

Development of MRI Contrast Agents Based On Iron Complexes



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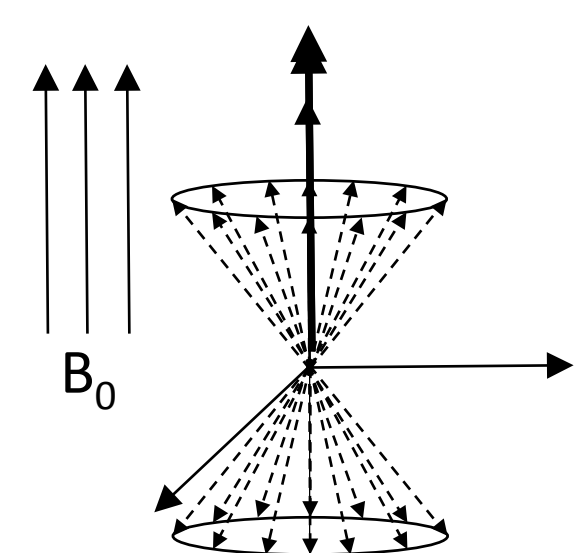
MRI & Contrast Agents

Overview:

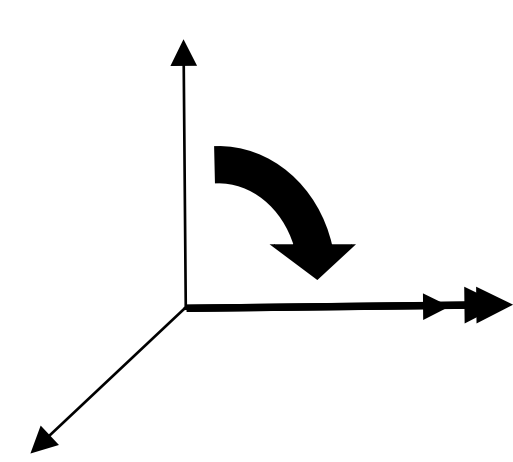
- MRI – Magnetic Resonance Imaging
- Magnetic field + radio frequency pulses
- Water hydrogen nuclei magnetic moment interacts with magnetic field
- Absorption and emission of energy through relaxation processes
- Contrast agent perturbs water's proton relaxivity through chemical interactions
- Results in different relaxation rates and subsequent image contrast on an MRI
- Contrast helps physicians diagnosis disease and better visualize abnormalities

MRI Relaxation Processes:

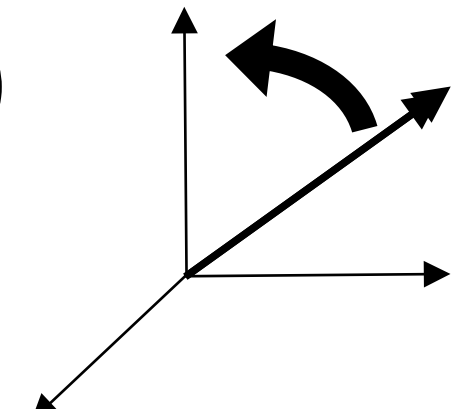
Net Magnetic moment alignment



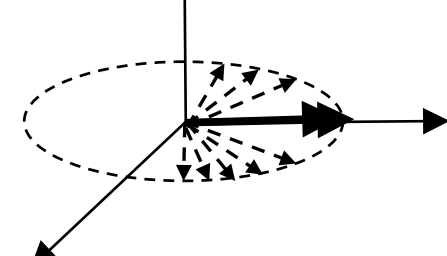
Radio wave Pulse Excitation



Longitudinal Relaxation (1/T₁)

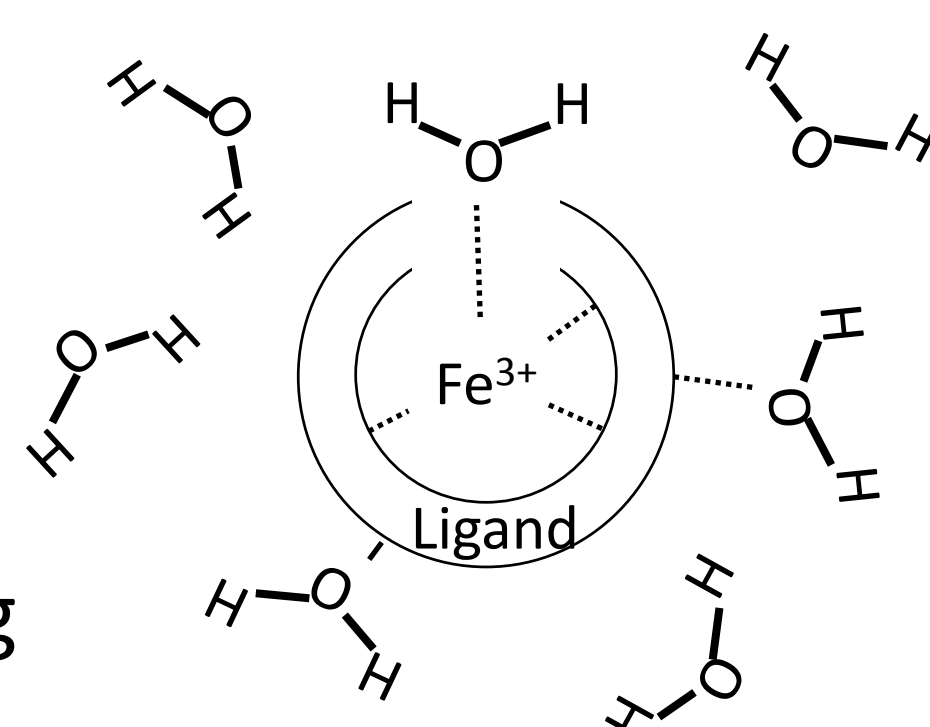


Transverse Relaxation (1/T₂)



Contrast Agent – Water Interactions:

- Inner Sphere (Coordination Bonding)
- Outer Sphere (H-bonding and proximity effects)



Methods – Data

Acquisition:

- 4.7 T MRI scanner and 9.4 T NMR Spectrometer
- Water enriched with ¹⁷O
- Gather variable temperature measurements
- Collect frequency shift data ($\Delta\nu_{\text{observed}}$ & $\Delta\nu_{\text{solvent}}$)
- Convert to reduced relaxivity data ($1/T_{2r}$)
- Fit data to equations to obtain information on water exchange rate constants

Modeling Contrast Agent Interactions:

- Swift – Connick Equations:

$$(1a) \quad \frac{1}{T_{2r}} = \frac{\pi}{P_m} * (\Delta\nu_{\text{observed}} - \Delta\nu_{\text{solvent}}) \\ = \frac{1}{\tau_m} * \frac{(T_{2m}^{-1} + T_{2m}^{-1} * \tau_m^{-1} + \Delta\omega_m^2)}{(T_{2m}^{-1} + \tau_m^{-1})^2 + \Delta\omega_m^2} + \frac{1}{T_{2os}}$$

$$(1b) \quad \frac{1}{T_{2r}} = \frac{\pi}{P_m} * (\Delta\nu_{\text{observed}} - \Delta\nu_{\text{solvent}}) \\ = \frac{1}{\tau_m} * \frac{\Delta\omega_m^2}{\tau_m^{-2} + \Delta\omega_m^2}$$

- Eyring Equations:

$$(2a) \quad \frac{1}{\tau_m} = k_{ex} = \frac{k_b * T}{h} * \exp\left(\frac{\Delta S^\ddagger}{R} - \frac{\Delta H^\ddagger}{R * T}\right)$$

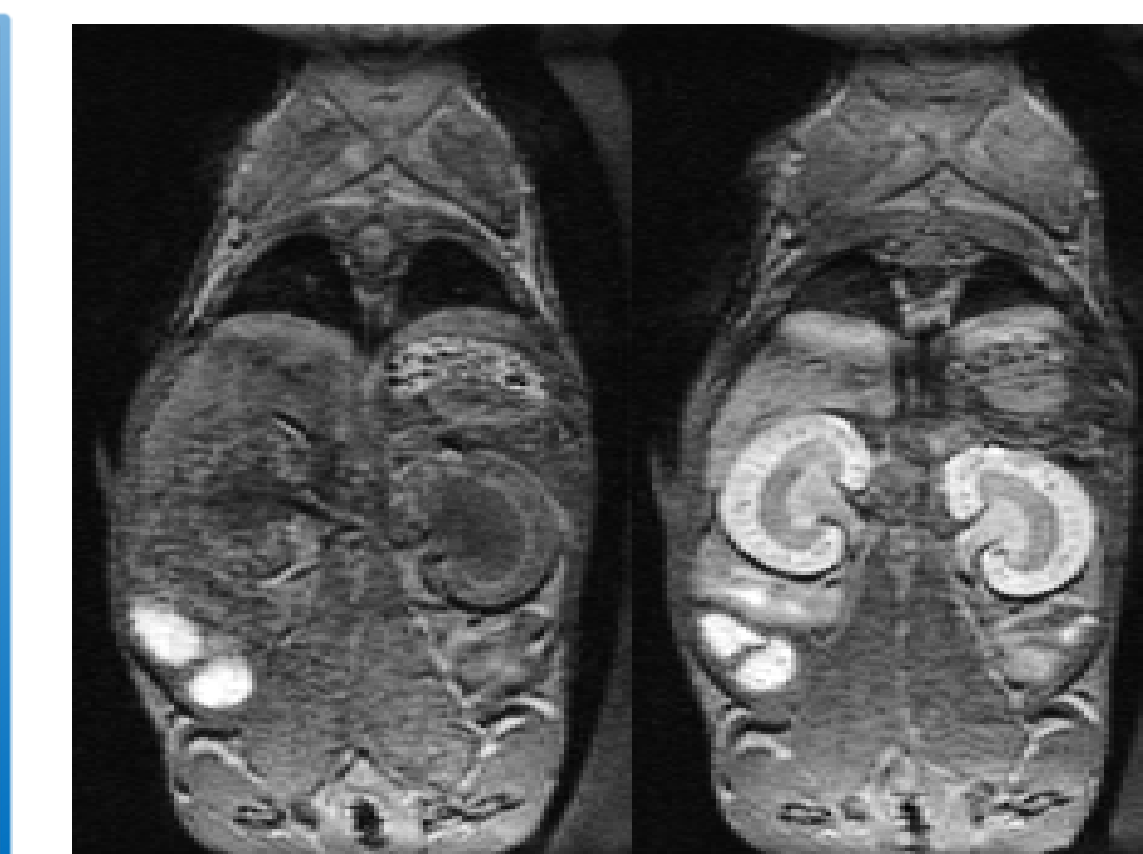
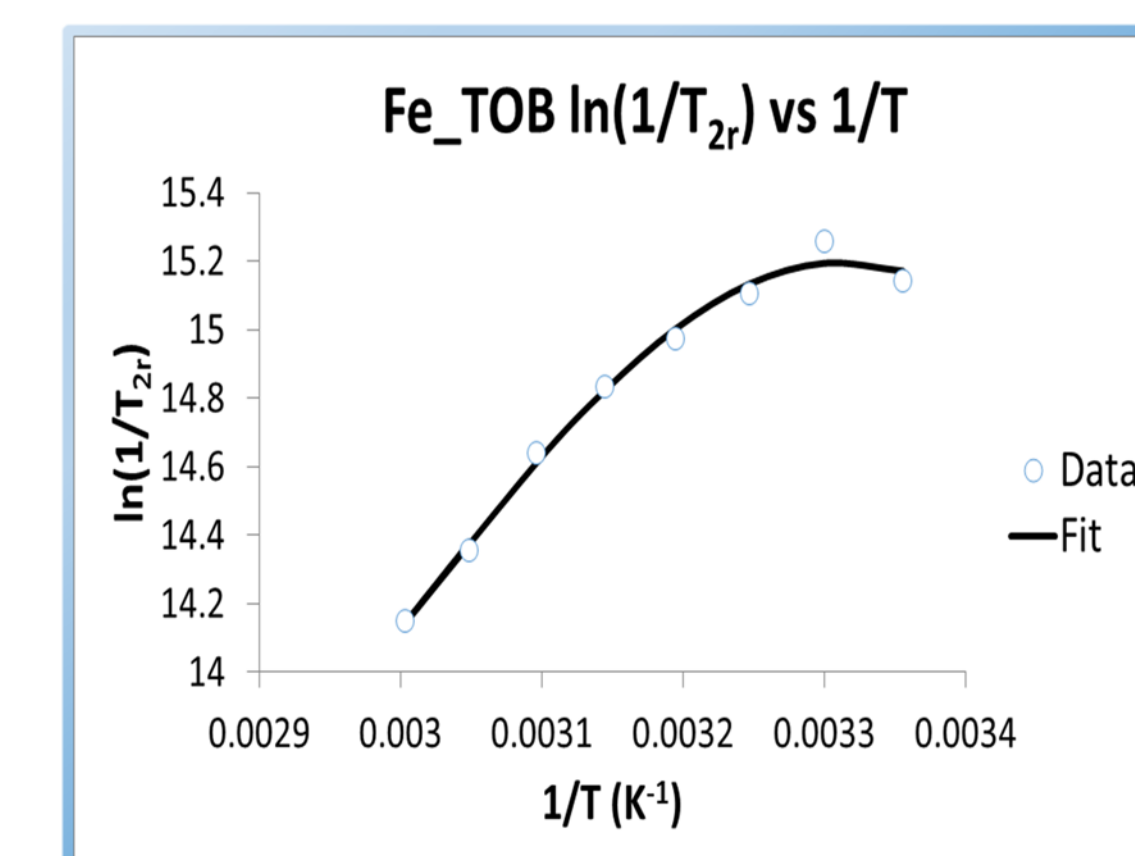
$$(2b) \quad \frac{1}{\tau_m} = k_{ex} = \frac{k_{ex}^{298}}{298.15} * T * \exp\left(\frac{\Delta H^\ddagger}{R} * \left(\frac{1}{298.15} - \frac{1}{T}\right)\right)$$

- Bloembergen Equations:

$$(3a) \quad \Delta\omega_m = \frac{g_L \mu_B S(S+1)B}{T} \left(\frac{A}{\hbar}\right)$$

$$(3b) \quad \Delta\omega_m = \frac{C}{T}$$

Results and Discussion:



- Fitting (left) of variable temperature ¹⁷O NMR shifts show an excellent fit of data points to equations 1b, 2b, and 3b
- *in vivo* MRI images before (center right) and after (right) contrast agent administration show a clear generation of contrast in the kidneys after 30 minutes

Conclusions:

- Iron agents generated kidney contrast, which was a desired result
- Fitting method was proven to be effective and reliable for modelling and activation parameter determination with the compounds tested
- k_{ex} was determined to be $15(\pm 2) * 10^5 \text{ s}^{-1}$
- Further studies and modeling of additional Fe(III) contrast agents are underway.
- Toxicology and pharmacology studies are warranted

References:

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