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NONLINEAR INTERACTION OF ELECTROMAGNETIC RADIATION AT THE CELL MEMBRANE LEVEL: RESPONSE TO STOCHASTIC FIELDS

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Abstract—A general rigorous analytic framework for computing the transmembrane potential shift resulting from the nonlinear voltage-current membrane relationship in response to wideband stochastic electromagnetic radiation is outlined, based on Volterra functional series. The special case of an insulated cylindrical cell with Hodgkin-Huxley membrane in an infinite homogeneous medium is worked out in detail, for the simplest case where the applied electric is normal to the cell axis, and independent from the axial coordinate. Representative computational results for a zero-average stationary band-limited white Gaussian incident field are illustrated and briefly discussed.

1. INTRODUCTION

The possible role of cell membranes as sites of *direct* interaction between electromagnetic (henceforth EM) fields and living systems, with specific reference to possible (albeit elusive) athermal and/or non-thermal effects[†], was perhaps first emphasized by Schwan throughout his seminal work on the subject [1, 2].

The possible relevance of *nonlinearity* in the cell-membrane voltage-current relationship was also early recognized [3, 4], and invoked, e.g., to explain EM-exposure induced changes in cytoplasmatic ion concentrations [5] and firing-potentials in excitable cells [6], as well

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† Non thermal effects are defined as those observed at such low exposure levels that, in the absence of any external temperature control, *no* macroscopic temperature change occurs *in vitro*, and no thermoregulatory reaction is observed *in vivo*.

as the different response observed to continuous-wave compared to low-frequency modulated radiation, possibly due to membrane-related rectification and demodulation [7].

In [8] a general framework for computing the change in the transmembrane potential of a cell exposed to a time-harmonic EM field was introduced, based on Volterra series (henceforth VS) expansions [9]. The same tool was subsequently adopted in [10, 11], and eventually applied in [12] and, independently, in [13], to solve the Hodgkin-Huxley equation [14] describing the membrane voltage-current relationship in excitable cells.

In [15], for the first time to the best of our knowledge, the Volterra series formalism was used to derive the power spectral density of the transmembrane potential response in a spherical cell with nonlinear membrane exposed to a wideband *stochastic* EM field, by solving a nonlinear boundary value problem. The non-trivial details of the formal derivation were not included in [15] due to space limitations. Here we present a full derivation for an insulated cylindrical cell with Hodgkin-Huxley (henceforth H-H) membrane, for the simplest two-dimensional case where the incident field is uniform along the cell axis.

This study is motivated by the possibility of modeling a variety of complex EM-polluted environments in terms of *stochastic* fields. The theoretical foundations for modeling EM fields in densely populated environments where a multitude of different EM sources, from narrowband to UWB, co-exist, were laid out by Middleton in a series of seminal papers [16–18]. According to [16], under these circumstances the field can be modeled as the superposition of a Gaussian stochastic process, representing the cumulative effects of a large number of weak sources (by the central limit theorem), and a Poisson (impulsive) one, produced by random strong transients (these latter may also originate a Gaussian process, if the product between their rate and their typical duration is a large number [18]).

Cell membranes exhibit electrical noise of endogenous origin [19]. Applied EM fields changing the level and spectral distribution of the transmembrane potential noise may thus affect cell homeostasis.

The effect of superimposed noise on the firing pattern of neurons is, e.g., highly non-trivial [20–23]. It has been even suggested that endogenous membrane noise may play an essential role in the operation of the nervous system, through the nonlinear stochastic resonance phenomenon [24, 25]. Numerical simulations supporting this suggestion [26] indicate that under suitable conditions, exogenous noise may induce firing activity in silent neurons and enhance the "detectability" of exogenous signals [27].

Investigating the electric response of cells to stochastic (noisy)

electromagnetic fields is thus a meaningful question. This paper is aimed at exploiting an electromagnetic modeling tool which may hopefully help further investigation about this issue.

The paper is accordingly organized as follows. In Section 2 the Volterra series representation of the membrane voltage-current density relationship is introduced, and the (spectral) Volterra series solution of the H-H equation, including the leading even and odd nonlinear response terms, is derived. In Section 3, the electromagnetic response of a (voltage clamped) cylindrical cell with non linear H-H membrane exposed to a linearly polarized EM field in a homogeneous medium is obtained. In Section 4 the average value and the power spectral density (henceforth PSD) of the nonlinear transmembrane (excess) potential for the simplest case of a (stationary, zero-average) white (band-limited) Gaussian noise field is computed. Numerical results are illustrated in Section 5 and discussed in Section 6. Conclusions and recommendations follow under Section 7.

2. NONLINEAR MEMBRANE VOLTAGE-CURRENT RELATIONSHIP

In the absence of an applied EM field, the transmembrane potential difference in a living cell takes the so-called resting value V_0 ($\sim 100\,\mathrm{mV}$ in a typical cell). When the impressed field is switched on, a *transmembrane excess potential* $\delta\phi$, and a transmembrane current density build up. These are related by a nonlinear functional relationship [3, 4] which can be conveniently expanded into a Volterra series [28]:

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

where[‡]

$$J_m^{(k)}(t) = \left(\frac{1}{2\pi}\right)^k \int_{-\infty}^{\infty} d\omega_1 \int_{-\infty}^{\infty} d\omega_2 \ldots \int_{-\infty}^{\infty} d\omega_k \; \Gamma^{(k)}(\omega_1, \omega_2, \ldots, \omega_k) \cdot \prod_{i=1}^{k} \delta\Phi(\omega_i) \exp(\imath\omega_i t), \tag{2}$$

$\delta\Phi(\omega)$ being the transmembrane excess potential Fourier transform. The Volterra series is adequate to model a general weakly nonlinear smooth relationship between the (local) transmembrane current density and voltage, including instantaneous (resistive) as well as non

[‡] Note that $[\Gamma^{(k)}] = \mathrm{ampere\,volt}^{-k}\,\mathrm{meter}^{-2}$.

instantaneous (reactive) nonlinearities [29]. The $\Gamma^{(k)}$ are referred to as the response kernels. The first order kernel is nothing but the usual (linear) transfer function.

2.1. The Hodgkin-Huxley Model

The H-H model was introduced in [14] as a phenomenological description of the nonlinear membrane voltage current relationship in excitable cells (e.g., neurons) [30]. Alternative (also phenomenological) models, including, among others, those of Fitzhugh-Nagumo [31] and Izhikevich [32], have been proposed later. The formalism expounded below may be adapted to these alternative models as well. Notwithstanding its venerable age, the H-H model is still widely used as a reference model [33], and has been ubiquitously adopted to model the nonlinear response of excitable cells exposed to EM radiation from extremely low frequencies up to the microwave range [34, 35]. According to the H-H model, the total transmembrane current density is

$$J_m = J_K + J_{Na} + J_l + \widetilde{C}\frac{d}{dt}\delta\phi, \tag{3}$$

where J_K, J_{Na} are the potassium and sodium ionic current densities, J_l is a leakage current density term, $\widetilde{C}$ the membrane specific capacitance ($\sim 10^{-2}\,\mathrm{Fm}^{-2}$ in a typical cell), and $\delta\phi$ is the transmembrane excess potential, viz.

$$\delta\phi = \phi(R^+) - \phi(R^-) - V_0, \tag{4}$$

$\rho = R^{\pm}$ identifying the outer/inner membrane surface, and V_0 being the resting potential. The current densities in (3) are given, according to [14], by

$$\begin{cases} J_K = g_K n^4(\delta\phi - V_K), \\ J_{Na} = g_{Na} h m^3(\delta\phi - V_{Na}), \\ J_l = g_l(\delta\phi - V_l), \end{cases} \tag{5}$$

where

$$\begin{cases} g_l = 3\,\mathrm{ohm}^{-1}\mathrm{m}^{-2}, \\ g_{Na} = 1200\,\mathrm{ohm}^{-1}\mathrm{m}^{-2}, \\ g_K = 360\,\mathrm{ohm}^{-1}\mathrm{m}^{-2}, \end{cases} \tag{6}$$

and

$$\begin{cases} V_l = 0.01059\,\mathrm{V}, \\ V_{Na} = 0.115\,\mathrm{V}, \\ V_K = -0.012\,\mathrm{V}. \end{cases} \tag{7}$$

In the original reference [14] the H-H model parameters (6) and (7) are given at 6.3°C. A discussion on how temperature affects the H-H

parameters can be found in [36]. The (dimensionless) coefficients m, n, h in (5) are obtained by solving the differential equations

$$\frac{du}{dt} = \alpha_u(1-u) - \beta_u u, \quad (u = m, n, h), \tag{8}$$

where[§]

$$\begin{cases} \alpha_n = \dfrac{1 - 0.1\overline{\delta\phi}}{10\exp\left(1 - 0.1\overline{\delta\phi}\right) - 1}, \\ \alpha_m = \dfrac{2.5 - 0.1\overline{\delta\phi}}{\exp\left(2.5 - 0.1\overline{\delta\phi}\right) - 1}, \\ \alpha_h = 0.07\ \exp\left(-0.05\overline{\delta\phi}\right), \end{cases} \tag{9}$$

and

$$\begin{cases} \beta_n = 0.125\exp\left(-0.0125\overline{\delta\phi}\right), \\ \beta_m = 4\exp\left(-0.055\overline{\delta\phi}\right), \\ \beta_h = \left[\exp\left(3 - 0.1\overline{\delta\phi}\right) + 1\right]^{-1}. \end{cases} \tag{10}$$

In (9), (10) $\overline{\delta\phi}$ is the dimensionless counterpart of $\delta\phi$. In view of Eqs. (8), (9), (10), the (dimensionless) coefficients m, n, h, and hence, via (5), the ionic current densities, and the total transmembrane current densities (3) are nonlinear functionals of $\delta\phi$, which can be written as VS as follows.

As a first step, we expand Eqs. (9) and (10) into McLaurin series

$$\alpha_{m,n,h} = \sum_{k=0}^{\infty} \alpha_{m,n,h}^{(k)} \delta\phi^k, \quad \beta_{m,n,h} = \sum_{k=0}^{\infty} \beta_{m,n,h}^{(k)} \delta\phi^k, \tag{11}$$

where the $\alpha_{m,n,h}^{(k)}$, $\beta_{m,n,h}^{(k)}$ coefficients are collected in Table 1, for $k = 0, 1, 2, 3$ and have dimensions V^{-k}. Next, we write the sought

Table 1. Expansion coefficients in Eq. (11).

k	0	1	2	3
$\alpha_n^{(k)}$	0.0581	3.3869	75.4738	493.8080
$\alpha_m^{(k)}$	0.2236	15.4131	461.3560	6897.23
$\alpha_h^{(k)}$	0.0700	−3.500	87.500	−1458.33
$\beta_n^{(k)}$	0.1250	−1.5625	9.7656	−40.6901
$\beta_m^{(k)}$	4.0000	−222.222	6172.84	−114312
$\beta_h^{(k)}$	0.0474	4.5177	204.458	5488.51

[§] Equations (9), (10) differ from those in [12] in view of the different units used here (MKSA).

solutions of Eqs. (8) in the form

$$u = u_{(0)} + \delta u, \quad (u = m, n, h) \tag{12}$$

where,

$$u_{(0)} = \frac{\alpha_u^{(0)}}{\alpha_u^{(0)} + \beta_u^{(0)}}, \tag{13}$$

and

$$\begin{aligned} \delta u \; = \; & \sum_{k=1}^{\infty} \left(\frac{1}{2\pi}\right)^k \int_{-\infty}^{\infty} d\omega_1 \int_{-\infty}^{\infty} d\omega_2 \ldots \int_{-\infty}^{\infty} d\omega_k \\ & \cdot \xi_u^{(k)}(\omega_1, \omega_2, \ldots, \omega_k) \prod_{n=1}^{k} \delta\Phi(\omega_n) \exp\left(\imath \omega_n t\right). \end{aligned} \tag{14}$$

Following [29], the Volterra kernels $\xi_u^{(k)}(\cdot)$ in (14) are obtained by first i) letting[‖]

$$\delta\phi(\omega) = 2\pi[A_1\delta(\omega - \Omega_1) + A_2\delta(\omega - \Omega_2) + \ldots + A_q\delta(\omega - \Omega_q)], \tag{15}$$

then ii) plugging Eqs. (11) to (15) into (8), and differentiating the resulting identity once with respect to each and any of the A_1, $A_2, \ldots, A_q$, and finally, iii) setting $A_1 = A_2 = \ldots = A_q = 0$. This yields a *linear* equation in $\xi_u^{(q)}(\Omega_1, \Omega_2, \ldots, \Omega_q)$. Letting successively $q = 1, 2, 3$ one accordingly gets, after some straightforward algebra

$$\xi_u^{(1)}(\Omega_1) = \left[\alpha_u^{(1)} - u_{(0)}(\alpha_u^{(1)} + \beta_u^{(1)})\right] \cdot \left[\alpha_u^{(0)} + \beta_u^{(0)} + \imath\Omega_1\right]^{-1}, \tag{16}$$

$$\begin{aligned} \xi_u^{(2)}(\Omega_1, \Omega_2) = & \left\{\alpha_u^{(2)} - u_{(0)}(\alpha_u^{(2)} + \beta_u^{(2)}) - \frac{1}{2}\left(\alpha_u^{(1)} + \beta_u^{(1)}\right)\right\} \\ & \cdot \left[\xi_u^{(1)}(\Omega_1) + \xi_u^{(1)}(\Omega_2)\right]\left[\alpha_u^{(0)} + \beta_u^{(0)} + \imath(\Omega_1 + \Omega_2)\right]^{-1}, \end{aligned} \tag{17}$$

$$\begin{aligned} \xi_u^{(3)}(\Omega_1, \Omega_2, \Omega_3) = & \left[\alpha_u^{(3)} - u_{(0)}(\alpha_u^{(3)} + \beta_u^{(3)}) - \frac{1}{3}\left(\alpha_u^{(2)} + \beta_u^{(2)}\right)\right. \\ & \left. \sum_{k=1}^{3} \xi_u^{(1)}(\Omega_k) - \frac{1}{3}\left(\alpha_u^{(1)} + \beta_u^{(1)}\right) \sum_{i,j=1\ldots3}^{i<j} \xi_u^{(2)}(\Omega_i, \Omega_j)\right] \\ & \cdot \left[\alpha_u^{(0)} + \beta_u^{(0)} + \imath(\Omega_1 + \Omega_2 + \Omega_3)\right]^{-1}. \end{aligned} \tag{18}$$

By using Eqs. (16)–(18) in (12)–(14), the ionic current densities in (5), and the total transmembrane current (3) can be cast in the Volterra

[‖] The Ω_i in (15) are purposely assumed as incommensurable.

series form (1), (2). The first three kernels are given explicitly in the Appendix. As noted in [4], the membrane specific capacitance may also exhibit nonlinear properties. The Volterra series approach summarized above can be easily extended to this more general case.

3. CYLINDRICAL CELL IN A HOMOGENEOUS MEDIUM

The Volterra series formalism can be used to solve the nonlinear boundary value problem of an insulated cell with nonlinear membrane in a uniform unbounded medium. The spherical cell case has been discussed in [15]. In this section we shall consider a cylindrical cell with radius R and membrane thickness $\delta \ll R$, exposed to a (plane wave) EM field whose wave vector is normal to the cell axis. The related boundary value problem, sketched in Fig. 1, is effectively 2-dimensional (z-independent) with no action potential propagation.

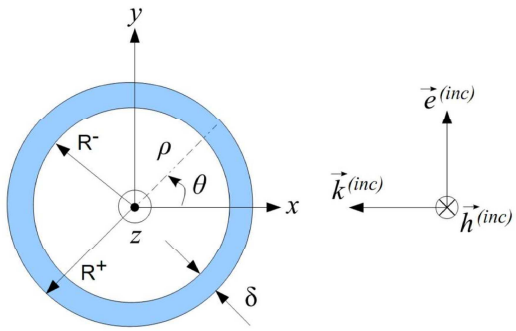

Figure 1. Geometry of problem and notation.

In view of the typical radii (1 μm to 1 mm) of a cell, a quasi-static analysis is appropriate up to 10^{10} Hz and above. Thus, all electrical quantities can be derived from a scalar potential

$$\phi(\vec{r},t) = \phi_0(\vec{r}) - Ae^{(inc.)}(0,t)\ \rho\ \sin\theta + \phi_s(\vec{r},t). \tag{19}$$

Here $e^{(inc.)}(0,t)$ is the (y-polarized) incident field

$$\phi_0(\vec{r}) = [1 - U(\rho - R)]V_0, \tag{20}$$

V_0 being the cell-resting potential, and $U(\cdot)$ Heaviside's step-function; $\phi_s(\cdot)$ is the scattered potential, which is a *nonlinear* functional of the incident field, viz.

$$\phi_s(\vec{r},t) = \sum_{m=1}^{\infty} A^m \phi_s^{(m)}(\vec{r},t). \tag{21}$$

The coefficient A in (19), (21) is used as a (dimensionless) book-keeping device, to be eventually set equal to one, which helps identifying the order of the various terms in the nonlinear response with respect to the incident field. For any A, the induced potential ϕ_s, and hence all terms $\phi_s^{(m)}$ in (21), must be a solution of Laplace equation, whence¶

$$\phi_s^{(m)}(\vec{r},t)=\begin{cases}\sum_{n=1}^{\infty}\left[c_n^{(m)}(t)\cos n\theta+s_n^{(m)}(t)\sin n\theta\right]\rho^n, & \rho<R\\ \sum_{n=1}^{\infty}\left[C_n^{(m)}(t)\cos n\theta+S_n^{(m)}(t)\sin n\theta\right]\rho^{-n}, & \rho>R\end{cases} \tag{22}$$

The unknown time functions $c_n^{(m)}(\cdot)$, $C_n^{(m)}(\cdot)$, $s_n^{(m)}(\cdot)$, $S_n^{(m)}(\cdot)$ can be found by enforcing continuity of the (radial, inward) current density across the cell membrane, viz.

$$\Sigma_{ext.} * \partial_\rho\phi|_{\rho=R^+} = \Sigma_{int.} * \partial_\rho\phi|_{\rho=R^-} = J_m(\delta\phi), \tag{23}$$

where $\Sigma_{ext.}$, $\Sigma_{int.}$ are the inverse Fourier transforms of the (complex) frequency domain conductivities of the external and intracellular medium, $R^{\pm}$ denote the outer/inner membrane surface, $*$ is time-convolution and $J_m(\delta\phi)$ is given by Eq. (1). For the sake of simplicity, we shall assume $\Sigma_{ext.}=\Sigma_{int.}=\Sigma$, which entails from the first equality in (23)

$$C_n^{(m)}(t)=-R^{2n}c_n^{(m)}(t),\quad S_n^{(m)}(t)=-R^{2n}s_n^{(m)}(t),\quad \forall m, \tag{24}$$

whence, using (19), (21), (22) and (24)

$$\begin{aligned}\delta\phi(\theta,t) &= \phi_s(R^+,\theta,t)-\phi_s(R^-,\theta,t)\\ &= -\sum_{m=1}^{\infty}A^m\left\{\sum_{n=1}^{\infty}2R^n\left[c_n^{(m)}(t)\cos n\theta+s_n^{(m)}(t)\sin n\theta\right]\right\}.\end{aligned} \tag{25}$$

In view of (21), 22), (24) and (25), the second equality in (23) yields the following equation, which holds true for any A within the circle of convergence of (21)

$$\begin{aligned}&\Sigma*\sum_{k=1}^{\infty}A^k\sum_{n=1}^{\infty}nR^{n-1}\left[c_n^{(k)}(t)\cos n\theta+s_n^{(k)}(t)\sin n\theta\right]\\ &-\delta_{k1}A\Sigma*e^{(inc.)}(t)\sin\theta\\ =\;& J_m\left(-\sum_{m=1}^{\infty}A^m\cdot\left\{\sum_{n=1}^{\infty}2R^n\left[c_n^{(m)}(t)\cos n\theta+s_n^{(m)}(t)\sin n\theta\right]\right\}\right).\end{aligned} \tag{26}$$

¶ The logarithmic $n=0$ terms are omitted from (22) in order to satisfy the condition of finiteness and regularity of the field at $\rho=0$ and $\rho\to\infty$.

The unknown functions $c_n^{(m)}(t)$ and $s_n^{(m)}(t)$ can now be expanded into Volterra series by letting[+]

$$c_n^{(m)}(t) = \left(\frac{1}{2\pi}\right)^k \int_{-\infty}^{\infty} d\omega_1 \int_{-\infty}^{\infty} d\omega_2 \ldots \int_{-\infty}^{\infty} d\omega_m \cdot \Xi_n^{(m)}(\omega_1, \omega_2, \ldots, \omega_m) \cdot \prod_{k=1}^{m} E^{(inc.)}(\omega_k) \exp(j\omega_k t), \quad (27)$$

and

$$s_n^{(m)}(t) = \left(\frac{1}{2\pi}\right)^k \int_{-\infty}^{\infty} d\omega_1 \int_{-\infty}^{\infty} d\omega_2 \ldots \int_{-\infty}^{\infty} d\omega_m \cdot \tilde{\Xi}_n^{(m)}(\omega_1, \omega_2, \ldots, \omega_m) \cdot \prod_{k=1}^{m} E^{(inc.)}(\omega_k) \exp(j\omega_k t), \quad (28)$$

where $E^{(inc.)}(\omega)$ is the Fourier transform of $e^{(inc.)}(0,t)$. The (spectral) kernels $\Xi^{(m)}(\omega_1, \omega_2, \ldots, \omega_m)$ and $\tilde{\Xi}^{(m)}(\omega_1, \omega_2, \ldots, \omega_m)$ are determined by letting

$$E^{(inc.)}(\omega) = 2\pi[A_1\delta(\omega - \Omega_1) + A_2\delta(\omega - \Omega_2) + \ldots + A_q\delta(\omega - \Omega_q)], \quad (29)$$

into (27) and (28), plugging into (26), and proceeding as already explained in connection with Eq. (15). One accordingly obtains, after some algebra

$$\tilde{\Xi}_1^{(1)}(\omega_1) = \frac{\sigma(\omega_1)}{\sigma(\omega_1) + 2R\Gamma^{(1)}(\omega_1)}, \quad (30)$$

$$\Xi_0^{(2)}(\omega_1, \omega_2) = R^2 \frac{\Gamma^{(2)}(\omega_1, \omega_2)}{2\Gamma^{(1)}(\omega_1 + \omega_2)} \tilde{\Xi}_1^{(1)}(\omega_1) \tilde{\Xi}_1^{(1)}(\omega_2), \quad (31)$$

$$\Xi_2^{(2)}(\omega_1, \omega_2) = -R \frac{\Gamma^{(2)}(\omega_1, \omega_2) \tilde{\Xi}_1^{(1)}(\omega_1) \tilde{\Xi}_1^{(1)}(\omega_2)}{\sigma(\omega_1 + \omega_2) + R\Gamma^{(1)}(\omega_1 + \omega_2)} \quad (32)$$

$$\begin{aligned} &\tilde{\Xi}_1^{(3)}(\omega_1, \omega_2, \omega_3) \\ &= \Big[\sigma(\omega_1+\omega_2+\omega_3) + 2R\Gamma^{(1)}(\omega_1+\omega_2+\omega_3)\Big]^{-1} \\ &\cdot \left\{ \sum_{(arg.\,perm.)} \left\{ \frac{2}{3}\Gamma^{(2)}(\omega_1, \omega_2+\omega_3) \tilde{\Xi}_1^{(1)}(\omega_1) \Big[R\Xi_0^{(2)}(\omega_2, \omega_3) \right.\right. \\ &\left.\left. - R^3 \Xi_2^{(2)}(\omega_2, \omega_3) \Big] \right\} + 6R^3 \Gamma^{(3)}(\omega_1, \omega_2, \omega_3) \prod_{i=1}^{3} \tilde{\Xi}_1^{(1)}(\omega_i) \right\}, \end{aligned} \quad (33)$$

[+] Note that $c_n^{(m)}$ and $s_n^{(m)}$ are measured in units of [volt meter^{-n}] whereas $\Xi_n^{(m)}$ and $\tilde{\Xi}_n^{(m)}$ are measured in [volt^{-m+1} meter^{m-n}].

$$
\begin{aligned}
&\tilde{\Xi}_3^{(3)}(\omega_1,\omega_2,\omega_3)\\
&= R\left[\sigma(\omega_1+\omega_2+\omega_3)+2R\Gamma^{(1)}(\omega_1+\omega_2+\omega_3)\right]^{-1}\\
&\cdot\left\{\sum_{(arg.\,perm.)}\left\{\frac{2}{3}\Gamma^{(2)}(\omega_1,\omega_2+\omega_3)\tilde{\Xi}_1^{(1)}(\omega_1)\tilde{\Xi}_2^{(2)}(\omega_2,\omega_3)\right\}\right.\\
&\left.-2\Gamma^{(3)}(\omega_1,\omega_2,\omega_3)\prod_{i=1}^{3}\tilde{\Xi}_1^{(1)}(\omega_i)\right\},
\end{aligned}
\tag{34}
$$

all other kernels of order ≤ 3 being identically zero.

In (31)–(34) σ is the spectral (frequency dependent) conductivity of the external and intracellular medium, and the sums in (33), (34) include all terms obtained from those explicitly written by permuting the frequency arguments in the factors. Knowledge of the kernels $\Xi_n^{(m)}(\cdot)$ and $\tilde{\Xi}_n^{(m)}(\cdot)$ allows finally to expand the transmembrane excess potential $\delta\phi$ into a Volterra series in the incident field, via Eqs. (22), (24), (27) and (28), yielding

$$
\delta\phi(\theta,t)=\sum_{m=1}^{\infty}\delta\phi^{(m)}(\theta,t),
\tag{35}
$$

where

$$
\begin{aligned}
\delta\phi^{(m)}(\theta,t) &= \left(\frac{1}{2\pi}\right)^m\int_{-\infty}^{\infty}d\omega_1\int_{-\infty}^{\infty}d\omega_2\ldots\int_{-\infty}^{\infty}d\omega_m\\
&\cdot Q^{(m)}(\theta;\omega_1,\omega_2,\ldots,\omega_m)\cdot\prod_{k=1}^{m}E^{(inc.)}(\omega_k)\exp(\imath\omega_k t),
\end{aligned}
\tag{36}
$$

with

$$
Q^{(1)}(\theta;\omega_1) = -2R\tilde{\Xi}_1^{(1)}(\omega_1)\sin\theta,
\tag{37}
$$

$$
Q^{(2)}(\theta;\omega_1,\omega_2) = -\Xi_0^{(2)}(\omega_1,\omega_2)-2R^2\Xi_2^{(2)}(\omega_1,\omega_2)\cos 2\theta,
\tag{38}
$$

$$
\begin{aligned}
Q^{(3)}(\theta;\omega_1,\omega_2,\omega_3) &= -2\left[R\tilde{\Xi}_1^{(3)}(\omega_1,\omega_2,\omega_3)\sin\theta\right.\\
&\left.+R^3\tilde{\Xi}_3^{(3)}(\omega_1,\omega_2,\omega_3)\sin 3\theta\right].
\end{aligned}
\tag{39}
$$

Equations (30) to (39) allow to compute the nonlinear transmembrane excess potential response up to 3rd order (included) in the incident field. Explicit expressions for the Q functions pertinent to the spherical cell case have been derived in [15].

4. NONLINEAR RESPONSE TO A WHITE GAUSSIAN FIELD

The Volterra series solution allows to write down the statistical moments of the nonlinear response as straightforward expansions involving the cumulants of the impressed field, when this latter is a stochastic process [37]. Here, as a simple model of a noisy EM environment, we shall consider a zero-average stationary Gaussian white noise EM field, which is entirely characterized by its first and second order moments, viz.

$$\langle e^{(inc.)}(t)\rangle = 0, \tag{40}$$

$$\langle e^{(inc.)}(t_1)e^{(inc.)}(t_2)\rangle = W_0\delta(t_1 - t_2). \tag{41}$$

where $\langle x\rangle$ denotes the expected value of x, and W_0 is the field power spectral density [$\mathrm{V^2m^{-2}sec}$]. The induced transmembrane excess potential average value and power spectral density can be easily obtained using (35)–(39) and capitalizing on Isserlis formulae [38],

$$\langle e^{(inc.)}(t_1)e^{(inc.)}(t_2)e^{(inc.)}(t_3)\rangle = 0, \tag{42}$$

and

$$\begin{aligned}&\langle e^{(inc.)}(t_1)e^{(inc.)}(t_2)e^{(inc.)}(t_3)e^{(inc.)}(t_4)\rangle\\ &= W_0^2\left[\delta(t_1-t_2)\delta(t_3-t_4)+\delta(t_1-t_3)\delta(t_2-t_4)+\delta(t_1-t_4)\delta(t_2-t_3)\right],\end{aligned} \tag{43}$$

yielding, after some simple algebra

$$\langle\delta\phi(\theta)\rangle = \frac{W_0}{2\pi}\left|\int_{-\infty}^{\infty} d\eta Q^{(2)}(\theta,\eta,-\eta)\right|, \tag{44}$$

$$\begin{aligned}\Pi(\omega,\theta) &= \mathcal{F}_{\tau\to\omega}\langle\delta\phi(\theta,t)\delta\phi(\theta,t+\tau)\rangle\\ &= W_0|Q^{(1)}(\theta,\omega)|^2 + \frac{W_0^2}{2\pi}\left\{2\int_{-\infty}^{\infty} d\eta\ |Q^{(2)}(\theta,\eta,\omega-\eta)|^2\right.\\ &\quad \left.+6\mathrm{Re}\left[Q^{(1)*}(\theta,\omega)\int_{-\infty}^{\infty} d\eta\ Q^{(3)}(\theta,\omega,\eta,-\eta)\right]\right\}.\end{aligned} \tag{45}$$

For a Gaussian colored noise the solution may be written basically in the same form, provided the linear response $Q^{(1)}$ in the above formulas is suitably modified.

5. NUMERICAL RESULTS

We present hereinafter some numerical results, based on the simplifying assumption that both the external and intracellular medium may be

modeled as ($0.1N_{eq}$ NaCl) saline solutions whose complex, frequency-dependent conductivity is computed using Stogryn's formulas [39], including some fixes and improvements from [40].

The most obvious effect of membrane nonlinearity is rectification, producing a DC component in the transmembrane excess potential, described by (44). The DC component (44) is maximum at $\theta = 0, \pi$. This maximum value, scaled to W_0 is shown in Fig. 2 as a function of the cell radius R.

All terms in the transmembrane excess potential PSD in (45) are also θ-dependent. The first term on the r.h.s. of (45) originates from the *linear* response kernel $Q^{(1)}$, while the second and third term stem from the leading (lowest order) even and odd nonlinear ($n.l.$) kernels, respectively.

In order to gauge the order of magnitude and relative weight of these terms, it is convenient to introduce the quantities

$$\Pi^{(linear)}(\omega) = \max_{\theta} |Q^{(1)}(\theta, \omega)|^2, \tag{46}$$

$$\Pi^{(n.l.)}_{odd}(\omega) = \max_{\theta} \left| \frac{3}{\pi} \mathrm{Re} \left[Q^{(1)*}(\theta, \omega) \int_{-\infty}^{\infty} d\eta Q^{(3)}(\theta; \omega, \eta, -\eta) \right] \right| \tag{47}$$

and

$$\Pi^{(n.l.)}_{even}(\omega) = \max_{\theta} \left| \frac{1}{\pi} \int_{-\infty}^{\infty} d\eta |Q^{(2)}(\theta, \eta, \omega - \eta)|^2 \right| \tag{48}$$

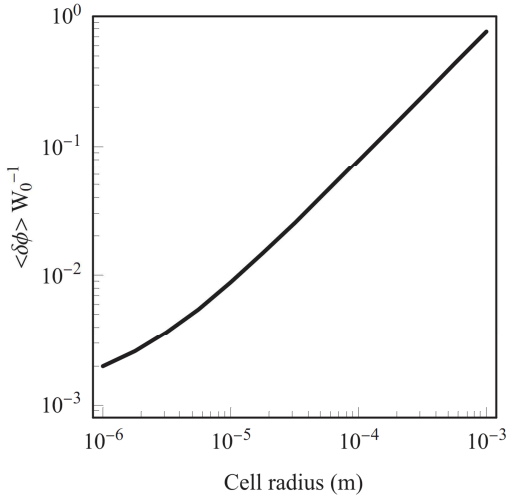

Figure 2. Scaled DC component of transmembrane excess potential at $\theta = 0, \pi$ as a function of cell radius.

which, apart from the factors W_0 and W_0^2, represent the extremal absolute values of the three θ-dependent terms in (45).

The function $\Pi^{(linear)}(\omega)$ is plotted in Fig. 3 as a function of frequency, in a double log-scale.

It is seen that for all cell radii, a well defined knee point exists across which the frequency dependence of $\Pi^{(linear)}(\omega)$ changes from essentially flat to $\propto f^{-2}$. The knee frequency as a function of the cell radius is plotted in Fig. 4, and is seen to scale roughly as R^{-1}.

The functions $\Pi_{odd}^{(n.l.)}(\omega)$ and $\Pi_{even}^{(n.l.)}(\omega)$ in Eqs. (47) and (48) are shown in Figs. 5 and 6, respectively. It is seen that $\Pi_{odd}^{(n.l.)}(\omega)$ is the leading nonlinear contribution to the transmembrane excess potential PSD, so that $\Pi_{even}^{(n.l.)}(\omega)$ can be neglected in (45).

It is interesting to compare the relative weights of the linear and nonlinear terms in (45). The linear term is dominant under ordinary conditions — and *must* be so in order for the Volterra series solution to be reliable. In the spirit of asymptotic approximation theory, the ratio $\Pi^{(linear)}/\Pi_{odd}^{(n.l.)}$ provides a loose estimate of the limiting value of W_0 which can be used in (45) for trustable results. Beyond this value, higher order terms can be no longer neglected. The reciprocal of this ratio is shown in Fig. 7.

In the low-end of the spectrum, below $\sim 10^4$ Hz, the ratio $\Pi_{odd}^{(n.l.)}/\Pi^{(linear)}$ is almost frequency-independent (see Fig. 7), being

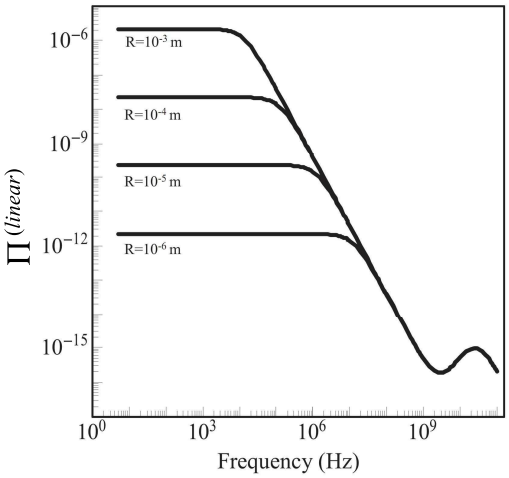

Figure 3. The $\Pi^{(linear)}$ function, Eq. (46), vs frequency, for some values of the cell radius R.

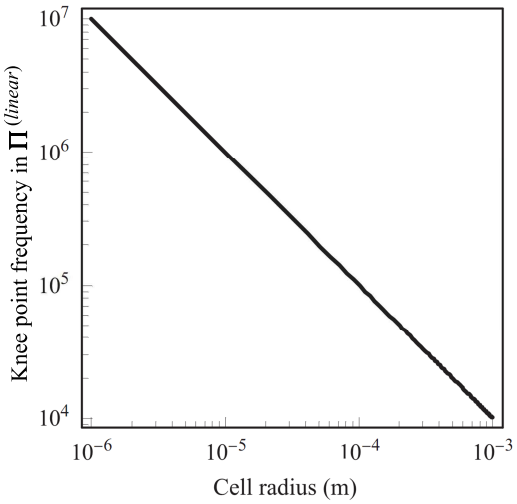

Figure 4. Knee frequency in Fig. 3 vs cell radius.

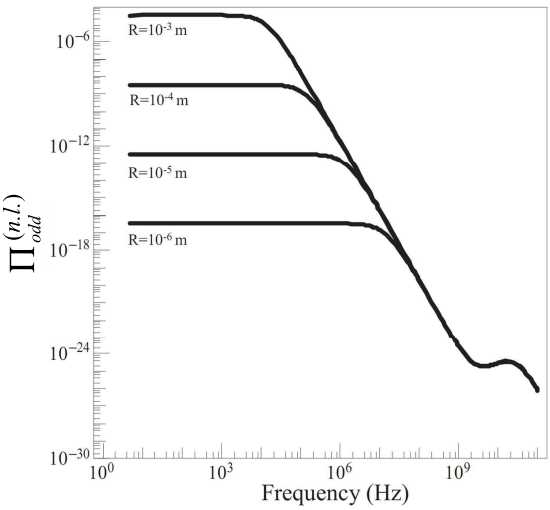

Figure 5. The $\Pi_{odd}^{(n.l.)}$ function, Eq. (47), vs frequency for some values of the cell radius R.

only a function of the cell radius R, and turns out to be well approximated by $\sim 10^{2\log(R)+7}$. At $f \sim 10^8$ Hz this ratio is $\approx 10^{-6}$ and becomes almost R-independent above this frequency, rolling off

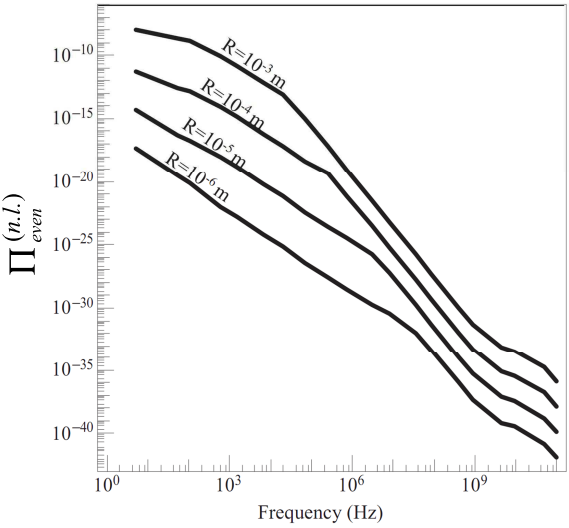

Figure 6. The function $\Pi_{even}^{(n.l.)}$, Eq. (48), vs frequency for some values of the cell radius R.

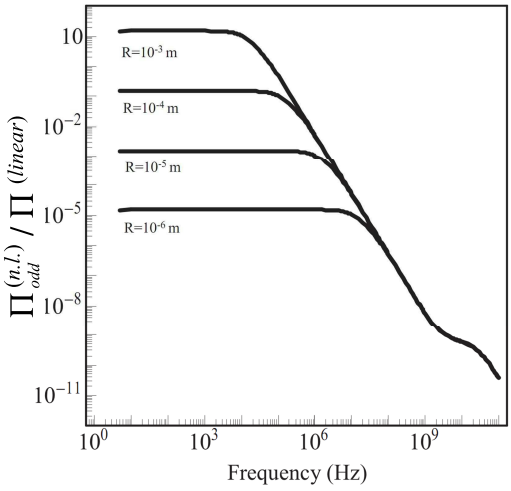

Figure 7. Ratio between the nonlinear and linear response coefficients $\Pi_{odd}^{(n.l.)}$ and $\Pi^{(linear)}$ in Eq. (45) vs frequency for some values of the cell radius R.

roughly as f^{-2}.

Figures 3 and 5 show that the induced transmembrane potential power spectral density is almost entirely confined, and essentially flat, in the low frequency part of the spectrum, up to some cell-radius dependent frequency in the 10^3–10^6 Hz range. Accordingly, the obtained results should remain valid for the more realistic case of a *band-limited* Gaussian EM field.

This low-pass behaviour is consistent with recent experimental findings indicating the absence of harmonic cell response to EM carriers in the mobile-telephone frequency bands [41, 42], and the presence of such responses to (very) low frequency fields [43, 44].

6. DISCUSSION

As stressed in Section 1, induced changes in the physiological level and frequency distribution of the membrane voltage noise are thought as being able of affecting cell homeostasis.

Endogenous cell membranes noise includes several terms of different origin [45]: i) thermal (Johnson) noise, ii) excess noise associated with fluctuations of the ionic currents through the membrane channels, iii) shot noise associated to the discrete nature of transmembrane charge carriers, iv) cross-talk noise due to the electrical activity of surrounding organs (e.g. heart and nervous system), etc. The first two mechanisms are credited as dominant under ordinary conditions, yielding, respectively, estimated r.m.s transmembrane excess potential fluctuations $\sim 2\,\mu$V and $\sim 10\,\mu$V [45].

We shall make the, admittedly crude, tentative assumption that a fiducial critical value of the r.m.s. transmembrane excess potential for the onset of sensible biological effects be ~ 10 times the size of typical endogenous fluctuations, i.e., $\sim 10^2\,\mu$V (see, e.g., [46, 47] for a discussion). The corresponding critical value $W_0^{(crit)}$ of the applied field power spectral density W_0 can be estimated from (45). For a cell radius of $R = 10^{-3}$ m, one gets $W_0^{(crit)} \sim 10^{-2}\,(\mathrm{V^2 m^{-2} sec^2})$, which corresponds, e.g., to a 10 V/m r.m.s. field in the effective (low-pass) cell-response band of 10^4 Hz.

Note that for the same W_0, the induced (nonlinear) transmembrane potential DC shift from Fig. 2 is negligible compared to the resting value V_0.

Understanding whether such crude estimates may have any relevance in connection with presumed biological effects of low-level (non-thermal) EM exposure would require substantial experimental work, well beyond the skills of the Authors and the scope of this paper,

which is merely aimed at providing a hopefully useful and sufficiently general modeling tool.

A well established conceptual and experimental framework exists for the measurement of membrane voltage noise [48–51], and several groups are presently engaged in the experimental study of membrane noise, and its changes under the action of external fields [52, 53]. We plan to establish a research cooperation with these groups, aimed at checking our results against experiments in a future paper.

On the other hand, the proposed approach is based on the highly trusted Hodgkin-Huxley nonlinear cell membrane model, and the widely used Volterra series framework for the analysis of nonlinear systems. This makes us confident that the present analysis may decently reflect our current modeling capabilities and understanding of the problem.

7. CONCLUSIONS AND FUTURE WORK

The transmembrane excess potential in a cylindrical cell with (nonlinear) Hodgkin-Huxley membrane induced by an applied electromagnetic field has been computed in analytic form, using nonlinear (Volterra) functional calculus. The leading odd and even nonlinear response terms have been explicitly derived for the simplest 2-dimensional case where the cell excitation is uniform along the cell axis (no action potential propagation). The spherical cell case can be studied along similar lines, and the relevant (qualitatively similar) results have been presented elsewhere [15].

The ideal relevant case of a white Gaussian incident field has been discussed in detail, being a possible simple model of a polluted electromagnetic environment.

The induced transmembrane potential power spectral density was found to be essentially confined to the low frequency part of the spectrum (where it looks almost flat), up to a frequency in the kHz to MHz range, depending on the cell radius.

Some order of magnitude estimates for the induced transmembrane-potential DC-shift and noise PSD have been discussed. The transmembrane voltage noise rms level of exogenous origin may exceed by one order of magnitude the endogenous one for an applied electric field $\sim 10\,\mathrm{V/m}$ spanning a $10^4\,\mathrm{Hz}$ bandwidth. The static shift in the transmembrane potential, on the other hand, turns out to be negligible under the same exposure conditions.

The proposed approach can be extended, in principle, to more complicated geometries (e.g., cells with internal organelles) and systems (e.g., cell aggregates, or tissues).

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APPENDIX A.

In the appendix we report the explicit formula for the kernels $\Gamma^{(1)}(\omega_1)$, $\Gamma^{(2)}(\omega_1,\omega_2)$, $\Gamma^{(3)}(\omega_1,\omega_2,\omega_3)$ in (2).

$$\begin{aligned}
\Gamma^{(1)}(\omega_1) &= j\omega_1\tilde{C}+g_l+g_K\left[n_{(0)}^4-4n_{(0)}^3V_K\xi_n^{(1)}(\omega_1)\right]+g_{Na}\\
&\quad\cdot\left[m_{(0)}^3h_{(0)}-m_{(0)}^3V_{Na}\xi_h^{(1)}(\omega_1)-3V_{Na}m_{(0)}^2h_{(0)}\xi_m^{(1)}(\omega_1)\right];\\
\Gamma^{(2)}(\omega_1,\omega_2) &= g_K\Big\{4n_{(0)}^3[\xi_n^{(1)}(\omega_1)+\xi_n^{(1)}(\omega_2)]-12n_{(0)}^2\\
&\quad\cdot V_K\xi_n^{(1)}(\omega_1)\xi_n^{(1)}(\omega_2)-8n_{(0)}^3V_K\xi_n^{(2)}(\omega_1,\omega_2)\Big\}+g_{Na}\\
&\quad\cdot\Big\{m_{(0)}^3[\xi_h^{(1)}(\omega_1)+\xi_h^{(1)}(\omega_2)]+3m_{(0)}^2h_{(0)}[\xi_m^{(1)}(\omega_1)+\xi_m^{(1)}(\omega_2)]\\
&\quad-2m_{(0)}^3V_{Na}\xi_h^{(2)}(\omega_1,\omega_2)-6m_{(0)}^2h_{(0)}V_{Na}\xi_m^{(2)}(\omega_1,\omega_2)\\
&\quad-6m_{(0)}h_{(0)}V_{Na}\xi_m^{(1)}(\omega_1)\xi_m^{(1)}(\omega_2)-3m_{(0)}^2V_{Na}\left[\xi_m^{(1)}(\omega_1)\right.\\
&\quad\left.\cdot\xi_h^{(1)}(\omega_2)+\xi_h^{(1)}(\omega_1)\xi_m^{(1)}(\omega_2)\right]\Big\};\\
\Gamma^{(3)}(\omega_1,\omega_2,\omega_3) &= g_K\Big\{12n_{(0)}^2\left[\xi_n^{(1)}(\omega_1)\xi_n^{(1)}(\omega_2)+\xi_n^{(1)}(\omega_2)\cdot\xi_n^{(1)}(\omega_3)\right.\\
&\quad\left.+\xi_n^{(1)}(\omega_3)\xi_n^{(1)}(\omega_1)\right]+8n_{(0)}^3\left[\xi_n^{(2)}(\omega_1,\omega_2)+\xi_n^{(2)}(\omega_2,\omega_3)\right.\\
&\quad\left.+\xi_n^{(2)}(\omega_3,\omega_1)\right]-8n_{(0)}^2V_K\left[\xi_n^{(1)}(\omega_1)\xi_n^{(2)}(\omega_2,\omega_3)+\xi_n^{(1)}(\omega_2)\right.\\
&\quad\left.\cdot\xi_n^{(2)}(\omega_3,\omega_1)+\xi_n^{(1)}(\omega_3)\xi_n^{(2)}(\omega_1,\omega_2)\right]-24n_{(0)}V_K\left[\xi_n^{(1)}(\omega_1)\right.\\
&\quad\left.\cdot\xi_n^{(1)}(\omega_2)\xi_n^{(1)}(\omega_3)+n_{(0)}^2\xi_n^{(3)}(\omega_1,\omega_2,\omega_3)\right]\Big\}+g_{Na}\Big\{3m_{(0)}^2\\
&\quad\cdot\left[\xi_m^{(1)}(\omega_1)\xi_h^{(1)}(\omega_2)+\xi_h^{(1)}(\omega_1)\xi_m^{(1)}(\omega_2)+\xi_m^{(1)}(\omega_2)\xi_h^{(1)}(\omega_3)\right.\\
&\quad\left.+\xi_h^{(1)}(\omega_2)\xi_m^{(1)}(\omega_3)+\xi_m^{(1)}(\omega_3)\xi_h^{(1)}(\omega_1)+\xi_h^{(1)}(\omega_3)\xi_m^{(1)}(\omega_1)\right]\\
&\quad+6m_{(0)}h_{(0)}\left[\xi_m^{(1)}(\omega_1)\xi_m^{(1)}(\omega_2)+\xi_m^{(1)}(\omega_2)\xi_m^{(1)}(\omega_3)+\xi_m^{(1)}(\omega_3)\right.
\end{aligned}$$

$$\cdot\xi_m^{(1)}(\omega_1)\Big]+6m_{(0)}^2h_{(0)}\left[\xi_m^{(2)}(\omega_1,\omega_2)+\xi_m^{(2)}(\omega_2,\omega_3)+\xi_m^{(2)}(\omega_3,\omega_1)\right]$$
$$+2m_{(0)}^3\left[\xi_h^{(2)}(\omega_1,\omega_2)+\xi_h^{(2)}(\omega_2,\omega_3)+\xi_h^{(2)}(\omega_3,\omega_1)\right]-12m_{(0)}h_{(0)}$$
$$\cdot V_{Na}\left[\xi_m^{(1)}(\omega_1)\xi_m^{(2)}(\omega_2,\omega_3)+\xi_m^{(1)}(\omega_2)\xi_m^{(2)}(\omega_3,\omega_1)+\xi_m^{(1)}(\omega_3)\right.$$
$$\left.\cdot\xi_m^{(2)}(\omega_1,\omega_2)\right]-6m_{(0)}^2V_{Na}\left[\xi_m^{(1)}(\omega_1)\xi_h^{(2)}(\omega_2,\omega_3)+\xi_h^{(1)}(\omega_1)\right.$$
$$\cdot\xi_m^{(2)}(\omega_2,\omega_3)+\xi_m^{(1)}(\omega_2)\xi_h^{(2)}(\omega_3,\omega_1)+\xi_h^{(1)}(\omega_2)\xi_m^{(2)}(\omega_1,\omega_3)$$
$$\left.+\xi_m^{(1)}(\omega_3)\xi_h^{(2)}(\omega_2,\omega_1)+\xi_h^{(1)}(\omega_3)\xi_m^{(2)}(\omega_1,\omega_2)\right]-6h_{(0)}V_{Na}$$
$$\cdot\xi_m^{(1)}(\omega_1)\xi_m^{(1)}(\omega_2)\xi_m^{(1)}(\omega_3)-6m_{(0)}V_{Na}\left[\xi_h^{(1)}(\omega_1)\xi_m^{(1)}(\omega_2)\xi_m^{(1)}(\omega_3)\right.$$
$$\left.+\xi_h^{(1)}(\omega_2)\xi_m^{(1)}(\omega_3)\xi_m^{(1)}(\omega_1)+\xi_h^{(1)}(\omega_3)\xi_m^{(1)}(\omega_2)\xi_m^{(1)}(\omega_1)\right]-6m_{(0)}^3$$
$$\left.\cdot V_{Na}\xi_h^{(3)}(\omega_1,\omega_2,\omega_3)-18m_{(0)}^2h_{(0)}V_{Na}\xi_m^{(3)}(\omega_1,\omega_2,\omega_3)\right\}.$$

Note in passing that letting $\xi_n^{(k)}=0$ (respectively, $\xi_m^{(k)}=\xi_h^{(k)}=0$), $k=1,2,3$, in the above formulas one may single out the contributions of the potassium (respectively, sodium) channels to the nonlinear response.

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