Billion-fold improvement in NMR sensitivity and study of metal-ion interaction with biomolecules

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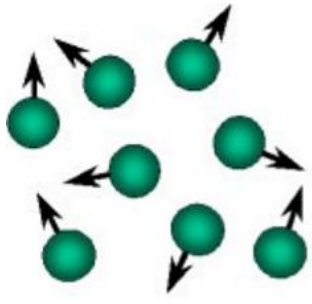
Outline

- NMR and its limits
- Paths to ultra-sensitivity:
  - Hyperpolarization with lasers
  - Radioactive probe nuclei
- Experiment
- Studies of metals in biology

Nuclear Magnetic Resonance

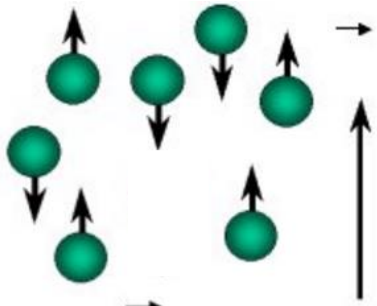
NMR: technique allowing identification of complex assemblies of atoms in molecules

- Participants:
  - Probe atoms (nuclear spin different from 0 = they can be oriented in magnetic fields)
  - Sample/ environment to be studied
- Magnetic field
  - Strong static field (B)
  - Weaker field oscillating at radio-frequency (MHz)



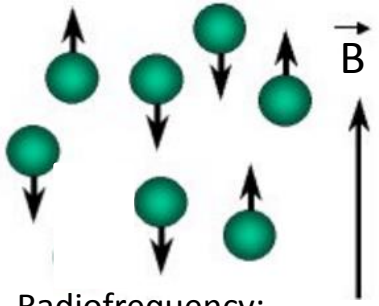
$\vec{B}_o = 0$

Randomly oriented

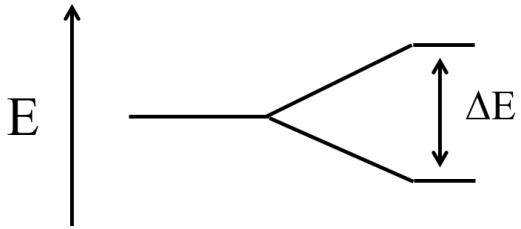


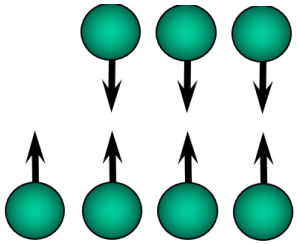
$\vec{B}_o > 0$

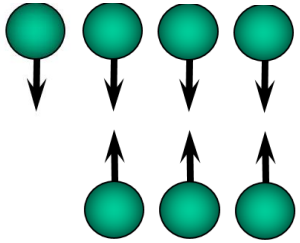
Highly oriented



Radiofrequency:
Change in orientation







NMR and role of metal ions in biology

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

- **Na(I), K(I), Mg(I), Cu(I), Zn(II):**
  - Among most abundant cations in living organisms
  - Right concentration crucial for correct functioning of cellular processes

- Challenges in studying them:
  - Often closed electron shells, thus invisible in many methods;
  - in NMR: almost invisible signals due to small abundance, spin > 1/2, and small sensitivity (due to small magnetic moment)

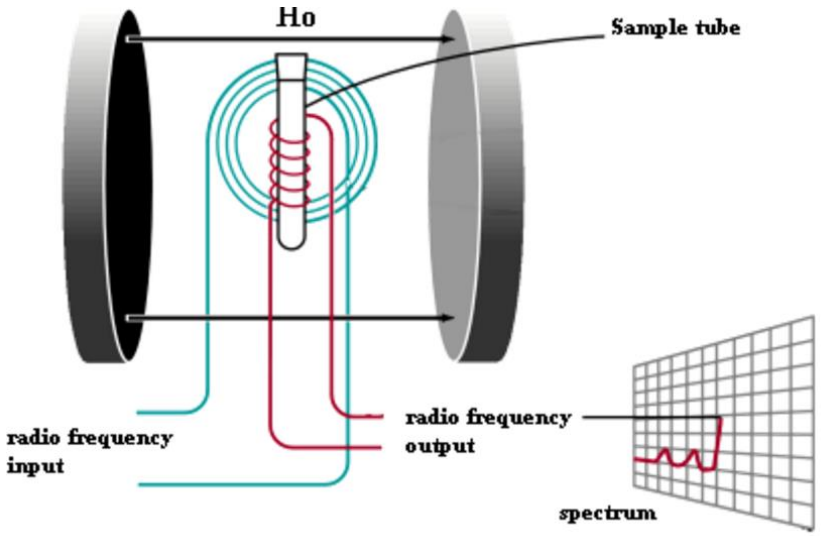
- Sensitivity of conventional NMR is very (or even too) low

=> ultra-sensitive NMR approaches needed

NMR limitation: sensitivity

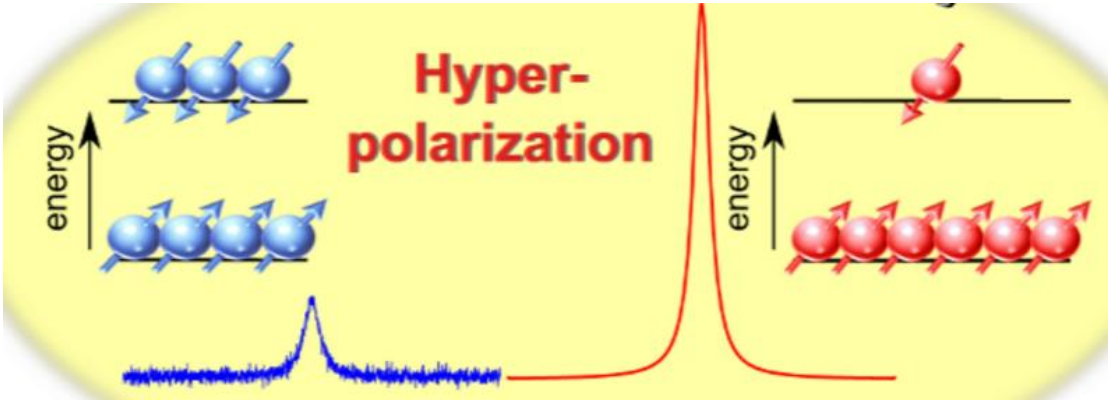
- Why is NMR so unsensitive
  - Small degree of (thermal) polarization
  - Inefficient detection

- Our combined paths to increase sensitivity
  - Hyperpolarization
  - Detection of particles



Hyperpolarization

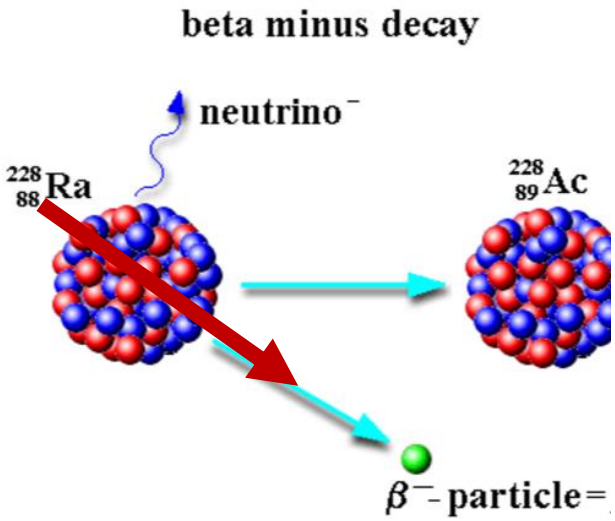
- Aligning almost all spins in one direction, e.g. using laser light
  - Laser-polarize Rb and transfer it to He to image patient lungs
- Works best for metal ions (alkali and alkali earth)
- Gain up to 10^5 in sensitivity

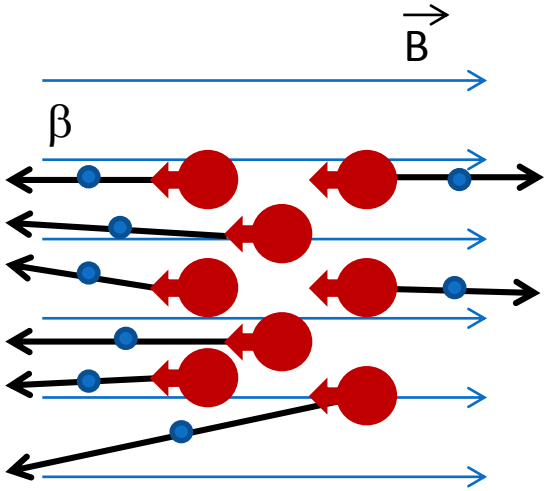


Detection of particles: beta decay

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

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

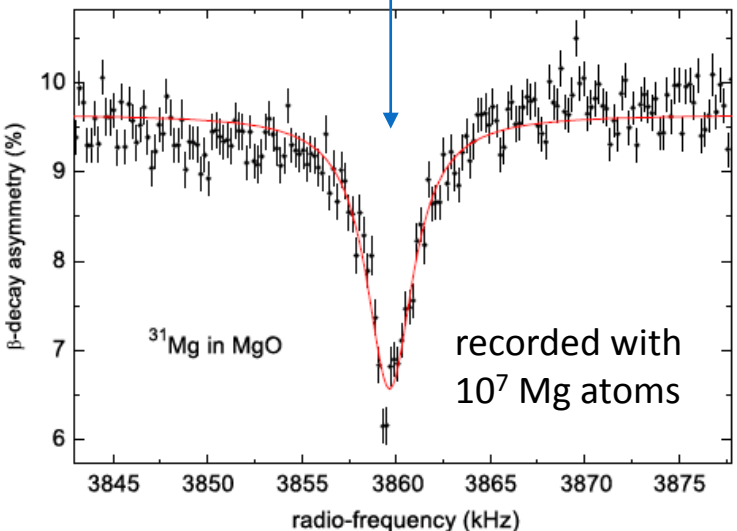


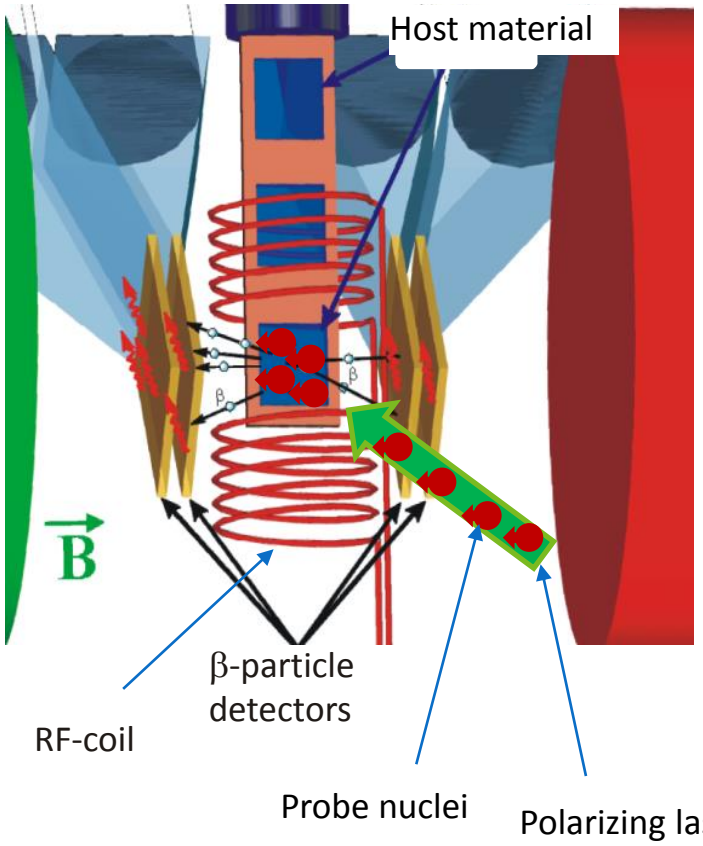


Beta-(detected) NMR

- Same principles as conventional NMR
- Ingredients:
  - Radioactive (short-lived) NMR-active atoms decaying via emission of beta particles
  - Beta particles emitted in spin direction
- Detection of resonance:
  - **Asymmetry in beta decay in space**
  - **At resonance: decrease in asymmetry**
- When combined with hyperpolarization

=> Beta-NMR can be up to 10^{10} more sensitive than conventional NMR





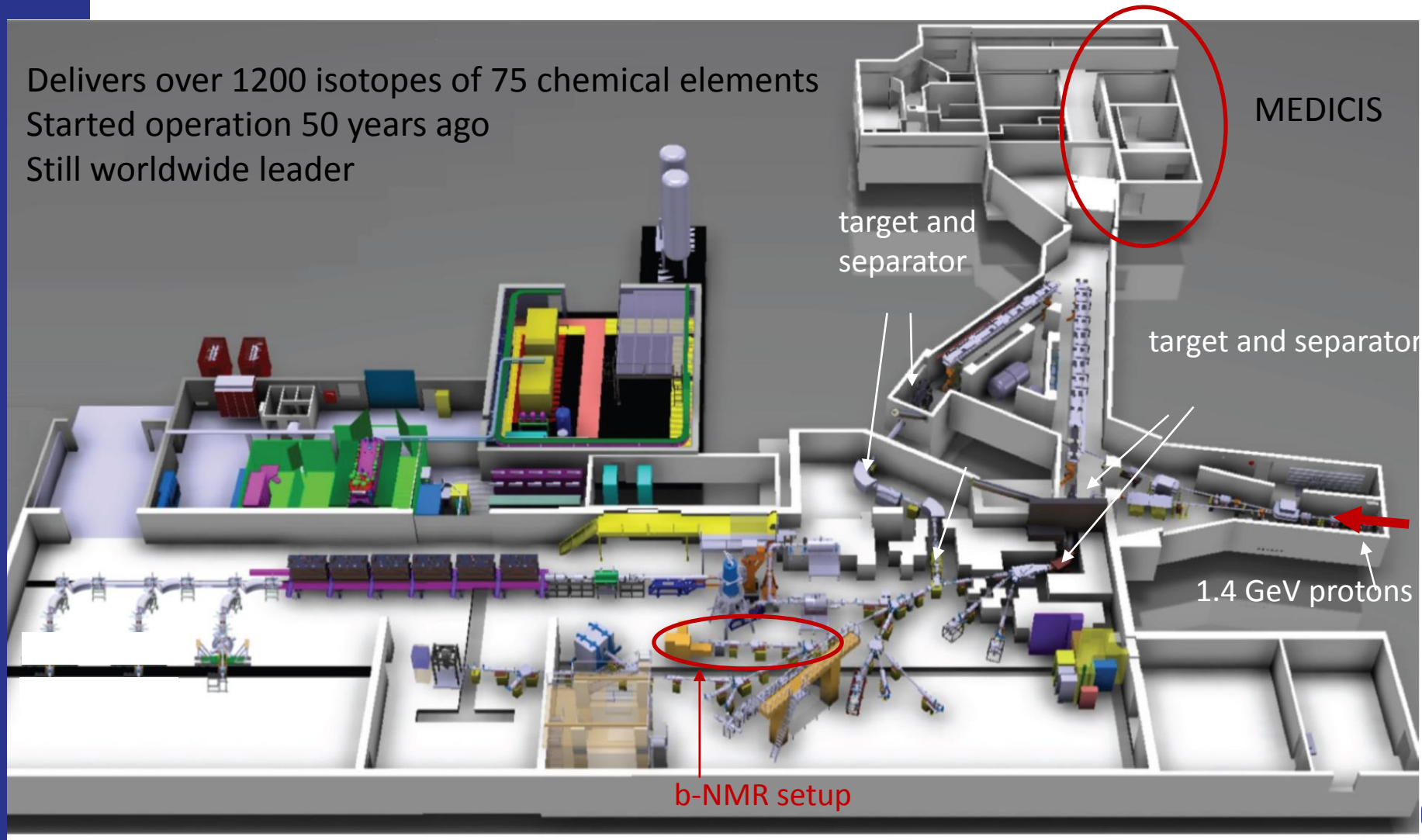
How to perform beta-NMR?

- How do I make radioactive nuclei?
- How do I hyperpolarize then?

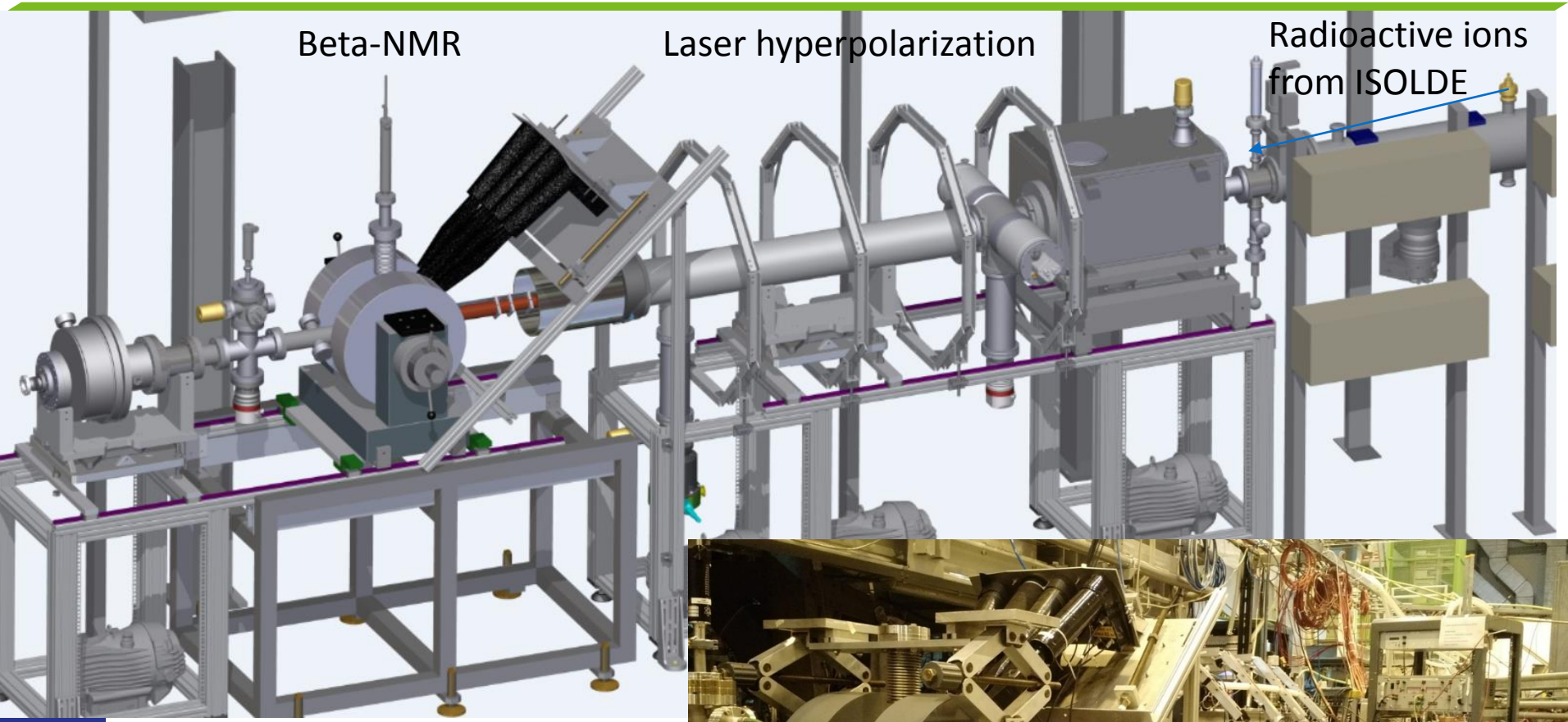
- How do I get them into my sample?
- How do they get to the biomolecule of interest?

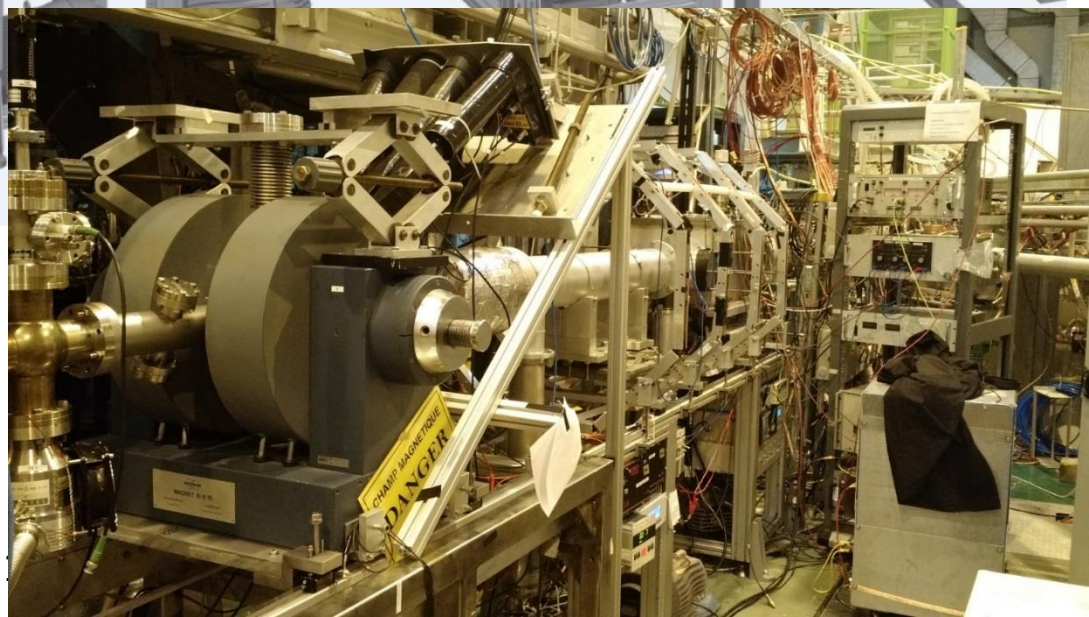
ISOLDE laboratory

CERN's facility for production and research with radioactive nuclei



Experimental setup

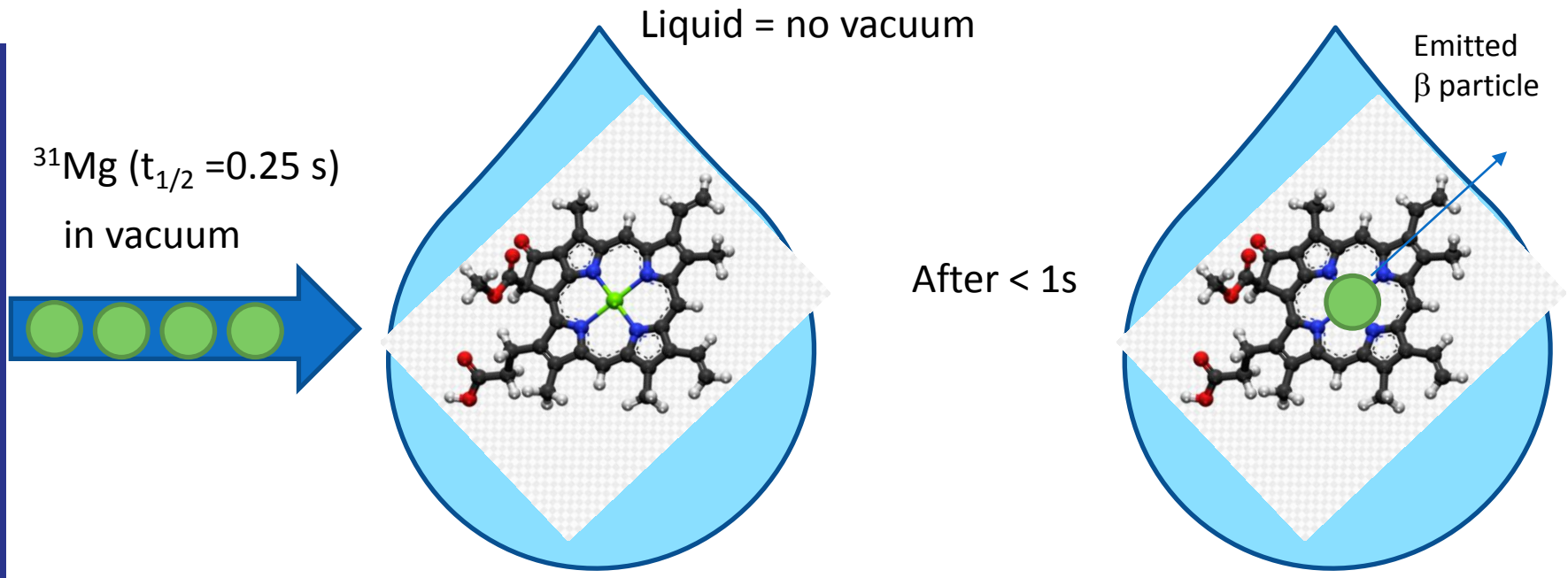




Polarization using lasers

M. Kowalska et al., Journal of Physics G, accepted (2017)

How to get to my sample?



Challenges and constraints:

- Vacuum/liquid interface with small probe-beam and polarization loss
- Quick transport and binding to biomolecule

Probe nuclei

Already laser-polarized at ISOLDE

Nucleus	Radioactive half-life	Nuclear spin
8Li	0.84 s	**2**
9Li	0.18 s	**3/2**
11Be	13.8	**1/2**
26Na	1.1 s	**3**
27Na	0.3 s	**5/2**
28Na	30 ms	**1**
29Mg	1.2 s	**3/2**
31Mg	0.25 s	**1/2**

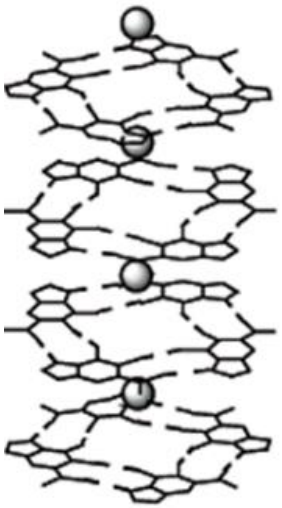
Planned

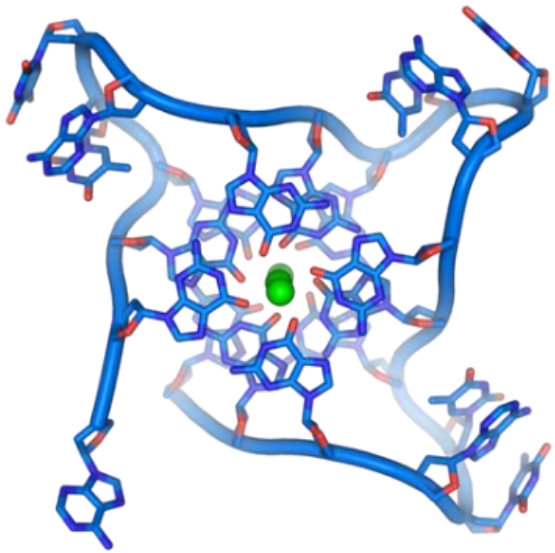
Nucleus	Radioactive half-life	Nuclear spin
37K	1.2 s	**3/2**
49K	1.3 s	**1/2**
39Ca	0.8 s	**3/2**
51Ca	0.36 s	**3/2**
58Cu	3.2 s	**1**
74Cu	1.6 s	**2**
75Cu	1.2 s	**5/2**
75Zn	10 s	**7/2**
75Zn*	5 s	**1/2**
77Zn	2 s	**7/2**
77Zn*	1.1 s	**1/2**

* Nuclear isomer = long-lived excited state

1st studies: Na+/K+ & G-quadruplexes

- DNA G-quadruplexes:
  - Guanine-rich fragments
  - Found in nature, e.g. in telomeres
  - Synthesised for novel applications
  - Binding alkali metals





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

- Aim
  - Show whether beta-NMR can address such systems
  - Benchmark results to several conventional liquid NMR studies
  - Determine binding sites and dynamics of Na+/K+ in different quadruplexes

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

Summary and outlook

- NMR is a powerful technique but it has a very limited sensitivity
- Hyperpolarization and detection of beta particles can give a billion times increase in NMR sensitivity
- Devoted experimental setup located at ISOLDE-CERN
- Preparing for the first experiments on Na/K and G-guadruplexes
- More chemical elements to be addressed soon