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CHIRANJEEV SAGAR

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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.

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PREEFACE

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 (^{1}H) 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 ^{1}H 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), ɣ-aminobutyric acid (GABA), glucose (Glc), glutamine (Gln), glutamate (Glu), glycerophosporylcholine (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 ±4% of error range over the simulated dataset. From our attempt, we have found that for residual waterpeak height <= 3* 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}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.