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Research Article

A Modular Multilevel Converter-Based Pulsed Electric Field Generator Design for Electroporation Applications

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***Abstract*—In this work, a modular multilevel converter-based pulsed electric field generator design is presented. In the proposed design, operation frequency is selected higher level compared to the similar works to provide new possibilities for better and healthy life. The pulse generation (PG) and the adapted modular multilevel converter (MMC) topology that is to be covered are introduced including the operating principles and very basic analysis. Finally, performance of the proposed MMC with four half bridge submodules is tested on a prototype built in laboratory. A bidirectional voltage is produced with 80 V amplitude pulsating at 100 kHz operation frequency.**

Index Terms— **Electroporation (EP), Modular multilevel converter (MMC), Pulsed Electric Fields (PEFs), pulse generation (PG).**

I. Introduction

FROM ELECTRIC fish to Lichtenberg figures the concept of electricity and life sciences had a certain space in the lives of humanity throughout history yet the knowledge of electricity and its interaction with tissues and cells was rather limited [1] [2]. The use of different kinds of electric fish, for instance, electric eel, catfish, and electric rays as therapeutic agents were reported in many historical records from different parts of the world from ancient Greece or Ancient Egypt to South American Indians [2]. For facial palsy and ptosis, a traditional Chinese prescription is stated in [2] suggesting an electric catfish tail is applied on the spot. According to [2], a torpedo, which is most probably prescribed by Hippocrates to Gallen, can deliver shocks of 45 volts of electricity whereas an electric eel from Amazon, the application of which is reported to treat gout by native South Americans by early explorers, can deliver up to 600 volts.

However, during those long centuries and broad application all around the world throughout a vast number of cultures from Islamic tradition to Roman medicine in the western part and China to South America to Eastern, our understanding of the concept is almost metaphysical and far from today's theories and thereby the control of the electricity is out of scope [1] [2] [3].

In the mid-18th century, the invention of the Leyden jar by Musschenbroek can be considered a turning point from this stagnant state to a fast transition of electricity to settle every aspect of our daily life, especially the controlled usage of electricity to live tissue [1] [2] [3]. However, the curious beginning of these applications, one of the first attempts includes some "party tricks" like Nollet's made of King's guards to leap simultaneously [3], with the observation of red spots by the application of discharge on the skin [3], this path leads to the way to Galvani's animal electricity [1] and finally the modern theories. In 1898, it is reported the application of electric fields as bactericidal to process water by G.W. Fuller [1]. At that point, neither the term electroporation nor the reversible and irreversible impacts resulting from the application of exogenous pulsed electric fields (PEFs) had been coined yet, this had to wait until the mid of the next century [1]. In 1948, Tiselius won Nobel Prize in chemistry due to his work on electrophoresis, the phenomenon, first described in 1807, basically points out that particles can be moved with the application of an external electric field [4]. Currently, there many techniques and modalities can be seen in different industries such as the food industry, environmental processes, as well as biotechnological and clinical applications like electrochemotherapy (ECT), gene electro transfer (GET), and nonthermal irreversible electroporation (NTIRE) for ablation of solid tumors [5].

Although there are some modalities like TTF (tumor treating fields) in which bio electrorheological models are applied to explain [6] [7], usually electro permeabilization, reversible electroporation (RE) and irreversible electroporation (IRE) are three key terms used to describe the main mechanisms practically employed [8]. Although there are still gaps in our understanding of the phenomena, there are major approaches that will be explained in a more detailed manner in this paper. In addition to theoretical explanations and mathematical models, there are different approaches to

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simulating the mechanism, like molecular dynamics.

From the electrogenesis process of electric fish to the static electricity of Leyden Jar there had not been much progress for long centuries on the other hand since the 18th century there is a progressive pace in the technical aspects of pulse generation. Conventional approaches like Marx or Blumlein generators [9] are still being applied in accord with the technological progress in power electronics as well as the manufacturing process in solid-state switches. In order to provide flexible and controllable pulse generation, modular multilevel converter (MMC) based power electronics is a good option to meet different application requirements. Each application can require different voltage level. Therefore, this work is focused on MMC based pulse generation.

In this paper, the first section shortly describes the basic electroporation mechanism. Later, pulse generation and pulse generators (PGs) are briefly explained. Finally, a prototype is built to validate the performance of the proposed MMC with four half bridge submodules adapted from [9] and [20]. In [9], pulse width modulation carrier repetition time is only 40 μs in the experimental pulse generator setup with three modules. Increasing operating frequency opens a new gate to answer the question of vitality as well as new possibilities for a better and healthy life yet. Therefore, in this work, the operation frequency is selected as 100 kHz. According to the measured results, bidirectional output voltage pulsating at 100 kHz is validated on the built prototype.

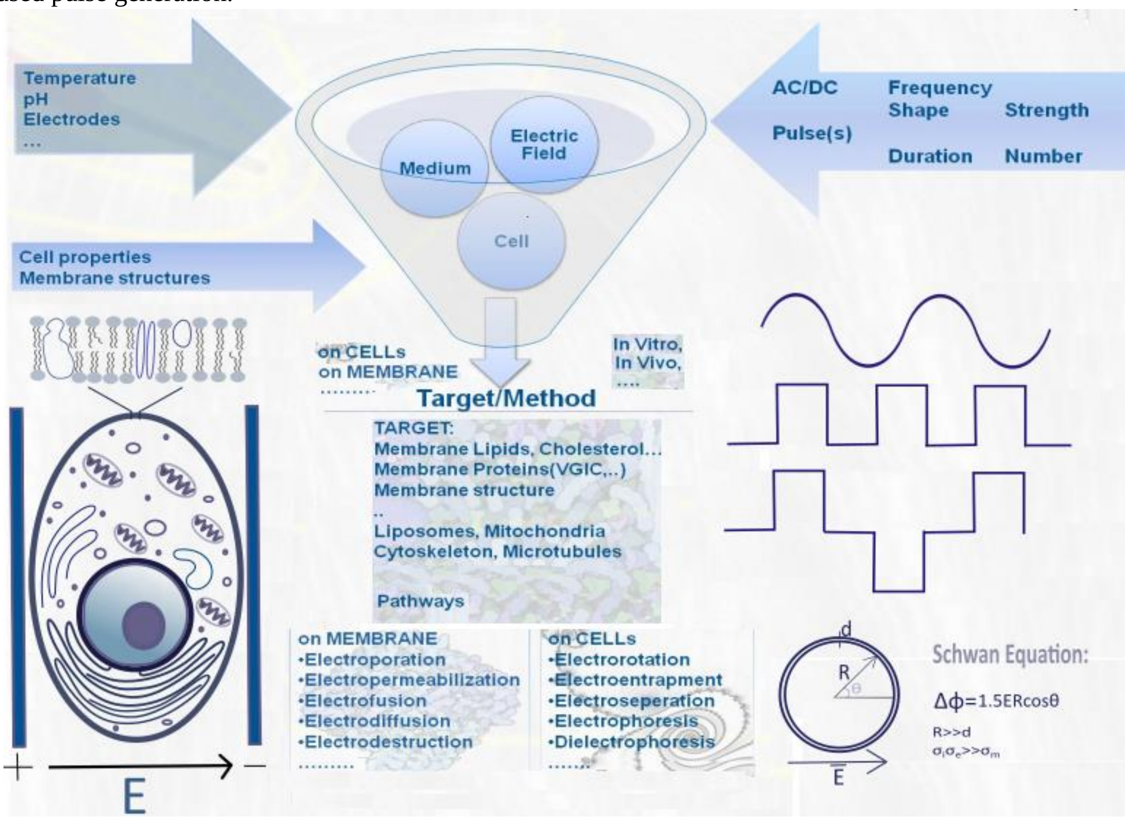

Fig. 1. Electric field applied on a single cell, Basic parameters, and Schwann equation.

II. Basic Electroporation Mechanism

As it is mentioned in the previous section there are vast numbers of applications covering life sciences and growing at a rapid rate since the second half of the 20th century. However, although it is widely applied there are still unknowns about the mechanism that explains how the phenomenon does work. Fortunately, the basic models are mostly able to describe the fundamental behavior. Certainly, it is not yet easy to observe the changes in and next to the cell membrane directly, the developments in new techniques and utilizing computational modeling applications we, humanity, understand the process better every day, with every new question that is raised due to new experiments there is a new answer is waiting for us to open a new window to comprehend the behavior of the cell, as well as the vitality as a concept.

Before diving into the mechanisms behind the pore formation on the plasma membrane of the cell, a quick review of a single cell would be a good starting point. Essentially, there are two distinct types of cells, eukaryotic and prokaryotic due to the organelles they own. Eukaryotic cells as in the case of human beings or plants, have organelles having their own membranes inside the cell whereas inside prokaryotic cells there are no membrane-bound organelles, like in bacteria. There can also be a cell wall in some bacteria species and plant cells but for simplicity, this would be out of our scope in this study. The plasma membrane is consisting of a phospholipid bilayer with hydrophilic polar heads pointing interior side of the cell (cytoplasm) and extracellular environment (suspension fluid, intracellular fluid, etc.) and hydrophobic tails between the polar heads as it is shown in Figure 1 [10]. There are protein-based structures forming channels, pumps, and gates as well as some other molecules like cholesterol or glycocalyces with various functions [10]. In this study, the model that would be studied assumes only the sandwich-like phospholipid bilayer with hydrocarbon tails between the polar heads [10] [11]. In essence, commonly accepted models defining the cell membrane behavior under an external electric field define a critical voltage over which pore formation models refer formation of water fingers through this bilayer first in hydrophobic character like a hole then transforming into hydrophilic character by changing electroporation or electro permeabilization as it is represented in [8]. The shift in the membrane potential difference exceeds the critical value in a very short time, in a range changing from nanoseconds to microseconds, before permeability is increased to a detectable level and during the pulse width, if the amplitude of the pulse remains above the critical value up to milliseconds permeability remains even intensify. After those initiation and expansion stages partial recovery (micro to milliseconds) and resealing (seconds to minutes) stages occur, and memory may hold for hours before the membrane turns to its normal state. Along with the mathematical models describe mainly the induced transmembrane voltage. However, other studies are taking into consideration the other kind of effects regarding the signal molecules, voltage sensors of membrane [12], mechanical effects [13], and remodeling the cytoskeleton [14] can be found throughout the literature on pulsed electrical field studies.

Fig. 1 visually summarizes this section as well as the common notion of the use of external electrical fields on living tissues and cells. In the top and the middle part, some basic factors that affect the procedure are reviewed quickly. There are mainly three elements describing the application: Electric fields, medium, and cell. Certainly, those can be extended considering the nature of the application. For example, as an applicator, a PEF (pulsed electric field) chamber can be used or electrodes with different structures that are made up of different materials, or the suspension medium for in vitro applications may change and affects the results. For in vivo tumor ablation, the target area would be much larger compared with a microfluidic or single-cell experiment, and so does the requirements. Depending on the frequency and the strength of the pulses applied, the target may change from cell membrane to cell organelles, or bio electrorheological effects on the cytoskeleton would become assertive. On the bottom left is a stylized single cell with its nucleus and some organelles, the electrical field is symbolically shown from the positive to the negative direction between the two electrodes, and the lipid bilayer with embedded molecules like proteins depicting cell membrane can be seen. On the right-hand side, one can see basic voltage applications on the electrodes that are affecting the nature of electrical fields formed between and sometimes among the electrodes. DC or AC form can be applied, and pulse shapes, widths, strength, polarity even pulse intervals between two successive pulses are reported to have resulted in significant differences depending on the application.

III. Pulsed Electric Field (PEF) Generators

In [15], pulse generation stages are listed under the name of pulsed power train diagram as follows: high voltage supply, energy storage, pulse compression stages, impedance matching, switch, and load. Although the fundamental mechanism, that is the application of the stored energy in a short time is the same, different approaches had been developed since the Leyden Jars of the 18th century. Marx generators, similar to Leyden Jars, were using capacitive storage and spark gaps when they are first invented [9][15]. Whereas transmission lines or Blumlein generators, although they are also among the conventional types, they take the advantage of inductive storage [15]. Today, soft switching techniques and/or resonant generators [16], solid-state pulsers [17], and wide bandgap-based designs [18][19] are joined in the methods and components. Moreover, different topologies originally designed for different purposes like modular multilevel converters used in high voltage direct current transmission lines have been able to be adapted to generate pulses [9].

A. *Modular multilevel converter topology with half bridge submodules for bipolar pulse generation*

In a typical half-bridge submodule (HB-SM), there are two switches and one capacitor as shown in Fig.2. Four HB-SMs has been interconnected to obtain bipolar waveforms in this study and that is adapted from [9], [20].

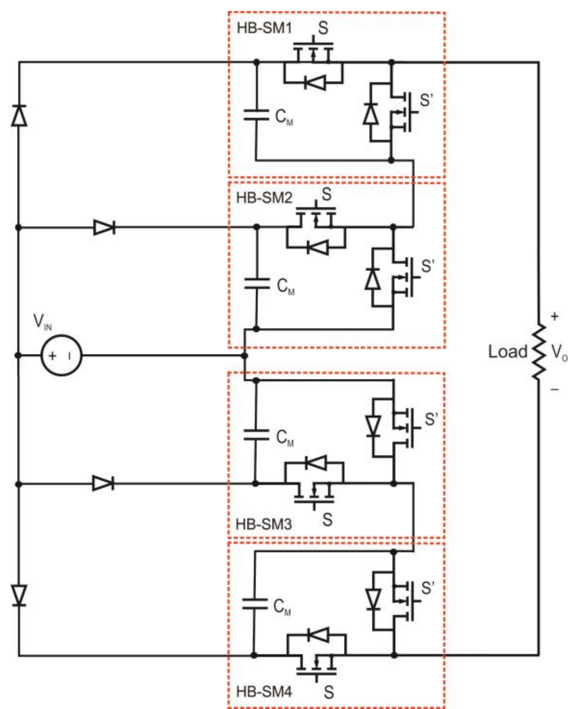

Fig. 2. Pulse generator with MMC topology in bipolar configuration with HB-SMs.

B. *Operating principles and brief analysis*

As mentioned before, each module is essentially composed of two switches S, $\bar{S}$ and a capacitor, C_M, that is pre-charged with voltage, V_{CM}, that is equal to the input voltage V_{in}. As it is shown in Fig. 2, employing interconnected four HB-SMs rectangular narrow pulses with amplitudes up to 2*V_{CM} to obtain bipolar outputs.

Pulse widths, and frequencies as well as the pulse shapes can be altered using different switching schemes. That is the reason the speed of the components and the technological advancements regarding those are critical to obtaining faster circuits and consequently narrower pulses.

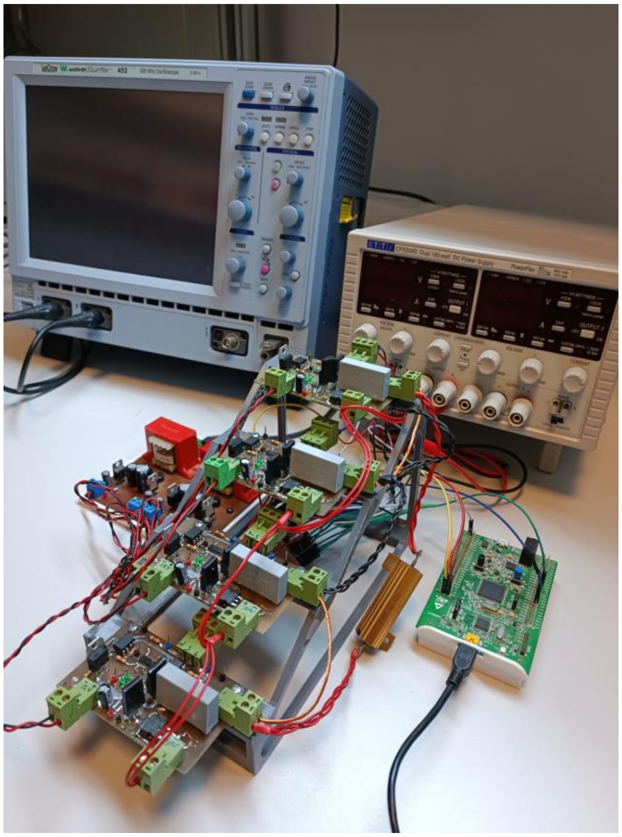

Fig. 3 The picture of the built MMC prototype with four submodules.

For each submodule, a diode is used to prevent the current flow back from the capacitors, these diodes are also known as directing/blocking diodes according to [9]. Using different switching schemes controlling S and $\bar{S}$, submodules can be activated or bypassed to obtain different voltage levels at the output. Activation is accomplished by the conduction of S while $\bar{S}$ is at the off state while for bypass of the submodule S is off and $\bar{S}$ is on. It is important to control the switches of the submodules that can be off at the same time but should not be on simultaneously to avoid short-circuiting the capacitor.

In order to produce positive pulse voltage at the load, S switches of HB-SM1 and HB-SM2 are on and their S' switches are off condition while S switches are off and S' switches are on in HB-SM3 and HB-SM4. Inversely, S' switches in HB-SM1 and HB-SM2 are on while S switches are off in HB-SM3 and HB-SM4 to produce negative pulse voltage at the load. However, it offers great flexibility the time constant of the circuit can become an issue, especially for fast-switching circuits for both charging and discharging cases.
The equivalent capacitor, $C_{eq\text{-}ch}$, for the general circuit in case of charging, can be approximated, considering the ideal conditions, as follows:

$$C_{eq\text{-}ch} = (2C_M) \tag{1}$$

The equivalent capacitor, $C_{eq\text{-}dis}$ for the positive or negative peak voltage case, i.e, for the discharge of all submodules simultaneously case, is:

$$C_{eq\text{-}dis} = C_M/2 \tag{2}$$

For a resistive load, an RC circuit would be formed and the capacitor voltage can be defined, having a well-known mathematical model with a time constant of *tau*(τ) equal to RC_{eq}.

IV. Experimental Results

The proposed MMC which has four half bridge modules and produces bidirectional voltage at the output is validated by a prototype built in the laboratory. A load resistance with 330 Ω is implemented at the output of the MMC prototype. STF19NF20 power MOSFETs are used for switching process and STPS30SM100S diodes are used to prevent reverse current from the capacitors. The operation frequency is selected high enough as 100 kHz. The input voltage is selected as 40 V, as scaled-down compared to real application requiring kVs, to provide safe operation in laboratory. The value of the capacitor used in each sub module is 1μF.

In the control circuit design, STM32F407VET6 microcontroller is used to produce required switching control signals. The control signals are isolated with optocoupler to prevent short-circuit of the capacitors. UCC27200 gate drivers are used to drive power MOSFETs. The picture of the built MMC prototype with four submodules is shown in Figure 3.

Fig. 4 shows gate driver signals, v_S, $v_{S'}$ applying to the S and S' in a half bridge module of built MMC. Fig. 5 is shows gate driver signals of three HB-SMs. $v_{S\text{-}HB\text{-}SM1}$ and $v_{S'\text{-}HB\text{-}SM2}$ are the control signals of HB-SM1. Each signal of HB-SMs is separately isolated from each other. The input signals of the drivers are isolated by optocouplers while the outputs are isolated by the using of a separate power supply for each driver. Fig. 6 shows the output voltage measured across the load. Bidirectional voltage at the output with 80 V magnitude is obtained. The capacitor voltage waveforms of four HB-SMs are given in Fig. 7. The charge and discharge of the capacitor are achieved for the required output voltage. Thus, bidirectional output voltage is produced with 80 V amplitude pulsating at 100 kHz operation frequency.

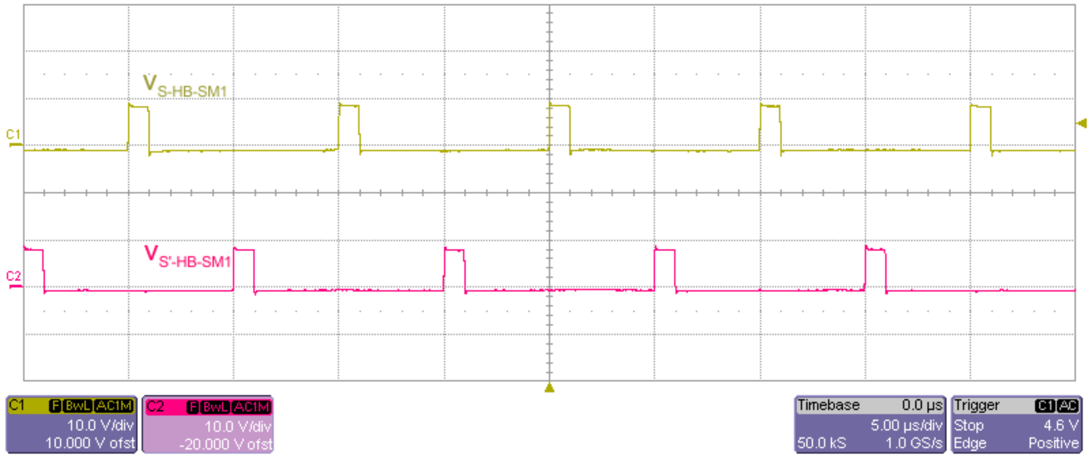

Fig. 4 The gate driver signals applying S and S' MOSFETs in a HB-SM.

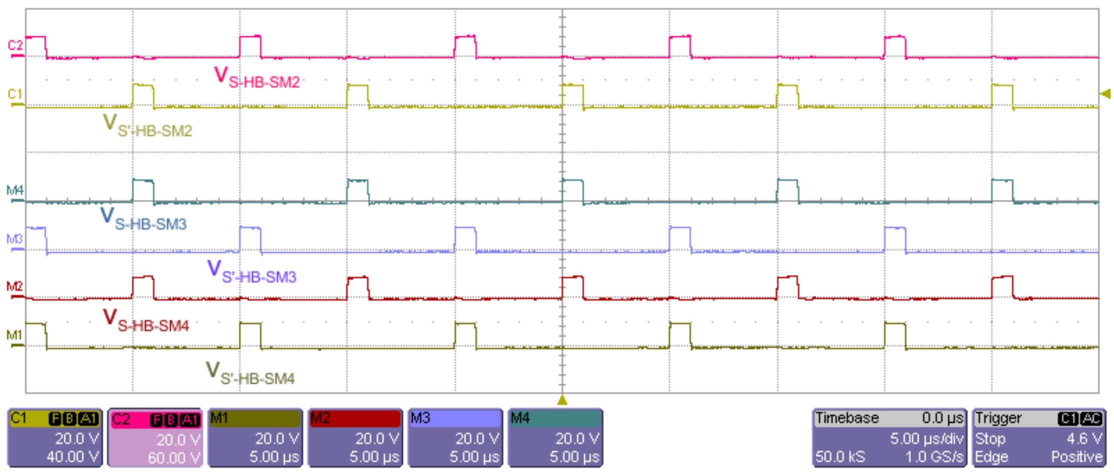

Fig. 5 The gate driver signals applying S and S' MOSFETs of three HB-SMs.

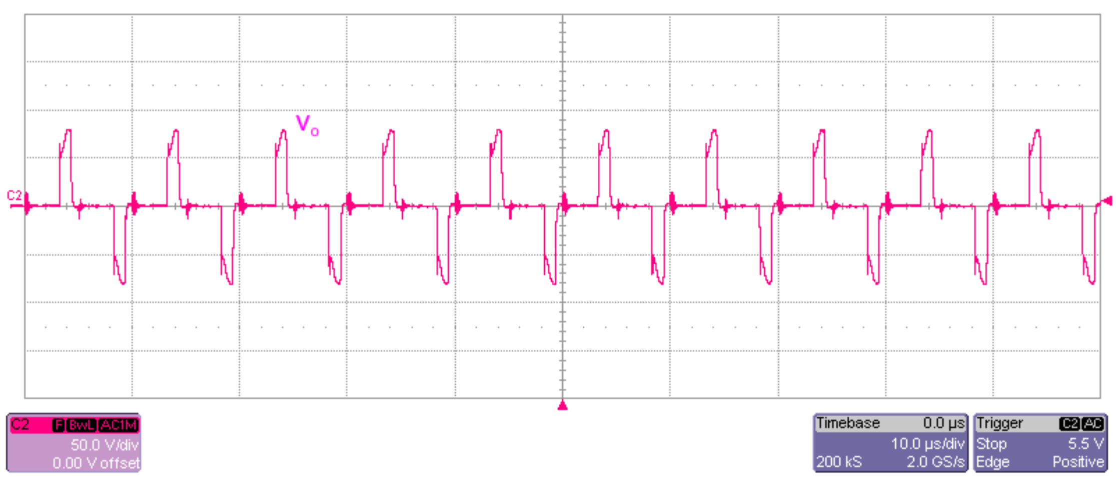

Fig. 6 Bidirectional output voltage measured across the load of proposed MMC with four HB-SMs.

(a)

(b)

Fig. 7. The capacitor and load voltage waveforms of the built MMC: (a) The load and capacitor voltage of HB-SM1 and HB-SM2, $v_{CM\text{-}HB\text{-}SM1}$ and $v_{CM\text{-}HB\text{-}SM2}$ (b) The load and capacitor voltage of HB-SM3 and HB-SM4, $v_{CM\text{-}HB\text{-}SM3}$ and $v_{CM\text{-}HB\text{-}SM4}$.

V. CONCLUSION

After a short opening about the use of electric fields throughout history and all around the cultures on the earth a brief introduction on the mechanism of cell membrane manipulation with exogenous electric fields. Later, the concepts about pulse generation and the topology to be discussed were quickly explained. Finally, a scaled-down prototype was built to validate the operation of the MMC with four half modules. According to obtained results, designed MMC provides bidirectional output voltage with 80 V magnitude, pulsating at 100 kHz operation frequency. Thus, scaled-down bidirectional pulse waveforms required for electroporation application was experimentally produced. When the proposed design is used in electroporation applications, it is expected that the operation at high frequency will provide new possibilities for better and healthy life. With the modular structure, MMC has flexible design advantages in case of any requirement in electroporation applications. The voltage sharing, scale and control of the proposed MMC can be easily modified with the modular structure.

Every discrepancy with models and practical experiments and every new question that arises from this work opens a new window even a gate deep inside the very foundation of our lives. The cell and organelles membranes play a key role to understand the whole features of the phenomena related to electrical fields and cell interaction. It is expected that the proposed MMC will be potential source for the future works of the electroporation pulse generator designers.

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Author contribution statements; Ovul Eski put contribution in literature searching, generating main ideas of this paper, analyzing of the proposed MMC with four half modules. Kemal Sahin put contribution in the building prototype and obtaining measurement results. Sevilay Cetin put contribution in the managing all stages in the paper.

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