DNA sequences with the same biological function are related to this biological function.

We feel that the special importance of this method lies in its capacity to detect functional relatedness among proteins which do not have significant similarity in the primary structure.

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A Note on the Noninvasive Estimation of Muscle Fiber Conduction Velocity

HOLGER BROMAN, GERARDO BILOTTO, AND CARLO J. DE LUCA

Abstract—**Average muscle action potential conduction velocity values were obtained during isometric constant-force contractions by a cross-correlation technique. To minimize the bias introduced by nondelayed activity appearing on the two myoelectric derivations, the signals were doubly differentiated. This arrangement effectively reduced the nondelayed activity and increased the accuracy of the estimate.**

INTRODUCTION

Using an invasive technique, in 1955, Buchthal, Guld, and Rosenfalck [1], [2] described action potential propagation velocities in human muscles *in situ*. Using a specially developed technique, Stalberg [3] performed an extensive study of the conduction velocity of single fiber action potentials in 1966. The first report of a noninvasive technique was published in 1970 by Lindström *et al.* [4]. These investigators estimated the conduction velocity by measuring the occurrence of "dips" in the power density spectrum of the surface detected myoelectric signal. These dips are caused by the sinusoidal transfer function of the differential electrode configurations used to detect the myoelectric signal.

In 1979 Lynn [5] introduced a direct on-line method of estimating the conduction velocity. This technique utilized the detection of zero crossings of two time-delayed waveforms of the myoelectric signal. To obtain consistent zero-crossing information from the myoelectric signals, an extremely narrow-band digital filter was employed. It was reported that in some records some waveform components of the two detected myoelectric signals were in phase, and thus nondelayed. This effect produced a skewing of the delay interval histograms which measure the time-shifted zero crossings. Lynn [5] reported this effect to be present under low-level muscle contractions and attributed it to interference or noise common to both electrode pairs. At higher levels of contraction, these errors were considered negligible. However, given Lynn's recording arrangement, with differential amplifiers, the recorded signals represent voltage differences appearing between the two electrode pairs. Therefore, any offsets along with any common noise appearing at the electrode surfaces would be expected to be effectively removed by the common mode rejection of the amplifiers. Thus, what appears in the recorded signals are simultaneous voltage differences which are probably due to nondelayed activity generated by the myoelectric signal. Lynn mentions that skewing of the delay interval histogram occurred in only a small number of cases. However, other investigators [6] have also reported similar difficulties.

Masuda *et al.* [7] reported a gradient threshold method of detection of zero-crossing points of the myoelectric signal for a time-delay measurement. This technique does not use an A/D converter or digital filters. Therefore, temporal accuracy of the measurement was improved since digitization was not required. Other investigators [8], [9] have tried to measure conduction velocities by stimulation of peripheral nerves and measuring the myoelectric response. These types of measurements are complicated since estimation of conduction velocity is influenced by both the unknown nerve conduction time and the unknown distance of the innervation zone of the muscle to the recording electrode.

Direct cross-correlation techniques for estimation of the conduction velocity have been used by other investigators [6], [10] utilizing digitization techniques and computation to obtain conduction velocity. A special device employing a cross-correlation technique was developed and constructed at the Department of Applied Electronics, Chalmers University of Technology, Göteborg, Sweden. This device, which operates in real time, employs two myoelectric signals and calculates the cross-correlation function at three lag points. The lag values are determined by a variable delay line, which is controlled by a feedback loop so that the cross-correlation value at the midpoint is maximized. Both the maximal correlation coefficient between the two myoelectric signals and the average conduction velocity of the muscle fiber action potentials are displayed.

The use of a cross-correlation approach rather than measurement of time between specific points along the two myoelectric signal waveforms, such as zero crossings (Masuda *et al.*), implies that one source of statistical variation has been avoided. The present technique uses a sign cross-correlation approach with a feedback to a variable delay line to estimate the lag between two input signals. The electrode configuration, shown in Fig. 1(a), has three separate silver bars as contact surfaces of dimension 1.0 cm × 1.0 mm separated by 1.0 cm. The middle contact is used as a common input for the differential amplifiers. Fig. 1(a) shows the arrangement of the differential amplifiers for the myoelectric signals. The ampli-

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H. Broman is with the Department of Applied Electronics, Chalmers University of Technology, Göteborg, Sweden.

G. Bilotto and C. J. De Luca are with the NeuroMuscular Research Center, Boston University, Boston, MA 02215, and the Liberty Mutual Research Center, Hopkinton, MA 01748.

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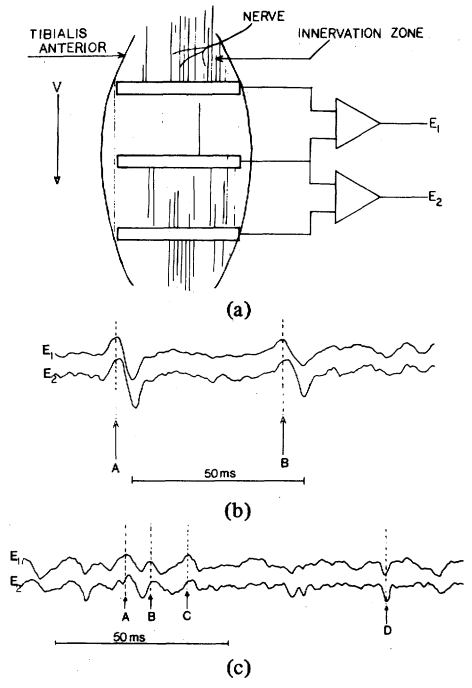

Fig. 1. (a) Schematic illustration of skeletal muscle, its innervation zone, and fiber direction. The horizontally oriented rectangular bars overlapping the muscle represent the three electrode contacts. The middle bar is common to the differential amplifiers. The vertical downward pointing arrow indicates the direction of propagation of the action potentials. (b) The myoelectric signals generated by the muscle are denoted as $E1$ and $E2$. These signals represent propagation of a single surface-recorded motor unit. Note the absence of nondelayed activity in these recordings. The signal $E2$ is a time displaced version of $E1$, as indicated by the two reference points A and B. (c) Shows interference EMG activity detected from a subject generating both delayed (A, B, C) and nondelayed activity (D).

fiers are ac coupled to eliminate offsets. The two signals $E1$ and $E2$ represent the first differentials of the myoelectric signal.

The two signals $E1$ and $E2$ then served as the input signals to the conduction velocity estimator for determining cross-correlation and actual conduction velocity. The estimator has a passband of 80–160 Hz, with slopes of +/- 18 dB/octave. The high bandlimit was chosen as low as 160 Hz to improve the signal-to-noise ratio. The low bandlimit was chosen as high as 80 Hz to eliminate frequency components that correspond to wavelengths that obviously cannot travel undistorted along the muscle fibers. The explanation is as follows. The well-known equation

$$v = \lambda * f \tag{1}$$

where v is the propagation velocity of the muscle fiber action potential, λ is the wavelength of the waveform component, and f is the frequency of the same waveform component, was the basis for the choice, as elaborated in the sequel.

Any frequency component of the myoelectric signal with a wavelength greater than the length of the muscle may exhibit reflections and other distortions. Reflections will generate wavefronts traveling in the reverse direction of original propagation along the muscle, and thus interfere with the measurement of muscle conduction velocity. Muscle conduction velocity measurement with a cross-correlation technique is dependent on two identical waveforms displaced in time and traveling in the same direction. Choosing 80 Hz as the lower cutoff frequency will attenuate some of the end effects, such as reflections, from the above type of component waveform in muscles with a length of less than 5 cm. Thus, a theoretical basis is established for the use of this bandwidth in this device and also by other investigators [5] utilizing similar types of measurements.

The tibialis anterior muscle was chosen for this investigation since its length was sufficient to allow electrode placement without overlap either with the innervation zone or the tendonous regions of the muscle. The location of the innervation zone was determined by one or both of the following methods. First, the motor point of the muscle was localized using superficial electrical stimulation. Second, the electrode was manipulated in the range from the motor point to the distal tendonous attachment of the muscle, during a low-level contraction, until the monitored myoelectric signals were similar in appearance but time delayed. Eight male subjects were tested with a range in age from 23 to 39 years.

Fig. 1(b) shows two differentially amplified signals $E1$ and $E2$ recorded from the surface of the tibialis anterior muscle during a static, i.e., isometric and isotonic, contraction. It is clearly seen that the two signals are time displaced with respect to each other. A typical correlation coefficient of 0.9 further confirms the visual observation that the signals are highly cross correlated. A simple calculation of the electrode contact separation divided by the time difference of these two waveforms provides the average conduction velocity of the muscle fiber action potentials. The electrode was thus placed on one side of the innervation zone to obtain action potentials mainly traveling in one direction.

Statement of the Problem

This technique of conduction velocity measurement was effective in determining the average muscle action potential propagation in only half of the subjects tested. The effectiveness was determined by comparing the resultant conduction velocity values to the values obtained by other investigators [1]–[6], [11]. In the other half of the tested subjects, conduction velocity estimates were extraordinarily large; estimates of up to 8 m/s were observed. These errors were consistently present in spite of intensive searches for electrode locations that would yield conduction velocity estimates reasonably close to those described in the literature. The normalized cross-correlation function had maximal values in the range of 0.6–0.9 during recording of either the reasonable estimates or the obviously erroneous values. Therefore, the correlation coefficient cannot be used as a sufficient condition for a criterion to accept or reject conduction velocity estimates.

Comparing Fig. 1(b), obtained from subjects whose conduction velocity estimates were in the range of 4 m/s, and Fig. 1(c), obtained in subjects with large values, the following observations can be made. Fig. 1(b) consistently shows a pattern of one signal being a delayed version of the other, and both show some superimposed noise. Fig. 1(c), however, shows that the two signals are a mixture of delayed and nondelayed activity. This nondelayed activity has been reported to be present in myoelectric signal recordings by other investigators [13]. The origin of this activity is unclear, however, its effects can readily be seen. Any estimation of conduction velocity will include the average time delay between the two myoelectric signals. To exemplify, given an interelectrode distance of 1 cm and a conduction velocity of 4 m/s, we would expect, in the absence of nondelayed activity, a peak of the cross-correlation function to occur at lag 2.5 ms. The half-value width of the peak is of the same order (see, for instance, [6]) varying to some degree with the filtering applied to the myoelectric signals. Thus, it is obvious that the appearance of nondelayed activity will skew the "true" peak of the cross-correlation function, and subsequently yield erroneously large conduction velocity estimates. Therefore, the objective is to decrease this type of activity to obtain a more reasonable estimate of conduction velocity.

Solution to the Problem

A signal processing scheme was employed to reduce the presence of nondelayed activity, as shown in Fig. 2(a). The electrode was modified to accommodate four silver bars of the

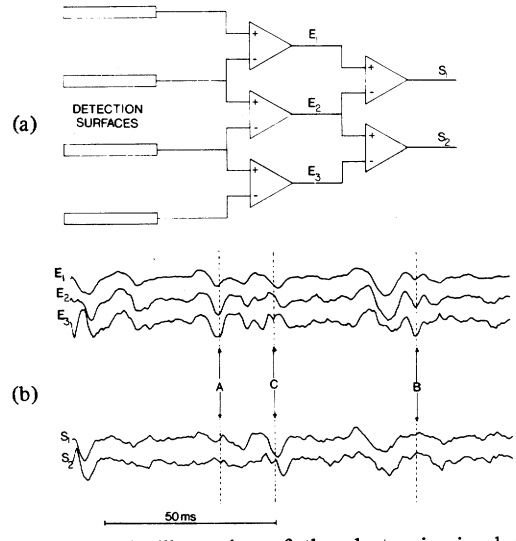

Fig. 2. (a) Schematic illustration of the electronic signal processing scheme required to reduce the presence of the nondelayed activity. Two layers of differential amplifiers are necessary. (b) The myoelectric signals recorded from the first and second layers are shown as $E1$, $E2$, and $E3$, and $S1$ and $S2$, respectively. Note the presence of nondelayed activity in the first differential signals at A and B, and the rejection of this activity in the second differential signals. On the other hand, the quality of the delayed activity is in some cases (such as in C) improved.

same dimension and spacing as shown in Fig. 1(a). With this modification, the myoelectric signal was doubly differentiated. In Fig. 2(a), $E1$, $E2$, and $E3$ represent the differentially amplified myoelectric signals which are then processed through a second layer of differential amplifiers. This second layer, due to its common mode rejection, reduces the common activity which appeared from the first layer of amplifiers. Fig. 2(b) shows an example of the first and second recorded differentials, respectively. Utilizing this approach, reasonable estimates of conduction velocity were obtained in all subjects tested. Subjects previously yielding extraordinarily large estimates now exhibited estimates in the range of 3.5–5 m/s for nonfatiguing contractions. These values agree well with previously reported estimates in the literature. The correlation coefficient exhibited the same range as before (0.6–0.9).

Discussion

Any technique for estimating the conduction velocity of muscle fibers from the myoelectric signal is dependent on the assumption that the signals detected via the electrodes are in fact transported along the muscle fibers and detected in this direction of propagation. The invalidation of this assumption, either by shortcomings of the employed technique or by the refractive properties of a nonhomogeneous and anisotropic medium such as muscle [14], [15], may be the underlying reason for inconsistent results obtained in some investigations [6].

These nonlinear properties of muscle may provide an impedance change for the action potentials traveling from the muscle surface to the electrode contacts located on the skin. Therefore, action potentials arriving at the two electrode contacts may have encountered different impedance pathways which may alter their magnitude and phase. These refractive properties may cause the arriving signals not to be perpendicular to the electrode contacts. A similar situation may also occur as muscle fibers are activated at different depths of the muscle. The deeper the muscle fibers, the greater is the probability that their signals will be significantly altered in propagation direction and phase. These nonlinear properties seem to be frequency dependent [14], [15]. Therefore, in some situations the signals detected by the surface electrode may not be an accurate representation of electrical activity transported along muscle fibers. The errors in conduction velocity values observed at the first layer of differential amplifier were not caused by line interference or noise common to both signals which Lynn used as an explanation in his study to explain skewing of some of the delay interval histograms.

Naeije and Zorn [6] recently reported that, in some of their subjects, muscle fiber conduction velocity was not observed to change during isometric fatiguing contractions. They thus concluded that conduction velocity does not change in some subjects performing fatiguing contractions. Such a conclusion is contradictory to our experience. Conduction velocity is always observed to decrease during fatiguing contractions if an appropriate methodology is utilized [16]. In the same study [16] we noticed, however, that decrease of the myoelectric conduction velocity cannot totally explain the observed shifts of the myoelectric power spectrum toward lower frequencies, and conclude that other phenomena, such as changes in firing patterns of active motor units, contribute to the overall spectral shifts.

The origin of the described nondelayed activity in two or several differentially derived myoelectric signals is not obvious. Any volume conducted contribution from a stationary source would be expected to be rejected by a high-quality differential amplifier. We therefore assume that the simultaneous activity is caused by transported signals whose wavefronts are not perpendicular to the long axis of the surface electrode. Such a situation might arise by inhomogeneity and anisotropic properties of the volume conductor [14].

It must be emphasized that this solution solves the problem of simultaneous activity as recorded from the tibialis anterior muscle. However, situations may arise where additional complications may interfere with the recording arrangements and, thus, one may still obtain incorrect measurements of conduction velocity.

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Comments on "Intermittent Drug Administration During Labor and Protection of the Fetus"

MICHAEL J. BENNETT

In the above paper,[1] the authors describe a system for intermittent injection of sedative drugs during labor, which they believe will minimize the transfer of drugs to the fetus. As a practicing anesthesiologist, I applaud any attempt to reduce drug doses in pregnant patients. However, while their device undoubtedly functions as stated, the method and study are flawed by serious errors of fact and interpretation. I wish to comment briefly on some of these.

While the authors do not refer to previous work, the idea originated, as far as I am aware, with Finster and his colleagues in 1966 [1]. These earlier authors presented no data in support of the idea. In 1978, Haram *et al.* [2] published a study of the method in which they state "Although . . . the evidence is not altogether conclusive, the transfer of DZ (diazepam) from the mother appears to be delayed when the intravenous injection is given during uterine contractions." In fact, these authors found no significant differences in mixed cord blood between groups with injections given during uterine contractions and injections given between contractions. Thus, evidence of benefit is altogether lacking in this earlier study.

A fundamental assumption of the method of Sande *et al.*[1] is that thiopental is ". . . rapidly removed from the blood system . . ." (and) ". . . fixed in the central nervous system." It is certainly true that thiopental is rapidly removed from the blood. It is redistributed to other tissues with a half-life of 6.8 min in normals [3]. However, it is not true that thiopental is fixed in the central nervous system. In fact, after a bolus injection, concentration of thiopental in the brain follows serum concentration with less than a 1 min lag [4]. Similarly, in the absence of labor, fetal serum thiopental concentration follows maternal serum concentration with, at most, a 1 min time lag [5]. Thus, since maternal serum thiopental concentration decreases with a 6.8 min half-life following a bolus injection, even if placental blood flow ceased entirely during the brief period of uterine contraction, 1.5 min every 6 min in Fig. 5 of the paper,[1] it appears unlikely to make any clinically significant difference in placental transfer.

Maternal doses of 3-4 mg/kg of thiopental are commonly used to induce general anesthesia for operative delivery and cause no appreciable decrease in Agpar scores [6], so the authors' observation of the lack of fetal effects of 3 mg/kg thiopental is hardly evidence that their system is effective in minimizing drug transfer to the fetus.

I will not comment on the sedative protocol used in this study except to say that it does not meet present day anesthetic or obstetric standards. The authors allude to this in their discussion of undesirable side effects.

Certainly, there is room in science for developments which contradict previously accepted dogma. However, if a study is to be accepted on these terms, it must meet at least the most obvious objections. A study comparing umbilical artery thiopental concentrations following cesarean section with maternal thiopental injections during and after uterine contractions would be one way to accomplish this.

While one could argue that the above considerations are not properly the province of biomedical engineers, I believe that we all have an obligation to avoid the dissemination of erroneous results and conclusions. I wish the authors well in their work, but hope that they will be somewhat more critical of their assumptions in the future.

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The author is with the Oregon Health Sciences University, Portland, OR 97201.

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Author's Reply[2]

The crux of the method presented in our paper[1] is the existence of drugs that are eliminated from the mother's bloodstream fast enough to enable uterine pressure peaks to act as barriers significantly reducing the total quantity of sedative transferred to the child. Dr. Bennett's reference to the article by Haram *et al.* [1] (which appeared after our own work had been concluded and our paper[1] submitted for publication) is thus a no-doubt unintentional red herring, since diazepam levels remain high in the bloodstream for days after administration [2], and it is therefore not surprising that no significant results were obtained using this drug.

Let us examine Dr. Bennett's main objection, that the half-life he accepts for the elimination of thiopental from the bloodstream, 6.8 min, is likewise too long for the method we have described to work. The figure of 6.8 $\pm$ 2.8 min reported by Burch and Stanski [3] for the rapid distribution half-life of thiopental is the result of fitting a triexponential equation to experimental data from 12 nonpregnant subjects. It was not stated how good the fit actually was, merely that it was significantly better than that of a biexponential equation. We have no wish to enter into polemics with Burch and Stanski, whose main objective was in any case, as the title of their article indicates, to investigate metabolism and protein binding. We would simply point out that their Fig. 5 shows the actual concentration of thiopental in the bloodstream (the variable we are primarily interested in is on the mother's side of the placenta) to fall from over 90 μg/ml 30 s after injection to little more than 30 μg/ml 60 s after injection. Whatever the physiological significance

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The author is with the Department of Electricity and Electronics, University of Santiago, Santiago, Spain.