Towards Closed-Loop Deep Brain Stimulation: Decision Tree-based Essential Tremor Patient's State Classifier and Tremor Reappearance Predictor

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Abstract— **Deep Brain Stimulation (DBS) is a surgical procedure to treat some progressive neurological movement disorders, such as Essential Tremor (ET), in an advanced stage. Current FDA-approved DBS systems operate open-loop, i.e., their parameters are unchanged over time. This work develops a Decision Tree (DT) based algorithm that, by using non-invasively measured surface EMG and accelerometer signals as inputs during DBS-OFF periods, classifies the ET patient's state and then predicts when tremor is about to reappear, at which point DBS is turned ON again for a fixed amount of time. The proposed algorithm achieves an overall accuracy of 93.3% and sensitivity of 97.4%, along with 2.9% false alarm rate. Also, the ratio between predicted tremor delay and the actual detected tremor delay is about 0.93, indicating that tremor prediction is very close to the instant where tremor actually reappeared.**

Index Terms— **Essential Tremor, Accelerometer, Surface EMG, Decision Tree, Gini index impurity function, Closed-loop Deep Brain Stimulation, Tremor Prediction.**

I. Introduction

Essential Tremor (ET) is a progressive neurological disorder of the central nervous system that occurs only when the affected muscle exerts effort. We will use *postural* to indicate posture tremor and *movement* to indicate kinetic tremor. The treatment of ET advanced stage patients may include surgical procedures, such Deep Brain Stimulation (DBS). DBS uses a surgically-implanted battery-operated pulse generator to provide high frequency electrical stimulation to the neurons that control movement. In current FDA-approved DBS systems, stimulation parameters are fixed over time and the stimulation is provided continuously, meaning that stimulation is not adapted to the patient's needs. In [1] we argued that, in order to design an adaptive closed-loop DBS system, suitable physiological signals that contain tremor information must be tracked during DBS-OFF periods, based on which stimulation is turned ON when tremor is predicted to be about to reappear; stimulation is then applied for a fixed amount of time, after which the cycle restarts. In [2] it was shown that DBS could be switched OFF for up to 50% of the time without patients experiencing any discomfort.

In [1] we designed a closed-loop ON-OFF DBS system based on surface electromyogram (sEMG) and accelerometer (Acc) signals measured non-invasively from the patient's symptomatic extremities. We extracted several features from the sEMG and Acc signals and manually designed thresholds for a tremor prediction algorithm that was shown to achieve an overall sensitivity of 100% along with an accuracy of 85.7% in ET trials; based on statistical tests, we concluded that the predicted tremor reappearance times differ from random prediction outcomes. Towards the design of a fully automated closed-loop DBS system suitable for commercial implementation, in [3] we developed a tremor predictor based on a feed-forward back-propagation Neural Network (NN), which achieved an overall sensitivity of 92.3% and accuracy of 75.8% when tested on 2 Parkinson's Disease (PD) patients. In [4] we proposed to improve the design of [3] by incorporating a Decision Tree (DT) based classifier to discriminate between movement and posture states for ET patients. In [4], the joint performance of state classifier and tremor predictor was not investigated, which is the main undertaking of this work.

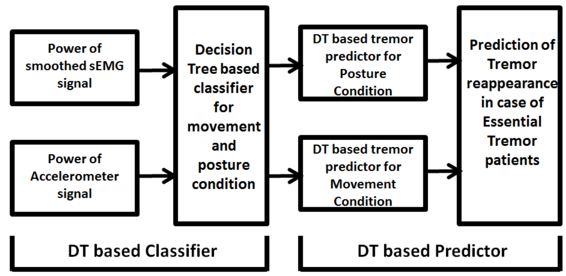

Fig. 1. Proposed algorithm: a DT-based classifier (to discriminate between movement and postural conditions) followed by two DT-based tremor predictors, one for movement condition and the other for posture condition.

Our main contribution is the development of an automated two-stage tremor predictor as shown in Fig. 1. The first stage is a DT-based classifier, to discriminate between movement and postural conditions based on the power of the sEMG and Acc signals as in [4]. The second stage consists of two DT-based tremor predictors (as opposed to a single NN-based predictor as in [3]), one designed for the movement condition and the other for the postural condition. The predictors' inputs are spectral and entropy measures derived from the sEMG and Acc signals. The algorithm was tested on 75 trials recorded from 3 ET patients, with 55% of the trails used for training and the rest for testing. The algorithm has an overall sensitivity of 97.4% and accuracy of 93.3%.

The rest of the paper is organized as follows. Section II describes the data set. Section III summarizes the parameter extraction methodology. Section IV describes the proposed algorithm. Section V presents the performance results followed by discussion.

Departments of: [1]Electrical and Computer Engineering, University of Illinois at Chicago, IL USA; [2]Neurosurgery, Johns Hopkins, Baltimore, MD USA. Contact author: P. Shukla *pshukl5@uic.edu*. The work of P. Shukla and D. Tuninetti was partially funded by NSF under award number 1134296; the contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NSF. Conversations with L. V. Metman, D. M. Corcos, and D. Graupe are greatly acknowledged.

II. Human Subjects and Data Recording Setup

Three ET patients treated with DBS were recruited for this study, two from Rush University Medical Center and one from University of Illinois at Chicago Hospital, with IRB protocol approved by the respective institution. In all patients the DBS electrodes (Medtronic DBS, lead model 3389) were stereotactically implanted in the ventral intermediate nucleus of the thalamus and had dominant tremor in one or both arms; the tremor was controlled by a combination of stimulation and medication. On the recording day, all the subjects were on their regular medication. Recordings were conducted in the Neural Control of Movement Laboratory at the University of Illinois at Chicago.

The data recording setup was as in [5]. The sEMG signal was recorded from the extensor digitorum communis of the forearm with the worst tremor, was amplified (gain set to 1,000) and then bandpass filtered between 20Hz and 450Hz (Delsys Inc., Boston, MA). Along with sEMG, the Acc signal was recorded with a calibrated Coulbourn type V94-41 miniature solid-state piezoresistive accelerometer with resolution 0.01g. There were 75 trials, each started with 20-50s of DBS and followed by a DBS OFF interval. Trials were in the one of the two conditions:

- Postural (P): Patients maintained their hand and wrist in a neutral, extended position level with the table surface
- Movement (M): Patients performed a voluntary movement such as reaching for their opposite shoulder.

III. Parameter Extraction

The input parameters for the proposed algorithm are as in [1], [3], [4] and are summarized next for completeness.

A. Input parameters for DT-based classifier

The *power of the raw sEMG and Acc signals*, used as inputs to the DT-based classifier, are calculated as

$$X_{P_\star}(i) = \int_{t_p(i)}^{t_p(i)+0.5} x_\star^2(t)\,\mathrm{d}t,\ \star = \mathrm{sEMG},\ \mathrm{Acc}, \quad (1)$$

where $x_{\mathrm{sEMG}}(t)$ and $x_{\mathrm{Acc}}(t)$ are the recorded sEMG and Acc signal, respectively, and $t_p(i) = t_0 + i\Delta$ for $i \in [0 : 80]$, t_0 is voluntary motion start time, i.e., the postural or movement condition start time for different trials, and $\Delta = 0.025$s is the size of the sliding window.

B. Input parameters for DT-based predictor

The tremor predictor inputs are a combination of spectral, entropy and recurrence measures from the *smoothed sEMG* signal obtained by averaging the raw signal over 1s windows and then sliding the window by 0.25s therefore generating a sample every 0.25s.

The *mean frequency* is the expected value of the frequency distribution over the spectrum range considered

$$F_{\mathrm{mean}} = \frac{\sum_{n=1}^{N} f_n P_n}{\sum_{n=1}^{N} P_n},\ N = 37, \quad (2)$$

where P_n is the power of a 1s window of the smoothed sEMG at frequency band centered around f_n, $n \in [1 : N]$, calculated by using a 512-point Fourier transform.

The frequency band of interest is from f_4 = 3Hz to f_{19} = 18Hz, which carries tremor information. For each band we calculate the power P_n; the frequency band with maximum power has index $i^\star = \arg\max_{n\in[4:19]}\{P_n\}$. The *peak frequency* and the *power at peak frequency*, whose utility is explained in [1], are respectively

$$F_{\max} = f_{i^\star}, \quad P_{\max} = \frac{P_{i^\star}}{\sum_{i\in[20:37]} P_i}. \quad (3)$$

In (3) $P_{\max}$ is normalized by the power of signal outside the tremor frequency range because the power at $F_{\max}$ must be compared over different trials, which might have significantly different power outside the range of interest.

The *mean power in n-th frequency band* is obtained by decomposing the smoothed sEMG signal into $M = 10$ frequency bands with Daubechies4 wavelets. Let $X_j(t)$ denote the signal in the j-th frequency band, $j \in [1 : M]$. The mean power in j-th frequency band is defined as

$$\overline{P_j} = \frac{1}{\Delta_T}\sum_{t\in\Delta_T} |X_j(t)|^2,\ \Delta_T = 1\mathrm{s}. \quad (4)$$

The *sample entropy* $\mathrm{SpEn}(U, m, r)$ for a time series U (here the smoothed sEMG signal) of length L involves two input parameters m and r, which are the pattern length and the similarity criterion, respectively. It is defined as

$$\mathrm{SpEn}(U, m, r) = \lim_{L\to\infty} -\log\frac{B_{m+1}(r)}{B_m(r)}, \quad (5)$$

where $B_{m+1}(r)/B_m(r)$ represents the conditional probability that the two sub-sequences of U matches point-wise for m points will also match within a tolerance r at the next point; therefore a lower $\mathrm{SpEn}(U, m, r)$ value reflects a high degree of regularity [6]. Here $m = 2, r = 0.14\sigma$, where σ is the standard deviation of the smoothed sEMG signal.

The *recurrence rate* involves the calculation of a recurrence matrix with elements, $R_{i,j}$, $(i, j) \in [1 : P], P = L - (E - 1)\tau$, for $U = \{x(i),\ i \in [1 : L]\}$ of length L considering $E = 5,\ \tau = 3,\ L = 1000$ as described in [7]. From $R_{i,j}$ the recurrence rate R is calculated as

$$\mathsf{R} = \frac{1}{P^2}\sum_{i,j} R_{i,j} \quad (6)$$

and quantifies possible non-linear synchronizations in the sEMG signal (it corresponds roughly to the probability that a specific state of the dynamical system, reconstructed using a method of delayed vector construction, will recur [7]).

IV. Proposed algorithm

A DT comprises three sets of nodes: root node n_R, intermediate nodes n, and terminal nodes n_T. This algorithm creates a binary tree by dividing an unclassified data set fed at root node n_R into smaller and smaller classified data based on the set of binary questions. Let $p(k|n)$ denote the *node proportions* for class $k \in [1 : 2]$ at node n, which is the estimated probability of class k within node n [8]. The *impurity* at node n is a non-negative function of the node proportions, in this work calculated by using Gini index [8]

$$i(n) = 1 - \sum_{k=1}^{2} \big(p(k|n)\big)^2. \tag{7}$$

By using a set of binary questions at each node, a set of binary splits are generated to divide the node n into a right node n_r and a left node n_l with proportions p_r and p_l, respectively [8]. The *goodness* of the split at a node n, is computed in terms of decrease in impurity as

$$\Delta i(s,n) = i(n) - p_l i(n_l) - p_r i(n_r),\ \forall s \in \mathcal{S}, \tag{8}$$

where $\mathcal{S}$ is a set of binary splits at each node n generated by a set of binary questions [8]. The split s^* is chosen among all splits $s \in \mathcal{S}$ as the one that gives the largest decrease in impurity in (8). The algorithm starts at the root node; based on $\Delta i(s^*, n_R)$, the root node n_R is split into two nodes n_l and n_r; the procedure is recursively continued on each node till no further decrease in impurity is possible on subsequent splits; the last node in this procedure is termed the terminal node n_T. The resulting tree is subjected to further optimization by pruning some of its sub-trees and nodes to reduces: (a) complexity and (b) over-fitting to the training data set so as to increase the classification accuracy during testing; here pruning is implemented by using the optimal pruning scheme in [8, Section 10.2]. First, the unclassified training data set is placed at the root node n_R; then based on binary questions, the data set is partitioned into smaller and smaller classified data sets as described above; finally, the maximum tree with several levels is built whose terminal nodes consists of a particular class samples and optimized by optimal pruning scheme.

The DT structure is built during the training phase and remain fixed in the testing phase. For both the classifier and tremor predictor, training is performed by using 10 out of 19 trials for ET patient 1 (Right Hand), 6 out of 10 trials for ET patient 1 (Left Hand), 9 out of 16 trials for ET patient 2, and 16 out of 30 trials for ET patient 3.

Our DT-based classifier, to discriminate between the movement (M) and postural (P) conditions, uses the power of raw sEMG signal $(X_{P_{\text{sEMG}}}(i))$ and of the Acc signal $(X_{P_{\text{Acc}}}(i))$ for $i \in [0:80]$, in (1). The input is the matrix $[X_{P_{\text{Acc}}}(i), X_{P_{\text{sEMG}}}(i)]_{i\in[0:80]}$ and the output is the vector $[y_i]_{i\in[0:80]}$ where $y_i \in \{\text{M}, \text{P}\}$.

Our DT-based predictor, uses as inputs the quantities in (2)-(6) computed from the smoothed sEMG. At time instant $l \in [1:4T]$, where T is an integer that equals the duration of a trial which is multiplied by 4 as we are generating parameter samples every 0.25s, the inputs is $X(i) = \Big[F_{\text{mean}}(i), F_{\max}(i), P_{\max}(i), \overline{P_j}(i), \text{SpEn}(U,m,r)(i), \mathsf{R}(i)\Big]$, and the output $Y(i)$ is $Y(i) = 0$ for *Non-Tremor* and $Y(i) = 1$ for *Tremor*. We use a sliding window processing of 0.25s; by training the algorithm to transition from *Non-Tremor* to *Tremor* at the time instant where tremor was visually detected, the prediction of tremor for some of the trials turned out to be 'delayed' by 0.5s to 2.5s; for this reason, we train the algorithm to transition from *Non-Tremor* to *Tremor* 2.5s before tremor was visually observed to capture the building up of the tremor. This procedure is depicted in Fig. 2. In Fig. 2 the six elements of the input vector at a particular time instance are indicated by arrows and the corresponding output is 1 (as this time instance lies in *Tremor* region).

V. Results and Discussion

The algorithm performance is evaluated by following [1]. Let T be the total duration of a trial. Let t_{on} and t_{off} be the times when DBS was switched ON and OFF, respectively. Let t_{tr} and t_{pr} be the times when tremor was detected and predicted using the DT-based algorithm, during the DBS-OFF period, respectively. During testing, the trials for which tremor was detected over the recorded interval after DBS was OFF, i.e., $t_{\text{tr}} < T$, were considered as tremor detected (TD) trials, otherwise as No-Tremor Detected (NTD) trials.

Classification of prediction outcomes for TD trials:

True positive (TP): if $[(t_{\text{tr}} > t_{\text{pr}})$ and $(t_{\text{tr}} - t_{\text{pr}}) < \max(5\text{s}, 0.5(t_{\text{pr}} - t_{\text{off}}))]$ or $[(t_{\text{tr}} < t_{\text{pr}})$ and $(t_{\text{pr}} - t_{\text{tr}}) < 1\text{s}]$, then the algorithm successfully predicts tremor.

False positive (FP): if $(t_{\text{tr}} > t_{\text{pr}})$ and $(t_{\text{tr}} - t_{\text{pr}}) > \max(5\text{s}, 0.5(t_{\text{pr}} - t_{\text{off}})]$, then the prediction is too early.

False negative (FN): if $(t_{\text{tr}} < t_{\text{pr}})$ and $(t_{\text{pr}} - t_{\text{tr}}) > 1\text{s}$, then the prediction is too late.

Classification of prediction outcomes for NTD trials:

True negative (TN): if the algorithm does not predict tremor over the interval $T - t_{\text{off}}$.

False positive (FP): if the algorithm predicts tremor over the interval $T - t_{\text{off}}$.

For the algorithm to perform well, the total number of TP and TN must be maximized while minimizing FP and eliminating FN. This would achieve the longest tremor-free interval when DBS is OFF. In order to quantify this we calculate the following performance metrics

$$\text{Sensitivity} = \frac{\#\text{TP}}{\#\text{TP} + \#\text{FN}}, \tag{9}$$

$$\text{Accuracy} = \frac{\#\text{TP} + \#\text{TN}}{\#\text{TP} + \#\text{TN} + \#\text{FP} + \#\text{FN}}, \tag{10}$$

$$\text{FalseAlarm} = \frac{\#\text{NTD} - \#\text{TN}}{\#\text{NTD}}, \tag{11}$$

$$\text{Mcc} = \frac{(\#\text{TP})(\#\text{TN}) - (\#\text{FP})(\#\text{FN})}{\sqrt{\begin{matrix}(\#TP + \#FP)(\#TP + \#FN)\\ (\#TN + \#FP)(\#TN + \#FN)\end{matrix}}}. \tag{12}$$

Mcc in (12) defines the Matthews correlation coefficient [9] which measures the quality of a binary classifier. The sensitivity in (9) should be very high (above 90%) as we do not want to miss any of the tremor events. Accuracy in (10), which is the ratio between the correctly predicted trials and the total number of trials, should be high (over 80%). The false alarm rate in (11) is proportional to the number of early tremor predictions in case of NTD trials and hence should be low (less than 20%). Furthermore, let $R_{\text{pd}} = \sum(t_{\text{pr}} - t_{\text{off}}) / \sum(t_{\text{tr}} - t_{\text{off}})$, where the summations

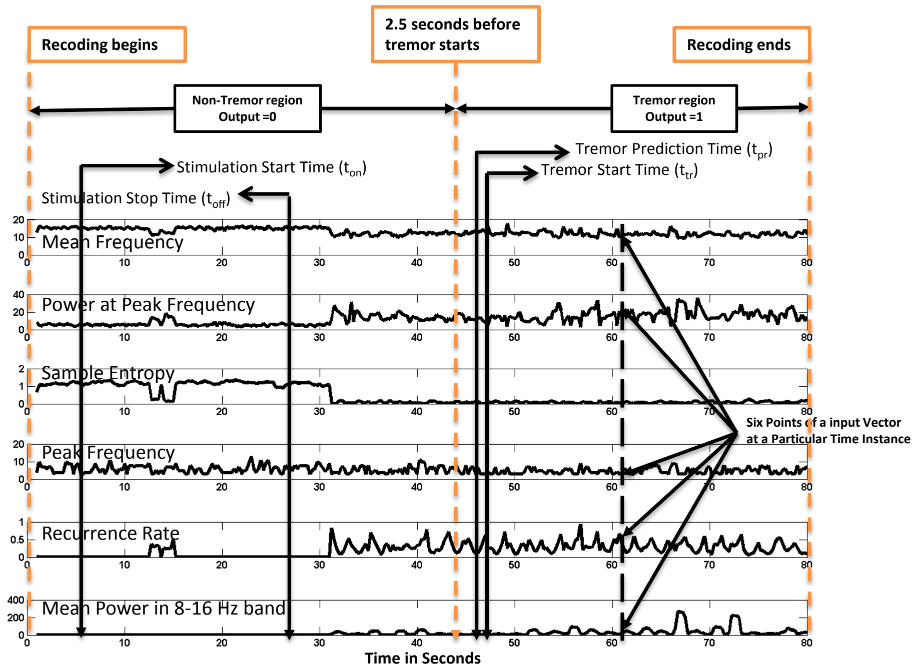

Fig. 2. Inputs and output for the DT-based predictor in a particular trial used for training. The bold vertical line, set at 2.5 sec before tremor was visually observed, divides the time series of the extracted parameters into Tremor (output equals 1) and No-Tremor regions (output equals 0). A time instance in the 'tremor region' is shown via a thin vertical line: the six elements of the corresponding input vector are indicated by six arrows, which results in a output equal to 1.

are over all the TD trials. For NTD trials we use $t_{\mathrm{tr}} = T - t_{\mathrm{off}}$, $t_{\mathrm{pr}} = \min(T, t_{\mathrm{pr}})$ because the tremor reappearance time is unknown. R_{pd} provides a measure of how good the prediction is, i.e., a higher value indicates that the predicted delay t_{pr} is closer to the actual delay t_{tr} which is desirable.

From, the prediction results for each ET patient and overall as summarized in Table I, we see that the proposed algorithm achieves an overall accuracy of 93.3%, which shows that in 93.3% of all ET trials, the DT based algorithm correctly predicts tremor. The DT based algorithm also achieves an overall sensitivity of 97.4%. For all except patient ET3 the algorithm achieves 100% sensitivity which indicates no miss in the tremor prediction in case of three ET patients. The high R_{pd} value (93.3%) along with low value of false alarm rate (2.9%) is achieved in all ET patients. The overall and individual Mcc values are greater than 0.75 which shows that there is strong correlation between prediction and actual classification. Moreover, for some performance indices we improved on our manual tremor prediction algorithm in [1] that achieved an overall accuracy of 85.7%, sensitivity of 100%, R_{pd} of 84.5%, Mcc of 0.71 and false alarm rate of 11.6% for ET trials. We have thus shown that by using parameters as in [1], we can design an automatic tremor prediction algorithm using DT type classifiers to effectively predict an incoming tremor in ET patients. For future work, we will also apply this algorithm to predict the tremor in case of PD patients.

TABLE I

PREDICTION RESULTS FOR EACH ET PATIENT AND OVERALL. LEGEND: N = TOTAL # OF TRIALS, A = ACCURACY IN %, S = SENSITIVITY IN %, FA = FALSE ALARM RATE IN %.

Patient	N	TP,TN,FP,FN	A	S	FA	Mcc	R_{pd}
ET1(Left)	10	7,2,1,0	90.0	100.0	0.0	0.76	81.7
ET1(Right)	19	7,11,1,0	94.7	100.0	0.0	0.90	96.8
ET2	16	11,4,1,0	93.8	100.0	20.0	0.86	89.9
ET3	30	12,16,1,1	93.3	92.3	0.0	0.86	95.8
Overall	75	37,33,4,1	93.3	97.4	2.9	0.87	93.3

REFERENCES

[1] I. Basu, D. Graupe, D. Tuninetti, P. Shukla, K. V. Slavin, L. V. Metman, and D. M. Corcos, "Pathological tremor prediction using surface electromyogram and acceleration: potential use in on-off demand driven deep brain stimulator design." *Journal of Neural Engineering*, vol. 10, 2013.

[2] D. Graupe, I. Basu, D. Tuninetti, P. Vannemreddy, and K. V. Slavin, "Adaptively controlling deep brain stimulation in essential tremor patient via surface electromyography." *Neurol Res.*, vol. 32, pp. 899–904, 2010.

[3] P. Shukla, I. Basu, D. Graupe, D. Tuninetti, and K. V. Slavin, "A neural network-based design of an on-off adaptive control for deep brain stimulation in movement disorders." in *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE*, 2012, pp. 4140–4143.

[4] P. Shukla, I. Basu, D. Graupe, D. Tuninetti, K. V. Slavin, L. V. Metman, and D. M. Corcos, "A decision tree classifier for postural and movement conditions in essential tremor patients." in *6th International IEEE Engineering in Medicine and Biology Society (EMBC) Conference on Neural Engineering*, 2013, pp. 117–120.

[5] M. M. Sturman, D. E. Vaillancourt, L. V. Metman, R. A. Bakay, and D. M. Corcos, "Effects of subthalamic nucleus stimulation and medication on resting and postural tremor in parkinson's disease." *Brain.*, vol. 127, pp. 2131–43, 2004.

[6] J. S. Richman and J. R. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy." *Am J Physiol Heart Circ Physiol.*, vol. 278(6), pp. H2039–49, 2000.

[7] C. L. Webber Jr and J. P. Zbilut, "Recurrence quantification analysis of nonlinear dynamical systems," *Tutorials in contemporary nonlinear methods for the behavioral sciences*, pp. 26–94, 2005.

[8] L. Breiman, J. Friedman, R. Olshen, and C. Stone, *Classification and Regression Tree*. Boca Raton, FL: CRC Press, 1984.

[9] P. Baldi, S. Brunak, Y. Chauvin, C. Andersen, and H. Nielsen, "Assessing the accuracy of prediction algorithms for classifiaction: an overview." *Bioinformatics.*, vol. 16, pp. 412–424, 2000.