Towards Fully Automated Closed-loop Deep Brain Stimulation in Parkinson's Disease Patients: a LAMSTAR-based Tremor Predictor

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Abstract— **This paper describes the application of the LAMSTAR (LArge Memory STorage and Retrieval) neural network for prediction of onset of tremor in Parkinson's disease (PD) patients to allow for on-off adaptive control of Deep Brain Stimulation (DBS). Currently, the therapeutic treatment of PD by DBS is an open-loop system where continuous stimulation is applied to a target area in the brain. This work demonstrates a fully automated closed-loop DBS system so that stimulation can be applied *on-demand* only when needed to treat PD symptoms. The proposed LAMSTAR network uses spectral, entropy and recurrence rate parameters for prediction of the advent of tremor after the DBS stimulation is switched off. These parameters are extracted from non-invasively collected surface electromyography and accelerometry signals. The LAMSTAR network has useful characteristics, such as fast retrieval of patterns and ability to handle large amount of data of different types, which make it attractive for medical applications. Out of 21 trials blue from one subject, the average ratio of delay in prediction of tremor to the actual delay in observed tremor from the time stimulation was switched off achieved by the proposed LAMSTAR network is 0.77. Moreover, sensitivity of 100% and overall performance better than previously proposed Back Propagation neural networks is obtained.**

Index Terms— **Parkinson's Disease, Tremor Onset Prediction, Closed-loop Deep Brain Stimulation, LAMSTAR Neural Network, Accelerometer, Surface EMG.**

I. INTRODUCTION

In the United States, more than one million people are afflicted with Parkinson's disease (PD), one of the most common neurodegenerative motor disorders. PD is due to the degeneration of dopamine-producing cells in the brain and is characterized by symptoms such as tremor, rigidity and bradykinesia. These debilitating symptoms gradually worsen over time, affecting the quality of life adversely. Although no permanent treatment is available for PD, the symptoms can be curbed medically or surgically. Levodopa-Carbidopa medication helps control the symptoms in the early stages of PD; however, as the disease advances, the effectiveness of these drugs reduces. Surgical procedures, like Thalamotomy and Deep Brain Stimulation (DBS), then need to be performed. With Thalamotomy, a target region is lesioned, and thus it is irreversible. With DBS, electrodes are stereotactically implanted in the Sub-Thalamic nucleus (STN) or the pars interna of the Globus Pallidus (GPi) for delivery of High Frequency stimulation (HFS). An Implantable Pulse Generator (IPG) is used to manually adjust the parameters of the HFS. Stimulation with a fixed set of parameters (amplitude 1-5 V, pulse duration 60-200 microseconds, and frequency of 120-180 Hz), determined by the clinician by assessment, is continuously applied to the target brain region. The battery of IPG usually lasts about 2 to 3 years and needs to be replaced surgically. DBS is a reversible procedure but may cause certain side-effects, such as speech slurring and dyskinesia. Over the past decade, it has become apparent that *on-demand* DBS may alleviate to a certain extent such side-effects while in addition improving IPG battery life and thus reducing the trauma of repetitive surgery [1], [2].

One of the primary symptoms of PD is tremor, a rhythmic involuntary oscillation with frequency range of 4-12 Hz, usually observed in the extremities. Among the PD symptoms, tremor is the first to reappear after discontinuation of DBS stimulation [3]. Tremor can be measured using non-invasive methods of surface electromyography (sEMG) and accelerometry (Acc). As reported in [4], in 3 out of 9 PD patients, the stimulation can be switched off for at least 50% of the time by accurately predicting the onset of tremor. Prediction of tremor with at least 90% sensitivity using sEMG and Acc signals was shown in [5], [6]. In [6], a manual algorithm was designed to predict tremor based on thresholding of different parameters. Since the thresholds were selected manually, it would be impossible to apply such method for each patient. A Back-Propagation neural network (BPNN) was proposed in [5] for fully automated tremor prediction; however, due to slow convergence, training the BPNN may be a slow process. In this work we aim to overcome the shortcomings of BPNN with a LAMSTAR Neural Network (LNN) [7].

A LNN has many practical advantages. It imitates the pattern learning capability of the human brain, can handle diverse data types for pattern recognition, has features for forgetting and for correlation between layers [7]. A LNN consists of multiple Self-Organizing Map (SOM) modules, each of which comprises of neurons competing based on the concept of Winner-Take-All (WTA). A feature given to the network for pattern-recognition is called a "sub-word" and the collection of features is called a "word". Each SOM module receives a sub-word for which its corresponding winner-neuron "fires". Based on the combination of winner neurons, the LNN network makes a decision. Here, the attributes given to the LNN for detecting the reappearance of tremor are the spectral, entropy and recurrence rate parameters calculated from the sEMG and Acc signals as in [6]. An improved sensitivity of 100% compared to previous results using Back Propagation network, as in [5], was achieved for this

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automated LAMSTAR based tremor predictor. LNN has also been reported to be 10 times faster than BPNN in training, as well as online operation. The fast retrieval feature for medical as well as other applications is extensively discussed in [7].

The rest of the paper is organized as follows. In Section II we discuss the method of data collection, parameter extraction and the LNN architecture in detail. In Section III we present the main result of the paper. Section IV concludes the paper.

II. Method

A. Data collection and feature extraction

Data collection was carried out at University of Illinois at Chicago (UIC) under the UIC-IRB 2008-0971. Recording of sEMG was performed on a female PD patient, who had previously undergone FDA-approved Medtronic DBS-system implantation in 2009, as described in [5], [6]. The patient had dominant tremor in the right hand which was controlled by medication and stimulation. On the recording day, the patient was on usual medication. Non-invasive sEMG electrodes were placed on the extensor digitorum communis (upper forearm) and the recording was done by a Delsys system (Delsys Inc., Boston, MA). The signal was amplified (gain set to 1000) and filtered (20-450 Hz). Acc was measured by a Coulbourn type V94-41 solid-state piezoresistive accelerometer placed at the tip of index-finger of the right hand. The two signals were sampled at 1000 Hz. The patient was comfortably seated with a supportive surface provided for the forearm. The patient was asked to perform two tasks: (i) to hold the right arm in an extended position, called as the "posture state" and (ii) to reach for the opposite shoulder or extension/flexion of the wrist, denoted as the "action state". Other than these states, the recording was also carried out for "rest state" where the patient had to completely relax the right arm and place it on the supportive surface. DBS stimulation was switched off for some time before each trial so that stimulation of a fixed duration could then be applied. The trial was then started with stimulation of 20 to 50 sec duration, followed by switching the DBS off until the tremor re-appeared.

Power of the raw extensor sEMG signal was calculated over 50 ms windows slid over each sample to smooth the signal, i.e., signal processing over 1-second windows, with a window shift of 0.25 second, thereby generating four samples every second. For fairness of comparison, we used as inputs for the LNN the same parameters calculated in [5], [6], as namely

- Spectral Analysis: Using 512-point Fourier transform, the power spectral density of smoothed sEMG was calculated over 1-second windows. Tremor information is concentrated in the 3-18 Hz frequency band; therefore, maximum power P_{max} and its corresponding frequency F_{max} are calculated over this band. Similarly these two values were also determined for the Acc signal. Daubechies Wavelet Transform (DWT) was applied to the smoothed sEMG signal to decompose it in 10 frequency bands. Of these, the frequency ranges 8-16 Hz and 16-32 Hz were found to be good parameters for tremor prediction.
- Entropy Analysis: as a measure of "randomness". The *wavelet entropy*, WtEn, quantifies the unpredictability or disorder in a signal. The *sample entropy*, $\mathrm{SpEn}(U, m, r)$, represents the conditional probability that the two sub-sequences of U, matching point-wise for m points, will also match at the next point within a tolerance r.
- Recurrence Rate Analysis: *Recurrence rate analysis* involves calculation of recurrence rates, measuring the probability of recurrence of a specific state of the dynamical system reconstructed using a method of delayed vector construction.

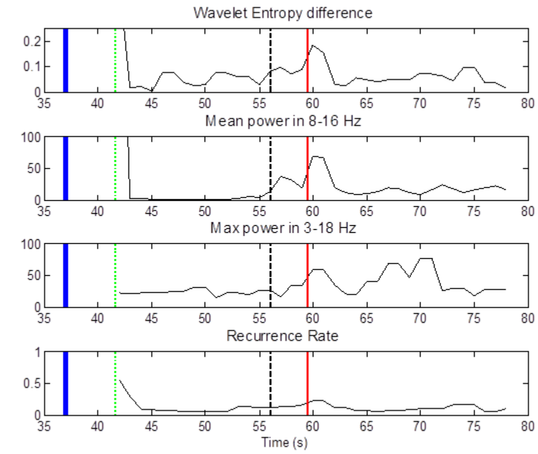

Fig. 1. The figure shows four of the parameters used in the LNN training. From top to bottom: sEMG Wavelet Entropy difference, sEMG Mean power in 8-16 Hz, Acc Maximum power in 3-18 Hz and sEMG Recurrence Rate calculated over 2 sec windows with an overlap of 1 sec. The bold blue line shows the end of stimulation, dotted green line shows start of the voluntary movement (in this instance, posture state) and the dashed black and the red lines show predicted and observed tremor, respectively.

Fig. 1 shows a representative plot of four of the parameters. In the figure, parameters show a trend before the tremor is observed, marked by the red vertical line. This trend is however not always observed in all trials.

B. LNN Architecture

LNN Inputs: The parameters described in Section II-A were further processed to obtain nine input features, which served as the subwords given to the LNN as shown in Fig. 2. These features were calculated over 8 samples or 2 sec windows. Windows overlapped over 1 sec; therefore, a set of 9 features was obtained every second. For entropy parameters, maximum value of sample entropy over each window and the decrease in sample and wavelet entropies compared to the previous window, were calculated. Mean values of power in 8-16 Hz and 16-32 Hz and the maximum value of power in 16-32 Hz over the 2 sec window were determined for sEMG. The rest of the spectral features, namely, F_{max} in the 2 sec window with maximum power and its corresponding P_{max} computed for Acc signal, were taken as two of the input features. Lastly, the maximum value of recurrence rate in the window was the ninth attribute considered for prediction of tremor.

Architecture: Fig. 2 shows the set-up of the LNN. The network is designed to have nine SOM modules with 11 neurons each and one output layer with two neurons. Each input word to the LNN consists of the nine features previously described. Each subword is given to its respective SOM layer. Based on the range of this input feature, a winner neuron of the SOM module fires. As shown in Fig. 2, the winner neurons from each SOM module are connected to the output neurons via link weights. The two neurons in the output layer, referred to as T and NT, correspond to the binary decision of "tremor predicted" or "tremor NOT predicted", respectively. This decision is made by comparing the sum of link weights from the nine winner neurons to the output neurons. If the sum of the link weights to the NT neuron is greater than or equal to the sum of link weights to the T neuron a decision of "tremor NOT predicted" is made, otherwise the decision is "tremor predicted".

We used approximately two-third of the 21 available trials for the considered PD patient for training and the remaining for testing. Training and testing are described next.

Training: During training, a word is input to the LNN that corresponds to the features of the sEMG and Acc signals at a given time point after DBS stimulation is switched off. Link weights from all the neurons to the two output neurons are initialized to zero at the beginning of training. After the winner neurons of the SOM modules fire and the decision is made based on the sum of link weights, a reward / punishment policy is applied. Different policies are applied for the Posture/Rest and Action states. If no tremor is predicted up to 5 sec before the tremor was actually observed, the link weights from the winner neurons to the NT output neuron are rewarded by Δ_L, and to the T output neuron punished by Δ_M. For early detection, the punishment ($4\Delta_M$ for Action mode and $6\Delta_M$ for Posture/Rest modes) is given to the link weight from the winner neurons to the NT output neuron; this is done so as to reduce the false alarm rate. In the last 5 sec window before the tremor appeared, if the tremor is predicted then the link weights from the winner neurons to T output neuron are rewarded by Δ_L and those to NT neuron are punished by Δ_M. Separate LNN networks were trained for the modes of Actions and Posture/Rest states because of the very different ranges the various features have in these states. The LNN was run for 200 iterations to ensure convergence.

Testing: The LNN performance was assessed based on sensitivity, accuracy and R-ratio, as in [5]. Sensitivity is defined as the percentage of true positives out of the sum of all true positives and false negatives. Accuracy is the percentage of correct decisions, i.e., true positives and true negatives out of all decisions. In this work, a true positive is defined if the tremor prediction was made at least 50% time through the tremor-free interval (as too early prediction defeats the purpose of on-demand closed-loop DBS). To evaluate the performance of the network, we also calculate R-ratio, which is the ratio of delay in tremor prediction from the time DBS stimulation was switched off to the delay in the tremor observation. This measure signifies how close to the actual observation is the tremor predicted by the LNN.

TABLE I
PERFORMANCE RESULTS FOR LAMSTAR NETWORK.

Trials	Total	Action	Posture	Rest
R-ratio	0.77	0.79	0.72	0.88
Accuracy	77%	60%	83.3%	100%
Sensitivity	100%	100%	100%	100%

III. RESULTS AND DISCUSSION

Nine parameters processed from the sEMG and Acc data were given to two separate LNNs based on the state of the limb being tested. The LNNs had the same basic structure of 9 SOM layers with 11 neurons each, as previously discussed. We trained and tested the LNNs for 21 trials of Action, Posture and Rest modes. Classification between the Action and Posture or Rest states has been previously shown in [8]. A state-classifier can be similarly implemented to recognize the mode, followed by selection of the corresponding LAMSTAR network. 100% sensitivity i.e. there were no 'misses', total accuracy of 77% and R-ratio of 0.77 were achieved for files of all modes combined. Detailed performance measures are given in Table I. The R-ratio value with LNN is greater than 0.7 for all modes. Accuracy with LNN is lowest in Action state, which is due to high false positive rate from early detections (which may be because voluntary movements are mistakenly classified as beginning of tremor). This aspect needs improvement and is currently under investigation. Since the current experimental set-up allows recording for approximately two hours without causing muscle fatigue, the number of trials for each state is limited. The accuracy of the LNN is expected to improve if the number of trials used for training the LNN for Action state is increased. Sensitivity with LNN is 100% for all modes, which is the most important performance factor since a 'miss' is not acceptable for tremor prediction applications.

IV. CONCLUSIONS

We presented here the initial progress towards developing a fully automated tremor predictor using a LAMSTAR neural network in order to overcome some of the limitations we encountered in our past work with Back Propagation network. Further improvement on our proposed design may be achieved by identifying other features characterizing the onset of tremor. Due to complete transparency of a LAMSTAR neural network, clusters of winner neurons during absence of tremor can be compared with the clusters at the advent of tremor. By recognizing this set of features, prediction can be improved by eliminating redundant SOM layers or features that may be obscuring the results. Clustering of the set of predicting neurons can be reinforced by adding

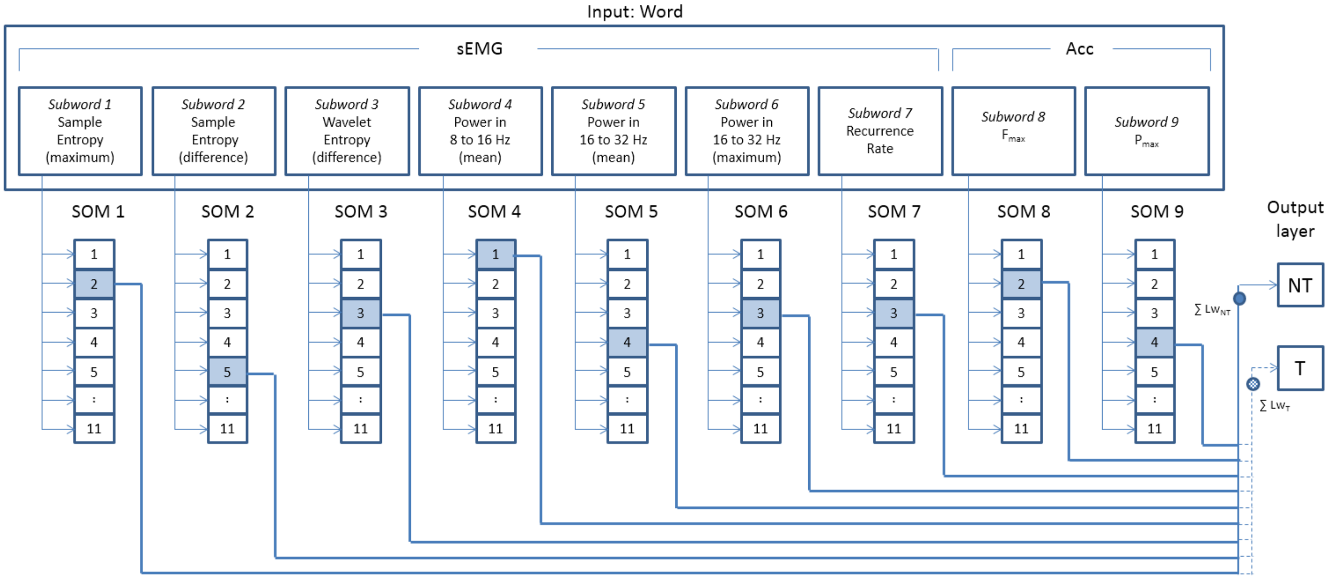

Fig. 2. Architecture of LNN: The figure shows the LAMSTAR neural network architecture. Nine input features or "subwords" are given to their respective SOM layers, which consist of 11 neurons each. Each of the neurons are connected to the output layer via Link weights. The decision of NT "No Tremor" neuron firing or T "Tremor" neuron firing is made by comparing the sum of link weights from the winner neurons to the output neurons, $\sum Lw_{NT}$ and $\sum Lw_{T}$ respectively. Output neuron corresponding to greater of the sums of link weights wins. Here, one instance of winner neurons of the nine SOM layers is shown with the shaded boxes representing the winner neurons at a time instant.

correlation links between related features. In future, we intend to compare the performance of the LAMSTAR neural network with other machine learning techniques such as Decision Tree Classifier and Support Vector Machine.

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