Theoretical Study of Transmembrane and Extracellular Potentials under Propagation Block Due to Geometrical Inhomogeneity

N. DIMITROVA

CLBA, Centre of Biology, Bulgarian Academy of Sciences, Acad. G. Bonchev str., bl 105, 1113 Sofia, Bulgaria

Abstract. A mathematical model was used to study transmembrane and extracellular potentials produced by active geometrically inhomogeneous excitable structures under conditions of propagation block. The structures were electrical analogues of intact or damaged unmyelinated nerve fibres, of the soma to axon transition, or of branching axons or dendrites. It was shown that: (1) damage to a cell is equivalent to the presence of a geometrical inhomogeneity, namely of a region of increased diameter; (2) propagation block caused by a geometrical inhomogeneity, results in: (a) a sharp decrease in the calculated transmembrane potential amplitude not only for the blocked region but also before it; (b) a considerable increase in the amplitude of both the negative phase of extracellular potentials at the points of the volume conductor preceding the blocked region and the first positive phase at points in the proximity of the region; (c) a more pronounced increase in the first positive phase amplitude at small radial distances, if the geometrical inhomogeneity is short compared with the length constant (λ); (3) the membrane damage results in recording of potentials resembling "giant" ones.

Key words: Mathematical model — Propagation block — Damage — Transmembrane potentials — Extracellular potentials

Introduction

Propagation block, as a mechanism for diminishing the spread of excitation, is an object of theoretical and experimental studies. Geometrical inhomogeneities affect the propagation of an action potential (Khodorov et al. 1969; Ramon et al. 1975; Dimitrova 1987, 1988) and may cause propagation block (Khodorov et al. 1969; Khodorov and Timin 1975; Dimitrova 1987).

As a rule, excitable structures are inhomogeneous. An inhomogeneity can be a geometrical one representing a region where the diameter changes (a soma to axon transition or branching of axons or dendrites) or it can be electrical

analogue of geometrical changes. For example, lack of longitudinal currents at insulated terminations of a skeletal muscle fibre (tendons) or at thin endings of dendrites or nerves (Rinzel 1976), is equivalent to a sharp decrease in the structure's diameter (Dimitrova 1988).

Damage to a structure can lead to physical, and consequently, to electrical contact between the intra- and extracellular media. When the damage is severe (for example, the structure is cut), the intracellular and extracellular potentials become equal, and the transmembrane potential tends to zero at the site of damage. As a first approximation, we classify such a damage as a disturbance of geometrical homogeneity.

The aim of the present paper was to study transmembrane and extracellular potentials produced by an excitable structure under action potential propagation block due to the presence of either a geometrical inhomogeneity or a disturbance of the homogeneity, as described above.

Materials and Methods

The method used was mathematical modelling. The transmembrane potentials were calculated on the basis of the Hodgkin—Huxley (1952) model by the method described by Joyner et al. (1978). This model was chosen because it describes well changes in the cable properties of excitable structures (Ramon et al. 1975). The structures were divided into equal segments 12.5 μm long; the time step was 10 μs, the temperature was 20 °C. The structures were "stimulated" by a rectangular pulse of current. The stimulus strength was of the order of 1.5 times the threshold value, and its duration was 200 μs. The membrane parameters used were the same as those typical for a giant axon (Hodgkin and Huxley 1952; Khodorov et al. 1969; Ramon et al. 1975). The following boundary conditions were used at the end of the structure:

$V_{i+1} = V_i$ — corresponded to the insulated end;

or $V_{i+1} = 0$ — corresponded to the grounded (damaged) end.

The following types of structures were studied: (1) a cylindrical fibre with the end grounded; the fibre diameter was 50 μm; (2) a cylindrical (initial) fibre interconnected with a region of increased diameter (d_r) terminated by the insulated or grounded end. The initial fibre diameter (d) was also 50 μm.

Inhomogeneous structures were characterized by the length (L) of the region of increased diameter and by the ratio of diameters (K_d) of the region and of the initial fibre $\left(K_d = \frac{d_r}{d}\right)$. When compared with their length constants (λ_r), the regions were short ($L = 10d$, $K_d = 10$ or $L = 25d$, $K_d = 20$) or long ($L = 112.5d \approx \lambda_r$, $K_d = 5$). The term "inhomogeneity" will be used to define the region of increased diameter throughout in the text.

The transition between the initial fibre and an inhomogeneity was always at the 350th segment (the axial distance from the point of stimulus application $z = 4.375$ mm). The structure's end was: at the 450th segment ($z = 5.625$ mm) for a cylindrical fibre with the end grounded, and for an inhomogeneity $25d$ long; at the 800th segment ($z = 10$ mm) for the longest inhomogeneity ($L = 112.5d$); and at the 390th segment ($z = 4.875$ mm) for the shortest one ($L = 10d$).

The extracellular potentials were calculated as described earlier (Dimitrova 1974; 1987), at

points with the following coordinates: the axial one (x) was from 2.6 to 6.8 mm in 0.3 mm steps, and the radial one (y) was 0.125; 0.5 and 2 mm. Only one wave of depolarization was taken into account when the extracellular potentials were calculated.

Results

1. *Fibre with grounded end*

In the region of the grounded end, the transmembrane potentials diminished sharply and simultaneously and tended to zero close to the end of the fibre (Fig. 1*A*1). Development of the action potential was blocked. In the region of the grounded end, the potential profile became considerably steeper (Fig. 1*A*2) than that in the middle portion of the fibre.

While the point of recording was moving axially from the area above the fibre to the grounded end and behind it, the extracellular potentials changed from triphasic — typical of a uniform infinitely long fibre (Dimitrova 1987) — to biphasic, positive-negative, and then to practically monophasic, positive (Fig. 2*A*). The changes in the number of phases were accompanied by alterations both in the negative and/or positive phase amplitude and in the duration of the phases. The amplitude changes were non-monotonous. The amplitudes first increased and then decreased. There were differences in the negative and positive phase amplitude alterations depending on the axial position of the point of observation. The points of the volume conductor at which the negative phase amplitude increased were closer to the site of stimulus injection than those for the positive phase.

The smaller the radial distance of the recording point from the fibre axis, the closer to the grounded (damaged) end was the point at which the maximum positive amplitude was recorded and the higher was the ratio between the maximum value of the "inhomogeneous" positive phase amplitude and that typical of the homogeneous fibre.

At higher radial distances, the axial positions of the points where the maximum negative or positive phase amplitude were observed, moved towards the point of stimulation and away from the fibre end, respectively. With increasing radial distance from the fibre axis, the region of biphasic potential recording was extended.

The duration of the extracellular potentials calculated for the region of the fibre end increased.

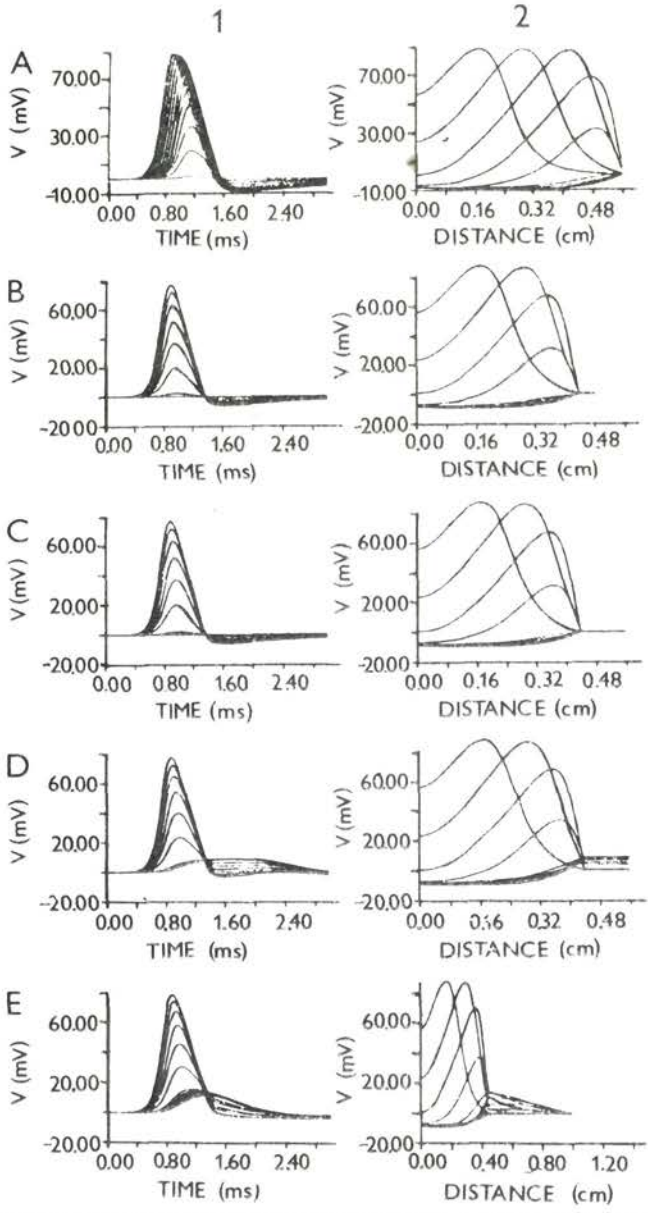

Fig. 1. Transmembrane potentials in time (1) and distance (2) domains. The potentials are shown for segments 270—360 at 10 segment steps and for times 0.6—2.4 ms at 0.2 ms steps, respectively. (*A*) — cylindrical fibre with the end grounded; (*B*) — cylindrical fibre interconnected with a short region of increased diameter ($L = 10\,d$, $K_d = 10$) and with the end grounded; (*C*) — as (*B*) but $L = 25\,d$, $K_d = 20$; (*D*) — as (*C*) but with the end insulated; (*E*) — cylindrical fibre interconnected with a long region of increased diameter ($L = 112.5\,d$, $K_d = 5$) with the end grounded.

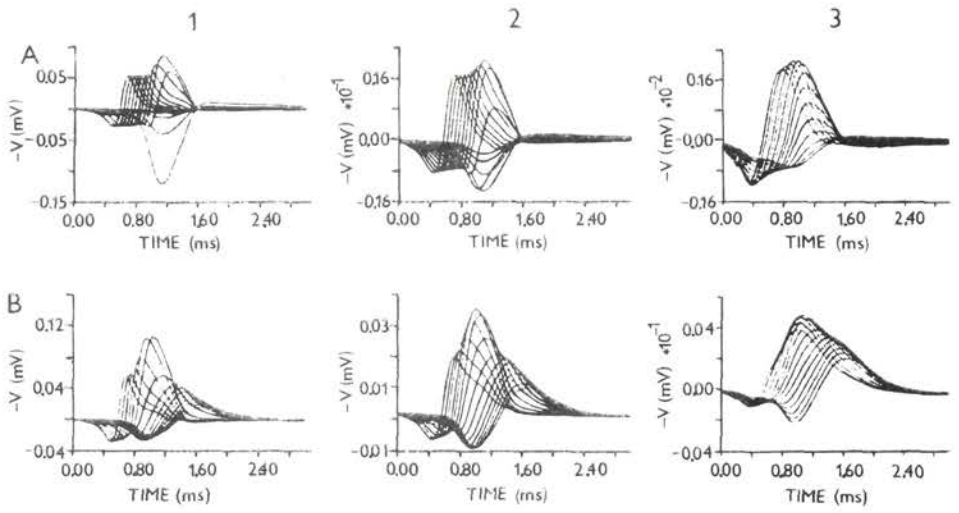

Fig. 2. Extracellular potentials calculated at different radial distances (y) of the observation point from the axis of the structure. Axial coordinates of the point are from 2.6 to 6.8 mm at 0.3 mm steps. (1) — $y = 0.125$ mm; (2) — $y = 0.5$ mm; (3) — $y = 2$ mm. (A) — cylindrical fibre with the end grounded; (B) — cylindrical fibre interconnected with a long region of increased diameter ($L = 112.5d$, $K_d = 5$).

2. *Fibre with a relatively short inhomogeneity*

Irrespective of both the boundary condition at the structure's end and the relation between L and K_d, the transmembrane potentials calculated for the structures with the short inhomogeneities were similar (Figs. 1*B*, *C*, *D*). Differences occurred only in the potentials calculated for the regions of both the inhomogeneity itself and a small portion of the fibre just before the inhomogeneity. If the structure's end was grounded, the potential along the membrane of the inhomogeneity was approximately zero (Fig. 1*B* and 1*C*). If the structure's end was insulated, the potential across the membrane at the inhomogeneity was approximately equal to that at the point just before the inhomogeneity (Fig. 1*D*). The axial alteration in the transmembrane potential profile along the membrane of the inhomogeneity was more pronounced if the end was grounded (this cannot be seen in the figures because of the scale used).

The character of the extracellular potentials (Fig. 3*A*, *B*, *C*) was the same as that described in the previous section; the only difference was in their amplitudes. The most pronounced changes in the amplitudes were typical of the structure with the longer inhomogeneity terminated by the grounded end (Fig. 3*B*).

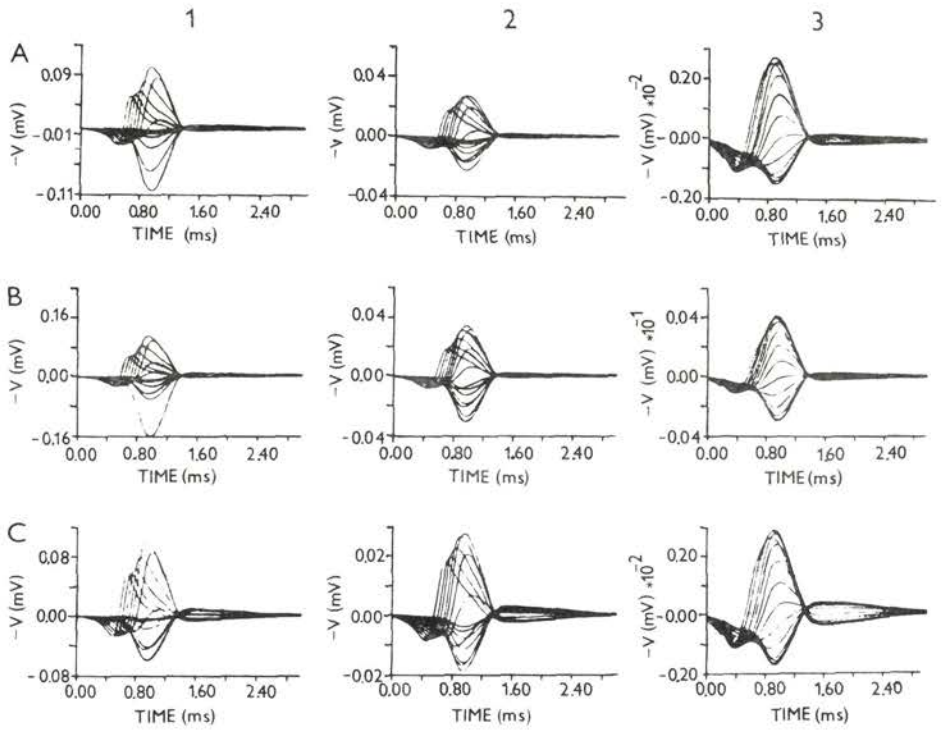

Fig. 3. As Fig. 2 but (*A*) — cylindrical fibre interconnected with a short region of increased diameter ($L = 10\,d$, $K_d = 10$) with the end grounded; (*B*) — as (*A*) but $L = 25\,d$, $K_d = 20$; (*C*) — as (*B*) but with the end insulated.

3. *Fibre with a long inhomogeneity ($L = 112.5\,d$, $K_d = 5$)*

The transmembrane potentials in the time domain (Fig. 1*E*1) were similar to those described above for a fibre with the inhomogeneity terminated by the insulated end (Fig. 1*D*1). In the distance domain the differences occurred in the region of increased diameter itself (Fig. 1*E*2). The potential profile seems to propagate gradually in this region.

Like the cases described above, the extracellular potential negative phase amplitude increased in the volume conductor region preceding the inhomogeneity (Fig. 2*B*). At all radial distances, however, this region was wider than that described in the previous cases.

There were substantial differences in the development of the positive phase of the extracellular potentials calculated in the region of the inhomogeneity. In contrast to all previous cases (Fig. 3), the amplitude of this phase increased at

higher radial distances only (Fig. 2*B*3). Over the region of increased diameter, the extracellular potentials were biphasic, positive-negative. There was a phase shift of the curves of the extracellular potentials calculated over the region of the inhomogeneity, resembling that typical of long normally conducting excitable structures.

Discussion

The propagation block examined in the present paper was caused by the presence of a supra-critical geometrical inhomogeneity (a specific region of increased diameter) or by a grounded end or by a combination of the two.

In terms of the cable theory, the block was due to a high electrical loading of the fibre in all these cases. The loading typical of a grounded end is the highest of all those typical of inhomogeneities examined in the present paper. In this sense, a grounded end can be classified as a geometrical inhomogeneity, namely as a region of increased diameter with $K_d = \infty$.

The geometry of the structures examined in the present paper* is analogous to that typical of the soma to axon transition or of branching axons or dendrites (Rall 1962; Dimitrova 1987, 1988) or of damaged structures. If a structure is damaged somewhere in its middle portion, and if the load tends to infinity (the resistance tends to zero) at the site of damage, then the excitation wave fails to propagate through the site. Then the potentials produced by the whole structure will be just the potentials produced by the initial portion of the structure, terminated by the damaged area.

Our study has shown that propagation block caused by a geometrical inhomogeneity is always accompanied by a dramatic decrease in the transmembrane potential amplitude and by a substantial increase in the amplitudes and durations of the extracellular potential phases.

In addition to the common features, there were differences in the nature of the development of the first positive phase when the extracellular potentials were calculated in the proximity of short and long inhomogeneities. The differences reflect pecularities of the development of the transmembrane potential profile in the two cases.

In structures where the propagation block results from the presence of a short geometrical inhomogeneity or of a grounded end, all the extracellular

* All the results obtained can be adopted for structures of any real size and corresponding geometrical properties (Dimitrova 1987)

potential changes are mainly due to the formation of a transmembrane potential profile which has effectively a static front fixed at the point of geometric change. This prevents development of the normal sequence (positive-negative-positive) of the extracellular potential phases typical of a propagating wave and leads to an increase in duration of each phase. As the static front is substantially steeper than the corresponding one typical of the homogeneous portion of the fibre, the amplitudes of the extracellular potentials calculated for the region of the inhomogeneity increase. This increase is more pronounced at smaller radial distances, in accordance with the results of Dimitrov and Dimitrova (1974).

When an inhomogeneity is long (commensurable with λ; $L = 112.5\,d$, $K_D = 5$ in our case), the potential profile is no longer static in relation to the site of the geometric change. Because of the membrane capacitance, a considerable portion of the transmembrane potential profile progressively "enters" the inhomogeneity, forming a relatively long depolarized zone there. The latter produces large additional negative potentials at volume conductor points before the site of geometric change. The point at which these negative potentials are maximal migrates from the site of geometric change to the site of fibre stimulation, when the radial distance of the recording point from the fibre axis increases (Dimitrov and Dimitrova 1974; Dimitrova 1987). As a result, at smaller radial distances, the additional potentials prevent the increase in the first positive phase near the site of increased diameter and produce a negative phase there (Fig. 2*B*).

The additional negative potential produced by a short or long inhomogeneity also causes a reduction in the amplitude of the first positive phase at those points of the volume conductor where the larger negative phase amplitudes were observed (Fig. 2*B*, 3).

At small radial distances, a very marked increase in the amplitude of the first positive phase is typical of damaged structures. Thus, any sufficiently severe damage to a homogeneous or inhomogeneous structure will transform the extracellular potential waveforms typical of such structures (Dimitrova 1987, 1988) in those which have both a prolonged duration and a large positive phase when the potentials are recorded close to the site of damage. Such a waveform transformation resembles the "giant" potentials recorded near the cell soma (Freygang 1958; Freygang and Frank 1959; Terzuolo and Araki 1961; Nelson and Frank 1964; Rosenthal 1971). There are, however, some differences between the potentials calculated in the present paper and the "giant" ones. There are also reasons for these differences: (1) in actual experiments which include recording of "giant" potentials, the cells are not damaged so severely as in our simulation; (2) the pressure of the electrode and the effect of penetrating the membrane with the other electrode (Terzuolo and Araki 1961; Murakami et al. 1961), etc. are likely to lead to changes in some membrane parameters that will affect the potentials.

References

Dimitrov G. V., Dimitrova N. (1974): Influence of the asymmetry in the distribution of the depolarized level on the extracellular potential field generated by an excitable fibre. Electromyogr. Clin. Neurophysiol. **14**, 255–275

Dimitrova N. (1974): Model of the extracellular potential field of a single striated muscle fibre. Electromyogr. Clin. Neurophysiol. **14**, 58–66

Dimitrova N. (1987): Mathematical modelling of intra- and extracellular potentials generated by active structures: effects of a step change in structure diameter. Gen. Physiol. Biophys. **6**, 19–34

Dimitrova N. (1988): Mathematical modelling of intra- and extracellular potentials generated by active structures with short regions of increased diameter. Gen. Physiol. Biophys. **7**, 401–412

Freygang W. H. (1958): An analysis of extracellular potentials from single neurons in the lateral geniculate nucleus of the cat. J. Gen. Physiol. **41**, 543–564

Freygang W. H., Frank K. (1959): Extracellular potentials from single spinal motoneurons. J. Gen. Physiol. **42**, 749–760

Hodgkin A. L., Huxley A. F. (1952): A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. (London) **117**, 500–544

Joyner R. W., Westerfield M., Moore J. W., Stockbridge N. (1978): A numerical method to model excitable cells. Biophys. J. **22**, 155–170

Khodorov B. I., Timin Y. N., Vilenkin S. Ya., Gulko F. B. (1969): Theoretical analysis of the mechanisms of conduction of a nerve pulse over an inhomogeneous axon. I. Conduction through a portion with increased diameter. Biofizika, **14**, 304–315 (in Russian)

Khodorov B. I., Timin E. N. (1975): Nerve impulse propagation along nonuniform fibres. Prog. Biophys. Mol. Biol. **30**, 145–184

Murakami M., Watanabe K., Tomita T. (1961): Effect of impalement with a micropipette on the local cell membrane. Study by simultaneous intra- and extracellular recording from the muscle fibre and giant axon. Jpn. J. Physiol. **11**, 80–88

Nelson P. G., Frank K. (1964): Extracellular potential field of single spinal motoneurons. J. Neurophysiol. **27**, 913–927

Rall W. (1962): Electrophysiology of a dendritic neuron model. Biophys. J. **2**, 145–167

Ramon F., Joyner R. W., Moore J. W. (1975): Propagation of action potentials in inhomogeneous axon regions. Fed. Proc. **34**, 1357–1363

Rinzel J. (1976): Simple model equations for active nerve conduction and passive neuronal integration. Lectures on mathematics in the life sciences. **8**, 125–164

Rosenthal F. (1971): Relationships between positive-negative extracellular potentials and intracellular potentials in Pyramidal tract neurons. Electroencephalogr. Clin. Neuro. **30**, 38–44

Terzuolo C. A., Araki T. (1961): An analysis of intra- versus extracellular potential changes associated with activity of single spinal motoneurons. Ann. N. Y. Acad. Sci. **94**, 547–558

Final version accepted June 8, 1988