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(54) **METHOD AND APPARATUS FOR CONTROLLED DELIVERY OF PULSED ELECTRIC FIELD ABLATIVE ENERGY TO TISSUE**
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(60) Provisional application No. 62/628,163, filed on Feb. 8, 2018.

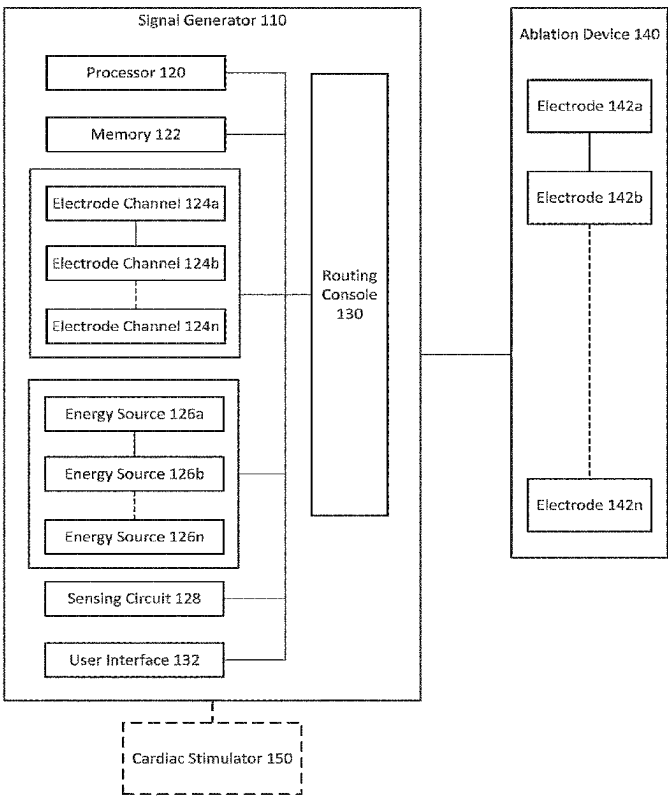
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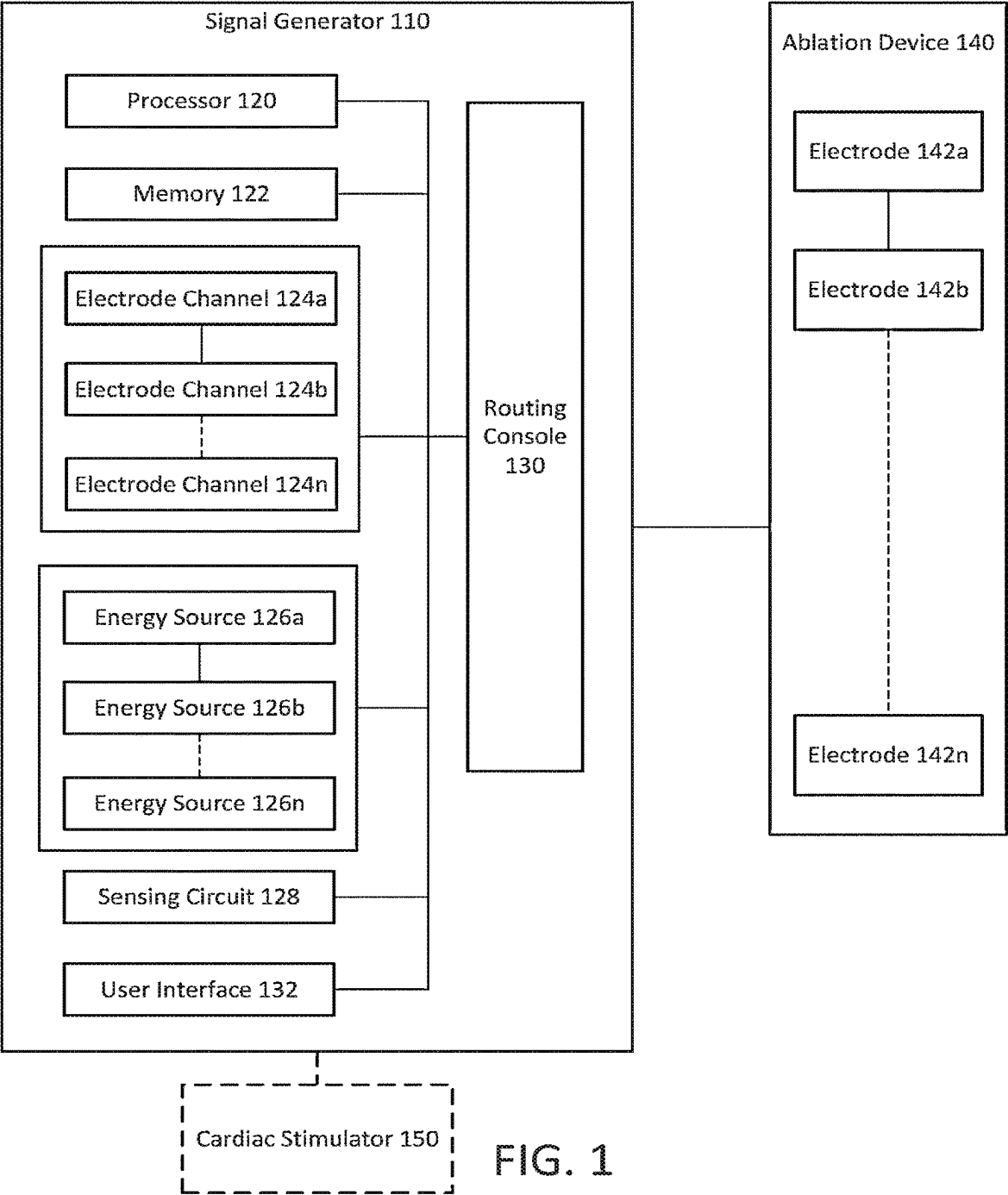
(57) **ABSTRACT**

Systems, devices, and methods for current control of energy delivery to ablate tissue are disclosed. A generator may include a set of electrode channels coupled to a set of electrodes during use. Each electrode channel from the set of electrode channels may include a first switch from a first set of switches and a second switch from a second set of switches. A set of energy sources may be coupled to a third set of switches. The third set of switches may be configured to switch from an OFF state to an ON state to couple the set of energy sources to the set of electrodes. A set of resistors may be coupled to the second set of switches. The second set of switches may be configured to switch from an OFF state to an ON state to couple the set of resistors to the set of electrodes.

100



100



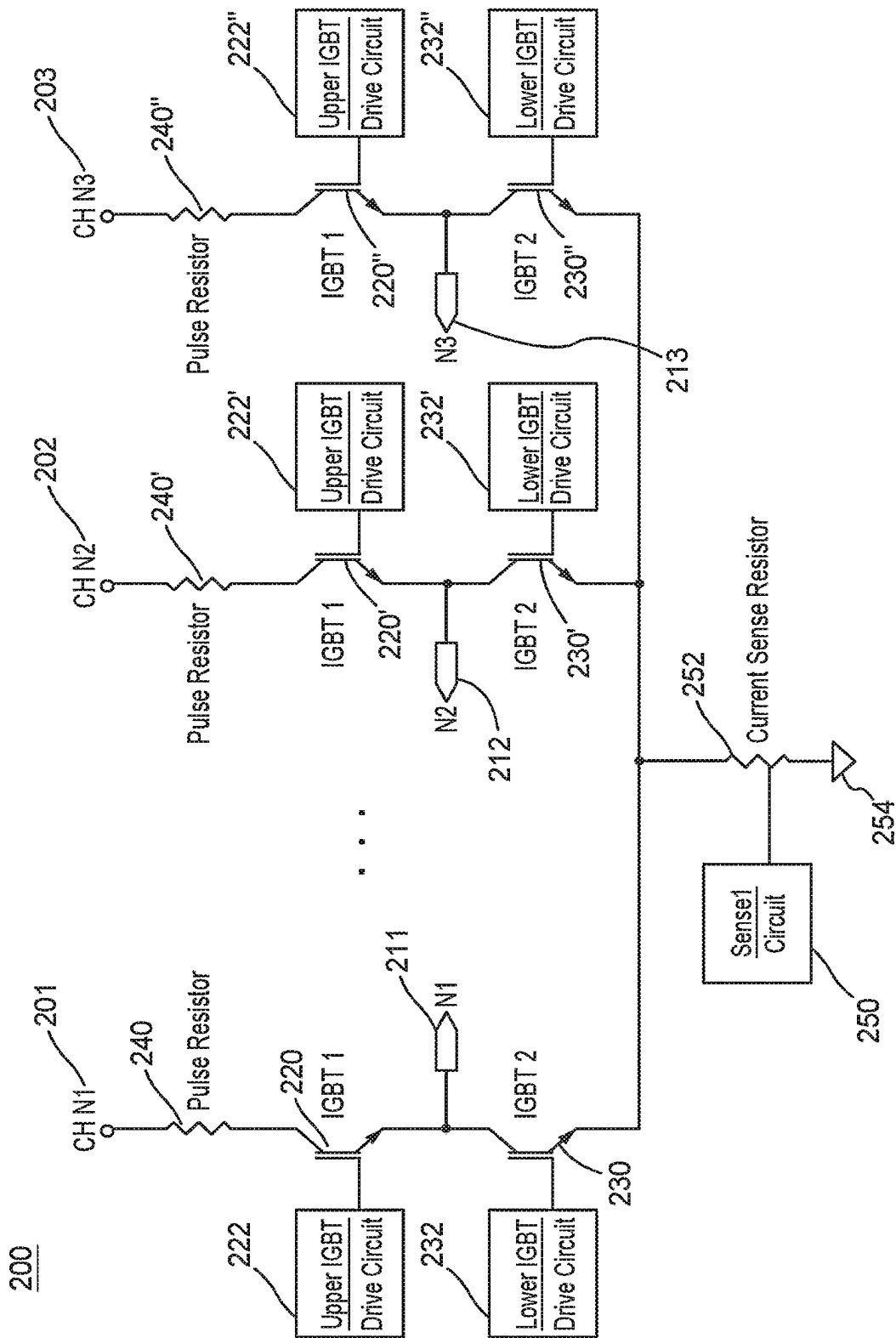


FIG. 2

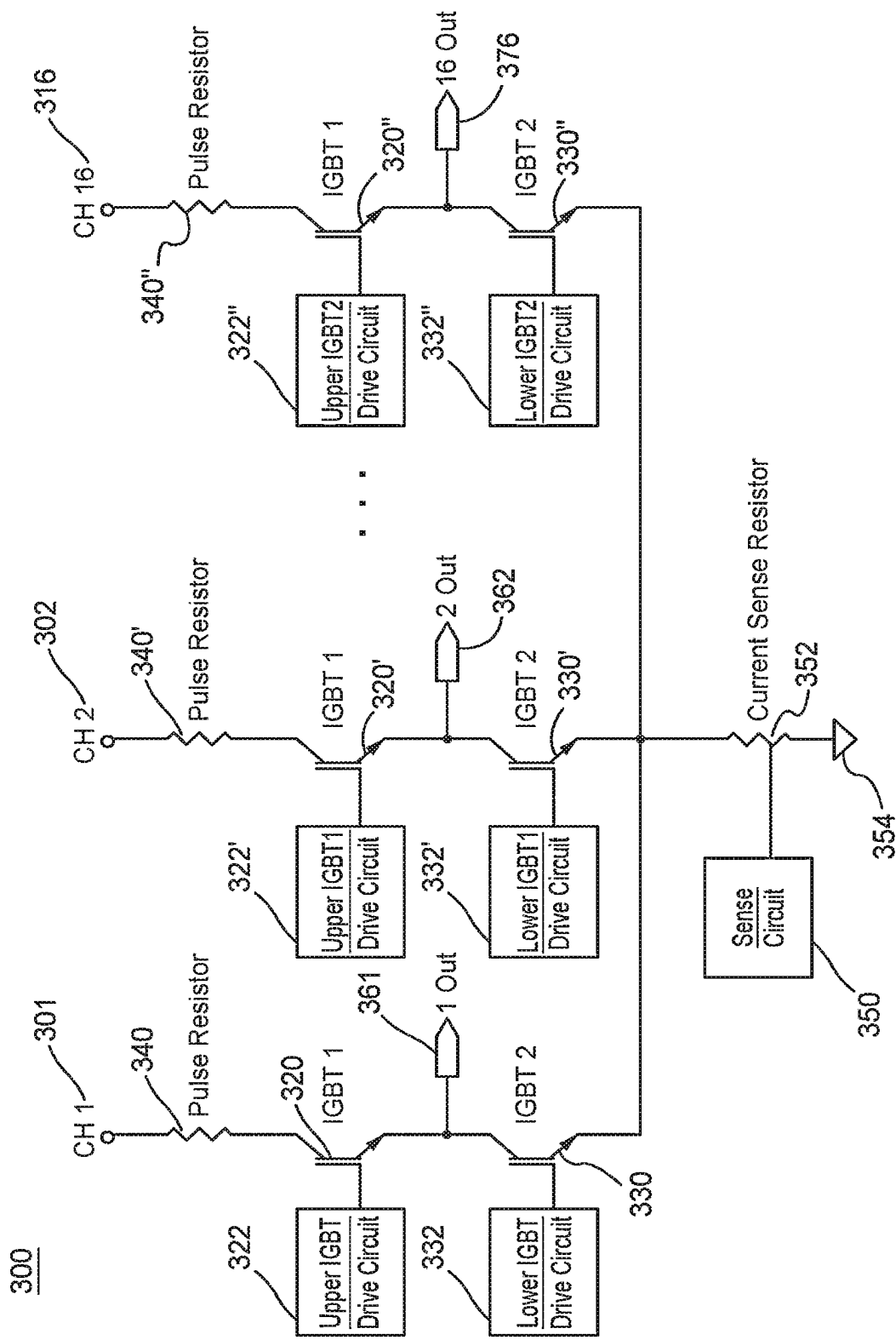


FIG. 3

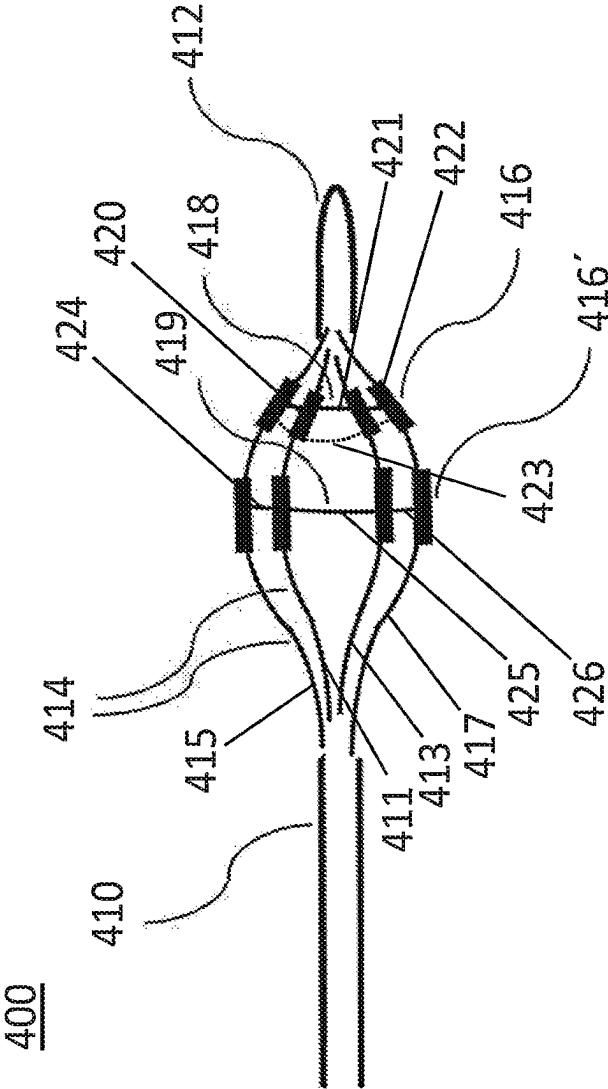


FIG. 4A

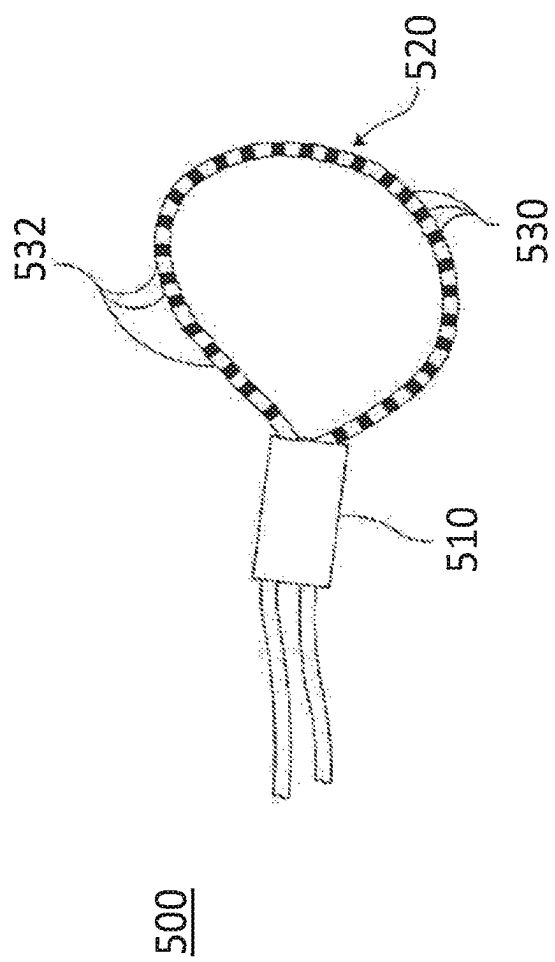


FIG. 5

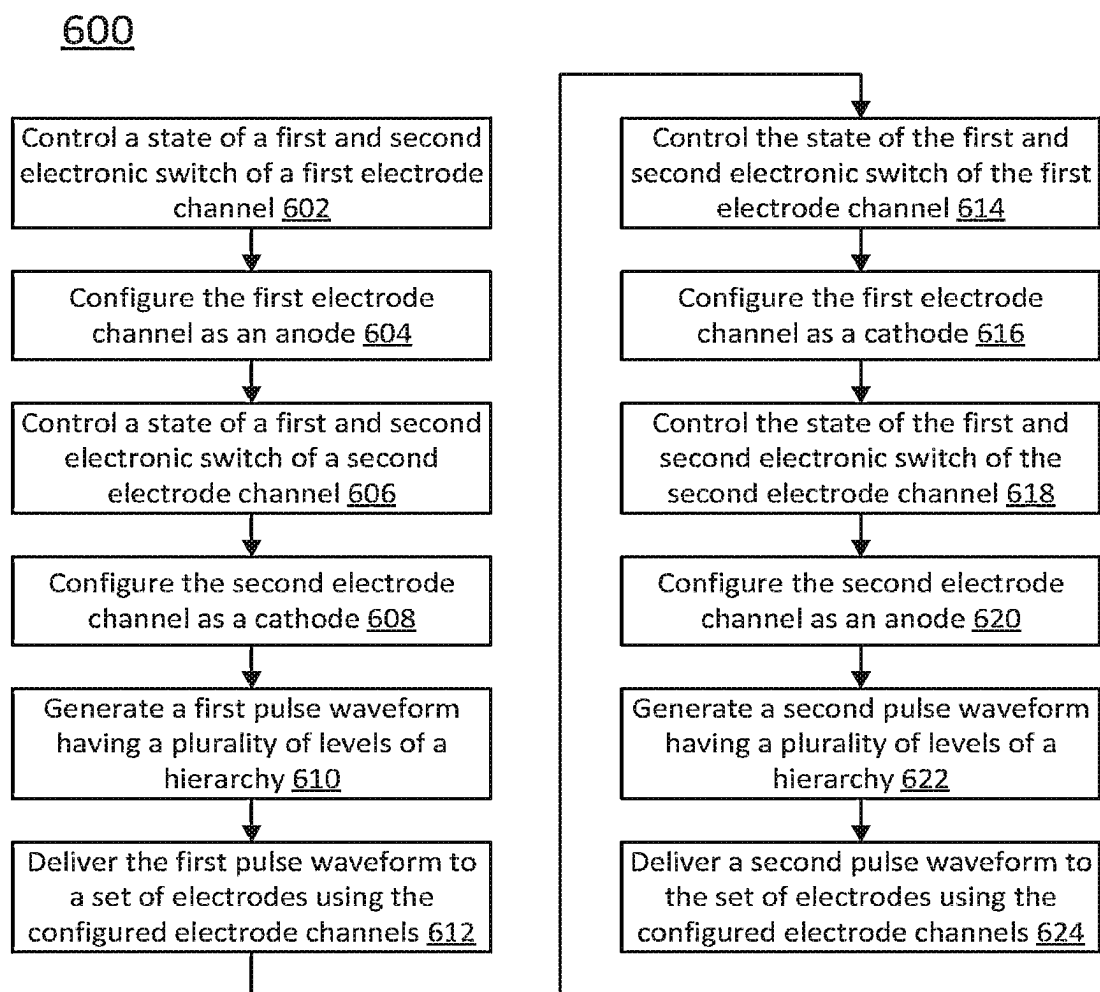


FIG. 6

700

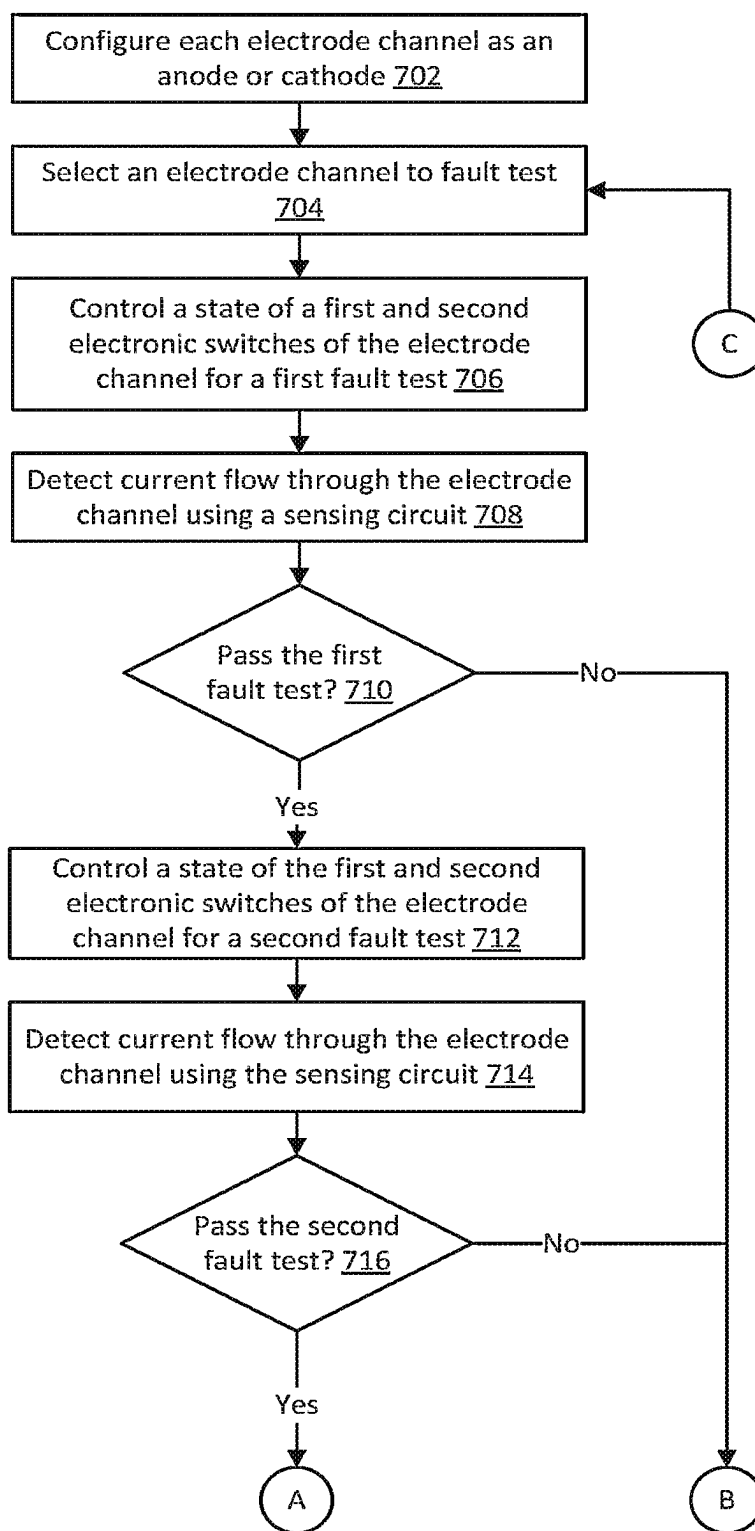


FIG. 7A

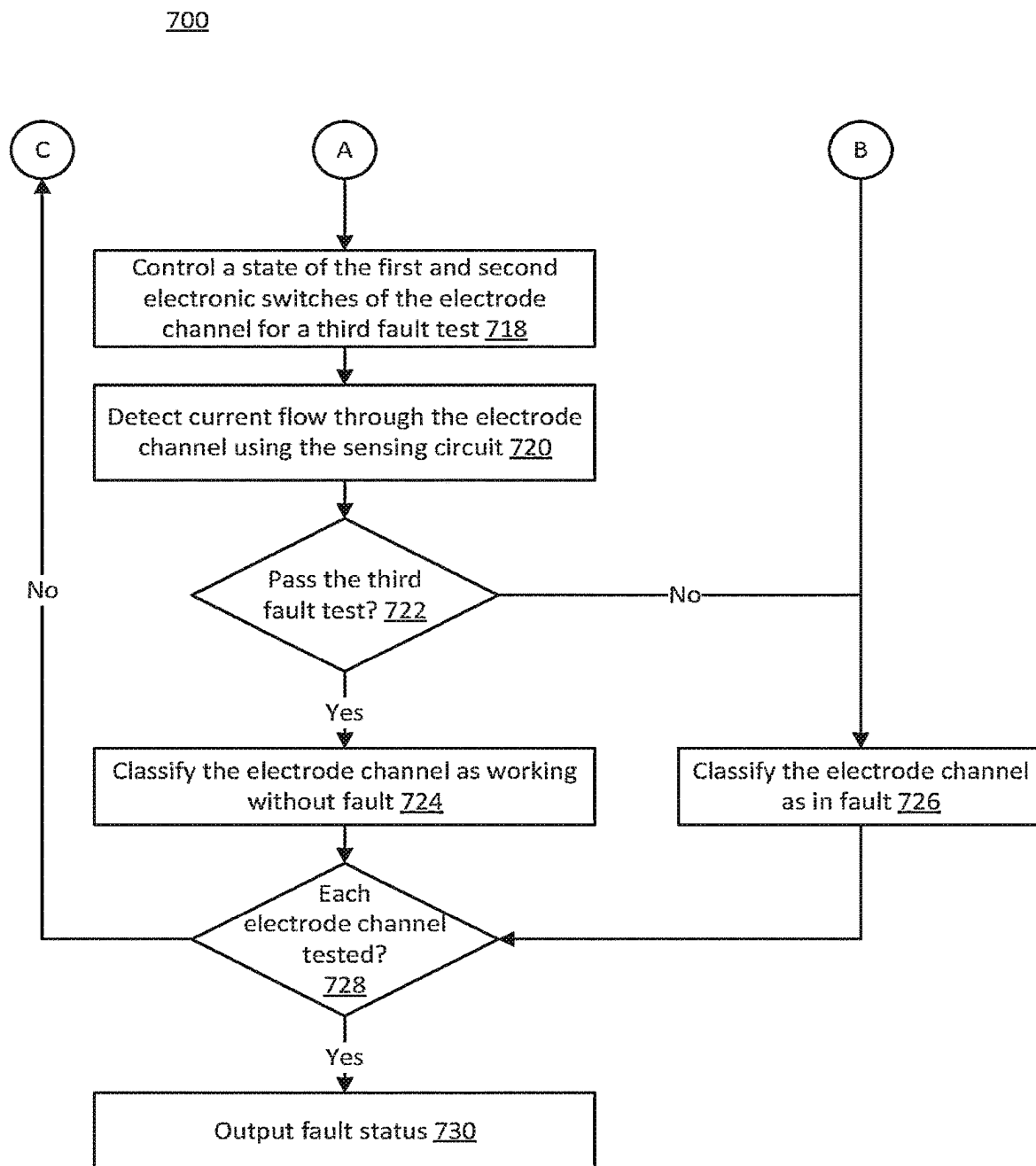


FIG. 7B

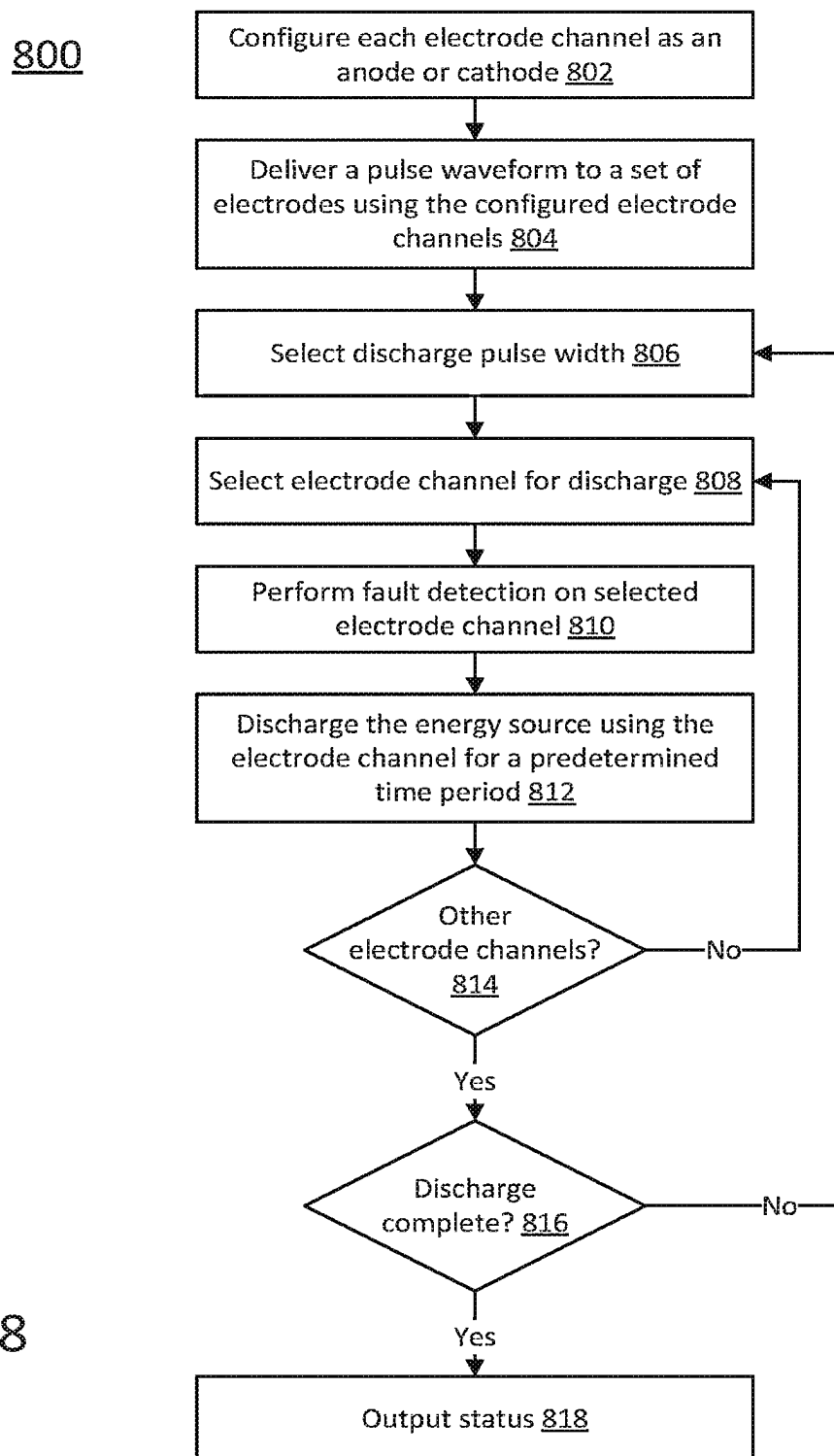


FIG. 8

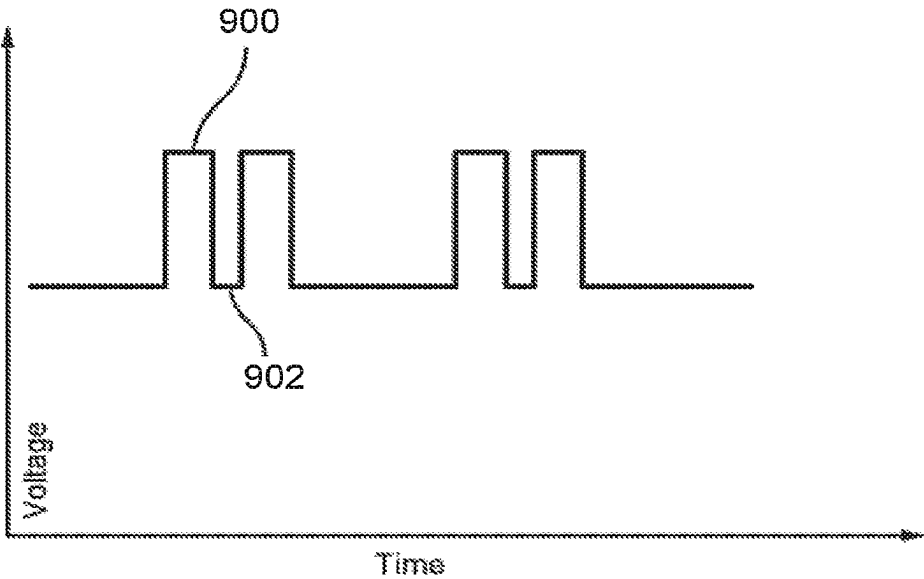


FIG. 9

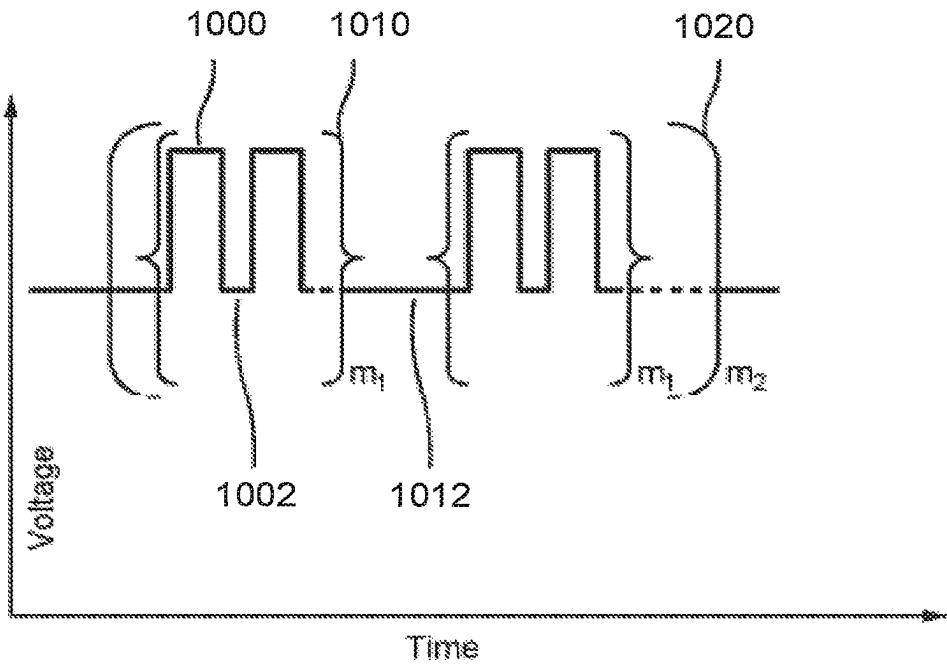


FIG. 10

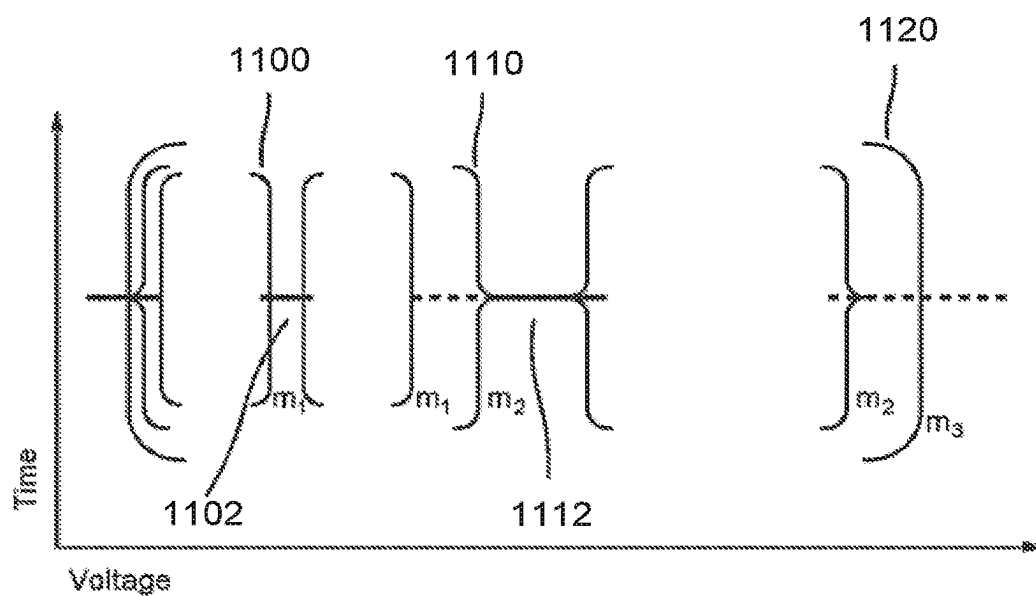


FIG. 11

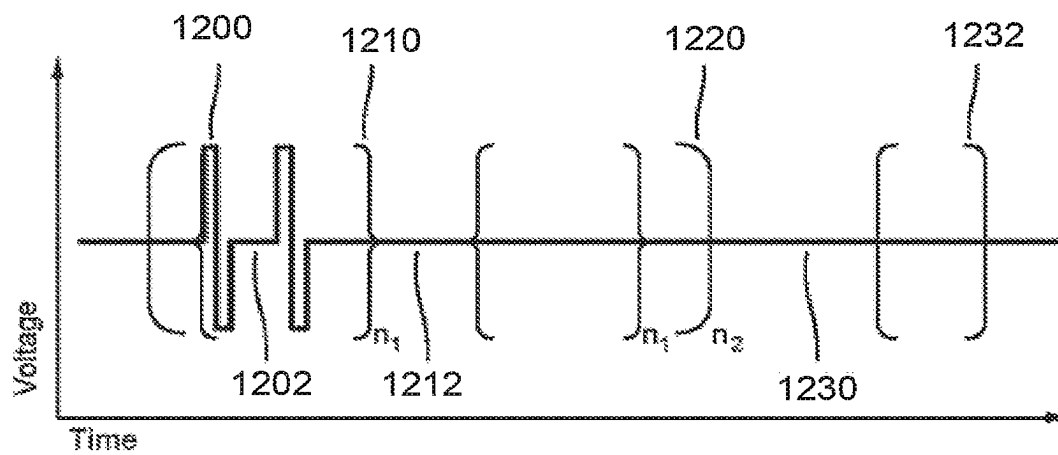


FIG. 12

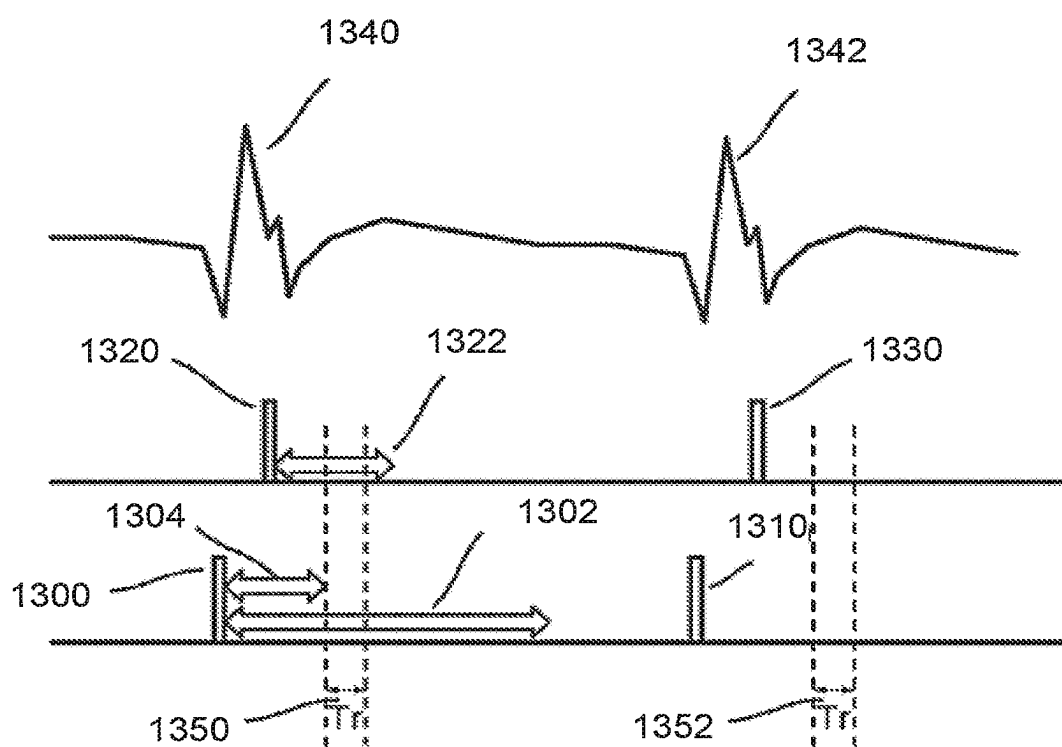


FIG. 13

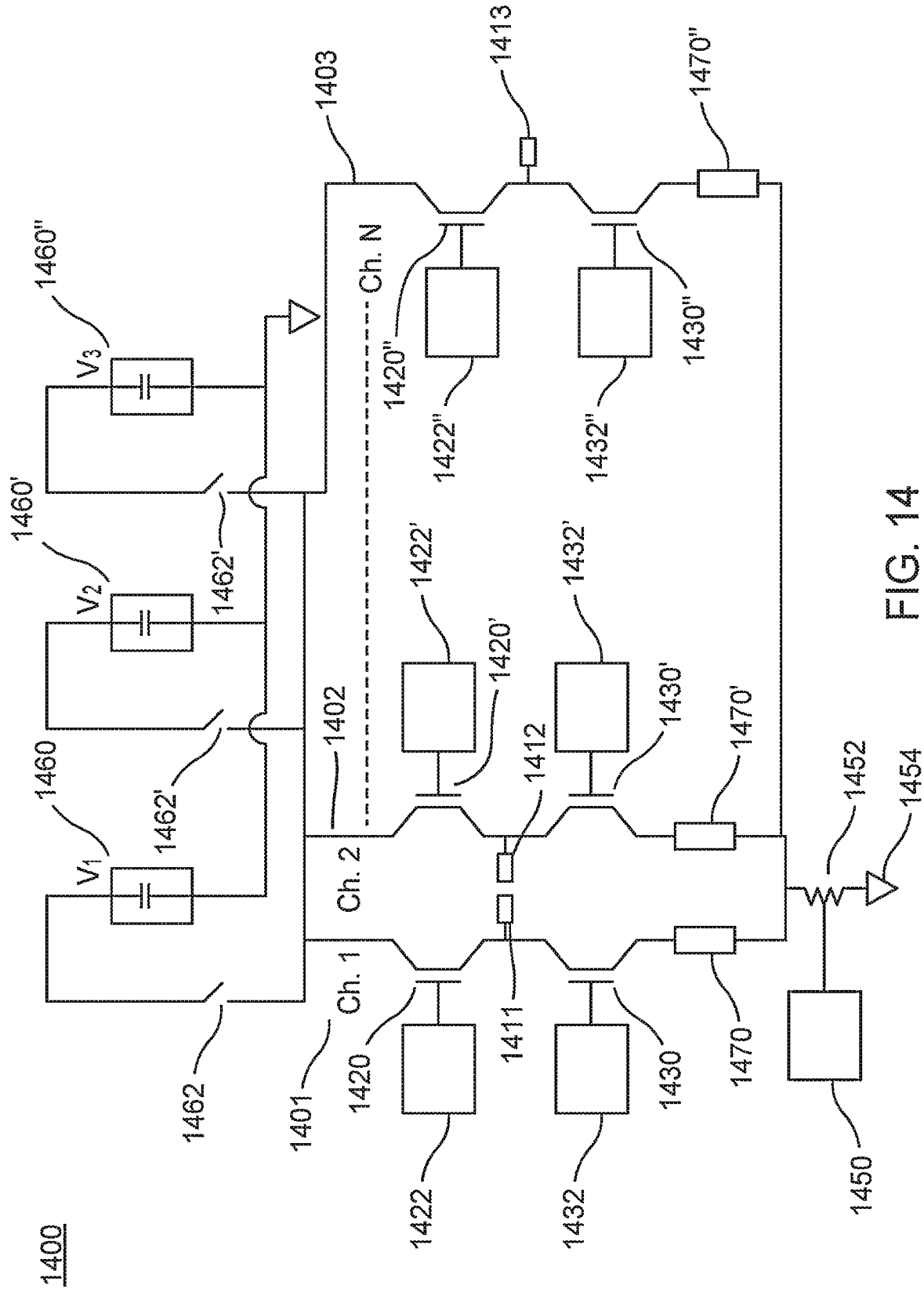


FIG. 14

1500

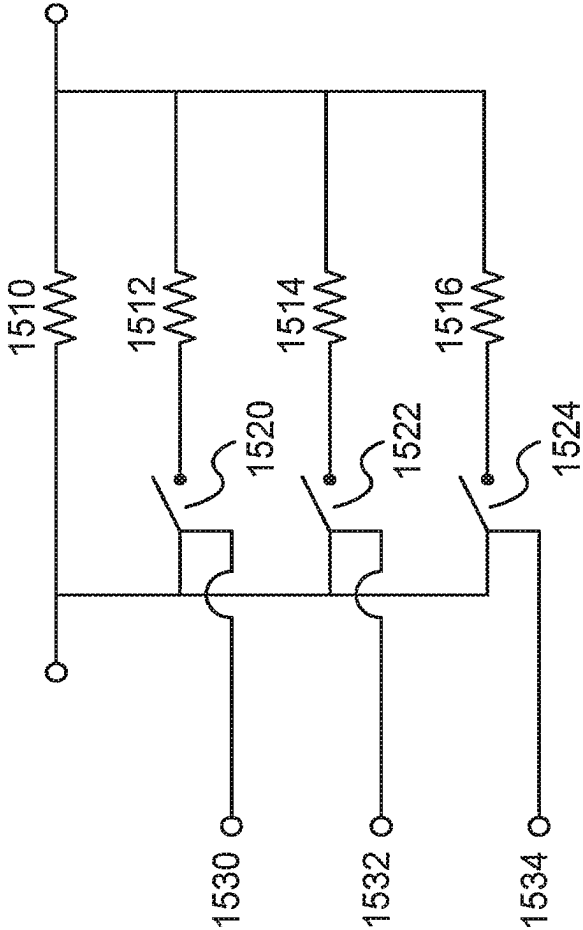
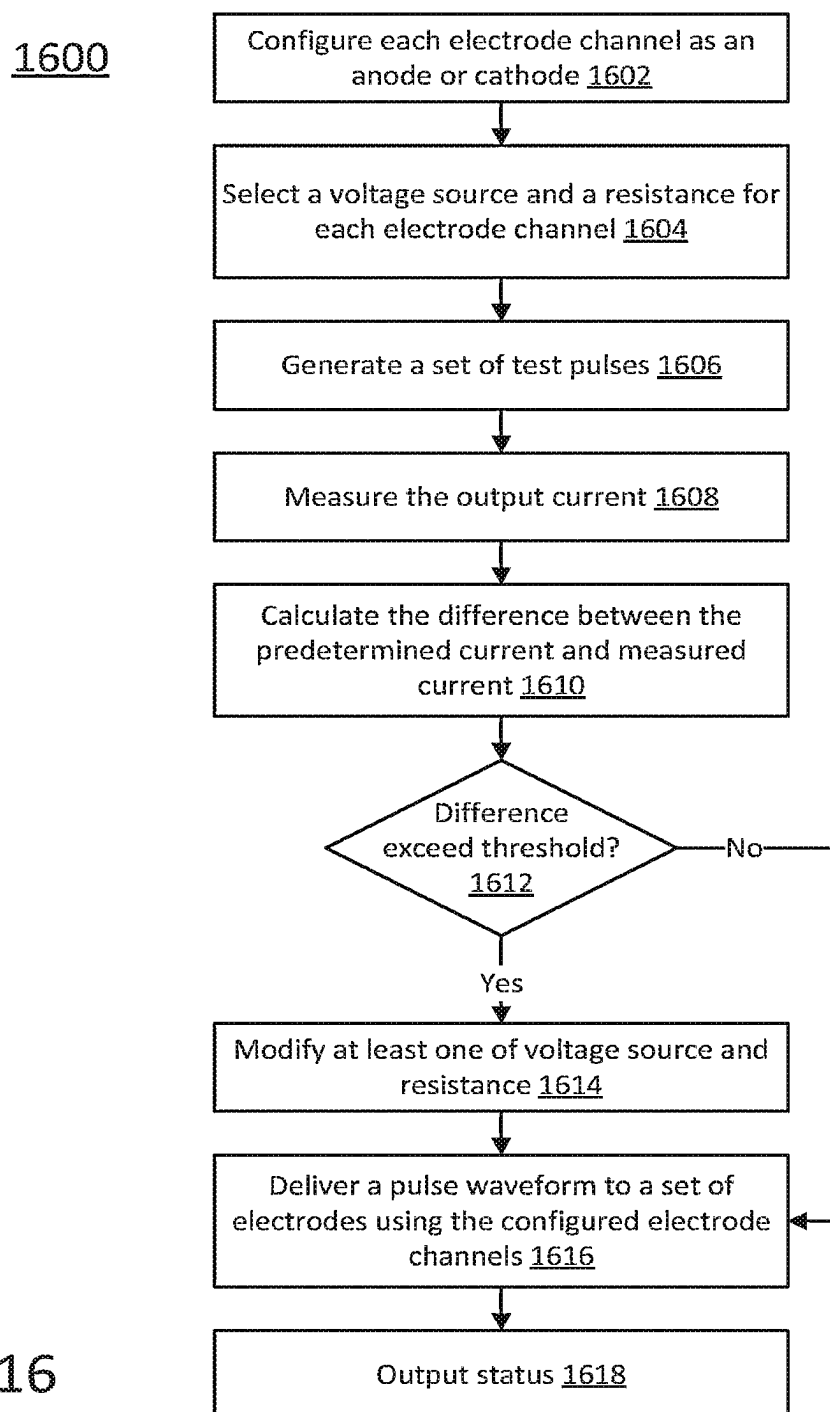


FIG. 15



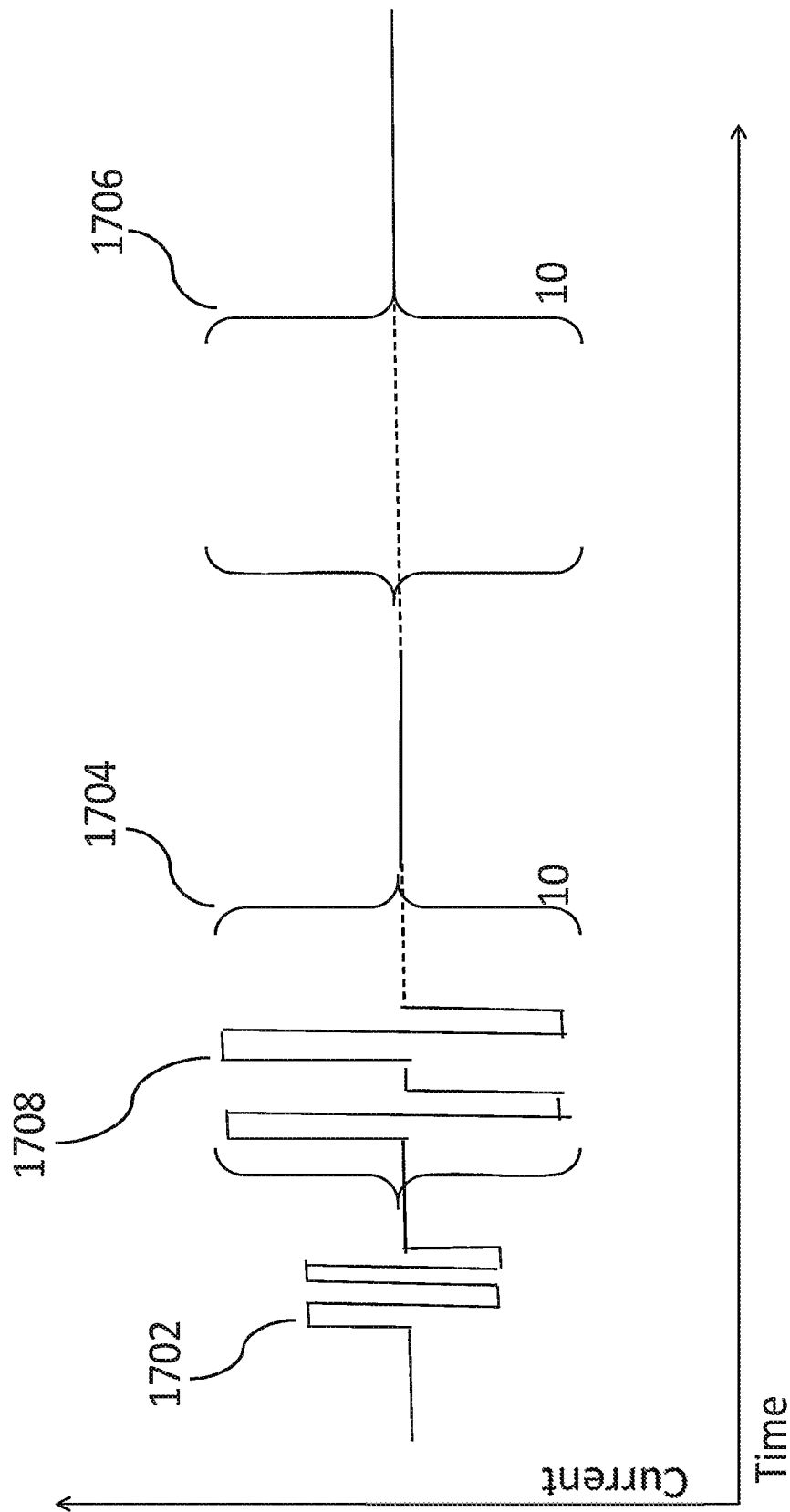


FIG. 17

**METHOD AND APPARATUS FOR
CONTROLLED DELIVERY OF PULSED
ELECTRIC FIELD ABLATIVE ENERGY TO
TISSUE**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

[0001] This application is a continuation of U.S. patent application Ser. No. 16/988,305, filed Aug. 7, 2020, issued as U.S. Pat. No. 12,295,637, which is a continuation of International Application No. PCT/2019/017322, filed Feb. 8, 2019, which claims priority to U.S. Provisional Application No. 62/628,163, filed Feb. 8, 2018, the disclosure of each of which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] The generation of pulsed electric fields for tissue therapeutics has moved from the laboratory to the clinic over the past two decades. Application of brief, high DC voltages to tissue may generate locally high electric fields typically in the range of hundreds of volts per centimeter that disrupt cell membranes by generating pores in the cell membrane. While the precise mechanism of this electrically-driven pore generation or electroporation continues to be studied, it is thought that the application of relatively brief and large electric fields generates instabilities in the lipid bilayers in cell membranes, causing the occurrence of a distribution of local gaps or pores in the cell membrane. Such electroporation may be irreversible if the applied electric field at the membrane is larger than a threshold value, leading to the pores remaining open, thereby leading to necrosis and/or apoptosis (cell death). Subsequently, the surrounding tissue may heal naturally.

[0003] Electroporation of tissue may be performed using electrode probes coupled to a high voltage generator for generation and delivery of brief, high voltage pulses, and may be limited by the capabilities of the generator. There is a need for measured and controlled delivery of high voltage application for tissue selectivity and safe energy delivery, such as in the context of ablation therapy for cardiac arrhythmias. Further, there is a need for measurement and control schemes capable of controlled delivery of energy for effective and safe medical procedures.

SUMMARY

[0004] Described herein are systems, devices, and methods for current control of energy delivery to ablate tissue through irreversible electroporation. Methods of adaptive adjustment of waveform amplitude are disclosed, wherein the current output of one or more channels may be measured and based on the measured set of current values, with the subsequent output of one or more channels adaptively controlled or modulated. The current output of a given channel may be adjusted by dynamically adjusting one or more of the voltage output and/or a suitable resistor or set of resistors in line with the output channel. The methods include various modes of control including adjusting pulse amplitude dynamically on a short time scale within the course of pulse delivery to a single set of electrodes.

[0005] Generally described herein are irreversible electroporation systems that may include a multi-channel voltage/signal generator and a programmable controller config-

ured to apply voltage pulses to a selected plurality or a subset of electrodes, with independent subset selections for anode and cathode electrode selections. The voltage waveform may be constructed as a hierarchical arrangement of multiplicities of voltage pulses organized in nested fashion. Levels of nesting of the pulses are disclosed together with a hierarchy of time intervals. The time intervals associated with the pulses and delays between pulses and delays between other elements of the hierarchy may be organized and the overall waveform may be designed to satisfy an inequality. The waveforms may be either monophasic (comprising a single electrical polarity) or biphasic (with alternating positive and negative polarities), or more generally a combination comprising both electrical polarities. While the electrodes may be disposed on a catheter device in some embodiments, in other embodiments they can be electrodes on other types of medical devices depending on the clinical application.

[0006] In some embodiments, the catheter devices used in these systems may be deployed epicardially or endocardially in cardiac applications. The waveforms may include predetermined parameters or may be automatically generated by a pulse generator and controller such that appropriate safety and timing constraints are satisfied.

[0007] Generally, a generator may include a set of electrode channels coupled to a set of electrodes during use. Each electrode channel from the set of electrode channels may include a first switch from a first set of switches and a second switch from a second set of switches. A set of energy sources may be coupled to a third set of switches. The third set of switches may be configured to switch from an OFF state to an ON state to couple the set of energy sources to the set of electrodes. A set of resistors may be coupled to the second set of switches. The second set of switches may be configured to switch from an OFF state to an ON state to couple the set of resistors to the set of electrodes. A processor may be coupled to the first set of switches and the second set of switches. The processor may be configured to set a subset of the third set of switches to the ON state to couple a subset of the energy sources to the electrode channels, and set a subset of the first set of switches to the ON state and a subset of the second set of switches to the ON state to configure a first subset of the electrode channels as anodes and a second subset of the electrode channels as cathodes. The processor may be further configured to deliver a pulse waveform to the first subset and the second subset of electrode channels using the subset of energy sources, such that electrodes coupled to the first subset and the second subset of electrode channels deliver energy to a target area.

[0008] In some embodiments, the processor may be configured to set the subset of the first set of switches and the subset of the second set of switches by setting, for each of the first subset of electrode channels and according to a first sequence, the first switch of that electrode channel to the ON state and the second switch of that electrode channel to the OFF state to configure that electrode channel as an anode. For each of the second subset of electrode channels and according to a second sequence, the first switch of that electrode channel may be set to the OFF state and the second switch of that electrode channel to the ON state to configure that electrode channel as a cathode, such that the respective electrode channels set according to the first sequence and the second sequence are paired for energy delivery.

[0009] In some embodiments, a sensing circuit may be configured to measure an output current of the set of electrode channels. The processor may be further configured to, in response to the output current measured by the sensing circuit being different from a predetermined output current, adjust at least one of a voltage delivered by the set of energy sources or a resistance of the set of resistors to adjust the output current measured by the sensing circuit closer to the predetermined output current. In some embodiments, the processor may be configured to adjust the at least one of the voltage or the resistance by (1) selecting one or more energy sources from the set of energy sources to deliver the pulse waveform, or (2) adjusting a resistance of one or more resistors from the set of resistors to be coupled to the set of electrodes. In some embodiments, the predetermined output current may be between about 5 Å and about 60 A. In some embodiments, the sensing circuit may be configured to detect electric arcing during use.

[0010] In some embodiments, the set of electrode channels may be arranged in parallel. In some embodiments, the processor may be further configured to set a resistance of the set of resistors between about 10 Ohms and about 600 Ohms. In some embodiments, the set of resistors may be configured to discharge excess energy from the set of energy sources. In some embodiments, the processor may be coupled to the first set of switches, the second set of switches, and the third set of switches via a set of drive circuits. The set of drive circuits configured to control the states of the first, second, and third sets of switches.

[0011] In some embodiments, the pulse waveform may include a first level of a hierarchy of the pulse waveform including a first set of pulses and a first time interval separating successive pulses, and a second level of the hierarchy of the pulse waveform including a plurality of first sets of pulses as a second set of pulses and a second time interval separating successive first sets of pulses. The second time interval being at least three times the duration of the first time interval. A third level of the hierarchy of the pulse waveform may include a plurality of second sets of pulses as a third set of pulses and a third time interval separating successive second sets of pulses. The third time interval being at least thirty times the duration of the second level time interval.

[0012] In some embodiments, a cardiac stimulator may be configured to generate a pacing signal for cardiac stimulation during use. The cardiac stimulator may be communicably coupled to the generator and further configured to transmit an indication of the pacing signal to the generator. The processor may be further configured to generate the pulse waveform in synchronization with the indication of the pacing signal, the synchronization including a pre-determined offset.

[0013] In some embodiments, the set of energy sources may be coupled to a collector terminal of the first set of switches and the set of resistors are coupled to an emitter terminal of the second set of switches. In some embodiments, each of the first set and the second set of switches is a bipolar junction transistor, a bipolar Field Effect transistor (Bi-FET), a power Metal Oxide Semiconductor Field Effect Transistor (MOSFET), or an Insulated-Gate Bipolar Transistor (IGBT). In some embodiments, each of the first set and the second set of switches may be an insulated-gate bipolar transistor.

[0014] In some embodiments, a generator may include a set of electrode channels coupled to a set of electrodes during use, a set of switches coupled to the set of electrode channels and configured to switch between an OFF state and an ON state, and a set of energy sources coupled to the set of electrode channels. A set of current control resistors may be coupled to the set of electrode channels. A set of current sensing resistors may be coupled to the set of electrode channels. A set of sensing circuits may be coupled to the set of current sensing resistors. A processor may be coupled to the set of switches and configured to set a state of a first subset of switches to configure a first subset of electrode channels as anodes and a second subset of electrode channels as a cathodes. A selected control parameter may be received via a user interface. A state of a second subset of switches may be set to select at least one energy source based on the selected control parameter to deliver a pulse waveform. The pulse waveform may be delivered to the set of electrodes using the first subset and the second subset of electrode channels, such that electrodes coupled to the first subset and the second subset of electrode channels deliver energy to a target area.

[0015] In some embodiments, each electrode channel from the set of electrode channels includes a first switch and a second switch from the set of switches. The processor may be configured to set the state of the first subset of switches by setting, for each of the first subset of electrode channels and according to a first sequence, the first switch of that electrode channel to the ON state and the second switch of that electrode channel to the OFF state to configure that electrode channel as an anode. For each of the second subset of electrode channels and according to a second sequence, the first switch of that electrode channel may be set to the OFF state and the second switch of that electrode channel may be set to the ON state to configure that electrode channel as a cathode, such that the respective electrode channels set according to the first sequence and the second sequence are paired for energy delivery. In some embodiments, the sensing circuit may be configured to measure an output current of the set of electrode channels. The processor may be further configured to, in response to the output current measured by the sensing circuit being different from a predetermined output current, adjust at least one of (1) a voltage delivered by the set of energy sources or (2) a resistance of the set of current control resistors in order to adjust the output current measured by the sensing circuit closer to the predetermined output current.

[0016] In some embodiments, the processor may be configured to adjust the at least one of the voltage or the resistance by setting a state of one or more switches to (1) select one or more energy sources from the set of energy sources to deliver the pulse waveform or (2) select one or more resistances of the set of current control resistors. In some embodiments, the predetermined output current may be between about 5 A and about 60 A. In some embodiments, the sensing circuit may be configured to detect electric arcing during use.

[0017] In some embodiments, the set of electrode channels may be arranged in parallel. In some embodiments, the processor may be further configured to set a resistance of the set of resistors between about 10 Ohms and about 600 Ohms. In some embodiments, the set of current control resistors may be configured to discharge excess energy from the set of energy sources. In some embodiments, the pro-

cessor may be coupled to the set of switches via a set of drive circuits. The set of drive circuits may be configured to control the state of the set of switches.

[0018] In some embodiments, the pulse waveform may include a first level of a hierarchy of the pulse waveform including a first set of pulses and a first time interval separating successive pulses, and a second level of the hierarchy of the pulse waveform including a plurality of first sets of pulses as a second set of pulses and a second time interval separating successive first sets of pulses. The second time interval being at least three times the duration of the first time interval. A third level of the hierarchy of the pulse waveform may include a plurality of second sets of pulses as a third set of pulses and a third time interval separating successive second sets of pulses, the third time interval being at least thirty times the duration of the second level time interval.

[0019] In some embodiments, a cardiac stimulator may be configured to generate a pacing signal for cardiac stimulation during use. The cardiac stimulator may be communicably coupled to the generator and further configured to transmit an indication of the pacing signal to the generator. The processor may be further configured to generate the pulse waveform in synchronization with the indication of the pacing signal. The synchronization may include a predetermined offset.

[0020] In some embodiments, the set of energy sources may be coupled to a collector terminal of the first set of switches and the set of resistors are coupled to an emitter terminal of the second set of switches. In some embodiments, each of the first set and the second set of switches is a bipolar junction transistor, a bipolar Field Effect transistor (Bi-FET), a power Metal Oxide Semiconductor Field Effect Transistor (MOSFET), or an Insulated-Gate Bipolar Transistor (IGBT). In some embodiments, each of the first set and the second set of switches may be an insulated-gate bipolar transistor. In some embodiments, the control parameter may be a current value. In some embodiments, the control parameter may be a voltage value.

[0021] Also described herein are methods that may include the steps of setting a state of a set of switches coupled to a set of electrode channels such that a first subset of electrode channels may be configured as anodes and a second subset of electrode channels may be configured as cathodes. Using a set of energy sources coupled to the set of electrode channels, a first pulse waveform may be delivered to the set of electrodes. An output current of the set of electrode channels may be measured using a sensing circuit coupled to the set of electrode channels. At least one of (1) a voltage delivered by the set of energy sources or (2) a resistance of a set of current control resistors coupled to the set of electrode channels may be adjusted based on the measured output current. After the adjusting, a second pulse waveform may be delivered to the set of electrodes such that the set of electrodes deliver energy to a target area. The second pulse waveform may have an amplitude different than the first pulse waveform.

[0022] In some embodiments, the first pulse waveform may include one or more test pulses for measuring the output current, and the second pulse waveform may be configured to ablate cardiac tissue. In some embodiments, the energy delivered by the set of electrodes generates irreversible electroporation in the targeted area. In some embodiments, each electrode channel from the set of electrode channels

includes a first switch and a second switch from the set of switches. The setting of the state of the set of switches may include setting, for each of the first subset of electrode channels and according to a first sequence, the first switch of that electrode channel to the ON state and the second switch of that electrode channel to the OFF state to configure that electrode channel as an anode. For each of the second subset of electrode channels and according to a second sequence, the first switch of that electrode channel is set to the OFF state and the second switch of that electrode channel is set to the ON state to configure that electrode channel as a cathode, such that the respective electrode channels set according to the first sequence and the second sequence are paired for energy delivery.

[0023] In some embodiments, adjusting values may be in response to the output current measured by the sensing circuit being smaller than a predetermined threshold value. In some embodiments, the predetermined output current may be between about 5 A and about 60 A. In some embodiments, a status of the current output may be presented using a user interface.

[0024] In one embodiment of the invention, the electrodes are catheter-based electrodes, or a plurality of electrodes disposed along the length of an elongate medical device, or along various portions of a medical device. The irreversible electroporation system described herein includes a voltage/signal generator and a controller capable of being configured to apply pulsed voltage waveforms to a selected plurality or a subset of electrodes. The controller is additionally capable of applying control inputs whereby selected pairs of anode-cathode subsets of electrodes can be sequentially updated based on a pre-determined sequence, and in one embodiment the sequenced delivery can be triggered from a cardiac stimulator or pacing system. In such embodiments, the ablation pulse waveforms are applied in a refractory period of the cardiac cycle so as to avoid disruption of the sinus rhythm of the heart. One example method of enforcing this is to electrically pace the heart with a cardiac stimulator and ensure pacing capture to establish periodicity and predictability of the cardiac cycle, and then to define a time window well within the refractory period of this periodic cycle within which the ablation waveform is delivered. In some embodiments, the pacing/stimulation function can be integrated in the generator console.

[0025] The pulsed voltage waveforms of the present invention are hierarchical in organization and have a nested structure. Further, they involve a sequence of groupings with a variety of associated timescales. Furthermore, the associated timescales and pulse widths, and the numbers of pulses and hierarchical groupings, are selected so as to satisfy one or more of a set of Diophantine inequalities involving the frequency of cardiac pacing.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] FIG. 1 is a block diagram of an electroporation system, according to embodiments.

[0027] FIG. 2 is a circuit diagram of a signal generator, according to embodiments.

[0028] FIG. 3 is a circuit diagram of a signal generator, according to other embodiments.

[0029] FIG. 4A is a side view of an ablation catheter, according to other embodiments.

[0030] FIG. 4B is a side view of an ablation catheter, according to other embodiments.

[0031] FIG. 5 is a partial close-up view of a central portion of an ablation catheter, according to other embodiments.

[0032] FIG. 6 illustrates a method for tissue ablation, according to embodiments.

[0033] FIGS. 7A-7B illustrate a method for fault detection, according to other embodiments.

[0034] FIG. 8 illustrates a method for energy discharge, according to other embodiments.

[0035] FIG. 9 is an example waveform showing a sequence of voltage pulses with a pulse width defined for each pulse, according to embodiments.

[0036] FIG. 10 schematically illustrates a hierarchy of pulses showing pulse widths, intervals between pulses, and groupings of pulses, according to embodiments.

[0037] FIG. 11 provides a schematic illustration of a nested hierarchy of monophasic pulses displaying different levels of nested hierarchy, according to embodiments.

[0038] FIG. 12 is a schematic illustration of a nested hierarchy of biphasic pulses displaying different levels of nested hierarchy, according to embodiments.

[0039] FIG. 13 illustrates schematically a time sequence of electrocardiograms and cardiac pacing signals together with atrial and ventricular refractory time periods and indicating a time window for irreversible electroporation ablation, according to embodiments.

[0040] FIG. 14 is a circuit diagram of a signal generator, according to embodiments.

[0041] FIG. 15 is a circuit diagram of a set of resistors, according to embodiments.

[0042] FIG. 16 illustrates a method for tissue ablation, according to embodiments.

[0043] FIG. 17 is a schematic illustration of a pilot waveform followed by biphasic pulses, according to embodiments.

DETAILED DESCRIPTION

[0044] Described herein are systems, devices, and methods for signal generation such as for delivery of pulsed electric fields to ablate tissue by irreversible electroporation. Generally, the systems, devices, and methods described herein may be used to generate large electric field magnitudes (e.g., electric fields of about 200 V/cm and above) to treat atrial fibrillation via irreversible electroporation, and/or provide a highly configurable a set of electrode channels (e.g., allow independent and arbitrary electrode selection), provide current control of energy delivery to one or more ablation devices, provide fault detection to the signal generator, and/or discharge excess stored energy to improve operational speed and reduce treatment time.

[0045] A tissue ablation system as described herein may include a signal generator having a set of energy sources, a set of electrode channels, a set of resistors coupled to each electrode channel of the set of electrode channels, and a processor configured to deliver a pulse waveform to a configurable set of electrode channels to deliver energy to a region of interest. The pulse waveforms disclosed herein may aid in therapeutic treatment of a variety of cardiac arrhythmias (e.g., atrial fibrillation). In some embodiments, in order to control the current output by an electrode channel, a set of energy sources may include a set of first switches and the set of resistors may include a set of second switches.

[0046] In one embodiment, in order to configure an electrode channel as an anode or cathode, the electrode channel

may include a drive circuit coupled to control an electronic switch. For example, an ON/OFF state for a set of electronic switches may be used to configure an electrode channel as an anode or cathode. In some embodiments, the electrode channel may be reconfigured as a cathode or anode for different pulses. The signal generator may include a set of electrode channels that may be coupled to respective electrodes of the same or different ablation device. In some embodiments, each electrode channel may be separately configured as a half-bridge amplifier while a pair of electrode channels may be collectively configured as a full bridge amplifier. As described herein, the number, configuration (e.g., anode, cathode), and operating mode (e.g., monophasic, biphasic) of the electrode channels may be independently controlled. In this manner, the generator may deliver different energy waveforms with different timings synergistically for electroporation of tissue.

[0047] In some embodiments, the signal generator may be configured to discharge excess stored energy (e.g., capacitive energy) to ground using the set of electrode channels that deliver pulse waveforms to the set of electrodes. Each energy source of the set of energy sources coupled to the electrode channels may include a capacitive element configured for storing energy. Each electrode channel may include a resistive element configured for discharging the capacitive element when the energy source is not in use (e.g., after applying ablative energy to tissue). For example, each energy source of the set of energy sources having excess energy stored in a corresponding capacitive element (e.g., after delivering a pulse waveform) may sequentially and over a set of cycles discharge a portion of the stored energy through the resistive element in each of the electrode channels until reaching a predetermined threshold. The signal generator may discharge this capacitor energy at faster rate by staggering the discharge period and rest period of each electrode channel and/or energy source. In some embodiments, the resistive element may include each of the sets of resistors coupled to each electrode channel of the set of electrode channels.

[0048] In some embodiments, the signal generator may perform one or more fault tests to classify a fault status of one or more electrode channels and thereby ensure proper operation of the signal generator. The signal generator may include a sensing circuit configured to detect current through each of the electrode channels. The processor may be configured to set one or more electronic switches of each electrode channel to predetermined states (e.g., test states) to allow the fault status of the electrode channel to be classified. Fault tests may be performed upon powering on the signal generator, such as for a Power on Self-Test (POST) and/or at predetermined intervals during use, such as during tissue ablation energy delivery and capacitor discharge.

[0049] The term “electroporation” as used herein refers to the application of an electric field to a cell membrane to change the permeability of the cell membrane to the extracellular environment. The term “reversible electroporation” as used herein refers to the application of an electric field to a cell membrane to temporarily change the permeability of the cell membrane to the extracellular environment. For example, a cell undergoing reversible electroporation may observe the temporary and/or intermittent formation of one or more pores in its cell membrane that close up upon removal of the electric field. The term “irreversible electroporation” as used herein refers to the application of an

electric field to a cell membrane to permanently change the permeability of the cell membrane to the extracellular environment. For example, a cell undergoing irreversible electroporation may observe the formation of one or more pores in its cell membrane that persist upon removal of the electric field.

[0050] Pulse waveforms for electroporation energy delivery as disclosed herein may enhance the safety, efficiency and effectiveness of energy delivery to tissue by reducing the electric field threshold associated with irreversible electroporation, thus yielding more effective ablative lesions with a reduction in total energy delivered. In some embodiments, the voltage pulse waveforms disclosed herein may be hierarchical and have a nested structure. For example, a pulse waveform may include hierarchical groupings of pulses having associated timescales. In some embodiments, the methods, systems, and devices disclosed herein may comprise one or more of the methods, systems, and apparatuses described in International Application Serial No. PCT/US2016/057664, filed on Oct. 19, 2016, and titled “SYSTEMS, APPARATUSES AND METHODS FOR DELIVERY OF ABLATIVE ENERGY TO TISSUE,” the contents of which are hereby incorporated by reference in its entirety.

[0051] In some embodiments, the systems may further include a cardiac stimulator used to synchronize the generation of the pulse waveform to a paced heartbeat. The cardiac stimulator may electrically pace the heart with a cardiac stimulator and ensure pacing capture to establish periodicity and predictability of the cardiac cycle. A time window within a refractory period of the periodic cardiac cycle may be selected for voltage pulse waveform delivery. Thus, voltage pulse waveforms may be delivered in the refractory period of the cardiac cycle so as to avoid disruption of the sinus rhythm of the heart. In some embodiments, an ablation device may include one or more catheters, guidewires, balloons, and electrodes. The ablation device may transform into different configurations (e.g., compact and expanded) to position the ablation device within an endocardial space. In some embodiments, the system may optionally include one or more return electrodes.

[0052] Generally, to ablate tissue, one or more catheters having one or more electrodes may be advanced in a minimally invasive fashion through vasculature to a target location. In a cardiac application, the electrodes through which a voltage pulse waveform is delivered may be disposed on an epicardial device or on an endocardial device. The methods described here may include configuring a first and second electrode channel of a set of electrode channels as a respective anode and cathode. Each electrode channel may include a drive circuit and an electronic switch configured to switch between ON and OFF states. The drive circuit may be configured to control the state of the electronic switch. A predetermined (e.g., test, or pilot) pulse waveform may be delivered to respective electrodes and current may be measured by a sensing circuit. The set of first and/or second switches may be controlled based on the measured current to select an energy source of the set of energy sources and/or at least one resistor of the set of resistors to output a predetermined current. A pulse waveform may be delivered to respective electrodes to ablate tissue using the first and second electrode channels. In some embodiments, the pulse waveform may include hierarchical waveforms to aid in tissue ablation and reduce damage to healthy tissue. In

some embodiments, the pulse waveform may be generated in synchronization with a pacing signal of the heart to avoid disruption of the sinus rhythm of the heart.

I. Systems

Overview

[0053] Disclosed herein are systems and devices configured for tissue ablation via the selective and rapid application of voltage pulse waveforms, resulting in irreversible electroporation. Generally, a system for ablating tissue described herein may include a signal generator and one or more ablation devices having one or more electrodes for the selective and rapid application of DC voltage to drive electroporation. As described herein, the systems and devices may be deployed epicardially and/or endocardially to treat atrial fibrillation. Each ablation device may be coupled to one or more electrode channels of the signal generator. Each electrode channel may be independently configured as an anode or cathode and a voltage pulse waveform may be delivered through one or more of the electrode channels in a predetermined sequence. In some embodiments, the electrode channels may be actively monitored and used for excess energy discharge of the set of energy sources. In some embodiments, a pacing signal for cardiac stimulation may be generated and used to generate the voltage pulse waveform in synchronization with the pacing signal.

[0054] FIG. 1 illustrates an ablation system (100) configured to deliver voltage pulse waveforms for tissue ablation. The system (100) may include a signal generator (110), ablation device (140), and optionally a cardiac stimulator (150). The signal generator (110) may be coupled to at least one ablation device (140), and optionally to the cardiac stimulator (150). The ablation device (140) may include a set of one or more electrodes (142).

Signal Generator

[0055] The signal generator (110) may be configured to generate pulse waveforms for irreversible electroporation of tissue, such as, for example, heart tissue. The signal generator (110) may be a voltage pulse waveform generator and deliver a pulse waveform to a set of electrodes (142a, 142b, . . . , 142n) of the ablation device (140). The signal generator (110) may generate and deliver several types of signals including, but not limited to, radiofrequency (RF), direct current (DC) impulses (such as high-voltage, ultra-short pulses used in electroporation), stimulus range impulses, and/or hybrid electrical impulses. For example, the signal generator (110) may generate monophasic (DC) pulses and biphasic (DC and AC) pulses. The signal generator (110) may include a processor (120), memory (122), a set of electrode channels (124a, 124b, . . . , 124n), a set of energy sources (126a, 126b, . . . , 126n), sensing circuit (128), routing console (130), and user interface (132). One or more signal generator components may be coupled using a communication bus. The processor (120) may incorporate data received from one or more of memory (122), electrode channels (124), energy sources (126), sensing circuit (128), routing console (130), user interface (132), ablation device (140), and cardiac stimulator (150) to determine the parameters (e.g., current, amplitude, width, duty cycle, timing, etc.) of the voltage pulse waveform to be generated by the

signal generator (110). The memory (122) may further store instructions to cause the processor (120) to execute modules, processes and/or functions associated with the system (100), such as pulse waveform generation and delivery, current sensing and control, electrode channel configuration, fault testing, energy discharge, and/or cardiac pacing synchronization. For example, the memory (122) may be configured to store anode/cathode configuration data, electrode channel configuration data, pulse waveform data, current data, fault data, energy discharge data, heart pacing data, patient data, clinical data, procedure data, and/or the like.

[0056] In some embodiments, the ablation device (140) may include a catheter configured to receive and/or deliver the pulse waveforms described herein. For example, the ablation device (140) may be introduced into an endocardial space of the left atrium and positioned to align one or more electrodes (142a, 142b, . . . , 142n) to heart tissue (e.g., one or more pulmonary vein ostia of the left atrium), and then deliver the pulse waveforms to ablate tissue. In another example, the ablation devices (140) may ablate tissue using an epicardial approach. The ablation device (140) may include one or more electrodes (142a, 142b, . . . , 142n), which may, in some embodiments, be a set of independently addressable electrodes. For example, the electrodes (142a, 142b, . . . , 142n) may be grouped into one or more anode-cathode subsets such as, for example, a subset including one anode and one cathode, a subset including two anodes and two cathodes, a subset including two anodes and one cathode, a subset including one anode and two cathodes, a subset including three anodes and one cathode, a subset including three anodes and two cathodes, and/or the like. The set of electrodes (142) may include any number of electrodes, for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, or more electrodes. In some embodiments, the methods, systems, and devices disclosed herein may comprise one or more of the methods, systems, and devices described in International Application Serial No. PCT/US17/12099, filed on Jan. 4, 2017, and titled “SYSTEMS, DEVICES, AND METHODS FOR DELIVERY OF PULSED ELECTRIC FIELD ABLATIVE ENERGY TO ENDOCARDIAL TISSUE,” and International Application Serial No. PCT/US2013/031252, filed on Mar. 14, 2013, and titled “CATHETERS, CATHETER SYSTEMS, AND METHODS FOR PUNCTURING THROUGH A TISSUE STRUCTURE AND ABLATING A TISSUE REGION,” the contents of which are hereby incorporated by reference in its entirety.

[0057] In some embodiments, the processor (120) may be any suitable processing device configured to run and/or execute a set of instructions or code and may include one or more data processors, image processors, graphics processing units, physics processing units, digital signal processors, and/or central processing units. The processor (120) may be, for example, a general purpose processor, Field Programmable Gate Array (FPGA), an Application Specific Integrated Circuit (ASIC), and/or the like. The processor (120) may be configured to run and/or execute application processes and/or other modules, processes and/or functions associated with the system and/or a network associated therewith (not shown). In some embodiments, the processor may comprise both a microcontroller unit and an FPGA unit, with the microcontroller sending electrode sequence instructions to the FPGA. The underlying device technologies may be provided in a variety of component types, e.g., metal-

oxide semiconductor field-effect transistor (MOSFET) technologies like complementary metal-oxide semiconductor (CMOS), bipolar technologies like emitter-coupled logic (ECL), polymer technologies (e.g., silicon-conjugated polymer and metal-conjugated polymer-metal structures), mixed analog and digital, and/or the like.

[0058] In some embodiments, the memory (122) may include a database (not shown) and may be, for example, a random access memory (RAM), a memory buffer, a hard drive, an erasable programmable read-only memory (EPROM), an electrically erasable read-only memory (EEPROM), a read-only memory (ROM), Flash memory, etc. The memory (122) may store instructions to cause the processor (120) to execute modules, processes and/or functions associated with the system (100), such as pulse waveform generation, electrode channel configuration, fault detection, energy discharge, and/or cardiac pacing.

[0059] In some embodiments, a set of electrode channels (124) may include a set of active solid-state switches. The set of electrode channels (124) may be configured in a number of ways, including independent anode/cathode configuration for each electrode channel. For example, the electrode channels (124a, 124b, . . . , 124n) may be grouped into one or more anode-cathode subsets such as, for example, a subset including one anode and one cathode, a subset including two anodes and two cathodes, a subset including two anodes and one cathode, a subset including one anode and two cathodes, a subset including three anodes and one cathode, a subset including three anodes and two cathodes, and/or the like. The set of electrode channels (124) may include any number of channels, for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, or more electrode channels. Energy delivery may use any combination of electrode channels (124) and any order for an energy delivery sequence. The energy delivered may be an RF and/or any tissue ablation energy. In some embodiments, the set of electrode channels may provide a discharge path to ground (e.g., capacitor discharge) for excess energy of an energy source (126). In some of these embodiments, excess energy may be discharged through the set of electrode channels (124) such that the signal generator (110) does not include a separate bleeder resistor and/or dump circuit, thereby reducing components count, generator size, cost, and/or manufacturing complexity.

[0060] The set of electrode channels (124) may be coupled to a routing console (130) to deliver energy to a set of electrodes (142) coupled to the routing console (130). The set of electrode channels (124) may be coupled to an energy source (126) of the set of energy sources to receive energy (e.g., a pulse waveform). Processor (120) may be coupled to each electrode channel (124) to configure an anode/cathode configuration for each electrode channel (124), which may be configured on a per pulse basis, per operator input, and/or the like. Furthermore, the processor (120) may be coupled to each energy source (126) to configure the set of electrode channels to a selected energy source. The processor (120) and energy source (126) may be collectively configured to deliver a pulse waveform to the set of electrodes (142) through the set of electrode channels (124). In some embodiments, each energy source may include a switch (e.g., electronic switch and drive circuit). In some embodiments, each electrode channel (124) may include an electronic switch (e.g., bipolar transistor) and a drive circuit, as described in detail herein. In some embodiments, each

electrode channel (124) may have a bootstrap configuration for low and high frequency operation. For example, the pulse duration of voltage pulses delivered through an electrode channel may be in the range of between about 1 microsecond and about 1000 microseconds. In biphasic mode, this corresponds to an approximate frequency range of between about 500 Hz and about 500 KHz for the frequency associated with the voltage pulses.

[0061] In some embodiments, each energy source (126) of the set of energy sources (126) may be configured to convert and supply energy to a set of electrodes (142) coupled to the signal generator (110). Each of the energy sources (126) of the signal generator (110) may include a DC power supply and be configured as an AC/DC switcher. In some embodiments, an energy source (126) of the signal generator (110) may deliver rectangular-wave pulses with a peak maximum voltage of about 7 kV into a device with an impedance in the range of about 30Ω to about 3000 Ω for a maximum duration of about 1000 μs. Pulses may be delivered in bursts, such as for example, in a sequence of between about 2 pulses and about 10 pulses interrupted by pauses of between about 1 ms and about 1000 ms. In one embodiment, the energy source may deliver about a 3 kV pulse at about 150 A. The set of energy sources (126) may include any number of energy sources, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, or more energy sources. In some of these embodiments, the energy source (126) may be configured to store energy. For example, the energy source (126) may include one or more capacitors to store energy from a power supply. While these examples are included for purely non-limiting illustrative purposes, it is noted that a variety of pulse waveforms with a range of pulse durations, intervals between pulses, pulse groupings, etc. may be generated depending on the clinical application.

[0062] In some embodiments, a sensing circuit (128) may be configured to determine an amount of current being delivered to a device coupled to the signal generator (110) (e.g., electrode (142) coupled to the electrode channel (124)). As described in more detail herein, the sensing circuit (128) may also be used to classify an electrode channel fault, monitor capacitor discharge, and/or sense arcing. In some embodiments, the sensing circuit (128) may be a direct current sensing circuit and/or a low-side sensing circuit. The sensing circuit may include one or more operational amplifiers, difference amplifiers (DA), instrumentation amplifiers (IA), and/or current shunt monitors (CSM).

[0063] In some embodiments, the routing console (130) may be configured to electrically couple a set of electrodes (142) of an ablation device (140) to a set of electrode channels (124). The routing console (130) may be configured to selectively deliver energy to the set of electrodes (142) using the set of electrode channels (124). One or more ablation devices (140) each having a set of electrodes (142) may be coupled to the routing console (130). The set of electrodes (142) may include any number of electrodes, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, or more electrodes.

[0064] In some embodiments, the electrode channels (124) configured for energy delivery (e.g., configured as an anode/cathode pair of electrode channels) may not be adjacent to each other. For example, the set of electrode channels (124) may include a set of N electrode channels (124n) in a linear array. In one embodiment, a first electrode channel may correspond to a first electrode channel (124a) in the linear

array of N electrode channels (124n). One or more of a second and third electrode channel (124b, 124c) may not be adjacent to the first electrode channel (124a) in the linear array of N electrode channels (124n).

[0065] A multi-electrode ablation device may allow targeted and precise energy delivery to tissue. In some embodiments, the electrodes (142) of an ablation device (140) may be configured for energy delivery (e.g., as an anode/cathode pair of electrodes (142)) and may be adjacent to each other within a linear array of the electrodes (142) in the ablation device (140). For example, an ablation device (140) may include a set of electrodes (142) as a linear array of N electrodes (142n). As discussed in more detail herein, FIG. 5 illustrates another embodiment of an ablation device (500) including a linear array of electrodes (530). The signal generator (110) coupled to the ablation device (140) may include a set of electrode channels (124) having N electrode channels (124n) corresponding to the N electrodes (142n) of the ablation device (140). In one embodiment, the first electrode channel (124a) of the N electrode channels (124n) may correspond to a first electrode (142a) in the linear array of N electrodes (142n). One or more of second and third electrode channel (124b, 124c) of the N electrode channels (124n) may not correspond to any of the electrodes adjacent to the first electrode (142a) in the linear array of N electrodes (142n).

[0066] Configurable electrode channel and electrode selection may provide flexibility in positioning the electrodes for ablating a desired region of interest. In one embodiment, the routing console (130) may couple to a set of 16 electrodes (142) of an ablation device (140). The routing console (130) may receive input from the processor (120) and/or user interface (132) for electrode channel selection and energy delivery to one or more electrodes (142). Additionally or alternatively, the routing console (130) may couple to a cardiac stimulator (150) and be configured to receive data from devices (e.g., heart pacing data from a pacing device) used for synchronization of a pulse waveform with a patient cardiac cycle.

[0067] In some embodiments, a user interface (132) may be configured as a communication interface between an operator and the system (100). The user interface (132) may include an input device and output device (e.g., touch surface and display). For example, patient data from memory (122) may be received by user interface (132) and output visually and/or audibly. The user may be prompted to input a desired current for energy delivery using the user interface (132). Electric current data from sensing circuit (128) may be received and output on a display of user interface (132). As another example, operator control of an input device having one or more buttons, knobs, dials, switches, trackball, touch surface, and/or the like, may generate a control signal to the signal generator (110) and/or ablation device (140).

[0068] In some embodiments, an input device of the user interface (132) may include a touch surface for operator input and may be configured to detect contact and movement on the touch surface using any of a plurality of touch sensitivity technologies including capacitive, resistive, infrared, optical imaging, dispersive signal, acoustic pulse recognition, and surface acoustic wave technologies. Additionally or alternatively, the user interface (132) may include a step switch or foot pedal.

[0069] In some embodiments, an output device of the user interface (132) may include one or more of a display device and audio device. The display device may include at least one of a light emitting diode (LED), liquid crystal display (LCD), electroluminescent display (ELD), plasma display panel (PDP), thin film transistor (TFT), and organic light emitting diodes (OLED). An audio device may audibly output patient data, sensor data, system data, other data, alarms, warnings, and/or the like. The audio device may include at least one of a speaker, piezoelectric audio device, magnetostrictive speaker, and/or digital speaker. In one embodiment, the audio device may output an audible warning upon detection of a fault in the signal generator (110).

[0070] In some embodiments, the signal generator (110) may be mounted on a trolley or cart. In some embodiments, the user interface (132) may be formed in the same or different housing as the signal generator (110). The user interface (132) may be mounted to any suitable object, such as furniture (e.g., a bed rail), a wall, a ceiling, or may be self-standing. In some embodiments, the input device may include a wired and/or wireless transmitter configured to transmit a control signal to a wired and/or wireless receiver of the signal generator (110).

[0071] In some embodiments, a cardiac stimulator (150) including a pacing device may be configured to generate a heart pacing signal to be delivered to a patient via the pacing device. An indication of the pacing signal may be transmitted by the cardiac stimulator (150) to the signal generator (110). Based on the pacing signal, an indication of a voltage pulse waveform may be selected, computed, and/or otherwise identified by the processor (120) and generated by the signal generator (110). In some embodiments, the signal generator (110) may be configured to generate the voltage pulse waveform in synchronization with the indication of the pacing signal (e.g., within a common refractory window). For example, in some embodiments, the common refractory window may start substantially immediately following a ventricular pacing signal (or after a very small delay) and last for a duration of between about 150 ms and about 250 ms thereafter. In such embodiments, an entire pulse waveform may be delivered within this duration. Heart pacing is described further herein with respect to FIG. 13.

[0072] In some embodiments, the systems described herein may include one or more sterile coverings configured to create a sterile barrier around portions of the system (100). In some embodiments, the system (100) may include one or more sterile coverings to form a sterile field. For example, a sterile covering may be placed between the ablation device(s) and the patient, forming a barrier between an interior, non-sterile side including the patient, signal generator, and ablation devices and an exterior, sterile side including the operator. Additionally or alternatively, components of the system (100) may be sterilizable. The sterile covering may include, for example, a sterile drape configured to cover at least a portion of a system component. In one embodiment, a sterile covering (e.g., sterile drape) may be configured to create a sterile barrier with respect to a user interface (132) of the system (100). The sterile drape may be clear and allow an operator to visualize and manually manipulate the user interface (132). The sterile covering may conform tightly around one or more system components or may drape loosely so as to allow components to be adjusted within the sterile field.

[0073] FIG. 14 illustrates a circuit diagram of an embodiment of a signal generator (1400) that may be structurally and/or functionally similar to signal generator (110). The signal generator (1400) may include one or more electrode channels Ch. 1 (1401) Ch. 2 (1402), . . . Ch. N (1403). The processor (120) and at least one of the energy sources (126) may be collectively configured to deliver a pulse waveform to the set of electrodes during use via one or more of the electrode channels (1401, 1402, 1403). For example, the processor (120) may electrically couple a voltage source (1460, 1460', 1460'') (e.g., capacitor bank) to the electrode channels (1401, 1402, 1403) by controlling each of a set of first switches (1462, 1462', 1462''). That is, each voltage source (1460, 1460', 1460'') includes a corresponding first switch (1462, 1462', 1462''). The switches described herein may be characterized by rapid response times, for instance 10 microseconds or faster to switch between ON and OFF states, more preferably 5 microseconds or faster, and still more preferably 2 microseconds or faster. This permits control of the output current in real time and over very short time scales, and also applies to a rapid pulsed electric field ablation delivery over a single set of electrodes or over a multiplicity of electrode sets. The first switch may be any type of suitable switch, including but not limited to one or more bipolar transistors, such as bipolar junction transistors or Bipolar Field Effect Transistors. In some embodiments, one or more of the first switches include insulated-gate bipolar transistors (IGBT's). The set of first switches may be controlled by, for example, a processor, a microcontroller, and/or a Field Programmable Gate Array (FPGA).

[0074] It should be appreciated that the signal generator (1400) may include N number of energy sources, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, or more energy sources. For example, the signal generator (1400) may include 3 voltage sources. For example, the signal generator (1400) may be configured to output voltages in the range of between about 500 V and about 3000 V, including all values and sub ranges in between. For example, the signal generator (1400) may be configured to output voltages in the range of between about 700 V and about 2400 V or between about 700 V and about 1800 V. In some embodiments, each of the voltage sources (1460, 1460', 1460'') may be configured to output different voltages to the electrode channels (1401, 1402, 1403). For example, each voltage source (1460, 1460', 1460'') may store different amounts of energy by including a different number of capacitors.

[0075] In some embodiments, the voltage levels to which the voltage sources may be charged may be determined based on input received from a user interface and/or from a microcontroller (not shown). For example, a user may input a voltage level of U_o . In response, the microcontroller may select a range of voltages between U_L and $U_{H,h}$ that includes U_o , and then select a set of voltages (e.g., V_1 , V_2 , V_3) within this range to charge the respective voltage sources to the respective set of voltage values. Based on the clinical application, a predetermined set of current values may be stored in memory and used by the microcontroller for the electrode sets used in the therapy delivery device connected to the generator. These predetermined current values may be considered as desired values of output currents from a therapy delivery standpoint, thus providing for a high confidence in safe and effective therapy delivery

when the output current of an electrode channel is near or substantially matches the predetermined current values.

[0076] FIG. 14 illustrates resistor (1470) coupled to the emitter terminal of the second electronic switch (1430). The resistor (1470) may be controlled by a processor (120) to provide variable resistance and control current flow in the output channels. FIG. 15 illustrates one embodiment of a resistors (1470) as a set of resistors/resistor bank (1500). The set of resistors (1500) includes a set of parallel resistors including a first resistor (1510), a second resistor (1512), a third resistor (1514), and a fourth resistor (1516) having respective resistances R1, R2, R3, R4, though it is understood that any suitable configuration of multiple resistors can be employed. Each of the second, third, and fourth resistors (1512, 1514, 1516) may include respective switches (1520, 1522, 1524), and switch controllers (1530, 1532, 1534). When two or more resistors (1510, 1512, 1514, 1516) are connected in parallel, the resistance of the electrode channel decreases, thereby increasing the current output (for a given voltage). In other words, connecting each switch progressively decreases the net resistance of the resistor (1500). The switches may be controlled or configured using a processor, microcontroller, and FPGA. The effective resistance of the set of resistors may be programmably controlled from a maximum of R1 (e.g., the resistance of the resistor 1510) to a minimum value of $(1/R1 + 1/R2 + 1/R3 + 1/R4)^{-1}$. Thus, for a given value of voltage V_i , the current in the output channel may range between a minimum value and a maximum value, depending on the additional impedance of tissue.

[0077] In some embodiments, the set of resistors (1470) may be configured to have a resistance in the range of between about 10 Ohms and about 600 Ohms, including all values and sub ranges in between. For example, the set of resistors (1470) may be configured to have a resistance in the range of between about 15 Ohms and about 360 Ohms or between about 15 Ohms and about 480 Ohms. It should be appreciated that each set of resistors (1470) may include N number of resistors in parallel, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, or more resistors. For example, each of the set of resistors may include 4 or 5 resistors. In some embodiments, as described in more detail herein, the set of resistors (1470, 1470', 1470'') may each be configured to discharge a capacitive element of the energy source when the energy source is not in use.

[0078] This configuration of independently selectable voltage sources and resistor values allows an output current of the signal generator (1400) to be controlled (following Ohm's law). The combination of independent voltage and resistor control allows a discrete set of current values to be output by the signal generator (1400). In some embodiments, the signal generator (1400) may generate a current output of between about 5 Å and about 60 A to apply at one or more of the electrode channels, including all values and sub ranges in between. For example, the signal generator (1400) may generate a current output of between about 5 Å and about 50 A.

[0079] The signal generator (200) may deliver biphasic (AC or DC) pulses where in some embodiments, after delivering a voltage pulse to the set of output channels (1411, 1412, 1413) with output channels (1411) as an anode and output channels (1412, 1413) as cathodes, the polarities are immediately reversed and a voltage pulse of opposite polarity is then delivered with output channel (1411) as a

cathode and output channels (1412, 1413) as anodes, and so on until a desired number of biphasic pulses has been delivered to the output channel set (1411, 1412, 1413) in the form of a suitable waveform. Subsequently (and possibly with a programmable time interval), a different set of device electrodes (or output channels) may be configured as anodes and cathodes, and the waveform may be delivered again over this new set of device electrodes. In this manner, the voltage waveform may be sequenced over any desired collection of electrodes. Generally, the processor (120) and energy sources (126) may be collectively configured to deliver the pulse waveform over a sequenced set of electrodes (142a, 142b, . . . , 142n).

[0080] In some embodiments, as described in more detail herein, the pulse waveform delivered using the signal generator (1400) may include a set of levels of a hierarchy and/or may be in synchronization with the indication of a pacing signal generated from a cardiac stimulator (150).

[0081] FIG. 14 illustrates each of the electrode channels having a similar circuit configuration that may be structurally and/or functionally similar to the electrode channels (124a, 124b, . . . , 124n). In some embodiments, each of the electrodes channels (1401, 1402, 1403) may be configured individually as a half bridge amplifier while a pair of the electrode channels may be collectively configured as a full bridge amplifier. The signal generators as described herein may include a flexibly programmable electrode configuration; various subsets of electrodes may be configured as anodes and cathodes dynamically and rapidly. Thus, in an ablation energy delivery process, energy may be delivered rapidly over a sequence of paired electrode subsets. In some cases, a given electrode may be configured as an anode, and shortly thereafter as a cathode, during the course of sequencing over a succession of paired electrode subsets. Likewise, a biphasic waveform may also be delivered with the help of this topology, where an initially given anode-cathode pair may be made to reverse polarity after a very brief switching time interval; repeatedly alternating the sequencing of anode/cathode selection may yield a biphasic or AC voltage pulse train. The signal generator (1400) may include N number of electrode channels, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, or more electrode channels. Described with reference to the first electrode channel (1401) for the sake of simplicity, each electrode channel may include a first electronic switch (1420) configured to switch between an ON state and an OFF state. A first drive circuit (1422) may be coupled to the gate terminal of the first electronic switch (1420) to control the state of the first electronic switch (1420). The first electrode channel (1401) further includes a second electronic switch (1430) configured to switch between an ON and an OFF state. A second drive circuit (1432) may be coupled to the gate terminal of the second electronic switch (1430) to control the state of the second electronic switch (1430). Each of the drive circuits (1422, 1432) may be coupled to and controlled by a processor (e.g., processor (120)). An output channel (1411) may be coupled to the emitter terminal of the first electronic switch (1420) and to the collector terminal of the second electronic switch (1430), and may form part of a current path for electrical currents to pass via electrodes on a medical device (not shown) through an electrical load (such as patient anatomy) to one or more output channels coupled to a second electrode channel as described below. The output

channel (1411) may be coupled to a first electrode such as a first electrode 142 (a) of ablation device (140).

[0082] Likewise, second and third electrode channels (1402, 1403) may include respective first electronic switches (1420', 1420''), each configured to switch between an ON state and an OFF state. First drive circuits (1422', 1422'') may be coupled to respective first electronic switches (1420', 1420'') to control the state of the first electronic switches (1420', 1420''). Output channels (1412, 1413) may be coupled between the emitter terminals of the first electronic switches (1420', 1420'') and the collector terminals of the second electronic switches (1430', 1430''). The output channels (1412, 1413) may be coupled to respective second and third electrodes, such as the second electrode (142b) and the third electrode (142c) of ablation device (140). The second and third electrode channels (1402, 1403) further include respective second electronic switches (1430', 1430'') configured to switch between an ON and an OFF state. Second drive circuits (1432', 1432'') may be coupled to the gate terminals of the second electronic switches (1430', 1430'') to control the state of the second electronic switches (1430', 1430''). Each of the drive circuits (1422', 1422'', 1432', 1432'') may be coupled to and controlled by a processor (e.g., processor (120)). The drive circuits controlled by the processor effectively comprise the routing console 130. As described above, the routing console may be configured to couple to a set of device electrodes connected to the output channels. Each electrode channel (1401, 1402, . . .) corresponds to a respective electrode (142a, 142b, . . .) of the set of device electrodes. As an exemplary illustration of waveform delivery, if switches (1420, 1430) are respectively in ON and OFF states, switches (1420', 1430') are respectively in OFF and ON states, and switches (1420'' and 1430'' are respectively in OFF and ON states, and all other switches of all other electrode channels are in an OFF state, a positive voltage pulse is delivered with output channel 1 (1411) as anode or positive terminal and with output channels 2 (1412 in FIG. 14) and N (1413 in FIG. 14) as cathodes or negative/ground terminals. Accordingly, channels 1 and 2 may be paired to drive a current through electrodes coupled to output channels (1411, 1412) (e.g., through tissue across the electrodes). In other words, current flows from output channel 1 across device electrodes (not shown) and through second electronic switch (1430') to ground via the set of resistors (1470').

[0083] The duration of the ON state of the switches determines the time width of the pulse. In this manner a sequence of pulses may be delivered over any sequence of anode-cathode pairings, including repeated pulsing of a given or particular anode-cathode combination. Waveform delivery may be interspersed over a sequence of electrodes with the architecture of the generator disclosed herein. While the example of electrode channel selection disclosed in the foregoing described the selection of one anode channel and two cathode channels, it should be clear that a variety of such anode-cathode combinations may be selected without limitation.

[0084] The electronic switches (1420-1420'', 1430-1430'') as described herein may include one or more bipolar transistors, such as bipolar junction transistors or Bipolar Field Effect Transistors. In some embodiments, one or more of the electronic switches include insulated-gate bipolar transistors (IGBT's). Such IGBT switches may be capable of handling the high instantaneous power associated with high voltages,

in the approximate range of about 50,000 W to about 300,000 W. An energy source (not shown) may be coupled to the collector terminals of the first electronic switches (1420, 1420', 1420'') of the electrode channels (1401, 1402, 1403). Each of the electrode channels (1401, 1402, 1403) may be coupled to a sensing circuit (1450) and current sense resistor (1452). In some embodiments, the sensing circuit (1450) may measure current flow through the current sense resistor (1452). The sensing circuit (1450) may be used to: measure output current, with this measurement used subsequently for current control; and detect excessively large or unsafe current levels, whereupon current output may be switched off completely. In some embodiments, the sensing circuit (1450) may be configured to detect arcing during use. In FIG. 14, the sensing circuit (1450) may be coupled between the emitter terminal of the second electronic switches (1430, 1430', 1430'') and ground (1454). Additionally or alternatively, each electrode channel (1401, 1402, 1403) may be coupled to a respective sensing circuit (1450) and current sense resistor (1452).

[0085] In some embodiments, as described with respect to FIGS. 14, a processor such as processor (120) coupled to the set of drive circuits (1422, 1432) may configure the first electrode channel (1401) as an anode. One or more of the second and third electrode channels (1402, 1403) may similarly be configured by the processor (120) as a cathode. In one embodiment, the first electrode channel (1401) may be configured as an anode by setting the first electronic switch (1420) of the first electrode channel (1401) to the ON state and by setting the second electronic switch (1430) of the first electrode channel (1401) to the OFF state. Each of the second and third electrode channels (1402, 1403) may be configured as a cathode by setting their respective first electronic switches (1420', 1420'') to the OFF state and setting their respective second electronic switches (1430', 1430'') to the ON state. In this manner, the electrode channels (1401, 1402) may, for example, form a current path to a tissue site (e.g., coupled to each of the output channels (1411, 1412) using the first electronic switch (1420) of the first electrode channel (1401) and second electronic switch (1430') of the second electrode channel (1402).

[0086] FIG. 2 illustrates a circuit diagram of an embodiment of a signal generator (200) that may be structurally and/or functionally similar to signal generator (110). The signal generator (200) may include one or more electrode channels (201, 202, 203). FIG. 2 illustrates each of the electrode channels having a similar circuit configuration that may be structurally and/or functionally similar to the electrode channels (124a, 124b, . . . , 124n). In some embodiments, each of the electrodes channels (201, 202, 203) may be configured individually as a half bridge amplifier while a pair of the electrode channels may be collectively configured as a full bridge amplifier. The signal generators as described herein may include a flexibly programmable electrode configuration; various subsets of electrodes may be configured as anodes and cathodes dynamically and rapidly. Thus, in an ablation energy delivery process, energy may be delivered rapidly over a sequence of paired electrode subsets. In some cases, a given electrode may be configured as an anode, and shortly thereafter as a cathode, during the course of sequencing over a succession of paired electrode subsets. Likewise, a biphasic waveform may also be delivered with the help of this topology, where an initially given anode-cathode pair may be made to reverse polarity after a very brief switching

time interval; repeatedly alternating the sequencing of anode/cathode selection may yield a biphasic or AC voltage pulse train. The signal generator (200) may include N number of electrode channels, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, or more electrode channels. Described with reference to the first electrode channel (201) for the sake of simplicity, each electrode channel may include a first electronic switch (220) configured to switch between an ON state and an OFF state. A first drive circuit (222) may be coupled to the gate terminal of the first electronic switch (220) to control the state of the first electronic switch (220). The first electrode channel (201) further includes a second electronic switch (230) configured to switch between an ON and an OFF state. A second drive circuit (232) may be coupled to the gate terminal of the second electronic switch (230) to control the state of the second electronic switch (230). Each of the drive circuits (222, 232) may be coupled to and controlled by a processor (e.g., processor (120)). An output channel (211) may be coupled to the emitter terminal of the first electronic switch (220) and to the collector terminal of the second electronic switch (230), and may form part of a current path for electrical currents to pass via electrodes on a medical device (not shown) through an electrical load (such as patient anatomy) to one or more output channels coupled to a second electrode channel as described below. The output channel (211) may be coupled to a first electrode such as a first electrode 142 (a) of ablation device (140).

[0087] Likewise, second and third electrode channels (202, 203) may include respective first electronic switches (220', 220''), each configured to switch between an ON state and an OFF state. First drive circuits (222', 222'') may be coupled to respective first electronic switches (220', 220'') to control the state of the first electronic switches (220', 220''). Output channels (212, 213) may be coupled between the emitter terminals of the first electronic switches (220', 220'') and the collector terminals of the second electronic switches (230', 230''). The output channels (212, 213) may be coupled to respective second and third electrodes, such as the second electrode (142b) and the third electrode (142c) of ablation device (140). The second and third electrode channels (202, 203) further include respective second electronic switches (230', 230'') configured to switch between an ON and an OFF state. Second drive circuits (232', 232'') may be coupled to the gate terminals of the second electronic switches (230', 230'') to control the state of the second electronic switches (230', 230''). Each of the drive circuits (222', 222'', 232', 232'') may be coupled to and controlled by a processor (e.g., processor (120)). The drive circuits controlled by the processor effectively comprise the routing console 130. As described above, the routing console may be configured to couple to a set of device electrodes connected to the output channels. Each electrode channel (201, 202, . . .) corresponds to a respective electrode (142a, 142b, . . .) of the set of device electrodes. As an exemplary illustration of waveform delivery, if switches (220, 230) are respectively in ON and OFF states, switches (220', 230') are respectively in OFF and ON states, and switches (220'' and 230'' are respectively in OFF and ON states, and all other switches of all other electrode channels are in an OFF state, a positive voltage pulse is delivered with output channel N (211) as anode or positive terminal and with output channels N+3 (212 in FIG. 2) and N+4 (213 in FIG. 2) as cathodes or negative/ground terminals. The duration of the ON state of the switches

determines the time width of the pulse. In this manner a sequence of pulses may be delivered over any sequence of anode-cathode pairings, including repeated pulsing of a given or particular anode-cathode combination. Waveform delivery may be interspersed over a sequence of electrodes with the architecture of the generator disclosed herein. While the example of electrode channel selection disclosed in the foregoing described the selection of one anode channel and two cathode channels, it should be clear that a variety of such anode-cathode combinations may be selected without limitation.

[0088] The electronic switches (220-220'', 230-230'', 320-320'', 330-330'') as described herein may include one or more bipolar transistors, such as bipolar junction transistors or Bipolar Field Effect Transistors. In some embodiments, one or more of the electronic switches include insulated-gate bipolar transistors (IGBT's). Such IGBT switches may be capable of handling the high instantaneous power associated with high voltages, in the approximate range of about 50,000 W to about 300,000 W. An energy source (not shown) may be coupled to the collector terminals of the first electronic switches (220, 220', 220'') of the electrode channels (201, 202, 203) through respective resistive elements (240, 240', 240''). As described herein in more detail, the resistive elements (240, 240', 240'') may each be configured to discharge a capacitive element of the energy source when the energy source is not in use. In some embodiments, the resistive element may have a resistance in the range of between about 5 Ohms and about 25 Ohms. Each of the electrode channels (201, 202, 203) may be coupled to a sensing circuit (250) and current sense resistor (252). In some embodiments, the sensing circuit (250) may be configured to detect arcing during use. In FIG. 2, the sensing circuit (250) may be coupled between the emitter terminal of the second electronic switches (230, 230', 230'') and ground (254). Additionally or alternatively, each electrode channel (201, 202, 203) may be coupled to a respective sensing circuit (250) and current sense resistor (252).

[0089] In some embodiments, as described with respect to FIGS. 1 and 2, a processor such as processor (120) coupled to the set of drive circuits (222, 232) may configure the first electrode channel (201) as an anode. One or more of the second and third electrode channels (202, 203) may similarly be configured by the processor (120) as a cathode. In one embodiment, the first electrode channel (201) may be configured as an anode by setting the first electronic switch (220) of the first electrode channel (201) to the ON state and by setting the second electronic switch (230) of the first electrode channel (201) to the OFF state. Each of the second and third electrode channels (202, 203) may be configured as a cathode by setting their respective first electronic switches (220', 220'') to the OFF state and setting their respective second electronic switches (230', 230'') to the ON state. In this manner, the electrode channels (201, 202) may, for example, form a current path to a tissue site (e.g., coupled to each of the output channels (211, 212) using the first electronic switch (220) of the first electrode channel (201) and second electronic switch (230') of the second electrode channel (202).

[0090] The processor (120) and energy source (126) may be collectively configured to deliver a pulse waveform to the set of electrodes during use via one or more of the electrode channels (201, 202, 203). The signal generator (200) may deliver biphasic (AC) pulses where in some embodiments,

after delivering a voltage pulse to the set of output channels (211, 212, 213) with output channels (211) as an anode and output channels (212, 213) as cathodes, the polarities are immediately reversed and a voltage pulse of opposite polarity is then delivered with output channel (211) as a cathode and output channels (212, 213) as anodes, and so on until a desired number of biphasic pulses has been delivered to the output channel set (211, 212, 213) in the form of a suitable waveform. Subsequently (and possibly with a programmable time interval), a different set of device electrodes (or output channels) may be configured as anodes and cathodes, and the waveform may be delivered again over this new set of device electrodes. In this manner, the voltage waveform may be sequenced over any desired collection of electrodes. Generally, the processor (120) and energy source (126) may be collectively configured to deliver the pulse waveform over a sequenced set of electrodes (142a, 142b, . . . , 142n).

[0091] In some embodiments, as described in more detail herein, the pulse waveform delivered using the signal generator (200) may include a set of levels of a hierarchy and/or may be in synchronization with the indication of a pacing signal generated from a cardiac stimulator (150).

[0092] FIG. 3 illustrates a circuit diagram of an embodiment of a signal generator (300) that may be structurally and/or functionally similar to signal generator (110). For example, the signal generator (300) may include one or more electrode channels (301, 302, 316) that may be structurally and/or functionally similar to the electrode channels (124a, 124b, . . . , 124n). For ease of explanation, unless explicitly noted otherwise, elements in FIG. 3 may have the same components, functionality, and/or values as discussed with respect to similar elements in FIG. 2. For example, the electrode channels (201, 202, 203) used to deliver pulse waveforms to a set of electrodes in FIG. 2 may be the same set of electrode channels (301, 302, 316) used for capacitive energy discharge in FIG. 3. The signal generator (300) may include one or more electrode channels (301, 302, . . . , 316) where FIG. 3 illustrates each of the electrode channels having a same circuit configuration. FIG. 3 illustrates 16 electrode channels, although it should be appreciated that the signal generator (300) may include N number of electrode channels, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, or more electrode channels. A first electrode channel (301) may include a first electronic switch (320) configured to switch between an ON state and an OFF state. A first drive circuit (322) may be coupled to the gate terminal of the first electronic switch (320) to control the state of the first electronic switch (320). The first electrode channel (301) may further include a second electronic switch (330) configured to switch between an ON and an OFF state. A second drive circuit (332) may be coupled to the gate terminal of the second electronic switch (330) to control the state of the second electronic switch (330). An output channel (361) may be coupled between the emitter terminal of the first electronic switch (320) and the collector terminal of the second electronic switch (330).

[0093] Likewise, a second and sixteenth electrode channel (302, 316) may include respective first electronic switches (320', 320'') configured to switch between an ON state and an OFF state. The first drive circuits (322', 322'') may be coupled to respective first electronic switches (320', 320'') to control the state of the first electronic switches (320', 320''). Output channels (362, 376) may be coupled between the emitter terminal of the first electronic switches (320', 320'')

and the collector terminal of the second electronic switches (330', 330''). The second and sixteenth electrode channels (302, 316) further include respective second electronic switches (330', 330'') configured to switch between an ON and an OFF state. A second drive circuit (332', 332'') may be coupled to the gate terminal of the second electronic switch (330', 330'') to control the state of the second electronic switch (330', 330''). Each of the output channels (361, 362, 376) may be coupled to respective electrodes on one or more medical devices (not shown). Each electrode channel (301, 302, 316) may thus correspond to a respective electrode of the set of electrodes on one or more medical devices.

[0094] The electronic switches as described herein may include one or more bipolar transistors. In some embodiments, one or more of the electronic switches include insulated-gate bipolar transistors. An energy source (not shown) may be coupled to the collector terminals of the first electronic switches (320, 320', 320'') of the electrode channel (301, 302, 316) through respective resistive elements (340, 340', 340''). The resistive elements (340, 340', 340'') may each be configured to discharge a capacitive element of the energy source when the energy source is not in use. Each of the electrode channels (301, 302, 316) may be coupled to a sensing circuit (350) and current sense resistor (352). In some embodiments, the sensing circuit (350) may be configured to detect arcing during use. In FIG. 3, the sensing circuit (350) may be coupled between the emitter terminal of the second electronic switches (330, 330', 330'') and ground (354). Additionally or alternatively, each electrode channel (301, 302, 316) may be coupled to a respective sensing circuit (350) and current sense resistor (352).

[0095] In some embodiments, as described with respect to FIGS. 1 and 3, the signal generator (110) may provide active monitoring of the electrode channels. For example, the processor (120) of the signal generator (110) may be configured to perform one or more fault tests to verify operation of one or more electrode channels (124a, 124b, . . . , 124n) (e.g., electronic switches and drive circuits), the energy source (126) (e.g., DC power supply), and sensing circuit (128) (e.g., arc detection). The fault tests may be performed on one or more electrode channels (124a, 124b, . . . , 124n) at predetermined intervals (e.g., upon startup before delivery of a pulse waveform, between delivery of pulse waveforms, when the energy source (126) is not in use). In some embodiments, the signal generator (300) may perform a series of fault tests on one or more electrode channels to classify a working state of one or more electrode channels. In one embodiment, after delivery of a pulse waveform to a set of electrodes (142a, 142b, . . . , 142n) at a first time, a first fault test may be conducted individually for one or more of the set of electrode channels (301, 302, . . . , 316). In some embodiments, the first fault test may include, for the first electrode channel (301), setting the first electronic switch (320) to the ON state and the second electronic switch (330) to the OFF state. A verification DC voltage may be applied to the first electrode channel (301) for fault testing. In one embodiment, the verification DC voltage may be about 50V. The first electrode channel (301) may be classified as passing the first fault test when substantially no current is detected by the sensing circuit (350) during the first fault test. The first electrode channel (301) may be classified as failing the first fault test (e.g., in fault) when a threshold current, for example a current of 10 mA or higher, is detected by the sensing circuit (350). In some embodiments, the

second fault test may include, for the first electrode channel (301), setting the first electronic switch (320) to the OFF state and the second electronic switch (330) to the ON state. The first electrode channel (301) may be classified as passing the second fault test when substantially no current is detected by the sensing circuit (350) during the second fault test. The first electrode channel (301) may be classified as failing the second fault test when a threshold current, for example a current of 10 mA or higher, is detected by the sensing circuit (350). In some embodiments, the third fault test may include, for the first electrode channel (301), setting the first electronic switch (320) to the ON state and the second electronic switch (330) to the ON state. The first electrode channel (301) may be classified as passing the third fault test when a predetermined amount of current is detected by the sensing circuit (350) during the third fault test and classified as failing the third fault test when the sensing circuit (350) detects a non-predetermined amount of current. For example, the predetermined amount of current (e.g., about 5 A) may be equal to a DC voltage output by the energy source (e.g., about 50 V) divided by a resistance of the resistive element (340) (e.g., about 10 Ω).

[0096] A failure in the first fault test may indicate a malfunction in the second electronic switch (330) and/or second drive circuit drive (332) (e.g., lower IGBT circuitry in FIG. 3) while a failure in the second fault test may indicate a malfunction in the first electronic switch (320) and/or first drive circuit (322) (e.g., upper IGBT circuitry in FIG. 3). A failure in the third fault test may indicate a malfunction in one or more of the energy source, sensing circuit, electronic switches, and drive logic. Accordingly, the fault tests may verify the individual and collective operation of upper and lower IGBT circuitry for a fault tested electrode channel. Each of the fault tests described herein may be performed for each electrode channel (301, 302, . . . , 316) at a predetermined interval.

[0097] In some embodiments, a fault test may be performed for an electrode channel (124) based on predetermined criteria (e.g., a predetermined number of pulses delivered, a predetermined amount of energy delivered, and/or the like). Each electrode channel or a subset of electrode channels may be verified. For example, fault tests may be performed on each electrode channel (124) configured as an anode, or for each electrode channel (124) after delivery of 5 pulses. In some embodiments, the fault tests may be conducted in conjunction with voltage pulse waveform delivery and capacitor discharge, as described in more detail herein.

[0098] The generation and delivery of high voltage pulse waveforms using a signal generator as described herein may lead to a set of energy sources (e.g., each having one or more capacitors) of the signal generator storing excess energy. This energy may be discharged to ground through a set of discharge pulses using the electrode channels. Discharge may be performed prior to delivering subsequent pulse waveforms. In other words, the electrode channels may be used to deliver tissue ablation energy to one or more electrodes as well as discharge excess energy to ground. This configuration may be used in place of a dump circuit and/or bleeder resistor circuit for discharging excess stored energy in the signal generator.

[0099] In some embodiments, as described with respect to FIGS. 1 and 3, each electrode channel (124) may sequentially partially discharge at least one of the energy sources

(126) to ground over a set of discharge cycles. For example, all of the energy sources (126) may be collectively partially discharged over a set of discharge cycles or a subset of the energy sources (126) may be collectively partially discharged over a set of discharge cycles. Each electrode channel (124) may be configured as a half bridge amplifier to partially discharge the energy source to ground. The energy source (126) may complete discharge of a predetermined amount of energy within seconds. As used herein, a discharge cycle refers to energy discharge of the energy source to ground using each of the electrode channels of the set of electrode channels. For example, energy may be partially discharged to ground one at a time through each electrode channel (124) of a signal generator (110). In some embodiments, fault detection may be performed on the electrode channels (124) at predetermined intervals (e.g., before each discharge cycle, after a predetermined number of discharge cycles, etc.) to ensure that energy discharge is performed as intended. As stored energy is reduced through discharging, a pulse width of a discharge pulse may be increased without causing damage to the electrode channels (124). For example, an initial, first amount of stored energy (e.g., about 3 kJ) of the energy source (126) may correspond to discharge pulses having a first predetermined pulse width (e.g., about 0.5 μ s). After discharge of the energy source to a second amount of stored energy, the pulse width of the discharge pulses may be configured to a second predetermined pulse width (e.g., about 2 μ s).

[0100] In some embodiments, the set of electrode channels illustrated in FIG. 3 may correspond to a set of discharge paths to ground to reduce an amount of stored energy of an energy source (126). In some embodiments, the first electrode channel (301) of the set of electrode channels (301, 302, . . . , 316) may be configured to partially discharge energy to ground after a delivering a pulse waveform to a set of electrodes (142). For example, the first electronic switch (320) may be set to the ON state and the second electronic switch (330) may be set to the ON state for a predetermined duration of time to at least partially discharge the energy source (126). This current through the first electrode channel (301) may be about equivalent to the DC voltage of the energy source (126) divided by a resistance of the resistive element (340). The first electrode channel (301) may discharge energy to ground using a predetermined pulse width (e.g., about 0.5 μ s).

[0101] Once the first electrode channel (301) partially discharges the energy source (126), each of the remaining electrode channels (302, . . . , 316) may be configured to partially discharge the energy source (126) one at a time in a manner analogous to the first electrode channel (301). In some embodiments, a channel inactive time period (e.g., dead time) may follow the partial energy discharge of an electrode channel. For example, a channel inactive time period following each electrode channel energy discharge may be about 100 μ s. In some embodiments, a discharge cycle inactive time period may follow each discharge cycle. For example, a discharge cycle inactive time period may be about 5 ms and may correspond to a bootstrap charge time. By staggering the discharge of each electrode channel, the signal generator (300) may discharge capacitor energy at a faster rate than conventional circuit topologies.

[0102] The set of electrode channels (124) may discharge the energy source to ground sequentially over a set of discharge cycles until reaching a predetermined energy

threshold. In some embodiments, energy discharge may be performed such that a pulse width increases over time or over each discharge cycle. The number of pulses may decrease as the pulse width may be between about 0.1 μ s and about 1 μ s and may be set between about 90 discharge cycles and about 130 discharge cycles; a second pulse width may be between about 1 μ s and about 5 μ s and may be set between about 80 discharge cycles and about 90 discharge cycles; a third pulse width may be between about 5 μ s and about 10 μ s and may be set between about 70 discharge cycles and about 80 discharge cycles; a fourth pulse width may be between about 10 μ s and about 15 μ s and may be set for about 70 discharge cycles or less; and a fifth pulse width may be between about 15 μ s and about 25 μ s and may be set for about 70 discharge cycles or less.

[0103] In one merely illustrative and non-limiting example, a set of 16 electrode channels may be used to discharge to ground an energy source of about 3 kJ at an average rate of about 1 kJ/sec such that the signal generator may complete discharge in about 3 seconds. In one embodiment, energy discharge may be configured as follows: a first pulse width of about 0.5 μ s may be set for about 110 discharge cycles over about 730 ms; a second pulse width of about 2 μ s may be set for about 80 discharge cycles over about 530 ms; a third pulse width of about 6 μ s may be set for about 73 discharge cycles over about 490 ms; a fourth pulse width of about 12.5 μ s may be set for about 70 discharge cycles over about 480 ms; and a fifth pulse width of about 25 μ s may be set over about 780 ms for any remaining discharge cycles left to complete the energy source discharge.

[0104] In some embodiments, fault detection as described herein may be performed on an electrode channel prior to a partial energy discharge using that electrode channel. If the electrode channel is determined to be in a fault state, the electrode channel may be excluded from the set of electrode channels used to discharge the energy source to ground and/or the fault status may be output to the operator. Verification of the electrode channels may be performed for each of the electrode channels or a subset of the electrode channels at predetermined intervals such as for: each energy discharge pulse; one or more discharge cycles (e.g., fault test the electrode channels after each cycle or every other cycle); pulse width transitions (e.g., fault detect the electrode channels between every increase in pulse width); and a predetermined time interval (e.g., fault test the electrode channels every 0.1 seconds, 0.25 seconds, 0.5 seconds, 1 second, etc.).

Ablation Device

[0105] The systems described here may include one or more multi-electrode ablation devices configured to ablate heart tissue for treating atrial fibrillation such as in a left atrial chamber of a heart. FIG. 4A illustrates an embodiment of an ablation device (e.g., structurally and/or functionally similar to the ablation device (140)) that may be configured to deliver voltage pulse waveforms using a set of electrodes to ablate tissue and electrically isolate a pulmonary vein. In some of these embodiments, the ablation device may be transformed from a first configuration to a second configuration such that the electrodes of the ablation device expand outward to contact a lumen or an ostium or an antrum of an orifice in tissue (e.g., pulmonary vein ostium or pulmonary vein antrum).

[0106] The ablation device (400) includes a catheter shaft (410) at a proximal end of the device (400), a distal cap (412) of the device (400), and a set of splines (414) coupled thereto. The distal cap (412) may include an atraumatic shape. A proximal end of the set of splines (414) may be coupled to a distal end of the catheter shaft (410), and a distal end of the set of splines (414) may be tethered to the distal cap (412) of the device (400). Each spline (414) of the ablation device (400) may include one or more independently addressable electrodes (416) formed on a surface of the spline (414). Each electrode (416) may include an insulated electrical lead configured to sustain a voltage potential of at least about 700 V without dielectric breakdown of its corresponding insulation. In other embodiments, the insulation on each of the electrical leads may sustain an electrical potential difference of between about 200V to about 1500 V across its thickness without dielectric breakdown. Each spline (414) may include the insulated electrical leads of each electrode (416) formed in a body of the spline (414) (e.g., within a lumen of the spline (414)). A set of spline wires (418, 419) may be electrically conductive and electrically couple adjacent electrodes (416) disposed on different splines (414). For example, the spline wire (418) (connecting electrodes (416)) and the spline wire (419) (connecting electrodes (416')) may extend in a transverse direction relative to a longitudinal axis of the ablation device (400).

[0107] FIG. 4A illustrates a set of splines (414) where each spline (414) includes a pair of electrodes (416 and 416') having about the same size, shape, and spacing as the electrodes (416 and 416') of an adjacent spline (414). In other embodiments, the size, shape, and spacing of the electrodes (416, 416') may differ. For example, the electrodes (416) electrically coupled to a first spline wire (418) may differ in size and/or shape from electrodes (416') electrically coupled to a second spline wire (419).

[0108] In some embodiments, the first spline wire (418) may include a first set of spline wires (420, 421, 422, 423), where each spline wire of the set of spline wires (420, 421, 422, 423) may couple electrodes (416) between a different pair of splines of the set of splines (414). In some of these embodiments, the set of spline wires (420, 421, 422, 423) may form a continuous loop between the electrodes (416) coupled thereto. Likewise, the second spline wire (419) may include a second set of spline wires (424, 425, 426), where each spline wire of the set of spline wires (424, 425, 426) may couple electrodes (416') across the set of splines (414). The second set of spline wires (424, 425, 426) may couple different electrodes (416') across the set of splines (414) than the first set of spline wires (420, 421, 422, 423). In some of these embodiments, the first set of spline wires (420, 421, 422, 423) may form a first continuous loop between the electrodes (416) coupled thereto and the second set of spline wires (424, 425, 426) may form a second continuous loop between the electrodes (416') coupled thereto. The first continuous loop may be electrically isolated from the second continuous loop. In some of these embodiments, the electrodes (416) coupled to the first continuous loop may be configured as anodes and the electrodes (416') coupled to the second continuous loop may be configured as cathodes. A pulse waveform generated by a signal generator may be delivered to the electrodes (416 and 416') of the first and second continuous loop. In some embodiments, the spline wires such as 421, 422, 423, etc. may be replaced by similar

electrical connections in the proximal part of the device (for example, in the device handle). For example, the electrodes (416) may all be electrically wired together in the handle of the device.

[0109] In another embodiment illustrated in FIG. 4B, the first spline wire (461) of the set of spline wires (461, 462) may couple electrodes (459) between a first spline (451) and a second spline (452) of the set of splines, and a second spline wire (462) of the set of spline wires (461, 462) may couple electrodes (460) between the third spline (453) and a fourth spline (454) of the set of splines. The electrodes (459) coupled by the first spline wire (461) and the electrodes (460) coupled by the second spline wire (462) may be configured as an anode and cathode respectively (or vice-versa). A pulse waveform may be delivered to the electrodes (459) coupled by the first spline wire (461) and the electrodes (460) coupled by the second spline wire (462). In some embodiments, instead of spline wires the electrical leads of at least two electrodes of the set of electrodes may be electrically coupled at or near a proximal portion of the ablation device, such as, for example, within a handle.

[0110] In other embodiments, referring to FIG. 4A, one or more of the spline wires (418, 419) may form a continuous loop between the electrically coupled electrodes (416). For example, a first set of spline wires (418) may form a first continuous loop between the electrodes (416) coupled thereto and a second set of spline wires (419) may form a second continuous loop between the electrodes (416) coupled thereto. In this case, the first continuous loop may be electrically isolated from the second continuous loop. In one embodiment, each of the electrodes (416) coupled to a first set of spline wires (418) may be configured as an anode while each of the electrodes (416) coupled to a second set of spline wires (419) may be configured as a cathode. Each group of electrically coupled electrodes (416) may be independently addressable. In some embodiments, instead of spline wires the electrical leads of at least two electrodes of the set of electrodes may be electrically coupled at or near a proximal portion of the ablation device, such as, for example, within a handle.

[0111] In other embodiments, the size, shape, and spacing of the electrodes (416) may differ. The ablation device (400) may include any number of splines, for example, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, or more splines. In some embodiments, the ablation device (400) may include 3 to 20 splines. For example, in one embodiment, the ablation device (400) may include between 4 and 9 splines.

[0112] For each of the ablation devices described herein, each of the splines may include a polymer and define a lumen so as to form a hollow tube. The one or more electrodes of the ablation device described herein may include a diameter from about 0.2 mm to about 2.5 mm and a length from about 0.2 mm to about 5.0 mm. In some embodiments, the electrode may include a diameter of about 1 mm and a length of about 1 mm. As the electrodes may be independently addressable, the electrodes may be energized in any sequence using any pulse waveform sufficient to ablate tissue by irreversible electroporation. For example, different sets of electrodes may deliver different sets of pulses (e.g., hierarchical pulse waveforms). It should be appreciated that the size, shape, and spacing of the electrodes on and between the splines may be configured to deliver energy sufficient to generate contiguous/transmural lesions in order to electrically isolate one or more pulmonary

veins. In some embodiments, alternate electrodes (e.g., all the distal electrodes) may be at the same electric potential, and likewise for all the other electrodes (e.g., all the proximal electrodes). Thus, ablation may be delivered rapidly with all electrodes activated at the same time. A variety of such electrode pairing options exist and may be implemented based on the convenience thereof.

[0113] For each of the ablation devices discussed herein, the electrodes (e.g., ablation electrode, return electrode) may include biocompatible metals such as titanium, palladium, silver, platinum or a platinum alloy. For example, the electrode may preferably include platinum or a platinum alloy. Each electrode may include an electrical lead having sufficient electrical insulation to sustain an electrical potential difference of at least 700V across its thickness without dielectric breakdown. In other embodiments, the insulation on each of the electrical leads may sustain an electrical potential difference of between about 200 V to about 2500 V across its thickness without dielectric breakdown, including all values and sub-ranges in between. The insulated electrical leads may run to the proximal handle portion of the catheter from where they may be connected to a suitable electrical connector. The catheter shaft may be made of a flexible polymeric material such as Teflon, Nylon, Pebax, etc.

[0114] FIG. 5 illustrates an embodiment of an ablation device (500) (e.g., structurally and/or functionally similar to the ablation device (140)) that may be configured to deliver voltage pulse waveforms generated by a signal generator (110) as described herein using a set of electrodes to ablate tissue which in some embodiments may generate a linear circumferential ablation lesion. The ablation device (500) may include a catheter (510) having a flexible elongate shaft (520). The elongate shaft (520) may be advanced and withdrawn from a lumen of the catheter (510). The flexibility of the catheter (510) may facilitate positioning of the electrodes (530) around asymmetric and/or complex contours. The elongate shaft (520) may include a set of electrodes (530) spaced apart along the elongate shaft (520). In some embodiments, the electrodes (530) may be integrally formed with the elongate shaft (520). Each of the electrodes (530) may be connected to a respective output channel of a signal generator. The electrodes (530) may be independently configured as an anode or cathode and configured to deliver a pulse waveform to target tissue to perform ablation. In some embodiments, the set of electrodes (530) may have a spacing (532) between electrodes configured to create a contiguous ablation lesion such as a circumscribing lesion around a left atrial target and pulmonary vein. In some embodiments, the ratio of the spacing (532) between consecutive electrodes (530) to the longitudinal length of each electrode may be less than about 3:1, and may be less than about 2:1.

II. Methods

[0115] Also described here are methods for delivering pulse waveform using the systems and devices described herein. Generally, the methods described here include configuring a set of electrode channels and output channels to deliver a voltage pulse waveform to one or more electrodes of an ablation device for tissue ablation. Some embodiments of the methods also describe signal generator fault monitoring and high energy discharge of an energy source (e.g., capacitor dump). These methods may allow arbitrary elec-

trode selection, provide fault detection, and improve operation speed for therapeutic procedures including atrial fibrillation. Additionally or alternatively, the pulse waveforms may include a set of levels of a hierarchy to reduce total energy delivery. Additionally or alternatively, a cardiac pacing signal may synchronize the delivered pulse waveforms with the cardiac cycle. The tissue ablation thus performed may be delivered in synchrony with paced heartbeats and with less energy delivery to reduce damage to healthy tissue. It should be appreciated that any of the ablation devices described herein may be used to ablate tissue using the methods discussed below as appropriate. For example, the methods disclosed herein are usable with any of the systems (100, 200, 300) and ablation devices (e.g., 140, 400, 500) described herein.

[0116] FIG. 6 is a method (600) for one embodiment of a signal generation process using the systems and devices described herein. The method (600) includes controlling a state of a first and second electronic switch of a first electrode channel (602). For example, step 602 may control a state of first electronic switch (220) and second electronic switch (230) of the first electrode channel (201) illustrated in FIG. 2. In some embodiments, a drive circuit (e.g., drive circuits (222, 232)) coupled to an electronic switch may be configured to control the state of the electronic switch. In some embodiments, the electronic switch may be configured to switch between an ON state and an OFF state using the drive circuit. The first electrode channel may be configured as an anode (604). A state of a first and second electronic switch of a second electrode channel may be controlled (606) by, for example, drive circuits controlling the ON/OFF states of respective electronic switches. The second electrode channel may be configured as a cathode (608).

[0117] In some embodiments, hierarchical voltage pulse waveforms having a nested structure and a hierarchy of time intervals, as described herein, may be useful for irreversible electroporation, as well as providing control and selectivity in different tissue types. In some embodiments, a first pulse waveform may be generated having a set of levels of a hierarchy (610). In some embodiments, a first level of a hierarchy of the first pulse waveform may include a first set of pulses, with each pulse having a pulse time duration. A first time interval may separate successive pulses. A second level of the hierarchy of the first pulse waveform may include a set of first sets of pulses as a second set of pulses with a second time interval separating successive first sets of pulses. The second time interval may be at least three times the duration of the first time interval. A third level of the hierarchy of the pulse waveform may include a set of second sets of pulses as a third set of pulses with a third time interval separating successive second sets of pulses. The third time interval may be at least thirty times the duration of the second level time interval. An energy source may deliver the first pulse waveform to a set of electrodes during use via the first electrode channel and the second electrode channel (612). The first pulse waveform may be delivered at a first time.

[0118] At a second time subsequent to the first time, the state of the first and second electronic switch of the first electrode channel may be controlled (614). The first electrode channel may be configured as a cathode (616). The state of the first and second electronic switch of the second electrode channel may be controlled (618). The second electrode channel may be configured as an anode (620). In

some embodiments, a second pulse waveform may be generated having a set of levels of a hierarchy (622), such as including the first, second, and third hierarchy levels described herein. The energy source may deliver the second pulse waveform to the set of electrodes during use via the first electrode channel and the second electrode channel at the second time (624).

Current Control

[0119] FIG. 16 illustrates a method (1600) for one embodiment of a current control process using the systems and devices described herein. The methods disclosed herein are usable with any of the systems (100, 200, 300, 1400) and ablation devices (e.g., 140, 400, 500) described herein. The method (1600) may optionally include configuring each electrode channel as an anode or cathode (1602), such as described in FIG. 6. The signal generator may be configured to select a voltage source from the set of voltage sources and a resistance from the set of resistors of an electrode channel (1604) to output a predetermined current from the signal generator. A set of test pulses having, for purposes of illustrative example, a microsecond pulse width may be output from the electrode channel (1606). The output current may be measured by, for example, a sensing circuit of the signal generator (1608). The difference between the predetermined current and measured current is calculated (1610). If the difference exceeds a predetermined threshold (1612—Yes), then at least one of the voltage source and resistance values are modified to reduce the calculated difference (1614). A pulse waveform may then be generated and output from the signal generator (1616). If the difference does not exceed a predetermined threshold (1612—No), then a pulse waveform may be delivered to a set of electrodes using the configured electrode channels (1616). The method of current control described herein may be performed without user input and may be quickly performed for each electrode channel before the delivery of a pulse waveform for electroporation. A status of the current output may be optionally displayed and/or output by a user interface (1618).

[0120] FIG. 17 illustrates a primary pulse waveform current output comprising two groups of pulses (1704, 1706). In this example, each group of pulses such as the first group (1704) comprises ten biphasic pulses (1708). In one embodiment of the invention, the primary waveform is preceded by a pilot waveform (1702) comprising a small set of pulses of some known voltage V and with measured amplitude I_o . Assume a current value of I_d is output across channels 1 and 2. Since the tissue response to modified voltage is generally linear, scaling the voltage to a value $V'=V*I_d/I_o$ will result in the desired output current I_d . The nearest voltage source V_i may be used to approximate V' , and the subsequent primary waveform voltage results in a current output (amplitude of primary pulses (1708)) that approximate the desired current output amplitude I_d . Thus, once a pilot pulse or pulse sequence (1702) is used to measure current, this measurement may then be used to set or control the voltage/current output of the subsequent primary or desired waveform output for therapy delivery. In various embodiments, the pilot pulse or pulse sequence may be used before the primary waveform output of every electrode set, or it can be used to precede the primary waveform output of only some of the electrode sets. In other embodiments, if the nearest voltage

source V , is not within range to provide the desired voltage value V' , the set of resistors (1470) may be used to scale the output current.

[0121] Defining the quantity

$$R_{\text{mod}} = (V' - V) / I$$

it can be shown that configuring the switches (1530, 1532, 1534) of a set of resistors (1510, 1512, 1514, 1516) to bring the resistor to a value closest to R_{mod} above will result in an output current value that is closer to the desired output value I_d . The granularity of the control in terms of achieving an output current value close to a desired value is determined by the number of discrete resistances in the set of resistors, and the number of voltage sources covering a desired range of voltage values. The number of pilot pulses used in the control scheme may be as small as one or two pulses, or it may be a larger number in a train of such pulses. The pilot pulses may include either monophasic or biphasic pulses. Likewise, the primary (therapy delivery) waveform may include monophasic or biphasic pulses, or any combination of the two without loss of generality.

Fault Detection

[0122] FIGS. 7A-7B illustrate a method (700) for one embodiment of a fault detection process using the systems and devices described herein. The methods disclosed herein are usable with any of the systems (100, 200, 300, 1400) and ablation devices (e.g., 140, 400, 500) described herein. The method (700) may optionally include configuring each electrode channel as an anode or cathode (702), such as described in FIG. 6. An electrode channel may be selected to fault test based on predetermined criteria as described herein. For example, an electrode channel may be selected for fault testing based on a number of pulses delivered by the electrode channel, an amount of energy delivered by the electrode channel, and/or the like. Furthermore, one or more electrode channels may be selected for fault testing upon powering on a signal generator and/or before delivery of a pulse waveform. Each electrode channel or a subset of electrode channels may be selected one at a time for fault testing. For example, fault tests may be performed on each electrode channel configured as an anode or each electrode channel configured as a cathode.

[0123] A state of a first and second electronic switch of the selected electrode channel may be controlled to perform a first fault test (706). For example, a first electronic switch may be set to the ON state and a second electronic switch may be set to the OFF state. Current through the selected electrode channel may be detected using a sensing circuit (708). The selected electrode channel may be classified by a processor (e.g., processor (120)) as passing the first fault test (710—Yes) when substantially no current is detected by the sensing circuit. A state of a first and second electronic switch of the selected electrode channel may be controlled to perform a second fault test (712). For example, a first electronic switch may be set to the OFF state and a second electronic switch may be set to the ON state. Current through the selected electrode channel may be detected using the sensing circuit (714). The selected electrode channel may be classified by the processor as passing the second fault test (716—Yes) when substantially no current is

detected by the sensing circuit. A state of a first and second electronic switch of the selected electrode channel may be controlled to perform a third fault test (718). For example, a first electronic switch may be set to the ON state and a second electronic switch may be set to the ON state. Current through the selected electrode channel may be detected using the sensing circuit (720). The selected electrode channel may be classified by the processor as passing the third fault test (722—Yes) when a predetermined amount of current is detected by the sensing circuit. For example, the predetermined amount of current may be equal to about a DC voltage output by the energy source divided by a resistance of a resistive element. The selected electrode channel passing each of the first, second, and third fault tests may be classified by the processor as working without fault (724). However, when the selected electrode channel fails to pass any of the first, second, and third fault tests (710—No, 716—No, 722—No), the selected electrode channel may be classified by the processor as in fault (726). A determination by the processor may be performed of whether each electrode channel has been fault tested (728), and the process may return to step 704 when another electrode channel is to be fault tested (728—No). Upon completing fault testing of each electrode channel to be tested (728—Yes), a fault status may be output (730).

Energy Discharge

[0124] FIG. 8 is a method (800) for one embodiment of an energy discharge process using the systems and devices described herein. The methods disclosed herein are usable with any of the systems (100, 200, 300, 1400) and ablation devices (e.g., 140, 400, 500) described herein. The method (800) may optionally include configuring each electrode channel as an anode or cathode (802) and delivering a pulse waveform using an energy source to a set of electrodes using the configured electrode channels (804). A discharge pulse width may be selected (806). In some embodiments, a discharge pulse width may be selected by a processor (e.g., processor (120)) based on an amount of energy stored in the energy source to be discharged to ground. For example, a higher amount of stored energy in the energy source may correspond to a narrower pulse width. In some embodiments, energy discharge may be performed upon completion of a treatment procedure (e.g., tissue ablation) and/or upon powering off of a signal generator (110). As energy is discharged to ground over a set of discharge cycles, the pulse width may be increased at predetermined intervals, such as those described herein. An electrode channel may be selected by the processor for discharge (808). Fault detection, as discussed with respect to FIGS. 7A-7B and as described herein, may optionally be performed on the selected electrode channel (810). When the selected electrode channel passes fault testing, the energy source may be discharged using the electrode channel for a predetermined time period (812). A determination by the processor may be performed of whether other electrode channels in the set of electrode channels have completed energy discharge (814). For example, a determination may be performed of whether a discharge cycle (e.g., discharge by each electrode channel in the set of electrodes) has been completed. The method may return to step 808 when one or more electrode channels remain in a discharge cycle (814—No). The method may proceed to step 816 when a discharge cycle has been completed (814—Yes). A determination by the processor

may be performed of whether the energy source has completed discharge (816). For example, a set of discharge cycles may be performed using the electrode channels until the energy source reaches a predetermined energy threshold. The method may return to step 806 when energy source discharge has not been completed (816—No). A status may be output (818) when energy source discharge has been completed (816—Yes).

Pulse Waveform

[0125] Disclosed herein are methods, systems and devices for the selective and rapid application of pulsed electric fields/waveforms to effect tissue ablation with irreversible electroporation. The pulse waveform(s) as disclosed herein are usable with any of the systems (100, 200, 300, 1400), ablation devices (e.g., 140, 400, 500), and methods (e.g., 600, 700, 800) described herein. Some embodiments are directed to pulsed high voltage waveforms together with a sequenced delivery scheme for delivering energy to tissue via sets of electrodes. In some embodiments, peak electric field values may be reduced and/or minimized while at the same time sufficiently large electric field magnitudes may be maintained in regions where tissue ablation is desired. This also reduces the likelihood of excessive tissue damage or the generation of electrical arcing, and locally high temperature increases. In some embodiments, a system useful for irreversible electroporation may include a signal generator capable of being configured to deliver pulsed voltage waveforms to a set of electrodes of an ablation device. In some embodiments, a processor of the signal generator is configured to control a set of electrode channels whereby selected pairs of anode-cathode subsets of electrodes may be sequentially triggered based on a pre-determined sequence, and in one embodiment the sequenced delivery may be triggered from a cardiac stimulator and/or pacing device. In some embodiments, the ablation pulse waveforms may be applied in a refractory period of the cardiac cycle so as to avoid disruption of the sinus rhythm of the heart. One example method of enforcing this is to electrically pace the heart with a cardiac stimulator (e.g., cardiac stimulator (150)) and ensure pacing capture to establish periodicity and predictability of the cardiac cycle, and then to define a time window well within the refractory period of this periodic cycle within which the ablation waveform is delivered.

[0126] In some embodiments, the pulsed voltage waveforms disclosed herein are hierarchical in organization and have a nested structure. In some embodiments, the pulsed waveform includes hierarchical groupings of pulses with a variety of associated timescales. Pulsed waveforms for electroporation energy delivery as disclosed herein may enhance the safety, efficiency and effectiveness of the energy delivery by reducing the electric field threshold associated with irreversible electroporation, yielding more effective ablative lesions with reduced total energy delivered. This in turn may broaden the areas of clinical application of electroporation including therapeutic treatment of a variety of cardiac arrhythmias.

[0127] FIG. 9 illustrates a pulsed voltage waveform in the form of a sequence of rectangular double pulses, with each pulse, such as the pulse (900) being associated with a pulse width or duration. The pulse width/duration may be about 0.5 microseconds, about 1 microsecond, about 5 microseconds, about 10 microseconds, about 25 microseconds, about 50 microseconds, about 100 microseconds, about 125 micro-

seconds, about 140 microseconds, about 150 microseconds, including all values and sub-ranges in between. The pulsed waveform of FIG. 9 illustrates a set of monophasic pulses where the polarities of all the pulses are the same (all positive in FIG. 9, as measured from a zero baseline). In some embodiments, such as for irreversible electroporation applications, the height of each pulse (900) or the voltage amplitude of the pulse (900) may be in the range from about 400 V, about 1,000 V, about 5,000 V, about 10,000 V, about 15,000 V, including all values and sub ranges in between. As illustrated in FIG. 9, the pulse (900) is separated from a neighboring pulse by a time interval (902), also sometimes referred to as a first time interval. The first time interval may be about 10 microseconds, about 50 microseconds, about 100 microseconds, about 200 microseconds, about 500 microseconds, about 800 microseconds, about 1 millisecond including all values and sub ranges in between, in order to generate irreversible electroporation.

[0128] FIG. 10 introduces a pulse waveform with the structure of a hierarchy of nested pulses. FIG. 10 shows a series of monophasic pulses such as pulse (1000) with pulse width/pulse time duration w , separated by a time interval (also sometimes referred to as a first time interval) such as (1002) of duration t_i between successive pulses, a number m_i of which are arranged to form a group of pulses (1010) (also sometimes referred to as a first set of pulses). Furthermore, the waveform has a number rn_2 of such groups of pulses (also sometimes referred to as a second set of pulses) separated by a time interval (1012) (also sometimes referred to as a second time interval) of duration t_2 between successive groups. The collection of m_2 such pulse groups, marked by (1020) in FIG. 10, constitutes the next level of the hierarchy, which may be referred to as a packet and/or as a third set of pulses. The pulse width and the time interval t_1 between pulses may both be in the range of microseconds to hundreds of microseconds, including all values and sub ranges in between. In some embodiments, the time interval t_2 may be at least three times larger than the time interval t_1 . In some embodiments, the ratio t_2/t_1 may be in the range between about 3 and about 300, including all values and sub-ranges in between.

[0129] FIG. 11 further elaborates the structure of a nested pulse hierarchy waveform. In this figure, a series of m_i pulses (individual pulses not shown) form a group of pulses (1102) (e.g., a first set of pulses). A series of m_2 such groups separated by an inter-group time interval (1110) of duration t_2 (e.g., a second time interval) between one group and the next form a packet (1110) (e.g., a second set of pulses). A series of m_3 such packets separated by time intervals (1112) of duration t_3 (e.g., a third time interval) between one packet and the next form the next level in the hierarchy, a super-packet labeled (1120) (e.g., a third set of pulses) in the figure. In some embodiments, the time interval t_3 may be at least about thirty times larger than the time interval t_2 . In some embodiments, the time interval t_3 may be at least fifty times larger than the time interval t_2 . In some embodiments, the ratio t_3/t_2 may be in the range between about 30 and about 800, including all values and sub-ranges in between. The amplitude of the individual voltage pulses in the pulse hierarchy may be anywhere in the range from 500 V to 7,000 V or higher, including all values and sub-ranges in between.

[0130] FIG. 12 provides an example of a biphasic waveform sequence with a hierarchical structure. In the example shown in the figure, biphasic pulses (1200) have a positive

voltage portion as well as a negative voltage portion to complete one cycle of the pulse. There is a time delay (1202) (e.g., a first time interval) between adjacent cycles of duration t_1 , and n_1 such cycles form a group of pulses (1210) (e.g., a first set of pulses). A series of n_2 such groups separated by an inter-group time interval (1212) (e.g., a second time interval) of duration t_2 between one group and the next form a packet (1220) (e.g., a second set of pulses). The figure also shows a second packet (1232), with a time delay (1230) (e.g., a third time interval) of duration t_3 between the packets. Just as for monophasic pulses, higher levels of the hierarchical structure may be formed as well. The amplitude of each pulse or the voltage amplitude of the biphasic pulse may be anywhere in the range from 500 V to 7,000 V or higher, including all values and sub-ranges in between. The pulse width/pulse time duration may be in the range from nanoseconds or even sub-nanoseconds to tens of microseconds, while the delays t_1 may be in the range from zero to several microseconds. The inter-group time interval t_2 may be at least ten times larger than the pulse width. In some embodiments, the time interval t_3 may be at least about twenty times larger than the time interval t_2 . In some embodiments, the time interval t_3 may be at least fifty times larger than the time interval t_2 .

[0131] Embodiments disclosed herein may include waveforms structured as hierarchical waveforms that include waveform elements/pulses at various levels of the hierarchy. The individual pulses such as pulse (1000) in FIG. 10 may include the first level of the hierarchy, and have an associated pulse time duration and a first time interval between successive pulses. A set of pulses, or elements of the first level structure, form a second level of the hierarchy such as the group of pulses/second set of pulses (1010) in FIG. 10. Among other parameters associated with the waveform are parameters such as a total time duration of the second set of pulses (not shown), a total number of first level elements/first set of pulses, and second time intervals between successive first level elements that describe the second level structure/second set of pulses. In some embodiments, the total time duration of the second set of pulses may be between about 20 microseconds and about 10 milliseconds, including all values and sub-ranges in between. A set of groups, second set of pulses, or elements of the second level structure, form a third level of the hierarchy such as the packet of groups/third set of pulses (1020) in FIG. 10. Among other parameters, there is a total time duration of the third set of pulses (not shown), a total number of second level elements/second set of pulses, and third time intervals between successive second level elements that describe the third level structure/third set of pulses. In some embodiments, the total time duration of the third set of pulses may be between about 60 microseconds and about 200 milliseconds, including all values and sub-ranges in between. The generally iterative or nested structure of the waveforms may continue to a higher plurality of levels, such as ten levels of structure, or more.

[0132] In some embodiments, hierarchical waveforms with a nested structure and hierarchy of time intervals as described herein may be useful for irreversible electroporation ablation energy delivery, providing a good degree of control and selectivity for applications in different tissue types. A variety of hierarchical waveforms may be generated with a suitable pulse generator of the type described in this disclosure. It is understood that while the examples herein

identify separate monophasic and biphasic waveforms for clarity, it should be noted that combination waveforms, where some portions of the waveform hierarchy are monophasic while other portions are biphasic, may also be generated/implemented.

[0133] In some embodiments, the ablation pulse waveforms described herein may be applied during the refractory period of the cardiac cycle so as to avoid disruption of the sinus rhythm of the heart. In some embodiments, a method of treatment may include electrically pacing the heart with a cardiac stimulator (e.g., cardiac stimulator (150)) to ensure pacing capture to establish periodicity and predictability of the cardiac cycle, and then defining a time window within the refractory period of the cardiac cycle within which one or more pulsed ablation waveforms may be delivered. FIG. 13 illustrates an example where both atrial and ventricular pacing is applied (for instance, with pacing leads or catheters situated in the right atrium and right ventricle respectively). With time represented on the horizontal axis, FIG. 13 illustrates a series of ventricular pacing signals (1300, 1310), and a series of atrial pacing signals (1320, 1330), along with a series of ECG waveforms (1340, 1342) that are driven by the pacing signals. As indicated in FIG. 13 by the thick arrows, there is an atrial refractory time window (1322) and a ventricular refractory time window (1302) that respectively follow the atrial pacing signal (1322) and the ventricular pacing signal (1300). As shown in FIG. 13, a common refractory time window (1350) of duration T , may be defined that lies within both atrial and ventricular refractory time windows (1322, 1302). In some embodiments, the electroporation ablation waveform(s) may be applied in this common refractory time window (1350). The start of this refractory time window (1322) is offset from the pacing signal (1300) by a time offset (1304) as indicated in FIG. 13. The time offset (1304) may be smaller than about 25 milliseconds, in some embodiments. At the next heartbeat, a similarly defined common refractory time window (1352) is the next time window available for application of the ablation waveform(s). In this manner, the ablation waveform(s) may be applied over a series of heartbeats, at each heartbeat remaining within the common refractory time window. In one embodiment, each packet of pulses as defined above in the pulse waveform hierarchy may be applied over a heartbeat, so that a series of packets is applied over a series of heartbeats, for a given electrode set. Similarly, a first waveform packet may be delivered successively over a first sequence of electrodes, followed by a second waveform packet delivered over a second sequence of electrodes, and so on; in some cases, it may even be convenient for the second sequence of electrodes to be different from the first sequence of electrodes. The architecture of the signal generator and routing console as disclosed herein permits the delivery of a variety of such hierarchical waveforms wherein waveform packet delivery to a given set of electrodes, in the sense disclosed herein, may be interspersed with waveform packet deliveries to a different set of electrodes. This modality of interspersed waveform delivery described herein may include monophasic, biphasic, and mixed pulses that include both monophasic and biphasic components.

[0134] It is understood that while the examples herein identify separate monophasic and biphasic waveforms, it should be appreciated that combination waveforms, where some portions of the waveform hierarchy are monophasic

while other portions are biphasic, may also be generated. A voltage pulse waveform having a hierarchical structure may be applied across different anode-cathode subsets (optionally with a time delay). As discussed above, one or more of the waveforms applied across the anode-cathode subsets may be applied during the refractory period of a cardiac cycle. It should be appreciated that the method steps described herein may be combined and modified as appropriate. Likewise, while the examples of electrode channel selection disclosed herein describe the selection of one anode and two cathode channels, it should be clear that a wide variety of channels may be selected to act as anodes or cathodes, without limitation.

[0135] As used herein, the terms “about” and/or “approximately” when used in conjunction with numerical values and/or ranges generally refer to those numerical values and/or ranges near to a recited numerical value and/or range. In some instances, the terms “about” and “approximately” may mean within +10% of the recited value. For example, in some instances, “about 100 [units]” may mean within +10% of 100 (e.g., from 90 to 110). The terms “about” and “approximately” may be used interchangeably.

[0136] Some embodiments described herein relate to a computer storage product with a non-transitory computer-readable medium (also may be referred to as a non-transitory processor-readable medium) having instructions or computer code thereon for performing various computer-implemented operations. The computer-readable medium (or processor-readable medium) is non-transitory in the sense that it does not include transitory propagating signals per se (e.g., a propagating electromagnetic wave carrying information on a transmission medium such as space or a cable). The media and computer code (also may be referred to as code or algorithm) may be those designed and constructed for the specific purpose or purposes. Examples of non-transitory computer-readable media include, but are not limited to, magnetic storage media such as hard disks, floppy disks, and magnetic tape; optical storage media such as Compact Disc/Digital Video Discs (CD/DVDs); Compact Disc-Read Only Memories (CD-ROMs), and holographic devices; magneto-optical storage media such as optical disks; solid state storage devices such as a solid state drive (SSD) and a solid state hybrid drive (SSHD); carrier wave signal processing modules; and hardware devices that are specially configured to store and execute program code, such as Application-Specific Integrated Circuits (ASICs), Programmable Logic Devices (PLDs), Read-Only Memory (ROM), and Random-Access Memory (RAM) devices. Other embodiments described herein relate to a computer program product, which may include, for example, the instructions and/or computer code disclosed herein.

[0137] The systems, devices, and/or methods described herein may be performed by software (executed on hardware), hardware, or a combination thereof. Hardware modules may include, for example, a general-purpose processor (or microprocessor or microcontroller), a field programmable gate array (FPGA), and/or an application specific integrated circuit (ASIC). Software modules (executed on hardware) may be expressed in a variety of software languages (e.g., computer code), including C, C++, Java®, Python, Ruby, Visual Basic®, and/or other object-oriented, procedural, or other programming language and development tools. Examples of computer code include, but are not limited to, micro-code or micro-instructions, machine

instructions, such as produced by a compiler, code used to produce a web service, and files containing higher-level instructions that are executed by a computer using an interpreter. Additional examples of computer code include, but are not limited to, control signals, encrypted code, and compressed code.

[0138] In some embodiments, the systems, devices, and methods may be in communication with other computing devices (not shown) via, for example, one or more networks, each of which may be any type of network (e.g., wired network, wireless network). A wireless network may refer to any type of digital network that is not connected by cables of any kind. Examples of wireless communication in a wireless network include, but are not limited to cellular, radio, satellite, and microwave communication. However, a wireless network may connect to a wired network in order to interface with the Internet, other carrier voice and data networks, business networks, and personal networks. A wired network is typically carried over copper twisted pair, coaxial cable and/or fiber optic cables. There are many different types of wired networks including wide area networks (WAN), metropolitan area networks (MAN), local area networks (LAN), Internet area networks (IAN), campus area networks (CAN), global area networks (GAN), like the Internet, and virtual private networks (VPN). Hereinafter, network refers to any combination of wireless, wired, public and private data networks that are typically interconnected through the Internet, to provide a unified networking and information access system.

[0139] Cellular communication may encompass technologies such as GSM, PCS, CDMA or GPRS, W-CDMA, EDGE or CDMA2000, LTE, WiMAX, and 5G networking standards. Some wireless network deployments combine networks from multiple cellular networks or use a mix of cellular, Wi-Fi, and satellite communication. In some embodiments, the systems, devices, and methods described herein may include a radiofrequency receiver, transmitter, and/or optical (e.g., infrared) receiver and transmitter to communicate with one or more devices and/or networks.

[0140] The specific examples and descriptions herein are exemplary in nature and embodiments may be developed by those skilled in the art based on the material taught herein without departing from the scope of the present invention, which is limited only by the attached claims.

We claim:

1. A generator for generating high voltage waveforms for tissue ablation through irreversible electroporation, the generator comprising:

during use, wherein each electrode channel from the set of electrode channels includes an output channel, wherein each output channel is configured to be coupled to an electrode during use;

a set of switches coupled to the set of electrode channels and configured to switch between an OFF state and an ON state, wherein each electrode channel from the set of electrode channels includes a first switch and a second switch from the set of switches, the first switch and the second switch connected in series in each electrode channel with the output channel therebetween;

a set of energy sources coupled to the set of electrode channel;

a processor coupled to the set of switches and configured to:

set one or more states of a first subset of switches to configure a first subset of electrode channels as anodes and a second subset of electrode channels as cathodes via controlling each of the first and second switches of the first subset of switches;

receive a selected control parameter via a user interface, wherein the control parameter is a current value or a voltage value;

set one or more states of a second subset of switches to select at least one energy source from the set of energy sources based on the selected control parameter to deliver a pulse waveform; and

deliver the pulse waveform to the set of electrodes using the first subset and the second subset of electrode channels, such that electrodes coupled to the first subset and the second subset of electrode channels deliver energy to a target area.

2. The generator of claim 1, wherein the processor is configured to set the state of the first subset of switches by:

setting, for each of the first subset of electrode channels and according to a first sequence, the first switch of that electrode channel to the ON state and the second switch of that electrode channel to the OFF state to configure that electrode channel as an anode; and

setting, for each of the second subset of electrode channels and according to a second sequence, the first switch of that electrode channel to the OFF state and the second switch of that electrode channel to the ON state to configure that electrode channel as a cathode, such that the respective electrode channels set according to the first sequence and the second sequence are paired for energy delivery.

3. The generator of claim 1, further comprising a set of current control resistors coupled to the set of electrode channels, and a set of sensing circuits, wherein the sensing circuit is configured to measure an output current of the set of electrode channels, the processor further configured to, in response to the output current measured by the sensing circuit being different from a predetermined output current, adjust at least one of a voltage delivered by the set of energy sources or a resistance value of the set of current control resistors in order to adjust the output current measured by the sensing circuit closer to the predetermined output current.

4. The generator of claim 3, wherein the processor is configured to adjust the at least one of the voltage or the resistance by setting a state of one or more switches to select one or more energy sources from the set of energy sources to deliver the pulse waveform or select one or more resistance values of the set of current control resistors.

5. The generator of claim 3 wherein the predetermined output current is between about 5 A and about 60 A.

6. The generator of claim 1, wherein the sensing circuit is configured to detect electric arcing during use.

7. The generator of claim 6, wherein the set of electrode channels are arranged in parallel.

8. The generator of claim 2, wherein the processor is further configured to set a resistance of the set of resistors between about 10 Ohms and about 600 Ohms.

9. The generator of claim 1, wherein the set of current control resistors are configured to discharge excess energy from the set of energy sources.

10. The generator of claim 2 wherein the processor is coupled to the set of switches via a set of drive circuits, the set of drive circuits configured to control the state of the set of switches.

11. The generator of claim 1 wherein the pulse waveform includes:

- a first level of a hierarchy of the pulse waveform including a first set of pulses and a first time interval separating successive pulses;
- a second level of the hierarchy of the pulse waveform including a plurality of first sets of pulses as a second set of pulses and a second time interval separating successive first sets of pulses, the second time interval being at least three times the duration of the first time interval; and
- a third level of the hierarchy of the pulse waveform including a plurality of second sets of pulses as a third set of pulses and a third time interval separating successive second sets of pulses, the third time interval being at least thirty times the duration of the second level time interval.

12. The generator of claim 11, further comprising a cardiac stimulator configured to generate a pacing signal for cardiac stimulation during use, the cardiac stimulator communicably coupled to the generator and further configured to transmit an indication of the pacing signal to the generator, the processor further configured to generate the pulse waveform in synchronization with the indication of the pacing signal, the synchronization including a pre-determined offset.

13. The generator of claim 11, wherein each switch of the first set of switches and the second set of switches includes an emitter terminal and a collector terminal, and wherein the set of energy sources are coupled to the collector terminals of the first set of switches and the set of resistors are coupled to the emitter terminals of the second set of switches.

14. The generator of claim 11 wherein each of the first set and the second set of switches is: a bipolar junction transistor, a bipolar Field Effect transistor (Bi-FET), a power Metal Oxide Semiconductor Field Effect Transistor (MOS-FET), or an Insulated-Gate Bipolar Transistor (IGBT).

15. The generator of claim 11, wherein each of the first set and the second set of switches is an insulated-gate bipolar transistor.

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