Investigating Solid-State NMR Recoupling Sequences

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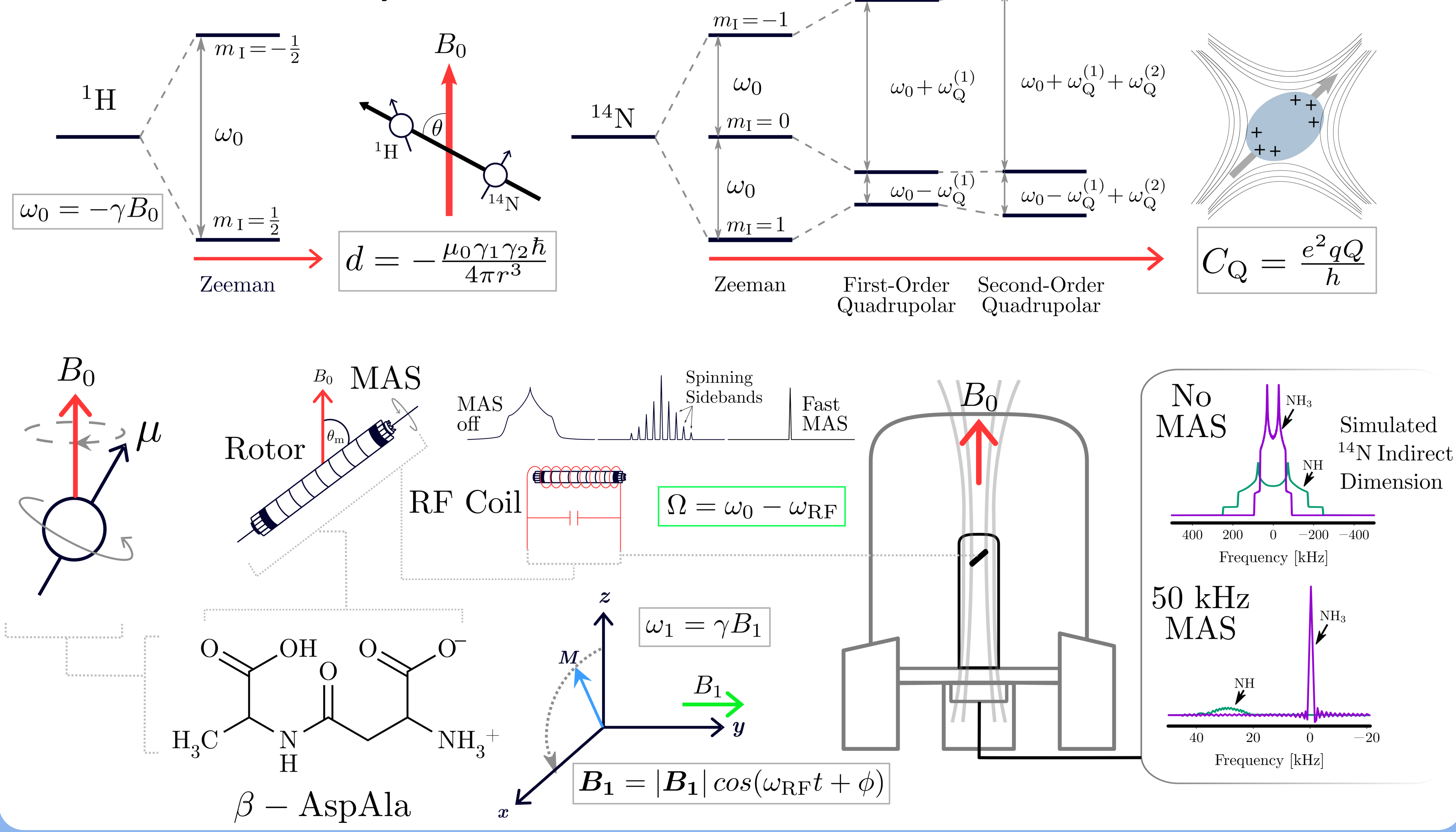
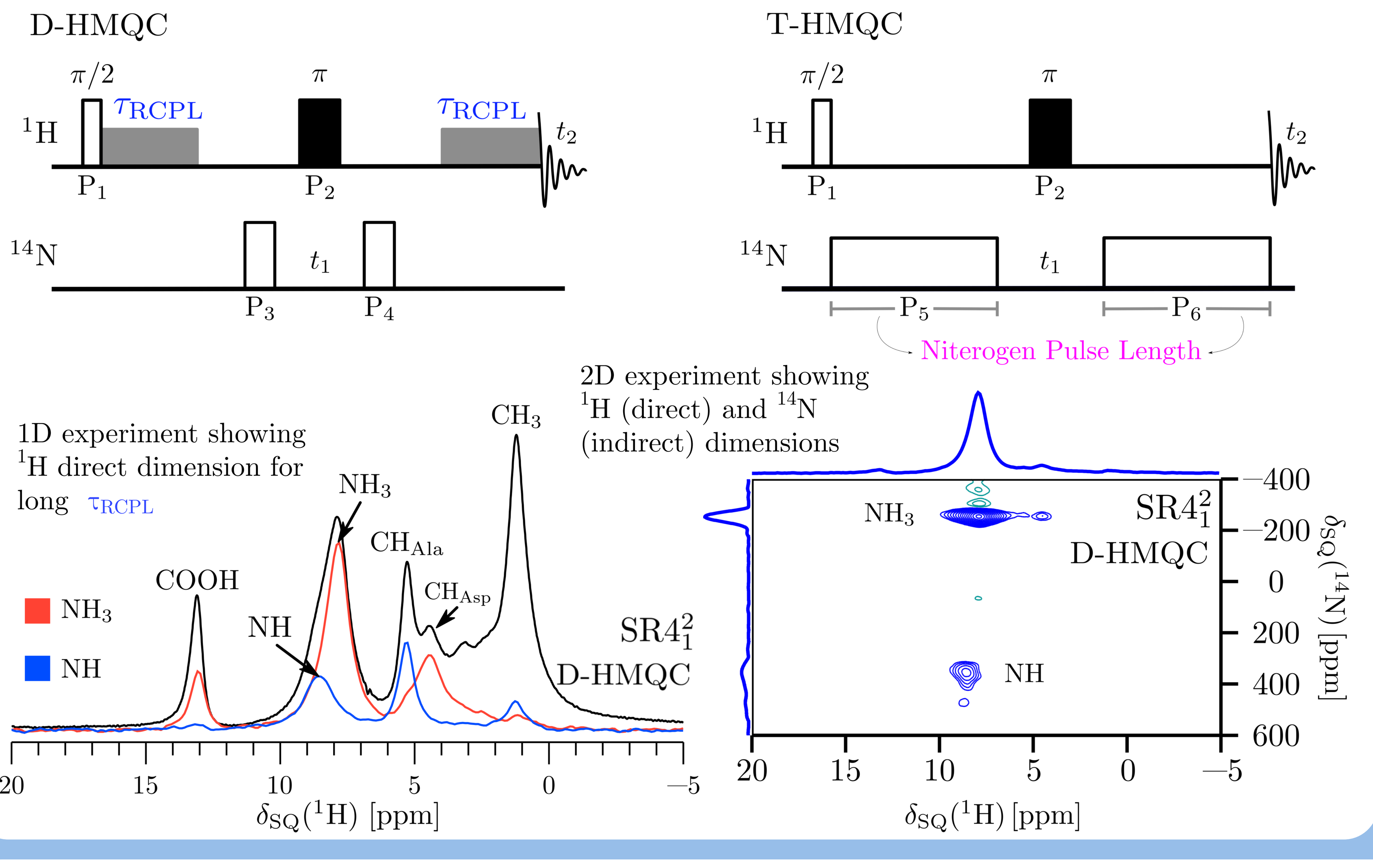
Solid State NMR, ¹H and ¹⁴N



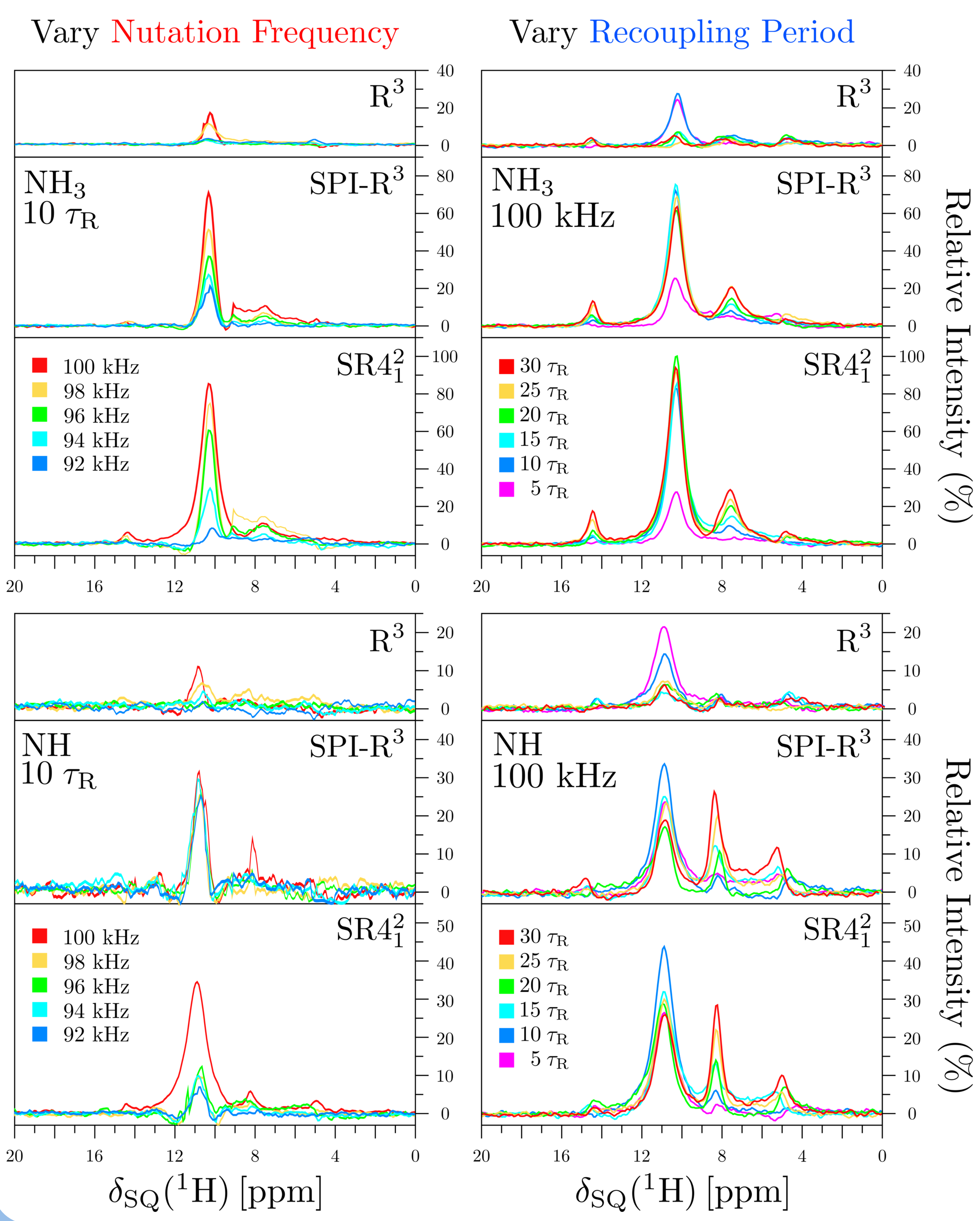
Outline

- Nitrogen environments are key to intermolecular hydrogen bonding which determine how molecules pack in e.g. active pharmaceutical ingredients (APIs). Many APIs however are provided in solid form therefore probing techniques such as Solid-State Nuclear Magnetic Resonance (NMR) provides a tool to understand the properties of these structures.
- This project considers the spin-1 ^{14}N isotope where the quadrupolar interaction makes direct observation difficult. Thus, indirect acquisition methods of ^{14}N spectra are explored and optimised.
- The dipeptide, β–Aspartyl Alanine (β–AspAla) containing two nitrogen sites: NH and NH_3 is spun at a Magic Angle Spinning (MAS) frequency of 50 kHz for a ^{1}H Larmor frequency of 500 MHz.
- The simulation package, SIMPSON (based on the Schrodinger equation and Density Operator theory), is used to compare experimental and simulated data.

- Two implementations of the ^{14}N –^{1}H Heteronuclear Multiple Quantum Correlation (HMQC) approach are investigated: Dipolar HMQC (D-HMQC) based on rotary resonance recoupling (R^3) methods (R^3 and SPI-R^3) and a symmetry based method ($SR4^2_1$), where the ^{1}H nutation frequency is set to twice the MAS frequency, and TRAnsfer of Populations in DOuble Resonance HMQC (TRAPDOR-HMQC), where pulsing is done on ^{14}N. The pulse sequences are:



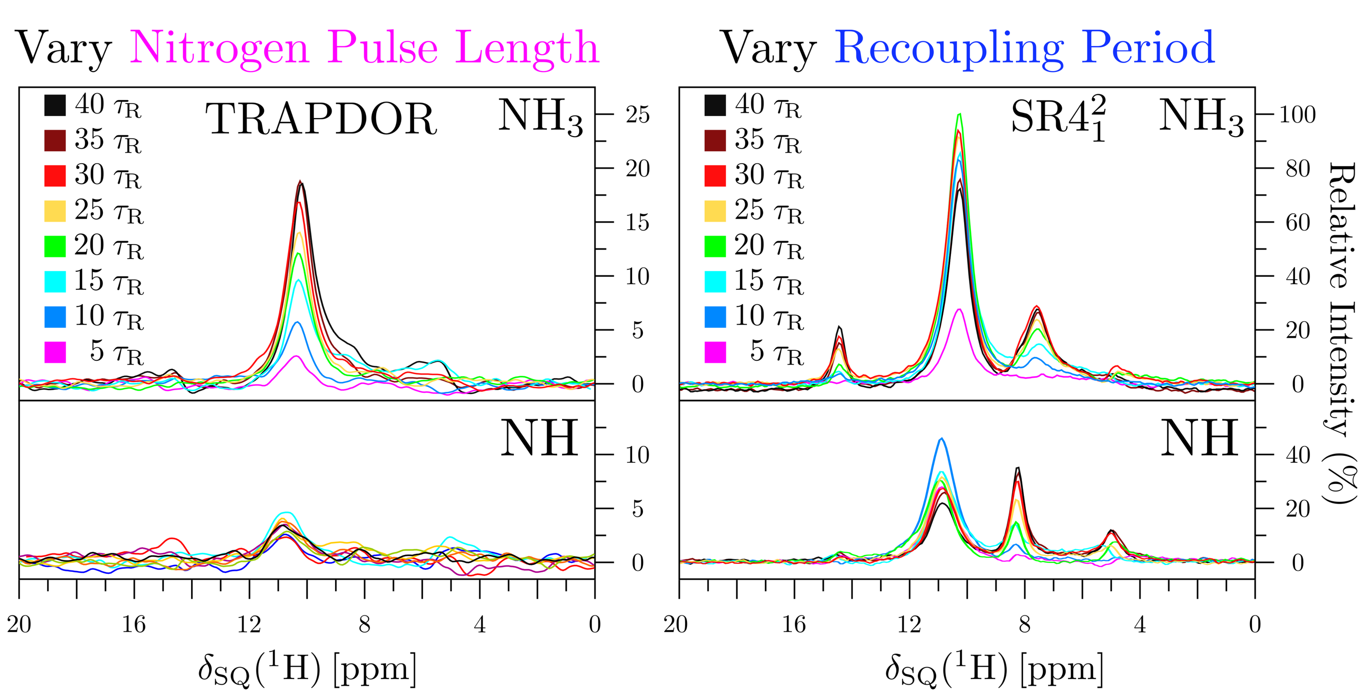
D-HMQC Experiments

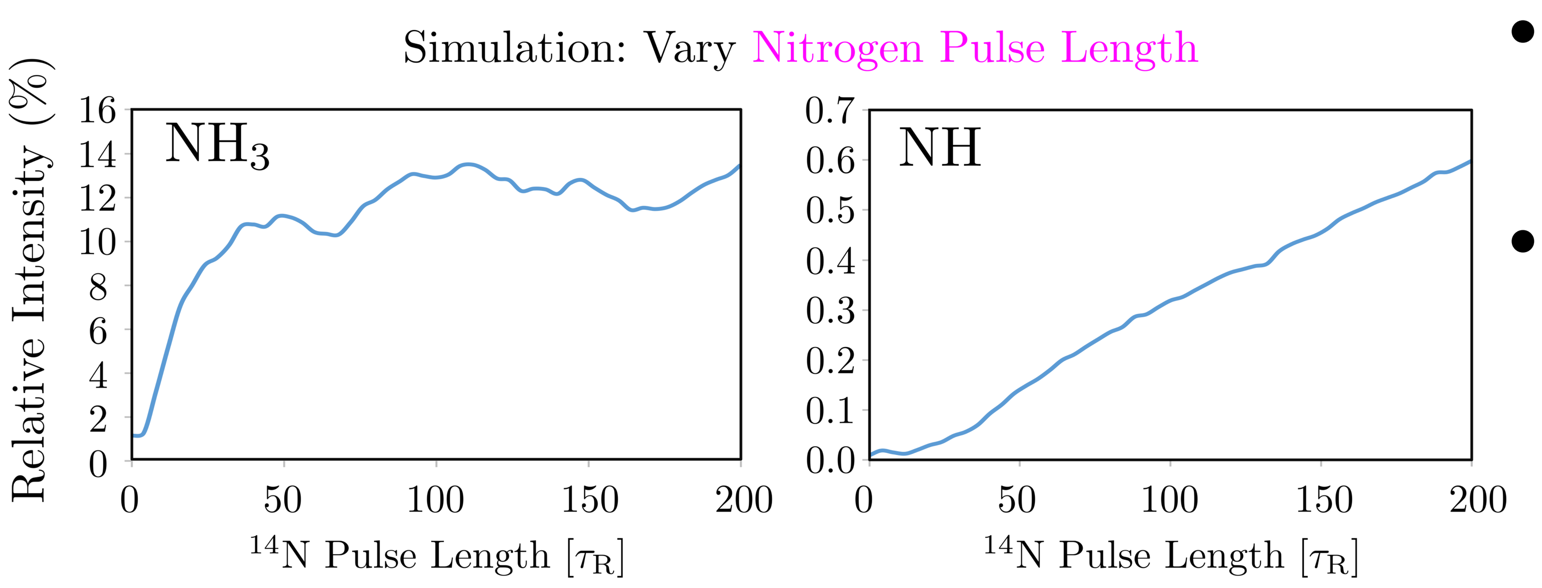


- The nutation frequency and the recoupling period was varied for both nitrogen environments across all three D-HMQC recoupling regimes.
- R^3 recoupling produces the least signal to noise ratio.
- The intensity of the peaks increased with the nutation frequency and a maximum is observed at twice the spinning frequency for all the recoupling regimes, as is expected.
- $SR4^2_1$ is found to be more sensitive to nutation frequencies for environments with a greater quadruple interaction than the other two R-based sequences.
- R^3 recoupling does not show as many neighbouring environments compared $SR4^2_1$ or SPI-R^3.

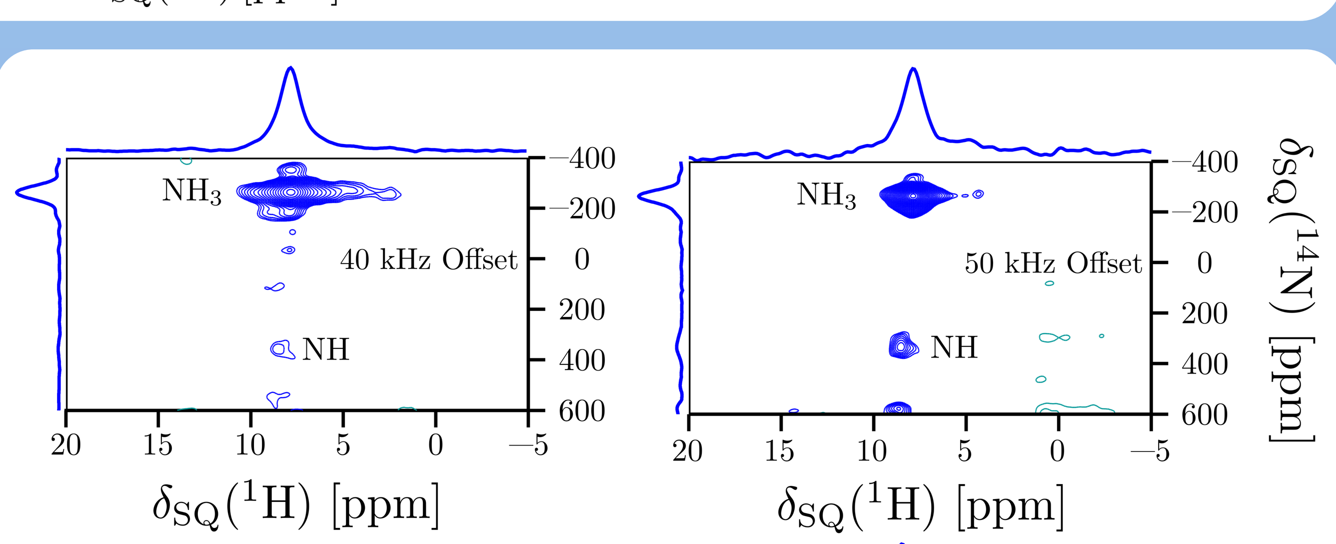
TRAPDOR-HMQC (T-HMQC)

- A ^{14}N RF pulse duration of 40 τ_R produces a comparable intensity to $SR4^2_1$ recoupling with a 5 τ_R recoupling period.
- For the same amount of recoupling applied, $SR4^2_1$ is the superior technique. However, the T-HMQC produces a smaller better signal to noise ratio compared to D-HMQC at similar peak intensities, suggesting that T-HMQC is a more efficient method.



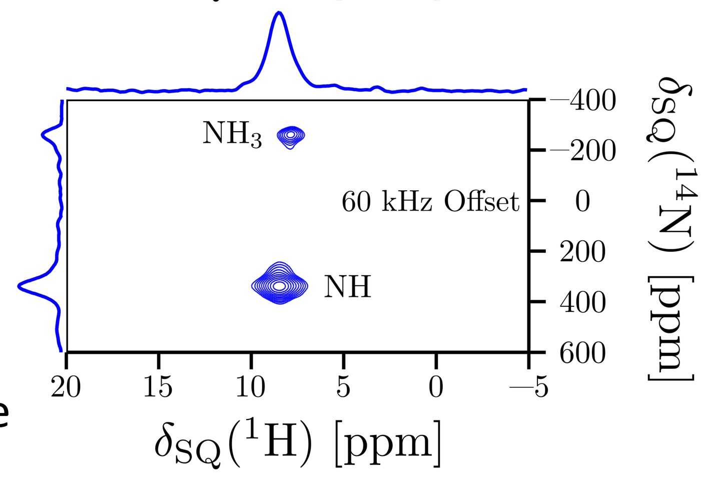


- SIMPSON simulation showing how intensity varies with ^{14}N pulse length.
- This indicates that T-HMQC, can reach higher intensities than $SR4^2_1$ for much longer recoupling periods. This could be something to investigate further for experiments.



50 kHz ^{14}N Nutation

Vary Offset



- The offset is the distance (in kHz) that the RF pulse is applied from the resonance peak.
- Varying the offset from 40 kHz to 60 kHz produces a change in the intensity of the relevant nitrogen environment. This is in agreement with that shown in [1].
- The ^{14}N nutation frequency shows a signal dependence on the excitation of the NH environment such that a 50 kHz nutation frequency produces batter signal than a 25 kHz nutation frequency does.

Conclusion and Outlook

- The methods presented offer insight into producing more sensitive ^{14}N –^{1}H spectra.
- Future experiments may include investigating what is seen for longer ^{14}N pulse lengths in the T-HMQC pulse sequence.
- Also, the simulations do not include effects of multi-spin dephasing. Future work should investigate if these effects can account for some of the discrepancies found between the data and simulations.

Reference

- [1] I. Hung and P. Gor'kov and Z. Gan. Efficient and Sideband-Free ^{1}H-Detected ^{14}N Magic-Angle Spinning NMR, *J. Chem. Phys.*, **151,** 154 (2019).