Towards Reproducible Computation in Magnetic Resonance Spectroscopy

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Towards Reproducible Computation in Magnetic Resonance Spectroscopy

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1 Abstract

Nuclear Magnetic Resonance Spectroscopy is an analytical technique which uses the properties of magnetic fields and the magnetic moment of the nucelus to identify and quantify the molecular composition of samples [13]. In the clinical domain, this technique can be used to identify and quantify the concentration of metabolites inside the brain in a specifically targeted voxel using MRI machines. However, quantifying these metabolites remains a challenging task and can be greatly dependent of the initial quality of the acquired spectrum [8], [3]. This work aims to link the quality of a nuclear magnetic resonance spectrum with the reliability of the metabolite concentration computed by the cQUEST algorithm.

La Spectroscopie par Résonance Magnétique Nucléaire est une technique analytique qui se repose sur les propriétés des champs magnétiques et du moment magnétique du noyeau atomique afin d'identifier et de quantifier la composition moléculaire d'échantillons [13]. Dans le domaine clinique, cette technique peut être utilisée pour identifier et quantifier la concentration de métabolites du cerveau au sein de voxels spécifiquement sélectionés en utilisant des machines IRM. Cependant, la quantification de ces métabolites reste une tâche difficile et peut être grandement dépendante de la qualité initiale du spectre acquis [8], [3]. Ce travail a pour objectif de relier la qualité du spectre de résonance magnétique nucléaire avec la fiabilité de la concentration en métabolite calculée par l'algorithme cQUEST.

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2 Acknowledgements

These 3 months at the CREATIS laboratory were a very enriching experience. I would like to thank Gaël Vila my supervisor who was always here to help me go through this project step by step with rigor, Hélène Ratiney for her expertise in magnetic resonance spectroscopy and the fascinating aspects of her field she made me discover, and Sorina Pop for her knowledge of software engineering and architecture with the VIP platform she manages.

Overall I was surrounded with very joyful and smart people, be it the other interns, the PhD students or permanent staff. It was a delight working here.

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3 Introduction

3.1 General context

This internship was conducted as part of my second year in the biomedical engineering track at the Phelma engineering school where I am specializing in medical imaging.

The internship took place at the CREATIS laboratory (Centre de Recherche en Acquisition et Traitement de l'Image pour la Santé) which is a Mixed Research Unit (UMR) between the CNRS, INSERM, INSA Lyon, Université Lyon I and Université Jean Monnet Saint-Etienne. It employs around 200 persons, including roughly 100 permanent staff (researchers, engineers, administrative staff) and 100 impermanent employees (PhD students, post-doctoral researchers and interns).

CREATIS hosts research groups focusing on medical imaging using MRI, ultrasounds, tomography, optics, simulations and machine learning.

I was an intern at VIP. VIP stands for Virtual Imaging Platform which is "a web portal for medical simulation and image data analysis" [1].

This platforms hosts several applications developed for medical imaging and clinical research such as magnetic resonance spectroscopy quantification algorithm. In October 2022, VIP counted 1445 registered users from 83 countries and approximately 20 applications available as a service. The team regularly performs technology watch and present their work at international conferences.

The platform members started a project within VIP named ReproVIP in january 2022. ReproVIP aims to study the reproducibility of computational workflows within the platform. Because these applications are complex and able to run on different machines, other scientists may have trouble reproducing the results presented on papers, which can hinder the ability to verify scientific results in peer reviewing and generally slow down scientific progress. This is a common problem amongst many fields in science, sometimes designated as a "Reproducibility Crisis"[2].

3.2 Organization

During the internship I was assigned many tasks. To keep track of what to do and follow the progress of the internship, I used Trello which is what the VIP team also uses. It

makes it possible to create cards with notes and organize them, the VIP team can also view them and add other cards.

There are roughly weekly scheduled meetings within the VIP team. When I had questions I could see my supervisor in his office or talk to him and other colleagues using Slack.

The studies that were conducted for this project rely heavily on computations over large amount of data. This was possible thanks to the distributed cloud computing EGI e-infrastructure on which the VIP platform is hosted. This is detailed in section 8.1.

3.3 Magnetic Mesonance Spectrocopy

Magnetic Resonance Spectroscopy (MRS) is a non-invasive analytical technique used in various scientific fields such as chemistry, biochemistry, and medicine. It exploits the magnetic properties of atomic nuclei. By subjecting a sample to a strong magnetic field and radiofrequency pulses, the nuclei within the sample resonate at specific frequencies, producing a unique spectrum. [13] In the case of a living organism the spectrum can be fitted and decomposed to reveal information about the types and quantities of different metabolites present in the sample. In medical applications, MRS can be used to study the composition of tissues -mainly metabolites- aiding in the diagnosis and monitoring of various diseases, such as cancer and neurological disorders. For instance a decrease in N-acetyl aspartate concentration is found in patients suffering from Gliomas, Radiation necrosis, Metastases and Lymphoma [14]

The most widely used software for "metabolite quantification" (i.e., estimating metabolite concentrations from a MR spectroscopy signal) is LCModel [4]. This internship work focuses on another software called cQUEST which will be discussed later.

3.4 Metabolite quantification in Magnetic Resonance Spectroscopy

The goal of metabolite quantification is twofold: firstly to identify the parts of the signal (in the time or frequency domain) which are caused by certain metabolites. Secondly to compute an estimate of the relative concentration of these metabolites in the selected region of interest.

These algorithms mostly work in the frequency domain by matching the spectrum with a database of known metabolite spectra. A single metabolite spectra is made of several peaks which overlap with other metabolites, the area underneath a metabolite spectrum is directly proportional to its concentration. The metabolite database used for fitting (also called metabolite basis set) can be either acquired from in-vitro experiments or quantum-mechanically simulated.

Some metabolites concentrations can be tied together, for instance the concentration of the sum of NAA and NAAG remains constant.

This fitting task is a non-linear least squares problem. In the case of the cQUEST algorithm, the Levenberg–Marquardt algorithm is used [8].

3.5 Internship subject

"Towards reproducible computation in magnetic resonance spectroscopy".
Magnetic resonance spectroscopy is used in preclinical studies to obtain concentrations of

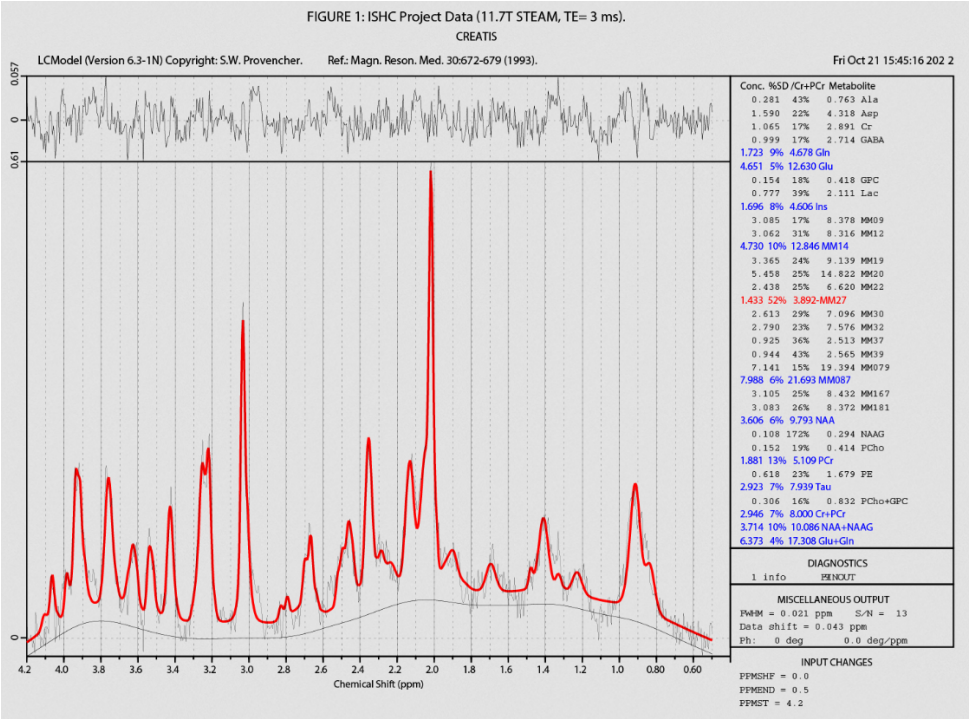

Figure 1: An MRS signal of a rat brain voxel acquired at 11.7T with the estimated metabolite concentrations computed by LCModel on the right.
The spectrum is fitted (red line) using a database of single metabolite spectrum that were either simulated or measured in-vitro.

metabolites in specifically targeted regions of an individual, in this case in rats brain.

The accuracy of metabolite quantification depends on the quality of the signal that was acquired. The spectrum noise levels and peak width play a role in the accuracy and reproducibility of quantification. [3]
The cQUEST [8] quantification software was developed by Hélène Ratiney. It relies on random seeding, which means that the quantification result can vary when it is run several times on the same data.

The goal of this internship is to study how the magnetic resonance signal quality affects both the accuracy of the metabolite quantification as well as the inter-execution variability on the same data for the cQUEST algorithm

In order to obtain lower noise in the spectrum, MR scientists perform several acquisitions of the same sample that are then averaged. However this is a time consuming process. This is why the final goal is to use these metrics to get a reproducibility or quality score to know when to stop averaging multiple MRS acquisitions when it gives a sufficient quality spectrum. If the quality calculations are done in real time in parallel to the acquisitions, this can speed up the process: researchers can stop MR acquisitions as soon as the signal quality is considered high enough for metabolite quantification.
The general plan of this internship is the following:

- Finding and testing indicators of signal quality. Using simulated spectra of varying quality.

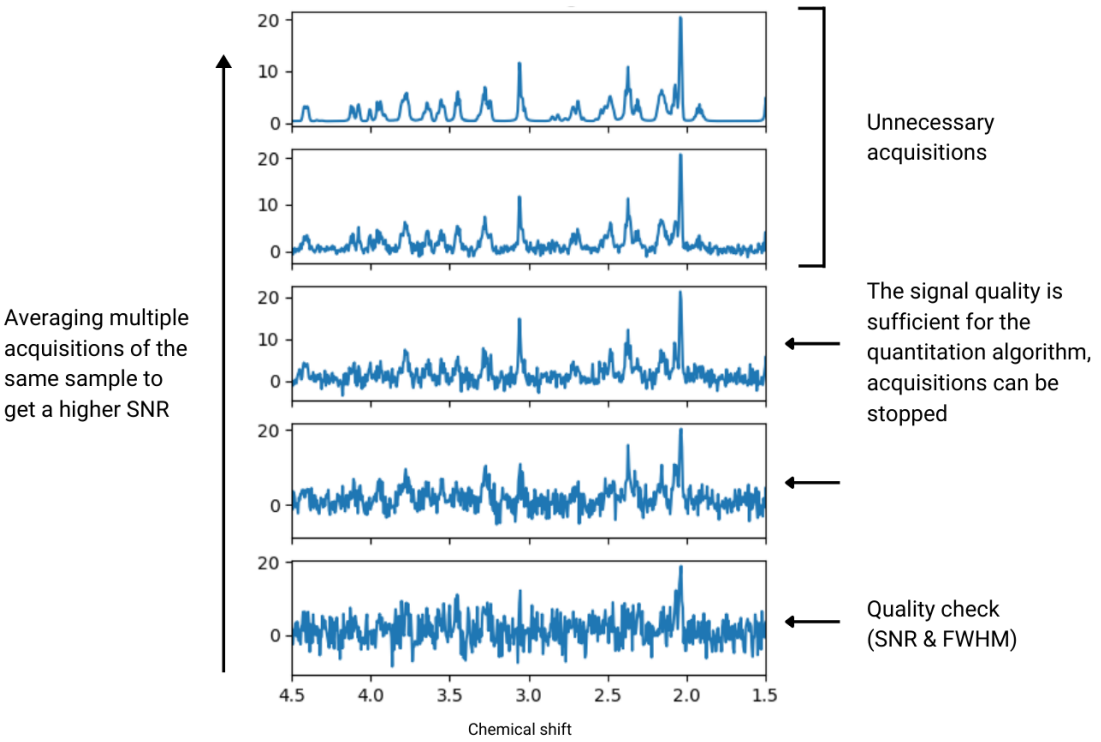

Figure 2: Overview of the final process. The key is to link spectrum quality with quantification accuracy in order to avoid unnecessary acquisitions.

- Running the quantification algorithm on the simulated spectra to link signal quality with quantification accuracy and reproducibility.
- Run the quantification algorithm on real world signals and link their quality with quantification accuracy and reproducibility.

4 Synthesis of MR Spectroscopy Signals for Simulation

4.1 Methods

In order to link the quality of the acquisition with the metabolite quantification quality, the first step is to simulate spectroscopic signals in order to have control over their quality by changing several parameters which are discussed below.

The spectroscopic spectrum of a rat brain can be reconstructed by a weighted sum of the free induction decay of the metabolites that make it up.

The benefit of this method is that a "noise-free signal" can be reconstructed and noise can be artificially added to precisely control the signal quality. One can also control the spectrum peak width (broadening) by apodizing the spectrum of each individual metabolite. Noise level and peak width (FWHM or Full Width at Half Maximum) are two signal quality indicators that were used throughout this work.

This was used to create a set of 100 signals with controlled varying quality. The cQUEST quantification algorithm was run on this set in order to link the signals quality with the reproducibility of metabolite quantification.

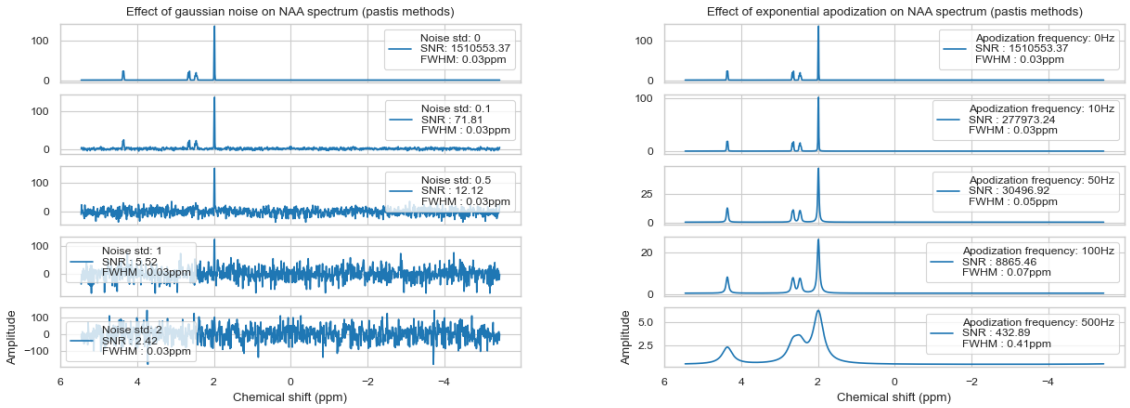

Figure 3: Apodization (peak broadening by multiplying the time signal with a decaying exponential) and adding artificial Gaussian noise of varying standard deviation to a single NAA metabolite signal

- Adding noise: A white gaussian noise of varying amplitude is added to the complex time-domain Free Induction Decay.
- Apodization: The complex time-domain Free Induction Decay is multiplied by a decaying exponential with a time constant that is equal to 1/d where d is the damping factor

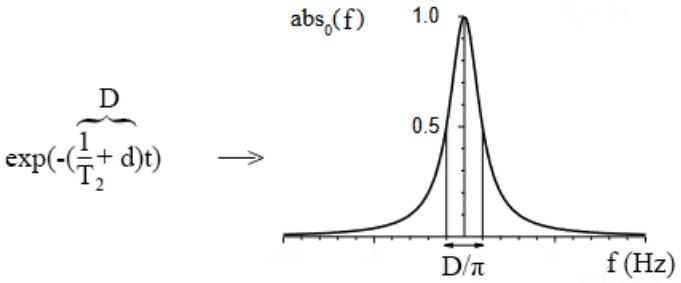

Figure 4: Apodization. Left: Free Induction Decay multiplied by a decaying exponential of time constant 1/d. Right: Fourier transform of the signal with it's FWHM.
Inspired from the Phelma NMR course handout (F. Hippert, T. Christen)

4.2 Results

The result is a set of 100 (10 noise levels * 10 apodization levels) simulated spectra based on a real one recorded on a rat brain at 11.7T.

5 Spectrum Quality

In order to link the reliability of quantification with signal quality the first step is to find and test indicators of signal quality. The main two indicators for MRS signal quality are the Signal-to-Noise Ratio (SNR) of a peak and the Linewidth, also called Full Width at Half Maximum (FWHM). [3] The goal here is to compare multiple methods of calculating

these indicators.

5.1 Signal-to-Noise Ratio

The level of noise in the spectrum can affect the reliability of the quantification.

Several methods were tested:

- SNR computed by the LCModel quantification algorithm: "the ratio of the maximum in the spectrum-minus-Baseline over the Analysis Window to twice the rms Residuals"[4].
- PASTIS (Processing ASsessment Technique for Improved Spectroscopy) [5] is a python library used to process magnetic resonance spectroscopy data.

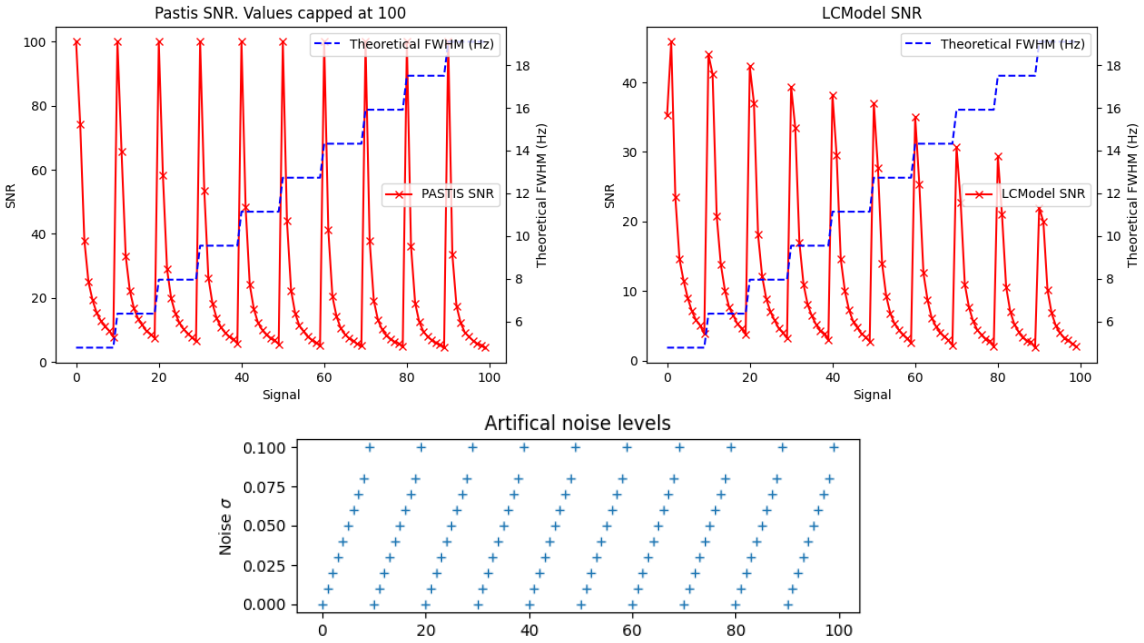

Figure 5: Comparison of SNR calculation method for different apodization (theoretical FWHM) and noise level of each signal represented at the bottom

Both methods behave similarly when adding noise and apodization. The PASTIS method returns very large values when no noise is added, which is why the values were capped at 100. For an equivalent level of noise, increased apodization tends to reduce the estimation of the SNR by both the PASTIS and LCModel method. event though noise is added after apodizing.

The PASTIS method has been chosen for SNR computation since it is faster to run compared to LCModel and yields closer results.

5.2 Linewidth

LCModel computes the linewidth on the most prominent peak of the spectrum, the precise method isn't detailed.

PASTIS computes the linewidth of a peak relative to its height without taking the baseline into account.

Finally, the Scipy [6] library uses peak prominence and analyse a window around the peak to take into account it's base.

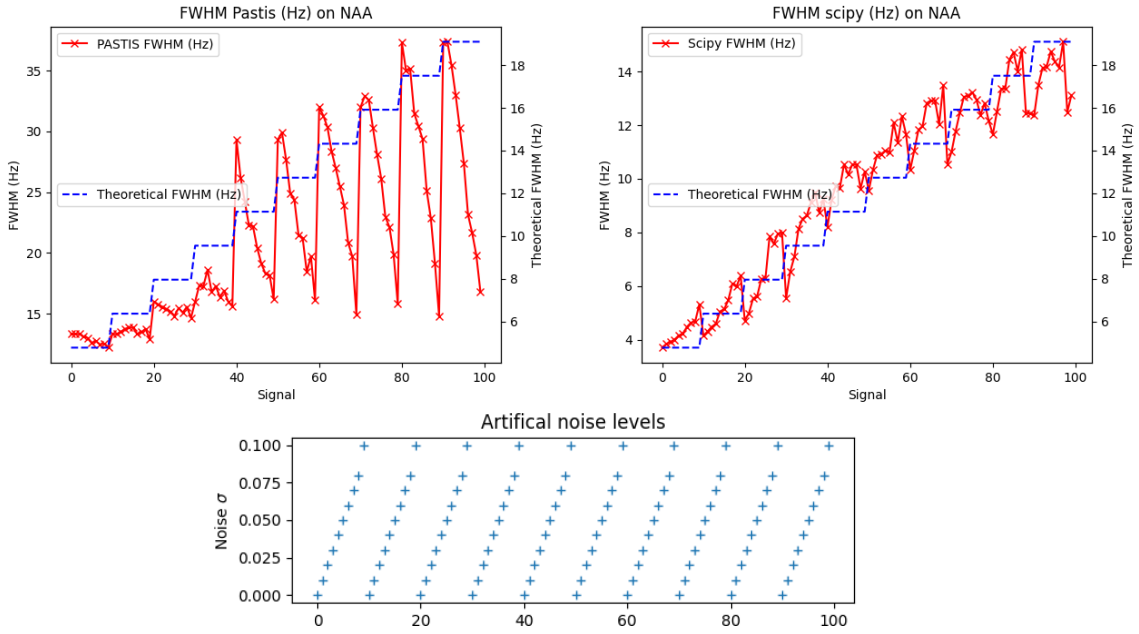

Figure 6: Comparison of FWHM calculation method for different apodization (theoretical FWHM) and noise levels represented at the bottom

In order to test which FWHM computation method should be used, the simulations were used to test the three methods and see how they respond to added noise and apodization. For each value of apodization, 10 values of noise were tested (from low to high in order). Each step of apodization (in blue) has 10 steps of noise.

The Scipy method seems to be the most accurate one:

- The computed FWHM (red curve) values range from 4 to 15Hz which corresponds to the theoretical (blue curve) ones (5 to 19Hz). The PASTIS method gives another range of values.
- The Scipy method follows the trend of increasing apodization whereas PASTIS doesn't after the fourth apodization value.
- The Scipy method is more robust to noise: increasing noise σ within an apodization value doesn't change as much as the PASTIS method

The Scipy method has therefore been chosen to compute FWHM values.

6 Quantification quality

The goal is to find criteria on the signal that predict a "good" quantification.

6.1 Indicators of quantification quality

6.1.1 Cramér-Rao bounds

Due to the constraints or MRS experiments (time, subject) it is often impossible to repeat the same acquisitions in order to get values of standard deviation for metabolite concentrations.

This is why the Cramér-Rao lower Bound (CRB) is widely used across the community to get a lower bound for the estimator of metabolite concentration.

$$Var(\hat{C}) \geq CRB$$

Where $\hat{C}$ is the estimator for the metabolite concentration C. CRBs are theoretical bounds computed during the quantification process by both LCModel and cQUEST.

6.1.2 Inter-execution variability

Since the cQUEST algorithm uses a random seed in the gradient descent used in the fitting process, different runs on the same data can yield different results. For each simulated spectrum, cQUEST was run 3 times for each signal. This is why a standard deviation σ is computed to have a value for inter-execution variability.

The initial quality of acquired spectra can have an effect on this inter-execution variability, it is therefore an indicator that is studied in this project.

6.2 Results on simulated signals

The quantification algorithms were run on the simulated MR spectra. The main benefit of using simulations in the first place before real world signals is to have more controlled data, especially without the macromolecules. Macromolecules add a large background signal of a very broad frequency range to the MR spectrum which can disturb metabolite quantification.

In order to get a statistically significant result, for each added noise value, 50 random noise sample were used. The cQUEST and LCModel quantification softwares were run on these simulations.

6.2.1 SNR and quantification quality

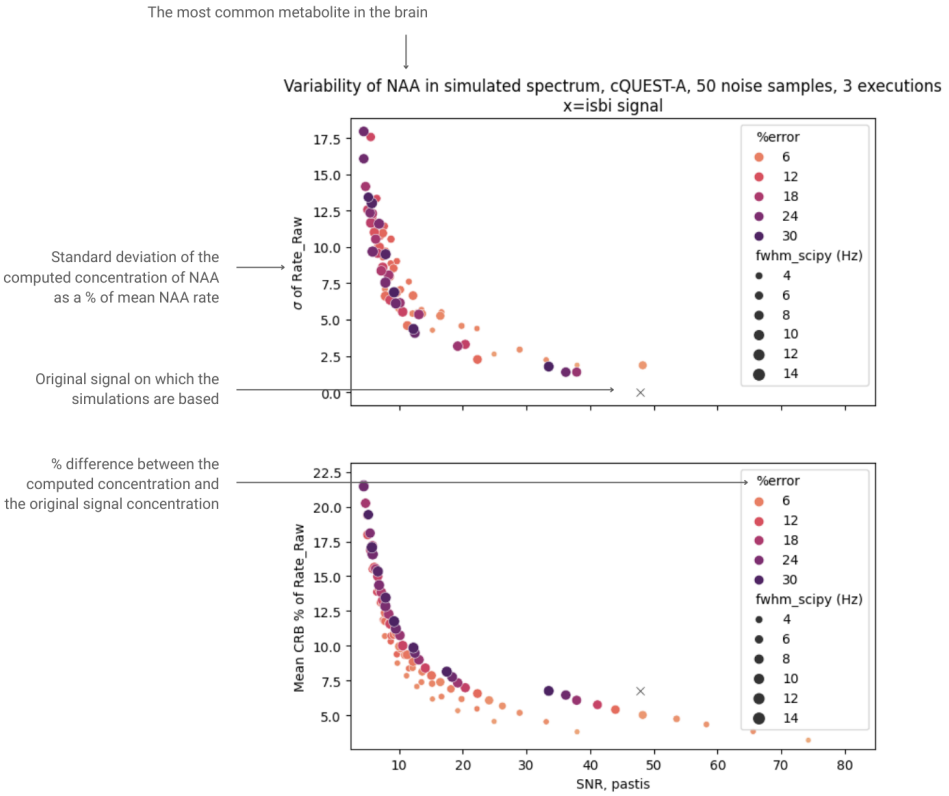

Figure 7: The relationship between the SNR and metabolite quantification quality using simulated spectra.

Figure 7 shows the relation between quantification quality and signal SNR, controlling for both signal peak width (represented by dot width) and the quantification error (dot color).

Firstly, the SNR is clearly linked to the Cramér-Rao bound (CRB) and to the standard deviation of the computed concentration because of the Cramér-Rao inequality. The two graphs show a similar trend and a comparable range of values.

Secondly, some spectra can have a high SNR and low CRB, yet the quantification error can be as high as 30% . In other words, the cQUEST algorithm has confidently made a wrong fit on those signals. The CRB can therefore be an insufficient indicator of quantification quality. The criterion to predict quantification quality from signal quality cannot depend on the SNR only but also on the FWHM.

6.2.2 FWHM and quantification quality

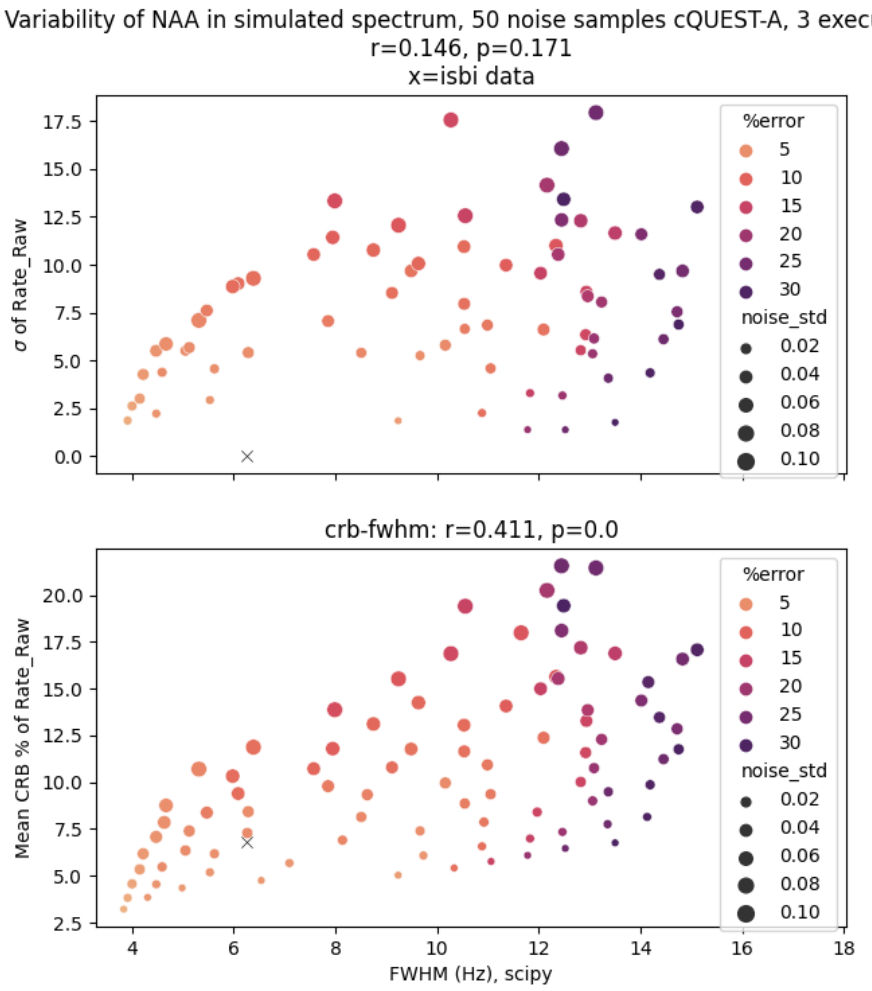

Figure 8: The relationship between the FWHM and metabolite quantification quality using simulated spectra.

On Figure 8, a low FWHM can be confidently linked to a low level of error in the quantification results. The FWHM is therefore also an indicator that can help discriminate good signals (Low CRB, STD and low error).

6.3 Criteria proposal and discussion

The proposed criteria for a good quality quantification is:

- Less than 10% Error
- Less than 10% CRB
- Less than 10% Standard deviation of Rate_Raw

Considering these criteria for the NAA metabolite, this results in signals with FWHM $<$ 6Hz and SNR $>$ 45

6.3.1 Thoughts on the Cramér-Rao inequality

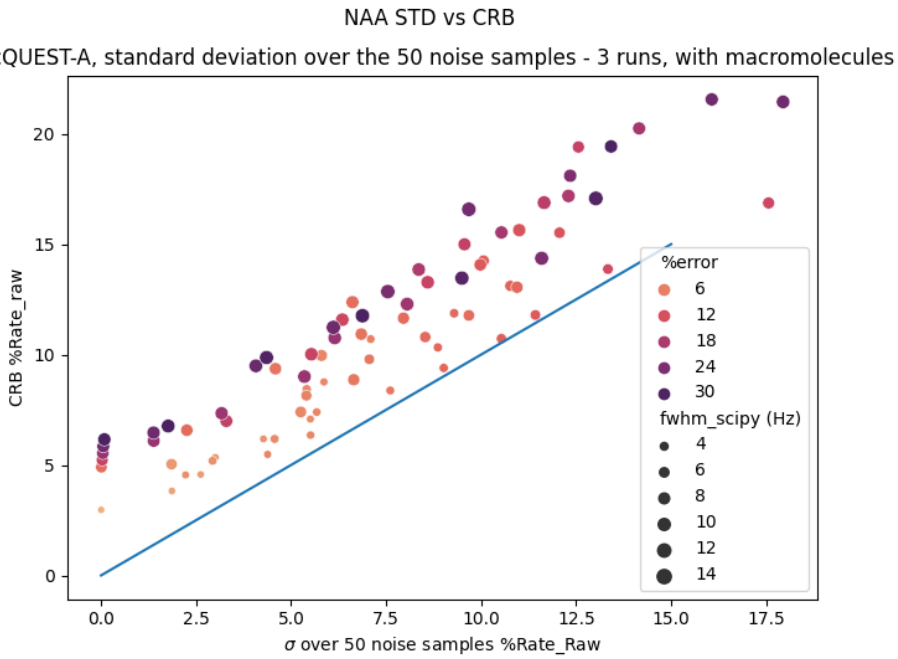

Figure 9: Showing the two quantification quality indicators: Cramér-Rao Bound (CRB) and standard deviation (σ). The blue line is the identity function.

The % error color corresponds to the ratio between the computed metabolite concentration and the expected (simulated) one.

This figure show that the Cramér-Rao inequality isn't respected especially for higher error values (The CRB should be lower than σ). This may be explained by the fact that either some hypothesis for the Cramér-Rao inequality aren't verified in this case or since σ is in this case an empirical value, it takes other factors into account. Diving deeper into the CRB calculation by cQUEST may be required to understand why it gives an unexpected relationship to the standard deviation for high-error signals.

7 Verifying the theory: case study

These criteria were constructed on simulated signals with a controlled quality. However real signals also present various artifacts as well as a baseline which is caused by macromolecules having short T2 decay time and therefore result in a very broad spectrum. Pre-recorded macromolecule signals are included in the cQUEST algorithm library it it to fit them, but the process is less reliable than for classical metabolites since they overlap a lot with the other molecules.

The final step is to verify if these criteria give similar results on real world signals and modify them if needed.

7.1 In-vivo magnetic resonance spectroscopy

The following paragraph describes a typical MRS acquisition on rat brain at the CREATIS lab.

The STEAM (STimulated Echo Acquisition Mode) MRS sequence is used. The main benefit of this sequence is to use very short echo time in order to catch metabolites with short T2 decay times which can be present in the brain.

Figure 10: 11.7T Bruker biospec 117/16 USR preclinical MRI machine, part of the PILoT imaging platform and its control room

Figure 11: Anesthesia machine using isoflurane

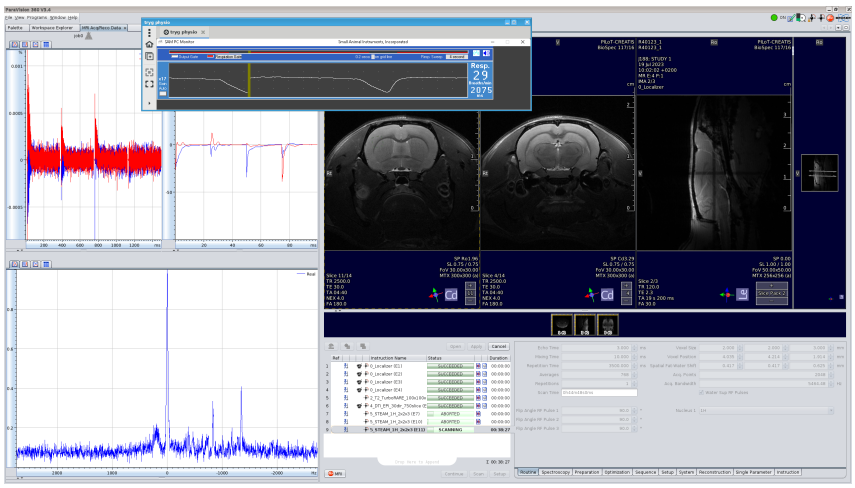

Figure 12: MRI control software.

The rat is maintained in an anesthesia state for the duration of the acquisitions. Inside the MRI control software the breathing pattern is constantly monitored in the window on the top. The signal from the four antennas if displayed in red on the top left corner. The MRS spectrum is automatically averaged over the multiple acquisitions in the bottom left corner. All successive acquisitions are kept in a dedicated rawdata file: they will be used in the analysis below.

- First the rat has to be anesthetized using isoflurane gas. For details on animal experiments at CREATIS see 9.2.
- Using a localizer MRI sequence (black and white images on figure 12), the animal has to be correctly positioned.
- The automatic adjustment of shimming parameters is launched. This ensures the most uniform magnetic field over region of interest.
- A region of interest (voxel) is selected for the STEAM MRS sequence.
- The STEAM MRS sequence is launched for the selected number of acquisitions.

7.2 Final analysis

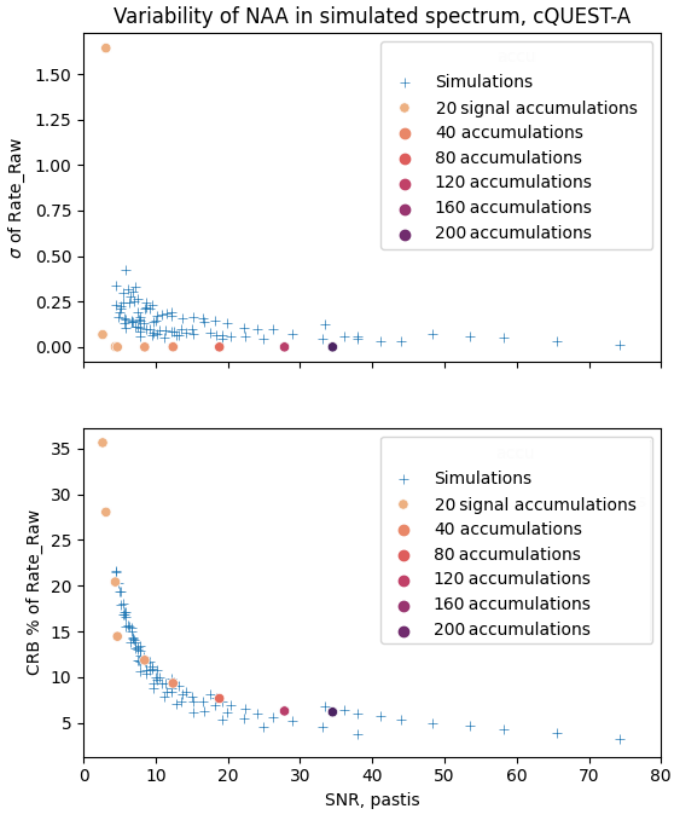

Figure 13: Effect of signal averaging on quantification quality and SNR compared to the simulations

A set of experimental data from a previous CREATIS study was used. It consists of a 15 min acquisition of 256 spectra using the STEAM sequence with a short echo time TE of 2ms on a rat whose brain received focal demyelination.

On the graph below, the round dots show the results for spectra with more and more acquisitions averaged together. The relation between CRB and SNR is similar to the simulations. However the standard deviation of Rate_Raw (standard deviation of the computed concentration of NAA, as a % of the mean NAA concentration) over multiple runs on the same data shows a more abrupt trend and lower values.

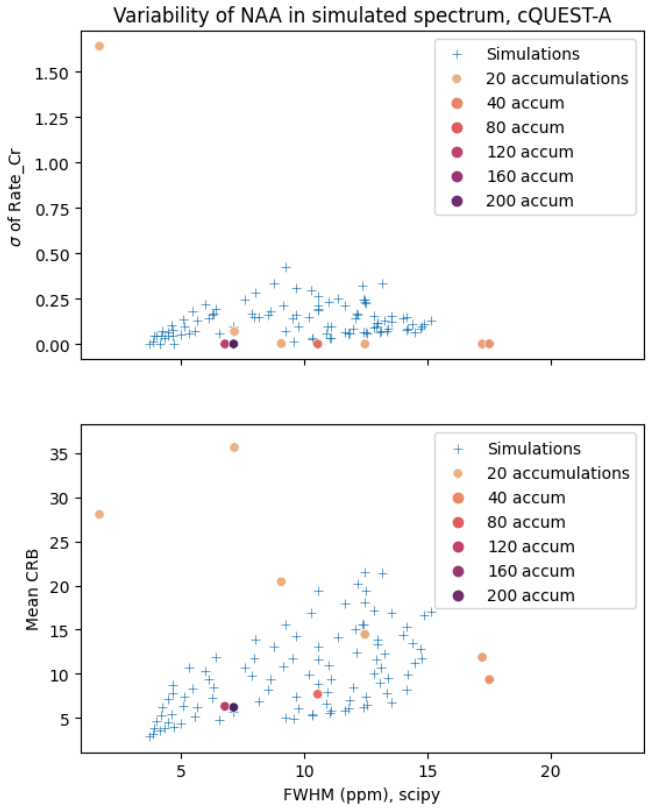

Figure 14: Effect of signal averaging on quantification quality and FWHM compared to the simulations

Conversely to the SNR, the FWHM showed very unexpected values. It is worth noting that real signals have artefacts as well as a "baseline" which is made of signals from macromolecules which maybe weren't present in the simulated spectra. The baseline could therefore be incorrectly "recognized" or fitted by the cQUEST algorithm which may skew the CRB values for instance. Moreover, despite the selection of the Scipy FWHM method which gave better results over the PASTIS FWHM method (figure 6), the selected method may still not be reliable enough for high noise values, which could explain the unsatisfying result of figure 14.

8 Conclusion

8.1 Discussion

Using the simulated spectra, the link between the signal-to-noise ratio and the Cramér-Rao Bound is in adequacy with what has been found by Kreis R. [3]. The link between FWHM and CRB is also similar to what has been found in the literature [3].

However using real world signals, only the link between the number of averaged acquisitions, signal-to-noise ratio and the Cramér-Rao Bound is in adequacy with what has been found by Kreis R. [3]. It is not the case for the FWHM.

The novelty of this study is the addition of inter-execution variability due to the nature

of the cQUEST algorithm, as well as the ability to perform large quantity of quantification executions on simulated spectra using the VIP and EGI platform.

8.2 Perspectives

Here is the suggested list of what could improve the results of this study:

- Finding a better FWHM calculation method or tweaking the parameters of peak finding to make it more robust to noise.
- Generating more signal accumulation steps by bootstrapping the set of individual acquired spectra to have a finer graph with more data.
- Testing different cQUEST fitting parameters can be a step towards having results closer to the simulation. In MR spectroscopy, trial and error is a common practice to perform a good metabolite quantification. This requires expertise on the fitting algorithm.

8.3 Aftermath

The entirety of code that was written as part of this internship is uploaded on an in2p3 Gitlab repository mainly in the form of Jupyter Notebooks in the hopes of it being used for further studies and a scientific publication under the ReproVIP project. Most of the tools for data analysis are now ready to be used and more studies can be easily conducted.

8.4 Final thoughts

Simulated MR spectra have led in this internship work to a better understanding of the way noise levels and peak width have an impact on the cQUEST quantification algorithm. However the use of real world signals did not give significant results compared to the simulation. I hope that the analysis material (e.g. code) written in the framework of this project will allow them to build on this topic. Ultimately, a better understanding of the quantification of metabolites using magnetic resonance spectroscopy will certainly have an impact in the clinical world. Researchers in vivo NMR spectroscopy continue their effort to promote spectroscopy in the medical world, which is less well known than MRI imaging, even though it can be performed with the same machines.

9 Miscellaneous

9.1 Tools and Scientific instruments

9.1.1 Software tools

The large majority of research within the team was done using Python, from writing signal processing tools to data analysis or APIs for other software.

The programs were enriched with text descriptions and step-by-step guides using Jupyter notebooks.

Large amount of data were manipulated using the pandas python library as well as Scipy and PASTIS

9.1.2 VIP and EGI

The VIP platform hosts various research applications which are either computed on CREATIS's servers or using EGI.

EGI - European Grid Infrastructure, is a federation of computing and storage resource providers. The applications which require more computing power such as the MRS quantifications from this internship project are therefore run on the distributed computing infrastructure provided by the EGI members.

9.1.3 MRI machine

The in-vivo acquisitions were performed on the 11.7T preclinical Bruker biospec 117/16 USR MRI machine. This instrument is part of PILoT (multimodal imaging platform at LyonTech) https://www.creatis.insa-lyon.fr/site7/en/PILoT This machine can perform scans on small mamals such as mice or rats.

9.2 Animal experiments

The CREATIS laboratory uses animals as part of research projects. There is an animal house hosted by INSA Lyon where they are taken care of. Animal experiments are regulated [11], scientists who conduct animal experiments have to follow a course each year to make sure they are up to date with regulations. They learn to recognize when the animal is in pain.

Scientist who work with animals have to follow the 3R rule which has been setup by the European Commission: Replacement, Reduction and Refinement: "Replacement can be defined as methods, strategies or approaches that do not involve the use of live animals. Reduction covers any approach that will result in fewer animals being used to achieve the same objective. Refinement signifies the modification of any procedures or practices from the time the experimental animal is born until its death to minimise its suffering and enhance its well-being, or by moving from species that are considered more sentient to those less sentient." [12]

The most used animals in CREATIS are rats (300g) and mice (20g).

9.3 Environmental impact

According to a study from the University of Melbourne [10], MRI is the imaging modality which has the biggest carbon footprint in Australia. An MRI machine on standby uses an average power of 9.06 kW and 15.36kW when doing a scan.

Note: Ideally, the computing of signal quality will be done in real time so that the acquisition can be stopped as soon as the quality is sufficient to give a reliable metabolite quantification. This can avoid unnecessary scans and help reduce the carbon footprint of MRS scans.

10 Bibliography

[1] https://www.creatis.insa-lyon.fr/vip/

[2] Baker, M. 1,500 scientists lift the lid on reproducibility. Nature 533, 452–454 (2016). https://doi.org/10.1038/533452a

[3] Kreis R. Issues of spectral quality in clinical 1H-magnetic resonance spectroscopy and a gallery of artifacts. NMR Biomed. 2004 Oct;17(6):361-81. doi: 10.1002/nbm.891. PMID: 15468083.

[4] LCModel & LCMgui User's Manual http://s-provencher.com/pub/LCModel/manual/manual.pdf

[5] https://crmbm.univ-amu.fr/softwares-pastis/

[6] https://scipy.org/

[7] Cudalbu, C., Behar, K. L., Bhattacharyya, P. K., Bogner, W., Borbath, T., de Graaf, R. A., ...Mlynárik, V. (2021). Contribution of macromolecules to brain 1H MR spectra: Experts' consensus recommendations. NMR Biomed., 34(5), e4393. doi: 10.1002/nbm.4393

[8] Ratiney H, Sdika M, Coenradie Y, Cavassila S, van Ormondt D, Graveron-Demilly D. Time-domain semi-parametric estimation based on a metabolite basis set. NMR Biomed. 2005 Feb;18(1):1-13. doi: 10.1002/nbm.895. PMID: 15660450.

[9] Cavassila S, Deval S, Huegen C, van Ormondt D, Graveron-Demilly D. Cramér-Rao bounds: an evaluation tool for quantification. NMR Biomed. 2001 Jun;14(4):278-83. doi: 10.1002/nbm.701. PMID: 11410946.

[10] McAlister S, McGain F, Petersen M, Story D, Charlesworth K, Ison G, Barratt A. The carbon footprint of hospital diagnostic imaging in Australia. Lancet Reg Health West Pac. 2022 May 3;24:100459. doi: 10.1016/j.lanwpc.2022.100459. PMID: 35538935; PMCID: PMC9079346.

[11] https://agriculture.gouv.fr/animaux-utilises-des-fins-scientifiques

[12] https://environment.ec.europa.eu/topics/chemicals/animals-science_en#the-three-rs

[13] Hippert F., Christen T. Nuclear Magnetic Resonance - Magnetic Resonance Imaging. Phelma course handout.

[14] Weinberg BD, Kuruva M, Shim H, Mullins ME. Clinical Applications of Magnetic Resonance Spectroscopy in Brain Tumors: From Diagnosis to Treatment. Radiol Clin North Am. 2021 May;59(3):349-362. doi: 10.1016/j.rcl.2021.01.004. Epub 2021 Mar 23. PMID: 33926682; PMCID: PMC8272438.

11 Abbreviations

CREATIS: Centre de Recherche en Acquisition et Traitement de l'Image pour la Santé
VIP: Virtual Imaging Platform https://vip.creatis.insa-lyon.fr/
EGI: European Grid Infrastructure, federation of computing and storage resource providers
MRS: Magnetic Resonance Spectroscopy
SNR: Signal-to-Noise Ratio
LW: Linewidth
FWHM: Full Width at Half Maximum (used as a quality indicator to get the width of a peak in the spectrum)
NAA: N-acetylaspartate
STEAM: an MRS sequence name STimulated Echo Acquisition Mode