Optimising NMR Spectroscopy through Method and Software Development

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Chapter 3

POISE

chpt:poise

This chapter describes the development of software for on-the-fly optimisation of NMR experimental parameters, titled POISE (*Parameter Optimisation by Iterative Spectral Evaluation*). The primary benefit of this is that parameters may be adjusted for individual spectrometers and samples, which may vary greatly in their chemical properties. POISE is primarily written in Python 3. In this chapter, I first provide some details about the implementation of POISE. The bulk of the text which follows is devoted to a number of applications in liquid-state NMR spectroscopy. At the end, the extension of the concept of on-the-fly optimisation to ESR spectroscopy is also briefly discussed: I contributed code for this, but the experimental ESR work and data analysis were carried out by Jean-Baptiste Verstraete (University of Oxford).

The work in this chapter forms the subject of two publications:

- Yong, J. R. J.; Foroozandeh, M. On-the-Fly, Sample-Tailored Optimization of NMR Experiments. *Anal. Chem.* **2021**, *93*, 10735–10739, DOI: 10.1021/acs.analchem.1c01767
- (JBV et al., manuscript submitted)

3.1 Introduction

ec:poise__introduction

In the previous chapter, I covered various approaches to improving pure shift NMR through the use of optimisation. Although the optimisation code written there was highly specialised and only designed to work on pure shift applications, it was envisioned that this optimisation approach could be applied to essentially *any* NMR experiment where parameter optimisation was required. In principle, this description is appropriate for *every* experiment: even the simplest pulse–acquire experiment can be optimised through the use of Ernst angle excitation. More complex examples, such as 2D experiments, typically have parameters which should be chosen to optimally match coupling constants (INEPT delay) or relaxation rates (NOE mixing time).

In practice, the need for accurate parameters is often 'solved' through the use of compromise values, which typically fall in the middle of an expected range for typical molecules. For example, these values may be stored as part of a parameter set designed to be reused. Alternatively, parameter values may be optimised 'by hand'. However, compared to this, the use of experimental optimisation has several benefits. It is:

1. *sample-specific*, and as long as the default values are within the optimisation bounds, the optimisation will yield performance which is no worse than the defaults;
2. more *robust* towards unusual molecular structures, which have physical or chemical properties which fall outside of an expected range;
3. *instrument-specific*, so can compensate for spectrometer imperfections.
4. *automated*, so does not require an expert to adjust parameter values manually, or even any user intervention for that matter;
5. *objective*, in that the quality of a spectrum can (in principle) be mathematically measured through a cost function; and
6. *rapid*, in that it uses an algorithm which is designed to achieve rapid decreases in the objective function: many 'manual' optimisations involve either trial-and-error or an exhaustive grid search (i.e. increasing a parameter value one step at a time), neither of which are efficient.

Despite these advantages, experimental optimisation of NMR parameters has seen only limited use. In fact, although there are several examples of such optimisations in laser,[2] nuclear quadrupole resonance,[3–5] and ESR[6] spectroscopies, the only direct parallel in NMR which I have found is that of the eDUMBO pulses for heteronuclear[7,8] and homonuclear dipolar[9] decoupling in solid-state MAS experiments. In this work, the Emsley group used 'direct spectral optimisation' (equivalent to what I call 'experimental optimisation') to determine the best coefficients for a

Fourier series pulse. The performance of these pulses was measured by a cost function which (primarily) took into account the intensity of the detected peaks: a larger intensity corresponds to better decoupling performance. Interestingly, the aim of using an experimental optimisation here was not to obtain sample-specific pulses (point (1)), but rather to account for the 'spectrometer response', i.e. instrumental non-idealities (point (3)). It was assumed that the compound used for the optimisation was a suitably representative choice, so that the optimisation result could simply be applied to other samples with no change.

The likely reason for the low popularity of experimental optimisations is *time*. In most cases, it is probably easier to run NMR optimisations in a theoretical manner, which can be much faster compared to the acquisition of a spectrum (depending on what simulations are involved), and also circumvents the effect of noise. Examples of such optimisations include the design of shaped pulses, either through optimal control theory[10–15] or by simple parameterisation:[16–21] these were briefly discussed in § 2.4.3. (In fact, even the aforementioned eDUMBO pulses were not *originally* designed as an experimental optimisation: they are actually an enhancement of the DUMBO decoupling schemes, which were optimised using numerical simulations.[22]) It is also possible to design entire pulse sequences using *in silico* optimisations:[23–27] this is essentially what I did with the dPSYCHE experiment (§ 2.6). However, doing this in an experimental fashion would almost certainly be prohibitively slow.

In this chapter, I aim to provide a convincing argument that experimental optimisation is not necessarily slow. In particular, I will show that it is often possible to devise optimisation routines which yield improved results in a matter of minutes. All the optimisations here are performed using a software package written by me, called POISE (Parameter Optimisation by Iterative Spectral Evaluation). POISE is open-source (`https://github.com/foroozandehgroup/nmrpoise`) and can be installed in a single step through `pip install nmrpoise`. Furthermore, it comes with extensive user documentation, both in the form of a text guide (`https://foroozandehgroup.github.io/nmrpoise`) as well as video (`https://www.youtube.com/watch?v=QTCeSCRZs4I`).

In contrast to previous work, which typically feature optimisations targeted at one specific application, I have endeavoured to make POISE as customisable and as broad as possible. This generality is what allows a single software package, POISE, to perform all the optimisations described in this chapter; it also means that other users can devise specific cost functions and optimisation procedures for their own use. Thus, *POISE is more than just the applications shown later in this chapter*: it is really a platform which makes it possible to carry out arbitrary optimisations on an NMR spectrometer.

3.2 Technical overview

sec:poise__technical

3.2.1 Fundamentals

ec:poise__fundamentals

3.2.2 Optimisation algorithms

bsec:poise__algorithms

3.2.3 Implementation details

:poise__implementation

3.2.4 What POISE is not

subsec:poise__notpoise

To round off this section on general principles of POISE, I want to make a note about several limitations of the approach chosen. Firstly, while generality is a strength in that POISE can be applied to a diverse range of NMR experiments, it can also be a weakness. POISE *always* follows the framework in FIG: in particular, it simply seeks to find the optimum $\mathbf{x}^*$, defined by

$$\arg\min_{\mathbf{x}} f(\mathbf{x}). \tag{3.1}$$ {eq:poise_argmin}

This rigidity in the underlying logic means that it is very conceivable that in specific instances, specialised optimisation routines which use customised strategies for data acquisition and analysis *can* outperform POISE in terms of speed and/or accuracy.

On top of this, in each function evaluation, the only information retained is the parameters $\mathbf{x}$ and the value of the cost function $f(\mathbf{x})$. The spectral data itself is not stored nor accumulated: thus, it is not possible to perform (for example) an 'optimisation' which collects scans until a certain SNR is reached, or one which collects t_1 increments of a 2D spectrum and performs non-uniform sampling (NUS) processing until the signal to artefact ratio is sufficiently high. In particular, I want to distinguish POISE from other types of 'optimisations' reported in the literature, which typically *accumulate* data points until a given confidence level is reached (e.g. through a model-fitting procedure). Such procedures have been performed before in the contexts of (for example) relaxation measurements[28,29] and undersampling in multidimensional NMR.[30–32]

Next, although POISE can in theory be used for optimisation of processing parameters (for example, by changing the 'acquisition' AU programme to perform only processing tasks), this usage is not considered here. Such optimisations can be more efficiently carried out on a personal computer, without requiring access to a spectrometer.

Having put forth a number of points in *support* of optimisation in the previous sections, it should be noted that there is always an inherent tradeoff against the time required for the optimisation itself. For example, it makes little sense to spend several minutes optimising the sensitivity of a pulse–acquire experiment: the time could simply be used to improve the SNR by collecting more scans. Thus, for practical use, it is imperative to make sure that the optimisation is either

fast, or solves a problem which cannot simply be tackled through signal averaging in the same amount of time. It is my hope that this is (broadly) true of the examples shown.

Finally, there is also the critical—though undeniably subjective—question of whether the optimisation is *worth it*: even if better results can be obtained in relatively short times, does this provide a substantial benefit over a 'compromise' value in a default parameter set?* I do not profess to have a definitive answer to this, and I leave the reader to form their own conclusions in the specific contexts where they may consider using POISE.

3.3 Applications

ec:poise__applications

3.3.1 Pulse width calibration

subsec:poise__pulsecal

`popt` vs `pulsecal`

3.3.2 Ernst angle optimisation

subsec:poise__ernst

Maths

3.3.3 NOE mixing time

subsec:poise__noe

Stuff

3.3.4 ASAP-HSQC excitation delay

subsec:poise__asaphsqc

INEPT

3.3.5 HMBC low-pass J-filter

subsec:poise__hmbc

Artefacts.

3.3.6 Inversion–recovery

subsec:poise__invrec

Stuff

*Of course, even though it is nowadays fashionable for authors to imply that their publications possess *great impact*, a similar argument can be applied to *many* scientific discoveries. To use an example from the next chapter, is it really necessary to acquire NOAH spectra when one can just acquire the standalone 2D experiments? I have seen arguments on both sides—some people simply do not need the speedups provided and do not want to spend the time to set up or troubleshoot new experiments.

3.3.7 Ultrafast NMR

subsec:poise__epsi

EPSI gradient imbalance

3.3.8 PSYCHE pure shift NMR

subsec:poise__psyche

J-refocusing

3.3.9 Solvent suppression

subsec:poise__solvsupp

Mouse

3.3.10 Diffusion NMR

ubsec:poise__diffusion

Automated DOSY

Probably a good idea to revisit (and understand) Iain's comments.

3.4 POISE for ESR

sec:poise__esrpoise

Need JB to write this section

3.5 References

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