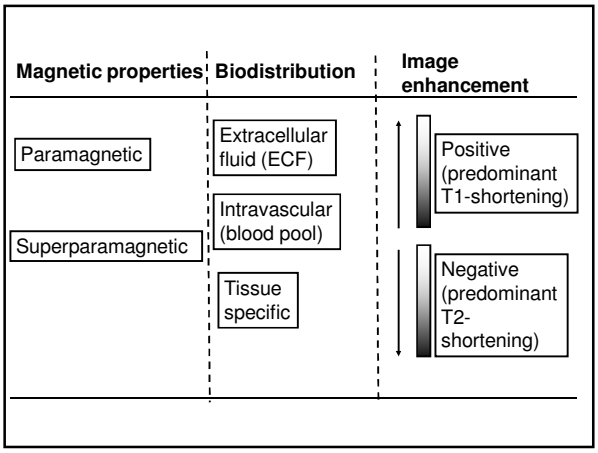
FYS-KJM 4740

MR-teori og medisinsk diagnostikk

Kap 11
MR kontrastmidler



MR Contrast Agents on the market or in clinical development*

Short Name	Generic Name	Trade Name	Enhancement Pattern (primary)
ECF agents:			
GdDTPA	gadopentetate dimeglumine	Magnevist	positive
GdDOTA	gadoterate meglumine	Dotarem	positive
GdDTPA-BMA	gadodiamide injection	Omniscan	positive
GdHP-DO3A	gadoterol injection	ProHance	positive
GdDTPA-BMEA	gadoversetamide	Optimark	positive
GdDO3A-butriol	gadobutrol	Gadovist	positive
GdBOPTA/Dimeg	gadobenate dimeglumine	MutliHance	positive
Organ specific agents:			
MnDPDP	mangafodipir trisodium	Teslascan	positive
GdEOB-DTPA	gadoxetic acid	Eovist	positive
GdBOPTA/Dimeg	gadobenate dimeglumine	MultiHance	positive
AMI-25	ferumoxides (SPIO)	Endorem/Feridex	negative
SHU 555A*	ferrixan (SPIO)	Resovist	negative
AMI-227#	Ferumoxtran	Sinerem/Combidex	negative
SHU 555 C*#	Ferucarotran		Positive/negative
Blood pool agents:			
MS-325		Angiomark	positive
gadomer-17		-----	positive
P792		-----	positive

* adapted from Rinck et al. 'Magnetic Resonance in Medicine' (2001) # = also blood pool agents

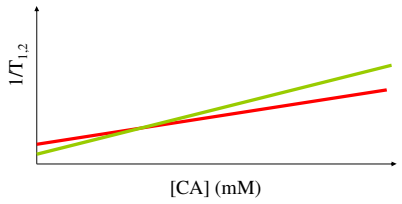
MR Contrast Agents (MRCA)

- A contrast agent is nothing more than a catalyst that decreases the T_1 and/or T_2 of the tissue protons
- T_1 and T_2 relaxation are NOT independent processes
- T_1 cannot be reduced without reducing T_2
- T_2 can be reduced without reducing T_1

Background & Theory

Contrast Agent Relaxivity *in vitro*

MRCA effectiveness (ability to alter $1/T_1$ and $1/T_2$) *in vitro* - in a homogeneous medium - is a linear function of [CA]:



Commonly use 'relaxation rate' ($1/T_{1,2}$) due to linear relationship with [CA]

Background & Theory

Contrast Agent Relaxivity *in vitro*

In vitro MRCA *relaxivity,* r_1 and r_2:

$$\frac{1}{T_{1,2}} = r_{1,2} \cdot [CA] + \left(\frac{1}{T_{1,2}}\right)_{pre}$$

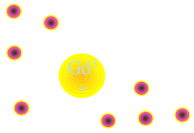
- $r_1 = T_1$ relaxivity; $r_2 = T_2$ relaxivity
- $r_{1,2}$ is due to dipolar (short range) interactions
- $r_{1,2}$ must be specified at a given temp, field stregth and medium

Contrast agents - basic principles

Two types of magnetic effects are used clinically to induce T_2- and T_1-shortening:

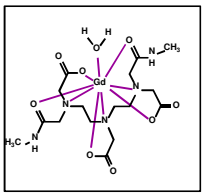
- Paramagnetism
- Superparamagnetism

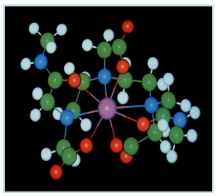
Paramagnetic ions



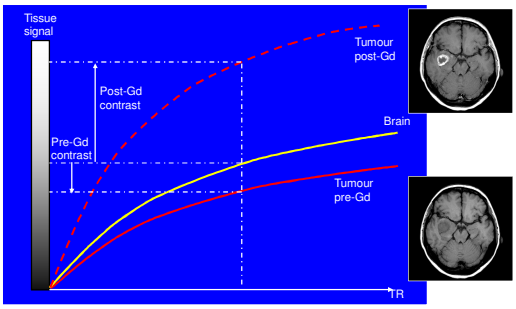
- Metal ions with unpaired electrons:
  - →gadolinium (Gd^{3+})
  - →iron (Fe^{2+} /Fe^{3+})
  - →manganese (Mn^{2+})
- Magnetic moment of unpaired electrons is >> magnetic moment of protons
- Dipolar magnetic interaction between electrons and water protons

Metal chelate – use of biocompatible ligand





Paramagnetic chelates enhance contrast in T1-w images



Paramagnetic ions

Typical in vitro relaxivity of small MW gadolinium chelates :

$r_1 \cong 4\ mM^{-1}s^{-1}$
$r_2 \cong 4.5\ mM^{-1}s^{-1}$

- Relaxivity is limited by rapid tumbling rate of the Gd-chelate
- T_1 relaxivity can be increased by selective binding to macromolecules (proteins) or by combinding multiple Gd-ions in a rigid structure (polymers)
- Will also modify biodistribution from extracellular to intravascular.

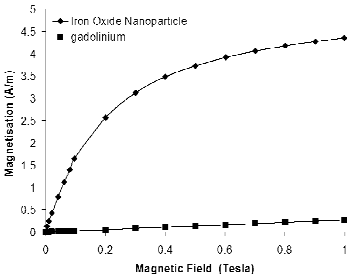
Superparamagnetic Iron Oxide Particles;

- Iron oxide particles (nanoparticles) made up of several thousand magnetic ions in the form of magnetite or maghemite crystals
- Much larger magnetic moment than paramagnetic agents
- Developed as liver/spleen/lymph node specific (T_2) or blood pool (T_1,T_2) agents
- Imaging effect and biodistribution is size dependent

Typical in vitro relaxivity of iron oxide nanoparticles :
$r_1 \cong 20\ mM^{-1}s^{-1}$
$r_2 \cong 40\ mM^{-1}s^{-1}$

Background & Theory

Iron oxides have much larger magnetic moment than gadolinium and are therefore much more potent relaxation enhancers



Dipolar relaxivity is a complex function of CA properties

$$r_1 = A\frac{q}{T_{1m} + \tau_m} \qquad r_2 = \frac{q}{\tau_m}\left[\frac{T_{2m}^{-2} + \tau_m^{-1}T_{2m}^{-1} + \Delta\omega_m^2}{(\tau_m^{-1} + T_{2m}^{-1})^2 + \Delta\omega_m^2}\right]$$

Important dependence of 'effective' correlation rate of molecule:

$$1/\tau_c = 1/\tau_r + 1/\tau_s + 1/\tau_m$$

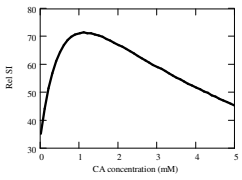
$1/T_{1m}$ and $1/T_{2m}$ dependent on spectral density functions of the form:

$$\frac{\tau_c}{1 + \omega_I^2\tau_c^2} \qquad \frac{\tau_e}{1 + \omega_S^2\tau_s^2}$$

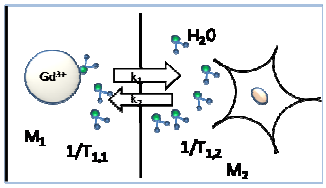
In vivo CA effects

e.g. spin echo sequence:

$$SI(C) = \rho\left(1 - \exp\left(-(R^\circ_1 + r_1 C)TR\right)\right)\exp\left(-(R^\circ_2 + r_2 C)TE\right)$$



Water exchange effects



$1/\tau = k_1 + k_2$

$$k_2 = k_1\frac{\xi_1}{\lambda - \xi_1}$$

Fast exchange: $\frac{1}{\tau} \gg 1/T_{1,1} - 1/T_{1,2}$

Slow exchange: $\frac{1}{\tau} \ll 1/T_{1,1} - 1/T_{1,2}$

Water exchange influence T1-relaxation:
Bloch equations including water exchange terms:

$$\frac{dM_1}{dt} = \frac{M_0 - M_1}{T_{1,1}} - k_1M_1 + k_2M_2$$

$$\frac{dM_2}{dt} = \frac{M_0 - M_2}{T_{1,2}} - k_1M_1 - k_2M_2$$

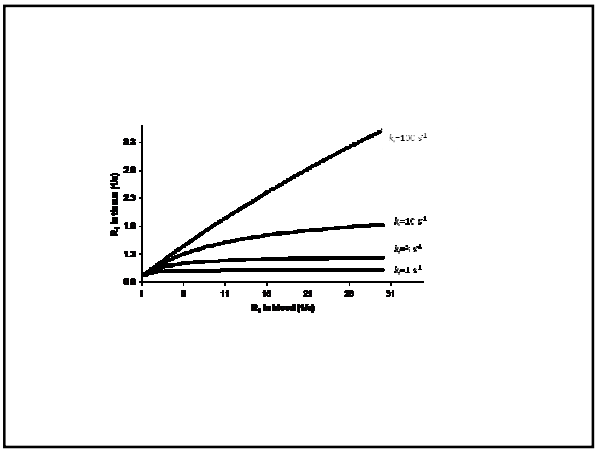
$$M(t) = M_0 + c_1\exp(-u_1t) + c_2\exp(-u_2t)$$

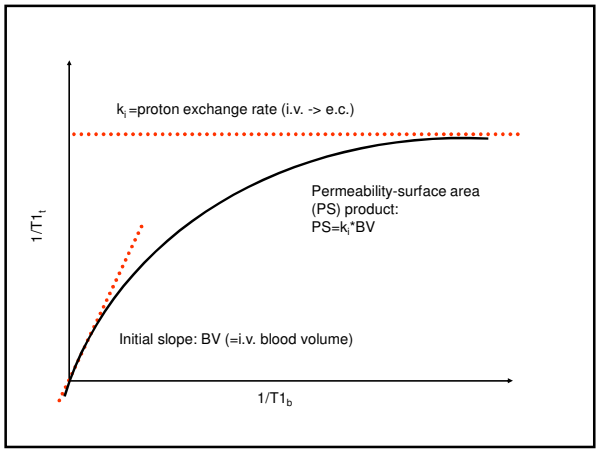
$$M(t) = M_0 + c_1\exp(-u_1t) + c_2\exp(-u_2t)$$

Mono-exp approximation:

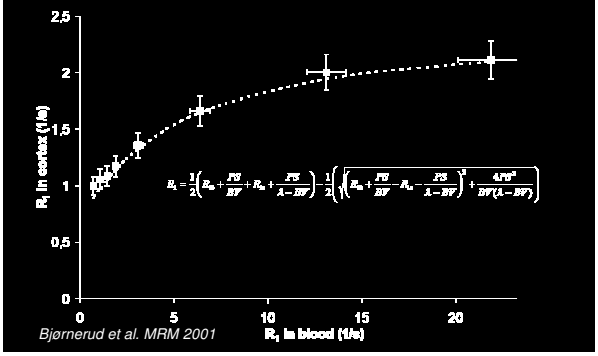
$$M(t) = M_0(1 - 2\exp(-R_1t))$$

$$R_1 \approx u_2 = \frac{1}{2}\left(R_{1,1} + k_1 + R_{1,2} + k_2\right) - \frac{1}{2}\sqrt{\left(R_{1,1} + k_1 - R_{1,2} - k_2\right)^2 + 4k_1k_2}$$



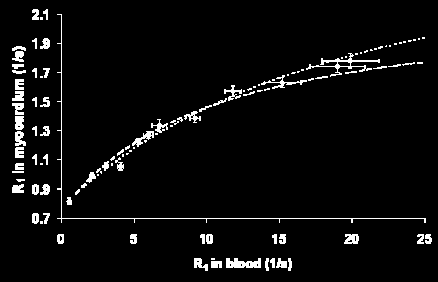


Results: renal cortex



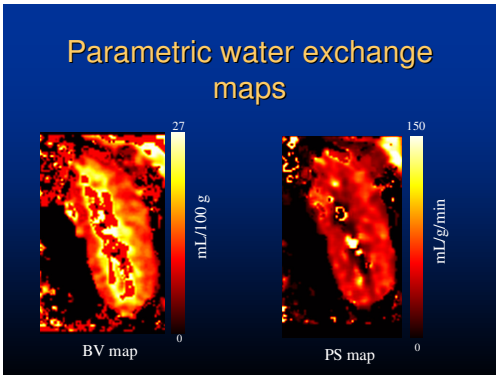
Bjørnerud et al. MRM 2001

Results: myocardium

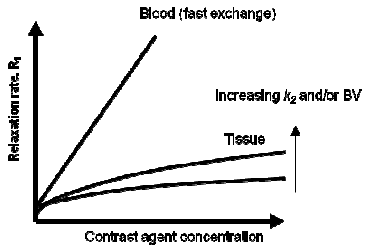


Bjørnerud et al. MRM 2002

Parametric water exchange maps



Summary – in vivo T1-effects of CA



Susceptibility induced relaxation:

$M_z=\chi H_0$ ($H=B_o/\mu_0$).

Langevin equation:

$$M = Nm\left[coth\left(\frac{\mu_0 m H_0}{k_B T}\right) - \left(\frac{k_B T}{\mu_0 m H_0}\right)\right]$$

For paramagnetic agents, Curie law approximation valid < 50 T …

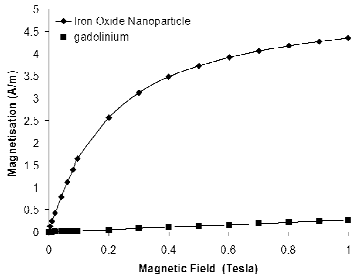
$$M = \frac{Nm^2\mu_0 H_0}{3k_B T} = \chi H_0$$

$$\Rightarrow \quad \chi = \frac{Nm^2\mu_0}{3k_B T}$$

Susceptibility constant

Background & Theory

Iron oxides have much larger magnetic moment than gadolinium and are therefore much more potent relaxation enhancers

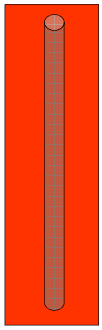


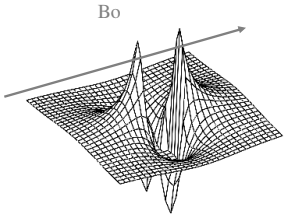
Background & Theory

Microscopic field inhomogeneities due to intravascular CA

Diamagnetic blood + CA

$M_i >> M_e$

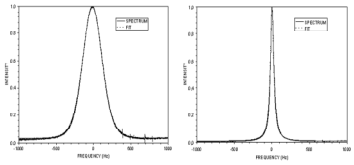




Susceptibility induced relaxation

$$S(TE,\omega) = S_0 \int_{-\infty}^{\infty} P(\omega)\exp(-j\omega TE)d\omega$$

P(ω) Gaussian or Lorentzian



Lorentzian lineshape

$$P(\omega) \propto \left[\frac{\sigma}{\sigma^2+\omega^2}\right]$$

$$S(TE,\omega) = S_0 \int_{-\infty}^{\infty}\left[\frac{\sigma}{\sigma^2+\omega^2}\right]\exp(-j\omega TE)d\omega$$
$$= S_0 \exp(-\sigma TE)$$

'Effective 1/T2* is proportional to linewidth of spectrum => monoexponential signal decay

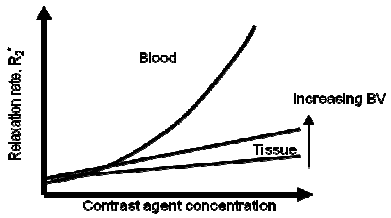
Gaussian lineshape

$$P(\omega) \propto exp\left(\frac{-\omega^2}{2\sigma^2}\right)$$

$$S(TE,\omega) = S_0 \int_{-\infty}^{\infty} exp\left(\frac{-\omega^2}{2\sigma^2}\right)\exp(-j\omega TE)d\omega$$
$$= S_0 \exp[-(\sigma TE)^2]$$

'Effective 1/T2* is proportional to σ^2TE : i.e. measured T2* is function of TE.

Summary – susceptibility induced relaxation



Advanced Applications of MR Contrast Agents

General requirement: estimate contrast agent concentration in vivo (at least to within a scaling constant)

T_1-based dynamic imaging

Most accurate approach: quantification of $1/T_1$

$$\Delta R_1(t) = R_1(t) - R_1{}^0 = C_i(t) r_1$$

Then, assuming fast water exchange: $C(t)=k\Delta R_1(t)$

Estimation of C(t) from T1-GRE sequence:

Requirement: TR<<T1 and TE<<T2* then:

$$SI \propto \frac{M_0 TR}{T_1}$$

T2/T2* based dynamic imaging

Assumption: monoexponential T2/T2* signal decay (Lorentzian lineshape)

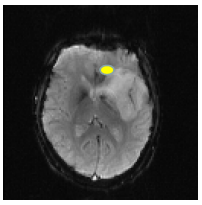
Then:

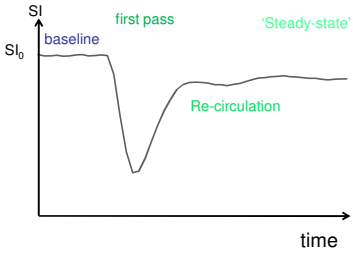
$$SI(t) = SI(0) f(M_0, T_1) \exp\left(-TE \cdot \Delta R_2(t)\right)$$

If T1-effects are negligible then:

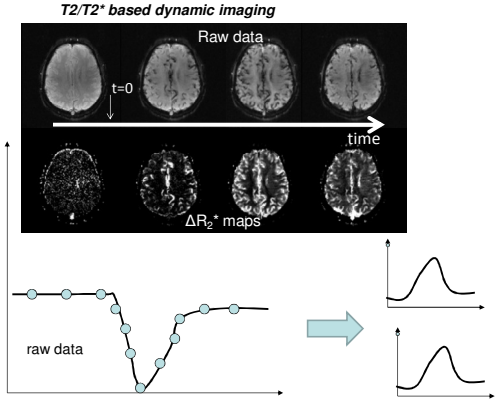
$$\Delta R_2(t) = k \ln\left(\frac{SI(t)}{SI(0)}\right) / TE \propto C(t)$$

DSC – dynamic signal change





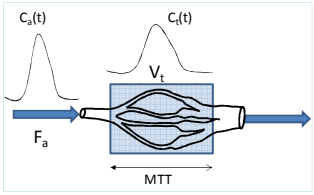
T2/T2* based dynamic imaging



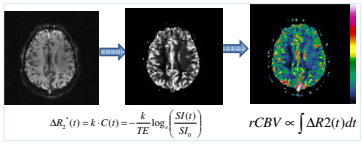
Perfusion imaging

Central volume principle:

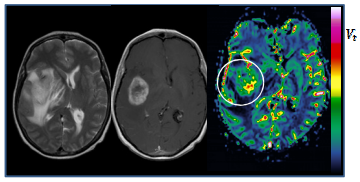
$$V_t = F_a \cdot MTT = \frac{F_a}{q_0}\int_0^\infty C_t(t)dt$$



Blood volume maps in tumor imaging:



$$\Delta R_2^*(t) = k \cdot C(t) = -\frac{k}{TE}\log_e\left(\frac{SI(t)}{SI_0}\right) \qquad rCBV \propto \int \Delta R2(t)dt$$



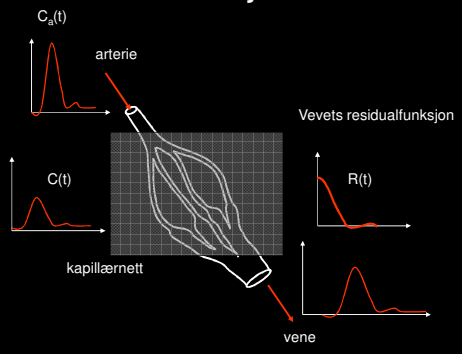
$$V_t = k\frac{\int_0^\infty C_t(t)dt}{\int_0^\infty C_a(t)dt} \propto \frac{\int \Delta R_{2t}(t)dt}{\int \Delta R_{2a}(t)dt}$$

Measurement of flow (perfusion) and MTT:

Introducing the *tissue residue function* R(t)

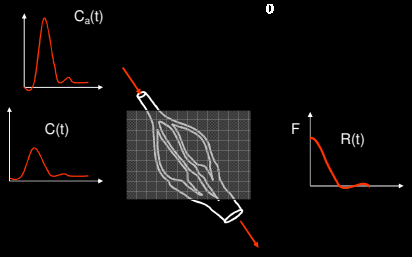
$$C_t(t) = F_t\int_0^t R(t-\tau)C_a(t)d\tau = F_t R(t) \otimes C_a(t)$$

Perfusjons-MR



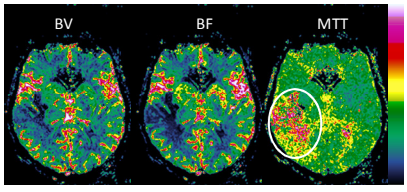
Standard dekonvolusjons-problem

$$\kappa C(t) = F\int_0^t C_a(\tau)R(t-\tau)d\tau$$

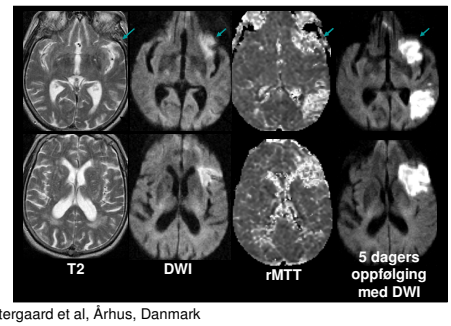


MR perfusjonsavbilding

MTT = V/F



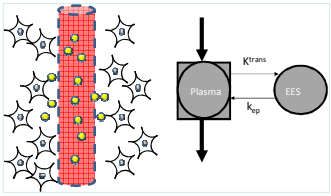
Slag: Forlenget MTT = area at risk



Østergaard et al, Århus, Danmark

Dynamic contrast enhanced imaging

Two-compartment model:



K^{trans} and K^{ep} related to 'leakiness of capillary wall

Dynamic contrast enhanced imaging

Two-compartment model:

$$\frac{dC_t}{dt} = K^{trans} C_p(t) - k^{ep} C_t(t)$$

$$C_t(t) = K^{trans} \int_0^t C_p(\tau) \exp[-k^{ep}(t-\tau)]\, d\tau$$

Transfer constants can be determined if C(t) can be measured in tissue and artery (AIF)

Dynamic contrast enhanced imaging

If not, need to assume $C_p(t)$ to be monoexponential

$$\frac{dC_t}{dt} = K^{trans} C_{p,0} \exp\left(-\frac{t}{T_{\frac{1}{2}}}\right) - k^{ep} C_t(t)$$

$$C_t(t) = \frac{K^{trans} C_{p,0}}{T_{1/2} - k^{ep}} \left[exp(-k^{ep} t) - exp\left(\frac{-t}{T_{1/2}}\right) \right]$$

Dynamic contrast enhanced imaging