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Modelling of the interaction between a ns electrical pulse and a biological cell

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Abstract

Ns electrical pulses can modify the membrane of some biological cell organites without noticeably altering the plasma membrane. The objective of this work deals with the development of numerical tools in order to compute and understand the influence of different parameters on the phenomena arising in the cell.

1. Introduction

Biological assemblies are known to be highly sensitive to electrical perturbations. High voltage pulses of microsecond or millisecond duration can interact with living organisms, allowing for example the modification of the cytoplasmic membrane structures in biological cells by processes. Such a modification is called electro-permeabilization or electroporation [1].

New applied developments are running in the fields of Biotechnology and clinical drug delivery. The safe use of these approaches requires a deep knowledge of the involved space and time dependent mechanisms. Both molecular dynamics and preliminary experimental approaches indicate that the key steps are present on the nanosecond time scale. Very recently, it was found that electromagnetic pulses of even shorter duration (order of 10 nanoseconds) can also modify the membranes of biological cell constituents such as the nucleus or the mitochondria without noticeably altering the plasma membrane [2], [3]. Results from the literature show that cancerous tumors can be reduced in size by applying a limited number of voltage pulses with very fast rise time and amplitude [4]. The published work also demonstrates very promising potential applications of these ultra short high voltage pulses for gene transfer.

The work will investigate the effects of the ultra short electromagnetic pulses on the behaviour of biological cells through experimental and modelling studies. Our investigations will be conducted with pulses of duration ranging from a few hundreds of picoseconds to a few tens of nanoseconds, with voltage amplitudes up to several hundreds of kilovolts per centimetre.

The general objective of this task deals with the development of the numerical basic tools in order to compute the different phenomena arising in the cell when exposed to a ns electrical pulse and to understand the influence of the main physical and electrical parameters on these phenomena.

2. Methods

The different phenomena arising in the cell when exposed to an electrical pulse are related to the pulse itself (type, field strength, pulse duration, rise and decay times), to the electrical properties of the cell, and to its geometric configuration (shape, type, contents).

Figure 1 depicts the simplest model of biological cell which consists of cells contents or a cytoplasm surrounded by a very thin, low-conductivity membrane, and placed in a conductive medium. Most cells in tissues are connected by gap junctions that permit some substances to be exchanged between cells, providing local cell communication. These gap junctions connect electrically the cells, thus increasing the sensitivity of the cell to externally applied electric fields.

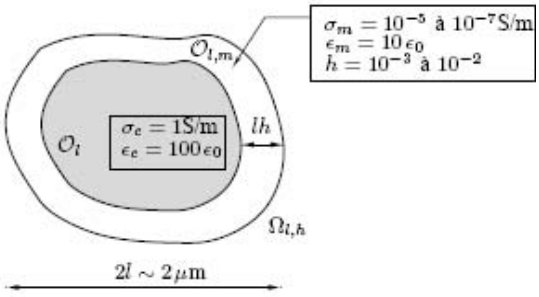

Figure 1 Cross section of simple procaryotic-type cell, with dimensions and electrical properties values.

Several approaches to simplified modelling of cells have previously been reported. For spherical cells, the transmembrane potential (TMP) can be estimated analytically by solving Laplace's equation [5]. The leaky cable model has also been used, such as R-C electrical network modelling. Since these approaches do not accurately predict the frequency behaviour of the cell [6], we will develop another approach, more rigorous, based on the numerical solving of the Maxwell's equations using both finite Differences Time Domain (FDTD) method and Finite Element Time Domain (FETD) method. This type of modelling is an interesting problem from both mathematical and numerical points of view: there is a high contrast

between the conductivities (10-7 S/m to 1 S/m) and between the dimensions (the membrane thickness is about 5 nm, compared to a 1 to 10 μm-diameter).

3. Results

In Figure 2, the frequency response of circular simple cell is shown. It is computed with a dielectric formulation in the frequency domain. The circular cell behaves as a low-pass filter and has one relaxation frequency. The curve describing the frequency behaviour of the cell for two values of membrane conductivity. In Figure 3, the time response of a spherical cell is shown for two conductivities of the extracellular medium.

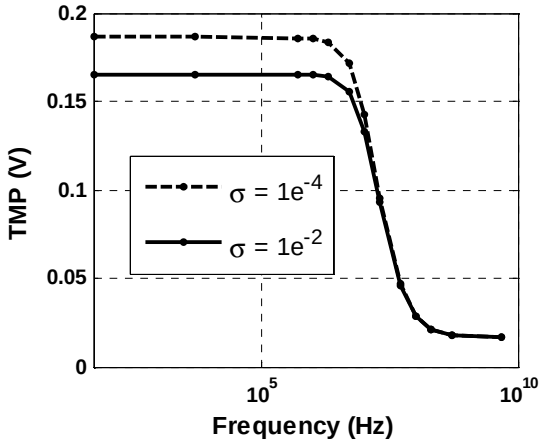

Figure 2 Frequency response of a spherical cell.

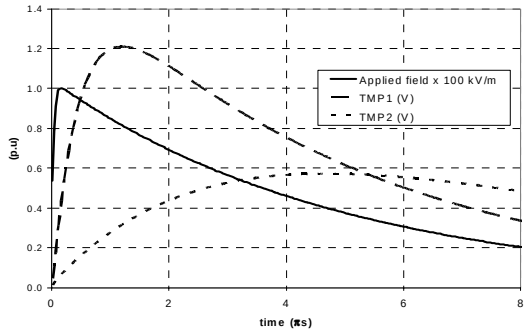

Figure 3 Transient applied field E (impulse wave) and the simulated TMP for two conductivities of extracellular medium: tmp1 (σ = 0.3 S/m), tmp2 (σ = 0.01 S/m).

4. Conclusion

Since the membrane is a really thin layer (5 nm compared to 1 μm) having a low conductivity (10^{-7} S/m against 1 S/m), its volume modelling requires a large mesh density in order to obtain accurate results. It will lead unavoidably to some limitations due to the large number of unknowns. That is the reason why an equivalent surface model will be developed, on the basis of previous works [7]. First results have already been obtained in 2D and in frequency domain [8]: they have to be generalized in 3D and in time domain, and implemented in both FDTD and FETD approaches.

From the biological point of view, it is interesting to characterize the specificity of the answers of each organelle to the ns pulse. Two effects may be obtained: the permeabilization of the mitochondria and the permeabilization of the nuclear envelope. These alterations will be assessed by using tools of cell biology. However only the consequence of the permeabilization may be experimentally revealed, and the transient phenomena can not be visualized. Comparison of numerical results with experimental results will finally be drawn in order to validate the numerical modelling. From this point, it will then be possible to have a good idea of the transient phenomena which will be made accessible by the modelling.

5. References

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