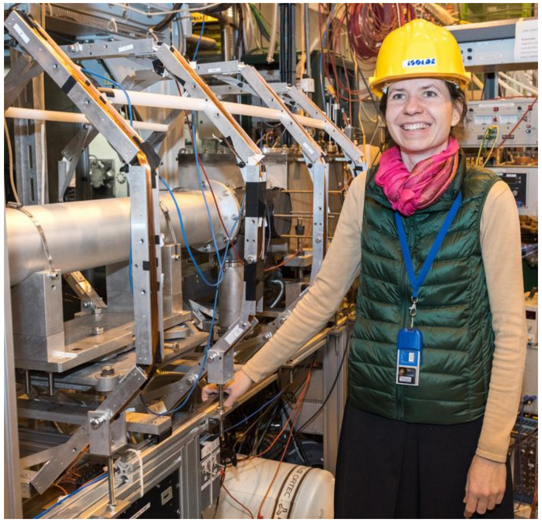
Przyspieszacze, detektory i radioaktywność w medycynie



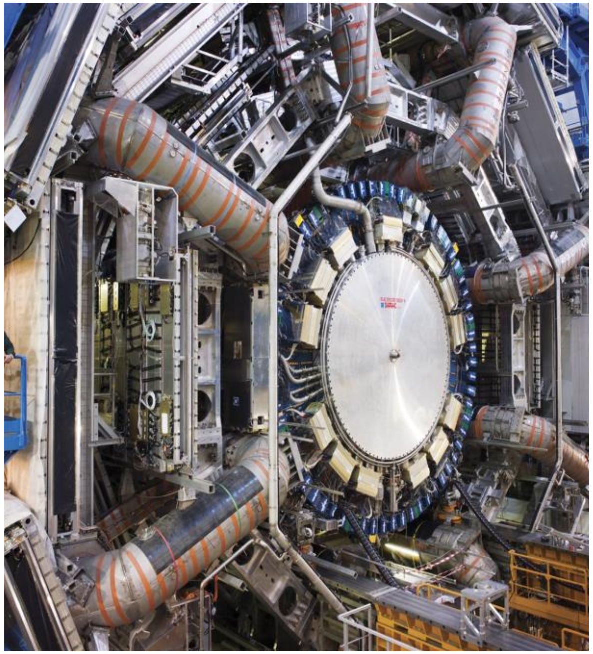
Sparks! Prezentacja o przyszłości detekcji i obrazowania

Magdalena Kowalska
CERN i Uniwersytet Genewski

Zastosowania badań postawowych w CERN

- CERN = największe laboratorium badań podstawowych na świecie
- Zrozumienie z czego się składa i jak powstał Wszechświat, wymaga:

Przyspieszaczy



Detektorów

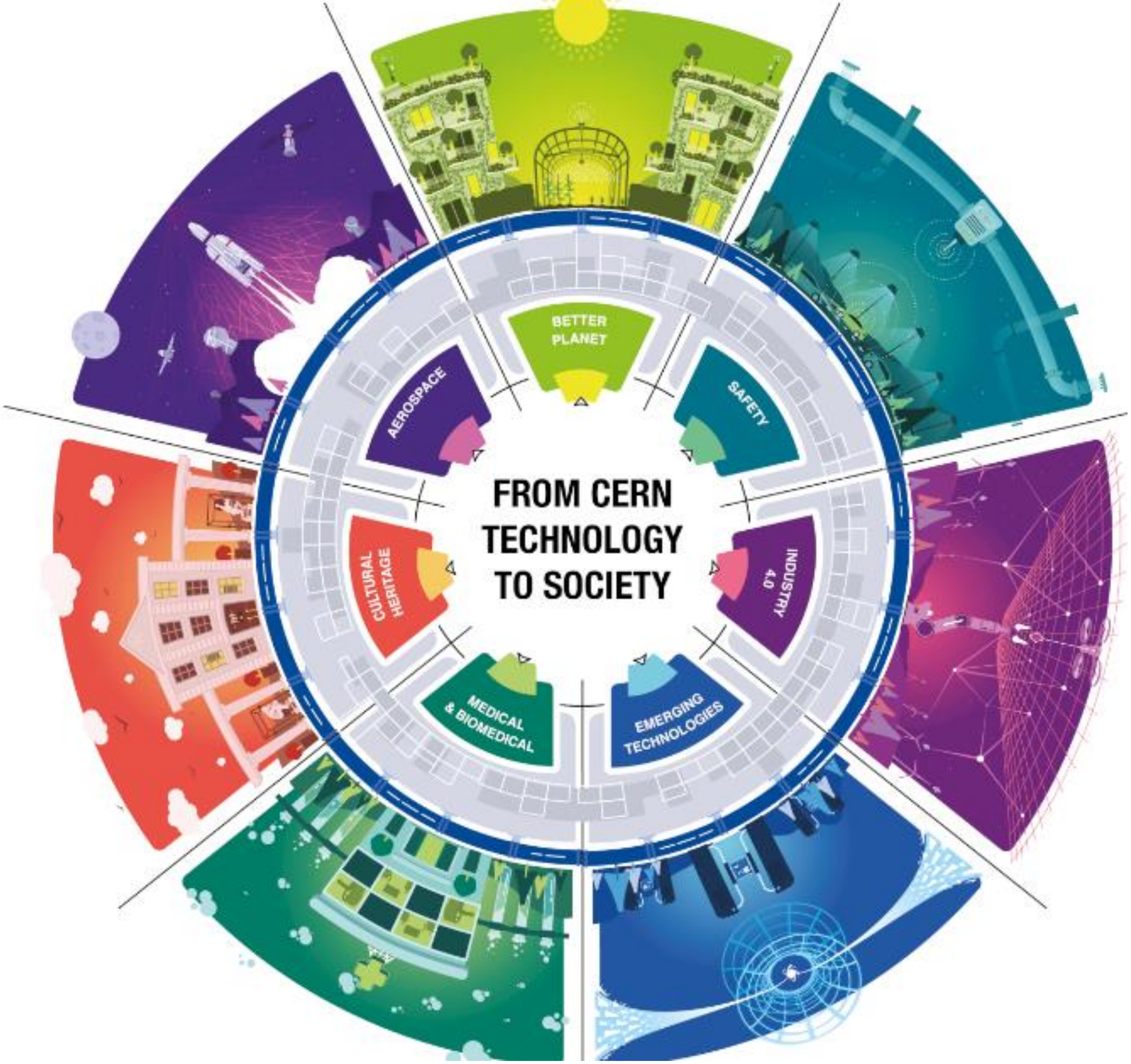
Promieniowania

(i technik informatycznych)

Te techniki mogą zostac ‚przetłumaczone’ w różne przydatne technologie:

Transfer wiedzy z CERN

- Dziedziny:
  - Przestrzeń powietrzna i kosmiczna
  - Opieka zdrowotna
  - Techniki cyfrowe
  - Środowisko
  - Technologie kwantowe

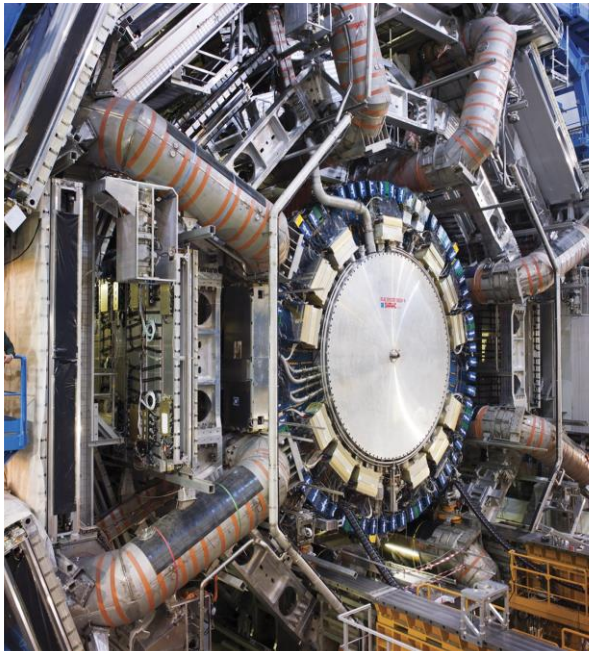


CERN Knowledge Transfer:
https://kt.cern/

Zastosowania w medycynie

- Użycie narzędzi CERN do polepszenia diagnozy i leczenia różnych chorób:

Przyspieszaczy

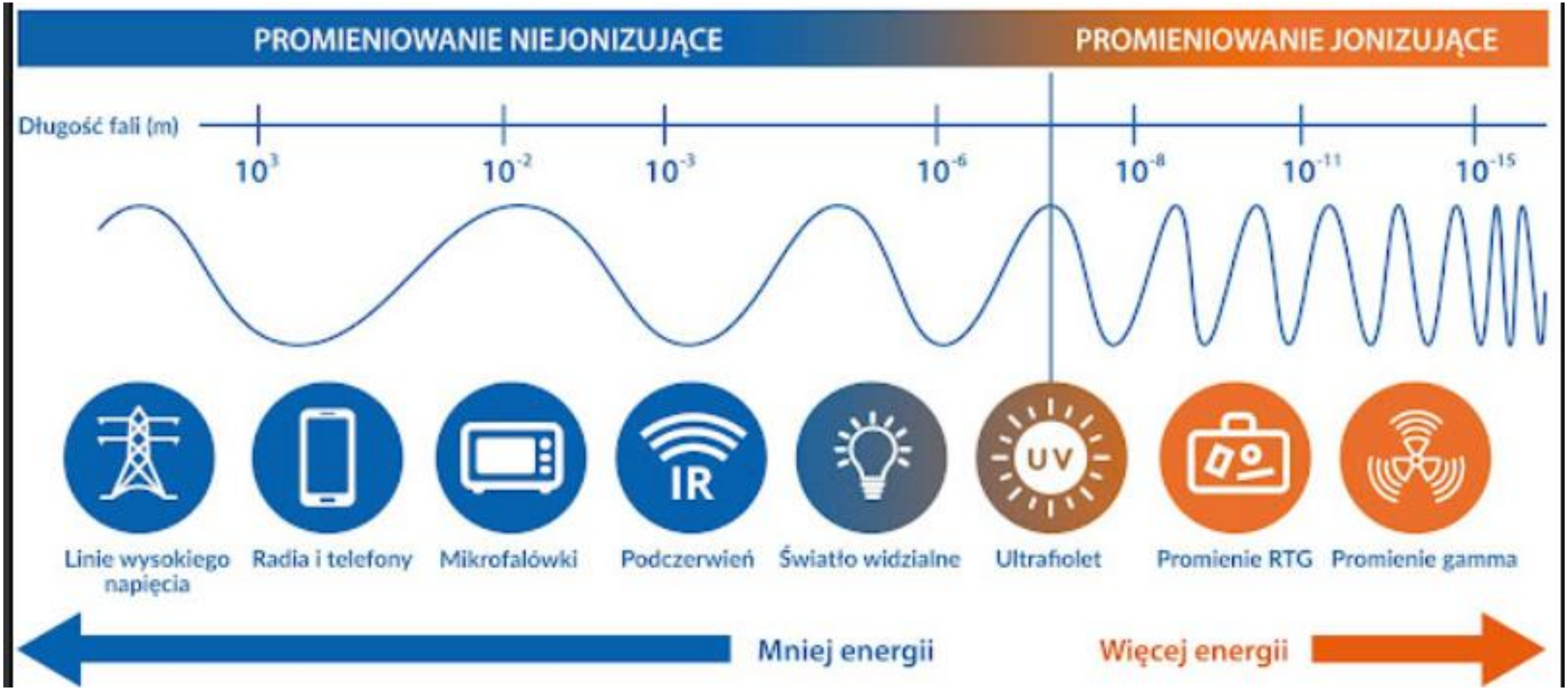


Detektorów

Promieniowania

- Silne strony:
  - Czuła detekcja promieniowania w celach diagnostycznych
  - Precyzyjne leczenie cząsteczkami i promieniowaniem

Promieniowanie jonizujące



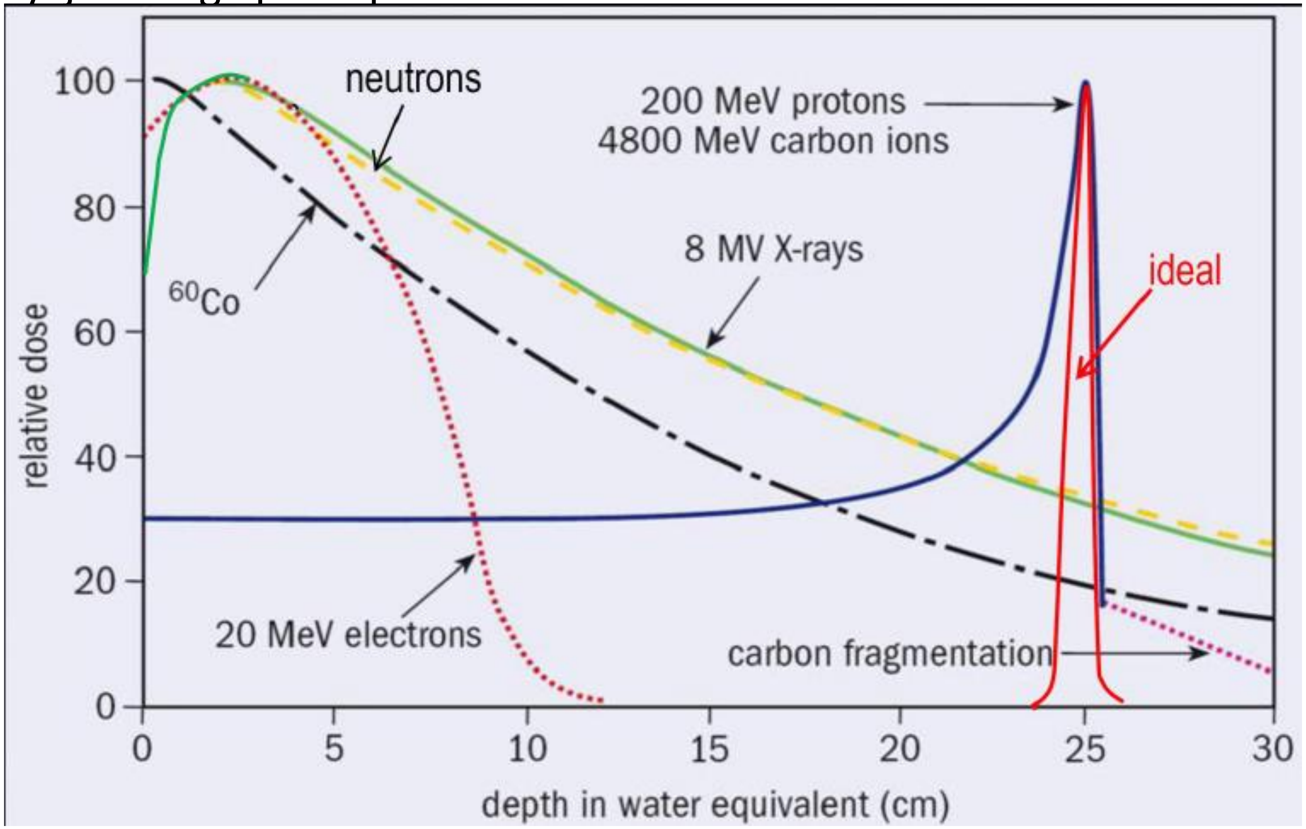
Cząstki :

- Beta (e- i e+)
- Protony, neutrony, cząstki alfa
- ‘cieżkie jony’ (12C, 16O, w przyszłości może nawet niestabilny 11C)

Przyspieszacze

Leczenie (raka) z wiązkami zewnętrznymi

- Depozycja energii przez promieniowanie w materii:

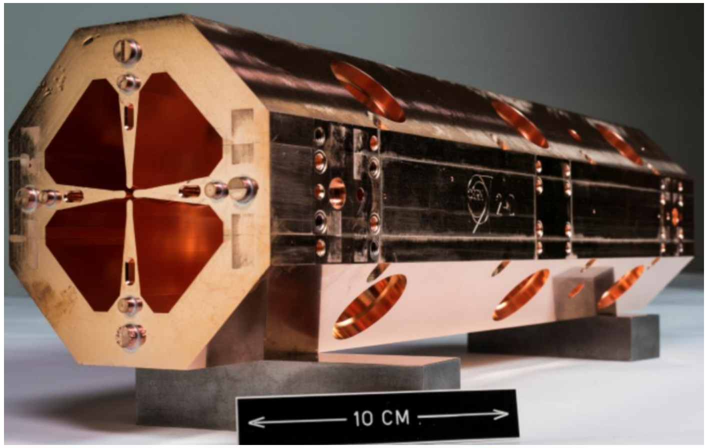


- Metoda:
  - Napromienianie z kilku stron, aby zmaksymalizować dawkę w objętości, która ma zostać wyleczona
  - Protony i „ciężkie jony” są najbardziej selektywne: największa dawka na końcu ścieżki cząstki

Diagnostyka i leczenie z przyspieszaczami

Przyspieszacze cząstek (z CERN):

- Produkcja izotopów PET i SPECT (cyklotrony przyszpitalne) do diagnostyki w madycynie nuklearnej
- Już używane do terapii hadronowej:
  - Leczenie raka i problemów z sercem z użyciem energetycznych wiązek protonów, jader deuteru, a nawet węgla
  - Energia depozytowana cm wgłab ciała, na końcu ‚trasy' cząstki



Tera foundation (U. Amaldi), CERN spin-off: ADAM

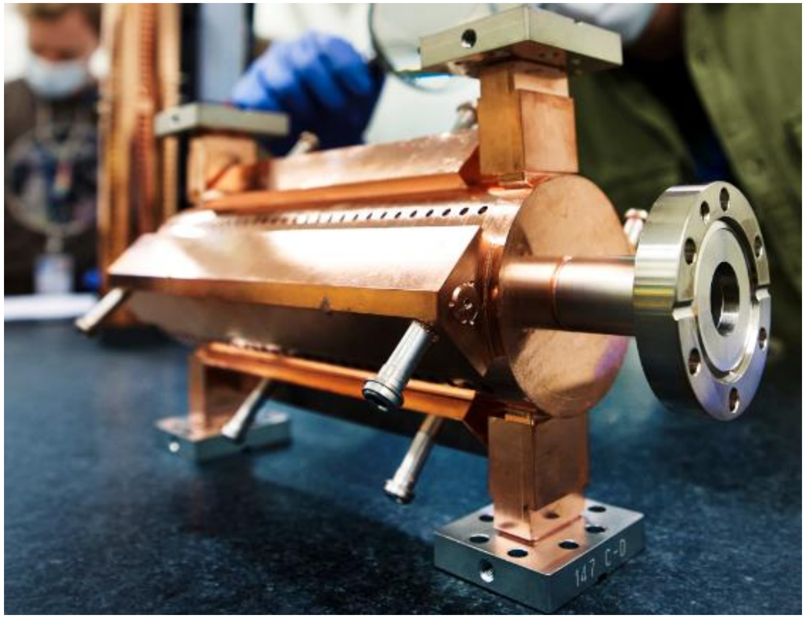
CNAO The National Center for Oncological Hadrontherapy Pavia, IT

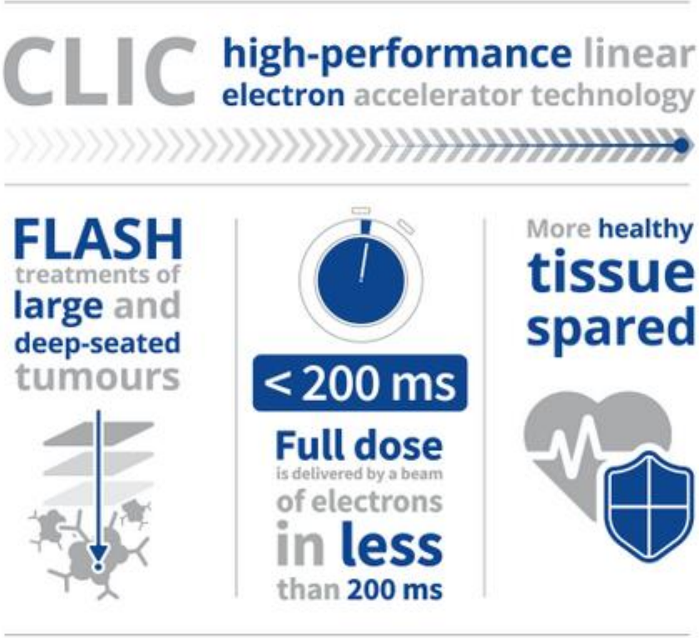
Połowa przyspieszaczy na świecie jest używana do zastosowań w medycynie

Diagnostyna i leczenie z przyspieszaczami

Kompaktowy przyspieszacz elektronów:

- W oparciu o R&D technologii CLIC (compact linear collider) w CERN
- FLASH: radioterapia w któtkimi pulsami
- Gotowy do zbudowania w Lozannie





CLIC high-performance linear electron accelerator technology

FLASH treatments of large and deep-seated tumours

< 200 ms

Full dose is delivered by a beam of electrons in less than 200 ms

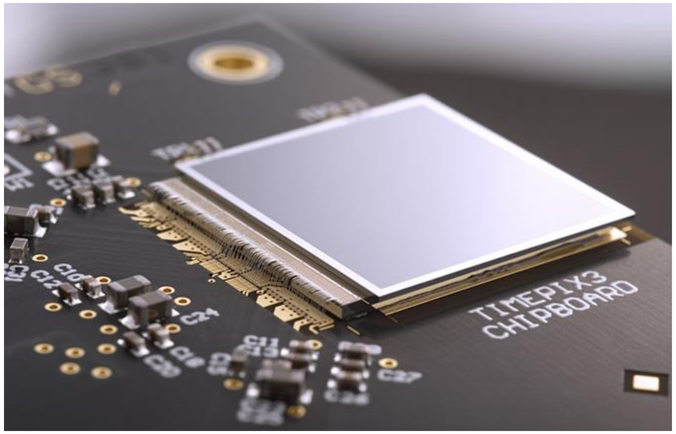
More healthy tissue spared

Video: https://videos.cern.ch/record/2295068

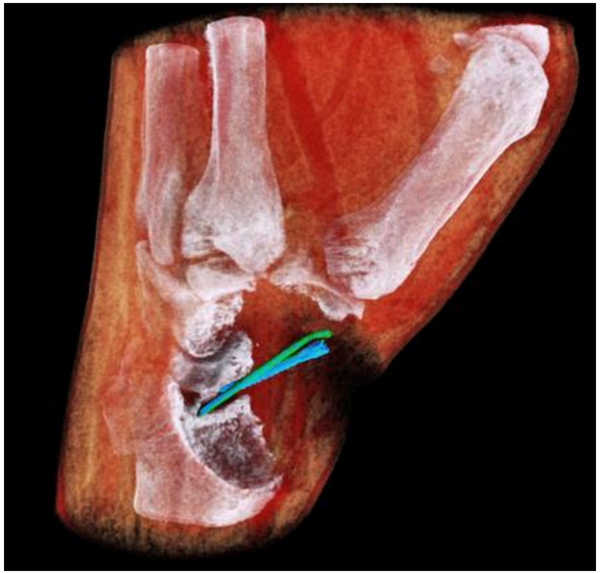
https://kt.cern/flash-radiotherapy

Detektory

Diagnoza z detektorami zliczającymi kwanty promieniowania Roentgenowskiego



- Kolaboracja MEDIPI i TIMEPIX w CERN
- Hybrydowe detektory o wysokiej zdolności rozdzielczej stworzone do śledzenia cząstek w LHC
- Aplikacje w wielu dziedzinach
- Zliczanie fotonów Rentgenowskich w diagnozie medycznej z użyciem tomografii komputerowej:
  - Niższe dawki
  - Wyższa rozdzielcośc przestrzenna
  - Rozdzielcośc w energii promieniowania
- 1st przenośny skaner CT w Europie

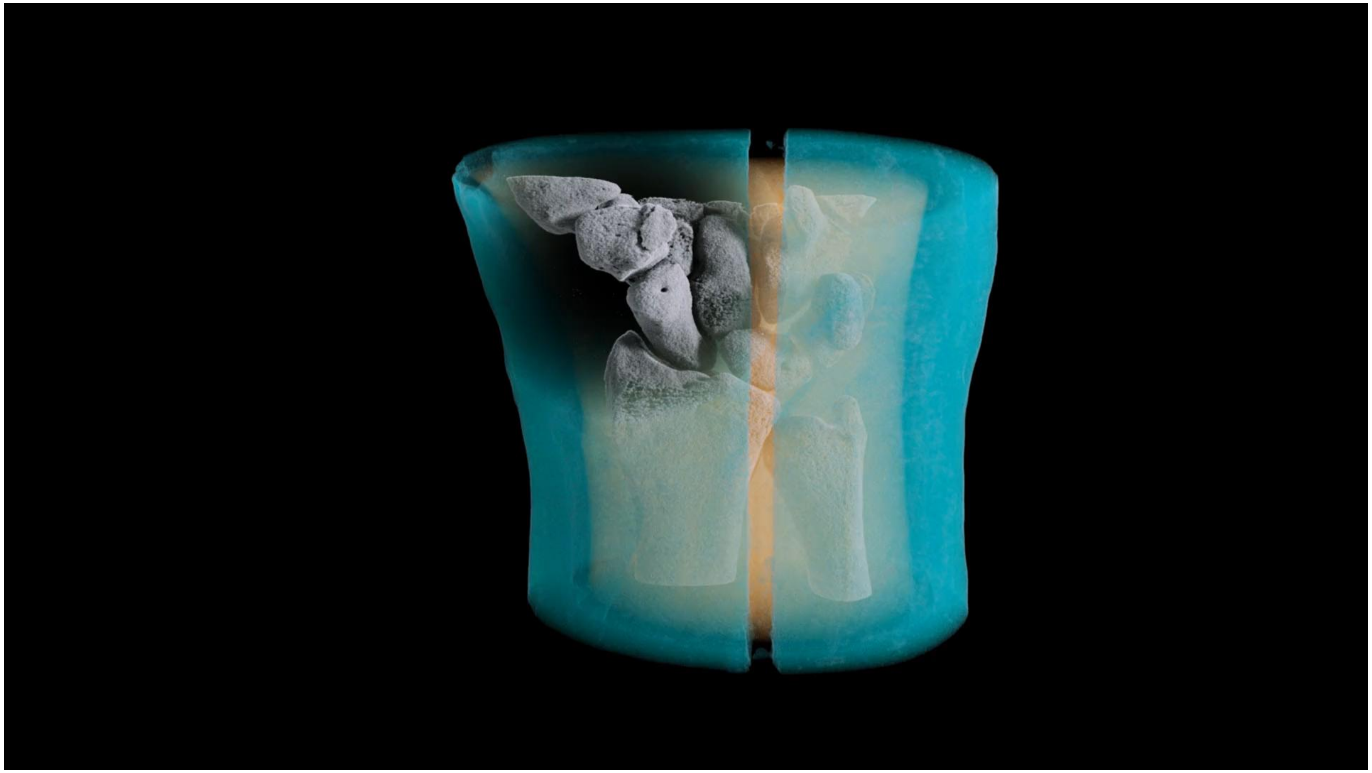


Śruba metalowa (niebieski), K- (zielony)

Transfer technologii n.p. do MARS, New Zealand, and Czechia

Tomografia komputerowa ze zliczaniem fotonów

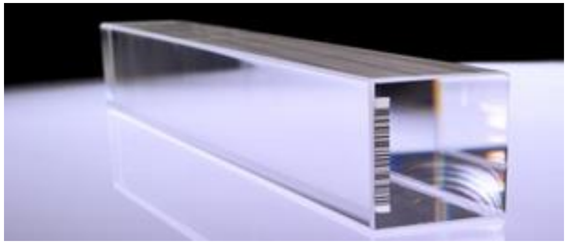
- Obraz przegubu:



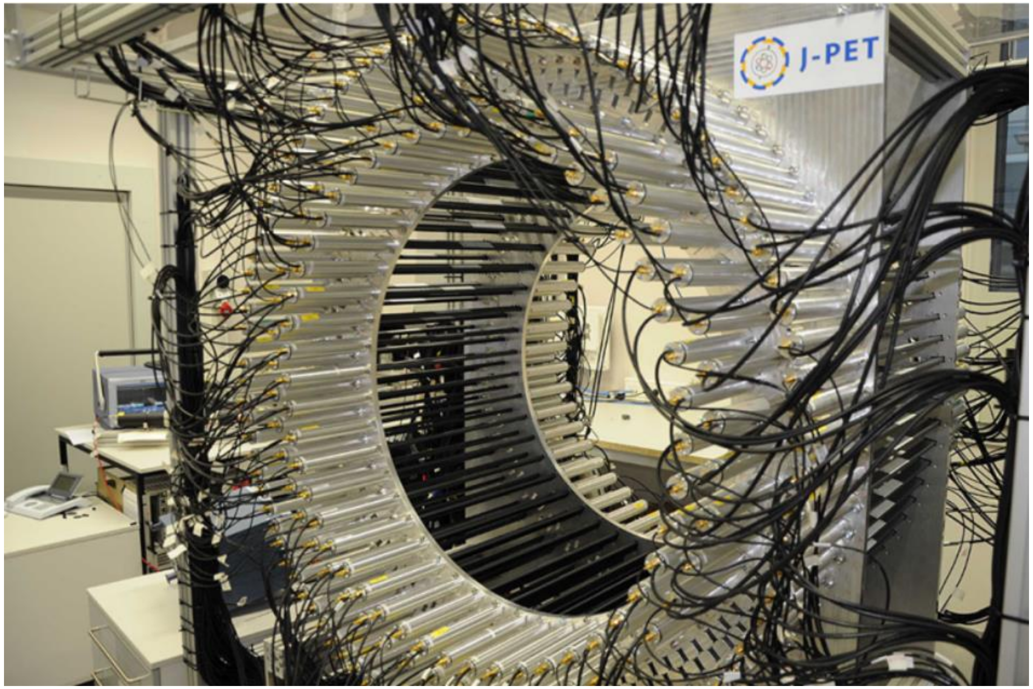
Source: MARS bioimaging

Detektory PET dla kwantów 511 keV

- Detektory z ns i ps rozdzielczością czasową – lepsza lokalizacja źródła fotonów anihilacyjnych:
  - Jak w trakerze ATLASu: monolityczne detektory krzemowe - projekt TT-PET UNIGE
  - Szybkie scyntyjujace kryształy z CMSu: CrystalClear w CERN
  - Jak w szybkiej jądrowej spektroskopii : U Complutense Madrid



- Tańsze materiały:
  - Scyntylatory organiczne: J-PET w Krakowie



Jądra niestabilne

Diagnostyka medyczna z izotopami nistabilnymi

- Diagnostyka z jądrami radioaktywnymi:
  - Jądro radioaktywne zwykle połączone chemicznie z biologicznym „ligandem”
  - „ligand” znajduje obszary do diagnozy: cukry lub peptydy trafiają do komórek, które ich najbardziej potrzebują, np. komórki rakowe
  - Emitowane promieniowanie wskazuje lokalizację interesującego regionu
  - Wydajne detektory cząstek wykrywają bardzo niskie, nieszkodliwe stężenia radioligandu (nM/pM)

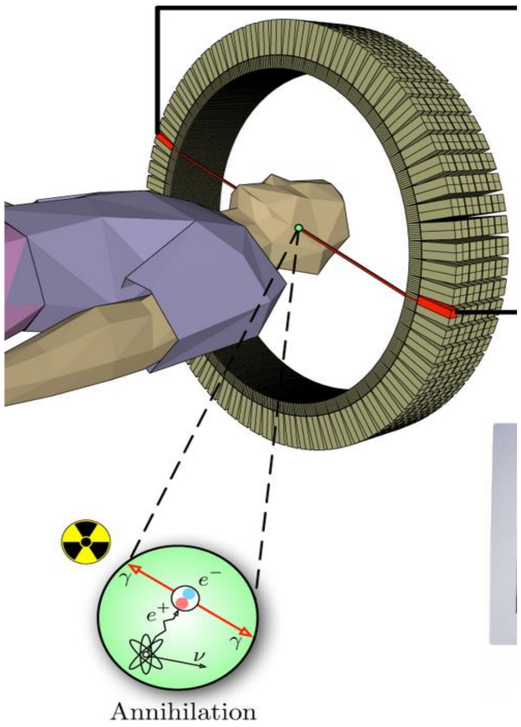
- Odpowiednie izotopy:
  - Izotop pierwiastka, który może wiązać się z ligandami biologicznymi
  - Czas życia wystarczająco długi do dostarczenia i wystarczająco krótki dla organizmu: godziny do dni
  - Odpowiedni rodzaj promieniowania i jego energia

- Wykrywanie: promieniowanie, nie cząstki, bo jest ono mniej zatrzymywane w ciele:
  - Promienie gamma z dekscytacji/rozpadu jądra lub z anihilacji emitowanej cząstki beta+

- Podejścia (medycyna nuklearna):
  - PET
  - SPECT

PET: pozytonowa tomografia emisyjna

- Sygnał z jąder emitujących beta+ (pozyton)
  - Emitowany pozyton zatrzymuje się po przebyciu kilku mm w tkance
  - Pozyton = antymateria, więc anihiluje z elektronem z sąsiedniej cząsteczki (E=mc2)
  - 2 promienie gamma o energii 511 keV są emitowane pod kątem 180 stopni
- Wykrywanie:
  - Na podstawie czasu i położenia trafień w detektorach identyfikuje się miejsce anihilacji



PET i CERN

- PET opracowano w Szpitalu Genewskim w 1977 r.
  - Pierwsze izotopy wyprodukowano w CERN

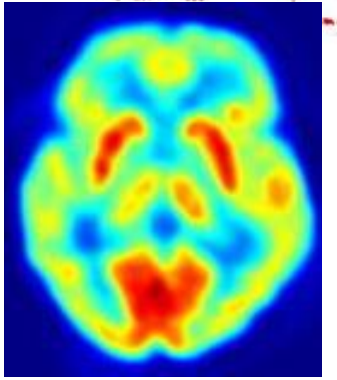
- Rozwój detektorów w CERN i okolicach
  - Działalność związana z CMS: CrystalClear
  - Szybka odpowiedź detektora -> lepsza lokalizacja
  - Tańsze, bardziej wydajne

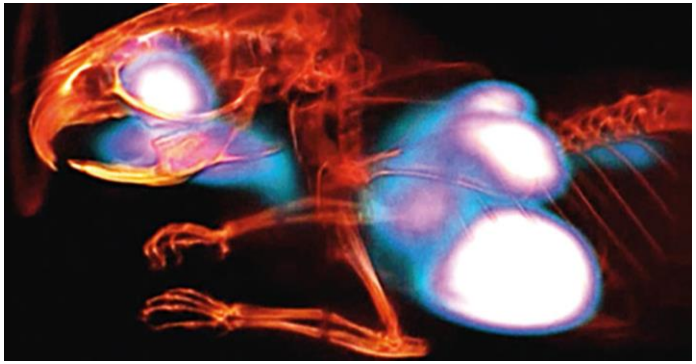
- Nowe izotopy PET:
  - ISOLDE i MEDICIS (siostra ISOLDE)

- Mocne strony:
  - Niezwykle czuła technika

- Względne słabości :
  - Rozdzielczość czasowa detektorów jest kluczowa -> można lepiej określić miejsce anihilacji
  - Koincydencja między 2 gamma: stosunkowo złożona rekonstrukcja maszyny i zdarzenia
  - e+ może przebyć kilka milimetrów przed anihilacją: ograniczenie rozdzielczości

SCAN OF MOUSE SKELETON . $5.7\ \mu Ci$, F^{18} (positron emission)
1 bin ≡ 1mm × 1mm. Plane spacing = 1 cm.

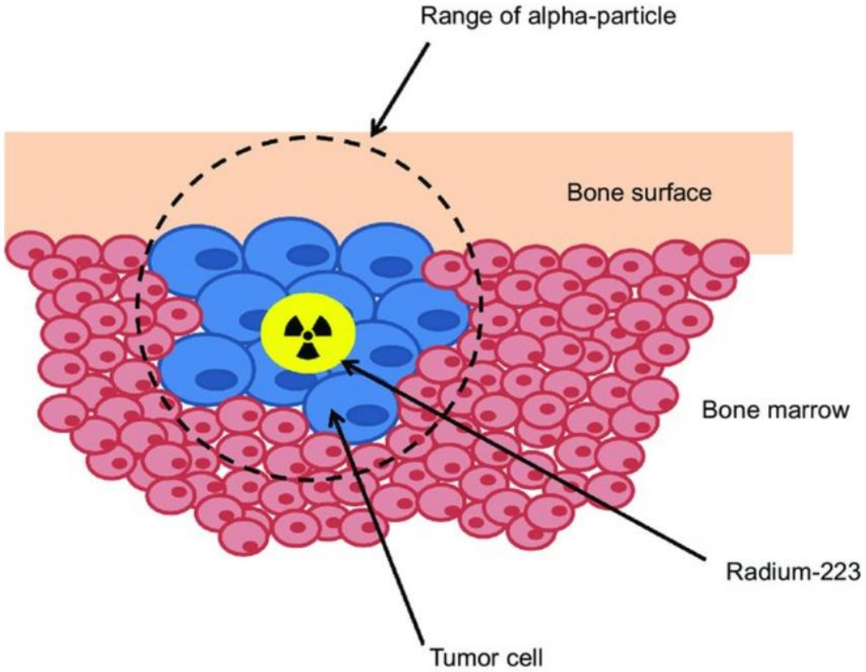


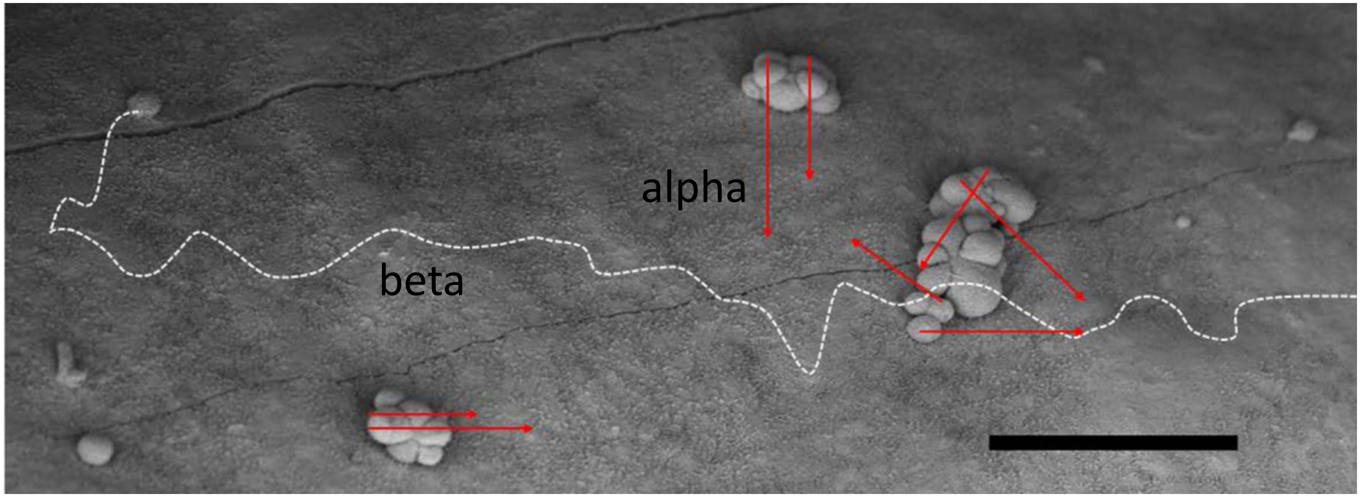


https://home.cern/news/news/knowledge-sharing/forty-years-first-pet-image-cern

Leczenie raka za pomocą radio-izotopów

- Leczenie poprzez uszkodzenie komórek (głównie DNA):
  - Promieniowania beta o wysokiej dawce
  - Promieniowanie alfa: cięższe, więc krótszy zasięg, ale wyższa śmiercionośniosc (dwu-niciowe uszkodzenie DNA)
- Dostarczanie izotopów do nowotworu – jak w diagnozie: połączenie z ligandem
- Izotop:
  - Odpowiedni okres półtrwania
  - Emisja alfa

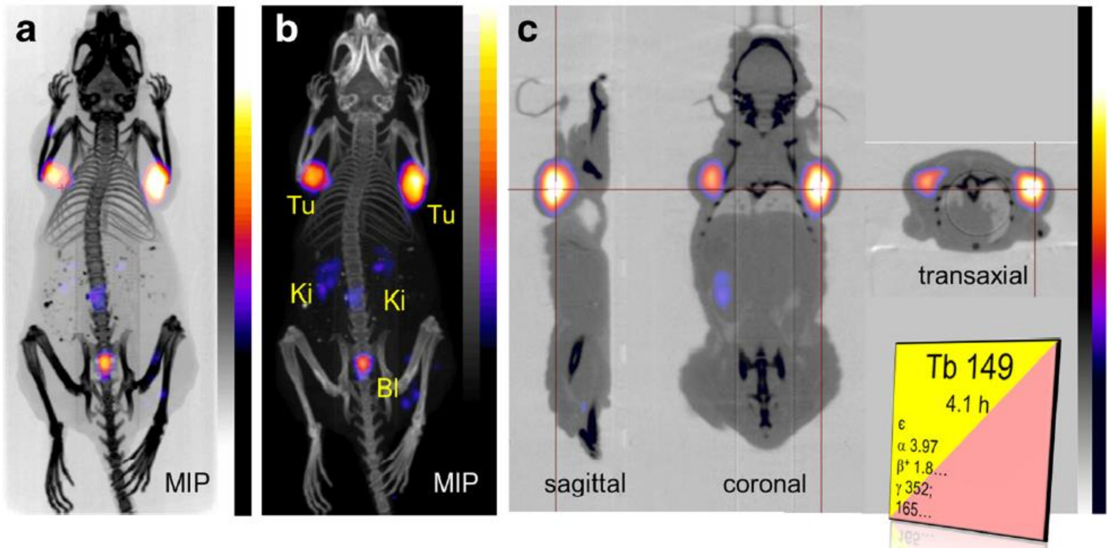


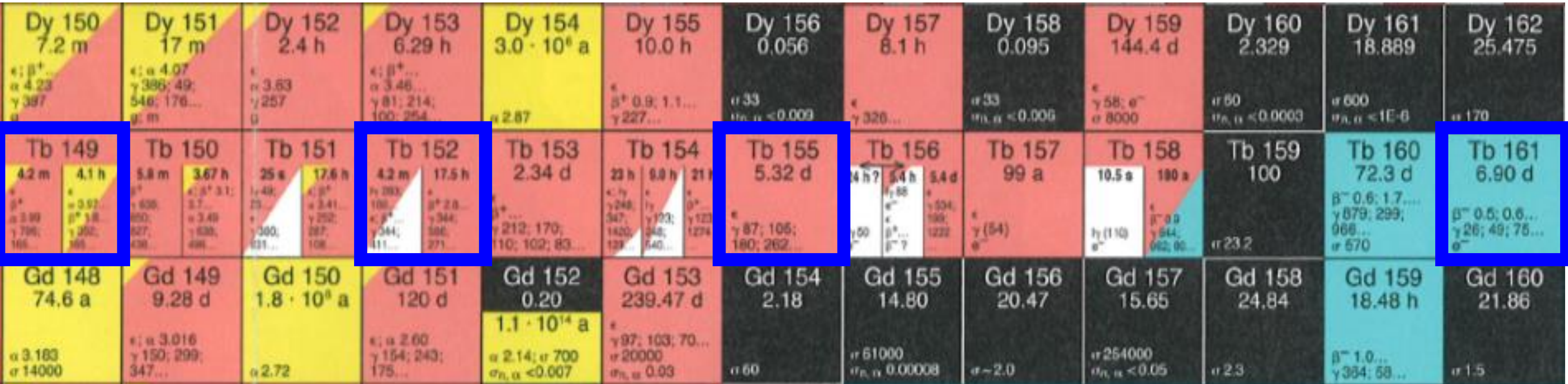


Teranostyka z izotopami niestabilnymi

- Teranostyka = teriapia i diagnostyka
  - Jeden izotop służy do diagnozy (np. PET)
  - Inny izotop tego samego pierwiastka: leczenie
- At ISOLDE and Medicis

After U. Koster, C Müller et al. 2012 J. Nucl. Med. 53, 1951

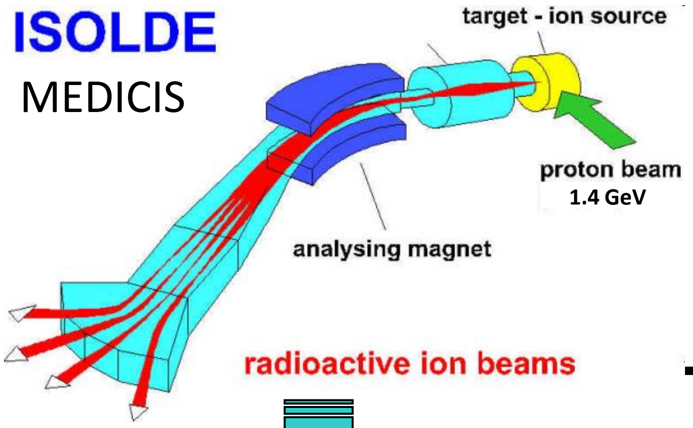




Dy 150 7.2 m ε; β^+... α 4.23 γ 397	Dy 151 17 m ε; α 4.07 γ 386; 49; 546; 176...	Dy 152 2.4 h ε α 3.63 γ 257	Dy 153 6.29 h ε; β^+... α 3.46... γ 81; 214; 100; 254...	Dy 154 $3.0 \cdot 10^6$ a α 2.87	Dy 155 10.0 h ε β^+ 0.9; 1.1... γ 227...	Dy 156 0.056 σ 33 $\sigma_{n,\alpha}$ <0.009	Dy 157 8.1 h ε γ 326...	Dy 158 0.095 σ 33 $\sigma_{n,\alpha}$ <0.006	Dy 159 144.4 d ε γ 58; e^- σ 8000	Dy 160 2.329 σ 60 $\sigma_{n,\alpha}$ <0.0003	Dy 161 18.889 σ 600 $\sigma_{n,\alpha}$ <1E-6	Dy 162 25.475 σ 170
Tb 149 4.2 m | 4.1 h	Tb 150 5.8 m | 3.67 h	Tb 151 25 s | 17.6 h	Tb 152 4.2 m | 17.5 h	Tb 153 2.34 d ε β^+... γ 212; 170; 110; 102; 83...	Tb 154 23 h | 9.0 h | 21 h	Tb 155 5.32 d ε γ 87; 105; 180; 262...	Tb 156 24 h? | 5.4 h | 5.4 d	Tb 157 99 a ε γ (54) e^-	Tb 158 10.5 s | 180 a	Tb 159 100 σ 23.2	Tb 160 72.3 d β^- 0.6; 1.7... γ 879; 299; 966... σ 570	Tb 161 6.90 d β^- 0.5; 0.6... γ 26; 49; 75... e^-
Gd 148 74.6 a α 3.183 σ 14000	Gd 149 9.28 d ε; α 3.016 γ 150; 299; 347...	Gd 150 $1.8 \cdot 10^6$ a α 2.72	Gd 151 120 d ε; α 2.60 γ 154; 243; 175...	Gd 152 0.20 $1.1 \cdot 10^{14}$ a α 2.14; σ 700 $\sigma_{n,\alpha}$ <0.007	Gd 153 239.47 d ε γ 97; 103; 70... σ 20000 $\sigma_{n,\alpha}$ 0.03	Gd 154 2.18 σ 60	Gd 155 14.80 σ 61000 $\sigma_{n,\alpha}$ 0.00008	Gd 156 20.47 σ ~2.0	Gd 157 15.65 σ 254000 $\sigma_{n,\alpha}$ <0.05	Gd 158 24.84 σ 2.3	Gd 159 18.48 h β^- 1.0... γ 364; 58...	Gd 160 21.86 σ 1.5

Nowe izotopy medyczne z CERN

i. Produkcja na ISOLDE

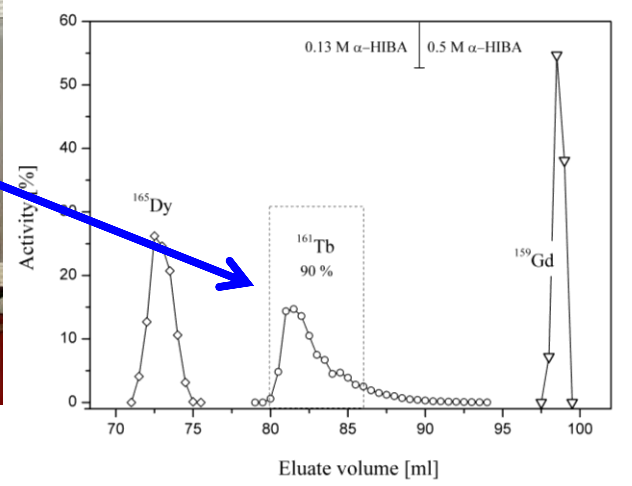


iv. Wstrzyknięcie do myszy

v. Obrazowanie PET/SPECT i leczenie nowotworów

ii. Transport do laboratorium PSI

iii. Oczyszczanie i znakowanie radiochemiczne

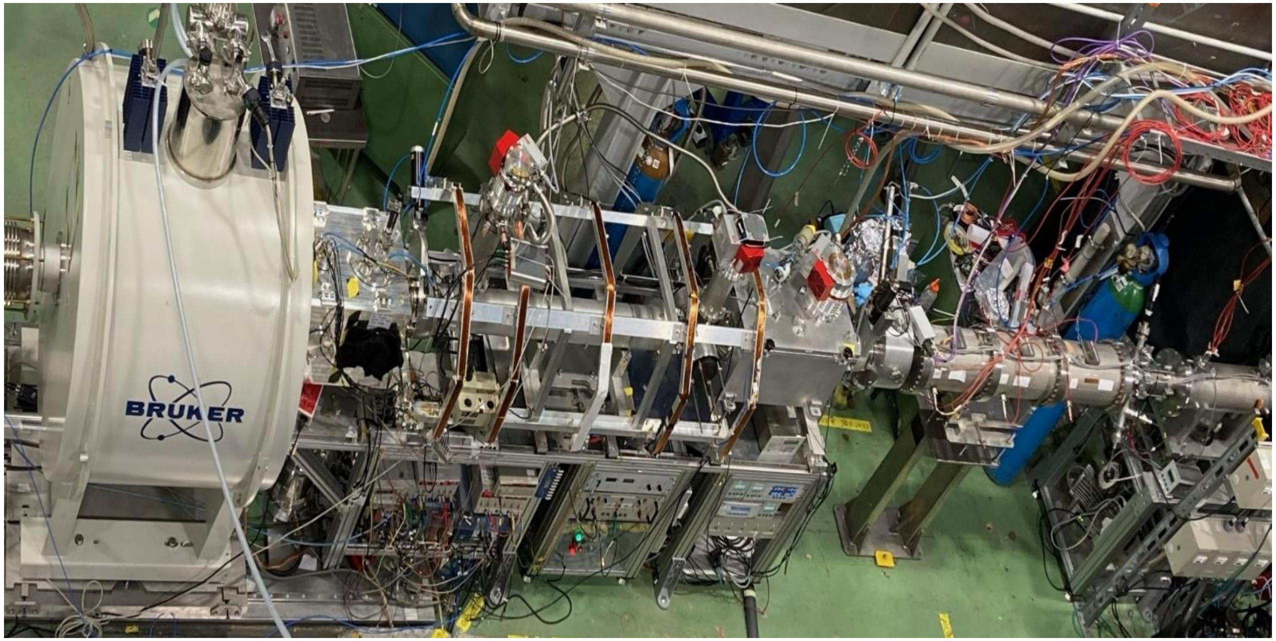


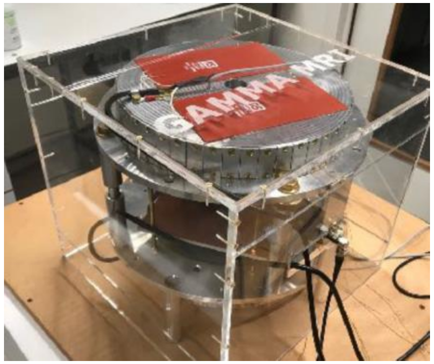
od U. Koster

C Müller et al. 2012 J. Nucl. Med. 53 1951

Ultra-czuły rezonans magnetyczny

- Moje własne projekty
- Magnetyczny rezonans jądrowy (NMR) i obrazowanie (MRI) z detekcją promieniowania
  - Zastosowanie niestabilnych jąder
  - Wykrywanie sygnału poprzez kierunek promieniowania, a nie odbiór sygnału w cewce
  - Do 10^{10} razy bardziej czuły niż konwencjonalny NMR
- Interdyscyplinarny zespół
  - Współpraca (np. z UAM Poznań)
  - Zastosowania w różnych dziedzinach

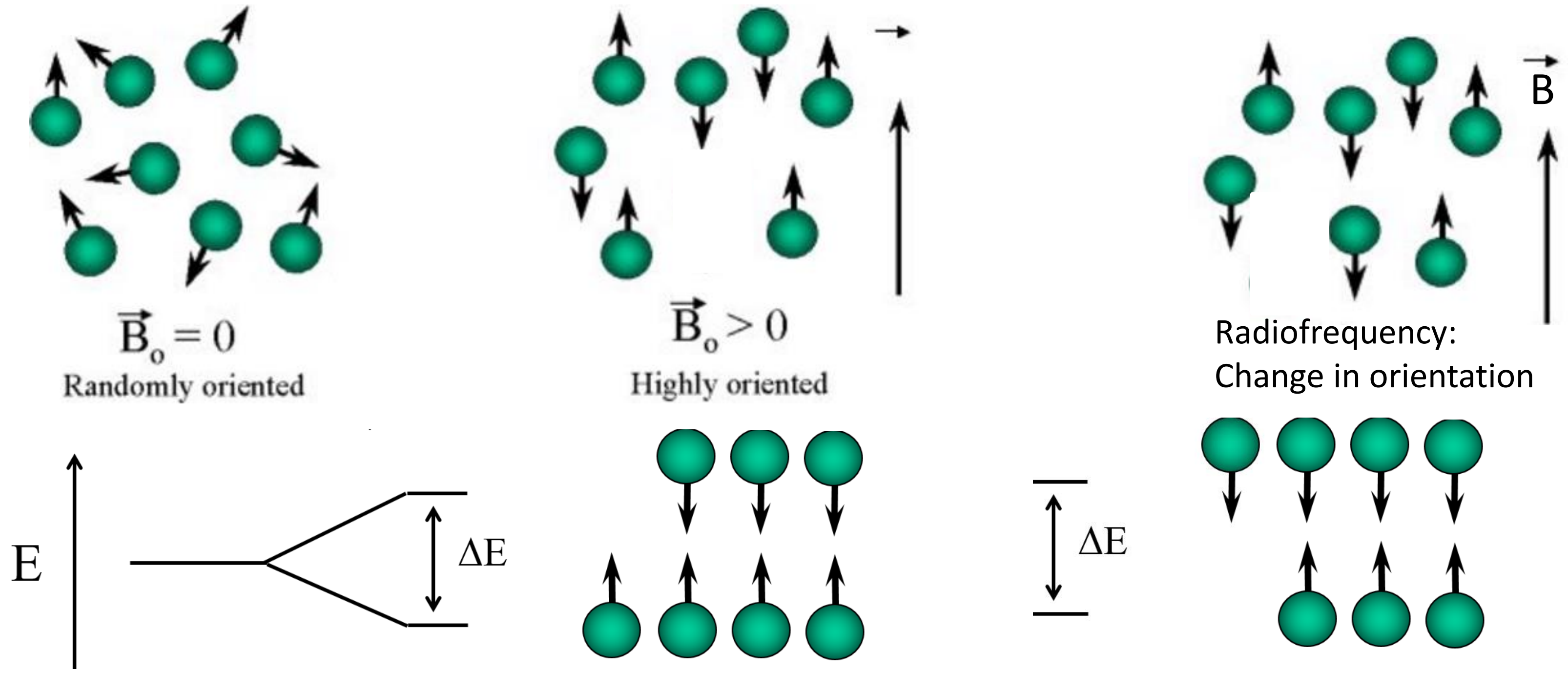




Linia na ISOLDE

Zasady magnetycznego rezonansu jądrowego

- Uczestnicy:
  - Jądra o spinie różnym od 0
  - Próbka/środowisko
- Pole magnetyczne
  - Silne pole statyczne (B0)
  - Słabsze pole prostopadłe (B1) oscylujące na częstotliwości radiowej (MHz)



Radiofrequency:
Change in orientation

Otoczenie wpływa na częstotliwość Larmora w polu magnetycznym (elektrony w cząsteczkach)

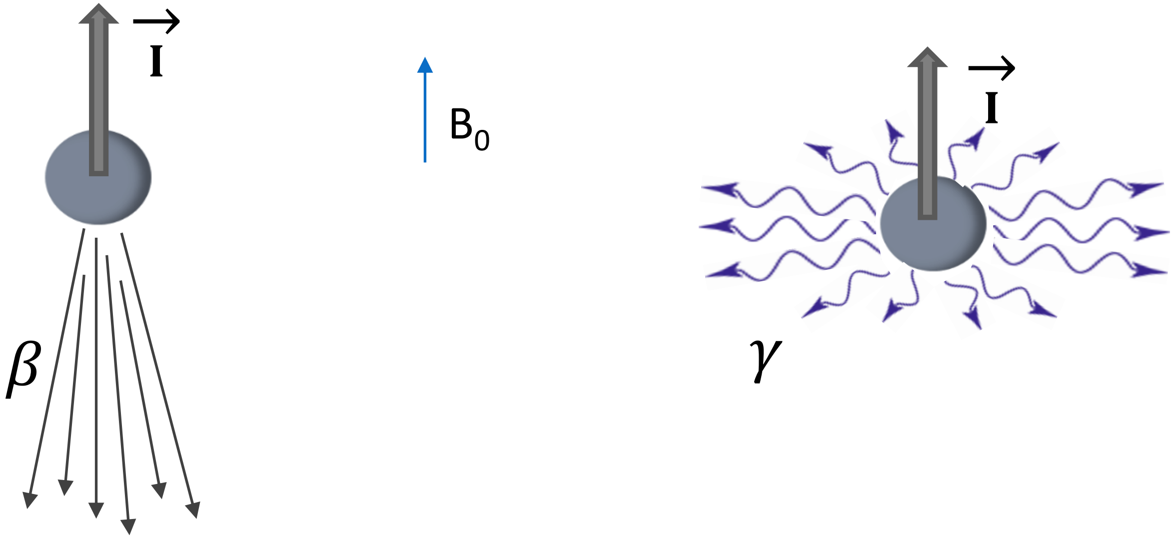
Spolaryzowane jądra niestabilne są specjalne

- **Ich rozpad beta i gamma jest anizotropowy w przestrzeni**

Emisja czastki beta,
dla jąder ze spinem >0

Emisja kwantu gamma,
dla jąder ze spinem >1/2

Niezachowanie parzystości
w odziaływaniach słabych,
eksperyment Pani Wu



zależą od poziomu i ‚stopnia’ polaryzacji spinu oraz
szczegółów przejścia jądrowego (początkowy spin, zmiana spinu)

- Zaobserwowana asymetria rozpadu może być wykorzystana do czułego magnetycznego rezonansu jądrowego

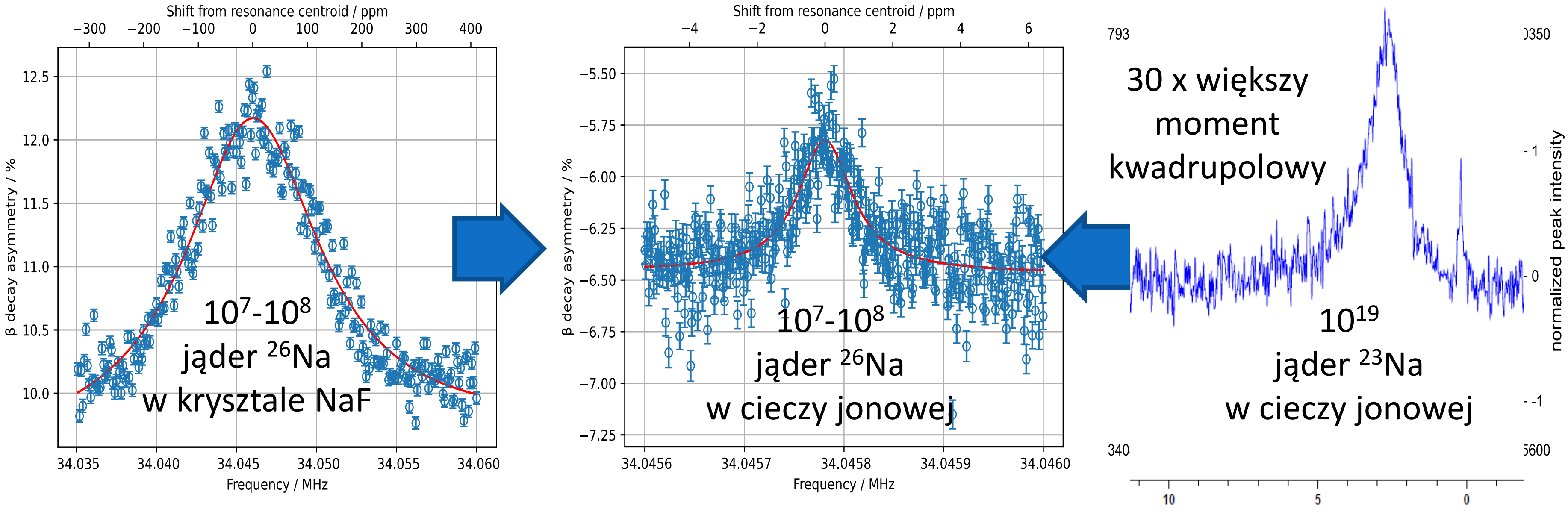
NMR jąder niestabilnych w cieczach

betaDropNMR

- NMR z detekcją cząstek beta (b-NMR) w próbkach ciekłych:
  - NMR: zmiana częstotliwości Larmora jądra przez sąsiednie molekuły na poziomie 10^{-6}
  - β-NMR: do 10^{10} bardziej czuła niż konwencjonaly NMR (sygnał zbierany z zaledwie 10^6 jąder)
  - NMR w cieczach: o wiele węższe rezonanse niż w ciałach stałych: 100-1000 większa precyzja (ok. 1 część na milion)

- Może dotyczyc pierwiastków chemicznych i próbek poza zasięgiem konwencjonalnego NMR
  - Np. interakcja jonów metali z biocząsteczkami

$^{26}_{11}\mathrm{Na}_{15}$ $t_{1/2} = 1.1$ s



10^7-10^8 jąder ^{26}Na w krysztale NaF

10^7-10^8 jąder ^{26}Na w cieczy jonowej

30 x większy moment kwadrupolowy

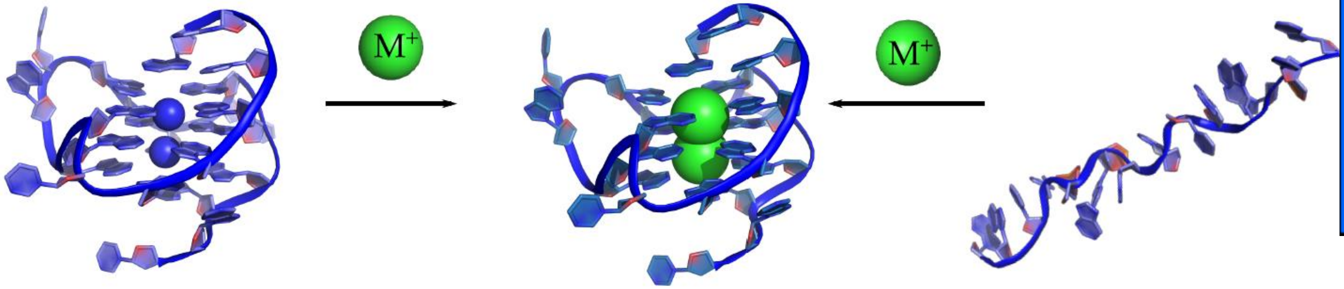
10^{19} jąder ^{23}Na w cieczy jonowej

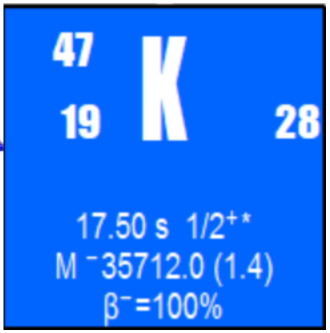
Harding, …, Kowalska, Phys. Rev. X., 10, 041061 (2020)

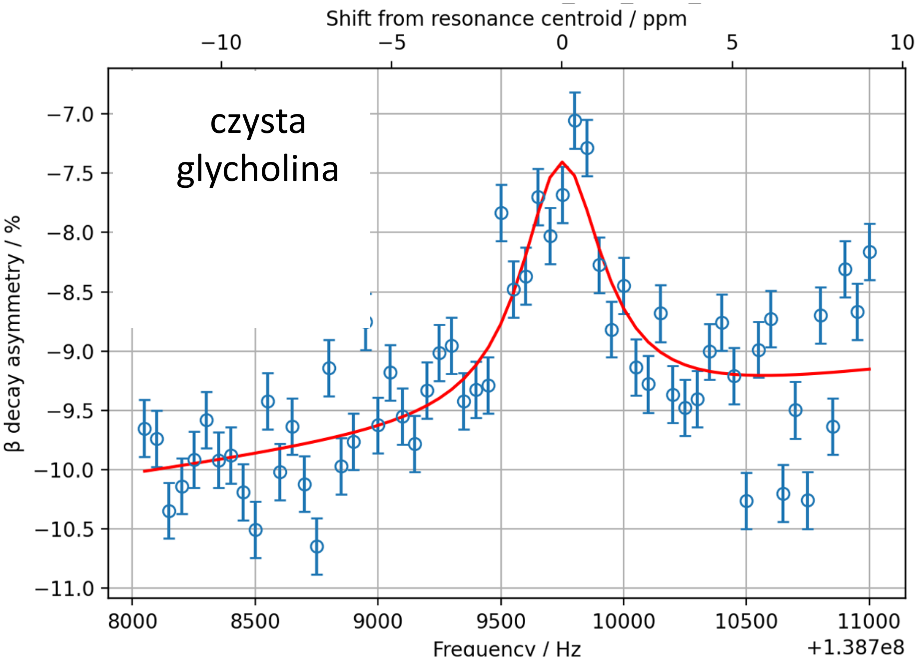
Wiązanie potasu z G-kwadrupleksami DNA

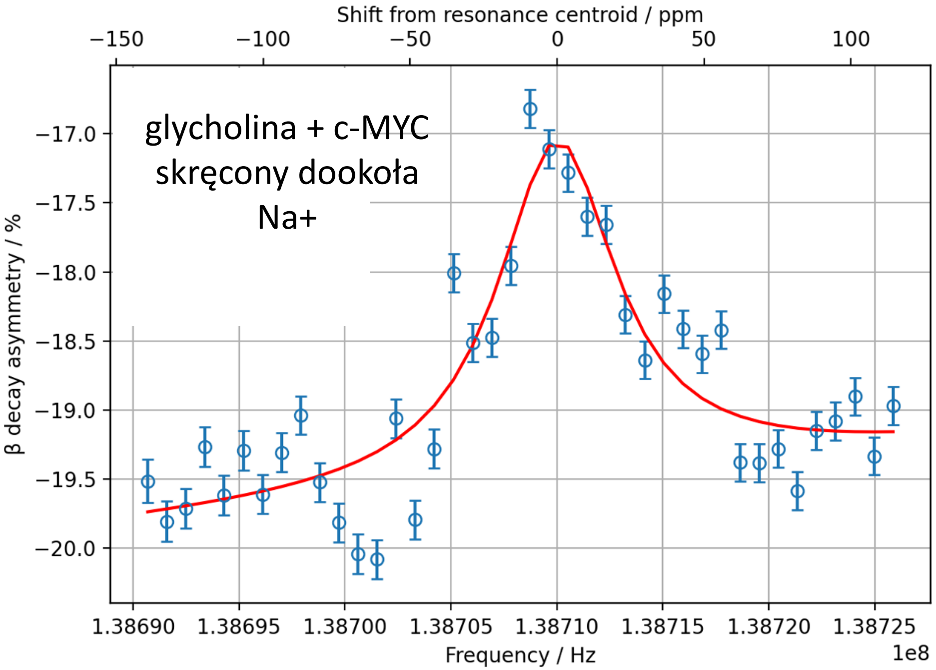
B. Karg

- G-kwadrupleksy:
  - obecne np. w telomerach, kluczowe: wiązanie z metalami alkalicznymi
- eksperymenty β-NMR: ^{47}K w roztworze DNA w glycholinie







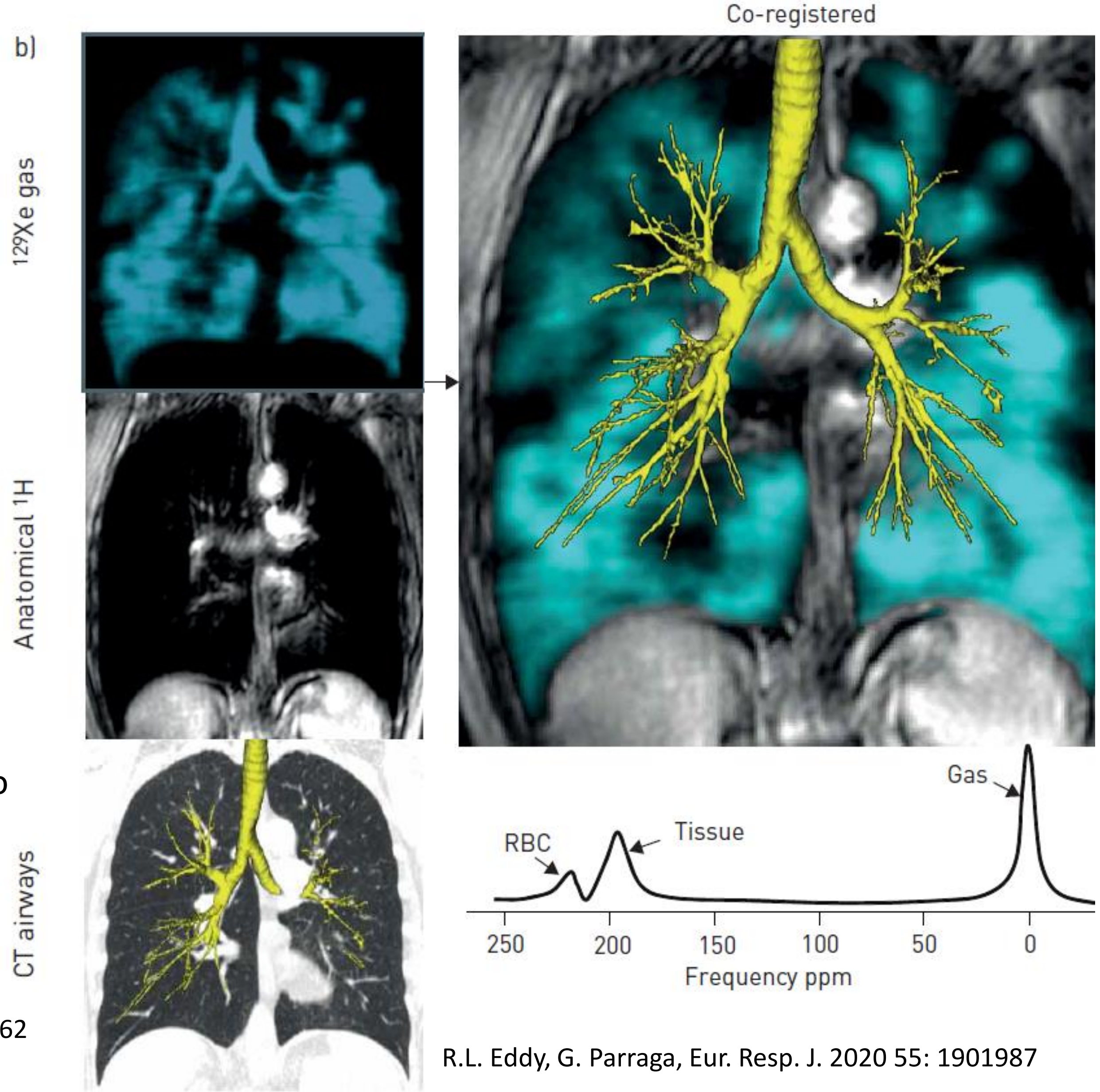


W obecności DNA: rezonans ^{47}K przesunięty i rozszerzony: wszczepiony K zastępuje Na w G-kwadrupleksie?

Rezonans magnetyczny ze stabilnym ^{129}Xe

- Dostarcza informacji o:
  - wentylacji płuc
  - mikrostrukturze tkanek
  - wymianie gazowej
- Cechy:
  - Czuły
  - Szybki (< 10 s)
  - Precyzyjny (3 mm)
  - Brak tła protonowego
  - Informacje chemiczne
- Zastosowania:
  - Choroby układu oddechowego
  - Nowe: obrazy czynnościowe silnie ukrwionych narządów: nerek, mózgu

J. Chacon-Caldera, Magn Reson Med. 2020;83(1):262
Y. Shepelytskyi, Magn Reson Med. 2022;88:83



R.L. Eddy, G. Parraga, Eur. Resp. J. 2020 55: 1901987

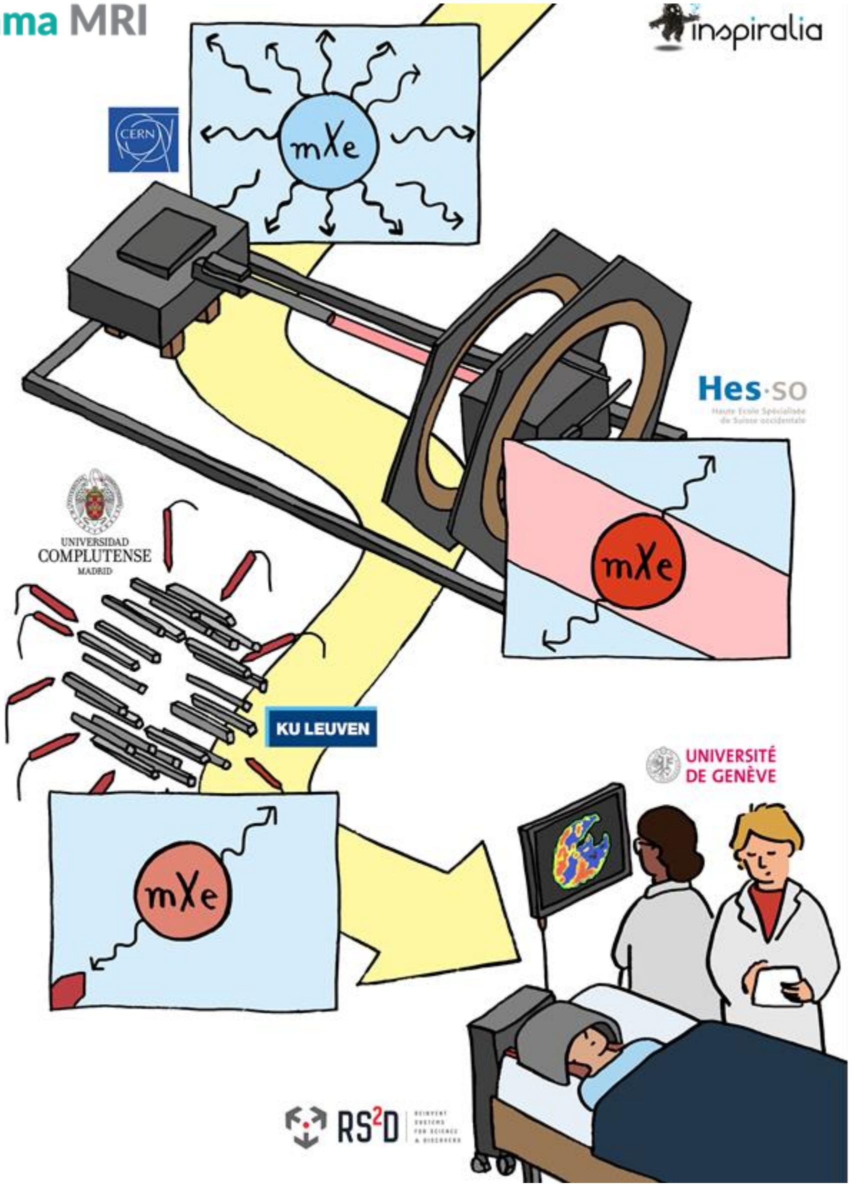
γ-MRI z długo-żyjącymi izomerami Xe

EU FET-OPEN

Gamma MRI

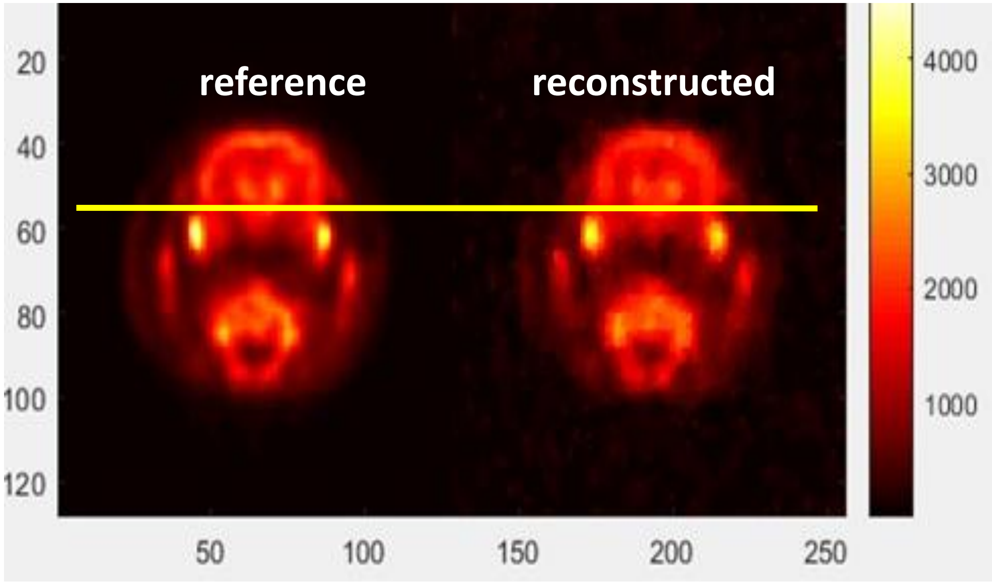
- Jednoczesne wykorzystanie czułości detekcji gamma (γ) + rozdzielczości przestrzennej i elastyczności MRI
  - Zastosowanie spolaryzowanych niestabilnych znaczników
  - Zwiększenie czułości MRI i rozdzielczości medycyny nuklearnej
  - Pozycjonowanie podane przez sekwencje MRI
  - Ilość znacznika podana przez stopień asymetrii emisji γ

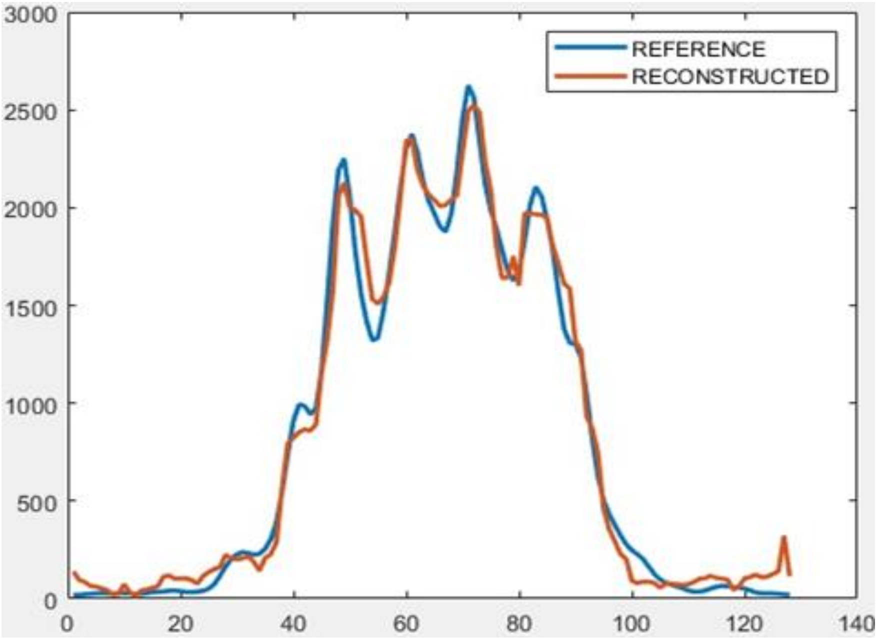
Prace nad prototypem trwają



Porównanie PET/SPECT/MRI/ γ-MRI

Technika	Aktywnośc	Czułośc	Rozdzielczośc
MRI	0	mM to µM	< 1 mm
HP ^{129}Xe MRI	0	100s of nM	< 1 mm
PET	~400 MBq	pM	1-3 mm
SPECT	500~1000 MBq	pM	1 mm
γMRI	1-10 MBq (1 mm rozdzielczość)	pM	< 1 mm (dla 10'tek MBq)





Oczekiwany sygnał w prototypie:
- mózg szczura z infuzją 10 MBq mXe, czas nagrywania 12 s
zrekonstruowany za pomocą skompresowanych strategii wykrywania w pikselach 0.5 mm

Podsumowanie

- Badania podstawowe CERN prowadzą do aplikacji medycznych z wykorzystaniem:
  - Akceleratorów
  - Detektorów
  - Jąder niestabilnych

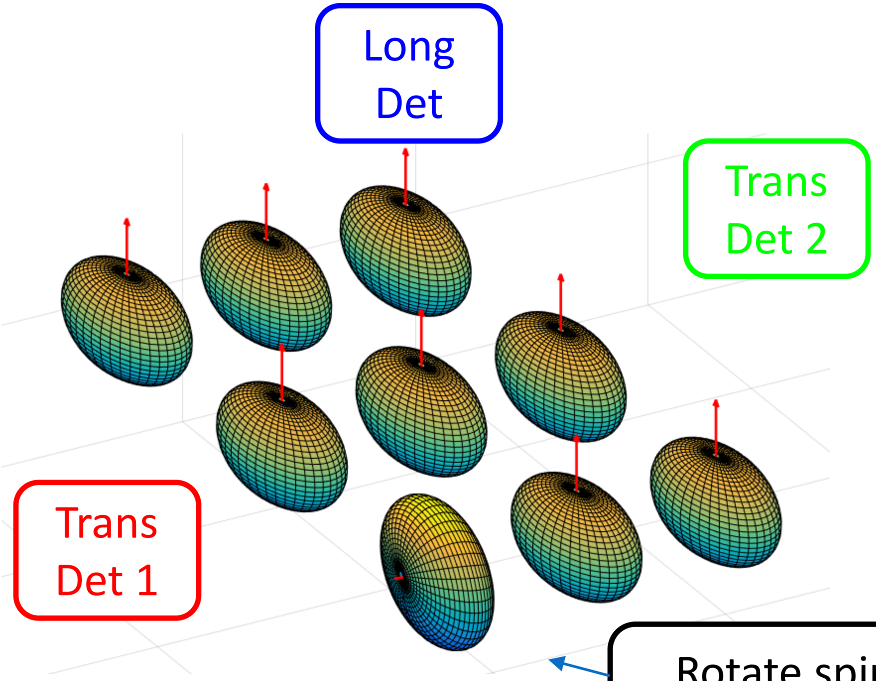
- Zainteresowanie: diagnostyka medyczna i leczenie

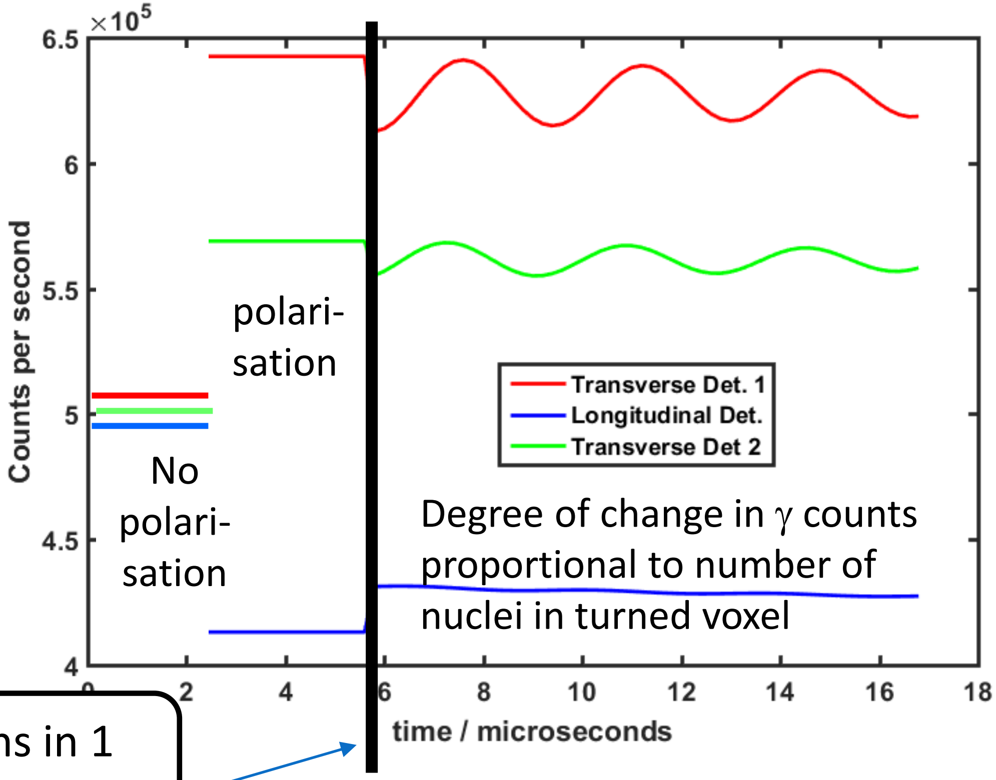
- Cel – urządzenia medyczne, które są:
  - MNIEJSZE
  - TAŃSZE
  - DOKŁADNIEJSZE
  - BARDZIEJ CZUŁE

- Wiele przykładów na różnych etapach dojrzałości

Gamma MRI – spatial resolution

- Pixel size
  - defined by slope of B-field gradients and spectral width of rf pulse
  - more nuclei -> smaller pixels possible up to B gradient and rf limit
- 1 pixel in resonance: change in gamma counts visible in each detector





Degree of change in γ counts proportional to number of nuclei in turned voxel

Rotate spins in 1 pixel by 90°

Simulations: R. Engel

Basic principle

Strength of unstable nuclei for life sciences:

- Efficient detection of decay radiation: PET, SPECT diagnostics with γ radiation
- Strong but localised damage: cancer therapy with α, β radiation
- Possibility to combine therapy and diagnostics: terranostics
  - PET/SPECT diagnosis + α, β treatment, e.g. 155Tb-SPECT, 152Tb-PET, 149Tb-α therapy
  - hadron therapy (and in-situ PET beam-deposition diagnosis) with 11C

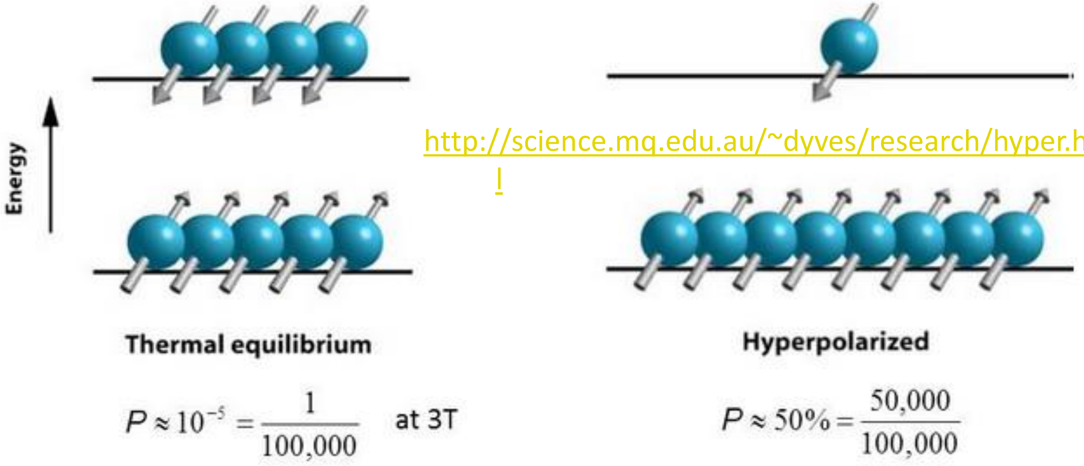
New here: anisotropic emission of radiation from spin-polarised nuclei

- Much higher sensitivity for spin-manipulating techniques:

=> Nuclear Magnetic Resonance (NMR) and Magnetic Resonance Imaging (MRI)

Radiation-detected NMR

Spin hyperpolarisation



$P \approx 10^{-5} = \frac{1}{100,000}$ at 3T

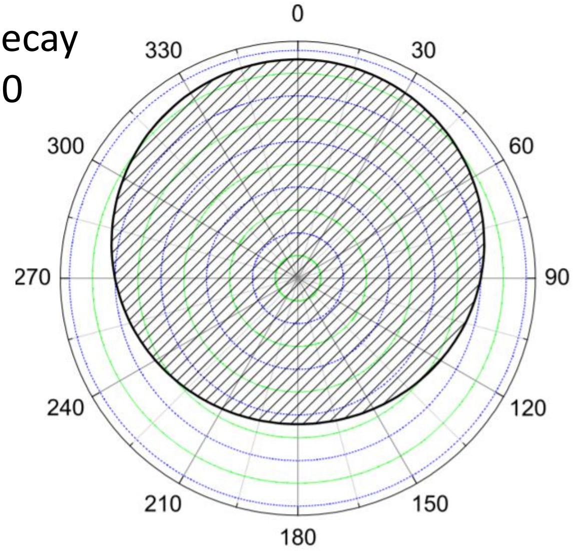
$P \approx 50\% = \frac{50,000}{100,000}$

http://science.mq.edu.au/~dyves/research/hyper.html

+ Decay anisotropy

β detector

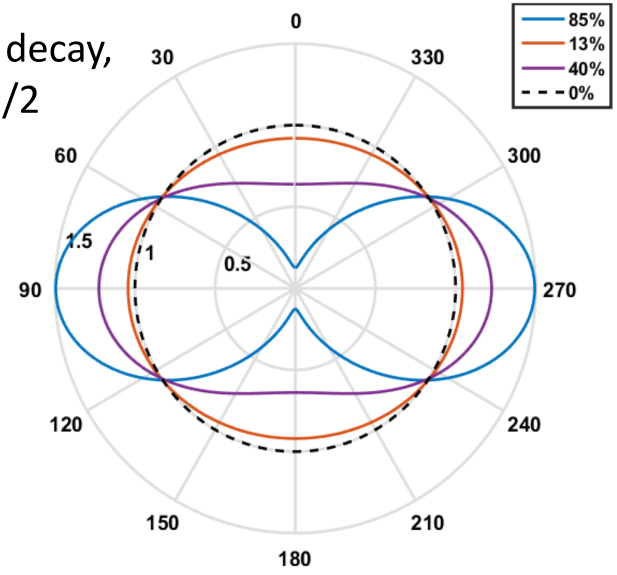
Beta decay
spin >0



β detector

B_0

Gamma decay,
spin >1/2

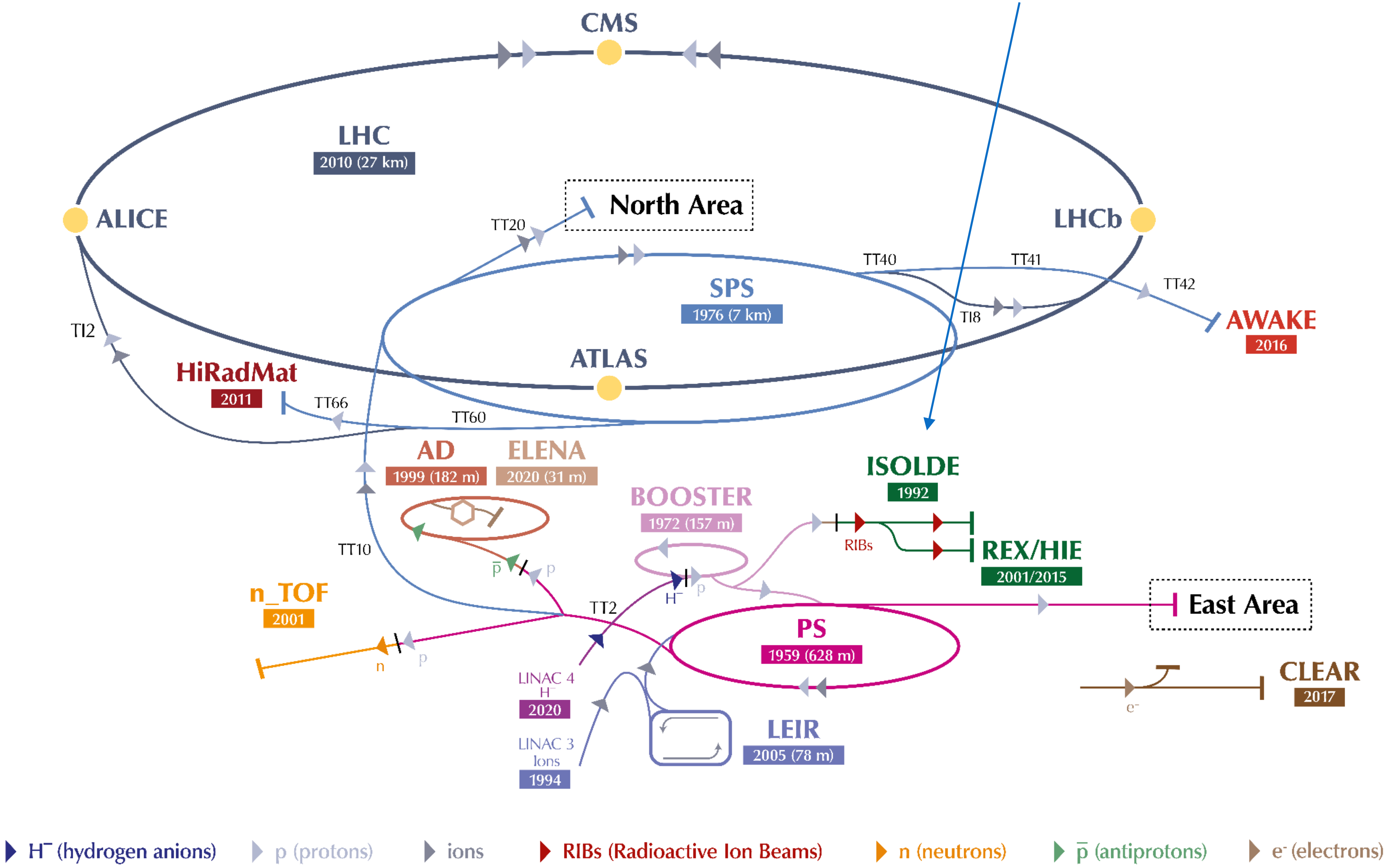


γ detector

γ detector

Experiments: ISOLDE lab at CERN

CERN facility for production and research with radioactive nuclei

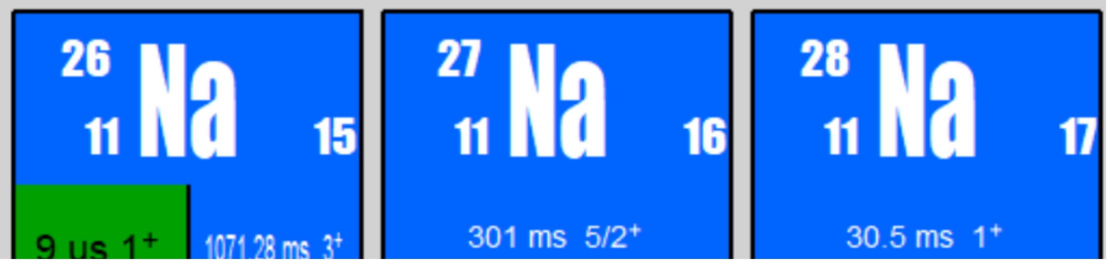


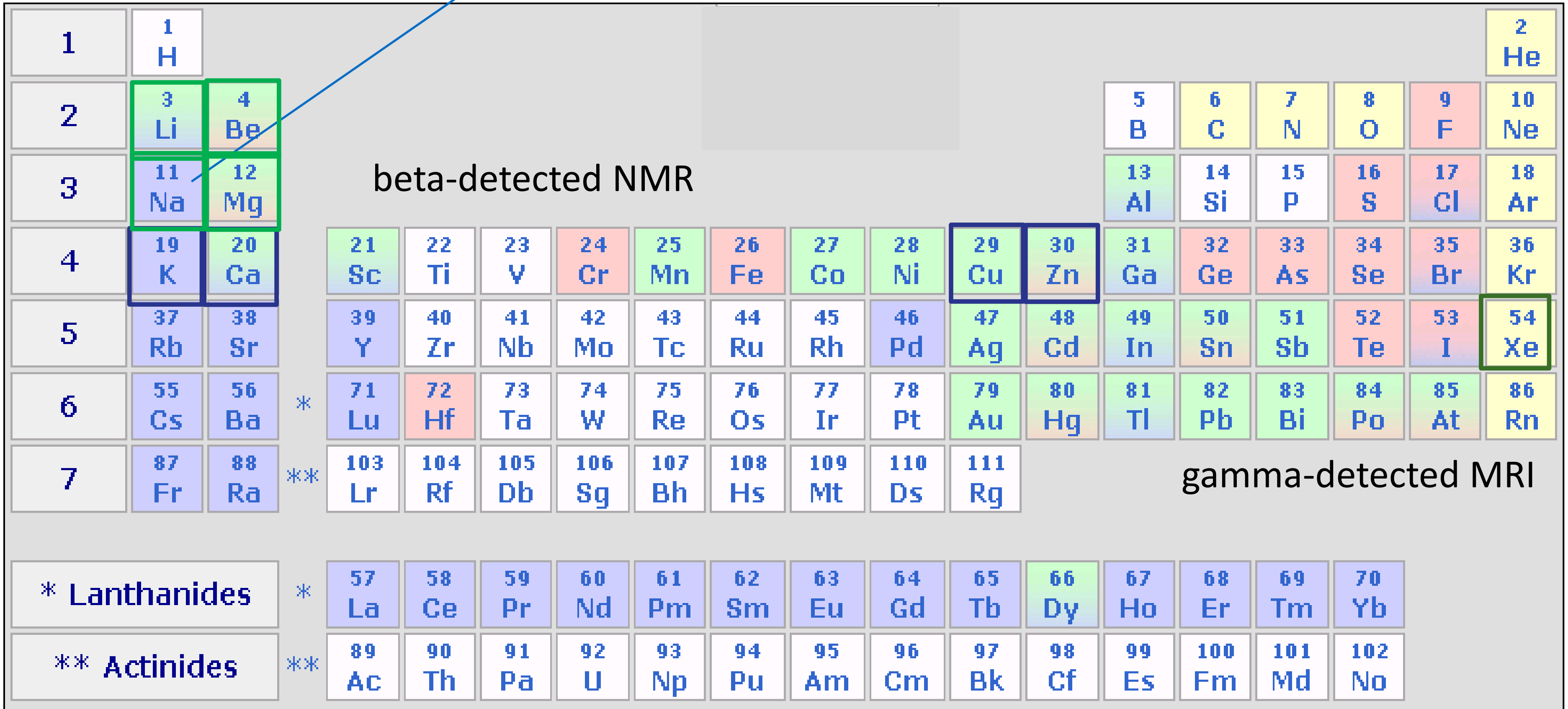
ISOLDE selection of radio-nuclei

- Over 1000 isotopes from 70 chemical elements used for experiments
  - Radioactive half-lives: >10 ms
- Interesting for life sciences

with radiation-detected NMR/MRI:

  - Already polarized
  - Planned



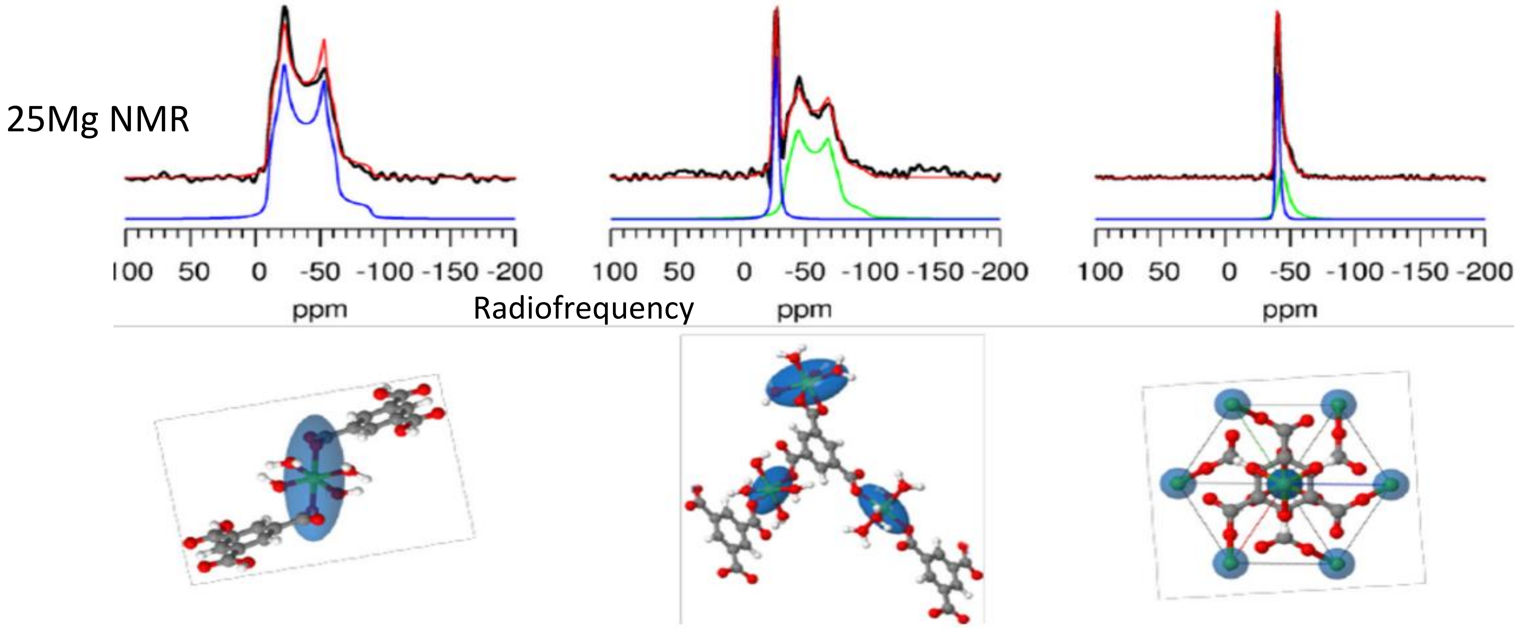


1	1 H																		2 He
2	3 Li	4 Be													5 B	6 C	7 N	8 O	9 F	10 Ne
3	11 Na	12 Mg													13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4	19 K	20 Ca		21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
5	37 Rb	38 Sr		39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
6	55 Cs	56 Ba	*	71 Lu	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
7	87 Fr	88 Ra	**	103 Lr	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg							
* Lanthanides			*	57 La	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb		
** Actinides			**	89 Ac	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No		

β-detected NMR and metals in biology

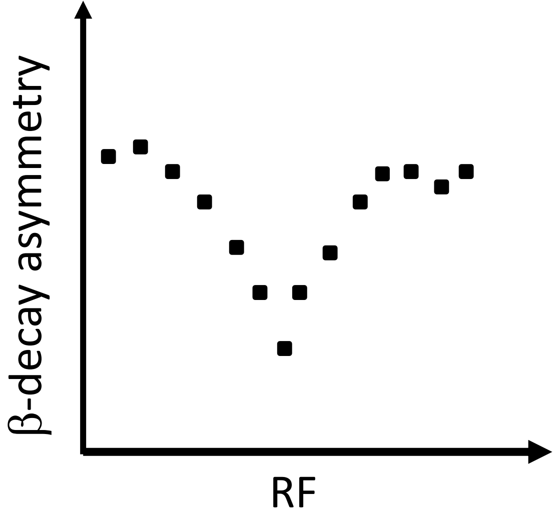
- Increase in sensitivity up to 10^9 times compared to conventional NMR
- Short-lived beta-particle-emitting probe nuclei
- Hyperpolarisation using e.g. lasers -> ideal for metals

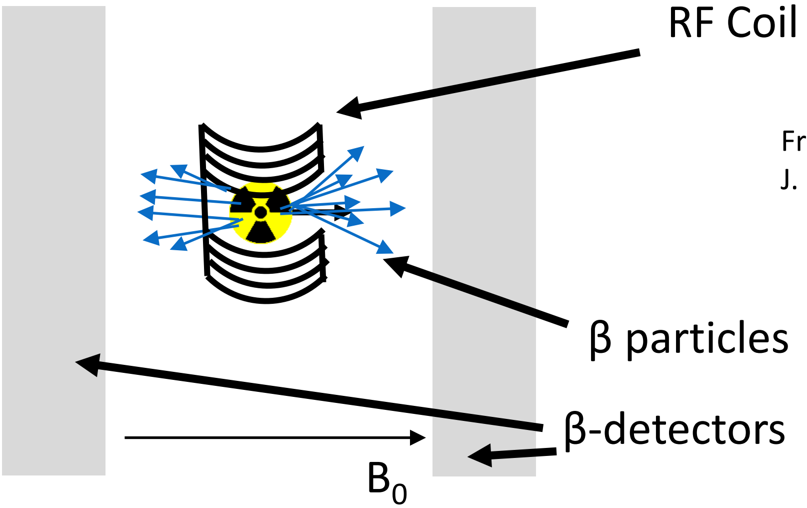
- NMR can provide info on location & evolution of metal-ion binding to biomolecules
  - NMR on 23Na, 25Mg, 63Cu, 67Zn bound to the biomolecule



- Challenges: almost invisible signals due to small abundance, spin >1/2, and small sensitivity
- Result: metal-ion-NMR used very rarely => sensitive NMR approach is needed

β-NMR spectra





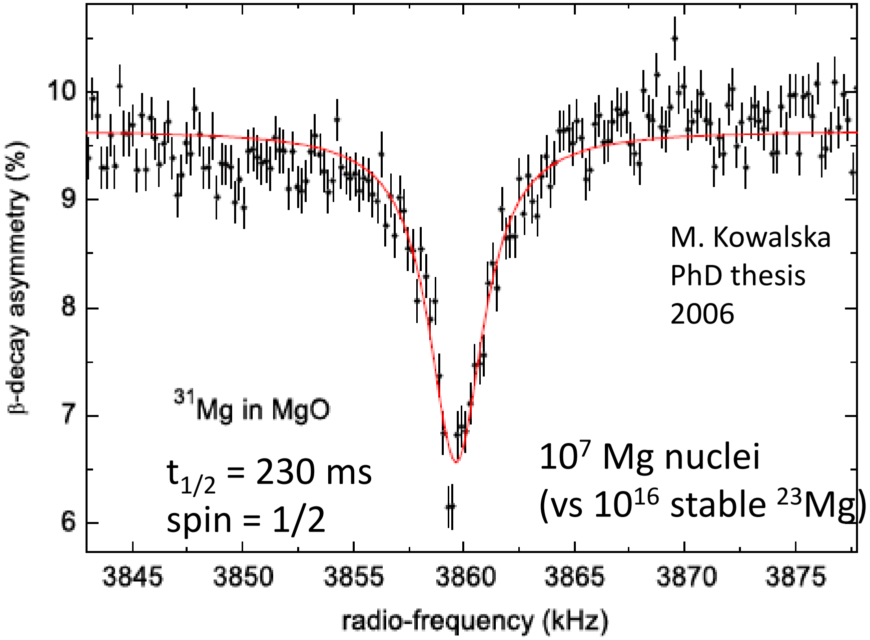
RF Coil

β particles

β-detectors

B_0

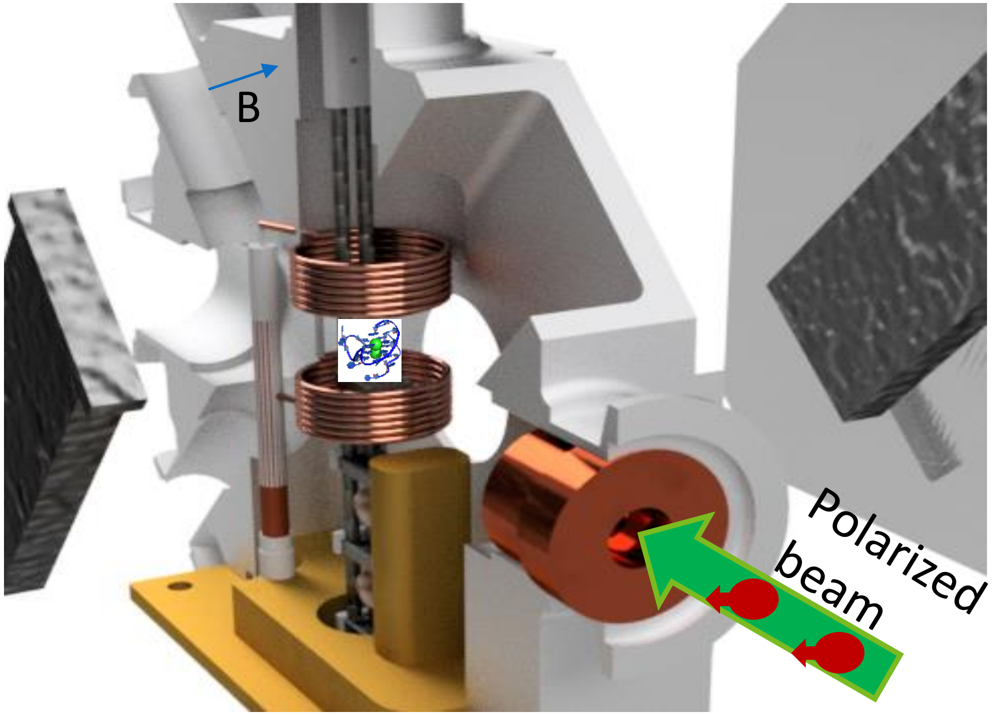
From
J. Croese



M. Kowalska
PhD thesis
2006

$t_{1/2}$ = 230 ms
spin = 1/2

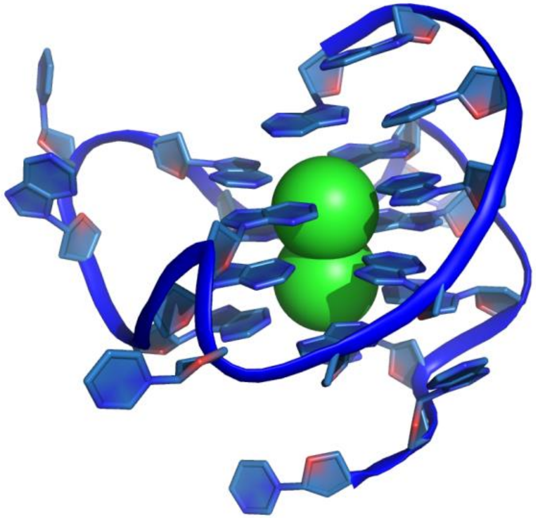
10^7 Mg nuclei
(vs 10^{16} stable ^{23}Mg)

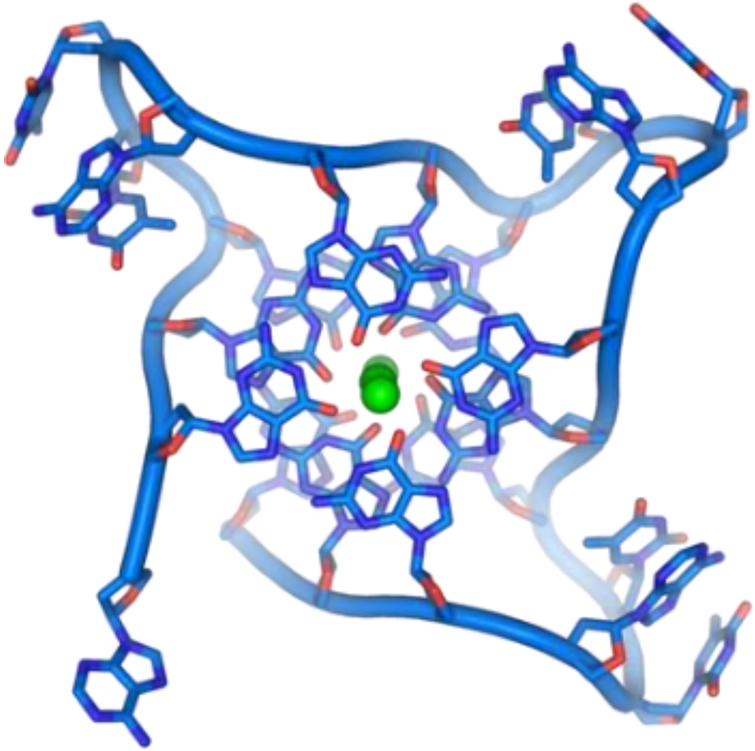


β-NMR 1st biological case

DNA G-quadruplexes and alkali metals

- DNA G-quadruplexes:
  - Guanine-rich DNA fragments
  - Found in nature, e.g. in telomeres





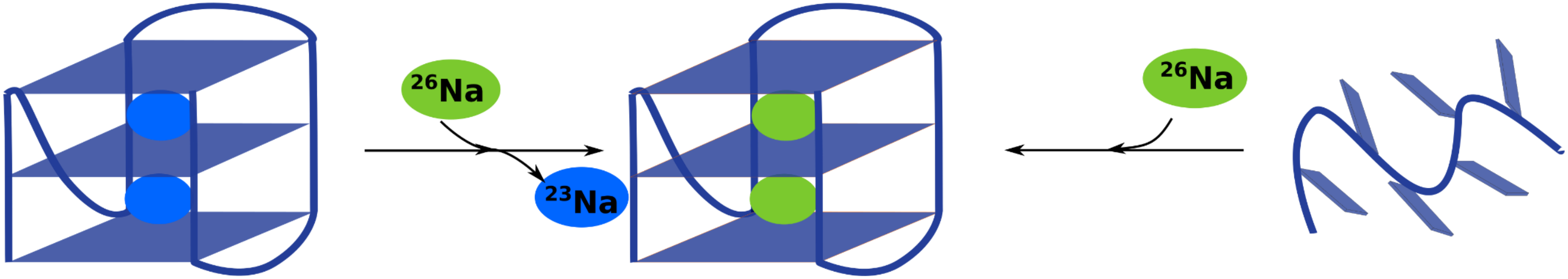
- Alkali metals (Na, K) in G-quadruplexes:
  - Important for their formation, stability and structural polymorphism
  - Until recently considered invisible in conventional Na+/K+ NMR

B. Karg, M. Kowalska et al, Proposal to the ISOLDE Scientific Committee, Jan 20

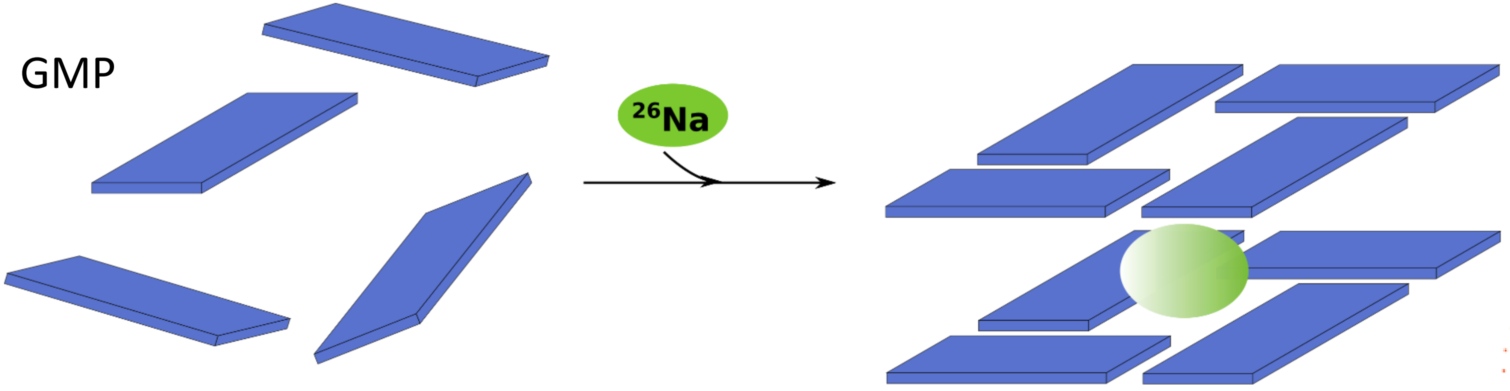
M. Trajkovski et al, J. Am. Chem. Soc. 134, 4132 (2012)

β-NMR and G-Quadruplexes

- Advantages:
  - Sensitivity: metal ions are easily visible, cleaner spectra
  - Smaller quadrupole moments -> longer relaxation and narrower spectra
  - Real-time: folding intermediates
- G-rich DNA



- GMP



- Experiments planned for summer 2021, after 2.5-year break in radioactive beams

γ-detected MRI and Xe imaging

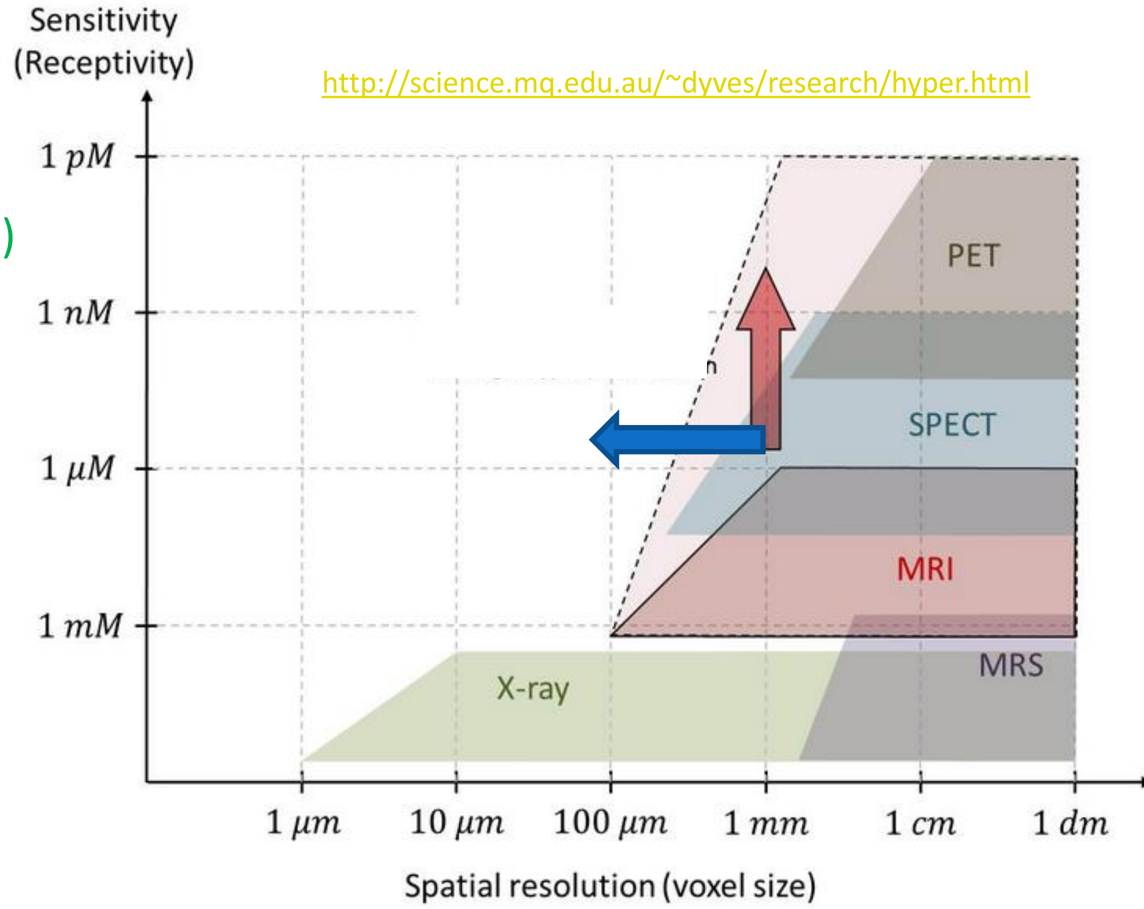
Aim: combine advantages of nuclear medicine and MRI in one modality

- Record MRI signals from PET/SPECT-type nuclei
- Hyperpolarize spins and observe asymmetry of gamma decay
- Result - high efficiency (γ detection) and high resolution (MRI)

- Gamma-MRI Equipment:
  - I>1/2 gamma-emitting nuclei
  - Spin-polarizer
  - MRI magnet
  - **Gamma detectors inside B field**

- **Shown to work in 2D by:**

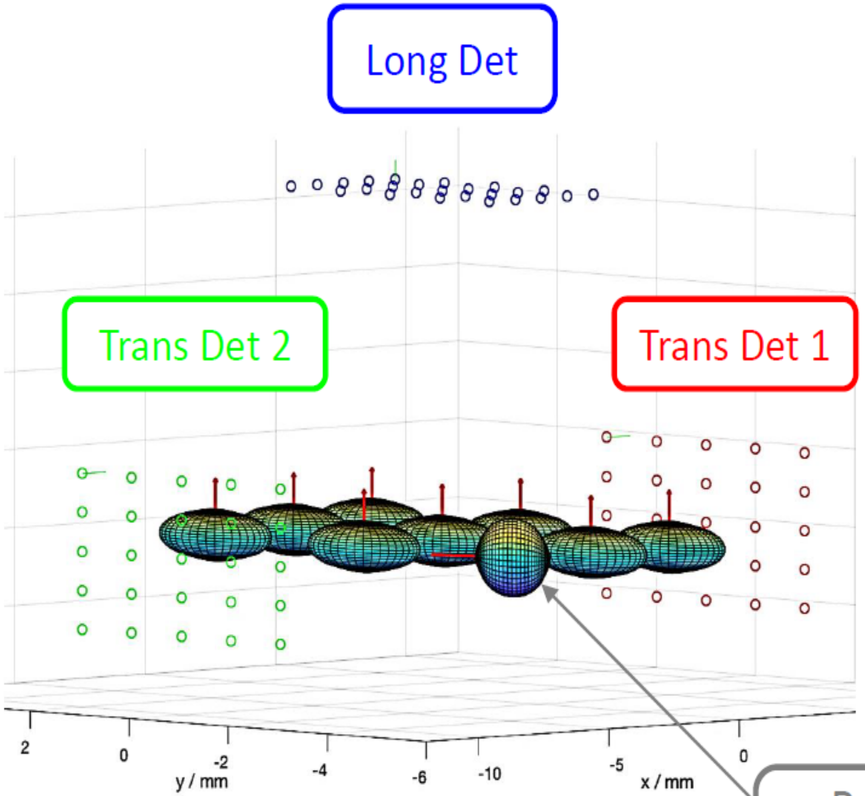
Y. Zheng, G.W. Miller, W.A. Tobias, G.D. Cates, Nature 537, 652 (2016)

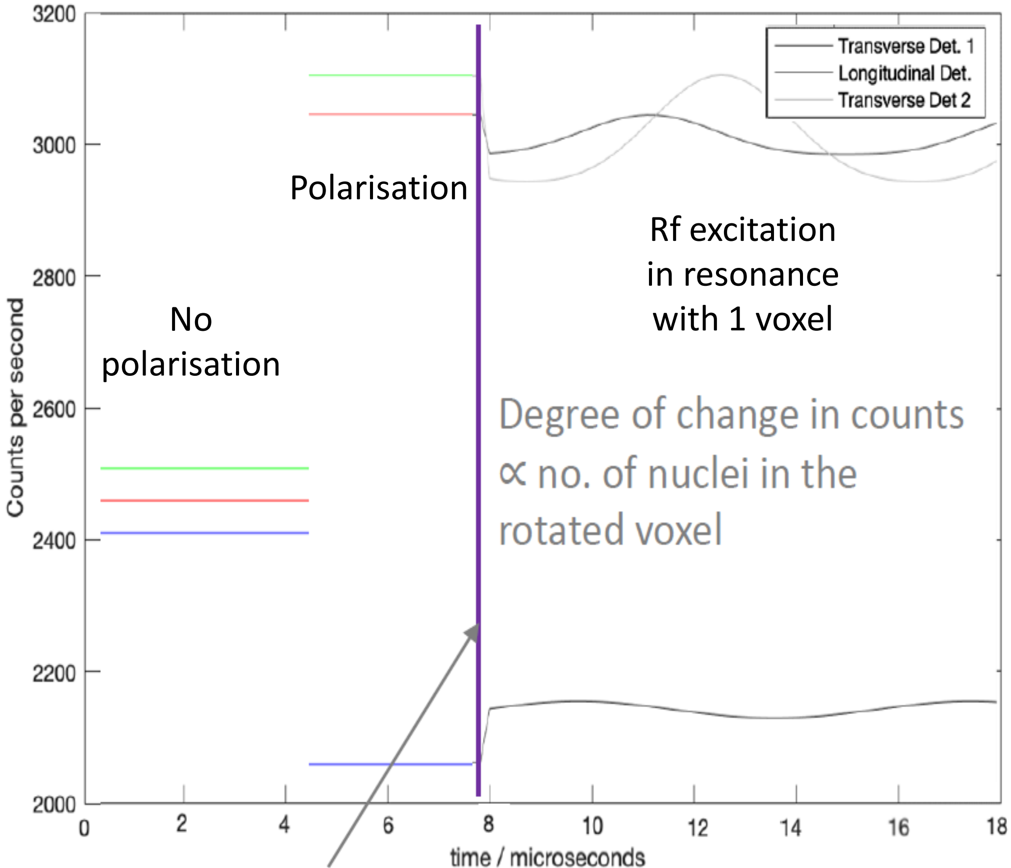


http://science.mq.edu.au/~dyves/research/hyper.html

γ-detected MRI – spatial resolution

- Pixel size
  - defined by slope of B-field gradients and spectral width of rf pulse
  - more nuclei -> smaller pixels possible up to B gradient and rf limit





Degree of change in counts ∝ no. of nuclei in the rotated voxel

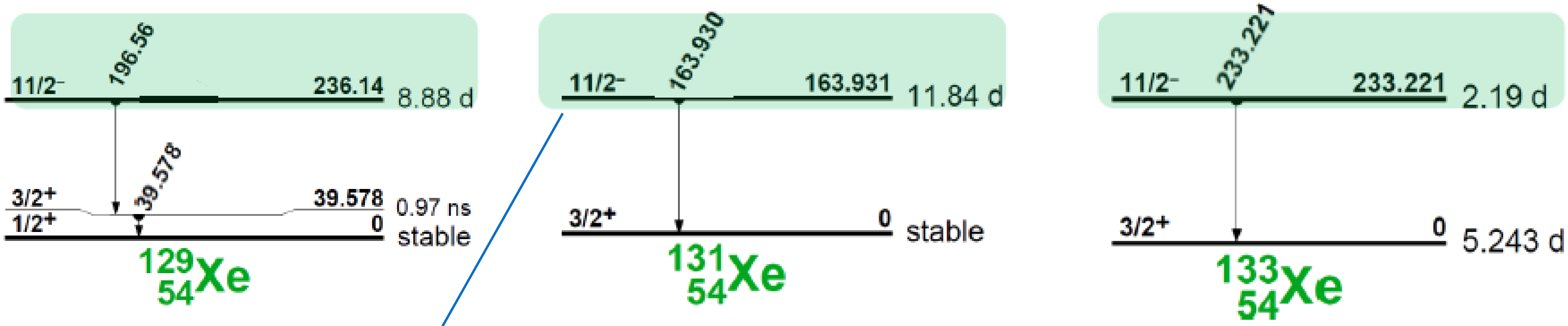
Rotate 1 voxel by 90° by application of RF pulse

Simulation software for anisotropic gamma decay by R. Engel and E.L. Wistrom

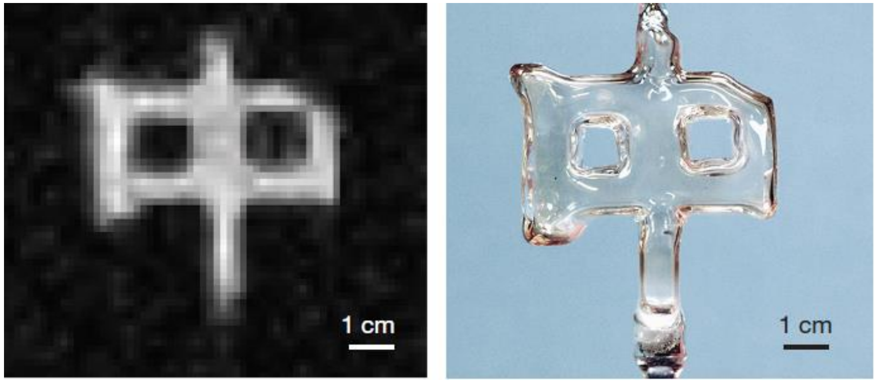
γ-MRI and lung & brain imaging

Imaging using long-lived ^{129m,131m,133m}Xe long-lived nuclear states (isomers):

- Xe: biologically neutral, yet binding to biomolecules and passing blood-brain barrier
- Stable ^{129}Xe used for MRI lung (and brain) imaging
- Unstable ^{133}Xe used for SPECT brain imaging



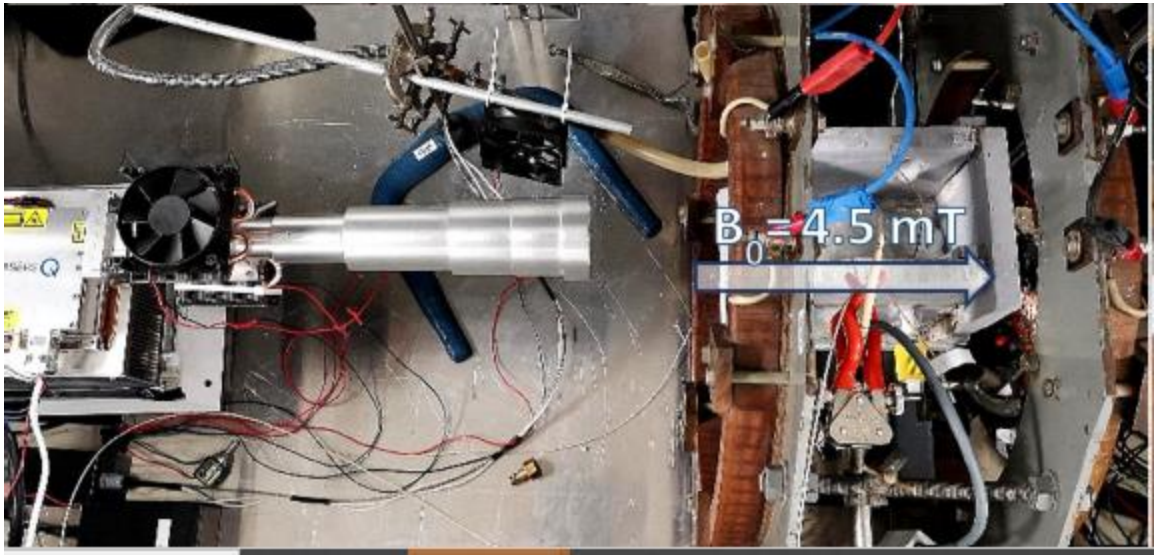
Gain: higher MRI sensitivity or higher nuclear-medicine resolution



Y. Zheng, G.W. Miller, W.A. Tobias, G.D. Cates, Nature 537, 652 (2016)

γ-MRI project status

- Unstable Xe production routes established: ISOLDE, ILL reactor (100-300 MBq)
- 1st tests of Xe polarisation in a compact setup



- 2018-21: CERN seed funding, small team funds from CERN, UNIGE, and HESSO (Geneva), and U Complutense (Madrid)
- April 2021: start of EU Future and Emerging Technologies project (FET-Open)
  - 3.4 MEUR to work on the g-MRI preclinical prototype
  - HESSO (Geneva), U Complutense, UNIGE, CERN, KU Leuven, RS2D, Inspiralia

Summary and outlook

- Unstable nuclei can offer more than diagnosis sensitivity and targeted treatment => decay anisotropy, when their spins are (hyper-)polarised

- Application: strongly increased NMR sensitivity
  - β–detected metal NMR to study metal-ion interaction with biomolecules
  - γ-detected Xe MRI for lung and brain imaging

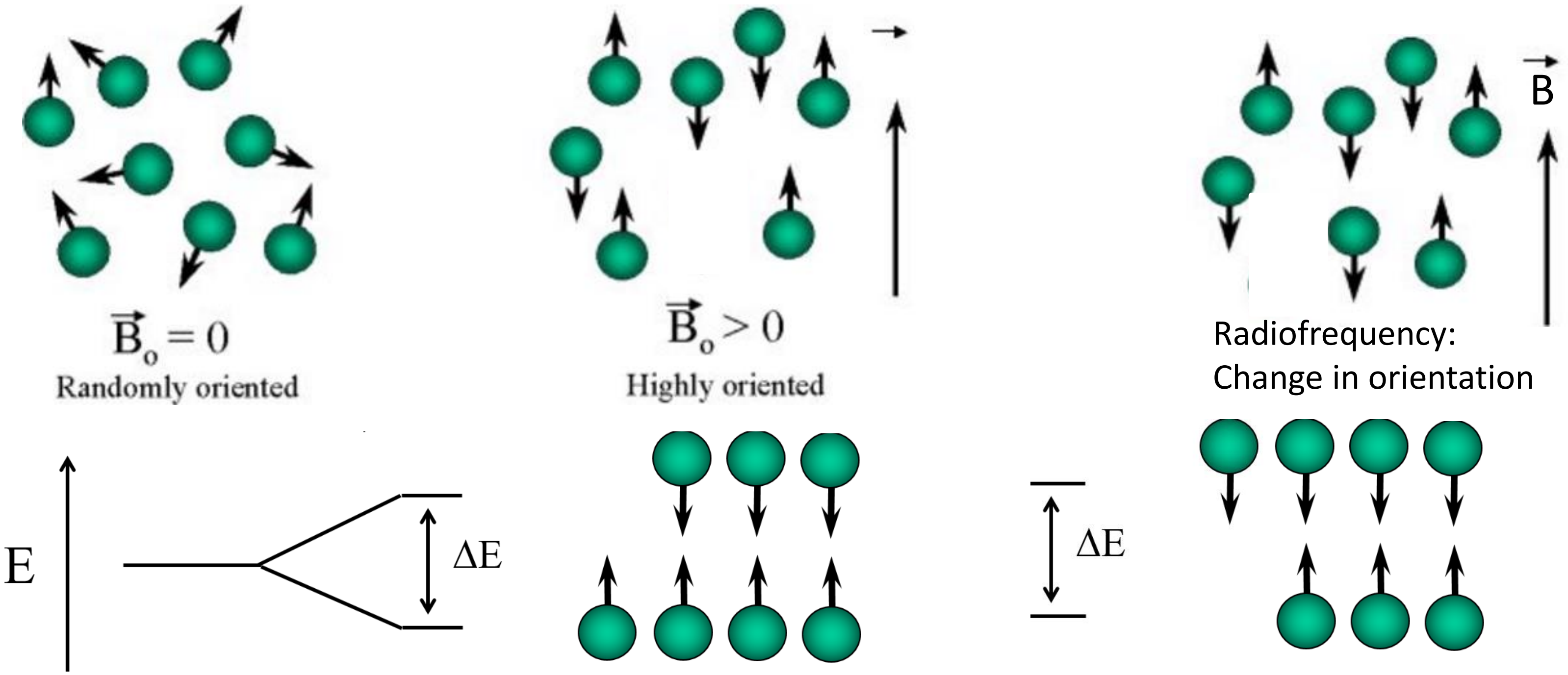
- Projects in their first stages:
  - Feasibility shown
  - Funding acquired

Stay tuned

Thanks to my collaborators and thank you for your attention

Principles of Nuclear Magnetic Resonance

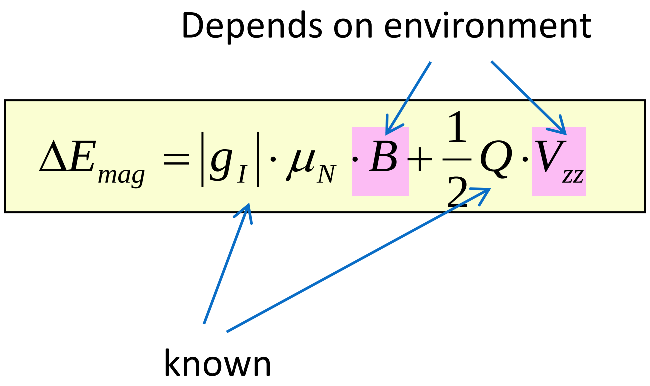
- Participants:
  - Probe nuclei with spin different from 0
  - Sample/ environment
- Magnetic field
  - Strong static field (B0)
  - Weaker perpendicular field (B1) oscillating at radio-frequency (MHz)



NMR in chemistry and biology

Most versatile method to study structure and dynamics of molecules in solution

- **Observables**: chemical shift (Larmor frequency) and relaxation times in different hosts
- **Determined properties**
  - local electronic environment (i.e. **number and type of coordinating groups**)

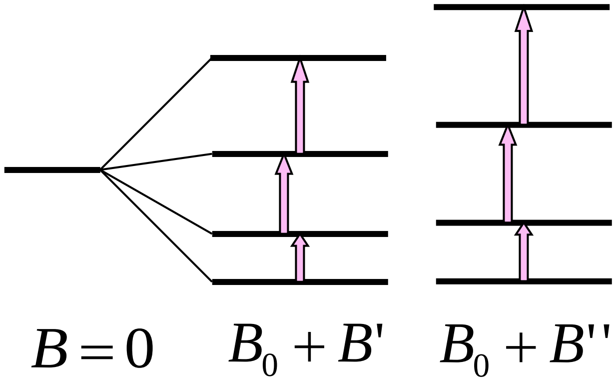


Depends on environment

$$\Delta E_{mag} = \left|g_I\right| \cdot \mu_N \cdot B + \frac{1}{2} Q \cdot V_{zz}$$

known

Same B, different shielding by host

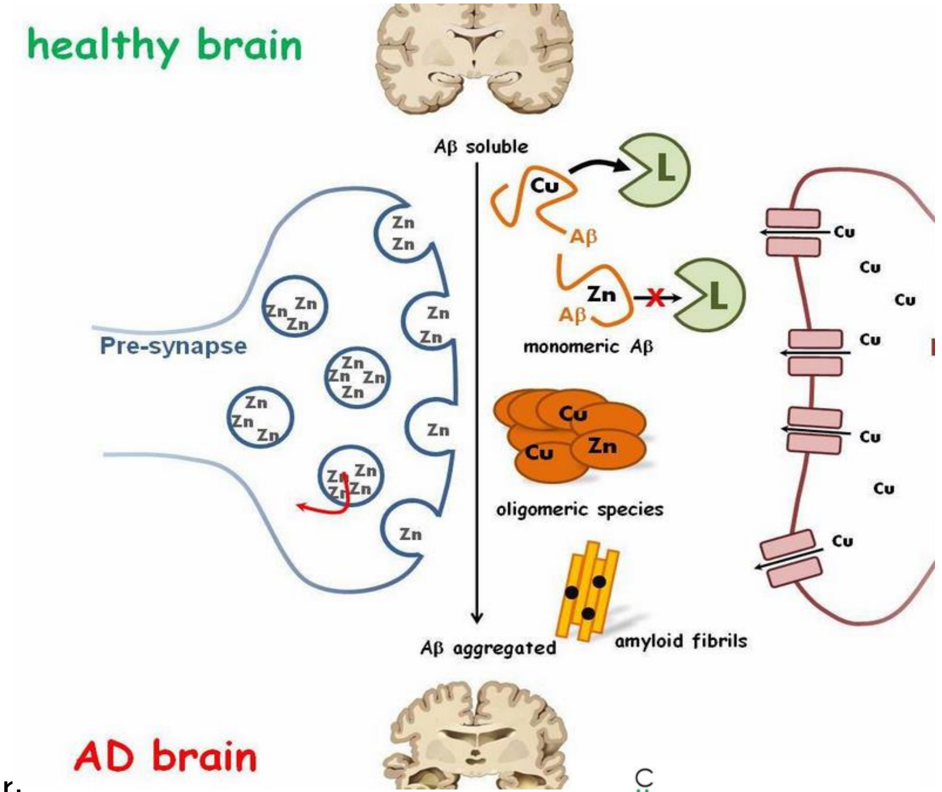


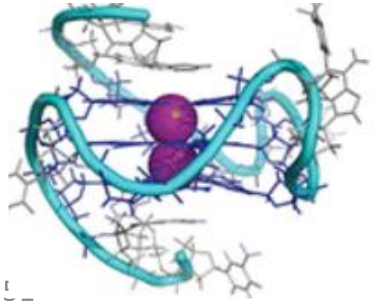
- **Derived information**:
  - Structure and dynamics of different biomolecules
  - kinetics and dynamics and ligand binding of the **metal ions and biomolecules**
  - 3D structure of proteins and **protein-metal complexes**

Metal ions in biology

- Role of metal ions in human body depends on adopted coordination environment

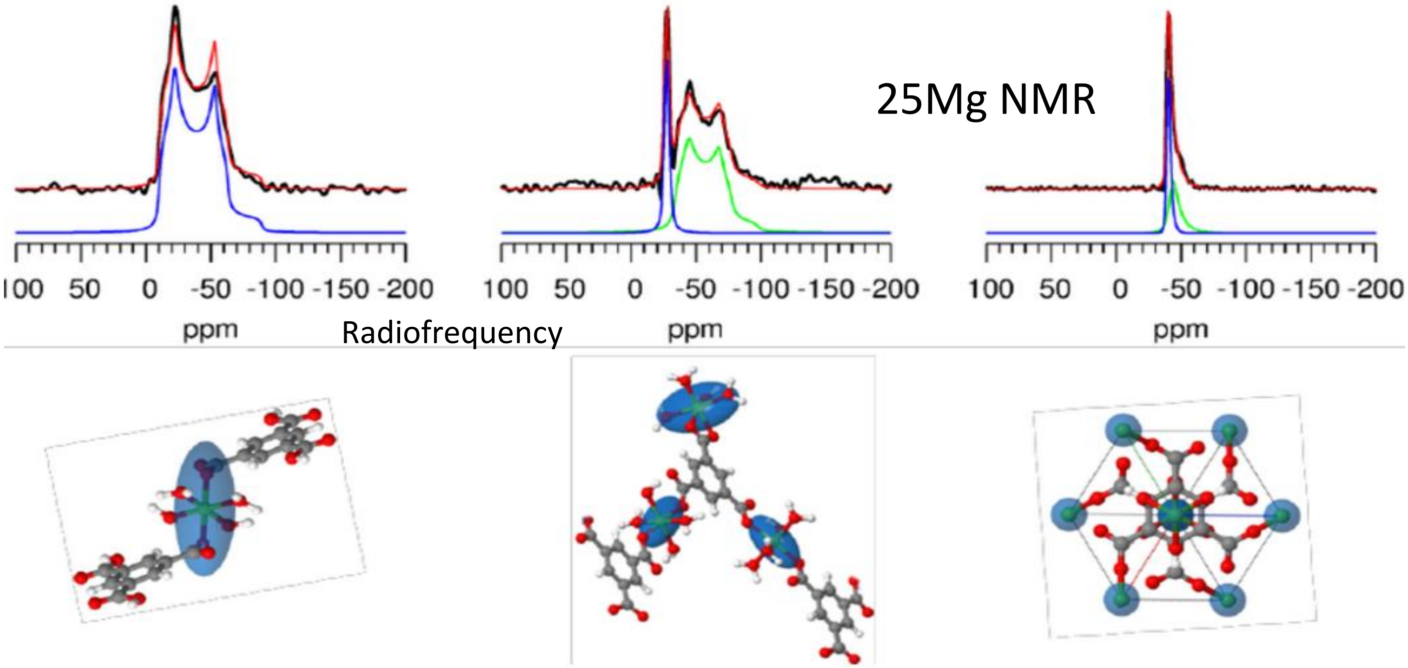
- Right concentration crucial for correct functioning of cellular processes
    - Na, K: transport of sugars and amino acids into cells; regulate flow of water across membranes
    - Mg: RNA- and DNA-processing enzymes and ribozymes
    - Cu: present in many enzymes involved in electron transfer and activation of oxygen
    - Zn: 2nd most abundant trace element in human body; catalytic and structural role, regulation of genetic message transcription and translation





Metal ions & NMR

- NMR can provide info on location & evolution of metal-ion binding to biomolecules
  - NMR on 23Na, 25Mg, 63Cu, 67Zn bound to the biomolecule



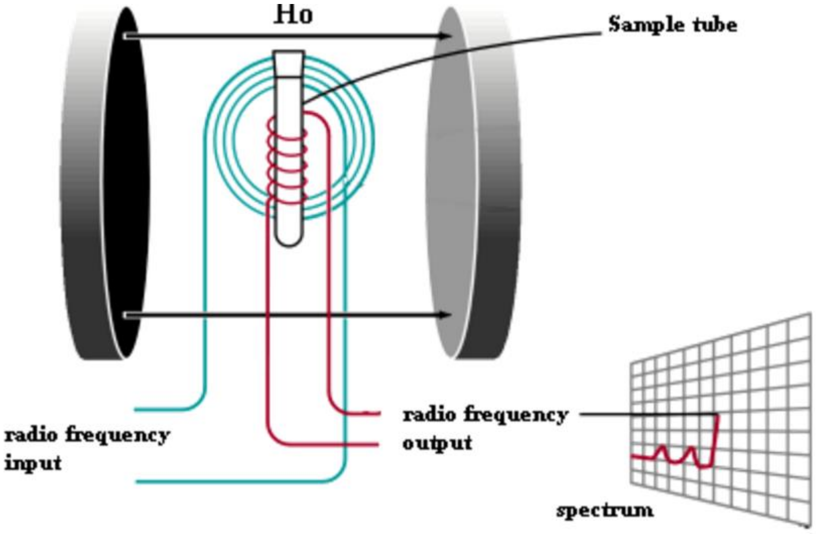
- Challenges: almost invisible signals due to small abundance, I>1/2, and small sensitivity (due to small magnetic moment)

- Result: metal-ion-NMR used very rarely

- In common with radioactive nuclei:
  - Small amount of nuclei so a sensitive NMR approach is needed

NMR limitation: sensitivity

- NMR is powerful but not sensitive
  - Small degree of spin polarization
  - Inefficient detection
- Our combined paths to increase sensitivity: beta-NMR and gamma-NMR/MRI
  - Hyperpolarization
  - Detection of asymmetry in beta decay



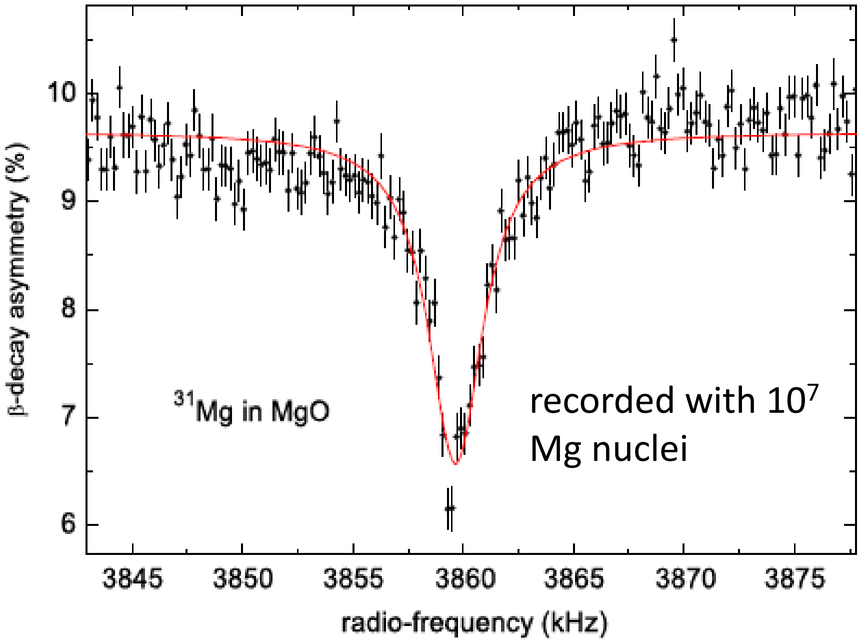
Ultrasensitive beta-detected NMR

- Addresses low sensitivity limitation of conventional NMR:
  - Low degree of polarization -> hyperpolarization
  - Inefficient resonance detection -> particle detection

=> up to **1e10** more sensitive than conventional NMR:

Example:

31Mg
T1/2 = 230 ms
I = 1/2

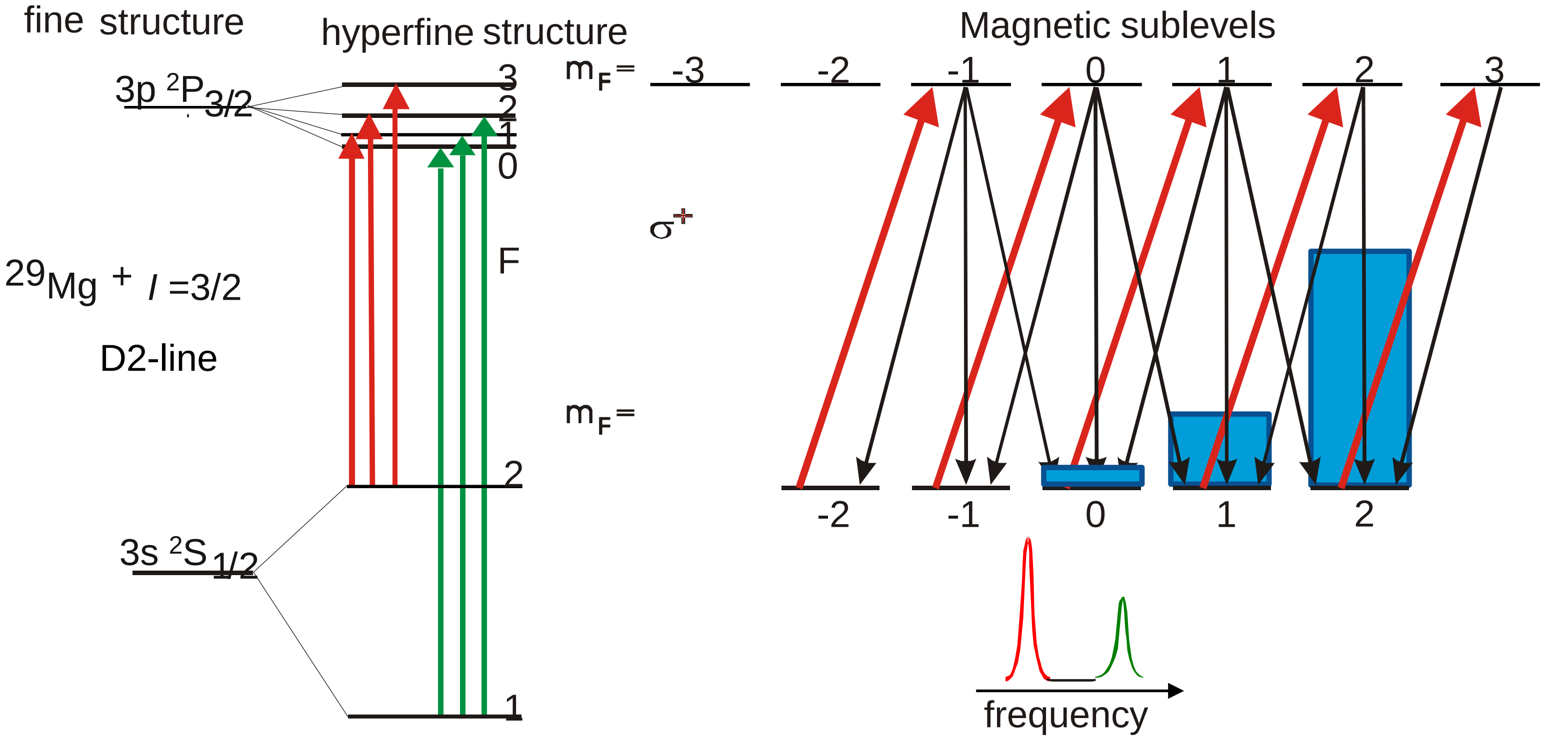


recorded with 10^7 Mg nuclei

M. Kowalska
PhD thesis
2006

Hyperpolarization: optical pumping

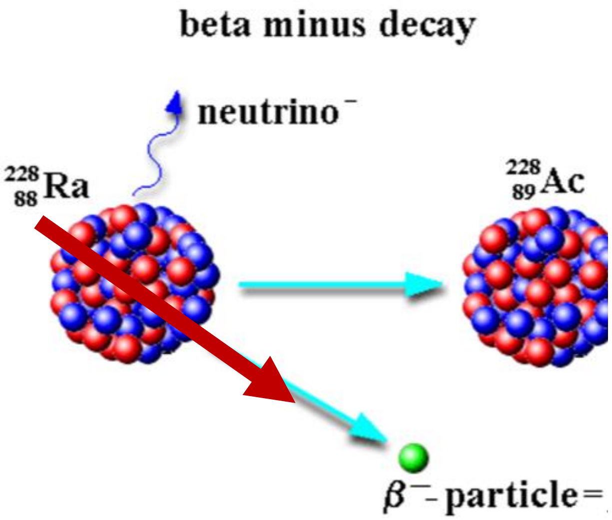
- Multiple excitation cycles with circularly-polarized light
- Photon angular momentum transferred to electrons and then nuclei
  - Works best for 1 valence electron
  - nuclear spin-polarization of 10-90%
  - Polarization buildup time < us

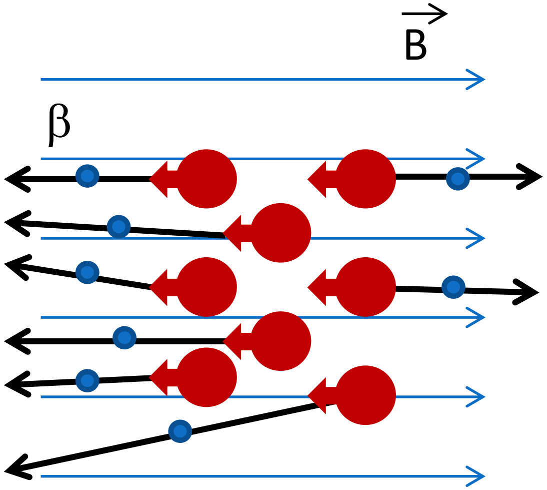


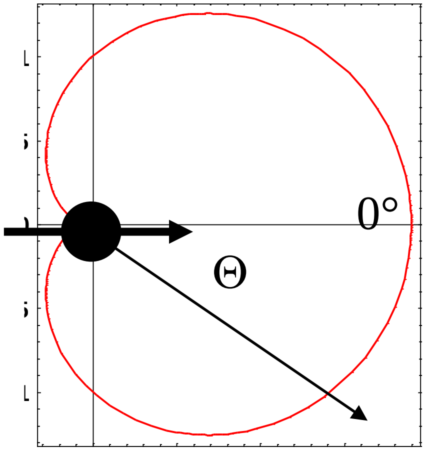
Detection of particles: beta decay

- Many unstable atomic nuclei decay by emitting a β particle (fast electron or positron)
- **Beta particles are emitted mostly in the direction of the spin**

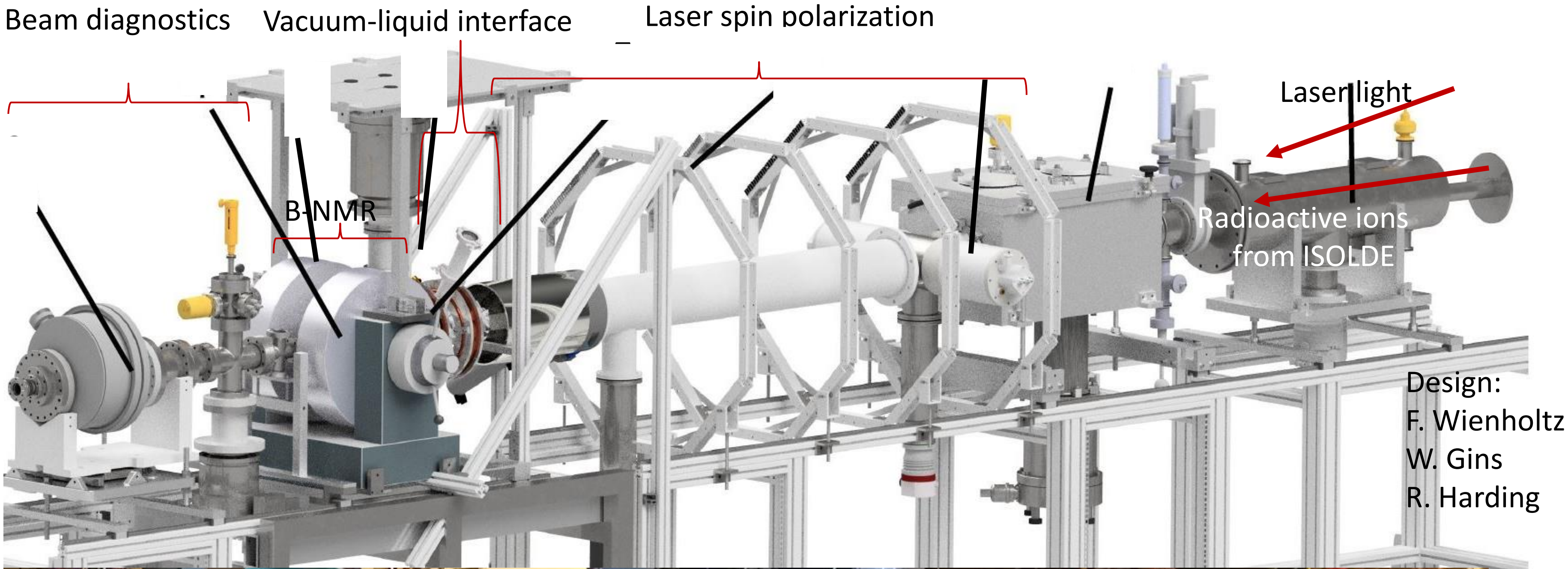
=> Gain in NMR detection efficiency: up to 10^5







Experimental setup

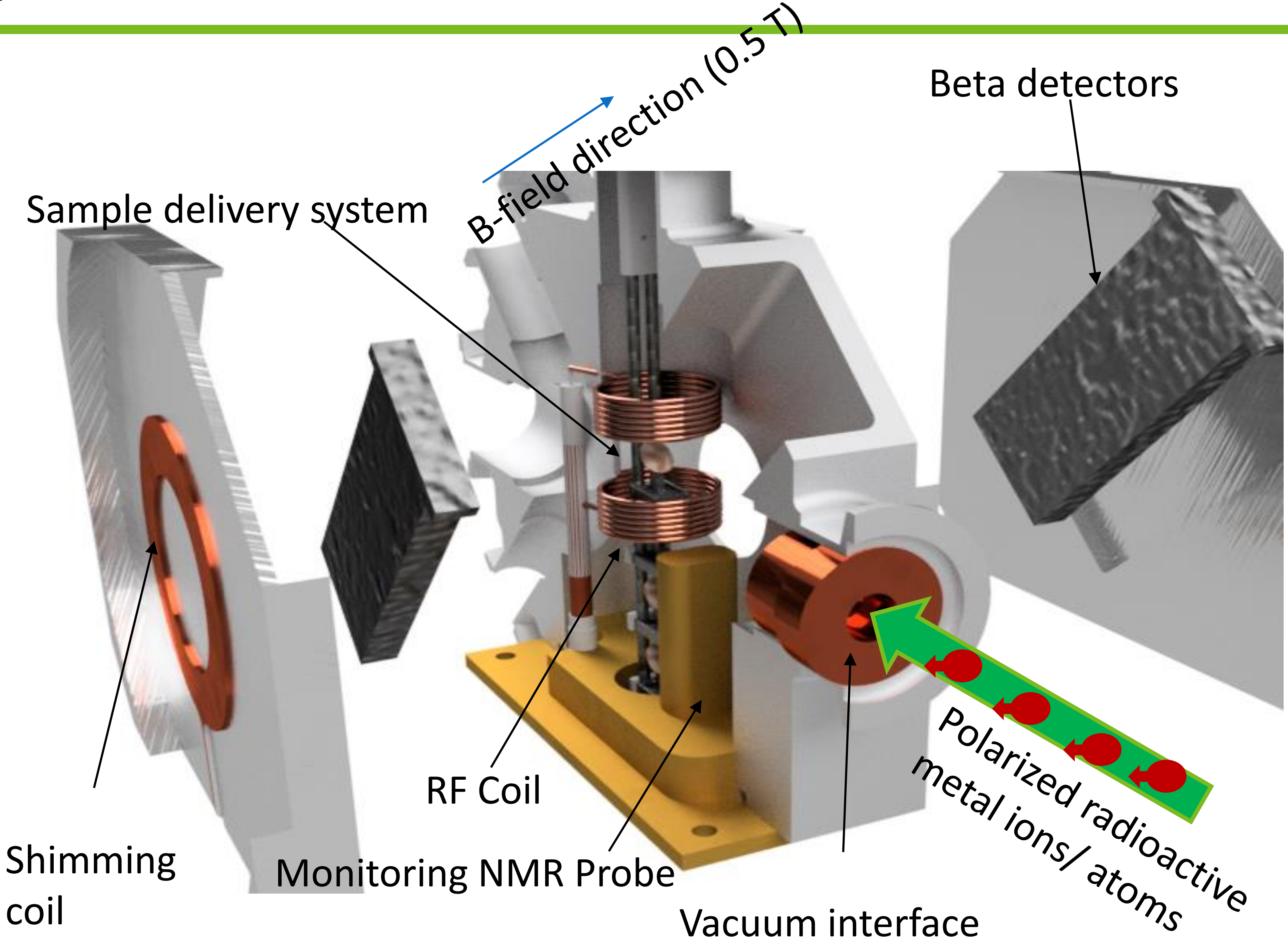


Design:
F. Wienholtz
W. Gins
R. Harding

M. Kowalska et al., J. Phys. G: Nucl. Part. Phys. 44 (2017) 084005
W. Gins et al., to be submitted to Nucl. Instr. and Meth. A

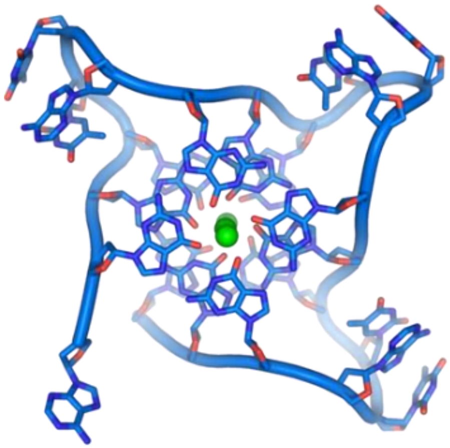
Designed and commissioned in 2016
First physics experiments in 2017
First biology-related experiments in 2018

Bio-Beta-NMR chamber



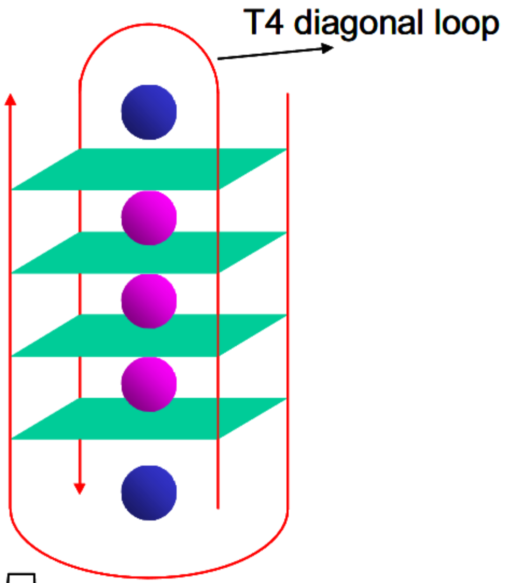
First bio-study: Na+ & G-quadruplexes

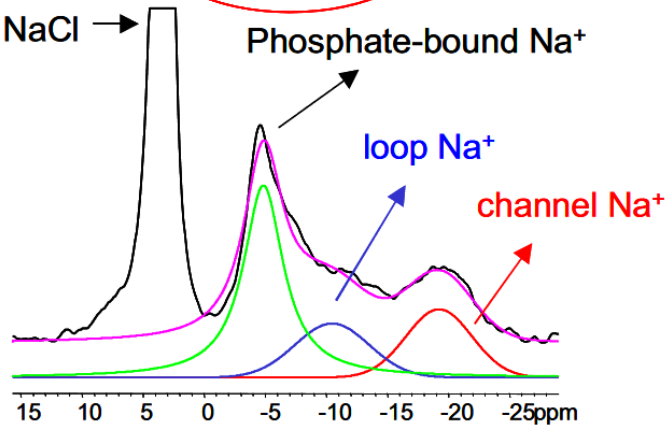
- DNA G-quadruplexes:
  - Guanine-rich DNA fragments
  - Found in nature, e.g. in telomeres or oncogenes
  - Synthesised for novel applications
  - Important in different diseases



- Alkali metals in DNA G-quadruplexes
  - Important for their formation, stability and structural polymorphism
  - Until recently considered invisible in conventional Na+/K+ NMR

One of few 23Na NMR GQ studies:
R. Ida, G. Wu, JACS, 2008



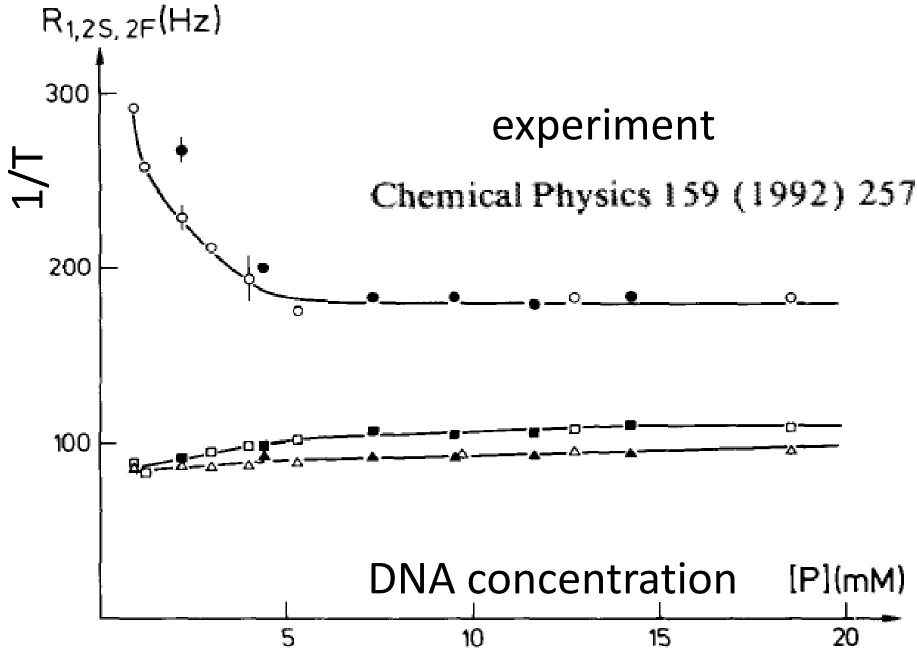


M. Kowalska et al, Proposal to the ISOLDE Scientific Committee, June 2017
M. Trajkovski et al, J. Am. Chem. Soc. 134, 4132 (2012)

NMR on Na+ and DNA interaction

- T1 relaxation measurements:
  - Quadrupole moment of 23Na interacts with electric-field inhomogeneities (gradients) in the environment
  - Longer T1 relaxation time: more homogenous environment
  - Shorter T1: less homogenous environment

- 23Na T1 measurements have been used to study:
  - Influence of drugs on DNA folding
  - Na binding site to DNA: grooves or backbone

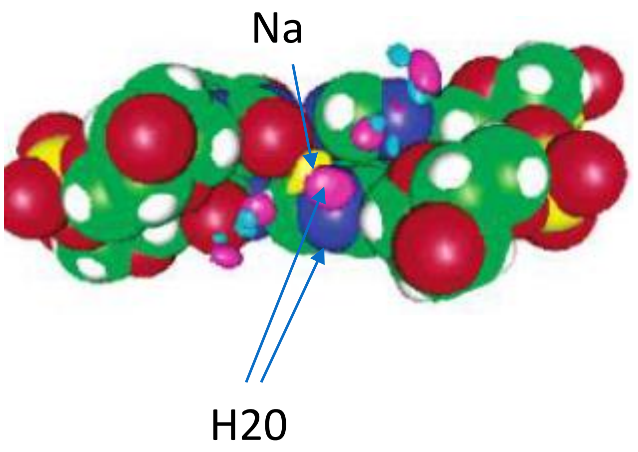


experiment

Chemical Physics 159 (1992) 257–267

simulations

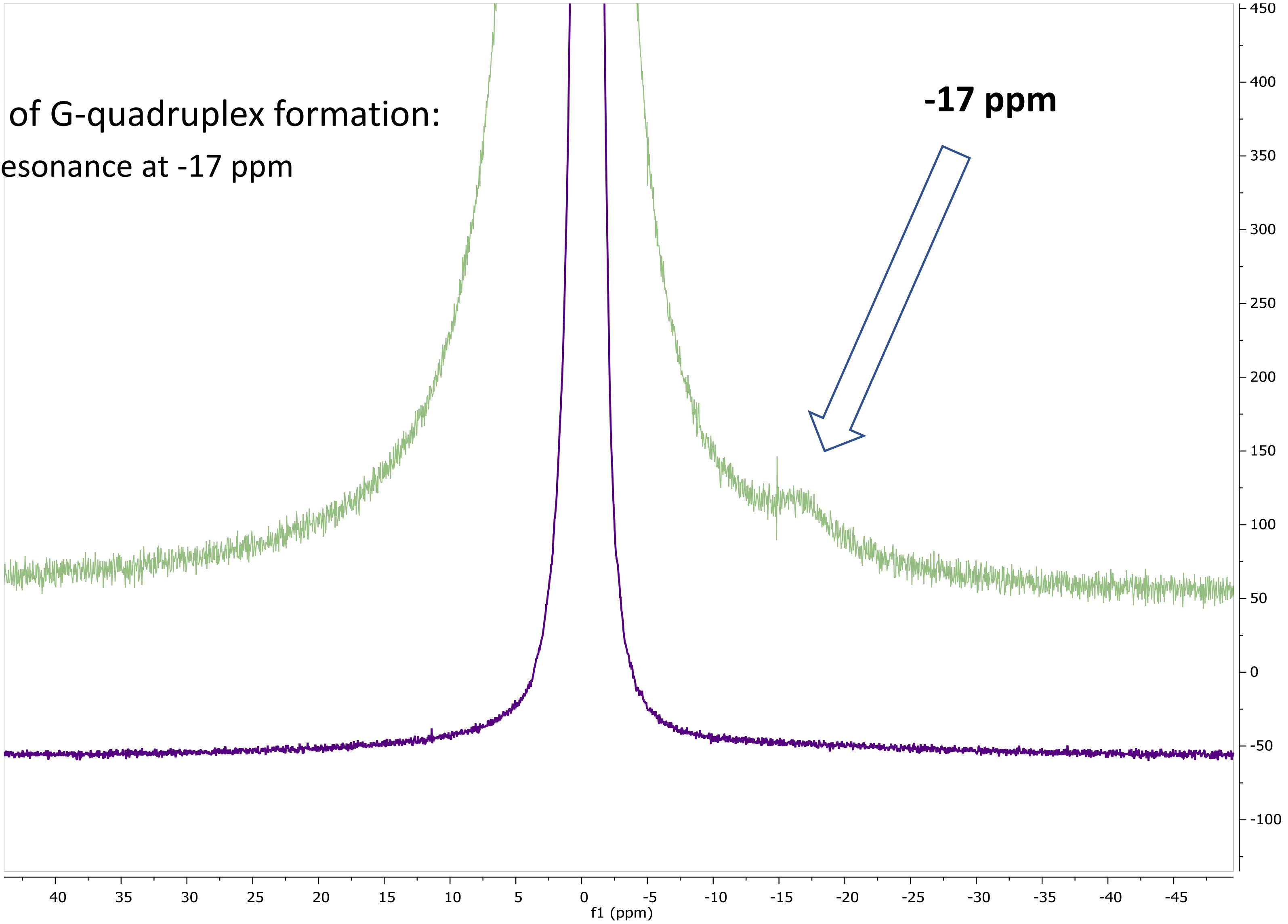
J. Phys. Chem. B **2004,** *108,* 16295



NMR on Na+ and G Quadruplexes

Conventional 23Na NMR

- Proof of G-quadruplex formation:
  - Resonance at -17 ppm

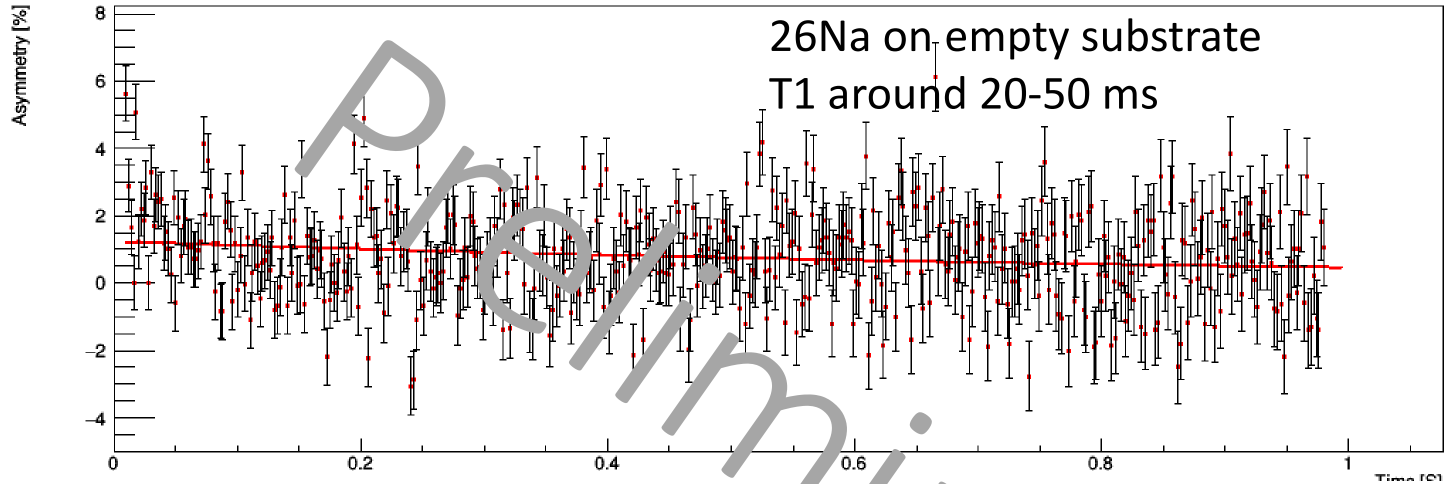


-17 ppm

0.7 M in H2O

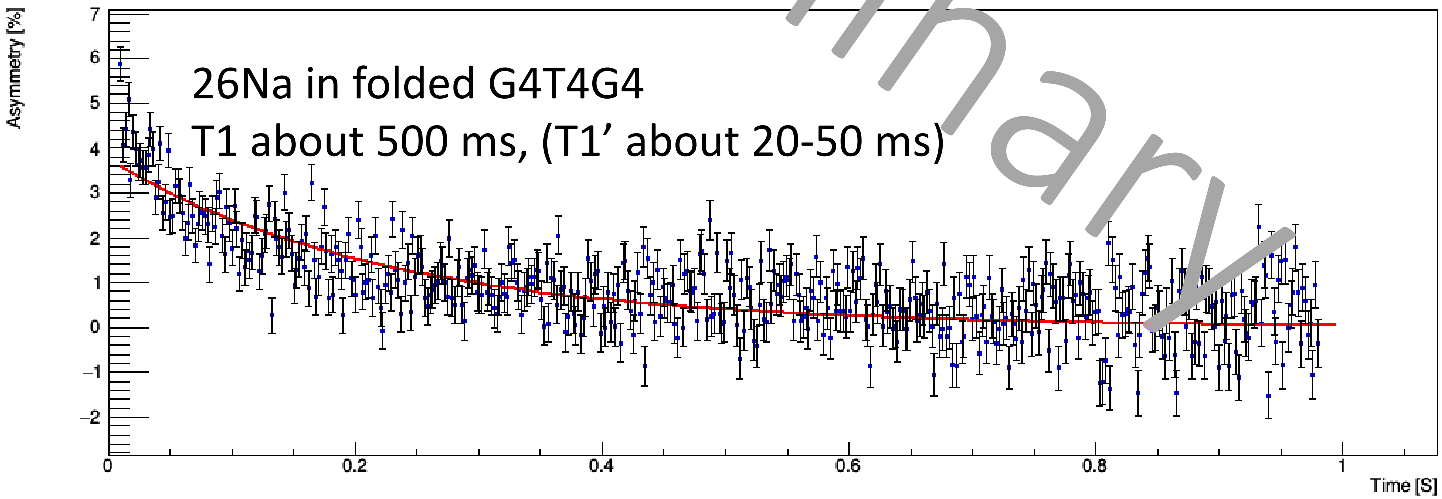
0.4 M in H2O

β-NMR: 26Na T1 in G4T4G4 G-quadruplex



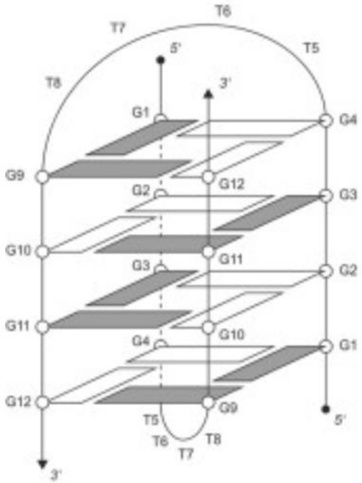
26Na on empty substrate
T1 around 20-50 ms

May 2018



26Na in folded G4T4G4
T1 about 500 ms, (T1’ about 20-50 ms)

Folded
G4T4G4
DNA sequence
on substrate



- T1 in presence of GQ quite long (due to relatively symmetric environment of GQ?)
- Calculations should help in more detailed interpretation
- Oct18 NMR spectra under analysis – probably too broad to see -17 ppm shift

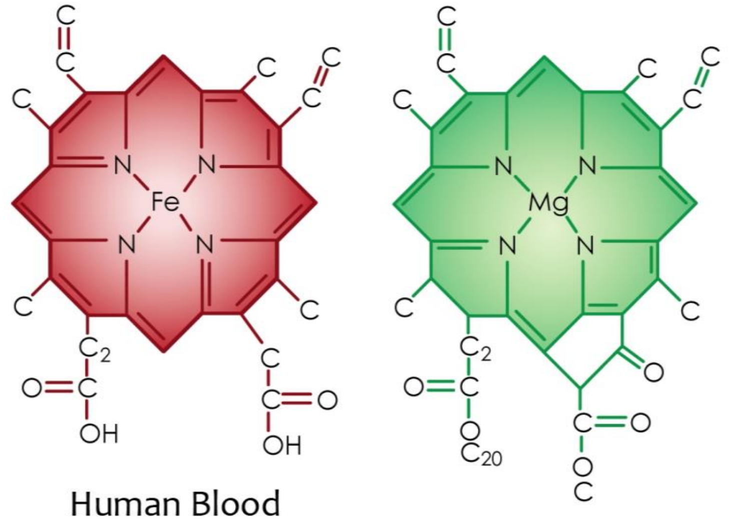
Beyond 2018

Already polarized at ISOLDE:

8,9Li
11Be
26-28Na
29,31Mg

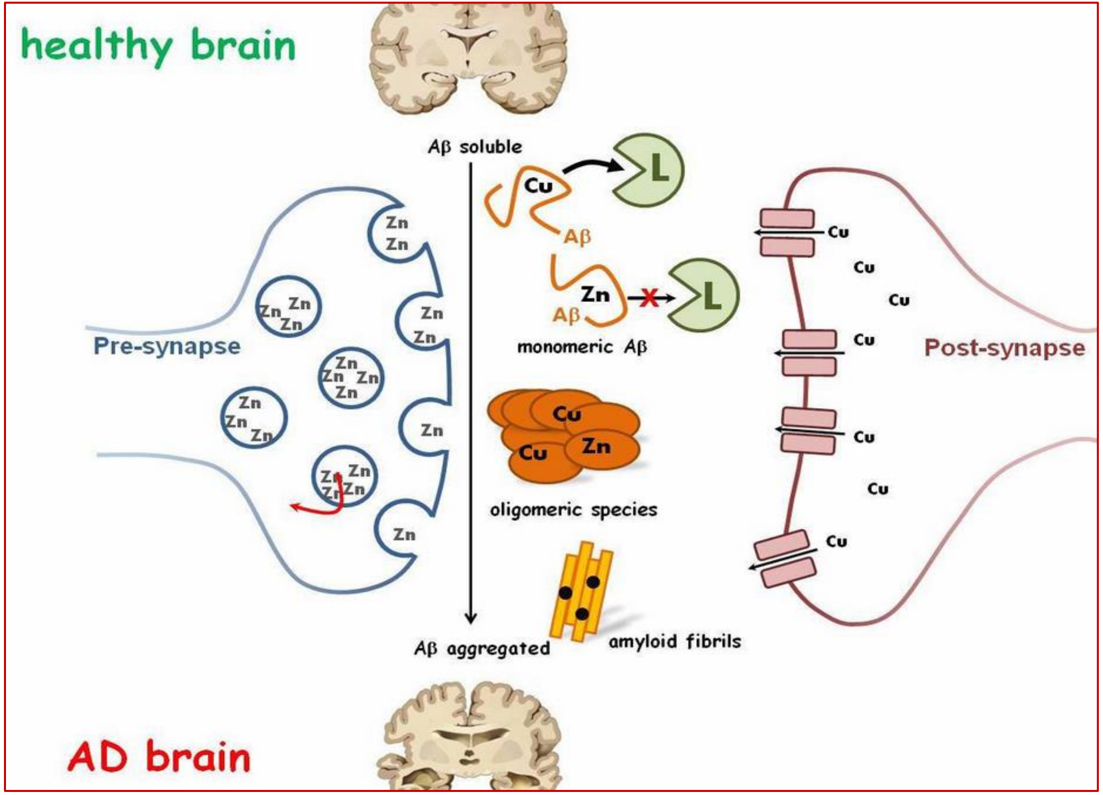
Feasible and planned soon:

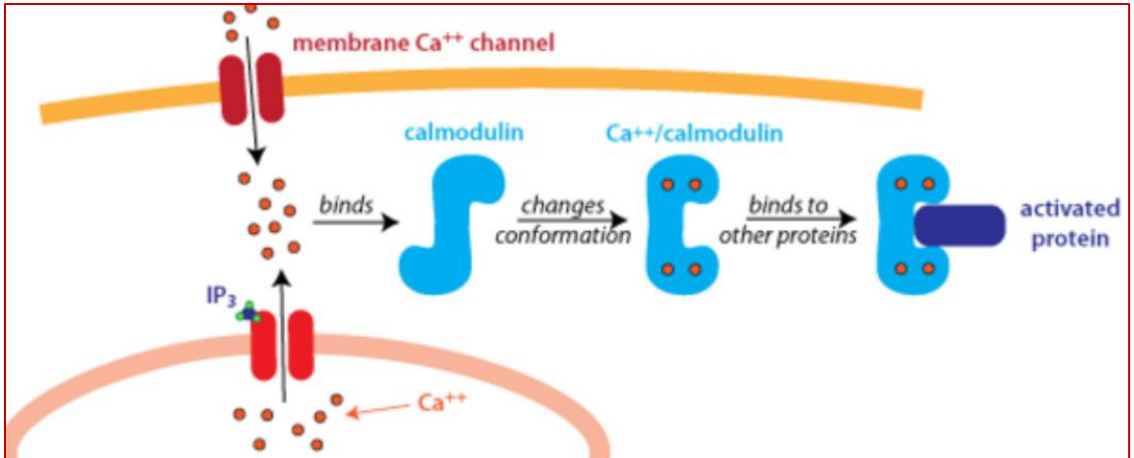
37,49K
39,51Ca
58,74,75Cu
75,77Zn



Human Blood Hemoglobin

Plant Chlorophyll

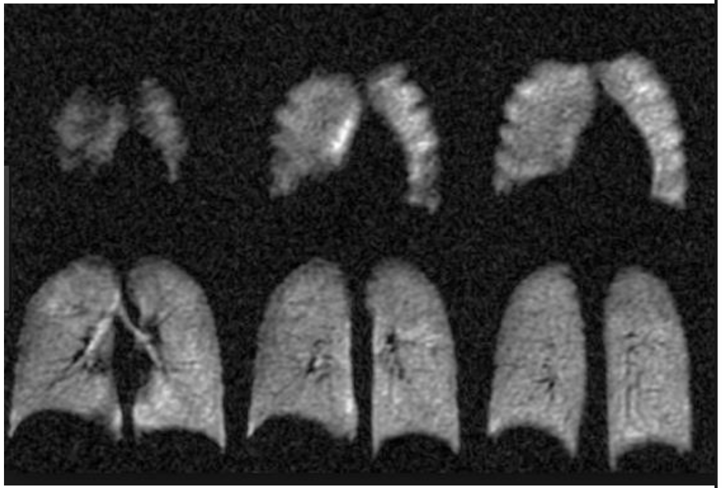




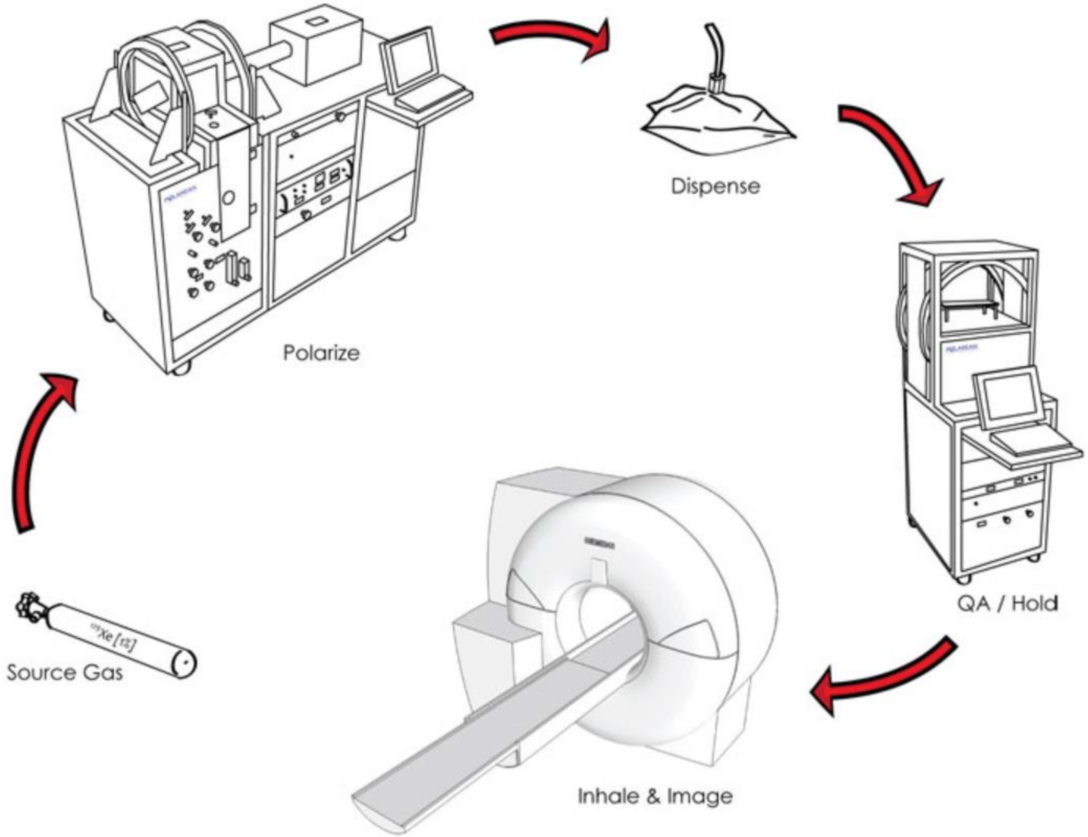
Magnetic resonance imaging

MRI with hyperpolarized nuclei

- MRI: high resolution, but small sensitivity
- Hyperpolarization: increase in sensitivity by up to 1e5
- Best example: 129Xe:
  - Polarized via spin-exchange with laser-polarized Rb
  - Applications: lung and brain MRI, encapsulation and use in body liquids



1st medical applications of 3He:
W. Heil et al, Mainz, Nature 1996

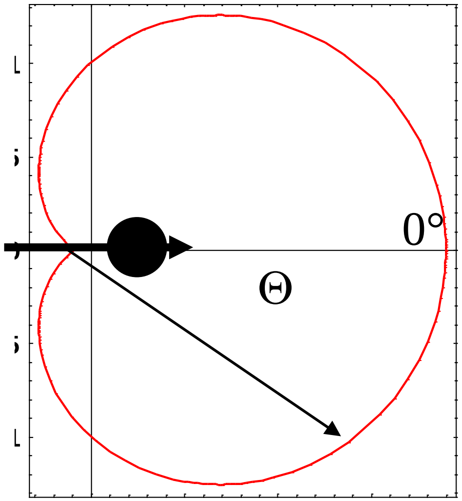


Gamma-decay asymmetry

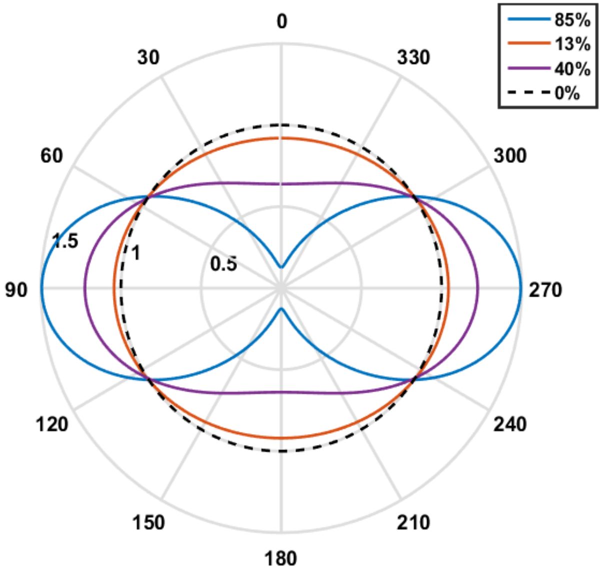
- Gamma rays emitted by de-exciting nuclear states are anisotropic in space:
  - I>1/2 nuclei
  - Asymmetry between spin direction and perpendicular to it

- Change of asymmetry -> very sensitive way to record NMR or MRI resonances
  - Increase in sensitivity: 1e5 vs hyperpolarized MRI with stable nuclei

Beta decay, I>0



Gamma decay, I>1/2



New modality: gamma-MRI

PET/SPECT and MRI have complementary features:

	Detection efficiency	Spatial resolution
PET and SPECT	high	Low (e.g. >5mm for 82Rb)
MRI	low	High

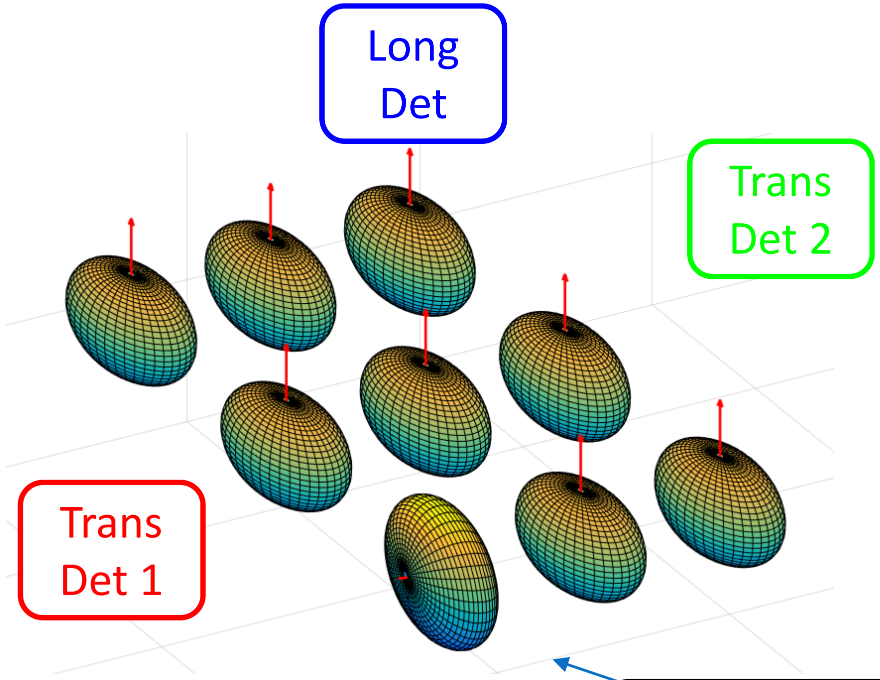
Solution: **gamma-MRI (or simultaneous SPECT-MRI):**

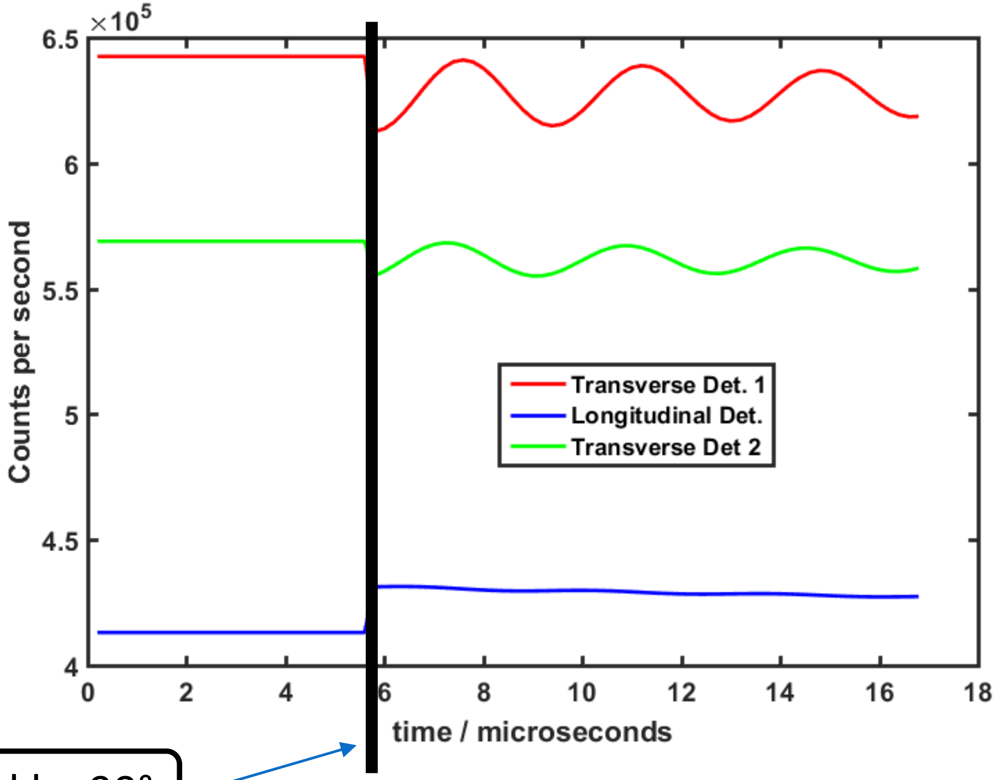
- What - Record MRI signals from PET/SPECT-type nuclei
- How - Hyperpolarize spins and observe asymmetry of gamma decay
- Result - high efficiency (gamma detection) and high resolution (MRI)
- Status: method shown to work: Y. Zheng, et al., Nature 537, 652 (2016)

- Gamma-MRI Equipment:
  - I>1/2 gamma-emitting nuclei
  - Spin-polarizer
  - MRI magnet
  - **Gamma detectors inside B field**

Gamma MRI – spatial resolution

- Pixel size
  - defined by slope of B-field gradients and spectral width of rf pulse
  - more nuclei -> smaller pixels possible up to B gradient and rf limit
- 1 pixel in resonance:
  - change in total gamma counts visible in each detector
  - Degree of change proportional to number of nuclei in addressed pixel



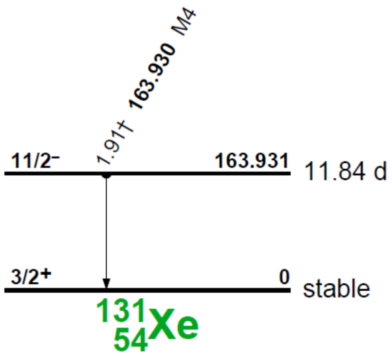


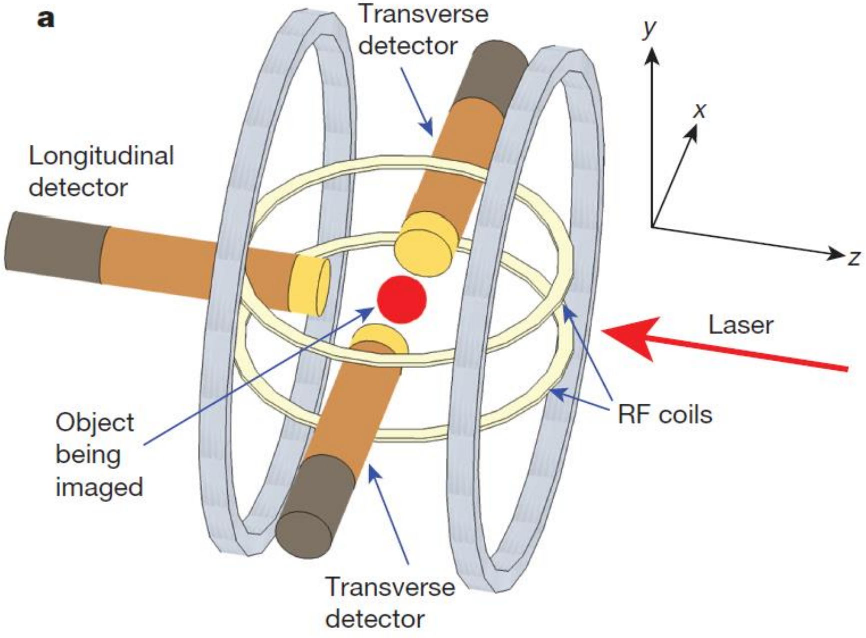
Rotate 1 pixel by 90°

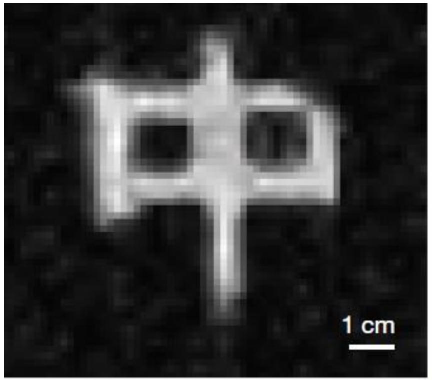
First gamma-MRI

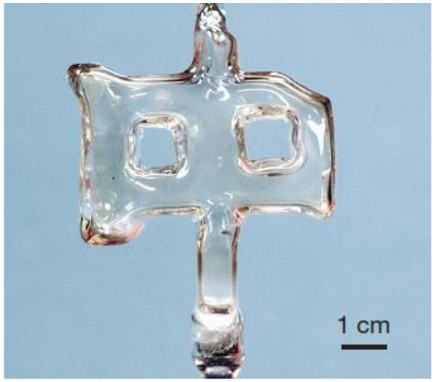
Y. Zheng, G.W. Miller, W.A. Tobias, G.D. Cates, Nature 537, 652 (2016)

- **131mXe**: t1/2 = 12 days
- **Setup:** low B-field
- **Results:** space-resolved signal (recorded pixel after pixel) with 1e13 nuclei vs 1e24 normally









Our gamma-MRI project

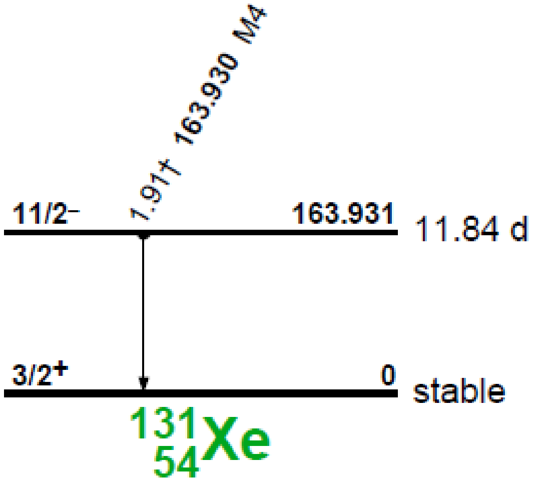
- Work on feasibility of the technique:
  - Use PET/SPECT isotopes or their isomeric states
  - Optimising rf pulses
  - Maintaining of polarization
  - First detectors

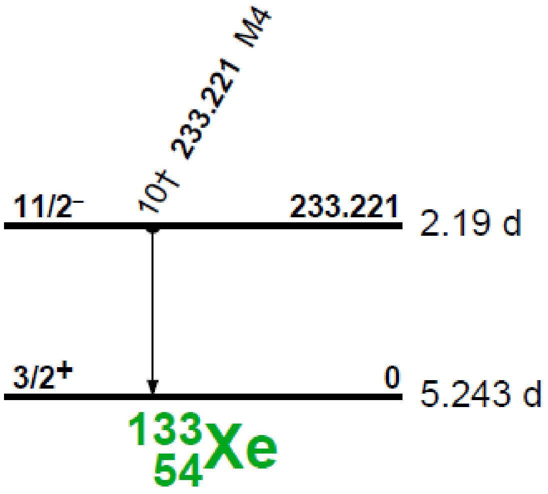
- => lower dose required to record signals

- Work on proof-of-principle experiment with commercial MRI scanner

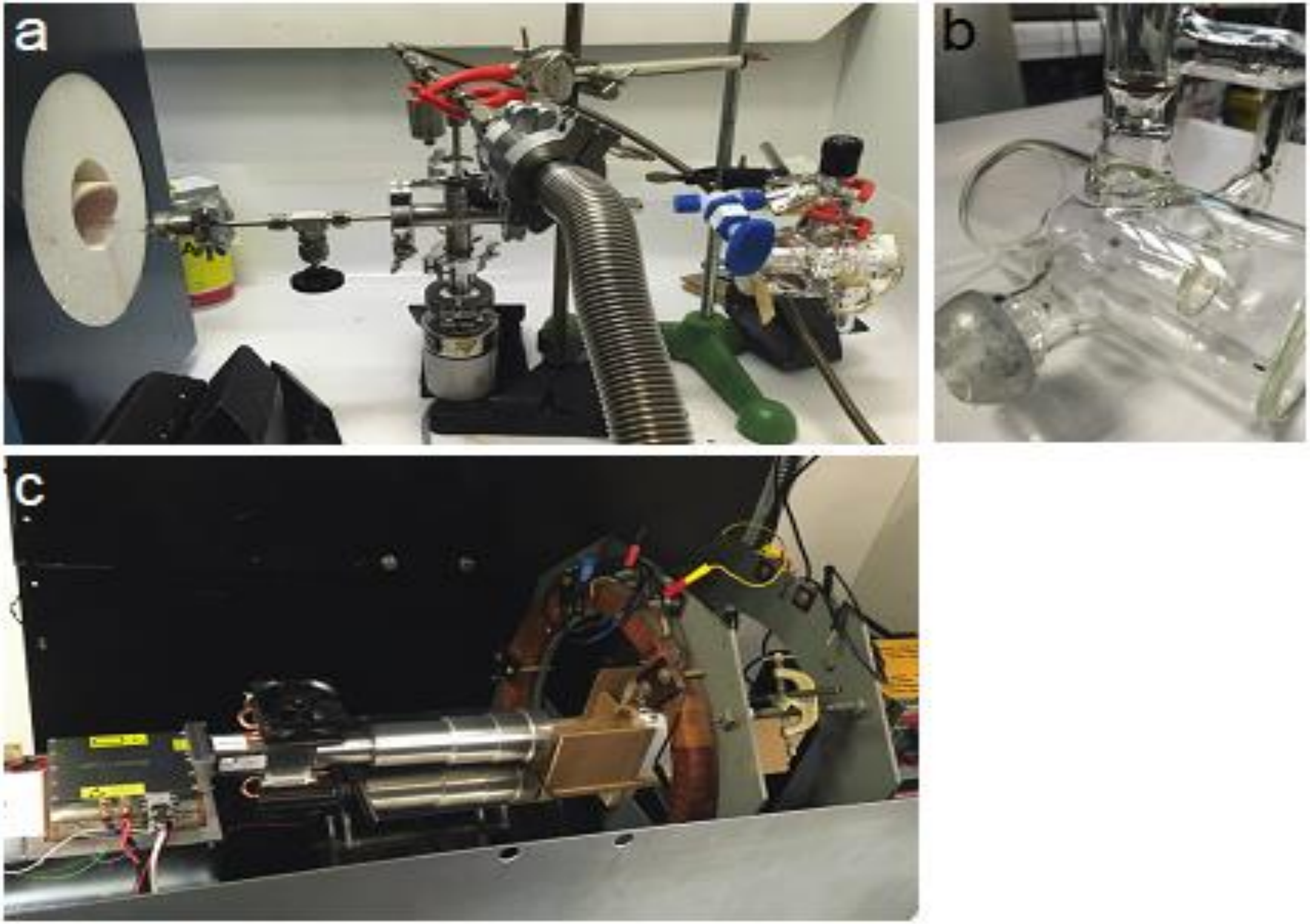
Our 1st isotopes

- Lung and brain studies





Our test gamma-MRI setup



Summary and outlook

- NMR in nuclear physics and biology
  - Valuable, very different, and facing same challenges – need for high sensitivity

- NMR and metal ions in biology
  - Sheds light on interactions with different biomolecules

- NMR low sensitivity can be increased by orders of magnitude with beta-NMR
  - Laser spin hyperpolarization
  - Detection of asymmetry in beta decay

- Beta-NMR in biological samples
  - Experimental setup at CERN
  - First biological experiments on Na interaction with DNA G-quadruplex structures

- More studies with Na and other metal ions coming up

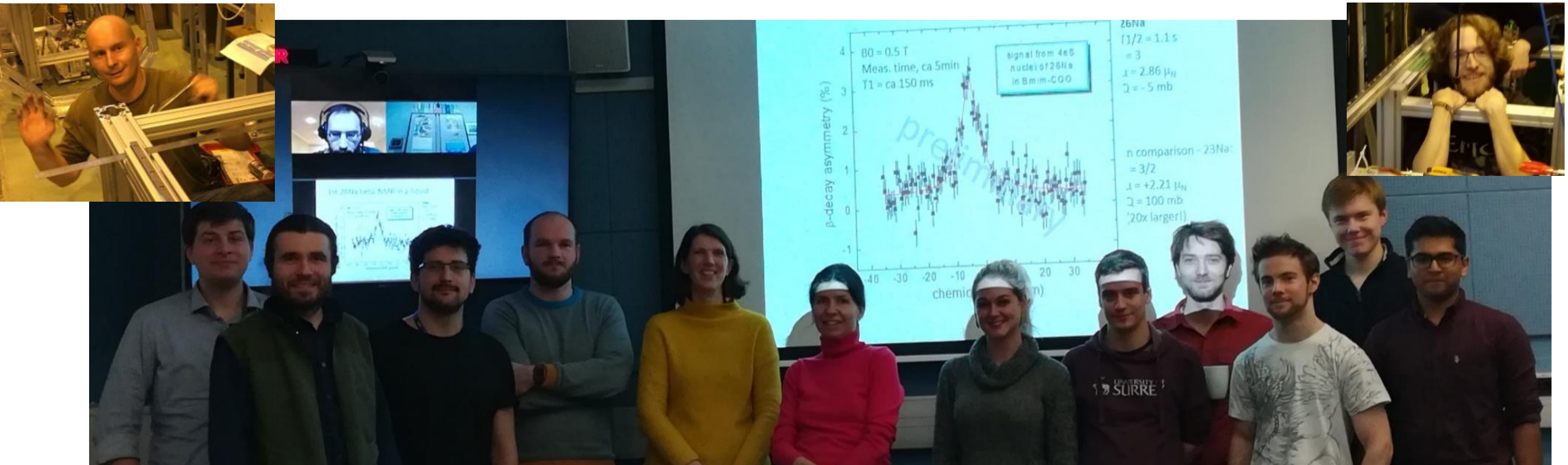
- Increase in MRI sensitivity with gamma-detected MRI
  - Ideal for noble gas imaging, e.g. He or Xe
  - Project starting in Geneva

Acknowledgements

Experimental setup:
CERN: J. Croese, R. Harding, S. Pallada, K. Dziubinska-Kuehn, F. Wienholtz, M. Jankowski, A. Javaji, P. Wagenknecht, R. Engel
KU Leuven: G. Neyens, W. Gins, F. Gustafsson, X. Yang, H. Heylen, A. Kanellakopoulos, V. Araujo Escalona
U Manchester/CERN: M. Bissell
AMU Poznan: M. Baranowski, M. Walczak
U Tennessee: M. Madurga Flores, X. Zhang
NPI Rez: D. Zakoucky

Biology (and conventional NMR):
NIC, Ljubljana: J. Plavec, V. Kocman
AMU Poznan: M. Kozak, J. Wolak, K. Szutkowski
U Copenhagen: L. Hemmingsen, F.H. Larsen,
UNIGE: L. Cerato, D. Jeannerat, E. Sistate

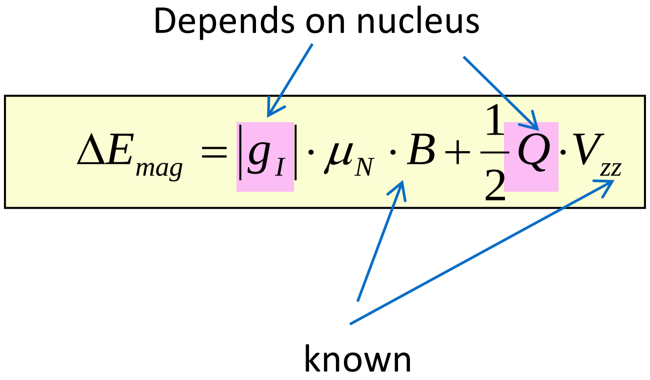
Gamma-MRI:
UNIGE/CERN: R. K. Kulesz
HESGE: J-N. Hyacinthe, E. Vinckenbosch
CERN: S. Pallada, J. Croese, T. Stora
Madrid: L. Fraile et al



NMR in nuclear physics

Method to determine precisely magnetic & quadrupole moments of short-lived nuclei

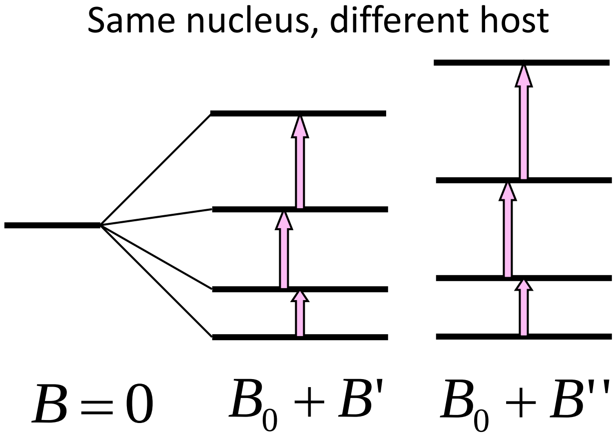
- **Observables**: Larmor frequency
- **Determined properties**
  - Magnetic dipole and electric quadrupole moment of the studied nucleus



Depends on nucleus

$$\Delta E_{mag} = |g_I| \cdot \mu_N \cdot B + \frac{1}{2} Q \cdot V_{zz}$$

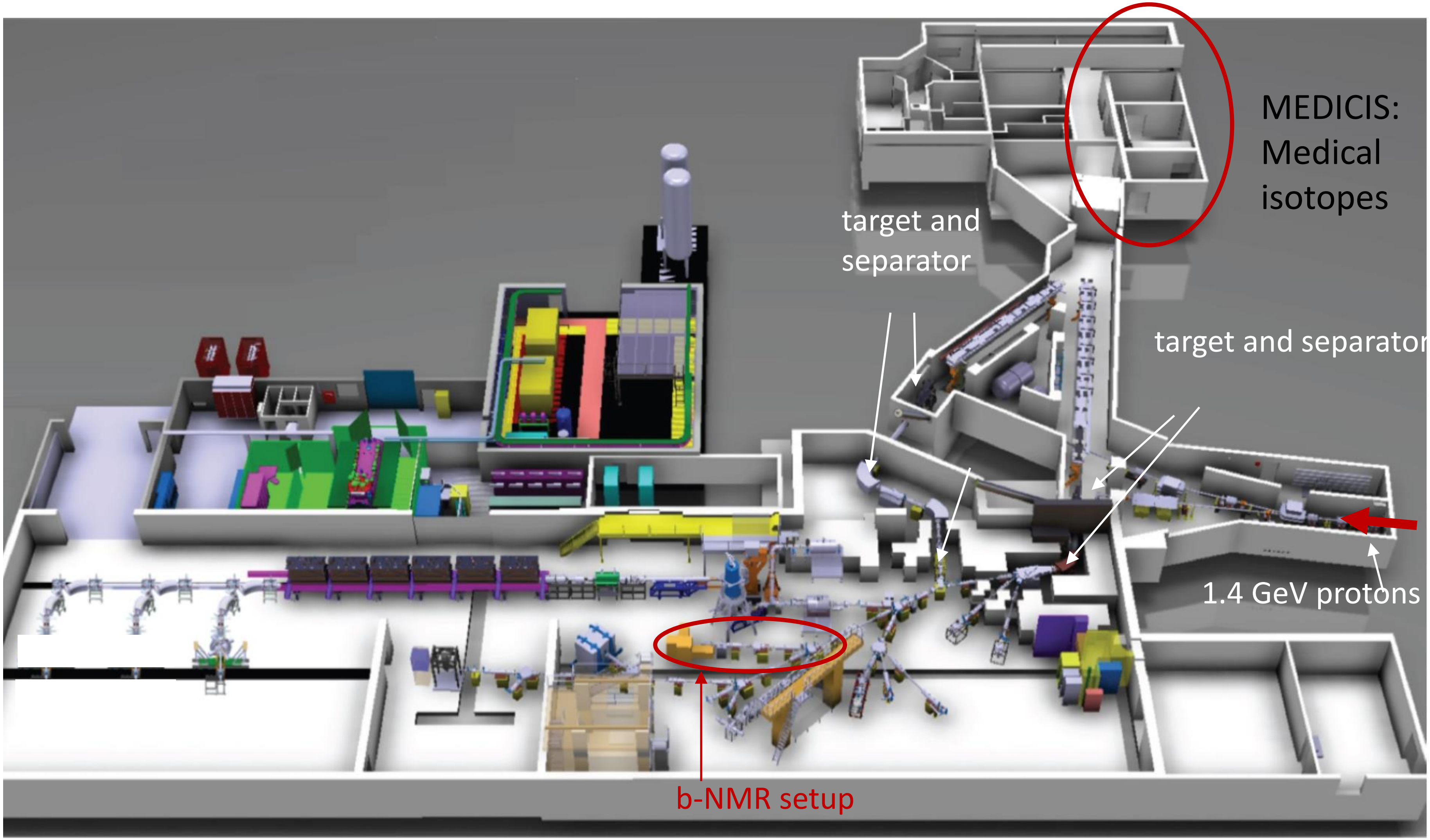
known



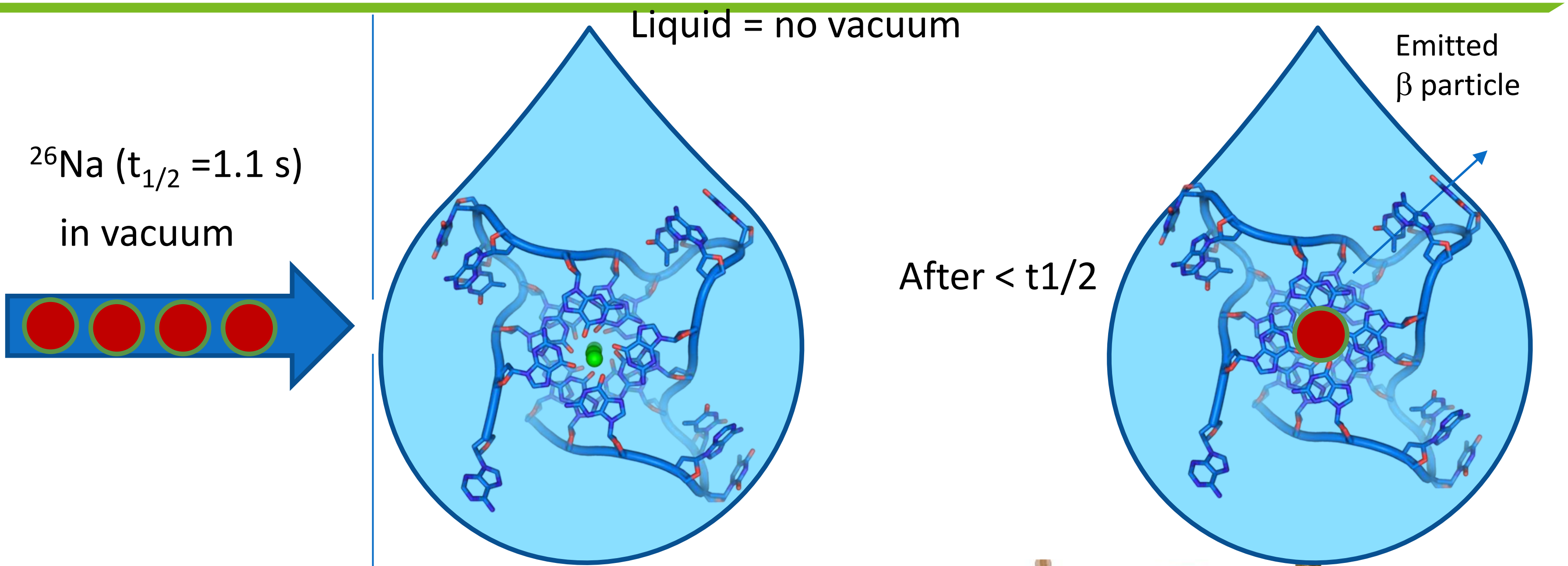
Same nucleus, different host

- **Derived information**:
  - Magnetic moment – orbitals occupied by valence nucleons
  - Quadrupole moment – collective properties

ISOLDE laboratory



Getting probe nuclei into liquid samples



^{26}Na ($t_{1/2}$ =1.1 s)

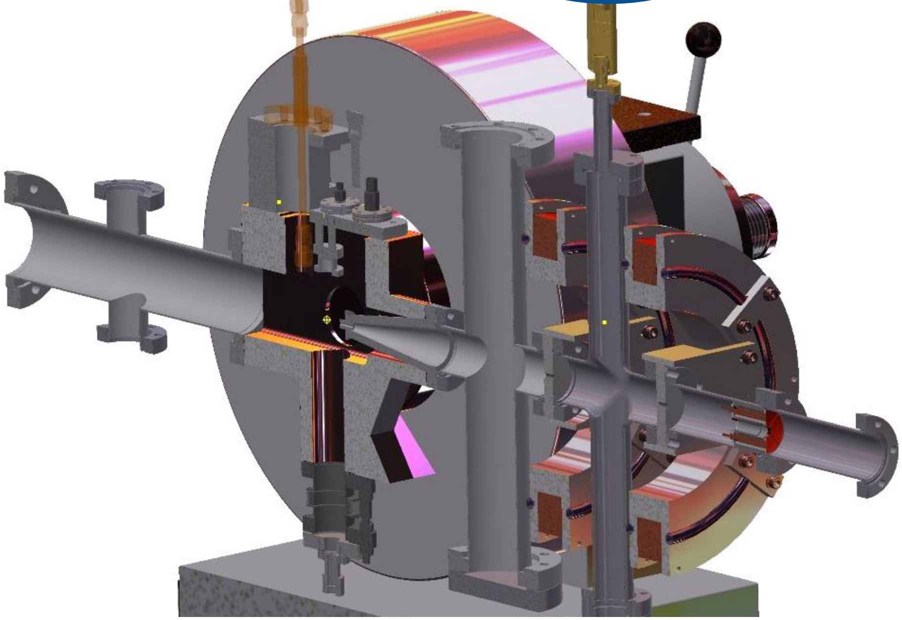
in vacuum

Liquid = no vacuum

After < t1/2

Emitted

β particle

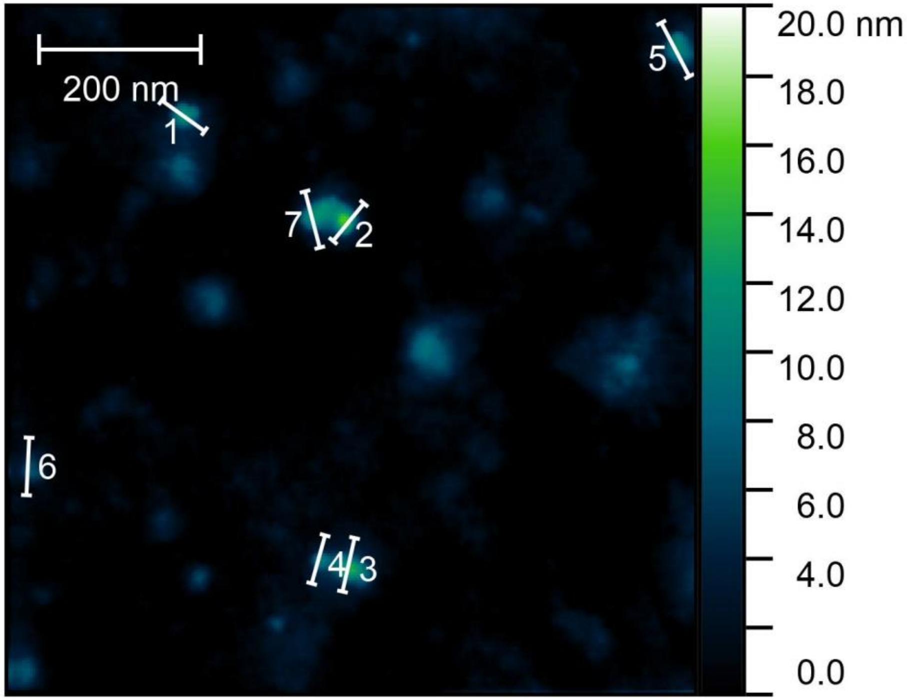


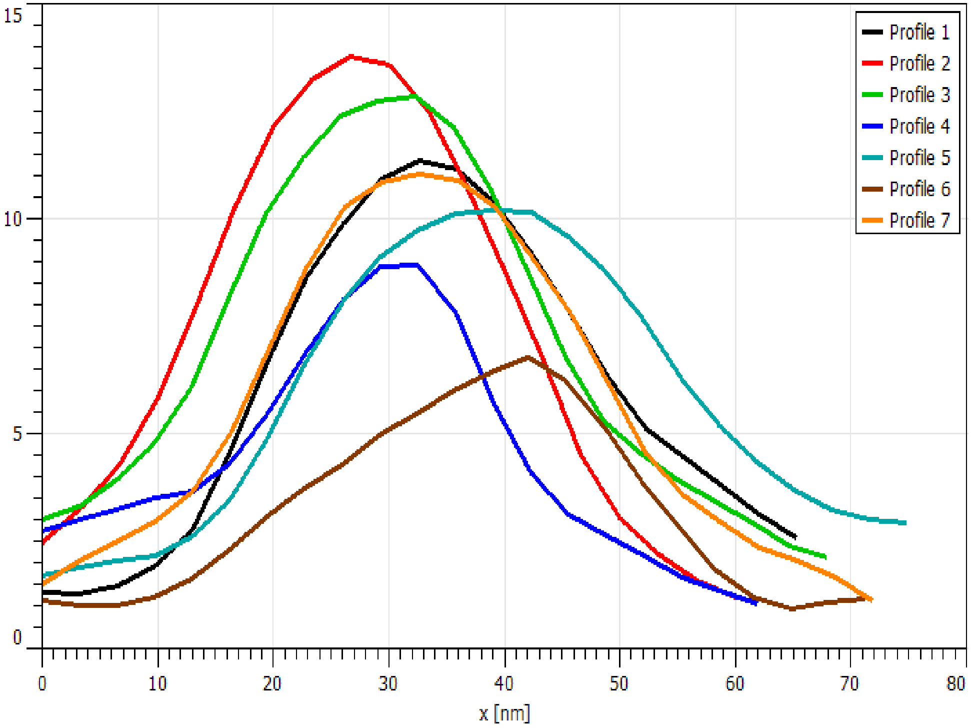
Challenges and constraints:

- Vacuum/liquid interface with little loss in atom beam and polarization
- Binding to biomolecule before decaying -> choose suitable systems to study

AFM measurements

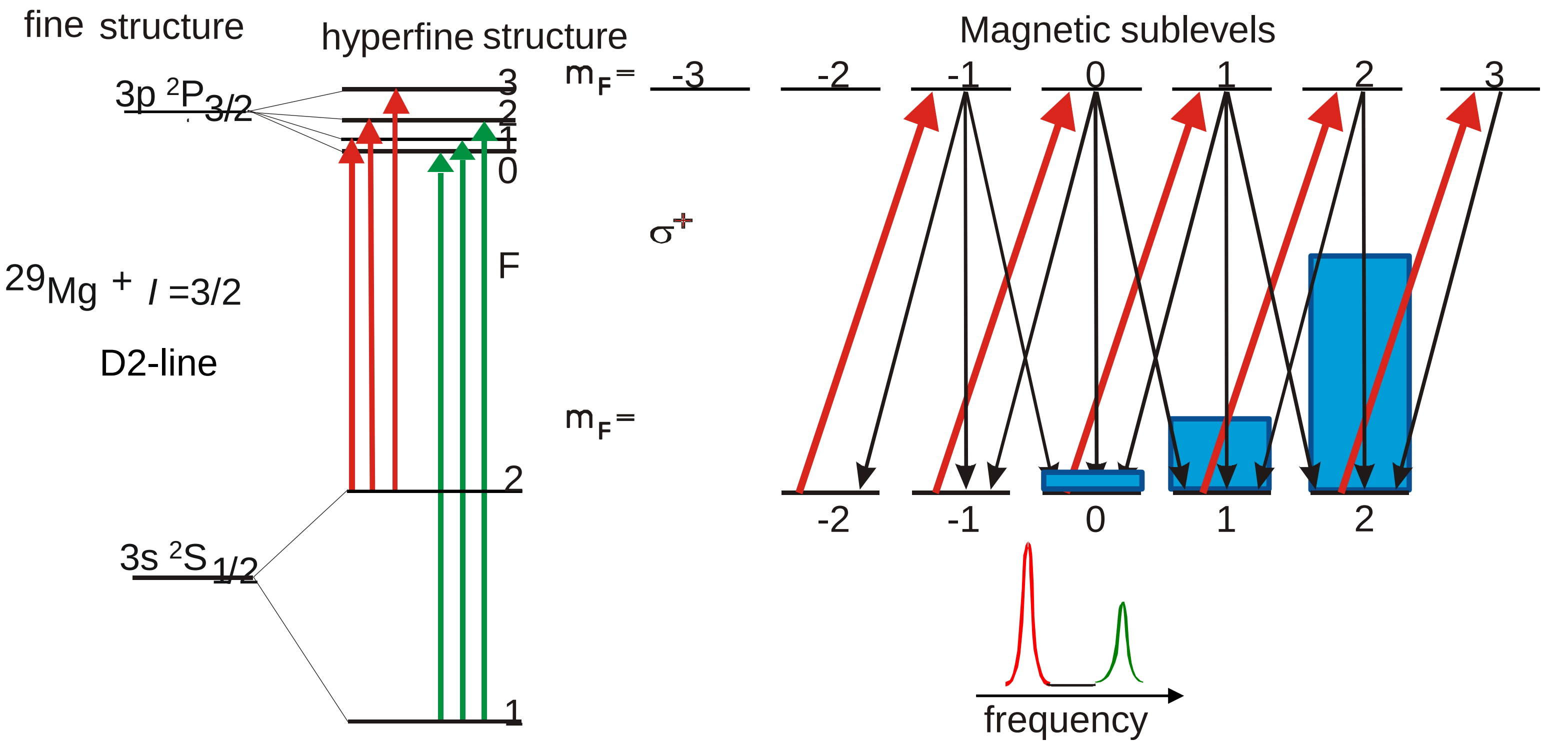
Folded G4T4G4 in Emim-DCA





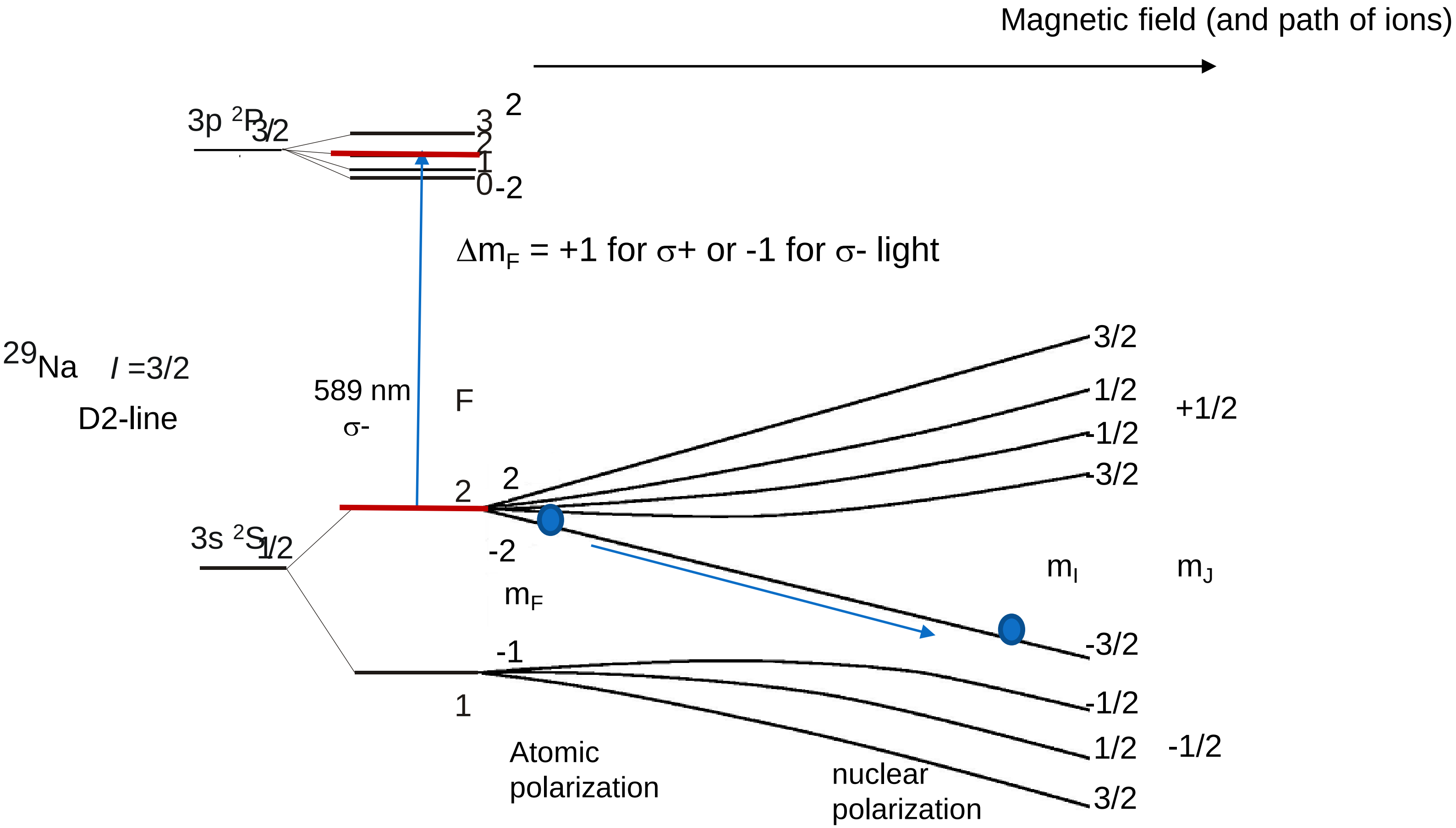
Hyperpolarization via optical pumping

- Multiple excitation cycles with circularly-polarized light
- Photon angular momentum transferred to electrons and then nuclei
  - Works best for 1 valence electron
  - nuclear spin-polarization of 10-90%
  - Polarization buildup time < us



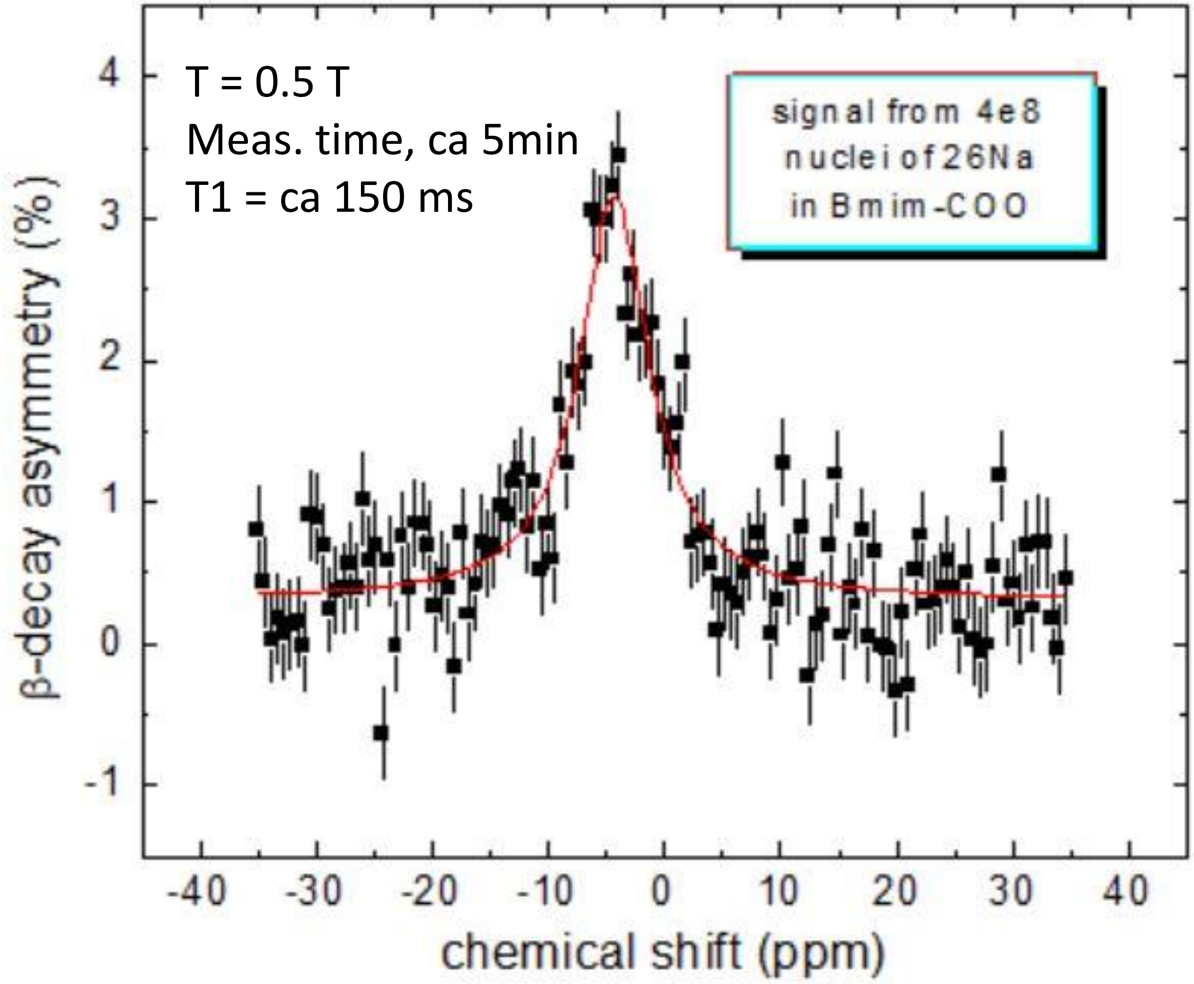
Optical pumping and nuclear spin

- Polarization of atomic spins with circularly polarized laser (ΔmF = +1 for σ+ or -1 for σ- light)
- Resulting polarization of nuclear spins via hyperfine interaction (PF->PI):
- Resulting beta-decay asymmetry



First NMR results in liquids

- Dec 2017: First Na beta-NMR signals in liquid hosts compatible with vacuum (ionic liquids)



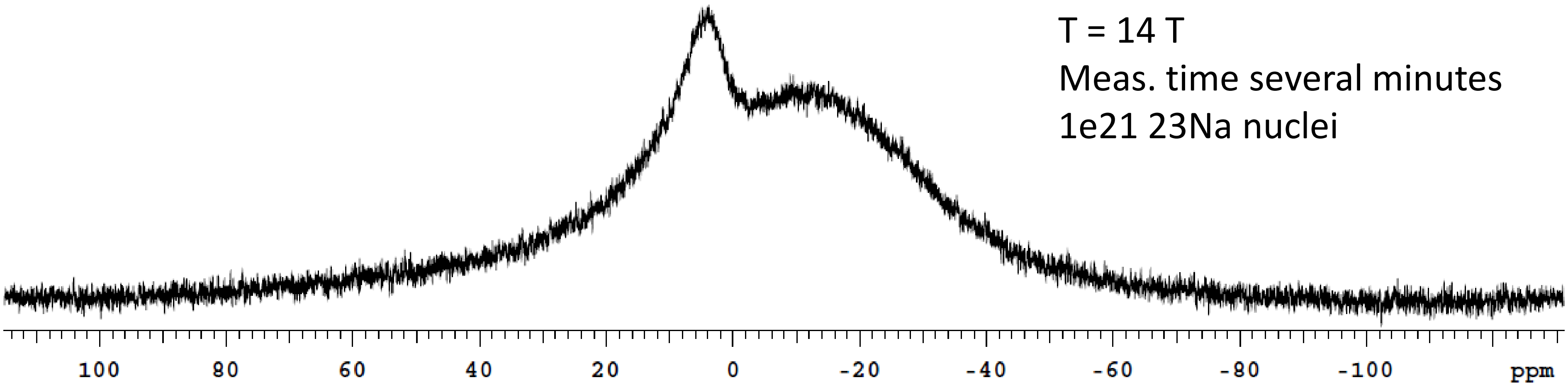
T = 0.5 T
Meas. time, ca 5min
T1 = ca 150 ms

26Na
T1/2 = 1.1 s
I = 3
$\mu = 2.86\ \mu_N$
Q = - 5 mb

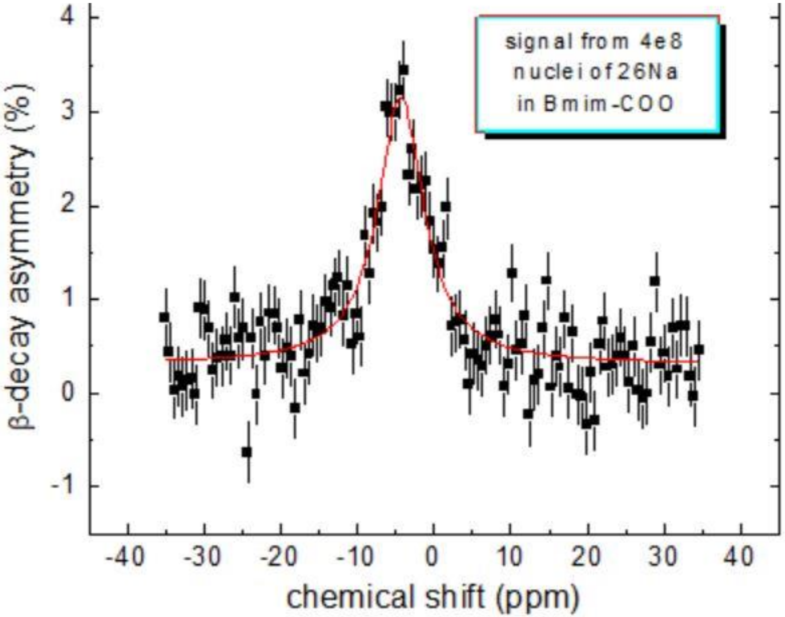
In comparison - 23Na:
I = 3/2
$\mu = +2.21\ \mu_N$
Q = 100 mb
(20x larger!)

Comparison to conventional NMR

- 23Na spectrum in Bmim-Ac ionic liquid (Bmim-COOH study ongoing)

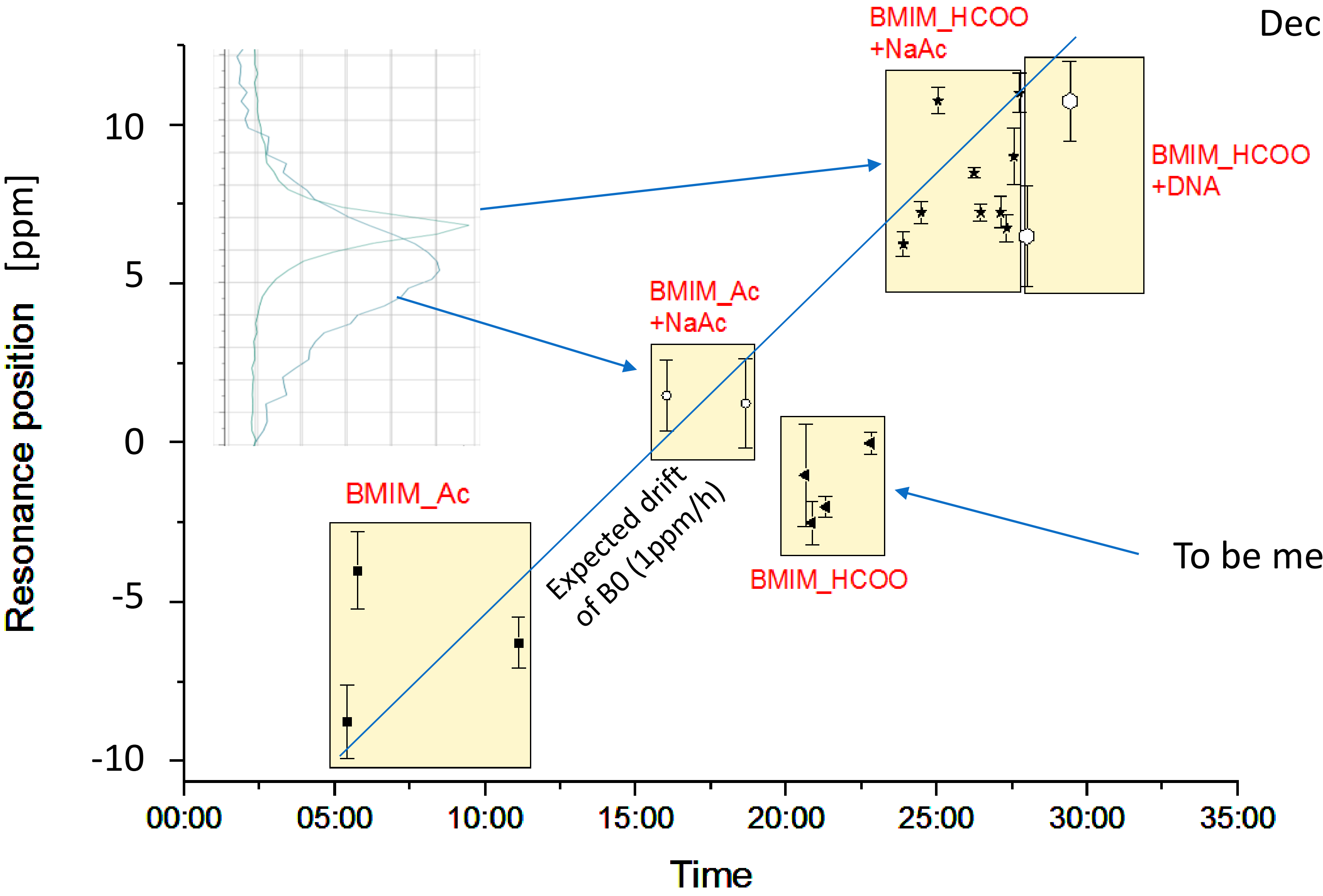


T = 14 T
Meas. time several minutes
1e21 23Na nuclei



Latest results

December 2017

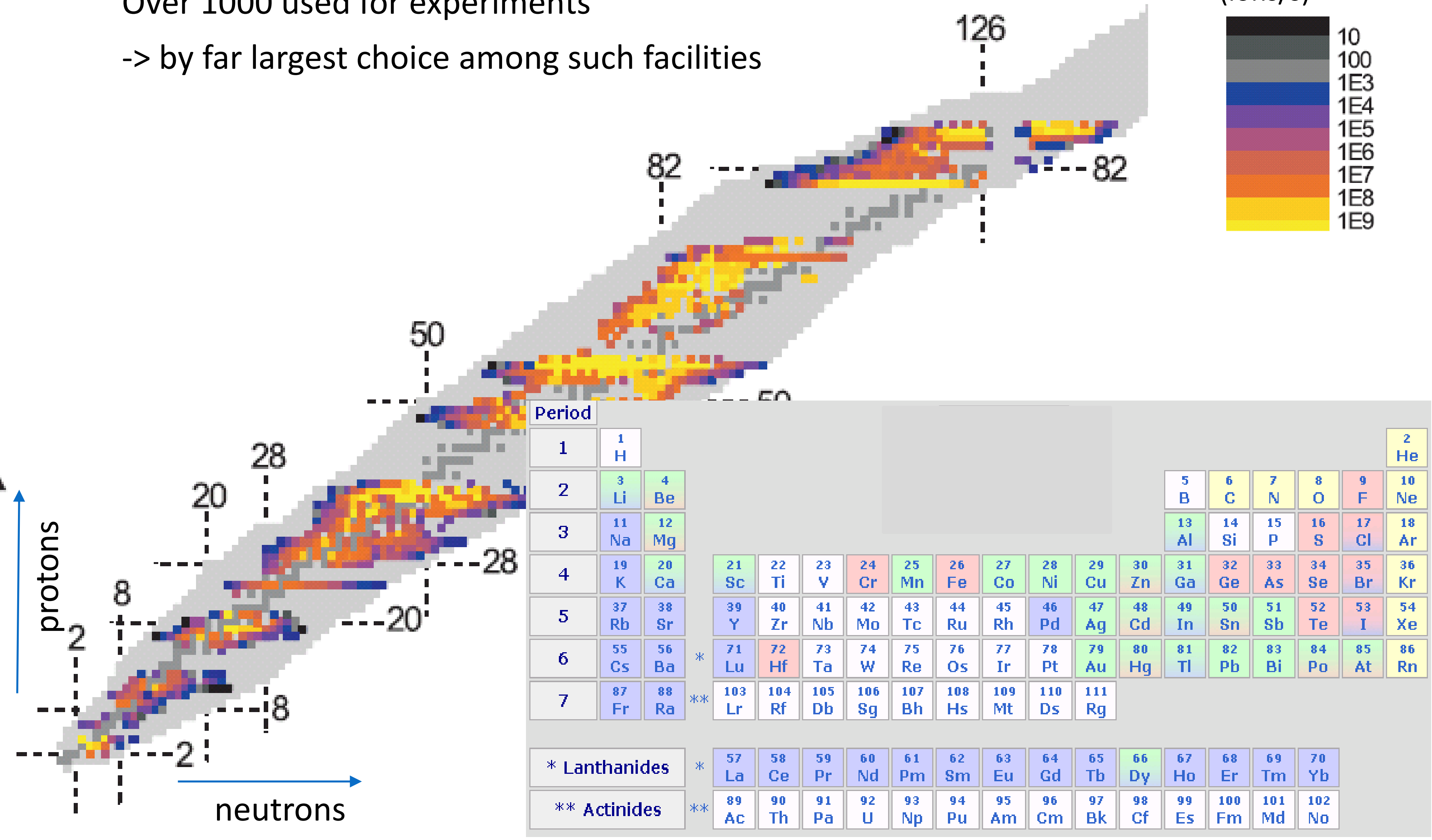


In addition: conventional 23Na studies performed 1.5 weeks ago

ISOLDE radionuclei

Nearly 1300 isotopes available from over 75 chemical elements
Over 1000 used for experiments

-> by far largest choice among such facilities

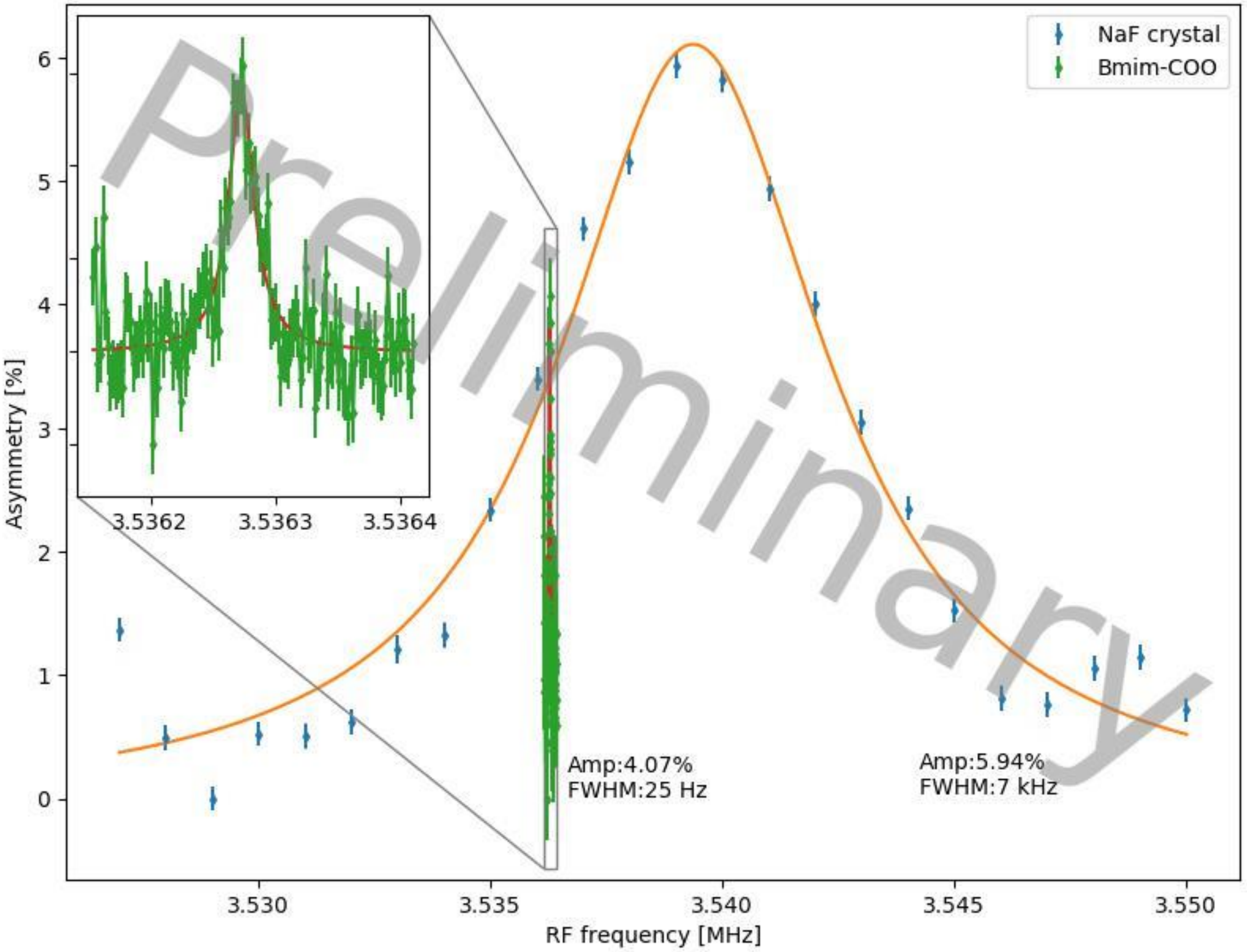


Period																			
1	1 H																		2 He
2	3 Li	4 Be												5 B	6 C	7 N	8 O	9 F	10 Ne
3	11 Na	12 Mg												13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4	19 K	20 Ca		21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
5	37 Rb	38 Sr		39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
6	55 Cs	56 Ba	*	71 Lu	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
7	87 Fr	88 Ra	**	103 Lr	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg							
* Lanthanides			*	57 La	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb		
** Actinides			**	89 Ac	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No		

Results: First Na beta-NMR in liquids

Solvent: ionic liquids (organic salts liquid at 1e-6 mbar vacuum)

Dec 2017



26Na

T1/2 = 1.1 s

I = 3

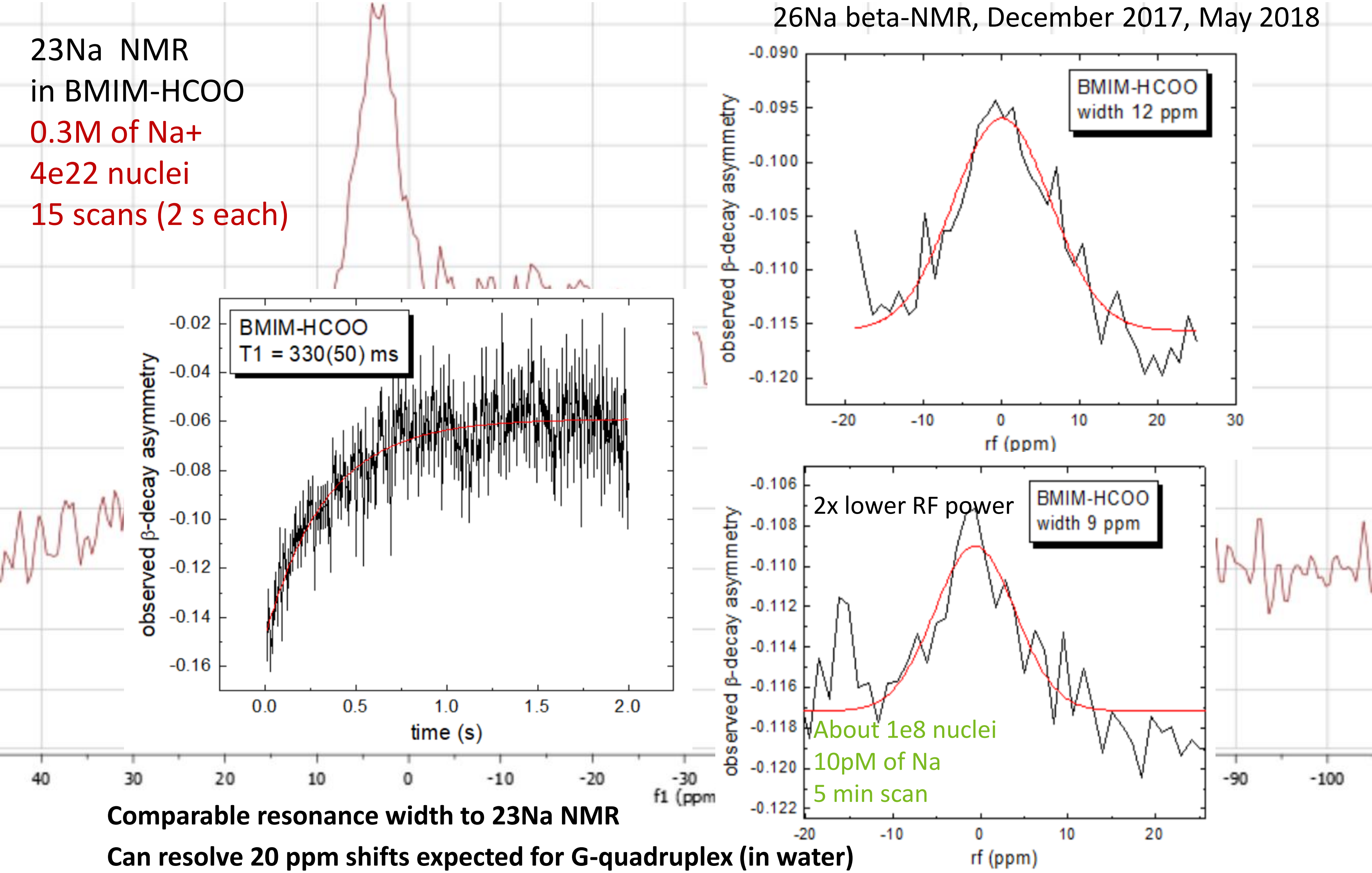
$\mu = 2.86\ \mu_N$

Q = - 5 mb

(20x smaller than 23Na)

Resonance much narrower than in solid samples used for nuclear physics

Conventional 23Na NMR vs 26Na beta-NMR



23Na NMR
in BMIM-HCOO
0.3M of Na+
4e22 nuclei
15 scans (2 s each)

26Na beta-NMR, December 2017, May 2018

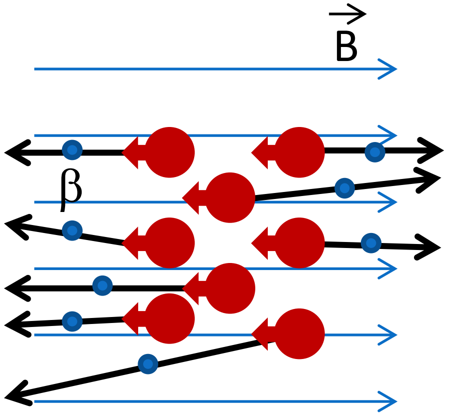
2x lower RF power

About 1e8 nuclei
10pM of Na
5 min scan

Comparable resonance width to 23Na NMR

Can resolve 20 ppm shifts expected for G-quadruplex (in water)

Asymmetry in beta-particle emission



Angular distribution of beta-radiation:

Velocity of beta-particle (v/c close to 1)

Angle between beta-particle emission and direction of spin polarization

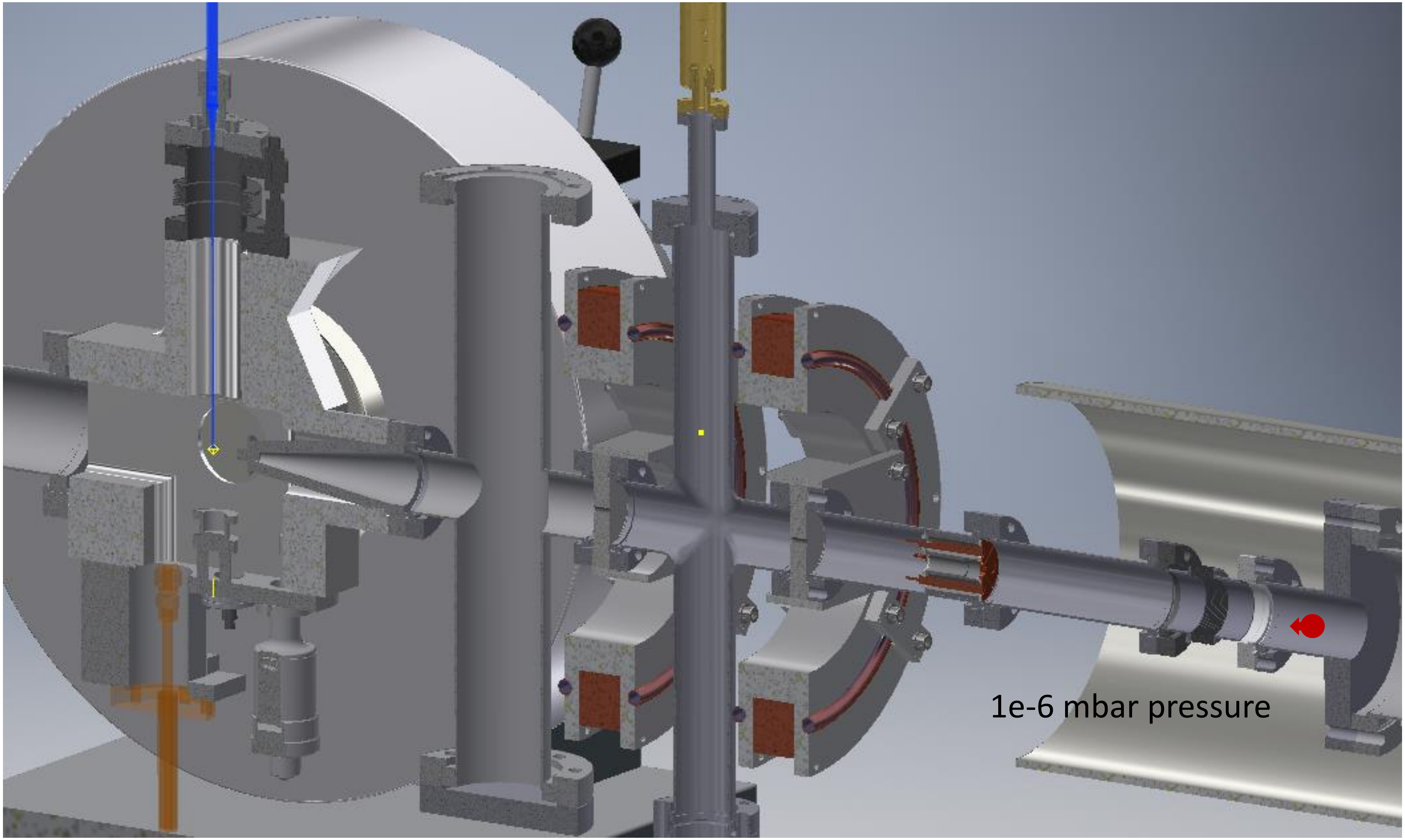
$$D(\Theta) = 1 + a\,\frac{v}{c}\,\frac{\langle I_z\rangle}{I}\cos(\Theta)$$

Asymmetry factor (-1,1), depends on details of beta decay

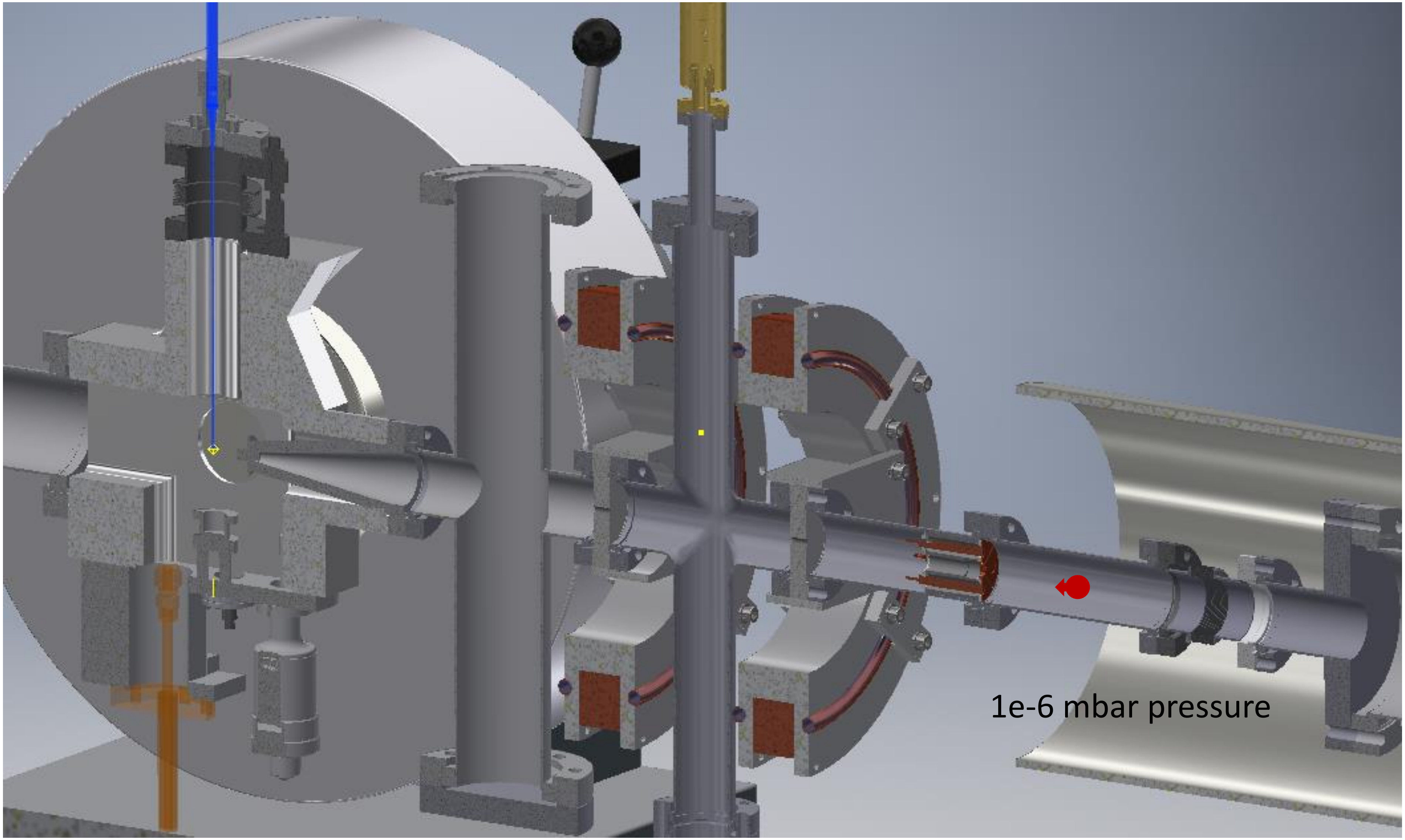
PI (0-100%): degree of spin polarization

Asymmetry factor for β-decay:
-1 for ΔI = -1
$I_i/(I_i + 1)$ for ΔI = +1
$-I_i/(I_i + 1)$ for ΔI = 0 (Gamow Teller)
0 for ΔI = 0 (Fermi)

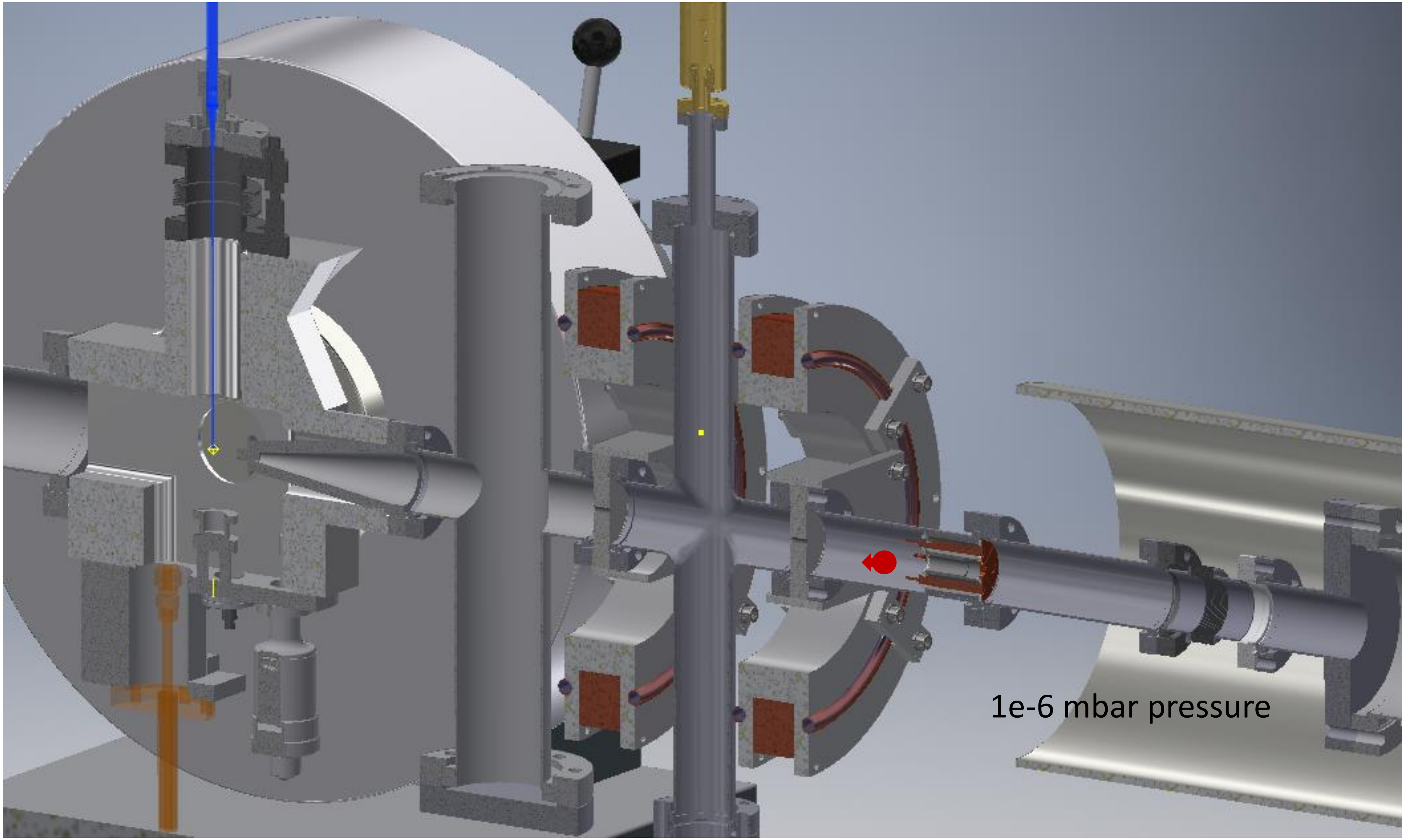
Measured β-decay asymmetry: $A = \frac{N(0°) - N(180°)}{N(0°) + N(180°)} = \frac{N_1 - N_2}{N_1 + N_2}$



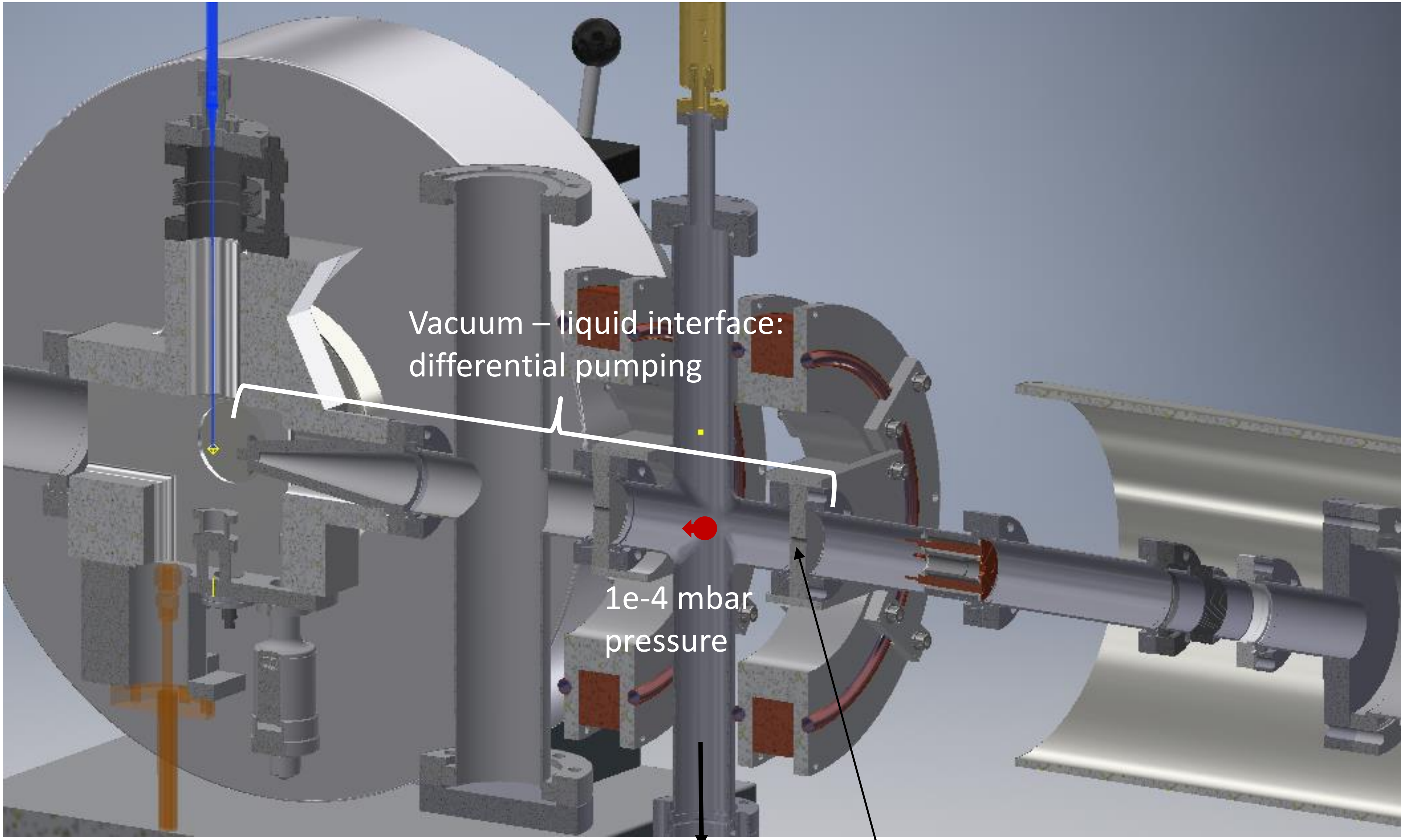
1e-6 mbar pressure



1e-6 mbar pressure



1e-6 mbar pressure

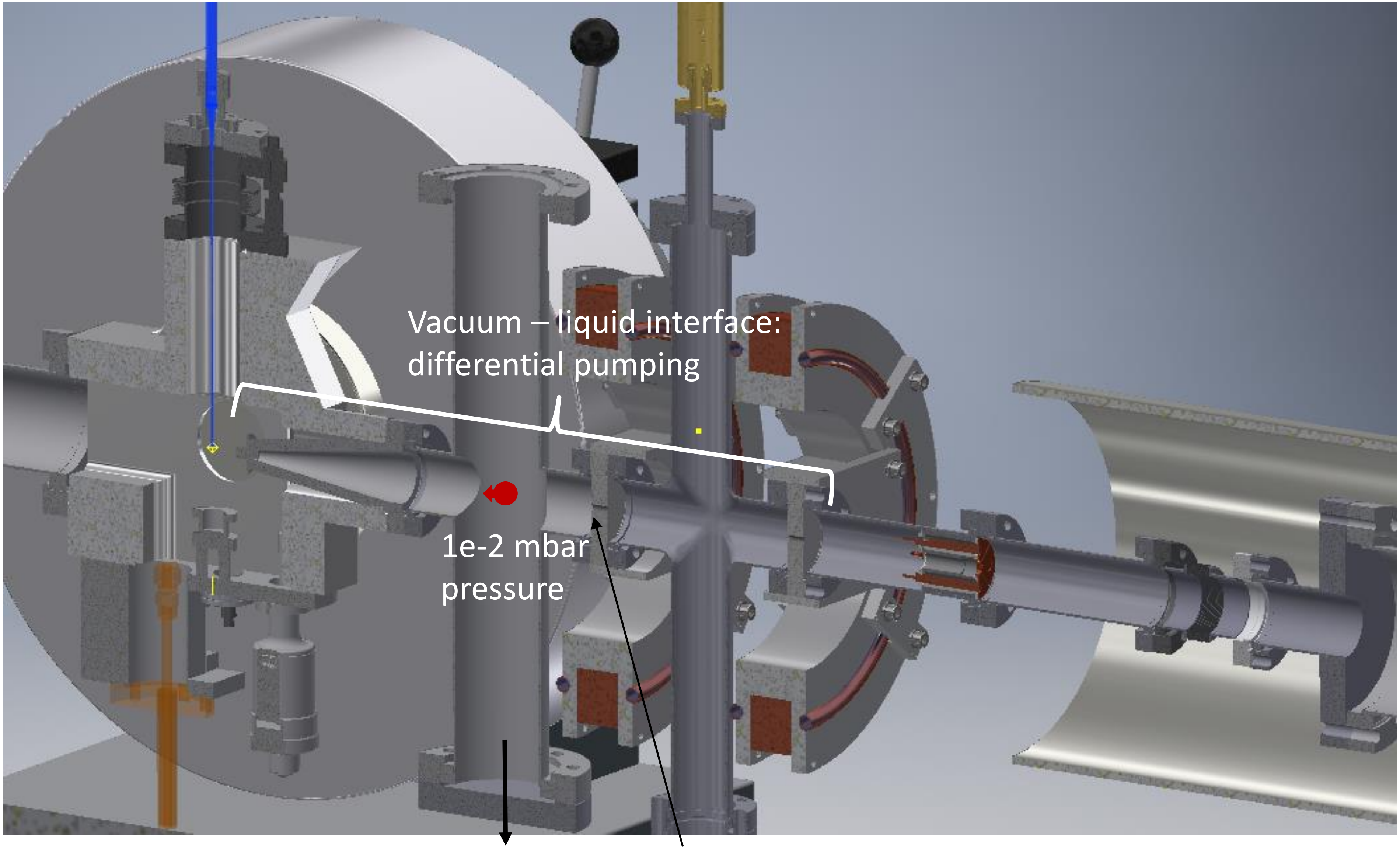


Vacuum – liquid interface: differential pumping

1e-4 mbar pressure

to vacuum pump

3 mm opening

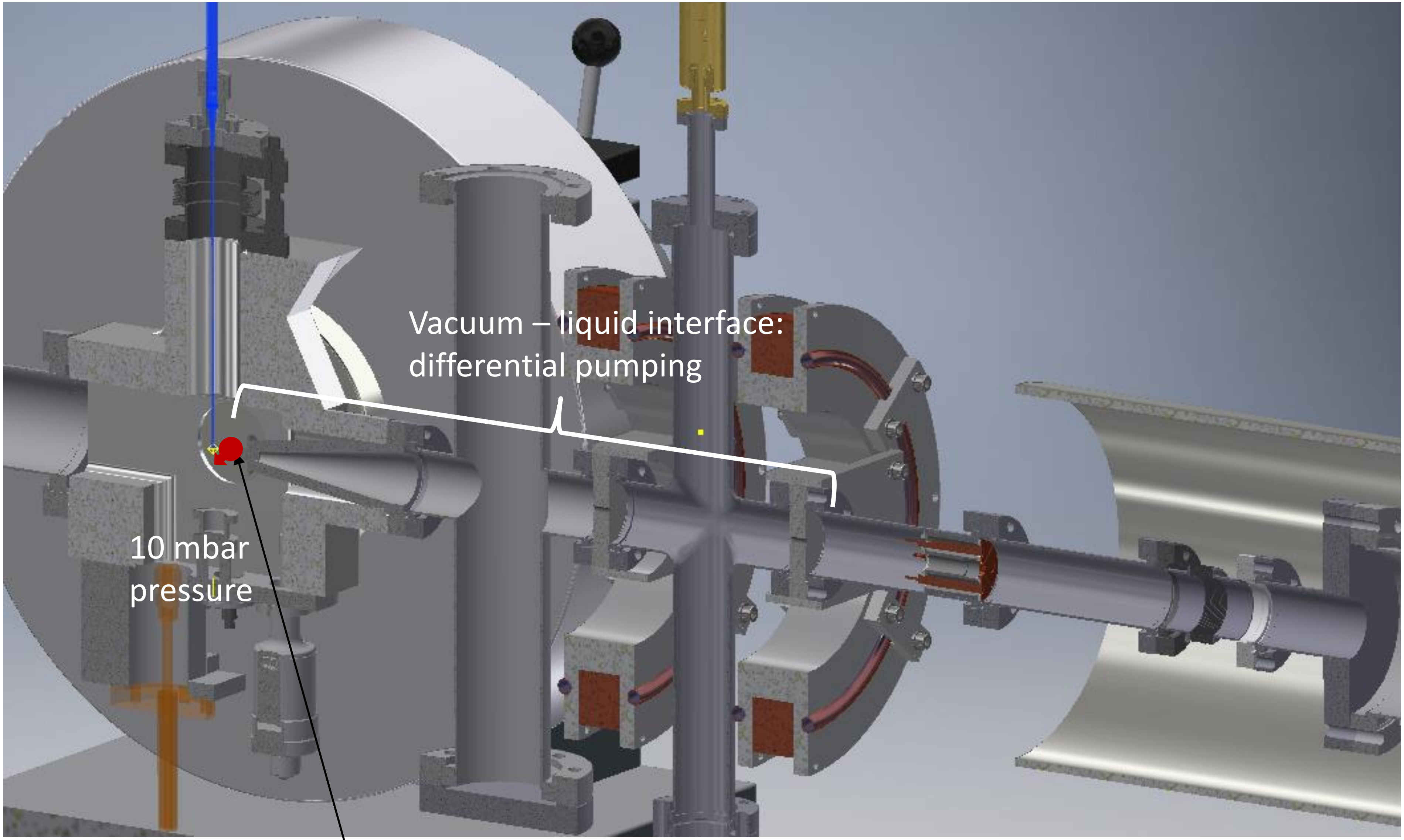


Vacuum – liquid interface: differential pumping

1e-2 mbar pressure

to vacuum pump

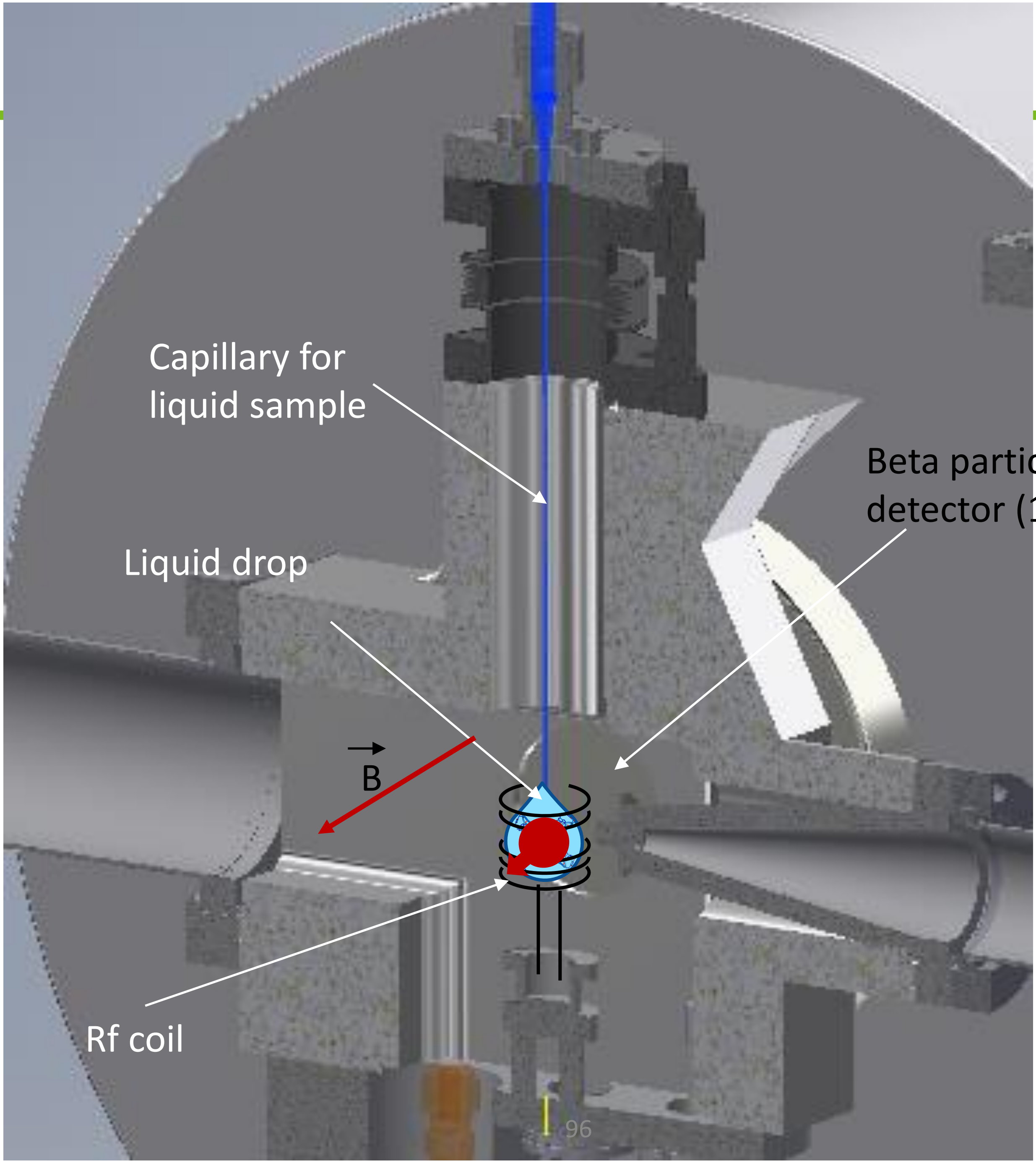
3 mm opening



Vacuum – liquid interface:
differential pumping

10 mbar
pressure

3 mm opening



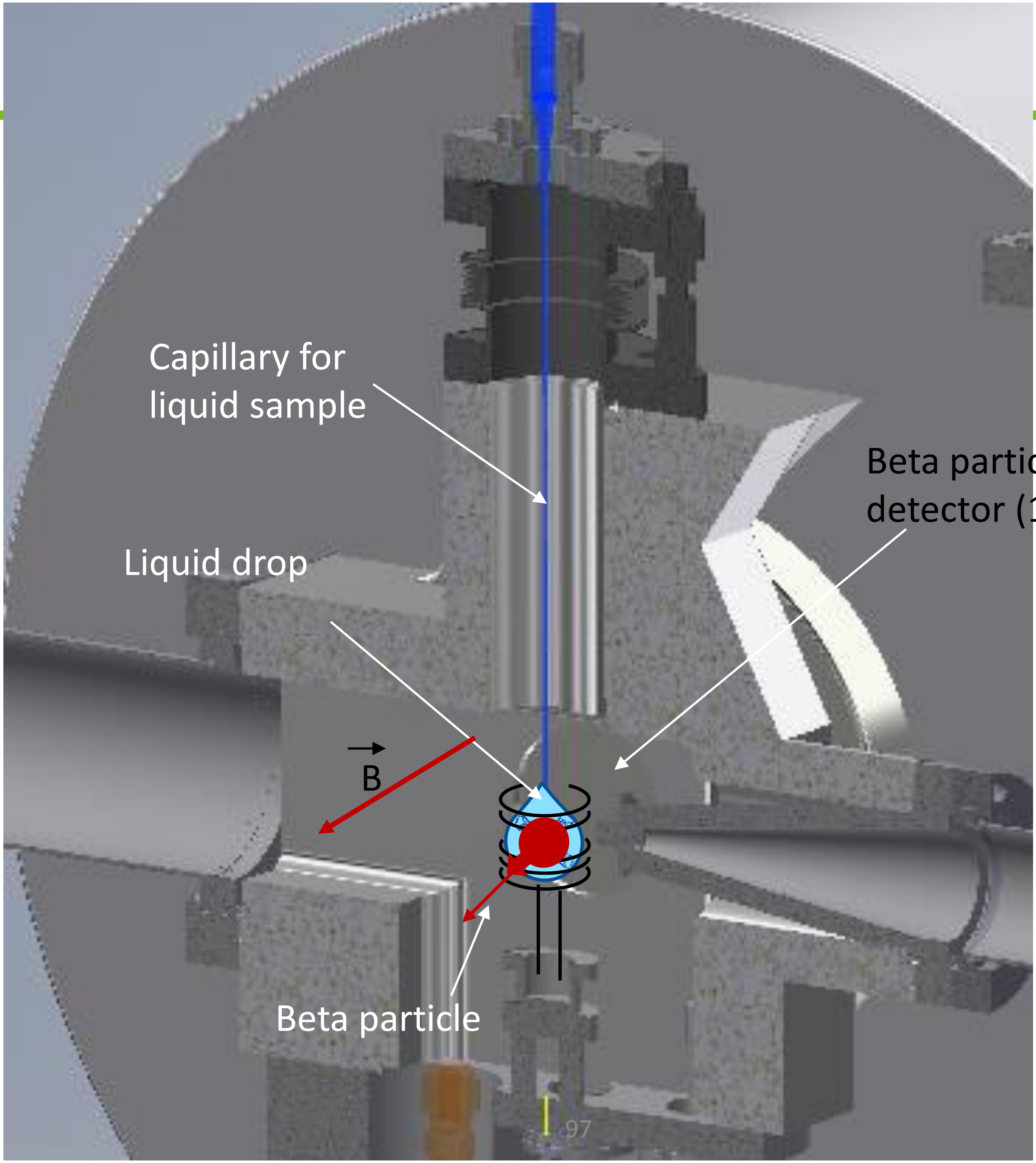
Capillary for liquid sample

Beta particle detector (180 deg)

Liquid drop

$\vec{B}$

Rf coil



Capillary for liquid sample

Liquid drop

Beta particle detector (180 deg)

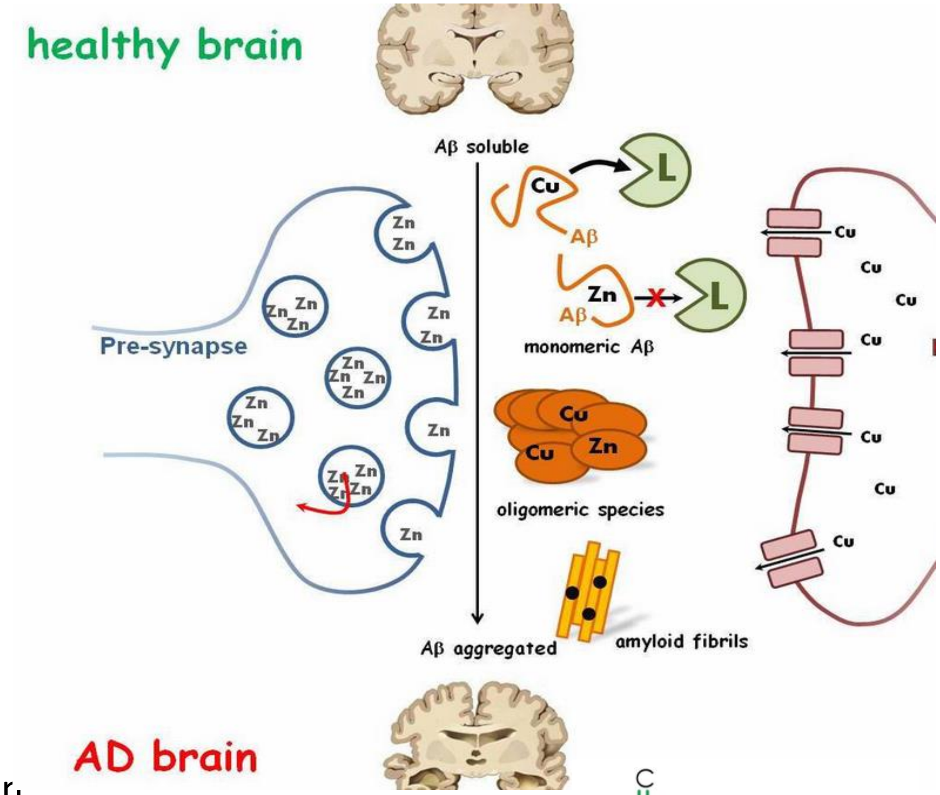
$\vec{B}$

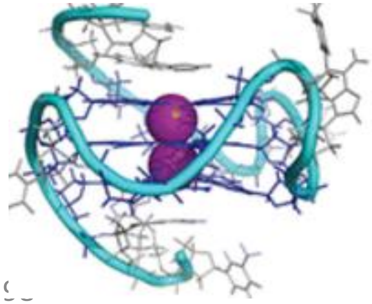
Beta particle

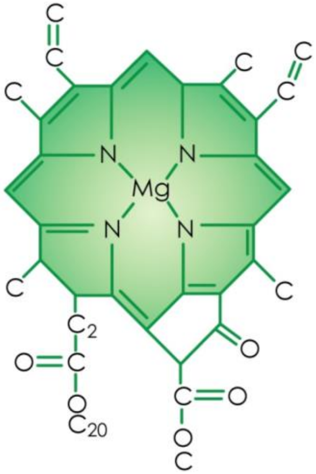
Studying metal ions in biology

- Role of metal ions in human body depends on adopted coordination environment

- Right concentration crucial for correct functioning of cellular processes
    - Na, K: transport of sugars and amino acids into cells; regulate flow of water across membranes
    - Mg: RNA- and DNA-processing enzymes and ribozymes
    - Cu: present in many enzymes involved in electron transfer and activation of oxygen
    - Zn: 2nd most abundant trace element in human body; catalytic and structural role, regulation of genetic message transcription and translation







Probe nuclei

Already polarized at ISOLDE

Nucleus	half-life	spin	magn mom (μ_N)	quadr mom (mb)	beta asym
8Li	0.84 s	**2**	1.65	31	5%
9Li	0.18 s	**3/2**	3.44	-31	
11Be	13.8	**1/2**	-1.68	0	1%
26Na	1.1 s	**3**	2.86	-5	30%
27Na	0.3 s	**5/2**	3.89	-7	30%
28Na	30 ms	**1**	2.43	40	40%
29Mg	1.2 s	**3/2**	0.98	160	3%
31Mg	0.25 s	**1/2**	−0.88	0	8%

Feasible and planned soon

Nucleus	half-life	Nuclear spin	magn mom (μ_N)	Quadr mom (mb)
37K	1.2 s	**3/2**	+0.20	
49K	1.3 s	**1/2**	+1.34	0
39Ca	0.8 s	**3/2**	1.02	+38
51Ca	0.36 s	**3/2**	-1.05	+36
58Cu	3.2 s	**1**	0.57	-150
74Cu	1.6 s	**2**	−1.07	260
75Cu	1.2 s	**5/2**	1.01	-270
75Zn	10 s	**7/2**		
75mZn	5 s	**1/2**		0
77Zn	2 s	**7/2**		
77mZn	1.1 s	**1/2**		0