Tremor severity rating by Markov chains
Fredrik Olsson* Alexander Medvedev*
*Department of Information Technology, Uppsala University, Sweden
(e-mails: fredrik.olsson@it.uu.se, alexander.medvedev@it.uu.se).

Abstract: The paper deals with mathematical modeling tools for tremor quantification, a problem arising in e.g. clinical applications and sports. Tremor is an involuntary repetitive movement of extremities, head, or trunk that occurs in disease but also in health, due to e.g. strain or fatigue. Quantification of tremor is traditionally performed by ocular observation, while numerous technologies based on wearable accelerometer data exist and have been tested in medical practice. The currently available approaches rely on spectral analysis that reduces a fundamentally nonlinear and non-stationary phenomenon to a linear combination of harmonic components. The classical nonlinear identification methods are as well of limited use because the underlying system is essentially autonomous and produces sustained oscillations without exogenous excitation. An alternative view on tremor is therefore adopted that treats the problem from a severity rating perspective aligned with clinical practices. The tremor amplitude is modelled by a Markov chain, where the states represent the predefined intervals of severity. A comparison with a previously developed event-based method of tremor quantification is provided on data collected using a smart phone in a patient diagnosed with Parkinson disease and undergoing Deep Brain Stimulation therapy. The experimental procedure is unobtrusive and can be implemented in a way that is transparent to the patient.

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1. INTRODUCTION

Tremor is a cardinal symptom in several neurological diseases, e.g. Parkinson’s disease (PD) and essential tremor (ET), Mario et al. (2000). These two examples of pathological conditions are especially illustrative with respect to symptom characterization. Rest tremor is reduced under voluntary movements and characteristic to PD, while ET patients typically exhibit action tremor that worsens in movement. Yet, both conditions can be present in the same patient. The time evolution of the tremor amplitude in the face of a voluntary movement is thus necessary to distinguish between rest tremor and action tremor.

Physiological tremor is always present in extremities, even of a healthy person, but becomes more prominent under strain, due to fatigue, emotional stress, or withdrawal of alcohol or drugs. Shooting (Lakie, 2010) and microsurgery (Riviere et al., 1998) are relevant examples of tasks where the performance is critically influenced by tremor.

Besides a purely biomechanical interest in explicating the mechanism of tremor, there is also a clinically relevant need of quantifying the severity of the motor symptom. In the latter case, unobtrusive tools of tremor quantification and characterization that do not demand active involvement of the patient are desirable.

Tremor quantification plays an important role in the individualization and optimization of treatments in PD and ET. Since monitoring of tremor can be performed in a unobstrusive manner, e.g. by means of the sensors of a smart phone or smart watch, it can be potentially used in tuning of the deep brain stimulation (DBS), see Cubo et al. (2017), Cubo et al. (2016), or in adjusting drug dosing to the severity of the symptom in a smart microtablet dispenser, Senek et al. (2017).

DBS is an established treatment in PD and ET, where implanted electrodes are utilized to chronically stimulate a certain target area in the brain in order to alleviate the symptoms of the disease. Primarily motor symptoms, such as tremor, are taken into account when optimizing the stimulation settings, due to their almost immediate response to a change in the stimulation. The DBS optimization is currently performed manually and attempts to exploit mathematical optimization are undermined by the model uncertainty, Cubo et al. (2018). Symptom quantification presents thus a feasible way of improving the fidelity of the patient-specific models, Cubo et al. (2017).

A natural description of tremor from a control engineering point of view is an orbitally stable limit cycle. This concept immediately highlights the nonlinear nature of the phenomenon. Yet, the frequency and amplitude of tremor change with time and posture. Selecting a mathematical model for tremor is therefore complicated by the lack of a standard modeling paradigm in time-varying systems.

Being a self-sustained nonlinear oscillation, tremor is suitably modeled as an autonomous system, Medvedev et al. (2017). This also presents a theoretical complication in estimating the tremor dynamics from measurements due to the lack of identifiability in absence of exogenous excitation. Note here that a voluntary movement can generally either amplify or subside tremor but is not accessible to direct measurement. Therefore, voluntary movement cannot serve as input in a classical system identification sense and
a more complex signal form of it does not produce more informative system output. On the contrary, it complicates the task of separating the effect of voluntary movement from that of tremor on the measured trajectory.

As the authors of Mario et al. (2009) point out, neither amplitude nor peak frequency provides reliable discrimination of the type of pathological tremor. Therefore, all the commonplace spectral analysis tremor quantification algorithms are only of limited use in this respect and other modeling paradigms than Fourier series are sought for. An event-based approach to modeling and quantifying tremor is proposed in Dimitrakopoulos et al. (2017), where the amplitude and timing of the extreme points of an estimated tremor trajectory are utilized. To keep in touch with the biomechanics underlying the phenomenon in question, the parameters of an autonomous nonlinear oscillator whose limit cycle captures the actual signal form of tremor can be estimated, Medvedev et al. (2017). Both methods can be readily implemented on a smart phone.

State-of-the-art computer-based analysis and objective quantification of tremor utilizes spectral analysis of measured waveforms and assumes the “wide-sense stationarity” of tremor, Mario et al. (2009). The actual non-stationarity of the tremor is tackled by taking into account the signal power within a frequency range close to the peak value, e.g. Dai et al. (2015).

Despite the findings in Mario et al. (2009), the frequency content is also used to distinguish voluntary motion from the motion due to pathological tremor. The spectrum of a voluntary motion lies at the frequencies below 3 Hz while pathological tremor gives rise to frequency components higher than 4 Hz, Heldman et al. (2011). The peak frequency value is used to differ between the types of pathological tremor. In Pierleoni et al. (2014), the following ranges are proposed: resting tremor (3-6 Hz), postural tremor (6-9 Hz), kinetic tremor (9-12 Hz).

In the present paper, tremor is quantified by modeling the deviation from a voluntary movement as a Markov process, whose states represent the predefined severity grades. A similar approach has been used in Rasku et al. (2008) and Hur et al. (2012) to model center of pressure (COP) trajectories in a human balance experiment. Just as tremor is a form of involuntary movement, the movement of the COP in standing human balance is an effect of involuntary body sway. Following Hur et al. (2012), the steady-state distribution of the Markov chain is studied and a set of parameters to quantify tremor is extracted from it.

The rest of the paper is organized as follows. The method proposed for tremor quantification from 3D inertial measurements is presented in Section 2. Experiments performed in a clinical environment during a DBS programming session are described in Section 3. The results of applying the tremor quantification method to the collected data are summarized and followed by a discussion in Section 4. Finally, conclusions are drawn and directions for future work are outlined in Section 5.

2. METHOD

This section describes a method of obtaining a 2D tremor signal representation from 3D inertial measurements as well as the use of Markov chains in modeling the steady-state of tremor. Sections 2.1-2.4 summarize previous work, see Dimitrakopoulos et al. (2017), Medvedev et al. (2017), to facilitate readability and provide suitable background.

The steps of the tremor quantification algorithm are:

**Step 1**: Data acquisition from the smart phone sensors

**Step 2**: Acceleration detrending and double integration

**Step 3**: Estimation of voluntary movement and extraction of tremor component

**Step 4**: Estimation of extreme points by detection of curvature maxima

**Step 5**: Tremor grading

Each algorithm step is described below in more detail.

2.1 Position estimation

The accelerometer measurements are modeled as

$$y_a(t) = R(t)(a(t) + g) + e_t,$$  \hspace{1cm} (1)

where \( t = 1, \ldots , N \) is a sample index that corresponds to a specific moment in time, \( a(t) \) is the acceleration of the sensor and \( g \) is the local gravitational acceleration, which is assumed to be known. Here, both \( a(t) \) and \( g \) are expressed in a global Earth-fixed reference frame. Since the measurements are in the local sensor frame, a rotation matrix \( R(t) \) that describes the transformation from the global frame to the sensor frame is needed. The measurements are assumed to be corrupted by zero-mean Gaussian noise, \( e_t \).

An estimate of the sensor acceleration \( \hat{a}(t) \) is calculated by first evaluating the rotation matrix \( \hat{R}(t) \). The smart phone used in the experiments is equipped with a gyroscope and a magnetometer in addition to the accelerometer. These sensors can be used together to estimate the orientation of the sensor with respect to the global frame and thus obtain an estimate \( \hat{R}(t) \) of the rotation matrix. Here an extended Kalman filter (EKF) with orientation deviation states is utilized, see Kok (2016), to yield \( \hat{R}(t) \). The acceleration of the sensor is then determined as

$$\hat{a}(t) = \hat{R}^T(t)y_a(t) - g.$$

The velocity and position estimates \( \hat{v}(t) \) and \( \hat{p}(t) \) can be produced by numerical integration

$$\hat{v}(t + 1) = \hat{v}(t) + T\hat{a}(t),$$

$$\hat{p}(t + 1) = \hat{p}(t) + T\hat{v}(t) + \frac{1}{2}T^2\hat{a}(t),$$

where \( T \) is the sample period and the sensor is assumed to be at rest in the beginning of the experiment, i.e. \( \hat{v}(1) = 0 \) and \( \hat{p}(1) = 0 \).

It is well known that position estimates obtained by pure integration are prone to drift and, as the noisy estimates \( \hat{a}(t) \) are integrated twice, errors will accumulate over time. In the experiments, this drift is alleviated by assuming a closed trajectory of the sensors, where the sensors return to the same position multiple times during the experiment. Removing a linear trend from the acceleration signal for each closed trajectory enforces the constraint that the sensor returns to the same position as in the beginning of the trajectory. Notice also that the estimation of the tremor movement is not sought in global coordinates but only relative to the voluntary movement.
The curvature of any trajectory $\gamma$ can be used to estimate the frequency of the tremor component. The 3D tremor signal is projected onto a plane, and the translational movement along the voluntary trajectory component, which allows the two horizontal components to be extracted as the 2D tremor signal $p_{3d}(t) = p_v(t) - \hat{p}(t)$. 

\[ p_{3d}(t) = \left( R_{2d}(t) \left[ p_{3d}(t) - \frac{p_{3d}(t) \cdot v_v(t)}{\|v_v(t)\|_2^2} v_v(t) \right] \right). \]  

(6)

The matrix $R_{2d}(t)$ rotates each projection into the horizontal plane, where the third element is zero. Here, the rotation $R_{2d}(t)$ is obtained as a sequence of rotations, that iteratively align the normal of each consecutive plane and finally performs one rotation to set the vertical component of all planes to zero.

### 2.4 Frequency estimate using curvature

The curvature of any trajectory $\gamma \in \mathbb{C}^2$ in a Euclidean space can be computed as

\[ \kappa = \sqrt{\|\gamma'\|^2 \|\gamma''\|^2 - (\gamma' \cdot \gamma'')^2}, \]  

(7)

where $\gamma'$ and $\gamma''$ are the first and second derivative of the trajectory. In the case at hand, $\gamma$ corresponds to the 2D tremor signal $p_{2d}$ and $\gamma'$, $\gamma''$ are obtained using numeric differentiation. Note that the curvature of the 3D position estimate $\hat{p}$ can be calculated by simply integrating $\hat{a}$ (corresponding to $\gamma''$) once to yield $\hat{v}$ (corresponding to $\gamma'$). This approach is implemented in Dimitrakopoulos et al. (2017) and does not rely on numerical differentiation.

The local maxima of $\kappa$ give the turning points of $\gamma$, i.e., those points, where the 2D tremor signal changes direction. Therefore, the time interval between the occurrences of three consecutive turning points is related to the instant frequency of the tremor signal. Specifically, the inverse of the time interval provides an estimate of the tremor frequency. Fig. 2 shows an example of a curvature plot for a 2D tremor signal and the extracted turning points. Here, a sliding window of nine samples is used to identify the local maxima. If the sample in the middle of the window is larger than the other samples, a local maximum is detected. Since the sensors sample at 100Hz, the largest detectable frequency is 12.5Hz, which is outside the tremor band.

### 2.5 Markov chain model

A Markov chain is a stochastic process that describes how the state $X_t$ of a dynamical system evolves over time, where the future state $X_{t+1}$ only depends on the current state. Specifically, the probability of transitioning from state $X_t = x_t$ to $X_{t+1} = x_{t+1}$ is given by

\[ p(X_{t+1} = x_{t+1} | X_t = x_t, X_{t-1} = x_{t-1}, \ldots, X_1 = x_1) = p(X_{t+1} = x_{t+1} | X_t = x_t), \]  

(8)

which is known as the Markov property. All states belong to the state-space, $x_{1:N} \in S = \{S_1, \ldots, S_M\}$. If $S$ consists of $M$ states, the transition probability matrix $P \in \mathbb{R}^{M \times M}$ can be formed, where each element

\[ P_{ij} = p(X_{t+1} = S_j | X_t = S_i), \quad i, j = 1, \ldots, M, \]  

(9)
stands for the probability of transitioning from the $i$:th state to the $j$:th state. The elements $P_{ij}$ are obtained from the 2D tremor signal by dividing the number of observed transitions from $S_i$ to $S_j$ by the total number of observations in $S_i$. Let

$$p(X_t) = [p(X_t = S_1) \ldots p(X_t = S_M)],$$  \hspace{1cm} (10)

denote the probability distribution of the state at time $t$, then it follows that

$$p(X_{t+1}) = p(X_t)P.$$  \hspace{1cm} (11)

If the Markov chain is irreducible and recurrent (Norris, 1998), the probability of the states to converge to the steady-state distribution $\pi$ as $t \to \infty$ satisfies

$$\pi = \pi P,$$  \hspace{1cm} (12)

which equality implies that $\pi$ is the left eigenvector of $P$ associated with the unit eigenvalue.

### 2.6 State selection

The state-space of the tremor Markov chain is modeled in the following way

$$S = \{S_i | d_{i-1} \leq \|p_{a2D}(t)\|_2 < d_i\}, \quad i = 1, \ldots, M$$  \hspace{1cm} (13)

$$d_i = ri, \quad r > 0,$$  \hspace{1cm} (14)

where each state $S_i$ corresponds to a set in $\mathbb{R}^2$, of points whose distance to the origin is bounded from below and above by the two disks with the radii $d_{i-1}$ and $d_i$, respectively. The radius of each state is set to a constant $r$, chosen by the user. A small $r$ increases the resolution provided by the state densities. However, $r$ and $M$ must be selected so that the Markov chain is irreducible and recurrent. These properties of a Markov chain mean that it is possible to reach any state in the state-space regardless of the initial state, or that there exists any positive finite integer $t$ such that

$$p(X_t = S_j|X_1 = S_i) > 0, \quad \forall i, j = 1, \ldots, M.$$  \hspace{1cm} (15)

Fig. 3 provides an example of patient data that illustrates how the tremor signal evolves within the state-space.

### 2.7 Tremor quantification parameters

The steady-state distribution $\pi$ captures the long-term behavior of tremor. To facilitate comparison between experimental data sets, the following parameters can be extracted from $\pi$ to quantify tremor severity.

**Mean distance:** The average distance between the actual and voluntary movement is defined as

$$d_{\text{mean}} = \frac{r}{M} \sum_{i=1}^{M} i\pi_i,$$  \hspace{1cm} (16)

where $\pi_i$ denotes the $i$:th element of $\pi$. A larger $d_{\text{mean}}$ means that the tremor amplitude is higher, driving the movement away from the intended voluntary trajectory.

**Standard deviation in distance:** A measure of uncertainty defined as

$$d_{\text{std}} = \sqrt{\frac{1}{M} \sum_{i=1}^{M} (ri - d_{\text{mean}})^2 \pi_i}.$$  \hspace{1cm} (17)

A larger $d_{\text{std}}$ indicates that the tremor amplitudes show more variation over the data set.

### 3. EXPERIMENT

The experimental data used in this study come from a PD patient with an implanted DBS system. The data were collected during a DBS programming session at the Uppsala University Hospital on May 30, 2017, under ethical approval obtained from Uppsala Ethical Review Board. The same data were also used in a previous study, Medvedev et al. (2017).

Inertial sensor and magnetometer measurements were collected using a Samsung Galaxy S5 mobile phone. The sampling rate of the sensors was 100 Hz. In each trial, the patient was instructed to pick up the phone from the table, lift it to the ear as if answering a phone call, and put it back on the table again. This movement was repeated three times per hand. The patient performed the trial with DBS turned off, with the original DBS setting, and with an alternative DBS setting that was tested during the session. This resulted in three independent data sets for each hand.

Notice that the above described test movement naturally arises in day-to-day handling of the phone and can be easily distinguished from other movements. Therefore, it can be utilized for non-obtrusive tremor monitoring.
is also reflected in the extracted parameters, where the curve a distinctly larger peak closer to the origin. This mass is more centered around small deviations, which gives a higher probability mass at larger deviations from the origin. The steady-state distribution of the 2D tremor signal was significantly smaller with DBS on. The standard deviation $d_{\text{std}}$ and similar $d_{95\%}$, characterizing how heavy the distribution tail is, also tends to be larger if the tremor is worse.

When comparing tremor severity with the DBS on and the DBS off, the difference is significant for both hands. However, it is more useful to study the difference between the DBS settings. Comparing the old setting with the new setting, it appears that the new setting performs worse, with a larger $d_{\text{mean}}$ and $d_{\text{std}}$ and similar $d_{95\%}$. During the experiment, it was also easy to visually distinguish between the DBS on and DBS off settings by just observing the patient. However, visually distinguishing between the two DBS settings was significantly more difficult. After the experiment, the patient indicated that the old setting felt better. So it was decided to revert back to the old settings. Notice here that tremor is only one symptom of PD and several other symptoms, as well as side effects of stimulation, are taken into account during DBS individualization.

The accuracy of the models may improve with longer experiments. The length of each experiment here was in the range of 14 s to 26 s per hand. However, longer experiments also mean an increased burden on the patient. Yet, a typical phone conversation is much longer than 30 s. In 2012, the average amount of time for a local wireless call was 1.80 min, see Statista (2017).

The state radius $r$ is in some sense limited by the length of the experiment, as one needs to choose $r$ large enough to render the Markov chain irreducible. It is expected that longer experiments would allow for smaller $r$ to be chosen, which would increase the resolution of the model. It would also be interesting to see how consistent the models constructed from short experiments are compared to models constructed from longer experiments. It may then be possible to find an ideal experiment length and a means of verifying the consistency of each model individually. Due to limited data to date, this analysis fell outside the scope of the present study. However, it is an extension worth considering in the future.

Histograms over the frequency estimates for the 2D tremor signals were obtained using the method described in Section 2.4 and are shown in Fig. 5. The frequency estimates were similar for all DBS settings and for both hands, and appear mostly within the range of 4 Hz to 12 Hz which is typical for pathological tremor in PD. This indicates that the extracted 2D tremor signal successfully captures the tremor that was present during the experiment.

4. RESULTS AND DISCUSSION

The steady-state distribution of the 2D tremor signal was computed for the three different DBS settings and for both hands separately, see Fig. 4. The parameters described in Section 2.7 were extracted from all distributions and are summarized in Table 1.

It can be seen that the steady-state distributions have higher probability mass at larger deviations from the origin, when DBS is turned off. With DBS on, the probability mass is more centered around small deviations, which gives the curve a distinctly larger peak closer to the origin. This is also reflected in the extracted parameters, where $d_{\text{mean}}$ is significantly smaller with DBS on. The standard deviations $d_{\text{std}}$ were also significantly smaller with DBS on, which is related to the distinct peaks with the probability mass concentrated closer to the mean. The third parameter, $d_{95\%}$, characterizing how heavy the distribution tail is, also tends to be larger if the tremor is worse.

5. CONCLUSIONS AND FUTURE WORK

This paper proposes an approach to modeling and quantifying hand tremor in PD. Measurements collected from inertial sensors and a magnetometer in a smart phone are used to obtain a 2D tremor signal, where the tremor component has been separated from the voluntary movement. The tremor component is then used to construct a Markov chain model that has its state-space defined by the tremor amplitude. Furthermore, a steady-state distribution describing the long-term behaviour of the Markov chain model is extracted together with a set of parameters to quantify the severity of tremor. The proposed tremor quantification method is unobtrusive as it only requires the patient to lift a smart phone, or a similar device, equipped
with the appropriate sensors. Handling a smart phone is usually part of patient’s day-to-day life. The developed method is applied to clinical data collected from a PD patient, with DBS implanted, for three different stimulation settings in the DBS system. For this particular data set, the proposed method provided tremor measures that agree with the clinical observations made during the experiment and support the DBS programming outcome.

The feasibility of the developed quantification method is illustrated on data collected during a DBS programming session but readily applies to dose titration in other PD or ET therapies. However, more experimental data is required for a thorough validation of the method and more experiments are planned in the future.

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