

ACKNOWLEDGMENTS

As my PhD journey nears an end, I begin my acknowledgement with sincere gratitude to my supervisor **Prof. Neeraj Sharma**, School of Biomedical Engineering, IIT (BHU), for his support and encouragement. He has helped and trained me in every possible way since the day I joined his lab. I am highly grateful to him for sharing with me his scientific knowledge which improved the quality of this thesis.

I am highly grateful to **Dr. Sanjeev Kr. Mahto**, Coordinator, School of Biomedical Engineering, IIT (BHU), for his motivation and support for the completion and submission of this thesis.

I take this opportunity to thank my Research Progress Evaluation Committee members, for their encouragements, support and guidance throughout my work.

I also express my sincere and warm thanks to all the Professors of the School of Biomedical Engineering for all their scientific counsels and suggestions leading to betterment of this scientific work. I express my heartfelt gratitude to the Director, IIT (BHU), Deans and Registrars of institute for their direct and indirect support. I am also thankful to Ministry of Human Resources and Development, Government of India for the financial support. I also thank the anonymous reviewers for sparing time to evaluate my thesis amidst their busy schedule.

Last but not the least I am truly thankful to my family and friends, who have supported me throughout the PhD journey and have selflessly been by my side to warrant a successful completion of this long journey.

CHIRANJEEV SAGAR

CONTENTS

<i>List of Figures</i>	<i>xi</i>
<i>List of Tables</i>	<i>xv</i>
<i>Preface</i>	<i>xvii</i>
<i>Abstract</i>	<i>xix</i>
Chapter 1. Introduction	1
1.1. Magnetic Resonance: An Introduction	1
1.1.1. Magnetic resonance spectroscopy (MRS)	4
1.1.2. SVS and MRSI	6
1.1.3. Acquisition parameters	7
1.1.4. Metabolites and Macromolecules	8
1.1.5. ^1H -MRS metabolites of interest	8
1.1.6. Macromolecules of interest in ^1H -MRS	10
1.2. Thesis Objectives	11
1.3. Thesis Contribution	12
1.4. Thesis Organization	13
Chapter 2. BACKGROUND OF METHODOLOGIES	15
2.1. Magnetic Resonance Spectroscopy	15
2.2. Sparsity in Signal Processing	17
2.3. Wavelet transform	18
2.3.1. Double Density Dual Tree Discrete Wavelet Transform (DDTDWT)	19
2.3.2. Rational-Dilation Wavelet Transform (RADWT)	20

2.3.3. Dual Tree Complex Wavelet Transform (DTCWT)	20
2.4. Wavelet thresholding	21
2.5. Machine learning	23
2.5.1. Support Vector Regressor	23
2.5.2. Random Forest	23
2.5.3. XGBoost	24
2.6. Deep Learning	
2.6.1. Convolutional Neural Network (CNN)	25
2.6.2. Long Short-Term Memory (LSTM)	27
2.6.3. U-Net	27
2.7. Review of previous works in MRS	31

Chapter 3. Sparsity based thresholding criterion for spurious echo removal and denoising MR spectra using rational-dilation wavelet transform

3.1. Introduction	37
3.2. Theory	38
3.2.1. Rational-Dilation Wavelet Transform (RADWT)	38
3.2.2. Sparsity measures ($L_{p,q}$ norm)	40
3.3. Thresholding criteria	43
3.3.1. Existing methods	43
3.3.2. Proposed criteria	44
3.3.3. Thresholding function	45
3.4. Method	46

3.4.1. Dataset used	46
3.4.2. Evaluation metrics	47
3.5. Experiments	48
3.6. Results and Discussion	49
3.7. Conclusion	54
Publication out of the study	55

Chapter 4. A Gradient boosted regression tree ensemble model using wavelet features for post-acquisition macromolecular baseline isolation from Brain MR spectra

4.1. Introduction	57
4.1.1. Theory	60
4.1.2. Wavelet transform	61
4.1.3. XGBoost	62
4.2. Methods	64
4.2.1. Simulation of dataset	64
4.2.2. <i>In-vivo</i> dataset	66
4.2.3. Fitting model architecture	66
4.3. Results and Discussion	69
4.3.1. MM isolation from noisy dataset: Comparison with different regression models	70
4.3.2. Parameterization of individual MMs from isolated MM spectra	72
4.3.3. Reconstructing Individual components from spectra of different noise level	75

4.3.4. MM isolation in the presence of Residual Waterpeak	76
4.4. Conclusion	78
Publication out of the study	79
Chapter 5: A hybrid deep learning approach to complete quantitation of proton magnetic resonance spectral peaks of the brain	
5.1. Introduction	81
5.2. Methods	83
5.2.1. Data augmentation and preparation	83
5.2.2. Model architecture	85
5.3. Results	88
5.3.1. Metabolite-MM isolation from spectra with different SNR	89
5.3.2. Relative peak amplitude estimation	92
5.3.3. Residual water removal	96
5.4. Discussion	97
5.5. Conclusions	99
Appendix	100
Publication in communication	102
Chapter 6: Conclusions and Future Scope	103
References	107

LIST OF FIGURES

Fig. 1.1.	Left: Transverse magnetization plot; Right: Longitudinal magnetization plot.	3
Fig. 1.2.	MR acquisition of the metabolite NAA. Left: real part of FID of metabolite ‘NAA’ (time-domain). Right: Real part of the Fourier transformed metabolite ‘NAA’ peaks.	5
Fig. 2.1.	A schematic of a residual connection implemented in a Deep Learning (DL) model. The activation function (f) used is ReLU, w_i is the weight at i^{th} layer, x is the input.	29
Fig. 2.2.	Attention modules used in a DL network. Left: Scaled Dot-Product Attention; Right: Multi-Head Attention module.	30
Fig. 2.3.	A standard architecture of inception module.	31
Fig. 3.1.	(a) Iterated filterbank for RADWT; (b) Analysis and Synthesis part of Filterbank	39
Fig. 3.2.	(a) RADWT frequency response of each of 15 levels of decomposition; (b) wavelet function resembling ‘Gabor’ function; (c) Fourier Transfer of wavelet function having Gaussian-like shape.	40
Fig. 3.3.	Visualization of spurious echo removal for comparison of different existing approaches: (a) Original signal with spurious echo; Spurious echo removal plot using different methods: (b) proposed method signal plot, (c) and (d) scalogram plot of (a) and (b); (e) using Minimax-soft thresholding, (f) using Minimax hard thresholding, (g) using SURE-soft thresholding, (h) using SURE hard thresholding, (i) using Srivastava et al. method signal plot, (j) corresponding	52

	scalogram plot.	
Fig. 3.4.	Denoising of Raman test signal by the proposed method.	54
Fig. 4.1.	Schematic of the steps followed for simulation of brain MRS spectra.	65
Fig 4.2.	Architecture of the proposed fitting model.	69
Fig 4.3.	Comparison of MM spectra isolation. In the figure panel, Ground Truth-MM for given noisy spectrum is compared with fitted MM spectra of different models respectively. Top left: Noisy spectrum with GT-MM; Top right: RF model fitted MM; Middle Left: SVR model fitted MM; Middle right: CNN model fitted MM; Bottom left: LSTM model fitted MM; Bottom right: Proposed method fitted MM. [Colour code - Blue: Noisy spectrum, Orange: GT-MM, Green: Fitted MM for the model, respectively].	73
Fig 4.4.	Isolation of MM spectra and Individual MM components from Spectra of variable noise levels. (a) 5dB, (b) 8dB, (c) 12 dB, (d) 15dB. The y-scale (amplitude) in Predicted MM and Recon: MM components plots of every figure have been scaled up for better visualization of isolated MM spectra and reconstructed Individual MM components.	76
Fig 4.5.	MM spectrum isolation from residual water peak included noisy MR spectra. Top: Noisy spectra with residual waterpeak; Middle: Superimposed individual components contribution of Metabolites, Macromolecular Baseline (GT) and Residual waterpeak, [Blue: Noisy spectrum, Green: GT-MM, Orange: Residual waterpeak]; Bottom: Isolated MM from nosiy spectra with residual waterpeak	77

(GT vs Proposed method) [Blue: GT-MM, Orange: Fitted MM from the proposed method].

- Fig 5.1. Inception module architecture for UNet encoder-decoder. (a) Wavelet residual inception module (used as 1st encoder block only), (b) Residual inception module for the rest encoder-decoder module. 86
- Fig 5.2. A schematic of the proposed model architecture for quantitation of MRS spectra. 89
- Fig 5.3. Comparative plots of the trained model performance: (a) loss function: mse (b) metric: accuracy 90
- Fig 5.4. Isolation of Metabolites and MMs from simulated test set brain MR spectra with different SNR: (a) 6 db, (b) 8 db, (c) 11 db, (d) 13 db. Each plot has five subplots: Noise degraded spectrum, overlapped ground truth and predicted metabolite spectra, overlapped ground truth and predicted MM spectra, overlapped noise added and noise removed, error between ground truth and predicted (Met+MM) spectra. 91
- Fig 5.5. Combined plot of individual peak estimates (ground truth vs. proposed): (a) metabolite peaks, (b) MM Peaks. [a.u.: arbitrary units, used for relative concentration estimate). 93-94
- Fig 5.6. Bland-Altman plot of individual peaks. (a) for Metabolite (b) for MMs. 95
- Fig 5.7. Isolation of Metabolites and MMs from simulated test set brain MR spectra with residual water peak at SNR: (a) 5 db, (b) 8 db. Each plot has five subplots: Noise degraded spectrum with residual waterpeak, 97

overlapped ground truth and predicted metabolite spectra, overlapped ground truth and predicted MM spectra, overlapped water + noise added and removed, error between ground truth and predicted (Met+MM) spectra.

LIST OF TABLES

Table 1.1:	A comparison between SVS and MRSI acquisition technique.	6
Table 2.1.:	A review of previous ML/DL based application in MRS analysis	34
Table 3.1:	Comparison of Peak amplitudes after denoising using different thresholds.	50
Table 3.2.:	Comparison results of different methods for denoising efficiency.	50
Table 4.1:	Parameters used to generate Macromolecular spectral baseline (expected at $B_0 = 3T$).	60
Table 4.2:	Hyperparameters for the proposed model.	68
Table 4.3:	Performance metrics of the models for MM isolation from noisy spectra.	71
Table 4.4:	MM peak parameterization: (mean over 500 simulated MMBL spectra)	74
Table 4.5:	Results for MM isolation from spectra with residual waterpeak.	77
Table 5.1:	Design and training parameters for inception modules used.	87
Table 5.2:	Comparative performance outcomes of the trained models	90
Table 5.3:	Performance evaluators for the peak amplitude estimation	93
Appendix Table 5.1:	Relative metabolite concentration range used in current study for the individual basis in simulating the brain spectra	100
Appendix Table 5.2:	Parameters used to generate Macromolecular spectral baseline (expected at $B_0 = 3T$).	101

PREFACE

This thesis is submitted for the degree of Doctor of Philosophy at Indian Institute of Technology (Banaras Hindu University), Varanasi. The research described herein was conducted under the supervision of Prof. Neeraj Sharma in the School of Biomedical Engineering, Indian Institute of Technology (Banaras Hindu University), Varanasi between July 2016 and July 2023.

To the best of my knowledge, this work is original, except where acknowledgements and references are made to previous work. Neither this, nor substantially similar thesis has been or is being submitted for any other degree, diploma, or other qualification at any other university.

ABSTRACT

MR Spectroscopy (MRS) is a non-invasive, ionizing radiation-free analytical MR technique to obtain information about a range of biochemicals, usually referred to as "metabolites" and "macromolecules" signals, from MR scanner. Proton MRS (^1H) is the most common technique used for tissue characterization of an organ in clinical setup complementing with MRI, which provide anatomical information. It presents an effective alternative method to biopsy for diagnosis of the tissues in the region of interest (ROI). The signals obtained are the sum of damped exponentials in time domain, called free induction decay (FID). Each individual exponential is associated with a particular ^1H nucleus of resonant frequency, uniquely defined by the local magnetic field depending upon the environment in which the molecule resides. The difference in these resonant frequencies, termed as 'Chemical Shift' and is the main basis of differentiation among biochemicals in MRS.

With the advancement in image processing and machine and deep-learning domains, use of image-based methodologies like MRI, CT, USG as non-invasive diagnostic tool in clinical set-up of healthcare has improved drastically. These tools have the shortcoming of generally providing anatomical profile through images. MRS, on the other hand, provides much detailed profile on a bio-chemical level, resembling *in-vivo* conditions non-invasively. This presents a fascinating area to study *in-vivo* condition non-invasively complementing MRI towards highly effective early diagnosis in healthcare. With technological advancements, MRS scan times have reduced exceptionally, increasing its usability and acceptability in the healthcare community. With the availability of more data and developments in the field of signal processing; ML, DL techniques have effectively worked in favour of MRS based research as well as clinical applications post-acquisition.

Biological signals like MRS signals are significant in analysing human physiological conditions. But these signals are susceptible to noise and artifacts and superimposition of a broad

macromolecular baseline with the metabolite components which can cause misinterpretation and subsequent incorrect diagnosis. In this thesis, we have attempted to create a single framework for the non-invasive, post-acquisition quantitation of biochemical components present in the MRS spectra such that it can be used in disease diagnosis. In this thesis, the analysis of degraded MR spectra was performed in three steps: noise and artifact removal, macromolecular spectra isolation from overlapped metabolite spectra, ultimately leading to a quantitation strategy for estimating individual metabolites and macromolecular components.

For different studies in this thesis, a basis-set of 18 individual metabolites [alanine (Ala), aspartate (Asp), creatine (Cr), γ -aminobutyric acid (GABA), glucose (Glc), glutamine (Gln), glutamate (Glu), glycerophosphorylcholine (GPC), glutathione (GSH), lactate (Lac), myo-inositol (mI), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), phosphoryl-choline (PCho), phosphorylethanolamine (PE), phosphocreatine (PCr), taurine (Tau)] were identified from literature review. The relative amplitude range for each metabolite was determined from the literature [26, 32-34]. Next, a basis-set for 17 MM components [$M_{0.94}$, $M_{1.22}$, $M_{1.43}$, $M_{1.70}$ (1.63, 1.68, 1.81), $M_{2.05}$ (1.99, 2.04), $M_{2.27}$, $M_{2.54}$, $M_{3.00}$, $M_{3.21}$ (3.11, 3.22, 3.27), $M_{3.71+}$ $M_{3.79}$, $M_{3.97}$] of gaussian lineshape were simulated with amplitude, linewidth and chemical shift parameters obtained from literature. Variation in the relative concentrations of different biochemicals is indicative of a specific medical condition or disease, and act as an important biomarker for detection and diagnosis.

To address the issue of noise and artifacts, a rational-dilation wavelet transform-based signal decomposition and a thresholding criterion designed using L_{pq} -norm-based sparsity measure of the decomposition levels of the signal was implemented and evaluated. Compared to the standard state-of-the-art methods, which are effective in denoising but can cause distortion of the signal at discontinuities, the proposed method can remove artifacts such as spurious echoes present in the MR signals and improve the signal SNR without distorting the signal. From this study, we also

took inferences that wavelet based multi-resolution decomposition can be used as an efficient feature descriptor for machine-, deep-learning models.

To address the issue of macromolecular baseline and metabolite spectra isolation from noisy MR spectra, which inherently is an inverse problem (explained in chapter 4), a novel approach of gradient boosted wavelet-feature tree model in a multioutput-regression framework for MRS spectral fitting was adopted, where the inverse problem was learned by training over wavelet coefficients of noisy spectral dataset simulated using basis-set of metabolites and macromolecules. The proposed method performed almost perfectly for the simulated dataset with smaller margins of error, compared to an equivalent CNN model. For the simulated test set, RMSE and SSIM of 0.1623 and 0.9571 respectively were obtained and RMSE of 0.2263 was obtained for *in-vivo* test set. The fitted peak amplitude for individual MM component lies within $\pm 4\%$ of error range over the simulated dataset. From our attempt, we have found that for residual waterpeak height $\leq 3 \times$ Highest peak of training spectra, our model is able to isolate MM spectra with little hyperparameter tuning of our model. The proposed model achieved an RMSE value of 0.2988 and SSIM of 0.8973 when the spectra was contaminated with residual water peak.

From the two previous studies, we understood the effectiveness of combining wavelet features in a learning-based framework for regression tasks. Therefore, for the goal of quantitation of MR spectra in a post-acquisition setup, we introduced more complex but efficient strategies like UNet structure for 1D-signals, residual modules, attention modules, inception module among other for our final study. a novel hybrid deep network of inception module-Unet architecture with residual connection and regression-dense layers has been proposed to isolate and quantify brain metabolites and macromolecules (MM) from a degraded, low SNR with baseline embedded, line-broadened spectra obtained from proton MR spectroscopy ($^1\text{H-MRS}$) in a clinical setting. In time domain, peak amplitude of individual biomarkers is directly proportional to their relative concentration. A set of degraded 30000 spectra with equivalent ground truths were simulated mimicking *in-vivo*

characteristics of brain MRS by using basis for individual metabolites and MMs for training and evaluation of the proposed model with train/validate/test set as 70/15/15 % ratio. The model performed accurately in isolating corrected metabolite and MM spectra with an accuracy of 99.19% on a trained model with validation loss of 0.0714 and test-set root mean-squared error (RMSE) of 0.2684. The structural similarity index (SSIM) between ground truth and isolated spectra was calculated with a mean value 0.9427 for metabolites, and 0.9506 for MM spectra. The peak amplitude estimated by regression-dense layer module from isolated spectra gave an RMSE value of 0.1807 for metabolites, and 0.0833 for MMs. For each metabolite/MM relative concentration or peak amplitude estimated, mean absolute percentage error (MAPE) was calculated. For all the 18 metabolites, the overall MAPE calculated was 9.03 %, with Ala, GABA, PCho, and NAAG having highest MAPE at 9.14, 10.44, 11.07, and 9.91 % respectively. For GSH, Gly, and NAA, MAPE were 8.48, 8.60, 7.29 and for rest of the metabolites, MAPE was below 5%. Similarly, for 17 estimated MM peak, the overall MAPE was 4.09% with $M_{1,22}$, $M_{3,27}$, $M_{3,79}$ having values above 5.5%. The rest of the MM peaks ranges between 2.21-3.9% of MAPE. The study results, therefore, support for an end-to-end deep learning model approach in quantitation of clinical degraded MR spectra for diagnostics and pathological studies. Small tests over datasets with water peak removed also gave encouraging results and scope for future developments to further reduce the acquisition times of an MRS scan.

Keywords: MRS, metabolites, signal processing, sparsity, L_{pq} -norm, spurious echo, macromolecules, complex wavelet, gradient boosting, feature extraction, inception model, UNet, attention, residual connection, peak estimation.