β NMR on liquid media for biophysics applications:

Billion-fold increase in NMR sensitivity

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Outline

1. **NMR** (physics and limits)

2. **Motivation** for β detected NMR at ISOLDE/CERN

3. **β NMR** (how to enhance sensitivity)

4. Experimental **setup at ISOLDE-CERN**

5. **Challenges** of β NMR when applied in **liquids**

6. β NMR studies in liquids with **Na+**

7. Summary

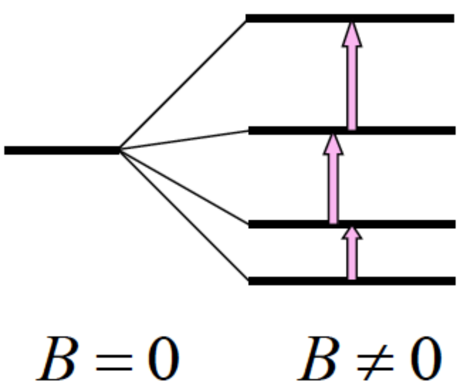
1. NMR

Nuclear Magnetic Resonance: Nuclear and **Hyperfine Interactions spectroscopic** technique

Nuclear Magnetic Resonance – NMR

(Zeeman splitting of nuclear levels)

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



Nucleus

Q, g_I, μ_N unknown

Biophysics (study of the medium)

Q, g_I, μ_N known

- Determine the **B modification** by the e- environment and the V_{zz} (EFG)

How to get a signal?

1. Polarization with strong magnetic field
2. Detection of RF signal in pick up coil

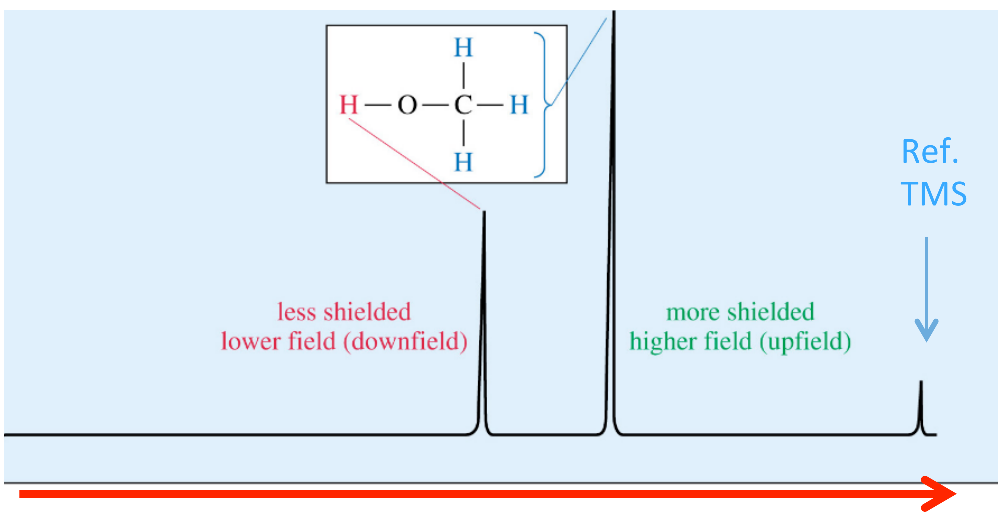
1.1 NMR in chemistry and biology

Most common NMR active nuclei: **^{1}H** and **^{13}C** NMR (both with I=1/2)

Other (e.g. **^{23}Na**, **^{25}Mg**, **^{63}Cu**, **^{65}Cu** and **^{67}Zn**) low sensitivity and broad peaks due to **small g** and **quadrupole interactions (I>1/2)**

NMR Observables:

- Chemical shift
- Relaxation times in different environments



Increased shielding by extranuclear electrons

Typical 1H NMR spectrum of Methanol

Different **shielding** of same type nuclei→ **different chemical shifts**

1.2 NMR limitations

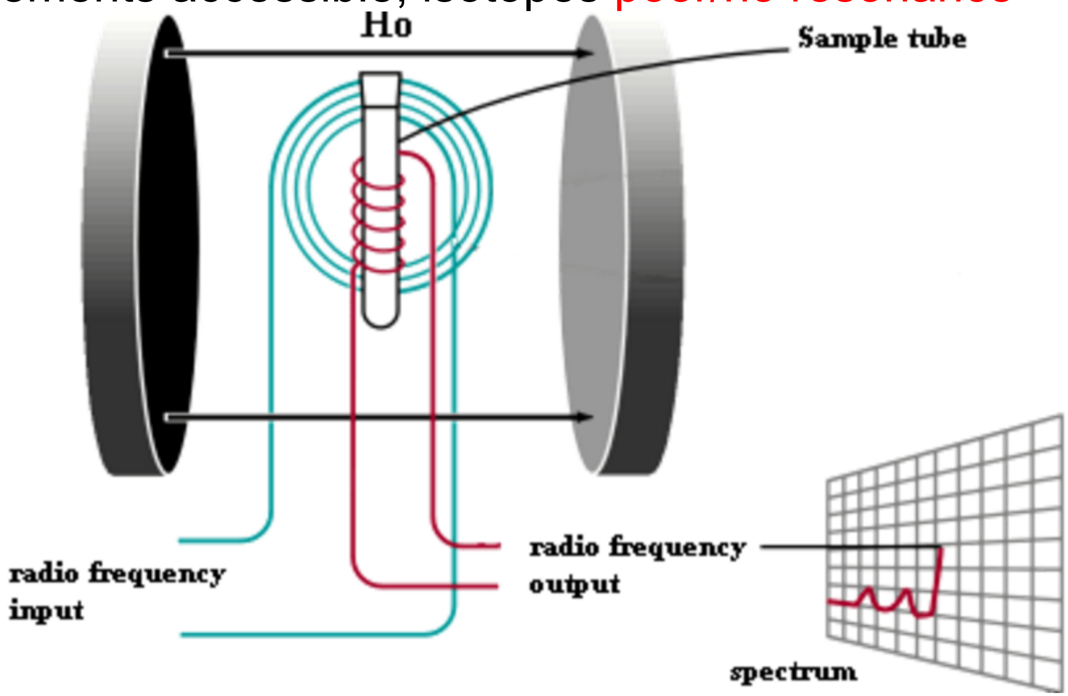
NMR is powerful but not sensitive especially for inorganic metal ions detection

Limitations

1. Small degree of polarisation (**<<1%**) (Boltzmann distribution), high B0 needed

2. Ineffective detection of resonances (RF pick up coil)

3. Not all elements accessible, isotopes poor/no resonance



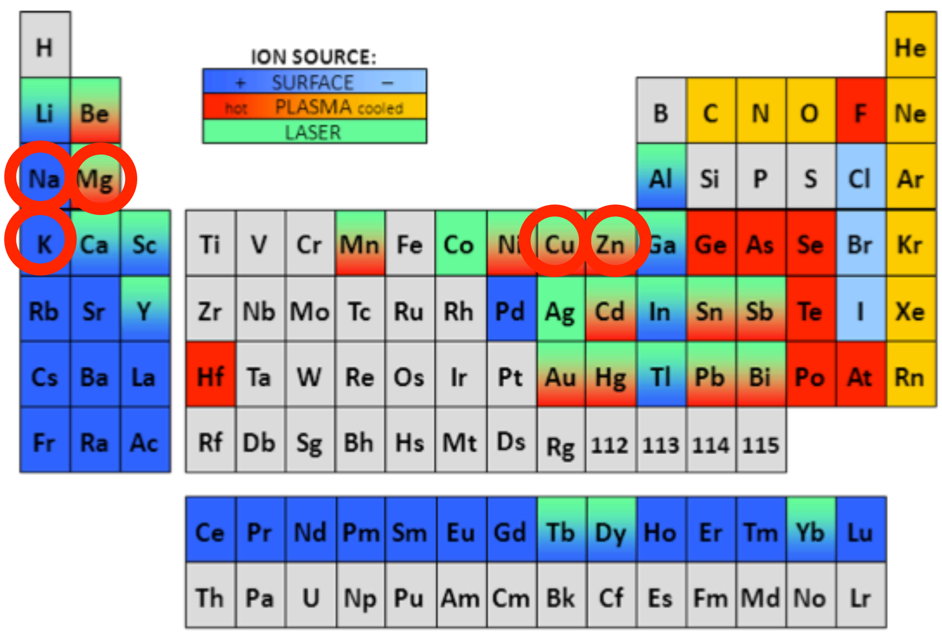
2. Our motivation

Develop NMR technique for direct studies of **metal ion** interactions with **biomolecules** in **solutions**

Some of the **most abundant cations** in humans**:**

Na(I), K(I), Mg(II), Zn(II), Cu(I), Cu(II)

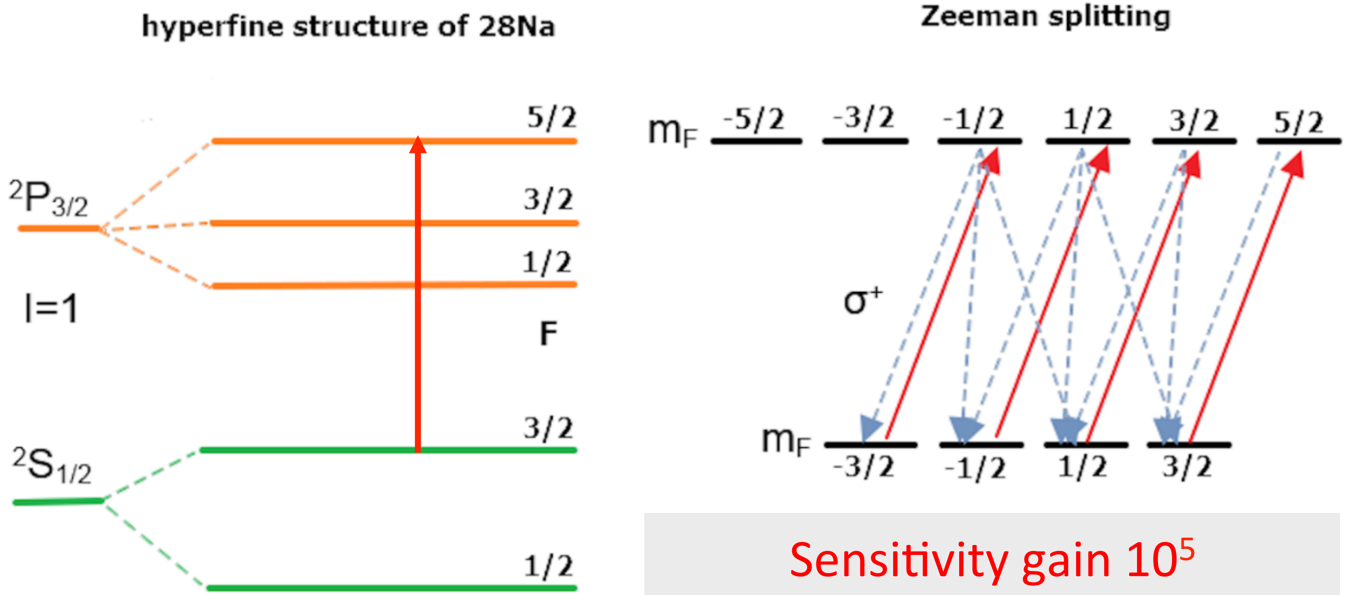
their right concentration is crucial for correct functioning of cellular processes



> 70 elements produced at ISOLDE

3.1 How to enhance sensitivity

1. Hyperpolarisation with lasers (1-100%)



Sensitivity gain 10^5

1. Polarize atomic spins (F)

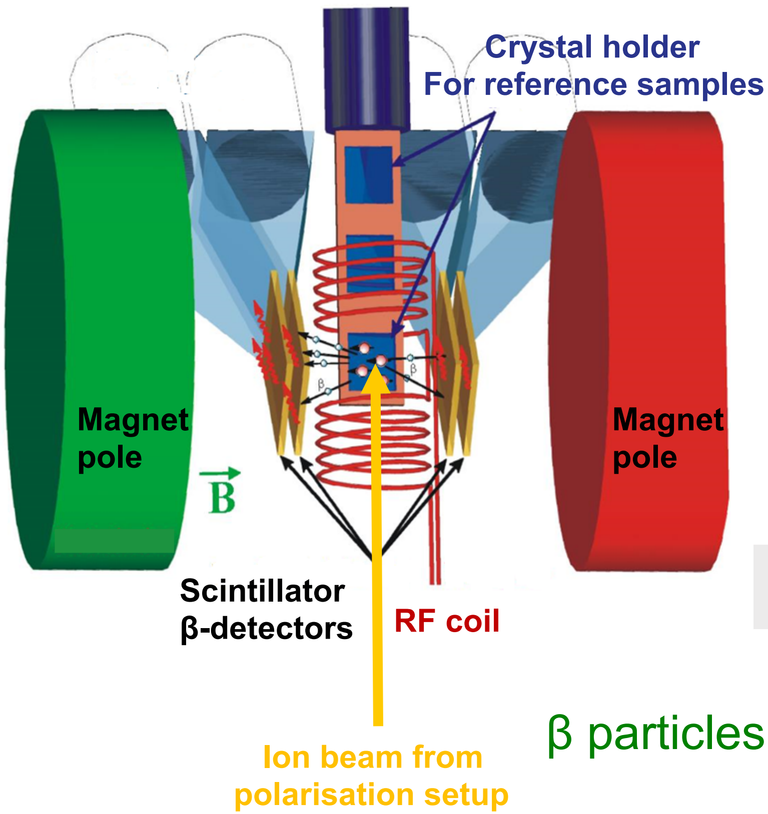
- Laser/atoms overlap
- circularly polarised light (σ+ or σ-) and decay ΔmF = 0, ± 1
- Repeat pumping-decaying cycle

2. Polarization of nuclear spins (I)

- Decouple atomic and nuclear spins with increasing B field
- Strong B0 field maintains the nuclear spin polarization

3.2 How to enhance sensitivity

2. β decay detection



Angular distribution of β radiation along spin axis

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

Sensitivity gain 10^5

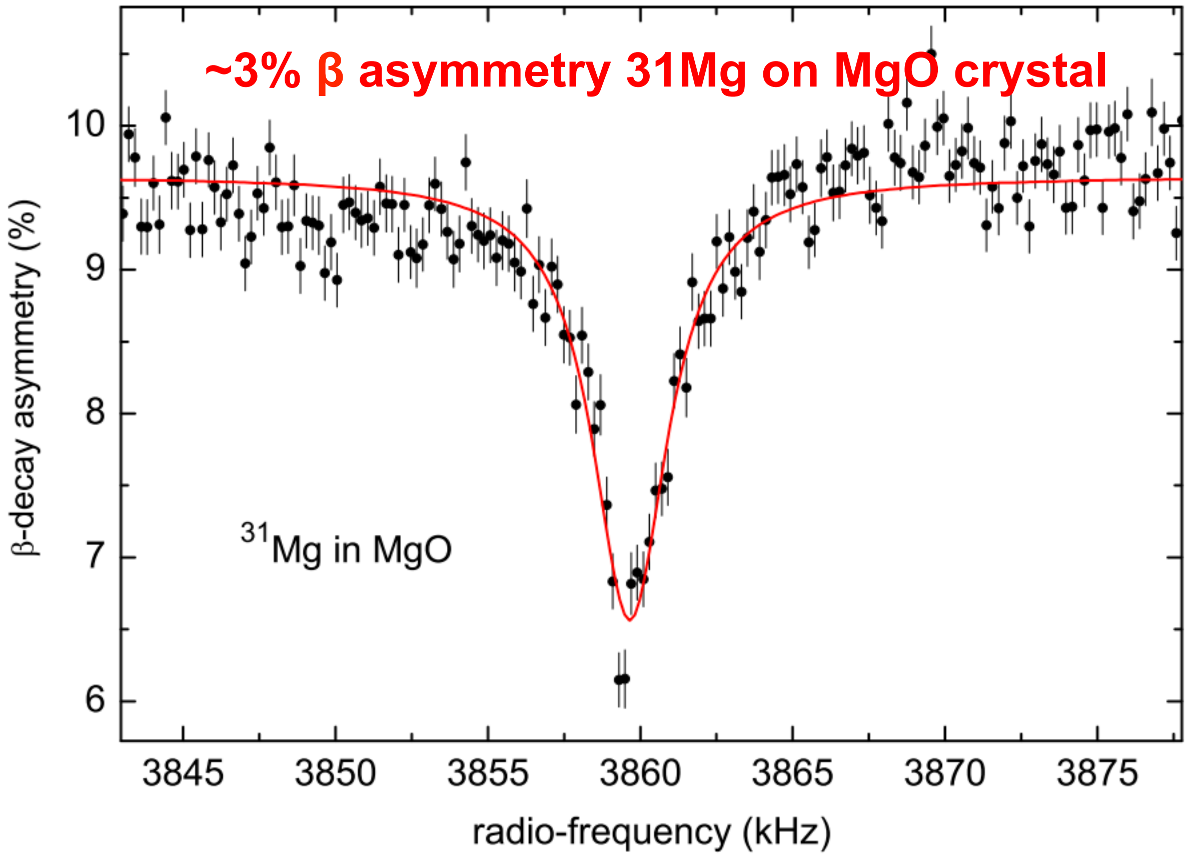
Probe nuclei

β particles mostly emitted in spin direction

β NMR Resonance detection

experimental β decay asymmetry loss when RF fits with resonance frequency

3.3 Typical β NMR spectrum

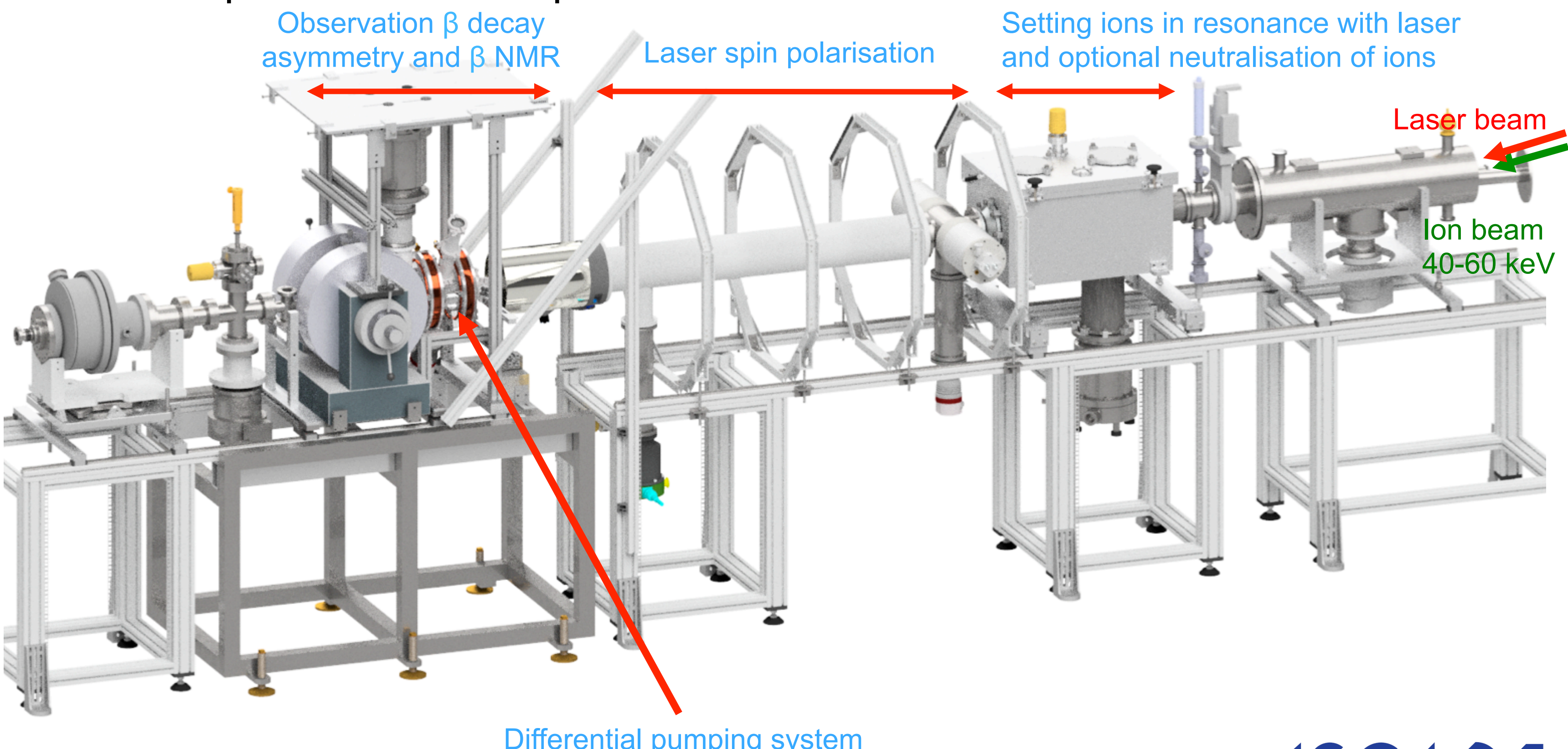


Magdalena Kowalska, PhD thesis

http://cds.cern.ch/record/983758?ln=en

4. β NMR setup at ISOLDE

- Commissioning run November 2016 with $^{26,28}Na$ radioactive beams in NaF crystal
- 1st successful tests with crystals and low vapour liquids in September 2017
- Next experiments with liquids December 2017

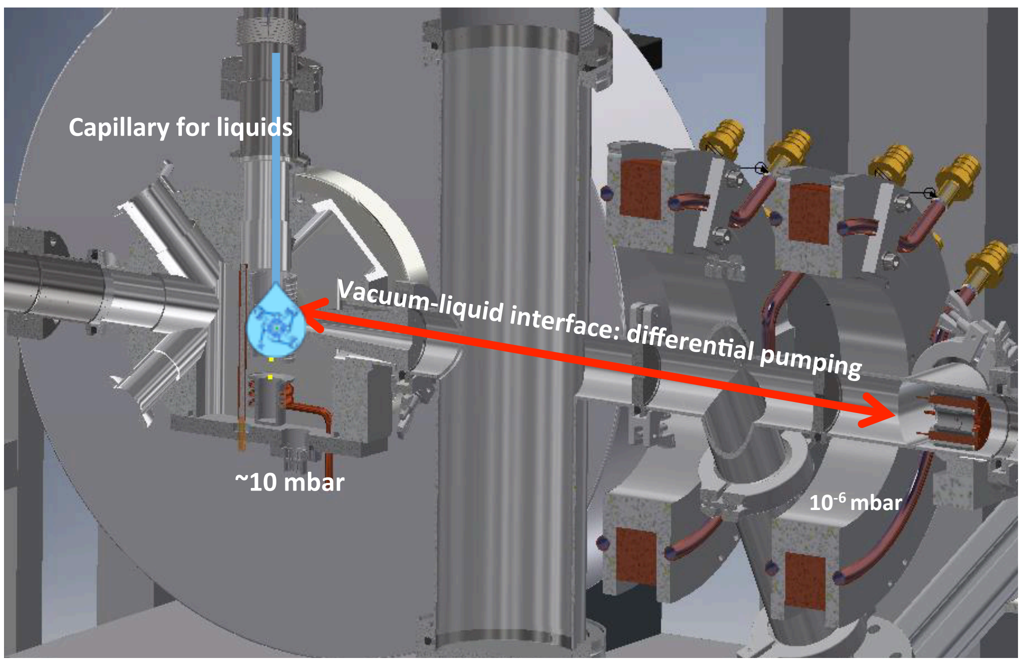


CAD design F. Wienholtz, R. Harding, W. Gins

5. Challenges with biological liquids

Radioactive beam from ISOLDE 10^{-6} mbar	Ion beam →	Experimental setup 10^{-6} mbar	Polarized beam →	NMR magnet and **chamber for liquids** **Water 1-10 mbar**

1. **Most liquids don't like vacuum (boiling or freezing)**
2. **Liquid drop formation and retain** at implantation site



CAD design R. Harding and M. Walczak,

Solutions

1. Use **low vapour pressure liquids compatible with 10^{-6} mbar**

2. Use **hydrophilic substrate** for keeping the liquid for hours

3. Design and build **new NMR chamber** and **Differential Pumping System**

ISOLDE

6.1 1st liquid β NMR studies with Na+

1st test run with liquids

1. Tested the **liquid handling system**
2. Tested the efficiency of the **differential pumping system**
3. Tested the new **RF setup** recording NMR signals on NaF crystal
4. Measured the relaxation times Na+ on crystal and liquid
5. 1st attempt to measure a NMR signal in liquids

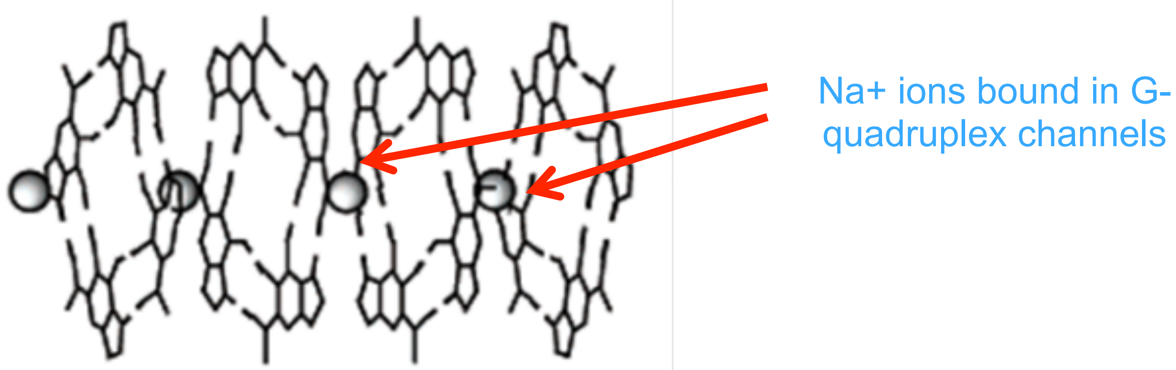
6.2 β NMR with Na+ in DNA structures

Next step DNA G-quadruplexes with Na^+

- Alkali metal ions (e.g Na^+ and K^+) important for formation, stability and structural polymorphism
- G-quadruplexes **bind strongly** to alkali metals and react fast (<1 s)

Goal

- Way and time scale Na^+ binds to G-quadruplexes



M. Kowalska et al, Proposal to the INTC, June 2017

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

6.3 More β NMR nuclei

What has been measured

Nucleus	T1/2	I	B asymmetry
8Li	0.84 s	2	5%
9Li	0.18 s	3/2	
11Be	13.8	1/2	1%
26Na	1.1 s	3	30%
27Na	0.3 s	5/2	30%
28Na	30 ms	1	40%
29Mg	1.2 s	3/2	3%
31Mg	0.25 s	1/2	8%

What we plan to measure

Nucleus	T1/2	I	Production + polarization
37K	1.2 s	3/2	Quite easy
49K	1.3 s	1/2	difficult
39Ca	0.8 s	3/2	difficult
51Ca	0.36 s		Quite difficult
58Cu	3.2 s	1	Quite difficult
74Cu	1.6 s	2	Quite difficult
75Cu	1.2 s	5/2	Quite difficult
75gZn	10 s	7/2	difficult
75mZn	5 s	1/2	difficult
77gZn	2 s	7/2	difficult
77mZn	1.1 s	1/2	difficult

Summary

- β detected NMR **1 billion times more sensitive** than NMR
- **Newly commissioned** setup in late 2016 at ISOLDE
- **Successful tests** liquid handling system, differential pumping and RF system late September 2017
- β NMR **Na^+ in DNA** coming soon!

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