Electroporation Pulse Generator for Biomedical Applications with Improved Output Voltage Ripple and Reduced Bus Capacitor

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[1] ***Abstract*— Electroporation is a promising cancer treatment based on applying short electric field pulses. In this context, highly versatile pulse generators are required to generate high-voltage low-ripple pulses in the µs range. In the past, several multi-level converters have been proposed to achieve this aim. Achieving constant output voltage and, consequently, electric field is essential to obtain predictable treatments and minimize the risks of tumor relapse. However, significant bus capacitance is required to achieve the required performance, leading to bulky equipment with serious safety implications due to the stored energy. In this letter, a high-performance pulse generator for electroporation is proposed that takes advantage of a multi-level structure with linear voltage regulation to achieve the desired performance with reduced bus capacitance. The proposed converter has been designed and tested experimentally during both laboratory and operation room treatments.**

Keywords—Pulse generator, electroporation, multi-level converter.

I. Introduction

Nowadays, cancer is one of the key societal challenges due to the wellbeing and economic implications of the derived set of diseases. Power electronics plays a key role in many of the treatments ranging from surgery using electrosurgical units to thermal treatments using radiofrequency or microwaves [1]. The complete set of available treatments includes radiation therapy, chemotherapy, immunotherapy and targeted therapies, among others.

Despite the number and specificity of the treatments have increased, there are still tumours that cannot be treated due to their nature or location. In this context, electroporation arises as a promising treatment with benefits in terms of patient recovery and treatment of difficult locations with no thermal effects. Electroporation is based on applying short electric field pulses to induce biological effects [2]. If these pulses are intense enough, the cell death is induced by combined necrosis-apoptosis mechanisms achieving irreversible electroporation (IRE, Fig. 1(a)).

IRE requires applying short voltage pulses in the µs range to generate electric fields above 1000 V/cm [3-5]. In the past, IRE generators have used capacitor discharge circuits with exponential decay waveforms or voltage source inverters with increased bus capacitance (IRE, Fig. 1(b)) [6-8] to achieve the desired voltage ripple Δv_{vs}. In the high voltage range, Marx generators have also been used, typically with limited current capabilities [9, 10]. To achieve reliable treatments despite the tissue impedance, a high bus capacitance is often required. It is important to note that achieving low voltage ripple is essential to ensure constant electric field and, as a consequence, a predictable treatment with lower risk of tumour relapse. This implies the use of bulky equipment that can limit mobility in the operation room and that poses safety risks due to the energy stored that can be dangerous in typical brain or liver treatments.

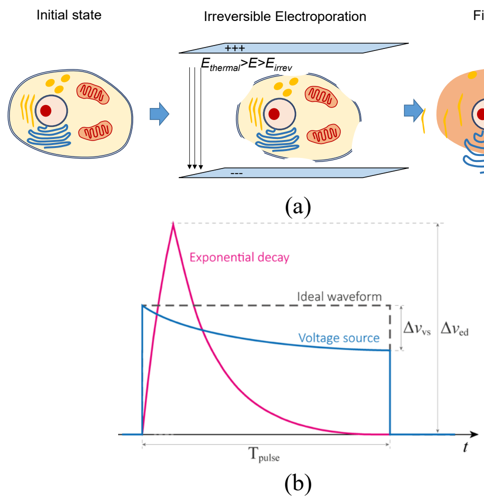


Fig. 1. Electroporation: (a) cellular electroporation process and (b) electroporation voltage pulses.

In order to achieve the desired performance, in the past, a versatile multi-level architecture was proposed to achieve the required performance [11, 12]. However, it requires a significant bus capacitance to ensure low output voltage ripple. This letter proposes a new multi-level structure with an improved indirect ac-ac power conversion stage featuring a linear voltage regulation stage that ensures almost-zero output voltage ripple with reduced capacitance. It is important to note that, as far as the authors know, no voltage droop compensation techniques are used in commercial clinical electroporators. As a consequence, large bus capacitors are used limiting power density, adding additional biological risks due to the energy stored, and limiting the treatment efficacy due to reduced electric field application.

The remainder of this letter is organized as follows. Section II presents the proposed topology and main waveforms. Section III presents the main experimental results both in laboratory and in operation room usage. Finally, Section III summarizes the conclusions of this letter.

[1] This letter follows the guidelines of the Special Section on Patent Related Short Articles and contains further developments made to the ideas patented in the granted patent [11], currently licensed to a US biomedical company.

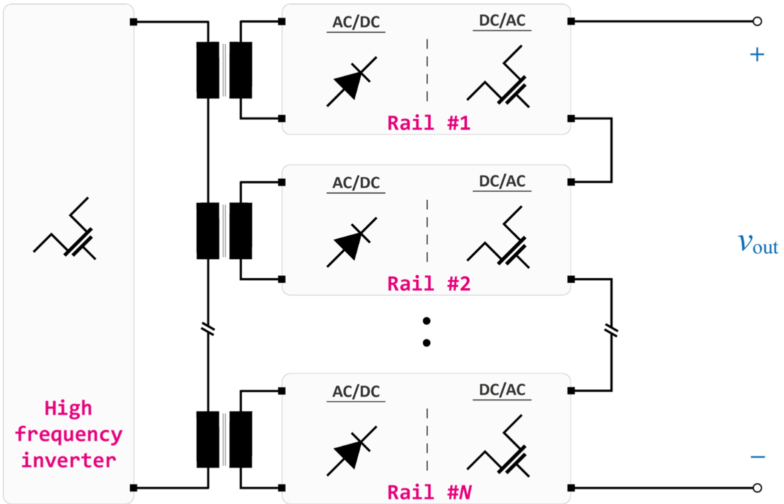


Fig. 2. Proposed patented generator architecture [11]: each rail contains a bus capacitor, C_b, to store the required energy.

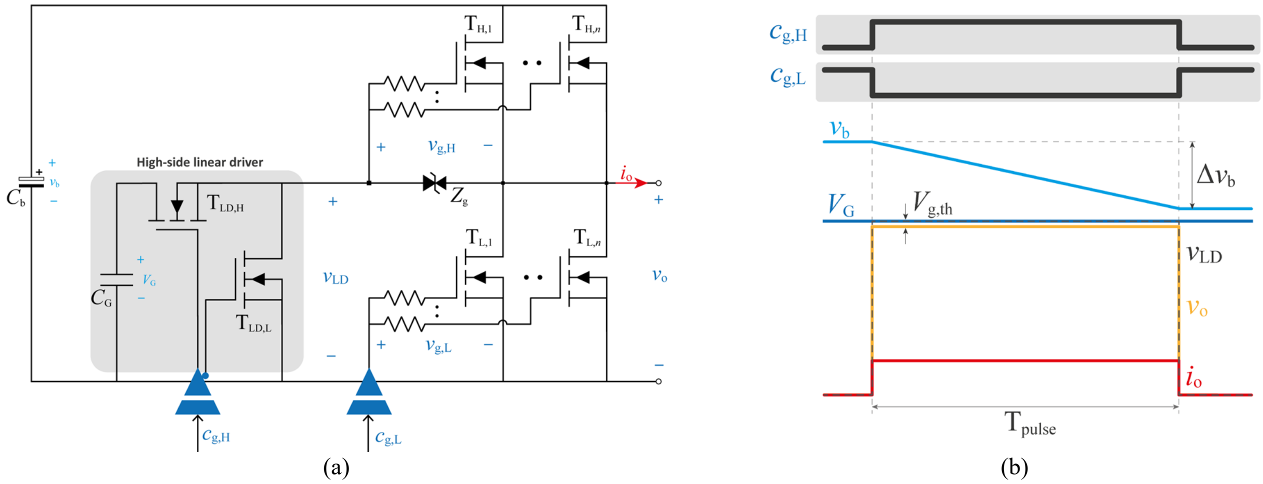


Fig. 3. Proposed upgraded full-bridge inverter cell with linear bus voltage control for improved voltage ripple: (a) topology and (b) main waveforms.

II. Proposed Pulse Generator

The proposed generator architecture is depicted in Fig. 2. It is composed of an isolated multilevel architecture so the output voltage v_{out} is the sum of the individual output voltage of each rail, 1 to n. A high frequency inverter and high frequency isolation transformers are used to power each individual rail to the desired voltage to perform the IRE treatment. Each rail comprises a high frequency rectifier plus a back-end full-bridge inverter that enables bipolar pulse generation. The latter is decupled using a bus capacitor, C_b, that ensures low-ripple output voltage.

This proposal includes an improved indirect ac-ac rail configuration that includes linear voltage regulation to achieve constant output voltage avoiding the need for large bus capacitance. The proposed rail structure is shown in Fig. 3, where only the output stage is shown and, for the sake of simplicity, only a half-bridge leg is represented. It comprises the use of a high-side linear drive to achieve the desired output voltage. The converter controls the voltage in C_G capacitor, V_G, using a boost stage to select the desired voltage, i.e. $V_G = \hat{v}_o + V_{g,th}$; where $\hat{v}_o$ is the desired peak output voltage and $V_{g,th}$ is the MOSFET gate threshold voltage. Then, the high-side linear driver achieves a linear regulation of the output voltage. By doing this, it is possible to obtain constant output voltage v_o by discharging the bus capacitor C_b through the output half-bridge composed of $T_{H,i}$ and $T_{L,i}$. It is important to note that C_b is charged at a voltage higher than the output voltage, so the voltage ripple at the output is negligible. Then, the output half-bridge devices are controlled by the digital control signals $c_{g,H}$ and $c_{g,L}$, and the applied gate voltages are $v_{g,H}$ and $v_{g,L}$, respectively. Using the proposed structure, the ripple in the bus voltage is

$$\Delta v_b = 1/C_b \int_{T_{pulse}} i_o(t)dt = Q_o/C_b \,. \qquad (1)$$

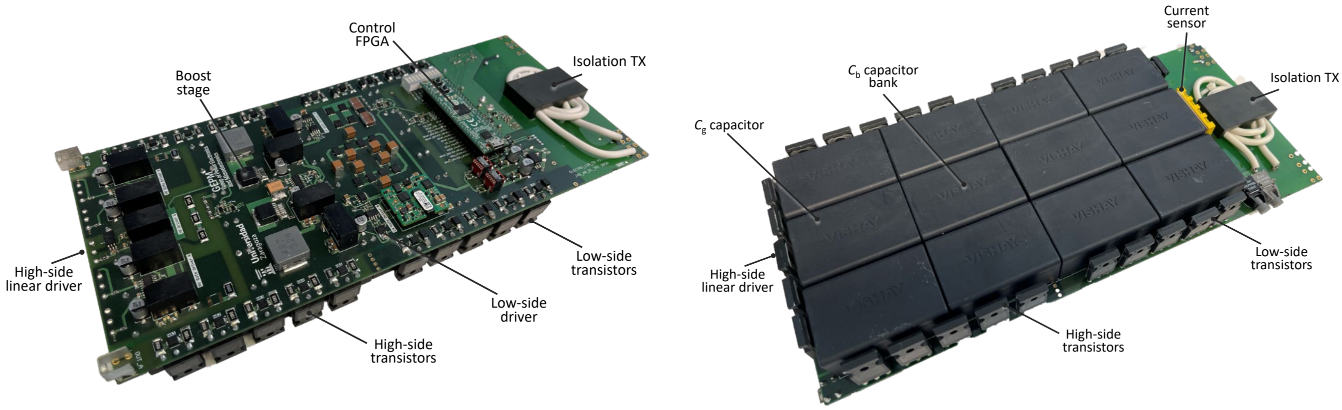
It is important to note that the bus voltage v_b must be above the desired output voltage, so the following condition must be fulfilled:

$$v_b \ge V_G + \Delta v_b = V_g + Q_o/C_b \,. \qquad (2)$$

Compared with the previous technologies (Fig. 1(b)), the proposed approach enables obtaining negligible output voltage ripple, leading to more effective treatments and, alternatively, reduced bus capacitance, for higher power density and safer treatments. These aspects are essential for modern IRE cancer treatments.

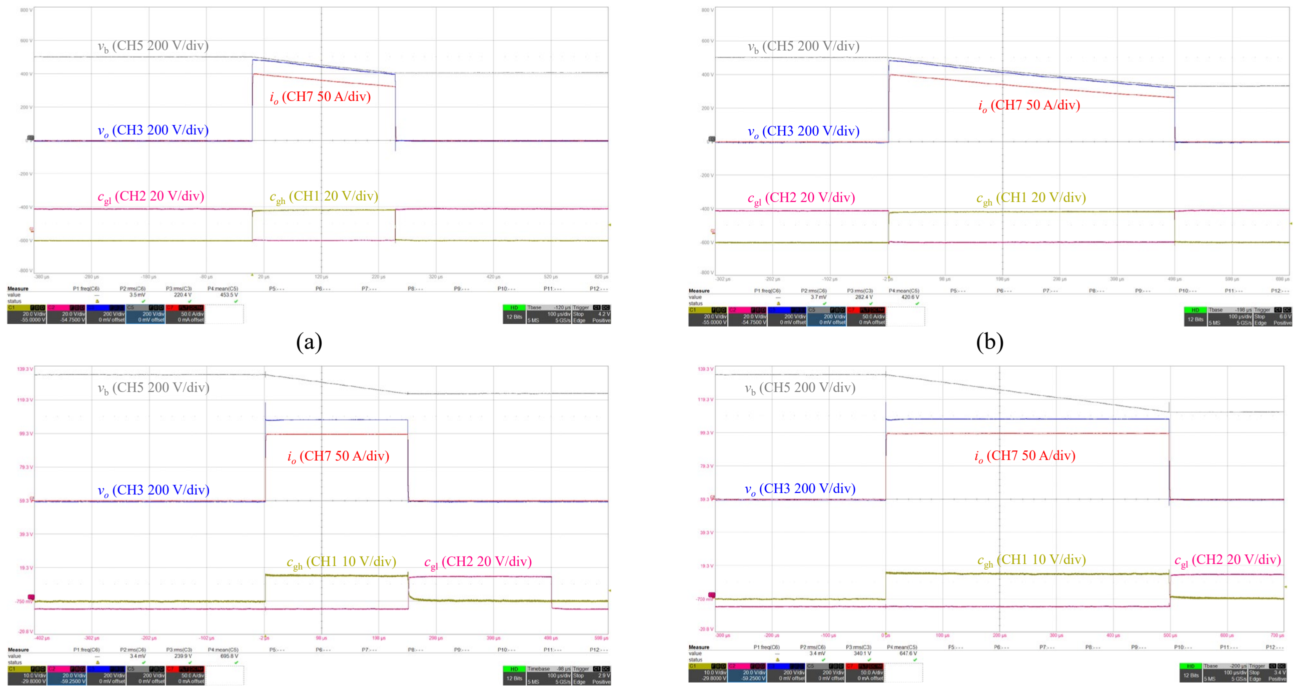
III. Implementation and Experimental Results

In order to prove the proper converter operation, a 7-level system has been designed to achieve 10 kVpp output voltage and 100 A output current. Fig. 4 shows a single rail board



(a) (b)

Fig. 4. Experimental prototype: (a) top and (b) bottom layers of a single ac-dc+dc-ac rail.



(a) (b) (c) (d)

Fig. 5. Main waveforms using a conventional voltage-source back-end inverter (a,b) and the proposed linearly regulated converter (c,d). From top to bottom: bus voltage (C5 200 V/div), output voltage (C3 200 V/div), output current (C7 50 A/div), and control signals (C1 10 V/div and C2 20 V/div).

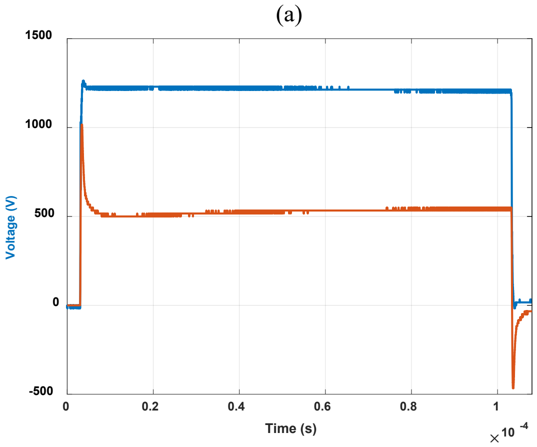
Table I. Design comparison per output module

Design criteria	Topology	Comparison	
		C_b	ΔV_o (%)
Equal capacitance	Previous multi-level structure	240 µF (12 · 20 µF)	5.8% @ 100 % $V_{o,max}$ 11.6% @ 50 % $V_{o,max}$ 23.3% @ 25 % $V_{o,max}$
	Proposed multi-level structure	220 µF (11 · 20 µF)	<1%@10-100% $V_{o,max}$
Equal voltage ripple 1%	Previous multi-level structure	1400 µF@ 100 % $V_{o,max}$ 2800 µF@ 50 % $V_{o,max}$ 6000 µF@ 25 % $V_{o,max}$	1%
	Proposed multi-level structure	220 µF@10-100% $V_{o,max}$	<1%

containing the PCB embedded high frequency isolation transformer, the diode rectifier and the proposed linearly regulated output full bridge. In the bottom layer, the bus capacitor can be seen.

The proposed topology has been implemented using IHW30N160R2 IGBTs from Infineon. Each individual rail is controlled by an FPGA that communicates using optic fibre with the control board. The control board enables communication with a PC to control the main treatment parameters including output voltage, number and length of pulses, and configuration of pulse trains. Besides, the output current is monitored for safety reasons both using an ADC and a fast comparator for fast disconnection in case an

(a)



(b)

Fig. 6. Experimental application of the proposed electroporation generator: (a) operation room and (b) applied pulses.

abnormal circumstance is detected during the treatment. The proposed generator also includes synchronization with ECG equipment if needed for a safe IRE treatment.

Fig. 5 shows the main waveforms of the proposed converter compared with the previous voltage-source inverter approach. Whereas in the previous topology the bus voltage discharges with the output current and, consequently, so does the output voltage (Fig. 5(a,b)), the improved linearly regulated configuration enables zero-ripple output voltage, providing improved performance for more reliable irreversible electroporation treatments.

In addition to this, Table I shows a design comparison of the proposed topology compared with the previous technology based in a voltage source full-bridge inverter proposed in [11, 12]. From this table, it is clear that the proposed topology achieves significant benefits in terms of output voltage ripple or, alternatively, in terms of reduced capacitance.

Finally, Fig. 6 shows the application of the proposed generator during clinical trials to determine the optimum electrical field pulse patterns and post-treatment liver regeneration [13]. All the procedures were approved by the Animal Experimentation Ethical Commission, University of Zaragoza (permit number: PII19/16), and all the experiments were performed in accordance with relevant guidelines and regulations. Fig. 6 (b) shows the voltage and current waveforms obtained when applying 3-cm parallel plates electrodes to pig liver tissue during in-vivo experiments. During these experiments, the correct voltage pulse generator operation was confirmed, proving the feasibility of the proposed approach.

IV. Conclusions

Electroporation is a promising cancer treatment technique that requires advanced power electronic converter to provide high performance and versatile pulse generation to develop effective treatments. In this letter, a versatile multi-level pulse generator has been presented featuring improved pulse generation. The proposed converter takes advantage of a linear output voltage regulation stage to achieve zero-voltage ripple with reduced bus voltage capacitance. This improves the performance and safety of the device while reduces its size for improved usability in medical environments. The proposed converter has been designed and implemented, and experimental verification has been conducted both in electronics laboratory and during in-vivo experimentation. As a result, the feasibility of this converter has been proved, and it has been established as a versatile tool for IRE treatment research and development.

Acknowledgement

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