MODELING, CONSTRUCTION AND CHARACTERIZATION OF A 66-kHz ULTRASOUND TRANSDUCER FOR CARDIAC EXPERIMENTATION

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ABSTRACT
In cardiology, diagnostic ultrasound is well established, whereas there is an unexplored potential for therapeutic applications. Searching for alternative devices that do not apply high intensity electric fields to the heart is interesting because these fields can damage myocytes due to electroporation, generating Ca2+ overload and even cell death. Power ultrasonic transducers, capable of generating high intensity acoustic fields, might be able to interfere with the cardiac activity. Modeling, construction and characterization of a 66-kHz ultrasound transducer are described. Experimental and theoretical acoustic impedance curves show good agreement. Power characterization confirmed the transducer stable behavior upon high electric drive. The transducer starts to produce cavitation when excited by an input voltage of 37Vpp. The ultrasonic transducer driven by a 25Vpp electric voltage (peak negative pressure of approximately 2.1kPa) was used to apply 66-kHz bursts to a perfused isolated rat heart, generating proarrhythmic effects. This is promising when it comes to therapeutic applications of ultrasound in cardiology, since arrhythmia-inducing agents might as well be antiarrhythmic. The developed transducer will be used for further investigation aiming to find a specific set of acoustical parameters able to interfere in the heart rate without damaging the cardiac tissue.

KEY WORDS
biosensors and transducers, ultrasound, therapy, cardiology.

1. Introduction
Ultrasound is a reliable and noninvasive technique that can be applied in medicine for both diagnosis and therapy. In diagnostic ultrasound, low intensity acoustic waves safely investigate biological tissues bringing back relevant information. Higher ultrasound intensities can alter tissue characteristics, and this is of interest for therapeutic applications, when the occurrence of bioeffects is desirable for tissue healing.

Specifically relating to cardiology applications, diagnostic ultrasound is highly recognized and accepted, while there is great potential for therapeutic applications. Examples are cardiac gene therapy [1], thrombolysis for acute coronary syndrome [2], ablation for treating arrhythmias [3], drug-free therapy for heart failure [4], ultrasonic pacing, as an alternative to electrical pacemakers [5], and ultrasonic defibrillation, as an alternative to electrical defibrillator [6].

Finding alternatives to devices that apply high intensity electric fields is relevant because these fields can produce reversible or permanent damage due to electroporation, generating electrical and contractile alterations, and even Ca2+ overload and cell death [7] [8]. Power ultrasound transducers, capable of generating high intensity acoustic fields, have great probability of producing effects on the cardiac activity. The objective of this work is to develop a power ultrasonic transducer to be applied in cardiac experimentation in rats. Transducer modeling, construction, characterization and preliminary application are described.

2. Methodology
2.1 Modeling, Construction and Characterization
The developed transducer was axisymmetrically modeled by using the finite element package ANSYS/Multiphysics. The finite element method is a generic numerical technique to find approximate solutions to partial differential equations with boundary conditions describing engineering problems. It divides the structural geometry into simpler elements, creating a mesh. For each element, the differential equations are solved, resulting in a final solution to the problem as a whole.

A finite element analysis can be divided into three main stages: pre-processing, solution and post-processing. During the pre-processing, the problem is defined by determining the geometry (Figure 1), the material properties (PZT-4 and aluminum), the element type (PLANE13 for piezoelectric and PLANE42 for structural element), the element dimension (\(\lambda/20\)) to be used to generate the mesh, and the boundary and loading conditions. Proceeding to the solution, the software solves a set of equations to obtain the nodal solutions. In the last
stage, post-processing, results for displacement distribution (structures), and for electric potential (piezoelectric elements) can be observed [9].

The Langevin transducer was modeled and constructed with two PZT-4 piezoceramic rings (Morgan, Fairfield, NJ, U.S.A.), with 25-mm external diameter, 12-mm internal diameter and 3.15-mm thickness, sandwiched between two aluminum structures and prestressed at 30 MPa. One of the aluminum masses was combined to an acoustic amplifier.

Once built, the transducer was conventionally characterized using an impedance meter (HP, 4194A, Palo Alto, CA, U.S.A.). It was also characterized with power application, using a scanning system that sweeps both frequency and electric voltage, available at the Acoustics Institute - CSIC, Madrid, Spain. The advantage of power characterization, as opposed to conventional impedance meter that apply only 0.1V, is that it simulates the real operation of power transducers. Exciting transducer with high electric voltages might generate instabilities due to heating effects. The resonance frequency and the electrical conductance are expected to drop for higher voltage inputs [10].

2.2 Application

The developed transducer was tested on a 12-month-old female Wistar rat heart with atria removed. This preliminary experiment was conducted in the Cardiovascular Research Laboratory at the State University of Campinas (LPCv/UNICAMP), Brazil. The experimental protocol (#1517-1) was approved by the Commission for Ethics in Animal Use of the Biology Institute (IB/UNICAMP). The rat was maintained at controlled temperature and 12-hour light/dark cycles in the Biomedical Engineering Center (CEB/UNICAMP), receiving food and water ad libitum. Euthanasia was performed through physical disruption of brain activity, caused by concussion, followed by exsanguination. Then, thoracotomy was carried out for removal of the functioning heart.

A cylindrical acrylic chamber was built to place the isolated heart. It had a removable base containing the cannula through which the nourishing solution flowed (Figure 2).

The aorta was cannulated into the inverted chamber base (Figure 3a) and the heart was rapidly perfused by a heparinized modified Krebs-Henseleit nutrient solution (composition: 115mM NaCl; 4.6mM KCl; 1.5mM CaCl$_2$.2H$_2$O; 1.2mM KH$_2$PO$_4$; 0.5mM NaHCO$_3$; 1.2mM MgSO$_4$.7H$_2$O; 11.1mM glucose). A stainless steel hook was inserted in the ventricle apex for force measurement, the chamber wall was screwed to the base, and the whole system was turned right side up. A cotton thread tied to the hook was connected to the force transducer, to which a 1.5-gf preload was applied. Using a gravity-driven flow system, at approximately 8 ml/min, carbogen-saturated (95%O$_2$ / 5%CO$_2$) Krebs-Henseleit solution at 30ºC was delivered to the spontaneously beating heart through the aorta (retrograde perfusion). The efflux solution in which the isolated heart remained immersed had the level maintained by a drainer connected to a vacuum pump. After allowing for a 30-minute stabilization of contractions, the ultrasound application was initiated (Figure 3c).
Figure 3. Experimental preparation. (a) Cannulating aorta on the inverted chamber base; (b) Isolated heart under retrograde perfusion, with the apex located on top, connected to the force transducer; (c) Ultrasound application through the acoustic window.

A 25V pp RF signal was used to continuously excite the 66-kHz ultrasonic transducer, which was coupled with gel to the chamber acoustic window. The isometric force transducer was previously calibrated by recording the polygraph feather deflection in response to a 0.5g mass for two different sensitivities (S50 e S100). The heart contraction strength was registered by the polygraph, which was coupled to the force transducer. The systolic tension and the heart rate were monitored. The block diagram represented in Figure 4 summarizes the experimental setup used to apply ultrasound to the heart.

3. Results

Loading the ANSYS data for electrical charge as a function of frequency into MatLab and differentiating with respect to time (i.e., multiplying by the imaginary angular frequency $j\omega$) results in the electric current. To obtain the electrical impedance, the same electric voltage applied during the simulation is divided by the electric current. The theoretical electrical impedance curve for magnitude as a function of frequency is displayed in Figure 5. The transducer resonance frequency is 66kHz, where the magnitude of the electrical impedance is minimum.

![Figure 4. Set up block diagram for in vitro preliminary test.](image)

![Figure 5. ANSYS: Theoretical electrical impedance. Magnitude x frequency.](image)
The constructed Langevin transducer, presented in Figure 6, was conventionally characterized using the impedance meter. The experimental electrical impedance curve for magnitude as a function of frequency is shown in Figure 7. The resonance frequency agrees with that previewed by the theoretical results.

![Figure 6. Ultrasound transducer (a) without and (b) with a delrin protection.](image)

![Figure 7. Experimental electrical impedance. Magnitude x frequency.](image)

Power characterization was performed in air and the results are expressed as electrical conductance (brightness) as a function of both frequency and the applied voltage (Figure 8). As the applied voltage rises, the resonance frequency is expected to drop due to losses. In fact, this happened, but to a little amount. Thus, the transducer has a very stable behavior at high electric drive, both in relation to electrical conductance and in relation to resonance frequency.

![Figure 8. Power characterization in air. Experimental electrical conductance (brightness) as a function of frequency and input voltage.](image)

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Following the power characterization, the transducer was tested for cavitation threshold. The transducer face was immersed in water and the input voltage was gradually increased. Cavitation started at a 37V<sub>PP</sub> input voltage.

In order to check the developed ultrasonic transducer applicability, it was preliminarily used on an isolated heart experiment. At approximately 2kPa peak rarefational pressure (25V<sub>PP</sub> input voltage), the ultrasonic energy interfered with the cardiac activity, when a single 66-kHz burst was applied for nearly 3 seconds. Arrhythmia was followed by post-extrasystolic potentiation of force (Figure 9).

![Figure 9. Isometric tension developed by an isolated, perfused rat heart. Reversible arrhythmia was induced at the onset of application of a 2kPa (peak negative pressure), 66-kHz ultrasound burst lasting 3 s. The timescale is compressed for the trace after ultrasound application was interrupted.](image)
4. Discussion

The available scientific literature indicates the ultrasound capability of treatment in cardiology. Moreover, it has been shown that ultrasound can reduce the electric excitation threshold [11] and produce positive inotropic effect in myocytes [12], by raising the calcium influx into the cells, thus increasing the intracellular calcium concentration [13] [14] [15].

A low frequency high power ultrasonic transducer was specifically developed to be applied in rat experimentation. Rat heart rates are much higher than human heart rates. In order to lower the heart frequency, atria were removed. Even without the right atrium, were the primary pacemaker (sinotriatral node) is located, the heart keeps beating spontaneously. This is probably due to the pacemaker activity of other cells, such as those from the atroioventricular node and the His-Purkinje conduction system.

A preliminary application of the transducer in rat heart in vitro showed some proarhythmic effects. This is promising when it comes to therapeutic applications of ultrasound in cardiology because arrhythmia-inducing agents might as well be antiarrhythmic. On the other hand, the proarhythmic effects might have been influenced by the chamber used to place the heart. Extrapolation of in vitro results to in vivo situations does not always work [16]. Homeostatic mechanisms are to be considered when the ultrasound is applied in vivo, condition in which the extracellular medium brings on protective responses in order to minimize the effects arising from the ultrasonic exposure.

It is known that depending on the set of applied acoustical parameters, ultrasound can even exert antagonistic actions, such as reestablishing blood flow (thrombolysis - low intensity waves) and stopping bleeding (hemostasis - high intensity waves) [17]. Thus, the occurrence of bioeffects depends on a combination of acoustical parameters, which should be found experimentally.

5. Conclusion

A 66-kHz power ultrasound transducer was modeled, constructed and characterized. Experimental and theoretical acoustic impedance curves show good agreement in relation to the transducer resonance frequency. When excited by an input voltage of $37 \text{V}_{pp}$, which results in an output negative pressure of approximately 3.1kPa, the transducer starts to produce cavitation.

The ultrasonic transducer driven by a $25 \text{V}_{pp}$ electric voltage was used to apply a single 66-kHz burst to a perfused isolated rat heart, and interfered with the cardiac activity, generating proarhythmic effects. The peak negative pressure was around 2.1kPa. The transducer will be used in the near future to investigate functional modifications produced on rat heart arising from ultrasonic exposure, aiming therapeutic applications of ultrasound in cardiology.

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References


