Lecture #15
NMR Relaxation Properties of Blood

• Topics
  – Hemoglobin and red blood cells
  – Blood oxygenation
  – BOLD
  – Hemorrhage

• References
Blood

• What are the $T_1$ and $T_2$ of human blood in vivo?

\[ T_1 \approx 1550 \text{ ms} \]
\[ T_2 \approx 165 \text{ ms} \ (\text{fully oxygenated}) \]

• Relaxation of blood depends on variety of physical parameters…
  – Field strength
  – Temperature
  – Integrity of erythrocytes (red blood cells)
  – Hematocrit
  – Chemical state of hemoglobin in red blood cells (oxy-, carboxy-, deoxy-, met-)

• We’ll start by focusing on normal physiological parameters at typical imaging field strengths.
  – 37°C, intact red blood cells, ~ 45% hematocrit, 0.5 T - 4 T
  – A particularly interesting parameter is the O₂ saturation
Hemoglobin

- The hemoglobin molecule contains 4 iron atoms that reversibly bind to $O_2$, $H_2O$, and other small molecules.
- Hb derivatives
  - oxy-, deoxy-, met-hemoglobin, hemichromes, ferritin, and hemosidrin.
  - These derivatives have different magnetic and NMR relaxation properties.

Hemoglobin consists of two alpha ($\alpha$) and two beta ($\beta$) subunits, each containing an iron-containing heme group to which oxygen ($O_2$) may bind.

The heme group consists of an iron (Fe) ion surrounded by a heterocyclic porphyrin ring.

Coordination (bonding) sites for Hb iron.
Oxy- vs Deoxy-hemoglobin

Loss of O$_2$ causes…
1. Magnetic change
2. Conformation change

- Oxy-hemoglobin is diamagnetic, while deoxy-hemoglobin is paramagnetic (4 upaired e$^-$s)
- However, conformational change block access to water.
- Without binding, water-(unpaired e$^-$) dipole interactions are too weak to contribute to T$_1$ relaxation.
- However, unpaired electrons in deoxyhemoglobin do produce large magnetic susceptibility gradients.

Local field distortions due to deoxy-Hb within RBCs dephases nearby H$_2$O molecules increasing T$_2$ and T$_2^*$ relaxation.
Compartmentalization

- The susceptibility effects of deoxyhemoglobin depends on both blood vessel and red blood cell (RBC) geometry, as this influences the pattern of the field gradients.

We’ll start here, modeling a RBC containing deoxy-Hb as having a bulk susceptibility shift relative to the surrounding plasma.
Blood

- Plasma is 95% water + some dissolved proteins
- Solid element in blood are primarily red blood cells
- Hemoglobin (Hb) contained within the red blood cells.
- Arterial blood Hb: 95/5 oxy/deoxy-hemoglobin
- Venous blood Hb: ~70/30 oxy/deoxy-hemoglobin

Water freely diffuses between the extra- and intra-cellular spaces
Blood $T_2$: Diffusion and Exchange

- In the deoxygenated state, the diffusion of water between plasma and erythrocytes results in dephasing and $T_2$ shortening.
- General model also includes diffusion through gradients

\[
\frac{1}{T_{2b}} = \frac{1}{T_{2o}} + \frac{1}{T_{2d}}
\]

Deoxygenation effect
- Exchange across erythrocyte membrane
- Diffusion through gradients within erythrocyte

$\tau_{ex} \approx 8 - 10$ ms  \hspace{1cm} $\Delta \omega \approx 1$ ppm

(fully deoxygenated blood)

Blood $T_2$ at 100% O$_2$ sat
Measuring the $T_2$ of Blood

Luz-Meiboom model:

\[
\frac{1}{T_{2b}} = \frac{1}{T_{2o}} + \frac{1}{T_{2d}} = \frac{1}{T_{2o}} + P_a (1 - P_a) \left[ \left( 1 - \frac{\%O_2}{100} \right) \alpha \omega_0 \right]^2 \tau_{ex} \left( 1 - \frac{2\tau_{ex}}{\tau_{180}} \tanh \frac{\tau_{180}}{2\tau_{ex}} \right)
\]

- Fraction of protons at one of the sites under exchange
- Dimensionless constant involving susceptibility of deoxyhemoglobin and RBC geometry

Want time between 180s, $\tau_{180}$, to be on the order of $\tau_{ex}$.
Estimating Oxygen Saturation of Blood in Vivo with MR Imaging at 1.5 T

Graham A. Wright, MSc • Bob S. Hu, MD • Albert Macovski, PhD

Table 2

<table>
<thead>
<tr>
<th>Subject</th>
<th>T2o (msec)*</th>
<th>τ180 (msec)</th>
<th>T2b (msec)</th>
<th>%HbO2</th>
<th>Aorta T2b (msec)</th>
<th>%HbO2</th>
<th>Superior Vena Cava T2b (msec)</th>
<th>%HbO2</th>
<th>Pulmonary Trunk T2b (msec)</th>
<th>%HbO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>224</td>
<td>6</td>
<td>223</td>
<td>97*</td>
<td>185</td>
<td>74</td>
<td>202</td>
<td>81</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>243</td>
<td>12</td>
<td>242</td>
<td>97*</td>
<td>175</td>
<td>75</td>
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<td>213</td>
<td>97*</td>
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<td>180</td>
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<tr>
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<td>194</td>
<td>97*</td>
<td>139</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>277</td>
<td>24</td>
<td>274</td>
<td>97*</td>
<td>171</td>
<td>77</td>
<td>186</td>
<td>79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* T2o chosen so that %HbO2 = 97% for blood in aorta for minimum τ180 used.
MR Oximetry

King C. P. Li, MD, FRCP (C) • Graham A. Wright, PhD2 • Lorie R. Pelc, PhD • Ronald L. Dalman, MD • Jean H. Brittain, MSEE • Herbert Wegmueller, MD3 • David T. Lin, BS • Curtis K. Song, BS

Radiology 1995; 194:321–325

Oxygen Saturation of Blood in the Superior Mesenteric Vein: In Vivo Verification of MR Imaging Measurements in a Canine Model

[Diagram of blood flow and measurement points]
Flow-independent Angiography

Application: deep vein thrombosis (DVT)
The BOLD Effect

• Blood Oxygen Level Dependent (BOLD) contrast generated via the relative amounts of oxy- and deoxyhemoglobin

• Is BOLD a $T_2$ or $T_2^*$ effect?

Anoxic mouse brain

– Large field inhomogeneities generated by deoxyhemoglobin within red blood cells
– These field gradients within the diffusion distance of water shorten blood $T_2$.
– In addition, field variations around deoxygenated blood extend well beyond the boundary of the blood vessels, resulting in $T_2^*$ shortening.

fMRI
T₂ and Diffusion

- Consider a single spherical magnetic inhomogeneity.

\[ \tau_D = \frac{R^2}{D} \quad \text{and} \quad \delta \omega = \gamma B_{eq}(R) \]

- Relative values of parameters determine effect on T₂ relaxivity.

- Examples
  - “Motionally averaged”: \( \delta \omega \tau_D \ll 1 \)
    \[ R_2 \approx 16\tau_D (\delta \omega)^2 / 135 \]
  - “Static”: \( \delta \omega \tau_D \gg 1 \)
    \[ R_2 \approx \left( \gamma \sigma_G^2 \right) D / 12 \]
  - “Intermediate”: \( \delta \omega \tau_D = 1 \)
SE vs GRE

- Previously we considered the effects of changing $\delta \omega$ (e.g. SPIOs vs Dy-DTPA); now let’s look at size effects.
- For a fixed diffusion coefficient, $D$, $\tau_D$ scales as $R^2$.
- Consider a spin-echo (SE) vs gradient-echo (GRE) acquisition. Assuming a Gaussian field distribution, one can show:

  - GRE: larger $R$ leads to increase $T_2$ relaxivity.
  - SE: $T_2$ relaxivity driven by long $\tau_D$ (i.e. large $R$) is refocused.

**FIG. 4.13.** A plot of Eq. 17 showing spin echo and gradient echo relaxation rates as a function of the correlation time, for a specific set of geometric variables: capillary diameter 5 $\mu$m, TE = 50 ms, and a field deviation of 0.75 mG.

**T₂⁻ vs T₂⁺-fMRI**

- For GRE images, large vessels are more efficient at increasing T₂ relaxivity, hence will dominate the typical GRE-based fMRI study.
- Although less sensitive, SE-fMRI better highlights small vessels as well as recovers signal from regions with poor homogeneity.

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Chiacchiaretta, et al., PLOS ONE | DOI:10.1371/journal.pone.0120398 March 6, 2015

“…Although less sensitive to BOLD functional signal, SE sequences have been proposed as a potential alternative to obtain increased functional localisation to the capillary bed, because static dephasing effects affecting the extravascular contribution around larger vessels are refocused by the 180° radiofrequency pulse...”

GE and SE functional connectivity maps, showing the following resting state networks: default mode network (DMN), executive control network (ECN), salience network (SN), dorsal attention network (DAN), sensorimotor network (SMN).
MRI of Hemorrhage: Overview

- Hemorrhage: escape of blood from vessels into surrounding tissues
- Collection of clotted blood is called a hematoma
- Appearance of hemorrhage on MRI is multifactorial
  - Hemoglobin chemical state
  - Microscopic structure of hematoma
- Hemorrhage constituents change over time

Complex changes in MRI contrast
MRI of Hemorrhage: Overview

**Oxyhemoglobin**
Hyperacute hemorrhage (<12 hr)
0 unpaired electrons - Diamagnetic
T1 (iso), T2/FLAIR (bright)
GRE (variable), DWI (bright)

**Deoxyhemoglobin**
Acute hemorrhage (12 hr - 2 d)
4 unpaired electrons - Paramagnetic
T1 (iso), T2/FLAIR (dark)
GRE (dark), DWI (dark)

**Methemoglobin (Intracellular)**
Early subacute hematoma (2 d - 1 wk)
5 unpaired electrons - Paramagnetic
T1 (bright), T2/FLAIR (dark)
GRE (dark), DWI (dark)

**Hemichromes**
Chronic hematoma center (> 1-2 mo)
0 unpaired electrons - Diamagnetic
T1 (dark), T2/FLAIR (bright)
GRE (bright), DWI (variable)

**Methemoglobin (Extracellular)**
Late subacute hematoma (1 wk - 2 mo)
5 unpaired electrons - Paramagnetic
T1 (bright), T2/FLAIR (bright)
GRE (bright), DWI (bright)

**Ferritin/Hemosiderin**
Chronic hematoma periphery (>1-2 mo)
$10^5$-$10^6$ unpaired electrons - Superparamagnetic
T1 (bright), T2/FLAIR (dark)
GRE (dark), DWI (dark)
• The electronic configuration of iron differs among the various hemoglobin species and is primarily responsible for their overall MR properties. The valence state – ferrous (Fe$^{+2}$) or ferric (Fe$^{+3}$) – is irrelevant; what matters is the number of unpaired electrons in the entire molecule.

• The magnetic susceptibility ($\chi$) is proportional to $N(N+2)$, where $N =$ the number of unpaired electrons.

• The $T_2$ relaxation rate, in turn, is proportional to the square of the magnetic susceptibility ($\chi^2$).
Hyperacute Hemorrhage: Oxyhemoglobin

- Hyperacute hematoma (<12 hr) consists of clotting RBCs with oxy-Hb predominant
- Dexoy-Hb formation starts to occur around the hematoma's periphery.

<table>
<thead>
<tr>
<th>MR Sequence</th>
<th>Hyperacute Hematoma Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1</strong></td>
<td>Isointense (to normal brain)</td>
</tr>
<tr>
<td></td>
<td>Central portions of hematoma with highest hematocrits may appear slightly hyperintense. Areas containing mostly serum, often at periphery, may be slightly hypointense.</td>
</tr>
<tr>
<td><strong>T2/FLAIR</strong></td>
<td>Mildly hyperintense</td>
</tr>
<tr>
<td></td>
<td>Areas with highest hematocrits may be isointense; pools of serum may be moderately to markedly hyperintense.</td>
</tr>
<tr>
<td><strong>GRE/SWI</strong></td>
<td>Hypointense rim due to early deoxy-Hb formation at periphery</td>
</tr>
<tr>
<td></td>
<td>Hypointense region may be more extensive in venous origin hematomas and in arterial hematomas several hours old.</td>
</tr>
<tr>
<td><strong>Diffusion</strong></td>
<td>Hyperintense (on DWI), hypointense (on ADC map)</td>
</tr>
<tr>
<td></td>
<td>Serum-containing areas are more “water-like” without diffusion restriction. Susceptibility artifact from deoxy-Hb may be seen at brain/hematoma interface.</td>
</tr>
</tbody>
</table>
Hyperacute Hemorrhage: Oxyhemoglobin

- Oxyhemoglobin is diamagnetic.
- Hematoma core is isointense to white matter on the $T_1$-weighted image.
- Mildly hyperintense on the $T_2$-weighted image representing oxy-hemoglobin.
- Some clot retraction has occurred with a hyperintense peripheral halo on the $T_2$-weighted image likely from edema.
- Even at this early stage, some transition to deoxyhemoglobin in the rim leads to hypointensity on the GRE image.
- DWI and ADC image shows restricted diffusion in the hematoma center due to reduced extracellular space and increased viscosity.
Acute Hemorrhage: Deoxyhemoglobin

- Acute hematoma (12 hr – 2 days) contains clotted RBCs with deoxy-Hb predominant, with deoxy-Hb forming in the periphery and spreading inward.
- Paramagnetic deoxy-Hb produces susceptibility-induced distortions of the local magnetic field, and water diffusion through these field variations induced T_2/T_2^* relaxation.
- Globin proteins inhibit water molecule access to the paramagnetic Fe^{2+}, hence outer sphere relaxation predominates, resulting in strong effects on T_2 with little or no change in T_1.

<table>
<thead>
<tr>
<th>MR Sequence</th>
<th>Acute Hematoma Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Isointense (to normal brain)</td>
</tr>
<tr>
<td></td>
<td>H_2O molecules cannot approach the paramagnetic centers of deoxy-Hb sufficiently closely for efficient T1 relaxation.</td>
</tr>
<tr>
<td>T2/FLAIR</td>
<td>Hypointense</td>
</tr>
<tr>
<td></td>
<td>Powerful paramagnetic effects of deoxy-Hb distort local fields around RBCs, causing accelerated dephasing and prominent T2-signal loss. (Halo of T2-bright edema may be seen in adjacent brain due to irritant effects of blood products.)</td>
</tr>
<tr>
<td>GRE/SWI</td>
<td>Hypointense</td>
</tr>
<tr>
<td></td>
<td>T2*-dephasing due to deoxy-Hb (same as for T2/FLAIR)</td>
</tr>
<tr>
<td>Diffusion</td>
<td>Hypointense (on both DWI and ADC maps)</td>
</tr>
<tr>
<td></td>
<td>Diffusion is actually restricted, but paradoxically dark appearance on DWI is a susceptibility artifact known as “T2-blackout”</td>
</tr>
</tbody>
</table>
Acute Hemorrhage:
Deoxyhemoglobin

- 18 hrs post hemorrhage.
- Hematoma isointense on T\textsubscript{1}.
- Strongly hypointense on T\textsubscript{2} and T\textsubscript{2}-FLAIR.
- Hyperintense peripheral halo on the T\textsubscript{2}-weighted image due to edema.
- Hypointensity on GRE due to T\textsubscript{2}* dephasing from deoxy-Hb confined in RBCs.
- DWI and ADC image shows dark center due to T\textsubscript{2}-blackout effect.
- Susceptibility artifacts (speckling) complicate ADC calculations.
Subacute Hemorrhage: Methemoglobin

- The early subacute phase (2 days - 1 week) is characterized by intracellular met-Hb.
- Fe$^{2+}$ to Fe$^{3+}$ transition induces crevices in the globin subunits allowing binding of water, driving inner sphere T$_1$ relaxation.
- met-Hb continues to be compartmentalized within the RBCs, and local magnetic susceptibility effects continue to drive T$_2$/T$_2^*$ relaxation.

(Aquo)-methemoglobin: the only blood product with short T$_1$
Subacute Hemorrhage: Methemoglobin

- 3 days post hemorrhage.
- Hematoma hyperintense on $T_1$ due met-Hb.
- Center strongly hypointense on $T_2$.
- Hyperintense peripheral halo on the $T_2$-weighted image due to edema.
- GRE shows even greater hypointensity in periphery due to accumulation of ferritin and hemosiderin.
- DWI and ADC image have dark centers due to $T_2$-blackout effect.
Intracellular vs Extracellular Methemoglobin

• Late subacute hematoma (~1 week and 2 months) characterized by lysis of RBCs.
• Inner sphere relaxation of met-Hb results in short $T_1$ values.
• Intracellular met-Hb has short $T_2/T_2^*$ due to strong local susceptibility-induced field distortions.
• Lysis of RBCs leads to uniformly distributed met-Hb, minimizing susceptibility effects. Local $T_2/T_2^*$-dephasing effects disappear and the hematoma now becomes bright on $T_2$ weighted images.

<table>
<thead>
<tr>
<th>MR Sequence</th>
<th>Late Subacute Hematoma Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Hyperintense (to normal brain)</td>
</tr>
<tr>
<td></td>
<td>$H_2O$ molecules have inner-sphere access to extracellular methemoglobin and its 5 unpaired electrons with resultant $T_1$ shortening.</td>
</tr>
<tr>
<td>T2/FLAIR</td>
<td>Hyperintense</td>
</tr>
<tr>
<td></td>
<td>Met-Hb is distributed uniformly in the water-containing extracellular hematoma cavity after RBC lysis. $T_2$-signal loss in early subacute hematoma stage due to intracellular compartmentalization of met-Hb has disappeared.</td>
</tr>
<tr>
<td>GRE/SWI</td>
<td>Hyperintense center, hypointense periphery</td>
</tr>
<tr>
<td></td>
<td>Center of hematoma is bright due to long $T_2$ of dissolved met-Hb. Periphery of hematoma is dark due to $T_2^*$-dephasing from superparamagnetic effects of accumulating ferritin/hemosiderin.</td>
</tr>
<tr>
<td>Diffusion</td>
<td>Hyperintense on DWI, iso- to hyperintense on ADC</td>
</tr>
<tr>
<td></td>
<td>Only slightly restricted diffusion remains (more than CSF, less than brain). Brightness on DWI is mostly &quot;$T_2$-shine-through&quot;.</td>
</tr>
</tbody>
</table>
Intracellular vs Extracellular Methemoglobin

- 3 weeks post hemorrhage.
- Center of hematoma hyperintense on both $T_1$ and $T_2$ due extracellular met-Hb.
- GRE shows hypointensity in periphery due to accumulation of ferritin and hemosiderin.
- ADC map shows center of the hematoma is isointense or even slightly higher intensity than brain.
- Bright DWI likely “$T_2$-shine-through”.
- Both the DWI and ADC images have a dark peripheral ring due to susceptibility effects of ferritin/hemosiderin.
Chronic hematoma

• ~ 2 months post the initial hemorrhage.
• Original cavity has collapsed, surrounding reactive edema has disappeared, RBCs have completely lysed, hemoglobin species have degraded, and heme iron has been released and deposited in the surrounding tissues.
• Center of old hematomas are water-like with long $T_1$, $T_2$, and ADC values.
• Periphery contain large, chunky metalloprotein complexes known as ferritin and hemosiderin, deposited by macrophages.
• Outside the central nervous system they are also scavenged by reticulo-endothelial system (RES) cells of liver, lymph nodes, and bone marrow.
• Ferritin and hemosiderin are superparamagnetic, and water molecules diffusing through these gradients resultant in $T_2/T_2^*$ dephasing.
• The iron centers of ferritin and hemosiderin are sequestered and do not allow close approach of water for inner sphere relaxation. Hence only a minimal $T_1$ shortening occurs.
Hemichromes

• Met-Hb is oxidatively denatured to form hemichromes
• Hemichromes are weakly diamagnetic and do not significantly influence the MR signal
• Hemichromes subsequently break down releasing free iron scavenged by macrophages and collected as ferritin/hemosiderin.
Ferritin vs Hemosiderin

- Ferritin, the principal iron storage molecule found in animal cells, is a protein shell packed with hundreds to thousandths of iron particles.
- Hemosiderin is an aggregate of hundreds to thousands of ferritin particles plus amorphous proteins and lipids.
- Both a superparamagnetic and collected by macrophases/glia/RES cells.
- Both ferritin and hemosiderin give rise to marked $T_2/T_2^*$ shortening.

Ferritin is a hollow protein shell composed of 24 subunits. Two subunits have been removed to allow visualization within the core where up to 4500 iron atoms can be stored.

Clumping of ferritin particles with amorphous protein to form hemosiderin aggregates.

Dark hemosiderin granules in Kupffer liver cells (Prussian blue stain).
Chronic hematoma

6 months post hemorrhage

CT  T₁  T₂

GRE  DWI  ADC

<table>
<thead>
<tr>
<th>MR Sequence</th>
<th>Chronic Hematoma Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T₁</strong></td>
<td>Hypointense center (compared to normal brain)</td>
</tr>
<tr>
<td></td>
<td>Reflects long T₁ values since old hematoma center is mostly H₂O with some dissolved proteins. Occasionally will be iso- or hyperintense if residual met-Hb or Fe^{2+} ions remain in solution (more common in subdural hematomas).</td>
</tr>
<tr>
<td><strong>T₂/FLAIR</strong></td>
<td>Hyperintense center</td>
</tr>
<tr>
<td></td>
<td>Reflects long T₂ values due to high H₂O content centrally. Periphery usually dark due to fibrotic response and T₂/T₂* shortening from hemosiderin.</td>
</tr>
<tr>
<td><strong>GRE/SWI</strong></td>
<td>Markedly Hypointense periphery</td>
</tr>
<tr>
<td></td>
<td>Dramatic T₂*-dephasing due to dense concentration of superparamagnetic ferritin and hemosiderin.</td>
</tr>
<tr>
<td><strong>Diffusion</strong></td>
<td>Hypo-/hyper-intense center (on DWI/ADC respectively)</td>
</tr>
<tr>
<td></td>
<td>High water content center shows only mildly restricted diffusion due to protein or fibrin. Periphery may be artifically hypointense due to “T₂-blackout” susceptibility artifact.</td>
</tr>
</tbody>
</table>
Next Lecture:
Cartilage