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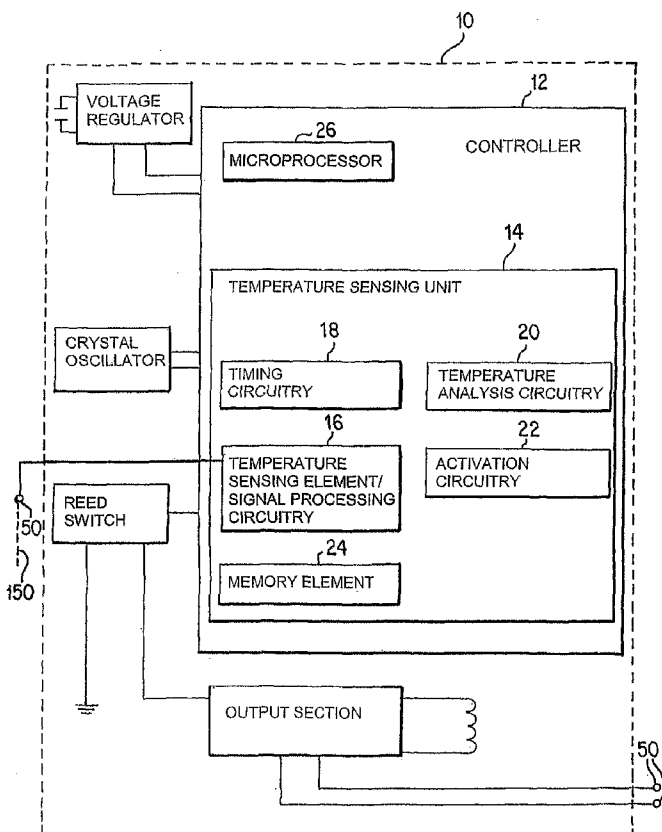
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- (71) Applicant (for all designated States except US): CYBERONICS, INC. [US/US]; 100 Cyberonics Blvd., Houston, TX 77058 (US).
- (74) Agent: SCOTT, Timothy, L.; 100 Cyberonics Blvd., Houston, TX 77058 (US).
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- (71) Applicant and
- (72) Inventor (for all designated States except US): ARMSTRONG, Randolph, K. [US/US]; 16807 Glenshannon, Houston, TX 77059 (US).

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(54) Title: NEUROSTIMULATOR WITH ACTIVATION BASED ON CHANGE IN BODY TEMPERATURE



(57) Abstract: Improved methods and devices are provided for detecting and/or predicting the onset of an undesirable physiological event or neural state, such as an epileptic seizure, to facilitate rapid intervention with a treatment therapy such as neurostimulation or drug therapy. The methods and devices involve monitoring the patient's body temperature, preferably by an implanted temperature sensor, to detect a sudden change in a body temperature parameter. The temperature parameter change may comprise an increase or decrease in the patient's body temperature, time rate of change of body temperature, or a difference in a moving average temperature for a first period from that of a second period. When a parameter change is detected that exceeds a threshold, neurostimulation therapy is delivered to a neural structure of the patient.

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# NEUROSTIMULATOR WITH ACTIVATION BASED ON CHANGES IN BODY TEMPERATURE

## BACKGROUND OF THE INVENTION

### 5           1. FIELD OF THE INVENTION

This invention relates generally to implantable medical devices, and more particularly to medical devices that may be activated or adapted to one or more physiological conditions in a patient in which the devices are implanted.

### 10           2. BACKGROUND

There have been many improvements over the last several decades in medical treatments for disorders of the nervous system, including epilepsy and other motor disorders, and conditions caused by or involving abnormal neural discharge. One of the more recently available treatments involves applying an electrical signal to reduce symptoms or effects of such neural disorders. For example, electrical signals have been successfully applied to neural tissue in the human body to provide various benefits, including reducing occurrences of seizures and/or improving or ameliorating other conditions such as depression. A particular example of such a treatment regimen involves applying an electrical signal to the vagus nerve of the human body to reduce or eliminate epileptic seizures, as described in U.S. Patent No. 4,702,254 to Dr. Jacob Zabara, which is hereby incorporated by reference in its entirety in this specification.

Electrical stimulation of the vagus nerve may be provided by implanting an electrical device underneath the skin of a patient, detecting a symptom or effect associated with the

condition, and delivering electrical stimulation pulses to the vagus nerve. Alternatively, the system may operate without a detection system if the patient has been diagnosed with epilepsy, and the device may simply apply a series of electrical pulses to the vagus nerve (or another cranial nerve) intermittently throughout the day, or over another predetermined time interval. Stimulation that involves a detection and/or sensing operation is referred to as active stimulation, while stimulation without a detection or sensing operation is known as passive stimulation.

Many implantable pulse generators used for electrical stimulation of neurological tissue operate according to a therapy algorithm programmed into the device by a health care provider such as a physician. One or more parameters of the therapy (e.g., current amplitude, pulse width, pulse frequency, and on-time and off-time) may thereafter be changed by reprogramming the neurostimulator after implantation by transcutaneous communication between an external programming device and the implanted neurostimulator. The ability to program (and later re-program) the implanted device permits a health care provider to customize the stimulation therapy to the patient's needs, and to update the therapy periodically should those needs change.

It is desirable, however, for an implantable medical device, such as a neurostimulator, to be able to provide active stimulation by automatically detecting one or more physiological parameters and responsively initiating a stimulation therapy specifically tailored to the physiological parameters detected, without the necessity of intervention by a health care provider. The detected parameters preferably indicate the onset or potential onset of an undesirable physiological event, such as an epileptic seizure. Detection of such physiological events is, however, complicated by physiological differences among patients.

### SUMMARY OF THE INVENTION

In one aspect, the present invention provides improved methods of detecting and/or predicting the onset of an undesirable physiological event or neural state, such as an epileptic seizure, in order to facilitate rapid intervention with a treatment therapy such as neurostimulation or drug therapy. In many instances, the temperature of a patient undergoing a physiological event such as an epileptic seizure undergoes a sudden, rapid fluctuation up or down shortly before or contemporaneous with seizure onset. In one embodiment, the invention comprises monitoring the patient's body temperature, preferably by an implanted temperature sensor, to detect a rapid change in a body temperature parameter that is incompatible with physical exercise or normal physiological conditions. The temperature parameter change may comprise an increase or decrease in the patient's body temperature, a time rate of change of body temperature exceeding a threshold level, or a difference in a moving average temperature for a first period from that of a second period.

The invention also provides methods of providing electrical neurostimulation therapy to treat an undesirable physiological event or neural state by responding to a detected temperature parameter change by initiating or altering a therapy regimen. In a preferred embodiment the responsive treatment comprises a neurostimulation therapy, more preferably electrical stimulation of a cranial nerve, and most preferably electrical stimulation of the vagus nerve. In one embodiment, the responsive treatment comprises initiating vagus nerve stimulation (VNS) according to programmed stimulation parameters. In an alternative embodiment, the responsive treatment comprises changing one or more parameters of an existing VNS regimen already implemented. The responsive treatment may, in a different embodiment, comprise initiating electrical stimulation to a trigeminal and/or a glossopharyngeal nerve of the patient rather than (or in addition to) the vagus nerve. In a still

further embodiment, the responsive treatment comprises providing a drug therapy from a drug pump coupled to the patient's body.

To provide a more efficacious temperature detection algorithm for the patient that reduces the likelihood of a false positive indication, the patient may be tested by one or more  
5 exercise, physiological or environmental tests to determine a maximum rate of temperature change associated with exercise or other physiological conditions (e.g., a rapid change in environmental temperature such as emerging from a temperature-controlled building into extremely hot or cold outside conditions). The maximum (and/or minimum) temperature, rate of temperature changes, moving average temperatures, and/or other temperature  
10 parameters occurring during the tests may be recorded and used in methods and devices of the present invention to ensure that the temperature parameter change detected and used to trigger neurostimulation is beyond a threshold value, which may correspond to normal physiological changes for the patient.

The precise mechanism for the temperature fluctuations that may function as a  
15 precursor of an epileptic seizure is not fully understood at present. Without being bound by theory, it is believed that such changes may arise from an instability of autonomic tone caused by electrical activity associated with a seizure. There is, however, uncertainty as to the relative contributions of the sympathetic and parasympathetic nervous system influences on autonomic tone. It is also possible that an instability of autonomic tone and temperature  
20 instability precede changes in the patient's electroencephalogram (EEG) readings or other physical manifestations of seizure activity, such as uncontrollable violent movements. In any case, if the responsive treatment can be implemented sooner, there will be a greater likelihood that the seizure (or other undesired physiological event or neural state) can be inhibited altogether, terminated sooner, or reduced in either severity or duration.

In another aspect, the present invention provides a neurostimulator system comprising a pulse generator capable of generating an electrical pulse to stimulate a neural structure (such as a cranial nerve) in a patient, a stimulation electrode assembly, and at least one temperature sensor element. The temperature sensor element may be considered as part of a temperature sensing unit that is, in turn, part of a controller for regulating how the neurostimulation therapy is applied to the neural structure.

The temperature sensing unit measures and analyzes body temperature to derive temperature parameters that may be used to initiate or alter a neurostimulation therapy when a temperature parameter exceeds a threshold value. The temperature parameters may include body temperature, rate of change of body temperature, or differences in moving average body temperatures over different time domains or intervals. In addition to the temperature sensing element, the temperature sensing unit preferably comprises timing circuitry for controlling the sampling rate at which temperature is sensed with the sensor element, temperature analysis circuitry for calculating temperature parameters and/or analyzing a temperature data stream from the temperature sensor element(s), and activation circuitry for initiating or altering a neurostimulation therapy. The controller is also preferably comprises a memory element for storing temperature data from the temperature sensing unit.

The temperature sensor element may comprise any of a number of different types of sensors, so long as it is capable of sensing temperature when implanted in the body of the patient. In one embodiment the sensor element comprises a silicon-based temperature sensor integrated into a microprocessor or other integrated circuit. In another embodiment, the temperature sensor may comprise an electrode or thermocouple coupled to the distal end of a lead whose proximal end is coupled to the pulse generator. In any event, the temperature sensor element is coupled to the pulse generator and senses a body temperature of the patient.

In preferred embodiments, the pulse generator comprises a biocompatible case enclosing and protecting a battery and the internal pulse generation circuitry such as the controller. In preferred embodiments, the pulse generator, stimulation electrode assembly, and controller (including the temperature sensing unit) are all implantable. In alternative  
5 embodiments, one or more of the components of the system may be external.

In a particular embodiment of the neurostimulation system, a temperature sensor provides a time series data stream of body temperature measurements for the patient, which is stored in a memory. The controller may be programmed to sample the temperature at a desired interval ranging from 0.01 seconds to one hour or more. In preferred embodiments,  
10 the temperature is measured at intervals from 0.5 seconds to 1 hour, and more preferably from 1 second to 30 minutes. Temperature analysis circuitry analyzes the temperature data stream to measure or calculate and store various temperature parameters, including body temperature, running averages of body temperature, and rates of change of body temperature over several time period domains that may range from one second to one hour or more.  
15 These time domains may comprise, without limitation, 1 second, 10 seconds, 15 seconds, 30 seconds, 1 minute, 2 minutes, 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 6 hours, and 24 hours.

In one embodiment, the temperature analysis circuitry determines and maintains a log of the minimum and maximum temperatures, running average temperatures, and rates of  
20 change of temperature over one or more time domains. Because individual temperature measurements may be highly variable, calculations of time rate of change of temperature may be based on moving averages rather than individual temperature readings. For example, a time rate of change for a 1 minute temperature domain may be calculated by comparing a moving average for a five second period with the five second moving average for the time



period exactly one minute prior to the first moving average. Similarly, a five minute time rate of change may be calculated by subtracting a moving average of a 1 second domain from a second 1 second moving average for a period exactly five minutes later and dividing the difference by five. Alternatively, individual temperature readings instead of moving averages  
5 may be used to calculate time rates of temperature change.

The temperature analysis circuitry may also calculate and compare shorter term running average temperatures (e.g., 10 seconds, 30 seconds) to longer term running averages (e.g., 10 minutes, 30 minutes, 1 hour). For example, a short term running average temperature for the previous 1 minute time domain may be continuously compared with a  
10 longer term running average for the past 10 minutes, and the difference may be stored.

One or more of temperature, time rate of change of temperature, or changes in running average temperature may be compared to thresholds of temperature, rate of change of temperature, or differences in running average temperature to provide an indication of the occurrence of an undesirable physiological event or neural state, such as onset of an epileptic  
15 seizure. The programmed threshold for temperature may be set at a temperature above normal body temperature or a higher temperature above a body temperature associated with exercise. In another embodiment, a temperature drop of even slightly below normal body temperature may be taken to indicate an undesirable medical condition. The threshold for time rate of change of temperature is preferably set at a rate that exceeds the rate of  
20 temperature change during periods of intense exercise. A negative threshold may also be set at a temperature drop exceeding that of moving from a warm environment to an extremely cold environment.

Changes in moving average temperatures may be compared to screen out changes associated with exercise periods and moving from a warm to a cold environment. These

thresholds may be set at a slope or grade representative of, for example, an increase or decrease in absolute temperature exceeding 1° F within 3 minutes or less. The foregoing examples are provided as nonlimiting examples only. In a preferred embodiment, the patient may be tested by monitoring body temperature after the device is implanted during several  
5 periods of exercise for short periods of time. In this manner maximum temperature parameters for normal physiological conditions may be easily determined and the thresholds programmed on an individual basis.

Once temperature parameter thresholds are established, parameters exceeding these thresholds may be detected by the temperature analysis circuit in conjunction with the  
10 temperature sensor. The temperature analysis circuitry preferably generates a therapy initiation signal and sends the signal to the activation circuitry for initiating or altering a neurostimulation therapy. In one embodiment, the signal simply causes the activation circuitry to activate the neurostimulation therapy according to the existing programming. In another embodiment, the activation circuitry alters the therapy by increasing or decreasing  
15 one or more stimulation parameters for a predefined period of time, such as changing the duty cycle from a stimulation on-time of 30 seconds to a stimulation on-time of 300 seconds for a period of thirty minutes, after which the on-time would be restored to 30 seconds. In a different embodiment, the activation circuitry alters the therapy by increasing the stimulation current by 0.5 milliamps for a similar time period before returning to the prior setting. It is  
20 believed that such a therapy initiation circuit, when implemented in a vagus nerve stimulator system, may inhibit, abort, or alleviate an epileptic seizure or other undesired physiological event.

Cranial nerve stimulation therapy is not harmful to the patient even if the therapy initiation signal is a false indication of the presence of an undesirable medical condition.

Accordingly, the device may also be programmed to initiate or alter neurostimulation therapy whenever one or more temperature parameters exceeds a threshold that may be consistent with an undesirable medical condition, without regard to whether or not the change may also be consistent with normal physiological activity. In this instance, temperature parameter thresholds may be established by a training protocol designed to determine temperature parameter fluctuations that may indicate an undesirable medical condition. The implantable neurostimulator may provide such a trained response by implementing a method that comprises sensing temperature with the temperature sensor, generating a time series of signals representative of the body temperature of the patient, and storing the time series temperature data stream in a memory. The method further comprises determining when an undesired physiological event has occurred in a patient, and providing an indication of the occurrence of the event to the controller. In response to the indication of the physiological event, the temperature analysis circuitry analyzes the stored time series temperature data stream for a predetermined time interval preceding (and possibly after) the event to determine temperature extrema, rates of temperature change, and differences in time weighted moving averages within that period, as one or more markers to predict the undesired physiological event (e.g., an epileptic seizure). The method also comprises continuing to monitor the temperature data stream for the presence of the marker(s) and, if one or more marker is present in the continuing data stream, initiating or altering the neurostimulation.

20 In another embodiment, the invention comprises a method of detecting and providing therapy for an undesired physiological event such as an epileptic seizure. The method comprises using a temperature sensing element to generate a time series of patient body temperature measurements, analyzing the time series of patient body temperature measurements to determine at least one temperature parameter, and delivering electrical

stimulation pulses to a cranial nerve when a change in the at least one temperature parameter exceeds a predetermined threshold change value. The time series of body temperature measurements may be stored in a memory element to facilitate the analysis of the data. The temperature parameter change may comprise an increase or decrease in the patient's body  
5 temperature, a time rate of change of body temperature over a first time domain, or a difference in a moving average temperature for a first period from that of a second period. The sensing element may comprise a temperature sensor incorporated into a microprocessor. The threshold value may comprise a value associated with the undesired physiological event.

In another embodiment, the invention comprises a method of detecting and providing  
10 therapy for an undesired physiological event indicated by a temperature marker. The method comprises sensing body temperature of a patient in a first temperature sensing step, generating a first time series temperature data stream for the patient, and storing the data stream in a memory. The method further comprises determining when an undesired physiological event has occurred, providing an indication of the occurrence of the undesired  
15 physiological event, and analyzing the time series temperature data stream for a predetermined time interval preceding said event to determine at least one temperature marker in the data stream associated with the event. Following determination of the temperature marker, the method comprises sensing body temperature of a patient in a second sensing step, generating a second time series temperature data stream for the patient,  
20 optionally storing the second time series data stream in a memory, and analyzing the second time series temperature data stream for the presence of the temperature marker. Finally, the method comprises initiating or altering a neurostimulation therapy in response to the detection of the temperature marker in the second time series data stream.

In another embodiment, the use of extra-physiologic changes in temperature parameters to detect an undesired physiological event may be augmented by one or more sensors for a different physiological parameter that is likewise subject to rapid fluctuation preceding or coincident with the occurrence of the undesired physiological event. In this  
5 embodiment, the invention provides an implantable neurostimulator comprising a pulse generator, a stimulation electrode assembly, a plurality of sensors coupled to the pulse generator, and a controller. The plurality of sensors are capable of sensing at least two physiological parameters selected from the group consisting of a temperature parameter, an  
10 action potential in a nerve tissue, a heart parameter, a blood parameter, and brain wave activity. In a preferred embodiment, at least one of the plurality of sensors comprises a temperature sensor for sensing body temperature of the patient and generating a time series of temperature data. The controller receives and analyzes the sensor signals from the plurality of sensors; and the pulse generator initiates or changes a neurostimulation therapy regimen in response to the controller's analysis.

15 The device may additionally be programmed to apply a periodic prophylactic stimulation of the nerve or nerve bundle to modulate its electrical activity in an appropriate manner for inhibiting seizures regardless of whether or not an excessive temperature change is detected.

20 Accordingly, it is a more specific aim of the present invention to provide methods and apparatus for automatically and selectively modulating the electrical activity of a cranial nerve, preferably the vagus nerve, in a predetermined manner in response to detection of a sudden change in a temperature parameter of the patient's body, to inhibit, abort or alleviate an undesirable physiological event. Detection of such a change of a temperature parameter

offers relative ease of detection, reliability as an indicator, and simplicity of the sensor and implant procedure.

### **BRIEF DESCRIPTION OF THE DRAWINGS**

5           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:

          Figure 1 is a stylized diagram of a prior art implantable medical device suitable for use in stimulating a vagus nerve of a patient, depicted as implanted into a patient's body and  
10    showing an external programming system;

          Figure 2 is a stylized diagram of an embodiment of an implantable medical device suitable for use in the present invention, with a temperature sensor integrally coupled to a pulse generator case;

          Figure 3 is a stylized diagram of another embodiment of an implantable medical  
15    device suitable for use in the present invention, with a temperature sensor at the distal end of a lead coupled to a pulse generator;

          Figure 4 is a block diagram of an implantable pulse generator in accordance with one illustrative embodiment of the present invention;

          Figure 5 illustrates an implantable pulse generator suitable for use in the present  
20    invention, showing the header and electrical connectors for coupling the device to a lead/electrode assembly;

          Figure 6 shows a lead and electrodes suitable for use in the present invention attached to a vagus nerve of a patient.

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, 5 but on the contrary, the intention is to cover all modifications, equivalents, and alternatives falling 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 10 clarity, not all features of an actual implementation are described in this specification. In the 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 15 the art having the benefit of this disclosure.

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 details of construction or design herein shown, other than as described in the claims 20 below. 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.

Figure 1 illustrates a prior art neurostimulation system for stimulation of the vagus nerve 100 of a patient. Pulse generator 10 is provided with a main body 30 comprising a case

or shell 27 (Figure 1) with a header 40 having one or more connectors 50 (Figure 5) for connecting to leads 60. The generator 10 is implanted in the patient's chest in a pocket or cavity formed by the implanting surgeon below the skin (indicated by a dotted line 90), similar to the implantation procedure for a pacemaker pulse generator. A stimulating nerve electrode assembly 70, preferably comprising an electrode pair 72, 74, is conductively connected to the distal end of an insulated electrically conductive lead assembly 60, which preferably comprises a pair of lead wires (one wire for each electrode of an electrode pair). Each lead wire in lead assembly 60 is attached at its proximal end to a connector 50 on case 27. The electrode assembly 70 is surgically coupled to a vagus nerve 100 in the patient's neck.

The electrode assembly 70 preferably comprises a bipolar stimulating electrode pair (Figure 6), such as the electrode pair described in U.S. Pat. No. 4,573,481 issued Mar. 4, 1986 to Bullara. Persons of skill in the art will appreciate that many electrode designs could be used in the present invention. The two electrodes are preferably wrapped about the vagus nerve, and the electrode assembly 70 is preferably secured to the nerve 100 by a spiral anchoring tether 76 (Figure 6) 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 60 is secured, while retaining the ability to flex with movement of the chest and neck, by a suture connection 80 to nearby tissue.

In one embodiment, the open helical design of the electrode assembly 70 (described in detail in the above-cited Bullara patent), which is self-sizing and flexible, minimizes mechanical trauma to the nerve and allows body fluid interchange with the nerve. The electrode assembly 70 preferably conforms to the shape of the nerve, providing a low stimulation threshold by allowing a large stimulation contact area with the nerve. In one



embodiment, the electrode assembly 70 comprises two electrode ribbons (not shown), of a conductive material such as platinum, iridium, platinum-iridium alloys, and/or oxides of the foregoing. The electrode ribbons preferably are individually bonded to an inside surface of an elastomeric body portion of the two spiral electrodes 72 and 74 (Figure 6), which may  
5 comprise two spiral loops of a three-loop helical assembly.

The lead assembly 60 may comprise two distinct lead wires or a coaxial cable whose two conductive elements are respectively coupled to one of the conductive electrode ribbons 72 and 74. One suitable method of coupling the lead wires or cable to the electrodes  
10 comprises a spacer assembly such as that disclosed in US 5,531,778, although other known coupling techniques may be used. The elastomeric body portion of each loop is preferably composed of silicone rubber, and the third loop 76 (which typically has no electrode) acts as the anchoring tether for the electrode assembly 70.

Referring to FIG. 4, distinct from the prior art, the pulse generator 10 of a preferred embodiment of the invention includes a controller 12 comprising a temperature sensing unit  
15 14 for measuring the body temperature of a patient at predetermined or programmable intervals. The TSU 14 includes a temperature sensor element 16 such as a thermocouple, electrode, or a temperature sensor included as part of a microprocessor 26 or integrated circuit, timing circuitry 18 for controlling the rate at which temperature measurements are taken, and analysis circuitry 20 for calculating a number of temperature parameters such as  
20 time-weighted moving average temperatures and time rates of change of temperature. The TSU 14 may also include activation 22 circuitry for deciding when to trigger a stimulation burst from the pulse generator 10. Finally, a memory element 24 is used in conjunction with (or as part of) TSU 14 for storing measured and calculated temperature data.

It will be appreciated by persons of skill in the art that one or more of the components of TSU 14 as depicted in Figure 4 may be depicted instead as other parts of the controller 12, or as other blocks within the stimulator 10, without lack of accuracy. For example, the timing circuitry and even the sensor element itself may be part of the microprocessor 26, and the 14 element may comprise a RAM or other memory device known in the art. In addition, 5 certain aspects of the invention may be implemented as hardware, firmware, software or combinations thereof. Persons of skill in the art will understand that circuit layout and hardware/firmware/software implementation decisions include numerous design choice issues, and unless specifically noted all such designs should be considered as falling within 10 the scope and spirit of the invention.

In certain embodiments of the invention, the temperature sensor element 16, such as sensor 110 (Figure 2) may be provided integrally with case 27 for sensing temperature under the control of the timing circuitry 18. Pulse generator 10 is typically implanted in the patient's body with a first side facing the patient's skin and a second side facing the interior 15 of the patient's body. Because the purpose of the sensor element 110 is to accurately measure the patient's core temperature, it is preferably located on the second side of pulse generator 10—facing the interior of the patient's body—to avoid temperature gradients induced from outside the patient's body.

In another embodiment, the temperature sensor element may comprise a 20 thermocouple 140 at the distal end of a lead wire 130 coupled to a connector 50 on the pulse generator 10, as shown in Figure 3. Alternatively, the thermocouple may be present at the distal end of a rigid member coupled to the pulse generator (not shown). More generally, by placing the sensor element at the distal end of a conducting and spacing element, a more reliable indication of core body temperature may be obtained by locating the sensor element

deeper insider the patient's body, thereby minimizing or removing altogether temperature effects from the exterior environment.

In a preferred embodiment, the temperature sensor element 16 comprises a silicon-based sensor element, preferably included as part of a microprocessor 26 or ASIC chip. Such a sensor element reduces the number of system components and consequently avoiding failure modes, such as fatigue-induced failure of a lead wire, associated with sensor elements spaced remotely from the pulse generator 10. In addition, by including the sensor element as part of an integrated circuit chip within the pulse generator case 27, the sensor element 16 is protected from the harsh environment of the patient's body, contributing to potentially longer life of the sensor element 16 and avoiding premature failure. Moreover, one or more of the other elements of the temperature sensing unit 14, i.e., the timing circuitry 18, the analysis circuitry 20, activation circuitry 22, and memory element 24, may also be included as part of the same microprocessor 26 or ASIC chip.

A view of the first side 29 (i.e., the side facing the skin of the patient) of an implantable pulse generator 10 according to certain embodiments of the invention is illustrated in FIG. 5. The generator 10 comprises a header 40 equipped with at least two connector sockets for coupling an electrode assembly 70 and a temperature sensing element 16 to connectors 50 on the pulse generator. In the embodiment of Figure 5, the electrode assembly 70 is coupled to a coaxial-type cable lead 60 that is connected to single connector socket having two connectors 50. A second connector socket is provided for connecting the proximal end of a second coaxial lead 130 to a pair of connectors 50, with the distal end of lead 130 being coupled in turn to a thermocouple 140 or other temperature probe, as shown in Figure 3. In other embodiments, the temperature sensor element 16 is provided as part of a microprocessor 26 or ASIC chip located inside case 27 of pulse generator 10, and one or two

connector sockets are provided in header 40 solely for connection to stimulation leads 60 (either a single coaxial socket or dual single-wire sockets).

In fully implantable embodiments, the invention provides active stimulation by sensing temperature parameters that may be associated with an undesired physiological event, such as an epileptic seizure, and automatically initiating or adjusting cranial nerve stimulation therapy in response. In preferred embodiments, the TSU 14 is able to specifically detect temperature parameters outside of the patient's normal physiologic temperature parameters, and automatically initiate therapy when it is determined that a change in the temperature parameter is likely to be associated with an undesired physiological event. The parameters may comprise body temperature, rate of change of temperature, and moving average temperature differences.

Referring again to Figure 4, in a particular embodiment of the neurostimulation system, a temperature sensor element 16 provides a time series data stream of body temperature measurement signals 150. The sampling rate of the time series data stream is controlled by timing circuitry 18, which preferably comprises registers allowing the sampling rate to be programmed by a user with external programming computer 160 and handheld programming wand 170. The data is preferably converted from analog to digital data by conventional digital-to-analog circuitry (not shown) and stored in memory element 24 for analysis by analysis circuitry 20. Alternatively, the temperature signal data stream may first be processed by analysis circuitry 20 (which in the alternative embodiment preferably comprises temporary memory storage capacity) and used to calculate one or more temperature parameters. The digital data, including both the temperature measurements and the calculated parameters, such as moving average temperatures and rates of change of temperature, are then stored in memory element 24.

The timing circuitry 18 preferably allows the temperature sampling rate to be programmed over a wide range of sampling rates, including rates ranging from more than 100 temperature measurements per second to less than 1 temperature measurement per hour. Although more precise indications of the occurrence of an undesired physiological event may be obtained at higher sampling rates, higher sampling rates require much higher power consumption and consequently significantly reduce battery life for a fully implantable system. Accordingly, sampling rates on the order of 1 second to 1 hour are most preferred. Extremely low sampling rates, such as one measurement each 30 minutes or hour, do not provide enough data to allow rapid temperatures to be detected, and thus are less preferred.

Temperature analysis circuitry 20 provides a desirable feature of the present invention. In particular, the circuitry determines one or more temperature parameters and compares those parameters to threshold values. If a parameter exceeds its threshold value, which indicates that an undesired physiological event may have occurred or may soon occur, cause controller 12 to generate stimulation signals for delivery to electrodes 72, 74 for stimulation of a cranial nerve.

In one embodiment, the temperature analysis circuitry 20 maintains a log of all temperature measurements for a predetermined log period, such as 24 hours, and also calculates and stores minimum and maximum temperatures, running average temperatures, and rates of change of temperature for several shorter time domains within the log period. As a nonlimiting example, for a system in which timing circuitry 18 provides a one minute sampling rate, analysis circuitry 20 may maintain a log of stored body temperature readings for the previous 1 hour, and may calculate and store rates of temperature change for the previous two minute, three minute and five minute periods based on the temperature readings for the most recent five minute period. If the temperature change for the previous two minute

period exceeds 1° F., or the previous five minute change exceeds 1.5° F., the activation circuitry may initiate stimulation of a vagus nerve of the patient. In addition, the analysis circuitry 20 may calculate a two minute, five minute, and ten minute running average body temperature reading for the most recent ten minute period. If the moving average  
5 temperature for the previous two minute period differs from that of either the five or ten minute moving average temperatures by more than 0.5° F., the activation circuitry may likewise initiate stimulation of a vagus nerve of the patient. It is understood that the time domains and temperature changes provided in the previous examples are exemplary only, and other time domains and temperature changes are within the scope of the invention.

10 In certain embodiments of the invention, maximum physiological temperature changes, rates of temperature change, and changes between moving average temperatures may be determined empirically for a patient by exercise tests after the neurostimulation system has been implanted in the body of the patient. For example, the patient may perform various exercise tasks, and the effects of the exercise tasks on the foregoing temperature  
15 parameters noted and stored by the temperature sensing unit 14. If, for example, the patient's temperature rises by 2.0° F. over a five minute period, a rate of temperature change exceeding 0.4° F./minute can be used as a threshold above which any rate change will trigger or alter (e.g., by extending the duration of) a neurostimulation therapy. Whether determined empirically or otherwise, temperature parameter thresholds are preferably set at a rate that  
20 exceeds the rate of temperature change during periods of intense exercise and rates associated with extreme environmental temperature differences.

False positive detections can be reduced by using a plurality of temperature parameter changes in excess of a threshold level, rather than a single temperature parameter. For example, TSU 14 can be programmed such that the analysis circuitry 20 will only initiate

stimulation if two temperature parameters exceed a threshold level. In a specific example, the analysis circuitry 22 could require that the current temperature exceed 100° F. and that the rate of temperature change for the most recent five minutes exceed 0.5° F/minute before generating a therapy initiation signal and transmitting it to the activation circuitry 22. In a different embodiment, the analysis circuitry may require that the rate of temperature change for the preceding three minute interval exceed 0.2° F/minute and that the moving average temperature for the preceding two minutes exceed the moving average for the preceding 10 minutes by 1.0° F before therapy is initiated.

The use of two or more temperature parameters to trigger therapy must be balance against the fact that failure to detect an imminent undesired physiological event such as an epileptic seizure results in a missed opportunity to abort the seizure. In general, the failure to abort a seizure is a worse therapeutic outcome than neural stimulation in response to false positives, because the latter is not likely to produce harmful side effects.

On the other hand, an overly high sensitivity can result in continuous or nearly continuous therapy, which is not desirable. Preferably, the time interval between consecutive applications of nerve stimuli should be programmed to assure that a suitable minimum off time is provided to prevent overstimulation of a neural structure.

Although a preferred embodiment and method have been described herein, it will be apparent to persons skilled in the art of the invention, from a consideration of the foregoing disclosure, that variations and modifications of the disclosed embodiment and method may be made without departing from the spirit and scope of the invention. Accordingly, it is intended that the invention shall be limited only to the extent required by the appended claims and the rules and principles of applicable law.

## CLAIMS

### WHAT IS CLAIMED:

1. A method of providing electrical neurostimulation therapy to a cranial nerve of a patient comprising:  
5 generating a time series of temperature data representative of the body temperature of the patient;  
determining a time rate of change of body temperature for the patient over at least one predetermined time period;  
comparing the time rate of change of the patient's temperature with a threshold time  
10 rate of change of temperature; and  
providing an electrical neurostimulation therapy to a cranial nerve of the patient if the time rate of change of the patient's body temperature exceeds said threshold time rate of change.
- 15 2. The method of claim 1, wherein said cranial nerve is selected from the group consisting of a vagus nerve, a trigeminal nerve, or a glossopharyngeal nerve.
3. The method of claim 1 wherein said step of providing an electrical neurostimulation therapy comprises changing a parameter of a neurostimulation therapy  
20 selected from the group consisting of current amplitude, a cycle on-time and a cycle off-time.
4. The method of claim 3 wherein said step of changing a parameter comprises increasing the current amplitude.



5. The method of claim 3 wherein said step of changing a parameter comprises increasing the cycle on-time.

6. The method of claim 1 wherein said at least one predetermined time period  
5 comprises a time period within the range of 15 seconds to 24 hours.

7 The method of claim 1 wherein said step of generating a time series of temperature data comprises sensing body temperature of the patient with an implanted temperature sensor.

10

8. The method of claim 7 further comprising the step of storing said time series temperature data in a memory.

9. The method of claim 7 wherein said step of determining a time rate of change  
15 of body temperature for the patient comprises determining a time rate of change over a plurality of time periods.

10. The method of claim 9 wherein said plurality of time periods comprise time periods selected from the group consisting of 15 seconds, 30 seconds, 1 minute, 2 minutes, 3  
20 minutes, 5 minutes, 10 minutes, 30 minutes, 1 hour, 3 hours, and 6 hours and 24 hours.

11. The method of claim 1 wherein said step of determining a time rate of change of body temperature comprises analyzing said time series of temperature data to determine a

maximum time rate of change in a selected time interval within said at least one predetermined time periods.

12. The method of claim 1 wherein said step of determining a time rate of change  
5 of body temperature comprises determining the difference between the temperature at the beginning of one of said at least one predetermined time periods and the temperature at the end of said one of said at least one predetermined time periods, and dividing said difference by the duration of said one of said at least one predetermined time periods.

10 13. The method of claim 1 wherein said step of determining a time rate of change of body temperature comprises determining the difference between the minimum temperature and the maximum temperature within one of said at least one time periods and dividing said difference by the time interval separating said minimum and said maximum temperatures.

15 14. The method of claim 1 wherein said threshold rate of change comprises a predetermined threshold rate of change.

15 15. The method of claim 1 wherein said threshold rate of change comprises a maximum rate of temperature change associated with physical exercise by the patient.

20

16. The method of claim 1 further comprising the step of testing the patient with an exercise test to determine a maximum rate of body temperature change over a predetermined exercise time period, and wherein said maximum rate of body temperature change comprises said threshold time rate of change.

17. A method of determining a physiological marker for an epileptic seizure in a patient comprising:

generating a first time series of temperature data representative of the body  
5 temperature of the patient,

determining when an epileptic seizure has occurred in the patient,

analyzing the time series temperature data for a predetermined time interval preceding the occurrence of the seizure to determine at least one temperature marker in the data stream as a predictor of an epileptic seizure.

10

18. The method of claim 17 further comprising the step of storing said time series temperature data in a memory.

19. The method of claim 17 wherein said step of determining at least one  
15 temperature marker comprises determining a maximum rate of change of temperature.

20. A method of providing electrical neurostimulation therapy to a cranial nerve of a patient comprising:

generating a first time series of temperature data representative of the body  
20 temperature of the patient;

determining when an undesired physiological event has occurred in the patient;

analyzing the first time series temperature data for a first predetermined time interval preceding the occurrence of the undesired physiological event to determine at least one temperature marker in the data stream as a predictor of the undesired physiological event;

generating a second time series of temperature data representative of the body of the temperature of the patient;

analyzing the second time series temperature data stream for the presence of the at least one temperature marker; and

5 providing an electrical neurostimulation therapy to said cranial nerve of the patient in response to detecting the presence of said at least one temperature marker in said second time series temperature data stream.

21. The method of claim 20 wherein said step of providing an electrical  
10 neurostimulation therapy to the patient comprises changing a parameter of a previous neurostimulation program to be applied to the patient.

22. The method of claim 20 wherein said cranial nerve is selected from the group  
15 consisting of the vagus nerve, the trigeminal nerve, and the glossopharyngeal nerve.

23. The method of claim 20 wherein said step of generating a first time series of  
temperature data comprises sensing body temperature of the patient with a temperature sensor  
at a desired sensing rate.

20 24. The method of claim 20 wherein said undesired physiological event is an epileptic seizure.

25. The method of claim 21 further comprising the steps of:

generating at least a third time series of data representative of a physiological parameter selected from the group consisting of an action potential in a nerve tissue, a heart parameter, a blood parameter, and brain wave activity;

analyzing the third time series data for a second predetermined time interval  
5 preceding the occurrence of the physiological event to determine at least a second marker in the third time series data stream as a predictor of the physiological event;

generating a fourth time series of data representative of the selected physiological parameter;

analyzing the fourth time series temperature data stream for the presence of the  
10 second marker; and

providing an electrical neurostimulation therapy to said cranial nerve of the patient in response to detecting the presence of said second marker in the fourth time series data stream.

26. The method of claim 25 wherein said electrical neurostimulation therapy is  
15 applied to the patient only in response to the detection of both of said temperature marker and said second marker.

27. A neurostimulator system for providing a neurostimulation therapy to a cranial nerve of a patient comprising:

20 a pulse generator capable of generating an electrical signal for stimulation of a cranial nerve in a patient,

a stimulation electrode assembly coupled to said pulse generator and to said neural structure for delivering said electrical signal to said neural structure,

a controller to regulate delivery of said electrical stimulation to said neural structure, said controller comprising a temperature sensing unit, said temperature sensing unit comprising

a temperature sensor element;

5 timing circuitry, said circuitry operating to control the rate at which said temperature element senses body temperature and to generate a first time series of temperature data preceding the occurrence of a physiological event and a second time series of temperature data after said event,

10 temperature analysis circuitry, said circuitry operating to analyze said first time series of temperature data to determine a marker of a physiological event, and said second time series of temperature data to detect the presence of said marker, and

activation circuitry for causing said pulse generator to provide said electrical signal to said cranial nerve if said marker is detected in said second time series of temperature data.

15

28. The neurostimulator system of claim 27 wherein said cranial nerve comprises at least one nerve selected from the group consisting of a vagus nerve, a trigeminal nerve, and a glossopharyngeal nerve.

20

29. The neurostimulator system of claim 27 wherein said pulse generator is implanted in said patient and said stimulation electrode assembly is coupled to said pulse generator by a lead assembly.

30. The neurostimulator system of claim 27 wherein said pulse generator is implanted in said patient and said stimulation electrode assembly is coupled to said pulse generator by a radio frequency transmitter and receiver.

5 31. The neurostimulator system of claim 27 wherein said temperature sensor comprises an implanted sensor coupled to said pulse generator by a lead assembly.

32. The neurostimulator system of claim 27 wherein said temperature sensor comprises a sensor that is part of an integrated circuit chip.

10

33. The neurostimulator system of claim 27 wherein said controller comprises hardware and at least one of firmware and software.

15 34. The neurostimulator system of claim 27, wherein said marker comprises a time rate of temperature change exceeding a threshold time rate of temperature change.

35. The neurostimulator of claim 34 wherein said threshold time rate of temperature change comprises a maximum time rate of temperature change associated with physical exercise by said patient.

20

36. The neurostimulator of claim 27 wherein said marker comprises a difference in moving average temperature from a first time domain to a second time domain.

37. The neurostimulator of claim 27 wherein said first time domain comprises ten minutes and a second time domain comprises two minutes.

38. The neurostimulator of claim 27, further comprising a memory element for  
5 storing temperature data.

39. A method of providing electrical neurostimulation therapy to a cranial nerve of a patient comprising:

generating a first time series of temperature data representative of the body  
10 temperature of the patient,

determining from the first time series of temperature data a body temperature parameter selected from the group consisting of a time rate of change of body temperature and a difference in a moving average body temperature for a first time domain and a moving average body temperature for a second time domain,

15 comparing the body temperature parameter to a threshold for the body temperature parameter, and

if the body temperature parameter exceeds said threshold, providing electrical neurostimulation pulses to a cranial nerve of the patient.

20 40. The method of claim 39, wherein said step of providing electrical neurostimulation pulses comprises changing a parameter of an electrical neurostimulation therapy to be delivered to said cranial nerve.



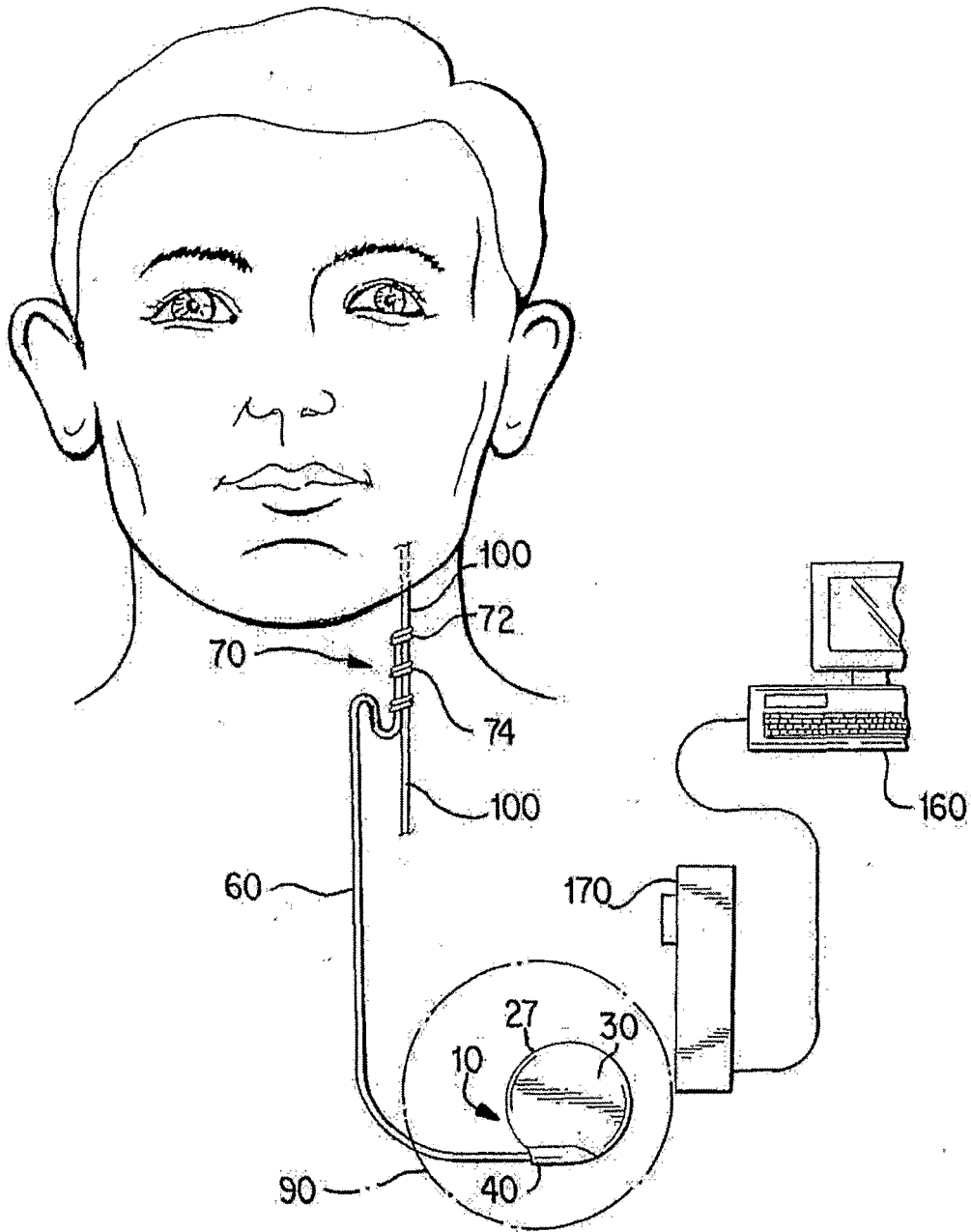


FIG. 1  
PRIOR ART

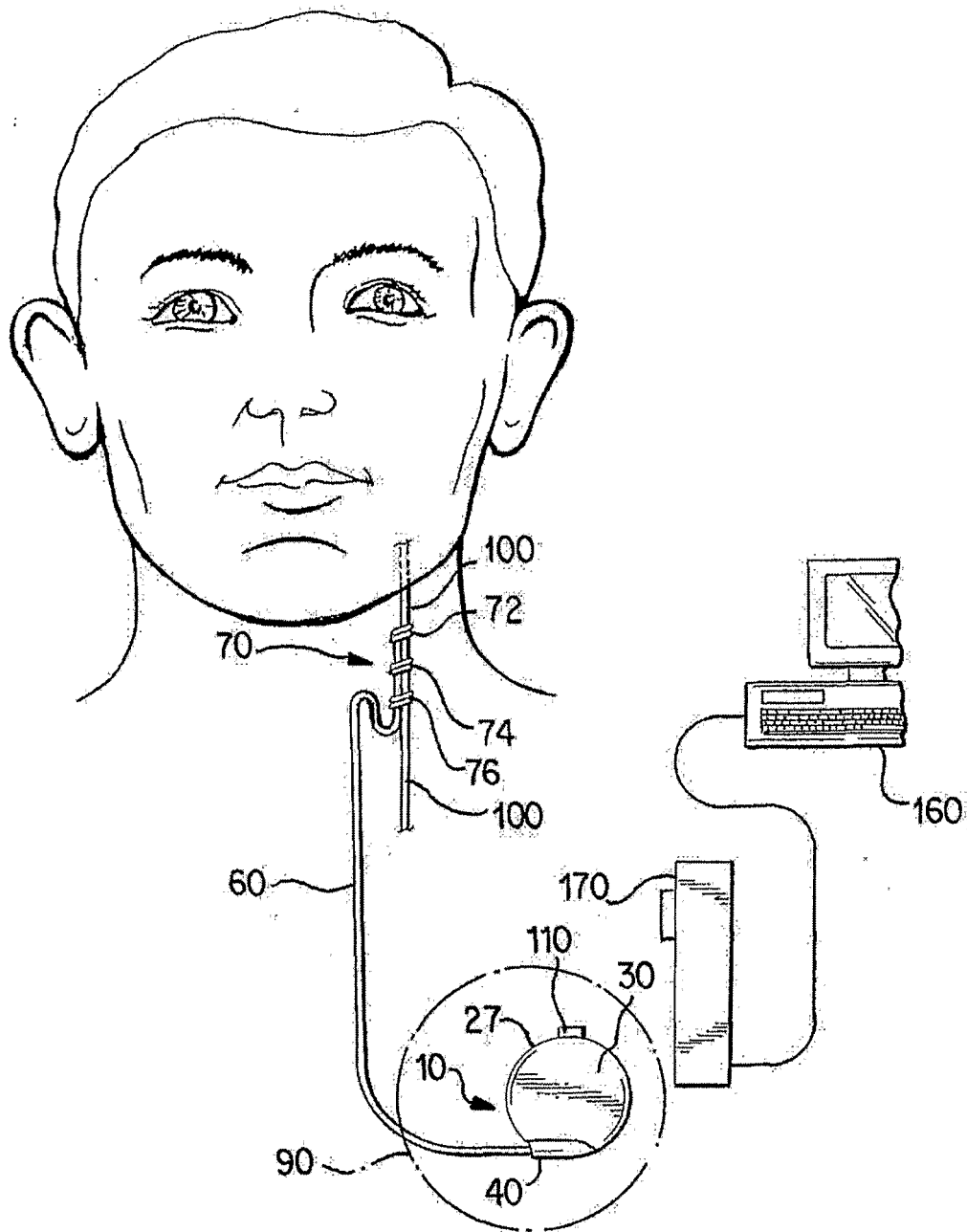


FIG. 2

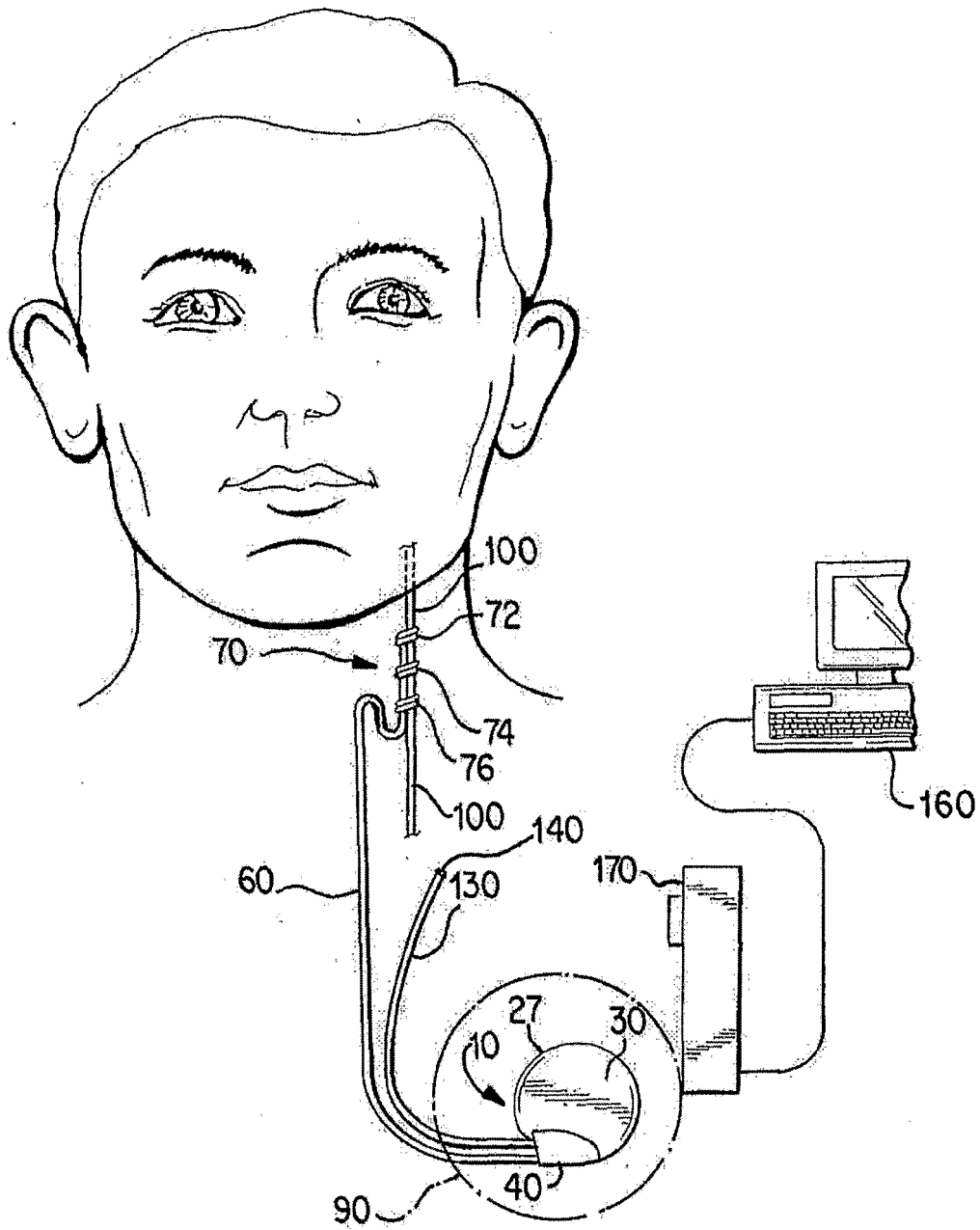
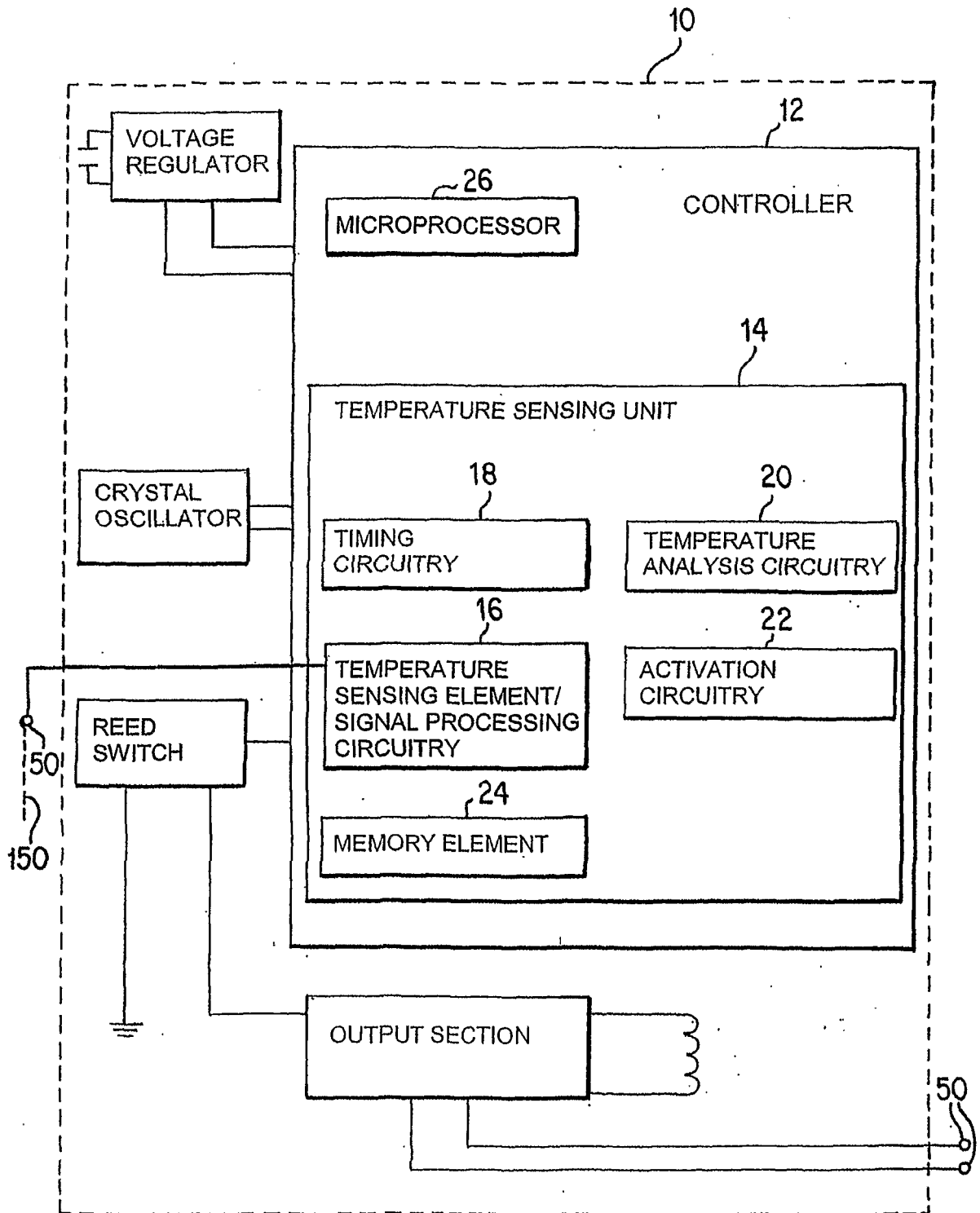


FIG. 3

FIG. 4



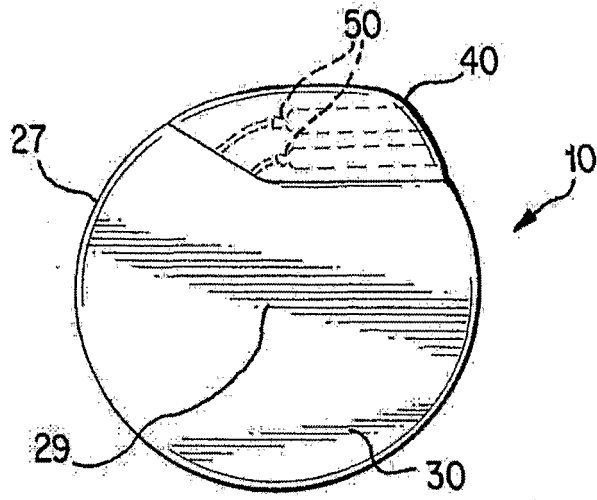


FIG. 5

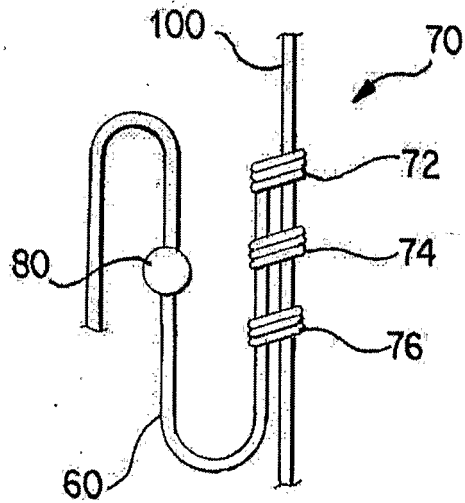


FIG. 6

# INTERNATIONAL SEARCH REPORT

International application No  
**PCT/US2005/044746**

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> A61N1/36      A61B5/00      A61N1/05		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols) A61N    A61B		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/000413 A (CHUNG, JONG-PIL; KANG, SUNG-MIN; KIM, YE-WON; LEE, CHONG-HYUN) 31 December 2003 (2003-12-31) page 1, lines 4-7 page 3, line 10 - page 6, line 25 figure 3	27-38
A	WO 01/28622 A (JOHNS HOPKINS UNIVERSITY) 26 April 2001 (2001-04-26) the whole document	27-38
A	US 6 248 080 B1 (MIESEL KEITH A ET AL) 19 June 2001 (2001-06-19) the whole document	27-38
A	WO 2004/036377 A (MEDTRONIC INC; OSORIO, IVAN; FREI, MARK, G; BHAVARAJU, NARESH, C; PETE) 29 April 2004 (2004-04-29) the whole document	27-38
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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. "&" document member of the same patent family	
Date of the actual completion of the international search	Date of mailing of the international search report	
4 April 2006	04/05/2006	
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  <b>Aronsson, F</b>	

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2005/044746

## 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.: **1-26, 39-40**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
  
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

International application No  
PCT/US2005/044746

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 2004000413	A	31-12-2003	AU	2003244244 A1		06-01-2004
			CN	1662277 A		31-08-2005
WO 0128622	A	26-04-2001	AU	1213401 A		30-04-2001
US 6248080	B1	19-06-2001	NONE			
WO 2004036377	A	29-04-2004	AU	2003287162 A1		04-05-2004
			EP	1558334 A2		03-08-2005



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 1-26,39-40

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Claims 1-16, 20-26 and 39-40 refer to therapeutic methods of treatment practised on the human or animal body, due to the delivery of neurostimulation therapy to a cranial nerve.

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

The subject-matter of claims 17-19 refers to diagnostic methods practised on the living human or animal body due to provision of results which on their own enable a decision to be made on the treatment necessary (treatment of epilepsy).

专利名称(译)	基于体温变化激活的神经刺激器		
公开(公告)号	<a href="#">EP1833556A1</a>	公开(公告)日	2007-09-19
申请号	EP2005849752	申请日	2005-12-09
[标]申请(专利权)人(译)	ARMSTRONG RANDOLPH K		
申请(专利权)人(译)	Cyberonics公司, INC. ARMSTRONG, 兰多夫K.		
当前申请(专利权)人(译)	Cyberonics公司, INC. ARMSTRONG, 兰多夫K.		
[标]发明人	ARMSTRONG RANDOLPH K		
发明人	ARMSTRONG, RANDOLPH K.		
IPC分类号	A61N1/36 A61B5/00 A61N1/05		
CPC分类号	A61B5/01 A61B5/4094 A61N1/36053 A61N1/36135		
优先权	11/009122 2004-12-10 US		
外部链接	<a href="#">Espacenet</a>		

#### 摘要(译)

提供了改进的方法和装置，用于检测和/或预测不期望的生理事件或神经状态（例如癫痫发作）的发作，以促进利用诸如神经刺激或药物治疗的治疗方法快速干预。该方法和装置涉及监测患者的体温，优选地通过植入的温度传感器，以检测体温参数的突然变化。温度参数变化可以包括患者体温的增加或减少，体温变化的时间速率，或第一时间段的移动平均温度与第二时间段的移动平均温度的差异。当检测到超过阈值的参数变化时，将神经刺激疗法递送至患者的神经结构。