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GaN-Based Versatile Waveform Generator for Biomedical Applications of Electroporation

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ABSTRACT Biomedical applications often require high-performance power supplies for diagnosis and treatment systems. In particular, modern electroporation techniques for cancer treatment require high-voltage generators with versatile waveform generation. In this context, sinusoidal waveform generation has been recently identified as beneficial for electrochemotherapy cancer treatments. This paper proposes the design of a high-voltage high-frequency arbitrary waveform generator taking advantage of Gallium Nitride (GaN) devices. The proposed converter has been designed and implemented, achieving a 1-MHz 2000-V output voltage. It has been electrically tested and applied to electrochemotherapy treatments in mice, demonstrating the feasibility of this proposal.

INDEX TERMS Electroporation, magnetic components, arbitrary waveform generators, capacitors, wide bandgap semiconductor, cancer treatment.

I. INTRODUCTION

High-voltage generators are required in a wide range of biomedical applications from diagnosis to treatment systems. Among these, electroporation [1], [2] is a promising cancer treatment technique which requires the application of a high-intensity electric field pulses to induce either reversible or irreversible processes (FIGURE 1) [3]. Electroporation is based on applying an intense electric field to induce biological changes in the desired tissue. If the electric field is below the reversibility threshold (E_{rev}, typically 500-1000 V), the cell recovers its initial state after the electroporation process. This process is called reversible electroporation (RE) and it is commonly used to improve drug absorption, for instance in electrochemotherapy treatments [4]–[6]. However, if the applied electric field is beyond that level, the process is irreversible, i.e. irreversible electroporation (IRE), and the process leads to the cell death by a combination of necrosis and apoptosis processes. This process is used for selective tissue ablation, always avoiding exceeding the thermal limit ($E_{thermal}$) that would lead to thermal ablation. IRE ablation has significant advantages [1], [7]–[10] including faster recovery and the avoidance of uneven treatments typical of thermal ablations made using radiofrequency or microwave technology.

Currently, electroporation treatments rely on the use of square-wave generators applying the waveforms described in FIGURE 2 (a) to (d), which include capacitor discharge circuits, and constant voltage circuits, both with unipolar or bipolar alternatives in order to avoid undesired effects of bias voltage [11]. However, recent studies have demonstrated the effectivity of applying high-voltage sinusoidal waveforms [12], [13] with lower harmonic content. These treatments require, however, new power electronics designs for enabling high-voltage sinusoidal waveform generation.

In the past, several attempts have been made providing versatile signal generators but with limited voltage/current amplitudes [14] or operating frequencies [15], [16], not fulfilling the requirements of electroporation applications. In [17], an accurate Josephson arbitrary generator is proposed, but limited to 1 V and 1 kHz. One of the few large-signal generators is detailed in [18]. However, it is

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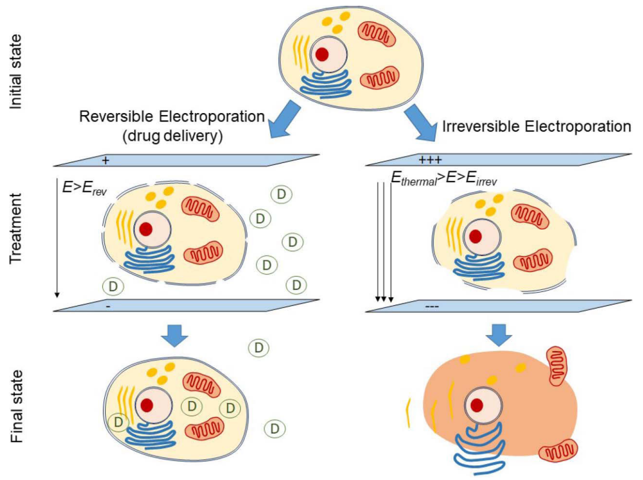

FIGURE 1. Cell electroporation: reversible (a) and irreversible (b) processes.

limited to sinusoidal waveforms and requires adapting the resonant tank, including frequency resolution and dynamic performance limitations.

The aim of this paper is to provide a versatile large-signal high-frequency arbitrary waveform generator taking advantage of the new wide bandgap (WBG) devices [19]–[22] and a multi-level topology [23]–[25]. Multi-level converters have been studied and applied in the past to related applications such as pulsed electric fields for water disinfection [26]–[30], among others. In this paper, GaN devices will be used to enable a fast-operation and high-performance high-voltage generator implementation achieving 2 kV pp output voltage, 10 A output current, and operating frequencies exceeding 1 MHz [31]. By using a high number of low-voltage levels, it will be possible to generate arbitrary waveforms with low distortion. The proposed generator is applied to a novel electrochemotherapy (ECT) treatment using sinusoidal waveform, where the electric field created by the proposed generator is applied to the tumours to increase their permeability to a chemotherapeutic agent (bleomycin). Thus, a more effective treatment is obtained with less side effects.

The remainder of this paper is organized as follows. Section II details the proposed power converter, including the proposed topology and modulation strategy. Section III details the main implementation and experimental results, including electrical test and results during in-vivo mice ECT experiment. Finally, the conclusions of this paper are drawn in Section IV.

II. PROPOSED POWER CONVERTER

In order to achieve a versatile high-voltage waveform generator, an isolated multi-level topology is proposed (FIGURE 3). It is composed of n levels operating at V_{bus} voltage, being possible to use low voltage devices in its implementation. Each sub-level features an isolated bus plus a super capacitor bank in order to be able to supply high pulsed current required for the electroporation applications. The output block is composed of a full-bridge topology, being able to supply bipolar output voltage. It is important to note that, this isolated structure provides inherent voltage balance between all the sub-levels.

The amplitude resolution of the proposed converter is defined by V_{bus}, whereas the maximum output voltage is, consequently, nV_{bus}. In order to improve the amplitude resolution and reduce the harmonic content, sinusoidal pulse-width modulation is applied during the level transitions (FIGURE 4). By doing so, high quality output signals can be obtained with a reduced number of required levels.

The temporal resolution of the proposed converter will depend on the switching frequency of the power devices. The higher the switching frequency, the lower the harmonic distortion in the output signal. For this reason, switching

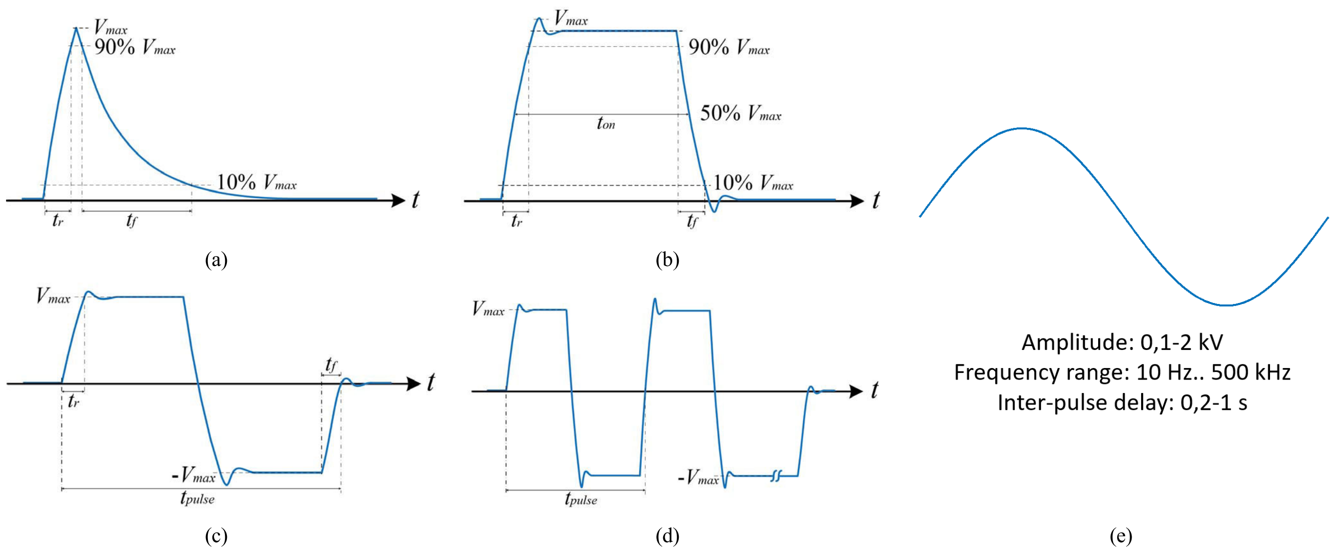

FIGURE 2. Output voltage waveforms applied during electroporation treatments: (a) capacitor discharge, (b) unipolar square-wave, (c) bipolar square-wave, (d) bipolar square-wave pulse train, and (e) recently proposed sinusoidal waveform.

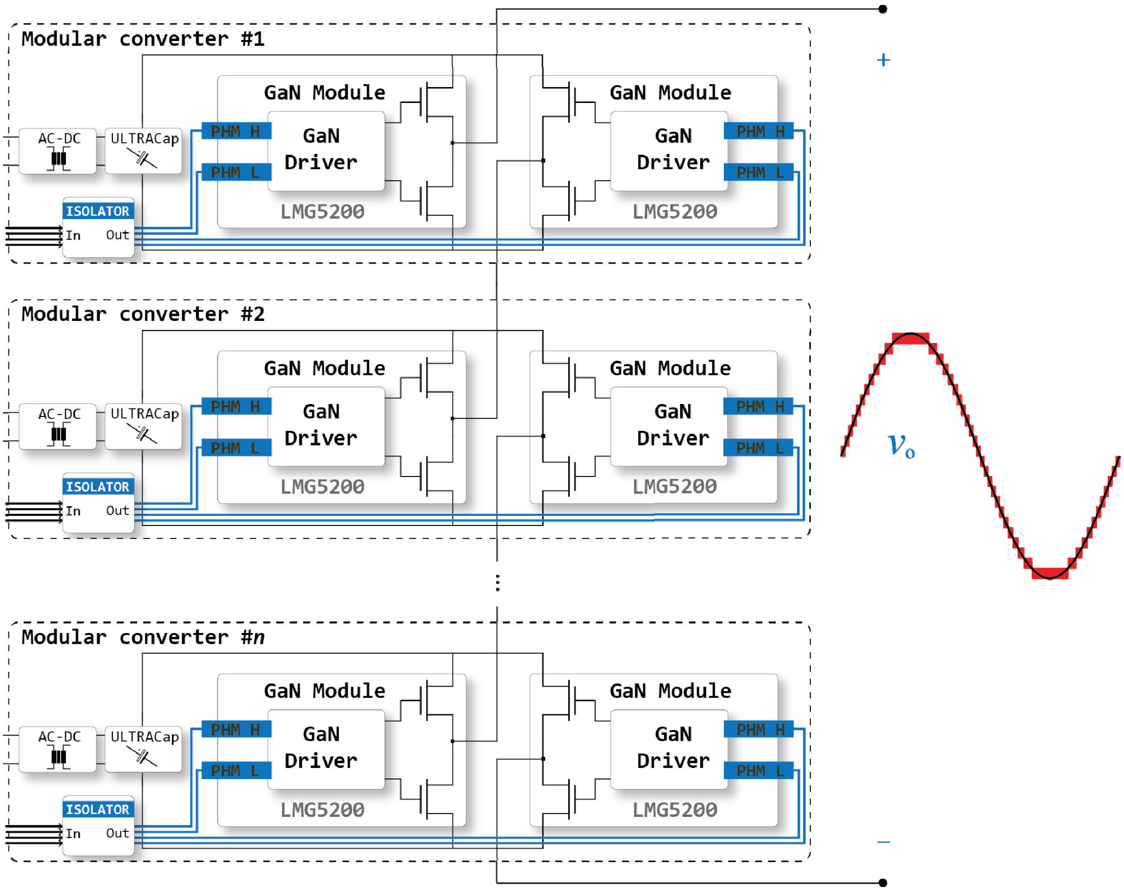

FIGURE 3. Proposed isolated multilevel inverter for versatile high-voltage waveform generation.

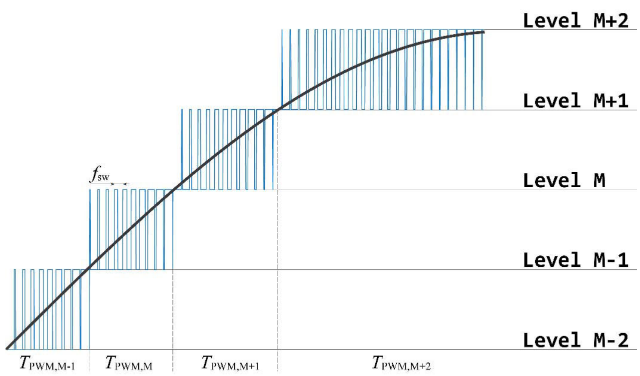

FIGURE 4. Total harmonic distortion of the output voltage as a function of the output amplitude and output sinusoidal waveform frequency.

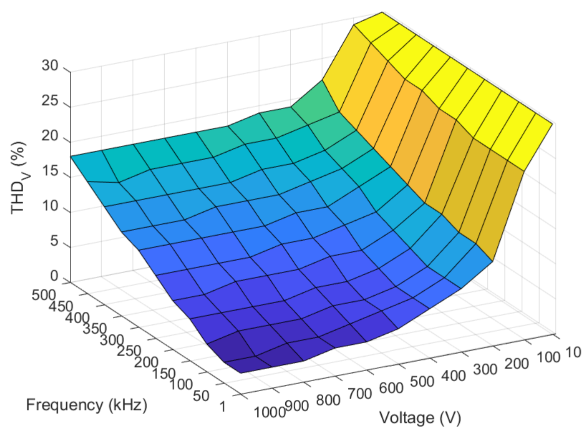

FIGURE 5. Proposed sinusoidal pulse width modulation (SPWM).

frequency will be maximized by using WBG devices in its implementation. Moreover, in order to balance power loss between the different sub-levels, their activation is sequentially alternated during each period of the output signal.

With these useful characteristics, any arbitrary waveform withing the voltage/current and frequency limits can be generated, including square, sinusoidal or pulsed-shaped waveforms, or complex modulations for advanced electropermeabilization techniques. It can be also applied to other industrial areas such as communications or audio for versatile and efficient power generation.

FIGURE 5 details an analysis on the influence of the output voltage amplitude and the sinusoidal output voltage frequency in the output voltage total harmonic distortion (THD_V) of the proposed converter. In this image, it can be seen that the THD_V increases linearly with the required frequency. Thus, the proposed GaN based implementation will enable operation at lower THD_V for a wider range of operating points. For the considered 1-MHz design, THD_V lower than 20% is obtained up to 500 kHz for the maximum output voltage, i.e. 2 kV pp. The influence of the required

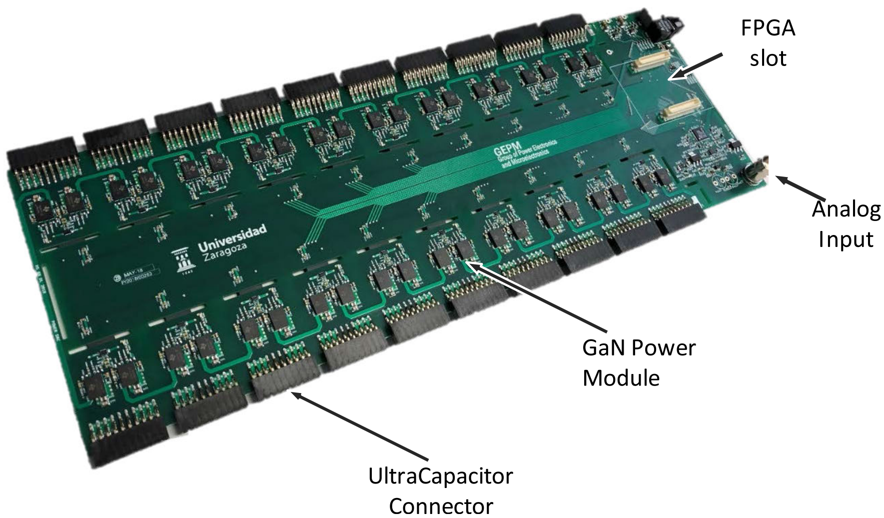

FIGURE 6. Experimental prototype.

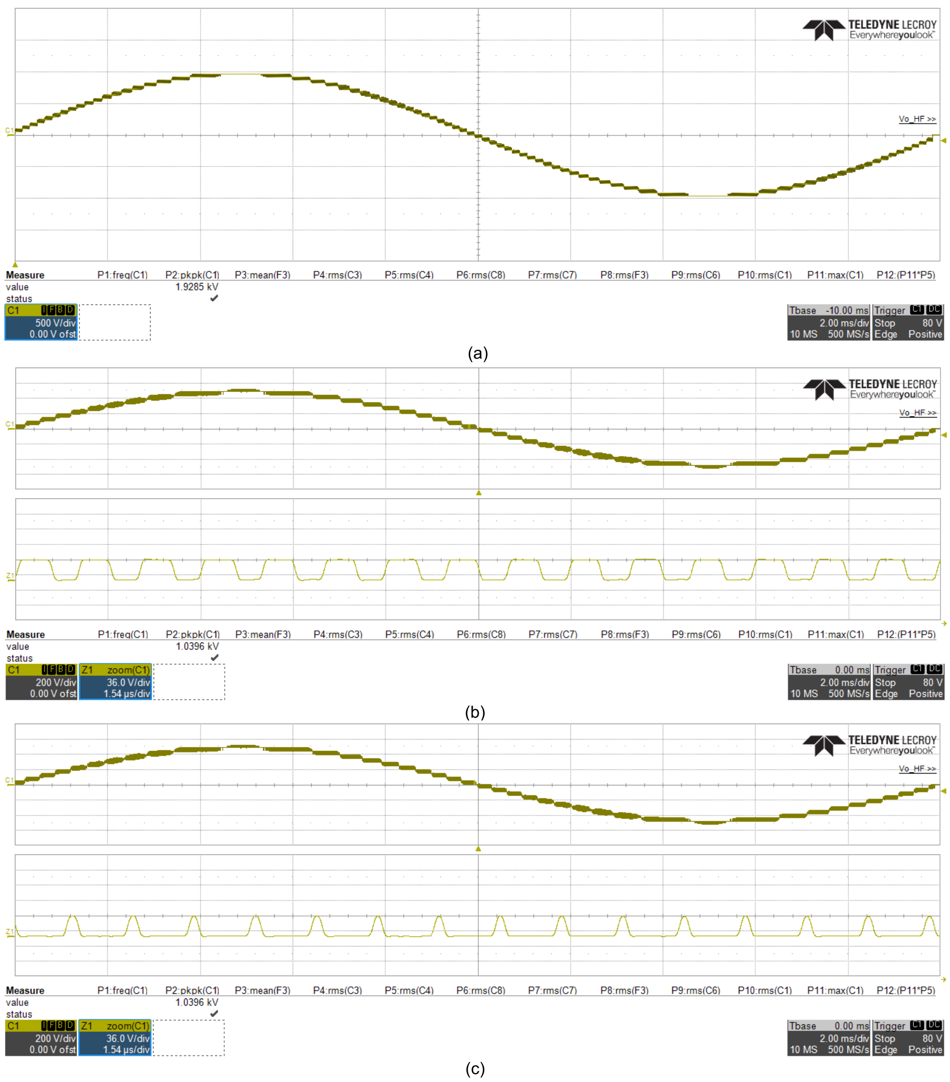

FIGURE 7. Experimental results: 50-Hz 2-kVpp output voltage (a) and detailed views of PWM modulation (b,c).

output voltage can also been analized, being the THD_V sevelry compromised when the required output voltage is close to the bus voltage of each level. Consequently, designs where the converter needs to operate in a wide range of ouput voltages will require a higher number of converter levels in order to ensure proper THD_V. For the proposed design,

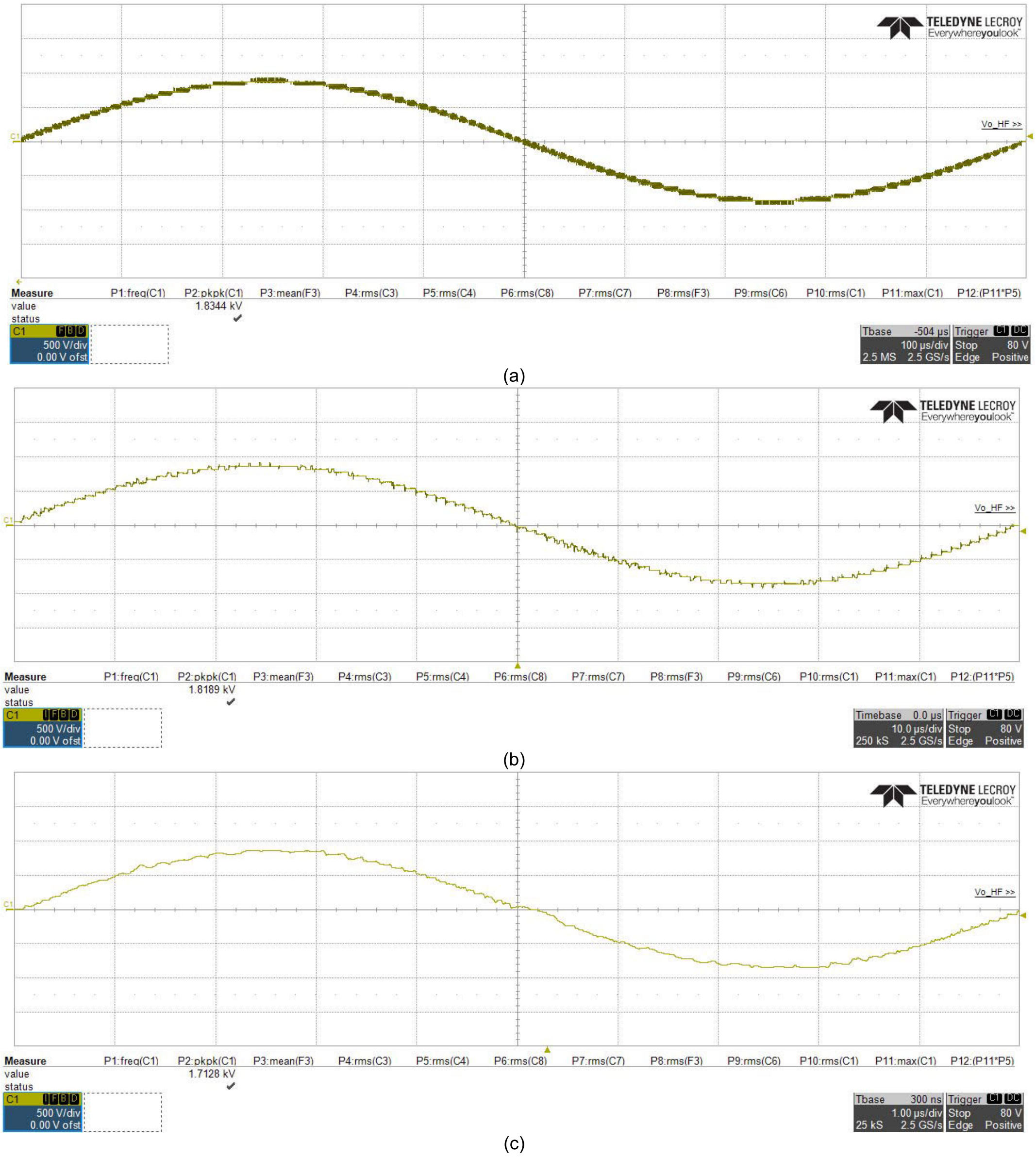

FIGURE 8. **Experimental results: High -voltage and high-frequency operation with 1 kHz (a), 10 kHz (b), and 100 kHz (c) output voltage waveforms.**

20 levels are considered, achieving THD_V lower than 20% in the 20%-100% output voltage range.

III. IMPLEMENTATION AND EXPERIMENTAL RESULTS

In order to test the feasibility of the proposed converter, an experimental prototype has been designed and built, which will be later used for clinical application of the new electroporation treatment. For the present study, the generator maximum ratings were fixed to sinusoidal waveforms up to 2 kV pp and 10 A to be provided in a wide range of frequencies from several Hz to hundreds of kHz. To meet these requirements, the proposed generator has been implemented featuring 20 sub-levels operating at a configurable bus voltage up to 60 V. As a result, a maximum 2400 V pp with a minimum resolution of 60 V is achieved. In order to achieve a good temporal resolution, 80-V LM5200 GaN devices from Texas Instruments have been selected. These devices provide on-resistance suitable for the application and fast switching capabilities, enabling high-frequency operation. Besides, these devices include the driving circuitry, providing a compact implementation, which is a key feature considering the high number of sub-levels. These devices allows providing at least 10-A worst case output current. Considering the frequency requirements of the application, 1 MHz switching frequency plus sinusoidal pulse density modulation has been considered in this design. FIGURE 6 shows the experimental prototype, including GaN devices and sockets for FPGA and capacitor bank connection.

FIGURE 7 shows representative results of the correct operation of the proposed converter. In figure, 50-Hz 2-kVpp output voltage waveform is synthesized, showing a detail of the PWM modulation applied to improve THD.

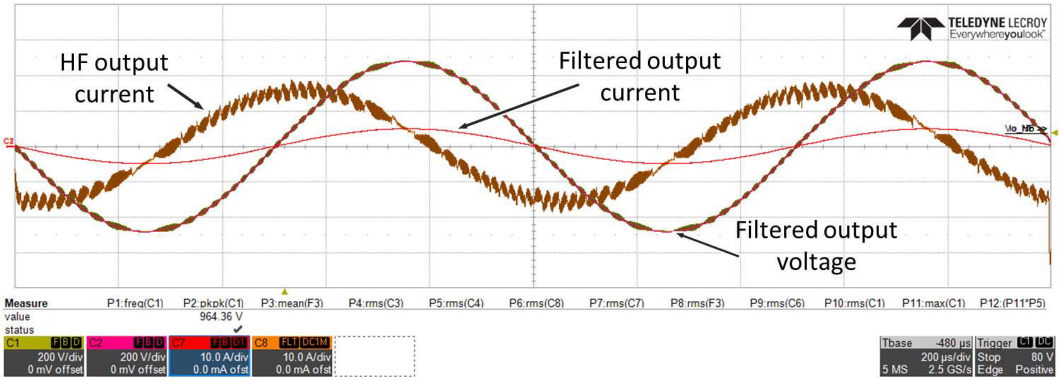

FIGURE 9. Experimental results: operation example with capacitive load.

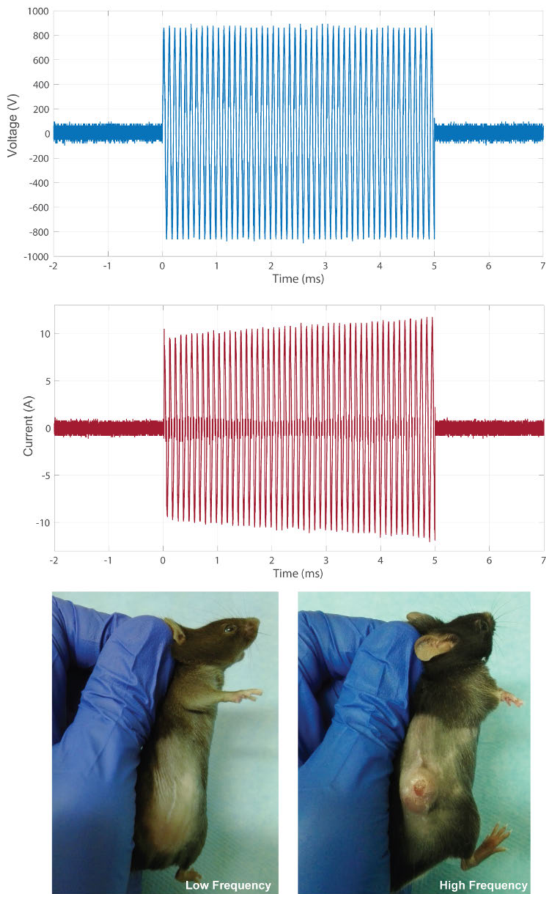

FIGURE 10. Experimental ECT results: applied voltage and current at 10 kHz before applying chemotherapy during the ECT treatment (a) and results of the application of low-frequency (10 kHz) and high-frequency (250 kHz) sinusoidal waveform in the ECT treatment (b).

After the correct converter operation is demonstrated, FIGURE 8 shows several examples of high-frequency operation synthesizing sinusoidal output voltage waveforms with frequency ranging from 1 kHz up to 100 kHz, taking advantage of the 1-MHz operation of the implemented GaN devices. Finally, FIGURE 9 shows an example of the converter operation with capacitive load. This experimental results proves the ability of the converter to operate with capacitive loads typical of electroporation processes, as well as the quality of the output signal, enabling the design of new electroporation treatments using high-voltage sinusoidal waveforms.

After the correct electrical performance was tested, the proposed converter was used in a proof of concept of a new ECT-based treatment [32]. This research was carried out at the Institute Gustave Roussy (UMR 8203-CNRS,Villejuif, France) following all the applicable ethical procedures (ethical evaluation approved by the CEEA 26, project number 2018_014_13409). The electric field pulses were locally applied to subcutaneous tumors in mice in combination with bleomycin. Stainless-steel parallel-plate electrodes were used (1 cm width, 1 mm thick and 4 cm long), interfaced with 2-m 5 kV-insultation wires to the developed generator. Besides, conductive gel (Asept Uni'Gel US, Aspet Inmed, France) was used to ensure correct electric field distribution. Different pulse durations, frequencies and amplitudes were assayed. FIGURE 10 (a) shows an example of the main waveforms during a single 5-ms 10-kHz sinusoidal burst ECT treatment. The correct generator operation as well as the evolution of the ECT treatment can be seen. As the electroporation process advances, the tissue conductivity increases as a result of increased tissue permeability, thus increasing the amplitude of the applied current. FIGURE 10 (b) shows an example of the experimental results several weeks after the treatment. As it can be seen, depending on the applied frequency, complete tumor regression can be achieved with sinusoidal waveforms. The complete set of in-vivo results is discussed in [32], together with additional electromagnetic analysis. The proof of concept showed less effectivity of the high frequency treatment at the same level of applied voltage, but more research is necessary to optimize the experimental parameters. These results are promising and highlight the potential of the proposed power converter for the research of future improved electroporation-based cancer treatments.

IV. CONCLUSIONS

This paper has proposed a GaN-based versatile waveform generator for biomedical applications. The proposed converter is based on an isolated multilevel structure featuring low-voltage GaN devices. Consequently, high output voltage can be achieved while operating at high frequency, enabling improved amplitude and temporal resolutions.

The proposed converter has been designed and implemented, following a 20-level structure operating at 1 MHz, with a maximum output voltage of 2000 V pp. After experimental results have proved the feasibility of this proposal, it has been applied to novel in-vivo electrochemotherapy treatments. The proposed converter has proved its correct operation as well as its effectivity as a research tool for future electroporation-based cancer treatments.

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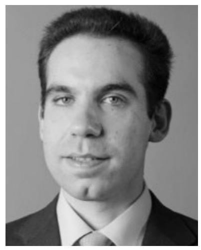

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