

Hyperpolarized ^{13}C MRI via dissolution Dynamic Nuclear Polarization

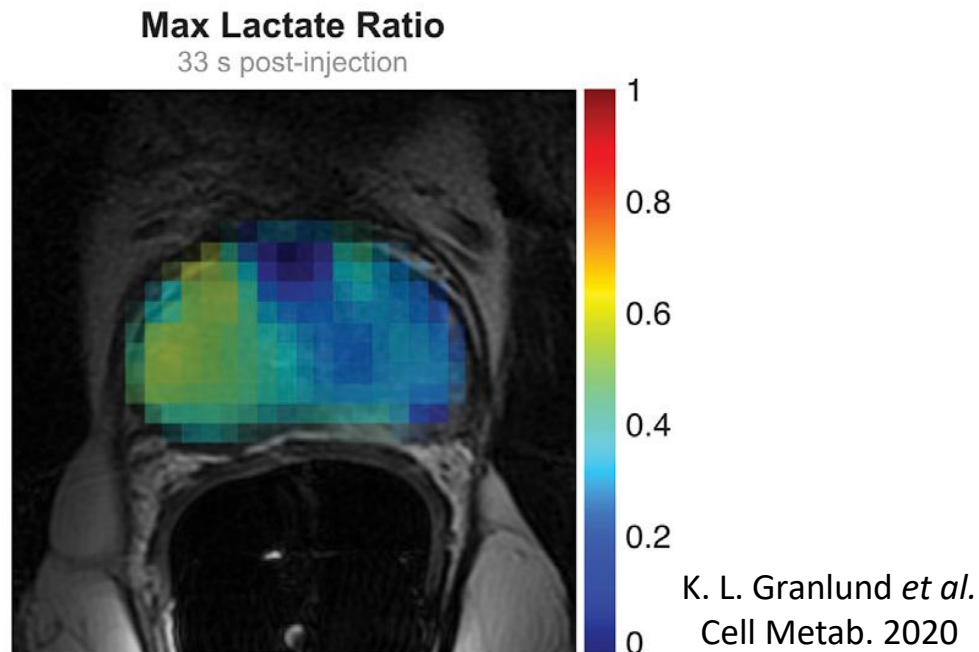
Arnaud Comment – Aarhus Training Course Oct 2026



GE HealthCare

Why hyperpolarizing ^{13}C ?

- No need to hyperpolarize ^1H since human body contains 40 M $^1\text{H}_2\text{O}$
- Other nuclei are however less concentrated and SNR is too low for MRI scans
- Carbon forms the backbone of most molecules involved in metabolic processes
- ^{13}C exhibits large chemical shift dispersion
- Real-time detection of metabolic fluxes
- High contrast-to-noise ratio images



G. D. Reed *et al.* IEEE T.
Med. Imaging 2014

Dynamic Nuclear Polarization (DNP)

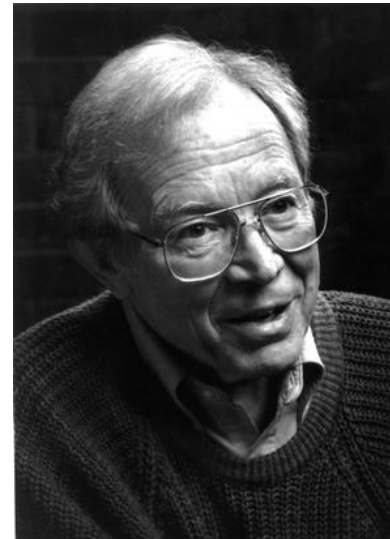
- In 1952, Overhauser predicted the possibility to transfer the large electron spin polarization to nuclear spins
- In 1953, Carver and Slichter demonstrated that nuclear spin polarization can indeed be enhanced by electrons in metals and liquids
- In 1957, Jeffries showed that nuclear spins can be polarized by electron spins using forbidden transitions in paramagnetic crystals
- In 1958, Abragam introduced the concept of “solid effect” to describe DNP in diamagnetic solids containing free radicals



Albert W. Overhauser



Charles P. Slichter



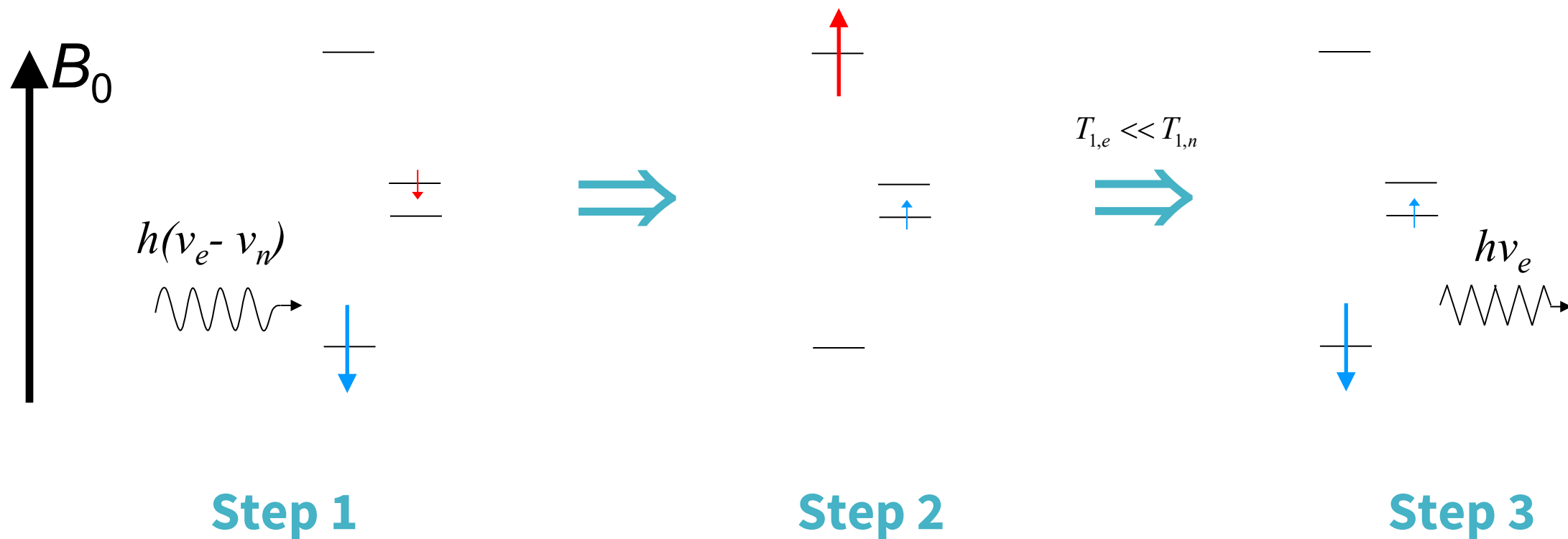
Carson D. Jeffries



Anatole Abragam

DNP by solid effect

- Polarization transfer through “forbidden” transitions



- Energy balance: $h(\nu_e - \nu_n) + h\nu_n = h\nu_e$

Thermodynamic description of solid effect

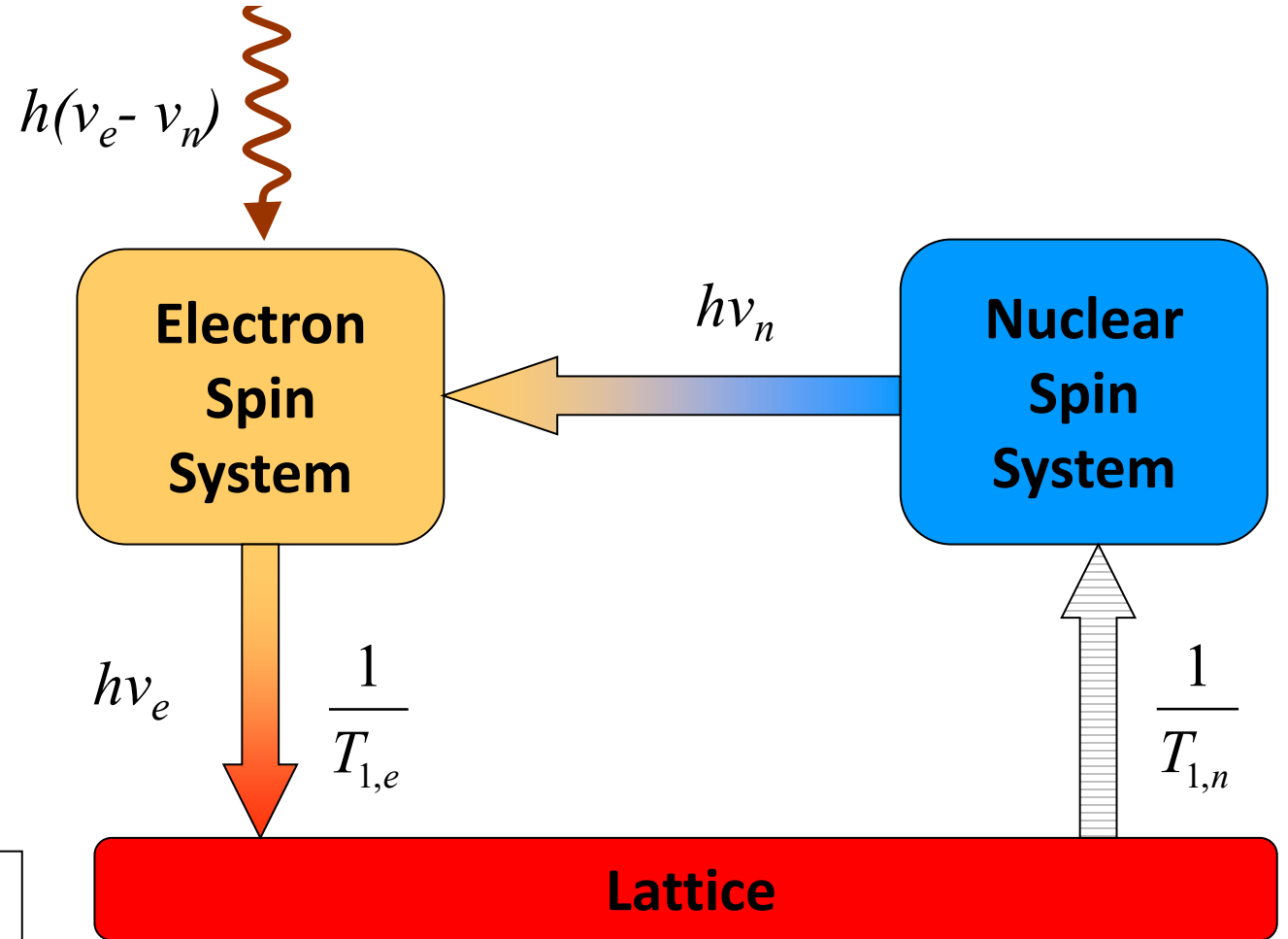
- Spin polarization:

$$\mathbf{P} = \frac{\hbar\gamma B_0}{2k_B \mathbf{T}}$$

- Spin temperature:

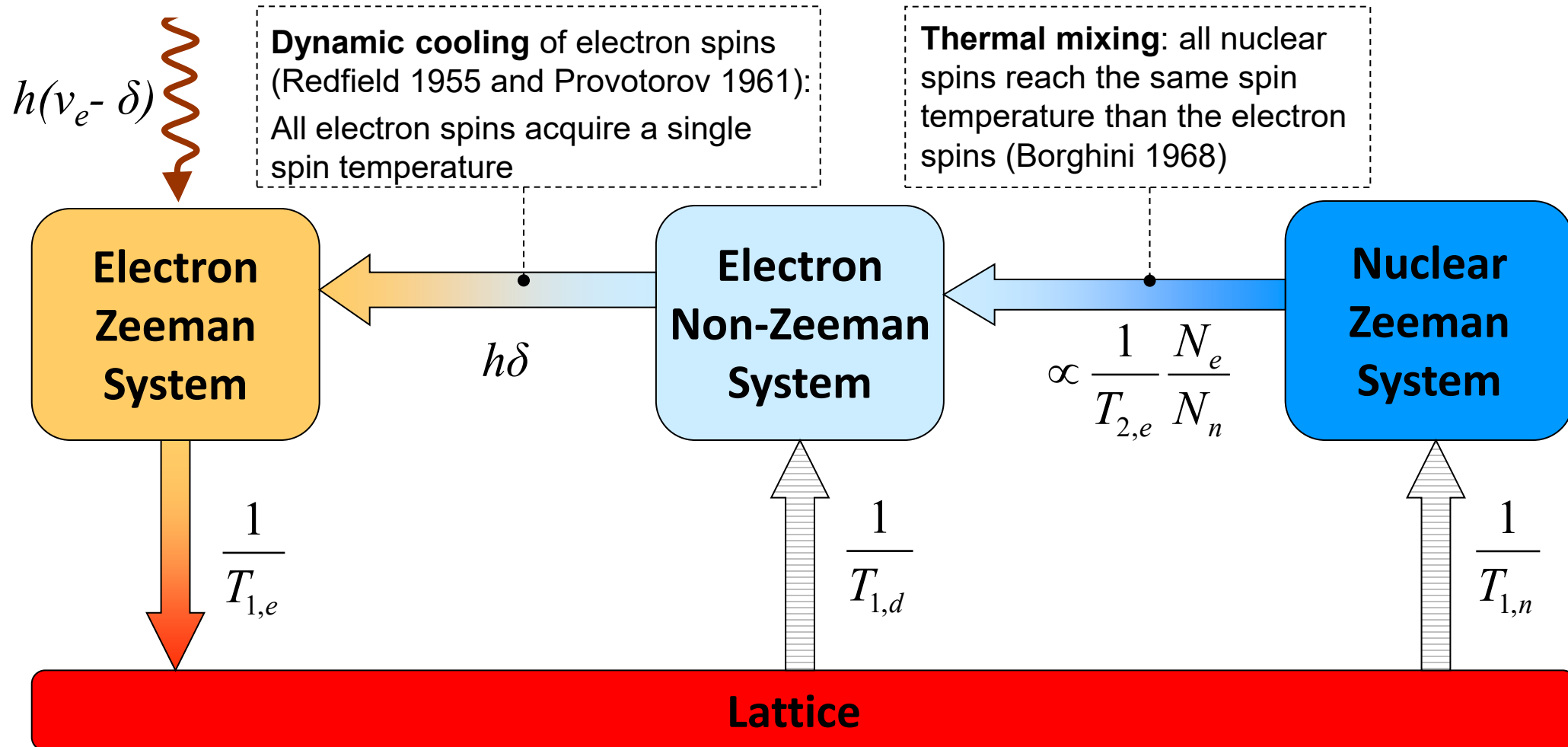
$$\mathbf{T}_S = \frac{\hbar\gamma B_0}{2k_B \mathbf{P}}$$

- Coolant: polarized electron spins
- Driving power: microwaves
- Dissipation: heat into liquid He bath



$T_{1,e}$ is much shorter than $T_{1,n}$

Thermodynamic description of thermal mixing

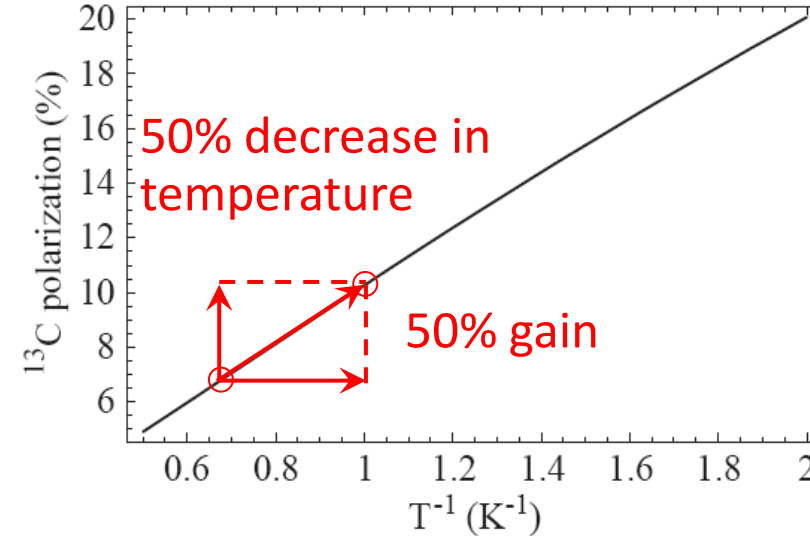
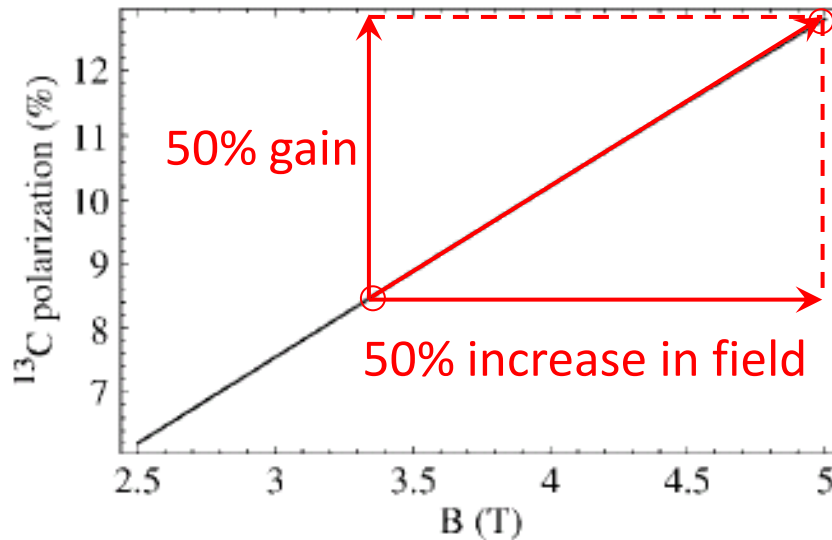


- Short $T_{2,e}$, $T_{1,e}$ and long $T_{1,n}$, $T_{1,d}$

Temperature and field dependence of DNP

- No quantitative theoretical model for DNP has been developed to date
- Qualitative trend provided by numerical solutions of Borghini model (Thermal mixing)

M. Borghini Phys. Rev. Lett 1968



A. Comment *et al.* Concepts Magn. Reson. 2007

- Experimental results match theoretical predictions

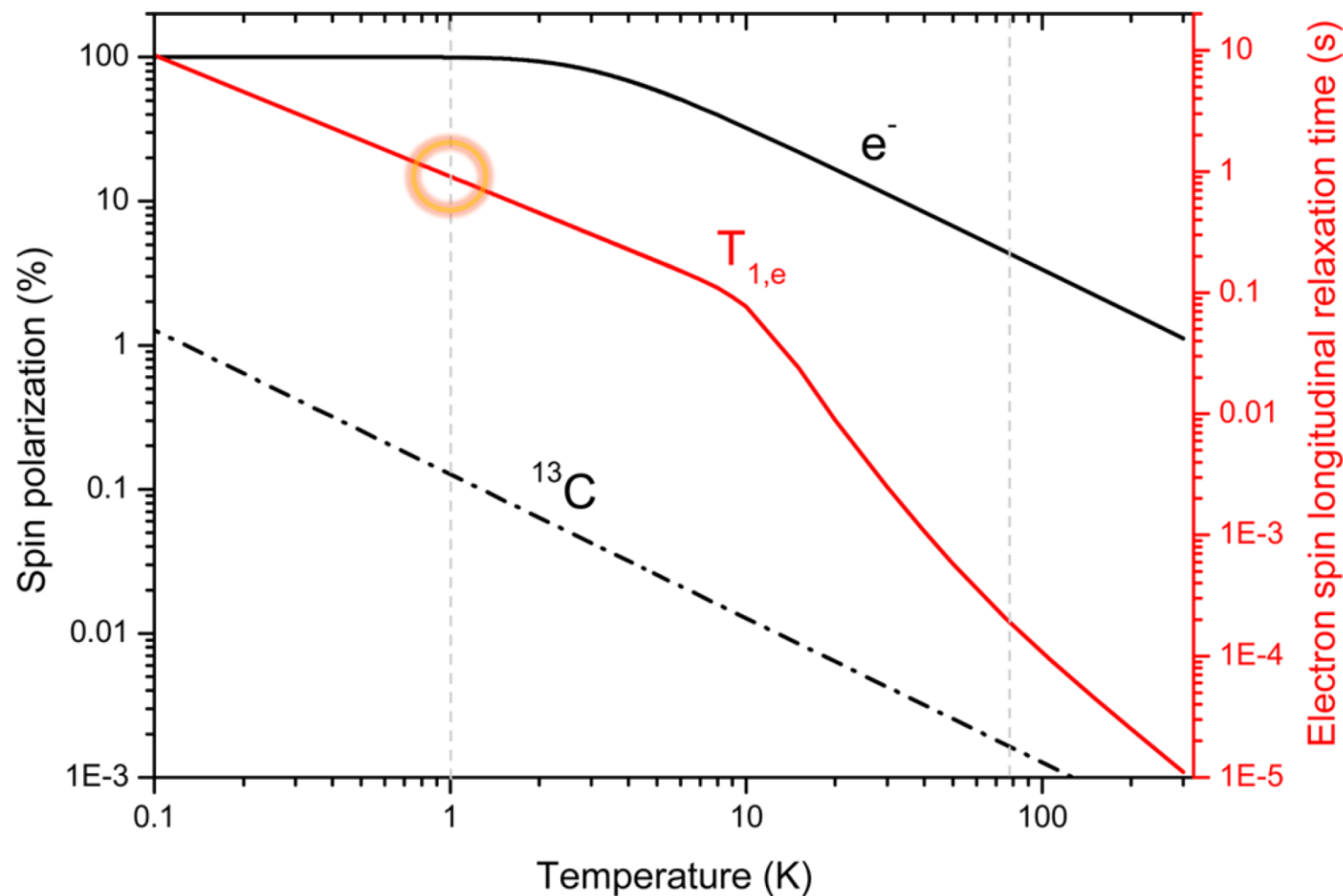
S. Jannin *et al.* J. Chem. Phys. 2008

What is the optimal temperature for DNP?

- In a field larger than 3 T, electron spins are polarized to ~100% below 2 K

$$P_{eq} = \frac{\hbar\gamma B_0}{2k_B T}$$

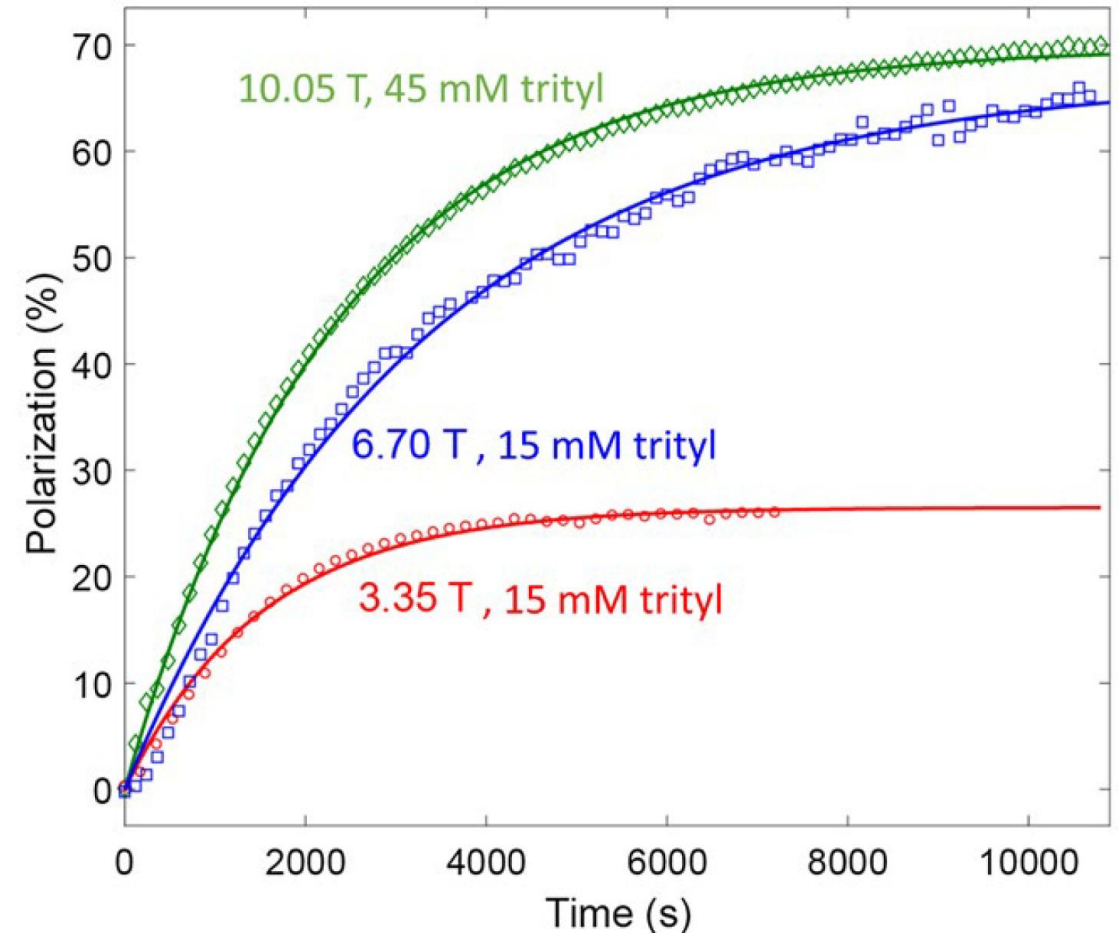
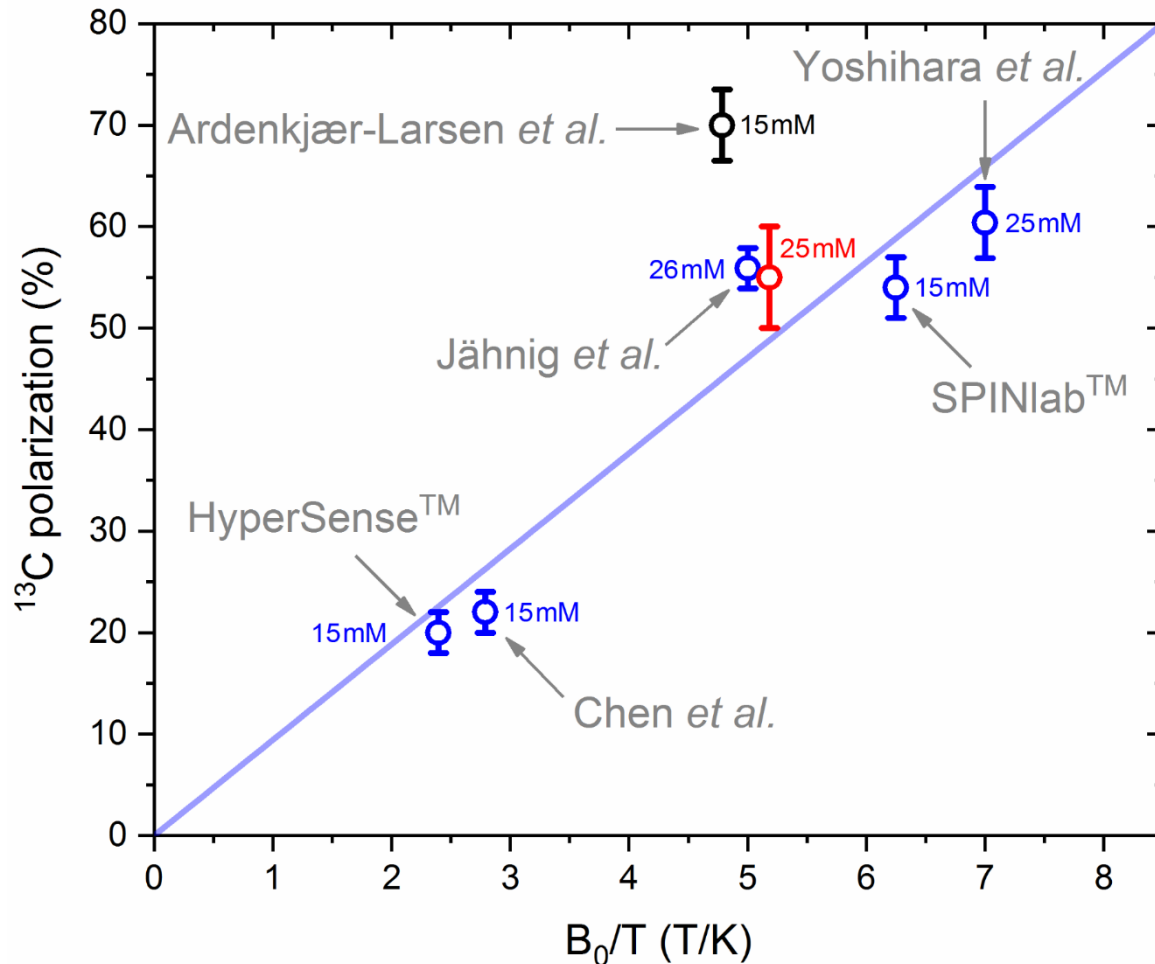
- For a given magnetic field (e.g. 5 T), the optimal temperature for DNP will mostly depend on $T_{1,e}$



A. Comment and M. E. Merritt, Biochem. 2014

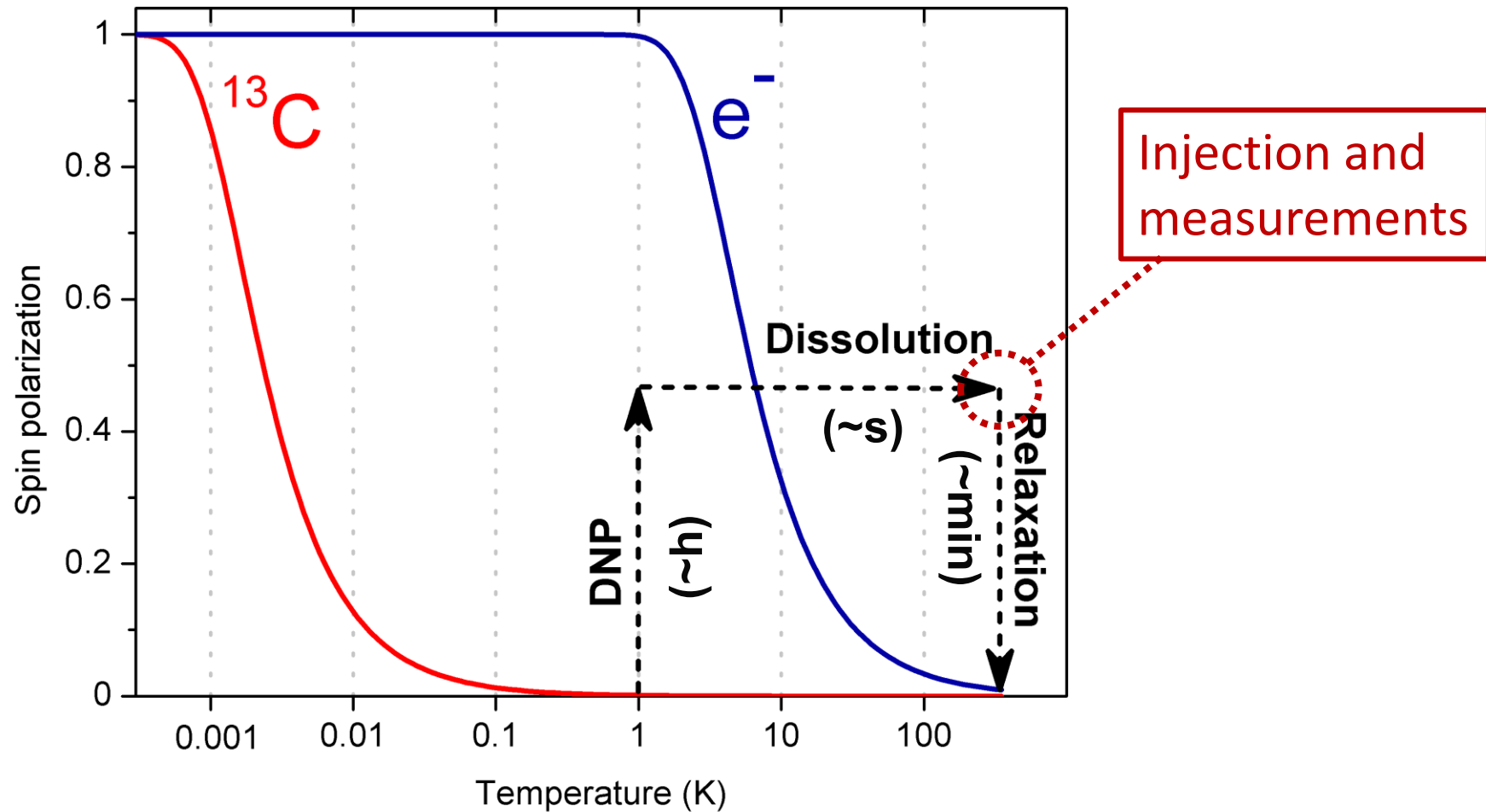
What is the ideal magnetic field for DNP?

- Because $T_{1,e}$ becomes too short at higher fields, higher EPA concentration is needed
- 7 T is most likely the optimal field



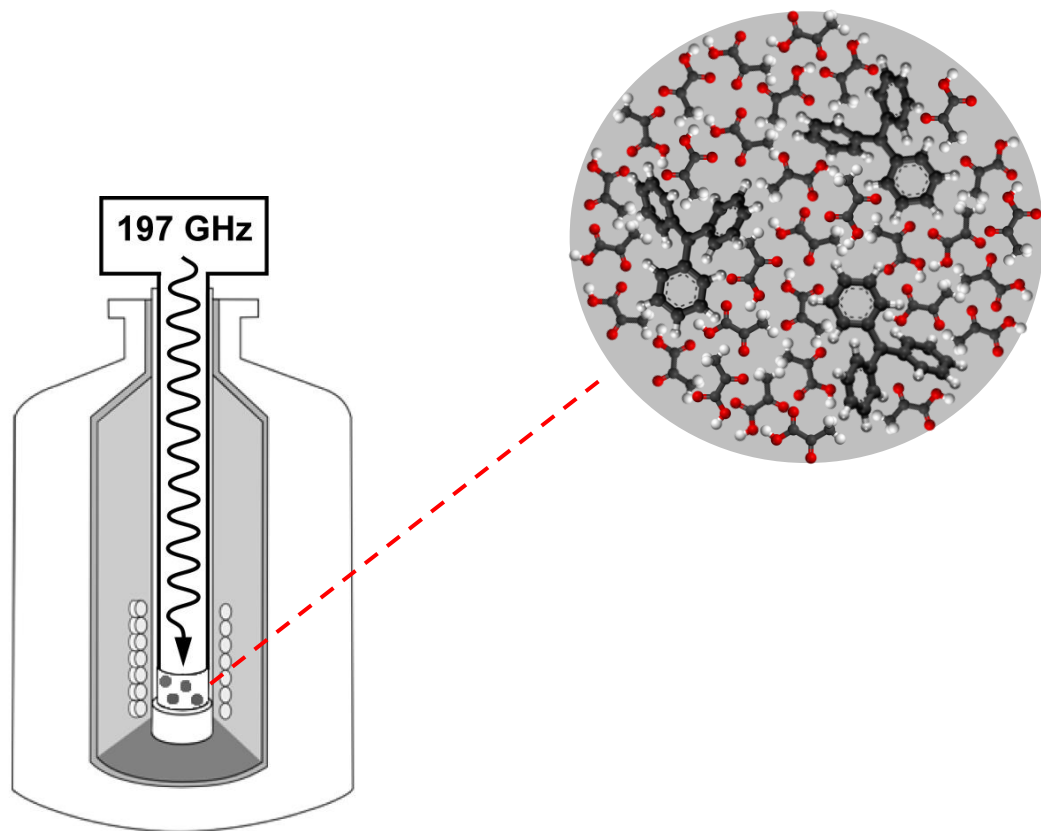
Dissolution DNP for Hyperpolarized ^{13}C MR

- Solid-to-liquid phase transition should be rapidly performed in high magnetic field environment to maintain enhanced nuclear spin polarization $\Rightarrow$ ***in situ* dissolution**

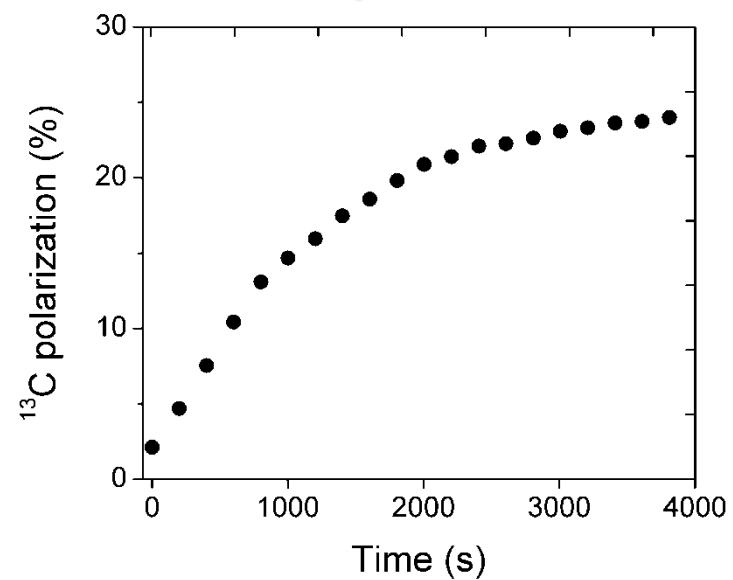
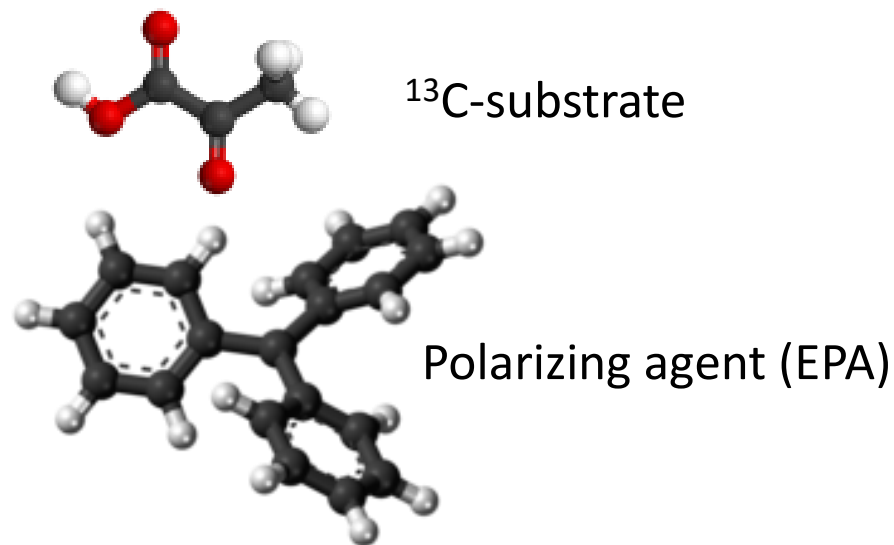


Preclinical in vivo studies

J.H. Ardenkjær-Larsen *et al.*, PNAS 2003



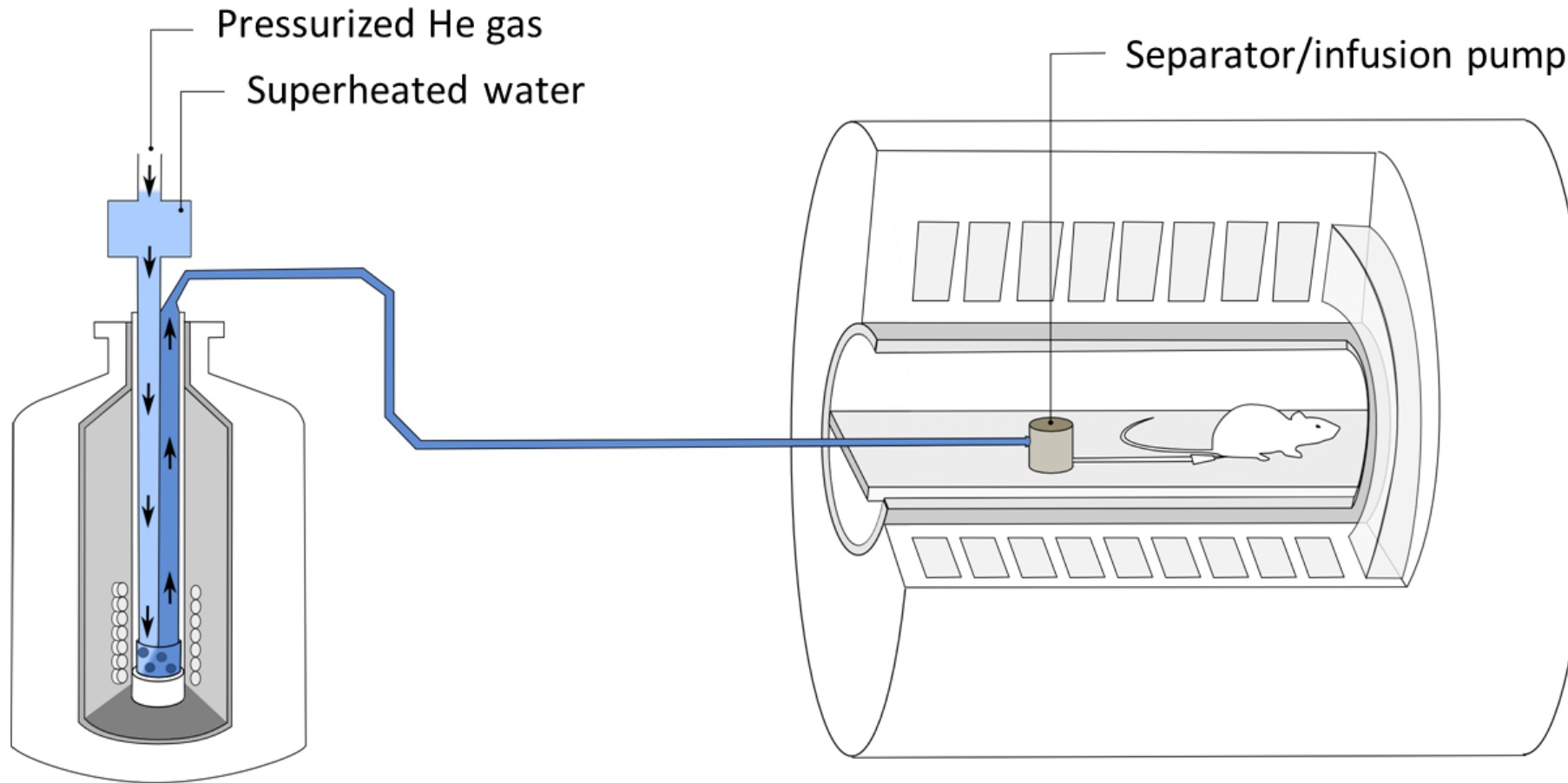
7 T / 1 K hyperpolarizer



Preclinical in vivo studies

A. Comment *et al.* Concepts Magn. Reson. 2007

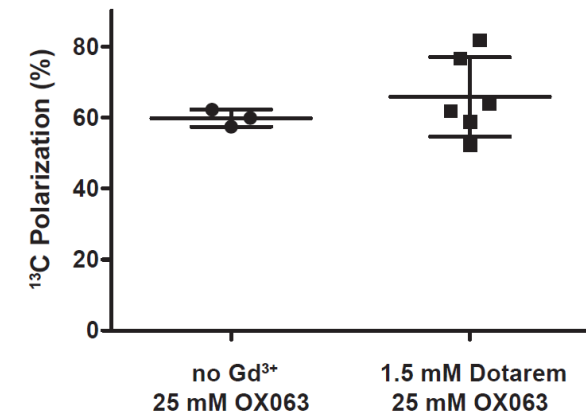
H.A.I. Yoshihara *et al.*, PCCP 2017



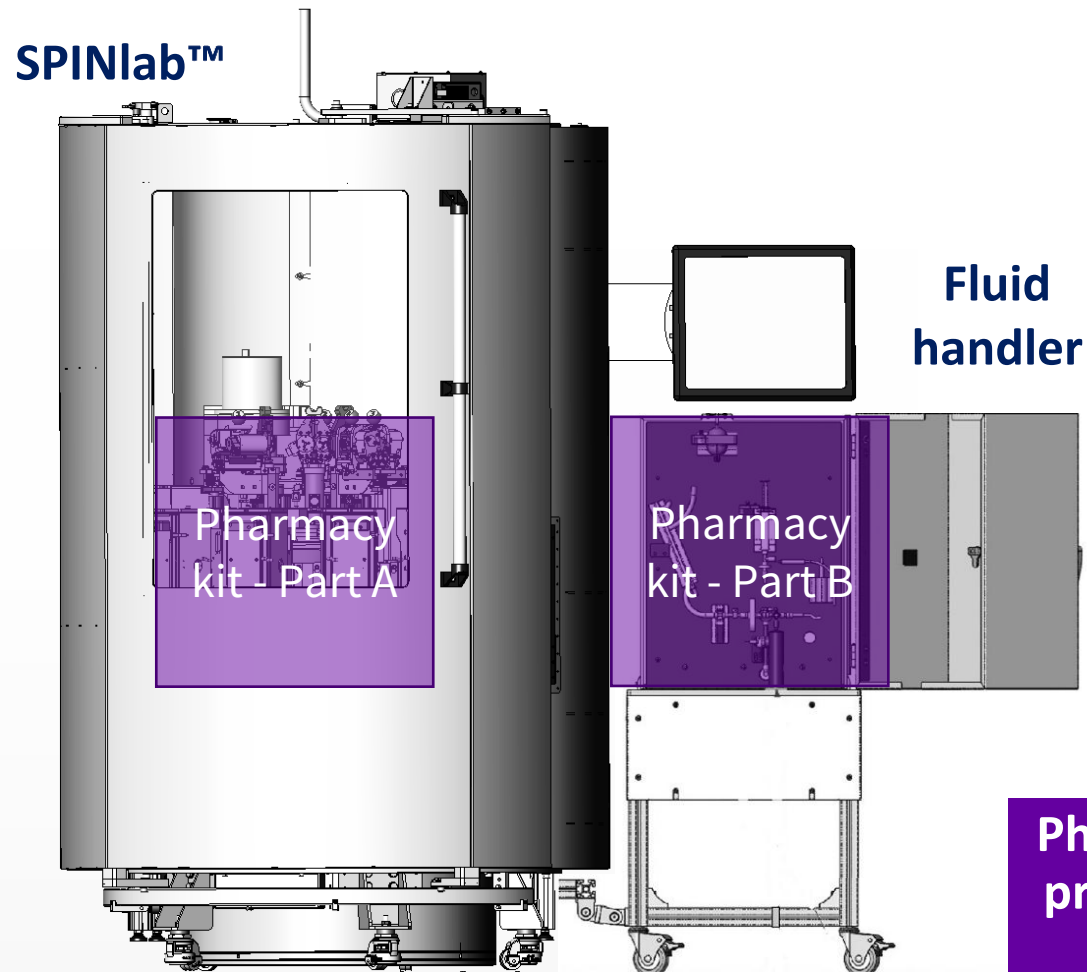
7 T / 1 K hyperpolarizer

3 s delay between dissolution and injection

Up to 80% polarization in
[1-¹³C]pyruvate
at time of injection



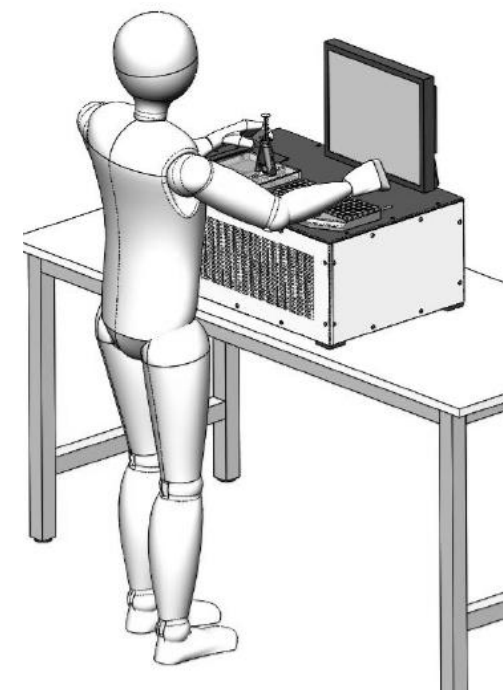
Hyperpolarized ^{13}C MRI - Hardware for clinical research



SIGNA™ Premier with MNS



Multi-Probe QC



Pharmacy kit (consumable) required for preparing injectable hyperpolarized ^{13}C probes

Clinical Hyperpolarized ^{13}C MR Study - Work Flow

Pharmacy kit fill

ISO7 cleanroom or biohood



1. Admix EPA with ^{13}C -pyruvate
2. Insert mixture in sample vial
3. Fill and assemble pharmacy kit

30 min/kit (can be frozen)

Load pharmacy kit in SPINlab

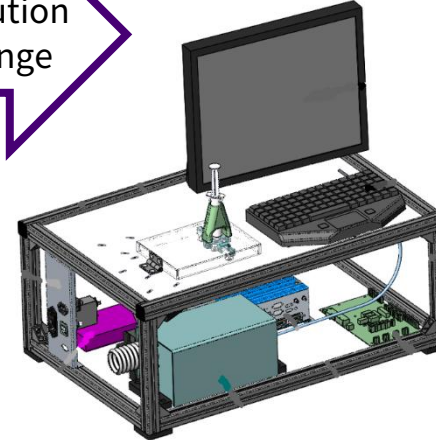
Hyperpolarization



1. Microwave irradiation
4 kits in parallel (3h/kit)
2. Dissolve sample in hot water

Draw solution into syringe

QC measurements



1. Draw aliquot from syringe
2. Measure pH, T, pyruvate and residual EPA concentrations

Within 1 min

Place syringe on power injector

^{13}C MRI



1. Inject ^{13}C -pyruvate solution
2. Perform ^{13}C MRI scans

Less than 5 min

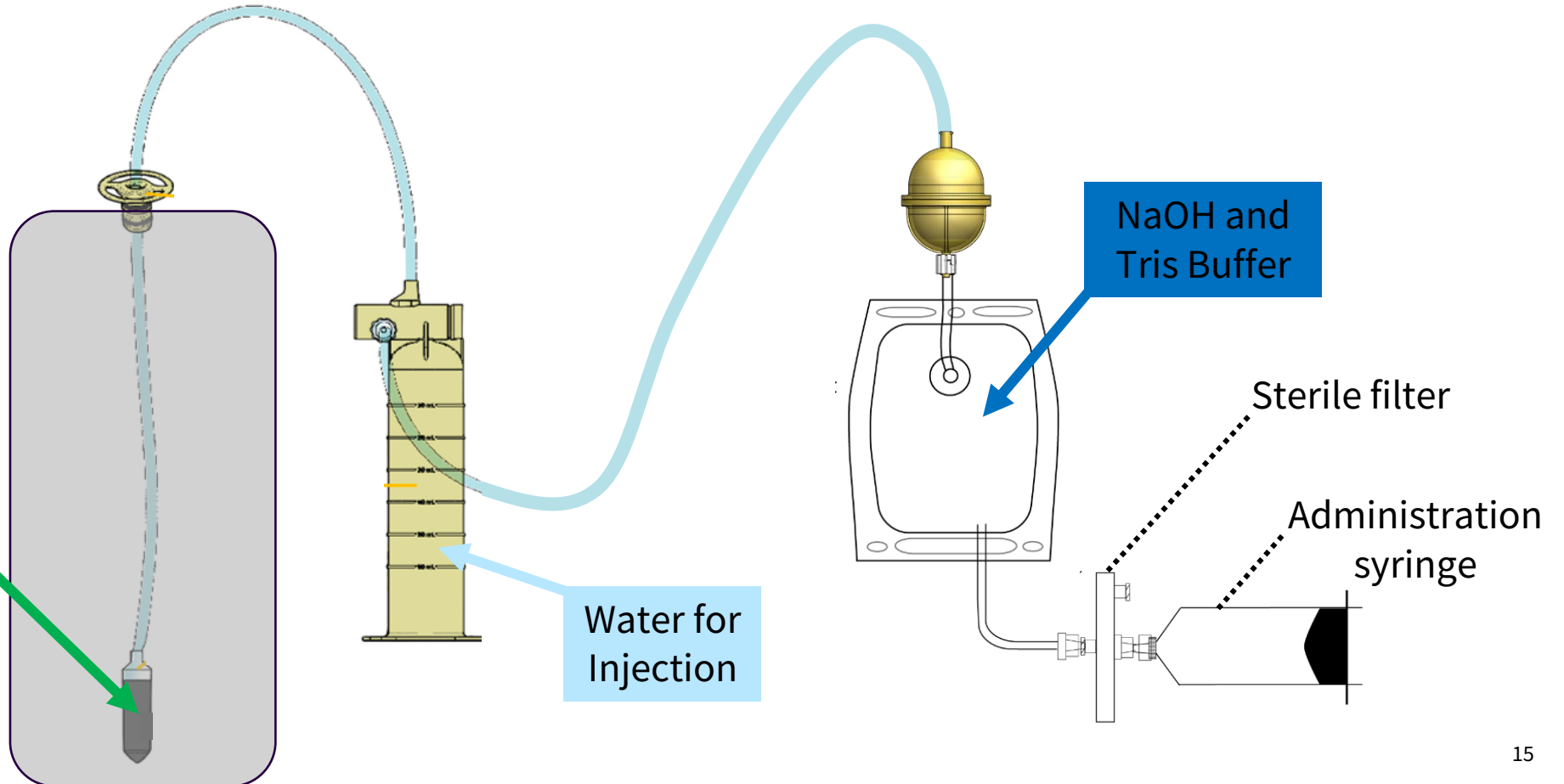
Pharmaceutical compounding to produce sterile ^{13}C -pyruvate solution

- Three starting components:
 - ^{13}C -pyruvic acid (1.15 mL) with EPA reagent (15 mM)
 - Water for injection (38 mL)
 - Excipient: NaOH solution (290 mM) with Tris buffer (160 mM) (36.5 mL)
- EPA reagent filtered down to few μm : strong safety profile with a margin of safety > 1,000 fold



Pyruvic acid
&
EPA (15 mM)

GMP facility



Clinical studies with SPINlab™

- Single-use pharmacy kits were designed for SPINlab™ because the concept one patient-one kit is the safest and widely accepted by regulatory bodies worldwide
- Neither severe nor moderate adverse events reported on all received data across about 2,500 injections of ^{13}C -pyruvate doses into human subjects
- Each single dose is QC'ed prior to injection (T, pH, ^{13}C -probe concentration, residual radical concentration)

SPINlab™



Hyperpolarized ^{13}C -pyruvate - All received data as of 31 Dec 2025				
	Volunteers with one or more injections	Volunteers with two or more injections	Volunteers with three or more injections	Volunteers with four or more injections
Healthy volunteers	463	218	52	35
Patient volunteers	1103	360	78	25
TOTAL	1566	578	130	60

Pharmacy kit



New PK to enable central aseptic filling, dose storage, and shipment

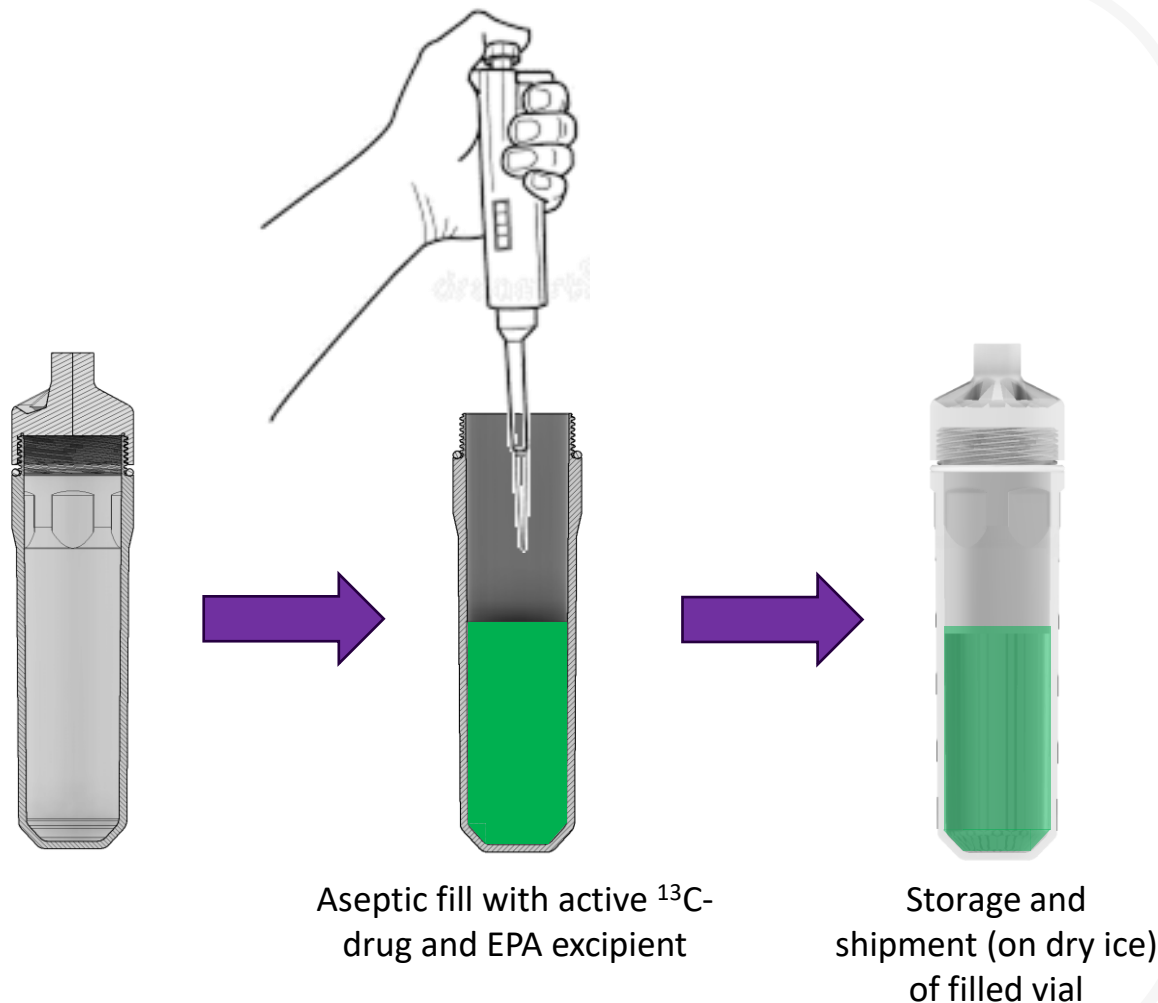
Benefits:

- No need for local specialized GMP facility
- Major step towards standardization and commercialization

Class II Biosafety cabinet
located in uncontrolled environment (MRI suite)



User removes cap and assemble
pharmacy kit in controlled environment 17

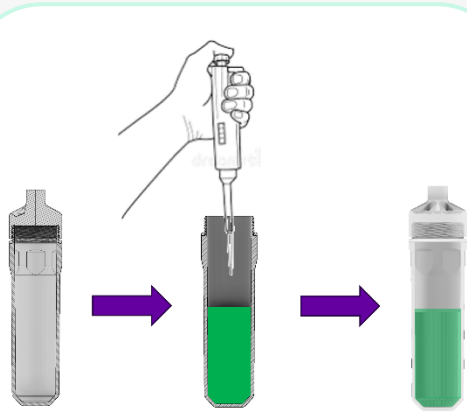


Aseptic fill with active ¹³C-
drug and EPA excipient

Storage and
shipment (on dry ice)
of filled vial

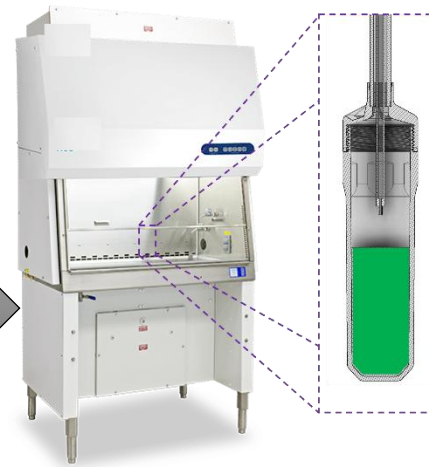
Clinical workflow for regulatory approval

GMP aseptic vial
fill with ^{13}C -probe

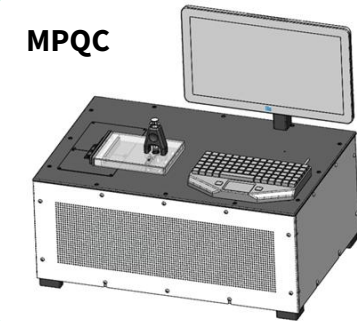


On-the day hospital assembly

Pharmacy kit assembly



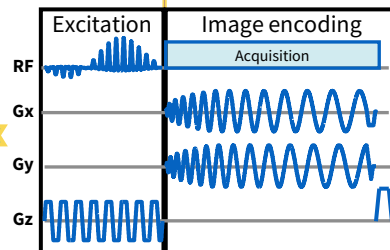
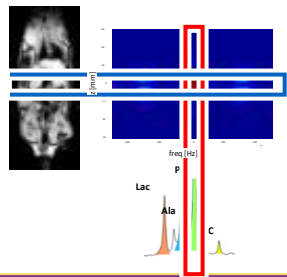
QC measurements



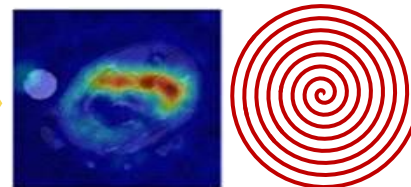
Hyperpolarised
 ^{13}C -pyruvate dose

Metabolic Imaging by Hyperpolarised ^{13}C MRI

Spectral-spatial excitation:
1 slice + 1 metabolite per exc



Single-shot readout (eg spiral)



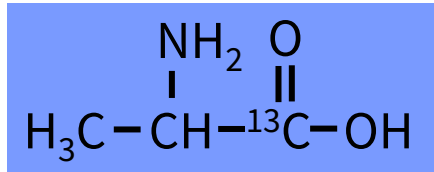
Dedicated RF coils
for ^{13}C MRI



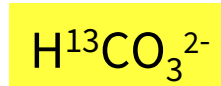
MR metabolic imaging with hyperpolarized ^{13}C -pyruvate

Resonances from $[1-^{13}\text{C}]$ pyruvate and its metabolic products are clearly separated at 3T

Alanine

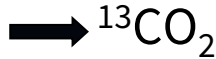
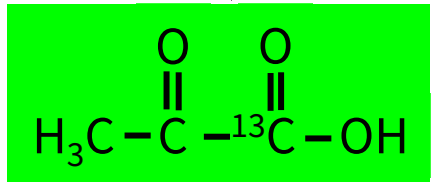


Bicarbonate

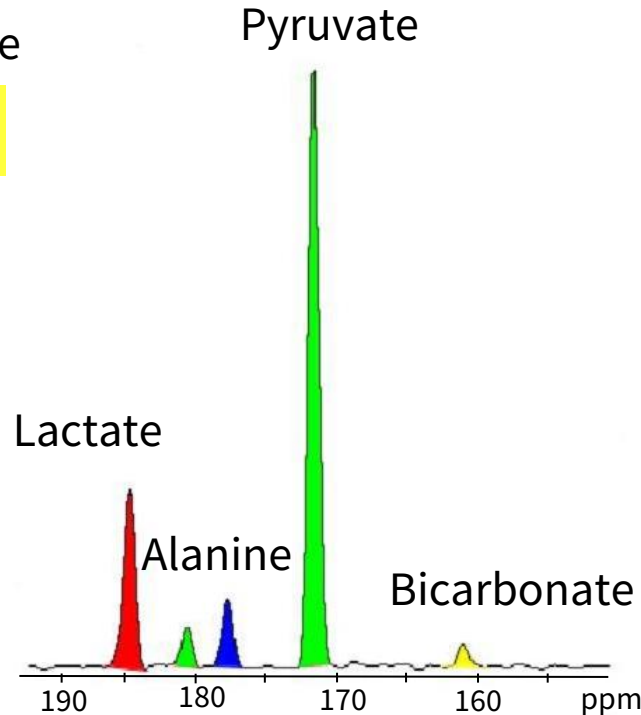
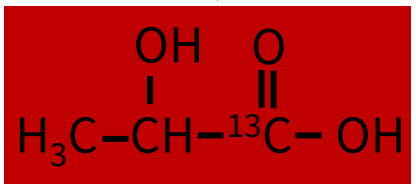


Pyruvate

Pyruvate

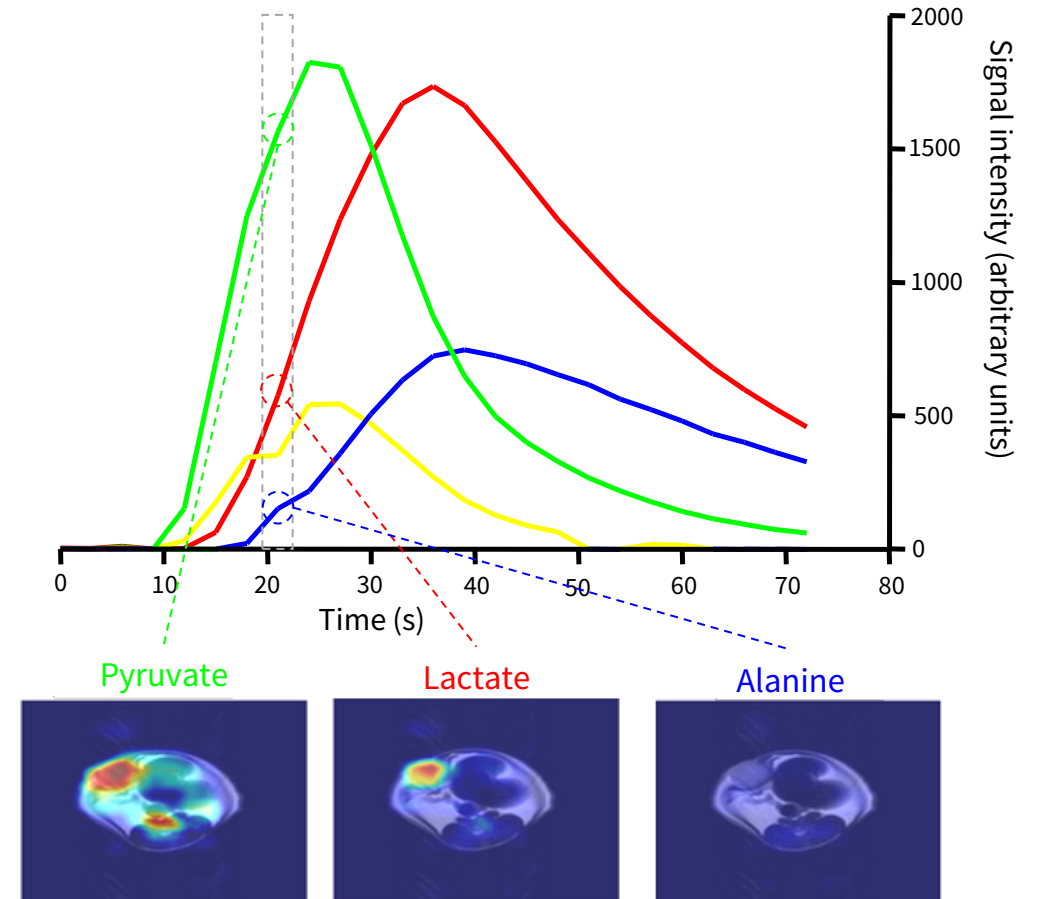


Lactate



Real-time MR metabolic imaging

Time course for substrate and products relates to metabolic fluxes

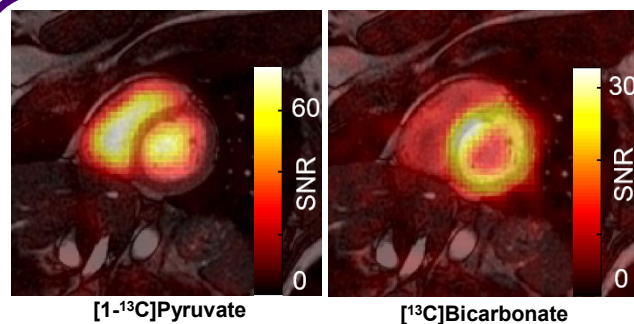


Enough signal to acquire image of individual metabolites at different time point

Clinical Studies

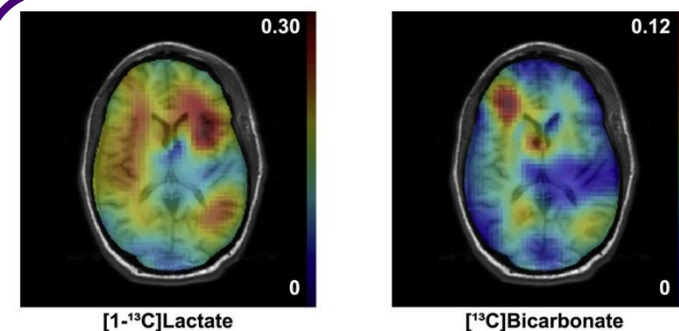
- Organs studied to date: prostate, brain, liver, heart, lung, spleen, kidney, pancreas, ... in fields including oncology, neurology and cardiology
- **Active surveillance & critical clinical decisions**
 - Tumor grading
 - Heart failure
 - Traumatic brain injury
- **Treatment response**
 - Radiotherapy
 - Chemotherapy
 - Immune therapy
 - Therapies targeting cardiac metabolism
- **Early detection**
 - Organ-specific tumors
 - Neurodegenerative diseases
 - Liver diseases

CARDIAC METABOLISM – SUNNYBROOK, TORONTO



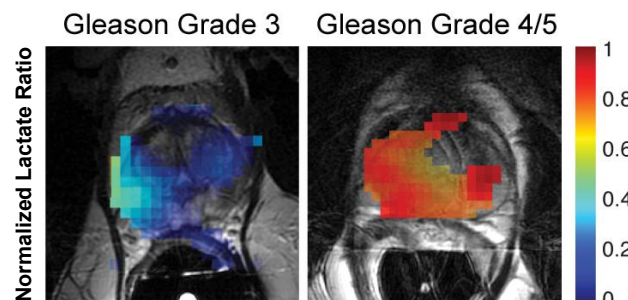
C. H. Cunningham *et al.*, Circ Res (2016)

TRAUMATIC BRAIN INJURY – UTSW, DALLAS



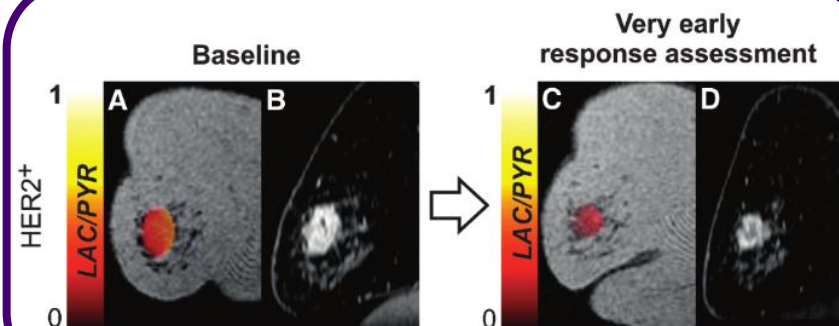
E. P. Hackett *et al.*, iScience (2020)

PROSTATE CANCER – MSKCC, NYC



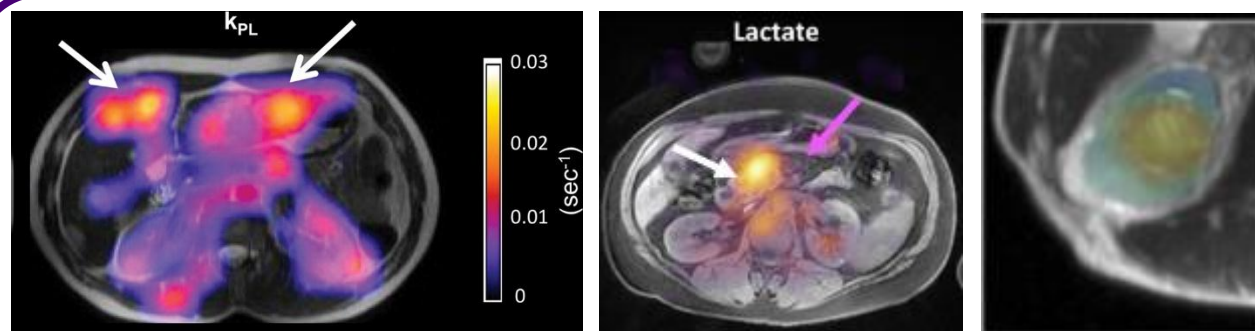
K.L. Granlund *et al.*, Cell Metab (2020)

BREAST CANCER – CAMBRIDGE, UK



R. Woitek *et al.*, Cancer Res (2021)

ABDOMINAL TUMORS (LIVER, PANCREAS, KIDNEY) – UCSF, SAN FRANCISCO and AARHUS, DENMARK



Z. J. Wang *et al.*, Radiology (2019)

Stødtkilde-Jørgensen *et al.*, JMIR (2020)

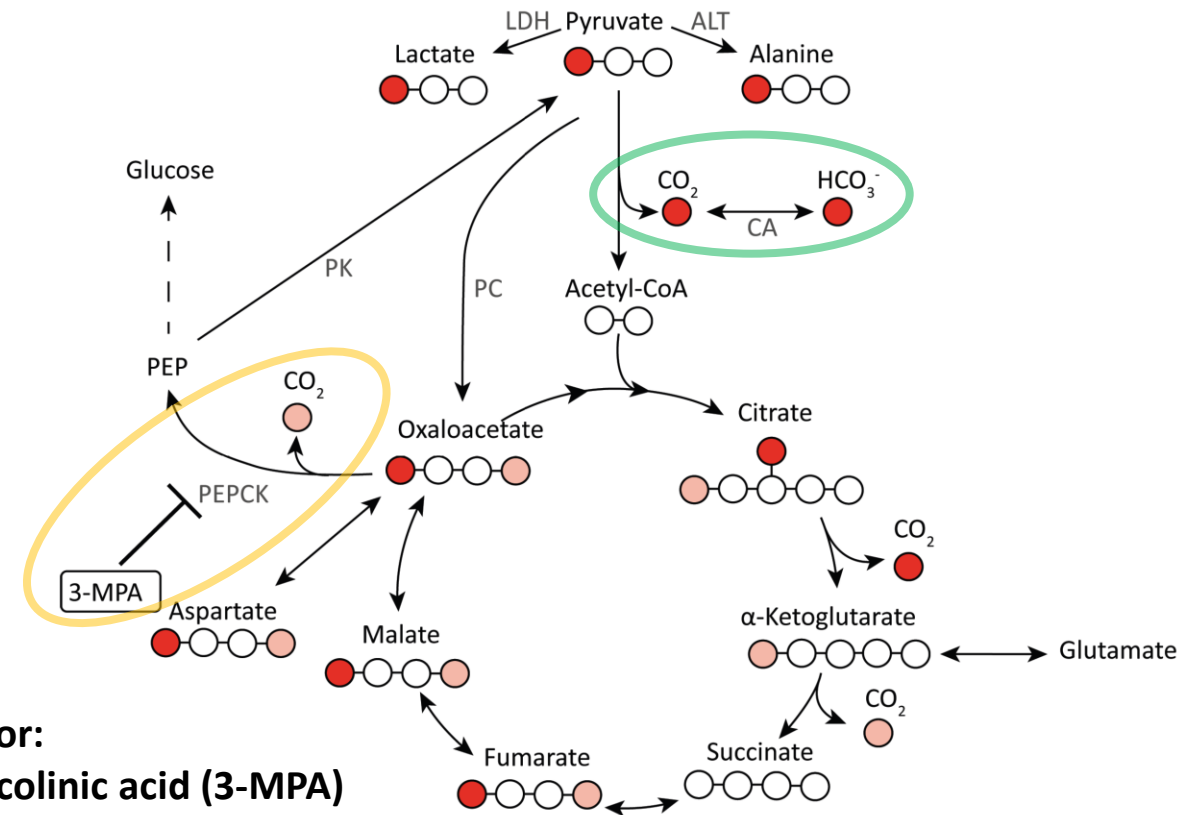
S. Tang *et al.*, Cancer (2021)

Can SNR be increased by increasing injected ^{13}C -probe dose?

- Pyruvate is typically injected at highly supraphysiological dose (about 10 times physiological dose in humans and up to 100 times in animals)
- This may alter the metabolic information obtained from the hyperpolarized ^{13}C scans

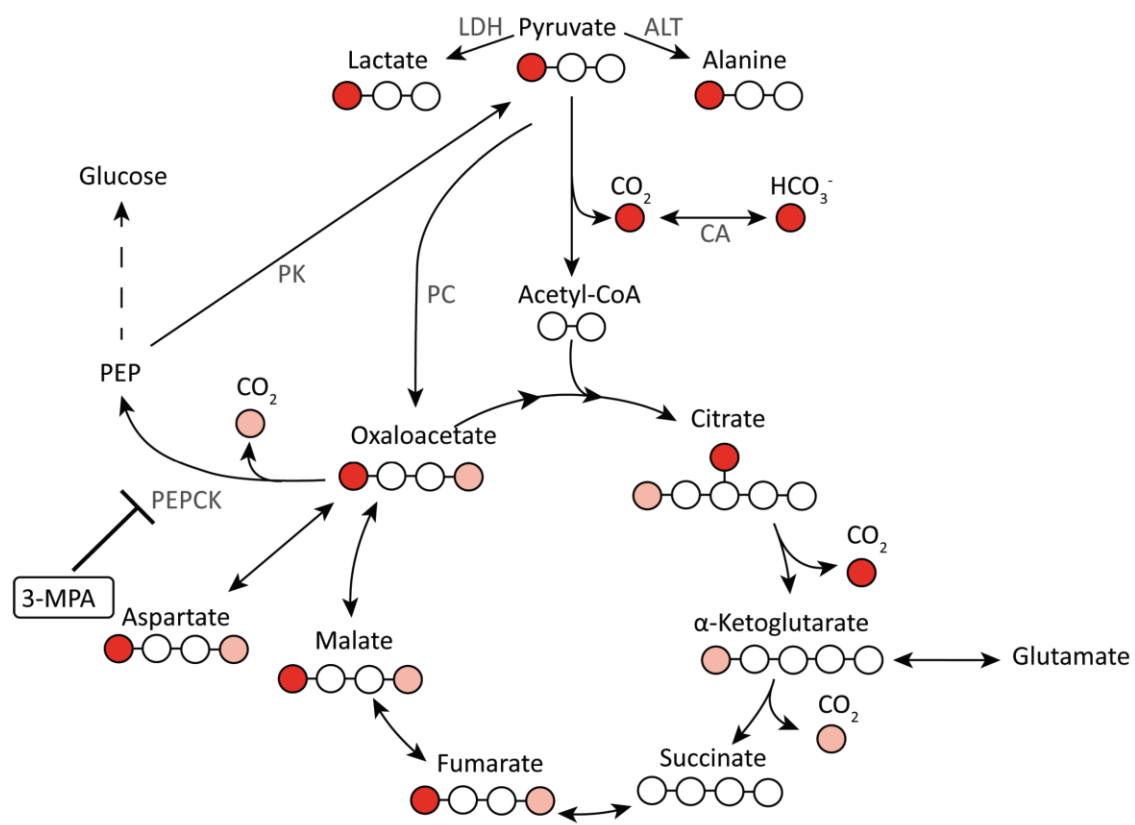
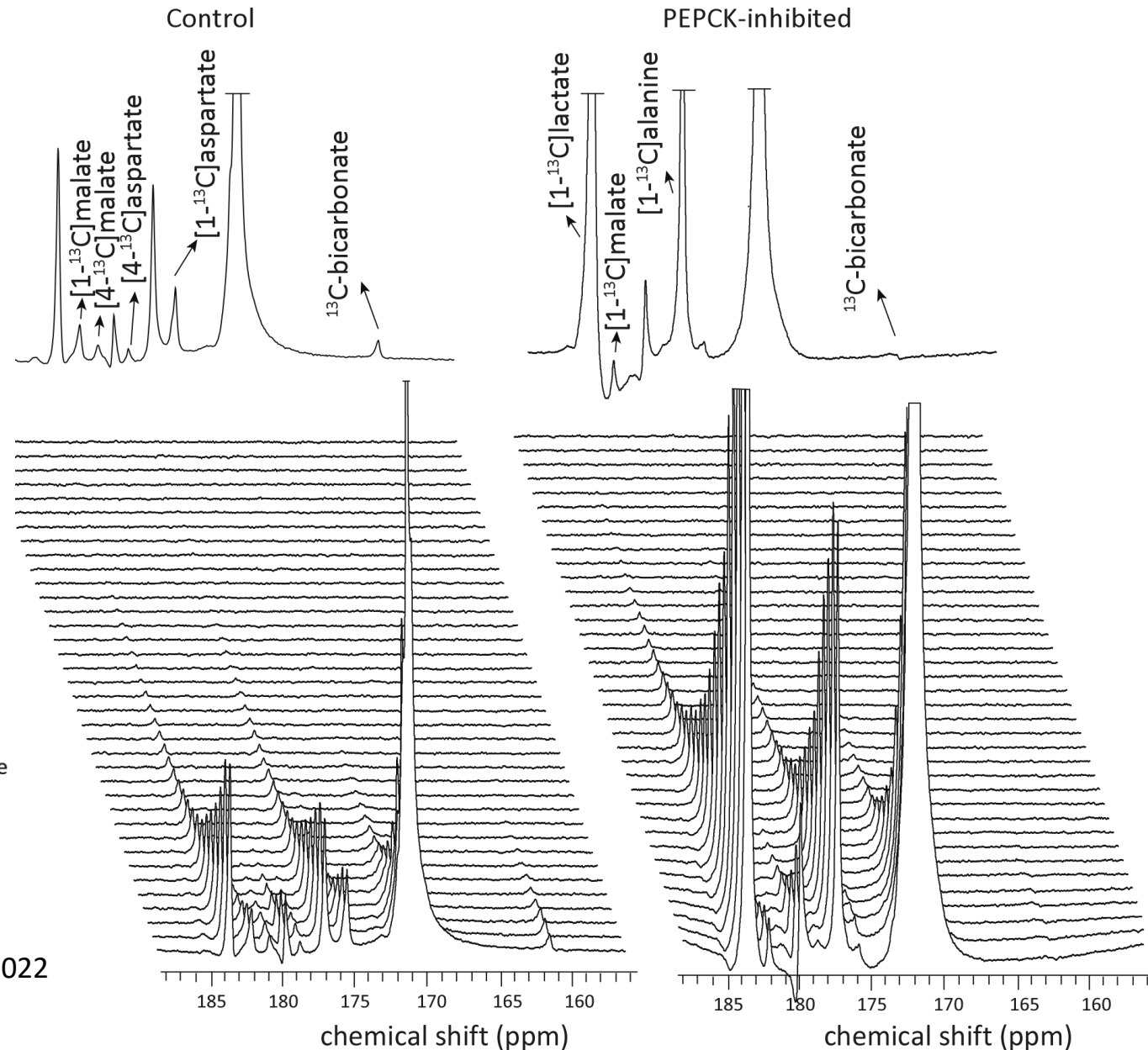
Case study: [1- ^{13}C]pyruvate liver metabolism in healthy rats

- ^{13}C -bicarbonate is from PDH activity in fed rats
- ^{13}C -bicarbonate signal is prominently from PEPCK activity in fasted rats



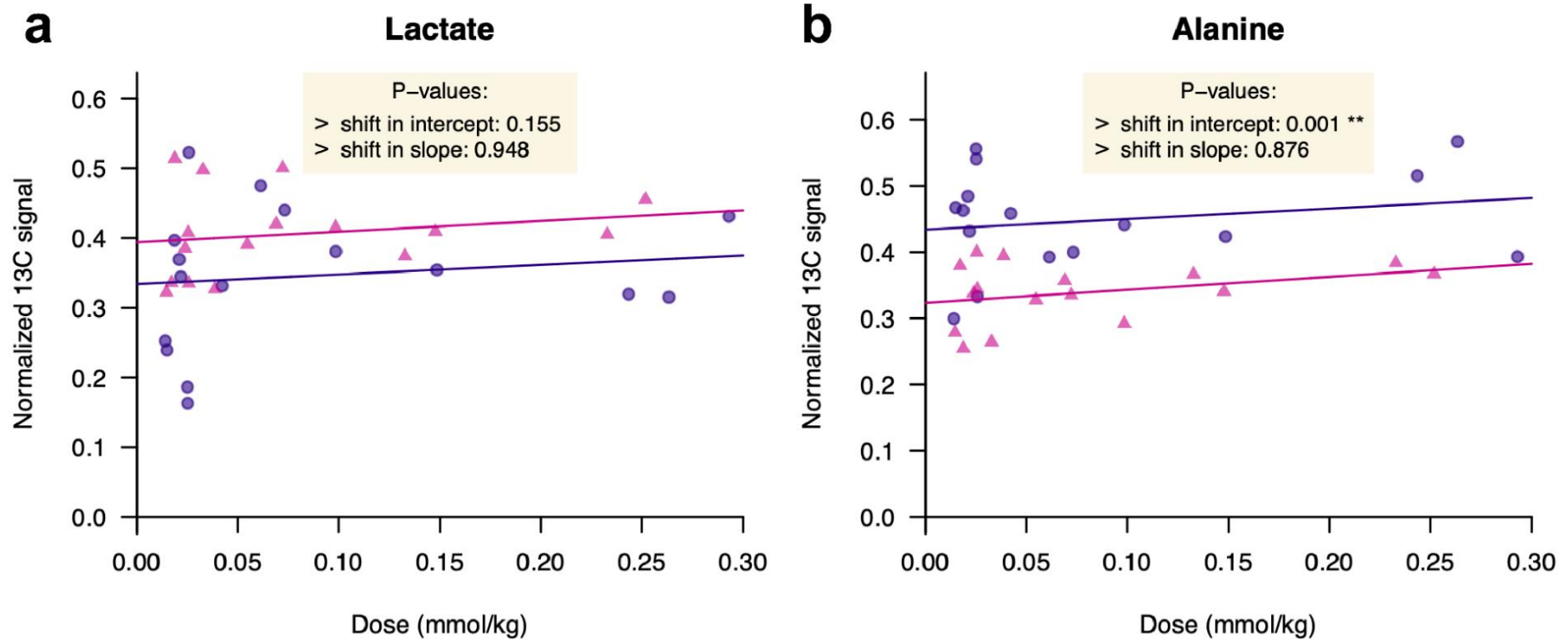
[1-¹³C]pyruvate liver metabolism in fasted rats

Significant decrease in bicarbonate levels only in FASTED rats

E. Can *et al.* Comm. Biol. 2022

Pyruvate dose study in rat liver

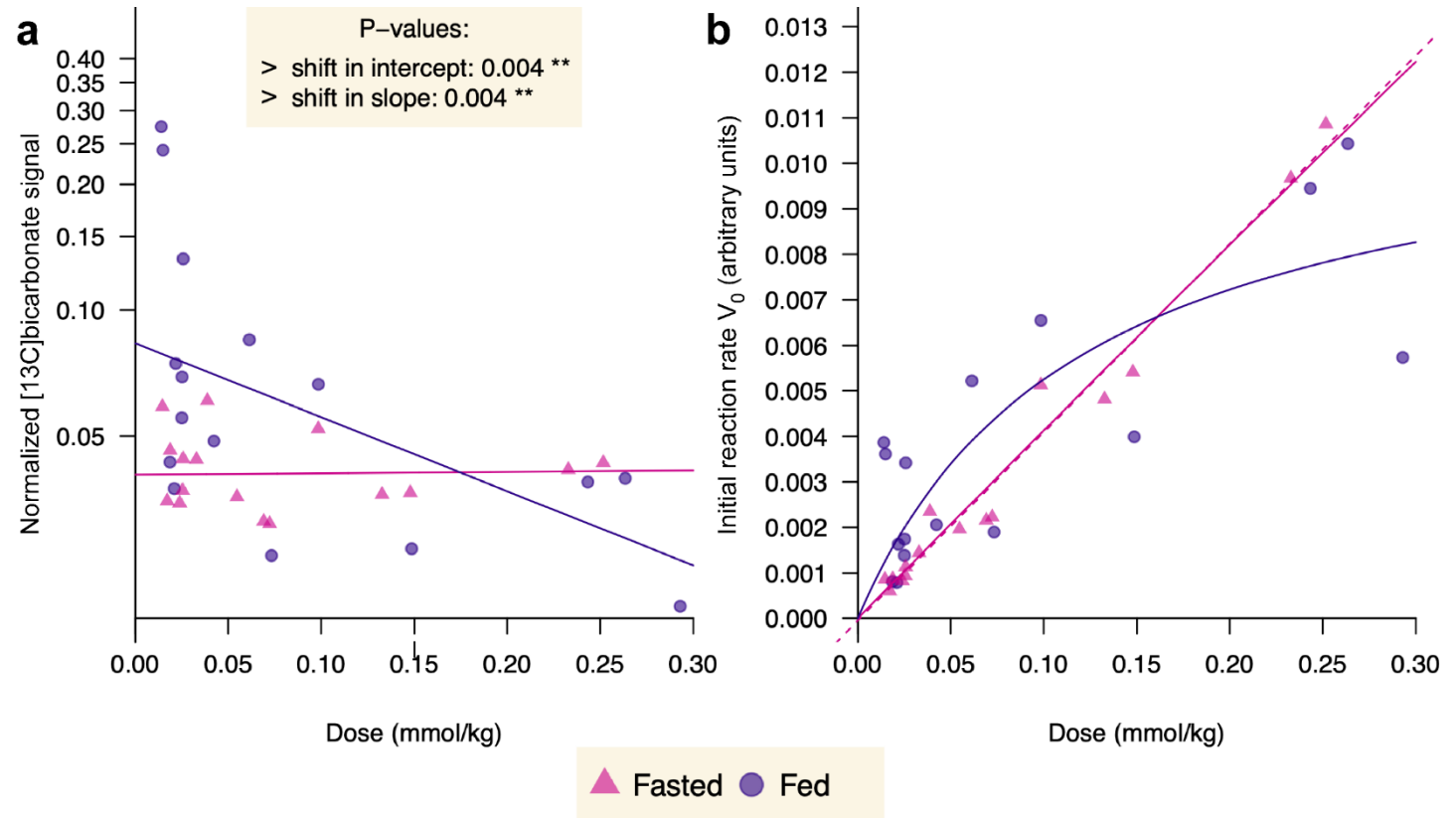
- Doses as low as 0.023mmol/kg were injected, leading to about 2 to 3-fold the normal basal physiological level
- Alanine decreases in fasted state for all doses (consistent with Hu *et al.*, Mol Imag Biol 2009)



E. Can *et al.* Comm. Biol. 2022

Pyruvate dose study in rat liver

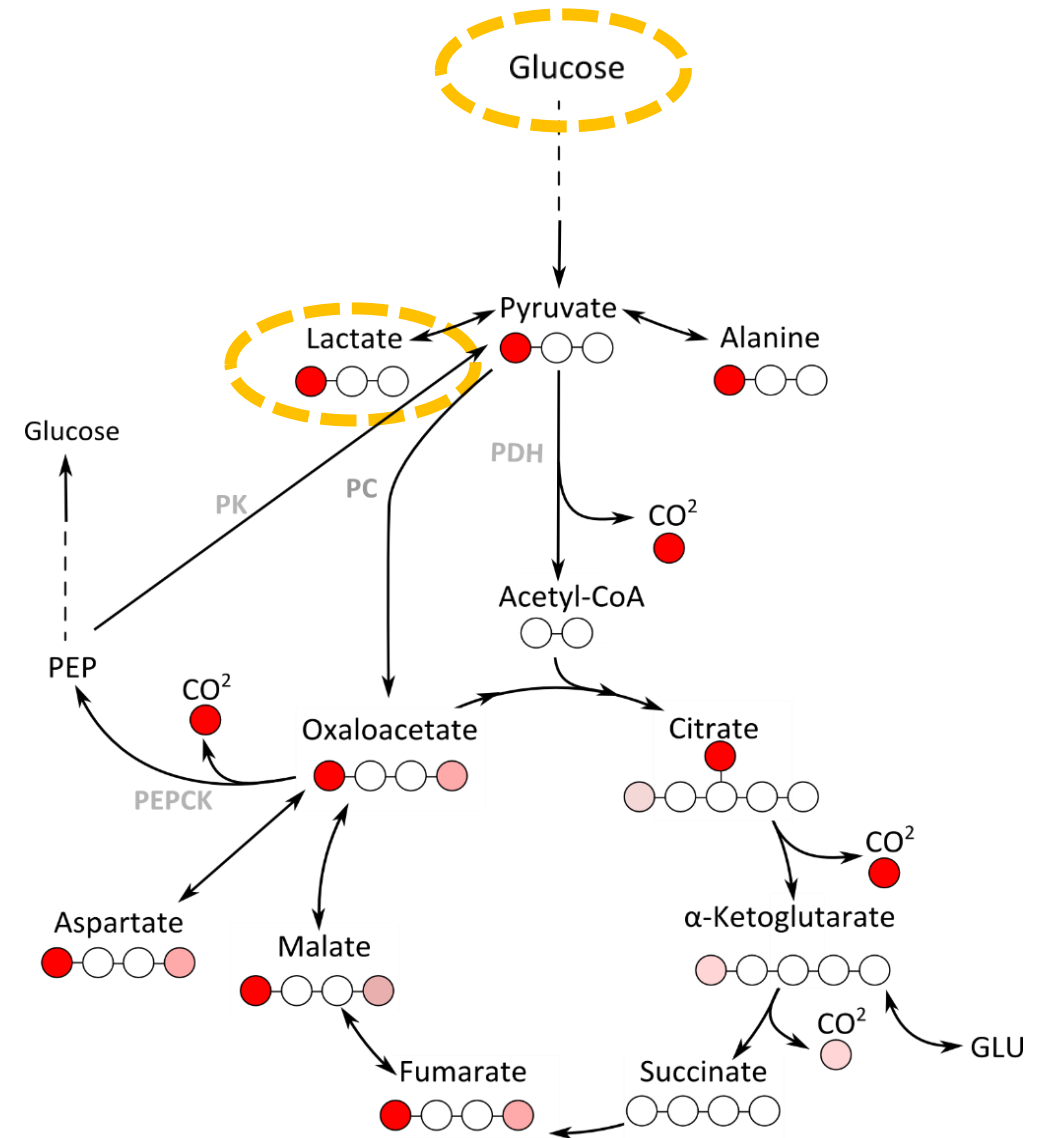
- Bicarbonate signal significantly decreases in fasted state but only apparent at lower doses
- PDH is most likely saturated at higher doses in fed state
- In fasted state, liver bicarbonate signal should provide a direct relation to flux through PEPCK
- **Results will depend on the dose in fed state**



E. Can *et al.* Comm. Biol. 2022

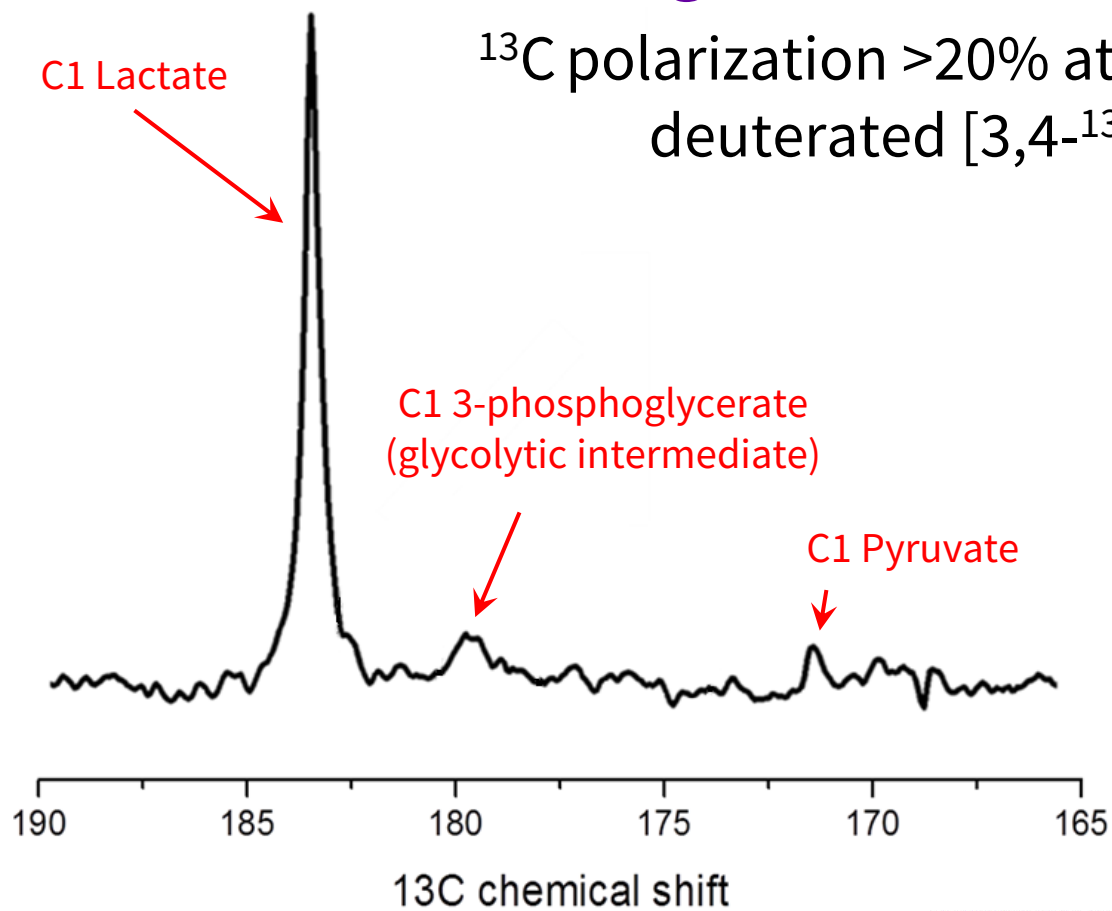
^{13}C -probes that can be injected at physiological doses

- Glucose and lactate blood concentration are on the order of mM
- Hyperpolarized ^{13}C -glucose and ^{13}C -lactate can be injected at physiological dose

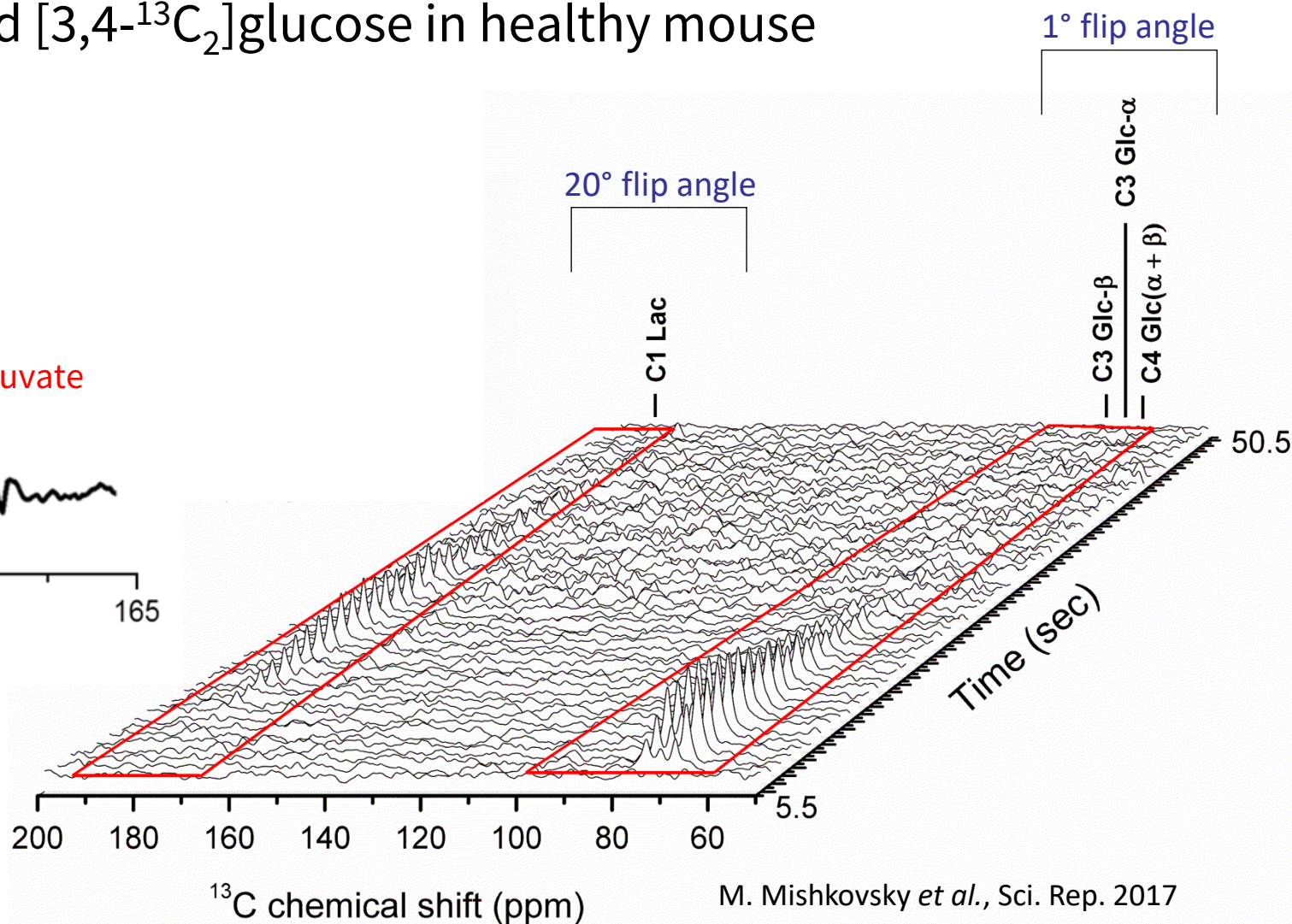


Real-time cerebral glucose metabolism

^{13}C polarization >20% at time of injection of hyperpolarized deuterated $[3,4-^{13}\text{C}_2]\text{glucose}$ in healthy mouse



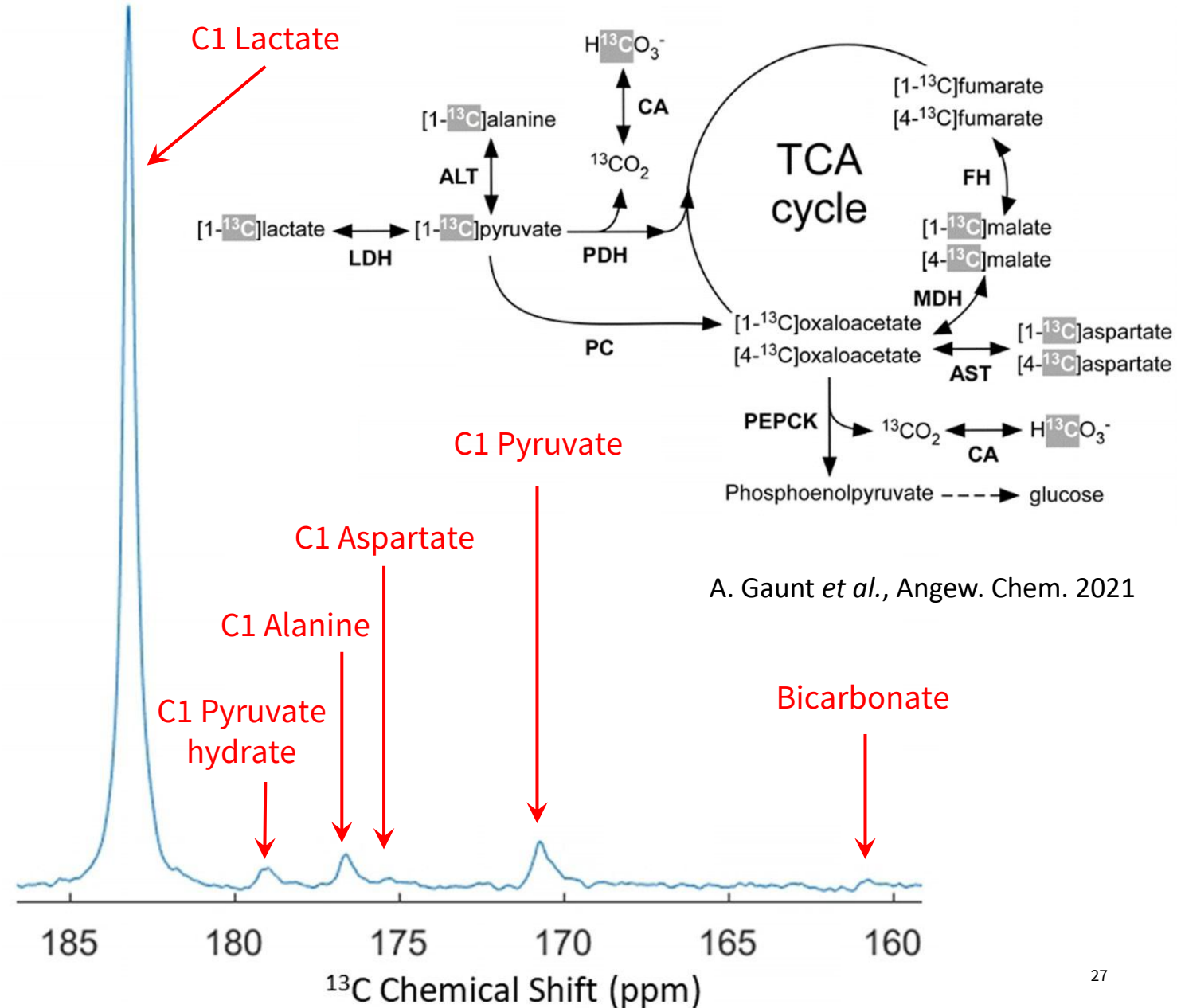
Lactate-to-pyruvate ratio
 17.6 ± 2 ($n = 5$)



M. Mishkovsky *et al.*, Sci. Rep. 2017

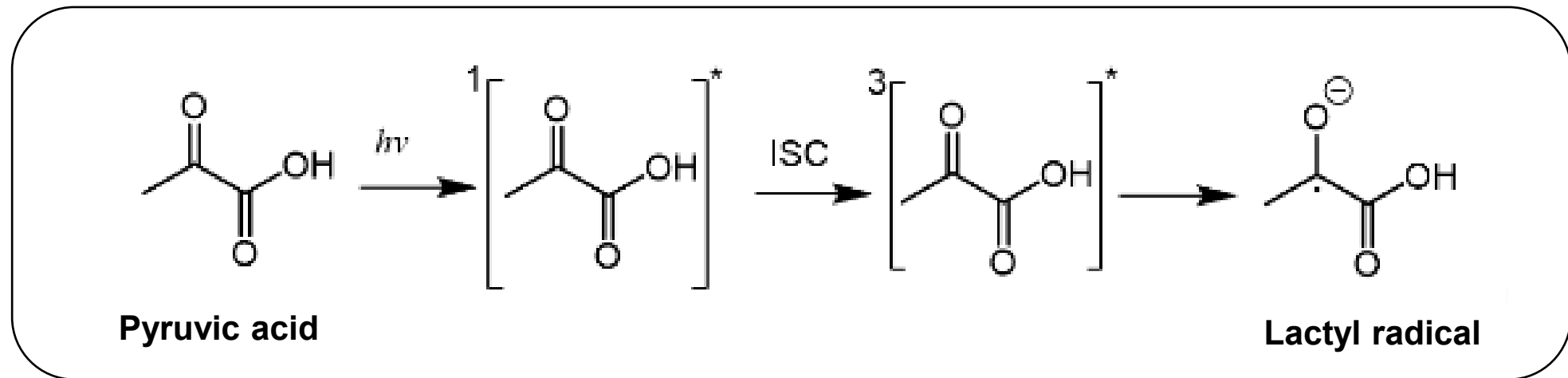
Real-time liver lactate metabolism

- Higher ^{13}C polarization allows injecting lower doses
- Injection of 1mL of a 40mM lactate solution in a 350g rat
- Plasma lactate concentration is on the order of 1.5mM, which is the physiological level in rats
- Lactate-to-pyruvate ratio is about 15, which is what one can expect in the rat liver.



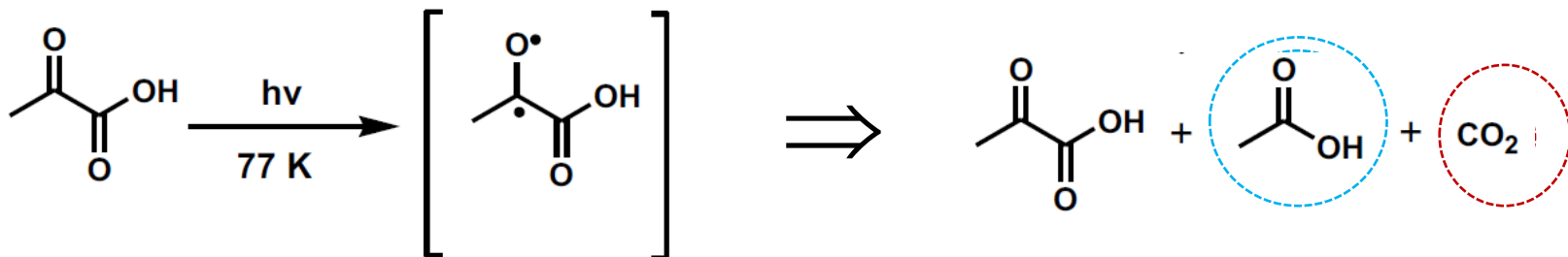
Minimizing delay between dissolution and injection into humans

- Rapid dissolution of large sample (1-2mL) + Neutralization (10s)
- Need to filter polarizing agents (radicals) out
- Transfer into QC syringe
- Fast Quality Control (T, pH, ^{13}C -probe concentration, residual radical concentration)
- Can photo-induced polarizing agents help?

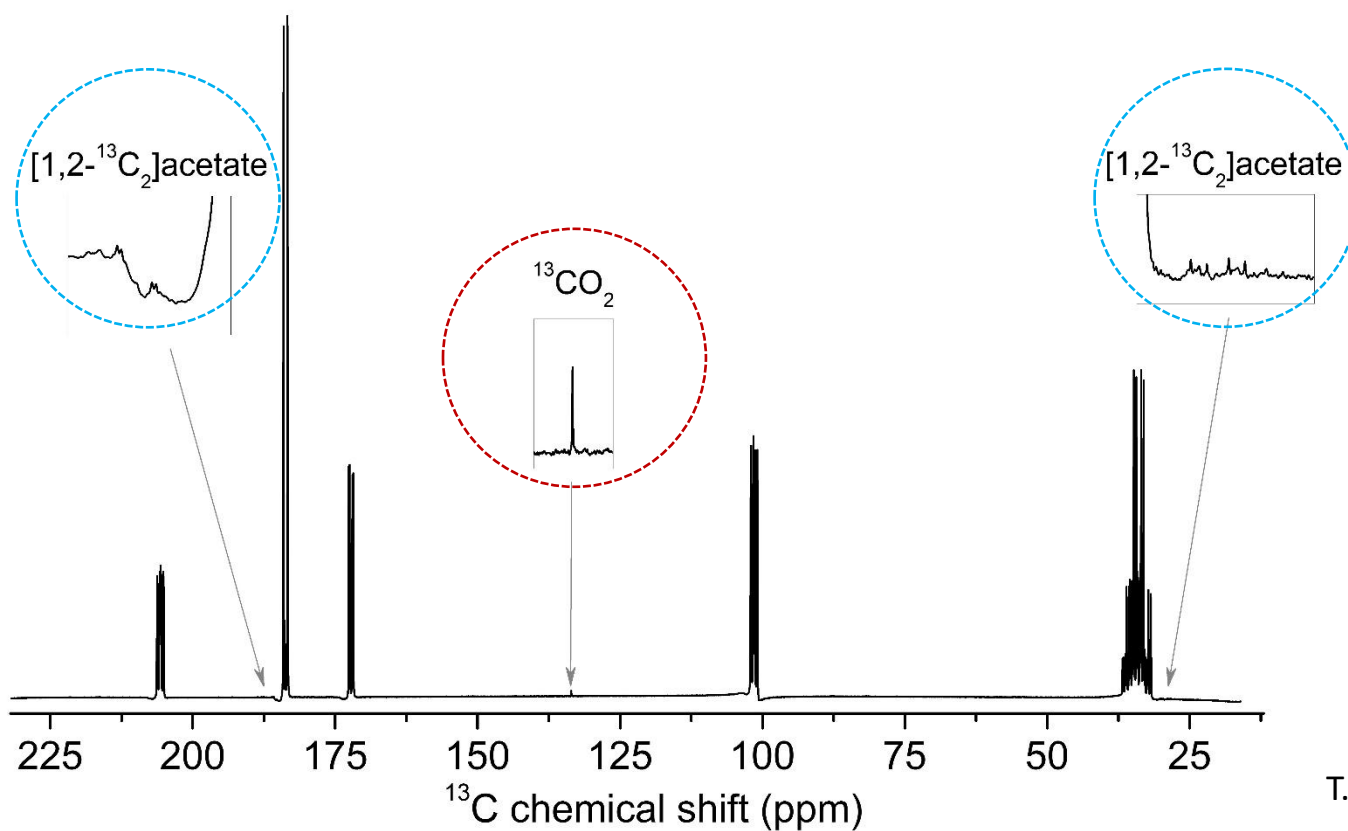


T. R. Eichhorn, *et al.*, PNAS 2013

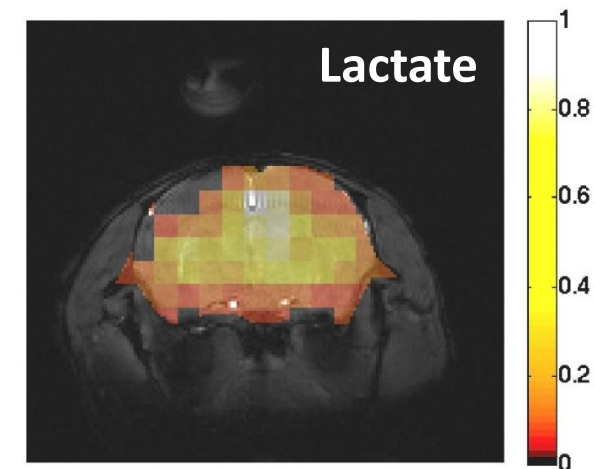
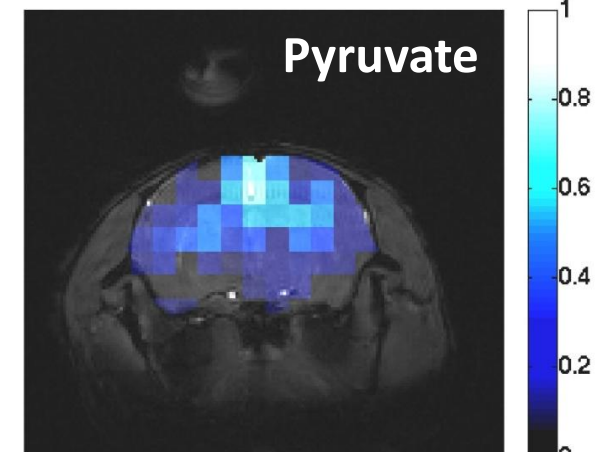
Spontaneous radical quenching upon dissolution



[U-¹³C]pyruvate and [U-¹³C]pyruvate hydrate



Hyperpolarized [1-¹³C]pyruvate in mouse head



Conclusions

- dDNP provides **high level of ^{13}C polarization** enabling metabolic imaging in humans and it is **safe and versatile**
- Depending on the metabolic pathways probed by HP ^{13}C -pyruvate, the supraphysiological dose from the bolus injection may not reflect the normal physiology: **HP ^{13}C -pyruvate is not a tracer and ^{13}C needs to be polarized to the highest level possible for ^{13}C MRI since low polarization cannot be compensated by increasing concentration (unlike in PET imaging)**
- Because of their higher normal plasma levels, HP ^{13}C -lactate and HP ^{13}C -glucose experiments can be performed while maintaining a physiological level but **low metabolic product pool sizes or shorter T_1 means that a large ^{13}C polarization is still required**
- Higher ^{13}C polarization can be obtained by improving solid-state DNP but also by **decreasing the delay between dissolution and injection**
- Photo-induced radicals would **remove the need for radical filtration** and enable producing purely endogenous imaging agents

Acknowledgments



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GE HealthCare

Albert Chen



CANCER
RESEARCH
UK

CAMBRIDGE
INSTITUTE



Rolf Gruetter
Christophe Roussel



Mathilde Lerche
Magnus Karlsson



Matthew Merritt



European Research Council



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SWISS NATIONAL SCIENCE FOUNDATION



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