Abstract: Electroporation is a pulsed electric field triggered phenomenon of cell permeabilization, which is extensively used in biomedical and biotechnological context. There is a growing scientific demand for high-voltage and/or high-frequency pulse generators for electroporation of cells (electroporators). In the scope of this article we have reviewed the basic topologies of nanosecond pulsed electric field (nsPEF) generators for electroporation and the parametric capabilities of various in-house built devices, which were introduced in the last two decades. Classification of more than 60 various nsPEF generators was performed and pulse forming characteristics (pulse shape, voltage, duration and repetition frequency) were listed and compared. Lastly, the trends in the development of the electroporation technology were discussed.

Keywords: electroporation; electroporators; nanosecond pulsed electric fields; nsPEF; pulsed power devices; high frequency; MOSFET; capacitor discharge; Blumlein; high-voltage generators

1. Introduction

High intensity pulsed electric fields (PEF) can trigger increased permeability of biological cells to exogenous molecules to which the cells were initially impermeable [1]. PEF polarizes the cell membrane, which causes reorientation of lipids and formation of pores [2,3], thus increasing molecular transport across the cell membrane [4,5]. In case of reversible electroporation (depends on pulse parameters), the cell membrane is then resealed [6]. As a result, there is a variety of electroporation applications, which include cancer treatment [7], gene delivery [8], food processing [9], biorefinery [10] and many other [11,12]. In each case, various PEF parameters are required, which establishes a challenge in generator design in terms of universality. The straightforward distribution of applications in the pulse amplitude–duration space is summarized in Figure 1 [13–19].

It can be seen that the majority of applications lie in the micro-millisecond range. Indeed, the range of longer but lower amplitude pulses dominated the field for decades, however, in the recent years the number of works focusing shorter (nanosecond) pulses increased significantly. The reason lies in the limitations of conventional microsecond range methodologies such as bioimpedance-dependent field distribution [20], Joule heating [21], muscle contractions [22], electrical breakdown [23] and oxidative stress [24]. Nanosecond pulses cannot solve all the problems completely, however, in many cases the negative factors are diminished. However, state-of-art pulsed power electronics are required for generators to form pulses up to tens of kV and hundreds of amperes in the nanosecond range. Therefore, the price and engineering complexity of such generators is high, nevertheless, the trends in applications of nanosecond PEF make it viable (Figure 2).
As it can be seen in Figure 2, there is a definitive rise in publications in the last decade, which partially is a consequence of better availability of pulse forming switches on the market. Development of laboratory grade generators for electroporation has intensified with the development of better semiconductors (i.e., silicon-carbide technology) [25]. Nevertheless, the number of papers focusing nanosecond pulse generators for electroporation is still low. A similar trend is observed in the frontier of short microsecond or sub-microsecond pulses using high frequency bursts (Figure 3), which possibly is a natural transition step from long micro-millisecond to the nanosecond range.

For the optimal effectiveness of the treatment many electroporation parameters must be adjusted, i.e., the pulse amplitude and duration, repetition frequency, waveform and number of pulses. As a result, universality of electroporators is important when a study of new phenomena and biological effects of PEF are established.
waveform, voltage amplitude and pulse widths. The pulse forming circuits of the electroporator can be developed with the pulse amplitude up to few kV and duration from tens of µs to seconds. These circuits can be enhanced by the application of modular approach, application of transformers, diodes or even by the application of in-house built topologies used for generator design [28,30,34–40].

In comparison, the selection of commercial high-voltage nanosecond pulsed electric field (nsPEF) electroporators is significantly lower [27,28]. Additionally, it is common, that the commercial devices have a limited range of available pulse durations and repetition frequencies, thus the device applicability is non-flexible. This is one of the main reasons, why the commercial electroporators are also not perfectly suited for electroporation research applications, where a wide parameters selection is desired. To sum up, the there is a growing scientific demand for nanosecond and high-frequency electroporators, which can, but are not limited, to deliver sub-microsecond range adjustable energy pulses. To cover the demand, the researchers develop in-house electroporators [29–33]. While the up to date review of commercial available PEF generators is available [27], there is no (at our knowledge) extensive overview of in-house built nanosecond and high-frequency electroporators. Currently, the works are mainly focused on the review of the general topologies used for generator design [28,30,34–40].

In the scope of this article, we reviewed the scientific papers reporting the developed nsPEF generators for electroporation in the last two decades. In addition, this article includes a summary and comparison of techniques used for the development of the PEF generator and the classification of generators is proposed based on the pulse forming circuit design. In total more than 60 in-house built nsPEF generators for electroporation applications were found, classified and compared.

2. Basic Generator Topologies

For electroporation research it is essential to have a pulse generator suitable to deliver controllable energy to biological tissue via application of repetitive electrical pulses with the predefined pulse waveform, voltage amplitude and pulse widths. The pulse forming circuits of the electroporator can be based on relatively simple circuits, which are discussed in the following works [15,26–28,34,38–42] and summarized in this section. The energy delivery can be provided by capacitor, inductor or transmission lines with the control of the switching element. These circuits can be enhanced by the application of
2.1. Pulse Forming Using Capacitor Discharge Circuits

A direct capacitor discharge pulse forming circuit concept is one of the most common, simple and oldest concepts for PEF pulse forming [15,43]. It is based on the transfer of energy stored in the capacitors into the load throughout well-defined voltage pulses. The pulse delivery is normally controlled with a semiconductor switch. Depending on the switch type or driving mode, the waveform is either rectangular (using metal–oxide–semiconductor field-effect transistors (MOSFETs) and insulated-gate bipolar transistors (IGBTs) [44]) or exponential decay wave (older concept typically used with thyristors [45]). In case of exponential decay pulses, the duration of the pulse (decay time) is defined by RC parameters of the discharge circuit, while in the case of rectangular pulses the parameters are mostly limited by the switch capabilities and the discharge capacitor value. The principle pulse forming circuit of capacitor discharge pulse generator is represented in Figure 4.

![Figure 4. The principle circuit of a direct capacitor discharge pulse generator.](image)

The pulse generator is composed of a variable high-voltage power supply V, a discharge capacitor C, a switch SW and optionally a resistor R. The direct capacitor discharge topology benefits from a simple and inexpensive design [38,43]. However, to ensure the rectangular wave delivery and limiting the pulse amplitude droop, a high capacity (μF to mF range) capacitor bank is required and the switch must withstand the full voltage amplitude. It limits the selection of available switches in case of high-voltage builds. In such a case, several series switches must be used, which results in increased complexity of the generator due to challenges in switch synchronization.

To overcome the limitations of the direct capacitor discharge concept, a more complex modular circuit topology can be used [46]. It provides voltage distribution between several switches and gives additional flexibility for the output pulse shape and amplitude. A simple example of a modular structure is presented in Figure 5.

The circuit includes several galvanically isolated high-voltage power supplies V1,2,...n. Each is controlled individually and can be set to a different amplitude. The voltages of the individual circuits contribute to the generation of a single output pulse at any time. The output voltage will be the sum of the voltages from separate stages, so adjusting the output voltage is possible. However, many stages are required to have enough output voltage levels, which consequently increases the cost of the device [38,39].

The Marx generator is an example of a modular circuit, however, due to high applicability it is often separated as an independent topology. Originally it was developed to test power grid high-voltage components and provide a capability to produce high-voltage pulses using a low-voltage DC supply. This topology has been adopted for PEF generation and widely used in electroporation applications [30,31]. The simplified circuit is represented in Figure 6.
The full Marx topology is based on separate stages/cells, where each stage has an energy storing capacitor C, a resistor R and a switch SW. The stages are charged in parallel from a direct current power supply V and subsequently connected in series with a load when the switches are triggered. In case of spark gaps the capacitors are fully discharged (decaying pulse), however the current and voltage flexibilities are high. For such a design, the pulse repetition rates are frequently in the order of several Hz, but the total charging voltage can reach tens or even hundreds of kV [47–49]. The voltage levels between 50 and 100 kV are most commonly used in industrial application [50–52]. In case when the semiconductor switches are used, a partial discharge of the capacitors can be achieved. The output voltages are frequently determined by the switch breakdown voltage and the number of stages, however, devices in the range of 1–6 kV are common [31,39,53].

In case the bipolar pulses are required to optimize the electroporation applications (e.g., food products treatment) [54,55], the direct capacitor discharge pulse generator concept can be enhanced with half-bridge or full-bridge circuit [56] as presented in Figure 7.

In both cases the generator can produce positive and/or negative high-voltage pulses. However, the half bridge topology has limitations in operation with capacitive-type of loads, hence full-bridge concept is more common. The increase of the number of the switches in a full-bridge concept brings additional operational flexibility similarly to the direct capacitor discharge topology. Moreover, to enhance the pulse control and scalability several half-bridge or full-bridge pulse forming circuits can be stacked in a modular approach [30,32,57]. Additionally, Marx generators can be arranged in a bridge configuration to enable the generation of bipolar pulses [30,31,58].

Nevertheless, independently on the topologies described above the capacitor discharge circuits are limited by switching dynamics of semiconductor devices, thus the minimal pulse durations are typically in the sub-microsecond range. In order to form shorter pulses (i.e., less than 100 ns) other electroporator topologies are required.

![Figure 5. The principle circuit of modular direct capacitor discharge pulse generator.](image)

![Figure 6. The circuit of pulse generator based on Marx topology.](image)
The transmission line discharge and pulse forming are controlled by the switch SW.

Impedance of biological tissue is often unknown, can vary from sample to sample and can be even more than the transmission line impedance, thus reflections of the voltage step at the load and at the open end of the lines of identical length \( l \). Both transmission lines are electrically connected at one end to a load and of rectangular high-voltage nsPEF pulses \[ 60–62 \]. The generator is based on the two transmission line pulse generator. Blumlein pulse generator is one of the most popular designs for the generation of bipolar half-bridge (a) and full-bridge (b) direct capacitor discharge pulse generator.

**2.2. Pulse Forming Circuit Topology Based on Transmission Lines**

The other group of pulse forming circuits is based on the charge and discharge of the transmission lines. This is a common type of circuit topology for generation of high-voltage pulses with less than 100 ns duration \[ 39,59 \]. As illustrated in Figure 8, the pulse forming circuit is composed of coaxial cable, which is used as a conductor of length \( l \) and charged through a resistor \( R \) to a voltage \( V \). The transmission line discharge and pulse forming are controlled by the switch SW.

![Circuit Diagram](image_url)

*Figure 7. The conceptual circuit of bipolar half-bridge (a) and full-bridge (b) direct capacitor discharge pulse generator.*

In order to form rectangular pulses the impedance of the load must match the characteristic impedance of the transmission line. However, load matching requirement by design limits the generator’s compatibility with dynamic loads since the impedance of the transmission line is dependent on the parameters of the cable.

The pulse amplitude of a single transmission line generator is limited to the half of the power supply voltage, while two or more lines must be used to match the pulse amplitude voltage to the power supply voltage (Figure 9). This type of configuration is known as a Blumlein transmission line pulse generator. Blumlein pulse generator is one of the most popular designs for the generation of rectangular high-voltage nsPEF pulses \[ 60–62 \]. The generator is based on the two transmission lines of identical length \( l \). Both transmission lines are electrically connected at one end to a load and discharged by closing the switch. If the load is mismatched (i.e., the load resistance is larger or smaller than the transmission line impedance), reflections of the voltage step at the load and at the open end of the transmission line will lead to a strain of consecutive decaying pulses \[ 42,63,64 \]. Hence, to generate rectangular wave pulse without any pulse reflections, the impedance of the load must be twice the impedance of the transmission line. This is not always an easy task to achieve, since the electrical impedance of biological tissue is often unknown, can vary from sample to sample and can be even dynamic during the pulse delivery \[ 38,65 \].

![Circuit Diagram](image_url)

*Figure 8. The conceptual circuit of a transmission line pulse generator.*
The switching element must withstand full high-voltage, which can be a challenge. On the other hand, instead, improved circuits are applied (i.e., the diode opening switch (DOS)).

After the switch SW1 is closed, the magnetic energy stored in the inductor reaches its maximum. At this point, the opening switch and the electric energy stored in the capacitor bank decreases. At the peak of sinusoidal current, energy storage and an inductor for secondary magnetic energy storage.

Lastly, the Blumlein generators are large dimension devices and have high demands for the electrical components. The usual concepts have a relatively short lifetime and operate in low repetition rate, while a rectangular wave pulse is typically delivered with a jitter [38,63]. However, with the latest modifications, Blumlein generators can now generate also a high-frequency (range of up to few MHz) output pulses with variable duration, amplitude and even polarity [38,60,63,66].

2.3. The Inductive Energy Discharge Pulse Generators

The third group of pulse generators is based on inductive energy discharge circuits, which transfer energy stored in the magnetic fields of coils into well-defined voltage pulses. The circuit concept is shown in Figure 10.

Figure 9. The conceptual circuit of a Blumlein pulse generator.

![Figure 9](image)

Figure 10. The conceptual circuit of an inductive energy discharge pulse generator.

![Figure 10](image)

The generator uses an AC power supply, a low voltage capacitor bank C for a primary electric energy storage and an inductor for secondary magnetic energy storage. When the switch SW1 is closed, the electric energy is discharged from the capacitor bank C into the inductor L. Hence, during the first quarter period of the sinusoidal AC-current, the magnetic energy stored in the inductor increases and the electric energy stored in the capacitor bank decreases. At the peak of sinusoidal current, the magnetic energy stored in the inductor reaches its maximum. At this point, the opening switch SW2 is activated and the current is abruptly interrupted influencing high rate of change of the magnetic flux \((dB/dt)\). Such a transient process induces voltage in the inductor, which is further discharged by a spark gap through the load [67].

The inductive energy discharge pulse generator has many drawbacks and is not used for electroporation research. Instead, improved circuits are applied (i.e., the diode opening switch (DOS)
After completing half of the period, the resonant network starts pumping the current through the presented in Figure 12.

Figure 11. The circuit of a diode opening switch generator.

The diode opening switch circuit is based on the DC voltage power supply V, which charges the capacitor bank C1 through the resistor R. When the capacitor is fully charged, the switch SW is closed and the energy in the capacitor C1 starts circulating in the resonant network (C1, C2, L1 and L2). After completing half of the period, the resonant network starts pumping the current through the diodes in the reverse direction. Ideally, the diode abruptly stops conducting and commutates the L2 current into the load. Therefore, this type of circuit is based on the saved energy transfer from inductor L2 to the load with a good repeatability [29].

Beside the application of diodes, it is also common that the inductive energy discharge pulse generator can be improved with the step-up pulse transformer. In this case the amplitude of the voltage pulse did not affect the opening switch [39]. A simplified transformer-based pulse forming circuit is presented in Figure 12.

Figure 12. The conceptual circuit of a transformers-based pulse generator.

Despite the advantages, the transformer-based pulse generator also has several issues, like core saturation, reset time after pulse delivery and distorted pulse shape because of the parasitic circuit elements. All these issues must be considered during the design of the pulse forming circuit [39]. On the other hand, the transformer based topology can be combined with the modular approach discussed before providing additional flexibility and pulse control [68].

3. Overview

3.1. Advantages and Disadvantages of the Typical Electroporator Concepts

The presented concepts of pulse generators demonstrate the diversity of techniques used for high-voltage pulse generation suitable for electroporation applications. All the techniques are summarized in the Figure 13.
Based on the energy storage, the pulse generators can be divided into three main groups: direct capacitor discharge, transmission line discharge and inductive storage discharge. Each has advantages and disadvantages, which are summarized in the Table 1.

Further, the in-house built nsPEF generators were analyzed and classified based on the switching type. The review focused only on nsPEF pulse generators, which were reported specifically for the application in the field of electroporation. We have included only the references where the reported duration of the pulse is in the sub-microsecond range (below 1 µs). In total 63 nsPEF generators for electroporation matched the requirements and are listed in Table 2. The devices are grouped based on the pulse forming circuit with the following parameters reported: pulse form, pulse duration, maximum pulse amplitude, pulse repetition frequency, switch type, switch model and additional remarks on the pulse form and topology in case the divergence from the usual performance is noticed.
Table 1. The comparison between the topologies of pulse generators used for electroporation.

| Concept          | Advantage                                                                 | Disadvantage                                                                |
|------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Direct Capacitor | Simple and inexpensive construction for systems up to 1 kV;              | High-voltage supply required;                                               |
|                  | Very flexible pulse shape control in the sub-microsecond–millisecond range; | Amplitude droop during the pulse;                                            |
|                  | Can operate in a high frequency range.                                    | High capacity capacitor banks are required for rectangular wave delivery into high loads; |
|                  |                                                                           | Switch must withstand full voltage amplitude or complex synchronization circuits are required in case of array of switches; |
|                  |                                                                           | Not suitable for sub-100 ns pulses.                                         |
| Non-Modular      | Non-Modular                                                               |                                                                              |
| Bipolar          | Positive and/or negative high-voltage pulses;                            | Switch synchronization is needed;                                           |
|                  | Highest pulse forming flexibility;                                        | Complex control systems;                                                    |
|                  | Capability to use asymmetrical pulses;                                    | Limited voltage handling capability;                                        |
|                  | Specific electrotransfer mechanisms can be triggered.                    | Not suitable for sub-100 ns pulses.                                         |
| Modular          | Applicable with low voltage switches and voltage supplies;               | Limited amplitude resolution;                                               |
|                  | Wide flexibility of pulse parameters;                                     | Complex control system;                                                     |
|                  | Arbitrary signal shape;                                                  | Switch synchronization is needed;                                           |
|                  | Easy to achieve high currents;                                            | Not suitable for sub-100 ns pulses.                                         |
|                  | Can operate in high frequency range.                                      |                                                                              |
| Marx Generator   | Applicable with low voltage switches and voltage supplies;               | Bulky structure;                                                            |
|                  | High voltages up to hundreds of kV;                                      | Voltage droop is common when high loads are used;                           |
|                  | High currents;                                                           | Limited high frequency capability;                                          |
|                  | Can generate sub-100 ns pulses.                                           | Electrode degradation in case of spark-gaps.                                 |
| Transmission line| Simple design;                                                            |                                                                              |
| Blumlein         | Commonly used for short pulse generation (sub-100 ns);                   | Load impedance matching requirement;                                        |
|                  | High-voltages and currents;                                               | Pulse width inflexibility (limited to transmission line);                   |
|                  | Can be used for bipolar pulses                                           | Relatively short lifetime;                                                   |
|                  |                                                                           | Most of the usual concepts operate in low repetition rate;                  |
|                  |                                                                           | Big dimensions of the generator.                                            |
| Resonant Circuit | High energy density pulsing can be ensured.                               | Not applicable for electroporation directly;                                |
|                  |                                                                           | Parasitic parameters affect the waveform;                                   |
|                  |                                                                           | Switch synchronization is needed;                                           |
|                  |                                                                           | Complex control system.                                                     |
| Inductive Storage| High energy density;                                                     |                                                                              |
| Diode Opening Switch | High density; Accessible electrical components; Variable load impedance; | Complicated design;                                                        |
|                  | Commonly used for short pulse generation (sub-100 ns);                   | Low output power;                                                          |
|                  | Fast repetition frequency.                                                | Switch synchronization is needed;                                           |
|                  |                                                                           | Complex control system;                                                    |
|                  |                                                                           | Complex switching and poor control of pulse durations.                      |
| Transformer based| High pulse amplitude;                                                     | Transient processes affect pulse waveform;                                 |
|                  | Applicable with low voltage switches;                                    | Core saturation and reset after pulse.                                      |
|                  | Flexible pulse amplitude.                                                |                                                                              |
Table 2. List of in-house developed nanosecond pulsed electric field (nsPEF) generators with their and pulse parameters for electroporation application.

| Circuit          | Reference | Pulse Form                  | Pulse Polarity | Pulse Duration | Maximum Amplitude | Repetition Frequency | Switch       | Switch Model       | Pulse Form and Topology Remarks                                                                 |
|------------------|-----------|-----------------------------|----------------|----------------|--------------------|----------------------|--------------|-------------------|-------------------------------------------------------------------------------------------------|
| Blumlein-type    | 2000 [73] | Gaussian                    | Unipolar       | 8 ns           | 30 kV              | -                    | Spark gap    | -                 | Pressurized spark gap                                                                            |
|                  | 2003 [40] | Gaussian                    | Unipolar       | 3–15 ns        | >10 kV             | -                    | Spark gap    | -                 | Distorted pulse shape                                                                            |
|                  | 2006 [64] | Rectangular                 | Unipolar       | 10 ns          | 40 kV              | -                    | Spark gap    | -                 | Distorted pulse shape                                                                            |
|                  | 2006 [64] | Rectangular                 | Unipolar       | 10–300 ns      | 1 kV               | 0–50 MHz             | MOSFET       | DE375-102N12A     | -                                                                                               |
|                  | 2007 [48] | Gaussian                    | Unipolar       | 50 ns          | 65 kV              | 10 Hz                | Spark gap    | -                 | Distorted pulse shape                                                                            |
|                  | 2007 [48] | Rectangular                 | Unipolar and bipolar | 20, 50, 75, 150, and 230 ns | <0.3 kV | 0–1.1 MHz | MOSFET | DE275-102N06A | High pulse amplitude droop                                                                        |
|                  | 2011 [75] | -                           | Unipolar and bipolar | 40–200 ns     | 1 kV               | 0–100 kHz           | -            | -                 | Pulse shape not specified                                                                       |
|                  | 2013 [63] | Gaussian                    | Bipolar        | 2 ns           | 650 kV             | -                    | Transistor   | HTS-UF           | Distorted pulse shape                                                                            |
|                  | 2014 [76] | Gaussian                    | Bipolar        | 20–100 ns      | 2 kV               | 0–(~3) kHz           | MOSFET       | DE475-102N21A     | Distorted pulse shape                                                                            |
|                  | 2016 [61] | Rectangular                 | Unipolar       | 100 ns         | 1.7 kV             | 0–(~3) kHz           | MOSFET       | -                 | Distorted pulse shape; Modular circuit                                                            |
|                  | 2017 [62] | Gaussian                    | Unipolar       | 20 ns          | 2.5 kV             | 0–10 kHz             | MOSFET       | DE475-102N21A     | -                                                                                               |
|                  | 2018 [77] | Gaussian                    | Unipolar and bipolar | 30 ns          | 10 kV              | 0–200 kHz            | MOSFET       | DE475-102N21A     | Modular                                                                                         |
|                  | 2019 [78] | Rectangular                 | Unipolar       | 30 ns          | 4 kV               | 1 kHz                | IGBT and spark gap | IRG4PH50K | Distorted pulse shape; With transformer                                                          |
|                  | 2020 [79] | Rectangular                 | Unipolar       | 5 ns           | 0.5 kV             | 0–10 MHz             | MOSFET       | IXZ631DF12N100    | Fixed pulse duration;                                                                            |
| Circuit | Reference | Pulse Form | Pulse Polarity | Pulse Duration | Maximum Amplitude | Repetition Frequency | Switch | Switch Model | Pulse Form and Topology Remarks |
|---------|-----------|------------|----------------|----------------|-------------------|---------------------|--------|--------------|--------------------------------|
| Transmission line | 2003 [40] | Gaussian | Unipolar | 150 ns | 12 kV | - | Spark gap | - | Distorted pulse shape |
| | 2010 [80] | Rectangular | Bipolar | 2 ns | 1.6 kV | 0–10 Hz | PCSS | - | Distorted pulse shape and laser triggering |
| | 2013 [81] | Rectangular | Bipolar | 10, 40, 60, 92 ns | 12.5 kV | - | Spark gap | - | Laser triggering |
| | 2018 [36] | Rectangular | Bipolar | 10, 60, 300 ns | 10 kV | - | Spark gap | - | Distorted pulse shape; Hybrid with resonant circuit |
| | 2019 [59] | Rectangular | Unipolar | 120, 160, 200, 300, 400 ns | 10 kV | - | Spark gap | - | Distorted pulse shape |
| | 2001 [49] | Gaussian | Unipolar | 2 ns | 2.6 kV | - | Spark gap | - | Distorted pulse shape |
| | 2003 [40] | Rectangular | Unipolar | 12 ns | 1 kV | - | MOSFET | DE275-501N16A | Distorted pulse shape |
| | 2004 [82] | Rectangular | Unipolar | 75 ns to 10 ms | 0.400 kV | 600 kHz | MOSFET | DYSRF DE275-501N16A | - |
| | 2004 [83] | Exponential | Unipolar | 100 ns to 100 µs | 0.3 kV | 0–2 kHz | IGRT | - | - |
| | 2004 [84] | Exponential | Unipolar | - | 3.4 kV | 0–1 kHz | BJTs | ZTX415 | Pulse rise time to 2 ns |
| | 2012 [85] | Gaussian | Bipolar | 2.5 ns | 1.66 kV | - | Optoelectronic | - | - |
| | 2014 [71] | Rectangular | Unipolar | 200 ns to 5 µs | 8 kV | 0–30 Hz | MOSFET | HTS 91-12 | - |
| | 2015 [86] | Rectangular | Unipolar | 38 ns to 7 µs | 0.5 kV | - | MOSFET | IRF740 | - |
| | 2016 [87] | Rectangular | Unipolar | 100 ns to 1 ms | 3 kV | 0–1 MHz | MOSFET | C2M0080120D | - |
| | 2017 [72] | Rectangular | Unipolar | 80 ns to 1 µs | 1.4 kV | 0–50 Hz | MOSFET | C2M1000170D | - |
| | 2019 [88] | Rectangular | Unipolar | 80 ns | 0.5 kV | - | MOSFET | - | - |
| Direct capacitor discharge | 2001 [49] | Gaussian | Unipolar | 6 ns | 6 kV | - | Spark gap and MOSFET | 40N160 | Distorted pulse shape |
| | 2007 [48] | Gaussian | Unipolar | 200 ns | 6 kV | - | Spark gap | - | Single pulse |
| | 2007 [89] | Gaussian | Unipolar | 1.3 ns | 1.1 kV | 0–200 kHz | Diode opening | SOT-22 Zetex FMMT417 | - |
| | 2008 [47] | Gaussian | Unipolar | 135–220 ps | 20–120 kV | 0–15 Hz | Peaking | - | - |
Table 2. Cont.

| Circuit                  | Reference | Pulse Form       | Pulse Polarity | Pulse Duration | Maximum Amplitude | Repetition Frequency | Switch   | Switch Model | Pulse Form and Topology | Remarks                                      |
|--------------------------|-----------|------------------|----------------|----------------|-------------------|----------------------|----------|--------------|------------------------|----------------------------------------------|
| 2011 [90]                | Rectangular | Bipolar | 100 ns | 1 kV | 1 kHz | MOSFET and JFET
|                          |           |                   |                |                |                   |                      |          |              |                        | Hybrid with Blumlein; Distorted pulse shape |
| 2012 [91]                | Rectangular | Unipolar | 200 ns to 1 µs | 8 kV | 0–1 kHz | MOSFET |
| 2013 [92]                | Rectangular | Bipolar | 300 ns to 10 µs | 4 kV | 0–40 kHz | IGBT IRGPS60B120KDP |
| 2015 [93]                | Gaussian | Unipolar | 600 ps | 31.2 kV | - | Spark gap | C2M0080120D |
| 2016 [94]                | Rectangular | Unipolar | 100 ns to 1 µs | 8 kV | 0–1 kHz | MOSFET |
|                          | Gaussian | Unipolar | 620 ps | 1 kV | 10 kHz | Avalanche transistors | FMMT417 |
|                          | Rectangular | Unipolar | 200 ns to 100 µs | 10 kV | 0–1 kHz | MOSFET C2M0280120D |
|                          | Rectangular | Bipolar | 100 ns to 1 µs | 3 kV | 0–1 kHz | MOSFET C2M0080120D | Voltage droop |
| 2016 [96]                | Rectangular | Unipolar and bipolar | 100 ns to 100 µs | 3 kV | 0–2 MHz | MOSFET C2M0080120D |
|                          | Gaussian | Unipolar | 300 ps | 1.6 kV | 0–10 kHz | Avalanche transistors | FMMT417 | Marx with gradient transmission |
| 2017 [99]                | Rectangular | Bipolar | 100 ns to 1 µs | 3 kV | 1 kHz | MOSFET C2M0080120D |
| 2017 [100]               | Gaussian | Unipolar | 400 ns to 20 µs | 6 kV | 0–100 MHz | IGBT IXYK 120N120C |
| 2018 [101]               | Gaussian | Unipolar | 350 ps | 3.1 kV | 0–10 kHz | Avalanche transistors | FMMT417 |
| 2018 [102]               | Rectangular | Bipolar | 200 ns to 1 µs | 2 kV | 0–1 kHz | MOSFET |
| 2019 [69]                | Rectangular | Bipolar | 500 ns to 1 ms | 15 kV | 10 kHz | MOSFET C2M0160120D |
| 2019 [29]                | Gaussian | Unipolar and bipolar | 8 ns | 6 kV | 0–3.5 kHz | MOSFET IXXD60951 andC2M0052120D | Fixed pulse duration |
| 2019 [103]               | Rectangular | Bipolar | 500 ns to 10 s | 5 kV | 0–0.5 MHz | MOSFET |
| 2020 [104]               | Rectangular | Bipolar | 500 ns to 5 µs | 10 kV | 0–0.5 MHz | MOSFET C2M0080120D |
| 2020 [70]                | Rectangular | Unipolar | 200 ns to 1 µs | 15.3 kV | 0–10 kHz | MOSFET C3M0005090J | Integrated with DOS circuit |
| 2005 [105]               | Gaussian | Unipolar and bipolar | 3.5 ns | 1.2 kV | 0–100 kHz | MOSFET APT10035JLL | DOS |
| 2007 [106]               | Gaussian | Unipolar | 20 ns | 4.5 kV | 20 Hz | IGBT CM300HA-12H | Distorted pulse shape; DOS with transformers |
| 2007 [106]               | Gaussian | Unipolar | 5 ns | 7.5 kV | 20 Hz | MOSFET APT10035 |
| 2009 [107]               | Gaussian | Unipolar | 5 ns | 4.4 kV | 0–3 MHz | MOSFET |
| 2009 [107]               | Gaussian | Unipolar | 2.6 ns | 1 kV | 0–3 MHz | MOSFET |
| 2010 [108]               | Gaussian | Unipolar | 50 ns | 30 kV | 0–0.5 kHz | Magnetic |
| 2012 [109]               | Gaussian | Unipolar | 50 ns | 1 kV | 0–0.5 kHz | MOSFET APT137M100L | DOS |
| 2019 [110]               | Rectangular | Unipolar | 23 ns | 8.2 kV | - | MOSFET C3M012090J | Hybrid with Blumlein |

1. PCSS – Photoconductive Semiconductor. 2. JFET – Junction Field Effect Transistor.
3.2. Classification of Available In-House Built Generators for nsPEF Electroporation

It was identified, that the traditional transmission line (including Blumlein-type) pulse forming circuits are no longer dominating in the nsPEF electroporation applications. The progress of semiconductor technologies enabled the development of cost effective, small-size and flexible sub-microsecond generators based on direct capacitor discharge topology. The Marx generator topology with new ultra-fast semiconductor switches forms a new leading technology trend now. In addition, there were few successful attempts to develop resonant-circuit nsPEF generators, which at the end were not followed by other researchers. Unpopularity of this topology is driven by the limited pulse duration flexibility and resulting Gaussian pulse shape.

All topologies demonstrate the possibility to produce high-voltage pulses, however, the transmission line (including Blumlein-type) topologies, which use spark gap switches, demonstrate a possibility to produce very high amplitude (peak voltages exceeding 10 kV) nsPEF rectangular wave pulses. Yet there is complexity associated with these designs and recent developments of Marx-bank \[69,70\] and other direct capacitor discharge circuits \[71\] indicate the growing availability of the off-the-shelf components fulfilling the high-voltage pulse delivery requirements. It is expected that the transmission line topologies will be pushed out of the sub-microsecond range due to a lack of flexibility, requirement of impedance matching and distorted waveforms. These drawbacks are not associated with the reported direct capacitor discharge circuits (including Marx-bank). However, the sub-100 ns pulses in the range of tens of kV are still yet hardly achievable by the direct capacitor discharge technology.

Indeed, for the high-voltage sub nsPEF pulse delivery, the switch performance and characteristics are crucial. The spark gap switches are fast and cost-effective for nsPEF generation, but these switches have a short lifetime due to electrode erosion, poor pulse duration control and can be frequently associated with turn-on jitter \[36\]. In contrast, the semiconductor switches offer high flexibility of pulse control, but are more constrained by high-voltage or current withstand limits as well as switch opening and closing times. A series connected switches can solve high-voltage limitation issues, but this increases the stray inductance, which is making the circuit slower.

One of the latest comparison between typical MOSFET, IGBT and bipolar junction transistor (BJT) switches was made in 2019 \[72\]. It was demonstrated that all three could ensure the breakdown voltage (collector–emitter or drain–source voltage) higher than 1 kV. However, the BJT switches, which among all would be the most cost-effective option, are slower than MOSFETs or IGBTs and cannot fulfill the nsPEF pulse forming requirements. It was demonstrated that only the high power MOSFETs can form pulses within the 100–300 ns range with the transition times (rise and fall time) faster than 100 ns \[72\]. More than a half of reported nsPEF electroporators (Table 2) use the MOSFET switch as a main pulse forming component.

The review indicates that the direct capacitor discharge topology is taking a lead in the nsPEF applications when the sub-microsecond pulse is required. In addition, the MOSFET switches are now the main technology to produce high-voltage nsPEF pulses in various circuit topologies. The spark gap switches are still applicable in case of a very high-voltage amplitude or ultra-short pulse duration (a few nanoseconds) \[64\]. Other types of switches (like photoconductive semiconductor, optoelectronic switch or even IGBT) are rarely applicable even if they also provide a capability to deliver ultra-short pulses. In all cases, the transient processes are triggered during the switch turn-on and turn-off, which negatively influence the pulse parameters. The proper compensation circuits must be applied to ensure system protection and the precise pulse waveform with constant pulse rise and fall times independently on the load/electrodes type \[111\].

4. Conclusions

The interest in shorter and higher intensity PEF pulses for electroporation is increasing, which leads to the growing demand for the nsPEF electroporators. Different techniques to design the pulse forming circuits for the nsPEF electroporators exist. Traditionally transmission line circuit topologies
were used, however, the recent development of SiC MOSFETs have resulted in the new wave of advanced direct capacitor discharge nsPEF electroporators with adjustable pulse parameters.

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