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A COMPUTATIONAL TECHNIQUE FOR DETERMINING THRESHOLD OF A MYELINATED NERVE FIBER FOR ARBITRARY ELECTRODE GEOMETRIES

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SUMMARY

A model of a myelinated nerve fiber is presented which allows the computation of current and potential at each of the nodes of Ranvier, prior to the initiation of an action potential, during constant-current stimulation through electrodes that are external to the fiber. A method for calculating threshold is demonstrated. Although the model is valid for arbitrary electrode geometries, results are presented in this paper only for bipolar electrodes oriented along the nerve. For this configuration, the variation in threshold with changes in electrode spacing is shown to have a minimum at about two internodal lengths. This result is compared with experimental data.

The model is presented as a tool which can be used to yield a better understanding of the influence of electrode geometry on the excitation process of myelinated nerve. Hopefully, this will eventually lead to an analytical method for the design of electrodes to be used in future applications of peripheral and central stimulation.

INTRODUCTION

Electrode design for neuro-stimulation has generally been determined by intuition, limited experimental data and the practicalities of fabrication rather than through analytical determination. This approach has been adequate in most current clinical applications, as efforts to develop workable, clinically-functioning stimulation systems have rightly concentrated on other problems of greater significance. But now as more sophisticated systems are being proposed, the need for a comprehensive analytical model of nerve stimulation becomes imperative.

Electrodes based on old designs, while partially effective, can no longer be relied on for future systems. Implanted battery-powered stimulators as well as micro-miniaturized external systems will require electrodes designed to minimize the current required for stimulation in order to reduce battery drain. As the clinical demand for more precise control of motor and sensory functions increases, electrodes must be designed to be very specific with regard to the neuronal populations excited. These and other equally important problems can be investigated only after an adequate analytical model has been developed.

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The purpose of this paper is to present and analyze a model for a myelinated nerve fiber which allows the computation of the transverse membrane current and membrane potential at each of the nodes of Ranvier following the application of a constant stimulus current. The model will predict both subthreshold response and the response up to the time of excitation for suprathreshold stimuli. Analytically determined strength-duration curves can be calculated for arbitrary electrode configurations.

MODEL

A myelinated nerve fiber can be approximated by the equivalent electrical network shown in Figure 1. The following assumptions have been made in deriving this model. The fiber is infinitely long, with nodes that are regularly spaced. Both internodal spacing and axon diameter are assumed to be proportional to fiber diameter. The myelin sheath is a perfect insulator so transverse membrane current flows only at the nodes. The electrical potential outside the fiber is determined only by the stimulus current, electrode geometry and tissue around the fiber, and it is not distorted by the presence of the fiber. This is reasonable since the dimensions of a single fiber are small and because our interest is limited to the period of time prior to excitation (before internally generated currents become significant). The small dimensions of the nerve also allow the simplification that the external surface of the membrane at any one node is at an equipotential. This implies that variations in the membrane current density over the nodal surface can be neglected.

In this paper, it will be assumed that the medium external to the nerve is infinite and isotropic. This assumption is not vital to the model, and both anisotropic and finite external mediums can be considered. Calculation of the potential throughout the medium, of course, becomes more complex as more realistic models for the external environment are formulated.

The internodal conductance G_a and the membrane capacitance C_m are constants for a given fiber diameter. For stimuli less than 80% of threshold, it can also be assumed that the membrane conductance G_m is constant. As threshold is approached, however, the membrane conductance at the node or nodes which are maximally depolarized begins to change markedly as the membrane becomes more permeable to sodium ions.

The accuracy of the assumption that G_m is constant for subthreshold stimuli is demonstrated in Figure 2. In this example, the fiber diameter is 20 µm and a monopolar electrode is located above and 1 mm away from one of the nodes. The change in membrane potential at this node is shown for a one millisecond pulse at various stimulus amplitudes. All responses are normalized by dividing the membrane potential by the stimulus current. Assuming G_m is constant at all nodes, it can be shown that the normalized response for all stimulus amplitudes, because of system linearity, is given by the single dashed line. Allowing G_m to vary as predicted by the Frankenhaeuser-Huxley equations for myelinated nerve membrane, we get the family of solid lines each representing a different stimulus amplitude. The threshold response at .127 ma is shown along with subthreshold responses at .126, .114 and .102 ma, the last two being 90% and 80% of threshold.

Obviously, as threshold is approached, the assumption that G_m is constant becomes invalid since the actual membrane potential deviates significantly from the result predicted by the linear model. The assumption is quite good, however, for subthreshold stimuli that are 80% or less than threshold. At 80% of threshold, the response obtained by assuming that membrane conductance is constant is within 3% of that predicted by the more exact representation over the entire one-millisecond period. The match is even better at lower stimulus levels. Similar results are obtained for shorter pulse durations.

In summary, the response to subthreshold stimuli is adequately modelled by the equivalent circuit shown in Figure 1 with all electrical components constant. For near-threshold and suprathreshold stimuli, the membrane conductance G_m at the node of maximum depolarization must be allowed to vary with membrane potential. G_m can still be considered to be constant, however, at the rest of the nodes. This simplifies computation considerably since the variation in G_m is modelled by a complex, nonlinear fourth-order differential equation. There will be some occasions (e.g., a monopolar electrode located exactly between two nodes)where the maximum depolarization occurs at two nodes. In these cases, G_m must be permitted to vary at both nodes.

In any case, the model is described by an infinite set of differential equations for the membrane potential at each of the nodes. An approximate solution of these equations can be obtained by selecting a finite set of differential equations that enclose the nodes of interest and then integrating the finite set. If the set of differential equations is large enough it can safely be assumed that the membrane potential at all nodes outside the selected set is zero. In practice, it has been found that selecting a set that includes ten nodes on either side of the cathode is more than adequate.

RESULTS

First, consider the subthreshold response of a 20 μm fiber with an internodal spacing of 2 mm to a monophasic, constant-current stimulus of 0.1 ma. The electrodes are assumed to be spherical, each located 1 mm from the nerve. The spacing between electrodes will be varied, but the cathode will be located directly over one of the nodes. For reference, each node is assigned a number with the node directly beneath the cathode taken to be 0.

The transverse membrane current at each node at 100 μsec for interelectrode spacings of 1, 3 and 5 mm is shown in Figure 3. Positive current indicates current flowing out of the nerve. As one would expect, the largest positive current occurs at node 0, the node closest to the cathode, while the largest negative currents occur near the anode. Currents at all other nodes are not very significant. Note that the positive current at node 0 increases as interelectrode spacing is increased.

These currents are not stationary with time. This can be seen in Figure 4 where the transverse membrane currents at nodes -4 to 2 are shown as a function fof time for an interelectrode spacing of 5 mm. The depolarizing current at node 0 falls from an initial value of 1780 picoamperes to a steady state value of 380 picoamperes. Most of this fall-off occurs during the first 20 μsec after the initiation of the stimulus current. Initially, current is positive only at nodes 0 and -4, however, the current at the nodes adjacent to node 0, while initially negative, becomes positive during the first 20 μsec. It is seen in this figure, that the nodal currents in response to a constant-current stimulus are far from constant--at least during the first 40 μsec.

It is also interesting to note that the average total current flowing through the nerve during a 100 μsec pulse is less than 7/1,000,000 of the applied stimulus current even though the electrodes are only 1 mm away.

The effect of these currents on the membrane potential is shown in Figure 5. Only node 0 shows significant depolarization, although node -4 is also depolarized. Nodes 1 and -1 are initially hyperpolarized, but both are depolarized later in time in response to the change in direction of current at these nodes which was seen in Figure 4.

It is clear from Figure 5 that excitation will initially occur at node 0. To calculate threshold, the membrane conductance of this node is allowed to vary in accordance with the Frankenhaeuser-Huxley equations. Current amplitude is then adjusted to find the minimum current that will produce an action potential at node 0. This value is threshold.

The following question will now be considered: how does threshold vary with the spacing between electrodes. The answer for a monophasic, constant-current 100 μsec pulse is shown by the solid line in Figure 6. The cathode is assumed to remain fixed above node 0 while the anode is moved along the length of the fiber. It is seen that a minimum is predicted at an interelectrode spacing of about 4 mm (a distance of two internodal lengths). This means that threshold for a bipolar electrode spaced 4 mm apart is 15% less than for a monopolar electrode. Threshold rises rapidly when the distance between electrodes becomes less than one internodal length. The fluctuations apparent in the curve are due to the anode passing over successive nodes.

The dashed line in Figure 6 is obtained by assuming that the membrane conductance is constant at all nodes (even at node 0) and that there is a critical value of membrane potential at which excitation will occur. The critical value used to calculate the dashed line is 24 mv. Good agreement is found between the two curves--there is less than a 3% error over the range of interelectrode spacing from 1 mm to infinity. This means that the constant conductance model can be used to determine threshold for various electrode configurations. This is a tremendous computational advantage since threshold can be determined from a single calculation of the subthreshold response, eliminating repeated iterative solutions of the nonlinear equations. It must be remembered, however, that the critical value of potential at which excitation is assumed to occur is a function of pulse duration.

The minimum in threshold versus interelectrode spacing predicted by the model has also been found experimentally. Threshold data for a frog sciatic nerve placed in saline with cylindrical electrodes next to the nerve are shown in Figure 7. Minimum threshold is obtained when the electrodes are approximately 8-10 mm apart. No attempt was made to determine the internodal length of those fibers with the lowest threshold so it is impossible to compare results directly. For the minimum to occur at two internodal lengths would require the internodal length to be 4-5 mm. This is not impossible, but does seem to be on the high side. Further experimental investigations will be carried out.

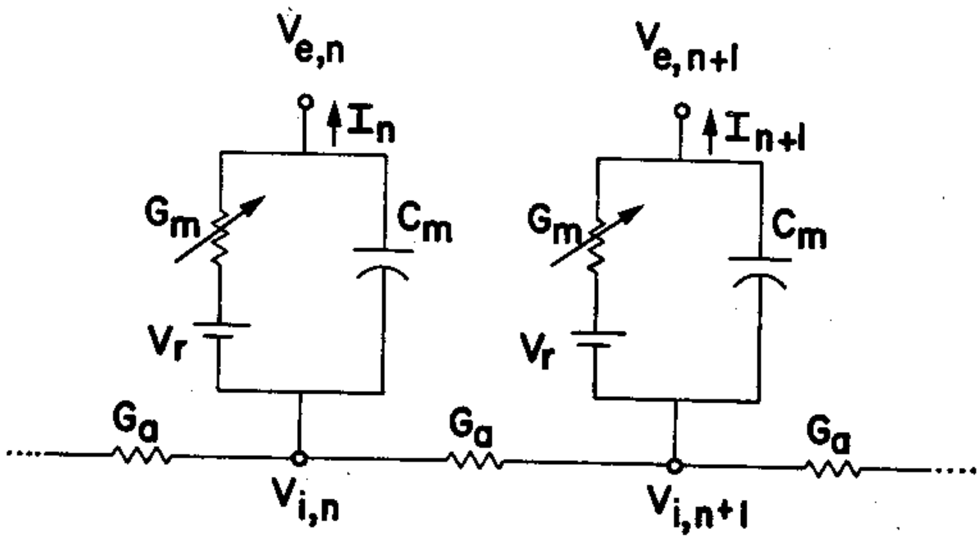


Fig. 1 Electrical network model for a myelinated fiber.

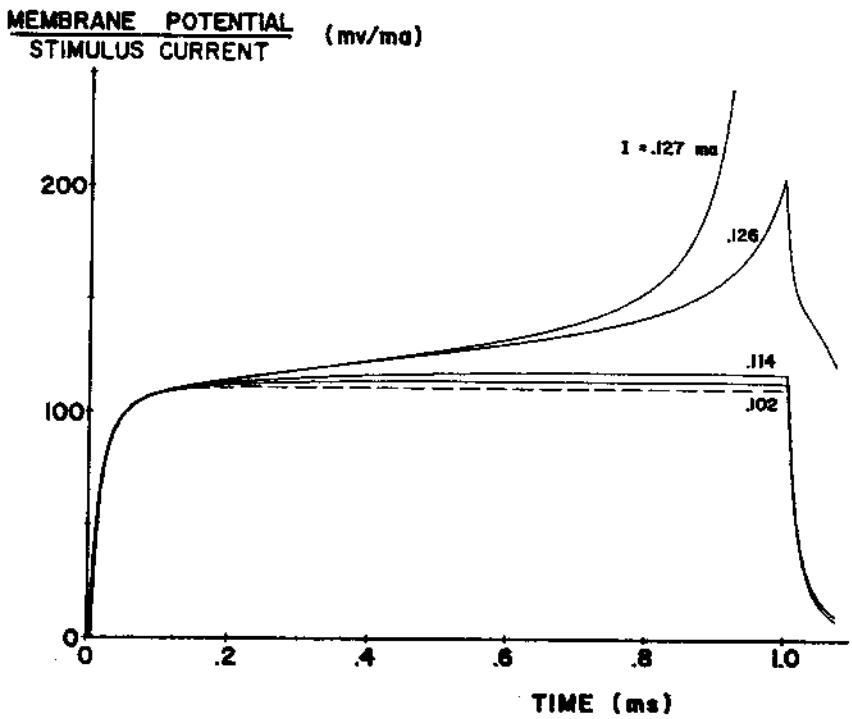


Fig. 2 Normalized potential at node beneath the cathode for a one-millisecond monophasic, constant-current stimulus. The threshold response (.127 ma) is shown along with subthreshold responses of .126, .114 and .102 ma, the last two being 90% and 80% of threshold. The dashed line is the normalized potential assuming linearity (constant membrane conductance). Note: Membrane potentials are shown as deviations from the resting potential.

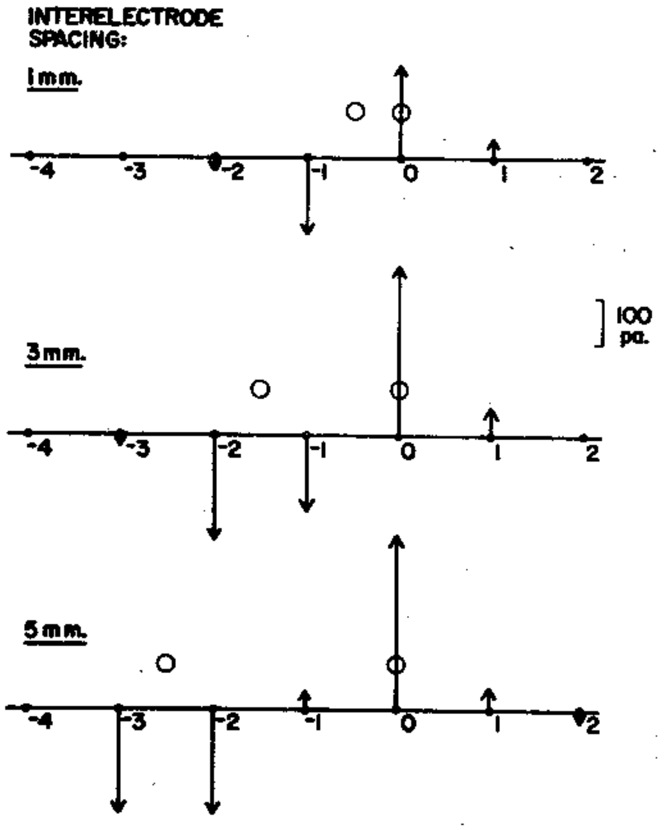


Fig. 3 Transmembrane current at nodes of a 20 μm fiber (intermodal spacing of 2 mm) at 100 μsec after a constant-current stimulus of 0.1 ma. Electrode position is indicated by the two circles above the nerve.

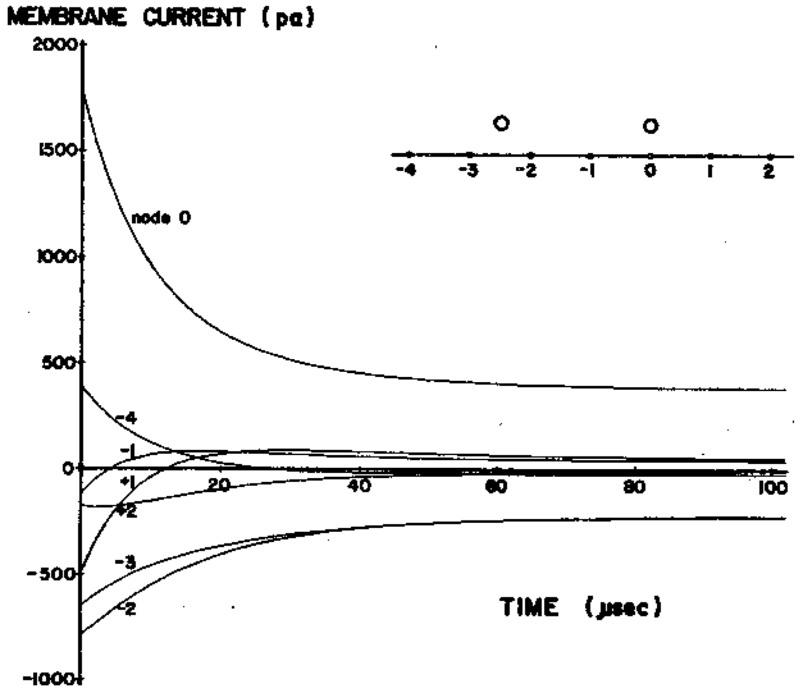


Fig. 4 Transmembrane current at nodes of a 20 μm fiber following a constant-current stimulus of 0.1 ma. Spacing between electrodes is 5 mm.

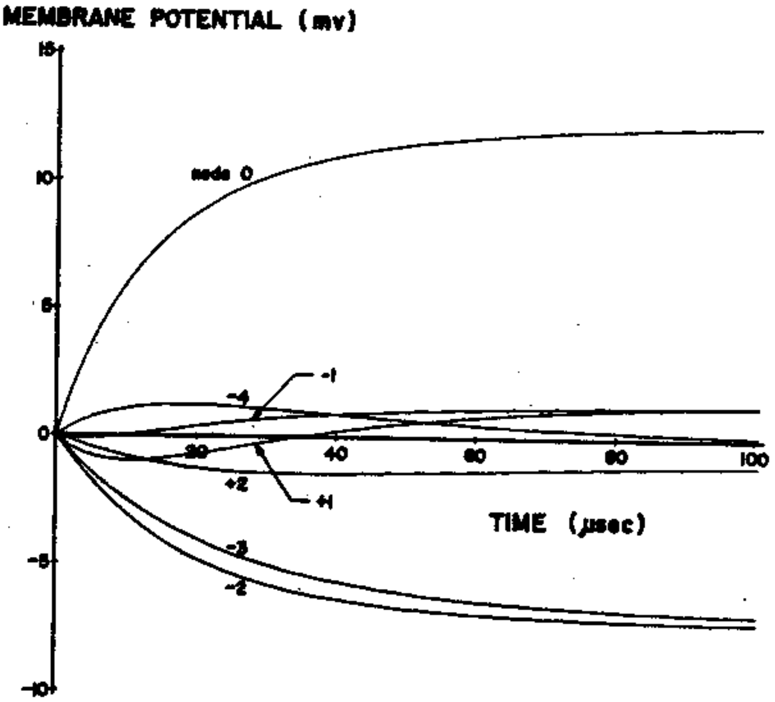


Fig. 5 Potential at nodes of a 20 μm fiber following a constant-current stimulus of 0.1 ma. Spacing between electrodes is 5 mm. Note: Membrane potentials are shown as deviations from the resting potential.

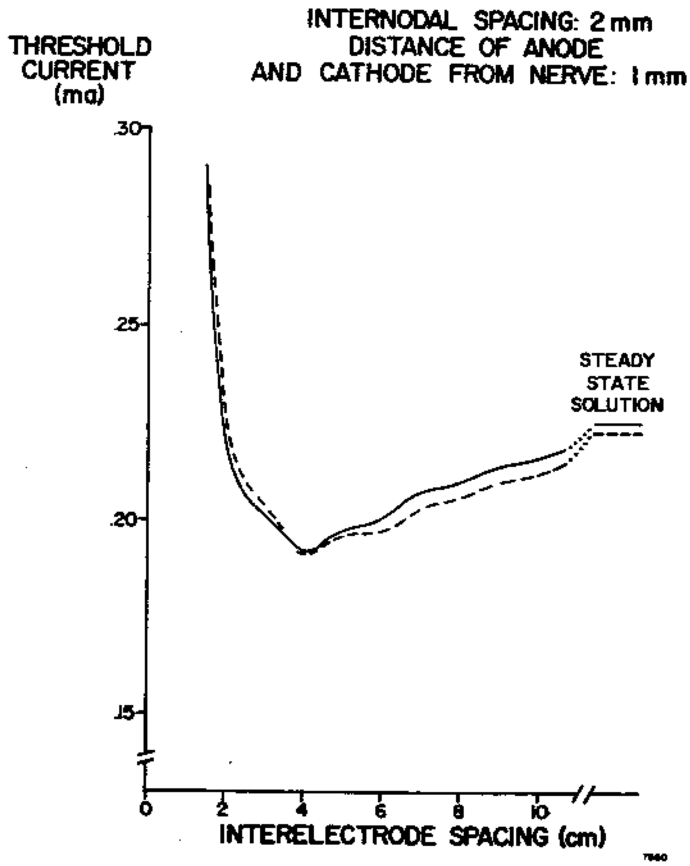


Fig. 6 Threshold as a function of spacing between bipolar electrodes (computer simulation). Dashed line indicates results obtained from linear model.

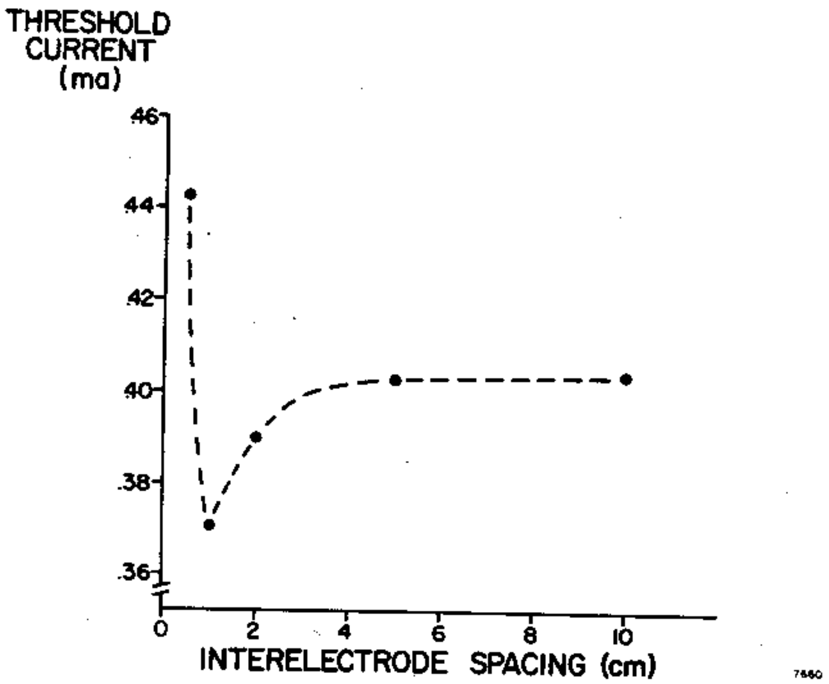
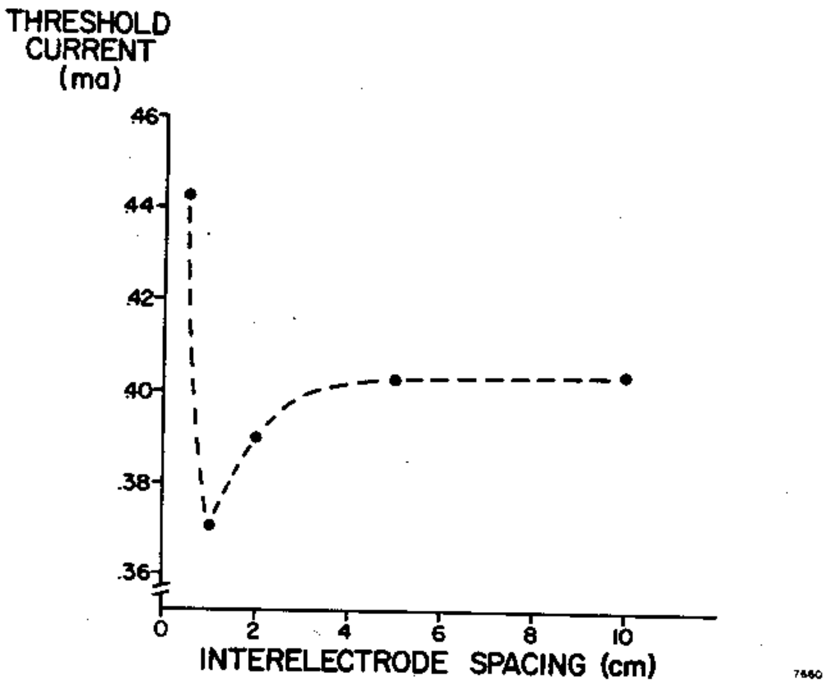


Fig. 7 Threshold as a function of spacing between bipolar electrodes (experimental data).



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