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DEEP LEARNING FOR SINGLE-VOXEL AND MULTIDIMENSIONAL MR-SPECTROSCOPIC SIGNAL QUANTIFICATION, AND ITS COMPARISON WITH NONLINEAR LEAST-SQUARES FITTING

HLUBOKÉ UČENÍ PRO KVANTIFIKACI JEDNOVOXELOVÝCH A MULTIDIMENZIONÁLNÍCH MR SPEKTROSKOPICKÝCH SIGNÁLŮ A JEHO SROVNÁNÍ S NELINEÁRNÍM FITOVÁNÍM METODOU NEJMENŠÍCH ČTVERCŮ

DOCTORAL THESIS
DIZERTAČNÍ PRÁCE

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Abstract

Preprocessing, analysis, and quantification of Magnetic resonance spectroscopy (MRS) signals are required for obtaining the metabolite concentrations of the tissue under investigation. However, a fast, accurate, and efficient post-acquisition workflow (preprocessing, analysis, and quantification) of MRS is challenging.

This thesis introduces novel deep learning (DL)-based approaches for preprocessing, analysis, and quantification of MRS data. The proposed methods achieved the objectives of robust data preprocessing, fast and efficient MR spectra quantification, *in-vivo* concentration quantification, and the uncertainty estimation of quantification. The results showed that the proposed approaches significantly improved the speed of MRS signal preprocessing and quantification in a self-supervised manner. Our proposed methods showed comparable results with the traditional methods in terms of accuracy. Furthermore, a standard data format was introduced to facilitate data sharing among research groups for artificial intelligence applications. The findings of this study suggest that the proposed DL-based approaches have the potential to improve the accuracy and efficiency of MRS for medical diagnosis.

The dissertation is structured into four parts: an introduction, a review of state-of-the-art research, a summary of the aims and objectives, and a collection of publications that showcase the author's contribution to the field of DL applications in MRS.

Keywords

MR spectroscopy, inverse problem, deep learning, machine learning, convolutional neural network, metabolite quantification, frequency and phase correction.

Abstrakt

Pro získání koncentrace metabolitů ve vyšetřované tkáni ze signálů magnetické rezonanční spektroskopie (MRS) je nezbytné provézt předzpracování, analýzu a kvantifikaci MRS signálu. Rychlý, přesný a účinný proces zpracování (předzpracování, analýza a kvantifikace) MRS dat je však náročný.

Tato práce představuje nové přístupy pro předzpracování, analýzu a kvantifikaci MRS dat založené na hlubokém učení (DL). Navržené metody potvrdily schopnost použití DL pro robustní předzpracování dat, rychlou a efektivní kvantifikaci MR spekter, odhad koncentrací metabolitů *in vivo* a odhad nejistoty kvantifikace. Navržené přístupy výrazně zlepšily rychlost předzpracování a kvantifikace MRS signálu a prokázaly možnost použití DL bez učitele. Z hlediska přesnosti byly získány výsledky srovnatelné s tradičními

metodami. Dále byl zaveden standardní formát dat, který usnadňuje sdílení dat mezi výzkumnými skupinami pro aplikace umělé inteligence. Výsledky této studie naznačují, že navrhované přístupy založené na DL mají potenciál zlepšit přesnost a efektivitu zpracování MRS dat pro lékařskou diagnostiku.
Disertační práce je rozdělena do čtyř částí: úvodu, přehledu současného stavu výzkumu, shrnutí cílů a úkolů a souboru publikací, které představují autorův přínos v oblasti aplikací DL v MRS.

Klíčová slova

MR spektroskopie, inverzní problém, hluboké učení, strojové učení, konvoluční neuronová síť, kvantifikace metabolitů, frekvenční a fázová korekce.

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CONTENTS

TABLES

1. INTRODUCTION

Magnetic resonance spectroscopy (MRS) has attracted the magnetic resonance (MR) community over the past seven decades [1]–[3]. A significant part of the interest in biomedical MRS stems from the possibility of non-invasive measurements of metabolites [3]. Information about tissue metabolites can help in clinical diagnostics. For instance, the detection of metabolic pathway changes may facilitate diagnosing disease in earlier stages before anatomy changes can be observed and thus enable more efficient treatment. This is demonstrated in glioma, a decrease of N-acetylaspartate (NAA) and creatine (Cr) concentrations and an increase of choline, lipids, and lactate predicts an increase in the glioma grade [1], [2].

Contrary to other diagnostic techniques such as Computed Tomography (CT) and Radionuclide imaging (e.g., Positron Emission Tomography (PET), Gamma camera), MRS emits no ionizing radiation to the subject, which enables follow-up studies [2].

It is possible to get various information using Spectroscopy (MRS) and Spectroscopic Imaging (MRSI) for atomic nuclei such as Proton (^{1}H), Phosphorus (^{31}P), Carbon (^{13}C), etc. The proton nucleus has the highest natural abundance (>99.9%) and intrinsic nuclear magnetic resonance (NMR) sensitivity (high gyromagnetic ratio) among all nuclei for MRS. Presently, the primary utilization of MRS in the clinical setting is centered around ^{1}H, with other nuclei being predominantly applied in preclinical and fundamental research. Although a number of brain metabolites can be identified with ^{1}H MRS, the quantity of substances assessable under *in vivo* conditions does not exceed 15-20, and is typically much lower. Further MR-visible nuclei with biochemical relevance have also demonstrated their value in providing information on tissue physiology and biochemistry [1]–[4]. Notably, the incorporation of non-^{1}H MRS in clinical practice has yet to become widespread, potentially due to the prerequisite of nonstandard hardware and specialized MRS techniques [3].

Recently, there has been a resurgence of interest in MRS within the MR community for clinical neuroscience and translational purposes [3]. This is largely due to the increased availability of high and ultrahigh-field scanners, and a better understanding of the role of metabolism in neuroenergetics and neurotransmission. Consequently, there has been a rise in the use of MRS for both typical clinical applications and neurological research, supported by advancements in acquisition and processing techniques [3].

However, MRS has some shortcomings that limit its routine use in clinical practice. Some of these are (i) MRS requires specialized equipment and software that are not widely available or standardized, (ii) MRS is time-consuming and prone to artifacts and noise that affect the quality and reliability of the spectra, (iii) MRS data analysis and interpretation are complex and require expert knowledge and skills [1], [5].

Deep learning (DL) has the potential to enhance the accuracy and efficiency of MRS by automating the data analysis, providing more reliable diagnoses, and enabling the use of MRS in routine clinical practice.

2. STATE OF THE ART OF DL IN MRS

The recent success of DL, one of the latest machine learning approaches, in a variety of tasks, including applications with a low signal-to-noise ratio (SNR) [6], [7], suggests that it might also handle the spectral analysis of an MRS signal. Supervised DL-based approaches have been used for ghosting artifacts detection and removal [8], spectral reconstruction [9], automatic peak picking [10], MRSI spatial resolution enhancement [11], localized correlated spectroscopy acceleration [12], metabolites and MM separation in MRS signals, the quantification and noise removal of MRSI signals [13], [14], and poor-quality spectra identification [15].

It has been shown that supervised DL can also be employed for FPC [16], [17] and could speed up FPC once it has been successfully trained. This supervised approach, using two separate networks in sequence to estimate frequency and phase, showed encouraging results. The first network was trained for frequency shift estimation using the magnitude of frequency- and phase-shifted spectrum as the input and the known frequency shift as the output. Subsequently, the second network was trained for phase shift estimation using real parts of the frequency-corrected spectrum as the input and phase shift as the output. In this approach, any error in the first step (frequency correction) may bias the phase shift estimation. Training two networks is a computationally expensive task. Moreover, the networks were trained in a supervised manner using simulated data. Any discrepancy between the *in-vivo* and the simulated spectra may result in errors in frequency and phase shift estimation. The true output values are unknown in MRS data, and obtaining hundreds of spectra with labeled frequency and phase shifts is almost infeasible. This makes it challenging to use supervised DL methods that rely on labeled transients. Self-supervised or unsupervised learning may eliminate the drawbacks of supervised learning.

Moreover, several studies demonstrated the potential of artificial neural networks for quantifying MR spectra. Hiltunen et al. [18] have demonstrated the feasibility of constructing a quantifying analyzer for long echo time (TE) in vivo proton MRS (1H NMR) spectra using artificial neural networks with magnitude spectra. Hatami et al. [19] and Lee et al. [20] applied supervised DL approaches to metabolite quantification and presented results comparable to conventional LCM approaches. Chandler et al. [21] also applied a supervised DL approach to study metabolite quantification in edited human brain MRS spectra. These studies utilized supervised learning approaches, in which the input and the output were simulated spectra and known values, respectively. The true output values are however unknown in *in-vivo* MRS data. Moreover, a network trained in a supervised manner using simulated data might be prone to overfit training data [22]; thus, any discrepancy between the *in-vivo* and the simulated training spectra, such as the presence of nuisance peaks,

frequency, and phase shifts, and line-broadening, may result in errors in metabolite quantification. Self-supervised learning may eliminate the drawbacks of supervised learning. Bhat et al. [23] investigated the application of a radial basis function neural network (RBFNN) for the automatic quantification of short echo time, multi-voxel, phased spectral data. Gurbani et al. [24] presented a self-supervised DL architecture that integrates a CNN with peak fitting for quantifying MR spectra. In their approach, a deep autoencoder is used as a framework for self-supervised or unsupervised learning. However, their method does not utilize the advantages of LCM such as fewer fitting parameters and realistic basis spectra. Table 1 provides a comparison of related work on MRS signal quantification using DL.

Even though DL algorithms have demonstrated equivalent quantitation performance to traditional methods, concerns have been raised about their robustness. Moreover, the effects of DL architectures, spectroscopic input types, and learning designs for optimal quantification in MRS of pathological spectra have not been investigated in previous studies and warrant further investigation.

Table 1 A summary of related work on MRS signal quantification using DL.

	Model architectures	**Input types**	**Learning process**	**Data type (training)**	**Prior metabolite resonances model**
Hiltunen et al. [18]	Shallow Neural Networks	Magnitude spectra (1D)	Supervised	Simulated	_
Bhat et al. [23]	Radial basis function neural network	Real part of spectra (1D)	Self-supervised	*In-vivo*	Lorentzian-Gaussian lineshape
Hatami et al. [19]	Convolutional neural network	Complex spectra (1D)	Supervised	Simulated	–
Lee et al. [20]	Convolutional neural network	Complex spectra (1D)	Supervised	Simulated	–
Chandler et al. [21]	Convolutional neural network	Real, imaginary and magnitude component of spectra (2D)	Supervised	Simulated	–
Gurbani et al. [24]	Convolutional neural network	Real part of spectra (1D)	Self-supervised	*In-vivo*	Lorentzian-Gaussian lineshape

3. AIMS OF THE DOCTORAL THESIS

The primary objective of this dissertation is to introduce and verify an advanced approach for rapid, efficient, and accurate quantification of metabolites using DL techniques in MRS. Moreover, this dissertation aims to construct a deep neural network that extracts features from FID signals, i.e., MRS signals in the time domain, for preprocessing and analyzing MRS data. The objectives of this research can be summarized as follows:

1. To develop a robust DL method for preprocessing MR data, including frequency and phase correction,
2. To design and implement a fast and appropriate DL-based approach for quantifying MR spectra,
3. To propose a self-supervised approach for quantifying concentrations in *in-vivo* spectra,
4. To propose a method for estimating the uncertainty of the concentration's estimation in DL-based methods.
5. To compare the effectiveness and reliability of DL-based methods with nonlinear least-squares (NLLS) fitting methods for quantification,
6. To propose a standard data format to facilitate data sharing among research groups for artificial intelligence applications.

4. SELECTED PUBLICATIONS

The present thesis is composed of six research papers (4 IF-journal publications, and 2 conference extended papers), which are interconnected in their scope and theme. The central focus of this work is the development of DL approaches for MRS data analysis, with a particular emphasis on frequency and phase correction, metabolite quantification, and data standardization.

MRS data preprocessing:
The first paper [25] presents a model-informed unsupervised DL approach to the frequency and phase correction of MRS signals. The feasibility and efficiency of physics-informed DL-based signal processing of MR spectroscopy data in an unsupervised manner were investigated. Simulated, phantom, and *in vivo* MEGA-edited MRS data were used in the study. This work aimed to solve the challenge of obtaining spectra with labels (i.e. spectra with labeled frequency and phase shifts) for the supervised DL approach to FPC.

Metabolite quantification (supervised DL approaches):
The next three papers focus on the development of supervised DL approaches to MRS signal quantification. The second paper [26] proposes a time-frequency analysis approach that leverages DL to produce highly accurate and robust MRS signal quantitation. This paper verified the hypothesis that DL in combination with time-frequency analysis can be used for metabolite quantification and yielded results more robust than DL trained with MR signals in the frequency domain [19]. This paper utilizes a CNN, but the training of CNNs is computationally intensive and its optimal architecture and hyper-parameters are not well understood. To address this issue, the third paper [27] utilizes a Wavelet Scattering Convolution Network (WSCN), which is a well-understood and computationally cheap. The WSCN approach achieved better quantification accuracy and computational efficiency compared to the CNN-based approach proposed in the second paper. The fourth paper [28] investigates the quantification of MR spectra by a supervised DL approach in an idealized setting, examining various forms of input, network architectures, optimization by ensembles of networks, and training bias. This work aimed to address concerns about the robustness of DL for MR spectra quantification.

Metabolite quantification (self-supervised DL approaches):
At the beginning of this Ph.D. study, the author was captivated by the idea of using supervised learning to solve complex problems in the quantification of MR spectra. The author spent several months exploring different supervised learning techniques and experimenting with

various datasets. However, as the author delved deeper into the subject, the author began to realize the limitations of supervised learning. At first, the author was hesitant to try self-supervised learning, as the author noticed that developing a neural network and training it in a self-supervised manner were much more challenging than supervised learning. However, the author quickly discovered that self-supervised learning offered a wealth of opportunities to explore new ideas and solve problems in innovative ways. With self-supervised learning, the author proposed a physics-informed DL approach to quantifying human brain metabolites from MRS data in the fifth paper [29]. The author ventured to develop an approach in which neural networks can learn in a self-supervised manner to solve an inverse problem for human brain metabolite concentration estimation.

The fourth and fifth papers shed light on a comparison between DL-based methods (supervised and self-supervised) and traditional methods (nonlinear least-squares fitting methods) for MRS data quantification. Additionally, the fifth paper's proposed method utilizes a physics-informed DL approach, allowing it to compute the Cramer-Rao lower bounds (CRLB) to estimate the uncertainty in concentration estimation. Table 2 provides a comparison of the author's work on MRS signal quantification using DL.

Table 2 A summary of our work on MRS signal quantification using DL.

	Model architectures	**Input types**	**Learning process**	**Data type (training)**	**Prior metabolite resonances model**	**Output of network**
Shamaei et al. [26]	Convolutional neural network	Complex time-frequency domain scalogram (wavelet coefficients) (2D)	Supervised	Simulated [a]	–	Amplitudes
Shamaei et al. [30]	Wavelet scattering network	Complex time-domain signal (FID) (1D)	Supervised	Simulated [b]	–	Amplitudes
Rizzo et al. [31]	Convolutional neural network	Complex spectra, time-frequency domain spectrograms (2D)	Supervised	Simulated [c]	–	Amplitudes
Shamaei et al.	Physics-informed	Complex time-domain signal	Self-supervised	Simulated [d] and *in-vivo*	Quantum-mechanics	Parameters of a

[29]	convolutional neural network	(FID) (1D)			simulated metabolite responses	complex model

[a] a combination of amplitude-scaled frequency-shifted damped metabolite basis set signals, the baseline (without noise).
[b] a combination of amplitude-scaled frequency-shifted phase-shifted damped metabolite basis set signals, the baseline and white noise.
[c] a combination of amplitude-scaled damped metabolite basis set signals, the baseline and white noise (all basis set signals share the same damping factor).
[d] a combination of amplitude-scaled frequency-shifted phase-shifted damped metabolite basis set signals, the baseline and white noise (all basis set signals share the same damping factor, frequency shift, and phase shift).

Standard data format to facilitate data sharing among research groups:
Finally, the sixth paper [32] advocates for a standard data format for MRS, which could facilitate data sharing and comparability across research groups for artificial intelligence applications.

Taken together, these papers present an overview of the state-of-the-art in DL approaches to MRS data analysis. They offer insights into the potential of these methods to improve the efficiency, reproducibility, and reliability of MRS data analysis, and highlight some of the challenges and opportunities that lie ahead in this rapidly evolving field. The thesis concludes with a synthesis of the key findings and recommendations for future research.

4.1 Paper 1 – Model-informed unsupervised deep learning approaches to frequency and phase correction of MRS signals

Citation

[1] Shamaei, A, Starcukova, J, Pavlova, I, Starcuk, Z. Model-informed unsupervised deep learning approaches to frequency and phase correction of MRS signals. Magn Reson Med. 2023; 89: 1221– 1236. doi:10.1002/mrm.29498

Paper contribution

The paper proposes and investigates the feasibility and efficiency of two novel unsupervised deep learning-based methods for frequency and phase correction (FPC) of magnetic resonance spectroscopy (MRS) data. These proposed methods utilize a priori physics domain knowledge to improve the performance of FPC. The paper presents the training, validation, and evaluation of these methods using simulated, phantom, and *in vivo* MEGA-edited MRS data. This study proposes a new measure to evaluate the FPC method performance and compares the performance of the proposed methods with other commonly used FPC methods. This study also evaluates the ability of the proposed methods to perform FPC at varying signal-to-noise ratios (SNR). Additionally, a Monte Carlo study is conducted to investigate the performance of the proposed methods. The contribution of the paper lies in the development and evaluation of two novel unsupervised deep learning-based FPC methods for MRS data, which can improve the accuracy and efficiency of FPC in various MRS applications.

4.2 Paper 2 – Deep Learning For Magnetic Resonance Spectroscopy Quantification: A Time-Frequency Analysis Approach

Citation

[2] Shamaei, Amirmohammad. Deep Learning For Magnetic Resonance Spectroscopy Quantification: A Time-Frequency Analysis Approach. In: *Proceedings II of the 26st Conference STUDENT EEICT 2020: Selected papers* [online]. Vysoké učení technické v Brně, Fakulta elektrotechniky a komunikačních technologií, 2020, s. 131-135 [cit. 2023-02-16]. ISBN 978-80-214-5868-0. Dostupné z: http://hdl.handle.net/11012/200638

Paper contribution

This paper explores the combination of deep learning and time-frequency analysis for more reliable metabolite quantification in magnetic resonance spectroscopy (MRS). This study verifies the hypothesis that this combination can produce more robust results than deep learning trained on MR signals in the frequency domain. The study uses the complex matrix of absolute wavelet coefficients for the time-frequency representation of the signal and implements convolutional neural networks (CNN) for deep learning. The paper also presents a comparison with DL used for the quantification of data in the frequency domain. Overall, the paper's contribution lies in providing an innovative approach to MRS quantification and advancing the understanding of the potential of deep learning and time-frequency analysis in this field.

4.3 Paper 3 – A Wavelet Scattering Convolution Network for Magnetic Resonance Spectroscopy Signal Quantitation

Citation

[3] Shamaei A., Starčuková J. and Starčuk Jr. Z. (2021). A Wavelet Scattering Convolutional Network for Magnetic Resonance Spectroscopy Signal Quantitation.In Proceedings of the 14th International Joint Conference on Biomedical Engineering Systems and Technologies - Volume 2: BIOSIGNALS, ISBN 978-989-758-490-9, pages 268-275. DOI: 10.5220/0010318502680275

Paper contribution

The paper's contribution is to explore the use of a Wavelet Scattering Convolutional Network (WSCN) for magnetic resonance spectroscopy (MRS) signal quantification. The paper highlights that the most widely used network for MRS signal quantification is the Convolutional Neural Network (CNN), but that its optimal architecture and hyper-parameters for MRS are not well understood. The paper shows that a WSCN, which is well-understood and computationally cheap, could yield more robust results for metabolite quantification than one of the quantitation methods based on model fitting (QUEST) and equivalent results to a CNN while being faster. The study investigates the effects of phase, noise, and macromolecule variation on the WSCN estimation accuracy. Overall, the paper's contribution is to propose an alternative deep learning approach to MRS signal quantification that is more computationally efficient and potentially more accurate than existing methods.

4.4 Paper 4 – Quantification of MR spectra by deep learning in an idealized setting: Investigation of forms of input, network architectures, optimization by ensembles of networks, and training bias.

Citation

[4] Rizzo, R, Dziadosz, M, Kyathanahally, SP, Shamaei, A, Kreis, R. Quantification of MR spectra by deep learning in an idealized setting: Investigation of forms of input, network architectures, optimization by ensembles of networks, and training bias. Magn Reson Med. 2022; 1- 21. doi:10.1002/mrm.29561

Paper contribution

The paper explores the application of deep learning (DL) architectures, spectroscopic input types, and learning designs for optimal quantification in magnetic resonance spectroscopy (MRS) of simulated pathological spectra. The study investigates 24 different DL architectures, with active learning through altered training and testing data distributions to optimize quantification performance. Ensembles of networks are explored to improve DL robustness and reduce the variance of estimates. The paper compares the performance of DL predictions and traditional model fitting (MF) using a set of scores. The results show that ensembles of heterogeneous networks that combine 1D frequency-domain and 2D time-frequency domain spectrograms as input perform best, and dataset augmentation with active learning can improve performance but gains are limited. MF is more accurate, although DL appears to be more precise at low signal-to-noise ratios (SNRs). However, the overall improved precision of DL predictions originates from a strong bias for cases with high uncertainty
toward the dataset the network has been trained with, tending toward its average value. The paper also highlights potential intrinsic biases on training sets, which are dangerous in a clinical context that requires the algorithm to be unbiased to outliers (i.e., pathological data). The contribution of the paper lies in providing a comprehensive evaluation of DL architectures and learning designs for MRS quantification, and highlighting the importance of unbiased and robust MRS quantification algorithms in a clinical context.

4.5 Paper 5 – Physics-informed Deep Learning Approach to Quantification of Human Brain Metabolites from Magnetic Resonance Spectroscopy Data.

Citation

[5] Shamaei, A, Starcukova, J, Starcuk, Z. Physics-informed deep learning approach to quantification of human brain metabolites from magnetic resonance spectroscopy data. Computers in Biology and Medicine. 2023; 158: 106837. doi: 10.1016/j.compbiomed.2023.106837

Paper contribution

The paper presents a novel, self-supervised deep learning (DL) method for the quantification of magnetic resonance spectroscopy (MRS) and magnetic resonance spectroscopic imaging (MRSI) data. This method is based on a linear combination model (LCM) and uses quantum-mechanics simulated metabolite responses and neural networks for the quantification of relative metabolite concentrations. The proposed DL-based method is evaluated and compared to traditional methods using simulated and publicly accessible *in-vivo* human brain MRS data. The paper also includes a novel adaptive macromolecule fitting algorithm. The performance of the proposed methods is investigated in a Monte Carlo study. The contribution of this paper lies in the development and evaluation of a self-supervised DL-based method for MRS data analysis that does not require ground truth fitted spectra, which is not always practical. This method can improve the accuracy and efficiency of MRS data analysis in various applications. To our knowledge, this is the first report showing the feasibility of the physics-informed self-supervised DL method for the quantification of MRS data.

4.6 Paper 6 – NIfTI-MRS: A standard data format for magnetic resonance spectroscopy

Citation

[6] Clarke, W, Mikkelsen, M, Oeltzschner, G, Bell T.K., Shamaei, A, Soher, B.J., Emir, U, Wilson, W. NIfTI-MRS: A standard data format for magnetic resonance spectroscopy. Magn Reson Med. 2022; 88: 2358- 2370. doi:10.1002/mrm.29418

Paper contribution

The contribution of this paper is the proposal of a standardized format, NIfTI-MRS, for magnetic resonance spectroscopy (MRS) data that incorporates essential spectroscopic metadata and additional encoding dimensions, and its implementation as an extension to the Neuroimaging informatics technology initiative (NIfTI) format. The standard format allows for easy data sharing, algorithm development, and integration of MRS analysis with other imaging modalities. The paper provides a detailed description of the NIfTI-MRS format specification, an open-source command-line conversion program to convert MRS data to NIfTI-MRS, and a dedicated plugin for FSLeyes, the FMRIB Software Library (FSL) image viewer for visualization of data in the proposed format. The paper also includes online documentation, 10 example datasets in the proposed format, and code examples of NIfTI-MRS readers implemented in common programming languages.

5. CONCLUSION

In summary, this dissertation aimed to develop a novel DL-based approach for rapid and accurate quantification of metabolites in magnetic resonance spectroscopy.
The proposed methods achieved the objectives of developing a robust DL method for preprocessing MR data [25], designing and implementing a fast and efficient DL-based approaches for quantifying MR spectra [26]–[29], investigating the applicability of the proposed approaches for quantifying concentrations in *in-vivo* spectra [29], and comparing the effectiveness and reliability of DL-based methods with NLLS fitting methods for quantification [28], [29].
The results of this study demonstrate that the proposed DL-based approaches can improve the speed and accuracy of MRS signal preprocessing and quantification in a self-supervised manner [29]. The performance of our methods on synthetic data is comparable with the traditional methods in terms of accuracy in a shorter amount of processing time. Furthermore, a standard data format was proposed to facilitate data sharing among research groups for artificial intelligence applications [32].
The results achieved in this research, corresponding to the objectives outlined in the Aims of the doctoral thesis section, can be summarized as follows:

1. Two novel unsupervised DL-based FPC methods for MRS data have been developed, which can improve the accuracy and efficiency of FPC in various MRS applications. The results have been published in an IF journal [Paper 1].

2. Fast and efficient DL-based solutions for quantifying MR spectra have been developed and tested on simulated and *in-vivo* data, and the results have been published in conferences and IF journals [Papers 2, 3, 4, and 5].

3. The applicability of the proposed self-supervised approach for quantifying relative concentrations in *in-vivo* spectra has been investigated [Paper 5].

4. The functionality of the proposed self-supervised approach has been extended to estimate the uncertainty of the concentration's estimation [Paper 5 and an abstract based on the findings of this thesis has been accepted for presentation at International Society for Magnetic Resonance in Medicine conference in 2023, in Toronto. Additionally, a manuscript based on this research is currently under preparation for submission to a high-impact factor journal.)].

5. A comprehensive comparison between DL-based methods and traditional NLLS fitting methods for MRS data quantification has been made, and the results have been published in two IF journals [Papers 4 and 5].

6. In collaboration with an international group of experts, a standard data format has been proposed to facilitate data sharing among research groups, and the results have been published in an IF journal [Paper 6]. The proposed format has been used in the present study for data sharing.

This research opens the door to further exploration of the applications of DL techniques in MR spectroscopy and spectroscopic imaging signal processing, potentially leading to significant advancements in medical diagnosis. Some potential applications of DL in MR spectroscopy and spectroscopic imaging for future work are:

Automated analysis: DL algorithms can be trained to automatically analyze MRS and MRSI data, reducing the time and effort required for manual analysis,
Improved signal-to-noise ratio: DL algorithms can be used to denoise MR signals [An abstract was presented by the author at the European Society of Magnetic Resonance in Medicine and Biology (ESMRMB) conference 2021], improving the signal-to-noise ratio and enabling higher-quality data,
Quantitative analysis: DL algorithms can be trained to perform quantitative analysis of MR spectroscopic data, allowing for the automated calculation of metabolite concentrations and other important parameters,
Image segmentation: DL algorithms can be used for automatic image segmentation, allowing for the separation of different tissues and structures within MR spectroscopic images,
Signal classification: DL algorithms can be trained to classify MRS signals based on specific features, allowing for improved diagnosis and treatment planning.

Overall, DL has the potential to significantly enhance the capabilities of MR spectroscopy and spectroscopic imaging in medical imaging. It is important to note that while DL can greatly aid in the analysis and interpretation of MR data, it should be used in conjunction with traditional methods and the expertise of experienced radiologists to ensure accurate and reliable results.

LITERATURE

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RESEARCH INTERESTS

Deep learning, Magnetic Resonance in Medicine, Self-Supervised Machine Learning

CONFERENCE PRESENTATIONS

Shamaei, A.M., Starčuková J., Radim Kořínek, and Starcuk Jr. Z., Magnetic Resonance Spectroscopic Imaging Data Denoising by Manifold Learning: An Unsupervised Deep Learning Approach, Poster presentation delivered in person at *ISMRMB 2022*, May, 2022.

Shamaei, A.M., Starčuková J. and Starcuk Jr. Z., Frequency and Phase Shift Correction of MR Spectra Using Deep Learning in Time Domain, Poster presentation delivered virtually at *ESMRMB 2021*, October, 2021.

Clarke, W., Bell, T., Emir, U., Mikkelsen, M., Oeltzschner, G., Rowland, B., **Shamaei, A.M**, Soher, B, Tapper, S., and Wilson, M, NIfTI MRS: A standard format for spectroscopic data, Poster presentation delivered in person at *ISMRMB 2021*, May, 2021.

Shamaei, A.M., Starčuková J. and Starcuk Jr. Z., A Wavelet Scattering Convolution Network for Magnetic Resonance Spectroscopy Signal Quantitation, Oral Presentation delivered virtually at *the 14th International Joint Conference on Biomedical Engineering Systems and Technologies*, Vienna, February, 2021, 10.5220/0010318502680275.

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PEER-REVIEWED PUBLICATION

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architectures, optimization by ensembles of networks, and training bias. Magn Reson Med. 2022; 1- 21. doi:10.1002/mrm.29561

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