Theoretical Evaluation of GSM/UMTS Electromagnetic Fields on Neuronal Network Response

Francesca Apollonio, Micaela Liberti, and Guglielmo D'Inzeo, *Member, IEEE*

***Abstract*—Understanding the modalities of interaction of electromagnetic (EM) fields with biological material is a key point in the identification of possible induced effects. An integrated approach to model EM fields interaction with biological systems is proposed in this paper. Here, a neuronal network is identified as the biological target. In this paper, for the first time, the possible effects of EM signals related to universal mobile telecommunication system and global system for mobile communication standard on the setup model are investigated.**

***Index Terms*—Bioelectromagnetic interaction, microwaves (MWs), mobile phones, modeling, neuronal network.**

I. Introduction

THE study of possible electromagnetic (EM) field effects on biological systems can be rigorously faced by a preliminary investigation on biophysical mechanistic basis of the interaction between the fields themselves and the biological structures involved. Since the beginnings of bioelectromagnetic studies, cellular membrane has been addressed as a primary site of interaction, leading to different models in literature. In particular, authors have chosen to perform analysis of this biological system as the only effective way to understand interactions with EM fields, in order to explain effects at cellular and tissue level [1], [2]. This approach is quite in accordance with a basic observation: the biophysical and biochemical physiological equilibriums are managed at cell and cell-membrane level. However, the cell membrane is not the basic biological unit for a bio-system, in fact, some other elementary structures exist with defined tasks and functional modalities. This leads to the determination of a biological scale of complexity that grows from the low biophysical level of ion-transport across cell membrane to the biological one of cellular cycles or signaling pathways. The structures and processes at each level of this scale, due to their electrical or polar nature, are identified as intrinsically sensitive to EM fields.

Apollonio *et al.* recently proposed an integrated approach to model EM fields interaction with biological systems [2]. This methodology implements the biological scale of complexity and evaluates the effects induced by the EM field on each component of the model up to the neuronal network level. In this paper, the authors investigate the possible effects of EM signals related to universal mobile telecommunication system (UMTS) and global system for mobile communication (GSM) standard on the setup model.

In the next two years, the new mobile telecommunication standard UMTS is going to establish itself as the third-generation technology, and services based on this standard will coexist with the current use of GSM second-generation technology. These standards greatly differ in frequencies and patterns used [time-division multiple access (TDMA) versus code-division multiple access (CDMA)], therefore, it seems interesting to evaluate how RF fields associated with such wireless technology can interact with biological systems and how the differences in the signal physical layer could eventually modify physiological conditions.

II. Materials and Methods

A. Neuronal Network Model

A quasi-realistic neural network has been used in order to investigate possible modifications in the electrical responses under EM exposure. We mainly consider the pattern of action potentials and back-propagating action potentials, in particular, inter-spike intervals (ISIs), spike coincidence, and synchronization of firing neurons, as macroscopic observables of possible metabolic changes within the neuron.

The task of connecting neuronal models has been resolved in [2], approaching the problem of signal propagation inside the axon on the basis of the core-conductor model [3]. The axon length can vary in a range between 1–100 mm. The overall effect of the neuronal axon can be taken into account by considering a pre-axon transmembrane voltage $V_{\rm pre}$ and a post-axon one $V_{\rm post}$, linked by the following relationship:

$$V_{\rm post} = V_{\rm pre} \exp\left(\frac{-x}{\lambda}\right) \tag{1}$$

where x is the axon length, and λ is determined referring to the resistive and dielectric characteristics of the axon. More specifically, referring to Fig. 1(a), it is possible to approximate the axon with a cylinder and, if r_i is the core resistance per unit length, r_e is the resistance of extracellular fluid per unit length, and r_m is the resistance across a unit length of passive membrane [3], it is possible to interconnect neuronal cells one another.

The model for the neuronal cell has to take into account the characteristic double layer of the cellular membrane responsible

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The authors are with the Center of Electromagnetic Fields and Biosystems and the Department of Electronic Engineering, University of Rome, "La Sapienza," 00184 Rome, Italy (e-mail: dinzeo@uniroma1.it).

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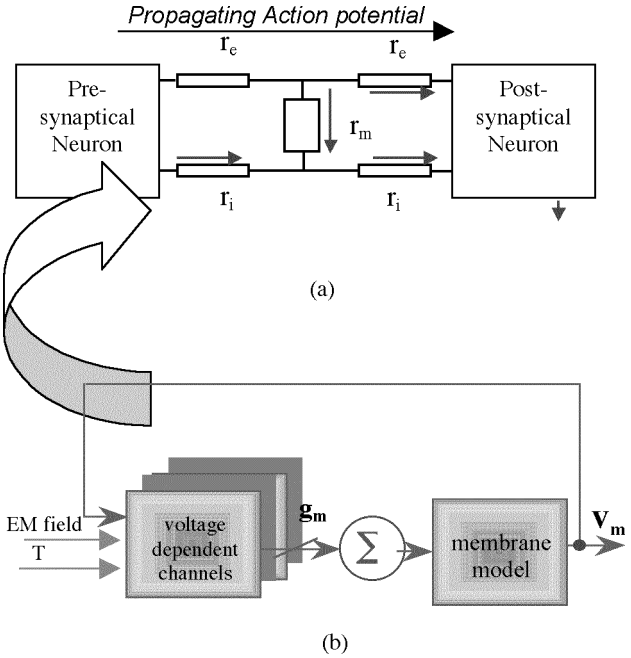

Fig. 1. Interconnection of neuronal models. (a) Network connection of two neurons. (b) Stochastic neuron model.

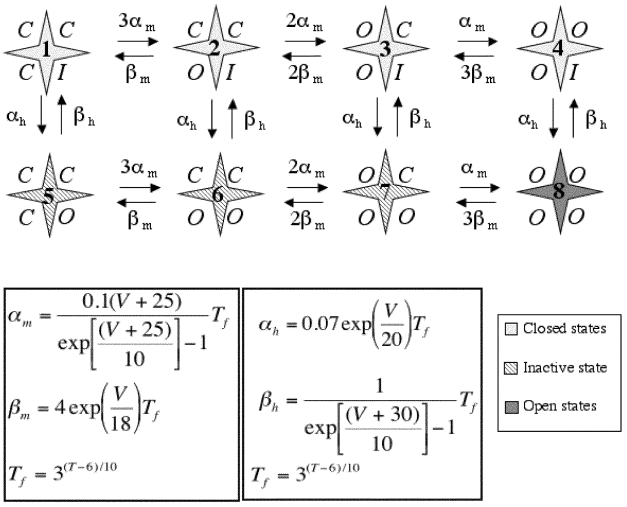

Fig. 2. State machine model for sodium voltage-dependent channel. Model topology: eight states, two different kinetics, transition rates.

for the insulation of the cytoplasm from the external environment, as well as several ionic channels, i.e., macromolecular structures through which ions can pass from the extracellular medium to the intracellular and vice versa. The electrical interpretation of the model gives rise to a lumped-element circuit for the neuron (the *deterministic neuron*) in which the double layer is represented by means of a capacitance, and ionic channels can be simulated by means of nonlinear resistances (ions moving through the membrane) and fixed potentials (different ion concentration inside and outside the cell) [4]. Results obtained with the lumped model give a good matching with experimental data [5]. Connecting several lumped-element models gives rise to the *deterministic neuronal network*. The response of the *deterministic neuronal network* to extremely low frequency (ELF) EM fields has been investigated in [2] using the lumped-element circuit able to simulate the behavior of silent and firing neuronal membranes. Nevertheless, such a model is not properly usable at RF frequencies due to the presence of the short-circuiting capacitance of the membrane.

In order to overcome this limit, a different way to model ionic channels has been introduced based on a Markov model approach [6]–[8]. The channel's behavior is fully defined by a set of N states, a transition rate matrix $\mathbf{Q}$, whose elements q_{ij} are the transition rates regulating the kinetic of the process, and a vector $\mathbf{P}(\mathbf{0})$, whose N elements are the occupancies for each state at the starting time $t = 0$. Each state in the model represents a possible conformation for the channel (open or closed), and transitions among states represent structural modifications associated to energetic changes. If the channel is considered ohmic (experimentations confirm this hypothesis with reasonable approximation [9]), the current flux through the channel at any instant is proportional to the probability for the system of being in an open state. A scheme reporting the different states and the matrix $\mathbf{Q}$ elements are reported in Fig. 2 for sodium, a voltage-dependent ionic channel used in the following. The channel is composed of four molecular subunits, whose structural conformations are responsible for channel opening or closing. As a consequence, the model has eight states with only one considered "*open*," which means conductive. Three subunits follow an m-like kinetics regulating fluctuations between open (O) and closed (C) states, while one subunit follow an h-like kinetics for the inactivating (I) process. The transition rates depend on membrane voltage V and on temperature T.

In order to evaluate the time course of channel gating, the channel is commonly supposed to be a zeroth-order Markov chain, stationary and ergodic, and the channel activity is represented by a random process where the aleatory variable is the dwell time in a certain state [10]. Under such hypotheses, it is possible to quantify the current flowing through the channel, as a function of the time t, by the evaluation of the probability of finding the system in the open state [10]–[12]. The model has been implemented and solved by means of a Monte Carlo technique, following the procedure summarized below:

1) single process simulation
   - identification of the current state of the channel;
   - evaluation of the dwell-time (T_d) in the current state by stochastic technique [10];
   - evaluation of the state that will be occupied after a time (T_d);
2) statistical averaging
   - realization of N single-process simulation;
   - evaluation of the open probability temporal evolution.

Once the dwell time in a certain state (T_d) has been determined as a function of transmembrane voltage and temperature, it is assumed that the channel is insensitive to an external stimulation for a time T_d, after which, returning to be sensitive, is ready for the evaluation of the next state. For this reason, providing that an appropriate time step is used in the numerical algorithm, the

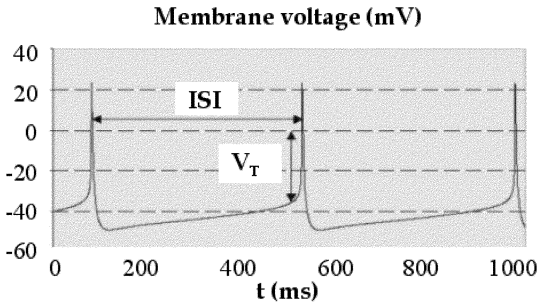

Fig. 3. Membrane voltage behavior. The parameters observed are ISIs, the distance between two subsequent spikes, and V_T membrane threshold, membrane value at which the spike starts.

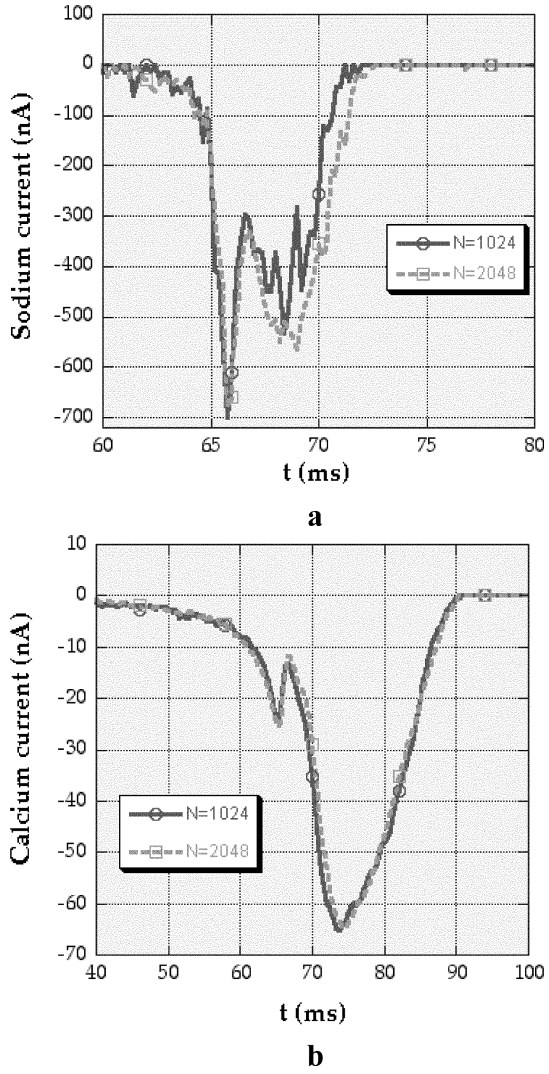

Fig. 4. Ionic currents calculated via Markov models with a different number of realizations N. (a) Sodium current with $N = 1024$ and $N = 2048$ realizations. (b) Calcium current with $N = 1024$ and $N = 2048$ realizations.

channel can be investigated even with high-frequency components. This explains how EM exposure even in the microwave (MW) range can be considered.

Ionic channels simulated through stochastic state machines have been introduced in the circuital model for a single neuron in [2]. Fig. 3 reports on the behavior of membrane voltage in physiological conditions. The integrated model obtained (*stochastic neuron*) is composed by cascading protein channel models, as sketched in Fig. 1(b), and can respond to RF fields like mobile telecommunication signals.

TABLE I
ISI AND V_T OF THE STOCHASTIC NEURON FOR DIFFERENT NUMBER OF REALIZATIONS

		N=1024	N=2048
ISI (ms)	Mean	438	439.25
	Dev std	21.4	11.47
V_T (mV)	Mean	- 49.23	- 49.06
	Dev std	0.77	1.5

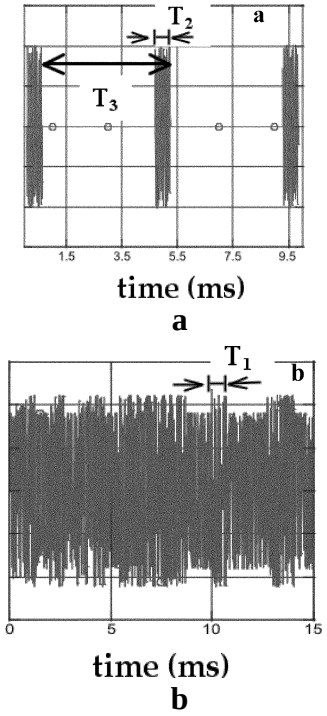

Fig. 5. Example of UMTS and GSM signals used for simulations. (a) T_2 is 0.546 ms (carrier on) and T_3 is 4.6 ms. (b) T_1 is 0.66 ms, in each timeslot T_1 power varies randomly of 1 dB and frequency varies of 5 MHz over 1940 MHz.

In this paper, the contribution of activated synapses to link several stochastic neurons has been taken into account, following the core-conductor approach previously introduced. The final result is a tissue network: the *stochastic neuronal network*. The more the ionic currents simulated with Markov models are similar to the currents generated in the deterministic model, the more the entire neuronal network works fine, thus giving realistic data. To this regard, a crucial point is played by the statistical averaging process of the ionic current Monte Carlo solution, in particular, the number of realization (N) of a single gating process. Fig. 4 reports on the sodium and calcium currents simulated in the stochastic neuron through Markov models with different values of N. It is possible to observe that increasing N from 1024 to 2048 realizations determines a reduction of "noise" in the current waveforms, particularly for the sodium current and, hence, a better approximation of the analytical curve. The resulting statistical parameters (mean value and standard deviation) of the ISI and threshold voltage are reported in Table I for both $N = 1024$ and $N = 2048$ realizations. The value of $N = 2048$ has been chosen for this study. In order to assess the connection, three neurons have

TABLE II
OUTPUT VARIABLES FOR THE DIFFERENT MODELS

	ISI				V_T			
	Mean	Stand. Dev.	% effect on mean	% effect on stand. dev	Mean	Stand. Dev.	% effect on mean	% effect on stand. dev
Unexposed	439.2	11.47	-	-	- 49.06	1.5	-	-
SIN900	439.5	11.15	0.07	- 2.7	- 49.41	1.7	0.7	13
GSM	438.2	11.28	- 0.2	- 1.6	- 48.86	1.4	- 0.4	- 6
UMTS	439.7	10.79	0.1	- 6	- 49.18	1.6	0.2	6

been considered and placed at a distance of 1 mm. Interest on stochastic models of nervous structures increased recently [13] and a complete simulation of the involved channels seems to be crucial [13], [14]. Such results [13] open the possibility of applying our approach to other kinds of nervous tissues.

Once defined, the physiological situation of a neuronal tissue with its own pattern of receptors and signaling transduction systems, the response of the network to high-frequency fields like UMTS and GSM signals have been investigated, comparing the results with a continuous wave (CW) signal.

B. EM Coupling

When dealing with a cell exposed to an EM field, in good approximation, the electric field value present on the membrane can be related to the transmembrane voltage, as shown in [15]. Following this assumption, the cell has been considered as a sphere of radius R of 40 μm covered by a membrane of very small thickness and with a capacitance $C_m = 0.1$ F/m^2, implying that the frequencies of interest for this study, i.e., the MW range, are above the β relaxation frequency for the cell.

At these frequencies, the membrane potential can be calculated approximately as follows:

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

where σ_c and σ_a are, respectively, the conductivity of the cytoplasm, equal to 1 S/m, and the conductivity of the extracellular fluid of 2 S/m [2], [16].

As stated previously, ionic channels coefficients α_i and β_i $(i = m, h)$ depend on the transmembrane voltage, which can be considered as the sum of two contributions: the first related to the physiological membrane values and the second related to a perturbing component due to the EM field acting on the cell [16]. Therefore, the EM field can be thought of as a perturbation of the equilibrium state that modifies ionic currents. In this context, ionic channels, as the elementary biological units, state the sensitivity of the model to the external perturbation. In order to establish which value of the membrane potential due to the EM field can be considered significant, a statistical methodology has been considered. The T-Student test,[1] commonly used to test whether the mean (or median) of a physical variable differs between two population groups, has been applied to the mean open probability of ionic channels, calculated with Markov models. The T-Student test gives as a result the p-value; if p is large $(p > 0.5)$, there is no evidence of a difference comparing the two different groups. In particular, considering as an example the potassium channel, the physiological and exposed situation have been compared for different values of induced membrane potential. Extremely significant values of $p < 0.0001$ have been obtained for a 20 μV of EM-induced voltage, solving the channel current with $N = 2048$ realizations; this means that the effect of the EM field on mean open probability is extremely significant when considering a superimposed voltage of 20 μV. Decreasing the intensity of EM-induced voltage, a reduction of significance (down to no significance) can be observed. Probably an increase of the realizations number N could drive to more performing sensitivity, but strongly raises the computational effort. This target is out of the scope of this paper.

[1]GraphPad Software Inc., San Diego, CA. © 1992–1998. [Online]. Available: http://www.graphpad.com

C. EM Signals

Apollonio *et al.* described the GSM standard and related signal used in their simulations in [2]. Here, an example is reported in Fig. 5(a).

Focusing attention on the UMTS standard, as reported in [17], the uplink (link from the mobile to base station) physical radio channel can be represented as follows. The uplink direction uses in-phase–quadrature (I–Q)/code multiplexing for user data and physical layer control information. The physical layer control information is carried by the dedicated physical control channel (DPCCH). The higher layer information (user data) is carried on one or more dedicated physical channel (DPDCH).

In this paper, only the DPDCH has been considered with a characterization based on two parameters: the frequency allocation and transmitting power. In particular, during each slot, a signal with a central frequency of 1940 MHz and a bandwidth of 5 MHz (distance between different carriers) is simulated in order to take into account a single transmitting channel; inside each slot, the power is considered constant, while moving from one slot to another the power is considered varying in a range of ± 1 dB of the maximum transmitting power, in order to take into account the mechanism of power control.

The resulting simulated signal is characterized by pseudonoise behavior, as evidenced in Fig. 5(b).

III. RESULTS

The proposed model is composed of different levels of the biological scale of complexity. As each level has its proper outputs, results for the single channels, isolated neuron, and three interconnected neurons will be reported. The exposure

TABLE III
STATISTICAL PARAMETERS FOR THE ISOLATED NEURON. MEAN VALUE, STANDARD DEVIATION, AND EFFECT OF EXPOSURE (DISPLACEMENT FROM THE UNEXPOSED SITUATION) FOR ISI AND V_T

	ISI				V_T			
	Mean	Stand. Dev.	% effect on mean	% effect on stand. dev	Mean	Stand. Dev.	% effect on mean	% effect on stand. dev
Unexposed	439.2	11.47	-	-	- 49.06	1.5	-	-
SIN900	439.5	11.15	0.07	- 2.7	- 49.41	1.7	0.7	13
GSM	438.2	11.28	- 0.2	- 1.6	- 48.86	1.4	- 0.4	- 6
UMTS	439.7	10.79	0.1	- 6	- 49.18	1.6	0.2	6

TABLE IV
STATISTICAL PARAMETERS FOR THE THREE CONNECTED NEURONS. MEAN VALUE, STANDARD DEVIATION, AND EFFECT OF EXPOSURE (DISPLACEMENT FROM THE UNEXPOSED SITUATION) FOR ISI AND V_T

	ISI				V_T			
	Mean	Stand. Dev.	% effect on mean	% effect on stand. dev	Mean	Stand. Dev.	% effect on mean	% effect on stand. dev
Unexposed	389.2	10.45	-	-	- 48.91	0.58	-	-
SIN900	386.6	11.01	- 0.6	5.3	- 48.8	0.76	0.2	31
GSM	388.6	10.66	- 0.15	5.6	- 48.8	0.53	0.2	- 8.6
UMTS	387.9	9.86	- 0.3	- 5.6	- 48.7	0.55	0.4	- 5.1

conditions considered in the following regarded: 1) a sinusoidal 900-MHz signal (SIN900), which takes into account the first generation of mobile communication signals (CW); 2) a GSM waveform, representative of pulsed signals; and 3) an UMTS signal for the last generation. In Table II, an attempt to organize the output variables observed for the single biological levels is reported.

Results of 3-s exposure for the potassium, sodium, and calcium channels have been observed for the exposed situation versus the physiological one, as the percentage of the effect on the mean value of the ionic current flowing through the channel itself. The effect obtained on the mean current value is very slight, less than 1%, and the variation on the current flowing in the channel due to the EM field is similar for both signals (GSM and UMTS) [18].

Regarding the isolated neuron and neuronal network, simulations have been realized for a 40-s exposure giving rise to almost 100 spikes. Results have been organized as follows for exposed and physiological situations:

- statistical analysis on the overall output (100 ISI);
- statistical analysis on incremental groups of spikes (1–10, 1–20, . . ., 1–100).

The results of the statistical analysis on the group of 100 spikes are reported in Tables III and IV, respectively, for the isolated neuron and network. These tables summarize mean values and standard deviations for both the ISI and threshold voltage V_T; the effect is expressed as a percentage of variation of the exposed variable from the physiological one. It is possible to observe that the effect is quite below 1% for mean values of the ISI and V_T, while it is around 6% (with a peak of 30%) for the standard deviation, indicating that the spreading of values around the mean is affected by the exposure signal more than the simple mean. To this regard a deeper analysis on standard deviation has been carried out, realizing an incremental statistics on spikes: first group from spike 1 to spike 10, second group from spike 1 to spike 20, and so on. Global results are reported in Figs. 6 and 7. A particular insight on the behavior of ISI standard deviation for the isolated neuron and neuronal network is reported in Fig. 6. First of all, it is possible to observe, both for the isolated neuron and network, that by comparing the exposed situations with the unexposed one, all the standard deviations, after an initial difference, tend to the unexposed values. However, while the isolated neuron standard deviation always increases, observing

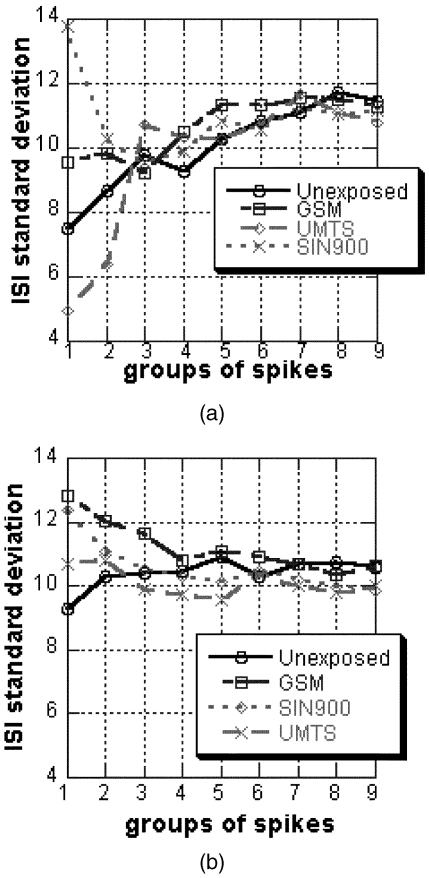

Fig. 6. ISI standard deviation for groups of incremental number of spikes. (a) Isolated neuron. (b) Stochastic network (three neurons).

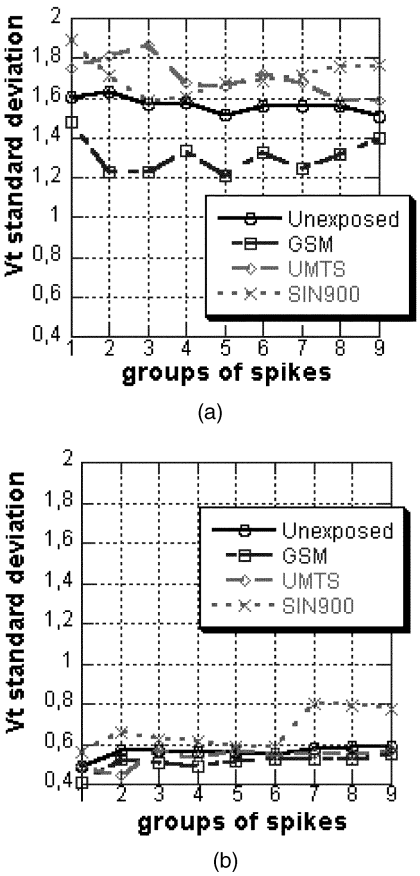

Fig. 7. V_T standard deviation for groups of incremental number of spikes. (a) Isolated neuron. (b) Stochastic network (three neurons).

the neuronal network, it can be seen that the standard deviation tends to reach a constant value after 60 spikes, indicating that a steady state has been reached. Fig. 7 refers to the behavior of V_T standard deviation; it is possible to observe an overall reduction of the values from isolated to connected neurons (from around 1.6 to 0.5). In summary, the standard deviation in the isolated neuron is more sensitive to the kind of signal: it presents, with respect to the unexposed reference, quite lower values for GSM and slight higher ones for UMTS and SIN900; such differences are not observed in the interconnected neurons. Examining in more detail the behavior of the standard deviation for ISI and V_T, it is possible to notice that interconnected neurons present a sort of synchronization that keep the values more similar in spite of the different kind of exposure.

IV. Conclusions

The approach proposed in this paper has allowed a quantitative evaluation of the effects at the neuronal network level induced by mobile systems, and can be a useful instrument for comparing different signal patterns and their impact on living systems. In general, it is possible to observe that moving from a microscopic to a more macroscopic biological level seems to imply a compensation of the EM fields' induced effects. This can lead to hypothesize a sort of "capability," proper of biological systems, to minimize the effects due to this kind of noninvasive perturbing action. However, in cases where temporal response is important, e.g., in sensory neuronal systems, the stochastic properties of the channels may play a key role in highlighting possible effects.

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Francesca Apollonio was born in Rome, Italy, in 1968. She received the Electronic Engineering degree and Ph.D. degree from the University of Rome "La Sapienza," Rome, Italy, in 1994 and 1998, respectively.

She began her research in the area of bioelectromagnetics in 1994. In 1995, she was with the Non-Ionizing Radiation Laboratory, ENEA Research Center, Rome, Italy, where she was involved with experimental dosimetry techniques. In 2000, she became a Researcher with the Department of Electronic Engineering, University of Rome "La Sapienza." She has been involved in research concerning biological effects of EM fields, in particular, her interests regard modeling the interaction mechanisms between EM fields and biological systems, molecular simulations, dosimetry techniques, and exposure system design.

Dr. Apollonio was the recipient of a 1995 Fellowship presented by the ENEA Research Center, Rome, Italy.

Micaela Liberti was born in Genova, Italy, in 1969. She received the Electronic Engineering degree from the University of Rome "La Sapienza," Rome, Italy, in 1995, and the Ph.D. degree in electronic engineering from the University of Rome "La Sapienza," Rome, Italy, in 2000. Her thesis concerned MW effects on enzyme kinetics in loaded liposomes.

From 2001 to 2002, she was a Post-Doctoral Fellow with the Italian Inter University Center of Electromagnetic Fields and Biosystems (ICEmB), University of Rome "La Sapienza." In 2002, she became a Researcher with the Department of Electronic Engineering, University of Rome "La Sapienza." Her scientific interests concern interaction mechanisms between EM fields and biological systems, dosimetric evaluation at microscopic levels, exposure system dosimetry, and design.

Dr. Liberti was the recipient of a 1996–1998 Fellowship presented by the Scientific Research Ministry for a National Research Program on Telemedicine.

Guglielmo D'Inzeo (M'83) was born in Milan, Italy, in 1952. He received the Electronic Engineer degree from the University of Rome, Rome, Italy, in 1975.

From the 1979 to 1985, he was Professore Incaricato with the University of Calabria (1979–1981) and with the University of Ancona (1980–1985). From 1986 to 1990, he was an Associate Professor of MWs measurements with the University of Rome, "La Sapienza," Rome, Italy. He is currently a Full Professor of Bioelectromagnetic Interaction with the University of Rome, "La Sapienza." Since 1997, he has been Chairman of the Electronic Engineering Department, University of Rome, "La Sapienza." Since 1999, he has been the Director of the Inter-University Centre for Electromagnetic Fields and Biosystems (ICEmB), University of Rome, "La Sapienza." He has authored or coauthored over 40 papers on international refereed journals and books. His research activities have concerned active and passive MWs component design and bioelectromagnetics. In MWs circuit design, he has focused his activities on planar circuit characterization using numerical techniques and on the design of monolithic amplifier circuits using new topologies. In the bioelectromagnetics area, his fields of interest are the interaction of EM fields with biological tissues, the effects of MWs and ELF fields on biological samples, and the modeling of the interaction mechanisms.

Prof. D'Inzeo served as secretary treasurer of the Middle and South Sections of the IEEE Microwave Theory and Techniques Society (IEEE MTT-S) from 1986 to 1988. He became a council member of the European Bioelectromagnetics Association (EBEA) in 1989. He served the Association as president from 1993 to 1998. From 1992 to 2000, he was the Italian representative of the COST 244 and COST 244B projects on "Biomedical Effects of Electromagnetic Fields" and was chairman of Working Group 3 (System Application and Engineering). In 1993, he acted as chairman of the Second International Meeting "Microwaves in Medicine" organized by the IEEE and Commission K (Electromagnetism in Biology and Medicine) of the International Scientific Radio Union (URSI). Since 1998, he has been the scientific director of Elettra 2000. Since 2001, he has been the national representative of the COST 281 project "Potential Health Effects from Emerging Wireless Communication Systems."