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(54) **SYSTEMS AND METHODS FOR CLOSED LOOP NEUROMODULATION**

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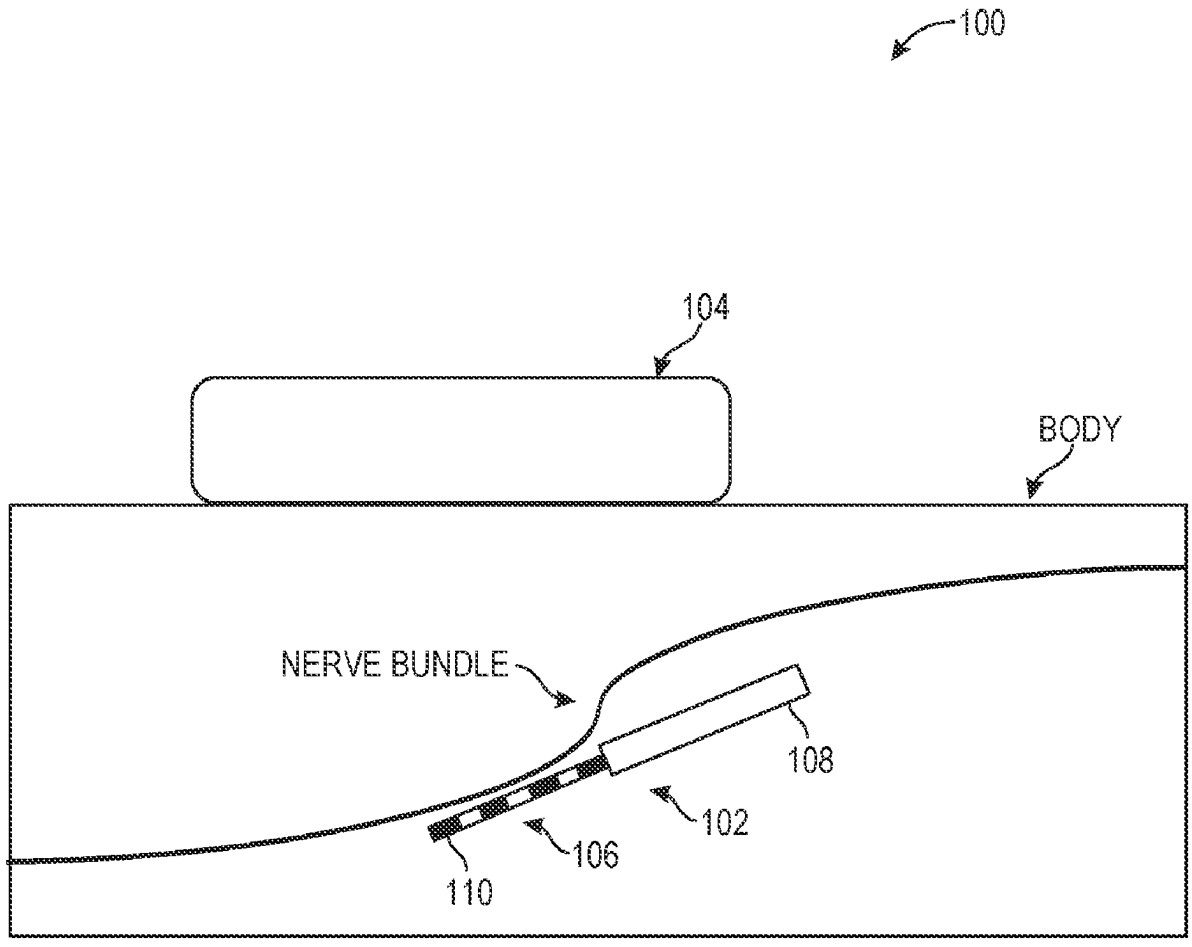
(57) **ABSTRACT**

A neuromodulation system includes an implantable neuromodulation device and an external unit. The neuromodulation device includes an electrode platform, a sensor/recorder coupled to the electrode platform, and a transceiver coupled to the sensor/recorder. The sensor/recorder senses electrical activity of tissue resulting from a delivery of a stimulation therapy to the tissue. The stimulation therapy is defined by a plurality of stimulation parameters, and the sensed electrical activity includes a stimulation response comprising an evoked stimulation response, a stimulation artifact, and an evoked compound action potential (ECAP) response. The transceiver transmits a sensed signal corresponding to the electrical activity. The externa unit includes a transceiver that receives the sensed signal from the neuromodulation device, and a processor that determines a measure based on the ECAP response and the evoked stimulation response; and determines whether to adjust one or more of the stimulation parameters of the stimulation therapy based on the measure.



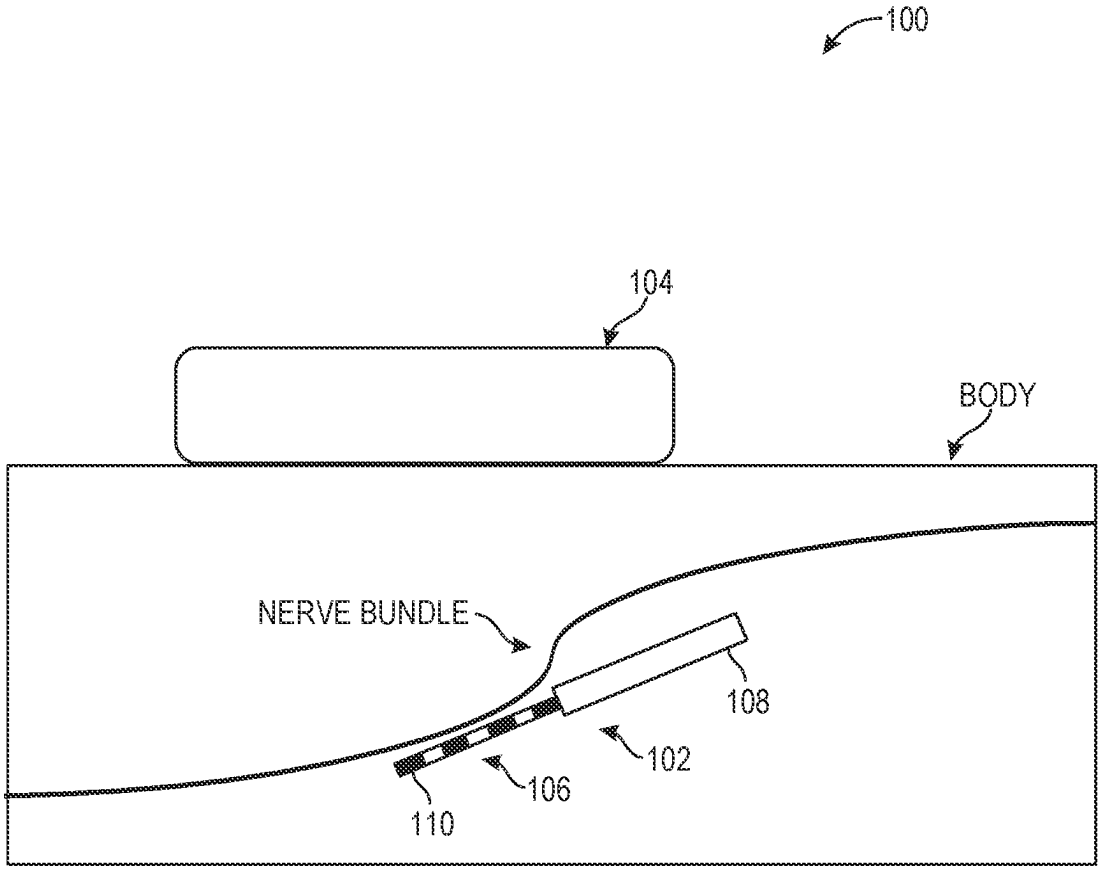


FIG. 1

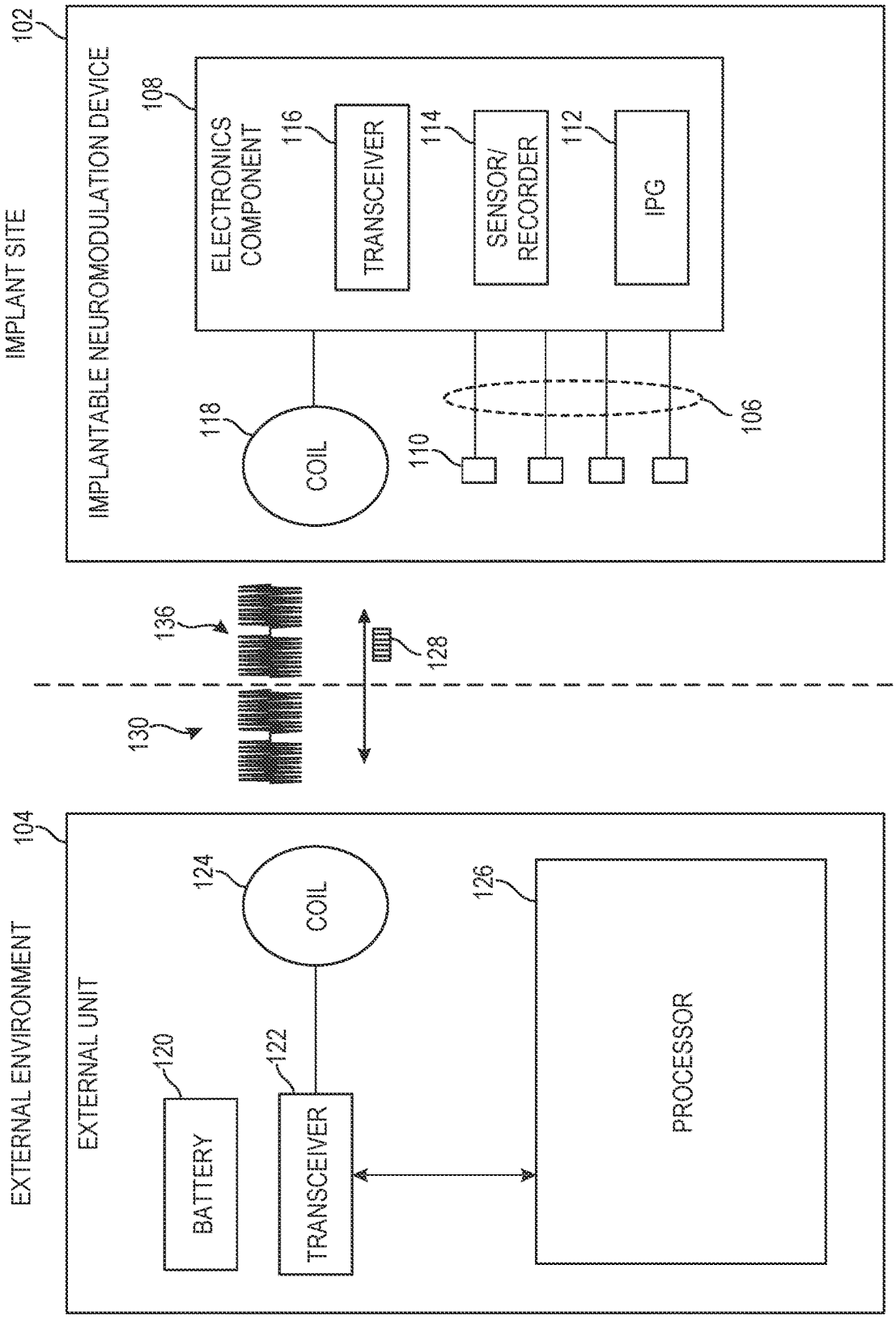

IMPLANT SITE
102
IMPLANTABLE NEUROMODULATION DEVICE
108
ELECTRONICS COMPONENT
116
TRANSCEIVER
114
SENSOR/ RECORDER
112
IPG
118
COIL
110
106
136
128
130
EXTERNAL ENVIRONMENT
104
EXTERNAL UNIT
124
COIL
126
120
BATTERY
122
TRANSCEIVER
PROCESSOR

FIG. 2

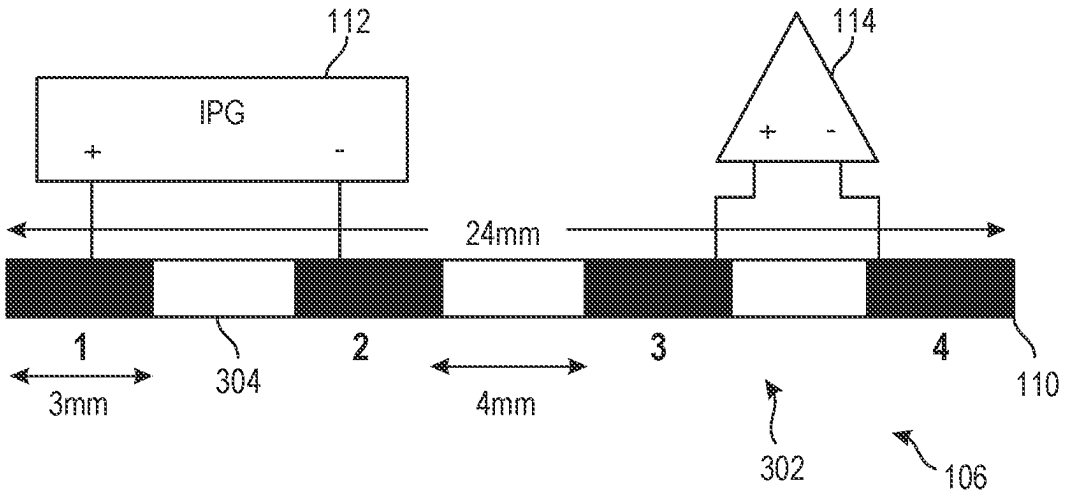


FIG. 3

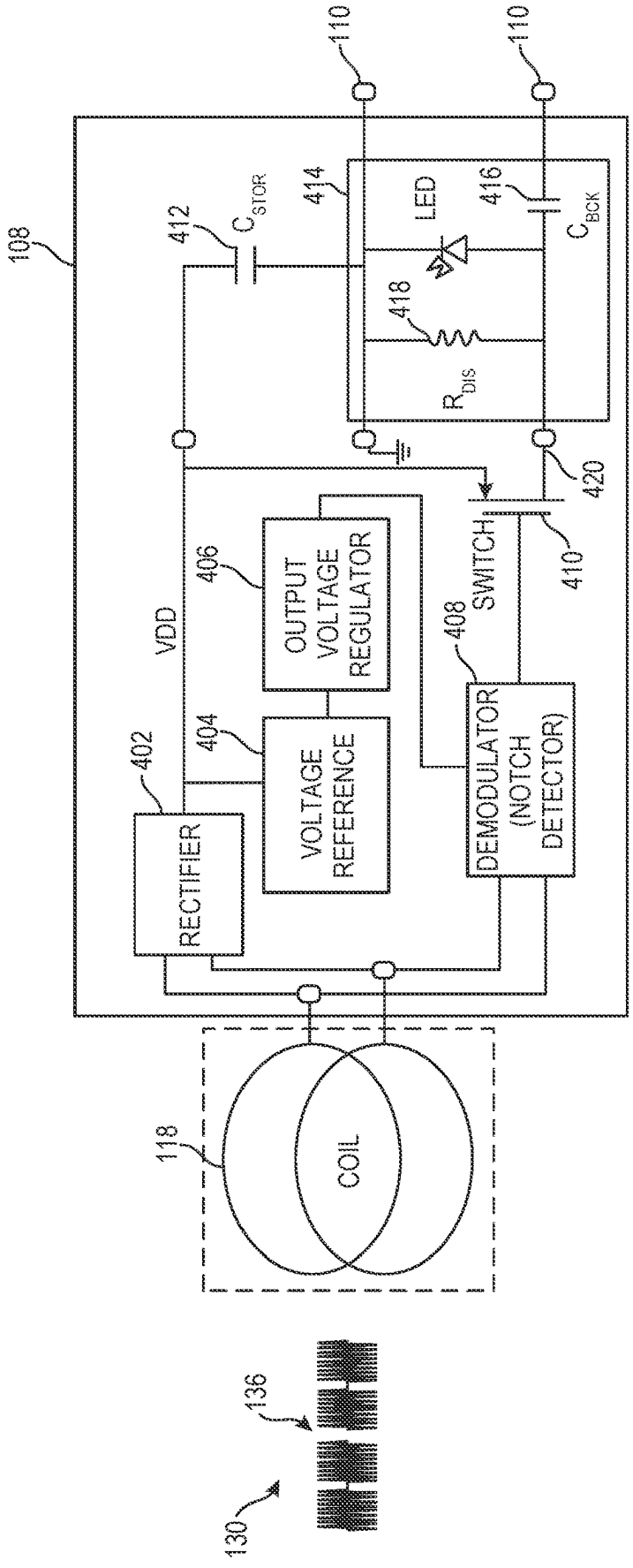

108
110
110
412
C_{STOR}
414
LED
416
C_{BCK}
418
R_{DIS}
420
410
SWITCH
408
406
OUTPUT VOLTAGE REGULATOR
VDD
404
VOLTAGE REFERENCE
402
RECTIFIER
DEMODULATOR (NOTCH DETECTOR)
118
COIL
136
130

FIG. 4

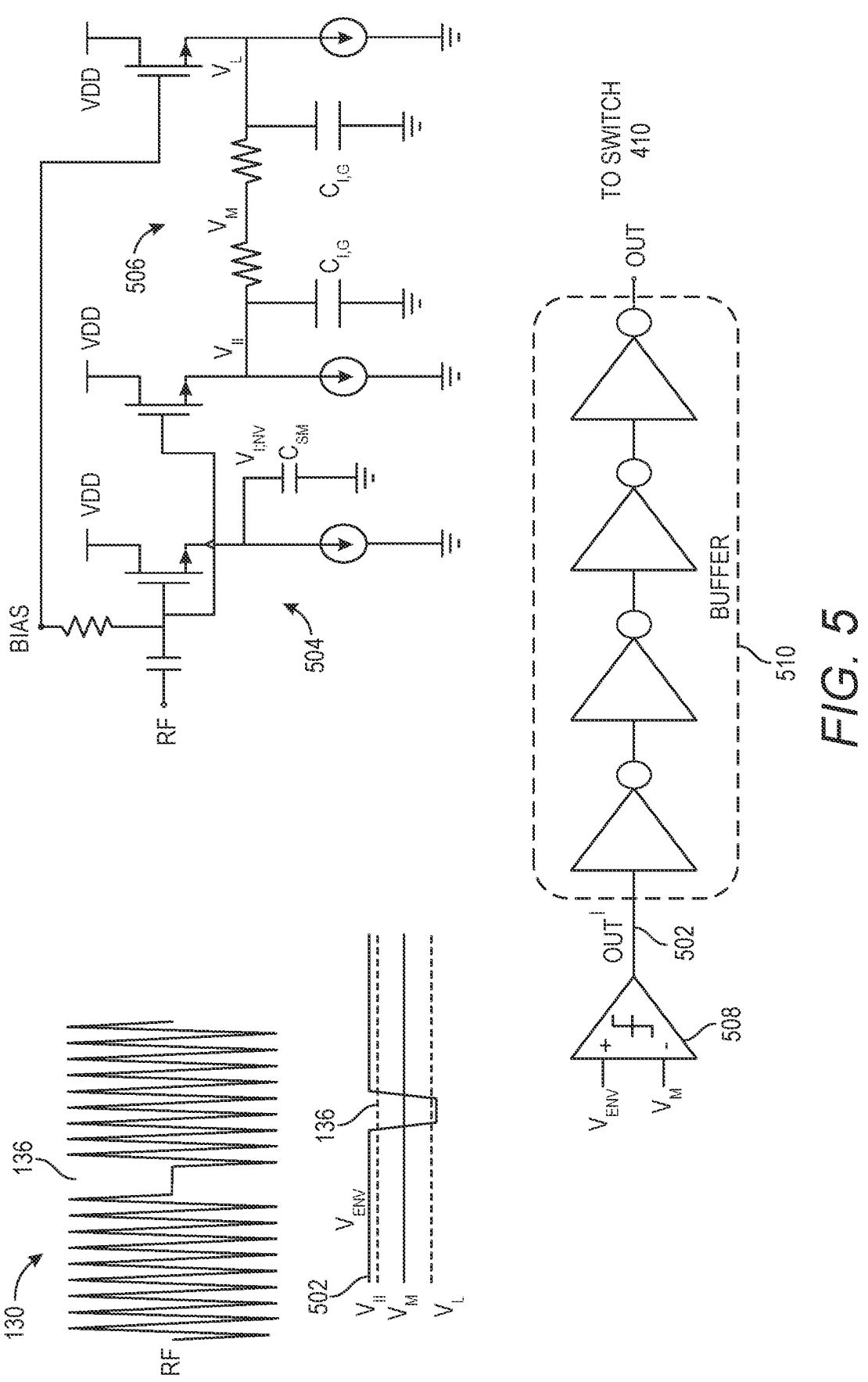

408
VDD
VDD
VDD
V_L
V_M
V_{ii}
$V_{i;INV}$
$C_{I,G}$
$C_{I,G}$
C_{SM}
506
504
BIAS
RF
TO SWITCH 410
OUT
BUFFER
510
OUT
502
508
V_{ENV}
V_M
130
136
RF
136
502
V_{ENV}
V_{ii}
V_M
V_L

FIG. 5

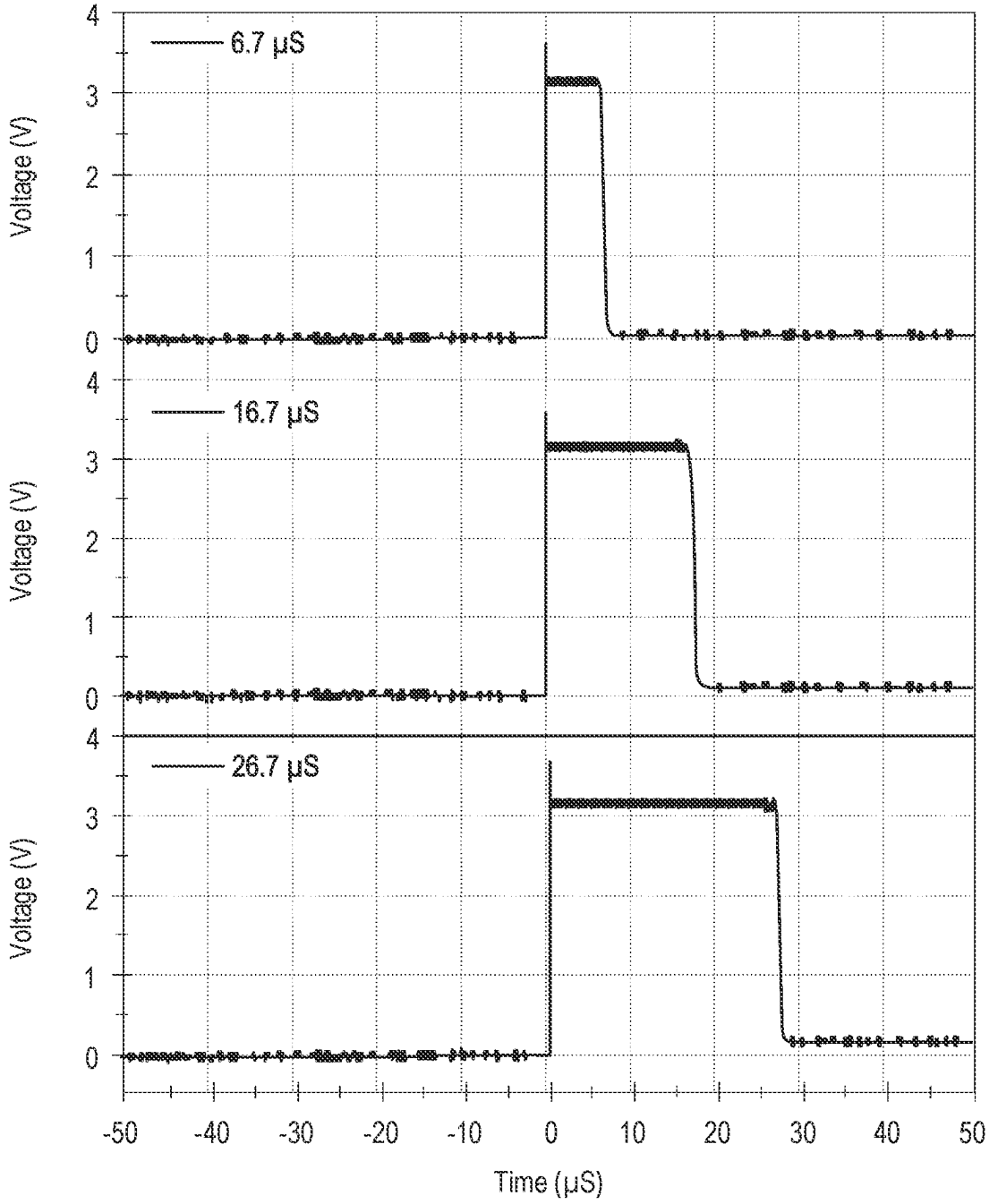


FIG. 6

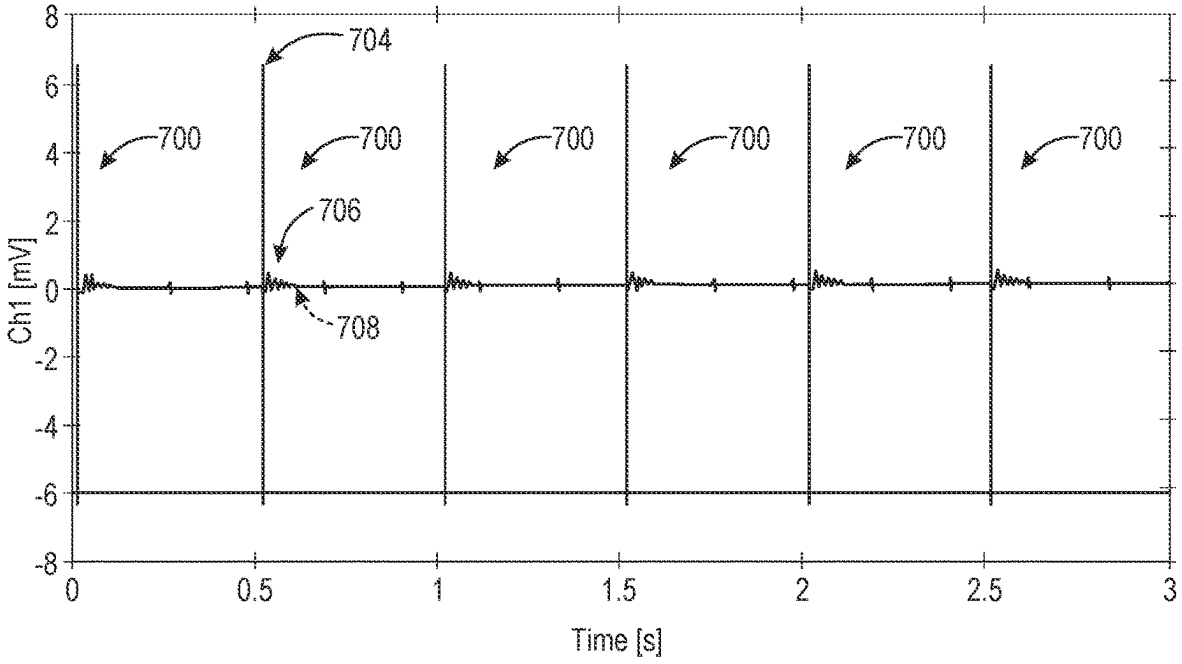

8
6
4
2
0
-2
-4
-6
-8
Ch1 [mV]
0
0.5
1
1.5
2
2.5
3
Time [s]
704
700
700
700
700
700
700
706
708

FIG. 7

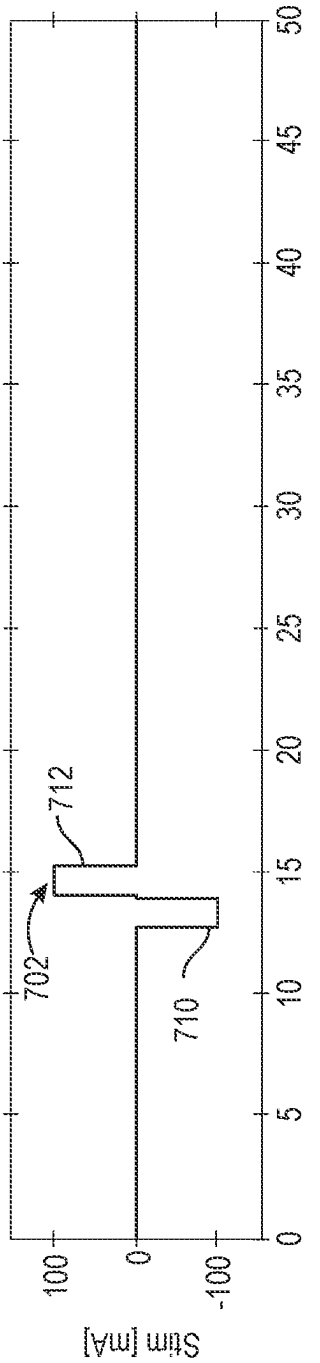

Stim [mA]
100
0
-100
0
5
10
15
20
25
30
35
40
45
50
Time [ms]
702
712
710

FIG. 8A

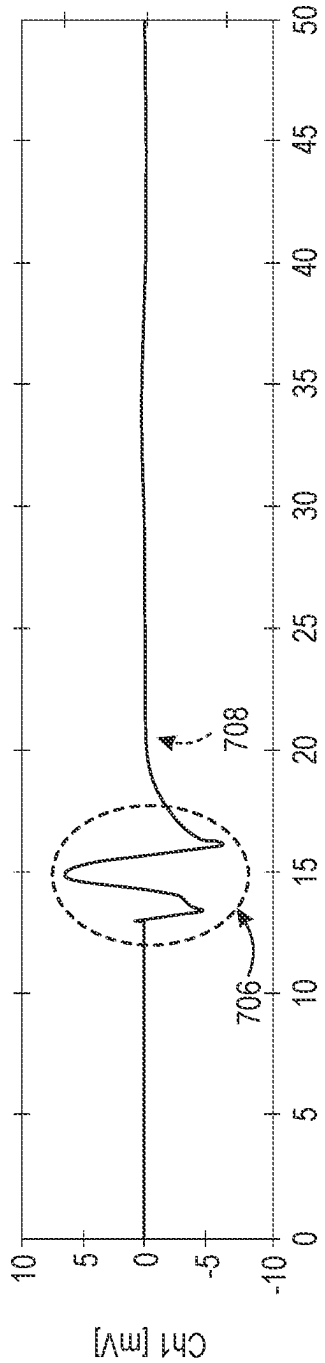

Ch1 [mV]
10
5
0
-5
-10
0
5
10
15
20
25
30
35
40
45
50
Time [ms]
708
706

FIG. 8B

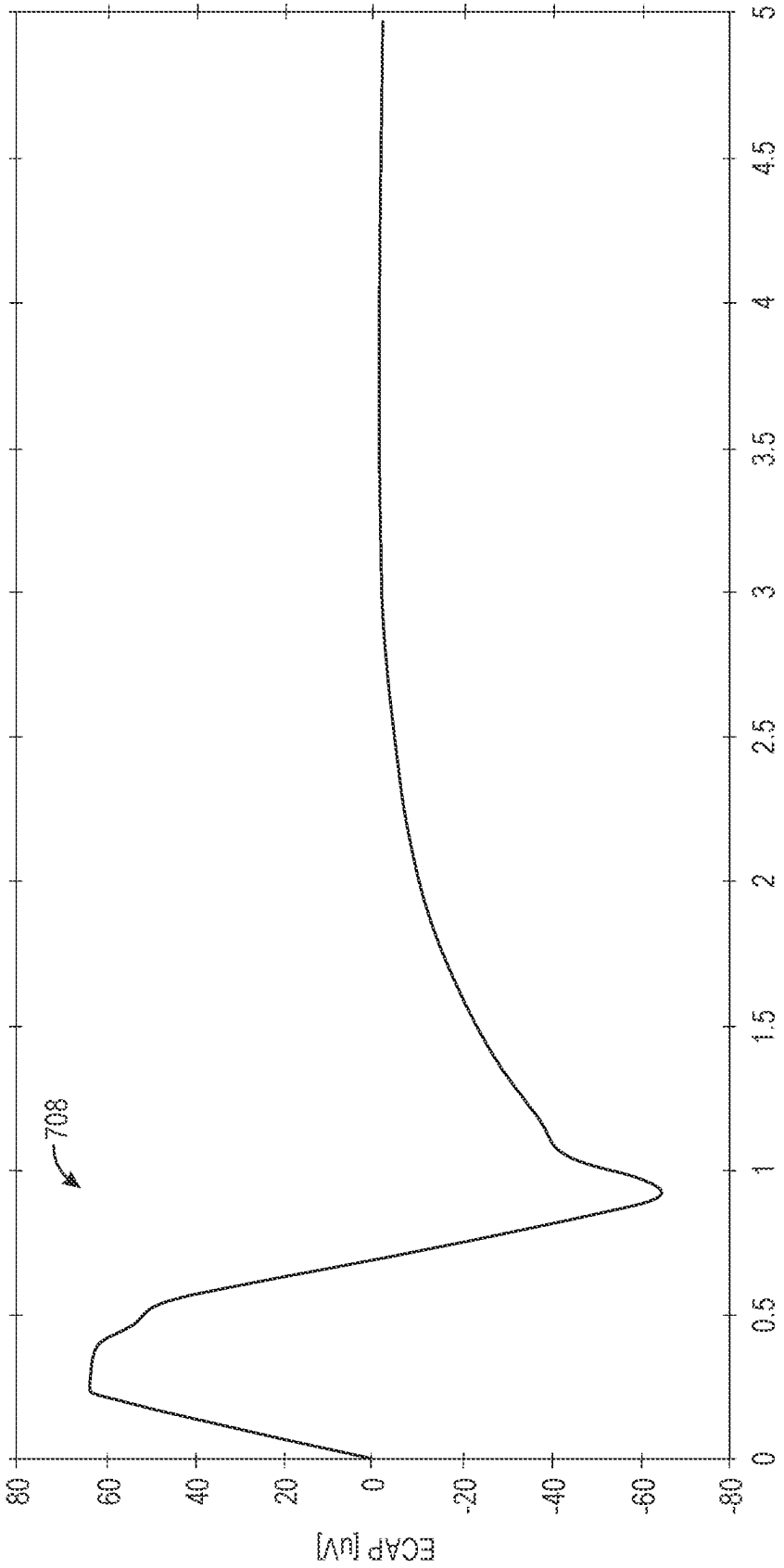


FIG. 9

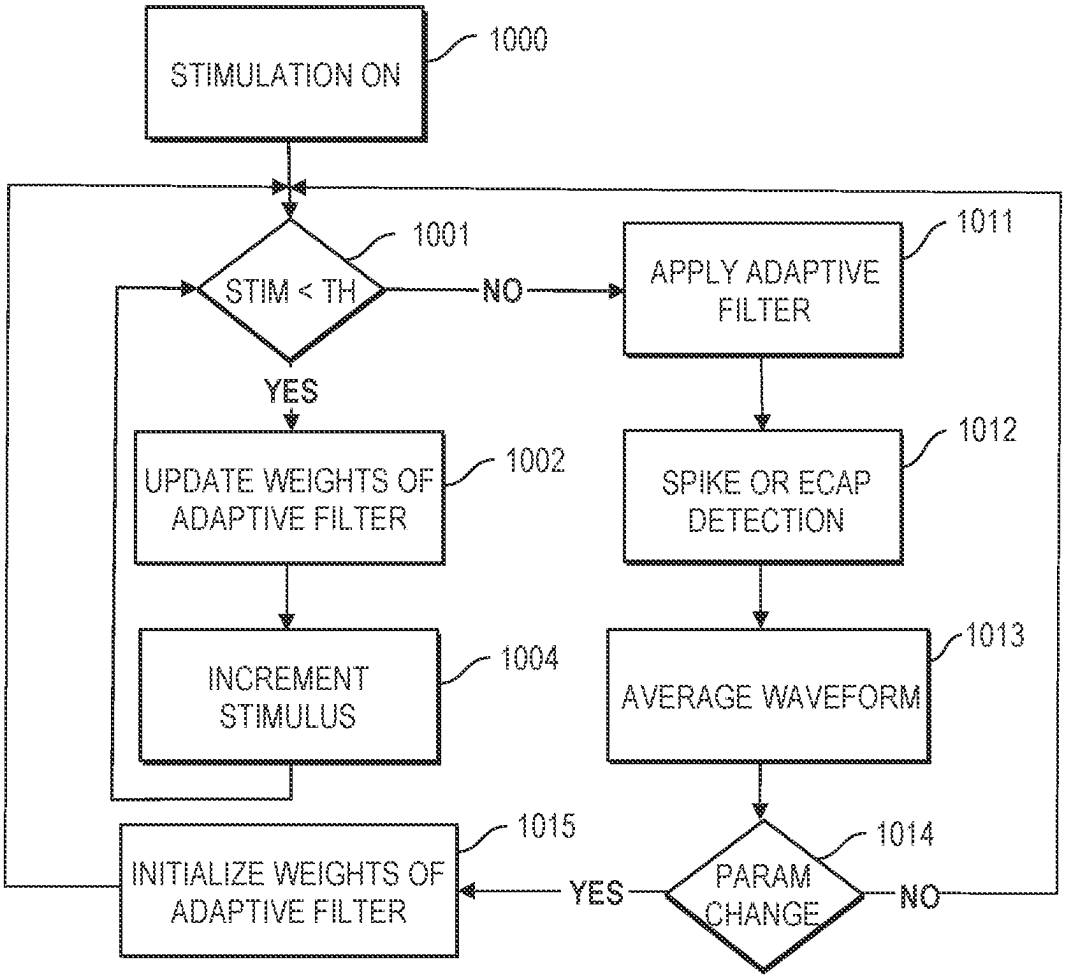

STIMULATION ON
1000
STIM < TH
1001
NO
YES
APPLY ADAPTIVE FILTER
1011
UPDATE WEIGHTS OF ADAPTIVE FILTER
1002
SPIKE OR ECAP DETECTION
1012
INCREMENT STIMULUS
1004
AVERAGE WAVEFORM
1013
INITIALIZE WEIGHTS OF ADAPTIVE FILTER
1015
YES
PARAM CHANGE
1014
NO

FIG. 10

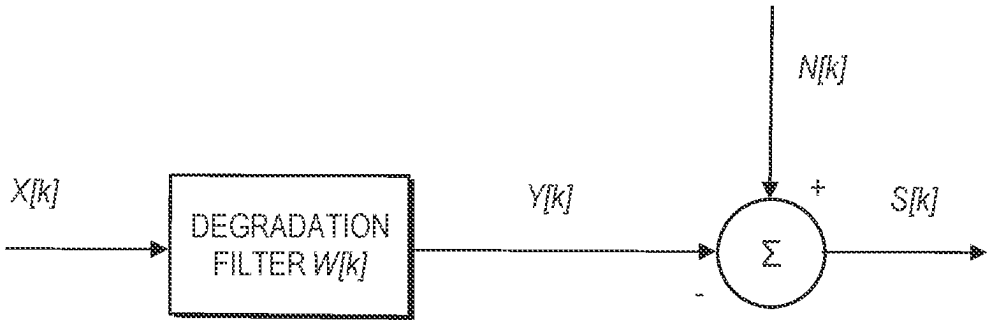


FIG. 11A

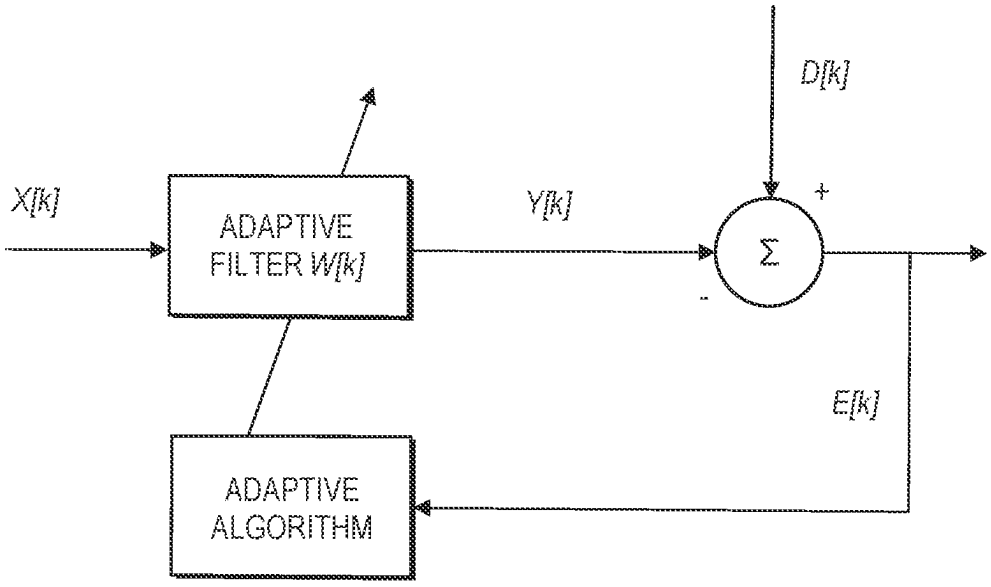


FIG. 11B

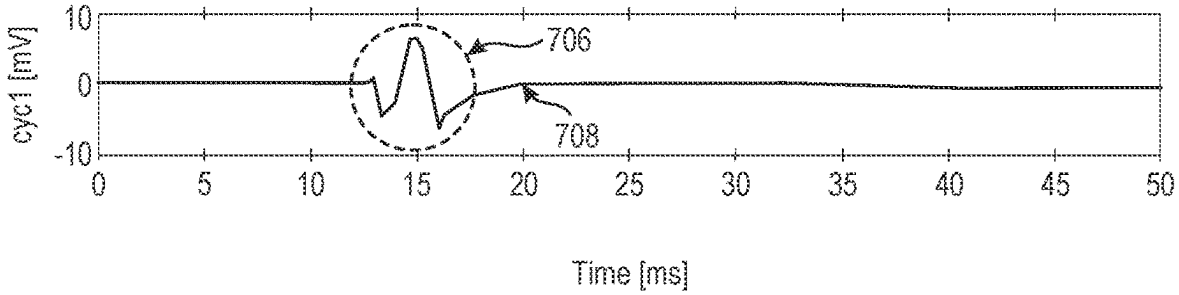


FIG. 12A

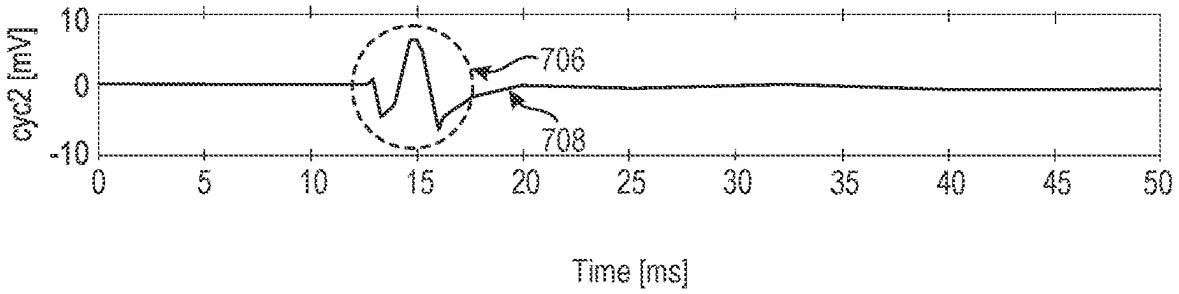


FIG. 12B

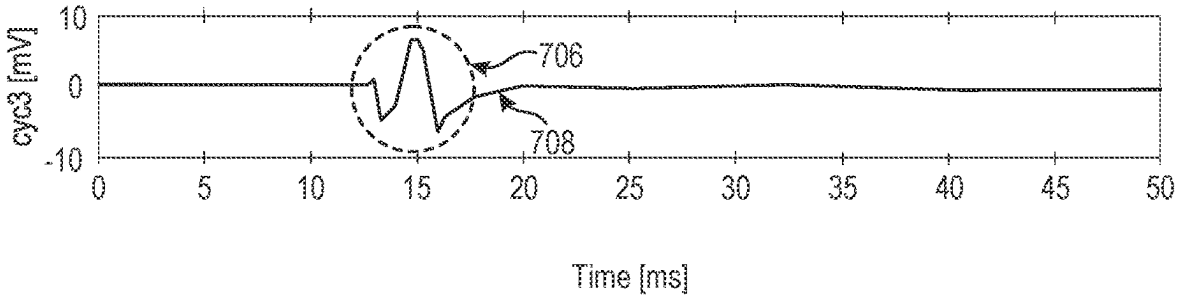


FIG. 12C

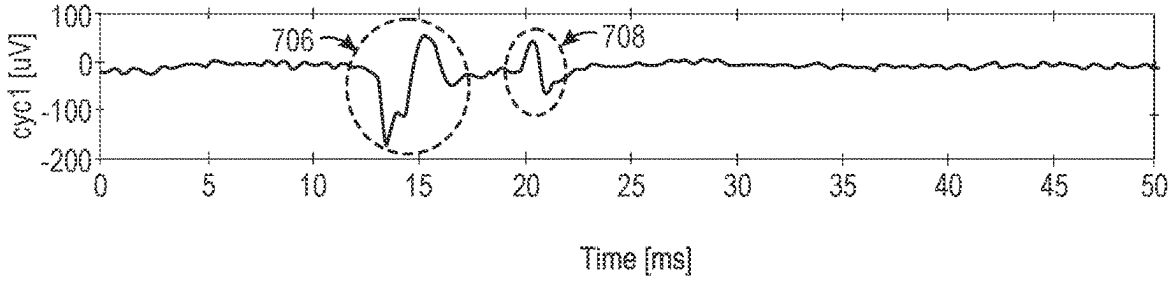


FIG. 13A

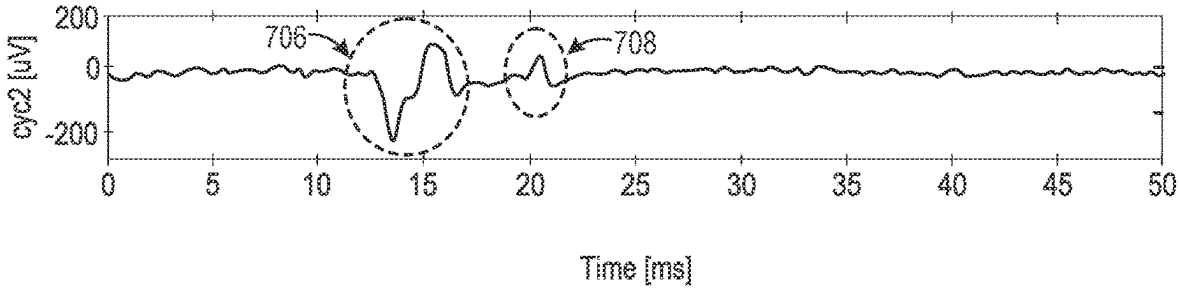


FIG. 13B

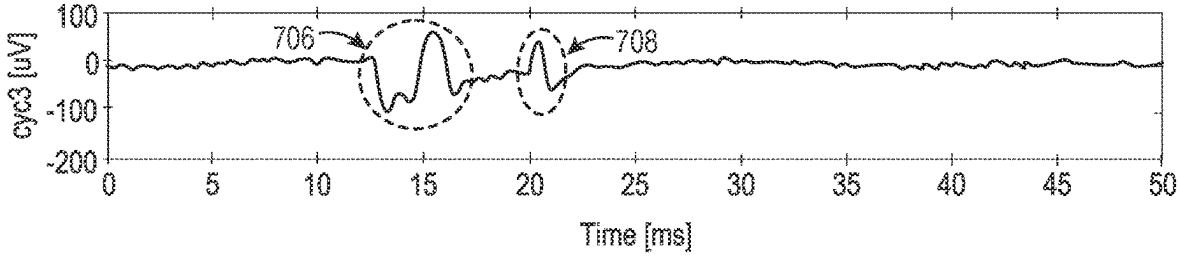


FIG. 13C

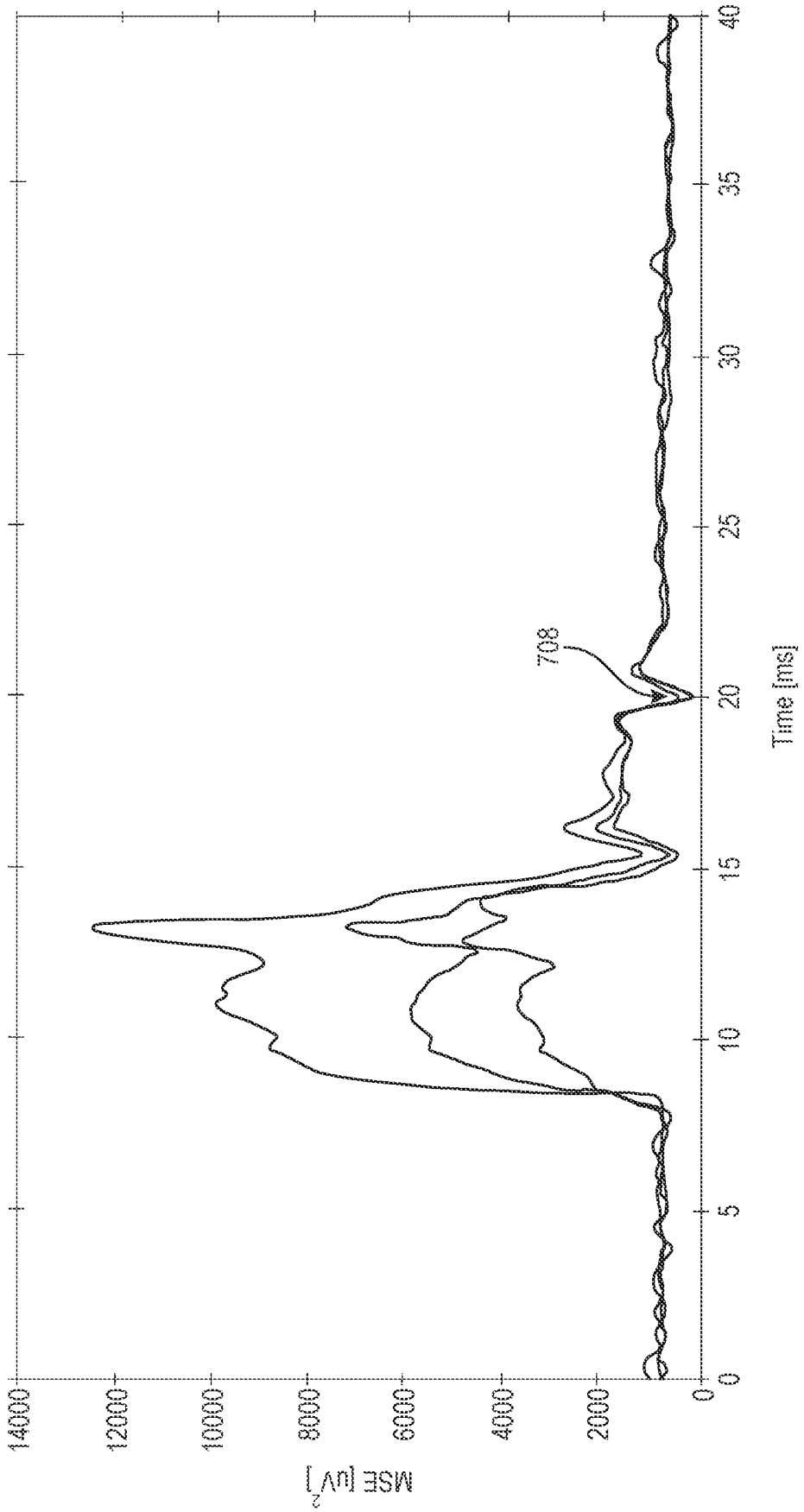

MSE [μV²]
14000
12000
10000
8000
6000
4000
2000
0
5
10
15
20
25
30
35
40
Time [ms]
708

FIG. 14

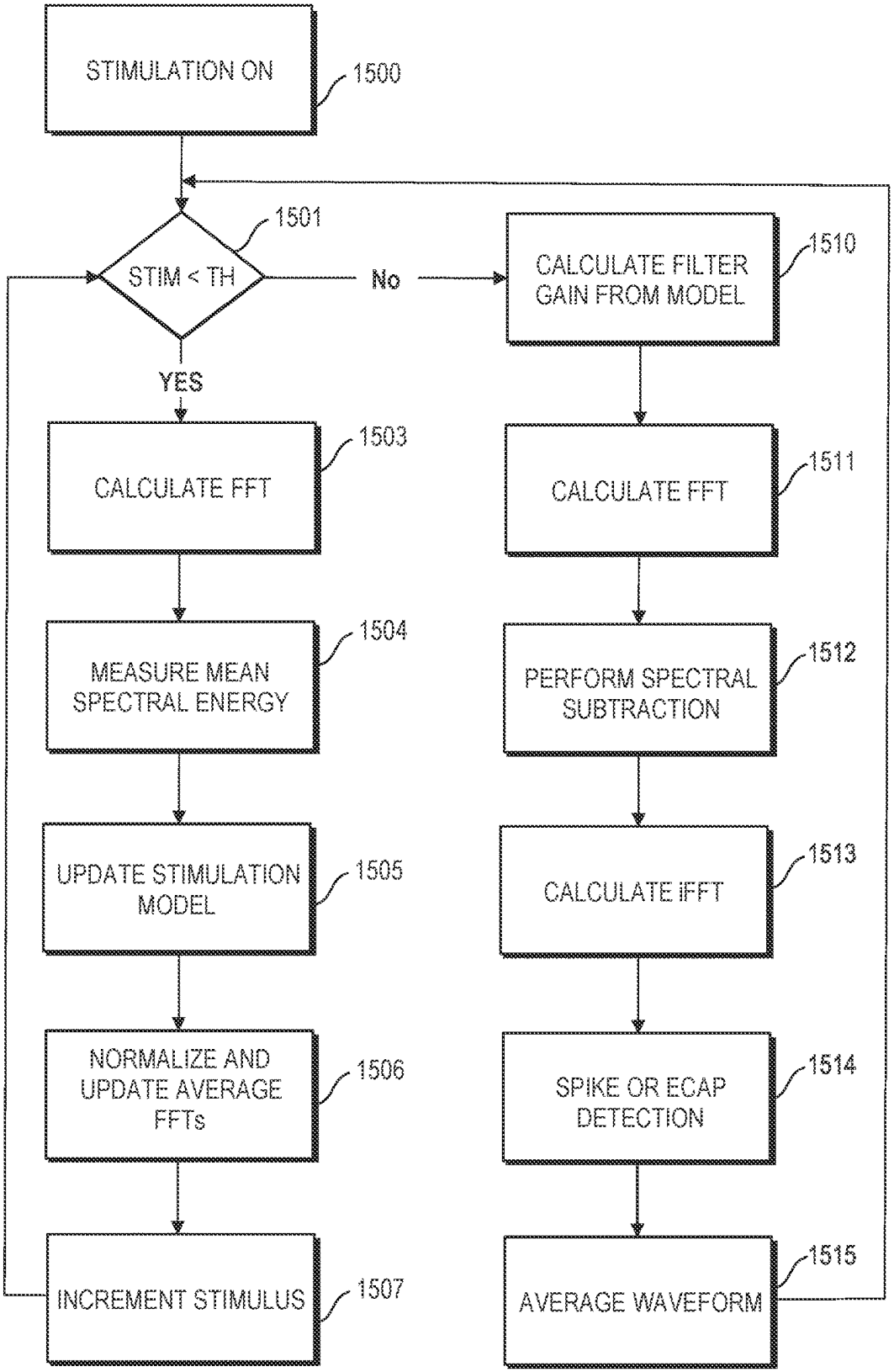

STIMULATION ON
1500
1501
STIM < TH
No
YES
CALCULATE FILTER GAIN FROM MODEL
1510
CALCULATE FFT
1503
CALCULATE FFT
1511
MEASURE MEAN SPECTRAL ENERGY
1504
PERFORM SPECTRAL SUBTRACTION
1512
UPDATE STIMULATION MODEL
1505
CALCULATE iFFT
1513
NORMALIZE AND UPDATE AVERAGE FFTs
1506
SPIKE OR ECAP DETECTION
1514
INCREMENT STIMULUS
1507
AVERAGE WAVEFORM
1515

FIG. 15

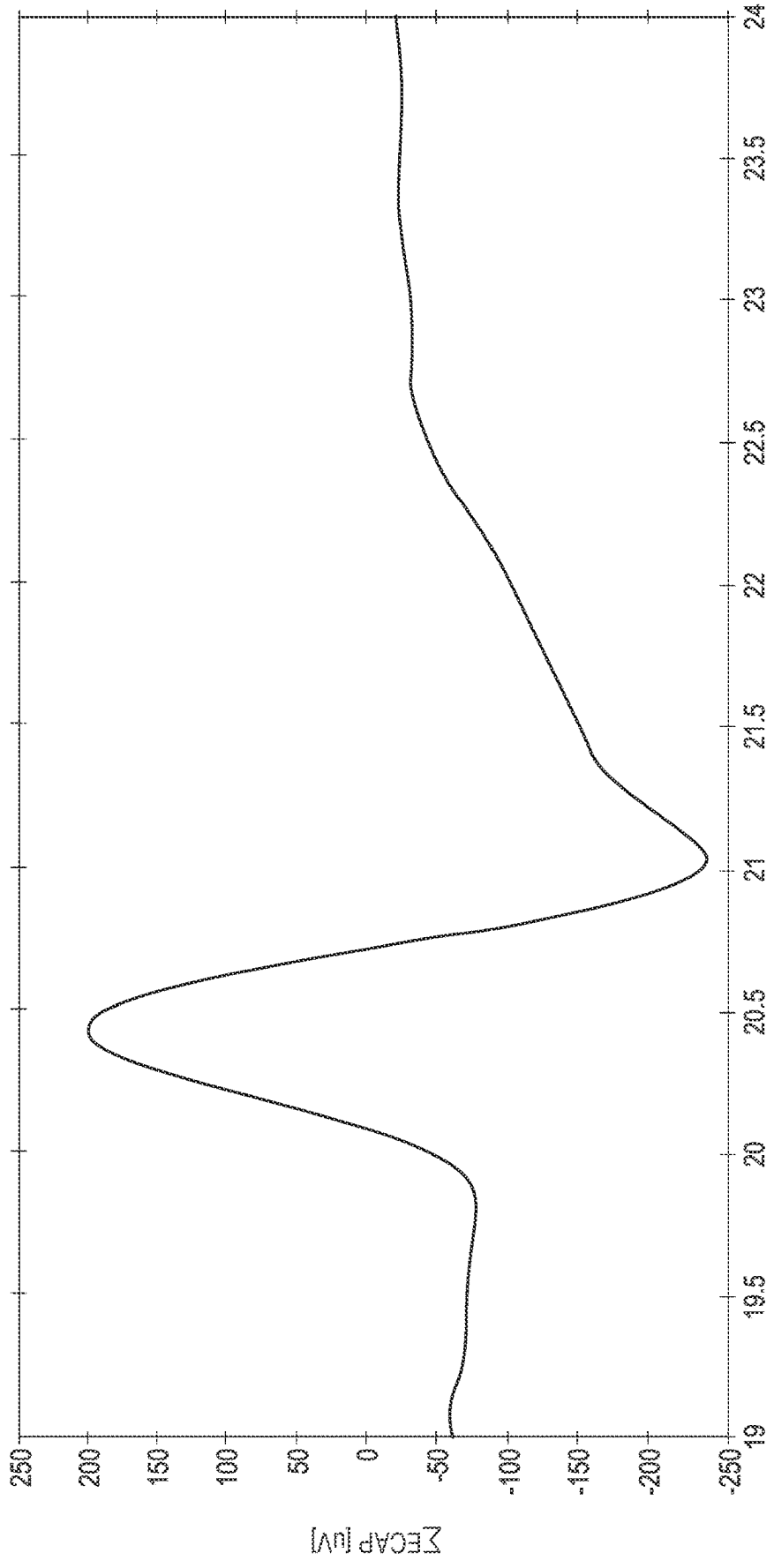

ΣECAP [uV]
250
200
150
100
50
0
-50
-100
-150
-200
-250
19
19.5
20
20.5
21
21.5
22
22.5
23
23.5
24
Time [ms]

FIG. 16

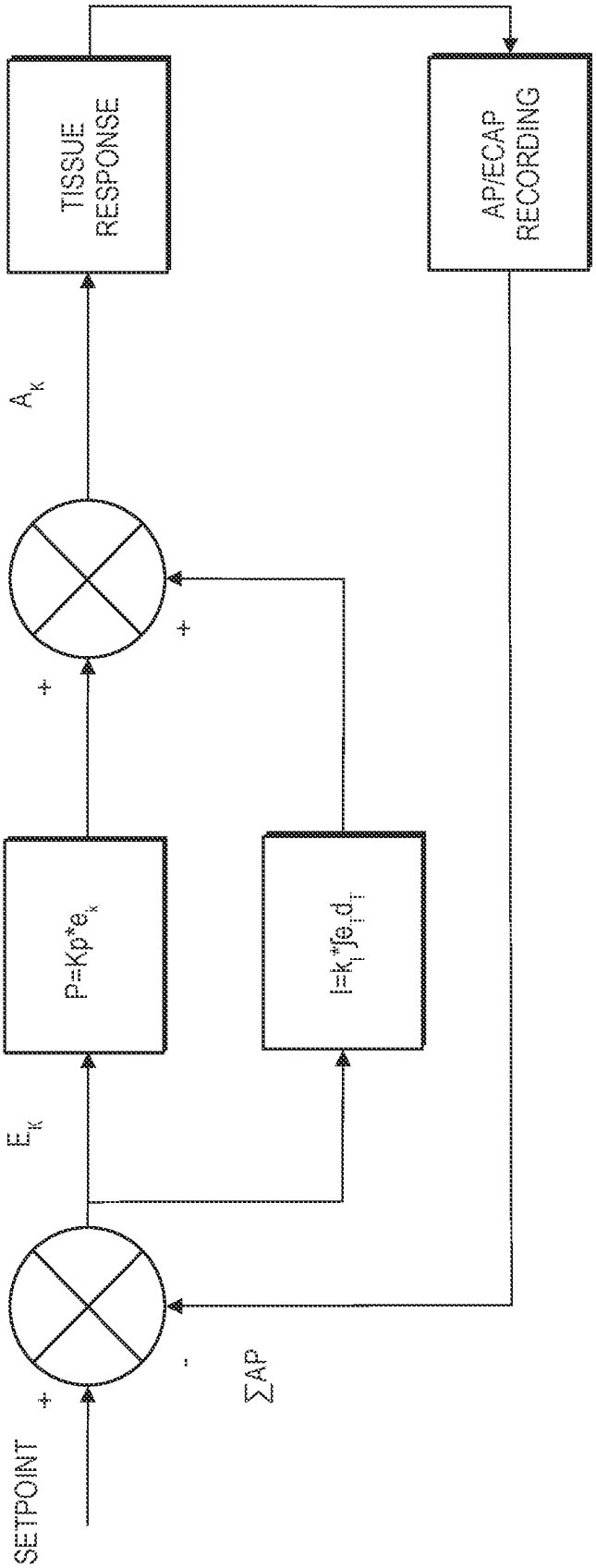

TISSUE RESPONSE
AP/ECAP RECORDING
A_K
+
+
$P=Kp*e_k$
$I=k_i*\int e_i.d_i$
E_K
+
-
SETPOINT
$\sum AP$

FIG. 17

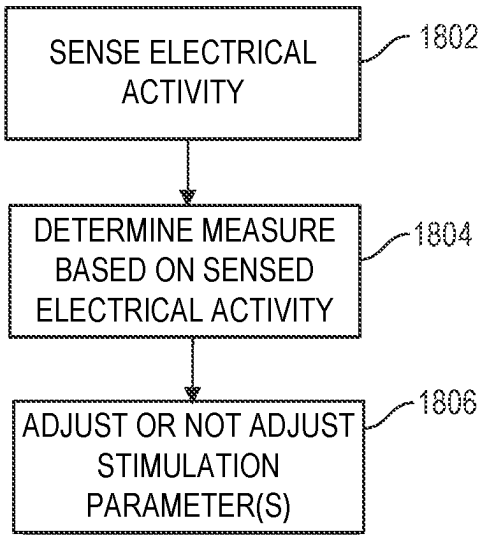

SENSE ELECTRICAL ACTIVITY
1802
DETERMINE MEASURE BASED ON SENSED ELECTRICAL ACTIVITY
1804
ADJUST OR NOT ADJUST STIMULATION PARAMETER(S)
1806

FIG. 18

SYSTEMS AND METHODS FOR CLOSED LOOP NEUROMODULATION

TECHNICAL FIELD

[0001] The present disclosure relates generally to neuromodulation systems and methods, and more particularly, to systems and methods for closed loop neuromodulation.

BACKGROUND

[0002] Neurostimulation therapies are often limited due to a loss of therapeutic effect over time. Habituation and desensitization with increasing tolerance to the neurostimulation therapy is a considerable challenge in the treatment of disorders such as chronic pain and urinary dysfunction. This effect is exacerbated with the use of static stimulation waveforms.

[0003] The current state of the art in peripheral nerve stimulation (PNS) to treat a range of chronic disorders, such as neuropathic pain and urinary disfunction, adopt open loop modalities, wherein the pulse generator output is a fixed waveform. While this approach is sufficient to provide therapeutic benefits, it is far from optimal, with adjustments to waveform amplitude performed by the patient. Variations in the electrical field at the nerve interface where the charge is delivered to a peripheral nerve fiber are common. Variations can be a result of changes in interface impedance, electrode movement and other interfering factors. Electrode movement can result from cardiac and respiratory motion or ambulation. This can impact the ability of the device to elicit an action potential (AP) response or provide the desired stimulation response consistently.

SUMMARY

[0004] The disclosure relates to a neuromodulation system that includes an implantable neuromodulation device and an external unit. The implantable neuromodulation device includes an electrode platform, a sensor/recorder coupled to the electrode platform, and a transceiver coupled to the sensor/recorder. The sensor/recorder is configured to sense electrical activity of tissue resulting from a delivery of a stimulation therapy to the tissue, wherein the stimulation therapy is defined by a plurality of stimulation parameters, and the sensed electrical activity includes a stimulation response comprising an evoked stimulation response, a stimulation artifact, and an evoked compound action potential (ECAP) response. The transceiver is configured to transmit a sensed signal corresponding to the electrical activity. The externa unit includes a transceiver configured to receive the sensed signal from the implantable neuromodulation device, and a processor configured to determine a measure based on the ECAP response and the evoked stimulation response; and to determine whether to adjust one or more of the plurality of stimulation parameters of the stimulation therapy based on the measure.

[0005] The disclosure also relates to a method of adjusting stimulation therapy delivered to tissue of a patient by an implanted neuromodulation device. The method includes a) sensing electrical activity of the tissue resulting from a delivery of a stimulation therapy to the tissue through an implanted neurostimulation device, wherein the stimulation therapy is defined by a plurality of stimulation parameters, and the sensed electrical activity includes a stimulation response comprising an evoked stimulation response, a stimulation artifact and an evoked compound action potential (ECAP) response. The method also includes b) determining a measure based on the ECAP response and the evoked stimulation response; and c) determining whether to adjust one or more of the plurality of stimulation parameters of the stimulation therapy based on the measure.

[0006] The disclosure also relates to an implantable neuromodulation device comprising an electrode platform, an implantable pulse generator coupled to the electrode platform, a transceiver, and a sensor/recorder coupled to the electrode platform and the transceiver. The implantable pulse generator is configured to deliver a stimulation therapy to tissue through the electrode platform, wherein the stimulation therapy is defined by a plurality of stimulation parameters. The sensor/recorder is configured to: compare the delivered stimulation therapy to an activation threshold that elicits an ECAP response for the patient; and in response to the stimulation therapy being above the activation threshold: sense electrical activity of the tissue resulting from the delivery of a stimulation therapy to the tissue wherein the sensed electrical activity includes a stimulation response comprising an evoked stimulation response, a stimulation artifact and an evoked compound action potential (ECAP) response; and transmit a sensed signal corresponding to the sensed electrical activity.

[0007] The disclosure also relates to an implantable neuromodulation device comprising an electrode platform, an implantable pulse generator, and a sensor/recorder coupled to the electrode platform. The implantable pulse generator is configured to deliver a stimulation therapy to tissue through the electrode platform, wherein the stimulation therapy is defined by a plurality of stimulation parameters. The sensor/recorder is configured to: sense electrical activity of the tissue resulting from the delivery of a stimulation therapy to the tissue wherein the sensed electrical activity includes a stimulation response comprising an evoked stimulation response, a stimulation artifact and an evoked compound action potential (ECAP) response; determine a measure based on the ECAP response and the evoked stimulation response; and determine whether to adjust one or more of the plurality of stimulation parameters of the stimulation therapy based on the measure.

[0008] The disclosure also relates to an external unit comprising a transceiver and a processor coupled to the transceiver. The transceiver is configured to receive a signal corresponding to sensed electrical activity of tissue resulting from a delivery of a stimulation therapy to the tissue by an implanted neuromodulation device. The stimulation therapy is defined by a plurality of stimulation parameters, and the sensed electrical activity includes a stimulation response comprising an evoked stimulation response, a stimulation artifact and an evoked compound action potential (ECAP) response. The processor is configured to: determine a measure based on the ECAP response and the evoked stimulation response, determine whether to adjust one or more of the plurality of stimulation parameters of the stimulation therapy based on the measure, and in response to determining to adjust one or more of the plurality of stimulation parameters, transmit stimulation information to the implanted neuromodulation device to adjust the one or more of the plurality of stimulation parameters.

[0009] It is understood that other aspects of apparatuses and methods will become readily apparent to those skilled in the art from the following detailed description, wherein

various aspects of apparatuses and methods are shown and described by way of illustration. As will be realized, these aspects may be implemented in other and different forms and its several details are capable of modification in various other respects. Accordingly, the drawings and detailed description are to be regarded as illustrative in nature and not as restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Various aspects of apparatuses and methods will now be presented in the detailed description by way of example, and not by way of limitation, with reference to the accompanying drawings, wherein:

[0011] FIG. **1** is an illustration of a neuromodulation system including an implantable neuromodulation device and an external unit positioned relative to a body.

[0012] FIG. **2** is a block diagram of the neuromodulation system of FIG. **1**.

[0013] FIG. **3** is a schematic illustration of components of the implantable neuromodulation device of FIG. **1**.

[0014] FIG. **4** is another schematic illustration of components of the implantable neuromodulation device of FIG. **1**.

[0015] FIG. **5** is an illustration of an example circuit architecture of components of the implantable neuromodulation device of FIG. **1**.

[0016] FIG. **6** includes illustrations of stimulation pulses output by an implantable neuromodulation device based on a signal transmitted by the external unit.

[0017] FIG. **7** is an illustration of a signal sensed and recorded by the implantable neuromodulation system of FIG. **1** that includes a series of six stimulation responses, each elicited by the delivery of an electrical stimulation pulse at or near a nerve bundle.

[0018] FIG. **8**A is an illustration of a stimulation pulse delivered by the implantable neuromodulation system of FIG. **1**.

[0019] FIG. **8**B is an illustration of stimulation artifact of a stimulation response elicited by the delivery of the electrical stimulation pulse of FIG. **8**A.

[0020] FIG. **9** is an illustration of an evoked compound action potential elicited by the delivery of an electrical stimulation pulse of FIG. **8**A.

[0021] FIG. **10** is a flowchart of a method quantifying the average energy in evoked compound action potentials in real-time.

[0022] FIG. **11**A is a block diagram illustration of a deconvolution based inverse filter that may be used to implement the method of FIG. **10**.

[0023] FIG. **11**B is a block diagram illustration of an adaptive filter that may be used to implement the method of FIG. **10**.

[0024] FIGS. **12**A-**12**C are illustrations of three consecutive evoked stimulation responses (or evoked neural responses), each with a corresponding stimulation artifact and evoked compound action potential (not visible).

[0025] FIGS. **13**A-**13**C are illustrations of the three consecutive evoked stimulation responses (or evoked neural responses) of FIG. **12** after filtering in accordance with the method of FIG. **10**, wherein the presence of the stimulation artifacts is reduced, and the evoked compound action potentials are now visible.

[0026] FIG. **14** is an illustration of the mean squared error minima identifying the beginning of each evoked compound action potential for the three consecutive cycles of FIG. **13**.

[0027] FIG. **15** is a flowchart of another method for quantifying the average energy in evoked compound action potentials in real-time.

[0028] FIG. **16** is an illustration of a running average of a set of evoked compound action potentials.

[0029] FIG. **17** is a block diagram illustration of a proportional-integral (PI) closed loop controller to maintain optimal stimulation amplitude.

[0030] FIG. **18** is a flowchart of a method of adjusting stimulation therapy delivered to tissue of a patient by an implanted neuromodulation device.

DETAILED DESCRIPTION

[0031] Neurostimulation therapies are often limited due to a loss of therapeutic effect over time. Habituation and desensitization with increasing tolerance to the neurostimulation therapy is a considerable challenge in the treatment of disorders such as chronic pain and urinary dysfunction. This effect is exacerbated with the use of static stimulation waveforms. By applying multiple stimulation waveforms or a more stochastic dynamic pattern of waveform, the loss of therapeutic benefit can be delayed or potentially eliminated. However, to quantify the effect of stimulation some form of feedback is necessary to determine if sufficient neural recruitment of target neural fibers has been achieved. For example, neural recruitment may be evidenced by an evoked stimulation response (also referred to herein as a neural response) sensed at or near the target neural fibers and captured by a neuromodulation device. Failure to recruit the target neural fibers will provide no therapeutic benefits, whereas exceeding the upper limits of the therapeutic window can increase the risk of tissue damage over time and can cause pain. Therapeutic window (or treatment window), as used herein generally means the range between the perception by a patient of paresthesia sensation onset and discomfort from stimulation.

[0032] The current state of the art in peripheral nerve stimulation (PNS) to treat a range of chronic disorders, such as neuropathic pain and urinary disfunction, adopt open loop modalities, wherein the pulse generator output is a fixed waveform. While this approach is sufficient to provide therapeutic benefits, it is far from optimal, with adjustments to waveform amplitude performed by the patient. Variations in the electrical field at the nerve interface where the charge is delivered to a peripheral nerve fiber are common. Variations can be a result of changes in interface impedance, electrode movement and other interfering factors. Electrode movement can result from cardiac and respiratory motion or ambulation. This can impact the ability of the device to elicit an action potential (AP) response or provide the desired stimulation response consistently. Therefore, by dynamically adjusting stimulation doses based on feedback, consistent neural recruitment is possible. Stimulation dose, as used herein means the type and/or pattern of stimulation that is delivered in order to evoke a neural response at the target fibers. The type of stimulation may be, for example, electrical pulse waveform stimulation, where a pulse is defined by amplitude and pulse width. The pattern of stimulation may be a single pulse, a pulse train (a series of stimulation pulses separated by a brief time interval specified by a frequency parameter) or continuous stimulation for a period of time.

[0033] A means of stimulation feedback is highly desirable to optimize therapy delivery. Fundamentally, feedback

to simply acknowledge neural recruitment could have significant benefits. One of the failures of occipital nerve stimulation (ONS) to treat migraine has been due to lead movement and migration resulting in a failure to recruit target neural fibers, while patients believed they were receiving therapy. Moreover, the introduction of new stimulation waveforms that stimulate at sub-paresthesia levels complicate open loop systems further, where it becomes increasingly more difficult for a patient to adjust their stimulation therapy effectively.

[0034] Evoked compound action potentials (ECAPs) (also referred to herein as evoked AP responses or just AP responses) generated through electrical stimulation are difficult to detect as they have a low amplitude relative to the stimulation artifact produced. Even with a recording system with a high signal-to-noise ratio (SNR), stimulation artifact is several orders of magnitude greater than the physiological response evidenced by ECAPs. Recording of ECAPs is less difficult when measuring downstream of stimulation sites. For example, if a target nerve fiber is stimulated 100 mm distance from the measuring site, and the type of nerve fiber has a slow propagation velocity, then the artifact generated by stimulation will have decayed by the time the evoked AP response reaches the measurement site. However, in PNS devices it is not possible to have a downstream measurement site. Therefore, in PNS devices measurement electrodes must reside adjacent to the stimulation electrodes, and as a result the ECAPs will therefore be obscured by stimulation artifact.

[0035] It is desirable to provide a neuromodulation system that senses evoked compound action potentials (ECAPs) relative to a target nerve, and uses ECAPs as feedback to determine if a stimulation therapy was successful in eliciting a neural response from the target nerve. It is also desirable to have in such a system, an implantable component that has sensing and stimulating electrodes adjacent each other as part of the same single array of contacts and a processing component, either implantable or external, configured to process neural responses sensed by the sensing electrodes to detect ECAPs.

[0036] Accordingly, in one aspect of the disclosure, a neuromodulation system records and measures physiologically elicited neural signals from electrodes adjacent to the stimulation electrodes. The neuromodulation system includes an implantable neuromodulation device with both sensing and stimulation electrodes as part of the same array. The electrodes can be in a cuff arrangement that is attached to the nerve or an array that resides alongside the nerve bundle. The implantable neuromodulation device and sensing electronics are hardwired and located at the nerve site.

[0037] The signals acquired from the sensing electrodes are processed in real-time to derive measures or biomarkers that may be used to control stimulation by the implantable neuromodulation device. To this end, the acquired signals may be transmitted to an externa unit that resides outside of the body. The acquired signals may correspond to electrical activity of neural tissue resulting from the delivery of a stimulation therapy by the implantable neuromodulation device. These electrical activity signals are referred to herein as stimulation response signals.

[0038] In some aspects the acquired stimulation response signals are processed by digital filters to remove stimulation artifact. Once stimulation artifact is removed the residual stimulation response signal is processed to locate single fiber action potentials (APs) or electrically evoked compound action potentials (ECAPs) wavelets. Measures or biomarkers may be derived from these action potentials and may be used as a means to quantify current stimulation therapy. In further aspects, stimulation therapy can be automatically controlled in real-time based on measures or biomarkers.

[0039] With reference to FIG. **1**, disclosed herein is a wireless neuromodulation system **100**. The neuromodulation system **100** includes an implantable neuromodulation device **102** configured to be implanted in a body adjacent a nerve bundle, and an external unit **104** configured to provide power to the implantable neuromodulation device, to receive and process signals from the implantable neuromodulation device, and to transmit stimulation information to the implantable neuromodulation device.

[0040] The implantable neuromodulation device **102** includes one or more electrode platforms **106** connected to an electronics component **108**. The one or more electrode platforms **106** include a number of electrodes **110**. While the example implantable neuromodulation device **102** shown in FIG. **1** includes a single electrode platform **106** with four electrode **110**, an implantable neuromodulation device **102** may be configured with additional electrode platforms, and the electrode platforms may be configured with more or less than four electrodes.

[0041] With reference to FIG. **2**, the electronics component **108** of the implantable neuromodulation device **102** includes an application specific integrated circuit (ASIC) that includes circuitry that functions as an implantable pulse generator (IPG) **112** that generates and outputs stimulation therapy through the electrodes **110** of the one or more electrode platforms **106**. The ASIC may include additional circuitry that functions as an electrophysiology signal sensor/recorder **114** that senses electrical activity of neural tissue captured through the electrodes **110** of the one or more electrode platforms **106** and stores records **128** of the electrical activity. The electronics component **108** also includes power and communication components, e.g., a transceiver **116** and an antenna **118**. In an embodiment, the antenna **118** is a coil. The power and communication components are configured to transmit the records **128** of electrical activity to the external unit **104**.

[0042] The external unit **104** includes a battery **120** and power and communications components, e.g., a transceiver **122** and an antenna **124**. In an embodiment, the antenna **124** is a coil. The external unit **104** also includes a processor **126** (also referred to as a microcontroller). In some embodiments the processor **126** is configured to control the power and communications components, e.g., a transceiver **122** and an antenna **124**, to transmit and modulate a carrier signal **130**, e.g., a radio-frequency (RF) signal, in a way that provides power to the implantable neuromodulation device **102** and provides stimulation information that controls the delivery of neurostimulation by the implantable neuromodulation device **102**.

[0043] In some embodiments, the stimulation information transmitted by the external unit **104** may specify neurostimulation settings or parameters, e.g., pulse width, pulse amplitude, etc., used by the implantable neuromodulation device **102** to deliver stimulation therapy. In this case, the stimulation information transmitted by the external unit **104** is used to program the implantable pulse generator **112** of the implantable neuromodulation device **102**. In some embodiments, instead of being used to program the implantable

pulse generator **112** of the implantable neuromodulation device **102**, the stimulation information transmitted by the external unit **104** controls the delivery of neurostimulation therapy by the implantable neuromodulation device in real time. In this case, the stimulation information transmitted by the external unit **104** controls the timing of neurostimulation therapy and the neurostimulation settings or parameters, e.g., pulse width, pulse amplitude, etc., of the therapy.

[0044] The processor **126** of the external unit **104** is also configured to process neural information included in electrical activity of neural tissue sensed by the electrode platform **106** of the implantable neuromodulation device **102** and received by the external unit **104** from the implantable neuromodulation device. To this end, the processor **126** is configured to sense and analyze evoked compound action potentials (ECAPs) resulting from delivery of stimulation therapy by the implanted neuromodulation device, and to initiate changes in neuromodulation therapy to ensure delivery of effective therapy, e.g., therapy that results in neural recruitment, and to ensure effective sensing of electrical activity resulting from delivery of therapy.

[0045] With reference to FIG. **3**, in some embodiments the electrode platform **106** of the implantable neuromodulation device **102** includes an electrode-bearing body **302** having four electrodes **110**. In some embodiments, the electrodes **110** are uniformly spaced apart and separated by non-conductive regions **304** of the electrode-bearing body **302**.

[0046] In the configuration shown in FIG. **3**, two electrodes **110** (electrode **1** and electrode **2**) are coupled to the IPG **112** of the electronics component **108** for purposes of delivery electrical stimulation pulses to the body, and two electrodes **110** (electrode **3** and electrode **4**) are coupled to the signal sensor/recorder **114** of the electronics component **108** for purposes of sensing and recording electrical activity of neural tissue resulting from the delivery of a stimulation therapy by the implantable neuromodulation device. Each possible combination of two electrodes **110** can be configured in unipolar and bipolar modes. In this example, electrodes **1** and **2** are configured for bipolar electrical stimulation and electrodes **3** and **4** are configured for bipolar recording. In other configurations utilizing one electrode as a reference with the remaining electrodes configured as working electrodes, unipolar signals can be recorded, thereby enabling multiple combinations of bipolar signals to be derived.

[0047] With reference to FIG. **2**, in some embodiments the implantable neuromodulation device **102** is configured to receive radio-frequency (RF) signals **130** (also referred to as Tx signals or incident signals) from the external unit **104** and to output stimulation pulses to an electrode **110** based on the RF signals. In some embodiments the RF signals are in a medical device radiocommunication (MedRadio) frequency range, e.g., 401-406, 413-419, 426-432, 438-444, and 451-457 MHz. To this end, the IPG **112** of the implantable neuromodulation device **102** may be configured to produce stimulation pulses having different pulse energies based on the characteristics or configuration of the RF signal **130**. For example, as disclosed later below the characteristics or configuration of the RF signal **130** may determine the widths and/or amplitudes (and thus the pulse energy) of a stimulation pulse. The implantable neuromodulation device **102** is also configured to harvest energy from the RF signals **130**. Details on the generation and output of stimulation pulses and energy harvesting may be found in International Publication Number WO 2021/055146, entitled "Wirelessly Powered Stimulator." Details may also be found in "A 430-MHz Wirelessly Powered Implantable Pulse Generator With Intensity/Rate Control and Sub-1 μA Quiescent Current Consumption," Honeming Lyu et al, IEEE Transactions on Biomedical Circuits and Systems, Vol. 13, No. 1, February 2019.

[0048] The processor **126** of the external unit **104** is configured to control the operation of the transceiver **122** to generate an RF signal **130** having a configuration that determines stimulation pulses energy and to transmit the RF signal to the implantable neuromodulation device **102**. As noted above, the configuration of the RF signal **130**, in turn, controls a characteristic, e.g., width and/or amplitude, of the stimulation pulse produced by the IPG **112** of the implantable neuromodulation device **102**. For example, with reference to FIG. **2**, notches **136** can be included in the RF signal **130** to control the width of stimulation pulses, and to control the rate at which stimulation pulses are output by the IPG **112**. A notch **136** may be included by reducing the amplitude of the RF signal **130** to a percentage of the peak amplitude that is used for purposes of energy harvesting by the implantable neuromodulation device **102**.

[0049] With reference to FIG. **4**, in some embodiments, the electronics component **108** includes a rectifier **402**, a voltage reference **404**, an output voltage regulator **406**, a demodulator **408**, a switch **410**, an energy storage capacitor **412**, and stimulation circuitry **414**. The electronics component **108** receives RF signals **130** through the antenna **118** of the implantable neuromodulation device **102**. The rectifier **402** is configured to rectify the RF signal **130** to generate an output voltage (VDD). Depending on the open/closed state of the switch **410**, the output voltage VDD is coupled to the energy storage capacitor **412** or to the stimulation circuitry **414**. When coupled to the energy storage capacitor **412**, the output voltage VDD charges the energy storage capacitor.

[0050] Continuing with reference to FIG. **4**, the output voltage VDD provided by the rectifier **402** is compared to a voltage reference **404** through the output voltage regulator **406**. To this end, the output voltage regulator **406** is configured to compare fractions of VDD with a constant voltage reference **404**. In some configurations, when the output voltage VDD exceeds a first threshold value, e.g., 19/12 of the voltage reference **404**, a discharge current path (not shown in FIG. **4**) is enabled to discharge excess charge from the energy storage capacitor **412**. When the output voltage VDD is less than a second threshold value, e.g., 19/16 of the voltage reference **404**, the output voltage regulator **406** disables the demodulator **408**. Circuitry within the output voltage regulator **406** sets the first and second threshold values of the voltage reference **404** to thereby regulate the amplitude of the stimulation pulse. For example, in one configuration, the amplitude may be regulated to be in the range of 2.7 volts and 3.6 volts.

[0051] As shown in FIG. **4**, the RF signals **130** are also received at the demodulator **408**. The demodulator **408** is configured to process the RF signals **130** to control the on/off state of the switch **410**. To this end, and with additional reference to FIG. **5**, the demodulator **408** is configured to output a timing signal **502** that replicates the timing of notches **136** present in the Tx signal **130**. In view of this functionality, the demodulator **408** may be referred to as a notch detector. The high end, low end, and transient envelope of the Tx signal **130** are denoted as V_H, V_L, and V_{ENV},

respectively in the timing signal **502**. The Tx signal **130** is input to circuitry **504** of the demodulator that includes a V_{ENV} detection branch, a V_H detection branch, and a V_L detection branch. The V_{ENV} detection branch may use a relatively small capacitor C_{SM} to extract V_{ENV} from the Tx signal, while V_H and V_L can be extracted on larger capacitors with and without the AC input, respectively. The average V_M, e.g., the average of the high end V_H and the low end V_L, can be obtained through a resistive divider **506**.

[0052] The average V_M is input to a comparator **508** and compared with V_{ENV} to reconstruct the timing of notches **136** included in the Tx signal **130**. Capacitors C_{SM} and C_{LG} can be selected to be e.g., 100 fF and e.g., 36 pF, respectively. As C_{SM}<<C_{LG}, the average V_M can be considered as constant so that the discharging and charging of C_{SM} determines the delays from the starting point of a notch **136** and the ending point of a notch, respectively. The timing signal **502** at the output of the comparator **508** can then be sharpened by a following buffer **510** and then provided to the input of the switch **410**.

[0053] With continued reference to FIGS. **4** and **5**, upon detection of a notch **136**, the demodulator **408** sets the switch **410** to a closed state and holds the switch in the closed state until the notch is no longer detected. During the time the switch **410** is closed, the output voltage VDD and the energy storage capacitor **412** are coupled to the stimulation circuitry **414** and a stimulation pulse is generated and delivered through the electrodes **110**. The duration of the notch **136** determines the pulse width of the stimulation pulse, and thus the pulse energy of the stimulation pulse. Examples of different stimulation pulses output by the IPG **112** of the implantable neuromodulation device **102** are shown in FIG. **6**, which includes waveforms of 6.7 μs, 16.7 μs, and 26.7 μs stimulation pulses respectively triggered by 10 μs, 20 μs, and 30 μs notches.

[0054] Regarding the stimulation circuitry **414** of the electronics component **108**, the circuitry includes a DC-block capacitor **416** and a discharge resistor **418**. The DC-block capacitor **416** is coupled to the output **420** of the switch **410** and to the electrode **110**. The DC-block capacitor **416** provides charge-neutralization and prevents any release of DC charge to the electrode **110**. The discharge resistor **418** nulls the accumulated charge on C_{BCK}.

[0055] FIG. **7** illustrates a series of six stimulation responses **700**, each elicited by the delivery of an electrical stimulation pulse at or near a nerve bundle. FIG. **8**A illustrates one cathodic electrical stimulation pulse **702**. FIG. **8**B illustrates a zoomed in portion of a resultant stimulation artifact **706** of a stimulation response elicited by the delivery of the electrical stimulation pulse of FIG. **8**A. FIG. **9** illustrates a typical AP response **708** elicited by the delivery of an electrical stimulation pulse of FIG. **8**A.

[0056] With reference to FIG. **7**, each of six stimulation responses **700** resulting from electrical activity sensed at the nerve bundle exhibit an evoked stimulation response **704**, a resultant stimulation artifact **706**, and an evoked compound action potential (ECAP) response **708** (not visible in FIG. **7** or **8**, but shown in FIG. **9**). ECAP responses **708**, also referred to herein as action potential (AP) responses, occur uniformly, potentially under cardiac autonomic control. The significant difference in stimulation artifact **706** and AP response **708** amplitude is salient.

[0057] With reference to FIGS. **8**A and **8**B, stimulation artifact **706** is evident from both negative stimulus pulse **710** and positive charge recovery pulse **712**. In the example of FIG. **8**B an AP response **708** is generated at 20 ms, however, it is not identifiable in this example as the AP response is in the u V range and stimulation artifact **706** occupies the mV range. The AP response **708** occurs at 20 ms which is 7 ms from the onset of stimulation pulse **702**. Therefore, the AP is propagating at ~2 m/s which is common for Aδ or C fibers which require 7 ms to travel the 14 mm between electrodes as shown in FIG. **2**.

[0058] With reference to FIG. **9**, the typical AP response **708** elicited through stimulation is measured during a period with minimal artifact and noise. In this example the AP response **708** waveform is ~60 μV peak-to-peak which is considerably lower amplitude than the stimulation artifact **706** shown in FIG. **8**B.

[0059] Because the stimulation artifact **706** is proportional to the charge delivered, which is dependent on the pulse amplitude and width of the stimulation pulse **702**, the stimulation artifact generated at increased amplitude can be predicted once the stimulation artifact characteristics recorded on the sensing electrodes are determined and modeled. This is crucial as any stimulation artifact **706** removal routine that is adapted in the presence of neural signals will likely attenuate or remove the neural components, e.g., the AP response **708**, of interest.

[0060] In accordance with embodiments disclosed herein, a stimulation response signal, such as illustrated in FIG. **7**, is processed to attenuate, or reduce the presence of stimulation artifacts **706** without attenuating the AP response **708**. Once stimulation artifacts **706** are attenuated or filtered from the stimulation response signal, the remaining signal is processed to locate the AP response **708**. As the stimulation (i.e., the delivery of electrical stimulation pulse **702**) is periodic, once the AP response **708** to such stimulation is identified, the exact time lag between the evoked stimulation response **704** and the AP response **708** can be measured and used to predict the location of the AP response **708** after the delivery of each electrical stimulation pulse **702** (or after the detection of the evoked stimulation response **704**).

[0061] Knowing the location or time of occurrence of the AP response **708** relative to the time of evoked stimulation response **704** is beneficial because signal processing can be applied to that particular time segment (the segment containing the AP response **708**). The AP response **708** may be used to quantify the overall neural response to the electrical stimulation pulse **702**. For example, if the electrical stimulation pulse **702** is too low there will not be a neural response. In other words, there would be no stimulation response **700** as shown in FIG. **7**. As another example, if the electrical stimulation pulse **702** is too high, a high amplitude evoked stimulation response **704** within the stimulation response **700** may be noted, which may be outside of the treatment window. As previously mentioned, treatment window generally means the range between the perception by a patient of paresthesia sensation onset and discomfort from stimulation. In the case of a high amplitude evoked stimulation response **704** outside the treatment window, the patient would experience discomfort.

[0062] With reference to FIG. **10**, a method of quantifying the average energy in evoked compound action potentials (ECAPs) in a signal representing sensed electrical activity of a nerve is now described. The method involves reducing the presence of stimulation artifact **706** in a signal representing sensed electrical activity of a nerve. The method may be

performed by the implantable neuromodulation device **102** of FIG. **1**, either alone or in conjunction with the external unit **104**. The implantable neuromodulation device **102** is configured to acquire the signal representing sensed electrical activity of a nerve, and to deliver stimulation therapy.

[0063] At block **1000**, an implanted neuromodulation device **102** is activated to output stimulation therapy in the form of electrical stimulation pulses **702**. For example, when treating pain, a patient may switch the device on when pain is excessive. The stimulation pulses **702** delivered by the device are defined by stimulation parameters e.g., pulse width, pulse amplitude, etc.

[0064] At block **1001**, the current parameters of the electrical stimulation pulses **702** are processed by the implanted neuromodulation device **102** to determine if a stimulation level provided by the stimulation parameters is below a known activation threshold that elicits an AP response **708**. To this end, the device may calculate an energy level for the electrical stimulation pulses **702** based on the parameters of the pulse. The known activation threshold is predefined and typically determined for a patient during a clinical programming session. The activation threshold may be adjusted during follow-up clinical sessions.

[0065] If the stimulation level provided by the stimulation parameters of the electrical stimulation pulse **702** is not below the activation threshold (in other words, it is above the activation threshold and thus elicits an ECAP or AP response **708**), the process enters a filtering operation or filtering mode. To this end, the process proceeds to block **1011**, where a signal representing sensed electrical activity of a nerve and acquired by the implanted neuromodulation device **102** is processed by an adaptive filter. The acquired signal representing sensed electrical activity of a nerve may correspond to a stimulation response **700** shown in FIG. **7** or zoomed in portion of the signal like the one shown in FIG. **8**B.

[0066] The main purpose of the filtering operation (block **1011**) is to significantly attenuate the stimulation artifact **706** generated through stimulation. The ECAP signals or AP responses **708** can be better derived if they are separated from the stimulation artifact **706** that is typically orders of magnitude greater than the physiological signal of interest, as illustrated in FIG. **7**. In one approach, a model is used to predict the location (time of appearance) of a stimulation artifact **706** in the recorded signal and perform a linear subtraction to thereby significantly attenuate or remove the stimulation artifact from the recorded signal.

[0067] As illustrated in FIG. **10**, when an electrical stimulation pulse **702** is applied (block **1000**) and is not below a threshold (block **1001**) that would elicit a physiological response i.e., an AP response **708**, the stimulation artifact **706** generated by a particular applied electrical stimulation pulse **702** having a pulse waveform is measured at the recording electrodes (electrodes **3** and **4** in FIG. **3**). The medium (e.g., neural fiber) effects between the stimulating electrodes (electrodes **1** and **2** in FIG. **3**) and recording electrodes (electrodes **3** and **4** in FIG. **3**) is modeled. A typical filter that preforms this modeling in real-time is an adaptive filter where the pulse waveform of the electrical stimulation pulse **702** delivered by the stimulating electrodes (electrodes **1** and **2** in FIG. **3**) is the input signal and the recorded signal sensed at the recording electrodes (electrodes **3** and **4** in FIG. **3**) is the reference signal.

[0068] The adaptive filter is one where the filter weights are adjusted in real-time to minimize the error between the input signals (the pulse waveform of the electrical stimulation pulse **702**) and reference signals as will be described below. If for example the adaptive filter has an FIR structure, then it can be described as follows where Nis the filter model order:

$$y[k] = \sum_{n=0}^{N-1} W[n]x[k-n]$$

[0069] At block **1012**, the filtered signal output by the adaptive filter is processed to detect AP responses **708**, where an AP response signal is detected for each stimulation response **700**. The AP response **708** may correspond to a signal like the one shown in FIG. **9**. Several methods can be employed to detect the AP response **708**. Given the fast conduction of AP response **708** on most neural fibers, the response will appear during stimulation. The AP response **708** can be measured in a time window with a fixed duration from the onset of a stimulation pulse **702**. Here the peak can simply be measured and used for titration on the next cycle. Methods such as cross-correlation techniques can be used to detect the AP response **708** waveform or spike, or simple threshold techniques. However, sufficient stimulation artifact **706** should be attenuated where the AP response **708** will be of greater amplitude than the stimulation artifact enabling a simple threshold detection approach.

[0070] At block **1013**, the detected AP responses **708** are processed to derive an average AP response signal using known waveform averaging techniques. If sufficient stimulation artifact **706** is removed the AP response **708** will be clear in the average waveform calculated in block **1013**. The average AP response signal may be used to derive a measure relative to the evoked stimulation response **704**. For example, a measure of relative amplitude between the average AP response signal and an average evoked stimulation response **704** may be a basis for adjusting or changing one or more stimulation parameters, e.g., a different pulse-width, duty cycle or stimulation frequency of the stimulation therapy.

[0071] At block **1014**, a determination is made to adjust one or more of the stimulation parameters defining the stimulation pulses **702** based on the measure obtained in the average waveform process of block **1013**. In some embodiments, at least one of the plurality of stimulation parameters (e.g., pulse amplitude, pulse width, duty cycle, stimulation frequency) may be decreased in response to the measure being above a first threshold. The first threshold may be an amplitude indicative of a stimulation therapy that is outside the treatment window of the patient so as to cause discomfort or pain. This may occur when the measure is based on high amplitude ECAP responses. The first threshold may be determined and set based on patient feedback to different stimulation therapies during implant of the implantable neuromodulation device, subject to post-implant updating based on subsequent patient feedback.

[0072] In some embodiments, at least one of the plurality of stimulation parameters (e.g., pulse amplitude, pulse width, duty cycle, stimulation frequency) may be increased in response to the measure being below a second threshold. The second threshold may be an amplitude indicative of a stimulation therapy that does not sufficiently elicit neural

activity. This may occur when the measure is based on low amplitude or no amplitude ECAP responses. The second threshold may be determined based on sensing and analysis of stimulation responses during implant of the implantable neuromodulation device, subject to post-implant updating based on subsequent sensing and analysis.

[0073] In some embodiments, the plurality of stimulation parameters may be left at current values in response to the measure being below the first threshold (so as not to cause patient discomfort or pain) and above the second threshold (so as to elicit sufficient neural activity).

[0074] If none of the stimulation parameters has changed the process returns to block **1001** where the stimulation parameters, e.g., pulse width, pulse amplitude, are reviewed again to confirm that the stimulation level provided by the stimulation parameters is below the activation threshold. The process then cycles through the filtering operation of blocks **1011**, **1012**, and **1013** where another signal representing sensed electrical activity of a nerve that is acquired by the device is processed.

[0075] Returning to block **1014**, if one or more of the stimulation parameters has changed the process proceeds to block **1015** where the adaptive filter weights are reset or initialized. The filter weights are reset to account for changes to characteristics of the stimulation artifact **706** that result from changes to the stimulation parameters.

[0076] The process then returns to block **1001** where the adjusted set of stimulation parameters are reviewed to determine if the stimulation level provided by the stimulation parameters is below the activation threshold. For example, if stimulation parameters are changed, where the level of stimulus is decreased either by reducing the duty cycle or amplitude for instance, the new set of stimulation parameters may fail to provide enough energy to elicit a nerve response.

[0077] At any time during the process of FIG. **10**, if the stimulation level is determined at block **1001** to be below the activation threshold, the process enters a learning operation or learning mode. To this end, the process proceeds to block **1002** where filter weights are updated. Algorithms such as a least mean squares (LMS) or recursive least square (RLS) algorithms are examples of routines to update weights of the adaptive filter (applied in block **1011**) by minimizing the error between the predicted and measured signal. In a dynamic system where the medium, e.g., neural fibers, may change slightly, for example pressure on the tissue, the characteristics of the medium may change. Therefore, updating the filter weights in real-time when new data is available enhances the performance of the adaptive filter and provides better approximations of the stimulation artifact **706**.

[0078] At block **1004**, the stimulation level is increased by an incremental amount by adjusting one or more of the stimulation parameters. For example, the level of stimulus may be increased by increasing the duty cycle or amplitude for instance. The process returns to block **1001**, where if the stimulation level is still below the activation threshold the process cycles through blocks **1002** and **1004** until the activation threshold is reached at block **1001**. To ensure physiological information of interest is not filtered, the learning algorithm corresponding to the blocks **1002**, **1004** loop is only applied when the stimulation levels are below the activation threshold for an AP response.

[0079] To adapt the filter characteristics when switching to filtering mode (blocks **1011**, **1012** and **1013**) when the stimulation level exceeds the activation threshold at block **1001**, a stimulation model is updated which is used to calculate the filter gain for new stimulation settings. This stimulation model can be a simple scalar coefficient that is updated or can utilize a curve fitting function, such as a second order polynomial or linear regression method.

[0080] An example of an inverse filter to process a discrete time-series that can be used for fast initialization of a set of Finite Impulse Response (FIR) filter coefficients (used to initialize weights in block **1015**) is illustrated in FIG. **11**A. The input signal x[k] is convolved with the degradation filter w[k] and the residual is compared to the reference s[k] to calculate an error e[k]. A linear Weiner filter with weights w[k] can approximate the degradation effect from tissue as the stimulation pulse x[k] is applied to bipolar electrodes **1** and **2** discussed earlier. The causal FIR Wiener filter can adopt least squares estimate with input matrix X, output vector y, to determine filter weights derived as follows:

$$W = (X^T X)^{-1} X^T y.$$

[0081] The output y[k] is the measured signal recorded from bipolar electrodes **3** and **4** described earlier. Such deconvolution filters are typically high-pass and can therefore amplify noise. In such circumstances it is advantageous to add noise to ensure a degree of noise reduction in the filter response by using s[k] to calculate the filter weights. The noise can be Gaussian or bandlimited Gaussian, where the noise signal n[k] is high pass filtered to create noise in the only the higher band, thereby creating attenuation at higher frequencies in the Wiener filter response, having a low pass effect. This requires a block estimation approach that is primarily suitable for initialization purposes.

[0082] An example of a real-time adaptive filter (applied in block **1011**) is illustrated in FIG. **11**B where the filter weights w[k] are adapted based on a learning algorithm such as the Least Means Square (LMS) or Recursive Least Square (RLS) methods. A cost function such as mean square error (MSE) is used to minimize the error between the filter residual y[k] and the desired signal d[k]. The desired signal is the measured stimulation artifact recorded between electrodes **3** and **4** in response to the stimulation waveform x[k]. When the MSE is at a minimum, the coefficients have converged, and the filter adequately models the characteristics of the tissue being stimulated. If the tissue changes due to electrode movement the filter will adapt. Convergence can occur quicker when initialized using the Wiener filter.

[0083] FIGS. **12**A-**12**C are illustrations of three consecutive evoked stimulation responses (or evoked neural responses), each with a corresponding stimulation artifact and evoked compound action potential (not visible). FIGS. **13**A-**13**C are illustrations of the three consecutive evoked stimulation responses (or evoked neural responses) of FIG. **12** after filtering in accordance with the method of FIG. **10**, wherein the presence of the stimulation artifacts is reduced, and the evoked compound action potentials are now visible.

[0084] It is evident from FIGS. **12**A-**12**C that no APs or ECAPs are visible, and the stimulation artifact **706** is approximately 7 mV peak-to-peak. With reference to FIGS. **13**A-**13**C, the result of filtering the stimulation artifact **706** from the stimulation response **700** waveforms with the adaptive filter is present where the stimulation artifact has

been reduced to approximately 100 μV peak-to-peak with a reduction of ~70:1. The AP response **708** signals are now evident at 20 ms with similar amplitude, and at a level that is identifiable. The AP response **708** signals can now be processed through spike sorting or template matching algorithms that can be applied to the filter residual to determine the presence and location of the AP response **708** elicited through stimulation.

[0085] For example, the results of a template matching routine are illustrated in FIG. **14** for each of the 3 cycles presented, using a MSE measurement to determine fit and location. The MSE approach clearly identifies the AP response **708** location onset at 20 ms where the error is a minimum for each cycle. This approach could be enhanced by combining the MSE method with a cross-correlation function, although cross-correlation can be erroneously impacted by amplitude.

[0086] With reference to FIG. **15**, another method of quantifying the average energy in AP response **708** in a signal representing sensed electrical activity of a nerve is now described. This method also involves reducing the presence of stimulation artifact **706** in a signal representing sensed electrical activity of a nerve.

[0087] In this method, a pseudo real-time approach is adopted that processes a segment of data as an alternative to a true real-time sample-by-sample strategy. This is acceptable as any adjustment to stimulation therapy can be performed in real-time prior to the next stimulation cycle. In circumstances where the frequency response of the medium (the neural fibers) being characterized is relatively static, it is often advantageous to perform filtering in the frequency domain, where instantaneous errors are eliminated.

[0088] At block **1500**, an implanted neuromodulation device **102** is activated to output stimulation therapy in the form of electrical stimulation pulses **702**. For example, when treating pain, a patient may switch the device on when pain is excessive. The stimulation pulses **702** delivered by the device are defined by stimulation parameters e.g., pulse width, pulse amplitude, etc.

[0089] At block **1501**, the current parameters of the electrical stimulation pulses **702** are processed by the device to determine if a stimulation level provided by the stimulation parameters is below a known activation threshold that elicits an AP response **708**. To this end, the device may calculate an energy level for the electrical stimulation pulses **702** based on the parameters of the pulse. The known activation threshold is predefined and typically determined for a patient during a clinical programming session. The activation threshold may be adjusted during follow-up clinical sessions.

[0090] If the stimulation level provided by the stimulation parameters of the electrical stimulation pulse **702** is below the activation threshold (in other words, it is not above the activation threshold and thus does not elicit an AP response), the process proceeds to block **1503** where a Fast Fourier Transform (FFT) is applied to an acquired stimulation response **700** signal to provide a frequency spectrum representation of the stimulation response signal.

[0091] At block **1504**, the mean energy of the frequency spectrum is calculated and stored.

[0092] At block **1505**, a stimulation model is adapted. The stimulation model is used to estimate the peak spectral energy based on the amplitude of the stimulus when attempting to filter the artifact. A spectral subtraction must be performed using an artifact spectrum that is obtained below the activation threshold to ensure the physiologic information is not present and therefore will not be removed following subtraction.

[0093] At block **1506**, the frequency spectra are averaged and normalized. This process has the effect of increasing the artifact to random noise ratio.

[0094] At block **1507**, one or more parameters of the stimulation therapy are changed in order to increase the stimulus being delivered, and the process returns to block **1501**. The loop of blocks **1503**, **1504**, **1505**, **1506**, **1507**, **1501** is repeated until the stimulation level provided by the stimulation parameters of the electrical stimulation pulse **702** is not below the activation threshold (in other words, it is above or exceeds the activation threshold and thus elicits an AP response), at which point the process proceeds to block **1510**.

[0095] At block **1510**, the stimulation model of block **1504** provides the spectral filter gain to block **1510**. As the mean spectral energy has been calculated for each increment in stimulus (at block **1507**) under the activation threshold, a simple model can be used (at block **1505**) to estimate the peak amplitude of artifact in the frequency domain with the current stimulus above the activation threshold. This could be a simple extrapolation.

[0096] At block **1511** an acquired stimulation response **700** signal that includes physiologic information and stimulation artifact **706** is transformed into the frequency domain by FFT.

[0097] At block **1512**, the normalized artifact averaged spectrum calculated in block **1505** is subtracted from the physiologic spectrum of block **1511**.

[0098] At block **1513**, the resultant is transformed back to the time domain by inverse FFT.

[0099] At block **1514**, the time domain signal resulting from inverse FFT (block **1513**) is processed to detect AP responses **708**, where an AP response signal is detected for each stimulation response **700**. The AP response **708** is detected based on a known time offset from the evoked stimulation response **704**. The AP response **708** may correspond to a signal like the one shown in FIG. **9**.

[0100] At block **1515**, the AP responses **708** detected in the block **1514** are processed to derive an average AP response signal using known waveform averaging techniques. The average AP response signal may be used to derive a measure relative to the evoked stimulation response **704**. For example, a measure of relative amplitude between the average AP response signal and an average evoked stimulation response **704** may be a basis for adjusting or changing one or more stimulation parameters, e.g., a different pulse-width, duty cycle or stimulation frequency of the stimulation therapy.

[0101] In the method of FIG. **15**, the loop taken when no AP response is elicited (outcome at block **1501** is "yes") estimates the stimulation-based degradation frequency spectrum (output of block **1503**). This estimated frequency spectrum is subsequently used in the loop taken when an AP response is elicited (outcome at block **1501** is "no") when at block **1512** the estimated spectrum from block **1503** is subtracted from the spectrum of the acquired stimulation response (output of block **1511**) to estimate the physiologic spectrum. The degradation spectrum (output of block **1503**) is multiplied by a gain function (block **1510**) based on the stimulation model (block **1505**) prior to spectral subtraction.

At block **1513**, the resultant spectrum is transformed back to the time-domain block by combining the filtered spectrum with the original phase of the recorded waveform, i.e., the acquired stimulation response signal.

[0102] Regarding blocks **1013** and **1515**, an example of averaging detected AP response **708** signals is illustrated in FIG. **16**. This represents five averaged cycles of the detected AP responses **708** at 20 ms. Applying a running average function enhances the SNR for every cycle and attenuates random noise and artifact. This averaged waveform can be used as a biomarker to evaluate the physiological response to stimulation.

[0103] The average waveform biomarker described above can provide biofeedback on response from stimulation. Such a marker can alert a patient to zones that could cause pain from stimulus, or conversely not provide a therapeutic effect, or fail to elicit a response at all. Keeping stimulation pulse **702** delivery within the therapeutic window is critical. Here stimulus can be automated by utilizing this biomarker as a process variable to maintain homeostasis by keeping titration levels at the optimal dose response level. An adaptive controller can be used that adjusts the level of stimulation based on this feedback to keep the response at the ideal desired level or setpoint. The stimulation is adapted based on the average waveform amplitude of AP responses **708**.

[0104] A classic Proportional-Integral (PI) controller, as illustrated in FIG. **17**, is an example of an approach to maintain the desired AP response **708** amplitude elicited from a stimulation pulse **702** at a controller setpoint. The error which is the difference between the average AP biomarker ZAP and the setpoint is multiplied by a proportional gain Kp, which adjusts the instantaneous error in proportion to the desired response. A running average of the error is also multiplied by the integral gain KI and summed with the P contribution. The adjusted stimulation amplitude Ak for the kth cycle is applied and resultant AP response **708** signal recorded and the biomarker ZAP calculated.

[0105] FIG. **18** is a flowchart of a method of adjusting stimulation therapy delivered to tissue of a patient by an implanted neuromodulation device. In some embodiments, the method is performed by a neuromodulation system **100** that includes the implanted neuromodulation device **102** and an external unit **104**, such as shown in FIGS. **1** and **2**. In some embodiments, the method is performed entirely by the implanted neuromodulation device **102**.

[0106] At block **1802**, electrical activity of the tissue resulting from a delivery of a stimulation therapy to the tissue through the implanted neuromodulation device **102** is sensed. For example, the electrical activity may be sensed by the implanted neuromodulation device **102**. This step of the method is referred to herein as "step a." The stimulation therapy delivered through the implanted neuromodulation device **102** is defined by a plurality of stimulation parameters, and the sensed electrical activity includes a stimulation response **700** having an evoked stimulation response **704**, a stimulation artifact **706**, and ideally an ECAP response **708**.

[0107] At block **1804**, a measure based on the ECAP response **708** and the evoked stimulation response **704** is determined. This step of the method is referred to herein as "step b." With reference to the series of blocks **1011**/**1012**/**1013** of FIG. **10**, in some embodiments, a measure based on the ECAP response **708** and the evoked stimulation response **704** is determined by obtaining an amplitude of the ECAP response **708**, obtaining an amplitude of the evoked stimulation response **704**, and calculating a relationship between the amplitude of the ECAP response and the amplitude of the evoked stimulation response. For example, the relationship may be a ratio of the amplitudes, such as an ECAP-amplitude/stimulation-response-amplitude ratio.

[0108] An amplitude of the ECAP response **708** may be obtained by applying a filter to the stimulation response (block **1011**) and locating the ECAP response **708** in the filtered stimulation response (block **1012**). The ECAP response **708** may be located by locating the ECAP response **708** relative to the evoked stimulation response **704** based on a known time offset. As described above with reference to FIG. **10**, the known time offset may be determined based on previously sensed electrical activity of the tissue resulting from stimulation therapy.

[0109] Once the ECAP response **708** is located in the filtered stimulation response (block **1012**), the amplitude of the ECAP response **708** can be derived from a waveform corresponding to the ECAP response. The amplitude of the ECAP response **708** may be derived from the waveform corresponding to the ECAP response **708** by calculating an average waveform from a plurality of ECAP responses (block **1013**), and deriving the amplitude from the average waveform.

[0110] Regarding the filter that is applied to the stimulation response (block **1011**), in some embodiments this filter is an adaptive filter having a plurality of filter weights that may be updated as needed. For example, in some instances an ECAP response **708** may not be present in the stimulation response **700**. This may occur, for example, when the stimulation therapy is below an activation threshold that elicits an ECAP response **708** for the patient (block **1001** outcome is "Yes"). In this case, the filter weights are updated. In some embodiments, the filter-weight update process is the loop of blocks **1002**/**1004**/**1001** in FIG. **10**, wherein the filter weights are updated (block **1002**) and one or more of the plurality of stimulation parameters is incrementally increased (block **1004**) until the stimulation therapy is not below the activation threshold that elicits an ECAP response **708** for the patient (block **1001** outcome is "No").

[0111] At block **1806**, after a measure based on ECAP response **708** is determined, a determination is made to adjust or not adjust one or more of the plurality of stimulation parameters of the stimulation therapy based on the measure (block **1014**). The step of the method is referred to herein as "step c." In some embodiments, at least one of the plurality of stimulation parameters (e.g., pulse amplitude, pulse width, etc.) is decreased in response to the measure being above a first threshold. As previously described, the first threshold may be an amplitude indicative of a stimulation therapy that is outside the treatment window of the patient so as to cause discomfort or pain. In some embodiments, at least one of the plurality of stimulation parameters (e.g., pulse amplitude, pulse width, etc.) is increased in response to the measure being below a second threshold. As previously described, the second threshold may be an amplitude indicative of a stimulation therapy that does not elicit neural activity (e.g., an ECAP response **708** for the patient). In some embodiments, the stimulation parameters are left at current values in response to the measure being below the first threshold and above the second threshold.

[0112] As previously described with reference to block **1804**, in some embodiments the filter that is applied to the stimulation response (block **1011**) to obtain the ECAP response **708** is an adaptive filter having a plurality of filter weights. In some embodiments, these filter weights are reset (block **1015**) depending on the outcome of block **1806**. For example, the filter weights may be reset when at least one of the plurality of stimulation parameters (e.g., pulse amplitude, pulse width, etc.) is decreased. The filter weights may also be reset when at least one of the plurality of stimulation parameters (e.g., pulse amplitude, pulse width, etc.) is increased.

[0113] As previously described, in some embodiments, the method of FIG. **18** is performed by a neuromodulation system **100** that includes an implanted neuromodulation device **102** and an external unit **104**. In one such an embodiment, the implanted neuromodulation device performs step a (block **1802**), while an external unit performs step b (block **1804**) and step c (block **1806**). As part of step a (block **1802**), the implanted neuromodulation device **102** transmits the sensed signal corresponding to the sensed electrical activity and the external unit **104** receives the sensed signal. The implanted neuromodulation device **102** may also deliver the stimulation therapy to tissue. Also as previously described, in some embodiments, the method of FIG. **18** is performed entirely by an implantable neuromodulation device **102**.

[0114] The various aspects of this disclosure are provided to enable one of ordinary skill in the art to practice the present invention. Various modifications to exemplary embodiments presented throughout this disclosure will be readily apparent to those skilled in the art. Thus, the claims are not intended to be limited to the various aspects of this disclosure but are to be accorded the full scope consistent with the language of the claims. All structural and functional equivalents to the various components of the exemplary embodiments described throughout this disclosure that are known or later come to be known to those of ordinary skill in the art are expressly incorporated herein by reference and are intended to be encompassed by the claims. Moreover, nothing disclosed herein is intended to be dedicated to the public regardless of whether such disclosure is explicitly recited in the claims. No claim element is to be construed under the provisions of 35 U.S.C. § 112, sixth paragraph, unless the element is expressly recited using the phrase "means for" or, in the case of a method claim, the element is recited using the phrase "step for."

1. A neuromodulation system comprising:

an implantable neuromodulation device comprising:

an electrode platform;

an pulse generator coupled to the electrode platform and configured to output a stimulation therapy through the electrode platform, wherein the stimulation therapy is defined by a plurality of stimulation parameters,

a sensor/recorder coupled to the electrode platform and configured to:

process the plurality of stimulation parameters to determine if the stimulation therapy is above a known activation threshold that elicits an evoked compound action potential (ECAP) response,

in response to the stimulation therapy being above the known activation threshold, sense electrical activity of tissue resulting from a delivery of a stimulation therapy to the tissue, wherein the sensed electrical activity includes a stimulation response comprising an evoked stimulation response, a stimulation artifact and an ECAP response,

in response to the stimulation therapy being below the known activation threshold, refrain from sensing electrical activity of the tissue resulting from the stimulation therapy, and adjusting one or more of the plurality of stimulation parameters until the stimulation therapy is above a known activation threshold; and

a transceiver coupled to the sensor/recorder and configured to transmit a sensed signal corresponding to the electrical activity; and

an external unit comprising:

a transceiver configured to receive the sensed signal from the implantable neuromodulation device; and

a processor configured to determine a measure based on the ECAP response and the evoked stimulation response; and to determine whether to adjust one or more of the plurality of stimulation parameters of the stimulation therapy based on the measure.

2. The neuromodulation system of claim **1**, wherein to determine a measure based on the ECAP response and the evoked stimulation response, the processor is configured to:

obtain an amplitude of the ECAP response; and

obtain an amplitude of the evoked stimulation response,

wherein the measure is a relationship between the amplitude of the ECAP response and the amplitude of the evoked stimulation response.

3. The neuromodulation system of claim **2**, wherein to obtain an amplitude of the ECAP response, the processor is configured to:

apply a filter to the stimulation response;

locate the ECAP response in the filtered stimulation response; and

derive the amplitude from a waveform corresponding to the ECAP response.

4. The neuromodulation system of claim **3**, wherein to locate the ECAP response, the processor is configured to locate the ECAP response relative to the evoked stimulation response based on a known time offset.

5. The neuromodulation system of claim **4**, wherein the processor is further configured to determine the known time offset based on previously sensed electrical activity of the tissue resulting from the stimulation therapy.

6. The neuromodulation system of claim **3**, wherein to derive the amplitude from a waveform corresponding to the ECAP response, the processor is configured to:

calculate an average waveform from a plurality of ECAP responses; and

derive the amplitude from the average waveform.

7. The neuromodulation system of claim **3**, wherein the filter is an adaptive filter having a plurality of filter weights, and the processor is further configured to, in response to the stimulation therapy being below an activation threshold that elicits an ECAP response:

update the plurality of filter weights.

8. The neuromodulation system of claim **7**, wherein to update the plurality of filter weights the processor is configured to:

incrementally increase at least one of the plurality of stimulation parameters and update the plurality of filter

weights until the stimulation therapy is not below the activation threshold that elicits an ECAP response.

9. The neuromodulation system of claim **2**, wherein to determine whether to adjust one or more of the plurality of stimulation parameters of the stimulation therapy based on the measure, the processor is configured to:

decrease at least one of the plurality of stimulation parameters in response to the measure being above a first threshold;

increase at least one of the plurality of stimulation parameters in response to the measure being below a second threshold; and

leave the plurality of stimulation parameters at current values in response to the measure being below a first threshold and above the second threshold.

10. The neuromodulation system of claim **9**, wherein the processor is further configured to, in response to one of decreasing at least one of the stimulation parameters or increasing at least one of the stimulation parameters, resetting one or more of a plurality of filter weights of an adaptive filter configured to be applied to the stimulation response.

11. (canceled)

12. A method of adjusting stimulation therapy delivered to tissue of a patient by an implanted neuromodulation device, wherein the stimulation therapy is defined by a plurality of stimulation parameters, the method comprising:

a) processing the plurality of stimulation parameters to determine if the stimulation therapy is above a known activation threshold that elicits an evoked compound action potential (ECAP) response;

b) in response to the stimulation therapy being above the known activation threshold:

i) sensing electrical activity of the tissue resulting from a delivery of a stimulation therapy to the tissue through the implanted neurostimulation device, wherein the sensed electrical activity includes a stimulation response comprising an evoked stimulation response, a stimulation artifact and an ECAP response;

ii) determining a measure based on the ECAP response and the evoked stimulation response; and

iii) determining whether to adjust one or more of the plurality of stimulation parameters of the stimulation therapy based on the measure; and

c) in response to the stimulation therapy being below the known activation threshold:

i) refraining from sensing electrical activity of the tissue resulting from the stimulation therapy; and

ii) adjusting one or more of the plurality of stimulation parameters until the stimulation therapy is above a known activation threshold.

13. The method of claim **12**, wherein determining a measure based on the ECAP response and the evoked stimulation response comprises:

obtaining an amplitude of the ECAP response; and

obtaining an amplitude of the evoked stimulation response,

wherein the measure is a relationship between the amplitude of the ECAP response and the amplitude of the evoked stimulation response.

14. The method of claim **13**, wherein obtaining an amplitude of the ECAP response comprises:

applying a filter to the stimulation response;

locating the ECAP response in the filtered stimulation response; and

deriving the amplitude from a waveform corresponding to the ECAP response.

15. The method of claim **14**, wherein locating the ECAP response comprises locating the ECAP response relative to the evoked stimulation response based on a known time offset.

16. The method of claim **15**, further comprising determining the known time offset based on previously sensed electrical activity of the tissue resulting from the stimulation therapy.

17. The method of claim **14**, wherein deriving the amplitude from a waveform corresponding to the ECAP response comprises:

calculating an average waveform from a plurality of ECAP responses; and

deriving the amplitude from the average waveform.

18. The method of claim **14**, wherein the filter is an adaptive filter having a plurality of filter weights, and further comprising, in response to the stimulation therapy being below an activation threshold that elicits an ECAP response for the patient:

updating the plurality of filter weights.

19. The method of claim **18**, wherein updating the plurality of filter weights comprises:

incrementally increasing at least one of the plurality of stimulation parameters and updating the plurality of filter weights until the stimulation therapy is not below the activation threshold that elicits an ECAP response for the patient.

20. The method of claim **13**, wherein determining whether to adjust one or more of the plurality of stimulation parameters of the stimulation therapy based on the measure comprises:

decreasing at least one of the plurality of stimulation parameters in response to the measure being above a first threshold;

increasing at least one of the plurality of stimulation parameters in response to the measure being below a second threshold; and

leaving the plurality of stimulation parameters at current values in response to the measure being below a first threshold and above the second threshold.

21. The method of claim **20**, further comprising, in response to one of decreasing at least one of the stimulation parameters or increasing at least one of the stimulation parameters, resetting one or more of a plurality of filter weights of an adaptive filter configured to be applied to the stimulation response.

22. The method of claim **12**, wherein:

steps a, bi, ci, and cii are performed by the implanted neuromodulation device; and

steps bii and biii are performed by an external unit; and

further comprising transmitting, by the implanted neuromodulation device, a sensed signal corresponding to the sensed electrical activity.

23. (canceled)

24. (canceled)

25. (canceled)

26. (canceled)

27. (canceled)
28. (canceled)
29. (canceled)
30. (canceled)
31. (canceled)

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