

Metabolite Quantification of 1H-MRSI spectra in Multiple Sclerosis: A Machine Learning Approach

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Synopsis

As an alternative to model-based spectral fitting tools, we introduce a machine-learning framework for estimating metabolite concentrations in MR spectra acquired from a homogeneous cohort of 42 patients with Secondary Progressive Multiple Sclerosis. Our framework based on random-forest regression performs a 42-fold cross validation on this dataset which involves (1) learning the spectral features from this cohort; (2) estimating concentrations and calculating relative error over the LCMoel estimates. Compared to the LCMoel, our method, after training, gives a low estimation error and a 60-fold improvement in estimation speed per patient.

Purpose

Multiple Sclerosis (MS) is an inflammatory neurological diseases affecting around 2.5 million people globally (www.mstrust.org.uk). Quantification of metabolites can yield important diagnostic information about disease progression for which model-based fitting tools such as the LCMoel [1] are widely used. Despite being the gold-standard, they require prior knowledge-tuning and can also be time-consuming. Prior work on healthy human brains has shown Random-Forest regression to perform the same quantification but at a faster speed [2]. The purpose of this work is to apply this method to a clinical setup involving MS-patients and address the limitations of parameter-tuning and speed of conventional fitting tools by validating on an extensive ¹H MRSI-MS dataset.

Methods

Random Forests [3] have been shown to be effective in a wide range of classification [4][5] and regression problems [2], including classification of MS-spectra [6]. These involve multiple forests comprising of a set of binary trees. For training, splits are created in each tree based on random subsets of the feature variables and piecewise linear regression is performed over the input data [2]. The process involves seeking best prediction at every node and using thresholding to further propagate data points till they reach the end of the tree. Subsequently the weighted average of the prediction from each tree is taken to give a single output estimate. In MRSI, the time-domain complex signal of a nucleus is given by:

$$S(t) = \int p(\omega) \exp(-i\Phi) \exp(-t/T_2^*) d\omega.$$

, and the corresponding frequency-domain spectrum is given by $S(\omega)$. As shown in Fig.1, we aim to perform the inverse signal-modeling where we have a training dataset, $D = (S_i(\omega), Y_i), i \in [1, N]$, where N is the total number of MS training spectra from 41 patients. $S_i(\omega)$ represents the training spectral data while Y_i represents the corresponding multi-parameter training labels. For our model, we consider the absolute concentrations of NAA, Cho, Cr, Myo-Inositol(ml) and Glutamate+Glutamine (Glx). Therefore, for a given spectrum $S_i(\omega)$, $Y_i = [NAA_i, Cho_i, Cr_i, mI_i, Glx_i]$. We run a K-Fold cross validation with 42 folds, number of trees = 100 and mTry = 128 to generate training sets using spectra from 41 patients and test on the spectra, $S_j(\omega)$, from the remaining patient to obtain concentration estimates \hat{Y}_j . The corresponding LCMoel fitted concentration labels Y_j serve as the ground-truth, $j \in [1, M]$ where M is the total number of test spectra. Error Calculation. For our experiments, we assess the absolute relative change in parameter estimates over the ground-truth values. Given the estimate \hat{Y}_j and the testing label Y_j , the estimate error for the parameter Y_j can be calculated as,

$$\hat{E}_j = \|\hat{Y}_j - Y_j\| / \|Y_j\|$$

Subjects. 42 patients (age 55+/-8) with SPMS (EDSS score 6+/-0.7) were recruited as part of the study. The patients underwent MRI examination at 3T, including T1w, T2w and FLAIR scans and proton semi-LASER MRSI with $TR/TE = 2000/43ms$ and 481 data points over spectral region-of-interest. An example has been shown in Fig.2. Prior work provides additional acquisition details [7]. The data was fitted using LCMoel and the voxels which did not pass the Cramer-Rao Lower Bound (CRLB) and visual quality tests were discarded (e.g. distorted baselines). There are no 'pure' lesion or non-lesion voxels and therefore all spectra are of mixed content. Total spectra per fold included approximately 4200 training and 100 test-spectra/patient respectively.

Results

We aim to get an error \hat{E}_j of < 15% for each of the metabolites per patient. The mean absolute relative error plots for all patients are shown in Fig.3. Using the Bland-Altman method [8], we observe a strong correlation between the LCMoel and RF estimates for a sample patient (Fig.4). \hat{E}_j for the same sample patient are within the acceptable range (especially for the major metabolites such as NAA, Choline and Creatine)(Fig.5).

Speed: **Training time** per fold is 3 minutes. While the LCMoel takes 10 minutes per patient for the metabolite quantification, our proposed framework, after training, takes only 10sec leading to a 60x improvement in speed

Discussion

An outlier high-error spectrum for a test-patient has been highlighted in Fig.4 which corresponds to the outlier whisker in Fig.5. The peaks in this spectrum are not well-defined and only few such spectra are present in the training set. The machine learning algorithm is therefore insufficiently trained on such spectra resulting in a high error. Future work would involve using a more robust approach such as deep-learning based methods to improve the accuracy of parameter estimation. Once a framework has been established, further work can be done on having a MS-specific simulated spectra model with wider variations in the spectral peak for parameter estimation to predict disease progression and the corresponding metabolite maps.

Acknowledgements

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Figures

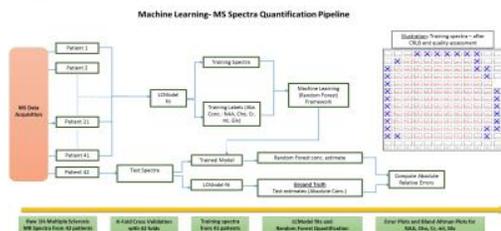


Fig.1: Pipeline for Machine Learning based quantification of MS spectra. Using the K-fold cross validation approach, this method is repeated using each of the 42 patient MS-spectra as test spectra.

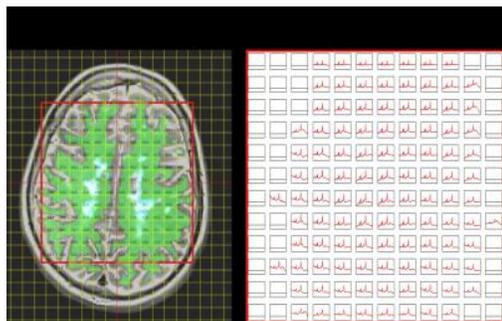


Fig.2: MRSI data acquired from an SPMS patient and the corresponding spectra after voxel-wise LCModel fitting [7].

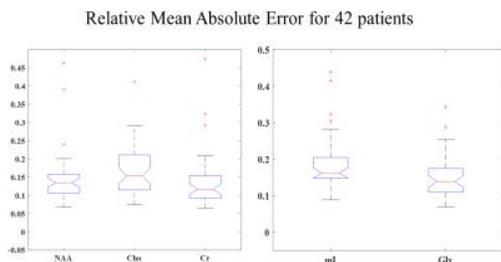


Fig.3: Absolute Relative Error box-plots for the entire 42-patient spectra dataset. The mean relative errors are: **(Left)** NAA (13.4%), Choline (13.8%), Creatine (10.8%); **(Right)** ml (14.7%), Glx (10.8%). 5 of the patient data included outlier spectra similar to the one shown in Fig. 4 which led to an overall increase in the mean relative errors for each of the metabolites.

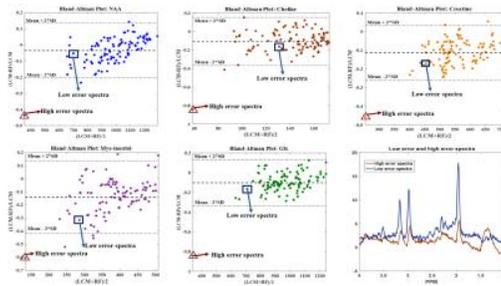


Fig.4: Bland-Altman[8] plots representing LCModel and Random Forest (RF) estimates of spectra from a sample MS-patient dataset. The X-Axis is the mean of the LCModel and RF estimate, while the Y-Axis represents the relative error of the RF estimate over the LCModel. **From (L-R):** Bland-Altman Plots for (*Top row*)- NAA, Choline and Creatine, (*Bottom row*)- myo-Inositol(ml) and Glx and spectra plots of outlier spectrum with high quantification error and one of the spectra with low quantification error (these are marked in the Bland-Altman plots within a red triangle and blue square respectively).

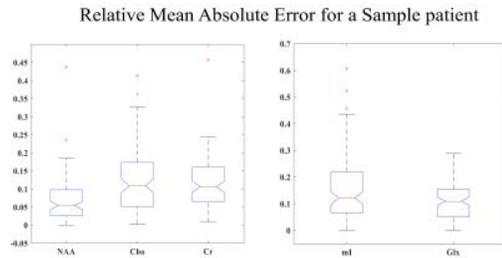


Fig.5: Absolute Relative Error box-plots for the sample patient spectra (same as in Fig. 4). The mean relative errors are: **(Left)** NAA (5.1%), Choline (10.4%), Creatine (10.2%); **(Right)** ml (11.5%), Glx (10.8%).