# Principles Underlying New Methods for Chronic Neural Recording

R. B. STEIN, D. CHARLES, L. DAVIS, J. JHAMANDAS, A. MANNARD, AND T. R. NICHOLS

SUMMARY: *Chronic recording is possible from nerve fibers which have grown through holes in an insulating medium (regeneration electrodes) or which are enclosed by an insulating sheath (cuff electrodes). Use of three electrodes in a balanced configuration permits good rejection of electromyographic (EMG) signals and other sources of electrical interference (fluorescent lights, 60 Hz signals from the mains, etc.). Equations are derived and tested for predicting the amplitude and form of the signals expected for a given cuff length and diameter. These equations can be used to design electrode units optimally for a given application. Finally, the use of transformers permits the neural signals to be carefully matched to the recording apparatus and further optimizes the neural signal-to-noise and signal-to-EMG ratios. Use of these methods in several physiological and clinical applications, as well as potential abuses, are discussed.*

RÉSUMÉ: *En enregistrement continu est possible à partir des fibres nerveuses qui se sont développées à travers les trous d'un médium isolé (électrodes de regénération) ou qui sont recouvertes d'une gaine isolée. L'utilisation de trois électrodes dans une configuration balancée permet un bon filtrage des signaux électro-myographiques (EMG) et d'autres sources d'interférence électrique (lumières fluorescentes, signaux 60 Hz, etc.). Des équations sont émises et vérifiées afin de prédire l'amplitude et la forme des signaux escomptés pour une longueur donnée de gaine ainsi que pour son diamètre. Ces équations peuvent être utilisées pour désigner optimalement des unités d'électrodes pour une application donnée. Finalement, l'utilisation de transformeurs permet aux signaux neuraux d'être soigneusement reliés à l'appareil d'enregistrement et de plus optimise les relations signal — bruit et signal — EMG. L'utilisation de ces méthodes dans plusieurs applications physiologiques et cliniques est discutée, ainsi que certains abus possibles.*

From the Departments of Physiology and Surgery, University of Alberta, Edmonton.

Reprint requests to Dr. R. B. Stein, Dept. of Physiology, Medical Science Bldg., University of Alberta, Edmonton, Canada T6G 2E1.

## INTRODUCTION

Advances in understanding the function of the nervous system have resulted from the application of microelectrode techniques to the brains of unanaesthetized, behaving animals (Evarts, 1966) and the peripheral nerves of man (Vallbo & Hagbarth, 1968; Vallbo, 1971). These advances have been particularly striking in understanding motor systems because of the obvious link between motor output and behaviour. However, microelectrodes are limited to use in acute experiments by two factors: their sensitivity to movement and their need to be carefully positioned by external devices. Both these limitations arise from the necessity that the tip of the microelectrode be very close to the nerve fiber being studied in order to ensure high signal-to-noise ratio. The noise level is determined mainly by the impedance of the microelectrode tip which must be quite high due to the small electrode size. Because the fluid surrounding the fiber represents a three-dimensional volume conductor, the signal amplitude will fall off steeply with distance from the nerve fiber. The amplitude will only exceed the noise level if the electrode diameter is comparable in size to the diameter of the fiber and within a distance equal to a few diameters from the fiber (Frank & Becker, 1964).

The problem of movement is more severe in recording from peripheral nerves than from neurons in the brain because the skull represents a point of fixation for a micro-drive. In either location long-term use is precluded by the need for positioning the electrode with external devices



https://doi.org/10.1017/S0317167100020333 Published online by Cambridge University Press

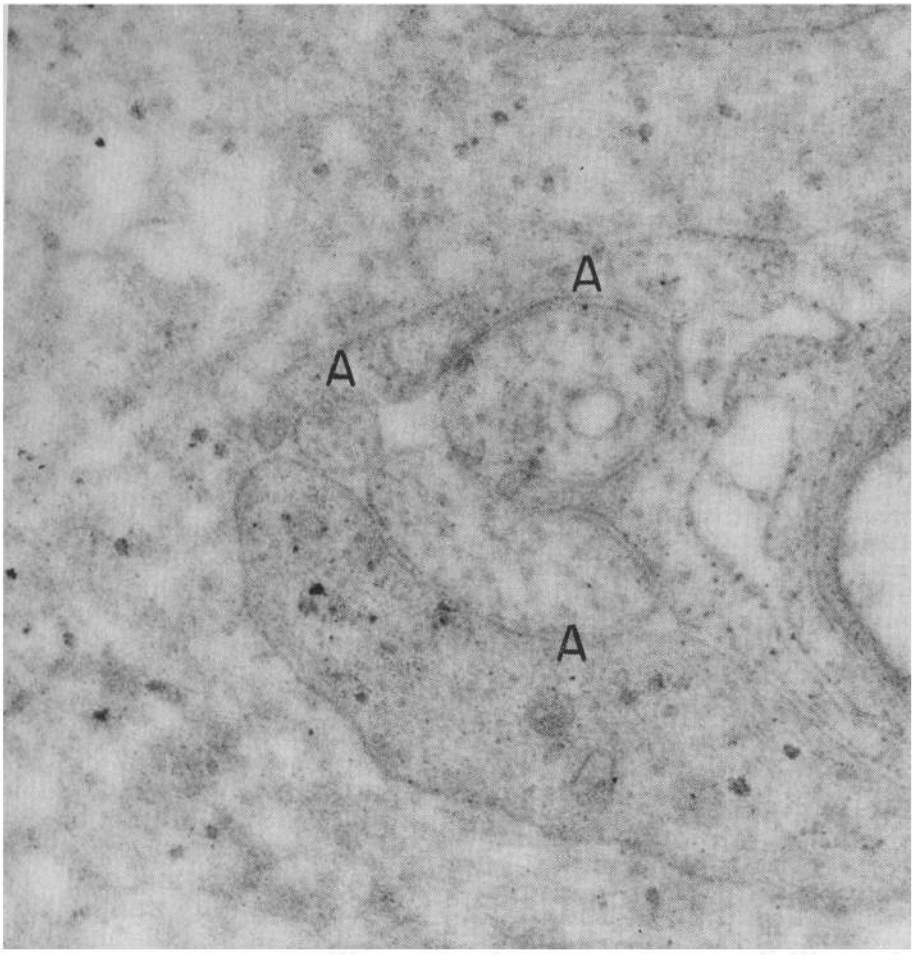


*Figure 1*—Electronmicrograph of small unmyelinated nerve axons in the cat which have grown through holes in a wafer. The wafers are similar to those used for regeneration electrode units in amphibia (Mannard et al., 1974) and had been placed between the cut ends of a partially transected sciatic nerve in the cat approximately four months before the nerve and wafer were fixed for histology. The letter A has been placed near the membranes of the three presumed nerve axons.

which means that there is a pathway for infection to enter the body.

Methods for chronic recording would permit 1.) the same fibers to be studied over a wider variety of conditions during development, conditioning, etc., and 2.) offer the possibility of prosthetic applications such as the control of artificial limbs by amputees, the control of the lower limbs in a paraplegic, etc. Recently, several reports (e.g., Wise et al., 1970; Sonn & Feist, 1974) have suggested using microelectronic techniques to fabricate arrays of microelectrodes which might be implanted. The use of multiple electrodes would permit simultaneous recording from several nerve cells, which has many advantages. Furthermore, if many electrodes are used, the probability is increased that some of the leads are close enough to nerve cells to obtain a reasonable signal-to-noise ratio. Nonetheless, the records shown in these reports are all from acute experiments and, to our knowledge, the possibility that connective tissue will grow around such an array and prevent good recordings chronically has not been eliminated. Finally, prosthetic applications of such electrode arrays may be limited since the high impedance of the electrodes will make the device sensitive to various sorts of electrical interference (fluorescent lights, motors, etc.) in environments other than carefully shielded rooms.

An alternative approach is to isolate a nerve fiber or fibers from the general body fluids by surrounding part of the fiber or fibers in an insulating medium. This technique, which will be referred to as placing the nerve in a *restricted extracellular space*, is well known to neurophysiologists who have for years recorded from nerve filaments in paraffin oil or other nonconductors. The challenge is to do this chronically without damaging nerve fibers and to choose the geometry of the recording arrangement so that the nerve signal is recorded above the noise while rejecting other sources of interference (e.g., EMG, movement artefacts, electrical interference). This article describes recent progress towards this goal and the principles underlying the methods being developed. A short account of some of these results has appeared elsewhere (Stein et al., 1975).

*Regeneration electrodes*

Our group succeeded in obtaining chronic recordings a couple of years ago (Mannard et al., 1974) from amphibian nerves using *regeneration electrode units**. These consist of a series of holes through a nonconductor, each of which has an electrode ending near the center of the hole. Regeneration electrode units were placed in the path of a partially transected sciatic nerve in an amphibian, *Xenopus laevis*. After a few months, recordings were made from sensory and motor fibers which had grown through the various holes. Unfortunately, we have not yet been able to reproduce these results in mammalian preparations because of 1.) the higher conduction velocity and hence lower spatial gradients in warm-blooded animals (see *Amplitude of neural signals*), 2.) the small size of the regenerated fibers, and 3.) the greater proliferation of connective tissue in mammals. The growth of connective tissue may block the holes before nerve ingrowth can take place.

Nonetheless, we have shown histologically (Fig. 1), as have others (Holz, 1974) that mammalian nerve

*U.S. patent pending



https://doi.org/10.1017/S0317167100020333 Published online by Cambridge University Press

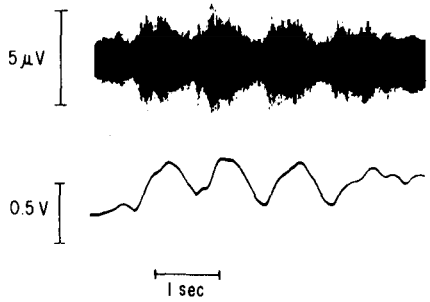


*Figure 2*—Neural signals recorded from the sciatic nerve of a cat walking on a treadmill (upper trace). The cat took three complete steps and then paused on the fourth step. The modulation of neural activity appears as a change in the envelope of the signals recorded at this sweep speed. Despite the small size of the signals (5 μ V), methods will be described later which permit these signals to be detected in the presence of EMG and other sources of interference. After full-wave rectification and low-pass filtering, a smooth signal can be obtained (lower trace) which might be used to control a prosthesis.

fibers do grow through such holes, although they tend to be small, unmyelinated fibers, or weakly myelinated fibers. The small size, together with the relatively higher conduction velocity at body temperature (see *Amplitude of neural signals)* makes it extremely difficult to record from such fibers. We are still attempting to optimize conditions for regeneration and recording so that the regeneration electrode units can be used in mammalian preparations.

*Cuff electrodes*

In the meantime, Hoffer et al. (1974) have demonstrated that it is possible to record chronically from mammalian nerve fibers if a length of nerve filament is dissected and placed in an insulating cuff. We have used cuffs of medical grade silastic, which are opened to insert the nerve and then sealed with silastic. The cuff contains one or more silver or platinum-iridium electrodes, so that recording can begin immediately from histologically normal fibers. The teflon-coated wires from one or more cuffs are further coated with silastic and led out to a twelve-pin integrated circuit socket. The socket is fixed with epoxy in the centre of a vitreous carbon Biosnap (Bentley Laboratories Inc., Irvine, Calif.) which is sutured into the skin overlying the hip. The vitreous carbon is a very hard, smooth material which is not rejected by the body and can be placed in the skin, even of human subjects, for years without infection Stanitski & Mooney, 1973). The entire implanted unit can be sterilized in an autoclave and contains only components which have been thoroughly tested for chronic use in animals and man.

Hoffer et al. (see also Brindley, 1972) indicate that chronic recording requires that the dissected filaments contain an undamaged blood supply. We have found (Stein et al., 1975) that with proper precautions recordings can be made from whole nerves as large as the sciatic nerve in the cat (3-4 mm in diameter), as shown in Fig. 2, which was recorded from a cat walking on a treadmill over a month after implantation. No special precautions were taken to shield either the motor driving the treadmill or other sources of interference (fluorescent lights, mains cords, etc.) in the environment. The methods we have used and the principles underlying them will now be described.

*Rejection of EMG*

If a whole nerve such as the sciatic nerve in the cat is stimulated, and recordings are made between an electrode in the limb and one in another part of the body, a large compound action potential (about 10 mV) is recorded (Fig. 3A). This is almost entirely due to the electrical activity of muscle (EMG) because of the much greater size and number of muscle fibers, compared to nerve fibers. If, however, a segment of nerve is enclosed in a non-conducting medium (paraffin oil or a cuff), the nerve signal recorded at the center of the length of nerve in the non-conducting medium can be detected (early wave in Fig. 3A). At the same time the indifferent electrode can be placed in the fluid nearby so that distant EMG sources will be picked up by both electrodes (Fig. 3B) and can be rejected by a differential amplifier (*common-mode rejection)*. The EMG is, however,

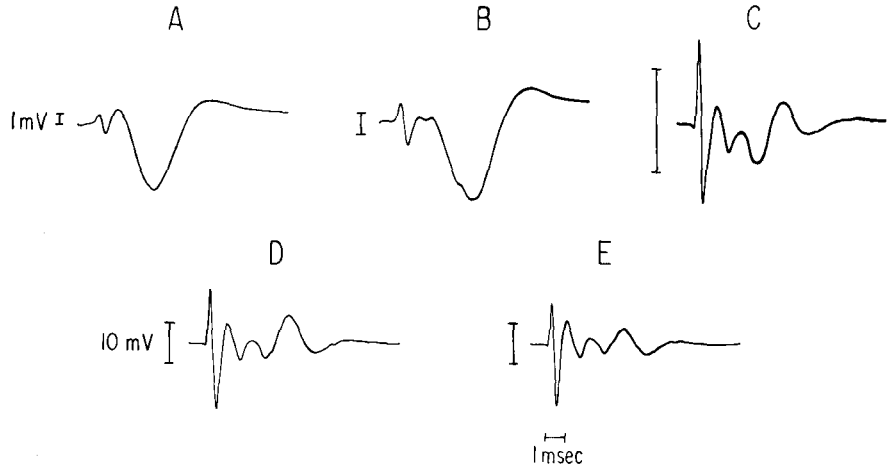


*Figure 3*—Compound action potential recorded by an electrode at the center of a cuff 4 cm in length around the sciatic nerve in the cat. The ventral roots supplying this nerve were stimulated and recording was carried out with respect to A) an electrode some distance away (about 20 cm), B) an electrode on the outside of the cuff, C) electrodes at the two inside edges of the cuff which were connected together (see Fig. 4). In D) and E) the configuration was the same as in C), but a transformer was used to amplify the signal in D) and further filtering was also done in E) to improve the neural signal (early, fast waves) with respect to the later, slower EMG waves. The vertical bar represents 1 mV for each part in the top half of this Fig. and 10 mV in the bottom half. The same time marker (1 msec) applies to all parts of the Fig. Some of the faster portions of these waveforms were strengthened to permit reproduction from the original photographs.



https://doi.org/10.1017/S0317167100020333 Published online by Cambridge University Press

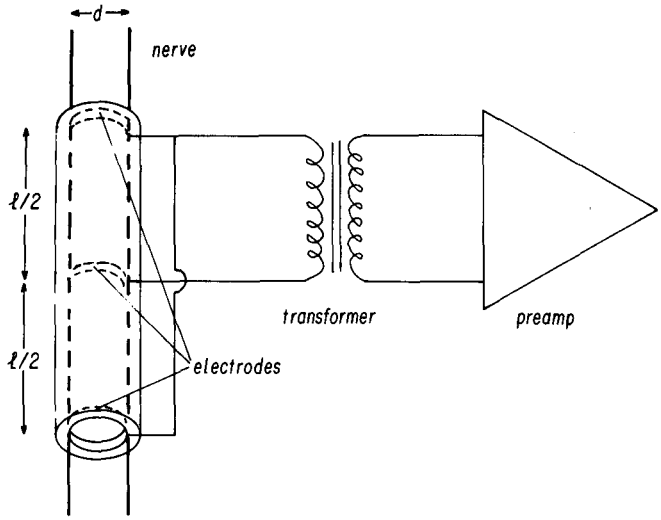


*Figure 4*—Method for recording using an insulating cuff with three electrodes around a nerve. The reasons for the recording configuration shown and the use of a transformer are described in the text.

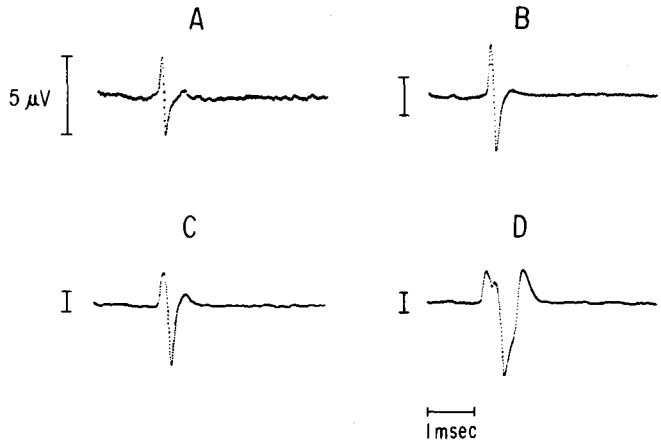


*Figure 5*—The effect of increasing the length of a nerve in a restricted extracellular space on the amplitude and waveform of recorded extracellular potentials from a single A $\beta$ fiber (conduction velocity = 64 m/sec). In this experiment varying lengths of the sural nerve in the cat were lifted from saline into paraffin oil. The lengths used were A) 0.4 cm, B) 1 cm, C) 1.8 cm, and D) 4.9 cm. The vertical bar in each case represents 5 $\mu$ V. The time scale is identical for each part of this Fig. Each part of the Fig. was obtained by averaging the responses to 512 stimuli applied to a dorsal root filament.

still large enough to swamp the neural component. Much better common-mode rejection can be obtained if two electrodes are built into the ends of the cuff (Fig. 4), and recording is carried out between the center of the cuff and the two ends which are shorted together (Fig. 3C).

The principle underlying this procedure is that once the two ends of the cuff are shorted together, there can be no potential gradient across the cuff. Hence, EMG currents will tend to flow around rather than through the cuff (the flow of current across the longitudinal resistance of the cuff requires a potential gradient according to Ohm's Law). Even though an electrode is placed around the nerve, this does not preclude some potential gradients in the radial direction and hence there is still some residual EMG. We have found that this residual EMG is minimized if the recording configuration is symmetrical. Assymetric placement of the internal electrode reduces the neural signal, which is generated by the current flow along the length of the nerve within the cuff, while increasing the EMG. The ratio of the neural signal to the EMG can be enhanced still further by carefully matching the input impedance of the recording apparatus to that of the electrodes being used. In Fig. 3D a Hammond audio transformer (Model 585D) has been placed between the recording electrodes and the preamp. This transformer amplifies the signals over ten times and has other desirable filtering properties which will be described later (*Amplification and filtering of neural signals*). Finally, the EMG is much slower in time course and hence contains lower frequency components than the neural signal. Fig. 3E shows the effect of applying a first-order high-pass filter with a half-power point of 300 Hz. There is now quite good rejection of EMG, and the neural signal stands out clearly. Thus, the large EMG components in Fig. 3A have been systematically reduced while the neural components have been enhanced until they stand out clearly in Fig. 3E. The same principles which are demonstrated for compound action potentials in Fig. 3 apply to data from single nerve fibers and now will be discussed in more detail in successive sections.

*Form of the neural signals*

Whether neural signals are recorded by means of regeneration electrodes, cuff electrodes, or simply by picking the nerve out of saline and into a non-conductor such as paraffin, the form of the action potential will be triphasic. Mathematically, what is recorded is the second difference between the voltage at the central electrode and the voltage at the two ends of the restricted extracellular space. In most cases the restriction will be cylindrical in form and the electrode will be placed in the center of the cylinder, as shown in Fig. 4. Then the voltage recorded will be (Stein & Pearson, 1971)

$$1.)\quad V(t) = c\,\{\tfrac{1}{2}V_m(t+\Delta t) - V_m(t) + \tfrac{1}{2}V_m(t-\Delta t)\}$$

where $V_m$ represents the intracellular potential in a nerve fiber, $\Delta t = l/2v$, $l$ is the length of the restriction in extracellular space, and $v$ is the conduction velocity of the nerve fiber. The form of the intracellular action potential and the constant $c$ can be determined by classical monophasic recording methods.

To do this, cats were prepared for recording acutely from peripheral



https://doi.org/10.1017/S0317167100020333 Published online by Cambridge University Press

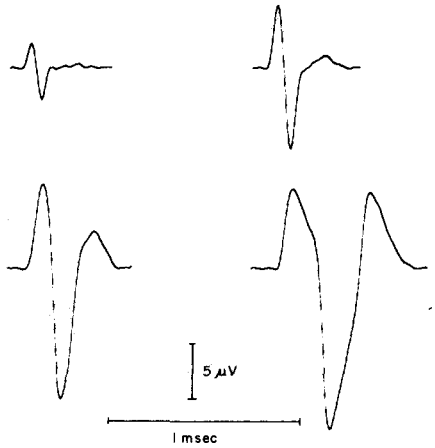


*Figure 6*—Action potentials computed for varying lengths of nerve in a restricted extracellular space using equation 1.) and the observed monophasic potentials. The lengths chosen, A) 0.6 cm, B) 1.3 cm, C) 2.6 cm, and D) 5.1 cm, are close to those used experimentally for the fiber shown in Fig. 5, so that a direct comparison between experiment and prediction is possible for this A β fiber.

nerves and a laminectomy was performed to expose sacral and lumbar roots. Nerves varying in diameter from the sural (0.5-1 mm) to the sciatic (3-4 mm) were either placed in a silastic cuff containing electrodes or lifted into a non-conducting medium (paraffin oil). Either dorsal or ventral roots were dissected until a filament was obtained which produced a single all-or-none action potential in the peripheral nerve, when the stimulus current was carefully graded. Body temperature and the temperature within the leg were monitored and maintained at 36 ± 1°C. The length $l$ of nerve in the restricted extracellular space was varied either by 1.) raising or lowering the nerve on a micromanipulator so that varying lengths were in paraffin, or 2.) using pairs of electrodes with different spacing in the nerve cuff, depending on the method of recording used. After recording several single units using various lengths of nerve, the nerve was ligated or cut, and the damaged end was lifted into paraffin. Recording between the proximal and distal ends of the length of nerve in the restricted extracellular space gave a classical monophasic action potential. Signal averaging (up to 1000 sweeps) was used to improve the signal-to-noise ratio of the signal unit potentials. This could be done during an experiment using a special purpose signal averager (Biomac 1000, Data Laboratories Ltd., Surrey, England), or at a later time by playing back the data recorded on an FM tape recorder (Hewlett-Packard Model 3960) into a Lab-8 computer system (Digital Equipment Co.) programmed for signal averaging (French, 1973).

The form of the monophasic action potential has a sharp rising edge and reaches a peak in less than 0.2 msec. This is followed by a slower repolarization. When the length of restriction is small, equation 1.) reduces to the second differential of the intracellular potential

2.) $$V(t) = \frac{c}{8}\left(\frac{l}{v}\right)^2 \frac{d^2V_m(t)}{dt^2},$$

after using the usual formula for a second differential

3.) $$\frac{d^2V_m(t)}{dt^2} = \lim_{\Delta t \to 0} \left\{ \frac{V_m(t+\Delta t) - 2V_m(t) + V_m(t-\Delta t)}{\Delta t^2} \right\}$$

The second differential of the monophasic waveform will have two prominent phases where abrupt changes in slope occur (at the beginning and end of the fast rising phase). The third phase will be much smaller (Fig. 5), due to the much more gradual change of slope at the end of the action potential.

*Amplitude of the neural signals*

As the length $l$ is increased the voltage increases as the square of the length, but the approximation in equation 2.) becomes less good (Fig. 5B). The third phase becomes more prominent and the action potential lengthens out (Fig. 5C). Eventually, equation 1.) predicts that the first and third phase will be equal and the second phase will be twice as great (Fig. 5D). Each will be a replica of the monophasic action potential and the peak-to-peak amplitude of the triphasic waveform will be 1.5 times that of the monophasic amplitude (Stein & Pearson, 1971).

The monophasic action potential ($V_1$) recorded clasically as described in the previous section is a scaled-down version of the intracellular action potential ($V_m$) and affected by the same constants as the triphasic potentials, i.e.,

4.) $$V_1 = c\, V_m.$$

Monophasic action potentials were recorded at the end of each experiment for all units studied. These potentials were then used to reconstruct the expected triphasic waveforms according to equation 1.) using a short computer program.

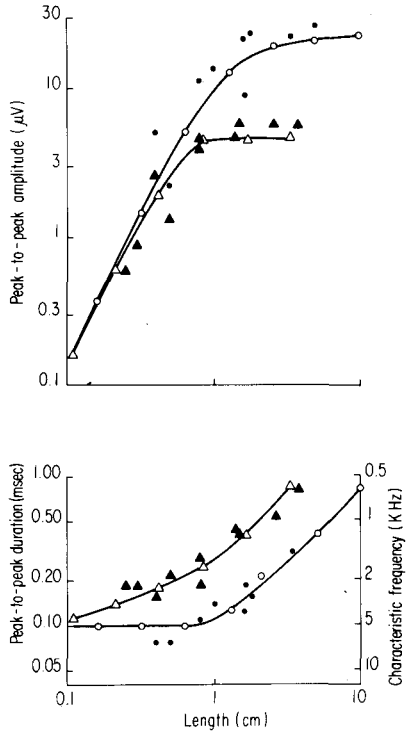


*Figure 7*—Variation of A) the peak-to-peak amplitude, and B) the peak-to-peak duration of two single units from the sural nerve in the cat. The faster-conducting unit (64 m/sec) is the same A β fiber (O and ●) shown in Figs. 5 and 6, while the slower unit (21 m/sec) is an A δ fiber. ( ▲ and △ ) from the same nerve. The lines have been fitted by eye through the computed values (open symbols). The filled symbols give the values measured experimentally which agree quite well with predictions. The characteristic or peak frequency expected in a frequency spectrum of the neural signal is also shown as a coordinate on the right side of the bottom part of this Fig. These values were calculated using equation 9).



https://doi.org/10.1017/S0317167100020333 Published online by Cambridge University Press

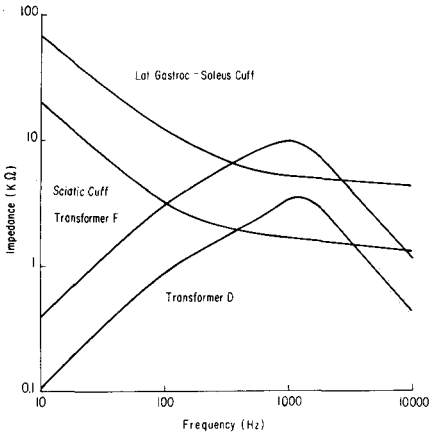


*Figure 8*—Magnitude of the impedances measured for two cuffs: one around the whole sciatic nerve and a second around the branch to lateral gastrocnemius and soleus muscles. Also shown are the impedances of two transformers (Hammond 585D and 585F) which were tested in the circuit shown in Fig. 4 for use with these cuffs. The ratio of turns on the secondary to that of the primary is 25.2 for the 585D transformer and 12.6 for the 585F transformer.

The computed waveforms agreed well with the experimentally measured triphasic potentials as shown in Fig. 6. From both the experimentally measured and the reconstructed triphasic potentials, the peak-to-peak amplitude and peak-to-peak duration could be measured (Fig. 7). These are compared for two units from the sural nerve in the cat. Note the close agreement, both for the peak-to-peak amplitude and for the time between the two most prominent peaks (peak-to-peak duration). The amplitude initially increases as the square of the length $l$ (a slope of 2 on the log-log plot of Fig. 7A), but begins to saturate beyond lengths of 1-3 cm, depending on the conduction velocity $v$. Increasing the length of a cuff beyond this value would not improve the signal levels, and since the duration begins to increase in proportion to $l$ (a slope of 1 on the log-log plot of Fig. 7B), it will become more difficult to separate the signals from the slower EMG waveforms (see *Amplification and filtering of neural signals).*

Note also the large difference in amplitude between fibers conducting at different velocities when long lengths are used, but the small difference when the length of restriction is small. This is because the parameter $c$ in equations 1) and 2) depends on the square of the ratio of the fiber diameter $a$ to the diameter $d$ of the restricted extracellular space (see Fig. 4 and Stein & Pearson, 1971).

If $a << d$, Stein & Pearson (1971) showed that equation 1.) becomes

5.) $$V \propto \left(\frac{a}{d}\right)^2 \Delta^2 V$$

The actual constant of proportionality will depend on the ratio of extracellular to intracellular conductivities, the percentage of the extracellular space within the restriction occupied by myelin and other factors. The difference notation ( $\Delta$ ) has also been introduced to shorten the expression 5.). To the extent that the conduction velocity $v$ is proportional to fiber diameter $a$ (Hursch, 1939; see Coppin & Jack, 1972, for conflicting evidence), simple expressions can be written from 5.) for the peak-to-peak amplitude $Vp$ of the waveforms in the limit of short and of long lengths $l$ in the restricted extracellular space

6.) $$Vp = k_1 \left(\frac{l}{d}\right)^2$$

for $l << 1$ cm. and

7.) $$Vp = k_2 \left(\frac{a}{d}\right)^2$$

for $l << 1$ cm. The values of the constants $k_1$ and $k_2$ can be determined empirically from data such as shown in Fig. 6. Typical values for nerves in cats were in the range $k_1 =$ 0.05-0.1 $\mu$ V and $k_2 =$ 0.1-0.2 V. If the single fiber has approximately the same longitudinal resistivity as the other material in the restricted extracellular space, the value of $k_2$ will be about equal to 1.5 times the intracellular action potential. The measured values of $k_2$ agree with this suggestion.

The values of $k_1$ are much smaller in warm-blooded animals such as cats than in cold-blooded animals such as amphibians because of the marked effect of conduction velocity on temperature. The higher $v$ at body temperature in mammals means that for a given $l$ the value of $\Delta t$ in equation 1.) will be smaller and hence $V(t)$ which depends on the second difference ( $\Delta t)^2$ will be correspondingly reduced. Even within a species $k_1$ and $k_2$ will not be rigorously constant because the duration of the action potential is well known to depend on conduction velocity or fibers diameter (see Fig. 7 and Paintal, 1966, 1967) and the assumption of linearity between conduction velocity and diameter may not be valid. We have not examined these factors in detail, but have been satisfied to obtain approximate values of $k_1$ and $k_2$ to use in the design of suitable electrodes. For example, if we construct a regeneration electrode with holes of diameter $d = 50$ $\mu$ m and length $l = 1$ mm, we would expect signal levels of 20 $\mu$ V or more from equation 6.). (There may, however, be significant differences in the

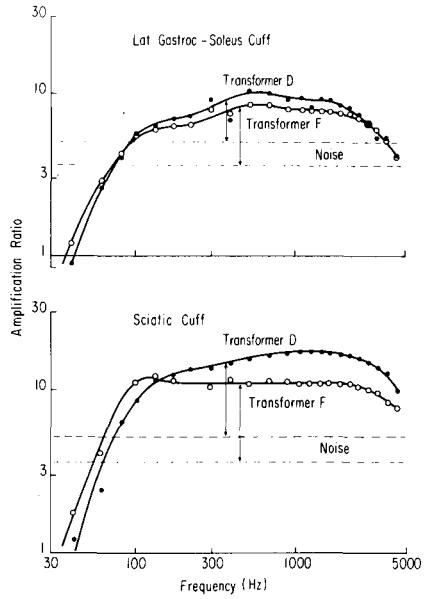


*Figure 9*—Amplification of neural signals (● and O) and noise (interrupted lines) by two transformers (Hammond 585D and 585F). The data points for each transformer have been fitted by eye with a smooth curve for clarity. The vertical lines connecting the signal level to the noise level for a given transformer indicate the improvement in signal-to-noise ratio at one frequency. As discussed in the text, transformer F was more suitable for use with the lateral gastrocnemius-soleus nerve, while transformer D was better with the sciatic cuff.



https://doi.org/10.1017/S0317167100020333 Published online by Cambridge University Press

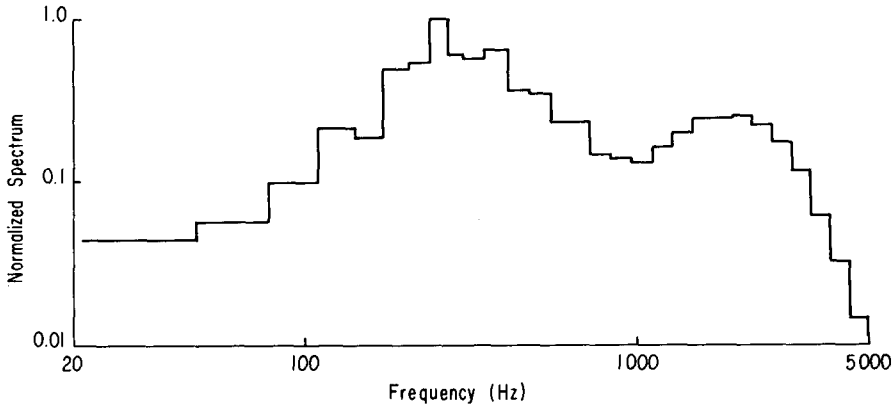


*Figure 10*—Power spectrum of signals recorded as shown in Fig. 2 from a cuff electrode while a cat was walking on a treadmill. The spectrum is usually measured in units such as $V^2/Hz$, but in this Fig. the data have been normalized with respect to the highest peak to show relative magnitudes. Even with the use of a transformer and some filtering the EMG peak between 100 Hz and 1000 Hz was greater in this example than the neural peak (near 2000 Hz). However, because of the ten-fold separation in frequency further filtering could be used to greatly reduce the EMG while preserving the neural components.

signal levels in normal and regenerated fibers.) On the other hand, if we install a cuff of 2 mm inside diameter snugly around a nerve, the expected signal amplitude, even from the largest fibers ($a = 20\mu$ m), will only be 15 $\mu$ V from equation 7) for very long cuffs. In order to record such small signals reliably in a chronic, behaving animal, several precautions are necessary, which will now be considered.

*Amplification and filtering of neural signals*

As indicated in an earlier section (*Rejection of EMG*), the large background EMG signals and other sources of noise (mains current, fluorescent lights, etc.) can be reduced by using the circuit shown in Fig. 4. Balancing takes place at three stages: 1) in the electrode array, by recording from the center electrode with respect to the two end electrodes, 2) by use of a transformer (Hammond 585D or 585F), 3) by use of a differential input to a standard low-noise physiological preamp (e.g. Grass Instruments Co., P15B).

The importance of a balanced electrode configuration in the rejection of EMG has already been demonstrated in Fig. 3. The use of the transformer has several functions. Most physiological preamplifiers have high input impedance ( $\geq 10$ M $\Omega$) and approach the minimum noise level theoretically possible (the so-called Johnson or thermal noise) with a high impedance source. However, these preamps are not optimized for low impedance sources. By using a transformer with a low impedance primary and a high impedance secondary the impedance can be matched to that which the preamplifier handles best. Secondly, in "stepping up" the impedance, the voltages recorded can also be amplified. The Johnson noise level increases only as the square root of the source impedance, so an increase in signal-to-noise ratio equal to the square root of the amplification ratio is possible. For this reason transformers have long been advocated for human sensory nerve action potential studies (Buchthal & Rosenfalck, 1966).

Finally, the transformer provides useful filtering, as illustrated in Figs. 8 and 9. This statement requires some explanation, since normally preamplifiers are designed to operate with a wide range of frequency cuts and high input impedance, so as to distort the biological signal as little as possible. The input stage is often directly coupled to the preparation, since capacitative coupling could be detrimental to the common-mode rejection of the preamp and may increase the noise level. Filtering is done at a later, less sensitive point in the circuit. However, with direct coupling, transients can cause blocking of the preamp for some time and low-frequency movement artefacts are also troublesome. However, these low-frequency artefacts and low-frequency components in the EMG are reduced by the filtering characteristics of the transformer.

Fig. 8 shows the impedance of typical cuff electrodes one month after implantation. There is a fairly constant resistance at high frequencies which is mainly due to the resistance of the fluid filling the cuffs and their fibers. The resistance of a cylinder of saline of resistivity $\rho$, length $l$ and diameter $d$ is (Mannard et al., 1974)

8.) $$R = \frac{\rho l}{\pi d^2}$$

The sciatic and lateral gastrocnemius-soleus nerve cuffs shown in Fig. 8 had lengths $l = 2.0$ cm and 1.2 cm, and diameters $d = 0.34$ cm and 0.15 cm respectively. If the effective resistivity were $\rho = 200$ $\Omega$-cm (Ruch & Patton, 1966), one would expect resistances of about $R = 1100\Omega$ and $3500\Omega$ from equation 8), in reasonable agreement with the observed values. Note, however, that the *effective* resistivity depends on the space occupied by the extracellular fluid (which has a relatively low resistivity), axoplasm and poorly-conducting materials such as myelin. The resistivity of the cuffs tends to increase with time, presumably due to the proliferation of connective tissue in the extra-cellular space.

In addition, the impedance varies inversely with frequency at the lower frequencies. This is presumably due to the capacitance of the electrode-saline interface (Robinson, 1968; Pollak, 1974). The capacitance of such an interface is actually quite complex in that the impedance varies as a fractional power of the frequency (Pollak, 1974). The capacitance also tends to increase with time after implantation. Finally, Fig. 8 shows the impedances of two



https://doi.org/10.1017/S0317167100020333 Published online by Cambridge University Press

transformers as a function of frequency. Note that the impedances are highest at frequencies just above 1 KHz, whereas at low frequencies the impedances are much lower than that of the electrodes. Since the capacitance of the electrode and the transformer are effectively in series, only a small fraction of the nerve voltage will be dropped across the transformer at low frequencies. This will not be true at frequencies where the impedance is higher, so the transformer serves as a band-pass filter. This is shown quantitatively in Fig. 9 by plotting total amplification of the electrodes plus transformer as a function of the frequency. The response is best at frequencies near 1 KHz and low-frequency signals such as 60 Hz interference, movement artefacts, and EMG are strongly rejected.

The frequency response curve was determined by stimulating through one cuff (e.g., lateral gastrocnemius-soleus) and recording the potential evoked in a second cuff (e.g., sciatic). The responses were averaged and the fast Fourier transformer was used to determine the magnitude of the components at each frequency 1) when the electrode was connected directly to the preamplifier, and 2) when the electrode was connected indirectly as shown in Fig. 4. The ratio of the magnitude of the components recorded with and without various transformers as a function of frequency was determined and is shown in Fig. 9. This ratio measures the extent to which a given frequency of signal will be amplified (ratio > 1) or attenuated (ratio < 1).

Note also in Fig. 9 that the two transformers behave differently with the two nerves. For a nerve with an impedance as high as that of the lateral gastrocnemius-soleus, there is little difference in the amplification of the signal, but the noise level is substantially greater with transformer D. Thus, transformer F provides the best signal-to-noise ratio, and the signal-to-noise ratio is substantially improved by this transformer in the range 100-4000 Hz. However, with a larger nerve such as the sciatic, and hence a lower impedance, transformer D provides a greater amplification of the neural components and better rejection of lower frequency signals such as the EMG. Thus, transformer D is preferable for use with the sciatic nerve. These brief comments should indicate how one can begin to match the recording apparatus to a given nerve so as to optimize the transmission of desired signals and reject unwanted frequency components.

Further filtering can, of course, be included in the preamplifiers to reject low-frequency signals. Fig. 10 shows the spectrum of the signals recorded from a cuff electrode on the sciatic nerve of a cat while it was walking. Two peaks are seen, one at 200-300 Hz corresponding to the EMG, and a second one near 2000 Hz due to the neural component. Even with the transformer and some filtering, the EMG component in this example is still dominant. The frequency at which the minimum occurs between the two peaks is near 1000 Hz. A high-pass filter with a suitable frequency cut could further reduce the EMG component in Fig. 10.

The peak frequency of the neural component will depend on the length of the cuff. For a neural waveform with a peak-to-peak duration $t_p$ msec. one might expect the peak frequency component $f_p$ in kHz to be

9.) $$f_p = \frac{1}{2t_p}$$

since the peak-to-peak measurement represents only half a cycle. This characteristic frequency is shown on the right of Fig. 7. The peak is relatively independent of cuff length until lengths are reached (approximately 1 cm) at which the waveform lengthens out markedly. The neural signals will then have lower frequency components and be relatively harder to distinguish from the EMG.

*Physiological and clinical applications*

At this stage of their development, we have been forced to consider mainly the technical aspects of these methods, so that reliable recordings can be obtained from freely-moving chronic animals. We have now had cuff electrodes implanted in cats and functioning for over six months, and have implanted up to four cuff electrodes in one animal. Once the method is developed and tested adequately, there are several immediate applications. Firstly, a rectified and filtered signal such as shown in Fig. 2 can be used to measure the relative activity of different nerves under different behavioural conditions. While techniques for single unit recording have added greatly to our knowledge of physiological mechanisms, there is also a need for methods of estimating the total amount of activity during normal function. The only available method has been to use gross surface electrodes. These electrodes record attenuated and distorted signals from a variety of sources which often cannot be clearly defined.

There are also recently developed methods of analysis using recordings from more than one electrode which are based on cross-correlation (Mann, 1973; Heetderks & Williams, 1975) and optimal filtering techniques (Roberts & Hartline, 1975). These techniques permit different groups of fibers to be distinguished on the basis of conduction velocity, waveform, etc. Thus, in addition to measuring the total nerve activity, this activity can be partitioned into one or more afferent and efferent components so that the function of different fiber groups can be studied in normal behaviour. This should be particularly useful in motor systems where the functions during posture and locomotion of various, clearly defined afferent and efferent groups of fibers are still controversial (Stein et al., 1973; Stein, 1974).

The methods also have obvious clinical applications, for example in prosthetics. An amputee may have stumps of some muscles which can provide signals to control a powered artificial limb. However, there will be no remnants of other, more distal muscles, even though the nerve fibers are still present. Cuff electrodes could provide a means of recording chronically from these nerve fibers and the signals would serve as a source for controlling other degrees of freedom in an artificial limb. Since



https://doi.org/10.1017/S0317167100020333 Published online by Cambridge University Press

the nerves are ligated, there would be no sensory information and the signals from the smaller $\gamma$-motoneurons are too small to be recorded in the larger human nerves. Thus, a good measure of $\alpha$-motoneuronal activity should be provided by the cuff electrodes. However, it remains to be shown that the signals from a ligated nerve are maintained more or less indefinitely at useful levels. Cuff electrodes may also be useful as a stimulating electrode on sensory nerves to provide feedback from the artificial limb, and thereby improve its effectiveness. These applications in basic physiological research and in clinical areas are being pursued vigorously by our group in Edmonton and others in various centers.

Finally, we wish to point out that we are aware of potential misuse developing in the future from refinements to this system. The degree of specificity and discreteness of stimulus site and recording site implied in the use of small nerve bundles will inevitably lead to increased interaction between the information flow within the human body and information systems outside the body. Neural signals which until now have been private information flowing within the individual are becoming accessible to outside monitoring and modification. We feel that such a powerful method for the control and modification of individual thought and behaviour will not go unnoticed by those who believe in the desirability of controlling the thought and behaviour of others. We openly welcome discussion on this matter, and encourage you to make suggestions both verbally and in print. We hope that other workers in this field will have the courage to mention this important potential abuse of their work. Hopefully a policy will be developed concurrently with the technological development which states that direct neural connections should be used for prosthetic aids only, and not for conditioning (including aversion therapy) or information retrieval not directly related to a prosthetic application (e.g., lie detection for governmental or employment purposes). In no case shall the privacy, dignity, freedom or individuality of the subject be compromised.

## DISCUSSION

*Jasper* (Montreal) commented on the distortion of the action potential which occurred with cuff electrodes. *Stein* replied that the actual form of the action potential was not important for his particular purposes. He was interested mainly in a signal of maximal amplitude which could be related to either the total level of voluntary contraction or the level of sensory feedback, depending on the nerve which was being used.

*Diamond* (Hamilton) questioned whether the placement of a chronic cuff around a nerve might interfere with axoplasmic transport. Stein thought this unlikely because the nerves continued to function in apparently normal fashion for prolonged periods of time while the cuff was on, and also because ultrastructural studies had not shown any significant differences between nerves with and without cuff.

## ACKNOWLEDGMENTS

We thank Dr. E. Sanders and Mrs. Y. Valgren for their help with histology, and Mr. A. R. Allen for assistance with some of the electrical measurements. We also thank Dr. C. De Luca and others at the Liberty Mutual Research Centre, Hopkington, Mass., for helpful comments. The research was supported in part by grants to Dr. Stein from the Medical Research Council of Canada and the Muscular Dystrophy Association of Canada.

## REFERENCES

BRINDLEY, G. S. (1972). Electrode arrays for making long-lasting electrical connexion to spinal roots. Journal of Physiology, 222, 135-136P.

BUCHTHAL, F. and ROSENFALCK, A. (1966). Evoked action potentials and conduction velocity in human sensory nerves. Brain Research, 3, 1-120.

COPPIN, C. M. L. and JACK, J. J. B. (1972). Internodal length and conduction velocity of cat muscle afferent nerve fibres. Journal of Physiology, 222, 91-93P.

EVARTS, E. V. (1966). Pyramidal tract activity associated with a conditioned hand movement in the monkey. Journal of Neurophysiology, 29, 1011-1027.

FRANK, K. and BECKER, M. C. (1964). Microelectrodes for recording and stimulation. In "Physical Techniques in Biological Research", edited by W. L. Nastuk. Academic Press, New York, Vol. 5A, pp. 22-87.

FRENCH, A. S. (1973). Averaging of neurophysiological data prior to frequency domain analysis. Computer Programs in Biomedicine, 3, 113-122.

HEETDERKS, W. J. and WILLIAMS, W. J. (1975). Partition of gross peripheral nerve activity into single unit responses by correlation techniques. Science (New York), 188, 373-375.

HOFFER, J. -A., MARKS, W. B. and RYMER, W. Z. (1974). Nerve fiber activity during normal movements. Society for Neuroscience (St. Louis Meeting), 4, 300.

HOLZ, A. (1974). Regeneration peripherer Nerven durch implantierte Vielfachcapillaren. Research in Experimental Medicine, 164, 321-323.

HURSCH, J. B. (1939). Conduction velocity and diameter of nerve fibers. American Journal of Physiology, 127, 131-139.

MANN, R. W. (1973). Prosthesis control and feedback via noninvasive skin and invasive peripheral nerve techniques. In "Neural Organization and Its Relevance to Prosthetics". Symposia Specialists, Miami, pp. 177-195.

MANNARD, A., STEIN, R. B. and CHARLES, D. (1974). Regeneration electrode units: implants for recording from single peripheral nerve fibers in freely moving animals. Science (New York), 183, 547-549.

PAINTAL, A. S. (1966). The influence of diameter of medullated nerve fibres of cats on the rising and falling phases of the spike and its recovery. Journal of Physiology, 184, 791-811.

PAINTAL, A. S. (1967). A comparison of the nerve impulses of mammalian non-medullated nerve fibres with those of the smallest diameter medullated fibres. Journal of Physiology, 193, 523-533.

POLLAK, V. (1974). Impedance measurements on metal needle electrodes. Medical and Biological Engineering, 12, 606-612.

ROBERTS, W. M. and HARTLINE, D. K. (1975). Separation of multi-unit nerve impulse trains by a multi-channel filter algorithm. Brain Research, in press.

ROBINSON, D. A. (1968). The electrical properties of metal microelectrodes. Proceedings of the Institute of Electrical and Electronic Engineering, 56, 1065-1071.

RUCH, T. C. and PATTON, H. D. (1965). "Physiology and Biophysics", Philadelphia & London, Saunders.

SONN, M. and FEIST, W. M. (1974). A prototype flexible microelectrode array for implant-prosthesis applications. Medical and Biological Engineering, 12, 778-791.

STANITSKI, C. L. and MOONEY, V. (1973). Osseus attachment to vitreous carbons. Journal of Biomedical Materials Research, Vol. 7. Biomedical Materials Symposium, 4, 97-108.

STEIN, R. B. (1974). Peripheral control of movement. Physiological Reviews, 54, 215-243.

STEIN, R. B., CHARLES, D., DAVIS, L., JHAMANDAS, J. and NICHOLS, T. R. (1975). A method for chronic recording from nerve fibres in experimental animals and man. Canadian Federation of Biological Societies 18, 39.

STEIN, R. B. and PEARSON, K. G. (1971). Predicted amplitude and form of extracellu-



https://doi.org/10.1017/S0317167100020333 Published online by Cambridge University Press

larly recorded action potentials from unmyelinated nerve fibres. Journal of Theoretical Biology, 32, 539-558.

STEIN, R. B. PEARSON, K. G., SMITH, R. S. and REDFORD, J. B. (1973). "Control of Posture and Locomotion", New York, Plenum Press.

VALLBO, Å. B. and HAGBARTH, K.-E. (1968). Activity from skin mechanoreceptors recorded percutaneously in awake human subjects. Experimental Neurology, 21, 270-289.

VALLBO, Å. B. (1971). Muscle spindle response at the onset of isometric voluntary contractions in man. Time difference between fusimotor and skeltomotor effects. Journal of Physiology, 218, 405-431.

WISE, K. D., ANGELL, J. B. and STARR, A. C. (1970). An integrated circuit approach to extracellular microelectrodes. Institute of Electrical and Electronic Engineering, Transactions on Biomedical Engineering, 17, 238-246.



https://doi.org/10.1017/S0317167100020333 Published online by Cambridge University Press