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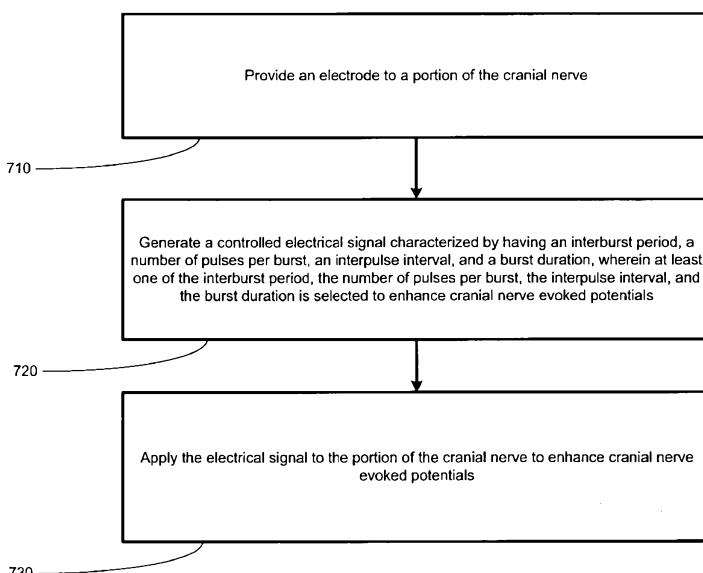
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(54) Title: MICROBURST ELECTRICAL STIMULATION OF CRANIAL NERVES FOR THE TREATMENT OF MEDICAL CONDITIONS



(57) Abstract: Disclosed herein are methods, systems, and apparatus for treating a medical condition in a patient using an implantable medical device by applying an electrical signal characterized by having a number of pulses per microburst, an interpulse interval, a microburst duration, and an interburst period to a portion of a cranial nerve of said patient, wherein at least one of the number of pulses per microburst, the interpulse interval, the microburst duration, or the interburst period is selected to enhance cranial nerve evoked potentials.

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## **MICROBURST ELECTRICAL STIMULATION OF CRANIAL NERVES FOR THE TREATMENT OF MEDICAL CONDITIONS**

### **BACKGROUND OF THE INVENTION**

5 The present application claims priority to prior copending United States patent application 60/787,680, filed March 29, 2006, entitled “Synchronized And Optimized Vagus Nerve Stimulation Method.”

10 The United States patent application entitled “Synchronization Of Vagus Nerve Stimulation With The Cardiac Cycle Of A Patient” by Arthur D. Craig and filed concurrently herewith is hereby incorporated herein by reference.

15 The PCT patent application entitled “Vagus Nerve Stimulation Method” by Arthur D. Craig and filed concurrently herewith is hereby incorporated herein by reference.

### **1. FIELD OF THE INVENTION**

20 This invention relates generally to medical device systems and, more particularly, to medical device systems for applying electrical signals to a cranial nerve for the treatment of various medical conditions, and for improved electrical signals in such systems.

### **2. DESCRIPTION OF THE RELATED ART**

25 Many advancements have been made in treating diseases such as depression and epilepsy. Therapies using electrical signals for treating these diseases have been found to effective. Implantable medical devices have been effectively used to deliver therapeutic stimulation to various portions of the human body (e.g., the vagus nerve) for treating these diseases. As used herein, “stimulation” or “stimulation signal” refers to the application of an electrical, mechanical, magnetic, electro-magnetic, photonic, audio and/or chemical signal to a neural structure in the patient’s body. The signal is an exogenous signal that is distinct from the endogenous electrical, mechanical, and chemical activity (e.g., afferent and/or efferent electrical action potentials) generated by the patient’s body and environment. In other words, the stimulation signal (whether electrical, mechanical, magnetic, electro-magnetic, photonic, audio or chemical in nature) applied to the nerve in the present invention is a signal applied from an 30 artificial source, e.g., a neurostimulator.

A “therapeutic signal” refers to a stimulation signal delivered to a patient’s body with the intent of treating a medical condition by providing a modulating effect to neural tissue. The effect of a stimulation signal on neuronal activity is termed “modulation”; however, for simplicity, the terms “stimulating” and “modulating”, and variants thereof, are sometimes used 5 interchangeably herein. In general, however, the delivery of an exogenous signal itself refers to “stimulation” of the neural structure, while the effects of that signal, if any, on the electrical activity of the neural structure are properly referred to as “modulation.” The modulating effect of the stimulation signal upon the neural tissue may be excitatory or inhibitory, and may potentiate acute and/or long-term changes in neuronal activity. For example, the “modulating” 10 effect of the stimulation signal to the neural tissue may comprise one more of the following effects: (a) initiation of an action potential (afferent and/or efferent action potentials); (b) inhibition or blocking of the conduction of action potentials, whether endogenous or exogenously induced, including hyperpolarizing and/or collision blocking, (c) affecting changes 15 in neurotransmitter/neuromodulator release or uptake, and (d) changes in neuro-plasticity or neurogenesis of brain tissue.

In some embodiments, electrical neurostimulation may be provided by implanting an electrical device underneath the skin of a patient and delivering an electrical signal to a nerve such as a cranial nerve. In one embodiment, the electrical neurostimulation involves sensing or detecting a body parameter, with the electrical signal being delivered in response to the sensed 20 body parameter. This type of stimulation is generally referred to as “active,” “feedback,” or “triggered” stimulation. In another embodiment, the system may operate without sensing or detecting a body parameter once the patient has been diagnosed with a medical condition that may be treated by neurostimulation. In this case, the system may apply a series of electrical pulses to the nerve (e.g., a cranial nerve such as a vagus nerve) periodically, intermittently, or 25 continuously throughout the day, or over another predetermined time interval. This type of stimulation is generally referred to as “passive,” “non-feedback,” or “prophylactic,” stimulation. The electrical signal may be applied by an IMD that is implanted within the patient’s body. In another alternative embodiment, the signal may be generated by an external pulse generator outside the patient’s body, coupled by an RF or wireless link to an implanted electrode.

30 Generally, neurostimulation signals that perform neuromodulation are delivered by the IMD via one or more leads. The leads generally terminate at their distal ends in one or more electrodes, and the electrodes, in turn, are electrically coupled to tissue in the patient’s body. For example, a number of electrodes may be attached to various points of a nerve or other tissue inside a human body for delivery of a neurostimulation signal.

While feedback stimulation schemes have been proposed, conventional vagus nerve stimulation (VNS) usually involves non-feedback stimulation characterized by a number of parameters. Specifically, conventional vagus nerve stimulation usually involves a series of electrical pulses in bursts defined by an “on-time” and an “off-time.” During the on-time, 5 electrical pulses of a defined electrical current (e.g., 0.5 - 2.0 millamps) and pulse width (e.g., 0.25 – 1.0 milliseconds) are delivered at a defined frequency (e.g., 20 – 30 Hz) for the on-time duration, usually a specific number of seconds, e.g., 10 - 60 seconds. The pulse bursts are separated from one another by the off-time, (e.g., 30 seconds – 5 minutes) in which no electrical signal is applied to the nerve. The on-time and off-time parameters together define a duty cycle, 10 which is the ratio of the on-time to the combination of the on-time and off-time, and which describes the percentage of time that the electrical signal is applied to the nerve.

In conventional VNS, the on-time and off-time may be programmed to define an intermittent pattern in which a repeating series of electrical pulse bursts are generated and applied to the vagus nerve 127. Each sequence of pulses during an on-time may be referred to 15 as a “pulse burst.” The burst is followed by the off-time period in which no signals are applied to the nerve. The off-time is provided to allow the nerve to recover from the stimulation of the pulse burst, and to conserve power. If the off-time is set at zero, the electrical signal in conventional VNS may provide continuous stimulation to the vagus nerve. Alternatively, the idle time may be as long as one day or more, in which case the pulse bursts are provided only 20 once per day or at even longer intervals. Typically, however, the ratio of “off-time” to “on-time” may range from about 0.5 to about 10.

In addition to the on-time and off-time, the other parameters defining the electrical signal in conventional VNS may be programmed over a range of values. The pulse width for the 25 pulses in a pulse burst of conventional VNS may be set to a value not greater than about 1 msec, such as about 250-500  $\mu$ sec, and the number of pulses in a pulse burst is typically set by programming a frequency in a range of about 20-150 Hz (i.e., 20 pulses per second to 150 pulses per second). A non-uniform frequency may also be used. Frequency may be altered during a pulse burst by either a frequency sweep from a low frequency to a high frequency, or vice versa. Alternatively, the timing between adjacent individual signals within a burst may be randomly 30 changed such that two adjacent signals may be generated at any frequency within a range of frequencies.

Although neurostimulation has proven effective in the treatment of a number of medical conditions, it would be desirable to further enhance and optimize neurostimulation for this

purpose. For example, it may be desirable to enhance evoked potentials in the patient's brain to aid in treating a medical condition.

### SUMMARY OF THE INVENTION

5       Applicant has discovered that it is possible to provide improved therapeutic neurostimulation treatments for a variety of medical conditions by a new type of electrical stimulation of the cranial nerves capable of providing enhanced evoked potentials in the brain. "Enhanced" in this context refers to electrical potentials evoked in the forebrain by neurostimulation that are higher than those produced by conventional neurostimulation, 10 particularly conventional VNS with an interpulse frequency of 20-30 Hz (resulting in a number of pulses per burst of 140-1800, at a burst duration from 7-60 sec). The electrical signal for this improved therapy is substantially different from the electrical signals in conventional VNS. In particular, electrical signals in the present invention are characterized by very short bursts of a limited number of electrical pulses. These shorts bursts of less than 1 second are referred to 15 hereinafter as "microbursts," and electrical stimulation applying microbursts to a cranial nerve is referred to as "microburst stimulation." By applying an electrical signal comprising a series of microbursts to, for example, a vagus nerve of a patient, enhanced vagal evoked potentials (eVEP) are produced in therapeutically significant areas of the brain. Significantly, eVEP are not produced by conventional vagus nerve stimulation.

20       As used herein, the term "microburst" refers to a portion of a therapeutic electrical signal comprising a limited plurality of pulses and a limited duration. More particularly, in one embodiment, a microburst may comprise at least two but no more than about 25 electrical pulses, preferably from 2 to about 20 pulses per burst, more preferably from 2 to about 15 pulses per burst. In one embodiment, a microburst may last for no more than 1 second, typically less 25 than 100 milliseconds, and preferably from about 10 msec to about 80 msec. A therapeutic electrical signal may comprise a series of microbursts separated from one another by time intervals known as "interburst periods" which allow a refractory interval for the nerve to recover from the microburst and again become receptive to eVEP stimulation by another microburst. In some embodiments, the interburst period may be as long as or longer than the adjacent microbursts separated by the interburst period. In some embodiments the interburst period may comprise an absolute time period of at least 100 milliseconds. Adjacent pulses in a microburst are separated by a time interval known as an "interpulse interval." The interpulse interval, together with the number of pulses and the pulse width of each pulse, determines a "microburst" 30

duration,” which is the length of a microburst from the beginning of the first pulse to the end of the last pulse (and thus the beginning of a new interburst period). In one embodiment, a microburst may have a microburst duration of 1.0 seconds or less (i.e., not greater than 1 sec), such as from about 2 msec to about 1 sec, and more preferably 100 msec or less, such as from about 5 msec to about 100 msec, and more preferably from about 10 msec to about 80 msec.

5 The improved electrical signals of the present invention are thus characterized by an interburst period, a microburst duration, a number of pulses per microburst, and an interpulse interval. The pulses in a microburst may be further characterized by a current amplitude and a pulse width.

Electrical stimulation according to the present invention may optionally include an on-time and

10 an off-time in which the microbursts are provided and not provided, respectively, to a cranial nerve. At least one of the interburst period, the burst duration, the number of pulses per microburst, the interpulse interval, the current amplitude, the pulse width, the on-time, or the off-time can be selected to enhance cranial nerve evoked potentials.

In one embodiment, the present invention provides a method of treating a patient having  
15 a medical condition by applying a pulsed electrical signal comprising a series of microbursts, wherein each of said microbursts has at least one characteristic selected from the group consisting of having from 2 pulses to about 25 pulses per microburst, having an interpulse interval of about 1 millisecond to about 50 milliseconds (such as from about 1 msec to about 10 msec), having a microburst duration of less than 1 sec, and being separated from an adjacent  
20 microburst by an interburst period comprising a time interval selected from the group consisting of A) the microburst duration or the microburst duration of the adjacent microburst and B) at least 100 milliseconds.

In one embodiment, the present invention provides a method of treating a medical condition of a patient with an electrical signal from an implantable medical device, comprising  
25 applying to a cranial nerve of a patient a pulsed electrical signal comprising a series of microbursts separated by interburst periods. Each microburst comprises a number of pulses per microburst, an interpulse interval, and a microburst duration. The microbursts are applied to a portion of a cranial nerve of said patient, wherein at least one of the interburst period, the microburst duration, the number of pulses per microburst, or the interpulse interval is selected to  
30 enhance cranial nerve evoked potentials.

In one embodiment, the present invention provides a method of treating a medical condition of a patient, comprising coupling at least one electrode to at least one cranial nerve of the patient, providing a programmable electrical signal generator coupled to the electrode, and generating a pulsed electrical signal comprising a series of microbursts separated by interburst

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periods. Each microburst comprises a number of pulses per microburst and an interpulse interval and has a microburst duration. The method further comprises selecting at least one of the interburst period, the number of pulses per microburst, the microburst duration, or the interpulse interval to enhance cranial nerve evoked potentials, and applying the pulsed electrical signal to the at least one electrode to treat the medical condition.

In one embodiment, the present invention provides a computer readable program storage device encoded with instructions that, when executed by a computer, perform a method, comprising generating an electrical signal comprising a series of microbursts separated by interburst periods, with each microburst comprising a number of pulses per microburst, an interpulse interval, and a microburst duration, wherein at least one of the interburst period, the number of pulses per microburst, the microburst duration, or the interpulse period is selected to enhance cranial nerve evoked potentials, and applying the electrical signal to a cranial nerve of the patient to treat the medical condition.

In one embodiment, the present invention provides a system for treating a medical condition of a patient, comprising at least one electrode coupled to at least one cranial nerve of a patient and an implantable device operatively coupled to the electrode and comprising an electrical signal generator capable of generating an electrical signal comprising a series of microbursts separated by interburst periods, with each microburst comprising a number of pulses per microburst, an interpulse interval and a microburst duration, and applying the electrical signal to a portion of a cranial nerve of said patient using the electrode, wherein at least one of the interburst period, the number of pulses per microburst, the interpulse interval or the microburst duration, is selected to enhance cranial nerve evoked potentials.

In one embodiment, the present invention provides a method of treating a medical condition in a patient using an implantable medical device, the patient having a cranial nerve, the method comprising:

applying to a selected location on the cranial nerve of the patient, an electrical signal characterized by having a plurality of microbursts and a number of pulses per microburst, wherein each microburst is separated from an adjacent microburst by an interburst period of at least 100 milliseconds, and wherein each microburst is patterned and comprises:

30 a plurality of pulses per microburst,

a plurality of interpulse intervals between adjacent pulses of the microburst of less than about 50 milliseconds, and

a microburst duration of not greater than 1 second,

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wherein at least one interpulse interval of the plurality of interpulse intervals in each microburst is selectively varied from the other interpulse intervals, and

wherein at least one of the number of pulses per microburst, the interpulse interval, the microburst duration, or the interburst period is selected to enhance cranial nerve evoked potentials within the patient.

In one embodiment, the present invention provides a method of treating a medical condition of a patient, comprising:

coupling at least one electrode to a selected location on at least one cranial nerve of the patient,

providing a programmable electrical signal generator coupled to the electrode,

generating an electrical signal characterized by having a plurality of microbursts and a number of pulses per microburst, wherein each microburst is separated from an adjacent microburst by an interburst period of at least 100 milliseconds, and wherein each microburst is patterned and comprises:

from 3 to 25 pulses per microburst

a plurality of interpulse intervals between adjacent pulses of the microburst of less than about 50 milliseconds, and

a microburst duration of not greater than 1 second,

wherein at least one interpulse interval of the plurality of interpulse intervals in each microburst is selectively varied from the other interpulse intervals, and

applying the electrical signal to the electrode to treat the medical condition.

In one embodiment, the present invention provides a system for treating a medical condition, comprising:

at least one electrode for coupling to at least one cranial nerve of a patient, and

an implantable device operatively coupled to the electrode and comprising an electrical signal generator for applying an electrical signal characterized by having a plurality of microbursts and a number of pulses per microburst, wherein each microburst is separated from an adjacent microburst by an interburst period of at least 100 milliseconds, and wherein each microburst is patterned and comprises:

from 3 to 25 pulses per microburst,

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a plurality of interpulse intervals between adjacent pulses of the microburst of less than about 50 milliseconds, and

a microburst duration of not greater than 1 second,

wherein at least one interpulse interval of the plurality of interpulse intervals in each

5 microburst is selectively varied from the other interpulse intervals, and

wherein at least one of the number of pulses per microburst, the interpulse interval, the microburst duration, or the interburst period is selected to enhance cranial nerve evoked potentials within the patient.

In one embodiment, the present invention provides a method of treating a medical 10 condition in a patient using an implantable medical device, the patient having a vagus nerve, the method comprising:

applying a first electrical signal to the vagus nerve of the patient during a first period, wherein the first electrical signal comprises a plurality of microbursts, wherein each microburst has more than about 50 pulses or has a burst duration of at least about 7 seconds, and

15 applying a second electrical signal to the vagus nerve of the patient during a second period, wherein the second electrical signal comprises a plurality of microbursts, wherein each microburst is separated from an adjacent microburst by an interburst period of at least 100 milliseconds, and wherein each microburst is patterned and comprises:

from 3 to about 25 pulses per burst,

20 a plurality of interpulse intervals between adjacent pulses of the microburst, wherein each interpulse interval is from about 1 millisecond to about 50 milliseconds, and wherein at least one interpulse interval of the plurality of interpulse intervals in each microburst is selectively varied from the other interpulse intervals, and

a burst duration from about 2 milliseconds to about 1 second.

25

#### BRIEF DESCRIPTION OF THE DRAWINGS

The invention may be understood by reference to the following description taken in conjunction with the accompanying drawings, in which like reference numerals identify like elements, and in which:

30 Figure 1 provides a stylized diagram of an implantable medical device implanted into a patient's body for providing a therapeutic electrical signal to a neural structure of the patient's body, in accordance with one illustrative embodiment of the present invention;

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Figure 2 is a block diagram of a medical device system that includes an implantable medical device and an external device, in accordance with one illustrative embodiment of the present invention;

Figure 3 illustrates an exemplary electrical signal of a firing neuron as a graph of voltage at a given location at particular times in response to application of an electrical signal to the nerve by the neurostimulator of Figure 2, in accordance with one illustrative embodiment of the present invention;

5 Figures 4A, 4B, and 4C illustrate exemplary waveforms for electrical signals for stimulating the cranial nerve for treating a medical condition, according to one illustrative embodiment of the present invention;

Figure 5 illustrates a flowchart depiction of a method for treating a medical condition, in accordance with an illustrative embodiment of the present invention;

10 Figure 6 illustrates a flowchart depiction of an alternative method for treating a medical condition, in accordance with an alternative illustrative embodiment of the present invention;

Figure 7 depicts a more detailed flowchart depiction of the step of performing a detection process of Figure 6, in accordance with an illustrative embodiment of the present invention;

15 Figure 8 shows a comparison of vagal evoked potentials (VEPs) with different stimulus timings;

Figure 9 illustrates synchronization of a vagal stimulus burst to the QRS wave of a patient's ECG;

Figure 10 illustrates the localization of an early VEP in the right thalamus and basal ganglia and a later VEP in the left insular cortex.

20 While the invention is susceptible to various modifications and alternative forms, specific embodiments thereof have been shown by way of example in the drawings and are herein described in detail. It should be understood, however, that the description herein of specific embodiments is not intended to limit the invention to the particular forms disclosed, but on the contrary, the intention is to cover all modifications, equivalents, and alternatives falling 25 within the spirit and scope of the invention as defined by the appended claims.

### **DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS**

Illustrative embodiments of the invention are described herein. In the interest of clarity, not all features of an actual implementation are described in this specification. In the 30 development of any such actual embodiment, numerous implementation-specific decisions must be made to achieve the design-specific goals, which will vary from one implementation to another. It will be appreciated that such a development effort, while possibly complex and time-

consuming, would nevertheless be a routine undertaking for persons of ordinary skill in the art having the benefit of this disclosure.

This document does not intend to distinguish between components that differ in name but not function. In the following discussion and in the claims, the terms “including” and “includes” are used in an open-ended fashion, and thus should be interpreted to mean “including, but not limited to.” Also, the term “couple” or “couples” is intended to mean either a direct or an indirect electrical connection. “Direct contact,” “direct attachment,” or providing a “direct coupling” indicates that a surface of a first element contacts the surface of a second element with no substantial attenuating medium there between. The presence of small quantities of substances, such as bodily fluids, that do not substantially attenuate electrical connections does not vitiate direct contact. The word “or” is used in the inclusive sense (i.e., “and/or”) unless a specific use to the contrary is explicitly stated.

The term “electrode” or “electrodes” described herein may refer to one or more stimulation electrodes (i.e., electrodes for delivering an electrical signal generated by an IMD to a tissue), sensing electrodes (i.e., electrodes for sensing a physiological indication of a patient’s body), and/or electrodes that are capable of delivering a stimulation signal, as well as performing a sensing function.

Cranial nerve stimulation has been proposed to treat a number of medical conditions pertaining to or mediated by one or more structures of the nervous system of the body, including epilepsy and other movement disorders, depression, anxiety disorders and other neuropsychiatric disorders, dementia, head trauma, coma, migraine headache, obesity, eating disorders, sleep disorders, cardiac disorders (such as congestive heart failure and atrial fibrillation), hypertension, endocrine disorders (such as diabetes and hypoglycemia), and pain, among others. See, e.g., U.S. Pats. Nos. 4,867,164; 5,299,569; 5,269,303; 5,571,150; 5,215,086; 5,188,104; 5,263,480; 6,587,719; 6,609,025; 5,335,657; 6,622,041; 5,916,239; 5,707,400; 5,231,988; and 5,330,515. Despite the numerous disorders for which cranial nerve stimulation has been proposed or suggested as a treatment option, the fact that detailed neural pathways for many (if not all) cranial nerves remain relatively unknown, makes predictions of efficacy for any given disorder difficult or impossible. Moreover, even if such pathways were known, the precise stimulation parameters that would modulate particular pathways relevant to a particular disorder generally cannot be predicted.

In one embodiment, the present invention provides a method of treating a medical condition. The medical condition can be selected from the group consisting of epilepsy, neuropsychiatric disorders (including but not limited to depression), eating disorders/obesity,

traumatic brain injury/coma, addiction disorders, dementia, sleep disorders, pain, migraine, endocrine/pancreatic disorders (including but not limited to diabetes), motility disorders, hypertension, congestive heart failure/cardiac capillary growth, hearing disorders, angina, syncope, vocal cord disorders, thyroid disorders, pulmonary disorders, and reproductive

5 endocrine disorders (including infertility).

In one embodiment, the present invention provides a method of treating a medical condition of a patient using an implantable medical device, comprising applying to a cranial nerve of a patient a pulsed electrical signal comprising a series of microbursts separated by interburst periods. In one embodiment, the interburst periods comprise at least 100 milliseconds each. In another embodiment, the interburst periods comprise at least the length of one of the 10 two microbursts separated by the interburst period. In another embodiment, the interburst period may be determined on a particular patient by providing microbursts separated by increasingly smaller interburst periods. The interburst period may be provided as any time interval greater than that at which the eVEP significantly diminishes or disappear. Each microburst comprises a 15 number of pulses per microburst, an interpulse interval, and has a microburst duration. In one embodiment, the number of pulses per microburst may range from 2 to about 25 pulses, and in another embodiment the number pulses per microburst may range from 2 to about 20 pulses, preferably from 2 to about 15 pulses. The microbursts are applied to a portion of a cranial nerve of the patient, and at least one of the interburst period, the number of pulses per microburst, the 20 interpulse interval, or the microburst duration are selected to enhance cranial nerve evoked potentials. Pulses within a microburst may also comprise a pulse width and a current amplitude. In an alternate embodiment, the method may also comprise an off-time, during which microbursts are not applied to the patient, and an on-time during which microbursts are applied to the patient.

25 It may be convenient to refer to a burst frequency, defined as 1 divided by the sum of the microburst duration and the interburst period, and it will be recognized by persons of skill in the art that the interburst period may alternatively be described in terms of a frequency of the pulses rather than as an absolute time separate one pulse from another.

In another alternate embodiment, the method may comprise, during a first period, 30 applying a primary mode of cranial nerve stimulation to a cranial nerve of the patient, such as conventional vagus nerve stimulation, and, during a second period, applying a secondary mode of cranial nerve stimulation to a cranial nerve of the patient, such as microburst stimulation. The conventional vagus nerve stimulation signal may be defined by a current amplitude, a pulse width, a frequency, an on-time and an off-time. The conventional vagus nerve stimulation

signal typically has more than about 50 pulses per burst and a burst duration of at least about 7 sec. In one embodiment, the first period corresponds to the on-time of conventional vagus nerve stimulation and the second time period corresponds to the off-time of conventional vagus nerve stimulation. In another embodiment, the first period and the second period can partially overlap.

5 In another embodiment, one of the first period or the second period can be entirely overlapped by the other of the first period or the second period.

The implantable medical device (IMD) system of one embodiment of the present invention provides for software module(s) that are capable of acquiring, storing, and processing various forms of data, such as patient data/parameters (e.g., physiological data, side-effects data, 10 such as heart rate, breathing rate, brain-activity parameters, disease progression or regression data, quality of life data, etc.) and therapy parameter data. Therapy parameters may include, but are not limited to, electrical signal parameters that define the therapeutic electrical signals delivered by the IMD, medication parameters and/or any other therapeutic treatment parameter. In an alternative embodiment, the term “therapy parameters” may refer to electrical signal 15 parameters defining the therapeutic electrical signals delivered by the IMD. Therapy parameters for a therapeutic electrical signal may also include, but are not limited to, a current amplitude, a pulse width, an interburst period, a number of pulses per burst, an interpulse interval, a burst duration, an on-time, and an off-time.

Although not so limited, a system capable of implementing embodiments of the present 20 invention is described below. Figure 1 depicts a stylized implantable medical system (IMD) 100 for implementing one or more embodiments of the present invention. An electrical signal generator 110 is provided, having a main body 112 comprising a case or shell with a header 116 for connecting to an insulated, electrically conductive lead assembly 122. The generator 110 is implanted in the patient's chest in a pocket or cavity formed by the implanting surgeon just 25 below the skin (indicated by a dotted line 145), similar to the implantation procedure for a pacemaker pulse generator.

A nerve electrode assembly 125, preferably comprising a plurality of electrodes having at least an electrode pair, is conductively connected to the distal end of the lead assembly 122, which preferably comprises a plurality of lead wires (one wire for each electrode). Each 30 electrode in the electrode assembly 125 may operate independently or alternatively, may operate in conjunction with the other electrodes. In one embodiment, the electrode assembly 125 comprises at least a cathode and an anode. In another embodiment, the electrode assembly comprises one or more unipolar electrodes.

Lead assembly 122 is attached at its proximal end to connectors on the header 116 of generator 110. The electrode assembly 125 may be surgically coupled to the vagus nerve 127 in the patient's neck or at another location, e.g., near the patient's diaphragm or at the esophagus/stomach junction. Other (or additional) cranial nerves such as the trigeminal and/or 5 glossopharyngeal nerves may also be used to deliver the electrical signal in particular alternative embodiments. In one embodiment, the electrode assembly 125 comprises a bipolar stimulating electrode pair 126, 128 (i.e., a cathode and an anode). Suitable electrode assemblies are available from Cyberonics, Inc., Houston, Texas, USA as the Model 302 electrode assembly. However, persons of skill in the art will appreciate that many electrode designs could be used in 10 the present invention. In one embodiment, the two electrodes are wrapped about the vagus nerve, and the electrode assembly 125 may be secured to the vagus nerve 127 by a spiral anchoring tether 130 such as that disclosed in U.S. Pat. No. 4,979,511 issued Dec. 25, 1990 to Reese S. Terry, Jr. and assigned to the same assignee as the instant application. Lead assembly 122 may be secured, while retaining the ability to flex with movement of the chest and neck, by 15 a suture connection to nearby tissue (not shown).

In alternative embodiments, the electrode assembly 125 may comprise temperature sensing elements and/or heart rate sensor elements. Other sensors for other body parameters may also be employed to trigger active stimulation. Both passive and active stimulation may be combined or delivered by a single IMD according to the present invention. Either or both modes 20 may be appropriate to treat a specific patient under observation.

In alternative embodiments, a sensor assembly 165, comprising a sensor lead assembly 162 and a sensor 160, may be employed to detect a body parameter of the patient.

The electrical pulse generator 110 may be programmed with an external device (ED) such as computer 150 using programming software known in the art. A programming wand 155 25 may be coupled to the computer 150 as part of the ED to facilitate radio frequency (RF) communication between the computer 150 and the pulse generator 110. The programming wand 155 and computer 150 permit non-invasive communication with the generator 110 after the latter is implanted. In systems where the computer 150 uses one or more channels in the Medical Implant Communications Service (MICS) bandwidths, the programming wand 155 may 30 be omitted to permit more convenient communication directly between the computer 150 and the pulse generator 110.

The therapeutic electrical stimulation signal described herein may be used to treat a medical condition by enhancing cranial nerve evoked potentials separately, or in combination with another type of treatment. For example, electrical signals according to the present

invention may be applied in combination with a chemical agent, such as various drugs, to treat various medical conditions. Further, the electrical stimulation may be performed in combination with treatment(s) relating to a biological or chemical agent. The electrical stimulation treatment may also be performed in combination with other types of treatment, such as magnetic

5 stimulation treatment.

Turning now to Figure 2, a block diagram depiction of the IMD 200 is provided, in accordance with one illustrative embodiment of the present invention. The IMD 200 (such as generator 110 from Figure 1) may comprise a controller 210 capable of controlling various aspects of the operation of the IMD 200. The controller 210 is capable of receiving internal data or external data and causing a stimulation unit 220 to generate and deliver an electrical signal to target tissues of the patient's body for treating a medical condition. For example, the controller 210 may receive manual instructions from an operator externally, or may cause the electrical signal to be generated and delivered based on internal calculations and programming. The controller 210 is capable of affecting substantially all functions of the IMD 200.

10 The controller 210 may comprise various components, such as a processor 215, a memory 217, etc. The processor 215 may comprise one or more microcontrollers, microprocessors, etc., capable of performing various executions of software components. The memory 217 may comprise various memory portions where a number of types of data (e.g., internal data, external data instructions, software codes, status data, diagnostic data, etc.) may be stored. The memory 217 may comprise one or more of random access memory (RAM) dynamic random access memory (DRAM), electrically erasable programmable read-only memory (EEPROM), flash memory, etc.

15 The IMD 200 may also comprise a stimulation unit 220 capable of generating and delivering electrical signals to one or more electrodes via leads. A lead assembly such as lead assembly 122 (Figure 1) may be coupled to the IMD 200. Therapy may be delivered to the leads comprising the lead assembly 122 by the stimulation unit 220 based upon instructions from the controller 210. The stimulation unit 220 may comprise various circuitry, such as electrical signal generators, impedance control circuitry to control the impedance "seen" by the leads, and other circuitry that receives instructions relating to the delivery of the electrical signal to tissue.

20 The stimulation unit 220 is capable of delivering an electrical signal over the leads comprising the lead assembly 122.

25 The IMD 200 may also comprise a power supply 230. The power supply 230 may comprise a battery, voltage regulators, capacitors, etc., to provide power for the operation of the IMD 200, including delivering the therapeutic electrical signal. The power supply 230

comprises a power source that in some embodiments may be rechargeable. In other embodiments, a non-rechargeable power source may be used. The power supply 230 provides power for the operation of the IMD 200, including electronic operations and the electrical signal generation and delivery functions. The power supply 230 may comprise a lithium/thionyl chloride cell or a lithium/carbon monofluoride (LiCF<sub>x</sub>) cell. Other battery types known in the art of implantable medical devices may also be used.

5 The IMD 200 may also comprise a communication unit 260 capable of facilitating communications between the IMD 200 and various devices. In particular, the communication unit 260 is capable of providing transmission and reception of electronic signals to and from an external unit 270, such as computer 150 and wand 155 that may comprise an ED (Figure 1).  
10 The communication unit 260 may include hardware, software, firmware, or any combination thereof.

In one embodiment, the IMD 200 may also comprise a detection unit 295 that is capable of detecting various patient parameters. For example, the detection unit 295 may comprise hardware, software, or firmware that is capable of obtaining and/or analyzing data relating to one or more body parameters of the patient. Based upon the data obtained by the detection unit 295, the IMD 200 may deliver the electrical signal to a portion of the cranial nerve to treat epilepsy, depression or other medical conditions. In one embodiment, the detection unit 295 may be capable of detecting a feedback response from the patient. The feedback response may 20 include a magnetic signal input, a tap input, a wireless data input to the IMD 200, etc. The feedback may be indicative of a pain and/or noxious threshold, wherein the threshold may be the limit of tolerance of discomfort for a particular patient. The term "patient parameters" may refer to, but is not limited to, various body parameters, which may in some embodiments involve sensors coupled to the IMD 200.

25 In another embodiment, the detection unit 295 may comprise hardware, software, or firmware that is capable of obtaining and/or analyzing data relating to one or more body parameters of the patient's cardiac cycle. Based upon the data obtained by the detection unit 295, the IMD 200 may deliver the electrical signal to a portion of the cranial nerve to treat epilepsy, depression or other medical conditions.

30 The external unit 270 may be an ED that is capable of programming electrical signal parameters of the IMD 200. In one embodiment, the external unit 270 is a computer system capable of executing a data-acquisition program. The external unit 270 may be controlled by a healthcare provider, such as a physician, at a base station in, for example, a doctor's office. In alternative embodiments, the external unit 270 may be controlled by a patient in a system

providing less control over the operation of the IMD 200 than another external unit 270 controlled by a healthcare provider. Whether controlled by the patient or by a healthcare provider, the external unit 270 may be a computer, preferably a handheld computer or PDA, but may alternatively comprise any other device that is capable of electronic communications and programming, e.g., hand-held computer system, a PC computer system, a laptop computer system, a server, a personal digital assistant (PDA), an Apple-based computer system, etc. The external unit 270 may download various parameters and program software into the IMD 200 for programming the operation of the IMD, and may also receive and upload various status conditions and other data from the IMD 200. Communications between the external unit 270 and the communication unit 260 in the IMD 200 may occur via a wireless or other type of communication, represented generally by line 277 in Figure 2. This may occur using, e.g., wand 155 (Figure 1) to communicate by RF energy with a generator 110. Alternatively, the wand may be omitted in some systems, e.g., systems in which external unit 270 operates in the MICS bandwidths.

15 In one embodiment, the external unit 270 may comprise a local database unit 255. Optionally or alternatively, the external unit 270 may also be coupled to a database unit 250, which may be separate from external unit 270 (e.g., a centralized database wirelessly linked to a handheld external unit 270). The database unit 250 and/or the local database unit 255 are capable of storing various patient data. This data may comprise patient parameter data acquired from a patient's body and/or therapy parameter data. The database unit 250 and/or the local database unit 255 may comprise data for a plurality of patients, and may be organized and stored in a variety of manners, such as in date format, severity of disease format, etc. The database unit 250 and/or the local database unit 255 may be relational databases in one embodiment. A physician may perform various patient management functions using the external unit 270, which 20 may include obtaining and/or analyzing data from the IMD 200 and/or data from the database unit 250 and/or the local database unit 255. The database unit 250 and/or the local database unit 255 may store various patient data.

One or more of the blocks illustrated in the block diagram of the IMD 200 in Figure 2, 25 may comprise hardware units, software units, firmware units, or any combination thereof.

30 Additionally, one or more blocks illustrated in Figure 2 may be combined with other blocks, which may represent circuit hardware units, software algorithms, etc. Additionally, any number of the circuitry or software units associated with the various blocks illustrated in Figure 2 may be combined into a programmable device, such as a field programmable gate array, an ASIC device, etc.

Figure 3 provides a stylized depiction of an exemplary electrical signal of a firing neuron as a graph of voltage at a given point on the nerve at particular times during the propagation of an action potential along the nerve, in accordance with one embodiment of the present invention. A typical neuron has a resting membrane potential of about -70 mV, maintained by transmembrane ion channel proteins. When a portion of the neuron reaches a firing threshold of about -55 mV, the ion channel proteins in the locality allow the rapid ingress of extracellular sodium ions, which depolarizes the membrane to about +30 mV. The wave of depolarization then propagates along the neuron. After depolarization at a given location, potassium ion channels open to allow intracellular potassium ions to exit the cell, lowering the membrane potential to about -80 mV (hyperpolarization). About 1 msec is required for transmembrane proteins to return sodium and potassium ions to their starting intra- and extracellular concentrations and allow a subsequent action potential to occur.

Referring again to Figure 1, the IMD 100 may generate a pulsed electrical signal in embodiments of the present invention for application to a cranial nerve such as vagus nerve 127

according to one or more programmed parameters. In one embodiment, the parameters defining the electrical signal may be selected from the group consisting of an interburst period, a number of pulses per burst, an interpulse interval, a burst duration, a current magnitude, a pulse width, an on-time, and an off-time. Suitable ranges for these parameters may comprise a variety of values. In particular, the interburst period in microburst signals according to the present invention may, in one embodiment, be 100 milliseconds or greater, preferably 100 milliseconds to 10 minutes, and more preferably 1 second to 5 seconds. In another embodiment, the interburst period may be equal to or greater than the microburst duration of one of the two adjacent microbursts that the interburst period separates. The number of pulses comprising a microburst may range from about 2 to about 25 pulses, such as from 2 to about 20 pulses, and more specifically from 2 to about 15 pulses. Suitable interpulse intervals in the present invention may range from about 1 millisecond to about 50 milliseconds, more preferably from about 2 milliseconds to about 10 milliseconds. Suitable microburst durations may range from about 2 msec to about 1 sec, preferably less than about 100 msec, more preferably from about 5 msec to about 100 msec, and even more preferably from about 10 msec to about 80 msec.

Ranges for current magnitude and pulse width may comprise values similar to those for conventional VNS signals, e.g., current magnitudes of 0.10 – 6.0 milliamps, preferably 0.25 – 3.0 milliamps, and more preferably 0.5 – 2.0 milliamps. Pulse widths may range from about 0.05 to about 1.0 milliseconds, preferably 0.25 to about 0.5 milliseconds. In view of the stated values of pulse width and interpulse intervals, a 2-pulse microburst could comprise a microburst

duration of as little as 1.1 milliseconds, while a microburst of 25 pulses could last as long as about 1275 milliseconds, although microburst durations of 100 milliseconds or less are preferred. In embodiments of the present invention, however, the microbursts are no greater than 1 second in duration.

5 In one embodiment, microburst signals of the present invention may be applied to the nerve continuously, with microbursts being applied to the nerve separated only by the interburst period (e.g., 1 to 5 seconds in a preferred embodiment). In an alternative embodiment, the concepts of “on-time” and “off-time” associated with conventional VNS therapy may be used to provide an on-time interval in which microbursts, separated by the interburst period, are applied 10 to the nerve for the duration of the on-time, followed by an off-time period in which no electrical signal is applied to the nerve. Thus, for example, a series of microbursts separated by an interburst period of 1 second, in which each microburst comprises 3 pulses separated by an interpulse interval of 5 msec, may be applied to a vagus nerve of the patient for an on-time of 5 minutes, followed by an off-time of 10 minutes in which no electrical signal is applied to the 15 nerve. In some embodiments, the on-time may range from about 100 msec to about 60 minutes. In such embodiments, the off-times may range from 200 msec to 24 hours or more.

In a further embodiment, during the off-time of the microburst stimulation, an alternative stimulation technique, such as conventional cranial nerve stimulation, can be performed. Conventional cranial nerve stimulation generally also involves an on-time and an off-time, and 20 the on-time of the microburst stimulation may be during the off-time of the conventional cranial nerve stimulation.

If both microburst stimulation and an alternative stimulation technique are performed, the on-times, the off-times, or both of the two stimulation regimes may partially or wholly overlap.

25 Exemplary pulse waveforms in accordance with one embodiment of the present invention are shown in Figures 4A-4C. Pulse shapes in electrical signals according to the present invention may include a variety of shapes known in the art including square waves, biphasic pulses (including active and passive charge-balanced biphasic pulses), triphasic waveforms, etc. In one embodiment, the pulses comprise a square, biphasic waveform in which 30 the second phase is a charge-balancing phase of the opposite polarity to the first phase.

In microburst stimulation according to the present invention, the microbursts are markedly shorter in both the number of pulses and the microburst duration compared to pulse bursts in conventional neurostimulation such as vagus nerve stimulation. While conventional VNS typically involves pulse bursts at a frequency of 20-30 Hz for a period of from 7-60

seconds (resulting in a burst having from 140-1800 pulses or more), microbursts according to the present invention, by contrast, can have a microburst duration from about 1 msec to no more than 1 second. Further, each microburst comprises at least 2 and about 25 pulses, with each of the pulses separated from an adjacent pulse by an interpulse interval of from about 1 to about 50  
5 milliseconds, more typically from about 2 to about 10 milliseconds. While the individual pulses in a microburst according to this aspect of the invention may resemble conventional VNS signal pulses in pulse width and pulse current, the number of pulses in a microburst is markedly smaller than in a pulse burst in conventional VNS therapy. Consequently, microbursts are also much shorter in duration (less than 1 second and typically less than 100 msec, such as from  
10 about 10 msec to about 80 msec) than pulse bursts in conventional neurostimulation therapy (at least 7 seconds and typically 20-60 seconds). Moreover, in most cases, the interpulse interval separating the pulses is shorter than in conventional neurostimulation (typically 2-10 msec for microbursts compared to 30-50 msec for conventional VNS). Pulse bursts of the present  
15 invention are termed “microbursts” because they are significantly shorter in both the number of pulses and the total microburst duration than conventional neurostimulation signals.

As noted, it has been discovered by the present inventor that microbursts according to this aspect of the invention are capable of providing an enhanced vagal evoked potential (eVEP) in the patient’s brain that is significantly greater than VEPs produced by conventional vagus nerve stimulation signals. This eVEP is attenuated, however, as the number of pulses increases  
20 beyond an optimal number of pulses. Thus, for example, in the monkey model discussed below, where a microburst exceeds 2-5 pulses, the eVEP begins to diminish, and if more than 15 pulses are provided, the eVEP is highly diminished. To maintain the eVEP effect, this aspect of the present invention requires a small number of pulses in a microburst as well as an interburst period separating each microburst from the adjacent microburst in order to allow the nerve a  
25 refractory space to recover from the microburst. Providing an appropriate interburst period ensures that the succeeding microburst in the electrical signal is capable of generating an eVEP. In one embodiment the interburst period is as long as or longer than the duration of the adjacent microbursts separated by the interburst period. In another embodiment, the interburst period is at least 100 milliseconds, such as from about 1 sec to about 5 sec. Each microburst comprises a  
30 series of pulses that, in some embodiments, are intended to mimic the endogenous afferent activity on the vagus nerve. In one embodiment the microbursts may simulate afferent vagal action potentials associated with each cardiac and respiratory cycle.

Although evoked potentials have been discussed above in the context of the vagus nerve, enhanced evoked potentials can be generated by microburst stimulation of any cranial nerve, e.g.

the trigeminal nerve or glossopharyngeal nerve, and remain within the spirit and scope of the present invention. Thus, while the present invention is presented, in certain embodiments, as providing microburst stimulation to a vagus nerve of a patient, microburst stimulation may also be applied to other cranial nerves, and particularly the trigeminal nerve and the glossopharyngeal 5 nerve.

The central vagal afferent pathways involve two or more synapses before producing activity in the forebrain. Each synaptic transfer is a potential site of facilitation and a nonlinear temporal filter, for which the sequence of interpulse intervals in a microburst can be optimized. Without being bound by theory, it is believed that the use of microbursts enhances VNS efficacy 10 by augmenting synaptic facilitation and “tuning” the input stimulus train to maximize the forebrain evoked potential.

For example, as shown in FIG. 8, the vagal evoked potential (VEP) measured in the monkey thalamus is barely visible if elicited by a single stimulus pulse on the vagus nerve (FIG. 8A) and it virtually disappears if the single stimuli are presented in a train at 30 Hz, as in 15 conventional neurostimulation (FIG. 8B). However, as shown in the series of traces in the middle and lower panels of the figure, the VEP is enormously enhanced (resulting in eVEP) and optimized by using a microburst of pulses (2-6 pulses, microburst duration  $\leq$  1 second, FIG. 8C) at appropriate interpulse intervals (in this case, 6.7 msec was optimal for the first interpulse interval, shown in FIG. 8D) and at an interburst period (i.e., burst frequency) that approximates 20 the electrocardiogram R-R cycle (the period between R-waves of consecutive heartbeats) in the monkey (in this case 0.3 Hz, shown as FIG. 8E).

The use of pairs of pulses is a standard physiological tool for producing central responses by stimulation of small-diameter afferent fibers. However, according to the present disclosure, a microburst with an appropriate sequence of interpulse intervals enormously enhances the effect 25 of neurostimulation. By selecting an appropriate interburst period, an electrical signal for neurostimulation may comprise a series of microbursts that each provide eVEP. As illustrated in FIG. 8, a microburst duration of  $>10$  msec produces a maximal VEP in the monkey and a first interpulse interval of  $\sim 6\text{-}9$  msec produces maximal facilitation, and so according to the present disclosure, a microburst of pulses with a total duration of  $\sim 10\text{-}20$  msec and with an interpulse 30 interval of  $\sim 6\text{-}9$  msec and subsequent microbursts of similar duration will produce an optimal VEP in the monkey model. Though not to be bound by theory, the eVEP may result because such a microburst simulates the pattern of action potentials that occur naturally in the small-diameter afferent vagal fibers that elicit the central response that the present enhanced and optimized therapy may evoke (see below). Selection of an appropriate interburst period to

separate one microburst from the next may be performed experimentally, although as previously noted, a refractory period of at least 100 msec (such as from 100 msec to 10 min, such as 1 sec to 5 sec) and at least equal to the microburst duration is most desired.

The sequence of interpulse intervals may vary with the patient's heart rate variability 5 (HRV) (reflecting cardiac and respiratory timing) and also between individual patients, and thus, in one embodiment, the number of pulses, on-time duration, off-time duration, microburst frequency, the interpulse interval, the interburst period, and the microburst duration may be optimized for each patient. As a standard microburst sequence for initial usage, a microburst of 2 or 3 pulses at interpulse intervals of 5-10 msec will approximate the short peak of endogenous 10 post-cardiac activity. The interburst period may also be determined empirically by providing microbursts with a steadily decreasing interburst period until the eVEP begins to decline. In one embodiment, the interpulse interval is a series of equal intervals (i.e., the simplest train) or increasing intervals, simulating the pattern of a decelerating post-synaptic potential, as 15 illustrated in FIG. 9. In an alternative embodiment, the interpulse intervals may decrease through the microburst, or may be randomly determined within a preselected range, e.g., 5-20 msec. This modification of conventional neurostimulation methodology may produce a significant enhancement of neurostimulation efficacy that is applicable to many different medical conditions.

The optimization may be accomplished by recording, using surface electrodes, a far-field 20 VEP, which originates from the thalamus and other regions of the forebrain, and varying the stimulus parameters in order to maximize the recorded potential. As illustrated in Figure 1, standard EEG recording equipment 194 and 16- or 25- lead electrode placement (of which five electrodes 190 are shown, with leads 192 in electrical communication with the EEG recording equipment 194), such as typically used clinically for recording somatosensory or auditory 25 evoked potentials, will enable the VEP to be recorded and identified as an EEG recording 198. Neurostimulation stimulus burst timing can be used to synchronize averages of 8 to 12 epochs, if desired. By testing the effects of varied numbers of pulses, interpulse intervals, microburst durations, and interburst periods in defining the microbursts, the peak-to-peak amplitude of the eVEP in a microburst can be optimized in each patient.

30 Neurostimulation can be optimized in individual patients by selected stimulus parameters that produce the greatest effect as measured with EEG surface electrodes. The current amplitude and pulse width is first optimized by measuring the size of the VEP elicited by individual pulses (as opposed to a microburst). The number of pulses, interpulse intervals, microburst durations, and interburst periods for the microbursts are then optimized using the current amplitude and

pulse width previously determined, by measuring the size of the eVEP induced by the microbursts.

Because the large eVEPs recorded in the thalamus, striatum, and insular cortex of the anesthetized monkey shown in FIG. 8, are large enough that if evoked in a human patient, the 5 eVEPs are observable in a standard EEG detected using electrodes adjacent to the human patient's scalp, the standard EEG may be used to indicate the effects of modifications to the signal parameters of the exogenous electrical signal. In this manner, the EEG may be used to optimize or tune the neurostimulation electrical signal parameters for microbursts empirically. Without being bound by theory, it is believed that the eVEP recorded in the right thalamus and 10 striatum is significant for the anti-epileptic effects of neurostimulation, whereas another potential (in the left insular cortex) is most significant for the anti-depression effects of neurostimulation. By using regional EEG localization on the right or left frontal electrodes (FIG. 10), the neurostimulation electrical signal parameters for microbursts according to this 15 aspect of the invention can be optimized appropriately by measuring the eVEP in these respective regions for individual patients.

The optimal microburst parameters for eliciting eVEPs from these two areas (right thalamus/striatum and left insular cortex, respectively) may differ. Both eVEPs are identifiable with EEG recording methods in awake human patients, so that the appropriate area may easily be used for parametric optimization in an epilepsy or depression patient.

20 The regional EEG localization represented in FIG. 10 allows the early VEP in the right thalamus and basal ganglia associated with the antiepileptic effects of neurostimulation to be distinguished from the later VEP in the left thalamus and insular cortex that may be associated with the treatment of other medical conditions.

25 In one embodiment, the present invention may include coupling of at least one electrode to each of two or more cranial nerves. (In this context, two or more cranial nerves mean two or more nerves having different names or numerical designations, and do not refer to the left and right versions of a particular nerve). In one embodiment, at least one electrode may be coupled to either or both vagus nerves or a branch of either or both vagus nerves. The term "operatively" 30 coupled may include directly or indirectly coupling. Each of the nerves in this embodiment or others involving two or more cranial nerves may be stimulated according to particular activation modalities that may be independent between the two nerves.

Another activation modality for stimulation is to program the output of the IMD 100 to the maximum amplitude which the patient may tolerate. The stimulation may be cycled on and off for a predetermined period of time followed by a relatively long interval without stimulation.

Where the cranial nerve stimulation system is completely external to the patient's body, higher current amplitudes may be needed to overcome the attenuation resulting from the absence of direct contact with the cranial nerve, such as vagus nerve 127, and the additional impedance of the skin of the patient. Although external systems typically require greater power consumption 5 than implantable ones, they have an advantage in that their batteries may be replaced without surgery.

Returning to systems for providing cranial nerve stimulation, such as that shown in Figures 1 and 2, stimulation may be provided in at least two different modalities. Where cranial nerve stimulation is provided based solely on programmed off-times and on-times, the 10 stimulation may be referred to as passive, inactive, or non-feedback stimulation. In contrast, stimulation may be triggered by one or more feedback loops according to changes in the body or mind of the patient. This stimulation may be referred to as active or feedback-loop stimulation. In one embodiment, feedback-loop stimulation may be manually-triggered stimulation, in which the patient manually causes the activation of a pulse burst outside of the programmed on-time/off-time cycle. The patient may manually activate the IMD 100 to stimulate the cranial nerve, such as vagus nerve 127, to treat an acute episode of a medical condition. The patient may also be permitted to alter the intensity of the signals applied to the cranial nerve within 15 limits established by the physician.

Patient activation of an IMD 100 may involve use of an external control magnet for 20 operating a reed switch in an implanted device, for example. Certain other techniques of manual and automatic activation of implantable medical devices are disclosed in U.S. Pat. No. 5,304,206 to Baker, Jr., et al., assigned to the same assignee as the present application ("the '206 patent"). According to the '206 patent, means for manually activating or deactivating the electrical signal 25 generator 110 may include a sensor such as piezoelectric element mounted to the inner surface of the generator case and adapted to detect light taps by the patient on the implant site. One or more taps applied in fast sequence to the skin above the location of the electrical signal generator 110 in the patient's body may be programmed into the implanted medical device 100 as a signal for activation of the electrical signal generator 110. Two taps spaced apart by a slightly longer duration of time may be programmed into the IMD 100 to indicate a desire to 30 deactivate the electrical signal generator 110, for example. The patient may be given limited control over operation of the device to an extent which may be determined by the program dictated or entered by the attending physician. The patient may also activate the IMD 100 using other suitable techniques or apparatus.

In some embodiments, feedback stimulation systems other than manually-initiated stimulation may be used in the present invention. A cranial nerve stimulation system may include a sensing lead coupled at its proximal end to a header along with a stimulation lead and electrode assemblies. A sensor may be coupled to the distal end of the sensing lead. The sensor 5 may include a cardiac cycle sensor. The sensor may also include a nerve sensor for sensing activity on a nerve, such as a cranial nerve, such as the vagus nerve 127.

In one embodiment, the sensor may sense a body parameter that corresponds to a symptom of a medical condition. If the sensor is to be used to detect a symptom of the medical condition, a signal analysis circuit may be incorporated into the IMD 100 for processing and 10 analyzing signals from the sensor. Upon detection of the symptom of the medical condition, the processed digital signal may be supplied to a microprocessor in the IMD 100 to trigger application of the electrical signal to the cranial nerve, such as vagus nerve 127. In another embodiment, the detection of a symptom of interest may trigger a stimulation program including different stimulation parameters from a passive stimulation program. This may entail providing 15 a higher current stimulation signal or providing a higher ratio of on-time to off-time.

Turning now to Figure 5, a flowchart depiction of a method for treating a medical condition, in accordance with one illustrative embodiment of the present invention is provided. An electrode may be coupled to a portion of a cranial nerve to enhance cranial nerve evoked potentials. In one embodiment, one or more electrodes may be positioned in electrical contact or 20 proximate to a portion of the cranial nerve to deliver a stimulation signal to the portion of the cranial nerve (block 710). The electrodes may be operatively coupled to at least one of a main trunk of the right or left vagus nerve, or any branch thereof. The IMD 100 may then generate a controlled electrical signal characterized by an interburst period, a number of pulses per microburst, an interpulse interval, and a microburst duration, wherein at least one of the 25 interburst period, the number of pulses per microburst, the interpulse interval, or the microburst duration is selected to enhance cranial nerve evoked potentials (block 720). This may include a predetermined electrical signal that is preprogrammed based upon a particular condition of a patient. For example, a physician may pre-program the type of stimulation to provide in order to enhance cranial nerve evoked potentials in the patient based upon data specific to the patient. 30 The IMD 100 may then generate a signal, such as a controlled-current microburst signal, to affect one or more portions of the neurological system of a patient.

The IMD 100 may then deliver the stimulation signal to the portion of the cranial nerve (block 730). The application of the electrical signal may be delivered to the main trunk of the right or left vagus nerve, or any branch thereof. In one embodiment, application of the

stimulation signal may be designed to promote an afferent effect. Further, the stimulation by the IMD 100 may reduce incidents or symptoms relating to a medical condition.

Additional functions, such as a detection process, may be alternatively employed with the embodiment of the present invention. The detection process may be employed such that an external detection or an internal detection of a bodily function may be used to adjust the 5 operation of the IMD 100.

Turning now to Figure 6, a block diagram depiction of a method in accordance with an alternative embodiment of the present invention is illustrated. The IMD 100 may perform a database detection process (block 810). The detection process may encompass detecting a 10 variety of types of vital signs or other body parameters of the patient. A more detailed depiction of the steps for performing the detection process is provided in Figure 7, and accompanying description below. Upon performing the detection process, the IMD 100 may determine if stimulation is indicated (block 820). Upon a determination that stimulation is not indicated, the detection process is continued (block 830).

Upon a determination that stimulation is indicated, a determination as to the type of 15 stimulation based upon data relating to the patient's condition is made (block 840). The type of stimulation may be determined in a variety of manners, such as performing a look-up in a look-up table that may be stored in the memory 217. Alternatively, the type of stimulation may be determined by an input from an external source, such as the external unit 270 or an input from 20 the patient. Further, determination of the type of stimulation may also include determining the location as to where the stimulation is to be delivered. Accordingly, the selection of particular electrodes, which may be used to deliver the stimulation signal, is made.

Upon determining the type of stimulation to be delivered, the IMD 100 performs the stimulation by delivering the electrical signal to one or more selected electrodes (block 850).

Upon delivery of the stimulation, the IMD 100 may monitor, store, or compute the results of the 25 stimulation (block 860). For example, based upon the calculation, a determination may be made that adjustment(s) to the type of signal to be delivered for stimulation, may be performed. Further, the calculations may reflect the need to deliver additional stimulation. Additionally, data relating to the results of stimulation may be stored in memory 217 for later extraction or 30 further analysis. Also, in one embodiment, real time or near real time communications may be provided to communicate the stimulation result or the stimulation log to an external unit 270.

Turning now to Figure 7, a more detailed block diagram depiction of the step of performing the detection process of block 810 in Figure 6, is illustrated. The system 100 may monitor one or more vital signs or other bodily parameters of the patient (block 910). This

detection may be made by sensors residing inside the human body, which may be operatively coupled to the IMD 100. In another embodiment, these factors may be performed by external means and may be provided to the IMD 100 by an external device via the communication unit 260. In one embodiment, the sensors include a strain gauge that may be used to determine 5 inspiration by identifying chest expansion. By detecting the onset of chest expansion, the strain gauge may detect the onset of inspiration. The strain gauge may also detect expiration by identifying when the chest is contracting.

Upon acquisition of various signals, a comparison may be performed comparing the data relating to the signals to predetermined, stored data (block 920). Based upon the comparison of 10 the collected data with theoretical or stored thresholds, the IMD 100 may determine whether an appropriate time to commence an on-time block has been reached (block 930). Based upon the determination described in Figure 7, the IMD 100 may continue to determine whether further stimulation is indicated, as described in Figure 6.

Additionally, external devices may perform such calculations and communicate the 15 results or accompanying instructions to the IMD 100. The IMD 100 may also determine the specific location or branch of the nerve to stimulate. The IMD 100 may also indicate the type of stimulation to be delivered. For example, a microburst electrical signal alone or in combination with another type of treatment may be provided based upon the quantifiable parameter(s) that are detected. For example, a determination may be made that a microburst electrical signal by 20 itself is to be delivered. Alternatively, based upon a particular type of medical condition, a determination may be made that a microburst electrical signal, in combination with a conventional therapeutic VNS signal, is desirable as a therapy for the patient.

All of the methods and apparatuses disclosed and claimed herein may be made and 25 executed without undue experimentation in light of the present disclosure. While the methods and apparatus of this invention have been described in terms of particular embodiments, it will be apparent to those skilled in the art that variations may be applied to the methods and apparatus and in the steps, or in the sequence of steps, of the method described herein without departing from the concept, spirit, and scope of the invention, as defined by the appended 30 claims. It should be especially apparent that the principles of the invention may be applied to selected cranial nerves other than, or in addition to, the vagus nerve to achieve particular results in treating patients having epilepsy, depression, or other medical conditions.

The particular embodiments disclosed above are illustrative only as the invention may be modified and practiced in different but equivalent manners apparent to those skilled in the art having the benefit of the teachings herein. Furthermore, no limitations are intended to the

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details of construction or design herein shown other than as described in the claims below. It is, therefore, evident that the particular embodiments disclosed above may be altered or modified and all such variations are considered within the scope and spirit of the invention. Accordingly, the protection sought herein is as set forth in the claims below.

5 As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude other additives, components, integers or steps.

Reference to any prior art in the specification is not, and should not be taken as, an acknowledgment, or any form of suggestion, that this prior art forms part of the common general

10 knowledge in Australia or any other jurisdiction or that this prior art could reasonably be expected to be ascertained, understood and regarded as relevant by a person skilled in the art.

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The claims defining the invention are as follows:

1. A method of treating a medical condition in a patient using an implantable medical device, the patient having a cranial nerve, the method comprising:

    applying to a selected location on the cranial nerve of the patient, an electrical signal

5   characterized by having a plurality of microbursts and a number of pulses per microburst, wherein each microburst is separated from an adjacent microburst by an interburst period of at least 100 milliseconds, and wherein each microburst is patterned and comprises:

    a plurality of pulses per microburst,

    a plurality of interpulse intervals between adjacent pulses of the microburst of

10   less than about 50 milliseconds, and

    a microburst duration of not greater than 1 second,

    wherein at least one interpulse interval of the plurality of interpulse intervals in each microburst is selectively varied from the other interpulse intervals, and

    wherein at least one of the number of pulses per microburst, the interpulse interval, the

15   microburst duration, or the interburst period is selected to enhance cranial nerve evoked potentials within the patient.

2. The method of claim 1, wherein the number of pulses per microburst is from 3 pulses to about 25 pulses.

20

3. The method of claim 1 or 2, wherein the number of pulses per microburst is from 3 to about 15 or the microburst duration is from about 10 milliseconds to about 80 milliseconds.

25   4. The method of any one of the preceding claims, further comprising providing an electrode, coupling said electrode to the cranial nerve, providing a programmable electrical signal generator coupled to the electrode, and wherein applying the electrical signal to a selected location on the cranial nerve comprises generating an electrical signal with the electrical signal generator and applying the electrical signal to the electrode.

30   5. The method of any one of the preceding claims, wherein the applying the electrical signal to a selected location on the cranial nerve is performed during a first period, and further comprising the step of applying a second electrical signal to the selected location on the cranial

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nerve using the electrode during a second period, wherein the second electrical signal has more than 50 pulses per burst or a burst duration of at least about 7 seconds.

6. The method of any one of the preceding claims, wherein applying said electrical signal to a cranial nerve comprises applying said electrical signal to a vagus nerve of the patient.

7. A method of treating a medical condition of a patient, comprising:  
coupling at least one electrode to a selected location on at least one cranial nerve of the patient,

10 providing a programmable electrical signal generator coupled to the electrode,  
generating an electrical signal characterized by having a plurality of microbursts and a number of pulses per microburst, wherein each microburst is separated from an adjacent microburst by an interburst period of at least 100 milliseconds, and wherein each microburst is patterned and comprises:

15 from 3 to 25 pulses per microburst

a plurality of interpulse intervals between adjacent pulses of the microburst of less than about 50 milliseconds, and

a microburst duration of not greater than 1 second,

wherein at least one interpulse interval of the plurality of interpulse intervals in each microburst  
20 is selectively varied from the other interpulse intervals, and

applying the electrical signal to the electrode to treat the medical condition.

8. The method of claim 7, wherein the electrical signal comprises a first electrical signal and the step of applying the electrical signal to a selected location on the cranial nerve is performed  
25 during a first period, and further comprising the step of applying a second electrical signal different from said first electrical signal to the cranial nerve using the electrode during a second period, wherein the second electrical signal has more than about 50 pulses per burst or a burst duration of at least about 7 seconds.

30 9. A system for treating a medical condition, comprising:  
at least one electrode for coupling to at least one cranial nerve of a patient, and  
an implantable device operatively coupled to the electrode and comprising an electrical signal generator for applying an electrical signal characterized by having a plurality of microbursts and a number of pulses per microburst, wherein each microburst is separated from

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an adjacent microburst by an interburst period of at least 100 milliseconds, and wherein each microburst is patterned and comprises:

from 3 to 25 pulses per microburst,

a plurality of interpulse intervals between adjacent pulses of the microburst of less than about 50 milliseconds, and

a microburst duration of not greater than 1 second,

wherein at least one interpulse interval of the plurality of interpulse intervals in each microburst is selectively varied from the other interpulse intervals, and

wherein at least one of the number of pulses per microburst, the interpulse interval, the

microburst duration, or the interburst period is selected to enhance cranial nerve evoked potentials within the patient.

10. The system for treating a medical condition of claim 9, wherein the electrode couples to at least one cranial nerve selected from the group consisting of the left vagus nerve, the right vagus nerve, the glossopharyngeal nerve, and the trigeminal nerve.

11. The system for treating a medical condition of claim 9 or 10, wherein the electrical signal generator is a programmable electrical signal generator.

20 12. The system for treating a medical condition of any one of claims 19 to 11, further comprising a detection communicator capable of delivering at least one signal to the electrical signal generator, and wherein the electrical signal generator is capable of applying the electrical signal on receipt of the at least one signal from the detection communicator.

25 13. A method of treating a medical condition in a patient using an implantable medical device, the patient having a vagus nerve, the method comprising:

applying a first electrical signal to the vagus nerve of the patient during a first period, wherein the first electrical signal comprises a plurality of microbursts, wherein each microburst has more than about 50 pulses or has a burst duration of at least about 7 seconds, and

30 applying a second electrical signal to the vagus nerve of the patient during a second period, wherein the second electrical signal comprises a plurality of microbursts, wherein each microburst is separated from an adjacent microburst by an interburst period of at least 100 milliseconds, and wherein each microburst is patterned and comprises:

from 3 to about 25 pulses per burst,

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a plurality of interpulse intervals between adjacent pulses of the microburst, wherein each interpulse interval is from about 1 millisecond to about 50 milliseconds, and wherein at least one interpulse interval of the plurality of interpulse intervals in each microburst is selectively varied from the other interpulse intervals, and

5 a burst duration from about 2 milliseconds to about 1 second.

14. A computer readable program storage device encoded with instructions for execution of a method, as claimed in any one of claims 1 to 8 and 13.

10 15. A method according to claim 1, 7 or 13, or a system according to claim 9, substantially as herein described.

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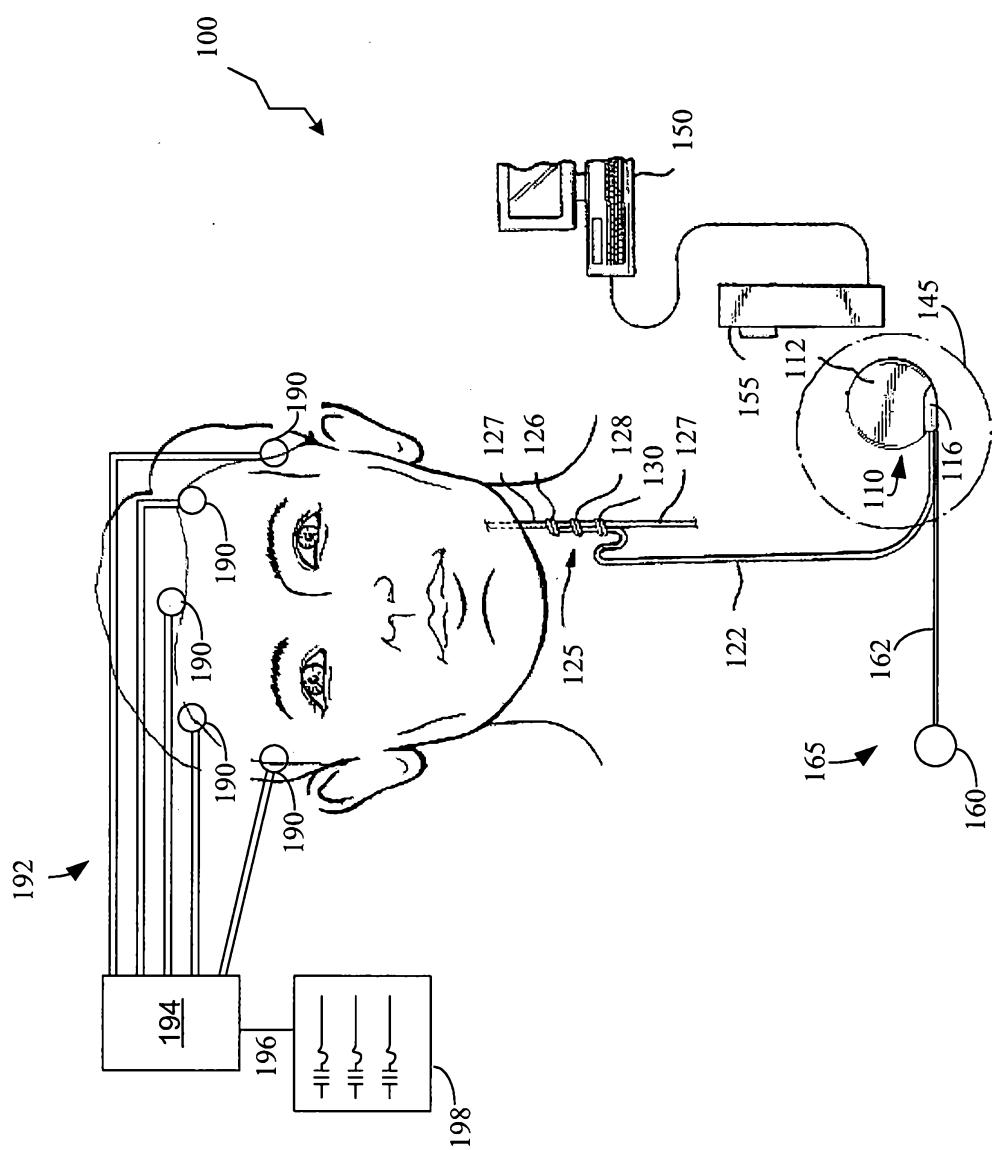
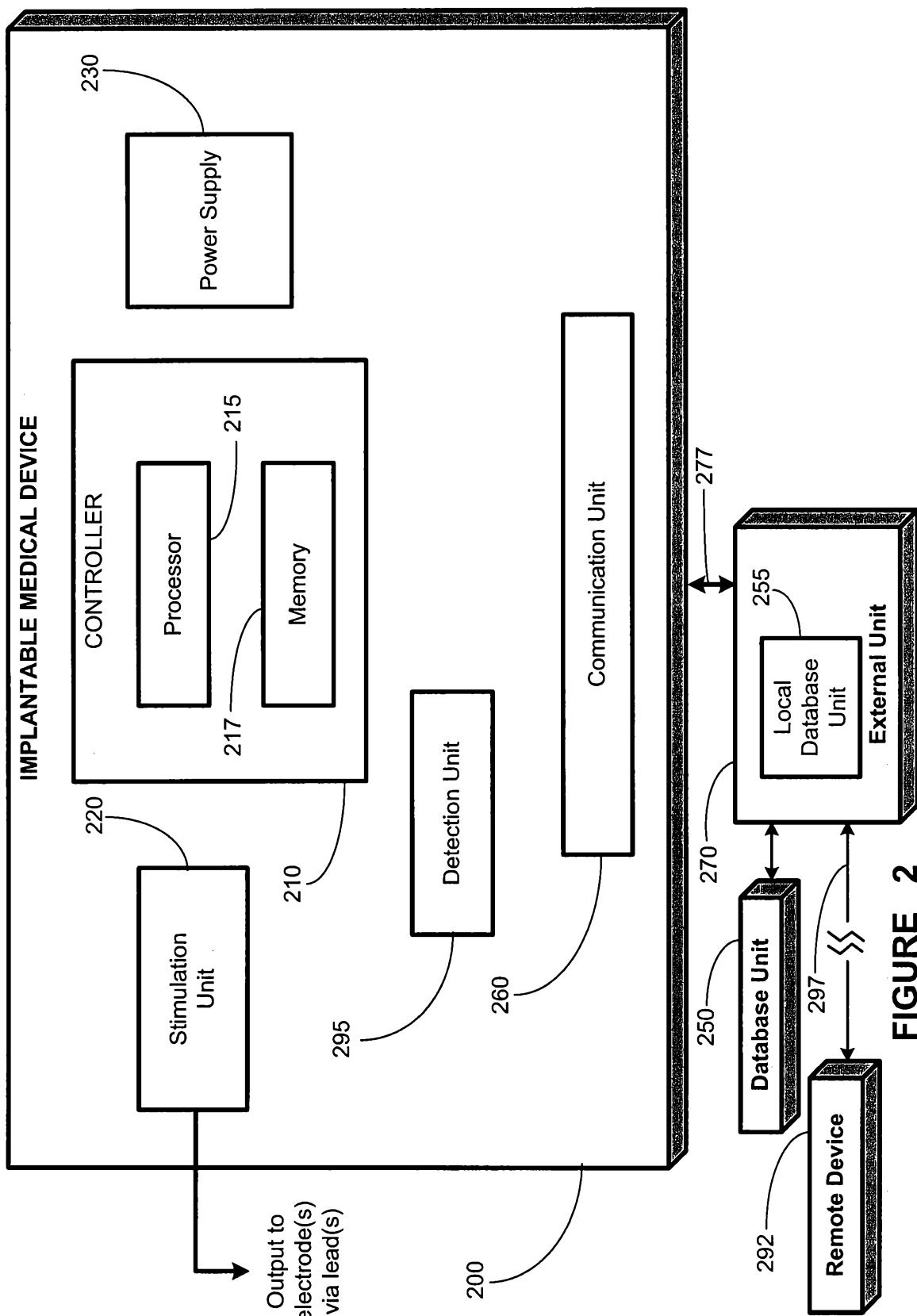


FIGURE 1



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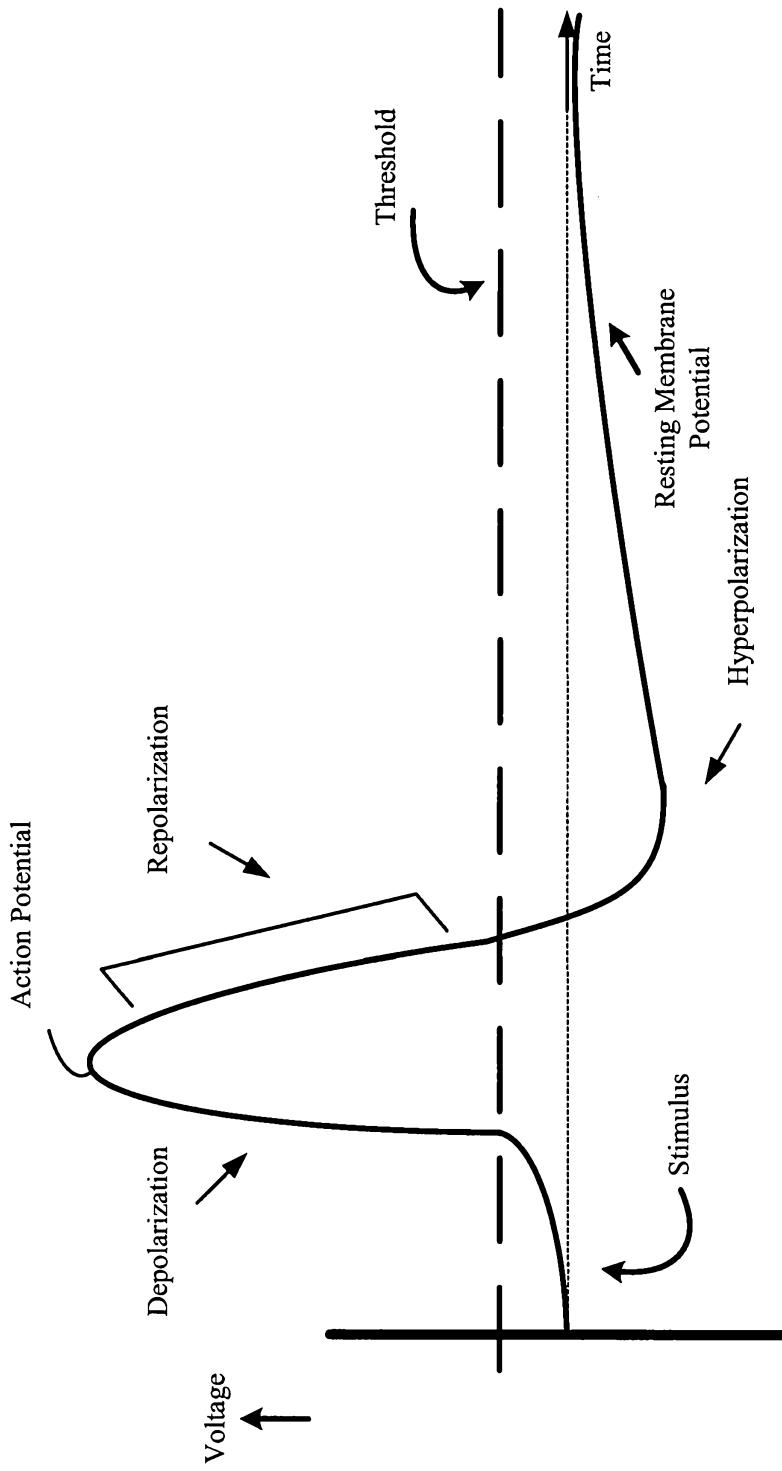
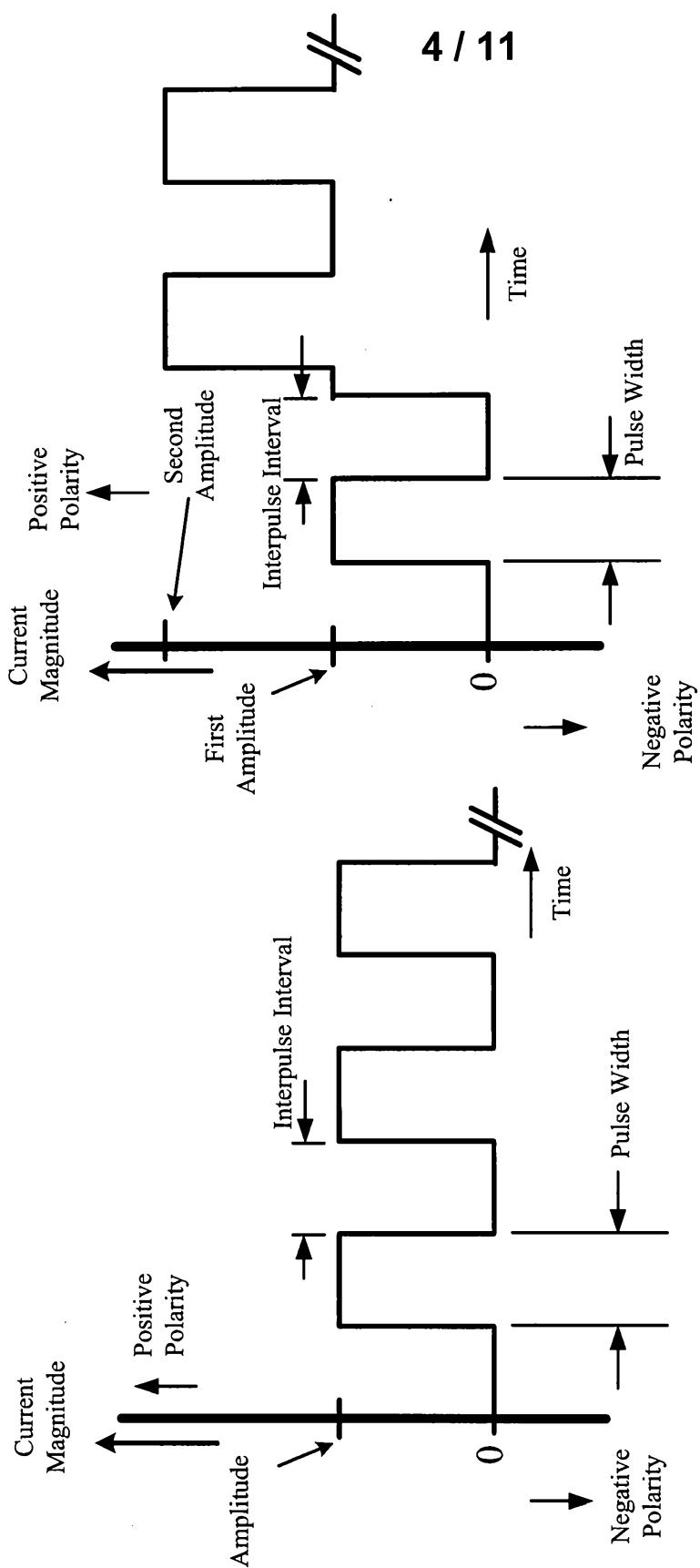


FIGURE 3



**FIGURE 4A**

**FIGURE 4B**

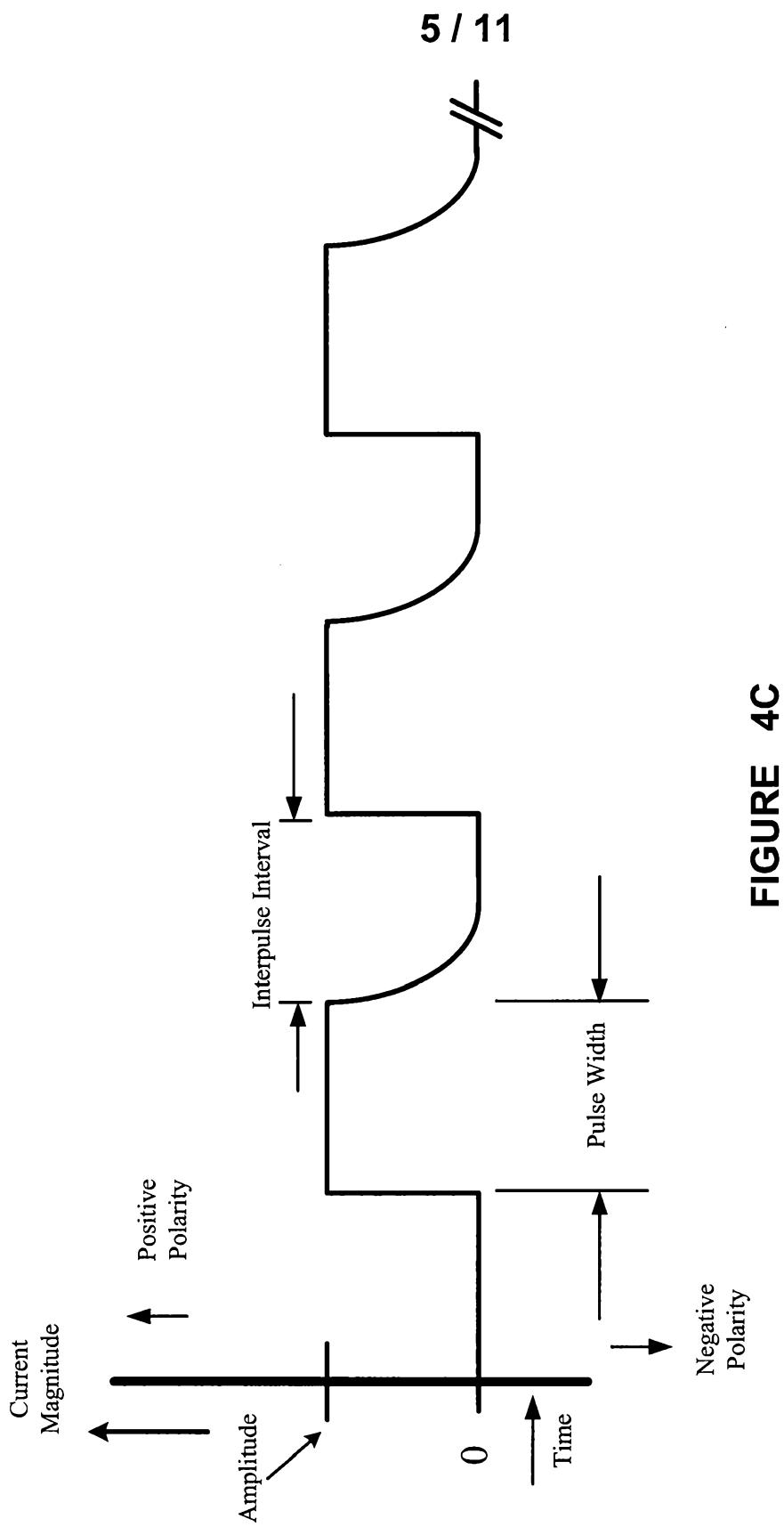


FIGURE 4C

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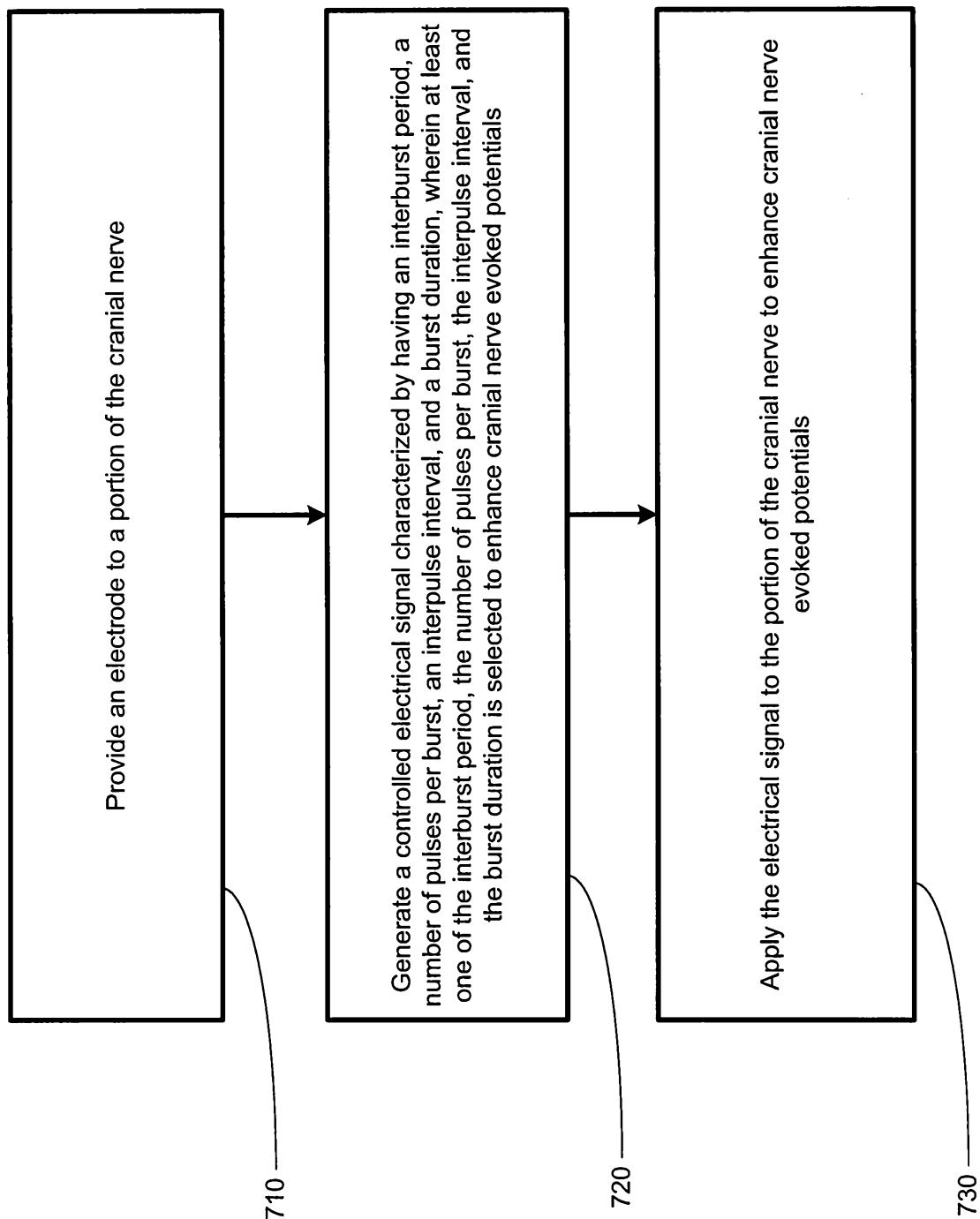


FIGURE 5

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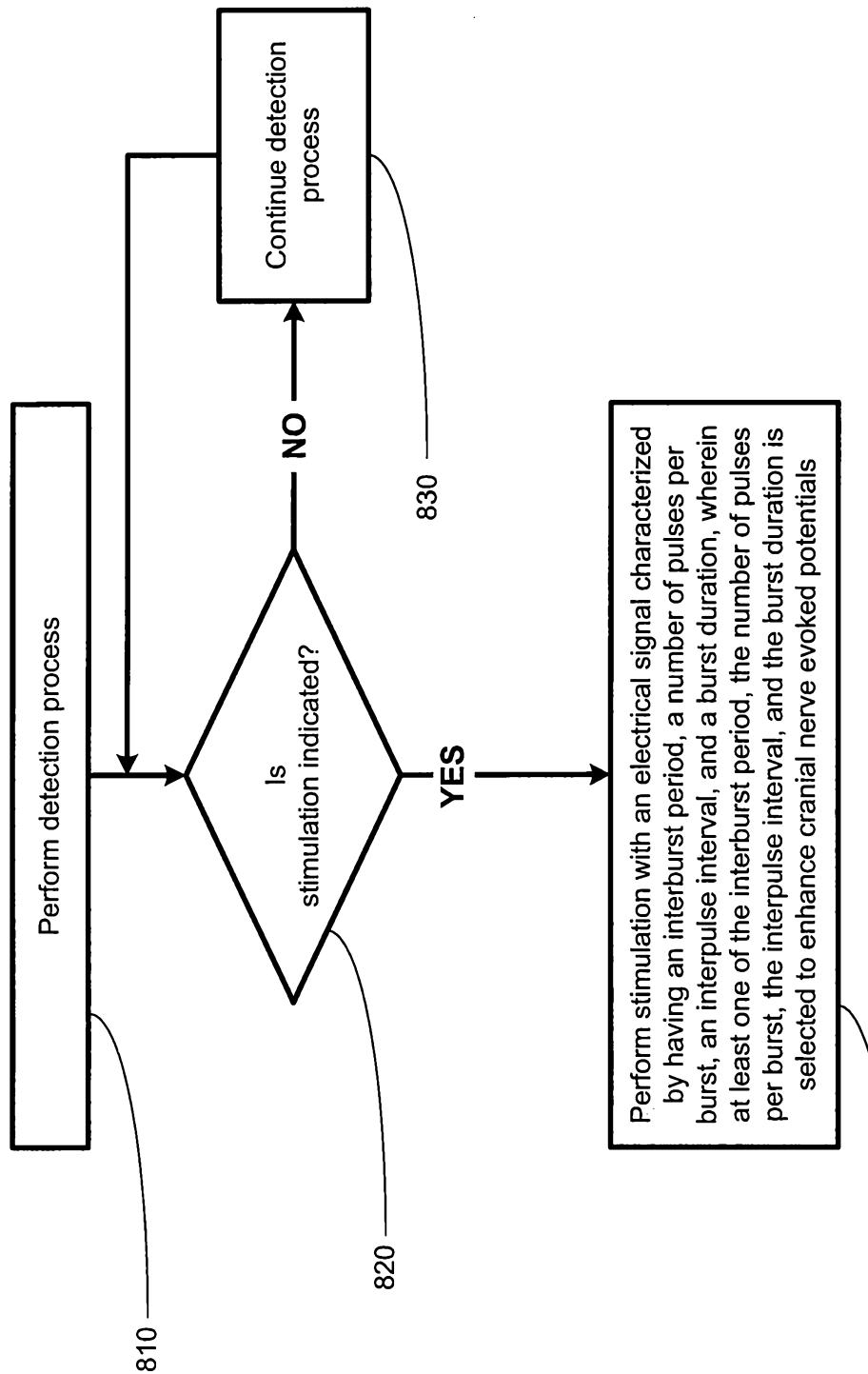


FIGURE 6

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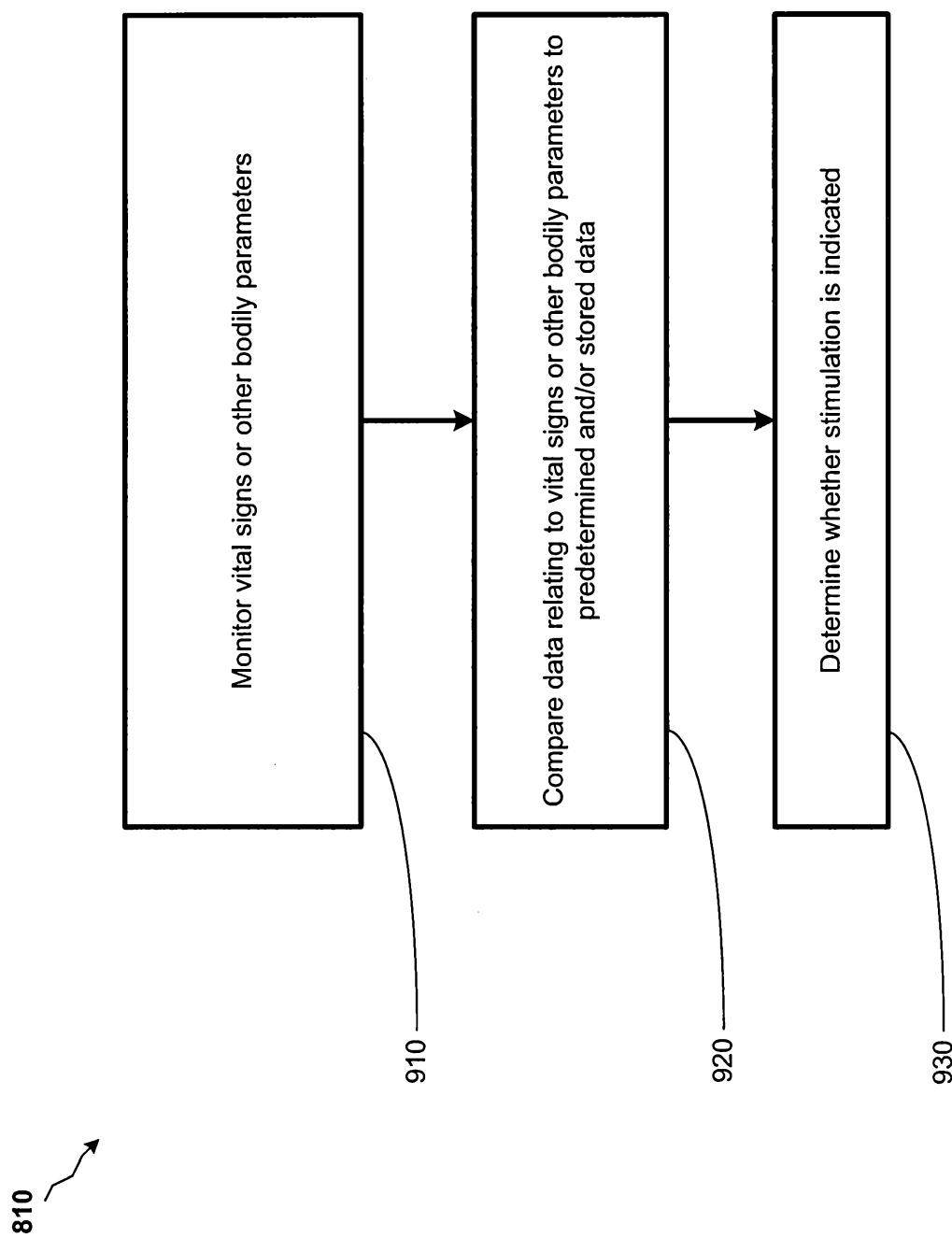


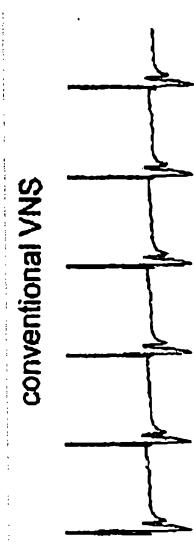
FIGURE 7

810



single pulse (every 4 sec)

FIGURE 8A



single pulse at 30 Hz (every 33 msec)

FIGURE 8B

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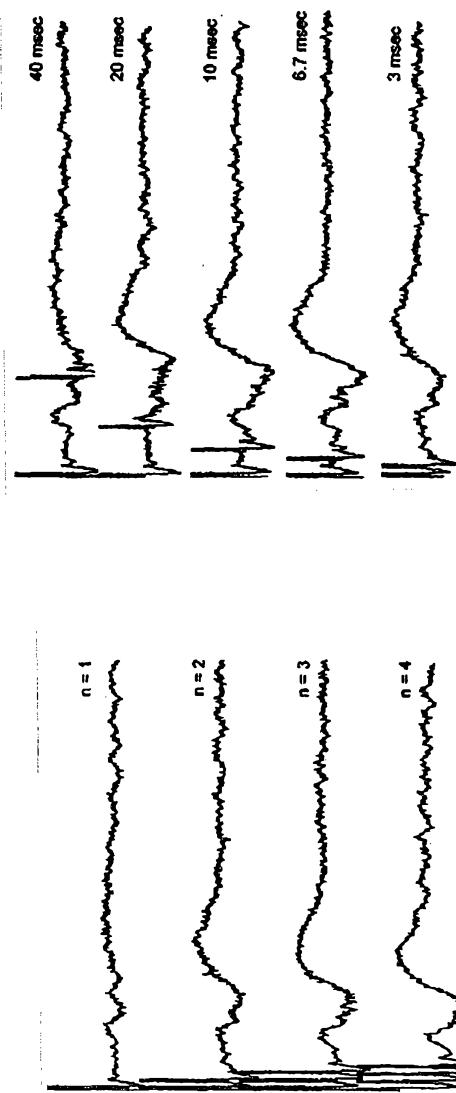
effect of burst duration (number of pulses)  
(3 msec interval; every 4 sec)

FIGURE 8C

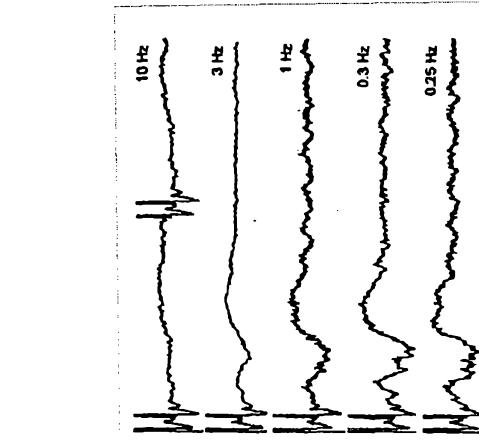
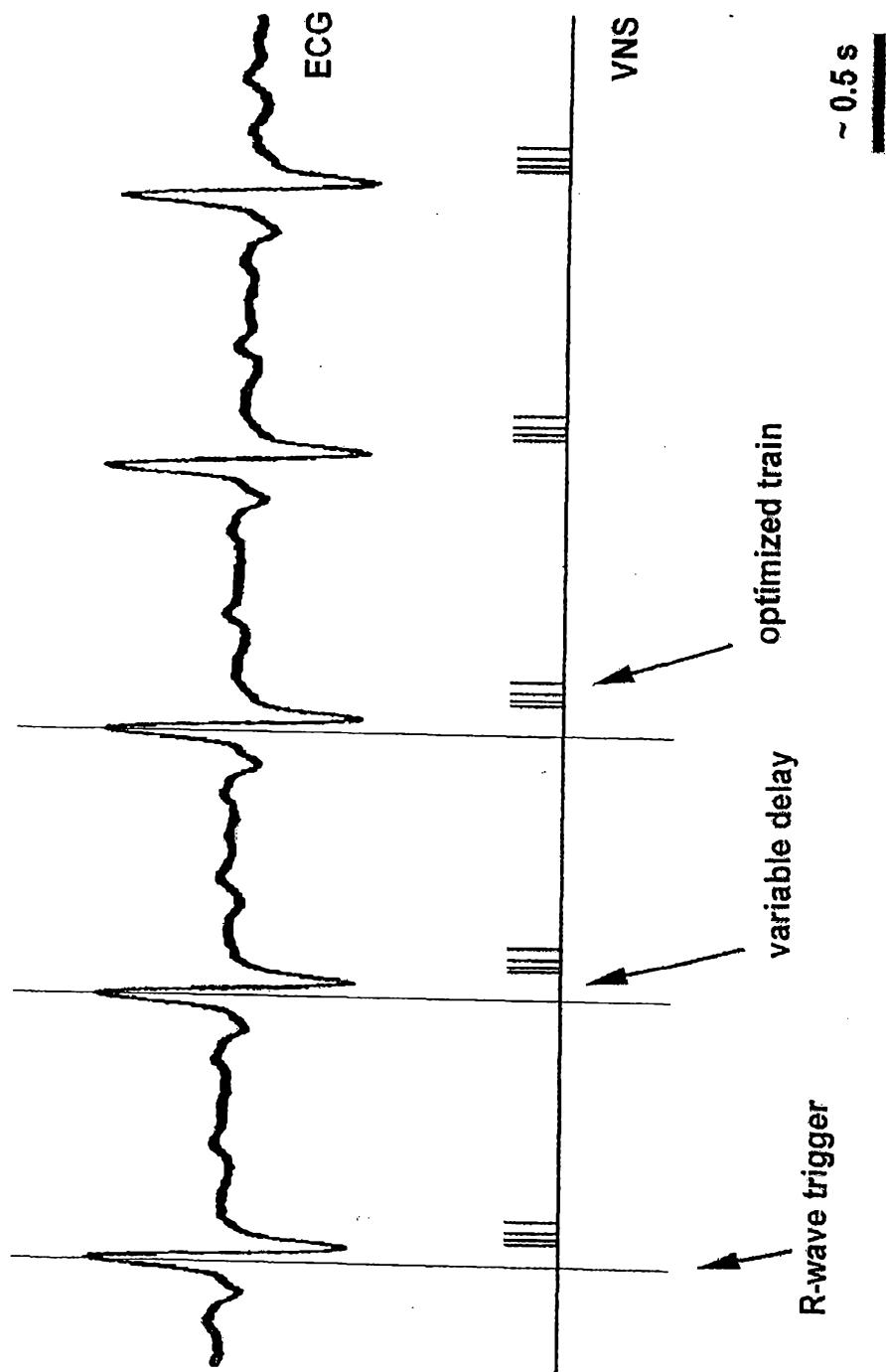
effect of interval between pulses  
(every 4 sec)

FIGURE 8D

effect of burst frequency  
(2 pulses at 6.7 msec interval)

FIGURE 8E

FIG. 9



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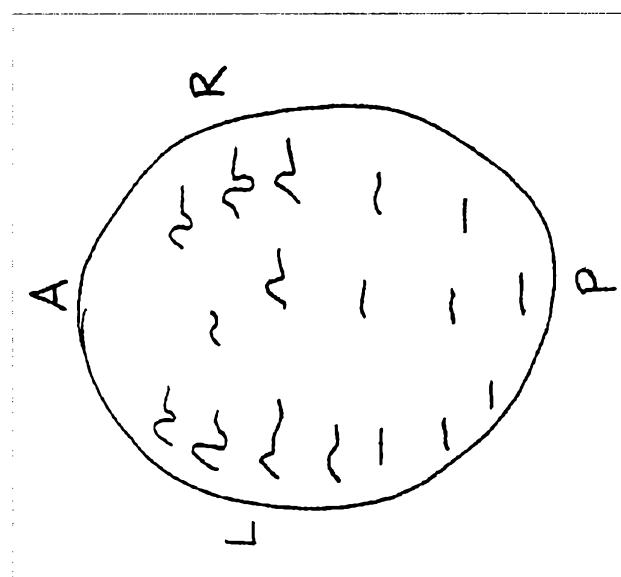


FIGURE 10