ELECTROMAGNETIC FIELDS IN BIOLOGICAL STUDIES

W. C. Parkinson

Department of Physics
University of Michigan
Ann Arbor, Michigan

For biological or cellular experiments using electromagnetic fields, it is essential that the parameters defining the field be carefully specified if the results are to be meaningful and are to be compared with the same experiment conducted in a different laboratory. The interaction of living systems with electric and magnetic fields can come only through forces exerted on the charges on the system. If the charges are stationary, the only origin of the force is the electric field. This electric field may be established by charge distributions, as in "capacitive plate" experiments, or by time-varying magnetic fields.

A geometry commonly used to produce time-varying magnetic fields consists of a pair of coaxial coils, each of equal radius and separated by a distance often equal to the radius. The electric field induced by a varying current in such a pair of coils varies both in space and in time. The electric field strength is zero on the axis of symmetry, and increases to a maximum near the radius of the coils. The strength is proportional to the time rate of change of the current in the coil, which depends not only on the amplitude and shape of the voltage pulse applied to the coil but also on the resistance and inductance of the coil.

The purpose of this article is to describe how these important physical parameters may be determined for both geometries.

Keywords – Pulsed electromagnetic fields, Capacitive plate experiments, Osteogenesis, Wound healing.

INTRODUCTION

There is now an extensive literature on the application of both steady and time-varying electric and magnetic fields to cellular systems in vivo and in vitro. That work in the field will expand is guaranteed by the exciting results obtained to date. Two examples will illustrate the point.

It has been determined experimentally that appropriate pulsed magnetic fields (1) as well as electric fields (2) promote osteogenesis and wound healing, and that direct current (DC) electric fields cause cultured epithelial cells (3,4) and cultured neural crest cells (5) to elongate perpendicularly to the field and migrate along the field. The fact that the exact mechanisms involved in these phenomena is not understood has led to a flurry of activity.

In many of the research publications describing results of the application of magnetic and electric fields to biological systems, the descriptions of the experimental arrangements do not permit determination of the critical physical parameters. As a result, it is not possible to compare quantitatively the results of an experiment carried out in one laboratory with those from another laboratory. The purpose of this article is to describe how to determine the one important parameter, the electric field, associated with the electric and magnetic field configurations commonly used.

The fact that the electric field is the dominant parameter in pulsed electromagnetic field (PEMF) experiments follows from the fact the interaction comes through forces exerted by the field on the electric charges contained in the atoms, molecules and larger components of the system. The force on these charges due to the applied or induced electric field E is $\boldsymbol{F} = \boldsymbol{qE}$, while that due to the magnetic field B is $\boldsymbol{F} = q\boldsymbol{v} \times \boldsymbol{B} = qvB\sin\theta$. If the charge is stationary, there is no magnetic force. At the very low velocities existing at the normal biological temperatures ($v = \sqrt{3kT/m}$), the magnetic force may be ignored. Thus, the magnetic field itself is not of interest, and a *changing* magnetic field is of interest only in that it induces an electric field. In any given experiment, there is a simple way to determine that the magnetic force can in fact be ignored. This is described below.

We look first at the electric fields, static and dynamic, produced by charge distributions, then at (induced) electric fields produced by time-varying magnetic fields.

ELECTRIC FIELDS FROM CHARGE DISTRIBUTIONS

Static Electric Fields

Consider the "capacitive plate" arrangement shown in Fig. 1a, where two parallel metal conducting plates in air or vacuum, each of area A, are spaced a distance d apart. If charges $+q$ and $-q$ are placed on the plates, the *electric field* between the plates will be essentially uniform (provided $d \ll \sqrt{A}$) and equal to $E = q/\epsilon_0 A$, where ϵ_0 is a proportionality constant, the permittivity of free space, and has the value 8.85×10^{-12} F/m. The direction of E is from the $+$ to the $-$ plate and perpendicular to the plates (Fig. 1b).

The potential difference between the plates is $V = \int \boldsymbol{E} \cdot \boldsymbol{dl} = qd/\epsilon_0 A$, and of course the usual way to put charge on the plates is to connect them to a power supply of voltage V (but they can be charged in other ways).
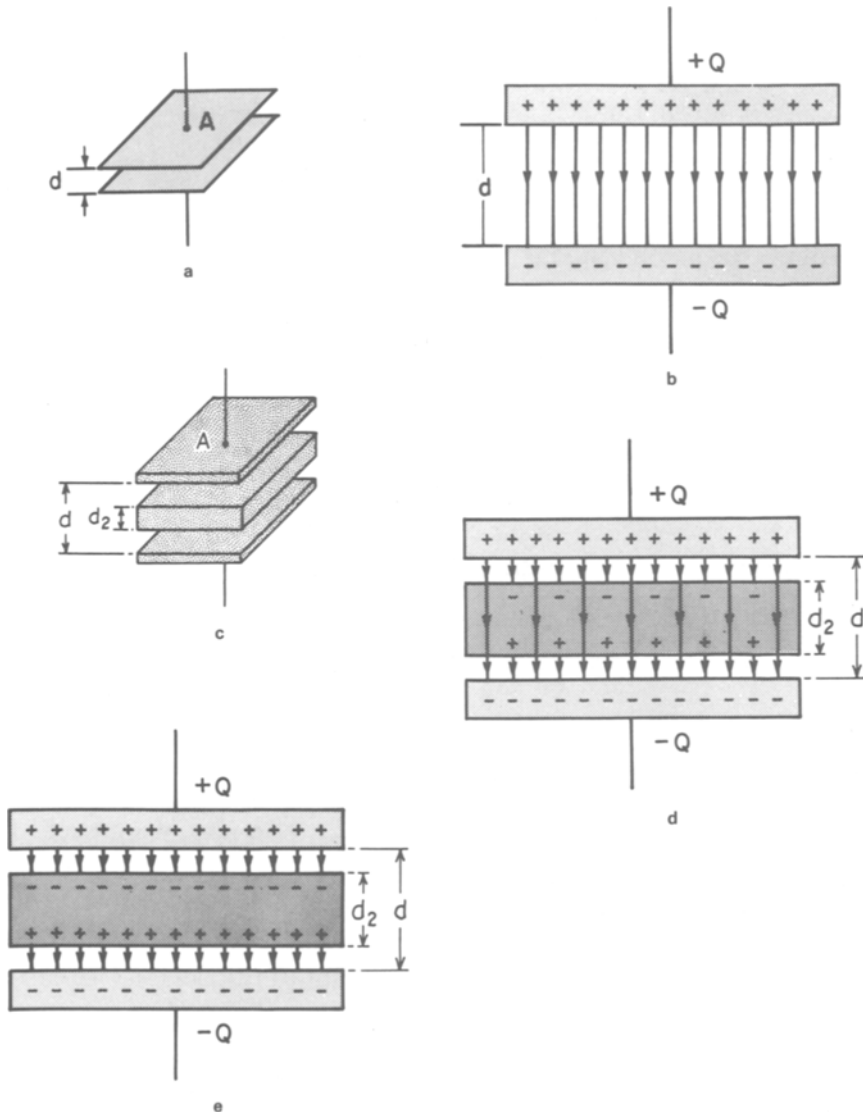
FIGURE 1. The electric field between parallel plates. The field between charged plates of area *A* spaced a distance *d* apart (a) is uniform as shown in (b). A dielectric inserted between the plates (c) reduces the field in the dielectric (d). The field in a conductor inserted between the plates is zero (e).

If a slab of nonconducting dielectric material of thickness d_2, such as glass or polystyrene, is placed between the plates, the electric field in the dielectric will be reduced to $E_2 = q/\kappa\epsilon_0 A$, where κ, the relative dielectric constant, is greater than unity and depends on the material (glass ~4.5, polystyrene ~2.6, water ~80). The reason the field is reduced in the dielectric medium

is that charges are induced on the surface of the electric in such a way as to oppose the field (Fig. 1d). A constant potential V applied to the plates will result in an electric field E_1 in the space d_1 between the plates and the dielectric ($d_1 = d - d_2$) of $E_1 = \kappa V/[\kappa d - d_2(\kappa -1)]$ and a field in the dielectric of $E_2 = V/[\kappa d - d_2(\kappa - 1)]$; the field in the dielectric is less than in d_1 (vacuum or air) by the factor κ as indicated above.

If now the dielectric is replaced by a conductor, say a piece of aluminum or a volume of culture medium, the field inside the conductor will be zero. The reason is that by definition a conductor contains free charges, charges (electrons or positive ions) that are free to move. They will move to the surface leaving zero field inside as shown in Fig. 1e. (The field inside must be zero or a free charge there would experience a force.) Thus, it is not possible in a static arrangement of capacitance plates to have an electric field in a conductor. Culture medium is a good conductor ($\sigma = 1$ mho/m for typical culture medium, 12 mho/m for 2 N NaCl, 3.5×10^7 mho/m for Al and of the order of 10^{-12} mho/m for an insulator such as polystyrene). If capacitive plates are used with a flask of culture medium fit snugly between them, the electric field is confined to the material of the flask, and the field in the medium is zero.

Stationary Electric Field in a Conducting Medium

A steady or stationary electric field can be produced in a conducting medium by passing a steady (DC) current through the medium. A conductor of conductivity σ, cross-sectional area A and length l will have a resistance $R = l/\sigma A$ Ω; and if a potential difference is maintained across the ends of the conductor, a current I will exist in it. The electric field will be $E = V/l = IR/l = I/\sigma A$. A charge q in the medium will then experience a force $F = qE$. In such experiments (4) it is important to restrict the current to low values to avoid ohmic (I^2R) heating of the medium. Small channels are usually provided: if $A \sim 10^{-2}$ cm^2, $l \sim 1$ cm, and $\sigma \simeq 10^{-2}$ mho/cm, a field of 10 V/cm is obtained for $I = 1$ *mA* with a power input to the channel of 10 mW (as will be shown in Fig. 3a).

Pulsed Electric Fields

If voltage pulses are applied to the capacitive plates of Fig. 1e, then the charges in the culture medium (conductor) must redistribute as the capacitance is alternately charged and discharged. This will produce a transient electric field (pulsed field) in the medium. The redistribution of charge takes time. This is characterized by a "relaxation time." The relaxation time is determined by the mobility of the charge carriers, which is related to the conductivity of the material. It can be shown (6) that the charge density (C/m^3) will be given by $\rho = \rho_0 e^{-\sigma t/\epsilon}$, where ρ_0 is the free charge density in the medium

at time $t = 0$, the time at which the voltage is changed. The relaxation time is the time required for ρ to fall to $1/e$ of its final value and is $\tau = \epsilon/\sigma$. If $\epsilon = \kappa\epsilon_0 = 80 \times 8.85 \times 10^{-12}$ and $\sigma = 1$ mho/m, then $\tau \simeq 7 \times 10^{-10}$ s for culture medium. For pure water $\tau \simeq 4 \times 10^{-8}$ s. These are short times; an ion with thermal velocity would move on the order of 1 μm in 10^{-9} s.

If capacitive plates are used with tissue culture dishes and culture medium, the charge which accumulates at the interfaces of the dielectrics and the conducting medium must redistribute each time the potential changes. The time associated with the redistribution is given above. When the voltage is applied, the initial electric fields are given by $\epsilon_1 E_1 = \epsilon_2 E_2$, as required by the condition of constant flux density. After the transient has died out and the voltage V is at a constant value, the current densities must be the same, or $\sigma_1 E_1 = \sigma_2 E_2$. To use a specific example, consider the geometry used by Korenstein et al. (7). [The electric fields in the cylindrical geometry used by Rodan et al. (8) cannot be easily evaluated. The use of the curved copper electrodes as they describe produces an electric field in the culture medium, which is a complicated function of the geometry.] In the Korenstein arrangement, two circular metal electrodes A, each 54 mm in diameter, one in close contact with the bottom of a petri dish P, the other coated with a very thin insulating layer of clear krylon, is in contact with the upper surface of the culture medium M as depicted in Fig. 2a. This arrangement forms a two-layer capacitor represented in Fig. 2b and c, where C_1 is the capacitance associated with the culture medium of depth $d_1 = 2.25$ mm and C_2 with the polystyrene bottom of the petri dish of thickness $d_2 = 1.25$ mm. Because the conductivity σ_1 of the medium is relatively large ($\sigma_1 \sim 2$ mho/m), R_1 will have a small value ($R_1 \sim 0.49$ Ω). While polystyrene is a very good insulator ($\sigma_2 \le 10^{-10}$) and R_2 can be taken as infinite, for the moment we consider it finite. The usual solution given when $t = 0$, the instant the switch S is closed, is

$$V_1 = V\left(\frac{R_1}{R_1 + R_2}\right)\left[1 - \left(1 - \frac{C_2 R_2}{\tau}\right)e^{-t/\tau}\right]$$

$$V_2 = V\left(\frac{R_2}{R_1 + R_2}\right)\left[1 - \left(1 - \frac{C_1 R_1}{\tau}\right)e^{-t/\tau}\right]\ ,$$

where

$$\tau = \frac{R_1 R_2 (C_1 + C_2)}{R_1 + R_2} = \frac{\epsilon_1 d_2 + \epsilon_2 d_1}{\sigma_1 d_2 + \sigma_2 d_1}\ .$$

If now we take $R_2 = \infty$ ($\sigma_2 = 0$), then

$$\tau = R_1(C_1 + C_2) = \frac{1}{\sigma_1}\left(\epsilon_1 + \epsilon_2 \frac{d_1}{d_2}\right)\ ;$$
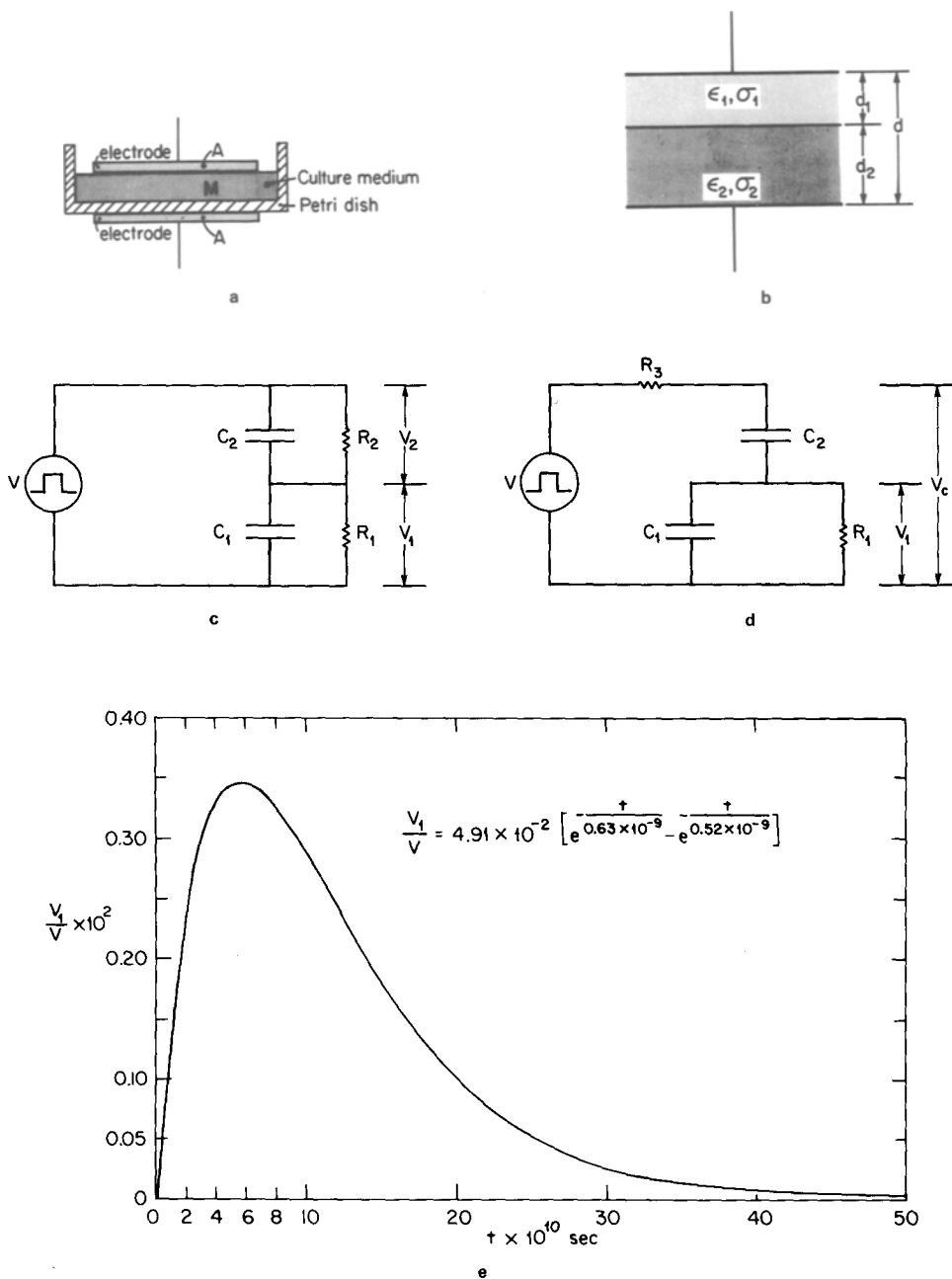
FIGURE 2. Geometry for a typical capacitive plate experiment. a: The geometry using a petri dish with culture medium and circular electrodes of area A. b: The capacitor equivalent. c: An incorrect equivalent circuit representation. d: A correct representation when $R_2 = \infty$ and the voltage generator V has a resistance R_3. e: The ratio of the voltage V_1 across the medium of conductivity σ_1 to the applied voltage V as a function of time. The electric field (for parallel plates) is V_1/d_1. Note particularly that the peak amplitude of V_1 is very small ($V/300$ for the example shown) and is of very short time duration, approximately 30×10^{-10} s.

The equation shown in panel e:

$$\frac{V_1}{V} = 4.91 \times 10^{-2} \left[e^{-\frac{t}{0.63 \times 10^{-9}}} - e^{-\frac{t}{0.52 \times 10^{-9}}} \right]$$

and when S is closed, V_1 and V_2 jump discontinuously to

$$V_1 = V\left(\frac{C_2}{C_1 + C_2}\right) \quad ; \quad V_2 = V\left(\frac{C_1}{C_1 + C_2}\right) .$$

The voltage V_1 decreases to zero and V_2 increases to $V_2 = V$ as $e^{-t/\tau}$. Thus, after a time corresponding to a few time constants τ, the field in the culture medium is zero and the potential V appears across C_2 (the polystyrene). The difficulty here is that this solution requires that the voltage generator deliver an infinite current initially to the capacitors. Since we are interested in what happens at the immediate times the generator switches polarity, it is important to include the impedance R_3, usually resistive, of the generator, as shown in Fig. 2d, where now it is assumed that the conductivity of the insulating material of C_2 is zero, i.e. $R_2 = \infty$. The solution for this circuit (see Appendix A) is

$$V_1 = V\frac{1}{R_3 C_1}\frac{\alpha_1 \alpha_2}{(\alpha_1 - \alpha_2)}(e^{-t/\alpha_1} - e^{-t/\alpha_2})$$

$$V_C = V\left\{1 - \frac{1}{R_1 C_1}\frac{\alpha_1 \alpha_2}{(\alpha_1 - \alpha_2)}\left[\left(1 - \frac{R_1 C_1}{\alpha_1}\right)e^{-t/\alpha_1} - \left(1 - \frac{R_1 C_1}{\alpha_2}\right)e^{-t/\alpha_2}\right]\right\} ,$$

where α_1 and α_2 are given by

$$2(\alpha_1, \alpha_2) = [R_1(C_1 + C_2) + R_3 C_2] \pm \sqrt{[R_1(C_1 + C_2) + R_3 C_2]^2 - 4R_1 R_3 C_1 C_2} ,$$

where for $2\alpha_1$ take the + sign and for $2\alpha_2$ take the negative sign. For the Korenstein geometry of Fig. 2a, $\alpha_1 \simeq 0.63 \times 10^{-9}$ s and $\alpha_2 \simeq 0.52 \times 10^{-9}$ s for $C_1 = 1140$ pF, $C_2 = 11$ pF, $R_3 = 52.3$ Ω and $R_1 = 0.5$ Ω. The values of C_1, C_2 and R_1 are calculated from the dimensions, conductivities and dielectric values given above. The value of R_3 typically is in the range of $10 \sim 100$ Ω. The potential across the culture medium that is proportional to E_1 ($E_1 = V_1/d_1$) is plotted in Fig. 2e. Note that the electric field does not rise discontinuously; further it persists for a very short time ($\sim 3 \times 10^{-9}$ s) compared to the width of the applied pulse (7) (25 μs) and is small ($V_1 \ll V$). It will reverse and be of the same form when the voltage pulse returns to zero. The field will persist for a longer time duration if C_1 is made smaller and C_2 larger, i.e. make the cross-sectional area of C_1 smaller, the depth of the medium greater and the bottom of the petri dish thinner.

There will be free charges at the interface, the number being determined by the applied voltage and the total capacitance, which for long times as compared to τ will be C_2. The number of unbound charges at the interface is then $Q' = Q/\kappa = \epsilon_0 Q/\epsilon$. Their effect on the cells plated on the surface should be similar to that of any charged substrate used to enhance adhesion in cell culture.

Clearly, the capacitive plate arrangement is not an effective way to produce pulsed electric fields. They can, however, be produced efficiently by using the conducting channel. If the voltage source is capacitively coupled to the channel, the DC current is guaranteed to be zero (Fig. 3a). The duration of the electric field pulse and the amplitudes in the forward and reverse directions are controlled by the time constant $\tau = RC$, where R is the resistance of the channel and C the coupling capacitor. Waveforms for the electric field are given in Fig. 3b for two values of t_p/τ. This assumes the resistance R of the channel of length l is much larger than the resistance of the electrodes. The expression for the electric field in the channel is
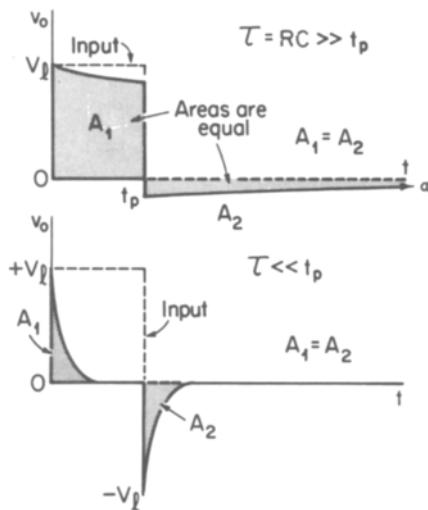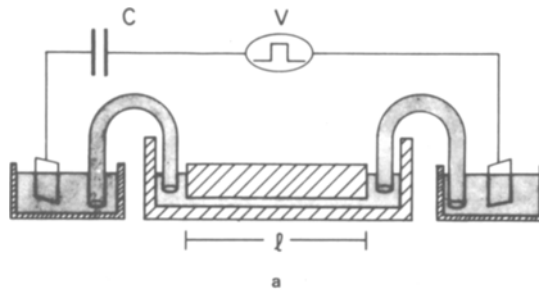
FIGURE 3. Geometry for producing pulsed electric fields in a conducting medium. a: A narrow channel of length l having resistance R is coupled through agar bridges to the electrodes. The rectangular voltage pulse V is coupled to the electrodes through the capacitance C. b: The voltage waveforms across the channel for two different time constants τ, where $\tau = RC$ and t_p is the time duration (width) of the voltage pulse V. There can be no DC current through the channel. The electric field is V_l/l and reverses in direction at $t = t_p$. The net field averaged over time is zero.

$$E = \frac{V_R}{l} = \frac{V}{l} e^{-t/\tau} \quad \text{for } t \leq t_p$$

$$E = \frac{V}{l} (e^{-t_p/\tau} - 1)e^{-(t-t_p)/\tau} \quad \text{for } t \geq t_p \; .$$

Note particularly that for any periodic waveform capacitively coupled to the channel, the average value of the electric field is zero; i.e. in Fig. 3b the areas A_1 and A_2 are equal.

Sinusoidal Electric Fields

If a sinusoidal voltage $V = V_0 \sin \omega t$ is applied to the circuit of Fig. 2d, the ratio of the voltage V_1 across the culture medium to the applied voltage will be

$$\left| \frac{V_1}{V} \right| = \frac{1}{\sqrt{(1 + R_3/R_1 + C_1/C_2)^2 + (\omega R_3 C_1 - 1/\omega R_1 C_2)^2}} \; .$$

For the values of R_1, R_3, C_1 and C_2 appropriate to the Korenstein arrangement, the ratio of V_1 to the applied voltage V at $f = 60$ Hz is $|V_1/V| = 2 \times 10^{-9}$, and for $f = 10^4$ Hz $|V_1/V| = 3.5 \times 10^{-5}$. Thus, there is essentially no electric field in the culture medium. Again this is due mainly to the low value of the resistance R_1.

A sinusoidal voltage applied directly to the channel of Fig. 3a, without the coupling capacitor, will produce an alternating electric field in the channel of $E = (V/l)\sin \omega t$.

MAGNETIC FIELDS AND INDUCED ELECTRIC FIELDS

General Remarks

Magnetic fields, both steady and time varying, are produced by currents (the field of a permanent magnet is produced by the electronic currents in the atoms). A configuration frequently used in PEMF experiments consists of two identical, coaxial coils separated by a distance d about equal to their radius a, similar to the well-known Helmholtz configuration illustrated in Fig. 4. Other coil shapes can and have been used, and for these the magnetic field B at any point is easily determined by measurement. However, it is not a simple matter to determine the induced electric field E (see below for further discussion). If a steady DC is sent through the circular coils (connected to be aiding), a steady magnetic field B will exist in the region of the coils. We will assume there is no ferromagnetic material such as iron in the vicinity. The magnitude and direction of B will vary from point to point and can
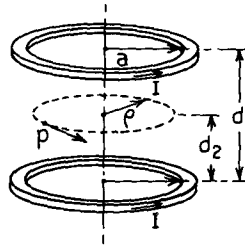
FIGURE 4. A current configuration frequently used for producing a magnetic field. Two identical coaxial coils, each of *N* turns, carrying a current *I* and having a mean radius *a*, are separated a distance *d*. If *d = a* the configuration is known as "Helmholtz coils." The magnetic field can be calculated (Appendix B) and is easily measured. If the current *I* varies with time, there will be an induced electric field which can also be calculated and easily measured (see text). The electric field is always zero on the axis. At a radius ρ, the field at every point *P* is tangent to the circle of radius ρ and lies in the plane of the circle parallel to the plane of the coils as shown.

be calculated (Appendix B). They can also be easily measured using commercially available gaussmeters.* There is no induced electric field in the region. That is, there is no electric field associated with a constant (unvarying in time) magnetic field; thus, there is no force acting on the charges in the biological system provided they are at rest.

If now the current in the coils is varied with time, either sinusoidally or pulsed, there will be both an induced electric field *E* which will vary with time and a magnetic field *B* which also will vary with time. The field *B* is proportional to the current *i*, while the field *E* is proportional to the time rate of change of the current, i.e. to di/dt. There are two points that have caused the difficulty in interpretation of data when either sinusoidal or pulsed voltages are used. First, there is no simple quantitative connection between the *voltage V* applied to the coils and fields *B* and *E*. It is necessary to know the current and the rate of change of current in the coils produced by *V*, and this depends on the inductance *L* and resistance *R* of the coils as well as the time variation in *V*. This is illustrated below. Second, while a loop of wire anywhere in the field will have induced across the open ends (Fig. 5a) a *voltage* $\mathcal{E} = -A(dB/dt)$, where *A* is the area of the loop perpendicular to the field *B*, this gives no quantitative information about the force on the charges, i.e. about the electric field at a given point. (The symbol $\mathcal{E}$ is used for induced voltage to distinguish it from the voltage *V* that is applied to the coils to cause the current.) If the loop is closed, the wire (or any conductor) will have a current induced in it due to *E* (not $\mathcal{E}$). The voltage (potential difference) measured between any two points *a* and *b* in Fig. 5b is not well defined. The reason is that the induced electric field is a nonconservative field, and therefore the potential difference depends on the path taken in moving from *a* to *b*. Thus,

---
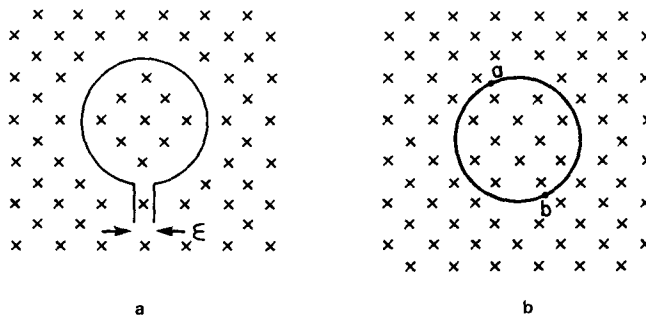
*Such as the model 750AR gaussmeter, RFL Industries, Boonton, NY.

FIGURE 5. Induced EMF. a: An open-loop conductor in a time-varying magnetic field will have an EMF ℰ induced across the open ends. The magnetic field is represented by the x's and is taken as perpendicular into the paper. b: For a closed conducting loop in a time-varying magnetic field there will be a current induced in the wire but the potential difference between any two points such as *a* and *b* is not well defined.

the induced electric field E at any point must in general be calculated. However, for coils with circular symmetry such as the Helmholtz configuration, the field can be determined from a measurement of the induced voltage in a circular loop of wire, but *only* if the loop is concentric with the axis of the field coils. If the loop is nonconcentric, a measurement of induced voltage ℰ gives $\int_c E \cdot dl$ around the loop, but this does not permit the electric field E to be determined at a given point because E is not the same at each point of the loop (as will be shown Fig. 7). Graphs for the calculation of E are given in Appendix B for circular coils.

It is important in the interpretation of experimental results to distinguish the variation of E in space, which depends on the geometry of the coil, and the variation of E with time, which depends on the shape of the applied voltage pulse V, the resistance R and the inductance L. The value of E at any point in space can in principle be calculated for coils of arbitrary shape [such as the EBI coil configuration – see e.g. Dierickx et al. (9)], but it is not easy. The problem is simplified if a pair of coaxial circular coils is used (Fig. 4). Even so the calculation is not elementary (see Appendix B), but once carried out results can be obtained for different-sized coils with relative ease using simple computer programs. Graphs of $E/(di/dt)$ and of (B_z/i) as a function of distance ρ from the axis are given in Fig. 6a and b for three planes parallel to the coils: on the midplane $G = 0.50$ corresponding to $d_2 = 0.5 \, d$; $G = 0.7$, $d_2 = 0.7d$; and $G = 0.9$, $d_2 = 0.9d_2$ (Fig. 4). Note particularly that E is zero on the axis and increases as ρ increases to approximately the value a and then decreases. This is the first and most important fact. Thus, if it is indeed the induced electric field E that is producing an effect on the cell activity, then the results will depend critically on the location of the cell in the coil geometry. Thus, in the limit of very small cells, there should be no
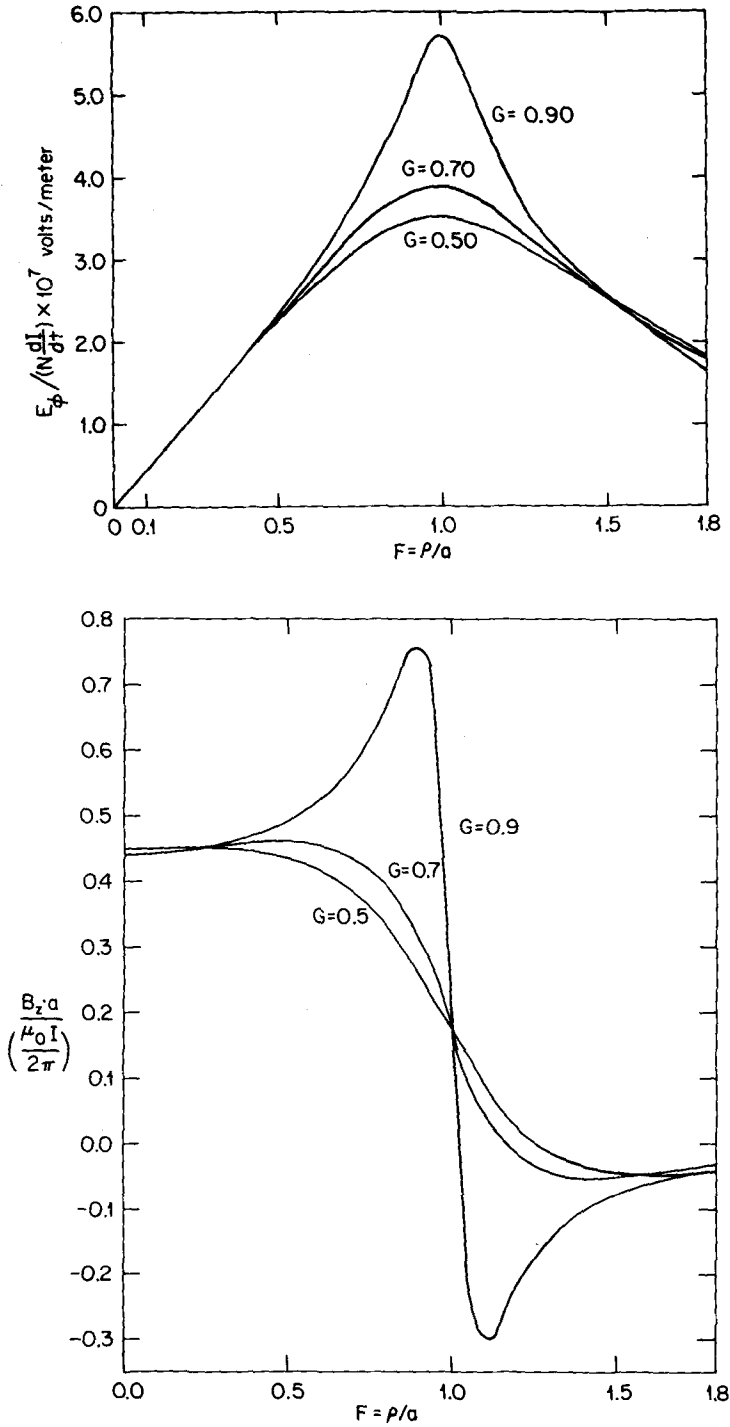
FIGURE 6. The fields of the current loops of Fig. 4. (a) The electric field as a function of radius ρ for three values of d_2 measured in units of the radius a $(G = d_2/d)$. The curve for the value $G = 0.50$ is in the plane midway between the coils. (b) The magnetic fields, calculated as a function of radius ρ for the same three values of G.

effect for cells exactly on the axis of the coils. The direction of the E field at any point P in Fig. 4 is in the plane parallel to the coils containing P and tangent to the circle of radius ρ. If each coil contains N turns, then the value of E will be N times that for a single loop. Thus, looking down on the plane containing P, the field E is perpendicular to the radius ρ at every point and at a fixed radius constant in magnitude (Fig. 7a). However, as shown in Fig. 7b, the field induced at each point on a circle with its center off axis is not tangent to the circle nor is it constant in magnitude. Thus, it is crucial to the interpretation of the results of any experiment using EMF that the position of a cell be accurately known with respect to the axis of symmetry of the coils.

Sinusoidal Voltages

A sinusoidal voltage V applied to the coils of Fig. 4 will result in a current i, which aside from a constant phase factor will also be sinusoidal and equal to $i = [V/\sqrt{R^2 + (\omega L)^2}]\sin\omega t$, where $\omega = 2\pi f$ is the angular frequency of the voltage source and R and L are the resistance and inductance of the two coils in series, respectively. The resistance and inductance are easily measured for the pair of coils using an impedance bridge.* The induced electric field, which is proportional to $(di/dt) = [\omega V/\sqrt{R^2 + (\omega L)^2}]\cos\omega t$, will be also sinusoidal. At a given point P (Fig. 4), the value of E and therefore the force on a charge at P will vary sinusoidally in time and will reverse in direction each half-cycle. The value can be obtained from the graph of Fig. 6a by using the above expression for (di/dt). Alternatively it can be measured very simply by using a circular pick-up coil of n turns and radius r accurately located with its axis coincident with the axis of the current coils. If the peak or maximum value of the voltage $\mathcal{E}$ induced in the coil is $\mathcal{E}_m$ (measured with an oscilloscope or high-impedance voltmeter), then the maximum value of the electric of field E_m at the radius $\rho = r/a$ is $E_m = \mathcal{E}_m/2\pi rn$ V/m, where r is the radius of the pick-up coil in meters. We find it convenient to wind several pick-up coils of different radii in shallow circular grooves in a Lucite plate that can be easily but accurately inserted in the field parallel to the current coils. This way it is a simple matter to measure the electric field at several radial points. A word of caution: The leads from the pick-up coils must be tightly twisted and brought well outside the field coils to avoid unwanted pick-up in the leads.

Pulsed Voltages

Consider now a pulsed voltage applied to the coils. The induced electric field E will depend not only on the time distribution of the voltage pulse, but also on R and L. It will not in general have the same waveform as V. As an example, if a step voltage pulse of amplitude V is applied at $t = 0$ and

---

*Such as the model 1650A impedance bridge, General Radio Company, Concord, MA.
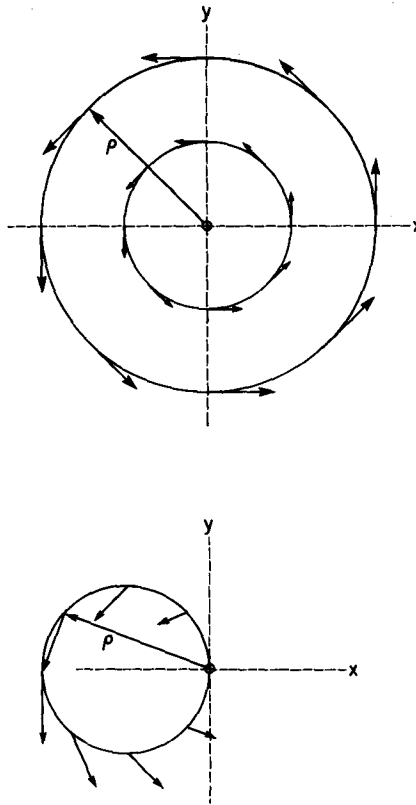
FIGURE 7. Electric field for the current loops of Fig. 4. (a) The field looking down the axis onto the plane containing the point *P*. The field strength is proportional to the length of the vectors (arrows) and is symmetrical about the axis of symmetry. (b) The electric field vectors around a circular loop centered off the axis of symmetry. Each vector has a length approximately proportional to the distance *ρ* from the origin 0 for *ρ* < *a* (see Fig. 6a) and is perpendicular to *ρ*. Note particularly the electric field is zero on the axis 0.

remains at *V* thereafter, the current *i* will rise exponentially from zero to the final value V/R with a time constant $\tau = L/R$, or $i = (V/R)(1 - e^{-t/\tau})$, as shown in Fig. 8a. If, however, a rectangular pulse of amplitude *V* and of duration t_p is applied to the same pair of coils, the resulting current is again given by $i = (V/R)(1 - e^{-t/\tau})$ for $\leq t_p$ but by $i = i_0 e^{-(t-t_p)/\tau}$ for $t \geq t_p$, where $i_0 = (V/R)(1 - e^{-t_p/\tau})$. A graph of *i* is given in Fig. 8b for three different values of the time constant *τ*. Because *B* is proportional to *i*, these graphs also give the time dependence of *B*.

The value of *E* is proportional to d*i*/d*t*, which for a step pulse is

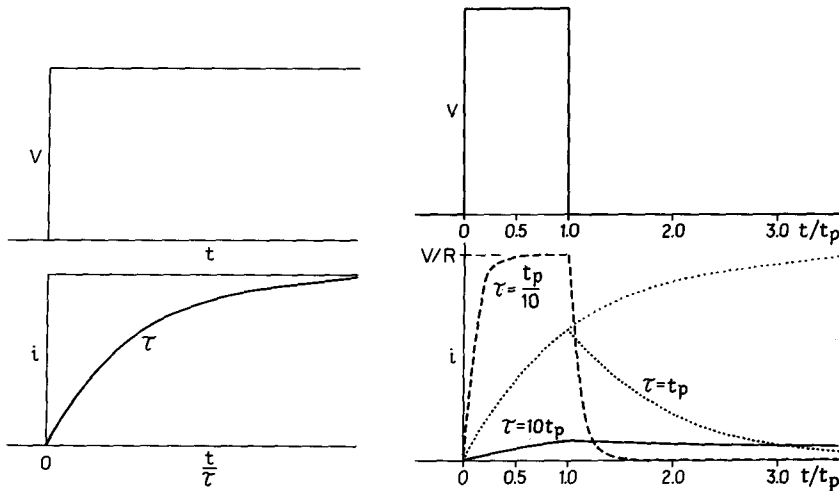$$\frac{di}{dt} = \frac{d}{dt}\left[\frac{V}{R}(1 - e^{-t/\tau})\right] = \frac{V}{L}e^{-t/\tau} \ .$$

FIGURE 8. The current in a coil due to an applied voltage V. (a) The current due to a step voltage V of infinite duration applied to a coil having resistance R and inductance L ($\tau = L/R$) increases exponentially from zero to a final value $i = V/R$ with the time constant τ. (b) The current waveforms resulting from a rectangular voltage pulse of amplitude V and duration t_p applied to coils having three different time constants. Note that the ordinate, the current i, has the asymptotic value V/R and at $t = 0$ has the slope $(di/dt) = V/L$. The maximum values of $i = V/R$ will of course be different for the three values of τ if R differs. The curve for $\tau = t_p$ will have reached at $t = t_p$ 63% of the final value for the step voltage of (a). It then decreases (decays) to zero with the time constant τ. Note that for $\tau = t_p/10$ the current essentially reaches its maximum value $i = V/R$, while for $\tau = 10t_p$ the current reaches only 9.6% of its maximum value. The current waveform can be measured on an oscilloscope by observing the voltage across a small resistance $R_s \ll R$ inserted in series with the coils. The effect if any of R_s on the waveform can be determined from the measured waveforms of the induced electric field with and without R_s in the circuit (see text).

For a rectangular pulse of duration t_p, it is

$$\frac{di}{dt} = \frac{V}{L} e^{-t/\tau} \text{ for } t \leq t_p$$

and

$$\frac{di}{dt} = \frac{V}{L}(1 - e^{-t_p/\tau})e^{-(t - t_p)/\tau} \text{ for } t \geq t_p \ .$$

Plots of di/dt are given in Fig. 9, which therefore give the time variation of E at any point in space. Note particularly that E reverses direction at $t = t_p$ no matter what the value of τ.

The value of the induced field E at any radius r is again easily measured using the same pick-up coils described above and a good oscilloscope. The time variation of E is the same as the induced voltage $\mathcal{E}$ observed on the scope, and the magnitude is again given by $E_m = \mathcal{E}_m/(2\pi rn)$.
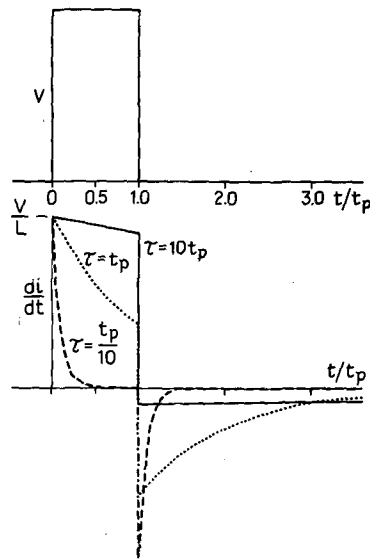
FIGURE 9. The time-rate of change of the current (di/dt) of Fig. 8b. The maximum value of the ordinate di/dt is V/L and will differ if L differs. The three curves as plotted are normalized to the same height to show their *relative* shapes. If each of the three time constants has the same value of R as shown in Fig. 8b the three values of L will be in the ratio $\frac{1}{10}$:1:10 and the values of (di/dt) = V/L at t = 0 will be in the ratio of 10:1:$\frac{1}{10}$. Note particularly that (di/dt) reverses direction at t = t_p. The net area under each curve is zero as is illustrated in Fig. 3b. The induced electric field is proportional to (di/dt); thus, it too must average to zero. The waveform can be observed on an oscilloscope using the pick-up coil of Fig. 5a. Because $\mathcal{E} = -n(d\phi/dt)$, a larger voltage will be observed if the pick-up coil contains several closely wound turns n. Since (dϕ/dt) is proportional to (di/dt), the waveform of the induced voltage is the same as (di/dt).

Forces, Impulses and Currents Due to E

The force on an ion due to the induced electric field is $\boldsymbol{F} = q \times \boldsymbol{E}$ where q is the net charge on the ion. For sinusoidal voltages and currents, the force reverses direction each half-cycle. For pulsed voltages the force, which is proportional to (di/dt), reverses direction at $t = t_p$ (Fig. 9). Further, the forces averaged over time in each direction are equal and the *net* force is zero. Saying it another way, the area under the (di/dt) curve above the axis is just equal to the area under the (di/dt) curve below the axis when taken over a complete cycle of the waveform. Note also that the area at any instant is

$$\int (\mathrm{d}i/\mathrm{d}t)\mathrm{d}t = \int_0^i \mathrm{d}i = i,$$ which is just the value of i plotted in Fig. 8.

Thus, the impulse, the time integral of the force, at any instant, is proportional to i, and when i returns to zero the impulse will have averaged to zero. Thus, the current waveform gives a good view of the time integral of the force as a function of time.

The induced electric field may cause currents in any conducting material

such as culture medium or tissue placed in the field. The induced currents are the result of the electric field exerting a force on the charge carriers, and they will in turn produce magnetic fields, cause ohmic heating of the material and, in the case of free ions as in the culture medium, result in transport of the ions.

The currents induced in a conducting medium, eddy currents, can in principle be calculated (see Chapter 10 of reference 13). The current density j in amperes per square meter is given by $j = \sigma E$, where σ is the conductivity in mho per meter and E the electric field in volts per meter induced by the changing magnetic field. In the case of a good conductor such as metal, the conductivity is large (for copper $\sigma = 5.8 \times 10^7$ mho/m) and the induced currents near the surface are large. These in turn produce magnetic fields that oppose the applied magnetic field, and as a result the induced currents do not penetrate far into the conductor. The measure of the penetration, the skin depth, is given by $\sqrt{2/(\omega\mu\sigma)}$ for a sinusoidal field of angular frequency ω, $\mu = 4\pi \times 10^{-7}$ being the permeability for nonmagnetic materials. At a frequency of 1 MHz, the skin depth for copper is 0.066 mm. Thus, at a depth of only 0.066 mm below the surface, the induced current is $1/e$ of its value on the surface. For culture medium and biological material, $\sigma \simeq 1$ mho/m and the corresponding skin depth is about 0.5 m. (This is the reason that microwave ovens work.) It is also because of the relatively small value of σ for biological material that the induced currents are small. For example, consider a petri dish plated with cells and covered with culture medium to a depth of 1 mm. The current density is 1 A/m^2 for $E = 1$ V/m. Thus, for a ring of culture medium of any radius and radial width 1 mm and depth 1 mm, the current for $E = 1$ V/m is only 1 μA. The ohmic heating is therefore negligible, and the alteration in the induced electric field due to these currents will be completely negligible. The correctness of this conclusion can be easily tested. If, while observing the EMF $\mathcal{E}$ induced in a pick-up coil of several turns placed in the center of the Helmholtz coils in an empty petri dish, culture medium is added to the dish, no measurable change in $\mathcal{E}$ is observed. It should be noted, however, that for high-field experiments, such as magnetically induced hyperthermia, heating will occur and electric field modification is possible.

For varying fields, either pulsed or sinusoidal, the transport for free ions must be oscillatory with no net displacement when averaged over a complete cycle. However, the induced electric field does have the potential for causing nonlinear effects for those ions not free to move equally in all directions, as e.g. in the vicinity of a cell membrane.

In any given experiment, it is relatively simple to determine whether a measured effect in an experiment employing a changing magnetic field is due to the induced electric field or to the magnetic field itself by comparing the measured effect for cells at a radius ρ with those on the axis at $\rho = 0$. Since at $\rho = 0$ the electric field is zero, any measured effect can be attributed to the magnetic field itself.

If in fact pulsed or sinusoidal EMFs have an effect on cellular function, then, in view of the above, the effect must come about owing to a nonlinear response of the cell. The exact mechanism for a nonlinear response is, of course, not known and is the subject of intensive ongoing research. The nonlinear response could exhibit itself in a variety of ways. One obvious mechanism is if the ion transport through the membrane is unilateral; i.e. an electrical force in one direction urges the transport through the membrane, but the reverse force has no effect. In this case, a sinusoidal induced electric field should produce the effect as well as a pulsed field. A second mechanism might result from the relative magnitudes of the forces; i.e. the force in one direction is large but acts for a short time compared with the much smaller reverse force acting for a much longer time ($\tau \gg t_p$) as shown in Fig. 9 for $\tau = 10t_p$. Thus, the membrane may react to an impulsive force. (An impulsive force is one that is applied for a time short compared with the response time of the object on which it acts. The classic example is the baseball bat meeting the baseball. The contact time is extremely short compared with the resulting flight time of the ball.) This could result in the redistribution of membrane proteins, which is known to have an effect on the growth and motility of certain cell types (10). In Fig. 9 for $\tau = L/R \gg t_p$, if L is small (thus R must be small), the value of $di/dt = (V/L)e^{-t/\tau}$ will be large, giving a large E on the rise of the pulse. This is the case for the "clinical" coils and waveforms of the EBI system of PEMF (11).

CONCLUSIONS

In experiments on cellular systems using EMFs, the electric field is the important parameter. If experiments are to be quantified and, most important, to be duplicated in other laboratories, it is essential not only that the geometry be specified but also the parameters that determine the electric field at the position of the cells. Owing to the relatively high conductivity of the culture medium, it is difficult to produce a significant electric field in capacitive plate experiments. The amplitude of the field is extremely small compared to the field in the insulating material, and it is of very short time duration. When time-varying magnetic fields are used to induce time-varying electric fields, it is essential that the position of the cells with respect to the geometry of the coils be carefully specified because the electric field E is a function of position and is zero on the axis of symmetry. The resistance and inductance as well as the voltage signal must be specified. It is also important that the experiment be shielded from stray or background EMFs.

Clearly some exciting experiments suggest themselves. If in fact the membrane transport is unilateral, or at least nonlinear, then measuring the uptake of growth factors as a function of pulse duration and amplitude and as a function of the amplitude and frequency of sinusoidal voltages should shed light on the mechanism.

APPENDIX A: CALCULATION OF E FOR A PARALLEL CAPACITIVE PLATE GEOMETRY

The value of the electric field as a function of time for the geometry of Fig. 2b, represented schematically in Fig. A-1, can be determined if the potential V_1 as a function of time is determined. Applying Kirchhoff's laws it follows from summing voltages around the loop containing C_1 that

$$V = iR_3 + \frac{1}{C_2}\int i\,dt + i_1 R_1 \tag{A-1}$$

and from the loop containing only C_1 and R_1 that

$$\frac{1}{C_1}\int i_3 dt = i_1 R_1 \ . \tag{A-2}$$

The current equation is

$$i = i_1 + i_3 \ . \tag{A-3}$$

Assume a solution to the equations of the form

$$i_1 = \frac{1}{(R_1)}[a + b_1 e^{-t/\alpha_1} + b_2 e^{-t/\alpha_2}] \ , \tag{A-4}$$

where the coefficients a, b_1, b_2, α_1 and α_2 must be determined. Let $R_1 C_1 = \tau_1$. Substituting the assumed value of i_1 in Eq. A-2, it follows that

$$i_3 = \tau_1 \frac{di_1}{dt} = -\frac{b_1}{R_1}\frac{\tau_1}{\alpha_1} e^{-t/\alpha_1} - \frac{b_2}{R_1}\frac{\tau_1}{R_1} e^{-t/\alpha_2}$$
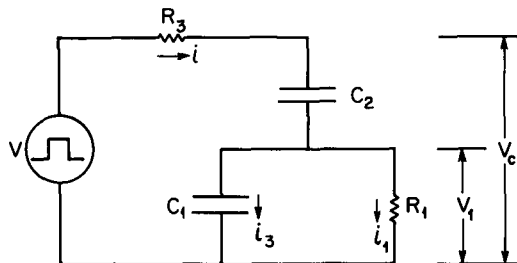

FIGURE A-1. The schematic diagram for the geometry of Fig. 2b including a voltage source V with internal resistance R_3.

and

$$i = i_1 + i_3 = \frac{a}{R_1} + \frac{b_1}{R_1}\left(1 - \frac{\tau_1}{\alpha_1}\right)e^{-t/\alpha_1} + \frac{b_2}{R_1}\left(1 - \frac{\tau_1}{\alpha_2}\right)e^{-t/\alpha_2} .$$

Substituting i, i_1 and i_3 in Eq. A-1, collecting coefficients and recognizing that the equation must hold for all times permits the coefficients to be determined. They are

$$a = 0 \text{ (there can be no DC current)}$$

$$b_1 = V\frac{R_1}{R_3}\frac{1}{\tau_1}\frac{\alpha_1\alpha_2}{(\alpha_1 - \alpha_2)} = -b_2$$

$$\alpha_1, \alpha_2 = \frac{[R_1(C_1 + C_2) + R_3C_2] \pm \sqrt{[R_1(C_1 + C_2) + R_3C_2]^2 - 4R_1R_3C_1C_2}}{2} ,$$

where the plus sign is taken for α_1 and the minus sign for α_2. The solutions for the currents are

$$i_1 = \frac{V}{R_3}\frac{1}{\tau_1}\frac{\alpha_1\alpha_2}{(\alpha_1 - \alpha_2)}[e^{-t/\alpha_1} - e^{-t/\alpha_2}]$$

$$i_3 = -\frac{V}{R_3}\frac{1}{\tau_1}\frac{\alpha_1\alpha_2}{(\alpha_1 - \alpha_2)}\left(\frac{\tau_1}{\alpha_1}e^{-t/\alpha_1} - \frac{\tau_1}{\alpha_2}e^{-t/\alpha_2}\right)$$

$$i = i_1 + i_3 = \frac{V}{R_3}\frac{1}{\tau_1}\frac{\alpha_1\alpha_2}{(\alpha_1 - \alpha_2)}\left[\left(1 - \frac{\tau_1}{\alpha_2}\right)e^{-t/\alpha_1} - \left(1 - \frac{\tau_1}{\alpha_1}\right)e^{-t/\alpha_2}\right] .$$

The electric field in the culture medium is

$$E_l = \frac{V_1}{d_1} = \frac{i_1R_1}{d_1} = \frac{V}{d_1}\frac{1}{R_3C_1}\frac{\alpha_1\alpha_2}{(\alpha_1 - \alpha_2)}(e^{-t/\alpha_1} - e^{-t/\alpha_2}) .$$

This solution is quite different from that of Korenstein et al. (7).

APPENDIX B: CALCULATION OF B AND E

The problem is to compute the magnetic induction B and the induced electric field E for a circular loop of varying current. The calculations are extended to a pair of coils each having many turns.

We begin with circular loop of current of radius a and ask for E and B at points P a distance ρ from the axis on a plane containing the x and z axes and at a distance Z above (or below) the plane of the loop. The geometry is shown in Fig. B-1.
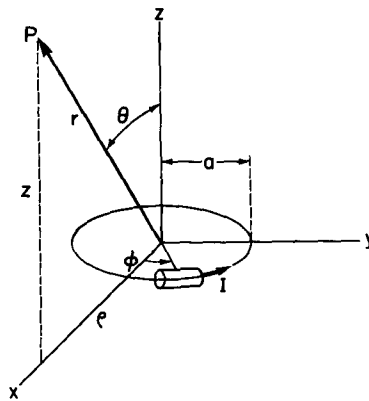
FIGURE B-1. The coordinate systems for calculating the electric and magnetic fields.

The magnetic field B and the induced electric field E can be expressed in terms of the vector potential A as

$$B = \text{curl } A$$

$$E = -\frac{\partial A}{\partial t} \quad .$$

The vector potential at the point P for the circular loop of current can be calculated, but it can not be evaluated in terms of the elementary functions. The result given by Jackson (12) for spherical coordinates is

$$A_\phi(r,\theta) = \frac{\mu_0 I}{\pi} \frac{a}{\sqrt{a^2 + r^2 + 2ar\sin\theta}} \left[\frac{(2 - k^2)K(k) - 2E(k)}{k^2} \right] ,$$

where

$$k^2 = \frac{4ar\sin\theta}{a^2 + r^2 + 2ar\sin\theta}$$

and $K(k)$ and $E(k)$ are the complete elliptic integrals of argument k. Tables of K and E are found in nearly all mathematical handbooks, but more conveniently they will be found in computer libraries and can be easily called into a program. Thus, A_ϕ, which depends only on geometry, can be evaluated. Since A_ϕ is directly proportional to the current I, and the electric field is given by $E_\phi = -\partial A_\phi/\partial t$, then the electric field is proportional to $(-dI/dt)$ and is therefore easily evaluated. It has the same spatial distribution as A_ϕ and depends only on the rate of change of I. A graph of $E_\phi/(dI/dt)$ is given

in Fig. B-2 in terms of two generic parameters, F and G. The height Z of the plane containing P above the circular current loop (Fig. B-1) is expressed in units of the radius a of the loop, $G = Z/a$. The distance of P from the axis of symmetry is $\rho = r\sin\theta$, and is also expressed in units of a, namely $F = \rho/a$. Thus, the graph of Fig. B-2 can be used to find the spatial dependence of E for a current loop of any radius. The direction of E lies in the horizontal plane containing P and is tangent the circle of radius ρ.

A second loop of current of the same radius a, coaxial with the first, a distance d above it and carrying the same current I (Fig. 4) will produce a vector potential which adds algebraically to that of the first. This follows since A_ϕ has the same value whether P is above or below the plane of the current loop. Thus, the two current loops carrying the same current in series aiding produce $A_\phi = A_{\phi1} + A_{\phi2}$. Since $G_1 = Z_1/a$ and $G_2 = Z_2/a$, the vector potential A_ϕ and therefore E can be readily evaluated from the graphs.
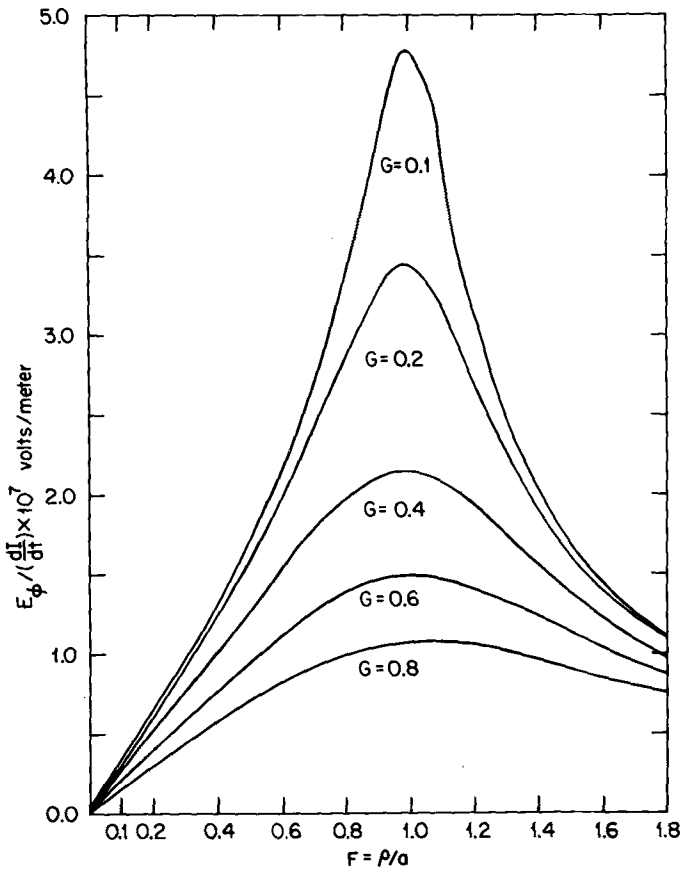

FIGURE B-2. Graph of the induced electric field $E_\phi/(dI/dt)$ for a single loop of current of radius a as a function of distance ρ (in units of a) from the axis in planes a distance $Z = G \cdot a$ above (or below) the plane of the current loop.

In general, rather than single current loops, coils of several turns N in each coil are used. The electric field E is then just N times that of the single loop. When several turns are used, the wire will fill an area, perhaps of rectangular shape as illustrated in cross section in Fig. B-3. It can be shown that if the values of ρ and Z are taken at the centers of the area, the calculated vector potential will be very close (within 1%) to the value calculated from the actual current distribution.

The magnetic field B can also be evaluated from $\boldsymbol{B} = \text{curl } \boldsymbol{A}$. The components in the r, θ and ϕ directions are

$$B_r = \frac{1}{r\sin\theta} \frac{\partial}{\partial\theta}(\sin\theta \; A\phi)$$

$$B_\theta = -\frac{1}{r}\frac{\partial}{\partial r}(rA_\phi)$$

$$B_\phi = 0 \; .$$

Rather than carrying out the indicated partial differentiation in spherical coordinates, it is more useful for the geometry of the coil pair to convert to cylindrical coordinates, using the coordinates ρ and z (Fig. B-1). The results for B_ρ and B_z for a single loop of current are given by Smythe (13) as

$$B_\rho = \frac{\mu_0 I}{2\pi} \frac{z}{\rho} \frac{1}{\sqrt{(a+\rho)^2 + z^2}}\left[-K(k) + \frac{a^2 + \rho^2 + z^2}{(a-\rho)^2 + z^2} E(k)\right]$$

$$B_z = \frac{\mu_0 I}{2\pi} \frac{1}{\sqrt{(a+\rho)^2 + z^2}}\left[K(k) + \frac{a^2 - \rho^2 - z^2}{(a-\rho)^2 + z^2} E(k)\right] \; ,$$

where

$$k = \frac{4a\rho}{\sqrt{z^2 + (a+\rho)^2}} \; .$$

Again these can be evaluated with a relatively simple computer program. The total field B for a single loop of current is found by combining B_ρ and

FIGURE B-3. A coil of rectangular cross section. The field due to an extended cross section containing N turns will be within 1% of the value calculated if all the turns are considered to be at the center of the area.

B_z in quadrature, the direction of B with respect to the plane of the coils being given by the angle $\tan^{-1}(B_z/B_\rho)$. The field for the two coils in series aiding is obtained by combining the components algebraically: $B_\rho = B_{\rho 1} + B_{\rho 2}$, $B_z = B_{z1} + B_{z2}$. Because the value of B is of itself of little interest and is so easily measured, it is not particularly useful to perform this calculation. A graph of the calculated value of Bz of a coil pair for three values of G is given in Fig. 6b.

REFERENCES

1. Basset, C. and L. Andrew. Pulsing electromagnetic fields: a new method to modify cell behavior in calcified and non-calcified tissues. *Calcif. Tissue Int.* 34:1–8, 1982.
2. Becker, R.O. Electrical osteogenesis – pro and con. *Calcif. Tissue Res.* 26:93–97, 1978.
3. Luther, P.W. and H.B. Peng. Changes in cell shape and actin distribution induced by constant electric fields. *Nature* 303:61–64, 1983.
4. Cooper, M.S. and R.E. Keller. Perpendicular orientation and directional migration of amphibian neural crest cells in dc electric fields. *Proc. Natl. Acad. Sci.* 81:160–164, 1984.
5. Erickson, C.A. and R. Nuccitelli. Embryonic fibroblast motility and orientation can be influenced by physiological electric fields. *J. Cell. Biol.* 98:296–307, 1984.
6. Scott, W.T. *The Physics of Electricity and Magnetism.* New York: John Wiley and Sons, 1959, p. 228.
7. Korenstein, R., D. Somjen, H.K. Fischler and I. Binderman. Capacitive pulsed electric stimulation of bone cells. *Biochim. Biophys. Acta* 803:302–307, 1984.
8. Rodan, G.A., L.A. Bourret and Louis A. Norton. DNA systems in cartilage cells is stimulated by oscillating electric fields. *Science* 199:690, 1978.
9. Dierickx, M., M. Hisenkamp, L. Rybowski and F. Burny. Electromagnetic and electric field configurations produced by two coils. *Acta Orthop. Scand.* 53 (suppl 196):19, 1982.
10. Nuccitelli, R. Transcellular ion currents: signals and effectors of cell polarity. *Mol. Cell Biol.* 2:451–481, 1983.
11. System 204, Electro-Biology Inc; 277 Fairfield Road, Fairfield, NJ 07006.
12. Jackson, J.D. *Classical Electrodynamics.* New York: John Wiley and Sons, 1975.
13. Smythe, W.R. *Static and Dynamic Electricity. 3rd ed.* New York: McGraw-Hill, 1968, p. 291.