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(71) Applicant: **CARDIAC PACEMAKERS, INC.** [US/US];  
4100 Hamline Avenue North, St. Paul, Minnesota 55112-  
5798 (US).

(72) Inventors: **AN, Qi**; 1815 113th CT NE, Blaine, Minnesota  
55449 (US). **MASKARA, Barun**; 1062 101st Lane NE,  
Blaine, Minnesota 55434 (US). **THAKUR, Pramodsingh**

**Hirasingh**; 10551 Kilbirnie Road, Woodbury, Minnesota  
55129 (US). **THOMPSON, Julie**; 261 Tanner Court,  
Circle Pines, Minnesota 55014 (US).

(74) Agents: **ARORA, Suneel** et al.; Schwegman, Lundberg &  
Woessner, P.A., P.O. Box 2938, Minneapolis, Minnesota  
55402 (US).

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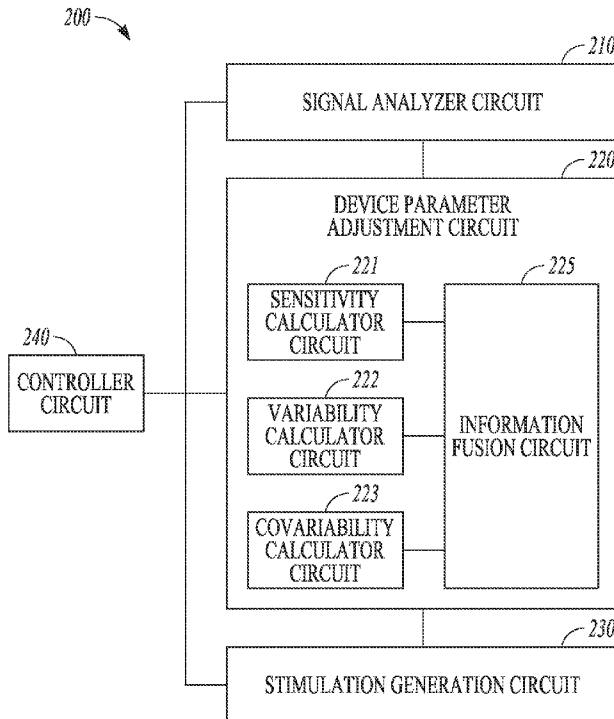


FIG. 2

(57) Abstract: Devices and methods for improving device therapy such as cardiac resynchronization therapy (CRT) by determining a desired value for a device parameter are described. An ambulatory medical device can receive one or more physiologic signals and generate multiple signal metrics from the physiologic signals. The ambulatory medical device can determine a desired value for a device parameter, such as a timing parameter used for controlling the delivery of CRT pacing to various heart chambers, using information fusion of signal metrics that are selected based on one or more of a signal metric sensitivity to perturbations to the device parameter in response to a stimulation, a signal metric variability in response to a stimulation, or a covariability between two or more signal metrics in response to a stimulation. The ambulatory medical device can program a stimulation using the desired device parameter value, and deliver the programmed stimulation to one or more target sites to achieve desired therapeutic effects.



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## MEDICAL DEVICE WITH MULTIPLE SENSOR FUSION

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### CLAIM OF PRIORITY

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application Serial Number 61/776,893, filed on March 12, 2013, which is herein incorporated by reference in its entirety.

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### TECHNICAL FIELD

[0002] This document relates generally to medical devices, and more particularly, to systems, devices and methods for improving a device therapy using multiple sensor metrics.

15

### BACKGROUND

[0003] Congestive heart failure (CHF) is a major health problem and affects over five million people in the United States alone. CHF is the loss of pumping power of the heart, resulting in the inability to deliver enough blood to meet the demands of peripheral tissues. CHF patients typically have enlarged  
20 heart with weakened cardiac muscles, resulting in reduced contractility and poor cardiac output of blood.

[0004] CHF is usually a chronic condition, but can occur suddenly. It can affect the left heart, right heart or both sides of the heart. If CHF affects the left ventricle, signals that control the left ventricular contraction are delayed, and the  
25 left and right ventricles do not contract simultaneously. Non-simultaneous contractions of the left and right ventricles further decrease the pumping efficiency of the heart.

### SUMMARY

30 [0005] CHF can be treated by cardiac pacing therapy. Pacing therapy to promote synchronization of heart chamber contractions for improved cardiac function is generally referred to as cardiac resynchronization therapy (CRT). Ambulatory medical devices such as cardiac pacemakers are capable of delivering CRT by pacing multiple heart chambers. Some ambulatory medical

devices can pace the heart chambers in a sequence that causes the heart chambers to contract in synchrony, thereby increasing the pumping power of the heart and delivering more blood to the peripheral tissues of the body. In the case of dyssynchrony of right and left ventricular contractions, a biventricular pacing therapy can be used to resynchronize the left and right ventricles. Bi-atrial pacing or pacing of all four heart chambers can also be used.

[0006] Improving the CRT therapy by determining desired CRT parameters involves determining desired pacing parameters, such as intervals between pacing pulses delivered to various heart chambers that provide effective CRT delivery. Due to the variation across patient population in their responses to CRT as well as the within-patient variation in optimal CRT setting as a result of, for example, changes in the patient's activity level, disease progression, medication, and general health condition, the patient response to CRT vary; and the therapy parameter need to be timely adjusted to provide and maintain desired cardiac function to the patient. The present inventors have recognized that there remains a considerable need of devices and methods that can automatically improve the device therapy by properly setting the CRT parameters on an individualized basis.

[0007] Various examples described herein can help improve the process of improving the device therapy such as cardiac resynchronization therapy (CRT). For example, an ambulatory medical device can receive one or more physiologic signals such as from a physiologic sensor and generate two or more signal metrics from the physiologic signals. The ambulatory medical device can include a device parameter adjustment circuit configured to determine a desired value for a device parameter, such as a timing parameter which can be used to control the delivery of CRT pacing to various heart chambers using information fusion. The device parameter adjustment circuit can include one or more of a sensitivity calculator circuit, a variability calculator circuit, or a covariability calculator circuit. The sensitivity calculator circuit can be configured to determine for at least two of the two or more signal metrics a respective sensitivity to a perturbation to the device parameter in response to stimulations. The variability calculator circuit can be configured to determine for at least two of the two or more signal metrics a respective variability in response to the stimulations. The covariability calculator circuit can be configured to determine

a covariability between at least two of the two or more signal metrics in response to the stimulations. An information fusion circuit can determine the desired device parameter value using one or more of the sensitivity, the variability, or the covariability. A controller circuit can program stimulations using the desired device parameter value, and a stimulation generation circuit can generate the programmed stimulations and deliver the stimulations to one or more target sites.

5 [0008] A method can include sensing one or more physiologic signals and generating two or more signal metrics from the physiologic signals. The method can include calculating a sensitivity of the signal metrics in response to stimulation with a perturbation to the device parameter, a variability of the signal metrics in response to the stimulation with a specified device parameter, and a covariability between two or more signal metrics in response to the stimulation with a specified device parameter. The method can then use one or more of the sensitivity, the variability, or the covariability to determine a desired value for the device parameter, such as a timing parameter which can be used to control the delivery of CRT pacing to various heart chambers. The method includes generating stimulations according to the desired value for the device parameter and delivering the stimulations the target sites.

10 [0009] Another method can include sensing one or more physiologic signals and generating two or more signal metrics from the physiologic signals, and determine a target directional vector using the difference between a first signal metric vector in response to stimulation when the device parameter is set to a first value, and a second signal metric vector in response to stimulation when the device parameter is set to a second value. Each signal metric vector comprises values of the two or more signal metrics measured during the respective stimulation. One of the first value or the second value of the device parameter includes a sub-optimal value. The method can construct a test signal metric vector in response to stimulation when the device parameter is set to a candidate value, and compute a projection of the test signal metric vector onto the target directional vector. When the projection meets a convergence criterion, the candidate value is determined to be a desired device parameter value. .

15 [0010] This Summary is an overview of some of the teachings of the present application and not intended to be an exclusive or exhaustive treatment of the present subject matter. Further details about the present subject matter are

found in the detailed description and appended claims. Other aspects of the invention will be apparent to persons skilled in the art upon reading and understanding the following detailed description and viewing the drawings that form a part thereof, each of which are not to be taken in a limiting sense. The scope of the present invention is defined by the appended claims and their legal equivalents.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Various embodiments are illustrated by way of example in the figures of the accompanying drawings. Such embodiments are demonstrative and not intended to be exhaustive or exclusive embodiments of the present subject matter.

[0012] FIG. 1 illustrates an example of cardiac rhythm management (CRM) system and portions of the environment in which the CRM system operates.

[0013] FIG. 2 illustrates an example of a device therapy adjustment circuit.

[0014] FIG. 3 illustrates an example of an information fusion circuit with signal metric selection.

[0015] FIG. 4 illustrates an example of an information fusion circuit with signal metric projection.

[0016] FIG. 5 illustrates an example of a method for determining a desired device parameter and stimulating a target site according to the desired device parameter.

[0017] FIG. 6 illustrates an example of a method for determining a desired value for a device parameter using a combination of signal metrics.

[0018] FIG. 7 illustrates an example of a method for determining a desired value for a device parameter using signal metric projection.

[0019] FIG. 8 illustrates an example of a method for adaptively determining a desired value for a device parameter.

## DETAILED DESCRIPTION

[0020] Disclosed herein are systems, devices and methods for improving a device therapy using multiple sensor metrics. The device therapy can include cardiac pacing therapy provided by an implantable medical device such as a pacemaker, an implantable cardioverter-defibrillator (ICD), or a cardiac resynchronization therapy (CRT) device. The improvement of the cardiac pacing therapy can include determining a desired value for a relative timing between a first event in a heart chamber and a second event in a different heart chamber, such as intervals between pacing pulses delivered to atria and ventricles that provide effective CRT delivery. The present document discussed methods and devices for improving the device parameters using multiple sensor metrics and information fusion. The methods and devices described herein can also be applicable to improving other device functions pertaining to an implantable medical device, including such as pacing therapy, defibrillation therapy, neural stimulation therapy, and patient diagnostics and stratifying a patient's risk of developing a disease or a condition, or to monitoring a patient's health status or response to a medical intervention.

[0021] FIG. 1 illustrates an example of a Cardiac Rhythm Management (CRM) system 100 and portions of an environment in which the CRM system 100 can operate. The CRM system 100 can include an ambulatory medical device, such as an implantable medical device (IMD) 110 that can be electrically coupled to a heart 105 such as through one or more leads 108A-C, and an external system 120 that can communicate with the IMD 110 such as via a communication link 103. The IMD 110 can include an implantable cardiac device such as a pacemaker, an implantable cardioverter-defibrillator (ICD), or a cardiac resynchronization therapy (CRT) device. The IMD 110 can include one or more monitoring or therapeutic devices such as a subcutaneously implanted device, a wearable external device, a neural stimulator, a drug delivery device, a biological therapy device, or one or more other ambulatory medical devices. The IMD 110 can be coupled to, or can be substituted by a monitoring medical device such as a bedside or other external monitor.

[0022] As illustrated in FIG. 1, the IMD 110 can include a hermetically sealed can 112 that can house an electronic circuit that can sense a physiologic signal in the heart 105 and can deliver one or more therapeutic electrical

stimulations to a target region, such as in the heart, such as through one or more leads 108A-C. The CRM system 100 can include only one lead such as 108B, or can include two leads such as 108A and 108B.

[0023] The lead 108A can include a proximal end that can be configured to be connected to IMD 110 and a distal end that can be configured to be placed at a target location such as in the right atrium (RA) 131 of the heart 105. The lead 108A can have a first pacing-sensing electrode 141 that can be located at or near its distal end, and a second pacing-sensing electrode 142 that can be located at or near the electrode 141. The electrodes 141 and 142 can be electrically connected to the IMD 110 such as via separate conductors in the lead 108A, such as to allow for sensing of the right atrial activity and optional delivery of atrial pacing pulses. The lead 108B can be a defibrillation lead that can include a proximal end that can be connected to IMD 110 and a distal end that can be placed at a target location such as in the right ventricle (RV) 132 of heart 105. The lead 108B can have a first pacing-sensing electrode 152 that can be located at distal end, a second pacing-sensing electrode 153 that can be located near the electrode 152, a first defibrillation coil electrode 154 that can be located near the electrode 153, and a second defibrillation coil electrode 155 that can be located at a distance from the distal end such as for superior vena cava (SVC) placement. The electrodes 152 through 155 can be electrically connected to the IMD 110 such as via separate conductors in the lead 108B. The electrodes 152 and 153 can allow for sensing of a ventricular electrogram (EGM) and can optionally allow delivery of one or more ventricular pacing pulses, and electrodes 154 and 155 can allow for delivery of one or more ventricular cardioversion/defibrillation pulses. In an example, the lead 108B can include only three electrodes 152, 154 and 155. The electrodes 152 and 154 can be used for sensing or delivery of one or more ventricular pacing pulses, and the electrodes 154 and 155 can be used for delivery of one or more ventricular cardioversion or defibrillation pulses. The lead 108C can include a proximal end that can be connected to the IMD 110 and a distal end that can be configured to be placed at a target location such as in a left ventricle (LV) 134 of the heart 105. The lead 108C can be implanted through the coronary sinus 133 and can be placed in a coronary vein over the LV such as to allow for delivery of one or more pacing pulses to the LV. The lead 108C can include an electrode 161 that can be located at a distal end of the lead 108C and

another electrode 162 that can be located near the electrode 161. The electrodes 161 and 162 can be electrically connected to the IMD 110 such as via separate conductors in the lead 108C such as to allow for sensing of the LV EGM and optionally allow delivery of one or more resynchronization pacing pulses from the LV.

[0024] The IMD 110 can include an electronic circuit that can sense a physiologic signal. The physiologic signal can include a EGM or a signal representing mechanical function of the heart 105. The hermetically sealed can 112 can function as an electrode such as for sensing or pulse delivery. For example, an electrode from one or more of the leads 108A-C can be used together with the can 112 such as for unipolar sensing of a EGM or for delivering one or more pacing pulses. A defibrillation electrode from the lead 108B can be used together with the can 112 such as for delivering one or more cardioversion/defibrillation pulses. In an example, the IMD 110 can sense impedance such as between electrodes located on one or more of the leads 108A-C or the can 112. The IMD 110 can be configured to inject current between a pair of electrodes, sense the resultant voltage between the same or different pair of electrodes, and determine impedance using Ohm's Law. The impedance can be sensed in a bipolar configuration in which the same pair of electrodes can be used for injecting current and sensing voltage, a tripolar configuration in which the pair of electrodes for current injection and the pair of electrodes for voltage sensing can share a common electrode, or tetrapolar configuration in which the electrodes used for current injection can be distinct from the electrodes used for voltage sensing. In an example, the IMD 110 can be configured to inject current between an electrode on the RV lead 108B and the can housing 112, and to sense the resultant voltage between the same electrodes or between a different electrode on the RV lead 108B and the can housing 112. A physiologic signal can be sensed from one or more physiological sensors that can be integrated within the IMD 110. The IMD 110 can also be configured to sense a physiologic signal from one or more external physiologic sensors or one or more external electrodes coupled to the IMD 110. Examples of the physiologic signal can include one or more of intrathoracic impedance, intracardiac impedance, arterial pressure, pulmonary artery pressure, RV pressure, LV coronary pressure, coronary blood temperature, blood oxygen saturation, one or more heart sounds,

physical activity or exertion level, posture, respiration, body weight, or body temperature.

[0025] The arrangement and functions of these leads and electrodes are described above by way of example and not by way of limitation. Depending on  
5 the need of the patient and the capability of the implantable device, other arrangements and uses of these leads and electrodes are possible.

[0026] As illustrated, the CRM system 100 can include a multi-sensor metrics based therapy adjustment circuit 113. The multi-sensor metrics based therapy adjustment circuit 113 can be configured to improve the therapy such as  
10 determining desired values for device parameters used for sensing a physiologic event, providing patient diagnostic information, assessing device operation and functionality, or controlling the generation and delivery of device therapy such as stimulations to the patient. One example of device parameter includes timing of the delivery of pacing pulses to the heart such as an atrial-ventricular delay  
15 (AVD). The AVD represents the latency between an intrinsically occurred atrial electrical activation signal ( $A_s$ ) such as sensed by the electrodes on the lead 108A and a subsequent ventricular pacing pulse ( $V_p$ ) such as delivered through the electrodes on the lead 108B, or between an atrial pacing pulse ( $A_p$ ) such as delivered through the electrodes on lead 108A and the subsequent  $V_p$ . In another  
20 example, the device parameter includes a left ventricular-right ventricular delay (VVD) which represents the latency between a left ventricular pacing pulse (LVp) such as delivered through the electrodes on the lead 108C a right ventricular pacing pulse (RVp) such as delivered through the electrodes on the lead 108B. In determining a desired value for a device parameter, the multi-  
25 sensor metrics based therapy adjustment circuit 113 can be coupled to one or more physiologic sensors or sensing electrodes such as the electrodes on one or more of the leads 108A-C and receive physiologic signals from the physiologic sensors or electrodes. In an example, the IMD 110 can program the stimulations (such as atrial pacing pulses, ventricular pacing pulses, cardioversion pulses, defibrillation pulses, or neural stimulations) and schedule the delivering of the  
30 stimulations using the desired device parameter value. Examples of the multi-sensor metrics based therapy adjustment circuit 113 are discussed below, such as with reference to FIGS. 2-4.

[0027] The external system 120 can allow for programming of the IMD 110 and can receives information about one or more signals acquired by IMD 110, such as can be received via a communication link 103. The external system 120 can include a local external IMD programmer. The external system 120 can include a remote patient management system that can monitor patient status or adjust one or more therapies such as from a remote location.

[0028] The communication link 103 can include one or more of an inductive telemetry link, a radio-frequency telemetry link, or a telecommunication link, such as an internet connection. The communication link 103 can provide for data transmission between the IMD 110 and the external system 120. The transmitted data can include, for example, real-time physiological data acquired by the IMD 110, physiological data acquired by and stored in the IMD 110, therapy history data or data indicating IMD operational status stored in the IMD 110, one or more programming instructions to the IMD 110 such as to configure the IMD 110 to perform one or more actions that can include physiological data acquisition such as using programmably specifiable sensing electrodes and configuration, device self-diagnostic test, or delivery of one or more therapies.

[0029] The multi-sensor metrics based therapy adjustment circuit 113 can be implemented at the external system 120, which can be configured to perform target event detection such as using data extracted from the IMD 110 or data stored in a memory within the external system 120. Portions of the multi-sensor metrics based therapy adjustment circuit 113 can be distributed between the IMD 110 and the external system 120.

[0030] Portions of the IMD 110 or the external system 120 can be implemented using hardware, software, or any combination of hardware and software. Portions of the IMD 110 or the external system 120 can be implemented using an application-specific circuit that can be constructed or configured to perform one or more particular functions, or can be implemented using a general-purpose circuit that can be programmed or otherwise configured to perform one or more particular functions. Such a general-purpose circuit can include a microprocessor or a portion thereof, a microcontroller or a portion thereof, or a programmable logic circuit, or a portion thereof. For example, a “comparator” can include, among other things, an electronic circuit comparator

that can be constructed to perform the specific function of a comparison between two signals or the comparator can be implemented as a portion of a general-purpose circuit that can be driven by a code instructing a portion of the general-purpose circuit to perform a comparison between the two signals.

5 [0031] FIG. 2 illustrates an example of a device therapy adjustment circuit 200, which can be an example of the multi-sensor metrics based therapy adjustment circuit 113. The device therapy adjustment circuit 200 can include a signal analyzer circuit 210, a device parameter adjustment circuit 220, a stimulation generation circuit 230, and a controller circuit 240.

10 [0032] The signal analyzer circuit 210 can receive one or more physiologic signals and generate two or more signal metrics from the physiologic signals. Examples of the physiologic signal can include EGM from the electrodes on leads 108A-C and the can 112, intrathoracic impedance, intracardiac impedance, arterial pressure, pulmonary artery pressure, RV  
15 pressure, LV coronary pressure, coronary blood temperature, blood oxygen saturation, heart sounds, posture, activity levels, or respiration signals including such as respiration rate or tidal volume. In an example, the signal analyzer circuit 210 can be configured to couple to one or more electrodes such as on one or more of the leads 108A-C and the can 112 connected to the IMD 110, or to  
20 couple to one or more physiologic sensors to sense one or more physiologic signals. In an example, the signal analyzer circuit 210 can be coupled to a memory circuit and receive the physiologic signals stored in the memory circuit. Examples of physiologic sensors include pressure sensors, flow sensors, impedance sensors, accelerometers, microphone sensors, respiration sensors,  
25 temperature sensors, and blood chemical sensors.

[0033] The signal analyzer circuit 210 can generate two or more signal metrics from the one or more physiologic signals. The signal metrics can represent a physiologic change in response to, for example, patient's disease progression, change in medication, change in health conditions, or change in  
30 posture or activity levels. The signal analyzer circuit 210 can be coupled to one or more physiologic sensors configured to sense the one or more physiologic signals. The physiologic sensors can be implanted inside a patient's body or external to the patient. In an example, the signal analyzer circuit 210 can generate one or more signal metrics from one sensor. For example, the signal

analyzer circuit 210 can receive a transthoracic impedance signal from the electrodes on one or more of the implantable leads such as 108A-C and the can 112, and generate a signal metric of direct-current (DC) impedance using the transthoracic impedance signal. In another example, the signal analyzer circuit 5 210 can receive a heart sound signal from an accelerometer coupled to the IMD 110, and generate two or more heart sounds metrics including, for example, S1 intensity, S2 intensity, S3 intensity, or timing metrics of the S1, S2, or S3 heart sound with reference to a fiducial point such as a P wave, Q wave, or R wave in an electrocardiogram (ECG) or an electrogram (EGM). In an example, the signal 10 analyzer circuit 210 can receive multiple physiologic signals from multiple sensors. For example, the signal analyzer circuit 210 can receive a blood pressure signal from a pressure sensor and generate two or more blood pressure signal metrics which can include systolic blood pressure, diastolic blood pressure, mean arterial pressure, and the timing metrics of these pressure 15 measurements with reference to a fiducial point.

[0034] The device parameter adjustment circuit 220, coupled to the signal analyzer circuit 210, can be configured to determine a desired value for a device parameter using the two or more signal metrics provided by the signal analyzer circuit 210. Examples of the device parameter can include parameters 20 used for sensing a physiologic event, providing patient diagnostic information, assessing device operation and functionality, or controlling the generation and delivery of device therapy such as stimulations to the patient. In an example, the device parameter adjustment circuit 220 can be configured to determine a desired value for a relative timing between a first event in a first site of the heart 25 and a second event in a second site of the heart. One example of the relative timing can include an atrial-ventricular delay (AVD) which represents the latency between an intrinsically occurred atrial electrical activation signal ( $A_s$ ) and a subsequent ventricular pacing pulse ( $V_p$ ), or between an atrial pacing pulse ( $A_p$ ) and the subsequent  $V_p$ . Another example of the relative timing can include 30 a left ventricular-right ventricular delay (VVD) which represents the latency between a left ventricular pacing pulse (LVp) and a right ventricular pacing pulse (RVp).

[0035] The device parameter adjustment circuit 220 can include one or more of a sensitivity calculator circuit 221, a variability calculator circuit 222, a

covariability calculator circuit 223, or an information fusion circuit 225. The sensitivity calculator circuit 221 can be configured to determine the sensitivity of a signal metric in response to stimulation programmed with a perturbation to the device parameter. In an example, stimulation with at least two distinct device parameter values can be delivered to a target site and the single receiver and analysis circuit 210 receives and measures the resultant signal metric values. The sensitivity calculator circuit 221 can determine the sensitivity of the signal metric using the comparison of the resultant signal metric values. In an example of determining a desired atrio-ventricular delay (AVD) to control the cardiac resynchronization therapy (CRT), the signal analyzer circuit 210 receives a heart sound signal and calculate S1 heart sound intensity (hereinafter "S1 intensity")  $\|S1\|_1$  when the AVD is set to a first value  $AVD_1$  and the S1 intensity  $\|S1\|_2$  when the AVD is set to a second value  $AVD_2$ ; and the sensitivity calculator circuit 221 can determine the sensitivity of S1 intensity to the perturbation of the AVD as the difference between  $\|S1\|_1$  and  $\|S1\|_2$  (i.e.,  $\|S1\|_1 - \|S1\|_2$ ) or as a relative change of S1 intensity with respect to the change of AVD (i.e.,  $(\|S1\|_1 - \|S1\|_2) / (AVD_1 - AVD_2)$ ). In an example, the sensitivity calculator circuit 221 can use more than two S1 intensity values  $\{\|S1\|_i\}$  corresponding to distinct AVD values  $\{AVD_i\}$  where  $i = 1, 2, \dots, N$ , ( $N > 2$ ) and determine the sensitivity of S1 intensity using as a linear or nonlinear combination of the pair-wise difference of S1 intensity values taken from  $\{\|S1\|_i\}$  (i.e.,  $\|S1\|_i - \|S1\|_j$ ), or a linear or nonlinear combination of the pair-wise relative change of S1 with respect to the respective change of AVD (i.e.,  $(\|S1\|_i - \|S1\|_j) / (AVD_i - AVD_j)$ ). In an example, under a particular AVD value, the sensitivity calculator circuit 221 can use a plurality of measurements of the S1 intensity such as taken at different time and determine a representative S1 intensity from the measurements, and use at least the representative S1 intensity to determine the sensitivity of S1 intensity.

**[0036]** The variability calculator circuit 222 can be configured to determine for at least two of the two or more signal metrics a variability in response to stimulation programmed with a specified device parameter. Alternatively, the signal metric variability can be computed during the baseline when no stimulation being delivered. Examples of the variability can include range, inter-quartile range, standard deviation, variance, sample variance, or other first-order, second-order, or higher-order statistics representing the degree

of variation. For example, in determining a desired value for the AVD using the S1 intensity, the variability calculator circuit 222 can perform a plurality of measurements of the S1 intensity when the implantable medical device delivers the stimulation to one or more regions of the heart with a predetermined AVD.

5 The variability calculator circuit 222 can determine the variability of the S1 intensity by computing a variance using the plurality of measurements of the S1 intensity.

[0037] The covariability calculator circuit 223 can be configured to determine covariability between the two or more signal metrics in response to stimulation with a specified device parameter. Examples of the covariability can include covariance or cross-correlation between any two of the two or more signal metrics, covariance matrix or cross-correlation matrix, sample covariance or sample cross-correlation matrix, and cross-spectrum or coherence as estimated in the frequency domain. The covariability calculator circuit 223 can determine the covariability between signal metrics using a plurality of measurements of at least two of the two or more signal metrics.

[0038] The two or more signal metrics used for covariability determination can be from the same physiologic signal. For example, the covariability calculator circuit 223 can determine the covariability between two or more heart sounds metrics, such as S1 intensity, S2 intensity, S3 intensity, or timing metrics of the S1, S2, or S3 heart sound with respect to a fiducial point such as a Q wave in an ECG or an atrial activation event in an EGM. In an example, the covariability calculator circuit 223 can determine the covariability between two or more signal metrics from different physiologic signals such as acquired from different physiologic sensors coupled to the signal analyzer circuit 210.

[0039] The information fusion circuit 225 can be configured to determine the desired device parameter value using one or more of the sensitivity for at least two of the two or more signal metrics, the variability for at least two of the two or more signal metrics, and the covariability between at least two of the two or more signal metrics. In an example, the information fusion circuit 225 can be configured to select one or more from a plurality of signal metrics based at least in part on a comparison of the sensitivity, the variability, the covariability, or any combination thereof. In an example, the information fusion circuit 225 can

determine a desired value for the device parameter using a combination of device parameter values estimated from two or more of the selected signal metrics. Examples of the information fusion circuit 225 are discussed below, such as with reference of FIGS. 4 and 5.

5 [0040] The stimulation generation circuit 230 can be configured to generate stimulations for stimulating a target site. In an example, the stimulation generation circuit 230 can generate one or more stimulation trains for stimulating one or more regions of a heart which can include a left ventricle, a right  
10 ventricle, a left atrium, a right atrium, a pulmonary artery, a septum between the left and right ventricles, or other epicardial or endocardial sites. In an example, the stimulation generation circuit 230 can generate one or more stimulation trains for stimulating one or more of a neural target including, for example, a baroreceptor regions, nerve trunk, or nerve bundles. The stimulation generation circuit 230 can be coupled to one or more of the implantable leads such as 108A-  
15 C to deliver the stimulations to the target sites.

[0041] The controller circuit 240 can be included with or coupled to the signal analyzer circuit 210, the device parameter adjustment circuit 220, and the stimulation generation circuit 230. In an example, the controller circuit 240 can adjust one or more programmable stimulation parameters when certain condition  
20 is met. Examples of the stimulation parameters can include stimulation pulse strength parameters, pulse waveform or morphology, and stimulation scheduling parameters. The stimulation pulse strength parameters can include, for example, a pulse amplitude, pulse width, pulse morphology, inter-pulse interval, pulse duty cycle, or pulse frequency. Pulse morphology can include a square wave,  
25 triangle wave, sinusoidal wave, or waves with desired harmonic components to mimic white noise such as indicative of naturally-occurring baroreflex stimulation. The stimulation pulse can be of one of multiphasic waves including biphasic, triphasic, or multiphasic waves. The therapy schedule parameters can include parameters controlling the time and duration of the stimulation pulse  
30 train. In an example, the controller circuit 240 can be configured to program the stimulations using the desired device parameter value provided by the device parameter adjustment circuit 220 and schedule the output of the stimulations from the stimulation generation circuit 230.

[0042] FIG. 3 illustrates an example of information fusion circuit 225, which can be an example of the information fusion circuit as illustrated in the device parameter adjustment circuit 220. The information fusion circuit 225 can be configured to select one or more signal metrics from a plurality of candidate  
5 signal metrics such as those generated by the signal analyzer circuit 210, and determine the desired device parameter using the selected signal metrics.

[0043] As illustrated in FIG. 3, the information fusion circuit 225 can include a signal metric reliability estimator circuit 310, a signal metric selector circuit 320, a metric-indicated device parameter determination circuit 330, and a  
10 metric-indicated device parameter fusion circuit 340. The signal metric reliability estimator circuit 310 can be configured to compute a signal metric reliability for a signal metric using at least one of the sensitivity such as from the sensitivity calculator circuit 221, the variability such as from the variability calculator circuit 222, or the covariability between the two or more signal  
15 metrics such as from the covariability calculator circuit 223. The signal metric reliability can be a quantity representing the responsiveness and consistency of the signal metric in response to the stimulation programmed with a specified device parameter. The signal metric selector 320 can be configured to select a subset from a plurality of candidate signal metrics using a comparison of the  
20 signal metric reliability of the signal metrics.

[0044] In an example, the signal metric reliability estimator 310 determines the signal metric reliability to be proportional to the signal metric sensitivity, such that a signal metric with a higher sensitivity can be more reliable for use in determining the desired value of the device parameter. For  
25 example, the signal metric reliability estimator circuit 310 can be configured to determine for the signal metric a first representative signal metric value  $\mu_1$  in response to the stimulation when the device parameter is set to a first value, and a second representative signal metric value  $\mu_2$  in response to the stimulation when the device parameter is set to a second value. The representative values  $\mu_1$   
30 and  $\mu_2$  can be a single measurement under respective device parameter value. The representative values  $\mu_1$  and  $\mu_2$  can also be determined from a plurality of measurements of the signal metric under respective device parameter value at different time, such as central tendency of the plurality of measurements. Examples of central tendency can include mean, median, weighted-mean, or

mode. The signal metric reliability estimator circuit 310 can then determine the signal metric reliability as the distance  $d_{12}$  between  $\mu_1$  and  $\mu_2$ , i.e.,  $d_{12} = |\mu_1 - \mu_2|$ .

[0045] In another example, the signal metric reliability circuit 310  
5 determines the signal metric reliability to be inversely proportional to the signal metric variability, such that a signal metric with a higher variability can be less reliable for use in determining the desired value of the device parameter. The signal metric reliability can also be determined to be proportional to the signal metric sensitivity and inversely proportional to the signal metric variability, such  
10 that a signal metric with high sensitivity and low variability can be more likely to be selected for use in determining the desired device parameter. For example, the signal metric reliability estimator circuit 310 can be configured to determine for each signal metric a first representative signal metric value  $\mu_1$  in response to the stimulation when the device parameter is set to a first value, and a second  
15 representative signal metric value  $\mu_2$  in response to the stimulation when the device parameter is set to a second value. The signal metric reliability estimator circuit 310 can further calculate a signal metric variability ( $\sigma$ ) using a plurality of measurements in response to the stimulation when the device parameter is set to a pre-determined value. Alternatively, the signal metric variability ( $\sigma$ ) can be  
20 computed during the baseline when no stimulation being delivered. The signal metric reliability estimator circuit 310 can then calculate a sensitivity-to-variability ratio (SVR) using the difference  $d_{12}$  and the variability  $\sigma$ , i.e.,  $SVR = d_{12}/\sigma$ .

[0046] The signal metric selector 320 can select the signal metric using  
25 the signal metric reliability provided by the signal metric reliability estimator 310. For example, the signal metric selector 320 selects the signal metric if the distance  $d_{12}$  meeting a reliability criterion such as  $d_{12}$  exceeding a reliability threshold, or if the SVR meeting a reliability criterion such as exceeding a reliability threshold.

30 [0047] The metric-indicated device parameter calculator 330 can be configured to determine for each of the selected signal metric a metric-indicated device parameter value. In an example, the metric-indicated device parameter calculator 330 can estimate the metric-indicated device parameter value by interpolating or extrapolating the relationship between the signal metric

measurements and the corresponding device parameter values. For example, in determining a desired AVD value, the metric-indicated device parameter calculator 330 can construct the relationship between the measurements of the S1 intensity in response to stimulation when the AVD is set to a number of values. The metric-indicated device parameter calculator 330 can create a regression model between the AVD and the S1 intensity, and estimate the S1 intensity-indicated AVD value using the created model. Examples of the regression model can include linear regression, polynomial regression, power regression, logistic regression, and other parametric and non-parametric models.

10 [0048] The metric-indicated device parameter fusion circuit 340 can be configured to determine a desired value for the device parameter using a combination of a subset or all of the metric-indicated device parameter values of the selected signal metrics. In an example, the metric-indicated device parameter fusion circuit 340 can determine the desired device parameter as the mean, or median, or mode of the metric-indicated device parameter values of the selected signal metrics. In an example, the desired device parameter can be a linear combination of the metric-indicated device parameter values of the subset of the selected signal metrics. In forming the linear combination, each metric-indicated device parameter value can be weighted by the corresponding signal metric reliability. The weight to each metric-indicated device parameter value can also be determined using the population data indicative of relative reliability of the signal metric. In an example, the metric-indicated device parameter fusion circuit 340 can be configured to receive from the system operator an input including a weight assigned to the metric-indicated device parameter value. In an example, the metric-indicated device parameter fusion circuit 340 can determine the desired device parameter value using nonlinear combinations of the metric-indicated device parameter values of the selected signal metrics. Examples of the nonlinear combination can include a decision tree, a neural network, a non-linear combination, or a multivariate regression model.

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30 [0049] FIG. 4 illustrates another example of the information fusion circuit 225, which can be an example of the information fusion circuit as a part of the device parameter adjustment circuit 220. The information fusion circuit 225 comprises a target signal metric change circuit 410, a memory circuit 420, and a signal projection calculator circuit 430.

[0050] The target signal metric change circuit 410 can be configured to generate a target directional vector representing cumulative change of the two or more signal metrics in response to the stimulation when the device parameter is changed from a first value to a second value. The target directional vector can be generated using at least one of the sensitivity of the two or more signal metrics such as provided by the sensitivity calculator circuit 221, the variability of the two or more signal metrics such as provide by the variability circuit 222, or the covariability between the two or more signal metrics such as provided by the covariability circuit 223. In an example, the target signal metric change circuit 410 can generate the target directional vector ( $v$ ) using a joint sensitivity computed from two or more signal metrics in response to the stimulation when the device parameter is changed from a first non-optimal value to a second sub-optimal value. The sub-optimal value can be chosen from the historical data such as therapy efficacy on the patient. In another example, the target signal metric change circuit 410 can generate the target directional vector ( $v$ ) using the joint sensitivity computed from the two or more signal metrics and the covariability between at least two of the two or more signal metrics such as a sample covariance matrix. The target signal metric change circuit 410 can further determine a unit target directional vector  $v_0 = v/||v||$  where  $||v||$  denotes the magnitude of  $v$ .

[0051] The memory circuit 420 can store a plurality of values for the device parameter, from which a desired value can be selected. The signal projection calculator circuit 430, coupled to the memory circuit 420 and the target signal metric change circuit 410, can be configured to receive one stored value for the device parameter at a time and measure the signal metrics in response to a stimulation programmed according to the received device parameter. For example, in determining a desired AVD value, the signal projection calculator circuit 430 can generate a signal metric vector ( $X_k$ ) that can include the measurements from a total of  $M$  signal metrics in response to stimulation programmed with AVD value ( $AVD_k$ ) taken from the memory circuit 420. The signal projection calculator circuit 430 can compute a projection ( $\Omega_k$ ) of the signal metric vector ( $X_k$ ) onto the target directional vector ( $v$ ) or the unit target directional vector ( $v_0$ ). In an example, the projection can be computed as a dot product between  $X_k$  and  $v_0$ , i.e.,  $\Omega_k = v_0^T X_k$ . The signal projection

calculator circuit 430 can sweep through the stored values of the device parameter and determine the desired device parameter based on the comparison of the resultant projections  $\{\Omega_k\}$ . In an example, the signal projection calculator circuit 430 determines the desired AVD as the one resulting in the largest projection  $\Omega_{\max}$ .

[0052] In another example, the signal projection calculator circuit 430 can be configured to adaptively determine a desired device parameter value. For example, the signal projection calculator circuit 430 can start with an initial value  $AVD_0$  and determine the resultant projection  $\Omega_0$  associated with the measurements of the signal metrics. The signal projection calculator circuit 430 can increase the AVD (i.e.,  $AVD_0 + \Delta$ ) or decrease the AVD (i.e.,  $AVD_0 - \Delta$ ) by a step size  $\Delta$ , and determine the resultant projection  $\Omega_1$ . The signal projection calculator circuit 430 can compare  $\Omega_1$  to  $\Omega_0$ , and adjust the AVD based on the comparison. For example, AVD can be decremented if  $\Omega$  increases from the previous value ( $\Omega_1 > \Omega_0$ ), and incremented if  $\Omega$  decreases from the previous value ( $\Omega_1 < \Omega_0$ ). The process can be continued until the resultant projection  $\Omega$  meets a convergence criterion (such as the difference between the present and the previous projections falls below a specified threshold value), where the corresponding AVD value can be determined to be the desired AVT value.

[0053] FIG. 5 illustrates an example of a method 500 for determining a desired device parameter and stimulating a target site according to the desired device parameter. In an example, the IMD 110, including its various examples discussed in this document, is programmed to perform method 500, including its various examples discussed in this document.

[0054] In an example, the method 500 can be used to determine a desired value for a relative timing between a first event in a first site of the heart and a second event in a second site of the heart. One example of the relative timing between the first and the second events can include an atrial-ventricular delay (AVD) which represents the latency between an intrinsically occurred atrial electrical activation signal ( $A_s$ ) and a subsequent ventricular pacing pulse ( $V_p$ ), or between an atrial pacing pulse ( $A_p$ ) and the subsequent  $V_p$ . Another example of the relative timing can include a left ventricular-right ventricular delay (VVD) which represents the latency between a left ventricular pacing pulse ( $LV_p$ ) and the subsequent right ventricular pacing pulse ( $RV_p$ ). The desired value of the

AVD or the VVD can then be used to program one or more stimulation trains to be delivered to one or more of the regions in the heart, such as right atrium (RA), left atrium (LA), right ventricle (RV), or left ventricle (LV), so as to restore the synchronization among various sites of the heart.

5 [0055] One or more physiologic signals can be sensed at 510. Examples of the physiologic signal can include one or more of intrathoracic impedance, intracardiac impedance, arterial pressure, pulmonary artery pressure, RV pressure, LV coronary pressure, coronary blood temperature, blood oxygen saturation, one or more heart sounds, physical activity or exertion level, posture, 10 respiration, body weight, or body temperature. The physiologic signals can be acquired by one or more physiologic sensors including, for example, pressure sensors, flow sensors, impedance sensors, accelerometers, microphone sensors, respiration sensors, temperature sensors, and blood chemical sensors. The physiologic sensors can be implanted inside a patient's body or external to the 15 patient. From the physiologic signals two or more signal metrics can be generated at 520. In an example, the physiologic signal can be a heart sound signal, and the heart sound metrics can include S1 intensity, S2 intensity, S3 intensity, or timing metrics of the S1, S2, or S3 heart sound with respect to a fiducial point such as a P wave or R wave on a ECG or an EGM. The signal 20 metrics can be obtained from two or more physiologic signals sensed by different physiologic sensors.

[0056] At 530, one or more of a sensitivity for a signal metric, a variability for a signal metric, or a covariability among two or more signal metrics can be calculated. In an example, the sensitivity can include difference 25 of the signal metric values in response to stimulation with the device parameter programmed to at least two different values. For example, the sensitivity of S1 intensity can be determined as the difference between the S1 intensity  $\|S1\|_1$  when the AVD is set to a first value  $AVD_1$  and the S1 intensity  $\|S1\|_2$  when the AVD is set to a second value  $AVD_2$ .

30 [0057] The variability can include a spreadness measure computed from a plurality of measurements of the signal metric in response to stimulation with a specified device parameter. In an example, the variability can be computed during the baseline when no stimulation is delivered. Examples of the variability can include range, inter-quartile range, standard deviation, variance, sample

variance, or other first-order, second-order, or higher-order statistics representing the degree of variation.

[0058] The covariability can include, for example, cross-correlation, covariance, covariance matrix or sample covariance matrix, cross-entropy, and mutual information computed using measurements from two or more signal metrics. The covariability can also include cross-spectrum and coherence as computed in the frequency domain. The two or more signal metrics used for covariability determination can be extracted from the same physiologic signal. For example, the signal metrics can include one or more heart sounds metrics extracted from a heart sound signal, such as the S1 intensity, S2 intensity, S3 intensity, or timing metrics of the S1, S2, or S3 heart sound with respect to a fiducial point. In an example of determining a desired AVD value, during the stimulation of one or more regions of the heart with a predetermined AVD, N ( $N \geq 2$ ) measurements for a total of M ( $M \geq 2$ ) signal metrics can be obtained. Let the  $n$ -th measurement of M signal metrics be denoted by a measurement vector  $X_n = [x_{1n}, x_{2n}, \dots, x_{Mn}]^T$ , where  $x_{mn}$  denotes the  $n$ -th measurement of the signal metric  $m$  ( $1 \leq m \leq M$ , and  $1 \leq n \leq N$ ), and “T” denotes transpose operation of a vector or a matrix. Then, all N measurements for all M signal metrics can be represented by an M-by-N measurement matrix  $X_{MN} = [X_1, X_2, \dots, X_N]$ . Let the mean of the N measurement for the signal metric  $m$  be denoted by  $\mu_m$  and the mean of all M signal metrics be denoted by the mean vector  $\mu = [\mu_1, \mu_2, \dots, \mu_M]^T$ , then the M-by-M sample covariance matrix  $C_{xx}$  representing multivariate variability can be computed as given in equation (1):

$$C_{xx} = \frac{1}{N-1} \sum_{n=1}^N (X_n - \mu) \cdot (X_n - \mu)^T \quad (1)$$

[0059] At 540, a desired value for the device parameter can be computed using, for example, one or more of the signal metric sensitivity, the variability, or the covariability. In an example, one or more signal metrics from a plurality of candidate signal metrics can be selected based on one or more of the signal metric sensitivity, the variability, or the covariability. The desired value for the device parameter can be computed using an information fusion method such as a linear or nonlinear combination of the signal-metric indicated device parameter values. Examples of the information fusion are discussed below, such as with reference of FIGS. 6 and 7.

[0060] On or more stimulation pulse trains can then be generated at 550 using the desired value of the device parameter, and delivered to a target site at 560 to achieved, for example, desired treatment. In an example, the stimulation pulse trains can be delivered to one or more regions of a heart including, for example, a left ventricle, a right ventricle, a left atrium, a right atrium, a pulmonary artery, a septum between the left and right ventricles, and other epicardial or endocardial sites. The stimulation pulse trains can also be delivered to a neural target including, for example, a baroreceptor regions, nerve trunk, and nerve bundles.

10 [0061] FIG. 6 illustrates an example of a method 640 for determining a desired value for a device parameter. The method 640 can be an example of 540. The method starts at 641 by computing a signal metric reliability (XR) for each of the candidate signal metrics. The signal metric reliability can be computed using one or more of the signal metric sensitivity, the variability, or the covariability provided at 530. In an example, the signal metric reliability can be proportional to the signal metric sensitivity. For example, in determining the reliability for a signal metric X, one or more measurements  $\{X\}_1$  can be generated in response to the stimulation when the device parameter is set to a first value ( $P_1$ ); and one or more measurements  $\{X\}_2$  can be generated in response to the stimulation when the device parameter is set to a second value ( $P_2$ ). A representative value  $\mu_1$  can be computed from the measurements  $\{X\}_1$  and a representative value  $\mu_2$  from the measurements  $\{X\}_2$ . The representative value  $\mu_1$  and  $\mu_2$  can be computed as mean, median, weighted-mean, mode, or other central tendency of respective measurements. The signal metric reliability (XR) can be proportional to a distance  $d_{12}$  between  $\{X\}_1$  and  $\{X\}_2$ , i.e.,  $XR = \alpha \cdot |\mu_1 - \mu_2|$  where  $\alpha$  is a scalar constant.

[0062] In another example, the signal metric reliability can be inversely proportional to the signal metric variability, such that a signal metric with a higher variability is less reliable for use in determining the desired value of the device parameter. The variability measure ( $\sigma$ ) can be computed using a plurality of measurements of the signal metric in response to the stimulation when the device parameter is set to a pre-determined value. In an example, the variability measure can be computed using the measurements  $\{X\}_1$ ,  $\{X\}_2$ , or measurements during the baseline when no stimulation is delivered. Examples of the variability

can include range, inter-quartile range, standard deviation, variance, sample variance, or other first-order, second-order, or higher-order statistics representing the degree of variation. The signal metric reliability (XR) can be proportional to the distance  $d_{12}$  between  $\mu_1$  and  $\mu_2$  and inverse proportional to  $\sigma$ . For example  
5 XR can be proportional to a sensitivity-to-variability ratio, i.e.,  $XR = \alpha \cdot |\mu_1 - \mu_2|/\sigma$ , where  $\alpha$  can be a scalar constant.

[0063] At 642, a signal metrics can be selected if the signal metric reliability meets a specified criterion. For example, a signal metric can be selected if the distance  $d_{12}$  exceeds a reliability threshold, or if the SVR exceeds  
10 a reliability threshold.

[0064] At 643, for each selected signal metric a metric-indicated device parameter value can be determined. In an example, the metric-indicated device parameter value can be determined using an extrapolation or interpolation of the relationship between the signal metric measurements and the corresponding  
15 device parameter values. For example, in determining the desired AVD value, an S1 intensity-AVD relationship can be constructed between the measurements of the S1 intensity in response to stimulation when the AVD is set to a number of values. The relationship can be represented by a regression model. Examples of the regression model can include linear regression, polynomial regression, power  
20 regression, logistic regression, and other parametric and non-parametric models. The S1 intensity-indicated AVD can then be determined using the extrapolation or interpolation using the regression model between the S1 intensity and the AVD values.

[0065] The desired device parameter value can then be determined at 644  
25 by combining the signal metric-indicated device parameter value of a subset or all of the selected signal metrics. In an example, the combination can include a linear combination of the metric-indicated device parameter values of the subset of the selected signal metrics. Each metric-indicated device parameter value can be weighted by the signal metric reliability associated with the respective  
30 selected signal metric. In an example, the combination can include a nonlinear combination of the metric-indicated device parameter value of the subset of the selected signal metrics, such as a decision tree, a neural network, a non-linear combination, or a multivariate regression model. The desired device parameter value can be used to generate stimulations at 550.

[0066] FIG. 7 illustrates an example of a method 700 for determining a desired value for a device parameter. In an example, the IMD 110, including its various embodiments discussed in this document, is programmed to perform method 700, including its various embodiments discussed in this document.

5 [0067] One or more physiologic signals are sensed at 710. The physiologic signals can be acquired by one or more physiologic sensors including, for example, pressure sensors, flow sensors, impedance sensors, accelerometers, microphone sensors, respiration sensors, temperature sensors, and blood chemical sensors. From the physiologic signals, two or more signal  
10 metrics can be generated at 720. In an example, signal metrics can include features representing a statistical or a morphological characteristic of the physiologic signal. The features can be extracted in time-domain, frequency-domain, or joint time-frequency domain. At 730, by setting the device parameter value to a first value ( $P_X$ ), a first signal metric vector  $X$  can be constructed. For  
15 example,  $X$  can include measurements of the two or more signal metrics in response to stimulation when the device parameter is set to  $P_X$ . At 740, by setting the device parameter value to a second value ( $P_Y$ ), a second signal metric vector  $Y$  can be constructed. The signal metric  $Y$  can include measurements of the two or more signal metrics in response to the stimulation when the device  
20 parameter is set to the value  $P_Y$ .

[0068] At 750, a target directional vector  $v$  can be generated using the signal metric vectors  $X$  and  $Y$ . The target directional vector can be generated using one or more of the sensitivity of the two or more signal metrics, the variability of the two or more signal metrics, or the covariability between the  
25 two or more signal metrics. In an example, the target directional vector can be computed using a joint sensitivity computed from the two or more signal metrics. In an example of determining a desired AVD value, the first signal metric vector  $X = [x_1, x_2, \dots, x_M]^T$  can be generated using the measurements from a total of  $M$  signal metrics in response to stimulation to one or more  
30 regions of the heart when the AVD is programmed to a first value  $AVD_X$ ; and the second signal metric vector  $Y = [y_1, y_2, \dots, y_M]^T$  can be generated using the measurements from the  $M$  signal metrics in response to stimulation when the AVD is programmed to a second value  $AVD_Y$ . In an example, the first value  $AVD_X$  can be arbitrarily selected, so that  $AVD_X$  can be less likely to be a

desired AVD value; and the second value AVD<sub>Y</sub> can be chosen as a sub-optimal AVD value determined based on, for example, therapy history, prior AVD adjustment, or using external information. The target signal metric change circuit 410 can determine the target directional vector (v) in the M-dimensional space as the vector from X to Y, i.e., v = Y-X. A unit target directional vector v<sub>0</sub> can be created as v<sub>0</sub> = v/||v|| where ||v|| represents the magnitude of vector v.

[0069] In another example, the target directional vector can be determined using the joint sensitivity computed from the two or more signal metrics and the covariability between two or more signal metrics. For example, the signal metric vector X can be repeatedly sampled for N times when AVD is set to AVD<sub>X</sub>, resulting in an M-by-N measurement matrix X<sub>MN</sub> = [X<sub>1</sub>, X<sub>2</sub>, ..., X<sub>N</sub>] representing the N repeated measurements of the M signal metrics in response of stimulation with AVD<sub>X</sub>. Similarly, the signal metric vector Y can be repeatedly sampled for N times when AVD is set to AVD<sub>Y</sub>, resulting in an M-by-N measurement matrix Y<sub>MN</sub> = [Y<sub>1</sub>, Y<sub>2</sub>, ..., Y<sub>N</sub>] representing the N repeated measurements of the M signal metrics in response of stimulation with AVD<sub>Y</sub>. A representative M-dimensional vector μ<sub>X</sub> can be computed using X<sub>MN</sub>, and a representative M-dimensional vector μ<sub>Y</sub> can be computed using Y<sub>MN</sub>. For example, μ<sub>X</sub> and μ<sub>Y</sub> can be computed as the mean of N measurements X<sub>MN</sub> = [X<sub>1</sub>, X<sub>2</sub>, ..., X<sub>N</sub>] and the mean of N measurements Y<sub>MN</sub> = [Y<sub>1</sub>, Y<sub>2</sub>, ..., Y<sub>N</sub>], respectively. A covariance matrix C can be generated using either X<sub>MN</sub> or Y<sub>MN</sub> or any combination of the repeated measurement of X and Y. The M-by-M covariance matrix C represents multivariate variability. In the M-dimensional signal metrics space, the M sensor readings at any given AVD can form an ellipse represented by covariance matrix C. For example, C can be computed using the N repeated measurement of M signal metrics X, as given in equation (2):

$$C = \frac{1}{N - 1} \sum_{n=1}^N (X_n - \mu_X) \cdot (X_n - \mu_X)^T \tag{2}$$

The target directional vector can then be determined using one or more of μ<sub>X</sub>, μ<sub>Y</sub>, or C. For example, the target directional vector v in the M-dimensional space can be computed as: v = C<sup>-1</sup>(μ<sub>Y</sub>-μ<sub>X</sub>). The target directional vector v implicitly

accounts for the sensitivity and the variability of the multiple signal metrics. A unit target directional vector  $v_0$  can be created as  $v_0 = v/\|v\|$ .

[0070] At 760, a test signal metric vector can be constructed. The test signal metric vector can comprise measurements from the two or more signal metrics in response to the stimulation when the device parameter is set to a specified value. In an example, a plurality of candidate device parameter values can be stored in a memory, and the test signal metric vector can be constructed in response to the stimulation when the device parameter is set to one of the candidate device parameter values. Then at 770, a projection of the test signal metric vector onto the target directional vector  $v$  can be computed. In an example, the projection can be computed as a dot product between the test signal metric vector and the unit target directional vector  $v_0$ . The projection can then be compared to a convergence criterion at 780. The candidate device parameter can be deemed the desired parameter value if the projection meets the convergence criterion. Otherwise, a different candidate device parameter value can be selected from the memory, and the resultant test signal metric vector can be projected to the unit target directional vector  $v_0$ . In an example, the method 700 sweeps through the candidate device parameter values in the memory and determines the desired device parameter as the one that maximizes the projection onto the unit target directional vector  $v_0$ .

[0071] FIG. 8 illustrates an example of a method 800 for adaptively determining a desired value for a device parameter. In an example, the IMD 110, including its various embodiments discussed in this document, can be programmed to perform method 800, including its various embodiments discussed in this document.

[0072] The device parameter can be initialized to  $P_0$  at 810 and the stimulation can be delivered to a target site in accordance with the initial value of the device parameter. The initial value of the device parameter can be chosen using empirical knowledge such as the historical performance of the stimulation therapy. At 820, a test signal metric vector  $X_k$  (which corresponds to the device parameter value  $P_k$ ) including measurements from  $M$  ( $M \geq 2$ ) signal metrics can be constructed. At 830, a target directional vector  $v$  can be generated, such as by using the joint signal metric sensitivity alone or in conjunction with the covariability among the  $M$  signal metrics, as discussed in 740. The test signal

metric vector  $X_k$  can be projected onto the target directional vector  $v$  (or the unit target directional vector  $v_0$ ) at 840. In an example, the resultant projection  $\Omega_k$  can be computed as dot product between the test signal metric vector  $X$  and the unit target directional vector  $v_0$ , i.e.,  $\Omega_k = v_0^T X_k$ . If the previous projection  $\Omega_{k-1}$  (which corresponds to a previous device parameter value  $P_{k-1}$ ) is available, a difference ( $\Delta\Omega$ ) between the current projection  $\Omega_k$  and the previous projection  $\Omega_{k-1}$ , defined as  $\Delta\Omega = |\Omega_k - \Omega_{k-1}|$ , can be computed at 850. The  $\Delta\Omega$  can then be compared to a convergence threshold at 860. If  $\Delta\Omega$  falls below the convergence threshold, then  $\Omega_k$  can be considered converged, and the present device parameter value  $P_k$  is deemed the desired value  $P_{opt}$ . Otherwise, the device parameter can be adjusted from  $P_k$  to the next value  $P_{k+1}$ . In an example, the update can be determined by equation (3):

$$P_{k+1} = P_k - \beta \cdot (\Omega_k - \Omega_{k-1}) \quad (3)$$

where  $\beta$  can be a positive scalar representing an adaptation rate. According to equation (3), the increment or decrement of device parameter value  $P$  can be proportional to the comparison of  $\Omega_k$  and  $\Omega_{k-1}$ . For example, if  $\Delta\Omega$  exceeds a convergence threshold and if  $\Omega_k > \Omega_{k-1}$ , which suggests that the projection increases as the device parameter changes from  $P_{k-1}$  to  $P_k$ , then at 880,  $P_{k+1}$  can be decremented. If, however,  $\Delta\Omega$  exceeds a convergence threshold and if  $\Omega_k < \Omega_{k-1}$ , which suggests that the projection decreases as the device parameter changes from  $P_{k-1}$  to  $P_k$ , then at 880,  $P_{k+1}$  can be incremented. For example, in determining the desired AVD value, AVD can be initialized to  $AVD_0$  which is comparable to the patient's intrinsic P wave to R wave interval. If at  $k$ -th iteration, the projection  $\Omega$  increases from the previous value ( $\Omega_k > \Omega_{k-1}$ ) and  $\Delta\Omega_k = |\Omega_k - \Omega_{k-1}|$  exceeds a convergence threshold, then at the next iteration,  $AVD_{k+1}$  can be decremented, i.e.,  $AVD_{k+1} = AVD_k - \beta \cdot \Delta\Omega_k$ . Because the update of AVD can be proportional to  $\Delta\Omega$ , as the  $\Omega_k$  gets closer to  $\Omega_{k-1}$ , the AVD gets fine-tuned to avoid missing the desired AVD due to a too large increment or decrement. The adjusted device parameter  $P_{k+1}$  can then be used in generating stimulation and deliver the stimulation to the target site at 890, and a new a test signal metric vector can be generated at 820.

[0073] The above detailed description includes references to the accompanying drawings, which form a part of the detailed description. The drawings show, by way of illustration, specific embodiments in which the

invention can be practiced. These embodiments are also referred to herein as “examples.” Such examples can include elements in addition to those shown or described. However, the present inventors also contemplate examples in which only those elements shown or described are provided. Moreover, the present  
5 inventors also contemplate examples using any combination or permutation of those elements shown or described (or one or more aspects thereof), either with respect to a particular example (or one or more aspects thereof), or with respect to other examples (or one or more aspects thereof) shown or described herein.

[0074] In the event of inconsistent usages between this document and  
10 any documents so incorporated by reference, the usage in this document controls.

[0075] In this document, the terms “a” or “an” are used, as is common in patent documents, to include one or more than one, independent of any other instances or usages of “at least one” or “one or more.” In this document, the  
15 term “or” is used to refer to a nonexclusive or, such that “A or B” includes “A but not B,” “B but not A,” and “A and B,” unless otherwise indicated. In this document, the terms “including” and “in which” are used as the plain-English equivalents of the respective terms “comprising” and “wherein.” Also, in the following claims, the terms “including” and “comprising” are open-ended, that  
20 is, a system, device, article, composition, formulation, or process that includes elements in addition to those listed after such a term in a claim are still deemed to fall within the scope of that claim. Moreover, in the following claims, the terms “first,” “second,” and “third,” etc. are used merely as labels, and are not intended to impose numerical requirements on their objects.

[0076] Method examples described herein can be machine or computer-  
25 implemented at least in part. Some examples can include a computer-readable medium or machine-readable medium encoded with instructions operable to configure an electronic device to perform methods as described in the above examples. An implementation of such methods can include code, such as  
30 microcode, assembly language code, a higher-level language code, or the like. Such code can include computer readable instructions for performing various methods. The code can form portions of computer program products. Further, in an example, the code can be tangibly stored on one or more volatile, non-transitory, or non-volatile tangible computer-readable media, such as during

execution or at other times. Examples of these tangible computer-readable media can include, but are not limited to, hard disks, removable magnetic disks, removable optical disks (e.g., compact disks and digital video disks), magnetic cassettes, memory cards or sticks, random access memories (RAMs), read only memories (ROMs), and the like.

[0077] The above description is intended to be illustrative, and not restrictive. For example, the above-described examples (or one or more aspects thereof) can be used in combination with each other. Other embodiments can be used, such as by one of ordinary skill in the art upon reviewing the above description. The Abstract is provided to comply with 37 C.F.R. §1.72(b), to allow the reader to quickly ascertain the nature of the technical disclosure. It is submitted with the understanding that it will not be used to interpret or limit the scope or meaning of the claims. Also, in the above Detailed Description, various features can be grouped together to streamline the disclosure. This should not be interpreted as intending that an unclaimed disclosed feature is essential to any claim. Rather, inventive subject matter can lie in less than all features of a particular disclosed embodiment. Thus, the following claims are hereby incorporated into the Detailed Description as examples or embodiments, with each claim standing on its own as a separate embodiment, and it is contemplated that such embodiments can be combined with each other in various combinations or permutations. The scope of the invention should be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. An ambulatory medical device, comprising:
  - a stimulation generation circuit configured to generate stimulations for stimulating a target site;
  - 5 a signal analyzer circuit configured to receive one or more physiologic signals and generate two or more signal metrics from the one or more physiologic signals;
  - a device parameter adjustment circuit configured to determine a desired device parameter value for a device parameter, the device parameter adjustment
  - 10 circuit including one or more of:
    - a sensitivity calculator circuit configured to determine for at least two of the two or more signal metrics a respective sensitivity to a perturbation to the device parameter in response to the stimulations;
    - a variability calculator circuit configured to determine for at least
    - 15 two of the two or more signal metrics a respective variability in response to the stimulations;
    - a covariability calculator circuit configured to determine a covariability between at least two of the two or more signal metrics in response to the stimulations; and
    - 20 an information fusion circuit configured to determine the desired device parameter value using at least one of the sensitivity, the variability, or the covariability; and
    - a controller circuit configured to be included with or coupled to the signal analyzer circuit, the device parameter adjustment circuit, and the
    - 25 stimulation generation circuit, the controller circuit configured to program or schedule delivery of the stimulations using the desired device parameter value.
2. The medical device of claim 1, wherein:
  - the stimulation generation circuit is configured to generate one or more
  - 30 stimulation trains for stimulating one or more regions of a heart; and
  - the device parameter adjustment circuit is configured to determine a desired value for a relative timing between a first event in a first site of the heart and a second event in a second site of the heart.

3. The medical device of any one of claims 1 or 2, comprising one or more physiologic sensors configured to be included with or coupled to the signal analyzer circuit, the one or more physiologic sensors configured to sense the one or more physiologic signals, wherein the signal analyzer circuit is configured to  
5 analyze the one or more physiologic signals from the one or more physiologic sensors.

4. The medical device of claim 3, wherein the one or more physiologic sensors include a physiologic sensor configured to sense a heart sound signal,  
10 and the signal analyzer circuit is configured to use the heart sound signal to generate one or more heart sounds metrics.

5. The medical device of any one of claims 1 through 4, wherein the information fusion circuit comprises:  
15 a signal metric reliability estimator circuit configured to compute a signal metric reliability for at least two of the two or more signal metrics using at least one of the sensitivity, the variability, or the covariability;  
a signal metric selector configured to select a subset from the two or more signal metrics using a comparison between the signal metric reliability of  
20 the two or more signal metrics;  
a metric-indicated device parameter determination circuit configured to determine for a signal metric of the selected subset a metric-indicated device parameter value; and  
a metric-indicated device parameter fusion circuit configured to  
25 determine the desired device parameter value using a combination of the metric-indicated device parameter values associated with the respective signal metrics of the selected subset.

6. The system of claim 5, wherein the signal metric reliability estimator  
30 circuit is configured to compute the signal metric reliability being proportional to the signal metric sensitivity.

7. The system of claim 5, wherein the signal metric reliability estimator circuit is configured to compute the signal metric reliability being inversely proportional to the signal metric variability.
- 5 8. The medical device of claim 5, wherein:  
the signal metric reliability estimator circuit is configured to determine, for at least two of the two or more signal metrics, a first representative signal metric value ( $\mu_1$ ) in response to stimulation when the device parameter is set to a first value, and a second representative signal metric value ( $\mu_2$ ) in response to  
10 stimulation when the device parameter is set to a second value; and  
the signal metric selector is configured to select the signal metric in response to a relative measure between  $\mu_1$  and  $\mu_2$  meeting a reliability criterion.
9. The medical device of claim 8, wherein:  
15 the signal metric reliability estimator circuit is configured to calculate, for at least two of the two or more signal metrics, a signal metric variability using a plurality of measurements in response to a stimulation when the device parameter is set to a specified value, and to calculate a sensitivity-to-variability ratio (SVR) using the relative measure between  $\mu_1$  and  $\mu_2$  and the signal metric  
20 variability; and  
the signal metric selector is configured to select the signal metric in response to the SVR meeting a reliability criterion.
10. The medical device of any one of claims 1 through 4, wherein the  
25 information fusion circuit comprises:  
a target signal metric change circuit configured to generate an target directional vector representing the change of the two or more signal metrics in response to the stimulation when the device parameter is changed from a first value to a second value, the target directional vector generated using at least one  
30 of the sensitivity, the variability, or the covariability;  
a memory circuit configured to store a plurality of values for the device parameter; and

a signal projection calculator circuit coupled to the memory circuit and the target signal metric change circuit, the signal projection calculator circuit configured to:

- 5                   determine, for a stored value of the device parameter, a signal metric vector comprising the values of the two or more signal metrics;
- compute, for a stored value of the device parameter, a projection of the signal metric vector onto the target directional vector; and
- determine the desired device parameter value of the device parameter in response to the projection meeting a specified criterion.

10

11.    A method for providing a device therapy, the method comprising:
- sensing one or more physiologic signals and generating two or more signal metrics from the one or more physiologic signals;
- determining a desired value for a device parameter using at least one of a
- 15    sensitivity of at least two of the two or more signal metrics in response to stimulation delivered using a perturbation to the device parameter, a variability of at least two of the two or more signal metrics in response to stimulation with a specified device parameter, or a covariability between the two or more signal metrics in response to stimulation with a specified device parameter;
- 20    generating stimulations using the desired device parameter value; and
- delivering the stimulations to a target site.

12.    The method of claim 11, wherein determining the desired value for the device parameter comprises determining a desired value for a relative timing
- 25    between a first event in a first site of the heart and a second event in a second site of the heart.

13.    The method of any one of claims 11 or 12, wherein sensing the one or more physiologic signals and generating two or more signal metrics comprising
- 30    sensing a heart sound signal and generating one or more heart sounds metrics.

14.    The method of any one of claims 11 through 13, wherein determining a desired value for a device parameter comprises:

computing a respective signal metric reliability for at least two of the two or more signal metrics using at least one of the sensitivity or the variability of the signal metric;

5 selecting a subset from the two or more signal metrics using a comparison between the signal metric reliability of the two or more signal metrics;

determining for a signal metric of the selected subset a metric-indicated device parameter value; and

10 determining the desired device parameter value using a combination of the metric-indicated devices parameter values associated with the respective signal metrics of the selected subset.

15 15. The method of claim 14, wherein computing the signal metric reliability comprises computing a reliability measure, the reliability measure being proportional to the signal metric sensitivity, or being inversely proportional to the signal metric variability, or being proportional to the signal metric sensitivity and inversely proportional to the signal metric variability.

20 16. The method of claim 14, wherein determining the desired device parameter value comprises a linear combination of the metric-indicated device parameter values associated with the respective signal metrics of the selected subset, each metric-indicated device parameter value weighted by the signal metric reliability corresponding to the selected signal metric.

25 17. The method of claim 14, wherein computing the signal metric reliability comprises:

30 generating one or more measurements  $\{X\}_1$  in response to stimulation when the device parameter is set to a first value and one or more measurements  $\{X\}_2$  in response to stimulation when the device parameter is set to a second value;

determining a representative value  $\mu_1$  from  $\{X\}_1$  and a representative value  $\mu_2$  from  $\{X\}_2$ ; and

determining a distance between  $\{X\}_1$  and  $\{X\}_2$  using  $\mu_1$  and  $\mu_2$ ;

and wherein selecting the subset from the two or more signal metrics comprises selecting the signal metric in response to the distance meeting a reliability criterion.

5 18. The method of claim 14, wherein computing the signal metric reliability comprises:

generating a plurality of measurements  $\{X\}_1$  in response to the stimulation when the device parameter is set to a first value and a plurality of measurements  $\{X\}_2$  in response to the stimulation when the device parameter is set to a second value;

10 determining a representative value  $\mu_1$  from  $\{X\}_1$  and a representative value  $\mu_2$  from  $\{X\}_2$ ;

determining a distance between  $\{X\}_1$  and  $\{X\}_2$  using  $\mu_1$  and  $\mu_2$ ;

determining a variability using measurements from  $\{X\}_1$  or  $\{X\}_2$ ; and

15 calculating a sensitivity-to-variability ratio (SVR) using the distance between  $\{X\}_1$  and  $\{X\}_2$  and the variability;

and wherein selecting the subset from the two or more signal metrics comprises selecting the signal metric in response to the SVR meeting a reliability criterion.

20 19. A method of adjusting a device parameter used for operating an ambulatory medical device, the method comprising:

sensing one or more physiologic signals and generating two or more signal metrics from the one or more physiologic signals;

25 constructing a first signal metric vector comprising values of the two or more signal metrics in response to stimulation when the device parameter is set to a first value, and a second signal metric vector comprising values of the two or more signal metrics in response to stimulation when the device parameter is set to a second value, one of the first value or the second value of the device parameter including a sub-optimal value;

30 determining a target directional vector using the difference between the first signal metric vector and the second signal metric vector;

constructing a test signal metric vector comprising values of the two or more signal metrics in response to stimulation when the device parameter is set to a candidate value;

computing a projection of the test signal metric vector onto the target directional vector; and

determining a desired value of the device parameter to be the candidate value in response to the projection meeting a convergence criterion.

5

20. The method of claim 19, wherein determining a target directional vector comprises:

generating, for at least two of the two or more signal metrics, a plurality of measurements  $\{X\}$  in response to stimulation when the device parameter is set to the first value and a plurality of measurements  $\{Y\}$  in response to stimulation when the device parameter is set to the second value;

10 determining a representative value vector  $\{\mu_X\}$  using the measurements  $\{X\}$ , the vector  $\{\mu_X\}$  comprising representative values of the two or more signal metrics;

15 determining a representative value vector  $\{\mu_Y\}$  using the measurements  $\{Y\}$ , the vector  $\{\mu_Y\}$  comprising representative values of the two or more signal metrics;

calculating a covariance matrix  $C$  using the measurements  $\{X\}$  of the two or more signal metrics or the measurements  $\{Y\}$  of the two or more signal metrics; and

20 determining a target directional vector using one or more of the vector  $\{\mu_X\}$ , the vector  $\{\mu_Y\}$ , or the covariance matrix  $C$ .

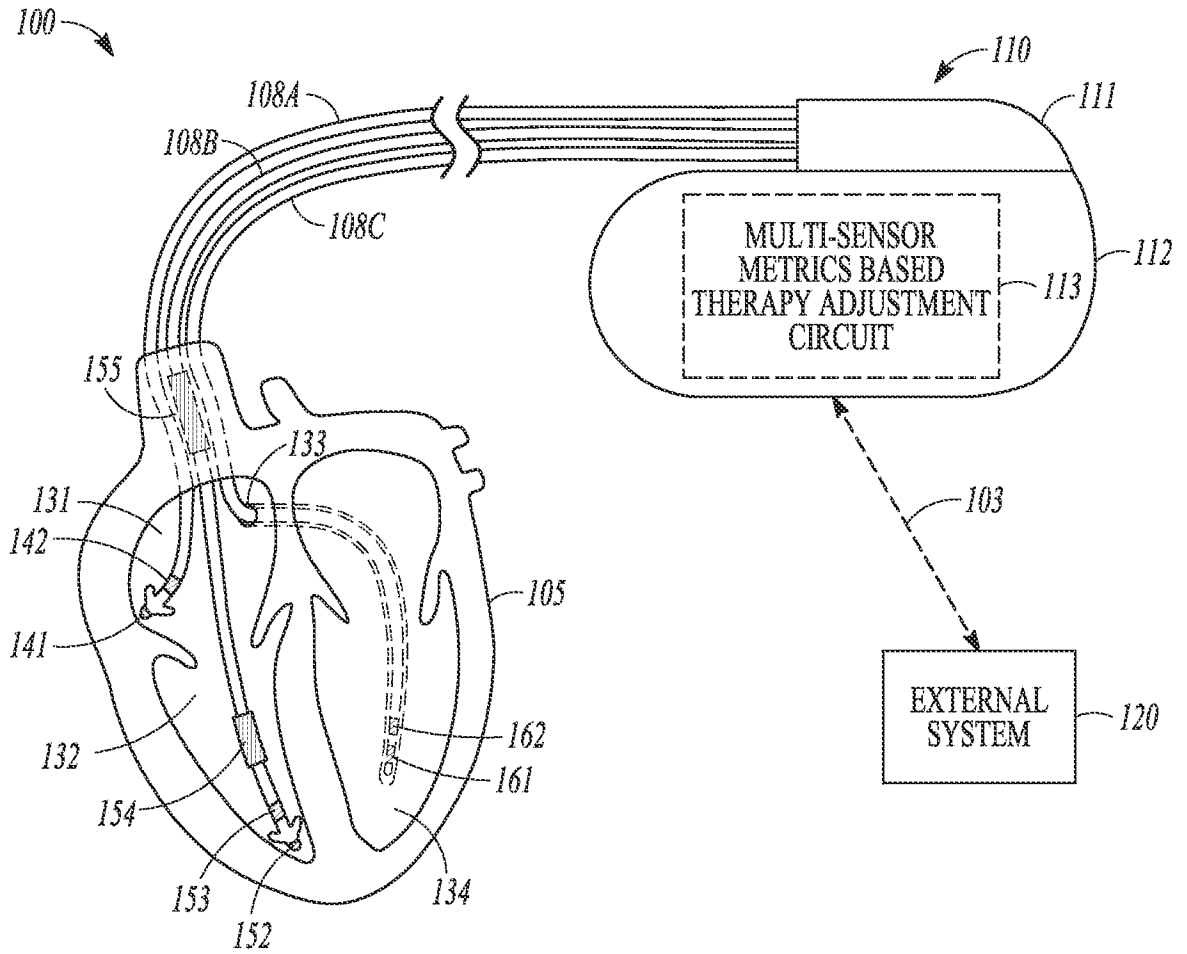
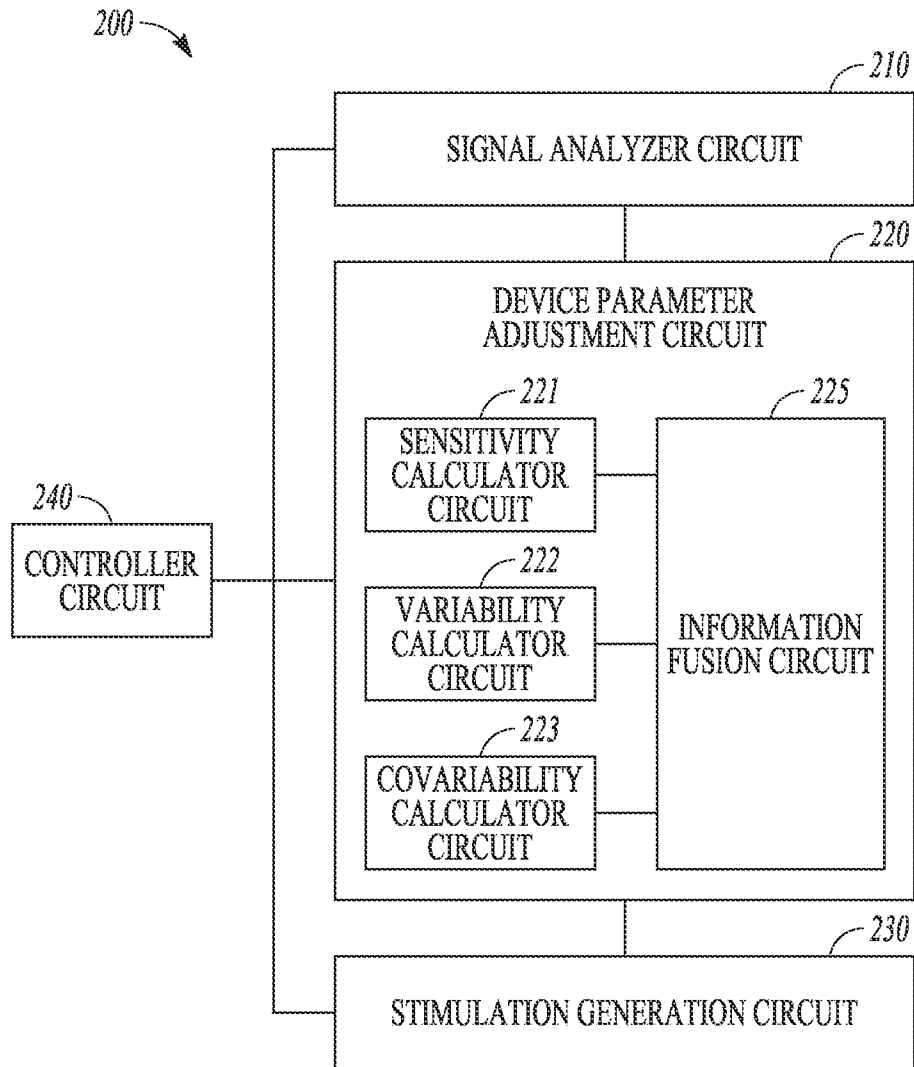


FIG. 1



**FIG. 2**

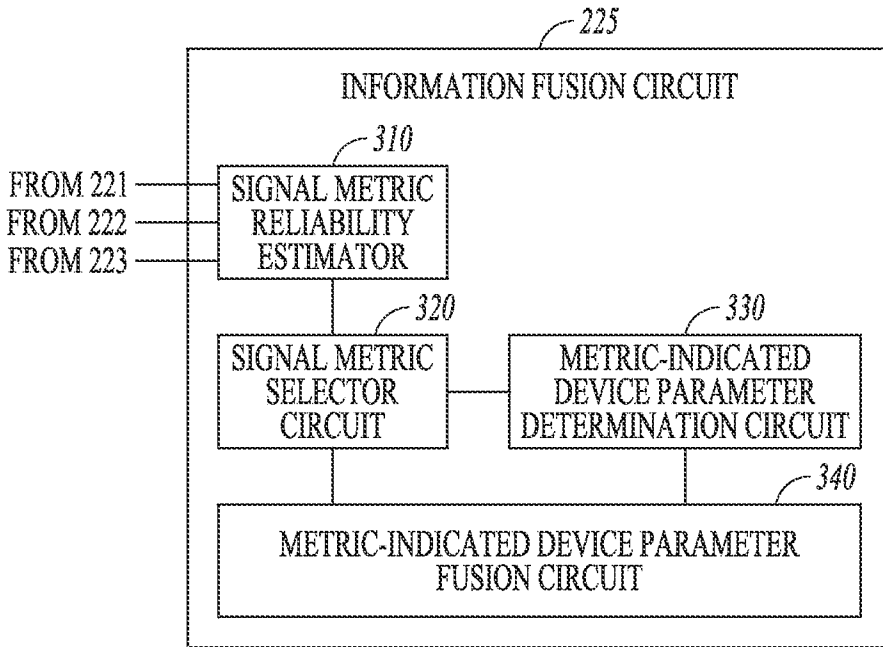


FIG. 3

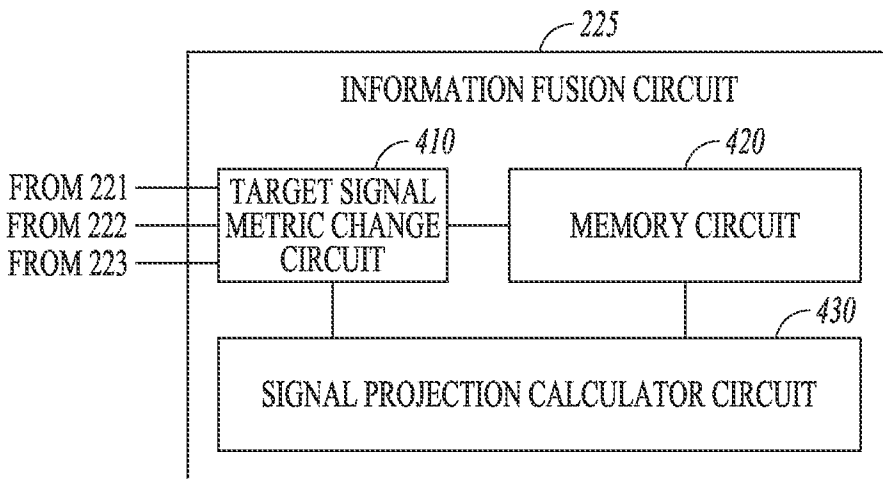
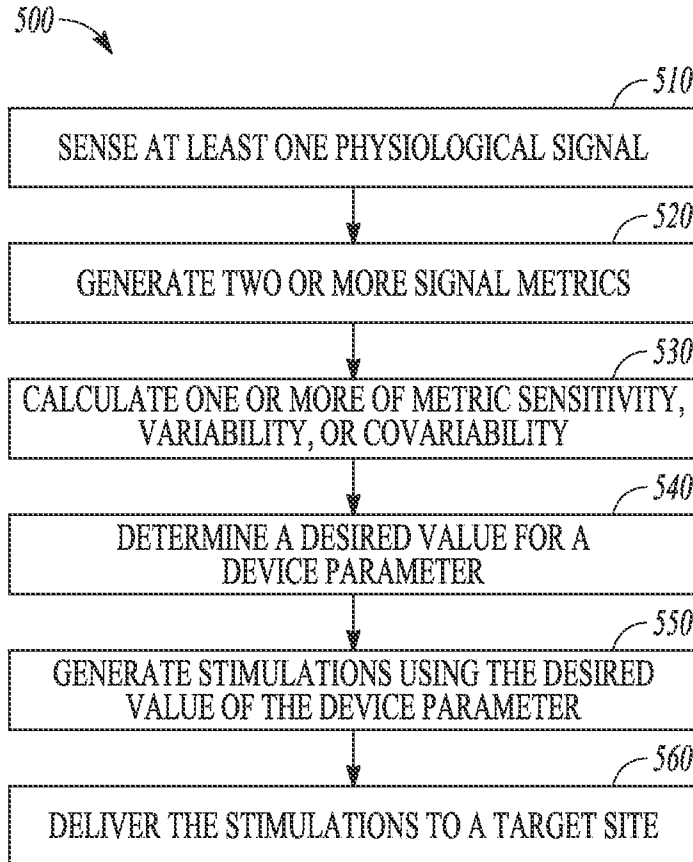
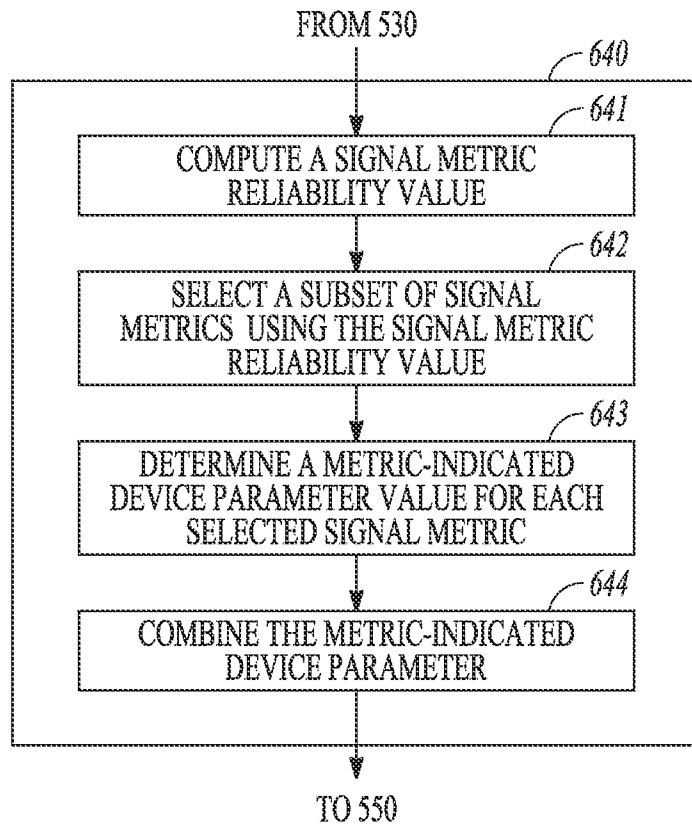


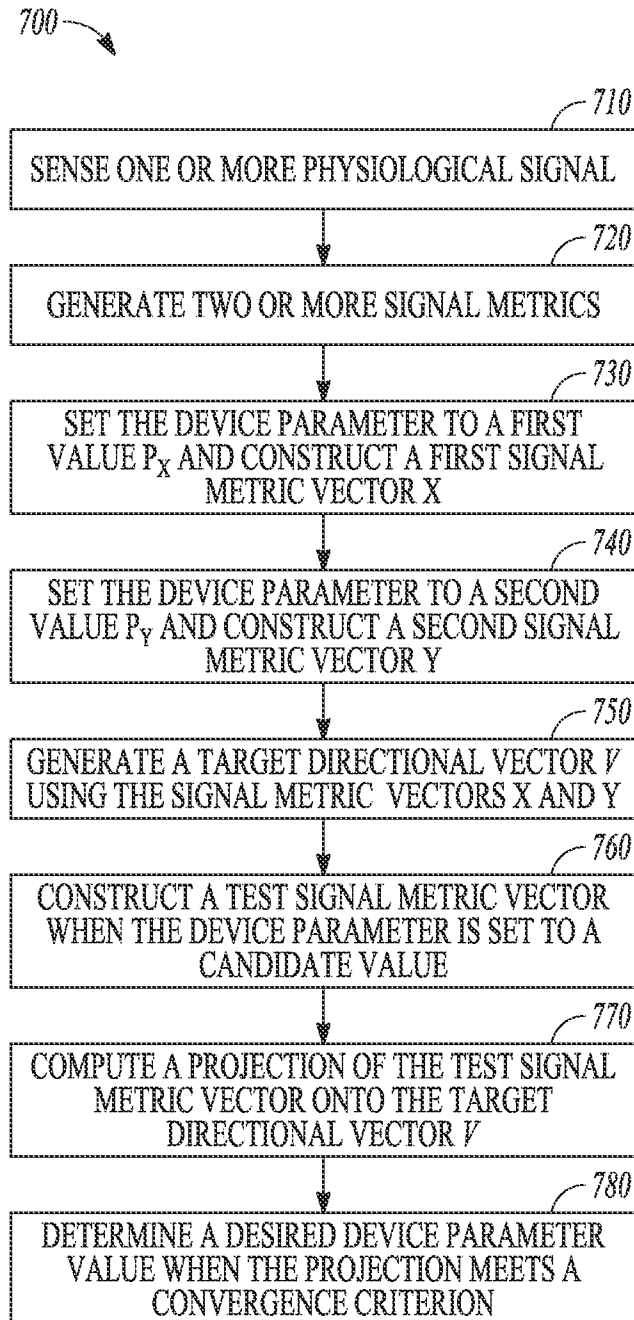
FIG. 4



**FIG. 5**



**FIG. 6**

**FIG. 7**

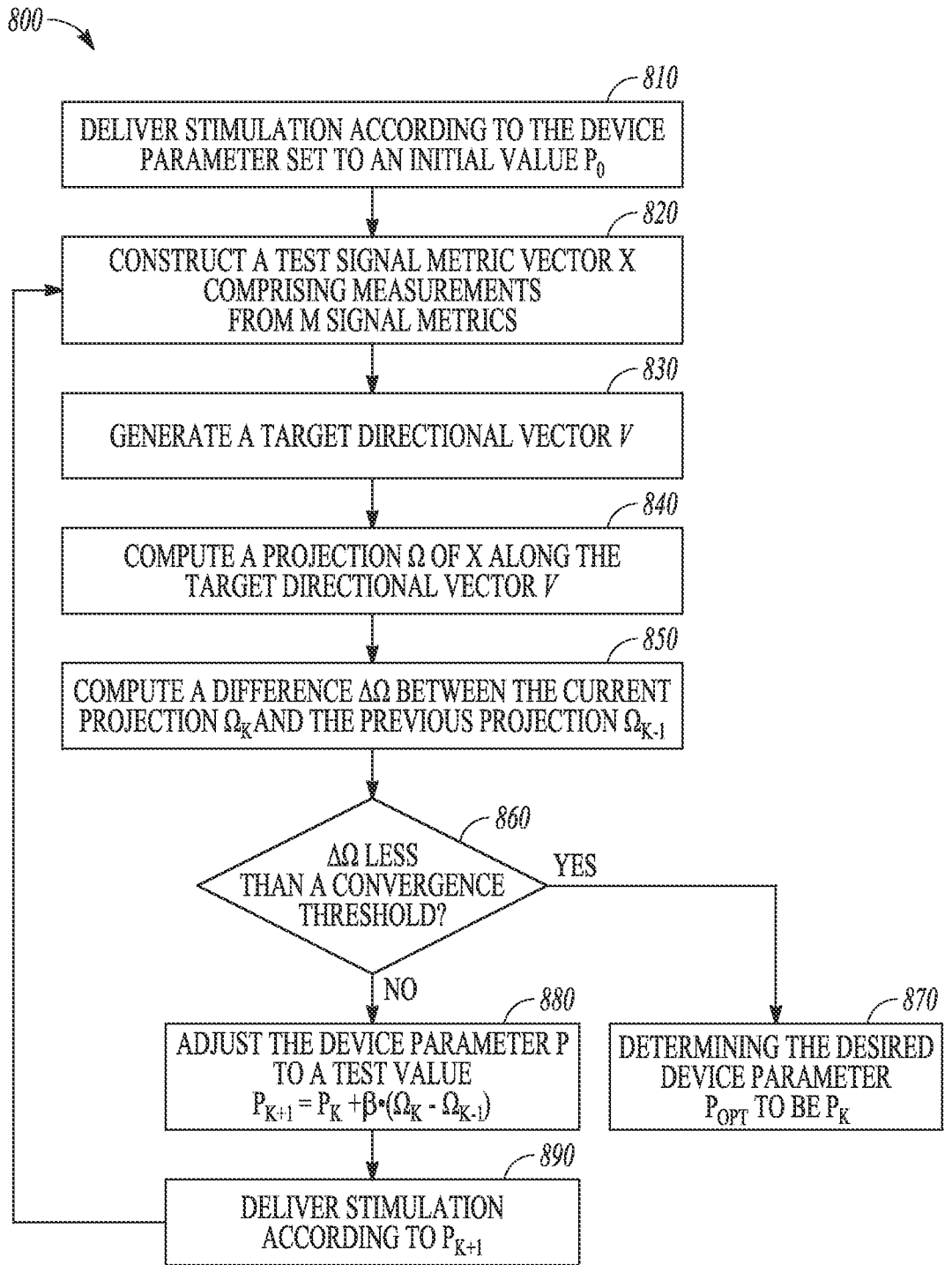


FIG. 8

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2014/021287

A. CLASSIFICATION OF SUBJECT MATTER  
INV. A61N1/05 A61N1/36 A61N1/365 A61N1/368 A61N1/37  
ADD.  
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED  
Minimum documentation searched (classification system followed by classification symbols)  
A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/274141 A1 (PATANGAY ABHILASH [US] ET AL) 28 October 2010 (2010-10-28)	1-4
A	abstract; figures 1-3, 6, 9 paragraphs [0045] - [0048], [0054] - [0061], [0081] - [0108]	5-10
X	US 2010/152796 A1 (SCHECTER STUART O [US]) 17 June 2010 (2010-06-17)	1-4
A	abstract; figures 1-2 paragraphs [0010] - [0013], [0023] - [0036], [0041] - [0044], [0055] - [0058]	5-10
X	US 2011/125208 A1 (KARST EDWARD [US] ET AL) 26 May 2011 (2011-05-26)	1-4
A	abstract; figures 1-3, 7A, 8 paragraphs [0011] - [0017], [0032] - [0051], [0073] - [0084]	5-10
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Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>
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Date of the actual completion of the international search  16 May 2014	Date of mailing of the international search report  26/05/2014
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Lahorte, Philippe
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2014/021287

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

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

1.  Claims Nos.: 11-20  
because they relate to subject matter not required to be searched by this Authority, namely:  
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy (Claim 11: "..."; claim 19: "A method for adjusting a device parameter used for operating an ambulatory medical device ... in response to stimulation when ...").
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

### Remark on Protest

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

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2014/021287

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/113890 A1 (CHO YONG K [US] ET AL) 6 May 2010 (2010-05-06)	1-4
A	abstract; figures 1-3, 5 paragraphs [0009] - [0013], [0019] - [0058] -----	5-10

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2014/021287
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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			JP 2012524615 A 18-10-2012
			US 2010274141 A1 28-10-2010
			US 2010274147 A1 28-10-2010
			WO 2010123749 A2 28-10-2010
			WO 2010123751 A1 28-10-2010
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US 2011125208	A1	26-05-2011	NONE
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US 2010113890	A1	06-05-2010	EP 2370161 A2 05-10-2011
			US 2010113890 A1 06-05-2010
			WO 2010051154 A2 06-05-2010
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