Quantifying Metabolism using Hyperpolarized MR

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There's more to MRI than $^1$H… but sensitivity is low

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Relative MR Frequency</th>
<th>Relative Abundance</th>
<th>NMR Receptivity</th>
<th>Atomic Fraction* Human Body</th>
<th>Common Targets (by NO means complete!)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H</td>
<td>100</td>
<td>99.98%</td>
<td>1</td>
<td>62%</td>
<td>Choline, Creatine, N-acetyl-aspartate, Lactate, Amino Acids (~mM)</td>
</tr>
<tr>
<td>$^{19}$F</td>
<td>94.094</td>
<td>100%</td>
<td>0.83</td>
<td>0.0012%</td>
<td>Fluorinated compounds</td>
</tr>
<tr>
<td>$^{31}$P</td>
<td>40.481</td>
<td>100%</td>
<td>0.066</td>
<td>0.22%</td>
<td>Phosphoethanolamine, a/b/g-ATP, phosphocholine, inorganic phosphate</td>
</tr>
<tr>
<td>$^{23}$Na</td>
<td>26.466</td>
<td>100%</td>
<td>0.092</td>
<td>0.037%</td>
<td>Sodium ion concentration intra/extracellular</td>
</tr>
<tr>
<td>$^{13}$C</td>
<td>25.145</td>
<td>1.11%</td>
<td>1.76x10^{-4}</td>
<td>12%</td>
<td>$^{13}$C-labeled substrates and their metabolic products; glycerols, citrate,…</td>
</tr>
<tr>
<td>$^{15}$N</td>
<td>10.137</td>
<td>0.37%</td>
<td>3.85x10^{-8}</td>
<td>1.1%</td>
<td>$^{15}$N-labeled … nitroxy radicals; NAA, glutamate, glutamine, choline</td>
</tr>
</tbody>
</table>

* By element, not by isotope
Dynamic nuclear polarization

With DNP, we achieve 30% polarization for $^{13}$C

- Compare to ~6ppm for $^{13}$C at 7T:
  \[ G \approx \frac{0.30}{0.000058} = 51,724 \]

- Compare to ~2.5ppm for $^{13}$C at 3T:
  \[ G \approx \frac{0.30}{0.0000248} = 120,967 \]

At thermal equilibrium, it would take >3 years to achieve the same signal to noise as a 1s measurement of HP-Pyr!
**Why pyruvate?**

- (Relatively) long half-life: $T_1 \sim 60$ s in vitro
- Rapid pharmacokinetics
- Key component at branching point of metabolism
- **First hyperpolarized injectable in humans**

**Glycolysis**

\[
\text{Glucose} + 2\text{Pi} + 2\text{ADP} + 2\text{NAD}^+ \rightarrow 2\text{Pyruvate} + 2\text{ATP} + 2\text{NADH} + 2\text{H}_2\text{O} + 2\text{H}^+
\]

**Challenges for imaging of HP Substrates:**

Measurement of the dynamic HP MRI signal is unlike traditional MRI:

- Signals are changing constantly
- Finite, nonrenewable magnetization
- $T_1$ relaxation
- Depleted with each measurement

Acquisition strategy must encode spatial & spectral information within constraints of biological activity!

And we need a way to quantify the interaction between these spin pools.
**Equations of motion: flux between chemical pools**

\[
LDH + NADH \rightleftharpoons NAD^+ + \text{Lactate}
\]

\[
V_{PL} = \frac{[LDH] (k_3[Pyr][NADH])}{k_2} + \frac{k_1[NADH]}{k_2} + \frac{k_3 k_4 [NADH][Pyr]}{k_4 k_2 [Lac]} \left(1 + \frac{[Pyr]}{k_i}\right)
\]

The apparent conversion rate depends on the reaction velocity (mol/s) and the probability that reagents are hyperpolarized:

\[
\frac{\partial P^*}{\partial t} = V_{PL} \frac{L^*}{P + P^*} - V_{PL} \frac{P^*}{P + P^*}
\]

Let \( k_{pl} = \frac{V_{PL}}{P + P^*} \),

\[
\frac{\partial L^*}{\partial t} = V_{PL} \frac{P^*}{P + P^*} - V_{PL} \frac{L^*}{L + L^*}
\]

Let \( k_{lp} = \frac{V_{PL}}{L + L^*} \).


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**What is the “best” model for signal evolution in vivo?**

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor/Product</td>
<td>2 spatial + 2 chemical</td>
<td>3 spatial + 2 chemical</td>
</tr>
<tr>
<td>Simplest</td>
<td>Separates intra- from extravascular agents</td>
<td>IV, EES, IC</td>
</tr>
<tr>
<td>Most widely used</td>
<td>Modest cost/complexity</td>
<td>Most accurate biophysical model</td>
</tr>
<tr>
<td>Over-estimates pyr in target tissue, under-estimates reaction rate</td>
<td></td>
<td>High cost/complexity, parm variations</td>
</tr>
</tbody>
</table>
What is the “best” model for signal evolution in vivo?

The general differential equation for models B-C:

\[ Y'(t) = AY(t) + V(t) \]

The general solution:

\[ Y(t) = e^{At}Y(t=0) + \frac{k_{ve}}{v_e} \int_0^t e^{A(t-\tau)}V(\tau)d\tau \]

PK model gives parameterized function of time

Special Case: Model B

1. \( k_{lp} = 0 \);
2. \( \text{Pyr}(t=0) = \text{Lac}(t=0) = 0 \);
3. \( \text{Lac}_{IV}(t) = 0 \)

\[ \text{Pyr}(t) = k_{ve} \int_0^t e^{-\alpha_p(t-\tau)} \text{Pyr}_{IV}(\tau)d\tau + v_b \text{Pyr}_{IV}(t) \]

\[ \text{Lac}(t) = \frac{k_{ve}k_{PL}}{\alpha_P - \alpha_L} \int_0^t [e^{-\alpha_L(t-\tau)} - e^{-\alpha_p(t-\tau)}] \text{Pyr}_{IV}(\tau)d\tau \]

Loss Terms:

\[ \alpha_p = \frac{k_{ve}}{1 - v_b} + R_{1,\text{Pyr}} + \frac{1 - \cos \theta}{TR} + k_{pl} \]

\[ \alpha_L = \frac{k_{ve}}{1 - v_b} + R_{1,\text{Lac}} + \frac{1 - \cos \theta}{TR} \]

Things we can measure; Unknowns to be determined

Model-Based Constrained Reconstruction

Prior knowledge from traditional MRI and a well-informed model of signal dynamics provide the link between undersampled, transient measurements.

Over the lifetime of these agents, we never acquire the same region of k-space twice!

Simulations can identify causes of bias and noise

- The difference between known conversion rate constant \((k_{pl})\) and the fit from noisy data inform on acquisition settings that may lead to higher errors

**Validation: dynamic multi-spectral phantoms**

New assays to quantify the accuracy of in vivo measurements will be crucial, particularly as this technology is deployed and tested in multiple labs and institutions.

Dynamic Signal Curves


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**Summary: Quantifying Metabolism using HP MR**

- Hyperpolarized substrates allow unprecedented insight into tumor physiology
- Pharmacokinetic models of substrate evolution provide a mechanism for quantitative analysis
  - Correct for influence of perfusion
  - Tells us how and why signals relate over all time
- A PK model with two spatial compartments provides reasonable compromise between simplicity and physiological accuracy
- Model-based constrained reconstruction of HP substrates allows acceleration in time domain and distribution of samples over kt-space
  - Fewer excitations preserve signal, enhance coverage, improve resolution
- Validation in simulation and in phantoms will be crucial!