MULTI-ELECTRODE NERVE STIMULATION: EXPERIMENTS AND SIMULATIONS

Veltink P.H., Alsté J.A. van

Biomedical Engineering Group,
Faculty of Electrical Engineering, University of Twente
Enschede, The Netherlands

ABSTRACT

Multi-electrode stimulation experiments were performed on rat nerves. Short term motor unit recruitment stability and muscle force addition were investigated. Furthermore, a simulation model of nerve stimulation and associated isometric muscle twitch force was developed. The model incorporated inhomogeneous and anisotropic nerve conduction, nerve fibre excitation, probability distributions of nerve fibre excitation parameters and a relation between nerve fibre excitation and isometric twitch muscle force. The results of the experiments showed a more stable recruitment and a better force addition for intrafascicular electrodes than for extraneural electrodes. Furthermore, for intrafascicular electrodes recruitment curves showed that not always thick nerve fibres were first recruited. The simulation results could explain some of the experimental results.

INTRODUCTION

Artificial nerve stimulation is used in implantable systems for Functional Neuromuscular Stimulation. These systems are designed to control the contraction of paralyzed skeletal muscles with the objective to obtain functional limb movements in stroke and spinal cord injured patients.

For nerve stimulation multi-electrode configurations are desirable to diminish fatigue and for changing the ratio of muscle force between different muscles. We investigated nerve stimulation in acute rat experiments and mathematical models.

EXPERIMENTAL METHODS

Experiments were done on hindlimb muscles of rats. The rats (Wistar, male, 3-4 months old, 0.30-0.35 kg) were anaesthetized with pentobarbital sodium. The initial dose was 70 mg/kg. On the average 15 mg/kg was given in addition every half hour. Atropine was given subcutaneously. The Peroneus Communis Nerve in the right hind limb was stimulated and the force of the Tibialis Anterior (TA) muscle and the Extensor Digitorum Longus (EDL) muscle were measured simultaneously under isometric condition. During stimulation of the Peroneus Communis Nerve spinal reflexes were not observed.

Stimulation was performed monopolar, using monophasic current pulses having a width of 60 µs. During a stimulation pulse the current remained constant. An indifferent electrode was placed in between muscles outside the stimulation region. Two electrode configurations were studied for stimulation: a four electrode intrafascicular configuration and a four electrode extraneural configuration (see figure 1). The four electrodes of the intrafascicular configuration consisted of 25 µm diameter stainless steel wires, insulated upto the tip, and were placed 100 µm apart. In some experiments also single 25 µm stainless steel wires were used for intrafascicular stimulation. Insertion of the intrafascicular electrodes was done by making an incision in the epineurium and piercing the perineurium. Sometimes also an incision had to be made in the perineurium. The four electrodes of the extraneural configuration consisted of 200 µm diameter stainless steel wires and were placed on the epineurium.

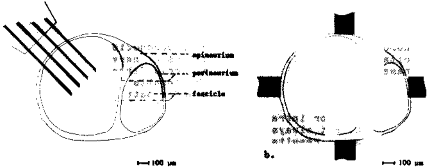


Figure 1: The electrode configurations and the stimulated nerve (drawn to scale):
a. intrafascicular electrode configuration, consisting of four 25 µm diameter stainless steel wires, placed 100 µm apart. The wires were insulated upto the tip.
b. extraneural electrode configuration, consisting of four 200 µm diameter stainless steel wires.
The nerve is drawn from a photograph of the cross-section of the N. Peroneus Communis of the rat.

Two stimulation experiments were performed with both electrode configurations: short term stability of motor unit recruitment and force addition when stimulating on two electrodes [1]. Short term stability of recruitment was investigated by generating single twitches at a low stimulation frequency (0.5 or 1.0 Hz). Stimulation was done several times at various stimulation pulse amplitudes. The twitch force amplitudes were measured. The addition of near tetanic forces for two electrodes was investigated by stimulating on single electrodes and on two electrodes simultaneously at a frequency of 70 Hz during about 0.5 s, with a phase lag between the two stimulation sequences of 180°. Force addition can provide information about overlap of recruited motor neuron groups. The intrafascicular electrode configuration was investigated at small force levels, corresponding to a few motor units. The extraneural electrode configuration was used also at medium and high force levels upto a quarter of the maximum force level per electrode.

MATHEMATICAL MODEL OF NERVE STIMULATION

We developed a model of nerve stimulation, consisting of four parts: the volume conduction model of the stimulated nerve describes the potential field in the nerve during stimulation. The second part describes the excitation of myelinated nerve fibres lying in the potential field inside the fascicle of the stimulated nerve. Furthermore, probability distributions of some nerve fibre excitation parameters were incorporated, and the last part of the model describes the isometric force amplitudes of muscle twitches when the stimulated nerve incorporates motoneurons of a muscle.

Volume conduction model of a stimulated nerve

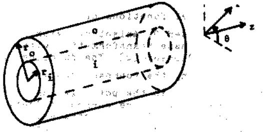


Figure 2: A two cylinder model of a nerve. The inner cylinder represents the boundary of the fascicle i. In between inner and outer cylinder the connective tissue o surrounding the fascicle is located. Outside the outer cylinder the extraneural medium e is situated.

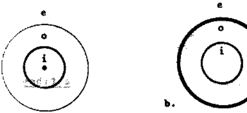


Figure 3: The electrode configurations considered:
a. an intrafascicular point electrode
b. an extraneural ring electrode.

We developed a volume conduction model of a stimulated nerve supposing a cylindrical symmetric nerve geometry with one fascicle (fig. 2). The medium i within the inner cylinder represents the fascicle. Medium o, in between inner and outer cylinder represents the connective tissue surrounding the fascicle. Medium e, external to the outer cylinder, represents the medium outside the nerve. Media o and e were assumed to be homogeneous, with conductivities σ_o and σ_e respectively. Medium i was supposed to be anisotropic with conductivity σ_{iz} in z direction and σ_{ir} perpendicular to this direction [2],[3]. A cylindrical coordinate system z, r, θ was used. Two cylindrical symmetric stimulation configurations were considered: an intrafascicular point electrode in the origin $r=o$, $z=o$ (fig. 3a), and an extraneural ring electrode $r=r_o$, $z=o$ (fig. 3b).

The electrical potential $V(z,r,\theta)$ fulfils the Laplace equation in cylindrical coordinates. The solution of this differential equation in the case of a cylindrical symmetric geometry is given by [2],[3]:

$$V(z,r,\theta)=\frac{1}{2\pi}\int_{-\infty}^{\infty}[g_0(k).I_0(|k|.r)+h_0(k).K_0(|k|.r)]e^{jkz}dk \tag{1}$$

I_0 and K_0 are modified Bessel functions of the first and second kind respectively and of order 0. Anisotropy within the fascicle can be included by a coordinate transformation within the fascicle, as described by Plonsey [2]. The functions $g_0(k)$ and $h_0(k)$ can be determined using the boundary conditions at the cylinder surfaces (continuity in the potential and normal current density), for $r=o$ and $r\to\infty$, and at the current injection point representing the electrode ($r=o$ for the intrafascicular point electrode and $r=r_o$ for the extraneural ring electrode). The boundary conditions were written in a matrix form and by matrix inversion the functions $g_0(k)$ and $h_0(k)$ were determined. From this, the electrical potential at any point was calculated.
In the stimulation model cathodic monophasic constant current pulses were simulated, having an amplitude A and a constant pulse width of 60 µs:

$$\begin{array}{lll} I(t & = -A & 0 <= t < 60\ \mu s \\ & = 0 & \text{otherwise} \end{array} \tag{2}$$

Model of the excitation of myelinated nerve fibres

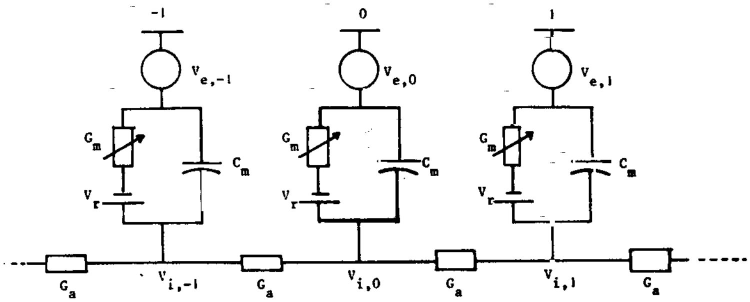


Figure 4: Network representation of a myelinated nerve fibre, as introduced by McNeal [4].

We used a model of excitation of myelinated nerve fibres as was described by McNeal [4]. The model was based on the work of

Frankenhaeuser and Huxley [5] who described the electrical behaviour of a node of Ranvier with a set of four non-linear differential equations. McNeal represented a myelinated nerve fibre by an electrical network (fig. 4). The nodes of Ranvier were modeled as lumped electrical components: membrane conductance G_m, nodal capacitance C_m and the nerve fibre resting potential V_r. Internally the nodes were connected via a conductance G_a. These components depended on the external myelin diameter D, which McNeal assumed to be proportional to the internodal length L. The nerve fibre model consisted of 11 nodes of Ranvier, numbered -5 to 5. Node 0, in the current injection plane perpendicular on the nerve fibres, was described by the Frankenhaeuser-Huxley equations [5]. G_m of the other nodes was taken constant.

We used the model of McNeal with the same parameter values, but the following exceptions:

- Since we were interested in the effects of cylindrical inhomogenities, we situated the nerve fibres in the inner cylinder of the volume conduction model as presented above and not in a homogeneous isotropic medium.
- Node 0 was not necessary in the current injection plane perpendicular to the nerve fibres. We defined node 0 as the node at the shortest distance L_0 from this plane (figure 5).
- Besides the membrane conductance of node 0 also the nodes -1 and 1 were described by the Frankenhaeuser-Huxley equations. The other 8 nodes were described with constant G_m.

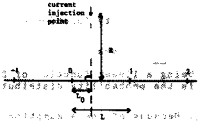


Figure 5: L_0 is the distance from the current injection plane perpendicular to the nerve fibres to the node lying nearest to that plane (node 0).

Probability distributions

When a nerve is stimulated, the exact position and characteristics of individual nerve fibres are unknown. In our model we assumed nerve fibre excitation to depend on four parameters: the external myelin diameter D, the distance r to the axis of fascicle cylinder, distance L_0 from node 0 to the current injection plane perpendicular on the fibre, and the stimulation pulse amplitude A. The internodal length L is assumed to be dependent on D. Because of cylinder symmetry, excitation probability does not depend on θ.

We defined a discrete sample space Ω, consisting of all the motoneurons in the stimulated nerve. On this sample space we define four random variables: $\underline{D}$, $\underline{r}$, L_0 and $\underline{A}$. $\underline{A}$ is the excitation amplitude, defined as the stimulation pulse amplitude above which a nerve fibre is excited, and below which it is not excited. $\underline{A}$ is a function of $\underline{D}$, $\underline{r}$ and $\underline{L_0}$.

For evaluation of the radius dependency of nerve fibre excitation for given diameter we define the function $g_{\underline{A}|\underline{D}}(r)$ by:

$$g_{\underline{A}|\underline{D}}(r) = f_{\underline{r}|\underline{D}}(r|D) \cdot \int_{-L(D)/2}^{L(D)/2} f_{\underline{L_0}|\underline{D},\underline{r}}(L_0|D,r) . F_{\underline{A}|\underline{D},\underline{r},\underline{L_0}}(A|D,r,L_0) . dL_0 \qquad (3)$$

$f_{\underline{r}|\underline{D}}(r|D)$ is the probability density function of $\underline{r}$ for given nerve fibre diameter D. Assuming the geometrical distribution of motoneurons of a certain diameter over the fascicle to be uniform and because of the cylinder symmetry assumed, we find a linear relation between radius r and $f_{\underline{r}|\underline{D}}(r|D)$.

$f_{\underline{L_0}}(L_0)$ is the probability density function of $\underline{L_0}$. We assume a uniform distribution of $\underline{L_0}$ between -L(D)/2 and L(D)/2, the internodal length L being a linear function of D.
$F_{\underline{A}|\underline{D},\underline{r},\underline{L_0}}(A|D,r,L_0)$ is the probability distribution function of $\underline{A}$ for given D,r and L_0. Because of the assumption that A only depends on D,r and L_0, this probability is 0 under a certain threshold $A_t(D,r,L_0)$ and 1 above this threshold.

Integration of $g_{\underline{A}|\underline{D}}(r)$ over r yields the excitation probability distribution $F_{\underline{A}|\underline{D}}(A|D)$ as a function of A for given D:

$$F_{\underline{A}|\underline{D}}(A|D) = \int_0^{r_i} g_{\underline{A}|\underline{D}}(r).dr \qquad (4)$$

$F_{\underline{A}|\underline{D}}(A|D)$ represents the recruitment curve for fibres with a given diameter D.

The probability of nerve fibre excitation $P_{exc}(A)$ for unknown values of D, r and L_0 and as a function of the stimulation pulse amplitude A equals the probability distribution function $F_{\underline{A}}(A)$.

$P_{exc}(A)$ can be expressed as follows:

$$P_{exc}(A) = F_{\underline{A}}(A) = \int_0^\infty f_{\underline{D}}(D).F_{\underline{A}|\underline{D}}(A|D).dD \qquad (5)$$

$f_{\underline{D}}(D)$ is the probability density function of $\underline{D}$. It might be obtained from a statistical analysis of nerve fibre diameters in many nerves.

Because the diameter dependency of nerve fibre excitation is important in the application for functional neuromuscular stimulation $g_{\underline{A}|\underline{D}}(r)$ and $F_{\underline{A}|\underline{D}}(A|D)$ were evaluated in our simulations.

A model for the amplitude of isometric twitch force

We define random variable $\underline{T}$, representing the amplitude of the isometric twitch force of the muscle activated by the stimulated nerve. Using (5), the expectation of T for a stimulation pulse amplitude A can be expressed as:

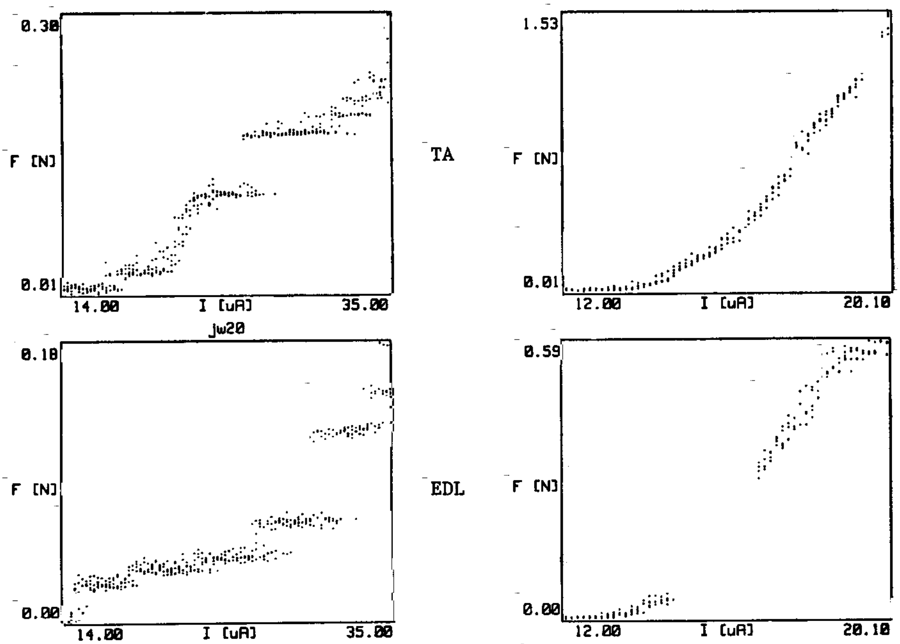
$$E[\underline{T}]\ (A) = \int_0^\infty M(D).f_{\underline{D}}(D).F_{\underline{A}|\underline{D}}(A|D).dD \qquad (6)$$

In (6) only the population of motoneurons within the nerve must be considered. A linear summation of the isometric twitch force of the motor units is assumed. According to literature the amplitude of the motor unit twitch force M(D) increases with the diameter D of the motoneuron innervating the motor unit [6].

RESULTS

Experimental results

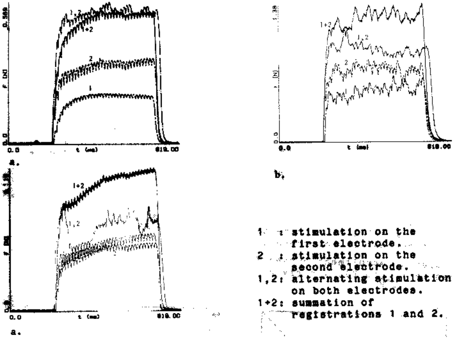
The recruitment curves clearly showed discrete force levels in part of the intrafascicular stimulation registrations. Not in all cases, because insertion of the intrafascicular electrodes without damaging the fascicle was difficult. A varying force step between successive force levels was seen, also at the beginning of the recruitment curves, indicating varying recruitment of thick and thin nerve fibres. Figure 6a gives an example of two recruitment curves simultaneously measured on the muscles TA and EDL during intrafascicular nerve stimulation. Discrete force levels can be seen, corresponding to the sum of the discrete motor unit contributions. The discrete force levels are more clearly recognizable for larger stimulation pulse amplitude range for the EDL muscle than for the TA muscle. Reasons could be the higher number of motor units and corresponding motoneurons for the TA muscle than for the EDL muscle or a non-uniform mixing of motoneurons of both muscles over the fascicle cross section. For extraneural electrodes discrete force levels were never clearly recognizable. Figure 6b gives a typical example. This difference points to a potentially more stable recruitment for intrafascicular stimulation than for extraneural stimulation.



a. b.

Figure 6: Typical results of twitch force amplitudes simultaneously measured on the TA and EDL muscles during stimulation of the N. Peroneus Communis of rat. The twitch amplitudes were determined several times for every stimulation pulse amplitude.
a. intrafascicular electrode.
b. extraneural electrode.

Stimulation on intrafascicular electrodes at 70 Hz often showed stable near tetanic force levels (figure 7a). When a stable near tetanic force level was obtained for the intrafascicular stimulation method, good summation was observed in part of the registrations. Apparently non-overlapping motor unit groups were not always recruited. For all combinations of two electrodes no systematic differences were observed in these results.



1 : stimulation on the first electrode.
2 : stimulation on the second electrode.
1,2: alternating stimulation on both electrodes.
1+2: summation of registrations 1 and 2.

Figure 7: Typical examples of near tetanic force registrations at 70 Hz stimulation frequency.
a. two stable registrations series for the intrafascicular electrode configuration.
b. extraneural electrode.

For extraneural electrodes, lack of recruitment stability was observed for near tetanic force registrations: recruitment was not stable. Figure 7b shows a typical example. Furthermore summation of force levels for combinations of two electrodes never was seen to be complete. In the first twitches the summation mostly was best. No systematic differences in force summation were observed for all possible combinations of two extraneural electrodes.

Simulation results

The nerve stimulation model described, was simulated on a hp9000/300 system programmed in PASCAL. Most of the parameter values of the volume conduction model of the nerve were obtained from literature. The conductivities $\sigma_{ir} = 0.08\ (\Omega m)^{-1}$ and $\sigma_{iz} = 0.5\ (\Omega m)^{-1}$ were obtained from Geddes and Baker [7]. The low extraneural conductivity $\sigma_e = 0.001\ (\Omega m)^{-1}$ models an almost electrical isolation of the nerve from the surrounding tissue, which corresponds to the stimulation conditions during our nerve stimulation experiments. The conductivity of the connective tissue surrounding the nerve fascicle was not found in literature. We assumed $\sigma_o = 0.1\ (\Omega m)^{-1}$, somewhat higher than the conductivity of fat, which is about $0.04\ (\Omega m)^{-1}$ according to Geddes and Baker. The radius of the inner cylinder $r_i = 0.5$ mm is in reasonable correspondence with the fascicle in the rat N. Peroneus Communis stimulated during our experiments (figure 1). Simulations were done for two values of the thickness of the extrafascicular connective tissue sheath $r_o - r_i$: 0.03 mm and 0.5 mm. We used as a criterium for nerve fibre excitation a membrane potential change of node 0 of more than 50 mV at 200 µs after the end of the 60 µs stimulation pulse.

Figure 8 shows $g_{\underline{A}|\underline{D}}(r)$ for the intrafascicular point electrode and the extraneural ring electrode at several values of D. The diagonal line represents excitation of all nerve fibres and corresponds to the probability density function of $\underline{r}$. Calculated recruitment curves for given nerve fibre diameters, as given by $F_{\underline{A}|\underline{D}}(A|D)$, are given in figure 9 for both values of $r_o - r_i$.

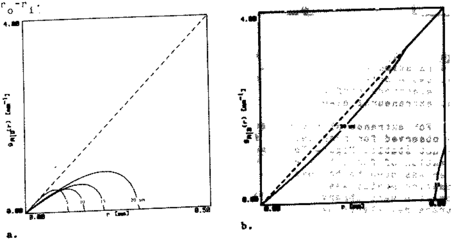
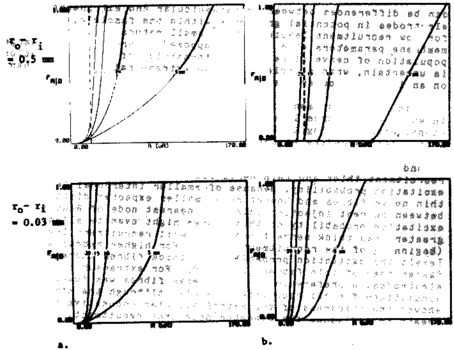


Figure 8: Excitation probability function $g_{\underline{A}|\underline{D}}(r)$ as a function of radius r at one stimulation pulse amplitude for four nerve fibre diameters D: 5, 10, 15 and 20 µm. $r_o - r_i = 0.5$ mm.

a. intrafascicular point electrode: the stimulation pulse amplitude is 20 µA.
b. extraneural ring electrode: the stimulation pulse amplitude is 29 µA.



<u>Figure 9</u>: Excitation probability distribution function $F_{A|D}(A|D)$ as a function of stimulation pulse amplitude A for four nerve fibre diameters D: 5, 10, 15 and 20 µm and for two values of the extrafascicular connective tissue sheath: $r_o - r_i$ = 0.5 mm and 0.03 mm.
a. intrafascicular point electrode.
b. extraneural ring electrode.
The dashed vertical lines marks the stimulation pulse amplitudes used in figure 8.

DISCUSSION

A more stable recruitment could be obtained with intrafascicular electrodes than with extraneural electrodes, despite the rather thin extrafascicular connective tissue sheath at some places around the nerve (figure 1). There are several possible explanations for this difference in stability: Simulations show that especially when only a small part of the motoneuron population is excited, the recruitment is less sensitive for changes of the extrafascicular connective tissue sheath when stimulating with an intrafascicular electrode than with an extraneural electrode (compare the results for $r_o - r_i$ = 0.5 mm and 0.03 mm in figure 9). In practice the conduction in the connective tissue sheath can vary with time, e.g. because of the influence of blood vessels and other structures in this sheath. Another reason for difference in recruitment stability can be differences between intrafascicular and extraneural electrodes in potential gradients within the fascicle, especially for low recruitment levels. When a small natural fluctuation of membrane parameters with time is supposed, there will be a larger population of nerve fibres around threshold, of which excitation is uncertain, when stimulating on an extraneural electrode than on an intrafascicular electrode.

In the recruitment curves of the intrafascicular electrodes in which clear force levels could be seen, not only big force steps, corresponding to thick nerve fibres, but also smaller steps, corresponding to thin nerve fibres, were observed, also at low recruitment levels. This corresponds to the diameter dependent recruitment curves found in the simulations. At small recruitment thick and thin nerve fibres have a comparable excitation probability. Because of smaller internodal length for thin nerve fibres and therefore a smaller expected distance between current injection point and nearest node of Ranvier, the excitation probability of thin fibres might even be slightly greater than thick nerve fibres for small recruitment levels (beginning of the recruitment curve). For higher recruitment levels the excitation probability of thick fibres increase much faster than of thin fibres (figure 9). For extraneural electrodes, a preference of thick nerve fibres was found in the simulations for all recruitment levels, although the simulations showed the thickness of the extrafascicular connective tissue sheath to influence the diameter dependent recuitment.

The simulations showed that the recruitment areas of thick nerve fibres were larger than of thin nerve fibres (figure 8). This indicates that overlap of recruitment areas of different stimulation electrodes is first to be expected for thick nerve fibres. We did not investigate this in our experiments.

REFERENCES

[1] P.H. Veltink, H.J. Hermens and J.A. van Alsté, "Multi-electrode intrafascicular and extraneural stimulation", Proc. 8th An. Conf. of the IEEE Eng. in Med. and Biol. Soc., Dallas, pp. 690-693, Nov. 1986

[2] R. Plonsey, "The Active Fiber in a Volume Conductor", IEEE Trans. Biomed. Eng., Vol. BME-21, pp. 371-381, 1974

[3] D.F. Stegeman, J.P.C. de Weerd and E.G.J. Eijkman, "A Volume Conductor Study of Compound Action Potentials of Nerve in situ: the Forward Problem", Biol. Cybernetics, Vol. 33, pp. 97-111, 1979

[4] D.R. McNeal, "Analysis of a Model for Excitation of Myelinated Nerve", IEEE Trans. Biomed. Eng., Vol. BME-23, pp. 329-337, 1976

[5] B. Frankenhaeuser and A.F. Huxley, "The Action Potential in the Myelinated Nerve Fibre of Xenopus Laevis as computed on the basis of Voltage Clamp Data", J. Physiol.,Vol. 171, pp. 302-315, 1964

[6] L.A. Geddes and L.E. Baker, "The Specific Resistance of Biological Material - A Compendium of Data for the Biomedical Engineer and Physiologist", Med. & Biol. Eng., Vol. 5, pp. 271-293, 1967

[7] E. Henneman, "Recruitment of Motoneurons: the Size Principle", in: J.E. Desmedt (Ed.), "Motor Unit Types, Recruitment and Plasticity in Health and Disease", Prog. Clin. Neurophysiol., Vol. 9, Basel, Karger, 1981,pp. 26-60