33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

A Modelling Study on Transmission of the Central Oscillator in Tremor by a Motor Neuron Pool

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Abstract— **In spite of decades of intense research, pathological tremors still constitute unknown disorders. This study addresses, based on a multi–scale model, the behavior of an entire pool of motor neurons in tremor, under the hypothesis that tremor is an oscillation of central origin commonly projected to all motor neurons that innervate a muscle. Our results show that under such conditions both paired discharges and enhanced motor neuron synchronization, two of the characteristic landmarks of tremor, emerge. Moreover, coherence and correlation analyses suggest that the central tremor oscillator is transmitted linearly by the motor neuron pool given that a small set (7 or 8) of motor neurons are sampled.**

I. INTRODUCTION

Tremor, defined as a rhythmic, involuntary movement of a body part, constitutes the most extended movement disorder, affecting 15 % of the people with age ranging between 50 and 89 years [1]. Pathological tremors, i.e. those that impair motor performance, may originate from up to 10 different conditions [2], none of them fully understood [3]. Nevertheless, it has been suggested that pathological tremors —henceforth simply referred to as tremors— arise from different combinations of 4 mechanisms: central neuronal oscillators, oscillations from distorted feedback and feedforward loops, oscillations due to reflexes, and mechanical oscillations [2]. The former is likely to be the major cause of tremors since, e.g. Parkinson's disease is thought to originate in the loop linking the cortex, basal ganglia and thalamus [4], while the olivocerebellar and thalamocortical loops are speculated to cause essential tremor [3].

A way to elucidate the underlying mechanisms of tremors may be to gain knowledge on the behaviour of motor units, given that the motor neuron output is possible to infer some of the properties of the synaptic input. Technical limitations in recording concurrently a meaningful portion of the motor neuron pool that innervates a muscle, however, greatly impede our understanding of motor unit behaviour in both physiological and pathological conditions [5]. Intramuscular recording with needle electrodes in tremor has suggested a series of features that may characterize motor unit behaviour in such condition, namely: i) the occurrence of paired or tripled discharges with short interspike interval, and ii) enhanced motor unit synchronization. Paired and tripled discharges have been reported both in those suffering from Parkinson's disease [6] and essential tremor [7], and in healthy individuals mimicking tremor [8]. Abnormally large motor unit entrainment has also been widely described [9], [10]. Both features are likely to arise from synaptic excitation and not from intracellular phenomena since, for example, spike doublets, as occasionally observed in healthy individuals, have much shorter inter–spike interval than paired discharges in tremor [11]. However, the limited amount of motor units that can be assessed through intramuscular electromyography, typically no more than 5 or 6 per contraction and recording electrode, hampers more exhaustive investigations of these observations. Computational models, on the other hand, may overcome this limitation, by systematically evaluating physiological hypotheses and contrasting the results obtained with experimental findings.

This work addresses the behavior of an entire motor unit pool in the presence of tremor based on a multi–scale model of tremor [12]. Such model incorporates both afferent and efferent synaptic input, and assumes that the pool receives a common supraspinal tremor input. Analysis of simulations with different frequencies and levels of voluntary contraction show enhanced motor neuron synchronization –when compared to non pathological conditions–, and suggest that the tremor may be linearly sampled by the motor neuron pool given that a small set of motor neurons are active.

II. METHODS

A. Simulation Model

We simulate with a multi–scale model of muscle pair during tremor [12] the first dorsal interosseus muscle, and its antagonist, the second palmar interosseus muscle. Briefly, the model comprises a representation of the motor neuron pool –120 motor neurons– that estimates continuously motor unit firings during dynamic contractions, based on the model described in [13]. This information, in turn, serves to simulate surface electromyography (sEMG) and limb mechanics. The net synaptic input to the motor neuron pool integrates information from muscle spindles and Golgi tendon organs, a volitional descending drive, a representation of the central oscillator of tremor, and synaptic noise. sEMG is calculated

The work presented in this paper has been carried out with the financial support from the Commission of the European Union, within Framework 7, specific IST programme "Accessible and Inclusive ICT", Target outcome 7.2 "Advanced self-adaptive ICT-enabled assistive systems based on non-invasive Brain to Computer Interaction (BCI)", under Grant Agreement number ICT-2007-224051, "TREMOR: An ambulatory BCI-driven tremor suppression system based on functional electrical stimulation."

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from a model of layer cylindrical volume conductor that comprises anisotropic muscle tissue and isotropic bone [14]. Limb mechanics are computed from a joint model that incorporates the viscoelastic properties of muscles, tendons, and other tissues.

We simulate tremor at three frequencies: 5, 8, and 11 Hz, covering the 3-12 Hz characteristic band of tremors [2], and three levels of voluntary activation: 0, 10, and 20 % of the maximum voluntary contraction (MVC). Model parameters are fixed to the same values as in [12].

B. Data Analysis

Motor unit synchronization is calculated with the strength of common input index (CIS) [15], an indicator of synchronization between pairs of motor units, which is computed from the cross–correlation histogram and its cumulative sum. The position and duration of the synchronous peak in the cross–correlation considered to be significant is obtained from the cumulative sum [16] when the latter goes over the mean of the baseline more than three standard deviations of the first 50 bins, [17]. We use 120 s of data and 1 ms bins.

Computation of correlation and coherence between motor unit spike trains (comprising a single or multiple motor units) and the central tremor serves to asses to what extent the latter is linearly transmitted by the motor neuron pool. Correlation between the synchronized motor unit spike train and the central oscillator gives a measurement of their linear coupling. We use the delay at maximum cross–correlation of the whole data span to align both signals. The motor unit spike train is previously smoothed. Coherence between a (single or composite) motor unit spike train and the central oscillator is employed to assess the relative influence of the tremor pacemaker with respect to other inputs [18]. Therefore, coherence gives an indication of the extent to what the input tremor signal is sampled by the motor neurons. Coherence provides a bounded measure of association between central activity and motor unit spike trains at each frequency, on a scale from 0 to 1. The coherence at a given frequency is considered to be significant when its value exceeds a certain confidence limit, calculated under the assumption of statistical independence. The confidence limit is obtained as in [19]; cross–spectra are computed in 1 s Hanning windows using zero padding to increase spectral resolution.

Results are given as mean $\pm$ standard deviation. Differences in two independent estimations of a variable are assessed with a Wilcoxon rank sum test.

III. RESULTS

Fig. 1 shows a representative simulation example, depicting limb angle and muscle force, which follow the typical sinusoidal shape of tremors, and the discharges of two motor neurons. The smaller motor neuron –number # 40– is recruited slightly before the larger one; both fire at least once per tremor burst. The smaller motor neuron shows three paired discharges with inter–spike interval (46.33 ± 9.07 ms) similar to what is reported in the literature [6], [7]. This suggests the model captures well the different behavior of small and large motor units in tremor: the former exhibit paired discharges while the latter do not [9].

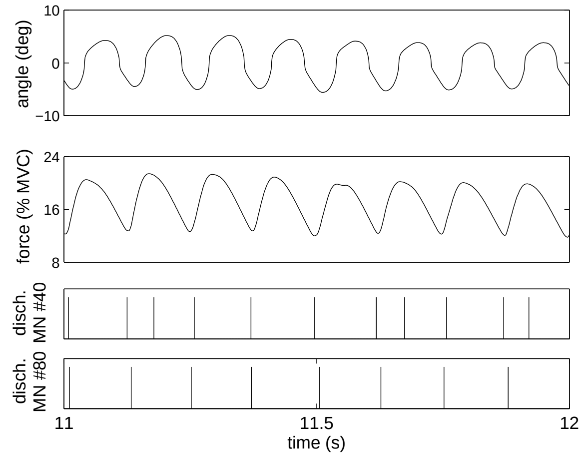

Fig. 1. Simulation example showing limb angle, muscle force and discharge time for two representative motor neurons during one tremor period. Simulation conditions: tremor frequency: 8 Hz, voluntary contraction: 10 % MVC.

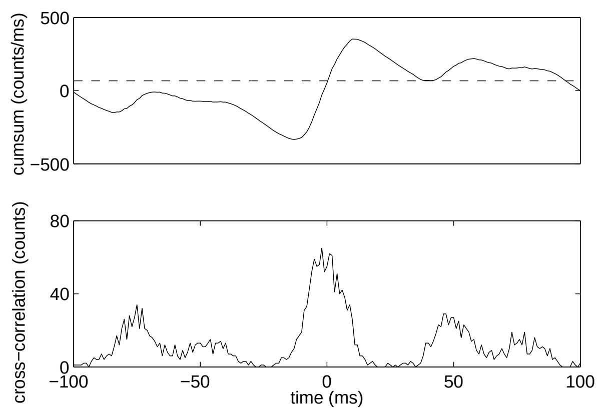

Fig. 2. Computation of the CIS. Top: cummulative sum (solid line) with significance threshold (dashed line). Bottom: cross–correlation histogram. Simulation conditions: tremor frequency: 8 Hz, voluntary contraction: 10 % MVC; motor neurons: # 40 and # 60.

Fig. 2 shows an example of cumulative sum and cross–correlation histogram employed to compute the CIS. There is an evident significant peak in the cross–correlation histogram, which yields a CIS of 8.225. For the case with no imposed tremor and same intensity of contraction, motor neuron synchronization is negligible since there is no significant portion of the cross–histogram; for all the pairs of motor neurons simulated (multiple of 10), the average CIS is 0.203 ± 0.159, in the range of what has been reported for the same muscle in healthy individuals [15].

Table I summarizes the CIS (for all motor neurons multiple of 10) for all simulated conditions. The amount of synchronization tends to increase clearly with the amount of voluntary contraction for 5 Hz tremor, whereas it becomes more independent from the volitional descending drive for 8

TABLE I

MOTOR NEURON SYNCHRONIZATION MEASURED BY THE CIS

Vol. contract. (% MVC)	Tremor frequency (Hz) 5	8	11
0	3.130 ± 2.344	6.230 ± 3.294	9.152 ± 3.211
10	5.859 ± 4.650	5.666 ± 3.907	8.530 ± 4.618
20	7.668 ± 5.426	7.769 ± 4.566	7.915 ± 4.310

and 11 Hz tremor. The general trend in the data is that synchronization becomes more frequency-independent with the volitional descending drive, mainly because more motor units exhibit a firing pattern aimed at maintaining the contraction, and less influenced by the commonly spread tremulous input. However, irrespectively from tremor frequency or contraction level, motor neuron synchronization is at least one order of magnitude larger than in the absence of tremor.

Regarding the correlation between motor unit spike trains and the tremor oscillator, it depends both on the level of voluntary contraction and the tremor frequency, though the latter has less influence on it, Table II. For a given tremor frequency, differences among motor units grow larger with the amount of voluntary contraction, reaching to a level where their distribution becomes exponential, as for the recruitment threshold [13]. The correlation descends as the voluntary contraction increases because more motor units in the pool are firing to sustain the desired contraction level. On the other hand, an increase in tremor frequency for the same voluntary contraction makes higher correlation appear, likely due a raise of the relative contribution of the tremor to the net synaptic input. Moreover, since according to the model the probability of a paired discharge to happen is larger at low tremor frequencies, the linear coupling between the oscillator and the spike train descends in this case due to the distortion of the waveform.

The correlation increases in an exponential manner as more motor units are considered in a composite spike train (CST). Fig. 3 shows an example in which no significant difference in correlation is observed for $n = 8$ motor neurons ($p < 0.95$). Table II summarizes the number of motor neurons (MNs in CST) that provide no significant difference with CSTs comprising more motor neurons ($p < 0.95$); the correlation given corresponds to this CST. As for single spike trains, the correlation tends to increase with tremor frequency, and to decrease with voluntary contraction for the same frequency. For all the simulations, 8 motor neurons (7.917 ± 0.996) are sufficient for the motor neuron pool to project linearly the central tremor to its output.

In all simulated conditions, significant coherence between single motor units and the tremor oscillator is only found at tremor frequency and its second harmonic, since odd harmonics are filtered out by the analysis itself, Fig. 4. This implies that the extent to which the common tremor input is transmitted to the output of a single motor neuron is very high when compared to other synaptic inputs [18].

Coherence spectra for CSTs comprising between 2 and 10 neurons follow the same exponential trend with increasing

TABLE II

CORRELATION BETWEEN SINGLE AND COMPOSITE SPIKE TRAINS AND THE CENTRAL TREMOR OSCILLATOR

Freq. (Hz)	Vol. Contract (% MVC)	Correlation with single MN	MNs in CST	Correlation with CST
	0	0.850 ± 0.136	9	0.774 ± 0.015
5	10	0.656 ± 0.200	8	0.890 ± 0.041
	20	0.388 ± 0.115	6	0.512 ± 0.038
	0	0.981 ± 0.015	9	0.985 ± 0.002
8	10	0.719 ± 0.207	8	0.937 ± 0.019
	20	0.509 ± 0.290	8	0.876 ± 0.034
	0	0.969 ± 0.028	8	0.974 ± 0.004
11	10	0.941 ± 0.069	8	0.972 ± 0.004
	20	0.861 ± 0.049	9	0.963 ± 0.003

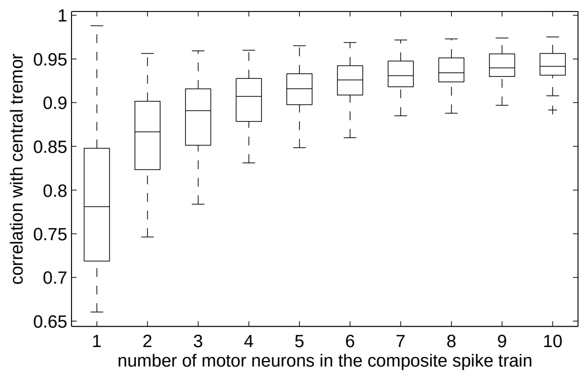

Fig. 3. Mean correlation between 80 random composite spike trains comprising from 1 to 10 motor units, and the central tremor oscillator. The central mark on each box is the median, the edges of the box the 25th and 75th percentiles, the whiskers extend to the most extreme data points not considered outliers; outliers are ploted individually (+). Simulation conditions: tremor frequency: 8 Hz, voluntary contraction: 10 % MVC.

number of neurons as the correlation. The frequency at which the peak coherence is found is always very close to that of the imposed tremor (< 0.244 Hz). Table III summarizes coherence both for single motor neurons and CSTs; again, the number of motor neurons considered is defined as the one that yields no significant difference ($p < 0.05$) with CSTs comprising more motor neurons; the coherence indicated corresponds to this CST. The results show more inter–frequency variation in the number of motor neurons required than for the correlation; however, the outcome is similar: 7 motor neurons (7.000 ± 2.296) provide maximum peak coherence with the central tremor oscillator, and this coherence is found near tremor frequency. Therefore, both correlation and coherence analyses suggest that a small set (7 or 8) of motor neurons are enough to transmit the tremor assuming it is commonly projected to the motor neuron pool. This result is similar to what has been recently demonstrated for the descending drive in healthy individuals [18].

IV. DISCUSSION

This study addresses the behavior of an entire pool of motor units in tremor based on a multi–scale model built upon physiological assumptions proposed in the literature. The simulation model implements afferent and efferent synaptic

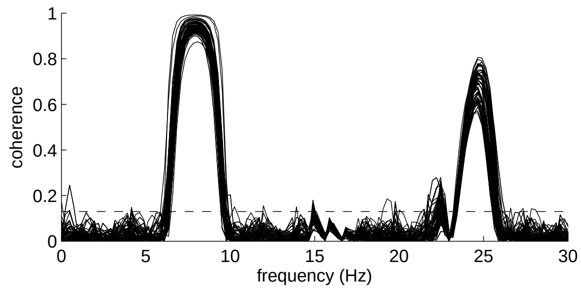

Fig. 4. Coherence between 80 motor unit spike trains and the central tremor oscillator (solid line), and 95 % confidence limit (dashed line). Simulation conditions: tremor frequency: 8 Hz, voluntary contraction: 10 % MVC.

TABLE III
COHERENCE BETWEEN SINGLE AND COMPOSITE SPIKE TRAINS AND THE CENTRAL TREMOR OSCILLATOR

Freq. (Hz)	Vol. Contract (% MVC)	Coherence with single MN	MNs in CST	Coherence with CST
5	0	0.955 ± 0.058	1	0.971 ± 0.030
	10	0.955 ± 0.014	8	0.978 ± 0.006
	20	0.936 ± 0.031	6	0.939 ± 0.021
8	0	0.976 ± 0.052	9	0.995 ± 0.001
	10	0.943 ± 0.032	8	0.977 ± 0.008
	20	0.886 ± 0.056	7	0.933 ± 0.024
11	0	0.931 ± 0.164	8	0.992 ± 0.002
	10	0.981 ± 0.015	6	0.989 ± 0.001
	20	0.956 ± 0.014	9	0.985 ± 0.002

inputs [12], and considers the tremor to be a common projection (with central origin) to the pool. Our results are consistent with experimental observations showing enhanced motor unit entrainment [9], [10], [6], and suggest that tremors are linearly transmitted by the motor neuron pool given that a small set of neurons are active. In our model, enhanced motor unit synchronization is a consequence of the common tremor input to the pool. Examination of coherence spectra and cross–correlograms for our data shows significant coherence and a broad central cross–correlogram peak, as it would be expected for a widespread oscillation coming from the central nervous system, [20]. This is indeed one of the two hypotheses proposed for enhanced motor unit entrainment in tremor, together with synchronization of synaptic inputs [10]. Regarding the linear transmission of the common tremor oscillator by a small set of motor neurons, this result is in agreement with a recent study showing a similar phenomenon for the volitional descending drive [18]. There, the authors demonstrate, based both on simulation and experimental data, that the same level of corticomuscular coherence is obtained for rectified sEMG and a composite spike train comprising a few motor neurons. Therefore, since coupling between the sensorimotor cortex and tremulous muscles has already been shown for Parkinson's disease [21] and essential tremor [22], one could speculate with similar levels of coherence between CSTs and electroencephalography.

In conclusion, our simulation study provides a description of the behavior of an entire motor unit pool in tremor, under the assumption that the tremor is a common (supraspinal) input to the pool. Under such hypothesis simulations show paired discharges and enhanced motor unit synchronization, the major characteristics described for tremors. Moreover, our data suggest that the tremor may be transmitted linearly given that a small set of motor neurons are active, as recently demonstrated for the volitional descending drive.

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