Contrast Agents in Magnetic Resonance Imaging

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Reasons for using contrast agents

- We need contrast to see structures
- Sometimes it's difficult to distinguish between different types of structures
What are contrast agents?

- Injected before MRI scan
  - Transportable
  - Region of interest
- Modify relaxation times
- Enhanced contrast
Basics

- 70% $\text{H}_2\text{O}$
- $B_0 (1.5 - 3) \text{T}$ aligns spins $\rightarrow M_z$
- Larmor frequency $\omega_0 = \gamma \cdot B_0$
- High frequency impulse $B_{\text{HF}}$ @ (5-100)MHz
$T_1$ Relaxation Time

- Recovery time of $M_z$
- Energy loss to lattice
- Spin-lattice Relaxation
- $T_1 = (0.5-5)s$
\( T_2 \) Relaxation Time

- Loss of \( M_{xy} \) coherence
- Energy exchange between spins
- Spin-Spin Relaxation
- \( T_2 = (1-200) \) ms
What can we do with the relaxation times?

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>$T_1$ value in ms</th>
<th>$T_2$ value in ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood (deoxygenated)</td>
<td>1350</td>
<td>50</td>
</tr>
<tr>
<td>Whole blood (oxygenated)</td>
<td>1350</td>
<td>200</td>
</tr>
<tr>
<td>Gray matter of cerebrum</td>
<td>920</td>
<td>100</td>
</tr>
<tr>
<td>White matter of cerebrum</td>
<td>780</td>
<td>90</td>
</tr>
<tr>
<td>Liver</td>
<td>490</td>
<td>40</td>
</tr>
<tr>
<td>Kidneys</td>
<td>650</td>
<td>60-75</td>
</tr>
<tr>
<td>Muscles</td>
<td>860-900</td>
<td>50</td>
</tr>
</tbody>
</table>
\( T_1 \)-weighted

- Short TR
  - different amounts of recovery
- Short TE
  - minimizes effect of \( T_2 \)
- Short \( T_1 \)
  - bright signal
$T_2$-weighted

- **Long TR**
  - minimizes effect of $T_1$

- **Long TE**
  - different amounts of decay

- **Short $T_2$**
  - dark signal
Perfect contrast agents

goes where you want it
not toxic
Large change in relaxation time
Contrast agents

- **T<sub>1</sub> contrast agents**
  - Positive agents
  - Shorten T<sub>1</sub> time
  - Increase signal
  - T<sub>1</sub> weighted images
  - Paramagnetic
  - Gadolinium Gd<sup>3+</sup>

- **T<sub>2</sub> contrast agents**
  - Negative agents
  - Shorten T<sub>2</sub> time
  - Decrease signal
  - T<sub>2</sub> weighted images
  - Ferro- or superparamagnetic nanoparticles
  - Magnetite Fe<sub>3</sub>O<sub>4</sub>
$T_1$ Contrast Agents

- Way to influence the water molecules

- Fluctuating field at Larmor frequency
  - Relaxation occurs

- Energy exchange Proton ↔ Lattice

- Normally: Protons
$T_1$ Contrast Agents

- Better way: Electrons
  - 660 times more powerful
- Gadolinium: 7-unpaired electrons
- 1 Million water molecules per second
- Gadolinium is toxic
- Use Gd chelates
- Stable complex
- Eliminated via the kidneys
T₂ contrast agents

- Iron Oxides
  - Magnetite Fe₃O₄

- Produce dark spots

- Superparamagnetic nanoparticles
Why so big?

1.5nm

Ferromagnetic or superparamagnetic particle

5nm - μm
$T_2$ contrast agents

- Protons with $\omega_L$
- Proton with $\omega_L + \Delta \omega$
- Proton with $\omega_L$ again but with phaseshift
- Out of phase

Strong magnetic field

Ferromagnetic or superparamagnetic particle

5nm - µm
Classification of nanoparticles

- Ultra-small superparamagnetic iron oxide nanoparticles USPIONs
- Superparamagnetic iron oxide nanoparticles SPIONs
- Micron-sized particles of iron oxide MPIO
Clearance

USPIOs

"long" circulation in the blood

(50-150)nm

SPIONs

smaller than 5nm

larger than 200nm
SPIONs

- ~200nm
- Uptake by phagocytic cells (Kupffer cells)
- Contrast between normal and abnormal tissue
USPIONs
How can we improve nanoparticles

- Before: biological distribution
  - Fate depends on: size, surface
  - Uptake by macrophages

- Now: “invade” the tumor cells
  - Need to optimize the nanoparticles
  - Long blood circulation

- “Stealthiness”
Coating

• Remember: superparamagnetic particles

• But Van der Waals forces

• e.g. Stabilize particle with Polymers
  – Reduce uptake by macrophages
  – Longer circulation

end-grafted

fully encapsulated
Multifunctionality

- Fluorophore
- Polymer Coating
- Therapeutic Agent
- MNP Core
- Permeation Enhancer
- Targeting Agent
Active Targeting

- Leaky blood vessels
- Targeting agents
  - open the door
- Releasing of therapeutic agent
- Destroy the cell
Conclusion

- Two types of relaxation time $T_1/T_2$
- Contrast agents increase contrast
- Agents decrease relaxation times
  - $T_1$: Gadolinium
  - $T_2$: Magnetite nanoparticles
- Size controls biodistribution
- Targeting contrast agents

- Physics will not change

- Future lies in the hands of chemists
Thank you!
References

● Papers

Joan Estelrich, Maria Jesus Sanches-Martin, Maria Antonia Busquets (2015): “Nanoparticles in magnetic resonance imaging: from simple to dual contrast agents”, in International Journal of Nanomedicine, 10, 1727-1740.


● Videos

MRI Imaging and Contrast Agents: https://www.youtube.com/watch?v=w7OwvjPLeyY
Nanoscale MRI Contrast Agents: https://www.youtube.com/watch?v=vgK9RIJKOnE
MR Contrast Agents Relaxivity: https://www.youtube.com/watch?v=Osx8Ced9Eyw
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Backup
Spin-Echo sequence (backup)
Why Magnetite? (backup)

**Fe\textsubscript{3+}[Fe\textsubscript{3+}Fe\textsubscript{2+}]O\textsubscript{4}**

in short Fe\textsubscript{3}O\textsubscript{4}

1/3 of the iron ions are Fe\textsuperscript{3+} in A sites
2/3 of the iron ions are Fe\textsuperscript{2+} and Fe\textsuperscript{3+} (50/50) in B sites

**Fe\textsuperscript{3+} Tetrahedral**

**Fe\textsuperscript{3+} Octahedral**

**Fe\textsuperscript{2+} Octahedral**

\[ 4\mu_B \]

28 per unit cell
Active Targeting (backup)

- Leaky vasculatures
- Targeting agents
  - open the door
- Receptor-mediated endocytosis
- Endosome breaks up
- Releasing of therapeutic agent