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Denison et al.

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(45) **Date of Patent: Nov. 26, 2013**

(54) **SEIZURE PREDICTION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1565 days.

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(22) Filed: **Apr. 30, 2007**

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(51) **Int. Cl.**
A61B 5/04 (2006.01)
A61B 5/00 (2006.01)

(52) **U.S. Cl.**
USPC **600/544**; 600/547

(58) **Field of Classification Search**
USPC 600/544, 545, 547; 607/45
See application file for complete search history.

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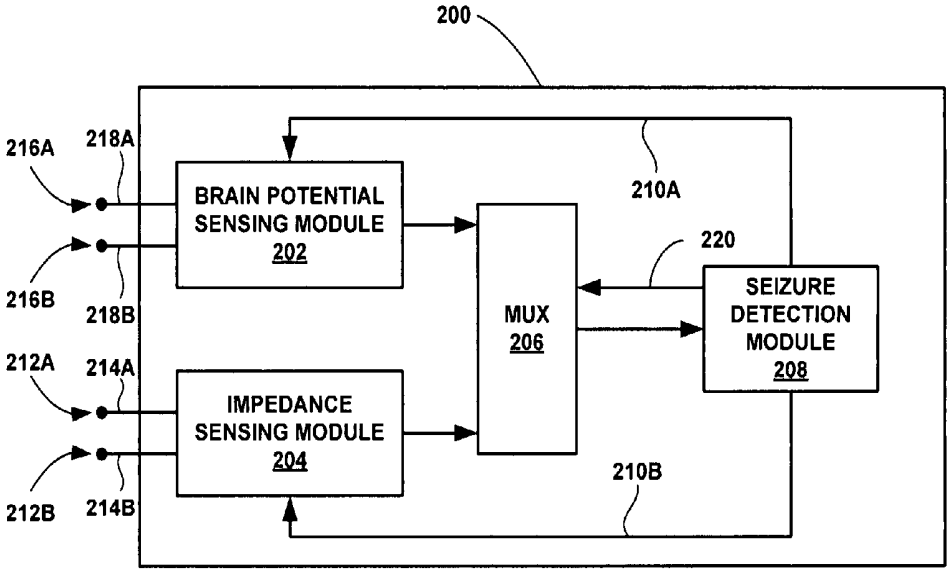
(74) *Attorney, Agent, or Firm* — Shumaker & Sieffert, P.A.

(57) **ABSTRACT**

Seizure prediction systems and methods include measuring impedance and a potential within a brain of a patient to determine whether the brain is in a state indicative of a possibility of seizure. In some embodiments, at least one of the measured impedance or the measured potential may be used as a primary indication of the brain state indicative of a possibility of seizure. In one embodiment, if one of the measured impedance or the measured potential indicates a seizure, the other measurement (impedance or potential) may be used to validate whether the brain is in the state indicative of the possibility of seizure.

52 Claims, 16 Drawing Sheets



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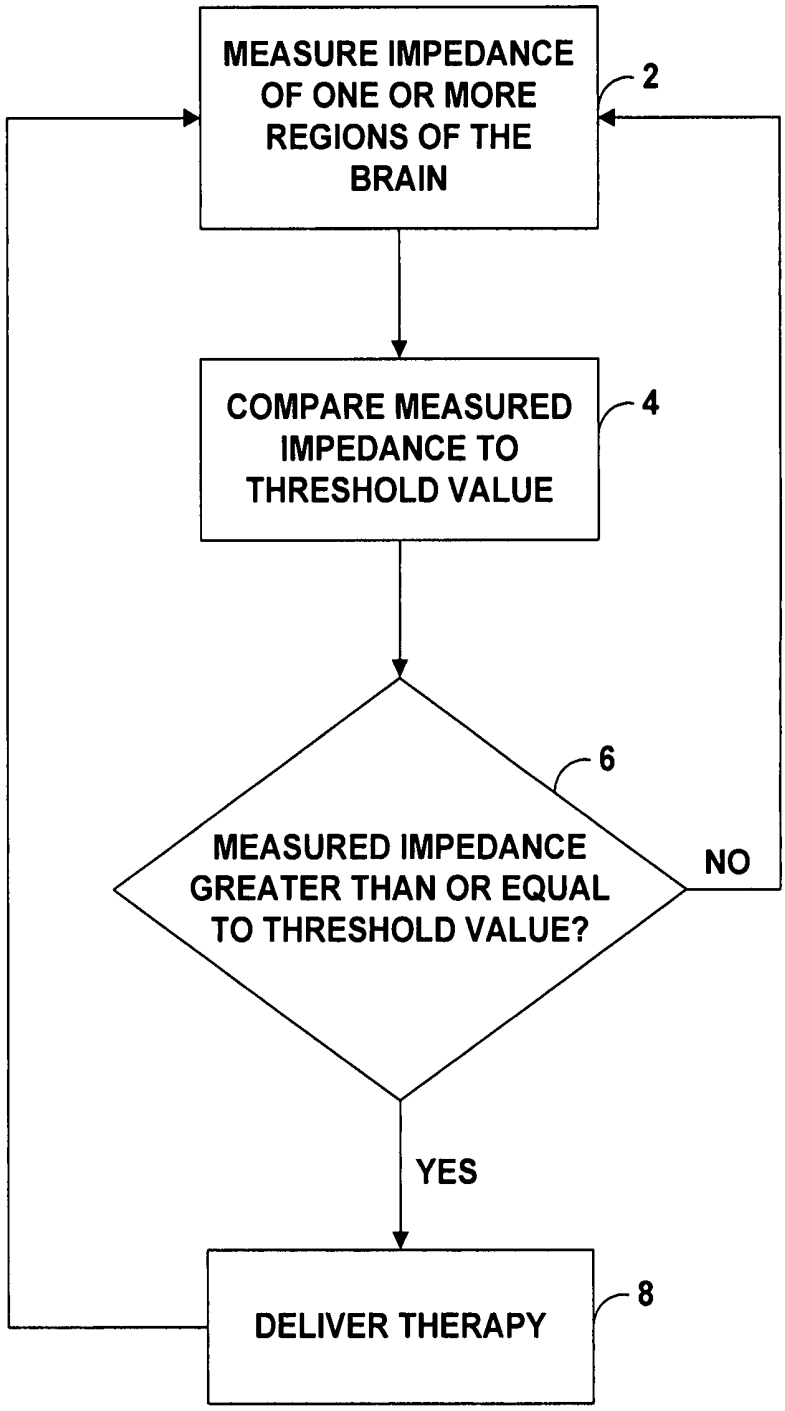
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2
COMPARE MEASURED IMPEDANCE TO THRESHOLD VALUE
4
MEASURED IMPEDANCE GREATER THAN OR EQUAL TO THRESHOLD VALUE?
6
NO
YES
DELIVER THERAPY
8

FIG. 1A

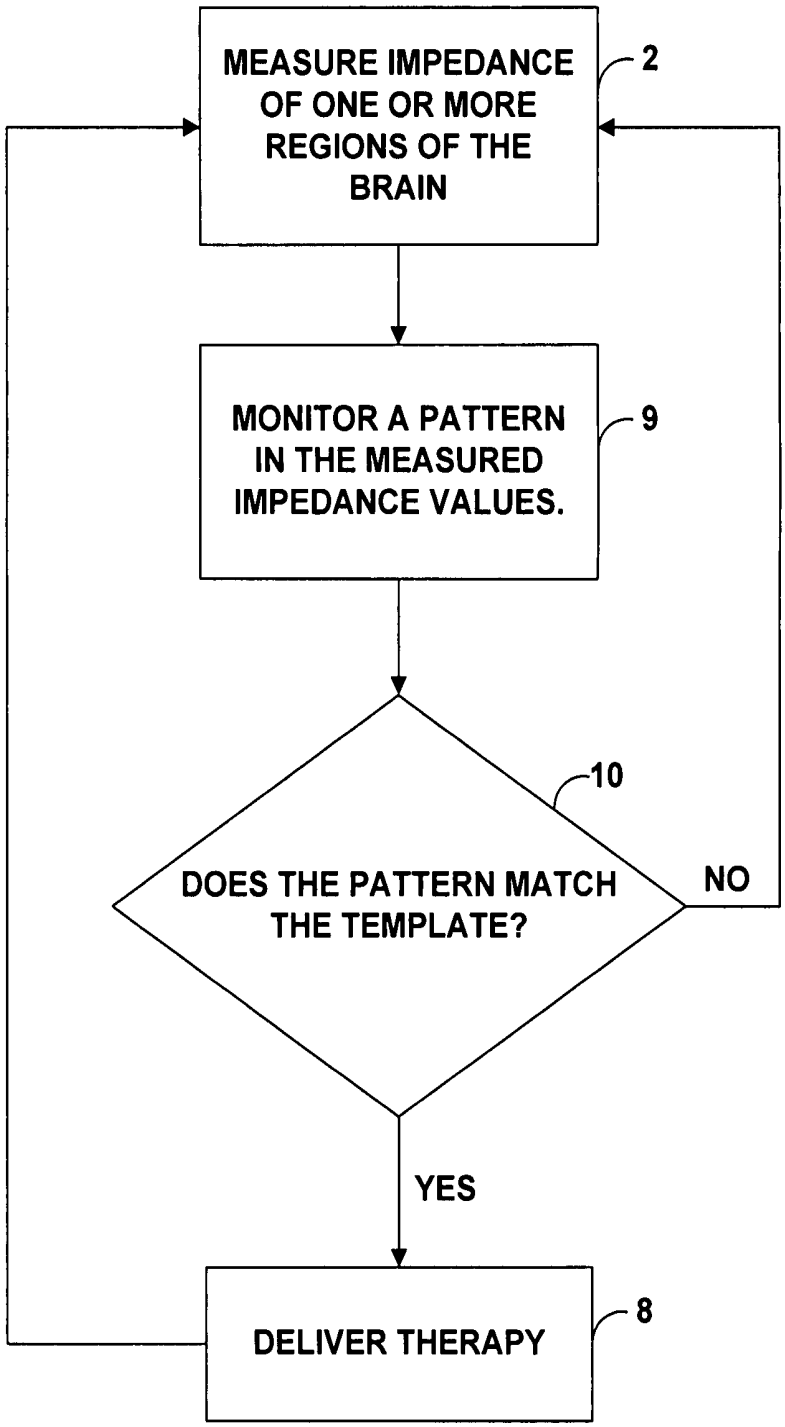
MEASURE IMPEDANCE OF ONE OR MORE REGIONS OF THE BRAIN
2
MONITOR A PATTERN IN THE MEASURED IMPEDANCE VALUES.
9
DOES THE PATTERN MATCH THE TEMPLATE?
10
NO
YES
DELIVER THERAPY
8

FIG. 1B

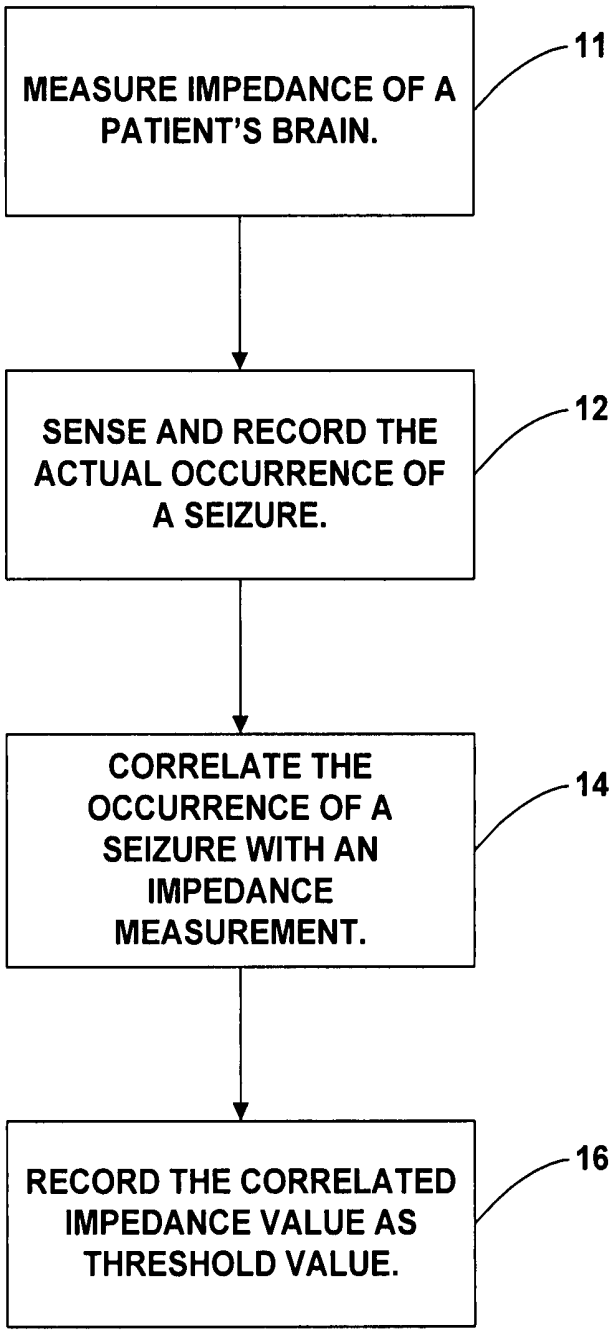
MEASURE IMPEDANCE OF A PATIENT'S BRAIN.
11
SENSE AND RECORD THE ACTUAL OCCURRENCE OF A SEIZURE.
12
CORRELATE THE OCCURRENCE OF A SEIZURE WITH AN IMPEDANCE MEASUREMENT.
14
RECORD THE CORRELATED IMPEDANCE VALUE AS THRESHOLD VALUE.
16

FIG. 2A

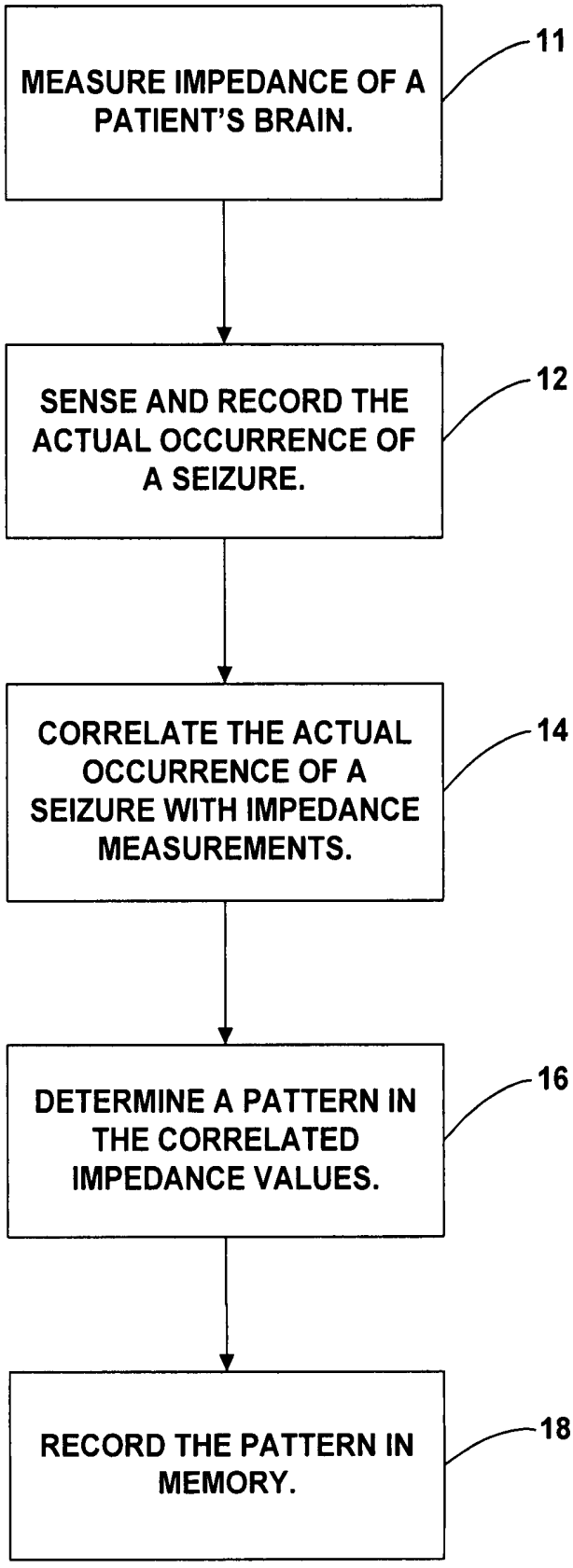
MEASURE IMPEDANCE OF A PATIENT'S BRAIN.
11
SENSE AND RECORD THE ACTUAL OCCURRENCE OF A SEIZURE.
12
CORRELATE THE ACTUAL OCCURRENCE OF A SEIZURE WITH IMPEDANCE MEASUREMENTS.
14
DETERMINE A PATTERN IN THE CORRELATED IMPEDANCE VALUES.
16
RECORD THE PATTERN IN MEMORY.
18

FIG. 2B

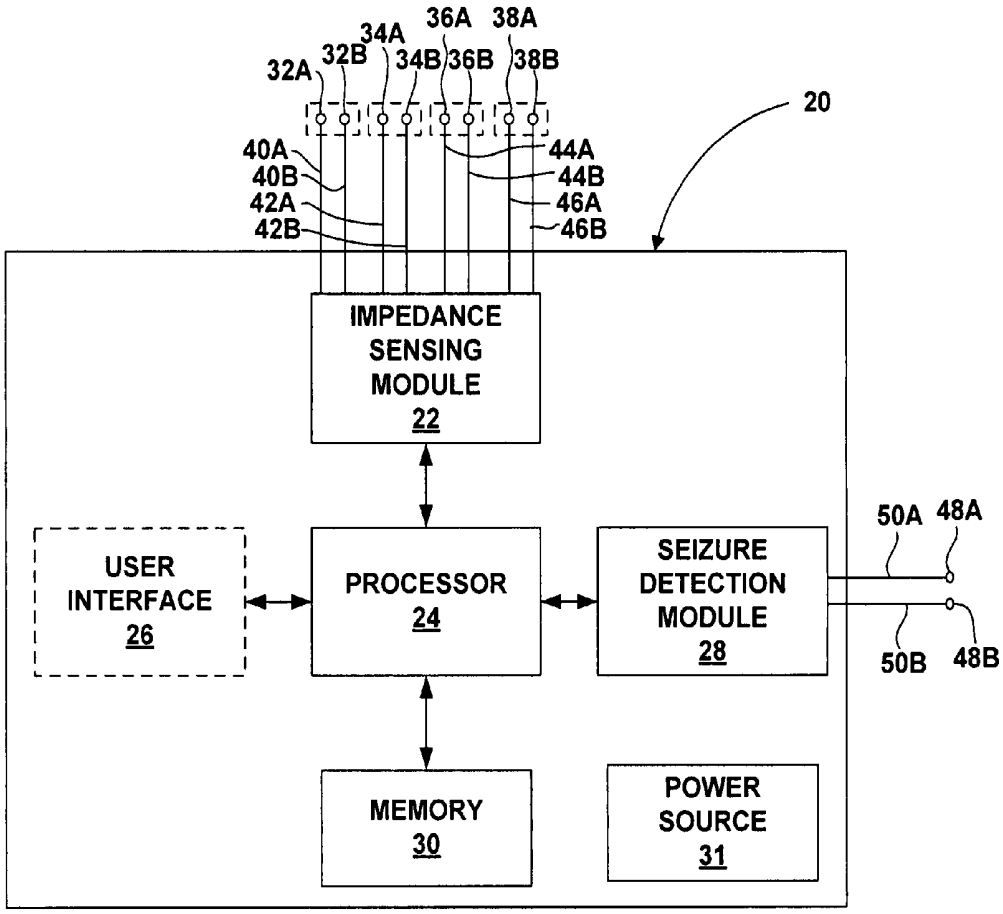
32A
32B
34A
34B
36A
36B
38A
38B
20
40A
40B
42A
42B
44A
44B
46A
46B
IMPEDANCE SENSING MODULE 22
USER INTERFACE 26
PROCESSOR 24
SEIZURE DETECTION MODULE 28
50A
48A
50B
48B
MEMORY 30
POWER SOURCE 31

FIG. 3

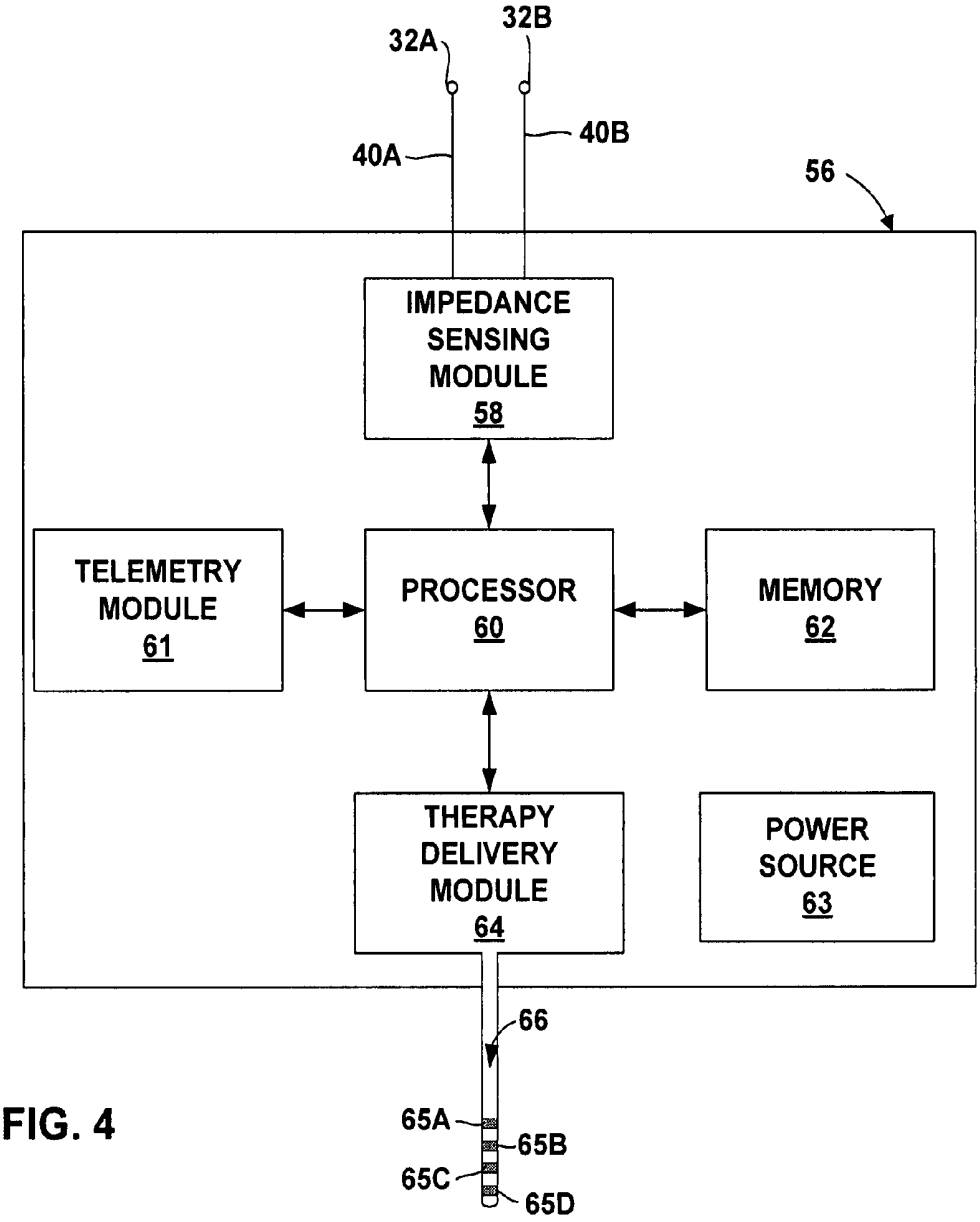
32A
32B
40A
40B
56
IMPEDANCE SENSING MODULE 58
TELEMETRY MODULE 61
PROCESSOR 60
MEMORY 62
THERAPY DELIVERY MODULE 64
POWER SOURCE 63
66
65A
65B
65C
65D

FIG. 4

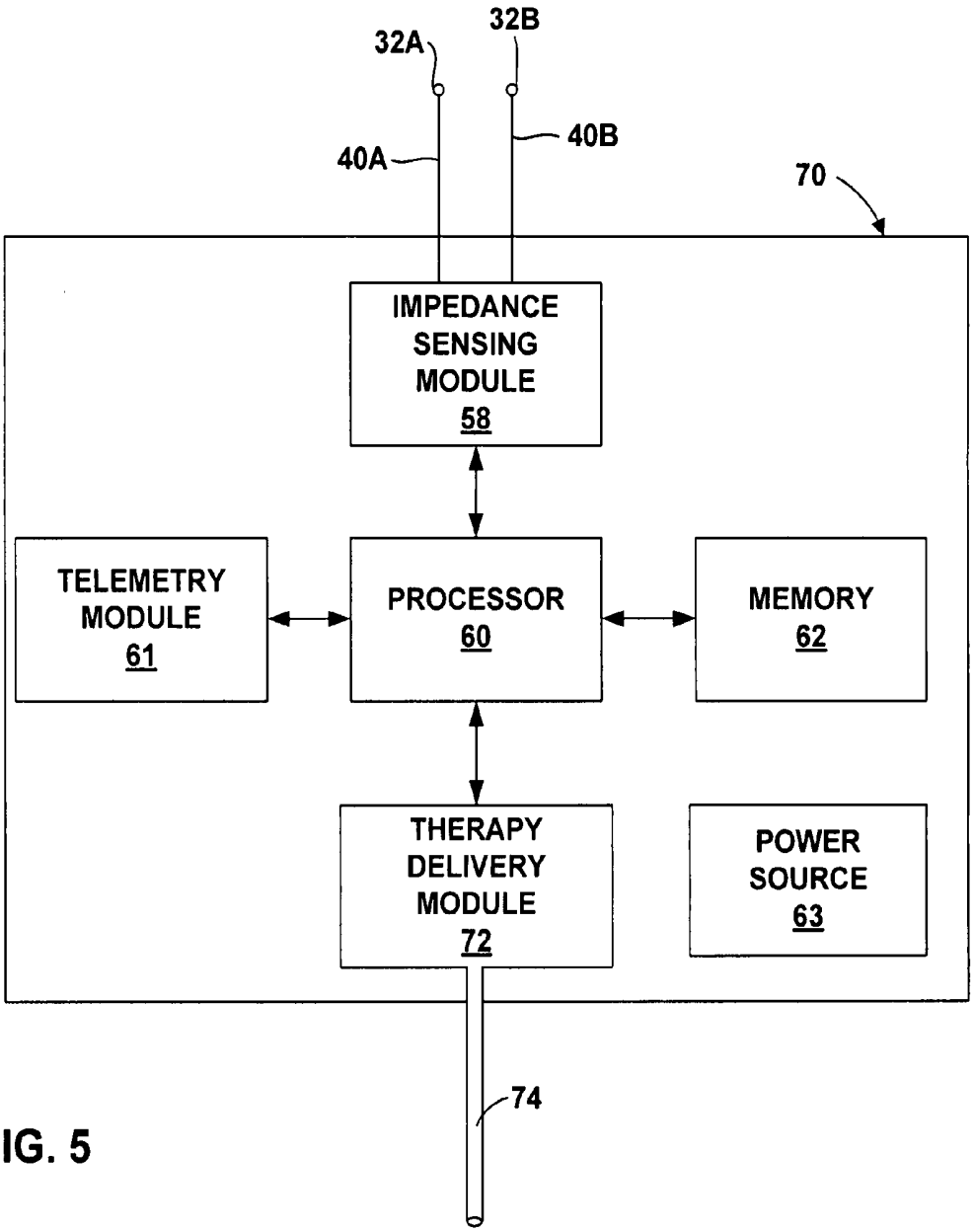
32A
32B
40A
40B
70
IMPEDANCE SENSING MODULE 58
TELEMETRY MODULE 61
PROCESSOR 60
MEMORY 62
THERAPY DELIVERY MODULE 72
POWER SOURCE 63
74

FIG. 5

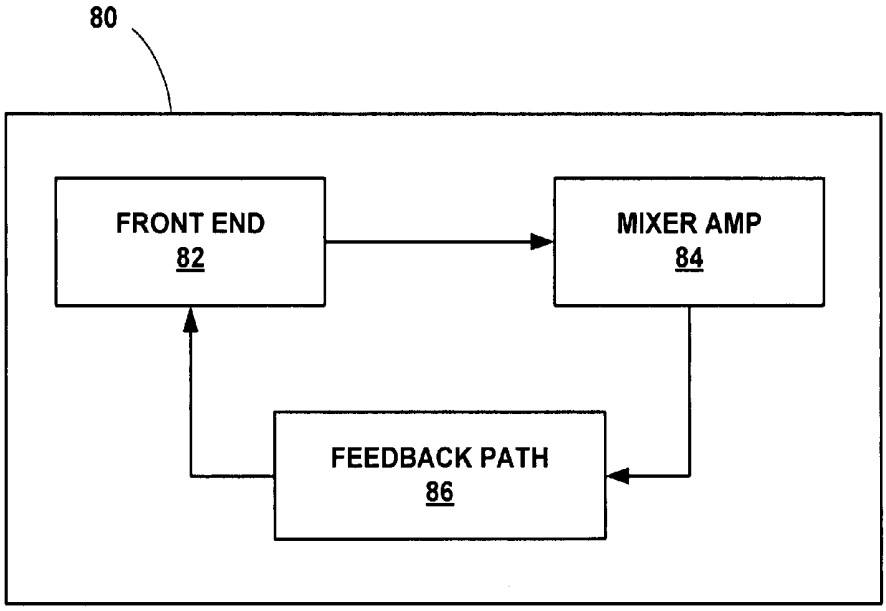
80
FRONT END
82
MIXER AMP
84
FEEDBACK PATH
86

FIG. 6

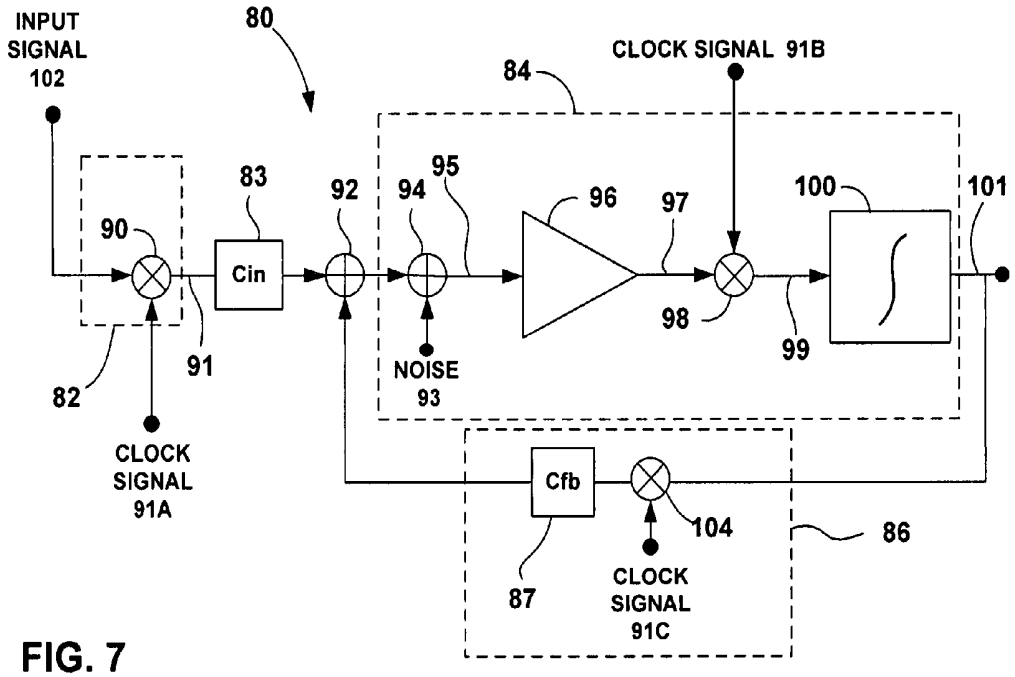
INPUT SIGNAL 102
80
84
CLOCK SIGNAL 91B
83
92
95
94
96
97
100
101
90
Cin
91
82
NOISE 93
98
99
CLOCK SIGNAL 91A
Cfb
104
86
87
CLOCK SIGNAL 91C

FIG. 7

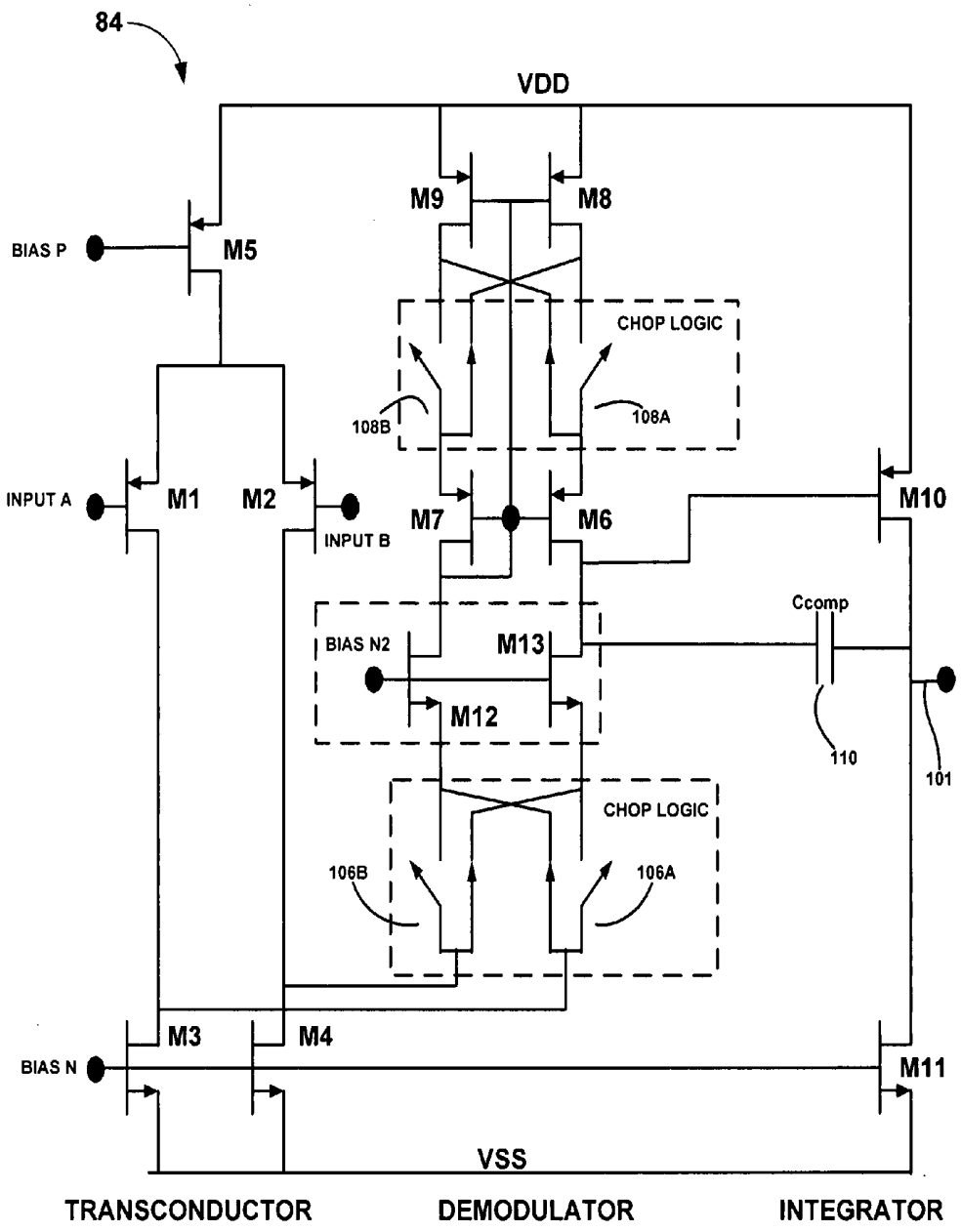
84
VDD
M9
M8
BIAS P
M5
CHOP LOGIC
108B
108A
INPUT A
M1
M2
INPUT B
M7
M6
M10
Ccomp
BIAS N2
M13
M12
110
101
CHOP LOGIC
106B
106A
M3
M4
BIAS N
M11
VSS
TRANSCONDUCTOR
DEMODULATOR
INTEGRATOR

FIG. 8

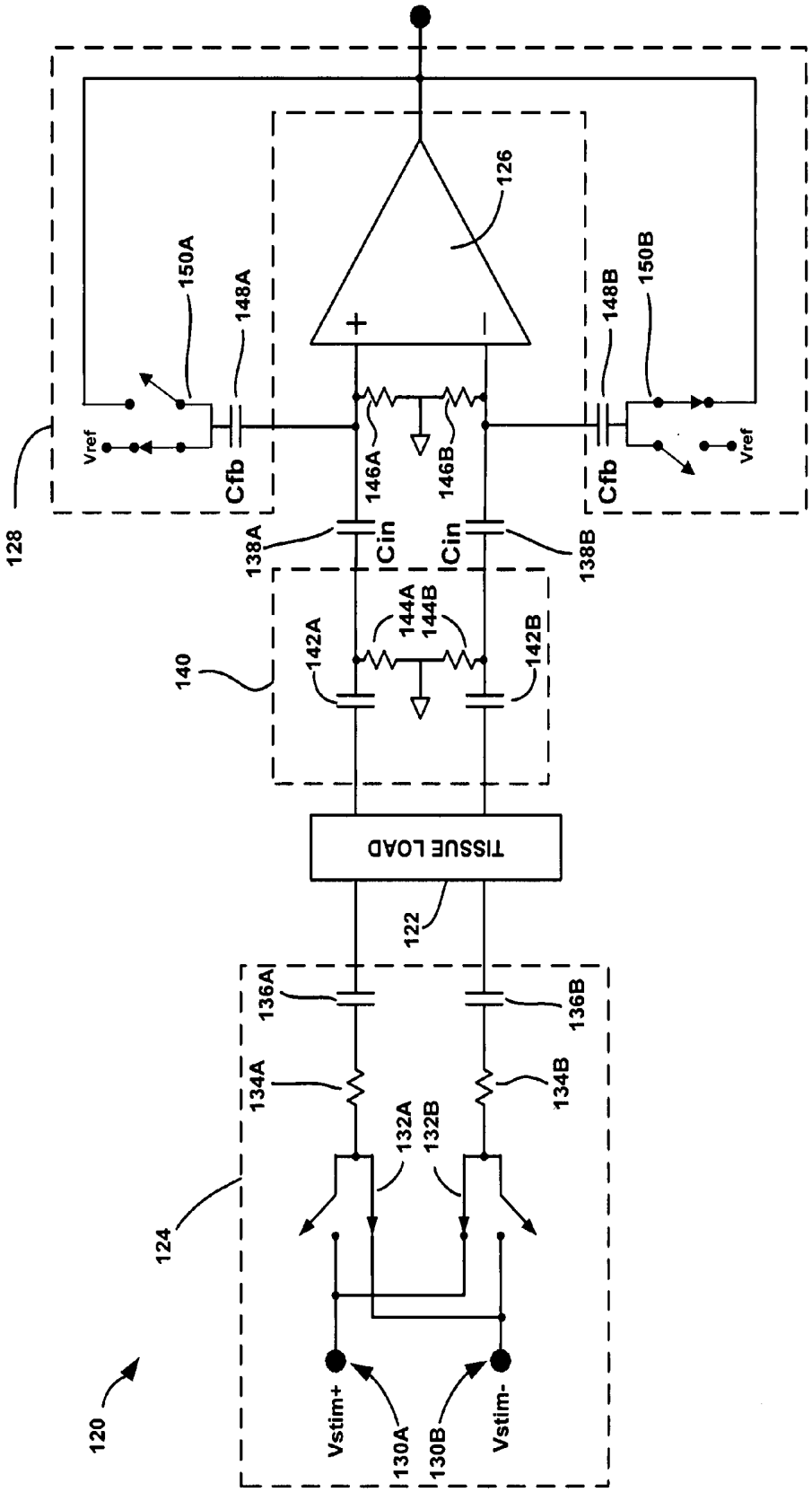
126
150A
148A
148B
150B
Vref
Cfb
Cfb
Vref
146A
146B
128
138A
Cin
Cin
138B
144A
144B
142A
142B
140
TISSUE LOAD
122
136A
136B
134A
134B
132A
132B
124
120
Vstim+
130A
130B
Vstim-

FIG. 9

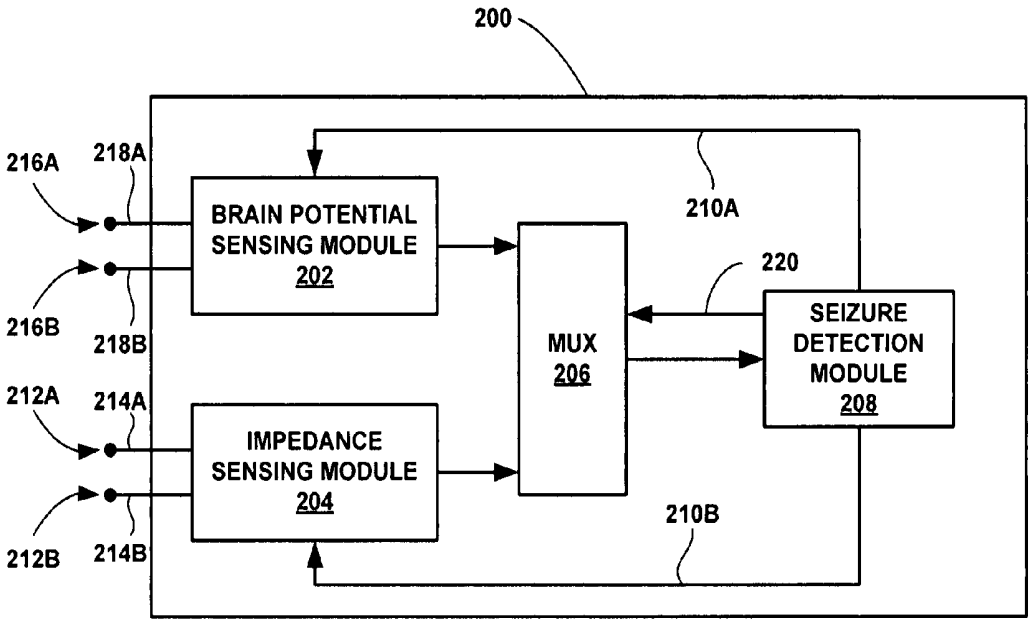
200
216A
218A
BRAIN POTENTIAL SENSING MODULE 202
210A
220
216B
218B
MUX 206
SEIZURE DETECTION MODULE 208
212A
214A
IMPEDANCE SENSING MODULE 204
210B
212B
214B

FIG. 10

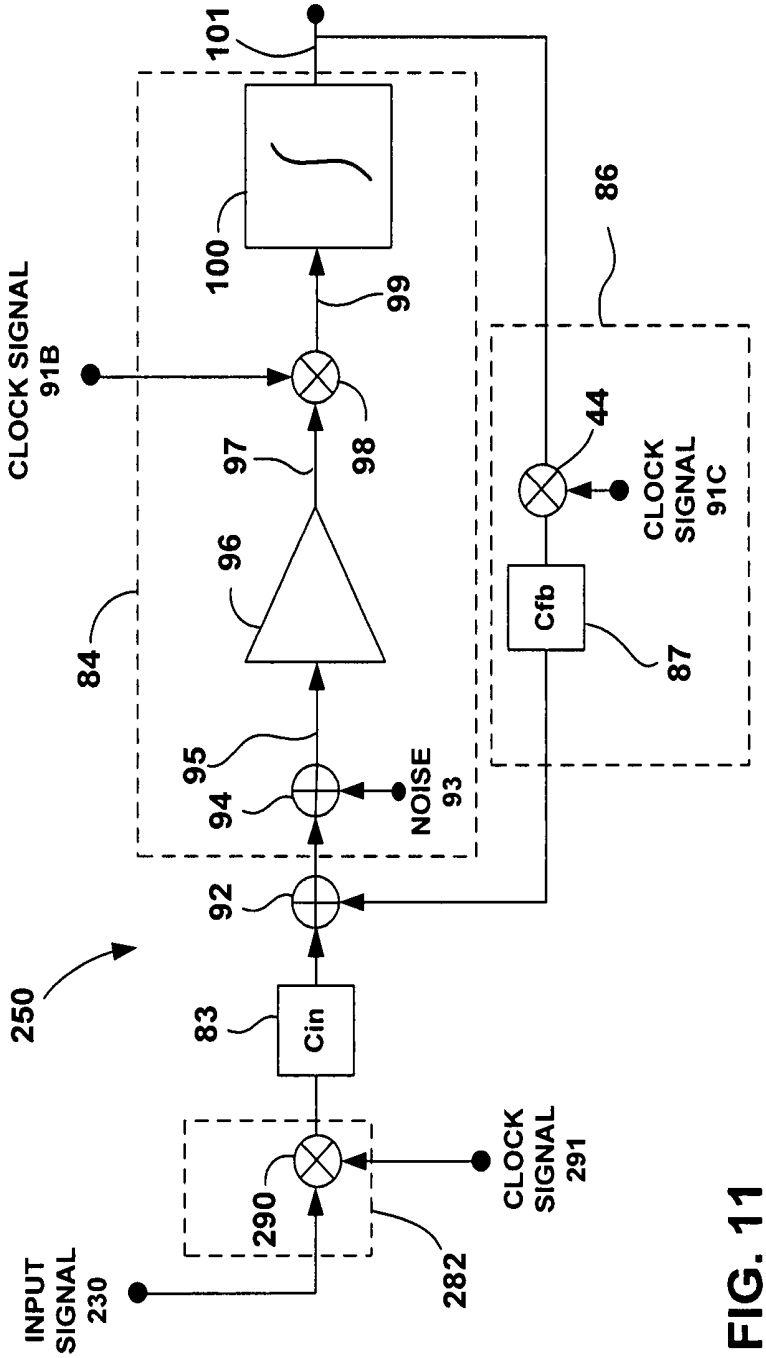
101
100
99
86
CLOCK SIGNAL 91B
97
98
44
CLOCK SIGNAL 91C
96
Cfb
84
87
95
NOISE 93
94
92
250
83
Cin
CLOCK SIGNAL 291
290
282
INPUT SIGNAL 230

FIG. 11

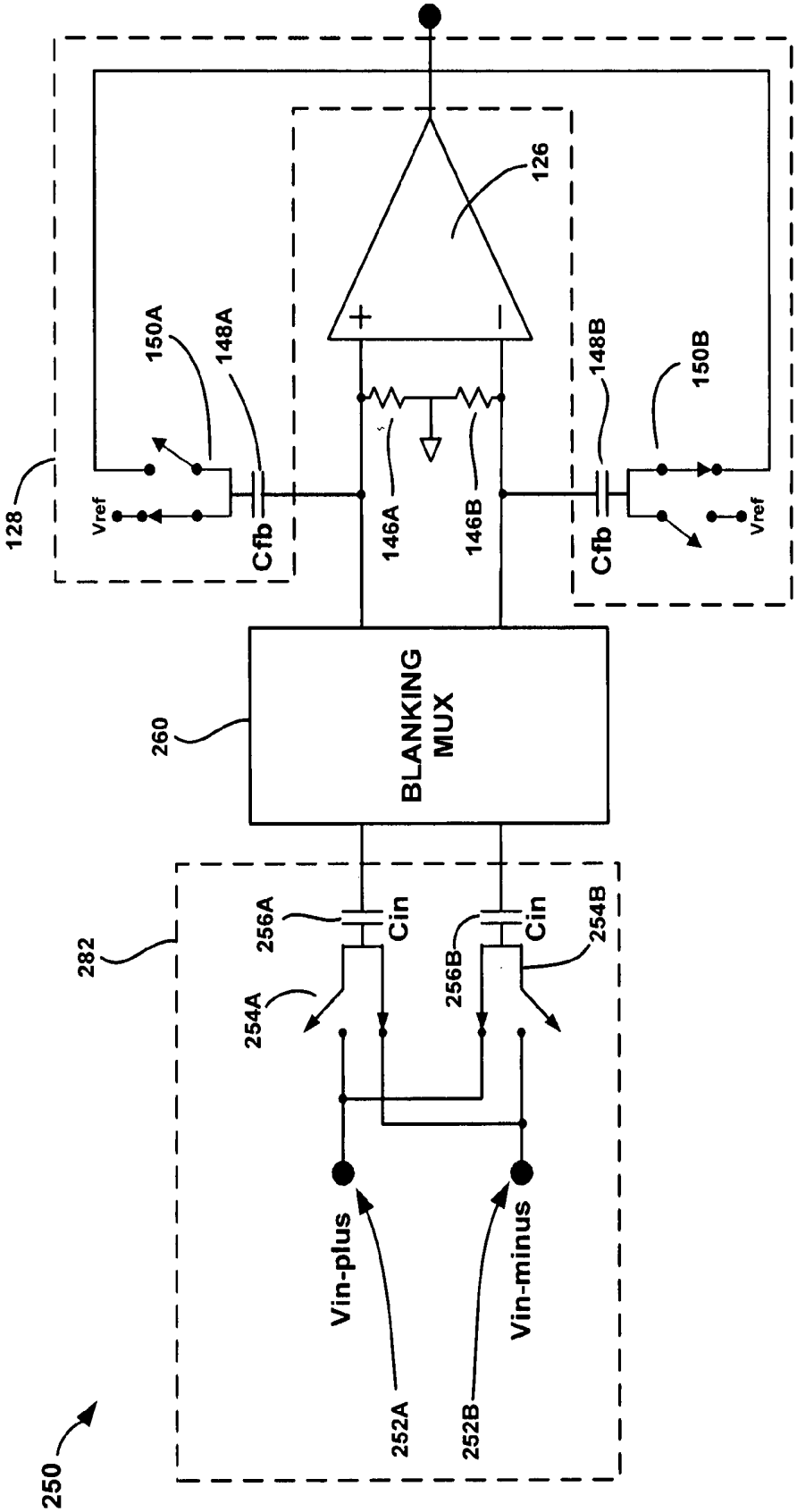
126
150A
148A
148B
150B
128
Vref
Cfb
146A
146B
Cfb
Vref
260
BLANKING MUX
282
256A
Cin
Cin
254B
254A
256B
Vin-plus
Vin-minus
252A
252B
250

FIG. 12

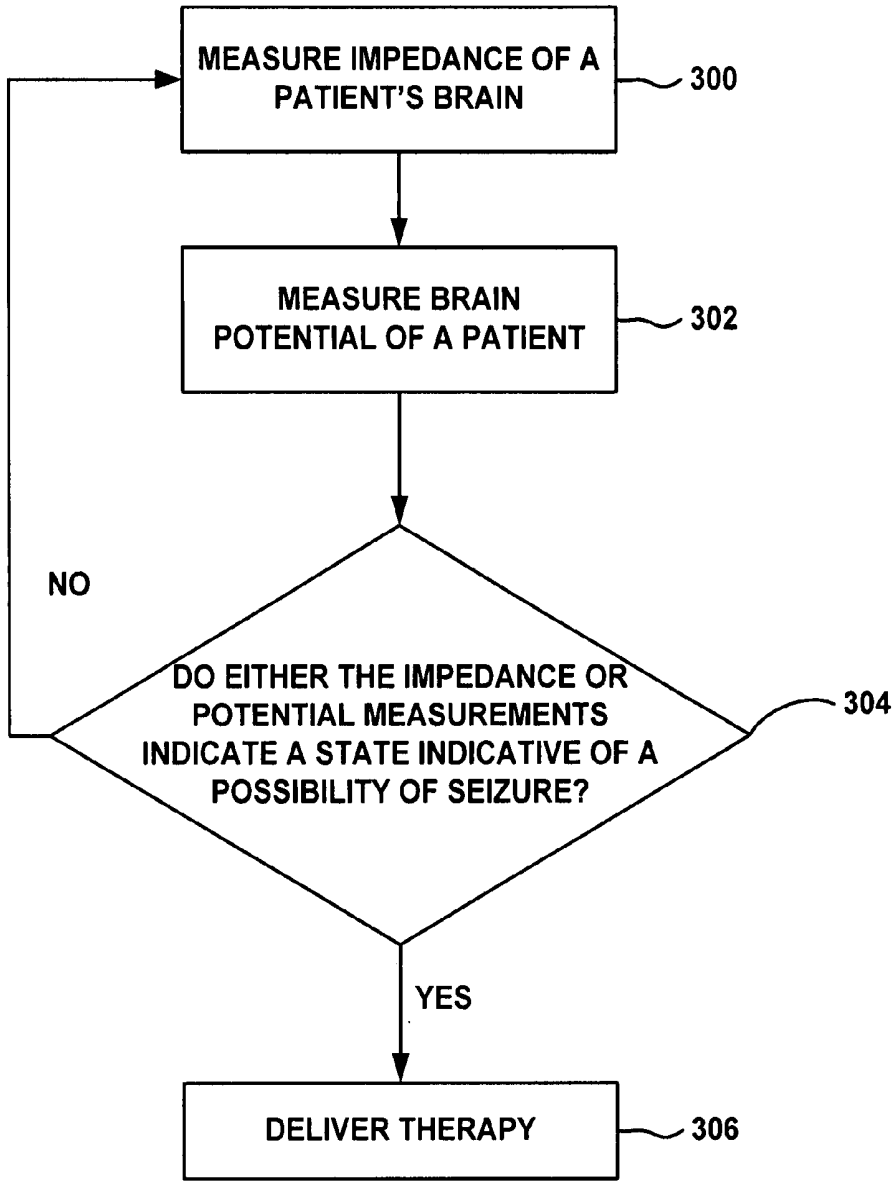
MEASURE IMPEDANCE OF A PATIENT'S BRAIN
300
MEASURE BRAIN POTENTIAL OF A PATIENT
302
NO
DO EITHER THE IMPEDANCE OR POTENTIAL MEASUREMENTS INDICATE A STATE INDICATIVE OF A POSSIBILITY OF SEIZURE?
304
YES
DELIVER THERAPY
306

FIG. 13

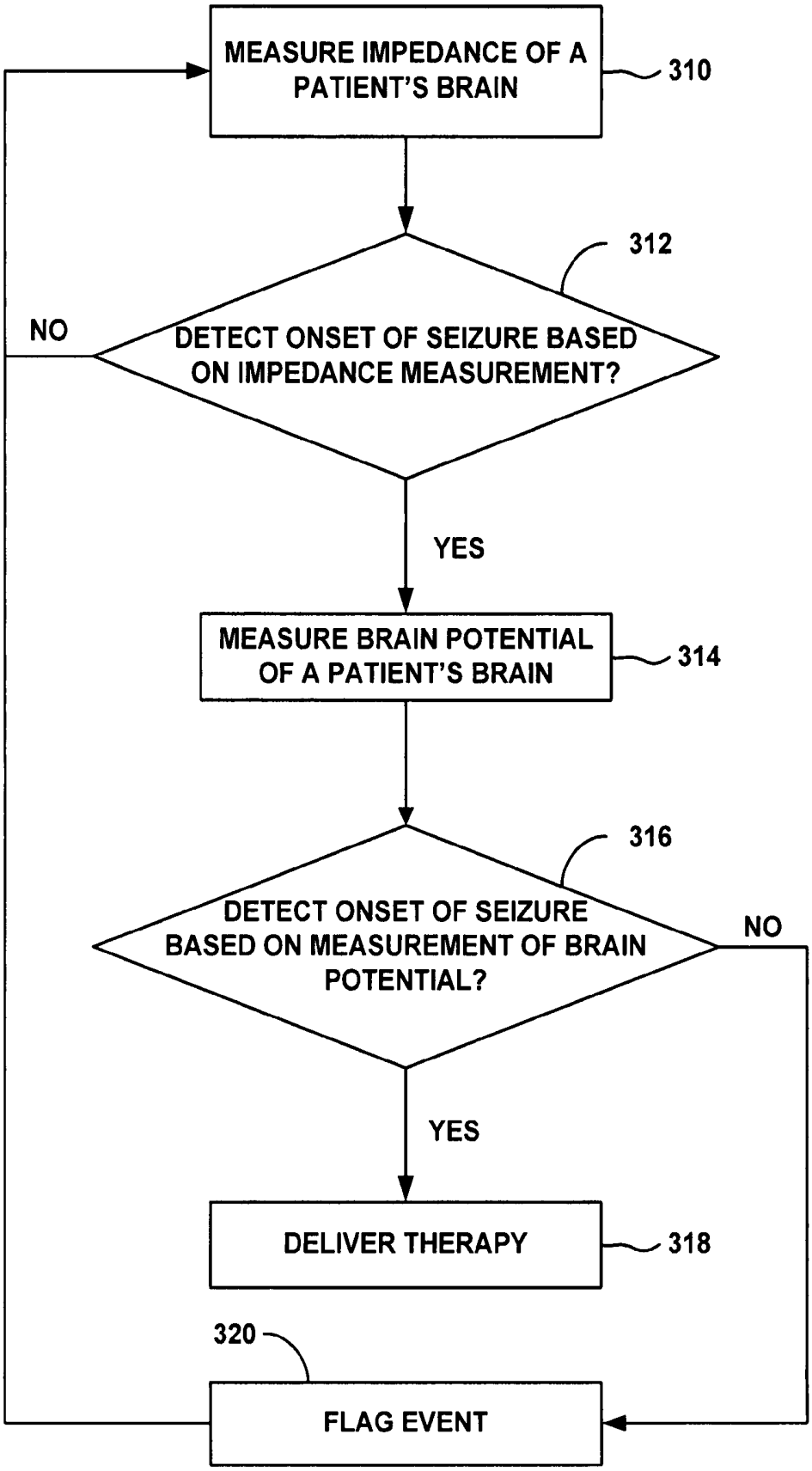
MEASURE IMPEDANCE OF A PATIENT'S BRAIN
310
312
DETECT ONSET OF SEIZURE BASED ON IMPEDANCE MEASUREMENT?
NO
YES
MEASURE BRAIN POTENTIAL OF A PATIENT'S BRAIN
314
316
DETECT ONSET OF SEIZURE BASED ON MEASUREMENT OF BRAIN POTENTIAL?
NO
YES
DELIVER THERAPY
318
320
FLAG EVENT

FIG. 14

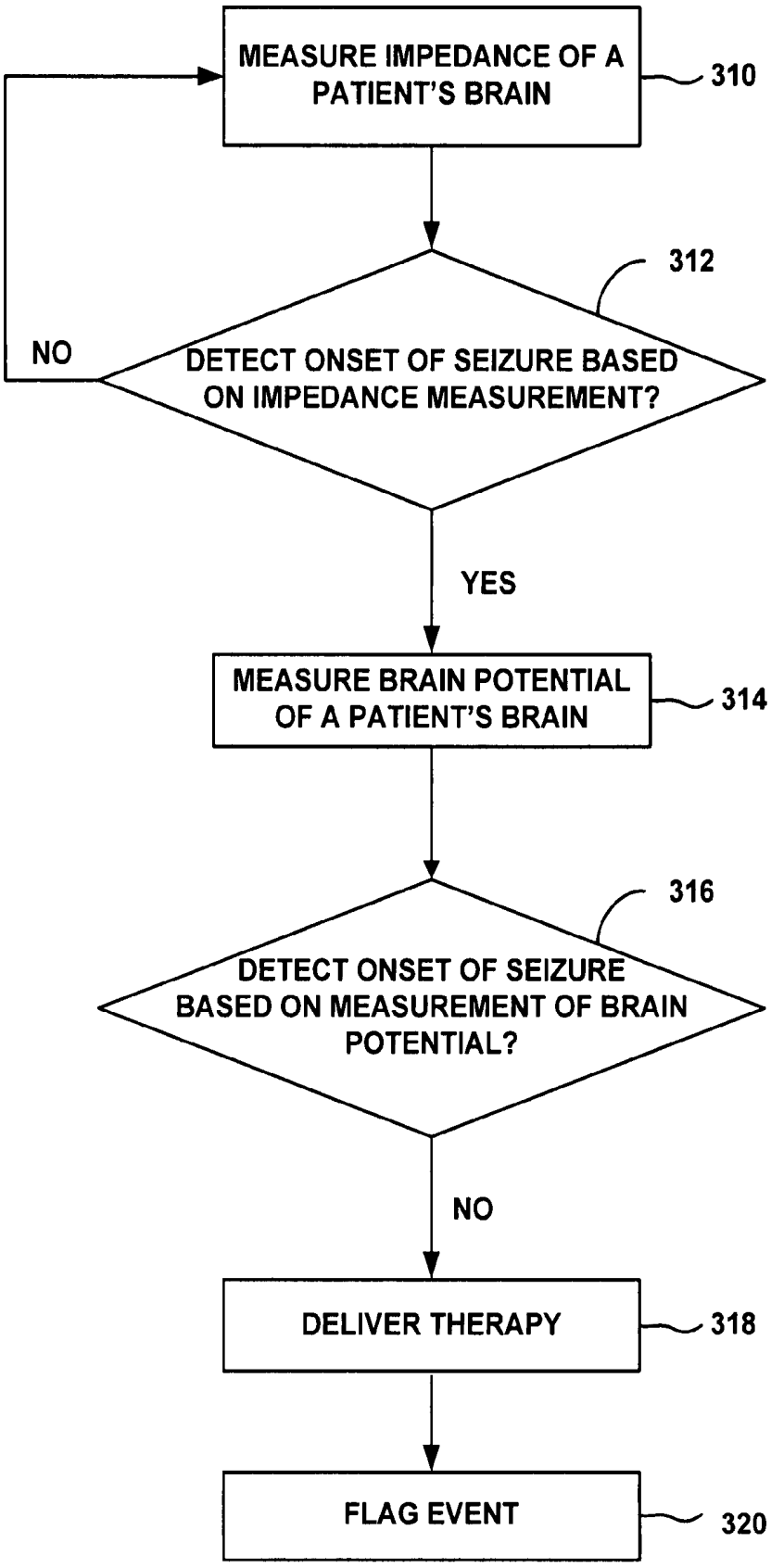
MEASURE IMPEDANCE OF A PATIENT'S BRAIN
310
312
DETECT ONSET OF SEIZURE BASED ON IMPEDANCE MEASUREMENT?
NO
YES
MEASURE BRAIN POTENTIAL OF A PATIENT'S BRAIN
314
316
DETECT ONSET OF SEIZURE BASED ON MEASUREMENT OF BRAIN POTENTIAL?
NO
DELIVER THERAPY
318
FLAG EVENT
320

FIG. 15

SEIZURE PREDICTION

TECHNICAL FIELD

The invention relates to physiological monitoring and, more particularly, physiological monitoring of the brain for seizure prediction.

BACKGROUND

Epilepsy is a neurological disorder characterized by the occurrence of seizures, although seizures may also occur in persons who do not have epilepsy. Seizures are typically attributable to abnormal electrical activity of a group of brain cells. A seizure may occur when the electrical activity of certain regions of the brain, or even the entire brain, becomes abnormally synchronized. The onset of a seizure may be debilitating. For example, the onset of a seizure may result in involuntary changes in body movement, body function, sensation, awareness or behavior (e.g., an altered mental state). In some cases, each seizure may cause some damage to the brain, which may result in progressive loss of brain function over time.

Attempts to manage seizures have included the delivery of electrical stimulation to regions of the brain and/or the delivery of drugs either orally or infused directly into regions of the brain. In electrical stimulation systems, a medical lead is implanted within a patient and coupled to an external or implanted electrical stimulator. The target stimulation site within the brain or elsewhere may differ between patients, and may depend upon the type of seizures being treated by the electrical stimulation system. In some therapy systems, electrical stimulation is continuously delivered to the brain. In other systems, the delivery of electrical stimulation is triggered by the detection or prediction of some event, such as the detection of a seizure by electroencephalogram (EEG) sensors within the brain.

In automatic drug delivery systems, a catheter is implanted within a patient and coupled to an external or implanted fluid delivery device. The fluid delivery device may deliver a bolus of an anti-seizure drug into the blood stream or into a region of the brain of the patient at regular intervals, upon the detection or prediction of some event, such as the detection of a seizure by EEG sensors implanted within the brain, or at the direction of the patient or clinician.

SUMMARY

In general, the invention involves techniques for monitoring the impedance of one or more regions of the brain of a patient to predict the likelihood of an onset of a seizure. It is believed that the impedance of one or more regions of the brain, or even the entire brain, is indicative of a physiological state of the brain, and may be monitored to determine whether the brain of a patient is primed for a seizure. That is, impedance of one or more regions of the brain may indicate whether an onset of a seizure is likely or whether a seizure is in progress. In some embodiments, the relationship between the measured impedance of the brain and an absolute threshold impedance value may be used to predict a seizure. For example, if an amplitude of the impedance signal is greater than or equal to a predetermined threshold, the brain may be in a state that indicates the possibility of the onset of a seizure.

In other embodiments, a measured impedance signal may be analyzed for slope, amplitude, temporal correlation or frequency correlation with a template signal, or combinations thereof in order to determine whether a seizure is likely to occur. For example, a trend in the measured impedance values may be compared to a predetermined template. For example, if rate of change (i.e., the slope) of the measured impedance over time correlates to the slope of a trend template, the brain may be in a state in which a seizure is likely. Alternatively, if inflection points in the impedance signal waveform substantially correlate to a template, the brain may be in a state in which a seizure is likely. Embodiments employing a temporal correlation technique may sample an impedance signal with a sliding window and compare the sample to a template to identify a signal that correlates well with the template. Embodiments employing a frequency correlation technique may include analyzing the impedance signal in the frequency domain to compare selected frequency components of the impedance signal to corresponding frequency components of the template signal.

Upon predicting the onset of a seizure by monitoring the impedance of one or more regions of the brain, therapy may be delivered to the patient in an attempt to prevent the seizure or mitigate the effects of the seizure. For example, electrical stimulation therapy or drug therapy may be delivered to the patient to return the brain to a state in which a seizure is less likely, thereby inhibiting the onset of the seizure and/or reducing the severity and/or duration of the seizure. In this way, impedance monitoring of the brain may be incorporated into a closed loop system for treating seizures. In addition or instead of delivering therapy, a an alarm may be provided upon the prediction of a seizure.

In some embodiments, the seizure prediction systems and methods include measuring impedance and a potential within a brain of a patient to determine whether the brain is in a state indicative of a possibility of seizure. In some embodiments, at least one of the measured impedance or the measured potential may be used as a primary indication of the brain state indicative of a possibility of seizure. In one embodiment, if one of the measured impedance or the measured potential indicates a seizure, the other measurement (impedance or potential) may be used to validate whether the brain is in the state indicative of the possibility of seizure.

In one embodiment, the invention is directed to a method comprising measuring an impedance of a brain of a patient and determining whether the brain is in a state indicative of a possibility of seizure based on the measured impedance.

In another embodiment, the invention is directed to a system comprising one or more electrodes implantable in a brain of a patient, an impedance sensing module that delivers an electrical stimulus to the brain via the electrodes to measure an impedance of the brain, and a processor coupled to the impedance sensing module. The processor receives impedance measurements from the impedance sensing module and determines whether the brain is in a state indicative of a possibility of seizure based on the measured impedance.

In another embodiment, the invention is directed to a system comprising means for measuring an impedance of a brain of the patient and means for determining whether the measured impedance indicates the brain is in a state indicative of a possibility of seizure.

In another embodiment, the invention is directed to a computer-readable medium containing instructions. The instructions cause a programmable processor to receive a signal indicative of a measured impedance of a brain of a patient and determine whether the brain is in a state indicative of a possibility of seizure based on the measured impedance.

In another embodiment, the invention is directed to a method comprising measuring an impedance of a brain of a patient, detecting an occurrence of a seizure, associating the occurrence of the seizure with at least one impedance mea-

surement, and recording the at least one impedance measurement associated with the occurrence of the seizure.

In another embodiment, the invention is directed to a system comprising an impedance sensing module that measures an impedance of a brain of a patient, a seizure detection module that detects an occurrence of a seizure, a memory, and a processor coupled to the impedance sensing module and the seizure detection module. The processor associates the occurrence of the seizure with at least one impedance measurement and records the at least one impedance measurement associated with the occurrence of the seizure in the memory.

In another embodiment, the invention is directed to a method comprising measuring an impedance of a brain of a patient, measuring a potential of the brain, and determining whether the brain is in a state indicative of a possibility of seizure based on the measured impedance and the measured potential.

In another embodiment, the invention is directed to a system comprising one or more electrodes implantable in a brain of a patient, a sensing module configured to measure a potential of the brain and deliver an electrical stimulus to the brain via at least some of the electrodes to measure an impedance of the brain, and a processor coupled to the sensing module. The processor receives impedance measurements and potential measurements from the sensing module and determines whether the brain is in a state indicative of a possibility of seizure based on the measured impedance and measured potential.

In another embodiment, the invention is directed to a computer-readable medium containing instructions. The instructions cause a programmable processor receive a first signal indicative of a measured impedance of a brain of a patient, receive a second signal indicative of a measured potential of the brain, and determine whether the brain is in a state indicative of a possibility of seizure based on the measured impedance and the measured potential.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1**A is a flow diagram illustrating a method for predicting seizure in a patient by measuring an impedance of the brain of the patient and comparing the measured impedance to a threshold value.

FIG. **1**B is a flow diagram illustrating another method for predicting seizure in a patient by measuring an impedance of the brain of the patient and comparing a pattern in the measured impedance to a template.

FIG. **2**A is a flow diagram illustrating a technique for determining one or more threshold values to compare to impedance measurements in order to predict a seizure.

FIG. **2**B is a flow diagram illustrating a technique for determining one or more trend templates to compare to a pattern of impedance measurements in order to predict a seizure.

FIG. **3** is a block diagram illustrating a medical device that may be used during a trial stage to determine the threshold impedance values or trend template that indicates a brain is in a state in which a seizure is likely.

FIG. **4** is a block diagram illustrating an embodiment of an implantable medical device that may be used to predict the onset of a seizure in a patient and deliver electrical stimulation therapy to the patient.

FIG. **5** is block diagram of another embodiment of a medical device that may be used to predict the onset of a seizure in a patient and deliver drug therapy to the patient.

FIG. **6** is a block diagram illustrating an embodiment of a chopper stabilized instrumentation amplifier, which may be incorporated into a medical device for measuring the impedance of a brain of a patient.

FIG. **7** is a block diagram illustrating a signal path flow of one embodiment of instrumentation amplifier that may be incorporated into an impedance sensing module of a medical device.

FIG. **8** is a circuit diagram illustrating a chopper-stabilized mixer amplifier forming part of an instrumentation amplifier.

FIG. **9** is a circuit diagram illustrating an instrumentation amplifier for measuring impedance across a brain tissue load.

FIG. **10** is a block diagram illustrating a medical device that may be used to predict seizure in a patient by measuring an impedance and a potential of the brain of the patient.

FIG. **11** is a diagram illustrating a signal flow path of a brain potential sensing module of the medical device in FIG. **10**.

FIG. **12** is a circuit diagram illustrating a chopper-stabilized instrumentation amplifier that may be incorporated into the brain potential sensing module.

FIG. **13** is flow diagram illustrating a method for predicting seizure in a patient based on an impedance measurement of the brain and a measurement of a brain potential.

FIG. **14** is flow diagram illustrating another method for predicting seizure in a patient based on an impedance measurement of the brain and a measurement of a brain potential.

FIG. **15** is flow diagram illustrating another method for predicting seizure in a patient based on an impedance measurement of the brain and a measurement of a brain potential.

DETAILED DESCRIPTION

Therapy delivery systems may be used to treat seizures to mitigate the effects of the seizure, shorten the duration of the seizure or to prevent the onset of seizures. In therapy systems in which the therapy (e.g., a drug or electrical stimulation) is delivered in response to the detection or prediction of a seizure, the timing of the therapy delivery is important to the efficacy of the therapy. The time required to analyze the input signals from sensors that are used to detect the seizure and produce an output which triggers the delivery of therapy are important factors in providing a warning to the patient of the onset of seizures, intervention of seizures or prevention of seizures. It is generally desirable to predict the onset of a seizure and deliver therapy to treat the seizure before the patient feels any effects (e.g., auras, changing in muscle tone, etc.) of the seizure or before any symptoms are seen by an observer. In addition, it is desirable to limit the number of false positives (i.e., the incorrect detection of a seizure), and false negatives (i.e., the failure to detect a seizure).

It is believed that the impedance of one or more regions of the brain, or even the entire brain, is indicative of a physiological state of the brain, and may be monitored to determine whether the brain of a patient is primed for a seizure. In particular, it is believed that the impedance of the brain is indicative of the electrochemical state and/or fluid distribution of the brain, which are both related to the onset of seizures. Certain impedance values within the brain may indicate that the brain is in a "bias" state, and that a seizure is likely to occur (i.e., there is a high probability of seizure). This bias state may occur just prior to an onset of a seizure when the brain is in a state in which a seizure is likely to occur. Thus,

the bias state may be indicative of a state within the brain indicative of a possibility of a seizure.

The present invention involves monitoring and analyzing impedance measurements of the brain to predict a seizure. Based on the prediction of a seizure, therapy may be delivered to a patient to help prevent the seizure or reduce the severity or duration of the seizure. In addition to the therapy delivery or instead of the therapy delivery, an alarm may be provided upon the prediction of the seizure, for example, to alert the patient to the possibility of an onset of a seizure. It is believed that detecting seizures by monitoring the impedance of the brain may help reduce the amount of delay before therapy is initiated compared to systems that rely on EEG sensing because changes in impedance of one or more regions of the brain may be an earlier indicator of the likelihood of a seizure.

Neurological disorders that cause seizures, such as epilepsy, may be generated in one or more of regions of the brain, which may differ between patients. The impedance in one or more of these "key regions" of the brain may be monitored. These "key regions" of the brain may be, for example, regions of the brain to which therapy is delivered in order to treat or prevent seizures. Examples of key regions of the brain include, but are not limited to, the cortex (e.g., front or motor cortex), brain stem, cranial nerves (e.g., the vagus nerve), or deep brain regions, such as the anterior thalamus, ventrolateral thalamus, globus pallidus, substantia nigra pars reticulata, subthalamic nucleus, neostriatum, cingulated gyrus or the cingulate gyrus.

As described in further detail below, an impedance signal may be analyzed using any suitable technique in order to determine whether the brain is in a state in which a seizure is likely to occur. For example, the instantaneous or average amplitude of impedance over a period of time may be compared to amplitude threshold. As another example, a slope of the amplitude of the signal over time may be compared to trend information or timing between inflection points or other critical points in the pattern of the amplitude of the impedance signal over time may be compared to trend information. As another example, the impedance waveform may be sampled with a sliding window and a correlation may be performed between the waveform and a stored template waveform. As another example, an amplitude of frequency components of the impedance waveform may be analyzed and compared to frequency components of template waveform.

FIG. **1**A is a flow diagram illustrating a method for predicting the onset of a seizure in a patient by measuring an impedance of the brain of the patient. The complex impedance of the brain of the patient is measured via an impedance sensing device, which may be implanted or may include both external and implanted components (**2**). In one embodiment, the impedance sensing device measures the impedance substantially continuously. In another embodiment, the impedance sensing device intermittently measures the impedance at a measurement frequency, such as, but not limited to, a frequency of about one hertz (Hz) to about 100 Hz.

Embodiments of a chopper stabilized instrumentation amplifier that may be incorporated into an impedance sensing device to amplify and filter sensor outputs are shown in FIGS. **6-8**, and described below. The chopper stabilized instrumentation amplifier may provide low noise measurement and help decrease the power consumption of the impedance sensing device, enabling the impedance sensing device to measure the impedance of the brain substantially continuously while still operating for several months or years relying on power from a finite power source, such as a rechargeable or non-rechargeable battery.

In order to measure the impedance of the brain, at least two electrodes are implanted within the relevant region(s) of the brain and coupled to an impedance sensing circuit. The relevant region(s) of the brain may be determined in a trial phase that precedes chronic implantation of the impedance sensing device and therapy delivery device. An example of a trial phase is shown in FIGS. **2**A-B. Complex impedance is a measure of the opposition to the stimulation current. Thus, stimulation current is delivered to the brain via the implanted electrodes in order to measure impedance of the brain.

The stimulation current may be relatively low to prevent inadvertent stimulation of tissue and to prevent the patient from feeling the stimulation current. For example, the stimulation current may be in a range of about 500 nanoamps (nA) to about 10 microamps (μA), although other stimulation currents may be used. The stimulation current that is delivered to measure impedance differs from that used to deliver stimulation therapy to the patient to prevent a seizure from occurring or to mitigate the effects of a seizure. In general, the stimulation current used for impedance measuring is at a relatively low current level and relatively high frequencies. Examples of frequencies that may be used for the input stimulation current to measure impedance of the brain include, but are not limited to range of about 1 kilohertz (kHz) to about 100 kHz, such as a range of about 4 kHz to about 16 kHz. In one embodiment, the stimulation current to measure impedance of the brain is about 12 kHz. Using stimulation currents having relatively high frequencies (e.g., 4 kHz or greater) to measure impedance helps prevent interference with other electrodes that may be implanted within the patient for delivery of electrical stimulation therapy or for sensing other physiological parameters, such as electroencephalogram (EEG) sensing.

It is believed that some frequency ranges may be more revealing of the impedance state of the region(s) of the brain for a particular patient than other frequency ranges. Thus, the impedance for the brain of a patient may be measured using stimulation currents modulated at frequencies in different frequency ranges. In addition, the optimal stimulation current frequency that is delivered to measure impedance of the brain may differ between patients and may depend on the region of the brain in which the impedance is measured.

The amplitude of the measured impedance signal is compared to a predetermined threshold (**4**). The relevant amplitude may be, for example, the instantaneous amplitude of an incoming impedance signal or an average amplitude of impedance over period of time. In one embodiment, the threshold value is determined during the trial phase that precedes implantation of a chronic therapy delivery device within the patient. In one embodiment, if the measured impedance is less than the threshold value (**6**), therapy is not delivered to the patient and the medical device continues measuring the impedance of the brain (**2**). On the other hand, if the measured impedance is greater than or equal to the threshold value (**6**), therapy is delivered to the patient in order to prevent the onset of the seizure, for example, by bringing the brain state to a "normal" state, i.e., a state in which a seizure is not likely to occur (**8**). The therapy may be delivered to the patient via a therapy delivery device that is separate from the impedance sensing device that measures the impedance. In other embodiments, a single medical device incorporates both a therapy delivery module and an impedance sensing device. In addition to or instead of delivering therapy to the patient, a patient alarm may be triggered in response to a measured impedance exceeding or equaling a threshold. Upon the impedance measurement exceeding or equaling a threshold, other actions may be triggered. For example, an implanted medical device or an external device, such as an

external programming device may also record date and time of the impedance measurements and/or the actual impedance measurements for future analysis by a clinician.

In some cases, the delivery of therapy may not inhibit the onset of the seizure, but may reduce the severity and/or duration of the seizure. While it is believed that an impedance value greater than or equal to a threshold value may be an indicator of an imminent seizure, in some cases, a measured impedance that is less than or equal to a threshold value may indicate an imminent seizure. In such cases, therapy is triggered if the measured impedance is less than or equal to the threshold value. Hence, the measured impedance may be compared to a threshold value to determine whether the impedance is greater than or less than the threshold value, as applicable for particular therapy criteria. After therapy is delivered to the patient (**8**), the medical device continues measuring the impedance (**2**). This closed loop may continue indefinitely. Alternatively, the current delivered to measure the impedance of the one or more regions of the brain may be applied for a limited period of time, such as periodically during relevant times during the day, or the algorithm employed by the medical device to measure the impedance and determine whether the impedance indicates a state within the brain that is indicative of a possibility of a seizure within the brain.

Typically, at least a part of the therapy delivery device is implanted within the patient. For example, if the therapy delivery device is an electrical stimulator, one or more medical leads including one or more electrodes for delivering electrical stimulation to the target tissue site within the body (e.g., brain) of the patient may be implanted within the patient and positioned to deliver stimulation directly to one or more regions of the brain. The one or more medical leads may also carry the electrodes used for measuring the impedance of the brain. Alternatively, one or more of the measurement electrodes may be deployed via different lead or formed on a housing associated with an implanted electrical stimulator or implanted sensing device, each of which may be referred to as an implantable medical device (IMD). As mentioned previously, electrical stimulator and sensing component may be combined in a common IMD. An electrical stimulator may be implanted within the patient or may be carried externally. If the electrical stimulator is implanted, the stimulator housing may include one or more electrodes for delivering electrical stimulation and/or sensing impedance.

In each of the embodiments discussed herein that include a medical device that is implanted in the patient's body, the implant site may be any suitable location, such as, but not limited to, in a pectoral region, upper back, lower back, lower abdomen, or buttocks. Alternatively, the medical device may be a cranial implant.

In another embodiment, in addition to or instead of delivering therapy to the patient when the measured impedance equals or exceeds a threshold value, a medical device may generate an alarm to indicate that there is an increased probability of a seizure. The alarm may be, for example, in the form of an audible sound, visual alert (e.g., a flashing light), a tactile alert (e.g., a mechanical vibration) or a combination of the audible, visual, and/or tactile alerts. Alternatively, other alerting techniques may be employed. The patient alarm may be useful if the patient is involved in an activity in which the patient and/or another person would be placed in a potentially harmful or compromising position if the patient experienced a seizure. The patient alarm may provide the patient with enough time to take measures to prevent any harm to himself or another person. For example, if the patient receives the seizure alarm while driving, the patient may pull over at the nearest available spot.

FIG. **1**B is a flow diagram illustrating another embodiment of method for predicting the onset of a seizure in a patient by measuring an impedance of the brain of the patient. The method shown in FIG. **1**B is similar to that shown in FIG. **1**A, except that rather than comparing the measured impedance to a threshold value (**4**) and delivering therapy (**8**) if the measured impedance is greater than or equal to the threshold value (**6**), the method shown in FIG. **1**B involves continuously monitoring a pattern (also referred to as a trend) in the measured impedance values (**9**). In this way, the method may use signal analysis techniques such as correlation to implement a closed-looped system for responding to the onset of a seizure.

If the pattern of the impedance measurements correlates well, i.e., matches, with a pattern template (**10**), therapy is delivered to the patient (**8**). In some embodiments, the template matching algorithm that is employed to determine whether the pattern matches the template (**10**) may not require a one hundred percent (100%) correlation match, but rather may only match some percentage of the pattern. For example, if the measured impedance values exhibit a pattern that matches about 75% or more of the template, the algorithm may determine that there is a substantial match between the pattern and the template. The pattern template may be generated in a trial phase, an example of which is shown in FIG. **2**B and described below. The template may be developed from recording the impedance activity prior to, and possibly during or after, an actual seizure. In one embodiment, a pattern for impedance values that characterize a brain state that will likely lead to a seizure is a rate of change of the impedance measurements over time. For example, a positive increase in the time rate of change (i.e., the slope or first derivative) of the impedance measurements may indicate a likelihood of a seizure, although a decrease (negative slope) in rate of change or another pattern may also be indicative of the likelihood of a seizure. Alternatively, if the time rate of change (i.e., the slope) of the impedance measurements matches or exceeds the time rate of change of the template, therapy may be delivered to the patient (**8**). The exact trend that is indicative of a brain state in which a seizure is likely may be determined during a trial phase, which is described below with reference to FIG. **2**B.

As various examples, the measured impedance signal may be analyzed for slope, amplitude, temporal correlation or frequency correlation with a template signal, or combinations thereof. If the measured impedance signal has a slope that exceeds a threshold, as mentioned above, a positive indication of seizure onset may be indicated. Alternatively, a correlation between inflection points in the amplitude waveform of the impedance signal or other critical points and a template may indicate a likelihood of a seizure onset.

For amplitude correlation, the amplitude of the measured impedance signal may be correlated with a threshold value, as described above. For temporal correlation, the signal may be sampled with a sliding window and compared to a template to identify a signal that correlates well with the template. For example, a processor of the implanted medical device or an external device may perform a correlation analysis by moving a window along a digitized plot of the amplitude of the measured impedance at regular intervals, such as between about one millisecond to about ten millisecond intervals, to define a sample of the impedance signal. The sample window is slid along the plot until a correlation is detected between the waveform of the template and the waveform of the sample of the impedance signal defined by the window. By moving the

window at regular time intervals, multiple sample periods are defined. The correlation may be detected by, for example, matching multiple points between the template waveform and the waveform of the plot of the impedance signal over time, or by applying any suitable mathematical correlation algorithm between the sample in the sampling window and a corresponding set of samples stored in the template waveform.

For frequency correlation, the impedance signal may be analyzed in the frequency domain to compare selected frequency components of the impedance signal to corresponding frequency components of the template signal. For example, one or more specific frequency bands may be more revealing than others, and the correlation analysis may include a spectral analysis of the impedance signal component in the revealing frequency bands. The frequency component of the impedance signal may be compared to a frequency component of a template.

In each of the embodiments described above, the one or more templates may be stored within the implanted medical device or an external device, such as a programming device for the implanted medical device. In some embodiments, different templates are employed and selected based on the patient physiological condition, which may be affected by, for example, the time of day or activity (e.g., sleeping, exercising, etc.).

FIG. **2**A is a flow diagram illustrating a technique for determining one or more threshold values to compare measured impedance values against in order to determine whether to deliver therapy to a patient. The absolute impedance value that indicates a high probability of seizure may differ depending on the patient. Factors that may affect the threshold value may include factors such as the age, size, and relative health of the patient. The threshold impedance values may even vary for a single patient, depending on fluctuating factors such as the state of hydration, which may affect the fluid levels within the brain of the patient. Accordingly, it may be desirable in some cases to measure the impedance of a particular patient over a finite trial period of time that may be anywhere for less than one week to one or more months in order to tune the trending data or threshold values to a particular patient.

It is also believed that it is possible for the relevant threshold values to be the same for two or more patients. In such a case, one or more previously generated threshold values may be a starting point for a clinician, who may adapt (or "calibrate" or "tune") the threshold values to a particular patient. The previously generated threshold values may be, for example, an average of threshold values for a large number (e.g., hundreds, or even thousands) of patients.

The impedance of a patient's brain is measured during a trial period of time (**11**). The impedance may be measured substantially continuously or at regular intervals, such as at a frequency of about 1 Hz to about 100 Hz. As previously discussed, the trial period may be anywhere from less than a week to one or more months. The trial period is preferably long enough to measure the impedance of the patient's brain at different hydration levels and during the course of different patient conditions (e.g., sleeping, exercising, eating, and so forth). As previously described, the impedance values may change depending on the fluid loading within the brain of the patient, which is typically not a constant value, as well as other known and/or unknown factors. In addition, it is also desirable for the trial period to span at least one seizure. Two or more seizures may be desirable in order to observe any possible fluctuations in the threshold values.

During the same trial period of time, the actual occurrence of a seizure is sensed and the date and time of the seizure are recorded (**12**). Any suitable technique may be used for detecting the actual occurrence of a seizure. In one embodiment, a system using known techniques of measuring and analyzing EEG or electrocorticogram (ECoG) waveforms may be used. EEG signals may be recorded via external or implanted electrodes, while ECoG signals, which are deep brain counterparts to EEG signals, typically require the implantation of electrodes on the surface of the brain itself or on the dura matter that surrounds the brain. In other embodiments, a system that detects an abnormal tremor or abnormal body movement, e.g., via one or more accelerometers may be used to detect the actual occurrence of a seizure. In yet another embodiment, a heart rate of the patient may be monitored, where a change in heart rate may indicate an onset of a seizure.

In another embodiment, a patient may provide feedback via a patient programmer or another device to indicate the occurrence of a seizure. The patient may, for example, press a button on a device prior to, during or after the actual occurrence of a seizure to cause the device to record the date and time, or alternatively, cause the medical device that includes the impedance sensing module to record the date and time of the seizure. As yet another alternative, the patient may manually input data relating to the date and time of the seizure into a device after the occurrence of the seizure. Patient feedback prior to the seizure may not be realistic or feasible because the patient typically cannot predict the onset of a seizure.

The impedance measurements are associated with the actual occurrence of a seizure (**14**) in order to determine the impedance value or values that are indicative of a brain state that may occur prior to the onset of a seizure. In one embodiment, a clinician or computing device may review the data relating to the occurrence of a seizure, and associate one or more impedance measurements with the occurrence of the seizure by matching the date and time of occurrence of the seizure with the impedance measurement that was recorded at substantially the same date and time, or within a certain range of the date and time. For example, the clinician may be interested in determining the impedance of one or more regions of the brain within a particular range of time prior to the onset of the seizure because such a time range may be more relevant to delivering preemptive therapy to prevent the onset of the seizure.

If more than one seizure occurred during the trial period, and the impedance values occurring within a certain time range prior to the onset of the seizure differ for each seizure, the clinician may average the impedance values or may use the lowest impedance value as the threshold value. Using the lowest impedance value is a conservative approach because although not all seizures occurred when the brain or region of the brain exhibited the lowest impedance value, at least one seizure occurred when the brain exhibited the lowest impedance value.

If the impedance was measured in more than one region of the patient's brain, the clinician may use the associated impedance measurements in order to determine which, if any, region exhibited changes in impedance prior to the actual occurrence of the seizure. If more than one region exhibited changes in impedance, the clinician may choose to monitor the region that exhibited the most consistent changes or greatest changes for the chronic impedance sensing and therapy delivery system. Alternatively, the impedance of more than one region of the brain may be monitored on a chronic basis (i.e., after the trial period when a therapy system is implanted in the patient for chronic therapy delivery).

After correlating the impedance measurements with the occurrence of a seizure, the clinician may record the relevant impedance values as the threshold value (**16**). Alternatively,

the correlation and threshold value recording may be automatically performed by a computing device or with the aid of a computing device.

FIG. **2**B is a flow diagram illustrating a technique for determining one or more trend templates to which a pattern in measured impedance values may be compared in order to predict a seizure. The technique shown in FIG. **2**B is similar that shown in FIG. **2**A, except that rather than associating the actual occurrence of a seizure with impedance measurements to determine a threshold value, the impedance measurements are associated with the seizure in order to determine a pattern or trend in the impedance measurements that occurred prior to the onset of the seizure. As with the threshold values, the trend in impedance measurements that indicates a high probability of seizure may differ depending on the patient. It is also believed that it is possible for the relevant trending data to be the same for two or more patients. In such a case, one or more previously generated trend templates may be a starting point for a clinician, who may adapt (or "calibrate" or "tune") the template to a particular patient.

In the technique shown in FIG. **2**B, after associating the actual occurrence of a seizure with more than one impedance measurement that was taken prior to the actual occurrence of the seizure (**14**), a pattern in the impedance values associated with the actual seizure may be determined (**16**). As previously discussed, the trend may be a rate of change, i.e., slope, of the impedance measurements, which are typically in the form of amplitude measurements, over time or a series of different slopes and transition points in a waveform of the impedance measurements. Thus, the associated impedance values would include the impedance values over a specific range of time prior to and possibly during the actual occurrence of the seizure. In one embodiment, the relevant period of time begins prior to the occurrence of the seizure and ends at the onset of the seizure. A pattern may be determined (**16**) by any suitable means. In one embodiment, the clinician may plot the impedance values over time and use the slope of the plot as the trend template. The slope of the plot represents the rate of change of the impedance values as a function of time. Alternatively, a computing device may generate the plot. After determining the relevant trend in impedance measurements that indicates the onset of a seizure, the clinician and/or computing device may record the trend in memory of a device and the trend may define a template for determining an onset of a future seizure (**18**).

In other embodiments, a pattern or trend other than a simple slope of the impedance measurements over time may define the template. For example, the template may include a series of different slopes and transition points in the waveform of the measured impedance.

FIG. **3** is a block diagram illustrating a medical device **20** that may be used during a first trial (or "learning") stage to determine the threshold impedance values or trend template to use in a system and method for treating seizures. In the example of FIG. **3**, medical device **20** includes impedance sensing module **22**, processor **24**, user interface **26**, seizure detection module **28**, memory **30**, and power source **31**. Medical device **20** may be used during a trial phase, e.g., prior to implantation of a chronic therapy delivery system for treating seizures.

Impedance sensing module **22** may include any suitable circuitry for measuring the impedance of the brain of a patient via one or more groups of electrodes **32**A-B, **34**A-B, **36**A-B, and **38**A-B that are implanted in different regions of the brain. Electrodes **32**A-B, **34**A-B, **36**A-B, and **38**A-B may be implanted to measure the impedance near key regions of the brain, which are regions of the brain that are relevant to the occurrence of seizures. The key regions of the brain may include, for example, regions of the brain to which therapy is delivered in order to treat or prevent seizures. Examples of key regions of the brain include the cortex (e.g., front or motor cortex), brainstem, cranial nerves (e.g., the vagus nerve), or deep brain regions, such as the anterior thalamus, ventrolateral thalamus, globus pallidus, substantia nigra pars reticulata, subthalamic nucleus, neostriatum, cingulated gyrus or the cingulate gyrus. In one embodiment, one or more sets of electrodes **32**A-B, **34**A-B, **36**A-B, and **38**A-B may be implanted to measure the impedance across the thalamus or cortex of the brain.

If a particular region of the brain is known to exhibit the most revealing changes in impedance values, the one or more groups of electrodes **32**A-B, **34**A-B, **36**A-B, and **38**A-B may be implanted in that region, rather than in different regions of the brain. Phantom lines indicating the grouping of the electrodes are shown in FIG. **3** for purposes of illustration. One example of a suitable impedance sensing circuit that may be included in impedance sensing module **22** is shown in FIGS. **6** and **7** and described below.

Each group of electrodes includes at least two electrodes in order to provide a current across tissue of the patient for the impedance measurement. At least one electrode of the group acts as an anode while the other electrode acts as the cathode. The stimulation current may be relatively low so that the patient does not feel the current. For example, the stimulation current may be in a range of about 500 nA to about 10 μA, although other stimulation currents may be used. Electrodes **32**A-B, **34**A-B, **36**A-B, and **38**A-B are electrically coupled to impedance sensing module **22** via conductors within implantable medical leads **40**A-B, **42**A-B, **44**A-B, and **46**A-B, respectively. In another embodiment, if medical device **20** is implanted within the patient, the housing of the medical device may be conductive or may include one or more electrodes that may act as an anode or cathode for delivering the impedance measuring stimulation current.

It may be desirable for electrodes **32**A-B to be implanted in the patient via a common burr cap hole, electrodes **34**A-B to be implanted via a common burr cap hole, and so forth with respect to electrodes **36**A-B and **38**A-B. In some embodiments, one or more electrodes in each group of electrodes **32**A-B, **34**A-B, **36**A-B, and **38**A-B may be disposed on a common housing of a cranial implant. The cranial implant may provide an advantage over leads in that the cranial implant may substantially fix the relative position of each electrode in the group of electrodes **32**A-B, **34**A-B, **36**A-B, and **38**A-B. That is, using electrodes **32**A-B as an example, when electrodes **32**A and **32**B are carried by a cranial implant, the cranial implant typically exhibits limited movement, and accordingly, electrodes **32**A and **32**B exhibit limited movement relative to each other.

Impedance sensing module **22** may provide processor **24** with a signal indicative of the measured impedance. Impedance sensing module **22** provides an impedance measurement by translating the impedance to an output voltage or current. The signal may be sent to processor **24** intermittently or near continuously. If a chopper stabilized instrumentation amplifier, such as the one shown in FIGS. **6** and **7**, is incorporated into impedance sensing module **22**, the amplifier amplifies and filters the output from electrodes **32**A-B, **34**A-B, **36**A-B, and **38**A-B to produce a stable, low noise signal with very low power requirements.

Processor **24** may include a microprocessor, a controller, a digital signal processor (DSP), an application specific integrated circuit (ASIC), a field programmable gate array (FPGA), discrete logic circuitry or the like. In some embodi-

ments, impedance sensing module **22** measures impedance by sending a known current across tissue of the patient, for example, from electrode **32**A to electrode **32**B, and determining the resulting voltage at electrode **32**B. In such embodiments, processor **24** may control the timing of the delivery of the stimulation current across electrodes **32**A-B, **34**A-B, **36**A-B, and/or **38**A-B, as well as the amplitude, pulse width, and rate of the stimulation current.

Processor **24** also controls seizure detection module **28**. Seizure detection module **28** implements any known methods for detecting the actual occurrence of a seizure. In one embodiment, seizure detection module **28** may include circuitry for measuring brain activity via EEG, which typically measures/monitors electrical activity of the brain by recording the voltage difference between electrodes placed on the scalp. In other embodiments, seizure detection module **28** includes circuitry for measuring brain activity via ECoG data, which typically measures/monitors electrical activity of the brain by recording the voltage difference between electrodes implanted subdurally or in the cerebral cortex of the brain. In the embodiment shown in FIG. **3**, electrodes **48**A-B are electrically coupled to seizure detection module **28** via leads **50**A-B. Electrodes **48**A-B may be implanted in some embodiments, and externally placed on the scalp of the patient in other embodiments.

Under the control of processor **24**, seizure detection module **28** may obtain EEG data, ECoG data, or other data indicative of seizures via electrodes **48**A-B and analyze the EEG, ECoG or other data using known techniques to determine when a seizure occurred. Processor **24** may receive a signal from seizure detection module **28** when an actual seizure occurred. Alternatively, processor **24** may receive EEG data, ECoG data, or other data from seizure detection module **28** and analyze the data to determine when a seizure occurred.

Many existing seizure prediction systems and methods rely on EEG data to determine when a seizure has started. In those existing systems, therapy may be delivered when the EEG data exhibits a certain characteristic. For example, in one seizure predicting procedure discussed in commonly-assigned U.S. Pat. No. 7,006,872, entitled, "CLOSED LOOP NEUROMODULATION FOR SUPPRESSION OF EPILEPTIC ACTIVITY," a seizure is predicted based on whether a sensed EEG starts to show synchrony as opposed to the normal stochastic features. In contrast, the present system and method monitors the impedance of the brain to predict the onset of a seizure before the actual occurrence of the seizure. It is believed that monitoring the impedance of the brain may be useful in predicting seizure before systems and methods monitoring EEG data. The earlier prediction of seizure provides a larger window of opportunity for delivering therapy to the patient to circumvent or preempt the seizure. An earlier detection of the seizure may help prevent delays in therapy delivery.

In addition, processing EEG data may consume more power than processing impedance data, at least with the impedance sensing circuitry shown in FIGS. **6** and **7** and described below. The lower power requirements of the present impedance-based system may help decrease the size of any medical devices incorporating the seizure prediction system as compare to those medical devices incorporating a seizure prediction system based on EEG data. Accordingly, a system relying on impedance to predict seizure may provide an additional advantage of decreasing the size of a medical device into which it is incorporated, which may be particularly beneficial in the case of an implanted medical device.

In an alternate embodiment, in addition to or instead of relying on EEG data, the occurrence of a seizure may be determined based on patient feedback. As described above, the patient may generate a patient marker via a patient programmer to record the date and time of a seizure. The patient marker may be created before, during or after the seizure. Regardless of the timing of the patient marker relative to the onset of the seizure, the patient marker alone should be sufficient data for the clinician or computing device to determine what impedance values are associated with the onset of a seizure.

Other techniques for determining when a seizure occurred may also be used. For example, other embodiments may include detection of abnormal tremor or abnormal body movement or monitoring the heart rate of the patient.

Processor **24** associates the actual occurrence of a seizure with impedance measurements (or signals representing the impedance measurements), and determines at least one threshold impedance value or a trend in impedance measurements that indicates a brain state indicative of a possibility of a seizure, such as a state just prior to the onset of a seizure. Processor **24** may use any of the techniques described above with respect to FIGS. **2**A and **2**B to find the relevant threshold value(s) or trends. For example, processor **24** may determine the rate of the change of the impedance values as a function of time during a time period beginning before the occurrence of the seizure. As another example, processor **24** may determine a threshold impedance value by associating one or more impedance measurements with the occurrence of the seizure by matching the date and time of occurrence of the seizure with the impedance measurement that was recorded at substantially the same date and time, or within a certain range of the date and time.

In some embodiments, processor **24** does not determine a threshold value or trend, but only stores the associated impedance measurements in memory **30** for later retrieval and analysis by a clinician, who may utilize another computing device to determine the threshold impedance value(s) or the relevant trends in impedance measurements. In addition to or instead of storing the associated impedance measurements, processor **24** may store all of the signals (or actual measured impedance values) from impedance sensing module **22**, as well as all of the signals from seizure detection module **28** in memory **30**.

Memory **30** of system **20** may include any volatile or non-volatile media, such as a RAM, ROM, NVRAM, EEPROM, flash memory, and the like. Memory **30** may also store program instructions that, when executed by processor **24**, cause impedance sensing module **22** to deliver stimulation to measure impedance of the brain and/or cause and seizure detection module **28** to sense seizures. Accordingly, computer-readable media storing instructions may be provided to cause processor **24** to provide functionality as described herein.

Impedance sensing module **22**, processor **24**, and seizure detection module **28** may be coupled to power source **47**. Power source **47** may take the form of a small, rechargeable or non-rechargeable battery, or an inductive power interface that transcutaneously receives inductively coupled energy. In the case of a rechargeable battery, power source **47** similarly may include an inductive power interface for transcutaneous transfer of recharge power.

Medical device **20** may be external to the patient and may utilize external electrodes **32**A-B, **34**A-B, **36**A-B, **38**A-B, and **48**A-B. Alternatively, electrodes **32**A-B, **34**A-B, **36**A-B, **38**A-B may be implanted while electrodes **48**A-B for seizure detection module **28** are external to the patient. As yet another alternative, all electrodes **32**A-B, **34**A-B, **36**A-B, **38**A-B, and **48**A-B may be implanted within the brain of the patient. In

embodiments in which medical device **20** includes both internal and external components, impedance sensing module **22**, processor **24**, user interface **26**, seizure detection module **28**, memory **30**, and/or power source **31** may be separate housings. The housings may be rigid or flexible, and may be fabricated from any suitable biocompatible material, such as titanium or silicone. For example, in embodiments in which electrodes **32**A-B, **34**A-B, **36**A-B, **38**A-B, which are electrically coupled to impedance sensing module **22**, are implanted within the patient, but electrodes **48**A-B, which are electrically coupled to seizure detection module **28**, are attached to an external surface of the patient, impedance sensing module **22** may be in a separate housing from the other components of medical device **20**. Impedance sensing module **22** may be implanted within the patient and telemetrically coupled to processor **24**, which may be in a housing carried externally.

User interface **26** is optional and is thus shown in phantom lines in FIG. **3**. In embodiments in which medical device **20** includes an external component, medical device **20** may include user interface **26** is optional. User interface **26** may include a display, input device (e.g., a keyboard, touch screen, buttons, a mouse, etc.) for a clinician to retrieve information from memory **30**, program processor **24**, and/or otherwise interact with processor **24**. Alternatively, the clinician may retrieve information from memory **30** and/or program processor **24** via wired or wireless telemetry.

FIG. **4** is a block diagram illustrating an embodiment of an implantable medical device (IMD) **56** that may be used to predict the onset of a seizure in a patient and deliver therapy to prevent the onset of the seizure or to otherwise mitigate the effects of the seizure. In other embodiments, implantable medical device **56** may include both implanted and external portions. Medical device **56** includes impedance sensing circuit **58**, processor **60**, memory **62**, and power source **63**, which may be the same as the impedance sensing circuit **22**, processor **24**, memory **30**, and power source **31**, respectively, of medical device **20**. Medical device **56** also includes telemetry module **61** and therapy delivery module **64**.

If medical device **56** includes more than one portion, the different portions may communicate via wired or wireless telemetry. For example, if impedance sensing module **58** is enclosed in a separate housing from processor **60** and therapy delivery module **64**, impedance sensing module **58** may provide processor **60** with impedance measurements via wireless telemetry.

As with impedance sensing module **22** of medical device **20**, impedance sensing module **58** may measure the impedance of the brain via electrodes **32**A-B, which are coupled to impedance sensing circuit **58** via leads **40**A-B. A relatively low stimulation current may be delivered across a region of the brain via electrodes **32**A-B. For example, the stimulation current may be in a range of about 500 nA to about 10 μA, although other stimulation currents may be used. If desired, multiple sets of electrodes may be used to sense the impedance in the same region of the brain or in multiple regions of the brain. By placing electrodes in more than one region in the patient's brain, the impedance at more than one region may be monitored. The impedance may be more revealing in one brain region than in other regions. In some embodiments, the housing of medical device **56** may include one or more electrodes for delivering stimulation current to measure impedance and/or at least a part of the housing of medical device **56** may be conductive act as an electrode. In those embodiments, impedance may be sensed via two or more electrodes on the housing of medical device **56** or via at least one electrode on the housing of medical device **56** and at least one of electrodes **32**A-B. Other sensing electrode arrangements may also be used.

Impedance sensing circuitry associated with sensing electrodes **32**A-B is provided within impedance sensing module **58**. In general, impedance sensing module **58** provides a measurement of an impedance of the brain by translating the sensed impedance to an output voltage or current. The output of impedance sensing module **58** may be received by processor **60**. Processor **60** may apply additional processing, e.g., convert the output to digital values for processing. In some embodiments, processor **60** stores the values in memory **62**, and/or transmits the values to an external programmer via telemetry module **61**. processor **60** may also control the timing of the delivery of the stimulation current via electrodes **32**A-B for measuring impedance.

Processor **60** also controls the delivery of therapy to the patient based on the output of impedance sensing module **58**. In one embodiment, processor **60** analyzes the measured impedance to determine whether the brain of the patient (i.e., one or more regions within the brain) is in a state indicative of a possibility of a seizure. If processor **60** determines the brain is the state indicative of a possibility of a seizure, processor **60** may generate a seizure indication. The seizure indication may be a value, flag, or signal that is stored or transmitted to indicate determination of a seizure. Therapy delivery module **64** or processor **60** may take action in response to the seizure indication. The generation of the seizure indication may cause, for example, therapy delivery module **64** to deliver therapy to the patient or cause processor **60** to generate an alarm or other notification that indicates the possibility that a seizure may occur. In some embodiments, processor **60** may record the seizure indication in memory **62** for retrieval and further analysis by a clinician. For example, seizure indications may be recorded over time, e.g., in a loop recorder, and may be accompanied by impedance values associated with the seizure indications. In general, the generation of the seizure indication may cause processor **60** to take some action or instruct another module **58**, **61** or **64** to take some action. Alternatively, impedance sensing module **58** or another module within medical device **56**, an external programming device, or another type of external computing device may include a processor that processes the impedance measurements and generates one or more seizure indications when the impedance measurements indicate the brain in the state that is indicative of a possibility of a seizure.

As other examples, processor **60** may receive the impedance measurements from impedance sensing circuit **58** and compare the measured impedance to one or more threshold values that were determined during a first stage of the therapy program using, for example, medical device **20** shown in FIG. **3**. For example, in one embodiment, when the measured impedance value is greater than or equal to the threshold value, processor **60** may control therapy delivery module **64** to deliver electrical stimulation therapy to the patient via electrodes **65**A-D of lead **66**. Alternatively, therapy delivery module **64** may deliver stimulation therapy via one or more electrodes on a housing of medical device **56**. For example, electrical stimulation may be delivered via two or more electrodes on the housing of medical device **56** or via at least one electrode on the housing (or a conductive housing itself) of medical device **56** and at least one of electrodes **65**A-B. Other stimulation electrode arrangements may also be used.

As another example, processor **60** may receive the impedance measurements from impedance sensing circuit **58** and compare the trend of the impedance measurements to one or more trend templates. Processor **60** may implement an algo-

rithm that recognizes a trend of impedance measurements that characterize a brain state that is predictive of the onset of a seizure. If the trend of the impedance measurements matches or substantially matches the trend template, processor **60** controls therapy delivery module **64** to deliver electrical stimulation to the patient via electrodes **65**A-D of lead **66** or via at least one electrode on the housing of medical device **56** or a conductive housing of medical device **56**. As previously described, instead of or in addition to delivering therapy in response to measured impedance measurements that substantially match the trend template, a patient alarm may be activated, processor **60** may record the date and time of the impedance measurements and/or the actual impedance measurements for future analysis by a clinician, a signal may be transmitted to another device (e.g., an external programming device) that records the date and time of the impedance measurements, and so forth.

In some embodiments, the electrical stimulation therapy is delivered to regions of the brain that are directly related to seizures. For example, electrical stimulation may be delivered to the thalamus or the cortex of the brain. Electrodes **65**A-D are electrically coupled to therapy delivery module **64** via conductors within lead **66**. In one embodiment, an implantable signal generator or other stimulation circuitry within therapy delivery module **64** delivers electrical signals (e.g., pulses or substantially continuous-time signals, such as sinusoidal signals) to a target stimulation site within the brain via at least some of electrodes **64** under the control of a processor **60**. The signals may be delivered from therapy delivery module **64** to electrodes **65**A-D via a switch matrix and conductors carried by lead **66** and electrically coupled to respective electrodes **65**A-D. The implantable signal generator within therapy delivery module **64** may be coupled to power source **63**.

The exact parameters of the stimulation therapy, such as the amplitude or magnitude of the stimulation signals, the duration of each stimulus, the waveform of the stimuli (e.g., rectangular, sinusoidal or ramped signals), may be specific for the particular target stimulation site (e.g., the region of the brain) involved as well as the particular patient. In the case of stimulation pulses, the stimulation therapy may be characterized by selected pulse parameters, such as pulse amplitude, pulse rate, and pulse width. In addition, if different electrodes are available for delivery of stimulation, the therapy may be further characterized by different electrode combinations. Known techniques for determining the optimal stimulation parameters may be employed. In one embodiment, electrodes **65**A-D are implanted to deliver stimulation therapy to an anterior nucleus of the thalamus of the brain of the patient, and stimulation therapy is delivered via a select combination of electrodes **65**A-D to the anterior nucleus with electrical stimulation including a frequency of 120 Hz, a voltage of about 4 volts, and a pulse width of about 100 microseconds. However, other embodiments may implement stimulation therapy including other stimulation parameters.

In the embodiment of FIG. **4**, lead **66** is substantially cylindrical. In other embodiments, lead **66** may be paddle-shaped (i.e., a "paddle" lead). Electrodes **65**A-D may be ring electrodes, segmented or partial ring electrodes. The configuration, type, and number of electrodes **65**A-D and leads **66** illustrated in FIG. **4** are merely exemplary. In other embodiments, two or more leads **66** may be coupled either directly or indirectly (e.g., via a lead extension) to therapy delivery module **64** of medical device **56**.

Processor **60** also controls telemetry module **61** to exchange information with an external programmer, such as a clinician programmer and/or patient programmer by wired or wireless telemetry. Processor **60** may control telemetry module **61** to communicate with the external programmer on a continuous basis, at periodic intervals, or upon request from the programmer. Telemetry module **61** may operate as a transceiver that receives telemetry signals from an external programmer and transmits telemetry signals to an external programmer. Telemetry module **61** may also include a transmitter to transmit signals from IMD **56** to an external programmer or to another IMD or external medical device.

In some embodiments, telemetry module **61** may include a chopper stabilized instrumentation amplifier, such as one shown in FIGS. **6** and **7**. More specifically, the receiver portion of telemetry module **61** may include the back end of a chopper stabilized instrumentation amplifier, referred to as a chopper stabilized mixer amplifier and feedback path, which produces a baseband signal from a received telemetry signal. The receiver portion is described in this disclosure as including only the back end (chopper stabilized mixer amplifier) because the corresponding front end is located in the transmitter portion of an external programmer or another device in communication with medical device **56**.

The receiver portion may also include a clock synchronizer that includes another chopper stabilized mixer amplifier, e.g., as further described in commonly-assigned U.S. patent application Ser. No. 11/700,404, entitled, "CHOPPER-STABILIZED INSTRUMENTATION AMPLIFIER," to Timothy J. Denison and filed on Jan. 31, 2007, U.S. patent application Ser. No. 11/700,738, entitled, "CHOPPER-STABILIZED INSTRUMENTATION AMPLIFIER FOR WIRELESS TELEMETRY," to Timothy J. Denison and filed on Jan. 31, 2007, and U.S. patent application Ser. No. 11/700,405, entitled, "CHOPPER-STABILIZED INSTRUMENTATION AMPLIFIER FOR IMPEDANCE MEASUREMENT," to Timothy J. Denison and filed on Jan. 31, 2007, the entire content of each of which is incorporated herein by reference. A chopper stabilized mixer amplifier as described in the aforementioned patent applications can produce an output that can be used by a phase lock loop to generate a correction signal that is used to synchronize the receiver portion of telemetry module **61** with the transmitter of the external programmer. The transmitter may include a front end of a chopper-stabilized instrumentation amplifier in the sense that it may include a first chopper stage that modulates an input signal with a radio frequency (RF) for transmission to an external programmer or another implanted or external medical device.

FIG. **5** is block diagram of another embodiment of an implantable medical device **70**, which is similar to medical device **56** of FIG. **4**. Unlike therapy delivery module **64** of FIG. **4**, which delivers electrical stimulation therapy to a patient via lead **66**, therapy delivery module **72** of FIG. **5** is configured to deliver a pharmaceutical agent to a patient via catheter **74** upon the prediction of a seizure. Catheter **74** may be any suitable fluid delivery conduit, and therapy delivery module **72** may be any suitable fluid delivery device, such as a drug pump. Upon detecting the onset of a seizure via impedance values measured by impedance sensing circuit **60**, processor **60** may control therapy delivery module **72** to deliver a bolus of a drug to the patient. The drug may be delivered directly to target tissue sites within the brain to mitigate the effects of a seizure or to prevent the onset of a seizure. Examples of suitable pharmaceutical agents for treating seizures include, but are not limited to, sodium valproate, benzodiazepine, barbiturates (e.g., Phenobarbital/primidone), ethosuximide, gabapentin, phenytoin, and carbamazepine.

FIG. **6** is a block diagram illustrating an embodiment of a chopper stabilized instrumentation amplifier **80**, which may

be incorporated into a medical device, for measuring the impedance of one or more regions of the brain of a patient. Instrumentation amplifier **80** may be included in impedance sensing modules **22** and **58** of medical devices **20** (FIG. **3**) and **56** (FIG. **4**), respectively. An instrumentation amplifier configured for impedance measurement and suitable for use as instrumentation amplifier **80** is described in further detail in the aforementioned, commonly-assigned U.S. patent application Ser. No. 11/700,404, entitled, "CHOPPER-STABILIZED INSTRUMENTATION AMPLIFIER," to Timothy J. Denison. Instrumentation amplifier **80** is configured to achieve stable measurement of impedance values of a brain of a patient at low frequency with very low power.

An impedance sensing module incorporating instrumentation amplifier **80** is alternating current (AC) coupled, which minimizes the possibility of stimulating tissue when delivering an impedance-measuring stimulation current to the tissue within the brain. In general, it is desirable to avoid inadvertently stimulating tissue with the stimulation current used for measuring impedance in order to prevent the patient from feeling the stimulation current (which differs from the stimulation current delivered for therapy delivery), and in order to inadvertently cause muscle or nerve stimulation. In addition, the AC coupling of the impedance sensing module helps prevent corrosion to the electrodes used to measure impedance (e.g., electrodes **32**A-B of FIGS. **3** and **4**).

Instrumentation amplifier **80** uses a differential architecture and a mixer amplifier to substantially eliminate 1/f noise, popcorn noise, and offset. Dynamic limitations, i.e., glitching, that result from chopper stabilization at low power are eliminated through a combination of chopping at low impedance nodes within a mixer amplifier **84** and feedback via feedback path **86**. The signal path of the instrumentation amplifier operates as a continuous time system, providing minimal aliasing of noise or external signals entering the signal pathway at the chop frequency or its harmonics. As a result, instrumentation amplifier **80** can provide stable measurements for low frequency signals, such as physiological signals and other signals having a frequency of less than approximately 100 hertz (Hz), and preferably less than or equal to approximately 2.0 Hz, and more preferably less than or equal to approximately 1.0 Hz, while operating under the constraints of a micro power system, e.g., drawing a supply current of less than or equal to approximately 2.0 microamps, and more preferably less than or equal to approximately 1.0 microamps, and requiring a supply voltage of less than or equal to approximately 2.0 volts, and more preferably less than or equal to approximately 1.5 volts.

As shown in FIG. **6**, instrumentation amplifier **80** includes front end **82**, mixer amplifier **84**, and feedback path **86**. In the example of FIG. **6**, front end **82** may provide a switched or static capacitive differential interface to mixer amplifier **84**, e.g., for measurement of a low frequency voltage amplitude. Front end **82** is configured for impedance measurement. Front end **82** couples a differential modulated (chopped) input signal that carries a low frequency signal of interest on a carrier (chopper) frequency. In other words, front end **82** shifts a low frequency signal that is subject to introduction of low frequency noise by mixer amplifier **84** to a carrier frequency at which the mixer amplifier **84** does not introduce substantial noise into the signal. The low frequency signal of interest may have, for example, a frequency within a range of approximately 0 Hz to approximately 100 Hz. In some embodiments, the carrier (chopper) frequency may be within a frequency range of approximately 4 kHz to 100 kHz. Front end **82** modulates the low frequency signal prior to introduction to mixer amplifier **84** so that the original baseband (low frequency) signal components are not corrupted by noise components introduced by mixer amplifier **84** at low frequency.

Noise generally enters the signal path of instrumentation amplifier **80** through mixer amplifier **84**. However, mixer amplifier **84** should not introduce noise to the modulated signal at the carrier frequency. Rather, the noise components are typically present at low frequency and may include 1/f noise or popcorn noise. In addition, noise in the form of dc offset cannot be introduced at the carrier frequency. Mixer amplifier **84** receives and amplifies the up-modulated input signal from front end **82**. Again, the up-modulated input signal is up-modulated to the chopper frequency to protect the input signal from low frequency noise and offset.

Mixer amplifier **84** demodulates the modulated input signal from the carrier frequency to the baseband of interest while upmodulating the mixer amp 1/f noise and offset out of the measurement band. Thus, the original low frequency signal components are demodulated back to baseband without the low frequency noise and offset components of the mixer amplifier **84**. Mixer amplifier **84** passes only the baseband signals, i.e., signals with frequency components of approximately 100 Hz or less, as output and substantially reduces or eliminates the noise components located at the carrier frequency. Thus, the output of instrumentation amplifier **80** contains the low frequency signal components of interest. In addition, mixer amplifier **84** provides a gain amplifier that amplifies the input signal. In this way, instrumentation amplifier **80** provides a low noise output while operating at low power.

Instrumentation amplifier **80** operates under the constraints of a micro power system and therefore has limited bandwidth. The limited bandwidth of instrumentation amplifier **80** can cause glitching or ripple in the passband of the output signal. As will be described, mixer amplifier **84** may have a modified folded cascode architecture that provides switching, e.g., via CMOS switches, at low impedance nodes. Switching at low impedance nodes enables chopping at higher frequencies where the only limitation would be the charge injection residual offset.

Feedback path **86** is coupled between the output of mixer amp **84** and front end **82** to reduce the ripple. Feedback path **86** may have a differential configuration that substantially eliminates glitching in the output signal by driving the net input signal to mixer amplifier **84** toward zero. In this way, feedback path **86** keeps the signal change at the input of mixer amplifier **84** relatively small in steady state. As a result, instrumentation amplifier **80** achieves a stable, low noise, low distortion output while operating at low power.

An impedance sensing module of a medical device may include multiple instrumentation amplifiers **80**. For example, multiple instrumentation amplifiers **80** may be provided in parallel to provide multiple sensing channels. The multiple sensing channels may sense impedance, e.g., at different positions or angles, or via different electrodes. In addition, multiple sensing channels may sense different types of physiological information in addition to impedance, such as electrocardiogram (ECG), electroencephalogram (EEG), electromyogram (EMG), pressure, motion, and the like.

Front end **82** of instrumentation amplifier **80** includes an impedance sensor. In particular, instrumentation amplifier **80** may form a biological impedance sensing device for measuring the impedance of tissue of a brain of a patient. In this way, instrumentation amplifier **80** may be incorporated into a system for detecting seizures and delivering therapy to prevent or otherwise treat the seizure, as described in this disclosure. The impedance sensor formed by front end **82** produces an AC modulated signal that is AC coupled to mixer amplifier **84**

through the tissue of the patient. In this case, front end **82** modulates stimulation current to modulate the amplitude of a tissue voltage signal, thereby chopping the impedance signal produced by application of the stimulation current source to the patient brain tissue. Thus, the patient is not exposed to a direct current (DC) signal. Moreover, the modulated signal may not substantially excite the tissue, thereby decreasing the likelihood that the patient may experience discomfort or other detrimental effects from the modulated signal.

According to another example embodiment, front end **82** of amplifier **80** may comprise a continuous time switched capacitor network. The switched capacitor network includes a differential set of switched input capacitors that toggle between input voltages at the positive and negative terminals of instrumentation amplifier **80**. By toggling the switched input capacitors at the chopper frequency, the differential input signal is chopped. In this manner, the differential input signal is up-modulated to the carrier frequency, yielding a modulated signal at the differential input of mixer amplifier **84**. Accordingly, the inputs to front end **82** may be from electrodes positioned to measure the impedance of a tissue site within the brain.

According to an additional example embodiment, feedback **86** may include a second feedback path (not shown in FIG. **6**) in addition to the previously described negative feedback path that reduces glitching in the output of instrumentation amplifier **80** and provides the nominal gain for amplifier **80**. This second feedback path provides negative feedback to allow for the construction of a high pass filter. The second feedback path is dominant at low frequencies, i.e., frequencies lower than the cutoff frequency, and the chopper stabilized negative feedback path is dominant at passband frequencies. The high pass filter may have a cutoff frequency approximately equal to, e.g., approximately 2.5 Hz, or 0.5 Hz, or 0.05 Hz. In this case, the first feedback path, i.e., the "chopper stabilizing" feedback path that eliminates glitching at the output, is dominant at pass band frequencies and the second "high-pass filter" feedback path is dominant at low frequencies. The corner frequency of the high pass filter in the second feedback path can be set by the scaling of feedback capacitors in the first feedback path and the time-constant of a switched capacitor integrator in the second feedback path. As one example, the high pass filter provided by this feedback path may be useful for filtering out electrode offsets. The second feedback path may include a high-pass integrator that is chopper stabilized for the lowest 1/f noise floor.

According to yet another embodiment, feedback **86** may include a third feedback path in addition to the first feedback path (not shown in FIG. **6**). The third feedback path provides positive feedback to increase the input impedance of instrumentation amplifier **80**. The increased input impedance is achieved by sampling the output of instrumentation amplifier **80** and applying a scaled charge to the input of the switched capacitors in front end **82** to provide compensatory charge at the sensor input. The scaled charge may be applied at a point in the signal flow prior to chopping of the input signal. The injected current effectively "replaces" charge lost during the sampling of input chopper capacitors in front end **82**. This charge replacement feedback may be considered similar to base current compensation. The positive feedback may increase the equivalent low-frequency input impedance of instrumentation amplifier **80** by an order of magnitude or more. This third feedback path may not be necessary in various applications. If increased input impedance is desired, however, this third feedback path can be readily added.

According to a further example embodiment, instrumentation amplifier **80** may include the previously described second and third feedback paths in addition to the first (chopper stabilizing) feedback path. In this case, the third feedback path does not tap off of the output signal of instrumentation amplifier **80** as previously described. Rather, the third, positive feedback path may tap off of an integrated signal provided by the second, high-pass filter feedback path. Accordingly, various combinations of first, second, and/or third feedback paths may be provided to address glitching, low frequency rejection, and/or amplifier input impedance. In each case, however, instrumentation amplifier **80** includes a front end **82** configured to apply a stimulation current for impedance measurement in combination with means for chopping the stimulation current to produce a chopped impedance signal for application to mixer amplifier **84**.

Instrumentation amplifier **80** can provide one or more advantages in a variety of embodiments. For example, as previously described, instrumentation amplifier **80** can achieve stable measurements at low frequency with low power. This is a result of the basic architecture of instrumentation amplifier **80**. As another advantage, on-chip, poly-poly capacitors may be used to implement feedback capacitors in instrumentation amplifier **80**. Poly-poly capacitors enable fast switching dynamics and can be formed on-chip with other amplifier components. A poly-poly capacitor may be formed on chip with other devices by combining two polysilicon electrodes and an intervening silicon dioxide dielectric. The gain of the instrumentation amplifier can be set by the ratio of the feedback capacitors to the input capacitors and centered around a selected reference voltage. Further, by modulating the input signal at front end **82**, the common mode input voltage can swing from rail to rail and mixer amplifier **84** is still able to extract a differential voltage. These advantages are merely exemplary and should be considered a subset of potential advantages provided by instrumentation amplifier **80**. Additional advantages are discussed in this disclosure or may occur to those skilled in the art upon consideration of this disclosure. Moreover, such advantages may not coexist in every embodiment.

FIG. **7** is a block diagram illustrating a signal path flow of one embodiment of instrumentation amplifier **80** that may be incorporated into impedance sensing modules **22** (FIG. **3**) or **58** (FIG. **4**). In general, a known stimulation current **102** is introduced across at least two electrodes positioned in the brain, and mixer amplifier **84** measures the resulting voltage. Based on the known stimulation current ISTIM and resulting voltage, instrumentation amplifier **80** may determine the impedance across the two electrodes, and accordingly, the impedance of the selected brain tissue.

In FIG. **7**, front end **82** includes modulator **90** for modulating a low frequency input signal **102** to produce modulated input signal **91**. Modulator **90** chops the input signal **102**, providing a chopped stimulation current for application across a tissue load. An input capacitance (Cin) **83** couples the output of modulator **90** to summing node **92**. For a differential input signal, Cin **83** may include a first input capacitor coupled to a first input of mixer amplifier **84** and a second input capacitor coupled to a second input of mixer amplifier **84**. Modulator **90** modulates a differential amplitude of input signal **102** to a carrier frequency provided by clock signal **91**A. Clock signal **91**A, like other clock signals described in this disclosure, may be a square wave signal that effectively multiplies the signal by plus 1 and minus 1 at a desired clock frequency. In this manner, module **90** chops the input signal **102** prior to application of the input signal to the tissue load and mixer amp **84**. Modulator **90** may, in some embodiments, comprise a pair of complementary metal oxide semiconductor (CMOS) single pole, double throw (SPDT) switches that

are driven by clock signal **91**A to modulate (chop) input signal **102** to the carrier frequency. The CMOS SPDT switches may be cross-coupled to each other to reject common mode signals.

In one example embodiment, the CMOS switches may be coupled to a set of differential capacitors to form a continuous time switched capacitor network that forms input capacitance Cin at the input of mixer amplifier **84**. In another example embodiment, the CMOS switches may be coupled to capacitors that AC couple modulated input signal **102** to the input of mixer amplifier **84**. In this case, front end **82** is an impedance sensor that modulates a stimulation current that is applied across tissue of a patient.

Feedback summing node **92** will be described below in conjunction with feedback path **86**. Summing node **94** represents the introduction of offset and 1/f noise within mixer amplifier **84**. At summing node **94**, the original baseband components of input signal **102** are located at the carrier frequency. The baseband signal components of input signal **102** may have a frequency within a range of approximately 0 Hz to approximately 100 Hz and the carrier frequency may be approximately 4 kHz to approximately 10 kHz. Noise **93** enters the signal pathway at summing node **94** to produce noisy modulated input signal **95**. Noise **93** may include 1/f noise, popcorn noise, offset, and any other external signals that may enter the signal pathway at low (baseband) frequency. At node **94**, however, the original low frequency components have already been chopped to a higher frequency band by modulator **90**. Thus, the low frequency noise **93** is segregated from the original low frequency components.

Mixer amplifier **84** receives noisy modulated input signal **95** from node **94**. In the example of FIG. **7**, mixer amplifier **84** includes gain amplifier **96**, modulator **98**, and integrator **100**. Amplifier **96** amplifies noisy modulated input signal **95** to produce amplified signal **97**. Modulator **98** demodulates amplified signal **97**. That is, modulator **98** modulates noise **93** up to the carrier frequency and demodulates the original baseband signal components from the carrier frequency back to baseband. Modulator **98** may comprise switches, e.g., CMOS SPDT switches, located at low impedance nodes within a folded-cascode architecture of mixer amplifier **84**. Modulator **98** is supplied with clock signal **91**B to demodulate amplified signal **97** at the same carrier frequency as clock signal **91**A. Hence, clock signals **91**A, **91**B should be synchronous with each other. In some embodiments, clock signal **91**A and clock signal **91**B may be the same signal, i.e., supplied by the same clock. In other embodiments, e.g., for measurement of reactance, the relative phasing of clock signals **91**A, **91**B and **91**C may be altered.

Integrator **100** operates on demodulated signal **99** to pass the low frequency signal components at baseband and substantially eliminate noise components **93** at the carrier frequency. In this manner, integrator **100** provides compensation and filtering. In other embodiments, compensation and filtering may be provided by other circuitry. However, the use of integrator **100** as described in this disclosure may be desirable. Feedback path **86**, as shown in FIG. **7**, provides negative feedback to the input of mixer amp **84** to reduce glitching in output signal **101**. In particular, feedback path **86** drives modulated signal **95** toward zero in steady state. In this way, feedback **86** keeps the signal change at the input to mixer amplifier **84** small. Feedback path **86** includes a modulator **104**, which modulates output signal **101** to produce a differential feedback signal **105** that is added to the signal path between front end **82** and mixer amplifier **84** at node **92**.

Feedback path **86** provides capacitor scaling versus the input capacitance Cin of mixer amplifier **84** to produce attenuation and thereby generate gain at the output of amplifier **80**. Accordingly, feedback path **86** may include a feedback capacitance (Cfb) **87** that is selected to produce desired gain, given the value of the input capacitance (Cin) **83** of mixer amplifier **84**. Integrator **100** may be designed to provide a stable feedback path **86** with acceptable bandwidth while also filtering out the upmodulated offset and 1/f noise from the measurement band.

Clock signal **91**C drives modulator **104** in feedback path **86** to modulate output signal **101** at the carrier frequency. Clock signal **91**C may be derived from the same clock as clock signal **91**B. However, because output signal **101** is single ended, feedback **86** includes two feedback paths that apply the negative feedback to the positive and negative input terminals of mixer amplifier **84**. Thus, the two feedback paths should be 180 degrees out of phase with each other, with one of the feedback paths modulating synchronously with modulator **98**. This ensures that a negative feedback path exists during each half of the clock cycle.

As an alternative, in some embodiments, mixer amplifier **84** may be configured to generate a differential output signal, rather than a single-ended output signal. A differential output signal may provide positive and negative outputs. In this case, feedback path **86** can feed back the positive output to the positive input of mixer amplifier **84** and feed back the negative output to the negative input of the mixer amplifier. For a differential output signal, feedback path **86** would modulate each of the positive and negative outputs. However, the positive and negative outputs could be modulated in-phase, rather than out of phase. Although a differential output is possible, a feedback path **86** configured to convert a single-ended output to differential feedback will be described herein for purposes of illustration.

In FIG. **7**, only the previously described negative feedback path **86** is shown. That is, the previously described feedback paths for increasing input impedance and constructing a high pass filter are excluded from FIG. **7**. These feedback paths are excluded in FIG. **7** because they are not necessary for proper operation of instrumentation amplifier **80**. However, the feedback paths may be included in other applications.

FIG. **8** is a circuit diagram illustrating an example embodiment of mixer amplifier **84** of instrumentation amplifier **80** in greater detail. As previously described, mixer amplifier **84** amplifies noisy modulated input signal **95** to produce an amplified signal and demodulates the amplified signal. Mixer amplifier **84** also substantially eliminates noise from the demodulated signal to generate output signal **101**. In the example of FIG. **8**, mixer amplifier **84** is a modified folded-cascode amplifier with switching at low impedance nodes. The modified folded-cascode architecture allows the currents to be partitioned to maximize noise efficiency. In general, the folded cascode architecture is modified in FIG. **8** by adding two sets of switches. One set of switches is illustrated in FIG. **8** as switches **106**A and **106**B (collectively referred to as "switches **106**") and the other set of switches includes switches **108**A and **108**B (collectively referred to as "switches **108**").

Switches **106** are driven by chop logic to support the chopping of the amplified signal for demodulation at the chop frequency. In particular, switches **106** demodulate the amplified signal and modulate front-end offsets and 1/f noise. Switches **106** are embedded within a self-biased cascode mirror formed by transistors M**6**, M**7**, M**8** and M**9**, and are driven by chop logic to up-modulate the low frequency errors from transistors M**8** and M**9**. Low frequency errors in transistors M**6** and M**7** are attenuated by source degeneration from transistors M**8** and M**9**. The output **101** of amplifier **96**

is at baseband, allowing an integrator formed by transistor M10 and capacitor 110 (Ccomp) to stabilize feedback path 86 (not shown in FIG. 8) and filter modulated offsets.

Mixer amplifier 84 has three main blocks: a transconductor, a demodulator, and an integrator. The core is similar to a folded cascode. In the transconductor section, transistor M5 is a current source for the differential pair of input transistors M1 and M2. In some embodiments, transistor M5 may pass approximately 800 nA, which is split between transistors M1 and M2, e.g., 400 nA each. Transistors M1 and M2 are the inputs to amplifier 84. Small voltage differences steer differential current into the drains of transistors M1 and M2 in a typical differential pair way. Transistors M3 and M4 serve as low side current sinks, and may each sink roughly 500 nA, which is a fixed, generally nonvarying current. Transistors M1, M2, M3, M4 and M5 together form a differential transconductor.

In this example, approximately 100 nA of current is pulled through each leg of the demodulator section. The AC current at the chop frequency from transistors M1 and M2 also flows through the legs of the demodulator. Switches 106 alternate the current back and forth between the legs of the demodulator to demodulate the measurement signal back to baseband, while the offsets from the transconductor are up-modulated to the chopper frequency. As discussed previously, transistors M6, M7, M8 and M9 form a self-biased cascode mirror, and make the signal single-ended before passing into the output integrator formed by transistor M10 and capacitor 110 (Ccomp). Switches 106 placed within the cascode (M6-M9) upmodulate the low frequency errors from transistors M8 and M9, while the low frequency errors of transistor M6 and transistor M7 are suppressed by the source degeneration they see from transistors M8 and M9. Source degeneration also keeps errors from Bias N2 transistors 66 suppressed. Bias N2 transistors M12 and M13 form a common gate amplifier that presents a low impedance to the chopper switching and passes the signal current to transistors M6 and M7 with immunity to the voltage on the drains.

The output DC signal current and the upmodulated error current pass to the integrator, which is formed by transistor M10, capacitor 110, and the bottom NFET current source transistor M11. Again, this integrator serves to both stabilize the feedback path and filter out the upmodulated error sources. The bias for transistor M10 may be approximately 100 nA, and is scaled compared to transistor M8. The bias for lowside NFET M11 may also be approximately 100 nA (sink). As a result, the integrator is balanced with no signal. If more current drive is desired, current in the integration tail can be increased appropriately using standard integrate circuit design techniques. Various transistors in the example of FIG. 6 may be field effect transistors (FETs), and more particularly CMOS transistors.

FIG. 9 is a circuit diagram illustrating an instrumentation amplifier 120 for measuring impedance across a tissue load 122. Tissue load 122 represents the tissue of a patient for which impedance is measured by instrumentation amplifier 120. Tissue 122 may be brain tissue. In general, it is important that instrumentation amplifier 120 does not stimulate excitable cells in the tissue or cause other detrimental effects such as electrode corrosion.

Instrumentation amplifier 120 may generally conform to instrumentation amplifier 80 described with reference to FIGS. 6-8. In the example of FIG. 9, instrumentation amplifier 120 applies synchronous detection principles to accurately measure the impedance of tissue load 122 with low power, inherent charge balancing, rejection of electrode potentials, and small stimulation currents. Instrumentation amplifier 120 is an example embodiment of previously described instrumentation amplifier 80. Like instrumentation amplifier 80, instrumentation amplifier 120 includes a front end 124, mixer amplifier 126, and feedback path 128. These features may generally correspond to front end 82, mixer amplifier 84, and feedback path 86 of instrumentation amplifier 80.

In FIG. 9, front end 124 includes input voltages Vstim+ and Vstim− at ports 130A and 130B (collectively referred to as "ports 130"), switches 132A and 132B (collectively referred to as "switches 132"), resistors 134A and 134B (collectively referred to as "resistors 134"), and capacitors 136A and 136B (collectively referred to as "capacitors 136"). In general, front end 124 modulates a stimulation current that creates a voltage on tissue load 122. The stimulation current may be applied across tissue load 122 via two or more electrodes, which may be mounted on one or more leads or carried on a surface of an implantable medical device housing. Similarly, the resulting voltage signal across tissue load 122 may be sensed by two or more electrodes deployed on one or more leads or on a device housing. The voltage on tissue load 122 is AC coupled to positive and negative inputs of mixer amplifier 126 by capacitors 138A and 138B (collectively referred to as "capacitors 138"), respectively. Thus, the tissue represented by tissue load 122 is not exposed to DC current. Moreover, the small modulated (AC) stimulation current, which may be approximately 10 μA or less, may not substantially excite the tissue represented by tissue load 122.

Switches 132 toggle between input voltages at ports 130 (Vstim+ and Vstim−) to generate stimulation current through resistor-capacitor (RC) pairs of resistor 134A and capacitor 136A and resistor 134B and capacitor 136B. Switches 132, resistors 134 and capacitors 136 may form an alternating current (AC) source that generates an ac stimulation current at a clock frequency for application to a load, such as 122. In particular, switches 132, resistors 134 and capacitors 136 form a modulator that modulates first and second voltages Vstim+ and Vstim− at the clock frequency to produce a chopped stimulation current for application to the load. The chopped stimulation current results in a chopped voltage signal across tissue load 122, which can then be used for impedance measurement. However, other types of ac current sources may be use to provide the ac stimulation current for impedance measurement.

The input voltages Vstim+ and Vstim− may be provided by regulated power supplies within a device in which instrumentation amplifier 120 is employed, such as an implantable medical device. Switches 132 open and close at a chopper frequency to, in effect, chop the input stimulation current delivered by input voltages at ports 130 via the RC pairs (134, 136) to measure tissue impedance. In this manner, front end 124 generates a modulated differential input signal that is processed by mixer amplifier 126 and feedback path 128. Stimulation currents at ports 130 may be provided by electrodes carried on leads that are connected to an electrical stimulator implanted within a patient. This is one example of delivery of stimulation current for impedance measurements. As an alternative, stimulation current for impedance measurement could be generated by one or more switched current sources. The reference voltages at ports 130 and the sizes of resistors 134 and capacitors 136 may be determined by the constraints on the stimulation current, linearity of the measurement, and the time constant of instrumentation amplifier 120 compared to the clock (not shown) that drives switches 132.

As an example, using a stimulation current of 10 μA, voltages at ports 130A and 130B may provide 2V and 0 V, respec-

tively, and resistors **134** may be selected as 100 kΩ resistors. Alternatively, using 2000 kΩ resistors yields a 0.5 μA stimulation current with 100 kΩ resistors. Using 10 nF capacitors for capacitors **136** results in a stimulation current having a time constant of 1 ms, which requires a stimulation current with a frequency of approximately 5 kHz to ensure minimal error from settling dynamics. The nonlinearity of the measurement, assuming 1 kHz loads, is bounded to under 0.5% in this case.

If high pass filtering is desired, the input to mixer amplifier **126** may include a high pass filter **140** and coupling capacitors **138**A, **138**B. In FIG. **9**, high pass filter **140** includes capacitors **142**A, **142**B (collectively referred to as "capacitors **142**") and resistors **144**A, **144**B (collectively referred to as "resistors **144**"). Resistors **146**A and **146**B (collectively referred to as "resistors **146**") control the voltage at the input of mixer amplifier **126**. Resistors **146** provide a DC conduction path that controls the voltage bias at the input of mixer amplifier **126**. In other words, resistors **146** may be selected to provide an equivalent resistance that is used to keep the bias impedance high. Resistors **146** may, for example, be selected to provide a 5 GΩ equivalent resistor, but the absolute size of the equivalent resistor is not critical to the performance of instrumentation amplifier **120**. In general, increasing the impedance improves the noise performance and rejection of harmonics, but extends the recovery time from an overload. To provide a frame of reference, a 5 GΩ equivalent resistor results in a referred-to-input (RTI) noise of approximately 20 nV/rt Hz with an input capacitance (Cin) of approximately 25 pF. In light of this, a stronger motivation for keeping the impedance high is the rejection of high frequency harmonics which can alias into the signal chain due to settling at the input nodes of mixer amplifier **126** during each half of a clock cycle.

Mixer amplifier **126** and feedback path **128** process the noisy modulated input signal to achieve a stable measurement of the differential voltage on tissue load **122** while operating at low power. Mixer amplifier **126** provides synchronous demodulation with respect to front end **82** and substantially eliminates noise, i.e., 1/f noise, popcorn noise, and offset, from the amplified output signal. Mixer amplifier **126** may be implemented using the modified folded-cascode architecture with switching at low impedance nodes.

As shown in FIG. **9**, feedback path **128** includes top and bottom feedback path branches that provide negative feedback and a single-to-differential interface. The top and bottom feedback path branches include capacitors **148**A and **148**B (collectively referred to as "capacitors **148**") which are connected to switches **150**A and **150**B (collectively referred to as "switches **150**"), respectively. Switches **150**A and **150**B are 180 degrees out of phase with each other and toggle between the output of mixer amplifier **126** and a reference voltage (Vref) to modulate the output of mixer amplifier **126**. Consequently, feedback path **128** provides negative feedback to keep the signal change at the input to mixer amplifier **126** small as previously described in this disclosure.

Switches **134**, switches **150**, and the switches at low impedance nodes in mixer amplifier **126** may be CMOS SPDT switches or other switches that provide fast switching dynamics. The transfer function of instrumentation amplifier **120** may be defined by the transfer function provided in equation (1) below, where Vout is the voltage of the output of mixer amplifier **126**, Cin is the capacitance of input capacitors **138**, ΔVin is the differential voltage at the inputs to mixer amplifier **126**, Cfb is the capacitance of feedback capacitors **148**, and Vref is the reference voltage that switches **150** mix with the output of mixer amplifier **126**.

$$Vout = Cin(\Delta Vin)/Cfb + Vref \quad (1)$$

From equation (1), it is clear that the gain of instrumentation amplifier **120** is set by the ratio of input capacitors Cin and feedback capacitors Cfb, i.e., capacitors **138** and capacitors **148**. The ratio of Cin/Cfb may be selected to be on the order of 100. Capacitors **148** may be poly-poly, on-chip capacitors or other types of MOS capacitors and should be well matched, i.e., symmetrical. Capacitors **138** and **148** may be poly-poly capacitors or other types of MOS capacitors and should be well matched, i.e., symmetrical. Capacitors **138** and **148** may be placed on chip with the other instrumentation amplifier components.

In operation, instrumentation amplifier **120** may fold electromagnetic interference (EMI) into the modulated input signal at the carrier frequency and odd harmonics. In order to determine if the channel is corrupted, the output of instrumentation amplifier **120** can be monitored with no stimulation current applied to front end **124**. Alternatively, spread-spectrum techniques may be used to break up the synchronous clock detection between front end **124** and mixer amplifier **126**. Spread-spectrum clocking breaks up the uncorrelated noise into a broadband noise signal that is substantially eliminated by mixer amplifier **126**, while maintaining the correlated impedance measurement.

The output of instrumentation amplifier **120** may be sent to an analog-to-digital converter (ADC) (not shown) that applies additional processing for measuring the impedance of tissue load **122**. The ADC may be located within an impedance sensing module or within a processor of a medical device. Further, when instrumentation amplifier **120** is implanted within a patient, the tissue-electrode interface (front end **124**) may be galvanically isolated from the measurement circuit (mixer amplifier **126** and feedback path **128**). Isolation helps to reject electrode polarization and ensure net charge balance across the electrodes.

FIG. **10** is a block diagram illustrating a medical device **200** that may be used to predict the onset of a seizure in a patient based on an impedance measurement of the brain of the patient and a measurement of an electrical potential of the brain. Example measurements of brain potential include EEG signals, ECoG signals, and other electrical signals that vary within the brain and indicate that the brain is in a state that indicates a possibility of an onset of a seizure. In general, medical device **200** may predict the onset of a seizure in a patient using a measurement of a brain potential in combination with any of the previously described techniques for predicting the onset of based on an impedance measurement of the brain of the patient. In different embodiments, the measured potential and measured impedance play different roles in the determination of whether the brain is in the state that indicates the possibility of a seizure. Some of the embodiments are described below. In each of the embodiments, however, medical device **200** measures an impedance of the brain of the patient and measures a brain potential of the patient, and predicts the onset of a seizure based on one or both of the measurements. In this way, medical device **200** may predict the onset of a seizure in a patient based on more than one parameter of the patient. In some embodiments, one type of measurements, i.e., impedance or brain potential, may be used to validate a brain seizure predicted based on the other type of measurement.

In the illustrated example of FIG. **10**, medical device **200** includes brain potential sensing module **202**, impedance sensing module **204**, multiplexer (MUX) **206**, and seizure detection module **208**. Generally, medical device **200** may operate similar to medical devices **20**, **56**, and **70** in FIGS. **3**,

4, and 5, respectively. That is, medical device **200** may be used during a first trial or learning stage to determine threshold values or trend templates to use for predicting the onset of seizures, or as an implantable medical device that predicts the onset of a seizure in a patient and takes some action in response to the seizure prediction. As previously described, the action may include delivering a therapy to the patient to prevent the onset of seizure or to otherwise mitigate the effects of the seizure or generating a notification to the patient or clinician that the seizure was predicted. Thus, although not illustrated in FIG. **10**, medical device **200** may include one or more of a processor, memory, telemetry module, user interface, power source, therapy delivery module, and therapy elements that deliver stimulation or drug therapy to the patient. These components are not shown in FIG. **10** in the interest of simplicity and to avoid redundancy in this disclosure.

Impedance sensing module **204** corresponds to and, therefore, operates in a similar fashion as impedance sensing modules **22** and **58** that are previously described with respect to FIGS. **3**, **4**, and **5**, respectively. In FIG. **10**, impedance sensing module **204** includes circuitry, such as circuitry illustrated in FIG. **9**, for measuring the impedance of the brain of a patient via electrodes **212**A and **212**B (collectively referred to as "electrodes **212**"), which are coupled to impedance sensing module **204** via leads **214**A and **214**B, respectively. Electrodes **212** represent one or more sets of electrodes that may be implanted in one or more regions of the brain that are relevant to the occurrence of seizures, such as the cortex (e.g., front or motor cortex), brainstem, cranial nerves (e.g., the vagus nerve), or deep brain regions, such as the anterior thalamus, ventrolateral thalamus, globus pallidus, substantia nigra pars reticulata, subthalamic nucleus, neostriatum, cingulated gyrus or the cingulate gyrus.

As previously described, a low stimulation current, e.g., a stimulation current in a range of approximately 500 nA to approximately 10 μA, may be delivered across one or more regions of the brain via electrodes **212**. Impedance sensing module **204** provides a measurement translating the impedance to an output voltage or current. When impedance sensing module **204** is implemented using the chopper stabilized instrumentation amplifier shown in FIGS. **6** and **7**, the output is a relatively stable low noise signal with very low power requirements.

Brain potential sensing module **202** may include any suitable circuitry for measuring a brain potential, such as circuitry for EEG or ECoG. In an example embodiment, the circuitry of module **202** may include a chopper stabilized instrumentation amplifier, such as the chopper-stabilized instrumentation amplifier shown in FIGS. **6** and **7**, to provide a stable, low noise signal with very low power requirements. In FIG. **10**, brain potential sensing module **202** measures a brain potential via electrodes **216**A and **216**B (collectively referred to as "electrodes **216**") which are coupled to module **202** via leads **218**A and **218**B, respectively. As with electrodes **212**, electrodes **216** represent one or more sets of electrodes. That is, in other embodiments, brain potential sensing module **202** may sense a potential of the brain of the patient via any suitable number of electrodes. One or more of the electrodes **216** may also be positioned on a housing of medical device **200**. Electrodes **216** may be implanted and/or external to the patient. For example, electrodes **216** may be placed externally on the scalp of the patient to obtain EEG data. Alternatively, electrodes **216** may be implanted subdurally or in the cerebral cortex of the brain to obtain ECoG data, or other brain potentials that can be measured to predict the onset seizures. As yet another alternative, electrodes **216** may include a set of implanted electrodes and a set of external electrodes attached to a scalp of the patient.

In embodiments in which electrodes **216** are implanted in a patient, electrodes **216** may be positioned in one or more regions of a brain of a patient in order to measure the potential of the one or more regions. Example regions include cortex (e.g., front or motor cortex), brainstem, cranial nerves (e.g., the vagus nerve), or deep brain regions, such as the anterior thalamus, ventrolateral thalamus, globus pallidus, substantia nigra pars reticulata, subthalamic nucleus, neostriatum, cingulated gyrus or the cingulate gyrus.

Electrodes **212** for measuring an impedance of the brain and electrodes **216** for measuring the potential of the brain may or may not be positioned in the same region of the brain of the patient. The impedance may be more revealing of a brain state indicative of a seizure in certain brain regions, while the potential may be more revealing in other brain regions, which may be different than that for the impedance measurements. Thus, in some embodiments, electrodes **212** and **216** are positioned in separate parts of the brain (or external to the brain in the case of electrodes **216**). However, in some embodiments, electrodes **212** and **216** may be implanted in the same region of the brain, in which case, a single set of electrodes may be coupled to brain potential sensing module **202** and impedance sensing module **204**. Other potential sensing electrode **16** arrangements may also be used.

As with some embodiments of medical devices **20**, **56**, and **70**, medical device **200** may, in some embodiments, include internal and external components. That is, in some embodiments, impedance sensing module **204**, brain potential sensing module **202**, MUX **206**, and/or seizure detection module **208** may be in different housings in order to allow some of the components to remain external to the patient while other components are implanted. For example, in embodiments in which electrodes **212** are coupled to impedance sensing module **204** and implanted within the patient, but electrodes **216** are attached to an external surface of the patient, impedance sensing module **204** may be in a separate housing from brain potential sensing module **202**. In such embodiments, impedance sensing module **204** may be implanted within the patient and telemetrically coupled to an external housing carrying brain potential sensing module **202** and other components necessary for the operation of medical device **200** as described.

Impedance sensing module **204** and brain potential sensing module **202** are coupled to seizure detection module **208** through MUX **206**. MUX **206** selectively applies the output of brain potential sensing module **202** and impedance sensing module **204** to seizure detection module **208**. In particular, MUX **206** may apply the output of modules **202** and **204** to seizure detection module **208** at substantially the same time, in an alternating fashion, in a pattern other than an alternating pattern, or under the control or request of seizure detection module **208**.

In the example of FIG. **10**, seizure detection module **208** controls MUX **206** via control signal **220**, brain potential sensing module **202** via control signal **210**A, and impedance sensing module **204** via control signal **210**B. Control signals **210**A and **210**B turn brain potential sensing module **202** and impedance sensing module **204**, respectively, on and off. That is, controls signals **210**A and **210**B control when modules **202** and **204**, respectively, operate. Control signal **220** controls MUX **206** to apply the output of one or both of modules **202** and **204** to seizure detection module **208**. In some embodiments, seizure detection module **208** may actively operate of

modules **202**, **204** and/or include separate ports to receive signals from modules **202**, **204**, in which cases MUX **206** may or may not be necessary.

In general, seizure detection module **208** determines whether the brain is in a state indicative of a possibility of a seizure based on the output of one or both of brain potential sensing module **202** and impedance sensing module **204**. In one embodiment, seizure detection module **208** detects the onset of a seizure based on the output of both of modules **202** and **204**. In this example embodiment, seizure prediction module **208** may monitor the output of one of modules **202** and **204** and, in response to detecting onset of a seizure based on the one output, requests MUX **206**, via control signal **220**, to apply the other output. As an example, MUX **206** may apply the output of impedance sensing module **204** to seizure detection module **208** until seizure detection module **208** detects the onset of a seizure based on the output of module **204**. Seizure detection module **208** may process the measured impedance using any one of the techniques described above in order to determine whether the measured impedance indicates the brain is in a state in which a seizure is possible. Until seizure detection module **208** detects an impedance measurement that indicates an onset of a seizure is likely, seizure detection module **208** may send control signal **210**A to brain potential sensing module **202** to cause module **202** to enter a sleep mode to conserve power.

Upon determining that the impedance measurements indicate a seizure is likely, seizure detection module **208** may then send control signal **220** to MUX **206** to cause MUX **206** to awake brain potential sensing module **202** and apply the output of brain potential sensing module **202** to its input. At substantially the same time, seizure detection module **208** may send control signal **210**B to impedance sensing module **204** to cause module **204** to enter a sleep state or mode to conserve power. Seizure detection module **208** processes the output of module **202** to validate the initial seizure prediction determination based on the measured impedance. In particular, seizure detection module **208** determines whether the potential measurements also indicate the brain is in the state in which a seizure is likely.

Seizure detection module **208** may employ techniques for determining whether the measured potential indicates the brain is in the state in which a seizure is likely that are similar to described above with respect to determining whether measured impedance indicates the brain is in the state. For example, in one embodiment, seizure detection module **208** compares an amplitude of the measured potential signal to a predetermined threshold. The relevant amplitude may be, for example, the instantaneous amplitude of an incoming potential signal or an average amplitude of the potential over period of time. In one embodiment, the threshold value is determined during the trial phase that precedes implantation of a chronic therapy delivery device within the patient.

In another embodiment, seizure detection module **208** correlates a pattern of the measured potential to a pattern template. If the pattern of the measured potential correlates well, i.e., matches, the pattern template, the measured potential indicates the brain is in the state that indicates a seizure is likely. In some embodiments, the template matching algorithm that is employed to determine whether the pattern matches the template (**10**) may not require a one hundred percent (100%) correlation match, but rather may only match some percentage of the pattern. For example, if the measured potential values exhibit a pattern that matches about 75% or more of the template, the algorithm may determine that there is a substantial match between the pattern and the template. The pattern template may be generated in a trial phase, such as by the potential activity prior to, and possibly during or after, an actual seizure. In one embodiment, a pattern for potential values that characterize a brain state that will likely lead to a seizure is a rate of change of the potential measurements over time. For example, a positive increase in the time rate of change (i.e., the slope or first derivative) of the potential measurements may indicate a likelihood of a seizure, although a decrease (negative slope) in rate of change or another pattern may also be indicative of the likelihood of a seizure. Alternatively, a time rate of change (i.e., the slope) of the potential measurements that matches or exceeds the time rate of change of the template may indicate a likelihood of a seizure. The exact trend that is indicative of a brain state in which a seizure is likely may be determined during a trial phase, as with the measured impedance processing techniques described above.

The measured potential signal from brain potential sensing module **202** may be analyzed for slope, amplitude, temporal correlation or frequency correlation with a template signal, or combinations thereof. The slope, amplitude, temporal correlation or frequency correlation with a template signal may be similar to the techniques described above with respect to determining whether the measured impedance indicates the brain is in the state that indicates a seizure is likely to occur.

When seizure detection module **208** determines the output of module **202** indicates a seizure is likely, seizure detection module **208** takes an action. The action may be at least one of sending a signal to memory (not shown) to record data related to the seizure, control a therapy delivery module (not shown) to deliver therapy to the patient or generate a notification to the patient or clinician. However, if seizure detection module **208** determines that the measured potential does not validate the initial seizure prediction made based on the measured impedance, seizure detection module **208** concludes that a seizure is not detected. Thus, in some embodiments, both the measured impedance from impedance sensing module **204** and the measured potential from brain potential sensing module **202** must indicate that an onset of a seizure is likely in order for seizure detection module **208** to conclude that the brain is in the state that indicates the possibility of a seizure. If only one of the measured impedance or the measured potential suggests the seizure is likely, module **208** may send a signal to memory to record data (e.g., the signals from impedance sensing module **204** that suggested the brain was in the state in which the seizure was likely and/or the signals from brain potential sensing module **202** that indicated a seizure was not likely) as a flagged event. The data may be stored for later retrieval and analysis by a clinician to review the source of the anomaly between the impedance and potential measurements.

In other embodiments in which the measured impedance and the measured potential must both indicate that an onset of a seizure is likely in order for seizure detection module **208** to conclude that the brain is in the state that indicates the possibility of a seizure, seizure detection module **208** may initially monitor the signal from brain potential sensing module **202**, rather than impedance sensing module **204** as in the previous embodiment. If seizure detection module **208** finds that the measured potential from brain potential sensing module **202** suggests the brain is in the state that indicates a likelihood of seizure, seizure detection module **208** may validate (or confirm) the initial determination by controlling MUX **208** to apply the output of impedance sensing module **204** to seizure detection module **208**. Seizure detection module **208** may then process the signal from impedance sensing module **204** to validate the initial seizure prediction, and conclude that the brain is in the state indicative of a seizure. If the measured

impedance does not support such a conclusion, seizure detection module **208** concludes that the brain is not in the state indicative of the seizure.

In another embodiment, seizure detection module **208** determines whether the brain is in the state indicative of a possibility of a seizure based on the output of one or both of modules **202** and **204**. In this embodiment, an output from one of brain potential sensing module **202** or impedance sensing module **204** may control the seizure prediction. Seizure detection module **208** makes an initial determination of whether the brain is in the state indicative of the possibility of the seizure based on either the measured potential from brain potential sensing module **202** or the measured impedance from impedance sensing module **204**. Upon making the initial seizure prediction, seizure detection module **208** may determine whether the other signal (i.e., either the signal indicative of measured impedance or brain potential) on which the initial determination was not based also indicates an onset of a seizure is possible. Thus, seizure detection module **208** may attempt to validate the initial seizure prediction. However, rather than concluding that the seizure is not likely if the second signal fails to validate the initial determination, the initial determination controls, and seizure detection module **208** sends a signal to memory (not shown) to record data related to the seizure, controls a therapy delivery module (not shown) to deliver therapy to the patient or generates a notification to the patient or clinician. In this case, if validation fails, seizure detection module **208** may nevertheless proceed with therapy but flag the recorded data so that a clinician can review the anomalous differences between the impedance and potential measurements, in terms of seizure indication.

In another embodiment, seizure detection module **208** determines whether the brain is in the state indicative of a seizure based on the output of one or both of modules **202** and **204**. In this embodiment, an output from one of brain potential sensing module **202** or impedance sensing module **204** may control the seizure prediction. As one example, MUX **206** may apply the outputs of modules **202** and **204** to seizure detection module **208** in an alternating fashion. In this example, modules **202** and **204** may operate at substantially the same time and MUX **206** may toggle between their outputs. Alternatively, seizure detection module **208** may control the operation of modules **202** and **204** via control signals **210**A and **210**B, respectively. In such an example, MUX **206** may be removed from medical device **200**. In any case, seizure detection module **208** receives the output of modules **202** and **204** in an alternating fashion. In other embodiments, seizure detection module **208** may receive the output of modules **202** and **204** in another pattern, such as, but not limited to two or more outputs from module **204** for a single output from brain potential sensing module **202**.

Seizure detection module **208** processes the received output signal using any of the previously described techniques, i.e., any of the previously described techniques for detecting onset of a seizure based on an impedance measurement or based on a measurement of a brain potential, such as a measurement of an EEG signal or ECoG signal. Seizure detection module **208** may output a signal that causes medical device **200** to take action in response to detecting onset of seizure based on the output of either of modules **202** and **204**. Alternatively, seizure detection module **208** may output a signal to take action in response to detecting onset of a seizure based on consecutively received signals from modules **202** and **204**.

The pattern exhibited by the measured impedance relative to the measured potential may be indicative of a brain state in which a seizure is likely to occur. For example, an increase in an amplitude of the impedance signal from impedance sensing module **204** and a subsequent (in time) decrease in the amplitude of the potential signal from brain potential sensing module **202** may indicate the brain state in which a seizure is likely to occur. However, other patterns and more complex patterns are possible. A pattern (or "trend") template may be generated during a trialing stage, in which the measured impedance and measured potential signals are correlated with an actual seizure in order to determine if a pattern, if any, is correlated with the occurrence of the seizure. If a pattern that indicates the brain state in which a seizure is likely to occur is generated during the trialing stage, the pattern may be stored within a memory of medical device **200** for use by seizure detection module **208**. Seizure detection module **208** may then use any of the template matching techniques to determine whether a pattern in the signal from impedance sensing module **204** relative to the signal from the brain potential sensing module **202** indicate the brain is in the state in which a seizure is likely to occur. Examples of suitable template matching techniques include the ones described above with respect to predicting a seizure based on an impedance measurement or a potential measurement.

As another example, MUX **206** may apply the outputs of modules **202** and **204** to seizure detection module at substantially the same time. It is recognized that MUX **206** and control signals **210**A and **210**B may be removed from medical device **200** in this example. In this example, brain potential sensing module **202** and impedance sensing module **204** operate at the same time and seizure detection module **208** monitors the outputs of modules **202** and **204** at substantially the same time. In this example, seizure detection module **208** may detect the onset of a seizure in a similar fashion with respect to the previous example, but monitors the output of modules **202** and **204** at substantially the same time instead of in an alternating fashion. That is, seizure detection module **208** monitors the output of modules **202** and **204** at substantially the same time and detects the onset of a seizure when the output of one of the modules indicates a seizure or when the output of both modules indicate the onset of seizure at substantially the same time. However, in some cases, the stimulation current delivered to brain tissue by impedance sensing module **204** for measuring impedance may interfere with the brain potential measurements. Brain potential sensing module **202** may be calibrated to generate a signal indicative of the potential of the brain by taking into consideration the impedance-measuring stimulation current delivered by impedance sensing module **204**.

In summary, one of modules **202**, **204** may be used as a primary triggering device for seizure prediction. If one of modules **202**, **204** indicates a seizure, the other device may be used to validate the seizure. If validation succeeds, therapy and/or data recording are applied. If validation fails, there are several possibilities. First, if validation fails, seizure detection module **208** may nevertheless proceed with therapy delivery (or adjustment) and/or data recording, but flag the event for later review in view of the differences between the outputs of the modules **202**, **204**. Alternatively, if validation fails, seizure detection module **208** may withhold delivery (or adjustment) of therapy and flag the event for later review in view of the differences between the outputs of modules **202**, **204**. In some embodiments, both modules **202**, **204** may be monitored on an alternating basis, or one of the modules may serve as a primary source that is monitored on continuing basis while the other module is only monitored for validation purposes. In each case, the module **202**, **204** that is not being monitored at a given time may be turned off or its output may be ignored. When its output is needed, a module **202**, **204** may be activated by seizure detection module **208**. In other

embodiments, more than two modules **202**, **204** may be applied to support more complex validation or analysis. For example, impedance, EEG signals, and ECoG signals could be monitored simultaneously, on an alternating basis, or for validation purposes.

Certain advantages may be provided by the various embodiments described in FIG. **10**. As an example, processing the output of only one of modules **202** and **204** at any give time may consume less power and result in a shorter latency between receiving the signal and detecting onset of a seizure than is possible when the output of modules **202** and **204** are processed at substantially the same time.

Although brain potential sensing module **202** and impedance sensing module **204** are shown to be two separate modules in the embodiment of medical device **200** shown in FIG. **10**, in other embodiments, brain potential sensing module **202** and impedance sensing module **204** may be incorporated into a common sensing module that is coupled to seizure detection module **208**. Brain potential sensing module **202** and impedance sensing module **204** may share circuitry or have separate circuitry.

FIG. **11** is a diagram illustrating a signal flow path for a chopper stabilized instrumentation amplifier **250** that brain potential sensing module **202** may include to generate a signal indicative of a measured potential of brain tissue. The signal flow diagram for instrumentation amplifier **250** may be substantially the same as that for instrumentation amplifier **80** in FIG. **7**, but with a different front end. Accordingly similar numbered components in FIG. **11** and FIG. **7** share similar functionality. In the interest of brevity and to avoid redundancy, the signal flow through mixer amplifier **84** and feedback path **86** is not described in detail. Instead, the flow of input signal **230** through front end **282** is described.

In FIG. **11**, front end **282** includes a modulator **290** for modulating an input signal **230** to produce modulated input signal **291**. Front end **282** may be coupled to a physiological sensor that generates an input signal **230** proportional to a sensed physiological parameter at its outputs. For example, input signal **230** may be a differential output signal from a pair of electrodes attached to an external surface of a patient or implanted within the brain of a patient, e.g., a pair of electrodes that sense EEG or ECoG signals.

Modulator **290** modulates a differential amplitude of input signal **230** to a carrier frequency provided by clock signal **291**. Clock signal **291**, like other clock signals described in this disclosure, may be a square wave signal that effectively multiples the signal by plus 1 and minus 1 at a desired clock frequency and is synchronous with clock signals **91**B and **91**C. In this manner, modulator **290** chops the input signal **230** prior to application of the input signal to mixer amp **84**. Modulator **290** may, in some embodiments, comprise a pair of complementary metal oxide semiconductor (CMOS) single pole, double throw (SPDT) switches that are driven by clock signal **291** to modulate (chop) input signal **230** to the carrier frequency. The CMOS SPDT switches may be coupled to a set of differential capacitors to form a continuous time switched capacitor network that forms input capacitance Cin at the input of mixer amplifier **84**. Additionally, the CMOS SPDT switches may be cross-coupled to each other to reject common mode

As previously described with respect to FIG. **7**, summing node **24** introduces offset and 1/f noise into the signal at the input to mixer amplifier **84** and mixer amplifier **84** produces a stable, low noise output signal. Mixer amplifier **84** may be implemented using the circuit illustrated in FIG. **8**. Feedback path **86** provides negative feedback that keeps the signal change small at the input to mixer amplifier **84** and, thus, substantially eliminates glitching that would otherwise result from the limited bandwidth of mixer amplifier **84**.

FIG. **12** is a circuit diagram illustrating chopper-stabilized instrumentation amplifier **250**. The architecture of instrumentation amplifier **250** may be substantially similar to instrumentation amplifier **120** shown in FIG. **9**. Accordingly, similar numbered components in FIG. **12** and FIG. **9** exhibit similar functionality.

In FIG. **12**, instrumentation amplifier **250** receives a differential voltage across its inputs **252**A and **252**B (collectively referred to as "inputs **252**"). Inputs **252**A and **252**B provide voltages Vin-plus and Vin-minus, respectively. For example, inputs **252** may be coupled to a pair of sensing electrodes, such as a pair of electrodes attached to an external surface of a patient or implanted within a region of the brain of the patient that generate EEG or ECoG signals.

Inputs **252**A and **252**B are connected to capacitors **256**A and **256**B (collectively referred to as "capacitors **256**") through switches **254**A and **254**B (collectively referred to as "switches **254**), respectively. Switches **2504** are driven by a clock signal provided by a system clock (not shown) and are cross-coupled to each other to reject common-mode signals. Capacitors **256** are coupled at one end to a corresponding one of switches **254** and to a corresponding input of mixer amplifier **126** at the other end. In particular, capacitor **256**A is coupled to the positive input of mixer amplifier **126**, and capacitor **126**B is coupled to the negative input of amplifier **126**, providing a differential input.

In FIG. **12**, switches **254** and capacitors **256** form front end **282**, which operates as a continuous time switched capacitor network as previously described with respect to FIG. **11**. Switches **254** toggle between an open state and a closed state in which inputs **252** are coupled to capacitors **256** at a clock frequency to modulate (chop) the signal at inputs **252** to the carrier (clock) frequency. As previously described, the signal at inputs **252** may be a low frequency signal within a range of approximately 0 Hz to approximately 100 Hz. The carrier frequency may be within a range of approximately 4 kHz to approximately 10 kHz. Hence, the low frequency sensor output is chopped to the higher chop frequency band.

Switches **254** toggle in-phase with one another to provide a differential input signal to mixer amplifier **126**. During a first phase of the clock signal, switch **254**A connects input **252**B to capacitor **256**A and switch **254**B connects input **252**A to capacitor **256**B. During a second phase, switches **254** change state such that switch **254**A couples input **252**A to capacitor **256**A and switch **254**B couples input **252**B to capacitor **256**B. Switches **254** synchronously alternate between the first and second phases to modulate the differential voltage at inputs **252** at the carrier frequency. The resulting chopped differential signal is applied across capacitors **256**, which couple the differential signal across the inputs of mixer amplifier **126**. Resistors **146**, mixer amplifier **126**, and feedback path **128** operate as previously described with respect to FIG. **9**.

As further shown in FIG. **12**, for applications in which instrumentation amplifier **250** provides an output in conjunction with a stimulation current being supplied to instrumentation amplifier **120** (FIG. **9**), blanking circuitry may be added to instrumentation amplifier **250** between coupling capacitors **256** and the inputs to mixer amplifier **126** to ensure that the input signal settles before reconnecting mixer amplifier **126** to front end **282**. For example, the blanking circuitry may be a blanking multiplexer (MUX) **260** that selectively couples and de-couples mixer amplifier **126** from front end **282**. This blanking circuitry selectively decouples the mixer amplifier from the differential input signal and selectively disables the

first and second modulators, i.e., switches **254**, **150**, e.g., during delivery of a stimulation current to instrumentation amplifier **120** which may be incorporated in impedance measurement module **204**.

Blanking MUX **260** is optional, but may be desirable in some cases. The clocks driving switches **254**, **150** to function as modulators cannot be simply shut off because residual offset voltage on mixer amplifier **126** may saturate the amplifier in a few milliseconds. For this reason, blanking MUX **260** may be provided to decouple amplifier **126** from the input signal for a specified period of time during and following application of a stimulation by a cardiac pacemaker or defibrillator, or by a neurostimulator.

To achieve suitable blanking, the input and feedback switches **254**, **150** should be disabled while mixer amplifier **126** continues to demodulate the input signal. This holds the state of the integrator within mixer amplifier **126** because the modulated signal is not present at the inputs of the integrator, while the demodulator continues to chop the DC offsets. Accordingly, blanking MUX **260** may further include circuitry or be associated with circuitry configured to selectively disable switches **254**, **150** during a blanking interval. Post blanking, mixer amplifier **126** may require additional time to resettle because some perturbations may remain. Thus, the total blanking time includes time for demodulating the input signal while the input and switches **254**, **250** are disabled and time for settling of any remaining perturbations. An example blanking time following application of a stimulation pulse may be approximately 8 ms with 5 ms for mixer amplifier **126** and 3 ms for the AC coupling components.

FIG. **13** is flow diagram illustrating a method for predicting seizure in a patient using one of an impedance measurement of a brain of a patient or measurement of a brain potential of the patient. The method illustrated in FIG. **13** may be implemented using medical device **200** and circuitry described in this disclosure. As shown in FIG. **13**, the method begins by measuring an impedance of a patient's brain (**300**) and measuring a brain potential of a patient (**302**). The impedance measurement and measurement of the brain potential may be obtained at the substantially the same time, in an alternating fashion, or in another pattern.

After the measurements have been obtained, any of the previously described techniques, e.g., correlation techniques, template matching techniques, thresholding techniques, and the like, may be used to determine whether either the measured impedance or the measured potential indicate the brain is in a state indicative of a possibility of a seizure (**304**). If the measurements were obtained at substantially the same time, separate techniques may be applied to each of the measurement in parallel or, alternatively, the techniques may be applied one after the other. As an alternative, if the measurements were obtained in an alternating fashion, the detection techniques may be applied in an alternating fashion as well. That is, after the impedance measurement is obtained, a correlation technique may be applied to the impedance measurement. While the correlation technique is executing, the measurement of the brain potential may be obtained. In this way, the measurements and processing techniques are performed in an alternating fashion.

When the seizure detection technique does not detect onset of a seizure, the method loops and steps **300**, **302**, and **304** are repeated. However, if the onset of a seizure is detected based on either of the measurements, therapy is delivered to treat the seizure. The therapy may be stimulation therapy, drug therapy, or a combination of both as described in this disclosure.

FIG. **14** is a flow diagram illustrating another technique for predicting a seizure in a patient based on an impedance measurement of the brain of a patient and a measurement of a brain potential of a patient. The technique illustrated in FIG. **14** may be implemented using medical device **200** and circuitry described in this disclosure. In the technique shown in FIG. **14**, seizure detection module **208** (FIG. **10**) determines that the brain of the patient is in a state indicative of a possibility of a seizure based on an initial seizure prediction based on measured impedance that is validated by a seizure prediction based on measured potential. In other embodiments, the initial seizure prediction may be based on the measured potential and validated with the measured impedance. As shown in FIG. **14**, seizure detection module **208** (or another processor) measures an impedance of a patient's brain (**310**) and applying one of the previously described techniques to detect an onset of a seizure based on the impedance measurement (**312**). If the measured impedance indicates that an onset of a seizure is not likely, seizure detection module **208** continues measuring the impedance of the brain (**310**). In this way, seizure detection module **208** monitors an impedance of the patient's brain until the impedance measurement indicates the onset of a seizure.

When the measured impedance indicates that the brain is in the state in which a seizure is likely, seizure detection module **208** measures a brain potential of the patient (**314**) and applying any of the previously mentioned techniques to detect onset of a seizure based on the measured potential (**316**). If seizure detection module **208** determines the measured potential indicates an onset of a seizure is likely, therapy is delivered to treat the seizure as previously described in this disclosure (**318**). Alternatively, data may be recorded in a memory of medical device **200** or seizure detection module **208** may generate a notification to a patient or clinician. If seizure detection module **208** determines that the measured potential does not indicate an onset of a seizure is likely, seizure detection module **208** flags the event for further analysis (e.g., by a clinician) (**320**). Flagging the event may involve storing the impedance and brain potential measurements and other data obtained at the time the measurements were taken. The method in FIG. **14** may decrease false positives by using a second measurement, e.g., a measurement of a brain potential or measurement of other electrical signal that indicates the onset of seizure, as a validation or confirmation step.

FIG. **15** is a flow diagram illustrating another technique for predicting a seizure in a patient based on an impedance measurement of the brain of a patient and a measurement of a brain potential of a patient. The technique illustrated in FIG. **15** is substantially similar to that shown in FIG. **14**, but rather than flagging an event if an initial seizure prediction is not validated, seizure detection module **208** merely attempts to validate the initial seizure prediction. In the technique shown in FIG. **15**, seizure detection module **208** measures impedance of the patient's brain (**310**), determines that the brain of the patient is in a state indicative of a possibility of a seizure based on an initial seizure prediction based on measured impedance (**312**), measures a potential of the brain (**314**), and attempts to validate the initial seizure prediction based on measured potential. If the potential measurements indicate that the brain is not in a state indicative of a possibility of a seizure (**316**), seizure prediction module **208** delivers therapy (**318**) and flags the event (**320**). In some embodiments, however, seizure prediction module **208** does not flag the event.

Various embodiments of the invention have been described. The invention may be embodied as a computer-readable medium that includes instructions to cause a proces-

sor to perform any of the methods described herein. These and other embodiments are within the scope of the following claims.

The invention claimed is:

1. A method comprising:

receiving, with a processor, impedance measurements indicative of an impedance of a brain of a patient, wherein the impedance of the brain is indicative of a physiological state of the brain;

receiving, with the processor, potential measurements indicative of a potential of the brain;

selecting, with the processor, a frequency component of a waveform of the impedance measurements from a plurality of frequency components of the waveform of the impedance measurements; and

determining, with the processor, whether the brain is in a state indicative of a possibility of a future seizure based on the potential measurements and the selected frequency component of the waveform of the impedance measurements.

2. The method of claim **1**, further comprising measuring, with a sensing module, the potential of the brain to generate the potential measurements by at least measuring the potential via at least one of electroencephalography (EEG) or electroencephalography (ECoG).

3. The method of claim **1**, further comprising measuring, with a sensing module, the potential of the brain to generate the potential measurements by at least measuring the potential of the brain at a different time than measuring the impedance of the brain to generate the impedance measurements.

4. The method of claim **1**, further comprising measuring, with a sensing module, the impedance of the brain of the patient to generate the impedance measurements and measuring the potential of the brain to generate the potential measurements by at least alternating between measuring the impedance of the brain and measuring the potential of the brain.

5. The method of claim **1**, wherein determining whether the brain is in the state indicative of a possibility of a future seizure based on the potential measurements and the selected frequency component of the waveform of the impedance measurements comprises:

determining whether the selected frequency component of the waveform of the impedance measurements indicates the brain is in the state indicative of the possibility of a future seizure; and

validating that the brain is in the state indicative of the possibility of a future seizure based on the potential measurements.

6. The method of claim **5**, wherein validating that the brain is in the state indicative of the possibility of a future seizure based on the potential measurements comprises determining whether the potential measurements indicate the brain is in the state indicative of the possibility of a future seizure.

7. The method of claim **6**, further comprising storing an indicator if the potential measurements do not indicate the brain is in the state indicative of the possibility of a future seizure.

8. The method of claim **1**, wherein determining whether the brain is in the state indicative of a possibility of a future seizure based on the potential measurements and the selected frequency component of the waveform of the impedance measurements comprises:

determining whether the brain is in the state indicative of the possibility of a future seizure based on the potential measurements; and

validating that the brain is in the state indicative of the possibility of a future seizure based on the selected frequency component of the waveform of the impedance measurements.

9. The method of claim **1**, further comprising comparing an amplitude of the waveform of the impedance measurements to a predetermined threshold value and determining whether the brain is in the state indicative of the possibility of a future seizure based on the comparison of the amplitude of the waveform of the impedance measurements to the predetermined threshold value.

10. The method of claim **1**, wherein determining whether the brain is in the state indicative of the possibility of a future seizure comprises comparing an amplitude of the potential measurements to a predetermined threshold value.

11. The method of claim **1**, further comprising comparing a trend in the waveform of the impedance measurements to a template and determining that the brain is in the state indicative of the possibility of a future seizure based on the comparison of the trend to the template.

12. The method of claim **1**, wherein determining whether the brain is in the state indicative of the possibility of a future seizure based on the potential measurements comprises comparing a trend in the potential measurements to a template.

13. The method of claim **12**, wherein the trend indicates a rate of change of the potential measurements over time.

14. The method of claim **1**, further comprising comparing a pattern of the impedance measurements relative to the potential measurements over time to a template and determining whether the brain is in the state indicative of the possibility of a future seizure based on the comparison of the pattern of the impedance measurements relative to the potential measurements over time to the template.

15. The method of claim **1**, wherein determining whether the brain is in the state indicative of the possibility of a future seizure comprises comparing the selected frequency component of the waveform of the impedance measurements to a corresponding frequency component of a waveform template.

16. The method of claim **1**, wherein determining whether the brain is in the state indicative of the possibility of a future seizure comprises determining a frequency component of a waveform of the potential measurements and comparing the frequency component of the waveform of the potential measurements to a corresponding frequency component of a waveform template.

17. The method of claim **1**, further comprising controlling a therapy delivery module to deliver therapy to the patient in response to determining the brain is in the state indicative of the possibility of a future seizure.

18. The method of claim **17**, wherein controlling the therapy delivery module to deliver therapy comprises controlling the therapy delivery module to deliver therapy to the patient in response to determining the brain is in the state indicative of the possibility of a future seizure based on one of the selected frequency component of the waveform of the impedance measurements or the potential measurements.

19. The method of claim **17**, wherein controlling the therapy delivery module to deliver therapy comprises controlling the therapy delivery module to deliver therapy to the patient in response to determining the selected frequency component of the waveform of the impedance measurements indicates the brain is in the state indicative of the possibility of a future seizure and the potential measurements indicate the brain is in the state indicative of the possibility of a future seizure.

20. The method of claim 1, further comprising generating a notification in response to determining that the brain is in the state indicative of the possibility of a future seizure.

21. The method of claim 1, further comprising measuring, with a sensing module, the impedance of the brain of the patient to generate the impedance measurements by at least measuring the impedance within at least one region of the brain, the region being selected from a group comprising: a cortex, brainstem, anterior thalamus, ventrolateral thalamus, globus pallidus, substantia nigra pars reticulata, subthalamic nucleus, neostriatum, cingulated gyrus or cingulate gyrus.

22. The method of claim 1, further comprising measuring, with a sensing module, the potential of the brain of the patient to generate the potential measurements by at least measuring the potential within at least one region of the brain, the region being selected from a group comprising: a cortex, brainstem, anterior thalamus, ventrolateral thalamus, globus pallidus, substantia nigra pars reticulata, subthalamic nucleus, neostriatum, cingulated gyms or cingulate gyrus.

23. The method of claim 1, further comprising measuring, with a sensing module, the potential of the brain of the patient to generate the potential measurements by at least measuring the potential within a same region of the brain in which the impedance is measured.

24. The method of claim 1, further comprising measuring, with a sensing module, the potential of the brain of the patient to generate the potential measurements by at least measuring the potential within a different region of the brain in which the impedance is measured.

25. The method of claim 1, further comprising measuring, with a sensing module, the impedance of the brain of the patient to generate the impedance measurements by at least:

generating an alternating current (ac) stimulation current at a clock frequency;

applying the stimulation current to a brain tissue load to produce a differential input signal;

amplifying the differential input signal in a mixer amplifier to produce an amplified signal;

demodulating the amplified signal in the mixer amplifier at the clock frequency to produce an output signal;

modulating an amplitude of the output signal at the clock frequency to produce a differential feedback signal; and

applying the modulated output signal as a differential feedback signal to the differential input signal via a first feedback path.

26. The method of claim 1, further comprising measuring, with a sensing module, the potential of the brain of the patient to generate the potential measurements by at least:

modulating an amplitude of a differential input signal indicative of the potential of the brain at a clock frequency to produce a modulated signal;

amplifying the modulated signal in a mixer amplifier to produce an amplified signal;

demodulating the amplified signal in the mixer amplifier at the clock frequency to produce an output signal;

modulating an amplitude of the output signal at the clock frequency; and

applying the modulated output signal as a differential feedback signal to the modulated input signal via a first feedback path.

27. A system comprising:

a sensing module configured to measure a potential of a brain of a patient, and measure an impedance of the brain, wherein the impedance of the brain is indicative of a physiological state of the brain; and

a processor coupled to the sensing module, wherein the processor is configured to receive impedance measurements and potential measurements from the sensing module, select a frequency component of a waveform of the impedance measurements from a plurality of frequency components of the waveform of the impedance measurements, and determine whether the brain is in a state indicative of a possibility of a future seizure based on the potential measurements and the selected frequency component of the waveform of the impedance measurements.

28. The system of claim 27, wherein the sensing module is configured to measure the potential of the brain via at least one of electroencephalography (EEG) or electrocorticography (ECoG).

29. The system of claim 27, wherein the sensing module comprises:

an impedance sensing module configured to measure the impedance of the brain, wherein the processor is configured to receive the impedance measurements from the impedance sensing module; and

a potential sensing module configured to measure the potential of the brain, wherein the processor is configured to receive the potential measurements from the potential sensing module.

30. The system of claim 29, further comprising:

a first set of electrodes coupled to the impedance sensing module; and

a second set of electrodes coupled to the potential sensing module.

31. The system of claim 29, wherein the impedance sensing module and the potential sensing module include common sensing circuitry.

32. The system of claim 27, wherein the sensing module is configured to measure the potential of the brain and measure the impedance of the brain at different times.

33. The system of claim 32, wherein the sensing module is configured to alternate between measuring the potential of the brain and measuring the impedance of the brain.

34. The system of claim 33, wherein the processor is configured to receive alternating potential measurements and impedance measurements from the sensing module and determine whether the brain is in the state indicative of the possibility of a future seizure based on a pattern in the potential measurements and impedance measurements.

35. The system of claim 27, wherein the processor is configured to determine whether the brain is in the state indicative of a possibility of a future seizure based on the potential measurements and the selected frequency component of the waveform of the impedance measurements by at least:

determining whether the selected frequency component of the waveform of the impedance measurements indicates the brain is in the state indicative of the possibility of a future seizure; and

validating that the brain is in the state indicative of the possibility of a future seizure based on the potential measurements.

36. The system of claim 27, wherein the processor is configured to determine whether the brain is in the state indicative of a possibility of a future seizure based on the potential measurements and the selected frequency component of the waveform of the impedance measurements by at least:

determining whether the potential measurements indicate the brain is in the state indicative of the possibility of a future seizure; and

validating that the brain is in the state indicative of the possibility of a future seizure based on the selected frequency component of the waveform of the impedance measurements.

37. The system of claim 27, wherein the processor is further configured to determine whether the brain is in the state indicative of the possibility of a future seizure by at least comparing an amplitude of the waveform of the impedance measurements to a predetermined threshold value.

38. The system of claim 27, wherein the processor is configured to determine whether the brain is in the state indicative of the possibility of a future seizure by at least comparing an amplitude of the potential measurements to a predetermined threshold value.

39. The system of claim 27, wherein the processor is configured to determine whether the brain is in the state indicative of the possibility of a future seizure by at least comparing a trend in the impedance measurements to a template.

40. The system of claim 27, wherein the processor is configured to determine whether the brain is in the state indicative of the possibility of a future seizure by at least comparing a trend in the potential measurements to a template.

41. The system of claim 27, wherein the sensing module is configured to generate the waveform of the impedance measurements, and wherein the processor is configured to determine whether the brain is in the state indicative of the possibility of a future seizure by at least analyzing the selected frequency component of the waveform of the impedance measurements and comparing the selected frequency component of the waveform of the impedance measurements to a corresponding frequency component of a waveform template.

42. The system of claim 27, wherein the sensing module is configured to generate a waveform of the potential measurements, and wherein the processor is configured to determine whether the brain is in the state indicative of the possibility of a future seizure by at least analyzing a frequency component of the waveform of the potential measurements and comparing the frequency component of the waveform of the potential measurements to a corresponding frequency component of a waveform template.

43. The system of claim 27, further comprising a therapy delivery module coupled to the processor, wherein the processor is configured to control delivery of therapy to the patient via the therapy delivery module in response to determining that the brain is in the state indicative of the possibility of a future seizure.

44. The system of claim 27, further comprising a notification device, wherein the processor is configured to activate the notification device in response to determining that the brain is in the state indicative of the possibility of a future seizure.

45. The system of claim 27, further comprising a therapy delivery module coupled to the processor, wherein the processor is configured to control delivery of therapy to the patient via the therapy delivery module in response to determining the brain is in the state indicative of the possibility of a future seizure based on one of the selected frequency component of the waveform of the impedance measurements or the potential measurements.

46. The system of claim 27, wherein the sensing module is configured to measure the impedance and the potential of a same region of the brain.

47. The system of claim 27, wherein the sensing module is configured to measure the potential in a first region of the brain and the impedance in a second region of the brain that is different than the first region.

48. The system of claim 27, wherein the sensing module comprises a chopper-stabilized instrumentation amplifier to measure the impedance of the brain, the instrumentation amplifier comprising:

an alternating current (ac) source configured to generate an (ac) stimulation current at a clock frequency for application to a brain tissue load;

a mixer amplifier coupled to receive a differential input signal from the brain tissue load in response to the stimulation current, wherein the mixer amplifier is configured to amplify the differential input signal to produce an amplified signal and demodulate the amplified signal at the clock frequency to produce an output signal;

a modulator configured to modulate an amplitude of the output signal at the clock frequency; and

a feedback path configured to apply the modulated output signal as a differential feedback signal to the differential input signal.

49. The system of claim 27, wherein the sensing module comprises a chopper-stabilized instrumentation amplifier to measure the potential of the brain, the instrumentation amplifier comprising:

a first modulator configured to modulate an amplitude of a differential input signal indicative of the potential of the brain at a clock frequency to produce a modulated signal;

a mixer amplifier configured to amplify the modulated signal to produce an amplified signal and demodulate the amplified signal at the clock frequency to produce an output signal;

a second modulator configured to modulate an amplitude of the output signal at the clock frequency; and

a feedback path configured to apply the modulated output signal as a differential feedback signal to the modulated input signal.

50. A non-transitory computer-readable medium comprising instructions that, when executed by a programmable processor, cause the programmable processor to:

receive impedance measurements indicative of an impedance of a brain of a patient, wherein the impedance of the brain is indicative of a physiological state of the brain;

receive potential measurements indicative of potential of the brain;

select a frequency component of a waveform of the impedance measurements from a plurality of frequency components of the waveform of the impedance measurements; and

determine whether the brain is in a state indicative of a possibility of a future seizure based on the potential measurements and the selected frequency component of the waveform of the impedance measurements.

51. The non-transitory computer-readable medium of claim 50, further comprising instructions that, when executed by the programmable processor, cause the processor to control a therapy delivery module to deliver therapy to the patient in response to determining that the brain is in the state indicative of the possibility of a future seizure.

52. The non-transitory computer-readable medium of claim 50, further comprising instructions that, when executed by the programmable processor, cause the processor to determine whether the brain is in the state indicative of a possibility of a future seizure based on the potential measurements and the selected frequency component of the waveform of the impedance measurements by at least determining whether the selected frequency component of the waveform of the impedance measurements indicates the brain is in the state indicative of the possibility of a future seizure and validating the determination based on whether the potential measurements indicates the brain is in the state indicative of the possibility of a future seizure.

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摘要(译)

癫痫发作预测系统和方法包括测量患者脑内的阻抗和电位，以确定大脑是否处于指示癫痫发作可能性的状态。在一些实施方案中，测量的阻抗或测量的电位中的至少一个可以用作指示癫痫发作可能性的脑状态的主要指示。在一个实施例中，如果测量的阻抗或测量的电位之一指示癫痫发作，则可以使用另一测量（阻抗或电位）来验证大脑是否处于指示癫痫发作可能性的状态。