



- (51) **International Patent Classification:**
A61N 1/372 (2006.01) *A61N 1/36* (2006.01)
- (21) **International Application Number:**
PCT/US2017/017412
- (22) **International Filing Date:**
10 February 2017 (10.02.2017)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
62/294,507 12 February 2016 (12.02.2016) US
- (71) **Applicant:** VERILY LIFE SCIENCES, LLC [US/US];
1600 Amphitheatre Parkway, Mountain View, CA 94043
(US).
- (72) **Inventors:** CONG, Peng; 1600 Amphitheatre Parkway,
Mountain View, CA 94043 (US). O'DRISCOLL, Steph-
en; 1600 Amphitheatre Parkway, Mountain View, CA
94043 (US). RAKHYANI, Anil, Kumar Ram; 1600 Am-
phitheatre Parkway, Mountain View, CA 94043 (US).
- (74) **Agents:** CHAPMAN, Ernest, F. et al.; Finnegan, Hender-
son, Farabow, Garrett & Dunner, LLP, 901 New York Av-
enue, NW, Washington, DC 20001-4413 (US).

(81) **Designated States** (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN,
KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA,
MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG,
NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS,
RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY,
TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,
ZA, ZM, ZW.

(84) **Designated States** (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report (Rule 48.2(g))

(54) **Title:** FOCUSED ELECTRIC FIELD NEUROSTIMULATION BY ONE OR MORE MICRO PARTICLES

(57) **Abstract:** A system and method for neurostimulation. The system may include a micro particle implantable into tissue. The micro particle may include a power system configured to receive wireless energy transmission, an electrode system having two electrodes, each electrode configured to transmit electrical pulses. The micro particle may also include a processing system configured to control the power system and the electrode system. The system may also include a central controller. The central control may include a power system configured to wirelessly power the micro particle, a communication system configured to wirelessly communicate with the micro particle, and a processing system configured to control the power system and communication system. The system may be configured to selectively stimulate a target location by virtue of the central controller being configured to instruct the two electrodes of the micro particle to transmit electrical pulses and modulate the electrical pulses to generate an electric field that focuses neurostimulation at the target location.



FOCUSED ELECTRIC FIELD NEUROSTIMULATION BY ONE OR MORE MICRO PARTICLES

BACKGROUND

Related Applications

[0001] This application claims priority to U.S. Provisional Application No. 62/294,507, filed February 12, 2016, which is incorporated herein by reference in the entirety.

Technical Field

[0002] The present disclosure relates generally to the field of focused electric field neurostimulation, and more particularly, focused electric field neurostimulation by one or more micro particles.

Background Description

[0003] The nervous system of a human has two main parts: the central nervous system (i.e., the brain and spinal cord) and the peripheral nervous system (i.e., the nerves that carry pulses to and from the central nervous system). The nervous system controls voluntary and involuntary actions of different body parts (e.g., muscles, limbs, organs, etc.) by transmitting and receiving signals to and from the different parts of the body. Efforts have been made to modulate nerve activity by way of pharmaceutical agents or neurostimulation to treat different conditions, diseases, and injuries for many years. For example, deep brain stimulation (DBS) has been used to treat Parkinson's disease, sacral nerve stimulation has been used to treat pelvic disorder and incontinence, and spinal cord stimulation has been used to treat ischemic disorders. Although these efforts in some case have produced some positive results, there is much room for significant advancement in the technology in order to improve the therapeutic effect, minimize the side effects, and make it more functional and viable as a long term solution. For example, the inability of current electrodes to accurately target specific nerves or nerve fibers limits the therapeutic effect of treatments while potentially producing side effects from inadvertent nerve stimulation. In addition, the large size of current wired electrodes and arrays and the wires connecting them to a central controller limit both the functionality and the suitability of these approaches to many applications.

SUMMARY

[0004] The present disclosure is directed to systems and methods for focused electric field neurostimulation generated by one or more micro particles.

[0005] In one aspect, the present disclosure is directed a system for neurostimulation. The system may include a micro particle implantable into tissue. The micro particle may include a power system configured to receive wireless energy transmission and an electrode system including two electrodes, each electrode configured to transmit electrical pulses. The micro particle may also include a processing system configured to control the power system and the electrode system. The system may also include a central controller. The central control may include a power system configured to wirelessly power the micro particle, a communication system configured to wirelessly communicate with the micro particle, and a processing system configured to control the power system and communication system. The system may be configured to selectively stimulate a target location by virtue of the central controller being configured to instruct the two electrodes of the micro particle to transmit electrical pulses and modulate the electrical pulses to generate an electric field that focuses neurostimulation at the target location.

[0006] In another aspect, the present disclosure is directed a system for neurostimulation. The system may include two micro particles implantable into tissue. The two micro particles may each include a power system configured to receive wireless energy transmission and an electrode system having an electrode configured to transmit electrical pulses. The micro particles may each also include a processing system configured to control the power system and the electrode system. The system may also include a central controller. The central controller may include a power system configured to wirelessly power the micro particles, a communication system configured to wirelessly communicate with the micro particles, and a processing system configured to control the power system and the communication system. The system may be configured to selectively stimulate a target location by virtue of the central controller being configured to cause the electrode of each micro particle to transmit modulated electrical pulses to generate an electric field that focuses neurostimulation at the target location.

[0007] In another aspect, the present disclosure is directed a method of neurostimulation. The method may include identifying a target location for neurostimulation by a micro particle having two electrodes that transmit electrical pulses. The method may further include selectively stimulating the target location by transmitting and modulating electrical pulses to generate an electric field that focuses neurostimulation at the target location. In certain embodiments, the neurostimulation may have no therapeutic effect. For instance, the neurostimulation may be for the sole purpose of detecting a response to the focused stimulation by the electric field.

[0008] In another aspect, the present disclosure is directed to a method of neurostimulation. The method may include identifying a target location for neurostimulation by two micro particles each having an electrode that transmits electrical pulses. The method may further include selectively stimulating the target location by transmitting and modulating electrical pulses to generate an electric field that focuses neurostimulation at the target location.

BRIEF DESCRIPTION OF DRAWINGS

[0009] Fig. 1 is a schematic of a neurostimulation system, according to an exemplary embodiment

[0010] Fig. 2 is a schematic illustration of a central controller, according to an exemplary embodiment.

[0011] Fig. 3 is a schematic illustration of a micro particle, according to an exemplary embodiment.

[0012] Figs. 4A, 4B, 4C, 4D, and 4E are pulse chart illustrations of different pulse widths, according to an exemplary embodiment.

[0013] Fig. 5 is a pulse chart illustration of different pulse polarities, according to an exemplary embodiment.

[0014] Fig. 6 is a pulse chart illustration of different pulse amplitudes, according to an exemplary embodiment.

[0015] Fig. 7 is a pulse chart illustration of different wave forms, according to an exemplary embodiment.

[0016] Fig. 8 is an illustration of a nervous system of a human.

[0017] Fig. 9 is an illustration of a pair of neurons of the nervous system of Fig. 8.

[0018] Fig. 10A, 10B, and 10C are schematic illustrations of one or more micro particles arranged to generate an electric field, according to exemplary embodiments.

[0019] Fig. 11 is a flow chart illustrating a method of neurostimulation, according to an exemplary embodiment.

DETAILED DESCRIPTION

[0020] A micro particle as described herein may be defined as a submillimeter implantable device, submillimeter device, or implantable device having an average diameter below 500 microns.

[0021] Neurostimulation as described herein may be defined as the delivery of electricity (e.g., electrical pulses) to a neuron, a nerve cell, or other target location of the nervous system intended to excite a neuron, a nerve cell, or other target location. The delivery of electricity may excite a nerve cell, for example, by inducing the flow of ions through the nerve cell membrane, which may trigger an action potential.

[0022] Fig. 1 shows a schematic diagram of a coordinated neurostimulation system 100, according to an exemplary embodiment. System 100 may include a central reader/controller, which will be referred to herein as a central controller 102. System 100 may also include one or more micro particles 104 configured to communicate with central controller 102. System 100 may be configured such that central controller 102 powers the micro particles 104 via wireless energy transmission. System 100 may be configured to wirelessly communicate with the micro particles 104, via wireless data links 106, without the use of leads as typically used for electrode stimulators. Central controller 102 and the micro particles may be configured to send and receive informational signals back and forth, which may include, for example, data, instructions, protocols, configurations, parameters, and the like. When the term information or informational signal(s) is used herein this may refer to one or more of the categories of information listed above.

[0023] In some embodiments, system 100 may include a single central controller 102 and a single micro particle 104. In some embodiments, system 100

may include a single central controller 102 and a plurality of micro particles 104. For example, in some embodiments, the number of micro particles 104 that system 100 includes may be 2 to 5, 6 to 10, 11 to 15, 16 to 20, 21 to 50, 51 to 100, or more. In some embodiments, system 100 may include multiple central controllers 102 and multiple micro particles 104. The number of central controllers 102 and multiple micro particles 104 may be determined and/or adjusted based on a number of variables, including for example, the body part that is to be stimulated, the function of the body part to be stimulated, the distance between the micro particles 104, the extent of damage to the person's nervous system, and the size and power of central controller 102. Although the following description is primarily directed to an embodiment of system 100 having more than one micro particle 104, the description is equally applicable to an embodiment of system 100 having just one micro particle 104, besides the description related to coordination of multiple micro particles 104.

[0024] Fig. 2 shows a schematic of central controller 102, according to an exemplary embodiment. Central controller 102 may be a portable or wearable device that a person may carry with them. Central controller 102 may include a processing system 108, a communication system 110, and a power system 112. Processing system 108 may be configured and responsible for controlling the overall operation of central controller 102 and coordinating the operation of the micro particles 104. Communication system 110 may be configured to wirelessly send informational signals to the micro particles 104 and receive informational signals from the micro particles 104. The power system 112 may be configured to power the central controller 102 and power the micro particles 104 using wireless energy transmission.

[0025] In some embodiments, central controller 102 may include additional components depending on desired functionality and/ or the needs of the implementation. By way of example, additional components include data ports, disk drives, a user interface, speaker(s), computer network interface(s), indicator light(s), and/or display. In some embodiments, central controller 102 may also include a wireless network adapter (e.g., WiFi) and an intelligent signal processor enabling secure data communication with other devices over the wireless network. The configuration of central controller 102 may be also be adjustable using any combination of hardware and software components.

[0026] Processing system 108 of central controller 102 may include one or more processors, including for example, a central processing unit (CPU) 114. The

CPU 114 may include any suitable type of commercially available processor or may be a custom design. Processing system 108 may include additional components, for example, non-volatile memory (e.g., a flash memory 116), volatile memory (e.g., a random access memory 118 (RAM)), and other like components, configured to store information (e.g., data, program instructions, sets of parameters, protocols, configurations, and the like) to enable the control and overall operation of central controller 102 and the micro particles 104.

[0027] Communication system 110 may utilize a variety of wireless data transmission methods for communicating back and forth with the micro particles 104 via one or more wireless data links 106 (see Fig. 1). For example, in some embodiments, communication system 110 may utilize radio data transmission, Bluetooth, near field communication (NFC), infrared data transmission, electromagnetic induction transmission, and/or other suitable transmission methods.

[0028] According to an exemplary embodiment, as shown in Fig. 2, communication system 110 of central controller 102 may utilize radio data transmission and include a number of components to support such transmission, such as a data encoder 120, a data decoder 122, a transmitter and a receiver or a transceiver 124, and/or an antenna 125. In some embodiments of communication system 110 may include two antennas, for example, one receiver antenna and one transmitter antenna. Also, in some embodiments, communication system 110 may be configured to transmit and receive data using a plurality of different wireless transmission methods.

[0029] Communication system 110 may be configured to establish data links between central controller 102 and the micro particles 104. Communication system 110 may be configured to transmit informational signals to the micro particles 104 while simultaneously receiving informational signals from the same or other micro particles 104. Processing system 108 may initiate the transmission of one or more informational signals to one or more of the micro particles 104 by conveying a message to the data encoder 120, which may then provide an encoded message to be transmitted through the antenna 125 via the transceiver 124. Processing system 108 may receive transmitted informational signals from the micro particles 104 when a transmission is received by the antenna 125 via the transceiver 124, which in some embodiments, may be decoded by the data decoder 122. Each micro particle 104 may be uniquely addressed, which may enable central controller 102 to individually

communication with each micro particle 104. Unique addressing of the micro particles 104 is described in more detail below. In some embodiments, data may be transmitted without encoding or decoding the data by communication system 110. Further, in some embodiments, recognition, pairing, or other signaling techniques may be used in place of addressing for transmitting data to and from micro particles 104.

[0030] Power system 112 may be configured to use wireless energy transmission to power the micro particles 104. In some embodiments, power system 112 may utilize, for example, inductive coupling, resonant inductive coupling, radio frequency, or the like to wirelessly transmit power.

[0031] According to an exemplary embodiment, as shown in Fig. 2, power system 112 may utilize resonant inductive coupling and may include a power source 126, an oscillator circuit 128, and/or a transmitting coil 130. Power source 126 may provide any suitable source of power, such as an AC source or a DC source. In some embodiments, the power source 126 may be, for example, a battery, a capacitor, a photovoltaic array, or the like. Oscillator circuit 128 may be powered by power source 126 and drive transmitting coil 130. In some embodiments, the signal from the oscillator circuit 128 may be amplified by a power amplifier 132 which may be coupled through, for example, a capacitor, to the transmitting coil 130. The transmitting coil 130 may be mutually coupled with the receiving coils on the micro particles 104, which will be discussed in more detail below. The coupled coils may transfer electromagnetic energy from the transmitting coil 130 through the body tissue to the receiving coils of the implanted micro particles 104 by way of mutual induction.

[0032] Fig. 3 shows a schematic diagram of an individual micro particle 104, according to an exemplary embodiment. Micro particle 104 may include a processing system 208, a communication system 210, a power system 212, and an electrode system 214. Processing system 208 may control the overall operation of the micro particle 104. Communication system 210 may communicate with central controller 102 by sending and receiving informational signals. The power system 212 may power the processing system 208, the communication system 210, and the electrode system 214 of the micro particle 104. The electrode system 214 may be controlled via the processing system 208 based on informational signals received from the central controller 102.

[0033] Processing system 208 may include a processor 216 configured to process, for example, data, instructions, protocols, configurations, and the like. For example, the processor 216 may receive informational signals containing instructions from the central controller 102 and based on the instructions control the operation of the electrode system 214 (e.g., stimulate nerve or sense nerve pulses).

[0034] Communication system 210 may utilize the same wireless data transmission method utilized by communication system 110 of the central controller 102. Communication system 210 may include an antenna 218 and a transceiver 220 to establish wireless communication with central controller 102. In order to minimize the number of components and size of the micro particles 104, antenna 218 and transceiver 220 may both be dual function, for example, each may receive and transmit signals. In some embodiments, communication system 210 may include a separate transmitter and a separate receiver rather than the dual function transceiver 220. Similarly, in some embodiments, communication system 210 may include a separate transmitter antenna and a separate receiver antenna rather than the dual function antenna 218. Although not shown, in some embodiments, communication system 210 may include an encoder and a decoder. In some embodiments, the encoder and/or decoder may be digital enabling better handling of signal attenuation. In some embodiments, all coding and decoding of the informational signals may be done by the central controller 102.

[0035] The power system 212 for micro particle 104, like the power system 112 for central controller 102 may use wireless energy transmission, including, for example, inductive coupling, resonant inductive coupling, radio frequency (RF) link, or the like to wirelessly transmit energy. Power system 212 may utilize the same wireless energy transmission method as power system 112 of central controller 102.

[0036] According to an exemplary embodiment, as shown in Fig. 3, power system 212 may utilize resonant inductive coupling. Power system 212 may include a receiving coil 222 that may be mutually inductively coupled to the transmitting coil 130 of central controller 102. In some embodiments, power system 212 may also include a power storage device 224 (e.g., battery, capacitor, or a power cell). The processing system 208, communication system 210, and the electrode system 214 may be powered by the energy received via the receiving coil 222. In some embodiments, power system 212 may also include a ground. Embodiments of power

system 212 utilizing an RF link for transmission of power may utilize a different type of antenna, thus eliminating the need for receiving coil 222.

[0037] The electrode system 214 may include a single electrode 226 or multiple electrodes. Each electrode 226 may be programmed to function as either a stimulating electrode for transmitting electrical pulses (e.g., input current or voltage pulse) or may be programmed to function as a sensing electrode for detecting electrical pulses transmitted along the neuron structure (e.g., axon, axon terminal, dendrites, etc.).

[0038] When programmed to function as a stimulating electrode 226, an electrode may be designated as either the cathode (i.e., negative) or the anode (i.e., positive). Embodiments of micro particle 104 where the electrode system 214 includes multiple electrodes 226, one electrode may be designated positive and one electrode may be set negative. In some embodiments where the electrode system 214 includes multiple electrodes 22, two or more of the electrodes may be designated positive or two or more of the electrodes may be designated negative.

[0039] The one or more electrodes 226 of electrode system 214 may be positioned at one or more locations about the micro particles 104. For example, for a cube shaped micro particle 104, one electrode 226 may be position on one side and one or more electrodes may be positioned on the other sides. For a spherical shaped micro particle 104, one or more electrodes 226 may extend, for example along a portion of the outer surface or in some embodiments the electrode may extend the full circumference around the sphere (e.g., ring shaped electrode).

[0040] In some embodiments, the orientation and direction electrode 226 is facing may be identifiable on the micro particle 104 and thus the electrode may be oriented during placement such that the electrode touches or faces a target location. In some embodiments, with more than one electrode, after placement of the micro particle 104 the active electrode may be advantageously selectable. For example, the electrode best oriented to stimulate a target location may be selected as the stimulating electrode.

[0041] In some embodiments, the orientation of the electrode 226 relative to a target location may be randomly determined based on the orientation of the micro particle 104 upon implantation. For example, some micro particles 104 may be positioned such that the electrode 226 is facing a target location while others may be positioned such that the electrode 226 is not generally facing a target location.

Stimulating of a target location even when an electrode 226 is not generally facing the target location may be achieved by selective neurostimulation targeting, which will be described in greater detail below.

[0042] The electrode system 214 may be configured to transmit one or more electrical pulses from the one or more electrodes 226. Although transmitting of multiple electrical pulses is primarily described herein, it is considered that in some embodiments a single electrical pulse may be transmitted from an electrode 226. Therefore, where multiple electrical pulses for neurostimulation are described, the description is equally applicable to embodiments where a single electrical pulse may be used for neurostimulation.

[0043] The characteristics of the electrical pulses may be defined by a set of parameters. The set of parameters may include, for example, a pulse width or pulse duration, a pulse polarity (e.g., cathodic or anodic), a pulse amplitude or power (e.g., voltage and/or current), a pulse frequency, and a pulse shape or waveform (e.g., rectangular, exponential, sinusoidal). The set of parameters defining the electrical pulses transmitted by electrode system 214 may be controlled or manipulated by central controller 102 or each individual micro particle 104.

[0044] In some embodiments, the pulse width or the pulse duration of the electrical pulses transmitted by the micro particles 104 may be controlled. For example, Figs. 4A-4E shows five different series of pulses, each having a different pulse width. The pulse width, as shown in Figs. 4A-4E may be represented as a duty cycle percentage between 0% and 100%. The series of pulses shown in Figs. 4b-4d that cycle on-off result in average voltages between full on and off determined by the pulse width. For example, the longer the duty cycle the closer the average voltage is to the on voltage. A 100% duty cycle would be equivalent to setting the voltage to the on voltage while a 0% duty cycle would be equivalent to grounding.

[0045] In some embodiments, the polarity of the electrical pulses (i.e., the pulse polarity) transmitted by the micro particles 104 may also be controlled. For example, the electrical pulses may be anodic phase (i.e., positive), cathodic phase (i.e., negative), or may be biphasic (i.e., switch between anodic and cathodic). For example, Fig. 5 shows square wave pulses where the first pulse is a cathodic phase and the second pulse is an anodic phase. Also illustrated in Fig. 5 is the pulse width and amplitude for the two pulses.

[0046] In some embodiments, the amplitude of the electrical pulses (i.e., the pulse amplitude A) transmitted by the micro particles 104 may also be controlled. This may be referred to as pulse amplitude modulation (PAM). The amplitude may be varied by varying the power (e.g., the voltage or the current) of the electrical pulses. For example, Fig. 6 shows square wave pulses where the pulse amplitude is modulated by increasing and decreasing the voltage both above and below zero volts producing an anodic phase pulse and cathodic phase pulse. The voltage may vary, for example, from about 10 mV to about 30 mV, about 10 mV to about 40 mV, about 10 mV to about 50 mV, about 20 mV to about 30 mV, about 20 mV to about 40 mV, or about 20 mV to about 50 mV. The range of amplitude or power by which electrode system 214 may stimulate a nerve cell may be less than that of current electrodes, which may reduce the risk of injury or atrophy to the nerve cell and surrounding tissue.

[0047] In some embodiments, the frequency of the electrical pulses (e.g., interval between pulses) transmitted by the micro particles 104 may also be controlled. In some embodiments, the frequency for a first series of pulses may be the same and then the frequency may be changed for a second series of pulses following the first series of pulses. In some embodiments, the frequency may change between each individual pulse. For example, as shown in Fig. 6, the duration between each pulse is different as demonstrated by the change in distance between each pulse along the time axis.

[0048] Although Figs. 4-6 illustrate only square waveform pulses, the shape of the electrical pulses are not limited to square waveforms. The pulse shape or waveform of the electrical pulses transmitted by the micro particles 104 may also be controlled. Fig. 7 shows a variety of different waveforms, which the micro particles 104 may utilize. For example, one or more electrical pulses may have a sinusoidal, a square, a ramp, a saw tooth, a triangular, an exponential rise, or an exponential decay waveform. In some embodiments, the wave form may be changed from one pulse to the next or it may remain the same for a first series of electrical pulses and then be changed for a second series of electrical pulses.

[0049] The above parameters may form a set of parameters that may be independently controlled and/or selected to define the electrical pulses transmitted by the micro particles 104 via the one or more electrodes 226. For example, one or more micro particles 104 may transmit electrical pulses defined by a set of

parameters, which includes a pulse width, a pulse polarity, a pulse amplitude, a pulse frequency, and a pulse shape or waveform. The set of parameters may include any combination of two or more of the above listed parameters.

[0050] The transmitting of the electrical pulses may generate an electric field. The direction of an electric field generated by a single positive point charge is radially outward while the direction of the electrical field of a single negative point charge is radially inward. When multiple charges or multiple electrodes are in proximity to one another the electric field produced by the multiple electrodes may be more complex depending on, for example, the number of electrodes, the charge of each electrode, the location of each electrode, and the magnitude of the current of each electrode. The electric field generated by the electrodes may be configured to stimulate and trigger an action potential of a nerve cell or a portion of a nerve cell. In some embodiments, a gradient of the electric field may trigger the action potential. Generating of the electric field and stimulating of a nerve cell will be discussed in further detail below.

[0051] Each micro particle 104 may be uniquely addressed. For example, each micro particle 104 may be uniquely electromagnetically addressed. Each micro particle may have a unique identification number that may be programmed into the non-volatile memory, hard coded, or generated during the electrical or mechanical fabrication. As a result of the unique addressing, central controller 102 may send unique informational signals to each individual micro particle 104. For example, central controller 102 may send a unique set of parameters for the electrical pulses for one or more individual micro particles 104. Similarly, central controller 102 may be able to individually identify informational signals received from each micro particle 104. In some embodiments, one or more of the micro particles 104 may have the same addressing so that the same information may be transmitted to multiple micro particles 104 at the same time.

[0052] Fig. 8 shows an illustration of a nervous system 300 of a human subject 302. Nervous system 300 is made up of two main parts: the central nervous system 304, which includes the brain 306 and the spinal cord 308, and the peripheral nervous system 310, which includes the nerves that go from the spinal cord to the arms, hands, legs, and feet. The peripheral nervous system 310 is made up of several nerve systems: the sensory nervous system, the motor nervous system, the somatic nervous system, and the autonomic nervous system. The sensory nervous

system includes sensor nerves that send information to the central nervous system 304 from internal organs or from external stimuli. The motor nervous system includes motor nerves that carry information from the central nervous system 304 to organs, muscles, and glands. The somatic nervous system includes somatic nerves that control skeletal muscle as well as external sensory organs. The autonomic nervous system includes autonomic nerves that control involuntary muscles (e.g., cardiac muscles).

[0053] The nervous system 300 is made up of billions of nerve cells, which may also be referred herein as neurons. Fig. 9 is an illustration of two interconnected nerve cells 312, which may be part of a network of interconnected nerve cells. Nerve cell 312 on the left as illustrated may be characterized as the transmitting nerve cell while nerve cell 312 on the right may be characterized as the receiving nerve cell. Each nerve cell 312, as shown in the Fig. 5, may include among other things, a nucleus 314, a cell body 316, an axon 318, axon terminals 319 and dendrites 320. The dendrites 320 collect electrical signals while the cell body 316 and nucleus 314 integrates the incoming signals and transmits outgoing nerve signals down the axon 318 to the axon terminals 319. The axon 318 may be surrounded by a myelin sheath 317 that facilitates transmission of nerve pulses to the axon terminals 319. The axon terminals 319 may pass the outgoing signal to dendrites 320 of the receiving cell. The electrical signals may be transmitted from the transmitting cell to the receiving cell across one or more synapses 322.

[0054] Nerve signals or pulses, which may also be referred to as action potential, is a coordinated movement of sodium and potassium ions across the cell membrane. The inside of a nerve cell is slightly negatively charged, for example, the resting membrane potential is about -70 to -80 mV. A stimulation (e.g., a mechanical, electrical, or chemical), which may also be referred to as a neurostimulation, can cause a few sodium channels in a small portion of the membrane to open and the position charge that they carry depolarizes the cell (i.e., makes the inside of the cell less negative). When the depolarization reaches a certain threshold value more sodium channels are opened enabling more sodium flow in and triggers an action potential. In other words, the inflow of sodium ions reverses the membrane potential in that area (i.e., making it positive inside and negative outside). When the electrical potential reaches about +40 mV inside, the sodium channels shut down and let no more sodium ions inside. The developing positive membrane potential causes

potassium channels to open and potassium ions leave the cell through the open potassium channels. The outward movement of the positive potassium ions makes the inside of the membrane more negative, repolarizing the cell. When the membrane potential returns to the resting value the potassium channels shut down and potassium ions can no longer leave the cell. This sequence of events occurs in a local area of the nerve cell membrane, but these changes get passed on to the next area of the nerve cell membrane, then to the next area, and so down the entire length of the axon. Thus, the action nerve pulse, nerve signal, or action potential gets transmitted (i.e., propagated) down the nerve cell and transmitted to other nerve cells through synapses. A typical nerve cell may have thousands of synapses enabling it to communication with thousands of other nerve cells, muscle cells, glands, etc.

[0055] The action potential is often referred to as an “all-or-none” response because once the membrane reaches a threshold, it will depolarize to +40 mV. Action potentials may be propagated rapidly. For example, typical neurons can conduct 10 to 100 meters per second depending on the diameter of the axon (i.e., larger axon produce faster propagation). Neurons may vary in size depending on the type of neuron. For example, some neurons have an average diameter of as little as about 5 microns while others may have an average diameter of about 100 microns. Neurons can vary structure and many neurons can be anatomically characterized as unipolar, multipolar, or bipolar.

[0056] When a portion of a person's nervous system becomes damaged (e.g., by disease or injury) or malfunctions, the voluntary or involuntary function of a person's body (e.g., limb or organ) may be restricted or a person may experience partial or total paralysis or dysfunction. System 100 may stimulate a function of a limb or an organ or treat a disease or condition by stimulating one or more nerves and in some embodiments sensing nerve pulses from one or more nerves using the micro particles 104. The electrical pulses transmitted from the micro particles 104 by electrode system 214 may generate an electric field, which may function as neurostimulation causing the sodium channels to open, depolarizing the cell and ultimately triggering a nerve pulse or action potential.

[0057] The neurostimulation of the electric field may be focused by modulating a number of different variables. For example, the number of electrodes, the positioning of the electrodes, the charge of the electrodes, and the current

supplied to the electrodes are some of the variables, which may be adjusted to focus the electric field.

[0058] In some embodiments, the number of electrodes generating the electric field may be 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments the number of electrodes generating the electric field may be 10 to 15, 15 to 20, or more. The number of micro particles 104 housing the electrodes 226 may also vary. For example, Fig. 10A shows a single micro particle 104 having two electrodes 226. In some embodiments, one of the electrodes shown in Fig. 10A may be designated positive and one may be designated negative and an electric field 251 may be generated by transmitting electrical pulses. The electric field may be modulated, for example, by changing the current (e.g., anodic current) supplied to the positive electrode. Fig. 10B shows another example where two micro particles 104 may each have an electrode and one may be designated positive and one may be designated negative, which generates for example, an electric field 252. Fig. 10C shows another example where four micro particles 104 may each have an electrode and three may be designated positive and one may be designated negative generating an electric field 253. In order to generate electric field 253, the current supplied to the bottom electrode 226 may be greater than the current supplied to the other positive electrodes 226. The focus of the electric field could also be changed by reassigning which electrodes 226 are positive and negative or by reducing or increasing the number of active electrodes.

[0059] An electric field may be generated by any number of micro particles 104 and electrodes 226. As discussed herein, a number of different variables may be modulated to focus the neurostimulation of the electric field. These variables may include the number of electrodes, the positioning of the electrodes, the charge of the electrodes, and the current supplied to the electrodes. In addition to current, other parameters associated with the electrical pulses may also be modulated to focus the neurostimulation of the electric field.

[0060] The electric fields focus and effectiveness in triggering an action potential may depend on one or more parameters of the electrical pulses. This is because different types of nerve cells and different portions of nerves cells have different levels of sensitivity to stimulation, which may depend on the parameters of the electrical pulses and the electric field generated. For example, some nerve cells may be activated based on the gradient of the electric field oriented parallel to the

axon of the nerve cell. Smaller diameter axons compared to larger diameter axons may be more effectively stimulated (i.e., have an increased sensitivity) to electrical pulses that are biphasic pulses with an exponentially decaying anodic phase. Some cell types demonstrate sensitivity to activation based on other parameters, for example, retinal cells demonstrate activation based on pulse frequency. For example, bipolar retinal cells may demonstrate increased sensitivity to sinusoidal pulses having a frequency of about 25 Hz, while ganglion cells may demonstrate increased sensitivity to sinusoidal pulses having a frequency of 100 Hz. Ganglion cells associated with other organs may also demonstrate increased sensitivity to frequency. For example, ganglion cells transmitting nerve pulses to the pancreas may also demonstrate a sensitivity to pulse frequency.

[0061] A target location (e.g., a nerve cell or portion of a nerve cell) may be defined as having an greater sensitivity to an electric field when the target location has a greater likelihood of an action potential being triggered at the target location by the electric field than an area surrounding the target location. This disparity in sensitivity based on the parameters of the electrical pulses may enable selective neurostimulation (i.e., targeting) of specific nerve cells or portions of nerve cells for neurostimulation and triggering of an action potential. For example, a specific nerve cell may be targeted for neurostimulation by transmitting electrical pulses with a specific set of parameters, to which generate an electric field that the targeted nerve cell has a greater sensitivity. In some embodiments, for example, this may include transmitting electrical pulses with a specific set of parameters to generate an electric field that have been determined to maximize the likelihood of triggering an action potential in the targeted nerve cell. In some embodiments, this may include transmitting electrical pulses that generate an electric field with a specific set of parameters that yield the greatest difference in likelihood of triggering an action potential between the targeted nerve cells and surrounding nerve cells. For example, this may include selecting a specific set of parameters that is known to yield a low probability of triggering an action potential in the surrounding nerve cells while yielding a higher likelihood of triggering an action potential in the targeted nerve cell, but the likelihood of triggering an action potential in the targeted nerve cell may not necessarily be maximized. As a result, there may be different set of parameters for maximizing the difference in likelihood of triggering an action potential between a

targeted nerve cell and a surrounding nerve compared to just maximizing the likelihood of triggering an action potential in the targeted nerve cell.

[0062] The greater sensitivity of the target nerve cell compared to the nerve cell in the surrounding area may be due to a variety of factors. For example, the target nerve cell may be a different type of nerve or different size (e.g., axon diameter), which as explained above can result in greater sensitivity to electrical pulses with certain parameters. Other information and testing may also be used to determine the set of parameters to which nerve cells have a greater sensitivity. This information and testing may include, for example, clinical testing and/or patient specific testing. Sensitivity may be measured and compared, for example, based on the flow of ions through the nerve triggered by electrical pulses and whether the flow of ions reaches the threshold to trigger an action potential. By targeting specific nerve cells, this method of selective neurostimulation by a focused electric field may reduce inadvertent or unintended stimulation (e.g., triggering of action potential) of surrounding nerves or portions of a nerve in the surrounding area.

[0063] Stimulating a nerve cell using an electric field may enable neurostimulation of nerve cells that are a distance from the one or more electrodes 226. In other words, generating an electric field may extend the distance or range two or more electrodes 226 may stimulate a nerve cell or portion of a nerve. The range of the electric field may enable neurostimulation of a nerve cell or portions of a nerve cell that are typically not accessible for neurostimulation due to the depth. For example, a nerve cell or portion of a nerve cell may not be accessible for neurostimulation if it is deep in the tissue and implanting an electrode in proximity to the nerve cell creates too high a risk of trauma.

[0064] The micro particles 104 may be implantable into the tissue of a person or animal. Implantation may be planned or more random. For example, in some embodiments the implantation may be planned such that individual micro particles 104 may be implanted at or proximate to specific nerves or portions of a nerve identified to control or transmit the nerve pulses that trigger the function which the system is trying to stimulate. In other embodiments, the general region of the target nerve or nerves may be known, but the micro particles 104 may be more randomly distributed in the region of the nerve or nerves rather than being individually placed at predetermined locations. In some embodiments, as illustrated in Fig. 9, micro particles 104 may be implanted near the dendrites 320, synapses

322, axons 318, or axon terminals 319, of one or more nerve cells 312. In some embodiments, the micro particles 104 may be implanted in a preplanned arrangement designed to enable focusing of the electric field on a nerve targeted for neurostimulation. In some embodiments, the micro particles 104 may be implanted to surround a nerve that is targeted for neurostimulation, but not positioned at or proximate the nerve due to the location of the nerve.

[0065] The micro particles 104 may vary in size. In some embodiments, for example, the average diameter of the micro particle 104 may be about 500 microns to about 400 microns, about 400 microns to about 300 microns, about 300 microns to about 200 microns, or about 200 microns or less. Generally, the micro particles may be about the size of a grain of sand. The minimal size of the micro particles will significantly reduce the likelihood of trauma compared to the larger prior art electrodes currently utilized. For example, prior art nerve cuffs designed to wrap around a peripheral nerve can cause trauma to the target nerve as well as the surrounding nerves during installation and operation due to the large size and complexity of the installation.

[0066] The microscopic size of the micro particles 104 enables more precise and refined placement (i.e., implantation) with respect to the corresponding microscopic nerve cells when compared to other electrodes that are an order of magnitude larger. For example, an electrode that is about 1 millimeter in diameter is 10 times the size of a nerve cell that has an average diameter of 100 microns. Thus, the 1 millimeter electrode covers the entire nerve cell and may even cover portions of neighboring nerve cells. In contrast, the micro particles 104 may be about the same order of magnitude of the nerve cell (e.g., 200 micron micro particle 104 and 100 micron nerve cell 312). Thus, the micro particle may be positioned more precisely in order to better focus an electric field for stimulating a specific nerve cell or portion of a nerve cell. In some embodiments, a micro particle 104 may be placed at or adjacent a specific portion of the nerve 312. For example, a micro particle may be placed at a dendrite branch or limb or may be placed along an axon 318 or at an axon terminal 319 of a nerve 312. In some embodiments, a micro particle 104 may be placed at or near a synapse 322 connecting two nerves 312. In some embodiments, the relative size of the micro particles 104 may allow placement further down the branches of the dendrites 320 or axon terminals 319. This may allow finer focus targeting by the electric field for neurostimulation.

[0067] More refined placement of the micro particles 104, which advantageously enables more refined targeting for neurostimulation by the electric field may reduce the potential for inadvertently stimulating nerve cells that were not intended, which in some cases may cause inadvertent function stimulation and other side effects. For example, stimulating the larger fibers of the Vagus nerve as part of treatment for epilepsy could inadvertently stimulate too broadly causing heart arrhythmias.

[0068] More refined placement of the micro particles 104 and closer proximity placement to the target nerve or portion of the nerve, in addition to reducing the likelihood for inadvertent nerve cell stimulation, also allows the strength of the electrical pulses transmitted from the micro particles 104 to be reduced. For example, the reduced size of the micro particles 104 allows for placement at closer proximity to the target portion of the nerve cell thereby enabling less power (e.g., voltage or current) to be used to stimulate the cell and trigger an action potential. Coulomb's law describes the relationship between distance and current intensity as $I = k(i/r^2)$. I = current required; k = constant; i = minimal current; r = distance from nerve. Thus, by reducing the distance from the nerve, the minimal current may be reduced. Reducing the strength of the electrical pulses and thus the electric field generated may be beneficial in some situations because electrical pulses and electric fields above certain thresholds can cause atrophy to the neural structures over time. Stimulating the nerve cells and triggering an action potential using less power (e.g., current and/or voltage) can reduce or prevent atrophy of the neural structures proximate to the micro particles.

[0069] System 100 as described herein may be utilized in a variety of methods for treating conditions related to nerve damage or nerve malfunction of humans or animals. Various methods of utilizing system 100 will now be explained with reference to Fig. 11.

[0070] According to an exemplary embodiment, system 100 may be utilized for a method 400 of neurostimulation. Method 400 may constitute a therapeutic program used for treating a patient who has a condition or disease or is experiencing loss of function or dysfunction of a limb, organ, or other body part. Method 400 may include identifying for neurostimulation one or more target locations at step 402. In some embodiments, the target locations may be one or more nerve cells associated with treating the condition or disease. In some embodiments, the target locations

may be one or more nerve cells that are associated with controlling a lost function of a limb, an organ, or other body part.

[0071] The scope of what constitutes a target location may vary. For example, a target location may be a specific nerve cell, a specific portion of a nerve cell (e.g., dendrite, axon, axon terminal, myelin sheath, or synapse), a cluster of nerve cells, or a region of tissue containing one or more nerve cells. In some embodiments, target locations may be adjacent or proximate to one another, for example, two adjacent nerve cells or an axon and axon terminal of the same nerve cell. In some embodiments, target locations may be a distance apart. In some embodiments, the distance apart may be, for example, less than, about 5 millimeters, about 10 millimeters, about 15 millimeters, about 20 millimeters, about 25 millimeters, or about 50 millimeters. In some embodiments, the distance apart may be, for example, greater than, about 5 millimeters, about 10 millimeters, about 15 millimeters, about 20 millimeters, about 25 millimeters, or about 50 millimeters.

[0072] Next, step 404 of method 400 may include distributing or implanting one or more micro particles 104 into the patient (e.g., the tissue). In some embodiments, distributing the one or more micro particles 104 may include placement of one or more individual micro particles in the vicinity of, a distance from, or surrounding one or more target locations. In some embodiments, distributing the one or more micro particles 104 to a target location may include directing them to a target location (e.g., a region) and within the region the one or more micro particles 104 may be more randomly distributed within the region. In some embodiments, distributing or placement of the micro particles 104 may be aided by imaging guidance. For example, a magnetic resonance imaging (MRI) system may be used to provide real-time visual feedback during the implanting of the micro particles.

[0073] The target locations can include the brain or the spinal cord (i.e., the central nervous system), peripheral nerves (e.g., the vagal nerve, the sciatic nerve), or individual organs at the nerve interface (e.g., the heart, the bladder, the pancreas). The target locations for distribution of the micro particles may include different types of nerves, for example, motor nerves, sensory nerves, or autonomic nerves. The nerve cells may be unipolar, multipolar, or bipolar.

[0074] In some embodiments, prior to distributing of the micro particles 104, method 400 may include initiating a startup of system 100, which may include powering up of the micro particles and testing the wireless communication between

central controller 102 and the micro particles 104. In some embodiments, powering up of the micro particles and testing of the wireless communication (i.e., startup) may be conducted after distribution of the one or more micro particles. In some embodiments, startup may be conducted for each micro particle after distribution of each micro particle.

[0075] Once the one or more micro particles are distributed and in position, step 406 of method 400 may include selectively stimulating at least one target location by transmitting electrical pulses and modulating the electrical pulses to generate an electric field that focuses neurostimulation at the target location. The focused neurostimulation from the electric field may trigger an action potential at the target location while simultaneously avoiding or reducing the likelihood of triggering an action potential at the surrounding area (e.g., neighboring nerve cells or neighboring nerve structure) due to the focused neurostimulation of the electric field. This may reduce or prevent inadvertent function stimulation and other side effects.

[0076] As discussed herein, a number of different variables may be modulated to focus the neurostimulation of the electric field. These variables may include the number of active electrodes, the positioning of the active electrodes, the charge of the electrodes, and the parameters of the electrical pulses (e.g., the current).

[0077] The number of active electrodes may be modulated by increasing or decreasing the number of electrodes transmitting electrical pulses. For example, not every electrode of every micro particle implanted needs to be active and transmitting electrical pulses. Instead, in some embodiments, initially a portion of the electrodes may be active enabling additional electrodes to be activated in order to better focus the neurostimulation of the electric field on a target location. In some embodiments, effective neurostimulation of a target location by the electric field may be achievable when with using only a portion of the electrodes 226 and/or only a portion of the micro particles 104.

[0078] The positioning of the active electrodes 226 generating the electric field may be modulated by changing which electrodes 226 are active. In addition to changing which electrodes are active, the charge of the active electrodes may also be changed to modulate the electric field. For example, an electrode 226 may be switched from active and positive to inactive or switched to a negative charge. In

another example, an electrode 226 may be switched from inactive to active and set as a negative charge or positive charge.

[0079] Modulating of the electrical pulses may also include varying one or more parameters of the electrical pulses. The parameters may include, for example, a pulse width, a pulse polarity, a pulse amplitude, a pulse frequency, and a pulse shape or waveform.

[0080] Modulating of the electrical pulses to focus the electric field may include adjusting of the different variables continuously or at a discrete interval. For example, adjustments may be made every 1 second, 5 seconds, 10 seconds, 30 seconds, 1 minute, 2 minutes, or more. In some embodiments, modulating of the electrical pulses may include cycling between different sets of variables and repeating the cycle, which generates a patterned electric field neurostimulation.

[0081] Transmitting and modulating the electrical pulses to focus the electric field may be initiated and controlled by central controller 102. For example, central controller 102 may selectively deliver power and information wirelessly to one or more micro particles 104. The information may include instructions for which electrodes are active, the charge of the active electrodes, the set of parameters for the electrical pulses. As described herein, each individual micro particle 104 may be uniquely addressed. Thus central controller 102 may transmit unique information to each micro particle 104.

[0082] In some embodiments, method 400 may also include selectively sensing responses to the neurostimulation of the one or more target locations at step 408. In some embodiments, sensing the response may include, for example, sensing the neurological response using one or more micro particles 104 configured for sensing, visually observing the response (e.g., movement of a limb), or clinical measuring the response (e.g., blood glucose monitoring or accelerometer monitoring).

[0083] For embodiments where the response may be sensed neurologically, central controller 102 may select which of the micro particles 104 senses nerve pulses. In some embodiments, central controller 102 may selectively instruct one or more micro particles 104 to switch from stimulating to sensing based on a stimulation protocol. In some embodiments, a micro particle 104 may stimulate and sense, for example, by using one electrode 226 to sense and another electrode 226 to stimulate. The nerve pulses may be sensed by one or more of the micro particles

104 and informational signals indicative of the sensed nerve pulse may be transmitted back to the central controller 102. In some embodiments, the sensed nerve pulses may be utilized to refine and modulate the electric pulses to better focus the electric field on the target location in order to improve efficacy of the treatment.

[0084] Central controller 102 may execute a therapeutic stimulation protocol configured to conduct a coordinated neurostimulation by one or more of the micro particles 104 at one or more of the target locations. For example, in some embodiments, central controller 102 may stimulate a first target location and then a second target location by modulating the electrical pulses such that the electric field first focuses neurostimulation at the first target location and then focuses neurostimulation at the second target location. In some embodiments, a first set of electrodes 226 may be used to stimulate the first target location and then the same set of electrodes may be used to stimulate the second target location. In some embodiments, a first set of electrodes 226 may be used to stimulate the first target location and then a second set of electrodes may be used to stimulate the second target location. Where different sets of electrodes are used, in some embodiments, one or more of the same electrodes may be part of both sets, or in some embodiments, none of the same electrodes may be part of both sets. In some embodiments, the electrical pulses may be modulated to focus the electric field to stimulate both the first target location and the second target location simultaneously.

[0085] In some embodiments, method 400 may include coordinated and repeated neurostimulation (e.g., step 406) and sensing (e.g., step 408). For example, method 400 may be utilized to stimulate a nerve pulse at one target location and to sense or measure a response at other nerve or target locations. More specifically, method 400 may include stimulating one or more target locations triggering nerve pulses and propagation of the nerve pulses, which may then be sensed downstream by one or more of the sensing micro particles 104. This coordinated neurostimulation and sensing may enable central controller 102 to calculate propagation behavior (e.g., timing, strength, etc.) of nerve pulses. In addition, the coordinated neurostimulation and sensing may enable central controller 102 to optimize the neurostimulation by the electric field to improve the therapeutic results.

[0086] For example, steps 406 and 408 may be repeated and in between steps the neurostimulation, sensing, and or identifying protocol may be adjusted in order to better achieve a desired result (e.g., stimulate a function of an organ or body part). The repeating of the steps and adjustment can act like a feedback control loop. In some embodiments, the adjustments made to optimize may include selectively adjusting the parameters or sets of parameters of the electrical pulses for one or more of the micro particles 104. In some embodiments, the adjustments made may include rearranging which one or more micro particles 104 may stimulate and which one or more micro particles 104 may sense. In some embodiments, the adjustments may include activating additional micro particles 104 for stimulating or sensing. In some embodiments, the adjustments may include repositioning one or more micro particles.

[0087] Method 400 and system 100 as described herein may be used in a variety of ways to therapeutically restore or improve function of an organ, a limb, or other body part by neurostimulation without inadvertently affecting other parts of the body by using micro particles to generated focused electric field for neurostimulation.

[0088] Although the present disclosure describes the use of system 100 and the corresponding methods primarily in reference to human patients, it is understood that system 100 and the corresponding methods may be employed with animals as well.

CLAIMS

1. A system for neurostimulation, comprising:
 - a micro particle implantable into tissue, the micro particle comprising:
 - a power system configured to receive wireless energy transmission;
 - an electrode system comprising two electrodes, each electrode configured to transmits electrical pulses;
 - and
 - a processing system configured to control the power system and the electrode system; and
 - a central controller comprising:
 - a power system configured to wirelessly power the micro particle;
 - a communication system configured to wirelessly communicate with the micro particle; and
 - a processing system configured to control the power system and the communication system;wherein the system is configured to selectively stimulate a target location by virtue of the central controller being configured to instruct the two electrodes of the micro particle to transmit electrical pulses and to modulate the electrical pulses to generate an electric field that focuses neurostimulation at the target location.
2. The system of claim 1, wherein the micro particle, in use, is implanted into tissue.
3. The system of claim 1 or 2, comprising a plurality of the micro particles, wherein the system is configured to focus neurostimulation by the electric field at the target location by instructing a first portion of the plurality of micro particles to transmit electrical pulses.

4. The system of claim 3, wherein the central controller is further configured to modulate the electrical pulses by changing from instructing the first portion of the plurality of microparticles to instructing a second portion of the plurality of micro particles to transmit the electrical pulses.
5. The system of claims 3 or 4, wherein the electrode system of at least one of the micro particles comprises an electrode for sensing nerve pulses generated in response to the neurostimulation of the target location.
6. The system of claim 5, wherein the central controller is further configured to modulate the electrical pulses based on the sensed nerve pulses generated in response to the neurostimulation of the target location.
7. The system of any of claims 1 to 6, wherein the central controller is further configured to modulate the electrical pulses by varying at least one parameter selected from the group: a pulse width, a pulse polarity, a pulse amplitude, a pulse shape, and a pulse frequency.
8. A system for neurostimulation, comprising:
 - two micro particles implantable into tissue, the two micro particles each comprising:
 - a power system configured to receive wireless energy transmission;
 - an electrode system comprising an electrode that transmits electrical pulses; and
 - a processing system configured to control the power system and the electrode system;
 - a central controller comprising:
 - a power system configured to wirelessly power the micro particles;
 - a communication system configured to wirelessly communicate with the micro particles; and
 - a processing system configured to control the power system and the communication system;

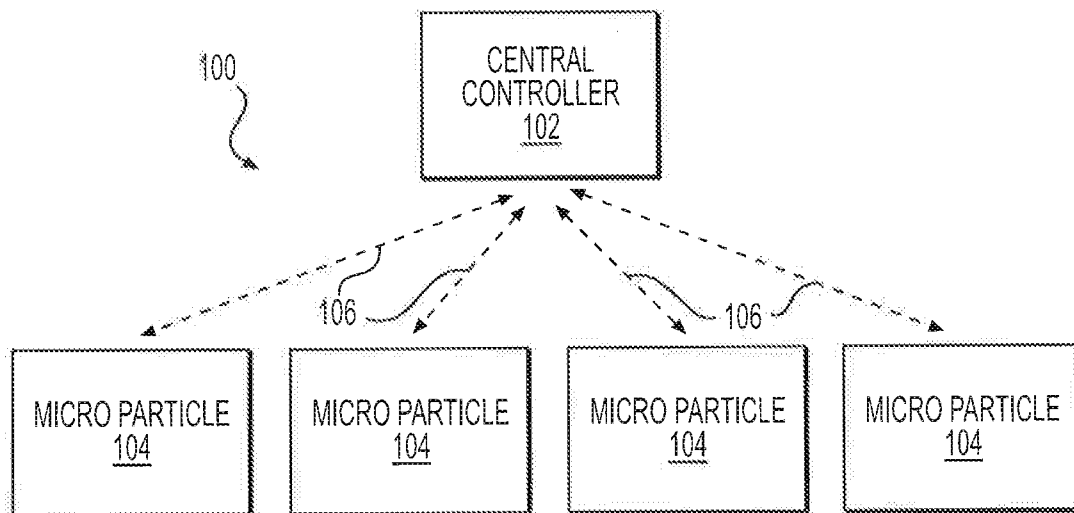
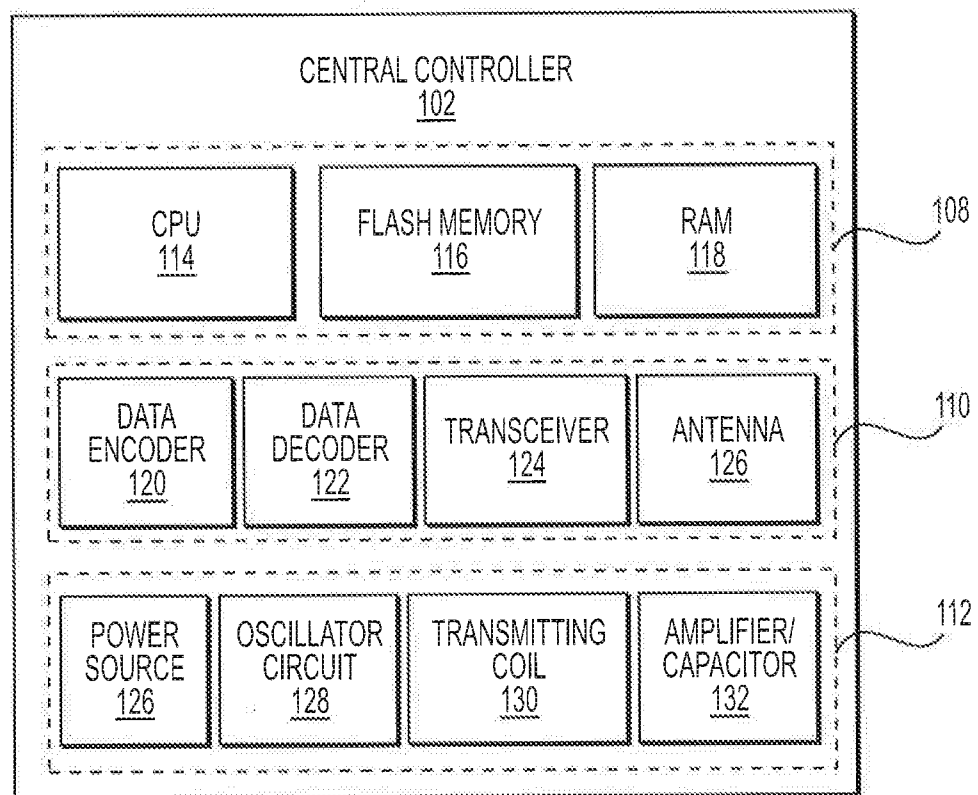
wherein the system is configured to selectively stimulate a target location by virtue of the central controller being configured to cause the electrode of each micro particle to transmit modulated electrical pulses to generate an electric field that focuses neurostimulation at the target location.

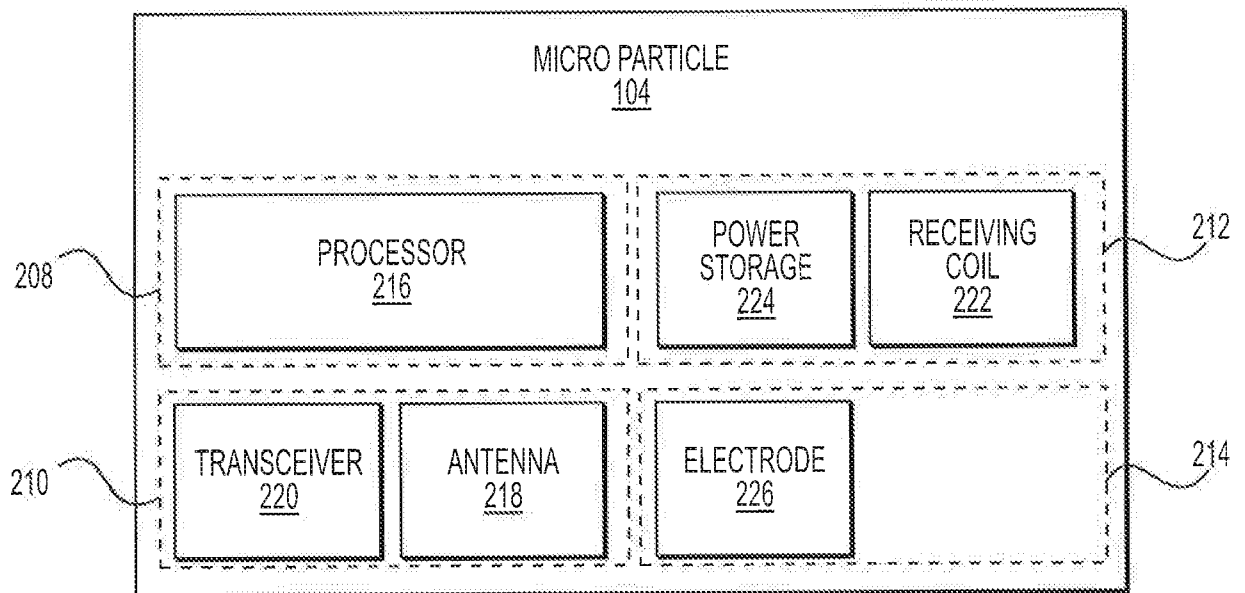
9. The system of claim 8, wherein the micro particles, in use, are implanted into tissue.
10. The system of claim 8, further comprising a plurality of the micro particles, wherein the system is configured to focus neurostimulation by the electric field at the target location by instructing a first portion of the plurality of micro particles to transmit electrical pulses.
11. The system of claim 10, wherein the central controller is further configured to modulate the electrical pulses by changing from instructing the first portion of the plurality of micro particles to instructing a second portion of the plurality of micro particles to transmit the electrical pulses.
12. The system of claims 10 or 11, wherein the central controller is further configured to modulate the electrical pulses by changing the charge of one or more of the plurality of micro particles.
13. The system of any of claims 8 to 12, wherein modulating the electrical pulses includes varying at least one parameter selected from: a pulse width, a pulse polarity, a pulse amplitude, a pulse shape, and a pulse frequency.
14. A method of neurostimulation, the method comprising:
 - identifying a target location for neurostimulation by a micro particle having two electrodes that transmit electrical pulses; and
 - selectively stimulating the target location by transmitting and modulating electrical pulses to generate an electric field that focuses neurostimulation at the target location.

15. The method of claim 15, further comprising selectively stimulating a second target location by modulating the electrical pulses to focus the electric field at the second target location.
16. The method of claims 15 or 16, further comprising selectively sensing a response to the neurostimulation and modulating the electrical pulses based on the response.
17. The method of claim 17, wherein sensing the response is measuring of a blood glucose.
18. The method of any of claims 15 to 18, wherein modulating the electrical pulses includes varying at least one parameter selected from the group: a pulse width, a pulse polarity, a pulse amplitude, a pulse shape, and a pulse frequency.
19. The method of any of claims 15 to 19, wherein the electrical pulses are modulated to produce a non-sequential patterned neurostimulation.
20. The method of any of claims 15 to 20, wherein the target location is the axon of a nerve cell.
21. The method of any of claims 15 to 22, further comprising modulating of the electrical pulses to generate an electric field that avoids stimulating an area surrounding the target location.
22. A method of neurostimulation, comprising:
 - identifying a target location for neurostimulation by two micro particles each having an electrode that transmits electrical pulses; and
 - selectively stimulating the target location by transmitting and modulating electrical pulses to generate an electric field that focuses neurostimulation at the target location.

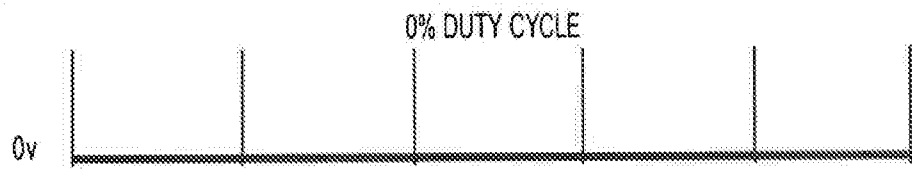
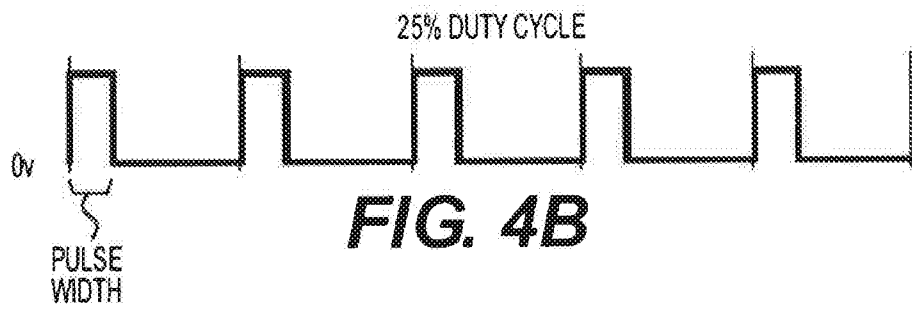
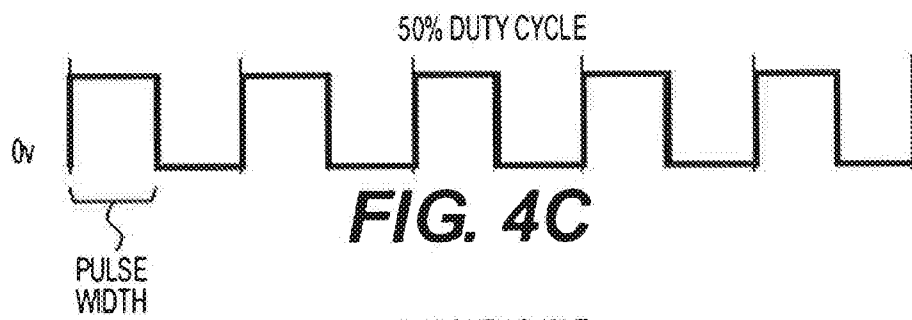
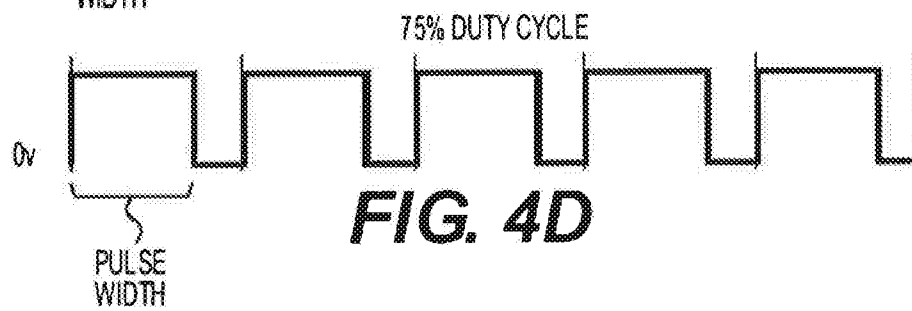
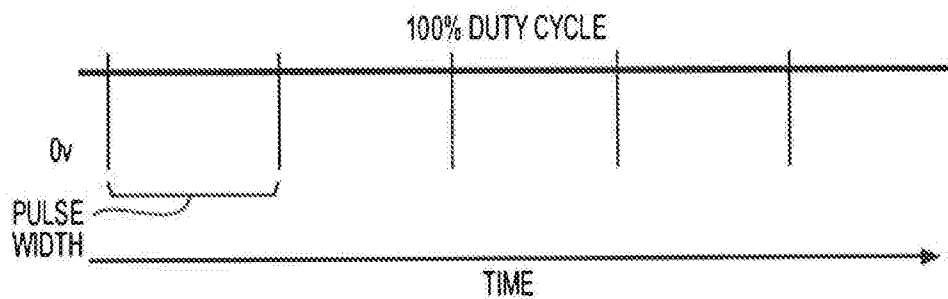
23. A modified nerve to which the micro particle of any one of claims 1 to 13 is attached, such that the one or more micro particles is in signaling contact with the nerve and so the nerve can be distinguished from the nerve in its natural state.
24. A modified nerve obtainable by stimulating neural activity of the nerve according to any one of claims 14 to 22.
25. A method of controlling a micro particle of any one of claims 1 to 13 that is in signaling contact with a nerve, comprising a step of sending control instructions to the micro particle, in response to which the micro particle applies a stimulatory signal to the nerve.

1 / 9

**FIG. 1****FIG. 2**

**FIG. 3**

3 / 9

**FIG. 4A****FIG. 4B****FIG. 4C****FIG. 4D****FIG. 4E**

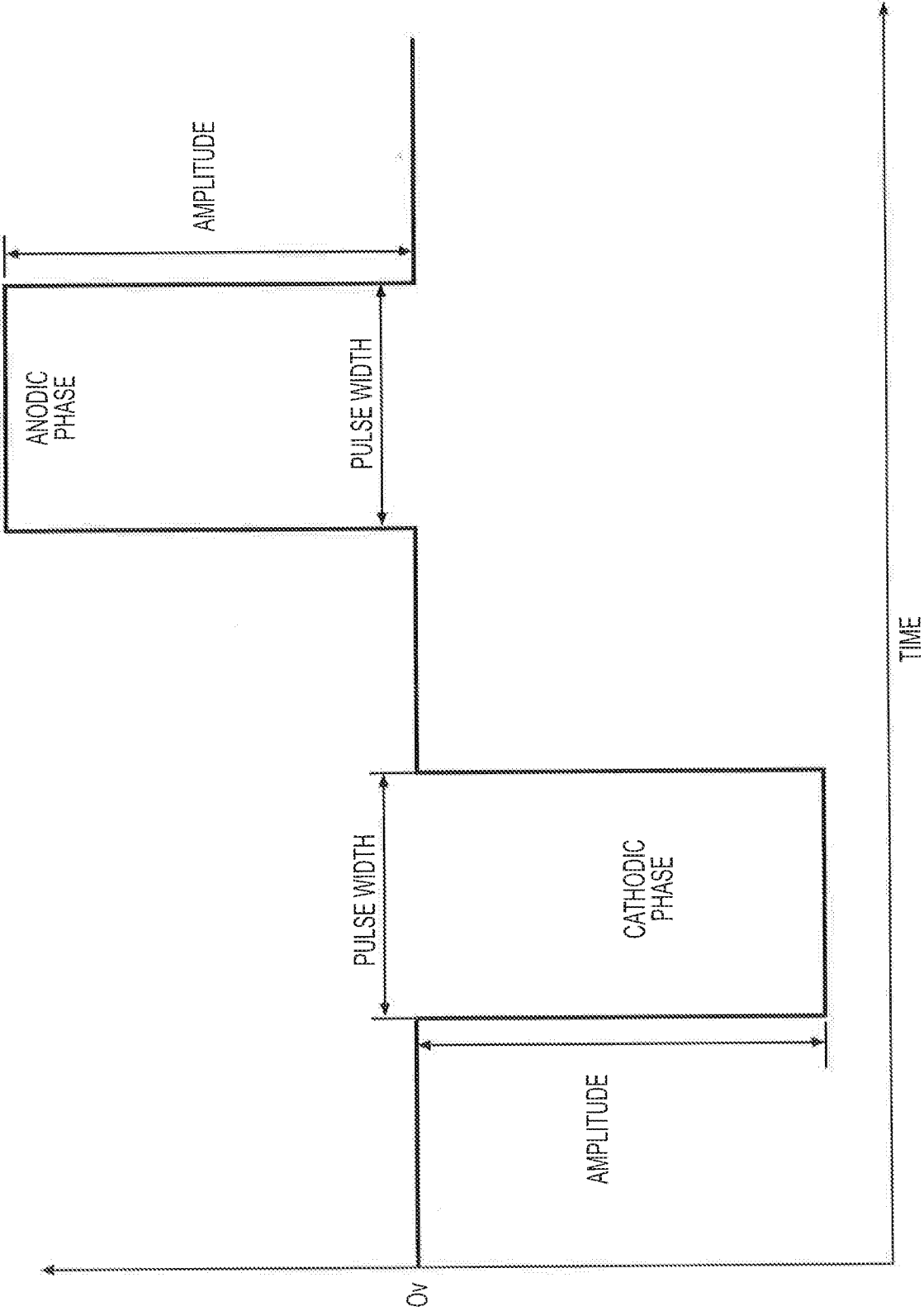


FIG. 5

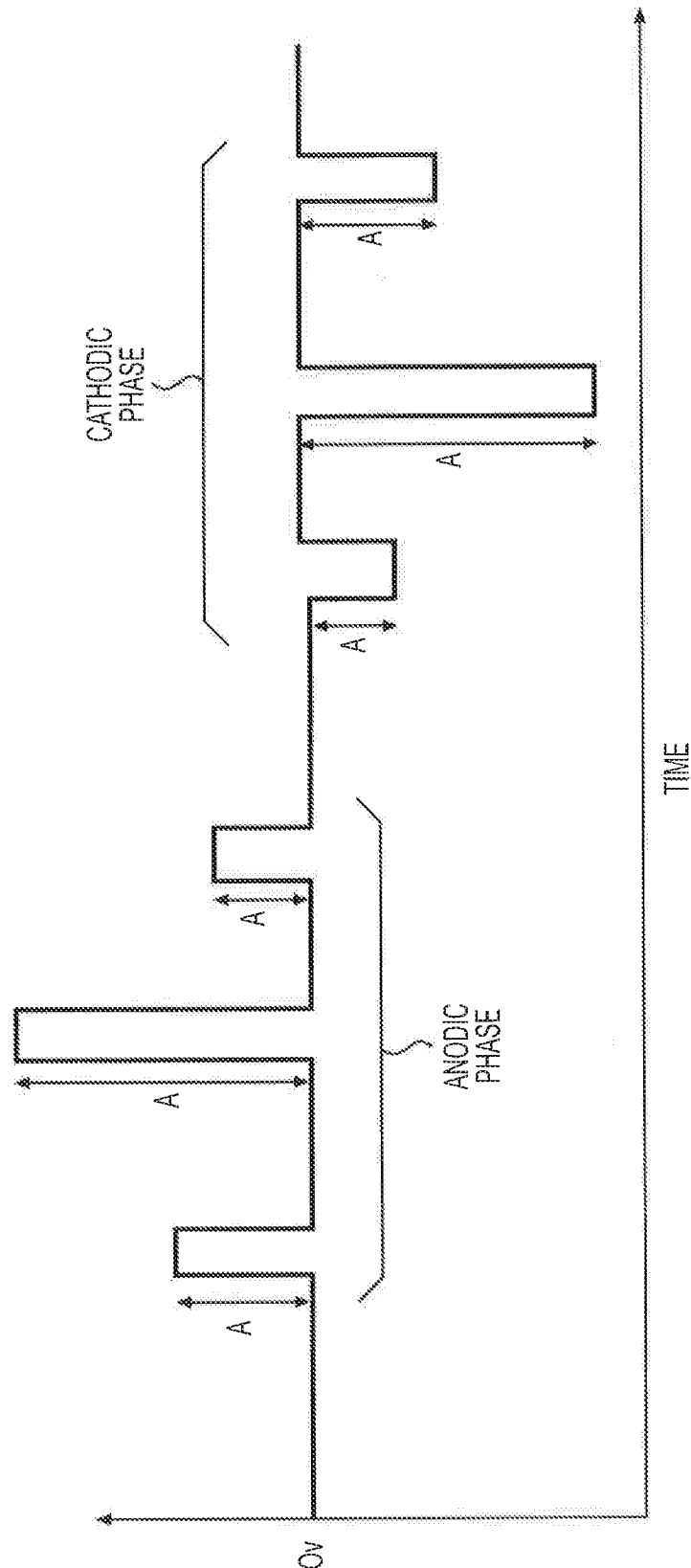
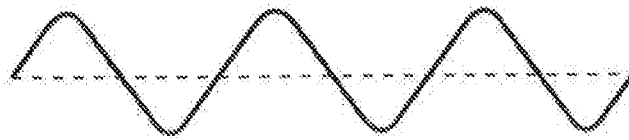
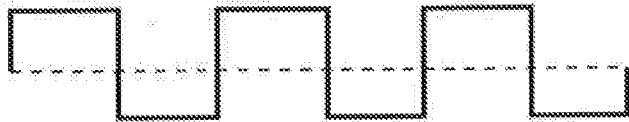


FIG. 6

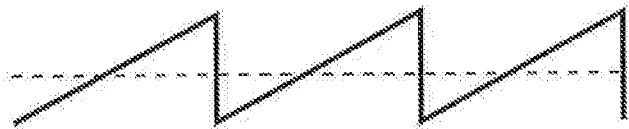
6 / 9



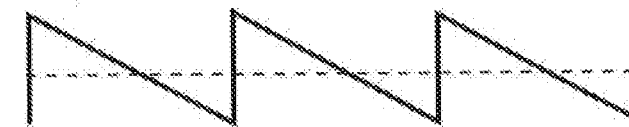
SINUSOIDAL



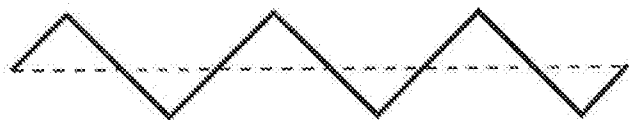
SQUARE



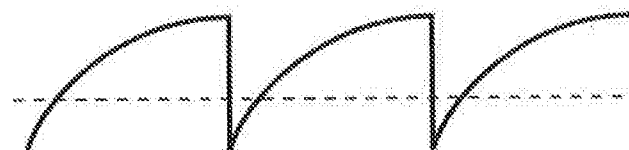
RAMP



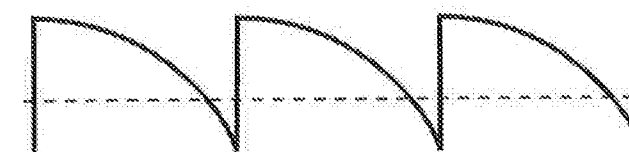
SAW TOOTH



TRIANGULAR

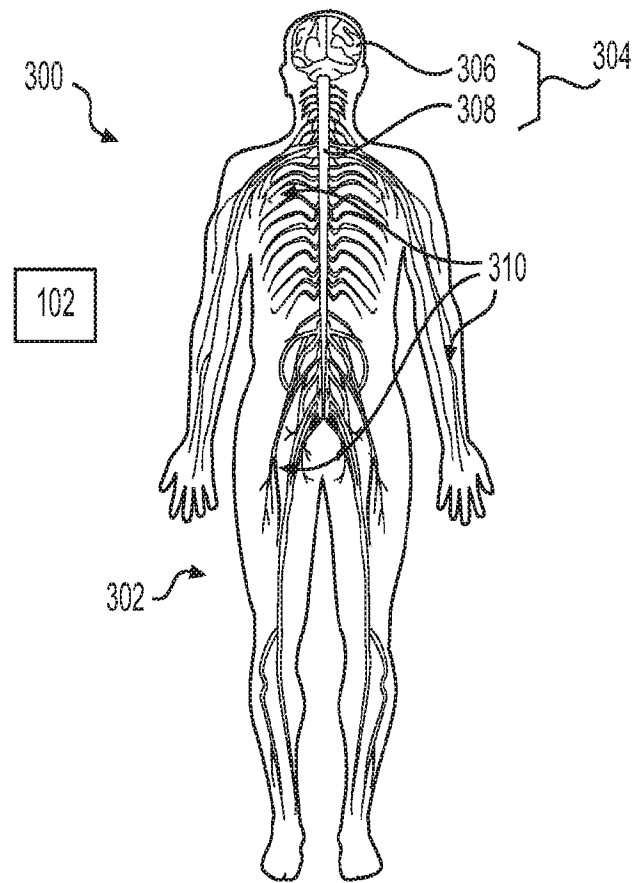
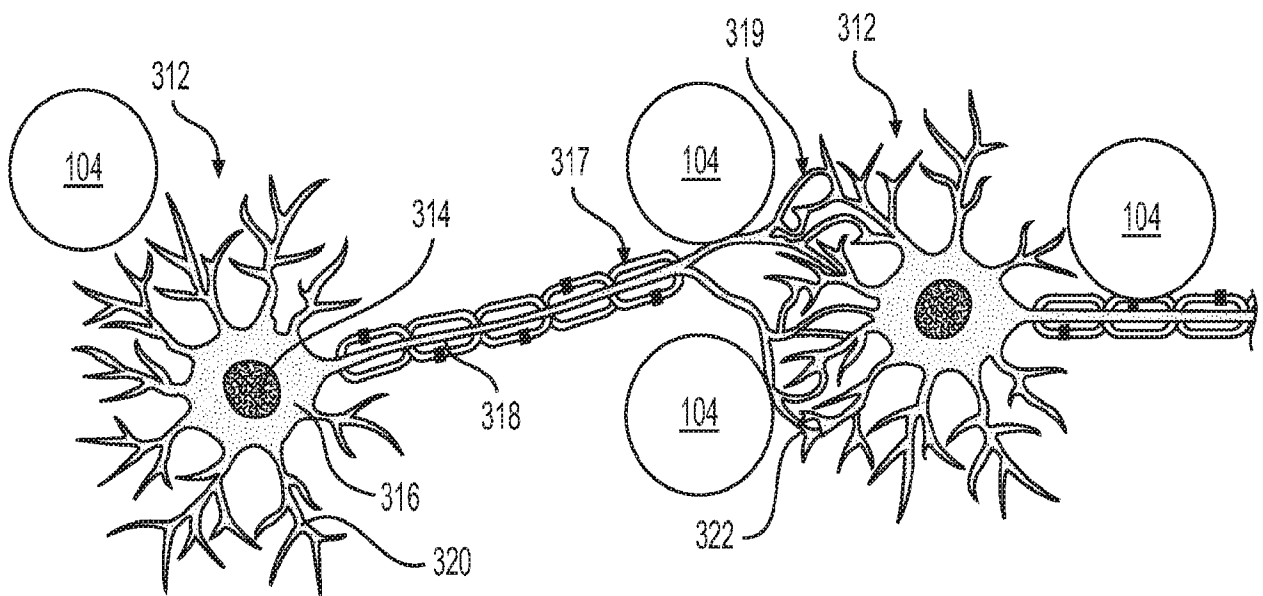


EXPONENTIAL
RISE



EXPONENTIAL
DECAY

FIG. 7

**FIG. 8****FIG. 9**

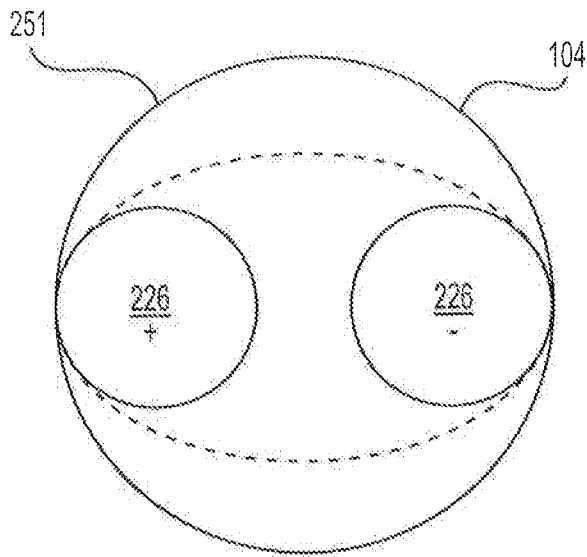


FIG. 10A

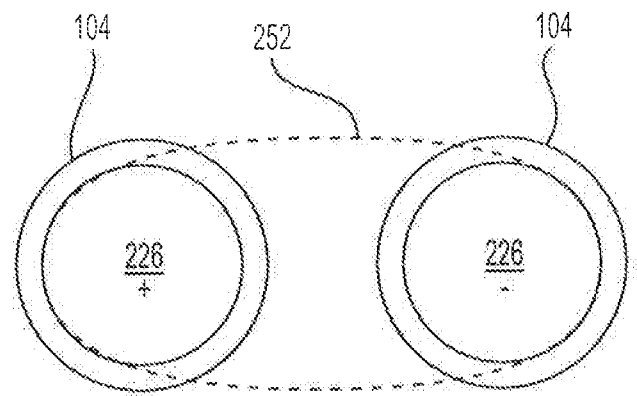


FIG. 10B

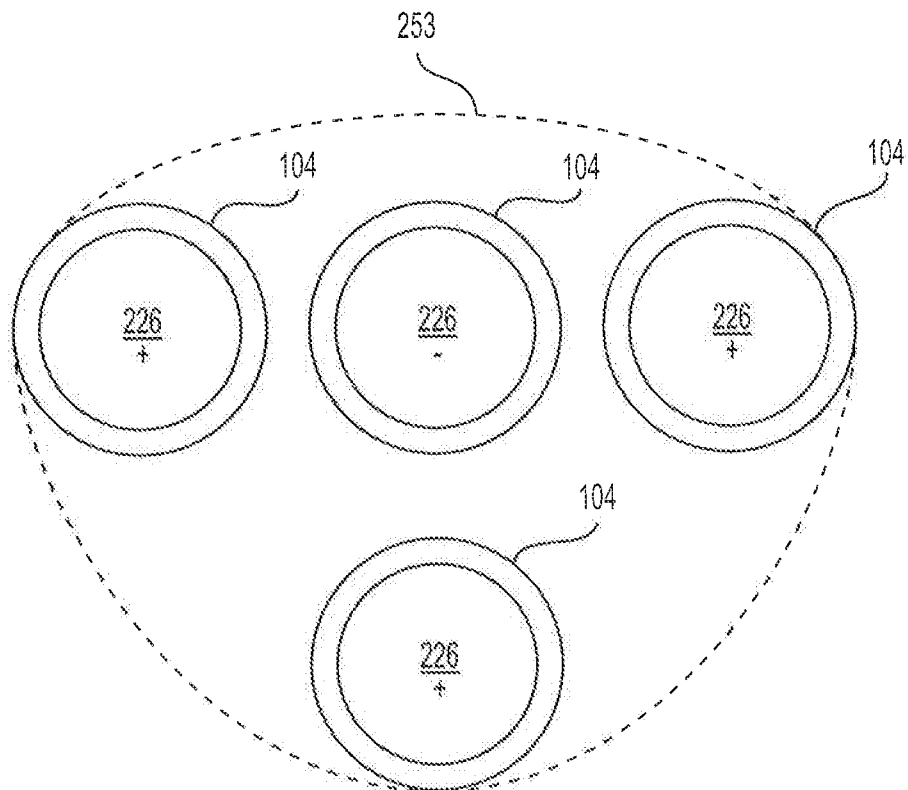
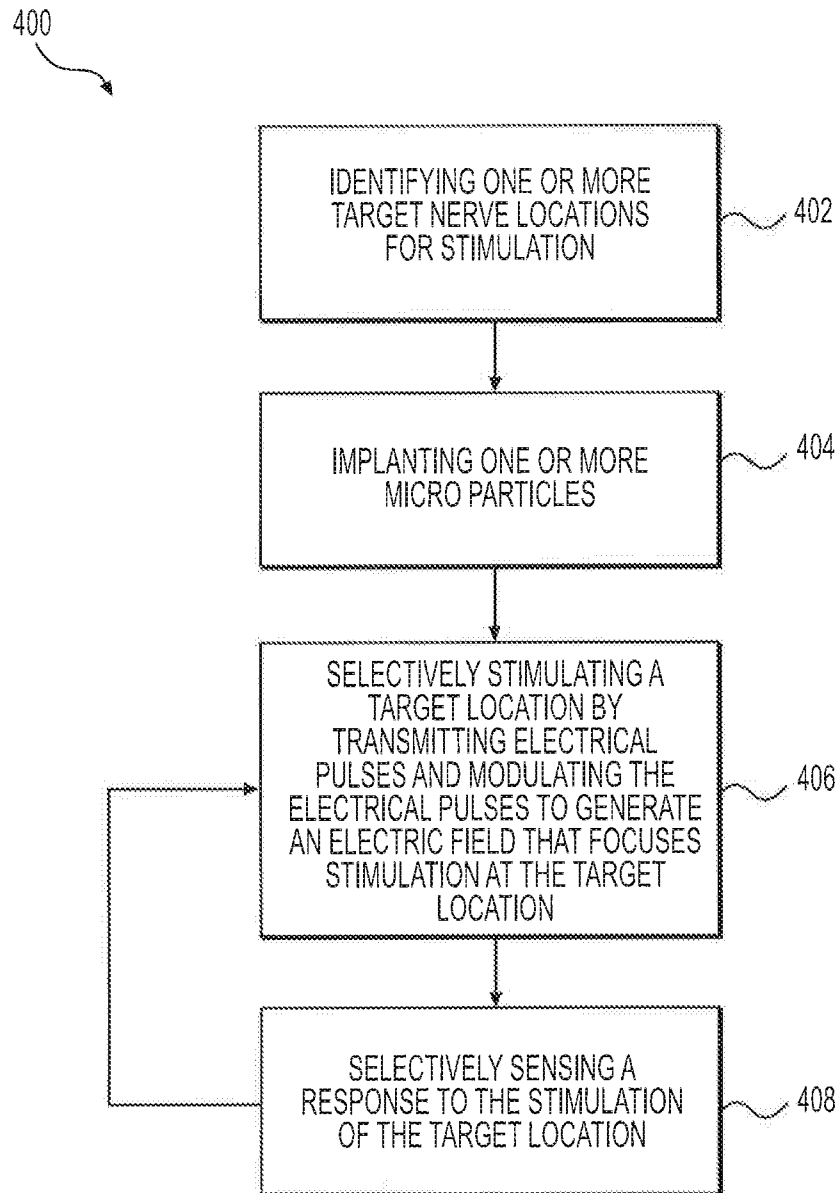


FIG. 10C

**FIG. 11**