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(54) **NERVE SIGNAL DIFFERENTIATION IN CARDIAC THERAPY**

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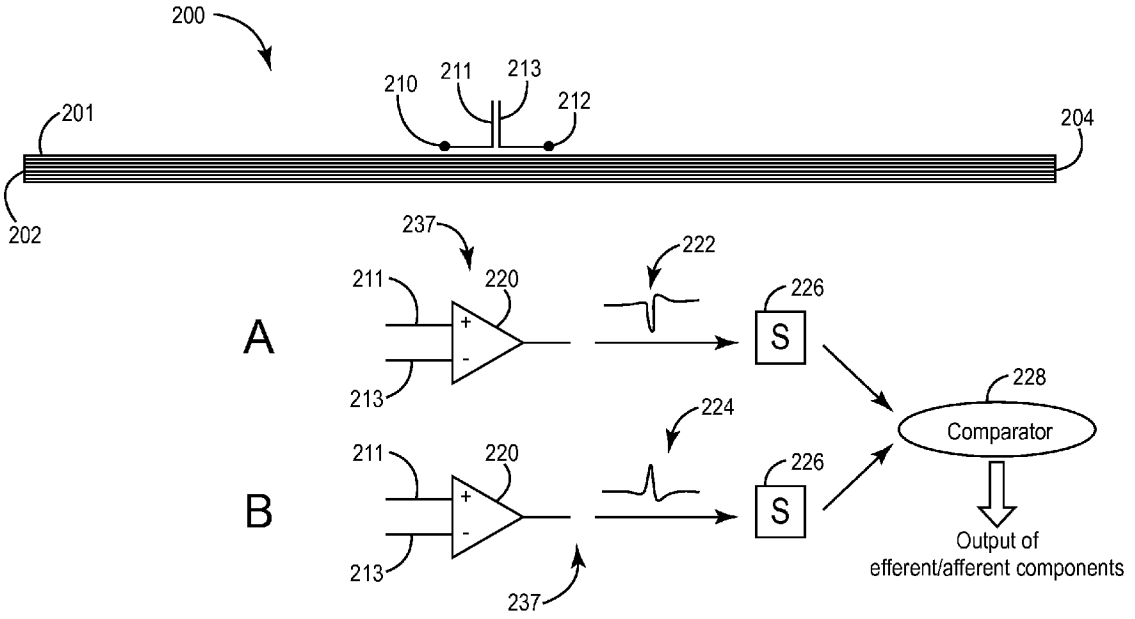
USPC **600/377**; 607/62

(57) **ABSTRACT**

Methods of nerve signal differentiation, methods of delivering therapy using such nerve signal differentiation, and to systems and devices for performing such methods. Nerve signal differentiation may include locating two electrodes proximate nerve tissue and differentiating between efferent and afferent components of nerve signals monitored using the two electrodes.



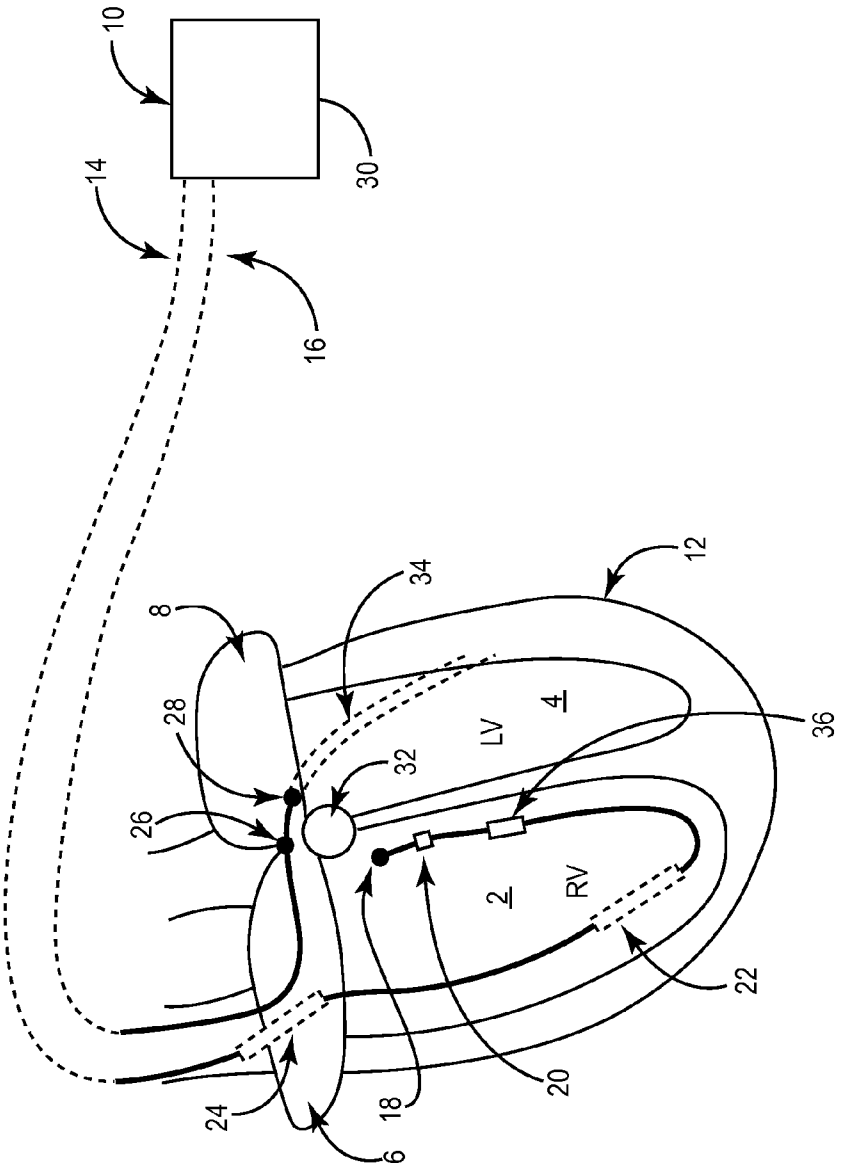


Fig. 1

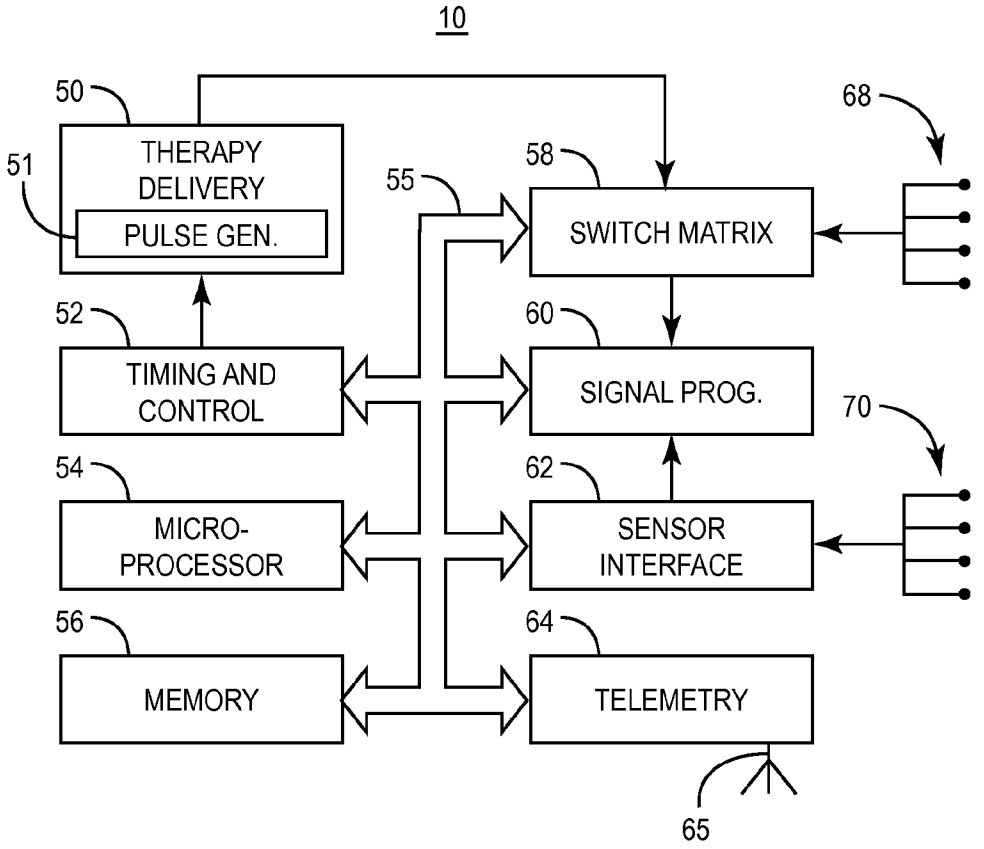

10
50
THERAPY DELIVERY
PULSE GEN.
51
52
TIMING AND CONTROL
54
MICRO-PROCESSOR
56
MEMORY
55
58
SWITCH MATRIX
60
SIGNAL PROG.
62
SENSOR INTERFACE
64
TELEMETRY
65
68
70

Fig. 2

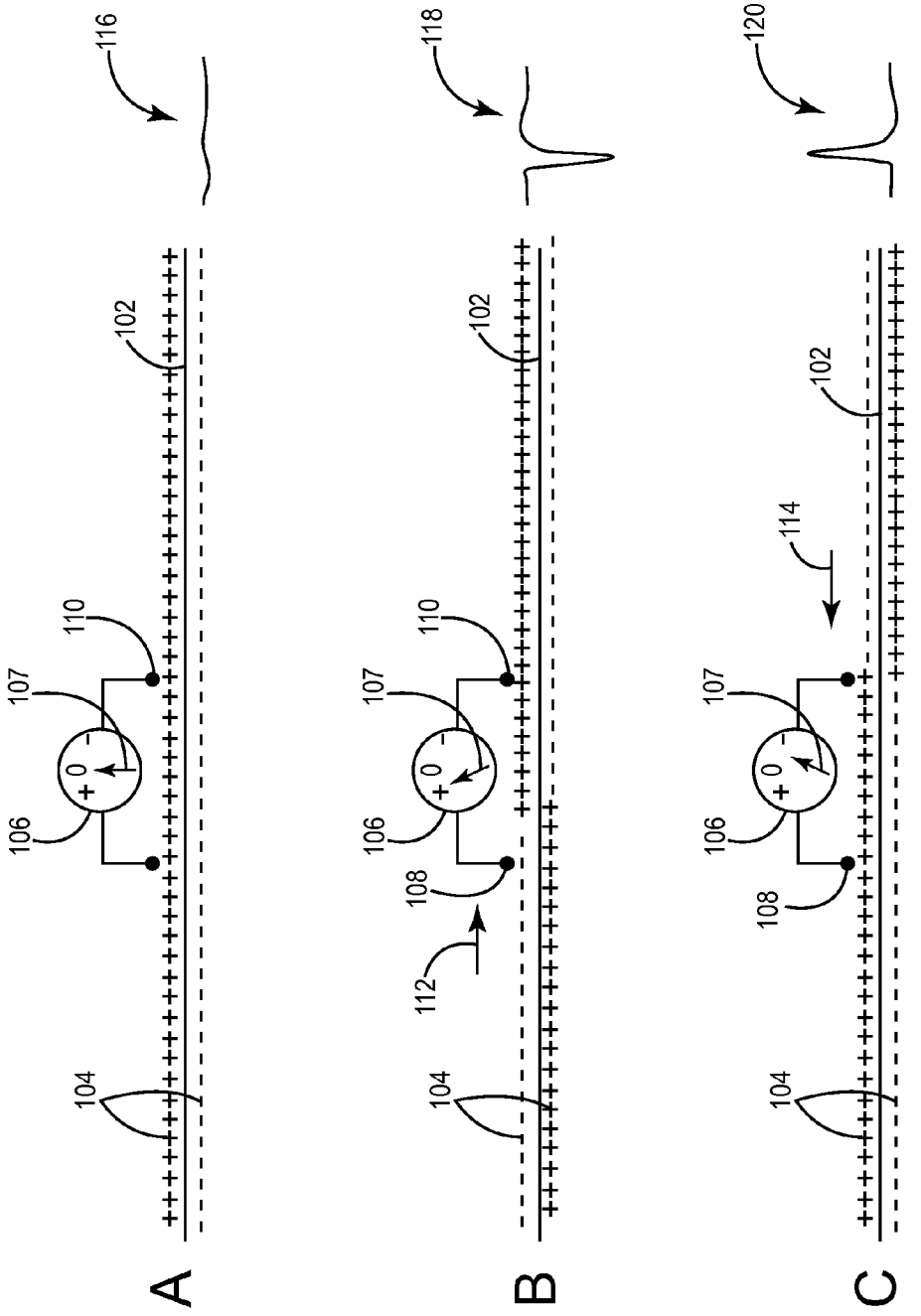


Fig. 3

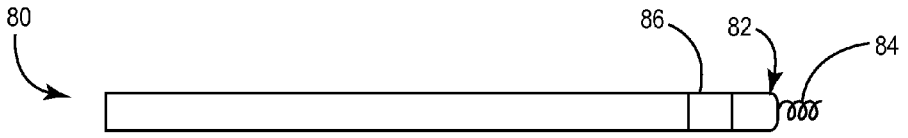


Fig. 4A

Fig. 4B

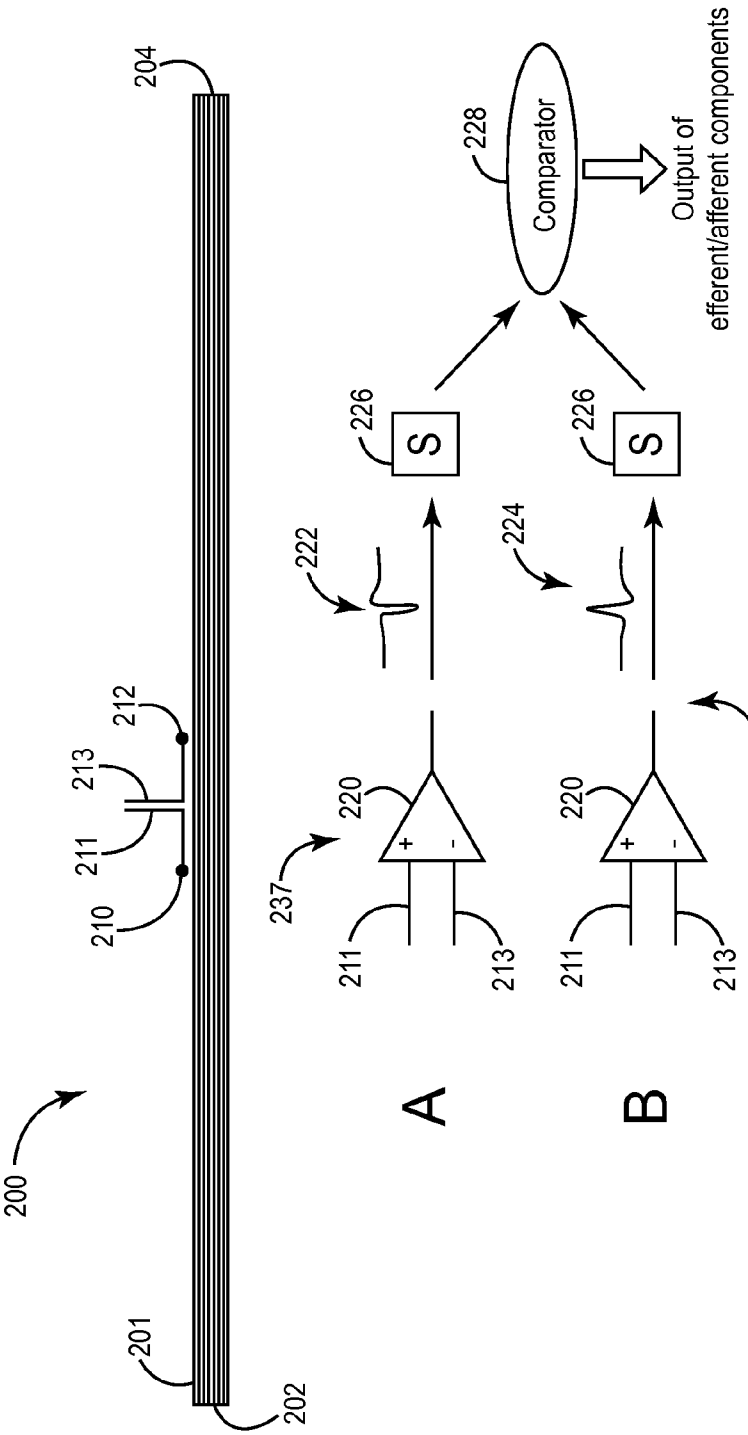

200
201
202
204
210
211
212
213
220
222
224
226
228
237
A
B
S
Comparator
Output of
efferent/afferent components

Fig. 5

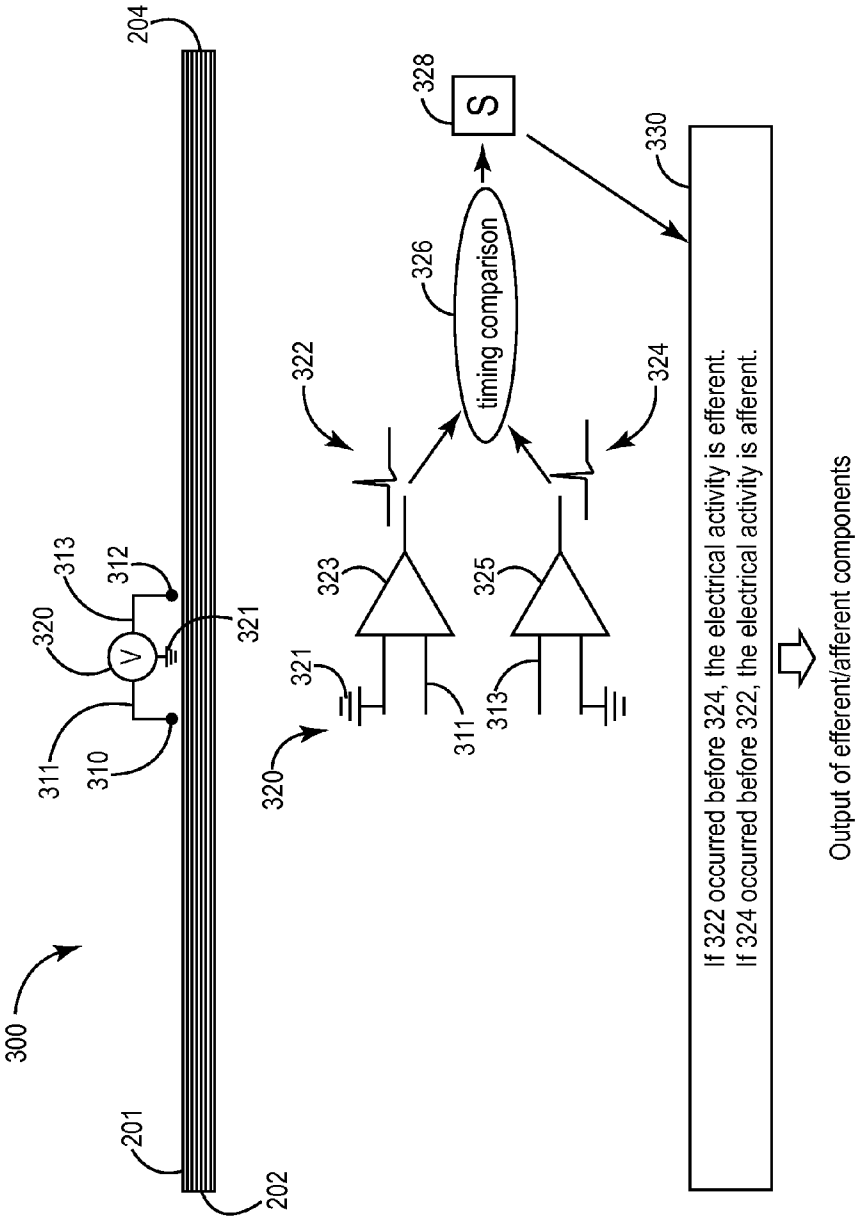

300
201
202
204
310
311
312
313
320
321
V
322
323
324
325
326
timing comparison
328
S
330
If 322 occurred before 324, the electrical activity is efferent.
If 324 occurred before 322, the electrical activity is afferent.
Output of efferent/afferent components

Fig. 6

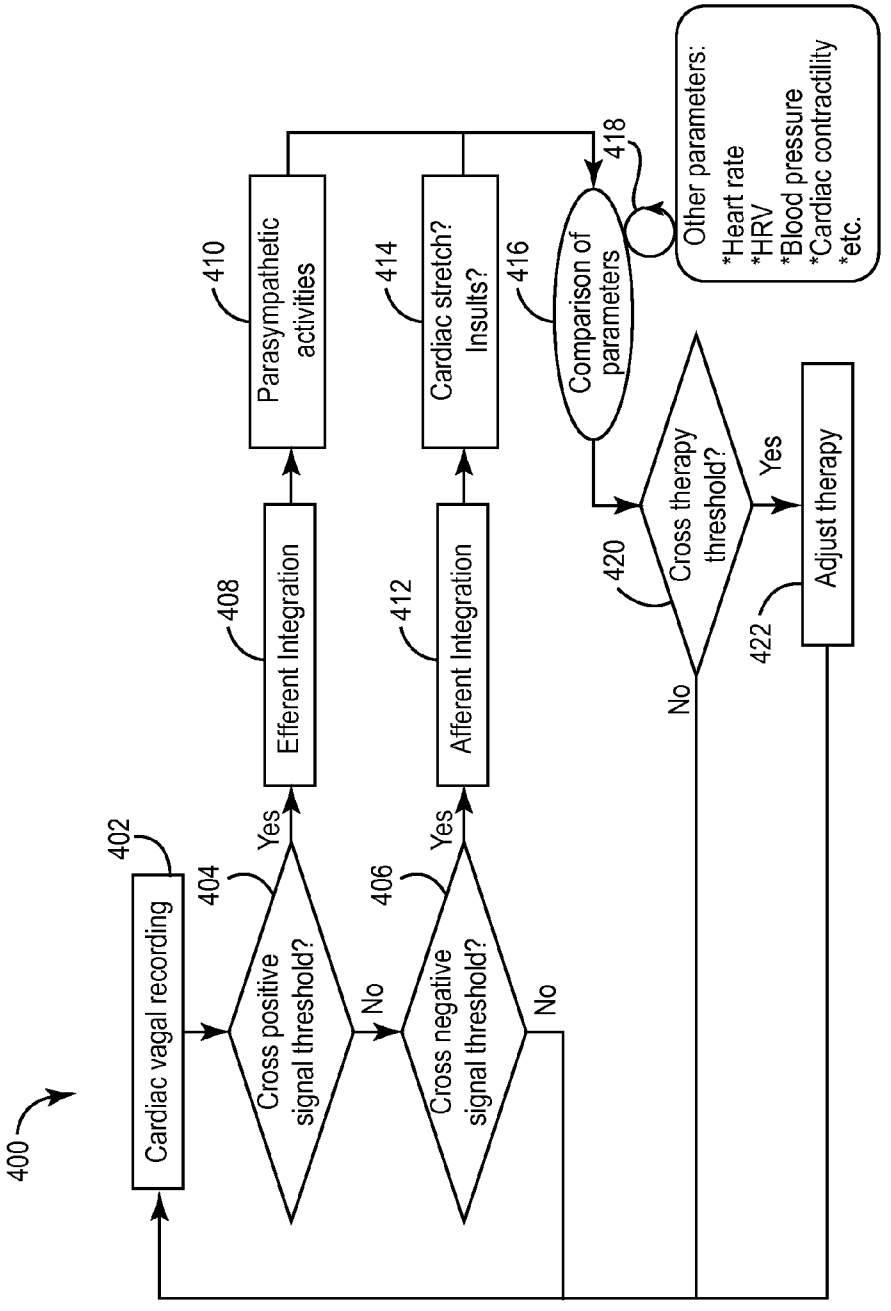

400
Cardiac vagal recording
402
Cross positive signal threshold?
404
Yes
No
Cross negative signal threshold?
406
Yes
No
Efferent Integration
408
Afferent Integration
412
Parasympathetic activities
410
Cardiac stretch? Insults?
414
Comparison of parameters
416
418
Other parameters:
*Heart rate
*HRV
*Blood pressure
*Cardiac contractility
*etc.
Cross therapy threshold?
420
Yes
No
Adjust therapy
422

Fig. 7

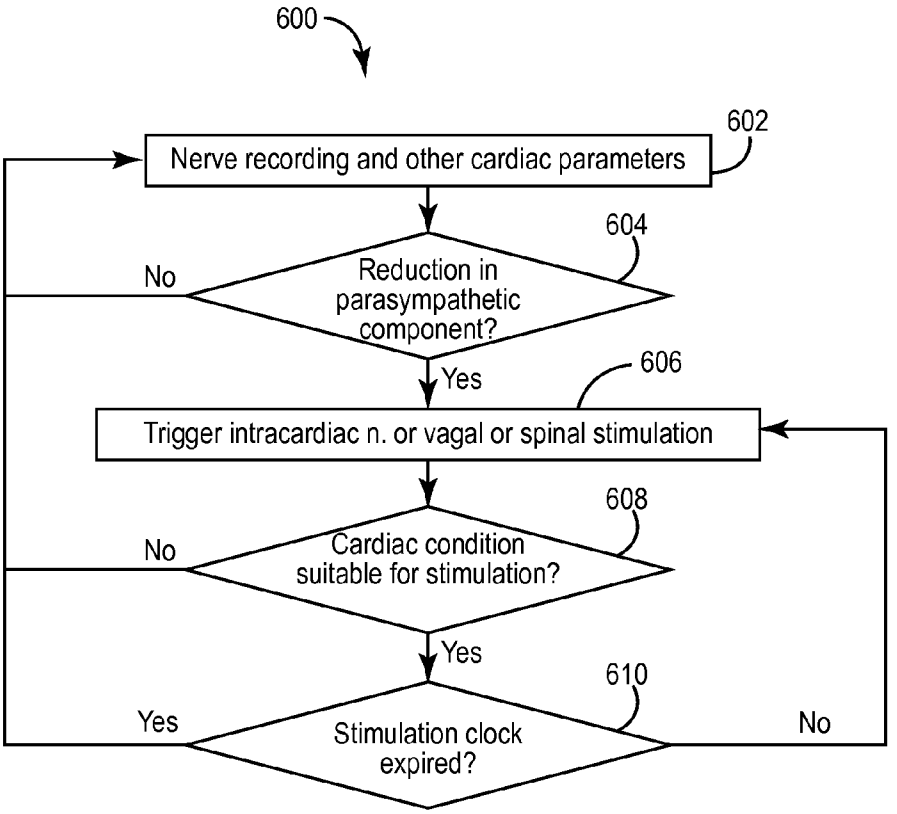

600
602
Nerve recording and other cardiac parameters
604
Reduction in parasympathetic component?
No
Yes
606
Trigger intracardiac n. or vagal or spinal stimulation
608
Cardiac condition suitable for stimulation?
No
Yes
610
Stimulation clock expired?
Yes
No

Fig. 8

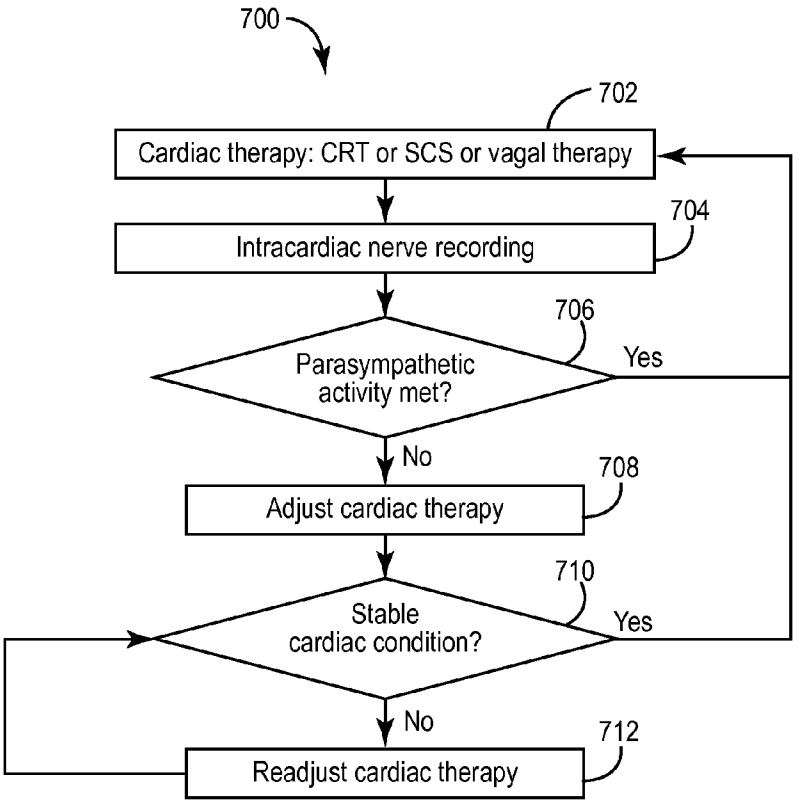

700
702
Cardiac therapy: CRT or SCS or vagal therapy
704
Intracardiac nerve recording
706
Parasympathetic activity met?
Yes
No
708
Adjust cardiac therapy
710
Stable cardiac condition?
Yes
No
712
Readjust cardiac therapy

Fig. 9

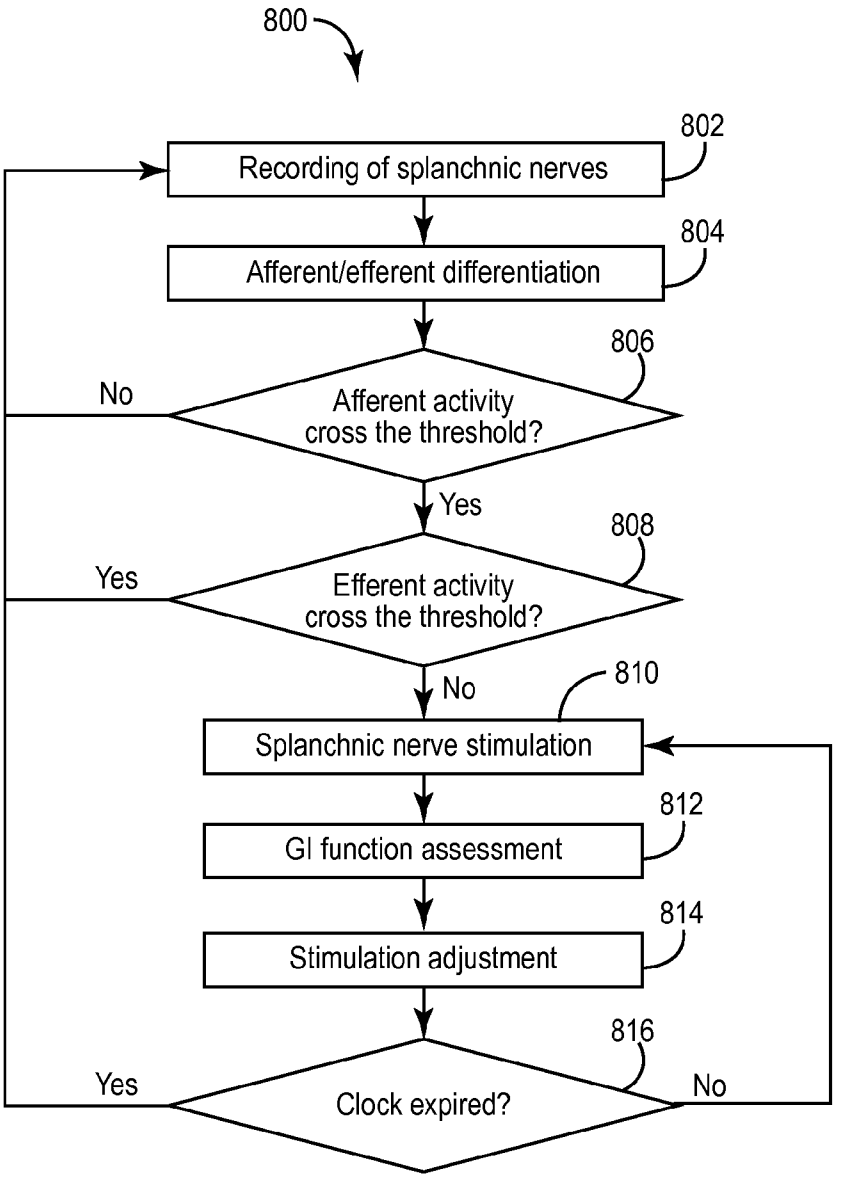

800
802
Recording of splanchnic nerves
804
Afferent/efferent differentiation
806
Afferent activity cross the threshold?
No
Yes
808
Efferent activity cross the threshold?
Yes
No
810
Splanchnic nerve stimulation
812
GI function assessment
814
Stimulation adjustment
816
Clock expired?
Yes
No

Fig. 10

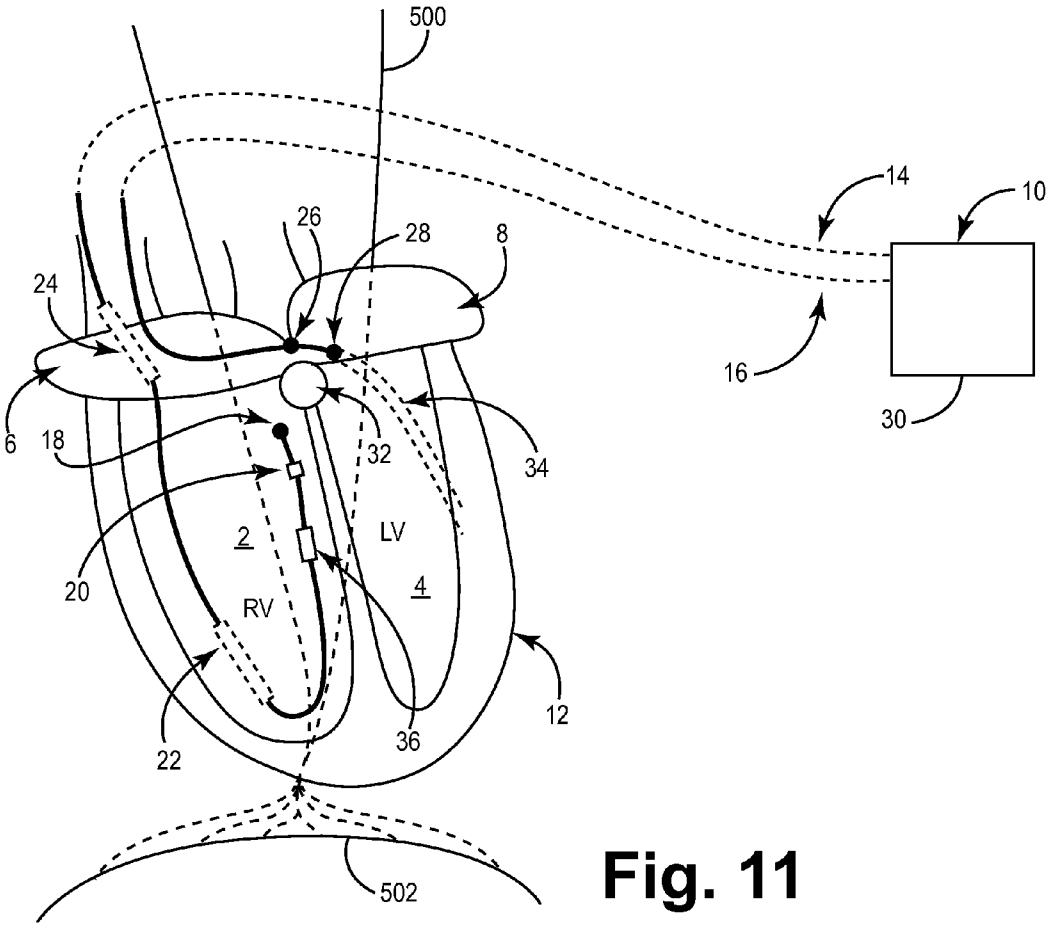


Fig. 11

NERVE SIGNAL DIFFERENTIATION IN CARDIAC THERAPY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a divisional of U.S. patent application Ser. No. 12/848,010, filed Jul. 30, 2010 entitled "NERVE SIGNAL DIFFERENTIATION IN CARDIAC THERAPY", herein incorporated by reference in its entirety.

BACKGROUND

[0002] The present disclosure relates to nerve signal differentiation; and, more particularly, delivering therapy using such nerve signal differentiation.

[0003] Nerve tissue contains both efferent fibers and afferent fibers. Electrical signals propagate from the central nervous system to tissue/organs along efferent fibers while electrical signals propagate from tissues/organs to the central nervous system along afferent fibers. The efferent and afferent fibers play different roles in neuronal regulation (e.g., regulation of the heart).

[0004] Further a variety of patient therapies exist that may benefit from nerve recordings. For example, certain therapies may be delivered based on such nerve recordings.

SUMMARY

[0005] The disclosure herein relates generally to devices and methods of analyzing nerve signals and/or delivering therapy based on nerve signals. For example, such methods and devices may differentiate between efferent and afferent components of a nerve signal for use with therapy, and further, may initiate or adjust therapy based on the efferent and/or afferent components.

[0006] An exemplary device for delivering therapy disclosed herein may include monitoring apparatus, a sensing module, a therapy delivery module, and a control module. The monitoring apparatus is configured to monitor physiological parameters of a patient and includes at least two electrodes configured to monitor electrical activity of the patient's vagus nerve. The sensing module is operably coupled to the monitoring apparatus and configured to receive the monitored physiological parameters. The therapy delivery module is configured to deliver cardiac therapy to the patient. The control module is operably coupled to the sensing module and to the therapy delivery module. Further, the control module is configured to differentiate between efferent activity and afferent activity of the monitored electrical activity of the patient's vagus nerve, analyze the monitored physiological parameters by at least determining whether the efferent activity of the electrical activity of the patient's vagus nerve is reduced over time, and initiate or adjust cardiac therapy to the patient if the efferent activity of the electrical activity of the patient's vagus nerve is reduced.

[0007] In one or more embodiments of the devices disclosed herein, the control module is further configured to determine whether the efferent activity of the electrical activity of the patient's vagus nerve is reduced by at least comparing the pulses per second of the efferent activity to a selected value or by at least comparing the pulses per second of presently-monitored efferent activity to the pulses per second of previously-monitored efferent activity. Further, the control module may be further configured to determine whether the monitored electrical activity of the patient's vagus nerve includes afferent activity and determine whether the efferent activity of the electrical activity of the patient's vagus nerve is reduced by at least comparing the efferent activity to the afferent activity.

[0008] Further, in one or more embodiments of the devices disclosed herein, the control module is further configured to determine whether the efferent activity of the electrical activity of the patient's vagus nerve is reduced by comparing the average amplitude of a selected frequency range of the efferent activity to a selected value, by comparing the average amplitude of a selected frequency range of the presently-monitored efferent activity to the average amplitude of the selected frequency range of previously-monitored efferent activity, by comparing the average power of a selected frequency range of the efferent activity to a selected value, or by comparing the average power of a selected frequency range of the presently-monitored efferent activity to the average power of the selected frequency range of previously-monitored efferent activity. Further, the cardiac therapy may include electrical stimulation to the patient's vagus nerve, and the control module may be further configured to deliver electrical stimulation to the patient's vagus nerve after a burst of efferent activity of the electrical activity of the patient's vagus nerve ceases.

[0009] Still further, in one or more embodiments of the devices disclosed herein, the physiological parameters further include electrical activity of the patient's heart and wherein the control module may be further configured to provide a function relating the status of the patient's vagus nerve to the electrical activity of the patient's heart for use in therapy, assess a status of the patient's vagus nerve using the monitored electrical activity of the patient's heart using the function, and initiate or adjust cardiac therapy to the patient based on the assessed status of the patient's vagus nerve.

[0010] An exemplary method of delivering therapy disclosed herein may include monitoring physiological parameters of a patient (i.e., where the physiological parameters include electrical activity of at least one nerve fiber of a patient) and determining whether the monitored electrical activity of the patient's vagus nerve includes efferent activity. The exemplary method further includes analyzing the monitored physiological parameters (e.g., analyzing the monitored physiological parameters may include determining whether the efferent activity of the electrical activity of the patient's vagus nerve is reduced over time) and initiating or adjusting cardiac therapy if the efferent activity of the electrical activity of the patient's vagus nerve is reduced.

[0011] In one or more embodiments of methods described herein, determining whether the efferent activity of the electrical activity of the patient's vagus nerve is reduced may include comparing the pulses per second of the efferent activity to a selected value, comparing the pulses per second of presently-monitored efferent activity to the pulses per second of previously-monitored efferent activity.

[0012] Further, in one or more embodiments of methods described herein, exemplary methods further include determining whether the monitored electrical activity of the patient's vagus nerve includes afferent activity. Thus, determining whether the efferent activity of the electrical activity of the patient's vagus nerve is reduced may include comparing the efferent activity to the afferent activity.

[0013] Still further, in one or more embodiments of methods described herein, determining whether the efferent activity of the electrical activity of the patient's vagus nerve is

reduced may include comparing the average amplitude of a selected frequency range of the efferent activity to a selected value, comparing the average amplitude of a selected frequency range of the presently-monitored efferent activity to the average amplitude of the selected frequency range of previously-monitored efferent activity, comparing the average power of a selected frequency range of the efferent activity to a selected value, and comparing the average power of a selected frequency range of the presently-monitored efferent activity to the average power of the selected frequency range of previously-monitored efferent activity.

[0014] Yet still further, in one or more embodiments of methods described herein, delivering cardiac therapy may include delivering electrical stimulation to the patient's vagus nerve, and the exemplary methods may further include delivering the electrical stimulation to the patient's vagus nerve for a selected period of time after a burst of efferent activity of the electrical activity of the patient's vagus nerve ceases. Further, the physiological parameters may further include electrical activity of the patient's heart, and the exemplary methods may further include: providing a function relating the status of the patient's vagus nerve to the electrical activity of the patient's heart for use in therapy, assessing a status of the patient's vagus nerve using the monitored electrical activity of the patient's heart using the function, and initiating or adjusting cardiac therapy to the patient based on the assessed status of the patient's vagus nerve.

[0015] The above summary is not intended to describe each embodiment or every implementation of the present disclosure. A more complete understanding will become apparent and appreciated by referring to the following detailed description and claims taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. **1** is a schematic diagram of an implantable medical device (IMD) operably coupled to a patient's heart.

[0017] FIG. **2** is a block diagram of the IMD shown in FIG. **9**.

[0018] FIG. **3** is a diagram of nerve signals propagating across a pair of electrodes.

[0019] FIGS. **4**A-**4**B depict two exemplary leads, respectively, that may include the electrodes shown in FIG. **3**.

[0020] FIG. **5** is a diagram illustrating an exemplary method of nerve signal differentiation using a bipolar electrode configuration.

[0021] FIG. **6** is a diagram illustrating an exemplary method of nerve signal differentiation using a unipolar electrode configuration.

[0022] FIG. **7** is a flow chart of an exemplary method of nerve signal differentiation and cardiac therapy adjustment based on nerve signals.

[0023] FIG. **8** is a flow chart of an exemplary method of initiating cardiac therapy based on nerve signals.

[0024] FIG. **9** is a flow chart of an exemplary method of adjusting cardiac therapy based on nerve signals.

[0025] FIG. **10** is a flow chart of an exemplary method of delivering and adjusting gastrointestinal therapy based on nerve signals.

[0026] FIG. **11** is a schematic diagram of an implantable medical device (IMD) operably coupled to a patient's heart and diaphram.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0027] In the following detailed description of illustrative embodiments, reference is made to the accompanying figures of the drawing which form a part hereof, and in which are shown, by way of illustration, specific embodiments which may be practiced. It is to be understood that other embodiments may be utilized and structural changes may be made without departing from (e.g., still falling within) the scope of the disclosure presented hereby.

[0028] Exemplary methods, devices, and systems are described with reference to FIGS. **1**-**10**. Elements or processes from one embodiment can be used in combination with elements or processes of the other embodiments, and that the possible embodiments of such methods, devices, and systems using combinations of features set forth herein is not limited to the specific embodiments shown in the Figures and/or described herein. Further, it will be recognized that the embodiments described herein may include many elements that are not necessarily shown to scale. Still further, it will be recognized that timing of the process operations and/or the size and shape of various elements herein may be modified but still fall within the scope of the present disclosure, although certain timing, one or more shapes and/or sizes, or types of elements, may be advantageous over others.

[0029] Referring to FIGS. **1**-**2**, IMD **10** is configured to monitor physiological parameters of the patient (e.g., the efferent and/or afferent of the electrical activity of the patient's nerves, the parasympathetic and/or parasympathetic signals of the patient's nerves) and to deliver therapy using two leads. Although the IMD **10** depicted in FIG. **1** uses two leads, a single lead or more than two leads may be used with the methods, devices, and systems described herein. For example, the IMD **10** may use one lead that includes a single electrode positionable near the atrioventricular node in the base of the right ventricle. The single electrode may be used for both either atrial or ventricular pacing/sensing and vagal recording/stimulation. Further, for example, the IMD **10** may use a first lead including an electrode for placement proximate a nerve a patient and a second lead including an electrode for placement proximate the same nerve of the patient but closer to the peripheral end of the nerve than the electrode of the first lead (e.g., for use in recording nerve signals and differentiating between efferent and afferent components of the nerve signals).

[0030] As shown, the IMD **10** is coupled to two transvenous leads: a right ventricular (RV) lead **14** and a coronary sinus (CS) lead **16**. RV lead **14** includes a distal tip electrode **18** deployed in the basal region of the right ventricle **2** in operative relation to the AV node **32**. Ring electrode **20** is spaced proximally from tip electrode **18** for use in bipolar sensing and pacing in the right ventricle **2**. According to one embodiment, tip electrode **18** may be used in conjunction with IMD housing **30** (for unipolar sense/stimulation) or ring electrode **20** (for bipolar sense/stimulation) for sensing ventricular signals, for detecting a ventricular rhythm, for delivering cardiac pacing pulses in the right ventricle, for monitoring the ST segment, for recording/monitoring the electrical activity of the vagus nerve, and for delivering vagal stimulation pulses in the right ventricle (e.g., for discriminating SVT and VT). RV lead **14** may further include coil electrodes **22** and **24** for use in delivering high-energy shock pulses for cardioversion and defibrillation therapies. Other embodiments may include additional electrodes adapted for sensing and stimulating the

right atrium **6**, either on a separate right atrial lead or included along RV lead **14**, recording the electrical activity of various nerves (e.g., the vagus nerve), etc. Further, such electrodes may be positioned relative to the SA node and or AV node for vagal stimulation or for recording/monitoring of the electrical activity of the vagus nerve (e.g., portions of the vagus nerve located in the heart **12**).

[0031] RV lead **14** further includes sensor **36** used for sensing signals other than cardiac electrical signals, such as mechanical signals, e.g., accelerometer sensing, hemodynamic pressure, flow, myocardial acceleration, heart sound, tissue perfusion, lung fluid status, etc., or blood chemistry signals, e.g., temperature, oxygen saturation, pH, etc. In one embodiment, sensor **36** is embodied as a pressure sensor (e.g., for monitoring various blood pressures and pressure drops) to, e.g., be used in verifying effective vagal stimulation. Further, for example, sensor **36** may be an oxygen sensor, as disclosed in U.S. Pat. No. 4,750,495 issued to Moore et al. on Jul. 31, 1989, a pressure transducer as disclosed in U.S. Pat. No. 4,485,813 issued to Anderson et al. on Dec. 4, 1984, a physical activity sensor as disclosed in U.S. Pat. No. 4,428,378, issued to Anderson et al on Jan. 31, 1984, or a ventricular impedance plethysmograph as disclosed in U.S. Pat. No. 4,535,774 issued to Olson on Aug. 20, 1985, all of which are incorporated herein by reference in their entireties.

[0032] Coronary sinus lead **16** is deployed in a cardiac vein **34** via the coronary sinus for positioning electrodes **26** and **28** in operative relation to the left chambers of heart **12**. In particular, in one embodiment, electrodes **26** and **28** are positioned near the AV node **32** to, e.g., allow electrical stimulation of the vagus nerve for discrimination of SVT and VT, for blocking conduction of the AV node **32**, etc. Further, electrode **26** may be positioned proximate the coronary sinus. Electrodes **26** and **28** may also be used for sensing cardiac signals and for delivering cardiac pacing pulses in the left ventricle **4**. It is recognized that coronary sinus lead **16** may carry additional electrodes such as a coil electrode for use in delivering high energy shock pulses, additional ring electrodes, and/or a tip electrode for cardiac sensing and pacing in the left atrium **8**.

[0033] Furthermore, the embodiments described herein are not limited for use with transvenous leads as shown in FIG. **1**. For example, other embodiments may include the use of epicardial electrodes positioned in operative relation to the fatty pad near the SA node and/or the fatty pad near the AV node. Further, subcutaneous electrodes may be incorporated on the housing **30** of IMD **10** and/or positioned on subcutaneous leads extending from IMD **10** for use in sensing cardiac signals and delivering electrical stimulation pulses, e.g., for delivering cardiac pacing and shock therapies. Numerous alternative electrode configurations may be appropriate for nerve recordings and vagal stimulation, including endocardial or epicardial electrodes deployed near or adjacent the SA nodal and/or AV nodal fatty pads or electrodes positioned along the vagus nerve branches.

[0034] FIG. **2** is a functional block diagram of IMD **10** shown in FIG. **1**. Although the IMD **10** has previously been described with respect to a patient's heart, IMD **10** may used for monitoring and delivering therapy to any organs or parts of a patient. IMD **10** generally includes timing and control circuitry **52** and an operating system that may employ microprocessor **54** or a digital state machine for timing sensing and therapy delivery functions and controlling other device functions in accordance with a programmed operating mode. Microprocessor **54** and associated memory **56** (e.g. read only memory, random access memory, etc.) are coupled to the various components of IMD **10** via a data/address bus **55**. IMD **10** includes therapy delivery module **50** for delivering a therapy, such as an electrical stimulation or drug therapy, under the control of timing and control circuitry **52**. Therapy delivery module **50** includes pulse-generating circuitry **51** for generating electrical stimulation pulses (e.g., bursts of electrical stimulation pulses) under the control of timing and control circuitry **52**. As will be described herein, pulse-generating circuitry **51** generates stimulation pulses for stimulating the vagus nerve.

[0035] For delivering electrical stimulation pulses, pulse-generating circuitry **51** may be coupled to two or more electrodes **68** via a switch matrix **58**. Switch matrix **58** is used for selecting which electrodes and corresponding polarities are used for delivering electrical stimulation pulses. Electrodes **68** may include lead-based electrodes, leadless electrodes incorporated on IMD **10**, and/or the IMD housing configured for use as a can or case electrode. Therapy delivery module **50** may further include high voltage circuitry for generating high voltage cardioversion/defibrillation shocks. Aspects of the present disclosure may be embodied in an implantable cardioverter defibrillator including high voltage circuitry as generally disclosed in U.S. Pat. No. 6,731,978 to Olson et al., incorporated herein by reference in its entirety.

[0036] Electrodes **68** may also be used for sensing electrical signals within the body, such as cardiac signals and/or nerve signals. Cardiac electrical signals are sensed using any of electrodes **68** for detecting the heart rhythm and determining when and what therapy is needed, and in controlling the timing of stimulation pulses. In other words, the IMD **10** includes monitoring apparatus, which includes electrodes **68** amongst other things. As will be described herein, cardiac electrical signals may be sensed following delivery of vagal stimulation for adjusting the vagal stimulation, for verifying the effectiveness of the vagal stimulation, and/or for detecting, and/or discriminating between cardiac conditions (e.g., SVT, VT/VF, etc.). Nerve signals are sensed using any of the electrodes **68** for detecting the electrical activity (e.g., parasympathetic activity, etc.) of various nerves.

[0037] Electrodes used for sensing and electrodes used for stimulation may be selected via switch matrix **58**. When used for sensing, electrodes **68** are coupled to signal processing circuitry **60** via switch matrix **58**. Processing circuitry **60** includes sense amplifiers and may include other signal conditioning circuitry and an analog to digital converter. In other words, the IMD **10** may include a sensing module, e.g., includes switch matrix **58**, signal processing circuitry **60**, etc. Electrically sensed signals may then be used by microprocessor **54** for detecting physiological events, such as detecting and discriminating cardiac arrhythmias. Further, the microprocessor **54** may have the ability to program amplifiers and other electronic circuits for monitoring neuronal signals (to, e.g., adjust the magnitude of the gain, the filtering, the sampling rate, etc.) and to processes raw data for integration, data analysis, and comparison of signals.

[0038] The monitoring apparatus of the IMD **10** may further include sensors **70** such as pressure sensors, accelerometers, flow sensors, blood chemistry sensors, activity sensors, and/or other physiological sensors known for use with IMDs. Sensors **70** are coupled to IMD **10** via a sensor interface **62** which provides sensor signals to signal processing circuitry **60**. Sensor signals are used by microprocessor **54** for detect-

ing physiological events or conditions. For example, IMD **10** may monitor heart wall motion, blood pressure, blood chemistry, respiration, and/or patient activity. Monitored signals may be used for sensing the need for delivering, adjusting, terminating, and/or initiating therapy under control of the operating system. In other words, the IMD **10** may include a control module, which may include the microprocessor **54** and memory **56** and may be configured using an operating system.

[0039] The operating system includes associated memory **56** for storing a variety of programmed-in operating mode and parameter values that are used by microprocessor **54**. The memory **56** may also be used for storing data compiled from sensed signals and/or relating to device operating history (e.g., nerve recording information, for use in differentiating between efferent and afferent components of a nerve recording, for use in delivering, adjusting, controlling, initiating, and/or terminating therapy) and/or for communicating such data outside of the patient (e.g., using telemetry communication out of recorded history on receipt of a retrieval or interrogation instruction).

[0040] IMD **10** further includes telemetry circuitry **64** and antenna **65**. Programming commands or data are transmitted during uplink or downlink telemetry between IMD telemetry circuitry **64** and external telemetry circuitry included in a programmer or home monitoring unit.

[0041] As described, IMD **10** is able to monitor and analyze electrical activity of a patient's nerve tissue. Nerve tissue (e.g., peripheral nerves or central nerve projections) contain both efferent fibers and afferent fibers. Electrical signals propagate from the central nervous system to tissue/organs along efferent fibers while electrical signals propagate from tissues/organs to the central nervous system along afferent fibers. The efferent and afferent fibers play different roles in neuronal regulation (e.g., regulation of the heart). The disclosure herein describes techniques and systems/devices to differentiate efferent components from afferent components in nerve recordings. For example, the efferent and afferent components (e.g., the action potential propagation directions) can be differentiated by analyzing the neuronal waveforms and propagation direction.

[0042] Further, the efficacy and efficiency of certain therapies may be improved using the differentiation of efferent and afferent components in nerve recordings. In at least one embodiment, assessment of vagal (parasympathetic) efferent activities in nerve recordings may be useful during neuromodulation.

[0043] The methods described herein may be implemented by various devices (e.g., implantable medical devices) and systems. For example, therapy systems such as therapy system **10**, shown and described in provisional application 61/299,816 filed on Jan. 29, 2010 and entitled THERAPY SYSTEM INCLUDING CARDIAC RHYTHM THERAPY AND NEUROSTIMULATION CAPABILITIES, is capable of implementing teachings of the present disclosure. Such devices and systems may include one or more leads, electronic circuits, power sources, sensors, electrodes, fluid delivery devices, etc. Further, such devices and systems may be configured to monitor one or more physiological parameters of a patient, e.g., electrical activity of a patient's heart, chemical activity of a patient's heart, chemical activity or pressure levels of a patient's gastrointestinal (GI) system, hemodynamic activity of a patient's heart, electrical activity of a patient's muscles, and electrical activity of a patient's nerves (e.g., vagus nerve, splanchnic nerves, etc.).

[0044] The electrical activity of a patient's heart may include one or more signals that may be monitored (e.g., using electrodes) from locations in or around the patient's heart. Using such monitored electrical activity of a patient's heart, certain metrics may be determined and collected (e.g., for analysis). For instance, the following metrics may be determined and collected using the electrical activity of the patient's heart: heart rate (HR), heart rate variability (HRV), heart rate turbulence (HRT), deceleration/acceleration capacity, T-wave alternans (TWA), electrocardiogram, P-wave to P-wave intervals (also referred to as the P-P intervals or A-A intervals), R-wave to R-wave intervals (also referred to as the R-R intervals or V-V intervals), P-wave to QRS complex intervals (also referred to as the P-R intervals, A-V intervals, or P-Q intervals), QRS-complex morphology, ST segment, T-wave changes, QT intervals, electrical vectors, etc.

[0045] The chemical activity of a patient's heart may include one or more chemical properties that may be monitored (e.g., using various sensors) from locations in or around the patient's heart. Using such monitored chemical activity of a patient's heart, certain metrics may be determined and collected (e.g., for analysis). For instance, the following metrics may be determined and collected using the chemical activity of the patient's heart: oxygen saturation, brain natriuretic peptide (BNP) (proteins/peptides) content, pH, lung fluid status, catecholamines, blood electrolytes (K+, Ca++, Na+, etc.), etc.

[0046] The hemodynamic pressure of a patient's heart may include one or more hemodynamic pressures that may be monitored (e.g., using various sensors) from locations in or around the patient's heart. Using such monitored hemodynamic pressures of a patient's heart, certain metrics may be determined and collected (e.g., for analysis). For instance, the following metrics may be determined and collected using the hemodynamic pressures of the patient's heart (e.g., using Medtronic OptiVol Fluid Status Monitoring): mean arterial pressure, diastolic blood pressure, systolic blood pressure, flow rates, pressure drops, heart sounds, lung sounds, tissue perfusion, intracardiac pressure, pulmonary vein pressure, cardiac imaging, etc.

[0047] The electrical activity of the patient's nerves may include one or more signals and may be monitored (e.g., using electrodes) from locations in or around one or more of the patient's nerves. Such signals may include parasympathetic and/or sympathetic signals propagating along efferent and afferent nerve fibers. In one embodiment, the electrical signals propagating along one or more nerve fibers of the patient's vagus nerve may be monitored. Further, using the methods and systems/devices described herein, the efferent and afferent components of the nerve signals may be differentiated such that, e.g. the efferent and the afferent components may be identified, monitored, and analyzed.

[0048] Three diagrams of nerve signals propagating across a pair of electrodes are depicted in FIG. **3**. Each of diagrams A, B, and C of FIG. **3** includes solid lines representative of the cell membrane of nerve fibers **102** and plus/minus symbols representative the cell membrane potential and its action potential propagation **104** along the respective nerve fibers **102**. Further, each of diagrams A, B, and C includes a first electrode **108**, a second electrode **110**, and a sensing module **106** configured to monitor the electrical signals captured by the first electrode **108** and the second electrode **110**. Referring

briefly to FIG. **1**, first electrode **108** is tip electrode **18** and a second electrode **110** can be ring electrode **20** on a single lead. The first electrode **108** and second electrode **110** may be located along the nerve fibers **102** such that the first electrode **108** is closer to a central end (i.e., corresponding to the direction towards the central nervous system of a patient) of the nerve fibers **102** than the second electrode **110** and the second electrode **110** is closer to a peripheral end (i.e., corresponding to the direction towards the tissue and/or organs of a patient) of the nerve fibers **102** than the first electrode **108**. In other words, the second electrode **110** may be located further along the nerve fibers **102** than the first electrode **108**.

[0049] Further, the first electrode **108** may be described herein as being located a selected distance away from the second electrode **110** such that the first electrode **108** and the second electrode **110** are spaced along the nerve fibers **102** as described herein (i.e., the first electrode **108** is located closer to the central end than the second electrode **110**). The selected distance may be about 1 millimeter (mm) to about 10 mm. If the electrodes are located too close to one another, the amplitude of the signals may be too small. Further, if the electrodes are located too far from one another, then the signals may be similar to a biphasic waveform with a positive portion and a negative portion spaced apart from one another.

[0050] Diagram A of FIG. **3** depicts an action potential of the nerve fibers **102** at rest. In other words, no electrical signals are propagating along the nerve fibers **102**. As a result, the sensing module **106** is not detecting either a positive or negative waveform (e.g., using the first electrode or the second electrode as shown by no voltage change between the first or second electrode **108**, **110**) as shown by the arrow indicator **107** within the sensing module **106** and the voltage versus time graph **116**.

[0051] Diagram B of FIG. **1** depicts an action potential of the nerve fibers moving from the central end to the peripheral end as shown by arrow **112**. In other words, electrical signals are propagating along the nerve fibers **102** from the central end to the peripheral end. As a result, the sensing module **106** is detecting a negative waveform (e.g., using the first electrode **108** and the second electrode **110** as shown by a voltage shift between the first and second electrode **108**, **110** with the first electrode **108** detecting the membrane potential change first) as shown by the arrow indicator **107** within the sensing module **106** and the voltage versus time graph **118**.

[0052] Diagram C of FIG. **1** depicts an action potential of the nerve fibers moving from the peripheral end to the central end as shown by arrow **114**. In other words, electrical signals are propagating along the nerve fibers **102** from the peripheral end to the central end. As a result, the sensing module **106** is detecting a positive waveform (e.g., using the first electrode **108** and the second electrode **110** as shown by a voltage shift between the first and second electrode **108**, **110** with the second electrode **110** detecting the membrane potential change first) as shown by the arrow indicator **107** within the sensing module **106** and the voltage versus time graph **120**.

[0053] Various leads may be used for recording/monitoring the electrical activity of one or more nerve tissues (e.g., stimulation leads, recording leads, therapy leads, etc.). Further, the process described herein may use one lead having two electrodes or two or more leads each having at least one electrode. Still further, the leads may have purposes other than nerve recording (e.g., muscle stimulation). Two exemplary leads **80**, **90** that may be used with the concepts depicted in and described with reference to FIG. **3**, as well as the methods described herein, are depicted in FIGS. **4**A and **4**B, respectively. The distal tip **82** of lead **80** (referred to as an intravascular pacing/recording lead) includes a screw-in electrode **84** (also referred to as a tip electrode) and a ring electrode **86**. Such electrodes **84**, **86** may be used for various nerve recordings and intravascular pacing/recording (e.g., be located proximate the fatty pad on the atrial epicardium).

[0054] The distal tip **92** of the lead **90** (referred to as a minimally invasive nerve recording patch lead) includes a first electrode **94**, a second electrode **96**, and a suturing hole **98**. The distal tip **92** may further include silicon insulation **95** surrounding the electrodes **94**, **96** and forming the suturing hole **98**. In at least one embodiment, the lead **90**, through minimally invasive surgery, may be sutured (e.g., using the suturing hole **98**) such that the electrodes **94**, **96** are located over a target location, e.g., a fatty pad or nerve bundle.

[0055] The electrodes of each lead **80**, **90** may be configured such that when the lead is located proximate nerve tissue, each electrode is located along the nerve tissue such that one electrode is located closer to a central end (i.e., corresponding to the central nervous system of a patient) and the other electrode is located closer to the peripheral end (i.e., corresponding to tissue and/or organs of a patient) of the nerve tissue Further, the leads **80**, **90** may be used in conjunction with each other. For example, the leads **80**, **90** can both be positioned proximate a nerve tissues such that an electrode of lead **80** is located closer to the central end of the nerve fiber than the electrode of lead **90** (such that the leads **80**, **90** may be used for nerve signal differentiation as described herein).

[0056] If the direction of lead placement cannot be determined at the time of implant (e.g., if the orientation of each electrode with respect to each cannot be determined such as which electrode is closer to the central end of the nerve fiber), then the signals recorded (e.g., electrical activity) on the electrodes may be correlated to certain physiological activities to determine the direction of lead placement. For example, if the lead is located proximate the vagus nerve and the electrical activity recorded on the electrodes is correlated to the slowing of the patient's heart rate, then the electrical activity may be assigned as efferent vagal activity and the electrode that first recorded the electrical activity may be assigned as being closer to the central end.

[0057] Some practical applications of the concepts depicted in and described with reference to FIG. **1** are described more specifically with reference to FIGS. **5**-**6**. For example, an exemplary method **200** of nerve signal differentiation using a bipolar electrode configuration (e.g., using two electrodes connected to single amplifier) is depicted in FIG. **5**. As depicted, the nerve fibers **201** extend from a central end **202** (i.e., corresponding to the nerve fibers projecting to the central nervous system of a patient) to a peripheral end **204** (i.e., corresponding to the nerve fibers projecting to tissue and/or organs of the patient). Such nerve fibers **201** may be part of any one or more portions or branches of a patient's nervous system such as, e.g., the brain, the cerebellum, the spinal cord, the intercostal nerves, the subcostal nerves, the lumbar plexus, the sacral plexus, the femoral nerves, the pudendal nerves, the sciatic nerves, the muscular branches of the femoral nerve, the saphenous nerve, the tibial nerve, the superficial peroneal nerve, the deep peroneal nerve, the common peroneal nerve, the ulnar nerve, the obturator nerve, the genitofemoral nerve, the iliohypogastric nerve, the median nerve, the radial nerve, the musculocutaneous nerve, the brachial plexus, the splanchnic nerves, etc.

[0058] In at least one embodiment, the nerve fibers **201** are part of the patient's vagus nerve. Parts of the patient's vagus nerve may be monitored (e.g., the same parts that may be used for vagal stimulation) proximate the sinoatrial (SA) nodal fatty pad, the atrioventricular (AV) nodal fatty pad and along the great vein, and coronary artery, the cervical vagus nerve (e.g., the right or left side), the fat pad located between the medial superior vena cava and aortic root (SVC-Ao fat pad), the fat pad superior to the right pulmonary artery, the fat pad at the IVC-left atrial junction (IVC-LA fat pad), the fat pad proximate the right pulmonary vein-atrial junction (RPV fat pad), the spinal cord (e.g., vertebral levels T1-T12, C1-C8, etc. such as described in U.S. Pat. App. Pub. No. 2002/0107552 A1 to Hill et al., which is incorporated herein by reference in its entirety), and additional intracardiac locations near the SA node, AV node, coronary sinus, and base of right ventricle.

[0059] The method **200** includes locating a first electrode **210** and a second electrode **212** along the nerve fibers **201** of a patient to capture the electrical activity propagating along the nerve fibers **201**. The first electrode **210** is located closer to the central end **202** of the nerve fibers **201** than the second electrode **212**. Conversely, the second electrode **212** is located closer to the peripheral end **204** of the nerve fibers **201** than the first electrode **210**. Further, for example, the first electrode **210** may be located about 1 mm to about 10 mm from the second electrode **212**. The first electrode **210** and the second electrode **212** may be located on the same lead or on different leads and operably coupled (e.g., electrically coupled) to an IMD or components thereof.

[0060] The first electrode **210** and second electrode **212** may be operably coupled (e.g., electrically coupled) to differentiation circuitry **237** for use in differentiating efferent and afferent activity. For example, as shown, the differentiation circuitry **237** includes at least an amplifier **220** (e.g., a component of an IMD) that is operably coupled to the first electrode **210** and the second electrode **212** via connections **211**, **213**, respectively (i.e., the first electrode **210** is operably coupled to the positive terminal of the amplifier **220** and the second electrode **212** is operably coupled to the negative terminal of the amplifier **220**). Further, connections **211**, **213**, as well as any electrical coupling or connection described herein, may be wired or wireless (e.g., using radio-frequency or optical transmission). When an electrical signal propagates from the central end **202** to the peripheral end **204** of the nerve fibers **201**, the amplifier **220** outputs a negative waveform **222** as shown in Diagram A thereby indicating that the electrical signal has an efferent component. When an electrical signal propagates from the peripheral end **204** to the central end **202** of the nerve fibers **201**, the amplifier **220** outputs a positive waveform **224** as shown in Diagram B thereby indicating that the electrical signal has an afferent component. Further, if the first electrode **210** and the second electrode **212** were coupled to the differentiation circuitry **237** oppositely (e.g., the first electrode **210** was operably coupled to the negative terminal of the amplifier **220** and the second electrode **212** was operably coupled to the positive terminal of the amplifier **220**), an efferent component would be indicated by a positive waveform while an afferent component would be indicated by a negative waveform. Furthermore, the amplifier **220** may possess a programmable gain and/or filtering features for optimal processing of nerve signals, and further for auto-adjusting the crossing threshold for collecting efferent or afferent signals. Moreover, electronic components (not shown) may be used in conjunction with the amplifier **220** to provide maximum or minimum derivatives of the nerve signal (e.g., the voltage of the signal) that relate to a fast change between the first and the second waveform of the nerve signals. Such derivatives may be used for integration and summary of the signals collected in a defined time window as described herein.

[0061] To determine whether the electrical signal includes efferent or afferent components, method **200** may integrate **226** the electrical signal (e.g., compute the area under the curve) to generate a signal value. The signal value may be compared **228** to one or more selected threshold values to determine whether the electric signal includes efferent or afferent activity (e.g., as opposed to background/baseline signals and/or noise). The threshold values may be about two to about three times a baseline value (e.g., the baseline value of electrical activity measured on the nerve fibers **201**). If the signal value is greater than the efferent threshold value, then the electrical activity is determined to contain efferent components. Efferent activity, in this configuration, generates a negative polarity, and therefore, the efferent threshold value may be a negative value or the absolute value of the electrical activity may be used in the comparison. If the efferent threshold value is a negative value, then instead of determining if the signal value is greater than the efferent threshold value, the method may determine if the signal value is less than the efferent threshold value. If the absolute value of the electrical activity is used in the comparison, then the method would determine if the signal value is greater than the efferent threshold value and whether the electrical activity has a negative polarity to determine that the electrical activity is efferent.

[0062] If the signal value is greater than the afferent threshold value, then the electrical activity is determined to contain afferent components. Afferent activity, in this configuration, generates a positive polarity, and therefore, the threshold value may be a positive value. As such, the method may determine if the signal value is greater than the afferent threshold value to determine if the electrical activity includes afferent activity. Such determinations of afferent or efferent activity may be reversed depending on the location of the electrodes, e.g., if the second electrode is located closer to the central end. Further, such differentiations between or determinations of efferent/afferent components may used, e.g., in delivering and/or adjusting therapy to a patient.

[0063] To recap, the method **200** may determine whether the electrical signals propagating along the nerve fibers **201** include efferent or afferent components. As such, a nerve signal (e.g., two recordings of the same nerve signal recorded at different locations along the nerve fibers **201**) may be inputted and a determination whether the electrical signals are efferent and/or afferent may be outputted.

[0064] In other words, the first electrode **210** and the second electrode **212** are operably coupled to differentiation circuitry **237** (e.g., a portion of an IMD, and which may include an amplifier **220**) that is configured to receive the electrical signals monitored by the first and the second electrodes **210**, **212**. Further, the differentiation circuitry **237** may include circuitry that is configured to determine whether an electrical signal propagating along the nerve fibers **201** monitored using the first and second electrodes **210**, **212** includes efferent activity (and/or afferent activity). In one or more embodiments, certain modules of an IMD may include the functionality of the differentiation circuitry **237**. For example, a control module of an IMD may be configured to compare the

electrical activity monitored by the first electrode to the electrical activity monitored by the second electrode and determine that the electrical signal includes efferent activity if the comparison between the electrical activity monitored by the first electrode to the electrical activity monitored by the second electrode generates a waveform having a particular polarity (e.g., positive or negative depending on the electrode configuration).

[0065] An exemplary method **300** of nerve signal differentiation using a unipolar electrode configuration is depicted in FIG. **6**. The method **300** may be used by itself, or in conjunction with method **200** depicted in FIG. **5** to, e.g., detect neuronal activation when efferent and afferent components occur at the exact same time. The nerve fibers **201** of FIG. **6** may be substantially similar to the nerve fibers **201** described herein with reference to FIG. **5**.

[0066] The method **300** includes locating a first electrode **310** and a second electrode **312** along the nerve fibers **201** of a patient to capture the electrical activity propagating along the nerve fibers **201**. The first electrode **310** is located closer to the central end **202** of the nerve fibers **201** than the second electrode **312**. Conversely, the second electrode **312** is located closer to the peripheral end **204** of the nerve fibers **201** than the first electrode **310**. The first electrode **310** and the second electrode **312** may be located on the same lead or on different leads and operably coupled to an IMD or components thereof.

[0067] The first electrode **310** and second electrode **312** may be operably coupled (e.g., electrically coupled) to a differentiation circuit **320** to differentiate between efferent and afferent components (e.g., a component of an IMD) via connections **311**, **313**, respectively. The differentiation circuit **320** may include a first amplifier **323** and a second amplifier **325**, each having a first input operably coupled to one of the electrodes **310**, **312** and a second input operably coupled to an electrical ground **321**. The first electrode **310** is electrically coupled (e.g., as an input) to the first amplifier **323**, and the second electrode **312** is electrically coupled (e.g., as an input) to the second amplifier **325**. The differentiation circuit **320** may further include filtering circuitry to filter any undesired electrical activity from the electrical signals monitored by the first and second electrodes **310**, **312**.

[0068] When an electrical signal propagates in either direction along the nerve fibers **201**, the first amplifier **323** outputs a positive waveform **322** and the second amplifier **325** outputs a positive waveform **324**. The timing of the waveforms **322**, **324** may be compared **326** e.g., to determine whether electrical activity is efferent or afferent, to determine the conduction velocity, etc., and the electrical signals may be integrated **328** similar to the integration **226** described herein with reference to FIG. **5** (e.g., the area under the curve for a period of time may be computed to generate a value).

[0069] Next, the method **300** may determine **330** whether the electrical signal that propagated along the nerve fibers **201** is efferent or afferent based on the timing comparison **326**. For example, if the electrical activity monitored by the first electrode **310** (e.g. waveform **322**) occurred before the electrical activity monitored by the second electrode **312** (e.g., waveform **324**), then the monitored electrical activity propagated from the central end **202** to the peripheral end **204** of the nerve fibers **201**, and therefore, the monitored electrical activity is efferent. Conversely, if the electrical activity monitored by the second electrode **312** (e.g., waveform **324**) occurred before the electrical activity monitored by the first electrode **310** (e.g. waveform **322**), then the monitored electrical activity propagated from the peripheral end **204** to the central end **202** of the nerve fibers **201** (in other words, from the right side of the figure to the left side), and therefore, the monitored electrical activity is afferent.

[0070] In other words, the timing difference of the action potential, or monitored electrical activity, between these two electrodes may be used to determine which direction the action potential propagates, e.g., if the electrode **310** detects the action potential earlier than electrode **312**, the propagation occurs from central end to the peripheral end, and such propagation is assigned as including efferent components. Vice versa, if the electrode **312** detects the action potential earlier than electrode **310**, the propagation is from the peripheral end to the central end, and such propagation is assigned as including afferent components. Often, due to the distance between the two electrodes being close, the velocity of nerve propagation being quick, and the use of a fast sampling rate, two connective action potentials monitored by the electrodes may overlap because the refractory period for nerves may be about 5 milliseconds to about 10 milliseconds.

[0071] Further, the unipolar recordings of method **300** may be used to determine action potential propagation velocity. For example, when the action potential propagates from central end **202**, electrode **310** will detect the action potential first, followed by the detection of action potential by the electrode **312**. A timing delay will exist between these two detections and the velocity of the action potential, or signal, is then determined by the time divided by the distance between these two electrodes.

[0072] Efferent and afferent signals traveling along nerve fibers **201** may also be differentiated by using processes (which, e.g., may be used in conjunction with the methods described herein) that take into account that fibers with different diameters and/or myelination (e.g., the thickness of the layer of myelin around the fiber) have different conduction velocities. For example, different classes and sub-classes (A-alpha, A-beta, A-gamma, A-delta, B, and C) of nerve fibers have different diameters and/or different levels of myelination. Further, each of the different types of fibers may conduct nerve signals corresponding to various functions of one or more physiological systems. As such, the conduction velocities, and thus the diameters, of the nerve fibers may be used to distinguish the different types of nerve signals being conducted over the nerve fibers. A-alpha fibers may have a diameter of about 12 to about 20 micrometers and a conduction velocity of about 70 meters per second to about 120 meters per second; A-beta fibers may have a diameter of about 5 micrometers to about 12 micrometers and a conduction velocity of about 30 meters per second to about 70 meters per second; A-gamma fibers may have a diameter of about 3 micrometers to about 6 micrometers and a conduction velocity of about 15 meters per second to about 30 meters per second; A-delta fibers may have a diameter of about 2 micrometers to about 5 micrometers and a conduction velocity of about 5 meters per second to about 30 meters per second; B fibers may have a diameter of about less than 3 micrometers and a conduction velocity of about 3 meters per second to about 15 meters per second; and C fibers may have a diameter of about 0.4 micrometers to about 1.2 micrometers and a conduction velocity of about 0.4 meters per second to about 2 meters per second.

[0073] For example, with respect to the vagus nerve, the A-alpha fibers of the vagus nerve may carry both efferent and

afferent activity, e.g., related to somatic motor functionality and parasympathetic sensory functionality. Further, for example, A-beta fibers of the vagus nerve may carry afferent activity, the A-gamma fibers of the vagus nerve carry efferent activity, and the A-delta fibers of the vagus nerve may carry afferent activity. Still further, for example, the B fibers of the vagus nerve may carry efferent activity, e.g., related to parasympathetic motor functionality, and the C fibers of the vagus nerve may carry both efferent and afferent activity, e.g., related to parasympathetic sensory functionality and parasympathetic motor functionality.

[0074] In at least one embodiment, it may be expected (e.g., depending on the electrode locations, signal filtering techniques, etc.) that the efferent activity (e.g., electrical activity of the vagus nerve traveling towards the heart propagates over smaller, less myelinated fibers and that afferent activity (e.g., electrical activity of the vagus nerve traveling away from the heart) propagates over large, myelinated fibers. As described, smaller, less myelinated fibers conduct action potentials more slowly than large, myelinated fibers. As a result, efferent activity and afferent activity may be distinguished and indentified using the monitored action potential's conduction velocity because efferent activity should travel slower than afferent activity.

[0075] In other words, the velocity of an action potential, or monitored electrical activity, calculated using the timing between the two electrodes **310**, **312** may be used to determine which direction the action potential propagates, e.g., if the velocity of the action potential is slower than an efferent threshold value or is within a range of efferent values, then the propagation is occurring from central end **202** to the peripheral end **204**, and such propagation is assigned as including efferent components. Vice versa, if the velocity of the action potential is faster than an afferent threshold value or is within a range of afferent values, then the propagation is occurring from the peripheral end **204** to the central end **202**, and such propagation is assigned as including afferent components.

[0076] The nerve signal differentiation methods **200**, **300** may be used in one or more therapy delivery methods (e.g., for adjustment of the therapy, initialization of the therapy, termination of the therapy, etc.). Further, the nerve signal differentiation methods as well as the other methods, systems, and devices herein may be used with any nerve signals of a patient (e.g., respiration nerve signals, muscle activity, etc.) and may be utilized in conjunction with any therapy, e.g., GI therapy (e.g., see FIG. **10**), muscle therapy, etc.

[0077] For example, the efferent and afferent components of a patient's vagus nerve may be used in cardiac therapy. A flow chart illustrating an exemplary method **400** of nerve signal differentiation and cardiac therapy adjustment based on nerve signals is depicted in FIG. **7**. The method **400** includes recording cardiac vagal signals **402** (e.g., the electrical activity of the patient's vagus nerve) with the systems and methods described herein, e.g., method **200** of FIG. **5**.

[0078] Concurrently or periodically, the method **400** may determine whether the recorded cardiac vagal signals have crossed a positive signal threshold **404**, which is similar to process step **228** described herein with reference to FIG. **5** except this system is configured such that positive electrical activity indicates efferent activity. The positive signal threshold may be a selected minimum value indicative of efferent integration (e.g., the positive signal threshold may be about two to about three times the baseline electrical activity the monitored nerve fibers). For example, if the recorded cardiac vagal signals exceed the positive signal threshold, then the recorded cardiac vagal signals may be efferent. In essence, the positive signal threshold may act to trigger further analysis of the presently recorded cardiac vagal signals for efferent components. Further, the positive signal threshold may also act as a filter, e.g., for filtering out undesired signals (e.g., too weak signals, signals operating at undesired frequencies, etc.).

[0079] If it is determined that the recorded cardiac vagal signals have crossed a positive signal threshold **404**, the method **400** may determine that the recorded cardiac vagal signals are efferent **408** similar to the processes of methods **200**, **300** described herein with reference to FIGS. **7-8**.

[0080] The method **400** may further determine whether the efferent components of the recorded cardiac signals include parasympathetic activity **410**. For example, determining whether the efferent components of the recorded cardiac signals include parasympathetic activity **410** may include correlating the efferent components to a slowing heart rate, decreased HRV, prolonged R-R intervals, prolonged P-R intervals, etc. If the efferent components of the recorded cardiac signals are correlated to a slowing heart rate, decreased HRV, prolonged R-R intervals, prolonged P-R intervals, etc., it may be determined that the efferent components include parasympathetic activity. In the case of monitoring the electrical activity of the vagus nerve, the method **400** may assume that all efferent components are parasympathetic activity.

[0081] The method **400** may also determine whether the recorded cardiac vagal signals have crossed a negative signal threshold **406**, which is similar to process step **228** described herein with reference to FIG. **5** except this system is configured such that negative electrical activity indicates afferent activity. Further, negative signal threshold step **406** may occur concurrently with process step **404** or after process step **404** (e.g., if it is determined that the recorded cardiac vagal signals have not crossed a positive signal threshold **404**). The negative signal threshold may be a selected minimum value indicative of afferent integration (e.g., the magnitude of the negative signal threshold may be about two to about three times the baseline electrical activity the monitored nerve fibers). For example, if the recorded cardiac vagal signals exceed the negative signal threshold (i.e., less than the negative signal threshold), then the recorded cardiac vagal signals may be afferent. In essence, the negative signal threshold may act to trigger further analysis of the presently recorded cardiac vagal signals for afferent components. Further, the negative signal threshold may also act as a filter, e.g., for filtering out undesired signals (e.g., too weak signals, signals operating at undesired frequencies, etc.).

[0082] If it is determined that the recorded cardiac vagal signals have crossed a negative signal threshold **406**, the method **400** may determine that the recorded cardiac vagal signals are afferent **412**. Afferent components of the cardiac vagal signals may be indicative of some cardiac conditions, e.g., such as myocardial ischemia or insult like over-stretch. As such, method **400** may analyze the physiological parameters of the patient to determine if the patient is undergoing any particular cardiac conditions **414** (e.g., ischemia, overload, tissue inflammation, cardiac stretch, cardiac insults, etc.) that, e.g., may be related to the afferent signals detected. If it is determined that the recorded cardiac vagal signals have not crossed a negative signal threshold **406**, the method **400** may return to recording cardiac vagal signals **402**.

[0083] After determining that the recorded cardiac vagal signals include either parasympathetic activity **410** or activity indicative of certain cardiac conditions **414**, the method **400** may conduct a comparison of physiological parameters **416** including the efferent signals and/or the afferent signals to determine whether the patient needs cardiac therapy, or in the case of ongoing cardiac therapy, needs an adjustment to the cardiac therapy. The physiological parameters may include the electrical activity of a patient's heart, chemical activity of a patient's heart, hemodynamic activity of a patient's heart, and electrical activity of the patient's vagus nerve as described herein.

[0084] Further, the physiological parameters may be compared to selected threshold values **420**. For example, each physiological parameter may be compared to a specific selected threshold value that represents a point at which either cardiac therapy for a patient should be started, or in the case of ongoing cardiac therapy, the cardiac therapy should be adjusted. If it is determined that cardiac therapy does not need to be adjusted or started based on the comparison to selected threshold values, the method **400** may return to recording cardiac vagal signals **402**.

[0085] If the comparison to selected threshold values determines that cardiac therapy needs be adjust or started, the method **400** may adjust (or start) the cardiac therapy **422**. The cardiac therapy may include the delivery of vagal stimulation (e.g., electrical stimulation to a patient's vagus nerve), electrical stimulation for pacing the patient's heart **12** (e.g., bradycardia pacing, cardiac resynchronization therapy, antitachycardia pacing (ATP), high-energy shock pulses for cardioversion/defibrillation therapy, and/or other pacing therapies), etc.

[0086] For example, the patient's R-R intervals may be compared to selected threshold values indicative of healthy cardiac function and/or cardiac conditions. If it is determined that the patient's R-R intervals are indicative of unhealthy cardiac function and/or treatable cardiac conditions, then the cardiac therapy may need to be adjusted.

[0087] As described herein, cardiac therapy may be initiated and/or adjusted based on nerve signal recordings (e.g., the parasympathetic component of a nerve signal). An exemplary method **600** of initiating cardiac therapy based on nerve signals is depicted in FIG. **8**. The method **600** may include data collection **602** (e.g., nerve recording and other cardiac parameters). Data collection **602** may include monitoring one or more physiological parameters of a patient, e.g., as described herein with reference to the IMD **10** of FIG. **1**. Specifically, however, the data collection **602** includes monitoring nerve signals (e.g., of the vagus nerve). Although not shown, the method **600** may include the processes described herein, e.g., with reference to FIGS. **5-6**, for identifying, processing, and/or filtering the efferent (or afferent) activity from the electrical activity of the nerve tissue (e.g., the vagus nerve).

[0088] Periodically or concurrently with the data collection **602**, the method **600** includes determining whether the efferent activity of the electrical activity of the patient's vagus nerve is reduced **604**. Determining whether the efferent activity of the electrical activity of the patient's vagus nerve is reduced **604** may be conducted using various processes. For example, the method may compare various parameters of the efferent activity to a selected value. Such parameters may include voltage, amplitude, frequency, pulses per heart beat, pulses per second, sum of integration, signal energy power of spectral analysis, timing of signals, and/or trend of nerve activity. The selected value may be a threshold representing the minimum or the maximum value of parasympathetic activity required for healthy cardiac function. In other words, if the patient's parasympathetic activity falls below a minimum selected value or exceeds a maximum selected value, it may be indicative of abnormal automatic nervous activities, unhealthy cardiac function, future cardiac conditions, and/or other organ problems. For example, the method may compare the pulses per second of the monitored efferent activity to a threshold value of about 3 pulses per second (e.g., the threshold value may be about 2 pulses per second to about 5 pulses per second depending on the patient, the physical activity of the patient, etc.). If the monitored efferent activity drops below 3 pulses per second, the method may determine that the efferent activity of the patient is reduced.

[0089] Further, for example, the method **600** may compare various parameters of the efferent activity presently being monitored or recorded to such parameters of efferent activity that have been previously recorded. Such parameters may include voltage, amplitude, frequency, pulses per heart beat, pulses per second, sum of integration, signal energy power using spectral analysis, timing of signals, and/or trend of nerve activity. In other words, the previously-monitored efferent activity may provide a baseline to which the presently-monitored efferent activity may be compared. If the presently-monitored efferent activity is less than the previously-monitored efferent activity (e.g., the previously-monitored efferent activity may have been analyzed and/or monitored previously), the presently-monitored efferent activity may be determined to be reduced, which therefore, may be indicative of abnormal automatic nervous activities, unhealthy cardiac function, risk of heart attack, future cardiac conditions, abnormal automatic activities to other organs like the GI system or somatic nerves to muscles.

[0090] Still further, for example, the method **600** may further identify, process, and/or filter the afferent activity/sympathetic activity from the electrical activity of the nerve tissue (e.g., the vagus nerve) and compare the efferent activity (and/or parasympathetic activity) of the electrical activity of the patient's vagus nerve to the afferent activity (and/or sympathetic activity) of the electrical activity of the patient's vagus nerve to determine if the efferent activity is reduced. Such comparison between efferent activity and afferent activity may compare various parameters (e.g., pulses per second), and further may not be a 1:1 comparison (e.g., each parameter may be multiplied, or transformed, for easier comparison).

[0091] In at least one embodiment, the amplitude (e.g., average amplitude over a selected time period) of a selected frequency range of the monitored efferent activity may be used to determine whether the efferent activity is reduced. For example, the method **600** may analyze the monitored efferent activity within the frequency spectrum to evaluate the amplitude in a selected frequency range (e.g., about 0.15 hertz to about 0.4 hertz, or high frequency (HF) band that, e.g., may be driven by respiration and may be derived mainly from vagal activity of the parasympathetic nervous system or about 0.04 hertz to about 0.15 hertz, or low frequency (LF) band that, e.g., may be derived from both parasympathetic and sympathetic activity and may reflect the delay in the baroreceptor loop), which is considered to purely reflect vagal activity. Further, the average amplitude of the selected frequency range of the presently-monitored efferent activity may be compared to a selected value or to the average amplitude of

the selected frequency range of previously-monitored efferent activity to determine whether the efferent activity of the electrical activity of the at least one nerve fiber is reduced.

[0092] In at least another embodiment, the power spectrum of the selected frequency range of the monitored efferent activity may be used to determine whether the efferent activity is reduced. For example, the method **600** may calculate the power (e.g., average area under the curve over time) of the monitored efferent activity in the selected frequency range. Further, the average power of the selected frequency range of the presently-monitored efferent activity may be compared to a selected value or to the average power of the selected frequency range of previously-monitored efferent activity to determine whether the efferent activity of the electrical activity of the at least one nerve fiber is reduced.

[0093] Further, a relation may exist between the power spectra of the monitored nerve signals (e.g., of a selected frequency range (e.g., about 0.15 hertz to about 0.4 hertz) and the patient's HRV. Using such a relation or transfer function (e.g., which may be predetermined (e.g., using data from a plurality of patients), created using data from the present patient, etc.), a patient's nerve signals or the status thereof (e.g., the power spectra of the nerve signals) may be calculated using the monitored HRV of the patient. In other words, a function may be provided (e.g., predetermined, calculated for a specific patient, etc.) relating the status of the patient's vagus nerve to the electrical activity of the patient's heart (e.g., the HRV of the electrical activity of the patient's heart) for use in therapy, assessing a status of the patient's vagus nerve using the monitored electrical activity of the patient's heart using the function, and initiating or adjusting cardiac therapy to the patient based on the assessed status of the patient's vagus nerve.

[0094] Further, in at least one embodiment, a comparison between efferent activity in general, average activity within a certain phase of the cardiac cycle, or efferent activity within a certain frequency band (e.g., HF or LF) may provide information about the intactness of the nerves innervating the heart. This could be indicative of nerve deterioration in certain cases, e.g., diabetes or cardiac infarct.

[0095] If it has been determined that there has not been a reduction in the parasympathetic component **604**, then the method **600** may return to data collection **602**. If it has been determined that there has been a reduction in the parasympathetic component **604**, then the method **600** may initiate the delivery of cardiac therapy **606**. Such therapy may include delivering vagal stimulation (e.g., electrical stimulation to a patient's vagus nerve), electrical stimulation for pacing the patient's heart **12** (e.g., bradycardia pacing, cardiac resynchronization therapy, ATP, and/or other pacing therapies), and/or other types of therapy like neuromodulation (e.g., spinal cord stimulation), etc. Further, in at least one embodiment, an IMD may be capable of delivering high-energy shock pulses for cardioversion/defibrillation therapy delivered in response to, e.g., tachycardia detections.

[0096] Further, the cardiac therapy may be delivered during or after the monitored nerve signals. For example, if the method is delivering vagal stimulation, the vagal stimulation may be delivered after a monitored burst of efferent and/or parasympathetic activity (e.g., vagal burst discharges) in order to, e.g., expand vagal excitation and effect. The cardiac therapy may start before the burst of nerve activity ceases or may start after the nerve activity ceases. For example, the method may deliver vagal stimulation for a selected period of time after a burst of efferent activity ceases.

[0097] After or during the delivery of cardiac stimulation **606**, the method **600** may determine whether the patient's cardiac condition is suitable for cardiac stimulation **608**. Determining whether the patient's cardiac condition is suitable for cardiac stimulation **608** may utilize the monitored physiological parameters (e.g., the electrical activity, chemical activity, hemodynamic information, and/or nerve activity of the patient's heart).

[0098] If it is determined that the patient's cardiac condition is not suitable for cardiac stimulation, the method **600** may return to data collection **602**. For example, determining whether the patient's cardiac condition is suitable for cardiac stimulation **608** may include analyzing the monitored physiological parameters for termination criteria. Analyzing such monitored physiological parameters may include determining whether the electrical activity of the patient's heart indicates a ventricular arrhythmia, determining whether the R-R intervals have not increased, and determining whether the P-R intervals have not increased. The method may then terminate the delivery of electrical stimulation to the vagus nerve if either the electrical activity of the patient's heart indicates a ventricular arrhythmia, the R-R intervals have not increased, or the P-R intervals have not increased. Further, for example, the method may include determining whether the patient's cardiac condition is worsening after the delivery of electrical stimulation to the patient's vagus nerve and terminating the delivery of electrical stimulation to the patient's vagus nerve if the patient's cardiac condition is worsening.

[0099] More details of methods of and devices for use in treating patients (e.g., using vagal stimulation) are described, e.g., in U.S. patent application entitled "VAGAL STIMULATION" to Ziegler et al. (Medtronic No. P0035129.00/M&R 134.03910101), U.S. patent application entitled "TERMINATION CRITERIA FOR VAGAL STIMULATION" to Kornet et al. (Medtronic Docket No. P0035322.00/M&R DOCKET NO. 134.03930101), U.S. patent application entitled "VAGAL STIMULATION FOR ARRHYTHMIA PREVENTION" to Zhou et al. (Medtronic Docket No. P0038318.00/M&R DOCKET NO. 134.04010101), U.S. patent application entitled "REGULATION OF PRELOAD" to Cornelussen et al. (Medtronic Docket No. P0038177.00/M&R DOCKET NO. 134.04020101), U.S. patent application entitled "VAGAL STIMULATION FOR TREATING MYOCARDIAL INFARCTION" to Zhou et al. (Medtronic Docket No. P0030271.00/M&R DOCKET NO. 134.04290101), U.S. patent application entitled "NERVE SIGNAL DIFFERENTIATION" to Zhou et al. (Medtronic Docket No. P0034839.00/M&R DOCKET NO. 134.03920101), and U.S. Provisional Pat. App. entitled "THERAPY USING PERTURBATION AND EFFECT OF PHYSIOLOGICAL SYSTEMS" to John Burnes et al. (Medtronic Docket No. P0029631.00/M&R DOCKET NO. 134.04160160), each of which are filed on the same date as the present application and are incorporated herein by reference in their entirety.

[0100] If it is determined that the patient's cardiac condition is suitable for cardiac stimulation, the method **600** may determine whether a stimulation clock (e.g., a timer that was started when the cardiac stimulation started) has expired **610**. If the stimulation clock **610** has expired, the method **600** may return to data collection **602**. If the stimulation clock has not expired, the method **600** may return to delivering cardiac stimulation **606**. In at least one embodiment, the stimulation

clock runs for about, e.g., 30 or 45 seconds. In other words, the method may terminate the delivery of electrical stimulation to the patient's vagus nerve after a selected time period has elapsed after the initiation of the delivery of electrical stimulation.

[0101] A flow chart illustrating an exemplary method **700** of adjusting cardiac therapy based on nerve signals is depicted in FIG. **9**. The method **700** includes delivering cardiac therapy **702**, e.g., vagal stimulation, cardiac resynchronization therapy, and/or spinal cord stimulation. The delivering of cardiac therapy **702** may be substantially similar to the delivery of cardiac therapy **606** described herein with reference to FIG. **8**.

[0102] Periodically or concurrently with the delivery of cardiac therapy **702**, the method **700** may record, or monitor, intracardiac nerve signals **704** (e.g., of the vagus nerve). Although not shown, the method **600** may include the processes described herein, e.g., with reference to FIGS. **5-6**, for identifying, processing, and/or filtering efferent and/or afferent activity from the electrical activity of the nerve tissue (e.g., the vagus nerve).

[0103] Using the monitored nerve signals, the method **700** may determine whether the parasympathetic activity of the nerve signals has been met **706**. In other words, the method **700** may include analyzing the monitored physiological parameters **706** after delivering cardiac therapy **702**. Such analyzing monitored physiological parameters may include determining whether the efferent activity of the electrical activity of the patient's vagus nerve is reduced. The processes in method **700** for determining whether the efferent activity of the electrical activity of the patient's vagus nerve is reduced may be similar to the processes described in method **600** of FIG. **8**.

[0104] If the parasympathetic activity of the nerve signals has been met, then the method **700** may return to delivering cardiac therapy **702**. If the parasympathetic activity of the nerve signals has not been met, then the method **700** may adjust the cardiac therapy **708**. In other words, the method **700** may adjust the cardiac therapy if the efferent activity of the electrical activity of the patient's vagus nerve is reduced. Adjusting the cardiac therapy **708** may include adjusting the voltage, amplitude, number of pulses per burst, burst frequency, pulse frequency, and pulse width of pacing or burst pacing therapy. Further, adjusting the cardiac therapy **708** may include triggering other neuromodulation therapy (e.g., spinal cord stimulation), drug pumps, or alerts to a patient to take medicine or rest (e.g., via telemetry). In at least one embodiment, adjusting the cardiac therapy may include determining if the vagal efferent components (e.g., sympathetic) are too high and delivering high frequency electrical pulses to the corresponding nerve through the same recording electrodes or different electrodes to block nerve conduction to, e.g., reduce the over-excited nerve activities.

[0105] If the cardiac therapy includes vagal stimulation, the parameters of such vagal simulation may be adjusted within certain ranges. Such parameters may include time (e.g., the vagal stimulation may be delivered for a selected time period), voltage (e.g., within a range of about 1 volt and about 8 volts), frequency of the pulses within a burst of pulses (e.g., within a range of about 1 hertz to about 150 hertz), frequency of the bursts (e.g., within a range of about 5 hertz to about 100 hertz), synchronization (e.g., with different portions of the electrical activity of the patient's heart), pulse width of each pulse (e.g., within a range of about 0.1 milliseconds to about 1 milliseconds), and number of pulses per burst (e.g., within a range of about 3 pulses to about 20 pulses), etc.

[0106] After the cardiac therapy has been adjusted, the method **700** may determine whether the patient has a stable cardiac condition **710**, e.g., using electrical activity, chemical activity, and/or hemodynamic activity of the patient's heart. Determining whether the patient has stable cardiac condition **710** may be substantially similar to determining whether the patient's cardiac condition is suitable for cardiac stimulation **608** as described herein with reference to FIG. **8**.

[0107] If it is determined that the patient has a stable cardiac condition, the method **700** may return to delivering cardiac therapy **702**. If it is determined that the patient does not have stable cardiac condition, the method **700** may readjust the cardiac therapy **712**, which may be substantially similar to adjusting cardiac therapy **708**. After the cardiac therapy has been readjusted **712**, the method **700** may again determine whether the patient has a stable cardiac condition **710**.

[0108] Although methods **600**, **700** are focused on cardiac therapy based on nerve activity, such methods are not limited to the delivery of cardiac therapy and may be used to treat other various conditions. For example, such methods may be used to treat and monitor organ functions in, e.g., the GI system, the bladder, various muscles, glands (e.g., for releasing hormones), etc.

[0109] One example where nerve recording and/or stimulation may be useful can be found in the GI system. The splanchnic nerves are paired nerves that contribute to the innervation of the viscera and carry fibers of the autonomic nervous system (efferent fibers) as well as sensory fibers from the organs (afferent fibers). One function of the splanchnic nerves is to regulate intestinal function. During proper functional digestion, sensors are stimulated in the intestine when food is moved into the intestine thereby triggering secretion of digestive enzymes and slowing contraction of intestinal muscles. As such, the sensing and stimulation of splanchnic nerves may help to regulate intestinal digestion.

[0110] Another function of the splanchnic nerves is to regulate bowel movements. When urine accumulates in bladder, sensors in bladder are stimulated by stretching and signals are propagated from such sensor to the spine and brain. Subsequently, efferent activity propagates from the brain to the bladder to trigger urination. If such efferent activity does not occur, the patient may not be able to urinate properly. As such, the sensing and stimulation of splanchnic nerves may help to regulate urination or other bowel movements.

[0111] In at least another embodiment, in the GI system, if the parasympathetic components of the autonomic nerves are too low, the GI system may, as described herein, not function appropriately, thus electrical stimulation of certain nerves (e.g., splanchnic nerves) may be triggered to increase parasympathetic tone for digestion and improve GI function. An example of a method of using nerve signals to deliver therapy to treat the GI system is described herein with reference to FIG. **10**.

[0112] A flow chart illustrating an exemplary method **800** of delivering and adjusting GI therapy based on nerve signals is depicted in FIG. **10**. The method **800** includes data collection **802**, which may include monitoring one or more physiological parameters of a patient, e.g., as described herein with reference to the IMD **10** of FIG. **1**. Specifically, however, the data collection **802** includes monitoring nerve signals of the splanchnic nerves. The method **800** may further include the processes described herein, e.g., with reference to FIGS. **5-6**,

for differentiating the efferent activity from the afferent activity within the electrical activity of the nerve tissue (e.g., the splanchnic nerves) **804**.

[0113] Periodically or concurrently with the data collection **802** and afferent/efferent differentiation **804**, the method **800** includes determining whether the afferent activity of the electrical activity of the patient's splanchnic nerves crosses a threshold **806**. Determining whether the afferent activity of the electrical activity of the patient's splanchnic nerves crosses a threshold value **806** may be conducted using various processes. For example, the method **800** may compare various parameters of the afferent activity to a selected threshold value. Such parameters may include voltage, amplitude, frequency, pulses per second, sum of integration, signal energy power of spectral analysis, timing of signals, and/or trend of nerve activity. The selected threshold value may be a threshold representing the minimum value of afferent activity required to indicate that food is located in the intestine. In other words, if the patient's afferent activity is above the selected threshold value, food may be present in the intestine, and conversely, if the patient's afferent activity is below the selected value, no food may be present in the intestine.

[0114] If the afferent activity of the splanchnic nerves crosses the threshold value, then the method **800** may determine if the efferent activity of the splanchnic nerves crosses another threshold value **808**. Such threshold determination may be similar to process step **806** for afferent activity but the threshold value **808** may be indicative of the minimum value required for proper digestive function in response to food being located in the intestine. If the patient's efferent activity is above the selected threshold value, then the body is responding effectively (e.g., delivering nerve signals to triggering secretion of digestive enzymes and slowing contraction of intestinal muscles) and the method **600** may return to data collection **802**. Conversely, if the patient's efferent activity is below the selected value, then the method **800** may deliver GI therapy **810**, e.g., electrical stimulation of the splanchnic nerve, which may be similar to the nerve stimulation **606** described herein with reference to FIG. **8**.

[0115] After the GI therapy **810**, the method **800** may assess the functionality of the patient's GI system **812**. Assessing the functionality of the patient's GI system **812** may include analyzing the monitored one or more physiological parameters, e.g., analyzing the electrical activity (efferent and/or afferent activity) of the splanchnic nerves. For example, if the efferent activity of the splanchnic nerves is still below the selected threshold value as utilized in process step **808**, then it may be determined that the GI therapy (e.g., splanchnic nerve stimulation) may need to be adjusted.

[0116] Adjusting the splanchnic nerve stimulation **814** may include adjusting the voltage, amplitude, number of pulses per burst, burst frequency, pulse frequency, and pulse width of pacing or burst pacing therapy, etc. For example, if it is determined that the efferent activity of the patient's splanchnic nerves is still too low, the method may supplement the efferent activity by delivering stimulation to the splanchnic nerves for a selected period of time after the efferent activity has ceased.

[0117] The method **800** may further determine whether a stimulation clock (e.g., a timer that was started when the GI therapy started) has expired **816**. If the stimulation clock **816** has expired, the method **800** may return to data collection **802**. If the stimulation clock has not expired, the method **800** may return to delivering GI therapy **810**. In at least one embodiment, the stimulation clock runs for about, e.g., 30 or 45 seconds. In other words, the method may terminate the delivery of GI therapy after a selected time period has elapsed after the initiation of the delivery of GI therapy.

[0118] One example of a medical device that may be used in carrying out the methods described herein for providing treatment is depicted in FIG. **1** as a schematic diagram of an implantable medical device (IMD).

[0119] The IMD **10** may be configured to monitor one or more physiological parameters of a patient (e.g., electrical activity of a patient's heart, chemical activity of a patient's heart, hemodynamic activity of a patient's heart, and electrical activity of the patient nerves). Although the IMD **10** has shown is configured to monitor the patient's heart, IMD **10** or similar devices may used for monitoring and delivering therapy to any organs or parts of a patient. In this example, the monitored physiological parameters, in turn, may be used by the IMD to detect various cardiac conditions, e.g., ventricular tachycardia (VT), ventricular fibrillation (VF), supraventricular ventricular tachycardia (SVT), atrial fibrillation (AF), atrial tachycardia (AT), ischemia/infarction, heart failure, etc., and to treat such cardiac conditions with therapy. Such therapy may include delivering vagal stimulation (e.g., electrical stimulation to a patient's vagus nerve), electrical stimulation for pacing the patient's heart **12** (e.g., bradycardia pacing, cardiac resynchronization therapy, ATP, and/or other pacing therapies), etc. Further, in at least one embodiment, the IMD **10** may be capable of delivering high-energy shock pulses for cardioversion/defibrillation therapy delivered in response to, e.g., tachycardia detections.

[0120] As used herein, "stimulation of the vagus nerve," also referred to herein simply as "vagal stimulation," refers to stimulation of neural tissue innervating the myocardium, directly or indirectly, e.g., stimulation of one or more of the vagus nerve or its branches (e.g., including the afferent and/or efferent fibers), the sinoatrial (SA) nodal fatty pad, the atrioventricular (AV) nodal fatty pad and along the great vein, the cervical vagus nerve (e.g., the right or left side), the fat pad located between the medial superior vena cava and aortic root (SVC-Ao fat pad), the fat pad superior to the right pulmonary artery, the fat pad at the IVC-left atrial junction (IVC-LA fat pad), the fat pad proximate the right pulmonary vein-atrial junction (RPV fat pad), the spinal cord (e.g., vertebral levels T1-T12, C1-C8, etc. such as described in U.S. Pat. App. Pub. No. 2002/0107552 A1 to Hill et al., which is incorporated herein by reference in its entirety), and additional intracardiac locations near the SA node, AV node, coronary sinus, and base of right ventricle.

[0121] One or more other embodiments of the present disclosure relates to sensing and stimulating a phrenic nerve of a heart failure patient with sleep apnea. In one or more embodiments, the LV lead **16** is placed in, around or near the phrenic nerve **500** that runs behind the left ventricle, as shown in FIG. **11**. The phrenic nerve **500** descends obliquely with the internal jugular vein (IJV) across the anterior scalene, deep to the prevertebral layer of deep cervical fascia and the transverse cervical and suprascapular arteries. Found in the middle mediastinum, both the left and right phrenic nerves run from C3, C4 and C5 along the anterior scalene muscle deep to the carotid sheath. The right phrenic nerve passes over the brachiocephalic artery, posterior to the subclavian vein, and then crosses the root of the right lung anteriorly and then leaves the thorax by passing through the vena cava hiatus opening in the diaphragm at the level of T8. The right phrenic nerve passes

over the right atrium. The left phrenic nerve passes over the pericardium of the left ventricle and pierces the diaphragm separately. The LV lead **16** can be placed around or near the left phrenic nerve. For example, the LV lead **16** can be placed within a few millimeters (mm) (e.g. about 5 mm or less than 5 mm) of the left phrenic nerve **500**.

[0122] After the LV lead has been properly placed, the therapy system or IMD **10** can monitor physiological conditions such as electrical activities from the phrenic nerve. By monitoring phrenic nerve activities and distinguishing the afferent/efferent nerve activities, as previously described, the IMD **10** can determine when and what electrical stimulation parameters to use during electrical stimulation to the phrenic nerve. For example, efferent components of phrenic nerve activity should have a certain burst frequency (e.g. 5 to 10 nerve discharges per burst, 12-16 bursts per minute) and magnitude (5-20 microvolts). When efferent components are weak (e.g. nerve discharge per second is 5 Hertz), especially in conjunction with too slow respiration (e.g. less than about 10 respirations per minute) and/or weak respiratory volume (e.g. about 500-800 milliliters per respiration cycle) relative to diaphragm **502**, IMD **10** then initiates or delivers electrical stimulation to the phrenic nerve **500** with a defined amplitude (e.g. 1-8 volts) and frequency (e.g. 10-20 Hertz per burst, 12 to 14 burst rate per minute, etc.), to modulate respiration rate and volume.

[0123] Alternatively, IMD **10** can detect a pattern of phrenic nerve **500** activities to determine whether there is sleep apnea characterized by irregularity in respiration rhythm and magnitude. Once detected, IMD **10** can deliver electrical stimulation to the phrenic nerve **500** via the LV lead **16** to correct sleep apnea, especially when the sleep apnea pattern is detected in conjunction with the occurrence of heart failure decompensation, the latter can be detected via Medtronic Optivol or pressure monitoring. IMD **10** then checks to verify that, for example, respiration rate has returned to a normal rate (e.g. 12-14 respiration per minute) or a normal rate for that specific patient. A patient with heart failure may not be able to achieve a normal respiration rate; however, as long as the patient's respiration rate is substantially improved (e.g. +/− a few respiration cycles from the previous state) through electrical stimulation, the IMD **10** may be deemed to achieved a desired result.

[0124] Skilled artisans appreciate that ranges provided herein for phrenic nerve stimulation are designated for adults and the ranges may be adjusted for other conditions (e.g. age of the patient or other factors). Additionally, it is appreciated that the LV lead **16** may be placed near both the phrenic nerve and the vagus nerve.

[0125] The methods described herein are intended to illustrate the general functional operation of the devices and/or systems described herein, and should not be construed as reflective of a specific form of software or hardware necessary to practice one or more of the methods described herein. It is believed that the particular form of software will be determined primarily by the particular system architecture employed in a device (e.g., an implantable medical device) and/or system and by the particular detection and therapy delivery methodologies employed by the device and/or system. Providing software to accomplish the described methods in the context of any modern implantable medical device, given the disclosure herein, is within the abilities of one of skill in the art.

[0126] Further, methods described in conjunction with flow charts presented herein may be implemented in a computer-readable medium that includes computer instructions or software for causing a programmable processor to carry out the methods described. Computer instructions are typically stored in a "computer-readable medium" such as random access memory (RAM). "Computer-readable medium" includes but is not limited to any volatile or non-volatile media, such as a RAM, read only memory (ROM), non-volatile random access memory (NVRAM), electrically erasable programmable read-only memory (EEPROM), compact disc read-only memory (CD-ROM)), flash memory, and the like. The instructions may be implemented as one or more software modules, which may be executed by themselves or in combination with other software.

[0127] The hardware used to the accomplish the described methods, may include any one or more of a microprocessor, a digital signal processor (DSP), a controller, an application specific integrated circuit (ASIC), a field programmable gate array (FPGA), or equivalent discrete or integrated logic circuitry. In one or more exemplary embodiments, the processor may include multiple components, such as any combination of one or more microprocessors, one or more controllers, one or more DSPs, one or more ASICs, or one or more FPGAs, as well as other discrete or integrated logic circuitry. The functions and processes described herein may be embodied as software, firmware, hardware, or any combination thereof. As used herein, the term "circuitry" may be implemented in software as executed by one or more processes, firmware, hardware, or any combination thereof.

[0128] All patents, patent documents, and references cited herein are incorporated in their entirety as if each were incorporated separately. This disclosure has been provided with reference to illustrative embodiments and is not meant to be construed in a limiting sense. As described previously, one skilled in the art will recognize that other various illustrative applications may use the techniques as described herein to take advantage of the beneficial characteristics of the apparatus and methods described herein. Various modifications of the illustrative embodiments, as well as additional embodiments of the disclosure, will be apparent upon reference to this description.

What is claimed is:

1. A device for differentiating between efferent and afferent components of electrical activity of at least one nerve fiber, wherein the at least one nerve fiber extends from a central end to a peripheral end, wherein the device comprises:

a first electrode configured to monitor electrical activity along the at least one nerve fiber;

a second electrode configured to monitor electrical activity along the at least one nerve fiber, wherein the first electrode is configured to be located closer to the central end of the at least one nerve fiber than the second electrode; and

differentiation circuitry configured to determine whether an electrical signal propagating along the at least one nerve fiber comprises efferent activity or afferent activity based on the electrical activity monitored using the first and second electrodes.

2. The device of claim **1**, wherein the device further comprises one or more leads, and wherein the first electrode and the second electrode are coupled to the one or more leads.

3. The device of claim **1**, wherein efferent activity is associated with a waveform having a first polarity and afferent

activity is associated with a waveform having a second polarity, and further wherein the differentiation circuitry is configured to:

compare the electrical activity monitored by the first electrode to the electrical activity monitored by the second electrode; and

determine that the electrical signal propagating along the at least one nerve fiber comprises efferent activity if the comparison between the electrical activity monitored by the first electrode to the electrical activity monitored by the second electrode generates a waveform having the first polarity.

4. The device of claim **3**, wherein the first polarity is negative.

5. The device of claim **1**, wherein the differentiation circuitry is further configured to:

compare the timing of the electrical activity monitored by the first electrode to the timing of the electrical activity monitored by the second electrode; and

determine that the electrical signal propagating along the at least one nerve fiber comprises efferent activity if the electrical activity monitored by the first electrode occurs before the electrical activity monitored by the second electrode.

6. The device of claim **1**, wherein the differentiation circuitry is further configured to:

calculate the velocity of the electrical activity monitored by the first and the second electrodes; and

determine that the electrical signal propagating along the at least one nerve fiber comprises efferent activity or afferent activity based on the calculated velocity of the electrical activity monitored by the first and the second electrodes.

7. The device of claim **6**, wherein efferent activity is associated with an action potential velocity within a first velocity range and afferent activity is associated an action potential velocity within a second velocity range, and wherein the differentiation circuitry is configured to determine that the electrical signal propagating along the at least one nerve fiber comprises efferent activity if the calculated velocity is within the first velocity range and to determine that the electrical signal propagating along the at least one nerve fiber comprises afferent activity if the calculated velocity is within the second velocity range.

8. The device of claim **1**, wherein the differentiation circuitry is configured to determine whether the electrical signal propagating along the at least one nerve fiber comprises efferent activity or afferent activity based on the electrical activity monitored within a selected frequency range.

9. A method of delivering therapy, wherein the method comprises:

monitoring physiological parameters of a patient, wherein the physiological parameters comprise electrical activity of at least one nerve fiber of a patient;

differentiating between efferent activity and afferent activity of the monitored electrical activity of the at least one nerve fiber resulting in data representative thereof; and

initiating or adjusting delivery of electrical stimulation to the at least one nerve fiber based on the data resulting from the differentiation.

10. The method of claim **9**, wherein the method further comprises determining whether the efferent activity of the electrical activity of the at least one nerve fiber is reduced over time based on the monitored electrical activity of the at least one nerve fiber, and wherein initiating or adjusting delivery of electrical stimulation to the at least one nerve fiber based on the data resulting from the differentiation comprises initiating or adjusting the delivery of electrical stimulation to the at least one nerve fiber if the efferent activity of the monitored electrical activity of the at least one nerve fiber is reduced.

11. The method of claim **9**, wherein determining whether the efferent activity of the monitored electrical activity of the at least one nerve fiber is reduced comprises comparing the pulses per second of the efferent activity to a selected value.

12. The method of claim **9**, wherein determining whether the efferent activity of the electrical activity of the at least one nerve fiber is reduced comprises comparing the pulses per second of presently-monitored efferent activity to the pulses per second of previously-monitored efferent activity.

13. The method of claim **9**, wherein determining whether the efferent activity of the electrical activity of the at least one nerve fiber is reduced comprises comparing the efferent activity of the electrical activity of the at least one nerve fiber to the afferent activity of the electrical activity of the at least one nerve fiber.

14. The method of claim **9**, wherein determining whether the efferent activity of the electrical activity of the at least one nerve fiber is reduced comprises comparing the average amplitude of a selected frequency range of the efferent activity to a selected value.

15. The method of claim **9**, wherein determining whether the efferent activity of the electrical activity of the at least one nerve fiber is reduced comprises comparing the average power of a selected frequency range of the efferent activity to a selected value.

16. A method of differentiating between efferent and afferent components of electrical activity of at least one nerve fiber, wherein the at least one nerve fiber extends from a central end to a peripheral end, wherein the method comprises:

locating a first electrode and a second electrode along the at least one nerve fiber, wherein the first electrode is located closer to the central end of the at least one nerve fiber than the second electrode;

monitoring the electrical activity of the at least one nerve fiber using the first electrode;

monitoring the electrical activity of the at least one nerve fiber using the second electrode; and

determining whether an electrical signal propagating along the at least one nerve fiber comprises efferent activity or afferent activity based on the electrical activity monitored using the first and second electrodes.

17. The method of claim **16**, wherein efferent activity is associated with a waveform having a first polarity and afferent activity is associated with a waveform having a second polarity, and wherein the method further comprises:

comparing the electrical activity monitored by the first electrode to the electrical activity monitored by the second electrode; and

determining that the electrical signal propagating along the at least one nerve fiber comprises efferent activity if the comparison between the electrical activity monitored by the first electrode to the electrical activity monitored by the second electrode generates a waveform having the first polarity.

18. The method of claim **17**, wherein the first polarity is negative.

19. The method of claim **16**, wherein the method further comprises:

comparing the timing of the electrical activity monitored by the first electrode to the timing of the electrical activity monitored by the second electrode; and

determining that the electrical signal comprises efferent activity if the electrical activity monitored by the first electrode occurs before the electrical activity monitored by the second electrode.

20. The method of claim **16**, wherein locating a first electrode and a second electrode along the at least one nerve fiber comprises locating the first electrode and the second electrode along at least one nerve fiber of the vagus nerve.

21. The method of claim **16**, wherein the method further comprises:

calculating the velocity of the electrical activity monitored by the first and the second electrodes; and

determining that the electrical signal comprises efferent activity or afferent activity based on the calculated velocity of the electrical activity monitored by the first and the second electrodes.

22. The method of claim **16**, wherein efferent activity is associated with an action potential velocity within a first velocity range and afferent activity is associated an action potential velocity within a second velocity range, and wherein determining that the electrical signal comprises efferent activity or afferent activity based on the calculated velocity of the electrical activity monitored by the first and the second electrodes comprises:

determining that the electrical signal comprises efferent activity if the calculated velocity is within the first velocity range, and

determining that the electrical signal comprises afferent activity if the calculated velocity is within the second velocity range.

23. The method of claim **16**, wherein determining whether an electrical signal propagating along the at least one nerve fiber comprises efferent activity or afferent activity based on the electrical activity monitored using the first and second electrodes comprises determining whether the electrical signal propagating along the at least one nerve fiber comprises efferent activity or afferent activity based on the electrical activity monitored within a selected frequency range.

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