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TReNDS - software for reaction monitoring with time-resolved non-uniform sampling

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NMR spectroscopy, used routinely for structure elucidation, has also become a widely applied tool for process and reaction monitoring. However, the most informative of NMR methods - correlation experiments - are often useless in this kind of applications. The traditional sampling of a multidimensional FID is usually time-consuming, and thus the reaction-monitoring toolbox was practically limited to 1D experiments (with rare exceptions, e.g. single-scan or fast-sampling experiments). Recently, the technique of time-resolved non-uniform sampling (TR-NUS) has been proposed, which allows to use standard multidimensional pulse sequences preserving the temporal resolution close to that achievable in 1D experiments. However, the method existed only as a prototype and did not allow on-the-fly processing during the reaction.

In this paper, we introduce TReNDS: free, user-friendly software kit for acquisition and processing of TR-NUS data. The program works on Bruker, Agilent and Magritek spectrometers, allowing to carry out up to four experiments with

Abbreviations: RM - reaction monitoring, CS - compressed sensing; NUS - non-uniform sampling, TReNDS - Time-Resolved N-Dimensional Spectroscopy

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interleaved TR-NUS. The performance of the program is demonstrated on the example of enzymatic hydrolysis of sucrose.

KEYWORDS
reaction monitoring, compressed sensing, non-uniform sampling, Time-Resolved N-Dimensional Spectroscopy

1 | INTRODUCTION

The application of NMR in reaction monitoring (RM) has recently been attracting growing attention [1, 2, 3, 4, 5, 6, 7, 8]. In most cases, RM-NMR relies on one-dimensional (1D) experiments (usually simple ^{1}H NMR) repeated in fixed time intervals.

Such an approach is fast, sensitive and quantitative, but fails for complex mixtures providing 1D spectra with severe peak overlap. Unfortunately, a common solution to the overlap problem - a multidimensional spectrum - cannot usually serve as a "snapshot" of the monitored process. The reason is the time-consuming sampling of a multidimensional evolution time space. Even for 2D experiments, the sampling can take minutes, which might cause too much averaging of the studied effects unless fast sampling[7] or single-scan[3] techniques are used.

A known solution to the problem of lengthy sampling is to omit a significant part of data during an experiment and reconstruct the missing points using mathematical algorithms. This approach, known as non-uniform sampling (NUS), is currently implemented in all major NMR software packages and routinely used by spectroscopists. Over the years, several NUS reconstruction algorithms have been developed, including: variants of CLEAN method[9, 10, 11, 12], maximum entropy[13, 14], SIFT method[15] and compressed sensing (CS, [16, 17]). Alternatively, one can "extrapolate" a conventionally sampled signal, as in linear prediction[18], covariance spectroscopy[19] or filter diagonalization[20] approaches.

An interesting time-resolved variant of NUS (TR-NUS) has been proposed by Mayzel et al.[21]. In this approach, the sampling is performed according to a shuffled non-uniform schedule in parallel to the chemical reaction occurring in the NMR tube. The acquired data is divided into overlapping subsets to form a stack of 2D NUS FIDs, and the reconstruction of the missing points is performed. A 2D case is schematically presented in Fig. 1a. For the acquisition, t_1 measurement points are chosen randomly from the whole possible range limited by its full grid. As the first stage of the processing, intersecting subsets are formed from the measured t_1 points. Then, data rows are ordered, and the reconstruction is carried out, giving a set of spectra characterizing the corresponding time moments.

In the original work[21], Mayzel et al. suggested to use multi-dimensional decomposition (MDD) to co-process the data of the subsets. The approach is very effective, but requires that peaks do not shift their positions from subset to subset. If this is not the case, one can apply CS methods to process each of the subsets separately[22].

Several examples of TR-NUS applications have been given in the recent years, studying, e.g.: biochemical reactions[21], protein unfolding[22], metabolism of yeasts[23] and bacteria [24], or a coherence transfer[25]. Up to now, however, the method has existed as a prototype and thus, despite its potential, has not been widely applied.

In this paper, we present TReNDS (Time-Resolved N-Dimensional Spectroscopy) - an open-source program for processing and display of TR-NUS data, combined with acquisition macros for spectrometers. The program is written in Python and exploits the CS module of the mddnmr package[26]. The pre- and post-processing of the NUS signal is performed using the nmrglue library[27]. The package also has an effective peak-tracking module allowing on-the-

fly analysis of the reaction progress. TReNDS is compatible with Bruker, Agilent, and Magritek spectrometers, and therefore opens up an avenue for applications of TR-NUS in a variety of scientific and industrial problems.

2 | INTERLEAVED ACQUISITION

The concept of interleaved multidimensional acquisition with real-time processing was introduced to protein NMR by Jaravine et al.[28]. In their work, the sampling of several multidimensional FIDs was performed by jumping between experiments and acquiring relatively few points of each signal.

However, the idea is not limited to protein studies and can provide many benefits in NMR of small molecules. Also, it fits very well to the concept of TR-NUS. Figure 1b presents the idea of interleaved NUS of two 2D FIDs.

Interleaved acquisition of several 2D experiments becomes the only reasonable approach when processes occurring in the sample cannot be easily repeated with exactly the same kinetics. Then, a conventional 2D spectra measured consecutively do not provide coherent dataset (for example, peaks from 2D HSQC and 2D HMBC do not match).

Significantly, one can measure 1D experiments between acquiring NUS points of 2D FIDs. It makes it possible to evaluate the rate of variations in a spectrum and to adjust the size of a subset for processing. As discussed before[25], the change of peak amplitudes within a subset of TR-NUS data results in t_1-noise. Thus, it is important to keep the subset size as small as possible. On the other hand, the mathematical conditions of CS reconstruction[29] require a minimum number of sampling points to make the reconstruction credible. The usual signal to thermal noise ratio also plays a role. So, there is an optimum to be found between the extremes of a too large and a too small subset, both bringing their own distortions. It is thus beneficial that the subset size is a processing parameter, not an acquisition parameter, and so it can easily be adjusted after the acquisition.

Finally, a practical remark should be added. In the procedure of interleaved acquisition one does not use steady-state scans before each “block” of collected data. This may lead to amplitude distortions in the first scans of the “block”, if interleaved experiments excite different nuclei and short interscan delays are set. In practice, however, we did not observe problems of this kind for a typical set of 1D ^{1}H and 2D ^{1}H-^{13}C experiments. Yet, a problem becomes pronounced, if data-saving following the acquisition of each “block“ takes too long. To avoid this, we recommend to use a local folder for the storage.

3 | FUNCTIONALITY

TReNDS package can control the acquisition of TR-NUS signals and process the collected data. The acquisition is controlled by spectrometer-specific macros that are independent from the processing interface. Such approach guarantees stability, as all numerically demanding functions e.g. CS processing, display of multiple spectra and peak-tracking belong to separate program.

The detailed instructions for acquisition, processing and display can be found in the software manual. Below, we mention only the principles of the procedures without going into the details, which may change in the next versions.

3.1 | Acquisition

TReNDS data is acquired in an interleaved manner by jumping between experiments and collecting 2 NUS points in each of them. Except for Magritek benchtop spectrometers, no modifications of pulse sequence codes are done - TReNDS exploits standard NUS implemented in Bruker and Agilent software. Two NUS points are collected in each

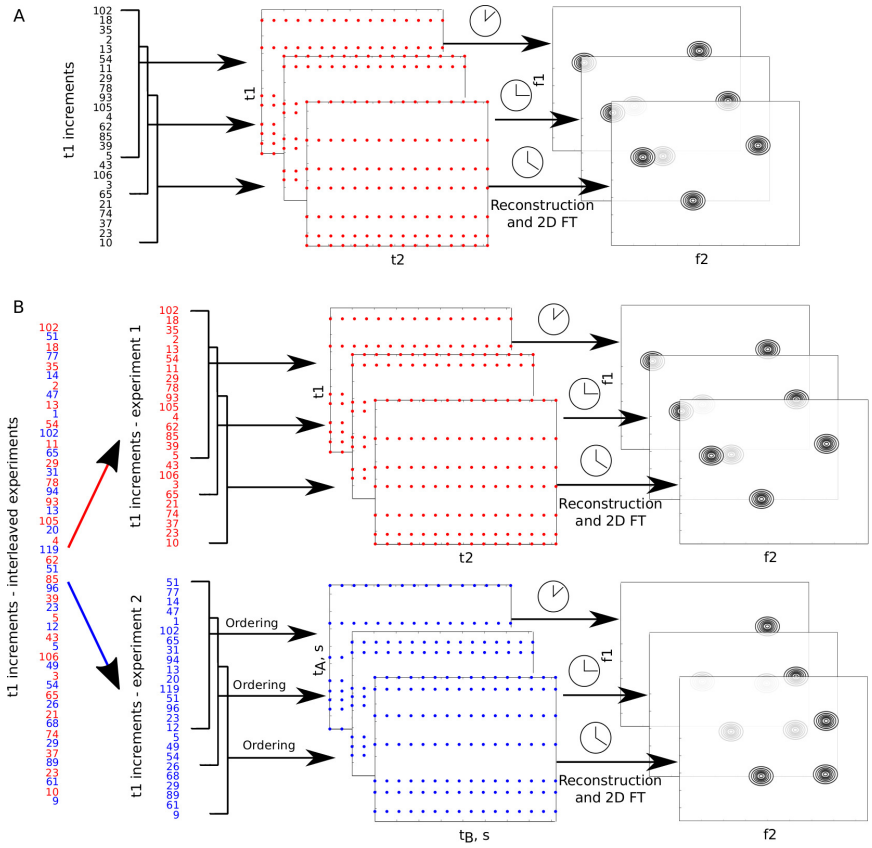

FIGURE 1 The sampling and processing schemes exploited in TReNDS. a) The concept of TR-NUS. Subsets of long NUS schedule are created, each forming a standard input to a CS reconstruction program. The resulting stack of spectra allows for continuous visualization of a process occuring in the sample in parallel to data acquisition. b) The idea of interleaved acquisition. The TR-NUS data is collected by jumping between NUS experiments (marked with blue and red). The datasets are separately processed and form a stack of spectra allowing to reflect the sample changes in various kinds of spectra.

step due to requirements of standard Agilent software (VnmrJ 4.2), which does not allow single-point NUS experiment. Figure 2a presents acquisition interface for Agilent and Bruker spectrometers.

The user has to prepare the “template” experimental setups which will be then run in TR-NUS mode. This is simple - it is enough to set standard experiments and enable NUS.

In the default mode, sampling of an indirect evolution time in one 2D experiment is interleaved with an acquisition of 1D spectra. The number of 2D spectra can be increased (up to 3). 1D dataset is collected before 2 NUS points of all 2Ds are measured. Optionally, 1D experiment can be removed from the loop.

The preparation stage includes also choosing a sampling schedule files and a number of “steps” i.e. the number of two-point loops to be acquired. The sampling schedule can be generated using any software (e.g. *nussampler* from MddNMR package, *Rowland Toolkit*[30] or *Schedule Generator* from hmsIST package[31]). Importantly, the schedule should be long enough to provide sampling coordinates for all “steps”.

3.2 | Processing

As mentioned above, the processing of NUS data can be performed using a variety of methods. TReNDS exploits algorithms from MddNMR software[26] - iterative soft thresholding[32, 16, 31] (IST) and iteratively re-weighted least squares[33, 16] (IRLS). While the latter algorithm is very effective (in terms of spectral quality) for low levels of sparseness, the former one is usually faster. We recommend IST for on-the-fly processing, but IRLS can be a method of choice for the ultimate processing of demanding datasets. Both algorithms look for the spectrum that fits to the measured data and has the lowest possible number of significant points (highest sparsity). This corresponds to solving the following minimization problem:

$$\underset{\boldsymbol{x}\in\mathbb{C}^n}{\operatorname{argmin}} \; ||\tilde{\boldsymbol{F}}\boldsymbol{x} - \tilde{\boldsymbol{y}}||_{\ell_2} + \lambda||\boldsymbol{x}||_{\ell_p} \tag{1}$$

where $\boldsymbol{x}$ is the spectrum, $\tilde{\boldsymbol{y}}$ is an undersampled FID signal, λ is a constant keeping balance between the agreement with the measured data (the first term) and spectral sparsity (the second term). $||...||_{\ell_p}$ denotes the norm, with $p = 1$ for IST algorithm and $0 < p \leq 1$ for IRLS algorithm.

For detailed explanations of the processing, see paper by Shchukina et al.[34].

Obviously, the concept of TR-NUS is compatible with other processing approaches, if they are fast enough to allow on-the-fly reaction monitoring.

In the standard mode, TReNDS reconstructs FID and displays the spectrum, after the data for at least one subset has been collected. The program automatically checks the data folder for the new data points and reconstructs consecutive frames of the TR-NUS spectrum. Figure 2b) presents processing interface of TReNDS.

3.3 | Data Visualization and Analysis

TReNDS software is capable of displaying up to three sets of 2D spectra and one 1D spectrum. As following subsets are reconstructed, slider "Frame No." on the display control panel increases its allowed values. The user can switch between the subsets with this slider. The subset (frame) number is synchronized for all the types of spectra.

Three 1D spectra are displayed for each frame: the one at the time moment corresponding to the beginning of its acquisition, the one in the middle, and the one at the end. Thus, the user can assess the spectral changes over the subset acquisition time and increase or decrease the size of the subset if needed. The height of the displayed 1D

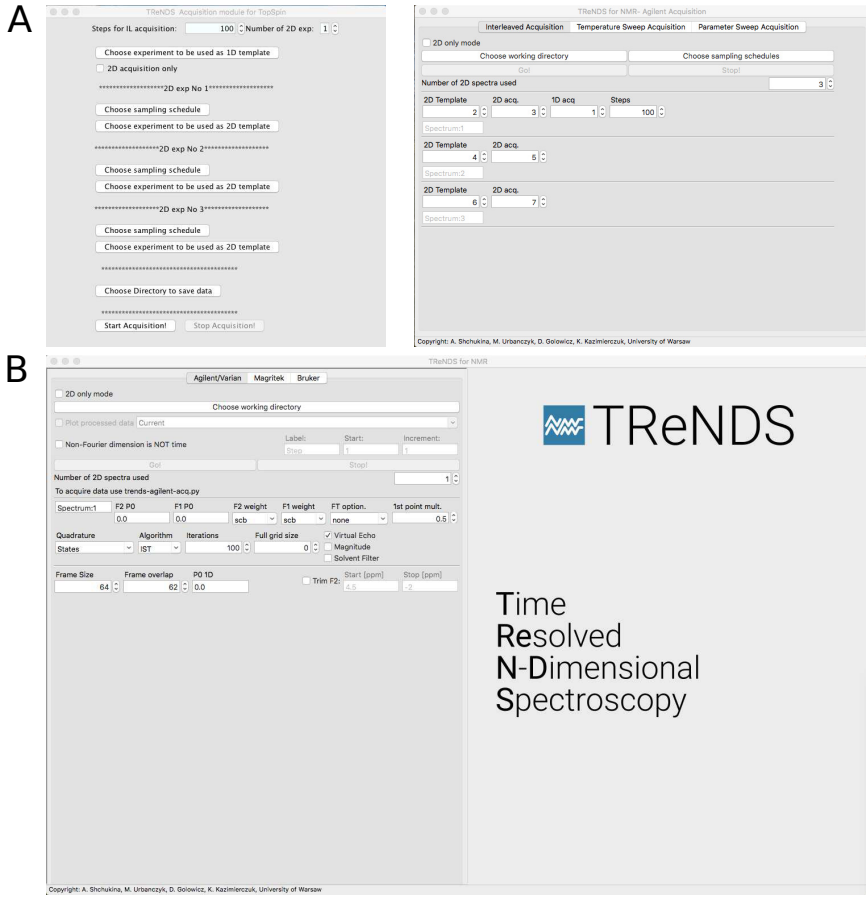

FIGURE 2 The TReNDS graphical user interface. a) Interfaces of acquisition macros for Bruker (left panel) and Agilent b) The processing interface

spectra can be adjusted. As for 2D spectra, the display settings (threshold and contour levels) for their contour plots can be adjusted for each spectrum type separately. TReNDS allows also the zero-order phasing of the spectra in all dimensions. After phase correction, all frames are recalculated.

One of the TReNDS trademarks is its ability to perform effective peak-picking, peak-tracking and intensity analysis on-the-fly. TR-NUS is particularly well suited for application requiring peak tracking, since peaks change their positions very slightly between consecutive frames.

The Figure 3 presents the scheme of TReNDS peak analyzer. Once a peak is selected for analysis in any of the frames, the software, first of all, performs automated peak picking in all the spectra of a given series; then, the correspondence between the found peaks is established, and each peak is assigned its unique number (peak tracking); finally, the selected peak is fitted with a 2D Lorentzian in each frame to find its height and full width at half maximum (FWHM) and, thus, its integral value. When the procedure has been carried out, a pop-up window appears with a plot of the integral of the peak throughout the frames. This plot can be fitted with function corresponding to the zero-order, first-order or second-order kinetics. The whole procedure takes seconds, or, for the biggest dataset that we have used (990 frames), a couple of minutes.

The user can choose between three intensity analysis modes of the peak analyzer: numerical integral, peak fit and peak height (no integration). While the integral of the peak theoretically gives a fuller picture of the chemical changes, it may be more beneficial to use the intensity in some cases (noisy spectra), as the estimation of the FWHM contributing to the integral can be distorted by the noise more than the intensity estimation.

The peak picking step is performed based on the threshold that is set for the display: only the spectral points that are above this threshold are considered as candidates for a peak. Thus, the software follows the human perception: it will "see" only the peaks that the user can see with the current display parameters. A "neighbor test" is used to check all the points above the threshold: if a point has higher intensity than all the points in its neighborhood of a given size (tunable by the user), it is considered a peak.

Peak tracking is based on the assumption that the time resolution (frame size and frame overlap) is high enough for the peaks to move gradually in small steps from frame to frame. With the peak lists for two successive frames at our disposal (step 1, peak picking, is already accomplished), the algorithm iterates over the peaks of the first frame to search for a peak of the second frame closest to the given one. The cases of peak appearance/disappearance are also taken into account: if the number of peaks increases, the peaks farthest from all the previous ones are considered "new", and if it decreases, the corresponding peaks from the former frame are considered "disappeared".

The procedure can be repeated any time from the very beginning, or only the third step (peak fitting) can be carried out for a newly selected peak if the user is satisfied with the threshold and the peak lists. If new frames have been added to the reconstructed sets since the last peak analysis, the procedure is repeated from the beginning anyway.

4 | EXAMPLE OF APPLICATION

As an example, we applied TReNDS to monitor enzymatic hydrolysis of sucrose with interleaved acquisition of 1D and 2D spectra, analyze peak intensities and calculate V_{max} of the reaction.

The sample was prepared by mixing stock solution of 2.0 M sucrose in D_2O with stock solution of enzyme in 1:1 volumetric ratio. Stock solution of enzyme was obtained by dissolving β-D-Fructofuranosidase (Sigma-Aldrich) in 95 mM acetate buffer (Sigma-Aldrich) (H_2O, pH = 5.2) to final concentration of 4.6 ug/mL. Due to high excess of the substrate, we expected long pseudo-zero order kinetics period for studied reaction.

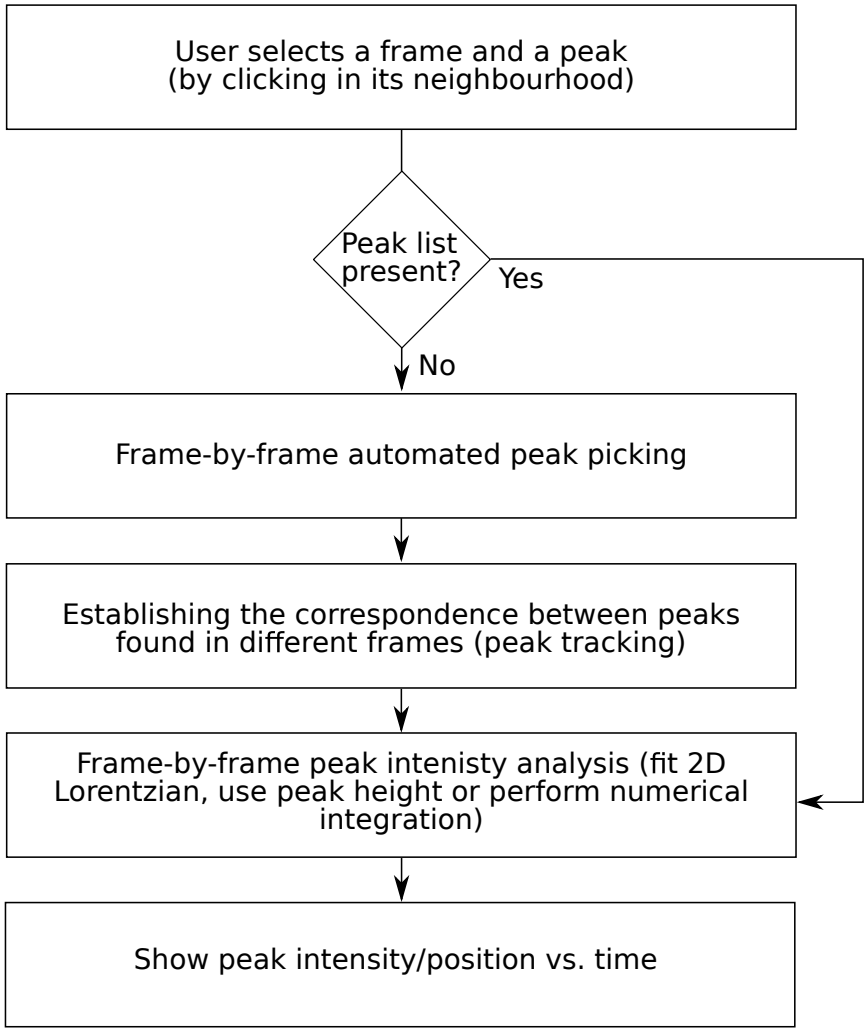

FIGURE 3 Scheme of peak-analyzing procedure in TReNDS.

After the preparation, the sample was quickly placed inside the magnet, all essential steps including probe tuning and shimming were carried on, and then interleaved acquisition employing TReNDS started. We performed the acquisition on Agilent 700 MHz spectrometer equipped with a room temperature HCN probe, as well as on Magritek Carbon 43 MHz benchtop spectrometer.

For the high-field NMR measurement, we interleaved 1D ^{1}H NMR spectrum with three 2D spectra: multiplicity edited ^{13}C HSQC, ^{1}H TOCSY, and ^{13}C HMBC. The spectra were acquired with two scans per increment for all 2D, and one scan for 1D. The relaxation delay was set to 1.5 s for every experiment. The NUS schedule consisted of 2048 points, while the full grid was 256 points. The total experimental time was approximately 26 hours.

The acquired data were processed in TReNDS. For TR-NUS reconstruction, we set the frame size to 64 points, and the frame overlap to 62 points. We used 200 iterations of IST algorithm to reconstruct every 2D spectrum. To speed up the processing, we trimmed the F2 dimension from 7 ppm to 2 ppm. We applied proper weighting functions to both dimensions of every 2D spectrum and magnitude mode for HMBC spectrum.

The reconstruction resulted in 992 spectra for each 2D dataset, providing temporal resolution of 92 seconds for all experiments. This gave opportunity to precisely track sucrose hydrolysis by observing spectral changes in 1D, TOCSY, HSQC and HMBC spectra simultaneously. Thus, we directly observed transformation of sucrose to D-fructose anomers and D-glucose anomers (Figure 4). Basing on acquired set of spectra and the fact that particular peaks appear or disappear, one can easily identify all signals.

The 'peak analysis' utility was used to integrate selected peaks above given threshold and to track their spectral positions. We calculated V_{max} of the enzymatic reaction from decaying signals of sucrose.

Due to severe peak overlap and strong water signal (no water suppression) in ^{1}H spectrum, only hydrogen attached to anomeric carbon of sucrose was well resolved and therefore used to calculate V_{max}. We present here that kinetic parameters (in our case V_{max}) can be also calculated from interleaved 2D spectra, taking advantage of superior peak resolution and temporal resolution similar to that used in classical reaction monitoring experiments (1D NMR). As an example we integrated selected peaks (Figure 5) from HSQC and HMBC spectra.

The reaction progress curve was linear for first 497 minutes (R^2=0.999 calculated from 1D spectrum) which corresponds to zero-order kinetics. The values of calculated V_{max} (M/s) from ^{1}H NMR and 2D spectra are: 9.7×10^{-6} (1D); $9{,}9 \times 10^{-6}$ (peak 1), 9.4×10^{-6} (peak 2), 8.9×10^{-6} (peak 3), 9.3×10^{-6} (peak 4), 1.0×10^{-5} (peak 5), 1.1×10^{-5} (peak 6), 1.2×10^{-5} (peak 7).

The same reaction was studied on Magritek 43 MHz spectrometer using TReNDS. In this case, we interleaved 1D ^{1}H NMR spectrum with 2D ^{13}C HSQC spectrum. We utilized NUS schedule consisting of 2048 points, while our interleaved 2D experiment had full grid of 128 points. ^{1}H NMR spectrum was acquired with 1 scan and ^{13}C HSQC with 8 scans per increment. The relaxation delay was set to 3.0 s. The frame size was set to 64 points with 62 points overlap. We applied 20 iterations of IRLS alghoritm to reconstruct every single 2D spectrum. Temporal resolution of resulting interleaved spectra was 109 s.

The low resolution dictated by low B_0 field combined with strong water signal make it impossible to find sufficiently well resolved peak in ^{1}H spectrum. However, in 2D we observed all sucrose peaks separated. We used 'peak height' utility to estimate V_{max} of the reaction, which is beneficial especially in low sensitivity measurments. Calculated V_{max} for one of the CH_2 signals was 1.2×10^{-5}, which is in agreement with high-field experiment results.

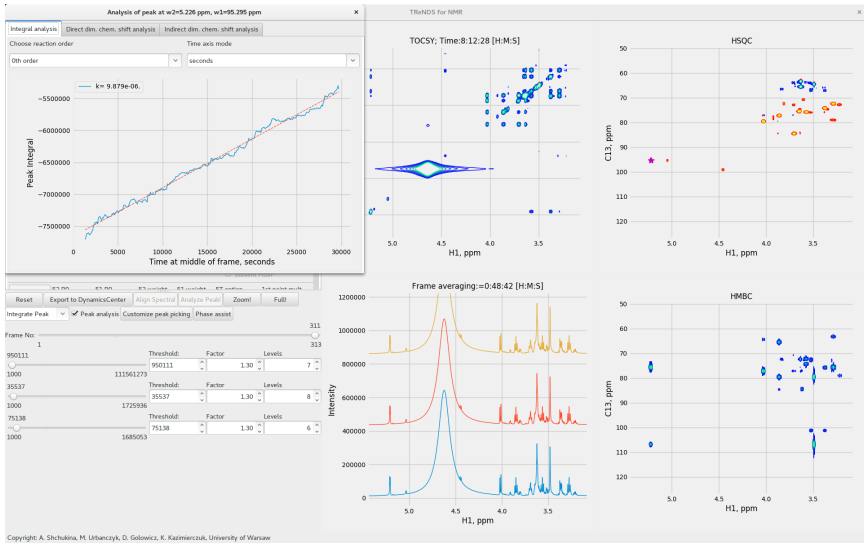

FIGURE 4 Sucrose hydrolysis monitored with TReNDS and peak analysis pop-up window.

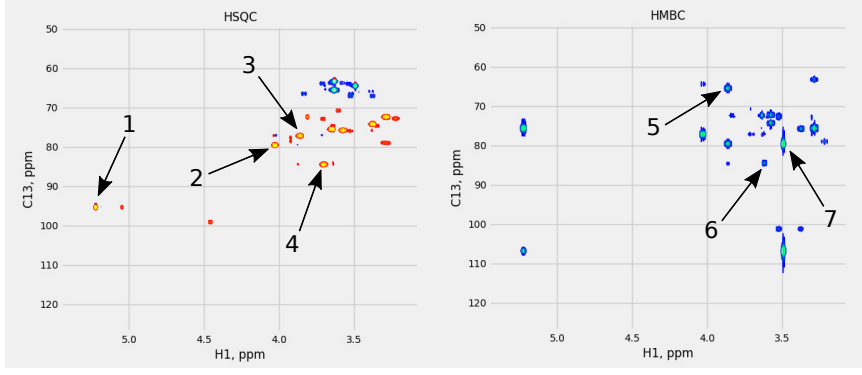

FIGURE 5 Selected 2D peaks for integration using TReNDS.

5 | POSSIBLE EXTENSIONS

TReNDS is an open-source, object-based software, which is easy to develop. Thus, we can envisage numerous possible improvements of the program, which can be implemented either by our group or other interested ones.

The main potential features include:

1. New processing algorithms. Low-rank reconstruction[35], maximum entropy[13] and other high-performance algorithms can be added to TReNDS interface in future.
2. The concept of moving-frame processing has recently been introduced into diffusion-ordered spectroscopy (DOSY)[36]. The interleaved acquisition can be extended to Laplace NMR.
3. The acquisition of pure-shift pseudo-2D spectra can also be performed in an interleaved manner, even employing some form of NUS (i.e., skipping certain "chunks" of an FID [7]).
4. Serial NMR data can be processed jointly, either by MDD[21] if peaks do not move or by Radon transform[37, 38] if they move linearly. Both tools could be implemented in TReNDS.
5. Finally, the interface could be adapted to spectra of dimensionalities higher than 2D, as in the solution by Jaravine et al.[28] mentioned above.

6 | CONCLUSIONS

We presented the software dedicated for acquisition and processing of time-resolved 2D spectra. The software allows easy process monitoring using standard pulse sequences. Since the acquisition is performed in an interleaved manner, spectra are acquired in parallel and effective interpretation of the changes in spectra can be performed by comparing time-profiles of changes for various peaks.

Supporting Information

The software can be downloaded from `trends.spektrino.com`. The software manual for TReNDS 1.0 is present in SI.

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Conflict of interest

Authors declare no conflict of interest.

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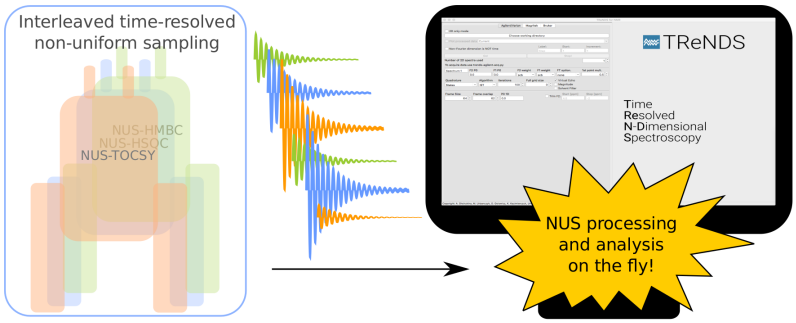
GRAPHICAL ABSTRACT



Time-resolved non-uniform sampling (TR-NUS) allows for reaction monitoring using multidimensional experiments. Here, we present TReNDS - the program for convenient setup and processing of TR-NUS measurement. The software performs spectral reconstruction and analysis including peak-peaking and tracking.