Methodology and applications of MRI with hyperpolarized C-13 and He-3 contrast agents

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Disclosures

• Hyperpolarized gases and $1^{-13}\text{C}$ Pyruvate are categorized by the FDA as investigational new drugs

• Consultant and Grantee of GE Healthcare, owner of the IP for the medical use of DNP and SEOP polarized agents
Outline

• Background
  – Hyperpolarization
  – Consequences

• Spin relaxation mechanisms
  – T1 relaxation mechanisms
    • Hyperpolarized Noble Gases
    • Hyperpolarized $^{13}$C Metabolites

• Correcting/exploiting signal decay mechanisms for imaging
  – Flip angle decay and correction
  – Oxygen induced decay and mapping
  – Diffusion signal decay
  – $^{13}$C compounds and metabolic imaging
Severe Gas Trapping in Asthma Subject

FEV1%pred = 94
RV/TLC = 0.27
(TLC - FVC) / TLC = 0.30

Gas trapping on MRI: left upper, lower lobe
right lower lobe

Abnormal MDCT: left upper, lower lobe
right upper, lower lobe

Ventilation defect score = 29
Tissue Susceptibility in the Lungs

\[ \frac{1}{T_2} \propto \eta \cdot \gamma \cdot \Delta \chi \cdot B_0 \]

\[ \eta = 1 - \frac{\rho_{\text{lung}}}{\rho_{\text{tissue}}} \]
Collaborations

- Department of Neurosurgery
  - Dr. Paul Clark
  - Tumor initiation by cancer stem cells isolated from glioblastoma multiforme
  - 22 CSC-LAP resistant (P4) MG1

Cage 1, Ear 1
T2 only, 1-5-2011
(2 weeks post-injection)

Injected 12-15-2010, MRI (T1-Gd enhanced) 2-8-2011
P4, 2x10^5 cells injected
Spectroscopic Imaging in Brain Glioma Model

Reference  Pyruvate  Lactate  Lactate/Pyruvate
Fig. 4. (A) $^{13}$C spectrum of urea (natural abundance $^{13}$C) hyper polarized by the DNP-NMR method. The concentration of urea was 59.6 mM, and the polarization was 20%. (B) Thermal equilibrium spectrum of the same sample at 9.4 T and room temperature. This spectrum is acquired under Ernst-angle conditions (pulse angle of 13.5° and repetition time of 1 s based on a $T_1$ of 60 s) with full $^1$H decoupling. The signal is averaged during 65 h (232,128 transients).

Golman et al. 2001
Hyperpolarization vs. Equilibrium Processes

• Definition of Polarization

\[ P_N = \frac{|N_+ - N_-|}{N_+ + N_-} = \frac{|N_+ - N_-|}{N} \]

• Polarization due to Boltzmann distribution for thermal equilibrium:

\[ P_B = \tanh \left( \frac{\gamma \hbar B_0}{2 k_B T} \right) \]

“Brute Force”:
- Increase field strength
- Increase N,
- Decrease T

Imaging of H-1
\[ P_N = P_{\text{Boltz}} \sim 10^{-6} \]

Increase polarization externally
Hyperpolarization Physics

- Increases net polarization up to 100,000 times thermal equilibrium
- Multiple approaches
  - Noble gas
    - Metastability exchange
    - Spin exchange optical pumping
  - Solid-State
    - Para-hydrogen induced polarization (PHIP)
    - Dynamic nuclear polarization (DNP)
Nuclear Magnetic Dipole Moment

Hydrogen

Helium

Helium-3
Polarized Gases: $^3\text{He}$ or $^{129}\text{Xe}$

**Spin-exchange optical pumping**

- **Cell Pressure:** 8 Atm
- **Cell Temperature:** ~160 °C
- **Laser Power:** ~40 W
- **Polarization:** 1-1.5 Liters @ 30-40% polarization in 18 hours

Walker and Happer, Reviews in Modern Physics, 1997
Spin-exchange optical pumping

Optical Pumping on Rb

Collisional Mixing

$m_J = -1/2$  $m_J = 1/2$

$2R_p$

$50\%$

$m_S = -1/2$  $m_S = 1/2$

$2S_{1/2}$

Quenching by $N_2$

Polarization Transfer

$H_a = A_a \mathbf{I}_a \cdot \mathbf{S} + g_s \mu_B S_z B_0 - \frac{\mu_a}{I_a} I_{ac} B_0$

Walker and Happer, Reviews in Modern Physics, 1997

Polarized Gases: $^3$He or $^{129}$Xe
Dynamic Nuclear Polarization (DNP): Solid State Hyperpolarization

- Hyperpolarization
  - Electron Polarization
    - $P_e = 92\%$ at $\sim 1.4K$
  - $^{13}C$ nuclei are very poorly polarized.
    - $^{13}C : P_c = < 0.06\%$ @ 1.4K, 3.35T
  - Irradiation at ESR freq $\sim 94$GHz (100mW)
- Carbon Polarization
  - $P_c = 20\text{-}30\%$

Ardenkær-Larsen et al. 2003
Dynamic Nuclear Polarization (DNP)

Coupled Energy States

Absorbance for Microwave Frequency Sweep

Farrar et al., Journal of Magnetic Resonance, 2000
DNP is versatile

- Can polarize $^{15}\text{N$, }^{1}\text{H, }^{13}\text{C}$
- Variety of $^{13}\text{C}$-labelled compounds:
  - $^{13}\text{C}$ Urea
  - $^{13}\text{C}_1$ Pyruvate, $^{13}\text{C}_2$ Pyruvate
  - $^{13}\text{C}_{1,4}$ Succinate
  - $^{13}\text{C}$ Bicarbonate...
Prototype Commercial SEOP System at UW-Madison

Vessel Containing He-3

Syringe System

HeliSpin, GE Healthcare
Prototype DNP System

- 3.35 Tesla, ~1.4 Kelvin, ~94 GHz irradiation, $e^-$ donor

- Rapidly warmed from 1.4K (dissolution) to 37°C
  - 30µl warmed using 4ml EDTA solution
  - Injected intravenously
Xenon-129 Polarizer Technology

- Fully automated operation with on-board diagnostics and data logging
- 50% polarization of two liters into four bags every twenty minutes
- Fast-track for FDA approval
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• **Correcting/exploiting signal decay mechanisms for imaging**
  – Flip angle decay and correction
  – Oxygen induced decay and mapping
  – Diffusion signal decay
  – $^{13}$C compounds and metabolic imaging
Classical Model of MRI: Magnetic Moments

Evolution of “ensemble” signal governed by T1 and T2 Relaxation
T1 Decay of Hyperpolarized Agents

- Non-equilibrium signal decays away at rate $1/T_1$
  - Not generated by the principal field, $B_0$ so signal to noise is largely independent of $B_0$
  - Once consumed, polarization does not recover
T1 Decay for Polarized Agents

After $t = T_1$, Signal is $\sim 37\%$

After $t = 2T_1$, Signal is $\sim 14\%$

Decay: $M_z(t) = M_{z,eq} e^{-kt/T_1}$

Recovery: $M_z(t) = M_{z,eq} (1 - e^{-t/T_1})$
T1 and T2 Decay in HP Gases

- T1 for $^3$He and $^{129}$Xe gas in the lungs is 20-30 s
  - Collisional interactions with O$_2$ (paramagnetic)

- Effective T2 shortened by diffusion and local susceptibility
Longitudinal Signal Decay

\[ M_z(n, \alpha) = M_o \cos^n(\alpha) \exp \left( -\frac{1}{\xi} \int_0^{nTR} \Gamma_{pO_2}(t) \, dt' \right) \]

\( n \) is the number of rf-pulses applied with flip angle \( \alpha \) and repetition time TR

\( \xi = 2.6 \text{ bar-s} \), and \( \Gamma_{pO_2} \) is the relaxation rate due to local pO\textsubscript{2}
T1 and T2 Decay in HP $^{13}$C Metabolites

- T1 varies widely depending on location in the molecule
  - Primarily dipole-dipole interactions*
  - Proximity to bound nuclei with magnetic moments shortens T1
  - Carbonyl, carboxyl or quaternary carbon positions (fumeric and pyruvic acid)
  - Deuterons

- T2 long in liquid state $\sim$4s

Where to $^{13}$C Label?

Example: Acetaminophen

<table>
<thead>
<tr>
<th>Carbon atom</th>
<th>T1 (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$30.11 \pm 2.41$</td>
</tr>
<tr>
<td>2, 6</td>
<td>$3.20 \pm 0.14$</td>
</tr>
<tr>
<td>3, 5</td>
<td>$3.04 \pm 0.14$</td>
</tr>
<tr>
<td>4</td>
<td>$26.77 \pm 2.40$</td>
</tr>
<tr>
<td>7</td>
<td>$37.44 \pm 4.85$</td>
</tr>
<tr>
<td>8</td>
<td>$6.86 \pm 1.46$</td>
</tr>
</tbody>
</table>
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Signal Decay Due to RF, Flip Angle

The graph shows the signal decay due to RF and flip angle over TR (time to repetition). The y-axis represents the signal intensity, ranging from 0 to 1000, and the x-axis represents TR ranging from 8 to 56. Two curves are plotted, one for 5° flip angle and another for 15° flip angle. The signal decreases as TR increases, indicating the decay effect of RF and flip angle on the signal intensity.
Impact on Resolution

Centric acquisitions in Rat Lungs

5 degrees

15 degrees
k-Space Acquisition

Phase
Encode

Sampled
Signal

DAQ

One line of k-space acquired per TR

Phase Direction

Frequency Direction
k-Space Signal
Flip angle optimization

Sample Times (s): 0.0, 3.6, 15.6, 43.9
Flip Angles (deg): 21.9, 34.2, 49.8, 90.0

<table>
<thead>
<tr>
<th>1D</th>
<th>2D 'equivalent'</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.9°</td>
<td>5.54°</td>
</tr>
<tr>
<td>34.2°</td>
<td>8.80°</td>
</tr>
<tr>
<td>49.8°</td>
<td>13.34°</td>
</tr>
<tr>
<td>90.0°</td>
<td>54.39°</td>
</tr>
</tbody>
</table>

Pyr

Lac
Variable Flip Angle

Increase the flip angle with TR:

- Current TR index, \( i \)
- \( N \) total TR’s

\[
\alpha_i = \text{atan}\left(\frac{1}{\sqrt{N-i}}\right)
\]

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HP He-3 MRI in Healthy Normal

Conventional MRI

He-3 MRI
Longitudinal Signal Decay

\[
M_z(n, \alpha) = M_o \cos^n(\alpha) \exp\left(\frac{-1}{\xi} \int_0^{nTR} \Gamma pO_2(t) dt'\right)
\]

Depolarization due to intermolecular interactions between O\textsubscript{2} and \textsuperscript{3}He:

Decay constant: \[\Gamma_{pO_2} = \frac{pO_2}{\xi}\] with \(\xi = 2.6\) bar\cdot s

Typical decay time: 13 s for \(pO_2\) of 200 mbar

Saam, Happer & Middleton; \textit{PRA} 52, 862 (1995)
Gas Exchange

- Ventilation/Perfusion Ratio
  - V/Q
  - Regulate gas exchange across the alveolar-capillary barrier

- Diffusion lung carbon monoxide (DLCO)

  Pulmonary perfusion

  Alveolar surface area (Emphysema)
Example Traces

\[ pO_2(t) = pO_2 - R t \]

- \( pO_2 = 100 \text{ mbar}, R = 0 \)
- \( pO_2 = 150 \text{ mbar}, R = 0 \)
- \( pO_2 = 200 \text{ mbar}, R = 0 \)
- \( pO_2 = 150 \text{ mbar}, R = -2 \text{ mbar/s} \)

Dependent on \( pO_2 \)

and

Dependent on ODR

Need large SNR
Multi-Slice Rabbit Data

Slice 1
Slice 2
Slice 3
Slice 4
Slice 5
Slice 6

Static 3He

V_A/Q

V_A/Q Hist

Counts
0 2 4 6 8 10 12
Counts
0 2 4 6 8 10 12
Counts
0 2 4 6 8 10 12
Counts
0 2 4 6 8 10 12
Counts
0 2 4 6 8 10 12
Counts
0 2 4 6 8 10 12

02/10/05
University of Pennsylvania
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Apparent Diffusion in Emphysema

ADC\textsubscript{Normal}

ADC\textsubscript{Diseased}

Leonhardt, 1986
Lung Microstructure

- Diffusion weighted imaging can provide structural information

Fain et al. Radiology 2006
Diffusion Weighting Gradient

Each measurement represents an entire volume

$q = \frac{\gamma G}{2\pi} (\delta - \varepsilon) \sqrt{\frac{\Delta - \delta / 3}{\Delta + \delta}}$

Correction term for $\delta \sim \Delta$.

Lori et at. JMR 2003
Retrospective Correction

Under-sampled acquisition

Projecions in plane

Diffusion Weighting

Projection number

Interleave DW

Use these unweighted images to correct for pO₂ and RF

q, mm⁻¹

0 0.18 0 0.35 0 0.54 0 0.73 0 0.91 0 1.1 0 1.3 0 1.5
RF and $T_1$ correction

RF and $pO_2$ are biggest sources of decay

Both vary spatially $\rightarrow$ pixelwise correction

Fit each pixel in the unweighted images to:\n
$$S_n = S_0 \ K^n$$

where,

$$K = \cos(\alpha) \ \exp(-TR/\ T_1)$$

Then correct all the images using the map of K.

\(^1\) Shanbhag et al. JMRI 2006
Regional Correction Map

Phantom validation

Methods

PVC and 290 μm acetal plates

Optical scan of plates

Photo of inside the phantom. End cap removed.

X<sub>RMS</sub> map

Single slice of 3D image

ROI X<sub>RMS</sub>

1390 (80) μm

126 (40) μm

Ideal X<sub>RMS</sub>

1373 μm

118 μm
Comparison of Diffusion Maps

Diffusion length $X_D$

9 year old
No asthma or HRV/wheeze

10 year old
Asthmatic

9 year old
HRV/wheeze before 3rd birthday

9 year old
Asthma & HRV/wheeze

175 μm

450 μm
Micro-Structure Dimension

$p = 0.009$

$p = 0.02$

$p = 0.004$

for equivalence of “both” and “neither”
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MR Spectroscopy and Chemical Shift Imaging (CSI)

Fourier Transform

Time domain

Frequency domain

FID $t$

FT

Pyruvate

Lactate

Alanine

Lac

Ala

Pyr

Spectrum
Chemical Shift Imaging (CSI)

3 spatial dimensions + spectral + time = 5 dimensions
IDEAL Results in Normal Liver (Mouse)

1 s scan
FOV = 10cm
Thickness = 2.5cm
TR = 25 ms
ΔTE = 0.74 ms
Multi-echo readout with flyback gradient, 10 echoes

Proton reference

Lactate x4
Pyr-H₂O x4

Alanine x4
Pyruvate
Gyromagnetic Ratio and Consequences

- $\gamma$ ratio of approximately 4 for carbon and proton:
  - $\gamma^{1}H = 42.576 \text{ MHz/T}$
  - $\gamma^{13}\text{C} = 10.705 \text{ MHz/T}$

- $k(t) = \gamma \int G(t) dt$

- Affects:
  - Detected signal strength
  - k-space navigation
  - RF excite profiles
Consideration: Field of View and $\gamma$

$\text{FOV} \ y = 1/\Delta ky$

$k(t) = \gamma \int G(t) \, dt$

X Gradient

Y Gradient
Radial was used to allow a large matrix size before the $^{13}$C γ reduction.

Multi echoes are acquired for spectral imaging.
Consideration: Reconstruction

Readout Trajectory  Proton k-space  FT  Proton Image

Carbon k-space  FT  Carbon Image

Applications: Motion Correction

Initial | Intermediate | Motion Corrected
---|---|---
Proton | | 
Carbon | | 

Simultaneous $^{1}$H/$^{13}$C Acquisition

- Sequential Gadolinium injection simultaneously affects $^{1}$H signal
  - Perfusion and vascularity
  - Gadolinium concentration (Cron, 1999)

\[ T_{1a} = \frac{-TR}{\ln \left( 1 - \frac{I_a}{I_b} \left( 1 - e^{-\frac{TR}{T_{1b}}} \right) \right) } \]

Dynamic image $I_a$
Known $T_1$ dynamic image $I_b$
Known $T_1$ map $T_{1b}$

Simplification from Cernicanu et al. 2006

Peterson, ISMRM 2010
Hyperpolarized $^{13}$C experiments

$$\text{Signal}_{\text{acquired}} = \text{Signal}_{\text{vasculature}} + \text{Signal}_{\text{extracellular}} + \text{Signal}_{\text{intracellular}}$$

*No contrast between compartments*

- Necessitates a simplified kinetic model with apparent rate constants
- Prohibits direct measurement of intracellular metabolism
Proposed approach: Isolating intracellular signal with gadolinium

- The decay rate of the $^{13}\text{C}$ spins will increase within the compartments containing Gd:
  - Vascular space in the brain
  - Vasculature and extracellular/extravascular space elsewhere

Inference of peaks from left to right:

1. intracellular lactate,
2. extracellular pyruvate hydrate,
3. intravascular pyruvate hydrate,
4. intracellular alanine,
5. extracellular pyruvate (the reference peak),
6. intravascular pyruvate, and
7. Urea reference material.
Hyperpolarized $^{13}$C has been applied to:

- Perform angiography with high contrast$^{1,2}$
- Measure pH in tumors$^3$
- Give indicator to treatment response$^6$
- Measure cardiac ischemia$^5$
- Measure cellular transport rates$^4$
- Display metabolic response to hypoxia$^4$

$^{1}$Mansson et al. 2006  $^{2}$Ishii et al. 2007  $^{3}$Gallagher et al. 2008  $^{4}$Harris et al. 2009  $^{5}$Golman et al. 2008  $^{6}$Day et al. 2007
Background on cellular metabolism

Oxidative vs. Anaerobic Glycolysis

Normal cells
- Oxidative Respiration (mitochondria)
- Glycolysis (cytosol)
- Aerobic Respiration

Tumor cells
- Glycolysis (cytosol)
- Anaerobic Respiration (cytosol)

Metabolic profile
- Normal cells: 60% Oxidative Respiration, 40% Glycolysis
- Tumor cells: 80% Glycolysis, 20% Anaerobic Respiration

Differentiated tissues
- In the presence of oxygen

Tumor cells
- In the absence of oxygen, with mitochondrial disorders

Mazurek, 2010
UCSF Press Release (RSNA)

“New prostate cancer imaging shows real-time tumor metabolism”
Improved approach: spectral spatial excitation

- Again, each species is alternately excited.
  - Pyruvate: 10° flip
  - Lactate: 30° flip

- New features
  - Spectral spatial excitation
  - Low bandwidth (2 kHz)
  - Centric encoding
  - 4 echoes (they’re free)

- Coronal 40 x 40 FOV
- 10 mm slice thickness
- 16 x 16 matrix
Images zero-filled to 128 x 128

- Note: Lactate was chemically shifted by $\frac{1}{4}$ FOV. Discontinuity in images reflects a corrective circular shift.
Imaging 7 days after left ureteral obstruction

- Images acquired at t = 20 seconds
- Mouse was fasted for 6 hours prior to imaging
Summary

• Hyperpolarized contrast agents provide multiple sources of contrast for functional studies
  – Noble gas applications to obstructive lung disease
  – $^{13}$C metabolites in cancer and other diseases of metabolism

• Challenging but increasing success in quantitative measurement of in vivo structure and function

• Increasing use in phenotyping disease and monitoring therapy, especially in the context of soft tissue anatomy
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Fain Lab 2010
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