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Toward Developing Robust Myotonic Dystrophy Brain Biomarkers using White Matter Tract Profiles Sub-Band Energy and A Framework of Ensemble Predictive Learning

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Abstract— **The myotonic dystrophies (DM1 and DM2) are dominantly inherited disorders that cause pathological changes throughout the body and the brain. DM patients have difficulties with memory, attention, executive functioning, social cognition, and visuospatial function. Quantifying and understanding diffusion measures along main brain white matter fiber tracts offer a unique opportunity to reveal new insights into DM development and characterization. In this work, a novel supervised system is proposed, which is based on Tract Profiles sub-band energy information. The proposed system utilizes a Bayesian stacked random forest to diagnose, characterize, and predict DM clinical outcomes. The evaluation data consists of fractional anisotropies calculated for twelve major white matter tracts of 96 healthy controls and 62 DM patients. The proposed system discriminates DM vs. control with 86% accuracy, which is significantly higher than previous works. Additionally, it discovered DM brain biomarkers that are accurate and robust and will be helpful in planning clinical trials and monitoring clinical performance.**

Clinical relevance— **Numerous DM patients experience neurological and cognitive effects that significantly influence their well-being. As new drug trials address the DM neurological symptoms, there is an urgent need for validated neurological biomarkers of DM. Further, defining quantifiable neural signatures of DM will help gain better insights into the disease pathophysiology and can lead to earlier diagnosis and more targeted treatment.**

I. INTRODUCTION

Myotonic dystrophies (DM) are highly variable inherited disorders that directly impact multiple organ systems including the brain. Central nervous system (CNS) manifestations in DM include decreases in attention, reduced visuospatial functioning, executive functioning, memory, and social cognition [1]. There is wide phenotypic variability in cognitive function, and evidence for a progressive component. Diffusion tensor imaging (DTI) shows decreased white matter (WM) connectivity in children and adults with DM, and magnetic resonance imaging (MRI) reveals decreased parietal, frontal, and temporal resting state metabolism [2]. Currently there are several experimental drugs being developed to benefit DM CNS symptoms, yet there are no validated CNS outcome measures ready for trials to demonstrate responsiveness to treatments.

Each major WM tract in the brain includes different populations of axons, and their health status can potentially unravel various cognitive and neurological alterations. Tract diffusion properties are used in clinical research to infer the neurobiology of different diseases. Fractional anisotropy (FA) is widely used to measure WM integrity along the tracts. FA provides useful information about fiber density and axonal diameter in WM and a decrease in its value suggests a loss of fiber tract integrity and WM damage. Previous studies show that FA values vary substantially within a tract and DM effects on the brain have little anatomical specificity [3]. Additionally, DM may strike at any local positions within the major WM tracts. Hence, diffusion properties of a tract should be represented with an array of measurements sampled at equidistant locations along the tract rather than representing a tract with mean diffusion measures. Furthermore, the DM characterization system should be able to learn local and global brain patterns simultaneously.

The main objective of this work was to design and develop a DM CNS characterization system to identify unique brain signatures of DM as neurological biomarkers, with the goal of identifying a combination of outcome measures for upcoming clinical trials. Therefore, we proposed a data-driven automated approach to efficiently identify equivalent WM structures in individuals with DM and healthy controls and measure multi-dimensional properties of the WM structures that are altered in DM patients. One main challenge of the DM characterization system is the sample size. MRI process is more complex and expensive than most imaging methods. Additionally, the prevalence of DM in the general population is about 1 in 8000 people [4]. Therefore, the size of DM brain imaging datasets is limited and small.

To deal with a small sample size and the need for both global and local features, an ensemble system is proposed, which uses time and spectral contents of FAs calculated for WM tracts to generate accurate and robust DM characterizations. The proposed method used Bayesian approach for the fusion function. Comparing to previous works [5], our method has three significant advantages. First, previous methods only analyzed global features of WM tracts, whereas our method uses both global and localized multi-scale features. Second, previous works only studied a few

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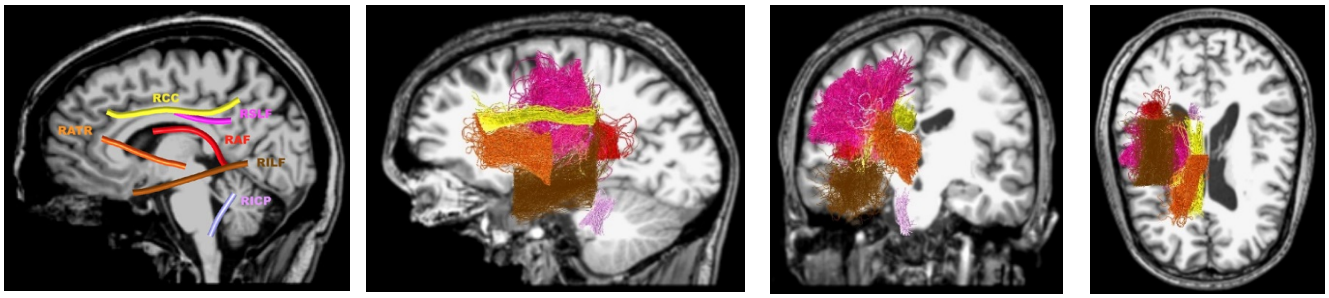

Fig. 1: Analyzed right tract FA profiles in different views.

number of WM tracts. In this work, 12 WM tracts underwent a comprehensive analysis. Third, uncertainties in data are accounted for in this work and instead of representing features and class labels by deterministic values, they are treated as probability distribution functions.

This paper is structured as follows. Section II describes the proposed system and presents details of the evaluation dataset. In section III the experimental results are presented and discussed. Lastly, final conclusions are presented in section IV.

II. Materials and Methods

Ensemble systems have been successfully applied in medicine with the goal of generating more accurate and robust predictions by combining the approximations of different models. In this work, a Bayesian random forest is proposed, which randomly samples many trees from a prior distribution, and subsequently performs a weighted ensemble of predictive probabilities. Details of each step are explained below.

A. Data Description and Pre-Processing

DTI scans and MRIs were acquired at the University of Minnesota (UMN) under an institutional review board (IRB) approved protocol using a Siemens 3T TIM trio scanner with a 12-channel receive only head coil [2]. Data was collected for 62 DM patients (46 DM1 and 16 DM2) and 96 controls. In this study, subjects had a genetic diagnosis or clinical diagnosis of DM1 or DM2 and they were between the ages of 18 and 60 years.

All scans were pre-processed using the reproducible tract profiles (RTP) methodology [6] at Stanford University. Scan preprocessing and tractography were handled in Flywheel, a neuroinformatics platform that utilizes Google Cloud Platform for cloud based analysis [6]. In the preprocessing phase, each T1w file was aligned to canonical anterior commissure - posterior commissure orientation using Vistasoft tool (`https://github.com/vistalab/vistasoft`) on a local machine. All scans were denoised using principal component analysis (PCA) [7] and went under Gibbs ringing correction [8], Eddy current correction [9] and bias correction via Advanced Normalization Tools (ANTs) [10]. FreeSurfer (`http://surfer.nmr.mgh.harvard.edu/`) was utilized for segmentation and region of interest (ROI) placement on each T1w acquisition.

The diffusion data was aligned and re-sliced using dtiInit and modeling was performed at voxel level to generate the FA data [6]. Previously determined ROIs were used to define tract locations using the automated fiber quantification (AFQ) method [11]. After the tract profiles were defined, individual tracts were calculated based on voxel-based metrics.

To decrease computational complexity, tracts were sampled along each fiber at 30 equidistant nodes. Diffusion properties were calculated by taking a weighted average across all streamlines belonging to each specific tract bounded by the same two ROIs used for that tract's segmentation. Each streamline's contribution to the average was weighed based on its Mahalanobis distance from the tract core [11]. This generated a downloadable file from Flywheel that included a Tract Profile showing variations along the central portion of each tract for each participant. Tract Profile data are composed of various metrics including radial diffusivity (RD), fractional anisotropy (FA), mean diffusivity (MD), and axial diffusivity (AD). In this work, FAs were used to study the white matter tracts.

We conducted a comprehensive analysis of the following twelve WM tracts: 1) Left Anterior Thalamic Radiation (LATR); 2) Right Anterior Thalamic Radiation (RATR); 3) Left Corpus Callosum (LCC); 4) Right Corpus Callosum (RCC); 5) Left Inferior Longitudinal Fasciculus (LILF); 6) Right Inferior Longitudinal Fasciculus (RILF); 7) Left Superior Longitudinal Fasciculus (LSLF); 8) Right Superior Longitudinal Fasciculus (RSLF); 9) Left Arcuate Fasciculus (LAF); 10) Right Arcuate Fasciculus (RAF); 11) Left Inferior Cerebellar Peduncle (LICP); and 12) Right Inferior Cerebellar Peduncle (RICP) (see Fig. 1).

The discrete wavelet transform (DWT), a multi-resolution time-frequency [12] analysis was used to represent the finer variations in the Tract FA Profiles at various scales. Daubechies mother wavelet was selected empirically considering its high correlation with Tract FA Profiles. To decrease dimensionality, each sub-band is represented by the standard deviation and mean of the absolute values of the coefficients in the sub-band and normalized sub-band energy (NSE), which is calculated by dividing the sub-band energy by the total energy.

B. Classification using Bayesian Random Forests

This work proposed a new method for the DM characterization task. This method is called the Bayesian stacked

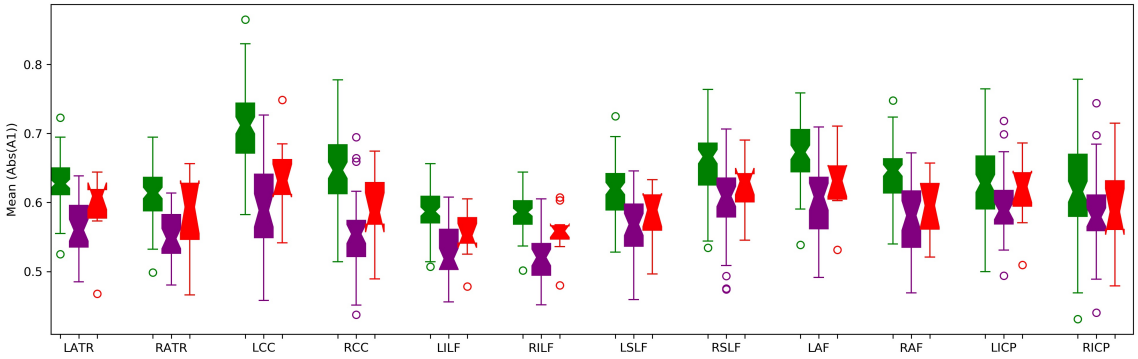

Fig. 2: Mean of the absolute values of the approximation sub-band level 1 (A1) coefficients. Green, purple, and red represent data from control, DM1, and DM2 subjects respectively.

random forest (BSRF), in which a set of random forests (RFs) are trained and applied in a sequential order and the Bayesian approach is used for the fusion function. The BSRF is designed based on the posterior probability, and predictions generated by the ensemble's classifiers represent the conditional terms. The first RF at the 0 level has only access to the WM tract data and RFs at higher levels use the approximation of the RF at the preceding level as additional input. This process refines the class decision and allows to correct errors made by classifiers of previous levels.

Let x be a new subject and y_i be the prediction made by the ith classifier, where $1 \leq i \leq B$. For the generic class C_k, the BSRF will assign the class that maximizes the probability in Eq.1. The conditional probabilities in Eq.1 are unknown, hence the Bayesian rules are used to approximate Eq.1 and generate Eq.2. To simplify Eq.2, the denominator is written as Eq.3. In this equation, M is the number of classes, which is equal to 3 (Control, DM1, and DM2). A conditional independence between the predictions of all the classifiers is assumed, hence Eq. 2 is simplified to Eq. 4. Consequently, to maximize Eq. 4, the numerator should be maximized with respect to k.

$$P\left(C_k|y_1,\ y_2,\ \ldots,\ y_B\right) \tag{1}$$

$$P\left(C_k|y_1,\ y_2,\ \ldots,\ y_B\right) = \frac{P\left(C_k\right) P(y_1,\ y_2,\ \ldots,\ y_B|C_k)}{P\left(y_1,\ y_2,\ \ldots,\ y_B\right)} \tag{2}$$

$$P\left(y_1,\ y_2,\ \ldots,\ y_B\right) = \sum_{l=1}^{M} P\left(y_1,\ y_2,\ \ldots,\ y_B|C_l\right) P\left(C_k\right) \tag{3}$$

$$P\left(C_k|y_1,\ y_2,\ \ldots,\ y_B\right) = \frac{P\left(C_k\right) \prod_{i=1}^{B} P(y_i|C_k)}{\sum_{l=1}^{M} \prod_{i=1}^{B} P\left(y_i|C_l\right) P\left(C_k\right)} \tag{4}$$

If one of the ensemble's classifiers generates a zero probability, the max rule is used instead of the product rule and the class with the maximum probability is selected as the final class label. This happens in a very rare situation as WM tracts are modified by the DM in a continuous way and changes induced by the disease process are also continuous in FA data. As a result, except for extreme cases, distinct borderlines between features extracted from FA data of WM tracts of DM1, DM2, and healthy controls cannot be identified and the generated probabilities are not zero for majority of subjects.

TABLE I: Performance indexes of the proposed DM characterization system and a previous effort.

DM Characterization System	Spc_{DM}	Spc_{Cont}	Sen_{DM}	Sen_{Cont}	A_T
Current Effort	84.90	88.46	74.19	93.75	86.07
Previous Effort [13]	72.11	75.55	70.10	77.31	73.71

III. Results and Discussion

This section presents the experimental evaluation results of the developed DM characterization system and compares current effort with a previous DM characterization system proposed in [13], which is based on resting state functional MRI analysis of the same patients used in this study.

The box plots of Fig. 2 show the distributions of one of the features extracted from the twelve WM tracts and used for the DM characterization task. These coefficients are the lowpass representation of the FAs calculated for the twelve WM tracts. The lowpass representation provides a smoother form of the FA signals and helps to study the long-term trend. Detail coefficients (Ds) of FA signals are also used in this analysis to study the short-term fluctuations caused by the disease process. The features explained in section II. A were calculated for the A1-A4 and D1-D4 sub-bands of the FA signals and were fed to the BSRF classifier.

Fig. 3 shows tract fractional anisotropy profiles for the left arcuate fasciculus (AF) of DM1 and DM2 patients included in the UMN dataset. In each plot, the black curve shows the control mean, and the lighter shades represent the interquartile range and the 10th-90th percentile range. The red curve shows FA values along the left AF in an individual with DM1/DM2. An interquartile range is a measure of where the bulk of the values lie and the 10th-90th percentile range is the difference between the 90th and 10th percentiles. Fig. 3 shows that DM changes in FA occur at specific positions within the Tract Profile, rather than along the entire tract.

Table I shows the performance of the proposed DM characterization system and a comparison between the accuracies obtained in this work and those reported in a previous study [13], using the same subjects. The developed system was assessed using five different performance measures: sensitivity

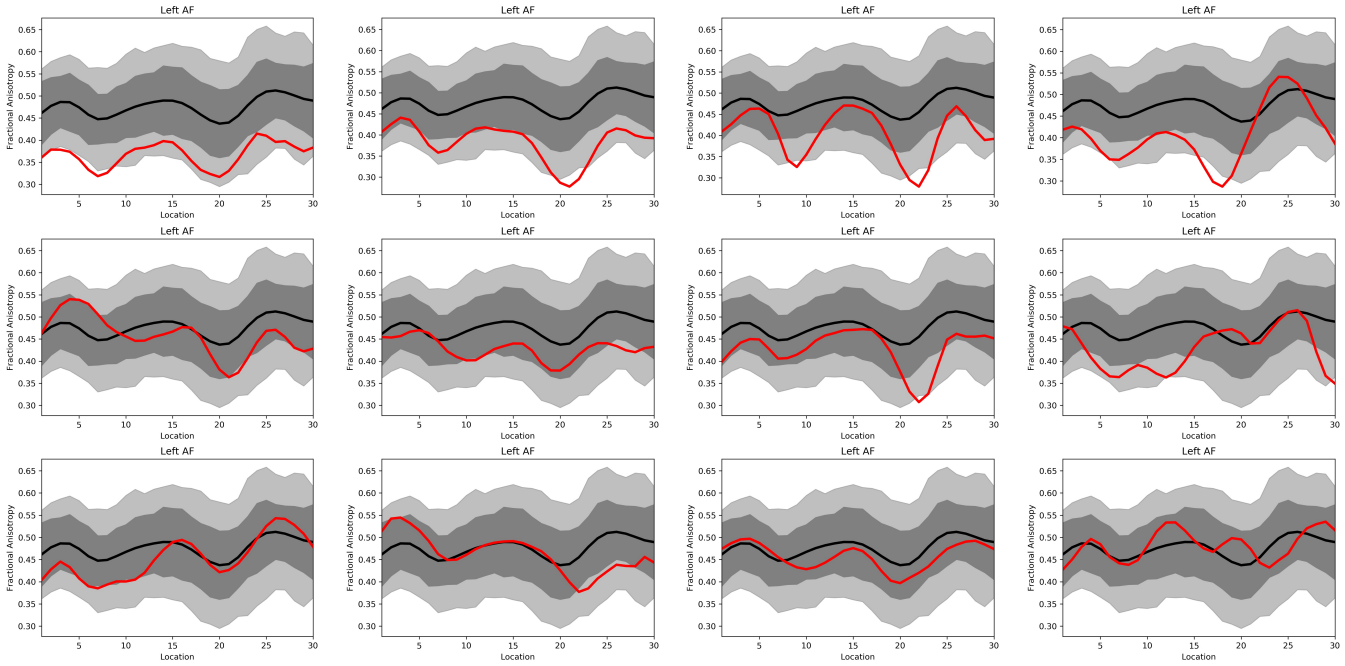

Fig. 3: Tract FA profiles for the left AF tract selected randomly from the UMN samples. The first and second row show samples that are correctly labeled by the proposed system as DM1 and DM2 respectively. The third row shows samples belonging to DM patients that are incorrectly labeled as controls.

of control and DM (Sen_{Cont}, Sen_{DM}), specificity of control and DM (Spc_{Cont}, Spc_{DM}), and total accuracy (A_T). As Table I shows, the performance of the proposed system is significantly higher than that of the previous effort. These results show that neurological biomarkers calculated based on the WM Tract Profiles (NSE, mean and standard deviation of the wavelet coefficients) can accurately characterize DM1 and DM2.

IV. CONCLUSIONS

In this work, a novel system was proposed to identify unique brain signatures of DM as neurological biomarkers, with the goal of identifying outcome measures for upcoming clinical trials. The proposed DM characterization system is based on a Bayesian stacked random forest and Tract Profiles sub-band energy and considers both long-term and short-term fluctuations caused by the disease process using wavelet approximation and detailed coefficients. In addition to the DM characterization task, this system can potentially provide multidisciplinary biomarkers that can help unravel our understanding of fatigue, sleepiness, attention, and circadian rhythms. We are optimistic that the results of this work can accelerate pharmaceutical research and, in turn, significantly help patients with DM.

REFERENCES

[1] Chad Heatwole, Rita Bode, Nicholas Johnson, Christine Quinn, William Martens, Michael P McDermott, Nan Rothrock, Charles Thornton, Barbara Vickrey, David Victorson, et al. Patient-reported impact of symptoms in myotonic dystrophy type 1 (prism-1). *Neurology*, 79(4):348–357, 2012.

[2] Jeffrey R Wozniak, Bryon A Mueller, Kelvin O Lim, Laura S Hemmy, and John W Day. Tractography reveals diffuse white matter abnormalities in myotonic dystrophy type 1. *Journal of the neurological sciences*, 341(1-2):73–78, 2014.

[3] Kees Okkersen, Darren G Monckton, Nhu Le, Anil M Tuladhar, Joost Raaphorst, and Baziel GM van Engelen. Brain imaging in myotonic dystrophy type 1: A systematic review. *Neurology*, 89(9):960–969, 2017.

[4] Tiina Suominen, Linda L Bachinski, Satu Auvinen, Peter Hackman, Keith A Baggerly, Corrado Angelini, Leena Peltonen, Ralf Krahe, and Bjarne Udd. Population frequency of myotonic dystrophy: higher than expected frequency of myotonic dystrophy type 2 (dm2) mutation in finland. *European journal of human genetics*, 19(7):776–782, 2011.

[5] Meghan R Swanson and Heather C Hazlett. White matter as a monitoring biomarker for neurodevelopmental disorder intervention studies. *Journal of neurodevelopmental disorders*, 11(1):1–11, 2019.

[6] Garikoitz Lerma-Usabiaga, Michael L. Perry, and Brian A. Wandell. Reproducible tract profiles (rtp): from diffusion mri acquisition to publication. *bioRxiv*, 2019.

[7] Jelle Veraart, Dmitry S Novikov, Daan Christiaens, Benjamin Ades-Aron, and Jan Sijbers Els Fieremans. Denoising of diffusion mri using random matrix theory. *Neuroimage*, 142:394–406, 2016.

[8] Elias Kellner, Bibek Dhital, Valerij G Kiselev, and Marco Reisert. Gibbs-ringing artifact removal based on local subvoxel-shifts. *International Society for Magnetic Resonance in Medicine*, 76(5):1574–1581, 2016.

[9] Jesper L R Andersson and Stamatios N Sotiropoulos. An integrated approach to correction for off-resonance effects and subject movement in diffusion mr imaging. *Neuroimage*, 125:1063–1078, 2016.

[10] Nicholas J Tustison, Brian B Avants, Philip A Cook, Yuanjie Zheng, Alexander Egan, Paul A Yushkevich, and James C Gee. N4itk: improved n3 bias correction. *IEEE Trans Med Imaging*, 29(6):1310–20, 2010.

[11] Jason D Yeatman, Robert F Dougherty, Nathaniel J Myall, Brian A Wandell, and Heidi M Feldman. Tract profiles of white matter properties: automating fiber-tract quantification. *PLoS One*, 7(11), 2012.

[12] Ingrid Daubechies. The wavelet transform, time-frequency localization and signal analysis. *IEEE transactions on information theory*, 36(5):961–1005, 1990.

[13] Tahereh Kamali, Katharine A Hagerman, John W Day, Jacinda Sampson, Kelvin O Lim, Bryon A Mueller, and Jeffrey Wozniak. Diagnosis of myotonic dystrophy based on resting state fmri using convolutional neural networks. In *2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, pages 1714–1717. IEEE, 2020.