Cell Membrane Nonlinear Response to an Applied Electromagnetic Field

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Abstract—**The transmembrane potential difference induced by an impressed electromagnetic field in a spherical homogeneous cell with nonlinear membrane is obtained by using the Volterra-series formalism. Some possible generalizations are suggested, and computed results are discussed.**

Key words—Biological effects; Cell membranes; Nonlinear response; Volterra series.

I. Introduction

CELLULAR [1], as well as intracellular (e.g., nuclear [2] and mitochondrial [3]), membranes exhibit distinct nonlinear electrical behavior, due to the potential barrier V_o resulting from the difference between inner and outer electrolytes and the action of ion-pumps [4].

The referred potential affects the cell *homeostasis*, and plays the key role in the physiology of excitable cells (e.g., neurons). Accordingly, cell membranes have been recently indicated as possible elicited sites of action for nonionizing electromagnetic radiation [5]–[11] to explain, e.g., a number of definitely nonthermal observed exposure effects on insulated living tissues [12]–[18] and systems [19]–[22].

The present paper is, to the best of our knowledge, the first rigorous attempt to study cell interaction with electromagnetic fields as a nonlinear boundary-value problem. This is done in the framework of the Volterra-Series Method, as formulated in [23]. Our results do confirm the relevance of nonlinear cell response.

The paper is organized as follows: Section II deals with nonlinear membrane modeling; the response of an insulated spherical cell is obtained in Section III; some representative computed results are presented in Section IV, and discussed in Section V.

II. Nonlinear Membrane Modeling

In the absence of an applied electromagnetic field, the transmembrane potential difference $\Delta\phi$ is equal to the cell resting potential $V^{(0)}$ (~ 100 mV, in a typical cell). When the field is applied, a *transmembrane excess potential* (henceforth abbreviated as TEP) $\delta\phi$ appears, viz.

$$\Delta\phi = V^{(0)} + \delta\phi. \tag{1}$$

As a result, a transmembrane current density J_m flows. We accordingly let

$$J_m = \sum_{k=1}^{\infty} J_m^{(k)} \tag{2}$$

where

$$J_m^{(k)} = \gamma_k \overset{(k)}{*} \left[\underbrace{\delta\phi, \cdots, \delta\phi}_{k \text{ factors}}\right] \tag{3}$$

$\overset{(k)}{*}$ denoting k-fold (time) convolution, viz.

$$\gamma_k \overset{(k)}{*} \left[\underbrace{\delta\phi, \cdots, \delta\phi}_{k \text{ factors}}\right] = \int_{-\infty}^{t} d\tau_1 \cdots \int_{-\infty}^{t} d\tau_k \, \gamma_k(\tau_1, \cdots, \tau_k) \cdot \delta\phi(t-\tau_1) \cdots \delta\phi(t-\tau_k). \tag{4}$$

Equation (2) is a Volterra functional expansion [23], [24] (Taylor series with memory), describing the most general local nonlinear noninstantaneous relationship between J_m and $\delta\phi$, in terms of the Volterra kernels γ_k. Note that the first term in (2) is the usual linear response. The Volterra kernels γ_k could be obtained, e.g., by solving into a Volterra series the celebrated Hodgkin-Huxley equation [25], possibly augmented to take into account the $\Delta\phi$-dependance of membrane (specific) capacitance [26]. This task is being presently accomplished [27], and will be the subject of a forthcoming paper.

Linearization of the HH equation about the resting state [28] yields the equivalent circuit shown in Fig. 1-Table I. This circuit does properly account for the "anomalous inductive reactance" phenomenon observed at *ELF* [29]; it doesn't conversely account for the observed *VLF*-dispersion of membrane (specific) conductance and capacitance [29]. The latter is usually explained in terms of surface-adsorbed ion-layers [30] and may be phenomenologically described by adding the Y_s branch shown dashed in Fig. 1-Table I [31]. The linearized equivalent circuit of Fig. 1 may be reasonably expected to be accurate over the whole RF range. Accordingly, letting $Y(\omega)$, its complex frequency-dependent admittance, and denoting as $\Gamma_1(\omega)$ the Fourier transform of $\gamma_1(\tau)$, we assume

$$\Gamma_1(\omega) = Y(\omega). \tag{5}$$

We turn now to the *nonlinear* features of cell membranes.

Area and thickness variations with applied voltage have been observed in thin-lipid artificial membranes at *ELF* [26], suggesting a voltage dependance of membrane capaci-

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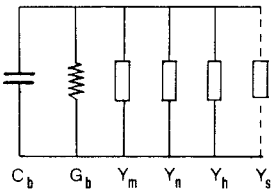

Fig. 1. Cell membrane linearized equivalent circuit.

tance of the form

$$C_m = C_o + \beta(\Delta\phi)^2 \tag{6}$$

(typical values: $C_o \sim 1\ \mu\text{F/cm}^2$, $\beta \sim 1.2\cdot 10^{-6}\ \mu\text{F/cm}^2\text{mV}^2$ [7]). Experimental evidence indicates that β is frequency dependent, and is negligible at and above ~ 100 KHz, in squid axon [32].

The current-voltage step-response of (space-clamped) squid axon membranes [33], on the other hand, is known to be fairly well approximated at late times (after ~ 10 ms, i.e., below ~ 100 Hz) by a nonlinear diode-like relationship of the form [33][1]

$$J_m = J_o[\exp(\delta\phi/V_T) - 1] \tag{7}$$

(typical values: $J_o \sim 10^{-6}$–10^{-5} A/cm^2; $V_T \sim 5$ mV [1]). The membrane pore conduction mechanism involves a number of characteristic times (ion-channel gating times [35], transit times [34], ion-pump characteristic times, etc.). At early times (before ~ 1 ms, i.e., above ~ 1 KHz), a substantially linear behavior is observed [33].

Accordingly, we assume that (6) and (7) provide a reasonably good description of membrane properties at frequencies below some 100 Hz; and that the (conduction plus displacement) transmembrane current density depends *linearly* on those spectral components of $\delta\phi$ whose frequency exceeds some 100 KHz. Hence, by denoting as $\Gamma_2(\omega_1, \omega_2)$ and $\Gamma_3(\omega_1, \omega_2, \omega_3)$ the (double, triple) Fourier transforms of $\gamma_2(\tau_1, \tau_2)$ and $\gamma_3(\tau_1, \tau_2, \tau_3)$, respectively, we get, omitting the details of the calculation

$$\Gamma_2(\omega_1, \omega_2) = \begin{cases} \dfrac{J_o}{2V_T^2} + j\,(\omega_1 + \omega_2)\cdot 2\beta V^{(0)}, & (2\pi)^{-1}(\omega_1 + \omega_2) < 100\ \text{Hz} \\ 0, & (2\pi)^{-1}(\omega_1 + \omega_2) > 100\ \text{KHz} \end{cases} \tag{8}$$

$$\Gamma_3(\omega_1, \omega_2, \omega_3) = \begin{cases} \dfrac{J_o}{6V_T^3} + j\,(\omega_1 + \omega_2 + \omega_3)\cdot\beta, & (2\pi)^{-1}(\omega_1 + \omega_2 + \omega_3) < 100\ \text{Hz} \\ 0, & (2\pi)^{-1}(\omega_1 + \omega_2 + \omega_3) > 100\ \text{KHz}. \end{cases} \tag{9}$$

Note that consistency between the 'exact' equation (5) and the linearized form of equations (6) and (7) in the static limit requires

$$J_o = V_T(G_b + G_m + G_n + G_h)$$
$$C_o = C_b + C_s - \beta|V^{(0)}|^2 \tag{10}$$

[1]In a more refined model, J_m would possibly be the sum of several diode-like terms, each related to some specific ion-channel. Such a generalization easily could be included.

TABLE I
CELL MEMBRANE LINEARIZED EQUIVALENT CIRCUIT ACCORDING TO [28], [31]

$Y_{m,n,h} = \dfrac{G_{m,n,h}}{1 + j\omega\tau_{m,n,h}}$ $Y_s = \dfrac{j\omega C_s}{1 + j\omega\tau_s}$	
$C_b = 0.5\ \mu\text{F/cm}^2$; $G_o = 0\ 6773\ 10^{-3}\ \Omega^{-1}/\text{cm}^2$	
$G_m = 0\ 0716\ 10^{-3}\ \Omega^{-1}/\text{cm}^2$, $\tau_m = 9.516$ ms	
$G_n = 0\ 8489\ 10^{-3}\ \Omega^{-1}/\text{cm}^2$, $\tau_n = 5\ 4586$ ms	
$G_h = -0\ 4316\ 10^{-3}\ \Omega^{-1}/\text{cm}^2$, $\tau_h = 0\ 2368$ ms	
$C_s = 0\ 4\ \mu\text{F/cm}^2$, $\tau_s = 5\ 10^{-2}$ ms	

where G_b, G_m, G_n, G_h, C_b, and C_s have been defined in Table I.

The problem is how to use the frequency domain *incomplete* knowledge of the second- and third-order Volterra kernels, provided by (8) and (9), plus the *full-spectrum* description of the first-order kernel, as represented by (5), for meaningful analysis of cell-membrane nonlinear response.

According to current opinions, as discussed in Section IV, relevant biochemical and/or CNS-behavioral effects could come from TEP intermodulation products at frequencies $\lesssim 100$ Hz. On the other hand, as shown in Section III, computation of nonlinear TEP responses to time-harmonic incident fields requires 1) knowledge of the first-order kernel at the incident frequencies, and 2) knowledge of the higher order kernels *only* at the intermodulation frequencies involved.

Equations (5), (8), and (9) do, therefore, contain sufficient information to study a number of suitably chosen meaningful cases, as, e.g., done in Section IV.

III. INSULATED SPHERICAL CELLS

We consider the simplest conceivable model of electromagnetic interaction with a living organism: a single spherical homogeneous cell, embedded in an infinite homogeneous medium, as depicted in Fig. 2.

Let $\{r, \theta, \phi\}$ a spherical cell-centered polar coordinate system, and assume a time-varying plane-wave incident field $\underline{e}^i$ linearly polarized along the polar axis.

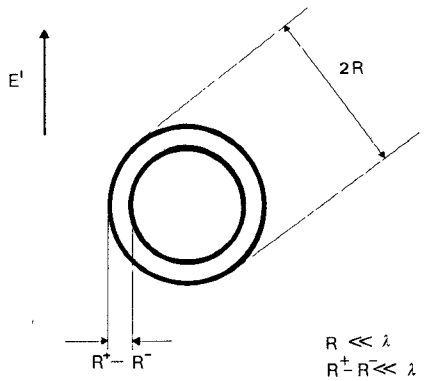

Fig. 2. Geometry of insulated spherical cell.

For typical cell diameters (from 1μ up to 1 mm) a quasi-static field analysis is appropriate up to frequencies ~ 10 GHz. Accordingly, all electrical variables of interest (e.g., fields, currents, etc.) may be derived from a single scalar potential, $\Phi(\underline{r}, t)$. Then, letting $\Phi_s(\underline{r}, t)$ the cell-induced potential, we have

$$\Phi(\underline{r}, t) = -e^i(t) r\cos\theta + \Phi_s(\underline{r}, t) \tag{11}$$

$$\nabla^2 \Phi(\underline{r}, t) = 0 \tag{12}$$

$$S_e * \left.\frac{\partial \Phi}{\partial r}\right|_{r=R+} = S_i * \left.\frac{\partial \Phi}{\partial r}\right|_{r=R-} = J_m \tag{13}$$

where S_e and S_i are the inverse Fourier transforms of the (complex) conductivities of the external and intracellular medium, respectively, $r = R+$ and $r = R-$ denote the outer and inner cell membrane surfaces, and J_m is the (inward) transmembrane current density, as defined by (3) and (1). Equation (13) holds true under the assumption of a purely radial transmembrane current flow.

To solve (12), together with the linear and nonlinear boundary conditions (13), we expand the cell-induced potential $\Phi_s(\underline{r}, t)$ into a Volterra series [23] with respect to the incident field, thus letting

$$\Phi(\underline{r}, t) = -Ae^i(t) r\cos\theta + \Phi_s(\underline{r}, t) \tag{14}$$

$$\Phi_s(\underline{r}, t) = \Phi^{(0)} + \sum_{m=1}^{\infty} A^m \Phi_s^{(m)}(\underline{r}, t) \tag{15}$$

where $\Phi^{(0)}$ is the cell resting-potential, viz.

$$\Phi^{(0)} = \begin{cases} -V^{(0)}, & r < R \\ 0, & r > R \end{cases} \tag{16}$$

$\Phi_s^{(m)}$ is a nonlinear homogeneous functional of degree m with respect to the incident field [23], and A is a dummy dimensionless variable, whose value may be finally set equal to one.

Inserting (14)–(16) into (12) and (13), and using (1)–(3), then repeatedly differentiating with respect to A, and finally letting $A = 0$, yields the following *hierarchy* of linear boundary value problems:

$$\nabla^2 \Phi_s^{(m)}(\underline{r}, t) = 0 \tag{17}$$

TABLE II
MULTIPOLE EXPANSION COEFFICIENTS, UP TO THIRD ORDER

$$c_1^{(1)} = \left[\hat{\sigma}_e \hat{\sigma}_1 + \hat{\gamma}_1 R\left(\hat{\sigma}_e + \hat{\sigma}_1/2\right)\right]^{-1}\left[\hat{\sigma}_e \hat{\sigma}_e + \hat{\gamma}_1 R(\hat{\sigma}_1 - \hat{\sigma}_e)/2\right] e^i$$

$$D_1^{(1)} = \frac{R^3}{2}\,\hat{\sigma}_e^{-1}\left[(\hat{\sigma}_1 - \hat{\sigma}_e) e^i - \hat{\sigma}_1 c_1^{(1)}\right]$$

$$c_0^{(2)} = \frac{1}{3}\,\hat{\gamma}_1^{-1}\hat{\gamma}_2\left[D_1^{(1)} R^{-2} - c_1^{(1)} R\right]^2$$

$$D_0^{(2)} = 0$$

$$c_2^{(2)} = \frac{2}{3} R^{-2}\left[2\hat{\sigma}_e \hat{\sigma}_1 + \hat{\gamma}_1 R\left(\hat{\sigma}_e + 2\hat{\sigma}_1/3\right)\right]^{-1}\hat{\gamma}_2 R\hat{\sigma}_e\left[D_1^{(1)} R^{-2} - c_1^{(1)} R\right]^2$$

$$D_2^{(2)} = -\frac{2}{3} R^5\,\hat{\sigma}_4^{-1}\hat{\sigma}_e\, c_2^{(2)}$$

$$c_1^{(3)} = R^{-1}\left[\hat{\sigma}_1\hat{\sigma}_e + \hat{\gamma}_1 R\left(\hat{\sigma}_e + \hat{\sigma}_1/2\right)\right]^{-1}\hat{\sigma}_e\left\{-2\hat{\gamma}_2 R\, c_0^{(2)}\left[D_1^{(1)} R^{-2} - c_1^{(1)} R\right] + \frac{4}{5}\hat{\gamma}_2 R\left[D_1^{(1)} R^{-2} - c_1^{(1)} R\right]\left[D_2^{(2)} R^{-3} - c_2^{(2)} R^2\right] + \frac{3}{5}\hat{\gamma}_3 R\left[D_1^{(1)} R^{-2} - c_1^{(1)} R\right]^3\right\}$$

$$D_1^{(3)} = -\frac{R^3}{2}\,\hat{\sigma}_e^{-1}\hat{\sigma}_1\, c_1^{(3)}$$

$$c_3^{(3)} = R^{-3}\left[3\hat{\sigma}_e\hat{\sigma}_1 + \hat{\gamma}_1 R\left(\hat{\sigma}_e + \frac{3}{4}\hat{\sigma}_1\right)\right]^{-1}\hat{\sigma}_e\left\{\frac{6}{5}\hat{\gamma}_2 R\left[D_1^{(1)} R^{-2} - c_1^{(1)} R\right]\left[D_2^{(2)} R^{-3} - c_2^{(2)} R^2\right] + \frac{2}{5}\hat{\gamma}_3 R\left[D_1^{(1)} R^{-2} - c_1^{(1)} R\right]^3\right\}$$

$$D_3^{(3)} = -\frac{3}{4} R^7\,\hat{\sigma}_e^{-1}\hat{\sigma}_1\, c_3^{(3)}$$

$$S_e * \left[-\delta_{m1} e^i(t)\cos\theta + \left.\frac{\partial \Phi^{(m)}}{\partial r}\right|_{r=R+}\right]$$

$$= S_i * \left[-\delta_{m1} e^i(t)\cos\theta + \left.\frac{\partial \Phi^{(m)}}{\partial r}\right|_{r=R-}\right]$$

$$= \gamma_1 * \delta\Phi^{(m)} + \sum_{k=1}^{m-1} \overset{(2)}{\gamma_2} * \left[\delta\Phi^{(k)}, \delta\Phi^{(m-k)}\right] + \cdots + \cdots + \overset{(k)}{\gamma_k} * \left[\underbrace{\delta\Phi^{(1)}, \cdots, \delta\Phi^{(1)}}_{k \text{ factors}}\right] \tag{18}$$

where

$$\delta\Phi^{(m)} = \Phi_s^{(m)}(R+) - \Phi_s^{(m)}(R-)$$

and δ_{mn} is the Kronecker symbol.

Equation (17) is solved by letting

$$\Phi_s^{(m)} = \begin{cases} \sum_{n=0}^{\infty} C_n^{(m)} r^n P_n(\cos\theta), & r < R \\ \sum_{n=0}^{\infty} D_n^{(m)} r^{-n-1} P_n(\cos\theta), & r > R \end{cases} \tag{19}$$

wherein $P_n(x)$ is the n-order Legendre polynomial, and the unknown expansion coefficients $C_n^{(m)}$ and $D_n^{(m)}$ are functions of time only.

Inserting (19) into (18) gives a hierarchy of *linear* functional equations in the $C_n^{(m)}$, $D_n^{(m)}$, whose formal solutions up to $m = 3$ have been collected under Table II, wherein the following shorthands have been used: $\hat{\sigma}_{i,e} = S_{i,e} *$, $\hat{\gamma}_k = \overset{(k)}{\gamma_k} *$, and $[\cdot]^{-1}$ denotes the inverse operator.

Several generalizations of the procedure just sketched may be easily implemented. Extension to multilayered spherical as well as cylindrical models (as, e.g., proposed in [36], in a linear circuit approximation) is straightforward, although the mathematics can grow pretty cumbersome. It is also quite possible to deal with eccentrical geometries, by following the alternative approaches described in [37], [38] for the linear case.

TABLE III
TEST CASES

	INCIDENT FIELD [V/m]	TRANSMEMBRANE EXCESS POTENTIAL: frequency	space pattern	maximum peak value [V] at f_o = 1 MHz, 2R = 1 mm	relative change with frequency	relative change with cell diameter
Test case I (1st Order Response)	monochromatic $e^i = E_1 \cos 2\pi f_0 t$	f_o	dipole	$5.01 \times 10^{-3} E_1$	fig. 3	fig. 4
Test case II (2nd Order Response)	monochromatic $e^i = E_1 \cos 2\pi f_0 t$	DC	monopole + quadrupole	$-3.005 \times 10^{-5} E_1^2$	fig. 5	fig. 6
	two-tone $e^i = E_1 \cos 2\pi f_1 t + E_2 \cos 2\pi f_2 t$, $f_1 = f_0 + \Delta f$, $f_2 = f_0$	$\Delta f = f_1 - f_2 = 10$ Hz		$1.293 \times 10^{-4} E_1 E_2$		
Test case III (3rd Order Response)	three-tone $e^i = E_1 \cos 2\pi f_1 t + E_2 \cos 2\pi f_2 t + E_3 \cos 2\pi f_3 t$, $f_1 = f_0 + \Delta f$, $f_2 = f_0 + 3\Delta f$, $f_3 = f_0$	$\Delta f = f_1 - f_2 = f_2 - f_3 = 10$ Hz	dipole + octupole	$3.987 \times 10^{-6} E_1 E_2 E_3$	fig. 7	fig. 8

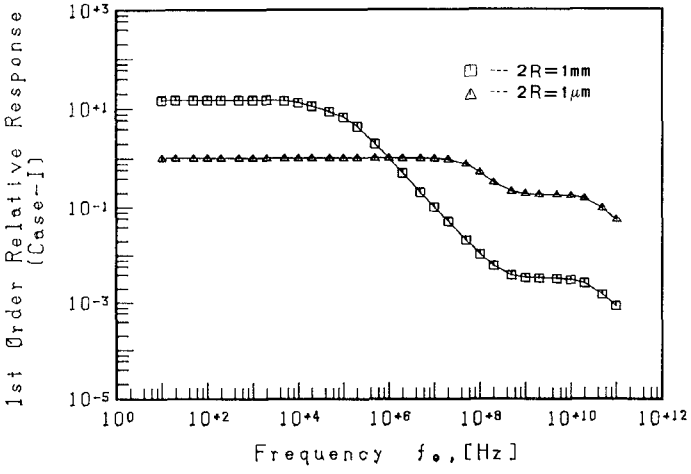

Fig. 3. First-order relative response (Case-I) as a function of frequency.

IV. COMPUTED RESULTS

The formal solutions collected in Table II allow, in principle, to compute the TEP response (up to third-order) to fairly general time-dependent fields, provided the cell-membrane Volterra kernels γ_k are known (see (1)).

For the special case where $\delta\phi$ is time-harmonic (such being the incident field), (4) algebrizes, and only discrete frequency-domain values of the (k-tuple) Fourier transforms of $\gamma_k(\tau_1, \cdots, \tau_k)$ do appear [23], [24].

In view of the incomplete knowledge represented by (5), (8), and (9), we shall confine our attention to time-harmonic incident fields, and compute, for a number of cases, some linear and nonlinear TEP responses as functions of the incident field strength, frequency, and cell diameter. They have been collected in Table III, which is also intended as a guide throughout Figs. 3–8.

The choice of the quoted nonlinear responses was suggested by the following arguments: a) dc TEP's as steady effects could produce long-term exposure damages; b) intermodulation TEP's close to EEG or "natural timer" frequencies [39], which cluster around ~10 Hz, could be particularly harmful.

For the sake of simplicity, both the external medium and the cell interior were modeled as 0.1 N_{eq} NaCl solutions at 37 °C, whose complex frequency-dependent conductivity was computed by means of Stogryn's formulas [40].

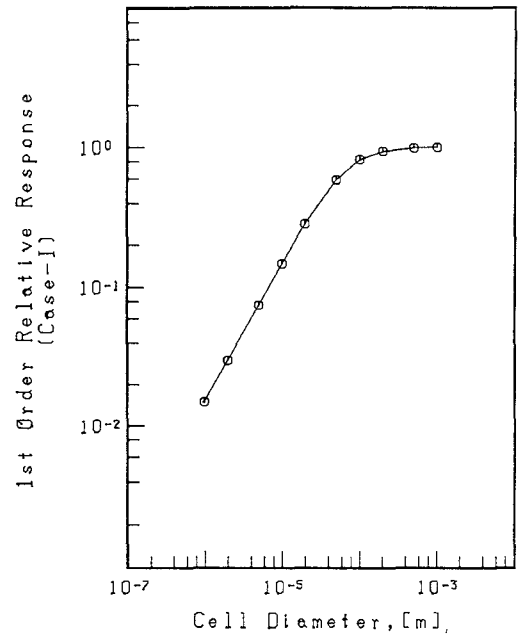

Fig. 4. First-order relative response (Case-I) as a function of cell diameter

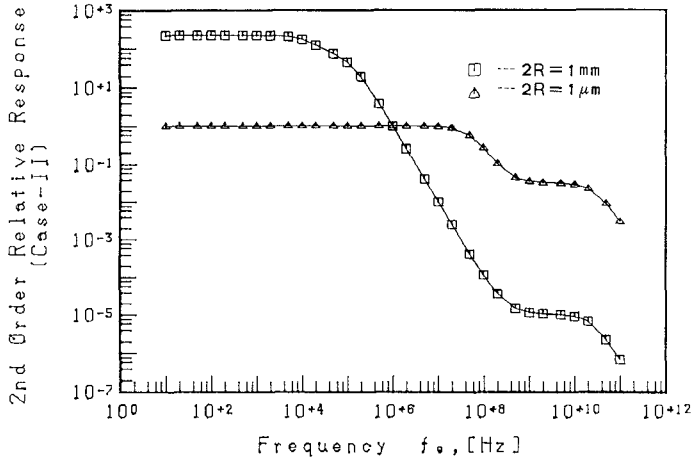

Fig. 5. Second-order relative response (Case-II) as a function of frequency.

All quoted TEP responses may be written as

$$\delta\phi = \delta\phi(2R_o, f_o) F(2R, f) \tag{20}$$

wherein $\delta\phi(2R_o = 1 \text{ mm}, f_o = 1 \text{ MHz})$ may be found in Table III, while $F(2R_o, f)$ and $F(2R, f_o)$ are plotted in Figs. 3, 5, and 7 and 4, 6, and 8, respectively. From our results, the following conclusions can be drawn:

a) induced TEP's ~1 mV (peak) ac, and ~100 μV dc, close to currently estimated threshold levels for detectable bioeffects [41]–[43] should be expected at field levels ~100 V/m, at $2R = 1$ mm below ~100 MHz.

b) at high frequencies, the TEP response becomes nearly independent of cell diameter. At low frequencies, larger cells (e.g., embryos, gametes, etc.) exhibit larger responses.

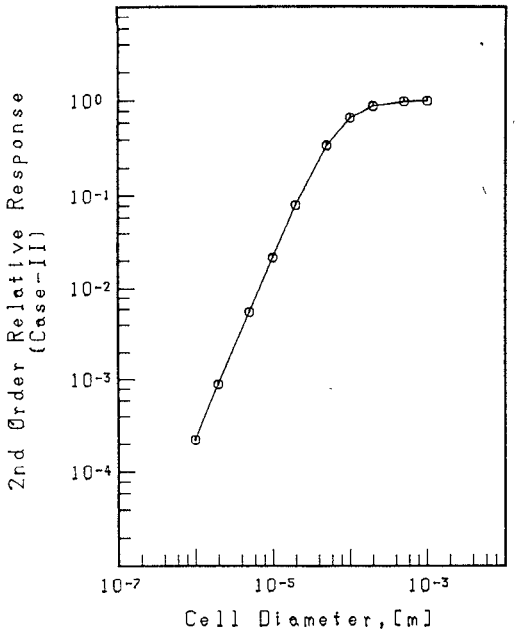

Fig. 6. Second-order relative response (Case-II) as a function of cell diameter.

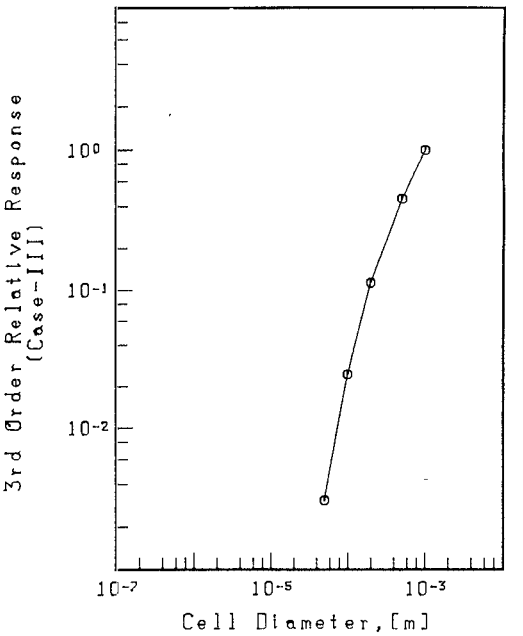

Fig. 8. Third-order relative response (Case-III) as a function of cell diameter.

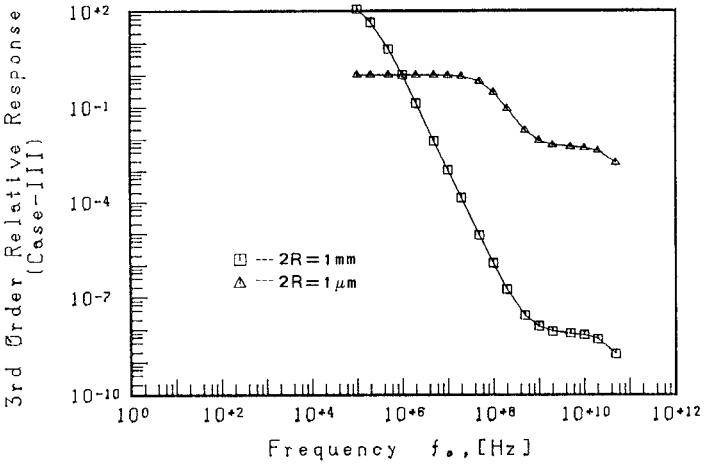

Fig. 7. Third-order relative response (Case-III) as a function of frequency.

V. Conclusions and Recommendations

We computed the response of a single cell. The case of a cell lattice (e.g., a living tissue) will be dealt with in a subsequent paper. No dramatic changes from present results should be expected, however.

Various possibly relevant phenomena, as, e.g., cell deformation (electrostriction), heating, and inhomogeneity, have not been included. A comprehensive description of cell interaction with EM fields, expectedly highly nonlinear, would benefit in our opinion of the Volterra series formalism.

It has been found that fields of 100 V/m may trigger detectable cellular effects, below 100 MHz. The obvious question is whether comparable fields may be produced inside a human body, by an unwanted exposure to man-made EM fields. Results in [44] indicate that fields 100 V/m in air (below current U.S. safety standards) could produce comparable intensities in selected spots (e.g., lung) of a piecewise-homogeneous body model, at ~80 MHz (first body resonance).

It is important to note, however, that the fields computed in [44] are macroscopic ones, i.e., space-average values over distances small compared to wavelength, *but not necessarily to cell size*. We remark that the possible relevance of local field changes over the space-scale of a cell, or possibly of the very ion channels, remains to be ascertained.

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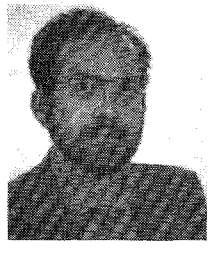

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