THE SPECIFICITY OF ELECTROMAGNETIC FIELD ACTION ON BIOELECTROCHEMICAL PROCESSES

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INTRODUCTION

The understanding of the modalities of interaction of electromagnetic (EM) fields with the biological material is a key point in the identification of possible induced effects. An important issue in this context is the possible capability of the EM field to induce an effect as an immediate consequence of the signal pattern specificity, i.e. selected amplitude and frequencies of the EM signal. This peculiarity of the interaction between EM fields and bioelectrochemical processes is most likely due to the high level of biological complexity, in which complex systems and non-linearities play an essential role. Here a methodology based on two essential steps is proposed with the aim of trying to explain the specificity of the EM action. The first point is the characterization of the 'primary interaction step', to be investigated at molecular or atomic level. The second one is related to the definition of a complete model able to simulate a tissue level, in particular a neuronal tissue, in which the biological information exchanged by cells is prevalently coded by electrophysiological processes.

MECHANISM OF INTERACTION

With regard to the characterization of the 'first interaction step', defined as the mechanism through which an EM field acts on a biological system, we believe that the first mechanism should be found at atomic or molecular level in the action of the EM field on the distribution of fixed charges of membrane proteins and of membrane double layer or alternatively on the dynamic process of ion binding to a receptor site. In this context the action is focussed on the chemical reaction of the ion binding. The problem of the ion dynamics in the proximity of a receptor site has been studied in literature by means of different classical and quantistic approaches, which using an approximate model of the receptor site are able to simulate dynamic processes with temporal scales of the order of channel gating times [1, 2].
Nevertheless in the chemical process of ion binding seems to be essential the reciprocal charge distributions of the two molecules involved, therefore a rigorous approach in the investigation of the binding process under the influence of an EM field, should consider molecular dynamics simulations based on quantistic considerations. In fact the binding mechanism is a chemical process which evolves in time, moreover during the process of binding the electronic distribution of both ligand and receptor site could be affected by each other and by the external field. Unfortunately this type of approach requires a strong computational effort even for molecular domains of few atoms, therefore a quantum-mechanical study has been carried out for the receptor site molecular conformation, considering the ligand moving on a fixed direction at different distances from the receptor site [3, 4].
The method used, the Perturbed Matrix Method (PMM), is based on perturbation theory in which the perturbing element is an electric field constant and locally homogeneous [5]. In particular the problem is first solved considering the system in an unperturbed situation: by means of a quantistic ab initio method, the Density Functional Theory (DFT), the minimal energy of the molecule is calculated. Then the perturbation, in presence of the electric field, is taken into account considering a perturbative term, which is generally represented by the product of the electric field and the dipole moment of the molecule, summed to the unperturbed hamiltonian operator. The problem is solved with a matrix notation, diagonalizing the hamiltonian perturbed matrix on the basis of the unperturbed eigenfunctions. The procedure implemented starts with a first quanto-mechanical calculation in order to obtain the optimised geometry of the system considered. Successively the diagonalization of the perturbed matrix is carried out for the different values of the applied electric field. The molecular system chosen as paradigmatic example of binding process is hemoglobin due to its chemical stability and to the huge number of experimental data present in literature. In particular its binding site, the imidazole-iron-porphyrin complex, indicated as FeP(Im) and two different ligands have been investigated: Fe^{2+} and CO. Results indicate that an electric field of at least 10^8 V/m is required in order to obtain a significative difference (15%) in the energy barrier of the chemical binding reaction, while electric fields of the order of 10^9 V/m could modify the conformational geometry of the molecule. Below these values, looking at energy curves and molecular geometry, the differences between exposed and not exposed can not be appreciated.

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MODELING BIOLOGICAL COMPLEXITY

Defining a complete model able to simulate the neuronal tissue level, in which the biological information exchanged by cells is prevalently coded by means of electrophysiological processes, is a task we are working on since 2000 [6].
The integrated approach proposed to model EM fields interaction with biological systems, reported in a schematic view in Fig. 1, is based on the evaluation of the electromagnetic field at cellular membrane level then on the evaluation of the effects induced on each component of the model growing from the low bio-physical level of ion channels to the biological one of neuron time behavior. In such an approach biological sub-systems, at each level of complexity, are represented by self-consistent models, whose validity can be experimentally verified, linked together so that the output of a lower level model represents an input for the upper level model. In this way, a global effect on the biological system may be quantitatively bound to the applied EM field through a chain of intermediate effects.
Regarding the specificity of the interaction mechanism between EM fields and neuronal processes, two elements seem to be essentials in order to be able to find an effect dependent in a selective way from amplitude and frequency of the exogenous signal: non-linearities and noise. Therefore from this point of view it is necessary to increase biological complexity in order to try to observe a selective effect. Nevertheless as previously outlined the transduction process from the EM field to the biological system is performed at atomic level, hence modeling the way in which the field acts on bioelectrochemical processes is a microscopic problem. In this context model integration becomes crucial: each level of the biological complexity modeled should incorporate in the right way the field and should well match experimental data.
A brief description of the different levels of the integrated model is given below.

Macromolecular Level

Applying Markov models to the simulation of the dynamic behaviour of membrane ionic channels has already allowed us to evaluate EM field action on macromolecular structures which regulate ion flux through cellular membrane, in particular voltage and ligand ionic channels [7, 8]. This technique which allows to obtain in a numerical way a current variable in time permits a direct comparison between theoretical and experimental results (patch-clamp recordings). More recently in order to improve the investigation into the interaction between protein channels and different kinds of EM signals, we have proposed methods for the analysis of ionic currents in the frequency domain. In fact it is of crucial importance to dispose of suitable techniques for analysing both simulated and measured currents, in order to evaluate possible effects, even of weak intensity, induced by the EM field. For this purpose the analysis by means of the power spectral density (PSD) seems to be particularly powerful, since it enables us to detect weak current oscillations, not otherwise detectable by first order statistical moments, evidencing distinct contributions of different kind of applied EM signals [9, 10].

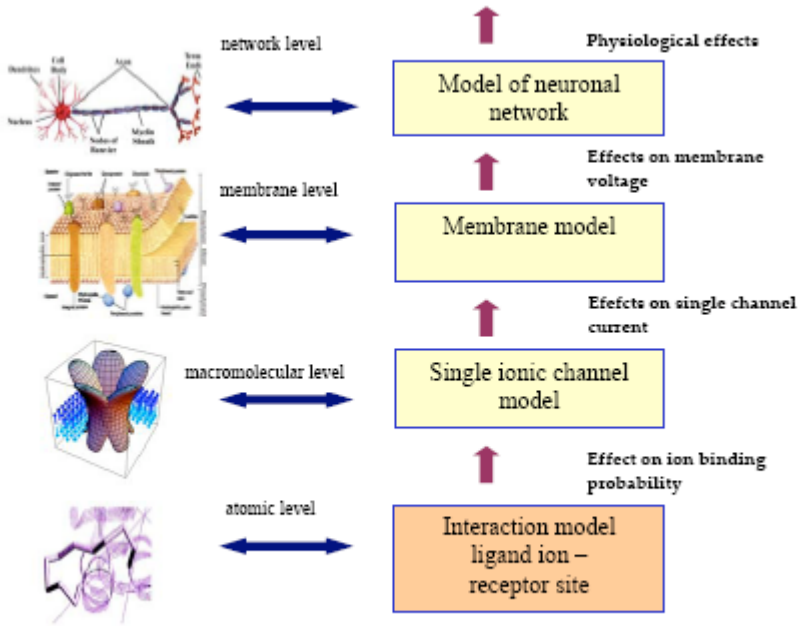

Fig. 1 Integrated model of interaction between electromagnetic fields and Nervous System.

Level of Cellular Membrane

At this level of complexity we refer to the stochastic neuronal model considering the Hodgkin-Huxley neuron in which channel noise is taken into account using Markov state machines for modeling both Potassium and Sodium currents. The used stochastic neuron model has been shown to describe typical neuron behaviors, such as noisy baseline, spontaneous isolated spikes, missing spike and unreliable response to repetitive stimulation. Due to its realistic behavior, stochastic neuron model is the best candidate to simulate the neuronal encoding of an exogenous EM signal. For this purpose, a 50 Hz sinusoidal signal was applied to the model and the output signal to noise ratio (SNR) was considered as a quantitative measure of the encoding of the signal in the spike train, for different channel noise levels. Reporting the SNR versus noise, i.e. channel number in the model, a typical bell-shaped curve, with a maximum in correspondence of a well defined internal noise level [11] is showed. This phenomenon, already evidenced in a neuron when an external Gaussian noise was applied, is known as stochastic resonance, and consists in the optimization of the response of a system to a subthreshold external stimulus, in correspondence of a particular amount of noise. This implies that neurons with different channels number and typology may detect EM signals differently, and the induced effects may also vary. Such a phenomenon is likely to depend on the mean synaptic current and on the EM frequency and amplitude.
A more accurate model of neuronal behaviors reproducing for example a variety of firing and bursting activities, is the double compartment neuron model, which accounts for both axo-somatic and dendritic areas related to various neuronal morphologies. The introduction of an EM field is clearly related to a modulation of the neuronal encoding process, dependent on field amplitude and frequency [12].

Multicellular Level

Multicellular level represents the highest level of the biological scale; in fact it is in this context in which biochemical and bioelectrics reactions due to cellular interconnections are taken into account.
The models proposed at this level of the biological scale represent coding and transmission processes of electrical pulses and will be used to determine if possible effects due to EM field on neuronal coding are feasible. First model taken into account is the one describing myelinic nervous fiber: the fiber will be based on a multi-compartment approach [12] showing the fiber divided in a sequence of adjacent compartments. Interconnection among neuronal cells will be further studied, in presence of EM field and noise, through the realization of two models, one representing a network afferent to peripheral nervous system (SNP) and the other relative to a cortical network affering to central nervous system (SNC) [13]. Results obtained in presence of EM field show for the peripheral network an amplification factor in the observable chosen, dependent on the number of network layers, maximum for specific values of synaptic conductance. For the network affering to central nervous system, a linear behavior is observed in the variations induced by high frequency field values while a synchronizing behavior is showed for selected values of field intensities in the low frequency range.

CONCLUSIONS

The proposed two-step methodology, investigation on the first mechanism of interaction at atomic and molecular level and modelization of the biological complexity integrating models of single sub-systems, seems to be appropriate way to reveal biological responses specifically related to the pattern of the exogenous EM signal.

REFERENCES

1. B. Bianco, A. Chiabrera, Biol & Bioener,1992. (28) pp. 355-365248101.
2. Chiabrera, B. Bianco, E. Moggia J.J. Kaufman, Bioelectromagnetics, 2000. (21), pp.312-324.
3. L. Dominici, F. Apollonio, G. d'Inzeo, M. Aschi, A. Amadei, Proc of the 6th Int. Congress of EBEA, Budapest, 2003. p. 99.
4. F. Apollonio, L. Dominici, S. Donatiello, G. d'Inzeo, BioeEm 2005. Dublin, June2005, pp 210-211.
5. M. Aschi, R. Spezia, A. Di Nola, A. Amadei, Chem. Phys. Lett. 2001. **344** pp. 374-380.
6. F. Apollonio, M. Liberti, G. d'Inzeo, L. Tarricone, IEEE Trans on MTT, 2000. **48** (11), pp. 2082-2093.
7. P. Bernardi, G. d'Inzeo, S. Pisa, IEEE Trans on Biomed Eng, 1994. **41** (2), p.125-133.
8. S. Bruna, M. Liberti, S. Giordano, E. Moggia, B. Bianco, G. d'Inzeo, IEEE MTT-S Int Micr Symp Dig, Phoenix 2001, pp. 162-166
9. A. Paffi, G. Cotignola, M. Liberti, F. Apollonio, G. d'Inzeo, EMC Symposium, Zurich, Feb. 2005, pp 137-140.
10. A. Paffi, G. Cotignola, M. Liberti, F. Apollonio, G. D'Inzeo, M. Mazzanti, BioEm 2005, Dublin, June.2005, pp 214-215
11. M. Giannì, A. Paffi,M. Liberti, F. Apollonio, G. d'Inzeo, 5th WSEAS International Conference on Power Systems and

Electromagnetic Compatibility, August 23-25 2005, Corfu, Greece.
12. A. Paffi, M. Giannì, F. Maggio, M. Liberti, F. Apollonio, G. d'Inzeo, accepted at XXVIIIth URSI General Assembly, 2005. October 23-29 New Delhi, India.
13. M. Giannì, F. Apollonio, M. Liberti , G. d'Inzeo, Abstract Book of XXVI Annual Meeting of Bioelectromagnetic Society, Washington DC, pp. 63-64, June 2004.
14. A.M. Tranquilli, F. Apollonio, M. Liberti , G. d'Inzeo , Abstract Book of XXVI Annual Meeting of Bioelectromagnetic Society, Washington DC, p. 295, June 2004.