TReNDS software for reaction monitoring by NMR

Acquisition & processing of time-resolved 2D spectra

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Nuclear magnetic resonance (NMR) spectroscopy is a main workhorse in the analysis of molecular structures. It can also visualize their dynamic changes, thus serving as a great reaction-monitoring tool. Here, we present a software package allowing to set up and process data from several interleaved time-resolved two-dimensional (2D) NMR spectra, extending the amount of information provided by the conventional approach based on 1D spectra.

Multidimensional NMR

Modern NMR spectroscopy is based on the measurement of time-domain free induction decay (FID) signals of nuclei having non-zero spin (most commonly 1H and 13C). Signals are converted into spectra by Fourier transform. Importantly, it is possible to generate interferograms - signals being a function of several time variables. It makes it possible to describe the topology and geometry of studied molecules, i.e., connections and distances between atoms. Unfortunately, sampling of even one additional (“indirect”) time dimension is costly: acquisition of a single 2D spectrum takes at least several minutes and one needs several different spectra providing complementary information. Thus, it is difficult to use 2D NMR as a “snapshot” technique in reaction monitoring. Many techniques have been proposed to alleviate this problem, usually by reconstructing part of the data using mathematical algorithms instead of measuring it experimentally.[1] However, till now it was rather cumbersome to employ them in the *online* mode, i.e., to process the data during the experiment.

Interleaved NUS acquisition

Our software package is called TReNDS: Time-Resolved N-Dimensional Spectroscopy. It is based on a special type of non-uniform sampling (NUS) - a time-resolved NUS [2].

NUS has often been used in multidimensional NMR experiments to accelerate their acquisition. It means skipping random rows of 2D or higher-dimensional NMR data with their subsequent

reconstruction (interpolation of data). We have employed compressed sensing (CS) reconstruction, which proved successful to NMR [3]: it relies on the assumption of spectral sparsity, i.e., the presence of only few peaks in a spectrum. As shown in many studies, the assumption is usually very well fulfilled.

In standard NUS, K random rows out of the full data grid of size N are sampled. In time-resolved NUS [2], in its turn, there is a long (of length >>N) shuffled list of indices of rows to be measured. Then, during the reconstruction process, the long list of the data lines is grouped into “frames” of length K (see Figure). They can also be overlapping, which hugely enhances the temporal resolution.

Moreover, TR-NUS allows the interleaved acquisition and our software gives an opportunity to switch from one type of NMR experiment to another between lines of data. Thus, we can acquire different kinds of NMR experiments simultaneously, which is a powerful advantage, since snapshots of the process are synchronised in time.

Processing

The processing contains two main parts: 1) the reconstruction of the undersampled data, 2) the tracking of spectral peaks throught the time series of spectra.

Importantly, the reconstruction can be carried out simultaneously to the acquisition, thus allowing for an early “snooping” into the chemical processes. As full reaction durations may reach tens of hours/days, it is highly convenient to have some preliminary information without waiting for the reaction to finish. This is provided by TReNDS!

Another benefit of the method is that the reconstruction is separated from the acqusition: we can perform the reconstruction multiple times with various parameters without the need to re-acquire any data. For details on the reconstruction, see [4].

A chemist is usually interested in the dynamics of changes of definite spectral peaks. The software allows for selecting a peak in a frame and acquiring its intensity and position changes throughout the available set of frames. This is done with a peak-tracking module, which takes into account the possibility of peak appearance/disappearence from frame to frame. Additionally, one can fit the peak intensity profiles to approximate the chemical kinetics rates.

Data visualization

TReNDS software contains a visualization block with the following main features:

- displaying up to three sets of 2D spectra and one 1D spectrum;

- sliders for frame number, threshold and contour levels for 2D spectra display; zoom/unzoom tools;
- a tool to select a peak for analysis
- pop-up window for peak analysis results

Besides, TReNDS provides a user-friendly interface for data acquisition as well as reconstruction.

System requirements

The acquisition module works with Bruker TopSpin 3.2 or higher, Magritek Spinsolve Expert and Agilent/Varian VNMRJ 4.2. The processing module works on Linux, macOS and Windows 10 systems.

Linux:

- Python 2.7 (For older systems we recommend Anaconda python distribution)
- Python Installer (pip) for the package installation

macOS:

- macOS 10.12 Sierra or higher (Package was not tested on earlier versions. However it should work properly with older versions)

Windows:

- Windows 10
- Activated Windows Subsystem for Linux (WSL instructions available at: https://docs.microsoft.com/en-us/windows/wsl/install-win10)

General to all systems requirements:

- The CS reconstruction uses popular MddNMR package (available at http://mddnmr.spektrino.com) therefore package have to be installed prior to usage of TReNDS.

Conclusion

Our software package TReNDS for chemical reaction monitoring with 2D NMR is an all-in-one tool for acquisition, on-the-fly processing, display and analysis of data. It also provides incomparably better time resolution that other known methods exploiting the concept of time-resolved non-unifrom sampling. It implements interleaved acquisition of NMR experiments allowing for the extraction of complementary types of information at the same time. The software has a user-friendly graphical interface.

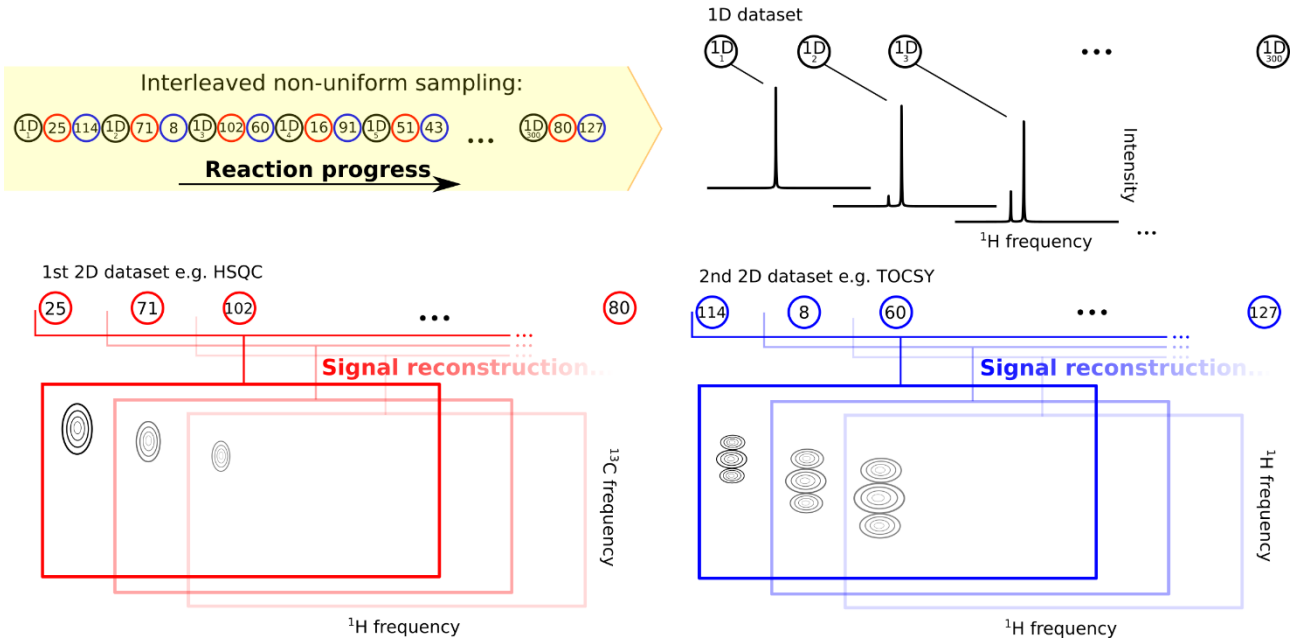

Fig 1: The idea of TR-NUS interleaved acquisition of 1D, 2D HSQC and 2D TOCSY spectra

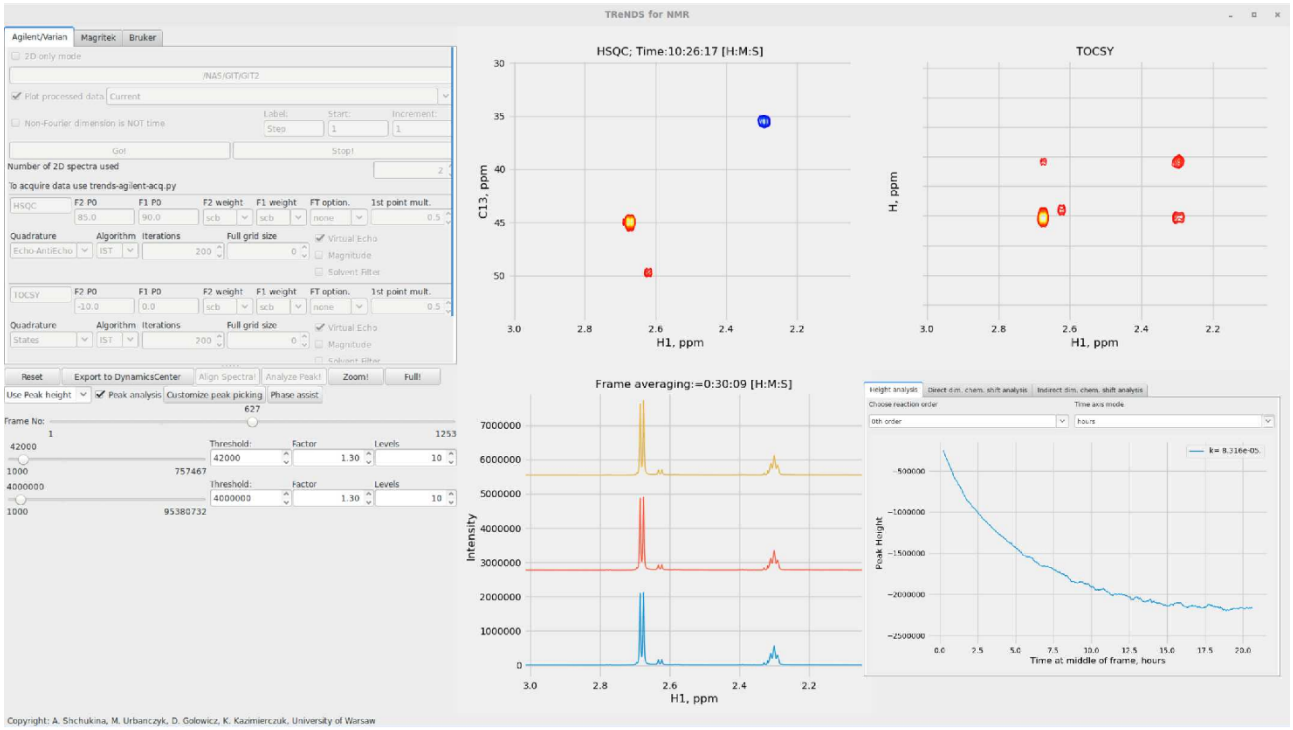

Fig. 2: The GUI of TReNDS package. Panels on the left contain TR-NUS processing parameters as well as standard NMR procedures – apodization, zero-filling etc. On the right 2D spectral snapshots obtained with interleaved HSQC and TOCSY spectra are presented as well as peak intensity plot. The aza-Michael addition of benzylamine and acrylamide was studied.

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Download the TReNDS package from http://trends.spektrino.com

[1] Gołowicz, D.; Kasprzak, P.; Orekhov, V.; Kazimierczuk, K.; Fast time-resolved NMR with non-uniform sampling, Progress in Nuclear Magnetic Resonance Spectroscopy, 2019, ISSN 0079-6565, https://doi.org/10.1016/j.pnmrs.2019.09.003.

[2] Mayzel, M.; Rosenlöw, J.; Isaksson, L.; Orekhov, V. Y. Time-Resolved Multidimensional NMR with Non-Uniform Sampling. J. Biomol. NMR 2014, 58, 129–139. https://doi.org/10.1007/s10858-013-9811-1

[3] Kazimierczuk, K.; Orekhov, V. Y. Accelerated NMR Spectroscopy by Using Compressed Sensing. Angew. Chem. Int. Ed. Engl. 2011, 50 (24), 5556–5559. http://doi.org/10.1002/anie.201100370

[4] Urbańczyk, M.; Shchukina, A.; Gołowicz, D.; Kazimierczuk, K. TReNDS—Software for Reaction Monitoring with Time-Resolved Non-Uniform Sampling. Magn. Reson. Chem. 2019, 57 (1), 4–12. https://doi.org/10.1002/mrc.4796