Towards sub-second metabolic imaging of cancer using hyperpolarized MRI

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Hyperpolarization of Nuclear Spin Alignment

\[ P \equiv \frac{N_{1/2} - N_{-1/2}}{N_{1/2} + N_{-1/2}} \approx \frac{\gamma \hbar B_0}{2kT} \]

For example, $^{13}\text{C}$ polarization = $2.5 \cdot 10^{-6}$ or 2.5 ppm at 3 T

P~1 or 1,000,000 ppm can be achieved by several methods
Exponential Decay of Hyperpolarized State
Benefits of Hyperpolarized MR

- Better signal to noise (SNR) and contrast to noise (CNR)
- Better temporal resolution
- Low field MRI scanners potentially give more SNR \textit{in vivo}!
- Faster & potentially cheaper examinations
- Sub-second metabolic imaging
Hyperpolarization (HP) Techniques

- DNP
- Polarization transfer from hyperpolarized $^{129}$Xe

Hyperpolarized $^{13}$C, $^{15}$N, $^{31}$P, etc.

- PASADENA or PHIP
- SABRE

para-$\text{H}_2$
Motivation: Complementary to Positron Emission Tomography (PET) Imaging of Cancer

Agent injection ➔ Agent uptake ➔ Imaging
Metabolic tracers in HP MRI and PET

Hyperpolarized MR tracer
\( ^{13}\text{C}\text{-pyruvate}, {^{15}}\text{N}\text{-choline, etc})

uptake and metabolism

metabolite

PET tracer
\( ^{18}\text{FDG}, {^{11}}\text{C}\text{-choline, etc.})

uptake and metabolism

tracer & metabolites

Image separation by Chemical Shift (CS)

Reconstructed Image
Sub-second $^{13}$C MRI

In vivo $^{13}$C sub-second image (0.3 s) of a rat brain, acquired 9 s after close-arterial injection of 1 ml, 25 mM hyperpolarized succinate (in color). The $^{13}$C image was overlaid on a coronal 1H fast gradient echo image with matching field-of-view (FOV) and slice location acquired prior to infusion to provide anatomical correlation (3D FIESTA, TR/TE = 6.3/3.1 ms, 5 x 5 x 5 mm³ spatial resolution, FOV = 220 mm/320 mm, 44 phase encoding steps/64 readout points, respectively).


Hyperpolarized MRI of phantoms

Sub-second $^{13}$C images of a partially filled syringe with 2 mL of 3.6 mM hyperpolarized ($P = 3\%$) contrast agent. $t_{90^\circ} = 107 \mu$s was used in balanced fast field echo (bFFE) or fssfp on 4.7 T Varian scanner (Vanderbilt University). Parameters: 50 kHz bandwidth, FOV 64x64 mm, 2x2 mm in-plane resolution, 0.64 ms acquisition time, TR=2 ms, TE=1 ms, imaging time for each image is 65 ms.

in vitro @ 4.7 T: faster and better
## PET vs. hyperpolarized (HP) MRI (future)

<table>
<thead>
<tr>
<th></th>
<th>PET-CT</th>
<th>Hyperpolarized MRI</th>
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<tbody>
<tr>
<td>Radioactive</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ionizing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Scan time</td>
<td>~20 min</td>
<td>Short (&lt;1 min)</td>
</tr>
<tr>
<td>Tracer uptake time</td>
<td>Long (~1 hour)</td>
<td>Short (&lt;5 min)</td>
</tr>
<tr>
<td>Fasting</td>
<td>5-6 h</td>
<td>Potentially none</td>
</tr>
<tr>
<td>Same day follow-up scan</td>
<td>No</td>
<td>Multiple</td>
</tr>
<tr>
<td>Treatment efficacy evaluation</td>
<td>1 month</td>
<td>minutes-hours</td>
</tr>
<tr>
<td>Sub-second metabolic imaging</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cancer diagnostic accuracy</td>
<td>&gt;93%</td>
<td>???</td>
</tr>
</tbody>
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Lactate Dehydrogenase (LDH) Imaging: $^{13}$C MR of injected hyperpolarized 1-$^{13}$C-pyruvate

pyruvate (pyr) $\rightarrow$ lactate (lac)

figure adopted from
Sensitivity and Lifetime

NMR Receptivity $\sim \gamma^3$

Hyperpolarized NMR Receptivity $\sim \gamma^2$
Proton detection of $^{13}\text{C}/^{15}\text{N}$ hyperpolarization

Polarization  Nucleus type: $^{1}\text{H}, ^{13}\text{C}$, etc.

Faraday Induction

Long lived low $\gamma$ nuclear spin states

PASADENA  More NMR sensitive protons

hyperpolarization  storage  detection

Vanderbilt University Institute of Imaging Science (VUINS)
Hyperpolarized $^1$H detection using INEPT

PHIP Hyperpolarization of HEP with 97% pH$_2$

Production of Hyperpolarized Tracer Compounds

a) The schematic of ParaHydrogen Induced Polarization (PHIP) leading to 20% hyperpolarization of 1-$_{13}$C carbon (red color); b) reference $^{13}$C spectrum of 170 millimoles of 1-$_{13}$C-acetate, 64 scans; c) $^{13}$C spectrum of 15 micromoles ($<$2 mg) of 20% hyperpolarized contrast agent with signal enhancement by $\sim$5,000,000 fold at 47.5 mT.

Detection Efficiency: 4.7 T vs. 0.047 T

The same sample with the same nuclear spin polarization!

**Sensitivity comparison of high and low field.** $^{13}$C spectroscopy of 1.0 g of sodium $^{1-13}$C-acetate solution in 2.8 mL 99.8% D$_2$O at 4.7 T (a) using multinuclear RF coil (Doty Scientific, SC) and at 47.5 mT (b) using multinuclear custom-built (Coffey A. M. et al. manuscript in preparation) RF coil. Identical $^{13}$C nuclear spin polarization was achieved by sample polarization at 4.7 T (a) and sample pre-polarization at 7 T (b). The latter used sample transfer from 7 T to 47.5 mT magnet. It is estimated that $^{13}$C polarization decays to the equilibrium level of that at 4.7 T during such sample transfer (data not shown). Both spectra are acquired with RF coils of similar diameter and similar parameters: spectra width = 10 kHz, no line broadening.

Coffey A. M. et al. manuscript in preparation
Low power < 1 W RF pulses and amplifier

A) RF circuit for a H/X probe on a 2 MHz spectrometer, where X = \(^{13}\text{C}\) or \(^{15}\text{N}\). Two single channel circuits share a common ground. The exterior \(^1\text{H}\) circuit consists of a Helmholtz coil. An interior \(^{13}\text{C}\) solenoid coil closely fits the reactor. B) Left shows direct detection of \(^{13}\text{C}\) reference spectrum of 0.13 moles of sodium \(1\text{-}^{13}\text{C}\) acetate in D\(_2\)O after 64 averages. Right shows hyperpolarized \(^{13}\text{C}\) spectrum of \(1\text{-}^{13}\text{C}\)-succinate-d\(_2\) (12\(\cdot\)10\(^{-6}\) moles in 4 mL H\(_2\)O) detected in situ with enhancement \(\varepsilon \sim 2,000,000\), polarization \(P = 8\%\). C) Frequency sweep responses of three channels: \(^1\text{H}\) at 2.020 MHz (left), \(^{13}\text{C}\) at 0.508 MHz (middle), and \(^{15}\text{N}\) at 0.2048 MHz (right).

Coffey, A. M. et. al
Experimental NMR Conference 2011
New Imaging Modalities?

If there is PET/CT, why not Hyperpolarized MRI/CT with low field MR?
Future/Ongoing Work

Goal 1: >50% polarization
- Polarization optimization & development: more QA

Goal 2: hyperpolarized biomarkers of cancer
- $5^{-13}C$-glutamine (elevated glutaminosis)
- $^{15}N$-choline (elevated choline kinase expression & activity)
- $1^{-13}C$-succinate (TCA cycle)
- $1^{-13}C$-lactate (TCA cycle)
- $1^{-13}C$-pyruvic acid (XIP technique)
- $1^{-13}C$-acetic acid (XIP technique)

Goal 3: Real time metabolic imaging in vivo
- purification of hyperpolarized contrast agents
- proton imaging of hyperpolarized metabolites
- low field imaging
Acknowledgements

my wife Elena M Oborina

Prof. John C. Gore (VUIIS)
Prof. Kevin Waddell (VUIIS)
Dr. Roman Shchepin (VUIIS)
Aaron Coffey (VUIIS and VU BME)
Diana Carver-Smith (VUIIS and VU Physics)
Raul Colon (VUIIS and VU Physics)
Dr. Sasidhar Tadanki & Ken Wilkens (Engineers @ VUIIS)
Dr. Donald Stec (VU)
Dr. Natalia Lisitza (Brigham & Women, Boston, MA)
Prof. Samuel Patz (Brigham & Women, Boston, MA)
Prof. Boyd Goodson & team (SIUC, Carbondale, IL)
Prof. Mike Barlow (University of Nottingham)
Prof. Matthew Merritt (UT South Western)
Dr. Bibo Feng (VUIIS) and Dr. Michael Nickels (VUIIS)

External Funding Support
NIH/NCI 1K99CA134749-01    NIH/NCI 5R00CA134749
NIH/NCI 3R00CA134749-02S1    Prevent Cancer Foundation