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To cite this article: Matej Kranjc et al 2013 J. Phys.: Conf. Ser. 434 012086

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Magnetic resonance electrical impedance tomography for determining electric field distribution during electroporation

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Abstract. Electroporation is a phenomenon caused by externally applied electric field to cells that results in an increase of cell membrane permeability to various molecules. Accurate coverage of the tissue with a sufficiently large electric field presents one of the most important conditions for successful membrane permeabilization. Applications based on electroporation would greatly benefit with a method for monitoring the electric field, especially if it could be done in situ. As the membrane electroporation is a consequence of an induced transmembrane potential, which is directly proportional to the local electric field, we have been investigating current density imaging and magnetic resonance electrical impedance tomography techniques to determine the electric field distribution during electroporation. In this paper, we present comparison of current density and electric field distribution in an agar phantom and in a liver tissue exposed to electroporation pulses. As expected, a region of increased electrical conductivity was observed in the liver tissue exposed to sufficiently high electric field but not in agar phantom.

1. Introduction
Electroporation is a phenomenon in which cells exposed to externally applied electric field of an adequate strength and duration increase their membrane permeability to various molecules, which are otherwise deprived of transmembrane transport mechanism [1–3]. Clinical applications, such as electrochemotherapy and non-thermal irreversible electroporation, both potent procedures used in solid tumor treatment, are being successfully introduced into clinical practice [4,5]. Therapies success depend on adequate electric field distribution in the tissue, which is currently determined by electrode positioning and by applied electric pulse amplitude, both obtained by treatment planning [6–8]. Even though treatment planning has already proved to have a great potential, its applicability is currently limited by conductivity data of tissues, especially within the tumor where heterogeneous and nonlinear conductivity was observed [9]. Poorly determined tissue conductivities and inaccurate electrode positions can result in an insufficient electric field coverage of the tumor and thus in a suboptimal treatment outcome [10].

As the membrane electroporation is a consequence of an induced transmembrane potential, which is directly proportional to the local electric field, we propose current density imaging (CDI) and magnetic resonance electrical impedance tomography (MREIT) techniques to determine the electric field distribution during electroporation [11]. CDI is a magnetic resonance imaging method for acquiring current density distribution inside conductive samples by measuring magnetic field changes
caused by applied current [12,13]. Tissue conductivity can be obtained by MREIT, a technique used for reconstruction of electrical conductivity inside a tissue by means of current density [14,15]. As the measurement of current density and electrical conductivity is performed during electric pulse delivery, determined electric field distribution includes all changes, which occur in tissue due to electroporation. In this paper we present comparison of current density and electric field distribution in an agar phantom and in a liver tissue exposed to electroporation pulses. We examined differences in the obtained current density and electric field distribution of non-biological tissue (agar) and biological tissue (chicken liver).

Electroporation applications such as electrochemotherapy and non-thermal irreversible electroporation would greatly benefit from conductivity imaging method such as MREIT. Reconstruction of electrical conductivity during electroporation pulse delivery together with measuring current density distribution using MREIT and CDI, respectively, would enable much needed in situ determination of an electric field distribution thus increasing and assuring the effectiveness of electroporation based treatments.

2. Materials and methods

All experiments were done in an acrylic glass container as shown in figure 1. The agar phantom was made of agar powder (Kemika, Croatia), 0.9 % NaCl saline solution (B. Braun, Germany) and distilled deionized water (B. Braun, Germany).

Evaluation of ex vivo monitoring of electric field distribution was done on a fresh chicken liver tissue. Temperature of the tissue was maintained at 4°C before the beginning of experiment when they were allowed to adjust to the room temperature. Tissues were sectioned in flat and cylindrical shaped samples with a diameter of 20 mm and placed in an acrylic glass container. Four needle electrodes measuring 1 mm in radius made of platinum-iridium alloy were inserted through the cover of the acrylic glass container into the phantom as shown in figure 1.

![Figure 1: Container (a) used in the study was made of the acrylic glass with four holes for electrodes (b). Either agar phantom or liver tissue (c) was placed inside. The container was inserted in the 25 mm RF probe (d).](image)

Electric pulse generator used for delivering electroporation pulses into the agar phantom and liver tissue was customized Cliniporator Vitae (IGEA, Carpi, Italy). The electric pulses with an amplitude of 1500 V were delivered between the diagonal electrodes of the imaging sample in sequences of four 100 μs long pulses separated by 100 μs intervals. Current density distribution and electrical conductivity were obtained in all experiments by the two-shot RARE current density magnetic resonance imaging sequence [16] and MREIT J-substitution algorithm [15], respectively. When both, current density distribution and electrical conductivity were obtained, Ohm’s law was used for calculating electric field inside the imaging sample as described in [11].
3. Results and discussion

As shown in figure 2, current density and electric field distribution within agar and liver during application of electroporation pulses were obtained successfully.

Figure 2: Electric current density distribution presented as a vector field (a and c) and electric field distribution (b and d) in agar phantom and liver tissue obtained by CDI and MREIT, respectively. Agar phantom and liver tissue were exposed to four 100 µs long electric pulses with an amplitude of 1500 V. Pulses were delivered between two needle electrodes (marked with + and −).

When we examined and compared results obtained in agar phantom and liver tissue we observed considerable differences, especially in the current density distributions (figure 2a and 2c). Current density distribution was uniformly distributed throughout the agar as dielectric properties of agar remained unchanged in spite of high electric field applied. On the contrary in the liver tissue, current density distribution was the highest between the electrodes where electrical conductivity was increased due to tissue changes associated to local tissue electroporation. Differences between electric field distributions (figure 2b and 2d) can be seen in pronounced alteration of field’s intensity in the case of the liver tissue (figure 2d). We stipulate this is a consequence of a dynamic process during which electric field is changing due to increasing tissue conductivity. Similar alterations can also be observed in sequential numerical modelling of electroporation [17].

As there is a great need for in situ determination of electric field distribution during electroporation pulse delivery, magnetic resonance electrical impedance tomography together with current density imaging could be of significant help in monitoring of electroporation based applications. The proposed method has been demonstrated to be feasible for determination of electric field during electroporation [11,18] and therefore a next step towards in vivo experiments can be taken.
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