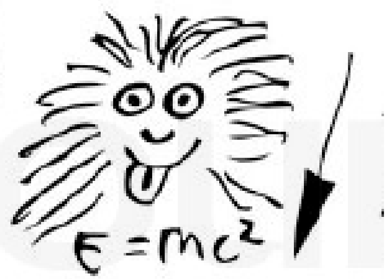
Incontri di Fisica Moderna

SUN
EARTH
E=mc²

Polarized is better: iperpolarizzazione dei nuclei per la diagnostica



Pietro Carretta
http://nmrphysics.unipv.it

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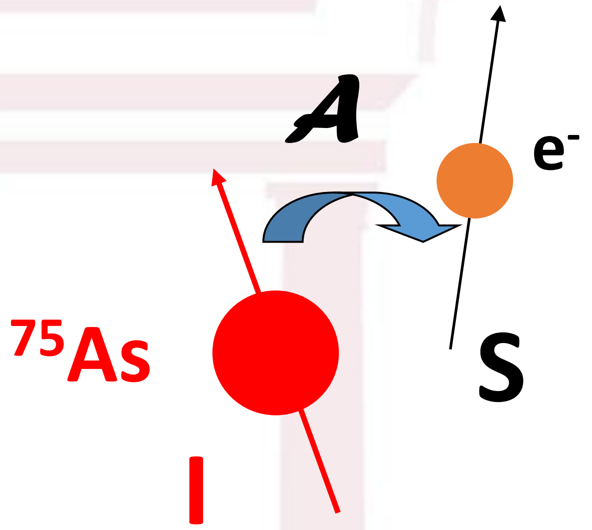
OUTLINE

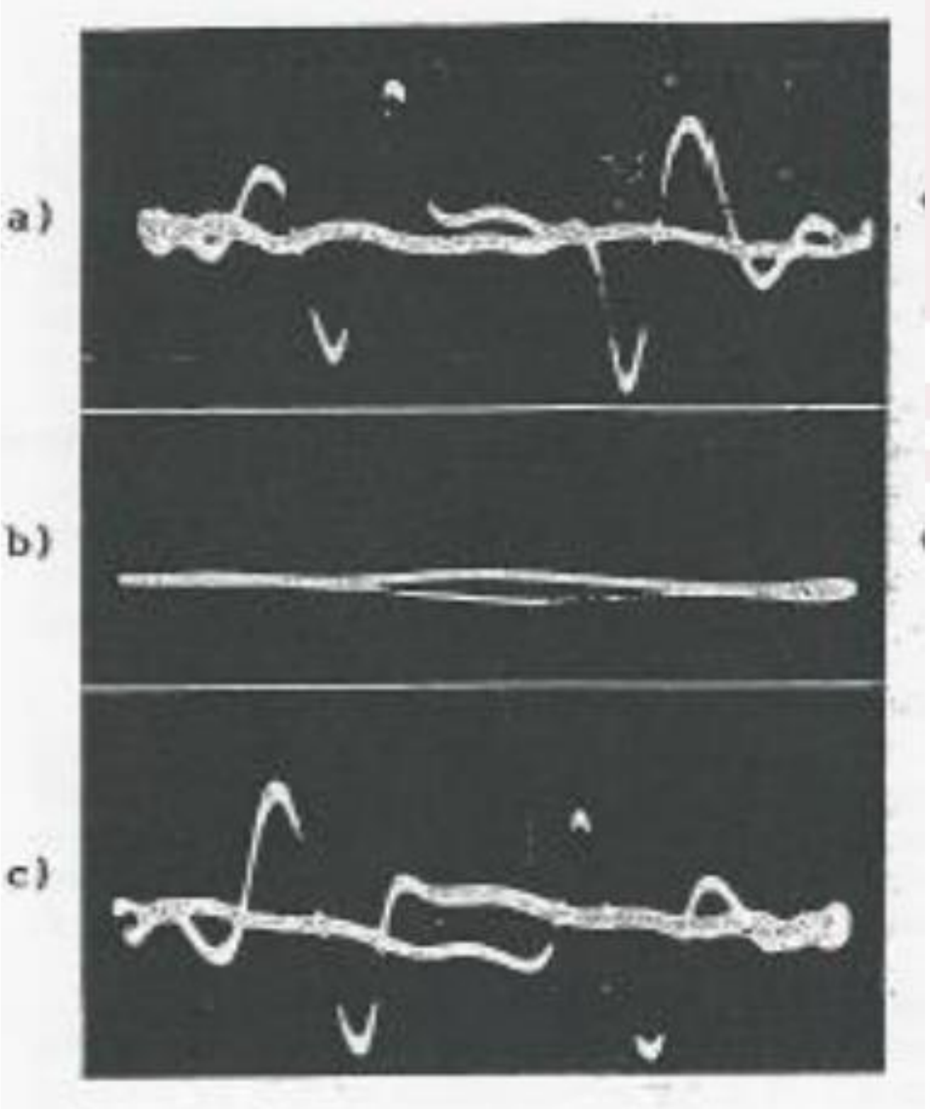
- Risonanza magnetica nucleare (NMR)
- Temperatura di spin
- Tomografia a risonanza magnetica (MRI)
- Iperpolarizzazione dei nuclei
- Imaging molecolare *in vivo*

$$\mu_I = \gamma\hbar I$$



La nascita del NMR in Europa

Luigi Giulotto



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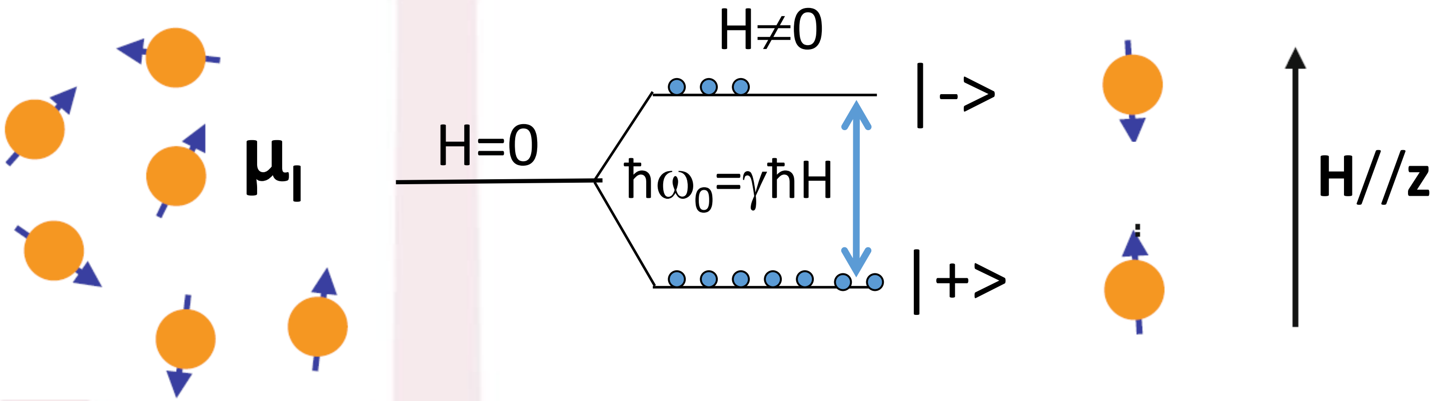
NMR oggi

-1 0
1 0
0 -1
0 1
Cantilever
Interferometer
Microwave coil
Magnetic tip
Resonant slice
Spin
z
y
x
ORS
MobiLab™ BLS

Cos’è l’NMR?

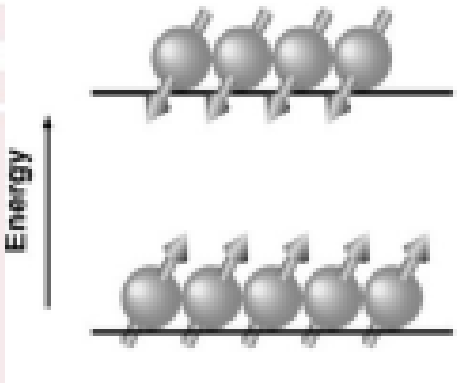
L’NMR studia l’evoluzione temporale della MAGNETIZZAZIONE nucleare determinata dalle interazioni a cui sono soggetti i nuclei.

$$\mathcal{H} = \mathcal{H}_Z + \mathcal{H}_{n-n} + \mathcal{H}_{n-e} + \mathcal{H}_{EFG}$$


μ_I
H=0
H≠0
$\hbar\omega_0=\gamma\hbar H$
|->
|+>
H//z

$$M_z = \mu_I \frac{N^+ - N^-}{N^+ + N^-} = \mu_I\, P(T, H)$$

$$M_z = \frac{N(\gamma\hbar)^2 J(J+1)\,H}{3kT}$$



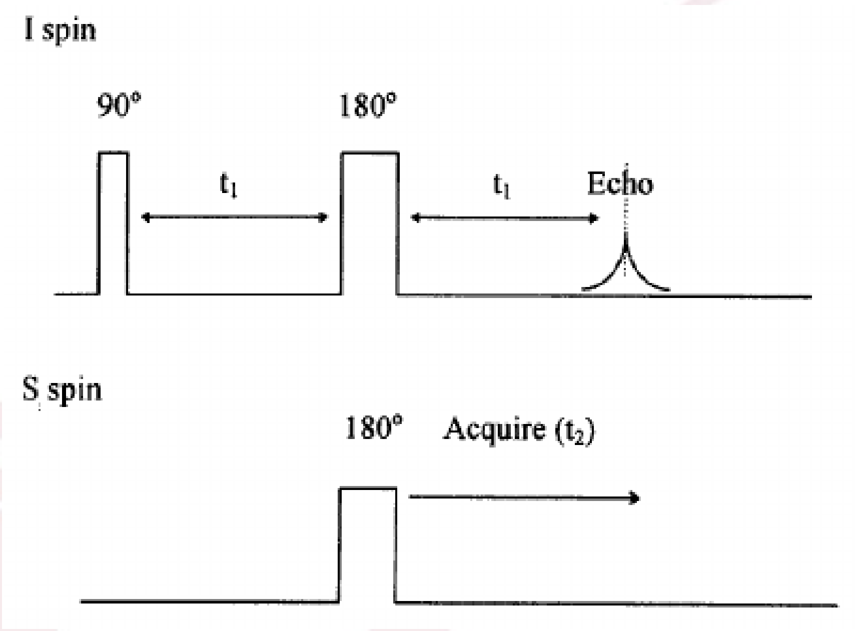
Thermal equilibrium

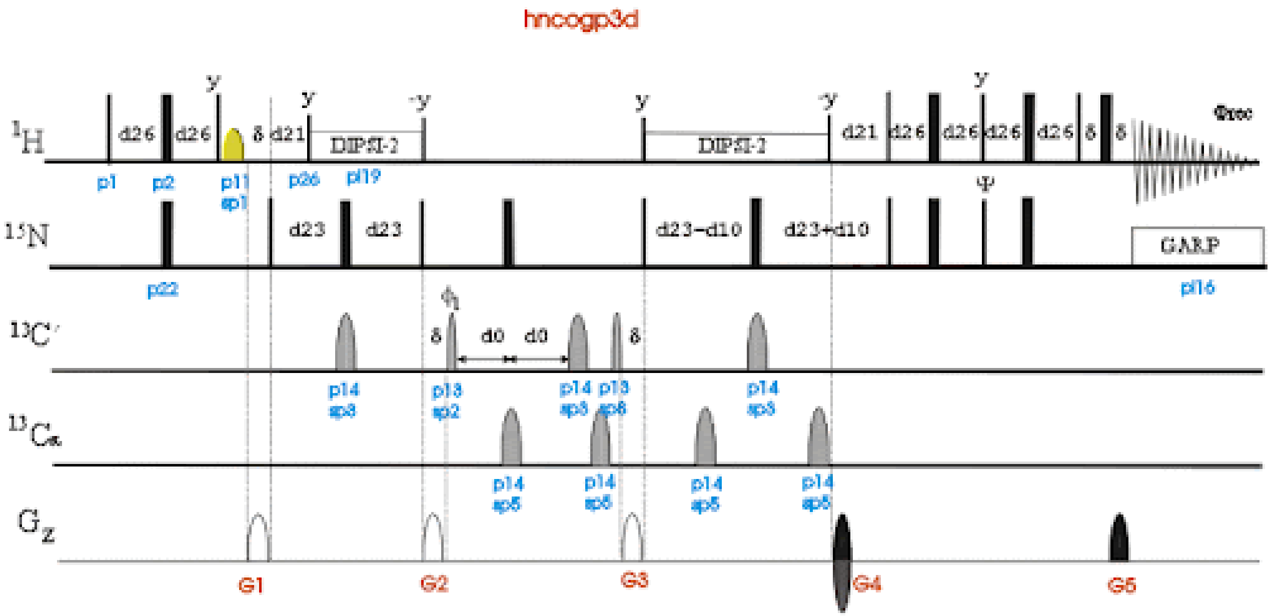
Nuclear magnetic moment $\vec{M}=\gamma\hbar\vec{I}$

Common NMR Active Nuclei

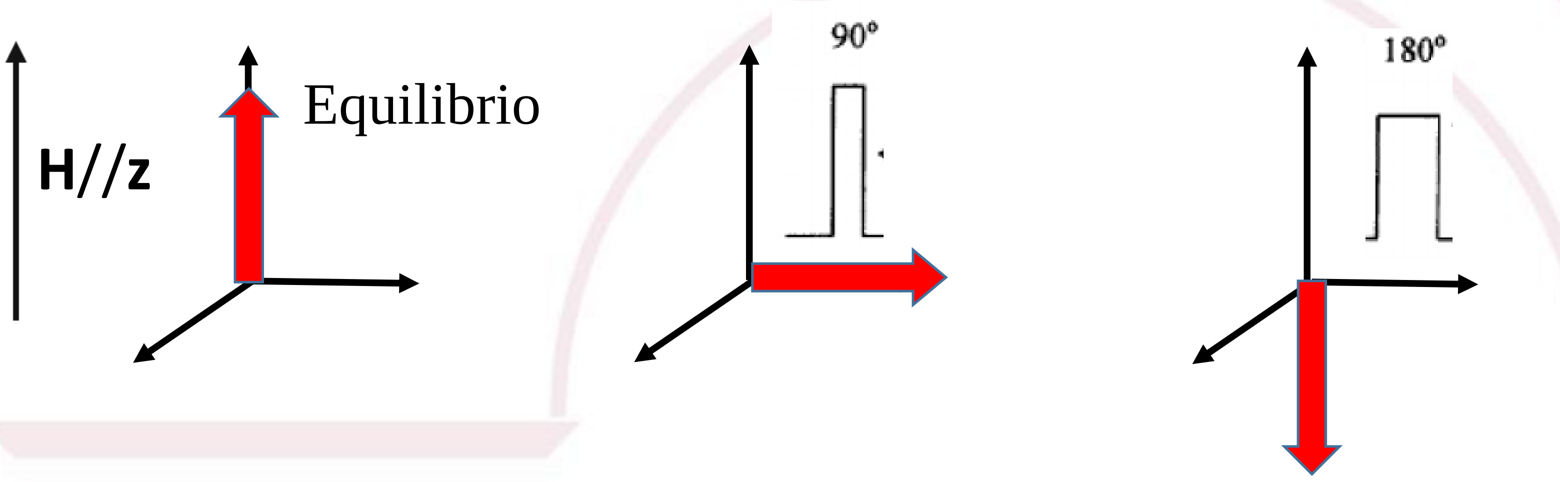
Isotope	Spin I	%age abundance	γ MHz/T
^{1}H	1/2	99.985	42.575
^{2}H	1	0.015	6.53
^{13}C	1/2	1.108	10.71
^{14}N	1	99.63	3.078
^{15}N	1/2	0.37	4.32
^{17}O	5/2	0.037	5.77
^{19}F	1/2	100	40.08
^{23}Na	3/2	100	11.27
^{31}P	1/2	100	17.25

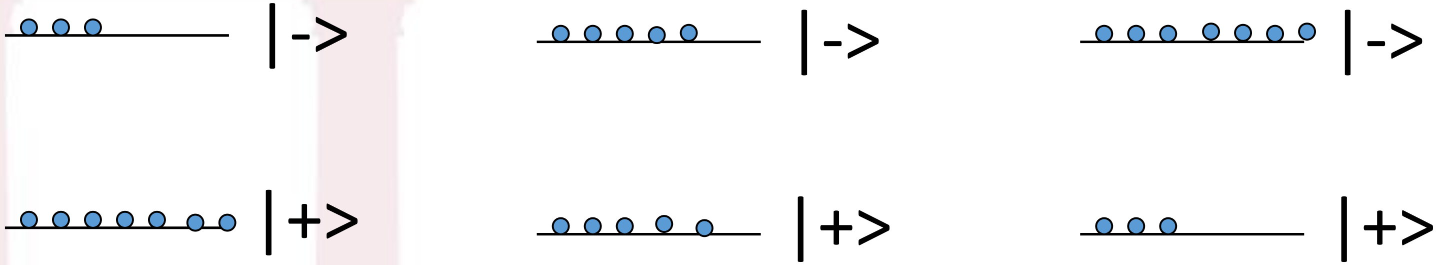
Come interrogare i nuclei? Impulsi RF


I spin
90°
180°
t_1
t_1
Echo
S spin
180°
Acquire (t_2)


hncogp3d
^{1}H
^{15}N
^{13}C'
^{13}Cα
G_z
d26
d26
δ
d21
DIPSI-2
DIPSI-2
d23
d23
d23-d10
d23+d10
d0
d0
GARP
p1
p2
p11 sp1
p26
pl19
p22
pl16
p14 sp3
p13 sp2
p14 sp3
p13 sp8
p14 sp3
p14 sp5
p14 sp5
p14 sp5
p14 sp5
y
-y
Ψ
ϕ_1
Φrec
G1
G2
G3
G4
G5

Impulsi RF e temperatura di spin


H//z
Equilibrio
90°
180°



$T_I = T_L$

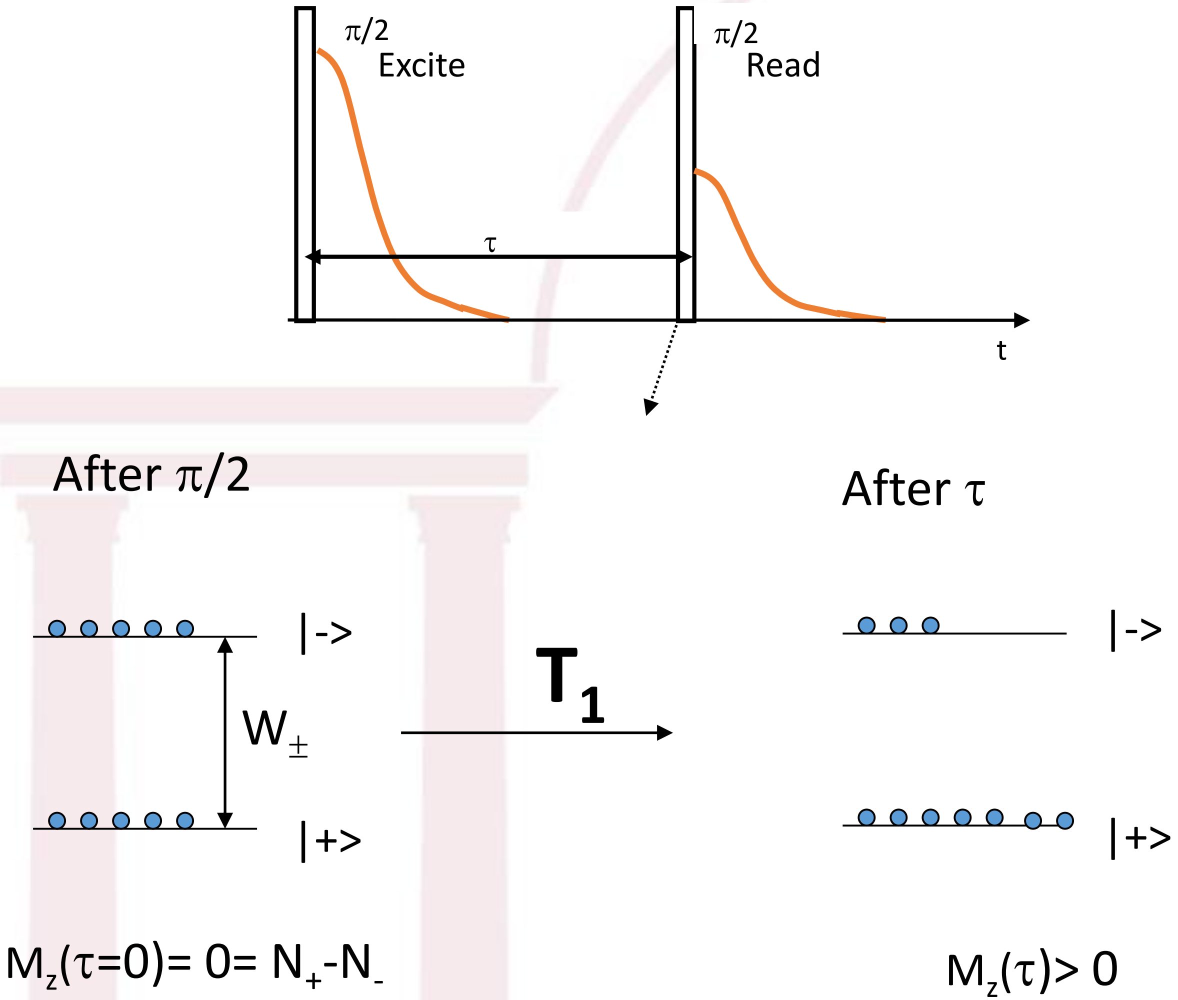
$T_I \rightarrow \infty$

$T_I = -T_L < 0$

L. Boltzmann

$$N_\pm = \frac{N \exp(-E_\pm / k_B T_I)}{Z}$$

Tempo di rilassamento T_1 ed effetto sul segnale


π/2
Excite
π/2
Read
τ
t
After π/2
After τ
|->
|+>
W±
T1
|->
|+>

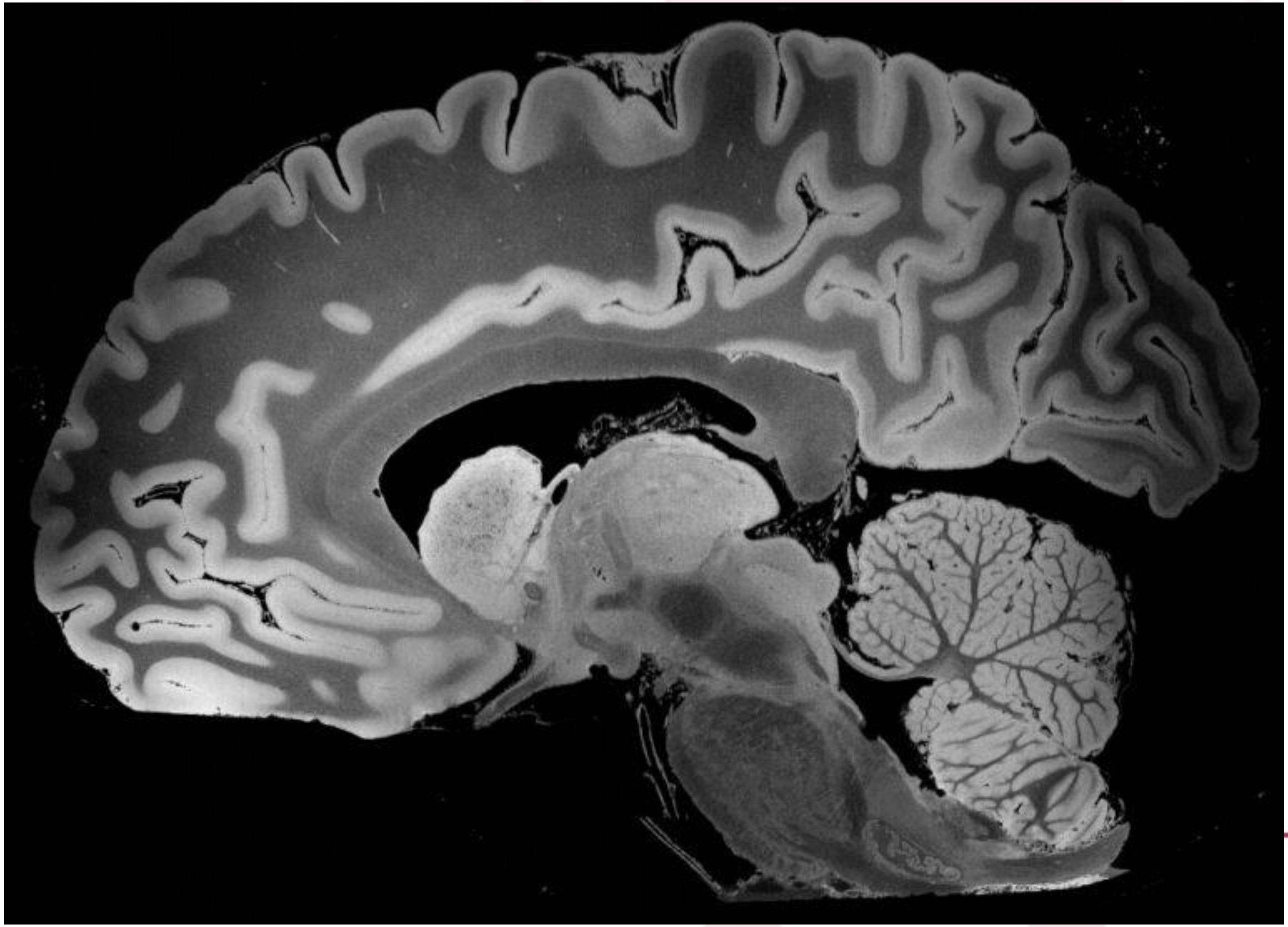
$M_z(\tau=0) = 0 = N_+ - N_-$

$M_z(\tau) > 0$

$$S_{NMR} \propto N\, P(T,H)\, f(T_1, T_2, t)$$

Tomografia MRI

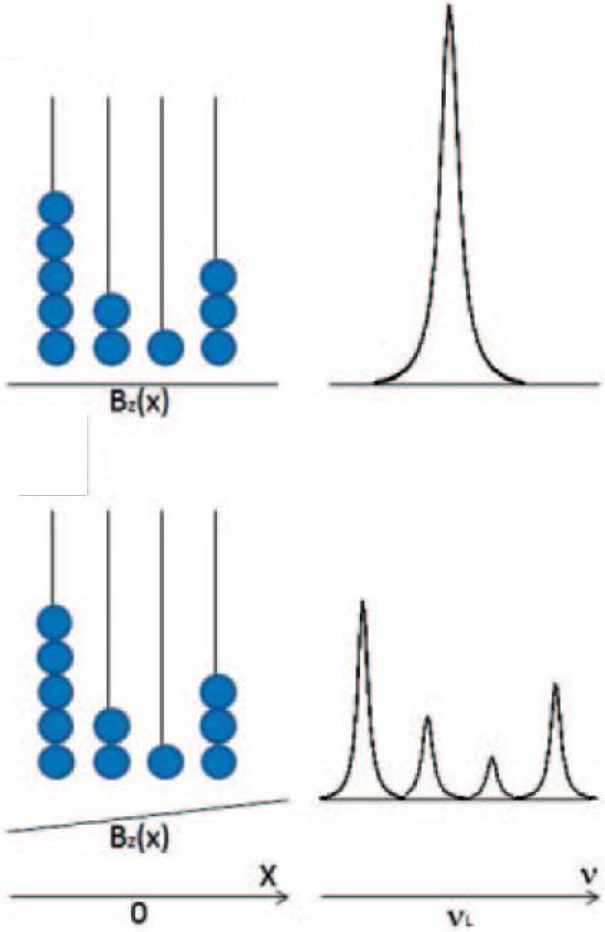
MRI sull’uomo: risoluzione fino a 100 μm in piano a 7 Tesla



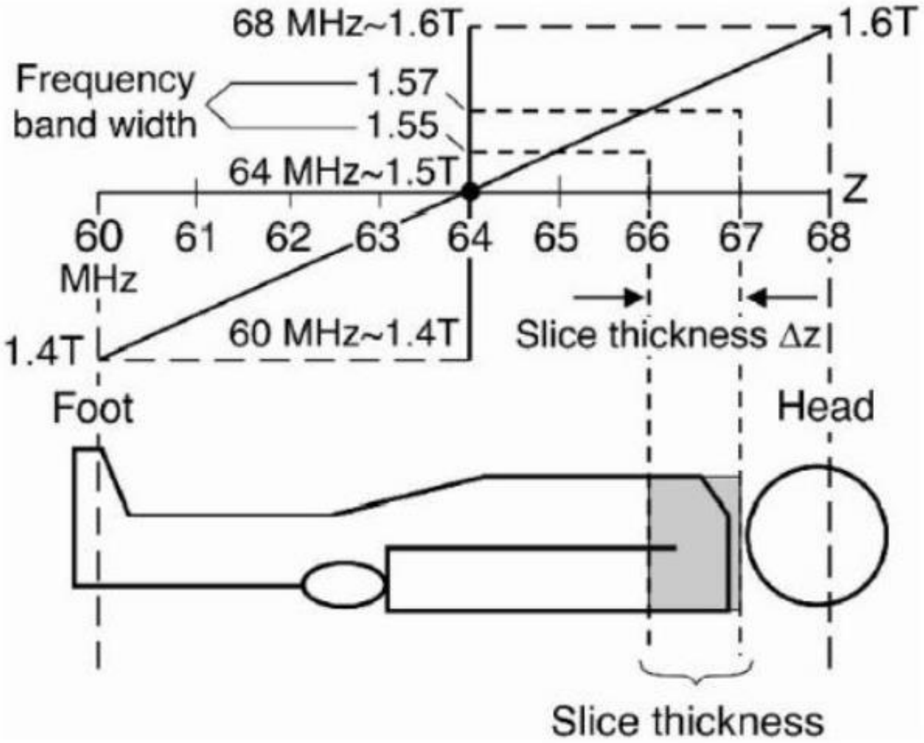
Brian L. Edlow et al., biorxiv:649822v1

Tomografia MRI

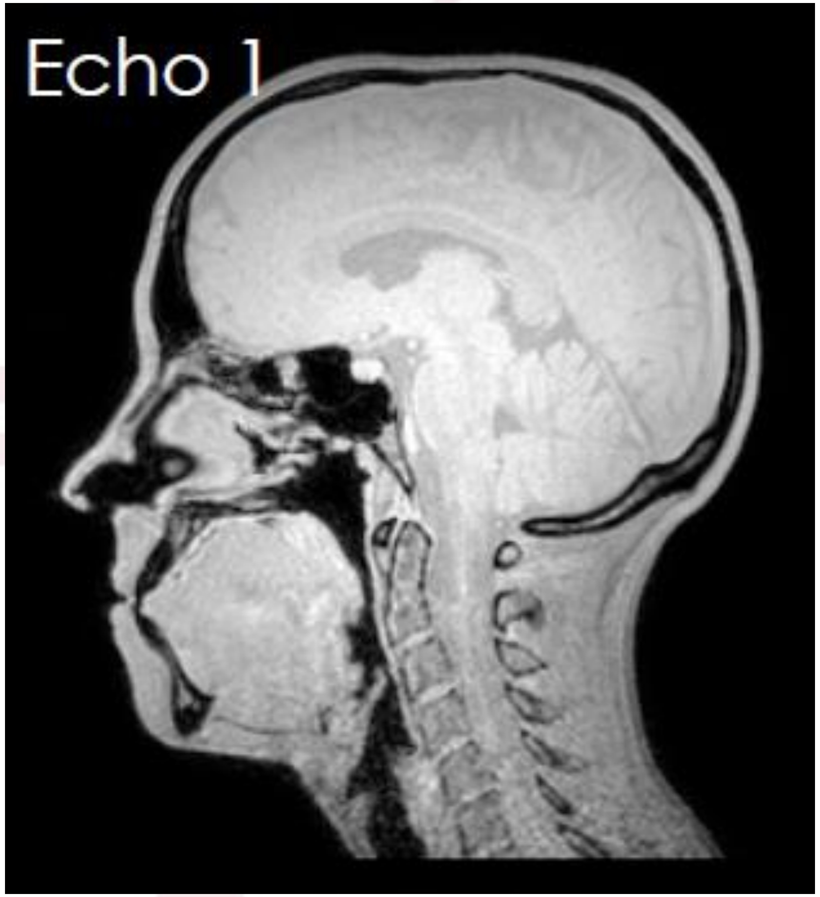
$\omega_0=\gamma B_0$


Bz(x)
Bz(x)
X
0
ν
νL

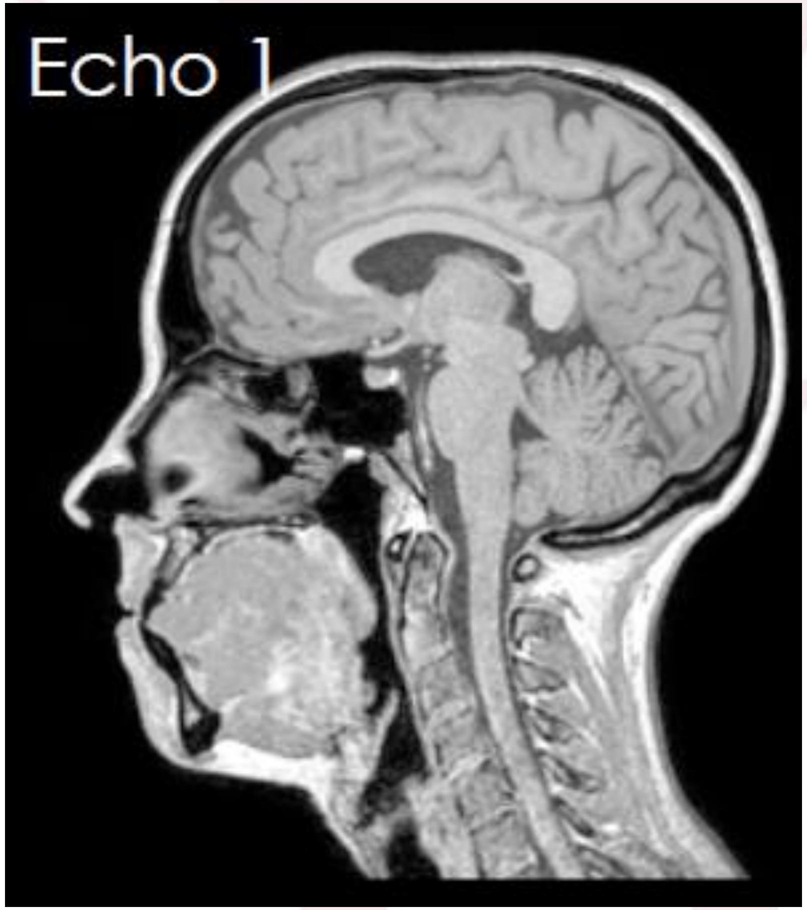
APPLICAZIONE DI G_z


68 MHz~1.6T
1.6T
Frequency
band width
1.57
1.55
64 MHz~1.5T
Z
60
MHz
61
62
63
64
65
66
67
68
1.4T
60 MHz~1.4T
Slice thickness Δz
Foot
Head
Slice thickness

Misure T_1 pesate



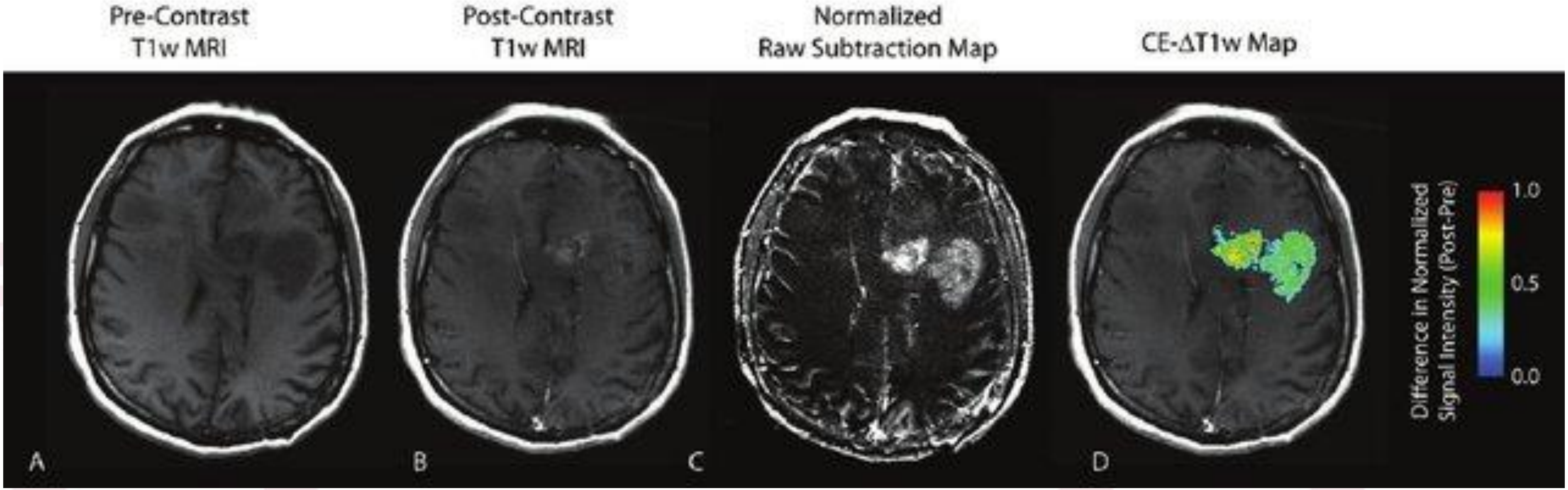
Densità protonica



T_1 pesata

Mezzi di contrasto per MRI

B.M.Ellingson et al. , Radiology 271, 200 (2014)

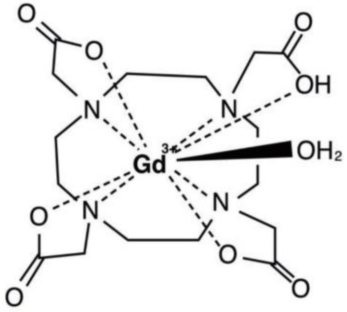

Pre-Contrast T1w MRI

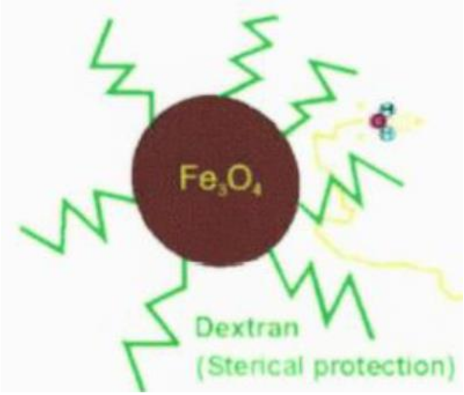
Post-Contrast T1w MRI

Normalized Raw Subtraction Map

CE-ΔT1w Map

A
B
C
D
Difference in Normalized Signal Intensity (Post-Pre)
1.0
0.5
0.0


O
O
N
N
OH
O
Gd3+
OH2
O
N
N
O
O
O


Fe3O4
Dextran
(Sterical protection)

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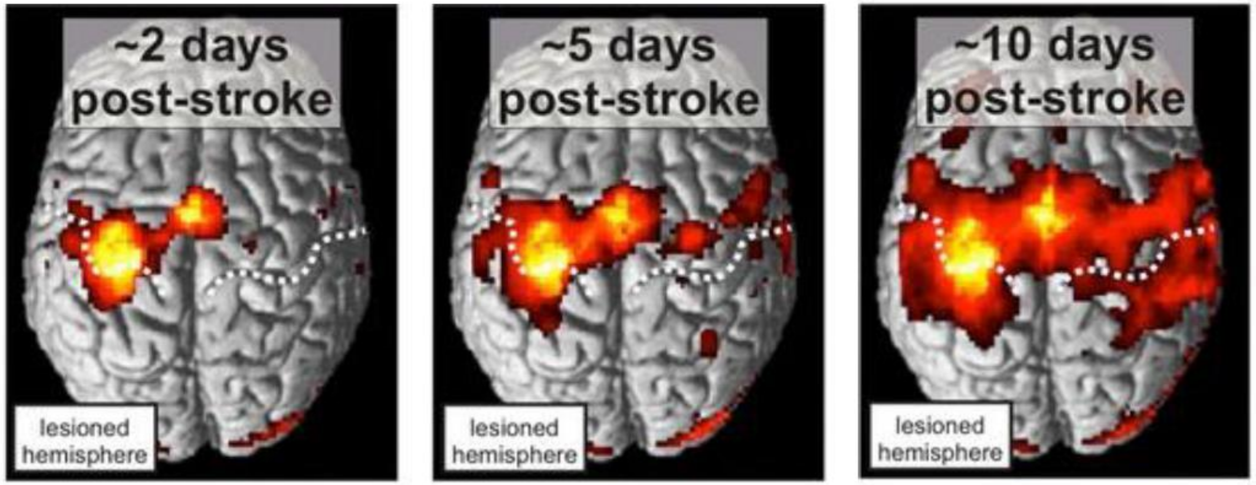
f-MRI


~2 days post-stroke
lesioned hemisphere
~5 days post-stroke
lesioned hemisphere
~10 days post-stroke
lesioned hemisphere

Riorganizzazione della corteccia motoria

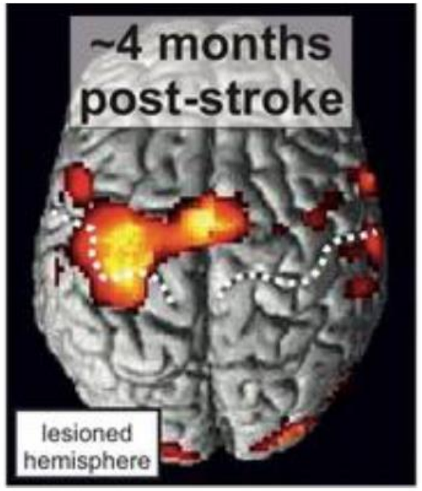
↓

- Attività bilaterale molto intensa
- Connettività interemisferica ridotta

Recupero

↓

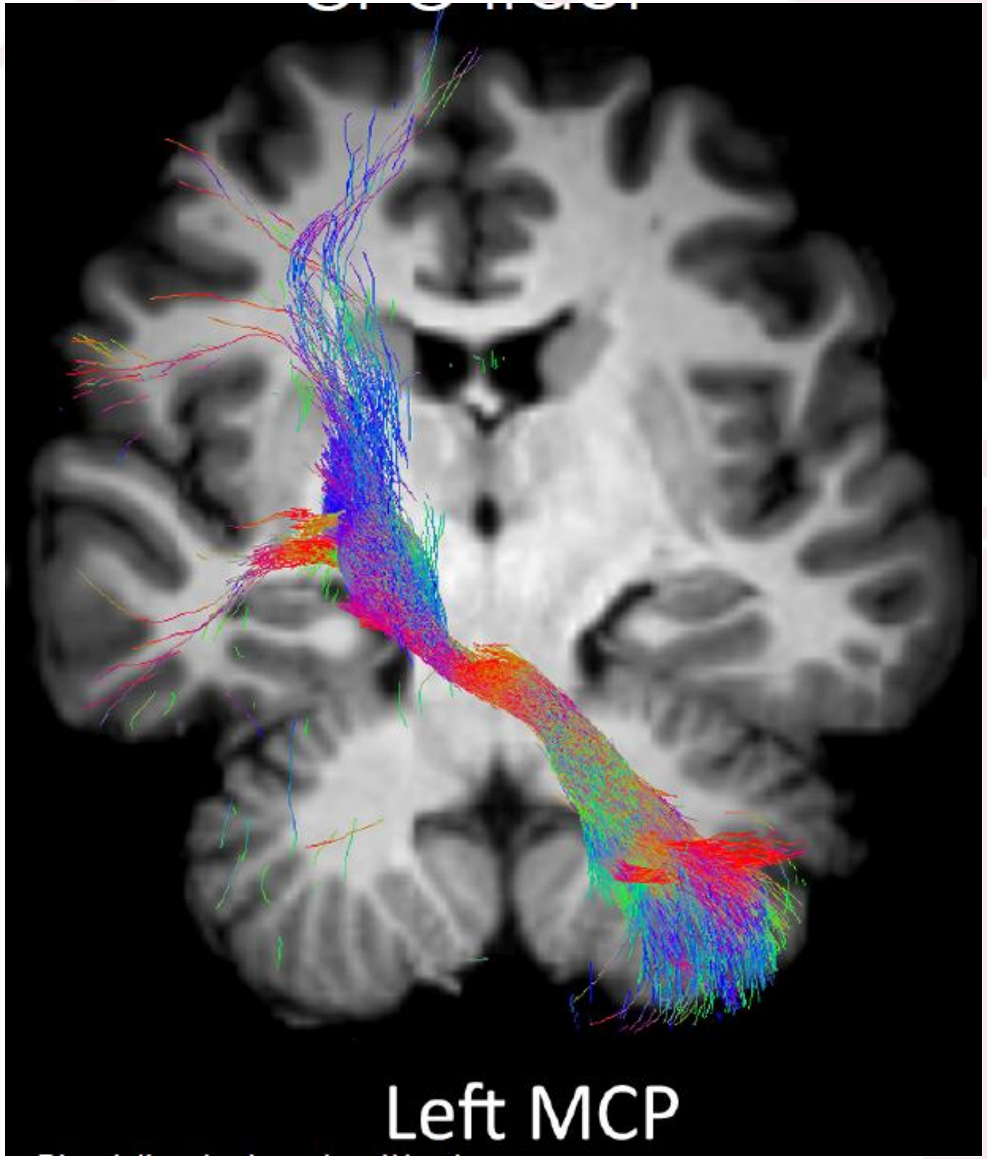
Intensità ridotta e parziale ritorno a un'attività unilaterale


~4 months post-stroke
lesioned hemisphere

Recupero:
- Reclutamento
- Focalizzazione

RS-fMRI: andamento della connettività funzionale durante il recupero

Trattografia DTI

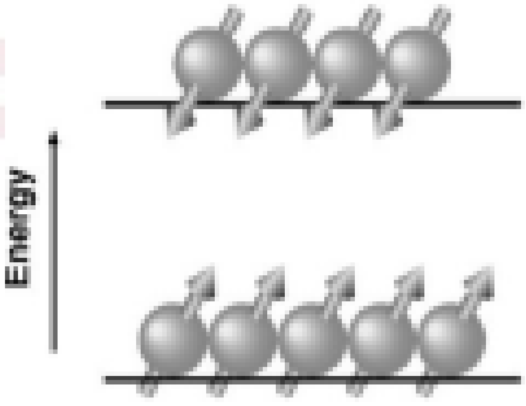


F. Palesi et al. (2014)

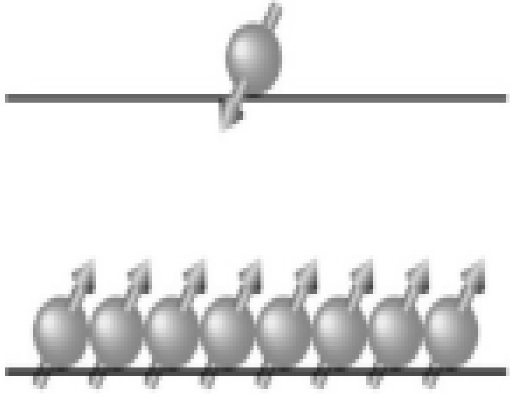
Problema Sensibilità →Iperpolarizzazione

$$\frac{N_+ - N_-}{N_+ + N_-} \cong 10^{-6}$$

At RT for H~Tesla



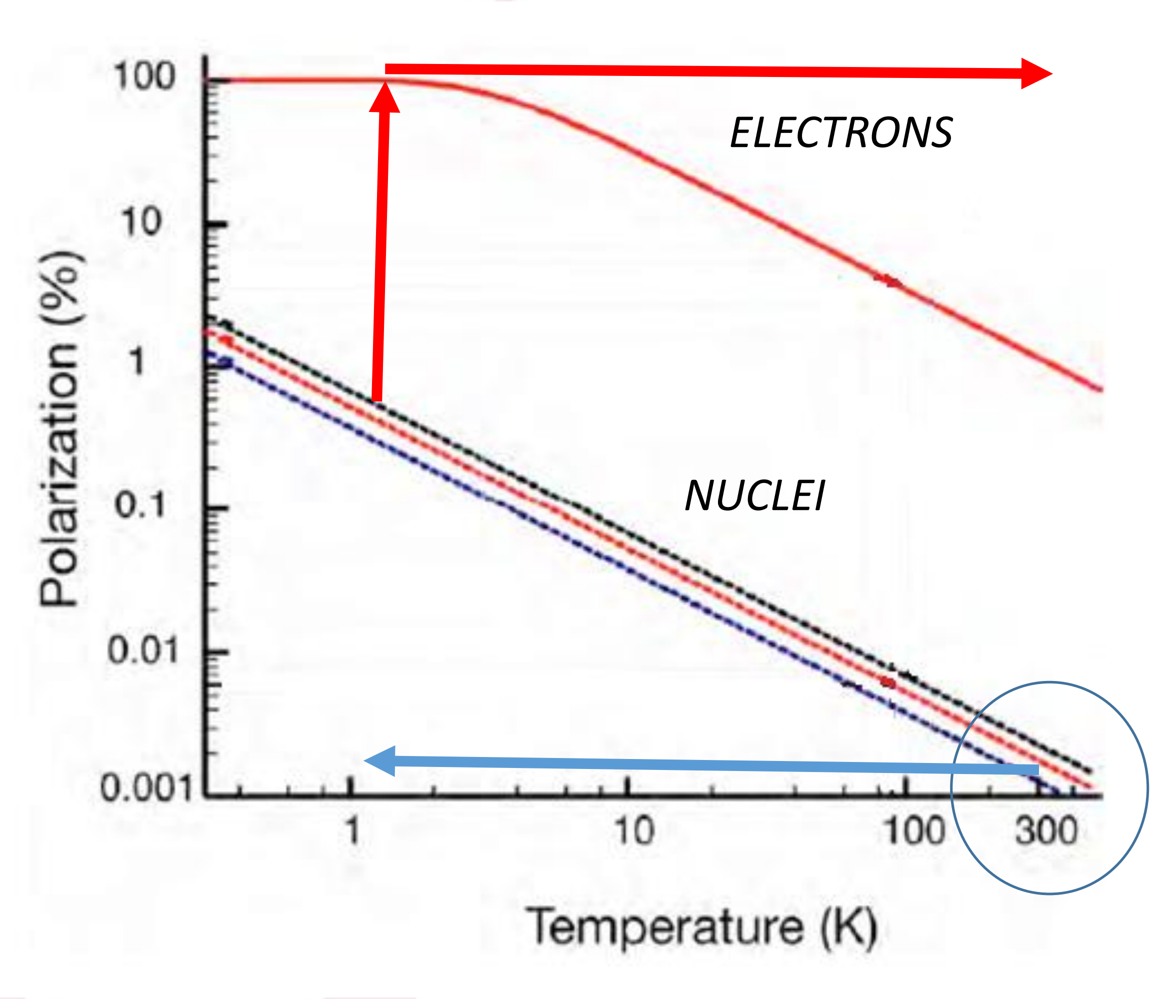
Thermal equilibrium

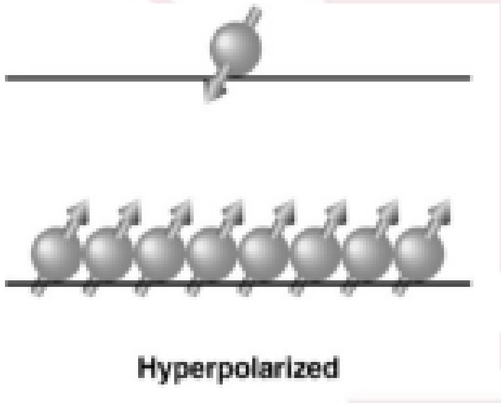


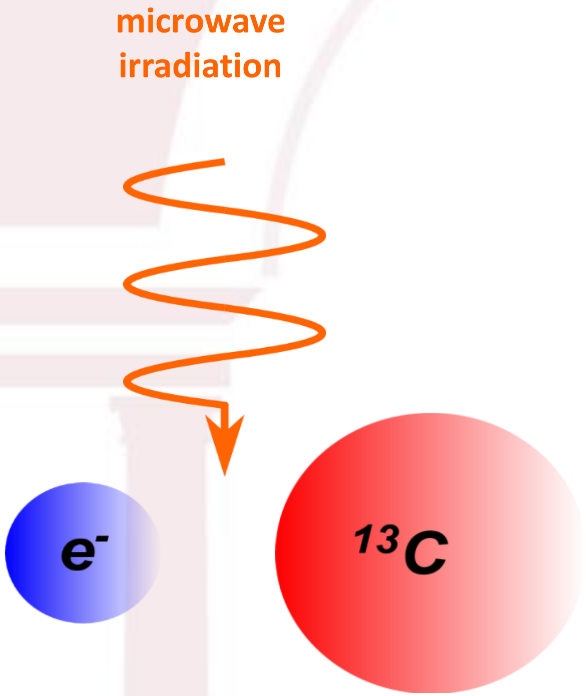
Hyperpolarized

HP
- **Non-equilibrio**
- **segnale $\sim\times10^5$**
- **T_1-limita tempo di vita**

Iperpolarizzazione dei Nuclei (DNP)

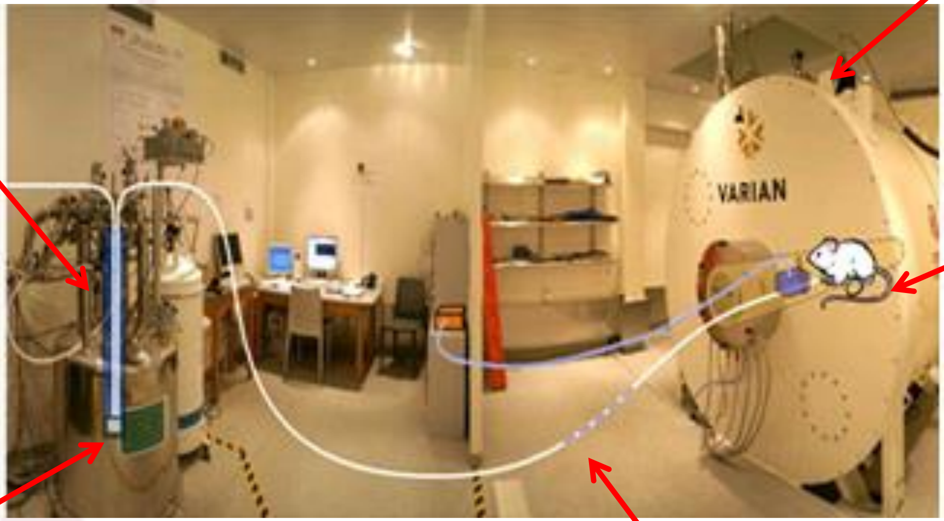



Hyperpolarized


microwave irradiation
e-
13C

For H=1 T only 1 nucleus over 10^6 contributes to the signal

Setup sperimentale



Apparato MRI

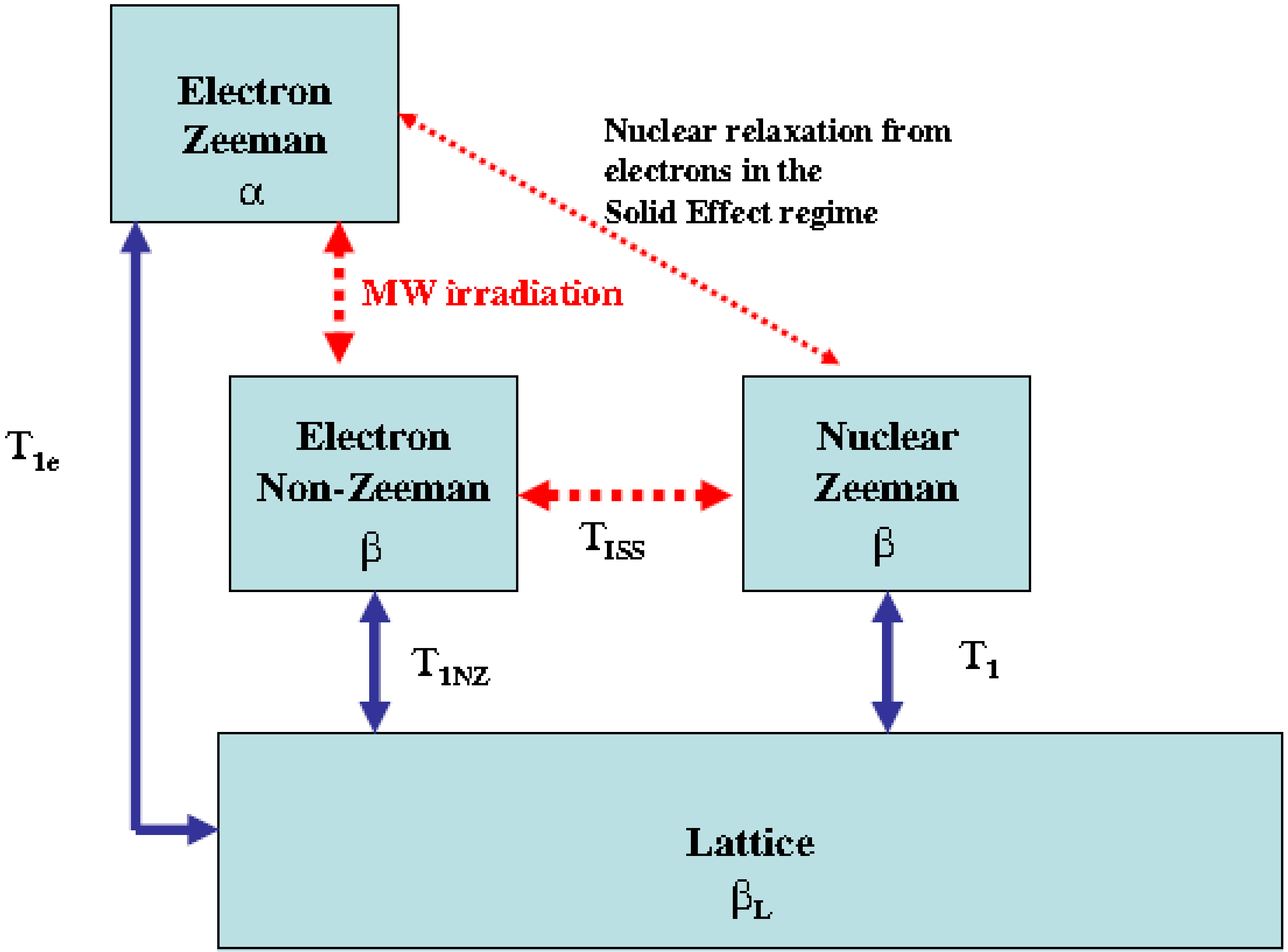
Sistema di diluizione

Iniezione *in vivo*

Polarizzatore

Tragitto del campione iperpolarizzato diluito

Descrizione Iperpolarizzazione: Thermal Mixing



Electron Zeeman
α

Nuclear relaxation from electrons in the Solid Effect regime

MW irradiation

T_{1e}

Electron Non-Zeeman
β

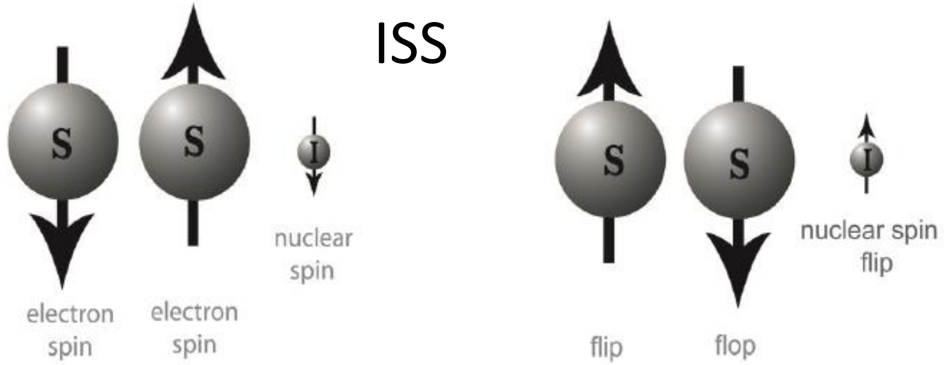
T_{ISS}

Nuclear Zeeman
β

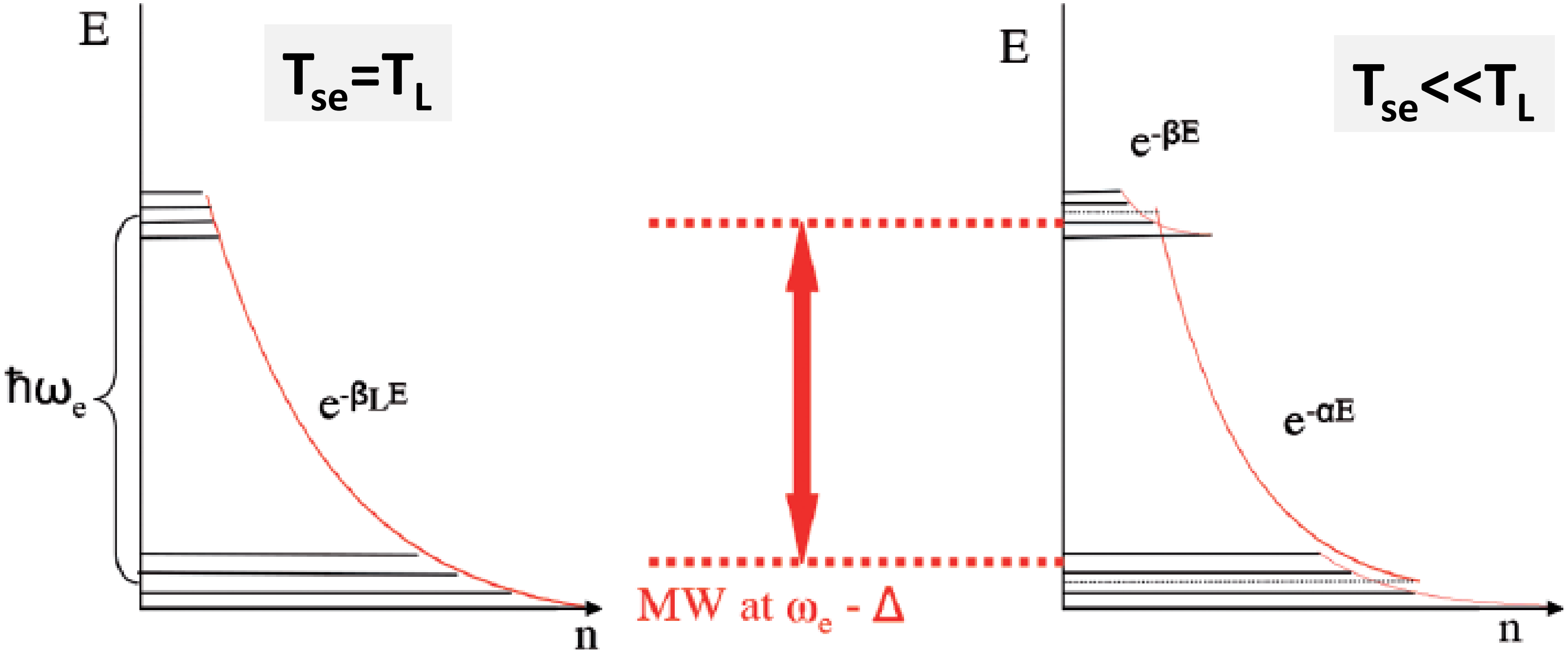
T_{1NZ}

T_1

Lattice
β_L

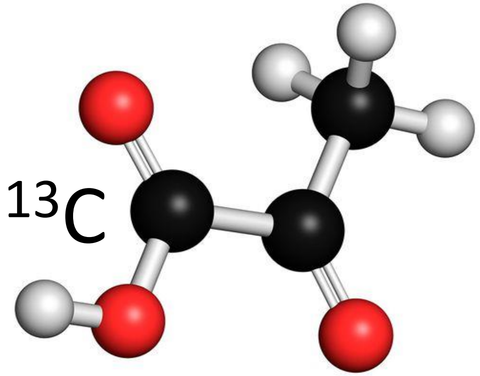

ISS
S
S
I
electron spin
electron spin
nuclear spin
S
S
I
flip
flop
nuclear spin flip

Raffreddamento degli spin elettronici


E
$T_{se}=T_L$
$\hbar\omega_e$
$e^{-\beta_L E}$
n
MW at $\omega_e - \Delta$
E
$T_{se}<<T_L$
$e^{-\beta E}$
$e^{-\alpha E}$
n

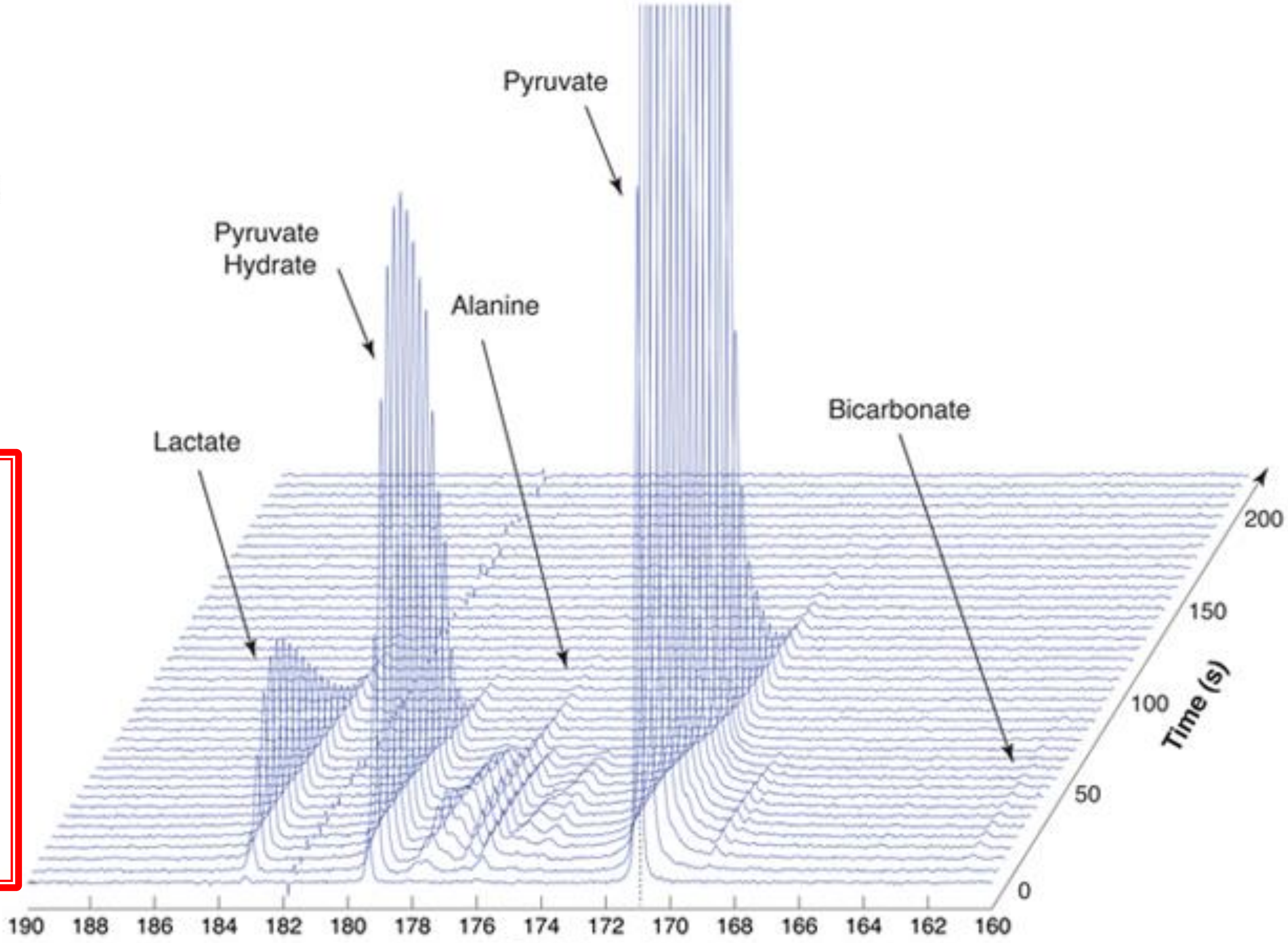
^{13}C Molecular Imaging

Acido Piruvico



^{13}C

- Assenza di background
- Risoluzione elevata del segnale proveniente da diverse molecole
- Molte molecole organiche facili da arricchire con ^{13}C



ω_0

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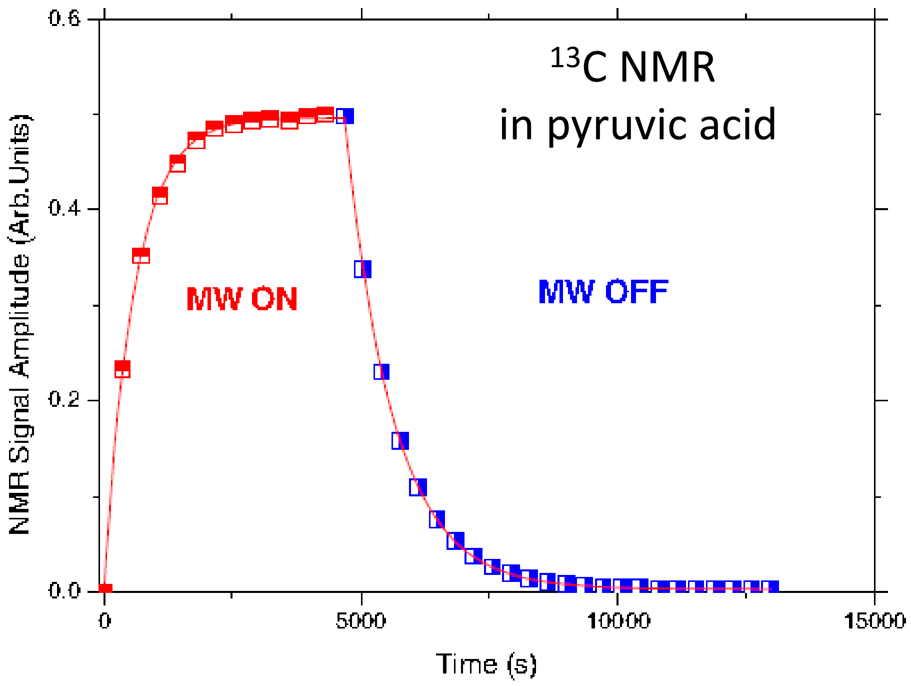
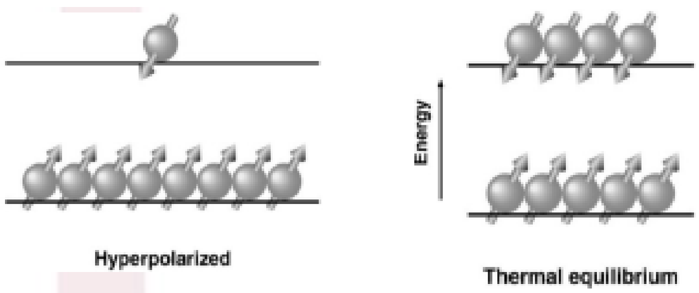
DNP - Imaging molecolare in medicina

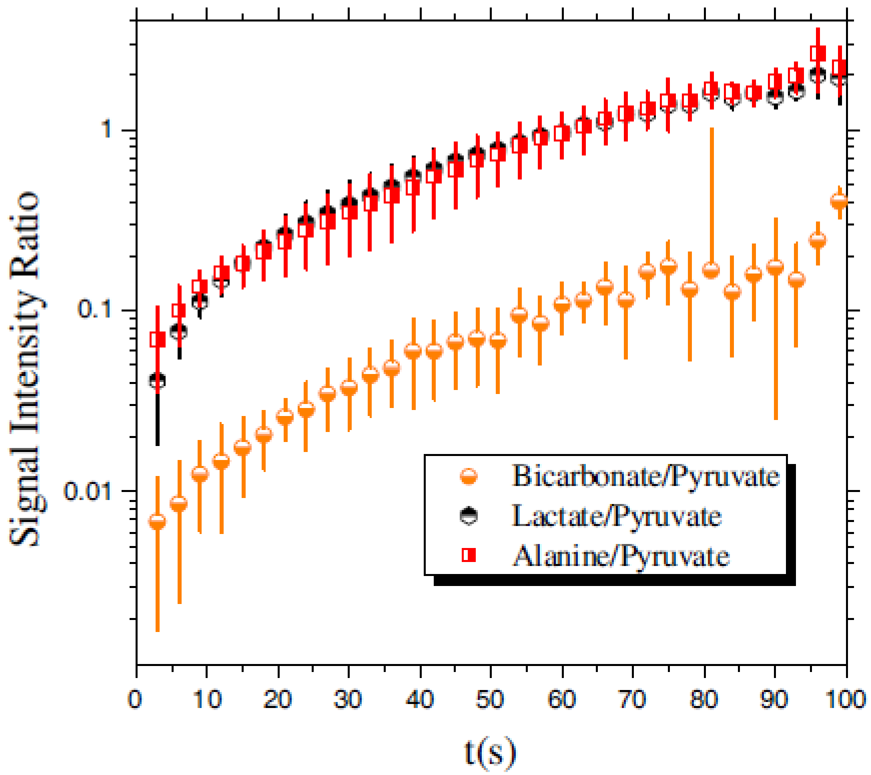
M.Filibian et al., PCCP 16, 27025 (2014)




Energy
Hyperpolarized
Thermal equilibrium

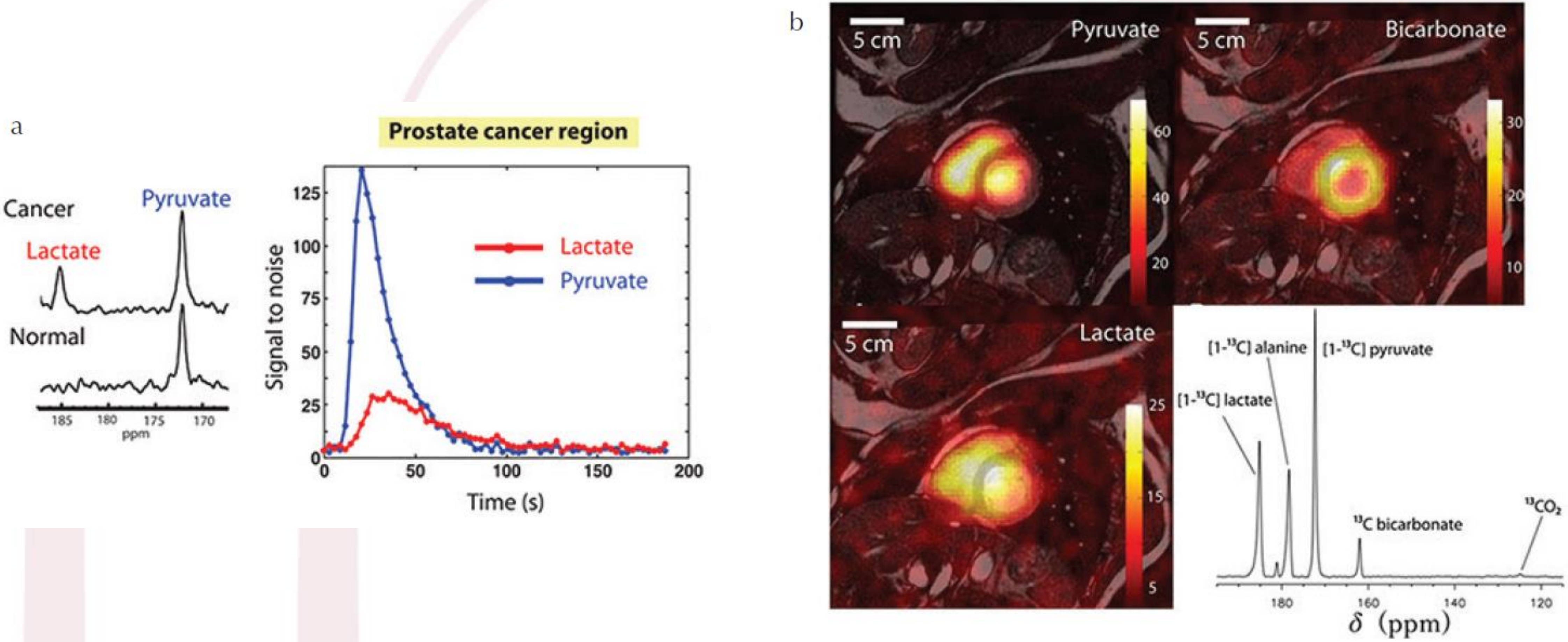
A.Lascialfari et al., Riv.N.Cim. 36, 211 (2013)

^{13}C *in vivo* MRS

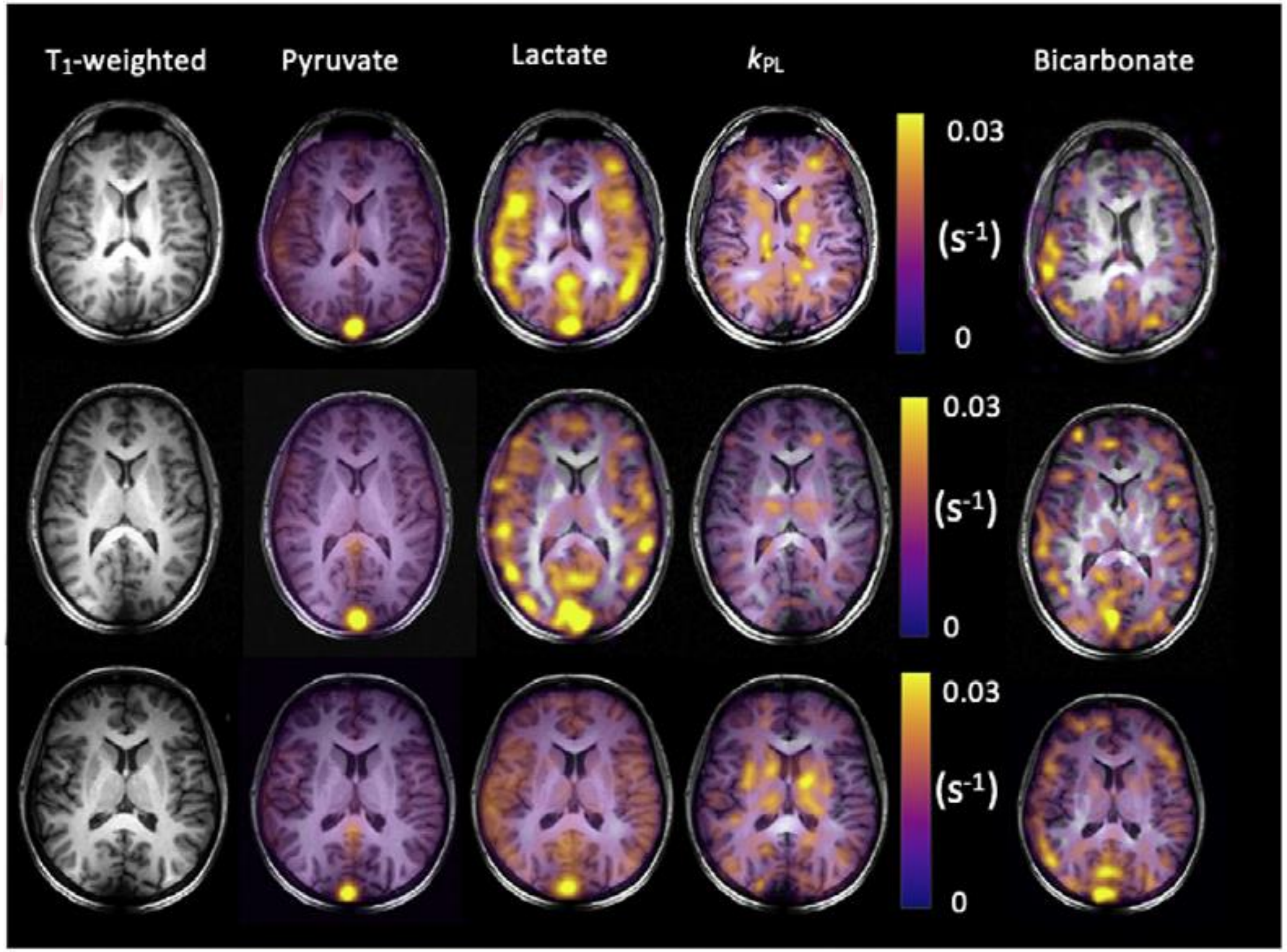


DNP- Imaging molecolare in medicina

N.J. Stewart and S.Matsumoto, doi:10.2463/mrms.rev.2019-0094


a
Cancer
Lactate
Pyruvate
Normal
185
180
175
170
ppm
Prostate cancer region
Signal to noise
Time (s)
Lactate
Pyruvate
0
25
50
75
100
125
0
50
100
150
200
b
5 cm
Pyruvate
60
40
20
5 cm
Bicarbonate
30
20
10
5 cm
Lactate
25
15
5
[1-^{13}C] alanine
[1-^{13}C] pyruvate
[1-^{13}C] lactate
^{13}C bicarbonate
$^{13}CO_2$
180
160
140
120
δ (ppm)

DNP-Imaging molecolare in medicina


T1-weighted
Pyruvate
Lactate
kPL
Bicarbonate
0.03
(s-1)
0
0.03
(s-1)
0
0.03
(s-1)
0

J.T. Grist et al., Neuroimage 189, 171 (2019)

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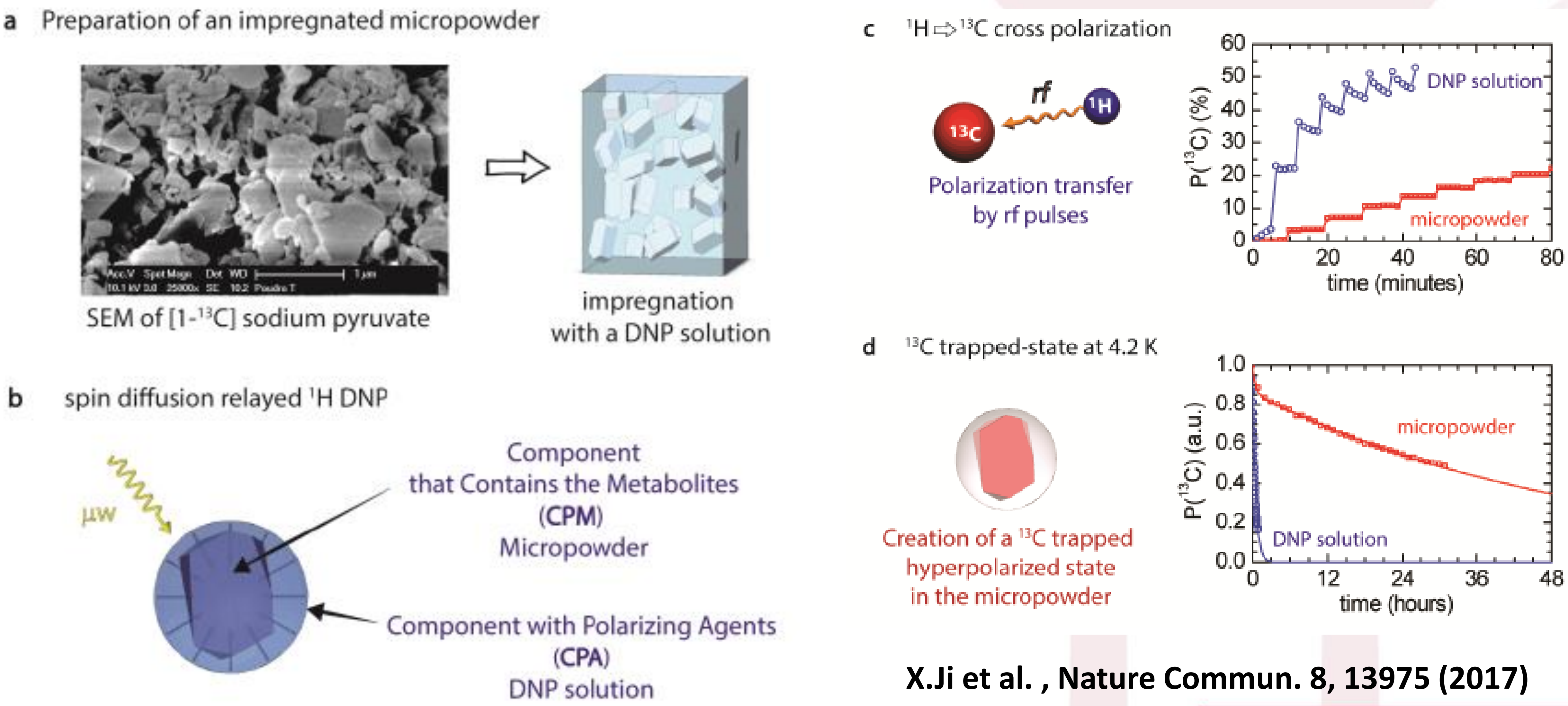
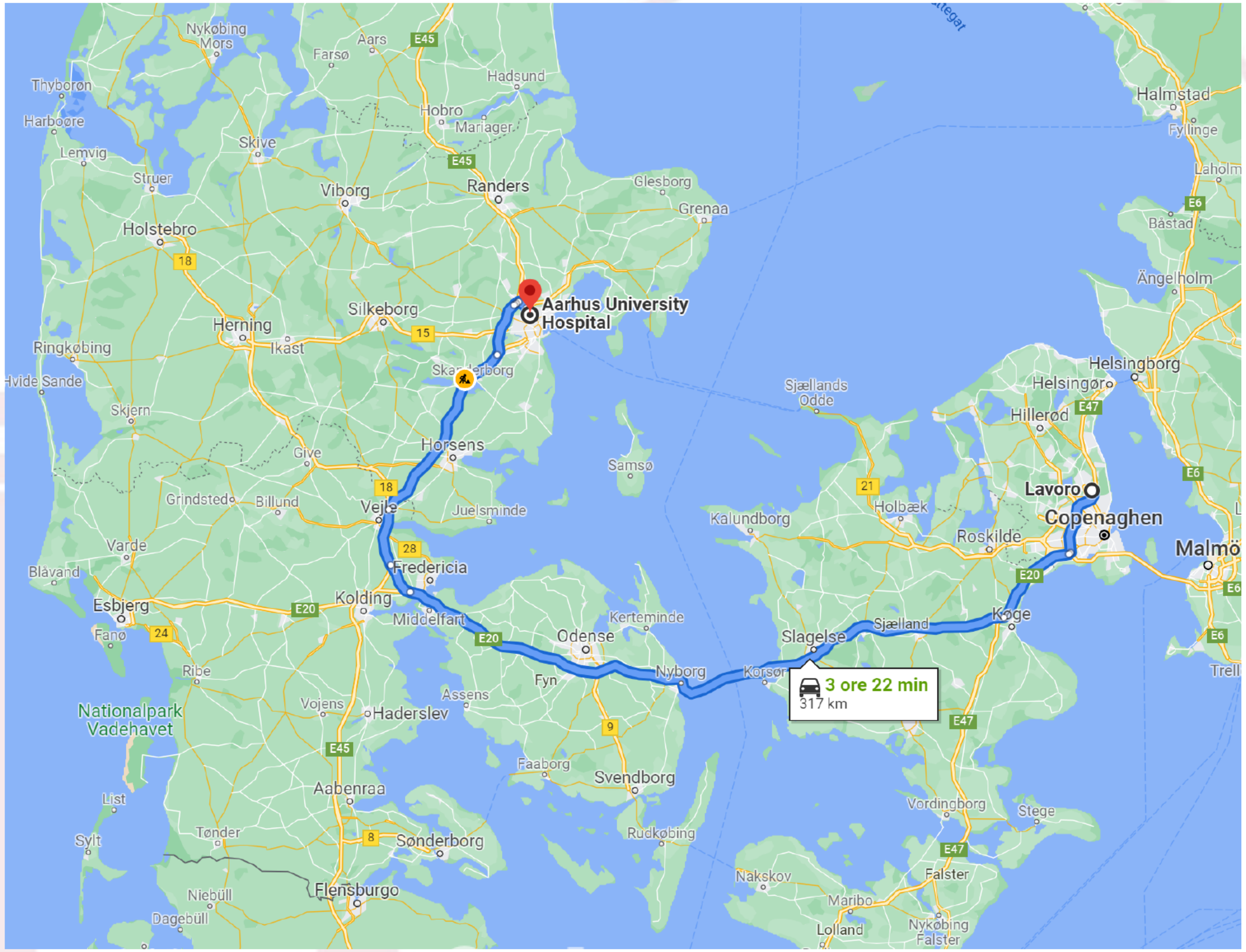
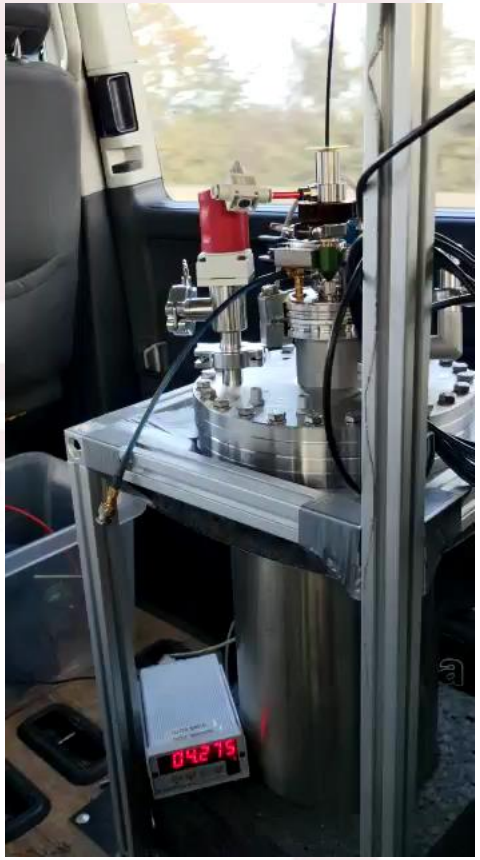
Remote DNP



X.Ji et al. , Nature Commun. 8, 13975 (2017)

Remote DNP


Aarhus University Hospital
Lavoro
Copenaghen
3 ore 22 min
317 km
Skanderborg
Horsens
Vejle
Fredericia
Kolding
Middelfart
E20
Odense
Nyborg
Korsør
Slagelse
Sjælland
Køge
Roskilde
Helsingør
Helsingborg
Hillerød
Malmö
Randers
Viborg
Silkeborg
Herning
Holstebro
Esbjerg
Sønderborg
Flensburgo
Svendborg
Samsø
Kalundborg
Holbæk
Halmstad



4 h and 320 km

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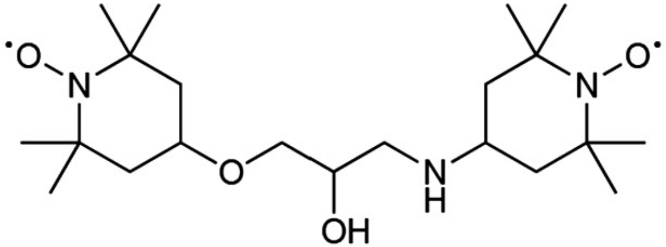
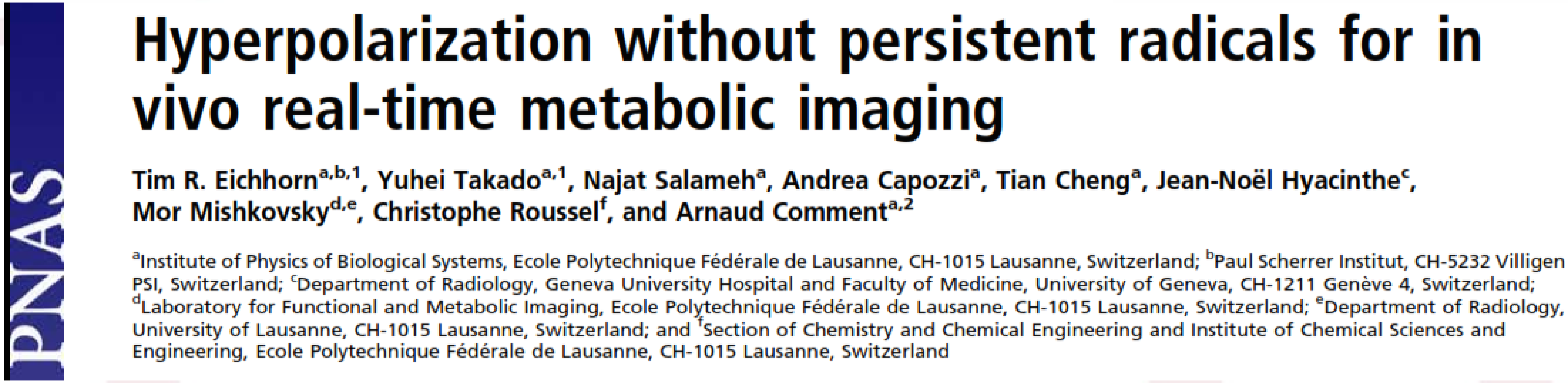
Thanks to Andrea Capozzi – DTU HYPERMAG

Radicali metastabili indotti da luce UV



TOTAPOL



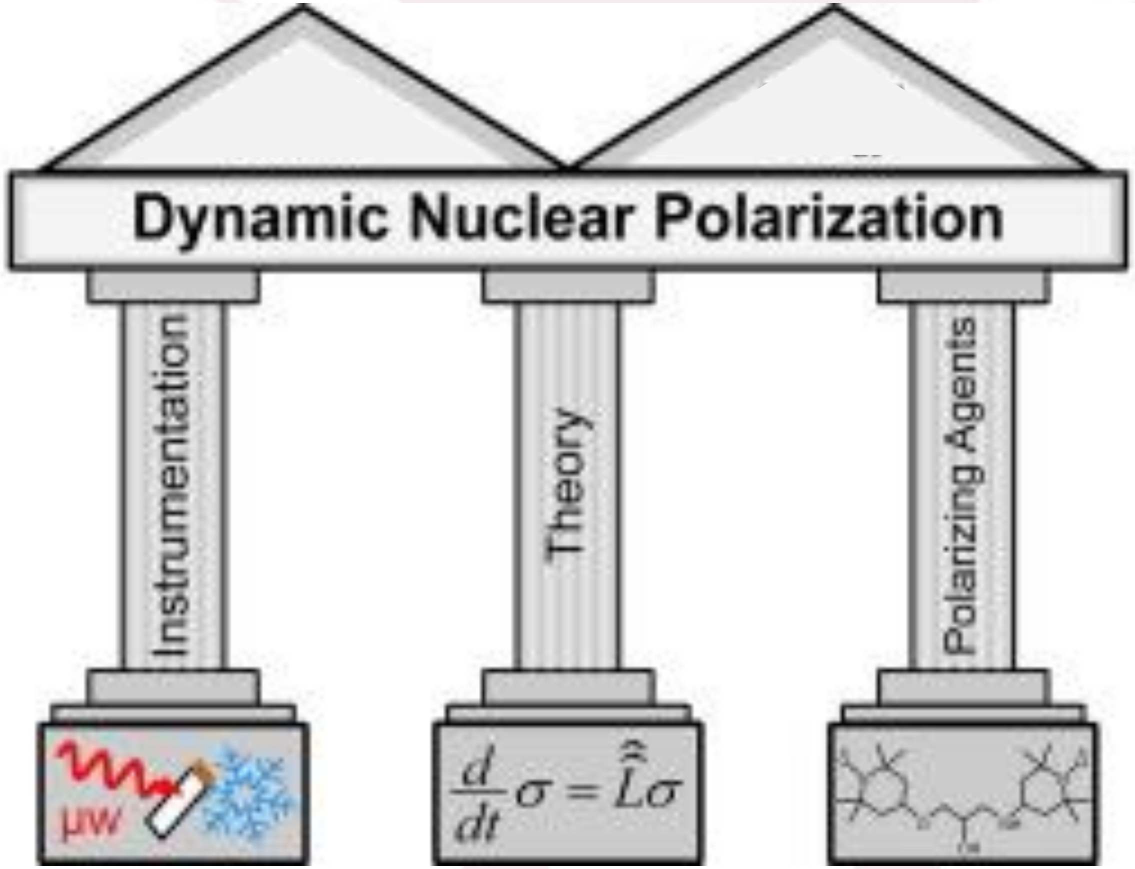
Hyperpolarization without persistent radicals for in vivo real-time metabolic imaging

Tim R. Eichhorn[a,b,1], Yuhei Takado[a,1], Najat Salameh[a], Andrea Capozzi[a], Tian Cheng[a], Jean-Noël Hyacinthe[c], Mor Mishkovsky[d,e], Christophe Roussel[f], and Arnaud Comment[a,2]

[a]Institute of Physics of Biological Systems, Ecole Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland; [b]Paul Scherrer Institut, CH-5232 Villigen PSI, Switzerland; [c]Department of Radiology, Geneva University Hospital and Faculty of Medicine, University of Geneva, CH-1211 Genève 4, Switzerland; [d]Laboratory for Functional and Metabolic Imaging, Ecole Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland; [e]Department of Radiology, University of Lausanne, CH-1015 Lausanne, Switzerland; and [f]Section of Chemistry and Chemical Engineering and Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland

Dynamic Nuclear Polarization

- **Fisica sperimentale**
- **Modellizzazione teorica**
- **Approccio fortemente multidisciplinare**


Dynamic Nuclear Polarization
Instrumentation
Theory
Polarizing Agents
μw
$\frac{d}{dt}\sigma = \hat{\hat{L}}\sigma$

NMR e MRI a Pavia

BRUKER
PharmaScan 70/16 US

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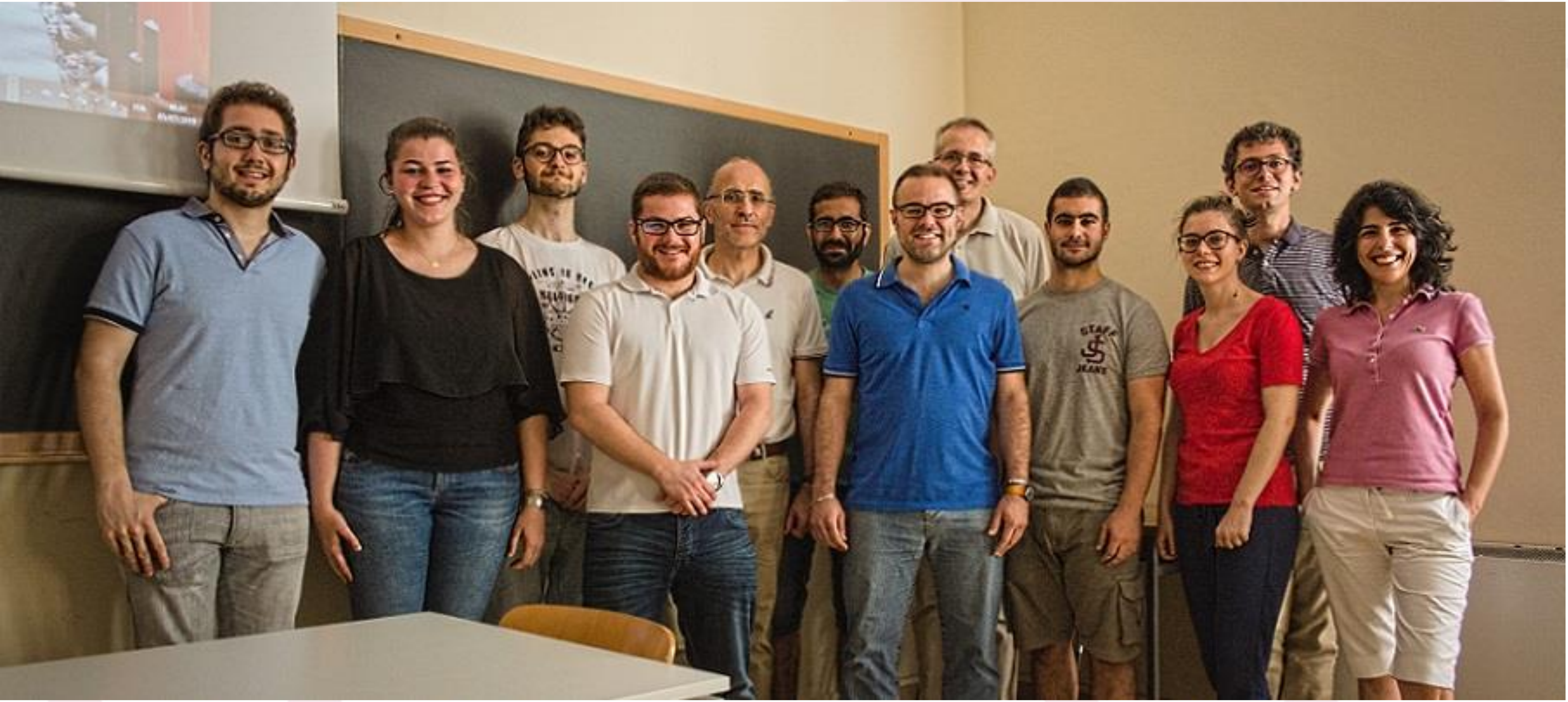

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GRAZIE PER L’ATTENZIONE

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