4D Electroacoustic Tomography (EAT) for Monitoring Electroporation Therapy

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ABSTRACT

Real-time monitoring of deep-tissue electric field distribution during electroporation therapy remains a significant clinical challenge. Electroacoustic Tomography (EAT) addresses this need by detecting ultrasound waves generated during pulsed electric energy induces cell membrane poration. Using a three-dimensional matrix array transducer, we demonstrate EAT's capability to visualize volumetric electric field distributions in real-time. A comprehensive database of EA signals was developed using square pulses ranging from 600-1000V with pulse widths of 60-150ns. To validate the 4D imaging capabilities, discrete pulse trains were delivered from 50 to 1000V at 50V increments, with universal back projection reconstructions effectively visualizing the source pressure distribution. Dynamic reconstructions clearly demonstrate electric field strength growth correlating with voltage increments. Our system's clinical viability has been validated through both in vivo murine studies using stable ablation energy and in vitro vegetable model experiments. Three-dimensional correlation between ablated regions and imaging intensity across multiple depths yielded structural similarity index (SSIM) values greater than 0.85, confirming EAT's ability to provide accurate dose maps. This work represents the first volumetric reconstruction of experimental electroporation using a planar ultrasound transducer system, establishing EAT as a viable deep-tissue monitoring modality for therapeutic electroporation procedures.

Keywords: Electroacoustic tomography, Electroporation, Pulsed ablation, Irreversible electroporation, In vivo dosimetry

1. INTRODUCTION

Due to the widespread adoption of electroporation, there has been growing interest in a deep-tissue electric field monitoring system. Electroporation therapy works to ablate a target region by generating an electric field of different energy to induce either reversible or irreversible cell membrane poration. This treatment methods differ based on the parameters of the applied electrical pulses (amplitude, pulse duration, repetition rate and number of pulses). By tuning these parameters, researchers can induce a targeted cell fate; weaker pulses can result in reversible (RE) membrane poration, whereas stronger ablations can cause cell death, known as irreversible electroporation (IRE). This therapy method has a wide range of applications from cancer ablation treatment to small porations for gene therapy[1-2].

Conventional IRE ablation treatments are limited by significant drawbacks with unintended thermal damage and severe muscle contractions. More recently, ultra-short pulse duration in the nanosecond range has shown much greater potential for clinical translation boasting reductions in Joule heating, oxidative damage, and muscle contraction. Ultra-short, pulsed IRE has even demonstrated tissue selectivity based on conductivity.

The pulsed electric energy induces thermoelastic expansion, generating ultrasound known as electroacoustic waves. Electroacoustic Tomography (EAT) is a novel *real-time* 3D ultrasound imaging method that can be used to visualize the electric field generated during pulsed electrical energy deposition[3]. Currently, clinical methods often result in incomplete and imperfect ablations. Simulation guided electroporation procedures have been shown to yield inconsistent results[4-5]. Our goal is to give clinicians verification that the applied ablation energy will result in a consistent targeted cell fate. By validating the electric field strength intraoperatively, electroacoustic tomography can offer a closed loop design for ablation procedures, leading clinical practice and improving clinical results. This technology effectively overcomes limitations inherent to existing approaches, providing precise real-time characterization of energy delivery and distinct visualization of treatment boundaries.

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2. METHODS

Electroacoustic tomography (EAT) is the detection of electric field distribution in soft tissue through measured acoustic pressure waves. During ablation, high-voltage electric pulses induce the emission of broadband ultrasound waves via thermoelastic expansion. Under the assumption of thermal and stress confinement, thermal diffusion and stress propagation during pulse delivery are negligible, resulting in an initial acoustic pressure that can be expressed as[3,6]:

$$p_0(r,t) = \frac{\beta(r)\sigma(r)}{\kappa(r)\rho(r,t)C_v(r)} E(r)^2 g(t) \tag{1}$$

where $\beta(r)$ is the thermal expansion coefficient, $\sigma(r)$ denotes the electrical conductivity, $\kappa(r)$ is the isothermal compressibility, $\rho(r,t)$ is the mass density, and $Cv(r)$ is the specific heat capacity at constant volume. Here, $E(r)$ represents the electric field strength at location r, and $g(t)$ denotes the temporal profile (characterized by shape and duration) of the applied electric pulse. Acoustic waves are then emitted from thermoelastic expansion within the tissue. This process is governed by the acoustic wave equation, which can be solved with Green's function formalism[3].

Figure 1 is an illustration of the 4D electroacoustic system. To acquire EA signal, a high-voltage nanosecond pulse generator (PGR-10KV-50R-01, Montena, Switzerland) is used to deliver treatment and trigger the ultrasound acquisition. Pulse events were synchronized by detecting triggers from the pulse generator and transmitting them to a delay generator (DG535, Stanford Research, USA) to output standard TTL signals for precise timing of data acquisition. The 256 ultrasound channels are amplified and output as RF data to the host computer for post-processing and reconstruction in MATLAB. By using a two-dimensional matrix array transducer, we demonstrate the ability for EAT to visualize the three-dimensional volumetric electric field distribution. To develop a database of observations, the pulse generator was used to deliver energy to two clinical electrode needles (20400107, AngioDynamics, USA) within a range of amplitude and pulse width parameters [600-1000V] [60-150ns]. The emitted ultrasound waves were observed with a custom 256-channel transducer array (Telemed) connected to a 256-parallel channel DAQ (Photosound)[7]. To study the differences between ultrasound emissions through several different media, we first conducted experiments in saline and then soft tissues of varied acoustic and conductive homogeneity. Delivery methods of pulsed ablation often vary by application and target. For IRE cancer treatments, nanoknife needles are used for minimally invasive pulse delivery; whereas, for intracardiac ablation procedures, contact electrodes at the end of catheters are used for ablation. All treatment methods show great potential for real-time monitoring with electroacoustic tomography.

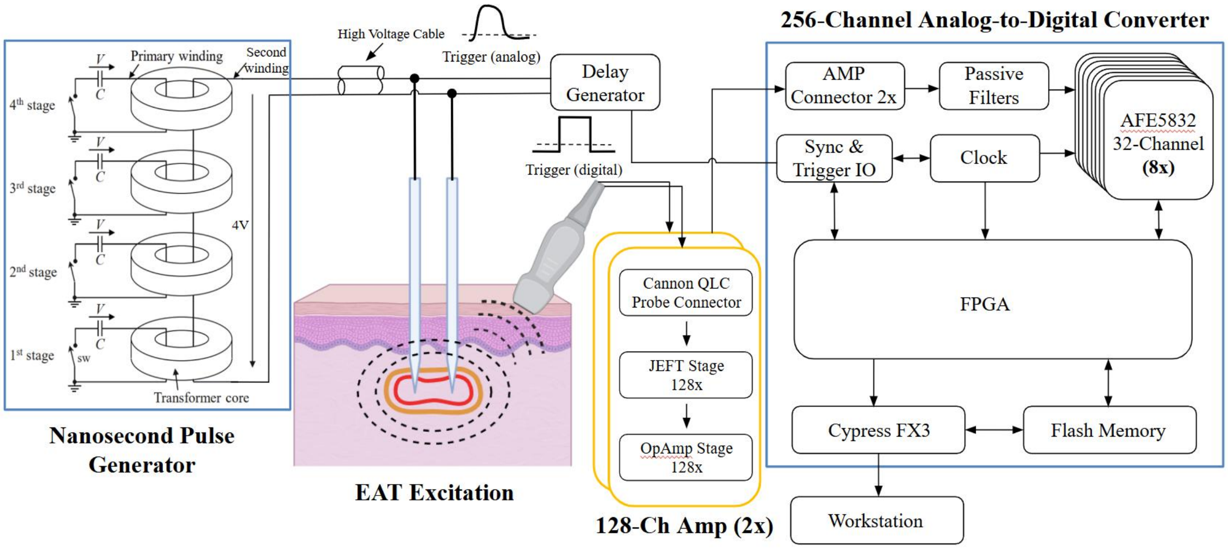

Figure 1. 4D Electroacoustic Tomography (EAT) system diagram.

3. RESULTS AND DISCUSSION

Volumetric frames are reconstructed using back-projection method. These volumes can be used to define the dimensionality of the effective electric field, allowing clinicians to be more certain about the resulting cell fate when ablating volumes. In Figure 2, we can see an idealized EA acquisition setup built in COMSOL Multiphysics software. On the right side of Figure 2, we can see the back-projected volume that was captured with this setup. This electroacoustic signal was captured by averaging 100 pulses with an ablation amplitude of 800V and pulse width of 60ns. At 40Mhz sampling frequency, this system is capable of generating precise volumetric reconstructions with a single ablation pulse. Here we can see the advantage of volumetric tomography. Post-processing allows the operator to rotate the resulting volume, offering integral perspectives of the electric field energy.

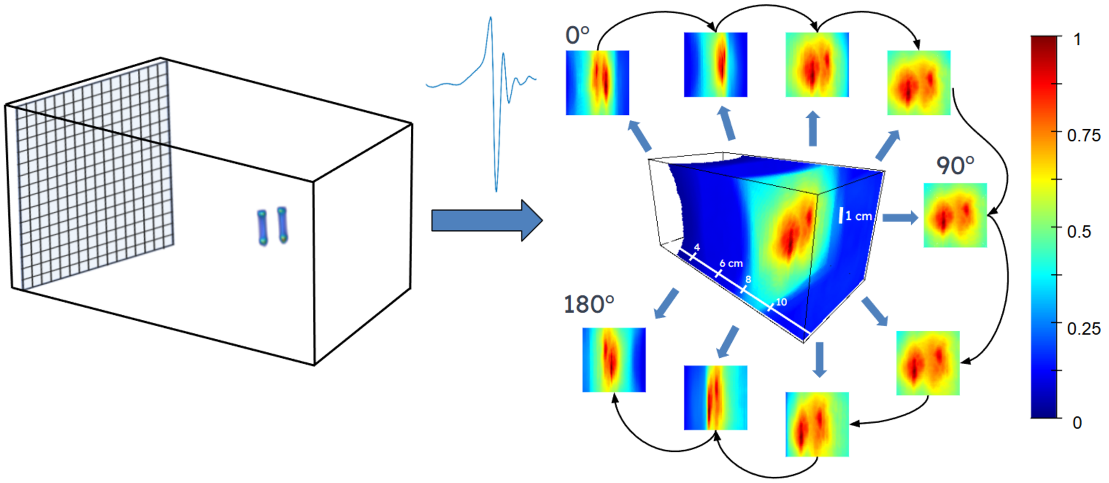

Figure 2. 3D Electroacoustic Tomography (EAT) universal back projection reconstruction of two electrodes in saline. EAT signals are acquired per pulse and are then averaged to improve signal clarity. Reconstructions are obtained through universal back projection methods. Pulse Parameters: 100 pulses of 60ns pulse duration and 800V pulse amplitude.

To demonstrate the *real-time* capabilities of EAT, we sought to receive ultrasound from a dynamic experiment that changes over time. To obtain this electroacoustic signal, a large frame buffer was filled by delivering discrete pulse trains from 50 to 1000V at increments of 50V. The resulting signal buffer contained information for 1900 unique electroporation pulses which can be reconstructed into 1900 unique volumetric frames. After separating the signal by the electroacoustic pulse amplitude and averaging them, we were left with 19 reconstructed intensity maps that represent each ablation pulse amplitude. A subset of these reconstructed volumetric frames can be seen in figure 3.

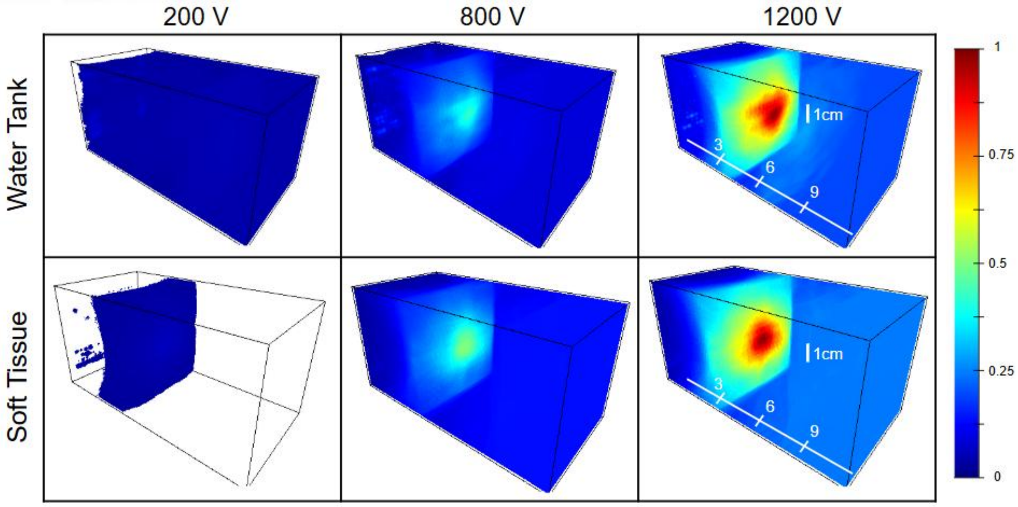

Figure 3. 4D EAT volumetric frames. Two electrodes were placed in the defined medium and the electric amplitude was increased over time in 100 pulse trains. RF data was reconstructed to visualize the electric field dose map at each discrete pulse amplitude.

To correlate the intensity of the electroacoustic dose maps with histopathology slices, we use an in vitro vegetable model, in this case a russet potato. Vegetable models have been shown to be great candidates for irreversible electroporation experiments because the flesh of the potato has levels of enzymatic action that makes it viable for TTC histopathology staining[8]. For this study, we sliced and stained a cylindrical volume of potato that was ablated at 4000V and 160ns pulse duration. Then, the lethally ablated regions were measured and correlated to the EAT volume at matching depths. This imaging method showed SSIM above 0.85, suggesting strong correlation with the ablation zone. These results support the idea that electroacoustic signals are produced by the electric field interaction with the target tissue.

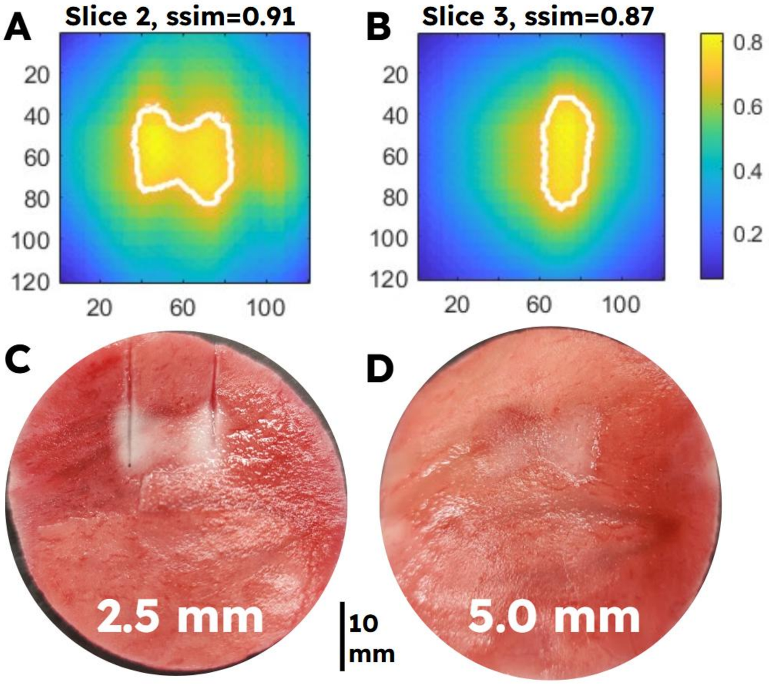

Figure 4. In vitro potato correlation. A reconstructed EAT volume was compared to the observed ablation zone within a potato. (A-B) Projections of reconstructed 3D EAT at defined depths. (C-D) TTC stained potato slices of ablated volume at defined depth; the white region indicates irreversibly ablated region of tissue.

4. CONCLUSION

Electroacoustic tomography is a promising emerging imaging technique that holds significant potential for real-time, in vivo dose monitoring during electroporation therapy. By correlating the electroacoustic signal to the ablative electric field strength, effective dose maps can address the clinical need for an intraoperative validation method. Real-time volumetric reconstructions of electric field energy can give interventionists the tools to better understand the underlying treatment. By support the growth of electroporation therapy, electroacoustic tomography can make a broad impact across the scientific and medical fields, improving protocols for cancer, cardiac, and cranial procedures. Incorporating this imaging method into electroporation therapy will improve treatment precision and enhance therapeutic outcomes, this would reduce the risk of incomplete ablations, reducing the burden on patients and clinicians alike.

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