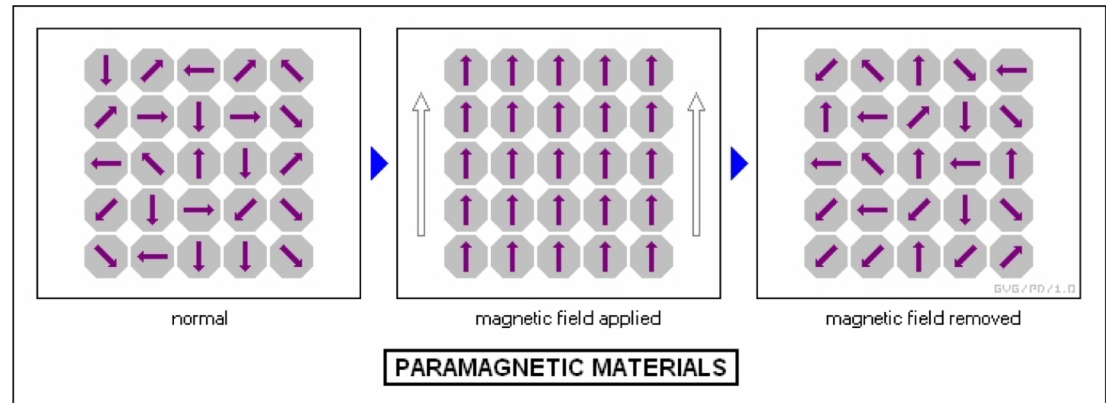
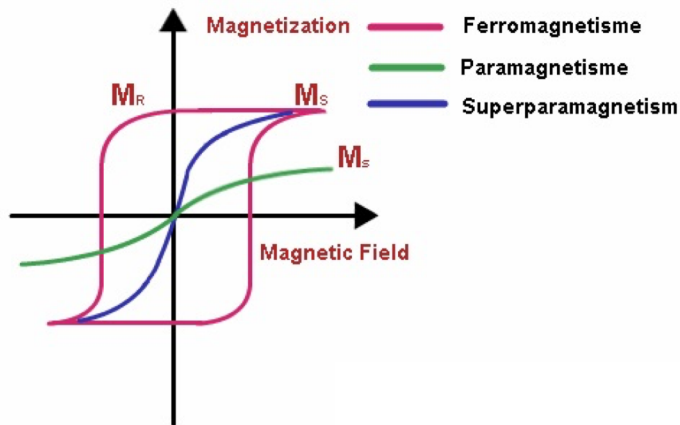


Lecture #12

Paramagnetic Relaxation Enhancement

- Topics
 - Paramagnetic contributions to relaxation
 - Paramagnetic metal ions
 - Gd³⁺-based T₁ 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

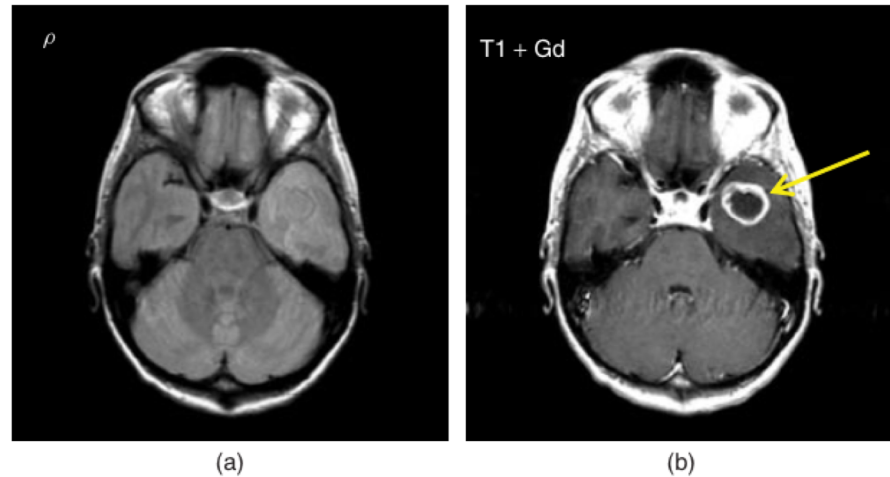


Figure 1.19 Images of a human brain with tumor without and with the Gd^{3+} chelate displaying the tumor with CA uptake in hypersignal.

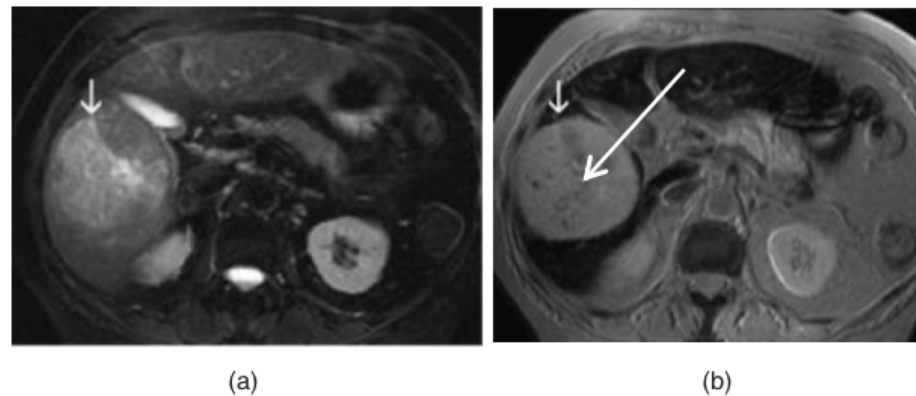


Figure 1.20 Images of a human liver without (a) and with (b) IO particles, displaying normal liver tissue with dark spots. Liver malign tumors don't uptake IO. Namkung et al. *Journal of Magnetic Resonance Imaging*, 25: 755–765 (2007).

Paramagnetic contributions to relaxivity

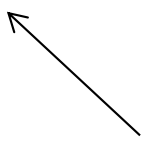
- The addition of a paramagnetic solute increases both $1/T_1$ and $1/T_2$ relaxation rates.
- Diamagnetic and paramagnetic contributions are additive.

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

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

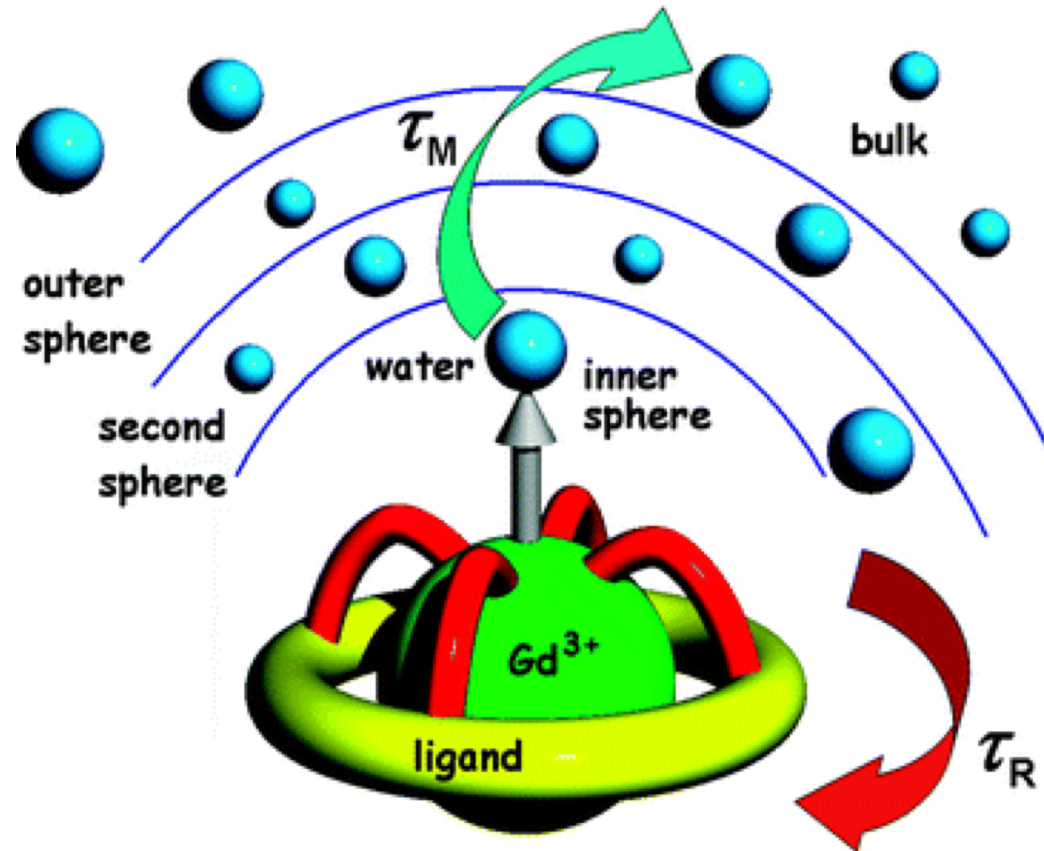
$$\frac{1}{T_i} = \frac{1}{T_{i,d}} + [M]R_i \text{ for } i = 1, 2$$

“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 \longrightarrow stochastic modulations \longrightarrow relaxation
- Exchange rates (μs to ms time scales) \ll 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:

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

Strength of the interaction

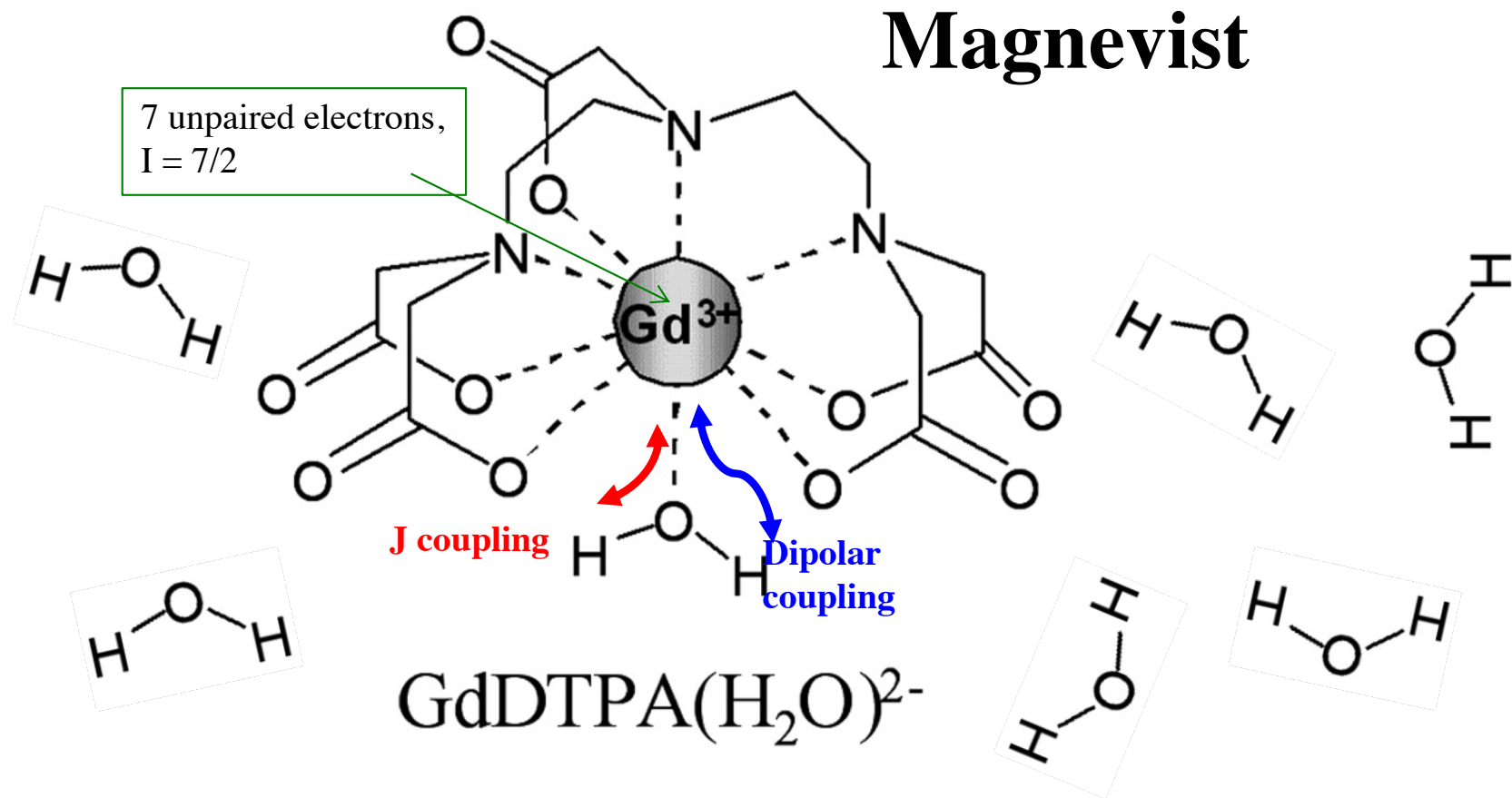
Difference frequency between exchange sites

1/exchange rate

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 $S > \frac{1}{2}$ 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...

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

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...

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

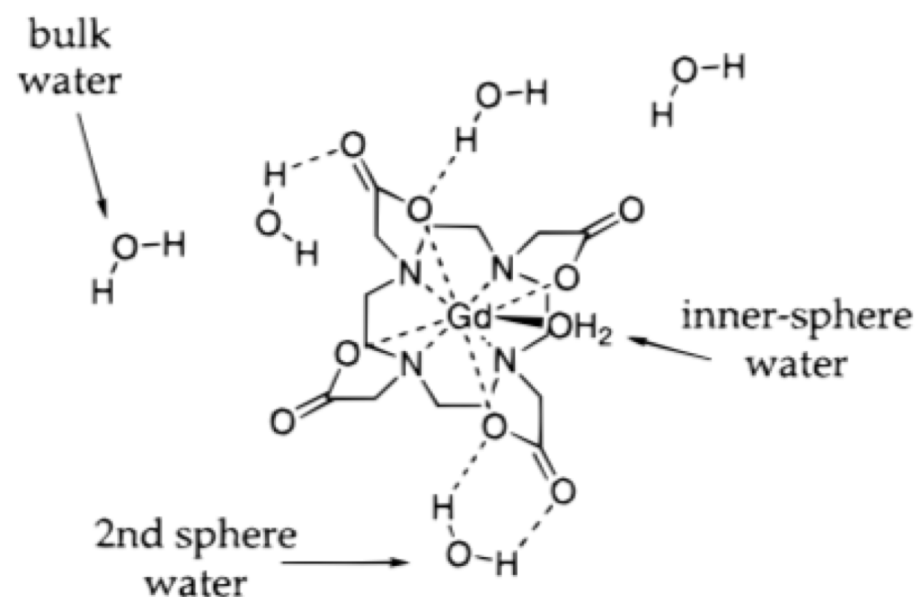
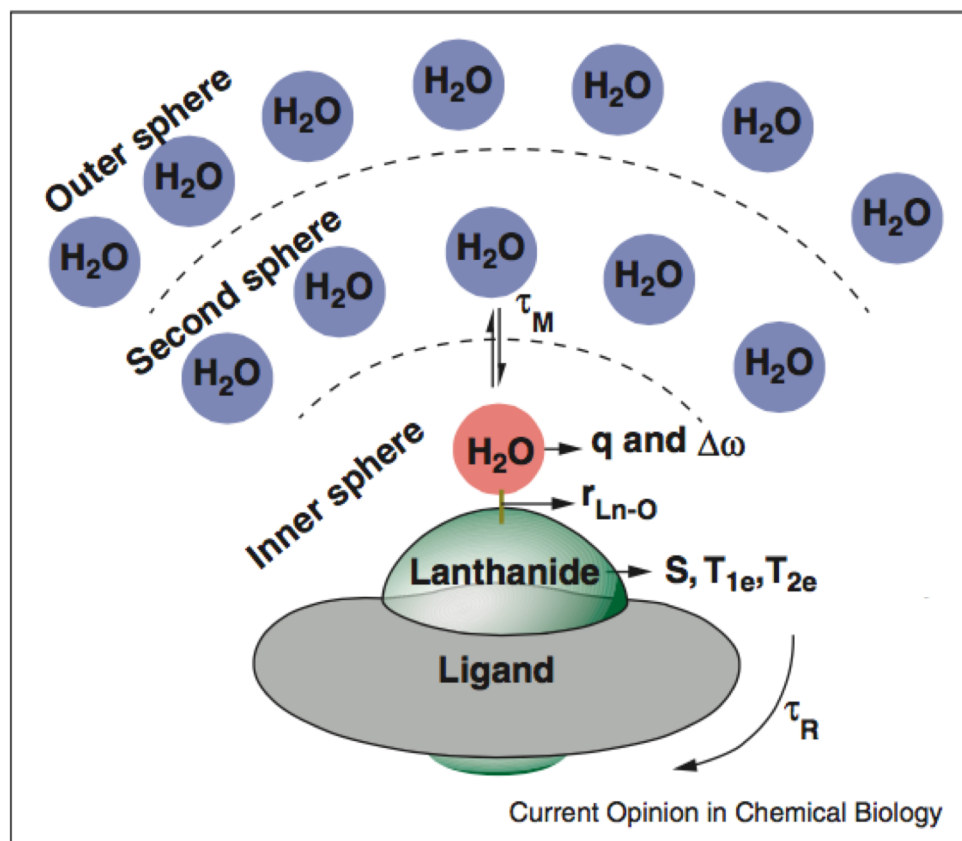
- The contribution to T_1 and T_2 relaxation (known as scalar relaxation of the 2nd kind) are:

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

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

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...

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

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

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

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

where M = ligand in paramagnetic 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

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

- Hence:

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

$\gamma_e B_0$ $\gamma_H B_0$

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

- The correlation times are quite interesting...

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

\swarrow \searrow
 water exchange time electron T_2

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

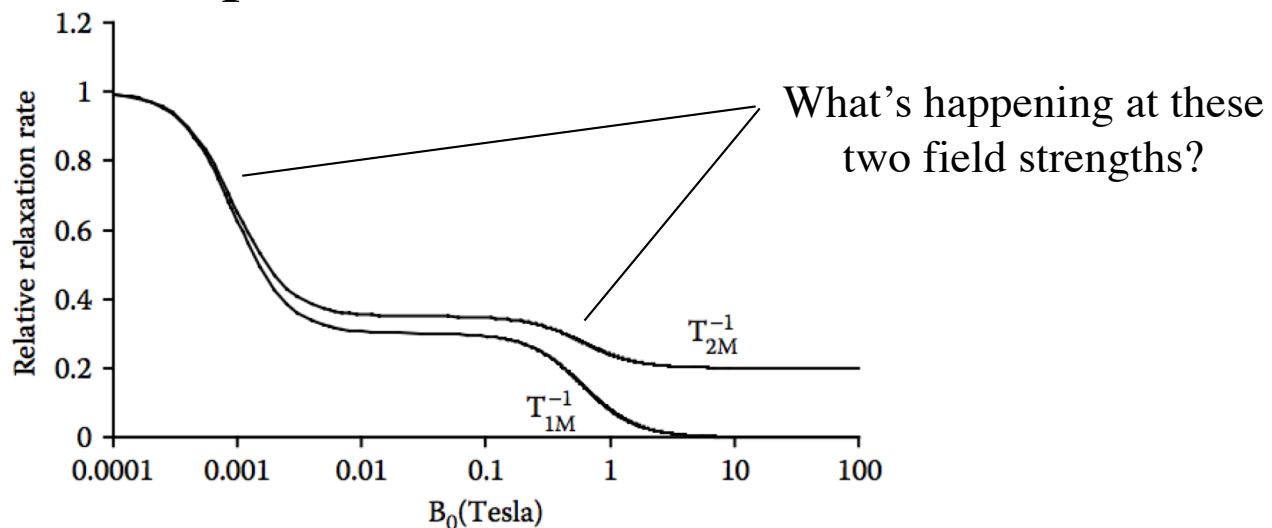
\swarrow
 electron T_1

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

\swarrow
 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.

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

Trace of transient ZFS tensor Correlation time for ZFS modulations, typically $\sim 10^{-9}$ s

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

Are these the same as those for nuclear relaxation via quadrupolar coupling?



SBM Theory: T_1

- The complete equations for the T_1 relaxation rate are...

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

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

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

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

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

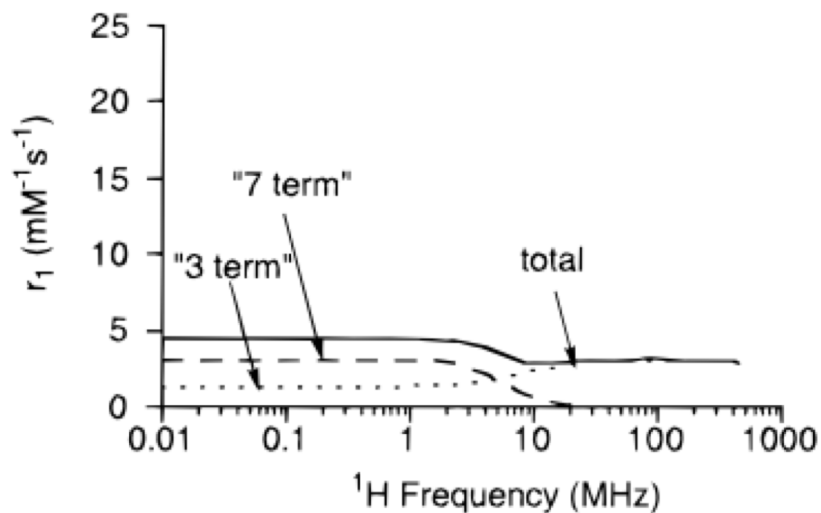
$$\tau_{ci}^{-1} = \tau_R^{-1} + \tau_M^{-1} + T_{je}^{-1}; j=1,2$$

- 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

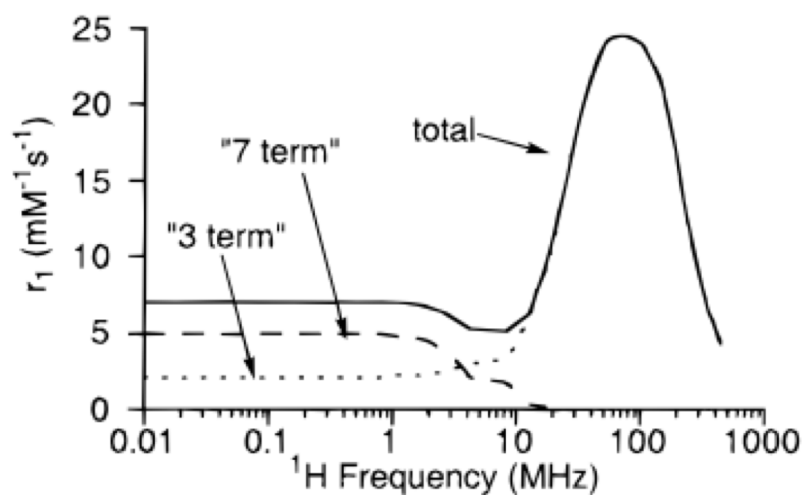
NMRD Curves Revisited

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

Examples



$$\tau_r = 0.1 \text{ ns}$$



$$\tau_r = 1 \text{ ns}$$

SBM Theory: T_2

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

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

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

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

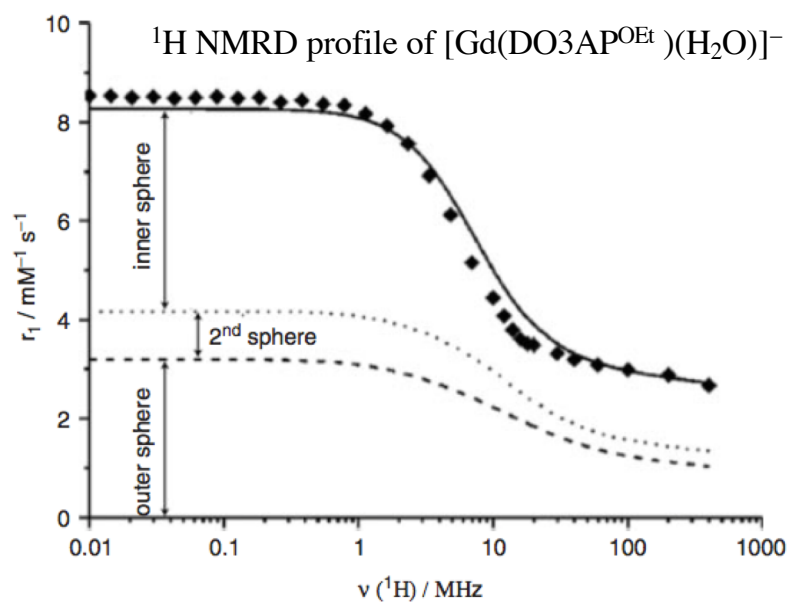
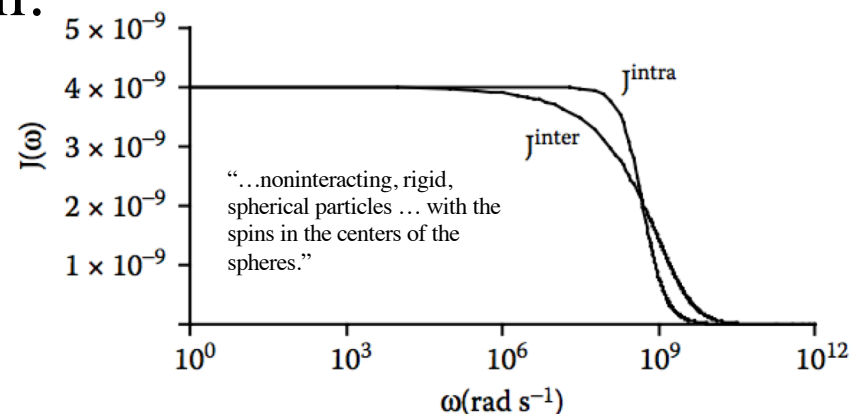
$$\tau_{e1}^{-1} = \tau_M^{-1} + T_{1e}^{-1}$$

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

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

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.

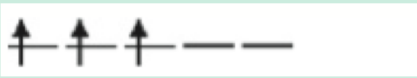
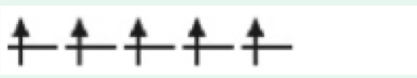
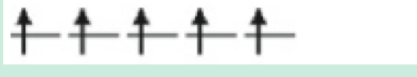
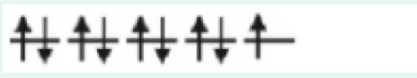
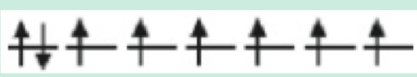
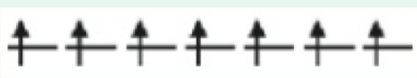
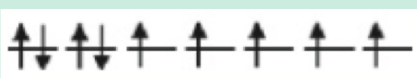


Lebduskova, et al., Dalton Trans. 2007, 493–501.

Paramagnetic Elements

1 H																	2 He	
		<input type="checkbox"/> Paramagnetic <input type="checkbox"/> Diamagnetic																
		<input type="checkbox"/> Ferromagnetic <input type="checkbox"/> Antiferromagnetic																
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne	
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar	
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr	
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe	
55 Cs	56 Ba	57 La	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn	
87 Fr	88 Ra	89 Ac																
			58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu		

Representative Metal Ions

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

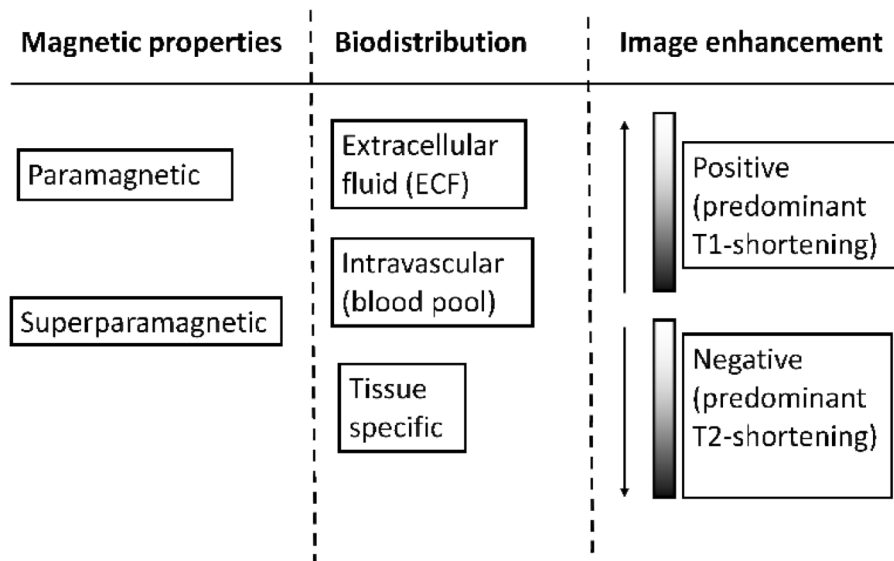
- Remember, MRI has good spatial resolution but low sensitivity.

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 $M_0 (1 - e^{-TR/T_1}) e^{-TE/T_2}$.
- 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

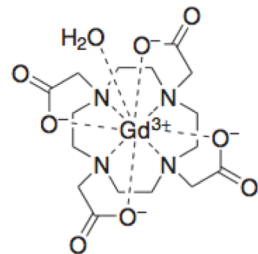
- MRI contrast agents must be both biocompatible pharmaceuticals and NMR relaxation probes
- Relaxivity
 - T_1 , T_2 , or T_2^* shortening
 - Typically need at least 10-20% increase in $1/T_1$ for robust detection.
- Specific in vivo distribution
- In vivo stability, excretability, lack of toxicity (acute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



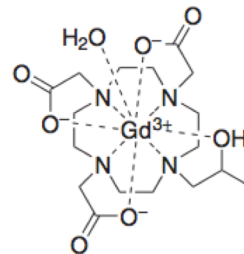
Types of MR Contrast Agents

- 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

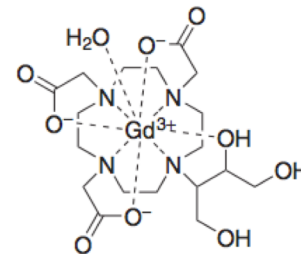
Clinically used Gd³⁺ chelates



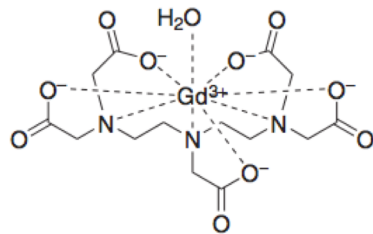
[Gd(DOTA)(H₂O)]⁻
Dotarem[®] (Guerbet S.A.)



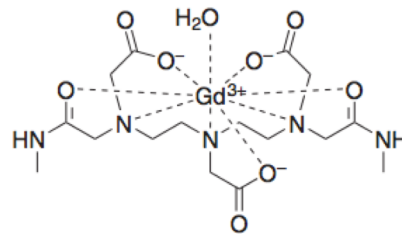
[Gd(HP-DO3A)(H₂O)]
ProHance[®] (Bracco)



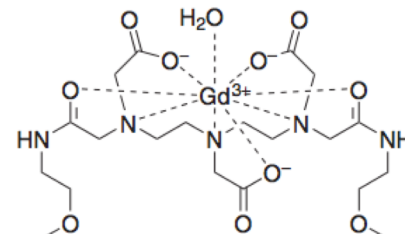
[Gd(DO3A-butrol)(H₂O)]
Gadovist[®] (Bayer Schering
Pharma AG, Bayer
Healthcare Pharmaceuticals)



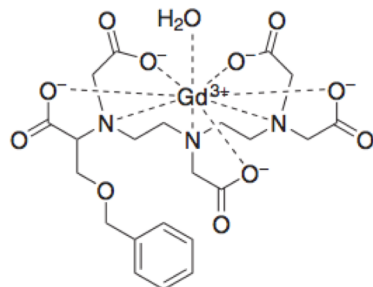
[Gd(DTPA)(H₂O)]²⁻
Magnevist[®] (Bayer Schering
Pharma AG, Bayer
Healthcare Pharmaceuticals)



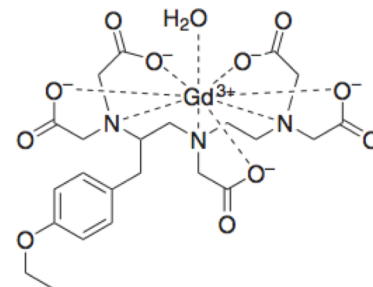
[Gd(DTPA-BMA)(H₂O)]
Omniscan[®] (GE Healthcare)



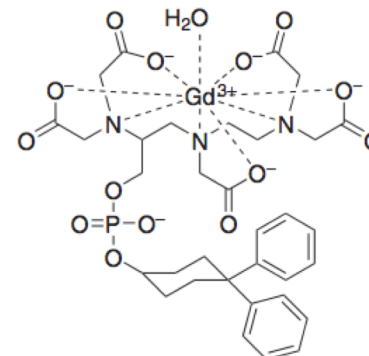
[Gd(DTPA-BMEA)(H₂O)]
OptiMARK[®] (Mallinckrodt Inc.)



[Gd(BOPTA)(H₂O)]²⁻
MultiHance[®] (Bracco)



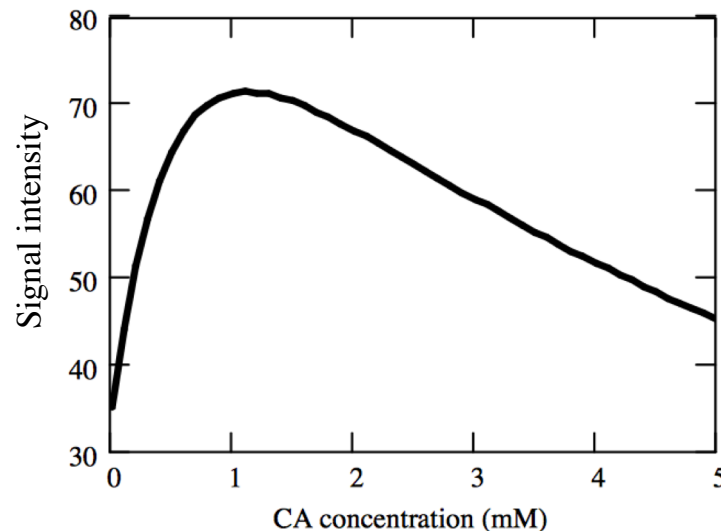
[Gd(EOB-DTPA)(H₂O)]²⁻
Primovist[®], Eovist[®] (Bayer
Schering Pharma AG, Bayer
Healthcare Pharmaceuticals)



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

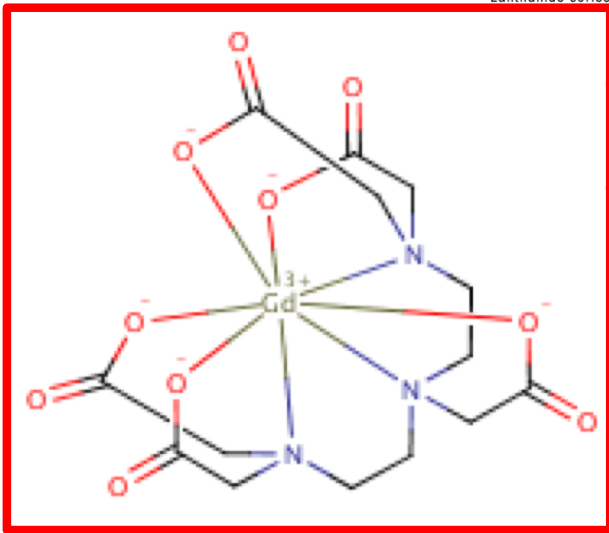
Doesn't Gd-DTPA also shorten T_2 ?

- Yes, but relaxation rates are additive
- In vivo tissue T_2 s are typically considerably shorter than T_1 s
- 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

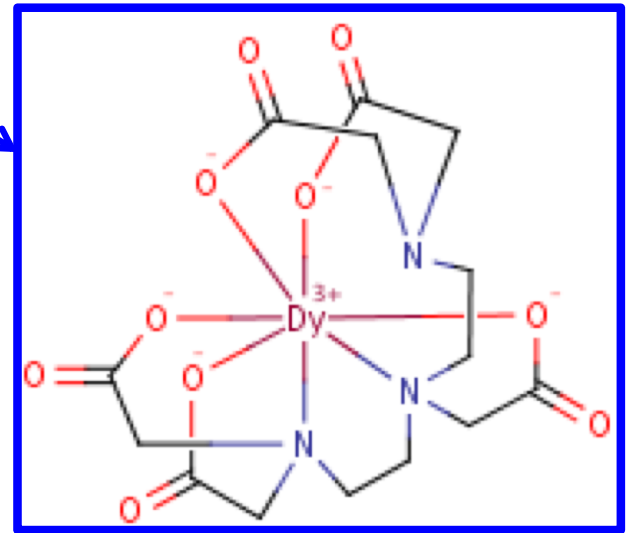
hydrogen 1 H 1.0079	helium 2 He 4.0026																												
lithium 3 Li 6.941	beryllium 4 Be 9.0122																												
sodium 11 Na 22.990	magnesium 12 Mg 24.305																												
potassium 19 K 39.098	calcium 20 Ca 40.078																												
rubidium 37 Rb 85.468	strontium 38 Sr 87.62																												
cesium 55 Cs 132.91	barium 56 Ba 137.33																												
francium 87 Fr [223]	radium 88 Ra [226]																												
scandium 21 Sc 44.956	titanium 22 Ti 47.887	vanadium 23 V 50.942	chromium 24 Cr 51.996	manganese 25 Mn 54.938	iron 26 Fe 55.845	cobalt 27 Co 58.933	nickel 28 Ni 58.693	copper 29 Cu 63.546	zinc 30 Zn 65.39	gallium 31 Ga 69.723	germanium 32 Ge 72.61	arsenic 33 As 74.922	selenium 34 Se 78.96	bromine 35 Br 79.904	krypton 36 Kr 83.80														
yttrium 39 Y 88.906	zirconium 40 Zr 91.224	niobium 41 Nb 92.906	molybdenum 42 Mo 95.94	technetium 43 Tc [98]	ruthenium 44 Ru 101.07	rhodium 45 Rh 102.91	palladium 46 Pd 106.42	silver 47 Ag 107.87	cadmium 48 Cd 112.41	indium 49 In 114.82	tin 50 Sn 118.71	antimony 51 Sb 121.76	tellurium 52 Te 127.60	iodine 53 I 126.90	xenon 54 Xe 131.29														
lanthanum 57 La 138.91	cerium 58 Ce 140.12	praseodymium 59 Pr 140.91	neodymium 60 Nd 144.24	promethium 61 Pm [145]	samarium 62 Sm 150.36	europium 63 Eu 151.96	gadolinium 64 Gd 157.25	terbium 65 Tb 158.93	ytterbium 66 Yb 173.04	lutetium 67 Lu 174.97	hafnium 72 Hf 178.49	tantalum 73 Ta 180.95	wolfram 74 W 183.84	reuterium 75 Re 186.21	osmium 76 Os 190.23	iridium 77 Ir 192.22	platinum 78 Pt 195.08	gold 79 Au 196.97	mercury 80 Hg 200.59	thallium 81 Tl 204.38	lead 82 Pb 207.2	bismuth 83 Bi 208.98	polonium 84 Po [209]	astatine 85 At [210]	radon 86 Rn [222]				
actinium 89 Ac [227]	thorium 90 Th 232.04	protactinium 91 Pa [231]	uranium 92 U 238.03	neptunium 93 Np [237]	plutonium 94 Pu [244]	americium 95 Am [243]	curium 96 Cm [247]	berkelium 97 Bk [247]	californium 98 Cf [251]	einsteinium 99 Es [252]	fermium 100 Fm [257]	mendelevium 101 Md [258]	nobelium 102 No [259]	lawrencium 103 Lr [260]	unlabeled 104 [261]	unlabeled 105 [262]	unlabeled 106 [263]	unlabeled 107 [264]	unlabeled 108 [265]	unlabeled 109 [266]	unlabeled 110 [267]	unlabeled 111 [268]	unlabeled 112 [269]	unlabeled 113 [270]	unlabeled 114 [271]	unlabeled 115 [272]	unlabeled 116 [273]	unlabeled 117 [274]	unlabeled 118 [275]



Useful T₁ agent

Gd³⁺: 7 unpaired e⁻ s
 $\mu = 7.9$
 $T_{1e} = \sim 1$ ns

Dy³⁺: 5 unpaired e⁻ s
 $\mu = 10.6$
 $T_{1e} = \sim 10^{-4}$ ns



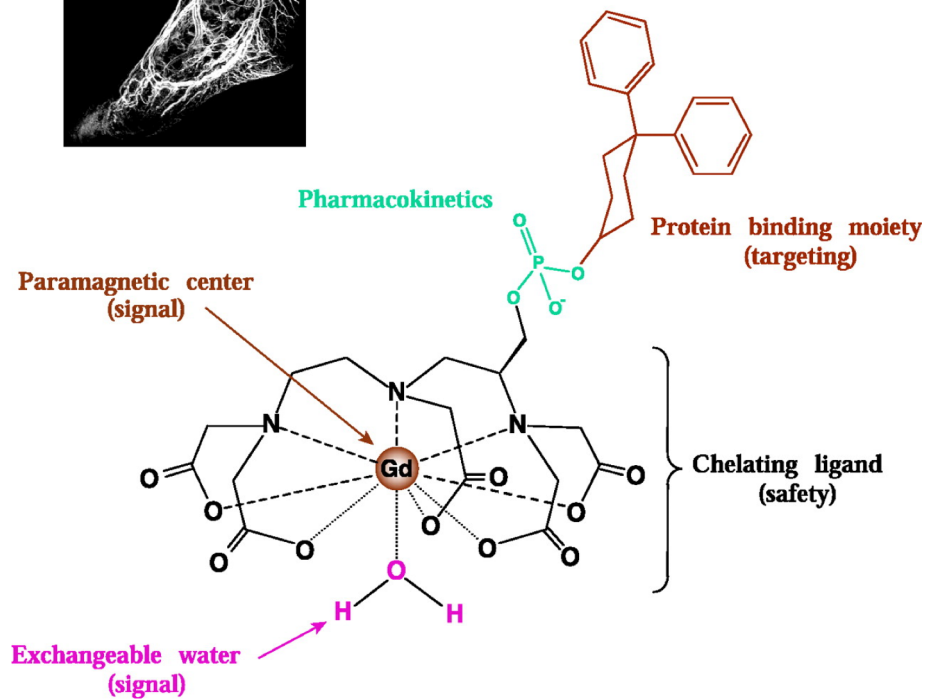
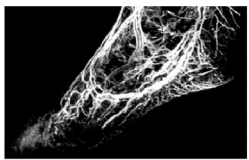
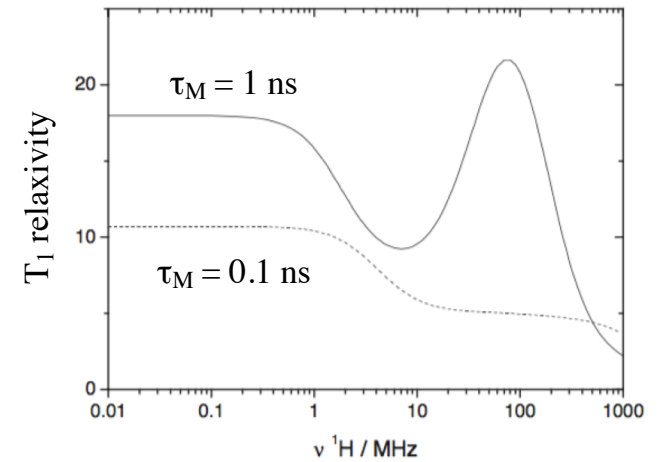
Not a useful T₁ agent



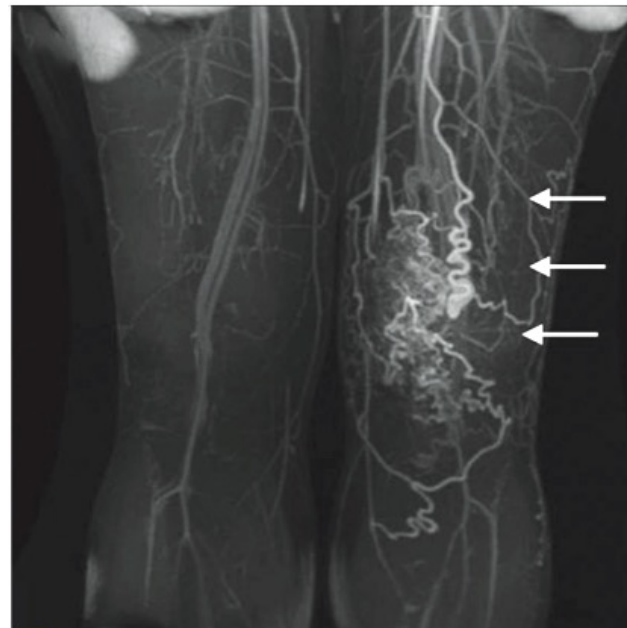
How might Dy³⁺ be best used as a contrast agent?

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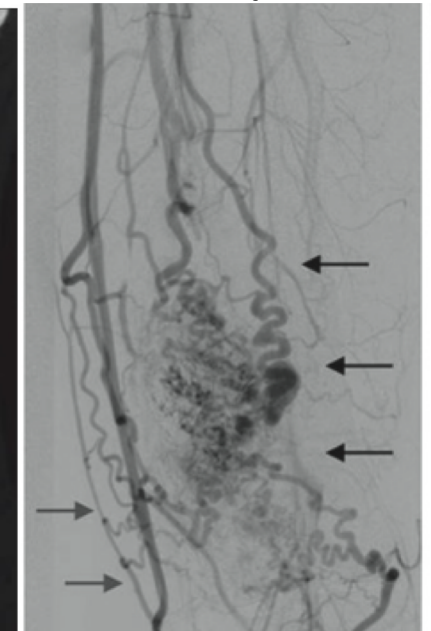
- Gd-DTPA bound to albumin
 - High T_1 relaxivity
 - Stays in the intravascular space



MRI



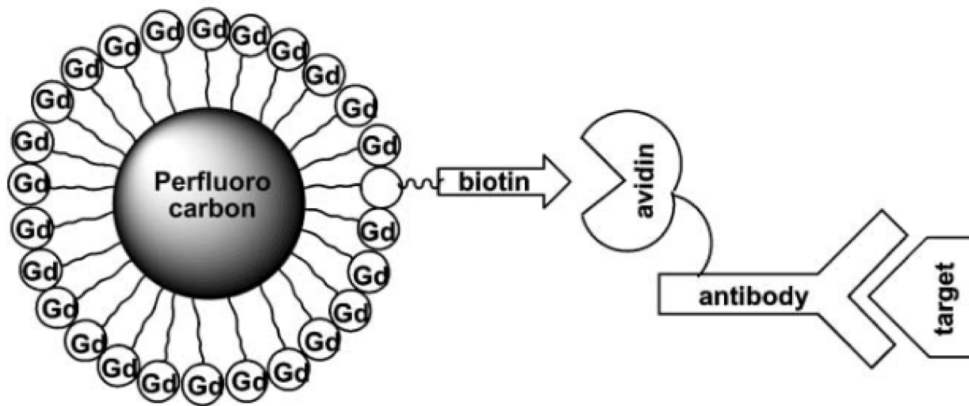
X-ray



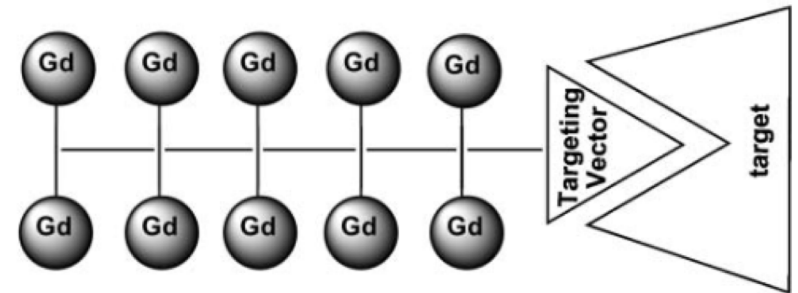
Lots of in vivo targeting strategies...

- A few examples

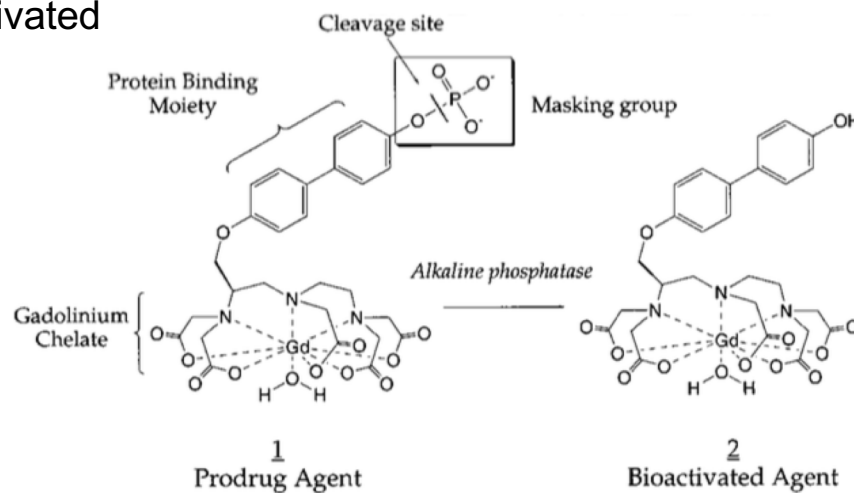
a) Targeted particle assembly:



b) Discrete targeted multimer:



c) Enzyme-activated

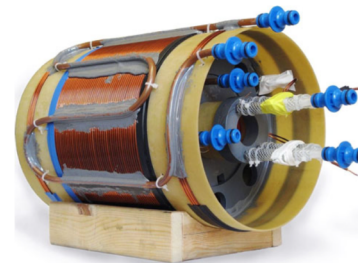
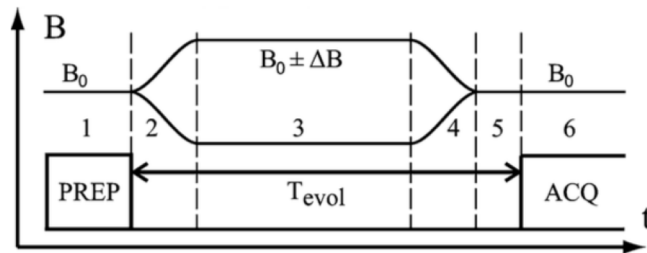


d) and many more

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

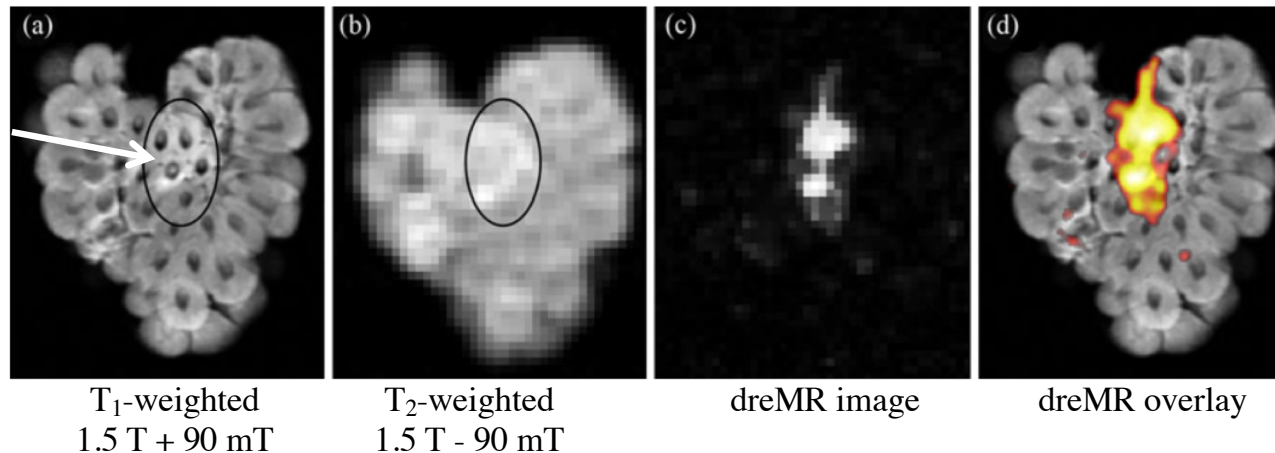
Jamu K. Alford,¹ Brian K. Rutt,¹⁻³ Timothy J. Scholl,¹ William B. Handler,¹ and Blaine A. Chronik^{1*}

- Contrast based on field dependence of T_1 relaxivity: $\frac{dR_1}{dB}$
- Hoelsher, et al, Magn, Reson Mater Phy, 2012.



Field-cycling insert coil

Raspberry injected with Gadoflurine



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