beta-NMR:
from nuclear physics to biology

Collaps – Collinear Laser Spectroscopy

CERN
D. Yordanov

KU Leuven
M. Bissell, G. Neyens

University of Mainz
R. Neugart

MPIK Heidelberg
K. Blaum

University of Copenhagen
M. Stachura, L. Hemmingsen

Free University Berlin
A. Gottberg

University of Saarland
K. Johnston

Magdalena Kowalska
CERN, PH-Dept

Outline

- NMR in nuclear physics and biology
- Metal ions in biology
- Ultra-sensitive beta-NMR
- Methods of spin polarization
- Challenge of beta-NMR in liquids
- Proof-of-principle experiment
- Outlook and summary

NMR in nuclear physics

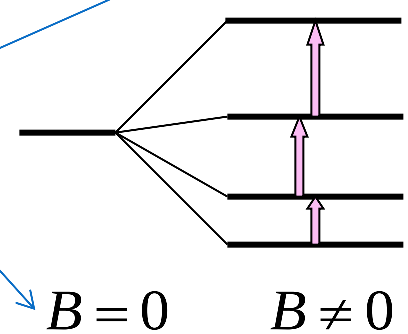
- **Observable**: Larmor frequency (for different nuclei in one host)
- **Determined properties**:
  - Precise values of electromagnetic moments of ground- and metastable-states of stable nuclei and radio-nuclides (**magnetic dipole** and **electric quadrupole** moment):
  - When combined with hyperfine structure determination => direct measurement of **nuclear spin**

$$\mu_I = g_I \cdot I \cdot \mu_N$$

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

(static) external magnetic field

Electric field gradient (in non-cubic host lattice)



- **Derived information**: comparison to nuclear models
  - μ_I: determination on the orbits occupied by valence protons and neutrons
  - Q: determination of nuclear deformation

NMR in (chemistry and) biology

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

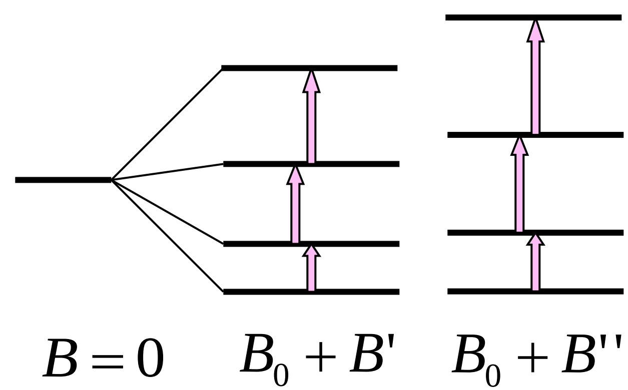
- **Observables**: chemical shift (Larmor frequency) and relaxation times in different hosts
- **Determined properties**
  - ➢ local electronic environment (i.e. **number and type of coordinating groups**)

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**: comparison to quantum-chemical models (e.g DFT)
  - ➢ kinetics and dynamics and ligand binding of the **metal ions and biomolecules**
  - ➢ 3D structure of proteins and **protein-metal complexes**

NMR and role of metal ions in biology

- Role of metal ions in human body depends on adopted coordination environment
- **Zn(II), Cu(I), Mg(II):** among most abundant cations in living organisms; right concentration is crucial for correct functioning of cellular processes
  - Mg: active in 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, involved in regulation of genetic message transcription and translation
- Challenges:
  - closed electron shells, thus invisible in many methods;
  - in NMR: almost invisible signals due to small abundance, I>1/2, and small sensitivity (due to small magnetic moment)

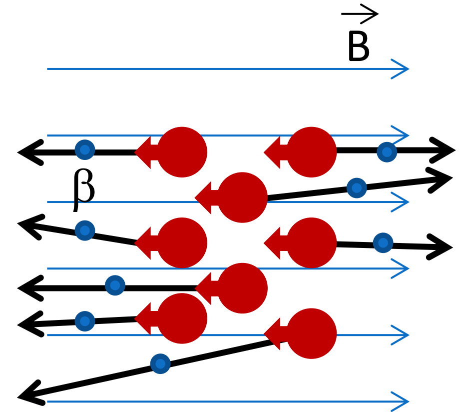
- Common features with NMR in nuclear physics:
  - Probe nuclei of interest are rare and give weak signals

- Sensitivity of conventional NMR is very (or even too) low, so it has to be enhanced => ultra-sensitive NMR approaches needed, e.g. **beta-detected NMR**

Beta-(detected) NMR

Weak interaction doesn’t conserve parity

- Anisotropic emission of beta particles from decay of polarized nuclei
- NMR resonance: destruction of asymmetry, observed as decrease in beta-decay asymmetry



Angular distribution of beta-radiation:

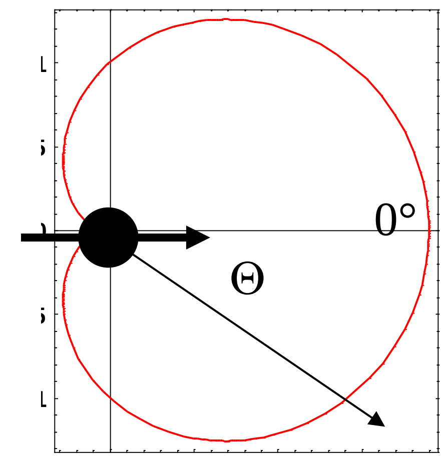
Velocity of beta-particle (v/c close to 1)

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



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

Conventional versus beta-NMR

	Conventional NMR	Beta-NMR
Polariza-tion	• << 1%: **Created inside** sample: (thermal occupation of levels in NMR magnetic field)	• 1%-100%: **Created outside** sample: (e.g. laser excitation)
Detection	• << 100% detection efficiency: Change of magnetization	• Up to 100% efficiency: Anisotropy of beta decay
Probe nuclei	• Stable or long-lived: ^{1}H, ^{13}C… • Need ~10^{17} in the sample	• Radioactive; ^{8}Li, ^{11}Be, ^{31}Mg, … • 10^{7} per resonance
Samples	Liquids, solids	Solids (until 2012)

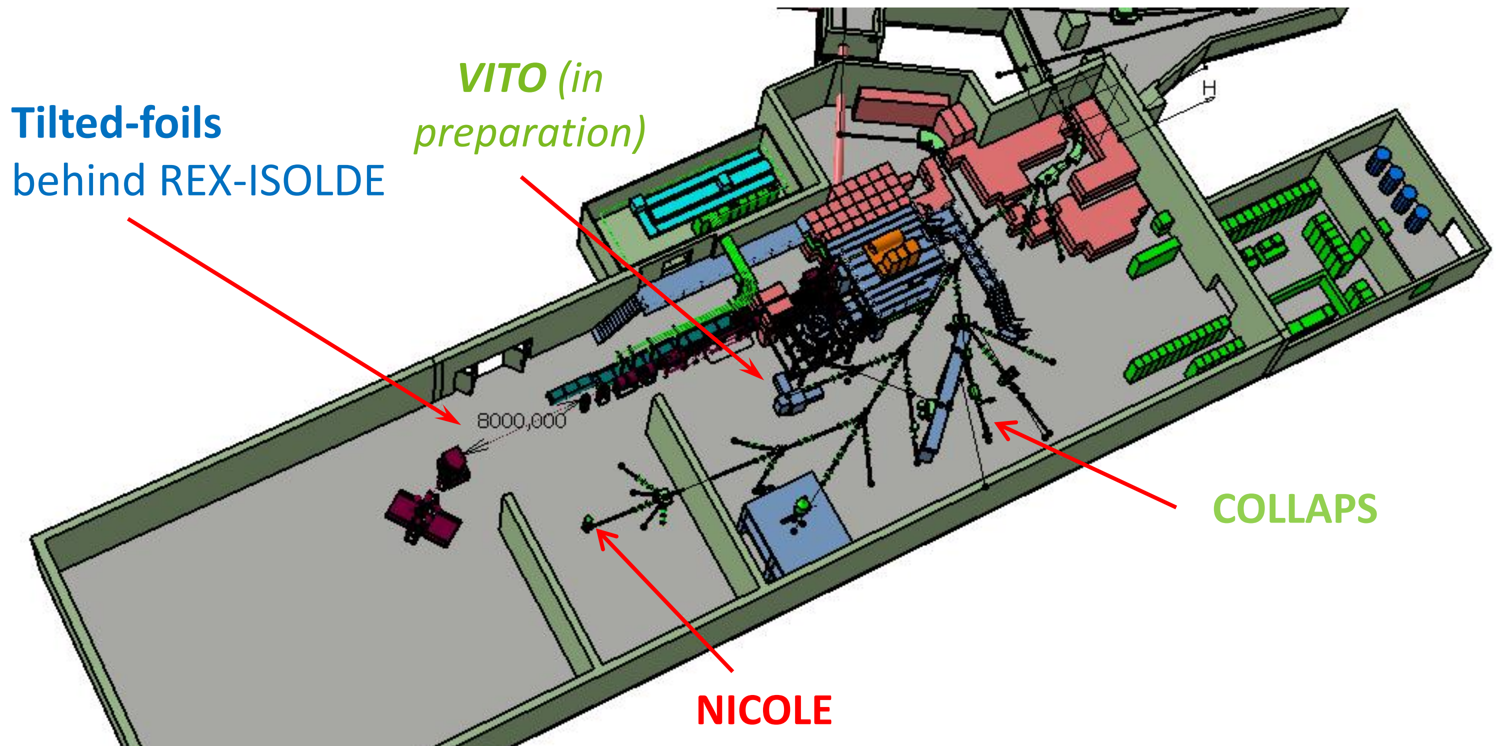
10 orders of magnitude higher sensitivity than conventional NMR
Dozens of different (radioactive) probe nuclei

ISOLDE

Beta-NMR: spin polarization

- Spin polarization to obtain large population differences:
  - Production mechanism -> versatile, but only at fragmentation facilities, low polarizations
  - Low temperature (subK) -> cannot perform studies on liquids
  - Passage via titled foils -> versatile, but so far low polarizations, work under way
  - **Optical pumping** -> dependent on laser scheme available, but high polarizations

- Techniques available at ISOLDE-CERN:



Towards beta-NMR in biology: in practice

- Simple idea:

Radioactive beam facility (e.g. ISOLDE) → Ion beam → Experimental setup for spin polarization → Polarized beam → NMR magnet and chamber with liquid sample

- Big challenge: radioactive beams like high vacuum; most liquids – don't

10^{-6} mbar → Ion beam → 10^{-5} – 10^{-6} mbar → Polarized beam → Water: 1-10 mbar; Glycerol: 10^{-2} mbar

- Suggested solution:

Radioactive beam facility → Optical pumping (well tested, high polarization) → **Differential pumping** → NMR magnet and chamber with liquid sample

Mg isotopes: good starting points

- Some history: M. Kowalska, talk at ENAM 2004 on:

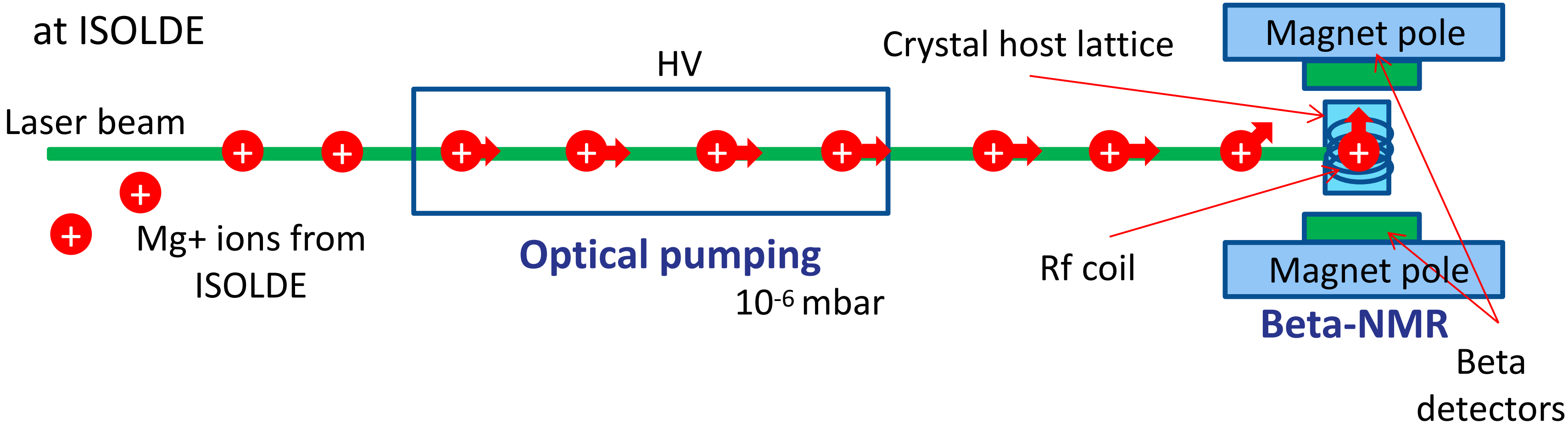
Laser and β-NMR spectroscopy on neutron-rich magnesium isotopes

Univ. Mainz: **M. Kowalska**, R. Neugart
K.U.Leuven: D.Yordanov, D. Borremans, P. Himpe, P. Lievens, S. Mallion, G. Neyens, N. Vermeulen
CERN: K. Blaum

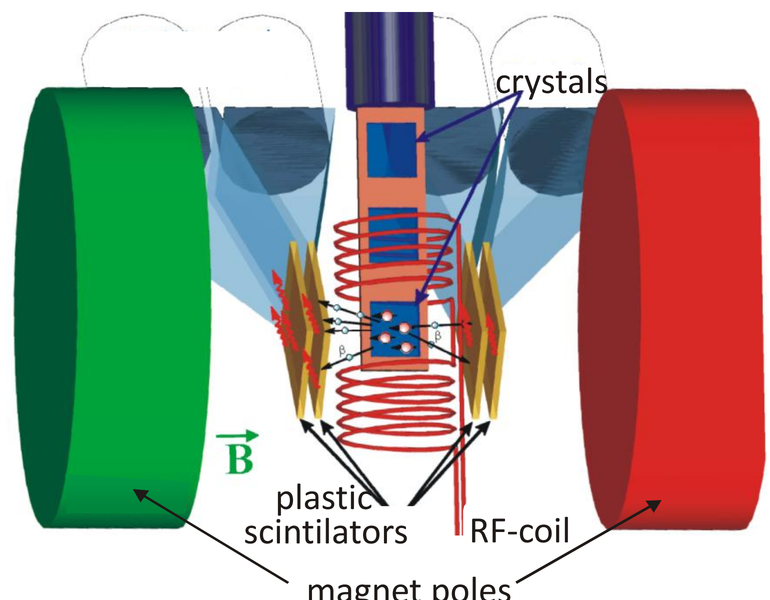
- First measurement of spins and moments of $^{29,31}Mg$ - my PhD thesis:
  - G. Neyens, M. Kowalska, D. Yordanov et al., Phys. Rev. Lett. 94, 022501 (2005)
  - M. Kowalska, D. Yordanov et al, Phys. Rev. C 77, 034307 (2008)

Experimental setup at the time

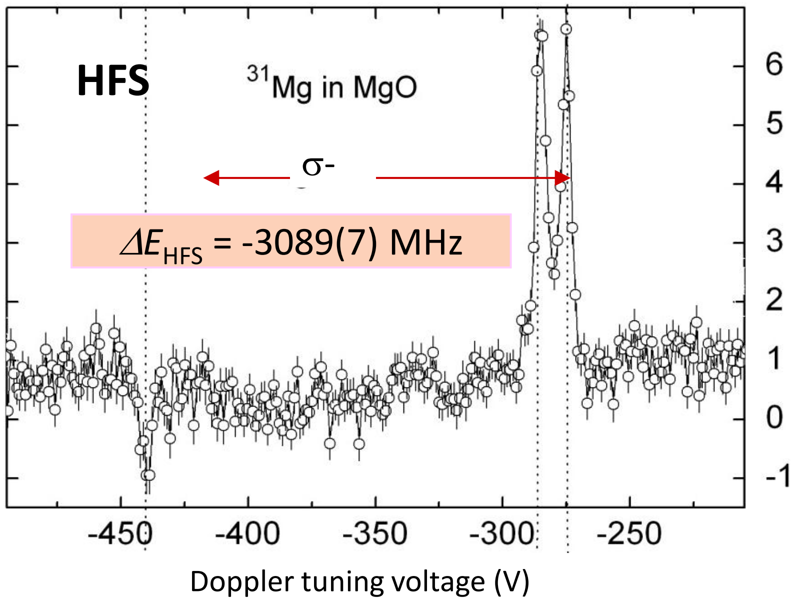
- COLLAPS setup for collinear laser spectroscopy at ISOLDE

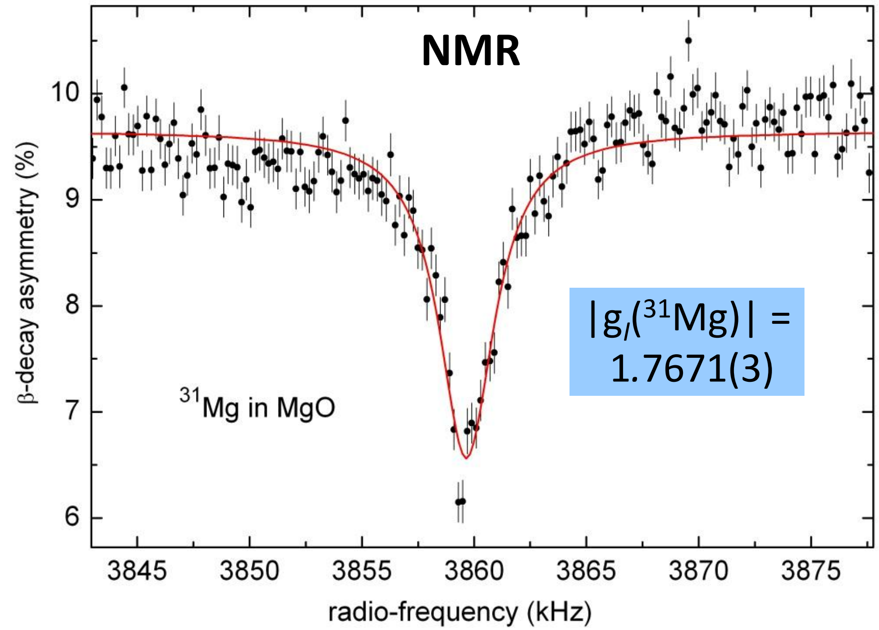


- Experimental procedure:
  - Optical pumping: polarization of atomic spins with laser light
  - HFS interaction = polarization of nuclear spins
  - Strong magnetic field: electron and nuclear spin decoupling
  - Nuclear spin polarization observed in beta-decay asymmetry



What did we learn?





Measured ground-state HFS and *g*-factor =
independent determination of nuclear spin
(with ^{25}Mg as reference for *A* and *g*)

$$\Delta E = g \cdot (I + 1/2) \cdot \frac{A_{ref}}{g_{ref}}$$

isotope	spin	μ (μ_N)
^{29}Mg	3/2 (*)	+0.9780(3)
^{31}Mg	1/2	-0.88355(15)
^{33}Mg (**)	3/2	−0.7456(5)

(*) confirms previous assignment from b-decay
(**) PhD thesis of D. Yordanov, DY et al, Phys. Ref. Lett. 99, 212501 (2007)

ISOLDE

What does it mean?

- **In nuclear physics:**
  - first spin and moment measurement for Mg isotopes around the "island of inversion"
  - 29Mg properties consistent with N=20 as good magic number
  - 31,33Mg: 2 neutrons across N=20 in ground state => inside the island
  - Contribution to the understanding of the "island of inversion" mechanism

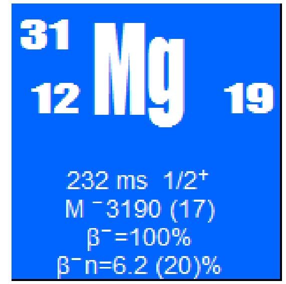
- **Towards biology applications**:
  - 31Mg is a spin 1/2 nucleus => no additional splitting in NMR: strong and clean signals
  - 31Mg is well produced (1e5 ions/s at ISOLDE) and gives high beta-asymmetries => beta-NMR resonances can be recorded quickly (a few min per scan)
  - 29Mg can serve as comparison: spin 3/2 (so quadrupole interaction present), weaker asymmetries but stronger production, so comparable time to record resonances
  - Interesting case: Mg cations play important roles in living organisms

- => ^{29,31}Mg are ideal cases to tests beta-NMR feasibility on liquid samples (towards applications in chemistry and biology)

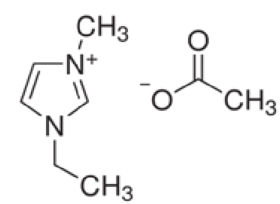
First beta-NMR in a liquid sample

- Proof-of-principle experiment (at ISOLDE)
  - Magnesium-31 beam
  - Spin polarization with lasers
  - Liquid host: ionic liquid (EMIM-Ac)
  - No biological hosts yet

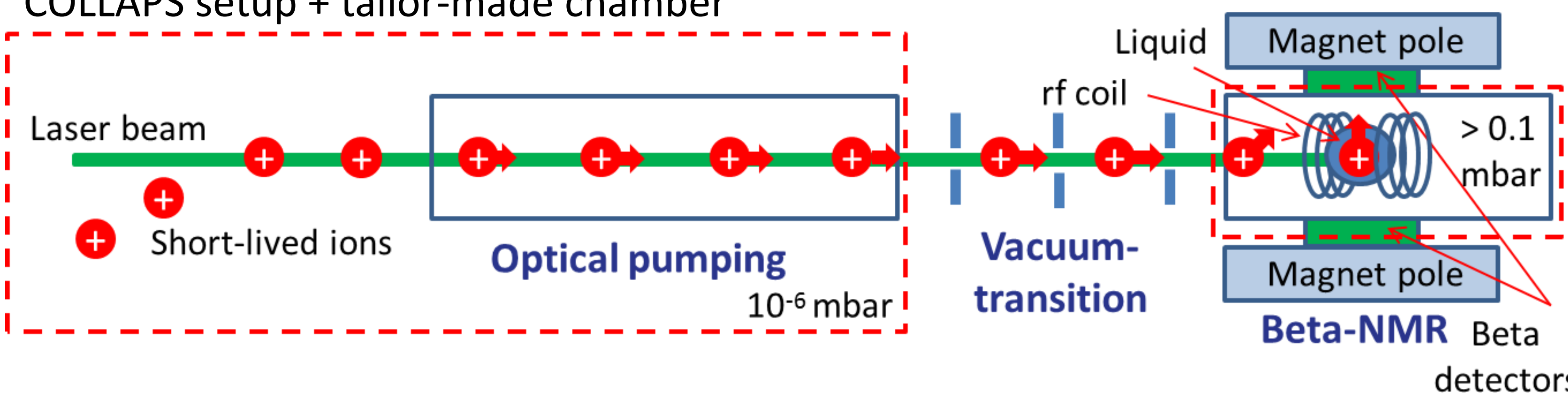
August 2012



EMIM-Ac



COLLAPS setup + tailor-made chamber

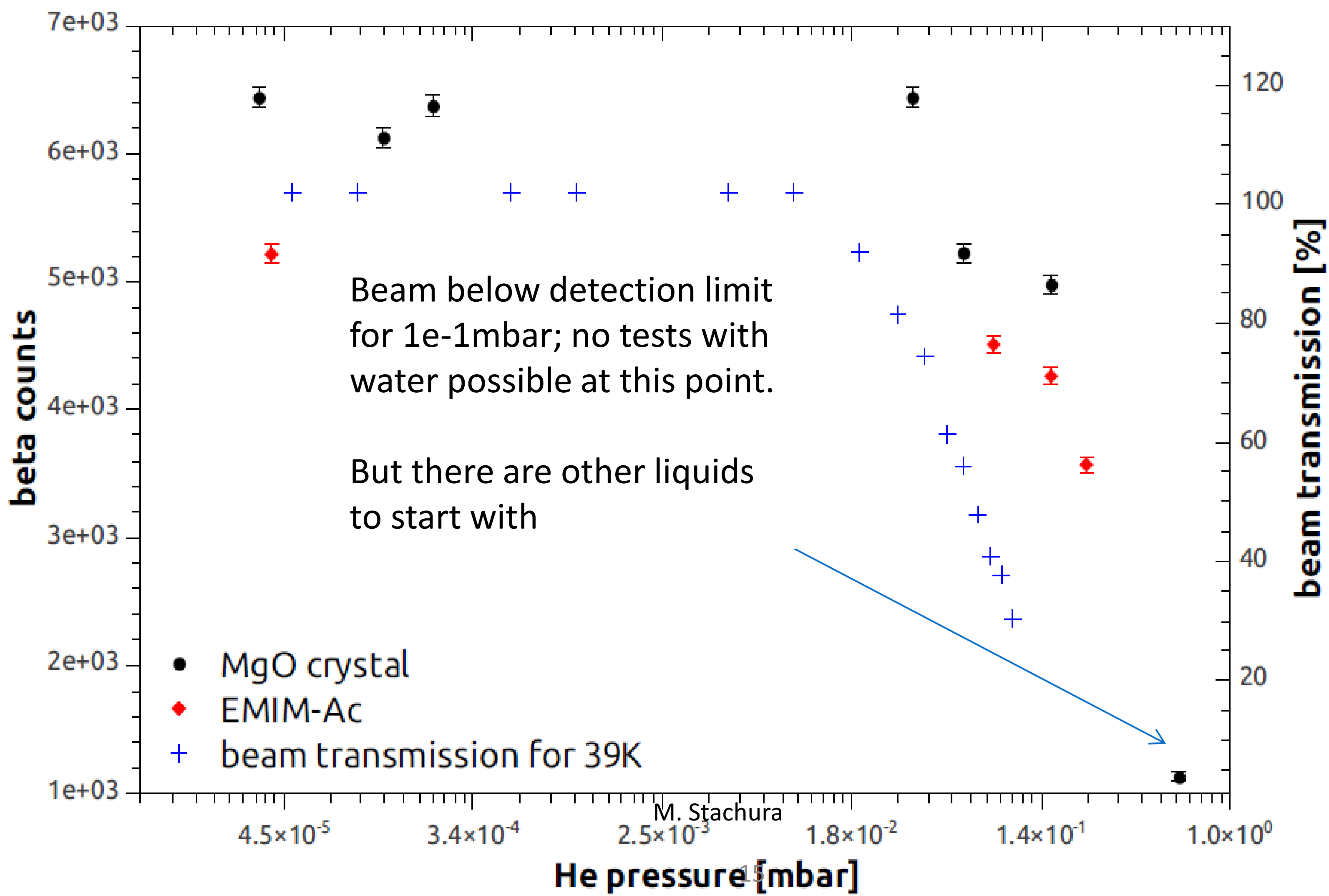


- Project: part of PhD thesis of M. Stachura (Copenhagen, supervisor L. Hemmingsen)
- Beta-NMR spectrometer and differential pumping designed by A. Gottberg (CERN, Madrid, Copenhagen)
- Optical pumping, beta detection and magnet: laser-spectroscopy setup (M. Kowalska, CERN and COLLAPS collaboration)

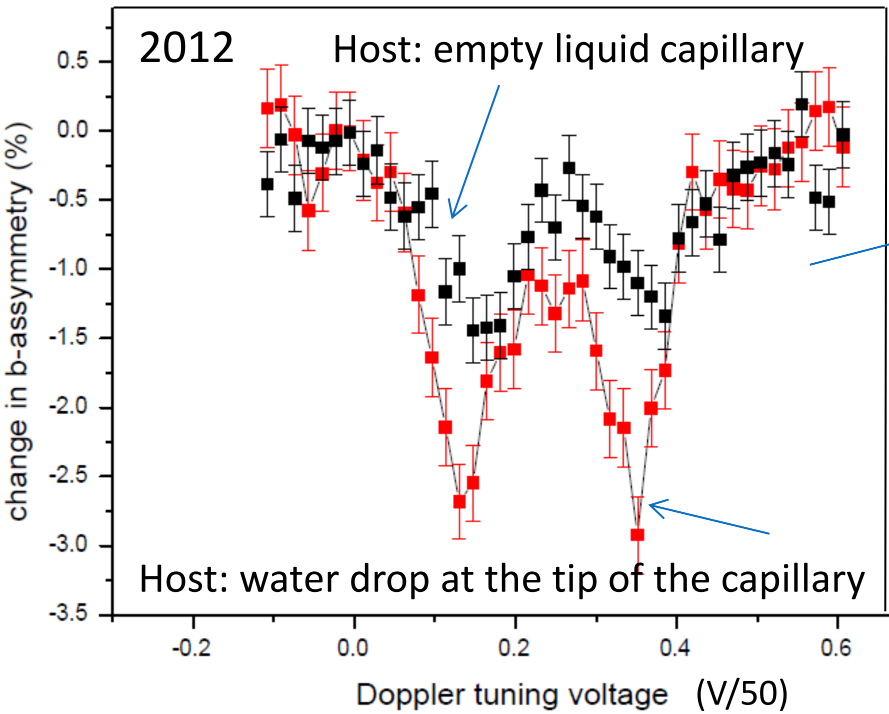
M. Stachura, L. Hemmingsen et al., Letter of Intent to the INTC, INTC-I-088 (2010)

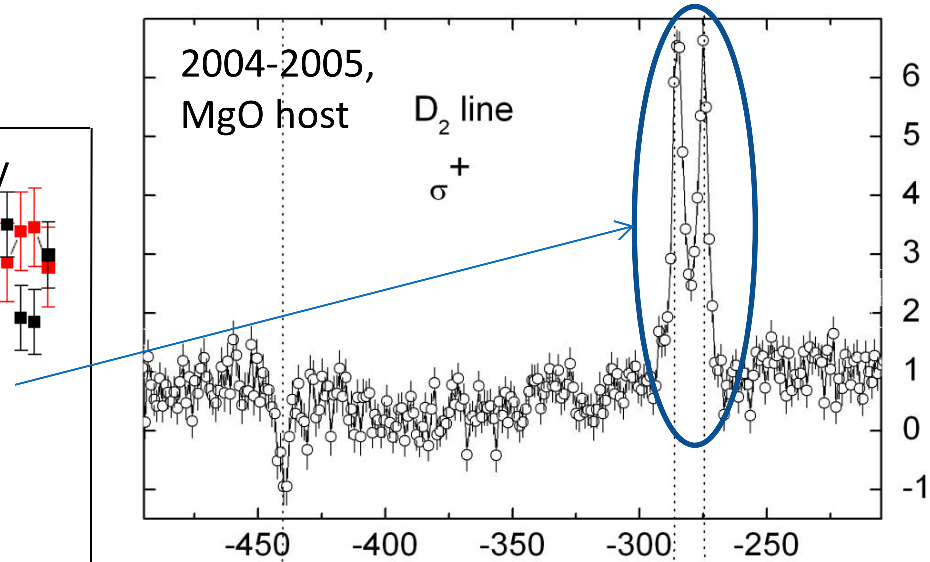
Ion beam transmission

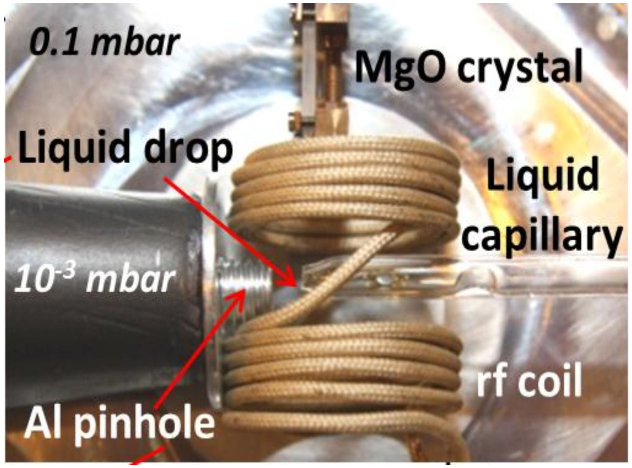
- 10^{-2} mbar just in front of liquid drop;
- 1-10 mbar in the last 2-3 mm to minimise beam losses



31Mg HFS in solid and liquid hosts



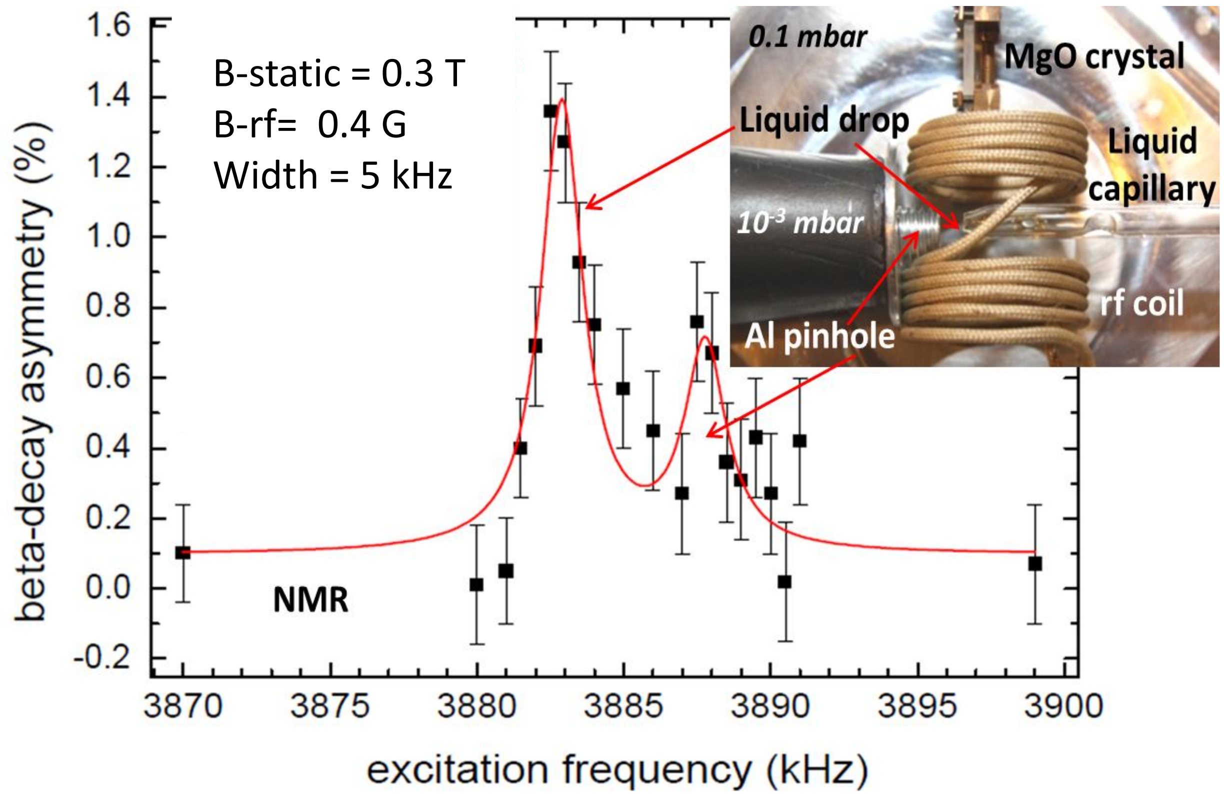




- Increase in beta-asymmetry amplitude in presence of liquid -> indirect proof that the ion beam reacts to the liquid

First beta-NMR in a liquid

- Data:
  - Several NMR spectra with high frequency modulation and 2 spectra with resonances resolved (no resonance frequency reference due to end of beamtime)



- Data interpretation:
  - NMR: observed frequency difference (chemical shift 1300 ppm) much larger than known chemical shifts in liquids (ca. 200 ppm), also quantum chemical calculations cannot find Mg binding sites producing such a shift
  - 2nd NMR resonance comes from metal capillary (Knight shift in metals – ca. 1000 ppm), where about 20% of ion beam is lost: artefact, but also internal frequency reference
  - Conventional NMR (at higher Mg concentration): also no 2nd resonance visible in liquid

A. Gottberg, M. Stachura, M. Kowalska, et. al., to be submitted to Angew. Chemie

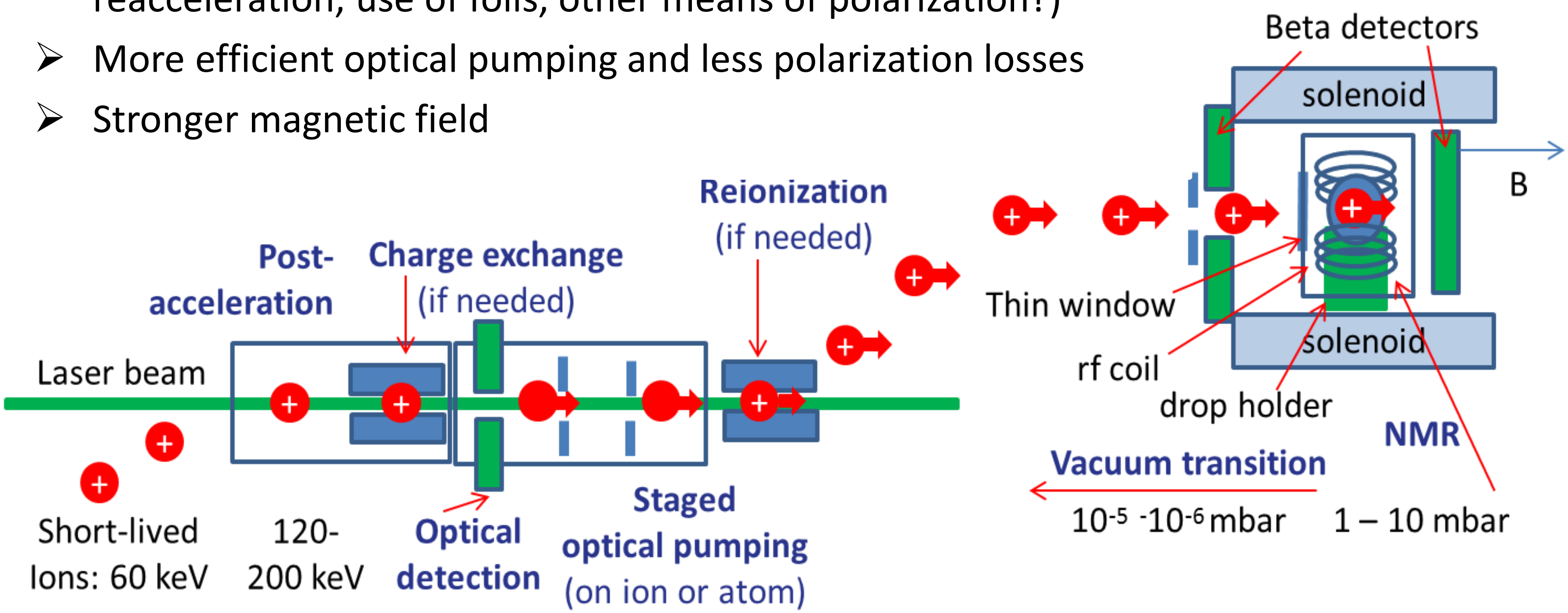
Where do we stand?

- Proof-of-principle system for beta-NMR in liquids exists
- First beta-NMR signal in a liquid recorded (but not in presence of a biomolecule)
- beta-asymmetry and beta-NMR signals observed up to 0.1 mbar pressure (not yet compatible with water)
- No detailed studies yet possible:
  - Influence of rest gas (so far – He)
  - Different liquid hosts and with biomolecules
  - Change of temperature and pH

- Open questions:
  - Will aqueous hosts be possible?
  - Will radionuclides host to biomolecules within their lifetime?
  - Will small chemical shifts be visible in beta-NMR?

Where are we going?

- Towards beta-NMR studies in biological hosts on Mg, Cu, and Zn cations:
  - Better vacuum-liquid interface (stronger differential pumping, beam reacceleration, use of foils, other means of polarization?)
  - More efficient optical pumping and less polarization losses
  - Stronger magnetic field



- More studies – scientific proposals :
  - ISOLDE: Further studies with Mg, Polarization tests with Cu
  - TRIUMF: tests of Mg polarization
- New VITO beamline at ISOLDE (M. Stachura et al):
  - PAC and beta-NMR in different vacuum environments
  - Devoted to material science, chemistry and biology, and nuclear structure

Summary

- NMR is a powerful method in nuclear physics and in biology
- Common requirement of high sensitivity calls for methods such as beta-NMR
- Recent beta-NMR studies of properties of Mg isotopes was very fruitful for nuclear-structure studies
- And it is promising for biology, but beta-NMR has never been used in liquid (body-like) hosts
- Proof-of principle experiment was performed at ISOLDE in 2012:
  - First liquid b-NMR signal was recorded
- Many challenges and work ahead but the goal is very motivating

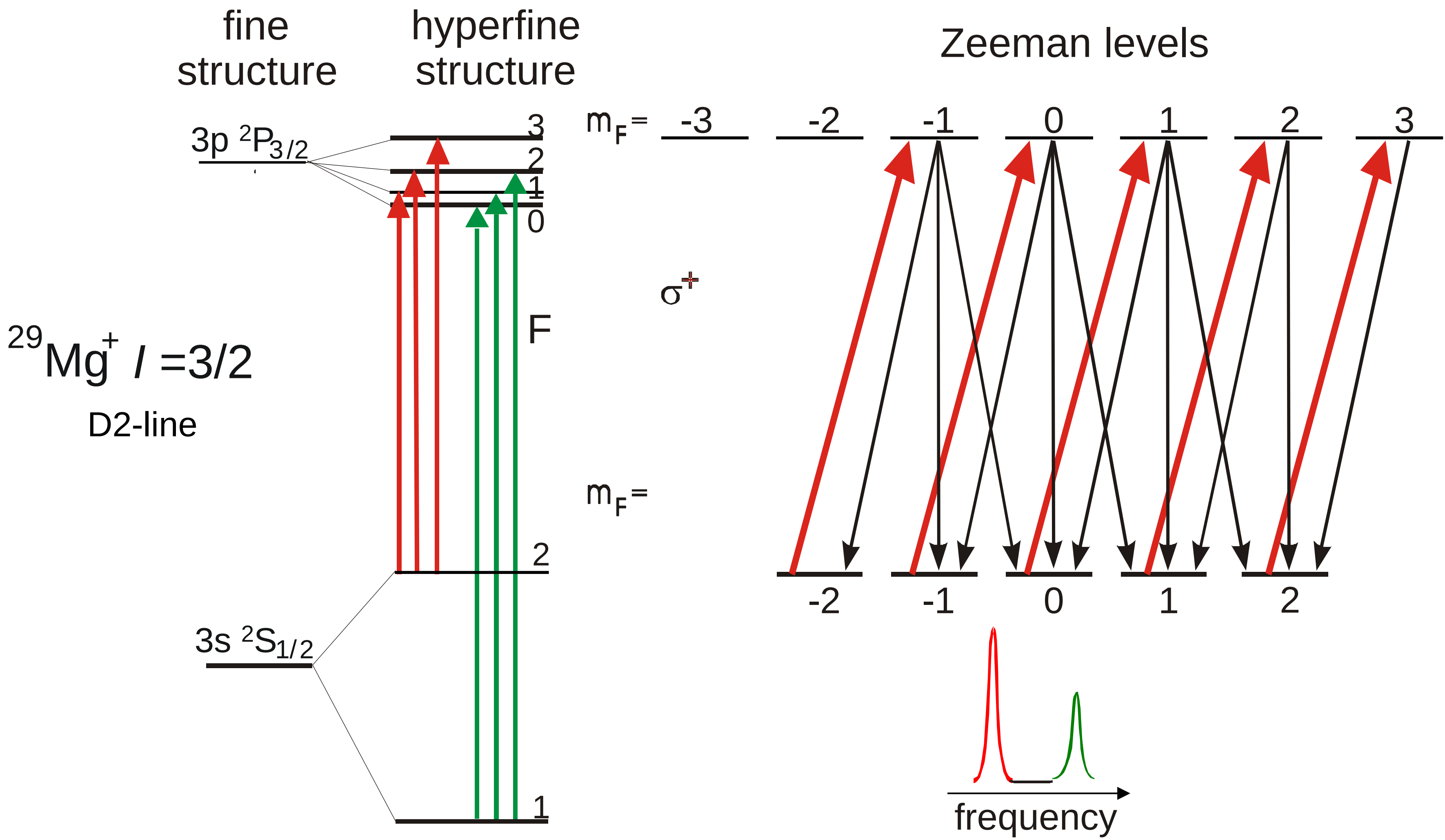
Thanks to my collaborators

and

thank you for your attention

M. Stachura, A. Gottberg, L. Hemmingsen, V. Arcisauskaite, M. L. Bissell, K. Blaum, A. Helmke, K. Johnston, K. Kreim, F. H. Larsen, R. Neugart, G. Neyens, D. Szunyogh, P. W. Thulstrup, D. T. Yordanov

Optical pumping and atomic spin polarization



σ+ circularly polarized light => Δm_F = +1
(or -1 for σ-) => atomic spin polarization

Mg$^+$: 280nm, UV

Zn and Cu isotopes

Backup slides

Chemical shift range for different metal ions:

^{67}Zn: 2700 ppm, from 0 to 2700 (calculations)

^{113}Cd: 650 ppm, from -650 to 0

^{199}Hg: 3500 ppm, from -3000 to 500

Zn candidates: (spin in brackets - not yet measured)

mass	spin	t1/2	production (ions/s)
73 gs	(1/2)	23 s	ca 1e6
77isomer	(1/2)	1 s	3e4
77 gs	(7/2)	2 s	7e6
79	(9/2)	1 s	1e6

Transition:
4s4p 3PJ=0,2 ->
4s6s 3S1 and 4s4d 3DJ
(300-335 nm)

Cu candidates: (all spins confirmed or measured at COLLAPS setup)

mass	spin	t1/2	production (ions/s)
58	1	3.4 s	3e5
73	3/2	4 s	4e6
74	2	1.6 s	6e5
75	5/2	1.2 s	1e5

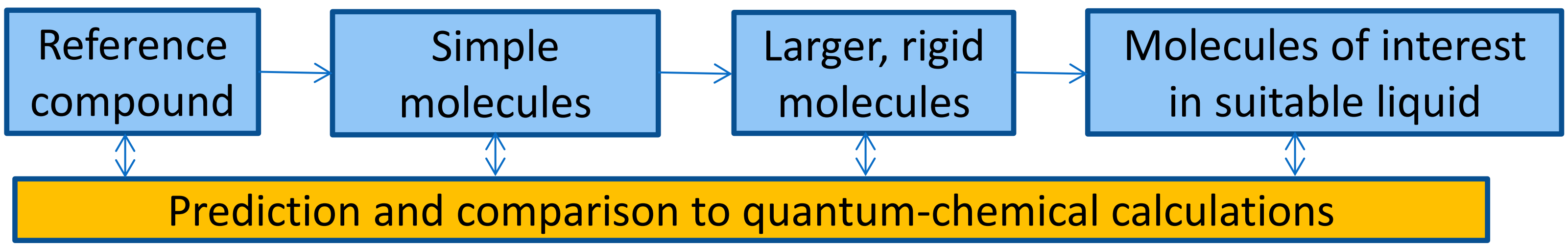
Transition:
2*S*1/2 gs -> 2*P*3/2
(324.754 nm)

Systematic approach

- Observables: chemical shifts, coupling constants, relaxation times

-> Metal coordination number, oxidation state, electronic configuration

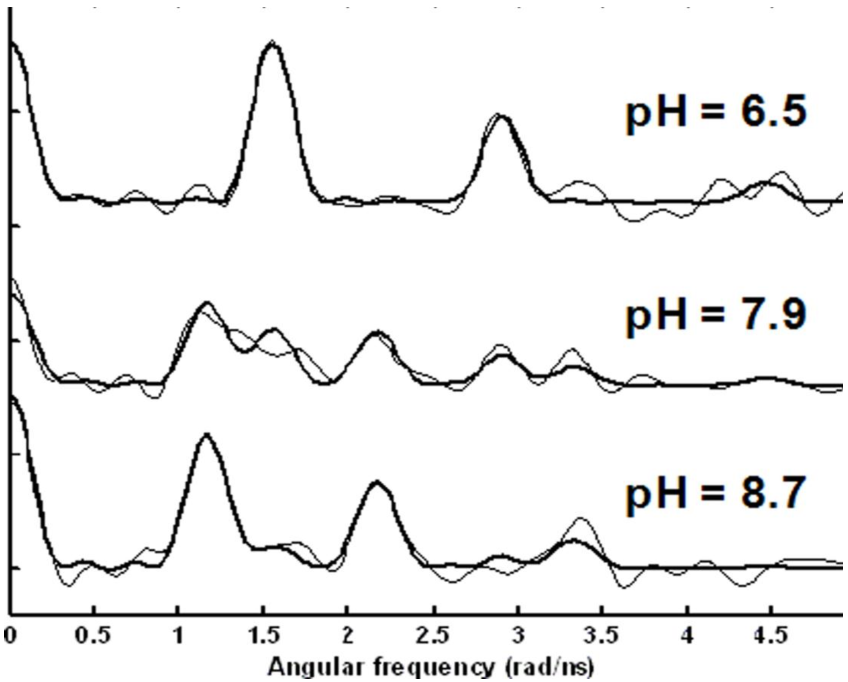
- Approach:

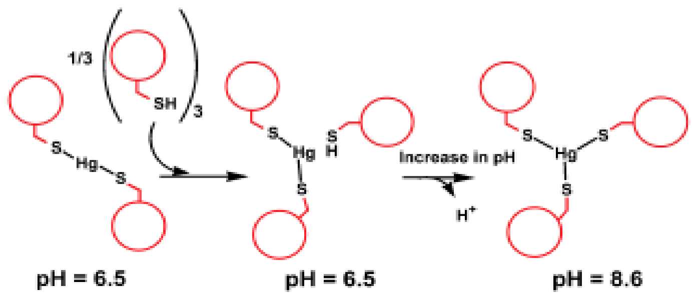


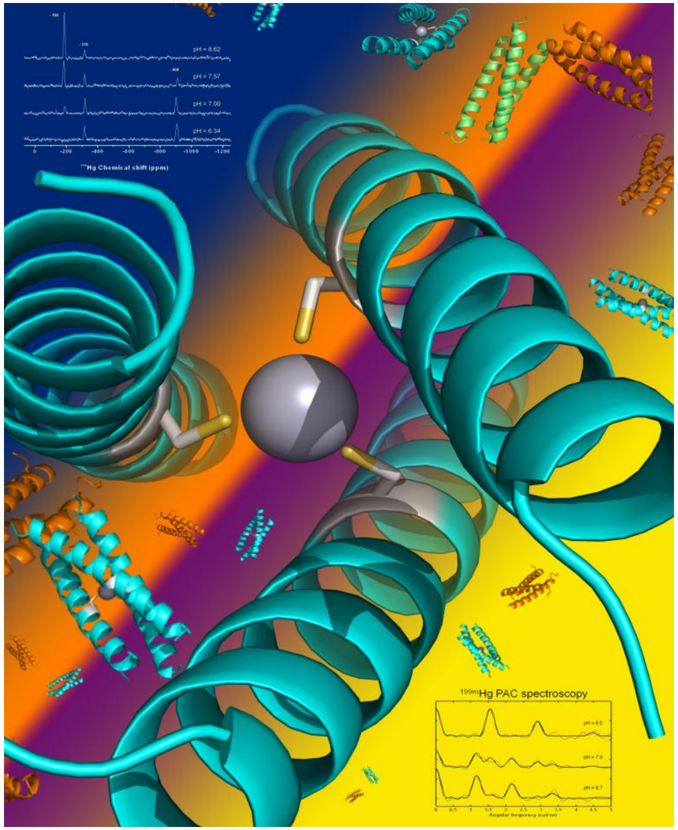
- **Long-term** – Studies on other biologically-relevant metal ions

Metal binding to proteins

- Studied with Perturbed Angular Correlation method







ISOLDE