Overview of bioelectromagnetic interactions models:

proposal for a unifying integrated methodology

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Introduction

Since the beginnings of bioelectromagnetic studies cellular membrane has been addressed as a primary site of interaction, leading to different models proposed in literature. In particular an analysis of this biological system seemed to be the only effective way to understand interactions between electromagnetic (EM) fields and biological systems.

The cell membrane in not the basic biological unit for a biosystem, in fact some other elementary structures exist with defined tasks and functional modalities and, because of their polar (or multipolar) nature, are intrinsically sensitive to EM fields.

Among the several possible microscopic sites of interest for such interaction protein channels in cell membranes are good candidates. These structures, regulating the ionic fluxes through cell membranes, play a major role in preserving the physiological values of transmembrane voltage, as well as the many consequent biochemical equilibria.

In the first part of this work an overview of the several models proposed in literature is presented following a structured matrix. In the second part an integrated approach to modelling EM interaction with biological systems is proposed. This methodology, which takes into account a unified model made up by specific component units for each biological level considered, is principally based on the evaluation of the effects induced by the field on each component of the model, growing from the low bio-physical level (ion-transport) to the biological one (cellular behaviour). The use of well assessed models for the simulations of each part allows both the evaluation of the effect at different level of complexity and the use of this effect as an input to the upper level. In such way it is possible to relate in a structured path of cascading models the different time constants that regulate each step.It is important to highlight how this approach can lead to a complete quantitative evaluation of the effects due to an EM source, taking into account all the bio-physical and bio-chemical phenomena.

Literature Overview

Interaction models proposed in literature are classifiable over the biological scale of complexity, specifically:

1. a biophysical level as to say ions and molecules moving towards and around the membrane,
2. protein and macromolecules level, with their selective functioning,
3. membrane, responsible of any information exchange between internal and external medium,
4. the whole cell, including its biochemical and metabolic functioning.

Authors have seen four principal kinds of modelling EM interaction: resonance mechanisms, coupling with non linear systems, effects controlled by the contemporary presence of electric and magnetic fields, and co-operative mechanisms due to interactions among several membrane components.

In the following a synthetic resume of principal approaches to the study of interaction mechanisms will be proposed; without any aim to be exhaustive it represents a structured overview of the existing bioelectromagnetic models of interaction citing only on the main related reference.

Ion-transport Modelling: The first modelling problem to be solved is to compute the dynamics of the messenger molecule while moving around the cell membrane in absence and in presence of exogenous EM exposure. Mechanisms able to model such kind of processes are intrinsically candidates to interact with any kind of fields, following the EM signal in its whole evolution in time. The output variables chosen for this level are typically the probability for a binding site to be occupied by the messenger molecule, the adsorbing and de-adsorbing times for the ion and its spatial position. In this contest three principal kind of modelling have been developed: free ions [1-4], ions under a central force [5] and ion binding in a realistic complex environment [6, 7].

Protein channel: Several approaches have been proposed till now to simulate the response of an ionic membrane channel to EM stimulation. Some models propose that typical windowing effect in frequency could be explained by the existence of resonating frequencies depending on structural characteristics of the examined system: mechanical (i.e. molecular length) and electrical (stochastic resonance) [8, 9]. A different view considered the channels as the non-linear "transducer" of EM external signals [10]. The induced oscillation of the membrane potential could influence the voltage sensing charged groups of the protein macromolecules that form voltage-sensitive ion channels; as a consequence a modification of the channel opening and closing probabilities is obtained. An alternative approach, has been proposed based on Finite States models [11, 12] (Markov or chemical kinetics). These models start from the evaluation of the current flowing through the single channel. This approach has been used in simulating the action of EM fields on each single channel.

Dynamical cell processes that underlie detection and amplification of environmental stimuli, are recognized to be organized through feedback coupled biochemical reactions. [13].

It has been suggested that solitons provide an explanation of the way signals are conducted through membranes. A chemical event, e.g. the arrival of a molecule on the receptor site, creates a soliton that propagates along the protein and through the membrane supplying energy for the second chemical event inside the cell. It is suggested that this process may be altered by the presence of external fields [14].

Membrane modelling: Referring to Hodgin&Huxley model for the neuronal membrane, some authors developed non-linear circuital models for this biological level [15-17]. Substantially they are composed of a circuital scheme representing the ionic currents crossing the membrane: each component in the circuital representation corresponds to a certain kind of current, due to a specific membrane channel family. These models are intrinsically able to demodulate ELF modulating components in an external signal but their limits are in the carrier frequency they detect: time constants involved in these processes are of order of milliseconds and the membrane capacitance shortcuts frequencies higher than some MHz.

A different approach has been proposed hypothesising a cooperative interaction arisen from different kind of excitation, each elective for different component or function of the cell membrane [18, 19].

Whole Cell: When dealing with highly complex biological structures as cells, a well defined biophysical model is hardly to achieve; therefore models proposed in literature focus their attention on the exchange processes of the cell with the external region, that take place by means of biochemical interactions. In this way a biochemical signalling path is taken into account in order to model metabolic functioning of the cell [20].

A unifying methodology

In this second part, a methodology will be proposed in order to include, in a structured path through the biological scale of complexity, all the approaches previously exposed.

A preliminary step consists in resolving the dosimetric problem that is the evaluation of EM. field at cellular level. In this work this microdosimetric procedure will not be explained in details [21].

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. In this way the whole system could be sensitive to EM fields in the large range of frequencies implied by any kind of exposure. The most microscopic level (ion binding) is characterised by time constants that lead the model to be sensitive to fields up to tens of Gigahertzs. Effects of such fields are the output of the model and input to the successive one, which in turn will have its outputs influenced by the field with respect to the physiological conditions. This approach permits to study effects of EM fields for a large range of frequencies on biological structures that, because of their dimensions, are characterised by high time constants. In fact it is possible to evaluate their interactions with the fields by means of the sensitive models of the microscopic levels. It is important for each step to identify an "output" variable of biological interest, so that relative changing of its value due to the EM exposure can be identified as the measure of the biological effectiveness of the exogenous field.

The authors applied this methodology in modelling a neuronal cell [22 and 23], resulting in a unified scheme for a single neuron. Two are the fundamental ideas:

A. First is to integrate the quantum modelling of the system constituted by a ligand ion (calcium ion: Ca^{2+}) and a cell membrane protein receptor (calmodulin) described in [6] in the analysis of a protein channel activity obtained by means of stochastic models of the channel as those developed in [11].
B. Second one consists in linking together the Markov modelling described for voltage dependent channels [11] with the membrane model [17] described in previous paragraph.

Implementation of the first idea has been presented in [22], where the calcium-controlled small conductance potassium channel (SK) is considered. SK channels are coassembled complexes of four pore-forming chains of Calmodulin (CaM). Experimental data support a model for channel activation in which Ca^{2+} binding to CaM induces conformational rearrangements in CaM that result in channel gating. It has been possible to assign an association level for the Ca^{2+} ion in each of the states through which the SK channel has been modelled by means of a Markov Model. Remembering the channel is controlled by four CaMs it has been possible to refer to a kinetic diagram for a single CaM whose kinetic parameters have the same physical meanings of the parameters provided by the ion-binding model.

Second idea has been further developed in [23, 24]. Here each branch in the circuit corresponds to the contribution of a large number of channels of the same kind. Neuronal modelling is developed through the integration with lower level models that can be gained 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 Markov Model approach.

It is important to note that a further result has been obtained: output parameter of the membrane model is the membrane voltage on which depends the metabolic force being one of the input parameters of the ion-binding model. In this way two feedback mechanism has been modelled: one for membrane voltage and the other one for Calcium concentration. Ability to adapt to external and physiological environment changes is the most specific peculiarity of biological systems and the real difficult characteristic to take into account, for this reason this model seems to be of particular interest.

Conclusions

In this work a classification has been proposed for available models of interaction of EM fields with cell membrane structures.

An integrated model from interaction with ions to cell membrane modifications has been proposed.

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