

GEMSTONE: ultra-selective NMR methods for complex spectra

Emma Gates

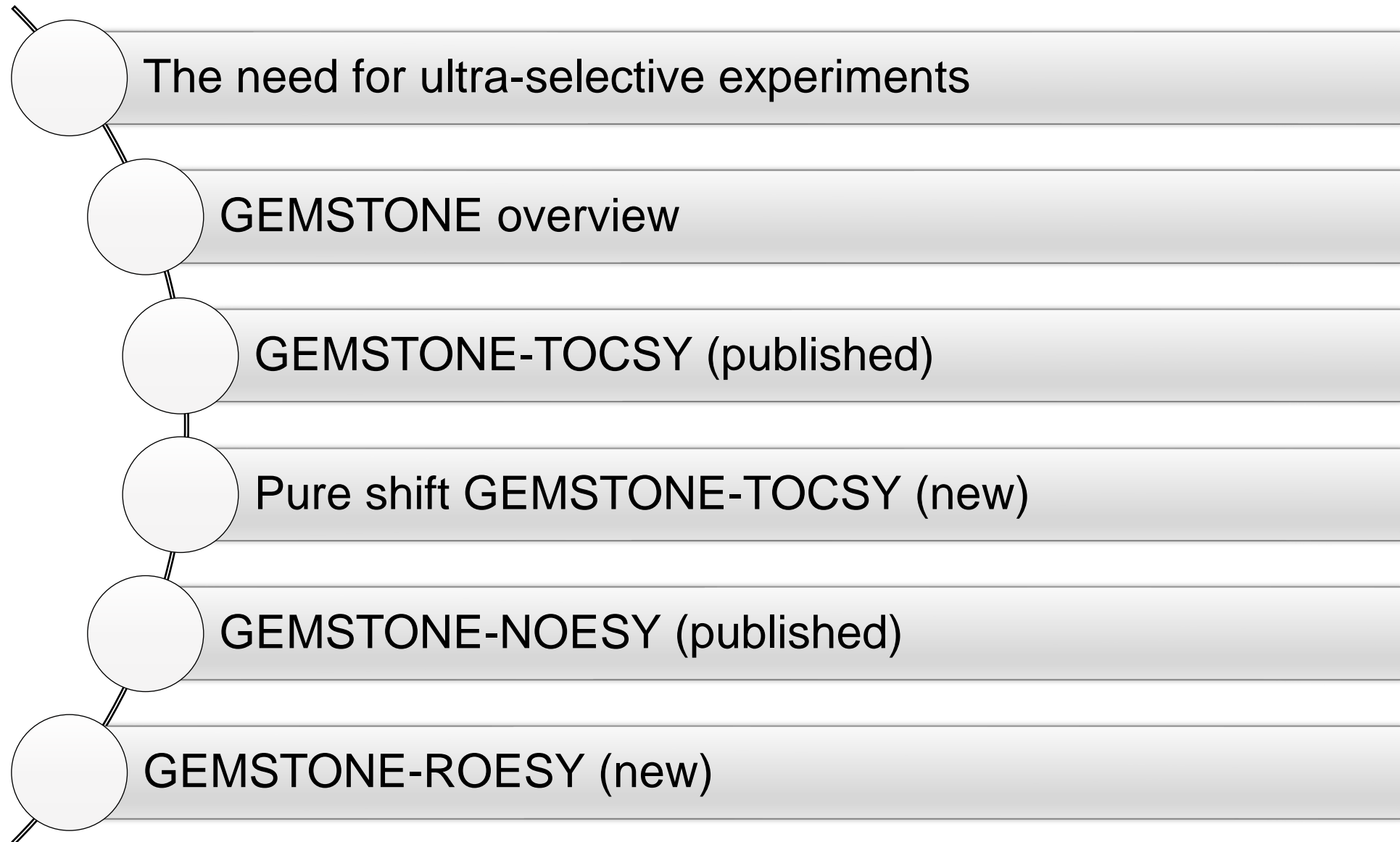
The University of Manchester

EUROMAR

Utrecht, Netherlands

13th July 2022

Presentation overview



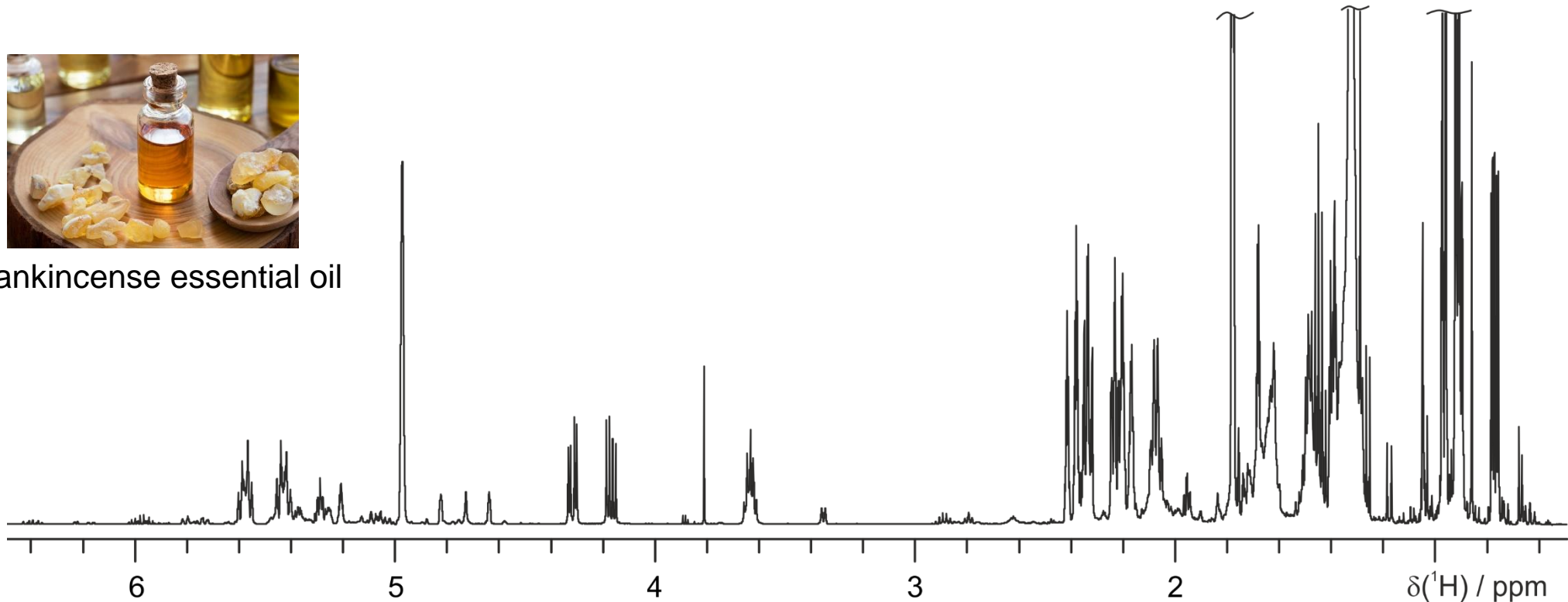
^1H NMR of complex systems

- ✓ Detailed structural information
- ✓ Qualitative and quantitative

- ✗ Narrow range of chemical shifts
- ✗ Multiplicity leads to overlap issues



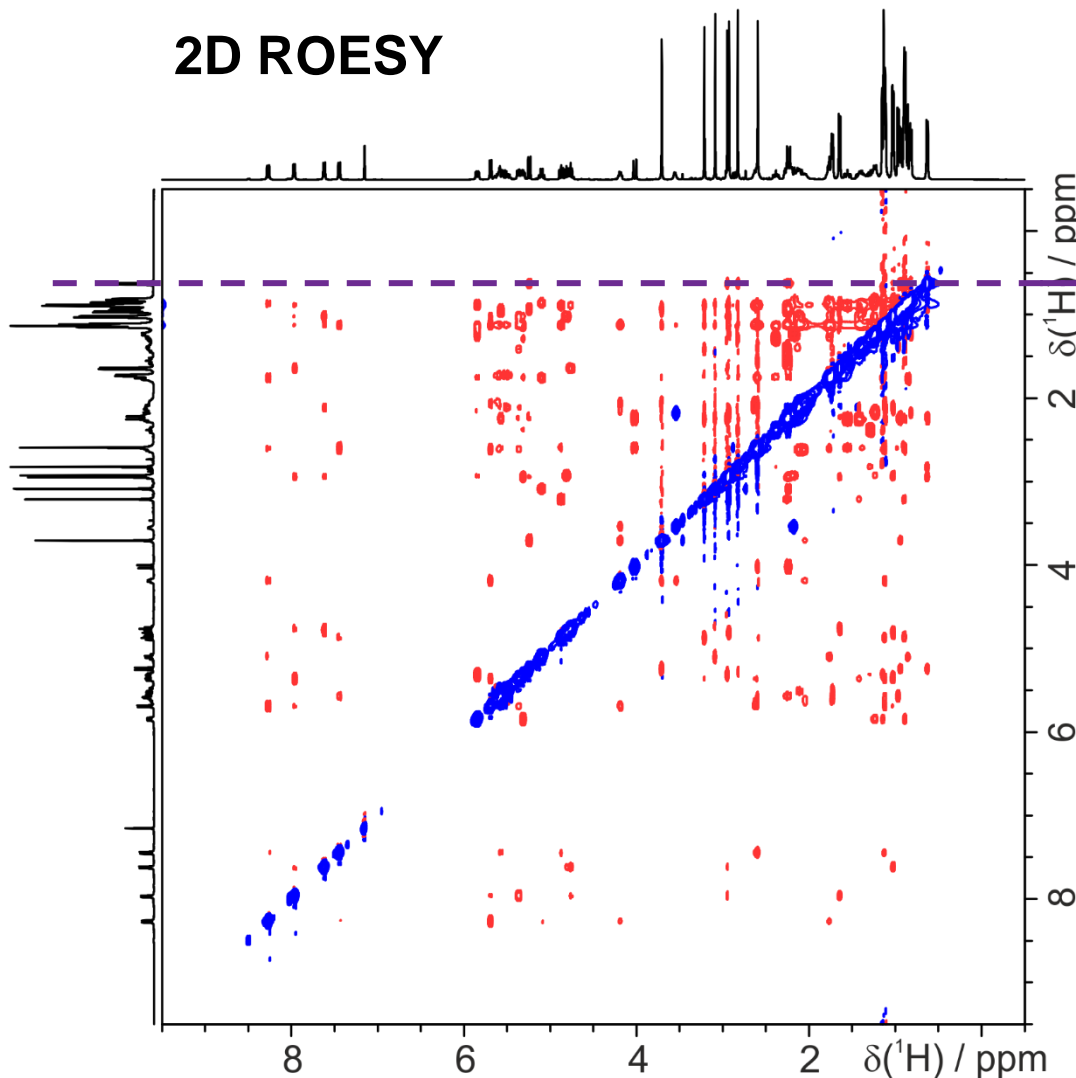
Frankincense essential oil



New methods are needed to circumvent spectral complexity and aid analysis

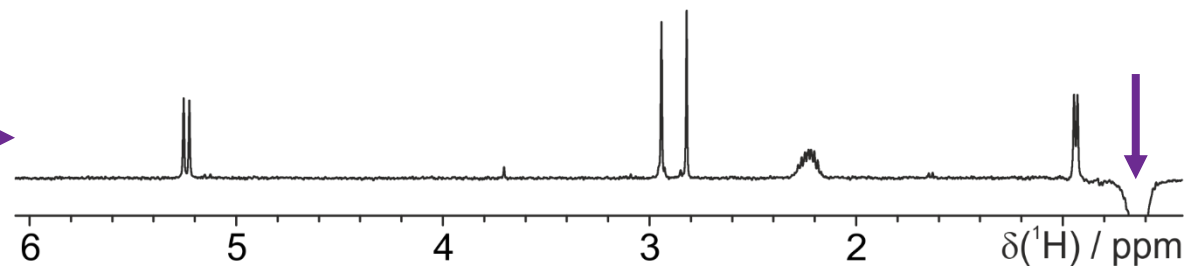
Overcoming overlap issues in ¹H NMR

2D ROESY

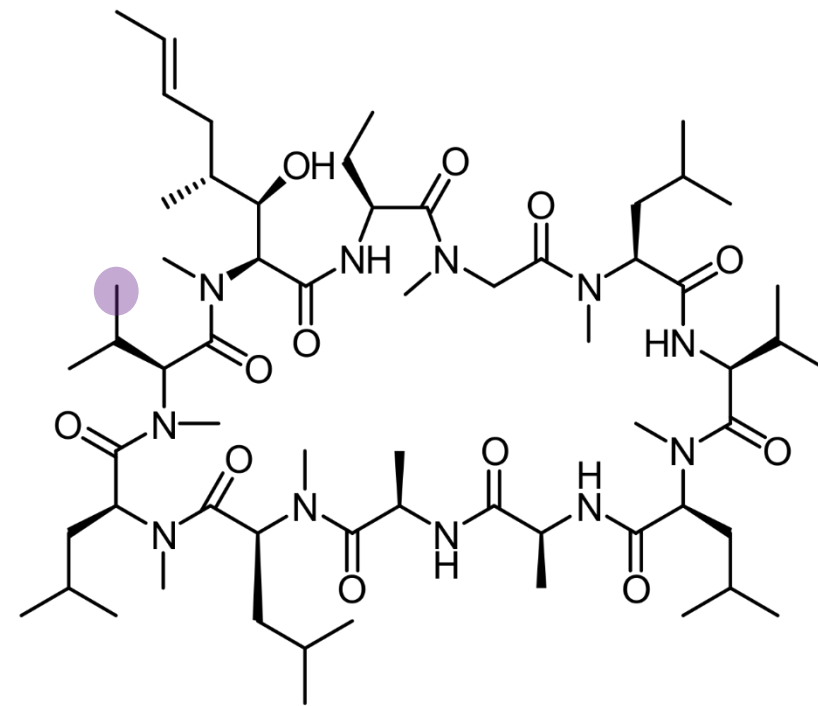


- ✓ Signals dispersed into multiple dimensions
- ✗ Long experiment time

Selective 1D ROESY

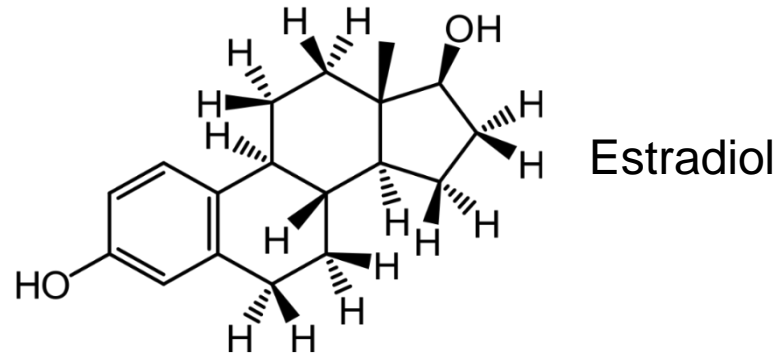


Cyclosporin

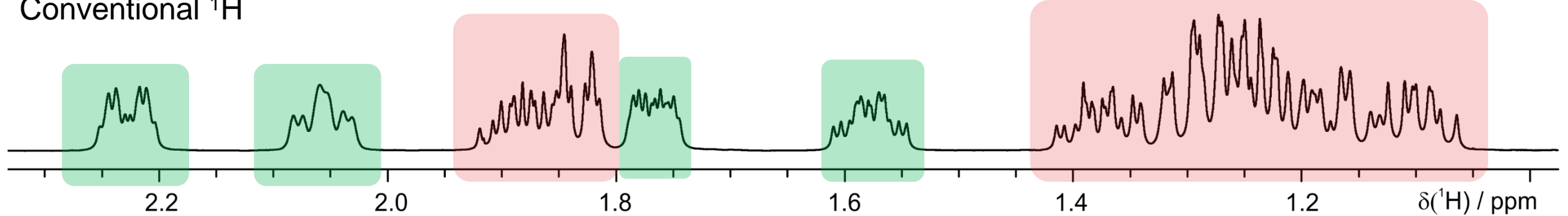


- ✓ Simplified subspectra
- ✓ Short experiment time
- ✗ Signal overlap hinders signal selection

Selective 1D methods

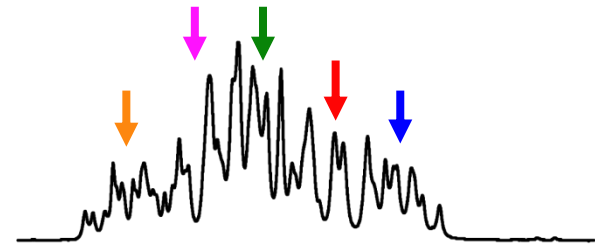


Conventional ^1H

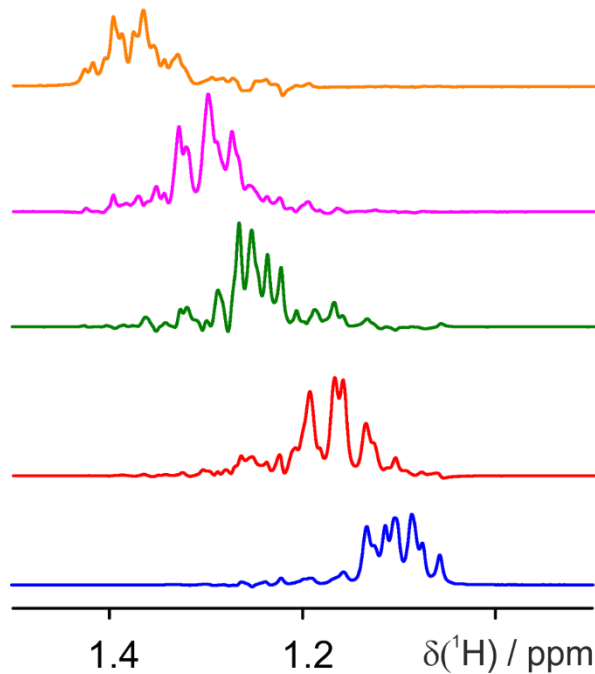


Selective 1D methods

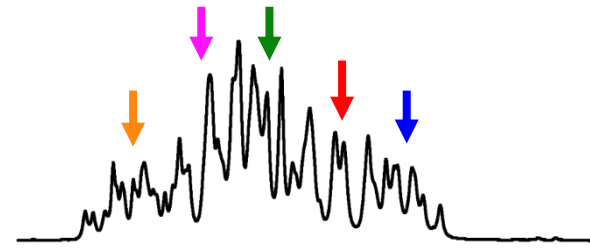
The Chemical Shift Selective Filter (CSSF) enables selection of a single multiplet even when severe signal overlap is present



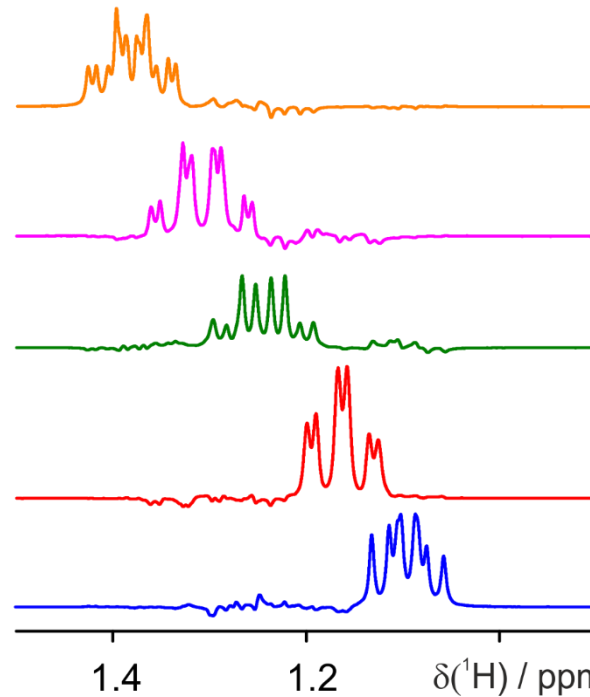
Conventional (<1 min)



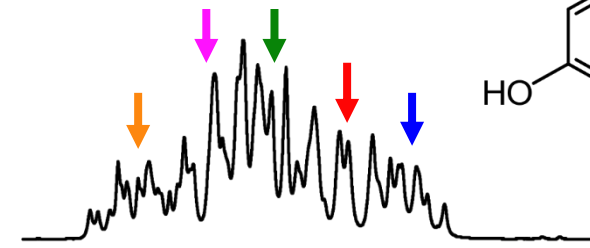
J. Magn. Reson., 1986, **70**, 106–133



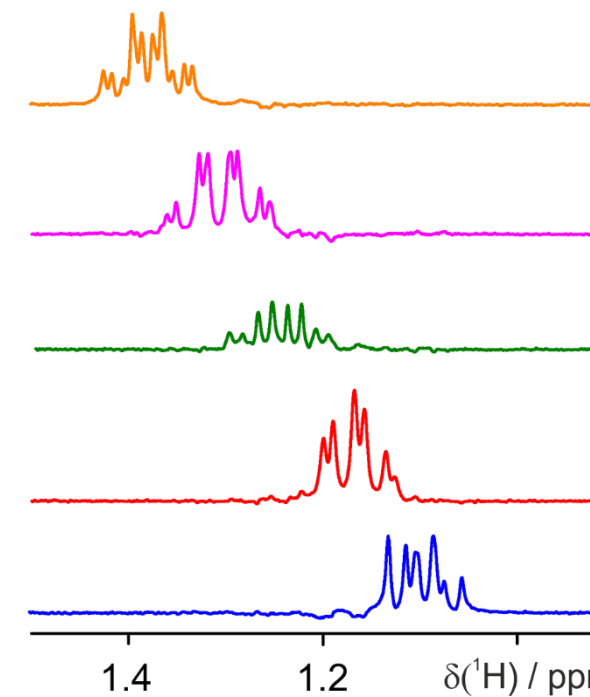
CSSF (~5 min)



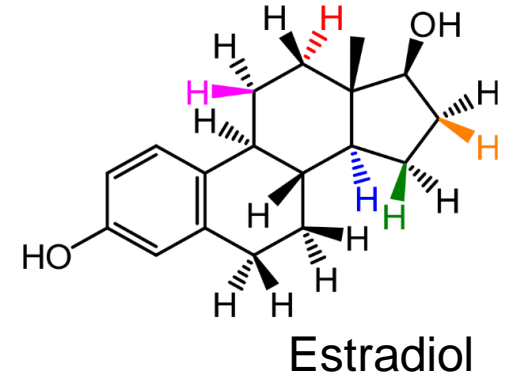
J. Magn. Reson., 2004, **170**, 97–103



GEMSTONE (<1 min)

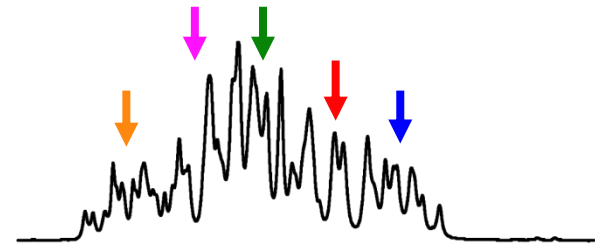
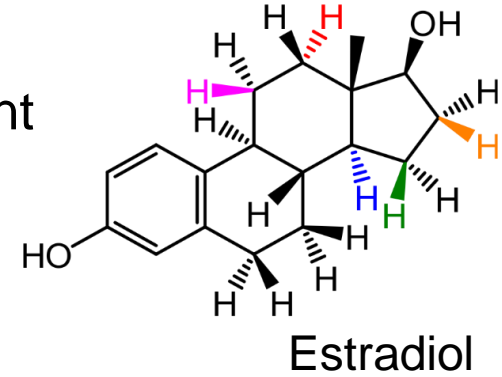


Angew. Chem. Int. Ed., 2021, **60**, 666–669

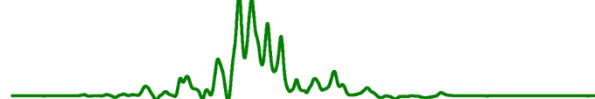
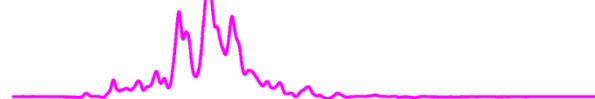


Selective 1D methods

Gradient-Enhanced Multiplet-Selective Targeted-Observation NMR Experiment (GEMSTONE) offers a single transient alternative approach to the CSSF experiment

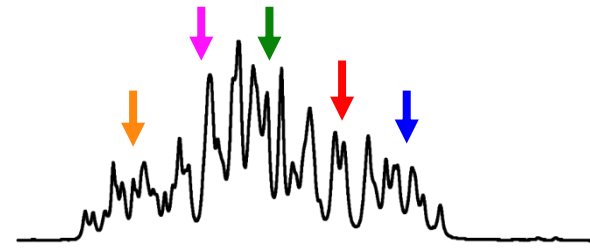


Conventional (<1 min)

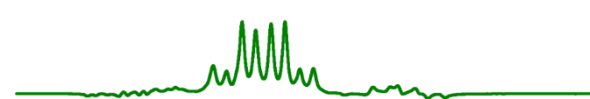
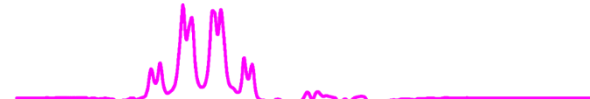


1.4 1.2 $\delta(^1\text{H}) / \text{ppm}$

J. Magn. Reson., 1986, **70**, 106–133

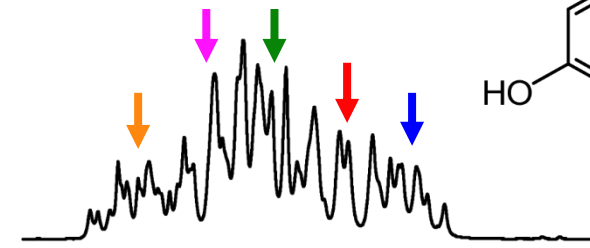


CSSF (~5 min)

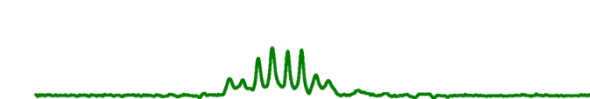


1.4 1.2 $\delta(^1\text{H}) / \text{ppm}$

J. Magn. Reson., 2004, **170**, 97–103



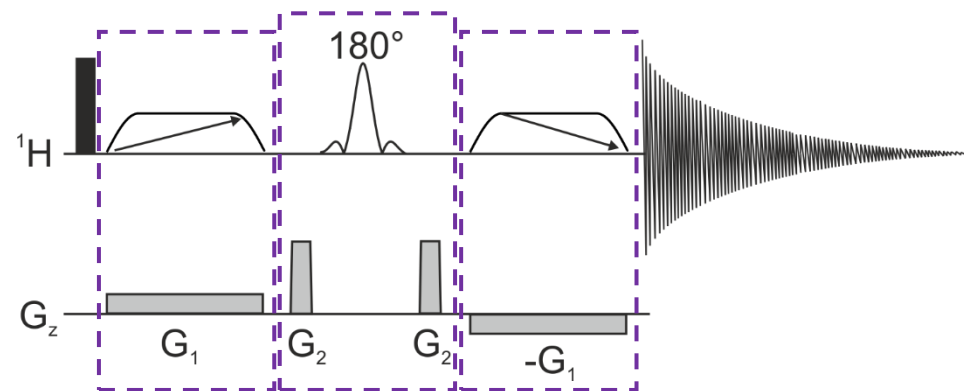
GEMSTONE (<1 min)



1.4 1.2 $\delta(^1\text{H}) / \text{ppm}$

Angew. Chem. Int. Ed., 2021, **60**, 666–669

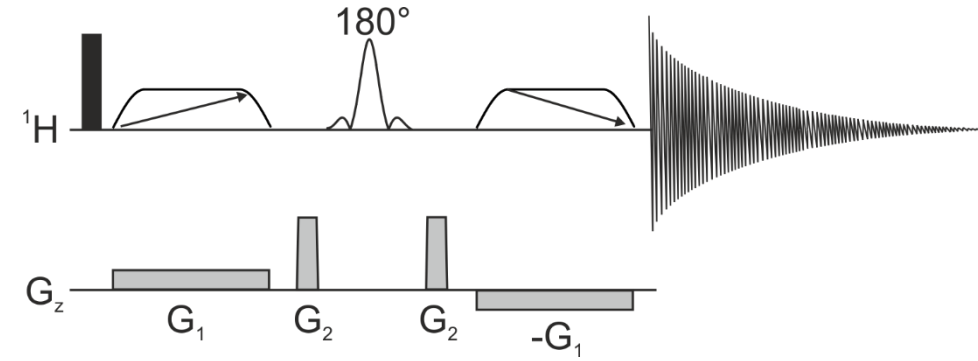
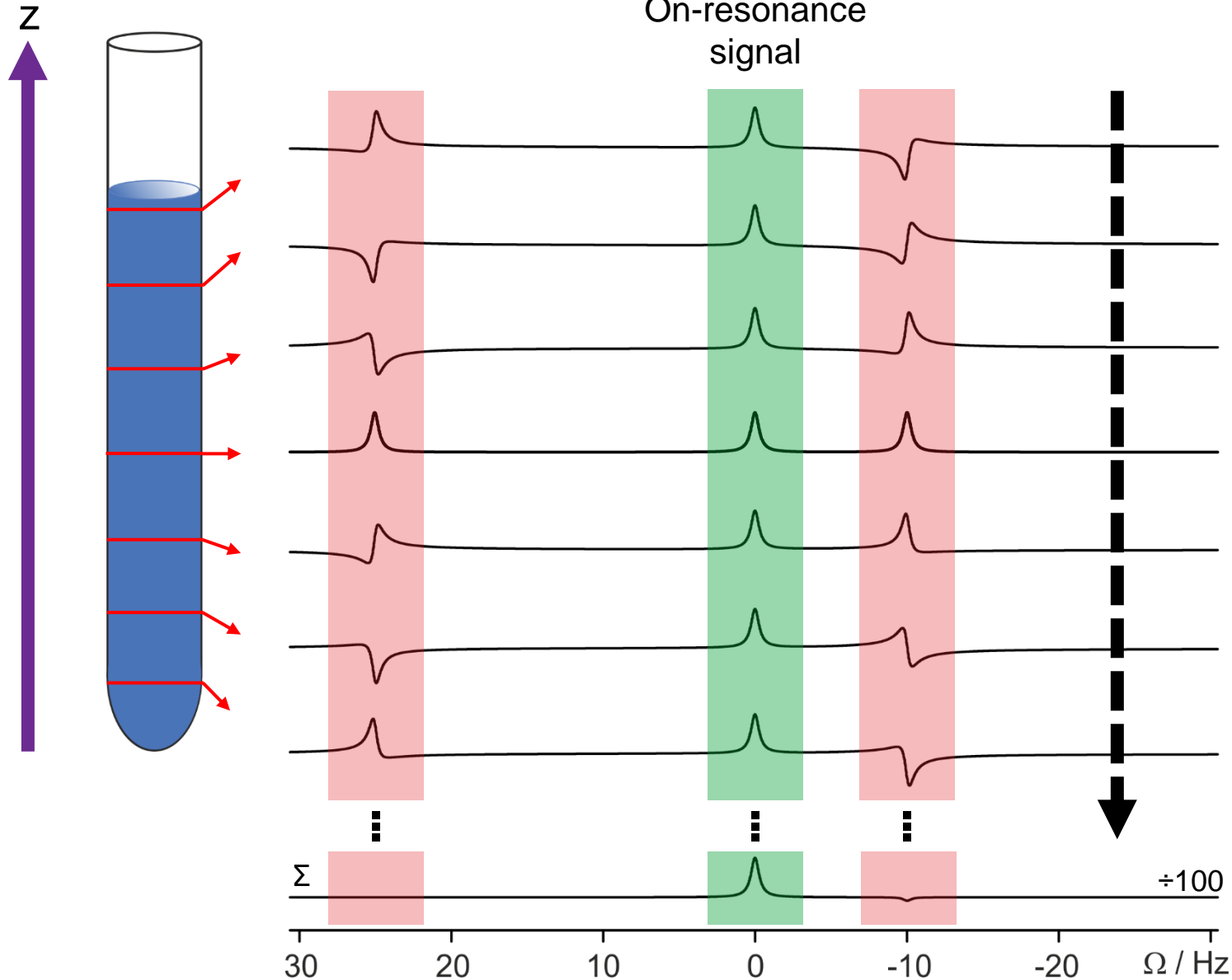
GEMSTONE overview



- Ultra-selective technique
- Swept-frequency pulses and G_1 gradients cause spatial encoding of signals
- On-resonance signals are retained, off-resonance signals are dephased
- The semi-selective 180° refocusing pulse refocuses J -modulation

GEMSTONE mechanism

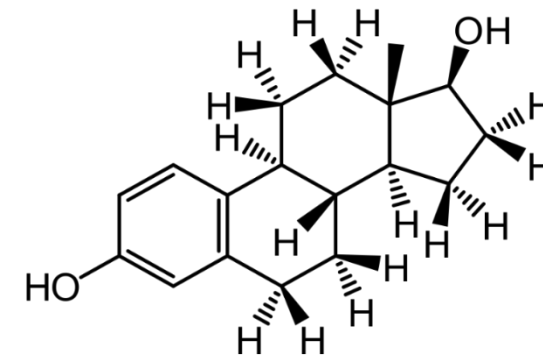
SPINACH simulations



- **On-resonance** signal retains the same phase throughout the NMR tube
 - **Off-resonance** signals acquire a spatially-dependent phase
- ⇒ Off-resonance signals average to zero over the length of the NMR tube

GEMSTONE setup

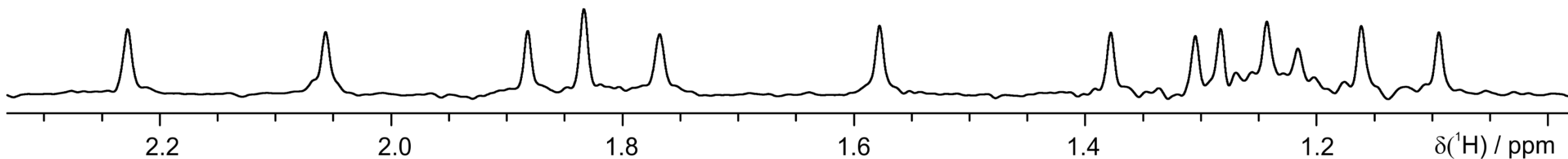
- Exact chemical shift information is required
- A pure shift experiment provides this



Conventional ^1H

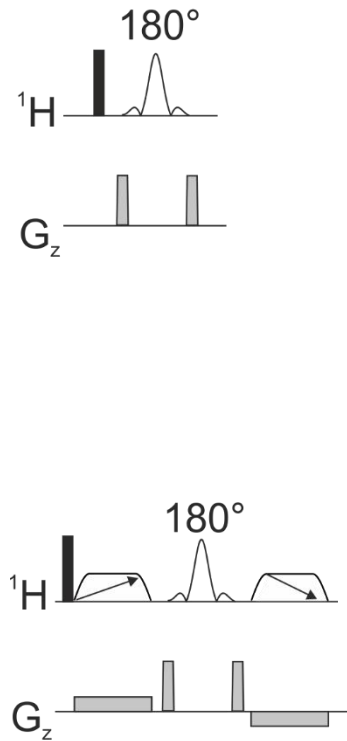


Pure shift ^1H

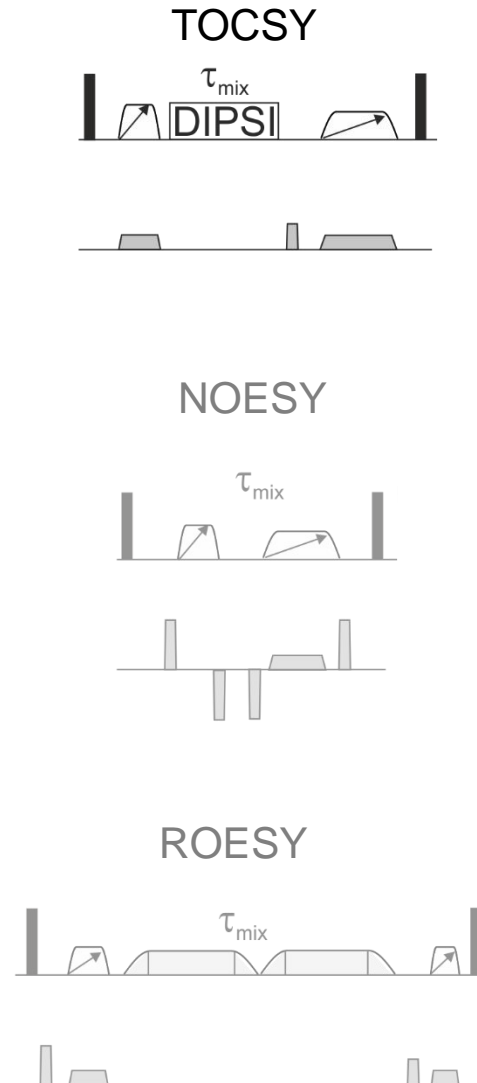


GEMSTONE experiments

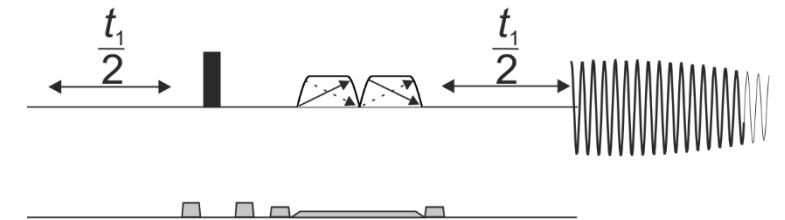
Signal selection



Mixing period

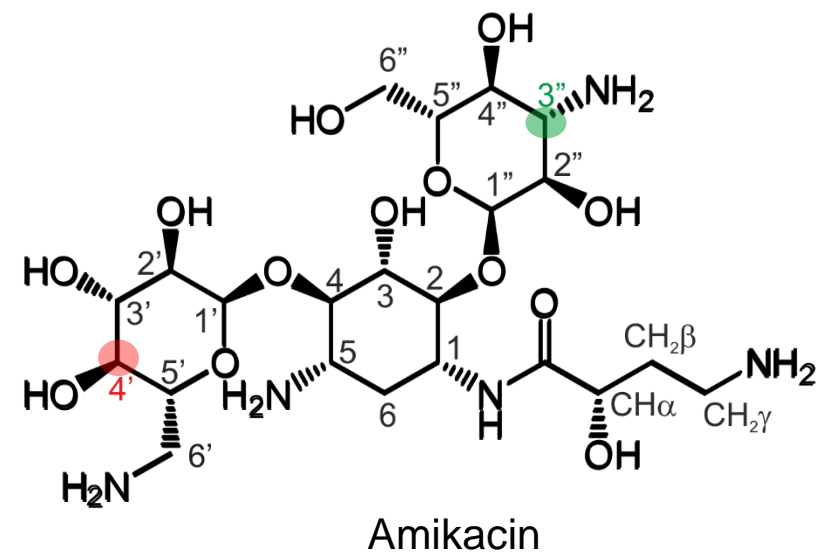
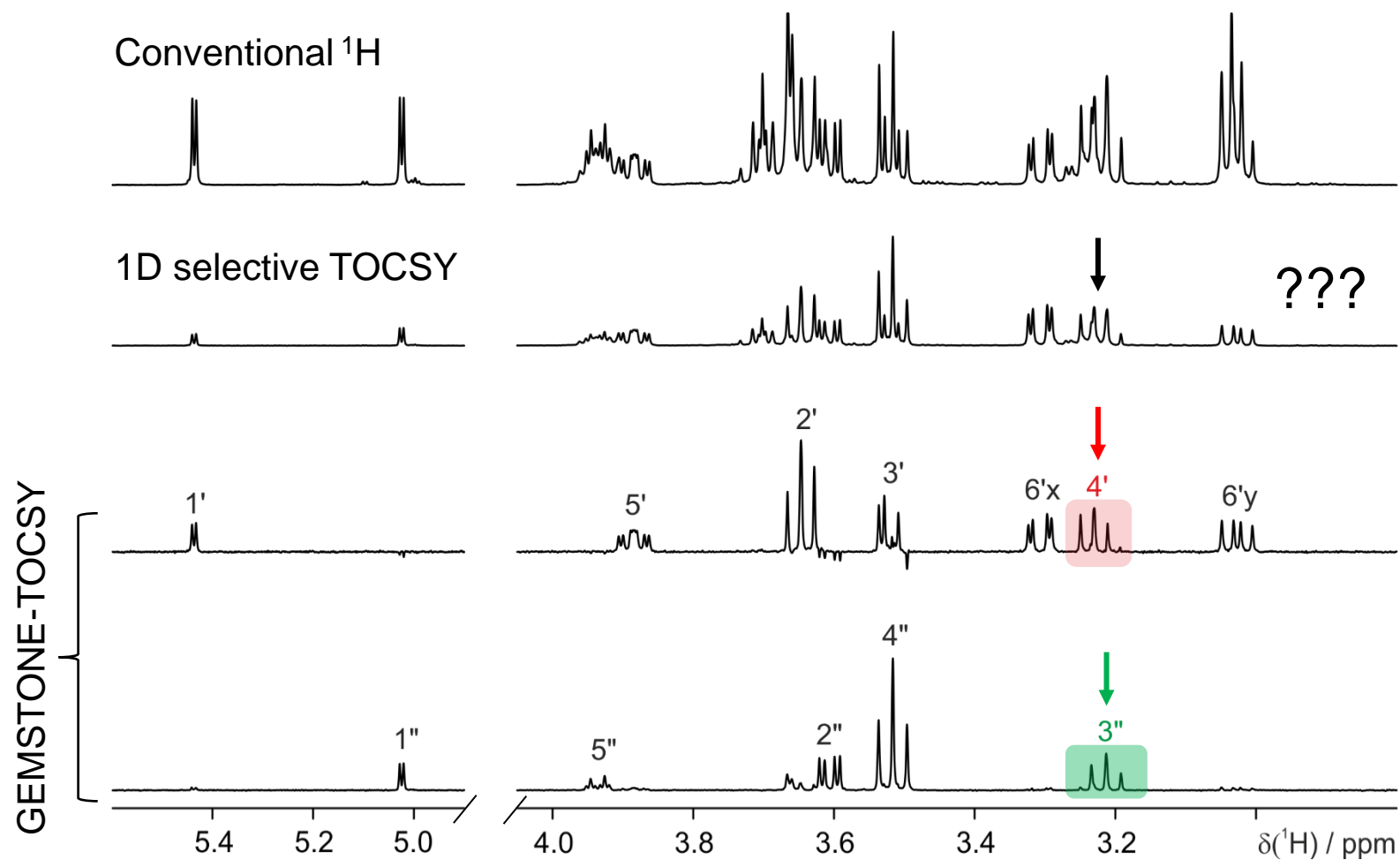


Pure shift



GEMSTONE-TOCSY

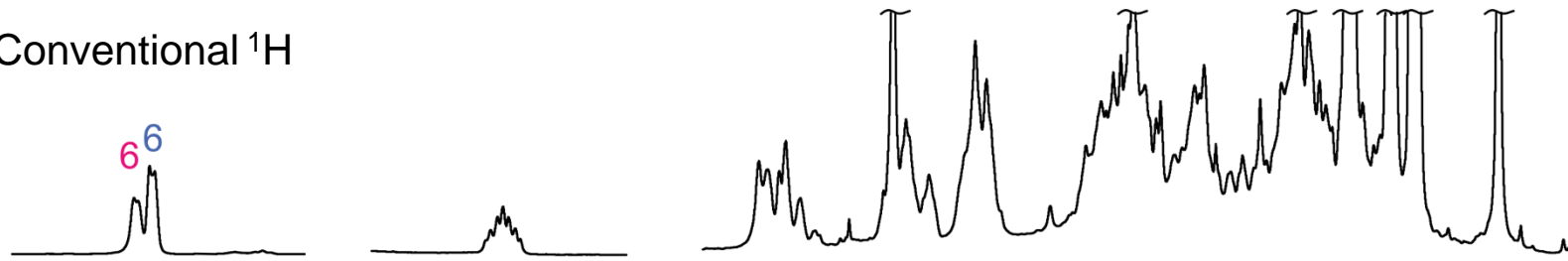
TOCSY experiments provide information about spin systems, aiding structure elucidation



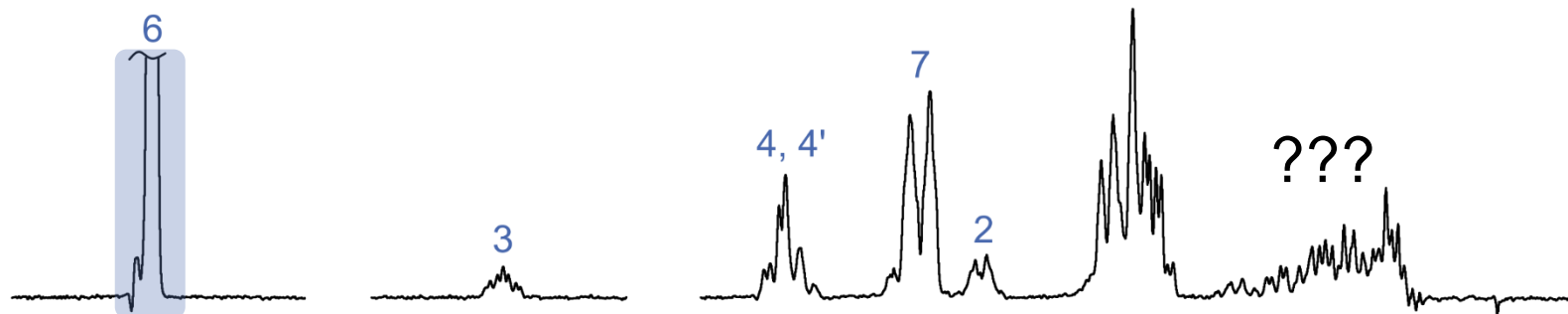
Pure shift GEMSTONE-TOCSY

TOCSY correlations are collapsed into singlets, increasing spectral resolution

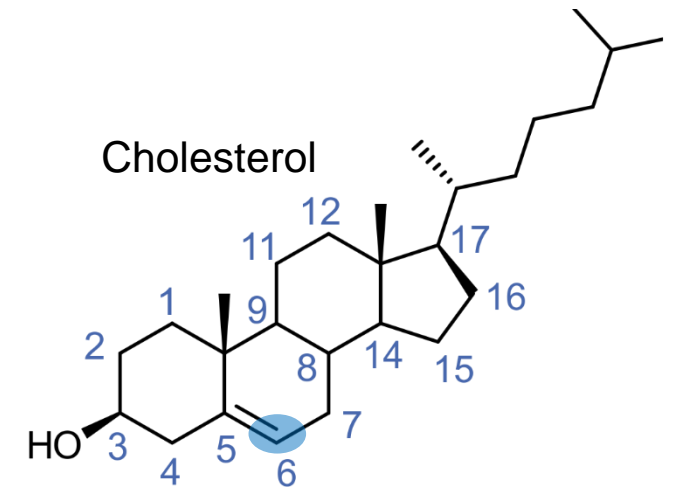
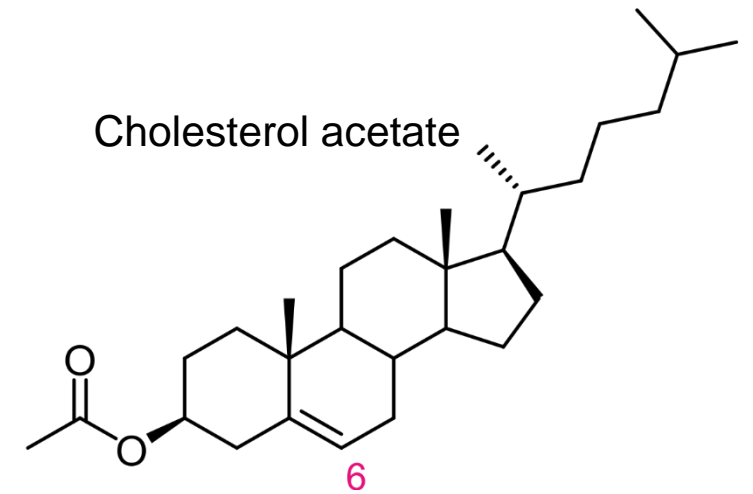
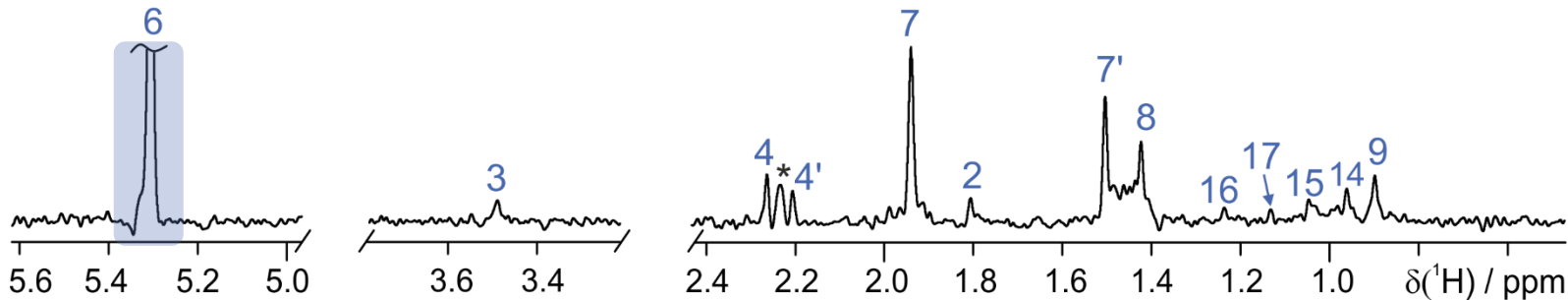
Conventional ^1H



GEMSTONE-TOCSY

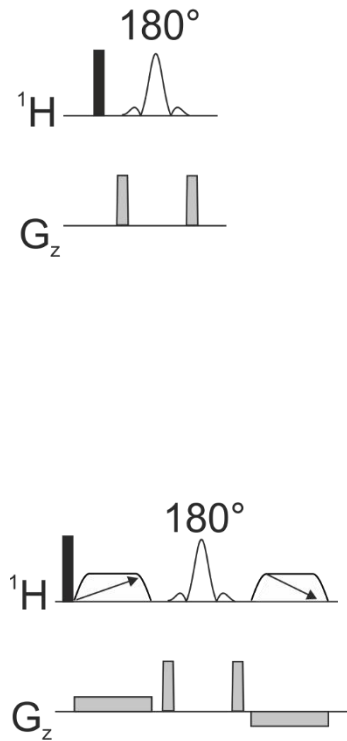


Pure shift GEMSTONE-TOCSY

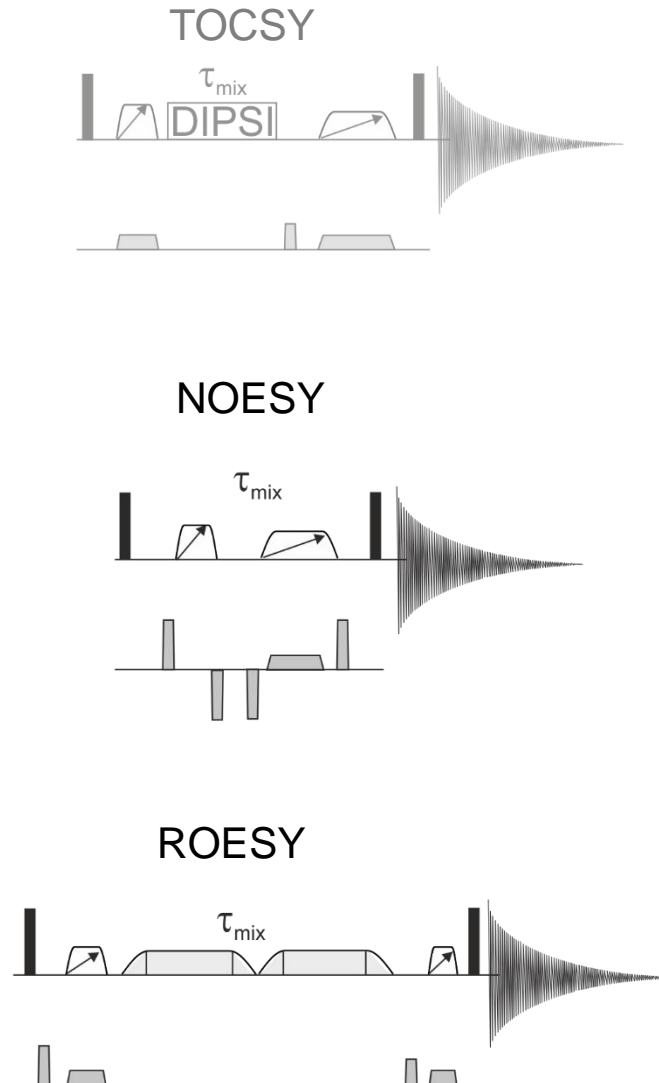


GEMSTONE experiments

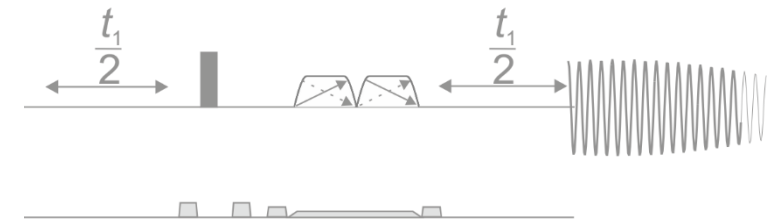
Signal selection



Mixing period

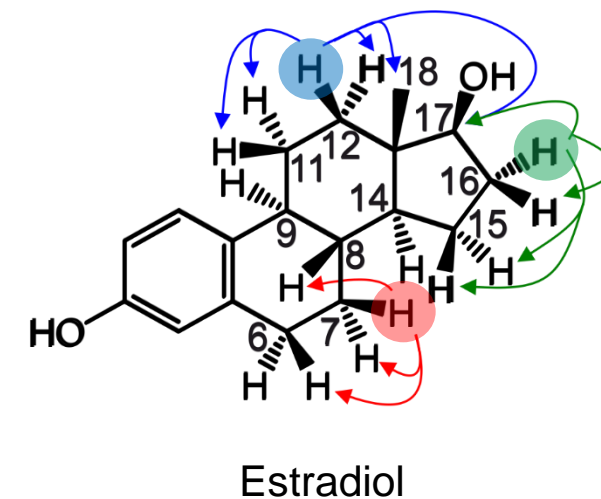
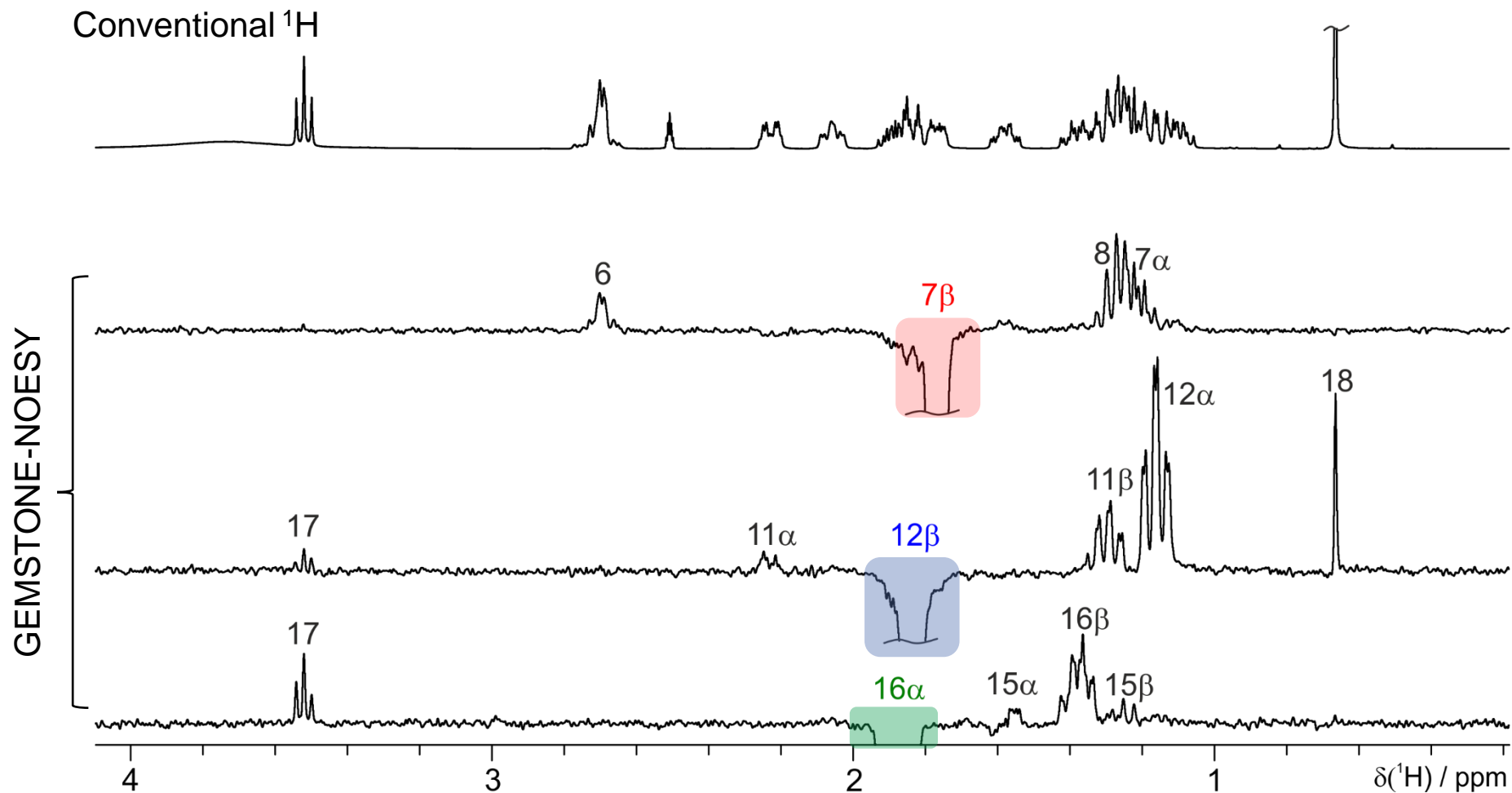


Pure shift



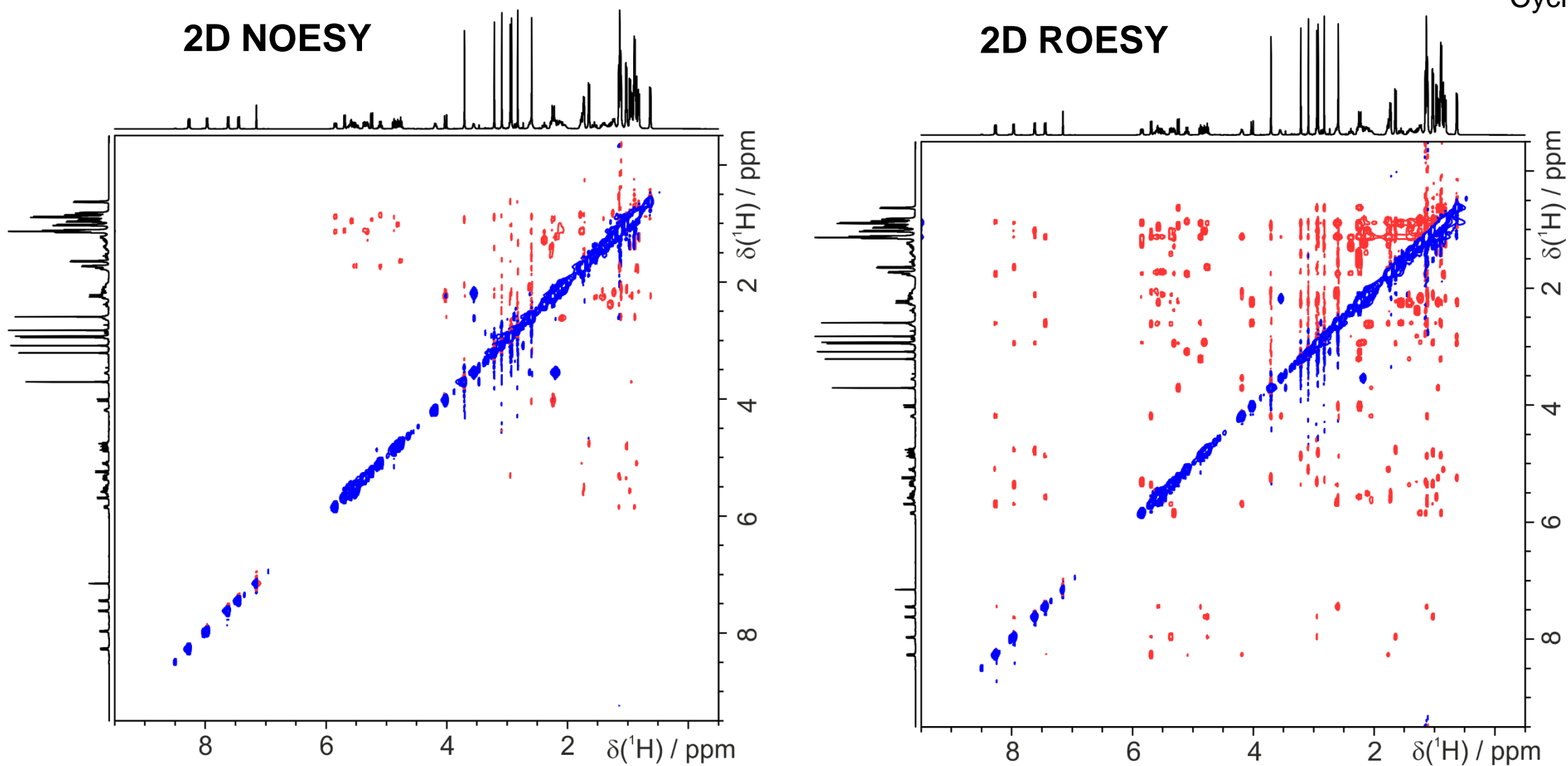
GEMSTONE-NOESY

NOESY experiments provide information about through-space interactions, aiding conformational analysis



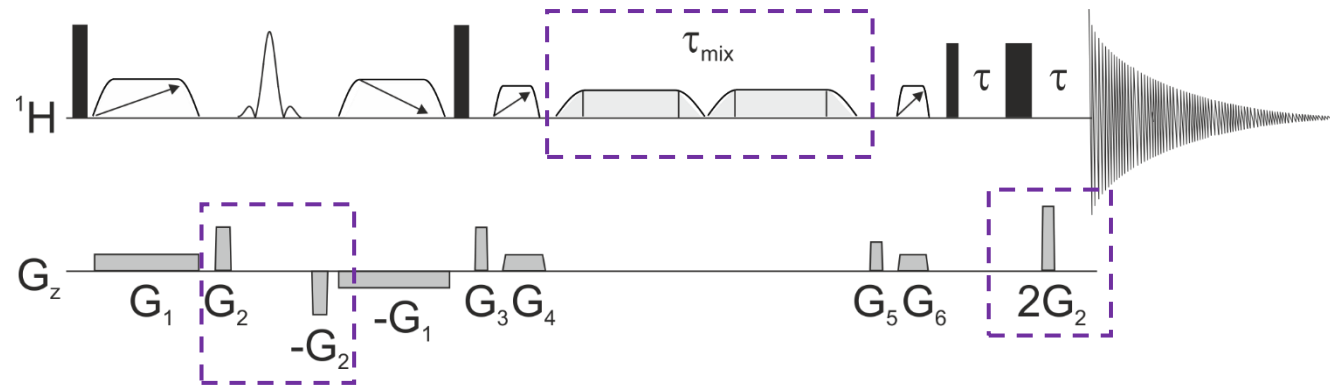
2D NOESY vs ROESY

Cyclosporin

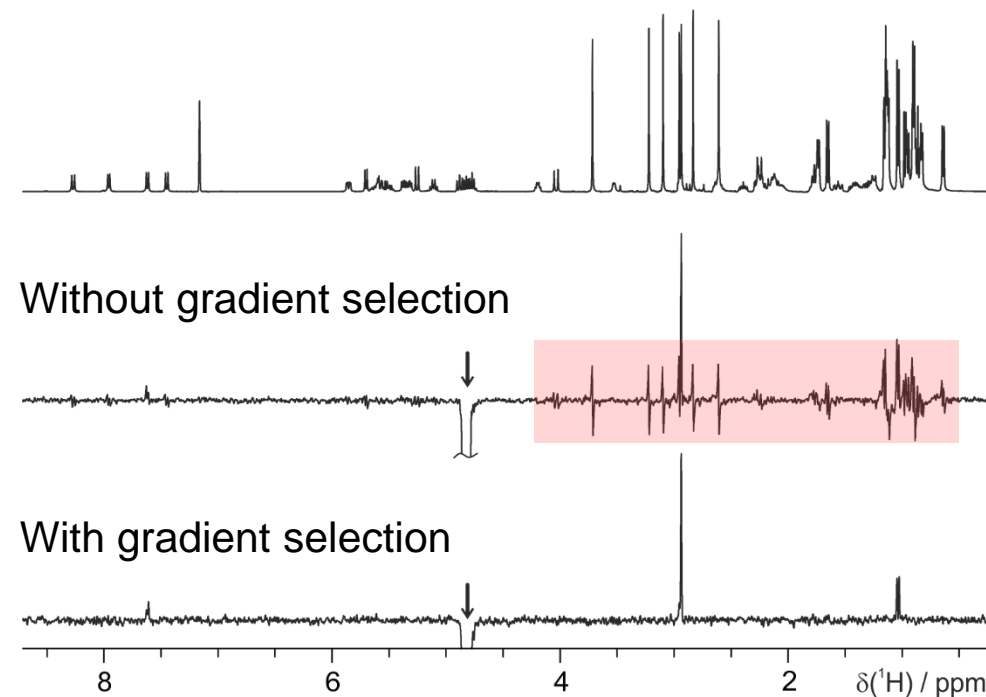


MW = 1202 g mol⁻¹, 400 MHz spectrometer, C₆D₆, 295 K

GEMSTONE-ROESY



- Ultra-selective 1D ROESY method
- The mixing period is based on the EASY-ROESY sequence
- Pulsed field gradients are used for coherence selection
- Spectra are free of subtraction artefacts

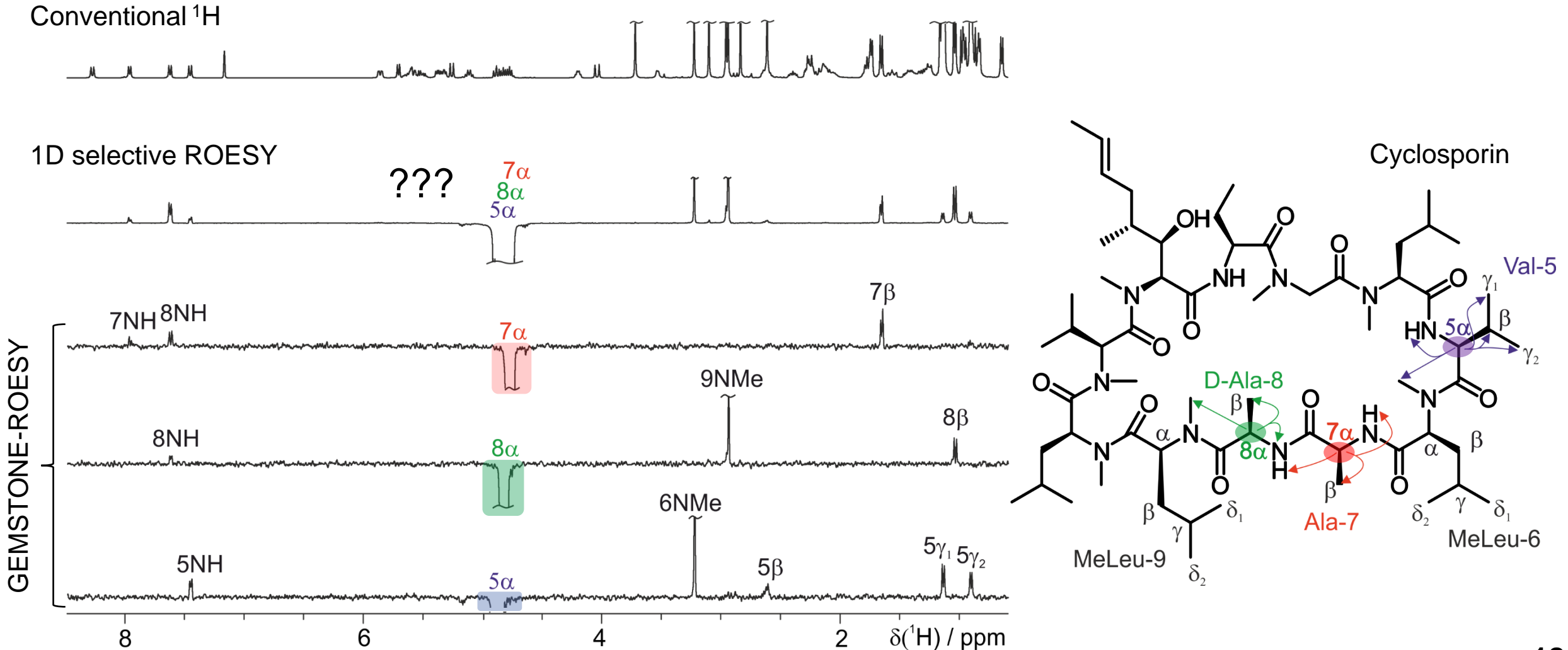


GEMSTONE-ROESY: Unpublished

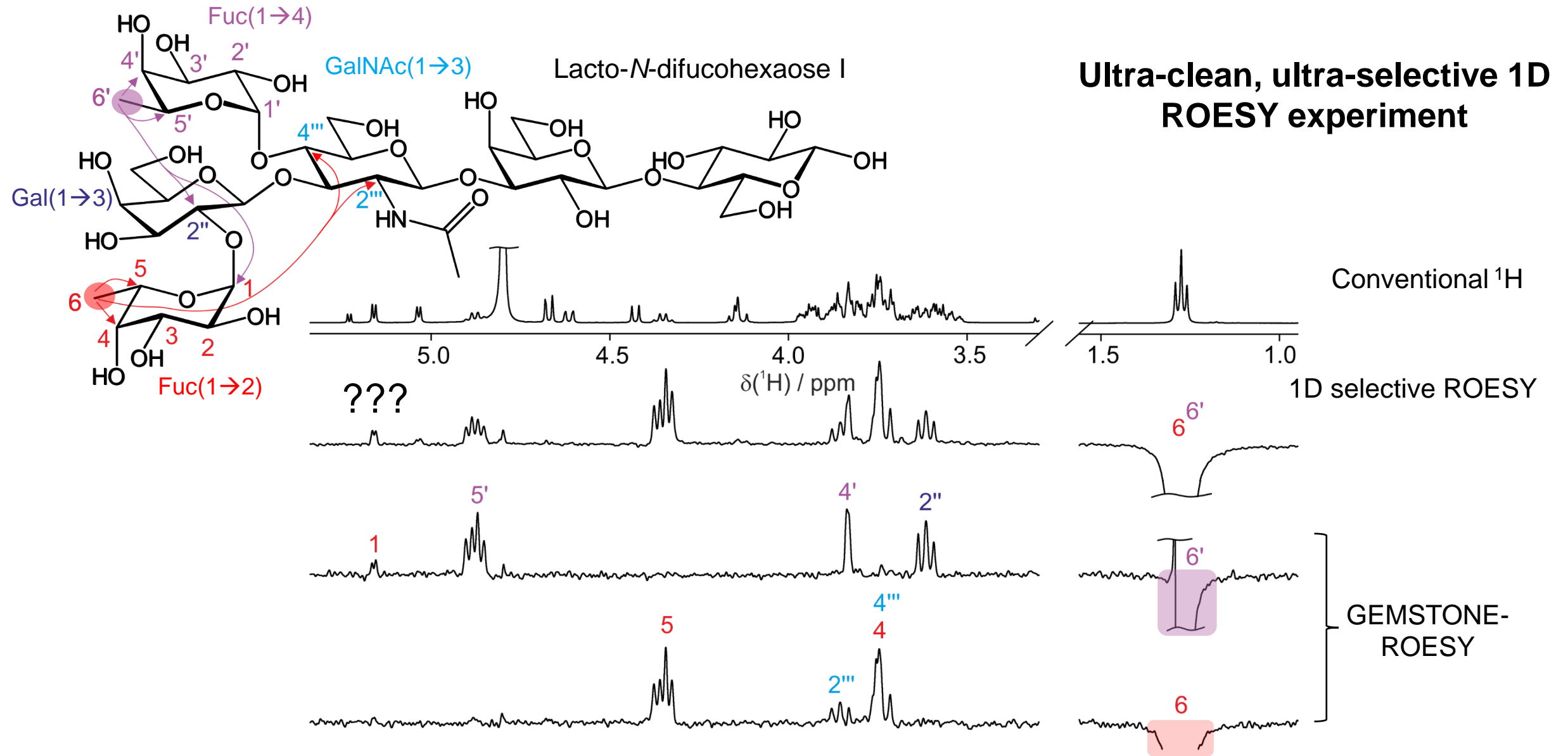
EASY-ROESY: *Eur. J. Chem.*, 2009, **15**, 585–588

GEMSTONE-ROESY

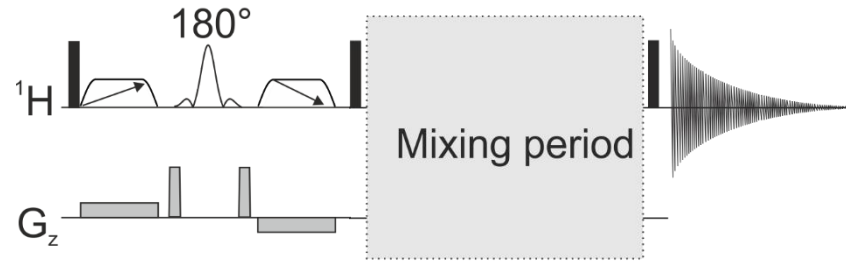
ROESY experiments provide information about through-space interactions for any size of molecule



GEMSTONE-ROESY

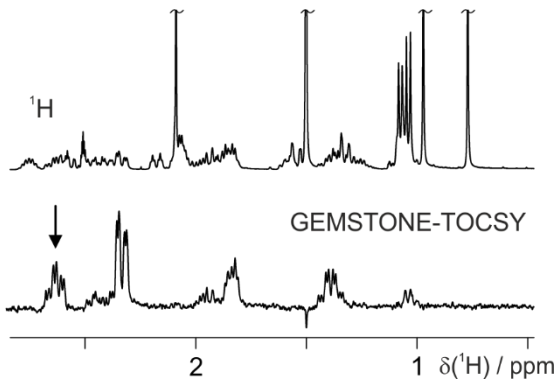


Summary



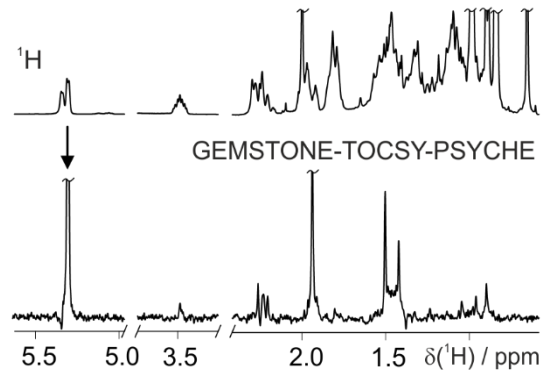
GEMSTONE

TOCSY



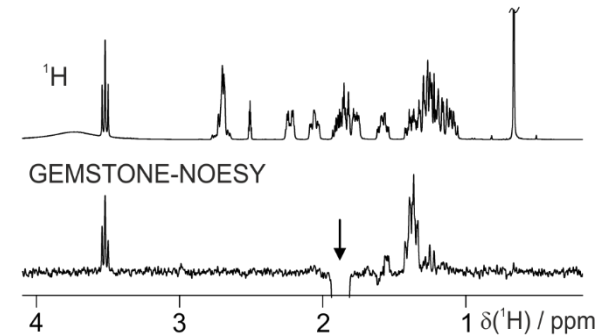
Chem. Commun., 2021, **57**,
2368–2371

TOCSY-PSYCHE



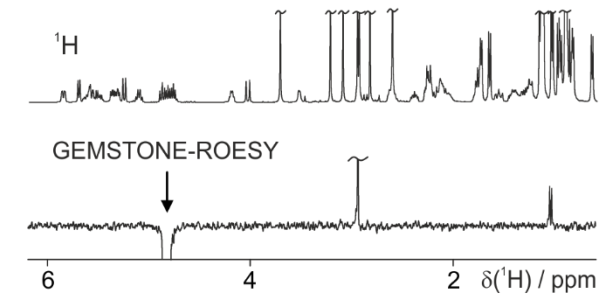
In preparation

NOESY



Angew. Chem. Int. Ed., 2021, **60**,
666–669

ROESY



In preparation

+ more ongoing projects!

Acknowledgements

University of Manchester

Dr. Laura Castañar Acedo

Dr. Ralph Adams

Prof. Gareth Morris

Prof. Mathias Nilsson

Marshall Smith



Johnson Matthey

Dr. Jonathan Bradley

Dr. Myron Johnson

Dr. Daniel Berry



Collaborators

Dr. Peter Kiraly (JEOL)

Dr. James Montgomery (University of Oxford)

Prof. Göran Widmalm (Stockholm University)



Manchester NMR Methodology Group at EUROMAR



Coral Mycroft

New NMR methods for structural analysis for fluorinated systems

Presented: 12th July, 11:35



Daniel Taylor

PO171

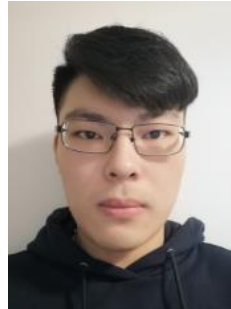
SABRE-enhanced real-time pure shift NMR spectroscopy



Howard Foster

PO316

Quantitative band-selective pure shift NMR



Runchao Li

PO330

Relaxational signal attenuation during selective refocusing pulses




Marshall Smith

PO344

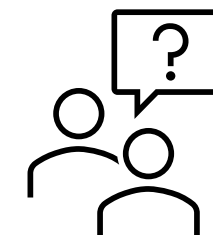
SCALPEL NMR: performing surgery on spectra of complex mixtures

Thank you for listening!

Any questions?

 @mancNMR
@emmagates441

emma.gates@postgrad.manchester.ac.uk

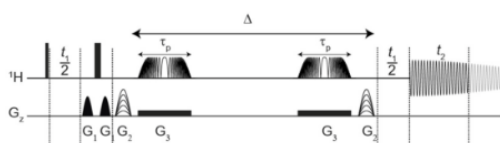


Published pulse sequences are available at: <https://nmr.chemistry.manchester.ac.uk>

Pulse Sequences

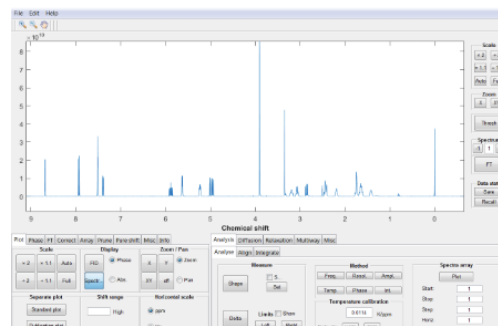
We are currently preparing many of our pulse sequences, parameter sets, example datasets and processing macros for the website. Some are available [here](#) but if you would like to use any of the other the sequences, as described in the [publications](#) section, please email us. The majority of sequences are available for Varian systems and we are gradually writing the Bruker variants.

The pulse sequences and any macros required for data conversion can be accessed from [this part](#) of the website.



Software

Software produced in-house, including The GNAT (General NMR Analysis Toolbox), the legacy DOSY Toolbox, and diffusion estimation.



Workshops and presentations

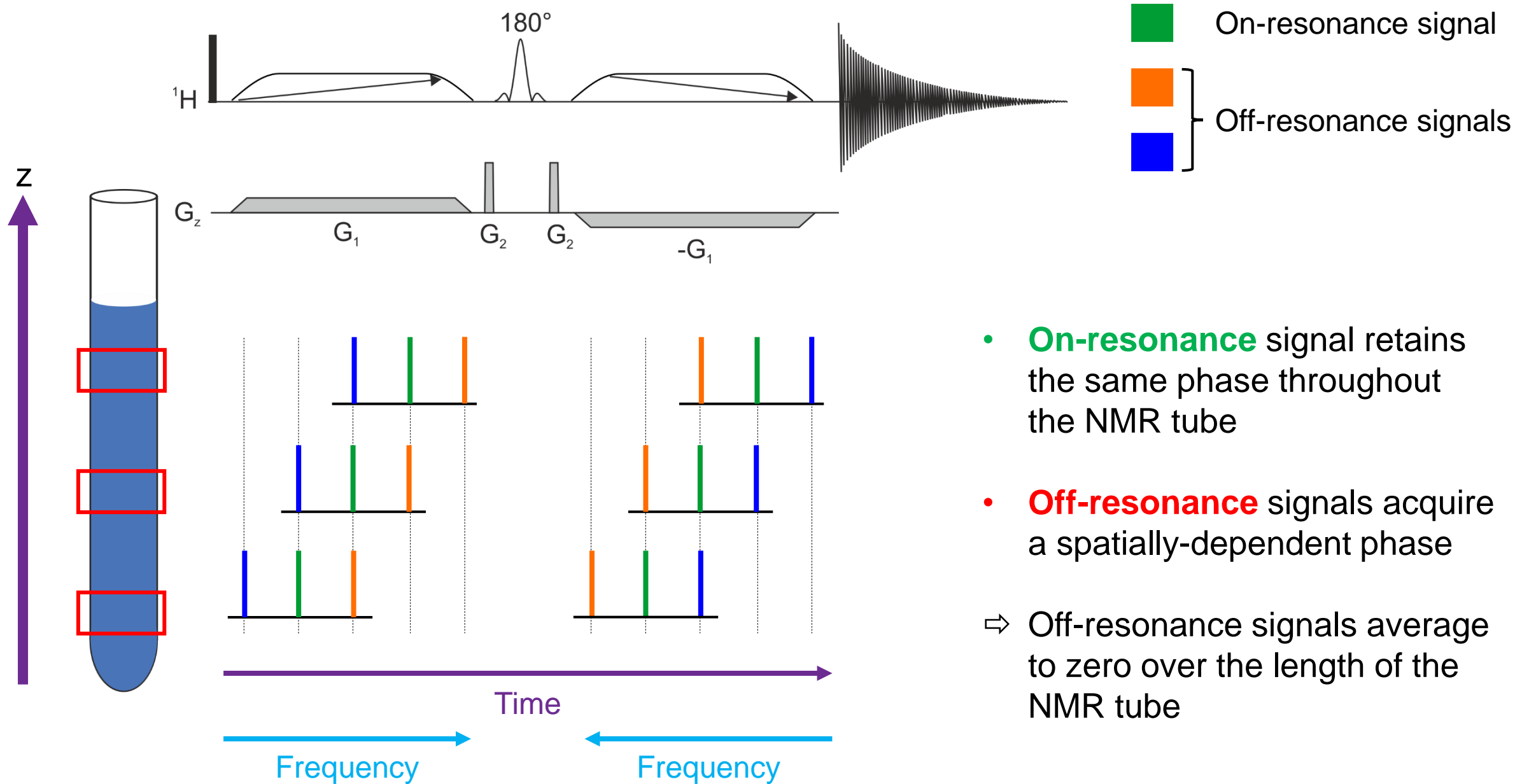
The slides from some of the workshops and presentations given by group members are available from [this part](#) of the website. There is a pure shift NMR package available for download as part of our 2017 workshop on pure shift NMR.



Posters



GEMSTONE mechanism



GEMSTONE excitation profile

The excitation profile of GEMSTONE is shown as a function of the total duration of the swept-frequency pulses

