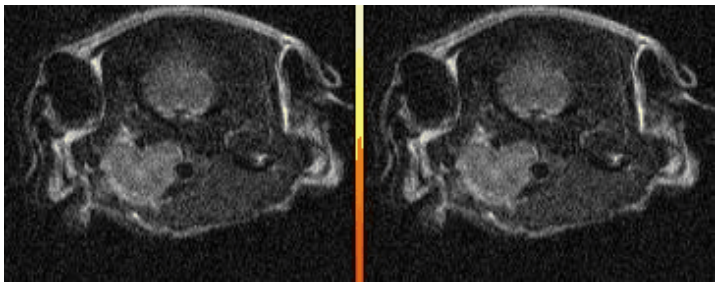
Quantifying Metabolism using Hyperpolarized MR



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

Nucleus	Relative MR Frequency	Relative Abundance	NMR Receptivity	Atomic Fraction* Human Body	Common Targets (by NO means complete!)
^{1}H	100	99.98%	1	62%	Choline, Creatine, N-acetyl-aspartate, Lactate, Amino Acids (~mM)
^{19}F	94.094	100%	0.83	0.0012%	Fluorinated compounds
^{31}P	40.481	100%	0.066	0.22%	Phosphoethanolamine, a/b/g-ATP, phosphocholine, inorganic phosphaste
^{23}Na	26.466	100%	0.092	0.037%	Sodium ion concentration intra/extracellular
^{13}C	25.145	1.11%	1.76×10^{-4}	12%	^{13}C-labeled substrates and their metabolic products; glycerols, citrate,..
^{15}N	10.137	0.37%	3.85×10^{-6}	1.1%	^{15}N-labeled … nitroxyl radicals; NAA, glutamate, glutamine, choline

* By element, not by isotope

Dynamic nuclear polarization

10158–10163 | PNAS | September 2, 2003 | vol. 100 | no. 18

Increase in signal-to-noise ratio of >10,000 times in liquid-state NMR

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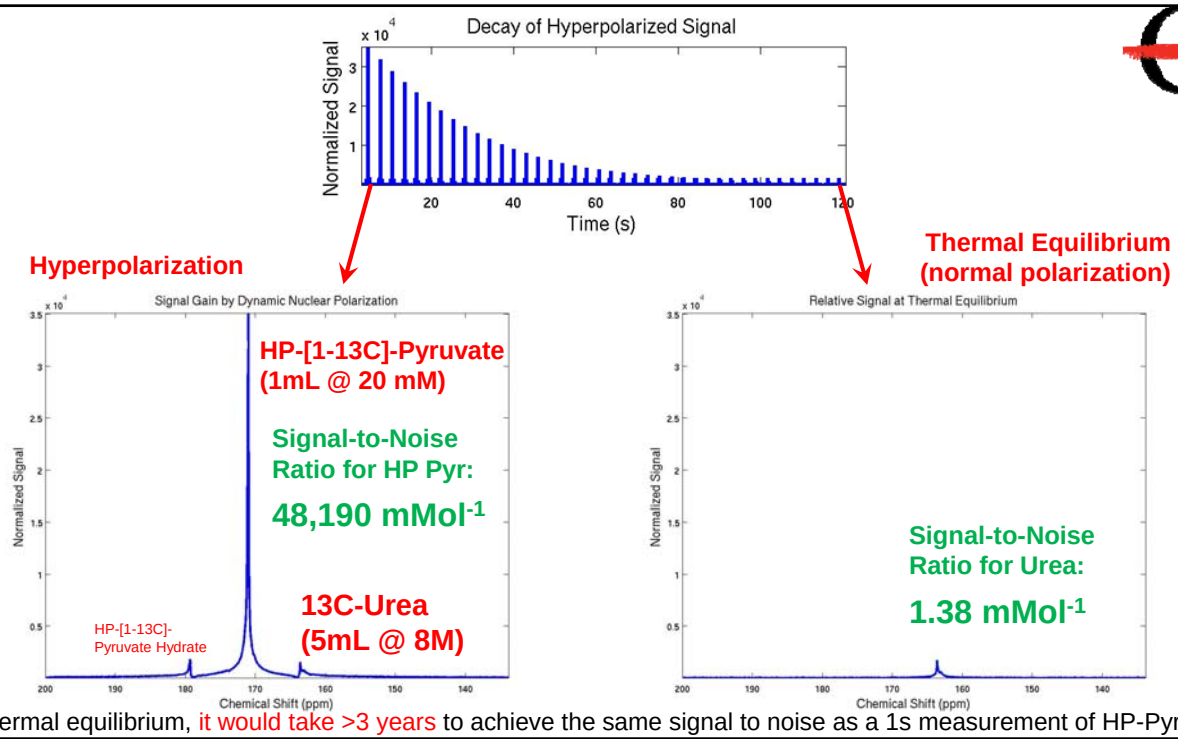
With DNP, we achieve 30% polarization for ^{13}C

- Compare to ~6pmm for ^{13}C at 7T:

$$G \approx \frac{.30}{.0000058} = 51{,}724$$

- Compare to ~2.5pmm for ^{13}C at 3T:

$$G \approx \frac{.30}{.00000248} = 120{,}967$$



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

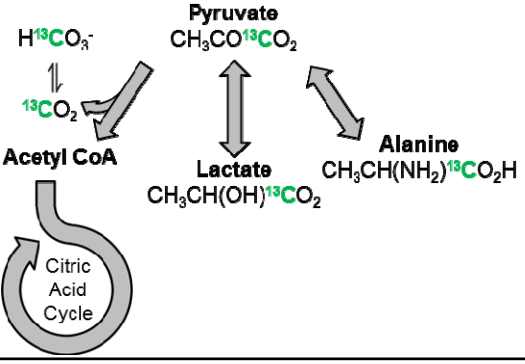
Why pyruvate?

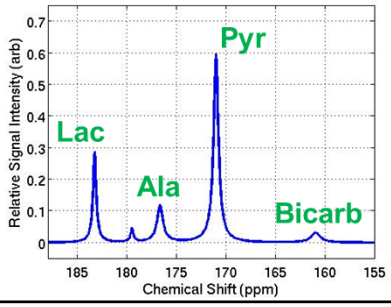
- (Relatively) long half-life: T1 ~ 60s in vitro
- Rapid pharmacokinetics
- Key component at branching point of metabolism
- **First hyperpolarized injectable in humans**

Glycolysis

Glucose
+ 2P_i + 2ADP + 2 NAD^+

2 Pyruvate
+ 2ATP + 2 NADH
+ 2 H_2O+ 2 H^+





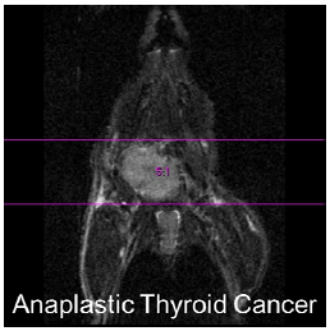
Challenges for imaging of HP Substrates:

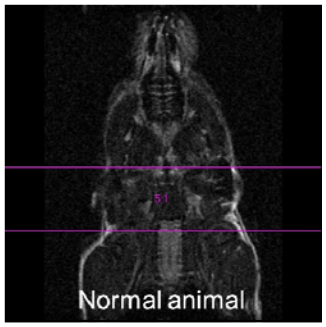
Measurement of the dynamic HP MRI signal is unlike traditional MRI:

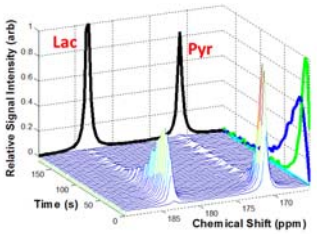
- Signals are changing constantly
- Finite, nonrenewable magnetization
- T1 relaxation
- Depleted with each measurement

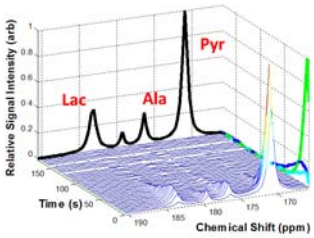
Acquisition strategy must encode spatial & spectral information within constraints of biological activity!

And we need a way to quantify the interaction between these spin pools.

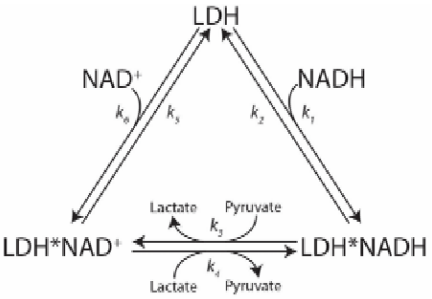








Equations of motion: flux between chemical pools



$$Pyruvate + NADH \overset{LDH}{\rightleftharpoons} NAD^+ + Lactate$$

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

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

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

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

Let

$$k_{pl} \equiv \frac{V_{PL}}{P+P^*}, \qquad k_{lp} \equiv \frac{V_{PL}}{L+L^*}$$

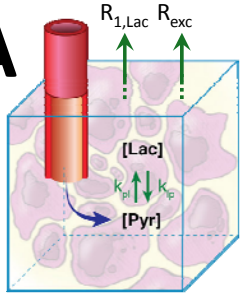
$$\frac{\partial P^*}{\partial t} = k_{lp}L^* - k_{pl}P^*$$

$$\frac{\partial L^*}{\partial t} = k_{pl}P^* - k_{lp}L^*$$

Walker CM, et al. *PLoS One*, 2013.

What is the "best" model for signal evolution in vivo?

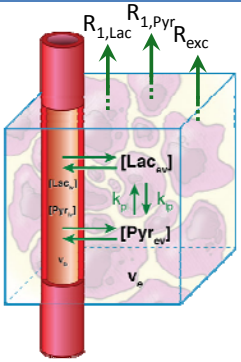
A



Precursor/Product

- Simplest
- Most widely used
- Over-estimates pyr in target tissue, under-estimates reaction rate

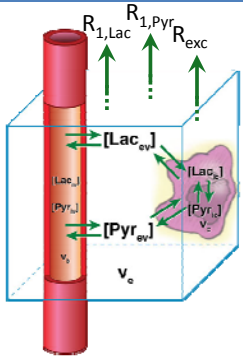
B



2 spatial + 2 chemical

- Separates intra- from extravascular agents
- Modest cost/ complexity

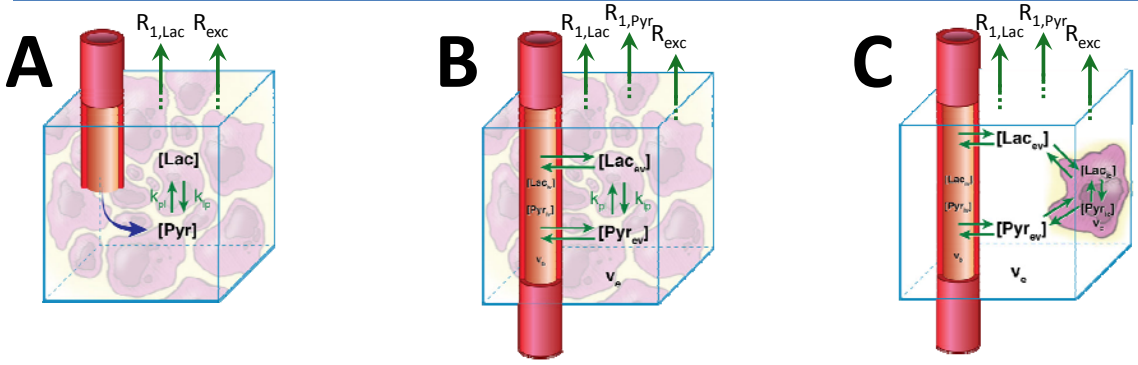
C



3 spatial + 2 chemical

- IV, EES, IC
- Most accurate biophysical model
- High cost/ complexity, parm variations

What is the "best" model for signal evolution in vivo?



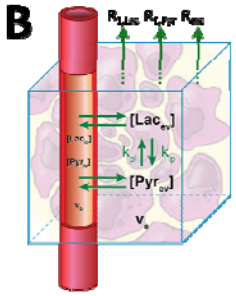
The general differential equation for models B-C:

$$\mathbf{Y}'(t) = \mathbf{A}\mathbf{Y}(t) + \mathbf{V}(t)$$

The general solution:

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

PK model gives parameterized function of time

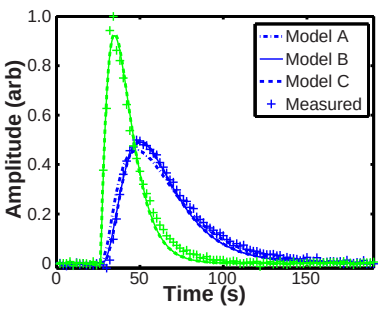


Special Case: Model B

(1) $k_{lp} = 0$; (2) $Pyr(t=0) = Lac(t=0) = 0$; (3) $Lac_{IV}(t) = 0$

$$Pyr(t) = k_{ve}\int_0^t e^{-\alpha_P(t-\tau)}Pyr_{IV}(\tau)d\tau + v_b Pyr_{IV}(t)$$

$$Lac(t) = \frac{k_{ve}k_{PL}}{\alpha_P - \alpha_L}\int_0^t \left[e^{-\alpha_L(t-\tau)} - e^{-\alpha_P(t-\tau)}\right]Pyr_{IV}(\tau)d\tau$$



Loss Terms:

$$\alpha_P = \frac{k_{ve}}{1-v_b} + R_{1,Pyr} + \frac{1-\cos\theta}{TR} + k_{pl}$$

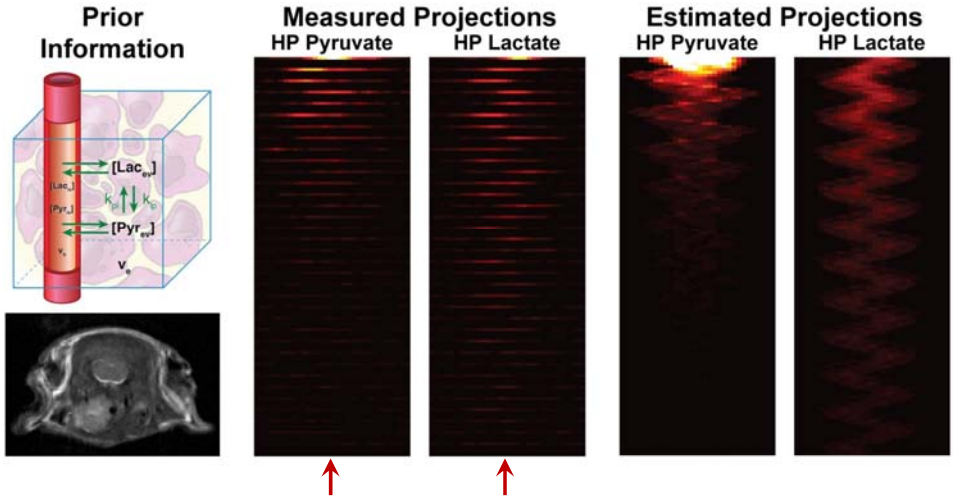
$$\alpha_L = \frac{k_{ve}}{1-v_b} + R_{1,Lac} + \frac{1-\cos\theta}{TR}$$

Things we can measure; Unknowns to be determined

Bankson JA, et al. *Cancer Research* 2015.

Model-Based Constrained Reconstruction

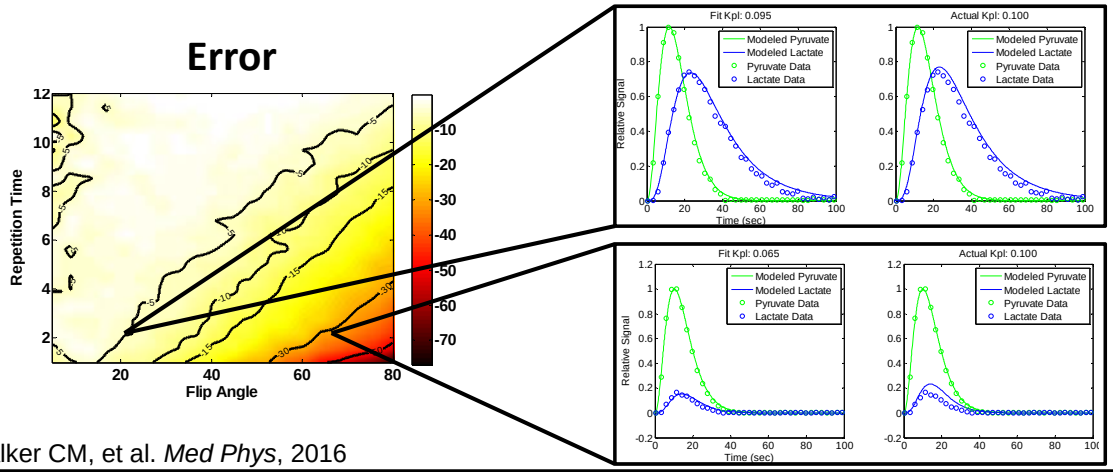
Prior knowledge from traditional MRI and a well-informed model of signal dynamics provide the link between undersampled, transient measurements.



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

Simulations can identify causes of bias and noise

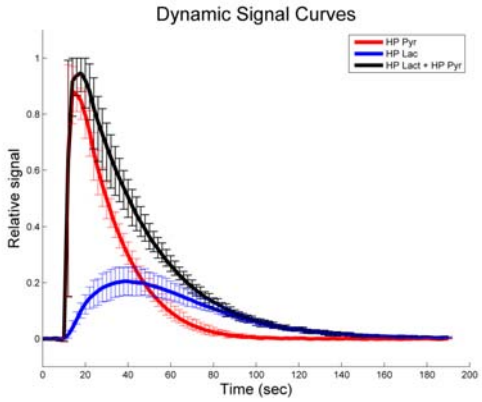
- The difference between known conversion rate constant (k_{pl}) and the fit from noisy data inform on acquisition settings that may lead to higher errors

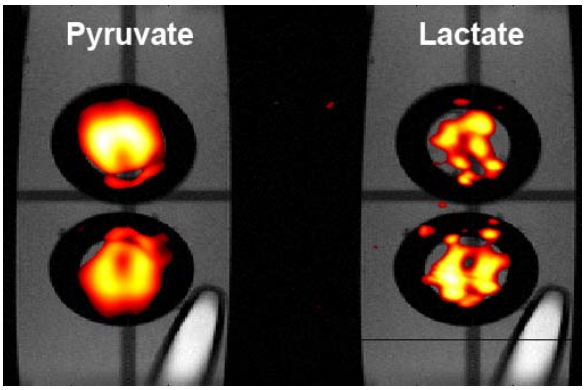


Walker CM, et al. *Med Phys*, 2016

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.





Walker CM, et al. *PLoS One*, 2013; Walker CM, et al. JoVE 2016.

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!