macromolecular Gd Agents

**Biodistribution/Clearance:** A clear priority for each contrast agent for diagnostic radiology is that it must be completely eliminated from the body within a reasonable time frame.



Macromolecular contrast agents are generally too large for glomerular filtration and must either be broken down or eliminated through the hepatobiliary system.

**Relaxivity:** Gadolinium ions bound to macromolecules have a longer rotational correlation time (i.e. closer to water's magnetic resonance), resulting in more efficient relaxation enhancement than Gd-DTPA.

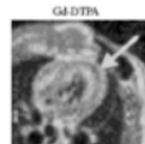
Macromolecular formulations also permit the binding of a large number of gadolinium containing groups to a single molecule leading to a higher relaxivity.

## Macromolecular Gadolinium Agents

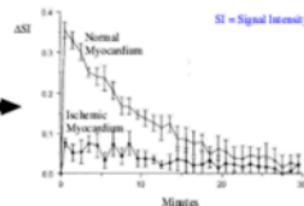
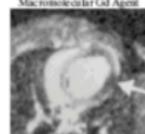
### Macromolecular Gd Agents: Applications

**Blood Pool Effects:** An ideal macromolecular agent remains intravascular and approximately at equal concentration for the period of the study.

As blood pool agents, macromolecular agents provide a simple and efficacious tool for the investigation of organ ischemia (i.e. reduced blood volume) - reduced tissue signal enhancement distal to occluded vessels.



The macromolecular Gd agent is far more effective at detecting ischemic tissue than Gd-DTPA.



# Macromolecular Gadolinium Agents

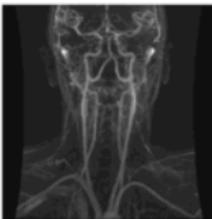
## Macromolecular Gd Agents: Applications

**Magnetic Resonance Angiography (MRA):** Unenhanced MRA has tremendous utility but suffers from a number of sensitivities (e.g. velocity range, motion-related artifacts).

A simple alternative lies in the use of macromolecular contrast agents combined with  $T_1$ -weighted imaging.



MRA of abdominal aorta



MRA of cervical and cerebral vasculature

Blood pool agent angiography are particularly pertinent to the imaging of tumor feeding vessels, since their complex flow patterns are not amenable to imaging via other methods.

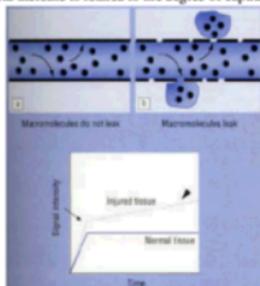
A disadvantage of macromolecule-enhanced angiography is that the signal in both the arteries and veins is elevated making it difficult to differentiate them.

## Macromolecular Gadolinium Agents

### Macromolecular Gd Agents: Applications

**Microvascular Permeability:** If capillary integrity is impaired, such as in malignancies or inflammatory diseases, macromolecular agents may slowly leak out of the intravascular compartment into the interstitial space.

The rate of enhancement increase is related to the degree of capillary hyperpermeability.

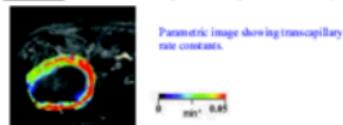


In certain tumor tissues there may be additional transport mechanisms referred to as vesiculovascular organelles, which permit the transit of macromolecules from the intravascular to extravascular spaces.

# Macromolecular Gadolinium Agents

## Macromolecular Gd Agents: Applications

**Parametric Mapping:** A parametric map is a synthesized image where the signal intensity of each pixel reflects the fractional blood volume or permeability-surface area (PS) of tissue.



The use of parametric imaging to provide estimates of capillary permeability has been applied to many diseases including:

- Lung injury: In acute alveolitis (inflammation of alveoli), there was an initial enhancement in contrast followed by a progressive enhancement, corresponding to capillary hyperpermeability.
- Ischemia: In some ischemia models there is a gradual increase in signal enhancement due to endothelial damage in the ischemic region leading to hyperpermeability.
- Liver transplant rejection: Rejected liver transplants have a significantly higher capillary permeability, a higher fractional blood volume, and blood mononuclear cell infiltration.
- Hyperpermeability is also seen in tumors, irradiated tissue, and sometimes following pharmaceutical interventions.

## Targeted Gadolinium-Based Contrast Agents

**Targeted Gd Contrast Agents** In nuclear medicine, nanomolar ( $10^{-9}$ ) or picomolar ( $10^{-12}$ ) concentrations of the radionuclide within the target tissue may be sufficient to image a lesion.

In MR, minimum concentrations of paramagnetic ions (i.e. Gd) are usually in the micromolar ( $10^{-6}$ ) range.

Nonetheless, although MR contrast agents need higher concentrations than radionuclides for imaging, MR has other advantages such as increased spatial resolution and anatomical information.

Targeted MR contrast agents can, in general, fall into three categories: small molecules, macromolecules, and particles.

**Targeted Small Molecules** Small molecules are generally defined as structures of less than several thousand Daltons (e.g. Gd-DTPA).

Small molecules are generally small enough to pass across the capillary fenestrations into the extracellular space.

Factors such as protein binding and lipophilicity enable these small molecule contrast agents to be targeted.

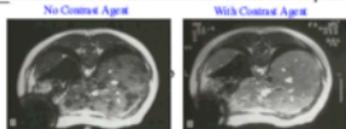
By substituting various functional groups on the chelate, lipophilicity and protein binding can be enhanced.

## Targeted Gadolinium-Based Contrast Agents

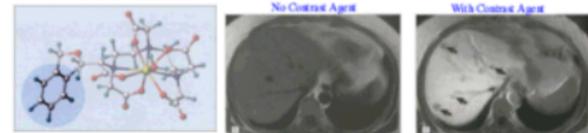
**Liver Targeted Small Molecules** Non-targeted agents such as Gd-DTPA and Gd-DO<sub>3</sub>A are hydrophilic and have relatively low protein binding and are therefore cleared via renal filtration.

Nonetheless, Gd-DTPA can still be used to look at liver lesions immediately after a bolus injection is administered.

But, if equilibrium is reached the lesions become less visible than in precontrast images.



An alternative to rapid scanning following a bolus injection is to use small molecular weight contrast agents (e.g. Gd-BOPTA) targeted to hepatocytes.

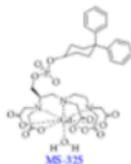


Gd-BOPTA enters hepatocytes by an organic anion transporter.

## Targeted Gadolinium-Based Contrast Agents

**Small Molecule Blood Pool Agents** Low molecular weight MR contrast agents can be retained within the intravascular space through reversible binding to albumin.

Albumin is too large to pass across the fenestrated capillaries into the extracellular space.



MR angiography with MS-325 shows narrowing of artery

Because the binding is non-covalent, the contrast agent may still be filtered by the glomeruli and excreted renally.

Since the rotational correlation time (tumbling rate) of the low molecular weight chelate is slowed by its association with the macromolecule albumin, its relaxivity is enhanced.

**Other Targeted Small Molecule Agents** Low molecular weight MR contrast agents have also been designed to accumulate in infarcted myocardial tissue, tumors, and bone marrow.

## Targeted Gadolinium-Based Contrast Agents

**Targeted Macromolecules** Large molecules or macromolecular MR contrast agents generally have molecular weights over 20,000 Daltons.

Their large size results in relative confinement within the intravascular space and often results in increased relaxivity due to rotational correlation effects.

The exact molecular weight that confers relative confinement of the contrast agent to the vascular space will vary depending on the charge and three-dimensional structure.

Macromolecules themselves may serve as the targeting moiety (e.g. antibodies) or as the scaffold to which targeting moieties are attached (e.g. polymers, liposomes)

**Gd-labeled Antibodies** Gd-labeled antibodies are unlikely to become useful for in vivo imaging since 1,000 to 10,000-fold higher concentrations of gadolinium are required for signal enhancement than can be delivered to cells by antibodies.

Further, the relaxivity of the Gd-labeled antibodies is similar to free Gd. This is because if the tether or linkage is flexible between the Gd and antibody, the rotational correlation time is not altered appreciably.

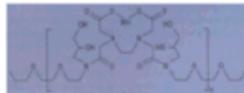
Only a limited number of chelates can be attached to each antibody without destroying the binding affinity of the antibody for its target.

To increase the amount of Gd bound to an antibody a polyfunctional linker can be constructed that is capable of binding many Gd ions (perhaps hundreds). However, the biodistribution and targeting will usually be compromised.

## Targeted Gadolinium-Based Contrast Agents

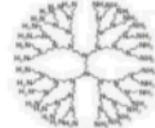
**Polymer-based Targeted Macromolecules** Polymers can be used as the scaffold to which targeting moieties and a large number of gadolinium chelates are attached. Some examples include:

**Copolymeric Chelates:** Copolymeric chelates are composed of repeating units of a linking monomer with a chelate monomer:



In the copolymeric chelate approach, since the chelate is part of the backbone, the construct tumbles slower and leads to significant contrast enhancements.

**Dendrimers:** Dendrimer agents have a branching appearance and exhibit very high relaxivities.



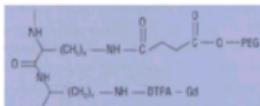
Compared with linear polymeric agents, which have some degree of polydispersity (varying molecular weights), dendrimers are nearly monodisperse.

## Targeted Gadolinium-Based Contrast Agents

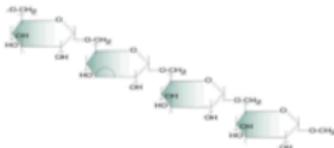
### Polymer-based Targeted Macromolecules

**Other Polymer-based Macromolecules:** Linear polymeric agents such as dextran and polylysine are often used as scaffolds for gadolinium chelates and targeting moieties.

In order to minimize toxicity of polylysine the **free amines** must be masked. This is usually accomplished using the linear molecule, polyethylene glycol (PEG).



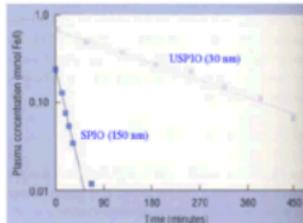
Dextran is widely used as a macromolecular scaffold for gadolinium because of its high capacity for **functionalization**.



## Targeted Gadolinium-Based Contrast Agents

**Targeted Particulate Contrast Agents** Size or particle diameter influences the biodistribution of particulate MR contrast agents.

Smaller particles (< 30 nm) tend to have **longer** intravascular residence times than larger particles (> 100 nm).



Larger particles tend to be more rapidly cleared from the blood by Kupffer cells and macrophages from the reticuloendothelial system (RES).

**Serum protein** binding also influences clearance by the RES. Opsonization by certain proteins leads to rapid clearance by the RES.

NOTE: The **spleen** has a larger fraction of RES elements than the liver, and agents cleared primarily by the RES tend to reach higher concentrations in the **spleen** than the liver.

## Targeted Gadolinium-Based Contrast Agents

**Circulation Time of Particulate Contrast Agents** As discussed the size of particles can be reduced to increase circulation time, but this may have only a minor prolonging effect.

Perhaps, more importantly, the **surface** characteristics of the particle can be modified to minimize absorption of serum proteins.

Neutral hydrophilic polymers (e.g. polyethylene glycol, PEG; dextran; starch) have been shown to be useful as coating agents in this regard.

PEG coated agents can have circulation times as long as **24 hours**.

### Examples of Particulate Contrast Agents

**Gd-Loaded Liposomes:** Liposomes can be used as carriers of paramagnetic ions. Paramagnetic chelates can be entrapped within the lipid vesicles.

Gd-loaded liposomes actually have a **reduced** relaxivity compared with free Gd-DTPA since water outside the liposome has much less contact with the Gd on the inside.

**Water flux** across the liposome membrane is rate limiting.

Smaller liposomes (< 100 nm) have a **higher** relaxivity than larger vesicles, since they have a greater surface area relative to internal volume.



## Targeted Gadolinium-Based Contrast Agents

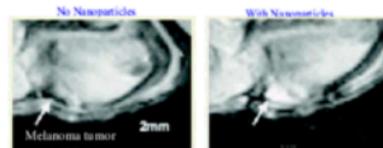
### Examples of Particulate Contrast Agents

**Surface-labeled Liposomes:** An alternative to liposomal entrapment is to incorporate Gd-chelates directly onto the lipid membrane.

With this format, chelates have good exposure to water and relaxivity is enhanced because of **slowed** rotational correlation time.

There is a size-related effect on relaxivity, the smallest liposomes (30 nm diameter) having the **highest** relaxivity, which may be related to steric hindrance of chelates and water exchange.

Some formulations of surface-labeled liposomes (i.e. lipid coated perfluorocarbons, 250 nm diameter) can carry up to **100,000** gadolinium molecules and targeting moieties.



## Targeted Gadolinium-Based Contrast Agents

### Examples of Particulate Contrast Agents

**Manganese Hydroxyapatite:** Manganese hydroxyapatite particles are prepared by precipitating calcium and phosphorous under controlled conditions.

By doping the particles with manganese ( $Mn^{2+}$ ) or substituting manganese for a portion of the calcium, paramagnetic hydroxyapatite particles are produced.

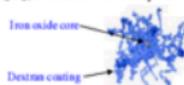
Smaller particles (<50 nm diameter) appear to have better relaxivity than larger particles, probably due to water flux, analogous to Gd-loaded liposomes.

One application for manganese hydroxyapatite particles is for imaging the liver and spleen, but coated particles can be prepared for targeting other organs.

PEG-coated manganese hydroxyapatite particles have a prolonged vascular distribution and can easily be modified to support specific ligands for targeting.

## Superparamagnetic Iron Oxides

**Iron Oxide Nanoparticles** Most superparamagnetic agents consist of an iron-oxide crystal comprised of  $Fe_3O_4$  and/or  $Fe_2O_3$ , coated in a biocompatible polymer matrix such as dextran.



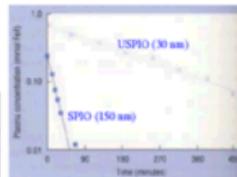
Without a coating material, iron oxide particles aggregate serum proteins and may activate the complement system.

Superparamagnetic agents can be divided into two main groups:

- Superparamagnetic iron oxides (SPIOs), which including coating are greater than 50 nm in diameter.
- Ultra-small superparamagnetic iron oxides (USPIOs), which are less than 50 nm in diameter

The difference in size is reflected in significant differences in the relaxivity constants  $R_1$  and  $R_2$  and in plasma half-life and biodistribution.

Iron Oxide	Inner Core Diameter	Particle Diameter	$R_1$ (mL · sec <sup>-1</sup> )	$R_2$ (mL · sec <sup>-1</sup> )
SPIO (Ferumoxide)	4.8 nm	150 nm	23.7	107.0
USPIO (Ferumoxtran)	4.9 nm	30 nm	22.7	53.1



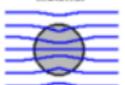
## Superparamagnetic Iron Oxides

**Superparamagnetic Agents** Superparamagnetic agents (e.g. iron oxide nanoparticles) are highly effective as contrast agents in MRI, with much higher relaxivities  $R_1$  and  $R_2$  than gadolinium chelates.

In most situations, it is the significant capacity of superparamagnetic agents to reduce the spin-spin ( $T_2$ ) relaxation time that is utilized.

The decrease in signal intensity is related to the inhomogeneity of the magnetic field produced around the magnetic particles.

### Superparamagnetic Material



The figure illustrates the effect of a superparamagnetic particle on the magnetic field flux lines.

Water molecules diffusing through these local gradients undergo fast  $T_2$  and  $T_2^*$  relaxation.

Superparamagnetic particles are therefore negative contrast agents, causing a reduction in the signal intensity in the tissues in which they accumulate.

The physico-chemical properties (i.e. size, surface properties, charge, etc.) of superparamagnetic agents not only effect the efficacy of the particles in MRI but also influence their stability, biodistribution, metabolism, and clearance.

## Superparamagnetic Iron Oxides

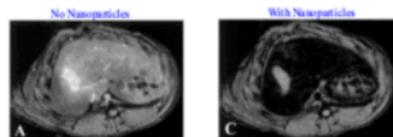
### Iron Oxide Nanoparticle Applications

**Gastrointestinal Tract:** The oral administration of iron-oxide nanoparticles coated with silicon (diameter of 300 nm) provides a significant improvement in the definition between the GI tract and surrounding organs.

The nanoparticles flow through and darken the stomach and the small intestines in 30 to 45 minutes.

By more clearly identifying the intestinal loops, the nanoparticles improve visualization of adjacent abdominal tissues such as the pancreas.

**Liver and Splenic Disease:** Following intravenous injection, nanoparticles (e.g. Ferumoxide, 150 nm diameter) are taken up by Kupffer cells of the healthy liver, increasing the contrast between healthy and diseased tissue which is devoid of Kupffer cells.



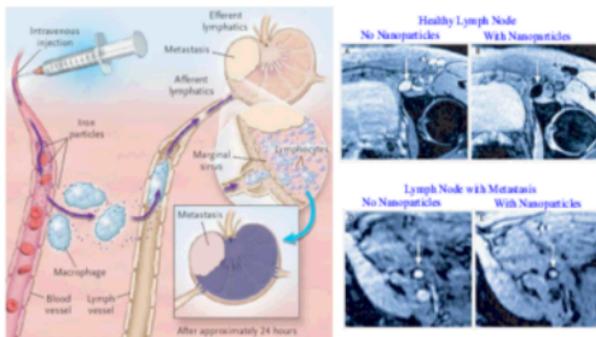
Another, more hepatocyte-specific agent that has been developed is arabinogalactane-labeled nanoparticles, which binds to asialoglycoprotein receptors present on normal hepatocytes.

## Superparamagnetic Iron Oxides

### Iron Oxide Nanoparticle Applications

**Lymph Node Diseases:** Long circulating nanoparticles (<30 nm) eventually gain access to the **interstitium**, drain through the lymphatic vessels and accumulate in the lymph nodes.

Lymph node **metastases** prevent accumulation of the nanoparticles in the node.



## Superparamagnetic Iron Oxides

### Iron Oxide Nanoparticle Applications

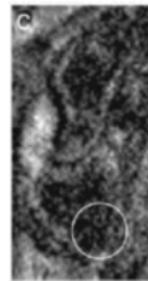
**Atherosclerosis/Inflammation:** Because of the long half-life of some nanoparticles (<30 nm), they can be taken up by **macrophages** in the whole body.

For example, it has been found that these long-circulating nanoparticles are phagocytosed by **macrophages** in atherosclerotic plaques.

Proton density weighted image of external and internal carotid artery



T2-weighted image 24 hours after administration of nanoparticles



Less of signal along vascular wall indicates accumulation of nanoparticles.

## Superparamagnetic Iron Oxides

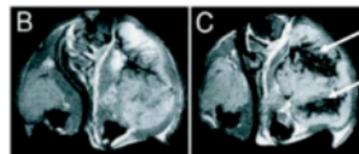
### Iron Oxide Nanoparticle Applications

**Blood Pool Agents:** Uptake of USPIOs (ultra small superparamagnetic iron oxides) by the liver and spleen is **quite low** and thus these nanoparticles remain in circulation for a very long time.

These characteristics have led to the use of USPIO as a blood pool agent.

**Cell Tracking:** Various immune cells as well as stem cells have been loaded with superparamagnetic contrast agents in order to track them in vivo.

Iron oxide loaded leukocytes and **T-cells** provide new avenues to target MR contrast agents to a variety of diseases including cancer, inflammation, and atherosclerosis.

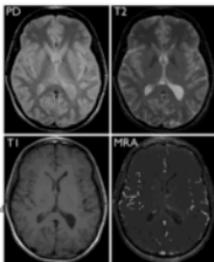
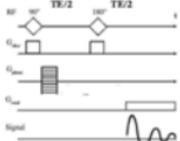


Antigen specific T-cells loaded with nanoparticles can be seen migrating to an antigen presenting tumor

T-cells are a subset of lymphocytes that play a large role in the immune response.

## T<sub>1</sub> and T<sub>2</sub> – weighted MRI

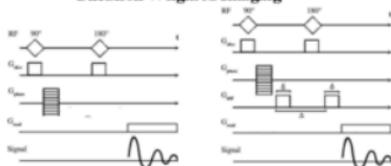
**Recall:** Simple T<sub>1</sub>, T<sub>2</sub> or PD contrast in MRI is generated by changing the TE and the TR.



<http://3d.med.utoronto.ca/med4100/Chw-Hom-MD-PAD-USP/>

Contrast	TR	TE	WM	GM	CNF
PD	long	short	dark*	intermed	intermed
T <sub>1</sub>	short	short	bright	intermed	dark
T <sub>2</sub>	med/long	long	dark	intermed	bright

## Diffusion Weighted Imaging



- Acquire multiple T<sub>2</sub>W images with increasing **diffusion gradients** during TE
- Images intensity is **attenuated** at higher gradient strengths and by faster diffusing water
- Calculate the **apparent diffusion coefficient** (ADC) by pixel-by-pixel image analysis:

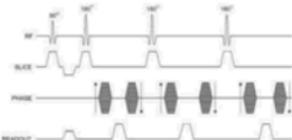
$$S_0 = S_0 \exp(-b \cdot \text{ADC}) \quad \text{ADC in m}^2/\text{s}^2$$

- where  $b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$ ,
- $S_0$  is the signal strength in a pulse sequence with a pair of balanced diffusion-sensitizing gradients of strength  $G$ , each of a duration  $\delta$  and with a delay  $\Delta$  between them.

Figure adapted from: Hagmann P et al. Radiographics 2005;25(2):229-233 © 2005 by Radiological Society of North America

## Fast Spin Echo

- Multispin echo technique – much more common than SE
- Number of variants: fast spin echo (FSE), turbo SE (TSE), rapid relaxation with relaxation enhancement (RARE).



- Ramp phase encode up and down on either side of data acquisition
- Collect FID after each 180° pulse at nTE.

Figure adapted from: [http://dx.doi.org/10.1007/978-1-4939-9888-8\\_1\\_10](http://dx.doi.org/10.1007/978-1-4939-9888-8_1_10)

## Diffusion-Weighted Imaging

One very important physical parameter that MRI can measure is the apparent **diffusion coefficient of water**.

The rate of water diffusion is often indicative of the health of tissues. For example, in conditions such as stroke, cells swell and cell membranes can rupture.

This means that water can diffuse much faster because there are fewer physical barriers.

The simplest pulse sequence used to measure diffusion is based on a spin-echo sequence, with symmetric “diffusion-encoding” gradients on each side of the 180° refocusing pulse.

The effect of the first diffusion gradient is to encode each proton with a certain phase in exactly the same mechanism as phase encoding.

If the **proton does not diffuse**, then the second diffusion-encoding gradient will impose equal and opposite phase on the proton so there is no net dephasing of the magnetization.

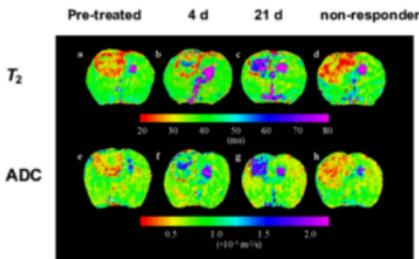
If the **proton, however, diffuses** to a different position in the time between the two encoding gradient pulses, then the proton magnetization is only partially rephased and there is a loss of signal.

The faster the proton diffuses the greater the loss of signal.



Diffusion-weighted image of a stroke

## Monitoring response to ganciclovir by changes in T<sub>2</sub> and ADC in BT4C rat brain tumors



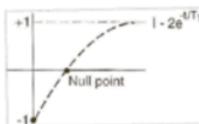
Papad, et al. Cancer Gene Therapy 5:101-109, 1998

## Basic Principles of MRI – Inversion Recovery

**Recall from Lecture 1:**

**Null Point** Following a 180° pulse, the point at which the signal crosses the zero line is called the null point.

At the null point the signal intensity is zero. The time is denoted T<sub>1</sub>(null). We can calculate the null point as follows:



$$\begin{aligned} \text{Signal Intensity} &= 0 = 1 - 2e^{-t/T_1} \\ \ln 1 &= \ln(2e^{-t/T_1}) \\ 0 &= \ln 2 + \ln(e^{-t/T_1}) \\ \ln 2 &= \frac{T_1(t)}{T_1} \end{aligned}$$

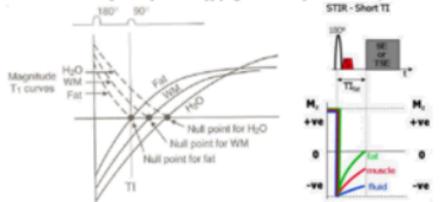
$$T_1(\text{null}) = 0.693T_1$$

The null point can be used to estimate the T<sub>1</sub> relaxation time!

## Basic Principles of MRI - Pulse Sequences

**Fat Suppression: STIR Imaging** STIR stands for short TI inversion recovery.

This inversion recovery technique entails applying the 90° RF pulse at the null point of fat.



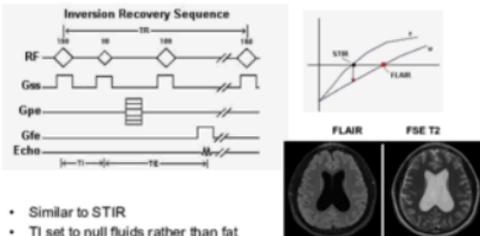
At the null point of fat, there will be no transverse magnetization from fat in the x-y plane (i.e. suppressed fat signal). However, water and other tissues will have their usual T<sub>1</sub> decay curve.

This technique is called STIR because fat has a very short T<sub>1</sub>, and a short TI must be chosen to null it.

Edwards et al. Journal of Cardiovascular Magnetic Resonance 2002, 4:88

## FLAIR - Fluid Attenuated Inversion Recovery

- FLAIR - Fast spin echo with TI set for fluid attenuation.



- Similar to STIR
- TI set to null fluids rather than fat
- In T2 weighted images, bright CSF becomes dark

http://www.scribbling.org/mri/pulseseqs.htm

## Diffusion tensor Imaging

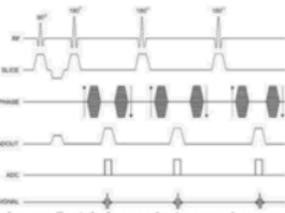
- Most commonly used for visualizing white matter in brain
- Based on the idea that water diffusion along the long axis of myelinated neuronal bundles should be much greater than diffusion in a perpendicular dimension



Fig. Brian Wandell, Stanford

## Diffusion tensor Imaging

- Use a diffusion-weighted fast spin echo pulse sequence
- Apply diffusion gradients in multiple directions (between 6 and 42).

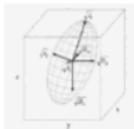


- Diffusion gradient during readout, ramp phase encode up and down on either side of data acquisition

Figure adapted from: [http://dtkb.berkeley.edu/mri/pulseseqs/fl\\_1.jpg](http://dtkb.berkeley.edu/mri/pulseseqs/fl_1.jpg)

## Diffusion tensor Imaging

- Use FSE to measure diffusion in multiple directions
- Construct diffusion tensor voxel by voxel
  - Diffusion tensor is approximately ellipsoid in shape
  - Represents mean distance that a water molecule will travel per unit time



DTI data are surfaces

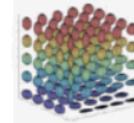


Fig. Brian Wandell, Stanford

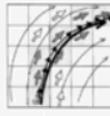
## Diffusion tensor tractography

- Fractional anisotropy
  - Normalized variance of the ellipsoid axis magnitudes

$$FA = \frac{\sqrt{3}}{2} \sqrt{\frac{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$



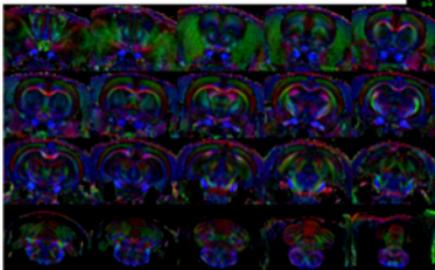
Modified algorithm



- FA = 0 for a sphere, 1 for a cylinder
- FA measures anisotropy, not direction!
- Use DT tractography to track fibers
- Numerous potential algorithms
  - Connect the voxels
  - FACT: Fiber assignment by continuous tracking
  - Path-Integral method (not shown)

Fig. Brian Wandell, Stanford

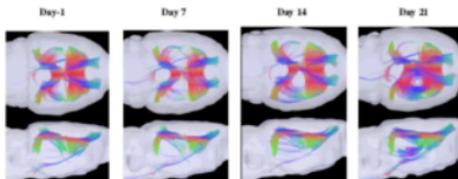
## FA Weighted Color Map



-shows voxel by voxel anisotropy in diffusion tensor

Kim et al., NMR in Biomedicine 2007

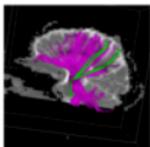
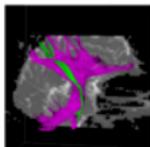
## Fiber tracts in a rat with 9L tumor



Kim et al., NMR in Biomedicine 2007

## Fiber-tracking in humans with amyotrophic lateral sclerosis (Lou Gehrig's disease)

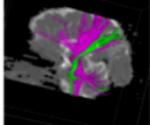
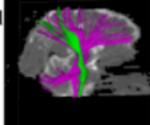
ALS



Muscle weakness and atrophy throughout the body due to the degeneration of the upper and lower motor neurons

■ Descending fibers  
■ CST cervical spinal Tract

Control

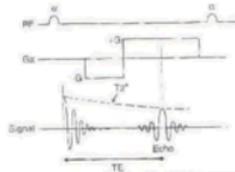


Reduced fiber tracts to motor cortex in ALS

Wang, et al., AJNR 2006;27:1234-8

## Gradient Echoes

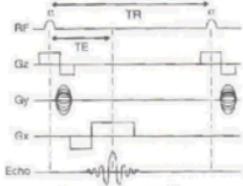
- Magnetization refocused by gradient – NOT by 180° pulse!



- Bilobed gradient dephases and rephases magnetization.
- Asymmetric, compensating
- Allows complete refocusing at TE
- No 180° pulse, so echo decay is  $T_2^*$ , not  $T_2$ .

## Gradient Echo Imaging

- Addition of Slice, Read and Phase encode gradients

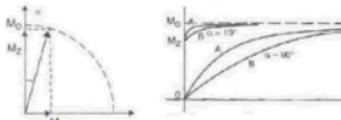


- Bilobed  $G_z$  gradient allows slice selection from the center of the pulse.
- Bilobed read gradient allows rephasing in the center of the echo.

FLASH (Fast low angle shot), SPGR (Spoiled Gradient Echo), and CE-FFE-T1 (Contrast Enhanced Fast Field Echo) or T1-FFE

## Advantage of Gradient Echo imaging

- Use a small flip angle to allow rapid imaging



- Small flip angle retains longitudinal magnetization
- Return to z axis is more rapid.
- Can use really short TR!!! (msec)
- But  $T_1$  weighting is reduced.