Occurrence of Widespread Motor-Unit Firing Correlations in Muscle Contractions: Their Role in the Generation of Tremor and Time-Varying Voluntary Force

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INTRODUCTION
The presence and degree of linear correlations between motor unit (MU) activities in a contracting muscle, and the phases of the correlated MUs, determine to a great extent the features of the muscle force waveform [and the electromyo-gram (EMG)]. At the same time, the detection of such synchrony and the estimation of its parameters can provide information on the neural processes that control the production of muscle force. In constant-force contractions, for example, MU correlations may play a key role in tremor generation and have been implicated in different hypotheses dealing with tremor mechanisms. Similarly, the analysis of MU correlations for muscle forces having various time courses, including complex ones, can provide information on the properties and interrelation of the synaptic inputs to the α-motoneurons, under general dynamic conditions.

Due to the above facts, the detection and measurement of synchrony within MU populations is an important task in the study of motor mechanisms. However, the estimation with traditional unit-to-unit (UTU) correlation analysis (Perkel et al. 1967) of the parameters of population synchrony, namely its extent (proportion of correlated units in the population), its strength (strength of correlations between units’ pairs), and the distribution of the units’ phases, is a complex task both experimentally and analytically. Until now, this difficulty has hindered the study of synchrony in MU populations.

Recent studies (Christakos 1994, 1997; Christakos and Giatroudaki 1998a,b; also see APPENDIX in Christakos et al. 1991) indicate a relatively simple method for detection of population synchrony and estimation of its parameters. This method uses a combination of unit-to-aggregate (UTA) coherence and correlation computations on a sample of pairs of simultaneously recorded unit and population-aggregate activities. UTA coherence computations provide information on the extent of synchrony and on the strength and its distribution within the population. UTA correlation computations yield an estimate of the distribution of the units’ phases, relative to the aggregate activity (common reference signal).

In the present study the firing behavior of MUs was examined during both static (constant force) and dynamic (quasi-sinusoidal or broadband random force) voluntary contractions of the first dorsal interosseus muscle of the hand in healthy adults. The emphasis was on the analysis of MU synchrony using the above method, where the units’ activities were trains of MU action potentials, and the population-aggregate activity was the muscle force signal (or the EMG). With regard to the dynamic contractions, this study is an extension of a previous investigation with sinusoidal forces (Iyer et al. 1994). Preliminary reports have been given in abstracts (Erimaki and Christakos 1998; Erimaki et al. 1998).
METHODS

The experiments were conducted on 10 neurologically normal volunteers (age 26 – 45), who assumed a comfortable sitting position. Their dominant hand and arm were secured on the lab bench, in front of the force transducer (WPI-Fort1000 and Harvard-Apparatus). The subjects exerted abduction force on a vertical plane with the lateral side of the horizontally extended index finger. The force was nearly isometric and mimicked the time course of a target curve that was displayed on the oscilloscope. The target curve was also presented to the subjects through earphones as a frequency-modulated tone. For static contractions, this curve was a horizontal line (constant force). For dynamic contractions, it was a sine wave (frequency in the band 1 – 4 Hz) or a broadband random signal (bandwidth from 0 to 3.5 Hz), both around a horizontal line representing a constant force level. The mean force level in static contractions was in the range 3–50% of maximal voluntary contraction (MVC). In dynamic contractions the force level was in the range 3–30% MVC, and the amplitude of the varying force was in the range 1–10% MVC.

The force signal was recorded together with multiunit activity from the first dorsal interosseus muscle of the hand (prime agonist), which was obtained by both intramuscular bifilar nichrome wire electrodes (40 μm) and surface Ag-AgCl disk electrodes. The data were digitized and stored on magnetooptical disks for off-line analysis using the program LabView. Discrimination of single MU spike trains in the intramuscular electrical activity was done by a threshold operation using the same program. This provided usually one and sometimes two or three MUs per recording. Spike trains were represented as sequences of 0’s and 1’s. All recorded signals, including the discrete sequences, were originally sampled at 5 kHz and subsequently low-pass filtered (cutoff 250 Hz) and resampled at 500 Hz for analysis (see Christakos et al. 1984). The filtering of data in this study (also in cases such as those of Figs. 2 and 3) was digital and introduced no time shifts.

Frequency-domain analysis, via the fast Fourier transform, included 1) segmentation of the original data series; 2) removal of mean, and windowing for each data segment; the data window used was a member of the algebraic family (see Durrani and Nightingale 1972) with a tapering between 40 and 60%; and 3) computation of auto- and cross-power spectra. From the latter, coherence estimates for pairs of activities were obtained as the squared modulus of the cross-spectrum divided by the product of the individual autospectra (Jenkins and Watts 1968).

In the study of MU correlations, the employed method utilizes the UTA (i.e., MU-to-force or MU-to-EMG) coherence and cross-correlation function. The results of mathematical analyses and computer simulations (Christakos 1994; 1997; Christakos and Giatroudaki 1998a,b; also see the APPENDIX in Christakos et al. 1991) have demonstrated that the UTA coherence function is almost zero for the uncorrelated units in a population. In contrast, the same function is nonzero at each frequency of synchrony for the units that are correlated to other units (unless the units’ phases within the population are very broadly distributed and the synchrony is very restricted). For any given unit, this nonzero value reflects the extent and strength of the unit’s correlations to other units.

These properties make the UTA coherence a useful tool for detection and measurement of population synchrony. Specifically, coherence computations on a sample of pairs of simultaneously recorded unit/po-pulation activities 1) enable the detection of population synchrony because the occurrence of even one nonzero (statistically significant) UTA coherence in the sample indicates the presence of a correlated subset to which the given unit belongs; 2) provide an estimate of the extent of synchrony, as the fraction of nonzero UTA coherences in the sample; and 3) furnish information on the strength of synchrony and its distribution within the population. Furthermore, UTA cross-correlation computations for the so identified correlated units in the sample yield an estimate of the distribution of the units’ phases, in the form of a histogram of units’ delays relative to the aggregate activity (reference signal).

According to the same analyses, for a narrow distribution of units’ phases at any given frequency of synchrony, the value of the UTA coherence is very close to the square of that of the UTA coherence, particularly if the extent of synchrony is large. This property follows easily from Eq. A4 in the APPENDIX of (Christakos 1997) and enables the estimation of the strength of synchrony in terms of UTA coherence estimates (also see DISCUSSION in that paper, and Christakos and Giatroudaki 1998a,b). In the present study, this rule has found wide application (see RESULTS).

Note that for the usual number of segments in the spectral analyses of this study (30 – 60), the threshold value for a significant coherence is in the range 0.04 to <0.1 (Jenkins and Watts 1968), when the estimates are obtained using rectangular windows. However, the nonrectangular window employed here reduces the number of the degrees of freedom, thus raising the threshold value for statistical significance. Therefore, a general criterion of 0.1 was used in the analysis that follows. In other words, marginally significant UTA coherences were considered zero. The justification for this is the square relationship that was found to hold for the units of this study between the values of the UTA and the UTA coherence (see preceding paragraph for conditions; also see RESULTS). Accordingly, a marginally significant UTA coherence implies very restricted correlations between unit pairs. It has to be emphasized that in any case, additional criteria have to be used regarding the significance of coherences at particular frequencies, such as replication and possible functional meaning.

RESULTS

Static contractions

The activities of all 114 recorded MUs from the 10 subjects were rhythmical (firing rates in the range 6.5–20 Hz), as was indicated by a dominant autospectral component at the mean firing rate of each MU, followed by smaller harmonic components, and also by a narrow, unimodal interspike interval histogram. Examples are shown in Figs. 1 and 2, where the MUs’ rates are 6.5 and 11 Hz, respectively (dashed lines). The presence and degree of MU synchrony was related to the type of muscle tremor that was present in a contraction in the following two basic ways:

(i) REGULAR AND LARGE TREMOR; STRONG AND WIDESPREAD MU SYNCHRONY. This tremor was manifested as a narrow (bandwidth of the order of 1–2 Hz) and large local peak in the force autospectrum, and occurred in all contractions of one subject (MG) and some contractions of five other subjects. Its frequency was somewhere in the band 6.5–9 Hz. An example from subject MG is shown in Fig. 1, where the frequency of the regular tremor is 6.5 Hz (dashed line).

Under this condition, the coherence to the force of all 40 recorded MUs from the 6 subjects (22 of which were from subject MG) displayed a narrow and large peak at the tremor frequency (values in the range 0.33–0.90, with an average of 0.57), and sometimes smaller harmonic peaks. In the example of Fig. 1, the MU fires at the tremor frequency, 6.5 Hz, and is highly coherent (value 0.89) with the force signal at that frequency. As explained in METHODS, these observations indicate the presence of widespread MU correlations at the frequency of the regular tremor. Note that for ½ of the 40 recorded MUs, the firing rate was higher than the frequency of tremor, and some of these MUs showed an additional autospectral component at the tremor frequency. An example is
shown in Fig. 3 (left column), where the MU has distinct autospectral components at its mean firing rate, 9 Hz (arrow), and at the tremor frequency, 6.5 Hz (right dashed line).

Examination of the time records, and also MU-to-force correlation analysis, revealed a clear tendency for MUs’ spikes to occur near the minima of the regular tremor oscillation. Examples are shown in the time records and cross-correlograms of Figs. 1 and 3. Accordingly, the correlated MUs were approximately in phase with each other at the tremor frequency. As explained in METHODS, for synchrony showing a high similarity of units’ phases and a large extent, the value of the UTU coherence is very close to the square of that of the UTA coherence. Thus from the above estimates of MU-to-force coherence, estimates of the coherence between MU pairs at the tremor frequency lie in the range 0.11–0.81 (average 0.35). Note that among the 40 MUs of the sample, there were 8 pairs and 2 triplets of simultaneously recorded MUs in different contractions of the 6 subjects. For each pair or triplet, the coherence of the individual MUs to tremor had similar, or comparable, values; and the coherence between these MUs at the tremor frequency was indeed close to the square of these values.

It seems, therefore, that in contractions showing narrowband tremor, MU synchrony is widespread and mostly strong, and the MUs are approximately in phase. The superposition of the nearly coincident twitches from the synchronous MUs forms the cycles of the regular and large tremor.

(I) IRREGULAR AND SMALL TREMOR: UNCORRELATED OR WEAKLY CORRELATED MU FIRING. This tremor was manifested as a broad and small local deflection or peak (bandwidth of several Hz) in the force autospectrum, somewhere between 6 and 13 Hz. It was observed in all contractions of one subject (SE) and in some contractions of eight other subjects, including five of the subjects of category (I). An example is shown in Fig. 2, where the broad tremor peak in the force autospectrum covers the band 8–12 Hz, and the frequency of the tremor oscillation in the time record of the high-pass filtered force signal (cutoff at 7 Hz) continuously varies within this band.

Under this condition, the coherence to the force of all 16 recorded MUs in different contractions of subject SE was zero in the band of tremor frequencies. The respective MU-to-force correlograms were practically flat, which is also indicative of a totally random phase relation between MU spikes and the irregular tremor oscillation. As explained in METHODS, these observations indicate a lack or sparsity of MU correlations in the contractions of this subject. A large fraction (50%) of the 16 MUs fired within the tremor frequency-band and therefore inevitably participated in the formation of the irregular tremor oscillation with their successions of partially fused twitches. It seems, therefore that the broadband tremor of this subject was basically produced by uncorrelated MUs firing within the tremor frequency-band.

For the eight other subjects, the situation was more complex. In two of them, the majority of the recorded MUs (31 of 40 MUs) also showed no coherence to the force in the band of tremor frequencies, and the respective MU-to-force correlograms were practically flat. An example is shown in Fig. 2 from one of these two subjects (EK), where the MU’s rate, 11 Hz (dashed line), falls...
within the tremor frequency-band. In agreement with these observations, the coherence between pairs of simultaneously recorded MUs in contractions of the subject of Fig. 2 (6 pairs of the 31 MUs) was also found to be zero in the band of tremor frequencies. Among the 31 MUs, a large fraction (35%) again fired within the tremor frequency-band and therefore participated with their uncorrelated contributions in the formation of the irregular tremor oscillation. It seems therefore that the broadband frequency content of the tremor in these contractions was again due to uncorrelated MU activities.

The remaining nine MUs from other contractions of the above two subjects, however, showed a clear coherence peak to the force, within the frequency band of the irregular tremor. The same was also true of all 18 MUs recorded from the other 6 subjects who showed irregular tremor. These coherence peaks were generally broader than the ones for regular tremor. The peak coherence values for the total of 27 MUs were in the range 0.18–0.47 (average 0.27, with only 3 values above 0.35), i.e., they were substantially smaller than those for regular tremor, also according to the Mann-Whitney test \( (P < 0.001) \). The same properties were indicated by small-amplitude, irregular oscillations in the respective MU-to-force correlograms. Therefore there was a contribution to the tremor in these contractions by correlated MUs (see METHODS), but the MU correlations were much weaker and their frequency band was broader than those for regular tremor.

Careful examination of the corresponding force autospectra revealed in some of them the presence of a distinct component within the frequency band of the irregular tremor, at the frequency of the MU-to-force coherence peak. In other words, the tremor in these contractions had a component that was due to MU correlations, and this component was not always discernible in the force autospectra. It is important to note that for the five subjects who also belonged to category (I), the frequency of this component was the same as that of their regular tremor. This identity implies a common origin for the distinct component and the regular tremor.

Examination of the time records revealed that this mixed tremor had a variable regularity. For the short time intervals where the tremor was more regular, a tendency for MUs’ spikes to occur near the minima of the tremor oscillation was evident in the time records and was also confirmed by correlation analysis. In other words, the correlated MUs were again in phase on average. The range of estimated coherence between MU pairs, obtained by squaring the above MU-to-force coherence estimates, is 0.03–0.22 (average 0.08). Note that for each of six pairs of simultaneously recorded MUs from five of the subjects, the coherence of the individual MUs to tremor again had comparable values; and the coherence between these MUs at the tremor frequency was close to the square of these values.

It seems therefore that under conditions of mixed tremor, MU synchrony is generally weak. The tremor then combines a broadband frequency content and a distinct component whose cycles are formed by partially overlapping twitches from weakly correlated MUs.

Finally, it is important to emphasize that whenever two or
three MUs were simultaneously recorded in a contraction (as described above, a total of 20 pairs and 2 triplets), their coherence to tremor had similar, or comparable, values, ranging from 0, for purely irregular tremor, to a large fraction of unity, for regular tremor. This suggests that, with respect to synchrony, active MUs behave in the same way. It thus supports the above conclusion about a lack or sparsity of MU correlations in the contractions where the recorded MUs showed no coherence to tremor. It should also be noted that in all cases studied, the values of the MU-to-force and the MU-to-EMG coherence were similar within the tremor frequency-band. Both coherences also had sometimes nonzero but small values in a low-frequency band near the origin, indicative of restricted correlations between MUs. Finally, the MU-to-EMG coherence often had significant but small values (usually below 0.20) within broad frequency-bands above 20 Hz.

Dynamic contractions

Under conditions of time-varying voluntary muscle force in eight of the subjects, the autospectrum of the force displayed a dominant component for quasi-sinusoidal variations (23 contractions), or a dominant broad peak for random, broadband variations (4 contractions), both in the corresponding frequency band. The firing of all 27 recorded MUs from the different subjects was modulated in the frequency band of the time-varying force, as was indicated in the MUs’ autospectra by a clear modulating component, or broad peak, and by a clear carrier component at the mean discharge rate of each MU. An example is shown in the left column of Fig. 3 for sinusoidal contractions at 1.5 Hz of the subject of Fig. 1, where the MU’s modulation frequency is 1.5 Hz (left dashed line) and the MU’s carrier rate is 9 Hz (arrow). As regards MU synchrony, the coherence to the force of all 27 recorded MUs from the different subjects was modulated in the frequency band of the time-varying force, as was indicated in the MUs’ autospectra by a clear modulating component, or broad peak, and by a clear carrier component at the mean discharge rate of each MU. An example is shown in the left column of Fig. 3 for sinusoidal contractions at 1.5 Hz of the subject of Fig. 1, where the MU’s modulation frequency is 1.5 Hz (left dashed line) and the MU’s carrier rate is 9 Hz (arrow).
MU-to-force correlation analysis verified this result and also provided estimates of MU phases. In the example of Fig. 3 (right column), the large oscillation at 1.5 Hz in the cross-correlogram of the MU to the low-pass filtered force (cutoff at 3 Hz) is indicative of strong correlations of the modulation of this MU to the sinusoidal force and to the modulations of other active MUs. The location of the central peak in this correlogram indicates a time advance of the modulation of this MU over the sinusoidal force of ~130 ms. Across subjects, the MU modulations were found to lead the quasi-sinusoidal force variations by 73–212 ms (sample of 23 MUs). This time advance 1 was similar at each modulation frequency for MUs of the same subject (it was also comparable across subjects) and 2 generally decreased as the modulation frequency and/or the modulation amplitude increased (i.e., as the speed of the contraction increased). For example, the time advance across subjects was in the range 179–212 ms for 1-Hz contractions (6 MUs), and 88–98 ms for 3-Hz contractions (3 MUs).

Accordingly, the distribution of the MUs’ phases at the modulation frequency is narrow (by the above estimates of MU time advances over the force signal, it only covers a small fraction of a modulation cycle). Therefore estimates of the coherence between MU modulations, obtained by squaring the above MU-to-force coherence estimates, lie in the range 0.09–0.83 (average 0.44). In other words, MU synchrony at the modulation frequency is widespread and mostly strong.

Finally, for 3 subjects who exhibited regular tremor in static contractions, the slowly varying force had superimposed regular tremor. In such situations, the coherence to the force of all 13 recorded MUs from these subjects showed a second narrow and large peak at the tremor frequency (values in the range 0.20–0.78, with an average of 0.44). An example is shown in Fig. 3 (right dashed line). Examination of the time records, as well as cross-correlation analysis between MUs and the high-pass filtered force, revealed again a tendency for MU spikes to occur near the minima of the tremor oscillation. In the example of Fig. 3, many of the spikes of the MU occur near the minima of the 6.5-Hz regular tremor of this subject (see the time record with the high-pass filtered force signal, where the cutoff was at 5.5 Hz; also see the corresponding MU-to-force correlogram).

Thus the MUs’ phase distribution at the tremor frequency was again narrow, and a range for the coherence between MUs, obtained by squaring the above MU-to-force coherence estimates, was 0.04–0.61 (average 0.22).

It seems therefore that in the presence of regular tremor during a contraction of time-varying strength, widespread and fairly strong MU correlations also exist at the tremor frequency, and the MU spikes are again in phase.

**Discussion**

Our observations indicate the occurrence of two types of widespread MU firing correlations, which can obviously coexist in a contraction.

In static contractions, MU correlations are associated with the presence of regular and large muscle tremor, and they are strong; or with the presence of a distinct component within the broad band of frequencies of the irregular tremor (somewhere in the range 6–13 Hz), in which case they are generally weak. In both cases, the correlations occur at the frequency of the regular tremor of a subject, even for MUs that fire at other, and possibly different, frequencies. A similar behavior, with strong MU correlations to the force, was reported by Elble and Randall (1976) under conditions of maximal-amplitude tremor, which in their experiments occurred for low to medium force levels. In our experiments, the regularity of tremor seemed to be the consistent and prominent feature associated with the presence of strong MU correlations, and the regular tremor could occur at various levels of contraction. However, for most subjects these levels also were low to medium.

The neuronal basis of physiological muscle tremor has been a question of recurring interest for many years. In this context, the presence and degree of MU correlations during tremor has been a matter of debate. As our observations make clear, the neuronal substrate of tremor can be quite different for different tremor types, and there seem to exist two extreme modes, as well as intermediate cases.

The first mode, which is the basis of broadband and small-amplitude tremor, involves uncorrelated discharges of MUs. The irregular tremor oscillation is then formed by the superposition of the successions of minimally fused twitches from the last-recruited, relatively large active MUs. These MUs fire rhythmically near their threshold rate (i.e., within the band of tremor frequencies), and their effects dominate over those of the other active MUs. Thus the broad tremor deflection, or peak, in the autospectrum of the force is formed by the superposition of the autospectral components that represent the rhythmical contributions of the large active MUs.

In other words, the generation and features of this tremor type are a consequence of (see Christakos 1982) 1) the actual distribution of filtering and firing properties of MUs (also see Allum et al. 1978) and 2) the central property of uncorrelated processes to preserve their frequency content on superposition (recall that the autospectrum of the sum of random processes is given as the sum of all auto- and cross-spectra of the processes, and the latter spectra are 0 when the processes are uncorrelated).

The second mode involves strongly correlated, and in-phase, MU activities. It is the basis of regular and large tremor, whose cycles are formed by the superposition of nearly coincident MU twitches from all, or most, active MUs (note, however, again the major role played by the large MUs). In terms of spectra, there is in this case a very large number of cross-spectral components, in addition to the above-mentioned autospectral ones. These components are at the frequency of the MU correlations, i.e., at the frequency of the regular tremor, and have large amplitudes, because of the strongly correlated and in-phase MU activities. The superposition of these components forms the narrow and large tremor peak in the force autospectrum, which dominates over the remaining tremor components.

Interestingly, the frequency of the regular tremor of a subject falls within the band of the subject’s irregular tremor. Different individuals can apparently show either type of tremor in a contraction, in which case one of these two modes dominates. But sometimes the point of operation is intermediate between these extreme modes. MU correlations are then generally weak, and the tremor combines 1) a broadband frequency content, due to the autospectral components of the large MUs, as above, and 2) a distinct component, which is due to the small cross-spectral components that reflect the weak MU correlations. This component again falls within the broad tremor-
band, but unlike the case of regular tremor, it has a small size. As a consequence, the tremor appears irregular both in the time records and in the force autospectra.

The mechanism of MU synchrony during tremor has also been a matter of controversy, and different hypotheses have been forwarded involving muscle spindles (see, e.g., Lippold 1970), Renshaw cells (Elble and Randall 1976), but also supraspinal structures (Llinas and Yarom 1986); for a review see Windhorst (1988). According to our data, the timing of the synchrony and the tremor combines well with the expected action of the muscle spindles, which tends to reinforce tremor. Specifically, tremor is reflected (see, e.g., Matthews 1981) through the action of these receptors in correlated, and nearly in-phase, oscillations in the membrane potentials of homonymous α-motoneurons. In situations where these oscillations have a large amplitude, and the correlations between them are strong, almost simultaneous discharges of the motoneurons occur near the depolarizing peaks of the cells’ membrane waves. Each such discharge triggers the MU twitches that form by their superposition the next cycle of the regular tremor. For small and weakly correlated such oscillations, the time relation between the superimposed MU twitches is more variable. The resulting force oscillation has then a small amplitude, shows a corresponding variability in frequency, and may only be evident over short periods of time in the tremor records.

Note that in this scheme the period of the regular tremor is composed of 1) the afferent and efferent conduction delays, and 2) the time interval from the initiation of the composite muscle twitch (that results from superposition of the synchronous MU twitches) to the point during the decrementing phase of this twitch where the spindles reach their maximal discharge. Thus the predicted tremor period is in the range of the actually observed ones.

Our observations in preliminary experiments using the ischemic maneuver (unpublished observations) are consistent with this scheme. They have demonstrated in three subjects that the blocking of the activities of the large afferent fibers from the spindles changes the tremor from regular, where MUs are strongly correlated, to irregular, where MU synchrony is much weaker or absent, while leaving the EMG level unchanged. On the other hand, removal of the occlusion reinstates both the weaker or absent, while leaving the EMG level unchanged. On the other hand, removal of the occlusion reinstates both the

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NOTE ADDED IN PROOF

In recent experiments in three subjects, the ischemic block during dynamic contractions showing regular tremor again drastically decreased, or abolished, the tremor synchrony, but did not reduce the synchrony of the MU modulations. These observations further argue for a different origin of the two types of synchrony.

REFERENCES
