

Mathematical Modelling of Intra- and Extracellular Potentials Generated by Active Structures with Short Regions of Increased Diameter

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Abstract. The Hodgkin—Huxley (1952) model was used to calculate intracellular potentials by the method of Joyner et al. (1978). Extracellular potentials were estimated on the basis of a mathematical model proposed by us. It has shown that, irrespective of practical isopotentiality of the membrane of a local inhomogeneity, the latter affects extracellular potentials in two ways: 1) through changes in the potential profile in the region of the structure before the inhomogeneity; 2) through its own potential profile. The first effect is considerably greater than the second one, but the second is greater than the effect of the equal portion of the thin fibre. Increase in the diameter or length of an inhomogeneity is combined with such changes in the potential profile, that the effect of the inhomogeneity on the extracellular potential amplitude is practically independent of its actual size. The extracellular potential waveform substantially depends on the ratio of the diameters of the two parts of the structure and on the position of the inhomogeneity in relation to the sealed structure end. Registration of the positive-negative potentials having a large positive phase should not be considered as an indication of passive properties of the structure.

Key words: Model — Intracellular potentials — Extracellular potentials — Active membranes — Local geometrical inhomogeneity

Introduction

An important result from the mathematical analysis of current flow in branching dendritic trees is the demonstration of a class of trees equivalent to a uniform cylinder (Rall 1959, 1962). The soma-dendrite complex of a motoneuron conforms well to that class. The equivalent cylinder theory has made it possible to model impulse conduction along such neurons (Dodge and Cooley 1973; Moore and Westerfield 1983; Moore et al. 1983).

There is another type of neuron having non-uniform distribution of den-

drites around the soma. A distinctive feature of such neurons' geometry is a narrowing of the structure in the region of their soma-dendrite complex. Purkinje cells of the cerebellum, Pyramidal cells of the cerebral cortex, supraoptic neurons, etc. belong to this class of structures. A thin fibre having a short region of increased diameter (local inhomogeneity) can be used as a first approximation of the axon-soma-dendrite complex in mathematical simulations of antidromic excitation of such cells. The short region could be formed by a respective increase/decrease in fibre diameter in the sites of transition from the axon to the soma and from the soma to the dendrites.

Effects of an increase/decrease in fibre diameter on the transmembrane potentials have been studied experimentally (Ramon et al. 1975) and theoretically (Khodorov et al. 1969; Pastushenko and Markin 1969; Goldstein and Rall 1974; Ramon et al. 1975; Joyner et al. 1978; Moore and Westerfield 1983; Moore et al. 1983; Dimitrova 1987). Bogoslovskaya et al. (1973) studied peculiarities of excitation wave propagation through local inhomogeneities formed by combinations of both changes in diameter. The authors theoretically showed that local inhomogeneities substantially increase the upper limit of the ratio of diameters in the in- and homogeneous parts of a structure ($K_d = d_i/d_h$), defined as a critical value for excitation propagation through an infinitely long inhomogeneity (Khodorov et al. 1969). Bogoslovskaya et al. (1973) found that the membrane is practically isopotential along a local inhomogeneity. Rall (1959) assumed the same for the soma membrane. Isopotential structures do not generate any extracellular potentials. According to Plonsey (1977) the power of the elementary sources generating extracellular potentials is proportional to the space derivative of the transmembrane potential $\left(\frac{\partial V_m}{\partial z}\right)$ and to the square of the structure diameter (d^2). Thus, the combination of the practical (but not the total) isopotentiality and the large diameter of a local inhomogeneity can be sufficient to produce a significant extracellular potential.

The aim of the present paper was to examine changes in both transmembrane and extracellular potentials generated by active structures having regions of increased diameter.

Materials and Methods

The Hodgkin—Huxley (1952) model was used to calculate transmembrane potentials. The partial differential equations were solved numerically as described by Joyner et al. (1978). Membrane parameters were as in the model of Hodgkin and Huxley (1952). Computations were obtained on a structure that consisted of a long homogeneous (h) fibre and a short region of increased (i) diameter. The ratio of the diameters of the two regions of the structure (d_i/d_h) was 2, 5 or 20. The length (L) of the region of increased diameter was $5d_h$ (from the 350th to the 370th segment) or $17.5d_h$

(from the 350th to the 480th segment). The region of increased diameter was in the middle or terminal part of the fibre. The boundary condition at the place of stimulus application was $V_{-1} = V_1$, and that at the structure end was $V_{L+1} = 0$ or $V_{L+1} = V_L$ (sealed end). The last conditions were used when the inhomogeneity was in the middle or terminal part of the structure, respectively. The time step was $10 \mu\text{s}$ and the segment length was $12.5 \mu\text{m}$. At any moment, the extracellular potentials were calculated on the basis of the distribution of the transmembrane potential profile along the structure. For a detailed description of the method of computations and validity of results irrespective of the actual structure size see Dimitrova (1987). This investigation was carried out with the assumption that the volume conductor was infinite, uniform and isotropic and that the coordinates of the stimulation point were $x = 0$ and $y = 0$. The radial distances from the structure axis to the point of registration were 0.125; 0.5 and 2 mm. The axial distances were varied and are listed under the figures.

Results

I. Transmembrane potentials

In the time domain, the transmembrane potentials calculated for a structure with a short (local) inhomogeneity are similar in their character to those calculated for structures with a long inhomogeneity (Khodorov et al. 1969; Dimitrova 1987). For any structure with a short region of increased diameter, it is possible to select such a structure with a long region of increased diameter that the transmembrane potentials in the two structures should be practically identical in shape (Figs. 1A1 and 1B1). In the distance domain, the transmembrane potentials are similar only in the regions before the inhomogeneities. When the region of increased diameter is short, its transmembrane potentials have a greater tendency to be simultaneous (Fig. 1A2) than when it is long (Fig. 1B2). An increase in the ratio of the diameters or a shortening of the region of increased diameter results in smaller variations of the transmembrane potentials along the inhomogeneity. The membrane tends towards isopotentiality.

The transmembrane potentials both in the time and distance domain are practically independent of the position of the local inhomogeneity in relation to the sealed structure end (Fig. 1C, D).

II. Extracellular potentials

1. Local inhomogeneity in the middle part of the structure.

Local inhomogeneities distort the simple triphasic waveform of the extracellular potentials generated by a long geometrically homogeneous fibre (Dimitrova 1987). A shift of the point of registration axially from the site of stimulation, towards the short region ($L = 5d_h$) of increased diameter, leads to changes in the negative and first positive phase amplitudes. The negative phase amplitude

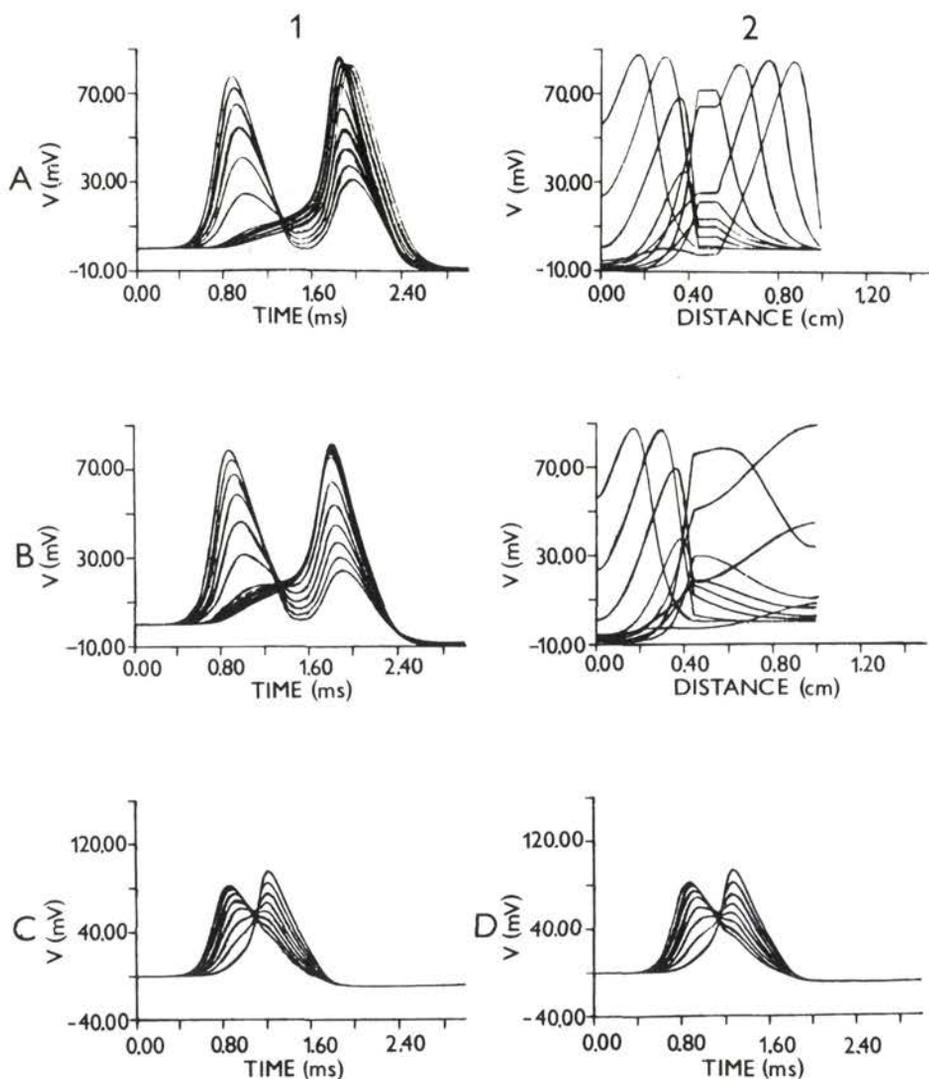


Fig. 1. Transmembrane potentials in the time and distance domain. (*A*) — local inhomogeneity is in the middle part of the structure, $L = 17.5 d_h$ (from the 350th to the 420th segment), $K_d = 20$; (*B*) — “infinitely” long inhomogeneity in the terminal part of the structure. $L = 112.5 d_h$ (from the 350th to the 800th segment), $K_d = 4.7$. Identical local inhomogeneities ($L = 5 d_h$) in the middle (*C*) and in the terminal (*D*) part of the structure. Transmembrane potentials are shown for segments 290—480 at every 10 (*A1* and *B1*), for segments 280—370 at every 10 (*C* and *D*) and for moments of time 0.6—2.4 ms at every 0.2 ms (*A2* and *B2*).

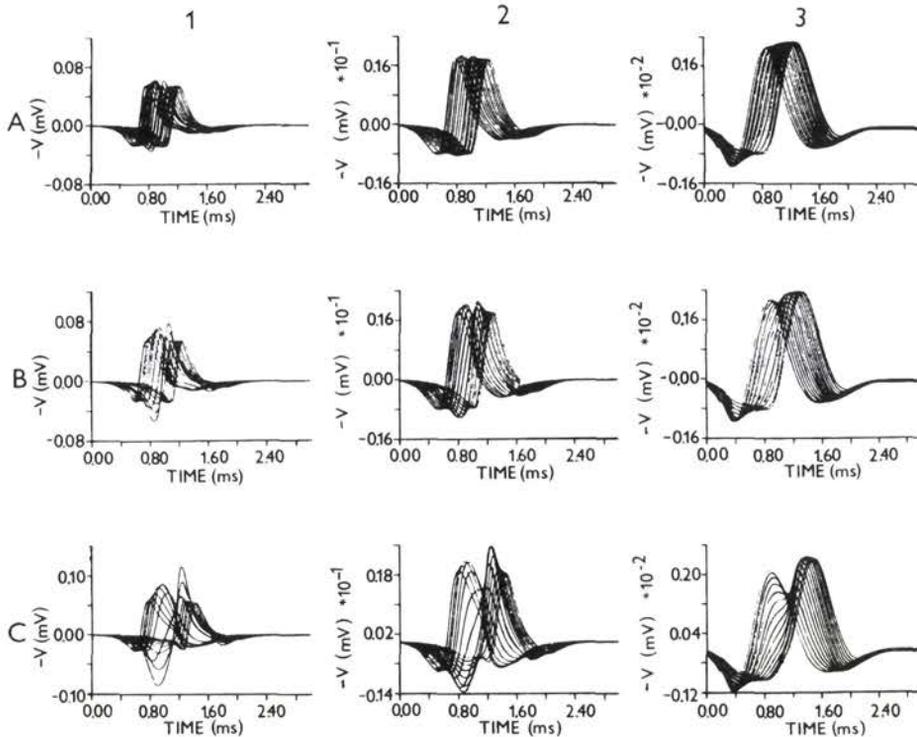


Fig. 2. Extracellular potentials vs. time. Local inhomogeneity ($L = 5d_h$) is in the middle part of the structure. Ratios of the diameters: (A) — $K_d = 2$; (B) — $K_d = 5$; (C) — $K_d = 20$. Radial distances of the point of "registration" (y) are: (1) — $y = 0.125$ mm; (2) — $y = 0.5$ mm; (3) — $y = 2$ mm. Axial distances (x) are: 3.1–5.9 mm at every 0.2 mm.

increases above the thin fibre, but decreases just before the inhomogeneity (Fig. 2A1). The first positive phase amplitude increases not only in the region before the inhomogeneity but also above it.

When the registration point shifts above or behind the region of increased diameter, the negative phase amplitude tends to the value typical of the homogeneous thin fibre and the first positive phase is deformed. The latter phenomenon is a result of changes in conduction velocity (Dimitrova 1987) during excitation propagation through the region of inhomogeneity.

An increase in the ratio of diameters amplifies changes in the negative and first positive phase amplitudes, described above (Figs. 2B1, 2C1). The relative alterations in the amplitudes are smaller at larger radial distances (Fig. 2, columns 2 and 3), particularly for the first positive phase amplitude. When the radial distance from the structure increases, the axial distance between the two

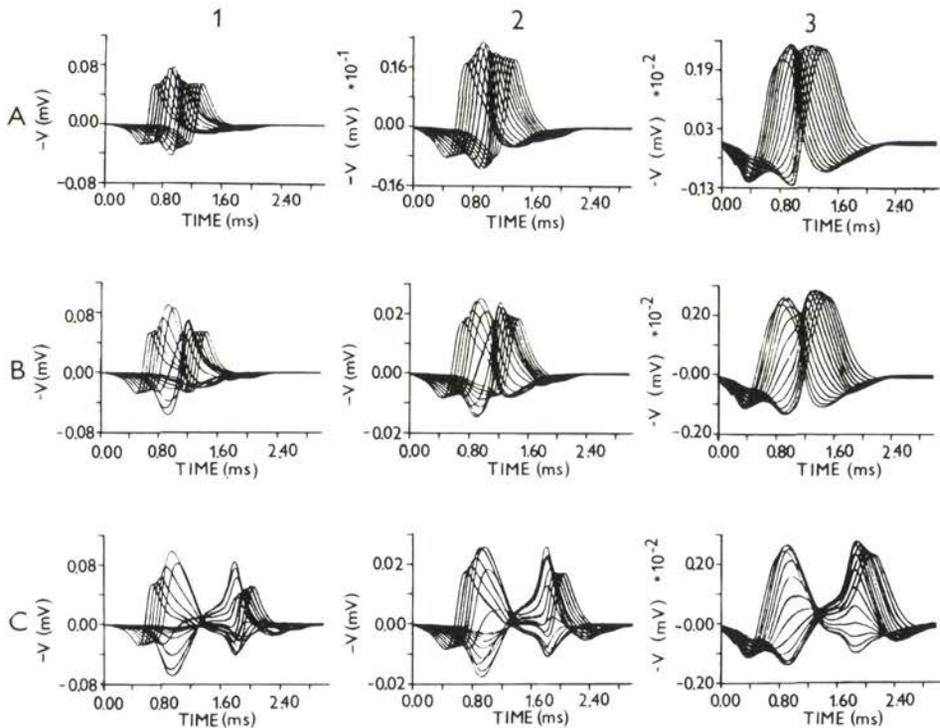


Fig. 3. Extracellular potentials vs. time. Local inhomogeneity ($L = 17.5d_h$) is in the middle part of the structure. Axial distances (x) are: 2.6–6.8 mm at every 0.3 mm. For other conditions see Fig. 2.

points where the maximum negative and first positive phase amplitudes are measured also increases.

A prolongation of the local inhomogeneity ($L = 17.5d_h$) leads to an approximately 10–20 percent increase in the amplitudes of the negative and first positive phases (compare Figs. 2 and 3) and to a slowing of the transmembrane potentials (Fig. 1A). The latter effect results in a prolongation of the extracellular potential phases.

An increase in the ratio of diameters ($K_d = 5$ or 20) produces a decremental retrograde wave that travels towards the stimulation point (Khodorov and Timin 1975; Goldstein and Rall 1974; Ramon et al. 1975; Dimitrova 1987). It leads to the generation of new peaks in the extracellular potentials (Fig. 3C). The peaks appear against a background of different extracellular potential components, that depends on position of the recording point in respect to the inhomogeneity. These components are: the second positive phase at points

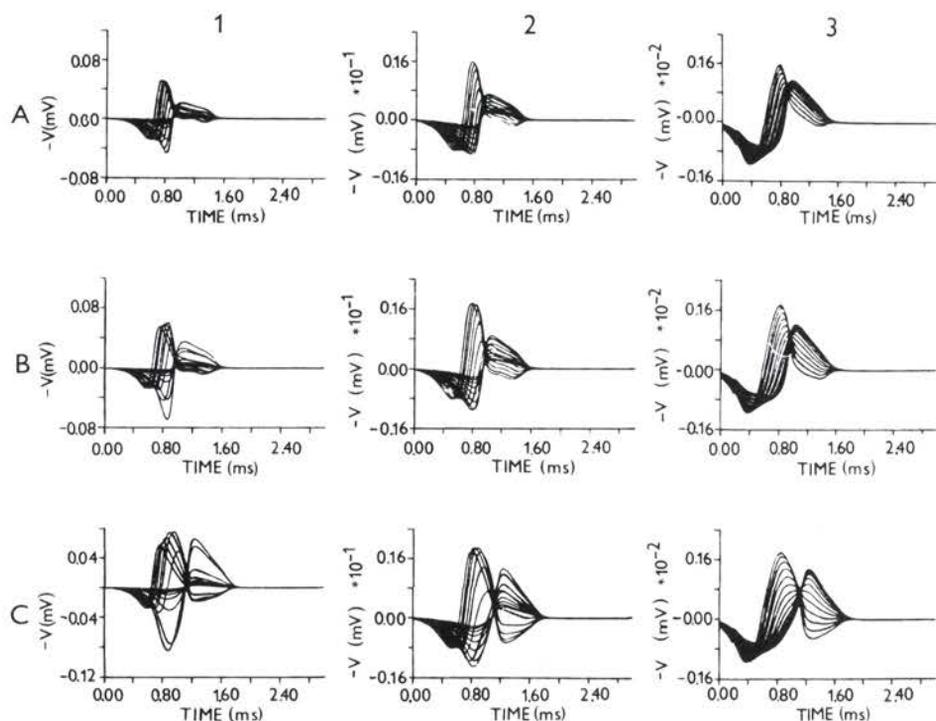


Fig. 4. Extracellular potentials vs. time. Local inhomogeneity ($L = 5d_h$) is in the terminal part of the structure. For details see Fig. 2.

before the region of increased diameter, the negative phase at points above it, and the first positive phase at points behind it.

The radial decline of extracellular potential components is smaller, when the region of increased diameter is longer (compare Figs. 2C and 3C).

2. Local inhomogeneity in the terminal part of the structure.

Everywhere in the area of inhomogeneity, the extracellular potentials are biphasic, positive—negative (Figs. 4 and 5), unlike the triphasic potentials described above. The first positive phase amplitude can be higher than that of the negative one.

Above the thinner part of the structures, the character of the alterations in the positive and negative phase amplitudes is similar to that described in the previous section. Differences only occur in the actual values of the amplitudes. The decrease of the negative phase amplitudes is more pronounced than their increase. When the inhomogeneity length is short and the ratio of diameters

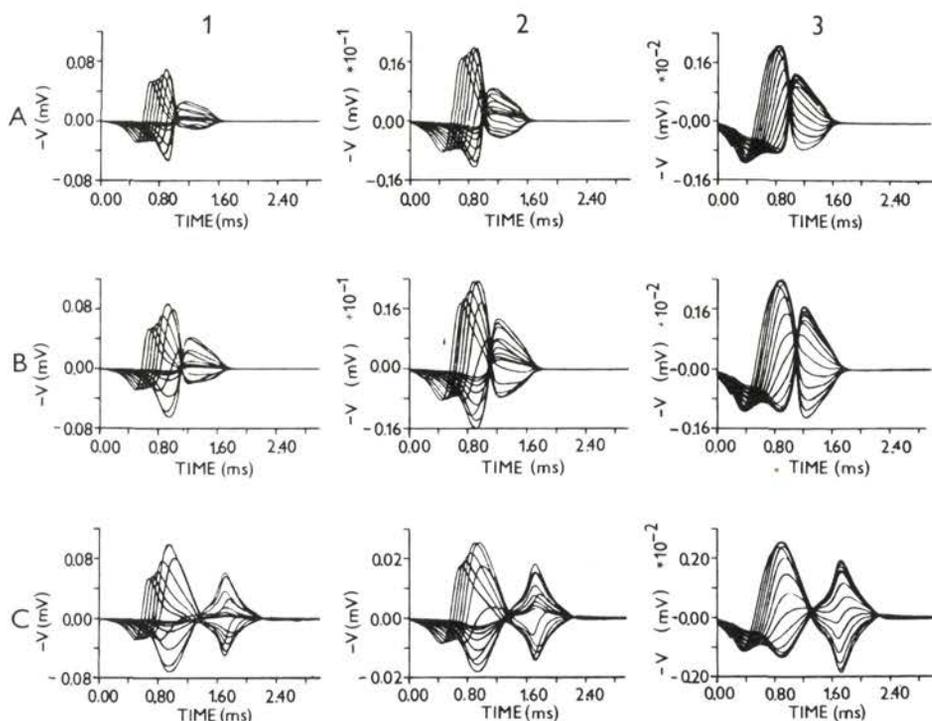


Fig. 5. Extracellular potentials vs. time. Local inhomogeneity ($L = 17.5d_h$) is in the terminal part of the structure. For details see Fig. 3.

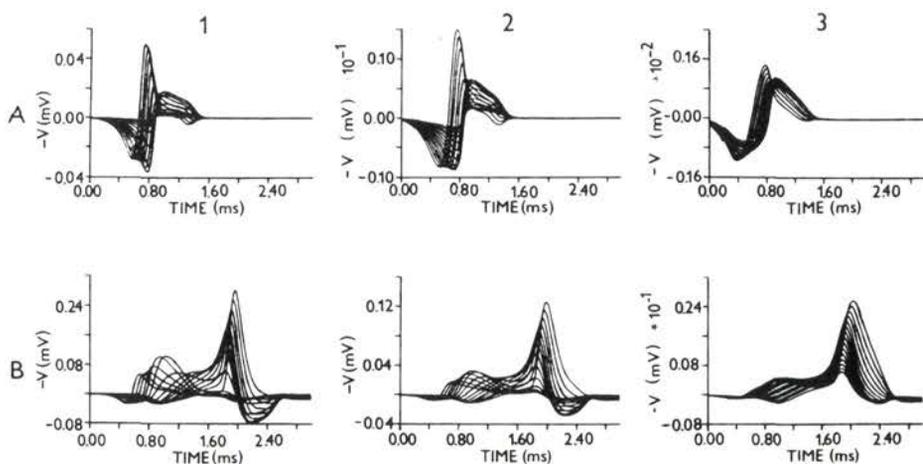


Fig. 6. Extracellular potentials vs. time. (A) — sealed end (the 370th segment) of the homogeneous fibre. For coordinates of the point of “registration” see Fig. 2; (B) — “infinitely” long inhomogeneity; $K_d = 4.7$. For coordinates of the point of “registration” see Fig. 3.

between the two regions is small, the amplitudes of the negative phase only decrease (Fig. 4A). The amplitude of the first positive phase increases more at lower and less at higher radial distances (compare Figs. 2 and 4; 3 and 5). The negative and first positive phases diminish both in the areas above and behind the inhomogeneity.

Changes in the inhomogeneity length or in the ratio of diameters between the two regions of the structure affect extracellular potentials in the manner described above.

Discussion

Our results have shown that, in structures with a local or infinitely long inhomogeneity, the character of transmembrane potentials in the time domain can be similar (Figs. 1A1 and 1B1). The relationship between the corresponding (K_d)s at which the potentials are similar, depends on the length of the short (local) inhomogeneity. Changes in the position of the short region of increased diameter in relation to the sealed structure end have no effect on transmembrane potentials calculated in the region of inhomogeneities (Figs. 1C and 1D). The similarity between the transmembrane potentials in the region before the inhomogeneities is a result of approximately equal effects (electrical loads) of the distal parts of the structures, including the inhomogeneities, on their proximal parts. In this sense, the effect of a sealed end is similar to that of a strong reduction in the structure diameter.

Due to the similarity between the transmembrane potentials, the extracellular potentials calculated in the regions of volume conductor preceding the inhomogeneities also have common features. The negative and positive phase amplitudes increase in this region. The main reason for this increase is the formation of steeper portions of the transmembrane potential profile in the regions of the structures before the respective inhomogeneities.

When the local inhomogeneity is in the terminal part of a structure, an additional increase in the first positive phase amplitude is obtained at small radial distances. The negative phase amplitude is reduced at all radial distances (compare Figs. 2 and 4; 3 and 5). This is due to the lack of a potential profile behind the end of the structure. If the profile had existed, it should have generated negative potentials in the area near (but before) the end of the fibre during formation of the first positive and negative phases (Dimitrova 1974). Fig. 6A demonstrates effect of the lack of a potential profile more clearly. The radius of the fibre corresponding to the Fig. 6A, is identical to that of the thinner part of the structures studied. The increase in the first positive phase amplitude is pronounced at small radial distances. At larger radial (and identical axial)

distances the first positive phase is generated earlier than at smaller ones and its formation can be complete before the potential profile begins to disappear (Fig. 6A3; Fig. 4 — column 3; Fig. 2 — column 3).

Above the region of increased diameter and behind it, the extracellular potentials depend considerably on the length of the inhomogeneity (compare Figs. 6B, 3C and 5C or Figs. 2 and 3; 4 and 5)*. The differences in extracellular potentials are due to those in the transmembrane potential profiles along the inhomogeneities and behind them (see, for example, Figs. 1A2 and 1B2).

A variation of the ratio of the diameters (K_d) over a wide range (from 2 to 20 in the present paper) induced small changes (≤ 20 percent) in the amplitude of the extracellular potentials calculated near a local inhomogeneity (Figs. 2, 3, 4, 5). This is in contrast to the more pronounced changes in the amplitude of the extracellular potentials calculated above a long inhomogeneity (Fig. 6B and Dimitrova 1987) and reflects differences in the power of the elementary generators, proportional to $d^2 \frac{\partial V_m}{\partial z}$ (Plonsey 1977). In case of a long inhomogeneity,

the power amplitude gradually increases from the value typical of the corresponding thin homogeneous fibre towards the constant value typical of the thick one. This increase occurs along a distance approximately equal to sum of 2 length constants (1 before and 1 behind the site of diameter increase). In case of a local inhomogeneity, differences only occur in the power calculated along the inhomogeneity. The power amplitude decreases in this region, whose length is considerably shorter than the length constant of the thicker portion of the structure. This decrease is a result of an increase in conduction velocity in the terminal part (Goldstein and Rall 1974) of the inhomogeneities. Irrespective of the ratio of the diameters (K_d) and of the length of a local inhomogeneity, an approximately equal range of alterations is a typical feature of the power amplitude calculated in the region of inhomogeneity. An increase in K_d or L is always accompanied by corresponding changes in $\frac{\partial V_m}{\partial z}$. Thus, the amplitude of

the extracellular potentials calculated near a local inhomogeneity, is less sensitive to changes in the geometrical parameters describing inhomogeneity, than the amplitude of the extracellular potentials calculated near a long one.

Our studies have shown that, in spite of the practical isopotentiality, the effect of a local inhomogeneity on extracellular potentials should not be neglected. A local inhomogeneity mainly affects such potentials in two ways: 1) through changes in the transmembrane potential profile before the inhomoge-

* Pay attention to similarity (Figs. 1A1 and 1B1) of the transmembrane potentials in the time domain for structures corresponding to Figs. 6B, 3C and 5C).

neity; 2) through its own potential profile. The second effect is substantially smaller than the first one, but larger than the effect of the equal portion of the thin homogeneous fibre.

Another conclusion concerns the effect of the structure sealed end. Our studies have shown that this effect is considerable for the extracellular, but not for the transmembrane potentials. Since any soma-dendrite complex is a relatively short portion of a neuron, experimentalists have to be very careful, when positive—negative potentials are recorded around such structures (Rosenthal 1971). Such potentials can be recorded around active structures near their terminal parts.

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