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Advances in 3D realistic modeling of cells for microdosimetry studies on PEF exposure

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Biomedical applications based on pulsed electric fields (PEFs) with µs duration and kV/m intensities (known as µsPEFs) are utilized to cause cell membrane electropermeabilization by creating a temporary increase in transmembrane potential (TMP) and enhancing membrane permeability, to allow the transport of genes, ions, and drugs across the membranes [1]. Recently, due to the growing need for efficient treatments for nerve diseases such as Parkinson's and spinal cord injury (SCI), researchers are directing their efforts toward the use of stem cells that can be differentiated through electrical stimulation [2].
In this context, an innovative approach is presented by the European RiseUp project, funded by the Future and Emerging Technologies (FET) Open of Horizon Europe Program 2020 [3]. The project's goal is to achieve neuronal regeneration after SCI through a biocompatible implantable device to electrically stimulate stem cells able to control their differentiation. In this regard, microdosimetric techniques are needed to give the distribution of the induced electrical quantities at the cell and subcellular levels, whose reliability lies in the use of cell models more and more realistic [4].
In this context, authors present a microdosimetric study related to µsPEFs application on stem cells, using advanced 3D realistic cell models including subcellular structures and internal organelles.
The 3D reconstruction process here fine-tuned is a semi-automatic procedure, composed of four steps: (i) image acquisition of cells decorated with different dyes to highlight selected internal organelles, using a confocal microscope (images collected by varying the z-quote); (ii) image pre-processing to improve the intensity contrast; (iii) segmentation step, using 3D Slicer v. 4.11, with the use of appropriate parameters, and 3D surface reconstruction of cell model; finally (iv) the model is optimized in Comsol Multiphysics v. 6.0.
For the microdosimetric study, the 3D model of the exposure system consists of two coplanar gold electrodes, placed on a polylactic acid (PLA) base, and covered by a culture medium. The 3D model of a stem cell with three compartments (cytoplasm, ER, and nucleus) is placed on top of the electrodes (nearly touching them). Dielectric properties used in the model to solve the EM problem with the AC/DC module of Comsol, are reported in [4]. A 100 µs pulse is delivered assuring an electric field of 50 kV/m between the electrodes.
Results show that the induced E-Field and TMP on cell membranes strictly depend on two parameters: the vicinity of the electrodes (due to the high non-uniformity of the E-field distribution generated by the system) and the irregularity of the cell compartments' shape [4]. In particular, close to the electrodes, TMP reaches values well above the electroporation threshold (1 V) [4]. While, thanks to the 3D realistic cell modeling, it is possible to provide an accurate spatial distribution of the E-field at the intracellular organelles level: for example, significant E-field variation, i.e. up to 70% on different regions of the ERplasm membrane, are present due to the irregular shape and to the corrugated surfaces of such subcellular structures. Data confirm the possibility to electroporate the stem cell using the µsPEF generated by the coplanar system and underline the importance of using realistic cell models with internal organelles to accurately validate experimental results with reliable numerical studies.

References

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