Integrated Models for the Analysis of Biological Effects of EM Fields Used for Mobile Communications

Francesca Apollonio, Micaela Liberti, Guglielmo d'Inzeo, and Luciano Tarricone

***Abstract*—The understanding of the modalities of interaction of electromagnetic (EM) fields with biological material is a key point in the identification of possible induced effects. Since the beginnings of bioelectromagnetic research studies, most of the attention has been focused on the effects on nervous systems and neuronal cells. The importance of this target has recently increased due to the wide diffusion of mobile terminals, used close to the head. In this paper, an integrated interaction model is proposed. The model, validated in each part of its components with experimental data, allows to obtain a quantitative link from the external applied field to the effects on neurons (isolated or linked to similar others). The models is firstly based on the evaluation of the EM field at cellular membrane level, then on the evaluation of the effects induced on each component of the model growing from the low biophysical level (membrane channels) to the biological one (neuron time behavior). The use of well-assessed models for the simulations of each part allows both the evaluation of the effect at different levels of complexity, and the employment of this effect acting as an input on the upper level. This approach allows, for the first time, a complete quantitative evaluation of the effects on neurons due to the fields from the existing mobile systems, and can be a useful instrument for the evaluation of the possible health impact of new technologies.**

***Index Terms*—Bioelectromagnetics, interaction modeling, ionic channel, mobile systems, neuron.**

I. Introduction

THE growing application of RF electromagnetic (EM) fields, connected to the large diffusion of mobile communications, and the linked questions arisen about consequences on population health, have recently given further improvement to research studies on the interaction of EM fields with biological systems.

Even though a lot of work has been done, there is still no complete assessed knowledge about this item. However, there is a general agreement [1], [2] about the importance of a correct evaluation of the mechanisms of interaction between EM fields and biological systems.

Possible effects on neuron activity have always represented a focal issue in this research field [3]–[6]. Mobile communications have given further improvement to neuronal studies considering that, for the first time in RF technology application, the RF source is so close to the exposed biological system, specifically the human brain.

To address the problem, on the basis of their previous experience [1], [7]–[15], the authors suggest that bioelectromagnetic (BEM) interaction studies should be approached following a procedure consisting of the following three main steps.

Step 1) Evaluation of the EM field distribution inside the biological target.

Step 2) Modeling of the interaction mechanism between fields and biological systems.

Step 3) Understanding of the physiological effects induced into the system by means of the above mentioned mechanisms.

A. Evaluation of the EM-Field Distribution

This step is fundamental. In fact, in order to interpret a biological effect, it is necessary to determine the internal field strength or the energy dose that can cause such an effect in the experimental subject. RF dosimetry is the quantification of the magnitude and distribution of absorbed EM energy within the exposed biological system [16]. Beside electric- and magnetic-field strength, a fundamental quantity at RF is the specific absorption rate (SAR) defined as the rate at which energy is absorbed per unit of mass. The problem can be approached by means of experimental and numerical techniques. For an overview of experimental dosimetry, see [16]. For numerical approaches, such as the finite-difference time-domain, finite-element method, or method of moments, it is possible to refer to [9], [17]–[21], just to mention some recent papers. In dosimetric studies, growing attention is given to the comparison among experimental and numerical results [22]. The importance of evaluating the field induced by an external EM source inside a biological system at a microscopic level has been perceived only recently [21], [23], [24]. In order to achieve this knowledge, it is crucial to relate the average field absorbed by the whole system, obtained by means of traditional dosimetry, to the local field induced inside cells and their compartments.

B. Modeling of the Interaction Mechanism

Several numerical models have been set up in order to understand how some parts of a complex biological system could interact with EM fields. The cell membrane has been identified as the primary target of the action of the EM fields on biological structures [25]. Starting from this consideration, structural

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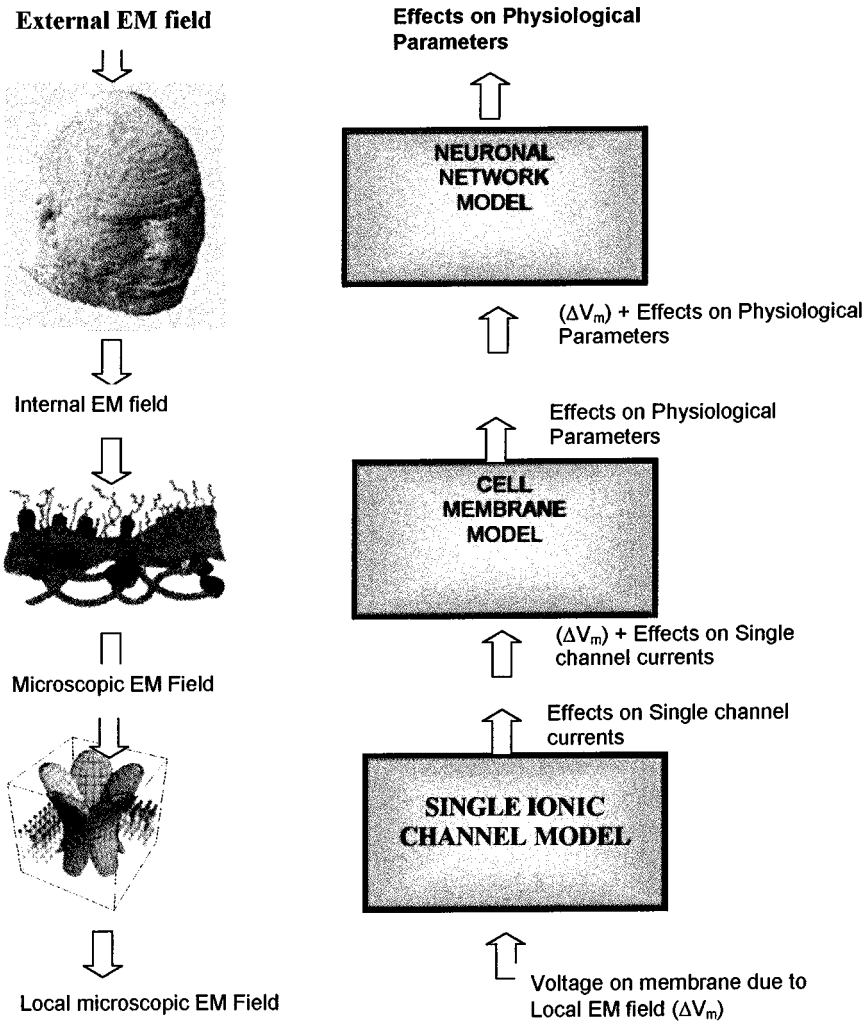


Fig. 1. Proposed procedure to gather inside BEM interactions. (a) Procedure to achieve the local microscopic field from a specific EM source. (b) Integrated way to evaluate biological effects at any level of complexity of the biological scale.

models for the cell membrane have been developed [26]–[28]. Single-membrane channel modeling has been outlined [29] to explain some experimental results [30]. Even more microscopic approaches have been proposed, such as molecular dynamics [31] and ligand ion-binding site process using quantum [32], [33] and Lorentz–Langevin [34] models.

C. Physiological Effects

At the moment, the third step is not so easily linked with the two previous ones. It can be performed with experimental tests [35] more often with theoretical analyses, but in both cases, without strong liaisons with the modeling used in the second step of the proposed procedure.

The whole modeling process and strategy proposed here can be schematically resumed in the flow-chart of Fig. 1. In Fig. 1(a), a starting point can be identified in the dosimetric evaluation of the EM-field distribution inside a subject exposed to an external EM source and, particularly, by means of numerical methods, in a region of tissue [8], [9], [17]–[20]. Successively, a dosimetric evaluation of the field distribution can be carried out at a more microscopic level, specifically around the cell membranes. From these first steps, the local microscopic field acting on a single protein channel can be evaluated. It is necessary to follow this descending procedure in order to achieve the local EM-field value in any point at any microscopic level.

After solving the dosimetric problem, it is necessary to consider the procedure in Fig. 1(b), describing the link among different functional models simulating, at specific levels of complexity, the behavior of the corresponding biological system.

The EM field could be considered acting as an additive component at each identified biological level. The output of each level is the input of the following one in the biological scale of complexity. The output of each step in the process is represented by the effects due to EM stimulation. As a first step, a local microscopic field is considered as input to the model of the single protein channels. Output parameters at this level are the modifications of the single-channel currents, which can alter the action potential behavior in a neuronal cell model. Different channel models can be inserted inside a cell membrane model and the action potential is the observed parameter. The output

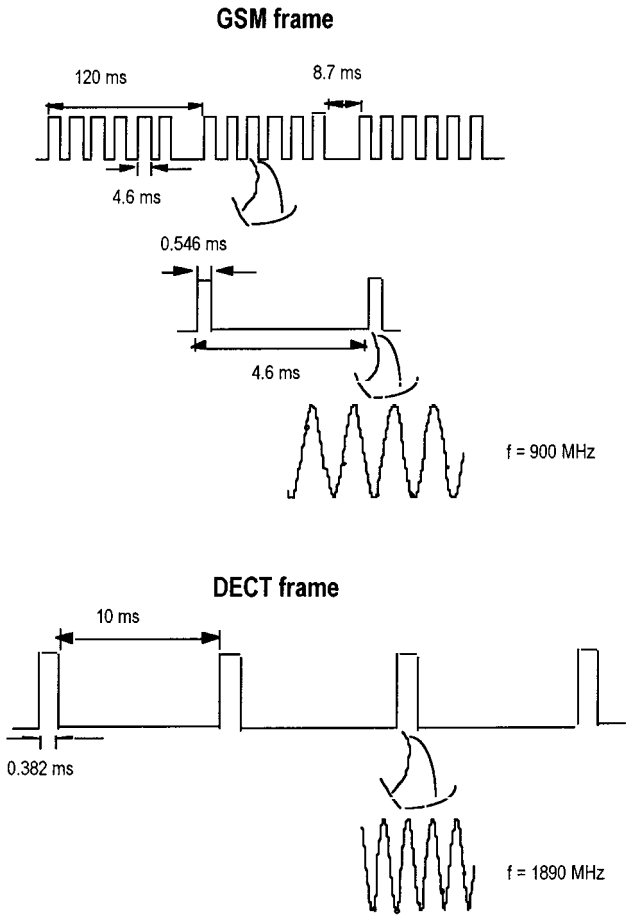


Fig. 2. Waveform parameters of GSM and DECT signals: low- and high-frequency contributions.

at cell level is the input to the neuronal network model, which evaluates the consequences of the EM stimulation at this level. The output at network level is represented by the action potential propagation.

Here, the results obtained implementing the chain in Fig. 1(b) are presented. This paper is organized as follows. In Section II, the EM sources specifically addressed are briefly introduced: those used in wireless communication, such as the standard GSM, and DECT. In Section III, a dielectric model suitable for a preliminary dosimetric evaluation of the EM field at the membrane level is briefly recalled. In Section IV, the microscopic model at channel level is described. In Section V, the derivation of a membrane model from single channel's models is reported. In Section VI, how a neuronal network can be modeled is described. Section VII presents results at the different levels (channel, cell, and network). Finally, conclusions are drawn in Section VIII.

II. EM Sources

In order to simulate the effects of GSM and DECT signals, their waveforms have been analyzed; Fig. 2 sketches the waveform parameters. "Pulsed" signals, as the GSM and DECT can be considered, usually consist of a single-frequency carrier (880–915 MHz for the GSM and 1880–1900 MHz for the DECT), shaped by a rectangular pulse train. This introduces low-frequency components in a signal spectrum, generally in the range of extremely low frequencies (ELFs). As can be seen from Fig. 2, the temporal evolution of a GSM signal is given by a repetition of a set of pulses every 120 ms and the single pulse is, in its turn, composed of a repetition of one burst every 4.6 ms. During each burst, the high-frequency component is transmitted. This type of periodicity gives rise to the low-frequency components of 8.3 Hz (from the period of 120 ms) and 217 Hz (from the period of 4.6 ms). The frame of the DECT signal is simpler: it is composed of a repetition of one pulse every 10 ms, each pulse carrying the high frequency contribution; in terms of low-frequency components, 100 Hz have to be considered. In the following paper, it seemed interesting to evaluate the biological response to the ELF components of GSM and DECT signals, even if the energy of such pulsed signals is around the carrier frequencies and, hence, around the high-frequency spectral components.

III. From the External EM Field to the Local Microscopic One

Once the EM source has been identified, the EM-field distribution inside the exposed biological system can be determined via macroscopic dosimetry [16]–[22], [8], [9]. In order to link this macroscopic evaluation with an equivalent information at a level of single cell and cellular compartments, a dielectric model of a cell has been developed.

The goal of such a model is the evaluation of the EM-field distribution at a microscopic level, and specifically around the membrane of a cell. The model considered in this paper is based on an approach proposed first in [27] and then a second time in [24]. Just recalling this second one, it is composed of four spherical concentric layers, with an external extracellular solution, as depicted in Fig. 3(a). The model characteristics are described in Table I.

The use of such a model, in conjunction with Mie's theory [36], allows the derivation of an analytical solution to the dosimetric problem. An example of the solution is given in Fig. 3(b), where the spatial variation of the EM-field level is evaluated for a plane wave incident upon the spherical model. Further studies and preliminary results about it can be found in [23] and [37]. Observing Fig. 3(b), it is possible to notice on the equatorial plane a strongly nonuniform distribution depending on the value of the angular position. It is possible to use this kind of spatial information to further improve dosimetric evaluation, attempting to obtain an effective EM field in the point of interest, down to the scale of single membrane macromolecules, e.g., like a protein channel.

IV. Microscopic Level

A. Protein Channel Modeling

Several approaches have been proposed up to now to simulate the response of an ionic membrane channel to EM stimulation. The first one was based on a "mechanical" vision where the gating of a channel is considered as the result of a mechanical flipping of parts of macromolecular structures, which are completely described by Newtonian equations [38]. Once the

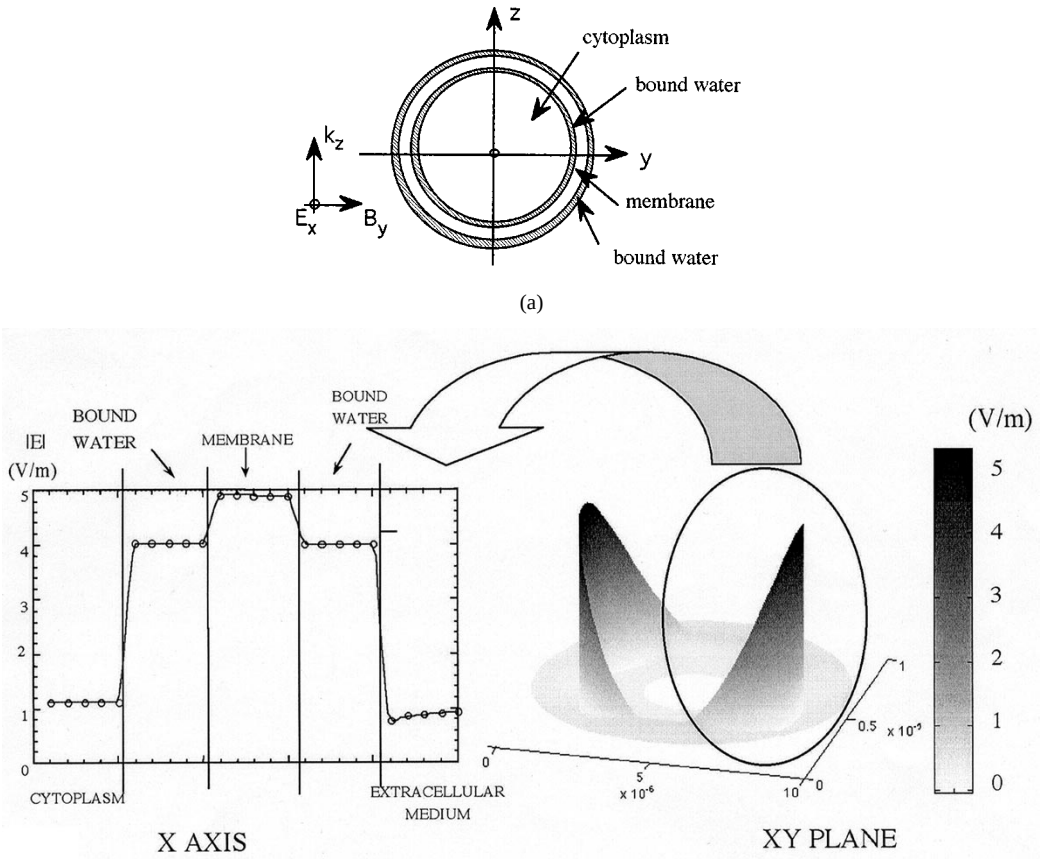


Fig. 3. (a) Five-layer cell model. (b) Results of E-field distribution onto the X–Y-plane, and particularly along the X-axis.

TABLE I
DIMENSIONS AND ELECTRICAL PARAMETERS OF THE CELL MODEL

	cytoplasm	inner bound water	membrane	outer bound water	extracell. medium
radius (m)	$3.499 \cdot 10^{-6}$	$3.5 \cdot 10^{-6}$	$3.51 \cdot 10^{-6}$	$3.511 \cdot 10^{-6}$	-
ε_ρ	48.677	6.851	11.3	6.851	70.87
σ (S/m)	1.3237	1.6266	0.0	1.6266	2.781

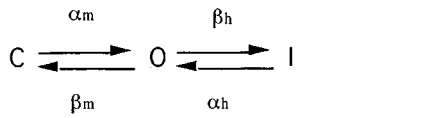
mass, initial energy (conformation), and resting potential are fixed, the dynamics of the gating site is completely determined in a given applied field. The typical windowing effect in frequency could, therefore, be explained by the existence of resonating frequencies depending on structural characteristics of the examined structure (just what happens for harmonic oscillations).

A different view was proposed by Cain [26], who focused on voltage-dependent channels, and considered the cell membrane as the nonlinear "transducer" of EM external signals. This approach has been proposed to explain the effects on neuronal cells of microwave (MW) fields [5], [28], [39], [40].

Unfortunately, these models suffer from some limitations. The former has a relatively small capability to take into account different field amplitudes, while the latter is not able to predict the well-known existence of a frequency sensitivity of the channel's response to EM stimulation [30]. Finally, both strategies do not allow the explanation of the conformational EM effects on the protein structure, and neither does the evaluation of the amount of energy transferred from the external field into the exposed site [29].

An alternative approach, suitable for these purposes, has been proposed basing on Markov models (MMs) [29]. These models start from the evaluation of the current flowing through the single channel. The typical pattern of a single-channel signal demonstrates that the channel can be considered as a "Boolean" device. Current flows through it or not. Two main conformations or states (closed or open) can be identified [41], even though inside each of these two groups many sub-states can exist, which correspond to different structural and conductance properties, related to different energetical situations for the channel.

This approach has been used by the authors in simulating the action of EM fields on each single channel [29], [42]. In such way, it is possible to achieve a real-time evaluation of single-channel behavior in EM fields' exposure conditions.



$$\alpha_m = \frac{10.0}{1.0 + 6671.6\, exp\ [-1.6\ log\,(V + 50)]}\, T_f$$

$$\beta_m = 0.06\,(V + 50)\, exp\ [-0.03\,(V + 50)]\ T_f$$

$$\alpha_h = [-0.075 exp\ [0.21\ log\,(V + 50)] + 0.21]\, T_f$$

$$\beta_h = \frac{0.8}{1.0 + 374163.73 exp\ [-2.8362\ log\,(V + 50)]}\, T_f$$

$$T_f = 3^{(T-6)/10}$$

Fig. 4. Calcium channel modeling: three-stage configuration and set of equations representing the kinetics of transitions between states. Voltage and temperature dependence is taken into account.

In the MM modeling, the single channel is a finite-state automaton. The channel is assumed to have a certain number N of admittable states (conformations). Each state corresponds to a discrete value of normalized conductance. Pairs of states are connected by a transition, and transition rates q_{ij} define the frequency of each transition in a unit of time. The channel's evolution is completely defined once the probability $p_i(t)$ is given for every state i in the model at $t = 0$. This probability, called *occupancy*, defines the probability that the system occupies state i at a given time t. In Fig. 4, an example of a three-state model is given. Two different closed conformations are considered. One is referred as the closed state, the other as the inactivated one.

Considering the channel as an ohmic device [43], the current flowing through the channel is proportional to the total open probability, as in the following relationship:

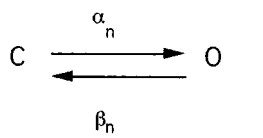
$$i(t_k) = V_m \sum_{i=1}^{N_o} g_j p_j(t_k) \tag{1}$$

where N_o is the number of open states, g_j is the conductance of the j-state, and V_m is the transmembrane voltage and $p_j(t_k)$ is the probability of state j at t_k fixed time. The time behavior of the occupancies is easily evaluated by using MMs. In fact, supposing the channel as a zeroth-order Markov chain, stationary and ergodic, and the occupancy a random variable, a random process can be generated, whose aleatory variable is the dwell time in each state. From such process, the occupancy of each state, at each time, can be derived as described in [29].

B. EM Field at Channel Level

As an example of modeling of the BEM interaction at channel level with the MM approach, calcium, sodium, and potassium channels have been examined. The Potassium channel can be modeled by using the two-state model in Fig. 5, and by using the equations of Hodgkin and Huxley [44] to define the transition rates as a function of temperature T (Kelvin degrees) and transmembrane voltage V_m.

Calcium and sodium channels are based on a three-state scheme (Figs. 4 and 6, respectively) and, in this case, Hodgkin and Huxley like equations were chosen to model the channel kinetics.

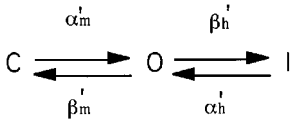


$$\alpha_n = \frac{0.01\,(V + 10)}{exp\left[\frac{(V + 10)}{10}\right] - 1}\, T_f$$

$$\beta_n = 0.125 exp\left[\frac{V}{80}\right] T_f$$

$$T_f = 3^{(T-6)/10}$$

Fig. 5. Potassium channel modeling: two-stage configuration and set of equations representing the kinetics of transitions between states. Voltage and temperature dependence is taken into account.



$$\alpha'_m = \frac{0.1\,(V + 25)}{exp\left[\frac{(V + 25)}{10}\right] - 1}\, T_f$$

$$\beta'_m = 4 exp\left[\frac{V}{18}\right] T_f$$

$$\alpha'_h = 0.07 exp\left[\frac{V}{20}\right] T_f$$

$$\beta'_h = \frac{1}{exp\left[\frac{(V + 30)}{10}\right] + 1}\, T_f$$

$$T_f = 3^{(T-6)/10}$$

Fig. 6. Sodium channel modeling: three-stage configuration and set of equations representing the kinetics of transitions between states. Voltage and temperature dependence is taken into account.

The external EM field can be considered as an additive perturbation of the transmembrane voltage. EM fields in the MW range can be considered. This is apparent once the model implementation has been quickly summarized.

As discussed in [29], the simulation is based at a certain time-step on the evaluation of: 1) current state of the channel; 2) dwell time (T_d) in the current state (the time the channel dwells in a certain state); and 3) next state, to be occupied after T_d time steps.

Extracting random numbers, 2) and 3) can be accomplished using simple formulas. This approach still holds when high frequencies stimulate the channel, assuming that an appropriate time step is used. Therefore, no theoretical limitations are cast on the use of the model for EM fields in a wide frequency range. The considered examples are referred to voltage-dependent channel. Similar considerations hold in the case of ligand-dependent channels. In such cases, as demonstrated in [45], the transition rate modifications due to EM effects can be estimated with suitable optimization strategies.

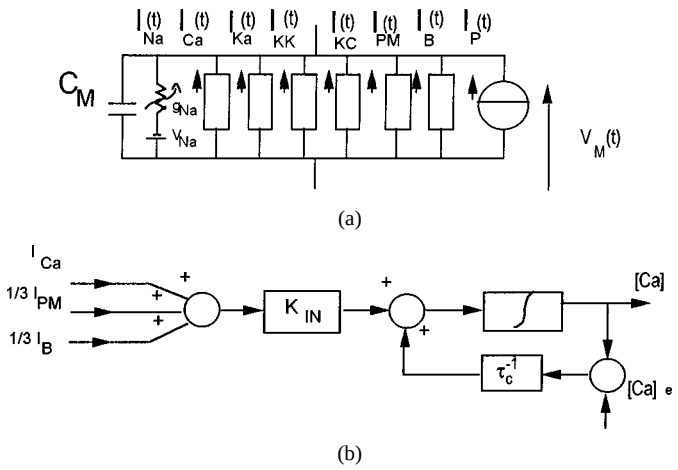


Fig. 7. Neuronal membrane electrical model representing the ionic currents crossing the membrane. (a) Circuit model. (b) Intracellular calcium concentration dynamics.

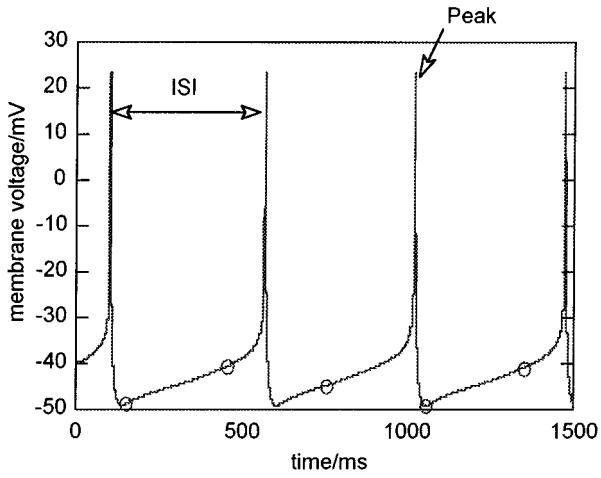


Fig. 8. Time behavior of the neuronal membrane voltage at $T = 20$ ∘C.

V. Macroscopic Level Membrane Modeling

The most innovative idea of this paper is linking together the modeling, as described in Section IV, with the membrane model described in this section. This means gathering together a large amount of single-channel MMs inside a global framework, which simulates the behavior of a cell membrane. This is exactly what happens in nature, where the cell membrane is basically composed of a lipid bilayer, with a huge number of ionic protein channels inside.

In the recent past [29], authors proposed a complete electrophysiological model (Fig. 7) of a neuronal cell membrane composed of a circuital scheme representing the ionic currents crossing the membrane, and of a block scheme sketching how the model takes into account the feedback action of intracellular calcium concentration [Ca]. Each component in the circuital representation corresponds to a certain kind of current (or membrane channel family). The basic equation for the circuit is Kirchhoff law

$$I_C + I_{\mathrm{Na}} + I_{\mathrm{Ca}} + I_{KA} + I_{KK} + I_{KC} + I_{PM} + I_B + I_S = 0 \tag{2}$$

where all these terms can be analytically described as a function of V_m [28], while the feedback action of [Ca] is described by the following equation (τ_a and K are analytically known constants):

$$\frac{d[\mathrm{Ca}]}{dt} = \frac{1}{\tau_a}\left([\mathrm{Ca}]_o - [\mathrm{Ca}]\right) + K\left(I_{\mathrm{Ca}} + \frac{1}{3}I_{PM} + \frac{1}{5}I_B\right). \tag{3}$$

Using this kind of modeling, it is possible to simulate the time behavior of membrane voltage, obtaining the shape of an action potential and its repetition in time, as shown in Fig. 8. The presence of synapses activity is taken into account in the model with suitable ionic channels, whose conductances follow a Poisson-type distribution. Results obtained have shown a good agreement with experimental data [6]. The reader may refer to [28] for details.

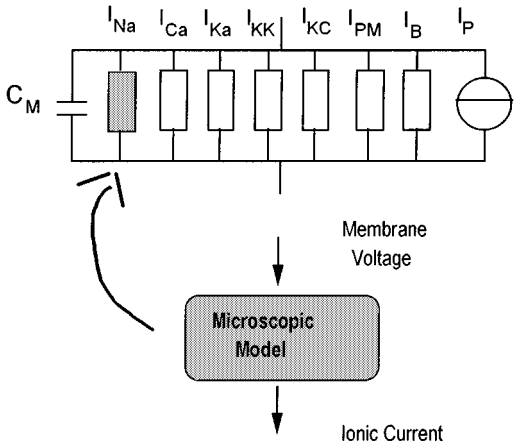


Fig. 9. Schematic representation of the procedure followed in the linking process between the patch membrance and single-channel model (example: sodium channel).

Here, it is put forward that the behavior of ionic channels in the membrane model is modeled with a statistical approach: each branch in the circuit corresponds to the contribution of a large number of channels of the same kind.

By substituting the building blocks of the macroscopic model (i.e., the branches representing populations of channels) with a large set of single channels of the same population each simulated with the MM approach [15]. This idea is sketched in Fig. 9. The proposed strategy, encapsulating micromodels in a more macroscopic framework, is referred to as MacroMM.

The MacroMM, thanks to the dependence of its building blocks on the transmembrane voltage V_m, is amenable to simulate the response of a whole neuronal cell membrane to an external EM stimulation.

The advantage of this approach is to couple the amenability of the macroscopic model to simulate a complex system, such as a whole membrane patch, with the suitability of microscopic MM for the investigation of physiological effects and interaction mechanisms at microscopic level.

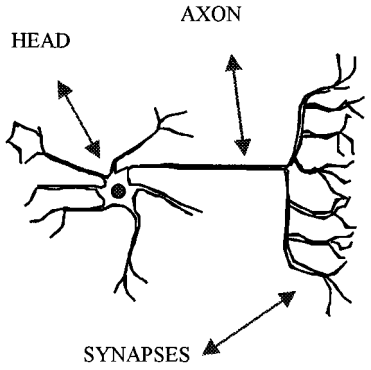


Fig. 10. Schematic representation of a neuronal cell.

VI. Network Level Neuronal Interconnection Modeling

A typical neuronal cell is sketched in Fig. 10. Three main regions can be identified: a head, an axon, and a synaptic region.

Modeling of the interconnection of two (or more) isolated neurons must cope with two main problems: 1) time needed to propagate the action potential through the neuronal axon and 2) simulation of the activation of a synapsis, and possible effects of external EM fields on it.

The problem of the signal propagation inside the axon can be approached thanks to the core-conductor model [46], and recalling that the action potential has the shape shown in Fig. 8. As shown, the signal has a time period [i.e., interspike interval (ISI)], which is of the order of milliseconds. The axon length can vary in a range between 0.5–5 mm. The overall effect of the neuronal axon can be taken into account by considering a pre-axon transmembrane voltage $V_{\rm pre}$, a post-axon voltage $V_{\rm post}$, and the following relationship:

$$V_{\rm post} = V_{\rm pre}\exp(-x/\lambda) \tag{4}$$

where x is the axon length, and λ is evaluated referring to the resistive and dielectric characteristics of the axon. More specifically, referring to Fig. 11, it is possible to approximate the axon with a cylinder, and if r_i is the core resistance per unit length, r_e the resistance of extracellular fluid per unit length, and r_m the resistance across a unit length of passive membrane [46], it is possible to have

$$I_{\rm syn\_post} = g_{\rm syn\_post}(V_{\rm pre}\exp(-x_1/\lambda) - V_{\rm syn\_post}) \tag{5}$$

where λ is

$$\lambda = \sqrt{\frac{r_m}{r_i + r_e}} \tag{6}$$

and $V_{\rm syn\_post}$ is the Nernst value for transmembrane voltage with respect to synaptic current. Equation (6) can be considered a boundary condition, to be added to the whole equation set of the MacroMM, so that isolated neuronal cells can be connected one another.

The MacroMM model can be considered as a black box, reproducing the physiological behavior of an isolated neuronal cell, and taking into account the contribution of activated synapses through the term I_S in the (2).

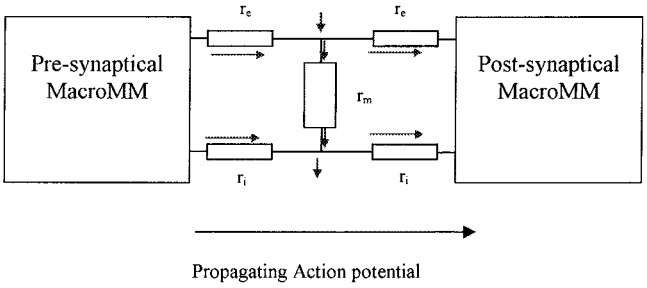


Fig. 11. Interconnection between presynaptic and postsynaptic neurons.

TABLE II
Cell Parameters for Applied Signal Voltage Calculations

Radius	C_m	σ_i	σ_a
40 μm	0.1 F/m^2	1 S/m	2 S/m

VII. Results

A. Induced Voltage and Effects

The amplitude of the external signal able to induce a transmembrane voltage of $V_m(t)$ is evaluated starting from dosimetric considerations on the maximum values allowed for the SAR in safety standards [47], [48]. The SAR is related to the internal electric field by means of the following relation:

$$\mathrm{SAR} = \frac{\sigma E^2}{\rho} \tag{7}$$

where σ is the conductivity and ρ is the mass density of the tissue: it is possible to derive a specific value for the internal electric field from the knowledge of SAR values. As stated previously, the presence of the electric field in the model is considered as a perturbation of the membrane voltage, hence, the internal electric field value must be related to the transmembrane voltage.

The cell can be considered as a sphere of radius R covered by a membrane of negligible thickness and capacitance C_m (F/m^2). The membrane potential V_m induced by the external field strength E is given by

$$V_m(\theta) \cong \frac{1.5ER\cos(\theta)}{1 + j\omega\tau} \tag{8}$$

where τ is the time constant for the beta dispersion and θ is the angle between the radius to a point on the membrane and the direction of the external field. At frequencies above the β relaxation frequency $1/2\pi\tau$, the membrane potential is approximately $V_m(\theta)$ [49]

$$V_m(\theta) \cong \frac{1.5E\cos\theta)}{\omega C_m\left[\dfrac{1}{\sigma_i} + \dfrac{1}{2\sigma_a}\right]} \tag{9}$$

where σ_i and σ_a are, respectively, the conductivity of the cytoplasm and the conductivity of the extracellular fluid (siemens per meter). In Table II, data used in our calculations are reported. Values of membrane voltage resulting from the previous relation are in the range of some millivolts depending on the actual SAR value. In particular, for SAR values of 2 W/kg averaged over

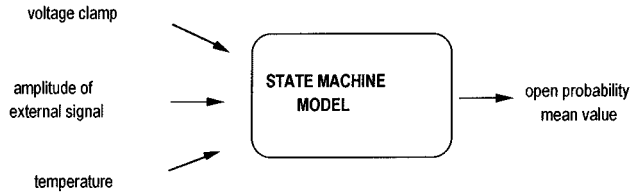


Fig. 12. Simple scheme describing the variables present in the simulations.

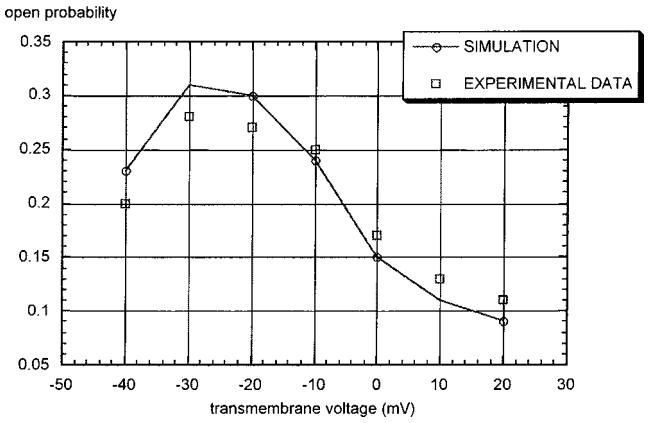


Fig. 13. Comparison between simulation results and experimental data for the calcium channel.

any 10 g of tissue (as stated in [47] and [48]), the resulting induced membrane voltage, at frequencies of interest of GSM and DECT standards, can be calculated to be of the order of millivolts.

The term "effect," used in the following discussion, is the relative variation of the output parameter, in the case of EM exposure, when compared with the physiological condition; e.g., in the case of the open probability of the channel as effect, in an analytical form, is intended as

$$\text{effect} = \frac{(p_o)_{\text{exp}} - (p_o)}{(p_o)}. \tag{10}$$

EM effects are included by evaluating their effect on transmembrane voltage $V_m(t)$.

Now, first the MM approach is going to be validated (Section VII-B.1) and effects of GSM and DECT high-frequency component on single channels will be studied later (Section VII-B.2). Finally, in Section VII-B.3, the effects of low-frequency components of these signals will be evaluated.

B. Protein Channel Models

Referring to Fig. 1, results of this section are relative to the most microscopic level described (i.e., protein channels). The protocol followed in these simulations can be introduced by the schematic representation of Fig. 12, in which both the inputs and outputs to the model are considered. The MM model for membrane channels can be considered as an electronic device in which the voltage clamp input represents a sort of a bias. The applied signal is represented as an additive voltage acting on the membrane, and the temperature represents an important variable, which should be considered in every physical situation.

Attention has been particularly focused on calcium, referring to the great amount of experimental and theoretical work that has been done in an attempt to gather insight into the macroscopic meaning of such ion measurements in biological systems [50], [51].

In particular, experimental data from Arber and Lin have shown the calcium intracellular concentration to be a key element for the field-induced modification on neuronal behavior [4].

1) Validation: First of all, the unexposed MM calcium channel has been validated. The open probability p_0 is numerically evaluated for different clamping voltages V_m. Once p_0 has been estimated, the current flowing through the channel can be derived.

For a complete discussion on this validation methodology, see [29]; as an example, in Fig. 13, a comparison is shown between results for the calcium channel and experimental data reported in [43]. It is apparent that there is a good agreement between theoretical and experimental data.

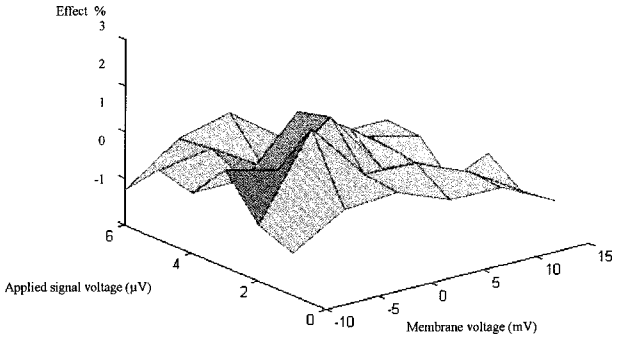
Similar validations have been performed for several other channels.

2) GSM and DECT: High-frequency components: First, an analysis of the channel response to the waveform of GSM and DECT signals has been accomplished. Due to the existing MW components, the model has to deal with such high-frequency signals; this requires both theoretical discussions and design improvements of the modeling technique.

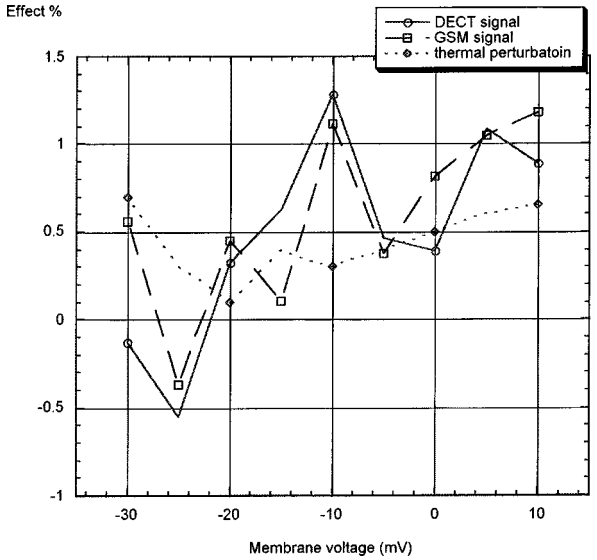
The effect of the RF on the gating of voltage-dependent channels has been analyzed for the case of the calcium channel. In Fig. 14(a), results of an exposure of the channel to a GSM signal are reported, varying both the values of the voltage clamp and the amplitude of the GSM signal. The response is complex and highly nonlinear. In Fig. 14(b), the effects on the calcium channels due to exposure, corresponding to a 1-μV perturbation of the membrane voltage, for the GSM signal, DECT signal, and thermal perturbation will be considered (see Section VII-A.1). As evident from this figure, the channel presents similar behavior for GSM and DECT exposure, while it has a different response to the thermal perturbation. Anyway, the effect is quite slight: 1.5%. Potassium channel presents similar responses. In Fig. 14(c), it is apparent that the sodium channel is more sensitive to such signals, with an effect of around 20%. The channel is sensitive to an applied signal voltage, but also to a membrane voltage, as shown in Fig. 14(c), where results are shown for applied voltage values of 0.1, 1, and 9 μV and for membrane voltage varying from -30 to 15 mV.

3) GSM and DECT: Low-frequency components: In Section VII-B.2, it has been shown that the overall GSM and DECT signals, when applied to the sodium channel, induce a maximum variation of around 20% in the opening probability and current fluxes. Anyway, our knowledge of the frame structure of GSM and DECT signals shows that several components in the ELF range (8, 100, and 217 Hz) are present. Therefore, in order to make an appropriate evaluation of the EM interaction and its effects, a further analysis must be performed considering only the low-frequency components in the stimulating signals.

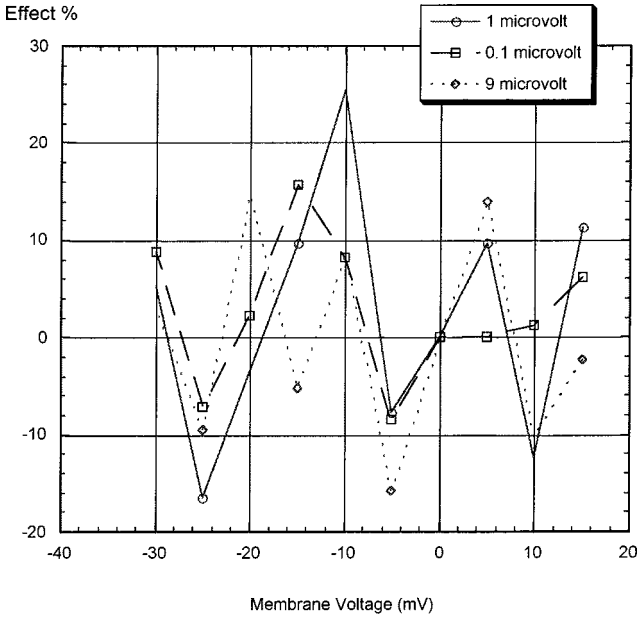
As a first evidence of the effects of the low-frequency component of "pulsed" signals on the gating of voltage-dependent



(a)



(b)



(c)

Fig. 14. (a) Calcium channel exposed to a GSM signal: high-frequency components. (b) Comparison between the GSM and DECT signals and thermal perturbation for the calcium channel at 1 μV of applied signal amplitude. (c) Effect of exposure to the DECT signal for the sodium channel: for 0.1, 1, and 9 μV of applied signal amplitude.

channels, Fig. 15 presents the results of an exposure of the calcium channel to the GSM signal, varying both the values of

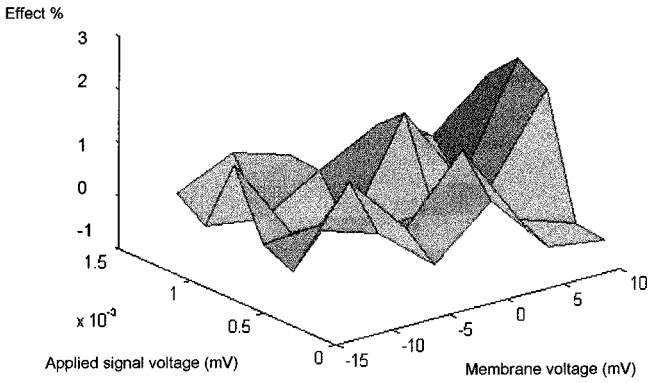


Fig. 15. Calcium channel exposed to the GSM signal: low-frequency components.

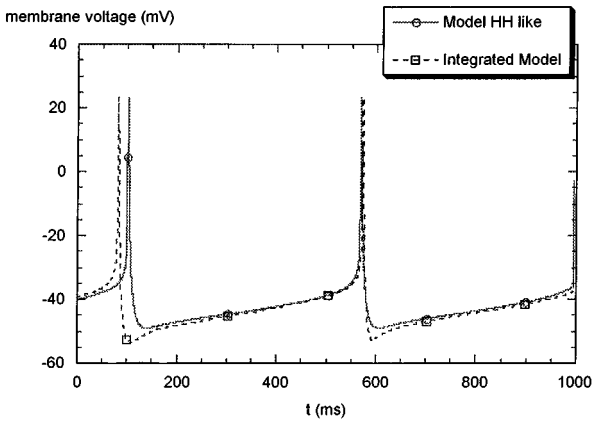


Fig. 16. Comparison between time behavior of the membrane voltage for a basic model and the MacroMM one.

the voltage clamp and the amplitude of the GSM signal (similar results have been obtained for the DECT). Even in the low-frequency range, an effect strongly dependent on a membrane voltage clamp is shown. Moreover, the open probability behavior is not very sensitive to the applied signal.

C. Whole Membrane Model

Results of this section are concerned with the biological level in the scale of complexity; specifically, referring to Fig. 1, to the second ascending step: cell membrane modeling, introduced in Section V.

1) Validation: In Fig. 16, it is shown how substitutions of branches in the macroscopic model corresponding to sodium, calcium and potassium currents, with the equivalent MMs, as described in Section V, do not significantly alter the time behavior of membrane voltage shown in Fig. 8. The macroMM gives results in quite good agreement with experimental data when an unexposed membrane is considered. Therefore, it is a suitable approach to integrate a different level of scale of BEM interaction.

2) Results on ISI: In Fig. 17, results are reported relative to the MacroMM: GSM and DECT signals act on the kinetics of the single channel. Results of such interactions are observed, at the level of the cellular membrane, as changes in the ISI. In particular, it is possible to note that lower values of the external signal give rise to higher variations of the ISI.

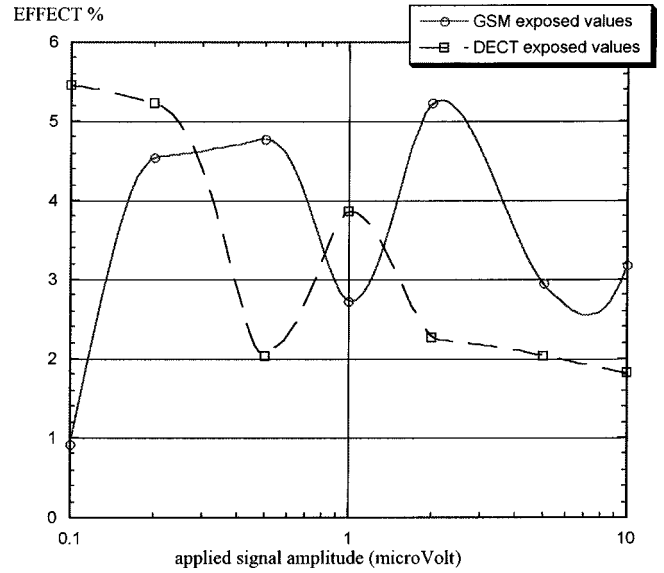


Fig. 17. Effects of GSM and DECT signals on ISI behavior.

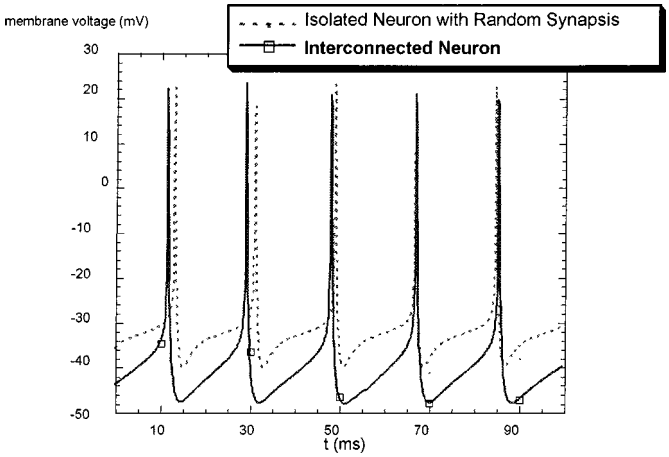


Fig. 18. Comparison between time behavior of membrane voltage for the basic model with random modeling of synaptic activity and the modeling of neuronal interconnection presented in this paper for a connection length of 1 mm.

D. Neuronal-Network model

The following results refer to the neuronal interconnection model presented in Section VI, applied to the basic model of an isolated neuron introduced in Section V [28].

1) Validation: In Fig. 18, a comparison is shown between neuronal activity from the basic model described in Section V and the neuronal activity obtained with the network modeling just mentioned, for a connection of 1-mm length. It is possible to see that the modeling of transmission of the action potential along the axon of the presynaptic neuron does no significantly alter the time behavior of membrane voltage. Therefore, the proposed model of network interconnection provides good agreement with experimental observations on single neuronal cells.

2) Results on a connected neuron: Due to the typical low-pass filtering behavior of a cell membrane, it is interesting to focus on low-frequency components of the two GSM and DECT signals considered. The behavior of the interconnected

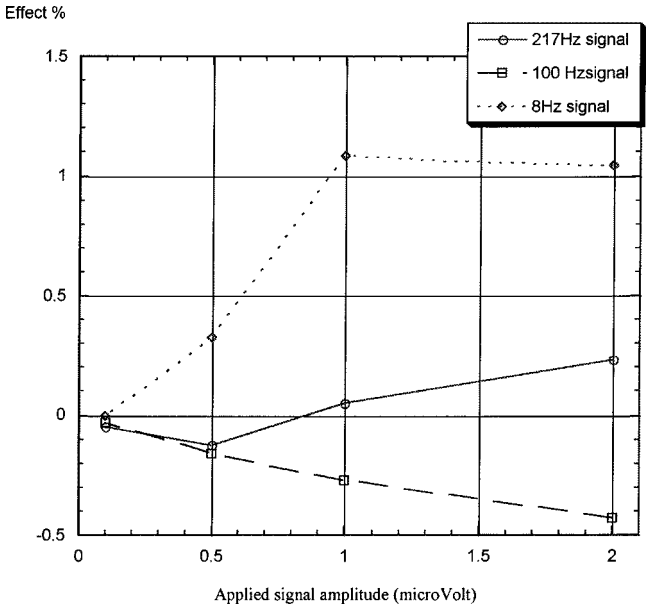


Fig. 19. Effects of low frequency of GSM and DECT signals on ISI behavior of connected cells.

neuron has been evaluated using the proposed model exposed at a frequency of 8.3 and 217 Hz for GSM signal and 100 Hz for the DECT signal. Results for 1-mm connection length are shown in Fig. 19. Maximum effects around 1% are observed on the ISI.

This is basically due to the existence of several feedback and channels interactions inside the cell membrane and at tissue level. This way, the potential high effect at the single-channel level compensate one another.

VIII. Conclusions

In this paper, it has been shown how the BEM interaction modeling can be approached, following a procedure consisting in linking several intermediate models in an integrated one. The output of each step in the process is considered as an input to the upper level. Different channel models can be inserted inside a cell membrane model, allowing for the evaluation of effects induced selectively on specific ions.

The output at the cellular level, which is a result by itself, can be considered as the input to a neuronal-network model, which evaluates the consequences of the EM stimulation at this level.

In such a way, a direct quantitative path is obtained from the external fields to the neurons behavior. Only a slight modification has been evidenced for the existing mobile technologies. Such modeling could be useful in *a priory* evaluation of the health impact of new proposed applications of EM fields.

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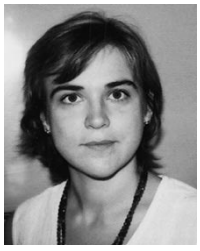

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