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Analysis and visualisation of tremor dynamics in deep brain stimulation patients

Abstract: Deep brain stimulation (DBS) is an established therapy for movement disorders such as in Parkinson's disease (PD) and essential tremor (ET). Adjusting the stimulation parameters, however, is a labour-intensive process and often requires several patient visits. Physicians prefer objective tools to improve (or maintain) the performance in DBS. Wearable motion sensors (WMS) are able to detect some manifestations of pathological signs, such as tremor in PD. However, the interpretation of sensor data is often highly technical and methods to visualise tremor data of patients undergoing DBS in a clinical setting are lacking. This work aims to visualise the dynamics of tremor responses to DBS parameter changes with WMS while patients performing clinical hand movements. To this end, we attended DBS programming sessions of two patients with the aim to visualise certain aspects of the clinical examination. PD tremor and ET were effectively quantified by acceleration amplitude and frequency. Tremor dynamics were analysed and visualised based on setpoints, movement transitions and stability aspects. These methods have not yet been employed and examples demonstrate how tremor dynamics can be visualised with simple analysis techniques. We therefore provide a base for future research work on visualisation tools in order to assist clinicians who frequently encounter patients for DBS therapy. This could lead to benefits in terms of enhanced evaluation of treatment efficacy in the future.

Keywords: Wearable motion sensors, movement disorders, tremor, deep brain stimulation, spectral estimation.

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1 Introduction

Pathological tremor is typically more pronounced at the upper limbs in patients with movement disorders such as PD and ET [1]. DBS is an established method for treating motor symptoms such as tremor in PD [2]. A series of visually guided hand movements (i.e. motor tasks) enable the physician to assess the severity of the motor symptoms and to adjust the DBS parameters [3]. This clinical evaluation is based on the observation of the tremor waveform, which is hard to detect visually for a precise DBS adaptation [4]. Physicians prefer objective and precise methods to solve these clinical questions [4]. In particular, methods to visualise tremor data of patients with DBS in a clinical setting are lacking.

Tremor is described by its characteristics in terms of frequency, amplitude and regularity [5]. PD tremor (3-6 Hz) typically occurs at rest. ET (2-7 Hz) is mainly characterised by an action tremor, which is further divided into postural and kinetic tremors [5]. A subtype of the kinetic tremor is the intention tremor, which increases towards the end of a visually-guided movement [6]. A clinical hand movement to evaluate this task-specific tremor is the finger-to-nose (FTN) motor task [6].

DBS programming is an empirical process under the visual guidance of an expert in movement disorders [2], [7]. The expertise on potential stimulation-induced side effects (SE) is essential to obtain a successful DBS therapy [7]. However, the absence of empirical data on the relationship between specific DBS parameters and the clinical response often limits the ability to select more efficient parameters [4]. WMS can provide reliable feedback of motor symptoms and may increase the therapeutic effect of DBS with less SE [4], [7]. It requires systematic steps to capture motor symptoms, an established signal processing pipeline and data analysis procedure, and suitable visualisation tools. The latter is still absent for tremor-dominant DBS patients in a clinical setting, although various authors have contributed to processing and analysis methods on accelerometer signals in a manner suited to the extraction of clinical parameters [5], [8].

2 Methods

In this work, we attended DBS programming sessions of two patients with the aim to visualise certain aspects of the clinical examination. The two patients followed the daily medication intake. Within the regular check-ups, the patients performed a series of motor tasks and the DBS parameters were adjusted by the trained physician in charge. The motor tasks complied with the standards of the International Parkinson and

Movement Disorder Society (MDS) to evaluate hand resting, postural, and intention tremor [1], [3], [6]. A motor task is defined as resting position (RP) when the arm/hand is lying on the table, as a postural position (PP) when the arm/hand is outstretched, and as FTN when touching the nose with the index finger. Each task starts from the resting position. We describe the methodology of the new approaches and results are illustrated by a collection of examples (in figures) of the two case studies. Note that the interpretation of sensor data is highly technical and its visualisation includes extensive staff time to process and analyse the data.

2.1 Data processing

Tremor was measured with a WMS (Shimmer3 IMU, Shimmer™ Corp., Ireland) attached to the patient's wrist. Unless otherwise specified, movement data was collected with a frequency of 200 Hz [9] and analysed offline with custom-written software in MATLAB™ (R2018a, MathWorks Inc., USA). Sensor data of the 3-axis accelerometer and 3-axis magnetometer of the inertial measurement unit (IMU) was used. For each patient, the data collection contained the time series data of the motor tasks to evaluate hand resting, postural, and intention tremor. The patients were asked to perform motor tasks two to three times and each movement was repeated several times in one session.

Acceleration signals were band-pass filtered (BPF) around the tremor frequency (3-pole Butterworth filter, 16 dB per octave). This frequency represents the sensor axis of the highest spectral peak in the Fast Fourier Transform (via visual inspection) obtained from the raw acceleration signal in the DBS off condition. The choice was confirmed post hoc by using the principle component analysis to find the sensor axis with the highest coefficient [10]. To capture the tremor frequency, low frequency high amplitude signals caused by voluntary movements (e.g. FTN motor task), and the high frequency low amplitude signals of physiological tremor (e.g. PP motor task), were removed. Low and high cut-off frequencies of the BPF were defined individually on the basis of test measurements and the literature [1].

Tremor dynamics were effectively quantified by acceleration amplitude and frequency [10]. Signals derived from the magnetometer provide additional information about the movement transitions. Statistical parameters, such as root mean square (RMS) amplitude, spectral peak frequency with position, and the area under the curve (AUC) in the power spectrum, were calculated. The standard deviation is equivalent to the RMS (mean value is removed).

The evolution of tremor power over time was derived from the BPF acceleration signal, and subsequently analysed by spectral estimation. Here, the magnitude squared of the short-time Fourier transform (STFT) represents the tremor power over time [11]. To reduce the spectral leakage, tremor signals were modified by Hann windowing [12]. The length of the window function depends on how fast the tremor is suppressed when the DBS parameters are changed. These response times may also differ within a patient (i.e. time to settle down to a steady state). Finally, tremor power was estimated from the area under the curve (AUC) within the BPF tremor frequency windows. STFT squared with an overlap of one data sample

was defined as the default setting and the calculated AUC values of each window consecutively arranged.

2.2 Tremor dynamics

Tremor dynamics were analysed based on setpoints, movement transitions and stability. A setpoint is defined as the lowest DBS amplitude needed to produce a complete (or near complete) loss of hand tremor that is observed by the physician. Setpoints were defined for the tasks to evaluate hand resting (RP motor task), postural (PP motor task), and intention tremor (FTN motor task). In the latter case, often the index finger and occasionally the hand tremble when both are in the vicinity of the nose [6]. Hence, setpoints were defined only in the vicinity of the nose during this motor task. The patient remained in this position for less than 3 s. Tremor responses to different DBS parameter settings were also quantified by the tremor power derived from the accelerometer signals. DBS parameters were decreased form their initial settings to find setpoints and increased to determine the thresholds at which SE such as headaches and tingling in the arm occur. Movement transitions were defined as a transition between two motor tasks such as RP to PP and RP to FTN. Tremor stability refers to the stability analysis of tremor amplitude and frequency.

3 Results

Set-points: The aim was to the find the setpoints in RP, PP and FTN motor tasks for each disease group and to fine-tune the DBS parameters in each setpoint. Figure 1 shows an example of the empirical search in PD to obtain a more effective stimulation amplitude guided by the physician. Typically, the amplitude is slightly above the setpoint.
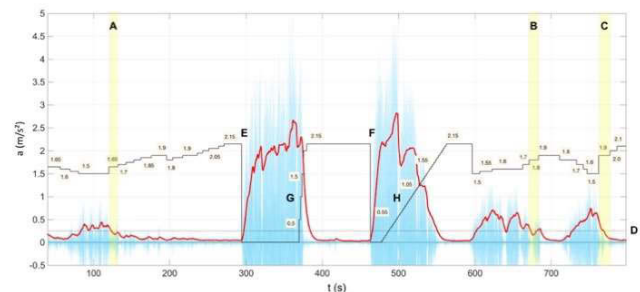

Figure 1: DBS programming in a PD patient with right hand resting tremor. Stimulation amplitude changes by the physician are shown as input step function (black signal). The tremor-dominant signal (Z-axis) depicted a tremor peak at about 4.2 Hz. Hence, the signal was narrow BPF between 3.8–4.6 Hz (blue signal). The tremor power (red signal) was computed as a feature based on the STFT. Initial settings of DBS parameters are 2.15 V, 130 Hz, and 60 μs (Medtronic™, lead 3389, C1- with 1513 Ω, C2- with 1493 Ω). Setpoint dynamics in RP (**A-C**) are between 1.65 V and 1.9 V for a threshold of about 0.25 m/s^2 (**D**). Note that the therapy limit was nearly reached as SE (e.g. muscle cramps) occurred at 2.2 V. DBS parameters were adapted with the clinician programmer device (N'Vision™, model 8840, Medtronic™ plc., Ireland) in step rates of 0.5 V, 0.1 V or 0.05 V. A tremor response time of approx. 2 s was observed (**E** and **F**) after switching off the initial stimulation of 2.15 V immediately. The amplitude auto-increase setting of the clinician

programmer was used for stimulation rates of 0.5 V each 2 s (**G**) and 0.05 V each 2 s (**H**). Data were sampled with 120 Hz and STFT settings with a window length of 192 samples used.

Movement transitions: An example for the analysis of the movement transition from rest-to-posture (RTP) and posture-to-rest (PTR) of an ET patient is depicted in Figure 2. This example shows the impact on subtle movements, such as holding an empty tea cup in the hand. The start and end time of each transition was determined by visual inspection. The results demonstrate that an intention tremor is followed by a postural tremor at the transition RTP.

Figure 2: Movement transitions of an ET patient with DBS therapy (Medtronic™, lead 3387, C1- with 1147 Ω, IPG+) and near-optimal stimulation settings (2.9 V, 130 Hz, 60 μs). The movement transitions of the right arm/hand from RTP (**A**) and PTR (**B**) are shown. The data were aligned on time axis to compare both transitions (indicated as yellow shaded box, **A** and **B**). Both signals (blue signals, **A** and **B**) represent the tremor dominant accelerometer axis (Z-axis, sensor mounted on wrist). Electromyography (EMG, Shimmer3 EMG, Shimmer™ Corp., Ireland) of the extensor carpi (EC) radialis and flexor carpi (FC) radialis muscles (red and green signals, **A** and **B**) were recorded additionally. A response time of about 2 s was measured when DBS was switched off. Notice that the acceleration signals were BPF between 2–7 Hz and EMG signals between 20–400 Hz with a sampling frequency of 1024 Hz. EMG signals were realigned and the averaged rectified RMS value with a window size of 512 samples was calculated. The PSD of the tremor signal (**C**, EMG not illustrated) is increased for the transition from PTR. This was observed in 3 ET patients holding an empty tea cup.

DBS parameter fine-tuning is shown in Figure 3a for the FTN motor task with its relative tremor power distribution in Figure 3b. This example refers to the ET patient in Figure 2 to analyse setpoints and movement transitions of the FTN motor task starting from RP. The stimulation amplitude with 3.6 V was defined as the setpoint to achieve a clinically evident effect reported by the patient and observed by the physician (Figure 3b). However, this near-optimal setpoint in relation to tremor suppression caused minor SE (paraesthesia and tingling in the right arm) once the stimulation was above 3.2V. A short-time increase was accepted by the patient.
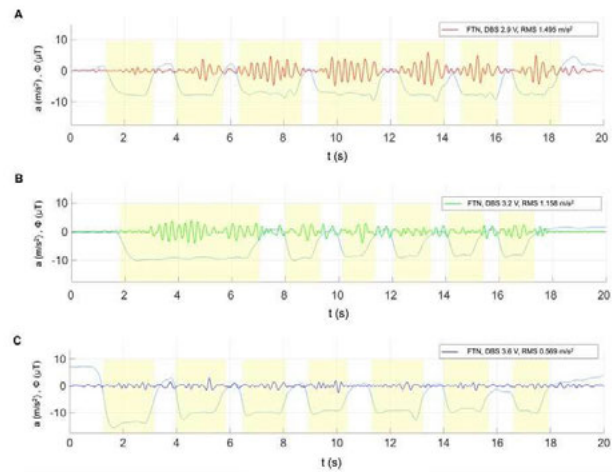

Figure 3a: DBS parameter adjustment for the FTN motor task of the ET patient in Figure 2. Times series data show the setpoint in the vicinity of the nose. Accelerometer signals of the right-hand tremor were BPF for the tremor-dominant axis (Z-axis of the red, green, and dark blue signal, **A-C**). A moving average filter was applied to the magnetic field signal to visualise the FTN trajectory (light blue signals, **A-C**). The setpoint in the vicinity of the nose is represented by the plateau of each FTN movement (magnetic field signal). In total, the 3 sessions with a series of 7 FTN movements were performed by the patient. Note that the patient was not able to perform one of the FTN movement correctly (first FTN trajectory in **B**). The DBS amplitude was increased afterwards to achieve the optimal performance for the FTN motor tasks, defined by its setpoint.
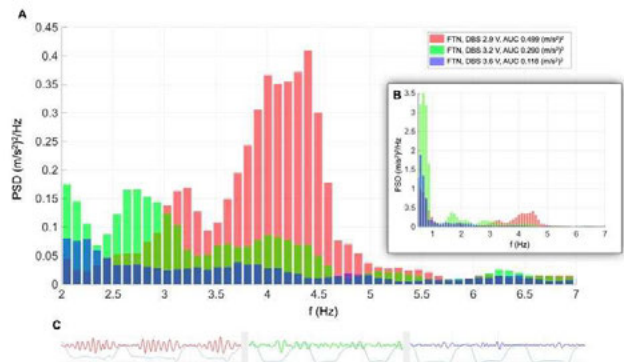

Figure 3b: Relative tremor power distribution of the FTN task (**A**). The voluntary movement frequency band decrease with an increase of relative power in the tremor frequency band (**B**). When tremor was absent lower frequencies significantly dominated during the FTN movement condition (**B**, PSD). Low frequency components became prominent which seems to act as a compensation mechanism. In (**C**) the data sequences (excerpt from Figure 3a) of a series of 3 FTN motor tasks are shown.

Results in Figure 2 and Figure 3 (a, b) are consistent with the literature. A previous study reported that the PD patients with isolated hand resting tremor continuously balance between tremor and tremor suppression during the transition from RP to movement [13]. Both states are expressed by power shifts between the low frequency band (voluntary

movements) and the tremor frequency band. Note that the visualisation of the FTN trajectory through the filtered magnetic field signal (Figure 3a) is a simple and effective technique to identify the motor task for processing of the acceleration data. This method has not been published in the literature.

Tremor stability: The term stability refers to the analysis of the tremor amplitude and frequency of the filtered accelerometer signals. Tremor time series data was analysed during DBS parameter changes and the evolution over time visualised by calculating the tremor-power. An example is shown in Figure 5.
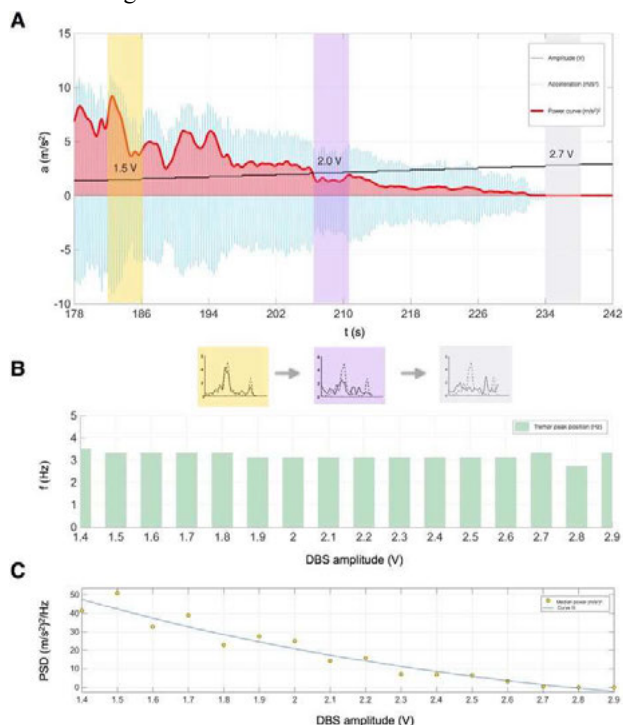

Figure 5: Tremor response to changes in DBS parameters of the ET patient in Figure 2. DBS amplitude changes (black, rate 0.1 V each 4 s) is illustrated for the BPF signal (blue) with its tremor power curve (red) (**A**). The tremor peak position (green) is stable in this patient (**B**). The patient's linear response of trembling to DBS changes is shown (linear regression, **C**). Note that the median values of the tremor power curve are presented for each segmented 4–s block (yellow points in **C**).

4 Discussion

The analysed data give an insight into tremor dynamics of DBS patients and its visualisation has not yet been published in the literature. Moreover, results of the two case studies are consistent with the literature. We visualise these results, which demonstrates that PD and ET patients with DBS therapy often balance between tremor and tremor suppression during the execution of movements, especially when non-optimal DBS parameters are set. A detailed interpretation of the tremor data, however, requires a larger cohort of patients. Moreover, the comparison between disease groups is challenging based on

the high variability in the motor symptoms. This requires a careful measurement protocol to collect data from patients with similar disease symptoms and progression. Hence, a study with several patients is planned in the future. The results of the two case studies were generated based on a time-intensive work to process, label, analyse and visualise the data; especially due to the manual DBS programming and synchronisation between the stimulation device and WMS. Finally, the visualisation methods provide a tool for future research work focused on tremor dynamics in DBS. Hence, the work will focus on a systematic data collection and evaluation in a larger study cohort.

Author Statement

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