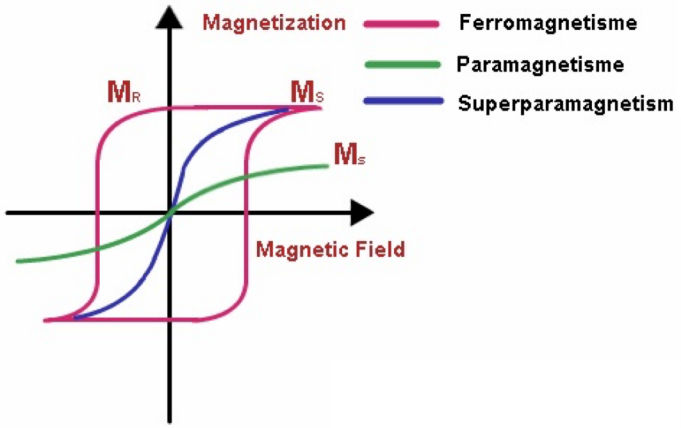
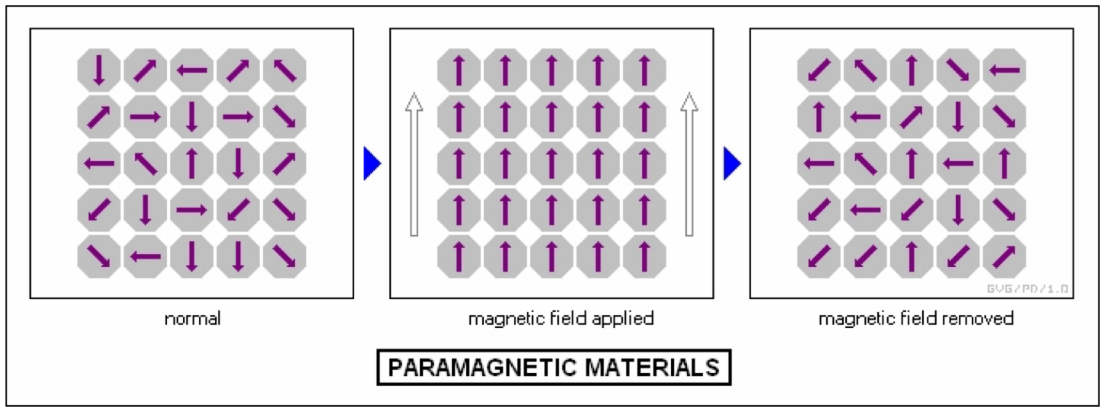
Lecture #12
Paramagnetic Relaxation Enhancement

- Topics
  - Paramagnetic contributions to relaxation
  - Paramagnetic metal ions
  - Gd^{3+}-based T_1 contrast agents
  - Research topic examples
- References
  - Kowalewski, Ch 15, pp 359-380.
  - Caravan, et al., "Gadolinium(III) Chelates as MRI Contrast Agents: Structure, Dynamics, and Applications", Chem. Rev. 1999, 99, 2293–2352.

Magnetism





Magnetic Property	Direction of Polarization (I) Relative to External Field	Relative Magnetic Susceptibility (χ) in ppm	Typical Materials
Diamagnetism	Opposite	−10	Water, fat, calcium, most biologic tissues
Paramagnetism	Same	+1	Molecular O_2, simple salts and chelates of metals (Gd, Fe, Mn, Cu), organic free radicals
Superparamagnetism	Same	+5000	Ferritin, hemosiderin, SPIO contrast agents
Ferromagnetism	Same	> 10,000	Iron, steel

Remember, for unpaired electrons: $\gamma_e = -658\gamma_H$

Paramagnetic materials effect both T_1 and T_2

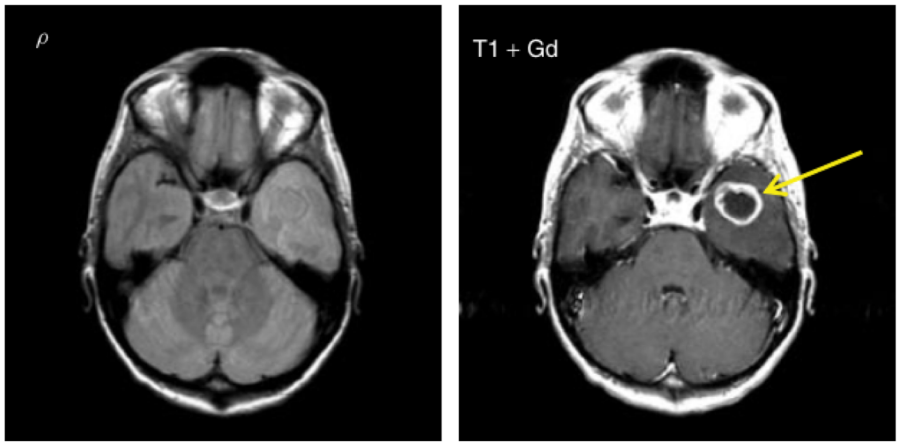


Figure 1.19 *Images of a human brain with tumor without and with the Gd^{3+} chelate displaying the tumor with CA uptake in hypersignal.*

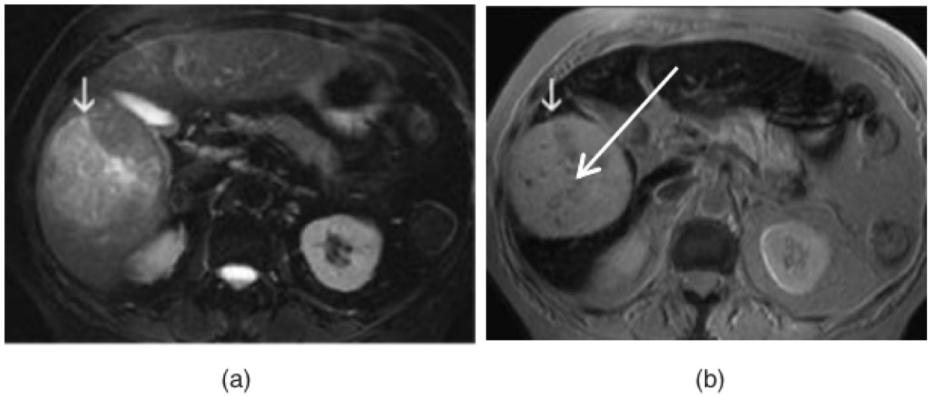


Figure 1.20 *Images of a human liver without (a) and with (b) IO particles, displaying normal liver tissue with dark spots. Liver malign tumors don't uptake IO. Namkung* et al. Journal of Magnetic Resonance Imaging, *25: 755–765 (2007).*

Paramagnetic contributions to relaxivity

- The addition of a paramagnetic solute increases both $1/T_1$ and $1/T_2$ relaxation rates.
- Diamagnetic and paramagnetic contributions are additive.

$$\frac{1}{T_i} = \frac{1}{T_{i,d}} + \frac{1}{T_{i,p}} \text{ for } i = 1, 2$$

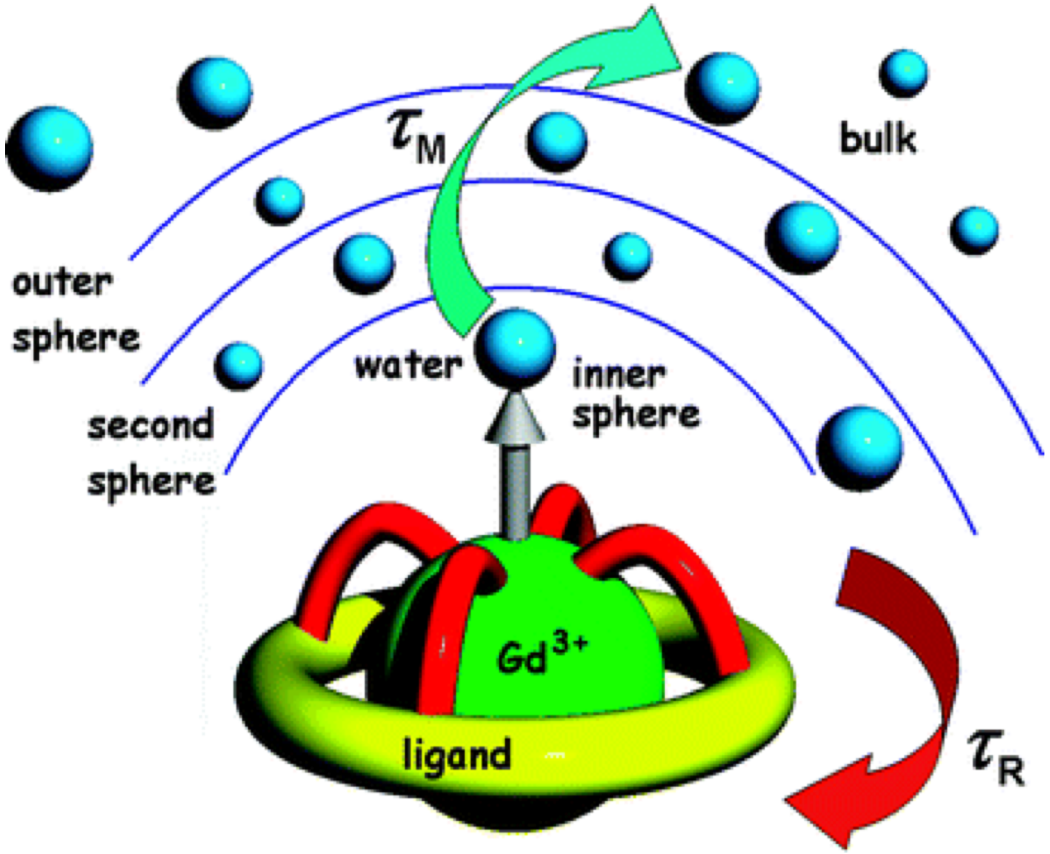
- Solvent relaxation rates are generally linearly proportional to the concentration of the paramagnetic species, [M].

$$\frac{1}{T_i} = \frac{1}{T_{i,d}} + [M]R_i \text{ for } i = 1, 2$$

"Relaxivity"

Water Interactions

- Nuclear spins see the lattice as the combined electron spin system and other molecular degrees of freedom.



$$\frac{1}{T_{i,p}} = \left(\frac{1}{T_i}\right)_{\text{inner}} + \left(\frac{1}{T_i}\right)_{\text{2nd}} + \left(\frac{1}{T_i}\right)_{\text{outer}} \quad \text{for } i = 1, 2$$

Review: Chemical exchange and τ_c

- Chemical exchange → stochastic modulations → relaxation
- Exchange rates (μs to ms time scales) << molecular tumbling
  - Too slow to effect anisotropic interactions such as CSA or dipole coupling
  - Can effect isotropic interactions such as chemical shift or J coupling
- Typically, chemical exchange induces a relaxation term of the form:

$$\frac{1}{T_{1,ex}} \propto A^2 \frac{\tau_{ex}}{1+(\Delta\omega)^2 \tau_{ex}^2}$$

1/exchange rate

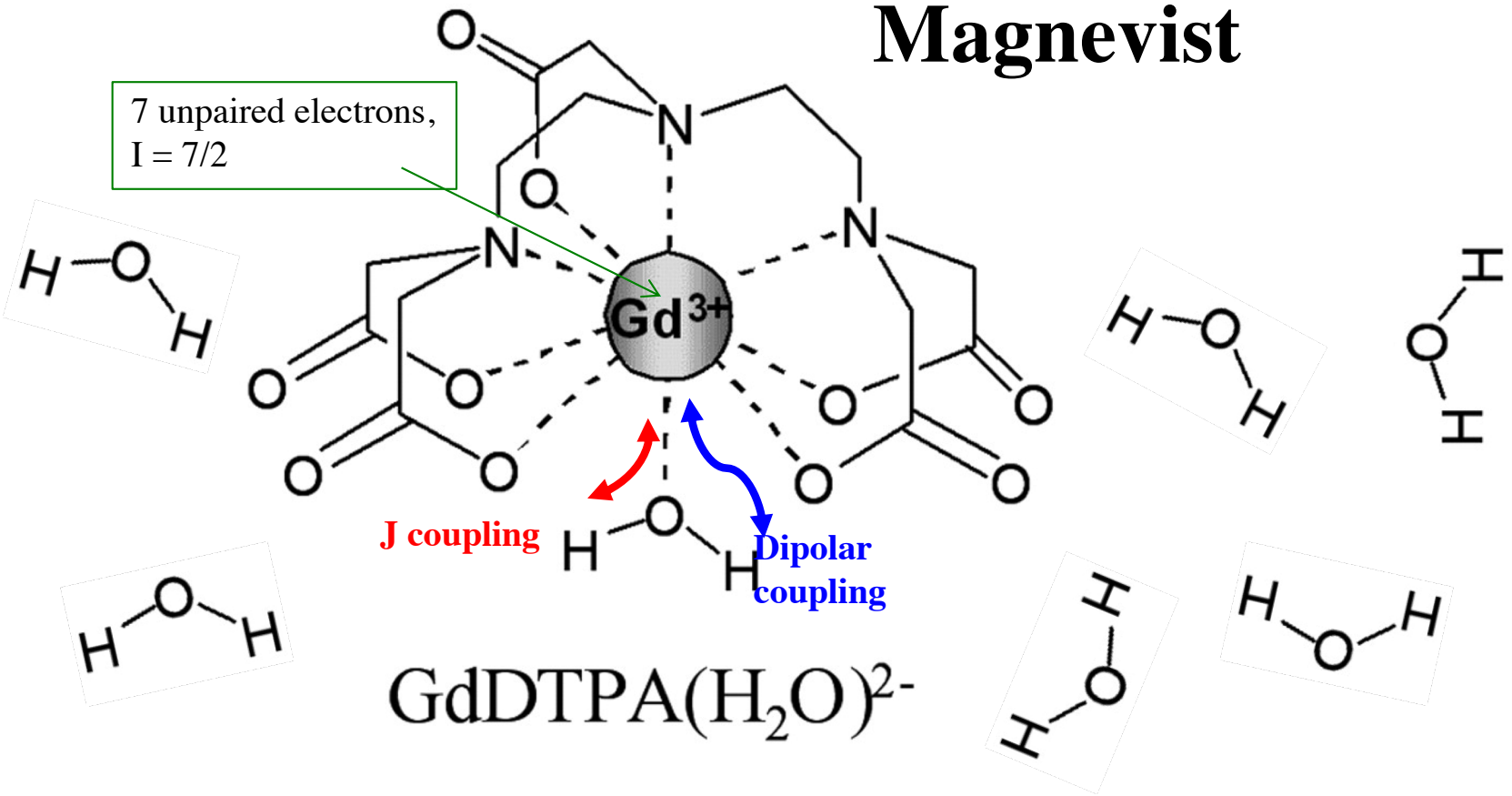
Strength of the interaction

Difference frequency between exchange sites

Hence, the exchange time can look just like a rotational correlation time!

Review: Nuclear-electron couplings

- In addition to chemical exchange, both J and dipolar coupling occur.



Review: Quadrupolar Coupling

- A spin S > ½ have a electrical quadrupolar moment due to their non-uniform charge distribution.

- This electrical quadrupole moment interacts with local electric field gradients
  - Static E-field gradients results in shifts of the resonance frequencies of the observed peaks.
  - Dynamic (time-varying) E-field gradients become a very effective relaxation mechanism.

- Quadrupolar coupling contribution to spin-lattice relaxation is…

$$\frac{1}{T_{1,Q}} \approx \frac{3\pi}{100}\frac{2S+3}{S^2(2S-1)}\left(\frac{e^2qQ}{\hbar}\right)^2\left(J(\omega_S)+4J(2\omega_S)\right)$$

Quadrupolar coupling constant

Electric field gradient term

Review: Scalar relaxation of the 1st kind

- Consider a J-coupled spin pair for which the S spin undergoes chemical exchange with an exchange time of τ_{ex}.
- The coupling constant between the *I* spin and a spin S_i becomes a stochastic function of time.
- As we have shown, this leads to a relaxation mechanism, known as scalar relaxation of the 1st kind given by:

$$\frac{1}{T_{1,I}} = \frac{8\pi^2 J^2 S(S+1)}{3} \frac{\tau_{ex}}{1+(\omega_I - \omega_S)^2 \tau_{ex}^2}$$

$$\frac{1}{T_{2,I}} = \frac{4\pi^2 J^2 S(S+1)}{3} \left(\tau_{ex} + \frac{\tau_{ex}}{1+(\omega_I - \omega_S)^2 \tau_{ex}^2} \right)$$

Review: Scalar relaxation of the 2nd kind

- For a system of J-coupled spins, where one of the spins, S, has a very short T_1= (e.g. spin S is quadrupolar coupled).
- We can analyze this system by assume the S spin is in continuous equilibrium with the lattice, in which case S magnetization becomes a perturbation in the Hamiltonian with correlation functions…

$$\left\langle S_z(t)S_z(t+\tau)\right\rangle = \frac{(2\pi J)^2 S(S+1))}{3} e^{-\tau/T_{1,S}} \quad \text{and} \quad \left\langle S_+(t)S_-(t)\right\rangle = \frac{(2\pi J)^2 S(S+1))}{6} e^{i\omega_s\tau} e^{-\tau/T_{2,S}}$$

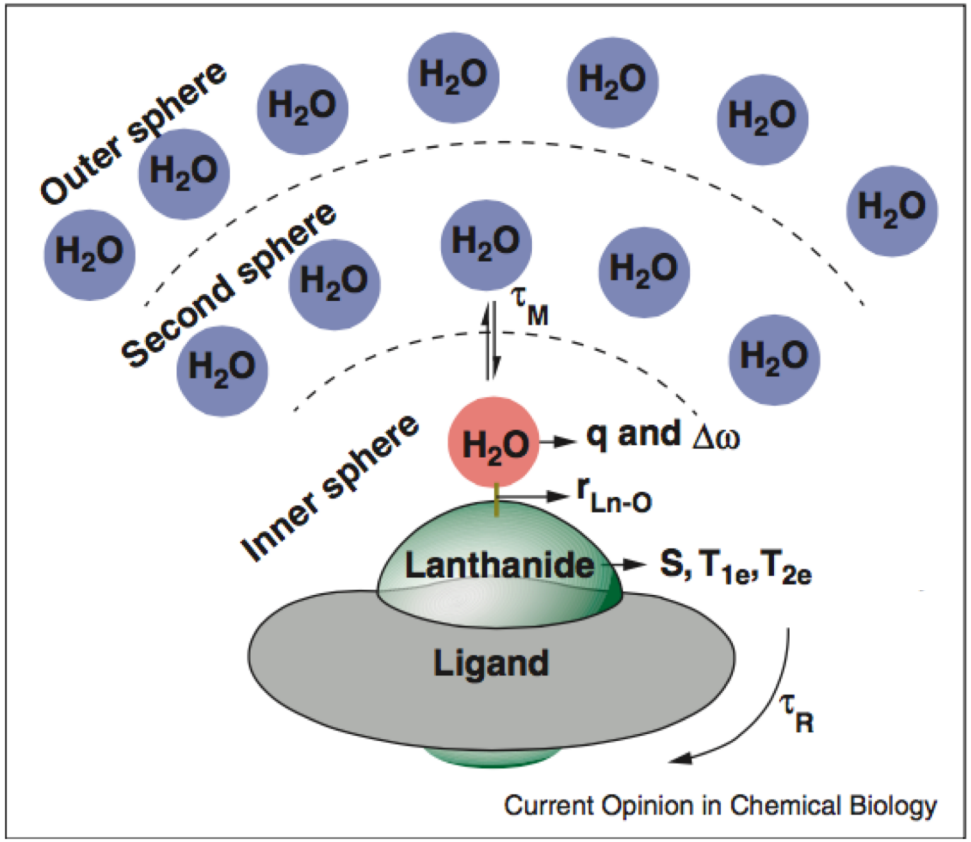
- The contribution to T_1 and T_2 relaxation (known as scalar relaxation of the 2nd kind) are:

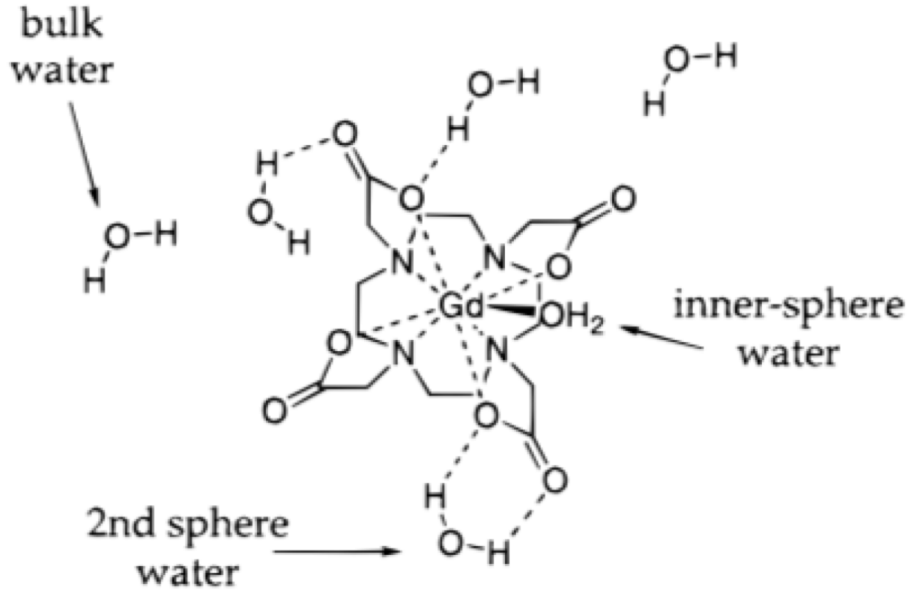
$$\frac{1}{T_1} = \frac{2(2\pi J)^2 S(S+1))}{3} \frac{T_{2,S}}{1+(\omega_I-\omega_s)^2 T_{2,S}^2}$$

$$\frac{1}{T_2} = \frac{(2\pi J)^2 S(S+1))}{3}\left(T_{1,S} + \frac{T_{2,S}}{1+(\omega_I-\omega_s)^2 T_{2,S}^2}\right)$$

Water Interactions

- Nuclear spins see the lattice as the combined electron spin system and other molecular degrees of freedom.





$$\frac{1}{T_{i,p}} = \left(\frac{1}{T_i}\right)_{\text{inner}} + \left(\frac{1}{T_i}\right)_{\text{2nd}} + \left(\frac{1}{T_i}\right)_{\text{outer}} \quad \text{for } i = 1, 2$$

Inner-Sphere Relaxation

- Chemical exchange contributes to inner-sphere relaxation.
- Excess spin-lattice relaxation rate, spin-spin relaxation rate, and measured chemical shift for the ligand due to the paramagnetic material are given by…

$$\left(\frac{1}{T_1}\right)_{\text{inner}} = \frac{P_M}{\tau_M + T_{1,M}}$$

$$\left(\frac{1}{T_2}\right)_{\text{inner}} = \frac{P_M}{\tau_M}\left(\frac{T_{2,M}^{-2} + \left(T_{2,M}\tau_M\right)^{-1} + \Delta\omega_M^2}{\left(T_{2,M}^{-1} + \tau_M^{-1}\right)^2 + \Delta\omega_M^2}\right)$$

$$\Delta\omega_P = \frac{P_M \Delta\omega_M}{\left(\tau_M / T_{2,M} + 1\right)^2 + \tau_M^2 \Delta\omega_M^2}$$

- inner-sphere *paramagnetic relaxation enhancement* (PRE)
- PRE normalized to 1 mM is called *relaxivity*.

where M = ligand in paramagentic complex

P_M = molar fraction of bound ligand nuclei

τ_M = lifetime of ligand in complex

Solomon-Bloembergen Theory

- Spin-lattice relaxation rate for the bound nuclei is a combination of…
  - Scalar coupling between nuclear and electron spins
  - Dipolar coupling between nuclear and electron spins

$$\Rightarrow \quad \frac{1}{T_{1,M}} = \left(\frac{1}{T_{1,M}}\right)_{SC} + \left(\frac{1}{T_{1,M}}\right)_{DD}$$

- Hence:

Scalar coupling / Dipolar coupling

$$\frac{1}{T_{1,M}} = \frac{2}{3}A_{SC}^2 S(S+1)\frac{\tau_{e2}}{1+(\omega_S-\omega_I)^2\tau_{e2}^2} + \frac{2}{15}\left(\frac{\mu_0}{4\pi}\right)^2\frac{\gamma_I^2\gamma_S^2\hbar^2}{r_{IS}^6}S(S+1)\left[\frac{\tau_{c2}}{1+(\omega_S-\omega_I)^2\tau_{c2}^2} + \frac{3\tau_{c1}}{1+\omega_I^2\tau_{c1}^2} + \frac{\tau_{c2}}{1+(\omega_S+\omega_I)^2\tau_{c2}^2}\right]$$

($\omega_S+\omega_I$: $\gamma_e B_0$, ω_I: $\gamma_H B_0$)

$$\frac{1}{T_{1,M}} \approx \frac{2}{3}A_{SC}^2 S(S+1)\frac{\tau_{e2}}{1+\omega_S^2\tau_{e2}^2} + \frac{2}{15}b_{IS}^2 S(S+1)\left[\underbrace{\frac{7\tau_{c2}}{1+\omega_S^2\tau_{c2}^2}}_{\text{“7-term”}} + \underbrace{\frac{3\tau_{c1}}{1+\omega_I^2\tau_{c1}^2}}_{\text{“3-term”}}\right]$$

- The correlation times are quite interesting…

$$\tau_{e2}^{-1} = \tau_M^{-1} + T_{2e}^{-1}$$

water exchange time / electron T_2

$$\tau_{e1}^{-1} = \tau_M^{-1} + T_{1e}^{-1}$$

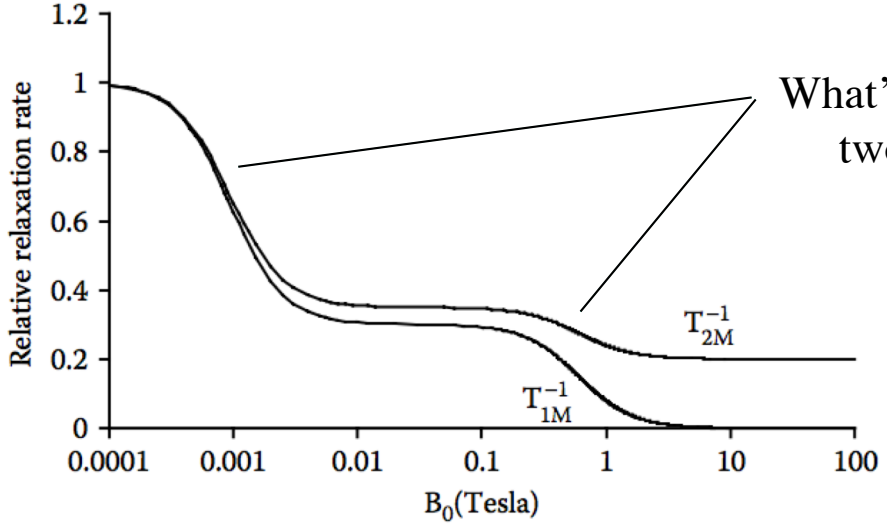
electron T_1

$$\tau_{ci}^{-1} = \tau_R^{-1} + \tau_M^{-1} + T_{je}^{-1};\ j = 1,2$$

rotational correlation time

NMRD Curves

- Typically, the scalar term is small compared to the dipolar coupling term (valid for Gd^{3+} but not necessarily Mn^{2+})
- If rotational correlation time dominates the dipolar coupling term, then the field dependence of the PRE is…



- The above plot is the behavior typically observed when constructing MRI phantom using e.g. $MnCl_2$ or $CuSO_4$.
- But what about T_{1e} and T_{2e}? Aren't these relaxation times themselves field dependent?

Solomon-Bloembergen-Morgan (SBM) Theory

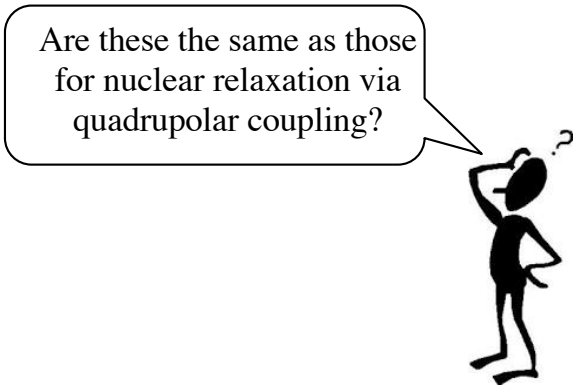
- SBM theory includes the field-dependence of the electron T_1 and T_2 relaxation times.
- Calculations of ESR relaxation rates are typically quite complicated.
- For the paramagnetic complexes using for MR contrast agents, electron relaxation rates are dominated by zero-field splitting (ZFS), the electron spin equivalent of nuclear quadrupolar coupling.

Trace of transient ZFS tensor

Correlation time for ZFS modulations, typically ~10^{-9} s

$$\frac{1}{T_{1,e}} = \frac{\Delta_t^2}{5}\left(\frac{\tau_v}{1+\omega_S^2\tau_v^2} + \frac{4\tau_v}{1+4\omega_S^2\tau_v^2}\right)$$

$$\frac{1}{T_{2,e}} = \frac{\Delta_t^2}{10}\left(3\tau_v + \frac{5\tau_v}{1+\omega_S^2\tau_v^2} + \frac{2\tau_v}{1+4\omega_S^2\tau_v^2}\right)$$



SBM Theory: T_1

- The complete equations for the T_1 relaxation rate are…

$$\frac{1}{T_{1,M}} \approx \frac{2}{3} A_{SC}^2 S(S+1) \frac{\tau_{e2}}{1+\omega_S^2 \tau_{e2}^2} + \frac{2}{15} b_{IS}^2 S(S+1) \left[\frac{7\tau_{c2}}{1+\omega_S^2 \tau_{c2}^2} + \frac{3\tau_{c1}}{1+\omega_I^2 \tau_{c1}^2} \right]$$

$$\tau_{e2}^{-1} = \tau_M^{-1} + T_{2e}^{-1} \qquad \frac{1}{T_{1,e}} = \frac{\Delta_t^2}{5} \left(\frac{\tau_v}{1+\omega_S^2 \tau_v^2} + \frac{4\tau_v}{1+4\omega_S^2 \tau_v^2} \right)$$

$$\tau_{e1}^{-1} = \tau_M^{-1} + T_{1e}^{-1}$$

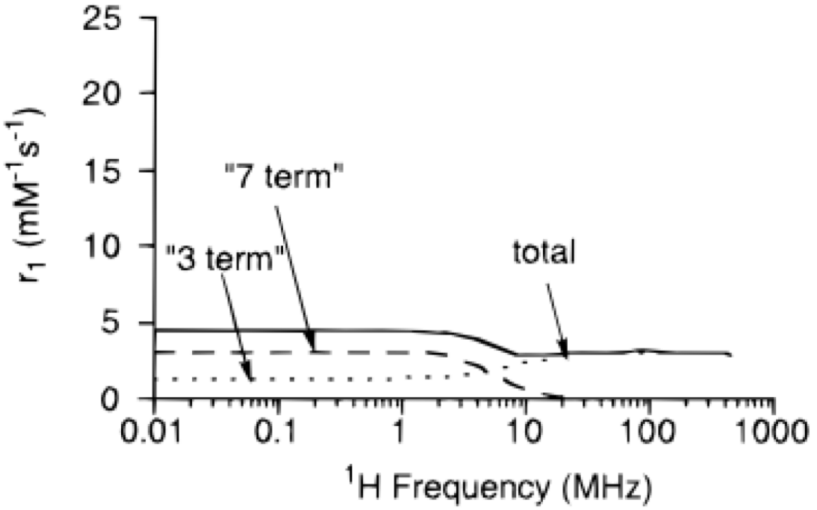
$$\tau_{ci}^{-1} = \tau_R^{-1} + \tau_M^{-1} + T_{je}^{-1};\ j = 1,2 \qquad \frac{1}{T_{2,e}} = \frac{\Delta_t^2}{10} \left(3\tau_v + \frac{5\tau_v}{1+\omega_S^2 \tau_v^2} + \frac{2\tau_v}{1+4\omega_S^2 \tau_v^2} \right)$$

- The SBM theory works reasonably well, but there are multiple extensions and modifications such as…
  - The Lipari-Szabo correction
  - The modified Florence approach
  - Swedish slow-motion theory

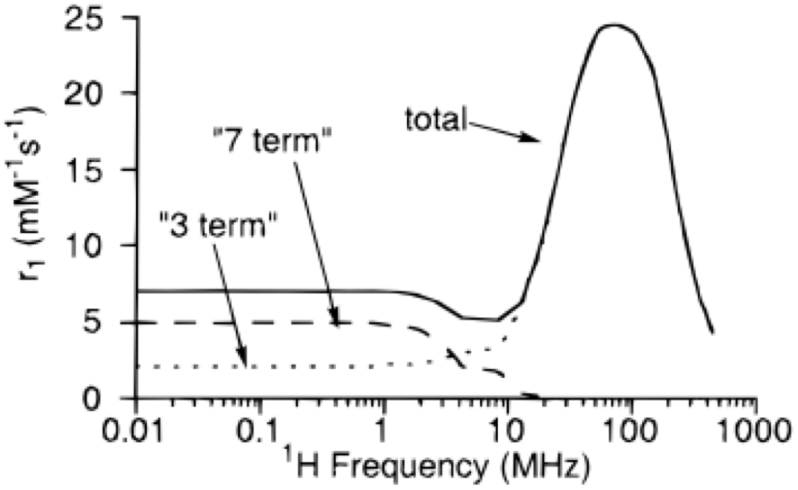
NMRD Curves Revisited

- Including the field-dependence of the electron relaxation rates can yield much more interesting relaxivity behavior.

Examples



$\tau_r = 0.1$ ns



$\tau_r = 1$ ns

SBM Theory: T_2

- For completeness, the equations for the T_2 relaxation rate is…

$$\frac{1}{T_{2,M}} \approx \frac{2}{3} A_{SC}^2 S(S+1)\left(\tau_{e1} + \frac{\tau_{e2}}{1+\omega_S^2\tau_{e2}^2}\right) + \frac{2}{15} b_{IS}^2 S(S+1)\left(4\tau_{c1} + \frac{3\tau_{c1}}{1+\omega_I^2\tau_{c1}^2} + \frac{13\tau_{c2}}{1+\omega_S^2\tau_{c2}^2}\right)$$

$$\tau_{e2}^{-1} = \tau_M^{-1} + T_{2e}^{-1}$$

$$\tau_{e1}^{-1} = \tau_M^{-1} + T_{1e}^{-1}$$

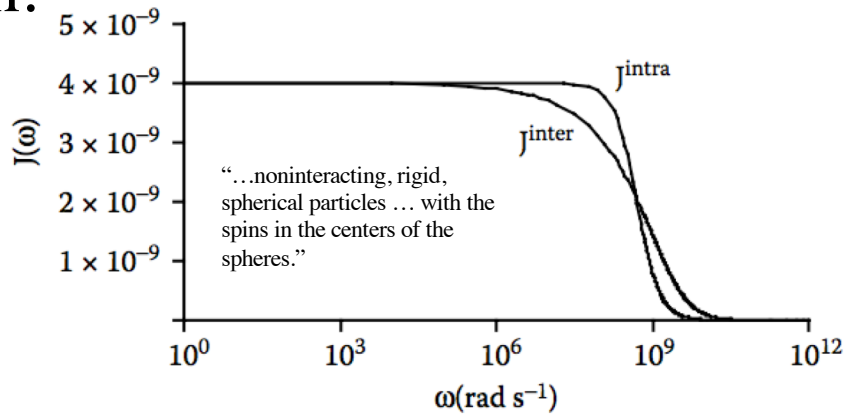
$$\tau_{ci}^{-1} = \tau_R^{-1} + \tau_M^{-1} + T_{je}^{-1};\ j = 1,2$$

$$\frac{1}{T_{1,e}} = \frac{\Delta_t^2}{5}\left(\frac{\tau_v}{1+\omega_S^2\tau_v^2} + \frac{4\tau_v}{1+4\omega_S^2\tau_v^2}\right)$$

$$\frac{1}{T_{2,e}} = \frac{\Delta_t^2}{10}\left(3\tau_v + \frac{5\tau_v}{1+\omega_S^2\tau_v^2} + \frac{2\tau_v}{1+4\omega_S^2\tau_v^2}\right)$$

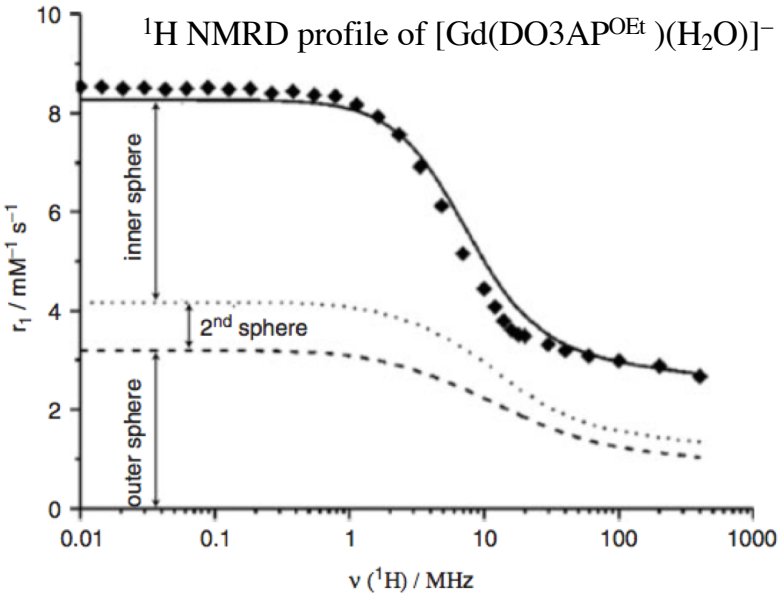
Outer-sphere Relaxation

- To compute outer sphere (intermolecular) relaxation effects, we need to use a more general correlation function which includes *r* changing with time due to translational diffusion.



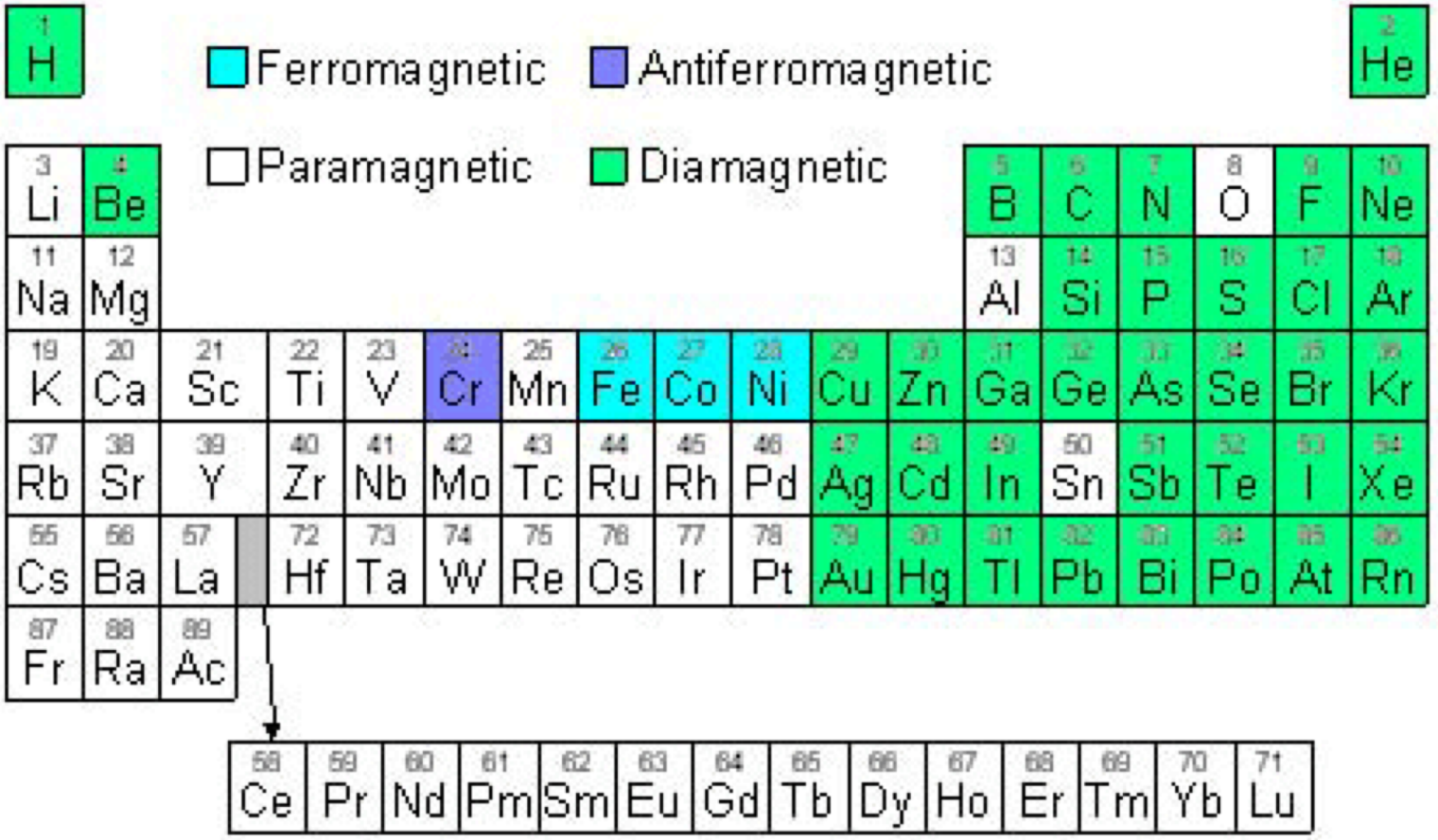
- Results in a modified spectral density function (see Kowalewski, Chp 3.5).

- For agents with water binding sites, relaxivity contributions from 2nd and outer sphere water are typically small.

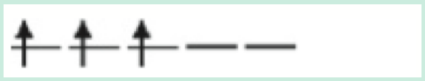
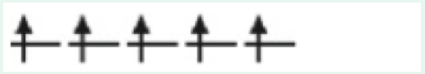
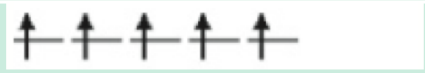
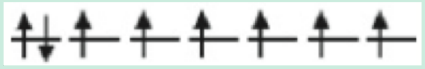
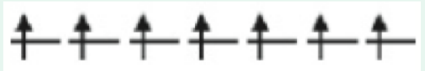
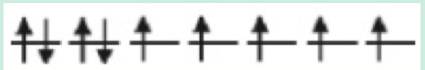


Lebduskova, et al., Dalton Trans. 2007, 493–501.

Paramagnetic Elements



Representative Metal Ions

Ion	Spin	Electron configuration	Magnetic moment	Electron T_1	ΔR_1 (0.5 T)	ΔR_2 (0.5 T)
$^{24}Cr^{3+}$	3/2		3.9	10^{-1} -1 ns	4.36	10.1
$^{25}Mn^{2+}$	5/2		5.9	1-10 ns	7.52	41.6
$^{26}Fe^{3+}$	5/2		5.9	10^{-1} -1 ns	8.37	12.8
$^{29}Cu^{2+}$	1/2		1.7	10^{-1} ns	0.83	0.98
$^{63}Eu^{3+}$	7/2		3.4	10^{-4} -10^{-3} ns	0.38	0.41
$^{64}Gd^{3+}$	7/2		7.9	1-10 ns	12.1	15.0
$^{66}Dy^{3+}$	5/2		10.6	10^{-4} -10^{-3} ns	0.56	0.56

- Magnetic moment due to both spin and orbital angular momentum
- Electron T_1
  - High symmetry: electric fields largely cancel.
  - Low symmetry: electric field gradients enhance quadrupolar relaxation.

Why do we need MR contrast agents?

- Remember, MRI has good spatial resolution but low sensitivity.

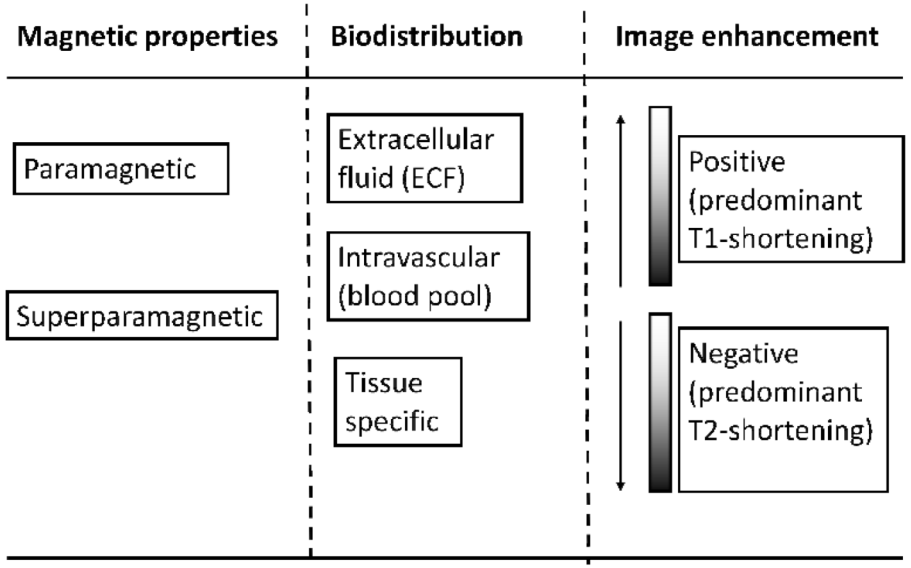
Modality	Spatial resolution	Dept	Temporal resolution	Sensitivity (mol/L)
PET	1–2 mm	No limit	10 s-min	10^{-11}–10^{-12}
SPECT	0.5–1 mm	No limit	min	10^{-10}–10^{-11}
MRI	25–100 μm	No limit	min-h	10^{-3}–10^{-5}
CT	50–200 μm	No limit	min	10^{-2}–10^{-4}
Ultrasound	50–500 μm	mm-cm	s-min	10^{-3}–10^{-4}

- MRI signal intensity is typically proportional to $M_0\left(1-e^{-TR/T_1}\right)e^{-TE/T_2}$.

- Idea of using paramagnetic salts to shorten water relaxation times goes all the way back to Bloch, Hansen, and Packard, Phys. Rev. 1948, vol. 70, p. 464.

In Vivo Requirements

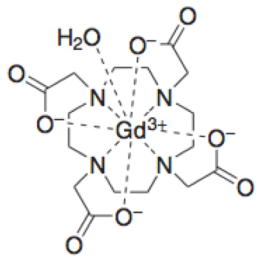
- MRI contrast agents must be both biocompatible pharmaceuticals and NMR relaxation probes
- Relaxivity
  - T_1, T_2, or T_2^* shortening
  - Typically need at least 10-20% increase in $1/T_1$ for robust detection.
- Specific in vivo distribution
- In vivo stability, excretability, lack of toxicity (acute and chronic)



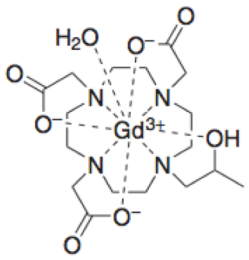
Types of MR Contrast Agents

- T_1 shortening agents
  - Clinical agents: Gd^{3+} based
  - Research: targeted and/or responsive agents, Mn^{2+} agents
- T_2, T_2^*,shortening agents
  - Clinical agents: Super-paramagnetic iron oxide (SPIO) nanoparticles
  - Research: targeted and/or responsive agents
- PARACEST agents

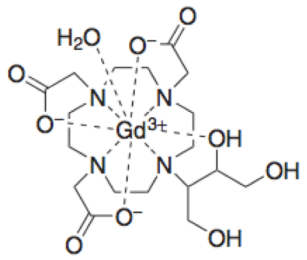
Clinically used Gd^{3+} chelates



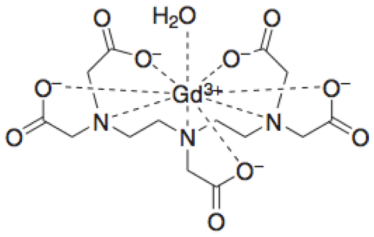
[Gd(DOTA)(H_2O)]$^-$
Dotarem® (Guerbet S.A.)



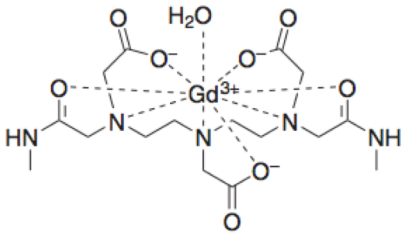
[Gd(HP-DO3A)(H_2O)]
ProHance® (Bracco)



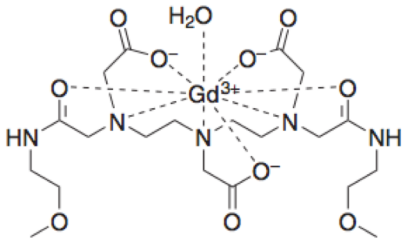
[Gd(DO3A-butrol)(H_2O)]
Gadovist® (Bayer Schering Pharma AG, Bayer Healthcare Pharmaceuticals)



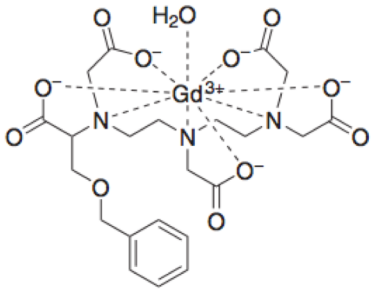
[Gd(DTPA)(H_2O)]$^{2-}$
Magnevist® (Bayer Schering Pharma AG, Bayer Healthcare Pharmaceuticals)



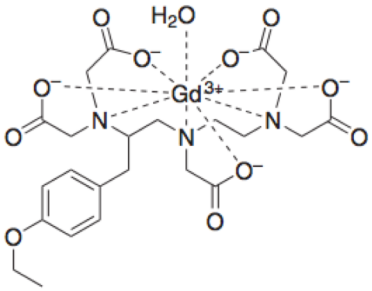
[Gd(DTPA-BMA)(H_2O)]
Omniscan® (GE Healthcare)



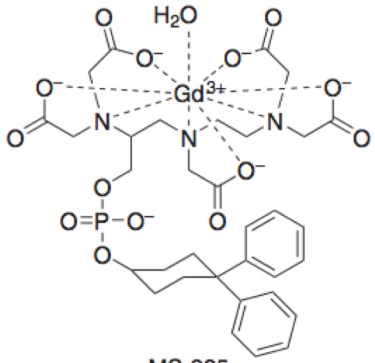
[Gd(DTPA-BMEA)(H_2O)]
OptiMARK® (Mallinckrodt Inc.)



[Gd(BOPTA)(H_2O)]$^{2-}$
MultiHance® (Bracco)



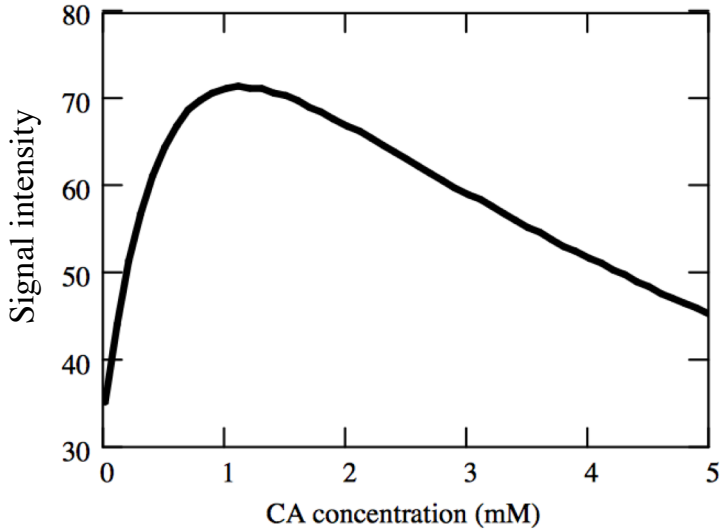
[Gd(EOB-DTPA)(H_2O)]$^{2-}$
Primovist®, Eovist® (Bayer Schering Pharma AG, Bayer Healthcare Pharmaceuticals)



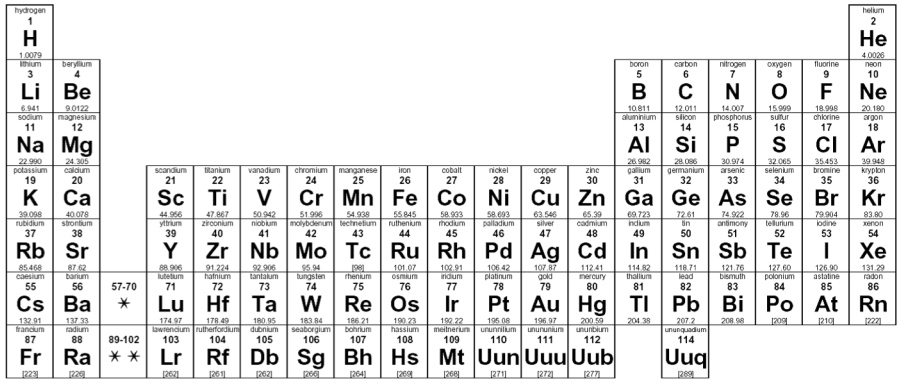
MS-325
ABLAVAR™ (formerly Vasovist®, AngioMARK®) (Lantheus Medical Imaging, Inc.)

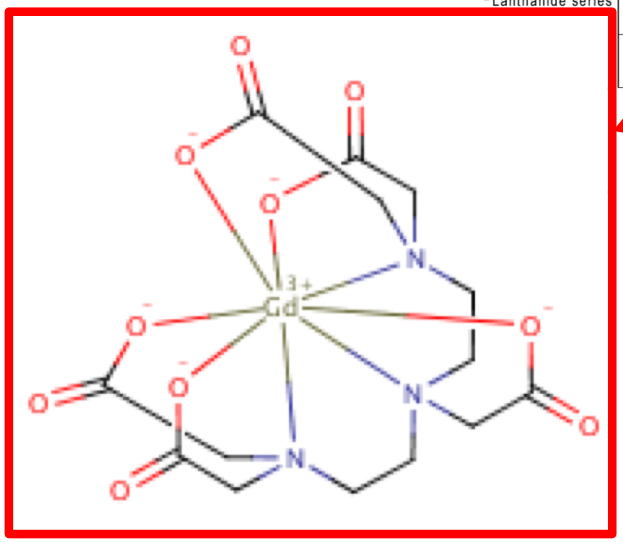
Doesn't Gd-DTPA also shorten T_2?

- Yes, but relaxation rates are additive
- In vivo tissue T_2s are typically considerably shorter than T_1s
- On a percentage basis, T_1 agents such as Gd-DTPA increase $1/T_1$ much more than $1/T_2$
- For a typical MRI sequence, signal is usually enhanced, unless the Gd-DTPA concentration gets very high.



Gd-DTPA vs Dy-DTPA





Gd^{3+}: 7 unpaired e^- s

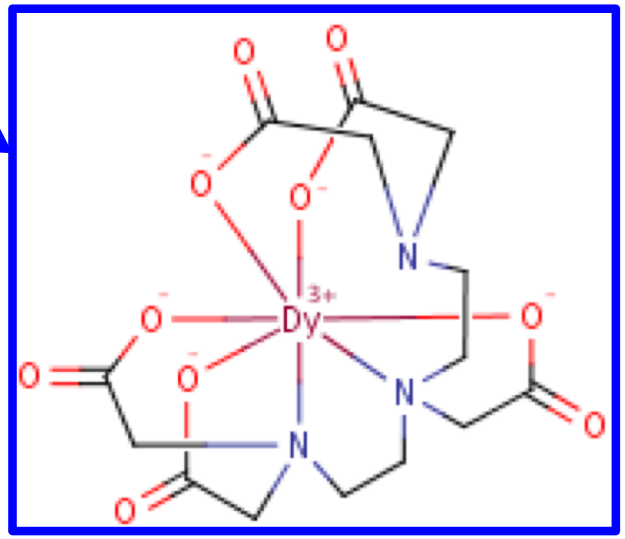
$\mu = 7.9$

T_{1e}= ~1 ns

Dy^{3+}: 5 unpaired e^- s

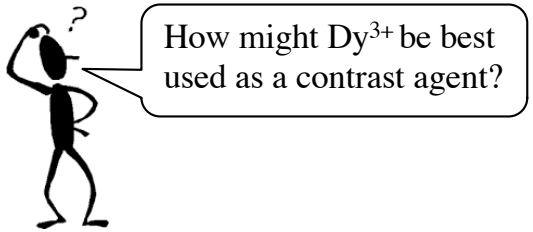
$\mu = 10.6$

T_{1e}= ~10^{-4} ns



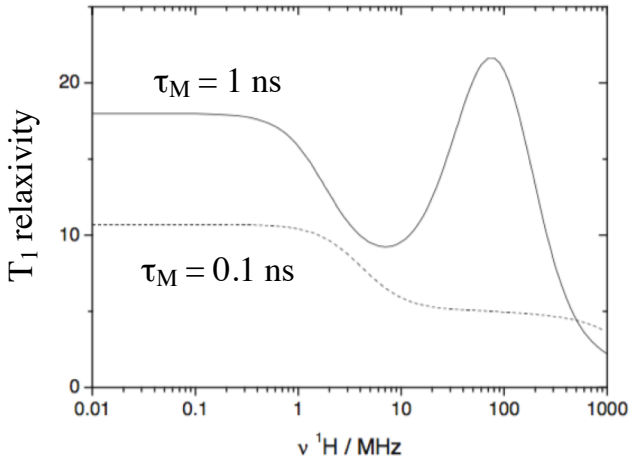
Useful T_1 agent

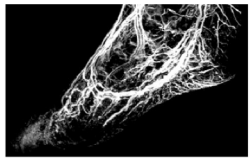
Not a useful T_1 agent



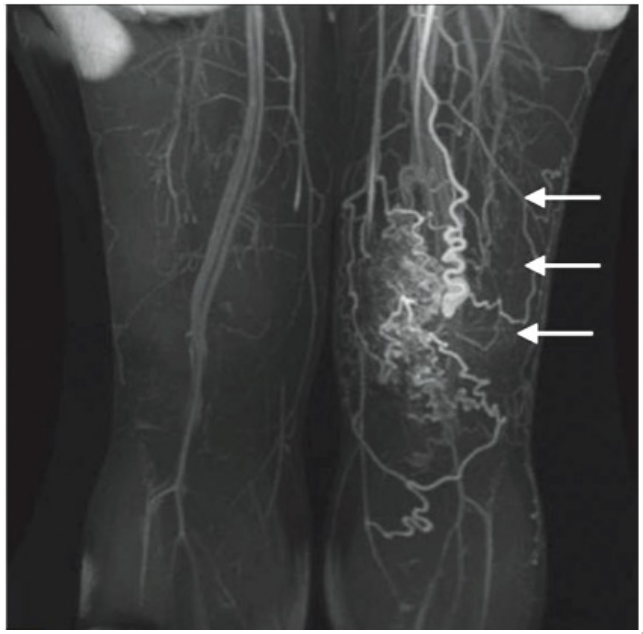
MS-325

- Gd-DTPA bound to albumin
  - High T_1 relaxivity
  - Stays in the intravascular space

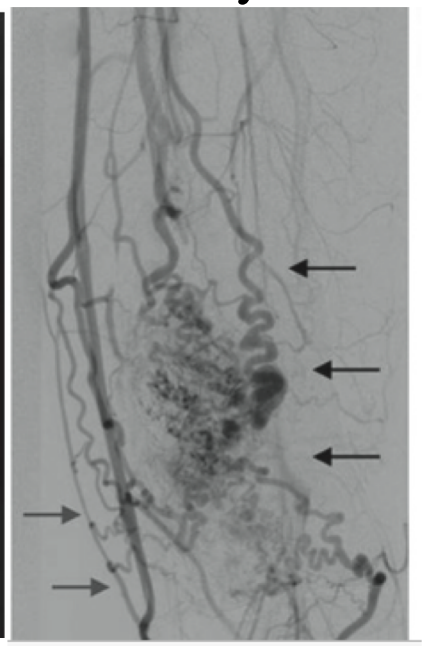




MRI



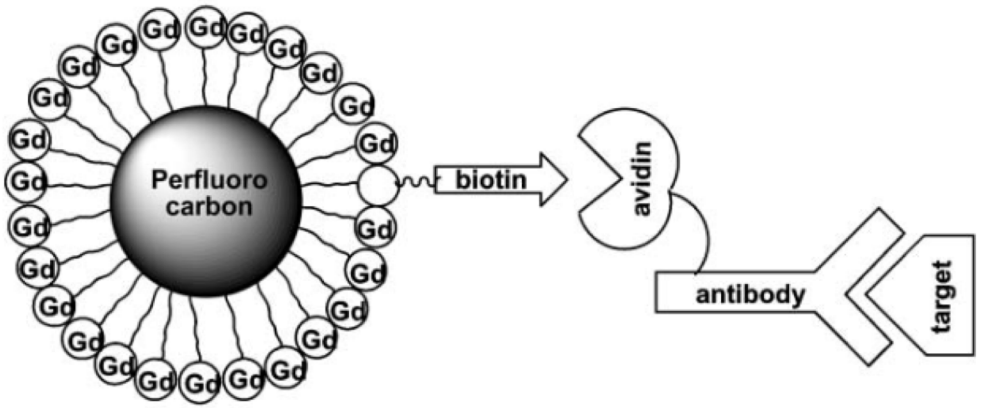
X-ray



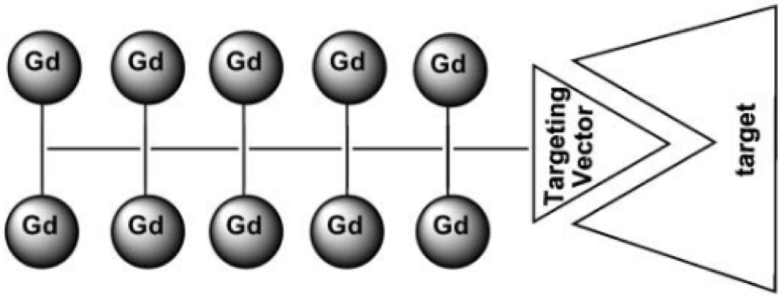
Lots of in vivo targeting strategies…

- A few examples

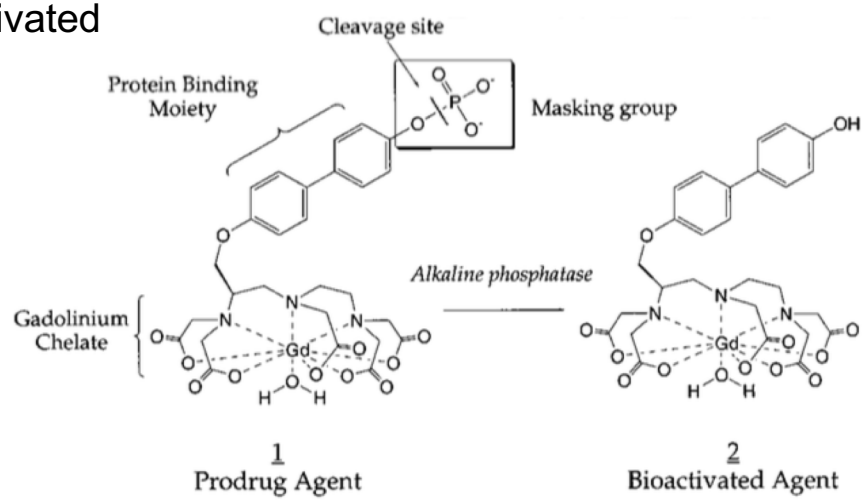
a) Targeted particle assembly:



b) Discrete targeted multimer:



c) Enzyme-activated



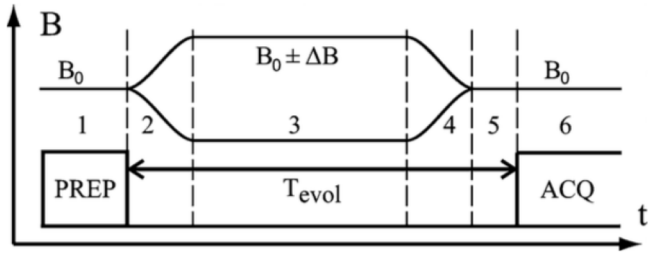
d) and many more

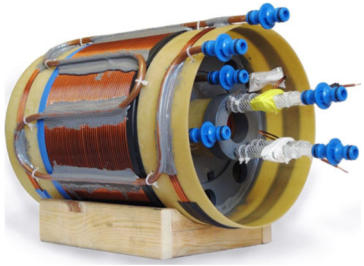
Magnetic Resonance in Medicine 61:796–802 (2009)

Delta Relaxation Enhanced MR: Improving Activation-Specificity of Molecular Probes through R_1 Dispersion Imaging

Jamu K. Alford,[1] Brian K. Rutt,[1–3] Timothy J. Scholl,[1] William B. Handler,[1] and Blaine A. Chronik[1*]

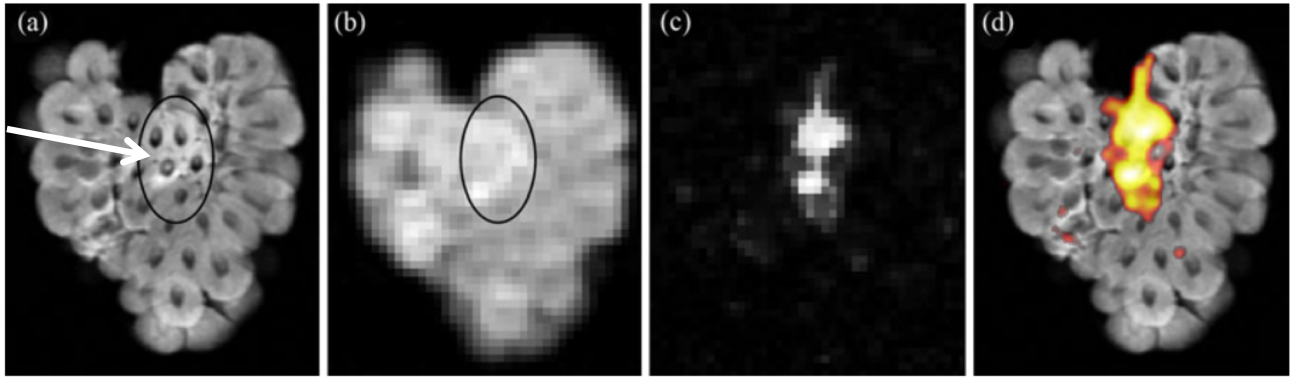
- Contrast based on field dependence of T_1relaxivity: $\frac{dR_1}{dB}$
- Hoelsher, et al, Magn, Reson Mater Phy, 2012.





Field-cycling insert coil

Raspberry injected with Gadoflurine



T_1-weighted 1.5 T + 90 mT

T_2-weighted 1.5 T - 90 mT

dreMR image

dreMR overlay

Next Lecture:
T_2, T_2^*, and PARACEST Contrast Agents