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Electrical Stimulation of Brain Localized without Probes—Theoretical Analysis of a Proposed Method

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A method of electrically stimulating neural elements confined within small volumes of brain at predetermined deep locations without employing probes is considered theoretically. The basic principle of the method is the partial rectification in the focal region of an ultrasonic field of the alternating current that flows in the entire brain, or a major portion thereof, in response to an externally applied electric field of the same freqeuncy. Since the magnitude of the electrical conductivity of the tissue varies with the temperature the adiabatic temperature, changes produced by the acoustic disturbance cause a periodic variation in the conductivity that results in a net unidirectional transfer of charge when the frequenices of the two fields are equal. The condition for stimulation is expressed quantitatively by a relation involving the amplitudes of the electric and acoustic field parameters, the thermal coefficient of electric conductivity of the tissue, the threshold quantity of charge that must be transferred unidirectionally per unit area to result in stimulation, the pulse duration, and a parameter that is determined by the geometric orientation of the electric and ultrasonic field vectors at the acoustic focus. Numerical calculations suggest that stimulation can be produced in the absence of thermal or other mechanisms of damage to the tissue. The values of the charge-stimulation and electrical-conductivity parameters employed in the calculations are derived from available experimental data.

INTRODUCTION

ALTHOUGH studies involving the stimulation of sites within the brain have yielded much information regarding its structural organization and mechanisms of operation, such work suffers from the considerable limitation that intervening brain must be penetrated by some type of probe (electrode, cannula, etc.) in order to provide the necessary localization of the stimulus to neural elements confined in relatively small interior volumes or regions. Although a multiplicity of sites can be stimulated along the course of a path of penetration, it is apparent that any method employing probes is severely limited by the number of sites that can be stimulated in one brain without imposing such extensive damage that the results obtained are either difficult to interpret or are meaningless for an undamaged brain. If localized electrical stimulation could be achieved without damage either at the site or along a path through the tissue to reach it, then a tool of considerable potential would be available for electrophysiological studies on the brain. This paper is concerned with a detailed theoretical analysis of a possible method of achieving this goal.

The determination of specific conditions, including values of electrical parameters used with specific electrode configurations, for achieving localized electrical stimulation of the brain has received the attention of a number of investigators (Lilly *et al.*,[1] Bickford *et al.*,[2] MacIntyre *et al.*,[3] Heath and Mickle,[4] and Phillips and Porter[5]). The stimulation of neural elements is produced by the unidirectional net transfer of sufficient quantity of electric charge, the magnitude of the charge depending in general on auxiliary experimental conditions. Quantitative studies of electrostimulation parameters such as pulse duration have

[1] J. C. Lilly, G. M. Austin, and W. W. Chambers, "Threshold Movements Produced by Excitation of Cerebral Cortex and Efferent Fibers With Some Parametric Regions of Rectangular Current Pulses (Cats and Monkeys)," J. Neurophysiol. 15 319 341 (1952).

[2] R. G. Bickford, M. C. Petersen, H. W. Dodge, and C. W. Semi-Jacobsen, "Observations on Depth Stimulation of the Human Brain Through Implanted Electrographic Leads," Proc. Staff Mtgs. Mayo Clinic 28, 181–187 (1953).

[3] W. J. MacIntyre, T. G. Bidder, and V. Rowland, "The Production of Brain Lesions with Electric Currents," Proc. Int. Biophys. Conf., 1st, 723–732, Plates 26–31 (1957).

[4] R. G. Heath and W. A. Mickle, "Evaluation of Seven Years Experience with Depth Electrode Studies in Human Patients," in *Electrical Studies on the Unanesthetized Brain*, E. R. Ramey and D. S. O'Doherty, Eds. (Paul B. Hoeber, Inc., New York, 1960), Chap. 11, pp. 214–242.

[5] C. G. Phillips and R. Porter, "Unifocal and Bifocal Stimulation of the Motor Cortex," J. Physiol. (London) 162, 532–538 (1962).

received the attention of some of these investigators.[1,6] These workers have demonstrated the importance of the unidirectional transfer process for stimulation. The importance of charge transfer, as compared with electrically produced thermal effects in the production of lesions, has received the attention of others (MacIntyre *et al.*,[3] Rowland[7]). In these latter studies, it has been demonstrated that conditions for repetitive stimulation exist in which relatively enormous amounts of charge can be transported in an alternating fashion (no net unidirectional transport) across tissue boundaries over time periods of hours to months, without causing damage. Lilly[6] has summarized in graphical form (Fig. 6.5 of referenced publication) information on the variation of the threshold charge transfer per pulse, using pulse pairs, as a function of the pulse duration. His graphical presentation shows where the threshold conditions for stimulation overlap those for the production of injury, electrolytic at long and thermal at short pulse durations. The range between approximately 0.03 and 10 msec is available for stimulation without concomitant injury, with the "safety factor" obviously dependent upon the specific choice of the value for the pulse duration.

It is apparent that if a method for producing partial rectification in any desired small volume of a high-frequency current field produced by appropriate means throughout an entire brain, or a large part thereof, were available that achievement of stimulation at localized deep sites without the use of probes would then become a distinct possibility. In order to accomplish this, it is necessary that the frequency of the electric (or magnetic) field that induces the current flow be high enough so that the charge transferred through tissue elements on each half-cycle is small as compared to that required for stimulation. Of course, the frequency should not be so high that penetration of the tissue in depth by the field is limited. However, this latter requirement is easily achieved for the method considered here.

The basic principle of the method, which is considered from a theoretical viewpoint in this paper, consists of the simultaneous application of an electric field, applied externally to the brain, and a focused ultrasonic field localized with the focus at the site desired for stimulation. In the simplest case, the frequencies of the electric and acoustic fields are equal. Since a traveling acoustic wave has associated with it a propagating alternating temperature variation, and since the electrical conductivity (and incidentally, the dielectric susceptibility) of media, including tissue, changes with the temperature, the acoustic field thus induces a periodic variation into the values of these parameters with the maximum variation occuring at the focus of the field. The amplitude of the variation in the focal region, as compared with that in the intervening tissue, is dependent upon the "gain" of the focusing system and the acoustic losses that occur in the tissue. Since the frequency of the electric field, and thus the currents produced in the tissue in response to it, and the frequency of the acoustic field are equal, it is apparent that the current that flows in the tissue at the focal center when the temperature is increased above the average value (that is, during a compressive half-cycle of the acoustic wave) is not equal to the current that flows in the opposite direction during a rarefaction half-cycle of the wave (that is, when the temperature is below the average value for the tissue). Thus a unidirectional transfer of charge occurs (the return part of the current loop lies off the focal center), that is, the charge transferred at the focal center during a compressive half-cycle of the sound wave is not equal to the charge transferred in the opposite direction during a rarefaction half-cycle; the magnitude of this unidirectional or rectified charge transfer is determined by various factors including: (1) the amplitude of the periodic temperature change in the sound-wave field at the focus, (2) the "linearity" of the brain tissue and coupling medium for the propagation of finite-amplitude acoustic waves,[8,9] (3) the magnitude of the acoustic absorption coefficient including its dependence on the frequency, (4) the magnitude of the electrical conductivity of the tissue and its coefficient of variation with temperature, and (5) the amplitude of the electrical field that induces the current flow in the tissue.

The feasibility of producing electrical stimulation at localized sites within the brain by the method outlined depends upon the magnitudes of the indicated parameters and their determination of the maximum values of the electric- and acoustic-field variables that can be employed. Therefore, it is necessary to consider quantitatively a number of different aspects of the proposed method, and all of those of evident importance are considered in this paper. An outline of these aspects, considered analytically in subsequent Sections, is now presented. First, it is convenient to express the conditions for electrical stimulation, based on the principle under consideration, in terms of a relation between electric-current density, acoustic sound-pulse amplitude (temperature, pressure), pulse length, and threshold value of electric charge that must be transferred unidirectionally in order to produce stimulation. The indicated relation serves to identify minimum values for combinations of the various field parameters that

[6] J. C. Lilly, "Injury and Excitation by Electric Currents, (A). The Balanced Pulsed-pair Waveform," in *Electrical Stimulation of the Brain*, D. E. Sheer, Ed. (University of Texas Press, Austin, Tex., 1961), pp. 60–64.

[7] V. Rowland, "Stereotaxic Techniques and the Production of Lesions," in *Neuroendocrinology*, L. Martini and W. F. Ganong, Eds. (Academic Press Inc., New York, 1966), Vol. 1, Chap. 4, pp. 107–137.

[8] F. E. Fox and W. A. Wallace, "Absorption of Finite Amplitude Sound Waves," J. Acoust. Soc. Amer. **26**, 994–1006 (1954).

[9] V. A. Krassilnikov, V. V. Shklovskaya-Kordy, and L. K. Zarembo, "On the Propagation of Ultrasonic Waves of Finite Amplitude in Liquids," J. Acoust. Soc. Amer. **29**, 642–647 (1965).

could result in stimulation. However, many such combinations are unacceptable because of various limiting factors—some associated with the sound field, others associated with the electric field.

For the sound field, it is necessary to choose a frequency sufficiently high to produce a small focal volume in order to appropriately confine the stimulation. Since ultrasonic absorption per unit path length increases linearly with the frequency in the range of possible interest, it is apparent that one upper limit to the frequency is determined by the magnitude of the absorption, the depth of the penetration desired, and the gain of the focusing system. In addition, since the sound levels that must be employed are high, it is necessary to take into account the transfer of energy that occurs, during propagation to the focus, from the fundamental frequency of the field to the harmonics. Also, the values of the parameters of the sound pulse must be below those that produce lesions either by thermal or nonthermal mechanisms (Fry,[10] and Barnard *et al.*[11]).

With respect to the electric field, it is necessary to consider possible difficulties associated with its application to the brain, such as field concentrations in the neighborhood of the electrodes and impedances associated with electrode interfaces (Schwan[12] and Schwan and Maczuk[13]). The effectiveness of the induced variation in electrical conductivity (recent experimental data obtained at this laboratory indicate that dielectric susceptibility changes are less important in the usable frequency range) in causing a periodic redistribution of the electric currents in the region of the focus must be evaluated. It is also necessary to compute the temperature rise produced in the tissue by the electric field and to consider the heat-exchange problem introduced by the application of the field to the entire brain or a reasonable fraction thereof. Quantitative analysis of these factors indicates limitations on the ranges of the values of the field parameters that can be used and thus identifies possible combinations that can be employed experimentally in attempting to stimulate.

I. ANALYSIS

Since the method under consideration employs focused ultrasound to produce localized stimulation and since the region to be activated is determined by the volume of the focal region, it is essential that the acoustic frequencies employed be such that the wavelength of the sound in the tissue is relatively small. That is, since the transverse diameter of the focal region is of the order of one-half wavelength, one should employ a frequency high enough so that a half-wavelength is of the order of the diameter of the tissue volume to be stimulated. However, it should be noted that for the transducer geometry normally employed to irradiate the brain, the longitudinal diameter of the focus is longer, in general, than the transverse diameter. (See, for example, Fry and Dunn.[14]) In addition, it is observed that since the magnitude of the absorption coefficient of the sound in the tissue increases with the frequency, it is not possible to decrease the diameter of the focal region indefinitely by the choice of higher frequencies. Based on this consideration alone, the useful frequencies for the intended purpose if penetration to the maximum depth is to be achieved in relatively large brains is between 1 and 10 MHz. (The wavelength in the brain at 1 MHz is approximately $1\frac{1}{2}$ mm.)

The formulas derived are applicable over a wide range of frequencies, but it is convenient for fixing the ideas to illustrate the relative magnitudes of many of the parameters by calculations made at one specific frequency. It is to be observed first that the mechanism considered here, and for the frequencies of immediate interest, one can confine the considerations to changes in the resistivity of the tissue induced by the acoustic field. At frequencies from 1 to 4 MHz, the specific electrical resistance (parallel-circuit representation) of mammalian brain gray matter is close to 250 $\Omega \cdot$cm at normal body temperature. This estimate is based on: values of the specific electrical impedance of rabbit cerebral cortex *in vivo* reported relatively recently by Ranck,[15] early data on minced human brain at 23°C reported by Rajewsky,[16] and on preliminary experimental measurements in the frequency range of interest on excised rat brain at this laboratory. The pertinent information in the second reference is listed by Schwan[17] in a comprehensive review chapter (see Table V of the reference) on methods of measuring biological impedances. The data by Ranck extend only to a frequency of 50 kHz, where the specific resistance is in the range 200 to 250 $\Omega \cdot$cm. However, the data of the earlier reference cover the range from 1 kHz to 100 MHz and, although not directly applicable, because of the *in vitro* minced state and lower temperature, it might be

[10] W. J. Fry, "Intense Ultrasound in Investigations of the Central Nervous System," Advan. Biol. Med. Phys. **6**, 281–348 (1958).

[11] J. W. Barnard, W. J. Fry, F. J. Fry, and R. F. Krumins, "Effects of High Intensity Ultrasound on the Central Nervous System of the Cat," J. Comp. Neurol. **103**, 459–484 (1955).

[12] H. P. Schwan, "Alternating Current Electrode Polarization," Biophysik **3**, 181–201 (1966).

[13] H. P. Schwan and J. G. Maczuk, "Electrode Polarization Impedance: Limits of Linearity," Proc. 18th Ann. Conf. Eng. Med. Biol., 18th IEEE-ISA 24 (1965).

[14] W. J. Fry and F. Dunn, "Ultrasound: Analysis and Experimental Methods in Biological Research," in *Physical Techniques in Biological Research*, W. L. Nastuk, Ed. (Academic Press Inc., New York, 1962), Vol. 4, Chap. 6, pp. 261–394.

[15] J. B. Ranck, Jr., "Specific Impedance of Rabbit Cerebral Cortex," Exp. Neurol. **7**, 144–152 (1963).

[16] B. Rajewsky, "Biophysikalische Grundlagen der Ultrakurzwellenwirkung in Lebenden Gewebe," in *Ultrakurzwellen, Band 1, Ergebnisse der Biophysikalischen Forschung* (George Thieme Verlag, Leipzig, Germany, 1939), Zweites Kapital, pp. 145, 147ff.

[17] H. P. Schwan, "Determination of Biological Impedances," in *Physical Techniques in Biological Research*, W. L. Nastuk, Ed. (Academic Press Inc., New York, 1963), Chap. 6, pp. 323–407.

used to conclude that the specific impedance does not increase in the frequency range from 100 kHz to 10 MHz.

Only preliminary dielectric susceptibility data are available for brain in the frequency range of interest. Measurements at this laboratory at 1 MHz indicate a value near 800 Ω·cm. This general magnitude is suggested also by measurements on brain made at higher frequencies and by data for other tissues on the frequency dependence of the dielectric constant. These latter extend over the frequency range from lower values to the range of interest here. Thus, in the absence of data on the variation with tissue composition, a choice of 2000 as an upper limit for the "average" dielectric constant of brain at 1 MHz is not unreasonable. It is of some interest to note that the dielectric constant is lower in value at higher frequencies—thus a value of 70 to 75 is listed by Schwan[17] for 100 MHz. It is apparent then that at 1 MHz the impedance of the parallel-capacitative branch of the equivalent electrical circuit for macroscopic size regions of brain tissue is at least several times the impedance of the resistive branch. Therefore, the principal attention in this paper is centered on the resistivity of the tissue as having significance with respect to the mechanism of stimulation considered here.[18]

In frequency ranges where the value of the resistivity of the tissue is essentially independent of the frequency, that is, not in relaxation regions (Schwan[17]), the temperature coefficient of the specific resistance is that characteristic of electrolytic solutions corresponding to the composition present in the tissue. A value of $-2\%/C^\circ$ would constitute a reasonable choice for brain tissue in the absence of specific information. However, since the operating frequencies of interest may be within or neighbor such a relaxation region, it is important to have at least rough measurements of the temperature dependence of the resistivity at hand for any specific frequency under serious consideration. Accordingly, measurements of the changes in resistance and reactance, as a function of the temperature, were made at this laboratory on a series of freshly excised rat brains. The data indicate that at a frequency of 1 MHz and at normal body temperature the *magnitude* of the change in specific resistance is at least $2\%/°C$.

As a result of the periodic temperature change that occurs in a sound field, it is apparent that the specific electrical conductivity of the brain at any position in the focal region of an ultrasound beam changes periodically at the frequency of the acoustic field. No data are available on the variation of the electrical conductivity of brain with pressure at the frequencies of interest here. However, since the measured variation with temperature at these frequencies shows that the temperature coefficient is close to that of a solution of NaCl at the concentration of this salt in the tissue, it might be argued that a similar situation would be expected of the pressure coefficient. E. L. Hixon has drawn the attention of the author to a paper by Fox, Herzfeld, and Rock published in 1946 that deals with the effects of ultrasonic fields on the conductivity of salt solution.[19] These authors employ in their calculations experimental values for the variation of the specific resistivity with pressure reported by Körber in 1909.[20] This latter author measured changes in specific resistance of solutions of various salts for a large range of concentrations as the pressure was varied up to 3000 kg/cm² and for a variety of temperatures. Calculations based on Körber's data show that if extrapolation of his results to tissue and to the frequencies of interest in this paper is possible, then at 40°C, the conductivity changes induced in the brain by the pressure variations in the sound field would be only slightly less than those due to the temperature variations in the field, and the two effects are additive. This dependence of the conductivity on the time can be expressed by the following relation:

$$\sigma=\sigma_0[1+(\Delta\sigma/\sigma_0)\sin\omega(t-x/v)], \qquad (1)$$

where the symbols denote the following: σ_0—electrical conductivity with no field present, $\Delta\sigma$—amplitude of the conductivity change[21], x—space coordinate in the direction of the beam axis, v—acoustic velocity, t—time, and ω—angular frequency.[21]

If an electrical field is superimposed on the tissue, then the current density $\mathbf{J}$ that results is related to the field vector $\mathbf{E}$ by the expression

$$\mathbf{J}=\sigma\mathbf{E}, \qquad (2)$$

when $\sigma=\sigma_0$, the corresponding value of the current density is designated by $\mathbf{J}_0$. The particular configuration of current-density changes that occurs in the region of the acoustic focus depends upon the relative orientation of the electric-field vector and the direction of the axis of the focused ultrasonic beam.

It follows from formulas for the current density as a function of position in the cross section of an electrical conductor that for the frequencies and tissue sizes (i.e., brain "diameters") of interest here, the current density does not vary appreciably because of the "skin effect." In this regard, it is appropriate, for estimating

[18] The subsequent analysis, with relatively minor changes, is applicable also at frequencies for which the specific reactance is comparable to or smaller than the specific resistance. However, the threshold values for the unidirectional charge transfer required for stimulation, in the formulas of the analysis developed here, are then not as readily identified with the values of threshold unidirectional charge obtained from the usual stimulation experiments employing rectangular current pulses (Lilly *et al.*[1] and Phillips and Porter[5]).

[19] F. E. Fox, K. F. Herzfeld, and G. D. Rock, "The Effect of Ultrasonic Waves on the Conductivity of Salt Solutions," Phys. Rev. **70**, 329–339 (1946).

[20] F. Körber, "Uber den Einfluss des Druckes auf das elektrolytische Leitvermögen von Lösungen," Z. Physik. Chem. 212–248 (1909).

[21] The amplitude change $\Delta\sigma$ is dependent on the space coordinate x because of the convergence and divergence of the beam.

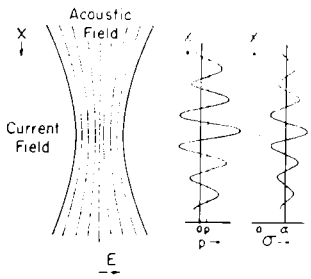

FIG. 1. Form of instantaneous pressure and conductivity distributions along axis of ultrasonic beam in focal region—electric-field vector perpendicular to axis of acoustic beam.

the magnitude of this effect, to employ the expressions that have been derived for cylindrical conductors (for example, see pp. 335–337 of Hund[22]); when this is done, it follows that for a frequency of 10 MHz and a brain "diameter" as large as that of the human that the difference in current density from the center to the periphery is no more than 1% because of the indicated effect, and therefore this constitutes no restriction on the stimulation method under consideration. Since the skin effect decreases as the frequency is reduced and also as the diameter of the brain becomes smaller, it follows that its effect is negligible for smaller brains at the frequencies of interest here.

Since the resulting response in current density for any orientation between electric-field vector and beam axis can be obtained by superimposing in appropriate fashion the current-density changes that occur in the two configurations shown in Figs. 1 and 2, we need consider only these two in detail. In Fig. 1, the electric-field vector is oriented at right angles to the acoustic-particle-velocity vector, which is along the direction of propagation. In Fig. 2, the electric-field vector is parallel to the acoustic-particle-velocity vector.

It is necessary now to derive for each of the two configurations a relation between the change in the magnitude of the electrical conductivity of the tissue in the focal region and the corresponding change in the magnitude of the current density which results. This is most appropriately obtained by analysis (in progress) based on the partial differential equation involving the potential function for the electric field and the gradient of the conductivity, but a simplified lumped-circuit analogy, not included here because of the length, does provide a way of estimating quantitatively the relation between fractional changes in conductivity and current density—that is, a means for evaluating the proportionality parameter F in the expression

$$|\Delta \mathbf{J}|/|\mathbf{J}_0| = F\Delta\sigma/\sigma_0. \tag{3}$$

When this is done, it follows that: For the configuration of Fig. 1,

$$0.7 \leq F_{\perp} < 1.0, \tag{4}$$

and for the configuration of Fig. 2,

$$F_{\parallel} \simeq 0.14. \tag{5}$$

[22] A. Hund, *Phenomena in High Frequency Systems* (McGraw-Hill Book Co., New York, 1936).

That the latter value is a conservative estimate is shown by the first numerical results obtained on the basis of the field type of analysis. This work indicates that the value of F listed here is low by almost a factor of 2.

From Eqs. 1–3, an expression is obtained for the magnitude of the current density J in terms of the amplitude of the electric field E_0 in the focal region:

$$J = \sigma_0[1+F(\Delta\sigma/\sigma_0)\sin\omega(t-x/v)]E_0\sin\omega t. \tag{6}$$

The current density that results in charge transfer to produce stimulation is the *unidirectional* component that flows during the entire duration of the current pulse, that is, the value of J from Eq. 6 averaged over the time of the pulse. (The unidirectional charge transferred during each half-cycle of the field is far below that needed to produce stimulation, as becomes apparent from the numerical calculations.) The magnitude, J_{DC}, of this component is evaluated then by integration of Eq. 6; for rectangular pulses, integration over one period yields the same result as integration over the entire duration of the pulse:

$$J_{DC} = \frac{\sigma_0 E_0}{T}\int_0^{\Upsilon}\left[1+F\frac{\Delta\sigma}{\sigma_0}\sin\omega\left(t-\frac{x}{v}\right)\right]\sin\omega t dt, \tag{7}$$

where Υ is equal to the period of the acoustic and electric fields. On evaluating this expression, one obtains

$$J_{DC} = J_0\left(\frac{\Delta\sigma}{\sigma_0}\right)\left(\frac{F}{2}\right)\cos\frac{\omega x}{v}, \tag{8}$$

where $J_0 = \sigma_0 E_0$. It should be noted that no loss of generality occurs by not inserting a specific phase angle in the argument of either of the trigonometric functions describing the acoustic or electric fields, since the expression $\omega x/v$ already constitutes a phase-angle shift. As Expression 8 indicates, the magnitude of the unidirectional component of the current density is dependent not only on the amplitude J_0 of the current density with the sound field absent and on the fractional change in conductivity produced by the sound field, but also on the phase difference between the acoustically induced change in the conductivity and the electric current produced by the electric field. The maximum value of the unidirectional rectified component of the current density is achieved at positions where $\cos\omega x/v$

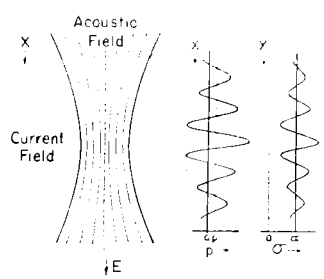

FIG. 2. Illustration of form of instantaneous pressure and conductivity distributions in focal region of ultrasonic beam—electric-field vector parallel to axis of acoustic beam.

is equal to 1. Since this rectified current density varies from 1 to 0 as a function of position in the tissue, it is appropriate to introduce a spatial average value $\mathbf{J}_{DC}$ such that, over a distance of one wavelength, comparable fractions of the tissue volume within which Eq. 8 applies experience rectified current densities greater and less than $\mathbf{J}_{DC}$—the average of one half-cycle of the cosine function is $2/\pi$. The size of the tissue volume experiencing more than the average current thus has the following dimensions: The transverse diameter at the position of the focal center is somewhat greater than the beam width (measured at the half-intensity contour, where the rectified component is equal to 0.707 of the axial value as compared to the average of $2/\pi$ for the cosine function), and is zero at a distance of 0.14λ from the middle of the focus along the beam axis. The neural elements in a series of similarly shaped volumes (the specific number depending on the dimension of the focus in the axial direction) of decreasing size, and spaced $\frac{1}{2}$ wavelength apart along the axis of the beam, would experience the necessary conditions for stimulation assuming that threshold conditions were constant throughout. It should be noted that the direction of the unidirectional current flow is, in general, immaterial from the viewpoint of stimulating nerve-cell bodies; and at different positions in the tissue, the unidirectional current component might well be oriented in different directions, but this is immaterial for stimulation if sufficient charge is transferred at each site. The expression for $\mathbf{J}_{DC}$ is then:

$$\mathbf{J}_{DC}=J_0(\Delta\sigma/\sigma_0)F/\pi. \tag{9}$$

Let η_s designate the electrical charge that must be unidirectionally transferred per unit area in order to achieve stimulation when t_s is the duration of the electric- and acoustic-field pulses (rectangular envelopes);

$$\eta_s=\mathbf{J}_{DC}t_s. \tag{10}$$

It is of interest to recall here that, in general, the value of η_s depends on the pulse duration (Lilly *et al.*[1]), but consideration of the specific form of this dependence is deferred until the end of this Section where numerical values of the parameters involved in the method of stimulation analyzed in this paper are presented. If the fractional change in electric conductivity from the acoustically undisturbed value is expressed in terms of the temperature amplitude, T, of the sound wave and the temperature coefficient of electrical conductivity, h, one obtains

$$\Delta\sigma/\sigma_0=hT. \tag{11}$$

The effect of the acoustic pressure on modifying the conductivity can be included by simply letting h designate the value of the temperature coefficient multiplied by a factor derived from the ratio of the magnitudes of the two field effects. Upon substitution for $\mathbf{J}_{DC}$ and $\Delta\sigma/\sigma_0$ from Eqs. 10 and 11 into Eq. 9, one obtains

$$J_0T=(\pi/F)(\eta_s/ht_s). \tag{12}$$

This expression (Eq. 12) thus constitutes the fundamental relation that must be satisfied between the current-density amplitude in response to the time-variable electric field, the temperature amplitude of the sound wave, the pulse duration of the acoustic and electric fields, the charge-stimulation parameter for the neural elements, and the temperature coefficient of electrical conductivity of the tissue. Of course, one can replace the temperature amplitude of the sound wave by well-known expressions involving acoustic pressure amplitude or intensity (Fry and Dunn[14]). If the pressure amplitude P is introduced, Eq. 12 is replaced by

$$\frac{J_0P}{\beta}\left(K_T-\frac{1}{\rho_0v^2}\right)=\frac{\pi}{F}\left(\frac{\eta_s}{ht_s}\right), \tag{13}$$

where β designates the coefficient of thermal expansivity, K_T the adiabatic compressibility, and ρ_0 the tissue density.

The relation between the pressure and temperature amplitudes employed here is that characteristic of a plane traveling wave; and it can be used as a good approximation to the relation existing between these amplitudes for the focused fields of interest here. Similarly, the sound intensity at the focus is expressed here in terms of the pressure amplitude by the relation that obtains for plane traveling waves—i.e.,

$$I\simeq P^2/2\rho_0v. \tag{14}$$

When the pressure amplitude from Eq. 14 is substituted into Eq. 13,

$$J_0I^{\frac{1}{2}}=\frac{\pi}{F}\,\frac{\eta_s}{(2\rho_0v)^{\frac{1}{2}}ht_s}\,\frac{\beta}{K_T-(1/\rho_0v^2)}. \tag{15}$$

Before considering a specific example, in order to illustrate the magnitudes of the quantities involved it is necessary to determine a value for η_s, the charge that must be transferred across unit area in the tissue in order to achieve stimulation.[23] The work of Lilly *et al.*,[1] in which the charge transferred via a pore electrode to stimulate motor cortical elements was determined as a function of the pulse duration over the range from 0.1 to 10 msec, shows quantitatively how the threshold charge (for just perceptible movement) decreases as the pulse length is shortened in the indicated interval. This dependence can be exhibited graphically as shown in

[23] In this regard, it should be noted that threshold unidirectional charge-transfer values derived from electrophysiological experiments in which no currents at frequencies of the order of a megacycle or higher are involved are appropriate, since it is the *duration* of the *rectified component* of the high-frequency current that is pertinent here and *not* its period.

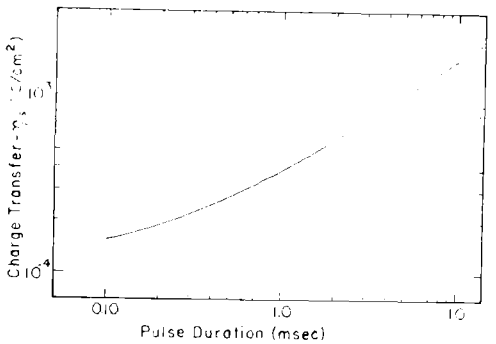

FIG. 3. Charge transferred per unit cross-sectional area of a cortical surface electrode as a function of pulse duration to induce stimulation—charge values calculated from experimental results of Lilly *et al.* (Eq. 19).

Fig. 3, where the charge at the pore face, in coulombs per square centimeter, is plotted as a function of the pulse duration in milliseconds. These charge-transfer values obviously represent *upper limits* to the threshold values in the tissue at the stimulated neural elements—i.e., the latter might well be considerably lower. However, the dependence upon pulse duration would be the same for threshold values and the curve of the Figure can thus be used for converting from values of the charge transfer deduced from the data of other investigators for specific pulse durations to derive corresponding values of the charge for different pulse durations in the interval covered by the graph. Before using the curve in this fashion, it is noted that no marked advantages, with respect to the charge required for stimulation, can be achieved by employing pulse durations shorter than 0.1 msec, as shown by additional measurements of Lilly.[6] (See Fig. 6.5 of the referenced publication.) A lower upper limit might well be expected in studies employing macroelectrodes, if the activity of single cortical neurons is observed; this is the case as shown by the work of Phillips and Porter.[5] These investigators recorded the activity of single pyramidal neurons in response to rectangular stimuli of 0.2 msec duration at a rate of 1 or 2/sec. The stimulus electrodes were chlorided silver balls of approximately $\frac{1}{2}$ mm diam applied directly to the cortex. It does not appear unreasonable to calculate a charge-transfer value on the basis of the minimum value of current that resulted in stimulation, as reported by Phillips and Porter,[5] 1.15 mA, since a charge-transfer value for stimulation computed using a current density at the electrode surface is obviously larger than threshold for pyramidal neurons. When the indicated value is employed, a charge transfer of $2.9(10)^{-5}$ C/cm² is calculated[24]; and since this is for 0.2-msec pulses, the graph of Fig. 3 yields by proportion the values listed in the second column of Table I for upper limits on the charge transfer for stimulation at the neuron membrane for the pulse lengths indicated in the first column.

TABLE I. Charge-transfer values for stimulation.[a]

t_s (msec)	η_s^+ (C/cm²)	ϵ_s^Δ (C/cm²)	η_s^∇ (C/cm²)
0.10	$2.4(10)^{-5}$		$0.64(10)^{-5}$
1.09	$6.2(10)^{-5}$	$1.28(10)^{-8}$	$1.7(10)^{-5}$
10.0	$25(10)^{-5}$		$6.6(10)^{-5}$

[a] +—Macroelectrode–electrode interface values. Δ—Microelectrode–transneuronal membrane values. ∇—Macroelectrode values at neural element.

First, it is of some interest to compare the value of η_s given in the Table for 1.09-msec pulses with the charge transferred to produce stimulation in deep brain in the experiments reported by Heath and Mickle.[4] At the surface of their 1-mm-diam ball electrode, this is $2.5(10)^{-4}$ C/cm² for 1-msec pulses (100 cps). This latter value is much greater than that listed in the Table, as probably would be expected from the indication of stimulation that was employed.

It is important from the viewpoint of obtaining better estimates of η_s to compare stimulation "threshold" charge-transfer values at macroelectrode surfaces with values calculated from microelectrode data. The following calculation employs microelectrode data reported by Frank and Fuortes[25] for cat motoneurons to derive values of η_s to compare with those given in Table I for pyramidal cells of the motor cortex of the cat. The rheobase currents determined by these investigators for the motoneurons they studied fall into two reasonably distinct ranges of values (see Table I of the cited paper). Only those units for which the time constant of the strength–latency curve is given in addition to the rheobase current are considered here. These motoneurons are their Nos.: 3, 7, 15, 16, 18, which exhibit rheobase values from 2.0 to $6.5(10)^{-9}$ A with an average rheobase of $3.7(10)^{-9}$ A and an average time constant of 1.09 msec, and their Nos.: 11 and 13, with rheobases of 18.1 and $12.0(10)^{-9}$ A and time constants of 1.73 and 0.68 msec. The much greater current values for Units 11 and 13 indicate that the measured currents were probably not confined to passage through the cell membrane and may well include leakage current around the shaft of the microelectrode, which the authors suggest as a source of error. In view of this data, it appears reasonable to conclude that the average value calculated for the rheobase of units 3, 7, 15, 16, and 18

[24] If one assumes that the current leaves the electrode over half of its surface, that is, that only half the area of the sphere is either in contact with tissue or covered with a film of salt solution, the corresponding value is $5.8(10)^{-5}$ C/cm². However, since it is the current density at the neural element that is the important factor, along with the pulse duration, in causing stimulation, the specific value calculated for the electrode interface is not of fundamental importance in this case; in fact, it does not influence the final choice of values for η_s to be used in the formulas relating sound field levels and current densities, as becomes apparent from the subsequent calculations.

[25] K. Frank and M. G. F. Fuortes, "Stimulation of Spinal Motoneurons with Intracellular Electrodes," J. Physiol. (London) 134, 451–470 (1956).

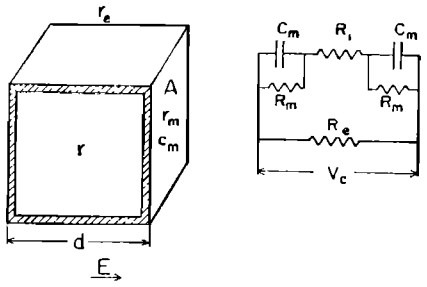

FIG. 4. Model of neuron in imbedded tissue and equivalent electric circuit.

is more nearly representative of the neurons than the average calculated by including the measurements on Units 11 and 13. Therefore, if one chooses, an effective surface area of $5(10)^{-4}$ cm^2 for the motoneuron (see, for example, Eccles[26]), one calculates [27,28] the threshold current i from

$$i=i_r/(1+e^{-t/\tau}). \tag{16}$$

For a pulse duration of 1.09 msec a value for the threshold charge-transfer parameter ϵ_a of Table I, $1.28(10)^{-8}$ C/cm^2 at the cell membrane for stimulation is computed.

In order to obtain an approximate relation between the charge transferred across the membrane of the cell body per unit area and that transferred per unit area of the brain substance when macroelectrodes are employed, let the neuron soma be represented by a cube equal in volume to that of the cell body and with one pair of parallel faces oriented with the normal in the direction of the electric field, as illustrated in Fig. 4. Then the equivalent circuit, also shown in the Figure, is appropriate for estimating the ratio of the charge that flows across the cell membrane per unit area and that which flows per unit area extraneuronally. Values for the parameters that characterize the electrical behavior of the neuron and the imbedding tissue for the stimulating pulse durations of interest here are estimated from the work of various investigators. From impedance measurements made on rabbit cerebral cortex, Ranck[29] derives values of these parameters that would suggest the following choices: $r_e=250$ $\Omega\cdot$cm, $r_i=100$ $\Omega\cdot$cm, $r_m=3000$ $\Omega\cdot$cm^2, $C_m=1.5$ μF/cm^2. The value 100 $\Omega\cdot$cm listed here for the internal resistivity is low as compared to the values characteristic of the cells of other tissues—Schwan indicates that an internal resistivity equal to about twice the external value is the usual situation. However, the following calculations are insensitive to the value of r_i—even a factor-of-5 increase in the value of this parameter, i.e., $r_i=500$ $\Omega\cdot$cm, makes no appreciable difference. With respect to r_m, a value of 1000 $\Omega\cdot$cm^2 was obtained for the motoneuron of the cat by Frank and Fuortes[25] from microelectrode data. Now the value of r_m, as derived by Ranck, is critically dependent on a knowledge of the volume fraction of neurons in the tissue, that is, a small error in this fraction results in a large error in the value of membrance resistance. So, it might well be argued that one should employ the 1000-$\Omega\cdot$cm^2 value for the numerical calculations of this paper. However, since lower values of r_m result in smaller values of the product of current and sound-level amplitudes requiring for stimulation, an intermediate value of 2000 $\Omega\cdot$cm^2 is chosen in order to be conservative in calculations.

The tissue volumes occupied by the neurons on one hand and all other elements on the other may well be about equal. Ranck lists a value of 40%–50% for the percentage of the tissue occupied by the neurons in rabbit cortex. However, it is apparent from the ensuing calculations that the conclusion that results is practically independent of the division of the tissue volume between neural elements and other components unless the neurons were to occupy almost the entire volume, which is certainly not the case. This independence results because the transneuronal impedance per unit area is large as compared to that of the extraneuronal tissue as can be seen from the following. For the purpose, let the cross-sectional areas associated with the intraneuronal and extraneuronal currents, flowing in response to the applied electric field, be equal, and let the cell bodies account for all the neural volume. Of course, neither of these assumptions corresponds to the actual situation; but the objective is to show first, that with a lower limit for the neural shunting impedance, the impedance of the extraneuronal tissue is much lower. Let

$$\begin{aligned} R_e&=250d=0.83\Omega,\\ R_i&=500d=1.65\Omega,\\ R_m&=2000\Omega,\\ C_m&=1.5\ \mu\text{F}. \end{aligned} \tag{17}$$

The value for d, $3.3(10)^{-3}$ cm, chosen here, is for pyramidal cortical neurons, since the conclusion derived in this case follows also for all smaller values of d, corresponding, for example, to smaller neurons, axons, and dendrites. The voltage difference V_C is Ed. At a frequency of $(10)^4$ cps, the transneuronal impedance via the capacitance elements is 25 times, and the transneuronal resistivity is several orders of magnitude times the parallel extraneuronal impedance. Therefore, it is apparent, unless the stimulating pulse has a major fraction of the energy in its frequency spectrum above the indicated frequency, that the average voltage

[26] J. C. Eccles, *The Physiology of Nerve Cells* (The Johns Hopkins Press, Baltimore, Md., 1957).

[27] The relation between the rheobase current i_r and the threshold current i for a pulse duration t for stimulation is given approximately by:

$$i=i_r/(1-e^{-t/\Upsilon}), \tag{16}$$

where Υ is the time constant. See, for example, Katz (Ref. 28).

[28] B. Katz, *Electrical Excitation of Nerve* (Oxford University Press, London, 1939).

[29] J. B. Ranck, Jr., "Analysis of Specific Impedance of Rabbit Cerebral Cortex," Exp. Neurol. 7, 153–174 (1963).

difference across the cell during the period of the pulse is essentially independent of the pulse duration.

Under the conditions just discussed, it is particularly easy to compare, at least approximately, the charge transferred per unit cross section of the tissue, in response to the applied electric field, with those charges transferred per unit area across the resistive and across the capacitative elements of the soma membranes of any subpopulation of neurons of diameter d. For the resistive paths, when t_p designates the pulse duration, these charge-transfer values are:

$$q_e \simeq t_p E d/R_e = t_p E/250 \tag{18}$$

for the extraneuronal medium, and

$$q_{ir} \simeq t_p E d/(2R_m + R_i) = t_p E d/(2R_m + 500d) \tag{19}$$

for the resistive elements of the membrane. For the dimensions of interest here, it is apparent from Eqs. 17 that $2R_m \gg R_i$, so Eq. 19 becomes

$$q_{ir} = t_p E d/2R_m = t_p E d/4000. \tag{20}$$

The corresponding charge transferred across the membrane via the capacitative elements is

$$q_{iC} = E d C_m/2(1 - e^{-2t_p/R_i C_m}). \tag{21}$$

In view of Eqs. 17 for pulse durations longer than $(10)^{-6}$ sec, Eq. 21 can be simplified to:

$$q_{iC} = E d C_m/2 = 0.75(10)^{-6} E d. \tag{22}$$

Both q_{iC} and q_{ir} are small as compared to q_e for the cases of interest, and this accounts for the large ratio, apparent from Table I (pulse duration of 1.09 msec), between the value $6.2(10)^{-5}$ C/cm² for η_s and the value $1.28(10)^{-8}$ C/cm² for ϵ_s. To calculate values for q_{ir} and q_{iC} from the former value, the ratios q_{ir}/q_e and q_{iC}/q_e are required. From Eqs. 18, 20, and 22,

$$q_{ir}/q_e = d/16 \tag{23}$$

and

$$q_{iC}/q_e = 1.9(10)^{-4} d/t_p. \tag{24}$$

For a pyramidal cell diameter, $d = 3.3(10)^{-3}$ cm and $t_p = 1.1(10)^{-3}$ sec, one obtains on identifying q_e with η_s,

$$q_{ir} = 2.1(10)^{-4} \cdot 6.2(10)^{-5} = 1.28(10)^{-8} \text{ C/cm}^2 \tag{25}$$

and

$$q_{iC} = [6.3(10)^{-3} \cdot 6.2(10)^{-5}]/1.1(10)^{-3} = 3.6(10)^{-8} \text{ C/cm}^2. \tag{26}$$

Now the sum of these two charge-transfer values, $4.8(10)^{-8}$ C/cm² is to be compared with the value $\epsilon_s = 1.28(10)^{-8}$ C/cm², which was obtained above from the microelectrode data. The ratio of these two values, $3\frac{3}{4}$, is then a value for the spreading factor by which the current density is reduced from the value at the electrode surface to the position of the pyramidal cell undergoing stimulation in the procedure of Phillips and Porter.[5] The value of this factor[30] is certainly reasonable from the viewpoint of the geometry involved—$\frac{1}{2}$-mm-diam electrode in contact with the surface of the cortex and pyramidal units lying approximately 1 mm below the surface. Evidence that cell bodies rather than fibers are excited at considerably lower values of charge transfer is furnished by the work of Asanuma and Sakata.[31] Using this factor, one can then calculate a value of η_s that is more nearly representative of that required at a pulse duration of 0.1 msec than the value of η_s given in the first column of Table I. This is $0.64(10)^{-5}$ C/cm², and it is an appropriate lower limit for η_s to insert into Eq. 12, 13, or 15 when calculating interrelated values of the current density and focal sound level to induce stimulation.

TABLE II. Values of acoustic- and electric-field parameters for stimulation of cortical pyramidal neurons (freq. 4 MHz).

Sound intensity I (W/cm²)	10 000	10 000	50 000	50 000
Pulse duration t_s (msec)	0.10	1.09	0.10	1.09
Current density[a] J_0 (A/cm²)	35	8.5	15.6	3.8
Relative orientation of fields	90°	90°	90°	90°
Temp. rise (electric) $(\Delta T)_e$ (C°)	3.7	1.9	0.74	0.38
Temp. rise (acoustic) $(\Delta T)_a$ (C°)	0.20	2.1	1.05	11.6
Temp. rise, total (C°)	3.9	4.0	1.8	12.0

[a] If the effect of the sound field pressure on the conductivity is included, as discussed above, calculated values of current density are reduced by a factor of almost two and, of course, the corresponding temperature increments, due to the electric field, are reduced by about four.

Now since unpublished data of this laboratory show that a sound level of 10 000 W/cm² at appropriate pulse durations for stimulation can be achieved at a frequency at least as low as 3 MHz (but not as low as 1.0 MHz) in the brain at the focus, an acoustic-pressure amplitude of 170 atm and a corresponding temperature amplitude of 0.38 C° can be achieved. The numerical values of the parameters employed here to interrelate the amplitudes of the acoustic-field variables are those characteristic of water at 38°C (see, for example, Fry and Dunn[14]); and the value of the thermal coefficient of electrical conductivity, h, is chosen equal to 0.02 as previously discussed. Inserting these values and those for η_s corresponding to pulse durations of 0.10 and 1.09 msec, as listed in the right-hand column of Table I, into Eq. 12 yields the current-density values required to stimulate cortical pyramidal cells when the axis of the focused ultrasonic beam is perpendicular to the direction of the electrical field—i.e., choosing $F = 0.75$ in view of Expression 4. In summary, several sets of conditions to stimulate cortical pyramidal neurons are given in Table II, where the tissue volume

[30] The factor is 7.5 if it is assumed that the current leaves the spherical electrode over only half of its surface.

[31] H. Asanuma and H. Sakata, "Function Organization of a Cortical Efferent System Examined with Focal Depth Stimulation in Cats," J. Neurophysiol. 30, 35–54 (1966).

involved is determined by the wavelength and the transducer aperture.

The last three rows of the Table are included to show the corresponding temperature increases calculated for the tissue caused by the absorption of energy from the electric and acoustic pulses since the values chosen for the stimulation parameters must be consistent with no thermal damage. In order to obtain specific numerical values for the temperature increase due to acoustic absorption, it is necessary to choose a specific frequency. Accordingly, a value of 4 MHz was chosen since this frequency is an appropriate operating choice from the viewpoint of other factors, as shown in this paper. The last row of the Table lists the total temperature rise in each case.

It is of interest to emphasize that the form of Relations 23 and 24 indicates that the conditions for stimulation depend upon the "diameter" of the neural element—if the diameter is doubled, the required value of the product of the acoustic pressure amplitude and the current density is halved, if the net charge transfer across the membrane per unit area to produce stimulation is invariant.

A second observation of some interest is suggested by Eqs. 23 and 24. As Lilly[6] has shown for pulse durations less than 0.1 msec, the macroelectrode charge transfer for stimulation tends to a constant value—i.e., the value of the quantity q_e required for stimulation is independent of the pulse length. Under such conditions, it follows from Eq. 24 that the charge transfer for the capacitative elements of the membrane increases in inverse proportion to the pulse duration while that transferred across the resistive elements, Expression 23, remains constant.[32] If one considers it unlikely that stimulation requires increasing amounts of charge transfer as the pulse length decreases, then it follows that the achievement of a "threshold" charge transfer across the *resistive* element of the membrane is the critical electrical factor involved in initiating stimulation.

II. AUXILIARY CONSIDERATIONS

A number of considerations bear upon the choice of frequency and sound level, at the focus in the tissue, for the ultrasonic field. With respect to the frequency, it is necessary, of course, that it equal the frequency of the electric field so that limitations on the parameters of the latter field imposed by the electrical characteristics of the tissue and accompanying media could influence the determination of the frequency for the acoustic field. However, it follows from the electric characteristics of the tissue that the only limitation on the choice of the frequency for the electric field is that it equal the frequency for the acoustic field. The minimum volume for the focus that can be achieved at a given depth in the tissue is determined by the wavelength of the acoustic radiation and by the diameter of the transducer. For the frequencies of interest here—a few megahertz and above—the volume of tissue in the "stimulation region" can be restricted to a tenth of a cubic millimeter (at 4 MHz) or less if desired at higher frequencies.

Since the sound levels that must be employed to achieve stimulation by the mechanism under consideration are extremely high, it is necessary to take into account the cavitation thresholds for both tissue and coupling media in selecting an appropriate frequency of operation. These threshold values are dependent on the manner in which the liquid is degassed and/or freed of nuclei that constitute sites for cavitation initiation. The threshold is dependent on: the viscosity of the medium, the frequency of the acoustic field, the pulse duration, the vapor pressure, the dissolved gas content, and possibly a number of other factors.[33] It has been shown by Esche[34] that the cavitation threshold for degassed water at room temperature rises rapidly at frequencies near 1.0 MHz and, in fact, is greater than 50 atm for this frequency. As the frequency is increased above this value, the threshold for water rises rapidly. With respect to the brain, the author and collaborators (Fry[10]) have shown that cavitation does not interfere with the achievement of sound-pressure amplitudes of the order of 50 atm (1000 W/cm^2) at 1.0 MHz for durations of the order of a second, but at 10 000 W/cm^2, the cavitation threshold is exceeded at this frequency for pulse durations as short as 1.0 msec (unpublished data). By comparison, at a frequency of 3.0 MHz by direct measurement (unpublished data), a level of 10 000 W/cm^2 can be sustained in brain for periods as long as 5 msec without evidence of cavitation.

The propagation of ultrasonic energy through tissue is accompanied by absorption and, for most soft tissues that have received attention thus far, including the brain, the absorption coefficient per unit pathlength is directly proportional to the frequency. The value of the absorption coefficient at a frequency of 1 MHz has been shown by Dunn[35] to be independent of the sound level for mouse spinal cord up to an intensity of 200 W/cm^2. It has also been shown that at this same frequency, sound levels up to 1000 W/cm^2 are achieved deep within cat and monkey brains when the loss along the transmission path through the tissue is calculated on the basis of the "low-level" absorption coefficient value (Fry[10]).

[32] It should be recalled here that Eqs. 23 and 24 are applicable only when the extraneuronal impedance is small as compared to the transneuronal value, so that the conclusion stated here is subject to this limitation.

[33] T. F. Hueter and R. H. Bolt, *Sonics* (John Wiley and Sons, Inc., New York, 1955).

[34] R. Esche, "Untersuchung der Schwingungsk Cavitation in Flussigkeiten," Akust. Beih 4, 208-218 (1952).

[35] F. Dunn, "Temperature and Amplitude Dependence of Acoustic Absorption in Tissue," J. Acoust. Soc. Amer. 34, 1545-1547 (1962).

In order to achieve ultrasonic intensities of the order of 10 000 W/cm², it is necessary to consider the transfer of energy from the fundamental frequency of the field to the harmonics as the sound propagates toward the focus. This energy loss from the fundamental frequency can be of comparable importance to the absorption loss in the tissue. Therefore, it is essential to evaluate the magnitude of this energy-transfer process as a function of the convergence of the field, the sound level at the focus, the operating frequency, and other parameters of the tissue that are important in determining its acoustic-propagation characteristics. This has been done, and typical results of the computations are shown in graphical form in Figs. 5 and 6. The deviation from the linear relation existing at low sound levels indicates energy loss by the transfer process. The results for two frequencies, 1.0 and 4.0 MHz, are given for two values of the absorption coefficient: that for water at approximately 20°C and an average for brain tissue at a temperature of 37°C. The transverse "diameter" of the focus is chosen in each case slightly greater than one wavelength, 0.16 cm at 1.0 MHz and 0.04 cm at 4 MHz. Results for a single focal length, 5.0 cm, are given. The quantity $Q_1(0)$ is proportional to the sound-pressure amplitude at the transducer face and $Q_1(5)$ is the corresponding value at the focus. The gain of the focusing system is simply the ratio of these two values. (Intensity gain is equal to the square of the ratio.) Of course, in any practical experiment arrangement, part of the sound path is in the coupling medium so the gain for a composite transmission path is required. Curves are shown for two aperture angles of the cone of convergence, 60° and 90°, and it is apparent that the deviation from linearity occurs at higher sound levels at the focus for the larger angle, indicating the desirability of using the largest angle consistent with the opening that can be made in the skull to reach the sites of interest. All of the curves correspond to cases where the second harmonic content at the transducer is zero. However, in order to show the effect of adding a small percentage of second harmonic, the dots adjacent to the solid curves show the results of calculations when a value of Q_2 (proportional to the sound-pressure amplitude of the second harmonic) equal to 2% of Q_1 is introduced at $x=0$.

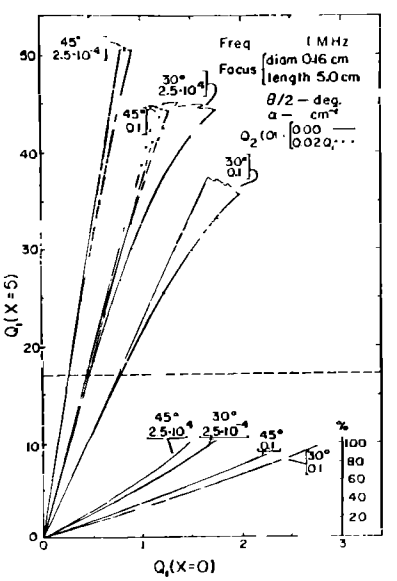

FIG. 5. Analytical results, frequency 1 MHz. Normalized pressure amplitude $Q_1(5)$ and percentage second harmonic at focus (lower set of curves) as a function of normalized pressure amplitude, $Q_1(0)$, before beam convergence taking into account energy transfer from fundamental and absorption. Curves shown for two values of the convergence aperture angle θ and pressure absorption coefficient α.

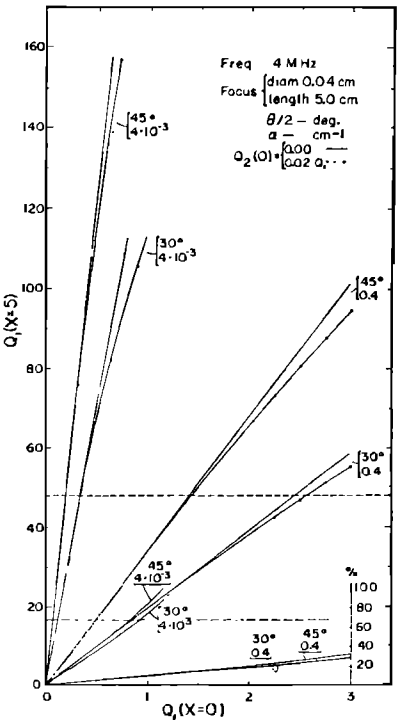

FIG. 6. Analytical results, frequency 4 MHz. Normalized pressure amplitude $Q_1(5)$ and percentage second harmonic at focus (lower set of curves) as a function of normalized pressure amplitude $Q_1(0)$ before beam convergence taking into account energy transfer from fundamental and absorption curves shown for two values of the convergence aperture angle, θ, and pressure absorption coefficient α.

Since a value of 10 000 W/cm², corresponding to a pressure amplitude of 171 atm, for the sound level at the focus, to produce stimulation by the mechanism analyzed in this paper, is an acceptable choice from the viewpoint of cavitation at a frequency of 3 MHz and above, and also from the viewpoint of tissue heating as discussed next, the value of $Q_1(5)=17.1$, which corresponds to this intensity level, is indicated by the horizontal lines on the graphs. It appears that 10 000 W/cm² can be achieved readily at the focus, insofar as limitations imposed by energy transfer to harmonics are concerned. For a cone of convergence for the beam of 90° apex angle, the curves of Figs. 5 and 6 yield for a sound level at the focus of 10 000 W/cm² a second harmonic content of about 5% at a frequency of 4 MHz and approximately 15% at 1 MHz. At the 50 000-W/cm² level, corresponding to $Q_1(5)=38.2$, the percentage of second harmonic is

about 15% at 4 MHz. As is discussed next, the use of such high sound levels at the focus at the higher frequencies would provide considerable advantages.

The choice of values for the acoustic-field parameters must be consistent with the avoidance of thermal damage to the brain, as already indicated. Therefore, it is necessary to calculate the heating produced by the acoustic pulse in the tissue at the focus. An upper limit for the increase in temperature that occurs can be obtained by assuming that no heat conduction takes place during the time of the pulse, and this assumption is not inaccurate because of the short pulse lengths employed. Under these conditions, the time rate of change of temperature is (Fry[10]):

$$dT/dt=\mu I/\rho C. \tag{27}$$

In this expression, the symbols designate: μ—intensity absorption coefficient per unit pathlength (centimeters^{-1}), ρC—heat capacity of the tissue per unit volume (joules/cubic centimeter), and I—sound intensity (watts/square centimeter). For a rectangular acoustic pulse of time duration t_s, the above expression yields

$$(\Delta T)_a=\frac{I}{\rho C}\int_0^{t_s}\mu dt, \tag{28}$$

where μ is a function of the temperature and $(\Delta T)_a$ designates the incremental change in temperature caused by the acoustic field. To obtain an estimate of the magnitude of the temperature increase in the tissue for specific conditions of irradiation at 37°C, one can choose the value for the heat capacity of the tissue equal to that of water and for μ a value of 0.20 times the frequency in megahertz. As a typical result: For a frequency of 4.0 MHz, an intensity of 10 000 W/cm^2, and a pulse duration of 1.09 msec, the maximum temperature rise in the tissue due to the absorption of acoustic energy is 2.1°C.

Ultrasound can also produce lesions in the central nervous system by "nonthermal" action (Fry[10]), and dosage studies indicate that, in this case, a linear relationship exists between sound-pressure amplitude and the reciprocal of the duration of exposure to result in a specific change in the tissue. These data have been obtained by irradiation of the young mouse spinal cord (Dunn and Fry[36]) for a variety of body temperatures of the animal. Extrapolation from the conditions under which the mice were irradiated (maximum intensity about 200 W/cm^2 and frequency of 1.0 MHz) to the conditions required for stimulation by the mechanism analyzed in this paper is too great a step to yield much confidence in derived values of the parameters for lesion production, by the nonthermal mechanism, at the high sound levels required—10 000 W/cm^2 or higher. However, such extrapolation does suggest that nonthermal lesions would not be produced under some of the conditions appropriate for stimulation, and this is experimentally verified by unpublished observations made at this laboratory—at 3.0 MHz and 10 000 W/cm^2, lesions are not produced for exposure times as long as 5 msec. Thus, it appears that an order-of-magnitude safety factor between the conditions for stimulation and "nonthermal" lesion production can be achieved.

The simplest method, in principle, of producing an electric field within a large fraction of the brain is to use metal electrodes (either insulated or noninsulated) in contact with Ringer's solution bridges, which are in turn in contact with the exposed dura or surface of the brain. The use of ionic conducting bridges to couple the electrical energy to the tissue eliminates fringe field effects at the brain surface. Such precautions are imperative since, although the current densities are of the same order as those at microelectrode tips when injecting neurons intracellularly,[37,38] the total electric power and the total current that must be transferred via an electrode when whole brains are involved are necessarily large. For example, a current density of 8.5 A/cm^2 throughout a brain volume of 25 cm^3 (squirrel monkey) corresponds to a pulse power of about 225 kW. These values indicate the desirability of employing even higher sound levels and thereby reducing the current density and total power required. However, the purpose here is to show that an acceptable set of values of the parameters for stimulation appears to exist and to leave for future combined experimental and theoretical study the choice of optimum sets.

The electrode polarization impedance (uninsulated metal) in contact with a salt solution is dependent on the value of the current density only for low densities. Schwan[12] has studied this electrode-polarization impedance phenomenon from both a theoretical and an experimental viewpoint, and it appears from his work at current densities lower than those of interest here that, as the current density increases to the relatively high values of the order of tens of amperes per square centimeter, the voltage drop across the polarization impedance will tend to a constant value independent of the current density.

One of the limitations on the parameters of stimulation for the method under consideration results because of heating of the tissue by the current that flows through the large tissue volume. This restricts

[36] F. Dunn and W. J. Fry, "An Ultrasonic Dosage Study: Functional Endpoint," in *Ultrasound in Biology and Medicine*, E. Kelly, Ed. (American Institute of Biological Science, Washington, D. C., 1957), pp. 226–235.

[37] High unidirectional current-density values are calculated from data available in the literature. For example, if the microelectrode current during injection is $5(10)^{-8}$ A and the inside diameter of the tip is 1.0 μ (see for example Coombs *et al.*, Ref. 38), the current density in the cell body at the electrode interface within the cytoplasm is 7 A/cm^2 and such current densities are applied for periods of time of the order of 1 min.

[38] J. S. Coombs, J. C. Eccles, and P. Fatt, "The Electrical Properties of the Motoneuron Membrane," J. Physiol. (London) 130, 291–325 (1955).

the frequency of stimulation since the heat is not so readily dissipated as that resulting from a very localized and restricted application of a stimulating electric current pulse, such as that at a probe electrode. In the latter case, the current densities can be quite high but the temperature in the region of the electrode returns rapidly between successive applications of the stimulating pulse because of the high-temperature gradient in the region of the electrode and the rapid exchange of blood at lower temperature from the immediate surroundings. Thus, the necessity of operating at higher sound levels and lower current densities is emphasized. For example, if the tissue can sustain a sound level at the focus of 50 000 W/cm^2 at an appropriately chosen frequency—e.g., 4 MHz—then the total electrical power for stimulation can be reduced by a factor of approximately 5 over that required at 10 000 W/cm^2. Values of the calculated temperature increase at the focus for this sound level are also included in Table II. The contribution to the temperature rise caused by the second harmonic of the acoustic field is calculated on the basis of a 90° cone of convergence for the beam. In this case, for a 50 000-W/cm^2 intensity of the fundamental, the heating at the focus due to the second harmonic of the field amounts to approximately 5% of that caused by the fundamental.

The temperature rise due to electrical heating during the period of a pulse is readily computed, if it is assumed that heat dissipation is absent, which is substantially the case for the short pulse times of interest. Then

$$(\Delta T)_e = J_0^2 R t_s / 2\rho C, \tag{29}$$

where R designates the resistivity of the tissue. Values for this temperature increment per pulse are also given in the Table, and the total temperature increase at the acoustic focus due to the combination of acoustic and electric absorption is listed.

III. CONCLUSIONS

(1) A quantitative expression is derived that constitutes the condition for electrical stimulation of neural elements in localized sites in the brain by externally applied, pulsed, high-frequency electric and acoustic fields. The magnitudes and configurations of the electric- and acoustic-field variables required are expressed in terms of the pertinent parameters of brain, including its electric and acoustic properties, and the threshold values of the stimulation paraments of the neural elements.

(2) Limitations on the energy content of the high-level electric and ultrasonic fields imposed by their heating actions and by nonthermal mechanisms of damage are considered. Energy transfer to the harmonics of an intense focused ultrasonic field is also discussed from the viewpoint of determining the conditions for achieving the requisite amplitudes of the acoustic field variables at the focus. Cavitation thresholds and electric polarization at electrode interfaces are also considered.

(3) An analysis of data available in the literature on stimulation of neural elements of the brain by macroelectrode and microelectrode methods is made in order to obtain values for the unidirectional charge-transfer parameter to result in neuron stimulation. Data on the variation of the threshold amplitude for stimulation by rectangular electric current pulses, applied via macroelectrode, as a function of the pulse length are combined with information on single neural units to provide values for the charge-transfer parameter to be employed in the expression constituting the condition for stimulation by the electroacoustic mechanism considered here.

(4) Acceptable values for the amplitudes of the electric- and acoustic-field parameters to be employed to stimulate cortical pyramidal neurons are presented.

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