Describing the Pulsed Output Voltage of a Medical Pulsed-Electric-Field Generator

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Abstract

Electroporation-based medical therapies are an evolving field of treatments used in the treatment of cancer or treatments which require the focused ablation of patient tissue. A clinical electroporator is a medical device which is used to create a pulsed output voltage that induces the biological phenomenon of electroporation in the tissue targeted during treatment. Examples of electroporation base therapies are electrochemotherapy (ECT) use to treat skin cancer or cardiac pulsed field ablation (PFA) used to treat cardiac arrhythmia. A pulsed-electric-field (PEF) generator is a subcomponent of a clinical electroporator which is responsible for creating the pulsed output voltage applied to the patient. The output voltage of a PEF generator is typically a very intense but short-duration voltage-controlled rectangular pulsed output. In this paper, the typical pulsed output voltage waveforms of different electroporation-based therapies are discussed. It is demonstrated there is a challenge in the field of electroporation-based therapies of how to adequately describe the pulsed output of clinical electroporators in an easy-to-interpret and unequivocal manner. A set of intuitive, unequivocal, measurable definitions of timing and amplitudes are proposed that can be used as a common definition set to overcome this problem. Examples of output waveforms for ECT and PFA electroporation-based therapy are discussed and described using the standard definition set. And experimental examples of pulsed outputs of a demo PEF generator are demonstrated.

Keywords: Terms, Definitions, Pulsed Electric Field, Electroporation, Pulsed Output, Pulsed Field Ablation, Electrochemotherapy

1 Introduction

Electroporation is a biological phenomenon where short-duration high-intensity $\bar{E}$-fields are applied to cells which induce the formation of nanopores in the membrane of the cells [1]. There are two types of electroporation, which are reversible (RE) electroporation and irreversible (IRE) electroporation. During RE electroporation, the pores which form in the cell membrane are temporary and only exist when the strong $\bar{E}$-field is applied to the cell. When the strong $\bar{E}$-field is removed, the pores in the cell membrane close, allowing the cell membrane to once again act as a protective barrier for the cell. The cell membrane's main function is to act as a protective barrier keeping harmful substances outside the cell. In medicine, this can present a challenge in drug delivery, as the cell membrane acts as an impermeable barrier to many drugs. However, with the use of RE electroporation, many previously impermeable drugs can become permeable due to the nanopores in the cell membrane.

This phenomenon can be very useful in cancer therapy such as electrochemotherapy (ECT) for skin cancer [2]. ECT is used in the treatment of skin cancer for tumours which are not suitable for surgical resection. The patient setting for a person undergoing a skin ECT treatment is shown in Fig. 1 where the patient is depicted to have a single skin cancer tumour on their neck. Skin ECT is provided in an outpatient setting under local anaesthetic.

During this treatment anti-cancer drugs are injected into the patient tumour. The drugs used are the same drugs used

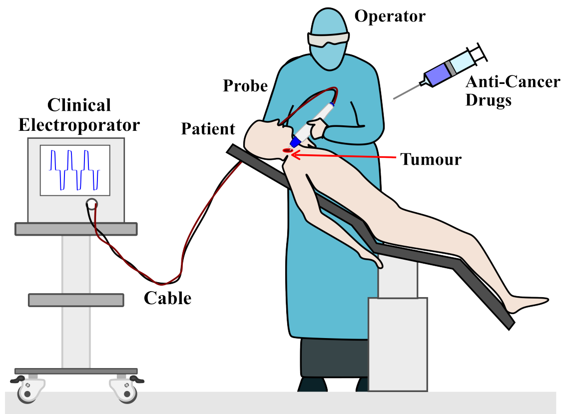


Fig. 1: Patient setting for electrochemotherapy.

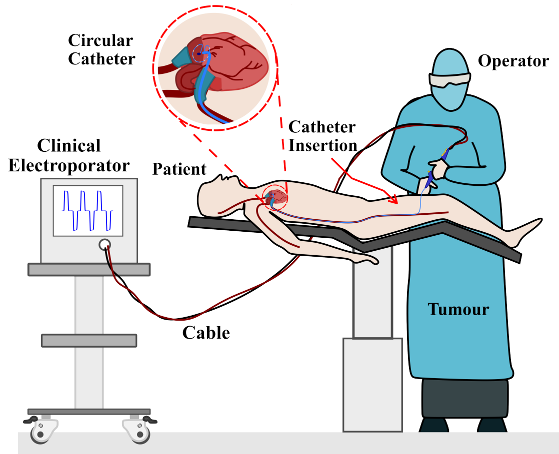


Fig. 2: Patient setting for cardiac pulsed field ablation.

in chemotherapy, hence the name electrochemotherapy. The operator then uses a device called a probe to connect the clinical electroporator to the tumour. The operator controls the clinical electroporator normally via a touchscreen interface and a footpedal to trigger the pulsed output. The clinical electroporator applies the pulsed output through the cable to the probe where it is applied to the tumour. This applies a high-intensity short-duration $\bar{E}$-field to the target tissue which induces RE electroporation in the tumour cells, allowing the anti-cancer drug to enter the tumour cells through the cell membrane and cause cell death.

During IRE electroporation a stronger $\bar{E}$-field is applied to cells. If the $\bar{E}$-field is applied for a sufficiently long time, the pores formed in the cell membrane become large enough to permanently damage the cell which induces cell death. The damage to the cell membrane is irreversible, hence the name irreversible electroporation. In medicine, irreversible electroporation can be used to ablate human tissue. An example of this is in the treatment of cardiac arrhythmia using pulsed field ablation (PFA) [3, 4]. Cardiac arrhythmia is a medical condition where a person has an abnormal heartbeat. Cardiac arrhythmia can be treated using PFA by ablating the heart tissue which causes the abnormal heart beat.

The typical patient setting of a PFA treatment for cardiac arrhythmia is shown in Fig. 2. Similar to skin ECT a clinical electroporator is used to generate a pulsed output. The operator inserts a catheter through the patients groin and navigates to the heart normally using a mapping system a hand-held mechanical device to guide the catheter. The catheter is used to apply the pulsed output from the clinical electroporator to the heart. A circular catheter is depicted in Fig. 2, similar to Medtronic's circular PFA catheter [3]. However other types of catheter's exist such as the lattice catheter [4] also from Medtronic. Different catheter designs typically require pulsed outputs with very different amplitude and timing specifications, and hence require different clinical electroporators which are specifically designed to each catheter or treatment.

The field of medical electroporation-based therapies is a wide and growing field including many more examples outside those of of the skin ECT and PFA for cardiac arrhythmia described here. Other examples of medical electroporation-based therapies include ECT to treat cancer in other organs such as the liver [5, 6], rectum [7] or oesophagus [8], the use of IRE electroporation to treat prostate cancer [9, 10] or chronic bronchitis [11] or to treat wounds [12] etc. The field of electroporation-based medical therapies suffers a common problem of poorly-defined description of the pulsed output of clinical electroporators. Different research groups or individuals practicing in the field apply equivocal and sometimes ambiguous descriptions of the pulsed output which can lead to confusion. In this paper, this problem is examined in more detail and a common definition set [13] is proposed for defining the timings and amplitudes of the pulsed output. The common definition standard is published separately as a standalone paper.

This paper is divided as follows; Section 2 is a problem statement which elaborates on the use of poorly-defined and equivocal terminology used to describe the pulsed output waveforms used in electroporation-based medical therapies. Section 3 gives the proposes solution to this problem to use a set of common definitions to describe the pulsed output which are intuitive, unequivocal and measurable. Section 4 gives examples of different pulsed outputs used in different medical electroporation-based therapies. Section 5 gives demonstrates experimentally measured pulsed outputs on a demo PEF generator. And lastly section 6 gives a conclusion.

2 The Problem Statement

The field of electroporation is plagued by different people using different terms and definitions in an equivocal and ambiguous fashion when describing the pulsed output. Terms such as pulse, burst, packet can all be used interchangeable by different authors with the same or different meanings. This practice makes it confusing for people who work in the field to compare work. Moreover it also makes it difficult to make a fair comparison of different clinical electroporators when reading and comparing their technical specifications.

2.1 Equivocal Magnitude-Related definitions

An example of this can be found when reading the IGEA technical specification for the Cliniporator VITAVE [14]. In the technical specification, a specification named *pulse amplitude* is described as having possible values of 400/730/900 V. However the term *pulse amplitude* is not described. And it is possible for two different people to read this term and apply two different meanings making the term equivocal.

For instance, consider the pulse voltage $v(t)$ depicted in Fig. 3 which has a maximum magnitude of V_{max} and a midpoint magnitude of V_{mid}. Without a standard definition set including a definition for the pulse amplitude term, it is conceivable that one reader may interpret the pulse amplitude to mean the maximum pulse magnitude while another reader may interpret the pulse amplitude to mean the midpoint pulse magnitude. Moreover, without adequate definitions of the foundation level terminology, it is not possible to form unequivocal definitions of more complex parameters such as distortion or accuracy.

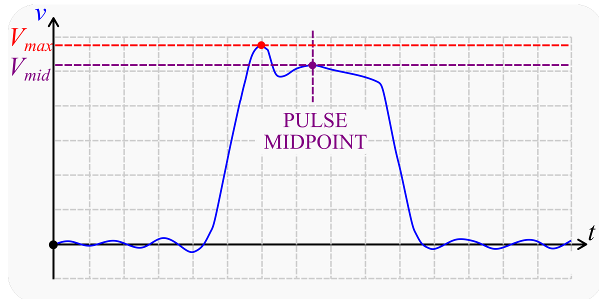


Fig. 3: The MAXIMUM and MIDPOINT MAGNITUDES of a PULSE $y(t)$.

2.2 Equivocal Time-Related definitions

A similar problem exists for time-related terminology used to describe the pulsed output. An example can be found here [15] where the authors describe the pulsed output of a PEF generator as a *"sequence of 20 biphasic bursts (100 µs duration)"*. The term *duration* here is highly ambiguous as it can mean several different time durations. Consider the three separate durations depicted in Fig. 4. It is unclear which if any of these definitions the authors may be referring to leading the reader to confusion and possible misinterpretation.

2.3 Equivocal Waveform-Related definitions

Moreover, the use of the term *biphasic* is equally ambiguous when used in this context describing a burst. The term biphasic is commonly used to describe the pulsed output of medical defibrillators [16]. When used to describe a defibrillator output, biphasic is used to describe a waveform with a magnitude which can easily be described by two distinct continuous functions during two distinct intervals in time when the defibrillator is supplying energy to the patient.

Similarly, the word monophasic is commonly used in defibrillation when referring to a pulsed output that can be described as a single continuous functions during a single interval when the defibrillator is supplying energy. And also,

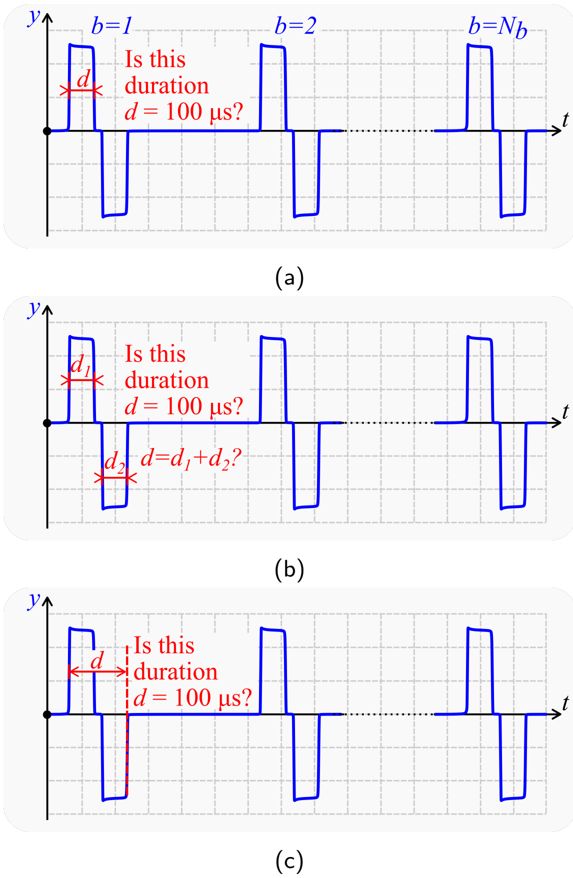


Fig. 4: Three possible interpretations of the meaning of duration d depicted separately in (a), (b) and (c).

the word triphasic can also be used to refer to a waveform that can be described as a three distinct continuous functions during a the distinct intervals when the defibrillator is supplying energy. A typical waveform of a monophasic, biphasic and triphasic defibrillator are shown in Fig. 5.

The defibrillation definition of the terms monophasic, biphasic and triphasic are intuitive, as the syllable *phasic* is used to refer to an interval in time, being derived from the word *phase* which is commonly used in mathematics to refer to time in units of radians. However, when the term *biphasic* is used to describe a burst waveform the use of the word becomes very misleading as it is open to multiple interpretations. The most common waveform of PEF generators is a burst. A burst is commonly and intuitively defined as a

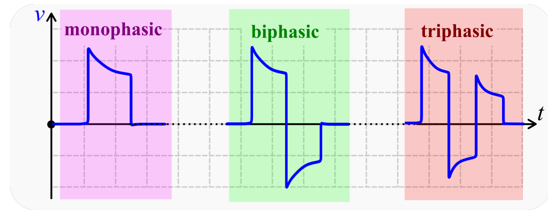


Fig. 5: The meaning of monphasic, biphasic and triphasic defibrillation waveshapes.

pulse train [17]. It is often the case in electroporation-related academic papers that the authors use the term biphasic to refer to bipolar pulse waveforms. Bipolar meaning a waveform which has both a magnitude with both positive and a negative polarity. Consider the three possibly-biphasic burst waveshapes shown in Fig. 6.

Fig. 6 (a) shows a burst train with voltage $v_1(t)$, where each burst in the train is a pulse train of two single pulses. The first pulse has a positive amplitude and the second pulse has a negative amplitude. There is no time separation between the first and second pulse within the burst. It is intuitive to call this waveform biphasic, as it can easily be described by two distinct continuous functions in two distinct intervals during the burst interval $[t_a \leq t < t_c]$ per equation 1.

$$\begin{aligned} v_1(t) &= V && \text{for} && t_a \leq t < t_b \\ v_1(t) &= -V && \text{for} && t_b \leq t < t_c \end{aligned} \tag{1}$$

Now consider the waveform $v_2(t)$ shown in Fig. 6 (b). It is unclear if this waveform can still be called biphasic. Each burst still consists of a bipolar pulse train with two single pulses. However, now the two single pulses are separated by a pulse separation time t_{ps}. Three separate continuous functions are now required to define the waveshape during the burst interval $[t_a \leq t < t_d]$ per equation 2.

$$\begin{aligned} v_2(t) &= V && \text{for} && t_a \leq t < t_b \\ v_2(t) &= 0 && \text{for} && t_b \leq t < t_c \\ v_2(t) &= -V && \text{for} && t_c \leq t < t_d \end{aligned} \tag{2}$$

As a result, it is unclear if this waveform is biphasic or triphasic which can lead to misinterpretation. A similar circumstance occurs for bursts with more than two single

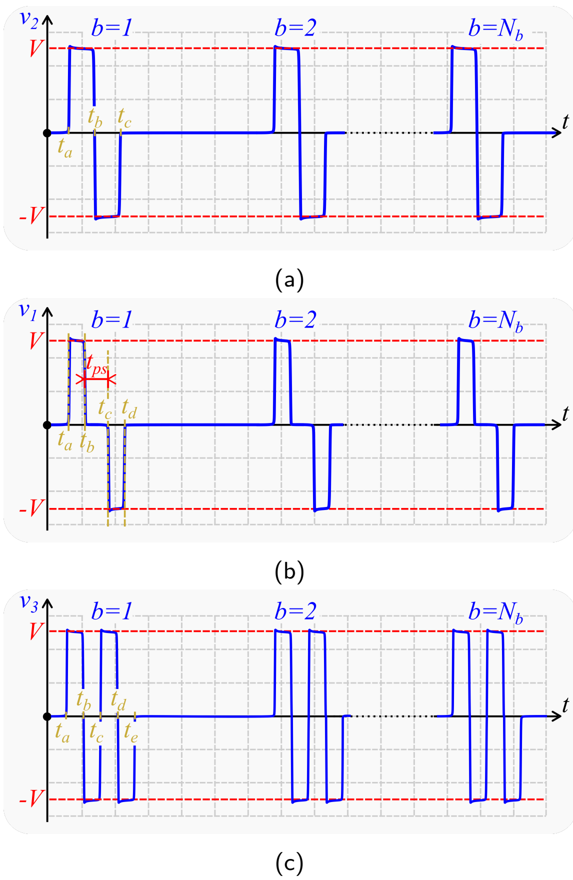


Fig. 6: Three possible interpretations of the meaning of term *biphasic* depicted separately in (a), (b) and (c).

pulses in the pulse train. Consider the waveform $v_3(t)$ depicted in Fig. 6 (c). In this example, each burst is a bipolar pulse train of four single pulses with no pulse separation. This waveform can be described by four separate continuous functions during the burst interval $[t_a \leq t < t_e]$ per equation 3.

$$
\begin{aligned}
v_3(t) &= V && \text{for} && t_a \leq t < t_b \\
v_3(t) &= -V && \text{for} && t_b \leq t < t_c \\
v_3(t) &= V && \text{for} && t_c \leq t < t_d \\
v_3(t) &= -V && \text{for} && t_d \leq t < t_e
\end{aligned} \tag{3}
$$

Hence, it is unclear if the term biphasic is still applicable to this waveform, or should it be described as *quadphasic*. Moreover, many readers commonly interprete all three of these waveforms as *biphasic*, while other readers hold true to the defibrillation meaning of biphasic and do not.

2.4 Unmeasurable Quantities

Another possible problem which which must be overcome when defining time durations, magnitude definitions or other quantities, is defining them in a manner that makes them measurable and doesn't open the possibility to measure the same parameter in multiple ways obtaining different results. This is a common problem for both time-related definitions and magnitude related-definitions. Consider Tab. 1 and Fig. 7 which attempt to define several time and magnitude parameters.

Tab. 1: Badly defined pulse parameters.

Parameter	Description
$t_{pos-width}$	The pulse width of the positive pulse.
$t_{pos-delay}$	The delay at 0V of the positive pulse, prior to switching negative.
$t_{neg-width}$	The pulse width of the negative pulse.
$t_{neg-delay}$	The delay at 0V of the negative pulse, prior to switching negative.
$V_{pos-amp}$	The target amplitude of the positive voltage pulse.
$N_{neg-amp}$	The target amplitude of the negative voltage pulse.

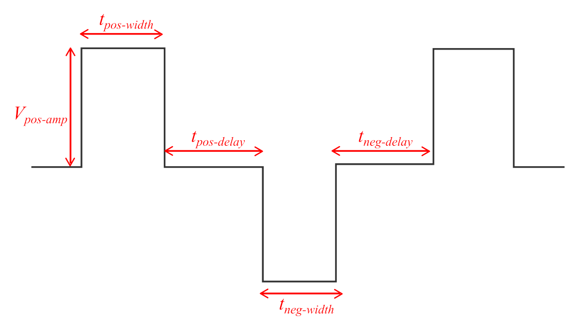


Fig. 7: An example of poorly-defined amplitude and timing definitions.

There are several issues with this set of definitions. However, the biggest problem being that many of these definitions cannot be measured. Consider the time duration $t_{pos-delay}$, which is defined at the instant the waveform is at 0 V, this time cannot actually be measured, as in a real measured waveform it's impossible to determine what are the instants that define the start and stop point of this measurement.

This problem is normally overcome by defining time instants at crossing points of a waveform. For example, rise time of a waveform is commonly defined as the time duration between the instants where the waveform's magnitude first crosses 10% and 90% of its final amplitude. However, for this definition to be unequivocal, there must be an unequivocal definition of the waveform's amplitude referenced by the rise-time definition. This practice is not the case for Tab. 1 and Fig. 7, which leads to unmeasurable definitions. This has a knock-on effect where engineers who create test plans, or write datasheets are forced to come up with their method to measure the defined parameter. This leads to the further problem where two different engineers can now measure the same defined parameter in two different manners obtaining two different results. For instance, the pulse width of a pulse could be measured as the time duration between the half-amplitude crossings of the pulse. This is a measurable definition. However a second engineer could also plausible measure pulse width as the duration between where the magnitude first crosses 10% of the amplitude and last crosses 10% of the amplitude. Hence, both engineers now measure different durations for the same definition.

3 The Proposed Solution

A standard set of terms and definitions to describe the pulsed output of PEF generators is required to overcome the issues with equivocal and unmeasurable definitions. As a result the author proposes the standard set of terms and definitions proposed in [13] as a suitable document. The purpose of this document is to provide a set of common definitions to enable efficient communication and fair comparison between different PEF generators. The document is also written as a possible base definition set which could be included in an collateral IEC60601 safety standard that covers clinical electroporators. The document is written to be compatible with the IEEE 1977 standard covering pulse terms [17]. However, the document differs from the IEEE standard to focus on the typical voltage-controlled burst-train output of PEF generators where each burst is a pulse train of rectangular pulses. The author has written the definition set so it may also be applied to current-controlled pulses or other types of pulses. And it is also written in such a way where it can be easily expanded to include other pulse waveforms, for instance a trapezoidal pulse definition can easily be added. All definitions have been written in a manner where they are intuitive, unambiguous and measurable. Important parameters which the author believes should be included in the technical specification of all clinical electroporators such as PULSE AMPLITUDE ACCURACY, DISTORTION and OVERSHOOT have also been included. Defined terms within the document are printed in SMALL CAPITAL to assist the reader in identifying them throughout the document. When normal case is used, the words have their normal English meaning. The same font style is followed in this paper.

3.1 Unequivocal and Intuitive Magnitude-Related Definitions

There are many different ways to define the magnitude of a pulse discussed in Section 2. The standard set of definitions overcomes this by defining separate definitions for all the terms PULSE AMPLITUDE Y, MAXIMUM PULSE MAGNITUDE Y_{max}, MINIMUM PULSE MAGNITUDE Y_{min}, MIDPOINT PULSE MAGNITUDE Y_{mid}, TOP MAGNITUDE Y_T and BASE MAGNITUDE Y_B for a waveform $y(t)$. Moreover, all terms are given a common mathematical notation such as Y or Y_{max} to enable the reader to easily identify the definitions in mathematical equations. Definitions are defined over a single pulse and to be as intuitive as possible to reduce the chances of misinterpretation, see for instance Fig. 8 which depicts the MAXIMUM PULSE MAGNITUDE Y_{max}, MINIMUM PULSE MAGNITUDE Y_{min} and MIDPOINT PULSE MAGNITUDE Y_{mid}, without having read the standard set of definitions, it is still intuitive to the reader the meanings of these terms.

Several possible ways exist to measure the amplitude of a waveform. The most common method used by oscilloscopes to determine amplitude is the histogram method [18]. It is also possible to use a the integral method defined in [13]. The author has chosen to use the integral method as it believed to be a more true measurement of PULSE AMPLITUDE of a rectangular pulse. The method works by defining a REFERENCE waveform which has the ideal shape of the pulse waveform. For instance a rectangular pulse $r(t)$ depicted in Fig. 9 has the shape of an ideal rectangle such that;

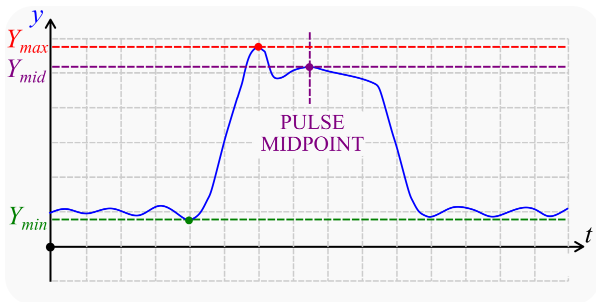


Fig. 8: The MAXIMUM Y_{max}, MINIMUM Y_{min} and MIDPOINT MAGNITUDES Y_{mid} of a PULSE $y(t)$.

$$
\begin{aligned}
r(t) &= Y_B && \text{for} && 0 \leq t < t_{m1} \\
r(t) &= Y_T && \text{for} && t_{m1} \leq t < t_{m2} \\
r(t) &= Y_B && \text{for} && t_{m2} \leq t < t_f
\end{aligned}
$$

where Y_B and Y_T are a constant numbers, the instants t_{m1} and t_{m2} are the mesial-line crossings of $y(t)$, and $t = 0$ and t_f are instants the initial and final data points in the set of known data points of the pulse waveform.

The TOP MAGNITUDE and BASE MAGNITUDE can be determined be finding values of Y_T and Y_B which satisfy the following integrals.

$$
Y_B = \frac{1}{t_1 + (t_f - t_2)} \left(\int_{t=0}^{t_1} y(t)\mathrm{d}t + \int_{t=t_2}^{t_f} y(t)\mathrm{d}t \right) \tag{4}
$$

$$
\int_{t=t_1}^{t_2} (y(t) - Y_B)\mathrm{d}t = \int_{t=t_1}^{t_2} (r(t) - Y_B)\mathrm{d}t \tag{5}
$$

The PULSE AMPLITUDE is then easily determined as $Y = Y_B - Y_T$. An iterative algorithm is required to simultaneously solve equations (4) and (5) to obtain Y_T and Y_B. An example of a suitable iterative algorithm is discussed in [19].

It is important to determine the difference between the REFERENCE $r(t)$ and SETPOINT $s(t)$ waveforms. The REFERENCE pulse $r(t)$ describes a pulse with the same PULSE AMPLITUDE and PULSE WIDTH as the measured pulse $y(t)$, but with an ideal shape. The conception of the REFERENCE waveform is necessary to determine the PULSE AMPLITUDE. Hence, with this set of definitions, it is possible to determine the voltage PULSE AMPLITUDE and the current PULSE

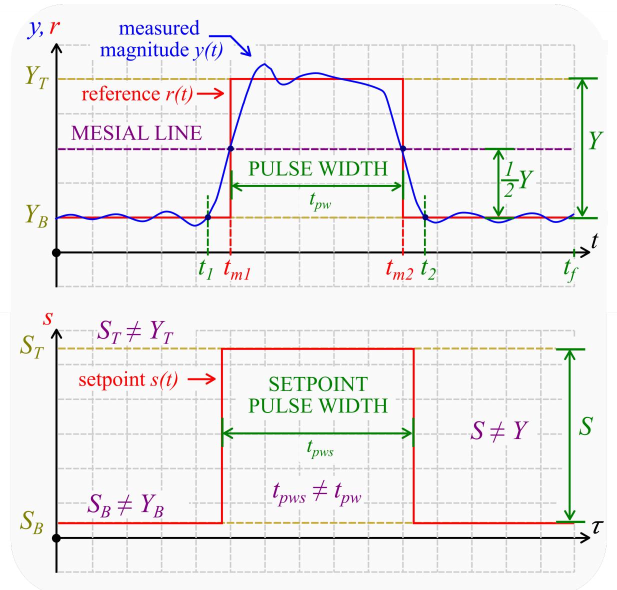


Fig. 9: The REFERENCE WAVEFORM $r(t)$ and SETPOINT WAVEFORM $s(\tau)$ of a RECTANGULAR PULSE with MAGNITUDE $y(t)$.

AMPLITUDE independent of knowing the SETPOINT. This is important, as there are many cases where no SETPOINT or desired quantity may exist for a certain parameter. For instance, if a clinical electropoator is commanded to output a voltage-controlled rectangular pulse it is clear a SETPOINT voltage PULSE AMPLITUDE must be defined. However in this case there is no SETPOINT value for the current PULSE AMPLITUDE, as the PULSE AMPLITUDE of the current varies as a function of the tissues conductivity which can be a range of values, however the PULSE AMPLITUDE of the current waveform can still be determined using the standard definition set by defining a REFERENCE waveform and using the integral method.

Moreover, it is equally important to separately define the SETPOINT waveform $s(t)$ to allow ACCURACY to be defined. The SETPOINT waveform is the waveform which has both the ideal shape and desired amplitude and timing parameters. The SETPOINT waveform of a rectangular pulse is also depicted in Fig. 9, but SETPOINT and REFERENCE waveforms have different amplitudes and timing parameters. This distinction between SETPOINT and REFERENCE enables the writer or reader to discuss accuracy. For instance, typically a clinical electroporator is commanded to output with a voltage-controlled uniform PULSED AMPLITUDE. So, you could command a setpoint PULSED AMPLITUDE of $S =$ 400 V. However, the measured PULSED AMPLITUDE may be a different number such as $Y = 440$ V, which can be determined be creating a REFERENCE waveform and using the integral method. Hence, it is now possible to define the PULSE AMPLITUDE ACCURACY as 40 V or 10 % when expressed as a percentage of the SETPOINT value.

3.2 Unequivocal and Intuitive Time-Related Definitions

Unequivocal timing definitions can be obtained by defining unequivocal timing instants. This is possible once unequivocal definitions for magnitudes exists, as then timing instants can be defined when the magnitude of a given waveform $y(t)$ crosses a certain magnitude reference line. The proposed standard definition set [13] defines timings over a single pulse, burst and burst train. The timing definitions over a single burst $y(t)$ are depicted in Fig. 10. All timing definitions are defined at magnitude crossing points. For example, the times PULSE SEPARATION, PULSE WIDTH and PULSE PERIOD are all defined between the instants of the half-amplitude crossings, given unequivocal definitions are provided for amplitude, the timing definitions are equally unequivocal. Moreover, the proposed definitions names are all very intuitive. PULSE SEPARATION is the time that separates a single pulse from another single pulse, PULSE WIDTH is the width of a single pulse, BURST WIDTH is the width of a single burst etc. A *pulse duration* is never defined as it was deemed too ambiguous.

3.3 Unequivocal Waveform-Related Definitions

Waveform-related definitions are also defined in [13] to avoid ambiguity between the meanings of terms such as PULSE, BURST or BURST TRAIN. Definitions for UNIPOLAR and BIPOLAR are included to enable writers describe pulse trains of with a magnitudes of only one or two polarities respectively. The terms *monophasic*, *biphasic* and *triphasic* have been excluded due to ease at which they can be misinterpreted.

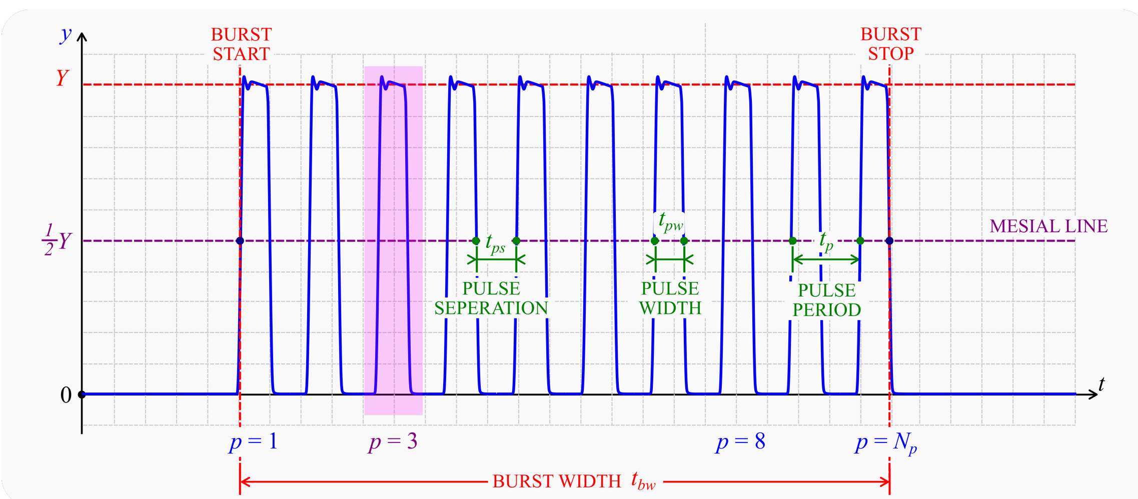


Fig. 10: A single UNIPOLAR BURST $y(t)$.

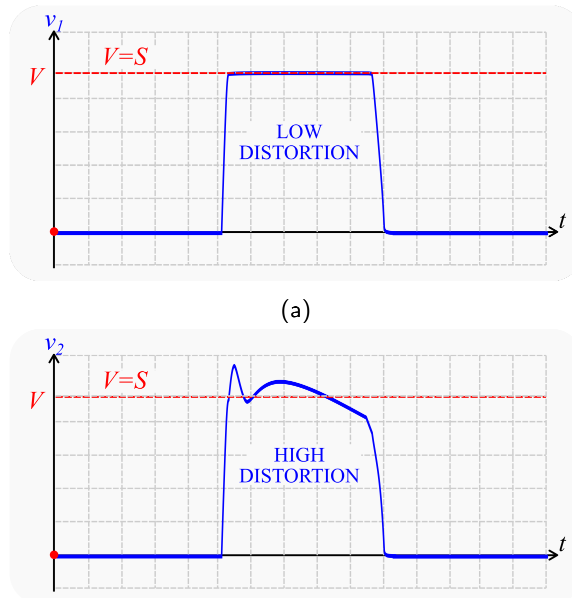
3.4 Important Parameters for Electroporation

The goal of a clinical electroporator is to excite the targeted tissue with the correct pulsed voltage to enable successful electroporation. Different electroporation-based therapies require specific $\bar{E}$-fields to enable successful electroporation. For ECT the ESOPE protocol asks for an $\bar{E}$-fields of 1000 V/cm [20]. Similarly, PFA normally requires an $\bar{E}$-field of 400 V/cm as this is the required level needed to IRE electroporate the myocardium cells in the heart [4]. In order to excite the cells with the correct $\bar{E}$-field magnitude, the clinical electroporator is required to produce a rectangular pulse with the right magnitude. Looking specifically at skin ECT, to induce an $\bar{E}$-field of 1000 V/cm, the clinical electroporator may be commanded to deliver a pulsed output with a PULSE AMPLITUDE of 400 V to probe. The relationship between the output voltage and $\bar{E}$-field is a function of the probe design and geometry. Although the clinical electroporator may be commanded to deliver 400 V the true pulsed output of the clinical electroporator is different from this number due to the finite accuracy of any real generator.

As a result, a standard definition for PULSE AMPLITUDE ACCURACY has been included in [13]. It is the authors opinion that this term should be characterized in the technical specification of any clinical electroporator to allow a fair comparison between clinical electroporators, and also to enable electroporation experiments to be more repeatible when repeated on different generators. A definition for ACCURACY in general has also been provided to allow for the characterization of other pulse parameters other than PULSE AMPLITUDE, for instance the ACCURACY of any SETPOINT timing parameter such as PULSE WIDTH may be determined also.

Although a clinical electroporator may have a very high PULSE AMPLITUDE ACCURACY, it is true the same clinical electroporator may have a very low distortion or a very high distortion output. This scenario is depicted in Fig. 11. It is unclear if a pulse with high accuracy but also high distortion can successfully electroporate targeted cells as well as a pulse with high accuracy and high distortion. Hence, definitions for DISTORTION have been included in [13] such as TOP DISTORTION, BASE DISTORTION and OVERSHOOT. It is the authors opinion these parameters should also be included in the technical specification of any clinical electroporator.

This sentiment has been mirrored in other published work which has called for the standardization of the functional requirements of clinical electroporators [21, 22].



(a)

(b)

Fig. 11: A single rectangular pulse with perfect accuracy and (a) low distortion and (b) high distortion.

4 Examples of Pulsed Outputs

In this section, the standard set of definitions [13] is used to describe some common pulsed outputs of clinical electroporators.

4.1 Pulsed Output for ECT per ESOPE

Per the ESOPE guidlines [20], skin ECT is performed by applying a PULSE TRAIN of eight single pulses with a PULSE WIDTH of 100 µs. The pulses may be repeated at a PULSE FREQUENCY of 1 Hz or 5 kHz. The pulse parameters for this output are provided in Tab. 2 and Tab. 3 for PULSE FREQUENCIES of 1 Hz and 5 kHz respectively.

Tab. 2: ESOPE pulse parameters for skin ECT at a 5kHz PULSE FREQUENCY.

Parameter	Description
Voltage PULSE AMPLITUDE	400 V
Burst Type	A single UNIPOLAR BURST
PULSE PERIOD	200 µs
PULSE FREQUENCY	5 kHz
PULSE WIDTH	100 µs
PULSE SEPERATION	100 µs
NUMBER OF PULSES	8
BURST WIDTH	1.5 ms

Tab. 3: ESOPE pulse parameters for skin ECT at a 1 Hz PULSE FREQUENCY.

Parameter	Description
Voltage PULSE AMPLITUDE	400 V
Burst Type	A single UNIPOLAR BURST
PULSE PERIOD	1 s
PULSE FREQUENCY	1 Hz
PULSE WIDTH	100 µs
PULSE SEPERATION	1 s
NUMBER OF PULSES	8
BURST WIDTH	7 s

4.2 Pulsed Output for ECT using HFIRE

Patients who undergo skin ECT are put under local anaesthetic only. As a result, patients can suffer pain or significant levels of discomfort during the treatment due to the application of electrical shocks from the clinical electroporator . In more recent times, the use of HFIRE pulses has been demonstrated to reduce patient pain [23]. HFIRE stands for high frequency reversible and/or irreversible electroporation. The term HFIRE does not mean a specific set of pulse parameters, instead it means a burst-train waveform with high PULSE FREQUENCY and low PULSE WIDTH.

4.3 Pulsed Output for Cardiac PFA with a Circular Catheter

The pulsed output of for cardiac PFA with a circular catheter described here [3] used the pulse parameters described in Tab. 5. Some pulse parameters had to be guessed as they were not published in [3]. Here we can see this burst-train is comprised of SWITCHED BIPOLAR BURSTS.

Hence, the standard set of definitions is suitable to describe the pulsed output waveform for many different types of electroporation-based therapies, including but not limited to skin ECT and cardiac PFA.

5 Experimental

Experimental work of a demo PEF generator described in this Section. A photo of the experimental setup is provided in Fig. 12. The prototype PEF generator is connected to different resistive loads through a different contactors contained in a 2U 19" rack. The different Rloads have similar resistance to that of human tissue.

The PEFG is commanded to output the different pulse parameters for skin ECT with ESOPE parameters defined in Tab.3 and HFIRE parameters defined in Tab. 4 into a 66.67

Tab. 5: Pulse parameters for cardiac PFA per [3].

Parameter	Description
Voltage PULSE AMPLITUDE	300 V to 700 V
Burst Type	SWITCHED BIPOLAR BURST
Burst Period	600 µs
Burst Frequency	1.67 kHz
Burst Separation	200 µs
Number of Bursts	60
Pulse Period (Guess)	10 µs
Pulse Frequency (Guess)	100 kHz
Pulse Width (Guess)	5 µs
Pulse Separation (Guess)	5 µs
Number of Positive Pulses	10
Number of Negative Pulses	10
Burst Width	400 µs
Burst-Train Width	35.8 ms

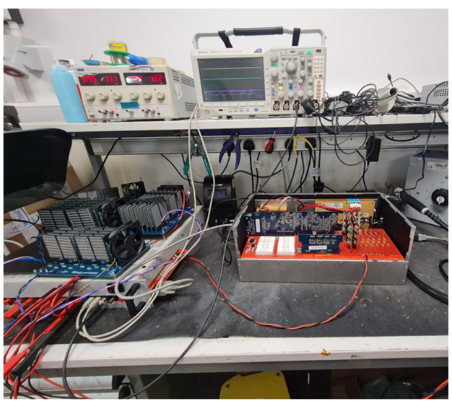
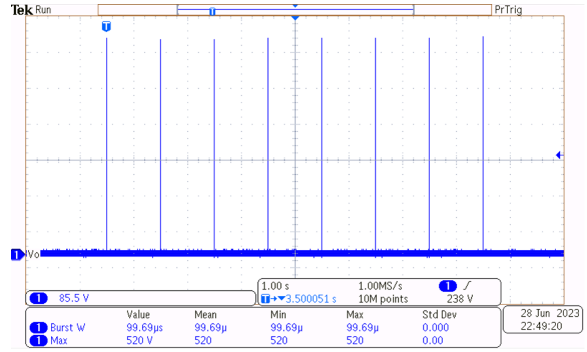


Fig. 12: A photo of the experimental setup.

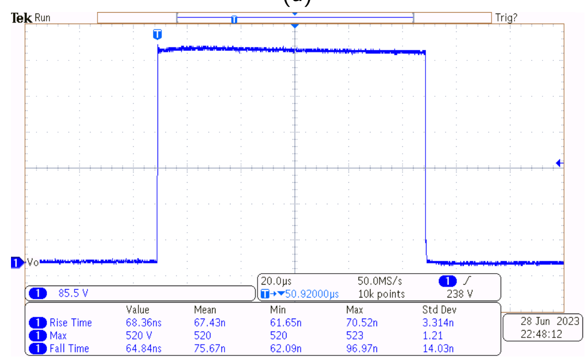
Ω Rload board. These values correspond to a current of 6 A.

Since the ESOPE pulse parameters are only a single BURST, this waveform is captured on the scope over the interval of a single BURST in Fig 13 (a) and over the interval of a single PULSE shown in Fig 13 (b).

The pulsed output for skin ECT using HFIRE consists of a BURST TRAIN with 30 BURSTS, where each burst is a SYMMETRICAL BIPOLAR BURST. This waveform is depicted in Fig 14 over the interval of the full BURST TRAIN in Fig 14 (a), the interval of a full BURST in Fig 14 (b), the interval of several PULSES in Fig 14 (c) and over the interval of a single PULSE in Fig 14 (d).



(a)



(b)

Fig. 13: Pulsed output for skin ECT using ESOPE at $f_p = 1$ Hz depicting an entire (a) BURST and (b) a single PULSE.

6 Conclusion

The work carried out in this paper focused on adequately describing the pulsed output of PEF generators used for medical electroporation-based therapies. Examples of electroporation based therapies were discussed including skin ECT and cardiac PFA. It was demonstrated the current field of electroporation-based medical therapies has set a low standard in adequately defining the technical specification of clinical electorporators and describing their pulse output in an unambiguous fashion. The widespread use of equivocal terms and definitions used to describe the pulsed output was discussed.

A set of standard definitions to describe the pulsed output of clinical electroporators was proposed. The new definition set was written to be easy-to-read and difficult to misinterpret. Definitions and terms included magnitude-related definitions for terms like PULSE AMPLITUDE, MAXIMUM MAGNITUDE etc, timing-related definitions including parameters such as PULSE WIDTH and BURST WIDTH etc as well as waveform-related definitions such as PULSE, BURST and BURST TRAIN. Moreover the need to include definitions for terms such as ACCURACY and DISTORTION was also discussed, calling for these parameters to be characterised in the technical specification of all clinical electroporators.

The set of standard definitions was used to describe some standard pulsed outputs of clinical electroporators, including the pulsed output used for skin ECT per ESOPE and using a HFIRE waveform. As well as an example of a pulse output used in cardiac PFA, demonstrating the set of standard definitions is useful at describing the pulsed outputs of many different types of electroporation-based therapies. Lastly experimental results were provided showing measured examples of the pulsed output of a demo PEF generator.

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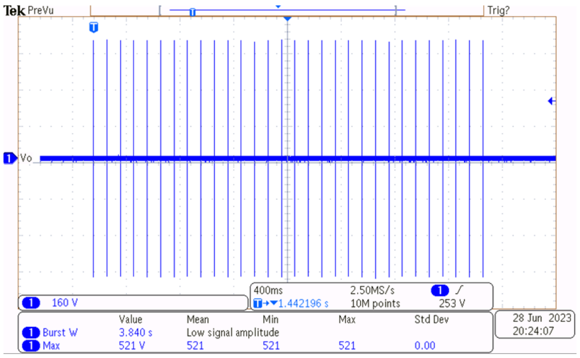
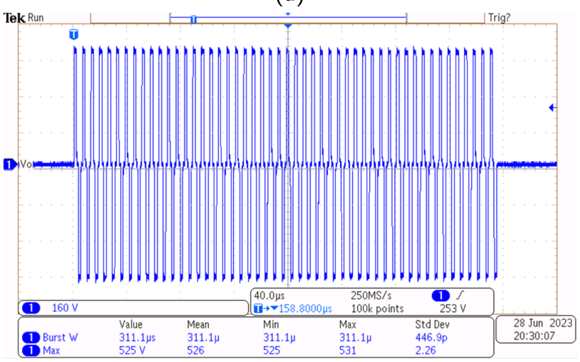


(a)



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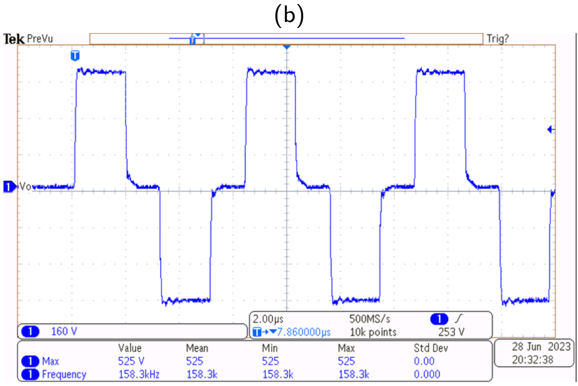

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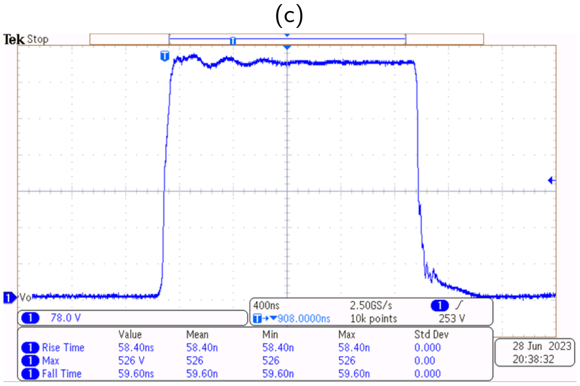

(d)

Fig. 14: Pulsed output for skin ECT using HFIRE depicting an entire (a) BURST TRAIN (b) BURST, (c) several single PULSES and (d) a single PULSE.