Optimising NMR Spectroscopy through Method and Software Development

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Chapter 4

NOAH

chpt:noah

This final—and long—chapter describes my work on *NOAH* (NMR by Ordered Acquisition using ^{1}H detection) *supersequences*, pulse sequences which record multiple 2D datasets ('*modules*') in the time required for one. This is an attractive NMR technique for several reasons: the time savings are clearly a key factor, but the flexibility of being able to combine almost any set of modules also makes NOAH supersequences applicable to a variety of contexts.

I begin by introducing the concepts underlying NOAH supersequences, as well as a general discussion of the time savings (and sensitivity per unit time) benefits thus realised. I then describe the GENESIS (GENEration of Supersequences In Silico) website, which allows users to generate Bruker pulse programmes for almost every imaginable NOAH supersequence. After this, my work on various aspects of the actual sequences themselves is described, with a special focus on newly developed and/or improved modules. Finally, the design of 'parallel' supersequences which use interleaved and/or time-shared modules is discussed.

This work was done in close collaboration with Ēriks Kupče (Bruker UK). However, all results and analysis shown in this chapter are mine, unless explicitly stated. The work in this chapter forms the subject of several publications:

- Yong, J. R. J.; Hansen, A. L.; Kupče, Ē.; Claridge, T. D. W. Increasing sensitivity and versatility in NMR supersequences with new HSQC-based modules. *J. Magn. Reson.* **2021**, *329*, 107027, DOI: 10.1016/j.jmr.2021.107027
- Kupče, Ē.; Yong, J. R. J.; Widmalm, G.; Claridge, T. D. W. Parallel NMR Supersequences: Ten Spectra in a Single Measurement. *JACS Au* **2021**, *1*, 1892–1897, DOI: 10.1021/jacsau.1c00423
- Yong, J. R. J.; Kupče, Ē.; Claridge, T. D. W. Modular Pulse Program Generation for NMR Supersequences. *Anal. Chem.* **2022**, *94*, 2271–2278, DOI: 10.1021/acs.analchem.1c04

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- Yong, J. R. J.; Kupče, Ē.; Claridge, T. D. W. Uniting Low- and High-Sensitivity Experiments through Generalised NMR Supersequences. **2022**, manuscript in preparation

The material in the introductory sections also closely follow two reviews which I have contributed to:

- Kupče, Ē.; Frydman, L.; Webb, A. G.; Yong, J. R. J.; Claridge, T. D. W. Parallel nuclear magnetic resonance spectroscopy. *Nat. Rev. Methods Primers* **2021**, *1*, No. 27, DOI: 10.1038/s43586-021-00024-3
- Yong, J. R. J.; Kupče, Ē.; Claridge, T. D. W. In *Fast 2D solution-state NMR: concepts and applications*, Giraudeau, P., Dumez, J.-N., Eds., forthcoming, 2022

4.1 Introduction

sec:noah__introduction

The characterisation of small molecules and biomolecules by NMR spectroscopy relies on a suite of standard 2D NMR experiments, which seek to detect heteronuclear scalar couplings (e.g. HSQC and HMBC), homonuclear scalar couplings (e.g. COSY and TOCSY), or through-space interactions (e.g. NOESY and ROESY). Although 2D experiments provide far superior resolution and information content compared to 1D spectra, they also require substantially longer experiment durations, as the indirect dimension must be constructed through the acquisition of many t_1 increments. This problem is further exacerbated by the fact that structural elucidation or verification often necessitates the acquisition of several different 2D experiments.

The acceleration of 2D NMR has thus proven to be a popular area of research, encompassing techniques such as non-uniform sampling (NUS),[7–10] fast pulsing (i.e. shortening of recovery delays),[11–14] ultrafast NMR,[5,15–19] Hadamard encoding,[20,21] and spectral aliasing.[22–24] All of these methods seek to directly speed up the acquisition of *individual* 2D spectra. In contrast, *multiple-FID techniques* such as time-shared NMR,[25,26] multiple-receiver NMR,[27–29] and—of course—NOAH supersequences,[5,30,31] instead aim to collecting multiple 2D spectra in (roughly) the time needed to acquire one 'conventional' 2D spectrum. This essentially amounts to an increase in *efficiency*, rather than pure speed.

4.2 Sensitivity analysis of NOAH supersequences

sec:noah__snr

General discussion of time savings and sensitivity analysis.

Should be very similar to RSC chapter

4.3 GENESIS: automated pulse programme creation

sec:noah__genesis

I think it makes sense to start with GENESIS;[3] that way everything else can be placed in context.

It's true that this was a full paper, but it included a lot of stuff which wasn't about the website itself—these will go into later sections.

4.4 Discussion of individual modules

sec:noah__modules

4.4.1 Sensitivity-enhanced HSQC

subsec:noah__sehsqc

^{13}C seHSQC

^{15}N seHSQC

4.4.2 HSQC-TOCSY

subsec:noah__hsqctocsy

HSQC + DIPSI + HSQC combos

Extension to HSQC-TOCSY

Cite ASAP work (Luy)

4.4.3 HSQC-COSY

subsec:noah__hsqccosy

Comparison of several versions of HSQC-COSY (JACS Au SI)

4.4.4 2DJ and PSYCHE

subsec:noah__2djpsyche

cnst37 scaling

SAPPHIRE

4.4.5 DQF-COSY

subsec:noah__dqfcosy

Once upon a time, I did some comparisons of States vs EA DQF-COSY. I think this section could probably be left out, though. The differences were *extremely* minor.

4.4.6 HMQC

subsec:noah__hmqc

Suppression of wing artefacts (GENESIS paper)

4.4.7 HMBC

subsec:noah__hmbc

Suppression of $^{1}J_{\mathrm{CH}}$ artefacts (GENESIS paper)

Investigation of gradient schemes (no difference was really observed, but that's fine)

Also ^{15}N HMBC

4.4.8 ADEQUATE

subsec:noah__adequate

Recent stuff.

4.5 Solvent suppression in NOAH

sec:noah__solvsupp

GENESIS paper.

4.6 NOAH with short recovery delays (???)

sec:noah__shortd1

I did like one bit of work on this a while ago. The idea is basically that the spectra are fine but SNR unsurprisingly suffers (in fact SNR/t also decreases).

It may be mildly interesting to compare this against the NORD experiments if I can get their pulse programmes to work... I don't expect the NORD sensitivity to be amazing but it should in fact be better than just doing NOAH with short d1.

It may equally be viable to just leave this entire section out of the thesis as I don't think it adds much...

4.7 Parallel and generalised NOAH supersequences

noah__parallel

Blah.

4.8 References

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