J-difference Editing Toolkit (JET)

TECHNICAL WHITE PAPER:
J-difference Editing Toolkit (JET) and the Novel Spectrum Registration Methods

OVERVIEW

The J-difference Editing Toolkit (JET) is a software package designed for the batch analysis of J-difference editing magnetic resonance spectroscopy (MRS) data, such as MEGA-PRESS MRS spectra. JET is capable to process raw data acquired from all major clinical (i.e., Siemens, GE, Philips) and preclinical (i.e., Bruker) MRI scanners. The first publicly available version (in 2020) of JET (JET v1.0) releases the Bruker-compatible functionalities, while the interface to the data from other vendors will be released in upcoming versions. JET is implemented in MATLAB, and is distributed as executables, except for the configuration functions being distributed as source code, allowing necessary users modifications. JET is fully automated and does not require user intervention to minimize software operator variances in MRS data quantification.

Prior to this first release, preliminary versions containing partial functionalities of JET has already been used in various studies and facilitated findings that reached publication (e.g., [1-2]). The major improvement in the current version beyond its ancestors is a more comprehensive and rigorous spectrum registration technique which will be introduced in great detail.

This technical white paper describes the purpose, scope, and especially the methods adopted in JET v1.0.

MODULES AND DATA STRUCTURE

The overarching purpose of JET is to provide a complete toolbox that performs registration and metabolite quantification in MR spectroscopy. The JET software consists of five sequential modules for data processing, while all data are stored under the same data structure (**Figure 1**).

MODULE 1: INITIALIZATION

The initialization module, as its name suggests, initializes the workspace to facilitate further data loading and processing. It defines where the raw data are located, where to save the report, where to store the processed data, etc.

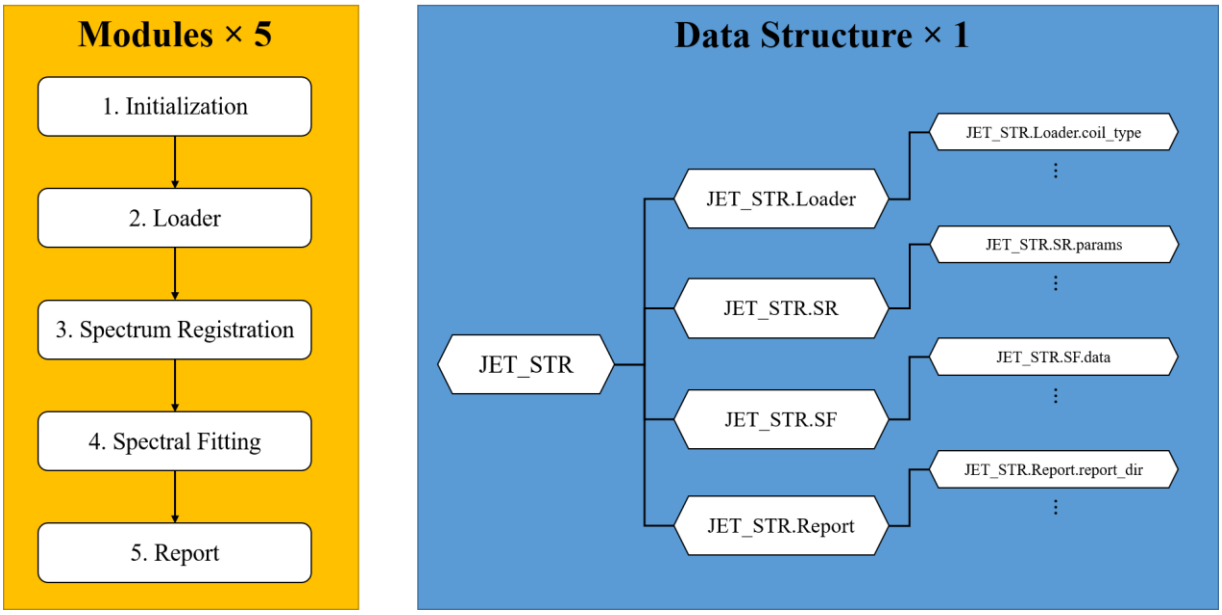


Figure 1. Overview of the modules and data structure in JET.

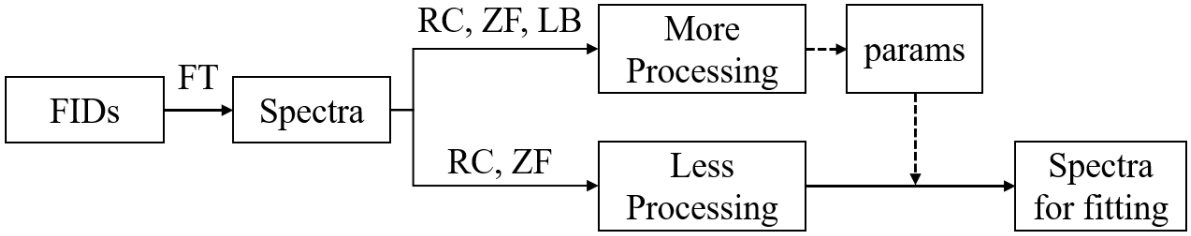
MODULE 2: LOADER

The loader module loads the data from external files into a common structure as defined in **Figure 1**. Two loading options have been implemented: 1) directly loading from raw data files and 2) converting from data structures processed by another software. Configurations are first initialized using approximated parameters and later updated with readouts from the loaded files or structures. Currently in JET v1.0, we have a loading interface specifically designed for data acquired with Bruker scanners, and a converter interface specifically designed for the GANNET [3] data structure. In the future releases, additional loaders and converters covering the other major vendors and software will be included.

MODULE 3: SPECTRUM REGISTRATION (SR)

In the most common schemes of MRS, two sets of acquisitions are performed: one in which a pair of frequency-selective editing pulses refocus the evolution of a coupling of interest (resulting in the ON data), and one in which the coupling is allowed to evolve without intervention (resulting in the OFF data) [4]. When analyzed in the frequency domain, the OFF spectra and the DIFF spectra (i.e., the difference between the ON and OFF spectra) are respectively used to quantify the concentrations of certain metabolites (e.g., Creatine and Choline with the OFF spectra and GABA and Glx with the DIFF

spectra). Such quantifications heavily rely on proper processing and accurate alignment among individual spectra.



RC: remove compensate points (typically first 68 points in FID)
ZF: zero-filling
LB: line-broadening
params: parameters of frequency and zero-order phase shift

Figure 2. Principle of JET spectrum registration.
In JET spectrum registration, two sets of spectra are processed and propagated throughout the process. The "more processing" version is used as a high-SNR representation with which the shifting parameters are calculated while the "less processing" version are corrected based on these calculated parameters and are subsequently used for spectra fitting.

The goal of JET spectrum registration is to combine each individual spectrum from all coil channels and repetitions, after proper removal of frequency and zero-order phase differences, to result in one single ON spectrum and one single OFF spectrum.

The principle of JET spectrum registration, as illustrated in **Figure 2**, is to use a line-broadened version of the spectra (higher SNR, less authentic) as a representation of the version without line-broadening (lower SNR, more authentic) to calculate the necessary frequency and phase shift, and then apply the shift to the more authentic version to prepare it as the input for spectral fitting. In this way we ensure minimal manipulation and great preservation of the signal.

The spectrum registration module consists of three steps: coil-channel combination, within-ON/OFF registration, and ON-to-OFF registration. The first two steps are performed separately on the ON and OFF spectra, whereas the last step intends to optimize over both the ON and OFF spectra together.

Module 3.1: Coil-channel Combination

The incoming data, whether they are the ON or the OFF spectra, shall be three-dimensional (3D) spectra of the following shape:

number of coil channels × number of repetitions × spectra length

Coil-channel combination aims to remove the frequency and phase differences that are specific to coil-channel but independent of repetitions. This step is applied to the ON and OFF spectra separately.
The strategy is to use the inter-repetition mean 2D spectra as the representation for each coil channel to calculate the coil-channel-specific corrections required, and apply these corrections over all repetitions in the same coil channel. The inter-repetition mean spectra has the following shape:

number of coil channels × spectra length

The specific procedures carried out include:

1. Use ACME [5] as phase correction initialization (**Figure 3, row 2**).
2. Use ICOSHIFT [6] as frequency correction initialization (**Figure 3, row 3**).
3. JET SR algorithm to correct for frequency and zero-order phase (**Figure 3, row 4**).
4. Channel combination by taking mean over coil channel.

The output of the coil-channel combination step is the 2D coil-channel combined spectra of the following shape:

number of repetitions × spectra length

The JET SR algorithm for coil-channel combination (applied separately to the ON and OFF spectra) uses a least square fitting method to minimize the difference between an iteratively updated *spectra template* and the *coil-channel-specific mean spectra* with three degrees of freedom: frequency, zero-order phase, and amplitude. This process estimates the necessary frequency, zero-order phase and amplitude for the correction, and such coil-channel-specific frequency and phase shifts are applied to every repetition within each coil channel to generate aligned spectra. In contrast, the amplitude corrections are only used to facilitate accurate estimation of frequency and phase shift, as well as for visualization and quantification of coil-channel sensitivity (**Figure 4, column 2**), but are not propagated to subsequent steps in order to ensure data authenticity (**Figure 4, column 3**).

- Here, the *spectra template*, unless otherwise defined, is approximated with the mean spectrum over the *coil-channel-specific mean spectra* at each iteration after the shift parameters calculated from the previous iterations are applied. As a result, the spectrum registration process is guiding the spectra to minimize the frequency and zero-order phase difference across coil channels.

- The *coil-channel-specific mean spectra* are taken as high-SNR representations of the spectra from each coil channel, such that we can generate more robust estimations of the coil-channel-specific shift parameters. After these parameters are faithfully estimated, they are applied to each individual spectrum within the respective coil channel for corrections.

Mathematically, in the JET SR algorithm for Coil-channel Combination, if we denote x as a spectrum to be registered, y as the template spectrum, and $\hat{y}$ as the numerically approximated template spectrum, we have

$$y(\Delta f, \Delta\varphi, A) = \text{fft}(A \cdot \text{ifft}(x) \cdot e^{2\pi(i \cdot t \cdot \Delta f \cdot B \cdot \Upsilon) + i \cdot \Delta\varphi})$$
$$\hat{y}(\widehat{\Delta f}, \widehat{\Delta\varphi}, \hat{A}) = \text{fft}(\hat{A} \cdot \text{ifft}(x) \cdot e^{2\pi(i \cdot t \cdot \widehat{\Delta f} \cdot B \cdot \Upsilon) + i \cdot \widehat{\Delta\varphi}})$$
$$\{\widehat{\Delta f}, \widehat{\Delta\varphi}, \hat{A}\} = \text{argmin}_{\widehat{\Delta f}, \widehat{\Delta\varphi}, \hat{A}}(||y - \hat{y}||^2)$$

where i denotes the unit imaginary number, t denotes the time in the time domain, B denotes the field strength, Υ denotes the gyromagnetic ratio of hydrogen, Δf denotes the actual frequency shift compared to the template, $\Delta\varphi$ denotes the actual phase shift compared to the template, A denotes the actual amplitude compared to the template, $\widehat{\Delta f}$ denotes the estimated frequency shift compared to the template, $\widehat{\Delta\varphi}$ denotes the estimated phase shift compared to the template, $\hat{A}$ denotes the estimated amplitude compared to the template.

The estimated $\widehat{\Delta f}$ and $\widehat{\Delta\varphi}$ are

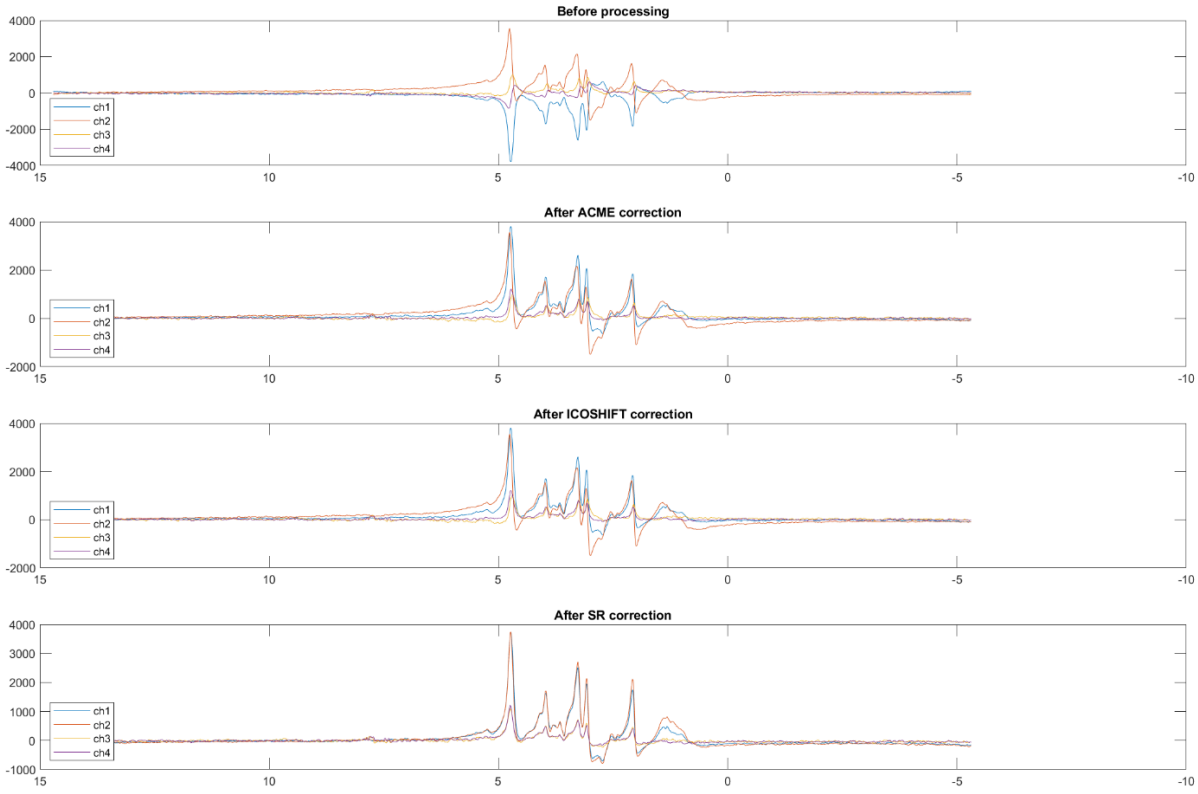


Figure 3. The evolution of sample OFF spectra during coil-channel combination.
Four-coil-channel OFF spectra, acquired with Bruker BioSpec 94/30 Cryoprobe, are used as an example to demonstrate the coil-channel combination process. The inter-repetition mean of each coil channel are shown in different colors. ACME (**row 2**) is used for initial phase correction while ICOSHIFT (**row 3**) is used for initial frequency correction. The JET SR algorithm (**row 4**) performs finer optimization over the

frequency and phase alignments. The unequal amplitudes of the spectra across coil channels result from the coil sensitivity difference, and are taken into account in the JET SR algorithm (to be addressed).

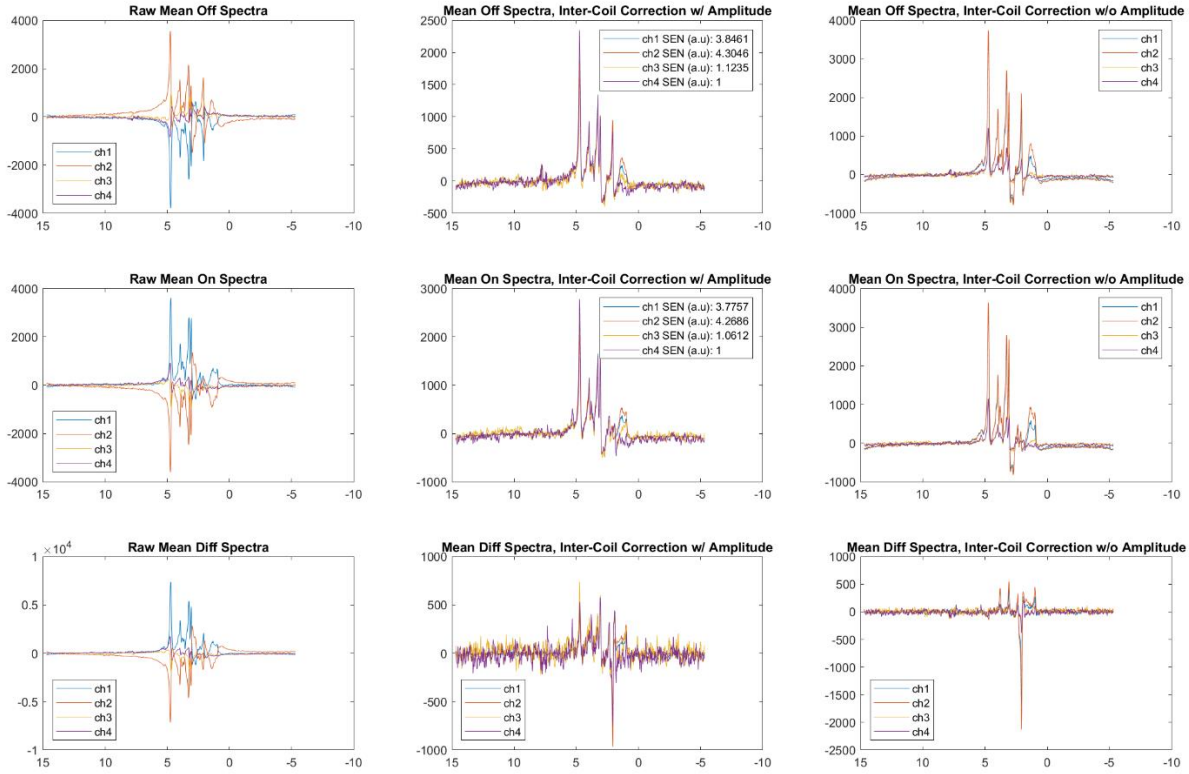


Figure 4. Handling unequal coil sensitivity during coil-channel combination.
Four-coil-channel ON, OFF, and DIFF spectra, acquired with Bruker BioSpec 94/30 Cryoprobe, are used as an example to demonstrate how JET handles unequal coil sensitivity during coil-channel combination. Amplitudes of the coil-channel-specific mean spectra are used as an additional degree of freedom during spectrum registration to ensure better estimation of shift parameters for frequency and phase alignment (**column 2**), but such amplitude corrections are not propagated to subsequent steps (**column 3**). As a beneficial side product of incorporating coil-channel-specific amplitudes into the spectrum registration among coil channels, coil sensitivities can be estimated (**row 1 and row 2 in column 2**).
Note: "w/ Amplitude" and "w/o Amplitude" in subfigure captions refer to whether the amplitude corrections are applied when generating the spectra in the subfigures. It does not refer to whether the amplitudes are used as a degree of freedom during parameter estimation.

Module 3.2: Within-ON/OFF Registration

The incoming data, whether they are the ON or the OFF spectra, shall be 2D spectra of the following shape:

$$\underline{\text{number of repetitions}} \times \underline{\text{spectra length}}$$

Within-ON/OFF registration aims to remove the frequency and phase differences that are specific to each repetition. This step is applied to the ON and OFF spectra separately.

The strategy is to use a repetition-wise smoothed 1D spectrum as the representation for each repetition to calculate the repetition-specific corrections required, and apply the corrections for each respective repetition. Each repetition-wise smoothed spectrum has the following shape:

$$1 \times \text{spectra length}$$

The specific procedures carried out include:

1. Use ACME [5] as phase correction initialization (**Figure 5, row 2**).
2. Use ICOSHIFT [6] as frequency correction initialization (**Figure 5, row 3**).
3. JET SR algorithm to correct for frequency and zero-order phase (**Figure 5, row 4**).

The output of the within-ON/OFF registration step is the 2D repetition-wise registered spectra of the following shape:

$$\text{number of repetitions} \times \text{spectra length}$$

We may as well take the mean over all repetitions at this step since spectra in all repetitions are registered already, but we nevertheless decide to save all spectra for data preservation purposes.

The JET Spectrum Registration algorithm for within-ON/OFF registration (applied separately to the ON and OFF spectra) uses a least square fitting method to minimize the difference between an iteratively updated *spectra template* and the *repetition-specific representative spectra* with two degrees of freedom: frequency and zero-order phase. This process estimates the necessary frequency and zero-order phase for the correction, and such repetition-specific frequency and phase shifts are applied to every repetition to generate aligned spectra.

- Here, the *spectra template*, unless otherwise defined, is approximated with the mean spectrum over the spectra from all repetitions at each iteration after the shift parameters calculated from the previous iterations are applied. As a result, the spectrum registration process is guiding the spectra to minimize the frequency and zero-order phase difference across repetitions.

- The *repetition-specific representative spectra*, implemented with inter-repetition gaussian-smoothing (smoothing over the time axis), are taken as high-SNR representations of the spectra from each repetition, such that we can generate more robust estimations of the repetition-specific shift parameters. After these parameters are faithfully estimated, they are applied to each individual spectrum for corrections.

- The optimization is not computed globally, but rather over the range of 0~4.5 ppm. This frequency range is adjustable.

Mathematically, in the JET SR algorithm for Within-ON/OFF Registration, if we denote x as a spectrum to be registered, y as the template spectrum, and $\hat{y}$ as the numerically approximated template spectrum, we have

$$y(\Delta f, \Delta\varphi) = \mathrm{fft}(\mathrm{ifft}(x) \cdot \mathrm{e}^{2\pi(i \cdot t \cdot \Delta f \cdot B \cdot \Upsilon) + i \cdot \Delta\varphi})$$
$$\hat{y}(\widehat{\Delta f}, \widehat{\Delta\varphi}) = \mathrm{fft}(\mathrm{ifft}(x) \cdot e^{2\pi(i \cdot t \cdot \widehat{\Delta f} \cdot B \cdot \Upsilon) + i \cdot \widehat{\Delta\varphi}})$$
$$\{\widehat{\Delta f}, \widehat{\Delta\varphi}\} = \mathrm{argmin}_{\widehat{\Delta f}, \widehat{\Delta\varphi}}(||y - \hat{y}||^2)$$

where i denotes the unit imaginary number, t denotes the time in the time domain, B denotes the field strength, Υ denotes the gyromagnetic ratio of hydrogen, Δf denotes the actual frequency shift compared to the template, $\Delta\varphi$ denotes the actual phase shift compared to the template, $\widehat{\Delta f}$ denotes the estimated frequency shift compared to the template, $\widehat{\Delta\varphi}$ denotes the estimated phase shift compared to the template.

Module 3.3: ON-to-OFF Registration and NAA Shifting

The incoming data, whether they are the ON or the OFF spectra, shall be 2D spectra of the following shape:

number of repetitions × spectra length

ON-to-OFF registration aims to remove the frequency and phase differences between the ON spectra and the OFF spectra. This step is applied to the ON spectra only. A follow-up NAA shifting step shifts the frequency of the ON and OFF spectra together using the N-acetylaspartate (NAA) peak as a reference.

The strategy is to use the mean over the ON spectra as a representation to calculate the repetition-specific corrections required, and apply the corrections for each respective repetition within the ON spectra. The mean spectrum has the following shape:

1 × spectra length

The specific procedures carried out include:

1. Use the mean of ON spectra and mean of OFF spectra to find the frequency and phase corrections required to match the former to the latter, and apply the correction over all repetitions of the ON spectra (**Figure 5, row 5**).
2. Use the mean of OFF spectra to find the frequency shift to align the NAA peak to 2 ppm, and apply the correction over all repetitions of both the ON and OFF spectra (**Figure 5, row 5**).
3. Take the mean over the ON spectra and the mean over the OFF spectra

The output of the ON-to-OFF registration and NAA shifting step are two 1D spectra each of the following shape:

1 × spectra length

The JET Spectrum Registration algorithm for ON-to-OFF registration (applied to the ON spectra only) uses a least square fitting method to minimize the difference between the *mean OFF spectrum* and the *mean ON spectrum* with two degrees of freedom: frequency and zero-order phase. This process estimates the necessary frequency and zero-order phase for the correction, and such repetition-specific frequency and phase shifts are applied to every repetition of the ON spectra to generate ON-OFF aligned spectra.

The optimization is computed over the following frequency ranges: -1~0 ppm, 3.05~3.3 ppm, 3.95~4.1 ppm, 6~6.5 ppm. These frequency ranges are adjustable.

Another special technique we use to ensure alignment between the ON and OFF spectra is to put a heavier weight on the optimization around the Creatine peak (3.05~3.3 ppm) for cleaner cancellation of the Creatine signal in the DIFF spectrum. In our default setting, a weighting 3 times heavier than usual is used over that frequency range. Again, this is adjustable.

Mathematically, in the JET SR algorithm for ON-to-OFF Registration, if we denote x as the template spectrum, y as a spectrum to be registered, and $\hat{y}$ as the numerically estimated spectrum, we have

$$y(\Delta f, \Delta\varphi) = \mathrm{fft}(\mathrm{ifft}(x) \cdot e^{2\pi(i \cdot t \cdot \Delta f \cdot B \cdot \Upsilon) + i \cdot \Delta\varphi})$$
$$\hat{y}(\widehat{\Delta f}, \widehat{\Delta\varphi}) = \mathrm{fft}(\mathrm{ifft}(x) \cdot e^{2\pi(i \cdot t \cdot \widehat{\Delta f} \cdot B \cdot \Upsilon) + i \cdot \widehat{\Delta\varphi}})$$
$$\{\widehat{\Delta f}, \widehat{\Delta\varphi}\} = \mathrm{argmin}_{\widehat{\Delta f}, \widehat{\Delta\varphi}}(||y - \hat{y}||^2)$$

where i denotes the unit imaginary number, t denotes the time in the time domain, B denotes the field strength, Υ denotes the gyromagnetic ratio of hydrogen, Δf denotes the actual frequency shift compared to the template, $\Delta\varphi$ denotes the actual phase shift compared to the template, $\widehat{\Delta f}$ denotes the estimated frequency shift compared to the template, $\widehat{\Delta\varphi}$ denotes the estimated phase shift compared to the template.

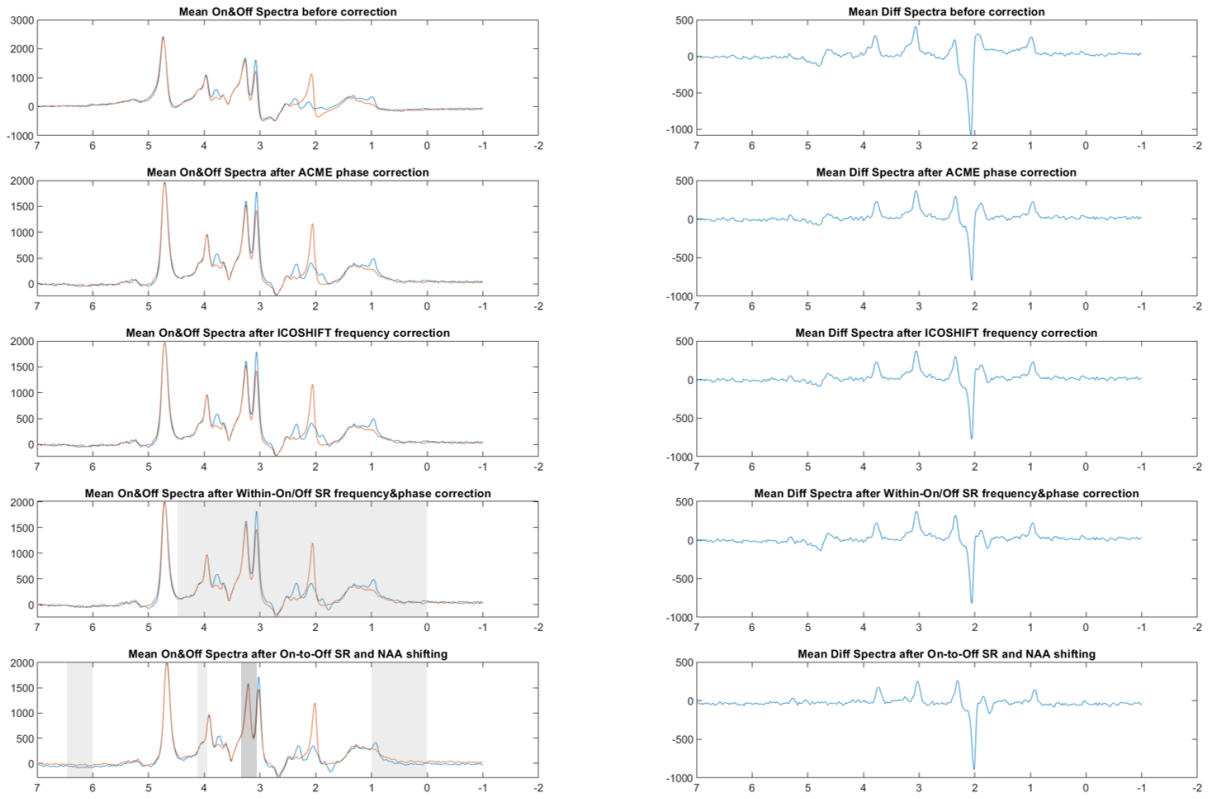


Figure 5. The evolution of sample spectra during within-ON/OFF registration and ON-to-OFF registration.
Four-coil-channel ON, OFF, and DIFF spectra, acquired with Bruker BioSpec 94/30 Cryoprobe, are used as an example to demonstrate the within-ON/OFF registration and ON-to-OFF registration processes. ACME (**row 2**) is used for initial phase correction while ICOSHIFT (**row 3**) is used for initial frequency correction. The JET SR algorithm performs finer optimization over the frequency and phase alignments, both to register the ON and OFF spectra separately (**row 4**) and to register the ON spectra to the OFF spectra (**row 5**). The JET SR algorithm is optimized over selected frequency ranges, as shown in the shaded regions in **row 4** and **row 5**. The frequency range being especially emphasized during optimization of On-to-Off registration is shown in darker shade in **row 5**.

MODULE 4: SPECTRAL FITTING

The goal of JET spectral fitting is to estimate metabolite concentrations.

The incoming data are one non-edited OFF spectrum (after all the proper processing of the JET spectrum registration) and one edited DIFF spectrum.

One popular approach for spectral fitting is to model the OFF and DIFF spectrum each as a linear combination of peaks with given shapes, for example Gaussian or Lorentzian peaks. However, this approach over-simplifies the diverse forms of the real-world

metabolite peaks. To address this issue, we use simulated metabolite basis sets [7] for spectral fitting.

Spectral quantification is performed by solving a separable nonlinear least-squares fitting problem using a modified variable-projection procedure (VARPRO) [8]. Line broadening, amplitude, frequency shift, phase shift, and linear baseline are incorporated as valid degrees of freedom during the fitting process. The OFF spectrum is used to quantify Choline, Creatine, and 1-Naphthaleneacetic acid (NAA), as shown in the right panel in **Figure 6**. The DIFF spectrum is used to quantify gamma-Aminobutyric acid (GABA) as well as Glutamate and Glutamine (Glx), as shown in the left panel in **Figure 6**.

For GABA, co-edition of macromolecule is not taken into account, so that only GABA+ is obtained. JET can further calculate the GABA ratios such as GABA+/GLX and GABA+/CR for cross-subject comparison.

The output of this step are the estimated metabolite levels, will are stored and displayed in the last module, the JET Report.

Mathematically, in the JET spectral fitting algorithm, if we denote y_{DIFF}, y_{OFF} respectively as the DIFF spectrum and OFF spectrum properly processed up until the beginning of the spectral fitting module, x_{Cho}, x_{Cr}, x_{NAA}, x_{GABA}, x_{Glx} as the simulated spectra for these five metabolites, and $\widehat{y_{DIFF}}$, $\widehat{y_{OFF}}$ respectively as the numerically fitted DIFF spectrum and OFF spectrum, we have

$$\begin{aligned} &y_{DIFF}[f_{DIFF\_metabolite}](\Delta A, \mathrm{R2}, \Delta f, \Delta\varphi, \mathrm{BL_{0th}}, \mathrm{BL_{1st}}) \\ &\quad = \mathrm{fft}\left(\mathrm{ifft}\left(x_{DIFF\_metabolite}\right) \cdot e^{-\mathrm{R2}\cdot t} \cdot e^{2\pi(i\cdot t\cdot \Delta f\cdot B\cdot \Upsilon)+i\cdot\Delta\varphi}\right) + \mathrm{BL_{0th}} + \mathrm{BL_{1st}} \cdot f \end{aligned}$$

$$\begin{aligned} &\widehat{y_{DIFF}}[f_{DIFF\_metabolite}]\left(\widehat{\Delta A}, \widehat{\mathrm{R2}}, \widehat{\Delta f}, \widehat{\Delta\varphi}, \widehat{\mathrm{BL_{0th}}}, \widehat{\mathrm{BL_{1st}}}\right) \\ &\quad = \mathrm{fft}\left(\mathrm{ifft}\left(x_{DIFF\_metabolite}\right) \cdot e^{-\widehat{\mathrm{R2}}\cdot t} \cdot e^{2\pi\left(i\cdot t\cdot \widehat{\Delta f}\cdot B\cdot \Upsilon\right)+i\cdot\widehat{\Delta\varphi}}\right) + \widehat{\mathrm{BL_{0th}}} + \widehat{\mathrm{BL_{1st}}} \cdot f \end{aligned}$$

$$\left\{\widehat{\Delta A}, \widehat{\mathrm{R2}}, \widehat{\Delta f}, \widehat{\Delta\varphi}, \widehat{\mathrm{BL_{0th}}}, \widehat{\mathrm{BL_{1st}}}\right\} = \mathrm{argmax}_{\widehat{\Delta A}, \widehat{\mathrm{R2}}, \widehat{\Delta f}, \widehat{\Delta\varphi}, \widehat{\mathrm{BL_{0th}}}, \widehat{\mathrm{BL_{1st}}}}\left(||y_{DIFF}[f_{DIFF\_metabolite}] - \widehat{y_{DIFF}}[f_{DIFF\_metabolite}]||^2\right)$$

$$\begin{aligned} &y_{OFF}[f_{OFF\_metabolite}](\Delta A, \mathrm{R2a}, \mathrm{R2b}, \Delta f, \Delta\varphi, \mathrm{BL_{0th}}, \mathrm{BL_{1st}}) \\ &\quad = \mathrm{fft}\left(\mathrm{ifft}\left(x_{OFF\_metabolite}\right) \cdot e^{-\mathrm{R2a}\cdot t} \cdot e^{(-\mathrm{R2b}\cdot t)^2} \cdot e^{2\pi(i\cdot t\cdot \Delta f\cdot B\cdot \Upsilon)+i\cdot\Delta\varphi}\right) + \mathrm{BL_{0th}} + \mathrm{BL_{1st}} \cdot f \end{aligned}$$

$$\begin{aligned} &\widehat{y_{OFF}}[f_{OFF\_metabolite}]\left(\widehat{\Delta A}, \widehat{\mathrm{R2a}}, \widehat{\mathrm{R2b}}, \widehat{\Delta f}, \widehat{\Delta\varphi}, \widehat{\mathrm{BL_{0th}}}, \widehat{\mathrm{BL_{1st}}}\right) \\ &\quad = \mathrm{fft}\left(\mathrm{ifft}\left(x_{OFF\_metabolite}\right) \cdot e^{-\widehat{\mathrm{R2}}\cdot t} \cdot e^{(-\widehat{\mathrm{R2}}\cdot t)^2} \cdot e^{2\pi\left(i\cdot t\cdot \widehat{\Delta f}\cdot B\cdot \Upsilon\right)+i\cdot\widehat{\Delta\varphi}}\right) + \widehat{\mathrm{BL_{0th}}} + \widehat{\mathrm{BL_{1st}}} \cdot f \end{aligned}$$

$$\left\{\widehat{\Delta A}, \widehat{\mathrm{R2a}}, \widehat{\mathrm{R2b}}, \widehat{\Delta f}, \widehat{\Delta\varphi}, \widehat{\mathrm{BL_{0th}}}, \widehat{\mathrm{BL_{1st}}}\right\} = \mathrm{argmax}_{\widehat{\Delta A}, \widehat{\mathrm{R2a}}, \widehat{\mathrm{R2b}}, \widehat{\Delta f}, \widehat{\Delta\varphi}, \widehat{\mathrm{BL_{0th}}}, \widehat{\mathrm{BL_{1st}}}}\left(||y_{OFF}[f_{OFF\_metabolite}] - \widehat{y_{OFF}}[f_{OFF\_metabolite}]||^2\right)$$

where i denotes the unit imaginary number, t denotes the time in the time domain, f denotes the frequency in the frequency domain, B denotes the field strength, Υ denotes the gyromagnetic ratio of hydrogen, Δf denotes the actual frequency shift compared to the template, $\Delta\varphi$ denotes the actual phase shift compared to the template, $\widehat{\Delta f}$ denotes

the estimated frequency shift compared to the template, $\widehat{\Delta\varphi}$ denotes the estimated phase shift compared to the template, $\mathrm{BL_{0th}}$ and $\widehat{\mathrm{BL_{0th}}}$ denote the true and estimated 0th-order baseline, $\mathrm{BL_{1st}}$ and $\widehat{\mathrm{BL_{1st}}}$ denote the true and estimated 1st-order baseline, $\mathrm{R2}$ and $\widehat{\mathrm{R2}}$ denote the true and estimated 1st-order Gaussian line broadening terms, $\mathrm{R2a}$ and $\widehat{\mathrm{R2a}}$ denote the true and estimated 1st-order Voigt line broadening terms, $\mathrm{R2b}$ and $\widehat{\mathrm{R2b}}$ denote the true and estimated 2nd-order Voigt line broadening terms, $[f_{DIFF\_metabolite}]$ and $[f_{OFF\_metabolite}]$ respectively denotes the frequency range for a particular metabolite (Cho, Cr and NAA for DIFF; Glx and GABA for OFF).

It shall be notices that spectral fitting over the DIFF spectrum and OFF spectrum are implemented under different settings. For DIFF fitting, Gaussian line broadening is implemented and numerically solved for. In contrast, for OFF fitting, Voigt line broadening is used instead.

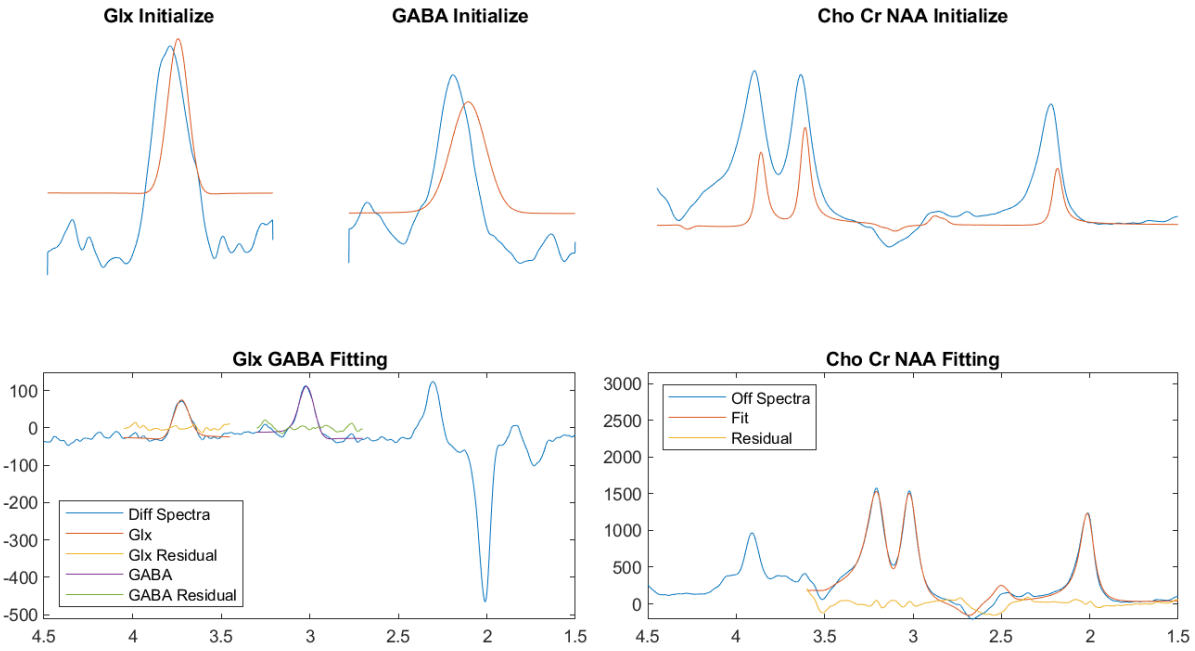


Figure 6. Demonstration of spectral fitting.
The DIFF spectrum is used to fit Glx and GABA, while the OFF spectrum is used to fit Choline, Creatine and NAA.

MODULE 5: REPORT

Each run of JET automatically generates a quality assurance summary report (left panel in **Figure 7**) and a metabolite quantification summary report (right panel in **Figure 7**). As

long as the data are provided correctly, analysis of data from each subject results in one run of JET.

The quality assurance summary report visualizes the quality of spectrum registration on the repetition level, allowing for visual inspections of the global and local patterns. The metabolite quantification summary report, on the other hand, records the quantified metabolite concentrations as generated in the previous spectral fitting step.

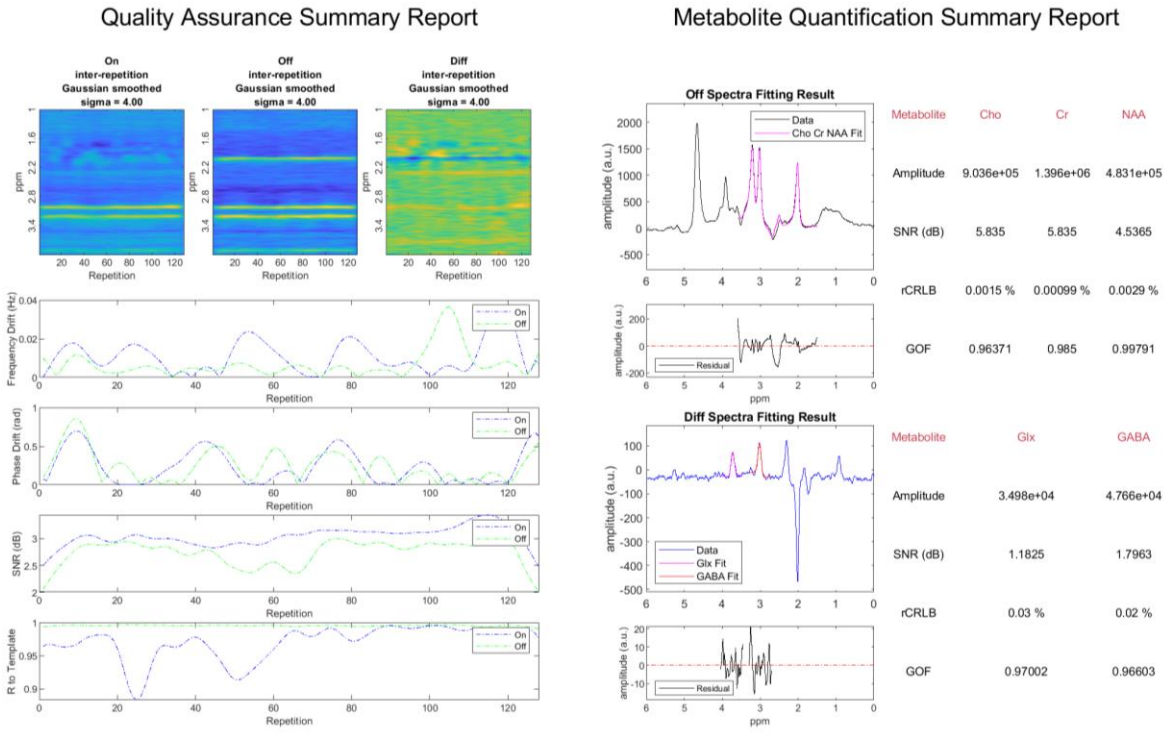


Figure 7. Sample JET reports.
A pair of reports will be generated each time the data from one subject is analyzed. The pair includes a quality assurance summary report (left panel) and a metabolite quantification summary report (right panel).

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References

[1] Riggle, Brittany A., et al. "MRI demonstrates glutamine antagonist-mediated reversal of cerebral malaria pathology in mice." Proceedings of the National Academy of Sciences 115.51 (2018): E12024-E12033.

[2] Provenzano, Frank A., et al. "Hippocampal pathology in clinical high-risk patients and the onset of schizophrenia." Biological Psychiatry 87.3 (2020): 234-242.

[3] Edden, Richard AE, et al. "Gannet: A batch-processing tool for the quantitative analysis of gamma-aminobutyric acid–edited MR spectroscopy spectra." Journal of Magnetic Resonance Imaging 40.6 (2014): 1445-1452.

[4] Harris, Ashley D., Muhammad G. Saleh, and Richard AE Edden. "Edited 1H magnetic resonance spectroscopy in vivo: Methods and metabolites." Magnetic Resonance in Medicine 77.4 (2017): 1377-1389.

[5] Chen, Li, et al. "An efficient algorithm for automatic phase correction of NMR spectra based on entropy minimization." Journal of Magnetic Resonance 158.1-2 (2002): 164-168.

[6] Savorani, Francesco, Giorgio Tomasi, and Søren Balling Engelsen. "icoshift: A versatile tool for the rapid alignment of 1D NMR spectra." Journal of magnetic resonance 202.2 (2010): 190-202.

[7] de Graaf, Robin A., Golam MI Chowdhury, and Kevin L. Behar. "Quantification of high-resolution 1H NMR spectra from rat brain extracts." Analytical chemistry 83.1 (2011): 216-224.

[8] Poullet, Jean-Baptiste, et al. "An automated quantitation of short echo time MRS spectra in an open source software environment: AQSES." NMR in Biomedicine: An International Journal Devoted to the Development and Application of Magnetic Resonance In vivo 20.5 (2007): 493-504.