Adaptive Control of Deep Brain Stimulator for Essential Tremor: Entropy-based Tremor Prediction Using Surface-EMG

Ishita Basu, Daniela Tuninetti, Daniel Graupe and Konstantin V. Slavin

Abstract— **Entropy, as a measure of randomness in time-varying signals, is widely used in areas such as thermodynamics, statistical mechanics and information theory. This paper investigates the use of two commonly employed entropy measures, namely Wavelet Entropy and Approximate Entropy, as a predictor of tremor reappearance in Essential Tremor patients; the predictor input is a raw surface-electromyographic (sEMG) signal measured from tremor affected muscles of patients implanted with a Deep Brain Stimulator (DBS). A combination of both types of entropy measure is shown to successfully predict the occurrence of tremor few seconds before its visual manifestation. This result can potentially lead to a novel sEMG-based adaptive on-off DBS controller that can be added on to existing open-loop DBS systems with minimal changes; an adaptive DBS system provides stimulation only when needed thereby reducing the risk of brain over stimulation, delaying DBS intolerance and prolonging DBS battery life.**

I. INTRODUCTION

Essential Tremor and current open-loop DBS. Essential Tremor (ET) is a progressive neurological disorder characterized by a rhythmic tremor (4-12 Hz) that is present only when the affected muscle is exerting effort [1] and can affect the arms, head (neck), jaw and voice as well as other body regions. ET is the most common movement disorder and an estimated five million Americans suffer from the disease. The pathophysiology of ET is not known. There is no cure for ET at present. If the tremor is severely disabling and drugs do not adequately relieve the symptoms, surgical procedures such as Deep Brain Stimulation (DBS) and thalamotomy [2] are considered. In DBS, an electric probe is placed in the Ventral Intermediate Nucleus (VIM) of the thalamus which is connected to a pacemaker placed near the collarbone. The probe stimulates the VIM with pulses of electricity which are thought to block the brain activity that causes tremor. Despite its clinical success, the mechanisms of DBS and its beneficial effects on ET patients are not well understood. As opposed to thalamotomy, DBS is controllable and its effects are reversible. Current DBS systems operate open-loop, that is, there is no feedback to determine the optimal stimulation parameters and/or when to stimulate. Hence, at present DBS operates continuously and unaltered over time as long as the battery lasts, regardless of the patients' instantaneous conditions and needs.

Next generation of sEMG-based closed-loop DBS. In order to adapt to the patients' condition, current DBS systems must be redesigned so as to include a closed-loop feedback control where the patients' tremor is continuously monitored and the stimulation adapted in response to its variations. To design an adaptively controlled closed-loop DBS system, it is necessary to find a suitable physiological signal that can be easily measured and has predictive information on tremor reappearance once DBS stimulation is stopped. The best feedback signal would be the actual neuronal brain activity measured from individual neurons (micro-recording) represented by the cell firing, or a group of neurons (macro-recording) represented by the local field potential. However, the measurement of these signals by means of DBS stimulation electrodes (during stimulation off times) require changes to the current Food and Drug Administration (FDA) approved DBS system; such a neuronal activity-based closed-loop DBS system would then require long testing and approval times thus delaying its commercialization. Alternatively, muscular activity measured by means of raw surface-electromyogram (sEMG) can be recorded non-invasively from tremor affected muscles and is known to carry predictive information on tremor reappearance [3]. Muscular activity can thus be used for adaptive on-off control of DBS. Moreover, an sEMG-based closed-loop DBS controller can be implemented as an add-on sub-system for the FDA-approved DBS systems by leveraging the currently available telemetry capabilities of DBS[1]. Indeed, the external sEMG sensors and the chest-implanted neurostimulator can exchange data through the existing telemetry/wireless link.

Advantages of sEMG. sEMG is a signal measuring muscle activity noninvasively using surface electrodes placed on the skin overlying the muscle [4]. sEMG has been successfully used as the information source for closed-loop control in several other problems, such as control of high-above-elbow prostheses , electrical stimulation in paraplegics [5], and to predict the onset of sleep apnea and hyperpnoea events [6]. The authors also showed in [3] that the lower frequency bands of sEMG, reconstructed by using a wavelet decomposition, contains predictive information about tremor reappearance in an ET patient with DBS implants, after the stimulation is switched off. As opposed to information obtained from mechanical or piezo-electric tremor sensors, sEMG integrates information of many motor-unit action potentials (MAUPs) in the cover-area of the sEMG sensors; since motor unit firing builds up gradually and not instantaneously, this build-up is observable by sEMG before tremor

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[1]Medtonic DBS system comprises a device called the physician programmer through which a clinician can adjust non-invasively the characteristics of the electrical pulses and transmit these changes via radio telemetry to the implanted neurostimulator.

symptoms are experience by the patient [3]. Moreover, the raw sEMG keeps the information over the whole frequency spectrum of the signal, which is imperative in prediction in control applications.

Our past work on predictive DBS control based on sEMG power. In [3], we decomposed the raw sEMG signal by using a Wavelet Transform (WT) and tracked the power fluctuations over time in four frequency bands (1-32 Hz). In some or in all the bands considered, power was shown to drop during a DBS-on period and to remain low for a significant amount of time during the following DBS-off period which corresponded to absence of tremor. A gradual power rise was shown to precede a visual reappearance of tremor and a sudden power increase was interpreted as voluntary movement. We successfully predicted tremor reappearance by comparing the instantaneous power level in frequency bands 4-8 Hz and 8-16 Hz with a (patient dependent) threshold.

Proposed work on predictive DBS control based on entropy index. In this paper, we propose a novel predictor for tremor reappearance with the following goals in mind:

GOAL 1: formally design a control algorithm based on our findings in [3] that eliminates the need of tracking the low frequency bands and adapting/estimating thresholds for each of them. Our goal is to find a single quantitative index that "summarizes" the predictive information of the low frequency bands of the raw sEMG signal.

GOAL 2: distinguish between different states a patient can be in, namely: a) rest and no tremor, b) voluntary movement and no tremor, c) tremor at rest or during voluntary movement. With our novel predictor we aim to be able to distinguish among these states.

We propose to use an *entropy* measure toward such goals.

Past work on entropy measures. Two types of entropy index have been proposed: *Wavelet Entropy* to capture information relating to power shifts in different frequency bands and *Approximate Entropy* to quantify the regularity and complexity of a time series signal [8]. These two measures are however not directly comparable. Wavelet Entropy has been widely used for analyzing electroencephalogram (EEG) signals to measure degree of similarity between different segments of the signal [9], for detecting different events such as seizures in epileptic patients [10]; it has also been used to analyze electrocardiogram (ECG) signals for detecting myocardial infarction [11]. It has been shown in [7] that tremor is characterized by an increased regularity in the corresponding sEMG signal as compared to sEMG without tremor which can be captured by the *Approximate Entropy* measure. It has also been used for similar analysis of EEG signals [12] and heart rate signals [13].

Main Contributions. The question we investigate here is whether either of these two types of entropy measure, or their combination, can be used to capture the changes in power in different frequency bands over time [3] and thus be used to predict an impending tremor before it actually visibly reappears (GOAL 1) and to efficiently differentiate between the patient's states (GOAL 2). We show that although each entropy measure captures similar kind of information, incorporating both of them makes the prediction more robust to errors in selection of algorithm parameters and allows to achieve both goals. We also show that the proposed entropy-based control outperforms the power-based control in [3].

Paper Organization. The paper is organized as follows: Section II introduces the entropy measures. Section III discusses the data recordings, the entropy calculation from the data sets, and the prediction procedure. Section IV presents the results of the detection algorithm and compares it with our earlier approach. Section V concludes the paper and points out interesting directions of future work.

II. SHANNON ENTROPY, WAVELET ENTROPY AND APPROXIMATE ENTROPY

The *(Shannon) entropy* is a measure of unpredictability and is often used to quantify the amount of order/disorder in a signal. In information theory, the entropy of a discrete random variable (RV) X is defined as [14]:

$$H(X) = -\sum_{i=1}^{N} p_i \log p_i \qquad (1)$$

where $p_i = \mathbb{P}[X = x_i]$, $i \in \{1,...,N\}$, is the probability mass function and N is the number of possible outcomes for X.

Based on (1), the *Wavelet Entropy* at time t of a time series signal $x(t)$, indicated as $H_{wt}(t)$, is defined as follows [9]: $x(t)$ is first decomposed into N frequency bands, indicated as $\{W_1(t),...,W_N(t)\}$, using a discrete WT and then the normalized power of $W_i(t)$ is computed as:

$$P_i(t) = \frac{|W_i(t)|^2}{\sum_{j=1}^{N} |W_j(t)|^2}, \ i \in \{1,...,N\}.$$

At each time instant t, $\{P_i(t), \ i \in \{1,...,N\}\}$ can be treated as a probability mass function whose entropy is given by (1) with $p_i = P_i(t)$, $i \in \{1,...,N\}$.

The computation of the *Approximate Entropy*, denoted as $\text{ApEn}(U,m,r)$, for a given time series $U = \{x(i), \ i \in \{1,...,L\}\}$ of length L involves two input parameters m and r, which are the pattern length and the similarity criterion, respectively. $\text{ApEn}(U,m,r)$ is evaluated as follows. Let $\mathbf{x}(i) = [x(i),...,x(i+m-1)]$ for $i \in \{1,...,L-m+1\}$ be a set of length-m vector sequences constructed from U. The ℓ_∞-distance between two such sequences $\mathbf{x}(i)$ and $\mathbf{x}(j)$ is: $d_\infty[\mathbf{x}(i),\mathbf{x}(j)] = \max_{k=1,...,m}|x(i+k-1) - x(j+k-1)|$. Let:

$$C_i^m(r) = \left|\left\{ j : \ d_\infty[\mathbf{x}(i),\mathbf{x}(j)] \leq r(L-m+1)^{-1} \right\}\right|$$

as number of patterns in $\mathbf{x}(i)$ that are similar to $\mathbf{x}(j)$ (given the "similarity criterion" r), $i,j \in \{1,...,L-m+1\}$ and let:

$$C^m(r) = (L-m+1)^{-1} \sum_{i=1}^{L-m+1} C_i^m(r).$$

The function $\text{ApEn}(U,m,r)$ is then defined as:

$$\text{ApEn}(U,m,r) = \log C^m(r) - \log C^{m+1}(r). \qquad (2)$$

Heuristically, given L data points, $\text{ApEn}(U,m,r)$ approximates the negative average logarithm of the conditional

probability that two sequences that are similar for m points remain similar within a tolerance r at the next point; a lower $\text{ApEn}(U,m,r)$ value reflects a high degree of regularity [8].

III. DATA SET AND METHODS

We use data obtained at the University of Illinois at Chicago (UIC). A series of sEMG recordings were done on a male patient, who underwent bilateral DBS implantation in the VIM in 2002, and has dominant tremor in his arms. The stimulation electrodes were regular implantable DBS electrodes (considered as macroelectrodes) which were inserted stereotactically through an Alpha-Omega Microdrive. The EMG equipment was a Neurotrek EMG System (Alpha-Omega, Israel), using noninvasive sEMG electrodes placed on the forearm muscles. There were two recording sessions about a month apart. The skin electrodes were placed on the patient's forearm, noting that in this patient tremors appeared first and almost solely on the forearms and then on hands. Here, we present results on data recorded during the second session. During this session, there were seven cycles of stimulation on and off with voluntary movement such as raising the arm and holding a glass of water and two cycles with writing task. Each cycle consisted of a stimulation-on duration followed by a stimulation-off duration. When the stimulation was off, the instant when tremor visibly reappeared, or writing worsened, was noted and then stimulation was switched on a few seconds after that.

The raw sEMG signal was recorded at a sampling rate of 12 KHz. The signal was first decimated to 2000 samples/s. It was then decomposed into nine frequency bands using a Daubechies4 wavelet. The Wavelet Entropy $H_{\text{wt}}(t)$ was calculated at each time point according to (1) and then averaged over time windows of half second duration. Furthermore, the decimated signal was low-pass filtered to retain frequency components up to 60 Hz and this signal was used for calculating the approximate entropy $\text{ApEn}(U,m,r)$. Following [13], we set $m = 2$, $N = 1000$ (0.5 s window), $r = 0.15\sigma$, where σ is the standard deviation (SD) of the corresponding windowed signal. The detection algorithm using either of the entropy measures involves finding an upper and a lower threshold and predicting an impending tremor whenever the entropy of the sEMG during the stimulus-off period lies in between these two thresholds for at least two consecutive windows (i.e for at least 1 s) and the absolute difference between the entropy at these consecutive time points must be lesser than a tolerance value which is estimated as the SD of the entropy of the sEMG measured during the preceding stimulus-on duration. The upper and the lower thresholds can be estimated from sEMG measured at rest and with voluntary movements when there is no tremor. These are expected to change over time with the progression of the disease and should be re-calculated offline after certain intervals (of the order of weeks/months). The lower threshold is required to prevent false detections due to voluntary movement without tremor. This algorithm was applied to both the entropy measures calculated from the seven cycles of recorded sEMG and the results are tabulated in the following section.

IV. RESULTS

In each recording cycle, the prediction algorithm described in Section III was applied to the entropy values calculated over an interval T_p, where T_p is the time interval during which the stimulation was off until tremor visibly reappeared and up to an additional two seconds following this event. Additionally, a prediction based on the power in frequency bands 4-8 Hz and 8-16 Hz was done as in [3] to compare performance with the novel entropy-based prediction scheme.

Table I shows the results with the Wavelet Entropy $H_{\text{wt}}(t)$ and with the approximate entropy $\text{ApEn}(U,m,r)$ considered separately and jointly, along with those with the power-based prediction of [3] (all times are expressed in seconds). Note that in the 3rd cycle, there are two time instants, 152 s and 163 s respectively, when tremor was visibly detected. The later instant corresponds to greater tremor than the former. The mean of the maximum and minimum entropy values over the stimulus-on periods over the 7 cycles were 0.5 and 0.04 for $\text{ApEn}(U,m,r)$ and 0.6 and 0.12 for $H_{\text{wt}}(t)$, respectively. Based on results in [7] a margin of 0.1 below the mean maximum entropy was allowed for determining the upper threshold and to prevent any confusion with voluntary movement, a larger margin of [0.26-0.28] was allowed for estimating the lower threshold. The upper and the lower thresholds for $H_{\text{wt}}(t)$ were thus set to 0.5 and 0.4, respectively, while those for $\text{ApEn}(U,m,r)$ where set to 0.4 and 0.3, respectively. Missed Detection (MD) in Table I means that tremor was not predicted during the interval T_p.

From the tabulated results, we see that by using $H_{\text{wt}}(t)$ there is correct detection in 5 out of 7 cycles. In the 2nd cycle, tremor is detected after its visible appearance while in the 3rd cycle there was missed detection over the period considered. On the other hand if we use the $\text{ApEn}(U,m,r)$ alone, there is missed detection in the 5th and 7th cycle. However, if we use both entropy measures and declare a detection if either measure detects a tremor, that is if we consider the union of each independent detection result, then we can get detection in all the cycles at least a few seconds before actual tremor visibly appears (column labeled "joint detection"). For comparison, also the times from the power-based prediction algorithm of [3] are reported (column labeled "power detection"). We can see that the joint detection algorithm performs better than the power based one as the former predicts an impending tremor closer to the actual tremor appearance time than the later for all the cycles except for the first one.

Fig. 1 shows the entropy values over portion of the stimulus-off duration for cycles 2 and 5. It depicts for these two cycles how the detection is more robust to the selection of the threshold values when both the entropy measures are used. During cycle 2, it can be seen that at around 89 s, two consecutive points of the $\text{ApEn}(U,m,r)$ lie very close to each other inside the detection band. However, for $H_{\text{wt}}(t)$, at around 90 s, there are three consecutive points close to each other with the 2nd point just missing the lower threshold. Hence, if the lower threshold were lower, there

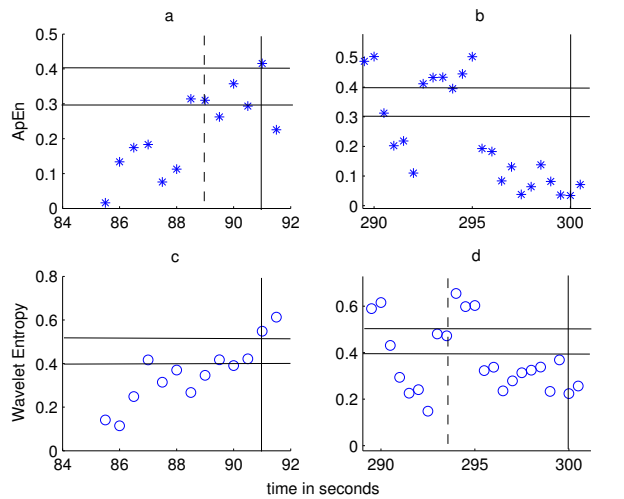| #	stim. off	visible tremor	ApEn detection	$H_{\mathrm{wt}}(t)$ detection	joint detection	power detection
1	40	45	42	45	42	44.5
2	85	91	89	92.5	89	88
3	146	152,163	151,158	MD	151,158	148
4	200	231	225	227	225	202
5	271	300	MD	293.5	293.5	273
6	360	389	389	382	382	365
7	440	454	MD	446	446	442
8*	503	509	504	504	504	504
9*	581	596	593	594.5	593	583

Fig. 1. ApEn (top) and $H_{\mathrm{wt}}(t)$ (bottom) during stimulus off interval for cycles 2(left) and 5(right). The solid horizontal lines denote the upper and lower threshold values used for predictions. The solid vertical lines indicate the time of tremor while the dashed vertical lines indicate time tremor predicted.

would actually be detection at this point. Similarly, in cycle 5, at around 292-294 s, there are four consecutive points in the ApEn(U,m,r) plot. There is a missed detection at this instant due to the upper threshold being lower than required for a successful detection. This is however taken care of by the $H_{\mathrm{wt}}(t)$. Thus, by taking the minimum between the tremor predicted time by either measure we neither get missed detection nor delayed detection.

We have designed a tremor prediction algorithm based on an entropy measure (GOAL 1) and have avoided false prediction due to presence of voluntary movements by using a lower threshold in the algorithm (GOAL 2). However, GOAL 2 has been addressed in a simple way and requires further work for more complex actions.

V. CONCLUSION AND FUTURE WORK

In this paper, we showed that entropy-type measures, specifically Wavelet and Approximate Entropy, can be used to design an effective adaptive controlled on-off DBS system where the stimulation is switched on when tremor is predicted to reappear. We also showed that a combination of both the entropy measures leads to the design of a more

robust predictor which outperforms previously proposed power-based predictor. This result can potentially lead to a novel sEMG-based adaptive on-off DBS controller which would provide stimulation only when needed and can be added on to existing open-loop DBS systems with minimal changes. We are currently recruiting more patients for testing the proposed detection algorithm on a wider range of dataset. As a direction of future work, we will look at adaptively modifying the prediction thresholds of the entropy-based predictor and to quantify the effect on the prediction time of the number of frequency bands used for the Wavelet Entropy and of the input parameters for the approximate entropy. We will also address GOAL 2 in more depth by classifying different states and complex actions based on entropy values. An artificial neural network can also be employed, using inputs from both the entropy parameters of this paper and the wavelet parameters [3], for combined prediction benefiting from both sets of parameters.

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