



## NMR

# Exploring 2D HSQC NMR

## A Comprehensive Guide Using Bruker Parameter Sets

Innovation with Integrity

### Introduction

Structural elucidation of unknown compounds can be effectively achieved using two-dimensional Heteronuclear Single Quantum Coherence (2D HSQC) NMR spectroscopy. Since its introduction, the HSQC pulse sequence has undergone numerous modifications aimed at improving sensitivity, resolution, efficiency, robustness, and overall performance.<sup>1</sup> This application note provides a comprehensive overview of 2D HSQC NMR applications using Bruker parameter sets. It is designed to assist both routine and advanced users in optimizing their experiments for structural analysis. For readers seeking a deeper understanding of the underlying principles, pulse sequence variants, and practical considerations, we recommend consulting specialized references that explore these aspects in greater detail.<sup>2</sup>

The diverse applications of HSQC NMR can be broadly categorized as follows:

#### 1. Structure Verification and Elucidation

- Conventional HSQC
- Sensitivity-enhanced HSQC
- Multiplicity-edited HSQC
- HSQC with COSY cross-peak suppression
- HSQC with Adiabatic Decoupling

#### 2. Accelerated HSQC Data Acquisition

- Non-Uniform Sampling (NUS) HSQC
- Ultrafast HSQC

#### 3. Highly-Resolved HSQC

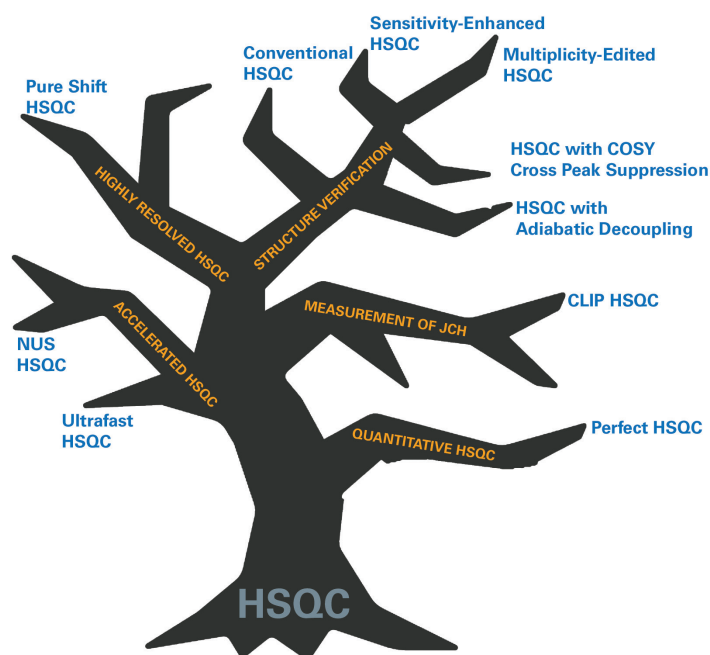
- Pure Shift HSQC

#### 4. HSQC for measurement of Heteronuclear Coupling Constants

- CLIP HSQC

#### 5. Quantitative HSQC

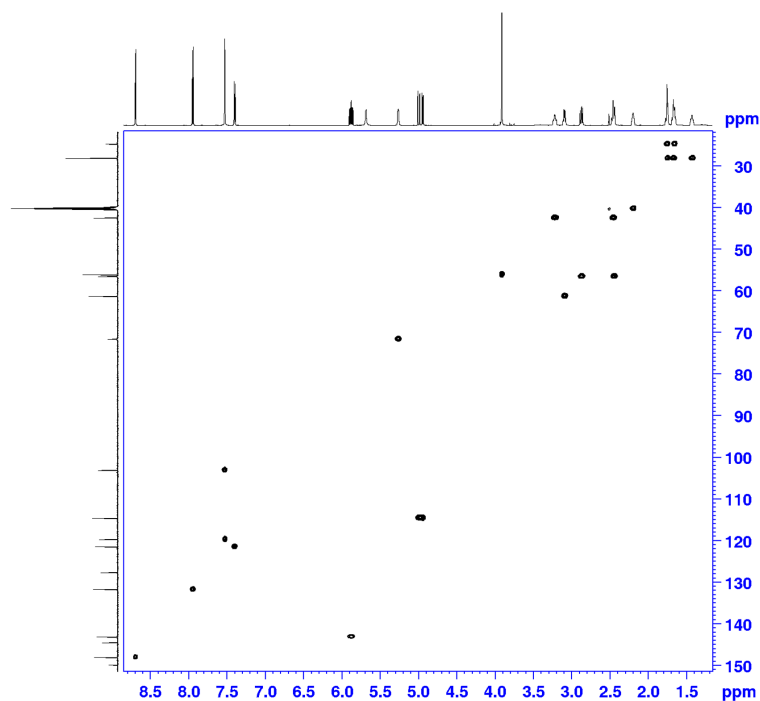
- Perfect HSQC



**Scheme 1:** Graphical representation of the various HSQC NMR experiments and their main applications

## 1. Structure Verification and Elucidation

### a. Conventional HSQC



**Figure 1:** 2D spectrum of conventional **HSQCETGP** of a 200 mM quinine solution in DMSO-d<sub>6</sub>

#### Application:

HSQC spectroscopy enables the correlation of proton chemical shifts (along the F2 axis) with the chemical shifts of the directly bonded carbon-13 nuclei (along the indirect F1 axis). This correlation is facilitated by the one-bond heteronuclear coupling constant, denoted as  $^1J_{\text{CH}}$ .

#### Example Spectrum:

Figure 1 shows a 2D HSQC spectrum (HSQCETGP) of 200 mM quinine in DMSO-d<sub>6</sub>. This is a gradient enhanced version of the conventional HSQC experiment.

#### Bruker Parameter Set:

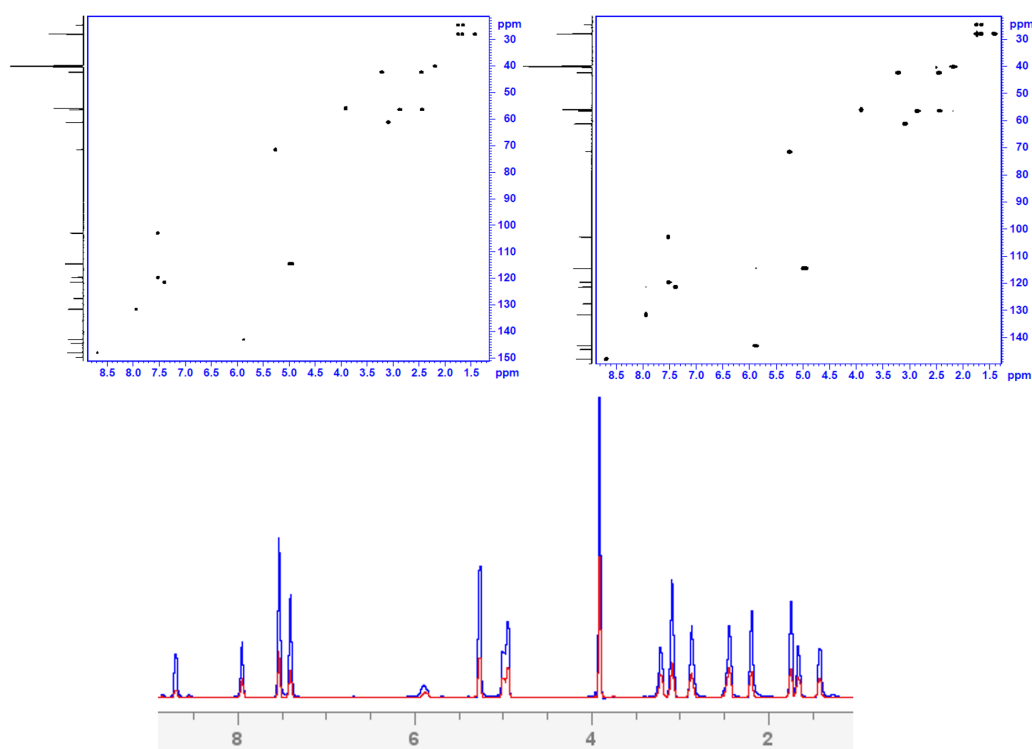
The relevant Bruker parameter files are located in the TOPSPINHOME/exp/stan/nmr/par directory. The conventional HSQC experiment is available under the parameter set name **HSQCETGP**.

#### Key Parameters:

The heteronuclear coupling constant (CNST2) is typically set to 145 Hz, reflecting the average heteronuclear one-bond coupling constant ( $^1J_{\text{CH}}$ ). This value may vary depending on the specific type of C-H bond being observed.

## 1. Structure Verification and Elucidation

### b. Sensitivity-Enhanced HSQC



**Figure 2:** Comparison of 2D HSQC spectra: the left panel shows the conventional HSQCETGP spectrum, while the right panel displays the sensitivity-enhanced HSQCETGPSI spectrum of 200 mM quinine in DMSO- $d_6$ . The bottom panel presents an overlay of 1D slices extracted from both spectra - HSQCETGP in red and HSQCETGPSI in blue - highlighting the enhanced signal intensity achieved with the sensitivity-improved method.

#### Application:

Sensitivity has long been a key challenge in NMR spectroscopy. Over the past few decades, researchers have introduced significant advancements to address this issue. One such improvement is the availability of sensitivity-enhanced parameter sets, such as HSQCETGPSI, which are designed to boost signal intensity. In sensitivity-enhanced pulse sequences, HSQC spectra acquired with a single scan may exhibit artifacts.

#### Example Spectrum:

Figure 2 presents a side-by-side comparison of the conventional HSQCETGP and the sensitivity-enhanced HSQCETGPSI spectra. The 2D spectra demonstrate the enhanced signal intensity provided by the HSQCETGPSI parameter set. Additionally, in the bottom panel, showing the overlaid 1D slices - red for HSQCETGP and blue for HSQCETGPSI - highlight the substantial gain in peak intensity provided by the sensitivity-optimized method.

#### Bruker Parameter Set:

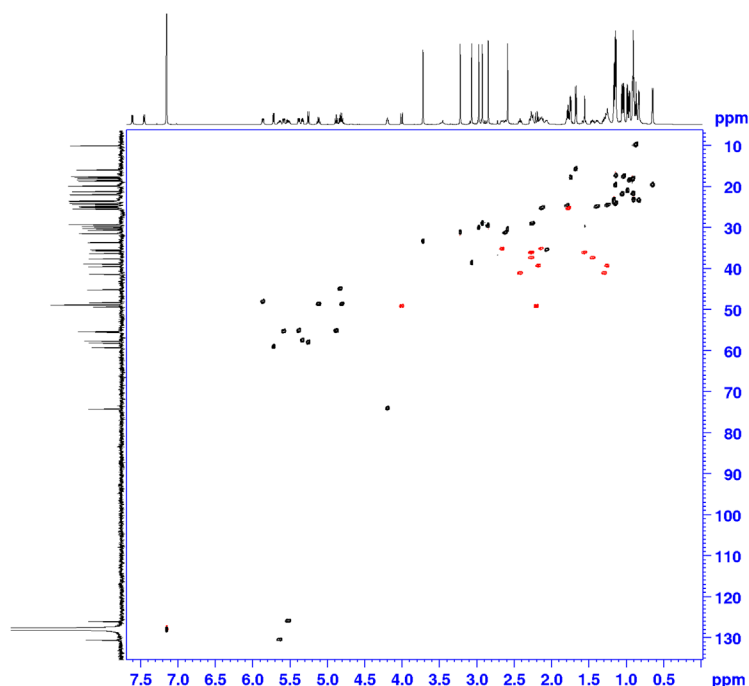
**HSQCETGPSI** - a sensitivity-enhanced version of the standard HSQC experiment.

#### Key Parameters:

Set the parameter  $d24 = 0.000862$  seconds which corresponds to the delay time calculated as  $d24 = 1/(8J)$  for XH couplings across all multiplicities.

## 1. Structure Verification and Elucidation

### c. Multiplicity-Edited HSQC



**Figure 3:** 2D multiplicity-edited HSQC spectrum of Cyclosporine (25 mM in Benzene- $d_6$ )

#### Application:

The edited HSQC experiment is a multiplicity-edited version of the standard HSQC, conceptually similar to DEPT (Distortionless Enhancement by Polarization Transfer) editing. By incorporating a dedicated editing period into the pulse sequence, it enables differentiation between CH, CH<sub>2</sub>, and CH<sub>3</sub> groups, providing valuable structural information, particularly in complex molecular systems.

#### Example Spectrum:

Figure 3 shows the 2D multiplicity-edited HSQC spectrum of cyclosporine. CH and CH<sub>3</sub> correlation peaks appear in black, while CH<sub>2</sub> peaks are highlighted in red, allowing for clear identification of protonated carbon types.

#### Bruker Parameter Set:

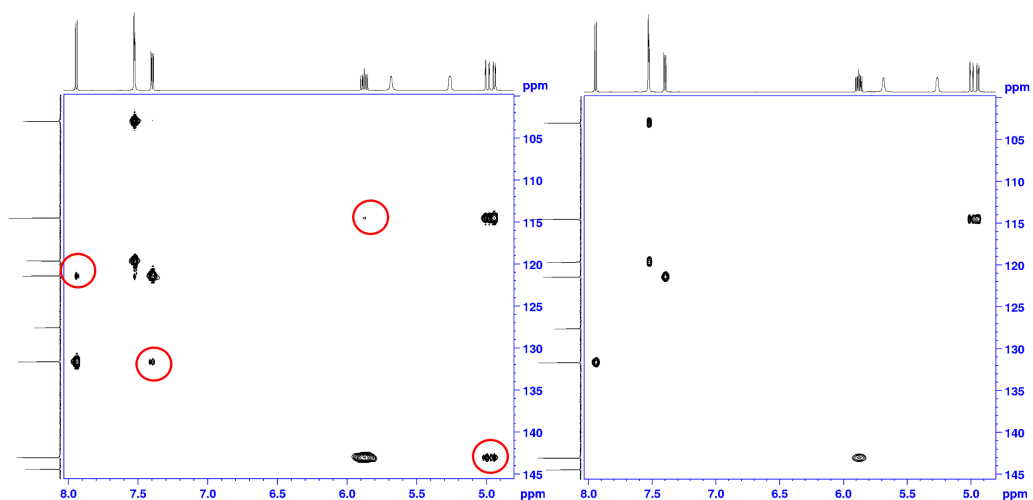
The multiplicity-edited HSQC experiment is available in the **HSQCEDETGPSISP** parameter set.<sup>4-6</sup>

#### Key Parameters:

d21: Set according to the desired multiplicity selection, calculated as  $d21 = 1/2J$ . For example, a value of 0.0036 seconds is commonly used and is derived from a  $^1J_{CH}$  value of 145 Hz. CNST2: Set to 145 Hz, representing the average one-bond  $^1J_{CH}$  coupling constant.

## 1. Structure Verification and Elucidation

### d. HSQC with COSY Cross-Peak Suppression



**Figure 4:** Comparison of 2D HSQC spectra of quinine acquired using two different parameter sets: HsQCETGpsisp2.2 (left), without COSY cross-peak suppression, and HsQCETGpsisp2.3 (right), with COSY cross-peak suppression. The COSY-suppressed version exhibits a cleaner spectrum, free from unwanted cross-peaks, enhancing interpretability.

#### Application:

In conventional HSQC experiments, cross peaks may arise not only between a proton and its directly bonded carbon but also between a proton and neighbouring carbons separated by two bonds. These additional signals result from residual COSY-type correlations between the protons of the neighbouring carbon nuclei.

The COSY-suppressed HSQC variant addresses this issue by eliminating the homonuclear proton to proton magnetization transfer, resulting in cleaner spectra that emphasize only the direct one-bond  $^1J_{CH}$  correlations.

#### Example Spectrum:

Figure 4 compares two 2D HSQC spectra of a 200 mM quinine solution DMSO- $d_6$ . The left panel shows the spectrum acquired using HsQCETGpsisp2.2, which does not include COSY suppression, while the right panel displays the spectrum from HsQCETGpsisp2.3, incorporating COSY suppression. The latter eliminates COSY-type artifacts, resulting in a cleaner and more interpretable spectrum.<sup>7-9</sup>

#### Bruker Parameter Set:

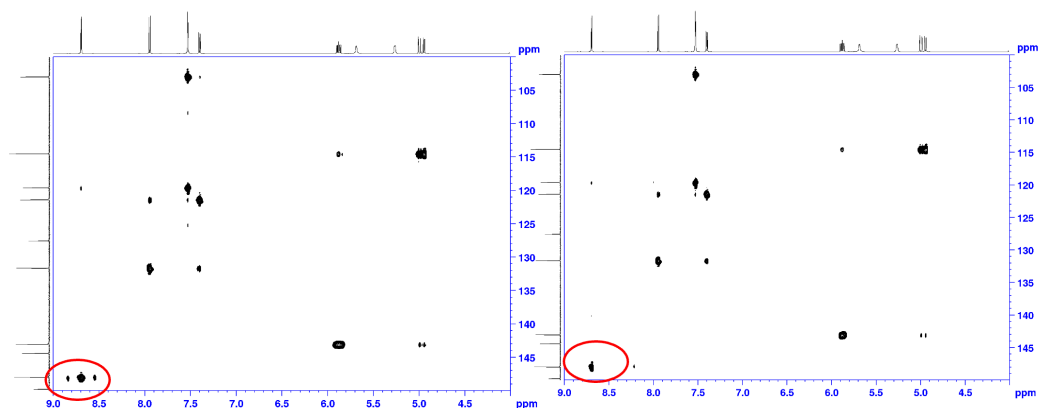
**hsqcedetgpsisp2.4** - a COSY suppressed, multiplicity-edited HSQC sequence

#### Key Parameters:

Set to desired CNST2 = J(XH), typically 145 Hz resulting in a d24 =  $1/8 \ ^1J_{CH}$  0.000862 seconds.

## 1. Structure Verification and Elucidation

### e. HSQC With Adiabatic Decoupling



**Figure 5:** 2D HSQC spectra of a 200 mM quinine sample in DMSO- $d_6$  acquired using rectangular decoupling (GARP, left) and adiabatic bilevel decoupling (bi\_p5m4sp\_4sp.2, right). At 147 ppm, the adiabatic decoupling spectrum shows complete suppression of decoupling sidebands, demonstrating superior performance compared to the conventional method.

#### Application:

Adiabatic pulses provide a highly effective solution for broadband heteronuclear decoupling, delivering significant improvements over conventional rectangular pulse methods. Their key advantage lies in their ability to uniformly invert spins across a wider X-nucleus bandwidth while operating at low radiofrequency (RF) power. This makes them particularly effective for decoupling over broad spectral ranges without excessive sample heating.

The adiabatic fast passage technique ensures consistent inversion efficiency, provided the adiabatic condition ( $\omega/\gamma B_0 \ll 1$ ) is satisfied - making the process largely independent of RF field strength. Compared to traditional rectangular pulses, adiabatic decoupling consumes less power, reduces thermal load on the sample, and improves both decoupling range and signal-to-noise ratio.

#### Example Spectrum:

Figure 5 compares 2D HSQC spectra acquired using conventional rectangular decoupling (GARP) and adiabatic bilevel decoupling method. The adiabatic method demonstrates superior decoupling efficiency, particularly at frequencies farther from the  $^{13}\text{C}$  transmitter offset, resulting in complete heteronuclear decoupling.

#### Bruker Parameter Set:

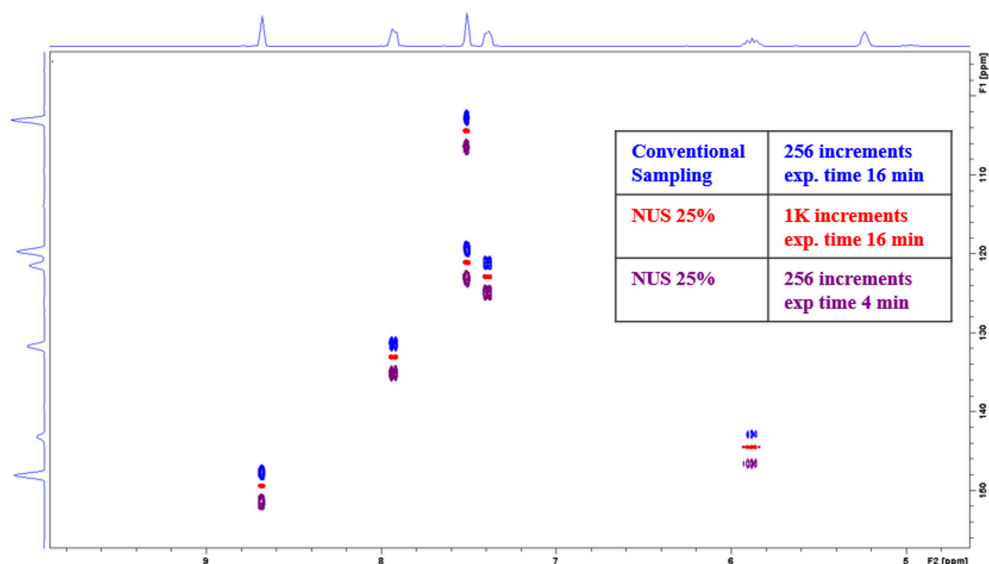
**HSQCETGPSISP.2\_ADIA** - a Bruker parameter set for adiabatic bilevel decoupling.<sup>10-12</sup>

#### Key Parameters:

CPDPRG2=GARP(conventional) and CPDPRG2= bi\_p5m4sp\_4sp.2 (adiabatic bilevel decoupling).

## 2. Accelerated HSQC Data Acquisition

### a. Non-Uniform Sampling (NUS) HSQC



**Figure 6:** Overlay of 2D HSQC spectra for a 50 mM quinine solution in DMSO- $d_6$ , comparing conventional and Non-Uniform Sampling (NUS) acquisition methods.

#### Application:

Enhancing resolution along the indirect dimension and minimizing acquisition time are key objectives in HSQC experiments. One effective strategy to achieve both is Non-Uniform Sampling (NUS). For small molecules, NUS can significantly shorten the duration of 2D HSQC experiments - often by up to 50% - by sampling only a fraction of the full data points. Alternatively, NUS can be leveraged to enhance spectral resolution along the indirect  $^{13}\text{C}$  dimension by reducing the number of  $t_1$  increments required.<sup>13-14</sup>

#### Example Spectrum:

Figure 6 compares 2D HSQC spectra of quinine acquired using both conventional and NUS techniques. Top (blue): Acquired with conventional sampling of 256  $t_1$  increments in 16 minutes. Middle (red): Acquired using NUS at 25% sampling of 1024 increments, also in 16 minutes, demonstrating enhanced resolution. Bottom (purple): Acquired using NUS at 25% of 256 increments, acquired in just 4 minutes, highlighting substantial time savings.

These results highlight how NUS can enhance resolution (as seen in the red spectrum) and reduce acquisition time (as seen in the purple spectrum), making it a valuable tool for efficient NMR data acquisition.

#### NUS set up in Topspin:

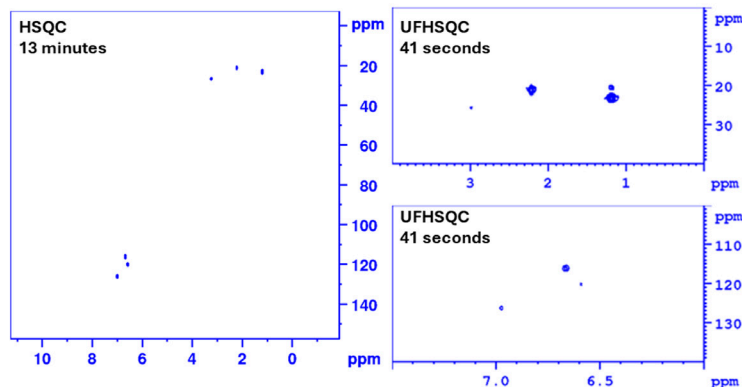
To configure NUS in Topspin, navigate to the AcqPars tab under the Experiment section and set FnTYPE to "non-uniform sampling". In the left-hand list, select NUS to access the NUS-specific parameters. NusAMOUNT [%] defines the percentage of sparse sampling (default is 25). NusPOINTS - Indicate the number of complex data points to be recorded. As a rule of thumb, the number of complex points should match the number of expected frequencies in the spectrum. Jsp [Hz] - J-coupling value (default is 0 Hz).

#### Targeted Acquisition (TA):

Bruker's Targeted Acquisition is an automated method that intelligently determines the optimal Non-Uniform Sampling (NUS) percentage on the fly. To perform a Targeted Acquisition, first configure your dataset for NUS by setting the FnType to "non-uniform sampling". Then, set NusAMOUNT to the maximum percentage of sparse sampling you wish to allow, for example to 100%. Assign the automation AU programs AUNM (acquisition) to "ta\_acqu", and AUNMP (processing) to "ta\_proc", then start the acquisition using the command "xaua". This streamlined workflow enables efficient data collection with minimal user input while maintaining high spectral quality.

## 2. Accelerated HSQC Data Acquisition

### b. Ultrafast HSQC



**Figure 7:** A comparative display of 2D HSQC spectra for the 2M Thymol sample in DMSO- $d_6$  showing the conventional HSQC on the left and the ultrafast HSQC on the right. Note the dramatic reduction in acquisition time of the ultrafast HSQC experiment.

#### Application:

Ultrafast NMR is an advanced technique that dramatically accelerates the acquisition of multidimensional NMR spectra. Unlike conventional methods that rely on multiple scans with incrementally varied evolution times, ultrafast NMR captures the entire dataset in a single scan using spatial encoding. This method encodes the nuclear spin evolution across different spatial positions within the sample, enabling rapid and efficient data collection.

Ultrafast NMR is especially valuable for investigating dynamic processes and real-time molecular interactions, making it a powerful tool in disciplines such as chemistry, biochemistry, and materials science. The technique was first introduced in 2002 by Lucio Frydman and colleagues as a revolutionary method for acquiring 2D NMR spectra in a single scan.<sup>15</sup>

#### Example Spectrum:

Figure 7 displays the UFHSQC spectrum of 2 M Thymol in DMSO- $d_6$ , acquired with SW(FT)=10 ppm, SW(UF)=40 ppm. The carbon frequencies are spatially encoded and thus appear in the spatially encoded UF (direct) dimension alongside the  $^1\text{H}$  dimension. Consequently, the HSQC spectrum is rotated by 90 degrees compared to a conventional HSQC. The entire acquisition was completed in under one minute.

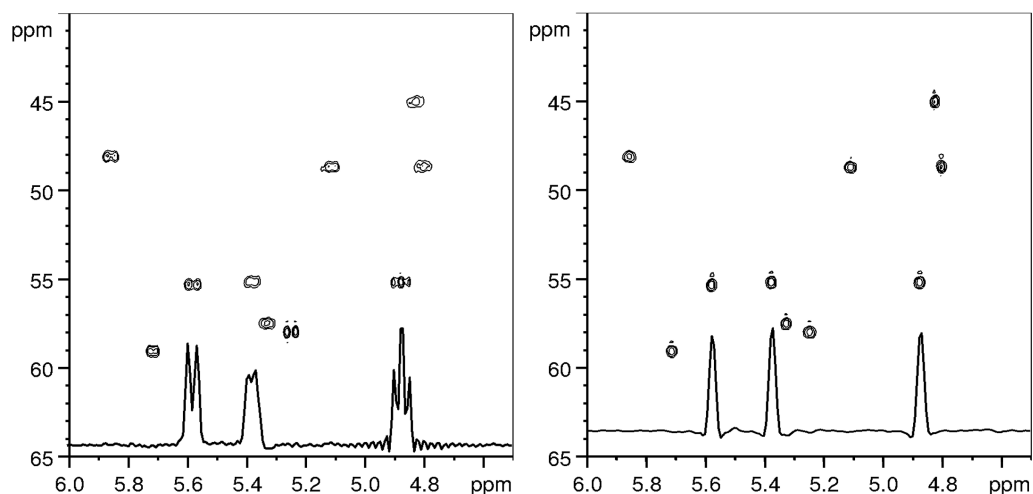
#### Work flow for running Ultrafast (UF) Experiments in TopSpin:

The **init\_uf** au program handles the set-up, while **proc\_uf** manages the processing. Basic instructions for these steps are outlined below, with more details to follow.

1. Use "rpar" to load your chosen experiment. Currently, four parameter sets are available: UFCOSY, UFTOCSY, UFDQS, and UFHSQC.
2. Please enter "init\_uf" in the TopSpin command line or initiate the experiment setup using "xaua":
  - a. Specify the spectral width in the UF dimension ( $^{13}\text{C}$  spectral range for HSQC spectra).
  - b. Indicate whether dummy scans should be acquired.
  - c. Indicate the offsets for the nuclei involved in the experiment ( $^1\text{H}$  and/or  $^{13}\text{C}$ ).
  - d. Start acquisition directly or with "zg".
3. Process with "xaup" or "proc\_uf": setup using "xaua":
  - a. The processed data within the primary experiment number includes frequency domain data in the direct UF dimension and time domain data in the indirect FT dimension.
  - b. A new experiment is created containing fully processed data in both dimensions (frequency domain data). The experiment number is expno+1000.
  - c. Automatic shearing of the data occurs if requested. Manual shearing is also possible; if uncertain, process with a zero shearing factor.
4. Final spectra calibration requires the usage of the au program "calib\_uf":
  - a. Create a peaklist containing only two 2D peaks for calibration purposes.
  - b. Type "calib\_uf" in the command line of TopSpin.
  - c. Provide the calibrated frequencies of the two peaks in both dimensions as input.

### 3. Highly-Resolved HSQC Using Pure Shift NMR

#### a. Pure Shift HSQC (PS-HSQC)



**Figure 8:** Comparison between conventional (left) and pure shift (right) HSQC spectra of Cyclosporine. The pure shift HSQC spectrum exhibits significantly enhanced peak resolution. One-dimensional proton slices extracted from the 2D-HSQC spectra are also shown, highlighting the improved spectral clarity in the pure shift experiment achieved by eliminating the homonuclear proton couplings.

#### Application:

Real-time pure shift acquisition offers a substantial improvement in spectral resolution and a modest enhancement in sensitivity compared to conventional HSQC experiments. Pure Shift NMR spectroscopy effectively suppresses homonuclear scalar couplings, enabling the acquisition of  $^1\text{H}$ - $^{13}\text{C}$  HSQC spectra that reflect only chemical shifts - free from multiplet structures - in both dimensions. This results in significantly cleaner and more interpretable spectra, representing a major advancement in resolution.

#### Example Spectrum:

Figure 8 is the view of the conventional (left) and pure shift (right)  $^1\text{H}$ - $^{13}\text{C}$  HSQC spectra of Cyclosporine. The pure shift spectrum demonstrates enhanced resolution by eliminating multiplet structures, allowing clearer identification of individual peaks.

#### Bruker Parameter Set:

The parameter set **HSQCEDETGPSISP2.2\_BBHD** enables the acquisition of an edited HSQC spectrum with broadband homonuclear decoupling, optimized for high-resolution in the direct  $^1\text{H}$  dimension (BBHD = BroadBand Homonuclear Decoupling).<sup>16-19</sup>

#### Key Parameters:

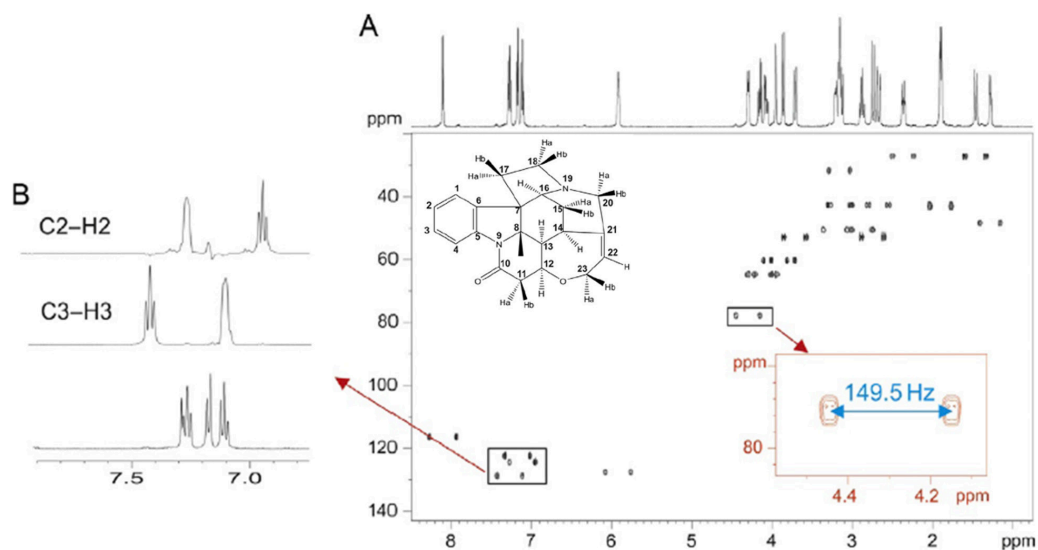
**AQ** (acquisition time): The acquisition time must be sufficiently long to achieve a meaningful increase in resolution, with an upper limit of <250 ms

**L0 (Number of Acquisition Blocks):** Increasing L0 helps suppress coupling evolution but may lead to line broadening due to cumulative imperfections in the refocusing blocks. Conversely, lower L0 values reduce the number of interruptions caused by the refocusing blocks but may result in more pronounced decoupling sidebands. In practice, L0 should be selected such that the resulting chunk size (D62) falls within the range of 20 to 40 ms.

**CPDPRG2:** This parameter must be set to GARP4 rather than an adiabatic decoupling sequence (e.g., p5m4sp\_4sp.2), as the short acquisition chunks used in this experiment cannot accommodate an adiabatic decoupling cycle.

## 4. HSQC for measurement of Heteronuclear Coupling Constants

### a. CLIP HSQC



**Figure 9:** (A) F2-coupled CLIP-HSQC spectrum of Strychnine recorded on a 500-MHz spectrometer. The one-bond  $^1J_{CH}$  coupling constants are clearly visible as large doublets along the direct dimension, as shown in the inset.

(B) One-dimensional slices extracted from the 2D spectrum, showing distorted signals caused by strong-coupling effects.

### Application:

A straightforward method for determining one-bond  $^1J_{CH}$  coupling constants is to analyse the detected dimension of a conventional HSQC experiment recorded without heteronuclear decoupling during proton acquisition. This approach is known as the F2-coupled CLIP-HSQC (Clean In-Phase Heteronuclear Single Quantum Coherence) experiment. CLIP-HSQC is a refined NMR technique designed to measure heteronuclear couplings between directly bonded nuclei, such as carbon and hydrogen. This method enhances spectral resolution by simplifying the multiple structures caused by proton-proton couplings. A recent development in this field is the real-time broadband proton homo decoupled CLIP-HSQC. This technique allows for the automated measurement of heteronuclear one-bond coupling constants with increased sensitivity and accuracy. The method involves a real-time acquisition protocol that minimizes systematic errors and speeds up the determination of coupling constant. Range of one-bond  $^1J_{CH}$  coupling constants are 120-250 Hz.

### Example Spectrum:

Figure 9 showing the conventional F2-coupled CLIP-HSQC spectrum of Strychnine. Section (A) : F2-Coupled CLIP-HSQC spectrum shows a conventional F2-coupled CLIP-HSQC spectrum of strychnine. The  $^1J_{CH}$  coupling constants are easily measurable due to the large doublet splitting observed along the proton (F2) dimension. The inset highlights one of these doublets, demonstrating the clarity and precision of the coupling constant measurement. The main advantages are direct and simple measurement of  $^1J_{CH}$  values, high digital resolution in the proton dimension and diastereotopic  $CH_2$  groups can be individually analyzed, aiding in detailed structural elucidation. Section (B) : 1D slices extracted from the 2D spectrum. These slices show distorted signals due to strong coupling effects. Strong coupling arises when the chemical shift difference between coupled protons is small relative to their coupling constant, leading to complex multiplet patterns.

### Bruker Parameter Set:

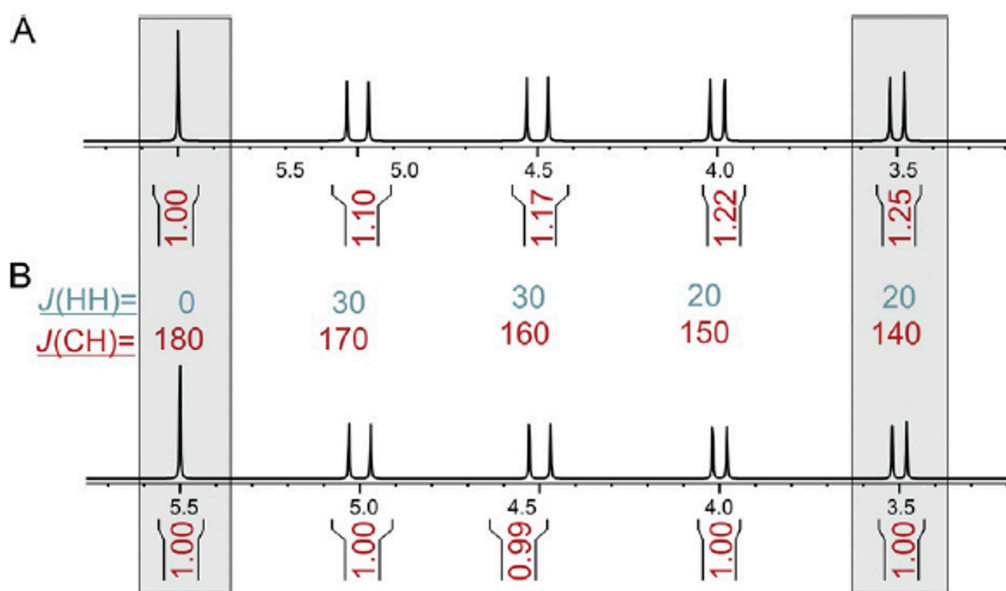
**HSQCCTETGPJCLR** - a specialized parameter set designed for measuring long-range heteronuclear coupling constants using a constant-time HSQC approach.<sup>20</sup>

### Key Parameters:

The following parameters were used in these experiments: Number of complex data points in  $^1H$  (F2) dimension : 2048. Number of t1 increments (F1 dimension) : 256. Number of scans per increment: 8. Relaxation Delay: 1.7 seconds.

## 5. Quantitative HSQC

### a. Perfect HSQC (J(HH)-Compensated INEPT)



**Figure 10:** From a single- $\Delta$  140-Hz Perfect-HSQC experiment. Results: A pure in phase spectrum was obtained. Figure A: Shows with peak volume differences up to 25% indicating some degree of intensity variation. Figure B: Shows significantly improved uniformity, with peak volume differences reduced to just 2% by combining four datasets recorded with different  $\Delta$  values.

#### Application:

In conventional HSQC spectra, peak intensities of different protons are variably modulated as a function of each individual  $J(\text{HH})$  coupling pattern. This non-uniform dependence introduces a common source of error in the integration and quantification of signal intensities. In contrast, the perfect-HSQC experiment which employs J-compensated INEPT transfers, addresses this issue by effectively suppressing  $J(\text{HH})$  modulations. As a result, it delivers more consistent and accurate peak intensities improving the reliability of quantitative NMR measurements.

#### Example Spectrum:

To evaluate the  $^1J_{\text{CH}}$ -compensated intensity strategy based on optimized selection of multiple polarization transfer delays, a perfect-HSQC spectrum was simulated for a spin system containing several protons with  $J(\text{HH})$  couplings ranging from 10 to 30 Hz and  $^1J_{\text{CH}}$  couplings between 120 and 180 Hz. In Figure 10A, a single- $\Delta$  140-Hz perfect-HSQC experiment, yields a pure in-phase spectrum, though with peak volume differences of up to 25% across the range of  $J_{\text{CH}}$  values. In contrast, Figure 10B presents the  $^1J_{\text{CH}}$ -compensated perfect-HSQC spectrum obtained by combining four datasets acquired with  $\Delta$  values of 2.94 ms (170 Hz), 2.86 ms (175 Hz), 2.86 ms (175 Hz), and 5.88 ms (85 Hz) where  $\Delta = 1/(2 \cdot ^1J_{\text{CH}})$ . This multi- $\Delta$  approach significantly improves uniformity, resulting in intensity differences of less than 2% across the entire  $^1J_{\text{CH}}$  range 120 and 180 Hz.

#### Bruker Pulse Sequence:

**hsqcetgppesp.2** - a Perfect Echo HSQC sequence designed to suppress  $J(\text{HH})$  coupling effects, enabling cleaner, in-phase spectra ideal for quantitative analysis.<sup>21</sup>

#### Key Parameters:

Different  $\Delta$  values can be set by adjusting CNST2 to 85, 170 or 175 Hz, respectively.

## Conclusions

Since its introduction over four decades ago, the HSQC pulse sequence has undergone extensive refinement, with ongoing innovations continuing to expand its capabilities. This application note has highlighted recent developments across a wide spectrum of HSQC methodologies, including structure verification and elucidation, accelerated data acquisition, high-resolution techniques, and quantitative approaches for precise measurement of  $^1J_{\text{CH}}$  coupling constants. A variety of Bruker parameter sets tailored to these applications have also been shown, along with representative spectra to demonstrate their effectiveness. These advancements underscore the dynamic nature of pulse sequence development, reaffirming HSQC's role as a versatile and evolving tool for addressing diverse analytical challenges in NMR spectroscopy.

HSQC Variant	Bruker Parameter Set
Conventional HSQC	HSQCETGP
Sensitivity-enhanced HSQC	HSQCETGPSI
Multiplicity-edited HSQC	HSQCEDETGPSISP
HSQC with COSY Cross Peak Suppression	hsqcedetgpsisp2.3 (Pulse Sequence)
HSQC with adiabatic Decoupling	HSQCETGPSISP2_ADIA
NUS Sampling	---
Ultrafast HSQC	UFHSQC
Pure Shift HSQC	HSQCEDETGPSISP2.2_BBHD
CLIP HSQC	HSQCCTETGPJCLR
Perfect HSQC	hsqcetgppesp.2 (Pulse Sequence)

**Table 1:** Table of Bruker HSQC NMR variants and their parameter sets

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