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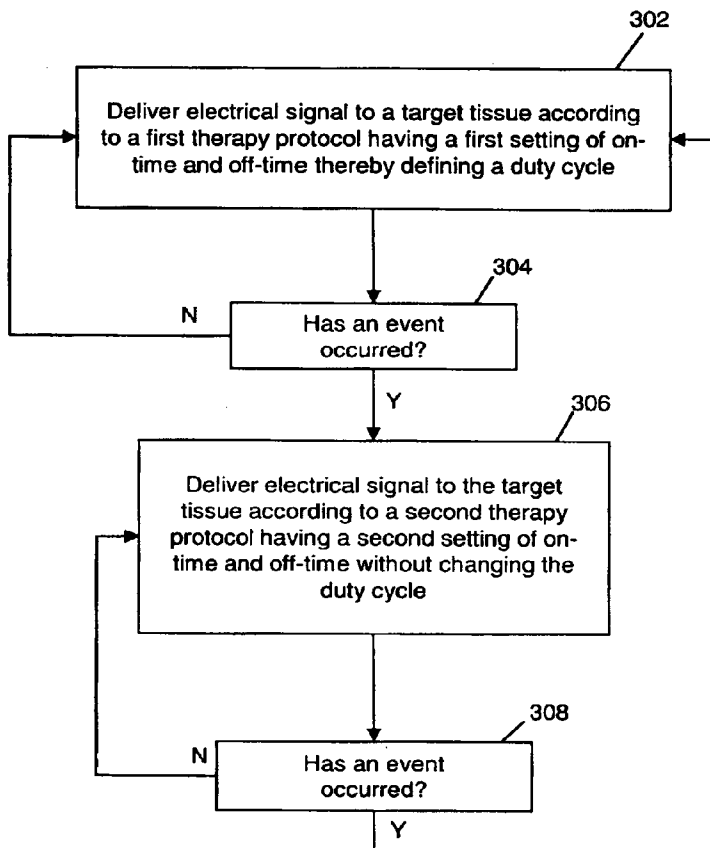
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- (71) Applicant (for all designated States except US): **CYBERONICS, INC.** [US/US]; 100 Cyberonics Blvd., Houston, TX 77058 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KOLAFA, Jerry, J.** [US/US]; 1310 Emily Morgan Circle, Richmond, TX 77469 (US). **MASCHINO, Steven, E.** [US/US]; 2501 Sand Bar Court, Seabrook, TX 77586 (US).
- (74) Agent: **SCOTT, Timothy, L.**; 100 Cyberonics Blvd., Houston, TX 77058 (US).

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[Continued on next page]

(54) Title: COMPENSATION REDUCTION IN TISSUE STIMULATION THERAPY



(57) Abstract: Methods and systems for reducing compensation of the body to therapy delivered by an implanted medical device are described herein. The disclosed techniques cause a change from one therapy protocol to another therapy protocol based on the occurrence of an event (e.g., time, user activations of a sensor, input from a physiological sensor, etc.). The therapy protocols of the implanted medical device differ in terms of the on-time and off-time, but effectuate the same or similar duty cycle.

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COMPENSATION REDUCTION IN TISSUE STIMULATION THERAPY

BACKGROUND

Technical Field

[0001] The subject matter of this disclosure generally relates to the field of implantable medical devices. More specifically, the present disclosure relates to reducing compensation in tissue stimulation therapy, and particularly electrical neurostimulation therapy.

Background Information

[0002] Implantable medical devices (IMDs) are used to treat a variety of diseases and disorders. Some types of IMDs apply an electrical signal to a patient's body tissue to which the IMD is coupled. For example, a neurostimulator can be coupled to a patient's vagus nerve to provide an electrical signal to the nerve to treat seizure disorders such as epilepsy. Providing an electrical signal to the vagus nerve can also be therapeutically beneficial to treat other conditions, including depression and various eating disorders such as bulimia nervosa.

[0003] The body is known to compensate or alter its response to repeated stimuli. For example, after receiving an electrical neurostimulation therapy over an extended period of time, the body may adapt or compensate in response to the repeated application of the electrical signal, thereby rendering the therapy provided by the IMD less beneficial. When this happens, a healthcare provider may adjust the operation of the IMD. An IMD adjustment may involve altering one or more operating parameters that define the electrical signal, such as current amplitude, pulse width, pulse frequency, on time, off time, etc. After the adjustment has been made to the electrical parameter(s), the body eventually may again compensate to the therapy provided by the IMD, thereby again rendering the therapy provided by the IMD less beneficial. Numerous adjustments may thus be required because the body may continually compensate to the therapy. Each IMD adjustment usually requires a visit to the physician that, for many patients, is time-consuming, expensive, and generally undesirable.

BRIEF SUMMARY

[0004] The present disclosure addresses the issues noted above by reducing or preventing the body from compensating to a given therapy protocol delivered by an implanted medical device. The disclosed techniques involve a change from a first therapy protocol to a second therapy protocol based on the occurrence of an event (e.g., an elapsed time interval, user activations of the therapy, input from a physiological sensor, etc.). The first and second therapy protocols differ in terms of the on-time and off-time, but effectuate the same or a similar duty cycle. Therapy protocols that have the same duty cycle, albeit with different settings for on-time and off-time, may result in similar therapeutic benefits to the patient. The implanted medical device preferably switches from the first such therapy protocol to the second before the body has a chance to compensate for the first therapy protocol.

[0005] In at least one embodiment, a method comprises delivering an electrical signal to a nerve according to a first setting of an on-time and off-time that defines a duty cycle. The method also comprises automatically changing the first setting to a second setting of on-time and off-time in response to an event. The second setting defines a duty cycle substantially equal to the duty cycle defined by the first setting.

[0006] In another embodiment, a system comprises a pulse generator that provides an electrical signal to a nerve and a controller coupled to the pulse generator. The controller causes the pulse generator to deliver an electrical signal to a nerve according to a first setting of an on-time and off-time that defines a duty cycle. In response to a first event, the controller also causes a change from the first setting to a second setting of an on-time and off-time that defines the same or similar duty cycle as defined by the first setting.

[0007] The foregoing has outlined rather broadly the features and technical advantages of the present invention in order that the detailed description of the invention that follows may be better understood. Additional features and advantages of the invention will be described hereinafter that form the subject of the claims of the invention. It should be appreciated by those skilled in the art that the conception and the specific embodiments disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present invention. It should also be realized by

those skilled in the art that such equivalent constructions do not depart from the spirit and scope of the invention as set forth in the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] For a detailed description of the preferred embodiments of the invention, reference will now be made to the accompanying drawings in which:

[0009] FIGURE 1 depicts, in schematic form, an implantable medical device, in accordance with a preferred embodiment of the invention, implanted within a patient and programmable by an external programming system;

[0010] FIGURE 2 is a block diagram of the implantable medical device of Figure 1 and comprising a user input sense device; and

FIGURE 3 illustrates a flow diagram of an embodiment of a method for treating or preventing compensation in tissue stimulation therapy.

NOTATION AND NOMENCLATURE

[0011] Certain terms are used throughout the following description and claims to refer to particular system components. 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 "comprising" 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 an indirect or direct electrical connection. Thus, if a first device couples to a second device, that connection may be through a direct electrical connection, or through an indirect electrical connection via other devices and connections. The terms "substantially the same as" and "substantially equal to," when used in conjunction with an electrical signal parameter such as duty cycle, refer to two parameters differing by no more than 25%, preferably no more than 10%, and more preferably by no more than 5%.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0012] The present invention is susceptible to implementation in various embodiments. The disclosure of specific embodiments, including preferred embodiments, is not intended

to limit the scope of the invention as claimed unless expressly specified. In addition, persons skilled in the art will understand that the invention has broad application. Accordingly, the discussion of particular embodiments is meant only to be exemplary, and does not imply that the scope of the disclosure, including the claims, is limited to specifically disclosed embodiments.

[0013] The following description is presented largely in terms of vagus nerve stimulation (“VNS”). However, the disclosure and claims that follow are not limited to VNS, and may be applied to the delivery of an electrical signal to modulate the electrical activity of other cranial nerves such as the trigeminal and/or glossopharyngeal nerves, or to other neural tissue such as one or more brain structures of the patient, spinal nerves, and other spinal structures. Further still, other embodiments of the invention can be implemented to stimulate tissue other than nerves or neural tissue, such as cardiac tissue, muscle tissue, connective tissue, or bone tissue.

[0014] As discussed above, it is known that the body compensates or alters its response in reaction to repeated electrical signals applied to a target tissue. In the case of neurostimulation therapy applied to a nerve, without being bound by theory the body may adapt by changes to the nerve itself (which may include structural and/or functional changes), changes in one or more brain centers involved in processing electrical signals from the nerve, or both. In addressing the problem of compensation or adaptation, various embodiments of the invention comprise an implantable medical device (IMD) that alters its therapy protocol to reduce or prevent the body from compensating to the therapy. The therapy protocol provided by the IMD comprises an electrical signal applied to a target tissue, with the signal characterized by a set of parameters. The parameters comprise, in at least some embodiments, pulse frequency, pulse width, current amplitude, on-time, and off-time. One therapy protocol differs from another therapy based on differences in the underlying parameters that define each therapy protocol. The “on-time” refers to the time period during which the IMD is actively stimulating tissue and the “off-time” refers to the time period in which no stimulation is provided.

[0015] In general, the IMD described herein provides a therapy protocol in which a therapy signal (which may comprise an electrical signal, a mechanical signal such as a vibration signal, an optical signal, a chemical signal, or another type of signal) is provided

to the target tissue for an on-time and then turned off (i.e., not provided to the target tissue) during an off-time. The therapy protocol then typically repeats itself over and over until the IMD is reprogrammed, or another intervention occurs, such as a manual intervention by the patient to temporarily deliver a different protocol for a short time period.

[0016] In electrical neurostimulation therapy such as vagus nerve stimulation therapy, the electrical signal is typically applied to the nerve as a pulsed electrical signal that is defined by a plurality of parameters. These may include current amplitude, pulse width, and pulse frequency. The electrical signal as thus defined is typically applied to the nerve in a series of pulses known as a burst. The burst is defined by an on-time, e.g., 30 seconds. For pulsed electrical signals, the on-time includes interpulse periods in which no electrical pulse is being applied to the nerve. The on-time period is followed by an off-time period in which no signal is applied to the nerve. The therapy is provided by cycling between on-time and off-time periods.

[0017] The “duty” cycle” of such a therapy protocol is the percentage of time in which the signal is being provided to the target tissue, i.e., it is the ratio of on-time to the sum of on-time and off-time. For example, a 50% duty cycle means that the on-time is equal to the off-time, and the electrical signal is being provided half of the time. It is important to note that where the signal is a pulsed signal, an electrical pulse is actually applied to the nerve for a small fraction of the total on-time. For example, in a 30 second burst (i.e., 30 second on-time) having a frequency of 20 Hz and a pulse width of 0.5 milliseconds, electrical charge is actually being delivered to the nerve for only 10 milliseconds (20 Hz X 0.5 milliseconds) each second of the burst, or 1% of the on-time. However, the entire 30 second on-time period is included in calculating the duty cycle. Thus, for pulsed electrical signals duty cycle is not the percentage of time that electrical charge is being delivered to the nerve, but the percentage of on-time to total time. In the alternative embodiment of non-pulsed signals, on the other hand, the duty cycle may equal the percentage of time that charge is delivered to the nerve.

[0018] Consistent with the foregoing, any given duty cycle can be implemented with a variety of different on-time/off-time patterns. For example, a 50% duty cycle can be implemented by a therapy protocol having an on-time of 10 seconds and an off-time of 10

seconds, as well as by a therapy protocol having an on-time of 15 seconds and an-off time of 15 seconds. Other therapy protocols having an equivalent duty cycle are obviously also available.

[0019] In accordance with some embodiments of the invention, the IMD automatically changes the on-time and off-time parameter settings periodically, without appreciably changing the duty cycle. It has been discovered that two or more therapy protocols having different on-time and off-time settings, while all other parameters remain substantially the same, including in particular duty cycle, may provide the same or similar therapeutic benefit to the patient while avoiding compensation for the signal that may reduce therapeutic benefit to the patient. Thus, in accordance with at least some embodiments, the IMD automatically changes the settings of on-time and off-time, while maintaining the duty cycle largely the same. Doing so reduces or avoids the body's tendency to compensate to the therapy protocol being delivered. That is, the body does not have a chance to compensate before the IMD changes the therapy protocol to a different therapy protocol with the same or a similar duty cycle. It has been discovered that where the duty cycle remains largely the same, the therapeutic efficacy to the patient likewise remains largely the same from one therapy to the next, but the tendency to compensate is reduced or eliminated. It is believed that such a periodically changing protocol may enable certain patients who would otherwise adapt to the therapy (thereby reducing or eliminating a therapeutic benefit) to instead maintain therapeutic efficacy.

[0020] Figure 1 illustrates an implantable medical device ("IMD") 110 implanted in a patient. The IMD 110 may be representative of any of a variety of medical devices that provide a signal (e.g., an electrical, mechanical, chemical, or optical signal) to a target tissue of a patient. At least one preferred embodiment of the IMD 110 comprises a neurostimulator for applying an electrical signal to a neural structure in a patient, particularly a cranial nerve such as a vagus nerve 113. A lead assembly 116 is coupled to the IMD 110 and includes one or more electrodes, such as electrodes 112 and 114. Lead 116 has a proximal end that connects to the IMD 110 and a distal end on which the electrodes are provided. The outer housing (or "can") 129 of the IMD 110 preferably is electrically conductive and thus may also function as an electrode. The electrodes, such as electrodes 112, 114 and can 129, can be used to apply an exogenous electrical signal

to and/or sense the electrical activity of the associated tissue (e.g., the vagus nerve 113). In one embodiment, a strain relief tether 115 comprises an attachment mechanism to help secure the lead assembly 116 to the nerve 113 and to provide strain relief. An example of a suitable strain relief tether is described in U.S. Pat. No. 4,979,511, incorporated herein by reference.

[0021] Figure 1 also illustrates an external programming system 120 comprising a programming device 124 coupled to a wand 128. The programming device 124 may comprise a personal computer, handheld computer (e.g., a personal digital assistant (PDA) device), or other suitable computing device consistent with the description contained herein. Methods and apparatus for communication between the IMD 110 and an external programming system 120 are known in the art. As explained below, in one embodiment the IMD 110 includes a transceiver (such as a coil) that permits signals to be communicated wirelessly and non-invasively between the external wand 128 and the implanted IMD 110. Via the wand 128, the programming system 120 generally monitors the performance of the IMD 110 and downloads new programming parameters (e.g., on-time, off-time, pulse width, current amplitude, and pulse frequency) into the device to alter its operation as desired.

[0022] Figure 2 shows a block diagram of one embodiment of the IMD 110. As shown, the IMD 110 comprises a system that includes a battery 230, a pulse generator 232, and a controller 234. Under the control of controller 234, the pulse generator 232 generates an electrical signal to apply to a target tissue (e.g., a vagus nerve 113) in a patient. The battery 230 provides power to both the pulse generator 32 and, via the pulse generator, to the controller 234. The controller 234 generally assists, controls, and/or programs the pulse generator 232. Controller 234 preferably comprises a central processing unit (CPU) 236 such as a low-power, mixed-signal microcontroller. In general, any suitable processor can be used to implement some or all of the functionality explained herein.

[0023] The CPU 236 preferably couples to one or more analog-to-digital converters (ADCs) 48 and storage 240. The storage 240 preferably comprises volatile and/or non-volatile memory. The non-volatile memory may comprise Flash memory. The volatile memory may comprise any suitable type of random access memory (RAM). The storage 240 is used to store code that is executed by the CPU 236. Such executable code may

be loaded into the IMD 110 during manufacturing and/or may be downloaded to the IMD from the programming system 120 after implantation. The executable code may be loaded into non-volatile memory and either executed directly from the non-volatile memory or copied to the volatile memory for execution therefrom.

[0024] The storage 240 or other storage (e.g., registers) in the pulse generator 232 may be used to store the parameter settings that define a therapy protocol or program. In accordance with a preferred embodiment of the invention, the IMD 110 may be programmed with a plurality of therapy protocols. The therapy protocols may be loaded into IMD 110 during manufacturing and/or downloaded to the IMD 110 from programming system 120 after implantation. The controller 234 can cause the pulse generator 232 to operate in accordance with any suitable therapy protocol from among one or more such protocols programmed into the IMD 110.

[0025] In a preferred embodiment, the IMD 110 includes a user input sensor 260 and a physiological sensor 262. Sensor 260 is used to sense an external user input such as a tap, a magnetic field, a sound, etc. Sensor 260 can be used to provide manual control of the IMD 110 by a person (e.g., the patient in which the IMD is implanted). The sensor 260 is preferably integrated within the IMD 110, but in alternative embodiments can be physically separate.

[0026] In at least one embodiment, user input sensor 260 comprises an implanted tap sensor such as an accelerometer. The tap sensor provides an electronic signal to the IMD 110 in response to a patient's physical tap or touching of the skin over the location of the implanted tap sensor. In another embodiment, the sensor 260 comprises a Reed switch that can be opened or closed by a magnet that is placed in close proximity to the IMD 110. In this embodiment, the patient may be provided with a magnet that when placed near the IMD provides a magnetic field as an input to the Reed switch, to thereby control one or more operations of the IMD 110.

[0027] Sensor 262 is sensitive to a physiological parameter of the patient in which the IMD 110 is implanted. Any number of such sensors may be included for sensing one or more physiological parameters of the patient's body functions. Physiological sensor(s) 262 may comprise any or all of the following non-limiting examples: electrodes that sense electrical activity, a pressure transducer, an acoustic element, a photonic element, a

blood pH sensor, a blood pressure sensor, a blood sugar sensor, and a body movement sensor. Accordingly, the sensors 262 that are coupled to the IMD 110 are capable of sensing one or more physiological parameters selected from the following exemplary list: an action potential in a nerve tissue, a heart parameter, a body temperature, a blood parameter (e.g., pH, pressure), food intake, gastric (e.g., stomach and/or intestinal) function, and brain activity.

[0028] Figure 3 illustrates a method 300 for reducing compensation of the patient's body to a therapy protocol performed by an IMD. In block 302, an electrical signal is delivered to a target tissue (e.g., a vagus nerve) by the IMD 110 according to a first therapy protocol having a first setting of on-time and off-time which defines a particular duty cycle. In block 304, the IMD 110 determines the occurrence of an event. In at least some embodiments, the event in block 304 comprises the expiration of a time period associated with the first on-time/off-time setting. That time period can be any fixed or programmable period of time such as 1 hour, 1 day, 1 month, etc. In other embodiments, the event may comprise a user activation parameter that is manually provided by a user to the user input sensor 260, or a physiological event that may be automatically sensed by physiological sensor 262 (Figure 2). Once the event is determined to have occurred in block 304, the IMD 110 at block 306 changes the first on-time/off-time setting to a second on-time/off-time setting while maintaining the same or a substantially similar duty cycle, and delivers to the target tissue an electrical signal according to a second therapy protocol employing the second on-time/off-time setting. As such, the therapy protocol changes in block 306 relative to the therapy protocol of block 302 but, with the duty cycle remaining the same, the therapeutic efficacy of the therapy protocol may be maintained or improved.

[0029] The IMD in block 308 again determines whether an event has occurred. The event in block 308 may comprise an event of the type referred to in regard to block 304, e.g., a time period associated with the second on-time/off-time setting or a physiological event sensed by physiological sensor 262. In one embodiment, the IMD 110 continues providing an electrical signal according to the second therapy protocol and the second on-time/off-time setting for a fixed or programmable period of time that may be the same as, or different from, a time period associated with the first on-time/off-time setting and the first therapy protocol. At the end of the time period for the second therapy protocol, control

reverts back to block 302 at which the process repeats. Each setting for on-time and off-time may be computed based on a prior setting.

[0030] In the embodiment of Figure 3, the IMD 110 thus provides an electrical signal to target tissue in alternating fashion in accordance with the first therapy protocol defined by a first on-time/off-time setting and then in accordance with the second therapy protocol defined by a second on-time/off-time setting. In other embodiments, more than two therapy protocols with the same or similar duty cycle can be implemented. For example, three therapy protocols can be implemented sequentially, each therapy being implemented for a specific period of time.

[0031] In accordance with some embodiments, the events occurring in blocks 304 and 308 may be other than time periods. In certain embodiments, the event may be indicated manually by a user via user input sensor 260. A user input such as a magnet may be used to signal any of a variety of user activation parameters, such as an indication of a binge/purge episode, a desire for therapy, or other parameters indicating an input from a user (e.g., the patient or a physician). In other embodiments, a physiological sensor 262 can be used to automatically detect one or more body parameters, changes of which in excess of a threshold value are the event. For example, the event may be physiological in nature such as, via a sensor 260 or 262, a bulimia patient bingeing and/or purging, either a single episode of bingeing and/or purging or bingeing and/or purging in excess of a predefined or programmable rate. Episodes of bingeing and/or purging can be detected by a variety of methods, including a manual indication by the patient or automatic detection of a body parameter such as swallowing, automatically detected gastric motility motion (e.g., stomach contractions), blood parameters such as a rapid increase in blood sugar or insulin secretion (which may be indicated either automatically via physiological sensor 262 or manually via user input sensor 260 after a conventional blood glucose test), sensed vagus nerve electrical activity, and other physiologically sensed body parameters. In some embodiments, the events in blocks 304, 308 comprise the determination that the patient has communicated (e.g., via tapping, a magnet, etc.) with a user input sensor 260 more than a threshold number of times in a given period of time. For example, a bulimia patient can manually activate the sensor 260 each time the patient feels a desire to binge or purge. If the rate at which the patient feels a need to binge and/or purge exceeds a

specified rate, the IMD 110 will automatically switch to the next scheduled therapy protocol.

[0032] In some embodiments as explained above, switching from one therapy protocol to the next can be based on time, based on a rate at which the user activates sensor 260, or based on a detection of physiological events (e.g., bingeing/purging). Further still, switching from one therapy protocol to the next can occur based on one or more of the expiration of defined time periods for each therapy protocol, manual activation of user input sensor 260, and/or detection of a physiological event. For example, the IMD 110 switches from one therapy protocol to another at defined time intervals, but one therapy protocol can be terminated prematurely in favor of the next scheduled therapy protocol if the user activates the sensor device 260 at a rate greater than a threshold rate.

[0033] In accordance with at least some embodiments, user input sensor 260 can also be used by a person (e.g., the patient in which the IMD 110 is implanted) to provide additional information to the IMD 110. In some embodiments, the IMD's controller 234 determines an action to be performed according to the number of user activations of the user input sensor 260. For example, a patient may activate the user input sensor device 260 once to signify the occurrence of a physiological or psychological event (e.g., the desire to binge or purge). The IMD 110 may then record in, for example, storage 240 that such an event has occurred. Such information can be used for a variety of purposes such as verifying the accuracy of what a bulimic patient reports to a healthcare provider regarding his or her desire to binge and purge.

[0034] In at least some embodiments, user activations of the user input sensor 260 can be performed to cause the IMD 110 to deliver an immediate stimulation. The number of user activations may encode the type of stimulation to be delivered. For example, three activations of sensor 260 in quick succession may cause the IMD 110 to deliver a larger stimulation level (e.g., greater current amplitude) than two activations of sensor 260 in quick succession.

[0035] Although the present invention and its advantages have been described in detail, it should be understood that various changes, substitutions and alterations may be made herein without departing from the spirit and scope of the invention as defined by the appended claims.

CLAIMS

What is claimed is:

1. A method of treating a patient, comprising:
delivering an electrical signal to a nerve according to a first setting of an on-time and off-time that defines a duty cycle; and
automatically changing said first setting to a second setting of on-time and off-time in response to a first event, wherein said second setting defines a duty cycle substantially equal to the duty cycle defined by said first setting.
2. The method of claim 1, wherein (b) further comprises sensing an occurrence of said first event following changing to said second setting and repeating (a) and (b).
3. The method of claim 1 wherein said first event comprises an expiration of a defined time period.
4. The method of claim 1, wherein said first event comprises a physiological or psychological event.
5. The method of claim 1, wherein said first event comprises a sensed user input.
6. The method of claim 1, further comprising automatically changing said second setting to a third setting of on-time and off-time in response to a second event, wherein said third setting defines a duty cycle substantially equal to the duty cycle defined by said first and second settings.
7. A system, comprising:
at least one electrode coupled to a nerve;
a pulse generator coupled to said at least one electrode, wherein said pulse generator provides an electrical signal to a nerve using said at least one electrode; and

a controller coupled to said pulse generator, wherein said controller causes said pulse generator to deliver said electrical signal to a nerve according to a first setting of an on-time and off-time that defines a first duty cycle and, in response to a first event, causes a change from said first setting to a second setting of an on-time and off-time that defines a second duty cycle that is substantially equal to the first duty cycle.

8. The system of claim 7, further comprising a user input sensor coupled to the controller, wherein said user input sensor senses a manual control input to control an operation of the pulse generator.

9. The system of claim 8, wherein said first event comprises a user activation parameter of said sensor in excess of an activation parameter threshold.

10. The system of claim 7, further comprising a physiological sensor coupled to the controller to control, at least in part, changing from the first setting to the second setting.

11. The system of claim 7 wherein said first event comprises an expiration of a defined time period.

12. The system of claim 11 further comprising a user input sensor capable of sensing a user input signal, and wherein said first event comprises at least one of an expiration of a defined time period and a sensed user input signal.

13. A method of treating a patient having a medical condition, comprising:
applying to a vagus nerve of the patient a first electrical signal defined by a first plurality of parameters comprising a first on-time and a first off-time defining a first duty cycle;

determining the occurrence of a first event and, in response to said first event
ceasing said step of applying said first electrical signal to said vagus nerve,
and

applying to said vagus nerve a second electrical signal defined by a second plurality of parameters comprising a second on-time and a second off-time defining a second duty cycle substantially the same as said first duty cycle.

14. The method of claim 13 wherein said first plurality of parameters comprises at least one of a first current magnitude, a first frequency, and a first pulse width, and said second plurality of parameters comprises at least one of a second current magnitude, a second frequency, and a second pulse width.
15. The method of claim 14 wherein at least one of said second current magnitude, said second frequency, and said second pulse width is the same as a respective one of said first current magnitude, said first frequency, and said first pulse width.
16. The method of claim 13 wherein said first event first is selected from the group consisting of the expiration of a defined time period, a physiological event, a psychological event, and a sensed user input.
17. The method of claim 13 further comprising:
 - detecting the occurrence of a second event, and in response to said second event
 - ceasing said step of applying said second electrical signal to said vagus nerve, and
 - applying said first electrical signal to said vagus nerve.
18. The method of claim 13 further comprising:
 - detecting the occurrence of a second event, and in response to said second event
 - ceasing said step of applying said second electrical signal to said vagus nerve, and
 - applying to said vagus nerve a third electrical signal defined by a third plurality of parameters comprising a third on-time and a third off-time characterized by a third duty cycle substantially the same as said first duty cycle.

19. The method of claim 13, wherein said second duty cycle differs from said first duty cycle by no more than 25%

20. The method of claim 13, wherein said second duty cycle differs from said first duty cycle by no more than 10%.

21. The method of claim 13, wherein said second duty cycle differs from said first duty cycle by no more than 5%.

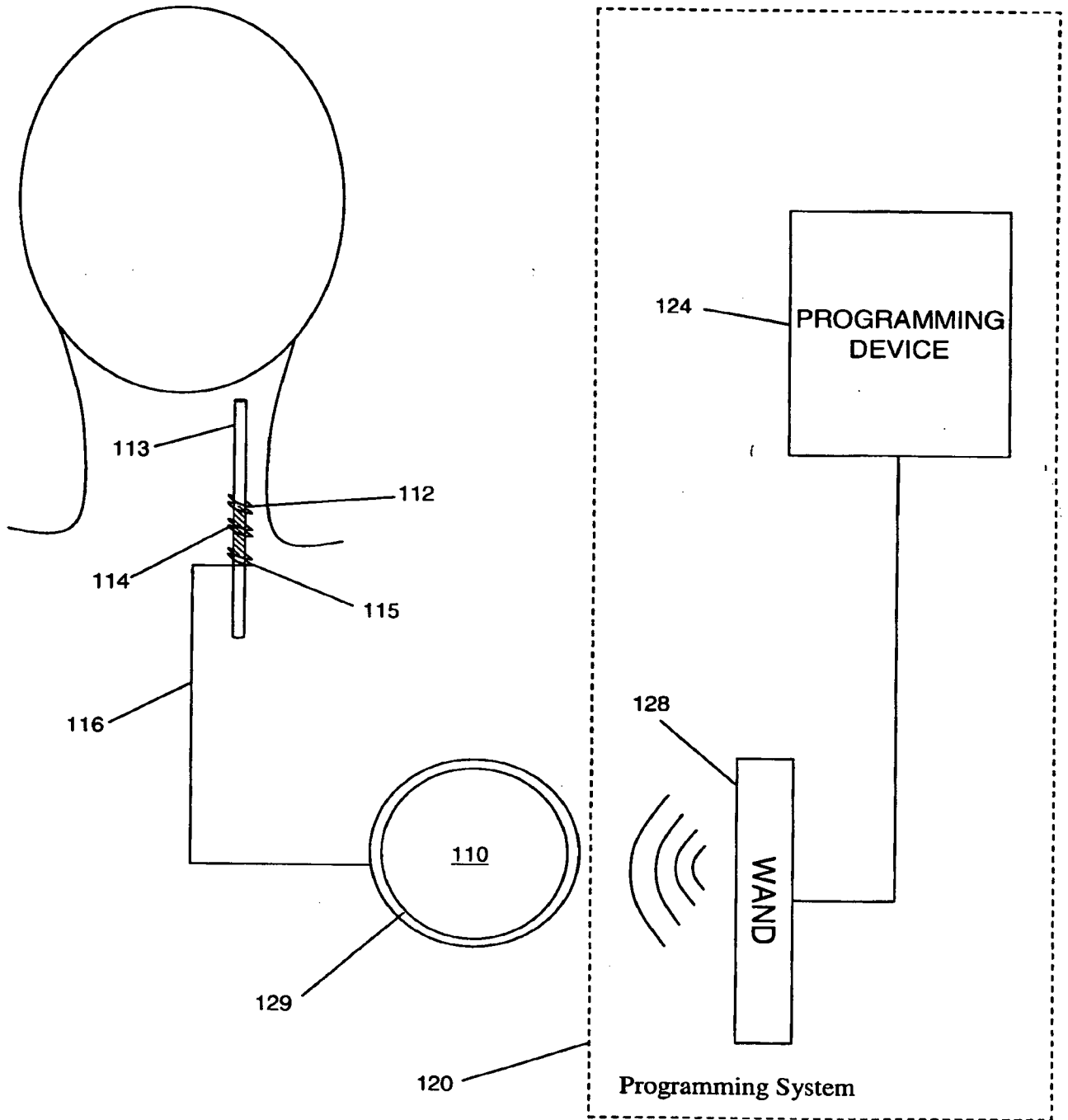


FIG. 1

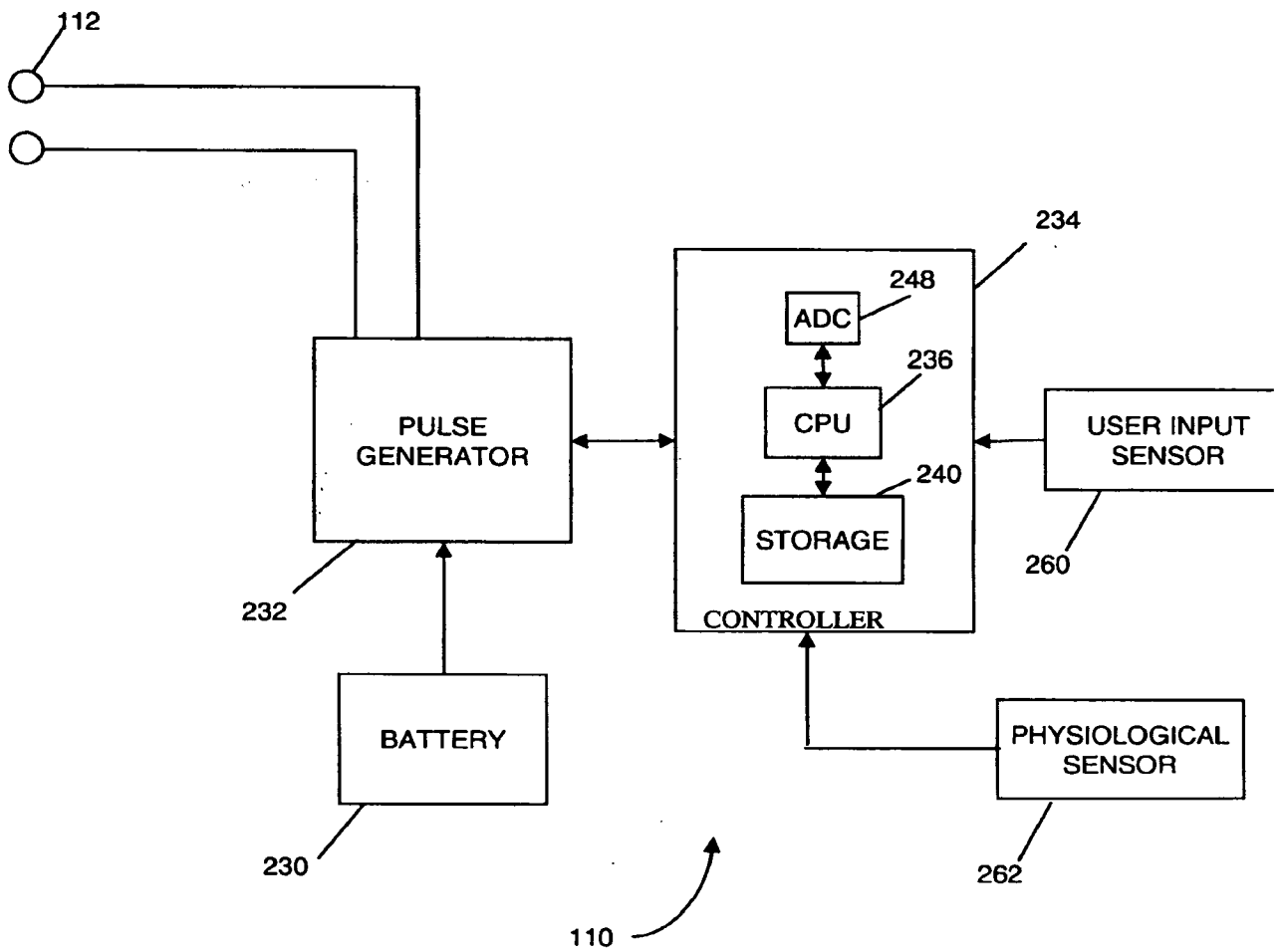


FIG. 2

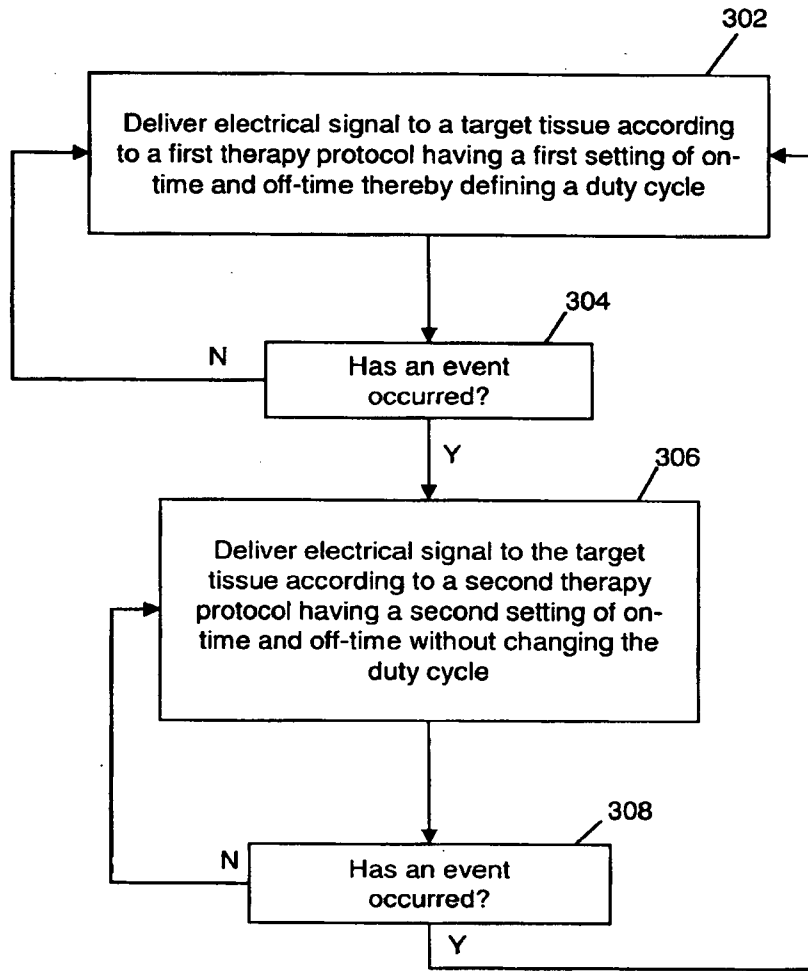


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/009723

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/36

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

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 practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/015153 A1 (GLINER BRADFORD E [US] ET AL) 19 January 2006 (2006-01-19) abstract paragraphs [0048], [0050] paragraphs [0059] - [0061] paragraphs [0063], [0065] - [0068] paragraphs [0073] - [0077], [0095] paragraphs [0099] - [0115] paragraphs [0125] - [0153], [0158] paragraphs [0161] - [0166] paragraphs [0185], [0189] - [0193] ----- -/--	7-12

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 document 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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

10 September 2007

Date of mailing of the international search report

17/09/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Ferrigno, Antonio

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/009723

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 2005/049649 A1 (LUDERS JURGEN [US] ET AL) 3 March 2005 (2005-03-03) abstract paragraphs [0023] - [0026] paragraphs [0031], [0034] paragraphs [0048], [0049] paragraphs [0053], [0054]	7-10
X	WO 2004/064918 A1 (DEPT OF VETERANS AFFAIRS REHAB [US] DEPT OF VETERANS AFFAIRS OFFIC [US]) 5 August 2004 (2004-08-05) abstract page 11, line 11 - page 12, line 24 page 17, line 21 - page 18, line 13 page 19, lines 13-25 page 23, lines 2-5 page 24, lines 14-23 page 25, line 4 - page 26, line 2	7-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/009723

Box 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.: 1-6, 13-21
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 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 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 fee, this Authority did not invite payment of any additional fee.
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.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2007/009723

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006015153 A1	19-01-2006	AU 2005275209 A1	23-02-2006
		CA 2573763 A1	23-02-2006
		EP 1786510 A2	23-05-2007
		WO 2006019764 A2	23-02-2006
US 2005049649 A1	03-03-2005	NONE	
WO 2004064918 A1	05-08-2004	NONE	