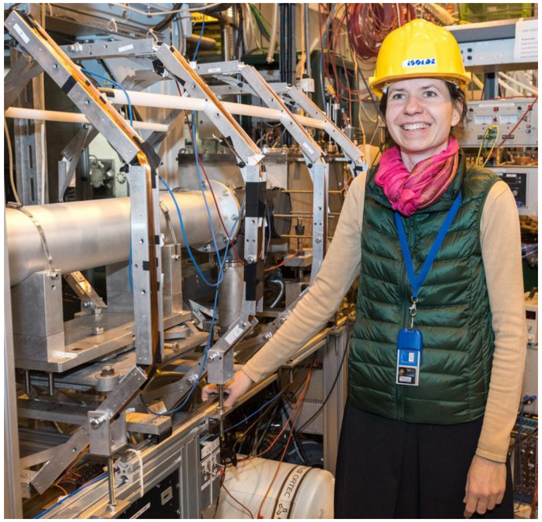
Przyspieszacze, detektory i radioaktywność w medycynie



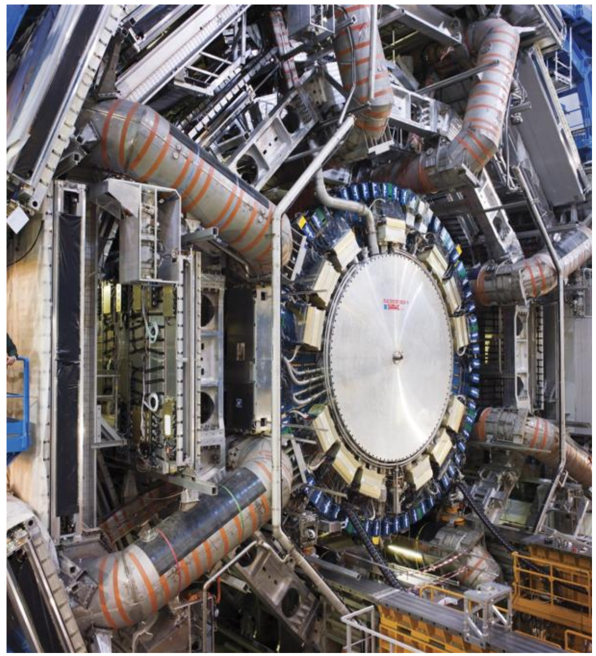
[Sparks! talk on Future of detection and imaging]

Prof. Magdalena Kowalska
CERN i Uniwersytet Genewski

Applications at CERN

- CERN = biggest basic science laboratory in world
- To understand what Universe is made of, requires:

Accelerators



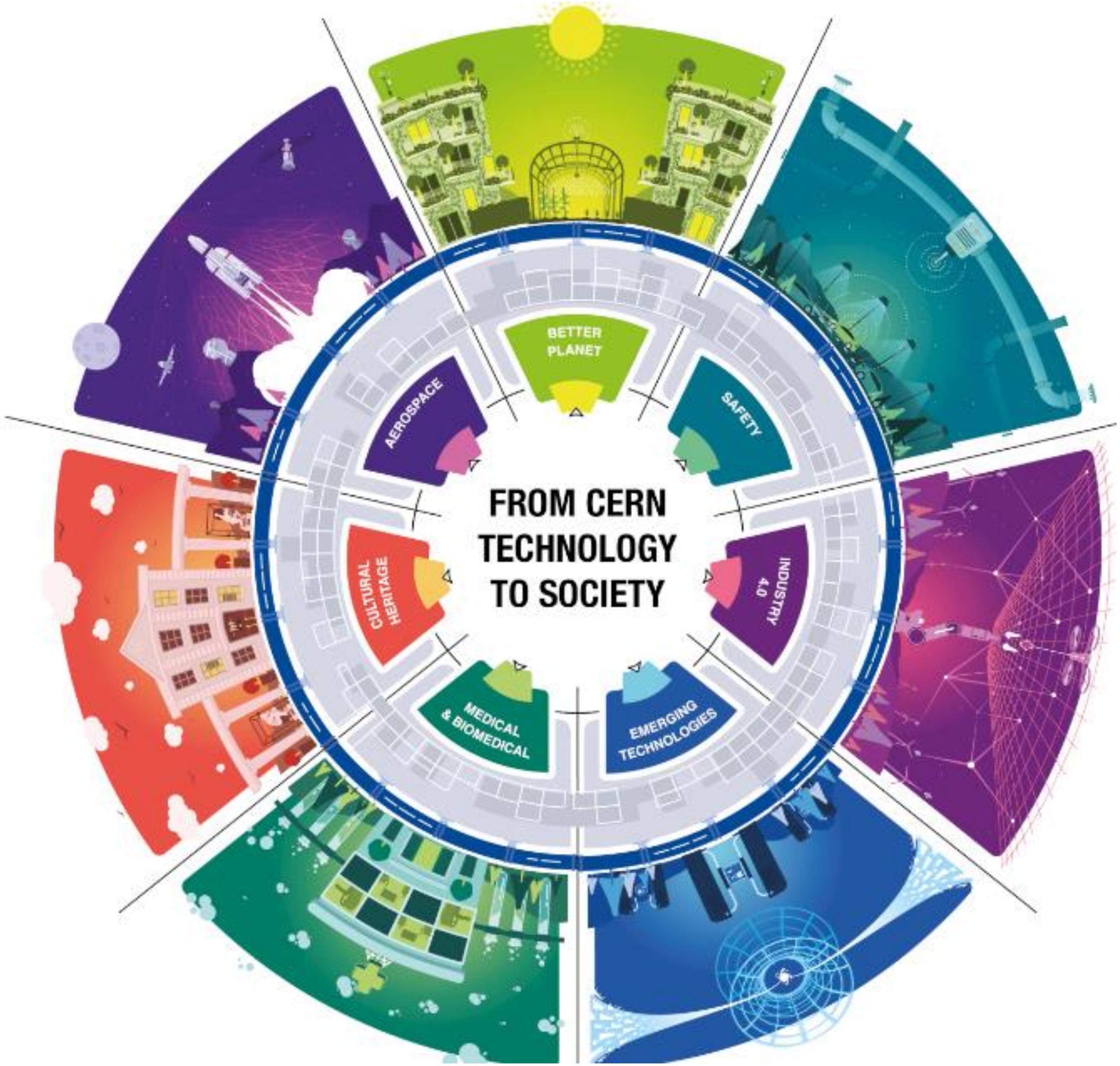
Detectors

Radiation

These tools can be translated into many useful technologies:

CERN technology transfer

- Fields:
  - Aerospace
  - **Healthcare**
  - Digital
  - Environment
  - Quantum



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

From basic science to medical applications

- People doing basic-science research:
  - are also part of society and are interested in medical care
  - often realise that our aims are the same as medical doctors:

- Provide healthcare approaches that are:
  - SMALLER
  - CHEAPER
  - MORE PRECISE
  - MORE SENSITIVE

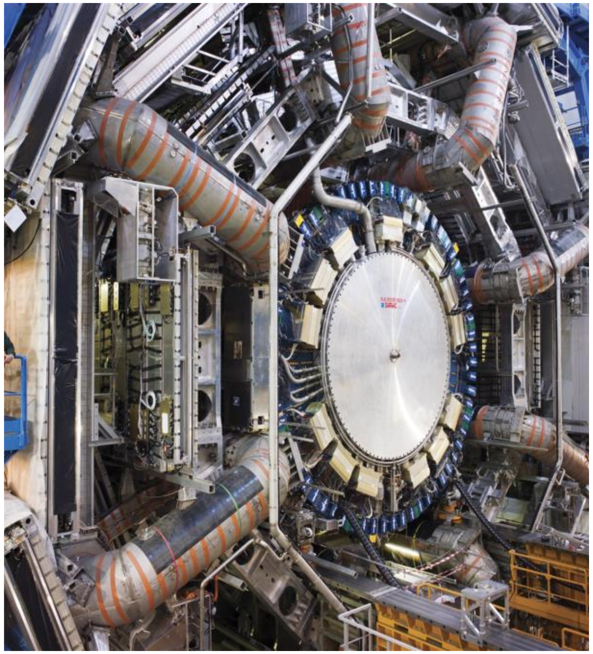
- We just might have a different view of how to achieve:
  - Bring the patient to the machine vs bring/scale the machine to the patient

- Working in interdisciplinary teams is the key for sussess

Medical applications at CERN

- Using CERN tools to improve diagnosis and treatment of diseases:

Accelerators

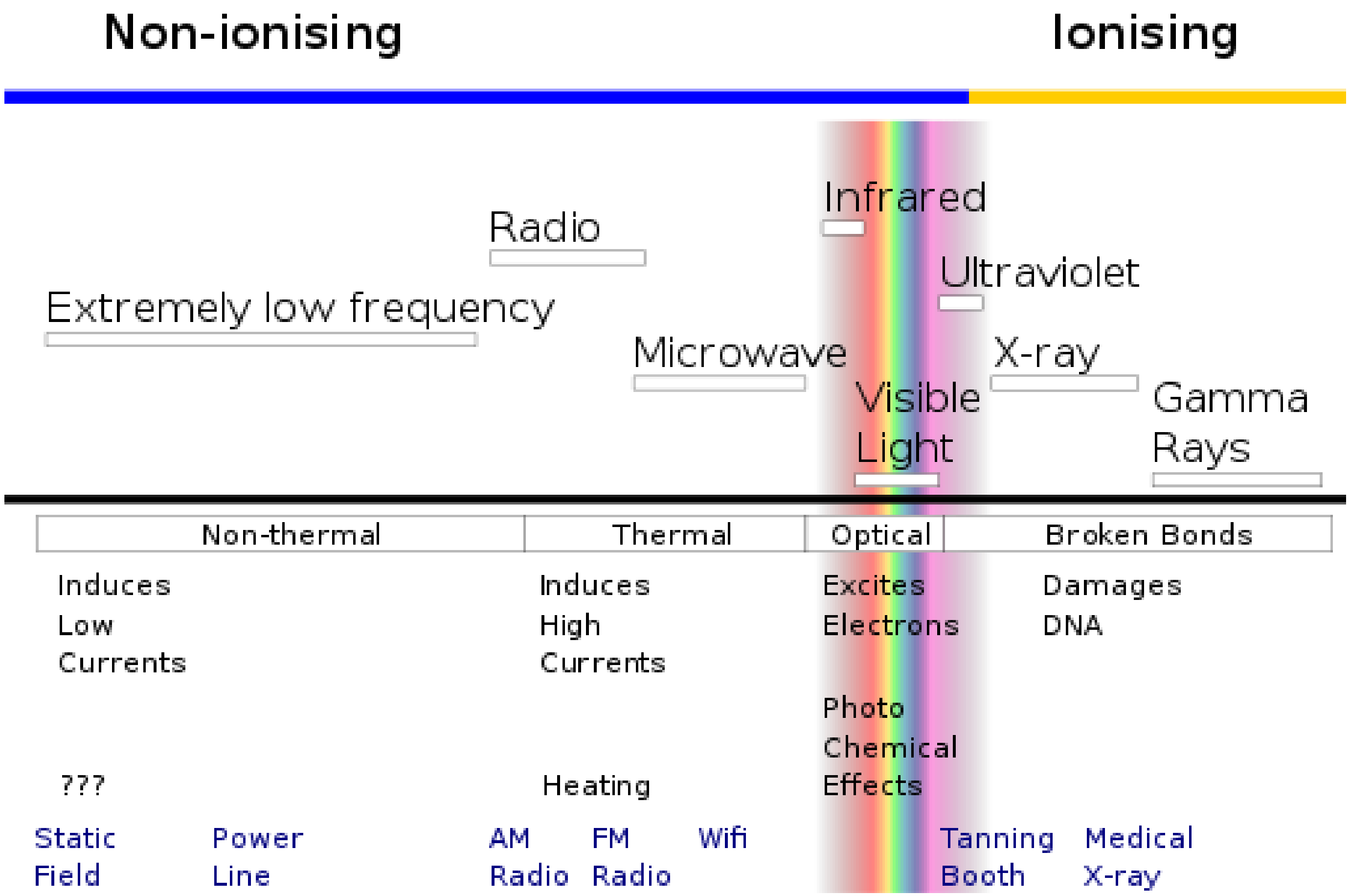


Detectors

Radiation

- Advantages:
  - Sensitive detection of radiation for diagnosis
  - Precise treatment with particles and radiation

Particles and ionising radiation



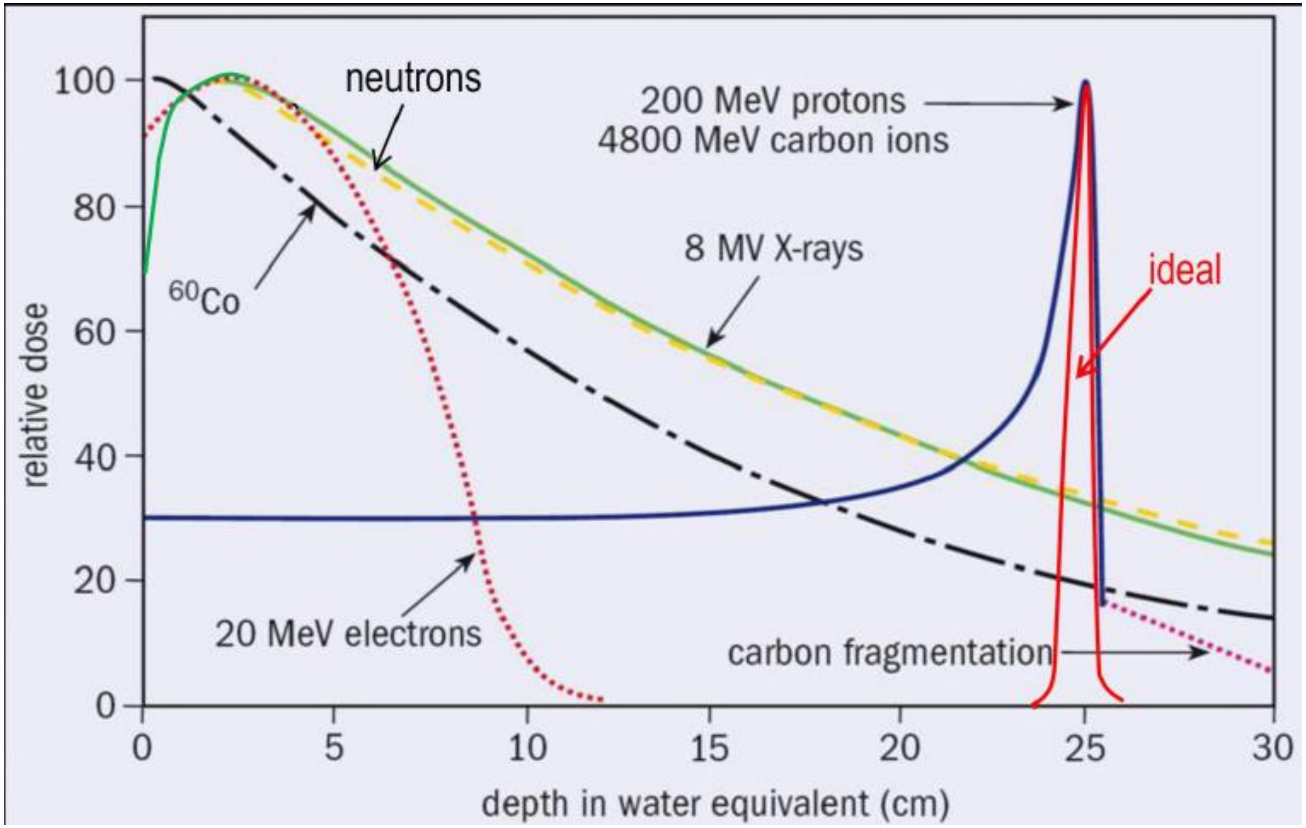
Particles:

- Beta (e- and e+)
- Protons
- ‘heavy ions’ (12C, 16O, in the future – also unstable 11C?)

Accelerators

(Cancer) treatment with external beams

- Energy deposited by radiation and particles in matter:

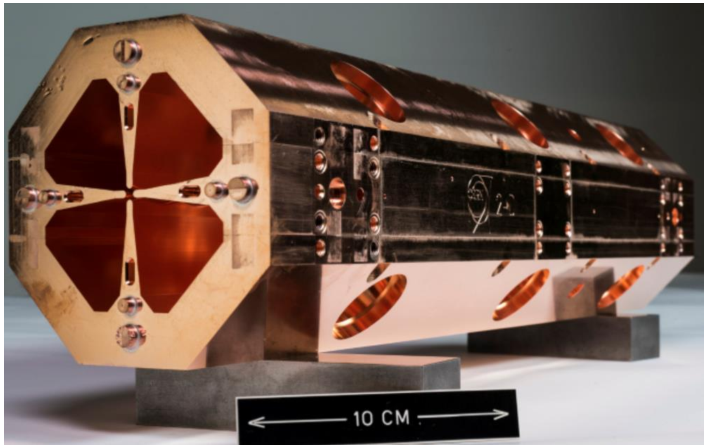


- Approach:
  - Irradiate from several side to maximise dose in volume to be healed (e.g. tumour)
  - Protons and ‘heavy ions’ most selective: most dose at the end of particle’s path

Diagnosis & treatment with accelerators

(CERN) particle accelerators:

- Production of isotopes for PET and SPECT (hospital cyclotrons) for nuclear-medicine diagnosis
- Already used for hadron therapy:
  - Cancer and cardiac-problem treatment with energetic beam of protons, deuterons, and even carbon ions
  - Energy deposited cm inside body, at the end of particle's path



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

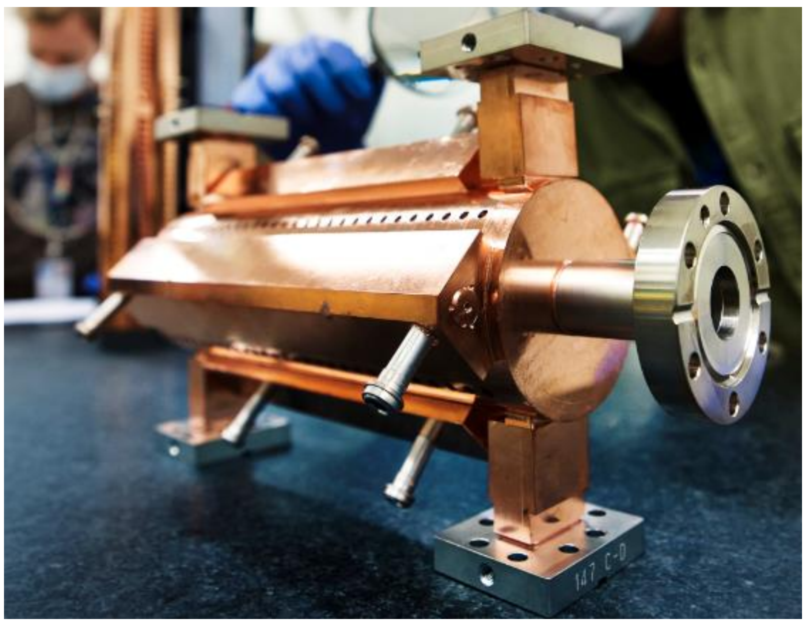
CNAO
The National Center for Oncological Hadrontherapy
Pavia, IT

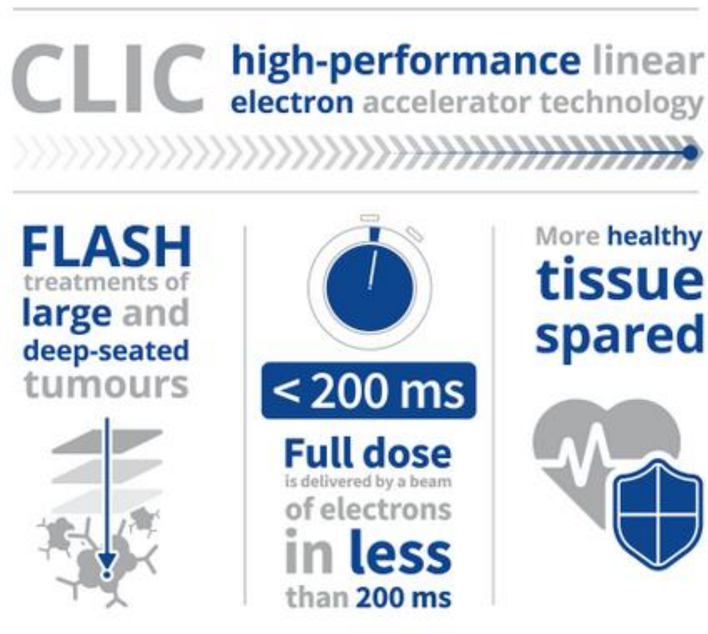
Half of accelerators in the world are used for medical purposes

Diagnosis & treatment with accelarators

Compact electron accelerator:

- Following CLIC (compact linear collider) R&D at CERN
- FLASH: short-pulse electron radiotherapy
- Facility to be built at Lausanne Hospital



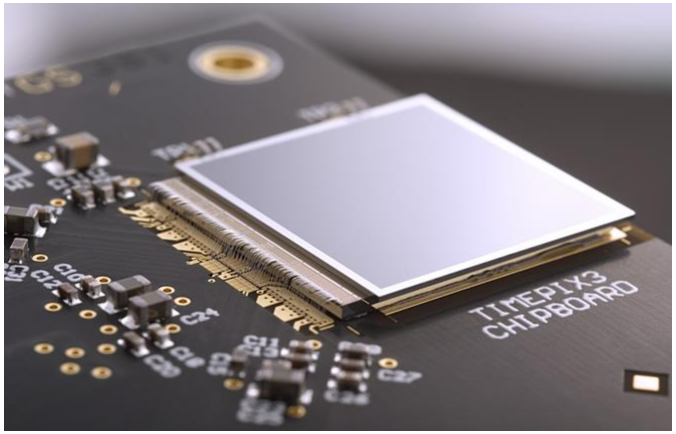


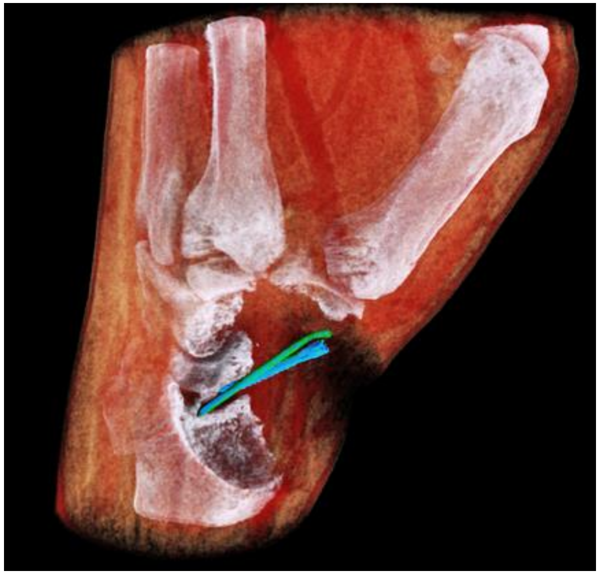
Video: https://videos.cern.ch/record/2295068

Detectors

Diagnosis with photon counting x-ray detectors

- MEDIPIX, TIMEPIX collaboration at CERN
- High-resolution hybrid pixel detectors for particle tracking at LHC
- Applications in many fields
- x-ray photon-counting in CT medical diagnosis:
  - Lower does
  - Higher spacial resolution
  - X-ray energy resolution
- 1st portable CT scanner in Europe in Lausanne



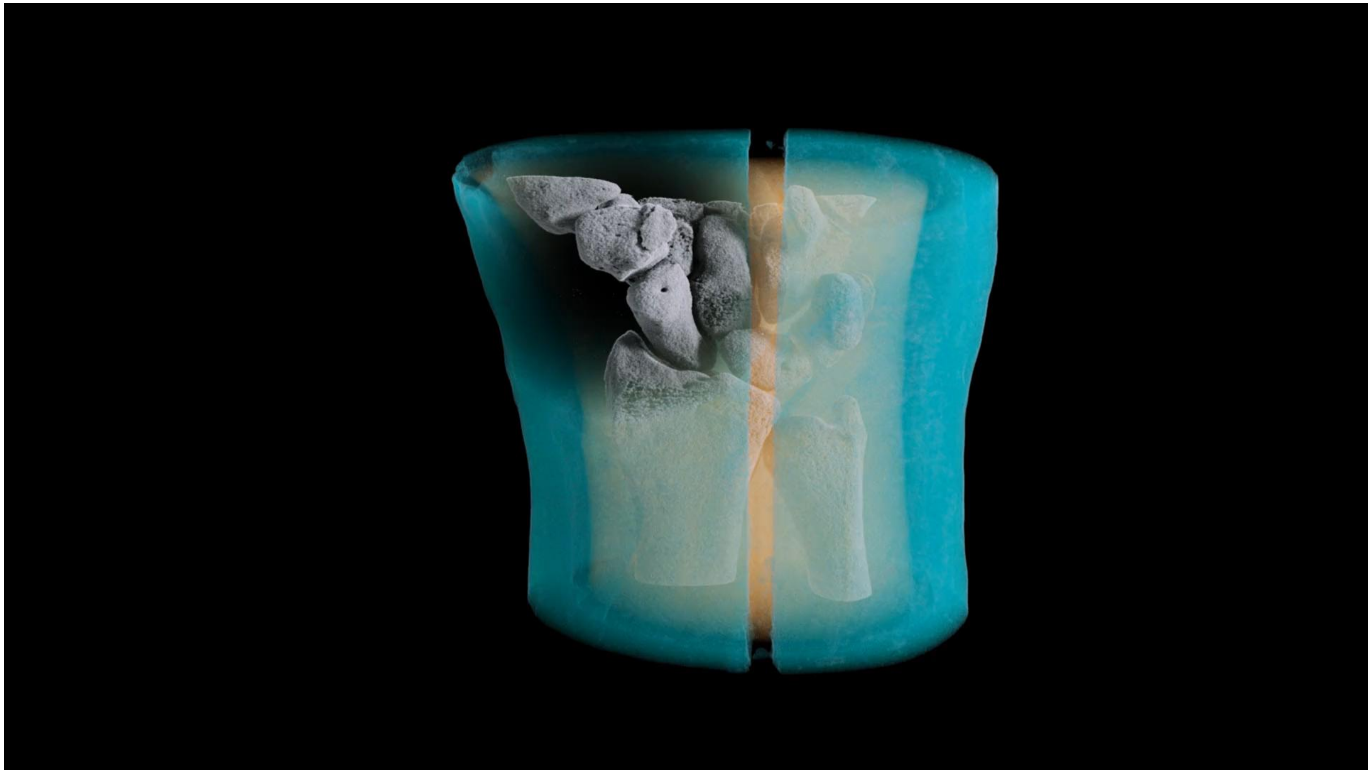


metallic screw (blue), K-wire (green)

Technology transfer e.g. to MARS, New Zealand, and Czechia

Computed tomography with photon counting

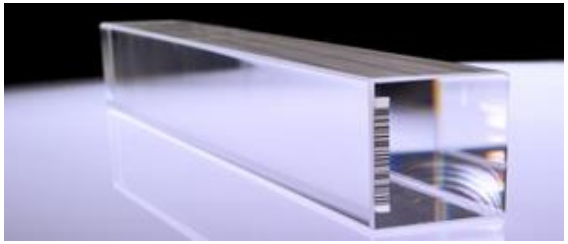
- Wrist image with colour x-ray:



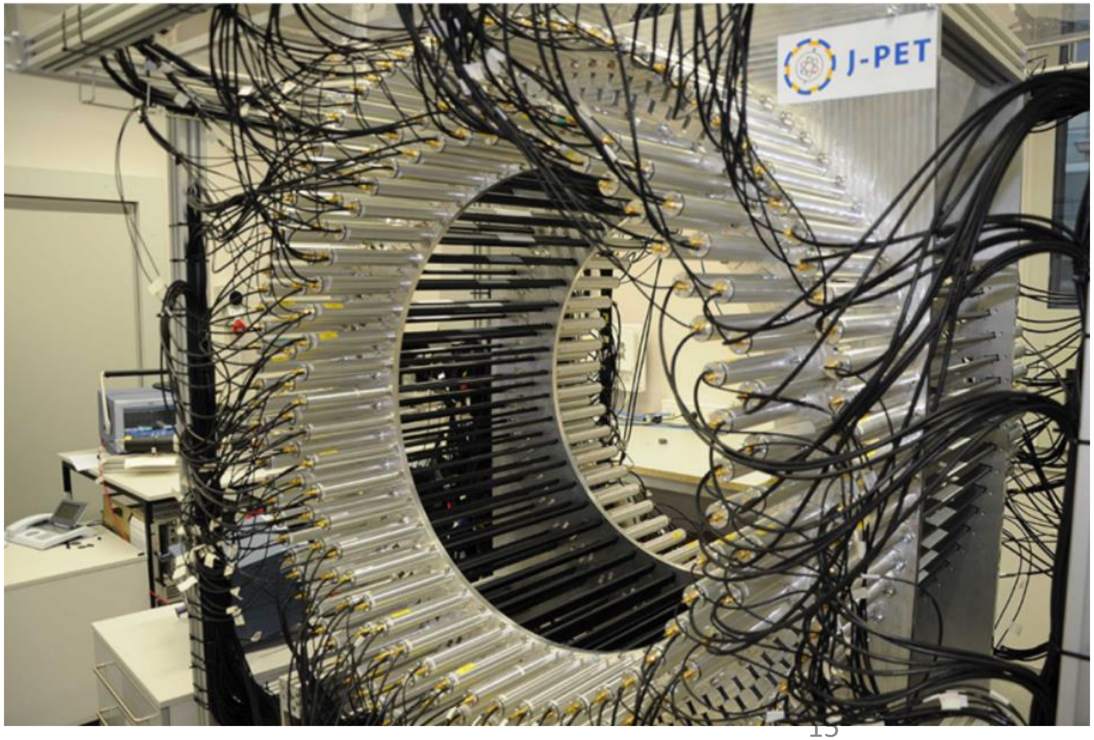
Source: MARS bioimaging

511-keV PET detectors from basic science

- Detectors with ns and ps time resolution - better localisation:
  - As in ATLAS tracer: monolytic Si detector – TT-PET project, Uni Geneva
  - Fast scintillating crystals from CMS: CrystalClear at CERN
  - As in nuclear fast timing: U Complutense Madrid



- Cheaper materials:
  - Organic scintillators: J-PET in Krakow



Radioactive nuclei

Medical diagnosis with unstable nuclei

- Diagnosis with radioactive nuclei:
  - Radioactive nucleus usually connected chemically to a biological ‘ligand’
  - ‘ligand’ finds areas to be diagnosed: sugars go to cells that need energy, e.g cancer
  - Emitted radiation shows the localisation of the interesting region
  - Efficient particle detectors detect very low unharmful nM or pM concentrations

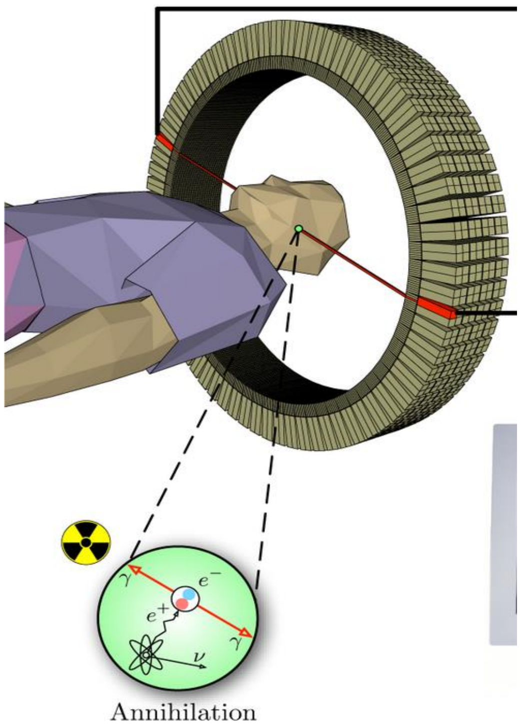
- Suitable isotopes:
  - Isotope of element that can bind to biological ligands
  - Lifetime long enough for delivery and short enough for a body: hours to days
  - Right type of radiation and its energy

- Detection: radiation not particles, because it gets stopped less in the body
  - Gamma rays from decay or annihilation of emitted beta+ particle

- Approaches (nuclear medicine):
  - PET
  - SPECT

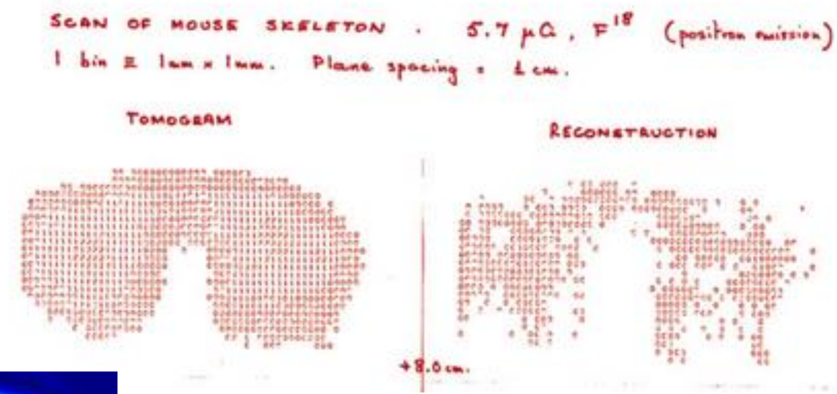
PET: Positron emission tomography

- Signal from beta+ (positron) emitting nuclei
  - Emitted positron stops after travel of some mm in tissue
  - Positron = antimatter, so it annihilates with an electron from a neighbouring molecule (E=mc2)
  - 2 gamma rays of 511keV are emitted at 180 degrees
- Detection:
  - Based on time and position of hits in detectors, place of annihilation is identified



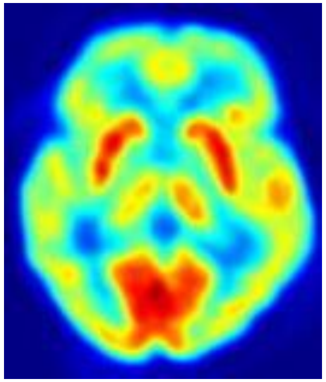
PET and CERN

- PET developed in Geneva Hospital in 1977
  - 1st isotopes were produced at CERN



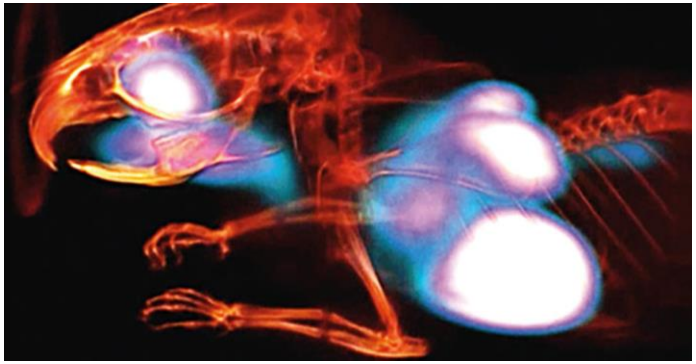
- Detector developments at CERN and around
  - CMS-related activity: CrystalClear
  - Fast response for localizing better
  - Cheaper, more efficient

- Novel PET Isotopes:
  - ISOLDE and MEDICIS (ISOLDE sister)



- Strengths:
  - Extremely sensitive

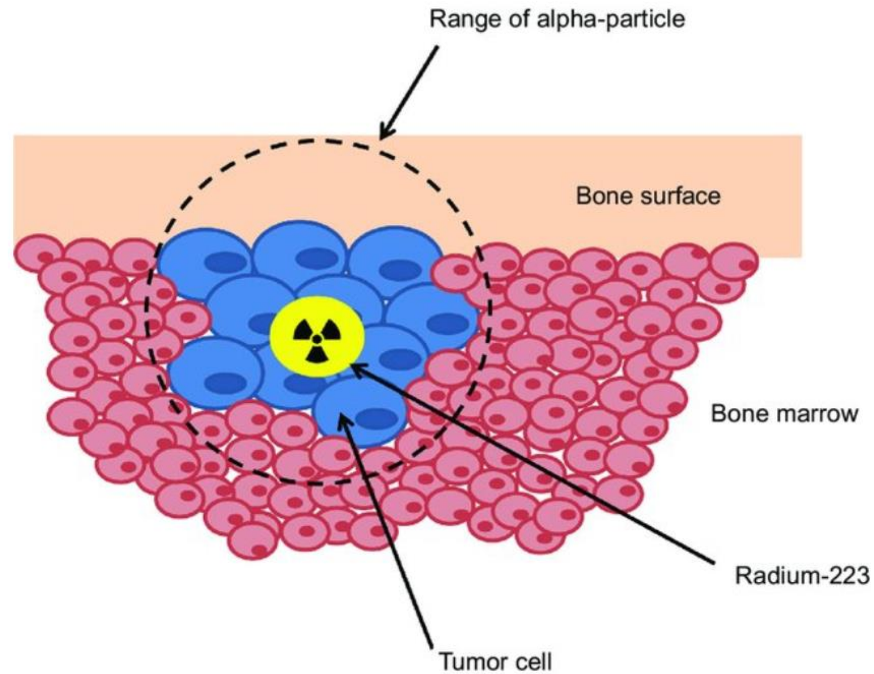
- Relative weaknesses:
  - Time resolution of detectors crucial -> can pinpoint annihilation location better
  - Coincidence between 2 gammas: relatively complex machine and event reconstruction
  - e+ can travel several mm before annihilating: limit in resolution

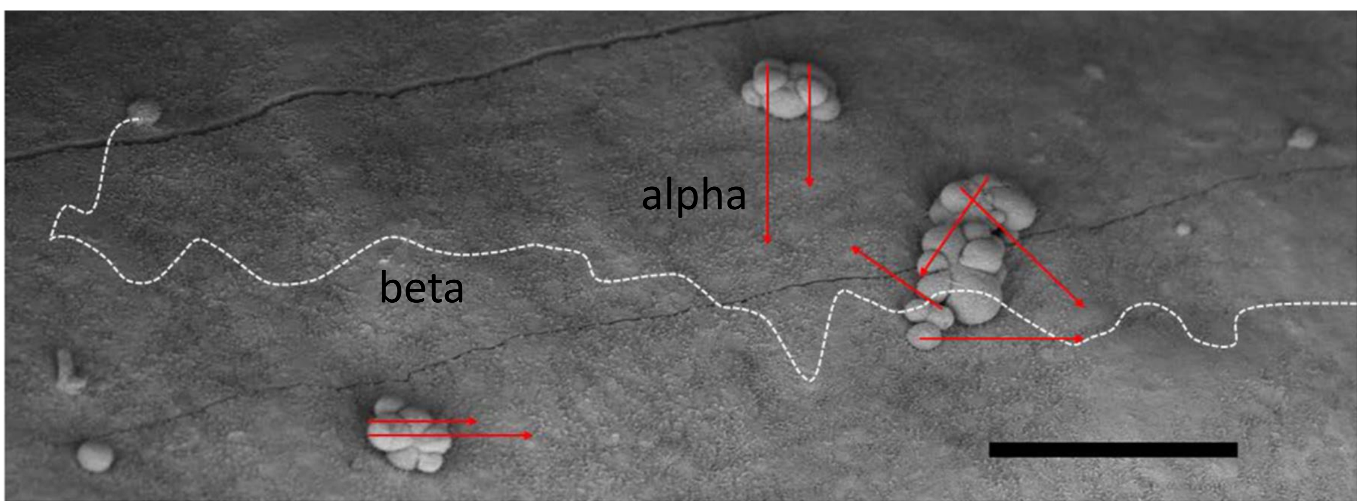


https://home.cern/news/news/knowledge-sharing/forty-years-first-pet-image-cern

Cancer treatment with radionuclei

- Treatment via cell (mostly DNA) damage:
  - High dose beta radiation
  - Alpha radiation: heavier, so shorter range but higher lethality
- Isotope delivery to cancer – as in diagnosis: connection to ligand
- Isotope:
  - Suitable half-life
  - Alpha emission

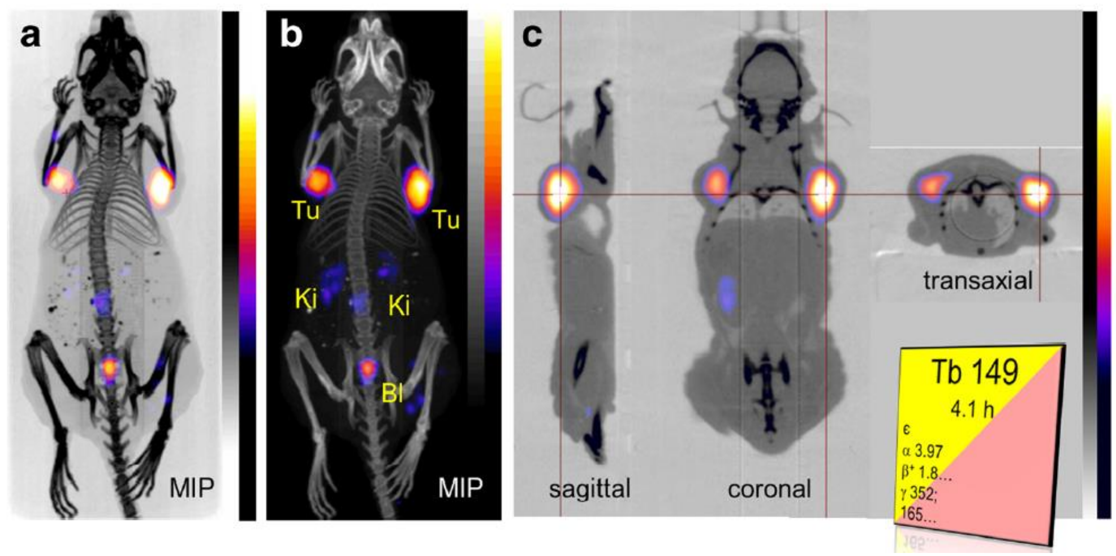


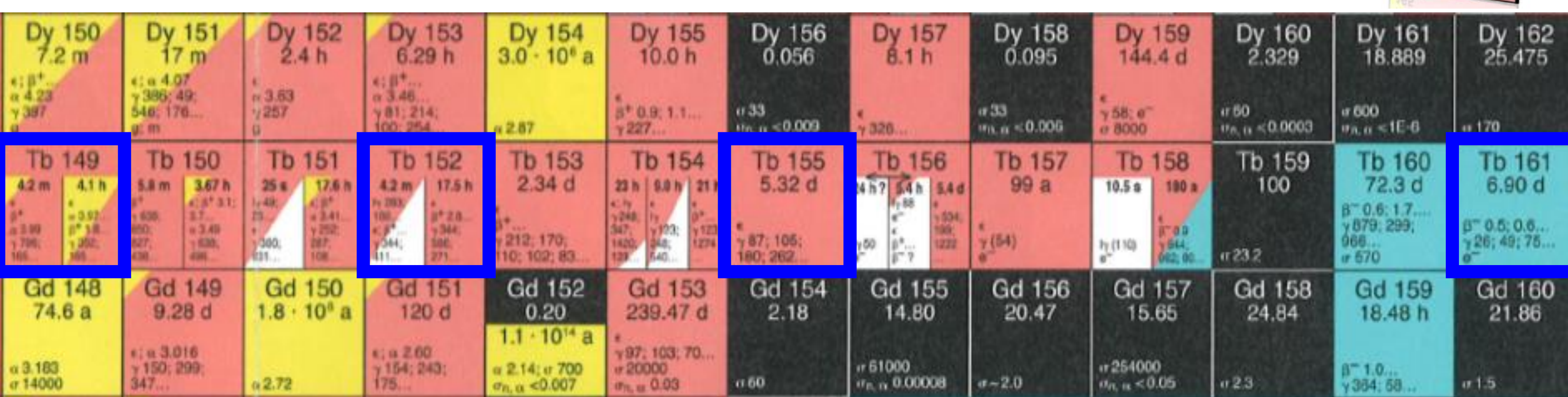


Theranostics with unstable nuclei

- Theranostics = therapy and diagnostics together
  - One isotope does diagnosis (e.g. PET)
  - Another isotope of the same element: treatment
- At ISOLDE and Medicis

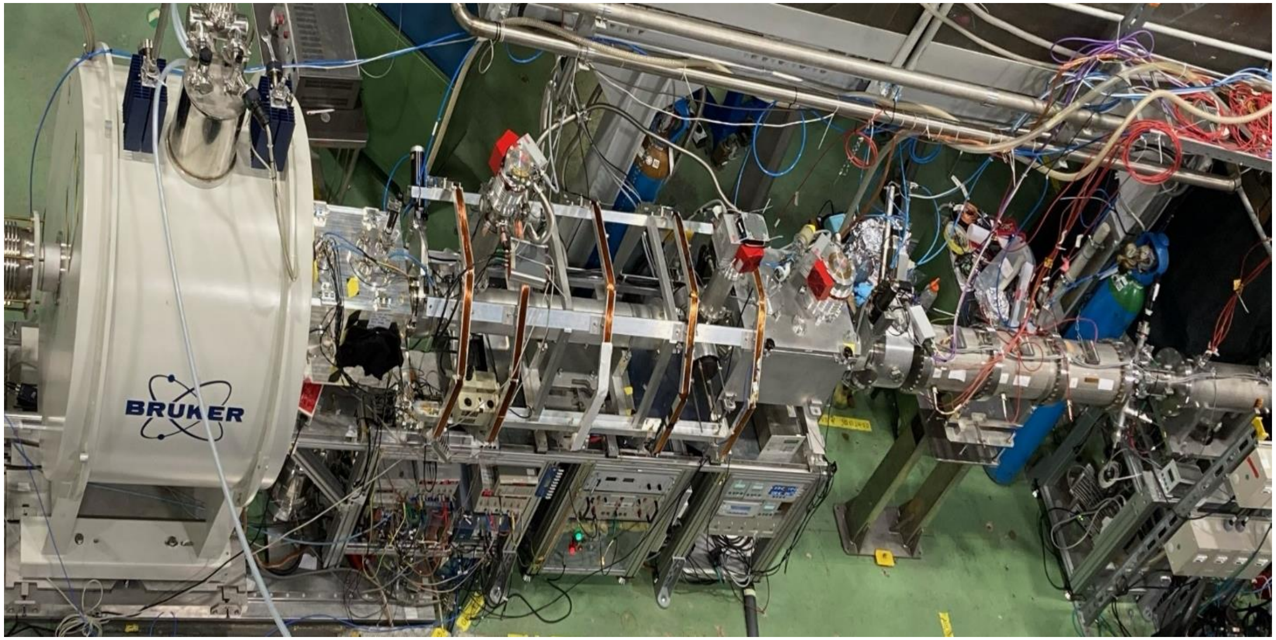
After U. Koster, C Müller et al. 2012 J. Nucl. Med. 53, 1951

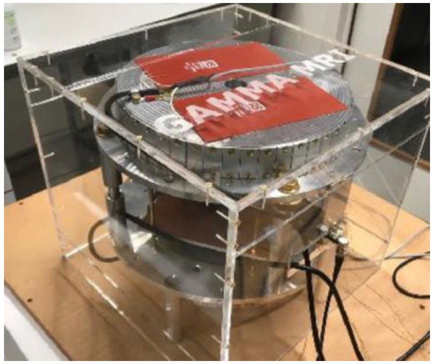




Ultrasensitive magnetic resonance imaging

- My own projects
- Radiation-detected Nuclear Magnetic Resonance (NMR) and Imaging (MRI)
  - Use of unstable nuclei
  - Signal detection via direction of radiation, not signal pickup in a coil
  - Up to 10^{10} more sensitive than conventional NMR
- Interdisciplinary team
  - Collaboration (e.g. with AMU Poznan)
  - Applications in different fields





Beamline at ISOLDE

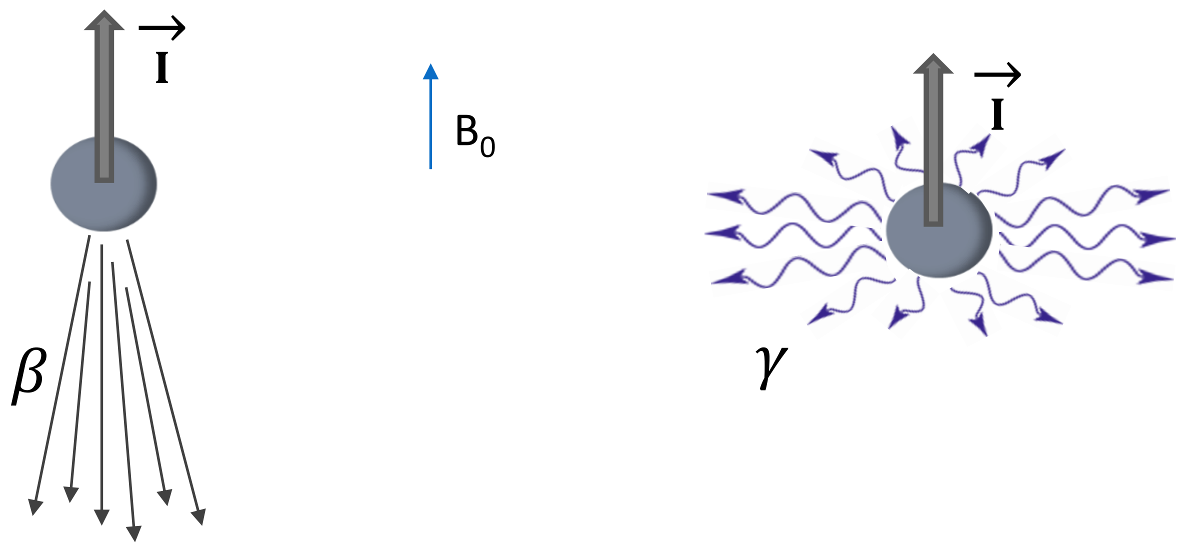
Why are polarized radio-nuclei special?

- **Their beta and gamma decay is anisotropic in space**

Beta decay, I>0

Gamma decay, I>1/2

Parity non-conservation of weak interaction, Mme Wu experiment

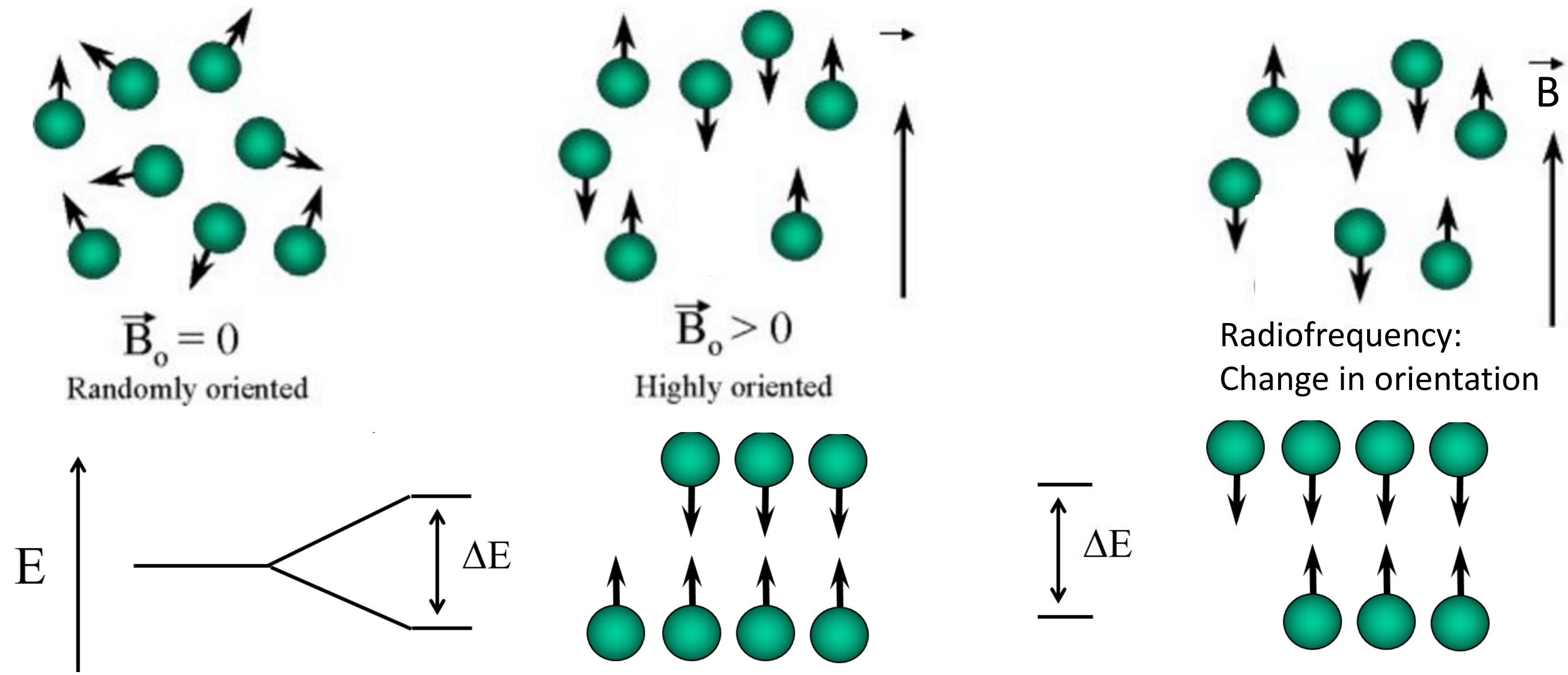


depend on degree and order of spin polarization and transition details (initial spin, change of spin)

- Observed decay asymmetry can be used to perform sensitive Nuclear Magnetic Resonance

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)



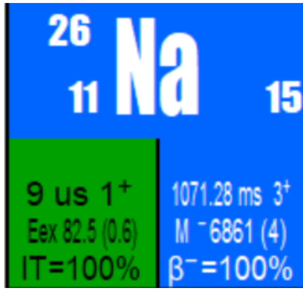
Larmor frequency in magnetic field is shifted by environment (electrons in molecules)

Radiation-detected NMR in liquid samples

betaDropNMR

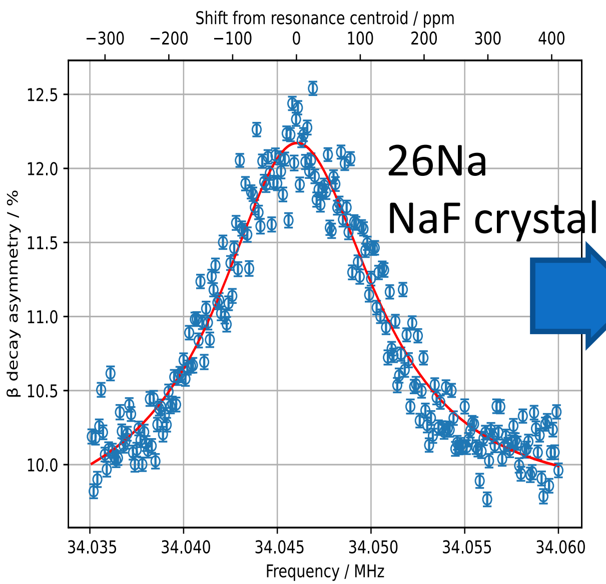
Beta-radiation detected NMR in liquids

- NMR: part per million shift in Larmor frequency due to direct environment of probe nucleus
- Up to billion times higher sensitivity than conventional NMR (down to 1e6 nuclei)
- much narrower resonances than in solids: 10^2-10^3 higher precision (part-per-million)



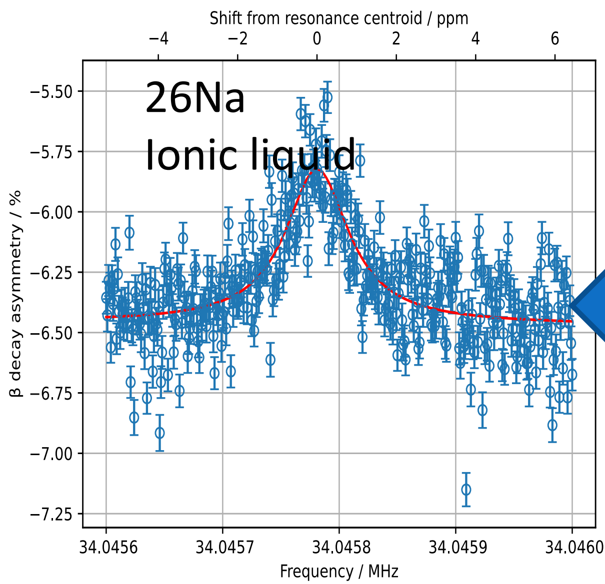
Can address chemical elements and samples inaccessible in conventional NMR

E.g metal-ion interaction with biomolecules



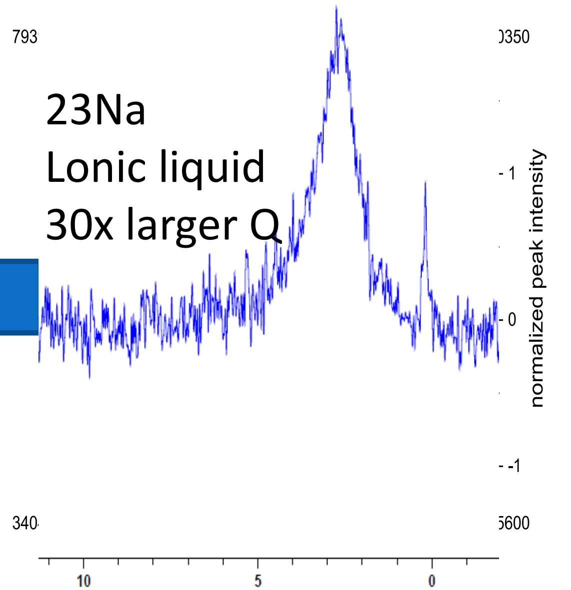
^{26}Na β-NMR in a NaF crystal

1e7-1e8 Na nuclei in sample



^{26}Na β-NMR in an ionic liquid

1e7-1e8 Na nuclei in sample



Conventional NMR scan of ^{23}Na (black)

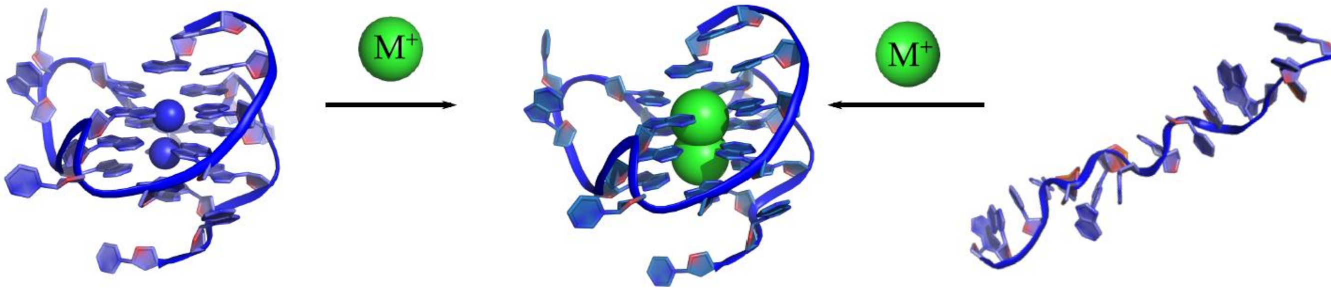
1e19 Na nuclei in sample

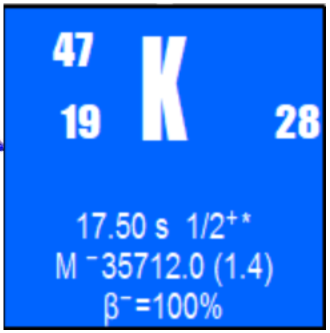
Harding, ..., Kowalska, Phys. Rev. X., 10, 041061 (2020)

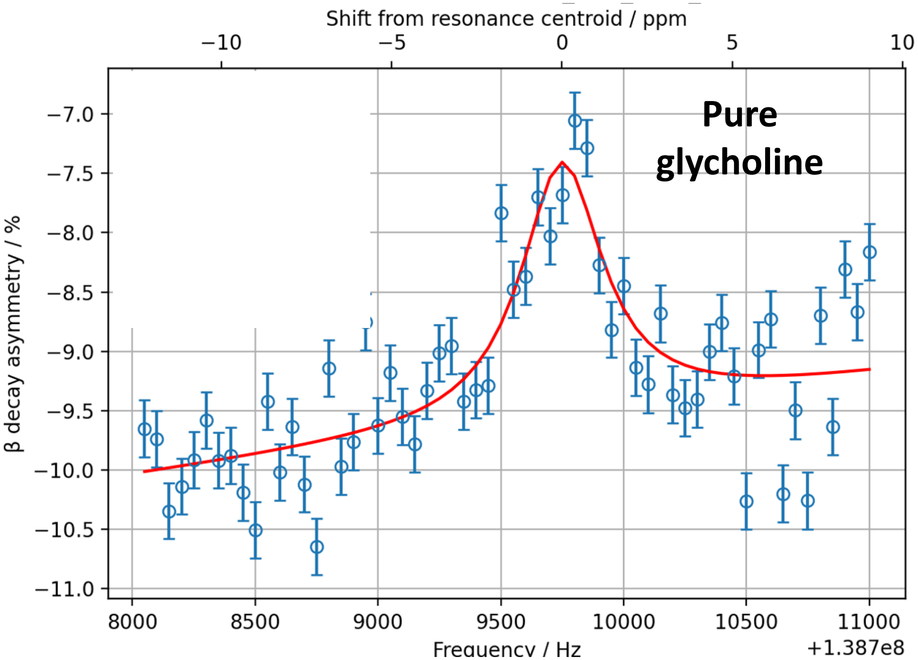
Potassium binding to DNA G-quadruplexes

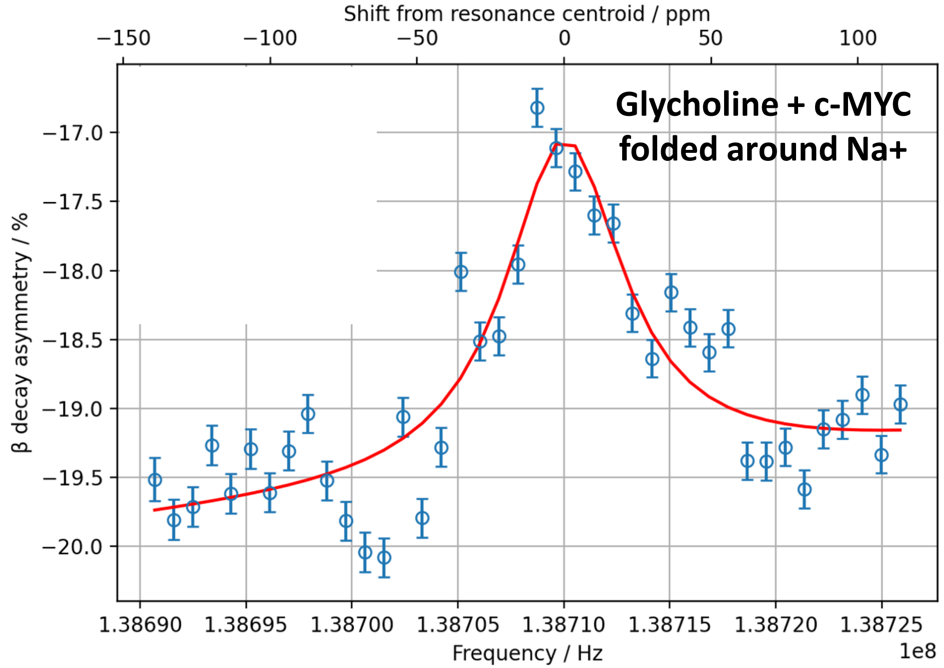
B. Karg

- G-quadruplexes:
  - present e.g in telomers, crucial: binding to alkali metals
- β-NMR experiments in 2022: ^{47}K implanted into glycholine DES + DNA





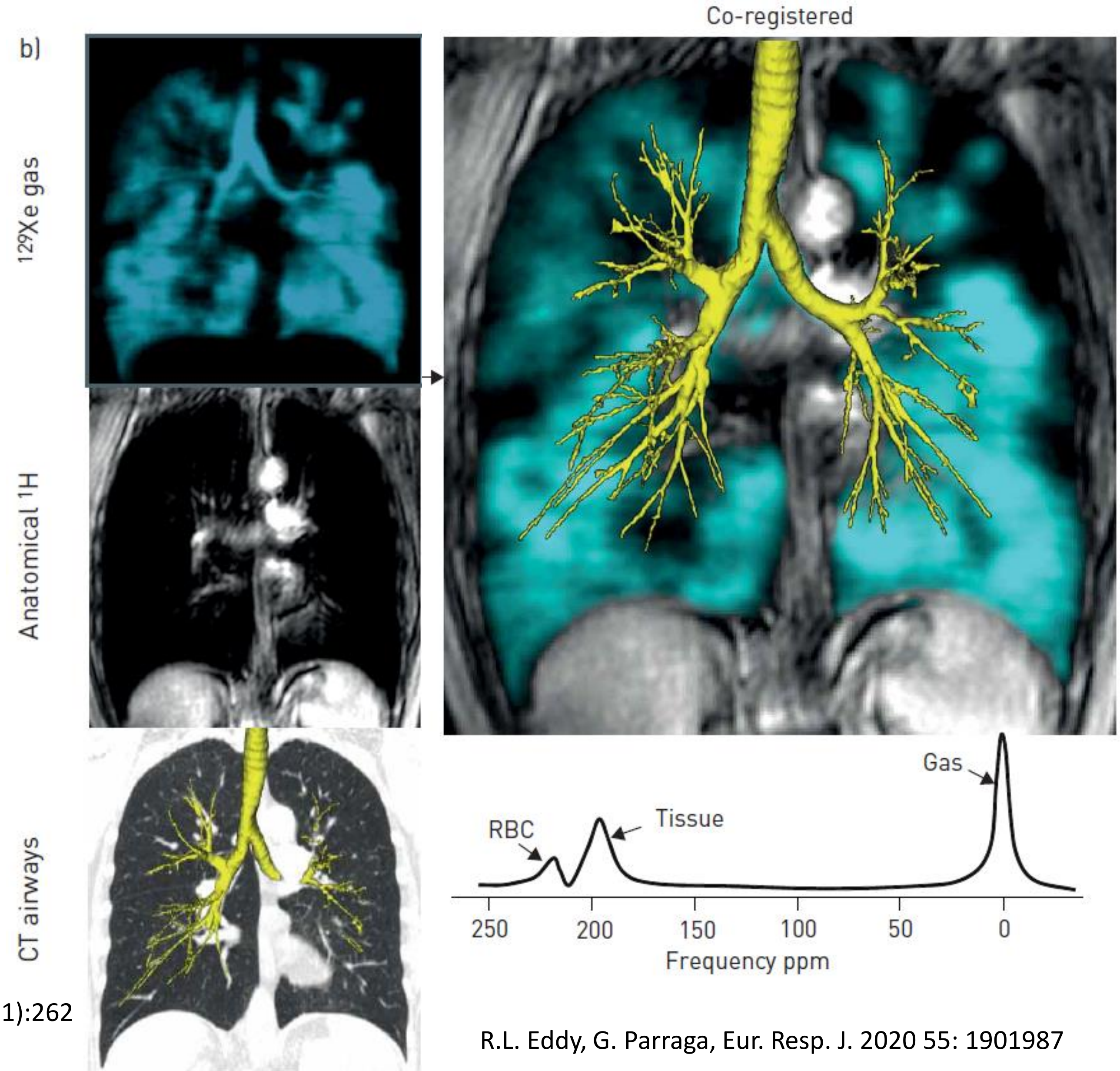




In presence of DNA: K resonance shifted and broadened: implanted K replaces Na inside G-quadruplex?

Stable ^{129}Xe Magnetic Resonance Imaging

- Provides information on:
  - pulmonary ventilation
  - tissue microstructure
  - gas exchange
- Features:
  - Sensitive
  - Fast (< 10 s)
  - Precise (3 mm)
  - No proton background
  - Chemical information
- Applications:
  - Respiratory diseases
  - Emerging: functional images of highly perfused organs: kidneys, brain



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

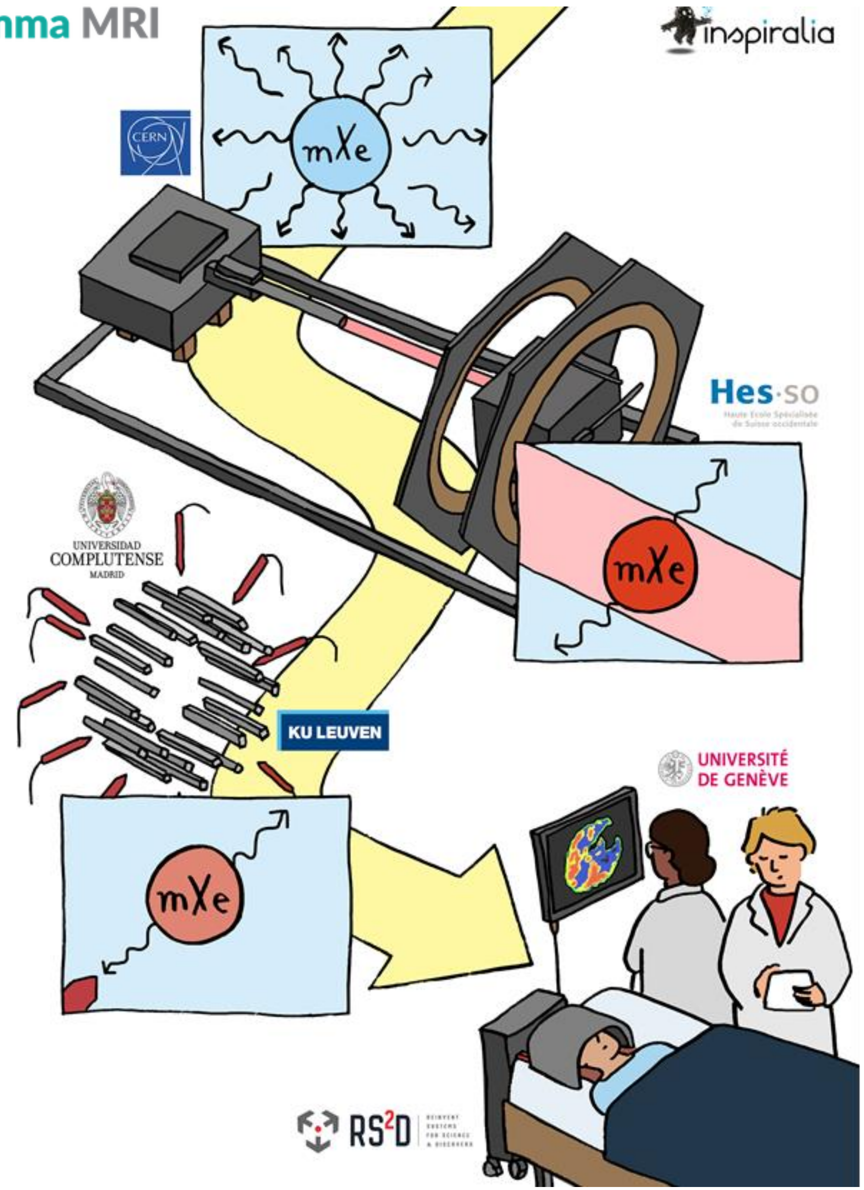
J. Chacon-Caldera, Magn Reson Med. 2020;83(1):262
Y. Shepelytskyi, Magn Reson Med. 2022;88:83

γ-MRI with long-lived Xe isomers

EU FET-OPEN

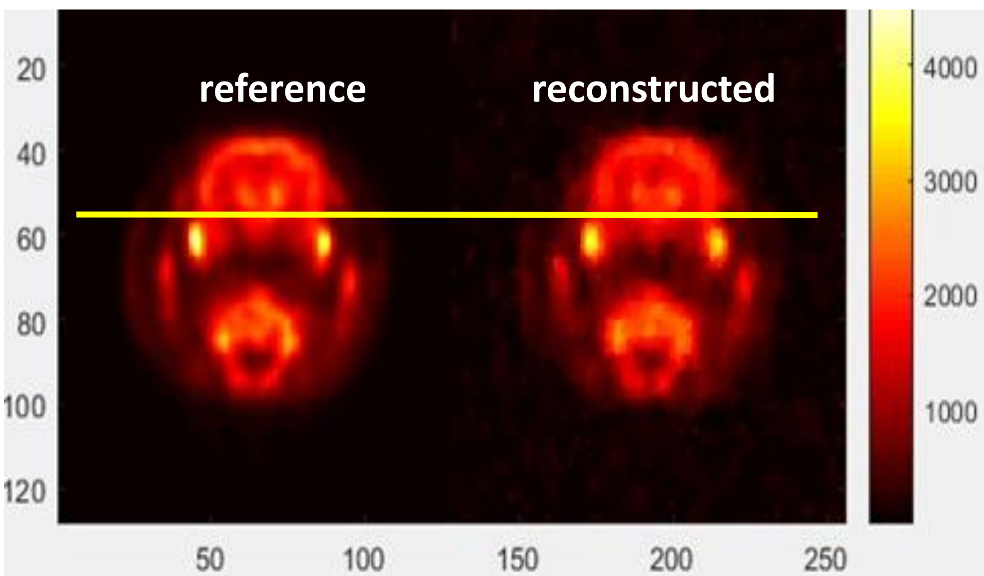
- Simultaneous exploitation of gamma (γ) detection sensitivity + spatial resolution and flexibility of MRI
  - Use of polarised unstable tracers
  - Increase MRI sensitivity and nuclear medicine resolution
  - positioning given by MRI sequences
  - tracer amount given by degree of asymmetry of γ-emission

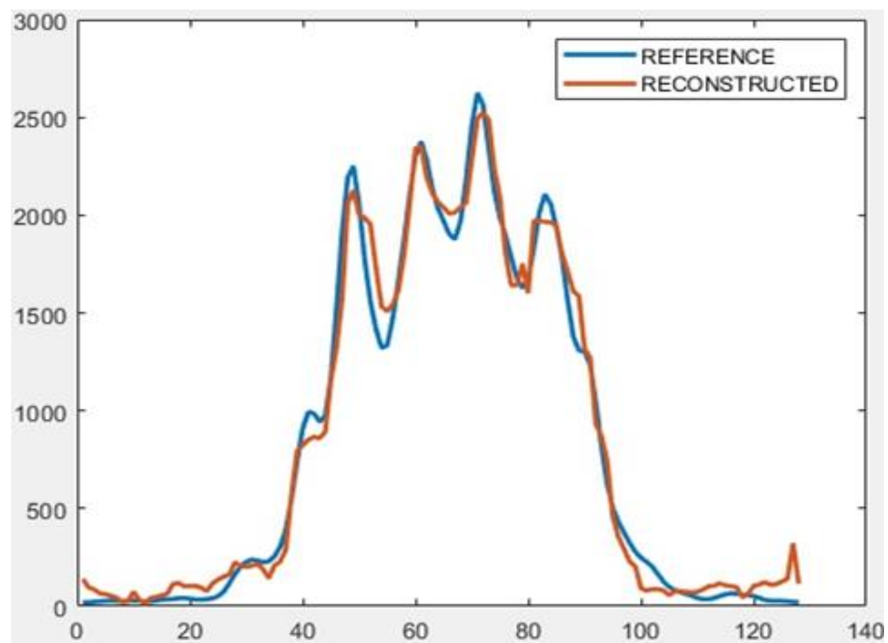
Work on prototype MRI device ongoing



Figures of merit

Technique	Activity	Sensitivity	Resolution
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 resolution)	pM	< 1 mm (for tens of MBq)





Expected signal in prototype:

- rat brain infused with 10 MBq of mXe, 12 s recording time
- reconstructed with compressed sensing strategies in 0.5 mm pixels

Summary

CERN basic science triggers medical applications from our:

- Accelerators
- Detectors
- Radionuclei

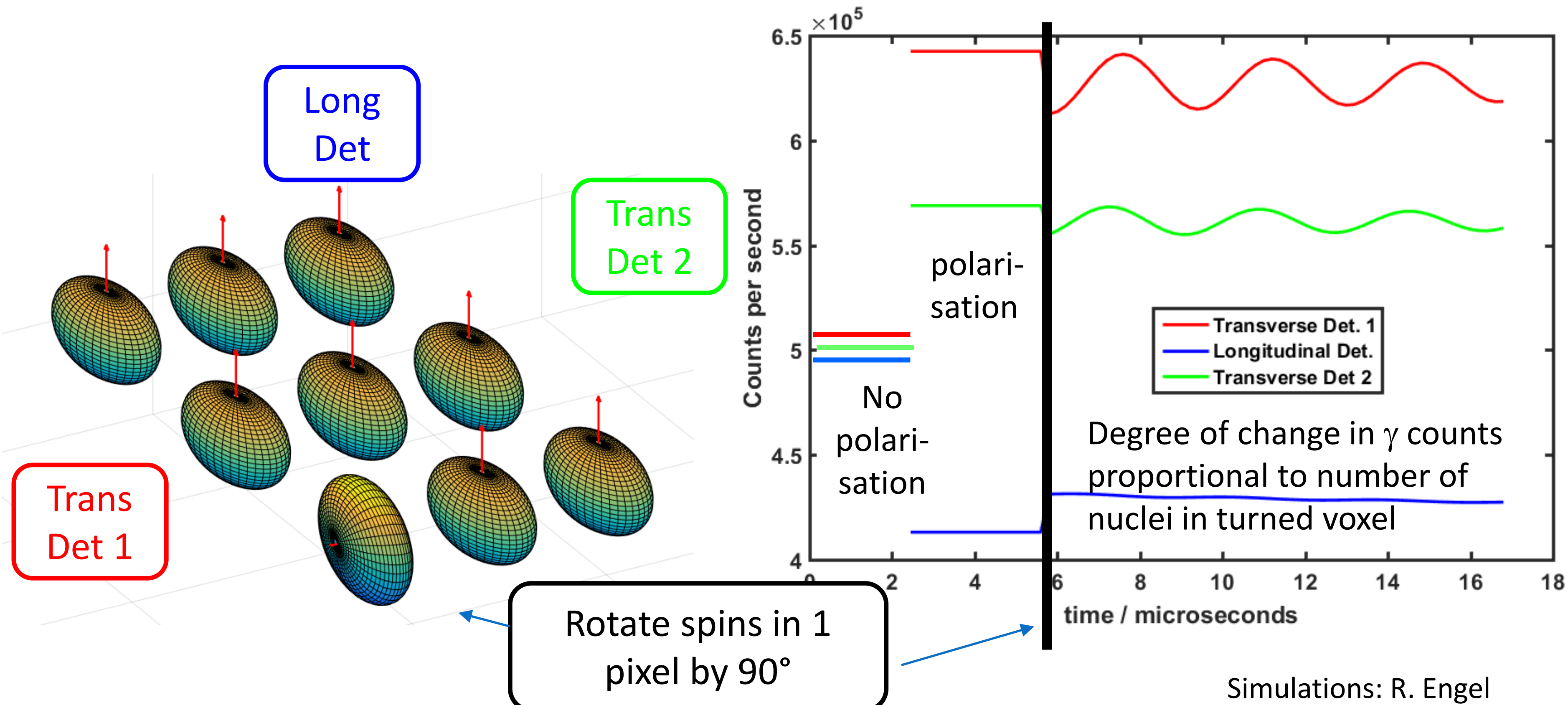
- Interest: medical diagnosis and treatment

- Aim – medical devices that are:
  - SMALLER
  - CHEAPER
  - MORE PRECISE
  - MORE SENSITIVE

- Many examples at different stages of maturity

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



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

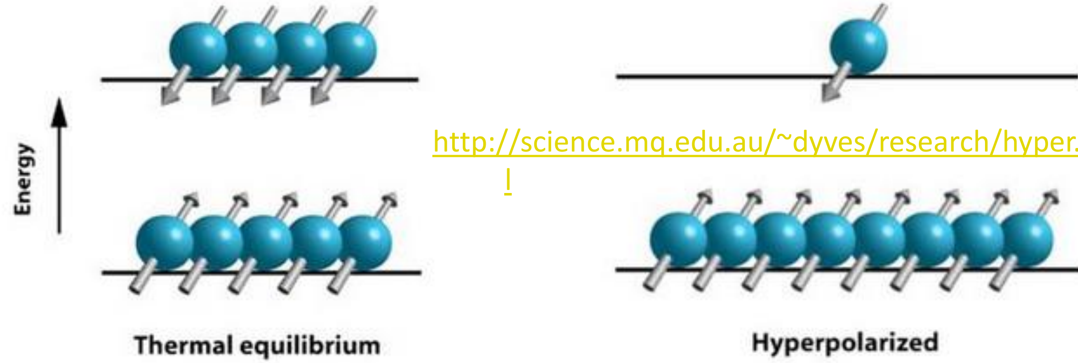
New here: anisotropic emission of radiation from spin-polarised nuclei

- Much higher sensitivity for spin-manipulating techniques:

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

Radiation-detected NMR

Spin hyperpolarisation



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

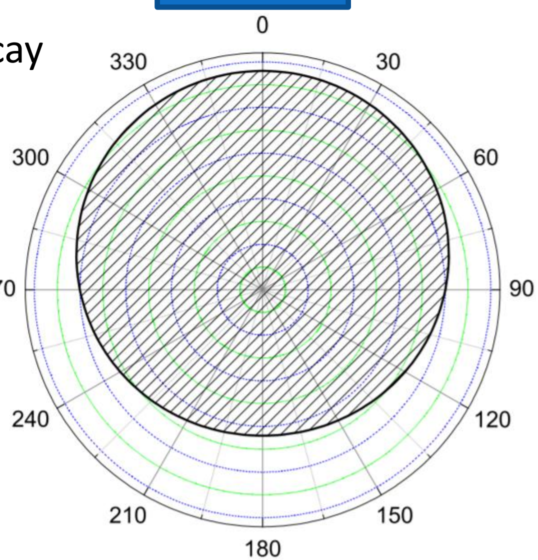
$P \approx 10^{-5} = \frac{1}{100,000}$ at 3T

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

+ Decay anisotropy

β detector

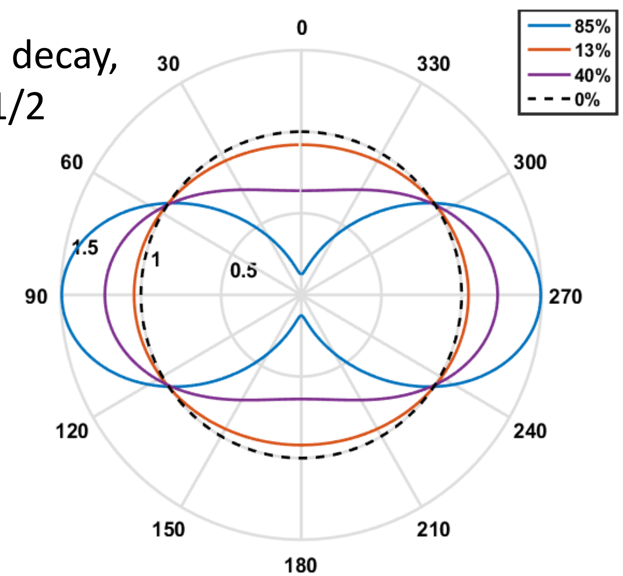
Beta decay
spin >0



β detector

B_0

Gamma decay,
spin >1/2

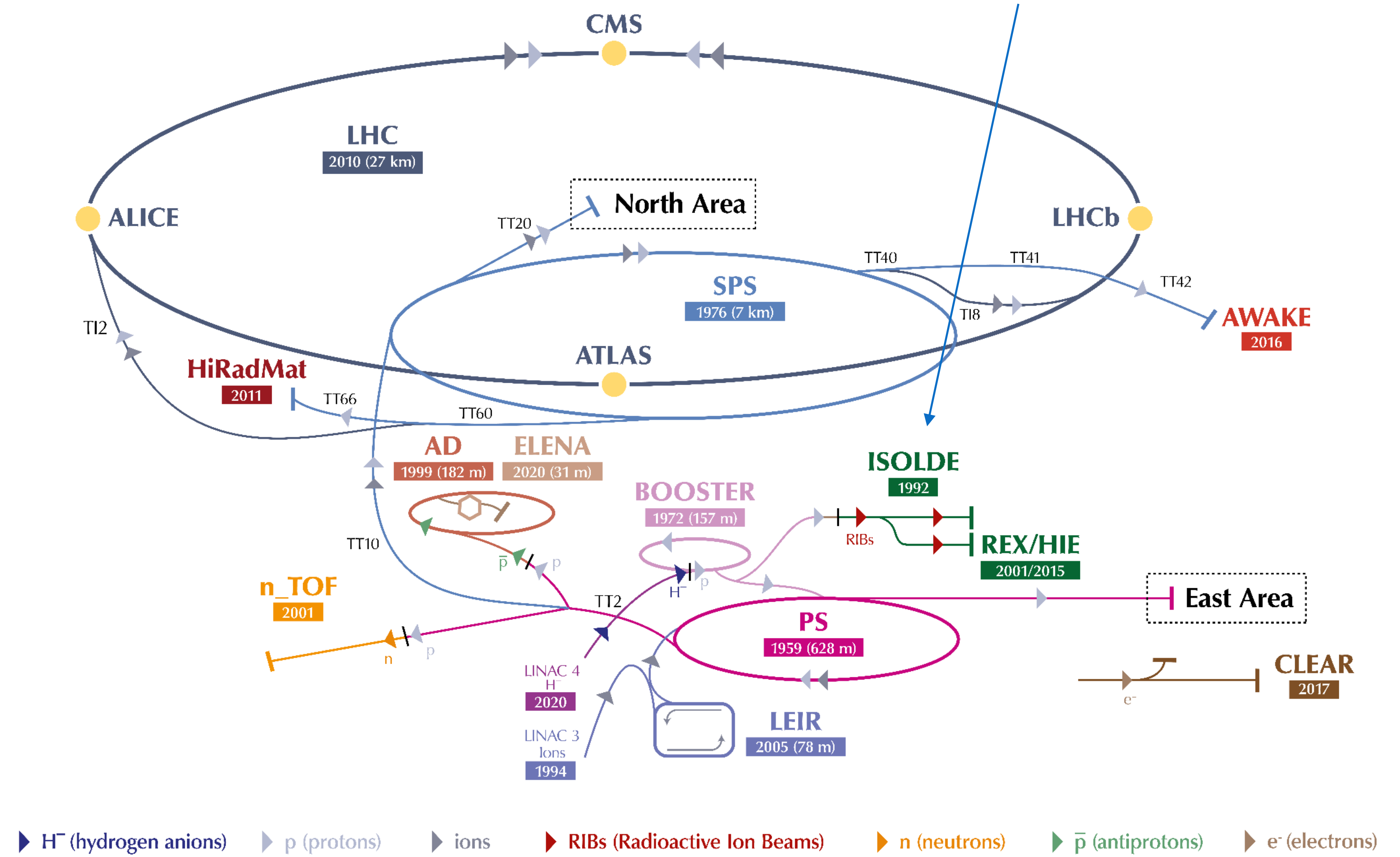


γ detector

γ detector

Experiments: ISOLDE lab at CERN

CERN facility for production and research with radioactive nuclei

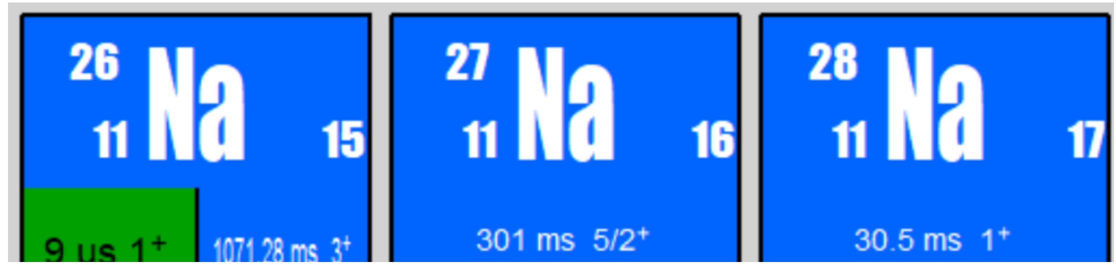


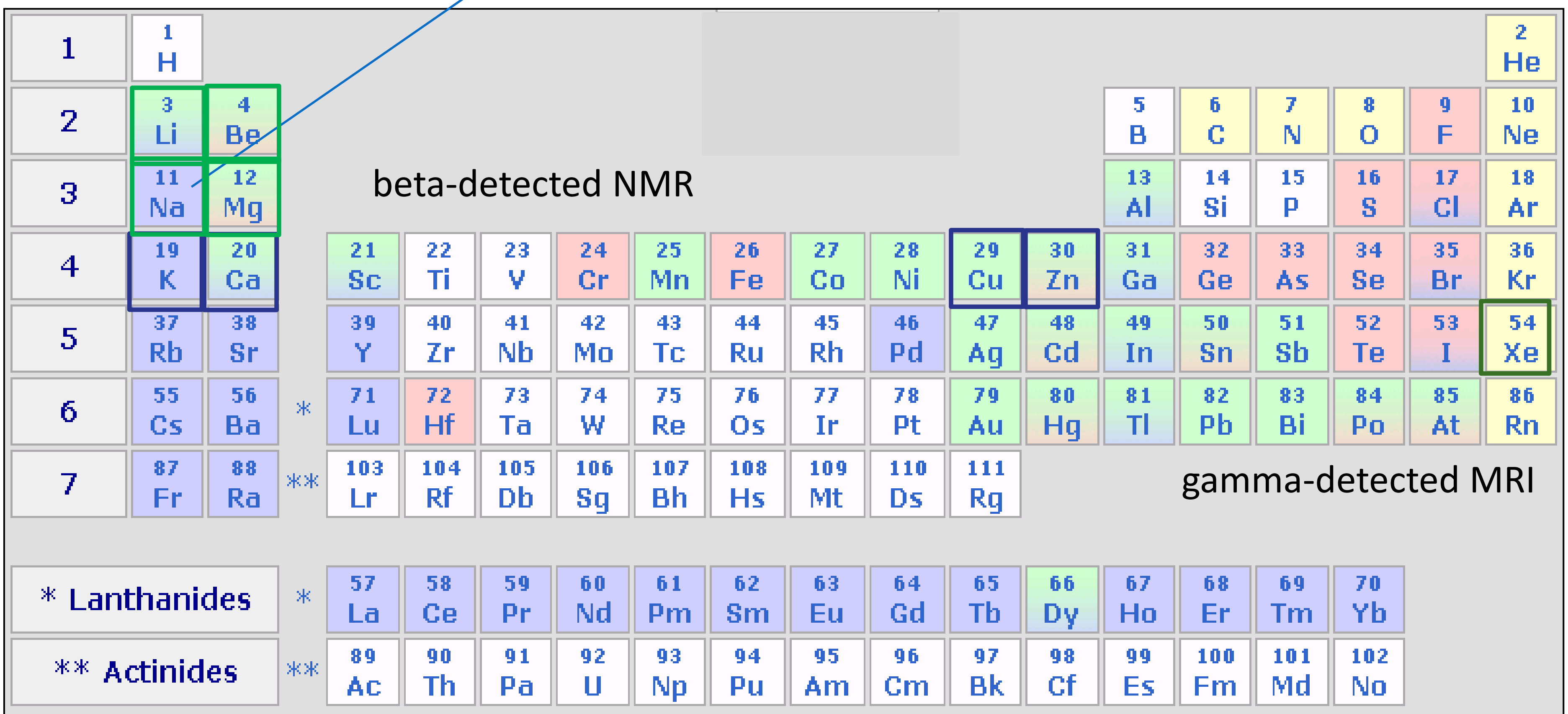
ISOLDE selection of radio-nuclei

- 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

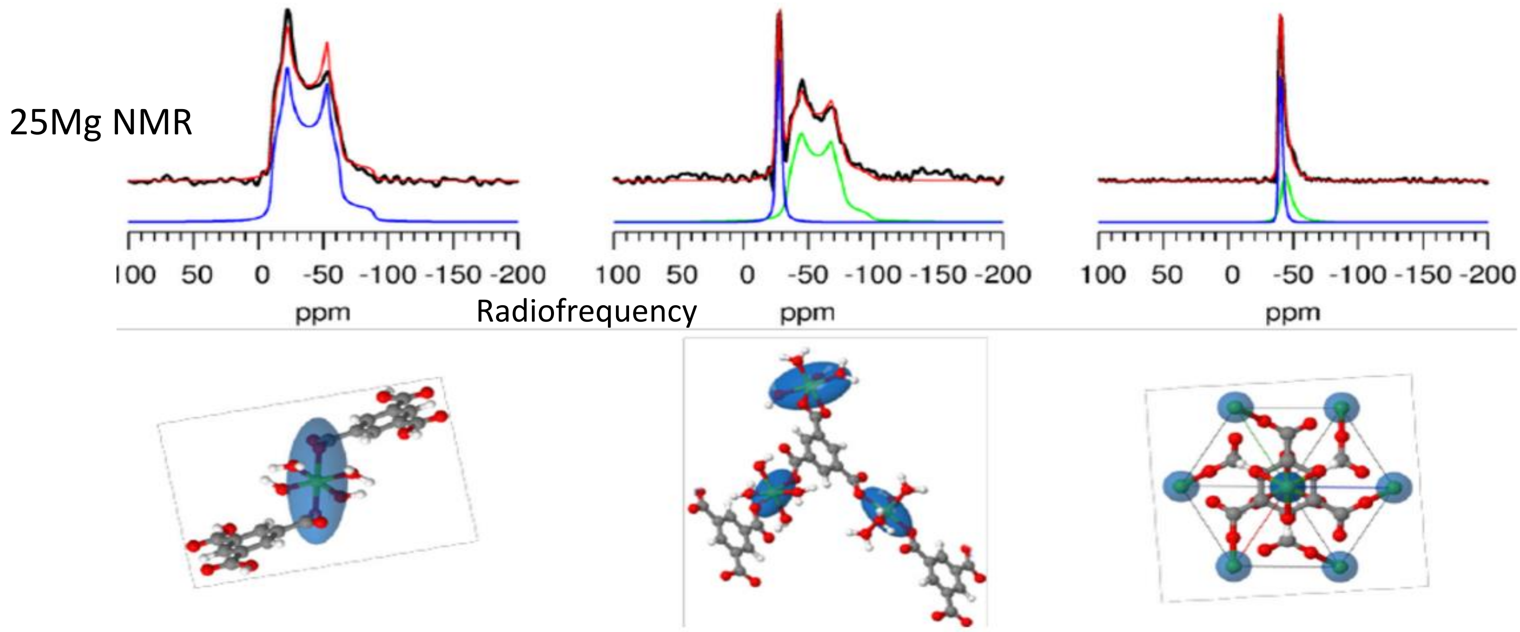




β-detected NMR and metals in biology

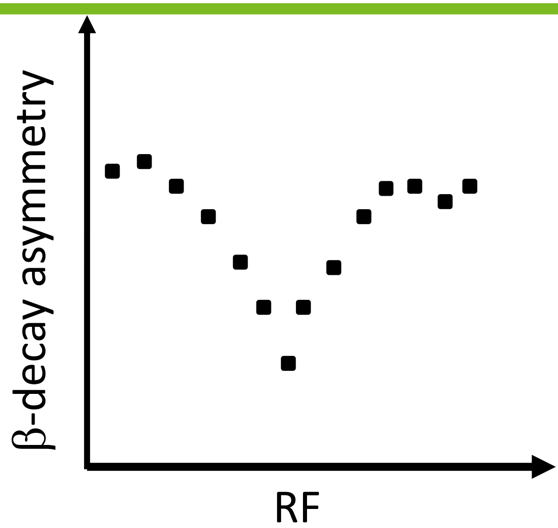
- Increase in sensitivity up to 10^9 times compared to conventional NMR
- Short-lived beta-particle-emitting probe nuclei
- Hyperpolarisation using e.g. lasers -> ideal for metals

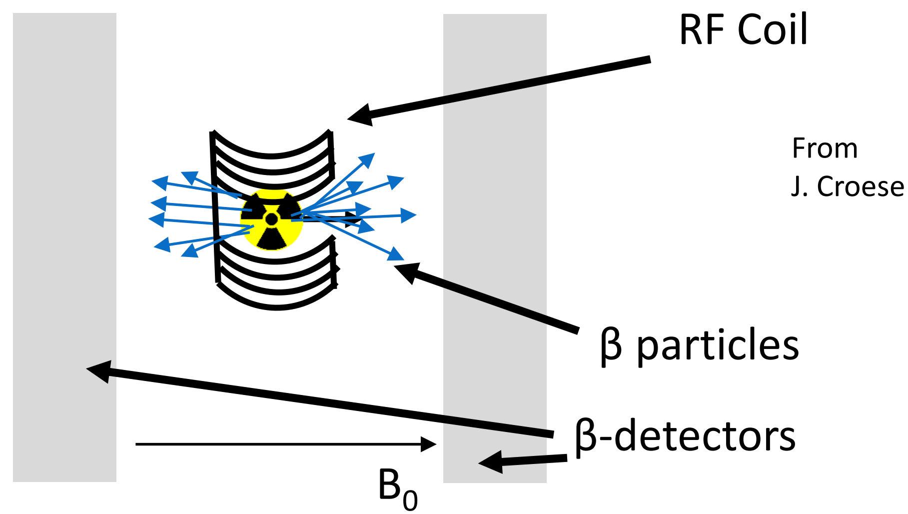
- NMR can provide info on location & evolution of metal-ion binding to biomolecules
  - NMR on 23Na, 25Mg, 63Cu, 67Zn bound to the biomolecule

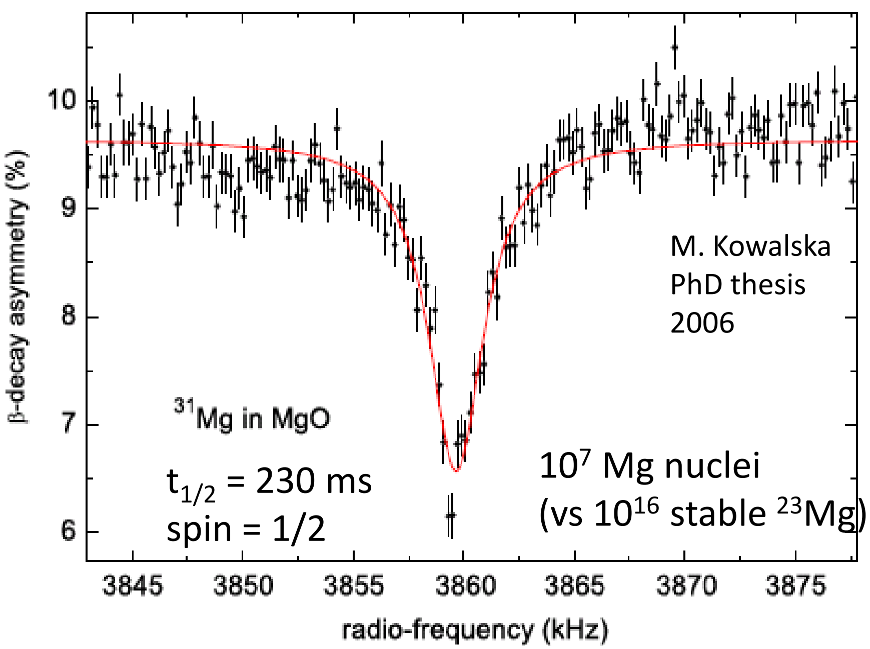


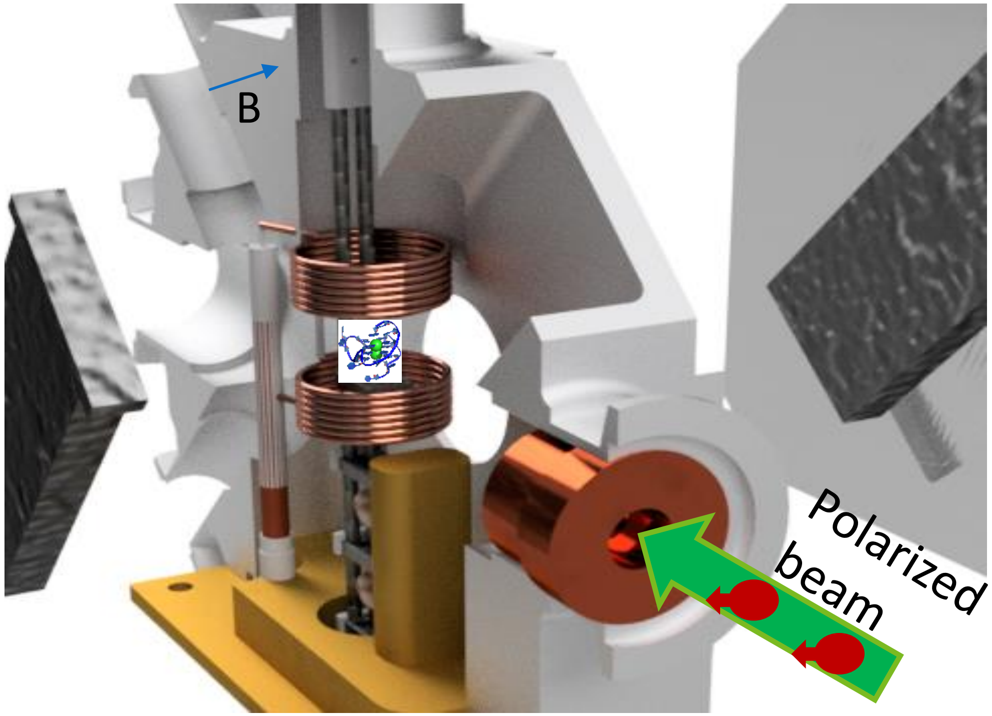
  - Challenges: almost invisible signals due to small abundance, spin >1/2, and small sensitivity
  - Result: metal-ion-NMR used very rarely => sensitive NMR approach is needed

β-NMR spectra





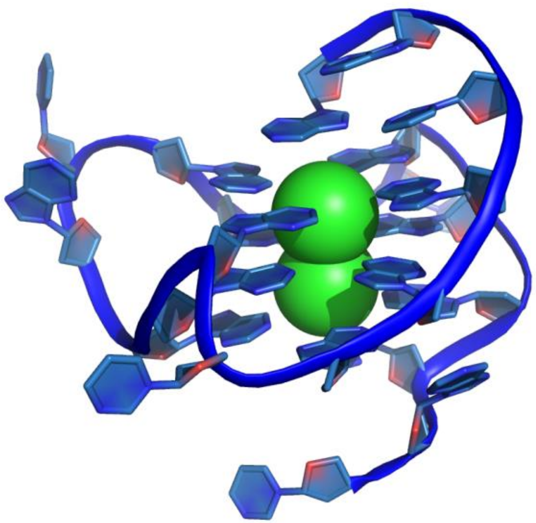


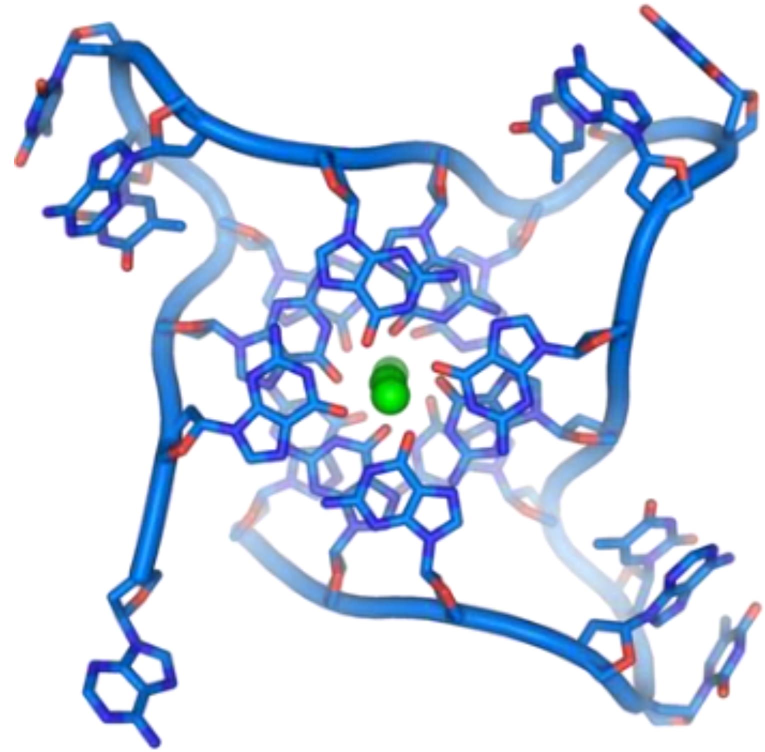


β-NMR 1st biological case

DNA G-quadruplexes and alkali metals

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



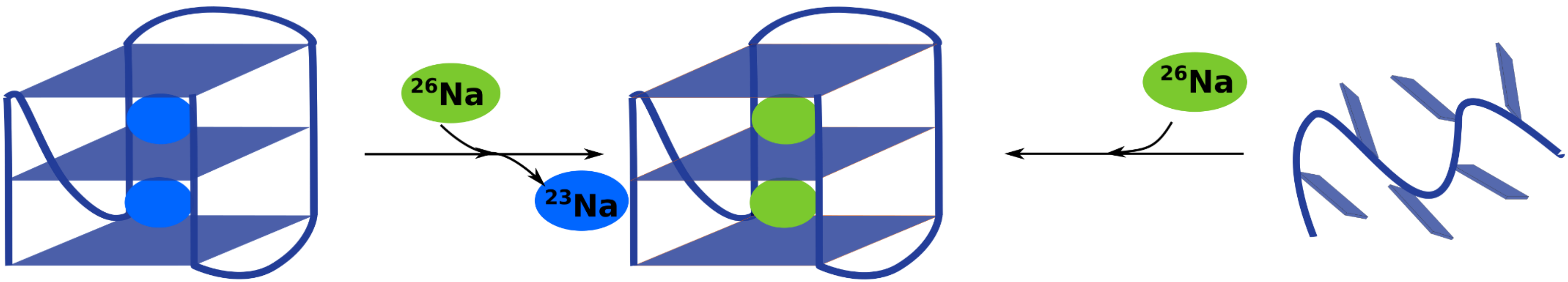


- Alkali metals (Na, K) in G-quadruplexes:
  - Important for their formation, stability and structural polymorphism
  - Until recently considered invisible in conventional Na+/K+ NMR

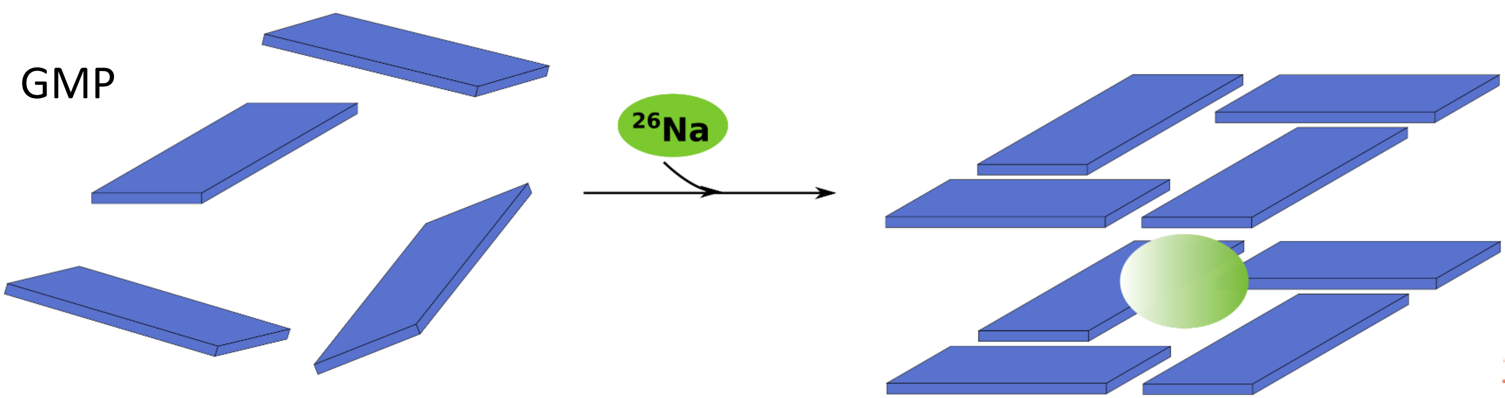
B. Karg, M. Kowalska et al, Proposal to the ISOLDE Scientific Committee, Jan 20
M. Trajkovski et al, J. Am. Chem. Soc. 134, 4132 (2012)

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

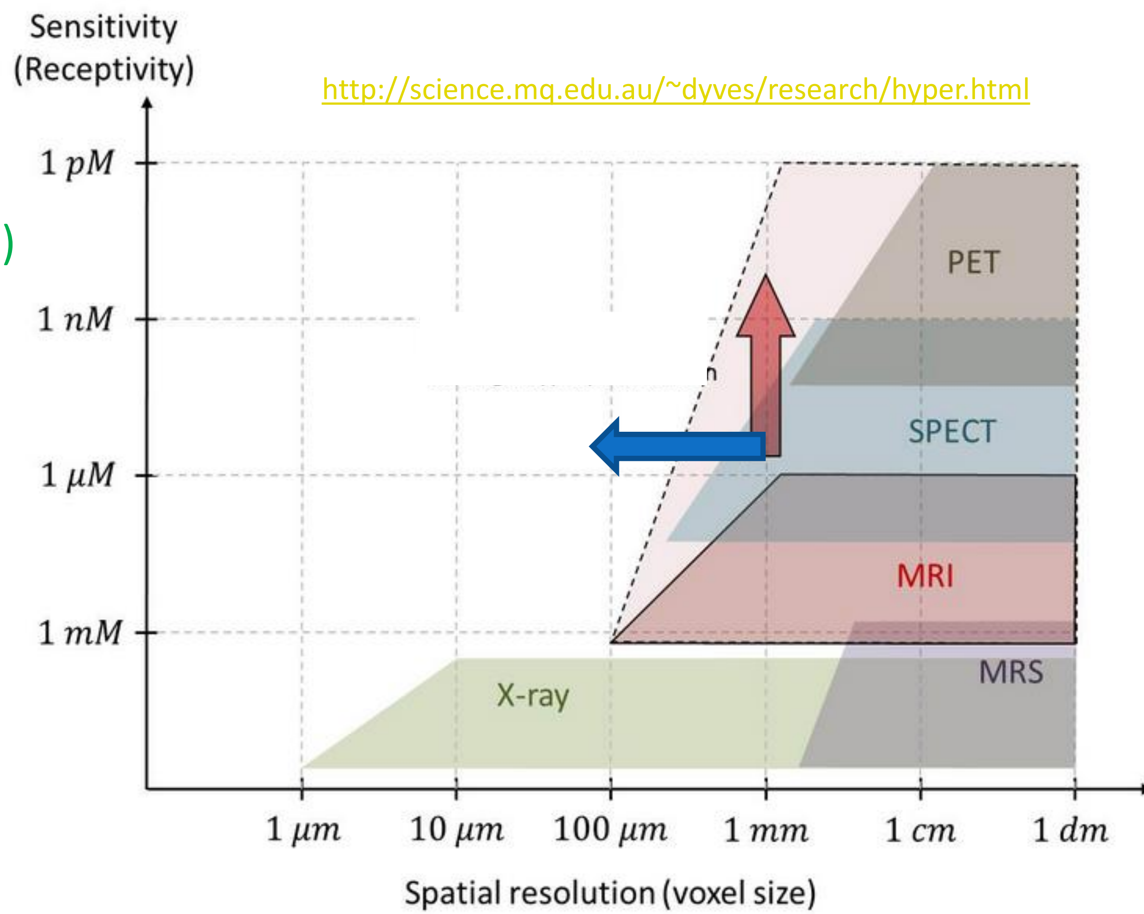
Aim: combine advantages of nuclear medicine and MRI in one modality

- 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**

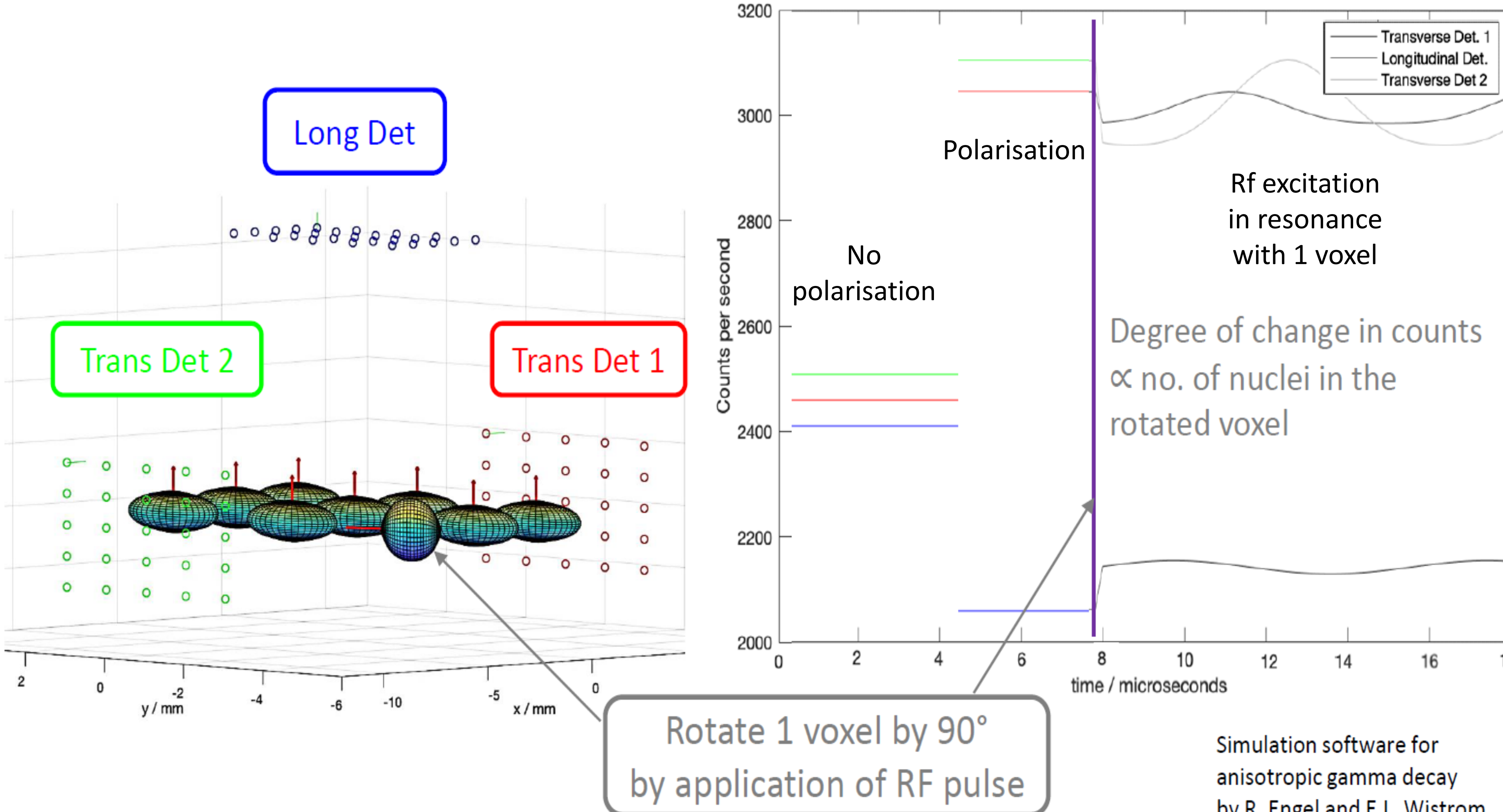
- **Shown to work in 2D by:**

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



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

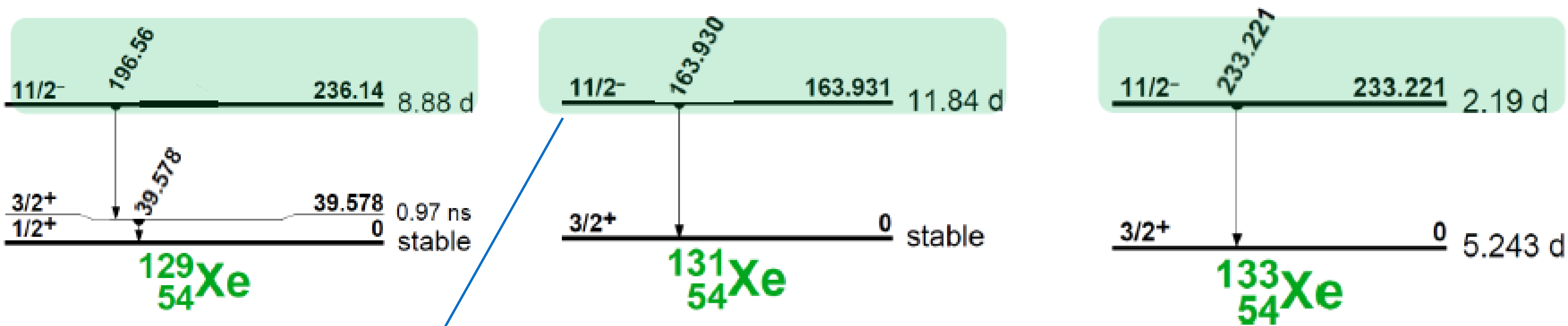


Simulation software for anisotropic gamma decay by R. Engel and E.L. Wistrom

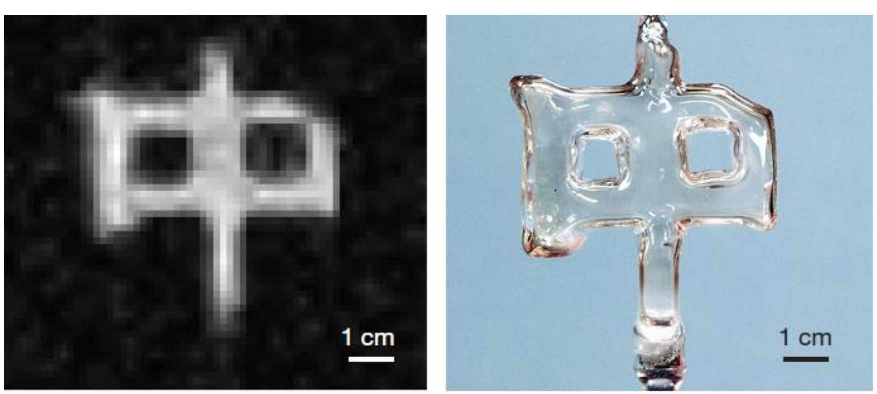
γ-MRI and lung & brain imaging

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



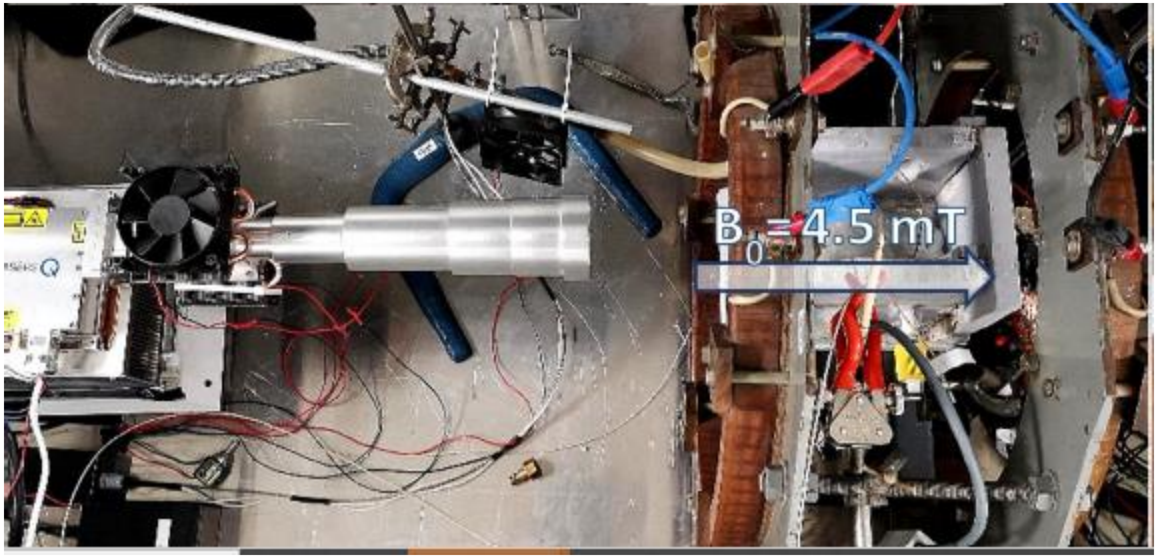
Gain: higher MRI sensitivity or higher nuclear-medicine resolution



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

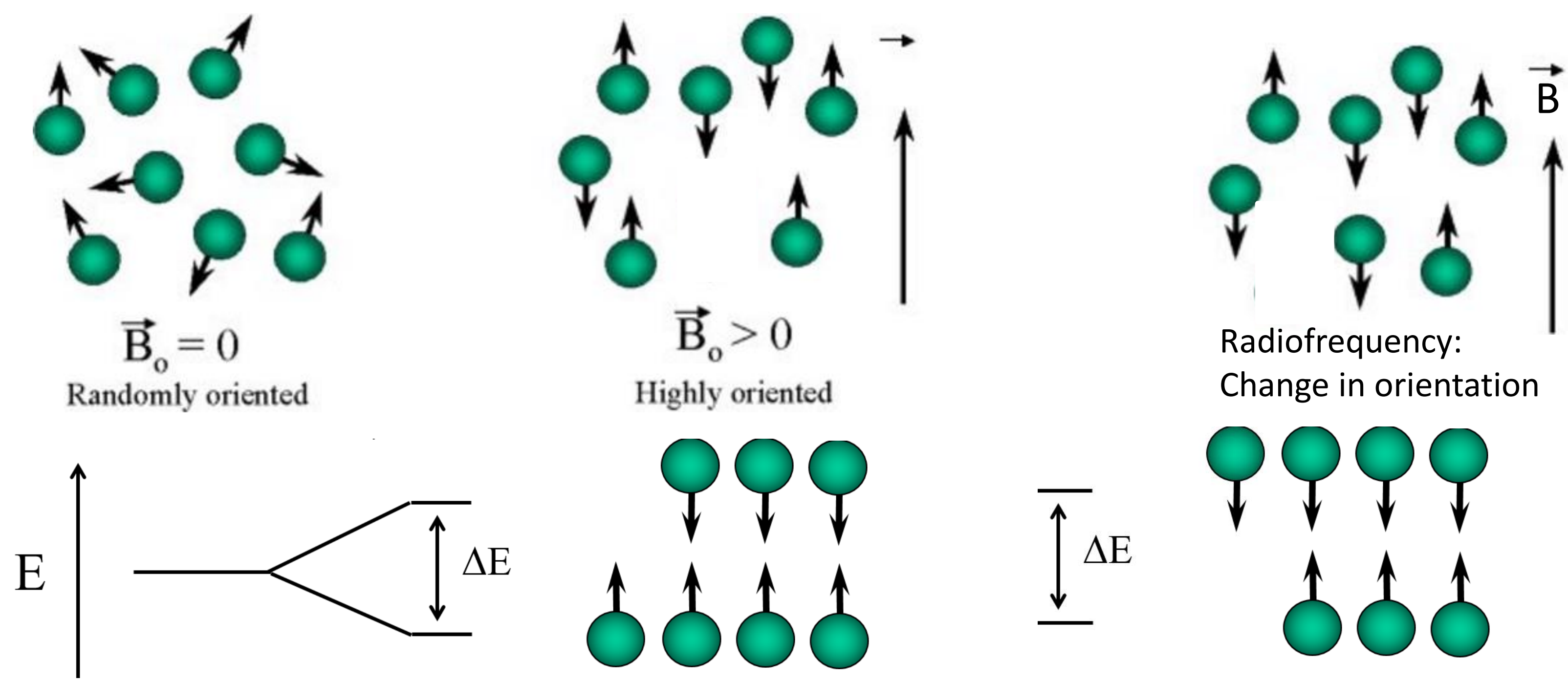
- Projects in their first stages:
  - Feasibility shown
  - Funding acquired

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

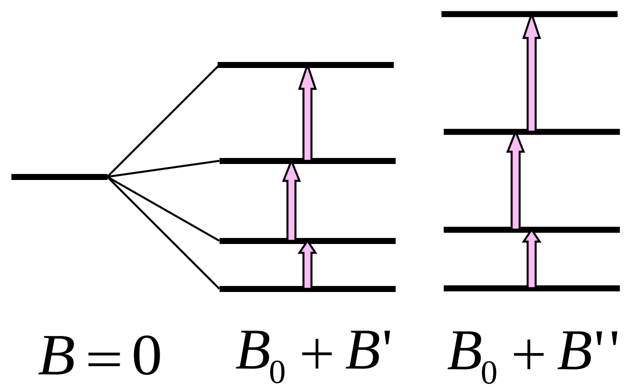
- **Observables**: chemical shift (Larmor frequency) and relaxation times in different hosts
- **Determined properties**
  - local electronic environment (i.e. **number and type of coordinating groups**)

Depends on environment

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

known

Same B, different shielding by host

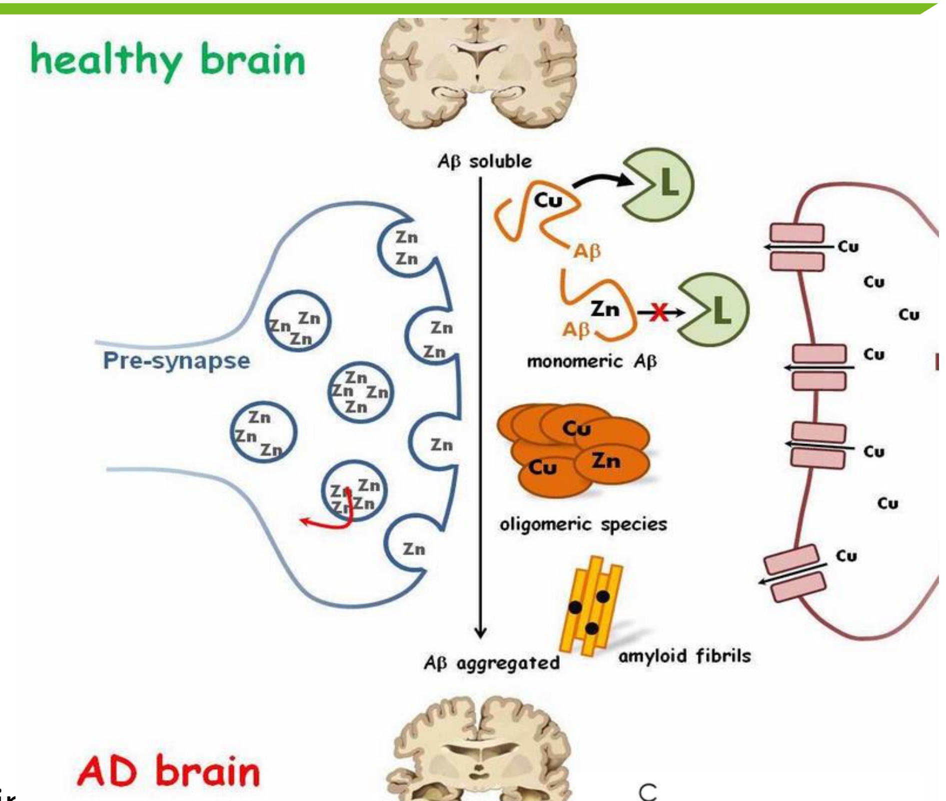


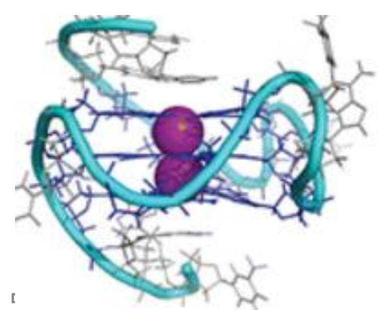
- **Derived information**:
  - Structure and dynamics of different biomolecules
  - kinetics and dynamics and ligand binding of the **metal ions and biomolecules**
  - 3D structure of proteins and **protein-metal complexes**

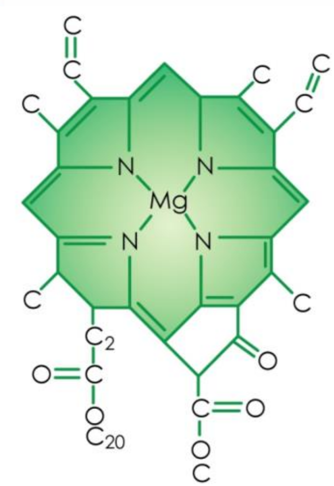
Metal ions in biology

- 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

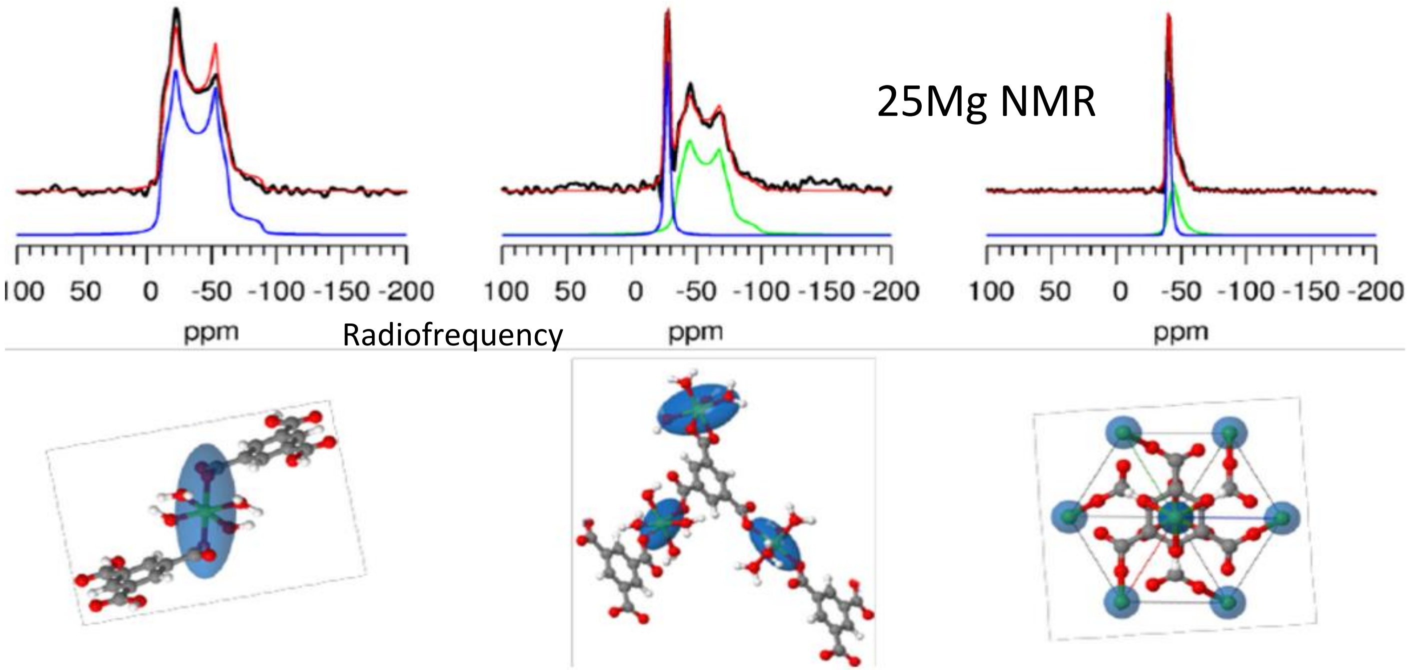






Metal ions & NMR

- 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)

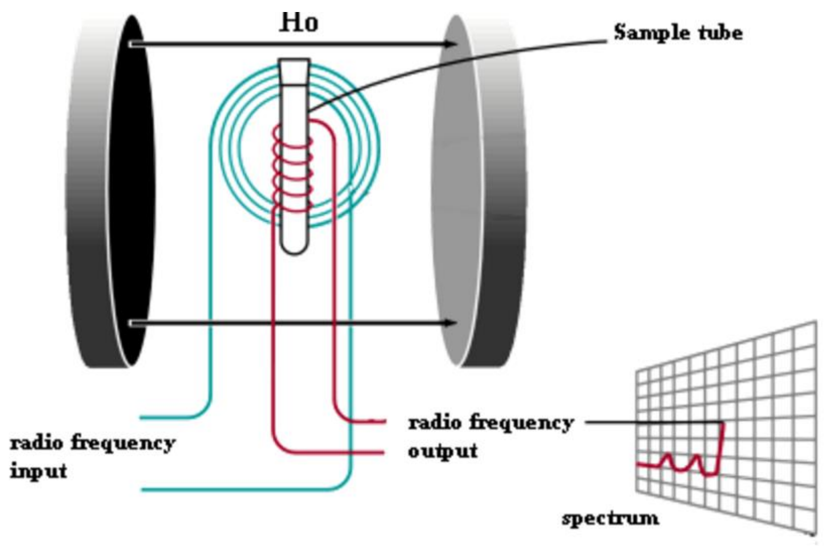
- Result: metal-ion-NMR used very rarely

- 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



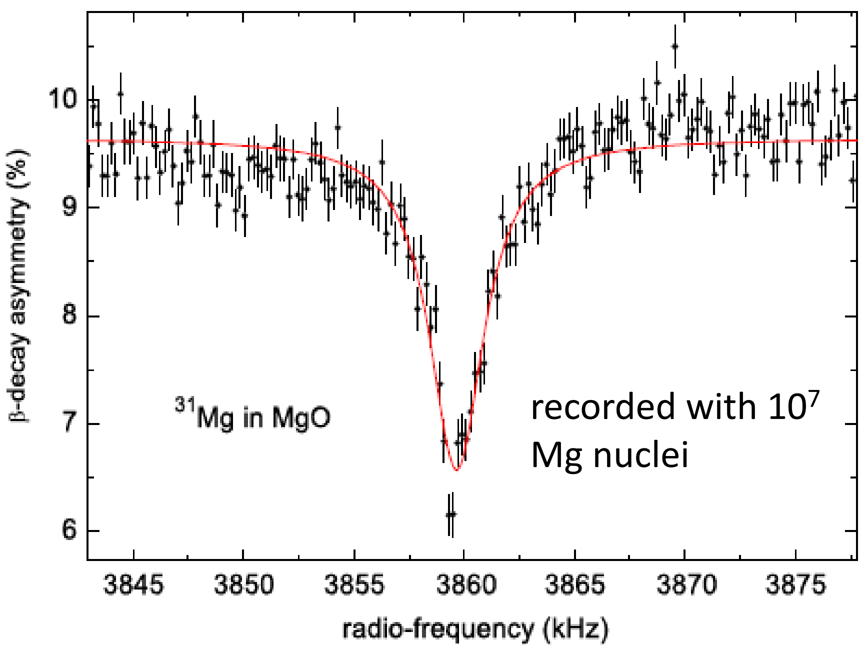
Ultrasensitive beta-detected NMR

- 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:

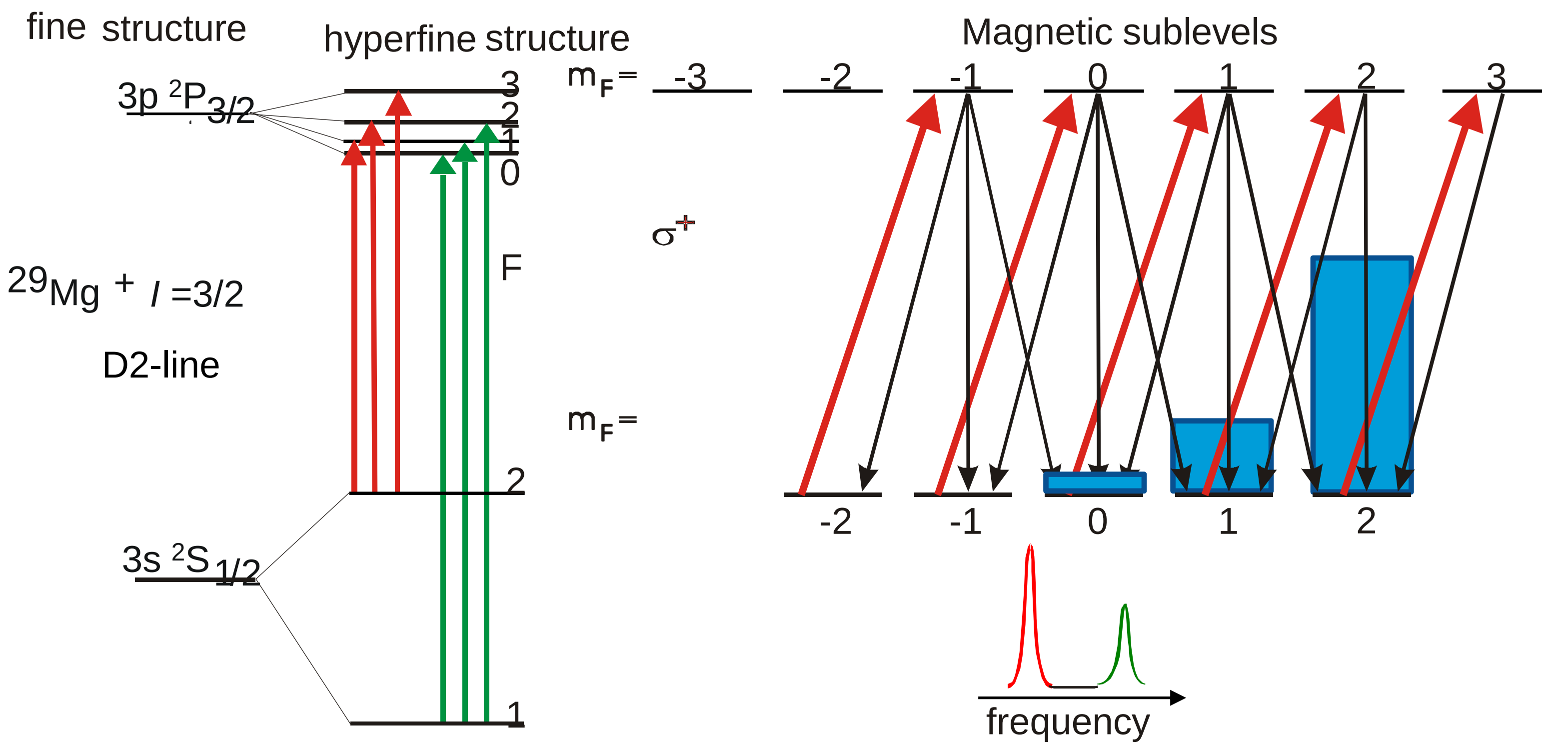
31Mg
T1/2 = 230 ms
I = 1/2



M. Kowalska
PhD thesis
2006

Hyperpolarization: optical pumping

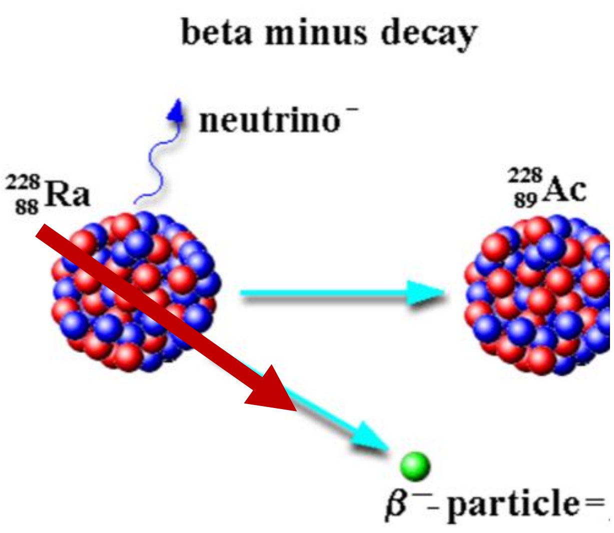
- Multiple excitation cycles with circularly-polarized light
- Photon angular momentum transferred to electrons and then nuclei
  - Works best for 1 valence electron
  - nuclear spin-polarization of 10-90%
  - Polarization buildup time < us

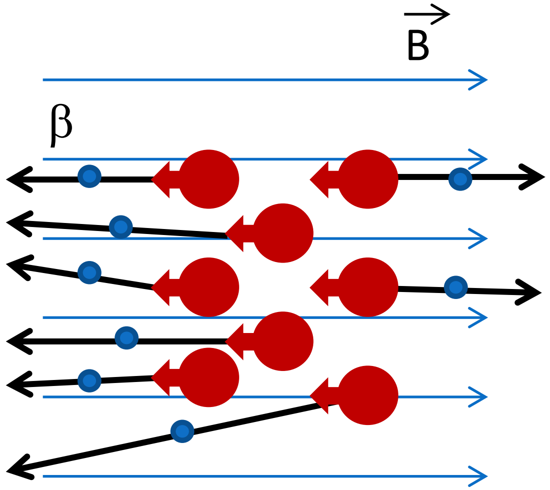


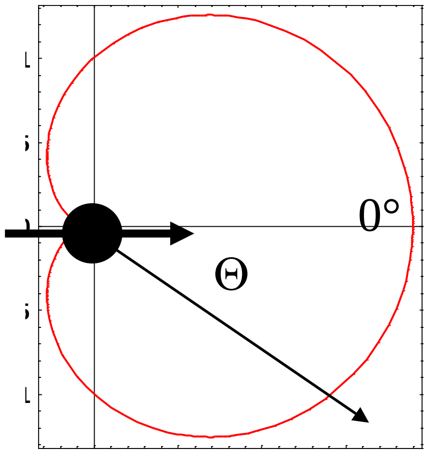
Detection of particles: beta decay

- 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**

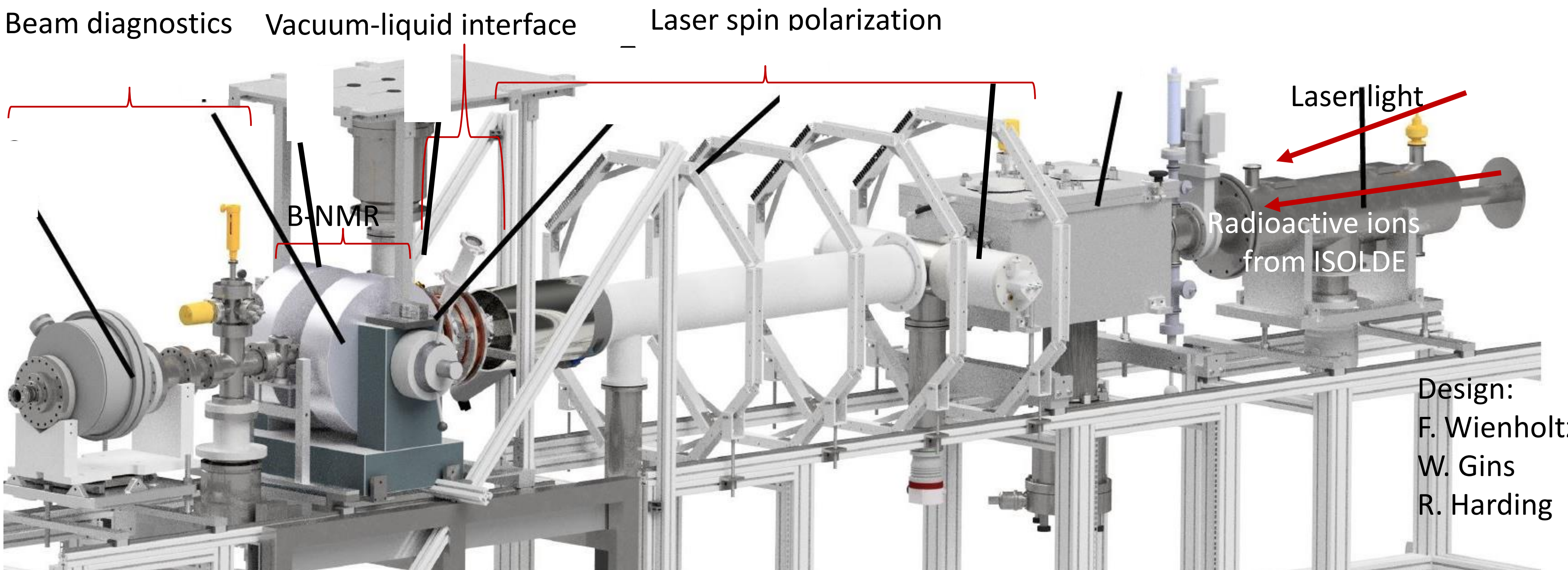
=> Gain in NMR detection efficiency: up to 10^5

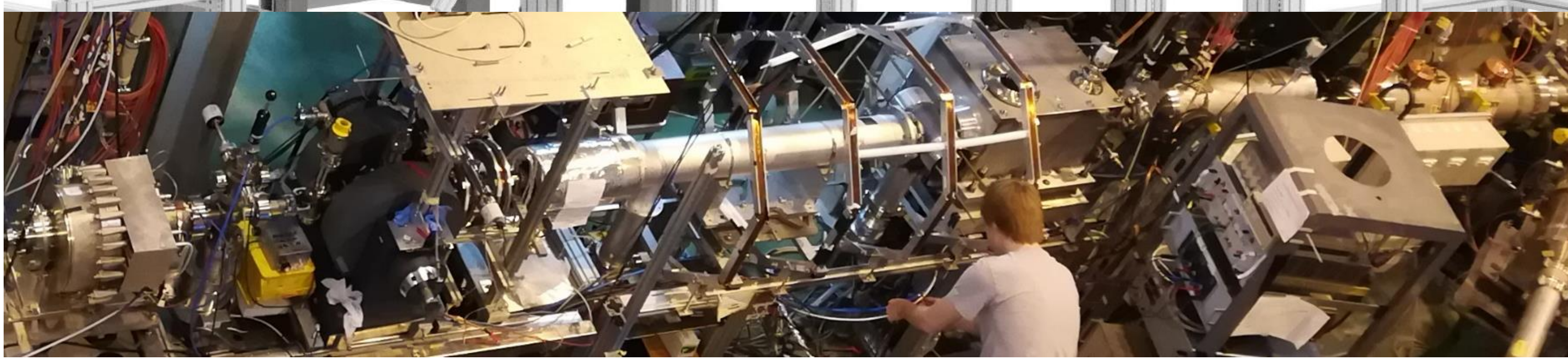






Experimental setup

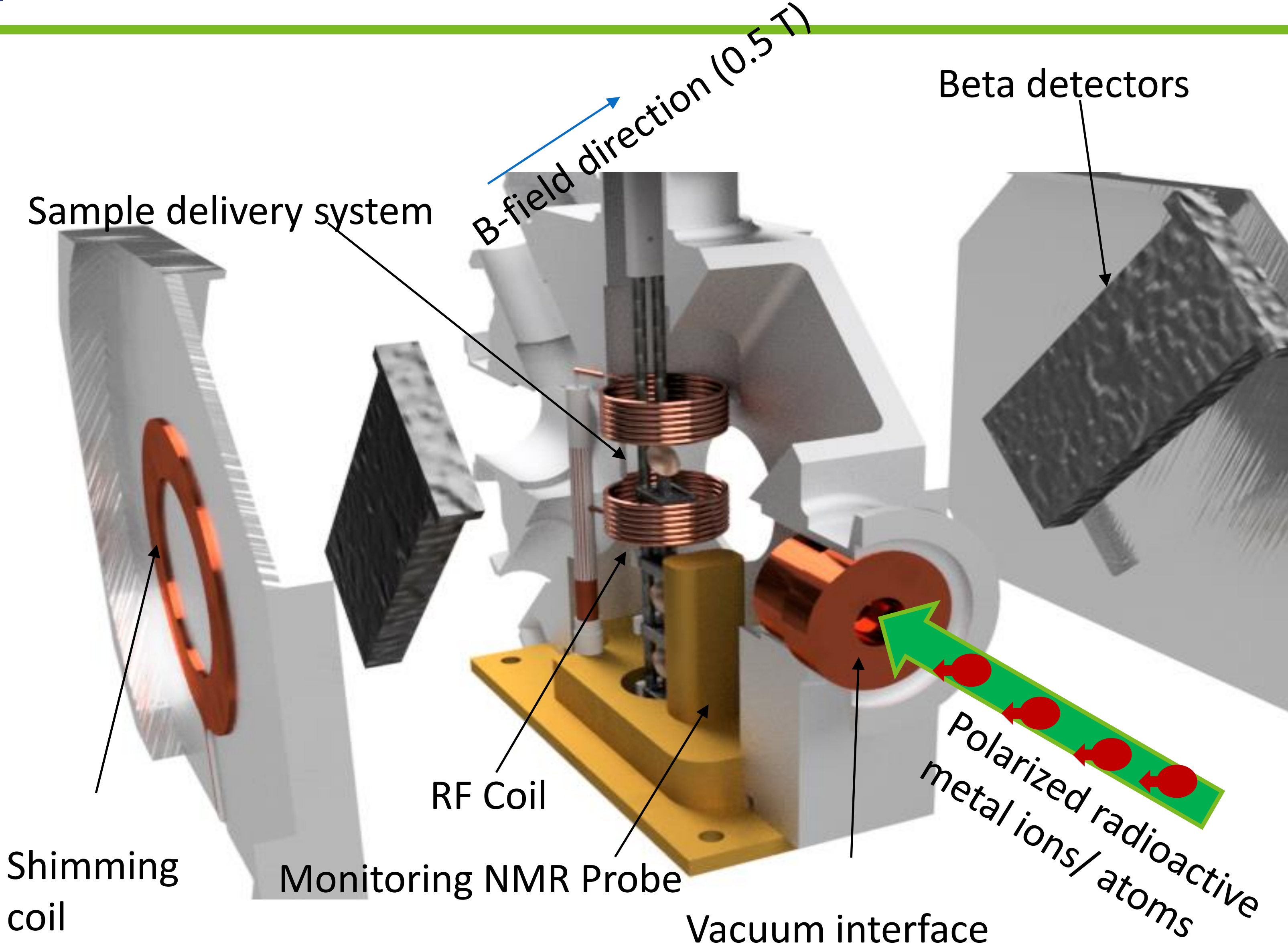




M. Kowalska et al., J. Phys. G: Nucl. Part. Phys. 44 (2017) 084005
W. Gins et al., to be submitted to Nucl. Instr. and Meth. A

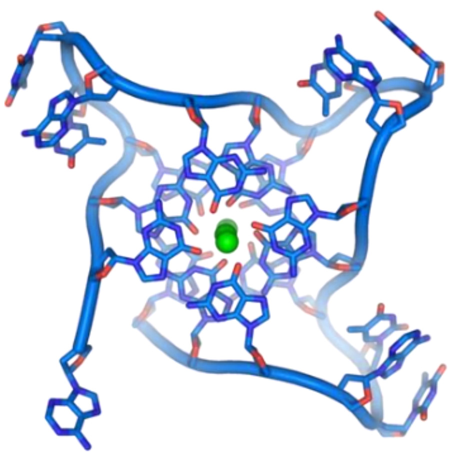
Designed and commissioned in 2016
First physics experiments in 2017
First biology-related experiments in 2018

Bio-Beta-NMR chamber



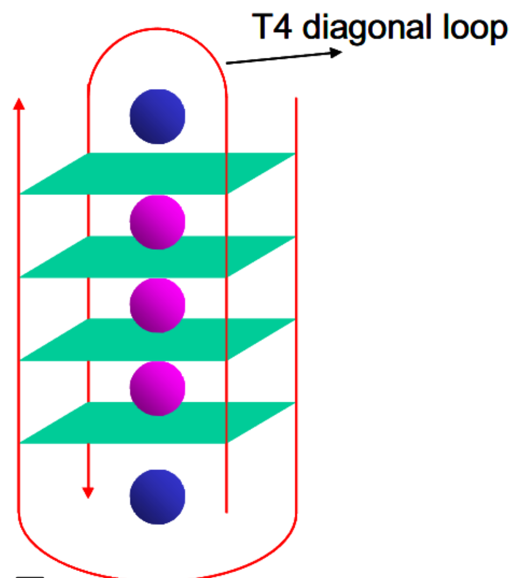
First bio-study: Na+ & G-quadruplexes

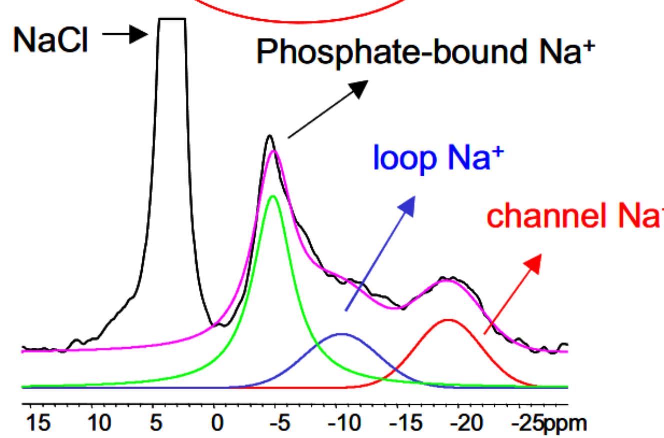
- DNA G-quadruplexes:
  - Guanine-rich DNA fragments
  - Found in nature, e.g. in telomeres or oncogenes
  - Synthesised for novel applications
  - Important in different diseases



- 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



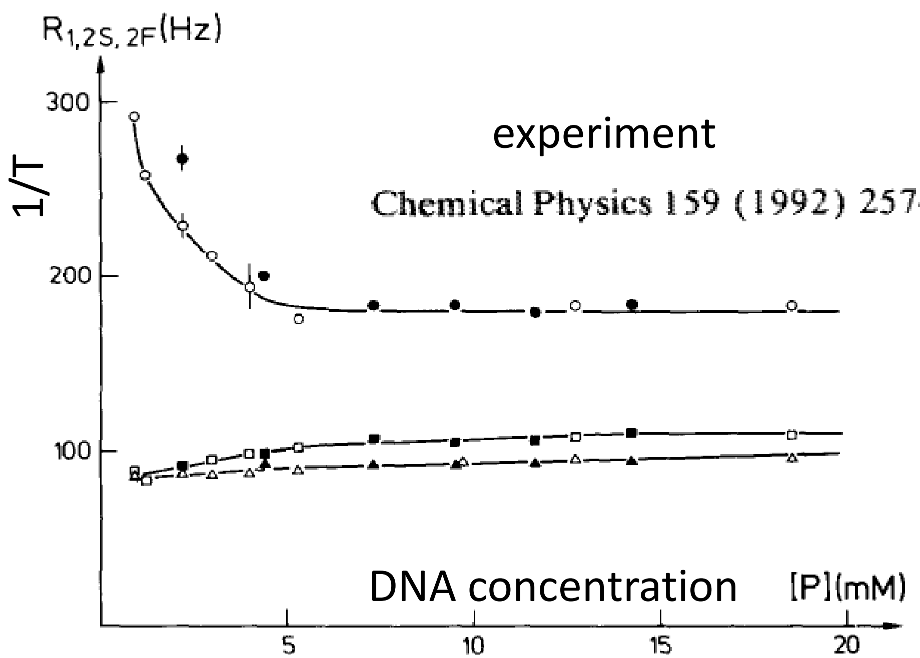


M. Kowalska et al, Proposal to the ISOLDE Scientific Committee, June 2017
M. Trajkovski et al, J. Am. Chem. Soc. 134, 4132 (2012)

NMR on Na+ and DNA interaction

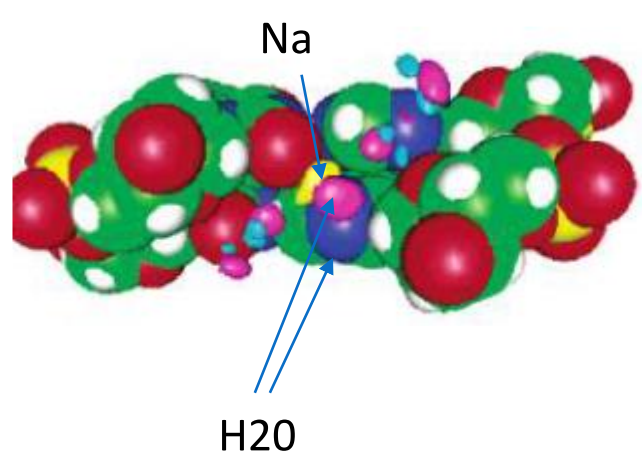
- T1 relaxation measurements:
  - Quadrupole moment of 23Na interacts with electric-field inhomogeneities (gradients) in the environment
  - Longer T1 relaxation time: more homogenous environment
  - Shorter T1: less homogenous environment

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



simulations

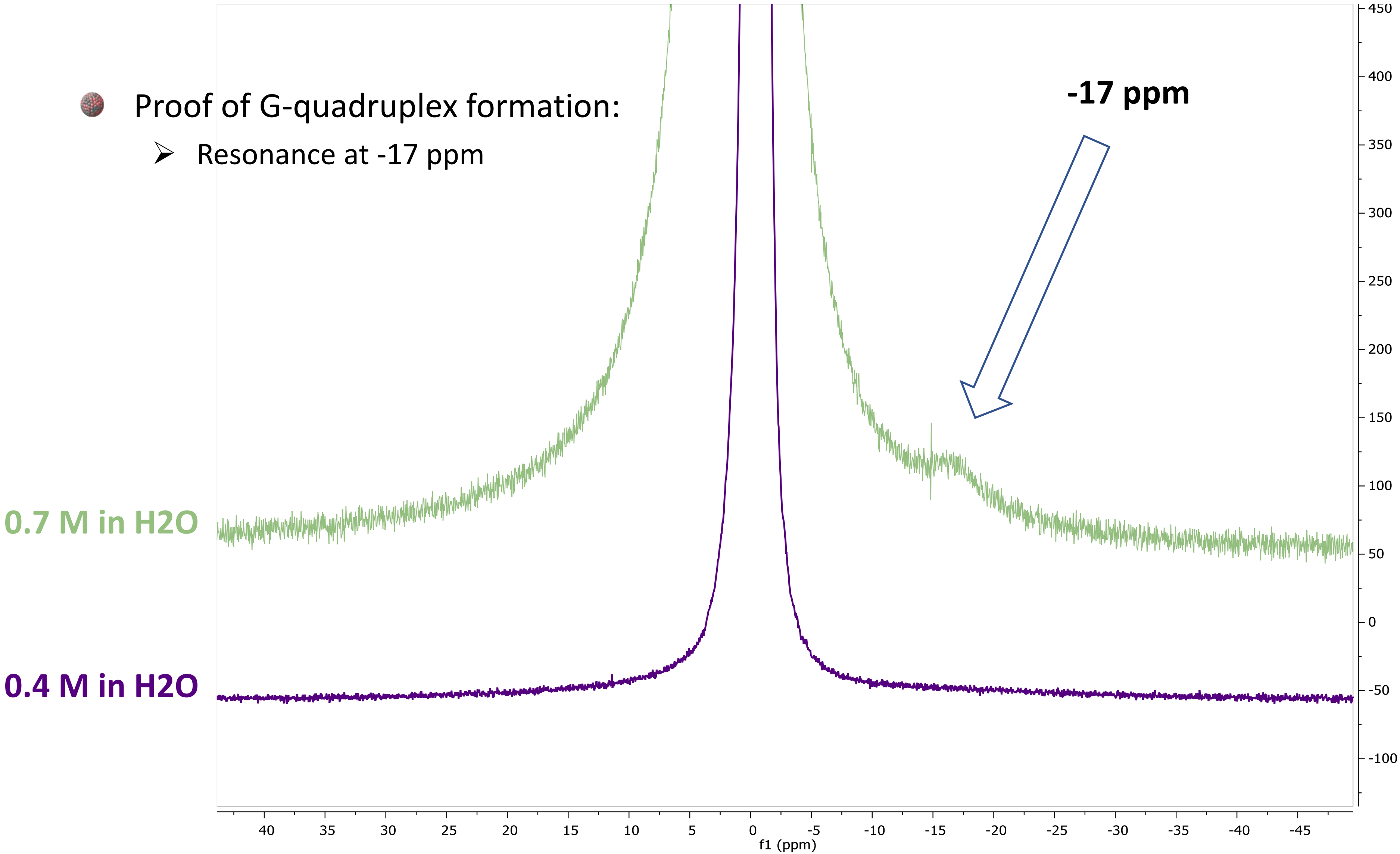
J. Phys. Chem. B **2004**, *108*, 16295



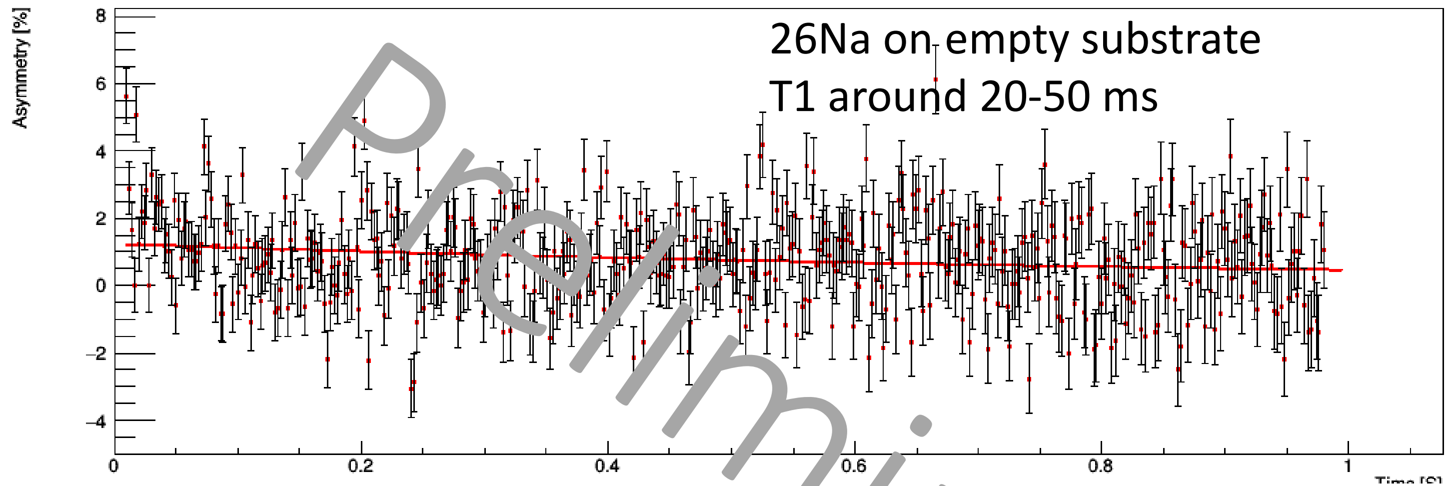
NMR on Na+ and G Quadruplexes

Conventional 23Na NMR

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

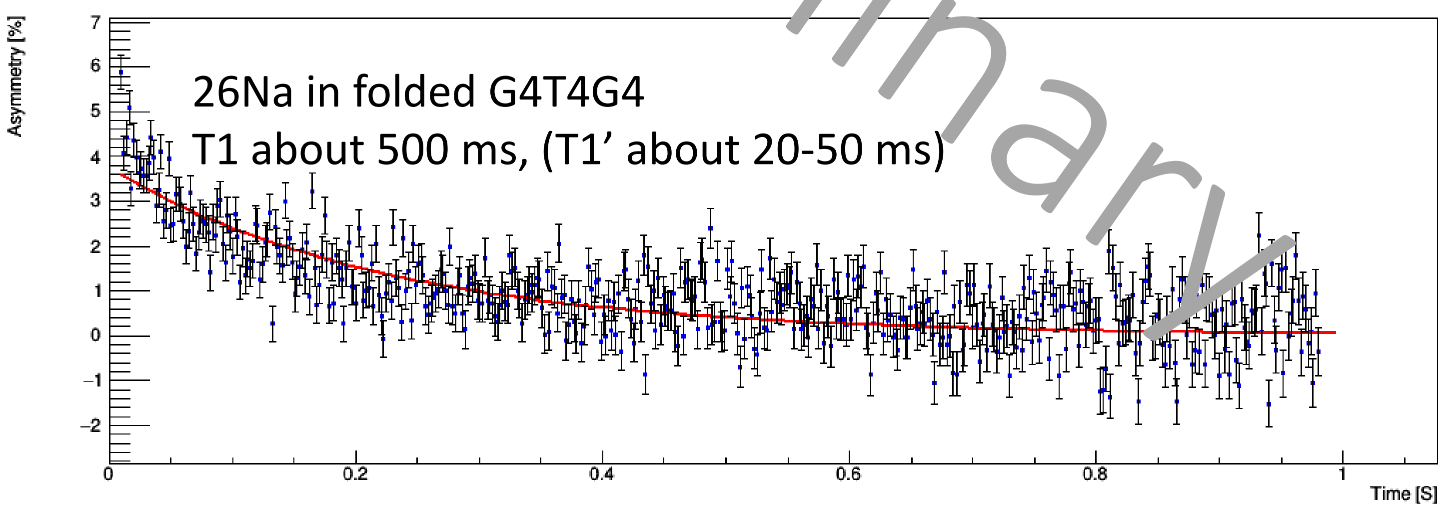


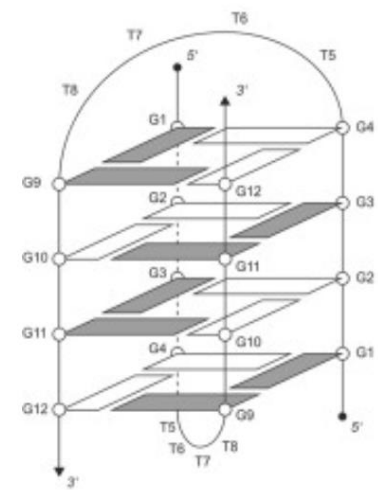
β-NMR: 26Na T1 in G4T4G4 G-quadruplex



May 2018

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

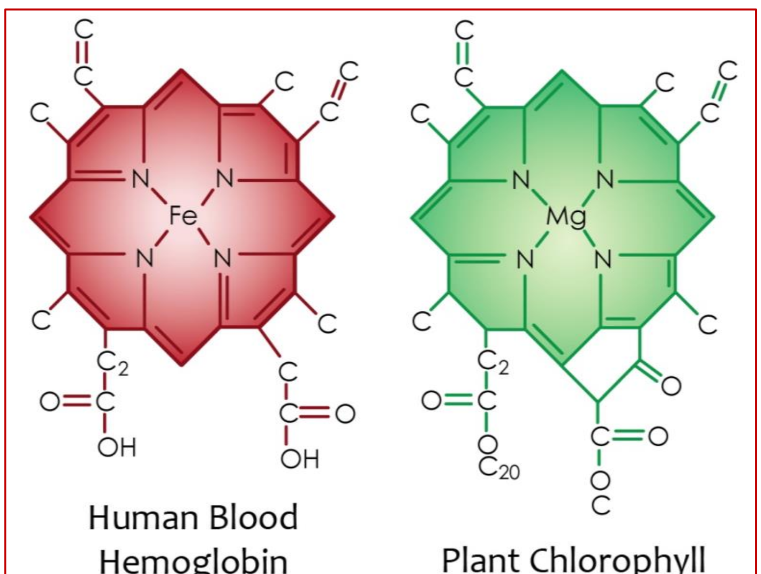
Feasible and planned soon:

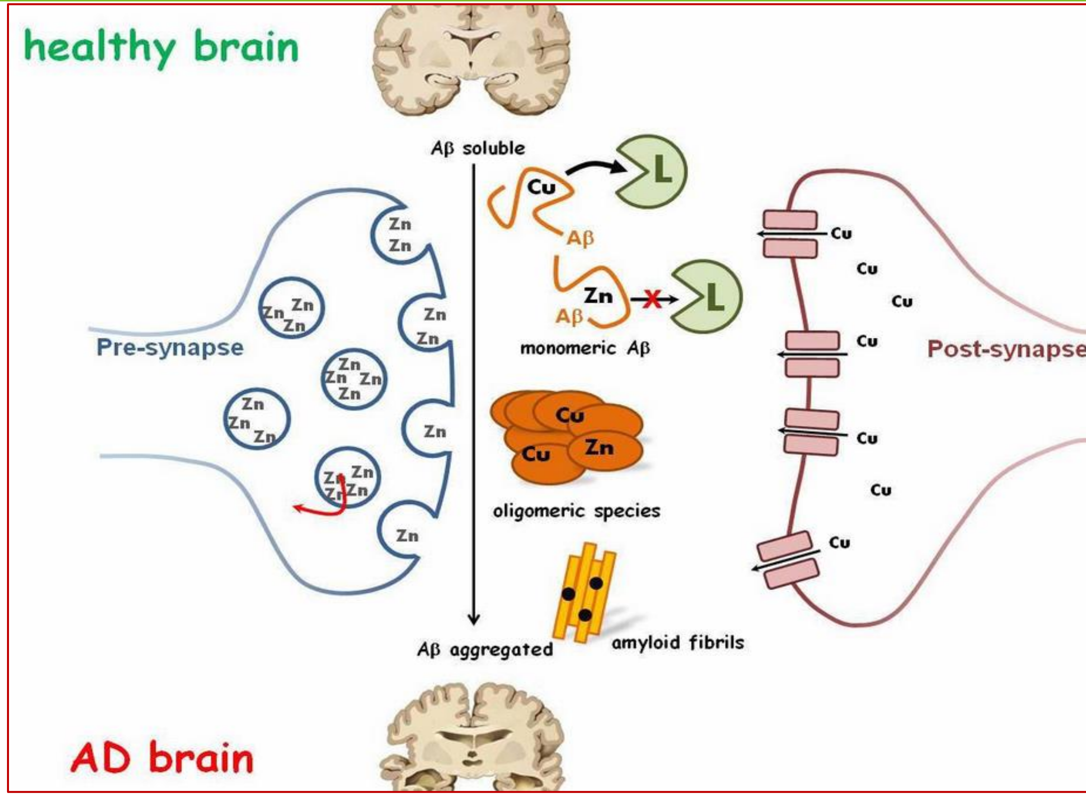
37,49K

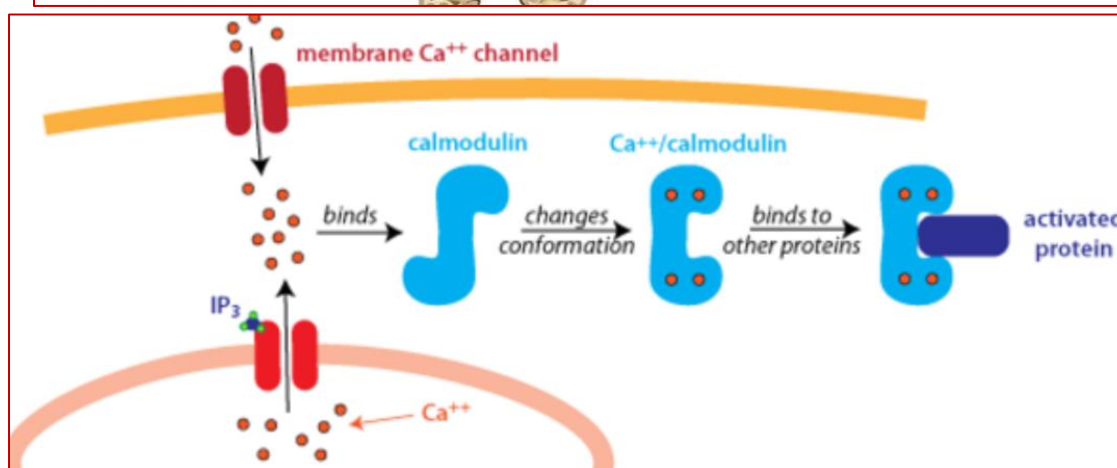
39,51Ca

58,74,75Cu

75,77Zn



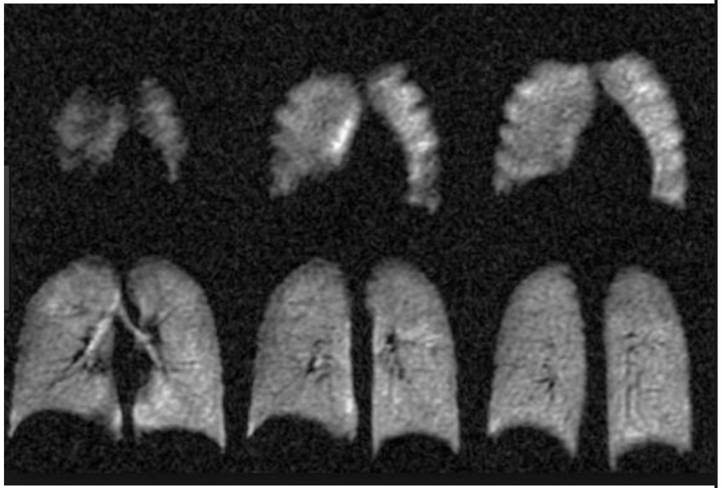




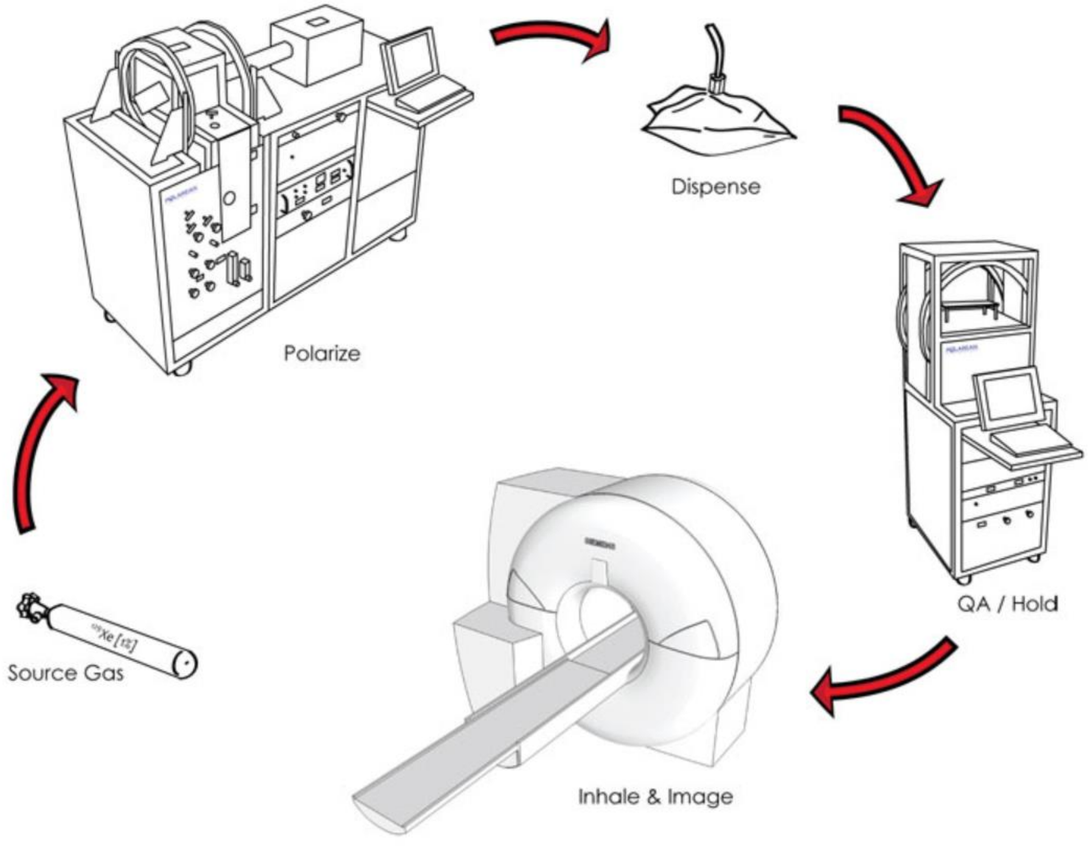
Magnetic resonance imaging

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



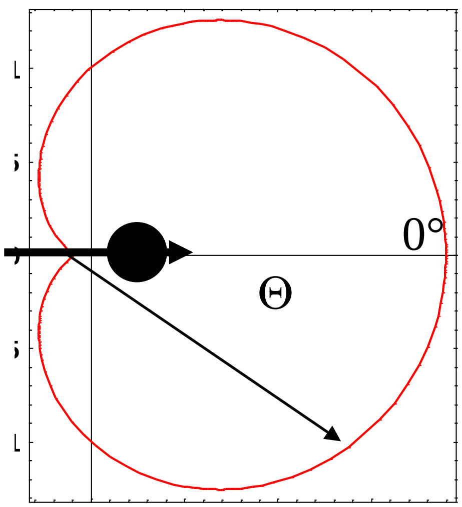
1st medical applications of 3He:
W. Heil et al, Mainz, Nature 1996



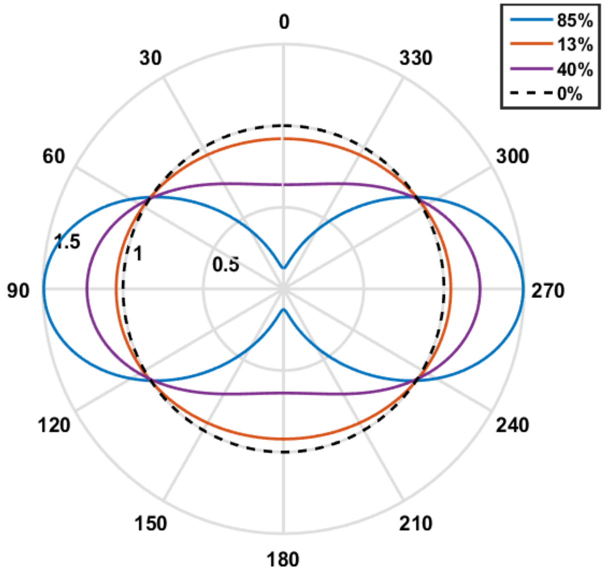
Gamma-decay asymmetry

- 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

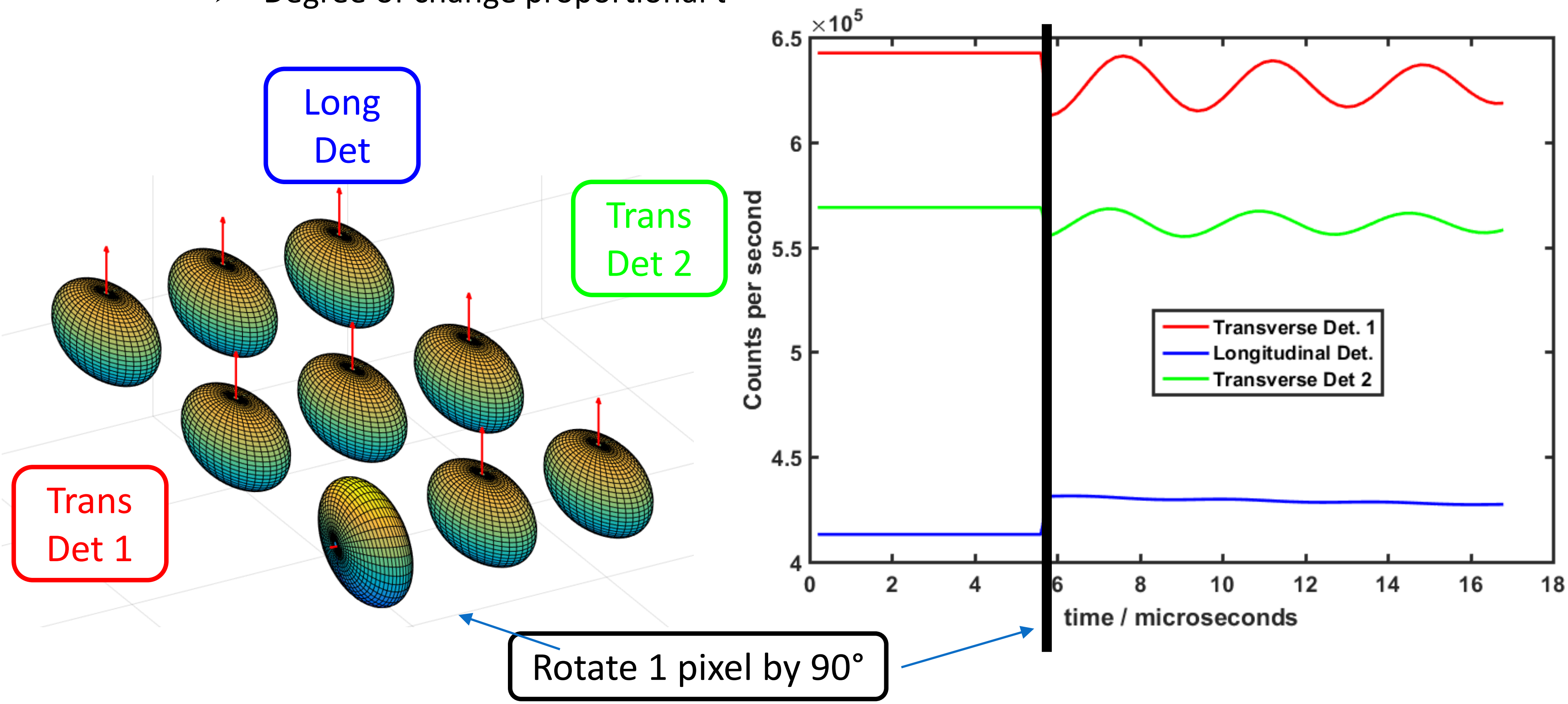
Solution: **gamma-MRI (or simultaneous SPECT-MRI):**

- 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

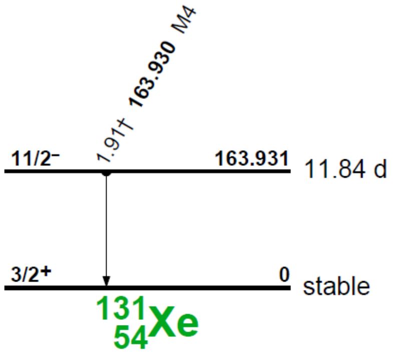
- Pixel size
  - defined by slope of B-field gradients and spectral width of rf pulse
  - more nuclei -> smaller pixels possible up to B gradient and rf limit
- 1 pixel in resonance:
  - change in total gamma counts visible in each detector
  - Degree of change proportional to number of nuclei in addressed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

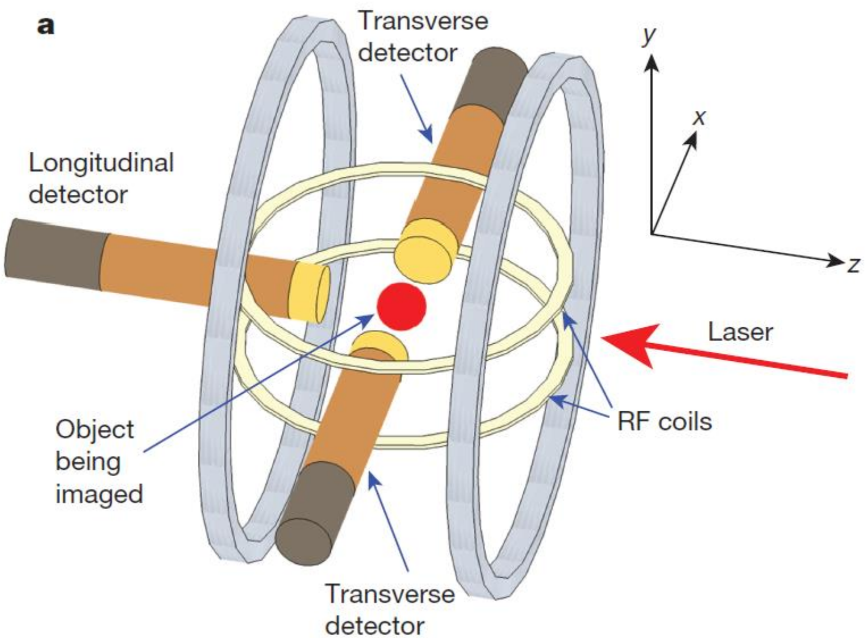


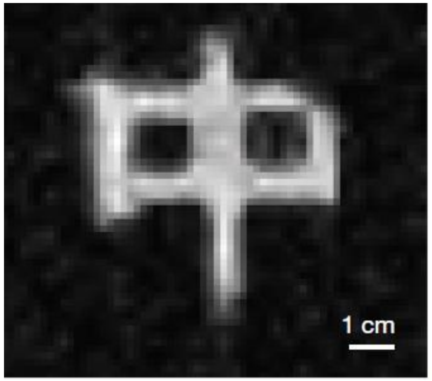
First gamma-MRI

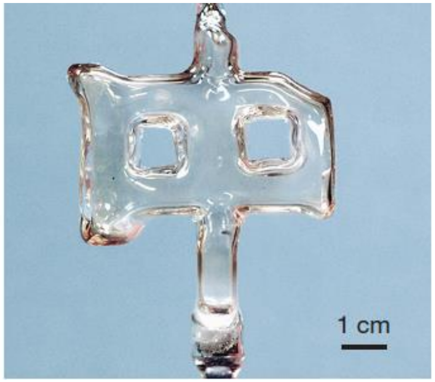
Y. Zheng, G.W. Miller, W.A. Tobias, G.D. Cates, Nature 537, 652 (2016)

- **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

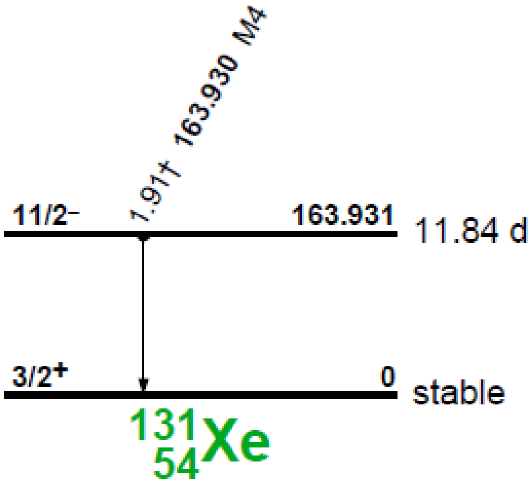
- Work on feasibility of the technique:
  - Use PET/SPECT isotopes or their isomeric states
  - Optimising rf pulses
  - Maintaining of polarization
  - First detectors

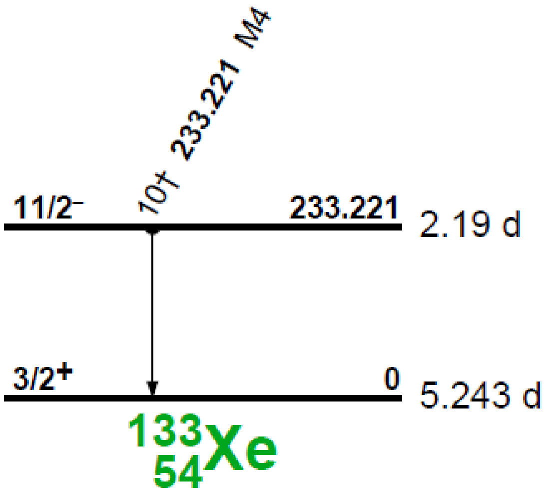
- => lower dose required to record signals

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

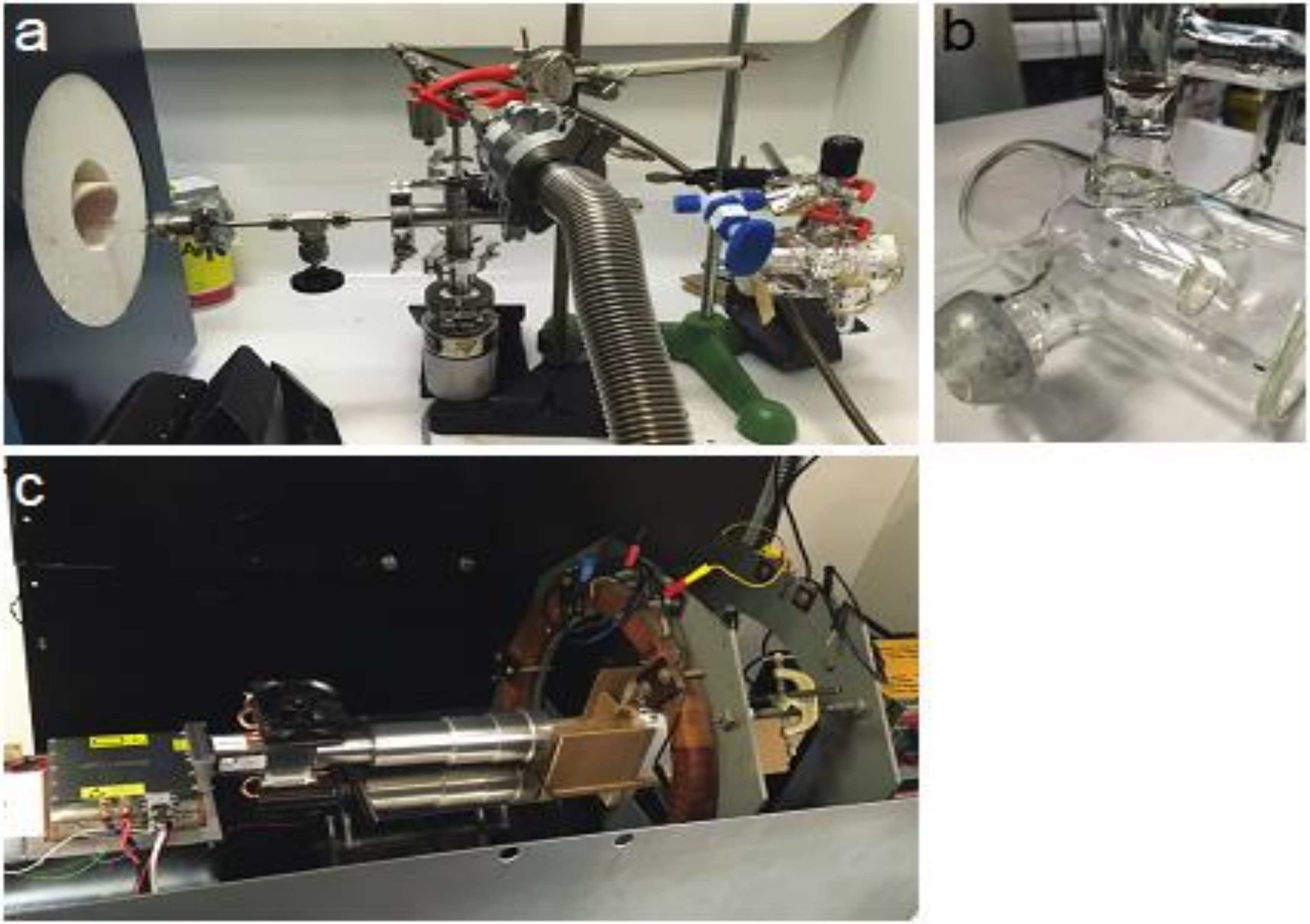
Our 1st isotopes

- 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
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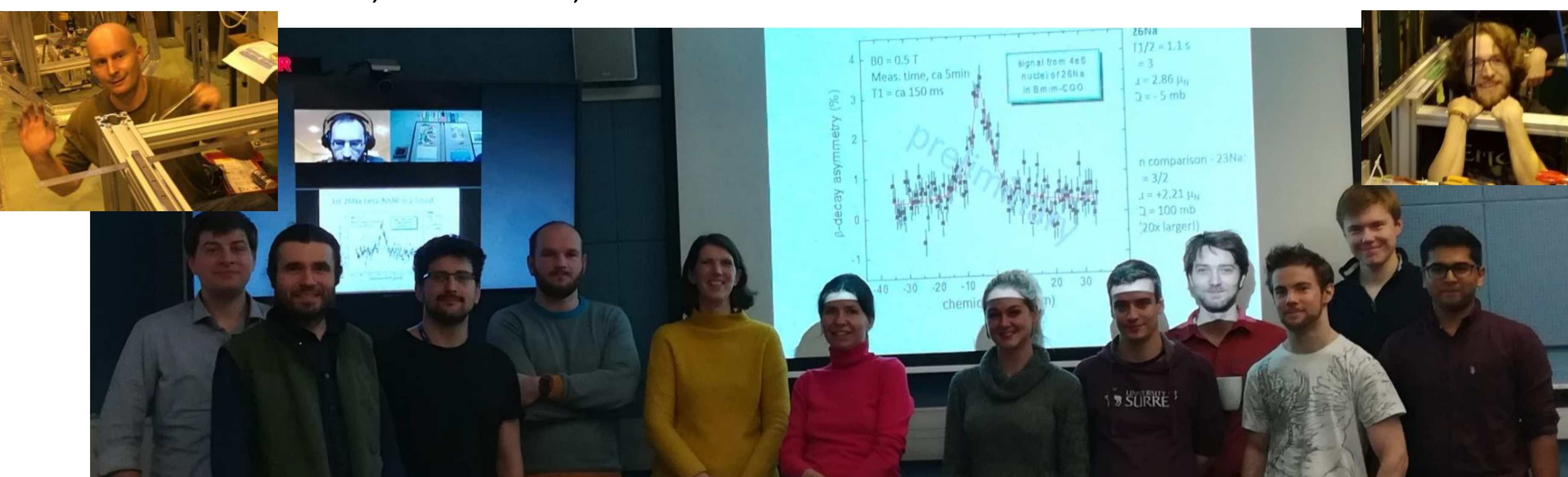
U Manchester/CERN: M. Bissell
AMU Poznan: M. Baranowski, M. Walczak
U Tennessee: M. Madurga Flores, X. Zhang
NPI Rez: D. Zakoucky

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

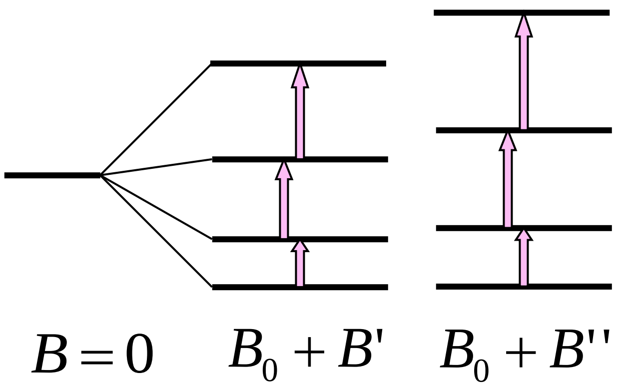
- **Observables**: Larmor frequency
- **Determined properties**
  - Magnetic dipole and electric quadrupole moment of the studied nucleus

Depends on nucleus

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

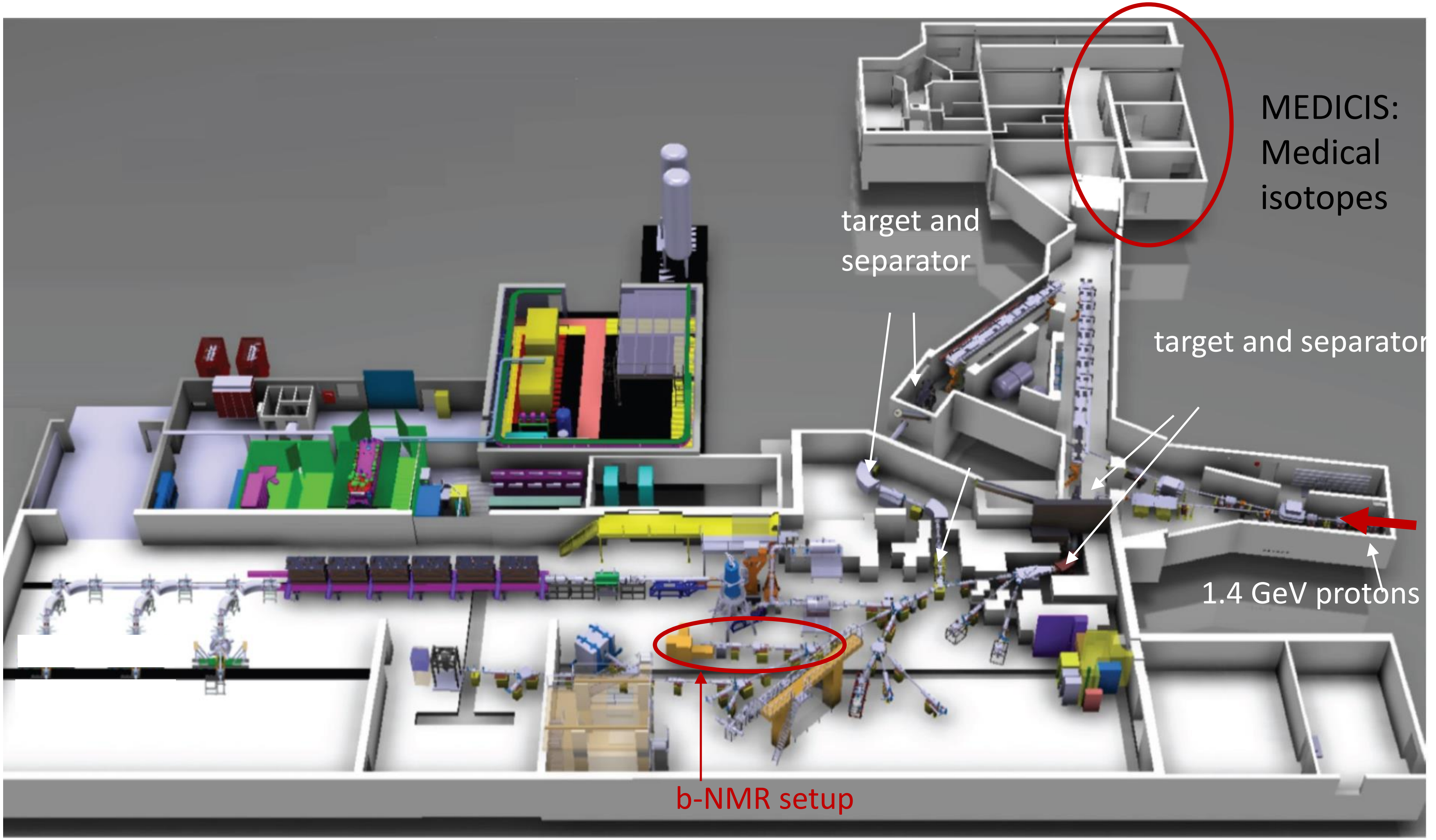
known

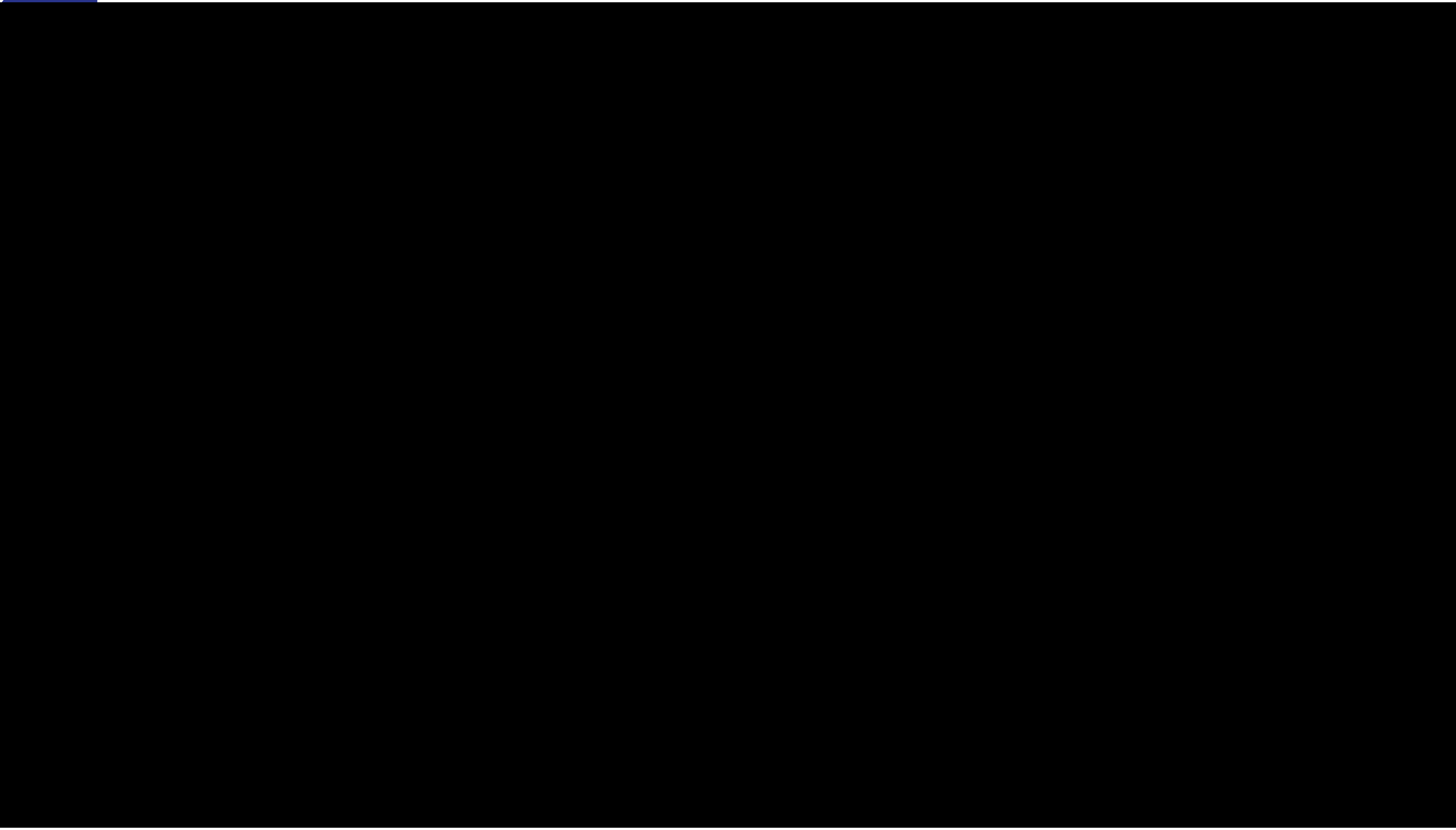
Same nucleus, different host



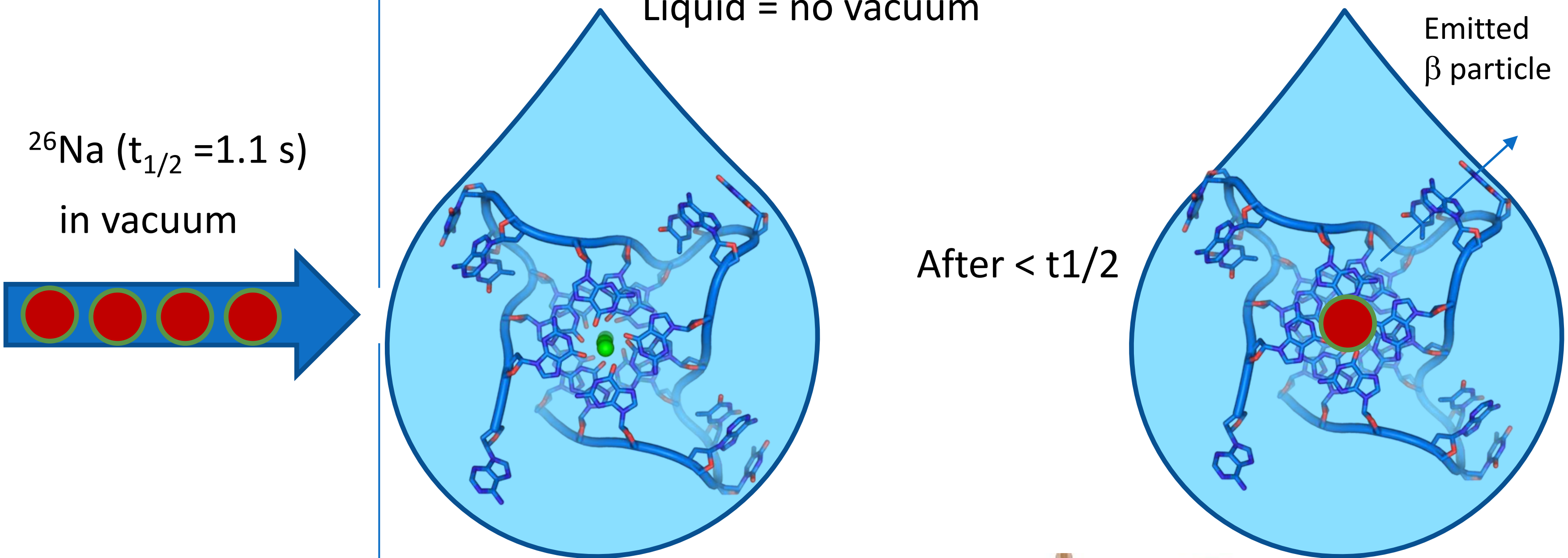
- **Derived information**:
  - Magnetic moment – orbitals occupied by valence nucleons
  - Quadrupole moment – collective properties

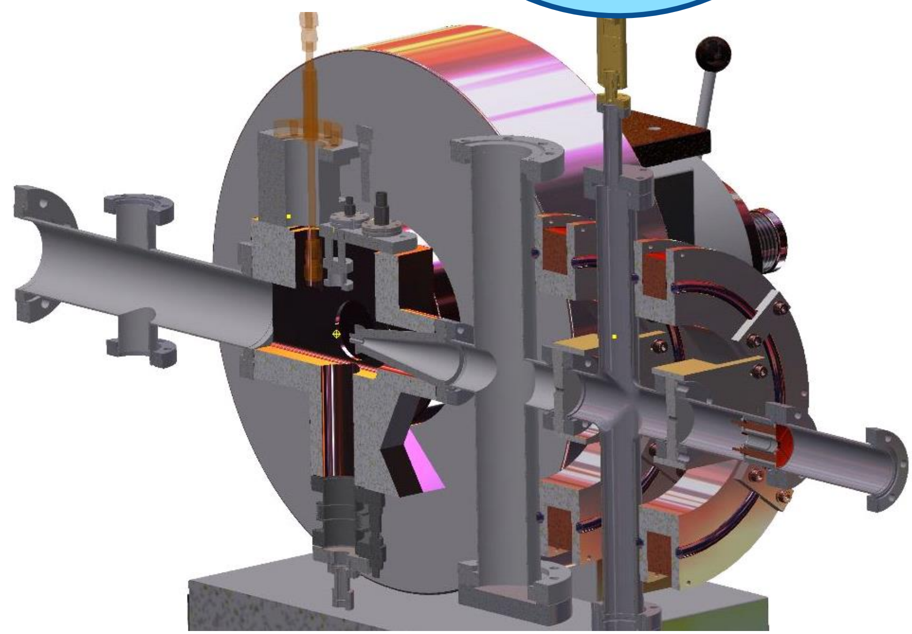
ISOLDE laboratory





Getting probe nuclei into liquid samples



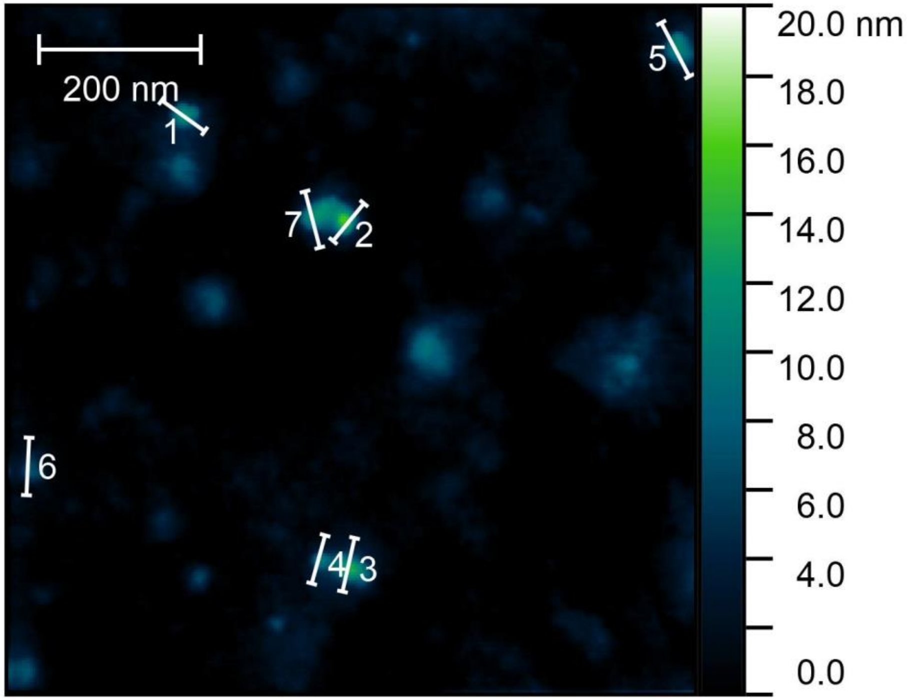


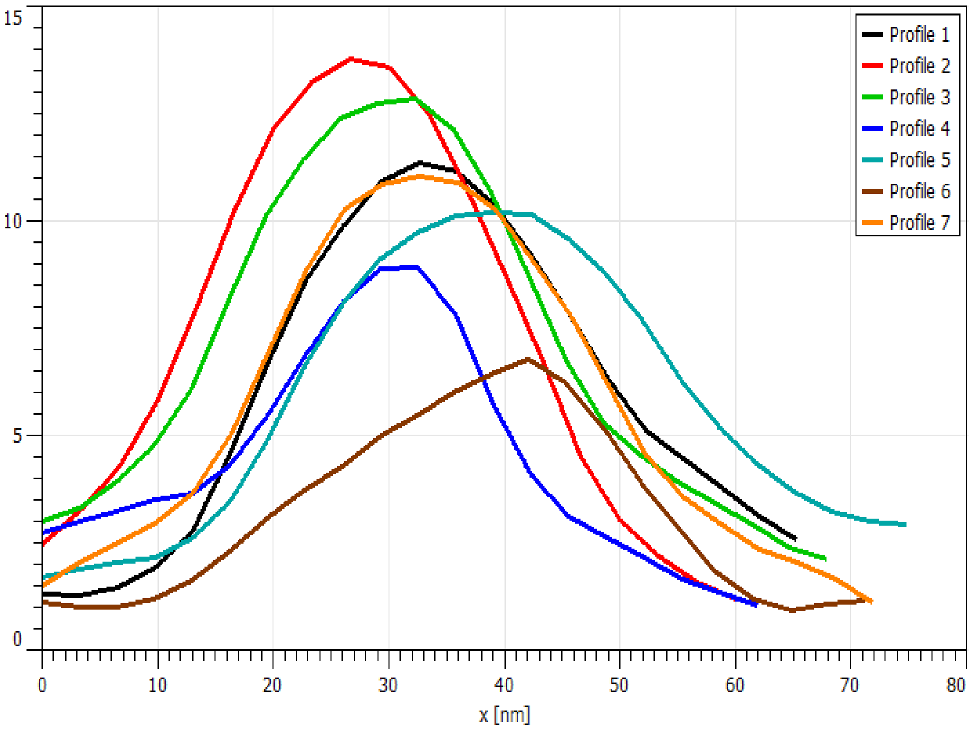
Challenges and constraints:

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

AFM measurements

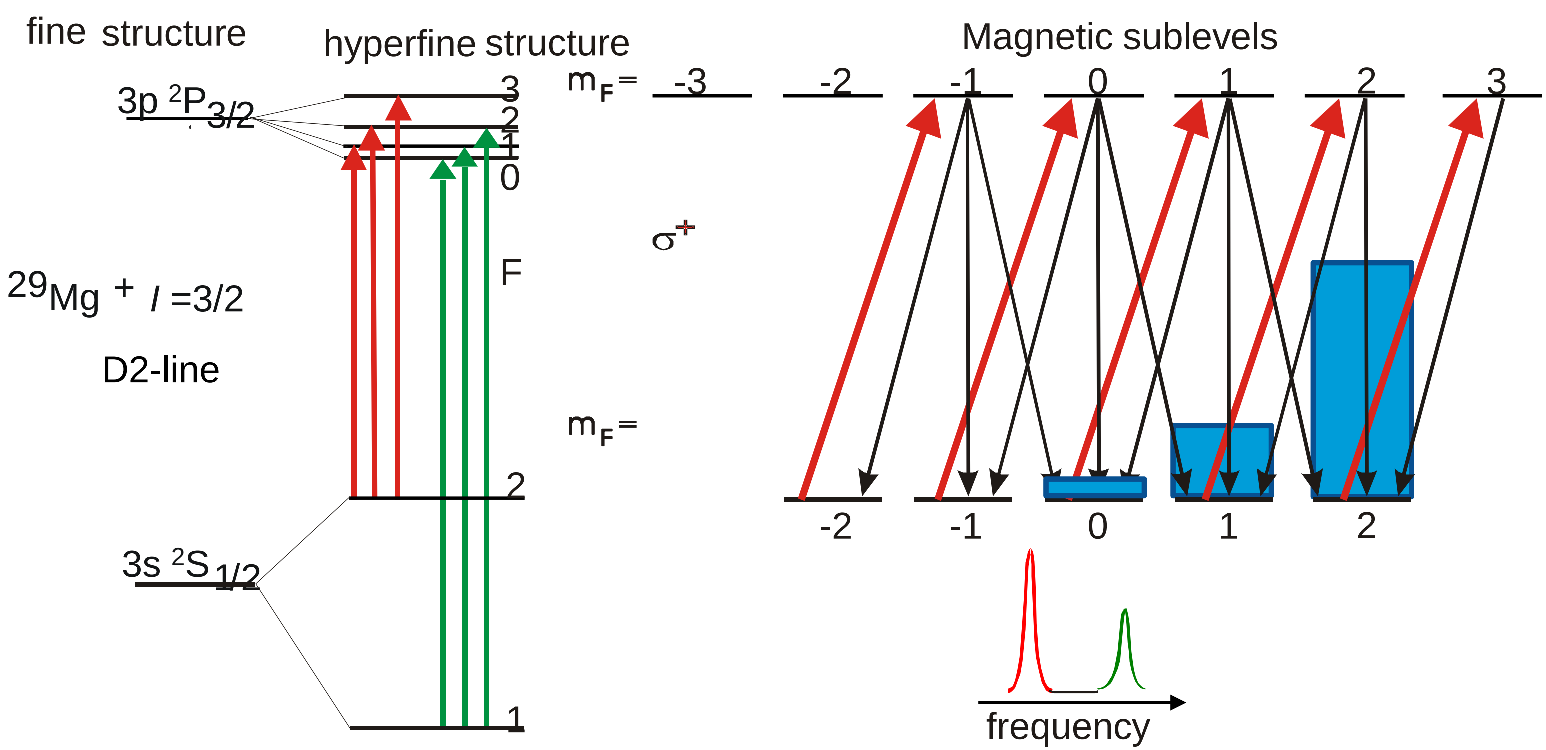
Folded G4T4G4 in Emim-DCA





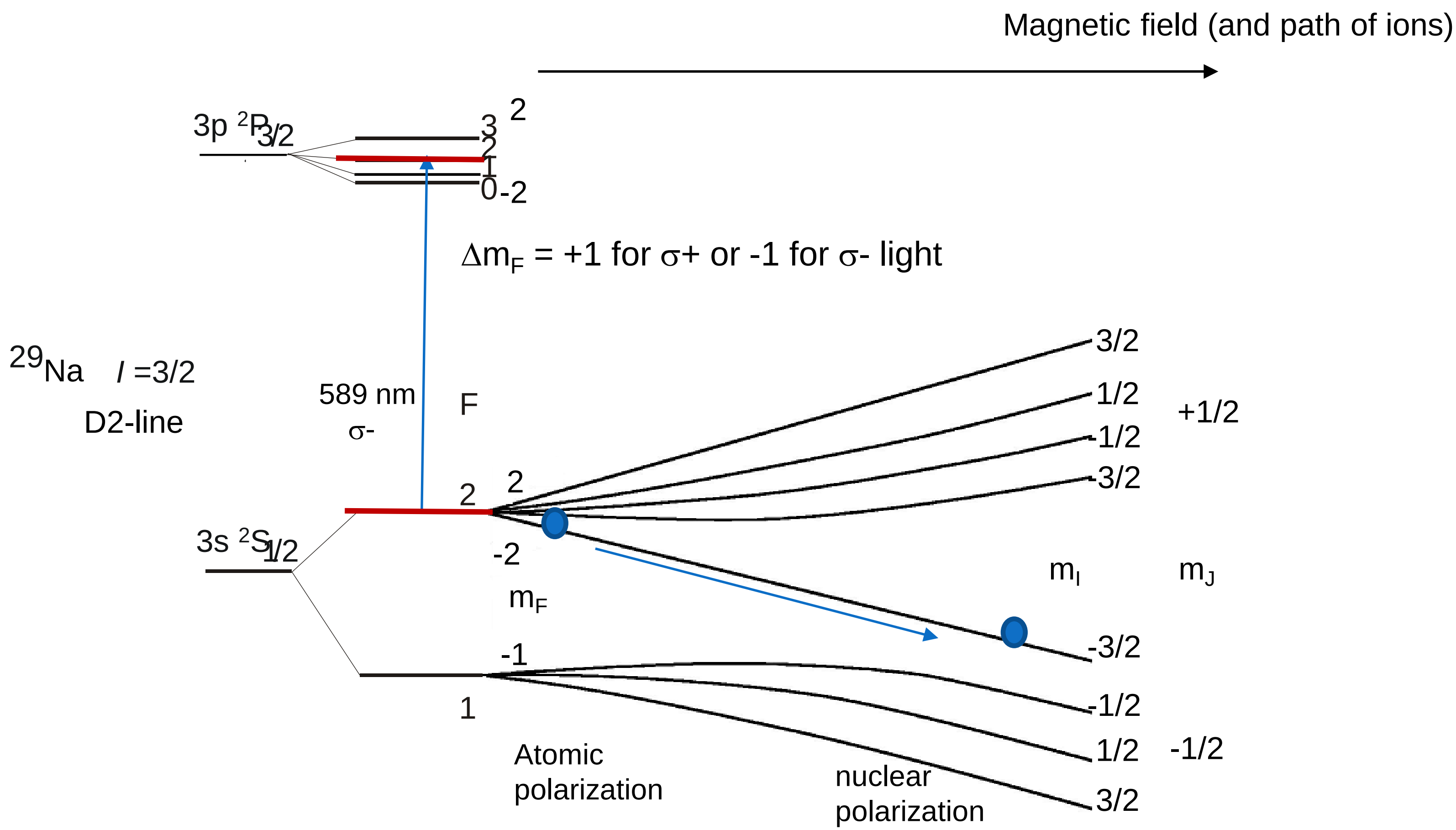
Hyperpolarization via optical pumping

- 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



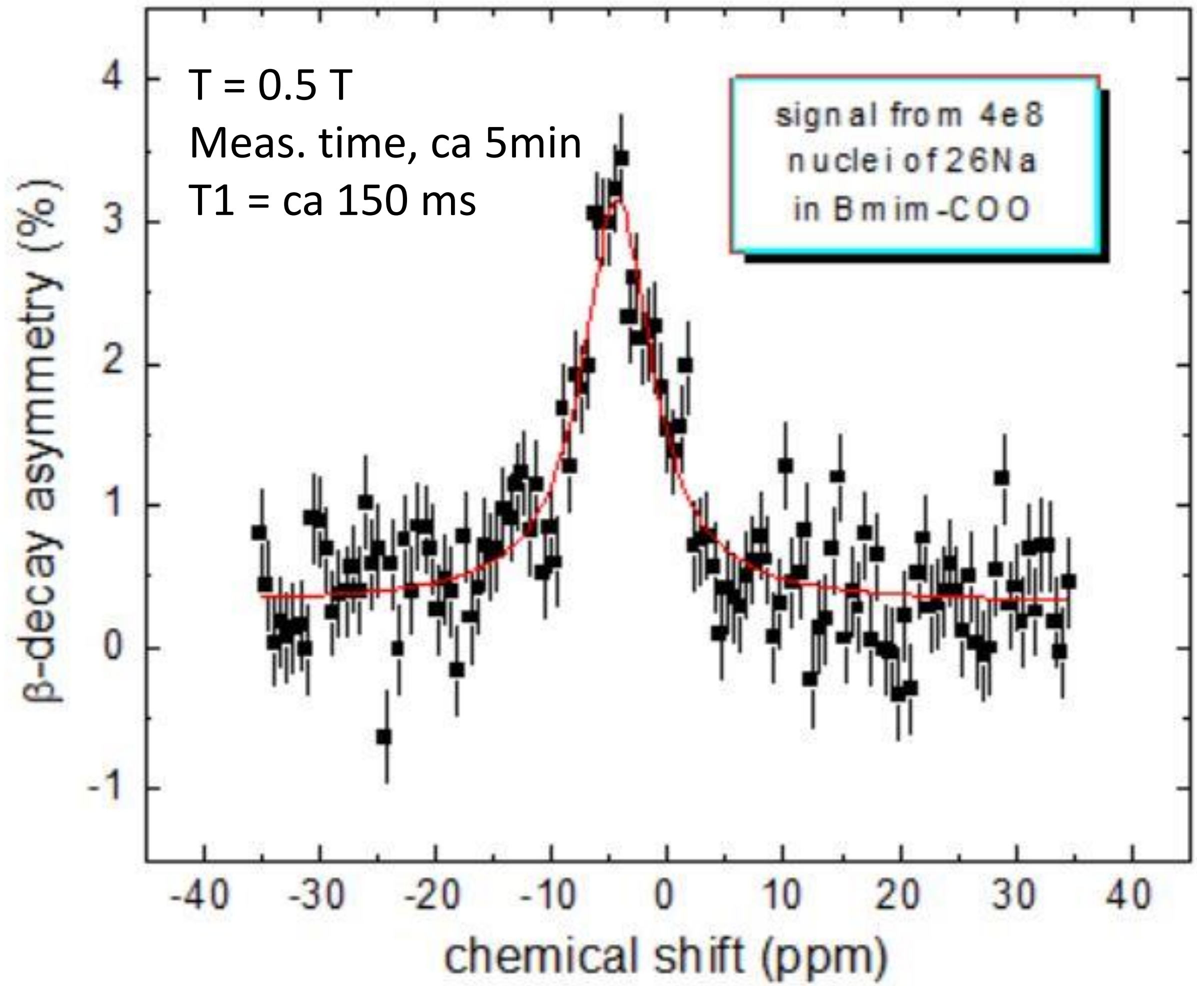
Optical pumping and nuclear spin

- Polarization of atomic spins with circularly polarized laser ($\Delta mF = +1$ for $\sigma+$ or -1 for $\sigma-$ 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)

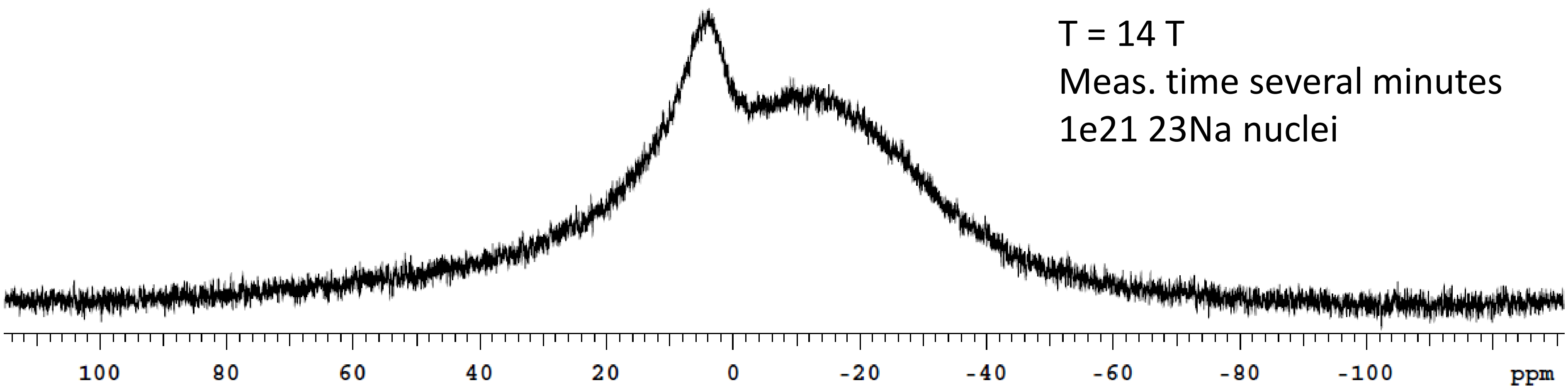


26Na
T1/2 = 1.1 s
I = 3
$\mu = 2.86\ \mu_N$
Q = - 5 mb

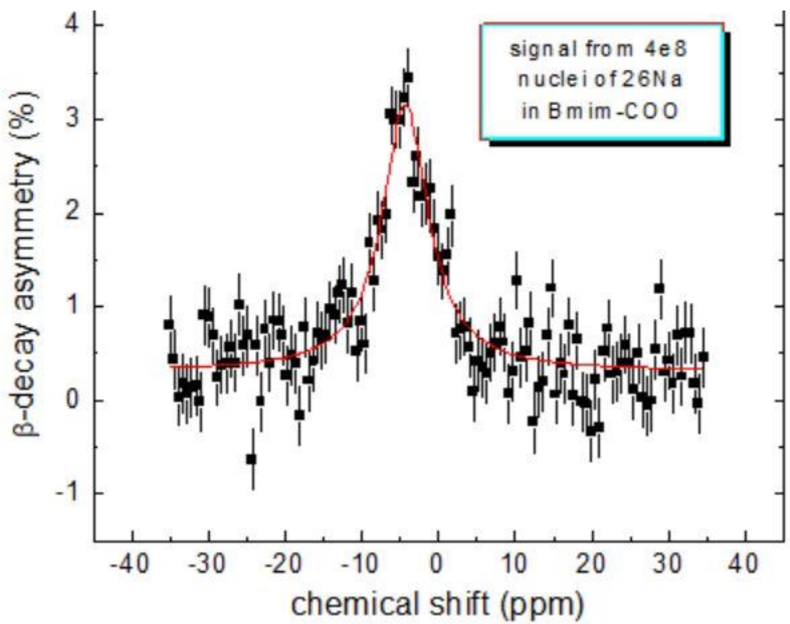
In comparison - 23Na:
I = 3/2
$\mu = +2.21\ \mu_N$
Q = 100 mb
(20x larger!)

Comparison to conventional NMR

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

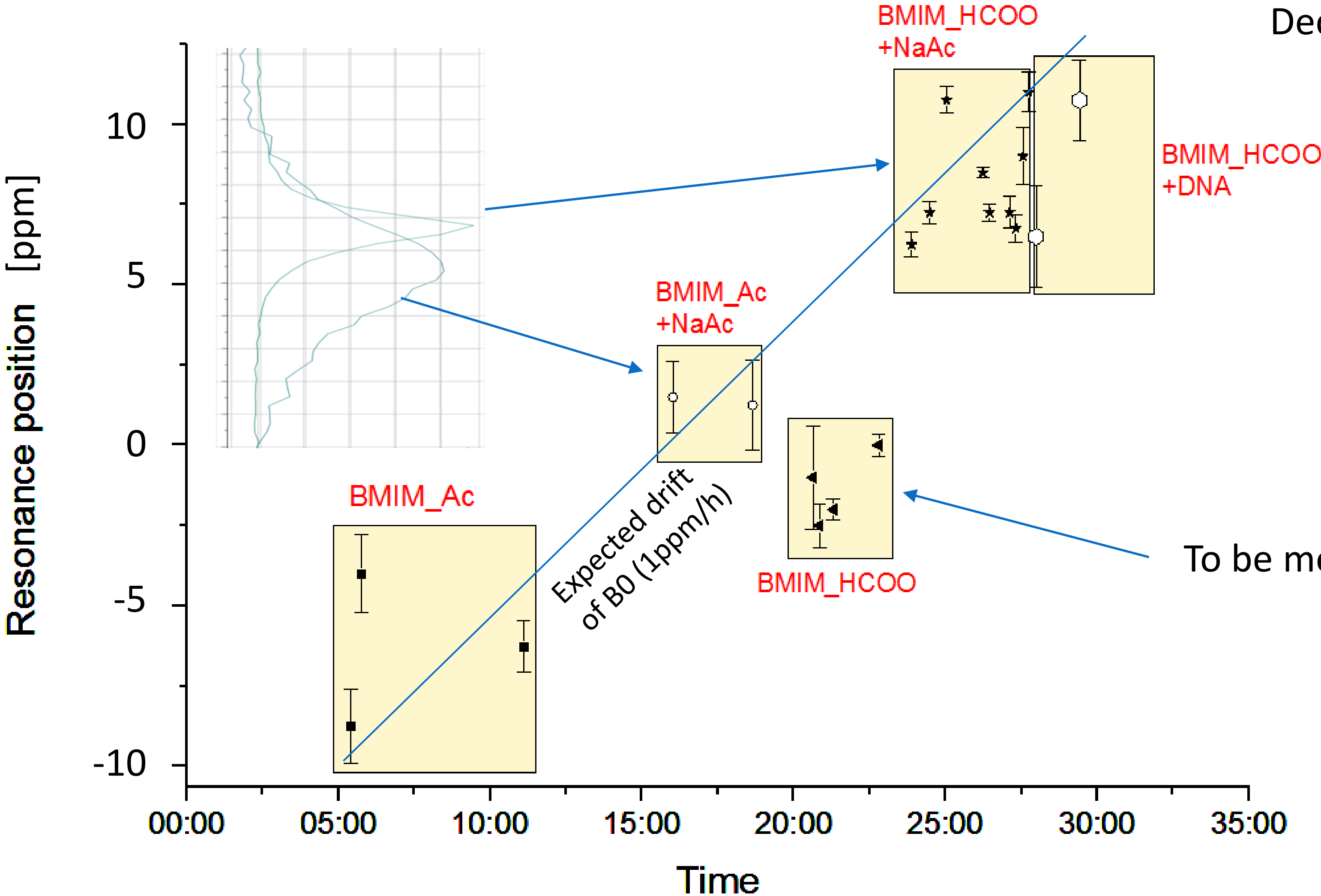


T = 14 T
Meas. time several minutes
1e21 23Na nuclei



Latest results

December 2017

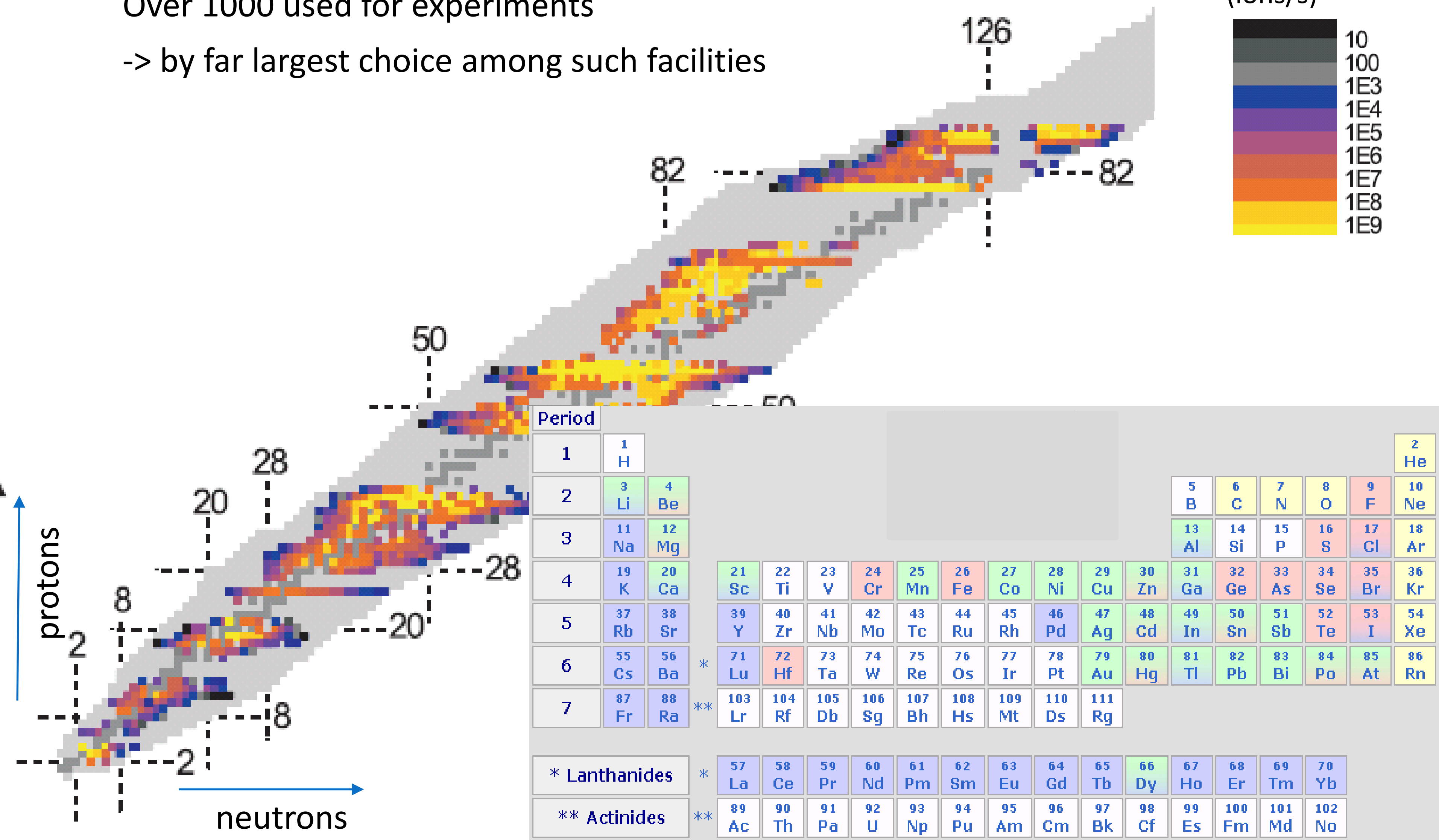


In addition: conventional 23Na studies performed 1.5 weeks ago

ISOLDE radionuclei

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

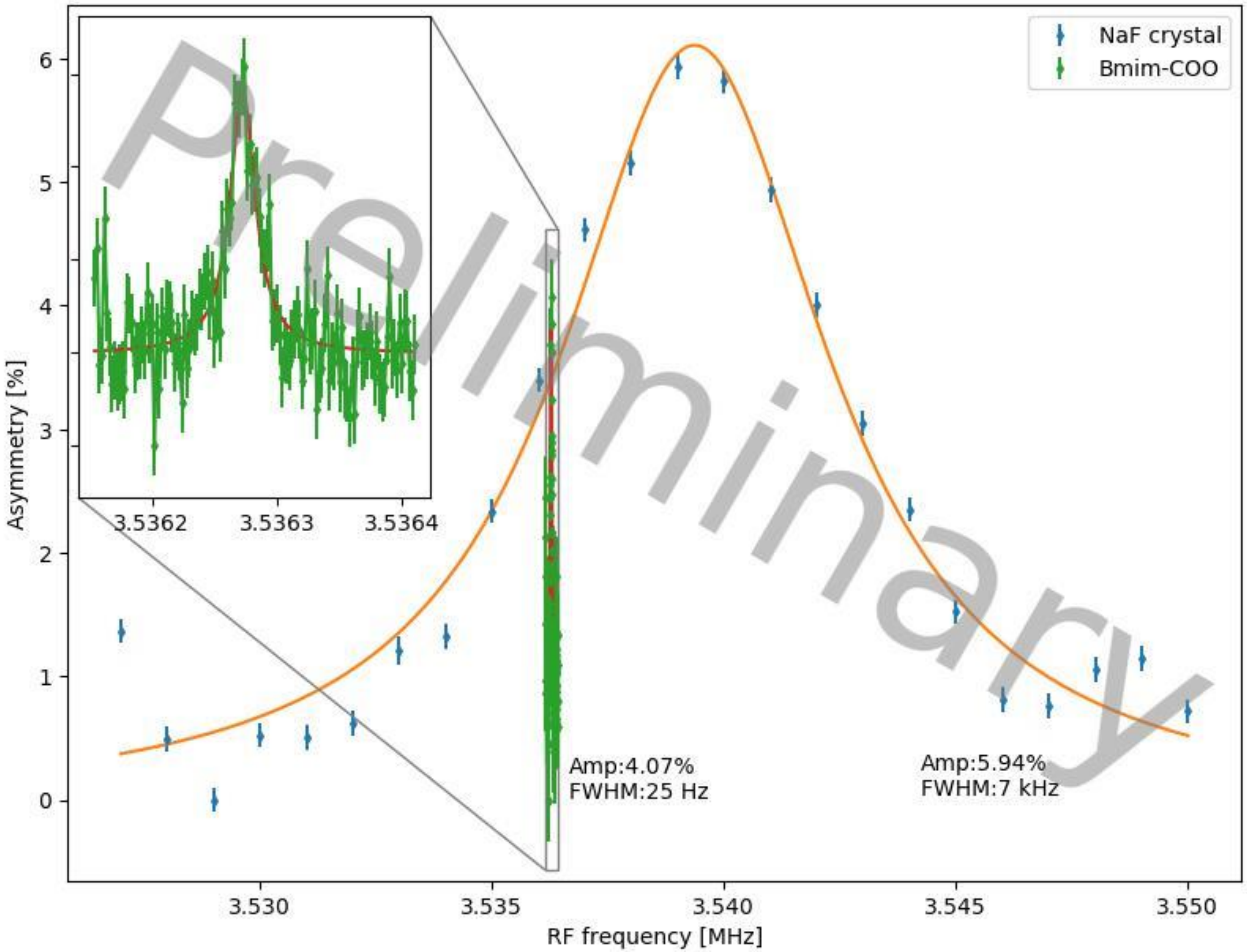
-> by far largest choice among such facilities



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

$\mu = 2.86\ \mu_N$

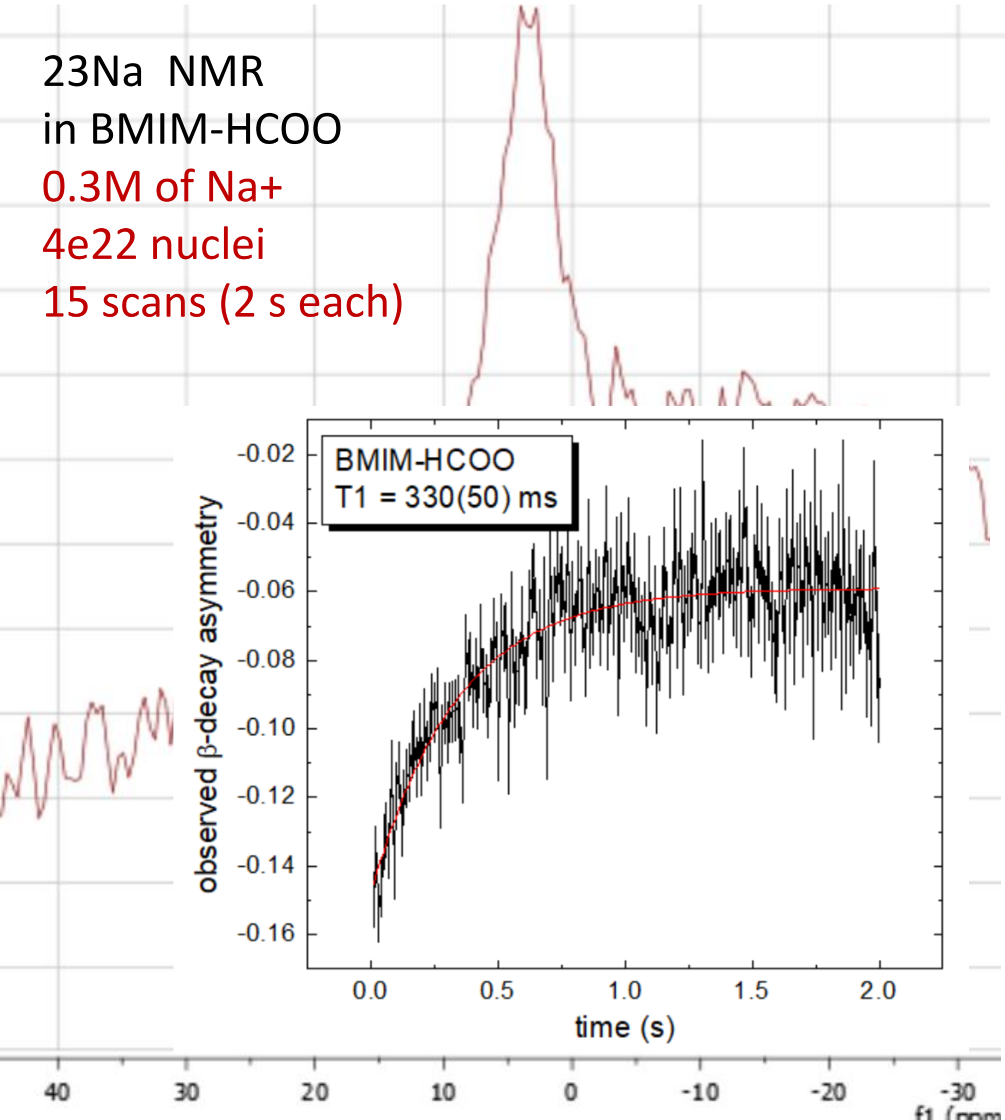
Q = - 5 mb

(20x smaller than 23Na)

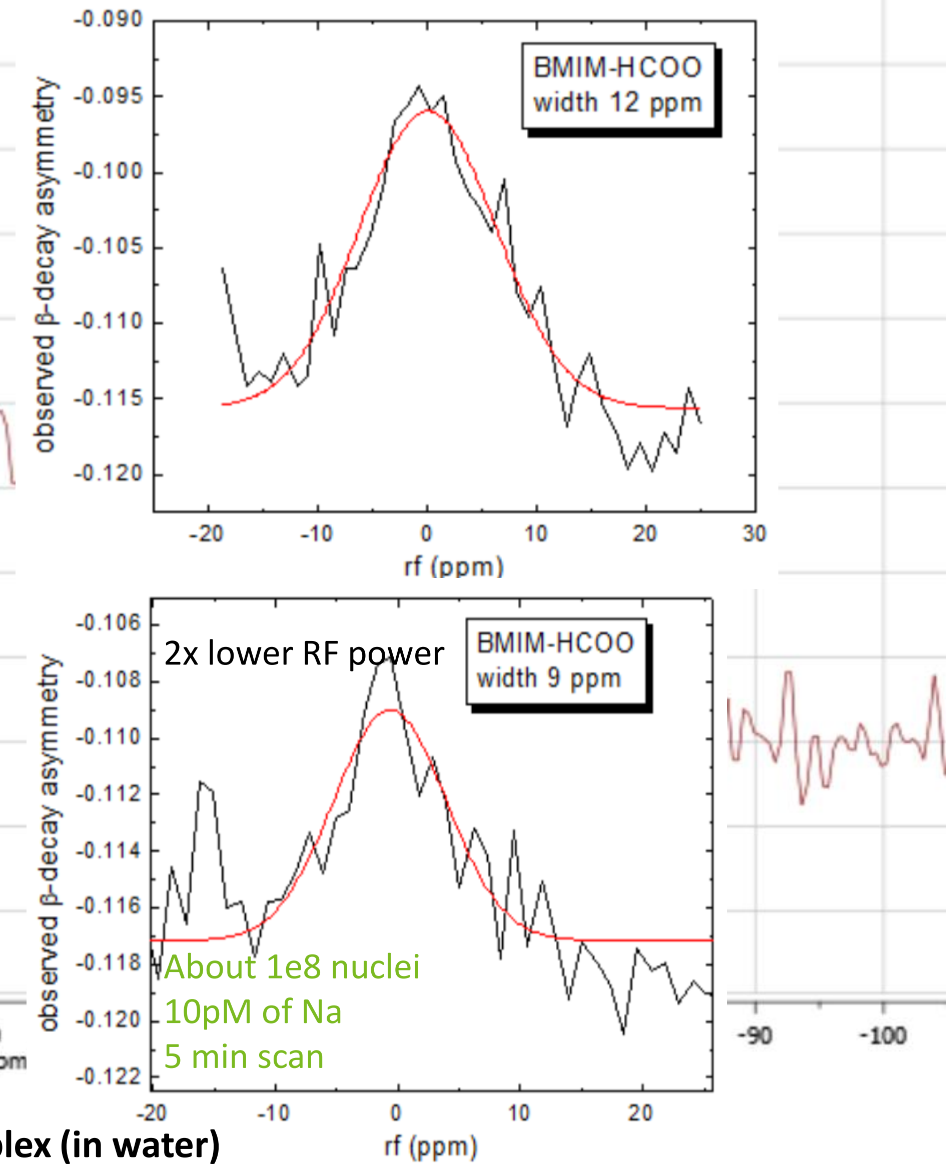
Resonance much narrower than in solid samples used for nuclear physics

Conventional 23Na NMR vs 26Na beta-NMR

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



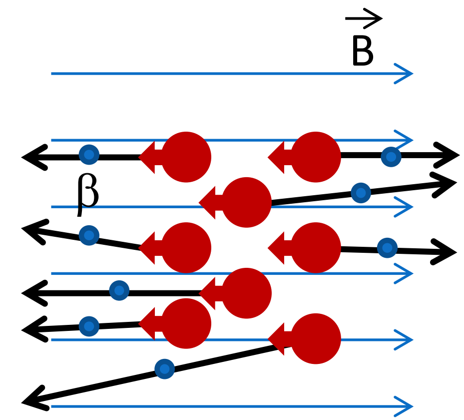
26Na beta-NMR, December 2017, May 2018



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:

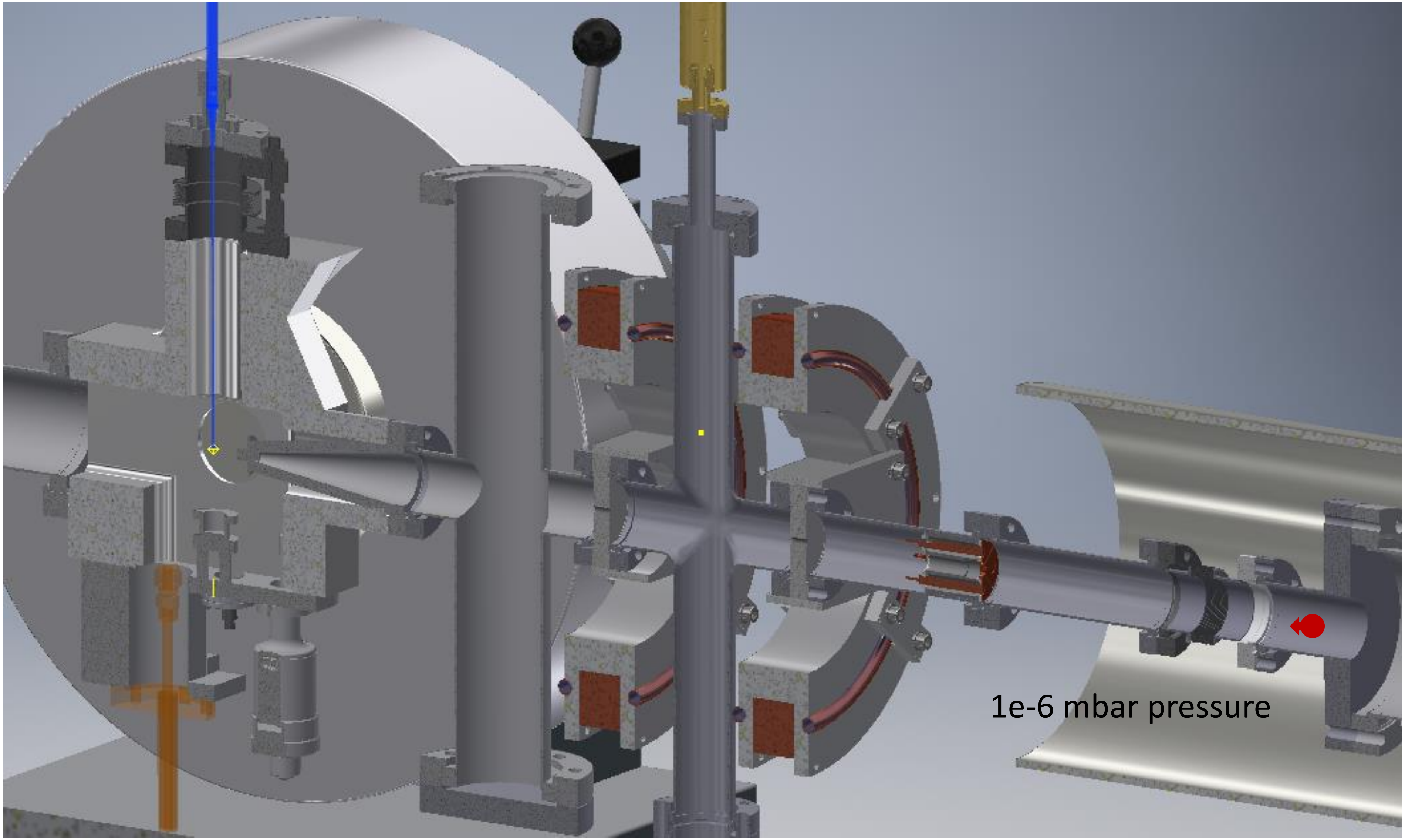
-1 for $\Delta I = -1$

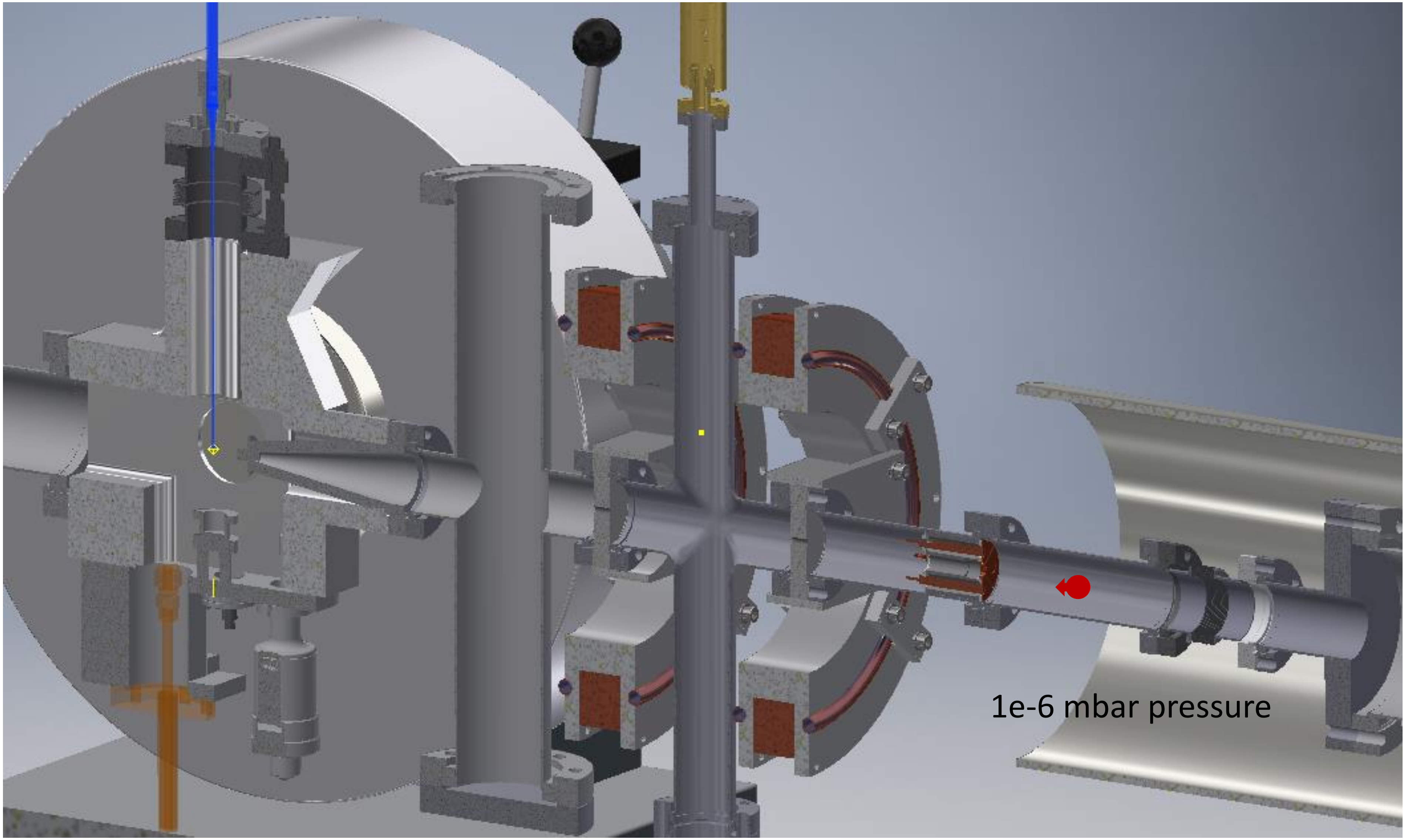
$I_i/(I_i + 1)$ for $\Delta I = +1$

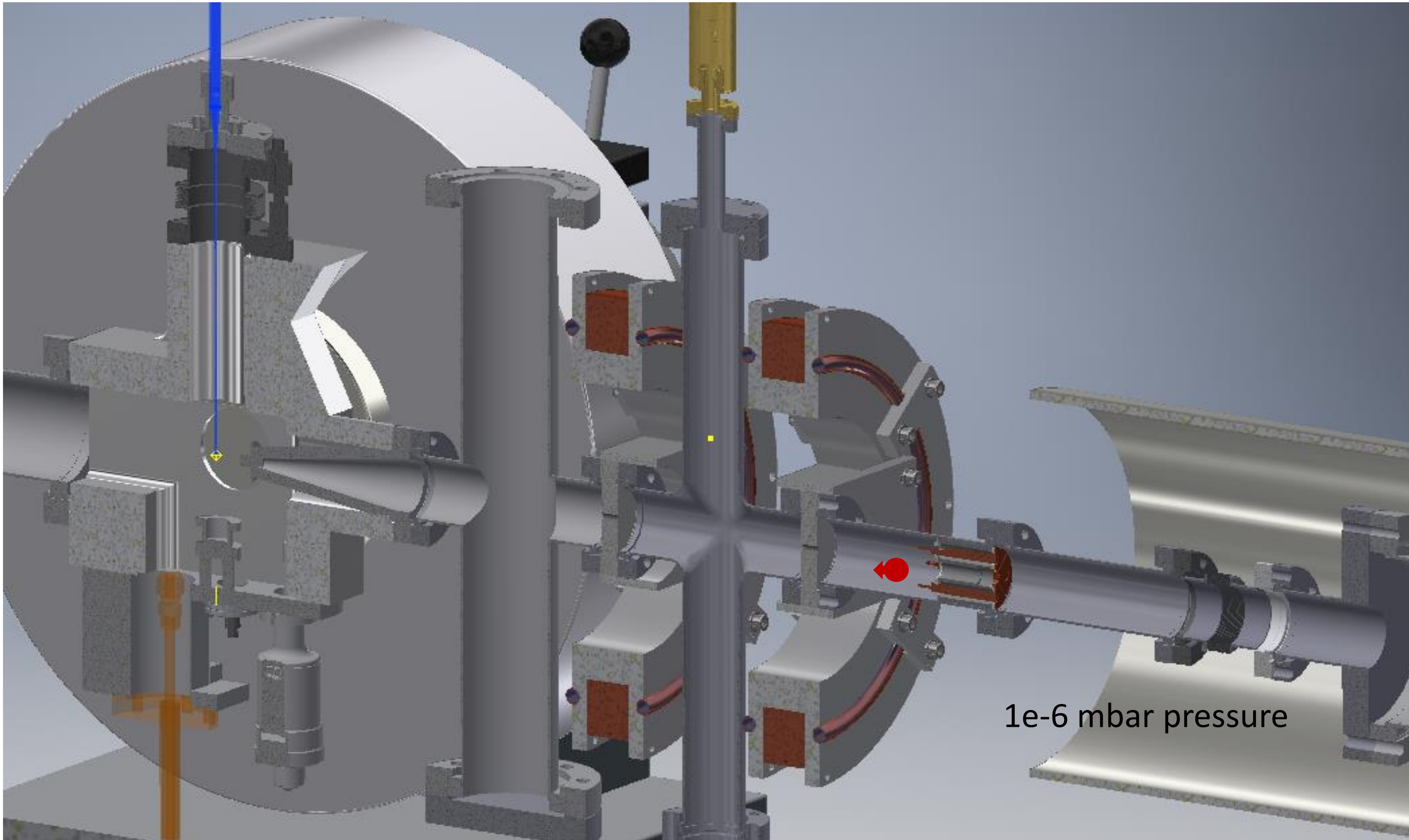
$-I_i/(I_i + 1)$ for $\Delta I = 0$ (Gamow Teller)

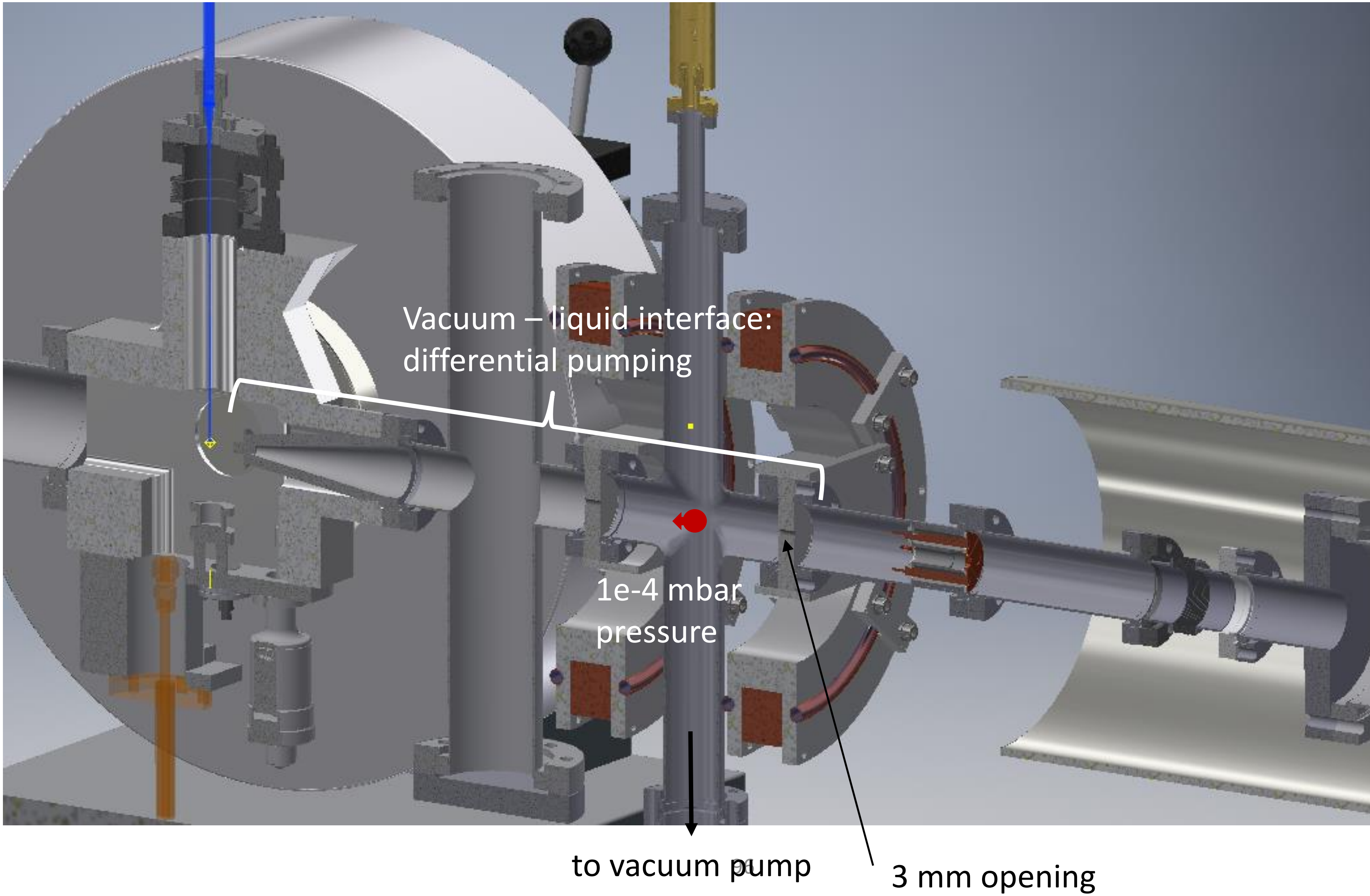
0 for $\Delta I = 0$ (Fermi)

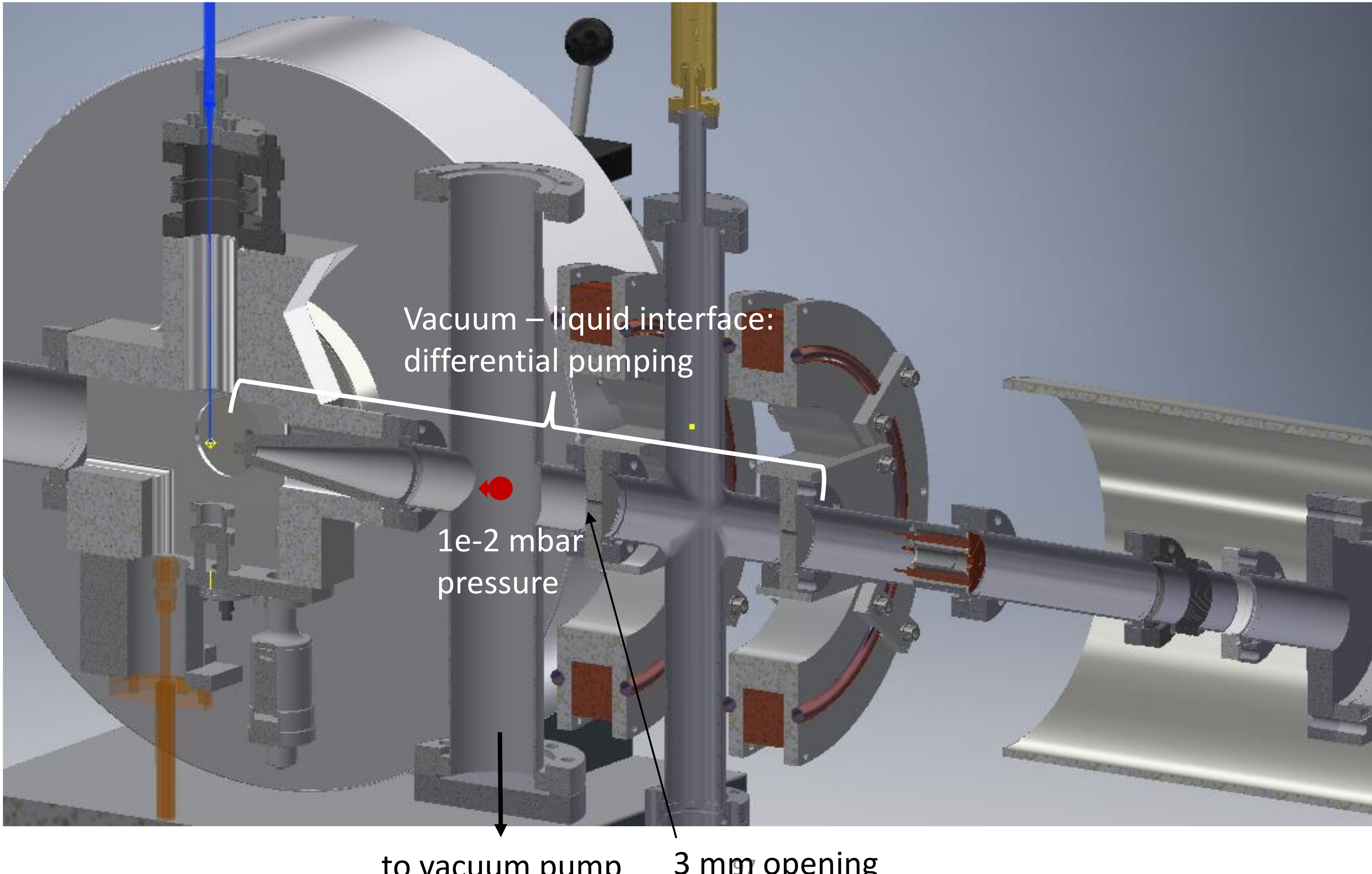
Measured β-decay asymmetry: $A = \dfrac{N(0°) - N(180°)}{N(0°) + N(180°)} = \dfrac{N_1 - N_2}{N_1 + N_2}$

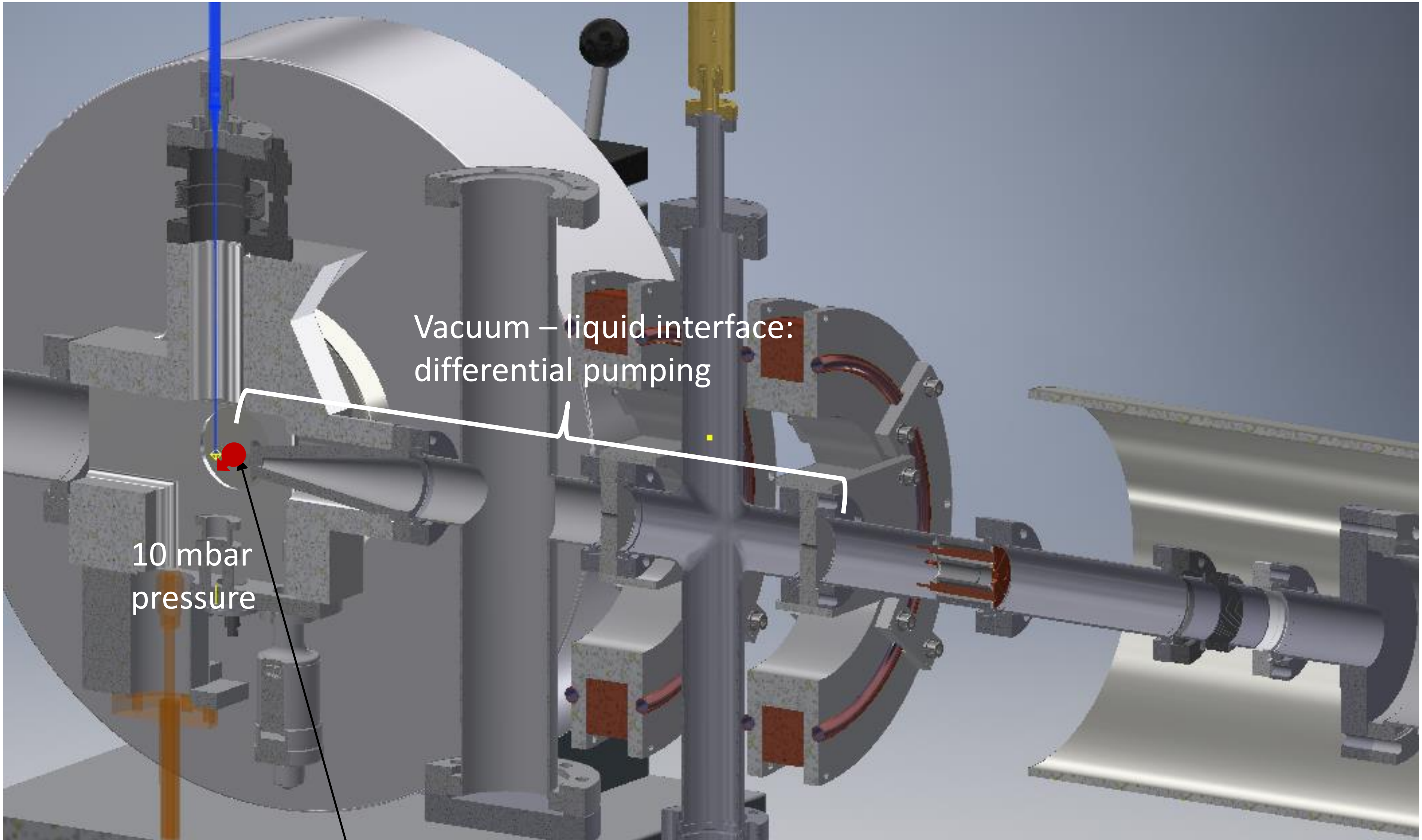

1e-6 mbar pressure


1e-6 mbar pressure

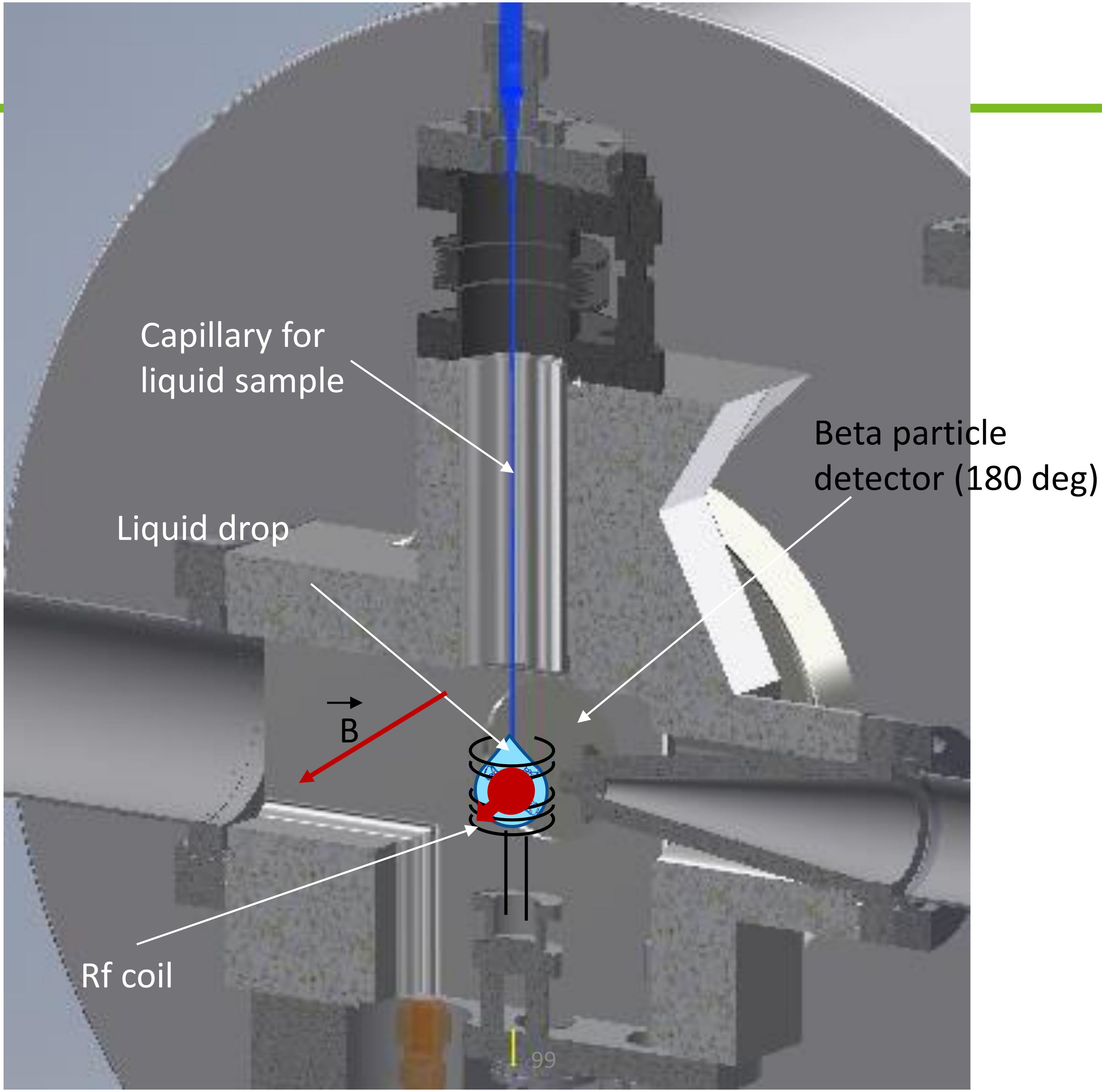

1e-6 mbar pressure

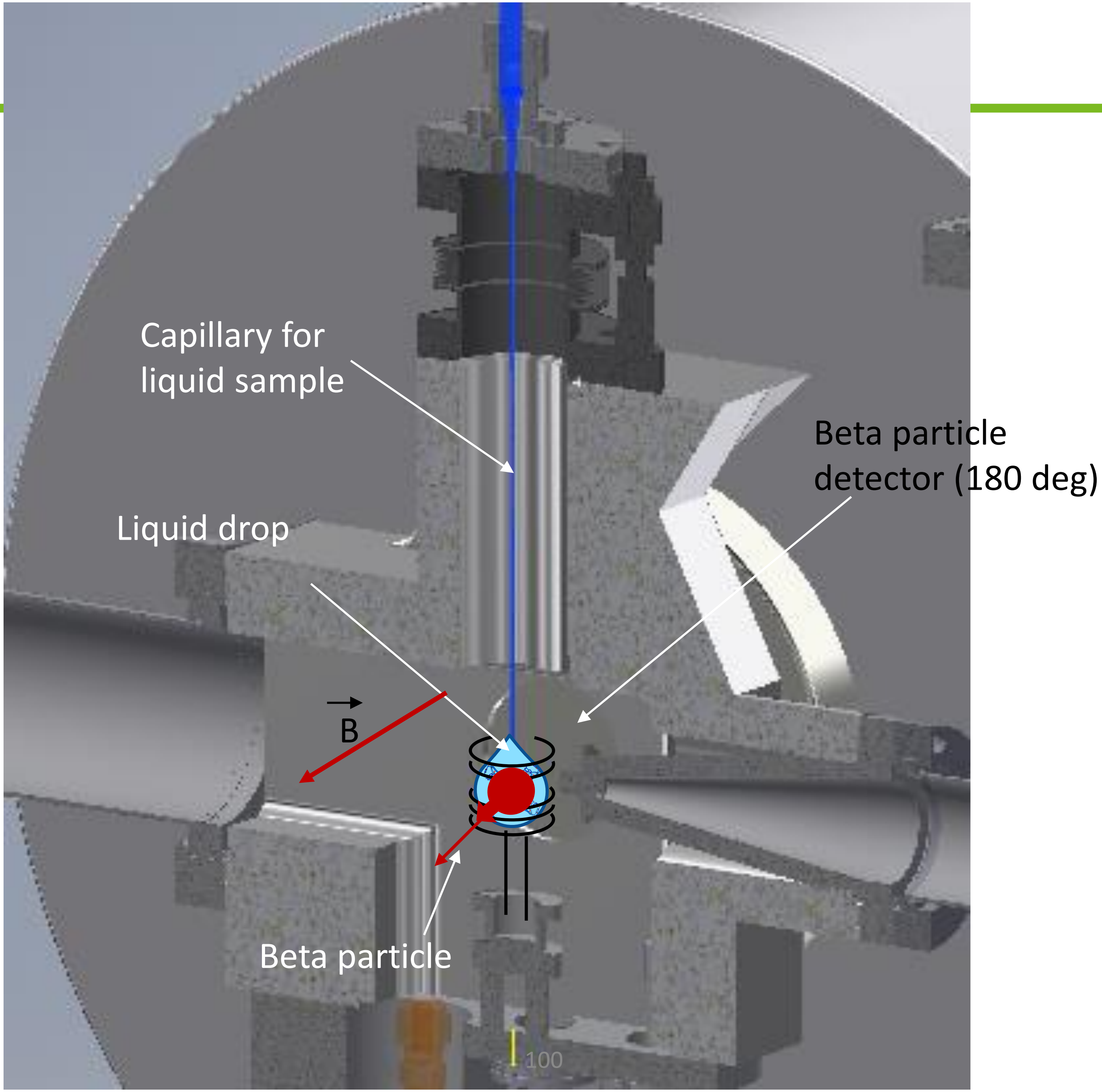

Vacuum – liquid interface:
differential pumping
1e-4 mbar
pressure
to vacuum pump
3 mm opening


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

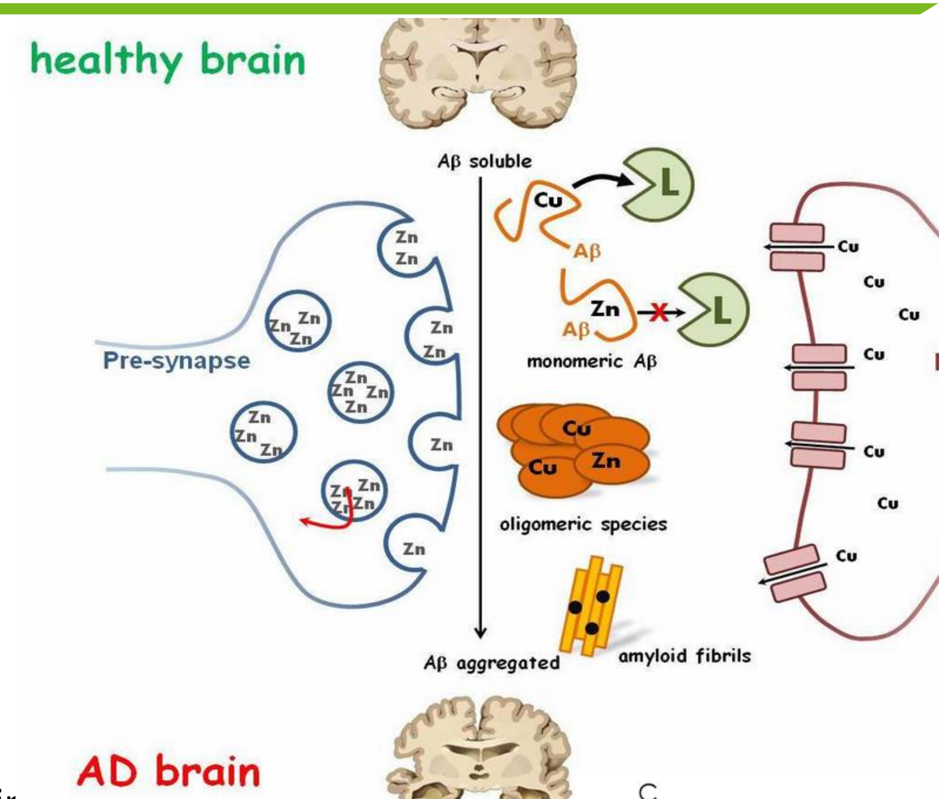

Capillary for
liquid sample
Beta particle
detector (180 deg)
Liquid drop
B
Rf coil

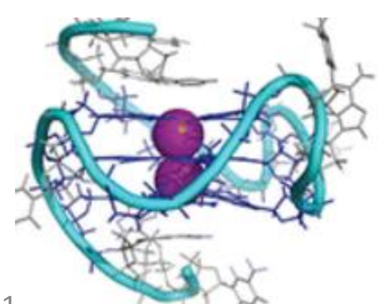

Capillary for
liquid sample
Beta particle
detector (180 deg)
Liquid drop
B
Beta particle
100

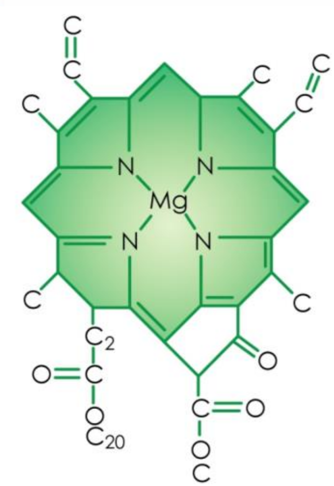
Studying metal ions in biology

- 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