



(51) International Patent Classification:

A61N 1/05 (2006.01) A61N 1/378 (2006.01)
A61N 1/36 (2006.01) A61B 5/04 (2006.01)
A61N 1/372 (2006.01)

(21) International Application Number:

PCT/US2017/018364

(22) International Filing Date:

17 February 2017 (17.02.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/296,306 17 February 2016 (17.02.2016) US

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(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:

— with international search report (Art. 21(3))

(54) Title: WIRELESS IMPLANT SYSTEMS FOR SENSING AND STIMULATING NERVES

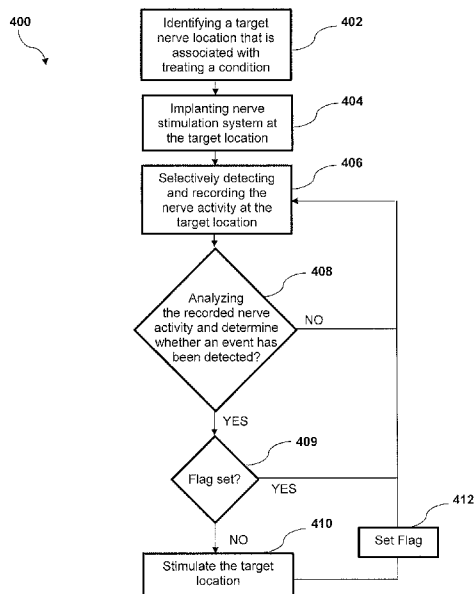


FIG. 9

(57) Abstract: A wireless implant system for neurostimulation is provided. The system may include a sensor configured to detect nerve activity of a nerve. The system may also include a stimulator comprising an electrode configured to transmit electrical pulses for stimulating the nerve. The system may further include a processor configured to interface with the sensor and the stimulator. The processor may be configured to analyze the nerve activity and determine whether an event has been detected, and if so, instruct the stimulator to stimulate the nerve.

WIRELESS IMPLANT SYSTEMS FOR SENSING AND STIMULATING NERVES**BACKGROUND****Related Applications**

[0001] This application claims priority to U.S. Provisional Application No. 62/296,306, filed February 17, 2016, which is incorporated herein by reference in the entirety.

Technical Field

[0002] The present disclosure relates generally to the field of neurostimulation, and more particularly, wireless implant systems for sensing and stimulating nerves.

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 electrical stimulation to treat different conditions, diseases, and injuries for many years. For example, nerve stimulator systems have been used to stimulate nerves of the peripheral nervous system to treat epilepsy, chronic pain, and other conditions. 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, current stimulators that time there stimulation at a fixed interval or stimulate on-demand may be limiting the therapeutic effect of treatments while potentially producing increased side effects. 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] In one aspect, the present disclosure is directed to a wireless implant system for neurostimulation of a nerve. The system may include a sensor configured to detect nerve activity of the nerve. The system may also include a stimulator comprising an electrode configured to transmit electrical pulses for stimulating the nerve. The system may also include a processor configured to interface with the sensor and the stimulator. The processor may be configured to analyze the nerve activity and determine whether an event has been detected, and if so, instruct the stimulator to stimulate the nerve.

[0005] In another aspect, the present disclosure is directed to a method of neurostimulation. The method may include identifying a target nerve location and implanting a neurostimulation system at the target location. The method may further include stimulating the target location if the event has been detected. In certain embodiments, the stimulation may have no therapeutic effect. For instance, the method may be used for the sole purpose of selectively detecting and recording nerve activity at the target location. The method may also be used for analyzing the recorded nerve activity and determining whether an event has been detected.

[0006] In another aspect, the present disclosure is directed to a wireless implant system for neurostimulation of a nerve. The system may include a sensor configured to detect nerve activity of the nerve. The system may also include a stimulator comprising an electrode configured to transmit electrical pulses for stimulating the nerve. The system may also include a processor that interfaces with the sensor and the stimulator. The system may further include a monolithic substrate on which the sensor, the stimulator, and the processor are formed. The processor may be configured to analyze the nerve activity and determine whether an event has been detected, and if the event has been detected, the processor is configured to instruct the stimulator to stimulate the nerve.

BRIEF DESCRIPTION OF DRAWINGS

[0007] Fig. 1 is an illustration of a nervous system of a human.

[0008] Fig. 2 is an illustration of a pair of neurons of the nervous system of Fig. 1.

[0009] Fig. 3 is a schematic of a neurostimulation system, according to an exemplary embodiment.

[0010] Figs. 4A, 4B, 4C, 4D, and 4E are pulse chart illustrations of different pulse widths, according to an exemplary embodiment.

[0011] Fig. 5 is a pulse chart illustration of different pulse polarities, according to an exemplary embodiment.

[0012] Fig. 6 is a pulse chart illustration of different pulse amplitudes, according to an exemplary embodiment.

[0013] Fig. 7 is a pulse chart illustration of different waveforms, according to an exemplary embodiment.

[0014] Fig. 8 is a flow chart illustrating a method of neuro stimulation, according to an exemplary embodiment.

[0015] Fig. 9 is a flow chart illustrating a method of neuro stimulation, according to an exemplary embodiment.

DETAILED DESCRIPTION

[0016] 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 or stimulate a nerve cell, for example, by inducing the flow of ions through the nerve cell membrane, which may trigger an action potential.

[0017] Fig. 1 shows an illustration of a nervous system 100 of a human subject 102. Nervous system 100 is made up of two main parts: the central nervous system 104, which includes the brain 106 and the spinal cord 108, and the peripheral nervous system 110, which includes the nerves that go from the spinal cord to the arms, hands, legs, and feet. The peripheral nervous system 110 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 104 from internal

organs or from external stimuli. The motor nervous system includes motor nerves that carry information from the central nervous system 104 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).

[0018] The nervous system 100 is made up of billions of nerve cells, which may also be referred herein as neurons. Fig. 2 is an illustration of two interconnected nerve cells 112, which may be part of a network of interconnected nerve cells. Nerve cell 112 on the left as illustrated may be characterized as the transmitting nerve cell while nerve cell 112 on the right may be characterized as the receiving nerve cell. Each nerve cell 112, as shown in the Fig. 2, may include among other things, a nucleus 114, a cell body 116, an axon 118, axon terminals 119 and dendrites 120. The dendrites 120 collect electrical signals while the cell body 116 and nucleus 114 integrates the incoming signals and transmits outgoing nerve signals down the axon 118 to the axon terminals 119. The axon 118 may be surrounded by a myelin sheath 117 that facilitates transmission of nerve pulses to the axon terminals 119. The axon terminals 119 may pass the outgoing signal to dendrites 120 of the receiving cell. The electrical signals may be transmitted from the transmitting cell to the receiving cell across one or more synapses 122.

[0019] 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 mV to -80 mV. A stimulation (e.g., a mechanical, electrical, or chemical) can cause a few sodium channels in a small portion of the membrane to open and the positive 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.

[0020] 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.

[0021] Neurostimulation has been used as a form of treatment for a variety of conditions. Some of these conditions include, for example, epilepsy, chronic pain, migraines, as well as other conditions. Most current nerve stimulators either stimulate the nerve on-demand (e.g., user initiated stimulation) or at a fixed interval. Some nerve stimulators use a sensor (e.g., accelerometer) to detect an episode (e.g., a seizure) and stimulate a nerve in response to the episode. Some other nerve stimulators use a sensor (e.g., ECG heart beat monitor) to determine when to stimulate. Although these treatment methods in some cases produce some positive benefits, the open loop or reactive nature of the control scheme may be less than optimal. The therapeutic benefit may be increased and/or the side effects may be decreased by improving the timing of the stimulation. For example, rather than stimulate a nerve at a fixed interval, on-

demand, or based on activity detected elsewhere in the body, the present disclosure describes an exemplary system and method for stimulating a nerve based on activity detected at the nerve.

[0022] Fig. 3 shows a neurostimulation system 300 for stimulating a nerve, according to an exemplary embodiment. System 300 may include a sensor 302, a stimulator 304, and a processor 306. Sensor 302 may be configured to monitor nerve activity of a nerve (e.g., 112). Stimulator 304 may be configured to stimulate the nerve and processor 306 may interface with sensor 302 and stimulator 304 and control the operation of system 300. In some embodiments, sensor 302, stimulator 304, and processor 306 may be formed on a monolithic substrate 308. In some embodiments, substrate 308, sensor 302, stimulator 304, and processor 306 may be an application specific integrated circuit (ASIC). The positioning of sensor 302, stimulator 304, and processor 306 on substrate 308 may vary. For example, sensor 302 and stimulator 304 may be formed on the inner surface of substrate 308 enabling direct contact or closer proximity to the nerve.

[0023] As shown in Fig. 3, substrate 308 may form a cuff-shape enabling system 300 to be wrapped around a nerve or portion of a nerve (e.g., an axon) when implanted, as shown in Fig. 2. In some embodiments substrate 308 may form another shape, for example, a partial cuff (e.g., half-cuff), a rectangle, square, sphere, or the like. In some embodiments, sensor 302, stimulator 304, and processor 306 may be located on one or more micro particles. In some embodiments, sensor 302 and stimulator 304 may be housed on separate substrates, which may be operably connected.

[0024] Sensor 302 may include one or more electrodes 310 positioned at one or more locations about substrate 308. Although the following description references just a single electrode 310, it is understood that it is equally applicable to a sensor 302 having multiple electrodes 310. Electrode 310 may be configured to monitor nerve activity at a nerve including, for example, chemical nerve activity, electrical nerve activity, or both. In some embodiments, sensor 302 may have one or more electrodes 310 for monitoring chemical nerve activity and one or more electrodes 310 for monitoring electrical nerve activity.

[0025] In some embodiments, sensor 302 may include additional types of sensing devices for monitoring nerve activity or other body activity. For example, in some embodiments, sensor 302 may include an accelerometer configured to detect certain body actions (e.g., seizures) or body positions.

[0026] Electrode 310 of sensor 302 may monitor electrical nerve activity by detecting and recording electrical nerve signals generated, transmitted, or received along the nerve structure (e.g., axon, axon, terminal, dendrites, etc.). System 300 may be configured such that electrode 310 may detect and record electrical nerve signals for a defined period, at a defined sample rate, and at a defined interval. For example, electrode 310 may detect and record electrical nerve signals for a period of 10 seconds at a sample rate of 1,000 samples per second at an interval of once every hour. The period, the sample rate, and the interval may all be varied. For example, the period may range from about 0.1 seconds to about 10 seconds if the primary objective is detecting action potentials, to about 1 second to about 60 seconds if the primary objective is measuring lower-frequency content on the nerve fibers. The sample rate may range, for example, from about 120 per second to about 10,000 per second depending on the frequency content of activity that is being detected. The interval may range, for example, from about 1 minute to about 1 hour, with the tradeoff being power consumption vs accuracy (e.g., probability of detecting an event). The nature of this tradeoff may depend on the precise nature of the event being detected.

[0027] Electrode 310 may monitor chemical nerve activity by detecting and recording the presence of a chemical at the nerve. For example, electrode 310 may be surface treated to be sensitive to the presence of one or more chemicals (e.g., dopamine or serotonin) such that the impedance of electrode 310 changes based on the presence of the chemical at the electrode. Thus, the presence of a chemical may be detected based on the change of the impedance of electrode 310. Like detecting the electrical nerve activity, system 300 may be configured such that electrode 310 may detect and record chemical nerve signals for a defined period, at a defined sample rate, and at a defined interval. The same ranges defined above for the period, the sample rate, and the interval are all applicable to detecting and recording of the chemical nerve activity as well.

[0028] Stimulator 304 may include one or more electrodes 312 for stimulating the nerve by transmitting electrical pulses (e.g., input current or voltage pulses) that excite the nerve by inducing a flow of ions through the nerve cell membrane. In some embodiments the electrode 312 may function as a cathode (i.e., negative electrode), an anode (i.e., positive electrode), or both (i.e., switch between). Embodiments where stimulator 304 includes multiple electrodes 312, one electrode may function as a cathode and another electrode may function as an anode. Electrode 312 of stimulator 304 when instructed to stimulate may transmit electrical pulses for a defined period have defined parameters. The defined period and the parameters of the electrical pulses may vary. For example, the defined period of stimulation may range from about 0.1 seconds to about 1 second, about 1 second to about 10 seconds, about 10 seconds to about 60 seconds, about 1 minute to about 5 minutes, about 5 minutes to about 10 minutes, or about 10 minutes or more. The electrical pulses parameters and how they may be varied will be discussed in further detail below.

[0029] Processor 306 may interface with sensor 302 and stimulator 304 and be configured to process, for example, data, instructions, protocols, configurations, and the like. For example, processor 306 may record the nerve activity detected by sensor 302 and based on the nerve activity determine computationally whether to stimulate the nerve via stimulator 304. For example, processor 306 may input the recorded data in an algorithm that detects whether an “event” has occurred, and if an event has occurred system 300 may stimulate the nerve via stimulator 304. The process of detecting an event and stimulating the nerve is discussed in further detail below.

[0030] Processor 306 may include one or more processors. In addition to processor 306, system may also include additional components, for example, non-volatile memory (e.g., a flash memory), volatile memory (e.g., a random access memory (RAM)), and other like components, configured to store information (e.g., data, program instructions, protocols, configurations, and the like) to enable the operation of system 300.

[0031] In some embodiments, operation of system 300 may be automatic after implantation. In other words, system 300 may operate without external input or control. In some embodiments, system 300 may include a communication circuit 314 configured

to enable transmitting and/or receiving of informational signals to and/or from a remote device, which may function as a controller. In some embodiments, system 300 may still operate automatically and communication circuit 314 may be configured just for transmitting data to the remote device enabling monitoring of the operation. In some embodiments, communication circuit 314 may be configured to transmit and receive data, for example, the recorded nerve activity and instructions for stimulating respectively. Thus, in some embodiments, system 300 may transmit the recorded nerve activity to a remote device that can determine computationally whether to stimulate the nerve and if it is determined that the nerve should be stimulated then the remote device can send an instruction to system 300 to stimulate.

[0032] Communication circuit 314 may be configured for wireless communication. Communication circuit 314 may utilize a variety of wireless data transmission methods for communication. For example, in some embodiments, communication circuit 314 may utilize radio data transmission, BLUETOOTH®, near field communication (NFC), infrared data transmission, electromagnetic induction transmission, and/or other suitable electromagnetic, acoustic, or optical transmission methods. Communication circuit 314 may include a number of components to enable and support wireless communication such as a data encoder, a data decoder, a transmitter and a receiver or a transceiver, and/or an antenna.

[0033] In some embodiments, system 300 may be locally powered by an onboard battery or other power storage device (e.g., a capacitor). In some embodiments, system 300 may be wirelessly powered or the onboard battery or power storage device may be wirelessly recharged. System 300 may be wirelessly powered or recharged using wireless energy transmission. In some embodiments, system 300 may utilize, for example, inductive coupling, resonant inductive coupling, radio frequency (RF) link, or the like to wirelessly transmit energy from a remote device to system 300.

[0034] As described herein, stimulator 304 may stimulate the nerve via electrode 312 by transmitting electrical pulses. Processor 306 may determine when to stimulate, the period of stimulation, and the parameters of the electrical pulses. The parameters of the electrical pulses defined by processor 306 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). Processor 306 may define or manipulate one or more of the electrical pulses parameters.

[0035] In some embodiments, the pulse width or the pulse duration of the electrical pulses transmitted by electrode 312 may be controlled. For example, Figs. 4A-4E show 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.

[0036] In some embodiments, the polarity of the electrical pulses (i.e., the pulse polarity) transmitted by electrode 312 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.

[0037] In some embodiments, the amplitude of the electrical pulses (i.e., the pulse amplitude A) transmitted by electrode 312 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 current both above and below zero mA producing an anodic phase pulse and cathodic phase pulse. The amplitude of the current may vary, for example, from about 100 μ A to 5 mA. The range of amplitude or power by which electrode 312 may stimulate a nerve cell may be less than that of the current electrodes, which may reduce the risk of injury or atrophy to the nerve cell and surrounding tissue.

[0038] In some embodiments, the frequency of the electrical pulses (e.g., interval between pulses) transmitted by electrode 312 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.

[0039] 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 electrode 312 may also be controlled. Fig. 7 shows a variety of different waveforms, which electrode 312 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.

[0040] The electrical pulses effectiveness in triggering an action potential may depend on the characteristics of the electrical pulses (i.e., the set of parameters). This is because different types of nerve cells and different portions of nerves cells have different levels of sensitivity to electrical pulse stimulation, which may depend on the parameters of the electrical pulses.

[0041] System 300 may vary in size. In some embodiments, for example, the average diameter of system 300 may be about 500 microns to about 5 mm, depending on the diameter of the nerve. The minimal size of system 300 will significantly reduce the likelihood of trauma compared to the larger prior art electrodes currently utilized. The size of system 300 may also enable more precise and refined placement with respect to the nerve structure compared to other electrodes that are an order of magnitude larger. System 300 may be positioned more precisely in order to sense and stimulate a specific nerve cell or portion of a nerve cell.

[0042] More refined placement of system 300, which advantageously enables more refined sensing and targeting of stimulation 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.

[0043] System 300 as described herein may be utilized to perform a variety of neurostimulation treatment methods for treating various conditions. Methods of utilizing system 300 and the operation of system 300 will now be explained with reference to Figs. 8 and 9.

[0044] According to an exemplary embodiment, system 300 may be utilized to perform a method 400 of neurostimulation. In some embodiments, method 400 may constitute a therapeutic treatment. Method 400 may include identifying a target nerve location associated with treating the condition at step 402. 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.

[0045] Next, step 404 of method 400 may include implanting system 300 into the patient at the target location. In some embodiments, this may include installing the substrate 308 around a nerve fiber or axon of a nerve. In some embodiments, implanting of system 300 may be aided by imaging guidance. For example, a magnetic resonance (MR) imaging system may be used to provide real-time visual feedback during the implantation of system 300.

[0046] In some embodiments, a plurality of target nerve locations may be identified at step 402, which are associated with treating a condition and thus a plurality of systems 300 may be implanted into the patient at the target locations.

[0047] The one or more 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.

[0048] In some embodiments, prior to implanting system 300, method 400 may include initiating a startup of system 300, which may include powering up system 300 and testing the operation including, for example, wireless powering or wireless communication if included as part of system 300. In some embodiments, powering up of system 300 and testing of the wireless communication (i.e., startup) may be conducted after implantation.

[0049] Once system 300 has been implanted, at step 406, method 400 may begin selectively detecting and recording nerve activity at the target location. Detecting the nerve activity may include detecting the chemical nerve activity and/or the electrical nerve activity. As described herein, the nerve activity may be detected and recorded for a defined period, at a defined sample rate, at a defined interval. For example, nerve activity may be detected and recorded for 10 seconds at a sample rate of 1000 samples per second at an interval of 10 minutes.

[0050] As described herein, system 300 may detect the chemical nerve activity by detecting the presence and/or quantity of a chemical at electrode 310 of sensor 302. Electrode 310 may be configured to be sensitive to the chemical. For example, electrode 310 may be surface treated to be sensitive to the chemical such that the impedance at the electrode changes based on the presence and/or quantity of chemical at the electrode. System 300 may be configured to use cyclical telemetry to detect the impedance changes and identify the presence and/or quantity of the chemical. Electrode 310 may be configured to be sensitive to a variety of chemicals, for example, dopamine, serotonin, or other organic chemicals, which may be present at a nerve.

[0051] As described herein, system 300 may also detect and record the electrical nerve activity of the target location (e.g., nerve) using sensor 302. Electrical nerve activity may be detected and recorded for a defined period, at a defined sample rate, and at a defined interval. For example, nerve activity may be detected and recorded for 10 seconds at a sample rate of 1000 samples per second at an interval of 10 minutes. The period, the sample rate, and/or the interval may all be varied. Between intervals, system 300 may be configured to enter a sleep mode to reduce power consumption and prolong battery life or reduce recharging frequency.

[0052] The electrical nerve activity may include lower-frequency content (e.g., waves) and higher-frequency content (e.g., action potential spikes). Processor 306 may be configured to filter the higher-frequency content and the lower-frequency content enabling the spikes to be identified and counted. For example, processor 306 may compute a spike per second value, which may be characterized as the “activity” of the nerve and a primary metric. Processor 306 may also compute sub-metrics based on the primary metric. For example, processor 306 may compute minimum and maximum values for the “activity” of the nerve. Processor 306 may also compute derivative values associated with the “activity” of the nerve. For example, in addition to computing the minimum and maximum number of action potentials, processor 306 may also compute or identify the magnitude of the action potentials, the duration between action potentials, or a pattern of the action potentials. Processor 306 may compute the average or the standard deviation for any or all of the different values.

[0053] Sensor 302 may also be configured to detect and record the local field potential, which is the electrophysiological signal generated by the summed electrical current flowing from the nerve and nearby nerves within the proximate area of the nerve tissue. Voltage may be produced across the area by the action potentials of the nerves and the voltage may vary based on the “activity” of the nerves. It has been observed in some types of nerves that the local field potential may synchronize nerve activity between adjacent nerves. This may enable specific patterns and coordination of action potential timing.

[0054] Following initial implantation and startup, system 300 may stay detecting and recording (i.e., step 406), and storing the data for an initialization period in order to collect an initial data set sufficient for evaluation. The initialization period may be adjustable. In some embodiments, the initialization period may be 1 hour, 12 hours, 24 hours, or more.

[0055] Following the completion of the initialization period, system 300 may proceed to step 408 and begin analyzing the recorded nerve activity to determine whether to stimulate the nerve. The determination of whether to stimulate the nerve may be based on whether one or more definable events have been detected. In some embodiments, processor 306 may determine (e.g., compute) whether an event has

been detected in the nerve by running the recorded data through an algorithm. In some embodiments, a remote device may receive the recorded data from system 300 and run the recorded data through the algorithm to determine whether and event has been detected.

[0056] A variety of different events may be defined based on different types of nerve activity. For example, events may be defined based on the chemical nerve activity, the electrical nerve activity, or a combination of both.

[0057] An event may be defined, for example, because a specific nerve activity has been identified to correspond with an optimal time for stimulating the nerve. The nerve activity corresponding with an optimal time for stimulating the nerve may be identified, for example, by analyzing a patient's recorded nerve activity history, timing of prior stimulations and the therapeutic effect and/or side effects of the stimulations. In some embodiments, an optimal time for stimulating may constitute a time at which the therapeutic effect is identified to be increased or maximized. In some embodiments, an optimal time for stimulating may constitute a time at which the side effects are identified to be decreased or minimized. In some embodiments, an optimal time for stimulating may be identified as a time at which the therapeutic effect is maximized and the side effects are minimized. In some embodiments, certain therapeutic effects are observed at certain times of day or correspond with specific (e.g., heightened or lessened) nerve activity.

[0058] Events defined based on the chemical nerve activity may include, for example, the detected presence of a chemical, the detected absence of a chemical, or the detected presence of a chemical above or below a certain threshold. Other events defined by the chemical nerve activity may also be defined.

[0059] A variety of events may be defined by the electrical nerve activity. For example, nerve activity (e.g., the spike rate) above or below a certain threshold may be defined as an event. In some embodiments, the magnitude or peak of the nerve activity may be defined as an event. In some embodiments, the magnitude or the frequency of the local field potential above or below a certain threshold may be defined as an event. It may also be possible to define the event as a high or low threshold of power in a given spectral envelope (e.g. 10-50 Hz, or 1000-5000 Hz). Furthermore, machine

learning may be used over time in conjunction with external measurements of therapeutic efficacy to trigger events based on specific patterns of activity (or specific patterns of action potentials) which are learned to be associated with improved therapeutic effects.

[0060] In some embodiments, an event may be defined based on a specific chemical nerve activity, a specific electrical nerve activity, or both. For example, an event may be defined as the presence of a chemical when the spike count is above a certain threshold, the absence of a chemical when the spike count is above or below a certain threshold, or the presence of a chemical above a certain threshold when the spike count is about a certain threshold.

[0061] A variety of factors may be considered when defining an event. For example, whether the target location is a nerve cell or a portion of a nerve cell, or whether the nerve cell is unipolar, multipolar, or bipolar may be considered when defining an event. In some embodiments, whether the target location is a motor nerve, sensory nerve, or autonomic nerve may be considered when defining an event. In some embodiments, whether the target location is part of the central nervous system or the peripheral nervous system may be considered. In some embodiments, the patient's condition being treated, or the physiology of the patient may also be considered. In some embodiments, processor 306 may update an event based on the detected and recorded nerve activity.

[0062] At step 408, after analyzing the nerve activity day, if no event is detected then system 300 may return to step 406 and continue detecting and recording the nerve activity at the defined interval. In between intervals, system 300 may be configured to sleep or hibernate in order to conserve power.

[0063] If an event is detected at step 408, then system 300 may proceed to step 410 and stimulate the target location (e.g., the nerve). In some embodiments, the stimulation (i.e., the duration and parameters of the electrical pulses) may be the same regardless of the event detected. In some embodiments, the stimulation (i.e., the duration and parameters) may vary depending on the event detected. For example, for an event associated with the chemical nerve activity the stimulation may be different than for an event associated with the electrical nerve activity.

[0064] In some embodiments, rather than processor 306 automatically triggering stimulation via stimulator 304 (i.e., proceeding to step 410) when an event is detected at step 408, processor 306 may instead transmit a signal via communication circuit 314 to a remote device, which may alert the patient to trigger the stimulation. Then the patient may trigger the stimulation utilizing the remote device.

[0065] In some embodiments, method 400 may be configured to limit the number of stimulations during a defined period. For example, as shown in Fig. 9, in some embodiments, method 400 may include a step 412 that sets a flag status after stimulation at step 410 and a step 409, which checks the flag status before stimulation. As a result, after stimulation occurs at step 410, the flag is set at step 412 preventing any further stimulation until the flag is cleared. System 300 and method 400 may be configured to clear the flag at a defined interval. For example, the flag may be cleared every 1 hour, every 6 hours, every 12 hours, or every 24 hours.

[0066] In some embodiments, system 300 may also be configured to receive input (e.g., biomarker data) from another sensor or external device and based on the data update what defines the event, the flag clearing interval, or the duration or parameters of the stimulation electrical pulses. For example, cytokine measurements from blood analysis may be an input biomarker that may be used to update what defines an event of the flag clearing interval.

[0067] Method 400 and system 300 as described herein may be used in a variety of ways to therapeutically treat different conditions. Although the present disclosure describes the use of system 300 and the corresponding methods primarily in reference to human patients, it is understood that system 300 and the corresponding methods may be employed with animals as well.

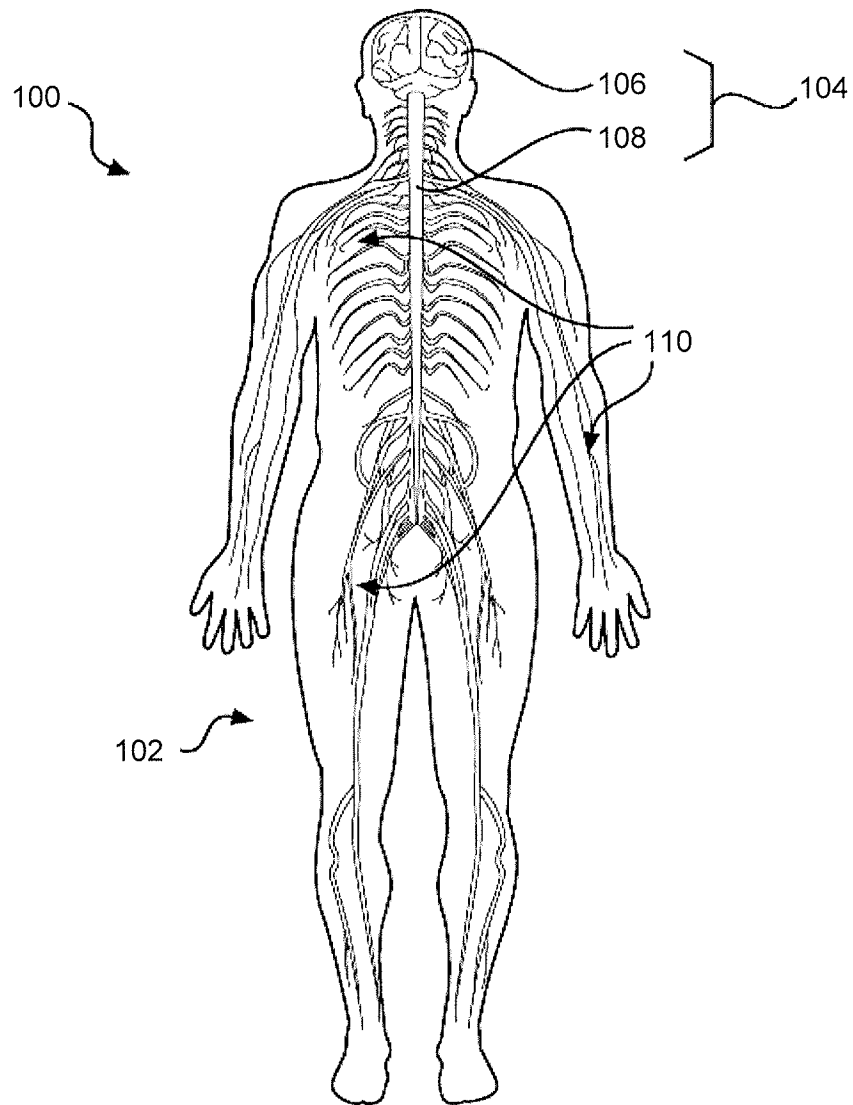
CLAIMS

1. A wireless implant system for neurostimulation of a nerve, comprising:
 - a sensor configured to detect nerve activity of the nerve;
 - a stimulator comprising an electrode configured to transmit electrical pulses for stimulating the nerve; and
 - a processor configured to interface with the sensor and the stimulator;wherein the processor is configured to analyze the nerve activity and determine whether an event has been detected, and if so, instruct the stimulator to stimulate the nerve.
2. The system of claim 1, wherein the nerve activity detected is electrical nerve activity.
3. The system of claim 1, wherein the nerve activity detected is chemical nerve activity.
4. The system of claim 3, where the chemical nerve activity is the presence of at least one of dopamine and serotonin.
5. The system of any of claims 2 to 4, wherein the sensor, the stimulator, and the processor are formed on a monolithic substrate as an integrated circuit.
6. The system of claim 5, wherein the substrate forms a cuff that is configured to be installed around one or more fibers of the nerve.
7. The system of any of claims 1 to 6, wherein the system is configured to be powered wirelessly via wireless energy transmission from a remote source.
8. The system of any of claims 1 to 7, further comprising a communication circuit configured to wirelessly communicate with a remote device.

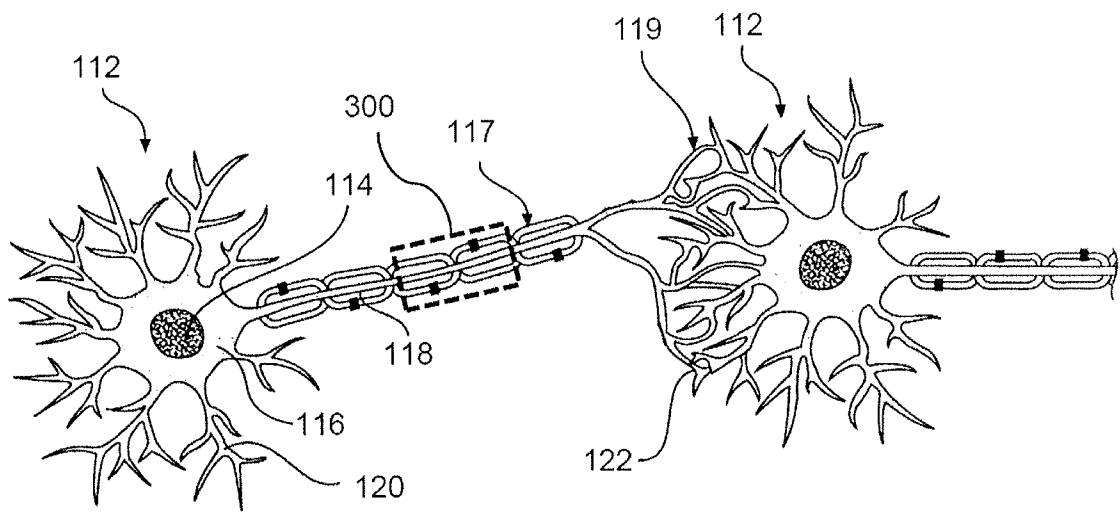
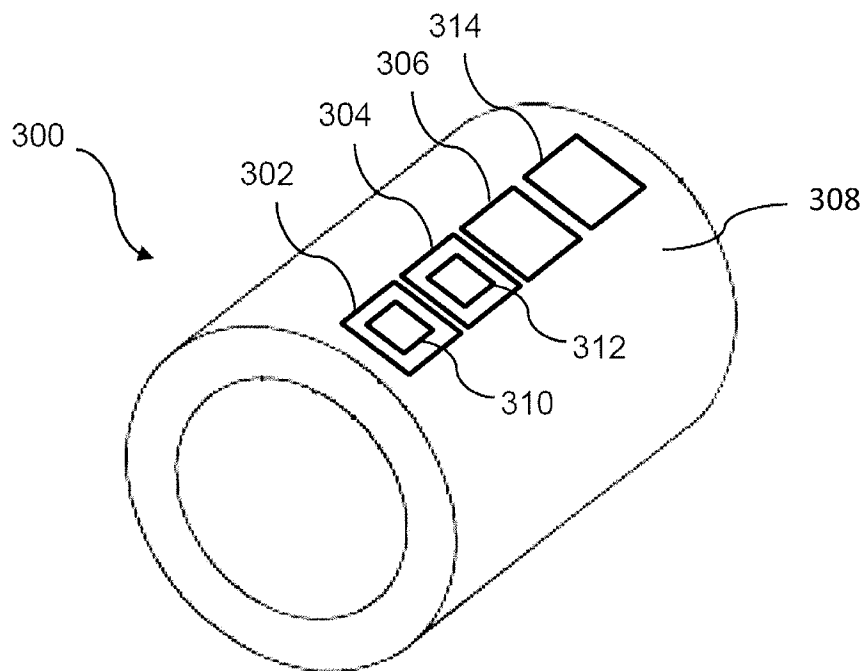
9. The system of claim 8, wherein the processor is configured to transmit information about the nerve activity to the remote device via the communication circuit.
10. The system of any of claims 1 to 9, wherein the event is defined by a specific nerve activity.
11. The system of any of claims 1 to 7 and 10, further comprising a communication circuit configured to wirelessly communicate with a remote device, wherein the processor is further configured to send an alert via the communication circuit to the remote device when an event has been detected and it is time to stimulate the nerve.
12. The system of any of claims 1 to 11, wherein the event is defined to correspond with an optimal time to stimulate the nerve.
13. The system of claim 12, wherein an optimal time to stimulate the nerve is when it increases the therapeutic effect or decreases the side effect.
14. A method of neurostimulation, comprising:
 - identifying a target nerve location;
 - implanting a neurostimulation system at the target location;
 - selectively detecting and recording nerve activity at the target location;
 - analyzing the recorded nerve activity and determining whether an event has been detected; and
 - stimulating the target location if the event has been detected.
15. The method of claim 14, wherein the event is defined to correspond with an optimal time to stimulate the nerve.
16. The method of claim 15, wherein an optimal time to stimulate the nerve is when it increases the therapeutic effects or decreases the side effects.

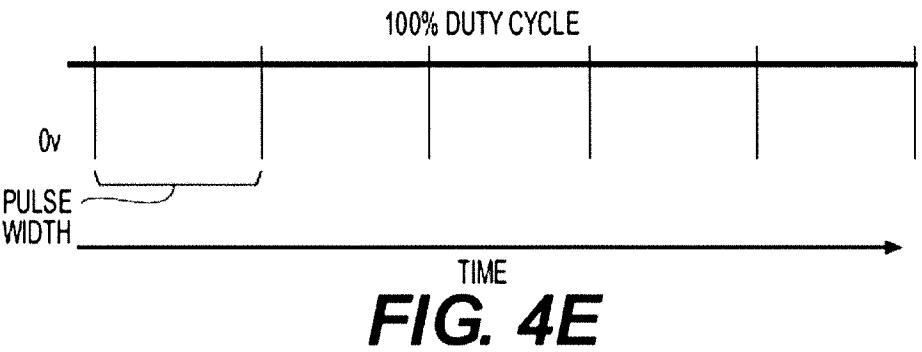
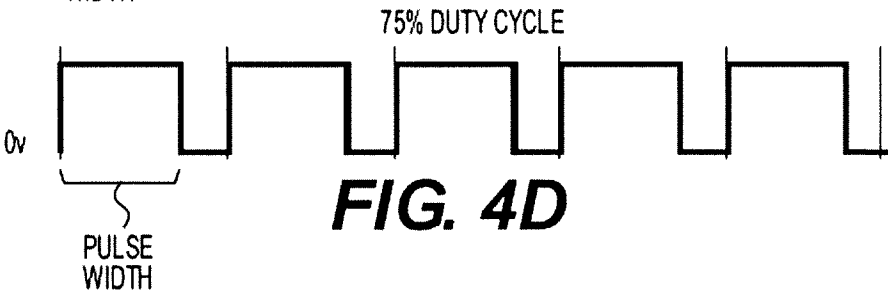
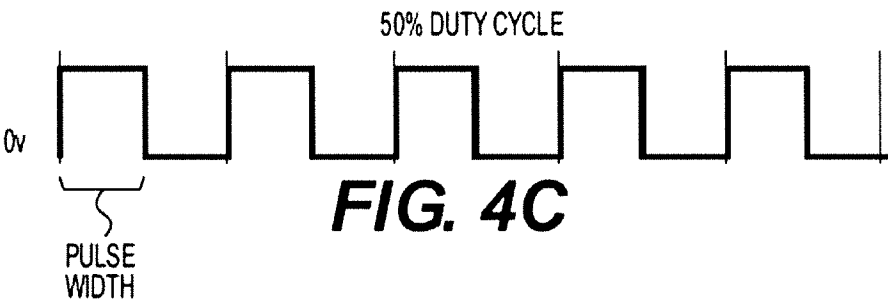
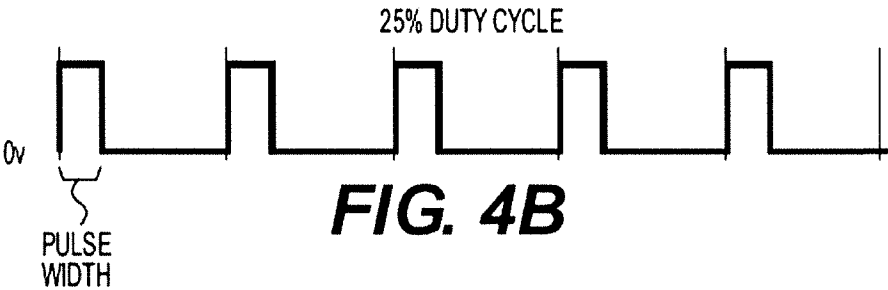
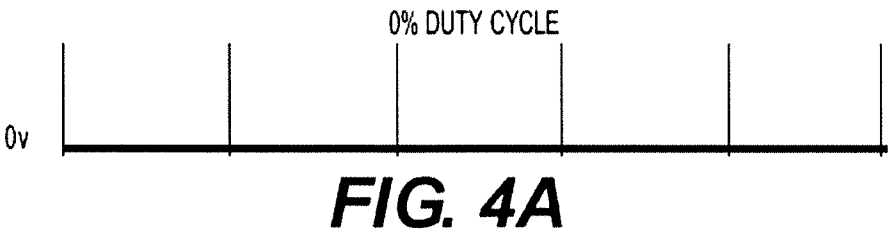
17. The method of any of claims 14 to 16, wherein the nerve activity is chemical nerve activity or electrical nerve activity.
18. The method of any of claims 14 to 17, further comprising transmitting the recorded nerve activity to a remote device, wherein the analyzing of the recorded nerve activity is performed by the remote device.
19. The method of any of claims 14 to 18, further comprising transmitting of a signal to a remote device when the event has been detected, which alerts a patient it is time to stimulate and the patient controls the stimulation.
20. A wireless implant system for neurostimulation of a nerve, comprising:
a sensor configured to detect nerve activity of the nerve;
a stimulator comprising an electrode configured to transmit electrical pulses for stimulating the nerve; and
a processor that interfaces with the sensor and the stimulator; and
a monolithic substrate on which the sensor, the stimulator, and the processor are formed;
wherein the processor is configured to analyze the nerve activity and determine whether an event has been detected, and
if the event has been detected, the processor is configured to instruct the stimulator to stimulate the nerve.

1/8

**FIG. 1**

2/8

**FIG. 2****FIG. 3**



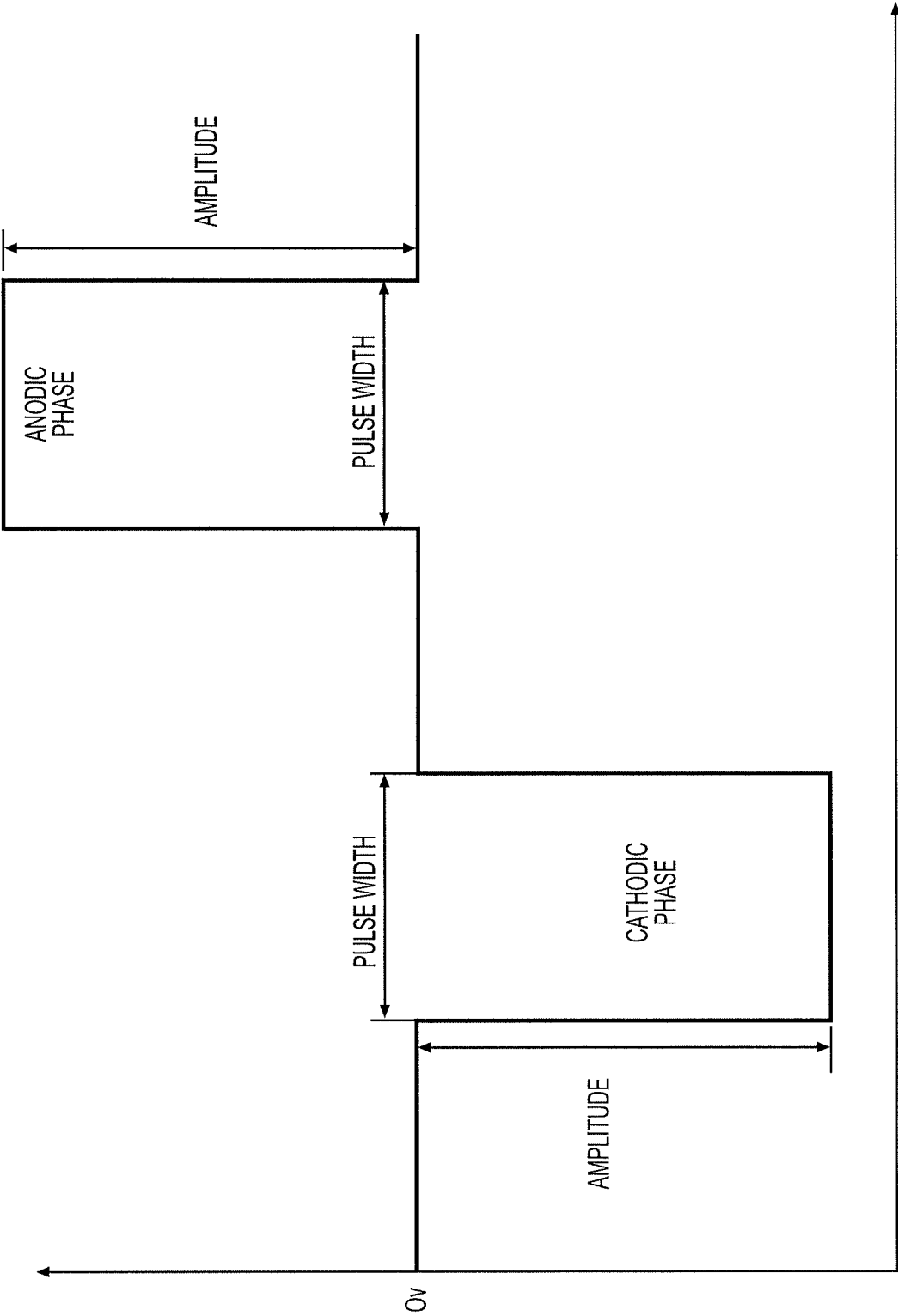


FIG. 5

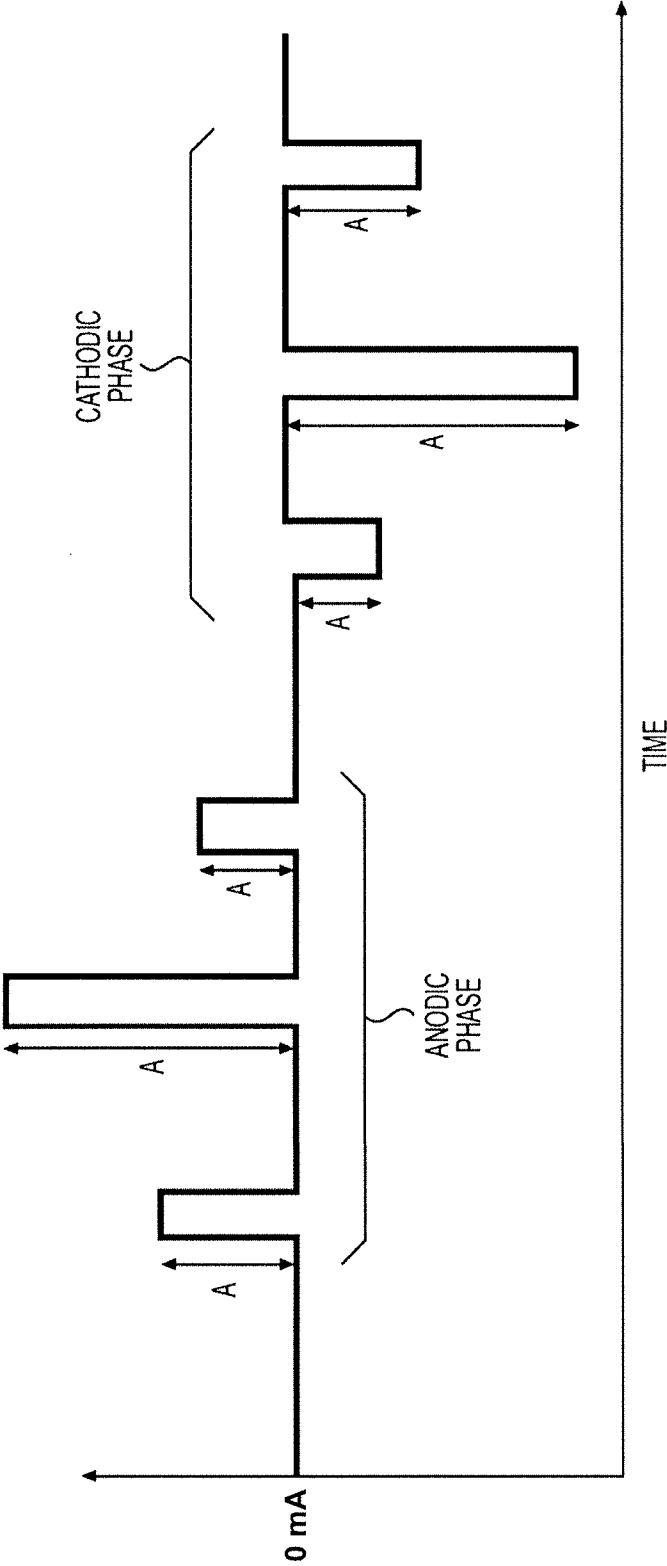
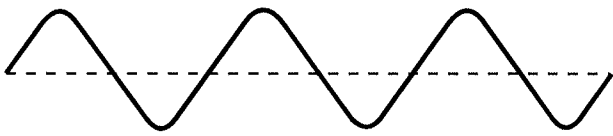
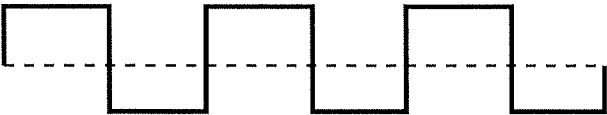


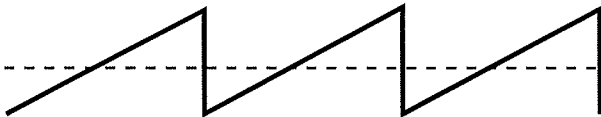
FIG. 6



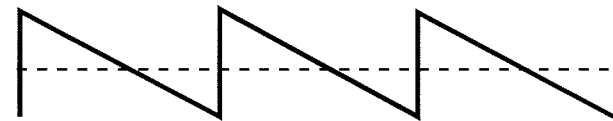
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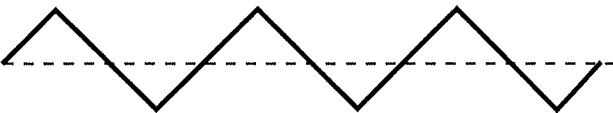
SQUARE



RAMP



SAW TOOTH



TRIANGULAR



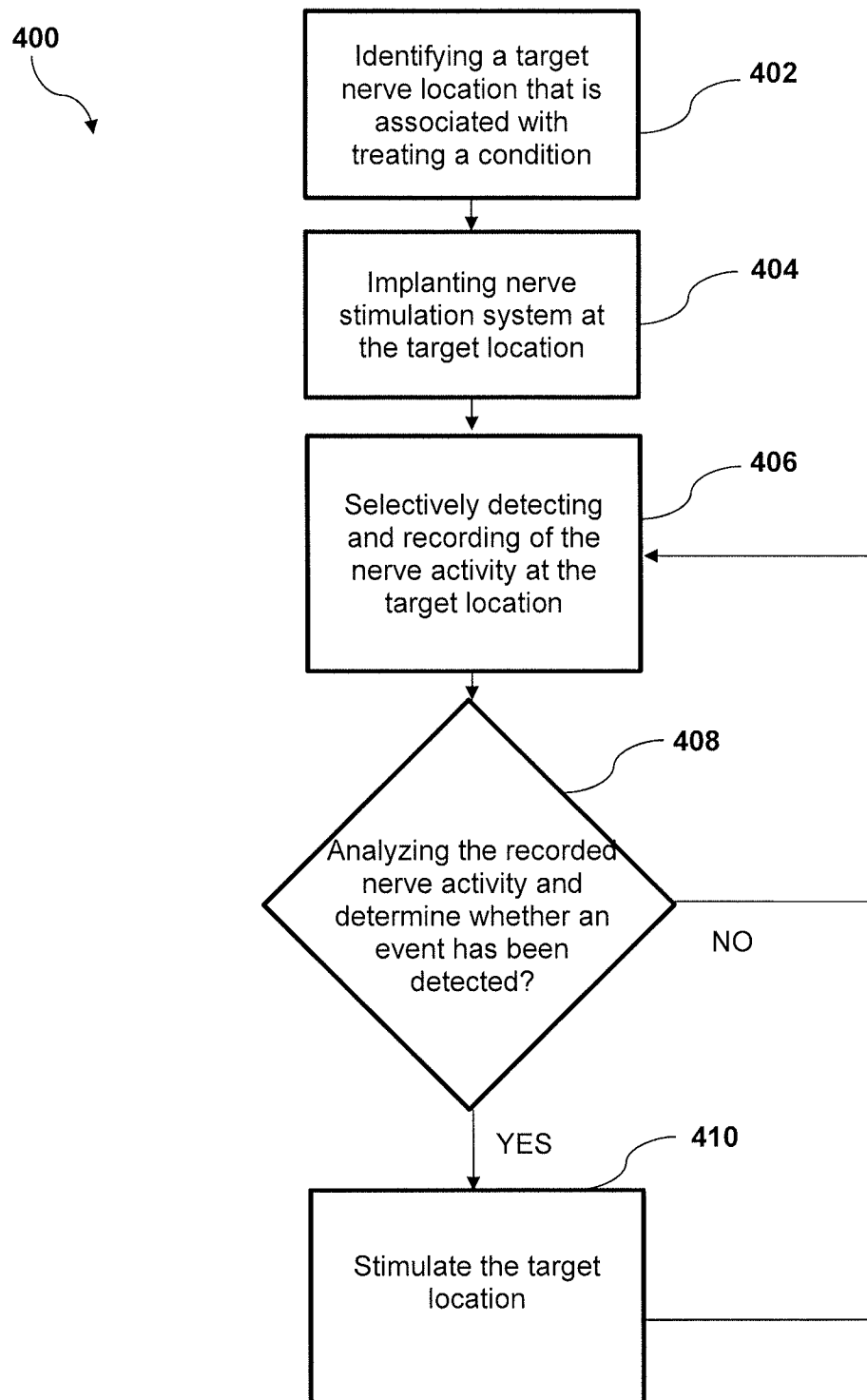
EXPONENTIAL
RISE

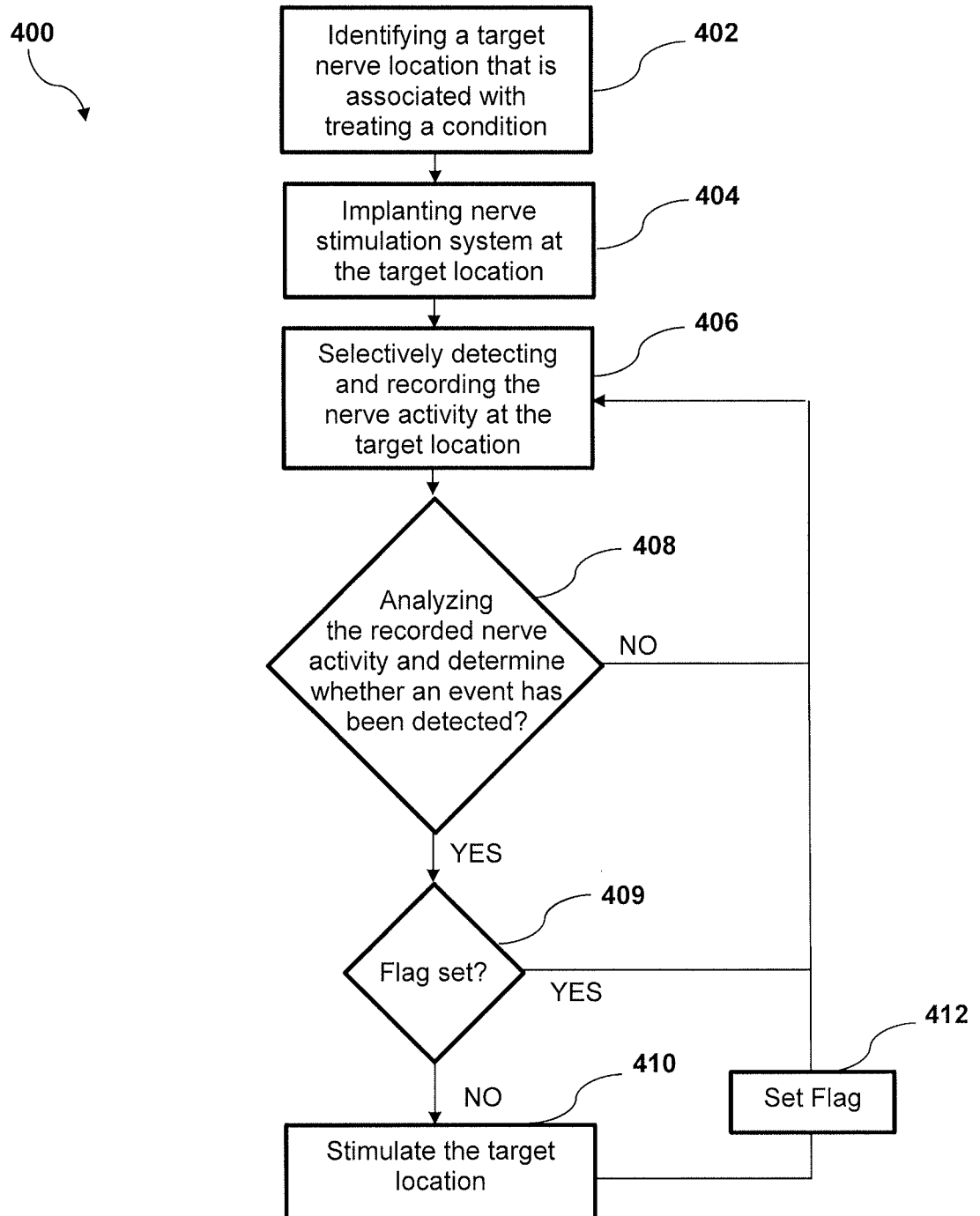


EXPONENTIAL
DECAY

FIG. 7

7/8

**FIG. 8**

**FIG. 9**

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/018364

A. CLASSIFICATION OF SUBJECT MATTER		
INV. A61N1/05	A61N1/36	A61N1/372 A61N1/378 A61B5/04
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) A61N A61B		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/300655 A1 (CHOLETTE MARTIN [US]) 4 December 2008 (2008-12-04) abstract; figures 2-, 5-7, 10-11 paragraphs [0034] - [0042], [0067] - [0072] -----	1-13,20
X	US 2008/319506 A1 (CAULLER LAWRENCE JAMES [US]) 25 December 2008 (2008-12-25) abstract; figures 1-2, 5, 11 paragraphs [0017] - [0024], [0032] - [0038] -----	1-13,20
X	US 2013/267816 A1 (EDER CLEMENS FLORIAN [GB]) 10 October 2013 (2013-10-10) abstract; figures 1-5, 12 paragraphs [0003], [0014] - [0018], [0022] - [0027], [0034], [0039], [0061] - [0063] ----- -/-	1-13,20
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 23 May 2017		Date of mailing of the international search report 02/06/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Lahorte, Philippe

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/018364

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/157141 A1 (CHIAO JUNG-CHIH [US] ET AL) 18 June 2009 (2009-06-18) figures 1-3, 11B, 28A-B, 29 paragraphs [0052] - [0053], [0080] - [0084], [0094], [0136] - [0138] -----	1-13,20
X	KR 2012 0053090 A (KNU INDUSTRY COOPERATION FOUND [KR]) 25 May 2012 (2012-05-25) the whole document -----	1,2, 5-10,20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/018364

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14-19
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery and therapy.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/018364

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008300655	A1	04-12-2008	NONE
US 2008319506	A1	25-12-2008	AU 2008268368 A1 31-12-2008 DE 112008001669 T5 12-05-2010 US 2008319506 A1 25-12-2008 US 2010069994 A1 18-03-2010 US 2012065701 A1 15-03-2012 WO 2009003025 A2 31-12-2008
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KR 20120053090	A	25-05-2012	NONE