Bioelectrochemistry 123 (2018) 77–87

Contents lists available at ScienceDirect

Bioelectrochemistry

journal homepage: www.elsevier.com/locate/bioelechem

Nanosecond bipolar pulse generators for bioelectrics

Shu Xiao *, Chunrong Zhou, Enbo Yang, Sambasiva R. Rajulapati

Frank Reidy Research Center for Bioelectrics, Department of Electrical and Computer Engineering, Old Dominion University, Norfolk, VA 23508, United States

ARTICLE INFO

Article history:
Received 21 November 2017
Received in revised form 3 April 2018
Accepted 24 April 2018
Available online 26 April 2018

Keywords:
Cancellation effects
Nanosecond pulses
Bipolar pulses
Multiphasic pulses

ABSTRACT

Biological effects caused by a nanosecond pulse, such as cell membrane permeabilization, peripheral nerve excitation and cell blebbing, can be reduced or cancelled by applying another pulse of reversed polarity. Depending on the degree of cancellation, the pulse interval of these two pulses can be as long as dozens of microseconds. The cancellation effect diminishes as the pulse duration increases. To study the cancellation effect and potentially utilize it in electrotherapy, nanosecond bipolar pulse generators must be made available. An overview of the generators is given in this paper. A pulse forming line (PFL) that is matched at one end and shorted at the other end allows a bipolar pulse to be produced, but no delay can be inserted between the phases. Another generator employs a combination of a resistor, an inductor and a capacitor to form an RLC resonant circuit so that a bipolar pulse with a decaying magnitude can be generated. A third generator is a converter, which converts an existing unipolar pulse to a bipolar pulse. This is done by inserting an inductor in a transmission line. The first phase of the bipolar pulse is provided by the unipolar pulse's rising phase. The second phase is formed during the fall time of the unipolar pulse, when the inductor, which was previously charged during the flat part of the unipolar pulse, discharges its current to the load. The fourth type of generator uses multiple MOSFET switches stacked to turn on a pre-charged, bipolar RC network. This approach is the most flexible in that it can generate multiphasic pulses that have different amplitudes, delays, and durations. However, it may not be suitable for producing short nanosecond pulses (<100 ns), whereas the PFL approach and the RLC approach with gas switches are used for this range. Thus, each generator has its own advantages and applicable range.

1. Introduction

Low intensity electric pulses with alternating polarities, such as RF emissions, have been widely studied and the outcomes have been low biological efficiency or no effect except for heating and a thermoelastic effect of RF heating [1–5]. With an increased electric field intensity and pulse duration, bipolar pulses in the range of hundreds of microseconds to sub-millisecond were used in electroporation. They were shown to be more effective in causing cell permeabilization than unipolar pulses [6], presumably because bipolar pulses alternate the exposure to both poles of the cells and increase the symmetry of permeabilization. They can also permeabilize non-spherical cells with a higher probability. Bipolar pulses may be a better option to energize electrodes than unipolar pulses. In a cell suspension, the ions released from aluminum and steel electrodes, including Al^{3+} and Fe^{2+} or Fe^{3+}, are lower when using bipolar pulses than monopolar sub-millisecond pulses [7], which reduces electrolytic contamination and toxicity of these ions. Bipolar pulses were used to reduce muscular contraction in irreversible electroporation (IRE) with a protocol known as HFIRE (High frequency IRE) [8,9]. In the nanosecond range, however, the higher efficiency of electropermeabilization for bipolar pulses is not observed. In fact, the permeabilization caused by one phase of the nanosecond bipolar pulse can be reduced or cancelled by the reversed phase [10]. Furthermore, phosphatidylserine (PS) externalization, nerve excitation and cell blebbing [11–15], can all be reduced or cancelled by applying reversed nanosecond pulses.

The level of cancellation depends on the magnitude of the reversed electric pulse. Having the same magnitude, despite the opposite polarity, may not necessarily induce a maximum cancellation. The cancellation also depends on how soon the reversed phase is applied after the first phase. It can be observed even 50 µs after the first pulse is applied [13]. While the cancellation is seemingly a universal phenomenon, there is an exception in that the activation of voltage gated calcium channels cannot be cancelled [16]. Thus, studying the biological responses to bipolar pulses becomes very important, as understanding the underlying mechanism may shed light on the selective response of cells to electric fields. Most importantly, the cancellation effects were found to exist only in the nanosecond pulse regime, making nsPEF (nanosecond Pulsed Electric Field) quite unique and distinct from longer pulses. Knowing the dependence of the cancellation effects on the pulse duration could be the key to understanding the mechanism of nanosecond cancellation.

* Corresponding author.
E-mail address: sxiao@odu.edu (S. Xiao).

https://doi.org/10.1016/j.bioelechem.2018.04.017
1567-5394/

To study the nanosecond bipolar cancellations, the bipolar pulse generator should be made available. The methods of generating bipolar pulses include pulse forming lines (PFLs) [17–19], the Marx generator [20], a totem-pole circuit [21] and an H-bridge circuit [22]. In our previous versions of bipolar pulse generators, we adopted these concepts. For example, bipolar 120-ns pulses (60 ns per phase) were produced by a bi-directional pulse-forming line that utilized MOSFET (Metal-Oxide-Semiconductor Field-Effect Transistor) switches and coaxial cable [10]. The circuitry to produce 600-ns bipolar pulses (300 + 300 ns) was based on an H-bridge voltage-source inverter (VSI) [11]. At one time, only the diagonal switch pairs were turned on to allow one polarity of the pulse generated. The timing was controlled by a digital delay generator. The H-bridge has the advantage of using only one power supply, but the load, which in that case was the electrode immersed in cell medium, has to be electrically floating. Two voltage measurement probes have to be employed simultaneously to measure the voltages at each of the electrodes and so a subtraction of the two gives the voltage across the electrodes. A different generator configuration, a totem-pole configuration, was used to produce bipolar pulses using two MOSFET switches and two separate power supplies [13–15]. One switch being turned on gives one polarity of the pulses. The load was grounded and so only one voltage probe was used to measure the voltage. Besides square waves, a bipolar damped sine wave and a unipolar half-cycle sine wave were generated by pulse generators that used IGBTs (Insulated-Gate Bipolar Transistor) as the primary switch in a damped RLC circuits. [12]. These methods in general were discussed in low voltage applications (<1 kV) for which a solid state switch with a hold-off voltage 1 kV was used. Also, very short bipolar pulse generators (±10 ns, for example) were not discussed. Whereas for high voltage and fast pulse generators, spark gap switches and stacked solid state switches can be used. In the context of studying cancellation effects, the techniques of generating high voltage (>1 kV), wide-range nanosecond (10 ns to ~1 μs) bipolar and multiphasic pulse generators are discussed in this paper. Specifically, a PFL, an RLC (resistor, inductance and capacitance) circuit, a unipolar to bipolar converter (UBC) and an RC network with stacking switches (RCNSS) are discussed. These methods rely on either pre-existing bipolar currents, such as in a transmission line, or the currents discharged from pre-charged bipolar capacitors. It is also possible to utilize the exchange of energy between an inductor and a capacitor, which causes an alternating current to flow in the load. The advantages and disadvantages of each method are discussed in order to provide biologists and engineers a good picture when it comes to the selection of the pulse generator.

2. Bipolar pulse generators

2.1. Switch considerations

In generating high voltage pulses, the switch performance is critical to the pulse risetime, pulse duration and repetition rate. In the nanosecond range, spark gap switches and MOSFETs are still the most useful switches, although vacuum switches such as thyratron, other solid-state switches like Field Ionization Dynistor (FID), IGBT, Semiconductor Opening Switch (SOS), photoconductive switch and avalanche transistor are also available [23–26]. Spark gaps are a fast, inexpensive and easy-to-build option for ultrafast nanosecond pulse generation, even though they introduce a turn-on jitter and voltage error and a short lifetime due to electrode erosion. A spark gap switch with a triggering mechanism can effectively lower the jitter and error, making it useful in high voltage, high current and fast switching. Because a spark gap is only capable of turning on and cannot be shut off, the pulse generator usually generates a fixed pulse duration. In contrast, MOSFETs can be programed to turn on and off by a low voltage gate signal, offering a flexibility of varying the pulse duration. The drawback is they have either a low voltage or a low current constraint. A high power operation therefore requires connecting MOSFETs in series to increase the switching voltage or in parallel to increase the current. But stacking MOSFETs can increase stray inductance, making the circuit slower. Therefore, it is preferable to use spark gap switches to generate short nanosecond pulses (<100 ns) and MOSFET switches to generate long nanosecond pulse (>100 ns).

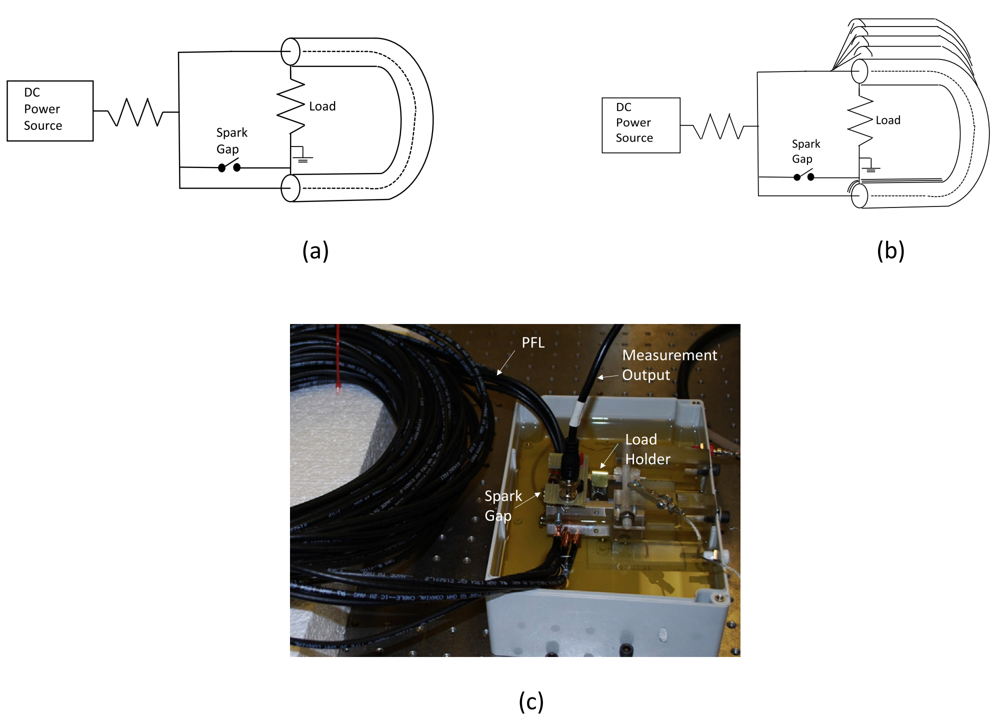

Fig. 1. A PFL for bipolar pulse generation. (a) A single transmission line. (b) A low-impedance line consisting of multiple transmission lines in parallel. (c) The actual generator configuration.