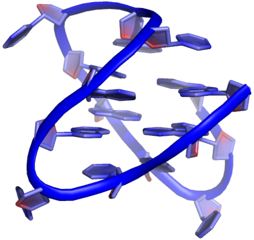
Addendum: Liquid β-NMR studies of the interaction of Na and K cations with DNA G-quadruplex structures

Spokesperson: Beatrice Karg, Magdalena Kowalska

February 9, 2022

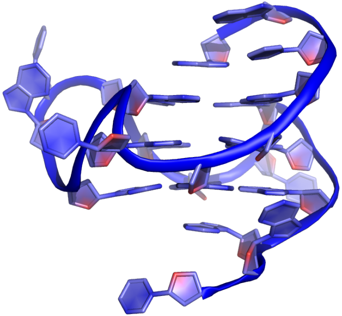
Quadruplex-DNA

Thrombin Binding Aptamer (*tba*)



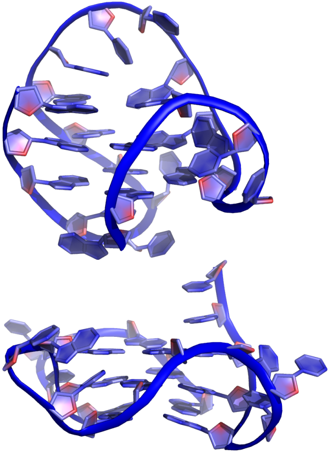
- therapeutic DNA from clinical trials
- 2 tetrads -> single ion binding site

c-myc



- oncogene promoter sequence
- most stable, fast kinetics

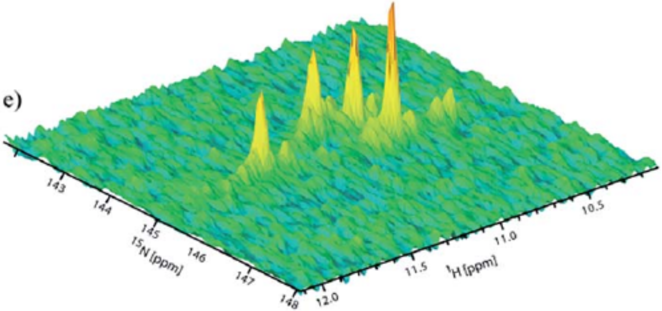
Human Telomeric (*ht*)



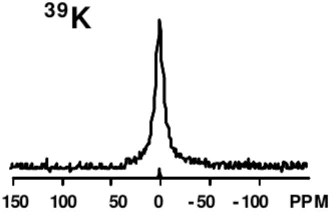
- native telomeric repeat
- structure cation-dependent

The Problems and the Unknowns

Signal overlap



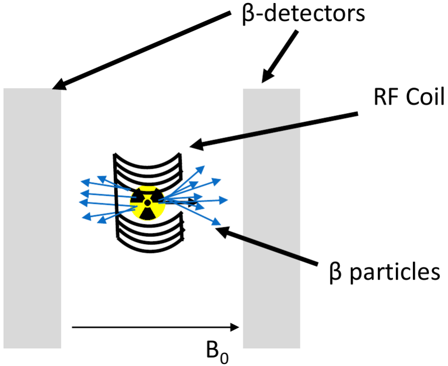
Weak & broad Resonances



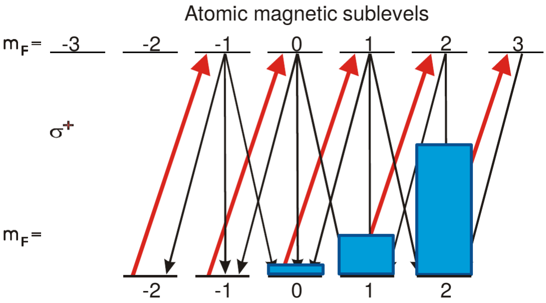
Left: Salgado et al., G-quadruplex DNA and ligand interaction in living cells using NMR spectroscopy, Chemical Science, 2015
Middle: Wong et al., Direct NMR detection of the "invisible" alkali metal cations tightly bound to G-quadruplex structures, Biochemical and Biophysical Research Communications, 2005

Sensitivity: β-NMR

β-detection - Emission Asymmetry

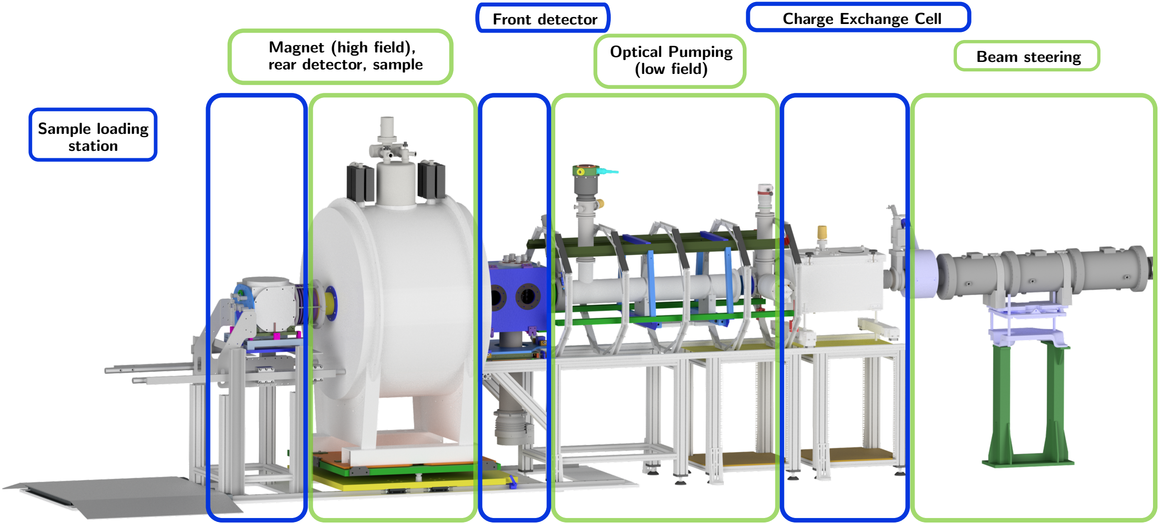


Hyperpolarization - Optical Pumping



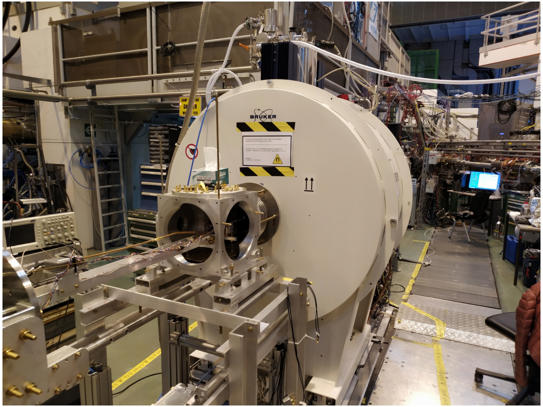
Harding et al., Magnetic moments of short-lived nuclei with part-per-million accuracy: Paving the way for applications of β-detected NMR in chemistry and biology,

The New Beamline

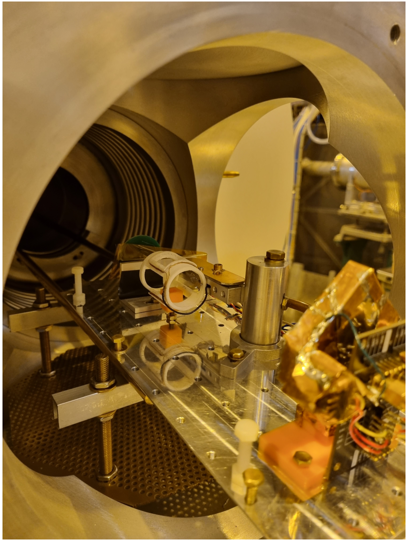


CAD-Design: N. Azaryan, Render: M. Jankowski

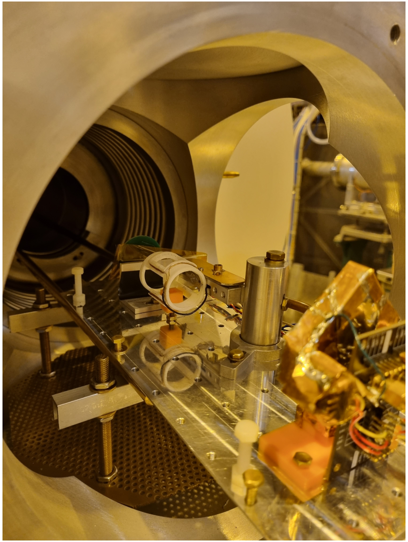
New Magnet



- 4.7T with sub-ppm homogeneity

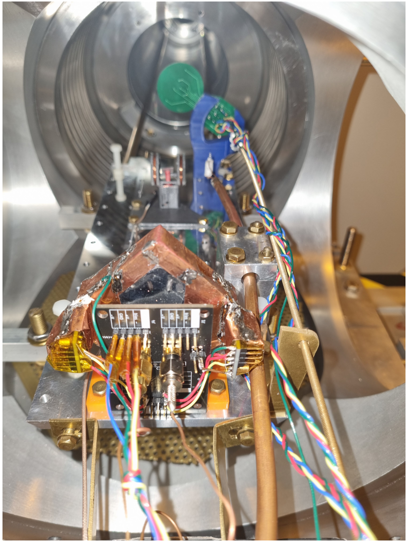


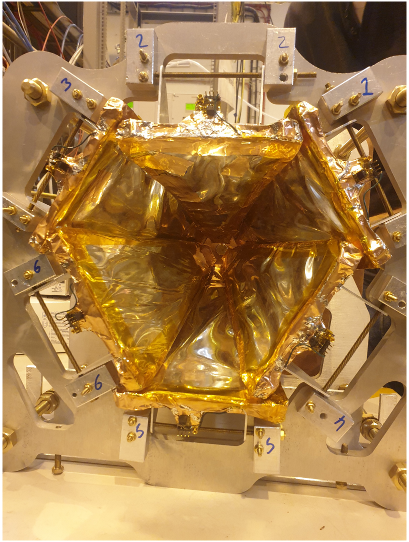
New Magnet



Coils by: M. Baranowski

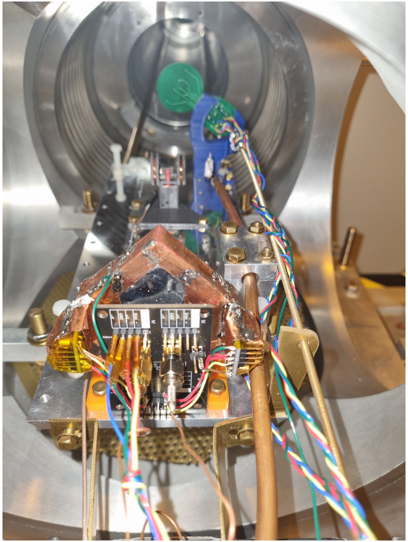
New Detectors

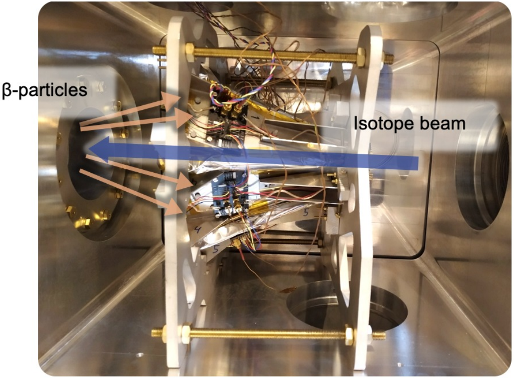




Developed and built by: M. Madurga-Flores, M. Myllymäki, S. Warren

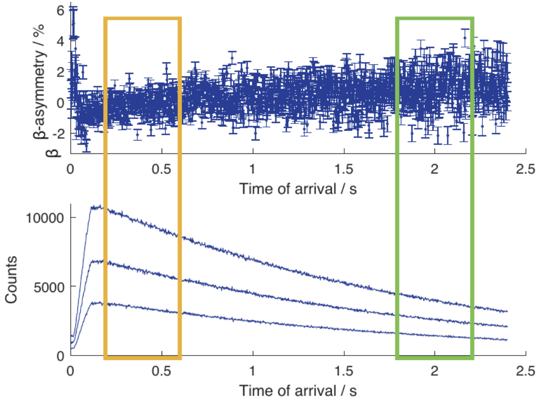
New Detectors





Developed and built by: M. Madurga-Flores, M. Myllymäki, S. Warren

New Data Acquisition System



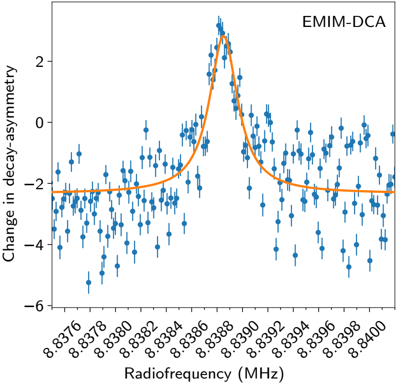
Time-resolved β-asymmetry and number of β-events for a hyperfine structure scan for data points in resonance with optical pumping laser

- combined data acquisition and control system
- FPGA-based 250 MHz 14-bit oscilloscope
- calculation of time-resolved properties for each beta-particle in real time (timestamp, amplitude, integral etc.)
- in-depth data analysis

Written by: M. Jankowski, J. Croese, H. Brand

Improvements

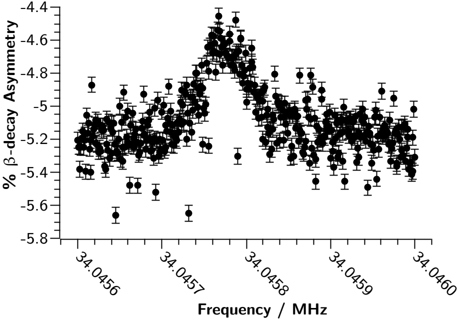
2018



	Frequency ν [Hz]
E2	8 838 838(10)

- Δ between samples: 9 Hz
- lowest FWHM: 201 ± 30 Hz

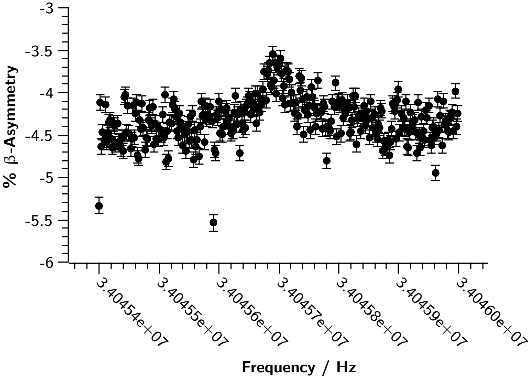
2021



	Frequency ν [Hz]	Uncertainty
E4	34045776.24	0.6

- Δ between single sample: < 6 Hz
- lowest FWHM: 38.5 ± 8.4 Hz

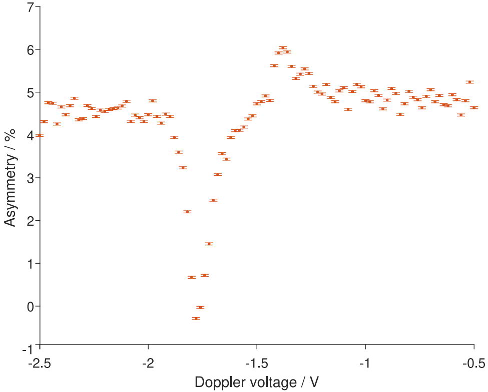
A look at Deep Eutectic Solvents

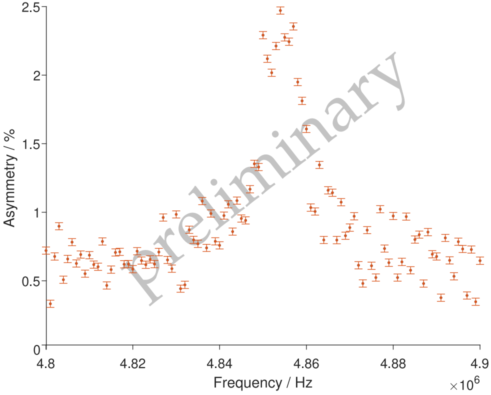


- (^{23}Na frequency: 34.045680 MHz)
- $\Delta\nu$ between solvents: 110 ± 0.5 Hz (chemical shift difference between solvents preserved)
- FWHM: $60 - 120$ Hz ± 10 Hz

Data-preparation: K. Dziubinska-Kühn

A new nucleus - Moving to ^{37}K





Data-preparation: M. Jankowski

Intended Runs

14 shifts for 1 run + remaining 14 shifts:

- 4 shifts: final testing/optimisation: detectors, sample holder, RF coil
- 10 shifts: polarisation and β-NMR on ^{49}K
- 14 shifts: final experiment (^{26}Na and/or ^{49}K with Quadruplex-forming oligonucleotides)

Technical:

- ^{26}Na: Ta, Ti, or UC_x target; ^{49}K: UC_x target
- yield: ^{26}Na: yield: 10^7 ions/s, ^{49}K: 2×10^4 ions/s

Summary

- successful ^{26}Na commissioning
- significantly reduced linewidth/uncertainty
- ^{37}K measured in crystal

- polarize and measure ^{49}K
- Oligonucleotide measurements with either Na/K

Properties of stable and radioactive isotopes relevant for this proposal

Nucleus	Radioactive half-life	Nuclear spin *I*	Magnetic moment (μ_N)	Quadrupole moment (mb)	Observed β-asymmetry
^{23}Na	-	3/2	2.217499(7)	104	-
^{26}Na	1.077 s	3	2.849378(20)	-5	25%
^{37}K	1.237 s	3/2	0.20320(6)	100	8-11%
^{39}K	-	3/2	0.39147(3)	60	-
^{49}K	1.260 s	1/2	1.33868(8)	-	-

Harding et al., Magnetic moments of short-lived nuclei with part-per-million accuracy: Paving the way for applications of β-detected NMR in chemistry and biology, http://arxiv.org/abs/2004.02820, 2020

Shidling et al., Precision half-life measurement of the β^+ decay of ^{37}K, Phys. Rev. C, 2014

Kopf et al., Optical pumping of short lived β-radioactive isotopes and the magnetic moment of 37K, Zeitschrift für Physik, 1969

Von Platen et al., Spin exchange polarization and hfs anomaly measurement of β-active 37K, Zeitschrift für Physik, 1971

Minamisono et al., Quadrupole moment of 37K, Physics Letters B, 2008

Carraz et al., The 49K beta decay, Physics Letters B, 1982

Number of Shifts

- for ^{49}K: UC_x (2×10^4 ions/s), record ^{49}K β-NMR resonances in crystal (establish polarization, then determine resonance frequency), ionic liquids/DES
- 1 shift at the start of every beamtime: establishing laser polarisation by HFS scans, optimising laser-atom overlap
- 0.3-0.5 shift (for each solvent and G4 configuration): measuring T_1 in one liquid sample, with different parameters optimised
- 0.5-1 shift for each solvent and G4 configuration: performing several NMR scans in one liquid sample (depending on the number of peaks and observed β-asymmetry)