

Cell Membrane Electroporation—Part 3: The Equipment

Key words: electrode, electroporator, pulse generator, safety standard

Introduction

As described in Part 1, a cell membrane can be made permeable to various molecules by carrying out a procedure called electroporation [1]. This procedure is being successfully used in biology, biotechnology, and medicine [2], [3]. It requires electroporators and electrodes. An electroporator generates short HV pulses of specific shape, amplitude, duration, number, and repetition frequency [4], and the pulses are applied to the target cells or load through the electrodes [5]. The energy delivered to the load is governed by the number of pulses and the pulse voltage, current, and duration. In biomedical applications that energy can be several joules; in biotechnology, where electroporation is used for treatment of agricultural products and water, it can be several kilojoules.

Cell membrane electroporation enables specific biomedical and biotechnological applications. To achieve this goal appropriate electroporation protocol needs to be followed. The diversity of electroporation applications and the range of targeted loads have led to numerous electroporation protocols and simultaneously to the development of many different electrodes and pulse generators [5]. In general electrodes can be classified according to the targeted load, i.e., cell suspension or tissue, and pulse generators can be classified according to the application, i.e., laboratory, clinical, or industrial. During pulse delivery the impedance of the load usually decreases, due to poration of the cell membranes by the electric field and increase in the load temperature. The impedance of the targeted load is inhomogeneous, especially in the case of tissue.

This article is the last in a series of three on electroporation. The first article [1] described the phenomenon from molecular to cellular level, the second [2] reviewed several interesting applications, and this article describes the equipment used in these applications. It starts with safety aspects and then describes electrodes and pulse generators in detail.

Safety, Standards, and Certification

Electroporators are HV pulse generators and therefore potentially hazardous for patients, operators, and nearby devices. Thus critical safety issues have to be considered, even for labo-

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Pulsed high-electric fields are used to electroporate biological cells. Here we describe different applicators and generators used in electroporation applications, with emphasis on clinical and industrial electroporators and safety issues.

ratory prototype electroporators. The most important safety issues are galvanic isolation, current and energy limitation, and fault operation.

Clinical and industrial electroporators are by law [6]–[8] obliged to meet the general standards written by technical committees of experts. The general standard for medical devices is

IEC60601-1 [9]. However, clinical electroporators must also meet collateral standards such as that for risk analysis ISO14971 [10], electromagnetic compatibility EN 55011 [11], medical software IEC62304 [12], and usability of the device IEC62366 [13].

The relevant competent body must certify that a device meets all the standards required by local law and is safe. In the European Union certified devices carry the CE (Conformance European) mark, and in USA and Canada certified devices carry the UL (Underwriters Laboratories), CSA (Canadian Standards Association), or ETL (Intertek Testing Services) marks.

Electrodes

Biological cells can be treated by electroporation in cell suspension or in tissue. Pulses from the electroporator generate an electric field around the electrodes. The electrode configuration and the homogeneity of the load impedance determine the distribution of the electric field, and its intensity is controlled by the pulse amplitude [14]–[16]. The choice of electrodes is governed by the targeted load and, unfortunately, often by pulse generator restrictions, e.g., maximum voltage or current, minimum impedance, and impedance matching. Impedance matching is especially important when nano- or picosecond pulses are applied to the targeted load. The choice of electrodes can also be influenced by biocompatibility requirements [17] and electrolytic dissolution of the target material [18]. The electrode housing, usually a plastic material, is used to define the electrode geometry and sometimes to prevent sparks.

Electrodes and Chambers for Cell Suspensions

Many different electrodes and chambers have been developed for *in vitro* electroporation. They can be divided into four main groups, namely single-cell chambers [19], micro-electrodes [20], [21], milli-electrodes [22], and flow-through chambers [23].

In the laboratory milli-electrodes are most frequently used. They usually consist of two approximately 1-cm-wide plate electrodes and a plastic holder that maintains an electrode separation of at least 1 mm [22]. Micro-electrodes, usually 1 cm wide glued onto cover glass [24] with electrode separation of 100 μm , permit observation of cells under the microscope during pulse delivery, which facilitates study of the dynamics of the observed phenomena [25]. A disadvantage is that the electric field surrounding the cells is inhomogeneous and sometimes poorly defined [26]. The electric field can be made more homogeneous by depositing different materials such as nickel [27], silver [28], gold [29], [30], or photoresist [31] on the cover glass. Micro-electrodes in parallel with inter-electrode distances of approximately 200 μm are used for fusion of large samples of cells [20].

Several single-cell (or patch-clamp electrode) chambers were developed during the last decade [32]–[34]. Electrodes built into flow-through chambers are used when large volumes of cells in solution are being electroporated. Existing flow-through chambers use either polyethylene or polypropylene as insulating materials, and stainless steel electrodes. Many products contain air bubbles that break down under the applied electric field. These bubbles must be removed by a degassing valve or the material

must be pressurized to shrink the gas bubbles [35], [36]. Metal release from the electrodes might be a problem when treating food [37].

Three main electrode configurations are used in flow-through chambers (Figure 1). The coaxial design (Figure 1A) has the advantage of easy construction but involves a cylindrical and hence inhomogeneous electric-field distribution. The field could be made more homogeneous by increasing the inner and outer diameters, but the increased electrode surface area would lower the impedance of the electrode system, making it suitable only for a low-conductivity load. The impedance might, however, be adapted by using short cylinder segments only.

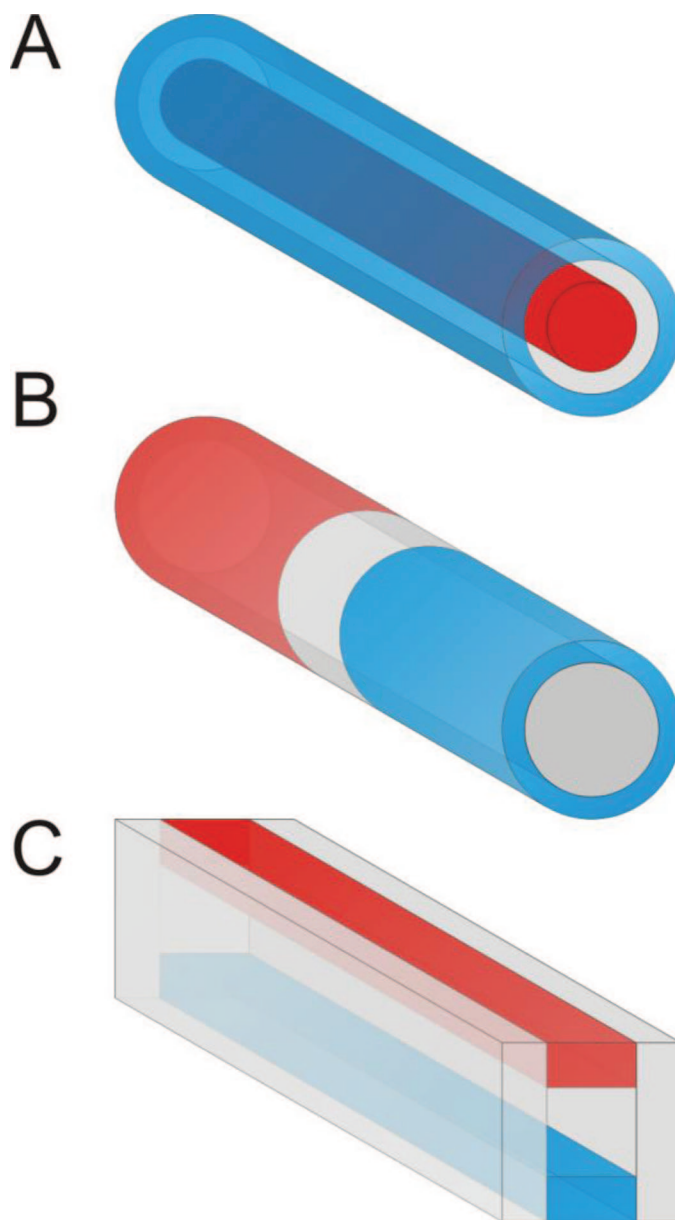


Figure 1. Basic electrode geometries of flow-through chambers: (A) coaxial, (B) collinear, and (C) planar. Red and blue areas represent opposite electrodes, and light gray areas represent insulating material such as plastic or Teflon.

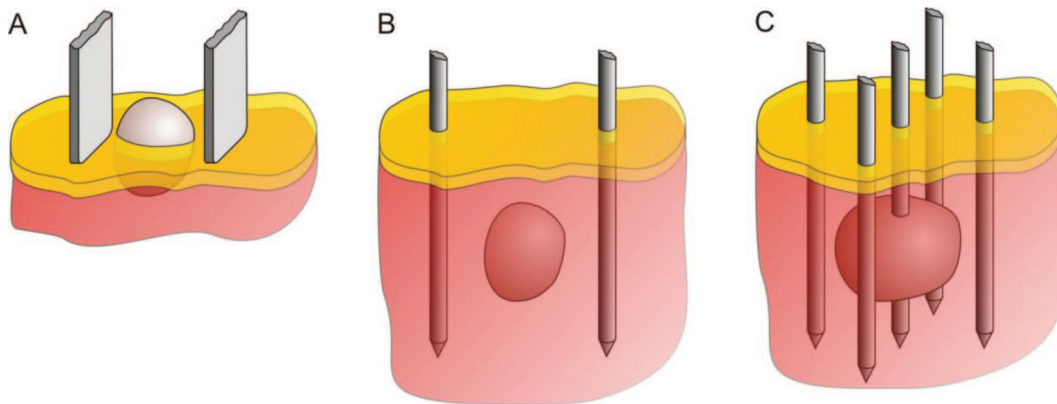


Figure 2. Electrodes used in clinics and *in vivo*. (A) Plate electrodes used for targeted tissue on the surface, (B) needle electrodes used for targeting deeper-seated tissue, and (C) multiple-needle electrodes used for targeting large volumes.

The collinear arrangement (Figure 1B) usually consists of three tube-like electrodes separated by insulating tubes. The inner electrode serves as the HV electrode and both outer tubes as ground electrodes, preventing current leakage out of the treatment area. The electric field is established mainly inside the cell solution in both insulating tubes, oriented in the direction of the flow. The impedance increases with the length of the chamber. The length of the insulating ring (gray area in Figure 1B) must be considerably greater than its diameter to achieve an acceptably homogeneous field distribution.

In the planar electrode design (Figure 1C) the electric field is applied using two or more plate electrodes in the direction normal to the mass flow. Since the impedance decreases with increasing length of the electroporation chamber, the length should be considerably larger than the electrode distance, in the interests of an acceptably homogeneous field distribution. To prevent current leakage a ground symmetric operation is advantageous.

Effective delivery of nanosecond pulses from the generator to the targeted cells requires that the impedance of the load be matched to the impedance of the generator. It is therefore necessary to evaluate the impedance of micro- [38] or milli-electrodes [39] and to calculate the electric field around the targeted cells. Research is continuing on the use of antennas to deliver sub-nanosecond pulses to the targeted cells [40].

Electrodes for Tissue

Electrodes used in clinics and *in vivo* are usually needles or plates, depending on the application site. Plates are commonly used for superficial tissues, as shown in Figure 2A. Needle electrodes are used to treat deep-seated tissue as shown in Figure 2B, and multiple-needle electrodes are used to treat a large volume of tissue as shown in Figure 2C. Multiple-needle electrodes are usually of linear or hexagonal arrangement (first and third on Figure 9A), or they can be arranged according to treatment plan [41]. Micro-needles are used to electroporate thin layers of skin but are still not as effective as multiple-array electrodes [42], [43].

Long single needles with insulating tubing, which allow application of the electric field only on the distal side of the needle, leaving the skin untreated, have been developed for deep-seated

tissue. Such electrodes are minimally invasive, reaching the tissue and ablating a considerable tissue volume (see also Figures 9 and 10) [44].

Electrodes applied to humans must be single use, with a reusable or integrated handle. The medical standards also require that the electrodes provide adequate insulation of the user. Other safety requirements concern the sterility and the biocompatibility of the materials used [45]. Electrodes are frequently of stainless steel (AISI 304 or 316) or titanium. Biocompatible plastic is used for the parts in contact with the patient. Sterility of the needles is achieved using γ -rays or ethylene oxide.

Pulse Generators

Reproducibility and efficacy of electroporation depend to a large extent on the applied electroporation signal being accurately reproducible. Since the electroporation process is driven by the local electric field, in most cases the output voltage is controlled. The electroporation signal is characterized by pulse amplitude and duration, number of pulses, pulse repetition frequency, and commutation sequence. Several different pulse shapes are used, usually exponential decay, square, and bell shaped (Figure 3).

Exponential Pulses

Exponential pulses (Figure 3A) are usually generated by a simple and inexpensive capacitor discharge circuit [46]–[48]. The capacitor (C) is charged to a preset voltage that sets the maximum amplitude (A_{\max}) of the pulse. C is then discharged through the load (Z_L). The time constant τ of the pulse = $C |Z_L|$. However, the impedance of a biological load decreases during pulse delivery [49] and can also vary from sample to sample. Thus τ also varies, and so most commercially available capacitor-discharge-based electroporators for laboratory use have a built-in resistance R connected in parallel with the load Z_L . The main purpose of this resistor is to limit the decrease in τ during the pulse. If $|Z_L| \geq 10R$, $\tau \approx RC$. However, considerable current can flow through R and thereby dissipate more than 90% of the pulse energy; this may be acceptable in laboratory settings but not in industrial applications.

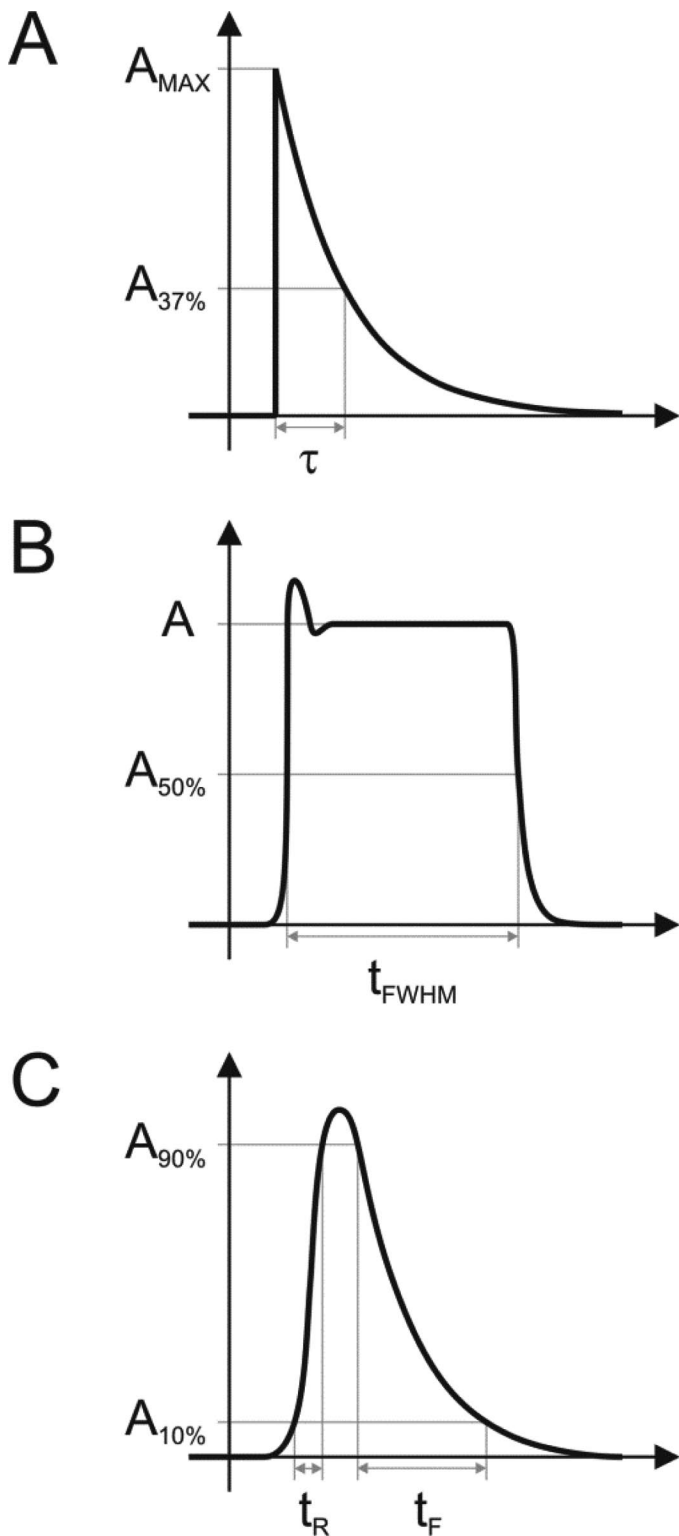


Figure 3. Amplitude and time parameters of electroporation pulses. (A) Exponential decay pulse characterized by maximum amplitude (A_{max}) and time constant (τ). (B) Square pulse characterized by amplitude (A) and pulse duration (t_{FWHM}). (C) Bell-shaped pulse characterized by maximum amplitude (A_{max}), rise time (t_R), and fall time (t_F).

A Marx generator (Figure 4) [50], [51] also generates exponentially decaying pulses. However, the capacitors (C) are charged in parallel through resistors (R) and then discharged in series through the load (Z_L) by switching on all switches (S) simultaneously. The maximum voltage applied to the load Z_L is the power supply voltage V multiplied by the number of capacitors, and the time constant $\tau = |Z_L| C/\text{number of capacitors}$.

Capacitor discharge circuits are the cheapest and the simplest electroporation circuits, per unit pulse energy. Nevertheless, their construction can still be challenging when HV or high-current pulses are required. If spark gaps are used as switches, the output amplitudes can reach a few megavolts and several kiloamperes [52]. The main problem is simultaneous switching of the spark gaps [53]. One of the best ways of doing this is by using a UV laser [54]. The pulse repetition frequency is usually below 100 Hz because of the long charging times.

Exponential pulses can be used to transfer DNA into cells (gene transfection). The transfer requires a HV component for permeabilization of cell membrane and a low-voltage tail necessary for electrophoretic drag of DNA [55]–[57]. However, the two components are not independent. The tail is desirable only in irreversible electroporation applications, as it greatly affects cell viability [58]. Cell viability is less important in gene transfection of bacteria but more important in gene transfection of valuable cells, for which square wave pulses are used more often [56], [59].

Square Pulses

Square pulses are usually characterized by the parameters shown in Figure 3B and by the rise (t_R) and fall (t_F) times shown in Figure 3C. In the case of square micro- and millisecond pulses, variation in t_R and t_F has no detectable effect on electroporation [60]. However, in the case of nano- and picosecond square pulses, the electroporation affects organelles (specialized substructure within a cell), and in plasma membranes may depend on t_R and t_F [61]. Micro- and millisecond square pulses are usually generated by a HV power supply switching circuit (Figure 5) [62], [63].

Usually, fast power MOSFET or insulated gate bipolar transistors are used as the switches. The amplitude of the pulse is determined by the variable power supply V (Figure 5), while pulse duration, pulse repetition frequency, and the total number of delivered pulses are defined by the switching sequence applied to the fast power switch S . The main problem is that electroporation pulses are high power and short duration. Thus all the energy required for the pulse delivered to the target must be generated and stored in the capacitor before delivery. Consequently, a voltage drop ΔV_L proportional to $t_p/(C |Z_L|)$ occurs during the pulse, where t_p is the duration of the pulse. In order to minimize this voltage drop a very large C is needed, but it is then more difficult to change the pulse amplitude between pulses. Consequently, square-wave pulse generators usually generate pulses with only one (preset) voltage. As it is usually required that each pulse have the same amplitude, another pulse can be delivered only after the capacitor is recharged to the preset voltage. Using MOSFETs or insulated gate bipolar transistors for the switch S , the output pulses can reach a few kilovolts and several amperes [64].

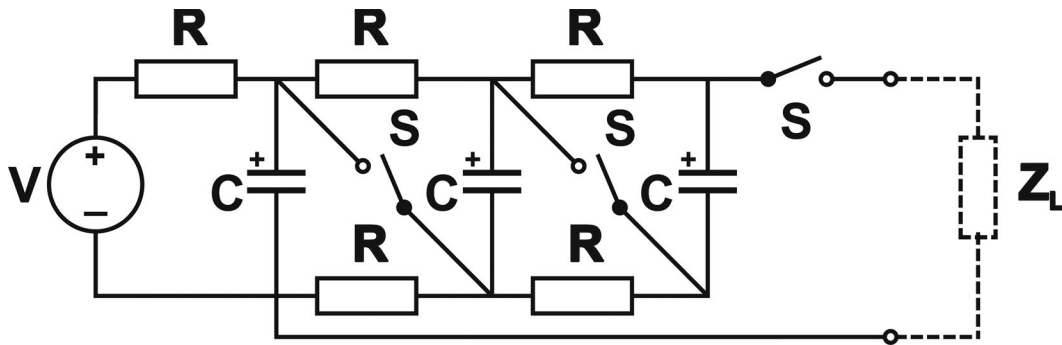


Figure 4. Marx generator for generation of exponentially decaying electroporation pulses.

Techniques used to generate nano- [26], [29], [65] and picosecond [66]–[68] square pulses differ significantly from those used to generate micro- and millisecond pulses, because HV switching components have turn-off times that are too long to form nano- or picosecond pulses. Pulse-forming networks are required, e.g., a transmission line. A transmission-line pulse generator (Figure 6) operates in two phases, namely charging and discharging. During the charging phase the switch S is turned off, and the variable HV power supply V charges the transmission line T through resistor (R) to a preset voltage. In the discharging phase the switch is turned on and the transmission line is discharged through the load (impedance Z_L). In order to generate square pulses without reflections, Z_L must match Z_0 , the impedance of the transmission line. The latter is given by $(L/C)^{0.5}$, where L and C are, respectively, the inductance and capacitance per meter length of the transmission line. The duration t_p of the pulse is $2l(\epsilon\mu)^{0.5}$, where l is the length of the transmission line and ϵ and μ are, respectively, the permittivity and permeability of the transmission-line insulation. The amplitude of the output pulse is $V/2$.

The Blumlein generator (Figure 7) is also used to form nano-second square pulses. During charging the switch S is turned off, and the variable HV power supply V charges the transmission lines T_1 and T_2 to a preset voltage. During discharging the switch is turned on, and the transmission lines are discharged through the load connected to the output. In order to generate square pulses without reflections, Z_L must be twice Z_0 . The duration of the pulse is again $2l(\epsilon\mu)^{0.5}$, but the amplitude of the output pulse is V .

Although the switching components for pulse-forming networks do not need a fast turn-off time, they need a fast turn-on time in order to form HV square-wave pulses (rather than bell-shaped pulses). MOSFETs can be used to achieve rise times of a few nanoseconds at voltages up to 1 kV, but spark gaps or photoconductive switches are preferable at higher voltages. The breakdown voltage of a spark gap can be controlled by gas pressure and gap distance [69]. To achieve very fast rise times with spark gaps, the gap distance should be small and the gas pressure high [26], or the gas should be replaced by a liquid dielectric [70]. The resistance of a photoconductive switch depends on the optical pulse energy [71]. The amplitude of the pulses formed by network generators, most often several kilovolts, is usually limited by the dielectric strength of the transmission lines.

Square-pulse generators are used for almost all electroporation applications, not only because they are simple and cheap, but also because they enable good control and reproducibility of the relevant electrical parameters. However, the load must be adjusted to the pulse-forming network impedance to avoid variable amplitude delivery to the load and pulse reflections. The latter would effectively prolong the pulses. The impedance of a biological load can be lowered by additional resistance in parallel, and the impedance of a transmission line can be lowered by adding identical transmission lines in parallel.

Other Generators

Many other concepts to generate electroporation pulses are used and thoroughly described elsewhere, e.g., diode opening switch generators [72], [73], and analog amplifiers to generate arbitrarily shaped pulses [4], [60], [74]–[77] with push-pull or full bridge circuits to generate both polarities [78]–[81].

Multi-Electrodes and Polarity Control

Electroporators (E_p) can be supplemented with an output commutator that can deliver electroporation pulses to multiple electrodes (E_x) and control the polarity of the pulses (Figure 8) [44]. A typical commutator has an integrated one-half bridge switch for each electrode. The half bridge switch is designed with two switches, one for the positive pole (S_p) and one for the negative pole (S_N). However, these two switches must never be active simultaneously because they would short-circuit the electroporator. If S_p or S_N is active, a positive or negative pole, respectively, is connected to the electrode; if both switches are

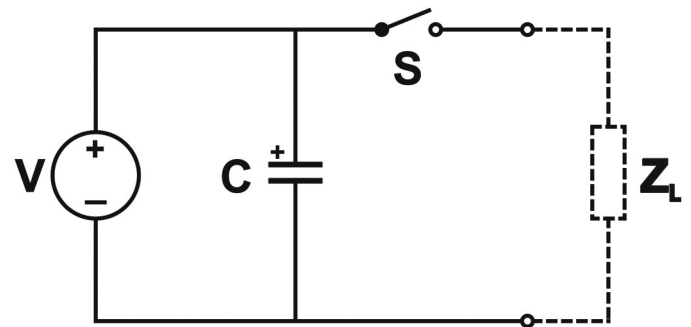


Figure 5. High-voltage power supply switching circuit for generation of square-wave electroporation pulses.

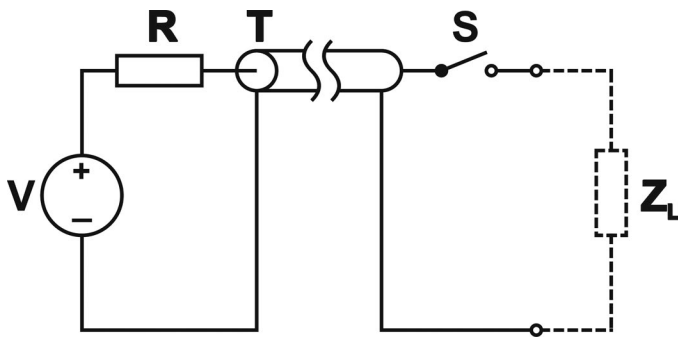


Figure 6. Transmission-line generator for generation of square-wave nanosecond electroporation pulses.

inactive, the electrode is in a high impedance state. Bipolar pulses can be generated using such a commutator by alternately changing the poles of paired electrodes. Bipolar pulses are used to increase the efficiency of electroporation [82] and to reduce electrolytic contamination [18]. Multiple-needle electrodes are used to treat larger tissue volumes *in vivo* [44], [83], [84].

Clinical Electroporators

Electroporators used in clinics must meet safety standards and must be certified for clinical use [64], [85]. They have been developed to treat tumors in association with drugs, such as bleomycin or cisplatin, using different protocols.

One of these devices is the Cliniporator, manufactured by IGEA SpA, Italy. It resulted from the European project Cliniporator (QLK-1999-00484). Following that project another EU-funded project [ESOPE (QLK-2002-02003)], a two-year prospective randomized clinical Phase 1-2 trial, was conducted [86]. It generated Standard Operating Procedures for Electrochemotherapy [87]. Today the Cliniporator is available in two different models, namely the Cliniporator 2 and the Cliniporator VITAE.

The Cliniporator 2 delivers electroporation in two different modalities, namely electrochemotherapy and gene electrotransfer. The power supply, controlled by a field-programmable gate

array to ensure maximum reliability, has two pulse generators, one for high voltage and the other for low voltage. Both generators use a HV analog amplifier [4] to ensure maximum stability of the square pulse shape, which is particularly important in gene electrotransfer mode. The maximum pulse amplitude is 1,000 V, with a maximum current of 20 A. The pulse repetition frequency is in the range 1 Hz to 5 kHz. The output is controlled by a circuit similar to a multi-electrode commutator, capable of switching the power between 7 independent channels (Figure 8).

Plate electrodes are used to treat cutaneous tissues and needle electrodes to penetrate the skin and to treat subcutaneous tissues and mucous membranes. The needles usually have linear or hexagonal geometry (first and third on Figure 9A). The hexagonal shape is preferred when a large area is to be treated. Sterile plates and needles can be plugged into a base that is attached to the electroporator (Figure 9A). Needles embedded in bases that fit around the finger (Figure 9B), and long needles with insulation sleeves and adjustable active lengths, have been developed (Figure 9C).

The Cliniporator 2 is provided with a trigger input to synchronize pulse delivery with the absolute refractory period of the heart. It is commonly used in more than 100 clinical centers of the European Community.

The Cliniporator VITAE is designed for use only in electrochemotherapy. It has two sections. The first, named PRE-SET, is used to treat superficial tissues and mucous membranes, similar to Cliniporator 2. The second, named CUSTOM, is used to treat deep-seated tumors and large tumors in bones and internal organs [88]. Each section is controlled by a field-programmable gate array, and its output circuit is of the same type as in Cliniporator 2. The PRE-SET section also uses the same generator as Cliniporator 2. The CUSTOM section uses a generator based on direct free discharge of capacitors into the load and can deliver pulses up to 3,000 V at 50 A with a pulse repetition frequency of 1 kHz. Not more than eight pulses are applied between each pair of electrodes. Several redundant circuits control the amount of energy delivered. Cliniporator VITAE is also provided with a trigger input to synchronize pulse delivery with the absolute refractory period of the heart. The PRE-SET section uses the

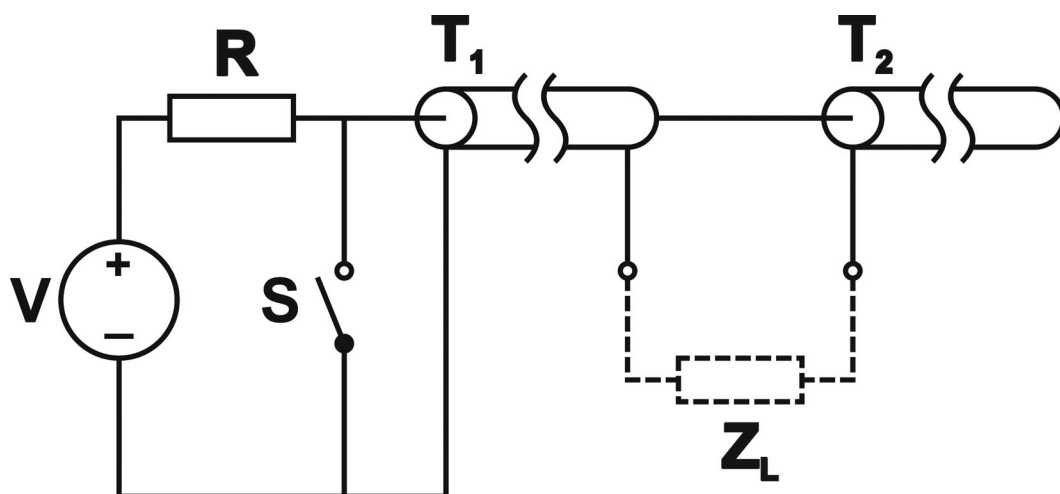


Figure 7. Blumlein generator for generation of square-wave nanosecond electroporation pulses.

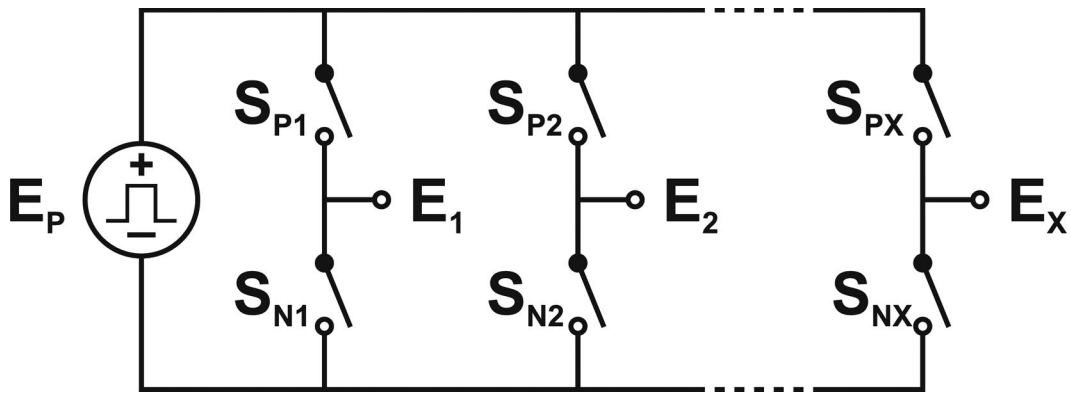


Figure 8. Commutator for multi-electrode and polarity control. Electroporators (E_p) can be supplemented with an output commutator that can deliver electroporation pulses to multiple electrodes (E_x) and control the polarity of the pulse.

same plate and needle electrodes as Cliniporator 2. The CUSTOM section uses long single-needle electrodes with insulating sleeves (Figure 9D) and active (uninsulated) end with a sharp tip for soft tissue applications, or trocar tips (drilling tips) for bones.

A new device named NanoKnife has also been developed to ablate soft tissue (including cancer) without using drugs. It relies on nonthermal tissue ablation resulting from irreversible electroporation [89]. Manufactured by Angiodynamics USA, it uses a pulse generator capable of delivering 10 to 100 pulses up to 3,000 V at 50 A through pairs of long needle electrodes [64]. Based on free discharge of capacitors, it is simple and efficient and does not require a HV amplifier. Since the pulse lengths are in the range 20 to 100 μ s, the final pulse is a good approximation to a square pulse, even for 50-A currents. Due to the large pulse energy, the system is equipped with fast-acting safety hardware circuits.

The electrodes are fully disposable, single, sterile, long needles exclusive to the NanoKnife (Figure 10). They have a trocar tip allowing better penetration and a movable insulated part al-

lowing adjustment of the length of the “active part” (uninsulated part) from 0 to 40 mm. The main application is the treatment of tumors in liver, prostate, lung, kidney, pancreas, and other areas, that otherwise would require open surgery. Other electroporation systems have been developed for DNA vaccination [90], gene or molecular electrotransfer, but they are currently used only for research.

Industrial Electroporators

HV and high-power electroporators are used in biotechnology to electroporate large volumes of liquid [51], [91]. Various switching elements and circuit configurations are possible.

Spark-gap switches are a classical switching element for pulsed power applications. They are easy to manufacture and can switch high voltage and high current at moderate cost. Electrodes manufactured from tungsten and copper and with Borda or Rogowski profiles ensure low and homogeneous wear across the electrode surface [92]. A disadvantage is a low repetition rate of order tens of hertz. Semiconductor switches such as insulated

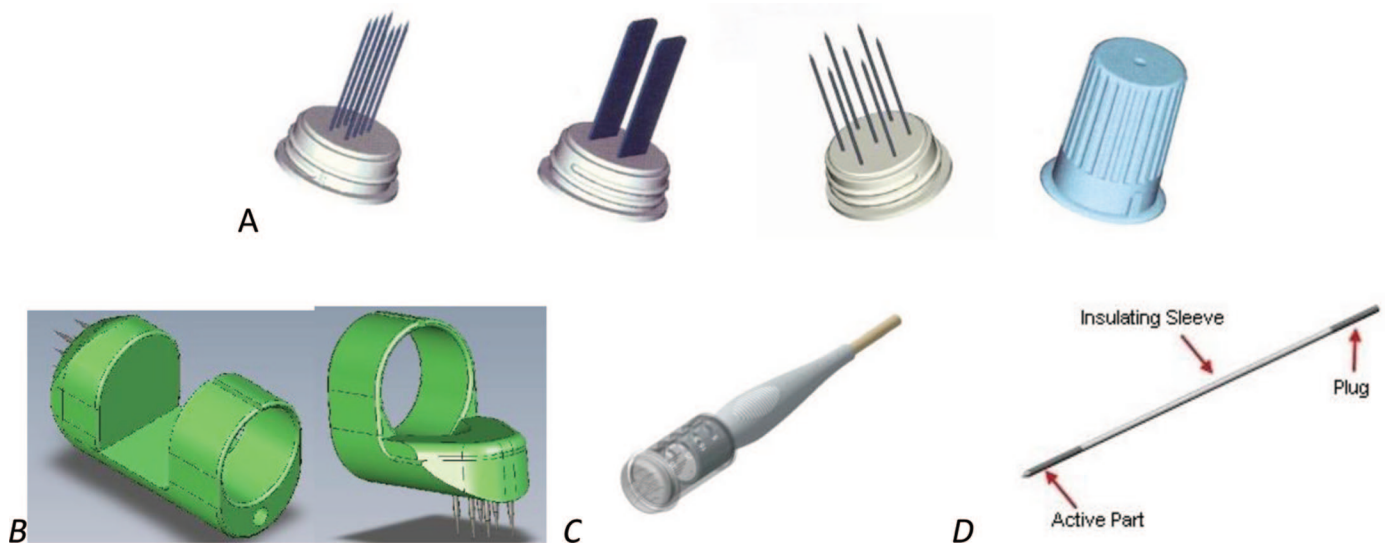


Figure 9. (A) Needle and plate electrodes used with Cliniporator 2. (B) Needle electrodes to be used with the fingers. (C) Long needle electrodes with adjustable active parts. (D) Needle electrode with insulating sleeve used with Cliniporator VITAE.

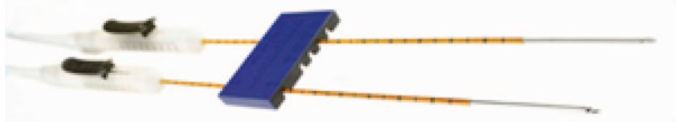


Figure 10. Applied part of the NanoKnife.

gate bipolar transistors and thyristors enable switching at repetition rates up to several tens of kilohertz but are limited with respect to switching voltage (kV) and current (kA) and are more costly than spark gaps per unit switched power.

For the treatment of small volumes of liquid, a pulse generator employing a step-up transformer and a semiconductor switch on the primary side could be used. This arrangement permits switching at voltages up to several kilovolts without stacking the switching elements in series. The output voltage of the transformer can be applied to an electroporation chamber with large distance between the electrodes. Since the primary current is larger than the secondary current through the electroporation chamber, switching at the primary side of the transformer involves higher switching currents, a limiting factor. It follows that this design is suitable only for electroporation chambers with high impedance.

Conclusions

Although many different commercial laboratory electroporators are available, researchers still need to develop custom-designed prototypes for their experiments. Low-cost, simple, easy-to-operate, and stable pulse generators can be developed for specific applications.

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