



University of California
San Francisco

Postprocessing Techniques: Fitting, Metabolic Modeling, & Denoising

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*University of Aarhus Training Course on Hyperpolarized ^{13}C &
 ^{129}Xe MRI: Moving to Clinical Use*

October 5th, 2026



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I have data... now what do I do with it?

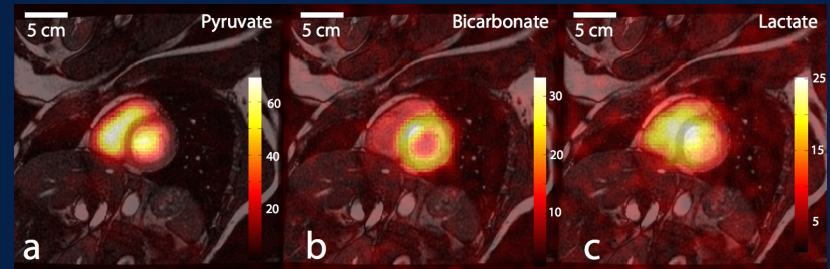
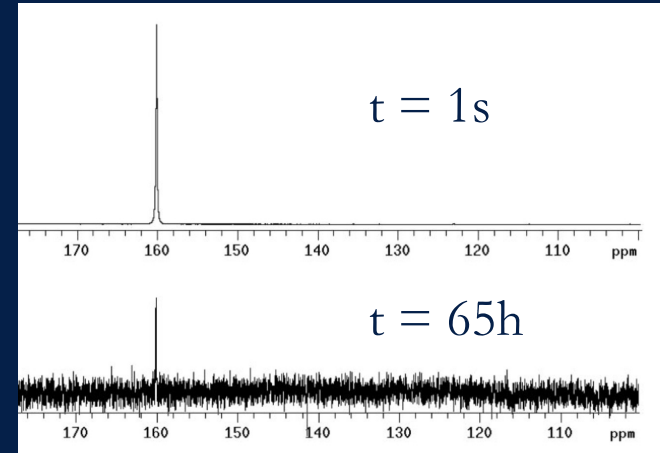
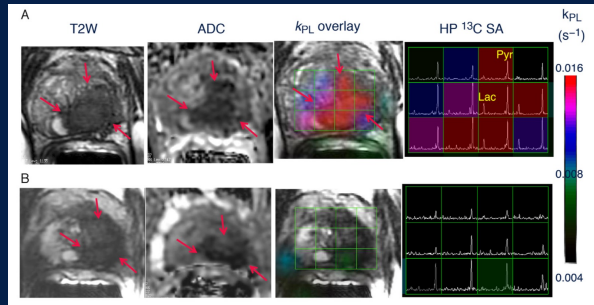
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October 6th, 2026

Hyperpolarization

- Hyperpolarization provides 10^4 - 10^5 increase in nuclear polarization¹
- With this increase in sensitivity, HP enables real-time metabolic imaging of ^{13}C substrates^{2,3,4}



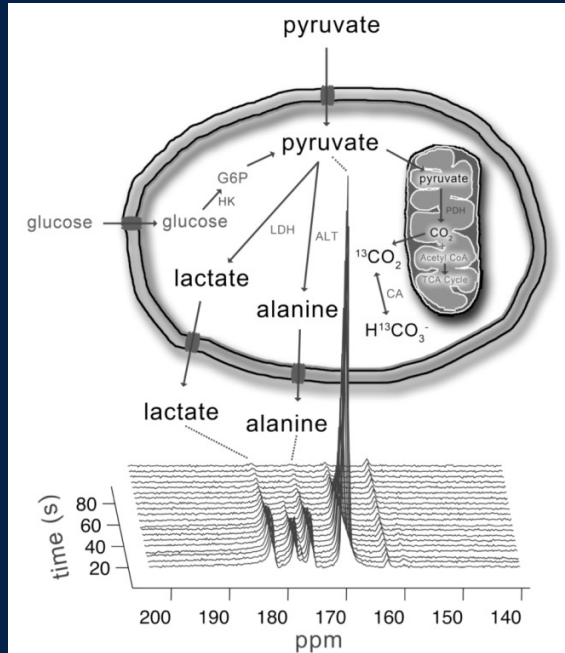
¹Ardenkjær-Larsen et al., PNAS 2003.

³Cunningham et al., Circ. Res. 2016.

²Nelson et al., STM 2013.

⁴Aggarwal et al., Eur. Ur. 2017

Hyperpolarized Metabolic Imaging



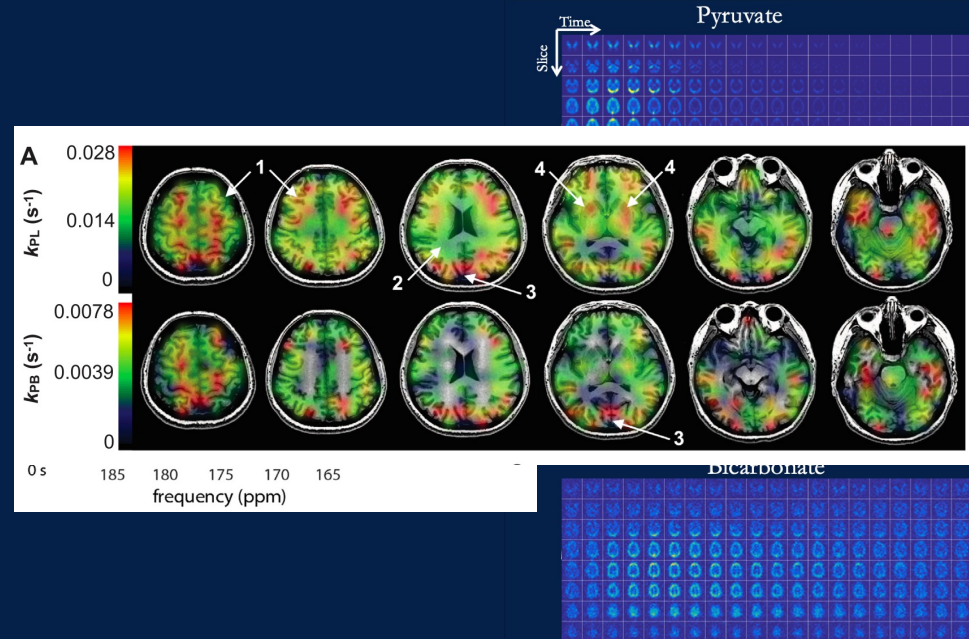
- Non-ionizing
- Endogenous compound
- Provides dynamic information on cellular metabolism (60-90s)
 - Both substrate uptake *and* metabolic conversion
- Quantify multiple enzymatic pathways in a single experiment

Learning Objectives

1. Learn how to process 5D metabolic data
2. Appreciate the tradeoffs between the different types of model-free metrics and kinetic models
3. Understand the basics of denoising hyperpolarized ^{13}C MRI data

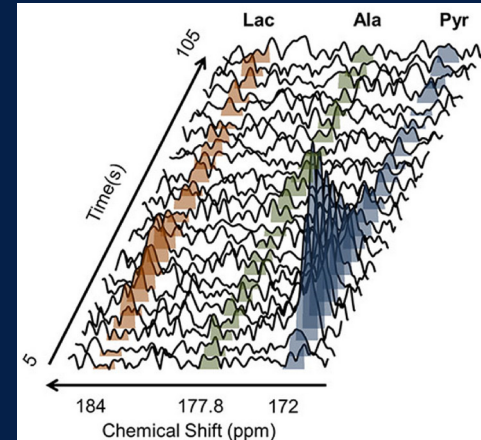
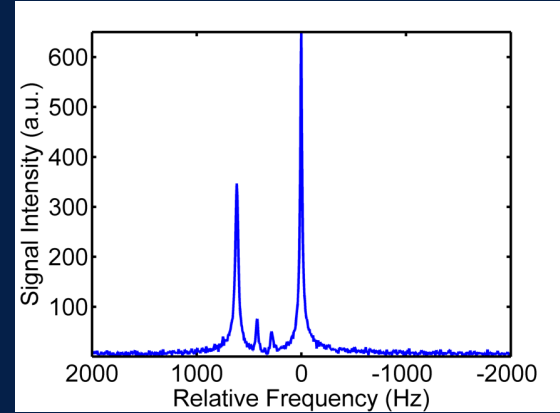
Data Visualization & Processing

- HP ^{13}C experiments have (up to) 5D data
 - 3 spatial [X, Y, Z]
 - 1 frequency (f)
 - 1 temporal (t)
- Want to eventually analyze this dataset. Need to:
 - Extract metabolite signals
 - Analyze data on a voxel (or ROI) basis to quantify metabolism



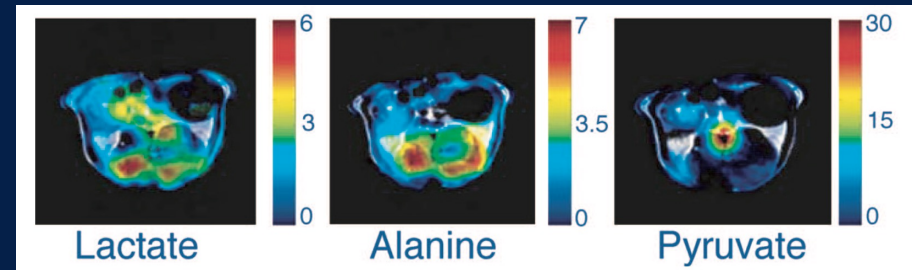
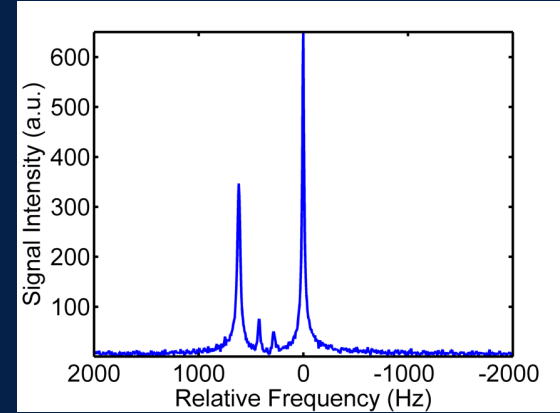
Data Extraction: Spectroscopy

- Metabolite signal must be extracted from spectra
- Magnitude data commonly used because of sparse spectrum, but leads to broader peaks
- For sparse HP spectra, have many options:
 - Peak integration – requires well-isolated peaks, no baseline distortion



Data Extraction: Spectroscopy

- Metabolite signal must be extracted from spectra
- Magnitude data commonly used because of sparse spectrum, but leads to broader peaks
- For sparse HP spectra, have many options:
 - Peak integration – requires well-isolated peaks, no baseline distortion
 - Model fitting - LCMoel¹, AMARES²



¹Provencher, MRM 1993.

²Purvis et al., PLoS one 2017

Data Extraction: Imaging

- Noise in MRI assumed to be zero-mean Gaussian
- Most imaging-based acquisitions analyze data in magnitude mode

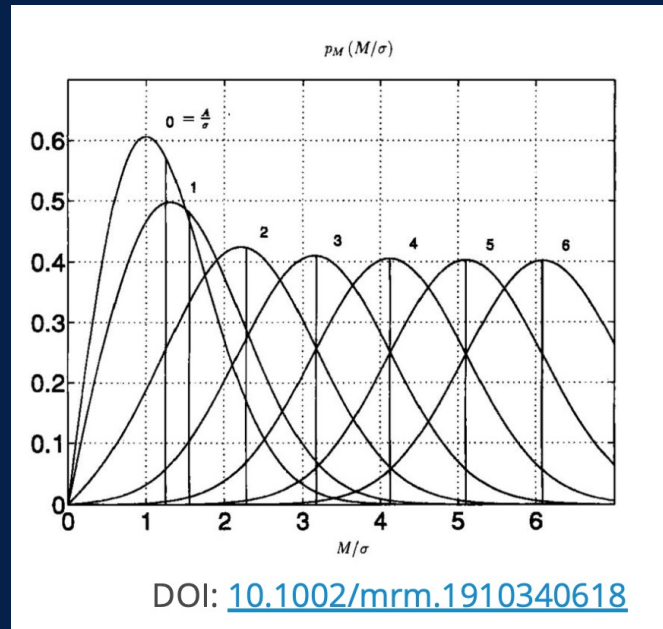
$$|M_{XY}| = \sqrt{M_x^2 + M_y^2}$$

- Results in Rician noise distribution.

- For high SNR, Rician SNR ~ Gaussian SNR
- For low SNR, introduces bias in the data

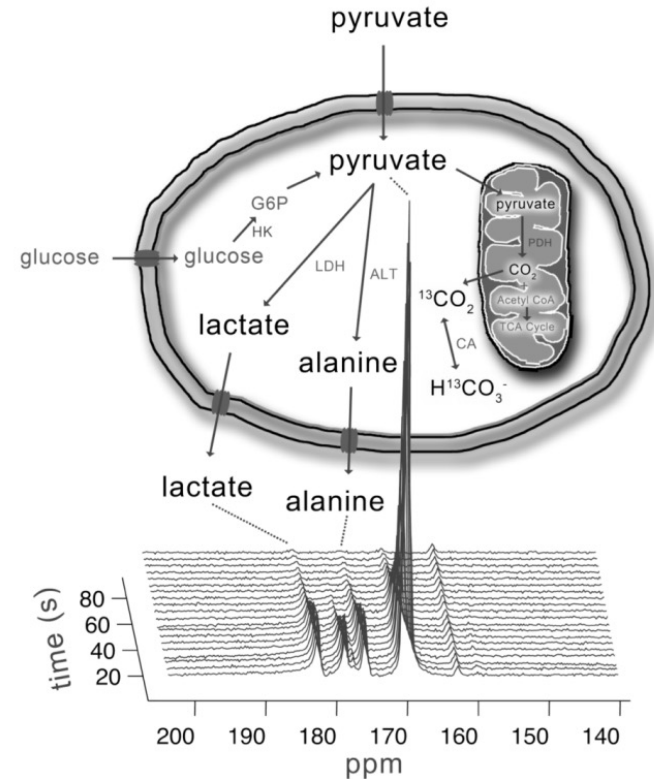
- What to do?

- Phase data if possible
- Some models can be adapted to account for Rician noise



How to Quantify Data

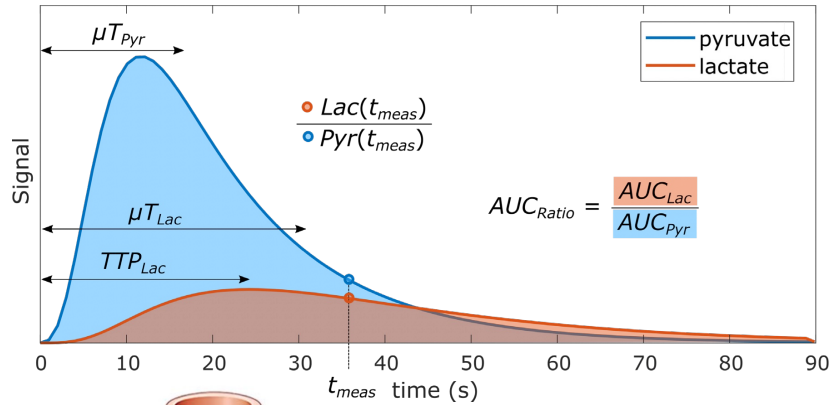
- Have extracted signal. Now what?
- Signal evolves continuously and dynamically during the experiment
 - T_1 decay
 - RF utilization
 - Metabolism
- How do we quantify metabolism and analyze our data?
 - Note that examples will be for HP ^{13}C pyruvate, but equally applicable to any other metabolically active substrate



How to Quantify Data

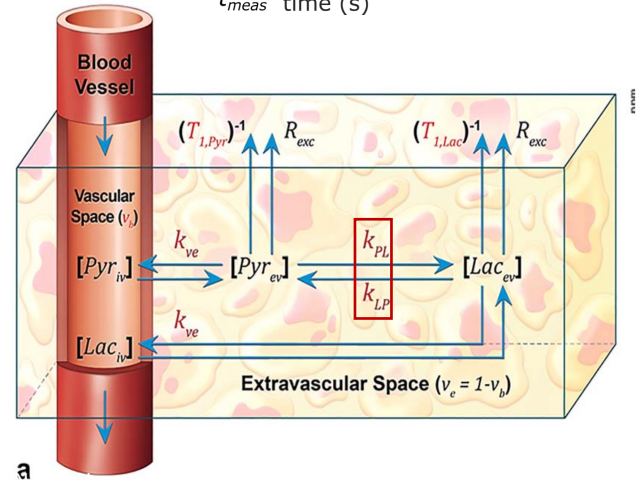
- Model-Free metrics

- Extract data directly from dynamic curves, no assumptions or models required



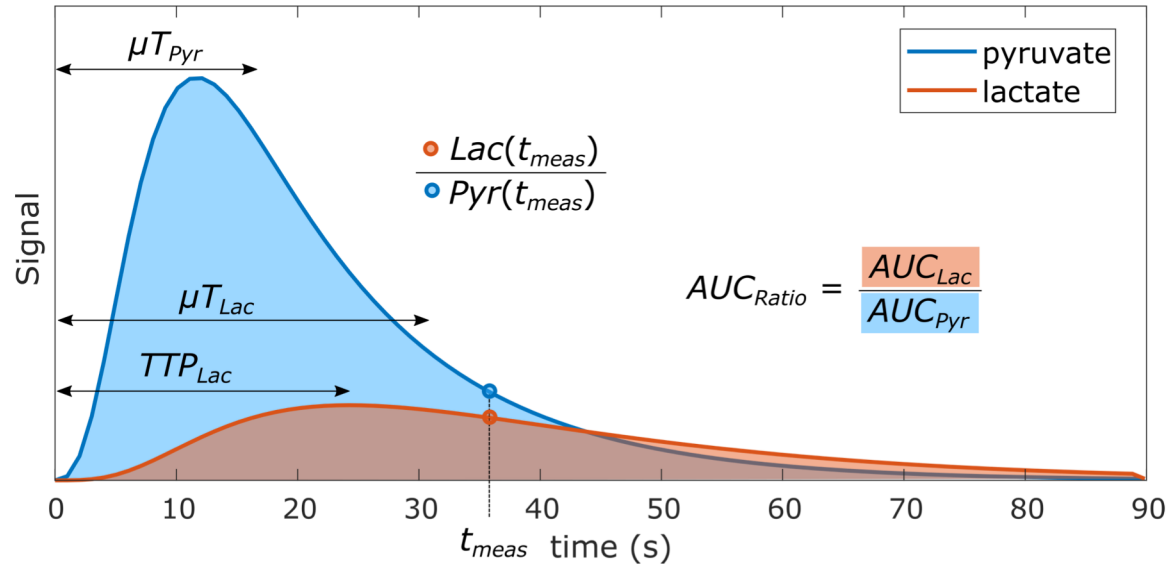
- Pharmacokinetic models

- PK models account for all sources of metabolism and loss of signal to quantify conversion of HP substrates



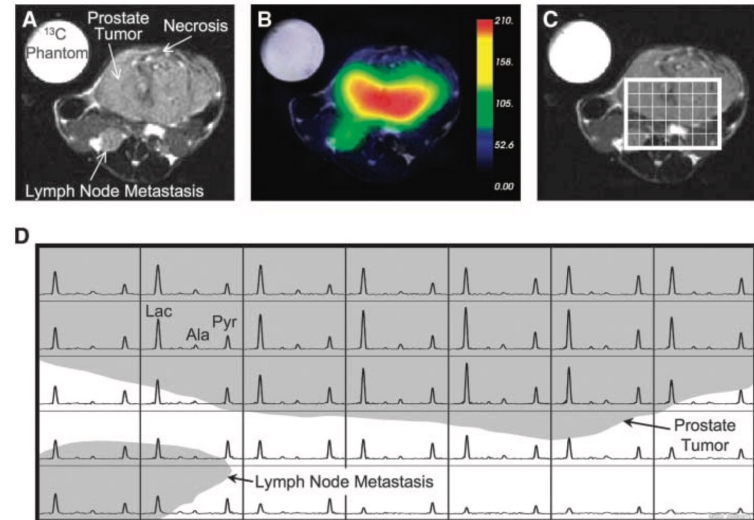
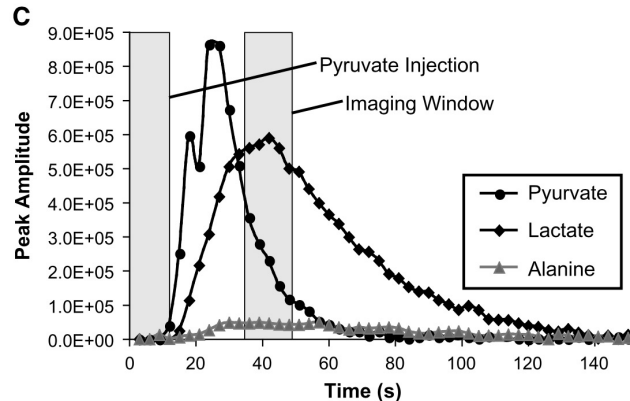
Model-free Metrics

- L/P ratio (single time-point)
- AUC L/P ratio (dynamics)
- Time-to-peak (TTP)
- Mean time (uT)



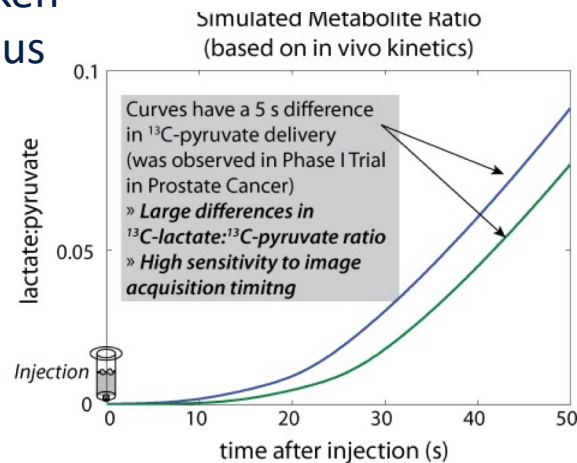
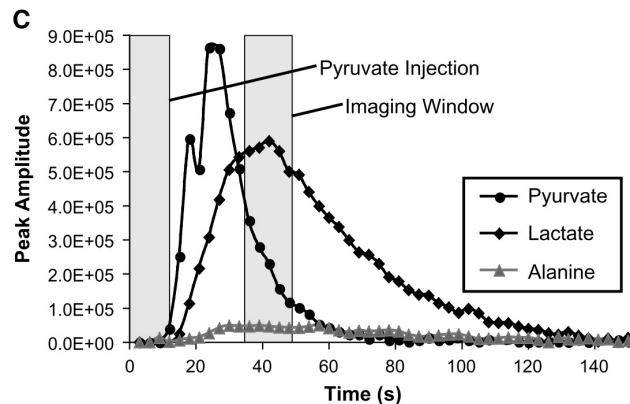
Ratiometric methods: Lactate/pyruvate (single time-point)

- Analyze metabolite ratios at single timepoint – simplest approach
- Has been used for 2D CSI data, pre-clinical applications when conditions are consistent
- Limitations?



Ratiometric methods: Lactate/pyruvate (single time-point)

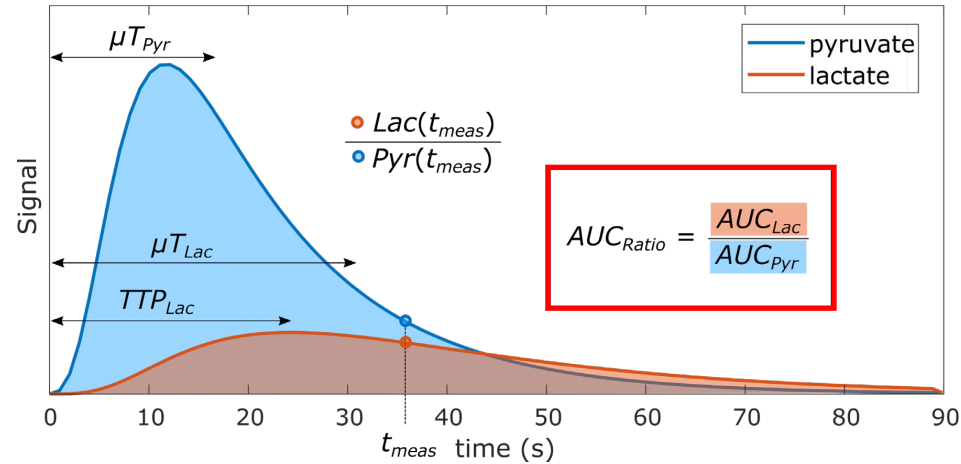
- Analyze metabolite ratios at single timepoint – simplest approach
- Has been used for 2D CSI data, pre-clinical applications when conditions are consistent
- Limitations?
 - Highly dependent on when the ratio is taken
 - Variability with experiment start time/bolus injection, perfusion



Metabolite Ratio (Dynamic Imaging)

- Area under the curve (AUC) ratio:
Acquire dynamic data then sum
signal before taking ratio
- Has been shown to be proportional
to pyruvate-to-lactate (k_{PL}) rate
constant from kinetic modeling

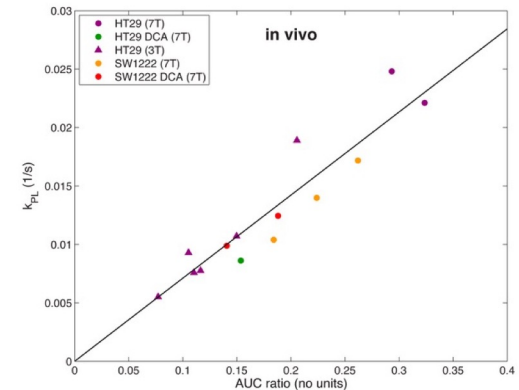
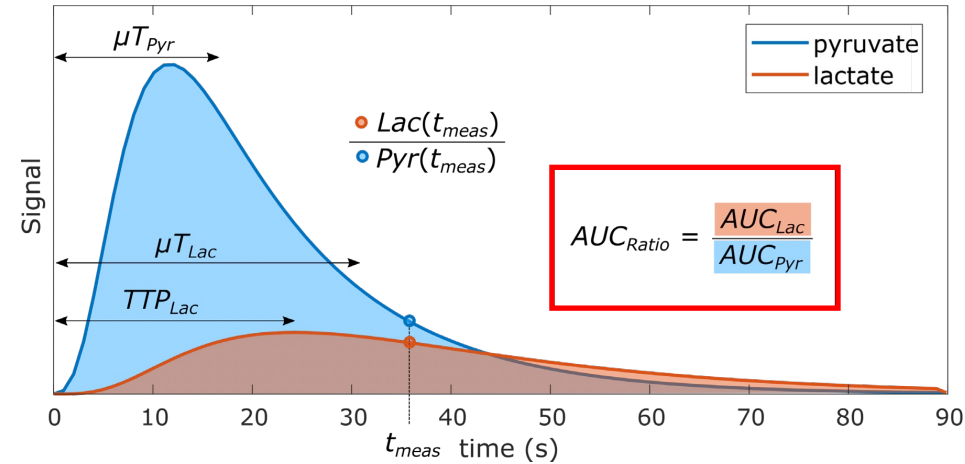
$$\frac{AUC(L)}{AUC(P)} = \frac{k_{PL}}{k_{LP} + r_L}$$



Metabolite Ratio (Dynamic Imaging)

- Pros:

- More robust to bolus, timing variation if entire kinetic curve is acquired
- Simple to calculate but still proportional to kinetic modeling rate constants under most conditions
 - Negligible back reaction ($k_{LP} \sim 0$), consistent $T_{1,L}$
- No assumption of input function shape

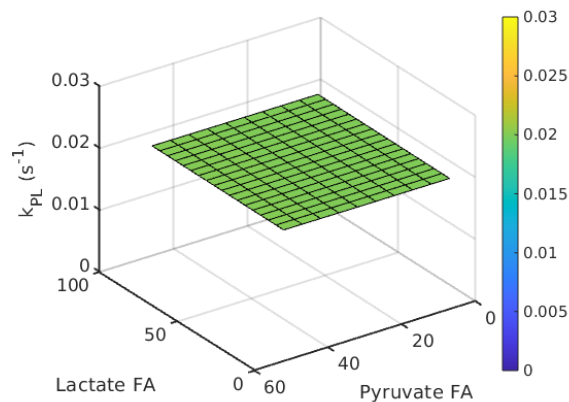
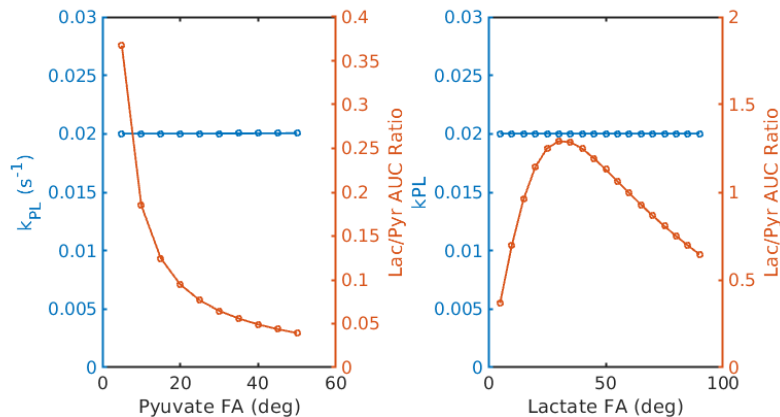
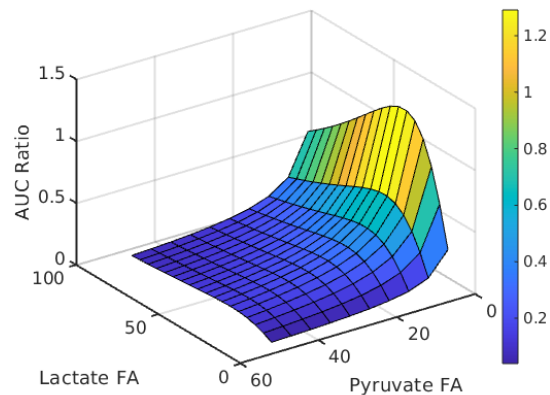


Metabolite Ratio (Dynamic Imaging)

- Cons:

- AUC ratio is strongly dependent on flip angle and cannot readily be compared across studies
- Proportionality between AUC ratio and k_{PL} breaks down when FA varies over time or with variations in bolus characteristics

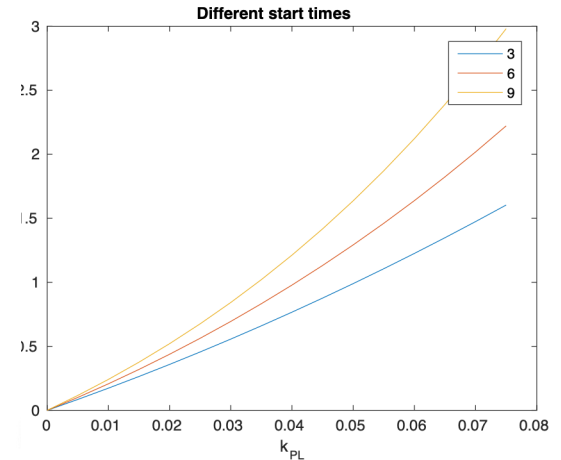
$$k_{PL} = 0.02 \text{ s}^{-1}$$



Metabolite Ratio (Dynamic Imaging)

- Cons:

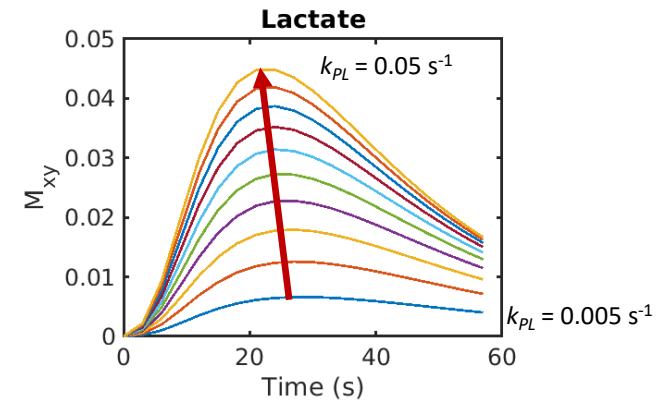
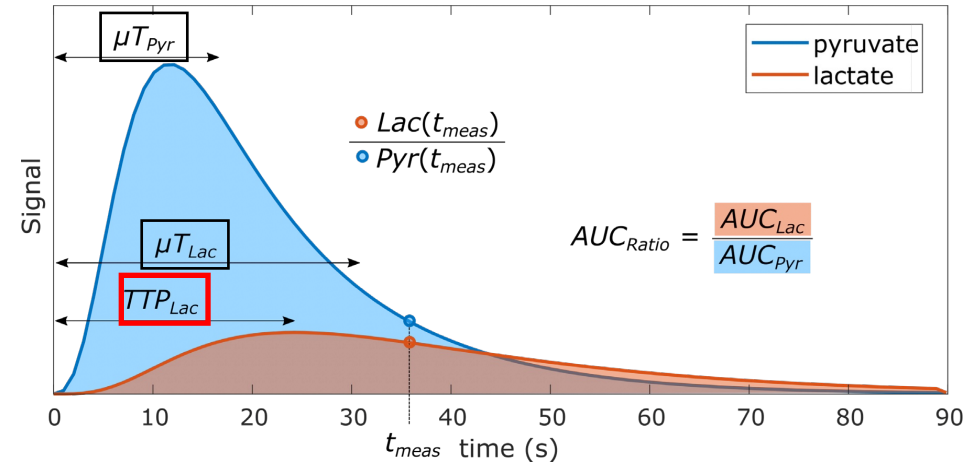
- AUC ratio is strongly dependent on flip angle and cannot readily be compared across studies
- Proportionality between AUC ratio and k_{PL} breaks down when FA varies over time or with variations in bolus characteristics
- Still sensitive to bolus timing if entire curve is not acquired



AUCratio simulation with
metabolite-specific
($\theta_{\text{pyruvate}} < \theta_{\text{lactate}}$),
constant-in-time flip angles

Dynamic Metrics

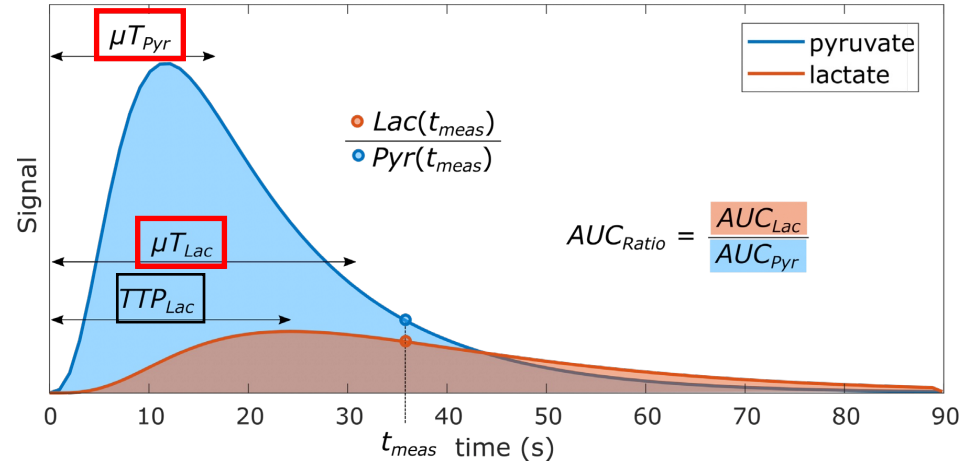
- Time to peak (TTP)
 - Time to peak for the metabolite kinetic curve
 - Lactate TTP inversely correlated to k_{PL}
- Limitations
 - Performs poorly with low SNR, coarse temporal resolution
 - Modest shift for large range of k_{PL}



Dynamic Metrics

- Mean arrival time (μT)
 - 'Center of mass' of dynamic curve

$$T_{\mu, \text{pyr}} = \frac{\sum_n P_S[n] t[n]}{\sum_n P_S[n]}$$

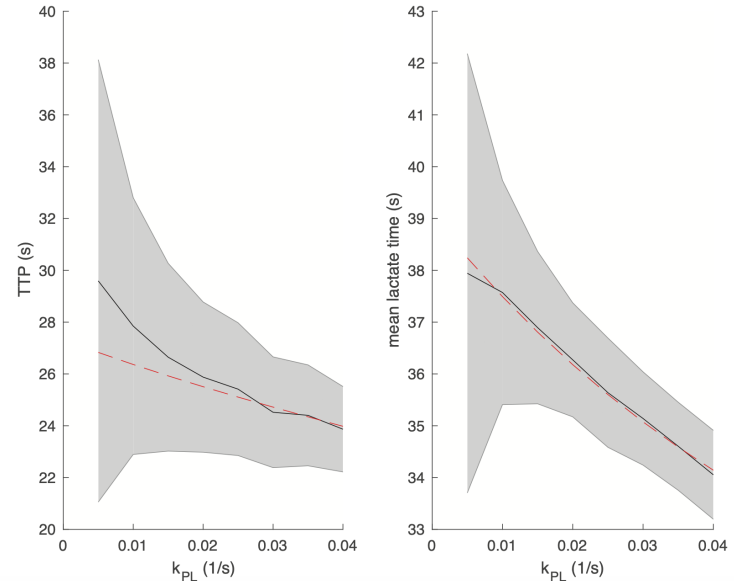


Dynamic Metrics

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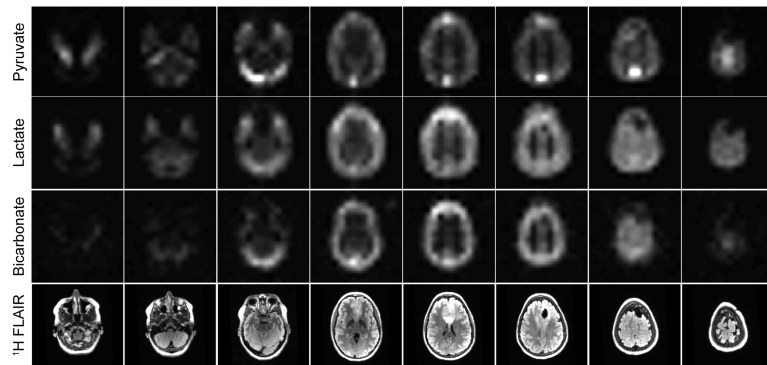
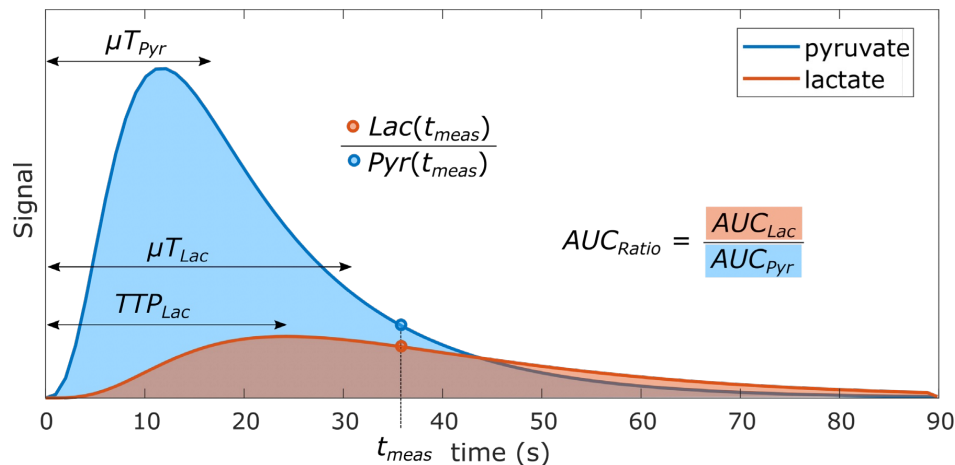
$$T_{\mu, \text{pyr}} = \frac{\sum_n P_S[n] t[n]}{\sum_n P_S[n]}$$

- Similar to TTP but more robust to low SNR
- Not as commonly used, but provides an estimate of arrival time (for substrate) or surrogate for metabolite TTP
- Also reflects anything that alters dynamic signal (T_1 , in/out-flow)



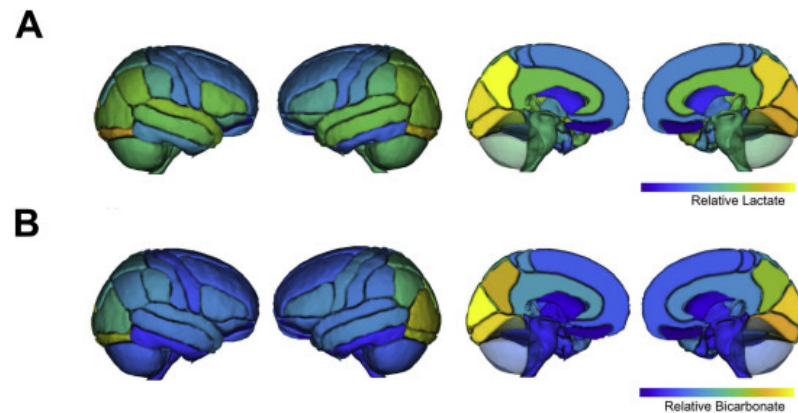
Metabolite Amplitudes

- All model-free approaches are either ratiometric or are derived from the general shape of the curve
- Why not use metabolite signal by itself?
- In general, too many sources of variations
 - Sensitive to the polarizer (polarization, time to injection)
 - Sensitive to scan setup (flip angles, coil shading)
 - Sensitive to biology (bolus injection rate, perfusion, transport into cell)



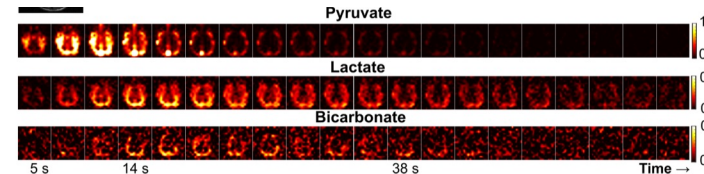
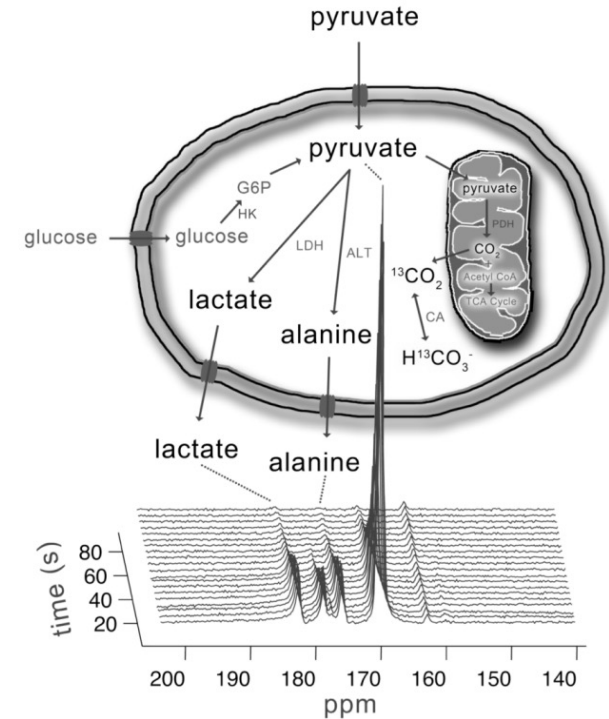
Metabolite Amplitudes

- All model-free approaches are either ratiometric or are derived from the general shape of the curve
- Why not use metabolite signal by itself?
- In theory, too many sources of variations
 - Sensitive to the polarizer (polarization, time to injection)
 - Sensitive to biology (bolus injection rate, perfusion, transport into cell)
 - Sensitive to scan setup (flip angles, coil shading)
- In practice, *can* use relative/normalized metabolite signal under specific conditions (e.g. lactate and bicarbonate 'topography' in human brain metabolism)



Kinetic/Pharmacokinetic modeling

- Pharmacokinetic (PK) models can be used to describe the fate of imaging agents in biological systems
- Provide a framework to understand, explain, and quantify signal evolution in vivo
- Data are fit to a model, which should account for
 - Sources of signal
 - Loss mechanisms (e.g. T1, flips)
 - Transition between spatial and **chemical pools**

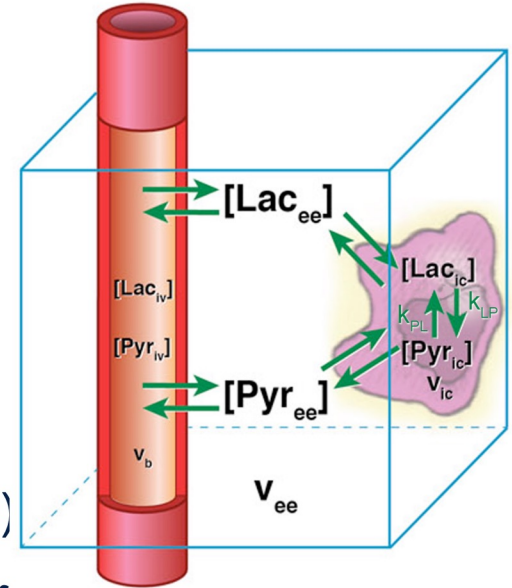


Kinetic Modeling: Three Compartments

- Three physical compartments, two chemical pools
- Include relationships between intracellular (*ic*) and extravascular, extracellular (*ee*) compartments:

$$\frac{\partial}{\partial t} \begin{bmatrix} Pyr_{ee}(t) \\ Lac_{ee}(t) \\ Pyr_{ic}(t) \\ Lac_{ic}(t) \end{bmatrix} = \begin{bmatrix} -\alpha_{P,ee} & 0 & \frac{k_{ecp}}{v_{ee}} & 0 \\ 0 & -\alpha_{L,ee} & 0 & \frac{k_{ecl}}{v_{ee}} \\ \frac{k_{ecp}}{v_c} & 0 & -\alpha_{P,ic} & k_{LP} \\ 0 & \frac{k_{ecl}}{v_c} & k_{PL} & -\alpha_{L,ic} \end{bmatrix} \begin{bmatrix} Pyr_{ee}(t) \\ Lac_{ee}(t) \\ Pyr_{ic}(t) \\ Lac_{ic}(t) \end{bmatrix} + \frac{k_{ve}}{v_{ee}} \begin{bmatrix} Pyr_{iv}(t) \\ Lac_{iv}(t) \\ 0 \\ 0 \end{bmatrix}$$

- Kinetic rate constant, k_{PL} (closest to enzyme kinetic rate)
- Also includes cellular transport rates (k_{ec}), more granular volume fractions (v_{ee} , v_{ic})
- Pros: Isolates metabolic conversion to intracellular space
- Cons: Requires additional model parameters

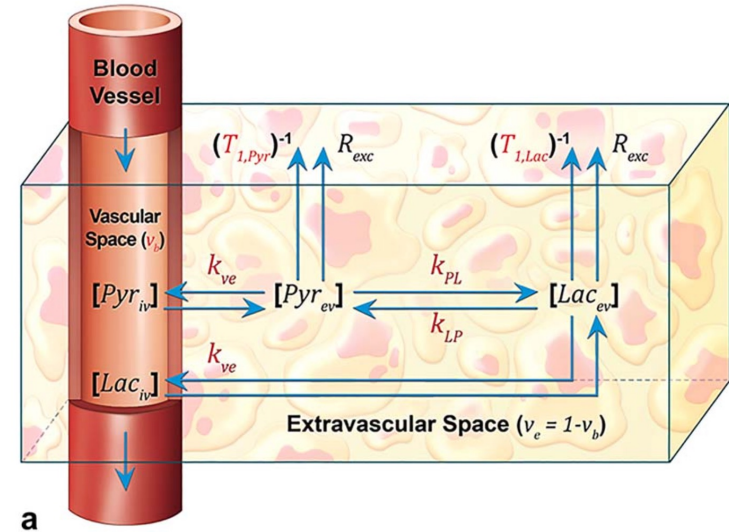


Kinetic Modeling: Two Compartments

- So a 3-compartment model is too complex. Can we simplify at all?
- Assume transport into cell is fast, need only two compartments

$$\frac{\partial}{\partial t} \begin{bmatrix} [Pyr_{ev}(t)] \\ [Lac_{ev}(t)] \end{bmatrix} = \begin{bmatrix} -\left(k'_{PL} + \frac{k_{ve}}{v_e} - R_{Pyr}\right) & k'_{LP} \\ k'_{PL} & -\left(k'_{LP} + \frac{k_{ve}}{v_e} - R_{Lac}\right) \end{bmatrix} \begin{bmatrix} [Pyr_{ev}(t)] \\ [Lac_{ev}(t)] \end{bmatrix} + \frac{k_{ve}}{v_e} \begin{bmatrix} [Pyr_{iv}(t)] \\ [Lac_{iv}(t)] \end{bmatrix}$$

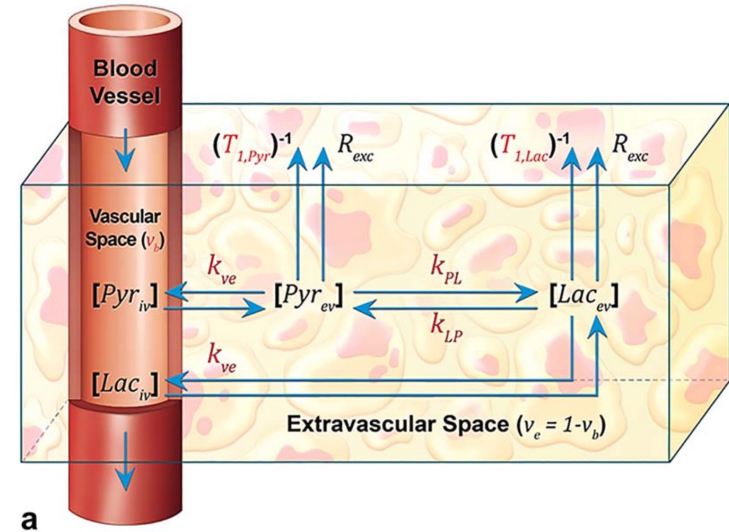
- More tractable, fewer unknowns. Includes extravasation (k_{ve}) rate and extravascular volume fraction (v_e)



Sun et al., MRM 2018

Kinetic Modeling: Two Compartments

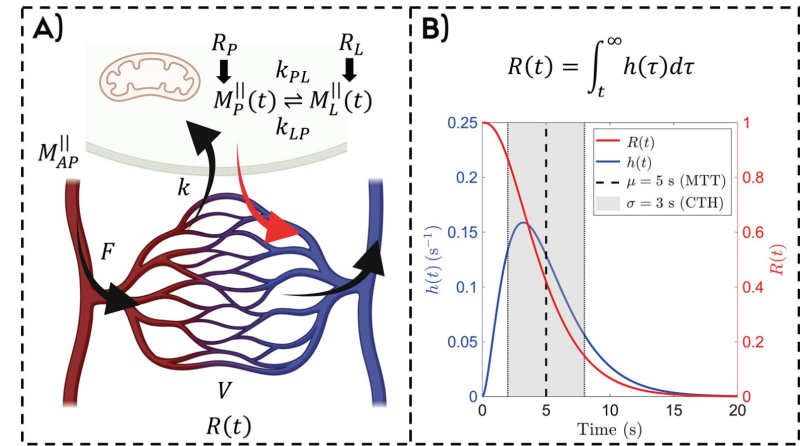
- Pros:
 - Best tradeoff between complexity and simplicity
 - Accounts for vascular fraction (substantial)
- Cons:
 - Requires extra parameters that are tricky to measure – fitting them increases model uncertainty
 - Pyruvate input function is required and can be difficult to measure



Sun et al., MRM 2018

Kinetic Modeling: Two Compartments

- Pros:
 - Best tradeoff between complexity and simplicity
 - Accounts for vascular fraction (substantial)
- Cons:
 - Requires extra parameters that are tricky to measure – fitting them increases model uncertainty
 - Pyruvate input function is required and can be difficult to measure
- New models being developed to disentangle capillary transit, extraction, relaxation, and metabolism¹

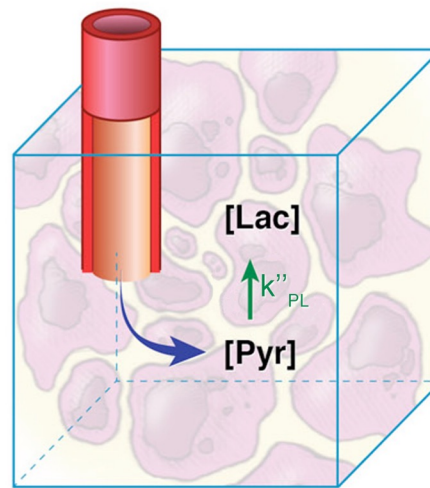


Christensen et al., MRM 2025

Kinetic Modeling: One Compartment (Precursor-Product)

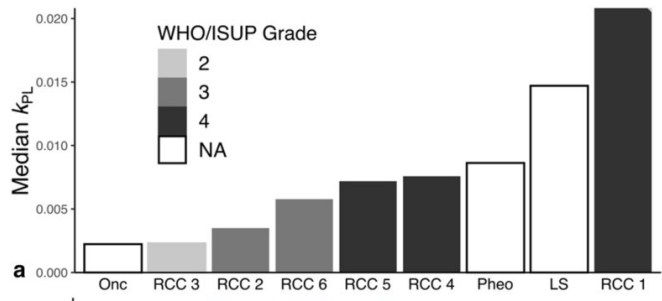
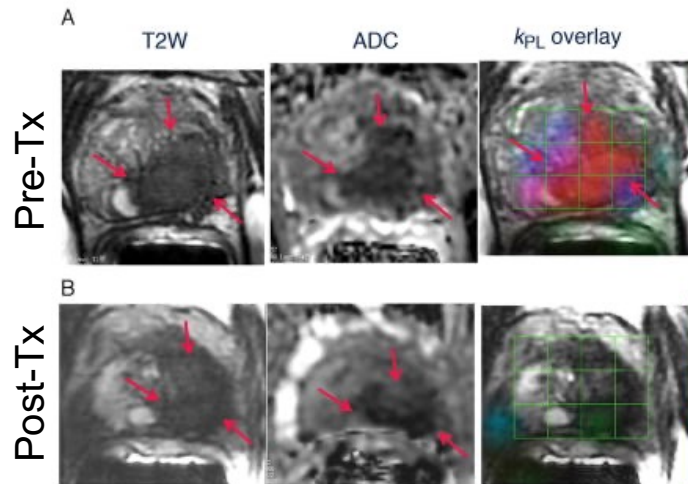
- Most common 'two site' model, with one physical compartment and two chemical pools
- Simple precursor-product relationship:

$$\frac{\partial Lac(t)}{\partial t} = k''_{PL} Pyr(t) - R_{Lac} Lac(t)$$



Kinetic Modeling: One Compartment (Precursor-Product)

- Pros:
 - Relatively robust
 - Fewer unknowns, limited prior knowledge needed
 - Readily extendable to multiple metabolites
- Cons:
 - Overly simplistic
 - Does not account for vasculature
 - k_{PL} is an apparent reaction rate, **not** an enzymatic rate
- Despite its simplicity, k_{PL} has shown promise as an imaging biomarker of tumor grade and treatment response^{1,2}

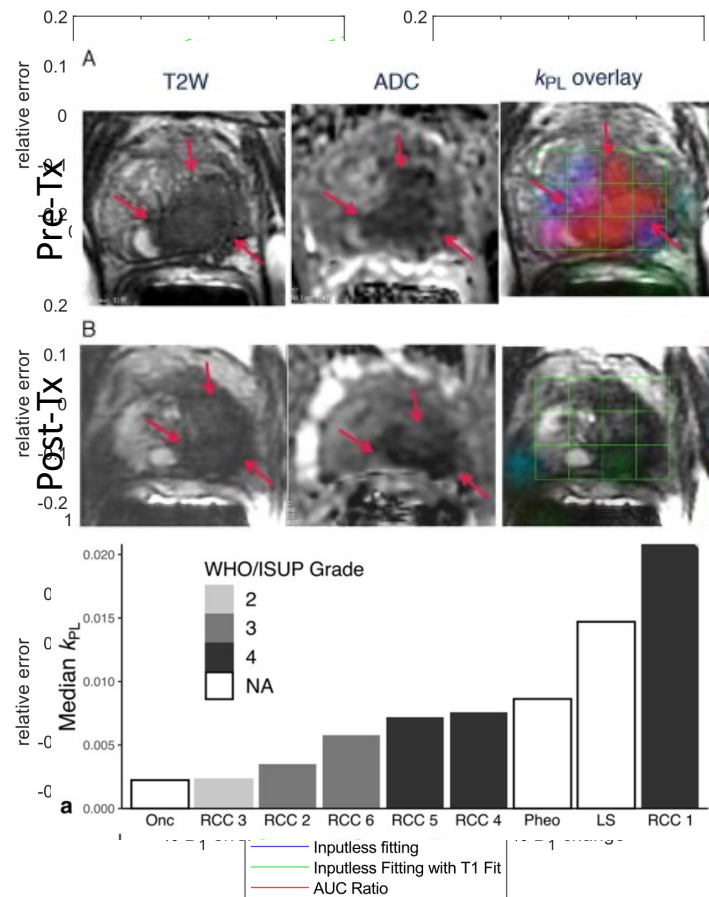


¹Aggarwal et al., Eur Urol 2017

²Ursprung et al., Cancers 2022

Quantification: Kinetic Modeling vs Model-Free

- Ultimately want to answer a scientific or clinical question
- Kinetic models are more invariant than AUC ratio to many experimental conditions and confounders
 - Rate constants are independent of FA
 - Invariant to bolus characteristics
- BUT, they require assumptions of their own
 - How many compartments?
 - Are R1 values known? What about the reverse reaction?
- Simulations are key to understanding the metric's sensitivity to noise, experimental variation, and model mismatch (e.g. error in T1, FA, etc)
- Lab this week will introduce you to the code behind the one-compartment model and show you how to setup your own Monte Carlo simulations



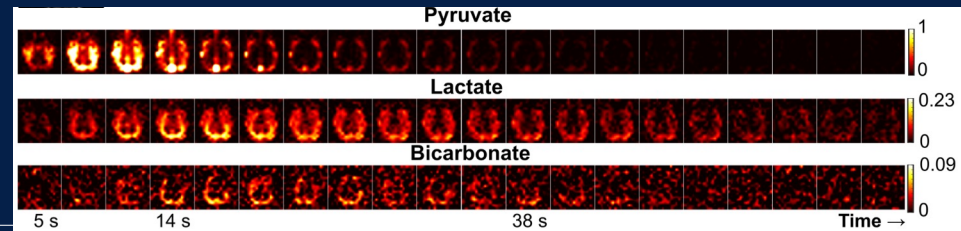
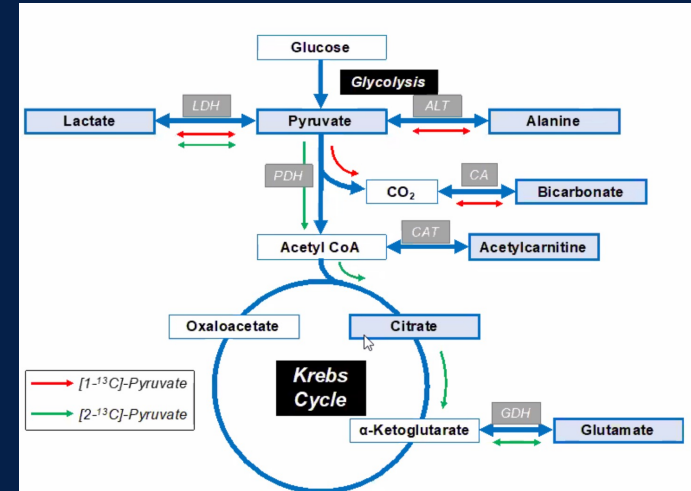


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Denoising HP ^{13}C Data

HP ^{13}C Data are SNR Limited

- So we can extract metabolite signals and quantify metabolism. Great!
- Despite the significant increase to polarization, often still SNR limited
 - Always want higher spatial resolution, more timepoints
- In particular, many metabolites have limited SNR for imaging
 - $[1-^{13}\text{C}]$ pyruvate $\rightarrow$ bicarbonate
 - $[2-^{13}\text{C}]$ pyruvate $\rightarrow$ TCA intermediates^{1,2}

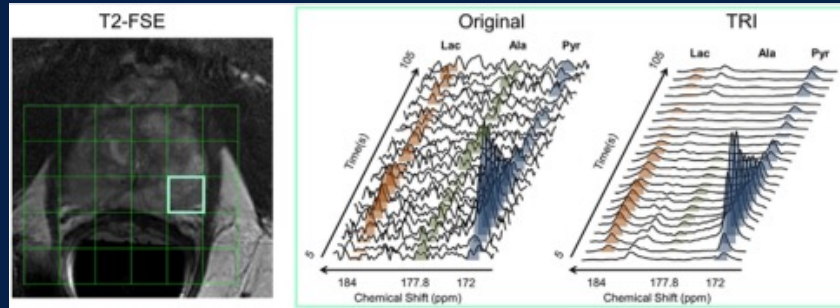


¹Josan et al., MRM: 2013.

²Chung et al., JMR 2019.

Denoising HP MRSI Data

- Denoising leverages the spatial, spectral, and dynamic information in an HP ^{13}C experiment
- Can provide significant SNR boost with less blurring/resolution loss than conventional filtering
 - Better quantification of low SNR metabolites
 - Finer resolution
 - Longer imaging window

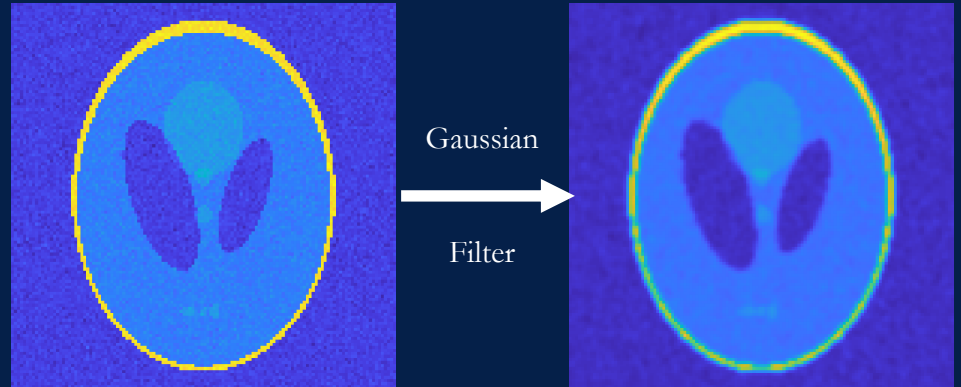


Approaches to Improving SNR

- Averaging

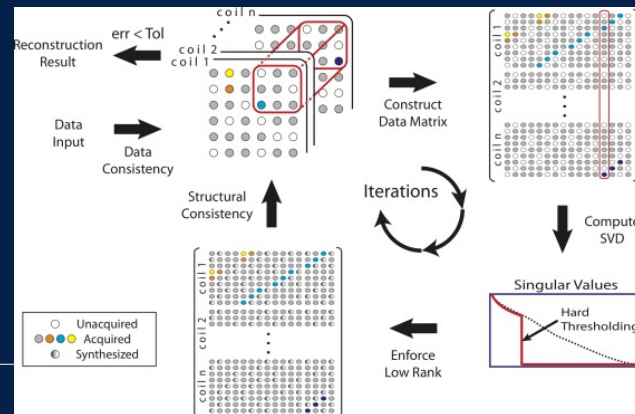
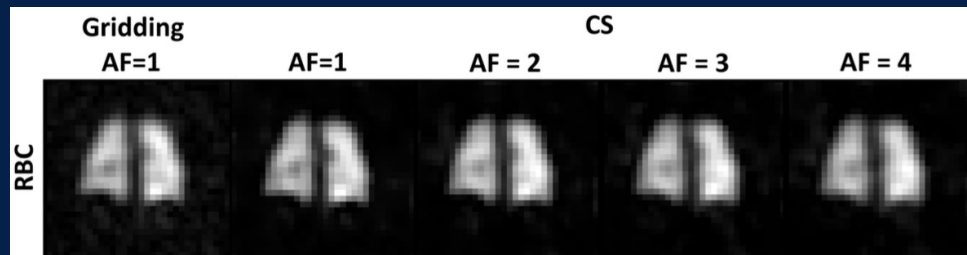
Approaches to Improving SNR

- ~~Averaging~~
- Filtering
 - Spectral/spatial apodization



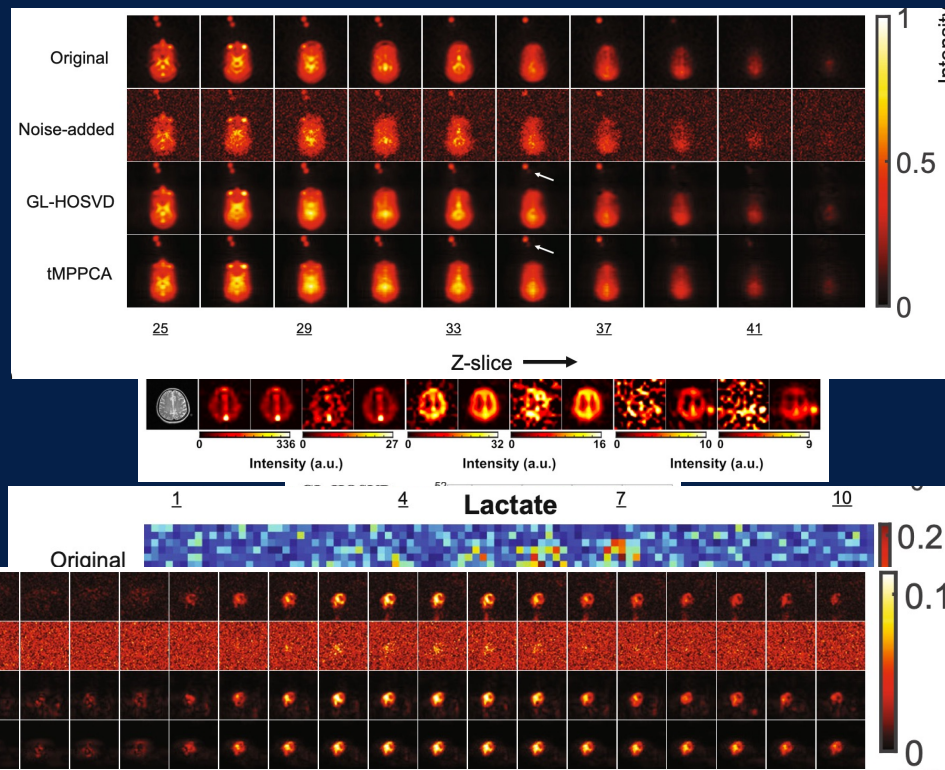
Approaches to Improving SNR

- ~~Averaging~~
- Filtering
- Exploit sparsity in some domain
 - Compressed-sensing
 - Low-rank matrix completion



Approaches to Improving SNR

- ~~Averaging~~
- Filtering
- Exploit sparsity in some domain
- Can exploit spatial/temporal correlation for image denoising (GL-HOSVD³, tMPPCA⁴, etc)
 - ¹H DWI¹
 - HP ¹³C MRI²⁻⁴
 - ... and other x-nuclei⁴



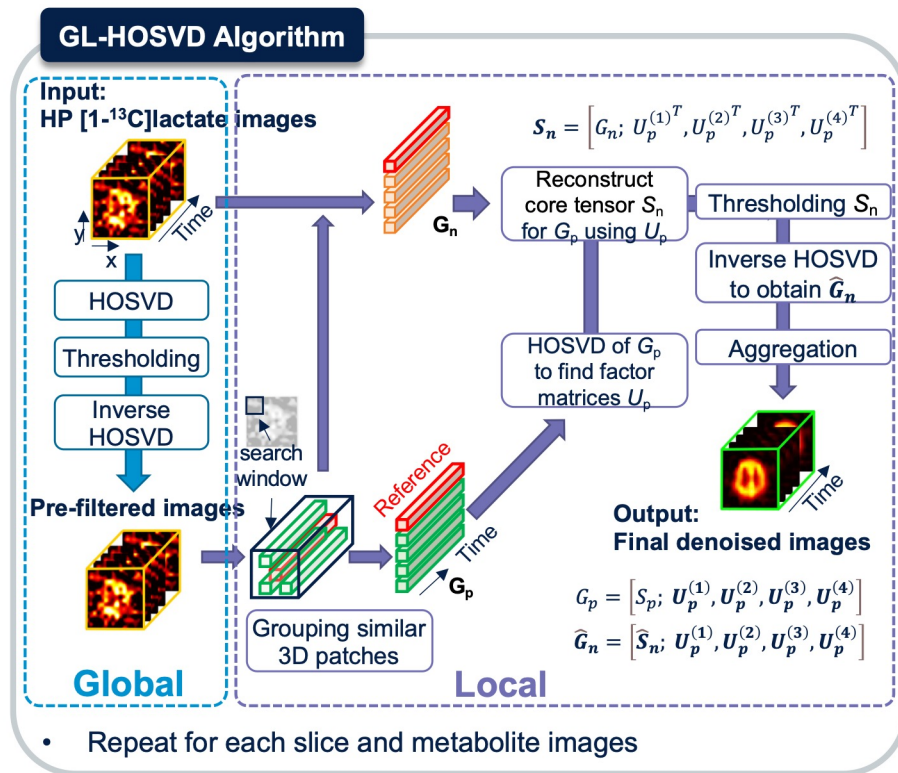
¹Zhang et al., Neuroimage 2017 ⁴Christensen et al., MRM 2023.

²Brender et al., Sci Rep 2019.

³Kim et al., MRM 2021

Patch-based HOSVD Denoising

Methods- Global-local Higher-Order Singular Value Decomposition (GL-HOSVD) algorithm



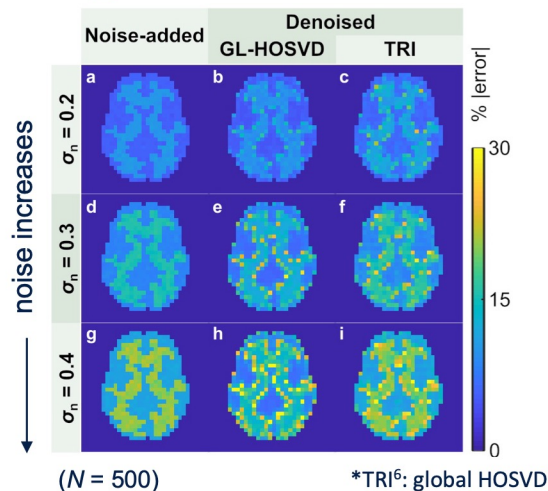
How to assess performance?

Results

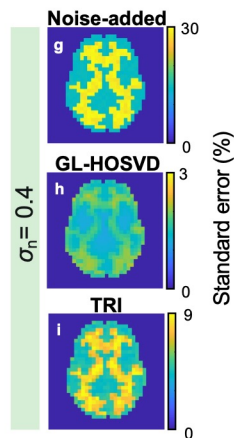
Assessment of Denoising Performance of GL-HOSVD

Accuracy of k_{PL} quantification

▪ k_{PL} bias

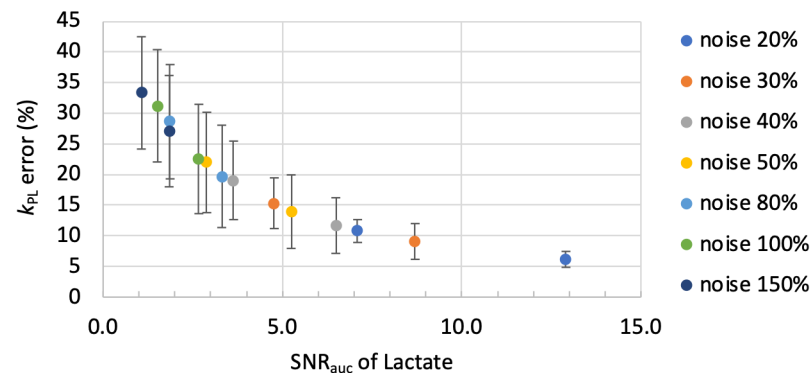


▪ k_{PL} precision



- **Lowest k_{PL} bias and highest k_{PL} precision from GL-HOSVD**
- High k_{PL} errors from GL-HOSVD at the interface between the white and gray matter

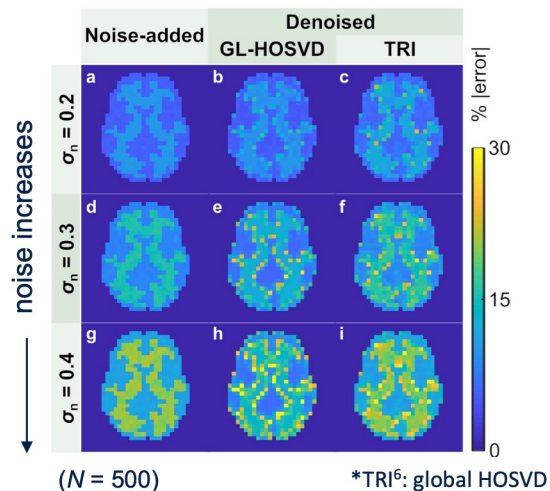
Accuracy of k_{PL} quantification



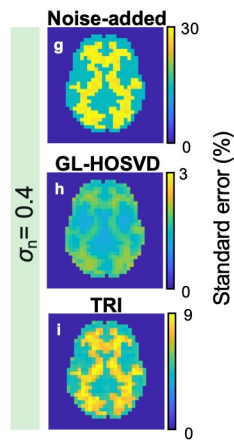
Results

Accuracy of k_{PL} quantification

k_{PL} bias

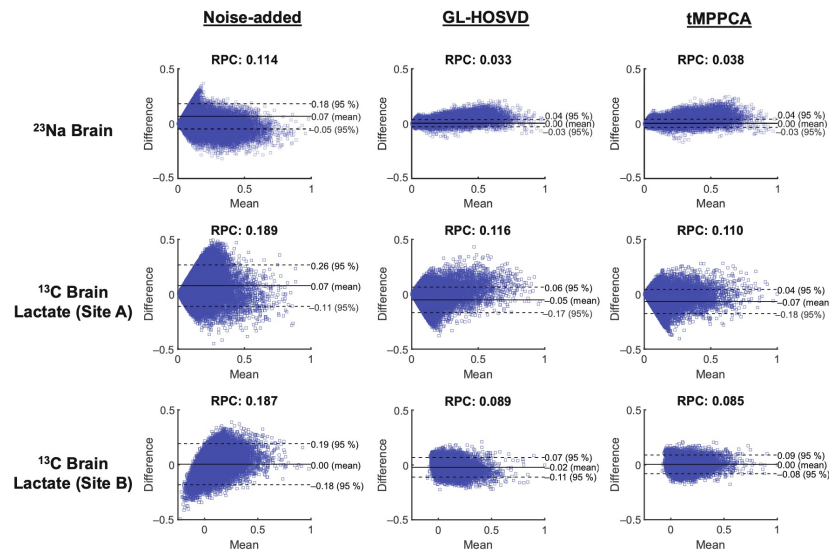


k_{PL} precision



- **Lowest k_{PL} bias and highest k_{PL} precision from GL-HOSVD**
- High k_{PL} errors from GL-HOSVD at the interface between the white and gray matter

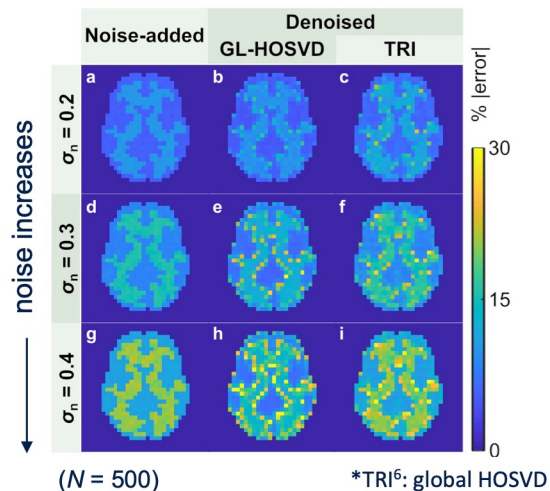
Signal quantification



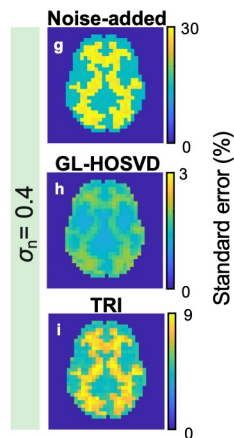
Results

Accuracy of k_{PL} quantification

k_{PL} bias

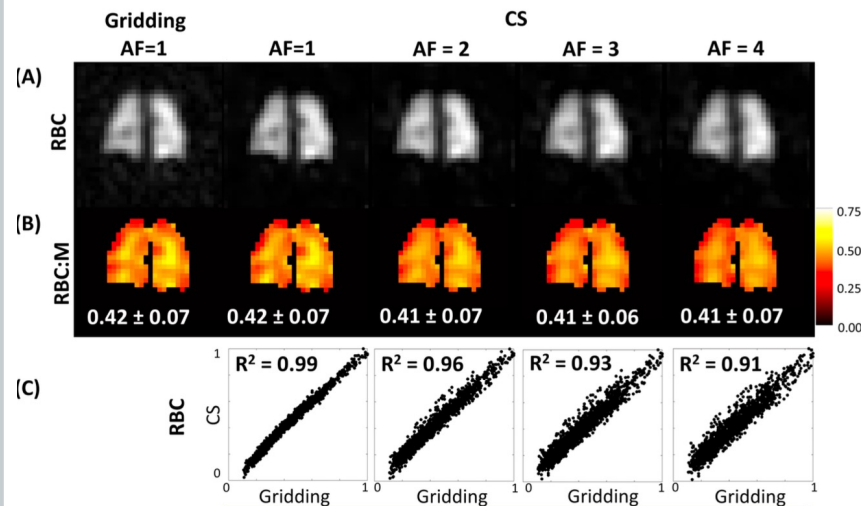


k_{PL} precision



- **Lowest k_{PL} bias and highest k_{PL} precision from GL-HOSVD**
- High k_{PL} errors from GL-HOSVD at the interface between the white and gray matter

RBC:Membrane quantification



Summary

- HP ^{13}C data needs to be processed properly to maximize accuracy
- Model-free and kinetic modeling approaches provide a way to quantify metabolism
 - Keep endpoint in mind - *“All models are wrong, but some are useful”*
 - For ^{13}C , not necessarily a one-size-fits-all approach – what works best for cell studies might not for multi-site clinical trials
 - Metabolite amplitudes: Use when presence alone is informative, or for standardized/calibrated acquisitions (cell studies, brain imaging)
 - AUC ratios: Use for dynamic acquisitions that captures the entire bolus; consistent flip angle schedule; more robust for very noisy data
 - Rate constants (k_{PL}): Use for dynamic acquisitions, particularly when bolus timing or flip angle schedules vary
- Further post-processing can ‘denoise’ HP data, enabling improved image quality and/or finer resolution
- In all cases, numerical simulations are key to understanding how parameters (both known and unknown) can influence quantification

Summary

- Code is available to get you started:
 - Quantification:
 - Model-free and one compartment kinetic models: <https://github.com/LarsonLab/hyperpolarized-mri-toolbox>
 - HEMEX (two compartment): <https://github.com/NichVC/HEMEX-HP>
 - Denoising:
 - GL-HOSVD: https://github.com/ykim-hmtrc/hp13c_EPI-hosvd_denoising
 - Tensor MPPCA: <https://github.com/sunenj/Tensor-MP-PCA>