Thermal and Nonthermal Mechanisms of Interaction of Radio-Frequency Energy with Biological Systems

Kenneth R. Foster, *Fellow, IEEE*

Invited Paper

Abstract—This paper reviews thermal and nonthermal mechanisms of interaction between radiofrequency (RF) fields and biological systems, focusing on pulsed fields with high peak power but low duty cycle. Models with simplified geometry are used to illustrate the coupling between external electromagnetic fields and the body, and with cellular and subcellular structures. Mechanisms of interaction may be linear or nonlinear with field strength, and thermal or nonthermal. Each mechanism is characterized by a threshold field strength (below which no observable response is produced) and time constant of response. Several classes of nonthermal mechanisms of interaction are well established; however, the anticipated thresholds for producing observable effects are expected to be very high. The bioeffects literature contains many open questions, including many reports of effects that are not clearly interpretable in terms of the mechanisms discussed in this paper.

Fig. 1.   Schematic showing different levels of field-tissue interaction. For a discussion of cutoff frequencies, see the text.

I. INTRODUCTION

SEVERAL thousand studies have examined the interactions between radio-frequency (RF) electromagnetic fields and biological systems, motivated both by beneficial applications and also possible hazards of such energy [1]. Most of these studies have employed continuous wave or pulsed sources with modest peak field strengths. Under such conditions, the dominant effects arise from thermal mechanisms.

The focus of this Special Issue is on nonthermal effects, i.e., effects produced directly by the applied fields rather than indirectly as a result of heating, particularly those that might be elicited by pulsed fields of very high peak strength. Several papers in this Special Issue concern possible biomedical applications of ultrawide-band (UWB) pulse generators, which can produce electric fields in air of tens of kV/m with risetimes of the order of 1 ns [2]. EMP simulators, which date back to the 1970's, can generate fields as high as 60–100 kV/m with pulse durations of 100–300 ns. The issue of nonthermal effects is also a factor in an ongoing debate about possible health risks of RF energy from communications systems. The problem is not whether effects exist (they surely do) but to understand their nature and anticipate the exposure conditions that will elicit them.

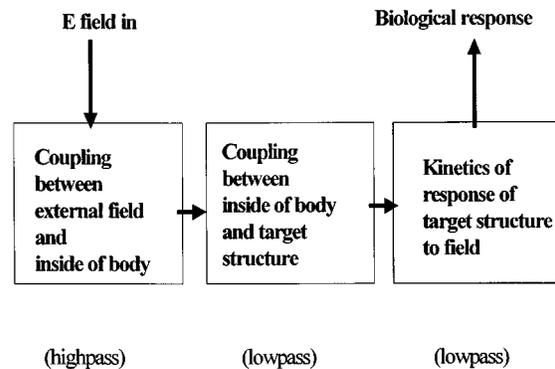This paper reviews interactions of electromagnetic fields with biological systems, focusing on the relation between external and internal field strengths and mechanisms of interaction. These two subjects are seldom discussed together. However, they are closely related, in that the field is typically specified in the air outside the body, whereas the field strength in tissue is the important dosimetric quantity. Most of the discussion concerns RF fields (3 kHz–300 GHz) but some discussion applies to pulsed fields with a broad spectrum, possibly including a dc component.

This paper reviews simple models that give insight into the orders of magnitude of phenomena, particularly as they relate to pulsed fields of high peak power but low duty cycle. Extensive reviews are available on dosimetry [3] and bioeffects and mechanisms of interaction [4]; see also the excellent but somewhat dated monograph [5]. The literature on biological effects of high-peak-low-average power RF pulses is sparse, however.

The interaction between RF energy and biological systems is a problem at three levels (Fig. 1). The first (macrodosimetry) concerns the relation between external fields and the resulting fields induced within the body on distance scales of centimeters or more. The second (microdosimetry) is the assessment of induced fields at the level of cellular or subcellular structures. The third is determining the biological response, if any, to the local field. Time or frequency enters at each level through the electromagnetic properties of the body (which are frequency-dependent) and the kinetics of the biological response.

II. ELECTRICAL PROPERTIES OF TISSUE

The bulk electrical properties of tissue have been reviewed elsewhere [6]; for a recent compilation of data see [7]. The bulk
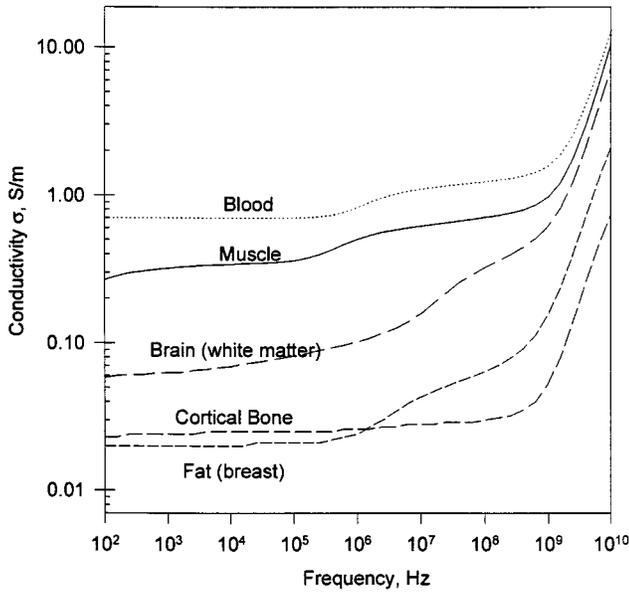
Fig. 2. Conductivity of tissues at body temperature. Adapted from [7]. The dielectric properties of tissues can vary by a factor of two or more, particularly at frequencies below 1 MHz. Fat and bone are particularly variable.

Fig. 3. Permittivity of tissues at body temperature. Adapted from [7].

electrical properties of tissues can be described by the complex permittivity ϵ^* or complex conductivity σ^*

$$\varepsilon^* = \varepsilon'\varepsilon_o + \sigma/s$$
$$\sigma^* = \sigma + s\varepsilon'\epsilon_o \qquad (1)$$

where σ is the conductivity (S/m), ϵ' is the relative permittivity (dimensionless), $\epsilon_o = 8.85$ pF/m (permittivity of vacuum) and $s = j\omega$ where ω is the radian frequency. The dielectric properties of fat and muscle are shown in Figs. 2 and 3. For most tissues, at frequencies <1 GHz, $\sigma > \omega\epsilon'\epsilon_o$ and the dielectric properties are primarily resistive. This formulation assumes that the dielectric properties of tissue are linear; some comments about nonlinear effects are presented below [6].

In terms of the these properties, the wavelength λ of an electromagnetic wave in tissue is

$$\lambda = \frac{c}{f \operatorname{Re} \sqrt{\varepsilon^*/\varepsilon_o}} \qquad (2)$$

and the $1/e$ penetration depth of the field L is

$$L = \frac{c}{2\pi f \operatorname{Im} \sqrt{\varepsilon^*/\varepsilon_o}} \qquad (3)$$

where c is the velocity of light in vacuum (Fig. 4).

The dielectric properties of tissue are highly dispersive (frequency dependent), arising from mechanisms that are discussed in detail in [6]. A major source of dispersion at low radio frequencies is associated with the charging of cell membranes, which have a low conductance but a capacitance of about 0.01 F/m^2. At low frequencies, cell membranes have a high impedance and current flows primarily through the extracellular space. Charge is accumulated against cell membranes, which imparts a large induced dipole moment to the
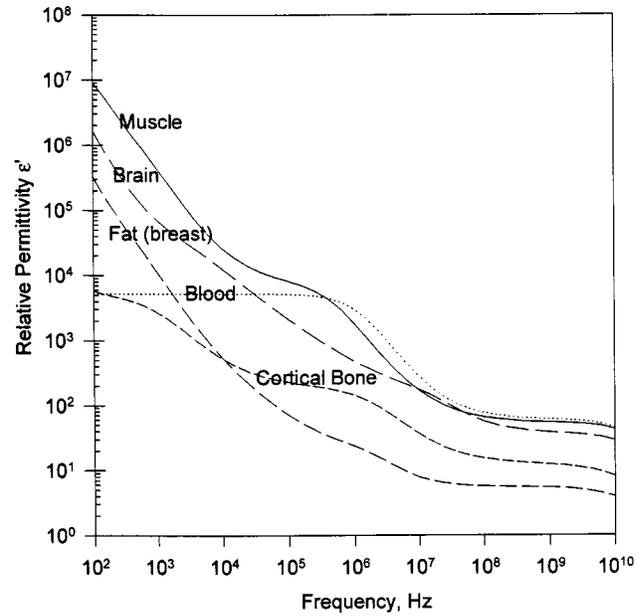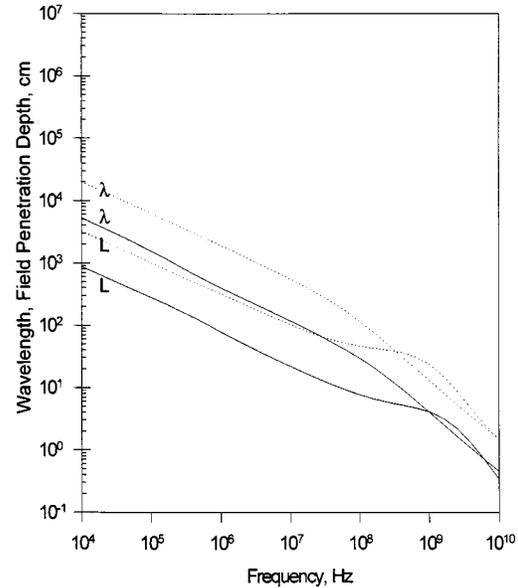

Fig. 4. Field penetration depth L and wavelength λ in muscle (solid line) and fat (dotted line). Calculated from data in [7].

cells, and consequently, a large permittivity to the bulk tissue. At higher frequencies, current flows through both intracellular and extracellular spaces. The result is a broad dispersion in the tissue properties, in the frequency range of about 0.1–1 MHz. At microwave frequencies (1–300 GHz), the bulk electrical properties of tissue are dominated by the water that constitutes about 80% of soft tissue by weight. Water undergoes a dielectric dispersion centered at 25 GHz (at 37 °C), which shows up as a pronounced increase in the conductivity of tissue above 1 GHz with a corresponding decrease in permittivity. At lower (audio) frequencies other polarization mechanisms, due to ionic effects, become apparent [6].

III. MACRODOSIMETRY: THE COUPLING OF EXTERNAL FIELDS TO THE BODY

The literature on macrodosimetry, including analytical, numerical, and experimental studies, is far too extensive to review here. Instead we consider a simple model that illustrates the relation between fields external to the body and those induced within it.

Consider a uniform sphere of radius R in air, subject to an incident plane wave of amplitude E_o. The field inside the sphere can be obtained analytically using Mie scattering theory [8]–[10]. The solution depends greatly on the wavelength λ of the radiation in the sphere as compared to the radius R.

A. Quasi-static Limit $(\lambda \gg R)$

In the limit of low frequencies, the induced electric field E_i in the sphere can be expressed as the sum of magnetic and electric dipole terms [8]

$$\bar{E}_i = E_o s \left[\frac{r}{2c} \left(\bar{x} \cos(\theta) - \bar{z} \sin(\theta) \cos(\phi) \right) + \frac{3\varepsilon_o}{\sigma_i^* + 2s\varepsilon_o} \bar{x} \right] \tag{4}$$

where r is the radial coordinate, and ϕ and θ are the angles with respect to the x and z axes.

Thus, in the quasi-static limit, the induced electric field in the object is the sum of electrically and magnetically induced contributions. If $\sigma_i \gg |s\varepsilon_o|$ (which is always the case for tissue) the ratio of the two contributions is approximately $\pi R \sigma_i / 6 c \varepsilon_o$ at $\theta = 0$. For a sphere of radius 0.15 m (similar to the radius of the human torso) and conductivity 0.5 S/m (similar to that of soft tissue), this ratio is approximately 15, i.e., the magnetic dipole term dominates.

These results can be extended to the case of homogeneous ellipsoids in an external field. For an ellipsoid oriented with (a) its major semiaxis parallel to the electric field, and (b) two equal semiminor axes, the electric dipole term becomes [11]

$$E_i = \frac{s\varepsilon_o E_o}{\chi(\sigma^* - s\varepsilon_o) + s\varepsilon_o} \approx \frac{s\varepsilon_o E_o}{\chi \sigma_i + s\varepsilon_i \varepsilon_o'}. \tag{5}$$

The "depolarization factor" χ is most compactly written as

$$\chi = \frac{x^6}{2} \int_0^\infty \frac{ds'}{(s' + x^4)(s' + x^2)\sqrt{(s' + x^4)}} \tag{6}$$

where $x = b/a$. The depolarization factor χ has the value $1/3$ for spheres, and 0.02 for an ellipsoid of axial ratio $1 : 6$ which approximates the shape of the human body. If the ellipsoid is oriented with a principal axis parallel to the external electric field, the internal field is uniform and parallel to the external field.

The electric dipole term can be written in the form of the transfer function of a high pass filter

$$E_i = \frac{E_\infty s\tau}{1 + s\tau} \tag{7}$$

where $E_\infty \approx E_o / \chi \epsilon_i'$ is the induced field in the limit of high frequencies and $\tau \approx \epsilon_i' \epsilon_o / \chi \sigma_i$ is a time constant for relaxation. For soft tissues with $\epsilon_i' = 100$ and $\sigma_i = 0.5$ S/m, τ is 5 ns for a sphere and 90 ns for an ellipsoid with axial ratio $1/6$. This corresponds to a cutoff frequency of about 2 MHz for the ellipsoid and about 30 MHz for the sphere. In the ellipsoid of axial ratio

$1/6$, at 60 Hz the internal electric field (electric dipole contribution) is smaller than the incident field by a factor of about 10^6.

Somewhat higher fields will be induced in the object if it is placed in contact with ground, due to image effects. For the ellipsoid of axial ratio $1/6$, this will result in an increase in the induced fields and relaxation time constant by a factor of about three. In addition, a "short circuit current" i_{sc} will flow between the object and ground. This current is approximately equal to the current density induced by the external field $(\sigma_i E_i)$ times the cross-sectional area of the ellipsoid, or [from (5)]

$$i_{sc} \approx \frac{\pi b^2 s\varepsilon_o E_o}{\chi}. \tag{8}$$

The above discussion was based only on the electric dipole term of the Mie scattering result, and is valid only in the low-frequency limit $\lambda \gg R$. As discussed below, these simple results give approximate values for peak induced field strengths even at higher frequencies.

B. Resonance Region $(\lambda \approx R)$

In this frequency range, the object exhibits electrical resonances due to wave propagation effects. The total energy absorbed by the object reaches a maximum near the resonant frequency. In the time domain, an impulse excitation will result in highly damped electrical oscillations in the sphere at the resonant frequency. For an adult human standing erect in a vertically polarized field, the first electrical resonance occurs at about 70 MHz (if the body is in free space) or 40 MHz (if it is in contact with ground). Parts of the body such as the head exhibit their own resonances at still higher frequencies [3]. In the resonance region, the pattern of induced fields in the object is very complex.

C. Quasi-Optic Range $(\lambda < R)$

In this frequency range, the transmitted wave inside the object propagates approximately as a plane wave. The field strength E_i just inside the surface for a normally incident wave is

$$E_i(\omega) = E_o(\omega) \frac{2}{1 + \sqrt{\varepsilon^*/\varepsilon_o}}. \tag{9}$$

Thus, $|E_i/E_o|$ is of the order of $1/3$ or less above 1 GHz. Broadband pulses show complex transmission effects in dispersive media such as tissue, with "precursors" and changes in shape of the propagating pulse [12], [13]. Such effects, however, do not have any apparent biological significance.

Experimental and computational studies by several groups confirm these results and fill in many important details. For example, Chen and Gandhi [14] calculated the induced fields and specific absorption rate (SAR) for idealized EMP's, using numerical models of the body with up to 45 000 cells. The exposure consisted of a half-cycle of 40-MHz sinewave (duration 12.5 ns, 1 kV/m peak field). The maximum induced currents were 3.9, 3.0, and 1.6 A in the ankles, heart, and neck, respectively. Assuming typical dimensions of these parts of the body and typical values for tissue conductivity, this corresponds to peak induced fields of about one-third of the external field strength, consistent with the results of the simple model presented above.

Several investigators have measured currents between the body and ground for human subjects exposed to RF fields, and the results are consistent with the simple model discussed above. In a human subject standing with bare feet on ground exposed to a vertically polarized 50-MHz field, Guy measured ground currents of 12 mA/(V/m) [15]. (Equation (8) yields 10 mA/(V/m), assuming $R = 0.15$ m and $\sigma_i = 0.5$ S/m.) In a grounded human subject exposed to vertically polarized EMP's of 10 kV/m, Gandhi *et al.* measured peak ground currents of 40 A, with the current pulses lasting some tens of nanoseconds [16]. The expected ground current depends on the time derivative of the field pulse, but the maximum currents [from (8)] will be less than 200 A.

The discussion above shows that the electric field induced inside the body by an external electric or magnetic field depends strongly on frequency and the geometry of the system. Because of the conductivity of body tissues, it is difficult to couple low frequency fields into the body through air, and dc fields are excluded entirely. In engineering terms, the body acts as a high-pass filter for external electric fields with a cutoff frequency in the low-megahertz range. This is significant because most biological responses to electric fields are quite slow.

IV. MICRODOSIMETRY: COUPLING OF FIELDS TO CELLULAR MEMBRANES

The second element of the "mechanisms" problem is to determine the coupling of a field to microscopic structures in the tissue, in particular, cell membranes. The following discussion extends that in Foster and Schwan [6]; see also [17]. The model consists of two concentric spherical shells in electrolyte, in an external electric field of unperturbed strength E_o (Table I). The shells have a thickness and specific capacitance comparable to those of cell membranes.

Laplace's Equation for this model can be solved readily using a computer algebra program (Maple, Waterloo Maple, Waterloo, ON, Canada). The full analytical results are lengthy and are not presented here.

The response of this system is characterized by four time constants. Two are of the form

$$\tau_1 = \tau_2 \approx \frac{\varepsilon_i \varepsilon_o}{\sigma_i} \approx 0.6 \text{ ns.} \qquad (10)$$

These represents "Maxwell–Wagner" dispersions, associated with the transition of the inner and outer media from principally conductive to principally capacitive in nature [6]. (At radian frequencies $>1/\tau_{1,2}$ the media are principally dielectric; at lower frequencies they are principally conductive and hence exclude fields.) The remaining two time constants describe the charging of the nuclear and plasma membranes through the electrolyte resistance, and are approximately

$$\tau_{\text{nuc}} \approx \frac{3R_{\text{nuc}}C_m}{2\sigma_i} \approx 0.05 \text{ } \mu\text{s} \qquad (11)$$

$$\tau_{\text{cell}} \approx \frac{3R_{\text{cell}}C_m}{2\sigma_i} \approx 0.15 \text{ } \mu\text{s} \qquad (12)$$

TABLE I
FIVE COMPARTMENT FOR CELL WITH
NUCLEUS IN EXTERNAL ELECTRIC FIELD

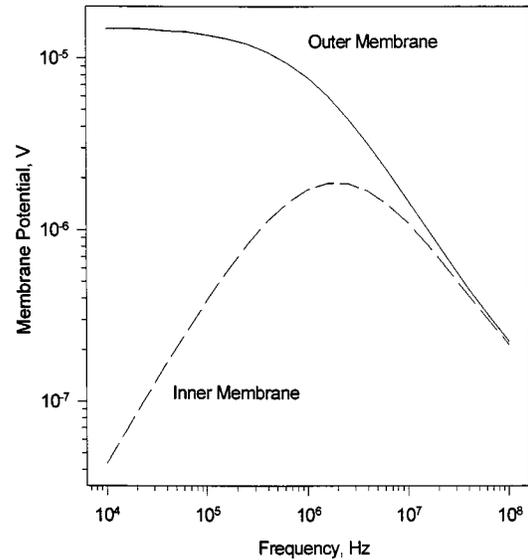| Compartment, Radii (all units in μm)	Relative Permittivity, Conductivity	Comments
$r > R_{\text{cell}}$ $R_{\text{cell}} = 10$ (cell radius)	78, 1 S/m	Electrolyte surrounding cell
$R_{\text{cell}} > r > R_{\text{cell}} - h$ $h = 0.01$ (membrane thickness*)	11.3, 0	Plasma membrane
$R_{\text{cell}} - h > r > R_{\text{nuc}}$ $R_{\text{nuc}} = 3$ (nuclear radius)	78, 1 S/m	Cytoplasm
$R_{\text{nuc}} > r > R_{\text{nuc}} - h$	11.3, 0	Nuclear membrane
$r < R_{\text{nuc}} - h$	78, 1 S/m	Nucleus

Fig. 5. Membrane potentials induced by a 1 V/m field in spherical cell model described in the text, versus frequency.

(where R_{cell} and R_{nuc} are the radii of the cell and nucleus, and C_m is the capacitance per unit area of the membrane; numerical values are given in Table I.)

Fig. 5 shows the induced potentials across the outer and inner membranes (at the poles of the cell) versus frequency, with an external (unperturbed) field of 1 V/m. The induced membrane potentials at other angles vary by a factor $\cos(\theta)$, where θ is the angle from the radius vector to the point on the membrane to the direction of the external field. The discussion below pertains to the peak induced membrane potentials, i.e., corresponding to $\theta = 0$.

The full analytical results can be approximated quite well in terms of simple transfer functions [6]:
membrane potential

$$V_m(s) \approx \frac{1.5R_{\text{cell}}}{1 + s\tau_{\text{cell}}} E_o(s) \qquad (13)$$

cytoplasmic field strength

$$E_{\mathrm{cyt}}(s) = \frac{s\tau_{\mathrm{cell}}}{1 + s\tau_{\mathrm{cell}}} E_o(s) \qquad (14)$$

nuclear field strength

$$\begin{aligned} E_{\mathrm{nuc}}(s) &= \frac{s\tau_{\mathrm{nuc}}}{1 + s\tau_{\mathrm{nuc}}} E_{\mathrm{cyt}}(s) \\ &= \frac{s\tau_{\mathrm{nuc}}}{(1 + s\tau_{\mathrm{nuc}})} \frac{s\tau_{\mathrm{cell}}}{(1 + s\tau_{\mathrm{cell}})} E_o(s) \end{aligned} \qquad (15)$$

nuclear membrane potential

$$\begin{aligned} V_{\mathrm{nuc}}(s) &\approx \frac{1.5 R_{\mathrm{nuc}}}{1 + s\tau_{\mathrm{nuc}}} E_{\mathrm{cyt}}(s) \\ &\approx \frac{1.5 R_{\mathrm{nuc}}}{1 + s\tau_{\mathrm{nuc}}} \frac{s\tau_{\mathrm{cell}}}{1 + s\tau_{\mathrm{cell}}} E_o(s). \end{aligned} \qquad (16)$$

These approximations were obtained by using the principle of superposition and are valid if the nucleus is much smaller than the cell. For the cell model considered here, they are in close numerical agreement with the full analytical solution shown in Fig. 5.

The above results have a simple physical interpretation. At low frequencies, the inside of the cell is shielded from the external field because of the conductivity of the inner medium. The potential drop across the outer cell membrane is comparable to the total voltage drop across the entire cell. At high frequencies, the membrane impedance is low and the potential drop across it is equal to the current density through the cell times the specific membrane impedance—a much smaller quantity.

Time-domain responses. For brief pulses, a more useful consideration is the impulse response, which is the inverse Laplace transform of the transfer function. The impulse response for the inner and outer membranes of the cell model (calculated by Maple from the full analytical solution) is shown in Fig. 6. This is, by definition, the response of the cell to a brief field pulse of infinitesimal duration, with an integrated field strength of 1 V s.

An approximate expression for the membrane potential $V_{m,\mathrm{impulse}}$ induced by a brief pulse $E_o(t)$ follows from (13):

$$V_{m,\mathrm{impulse}} = \frac{1.5 R_{\mathrm{cell}}}{\tau_{\mathrm{cell}}} e^{-t/\tau_{\mathrm{cell}}} \int E_o(\xi)\, d\xi \qquad (17)$$

where the pulse duration is assumed to be much less than τ_{cell} and ξ is a dummy variable of integration. Thus, a pulse with a dc component will induce a membrane potential that is proportional to its impulse strength [the integral in (17)], which persists for times of the order of τ_{cell}. In the absence of a dc component, the induced membrane potential persists only as long as the incident pulse.

Equations (13) and (17) imply that the peak membrane potential induced by a brief rectangular pulse E_{pulse} and duration $\tau_{\mathrm{pulse}} \ll \tau_{\mathrm{cell}}$, will be the same as the steady-state potential induced by a constant field E_{steady}. if

$$E_{\mathrm{pulse}} \approx E_{\mathrm{steady}} \frac{\tau_{\mathrm{cell}}}{\tau_{\mathrm{pulse}}}. \qquad (18)$$
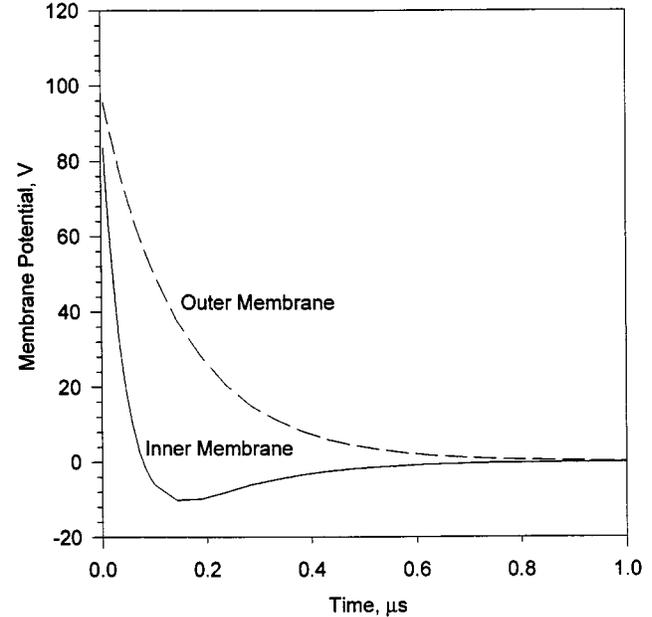

Fig. 6. Impulse response for the membrane potentials in the spherical cell model discussed in the text.

This inverse relation between the induced membrane potential and pulsewidth has a counterpart in the strength-duration function of excitable cells (i.e., the threshold for eliciting an action potential as a function of pulsewidth), which has been studied by electrophysiologists since the early 1900's [18]. For a nonrectangular pulse, E_{pulse} would be replaced by an effective pulse amplitude equal to the impulse strength divided by some measure of the pulsewidth. This underscores once again that only the low-frequency components of the pulse are effective in changing the membrane potential.

All of the above discussion assumes that the system is linear. For very strong fields, sufficient to rupture cell membranes, or cause dielectric saturation or dielectric breakdown, this assumption will obviously fail. At low frequencies, nonlinearities in the dielectric response can also occur due to membrane excitation and other mechanisms [6]. These effects are not observed under usual experimental conditions (involving RF fields at modest levels) but may be a factor in some experiments involving very strong pulsed fields.

V. INTERACTION MECHANISMS

The third element of the problem is to elucidate the biophysical mechanisms by which applied fields may elicit biological responses. Many mechanisms, both thermal and nonthermal,[1] and linear and nonlinear, are well established by which electromagnetic fields can interact with biological systems. Whether they can produce observable effects at practical exposure levels is a different matter entirely. The following discussion reviews several well established mechanisms for interaction, focusing

[1]As used above, "nonthermal" refers to the mechanism of interaction, not to the magnitude of temperature increase from the exposure. Some authors use "nonthermal" instead to refer to effects observed in the absence of what the investigator considers to be a biologically significant temperature increase, even though the mechanism for the effect may be unknown. The dual use of the term, sometimes in the same paper, is a potential source of ambiguity.

on the anticipated amplitude and frequency thresholds for responses.

A. Thermal Mechanisms

Biological effects might result from bulk temperature increase, or from the rate of temperature increase, even though the bulk temperature rise might be small. The appropriate dosimetric quantity for such effects is the specific absorption rate (SAR) in W/kg, a measure of absorbed power.

1) Bulk Temperature Rise: A brief pulse that deposits 1 Joule/kg will produce a transient increase in temperature of approximately $3 \cdot 10^{-4}$ K in soft tissue such as muscle. A continuous-wave RF field of 30 V/m (at 1 GHz) will produce an SAR of about 1 W/kg, which corresponds roughly to the basal metabolic rate of humans. Fields of this order, if sustained in tissue for sufficient times, can be expected to produce thermally significant heating in humans.

Biological processes vary greatly in their sensitivity to temperature. The threshold for cutaneous sensation of warmth from brief (3 s) pulses of microwave energy corresponds to skin temperature increases of about 0.07 K [19]. At another extreme, mammalian tissues can withstand brief (<1 s) temperature increases of several tens of degrees without observable thermal damage [20].

2) Rate of Temperature Increase: Several biological effects are elicited by pulsed RF energy, which are associated with the rate of temperature increase:

Thermoelastic expansion and microwave hearing. Transient heating of tissue can generate acoustic signals (due to thermal expansion of tissue water) which can elicit auditory sensations in an exposed individual, an effect called microwave hearing [21].

For brief pulses, the magnitude P_o of the thermoelastic pressure transient is of the order of

$$P_o = \frac{c_s \beta SR \rho}{C_p J} \tag{19}$$

where R is the diameter of the heated region, S is the SAR, β is the volumetric thermal expansion coefficient, c_s is the velocity of sound, C_p is the heat capacity, and J is the mechanical equivalent of heat.

The microwave auditory effect is produced by radar-like pulses, i.e., brief (1–10 5μs) pulses with carrier frequencies of 1–10 GHz and peak incident power densities of about 10^4 W/m^2. The resulting increase in tissue temperature is very small (a few microdegrees after each pulse) but the rate of heating is high (typically 1–10 K/s). The resulting sound transients exceed 100-dB peak sound pressure and are audible through bone conduction hearing. Clearly, any form of pulsed energy will generate acoustic transients in tissue through this thermal mechanism, which may or may not be audible. The acoustic transients produced by realistic RF sources are far below levels expected to damage tissue. They are audible because of the exquisite sensitivity of the human auditory system.

Thermally induced membrane depolarization. Wachtel and colleagues have reported that a single pulse of microwave energy lasting 0.1 s with a peak SAR of about 40 000 W/kg will
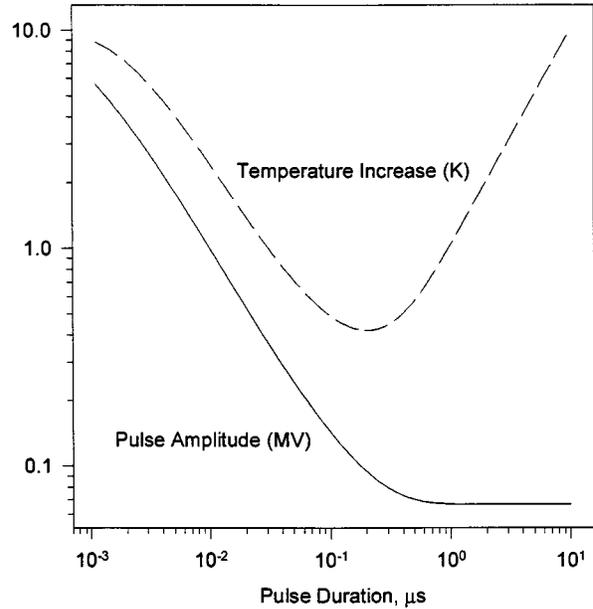

Fig. 7. Amplitude of a rectangular pulse (MV/m) needed to induce a 1 V potential in the outer cell membrane, for the spherical cell model discussed in the text. Also shown is the transient temperature increase in the cell and surrounding medium produced by the pulses (see text). For a given induced membrane potential, the least heating occurs when the pulse length is comparable to the membrane charging time constant. In calculating the temperature increases, typical thermal properties of biological media were assumed.

cause a temporary cessation in the firing of the pacemaker neurons of *Aplysia*. Such a pulse will induce a temperature increase of about 1 K, at a rate of 10 K/s [22]. The same group also reported "multiphasic body movements" in mice whose heads were exposed to intense microwave pulses at a total energy of 500–1000 J/kg. [23], which corresponds to a transient temperature rise of 0.1–0.2 °C during each pulse, with a corresponding a rate of temperature increase of several degrees per second. A simple analysis, based on the Nernst equation, suggests that such rapid thermal transients will lead to significant changes in cell membrane potentials [24].

B. Membrane Excitation and Breakdown

Two well-established mechanisms for biological effects of electric fields are electroporation [25] and membrane excitation [26]. Membrane excitation is a comparatively slow process (the response time of ion gates in cell membranes is in the range 0.1–1 ms) and its threshold rises quickly with frequency above about 1 kHz.

By contrast, electrical breakdown of cell membranes (electroporation) is a very fast process, which has been demonstrated with field pulses as short as 10 ns in artificial membranes [27]. The threshold for electroporation (even for such short pulses) corresponds to induced membrane potentials of the order of 1 V. To produce such effects in a spherical cell of 10 μm radius, (13) suggests that field levels of the order of 50 000 V/m would be required outside the cell, maintained for longer than $\tau_{\text{cell}} \approx 0.15\,\mu$s.

Provided they have a dc component, very short pulses can also cause membrane breakdown. For the example considered

above, the threshold for electroporation corresponds to an impulse strength of approximately (50 000 V/m)(0.15 μs) or about 0.01 V s/m. Fig. 7 shows the pulse amplitude needed to induce a 1-V membrane potential in the spherical cell model, together with the temperature increase after each pulse (based on thermal properties of biological media). For these (rectangular) pulses, electroporation is most efficient (least heating per pulse) when the pulsewidth is of the order of τ_{cell}.

A few studies have been reported on electroporation with short broad-band pulses. Schoenbach *et al.* [28] reported destruction (presumably due to electroporation) of *E. coli* cells exposed to brief (tens of microseconds to tens of nanoseconds) broadband electric field pulses as strong as 6 MV/m applied directly to the cell suspension (!). The threshold for cell destruction varied much more slowly as a function of pulsewidth than simple inverse behavior predicted by the model discussed above. In part this may reflect the complex dielectric properties of the bacteria, which exhibit a broad dielectric dispersion arising from the presence of cell walls and other structures. Apart from any practical applications (e.g., sterilizing media), electroporation using short broadband pulses may be useful for studying the electrical properties of cells themselves.

C. Direct Electrical Forces on Cells or Cell Constituents

Electric fields either exert forces on charges, as well as on uncharged particles through induced dipole moments. Such forces can be ranked according to the order of interaction (and generally in order of decreasing strength): field-charge interactions, field-permanent dipole moment interactions, and field-induced dipole moment interactions. In each case, the threshold field strength needed to produce an observable effect is determined by the need to overcome random thermal agitation. The response time of the target structure is determined by viscous drag or other mechanical forces on the particle, and results in a cutoff frequency for the response.

Field-charge interactions. Electric fields exert forces on charges and in principle will displace them. However, under realistic exposure conditions the resulting displacements are very small, and overwhelmed by thermal agitation. For example, the mobility of simple ions in an aqueous electrolyte solution is of the order of 10^{-7} (m/s)/(V/m). Thus, a field of 1 kV/m will induce a velocity of ~10^{-4} m/s in a small ion in electrolyte. This is eight to nine orders of magnitude below the root-mean-square velocity of the same ion due to Brownian motion.

Field-permanent dipole interactions. A molecule or colloidal particle can have a permanent dipole moment μ due to a distribution of fixed charges in it. An electric field E will induce a torque $E\mu\cos(\theta)$, where θ is the angle between the field and the dipole moment, which will tend to align the particles with the field. The response time τ is determined by viscous drag on the particle. From Stokes' law

$$\tau = \frac{4\pi\eta a^3}{kT} \tag{20}$$

where a is the radius of the dipole, η the viscosity of the medium, k is Boltzmann's constant, and T is the absolute temperature. The mean orientation of the particles is determined by the strength of the interaction (which is of the order of μE) as compared to the mean thermal energy kT. In general, larger particles have larger dipole moments (and can be oriented by weaker fields) but their response time is slower (Table II). A whole literature exists on the use of pulsed dc or gated RF fields to produce partial alignment of molecules and colloidal particles [29], but clearly the required field strengths are very high.

Electric field-induced dipole interactions. Electric fields will also exert forces and torques on uncharged objects due to field-induced dipole interactions (due to the polarizabilty α of the particles). Thus, the induced dipole moment μ_p is

$$\mu_p = \alpha E \tag{21}$$

and the force on the particle is

$$f = \alpha E \frac{dE}{dx}$$
$$= \frac{\alpha}{2}\frac{dE^2}{dx}. \tag{22}$$

The polarizability α of a spherical particle of radius r is given by

$$\alpha = 4\pi\epsilon_m r^3 \operatorname{Re}(u^*) \tag{23}$$

where u^* is the Clausius-Mossotti ratio

$$u^* = \frac{\varepsilon_p^* - \varepsilon_m^*}{\varepsilon_p^* + 2\varepsilon_m^*} = \frac{\sigma_p^* - \sigma_m^*}{\sigma_p^* + 2\sigma_m^*} \tag{24}$$

and the subscripts p and m indicate the particle and surrounding medium. If the particle is electrically anisotropic, the field may also exert a torque on it through its interaction with the polarizability tensor. The force depends on the dielectric properties of the medium and particle, which enter through the quantity $\mathbf{u}^*$, and this factor varies within narrow limits. Unlike the other forces considered above, field-induced dipole forces are quadratic in field strength. Thus, the force generated by RF fields will have a dc component. This provides a mechanism for eliciting slow biological responses using high frequency fields.

Field-induced dipole ("dielectrophoretic") forces find practical application in the manipulation of cells, for example by causing them to line up in the "pearl chain" effect [30] before electroporation [31], [32]. The pearl chain effect generally requires field strengths above 1 kV/m at frequencies below ca. 1 MHz. The response time (of the order of 1 s for typical cells) is determined by complex hydrodynamic factors, and depends on field strength. The combination of high threshold and slow response generally means that heating effects are significant, and experiments on these phenomena are generally done using small chambers with good thermal control.

Electrode effects. If current is passed into the biological object through electrodes, electrochemical reactions will necessarily occur at the electrode-tissue interface. Particularly if the current has a dc component, such reactions can change pH, pO_2, and introduce a variety of biologically active ions into the

TABLE II
THRESHOLD FIELD STRENGTHS AND RELAXATION FREQUENCY FOR
SEVERAL MOLECULES.

Molecule	Dipole Moment μ (Debye)	Relaxation Frequency	E_{th} V/m
Water	1.8	20 GHz	$7 * 10^8$
Hemoglobin	170	ca. 1 MHz	$7 * 10^6$
DNA	~ 100,000 (varies)	< 1 kHz	>10,000

medium, some of them toxic [33]. Electrode impedance properties are strongly nonlinear, and rectification or generation of harmonics can occur. Electrode effects are an obvious potential cause of effects (or artifacts, depending on one's perspective) in studies in which RF fields are applied directly to biological preparations via electrodes.

The mechanisms described above are well established and noncontroversial. In addition, the scientific literature abounds with proposals for mechanisms, sometimes by highly respected physicists, for biological effects of RF energy at low exposure levels. This includes a theory for resonance-type effects reported from millimeter waves [34] or proposed mechanisms for biological damage from ultrawide-band pulses [35]. Many of these theories are experimentally unsupported, not accompanied by quantitative estimates of response times and thresholds, or can be challenged on obvious theoretical grounds [36] and they remain unpersuasive and controversial.

VI. THE "MECHANISMS PARADOX"

As the above discussion shows, there are many mechanisms, both linear and nonlinear, thermal and nonthermal, by which RF or broadband electric fields can interact with biological materials. But careful analysis, that properly accounts for the strength of the interaction and dissipative effects, leads to high anticipated thresholds for producing observable effects. This arises in part from the nature of the coupling of external fields to the body, and in part from the strength of the interaction and the kinetics of response.

Indeed, the (very limited) studies to date have failed to disclose striking effects in animals exposed to ultrawide-band or EMP pulses (e.g., [37]–[39]), with field strengths (measured outside the body) of the order of tens of kV/m (ultrawide-band pulses) to hundreds of kV/m (EMP). The studies (e.g., by Schoenbach et al., [28]) that did report clear-cut effects utilized much stronger fields, applied directly to the preparation. Ultrawide-band and EMP pulses are clearly far more effective in damaging electronics (one of the purposes for which the technologies were developed) than in damaging biological cells. None of the considerations presented above suggest the possibility of nonthermal effects from the much weaker fields used in communications systems.

Paradoxically, many effects, sometimes at low exposure levels, of RF energy have been reported in the literature that clearly are not explicable in terms of the biophysical mechanisms discussed above. For example, many therapeutic effects of millimeter waves have been reported by investigators in the former Soviet Union. Many of these effects involve low

exposure levels (<0.1 W/m^2), at frequencies where the energy barely penetrates the (dead) outer layers of the skin [40], [41].

This paradox might be resolved in two ways. On the one hand, biophysical theory is surely not complete, and one can take for granted that interesting new mechanisms of interaction will be discovered. On the other hand, the experimental evidence is frequently unclear. Many studies that report effects are exploratory in nature, or subject to technical criticism, or the effects are close to the limits of statistical detection. Many reported effects find conventional explanations or simply disappear when followup studies are conducted under better controlled conditions [42]. It is the continued interplay of theory and experiment that creates reliable knowledge, and this has not even begun for many reported bioeffects. Given sufficient field strengths, however, there is no question that a range of effects will be produced. The issue then is to make productive use of them.

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Kenneth R. Foster (M'77–SM'81–F'88) received the Ph.D. degree in physics from Indiana University in 1971.

He served from 1971 to 1976 with the U.S. Navy at the Naval Medical Research Institute. Since 1976 he has been with the Department of Bioengineering at the University of Pennsylvania, Philadelphia, where he is presently a Professor and Undergraduate Curriculum Chair of Bioengineering. For all of this time he has been engaged in studies on the interaction of nonionizing radiation and biological systems, including studies on mechanisms of interaction and biomedical applications of radiofrequency and microwave energy. In addition he has written widely about scientific issues related to possible health effects of electromagnetic fields. He has published approximately 90 technical papers in peer reviewed journals, numerous other articles, and is the author of two books related to technological risk and the law. His latest book is *Judging Science* (Cambridge, MA: MIT Press, April 1997).

Dr. Foster was Chair of the IEEE EMBS Committee of Man and Radiation from 1997 to 1999, and in 1997 and 1998, served as President of the IEEE Society on Social Implications of Technology.