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Bolea et al.

(54) **OBSTRUCTIVE SLEEP APNEA TREATMENT DEVICES, SYSTEMS AND METHODS**

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(73) Assignee: **Apnex Medical, Inc.**

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Related U.S. Application Data

(63) Continuation of application No. 12/835,984, filed on Jul. 14, 2010, which is a continuation of application No. 11/907,532, filed on Oct. 12, 2007, now Pat. No. 7,809,442.

(60) Provisional application No. 60/851,386, filed on Oct. 13, 2006, provisional application No. 60/918,257, filed on Mar. 14, 2007.

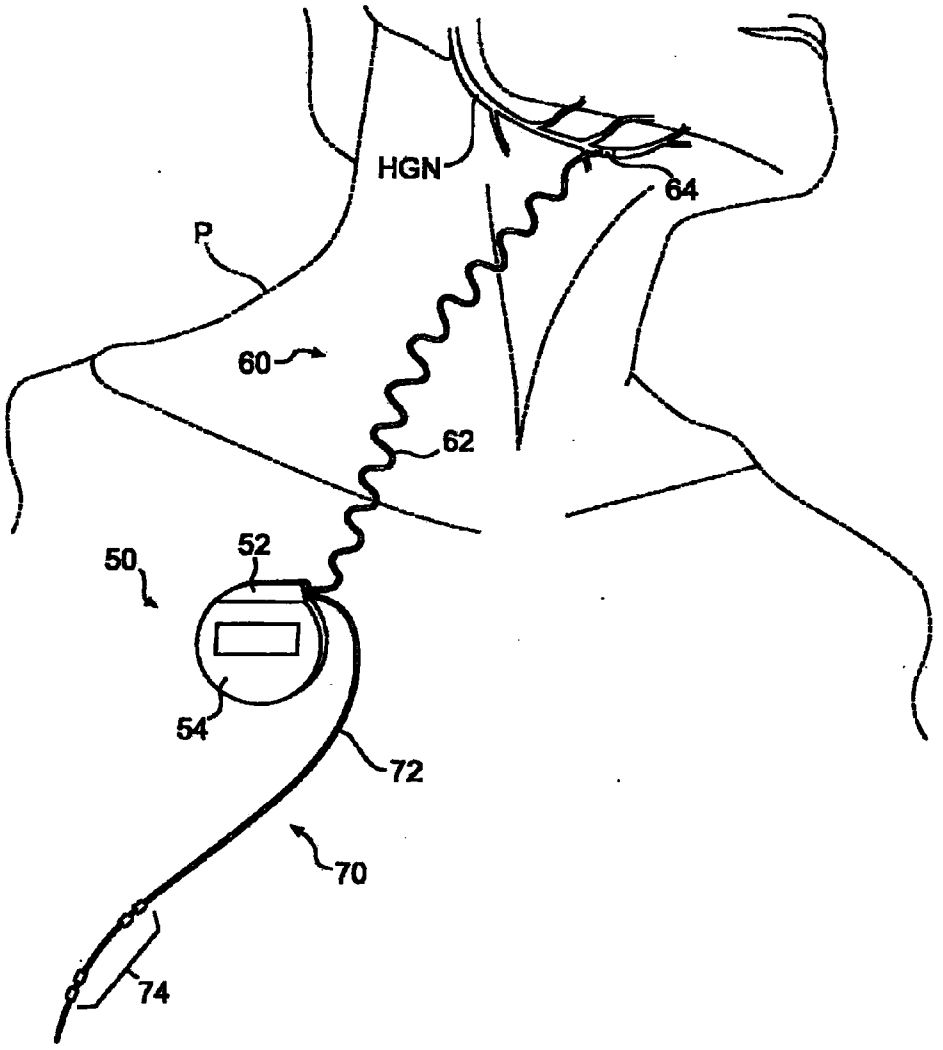
Publication Classification

(51) **Int. Cl.**
A61N 1/372 (2006.01)

(52) **U.S. Cl.** **607/42**

(57) **ABSTRACT**

Devices, systems and methods for nerve stimulation for OSA therapy.



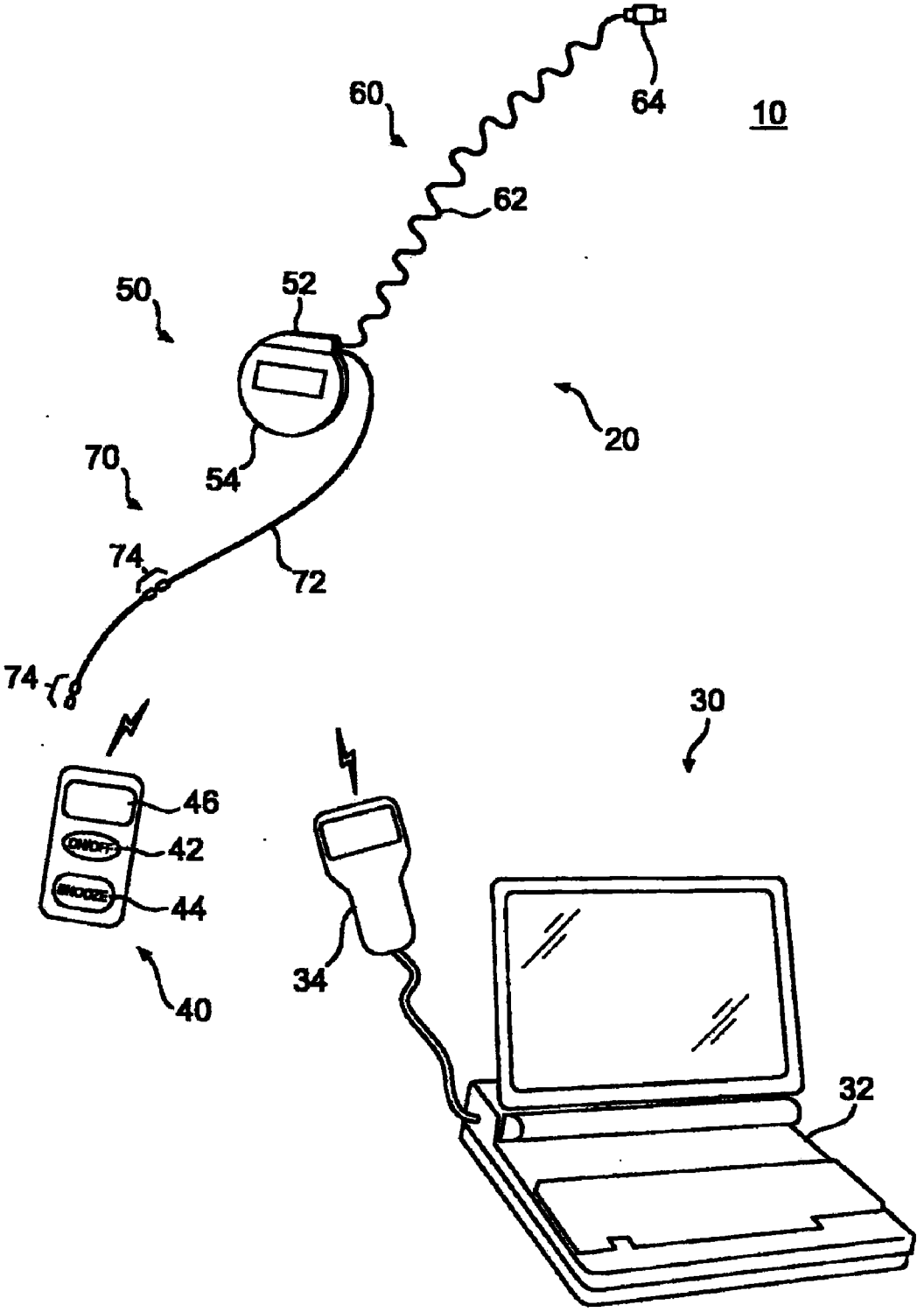


FIG. 1

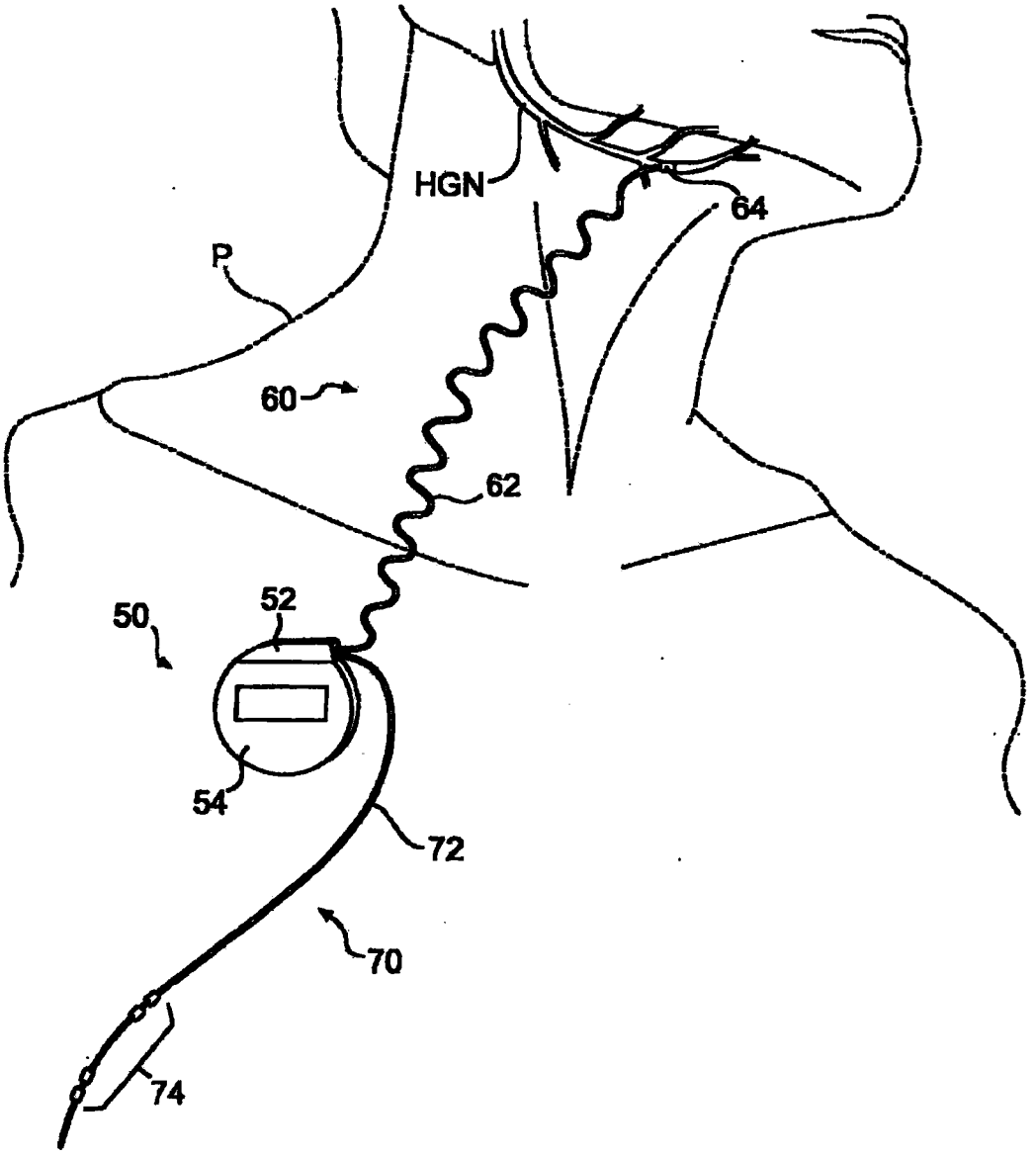


FIG. 2

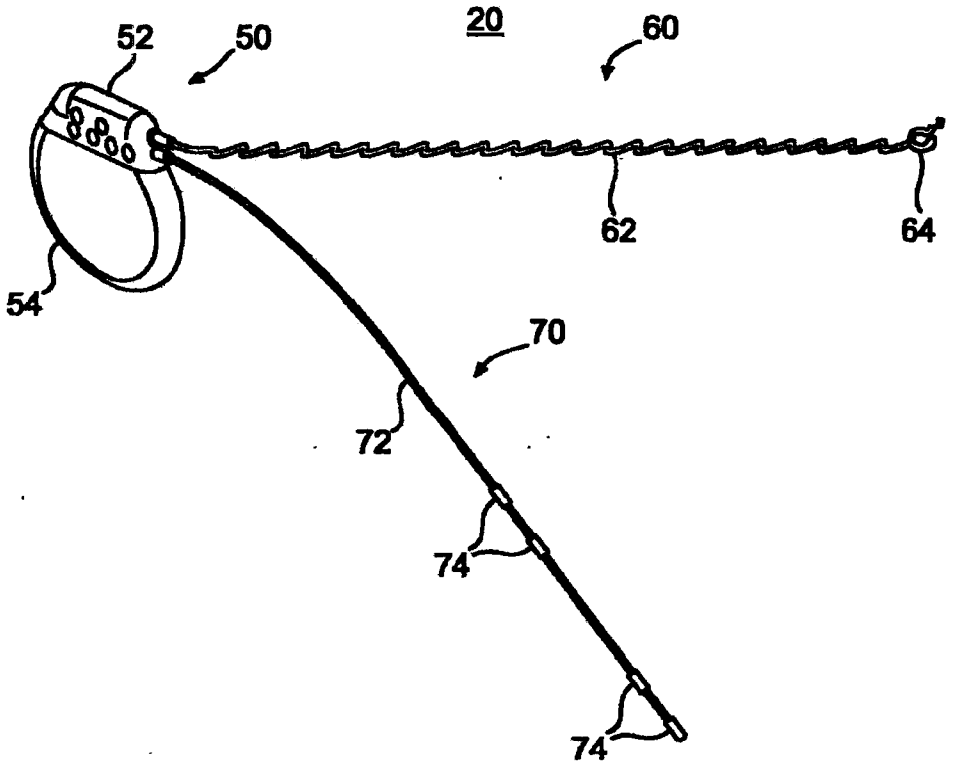


FIG. 3

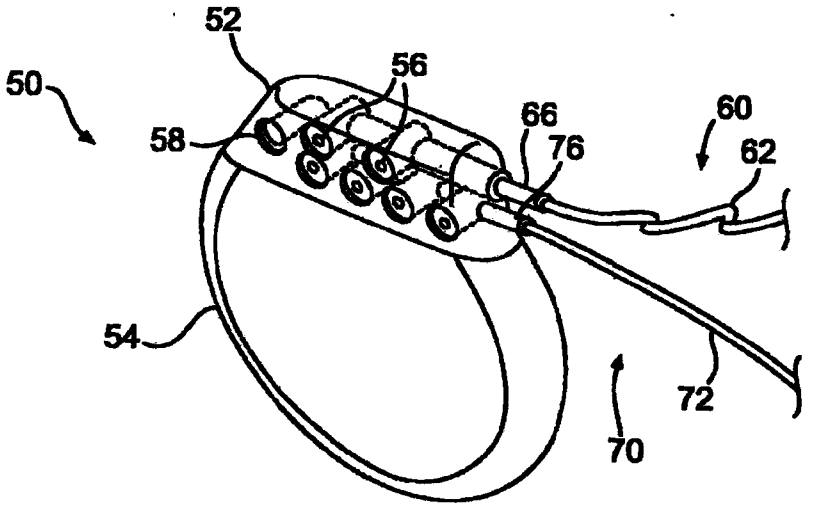


FIG. 4

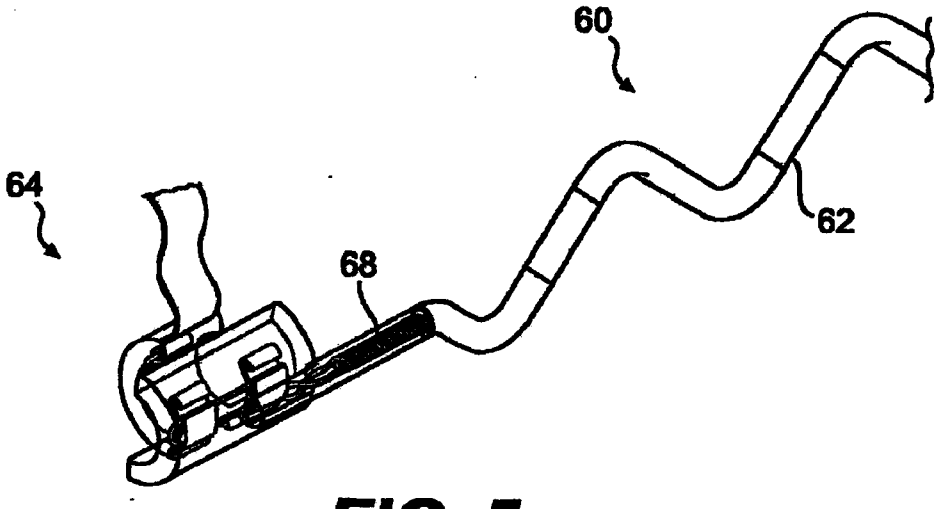


FIG. 5

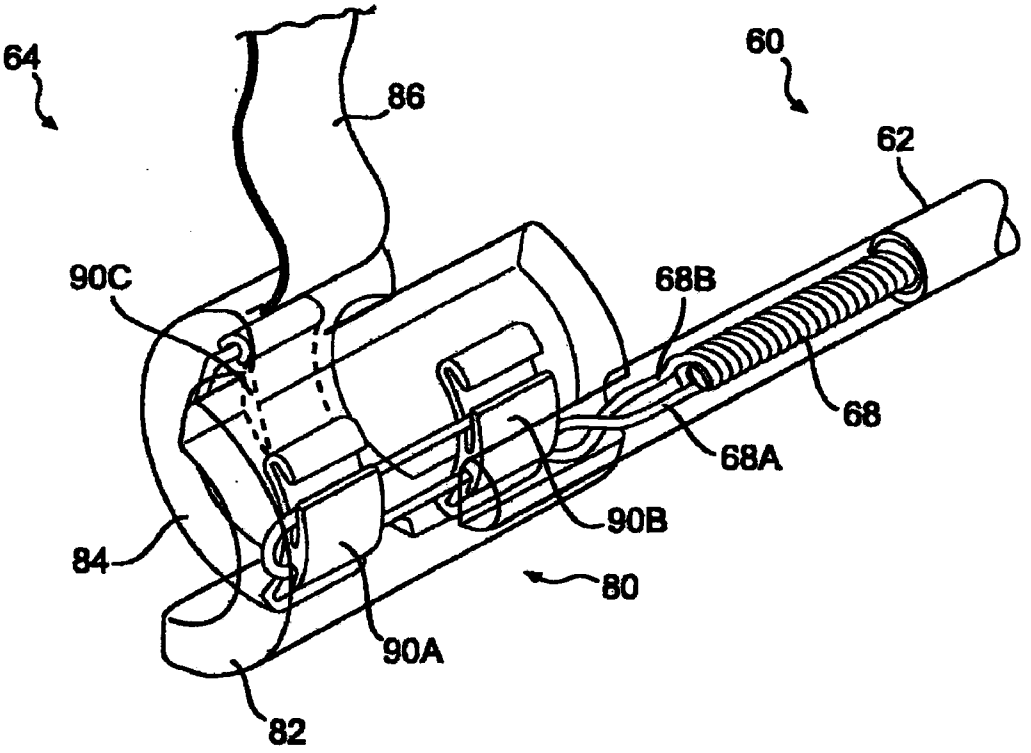


FIG. 6

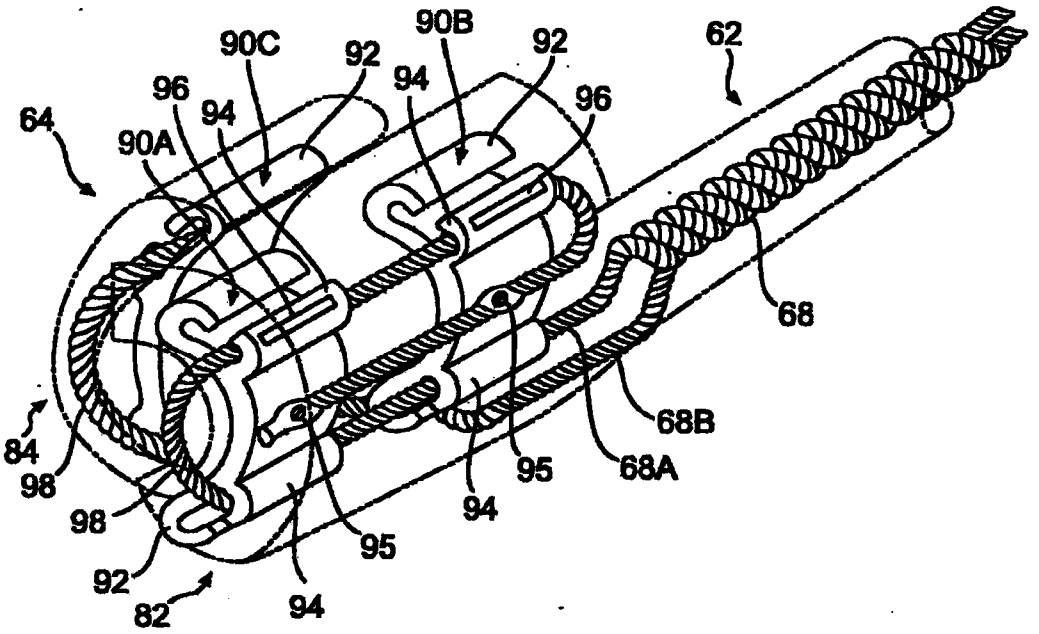

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FIG. 7

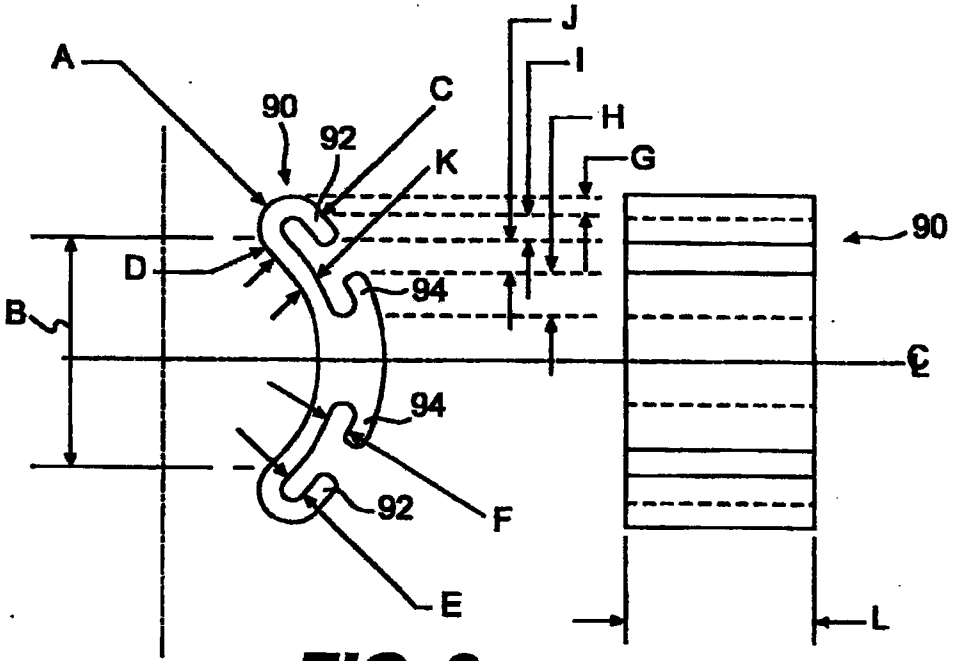
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FIG. 8

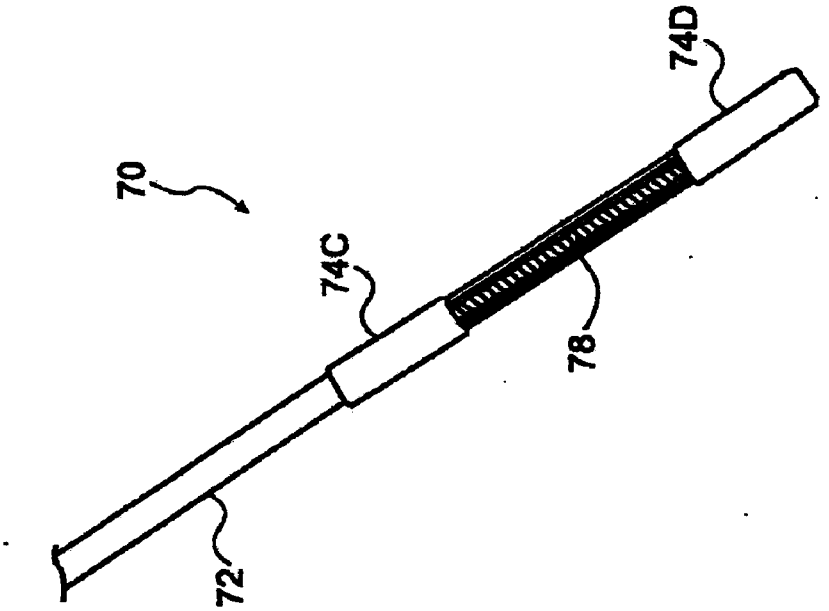


FIG. 9B

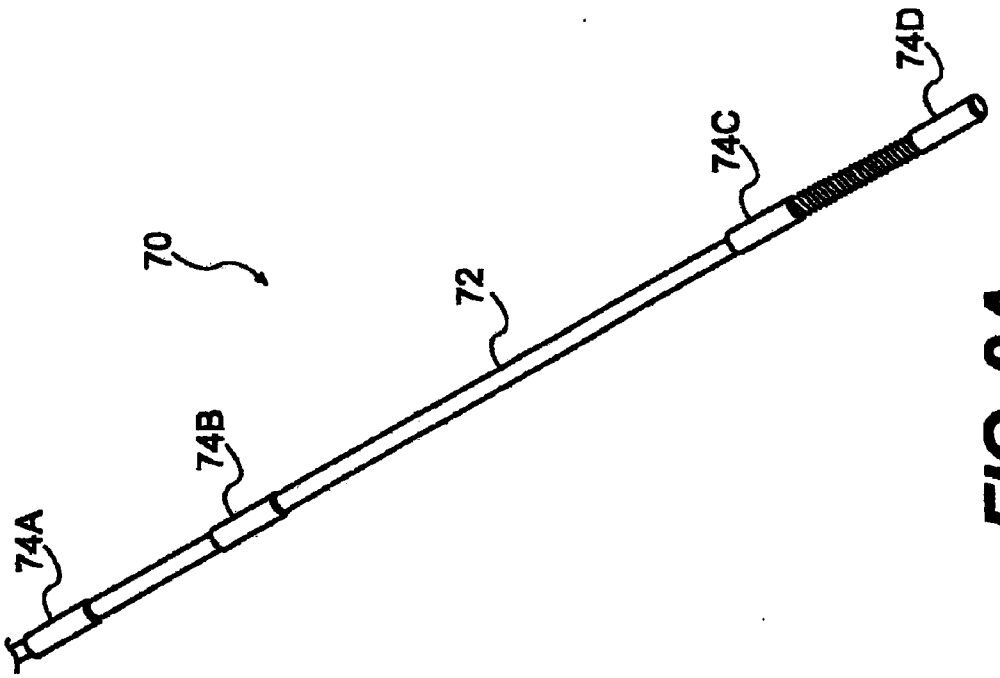


FIG. 9A

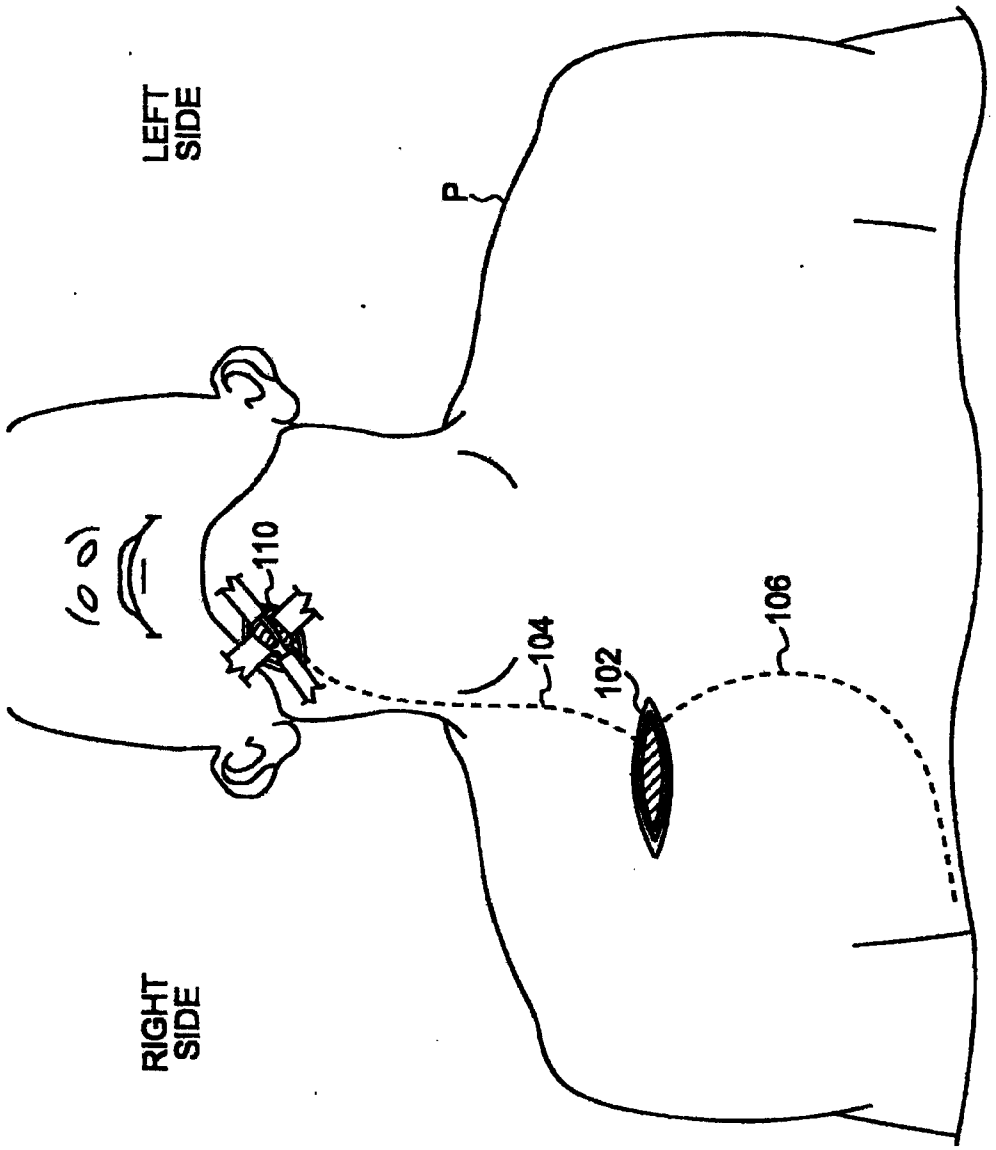


FIG. 10

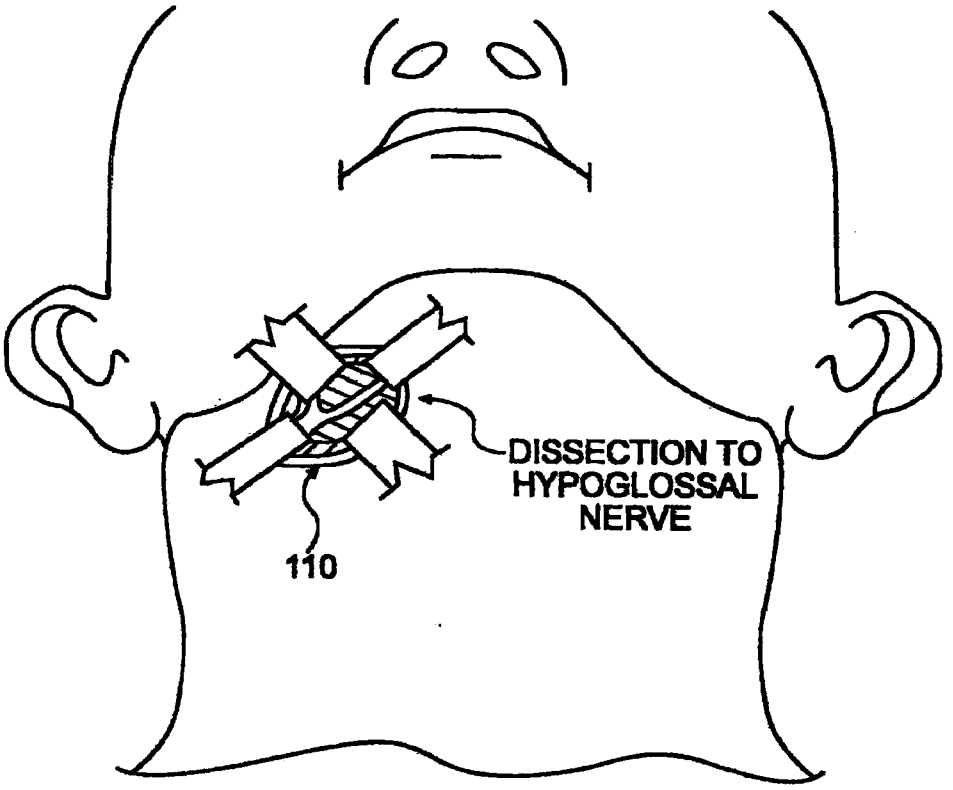


FIG. 11A

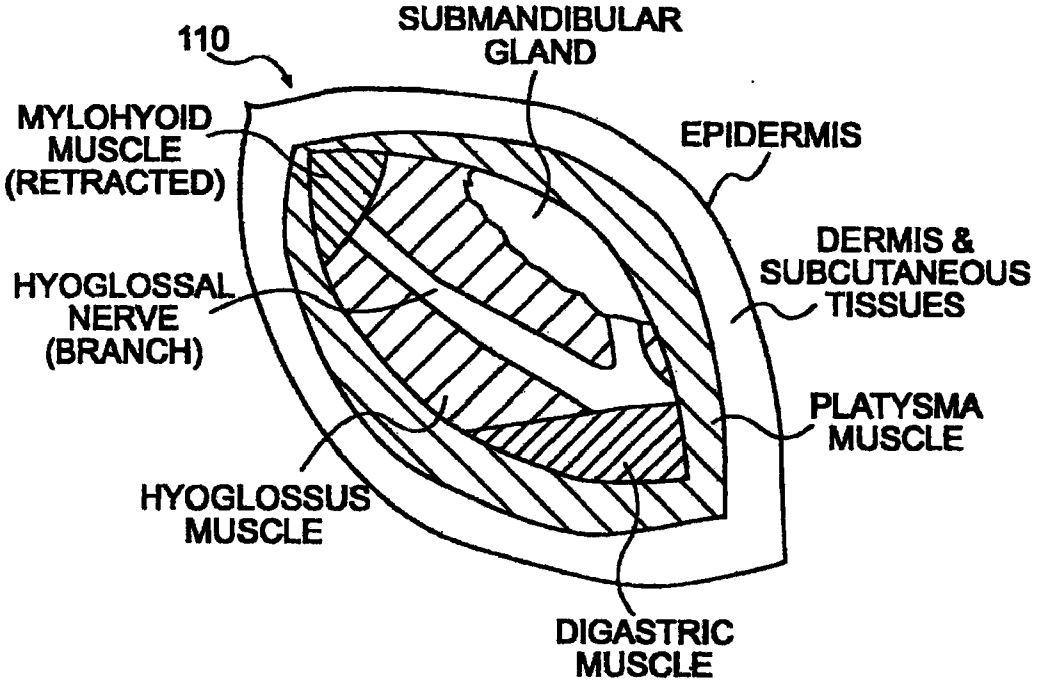
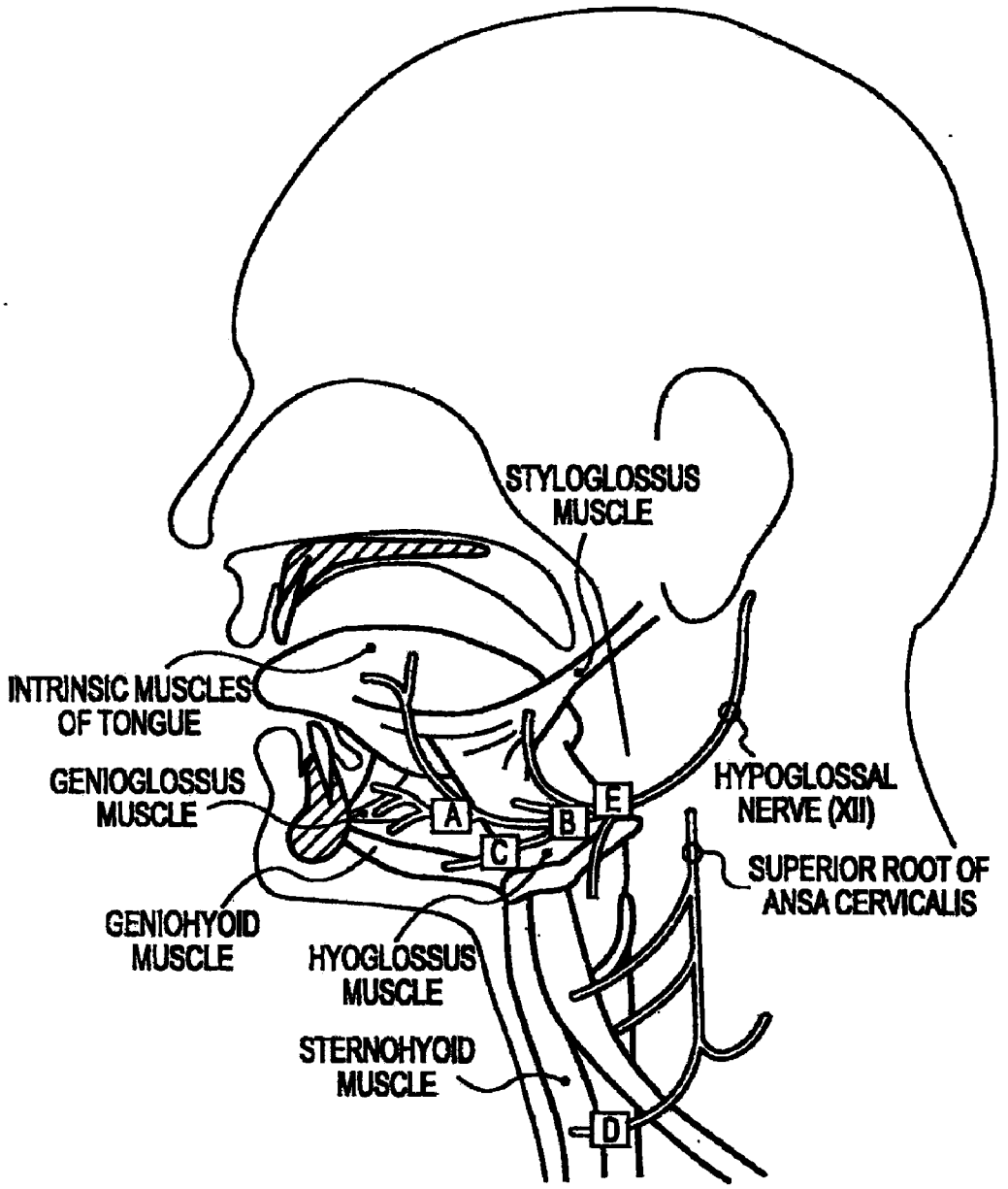


FIG. 11B


STYLOGLOSSUS MUSCLE
INTRINSIC MUSCLES OF TONGUE
GENIOGLOSSUS MUSCLE
HYPOGLOSSAL NERVE (XII)
SUPERIOR ROOT OF ANSA CERVICALIS
GENIOHYOID MUSCLE
HYOGLOSSUS MUSCLE
STERNOHYOID MUSCLE
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B
C
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FIG. 12

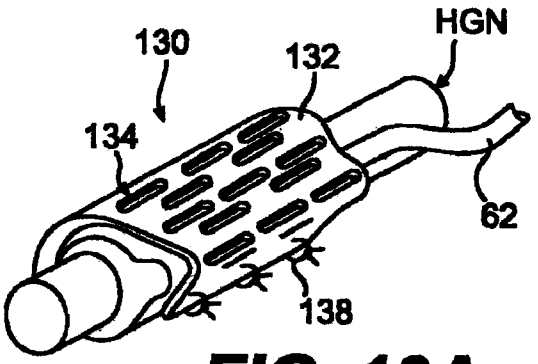

FIG. 13A

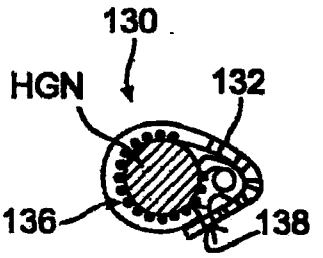

FIG. 13B

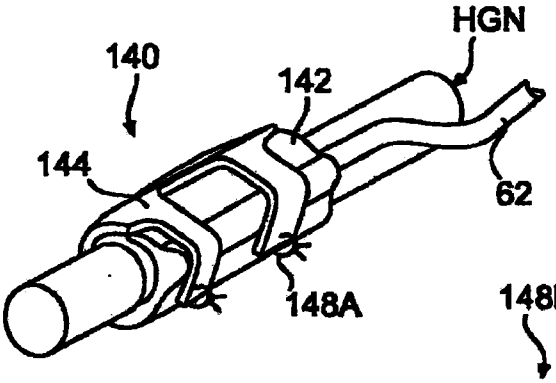

FIG. 14A

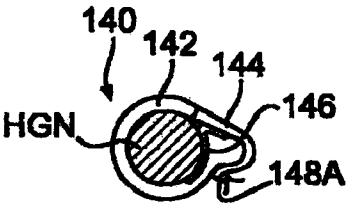

FIG. 14B

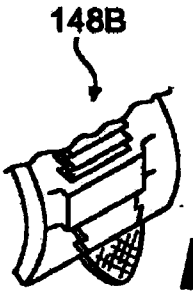

FIG. 14C

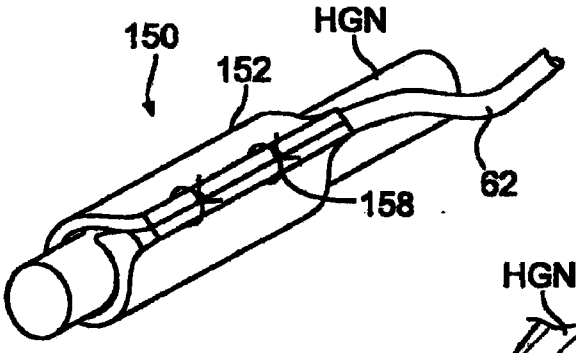

FIG. 15A

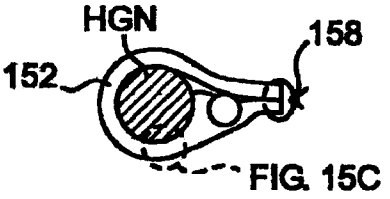

FIG. 15B

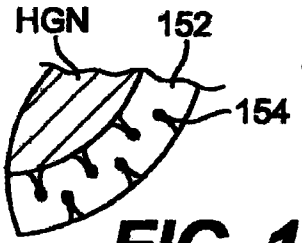

FIG. 15C

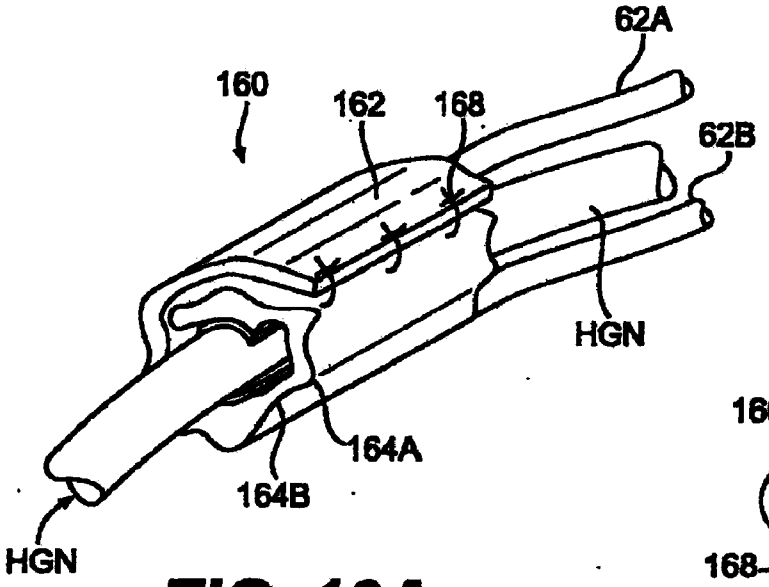

FIG. 16A

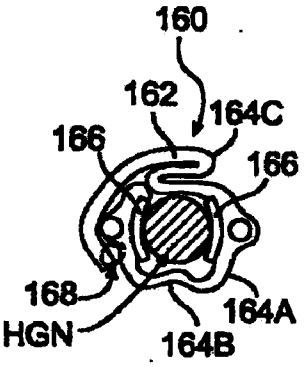

FIG. 16B

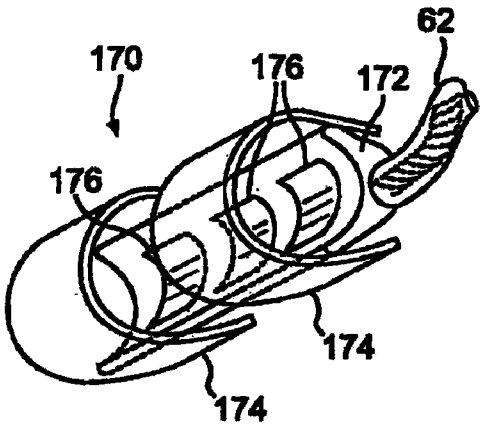

FIG. 17

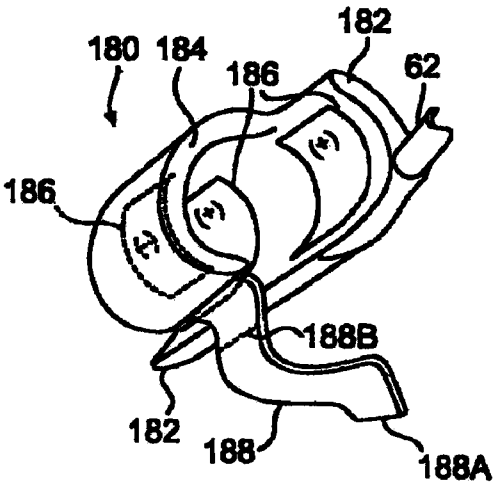

FIG. 18

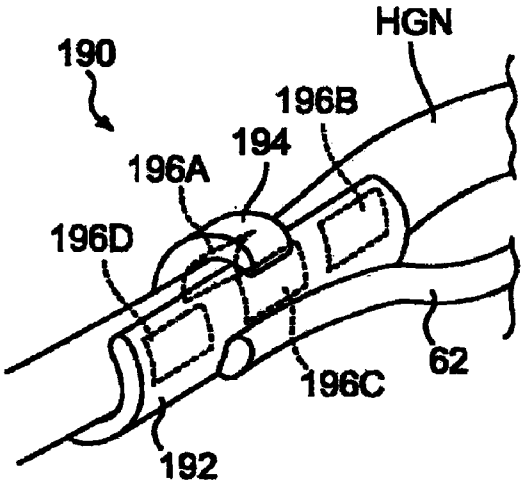

FIG. 19A

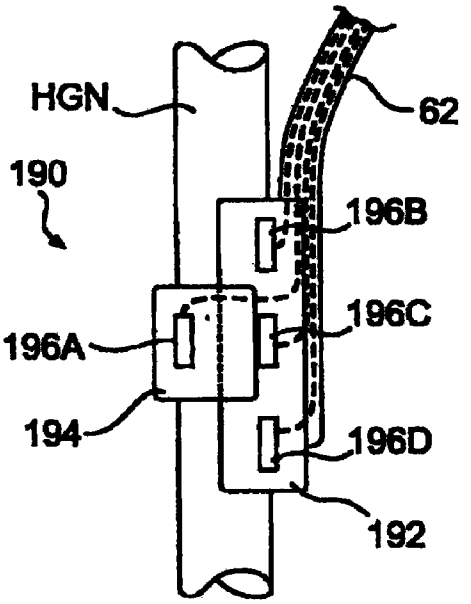

FIG. 19B

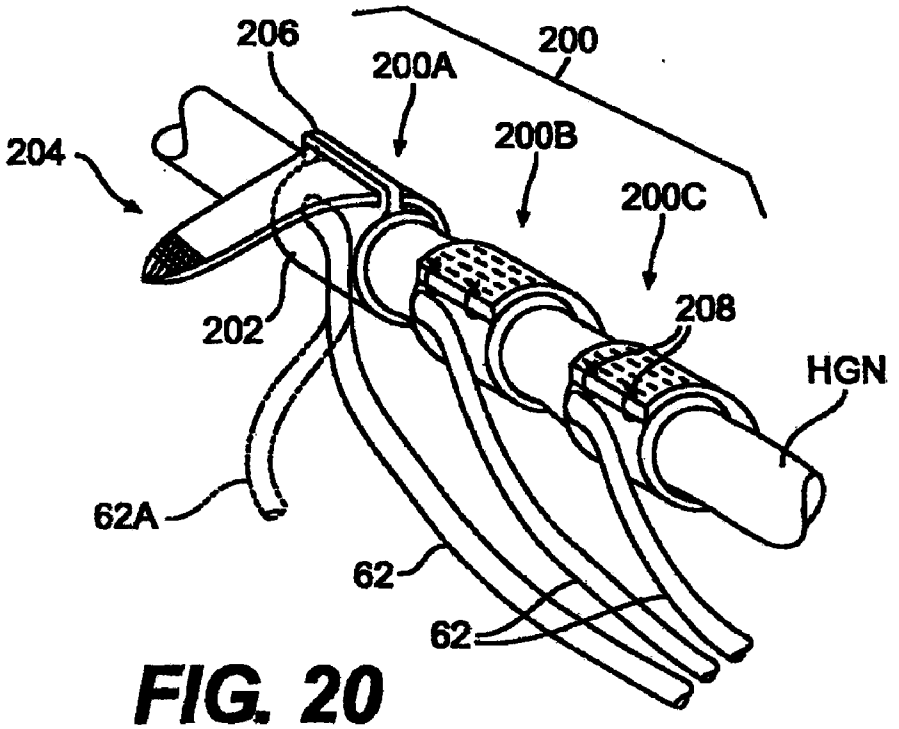

FIG. 20

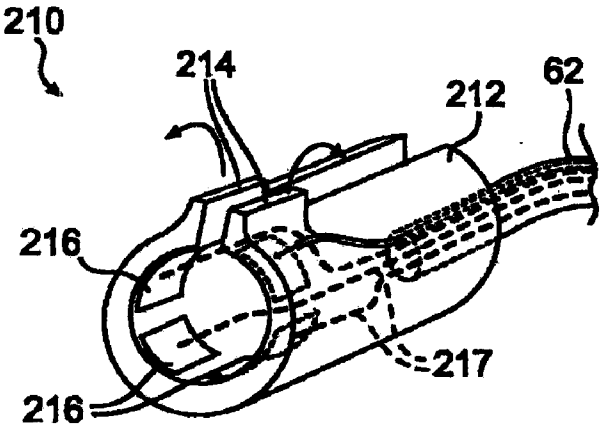

FIG. 21A

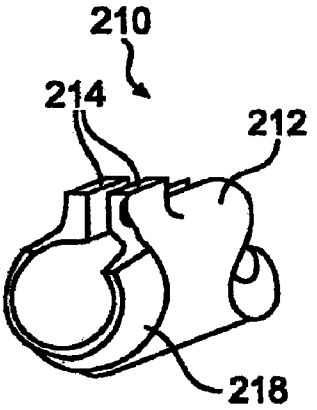

FIG. 21B

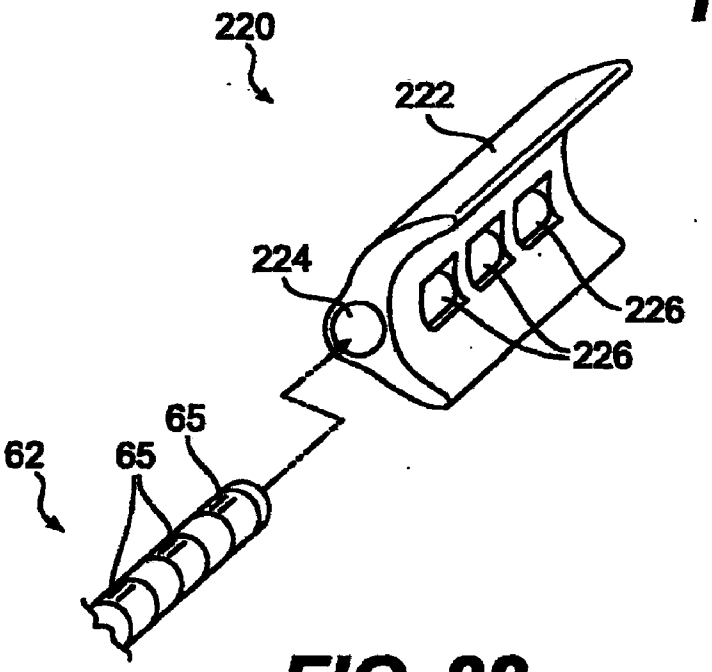

FIG. 22

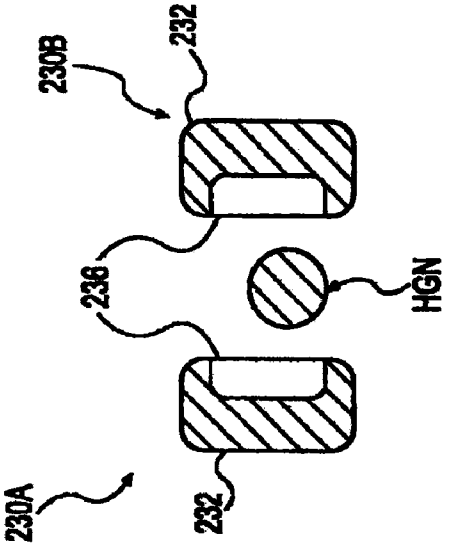

FIG. 23B

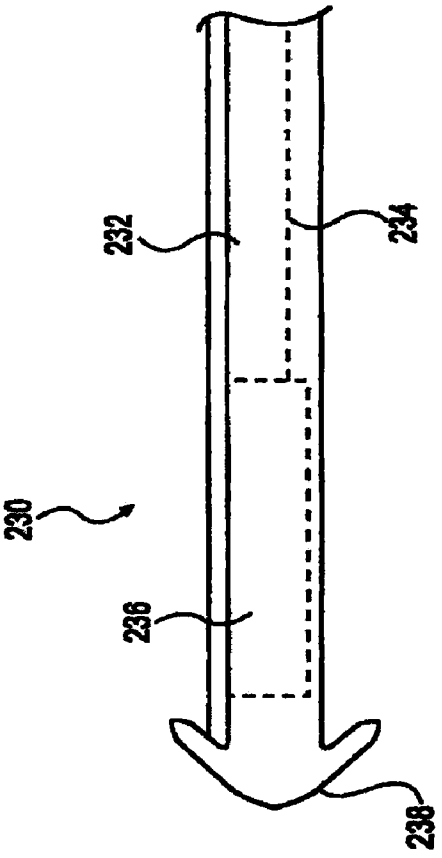

FIG. 23A

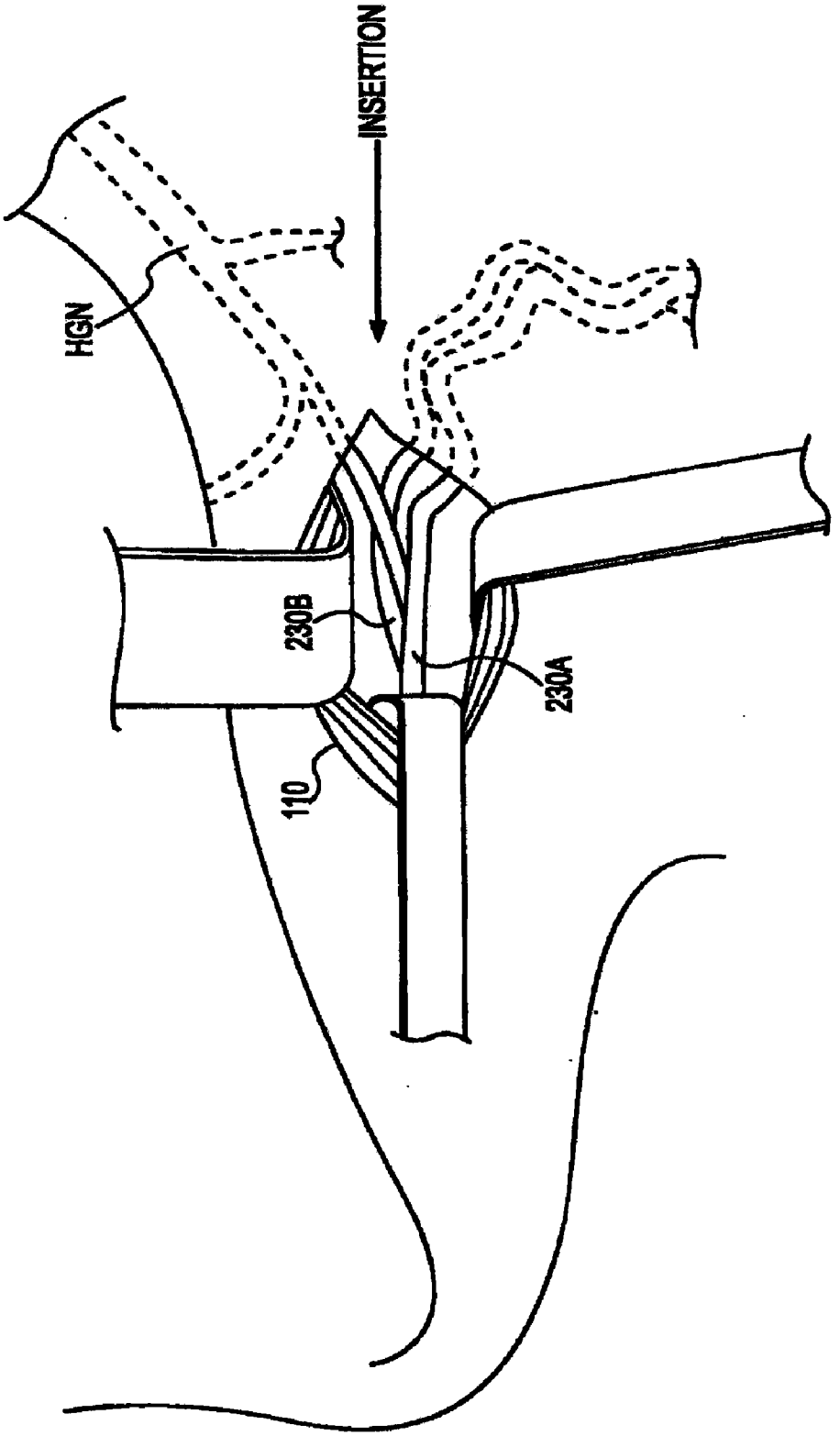

FIG. 23C

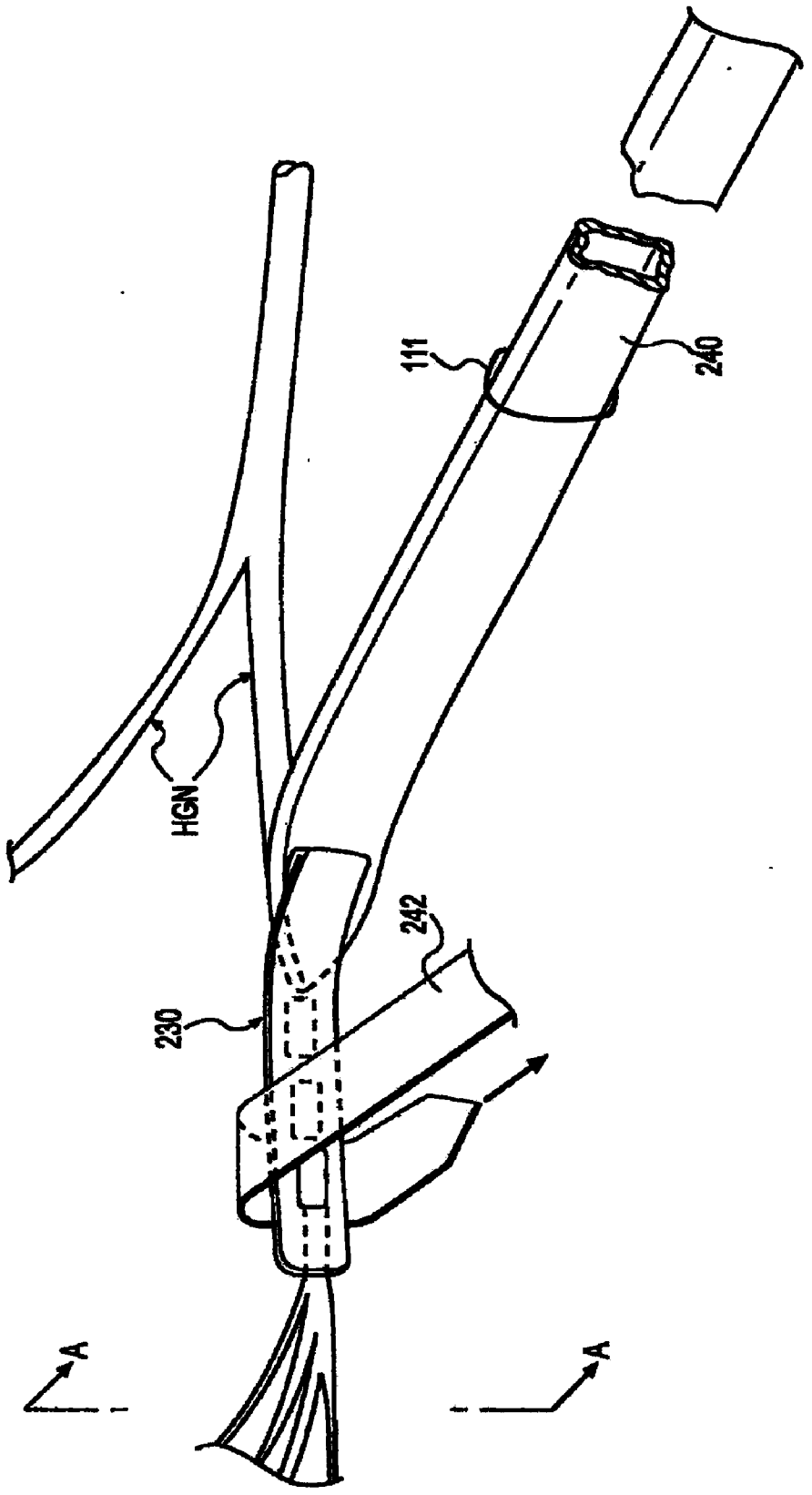

FIG. 24A

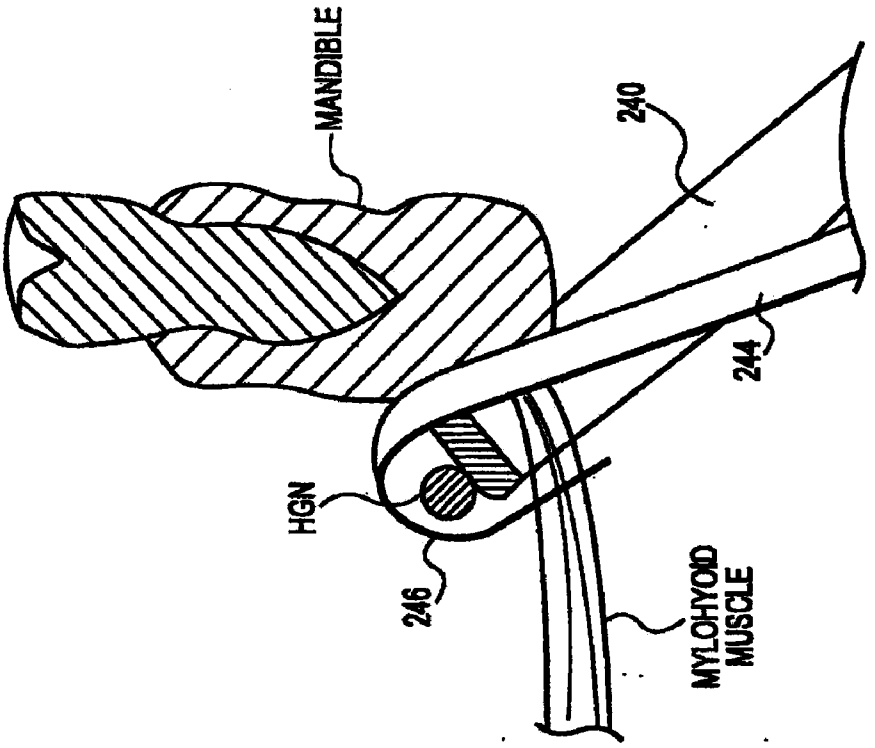

FIG. 24C

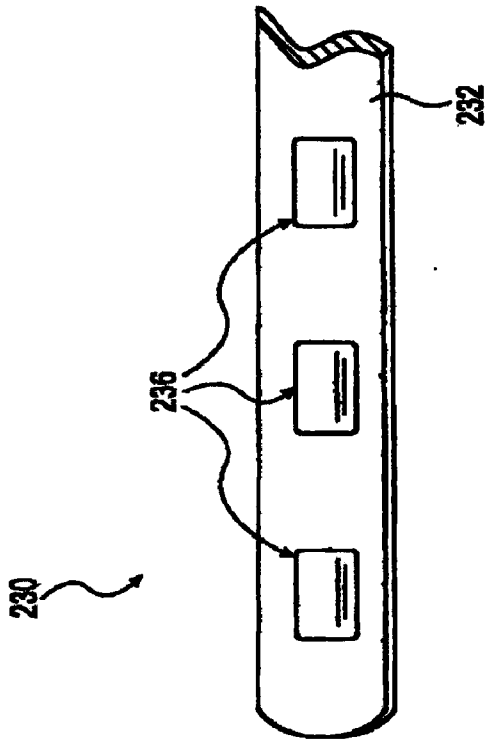

FIG. 24B

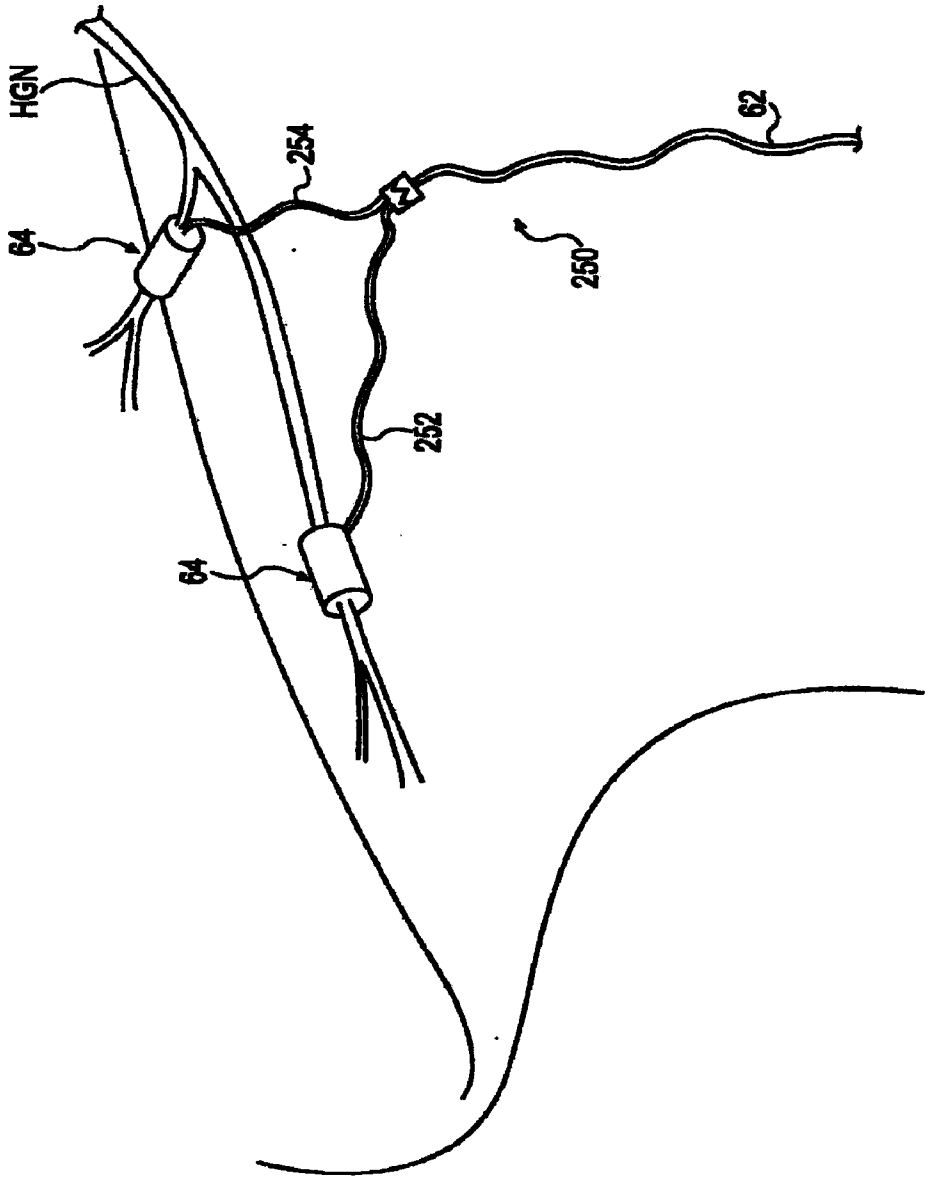

FIG. 25

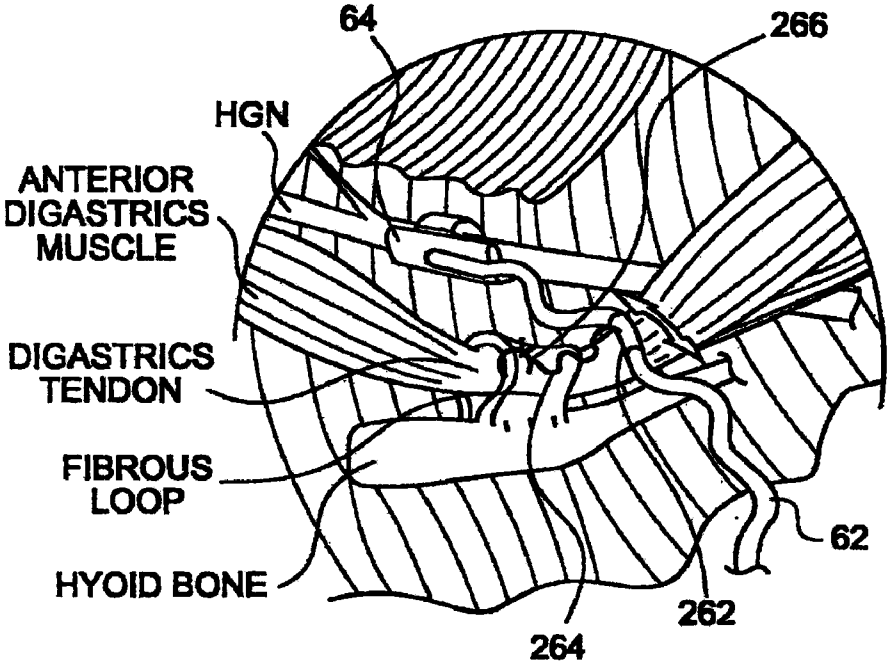

FIG. 26A

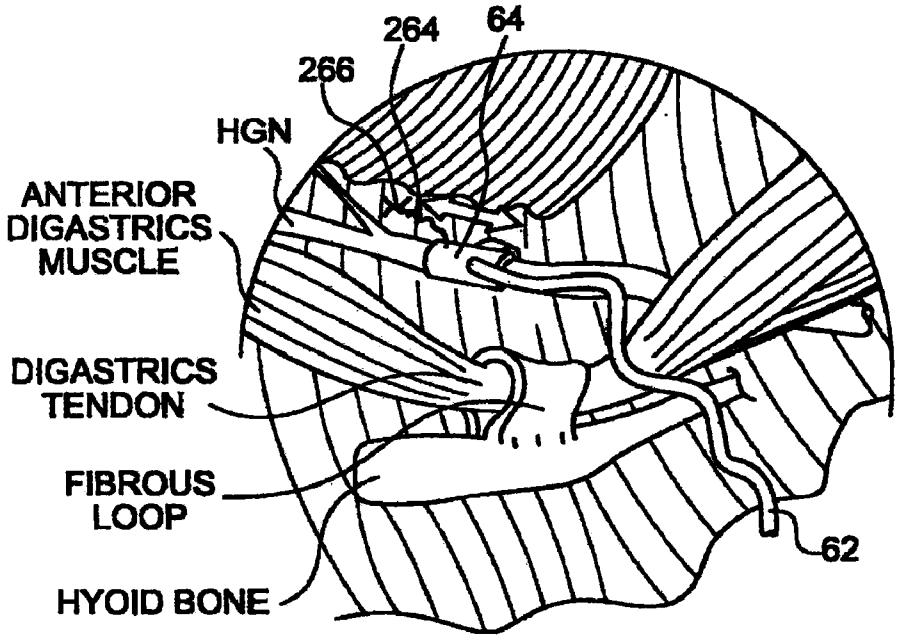

FIG. 26B

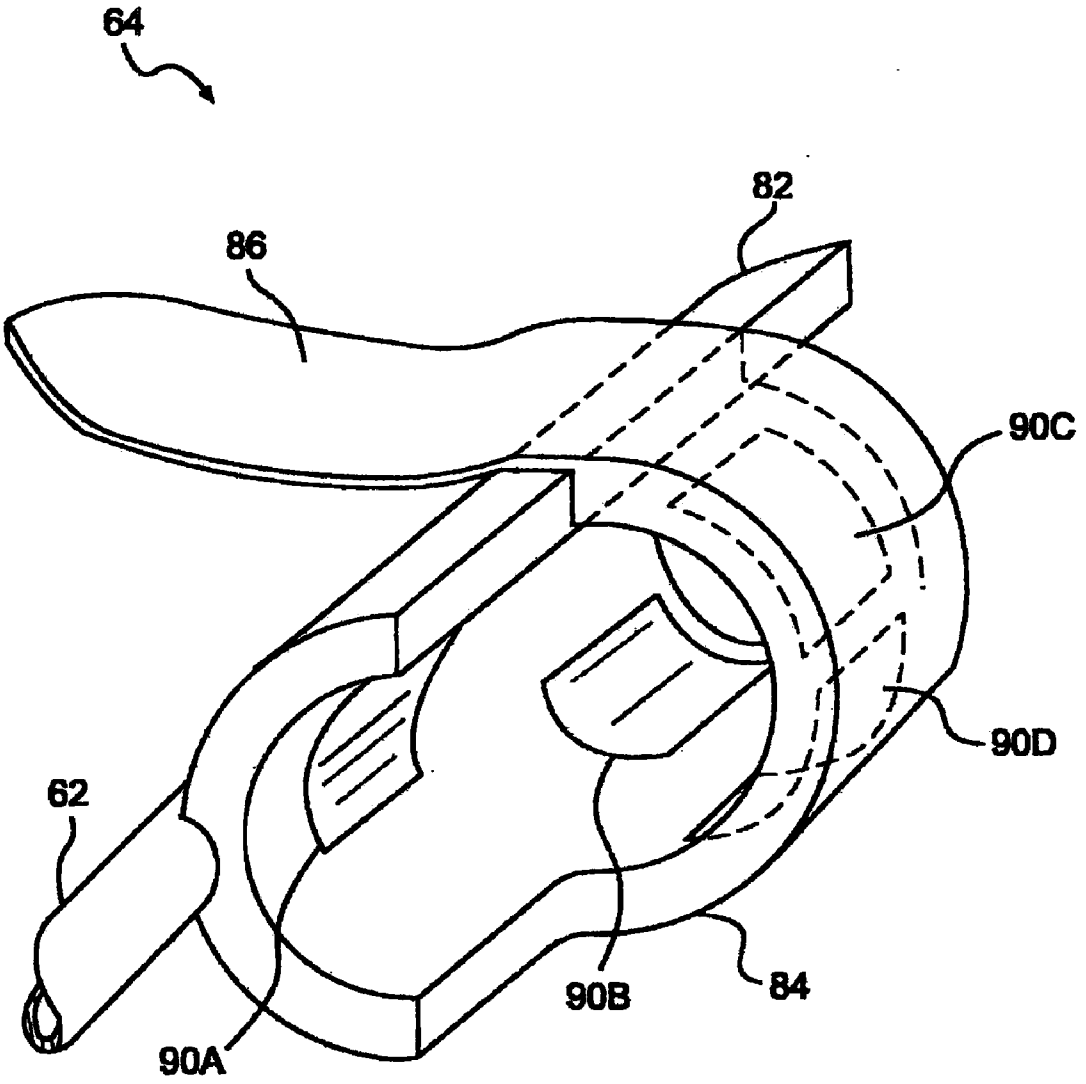

FIG. 27A

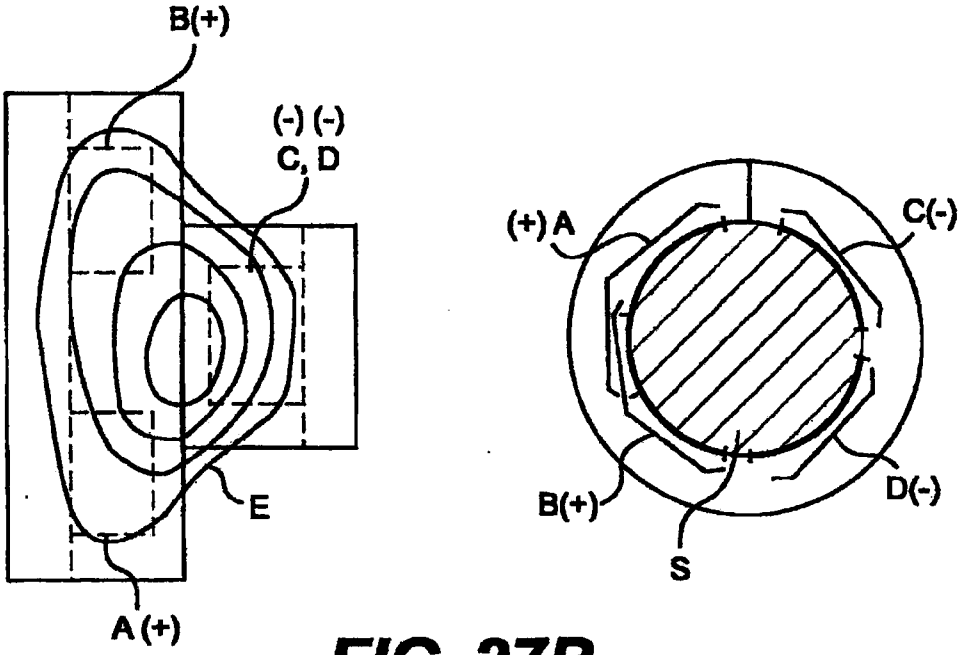

FIG. 27B

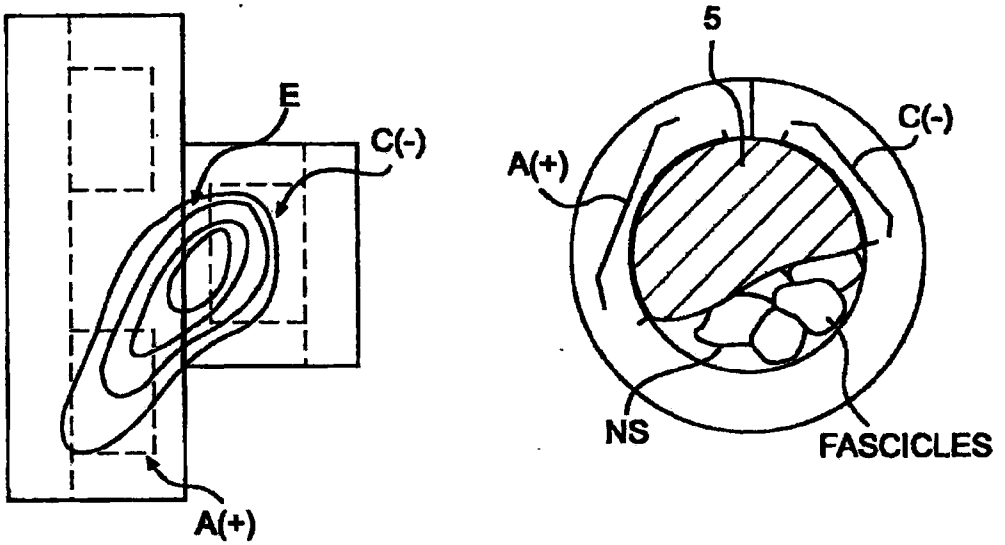

FIG. 27C

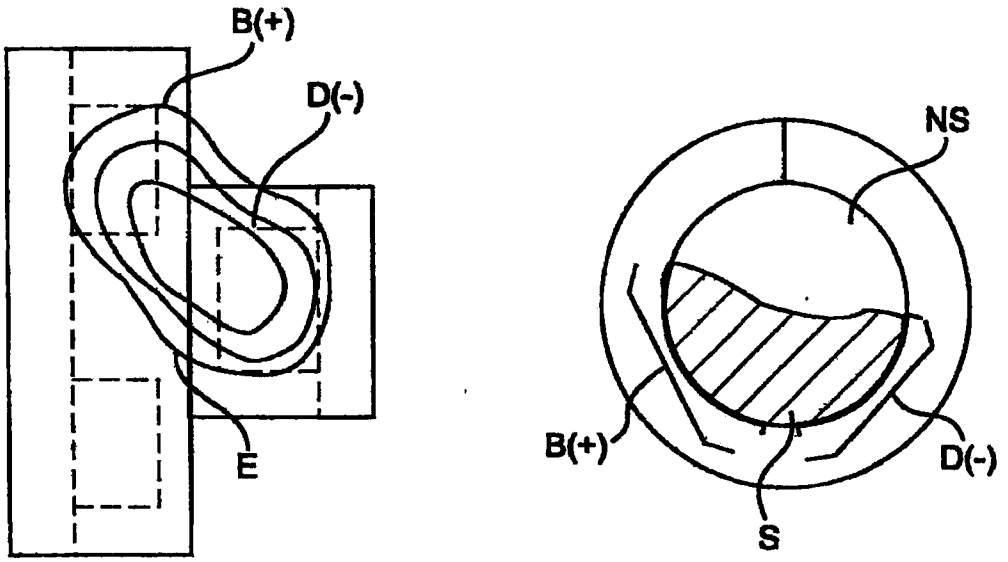

FIG. 27D

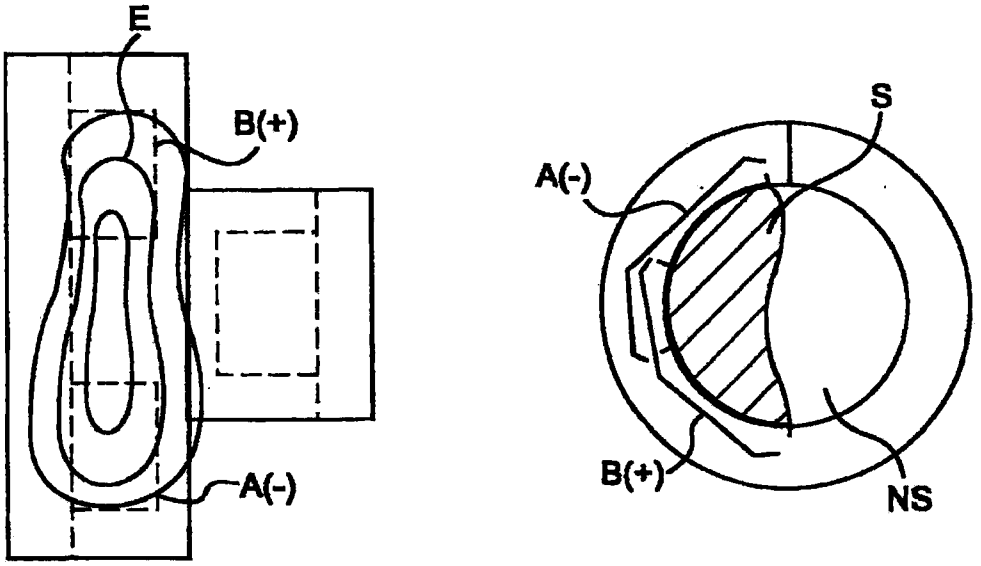

FIG. 27E

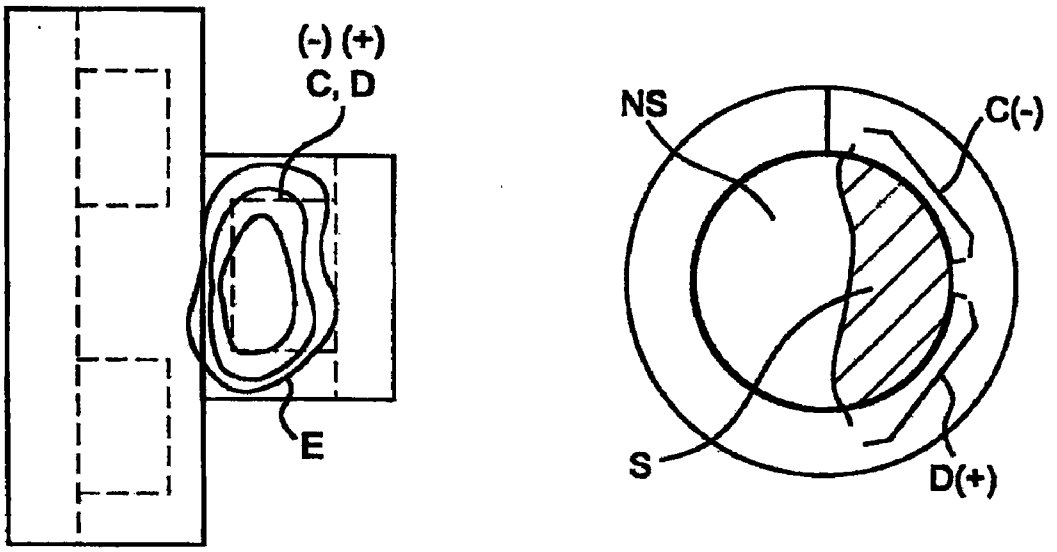

FIG. 27F

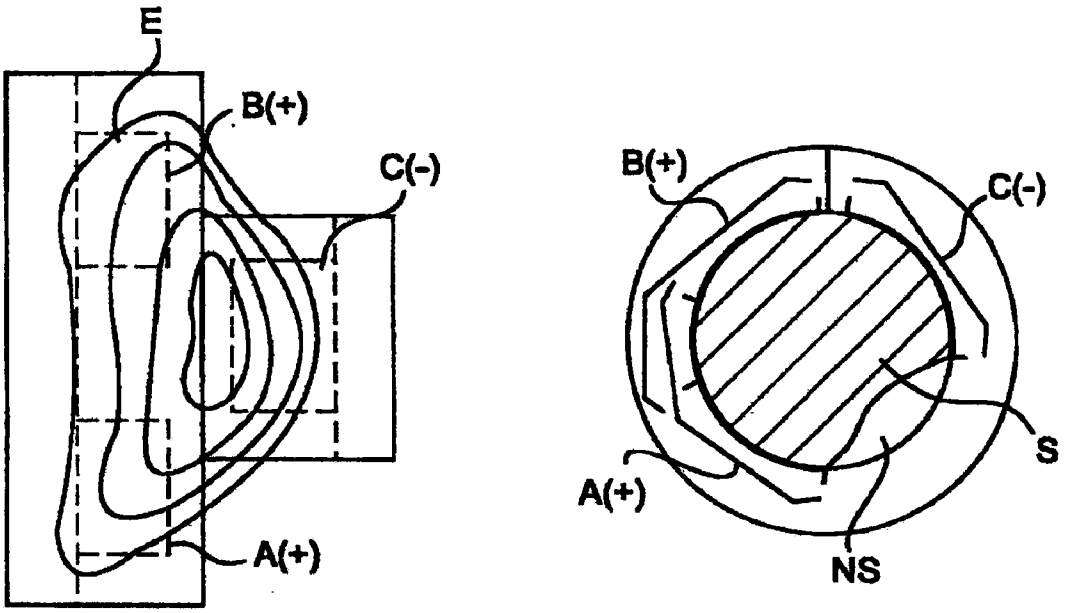

FIG. 27G

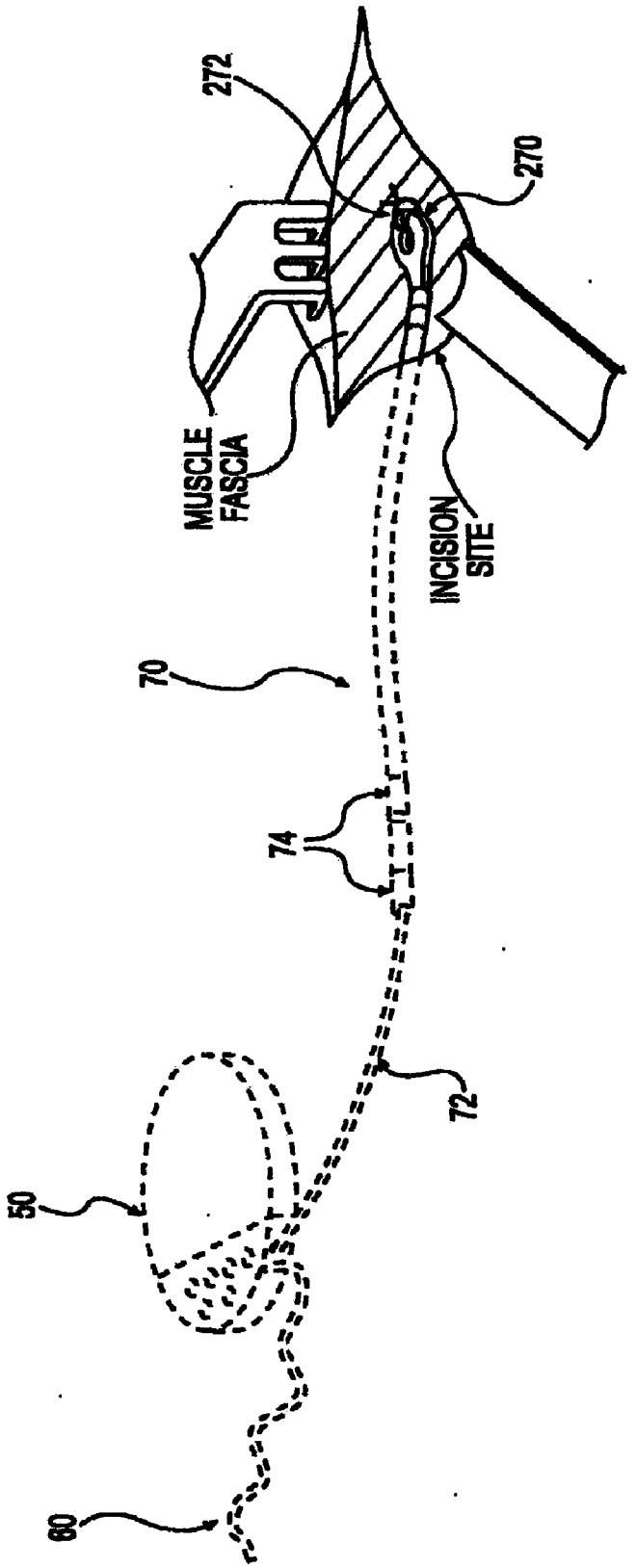

FIG. 28

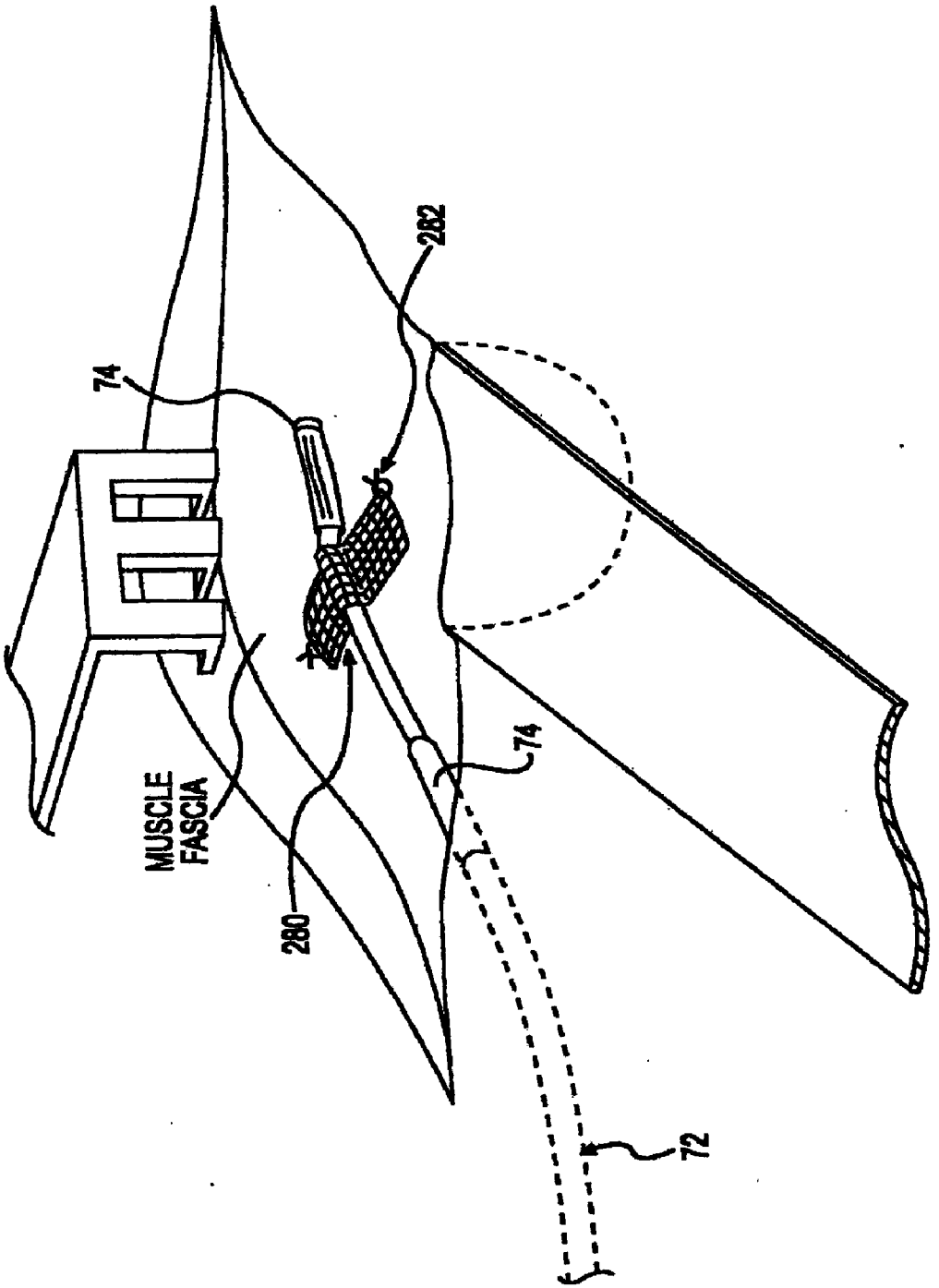

FIG. 29A

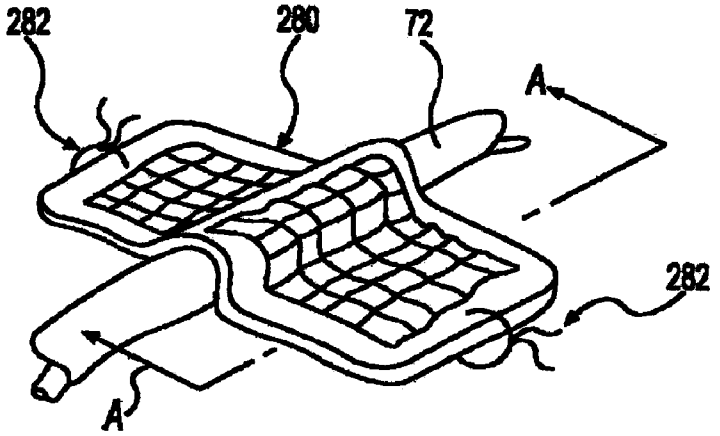

FIG. 29B

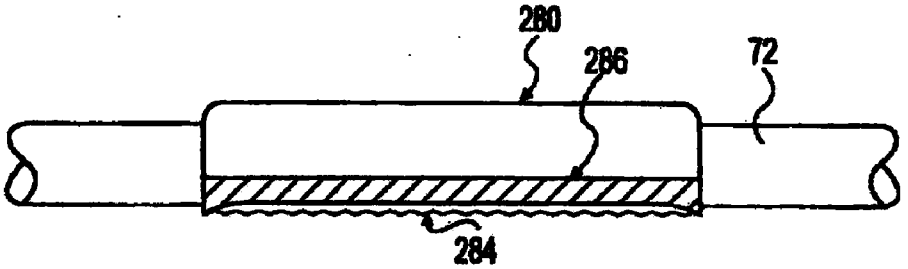

FIG. 29C

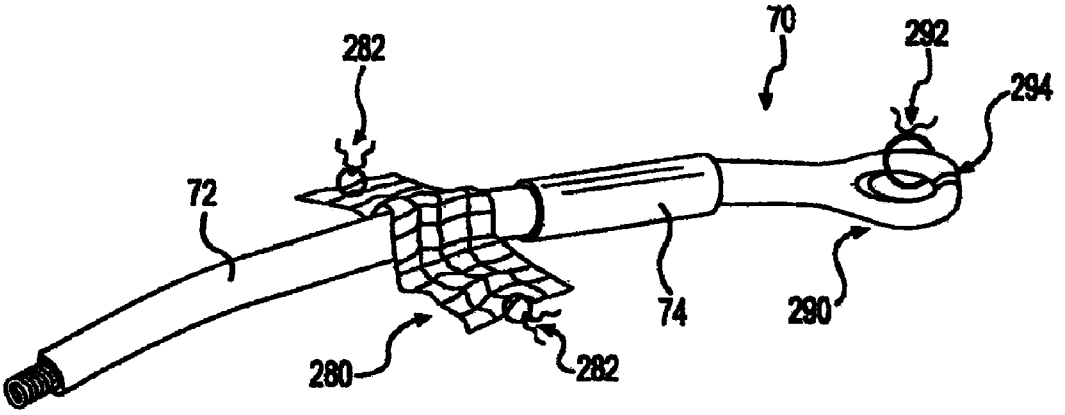

FIG. 30

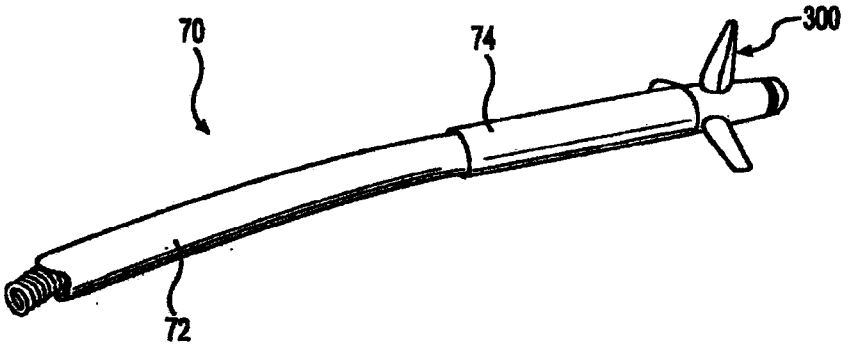

FIG. 31A

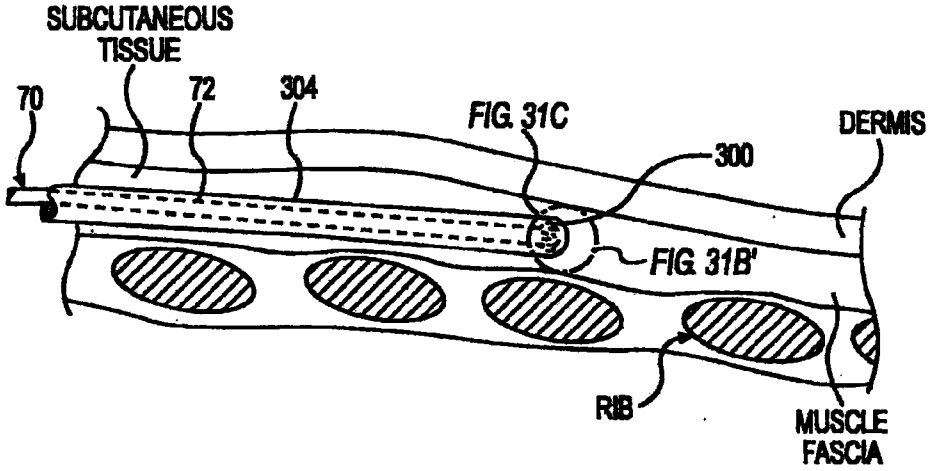

FIG. 31B

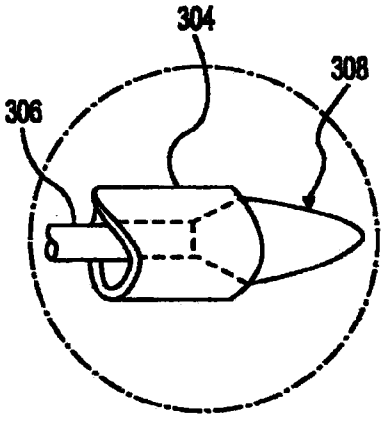

FIG. 31B'

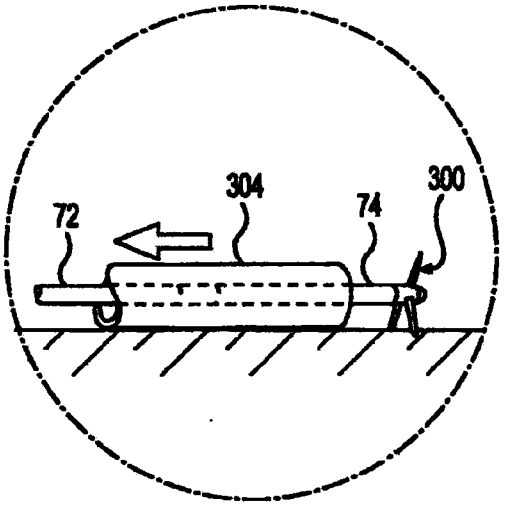

FIG. 31C

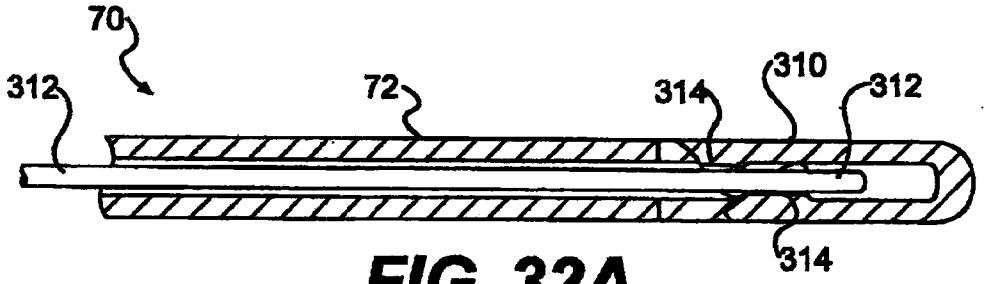

FIG. 32A

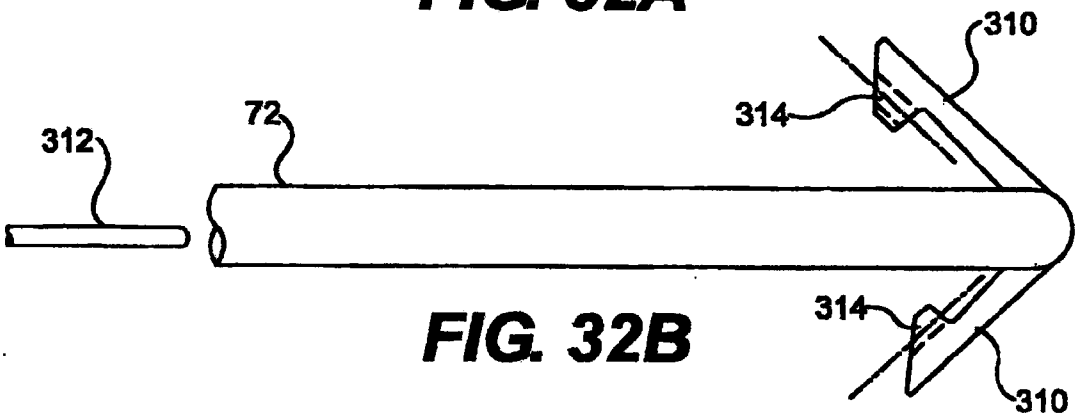

FIG. 32B

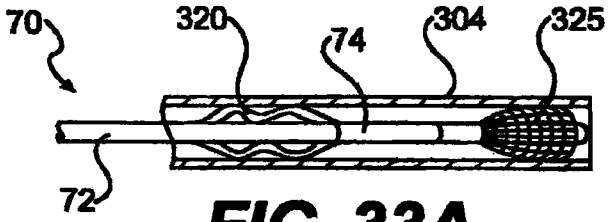

FIG. 33A

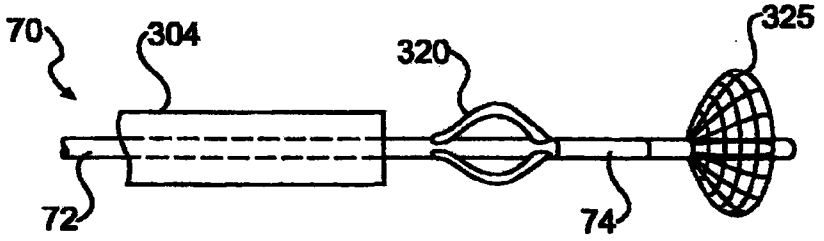

FIG. 33B

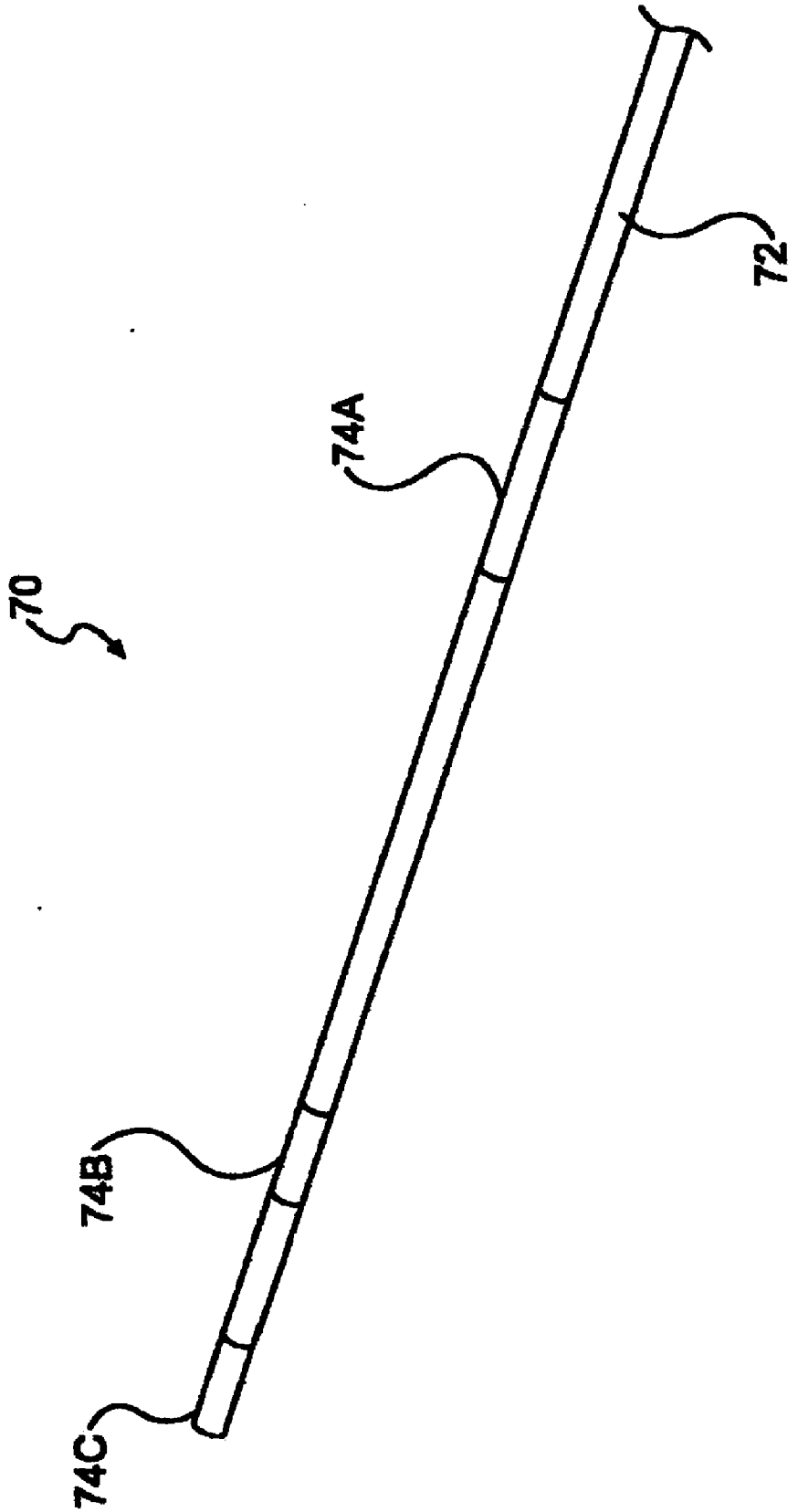

FIG. 34

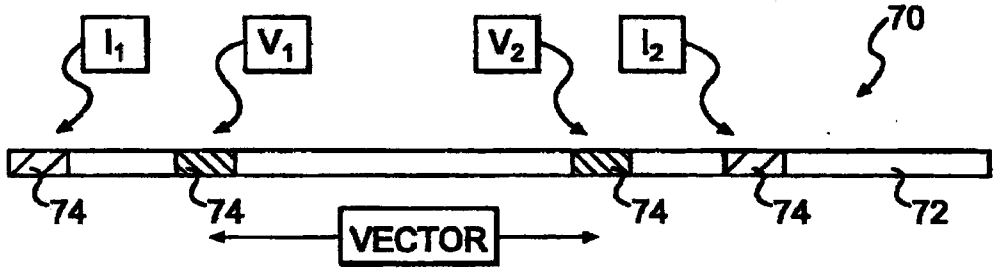

FIG. 35A

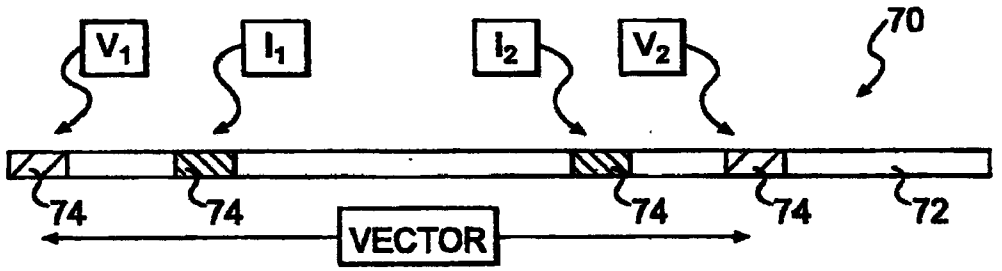

FIG. 35B

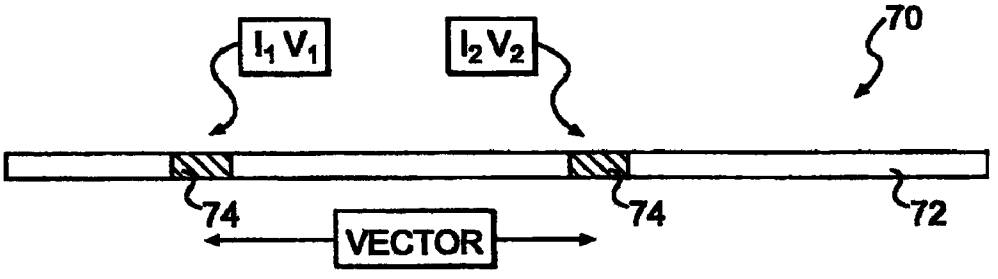

FIG. 35C

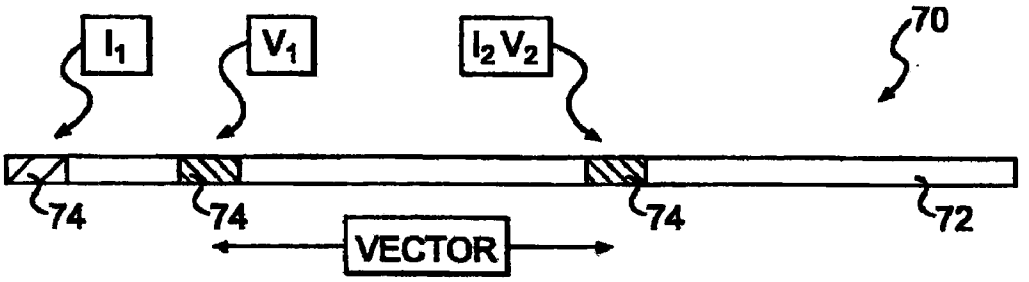

FIG. 35D

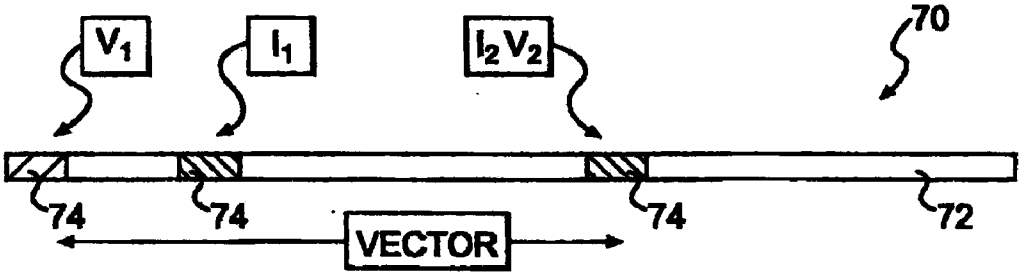

FIG. 35E

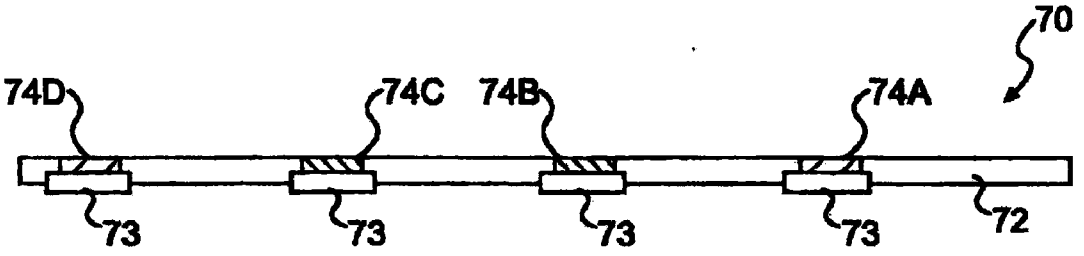

FIG. 36

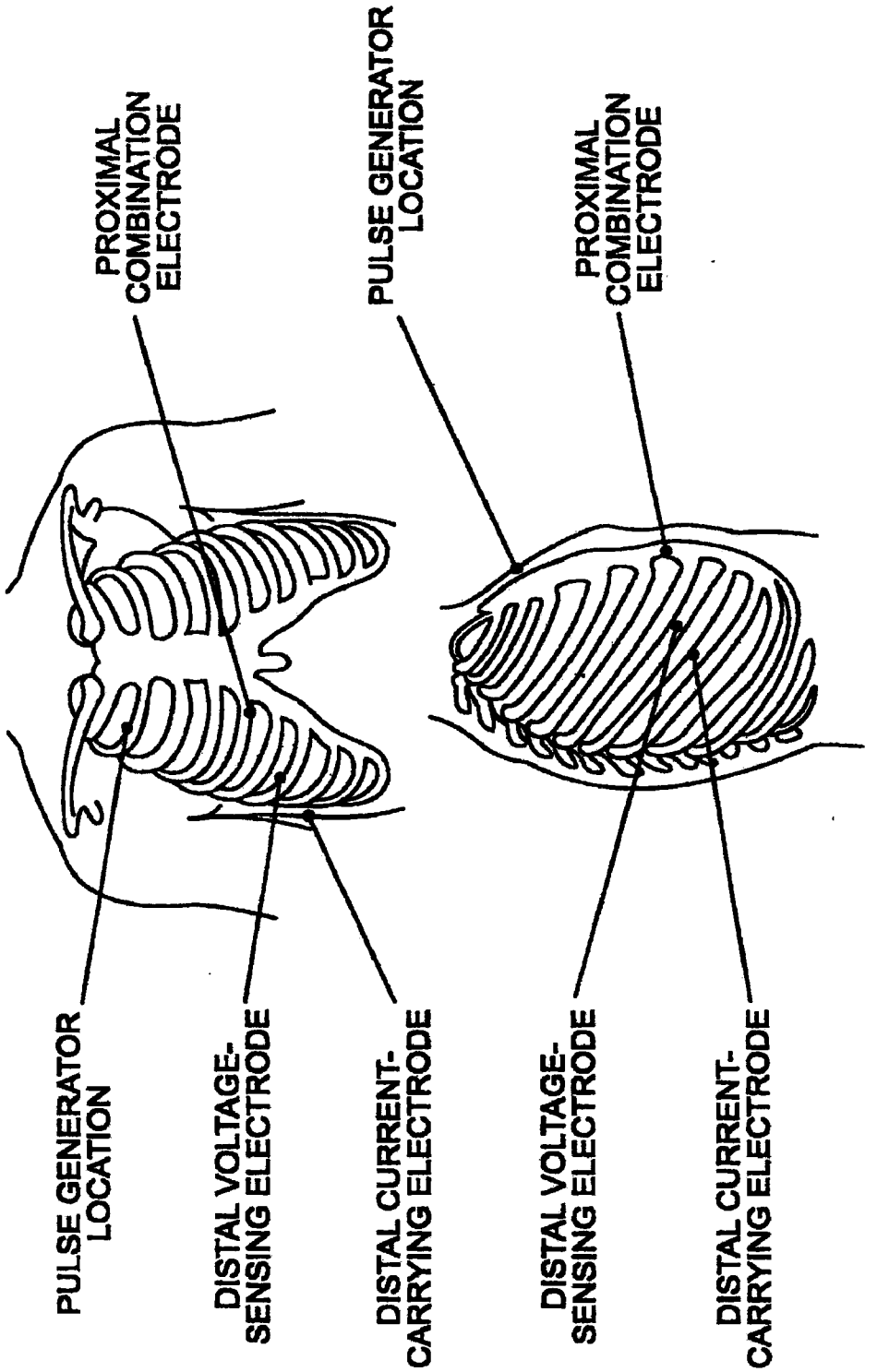
PROXIMAL COMBINATION ELECTRODE
PULSE GENERATOR LOCATION
PROXIMAL COMBINATION ELECTRODE
PULSE GENERATOR LOCATION
DISTAL VOLTAGE-SENSING ELECTRODE
DISTAL CURRENT-CARRYING ELECTRODE
DISTAL VOLTAGE-SENSING ELECTRODE
DISTAL CURRENT-CARRYING ELECTRODE

FIG. 37

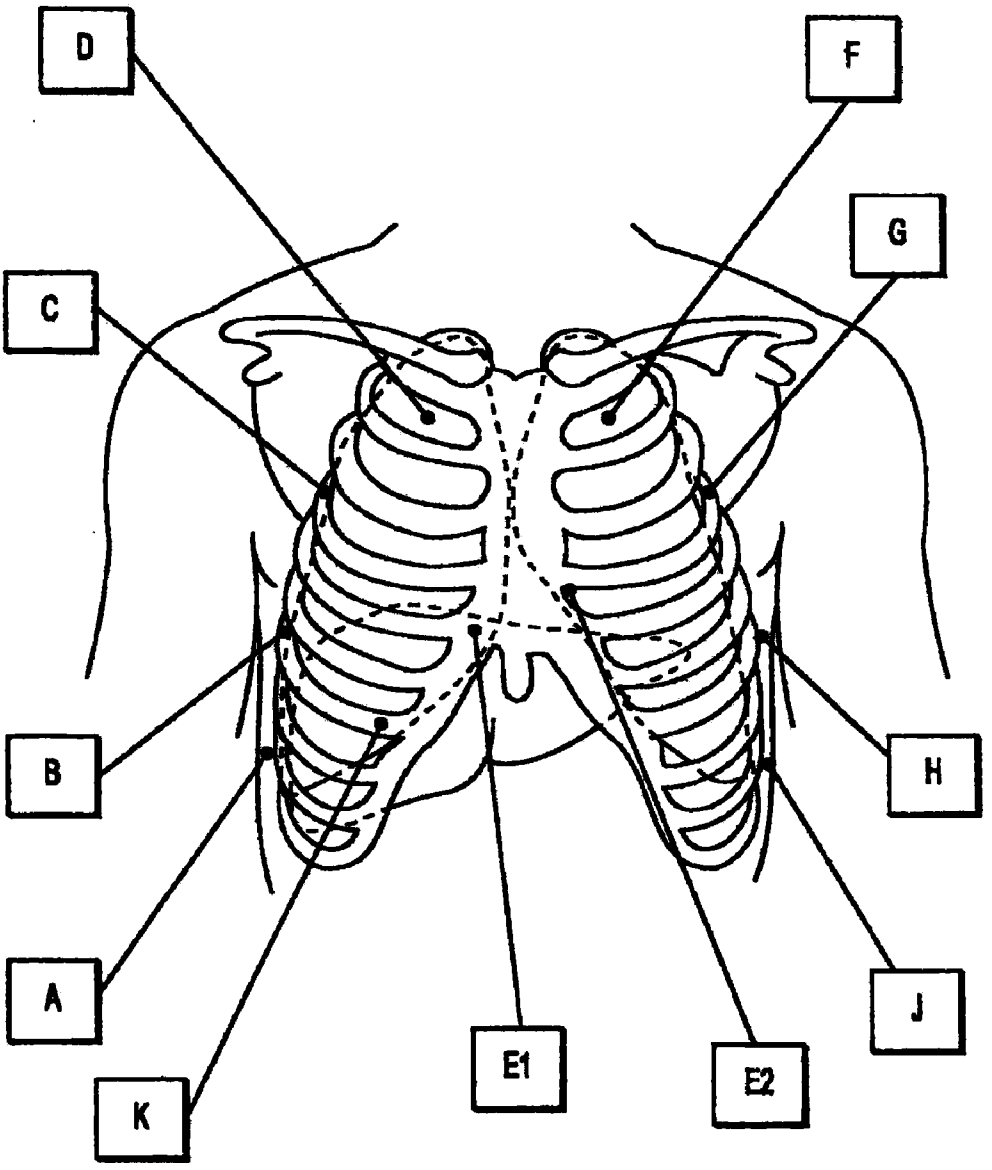

FIG. 38A

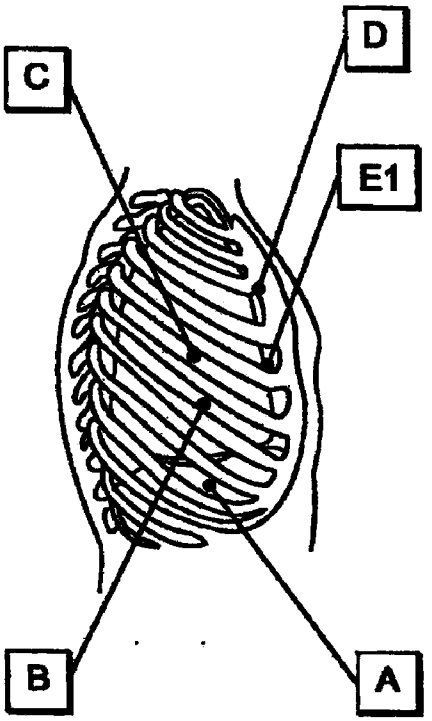

FIG. 38B

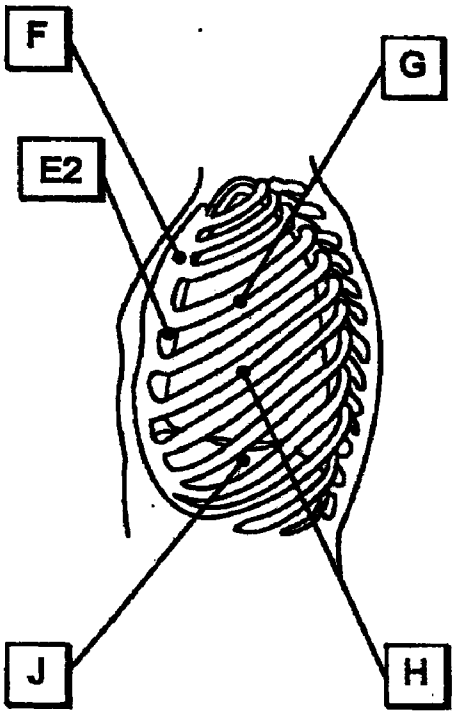

FIG. 38C

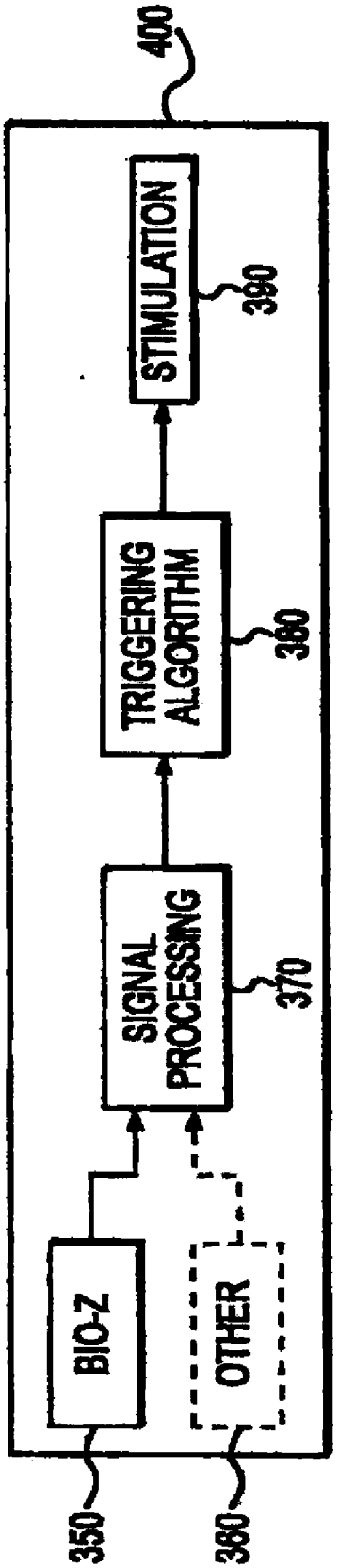
400
STIMULATION
390
TRIGGERING ALGORITHM
380
SIGNAL PROCESSING
370
BIO-Z
OTHER
350
360

FIG. 39

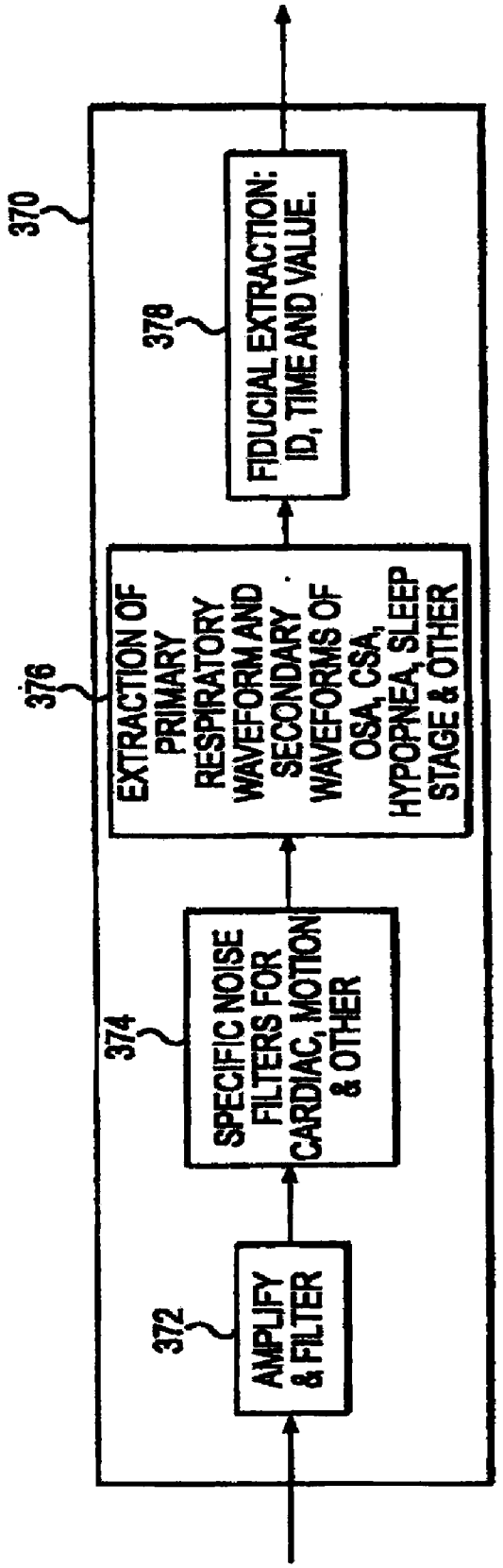
370
372
AMPLIFY & FILTER
374
SPECIFIC NOISE FILTERS FOR CARDIAC, MOTION & OTHER
376
EXTRACTION OF PRIMARY RESPIRATORY WAVEFORM AND SECONDARY WAVEFORMS OF OSA, CSA, HYPOPNEA, SLEEP STAGE & OTHER
378
FIDUCIAL EXTRACTION: ID, TIME AND VALUE.

FIG. 40

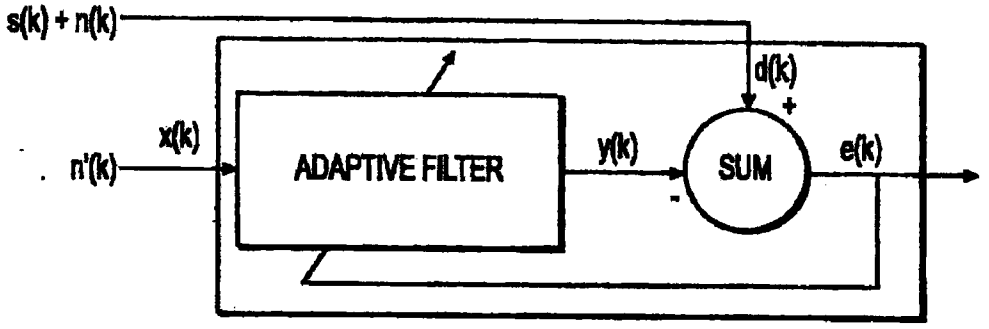

FIG. 41

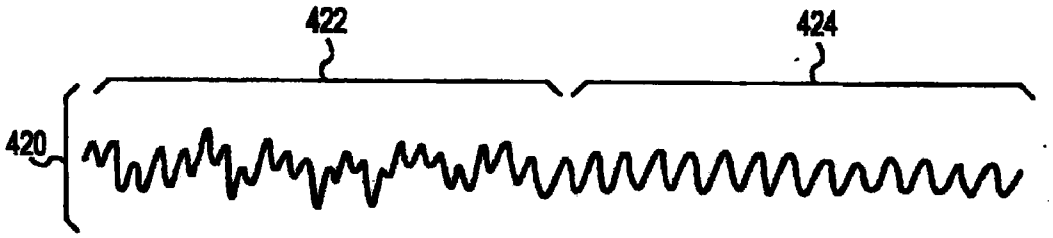

FIG. 42

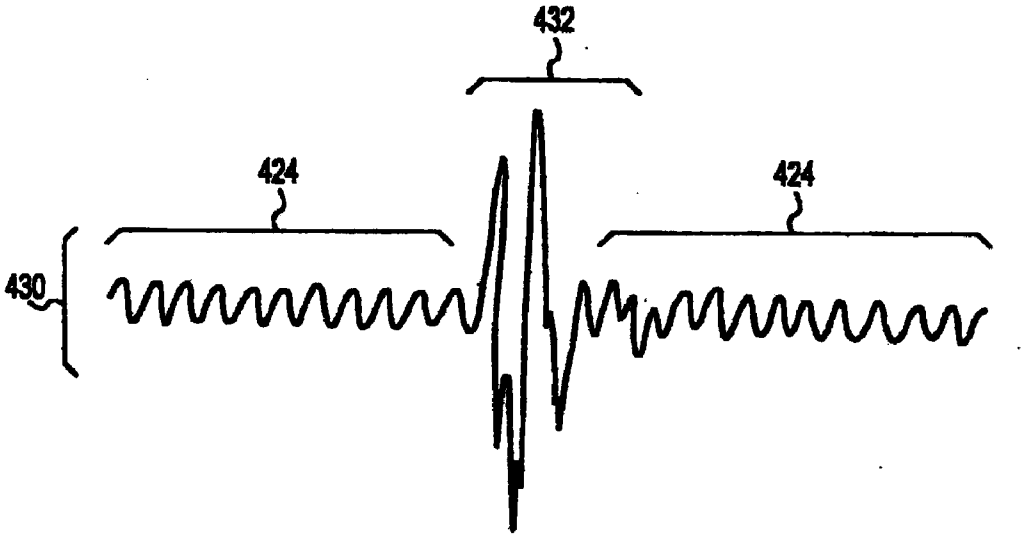

FIG. 43

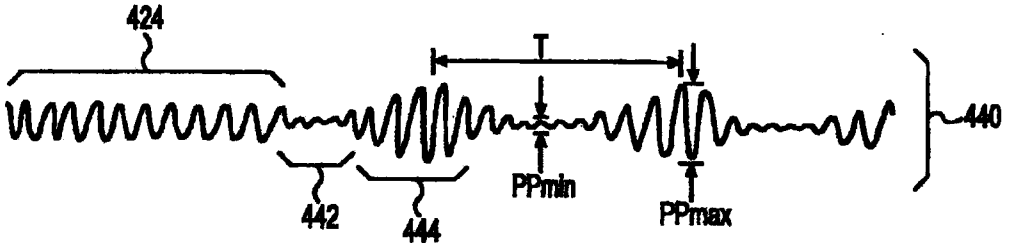

FIG. 44

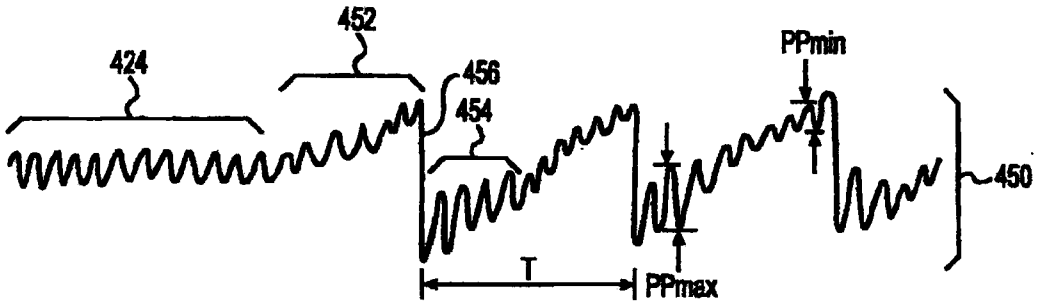

FIG. 45

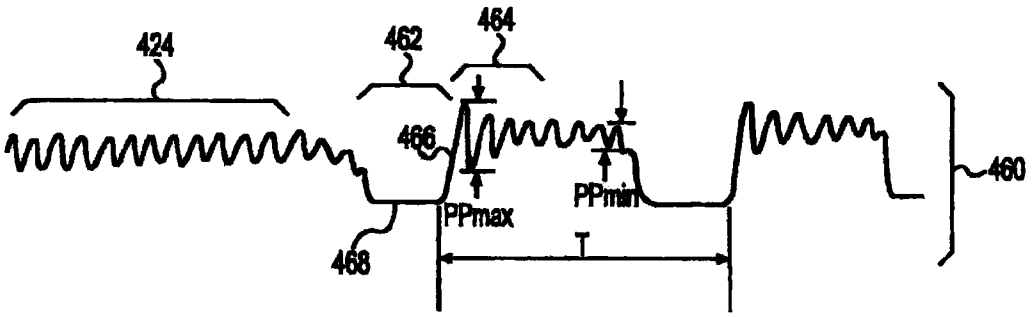

FIG. 46

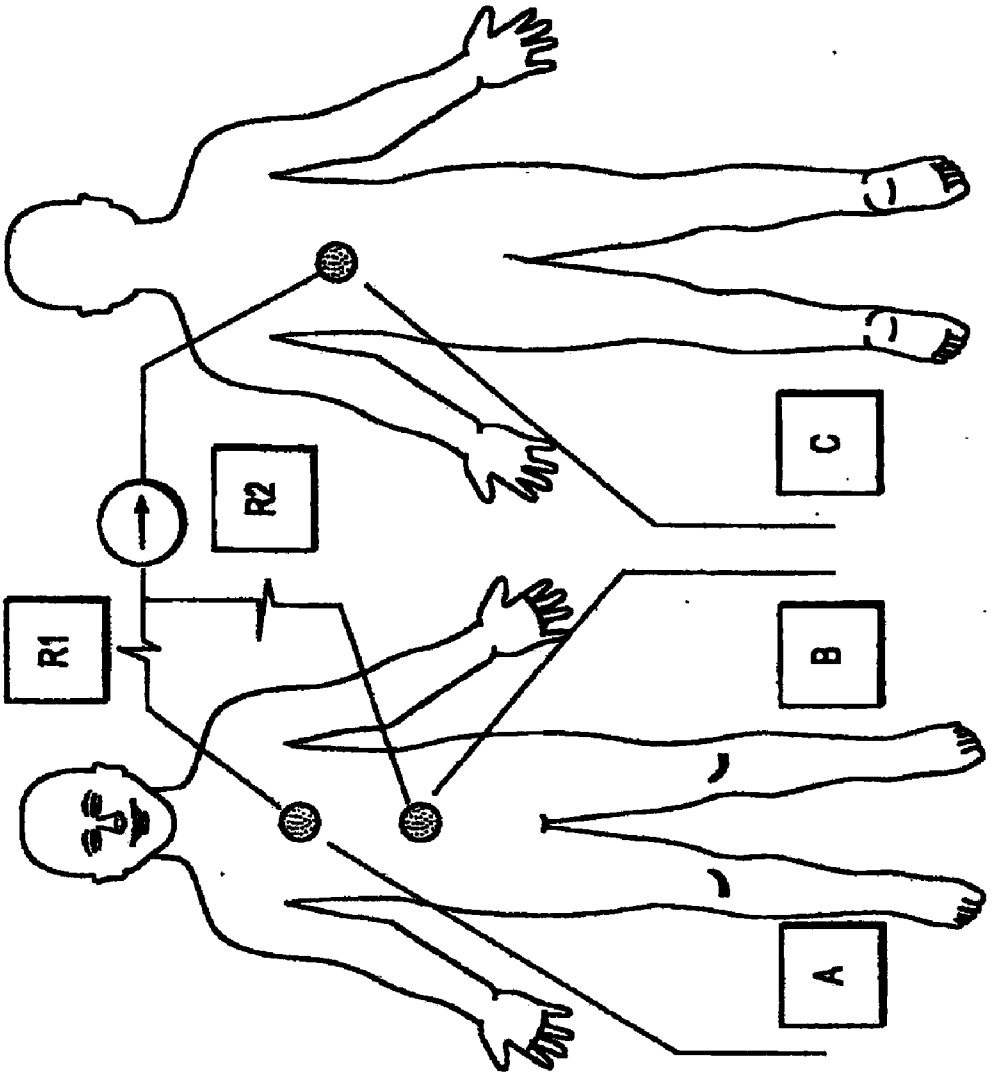

FIG. 47

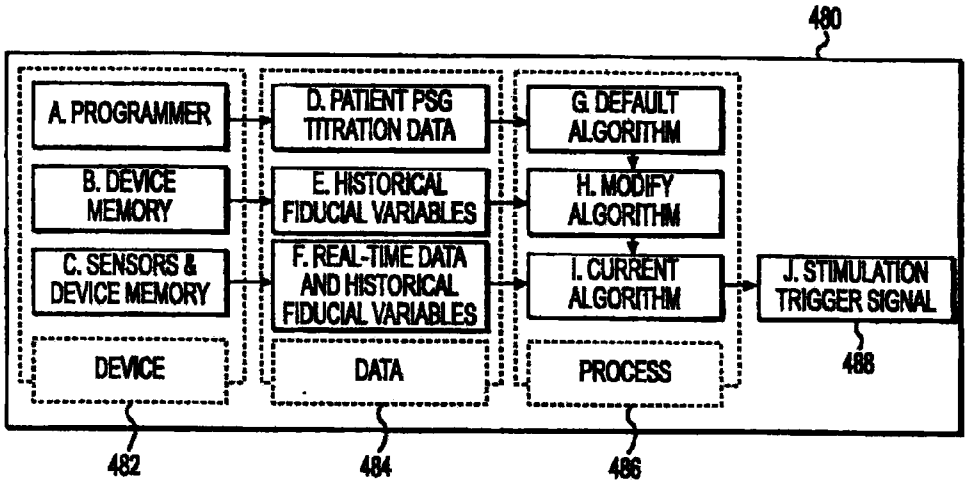

FIG. 48

REFERENCE MARKER ON GRAPH	VARIABLE NAME	VALUE & TIME OF EVENT
T	T	TIME OF ONSET OF INSPIRATION AS INDICATED BY PRESSURE SENSOR IN-LINE WITH AIRFLOW.
	T.est	ESTIMATED ONSET AS CALCULATED FROM HISTORICAL FIDUCIAL VARIABLES.
	T. pred	PREDICTED ONSET AS CALCULATED FROM REAL-TIME DATA AND HISTORICAL FIDUCIAL VARIABLES.
A	Vmax t.Vmax	POSITIVE PEAK OF PRIMARY SIGNAL
B	Vmin t.Vmin	MINIMUM OF PRIMARY SIGNAL BETWEEN SUCCESSIVE POSITIVE PEAKS
C	dV.in t.dV.in	MOST POSITIVE 1ST DERIVATIVE DURING INSPIRATION
D	dV.ex t.dV.ex	MOST NEGATIVE 1ST DERIVATIVE DURING EXPIRATION
E	D2V.in t.d2V.in	MOST POSITIVE 2ND DERIVATIVE DURING INSPIRATION. THIS TYPICALLY OCCURS SOON AFTER ONSET OF INSPIRATION.
F	d2V.pk t.d2V.pk	MOST NEGATIVE 2ND DERIVATIVE SLOPE. THIS OCCURS AT OR NEAR THE POSITIVE PEAK OF PRIMARY SIGNAL.
G	d2V.ex t.d2V.ex	MOST POSITIVE 2ND DERIVATIVE FOLLOWING INSPIRATION. THIS TYPICALLY OCCURS NEAR THE OFFSET OF EXPIRATION.
C2	V.in50 t.V.in50	THE POINT AT WHICH THE PRIMARY SIGNAL'S MAGNITUDE IS 50% BETWEEN POSITIVE PEAK AND PRECEEDING MINIMUM.
D2	V.ex50 t.V.ex50	THE POINT AT WHICH THE PRIMARY SIGNAL'S MAGNITUDE IS 50% BETWEEEN POSITIVE PEAK AND FOLLOWING MINIMUM.

FIG. 49

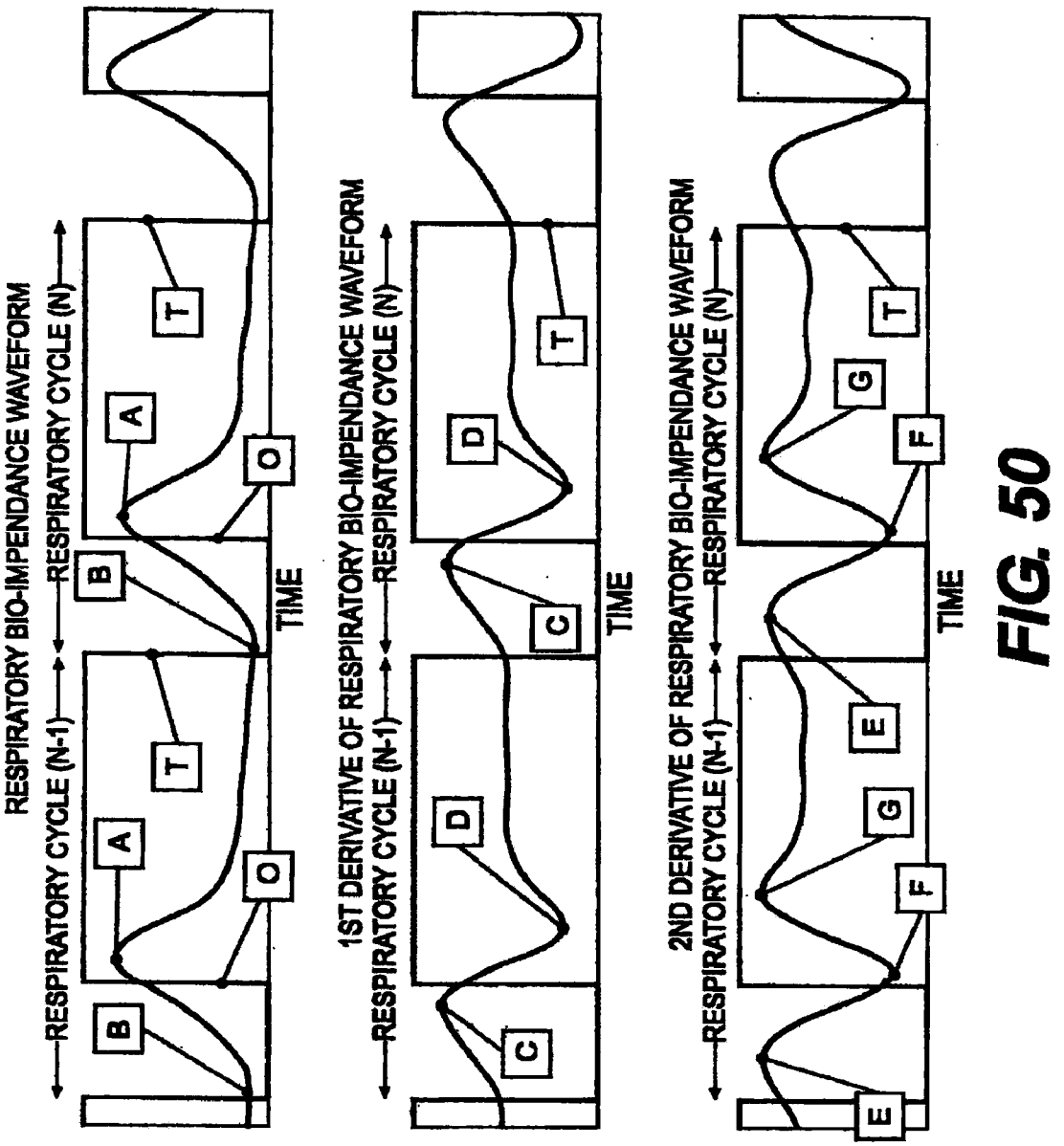
RESPIRATORY BIO-IMPENDANCE WAVEFORM
RESPIRATORY CYCLE (N-1)
RESPIRATORY CYCLE (N)
TIME
1ST DERIVATIVE OF RESPIRATORY BIO-IMPENDANCE WAVEFORM
RESPIRATORY CYCLE (N-1)
RESPIRATORY CYCLE (N)
TIME
2ND DERIVATIVE OF RESPIRATORY BIO-IMPENDANCE WAVEFORM
RESPIRATORY CYCLE (N-1)
RESPIRATORY CYCLE (N)
TIME
A
B
C
D
E
F
G
O
T

FIG. 50

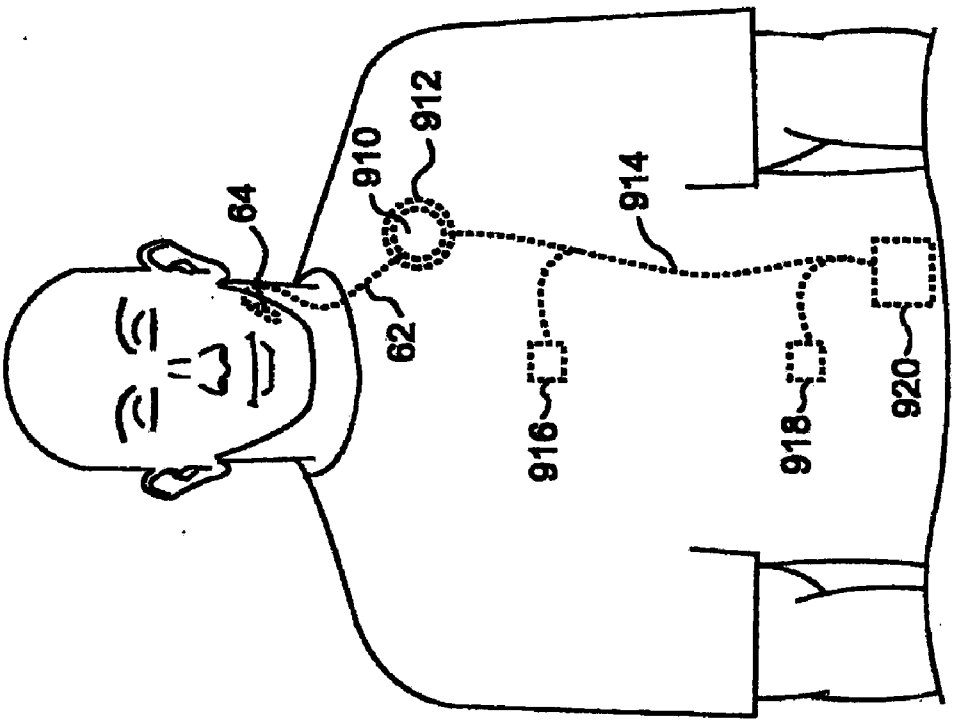

FIG. 51B

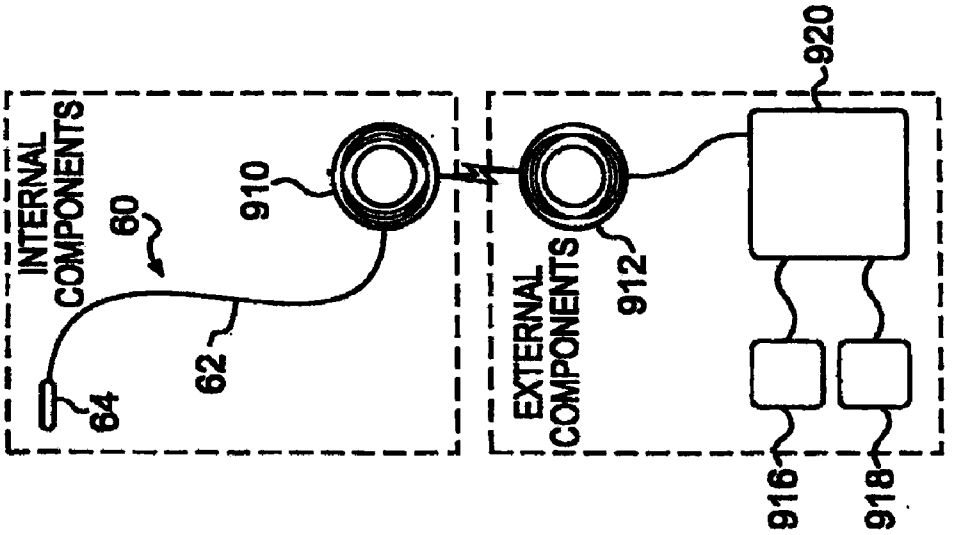

FIG. 51A

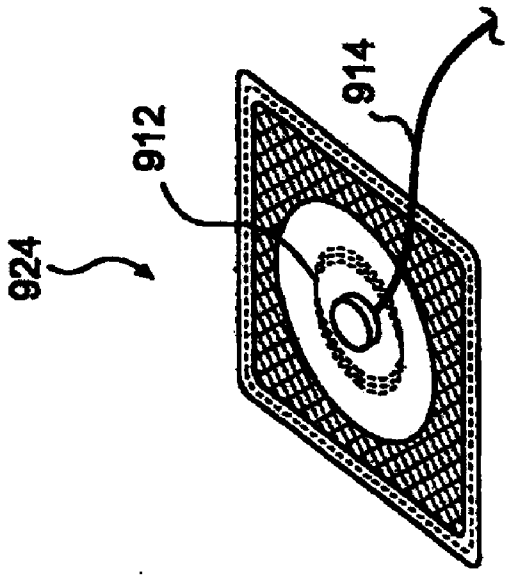

FIG. 51D

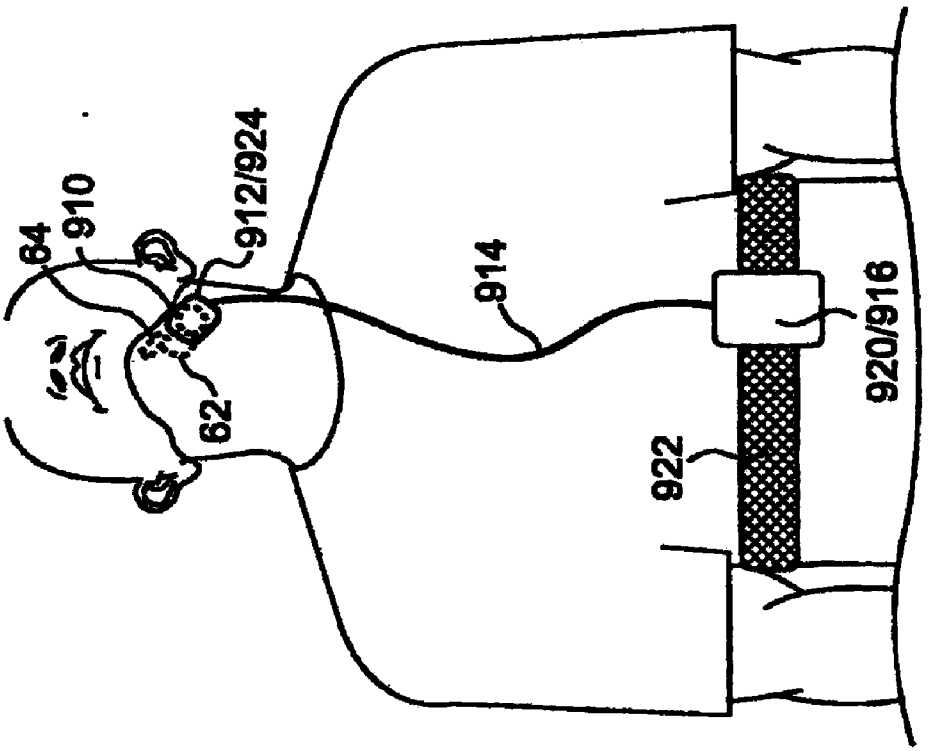

FIG. 51C

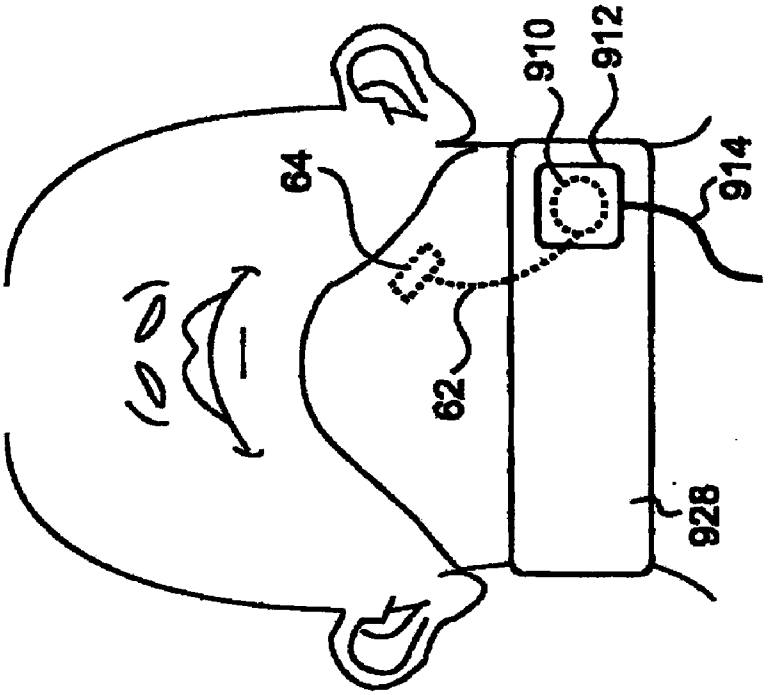

FIG. 51F

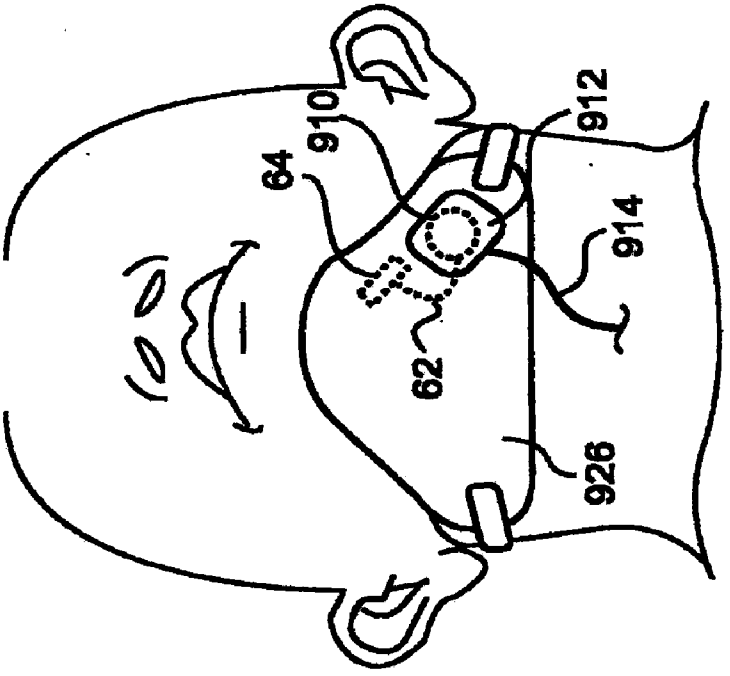

FIG. 51E

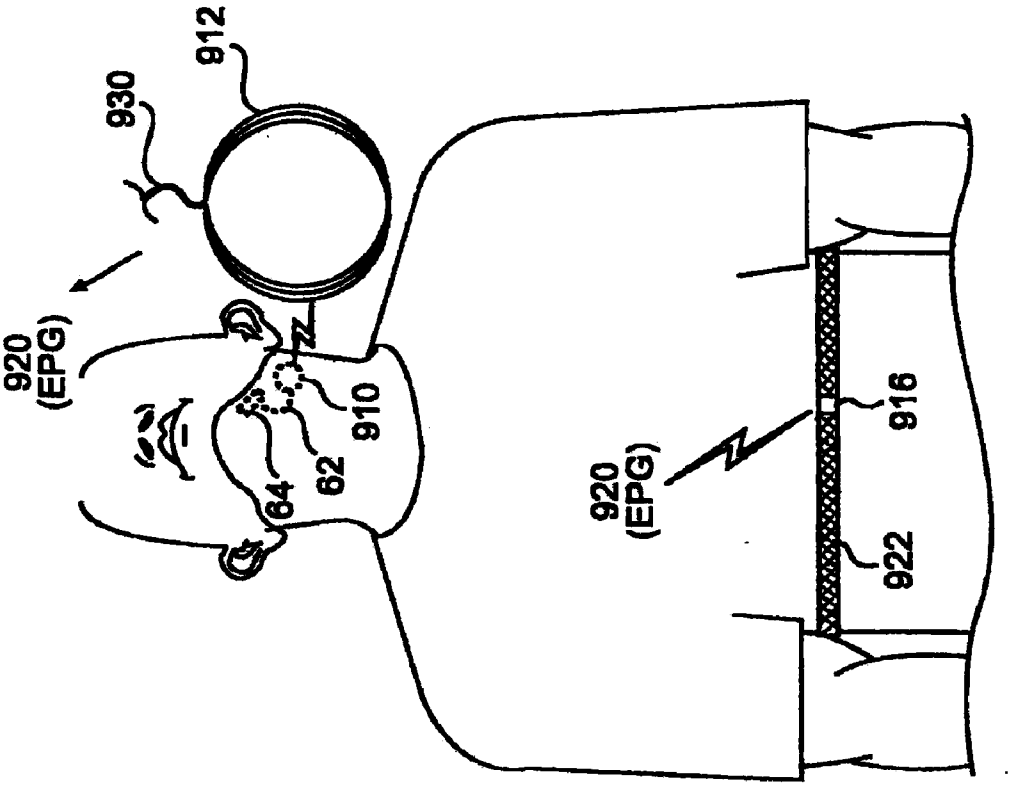

FIG. 51G

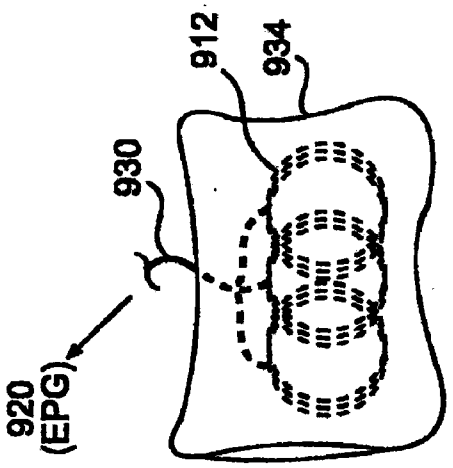

FIG. 51I

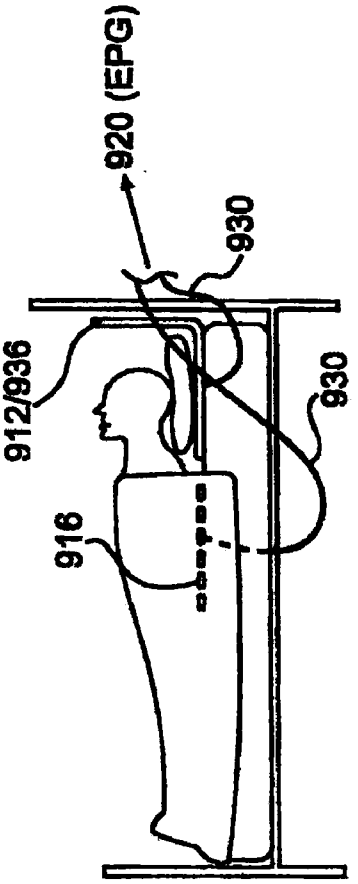

FIG. 51J

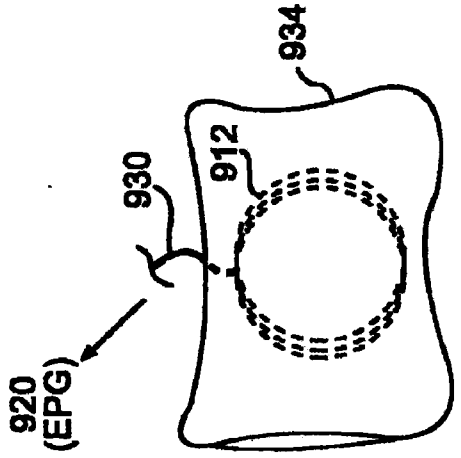

FIG. 51H

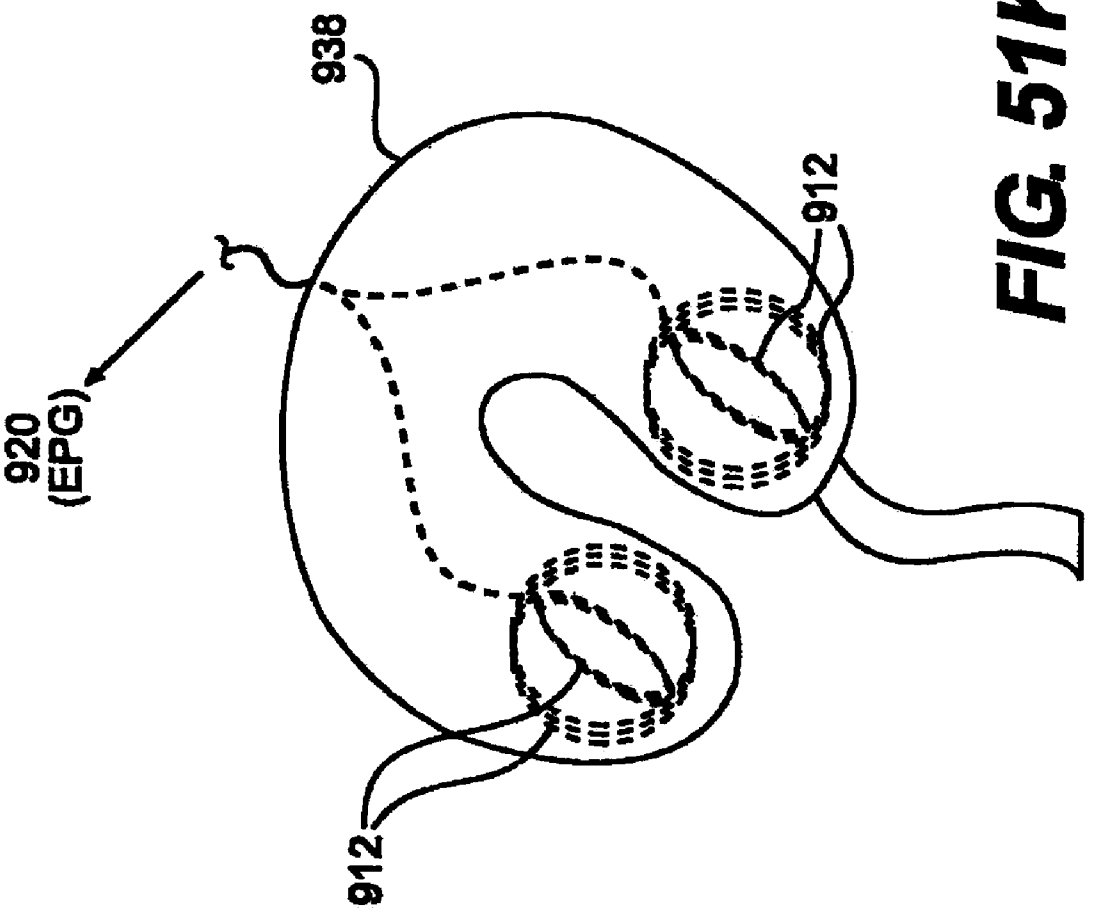

FIG. 51K

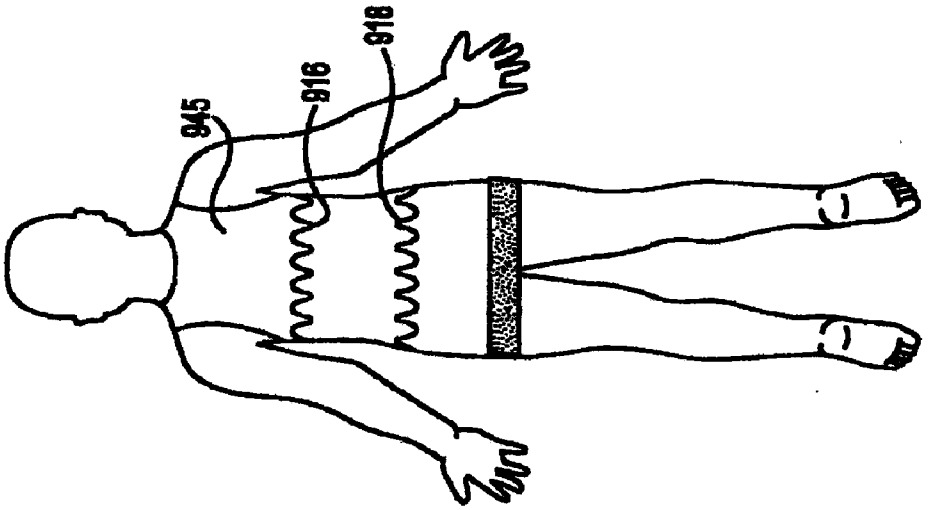

FIG. 51M

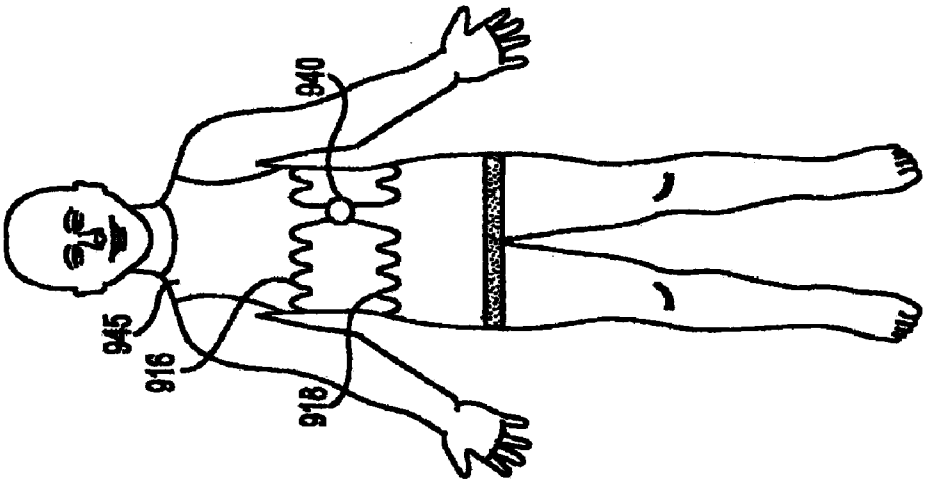

FIG. 51L

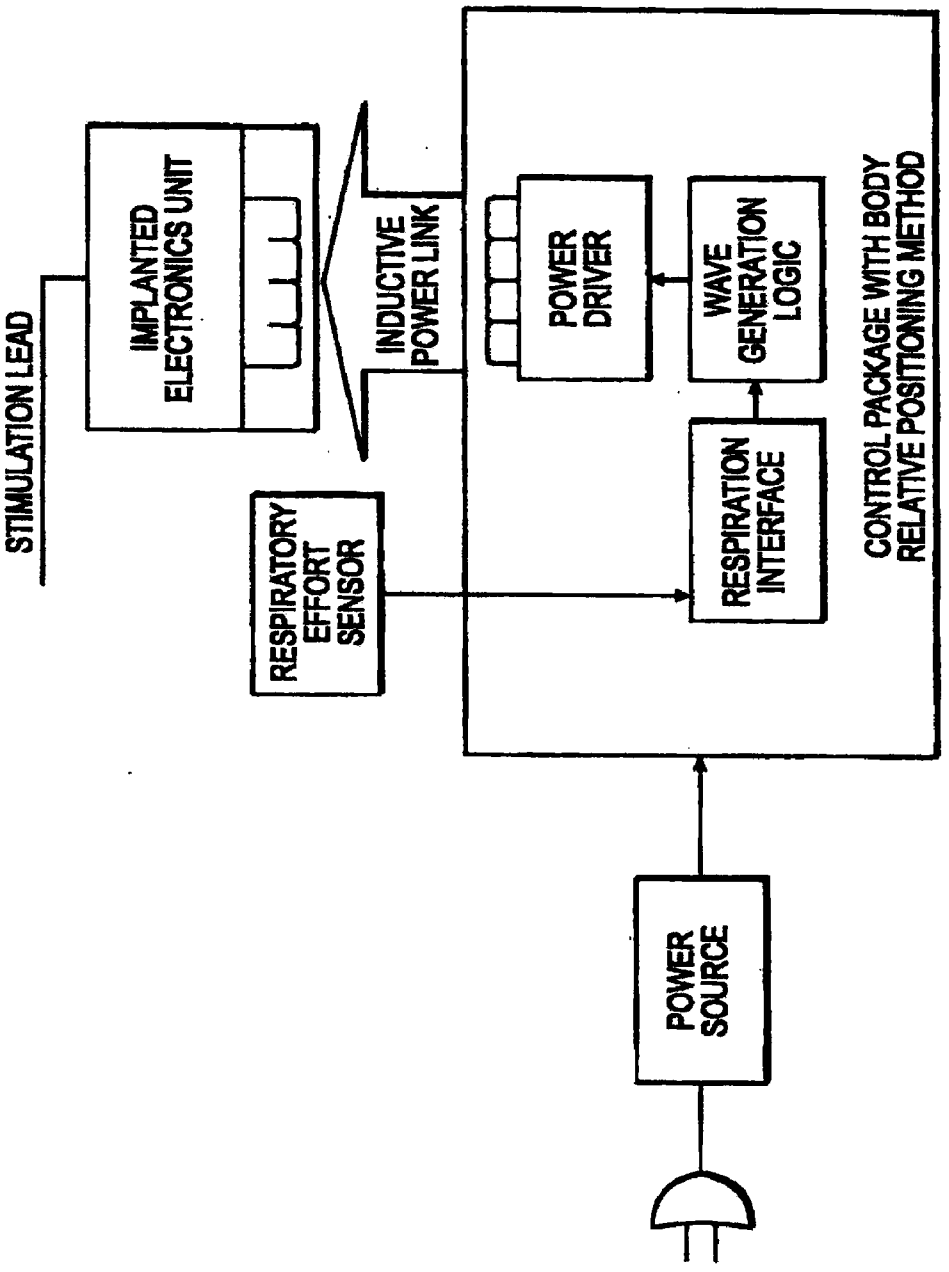
STIMULATION LEAD
IMPLANTED ELECTRONICS UNIT
INDUCTIVE POWER LINK
POWER DRIVER
WAVE GENERATION LOGIC
RESPIRATORY EFFORT SENSOR
RESPIRATION INTERFACE
CONTROL PACKAGE WITH BODY RELATIVE POSITIONING METHOD
POWER SOURCE

FIG. 52A

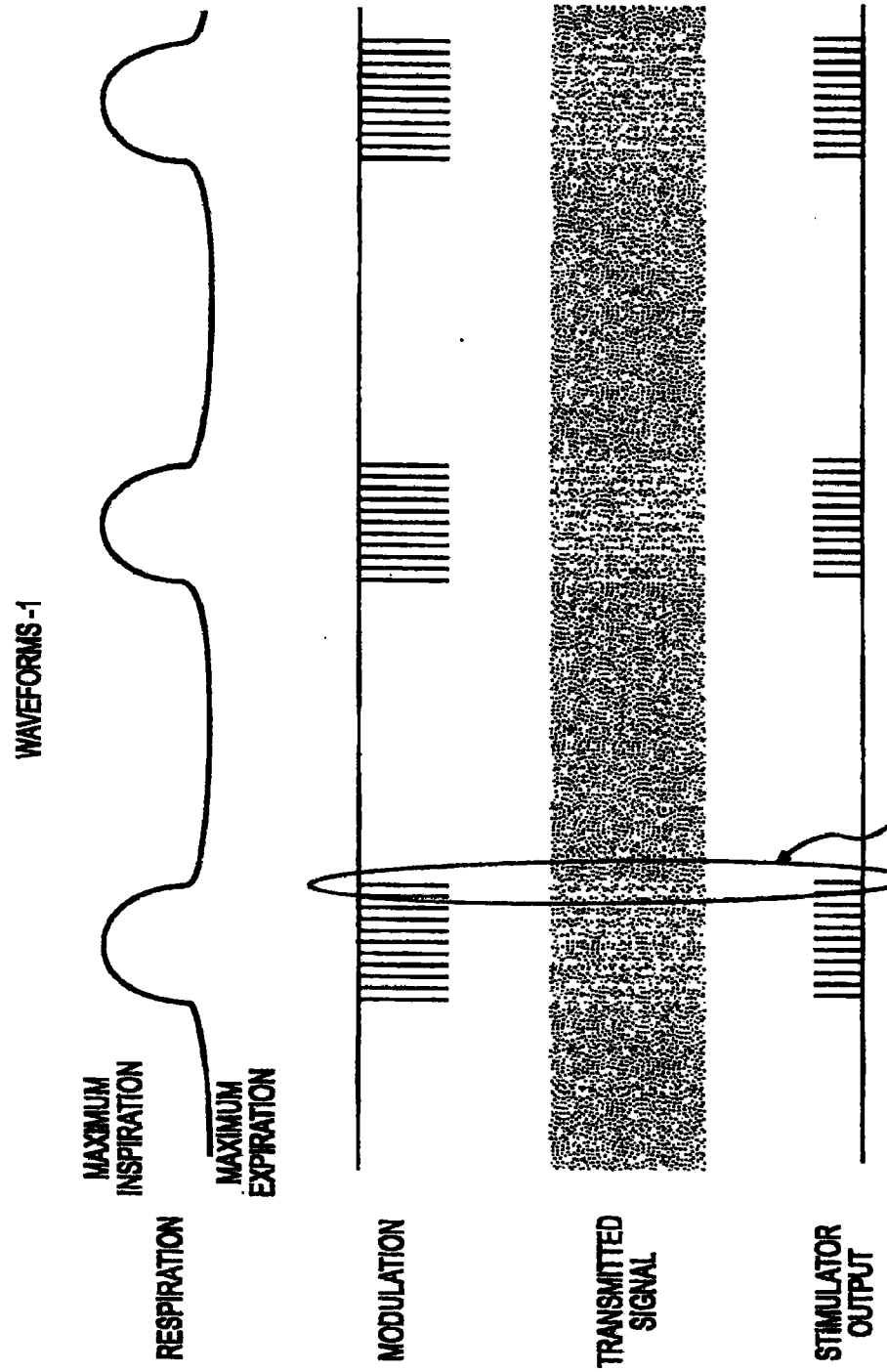
WAVEFORMS -1
MAXIMUM INSPIRATION
MAXIMUM EXPIRATION
RESPIRATION
MODULATION
TRANSMITTED SIGNAL
STIMULATOR OUTPUT
SEE WAVEFORMS - 2

FIG. 52B

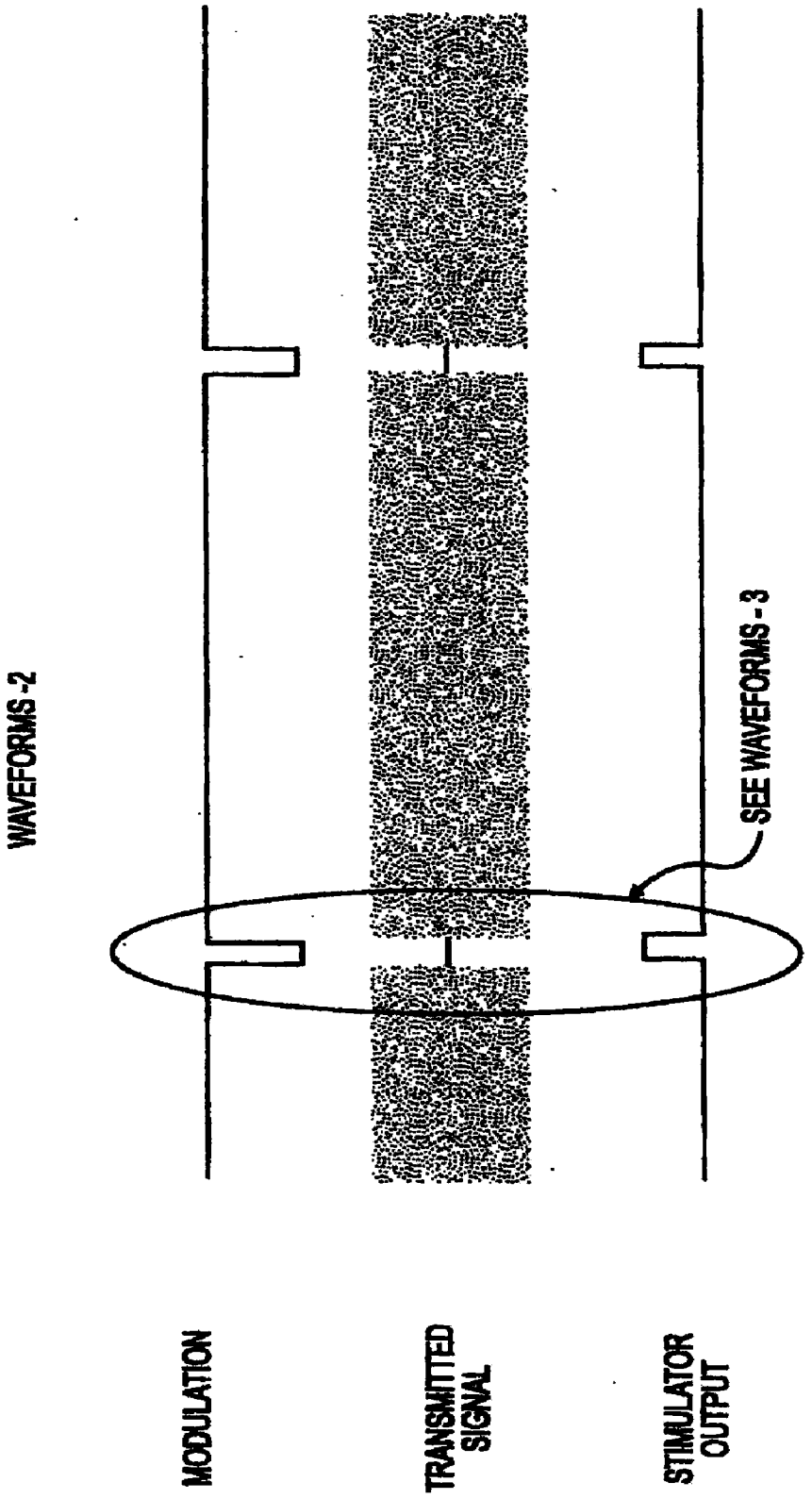
WAVEFORMS -2
SEE WAVEFORMS - 3
MODULATION
TRANSMITTED SIGNAL
STIMULATOR OUTPUT

FIG. 52C

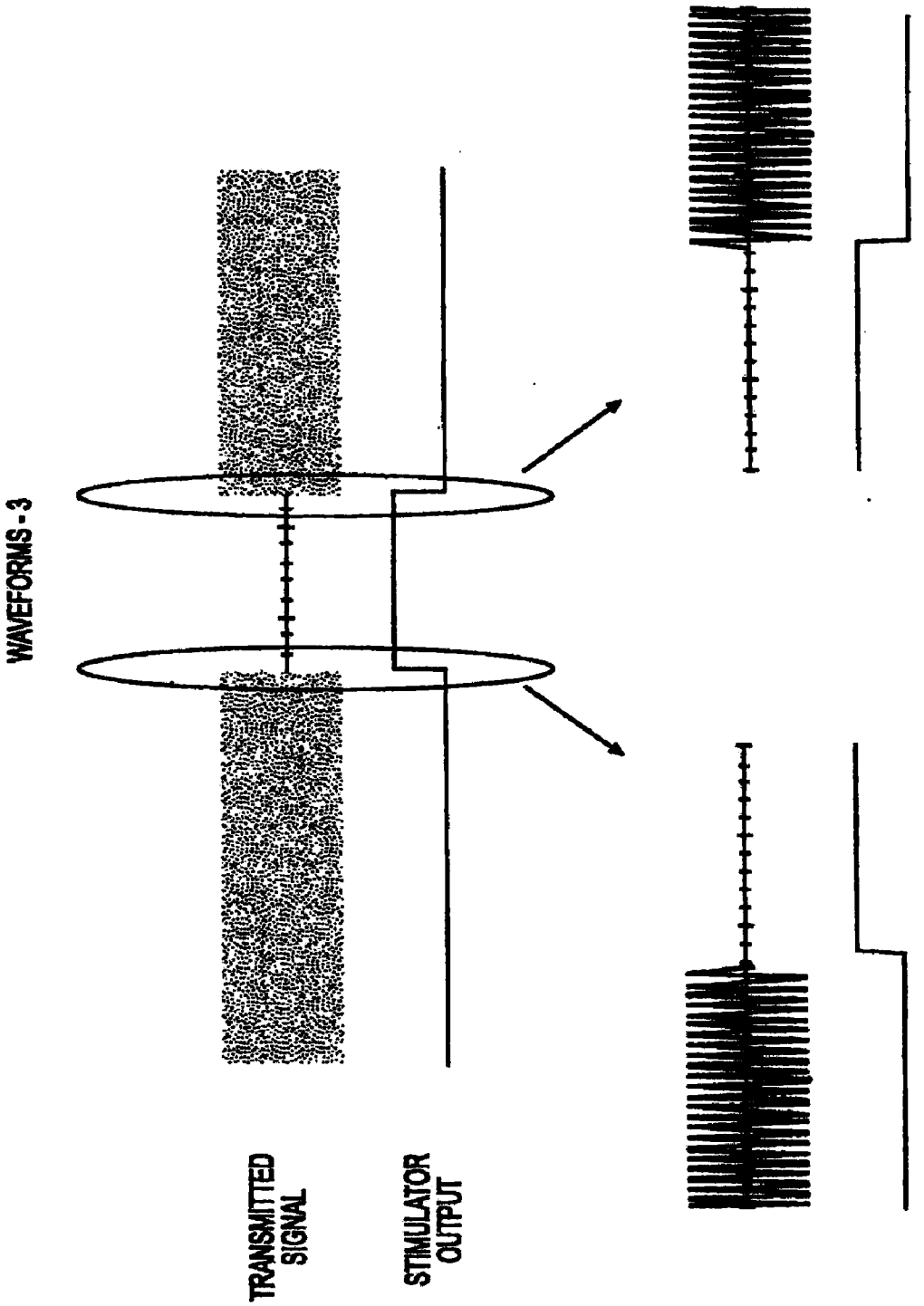

FIG. 52D

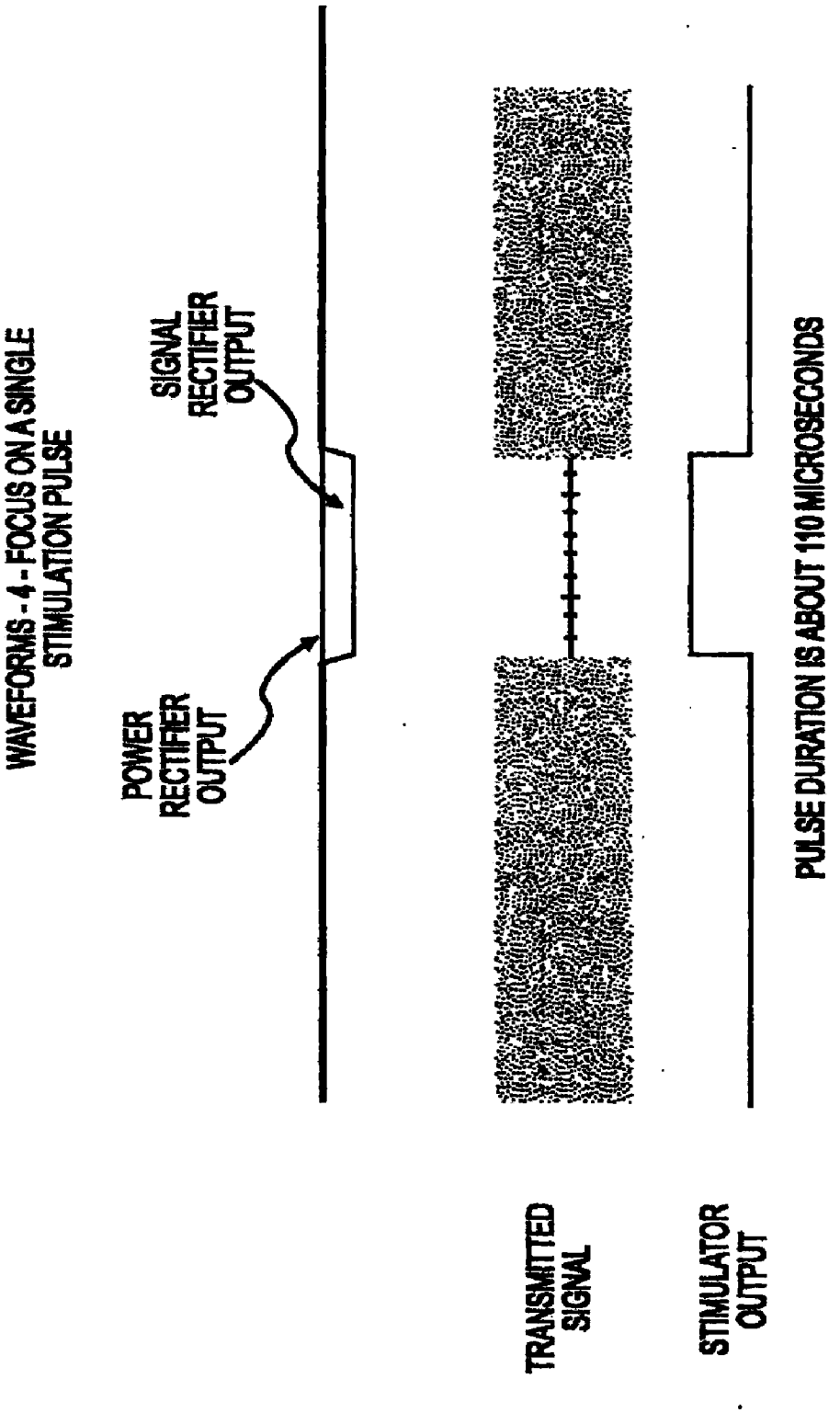
WAVEFORMS - 4 - FOCUS ON A SINGLE STIMULATION PULSE
SIGNAL RECTIFIER OUTPUT
POWER RECTIFIER OUTPUT
TRANSMITTED SIGNAL
STIMULATOR OUTPUT
PULSE DURATION IS ABOUT 110 MICROSECONDS

FIG. 52E

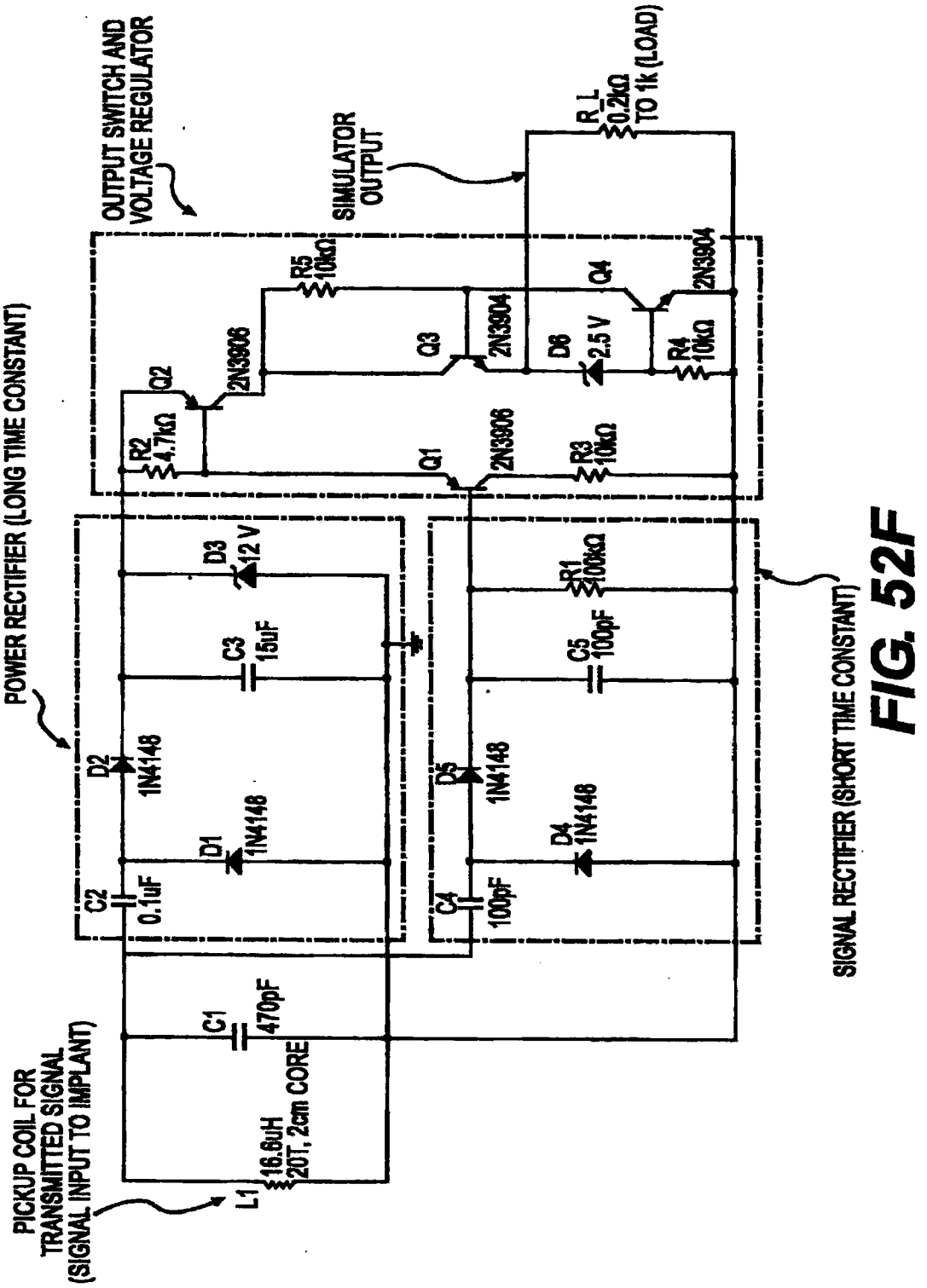
OUTPUT SWITCH AND VOLTAGE REGULATOR
SIMULATOR OUTPUT
R_L 0.2kΩ TO 1k (LOAD)
R5 10kΩ
Q4 2N3904
Q3 2N3904
D6 2.5 V
R4 10kΩ
Q2 2N3906
R2 4.7kΩ
Q1 2N3906
R3 10kΩ
POWER RECTIFIER (LONG TIME CONSTANT)
D3 12 V
C3 15uF
D2 1N4148
D1 1N4148
C2 0.1uF
R1 100kΩ
C5 100pF
D5 1N4148
D4 1N4148
C4 100pF
SIGNAL RECTIFIER (SHORT TIME CONSTANT)
C1 470pF
L1 16.6uH 20T, 2cm CORE
PICKUP COIL FOR TRANSMITTED SIGNAL (SIGNAL INPUT TO IMPLANT)

FIG. 52F

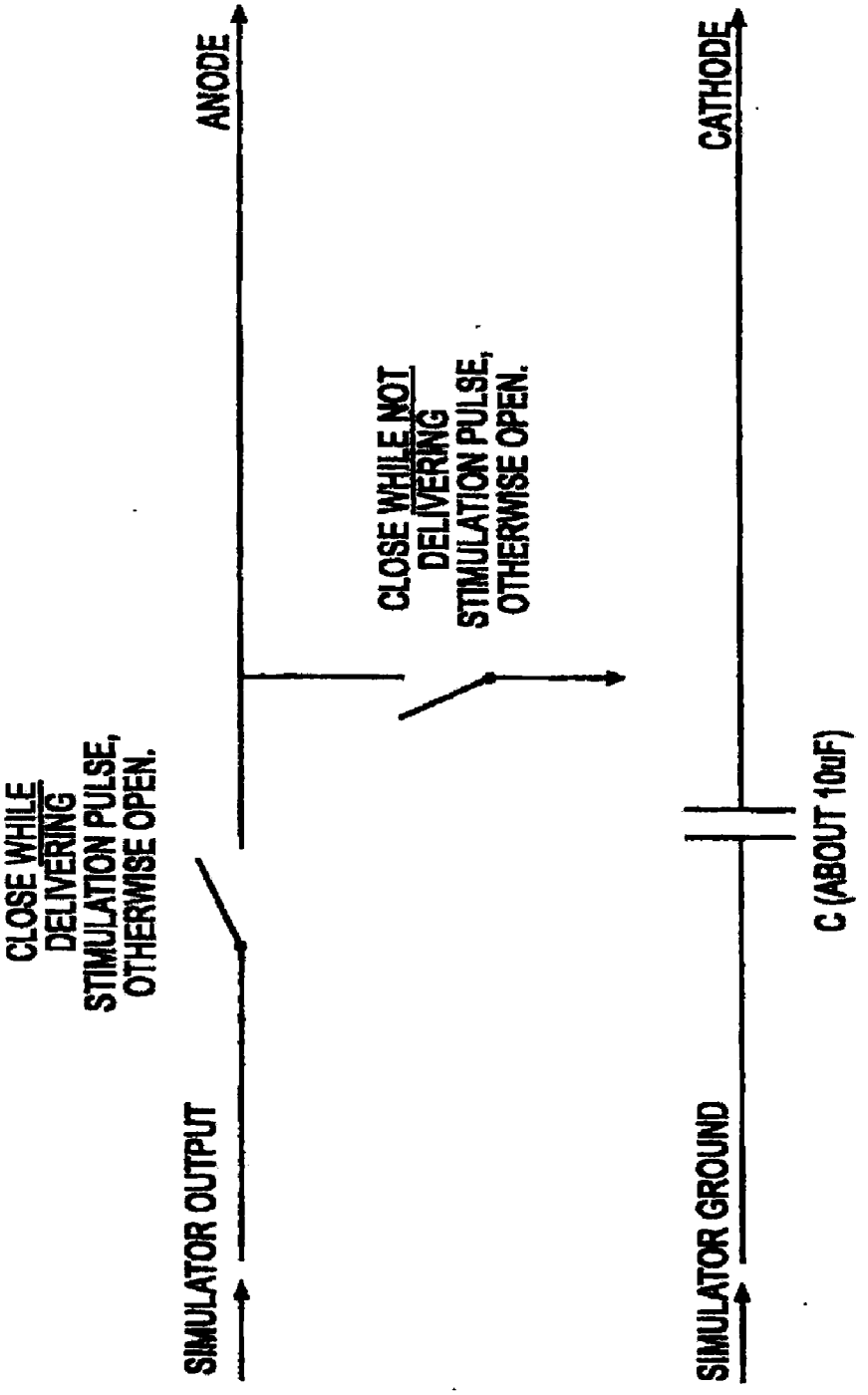
SIMULATOR OUTPUT
CLOSE WHILE DELIVERING STIMULATION PULSE, OTHERWISE OPEN.
ANODE
CLOSE WHILE NOT DELIVERING STIMULATION PULSE, OTHERWISE OPEN.
CATHODE
SIMULATOR GROUND
C (ABOUT 10uF)

FIG. 52G

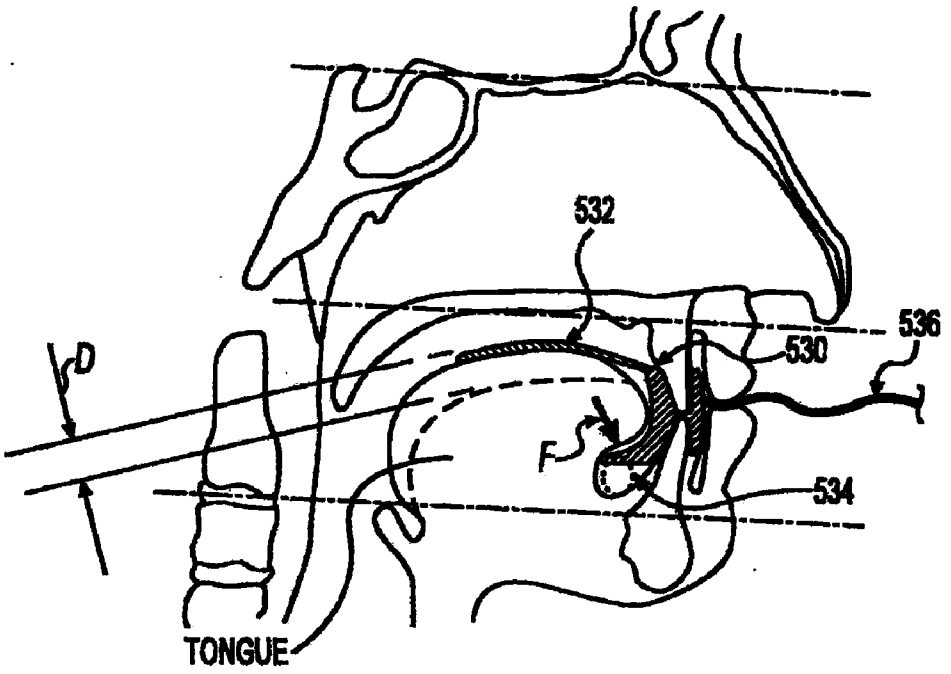

FIG. 53

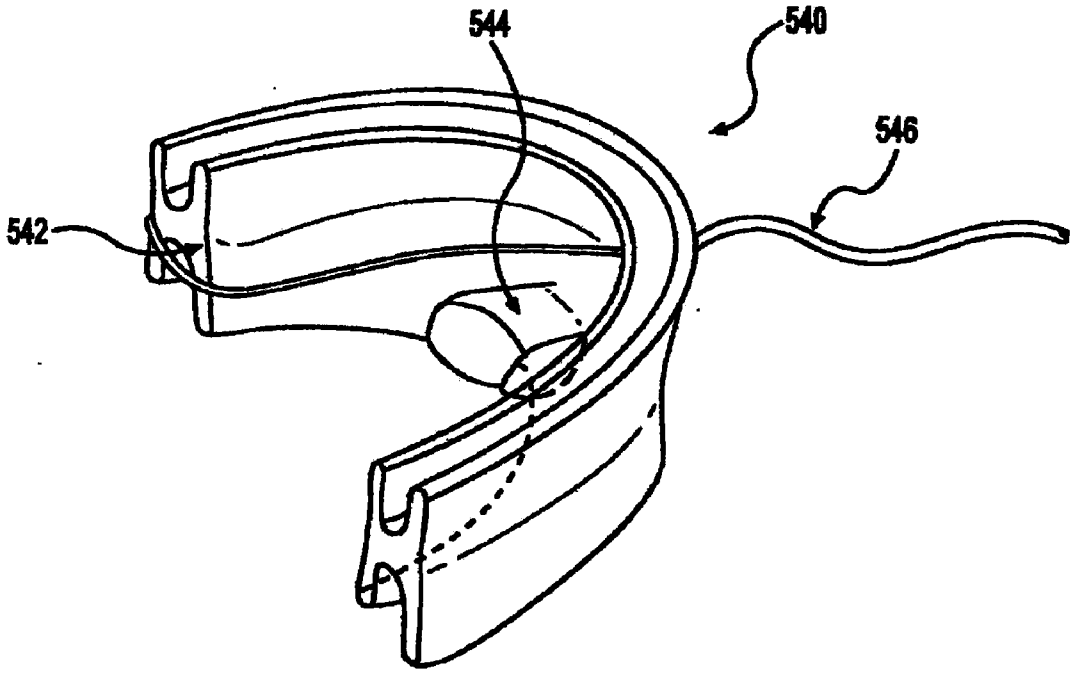

FIG. 54

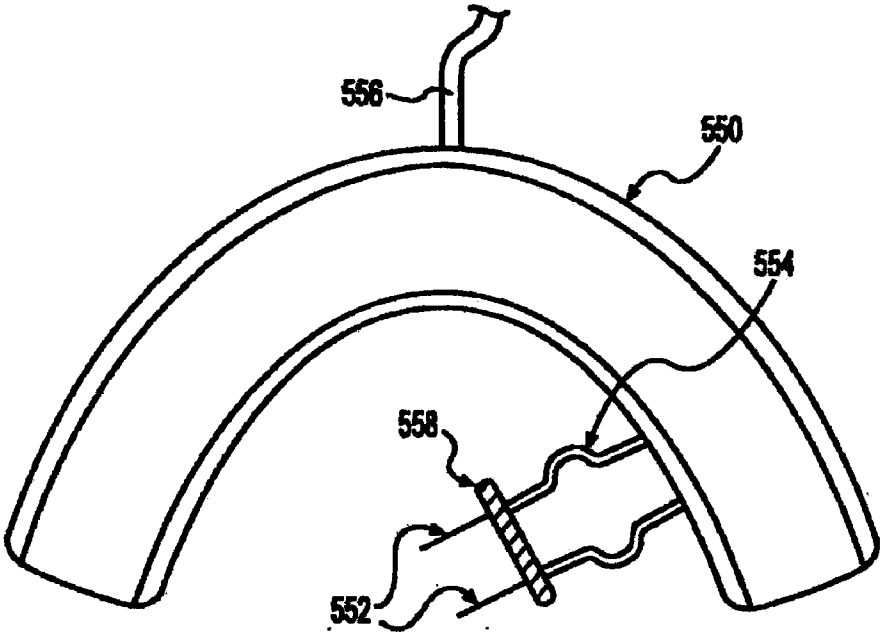

FIG. 55

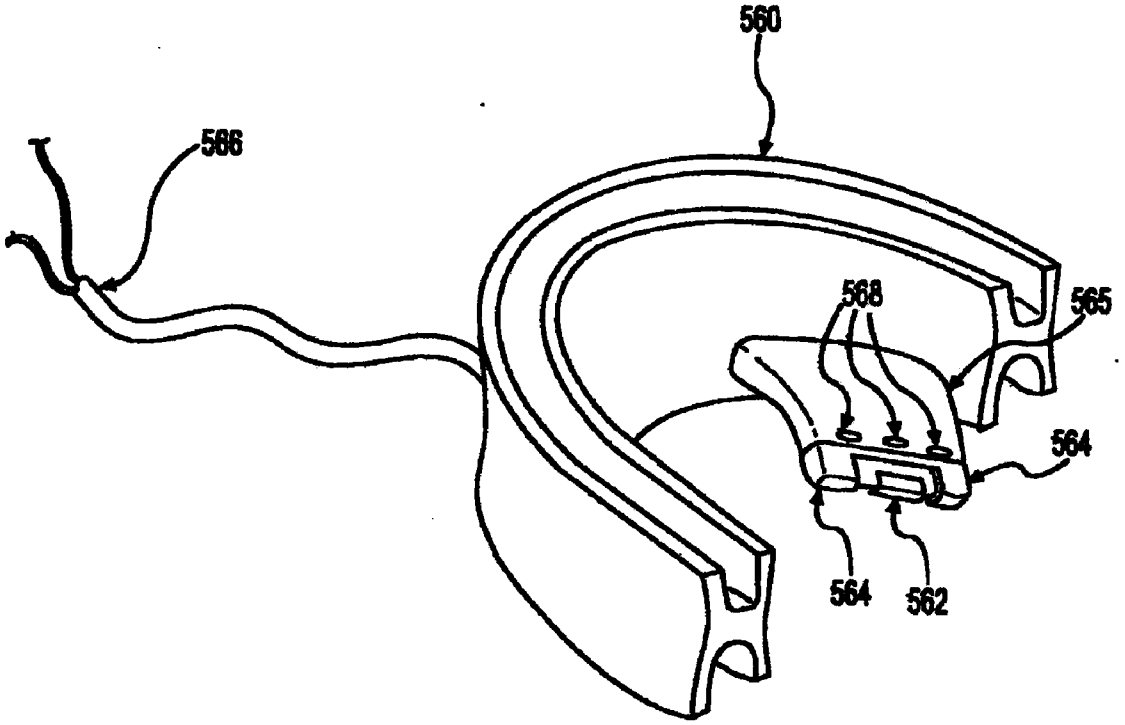

FIG. 56

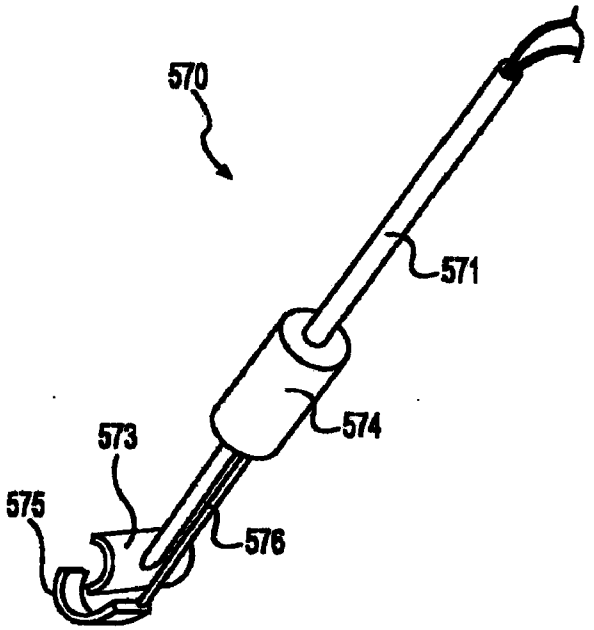

FIG. 57A

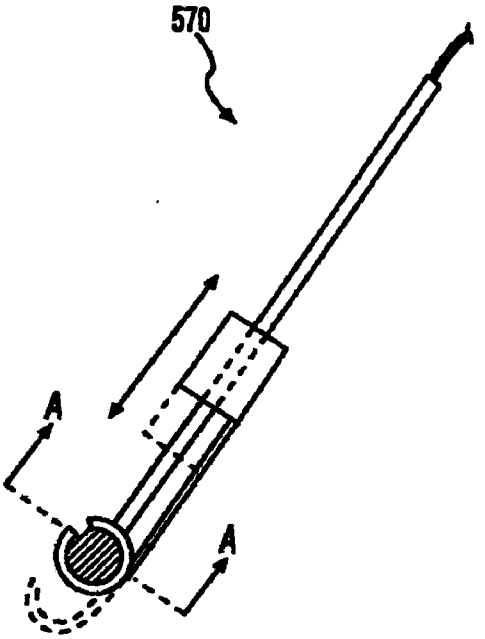

FIG. 57B

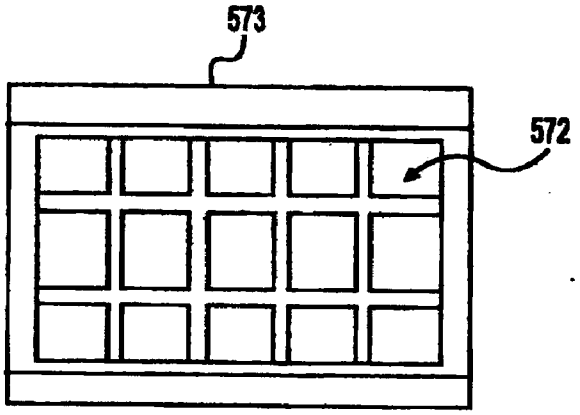

FIG. 57C

OBSTRUCTIVE SLEEP APNEA TREATMENT DEVICES, SYSTEMS AND METHODS

[0001] The present case claims the benefit of U.S. Provisional Patent Application No. 60/851,386 filed Oct. 13, 2006 and U.S. Provisional Patent Application No. 60/918,257 filed Mar. 14, 2007, both titled OBSTRUCTIVE SLEEP APNEA TREATMENT DEVICES, SYSTEMS AND METHODS, the entire disclosures of which are fully incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The inventions described herein relate to devices, systems and associated methods for treating sleeping disorders. More particularly, the inventions described herein relate to devices, systems and methods for treating obstructive sleep apnea.

BACKGROUND OF THE INVENTION

[0003] Obstructive sleep apnea (OSA) is highly prevalent, affecting one in five adults in the United States. One in fifteen adults has moderate to severe OSA requiring treatment. Untreated OSA results in reduced quality of life measures and increased risk of disease including hypertension, stroke, heart disease, etc.

[0004] Continuous positive airway pressure (CPAP) is a standard treatment for OSA. While CPAP is non-invasive and highly effective, it is not well tolerated by patients. Patient compliance for CPAP is often reported to be between 40% and 60%.

[0005] Surgical treatment options for OSA are available too. However, they tend to be highly invasive (result in structural changes), irreversible, and have poor and/or inconsistent efficacy. Even the more effective surgical procedures are undesirable because they usually require multiple invasive and irreversible operations, they may alter a patient's appearance (e.g., maxillo-mandibulary advancement), and/or they may be socially stigmatic (e.g., tracheostomy).

[0006] U.S. Pat. No. 4,830,008 to Meer proposes hypoglossal nerve stimulation as an alternative treatment for OSA. An example of an implanted hypoglossal nerve stimulator for OSA treatment is the Inspire™ technology developed by Medtronic, Inc. (Fridely, Minn.). The Inspire device is not FDA approved and is not for commercial sale. The Inspire device includes an implanted neurostimulator, an implanted nerve cuff electrode connected to the neurostimulator by a lead, and an implanted intra-thoracic pressure sensor for respiratory feedback and stimulus trigger. The Inspire device was shown to be efficacious (approximately 75% response rate as defined by a 50% or more reduction in RDI and a post RDI of ≦20) in an eight patient human clinical study, the results of which were published by Schwartz et al. and Eisele et al. However, both authors reported that only three of eight patients remained free from device malfunction, thus demonstrating the need for improvements.

SUMMARY OF THE INVENTION

[0007] To address this and other unmet needs, the present invention provides, in exemplary non-limiting embodiments, devices, systems and methods for nerve stimulation for OSA therapy as described in the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] It is to be understood that both the foregoing summary and the following detailed description are exemplary. Together with the following detailed description, the drawings illustrate exemplary embodiments and serve to explain certain principles. In the drawings:

[0009] FIG. **1** is a schematic diagram showing a fully implanted neurostimulator system with associated physician programmer and patient controller for treating obstructive sleep apnea;

[0010] FIG. **2** is a schematic diagram showing the implantable components of FIG. **1** implanted in a patient;

[0011] FIG. **3** is a perspective view of the implantable components shown in FIG. **1**;

[0012] FIG. **4** is a detailed perspective view of the implantable neurostimulator (INS) shown in FIG. **3**;

[0013] FIG. **5** is a detailed perspective view of the nerve cuff electrode and lead body shown in FIG. **3**;

[0014] FIG. **6** is a close-up detailed perspective view of the nerve cuff electrode shown in FIG. **3**;

[0015] FIG. **7** is a detailed perspective view of the internal components of the nerve cuff electrode shown in FIG. **6**;

[0016] FIG. **8** shows side and end views of an electrode contact of the nerve cuff electrode shown in FIG. **7**;

[0017] FIGS. **9**A and **9**B are perspective views of the respiration sensing lead shown in FIG. **3**;

[0018] FIG. **10** schematically illustrates surgical access and tunneling sites for implanting the system illustrated in FIG. **2**;

[0019] FIGS. **11**A and **11**B schematically illustrate dissection to a hypoglossal nerve;

[0020] FIG. **12** schematically illustrates various possible nerve stimulation sites for activating muscles controlling the upper airway;

[0021] FIGS. **13-22** are schematic illustrations of various stimulation lead body and electrode designs for use in a neurostimulator system;

[0022] FIGS. **23-24** schematically illustrate alternative implant procedures and associated tools for the stimulation lead;

[0023] FIG. **25** schematically illustrates an alternative bifurcated lead body design;

[0024] FIGS. **26**A-**26**B schematically illustrate alternative fixation techniques for the stimulation lead and electrode cuff;

[0025] FIGS. **27**A-**27**G schematically illustrate field steering embodiments;

[0026] FIGS. **28-33** schematically illustrate alternative fixation techniques for the respiration sensing lead;

[0027] FIGS. **35**A-**35**E and **36** schematically illustrate alternative electrode arrangements on the respiration sensing lead;

[0028] FIGS. **37** and **38**A-**38**C schematically illustrate various anatomical positions or bio-Z vectors for the electrodes on the respiration sensing lead;

[0029] FIGS. **39-46** schematically illustrate alternative respiration signal processing techniques;

[0030] FIG. **47** schematically illustrates an alternative respiration detection technique;

[0031] FIGS. **48-50** schematically illustrate alternative stimulation trigger algorithms;

[0032] FIGS. **51**A-**51**M are schematic illustrations of various external (partially implanted) neurostimulation systems for treating obstructive sleep apnea;

[0033] FIGS. **52**A-**52**G are schematic illustrations of a specific embodiment of an external (partially implanted) neurostimulation system;

[0034] FIGS. **53-56** schematically illustrate alternative screening tools; and

[0035] FIGS. **57**A-**57**C schematically illustrate alternative intra-operative tools.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0036] The following detailed description should be read with reference to the drawings in which similar elements in different drawings are numbered the same. The drawings, which are not necessarily to scale, depict illustrative embodiments and are not intended to limit the scope of the invention.

[0037] Description of Fully Implanted Neurostimulator System

[0038] With reference to FIG. **1**, a neurostimulator system **10** including implanted components **20**, physician programmer **30** and patient controller **40** is shown schematically. The implanted components of the system **10** may generally include an implanted neurostimulator (INS) **50** (a.k.a., implanted pulse generator (IPG)), an implanted stimulation lead (or leads) **60**, and an implanted respiration sensing lead (or leads) **70**. The INS **50** generally includes a header **52** for connection of the leads **60**/**70**, and a hermetically sealed housing **54** for the associated electronics and long-life or rechargeable battery (not visible). The stimulation lead **60** generally includes a lead body **62** with a proximal connector and a distal nerve electrode cuff **64**. The respiration sensing lead **70** generally includes a lead body **72** with a proximal connector and one or more sensors **74** disposed on or along a distal portion thereof. Suitable designs of the INS **50**, stimulation lead **60** and respiration sensing lead **70** are described in more detail hereinafter.

[0039] As shown in FIG. **2**, and by way of example, not limitation, the implanted components **20** (shown faded) of the neurostimulator system **10** are implanted in a patient P with the INS **50** disposed in a subcutaneous pocket, the stimulation lead body **62** disposed in a subcutaneous tunnel, the nerve cuff electrode **64** disposed on a nerve (e.g., hypoglossal nerve (HGN)) innervating a muscle (e.g., genioglossus muscle, not shown) controlling the upper airway, the respiration sensing lead body **72** disposed in a subcutaneous tunnel, and the respiration sensors **74** disposed adjacent lung tissue and/or intercostal muscles outside the pleural space.

[0040] Generally, electrical stimulus is delivered by the INS **50** via the stimulation lead **60** to a nerve innervating a muscle controlling upper airway patency to mitigate obstruction thereof. To reduce nerve and muscle fatigue, the stimulus may be delivered for only a portion of the respiratory cycle, such as during inspiration which corresponds to negative pressure in the upper airway. Stimulation may be thus triggered as a function of respiration as detected by respiration sensing lead **70** in a closed-loop feedback system. By way of example, the stimulus may be triggered to turn on at the end of expiration (or at the beginning of inspiration), and triggered to turn off at the beginning of expiration (or at the end of inspiration). Triggering the stimulus as a function of expiration improves capture of the entire inspiratory phase, including a brief pre-inspiratory phase of about 300 milliseconds, thus more closely mimicking normal activation of upper airway dilator muscles. Over-stimulation may cause nerve and/or muscle fatigue, but a 40% to 50% duty cycle may be safely tolerated, thus enabling limited over-stimulation. As an alternative, stimulus may be delivered independent of actual respiration wherein the stimulus duty cycle is set for an average inspiratory duration at a frequency approximately equal to an average respiratory cycle.

[0041] Stimulus may be delivered to one or more of a variety of nerve sites to activate one muscle or muscle groups controlling patency of the upper airway. For example, stimulation of the genioglossus muscle via the hypoglossal nerve moves or otherwise stiffens the anterior portion of the upper airway, thereby decreasing the critical pressure at which the upper airway collapses during inspiration and reducing the likelihood of an apnea or hypopnea event occurring during sleep. Because the systems described herein work at the level of the tongue, it may be desirable to combine this therapy with a therapy (e.g., UPPP or palatal implant) that work at the level of the soft palate, thus increasing efficacy for a broader range of patients.

[0042] With reference back to FIG. **1**, the physician programmer **30** may comprise a computer **32** configured to control and program the INS **50** via a wireless link to a programming wand **34**. The physician programmer **30** may be resident in a sleep lab where the patient undergoes a polysomnographic (PSG) study during which the patient sleeps while the INS **50** is programmed to optimize therapy.

[0043] The patient controller **40** may comprise control circuitry and associated user interface to allow the patient to control the system via a wireless link while at home, for example. The patient controller **40** may include a power switch **42** to turn the system on and slowly ramp up when the patient goes to sleep at night, and turn it off when the patient wakes in the morning. A snooze switch **44** may be used to temporarily put the INS **50** in standby mode for a preprogrammed period of time to allow the patient to temporarily wake, after which the INS **50** turns back on and ramps up to the desired stimulus level. A display **46** may be provided to indicate the status of the INS **50** (e.g., on, off or standby), to indicate satisfactory wireless link to the INS **50**, to indicate remaining battery life of the INS **50**, etc. The patient controller may also have programmability to adjust stimulus parameters (e.g., amplitude) within pre-set range determined by the physician in order to improve efficacy and/or to reduce sensory perception, for example. Optionally, the patient controller **40** may be configured to function as the programming wand **34** of the physician programmer **30**.

[0044] With reference to FIG. **3**, the implanted components **20** are shown schematically with more detail. The implanted components include INS **50**, stimulation lead **60**, and respiration sensing lead **70**. The INS **50** includes header **52** and housing **54**. The stimulation lead **60** includes lead body **62** and nerve cuff electrode **64**. The respiration sensing lead **70** includes lead body **72** and respiration sensors **74** (e.g., impedance sensing electrodes).

[0045] With reference to FIG. **4**, the INS **50** is shown schematically in more detail. The INS **50** includes header **52** that may be formed using conventional molding or casting techniques and may comprise conventional materials such as epoxy or polyurethane (e.g., Tecothane brand polyurethane). The housing **54** may be formed using conventional stamping or forming techniques and may comprise conventional materials such as titanium or ceramic. The housing **54** may include

one or more isolated electrodes, and/or if a conductive material is used for the housing **54**, the housing **54** may comprise an electrode, which may be used for respiratory sensing, for example. The housing **54** may be hermetically sealed to the header **52** using conventional techniques. The header **52** may include two or more receptacles for receiving the proximal connectors **66**/**76** of the stimulation lead body **62** and respiration sensing lead body **72**. The connectors **66**/**76** may comprise a conventional design such as IS**1** or other in-line designs. The header **52** may also include set screw seals and blocks **56** for receiving set screws (not shown) that establish electrical contact between the INS **50** and the conductors of the leads **60**/**70** via connectors **66**/**76**, and that establish mechanical fixation thereto. Some electrical contact may be achieved through spring type or cam-locked mechanisms. As shown, two set screw arrangements **56** are shown for the stimulation lead **60** and four set screw arrangements **56** are shown for the respiration sensing lead **70**, but the number may be adjusted for the number of conductors in each lead. A hole **58** may be provided in the header **52** for securing the INS **50** to subcutaneous tissue using a suture at the time of implantation.

[0046] The INS **50** may comprise a conventional implanted neurostimulator design used in neurostimulation applications, such as those available from Texcel (US), CCC (Uruguay) and NeuroTECH (Belgium), but modified for the present clinical application in terms of stimulation signal parameters, respiratory signal processing, trigger algorithm, patient control, physician programming, etc. The INS may contain a microprocessor and memory for storing and processing data and algorithms. Algorithms may be in the form of software and/or firmware, for example. One of several different embodiments of the neurostimulator may be implemented. For example, the neurostimulator may be an internal/implanted neurostimulator (INS) powered by a long-life primary battery or rechargeable battery, or an external neurostimulator (ENS) wirelessly linked (e.g., inductive) to an implanted receiver unit connected to the leads. The INS (or the receiver unit of the ENS) may be implanted and optionally anchored in a number of different locations including a subcutaneous pocket in the pectoral region, the dorsal neck region, or cranial region behind the ear, for example.

[0047] The INS **50** may include a long-life battery (not shown) which requires periodic replacement after years of service. Alternatively, the INS may include a rechargeable power source such as a rechargeable battery or super capacitor that is used instead of the long-life battery. To facilitate recharging, the INS may include a receiver coil inductively linked to a transmitter coil that is connected to a recharging unit powered by a larger battery or line power. Because the patient is stationary while sleeping, recharging may be scheduled to occur sometime during sleep to eliminate the need to carry the recharging unit during daily activities. The transmitter coil and the receiver coil may be arranged coaxially in parallel planes to maximize energy transfer efficiency, and may be held in proximity to each other by a patch, garment, or other means as described with reference to the external neurostimulator embodiments. Other examples of neurostimulator designs will be described in more detail hereinafter.

[0048] With reference to FIG. **5**, the stimulation lead **60** may comprise a variety of different design embodiments and may be positioned at different anatomical sites. For example, a nerve cuff electrode(s) **64** may be attached to a nerve(s) innervating musculature affecting patency of the upper airway. As an alternative or in addition, the nerve cuff electrode **64** may be replaced with an intramuscular electrode and placed directly in the musculature affecting patency of the upper airway. The nerve electrode **64** may be attached to a specific branch of a nerve innervating the desired muscle(s), or may be attached to a proximal trunk of the nerve in which a specific fascicle innervating the desired muscle(s) is targeted by steering the stimulus with multiple electrodes. One or more electrodes may be used for attachment to one or more portions of nerves on one side (unilateral) of the body, or one or more electrodes may be used for attachment to one or more portions of nerves on both sides (bilateral) of the body. Variations in lead body **62** and electrode **64** design as well as variations in the target stimulation site or sites will be described in more detail hereinafter.

[0049] With continued reference to FIG. **5**, the lead body **62** may be sigmoid shaped, for example, to reduce strain applied to the cuff electrode **64** when the lead body **62** is subject to movement. The sigmoid shape, which may alternatively comprise a variety of other waveform shapes, may have a wavelength of approximately 1.0 to 15 cm, and an amplitude of approximately 0.75 to 1.5 cm, for example. The lead body **62** may comprise a tubular jacket with electrical conductors **68** extending therein. The tubular jacket may comprise extruded silicone having an outside diameter of approximately 0.047 inches and an inside diameter of approximately 0.023 inches, for example. The tubular jacket may optionally have a covering of co-extruded polyurethane, for example, to improve durability. The conductors **68**, shown in a transparent window in the jacket for purposes of illustration only, may comprise a bifilar coil of insulated (e.g., ETFE) braided stranded wire (BSW) of MP35NLT material. The number of conductors **68** is shown as two, but may be adjusted depending on the desired number of independent electrodes used.

[0050] With reference to FIG. **6**, the nerve cuff electrode **64** may comprise a cuff body **80** having a lateral (or superficial) side **82** and a medial (or contralateral, or deep) side **84**. The medial side **84** is narrower or shorter in length than the lateral side **82** to facilitate insertion of the medial side **84** around a nerve such that the medial side is on the deep side of the nerve and the lateral side is on the superficial side of the nerve. This configuration reduces the dissection of nerve branches and vascular supply required to get the cuff around a nerve. For the nerve cuff implant sites discussed herein, the medial side **84** may have a length of less than 6 mm, and preferably in the range of approximately 3 to 5 mm, for example. The lateral side **82** may have a length of more than 6 mm, and preferably in the range of approximately 7 to 8 mm, for example. The cuff body **80** may be compliant and may be available in different sizes with an inside diameter of approximately 2.5 to 3.0 mm or 3.0 to 3.5 mm, for example. The cuff size may also be adjusted depending on the nominal diameter of the nerve at the site of implantation. The cuff body **80** may have a wall thickness of approximately 1.0 mm and may be formed of molded silicone, for example, and may be reinforced with imbedded fibers or fabrics. An integral tow strap **86** may be used to facilitate wrapping the cuff around a nerve by first inserting the strap **86** under and around the deep side of the nerve and subsequently pulling the strap to bring the medial side **84** in position on the deep side of the nerve and the lateral side **82** on the superficial side of the nerve.

[0051] With continued reference to FIG. **6**, the nerve cuff electrode **64** includes electrode contacts **90**A, **90**B, and **90**C imbedded in the body **80** of the cuff, with their inside surface

facing exposed to establish electrical contact with a nerve disposed therein. A transverse guarded tri-polar electrode arrangement is shown by way of example, not limitation, wherein electrode contacts **90**A and **90**B comprise anodes transversely guarding electrode contact **90**C which comprises a cathode.

[0052] With this arrangement, the anode electrodes **90**A and **90**B are connected to a common conductor **68**A imbedded in the body **80**, and the cathode electrode **90**C is connected to an independent conductor **68**B extending from the lateral side **82** to the medial side **84** and imbedded in the body **80**. By using the conductors **68** to make connections within the body **80** of the cuff **64**, fatigue stresses are imposed on the conductors rather than the electrode contacts **90**A, **90**B and **90**C.

[0053] With additional reference to FIGS. **7** and **8**, the electrode contacts **90**A, **90**B and **90**C may thus be semi-circular shaped having an arc length of less than 180 degrees, and preferably an arc length of approximately 120 degrees, for example. Each electrode **90** may have two reverse bends (e.g., hooked or curled) portions **92** to provide mechanical fixation to the body **80** when imbedded therein. Each electrode **90** may also have two crimp tabs **94** defining grooves thereunder for crimping to the conductors **68** or for providing a pass-through. As shown in FIG. **7**, conductor **68**A passes through the grooves under the lower crimp tabs **94** of electrodes **90**B and **90**A, loops **98** around through the grooves under the upper crimp tabs **94** of electrodes **90**A and **90**B, is crimped **96** by the upper tabs **94** of electrodes **90**A and **90**B to provide mechanical and electrical connection, is looped again back between the crimp tabs **94** on the outside of the electrode contact **90**, and is resistance spot welded **95** to provide redundancy in mechanical and electrical connection. Also as shown in FIG. **7**, conductor **68**B passes through the groove under the lower crimp tab **94** of electrode **90**C, loops around through the groove under the upper crimp tab **94** of electrode **90**C, and is crimped by the upper tab **94** of electrode **90**C to provide mechanical and electrical connection. This arrangement avoids off-axis tensile loading at the crimp sites **96** which may otherwise fail due to stress concentration, and the looped portion **98** provides additional strain relief. FIG. **8** provides example dimensions (inches) of an electrode contact **90** for a 25 mm inside diameter cuff, wherein the electrode is formed of 90/10 or 80/20 platinum iridium alloy formed by wire EDM, for example.

[0054] With reference to FIGS. **9**A and **9**B, a distal portion of the respiration sensing lead **70** and a distal detail of the sensing lead **70**, respectively, are shown schematically. In the illustrated embodiment, the respiration sensing lead **70** and associated sensors **74** are implanted as shown in FIG. **2**. However, the respiration sensors) may comprise a variety of different design embodiments, both implanted and external, and may be positioned at different anatomical sites. Generally, the respiratory sensor(s) may be internal/implanted or external, and may be connected to the neurostimulator via a wired or wireless link. The respiratory sensor(s) may detect respiration directly or a surrogate thereof. The respiratory sensor(s) may measure, for example, respiratory airflow, respiratory effort (e.g., diaphragmatic or thoracic movement), intra-pleural pressure, lung impedance, respiratory drive, upper airway EMG, changes in tissue impedance in and around the lung(s) including the lungs, diaphragm and/or liver, acoustic airflow or any of a number other parameters indicative of respiration. Detailed examples of suitable respiration sensing leads and sensors will be described in more detail hereinafter.

[0055] With continued reference to FIGS. **9**A and **9**B, the respiration sensing lead **70** includes a lead body **72** and a plurality of respiration sensors **74**A-**74**D comprising ring electrodes for sensing bio-impedance. The lead body **72** of the respiration sensing lead **70** may include a jacket cover comprising an extruded silicone tube optionally including a polyurethane cover (**80**A durometer), or may comprise an extruded polyurethane tube (**55**D durometer). The ring electrodes **74**A-**74**D may comprise 90/10 or 80/20 platinum iridium alloy tubes having an outside diameter of 0.050 inches and a length of 5 mm, and secured to the jacket cover by laser welding and/or adhesive bonding, for example. The lead body **72** may include a plurality of conductors **78** as seen in the transparent window in the jacket cover, which is shown for purposes of illustration only. The conductors **78** may comprise insulated and coiled BSW or solid wire (optionally DFT silver core wire) disposed in the tubular jacket, with one conductor provided for each ring electrode **74**A-**74**D requiring independent control. Generally, the impedance electrodes **74**A-**74**D may comprise current emitting electrodes and voltage sensing electrodes for detecting respiration by changes in bio-impedance. The number, spacing, anatomical location and function of the impedance electrodes will be described in more detail hereinafter.

[0056] Description of Implant Procedure

[0057] With reference to FIG. **10**, surgical access sites are schematically shown for implanting the internal neurostimulator components **20** shown in FIG. **1**. The internal neurostimulator components **20** may be surgically implanted in a patient on the right or left side. The right side may be preferred because it leaves the left side available for implantation of a pacemaker, defibrillator, etc., which are traditionally implanted on the left side. The right side may also be preferred because it lends itself to a clean respiratory signal less susceptible to cardiac artifact and also offers placement of respiratory sensors across the interface between the lung, diaphragm and liver for better detection of impedance changes during respiration.

[0058] With continued reference to FIG. **10**, the INS (not shown) may be implanted in a subcutaneous pocket **102** in the pectoral region, for example. The stimulation lead (not shown) may be implanted in a subcutaneous tunnel **104** along (e.g., over or under) the platysma muscle in the neck region. The respiration sensing lead (not shown) may be implanted in a subcutaneous tunnel **106** extending adjacent the ribcage to an area adjacent lung tissue and/or intercostal muscles outside the pleural space. The nerve cuff electrode (not shown) may be attached to a nerve by surgical dissection at a surgical access site **110** proximate the targeted stimulation site. In the illustrated example, the target nerve is the right hypoglossal nerve and the surgical access site is in the submandibular region.

[0059] With reference to FIGS. **11**A and **11**B, a surgical dissection **110** to the hypoglossal nerve is shown schematically. A unilateral dissection is shown, but a bilateral approach for bilateral stimulation may also be employed. Conventional surgical dissection techniques may be employed. The branch of the hypoglossal nerve (usually a medial or distal branch) leading to the genioglossus muscle may be identified by stimulating the hypoglossal nerve at different locations and observing the tongue for protrusion.

Because elongation and/or flexion may be mistaken for protrusion, it may be desirable to observe the upper airway using a flexible fiber optic scope (e.g., nasopharyngoscope) inserted into the patient's nose, through the nasal passages, past the nasopharynx and velopharynx to view of the oropharynx and hypopharynx and visually confirm an increase in airway caliber by anterior displacement (protrusion) of the tongue base when the nerve branch is stimulated.

[0060] The implant procedure may be performed with the patient under general anesthesia in a hospital setting on an out-patient basis. Alternatively, local anesthesia (at the surgical access sites and along the subcutaneous tunnels) may be used together with a sedative in a surgical center or physician office setting. As a further alternative, a facial nerve block may be employed. After a post-surgical healing period of about several weeks, the patient may return for a polysomnographic (PSG) test or sleep study at a sleep center for programming the system and titrating the therapy. A trialing period may be employed prior to full implantation wherein the hypoglossal nerve or the genioglossus muscle is stimulated with fine wire electrodes in a sleep study and the efficacy of delivering stimulus to the hypoglossal nerve or directly to the genioglossus muscle is observed and measured by reduction in apnea hypopnea index, for example.

[0061] Other nerve target sites are described elsewhere herein and may be accessed by similar surgical access techniques. As an alternative to surgical dissection, less invasive approaches such as percutaneous or laparoscopic access techniques may be utilized, making use of associated tools such as tubular sheaths, trocars, etc.

[0062] Description of Alternative Stimulation Target Sites

[0063] With reference to FIG. **12**, various possible nerve and/or direct muscle stimulation sites are shown for stimulating muscles controlling patency of the upper airway. In addition to the upper airway which generally includes the pharyngeal space, other nerves and dilator muscles of the nasal passage and nasopharyngeal space may be selectively targeted for stimulation. A general description of the muscles and nerves suitable for stimulation follows, of which the pharyngeal nerves and muscles are shown in detail in FIG. **12**.

[0064] Airway dilator muscles and associated nerves suitable for activation include are described in the following text and associated drawings. The dilator naris muscle functions to widen the anterior nasal aperture (i.e., flares nostrils) and is innervated by the buccal branch of the facial nerve (cranial nerve VII). The tensor veil palatine muscle functions to stiffen the soft palate and is innervated by the medial (or internal) pterygoid branch of the mandibular nerve. The genioglossus muscle is an extrinsic pharyngeal muscle connecting the base of the tongue to the chin and functions to protrude the tongue. The genioglossus muscle is typically innervated by a distal or medial branch (or branches) of the right and left hypoglossal nerve. The geniohyoid muscle connects the hyoid bone to the chin and the sternohyoid muscle attaches the hyoid bone to the sternum. The geniohyoid muscle functions to pull the hyoid bone anterosuperiorly, the sternohyoid muscle functions to pull hyoid bone inferiorly, and collectively (i.e., co-activation) they function to pull the hyoid bone anteriorly. The geniohyoid muscle is innervated by the hypoglossal nerve, and the sternohyoid muscle is innervated by the ansa cervicalis nerve.

[0065] By way of example, a nerve electrode may be attached to a specific branch of the hypoglossal nerve innervating the genioglossus muscle (tongue protrude), or may be attached to a more proximal portion (e.g., trunk) of the hypoglossal nerve in which a specific fascicle innervating the genioglossus muscle is targeted by steering the stimulus using an electrode way. Activating the genioglossus muscle causes the tongue to protrude thus increasing the size of anterior aspect of the upper airway or otherwise resisting collapse during inspiration.

[0066] As an alternative to activation of any or a combination of the airway dilator muscles, co-activation of airway dilator and airway restrictor or retruder muscles may be used to stiffen the airway and maintain patency. By way of example, a nerve electrode may be attached to specific branches of the hypoglossal nerve innervating the genioglossus muscle (tongue protruder), in addition to the hyoglossus and styloglossus muscles (tongue retruders), or may be attached to a more proximal portion (e.g., trunk) of the hypoglossal nerve in which specific fascicles innervating the genioglossus, hyoglossus and styloglossus muscles are targeted by steering the stimulus using an electrode array. Activating the hyoglossus and styloglossus muscles causes the tongue to retract, and when co-activated with the genioglossus, causes the tongue to stiffen thus supporting the anterior aspect of the upper airway and resisting collapse during inspiration. Because the tongue retruder muscles may overbear the tongue protruder muscle under equal co-activation, unbalanced co-activation may be desired. Thus, a greater stimulus (e.g., longer stimulation period, larger stimulation amplitude, higher stimulation frequency, etc.) or an earlier initiated stimulus may be delivered to the portion(s) of the hypoglossal nerve innervating the genioglossus muscle than to the portion (s) of the hypoglossal nerve innervating the hyoglossus and styloglossus muscles.

[0067] With continued reference to FIG. **12**, examples of suitable nerve stimulation sites include B; A+C; A+C+D; B+D; C+D; and E Sites B and E may benefit from selective activation by field steering using an electrode array. As mentioned before, nerve electrodes may be placed at these target nerve(s) and/or intramuscular electrodes may be placed directly in the muscle(s) innervated by the target nerve(s).

[0068] Site A is a distal or medial branch of the hypoglossal nerve proximal of a branch innervating the genioglossus muscle and distal of a branch innervating the geniohyoid muscle. Site B is a more proximal portion of the hypoglossal nerve proximal of the branches innervating the genioglossus muscle and the geniohyoid muscle, and distal of the branches innervating the hyoglossus muscle and the styloglossus muscle. Site C is a medial branch of the hypoglossal nerve proximal of a branch innervating the geniohyoid muscle and distal of branches innervating the hyoglossus muscle and the styloglossus muscle. Site D is a branch of the ansa cervicalis nerve distal of the nerve root and innervating the sternohyoid. Site E is a very proximal portion (trunk) of the hypoglossal nerve proximal of the branches innervating the genioglossus, hyoglossus and styloglossus muscles.

[0069] Activating site B involves implanting an electrode on a hypoglossal nerve proximal of the branches innervating the genioglossus muscle and the geniohyoid muscle, and distal of the branches innervating the hyoglossus muscle and the styloglossus muscle.

[0070] Co-activating sites A+C involves implanting a first electrode on a hypoglossal nerve proximal of a branch innervating the genioglossus muscle and distal of a branch innervating the geniohyoid muscle, and implanting a second electrode on the hypoglossal nerve proximal of a branch

innervating the geniohyoid muscle and distal of branches innervating the hyoglossus muscle and the styloglossus muscle.

[0071] Co-activating sites A+C+D involves implanting a first electrode on a hypoglossal nerve proximal of a branch innervating the genioglossus muscle and distal of a branch innervating the geniohyoid muscle; implanting a second electrode on the hypoglossal nerve proximal of a branch innervating the geniohyoid muscle and distal of branches innervating the hyoglossus muscle and the styloglossus muscle; and implanting a third electrode on a branch of an ansa cervicalis nerve distal of the nerve root and innervating the sternohyoid.

[0072] Co-activating sites B+D involves implanting a first electrode on a hypoglossal nerve proximal of branches innervating the genioglossus muscle and the geniohyoid muscle, and distal of branches innervating the hyoglossus muscle and the styloglossus muscle; and implanting a second electrode on a branch of an ansa cervicalis nerve distal of the nerve root and innervating the sternohyoid.

[0073] Co-activating sites C+D involves implanting a first electrode on a hypoglossal nerve proximal of a branch innervating the geniohyoid muscle, and distal of branches innervating the hyoglossus muscle and the styloglossus muscle and implanting a second electrode on a branch of an ansa cervicalis nerve distal of the nerve root and innervating the sternohyoid.

[0074] Activating site E involves implanting an electrode on a hypoglossal nerve proximal of the branches innervating the genioglossus, hyoglossus and styloglossus muscles; and selectively activating (e.g., by field steering) the genioglossus muscle before or more than the hyoglossus and styloglossus muscles.

[0075] Description of Alternative Nerve Electrodes

[0076] Any of the alternative nerve electrode designs described hereinafter may be employed in the systems described herein, with modifications to position, orientation, arrangement integration, etc. made as dictated by the particular embodiment employed. Examples of other nerve electrode designs are described in U.S. Pat. No. 5,531,778, to Maschino et al., U.S. Pat. No. 4,979,511 to Terry, Jr., and U.S. Pat. No. 4,573,481 to Bullara, the entire disclosures of which are incorporated herein by reference.

[0077] With reference to the following figures, various alternative electrode designs for use in the systems described above are schematically illustrated. In each of the embodiments, by way of example, not limitation, the lead body and electrode cuff may comprise the same or similar materials formed in the same or similar manner as described previously. For example, the lead body may comprise a polymeric jacket formed of silicone, polyurethane, or a co-extrusion thereof. The jacket may contain insulated wire conductors made from BSW or solid wire comprising MP35N, MP35N with Ag core, stainless steel or Tantalum, among others. The lead body may be sigmoid shaped to accommodate neck and mandibular movement. Also, a guarded cathode tri-polar electrode arrangement (e.g., anode-cathode-anode) may be used, with the electrodes made of 90/10 or 80/20 Par alloy with silicone or polyurethane backing.

[0078] With specific reference to FIGS. **13**A and **13**B, a self-sizing and expandable design is shown to accommodate nerve swelling and/or over-tightening. FIG. **13**A shows a perspective view of a nerve electrode cuff **130** on a nerve such as a hypoglossal nerve, and FIG. **13**B shows a cross-sectional view of the nerve cuff electrode **130** on the nerve. In this embodiment, the implantable nerve cuff electrode **130** comprises a complaint sheet wrap **132** configured to be wrapped about a nerve and secured thereto by connecting opposite portions of the sheet by sutures **138**, for example. The sheet **132** includes a plurality of radially and longitudinally distributed fenestrations **134** to allow expansion of the sheet **132** to accommodate nerve swelling and/or over tightening. Electrode contacts **136** comprising a coil, foil strip, conductive elastomer or individual solid conductors may be carried by the sheet **132** with an exposed inside surface to establish electrical contact with the nerve.

[0079] With specific reference to FIGS. **14**A-**14**C, another self-sizing and expandable design is shown to accommodate nerve swelling and/or over-tightening. FIG. **14**A shows a perspective view of a nerve electrode cuff **140** on a nerve such as a hypoglossal nerve, and FIG. **14**B shows a cross-sectional view of the nerve cuff electrode **140** on the nerve. In this embodiment, the implantable nerve cuff electrode **140** comprises a complaint sheet wrap **142** configured to be wrapped about a nerve and secured thereto by connecting opposite portions of the sheet by sutures **148**A, or by a buckle **148**B as shown in FIG. **14**C, for example. The opposite portions of the sheet **142** comprise one or more narrow strips **144** integral with the sheet **142** to allow expansion and to accommodate nerve swelling and/or over tightening. Electrode contacts **146** comprising a coil, foil strip, conductive elastomer or individual solid conductors may be carried by the sheet **142** with an exposed inside surface to establish electrical contact with the nerve.

[0080] With specific reference to FIGS. **15**A-**15**C, another self-sizing and expandable design is shown to accommodate nerve swelling and/or over-tightening. FIG. **15**A shows a perspective view of a nerve electrode cuff **150** on a nerve such as a hypoglossal nerve, and FIG. **15**B shows a cross-sectional view of the nerve cuff electrode **150** on the nerve. In this embodiment, the implantable nerve cuff electrode **150** comprises a complaint sheet wrap **152** configured to be wrapped about a nerve and secured thereto by connecting opposite portions of the sheet **152** by sutures **158**, for example. The opposite portions of the sheet **152** are offset from the nerve and a thickened portion of the sheet **152** fills the offset space. The offset distance reduces the amount of compressive force that the electrode cuff can exert on the nerve. To further reduce the pressure on the nerve, the sheet **152** includes a plurality of radially distributed slits **154** extending partly through the thickness of the sheet **152** to allow expansion and to accommodate nerve swelling and/or over tightening.

[0081] With specific reference to FIGS. **16**A and **16**B, another self-sizing and expandable design is shown to accommodate nerve swelling and/or over-tightening. FIG. **16**A shows a perspective view of a nerve electrode cuff **160** on a nerve such as a hypoglossal nerve, and FIG. **16**B shows a cross-sectional view of the nerve cuff electrode **160** on the nerve. In this embodiment, the implantable nerve cuff electrode **160** comprises a complaint sheet wrap **162** configured to be wrapped about a nerve and secured thereto by connecting opposite portions of the sheet **162** by sutures **168**, for example. The sheet **162** includes a plurality of radially distributed and longitudinally extending convolutions **164** that may comprise alternative thick **164**A and thin **164**B portions in the sheet **162** and/or overlapping portions **164**C of the sheet **162** to allow expansion and to accommodate nerve swelling and/or over tightening. Electrode contacts **166** comprising a coil, foil strip, conductive elastomer or individual solid con-

ductors may be carried by the sheet **162** with an exposed inside surface to establish electrical contact with the nerve. Nerve cuff electrode **160** may accommodate one or two lead bodies **62**A, **62**B for connection to the electrode contacts **166** on the same or opposite sides of the nerve.

[0082] With reference to FIG. **17**, a modular nerve electrode cuff **170** is shown that includes a semi-cylindrical body portion **172** with an array of electrode contacts **176** with separate insulative strips **174** for placement on the deep (contralateral side) of the nerve, which typically has more nerve branches and connecting blood vessels. In this embodiment, independent placement of the electrode body **172** on the superficial (lateral) side of the nerve and placement of the insulative strips **174** on the deep (contralateral) side of the nerve minimizes dissection. The strips **174** may be connected to the electrode body **172** by sutures or buckles as described previously. This embodiment is also self-sizing to accommodate nerve swelling and/or over-tightening.

[0083] With reference to FIG. **18**, a nerve cuff electrode **180** is shown that has a cuff body with a relatively wide semi-cylindrical lateral side **182** and a relatively narrow semi-cylindrical medial side **184** that may extend through a small fenestration around the deep (contralateral) side of a nerve to securely and gently grasp the nerve while minimizing dissection. In the illustrated example, the lateral side **182** carries two anode electrode contacts **186** and the medial side **184** carries one cathode electrode contact **186** in an arrangement that may be referred to as transverse guarded tri-polar. A tow strap **188** is provided for inserting the medial side **184** around the deep side of the nerve. The tow strap **188** may be integrally formed with the medial side **184** of the cuff body, and may include a reinforced tip **188**A with a serrated or marked cut line **188**B.

[0084] With reference to FIGS. **19**A and **19**B, a nerve cuff electrode **190** is shown that has a cuff body with a relatively wide semi-cylindrical lateral side **192** and a relatively narrow semi-cylindrical medial side **194** that may extend through a small fenestration around the deep (contralateral) side of a nerve to securely and gently grasp the nerve while minimizing dissection. In the illustrated example, the lateral side **192** carries one cathode electrode contact **196**C and two guarding anode electrode contacts **196**B and **196**D, and the medial side **194** carries one anode electrode contact **196**A in an arrangement that may be referred to as transverse and longitudinal guarded quad-polar. The provision of guarding electrode contacts **196**B and **196**C reduces extrinsic stimulation due to the lack of insulative material on the medial side **194**. The embodiments of FIGS. **18**, **19**A and **19**B illustrate two different electrode contact arrangements, but the number and arrangement may be modified to suit the particular application.

[0085] With reference to FIG. **20**, a nerve cuff electrode array **200** is shown that utilizes a series of relatively narrow independent cuffs **200**A, **200**B and **200**C with corresponding independent lead bodies **62**. Providing a series of relatively narrow independent cuffs **200**A, **200**B and **200**C minimizes the required dissection around the nerve for implantation thereof. Also, the series of independent cuffs **200**A, **200**B and **200**C allows more selectivity in electrode placement to adjust for anatomical variation or multiple target stimulation sites, for example. Providing multiple independent lead bodies **62** allows for more options in routing and placement of the individual lead bodies **62** (e.g., alternate placement of lead body **62**A) and also prevents tissue encapsulation around the lead bodies **62** from collectively affecting encapsulation of the nerve cuffs **200**. Each of the cuffs **200**A, **200**B and **200**C may include a cuff body **202** with one or more imbedded electrode contacts (not shown) and a tow strap **204** as described before. Also, each of the cuffs **200**A, **200**B and **200**C may include suture **208** or a buckle **206** to lock onto the tow strap **204** for connecting opposite ends of the body **202** around the nerve.

[0086] With reference to FIGS. **21**A and **21**B, a nerve cuff electrode **210** is shown with multiple electrode contacts **216** radially spaced around the inside surface of a compliant split cuff body **212** to establish multiple electrical contact points around the circumference of the nerve. Each of the electrode contacts **216** may be connected to independent conductors in the lead body **62** via axially extending wires **217**. This arrangement allows for field steering as discussed herein. The compliant split cuff body **212** together with axially extending wires **217** allows for self-sizing to accommodate nerve swelling and/or over-tightening. One or more pairs of tabs **214** extending from opposite end portions of the cuff body **212** may be connected by a suture (not shown) as described herein. As shown in FIG. **21**B, the proximal and distal ends of the cuff body **212** may have tapered thickness extensions **218** to provide strain relief and reduce mechanical irritation of the nerve due to contact with the edge of the cuff.

[0087] With reference to FIG. **22**, a nerve cuff electrode **220** is shown with a separable lead **62** in what may be referred to as a modular design. In this embodiment, the nerve cuff electrode **220** includes a semi-circular flexible cuff body (or housing) **222** with a receptacle **224** configured to accommodate a distal end of a lead body **62** therein. The receptacle **224** may provide a releasable mechanical lock to the lead body **52** as by a press fit, mating detents, etc. The distal end of the lead body **62** carries an array of ring electrodes **65**, with windows **226** provided in the cuff body **222** configured to align with the ring electrodes **65** and permit exposure of the ring electrodes **65** to the nerve to establish electrical connection therebetween. The cuff body **222** may be attached to the nerve or simply placed adjacent the nerve. Any of the cuff designs described herein may be provided with a receptacle to accommodate a removable lead body. This embodiment allows post-operative removal of the lead body **62** without removal of the cuff **220**, which may be beneficial in revision operations, for example.

[0088] Description of Alternative Implant Procedure for the Stimulation Lead

[0089] With reference to FIGS. **23**A-**23**C, an insertable paddle-shaped lead **230** design is shown. The insertable lead **230** may have a paddle-shape (rectangular) cross-section with a tubular jacket **232** and one or more conductors **234** extending trough to one or more distally placed electrode contact(s) **236**. The electrode contact(s) **236** may be imbedded in a molded distal end of the jacket **232** such that the electrode contact **236** has an exposed surface to face the nerve when implanted as shown in FIG. **23**B. The space between the nerve and electrode is shown for purposes of illustration only, as the electrodes may be placed in direct contact with the nerve. Soft tines **238** may be integrally formed at the distal end of the tubular jacket **232** for purposes of mild fixation to tissue when implanted. The insertable lead **230** is configured to be placed adjacent to the nerve (thereby negating the need for a cuff) by inserting the lead **230** at the surgical access site **110** and following the nerve distally until the electrode contacts **236** are placed adjacent the target stimulation site. The insertable lead **232** may be used alone or in conjunction with

another lead as shown in FIGS. **23**B and **23**C. In the illustrated example, a first lead **230**A is inserted along a superficial side of the nerve and a second lead **230**B is inserted along a deep side of the nerve.

[0090] A method of implanting lead **230** may generally comprise accessing a proximal extent of the nerve by minimal surgical dissection and retraction of the mylohyoid muscle as shown in FIG. **23**C. Special tools may alternatively be employed for percutaneous or laparoscopic access as shown and described with reference to FIGS. **24**A-**24**C. Subsequently, two paddle-shaped leads **230** with distal electrode contacts **236** may be inserted into the surgical access site and advanced beyond the access site along a distal aspect of the nerve to the desired stimulation site on either side of the nerve. These techniques minimize trauma and facilitate rapid recovery.

[0091] A less invasive method of implanting a paddle-shaped lead **230** is shown in FIGS. **24**A-**24**C. In this embodiment, a rectangular tubular trocar **240** with a sharpened curved tip is placed through a percutaneous access site **111** until a distal and thereof is adjacent the superficial side of the nerve. A paddle-shaped lead **230** is inserted through the lumen of the trocar **240** and advanced distally beyond the distal end of the trocar **240** along the nerve, until the electrode contacts **236** are positioned at the target stimulation site. As shown in FIG. **24**B, which is a view taken along line A-A in FIG. **24**A, the insertable lead **230** includes multiple electrode contacts **236** in an anode-cathode-anode arrangement, for example, on one side thereof to face the nerve when implanted. In this embodiment, tines are omitted to facilitate smooth passage of the lead **230** through the trocar. To establish fixation around the nerve and to provide electrical insulation, a backer strap **242** of insulative material may be placed around the deep side of the nerve. To facilitate percutaneous insertion of the backer **242**, a curved tip needle **244** may be inserted through a percutaneous access site until the tip is adjacent the nerve near the target stimulation site. A guide wire **246** with a J-shaped tip may then be inserted through the needle **244** and around the nerve. The backer **242** may then be towed around using the guide wire **246** as a leader, and secured in place by a buckle (not shown), for example.

[0092] With reference to FIG. **25**, a bifurcated lead **250** is shown to facilitate separate attachment of electrode cuffs **64** to different branches of the same nerve or different nerves for purposes described previously. Any of the nerve cuff electrode or intramuscular electrode designs described herein may be used with the bifurcated lead **250** as shown. In the illustrated example, a first lead furcation **252** and a second lead furcation **254** are shown merging into a common lead body **62**. Each furcation **252** and **254** may be the same or similar construction as the lead body **62**, with modification in the number of conductors. More than two electrode cuffs **64** may be utilized with corresponding number of lead furcations.

[0093] Description of Stimulation Lead Anchoring Alternatives

[0094] With reference to FIGS. **26**A and **26**B, an elastic tether **264** with a limited length is utilized to prevent high levels of traction on the electrode cuff **64** around the hypoglossal nerve (or other nerve in the area) resulting from gross head movement. In other words, tether **264** relieves stress applied to the electrode cuff **64** by the lead body **62**. FIGS. **26**A and **26**B are detailed views of the area around the dissection to the hypoglossal nerve, showing alternative embodiments of attachment of the tether **264**. The proximal end of the tether **264** may be attached to the lead body **62** as shown in FIG. **26**A or attached to the electrode cuff **64** as shown in FIG. **26**B. The distal end of the tether **264** may be attached to the fibrous loop carrying the digastrics tendon as shown in FIG. **26**A or attached to adjacent musculature as shown in FIG. **26**B.

[0095] By way of example, not limitation, and as shown in FIG. **26**A, a tubular collar **262** is disposed on the lead body **62** to provide connection of the tether **262** to the lead body **62** such that the lead body **62** is effectively attached via suture **266** and tether **264** to the fibrous loop surrounding the digastrics tendon. The tether **264** allows movement of the attachment point to the lead body **62** (i.e., at collar **262**) until the tether **264** is straight. At this point, any significant tensile load in the caudal direction will be borne on the fibrous loop and not on the electrode cuff **64** or nerve. This is especially advantageous during healing before a fibrous sheath has formed around the lead body **62** and electrode cuff **64**, thus ensuring that the cuff **64** will not be pulled off of the nerve. It should be noted that the length of the tether **262** may be less than the length of the lead body **62** between the attachment point (i.e., at collar **262**) and the cuff **64** when the tensile load builds significantly due to elongation of this section of lead body **62**.

[0096] The tether **264** may be formed from a sigmoid length of braided permanent suture coated with an elastomer (such as silicone or polyurethane) to maintain the sigmoid shape when in the unloaded state. The tether **264** may also be made from a monofilament suture thermoformed or molded into a sigmoid shape. The distal end of the tether **264** may be attached to the fibrous loop using a suture **266** or staple or other secure means. Note that the tether **264** may be made from a biodegradable suture that will remain in place only during healing.

[0097] Also by way of example, not limitation, an alternative is shown in FIG. **26**B wherein the tether **264** is attached to the electrode cuff **64**. The distal end of the tether **264** may be attached to the adjacent musculature by suture **266** such the musculature innervated by branches of the hypoglossal nerve or other musculature in the area where the electrode cuff **64** is attached to the nerve. The tether **264** ensures that the electrode cuff **64** and the hypoglossal nerve are free to move relative to the adjacent musculature (e.g., hyoglossal). As significant tensile load is applied to the lead body **62** due to gross head movement, the tether **264** will straighten, transmitting load to the muscle rather then to the nerve or electrode cuff **64**.

[0098] Description of Field Steering Alternatives

[0099] With reference to FIGS. **27**A-**27**G, a field steering nerve cuff electrode **64** is shown schematically. As seen in FIG. **27**A, the nerve cuff electrode **64** may include four electrode contacts **90**A-**90**D to enable field steering, and various arrangements of the electrode contacts **90**A-**90**D are shown in FIGS. **27**B-**27**G. Each of FIGS. **27**B-**27**G includes a top view of the cuff **64** to schematically illustrate the electrical field (activating function) and an end view of the cuff **64** to schematically illustrate the area of the nerve effectively stimulated. With this approach, electrical field steering may be used to stimulate a select area or fascicle(s) within a nerve or nerve bundle to activate select muscle groups as described herein.

[0100] With specific reference to FIG. **27**A, the nerve cuff electrode **64** may comprise a cuff body having a lateral (or superficial) side **82** and a medial (or contralateral, or deep) side **84**. The medial side **84** is narrower or shorter in length than the lateral side **82** to facilitate insertion of the medial side

84 around a nerve such that the medial side is on the deep side of the nerve and the lateral side is on the superficial side of the nerve. An integral tow strap **86** may be used to facilitate wrapping the cuff around a nerve. The nerve cuff electrode **64** includes electrode contacts **90**A, **90**B, **90**C and **90**D imbedded in the body of the cuff, with their inside surface facing exposed to establish electrical contact with a nerve disposed therein. Electrode contacts **90**A and **90**B are longitudinally and radially spaced from each other. Electrode contacts **90**C and **90**D are radially spaced from each other and positioned longitudinally between electrode contacts **90**A and **90**B. Each of the four electrode contacts may be operated independently via four separate conductors (four filar) in the lead body **62**.

[0101] With specific reference to Ewes **27**B-**27**G, each includes a top view (left side) to schematically illustrate the electrical field or activating function (labeled E), and an end view (right side) to schematically illustrate the area of the nerve effectively stimulated (labeled S) and the area of the nerve effectively not stimulated (labeled NS). Electrodes **90**A-**90**D are labeled A-D for sake of simplicity only. The polarity of the electrodes is also indicated, with each of the cathodes designated with a negative sign (−) and each of the anodes designated with a positive sign (+).

[0102] With reference to FIG. **27**B, a tripolar transverse guarded cathode arrangement is shown with electrodes C and D comprising cathodes and electrodes A and B comprising anodes, thus stimulating the entire cross-section of the nerve.

[0103] With reference to FIG. **27**C, a bipolar diagonal arrangement is shown with electrode C comprising a cathode and electrode A comprising an anode, wherein the fascicles that are stimulated may comprise superior fascicles of the hypoglossal nerve, and the fascicles that are not stimulated may comprise inferior fascicles of the hypoglossal nerve (e.g., fascicles that innervate the intrinsic muscles of the tongue).

[0104] With reference to FIG. **27**D, another bipolar diagonal arrangement is shown with electrode D comprising a cathode and electrode B comprising an anode, wherein the fascicles that are stimulated may comprise inferior fascicles of the hypoglossal nerve.

[0105] With reference to FIG. **27**E, a bipolar axial arrangement is shown with electrode A comprising a cathode and electrode B comprising an anode, wherein the fascicles that are stimulated may comprise lateral fascicles of the hypoglossal nerve.

[0106] With reference to FIG. **27**F, a bipolar transverse arrangement is shown with electrode C comprising a cathode and electrode D comprising an anode, wherein the fascicles that are stimulated may comprise medial fascicles of the hypoglossal nerve.

[0107] With reference to FIG. **27**G, a modified tripolar transverse guarded cathode arrangement is shown with electrode C comprising a cathode and electrodes A and B comprising anodes, thus stimulating the entire cross-section of the nerve with the exception of the inferior medial fascicles.

[0108] Description of Respiration Sensing Lead Anchoring Alternatives

[0109] With reference to the following figures, various additional or alternative anchoring features for the respiration sensing lead **70** are schematically illustrated. Anchoring the respiration sensing lead **70** reduces motion artifact in the respiration signal and stabilizes the bio-impedance vector relative to the anatomy.

[0110] In each of the embodiments, by way of example, not limitation, the respiration sensing lead **70** includes a lead body **70** with a proximal connector and a plurality of distal respiration sensors **74** comprising ring electrodes for sensing bio-impedance. The lead body **72** of the respiration sensing lead **70** may include a jacket cover containing a plurality of conductors **78**, one for each ring electrode **74** requiring independent control. Generally, the impedance electrodes **74** may comprise current emitting electrodes and voltage sensing electrodes for detecting respiration by changes in bio-impedance.

[0111] With reference to FIGS. **28**-**33**, various fixation devices and methods are shown to acutely and/or chronically stabilize the respiratory sensing lead **70**. With specific reference to FIG. **28**, the INS **50** is shown in a subcutaneous pocket and the stimulation lead **60** is shown in a subcutaneous tunnel extending superiorly from the pocket. The respiration sensing lead **70** is shown in a subcutaneous tunnel superficial to muscle fascia around the rib cage. A suture tab or ring **270** may be formed with or otherwise connected to the distal end of the lead body **72**. Near the distal end of the lead **70**, a small surgical incision may be formed to provide access to the suture tab **270** and the muscle fascia under the lead **70**. The suture tab **270** allows the distal end of the lead **70** to be secured to the underlying muscle fascia by suture or staple **272**, for example, which may be dissolvable or permanent. Both dissolvable and permanent sutures/staples provide for acute stability and fixation until the lead body **72** is encapsulated. Permanent sutures/staples provide for chronic stability and fixation beyond what tissue encapsulation otherwise provides.

[0112] With reference to FIGS. **29**A-**29**C, a fabric tab **280** may be used in place of or in addition to suture tab **270**. As seen in FIG. **29**A, the fabric tab **280** may be placed over a distal portion of the lead body **72**, such as between two distal electrodes **74**. A small surgical incision may be formed proximate the distal end of the lead **70** and the fabric tab **280** may be placed over the over the lead body **72** and secured to the underlying muscle fascia by suture or staple **282**, for example, which may be dissolvable or permanent, to provide acute and/or chronic stability and fixation. With reference to FIGS. **29**B and **29**C (cross-sectional view taken along line A-A), the fabric tab **280** may comprise a fabric layer (e.g., polyester) **284** to promote chronic tissue in-growth to the muscle fascia and a smooth flexible outer layer (silicone or polyurethane) **286** for acute connection by suture or staple **282**.

[0113] With reference to FIG. **30**, lead **70** includes a split ring **290** that may be formed with or otherwise connected to the distal end of the lead body **72**. The split ring **290** allows the distal end of the lead **70** to be secured to the underlying muscle fascia by suture or staple **292**, for example, which may be dissolvable or permanent. The ring **290** may be formed of compliant material (e.g., silicone or polyurethane) and may include a slit **294** (normally closed) that allows the lead **70** to be explanted by pulling the lead **70** and allowing the suture **292** to slip through the slit **294**, or if used without a suture, to allow the ring to deform and slide through the tissue encapsulation. To further facilitate explantation, a dissolvable fabric tab **282** may be used to acutely stabilize the lead **70** but allow chronic removal.

[0114] With reference to FIGS. **31**A-**31**C, deployable anchor tines **300** may be used to facilitate fixation of the lead **70**. As seen in FIG. **31**A, the self-expanding tines **300** may be molded integrally with the lead body **72** or connected thereto

by over-molding, for example. The tines **300** may comprise relatively resilient soft material such as silicone or polyurethane. The resilient tines **300** allow the lead **70** to be delivered via a tubular sheath or trocar **304** tunneled to the target sensing site, wherein the tines **300** assume a first collapsed delivery configuration and a second expanded deployed configuration. As seen in FIG. **31**B, the tubular sheath or trocar **304** may be initially tunneled to the target site using an obtruator **306** with a blunt dissection tip **308**. After the distal end of the tubular sheath **304** has been tunneled into position by blunt dissection using the obtruator **306**, the obtruator **306** may be removed proximally from the sheath **304** and the lead **70** with collapsible tines **300** may be inserted therein. As seen in FIG. **31**C, when the distal end of the lead **70** is in the desired position, the sheath **304** may be proximally retracted to deploy the tines **300** to engage the muscle fascia and adjacent subcutaneous tissue, thus anchoring the lead **70** in place.

[0115] With reference to FIGS. **32**A and **32**B, an alternative deployable fixation embodiment is shown schematically. In this embodiment, self-expanding tines **310** are held in a collapsed configuration by retention wire **312** disposed in the lumen of the lead body **72** as shown in FIG. **32**A. Each of the tines **310** includes a hole **314** through which the retention wire **312** passes to hold the tines **310** in a first collapsed delivery configuration as shown In FIG. **32**A, and proximal withdrawal of the retention wire **314** releases the resilient tines **310** to a second expanded deployed configuration as shown in FIG. **32**B. The lead **70** may be tunneled to the desired target site with the tines **310** in the collapsed configuration. Once in position, the wire **312** may be pulled proximally to release the tines **310** and secure the lead **70** to the underlying muscle fascia and adjacent subcutaneous tissue to establish fixation thereof.

[0116] With reference to FIGS. **33**A and **33**B, another alternative deployable fixation embodiment is shown schematically. In this embodiment, self-expanding structures such as one or more resilient protrusions **320** and/or a resilient mesh **325** may be incorporated (either alone or in combination) into the distal end of the lead **70**. By way of example, not limitation, resilient protrusions **320** may comprise silicone or polyurethane loops and resilient mesh **325** may comprise a polyester fabric connected to or formed integrally with the lead body **72**. Both the resilient protrusions **320** and the resilient mesh **325** may be delivered in a collapsed delivery configuration inside tubular sheath **304** as shown in FIG. **33**A, and deployed at the desired target site by proximal retraction of the sheath **304** to release the self-expanding structures **320**/**325** to an expanded deployed configuration as shown in FIG. **33**B. Both the resilient protrusions **320** and the resilient mesh **325** engage the underlying muscle fascia through tissue encapsulation and adjacent subcutaneous tissues to provide fixation of the lead **70** thereto.

[0117] Other fixation embodiments may be used as well. For example, the fixation element may engage the muscle fascia and adjacent subcutaneous tissues or may be embedded therein. To this end, the electrodes may alternatively comprise intramuscular electrodes such as barbs or helical screws.

[0118] Description of Respiration Sensing Electrode Alternatives

[0119] A description of the various alternatives in number, spacing, anatomical location and function of the impedance electrodes follows. Generally, in each of the following embodiments, the respiration sensing lead includes a lead body and a plurality of respiration sensors comprising ring electrodes for sensing bio-impedance. The lead body may include a plurality of insulated conductors disposed therein, with one conductor provided for each ring electrode requiring independent connection and/or control. The impedance electrodes may comprise current emitting electrodes and voltage sensing electrodes for detecting respiration by changes in bio-impedance.

[0120] With reference to FIG. **34**, the distal portion of a respiration sensing lead **70** is shown by way of example, not limitation. The respiration sensing lead **70** includes a lead body **72** with a proximal connector and a plurality of distal impedance electrodes **74**. In this example, the lead body **72** and electrodes **74** are cylindrical with a diameter of 0.050 inches. The distal current-carrying electrode **74**A may be 5 mm long and may be separated from the voltage-sensing electrode **74**B by 15 mm. The distal voltage sensing electrode may be 5 mm long and may be separated from the proximal combination current-carrying voltage-sensing electrode **74**C by 100 mm. The proximal electrode **74**C may be 10 mm long. The proximal portion of the lead **70** is not shown, but would be connected to the INS (not shown) as described previously. The lead body incorporates a plurality of insulated electrical conductors (not shown), each of which correspond to an electrode **74**A-**74**C. The electrodes and conductors may be made of an alloy of platinum-iridium. The lead body **72** may comprise a tubular extrusion of polyurethane, silicone, or a co-extrusion of polyurethane over silicone. The conductors may be formed of multi-filar wire coiled to provide extensibility for comfort and durability under high-cycle fatigue.

[0121] With reference to FIGS. **35**A-**35**E, the position of the electrodes **74** may be characterized in terms of bio-impedance or bio-Z vectors. The bio-Z vector may be defined by the locations of the voltage-sensing electrodes (labeled V_1 & V_2). The voltage-sensing electrodes may be located on either side of the current-carrying electrodes (labeled I_1 & I_2). For example, it is possible to locate either one or both of the voltage-sensing electrodes between the current-carrying electrodes as shown in FIG. **35**A (4-wire configuration (I_1–V_1–V_2–I_2)), and it is possible to locate either one or both of the current-carrying electrodes between the voltage-sensing electrodes as shown in FIG. **35**B (inverted 4-wire configuration (V_1–I_1–I_2–V_2)). While at least two separate electrodes (I_1 & I_2) are required to carry current and at least two separate electrodes (V_1 & V_2) are required to measure voltage, it is possible to combine the current carrying and voltage sensing functions in a common electrode. Examples of combining voltage sensing and current carrying electrodes are shown in FIGS. **35**C-**35**E. FIG. **35**C (2-wire configuration (I_1V_1–I_2V_2)) shows combination electrode I_1V_1 and I_2V_2 where each of these electrodes is used to carry current and sense voltage. FIGS. **35**D (3-wire configuration (I_1–V_1–I_2V_2)) and **35**E (inverted 3-wire configuration (V_1–I_1–I_2V_2)) show combination electrode I_2V_2 which is used to carry current and sense voltage.

[0122] With reference to FIG. **36**, insulative material such as strips **73** may cover one side of one or more electrodes **74**A-**74**D to provide directional current-carrying and/or voltage-sensing. The insulative snips may comprise a polymeric coating (e.g., adhesive) and may be arranged to face outward (toward the dermis) such that the exposed conductive side of each electrode **74** faces inward (toward the muscle fascia and thoracic cavity). Other examples of directional electrodes would be substantially two-dimensional electrodes such as discs or paddles which are conductive on only one side.

Another example of a directional electrode would be a substantially cylindrical electrode which is held in a particular orientation by sutures or sutured wings. Another example of a directional electrode would be an electrode on the face of the implanted pulse generator. It would likely be desirable for the pulse generator to have a non-conductive surface surrounding the location of the electrode.

[0123] In addition to the cylindrical electrodes shown, other electrode configurations are possible as well. For example, the electrodes may be bi-directional with one planar electrode surface separated from another planar electrode surface by insulative material. Alternatively or in combination, circular hoop electrodes may be placed concentrically on a planar insulative surface. To mitigate edge effects, each electrode may comprise a center primary electrode with two secondary side electrodes separated by resistive elements and arranged in series. An alternative is to have each primary current-carrying electrode connected by a resistive element to a single secondary side electrode. The conductive housing of the INS **50** may serve as an current-carrying electrode or voltage-sensing electrode. Alternatively or in addition, an electrode may be mounted to the housing of the INS **50**.

[0124] Because bio-impedance has both a real and imaginary component, it is possible to measure the bio-Z phase as well as magnitude. It may be preferable to extract both magnitude and phase information from the bio-Z measurement because the movement of the lung-diaphragm-liver interface causes a significant change in the phase angle of the measured impedance. This may be valuable because motion artifacts of other tissue have less impact on the bio-Z phase angle than they do on the bio-Z magnitude. This means the bio-Z phase angle is a relatively robust measure of diaphragm movement even during motion artifacts.

[0125] An example of a bio-Z signal source is a modulated constant-current pulse train. The modulation may be such that it does not interfere with the stimulation signal. For example, if the stimulation signal is 30 Hz, the bio-Z signal source signal may be modulated at 30 Hz such that bio-Z and stimulation do not occur simultaneously. The pulses in the pulse train may have a pulse width between 1 uS to 1 mS, such as 10 uS. The pulses may be separated by a period of time roughly equal to the pulse width (i.e., on-time of the pulses). The number of pulses in a train may be determined by a trade-off between signal-to-noise and power consumption. For example, no more than 100 pulses may be necessary in any given pulse train. The magnitude of current delivered during the pulse on-time may be between 10 uA and 500 uA, such as 50 uA.

[0126] Other wave forms of bio-Z source signal may be used, including, without limitation, pulse, pulse train, biphasic pulse, biphasic pulse train, sinusoidal, sinusoidal w/ramping, square wave, and square w/ramping. The bio-Z source signal may be constant current or non-constant current, such as a voltage source, for example. If a non-constant current source is used, the delivered current may be monitored to calculate the impedance value. The current-carrying electrodes may have a single current source, a split-current source (one current source split between two or more current-carrying electrodes), or a current mirror source (one current source that maintains set current levels to two or more current-carrying electrodes). Different characteristics of the sensed signal may be measured including, without limitation, magnitude, phase shift of sensed voltage relative to the current source signal, and multi-frequency magnitude and/or phase shift of the sensed signal. Multi-frequency information may be obtained by applying multiple signal sources at different frequencies or a single signal source which contains two or more frequency components. One example of a single multi-frequency source signal is a square wave current pulse. The resultant voltage waveform would contain the same frequency components as the square wave current pulse which would allow extraction of Bio-Z data for more than a single frequency.

[0127] With reference to FIG. **37**, the bio-Z vector may be oriented with regard to the anatomy in a number of different ways. For example, using the electrode arrangement illustrated in FIG. **34** and the anatomical illustration in FIG. **37**, the bio-Z vector may be arranged such that the proximal combination electrode is located just to the right of and above the xiphoid below the pectoral muscle between the 5^{th} and 6^{th} ribs and the distal current-carrying electrode is located mid-lateral between the 7^{th} and 8^{th} ribs, with the distal voltage-sensing electrode positioned between the 6^{th} and 7^{th} ribs 10 mm proximal of the distal current-carrying electrode. This arrangement places the electrodes along the interface between the right lung, diaphragm and liver on the right side of the thoracic cavity. The lung-diaphragm-liver interface moves relative to the bio-Z vector with every respiratory cycle. Because the lung has relatively high impedance when inflated and the liver has relatively low impedance due to the conductivity of blood therein, this bio-Z vector arrangement across the lung-diaphragm-liver interface provides for a strong respiratory signal that is indicative of changes between inspiration and expiration. In addition, because the heart is situated more on the left side, positioning the bio-Z vector on the right side reduces cardiac artifact. The net result is a bio-Z vector that provides an excellent signal-to-noise ratio.

[0128] A variety of different bio-Z vector orientations relative to the anatomy may be employed. Generally, bio-Z vectors for monitoring respiration may be located on the thorax. However, bio-Z electrodes located in the head and neck may also be used to define respiratory bio-Z vectors. By way of example, not limitation, the bio-Z vector may be arranged transthoracically (e.g., bilaterally across the thorax), anteriorly on the thorax (e.g., bilaterally across the thoracic midline), across the lung-diaphragm-liver interface, perpendicular to intercostal muscles, between adjacent ribs, etc. A single bio-Z vector may be used, or multiple independent vectors may be used, potentially necessitating multiple sensing leads. One or more bio-Z sub-vectors within a given bio-Z vector may be used as well.

[0129] With reference to FIGS. **38**A-**38**C, thoracic locations defining examples of bio-Z vectors are shown schematically. FIG. **38**A is a frontal view of the thorax, FIG. **38**B is a right-side view of the thorax, and FIG. **38**C is a left-side view of the thorax. In each of FIGS. **38**A-**38**C, the outline of the lungs and upper profile of the diaphragm are shown. As mentioned previously, a bio-Z vector may be defined by the locations of the voltage-sensing electrodes. Thus, FIGS. **38**A-**38**C show locations for voltage sensing electrodes which would define the bio-Z vector.

[0130] By way of example, not limitation, the following bio-Z vectors may be effective for monitoring respiration and/or for measuring artifacts for subsequent removal of the artifact from the respiration signal. Vector C-G is across the upper left and upper right lobes of the lungs, and provides a good signal of ribcage expansion with moderate cardiac artifact. Vector D-F is a short-path version of C-G that provides a

good respiratory signature largely correlated with ribcage expression, with less cardiac artifact than C-G, but may be sensitive to movement of arms due to location on pectoral muscles. Vector C-D is a short-path ipsilateral vector of the upper right lung that may be sensitive to arm movement but has less cardiac artifact. Vector B-H is a transverse vector of thoracic cavity that captures the bulk of the lungs and diaphragm movement, but may have relatively large cardiac artifact. Vector A-E ipsilateral vector across the lung-diaphragm-liver interface. Because the liver is higher in conductivity and has a different impedance phase angle than the lung, vector A-E**1** yields a good signal on both bio-Z magnitude and phase with limited cardiac artifact. Vector B-K is an ipsilateral vector across the lung-diaphragm-liver interface that is substantially between a common set of ribs with a current path that is mostly perpendicular to the intercostal muscles. Because resistivity of muscle is much higher perpendicular to the muscle direction than parallel, vector B-K reduces current-shunting through the muscle which otherwise detracts from the signal of the lung-diaphragm-liver interface. Vector A-K is an ipsilateral vector across the lung-diaphragm-liver interface similar to vector A-E**1** but is more sensitive to movement of the lung-diaphragm-liver interface than to changes in resistivity of the lung-diaphragm-liver interface due to inspired air volume and is thus a good indicator of diaphragm movement. Vector B-E**1** is a vector across the middle and lower right lung and is good for detecting diaphragm movement with little cardiac artifact. Vector C-E**1** is a vector across the upper and middle right lung and is also good for detecting diaphragm movement with little cardiac artifact. Vector D-E**1** is a vector across the upper right lung with little cardiac artifact Vector A-D is an ipsilateral across a substantial portion of the right lung and diaphragm with little cardiac artifact, but may be susceptible to motion artifact due to arm movement. Vector E**1**-E**2** is a vector across the heart and provides a good cardiac signal that may be used for removing cardiac artifact from a respiratory signal. Vector E**2**-J is a vector across the lung-diaphragm-stomach interface that provides a good measure of diaphragm movement using bio-Z phase vs. magnitude because the stomach has almost no capacitive component and generally low conductivity.

[0131] The respiratory bio-Z signal is partly due to the resistivity change which occurs when air infuses lung tissue, partly due to the relative movement of electrodes as the rib cage expands, and partly due to the displacement of other body fluids, tissue and organs as the lungs move along with the ribcage and diaphragm. As described above, each vector measures certain of these changes to different extents. It may be desirable, therefore, to combine vectors which have complementary information or even redundant information to improve the respiratory information of the bio-Z signal. To this end, multiple vectors may be used. For example, one vector may be used to sense changes in the lung-diaphragm-liver interface and a second vector may be used to detect changes (e.g., expansion, contraction) of the lung(s). Examples of the former include A-K, B-K, A-E**1**, B-E**1**, and A-B. Examples of the later include D-F, B-D, C-G, D-E**1**, and C-E**1**. Note that some vector combinations which share a common vector endpoint such as A-E**1**, D-E**1** and B-E**1**, B-D may use a common electrode which would simplify the respiratory sensing lead or leads.

[0132] An advantage of using the lung-diaphragm-liver interface vector is that it provides a robust signal indicative of the movement of the diaphragm throughout the respiratory cycle. The liver is almost two times more electrically conductive than lung tissue so a relatively large bio-Z signal can be obtained by monitoring the movement of the lung-diaphragm-liver interface. Because the liver functions to filter all the blood in the body, the liver is nearly completely infused with blood. This helps to dampen out the cardiac artifact associated with the pulsatile flow of the circulatory system. Another advantage of this location is that vectors can be selected which avoid significant current path through the heart or major arteries which will help reduce cardiac artifact.

[0133] It is worth noting that diaphragm movement is not necessarily synchronous with inspiration or expiration. Diaphragm movement typically causes and therefore precedes inspiration and expiration. Respiratory mechanics do allow for paradoxical motion of the ribcage and diaphragm, so diaphragm movement is not necessarily coincident with inspiration. During REM sleep, the diaphragm is the dominant respiratory driver and paradoxical motion of the ribs and diaphragm can be problematic, especially if movement of the ribcage is being relied upon as an inspiratory indicator. Monitoring the diaphragm for pre-inspiratory movement becomes especially valuable under these circumstances. Bio-Z monitoring of the diaphragm can be used as a more sophisticated indicator of impending inspiration rather than the antiquated approach of desperately trying to identify and respond to inspiration in pseudo-real time based on sensors which are responding to characteristics of inspiration.

[0134] For purposes of monitoring respiration, it is desirable to minimize shunting of the electrical current through tissues which are not of interest. Shunting may result in at least two problems: reduced signal from the lungs; and increased chance of artifacts from the shunted current path. Skeletal muscle has non-isotropic conductivity. The muscle's transverse resistivity (1600 ohm-cm) is more than 5 times its longitudinal resistivity (300 ohm-cm). In order to minimize the adverse effect of shunting current, it is desirable to select bio-Z sensing vectors which are perpendicular to muscle structure if possible. One such example is to locate two or more electrodes of a bio-Z sensing array substantially aligned with the ribs because the intercostal muscles are substantially perpendicular to the ribs.

[0135] Description of Respiration Signal Processing

[0136] With reference to FIG. **39**, the neurostimulation system described herein may operate in a closed-loop process **400** wherein stimulation of the targeted nerve may be delivered as a function of a sensed feedback parameter (e.g., respiration). For example, stimulation of the hypoglossal nerve may be triggered to occur during the inspiratory phase of respiration. Alternatively, the neurostimulation system described herein may operate in an open-loop process wherein stimulation is delivered as a function of preset conditions (e.g., historical average of sleeping respiratory rate).

[0137] With continued reference to FIG. **39**, the closed-loop process **400** may involve a number of generalized steps to condition the sensed feedback parameter (e.g., bio-Z) into a useable trigger signal for stimulation. For example, the closed-loop process **400** may include the initial step of sensing respiration **350** using bio-Z, for example, and optionally sensing other parameters **360** indicative of respiration or other physiologic process. The sensed signal indicative of respiration (or other parameter) may be signal processed **370** to derive a usable signal and desired fiducials. A trigger algorithm **380** may then be applied to the processed signal to control delivery of the stimulation signal **390**.

[0138] With reference to FIG. **40**, the signal processing step **370** may include general signal amplification and noise filtering **372**. The step of amplification and filtering **372** may include band pass filtering to remove DC offset, for example. The respiratory waveform may then be processed to remove specific noise artifacts **374** such as cardiac noise, motion noise, etc. A clean respiratory waveform may then be extracted **376** along with other waveforms indicative of specific events such as obstructive sleep apnea (OSA), central sleep apnea (CSA), hypopnea, sleep stage, etc. Specific fiducial points may then be extracted and identified (e.g., type, time, and value).

[0139] The step of removing specific noise artifacts **374** may be performed in a number of different ways. However, before signal processing **374**, both cardiac and motion noise artifact may be mitigated. For example, both cardiac and motion noise artifact may be mitigated prior to signal processing **374** by selection of bio-Z vectors that are less susceptible to noise (motion and/or cardiac) as described previously. In addition, motion artifact may be mitigated before signal processing **374** by minimizing movement of the sensing lead and electrodes relative to the body using anchoring techniques described elsewhere herein. Furthermore, motion artifact may be mitigated prior to signal processing **374** by minimizing relative movement between the current-carrying electrodes and the voltage-sensing electrodes, such as by using combined current-carrying and voltage-sensing electrodes.

[0140] After cardiac and motion artifact has been mitigated using the pre-signal processing techniques described above, both cardiac and motion artifact may be removed by signal processing **374**.

[0141] For example, the signal processing step **374** may involve the use of a low pass filter (e.g., less than 1 Hz) to remove cardiac frequency noise components which typically occur at 0.5 to 2.0 Hz, whereas resting respiration frequency typically occurs below 1.0 Hz.

[0142] Alternatively, the signal processing step **374** may involve the use of a band pass or high pass filter (e.g., greater than 1 Hz) to obtain a cardiac sync signal to enable removal of the cardiac noise from the bio-Z signal in real time using an adaptive filter, for example. Adaptive filters enable removal of noise from a signal in real time, and an example of an adaptive filter is illustrated in FIG. **41**. To remove cardiac artifact from the bio-Z signal which contains both cardiac noise n(k) and respiratory information s(k), a signal n'(k) that represents cardiac noise is input to the adaptive filter and the adaptive filter adjusts its coefficients to reduce the value of the difference between y(k) and d(k), removing the noise and resulting in a clean signal in e(k). Notice that in this application, the error signal actually converges to the input data signal, rather than converging to zero.

[0143] Another signal processing technique to remove cardiac noise is to combine signals from two or more bio-Z vectors wherein respiration is the predominate signal with some cardiac noise. This may also be used to reduce motion artifact and other asynchronous noise. Each of the two or more signals from different bio-Z vectors may be weighted prior to combining them into a resultant signal Vw(i). If it is assumed that (a) the respiratory bio-impedance is the largest component in each measured vector, (b) the non-respiratory signal components in one vector are substantially independent of the non-respiratory components in the other vector, and (c) the ratio of the non-respiratory component to the respiratory components in one vector is substantially equal to the same ratio in the other vector, then a simple weighting scheme may be used wherein each signal is divided by it's historic peak-to-peak magnitude and the results are added. For example, if M_A=historical average peak-to-peak magnitude of signal from vector A, M_B=historical average peak-to-peak magnitude of signal from vector B, $V_A(i)$=data point (i) from vector A, $V_B(\ )$=data point (i) from vector B, then the resultant signal $V_W(i)$ (i.e., weighted average of A & B for data point (i)) may be expressed as $V_W(i)=V_A(i)/M_A+V_B(i)\ M_B$.

[0144] Yet another signal processing technique for removing cardiac noise is to subtract a first signal that is predominantly respiration from a second signal that is predominantly cardiac. For example, the first signal may be from a predominantly respiratory bio-Z vector (e.g., vector B-H) with some cardiac noise, and the second signal may be from a predominantly cardiac bio-Z vector (e.g., vector E**1**-E**2**) with some respiration signal. Each of the two signals from the different bio-Z vectors may be weighted prior to subtracting them. The appropriate weighting may be determined, for example, by calculating the power density spectra in the range of 2-4 Hz for a range of weighted differences across at least several respiratory cycles. A minimum will occur in the power density spectra for the weighted averages which are sufficiently optimal.

[0145] Motion artifact may be removed by signal processing **374** as well. Motion artifact may be identified and rejected using signal processing techniques such as monitoring voltage magnitude, testing the correlation of magnitude and phase, and/or testing correlation at two or more frequencies. Motion artifacts may cause a large change in measured bio-impedance. A typical feature of motion artifacts is that the voltage swings are much larger than respiration. Another feature is that the voltage changes are highly erratic. Using these characteristics, which will be described in more detail below, motion artifact may be removed from the respiration signal.

[0146] The step of extracting waveforms indicative of respiration and other events **374** may be better explained with reference to FIGS. **42-46** which schematically illustrate various representative unfiltered bio-Z signals. FIG. **42** schematically illustrates a bio-Z signal **420** with representative signatures indicative normal respiration (i.e., event free) during an awake period **422** and a sleeping period **424**. FIG. **43** schematically illustrates a bio-Z signal **430** with representative signatures indicative of normal respiration during sleeping periods **424** interrupted by a period of motion **432** (i.e., motion artifact). FIG. **44** schematically illustrates a bio-Z signal **440** with representative signatures indicative of normal respiration during a sleeping period **424** followed by periods of hypopnea (HYP) **442** and recovery **444**. FIG. **45** schematically illustrates a bio-Z signal **450** with representative signatures indicative of normal respiration during a sleeping period **424** followed by periods of obstructive sleep apnea (OSA) **452** and recovery **454** (which typically includes an initial gasp **456**). FIG. **46** schematically illustrates a bio-Z signal **460** with representative signatures indicative of normal respiration during a sleeping period **424** followed by periods of central sleep apnea (CSA) **462** (which typically includes a cessation in breathing **468**) and recovery **464**.

[0147] The step of extracting **374** waveform data indicative of an awake period **422** vs. a sleep period **424** from a bio-Z signal **420** may be explained in more detail with reference to

FIG. **42**. In addition, the step of filtering **372** waveform data indicative of motion **432** from a bio-Z signal **430** may be explained in more detail with reference to FIG. **43**. One way to determine if a person is awake or moving is to monitor the coefficient of variation (CV) of sequential peak-to-peak (PP) magnitudes over a given period of time. CV is calculated by taking the standard deviation (or a similar measure of variation) of the difference between sequential PP magnitudes and dividing it by the average (or a similar statistic) of the PP magnitudes. N is the number of respiratory cycles which occur in the selected period of time.

[0148] The CV may be calculated as follows:

$$CV = \frac{sd(dPP)}{\overline{PP}}$$

[0149] Where:

$$sd(dPP) = \sqrt{\frac{\sum_{i=1}^{N}(dPP_i - \overline{dPP})}{(N-1)}}$$

$$\overline{dPP} = \frac{\sum_{i=1}^{N}(dPP_i)}{(N)}$$

$$dPP_i = PP_{i+1} - PP_i$$

$$\overline{PP} = \frac{\sum_{i=1}^{N}(PP_i)}{(N)}$$

[0150] Generally, if the CV is greater than 0.20 over a one minute period then person is awake. Also generally, if the CV is less than 0.20 over a one-minute period then person is asleep. These events may be flagged for the step of fiducial extraction **378** wherein data (e.g., event duration, CV, PP range, PPmin, PPmax, etc.) may be time stamped and stored with an event identifier. If CV is greater than 1.00 over a 20 second period then body movement is affecting the bio-Z signal. By way of example, not limitation, if body movement is detected, then (a) stimulation may be delivered in an open loop fashion (e.g., based on historical respiratory data); (b) stimulation may be delivered constantly the same or lower level; or (c) stimulation may be turned off during the period of movement. The selected stimulation response to detected movement may be preset by the physician programmer or by the patient control device. Other stimulation responses may be employed as will be described hereinafter.

[0151] In each of FIGS. **44-46**, maximum and minimum peak-to-pea magnitudes (PPmax and PPmin) may be compared to distinguish hypopnea (HYP), obstructive sleep apnea (OSA), and central sleep apnea (CSA) events. Generally, PP values may be compared within a window defined by the event (HYP, OSA, CSA) and the recovery period thereafter. Also generally, the window in which PP values are taken excludes transitional events (e.g., gasp **456**, **466**). As a general alternative, peak-to-peak phases may be used instead of peak-to-peak magnitude. The hypopnea and apnea events may be flagged for the step of fiducial extraction **378** wherein data (e.g., event duration, CV, PP range, PPmin, PPmax, etc.) may be time stamped and stored with an event identifier.

[0152] A typical indication of hypopnea (HYP) and apnea (OSA, CSA) events is a recurrent event followed by a recovery. The period (T) of each event (where PP oscillates between PPmax and PPmin and back to PPmax) may be about 15 to 120 seconds, depending on the individual. The largest PP values observed during hypopneas and apneas are usually between 2 and 5 times larger than those observed during regular breathing **424** during sleep. The ratio of the PPmax to PPmin during recurrent hypopnea and apnea events is about 2 or more. During the event and recovery periods (excluding transitional events), PP values of adjacent respiratory cycles do not typically change abruptly and it is rare for the change in PP amplitude to be more than 50% of PPmax. One exception to this observation is that some people gasp **456**, **466** (i.e., transitional event) as they recover from a CSA or OSA event.

[0153] The ratio of successive PP magnitudes during normal (non-event) sleep **424** is mostly random. The ratio of successive PP magnitudes during apnea and hypopnea events will tend to be a non-random sequence due to the oscillatory pattern of the PP values. Recurrent apneas and hypopneas may be diagnosed by applying a statistical test to the sequence of successive PP ratios.

[0154] The step of extracting **374** waveform data indicative of an hypopnea event **442** from a bio-Z signal **440** may be explained in more detail with reference to FIG. **44**. The ratio of PPmax to PPmin during recurrent hypopneas is typically between 2 and 5. This is in contrast to CSA's which have very small PPmin due to the complete cessation of breathing. This results in CSA's having PPmax to PPmin ratios larger than 5. Accordingly, hypopnea events may be detected, identified and flagged for the step of fiducial extraction **378** wherein data (e.g., event duration, CV, PP range, PPmin, PPmax, etc.) may be time stamped and stored with an event identifier.

[0155] The step of extracting **374** waveform data indicative of an OSA event **452** from a bio-Z signal **450** may be explained in more detail with reference to FIG. **45**. The sharp change **456** in the bio-Z respiratory magnitude due to OSA is typically in the range of 1 to 4 times the magnitude of the peak-to-peak respiratory cycle magnitude. The sharp change **456** typically takes less than 5 seconds to occur. OSA tends to occur in a recurring sequence where the period (T) between sequential events is between 15 and 120 seconds. A one-minute period is commonly observed. According to these characteristics, OSA events may be detected, identified and flagged for the step of fiducial extraction **378** wherein data (e.g., event duration, CV, PP range, PPmin, PPmax, etc.) may be time stamped and stored with an event identifier.

[0156] The step of extracting **374** waveform data indicative of a CSA event **462** from a bio-Z signal **460** may be explained in more detail with reference to FIG. **46**. The behavior of the Bio-Z signal throughout recurrent CSA events differ from other hypopnea and OSA in three ways. First, during CSA there is complete cessation of respiratory activity which results in a flat Bio-Z signal. This means the ratio of PPmax to PPmin is typically greater than 5 during recurrent CSA events. The duration of the estimated respiratory cycle may also be used to distinguish between CSA from OSA and hypopnea. The lack of respiratory activity during CSA results in an inflated estimate for the respiratory cycle period. The PP typically does not vary by more than 50% for successive cycles. The respiratory cycle duration during a CSA event is more than twice as long as the duration of the respiratory

cycles preceding the CSA event Second, during CSA the Bio-Z magnitude will drift outside the PP magnitude range observed during respiration. It has been observed that with the onset of central sleep apnea (CSA) the magnitude and phase of the Bio-Z signal settle to a steady-state value outside the peak-to-peak range observed during the normal respiratory cycle during sleep. Third, upon arousal from CSA a person will typically gasp. This gasp results in a large PP. The PP of the first respiratory cycle following the CSA event and the PP observed during the CSA (which is essentially noise) will exceed 50% of PPmax.

[0157] With continued reference to FIG. **46**, the flat portions **468** of the data traces are periods of respiratory cessation. Upon arousal the subject gasps **466** and the raw bio-Z signal resumes cyclic oscillation above the static impedance level observed during CSA. According to these characteristics, CSA events may be detected, identified and flagged for the step of fiducial extraction **378** wherein data (e.g., event duration, CV, PP range, PPmin, PPmax, etc.) may be time stamped and stored with an event identifier.

[0158] The step of extracting **374** waveform data indicative of sleep stage (e.g., rapid eye movement (REM) sleep vs. no-rapid eye movement (NREM) sleep) may be performed by comparing the phase difference between a first vector and a second vector wherein the first bio-Z vector is along the lung-diaphragm-liver interface (e.g., vector A-K or vector B-K) and the second bio-Z vector is about the lung(s). Examples of the first bio-Z vector include A-K, B-K, A-E**1**, B-E**1**, and A-B. Examples of the second bio-Z vector include D-F, B-D, C-G, D-E**1**, and C-E**1**. Note that some vector combinations which share a common vector endpoint such as A-E**1**, D-E**1** and B-E**1**, B-D may use a common electrode and to simplify the respiratory sensing lead or leads. Typically, during NREM sleep, the two vectors are substantially in phase. During REM sleep, the diaphragm is the primary respiratory driver and a common consequence is paradoxical motion of the ribcage and diaphragm (i.e., the two vectors are substantially out of phase). This characteristic would allow for an effective monitor of a person's ability to reach REM sleep. Accordingly, REM and NREM sleep stages may be detected, identified, and flagged for the step of fiducial extraction **378** wherein characteristic data (e.g., event duration, phase, etc.) may be time stamped and stored with an event identifier.

[0159] An alternative method of detecting an OSA event is to make use of a split current electrode arrangement as shown in FIG. **47** which shows the positions of three electrodes on the subject. Electrode A may be above the zyphoid, electrode B may be just above the belly button, and electrode C may be on the back a couple of inches below electrode A. Electrodes A and B are connected to a common constant current source through resistors R**1** and R**2**. The voltage measured across the current source is a measure of the bio-impedance during normal respiration. The voltage across R**1** is an indicator of the paradoxical motion associated with apnea. An unbalanced current split between R**1** and R**2** resulting in large bio-Z voltage swings is indicative of OSA. During normal respiration or even very deep breaths the is almost no effect on the apnea detection channel. Accordingly, OSA events may be detected, identified, and flagged for the step of fiducial extraction **378** wherein characteristic data (e.g., event duration, voltage swing magnitude, etc.) may be time stamped and stored with an event identifier.

[0160] Generally, the extracted **378** waveform and event data may be used for therapy tracking, for stimulus titration, and/or for closed loop therapy control. For example, data indicative of apneas and hypopneas (or other events) may be stored by the INS **50** and/or telemetered to the patient controlled **40**. The data may be subsequently transmitted or downloaded to the physician programmer **30**. The data may be used to determine therapeutic efficacy (e.g., apnea hypopnea index, amount of REM sleep, etc.) and/or to titrate stimulus parameters using the physician programmer **30**. The data may also be used to control stimulus in a closed loop fashion by, for example, increasing stimulus intensity during periods of increased apnea and hypopnea occurrence or decreasing stimulus intensity during periods of decreased apnea and hypopnea occurrence (which may be observed if a muscle conditioning effect is seen with chronic use). Further, the data may be used to turn stimulus on (e.g., when apnea or hypopnea events start occurring or when motion artifact is absent) or to turn stimulus off (e.g., when no apnea or hypopnea events are occurring over a present time period or when motion artifact is predominant).

[0161] Description of Stimulus Trigger Algorithms

[0162] As mentioned previously with reference to FIG. **39**, the neurostimulation system described herein may operate in a closed-loop process wherein the step of delivering stimulation **390** to the targeted nerve may be a function of a sensed feedback parameter (e.g., respiration). For example, stimulation of the hypoglossal nerve may be triggered to occur during the inspiratory phase of respiration. In a health human subject, the hypoglossal nerve is triggered about 300 mS before inspiration. Accordingly, a predictive algorithm may be used to predict the inspiratory phase, and deliver stimulation accordingly. FIG. **48** schematically illustrates a system **480** including devices, data and processes for implementing a self-adjusting predictive trigger algorithm.

[0163] The system components **482** involved in implementing the algorithm may include the physician programmer (or patient controller), INS and associated device memory, and the respiratory sensor(s). The sensors and device memory are the sources of real-time data and historical fiducial data which the current algorithm uses to generate a stimulation trigger signal. The data **484** utilized in implementing the algorithm may include patient specific data derived from a sleep study (i.e., PSG data), data from titrating the system post implantation, and historic and real-time respiratory data including respiratory and event fiducials. The processes **486** utilized in implementing the algorithm may include providing a default algorithm pre-programmed in the INS, patient controller or physician programmer, modifying the default algorithm, and deriving a current algorithm used to generate a trigger signal **488**.

[0164] More specifically, the processes **486** utilized in implementing a predictive trigger algorithm may involve several sub-steps. First, a default algorithm may be provided to predict onset of inspiration from fiducial data Selecting an appropriate default algorithm may depend on identifying the simplest and most robust fiducial data subsets which allow effective prediction of onset. It also may depend on a reliable means of modifying the algorithm for optimal performance. Second, modification of the default algorithm may require a reference datum. The reference datum may be the estimated onset for past respiratory cycles. It is therefore useful to precisely estimate inspiratory onset for previous respiratory cycles from historical fiducial data. This estimation of

inspiratory onset for previous respiratory cycles may be specific to person, sensor location, sleep stage, sleep position, or a variety of other factors. Third, the current algorithm may be derived from real-time and historical data to yield a stimulation trigger signal **488**.

[0165] With reference to FIG. **48**, a self adjusting predictive algorithm may be implemented in the following manner.

[0166] The Programmer block is illustrates means by which PSG-derived data may be uploaded into the device.

[0167] The Sensors and Device Memory block includes the sources of real-time data and historical fiducial variables which the current algorithm uses to generate a stimulation trigger signal.

[0168] The Patient PSG Titration Data block includes conventional polysomnographic (PSG) data obtained in a sleep study. A self-adjusting predictive algorithm utilizes a reference datum to which the algorithm can be adjusted. Onset may be defined as onset of inspiration as measured by airflow or pressure sensor used in a sleep study, for example. Estimated Onset may be defined as an estimate of Onset calculated solely from information available from the device sensors and memory. To enable the predictive algorithm to be self-adjusting, either Onset or Estimated Onset data is used. During actual use, the implanted device will typically not have access to Onset as that would require output from an airflow sensor. The device then may rely on an estimate of Onset or Estimated Onset. The calibration of Estimated Onset to Onset may be based on PSG data collected during a sleep study. The calibration may be unique to a person and/or sleep stage and/or sleep position and/or respiratory pattern.

[0169] The Historical Fiducial Variables block represents the Historical Fiducial Variables (or data) which have been extracted from the bio-Z waveform and stored in the device memory. This block assumes that the raw sensor data has been processed and is either clean or has been flagged for cardiac, movement, apnea or other artifacts. Note that fiducial data includes fiducials, mathematical combinations of fiducials or a function of one or more fiducials such as a fuzzy logic decision matrix.

[0170] The Real-Time Data and Historical Fiducial Variables block incorporates all the information content of the Historical Fiducial Variables block and also includes real-time bio-Z data.

[0171] The Default Algorithm block represents one or more pre-set trigger algorithms pre-programmed into the INS or physician programmer. The default algorithm used at a specific point in time while delivering therapy may be selected from a library of pre-set algorithms. The selection of the algorithm can be made automatically by the INS based on: patient sleep position (position sensor), heart rate (detectable through the impedance measuring system) or respiration rate. Clinical evidence supports that the algorithm used to predict the onset of inspiration may be dependant on sleep position, sleep state or other detectable conditions of the patient.

[0172] The Modify Algorithm block represents the process of modifying the Default Algorithm based on historical data to yield the Current Algorithm. Once the calibration of Estimated Onset to Onset is resident in the device memory it can be used to calculate Estimated Onset for past respiratory cycles from Fiducial Variables. The variable used to represent the Estimated Onset will be TEST or TEST(i) where the "i" indicates the cycle number. Note that Estimated Onset is calculated for past respiratory cycles. This means that sensor fiducial variables which either proceed or follow each Onset event may be used to calculate the Estimated Onset.

[0173] The Current Algorithm block represents the process of using the Modified Default Algorithm to predict the next inspiratory onset (Predicted Onset). The Predicted Onset for the next respiratory cycle may be calculated from real-time data and historical fiducial variables. The calculation may be based on the Modified Default Algorithm. Modification of the Modified Default Algorithm to derive the Current Algorithm may be dependent on the calibration of Estimated Onset to Onset which was input from the physician programmer and may be based on comparison of real-time bio-Z data to data collected during a PSG titration study. The Current Algorithm may use historic and/or real-time sensor fiducial variables to predict the next onset of inspiration. This predicted onset of inspiration may be referred to as Predicted Onset. The variable used to represent Predicted Onset may be TPRED or TPRED(i) where the "i" indicates the respiratory cycle.

[0174] The Stimulation Trigger Signal block represents the Current Algorithm generating a trigger signal which the device uses to trigger stimulation to the hypoglossal nerve.

[0175] FIG. **49** is a table of some (not all) examples of waveform fiducials which can be extracted from each respiratory cycle waveform. For each fiducial there is a magnitude value and a time of occurrence. Each waveform has a set of fiducials associated with it. As a result, fiducials may be stored in the device memory for any reasonable number of past respiratory cycles. The values from past respiratory cycles which are stored in device memory are referred to as Historical Fiducial Variables.

[0176] The graphs illustrated in FIG. **50** are examples of fiducials marked on bio-Z waveforms. The first of the three graphs illustrate the bio-impedance signal after it has been filtered and cleared of cardiac and motion artifacts. The first graph will be referred to as the primary signal. The second graph is the first derivative of the primary signal and the third graph is the second derivative of the primary signal. Each graph also displays a square wave signal which is derived from airflow pressure. The square wave is low during inspiration. The falling edge of the square wave is onset of inspiration.

[0177] Due to the fact that it may be difficult to identify onset of inspiration in real-time from respiratory bio-impedance, a goal is to construct an algorithm which can reliably predict onset of inspiration "T" for the next respiratory cycle from information available from the current and/or previous cycles. A reliable, distinct and known reference point occurring prior to onset of inspiration, "T", is "A", the peak of the primary signal in the current cycle. As can be seen in FIG. **50**, the upper peak of the bio-Z waveform "A" approximately corresponds to the onset of expiration "O". A dependent variable $t_{T\text{-}PK}$ is created to represent the period of time between the positive peak of the primary signal for the current cycle, t.Vmax(n), indicated by "A_n" on the graph, and onset of inspiration for the next cycle, t.onset(n+1), indicated by "T" on the graph. The variable $t_{T\text{-}PK}$ may be defined as:

$$t_{T\text{-}PK}=t.\text{onset}(n+1)-t.V\text{max}(n)$$

[0178] Note that t.Vmax could be replaced by any other suitable fiducial in defining a dependent variable for predicting onset.

[0179] A general model for a predictive algorithm may be of the following form:

[0180] $t_{T\text{-}PK}$=f(fiducials extracted from current and/or previous cycles)

[0181] A less general model would be to use a function which is a linear combination of Fiducial Variables and Real-Time Data.

[0182] The following fiducials may be both highly statistically significant and practically significant in estimating T:

[0183] t.Vmax(n)=the time where positive peak occurs for the current cycle;

[0184] t.dV.in(n)=the time of most positive 1^{st} derivative during inspiration for the current cycle; and

[0185] t.Vmax(n−1)=the time of positive peak for the previous cycle.

[0186] This model can be further simplified by combining the variables as follows:

$$\Delta t.pk(n)=t.V\max(n)-t.V\max(n-1)$$

$$\Delta t.in(n)=t.V\max(n)-t.dV.in(n)$$

[0187] Either Δt.pk(n) or Δt.in(n) is a good predictor of Onset.

[0188] The following example uses Δt.pk(n). The time from a positive peak until the next inspiration onset can be estimated by

$$T=t.V\max(n)+k0+k1*\Delta t.pk(n)$$

[0189] The coefficients k**0** and k**1** would be constantly modified by optimizing the following equation for recent historical respiratory cycles against T_{est}:

$$T_{est}=t.V\max(n)+k0+k1*\Delta t.pk(n)$$

[0190] Thus, the predictive trigger time T_{pred} may be determined by adding $t_{T\text{-}PK}$ to the time of the most recent peak (PK) of the bio-Z signal, where:

$$t_{T\text{-}PK}=k0+k1*\Delta t.pk(n)$$

[0191] The predictive equation we are proposing is based on the fact that the very most recent cycle times should be negatively weighted Regression analysis supports this approach and indicates a negative weighting is appropriate for accurate prediction of onset. Thus, predicting onset is more effective if the most recent historical cycle time is incorporated into an algorithm with a negative coefficient.

[0192] Description of External (Partially Implanted) System

[0193] With reference to FIGS. **51**A and **51**B, an example of an external neurostimulator system inductively coupled to an internal/implanted receiver is shown schematically. The system includes internal/implanted components comprising a receiver coil **910**, a stimulator lead **60** (including lead body **62**, proximal connector and distal nerve electrode **64**). Any of the stimulation lead designs and external sensor designs described in more detail herein may be employed in this generically illustrated system, with modifications to position, orientation, arrangement, integration, etc. made as dictated by the particular embodiment employed. The system also includes external components comprising a transmit coil **912** (inductively linked to receiver coil **910** when in use), an external neurostimulator or external pulse generator **920** (ENS or EPG), and one or more external respiratory sensors **916**/**918**.

[0194] As illustrated, the receiver coil **910** is implanted in a subcutaneous pocket in the pectoral region and the stimulation lead body **62** is tunneled subcutaneously along the platysma in the neck region. The nerve electrode **64** is attached to the hypoglossal nerve in the submandibular region.

[0195] The transmitter coil **912** may be held in close proximity to the receiver coil **910** by any suitable means such as an adhesive patch, a belt or strap, or an article of clothing (e.g., shirt, vest, brazier, etc.) donned by the patient. For purposes of illustration, the transmitter coil **912** is shown carried by a t-shirt **915**, which also serves to carry the ENS **920** and respiratory sensor(s) **916**, **918**. The ENS **920** may be positioned adjacent the waist or abdomen away from the ribs to avoid discomfort while sleeping. The respiratory sensor(s) **916**, **918** may be positioned as a function of the parameter being measured, and in this embodiment, the sensors are positioned to measure abdominal and thoracic/chest expansion which are indicative of respiratory effort, a surrogate measure for respiration. The external components may be interconnected by cables **914** carried by the shirt or by wireless means. The shirt may incorporate recloseable pockets for the external components and the components may be disconnected from the cables such that the reusable components may be removed from the garment which may be disposed or washed.

[0196] The transmitting coil antenna **912** and the receiving coil antenna **910** may comprise air core wire coils with matched wind diameters, number of wire turns and wire gauge. The wire coils may be disposed in a disc-shaped hermetic enclosure comprising a material that does not attenuate the inductive link, such as a polymeric or ceramic material. The transmitting coil **912** and the receiving coil **910** may be arranged in a co-axial and parallel fashion for coupling efficiency, but are shown side-by-side for sake of illustration only.

[0197] Because power is supplied to the internal components via an inductive link, the internal components may be chronically implanted without the need for replacement of an implanted battery, which would otherwise require re-operation. Examples of inductively powered implantable stimulators are described in U.S. Pat. No. 6,609,031 to Law et al., U.S. Pat. No. 4,612,934 to Borkan, and U.S. Pat. No. 3,893,463 to Williams, the entire disclosures of which are incorporated herein by reference.

[0198] With reference to FIGS. **51**C-**51**G, alternative embodiments of an external neurostimulator system inductively coupled to an internal/implanted receiver are schematically shown. These embodiments are similar to the external embodiment described above, with a few exceptions. In these embodiments, the receiver coil **910** is implanted in a positioned proximate the implanted stimulation lead body **62** and nerve electrode **64**. The receiver coil **910** may be positioned in a subcutaneous pocket on the platysma muscle under the mandible, with the lead body **62** tunneling a short distance to the nerve electrode **64** attached to the hypoglossal nerve. Also in these embodiments, the respiratory sensor(s) **916**/**918** may be integrated into the ENS **920** and attached to a conventional respiratory belt **922** to measure respiratory effort about the abdomen and/or chest. An external cable **914** connects the ENS **920** to the transmitter coil **912**.

[0199] In the embodiment of FIG. **51**D, the transmitter coil **912** is carried by an adhesive patch **924** that may be placed on the skin adjacent the receiver coil **910** under the mandible. In the embodiment of FIG. **51**E, the transmitter coil **912** is carried by an under-chin strap **926** worn by the patient to

maintain the position of the transmitter coil **912** adjacent the receiver coil **910** under the mandible. In the embodiment of FIG. **51**F, the receiver coil **910** may be positioned in a subcutaneous pocket on the platysma muscle in the neck, with the lead body **122** tunneling a slightly greater distance. The transmitter coil **912** may be carried by a neck strap **928** worn by the patient to maintain the position of the transmitter coil **912** adjacent the receiver coil **910** in the neck.

[0200] With reference to FIGS. **51**G-**51**K, additional alternative embodiments of an external neurostimulator system inductively coupled to an internal/implanted receiver are schematically shown. These embodiments are similar to the external embodiment described above, with a few exceptions. As above, the receiver coil **910** may be positioned in a subcutaneous pocket on the platysma muscle under the mandible, with the lead body **62** tunneling a short distance to the nerve electrode **64** attached to the hypoglossal nerve. However, in these embodiments, the ENS **920** (not shown) may be located remote from the patient such as on the night stand or headboard adjacent the bed. The ENS **920** may be connected via a cable **930** to a large transmitter coil **912** that is inductively coupled to the receiver coil **910**. The respiratory sensor **916** may comprise a conventional respiratory belt **922** sensor to measure respiratory effort about the abdomen and/or chest, and sensor signals may be wirelessly transmitted to the remote ENS **920**. As compared to other embodiments described above, the transmitter coil **912** is not carried by the patient, but rather resides in a proximate carrier such as a bed pillow, under a mattress, on a headboard, or in a neck pillow, for example. Because the transmitter coil **912** is not as proximate the receiver coil as in the embodiments described above, the transmitter coil may be driven by a high powered oscillator capable of generating large electromagnetic fields.

[0201] As shown in FIG. **51**H, the transmitter coil **912** may be disposed in a bed pillow **934**. As shown in FIG. **51**I, the transmitter coil **912** may comprise a series of overlapping coils disposed in a bed pillow **934** that are simultaneously driven or selectively driven to maximize energy transfer efficiency as a function of changes in body position of the patient corresponding to changes in position of the receiver coil **910**. This overlapping transmitter coil arrangement may also be applied to other embodiments such as those described previously wherein the transmitter coil is carried by an article donned by the patient. In FIG. **51**J, two or more transmitter coils **912** are carried by orthogonal plates **936** arranged as shown to create orthogonal electromagnetic fields, thereby increasing energy transfer efficiency to compensate for movement of the patient corresponding to changes in position of the receiver coil **910**. FIG. **513** also illustrates a non-contact respiratory sensor **916** arrangement as utilized for detecting sudden infant death syndrome (SIDS). As shown in FIG. **51**K, two orthogonal transmitter coils **912** are located on each side of a neck pillow **938**, which is particularly beneficial for bilateral stimulation wherein a receiver coil **910** may be located on either side of the neck.

[0202] With reference to FIGS. **51**L (front view) and **51**M (rear view), external respiratory effort sensors **916**/**918** are schematically shown incorporated into a stretchable garment **945** donned by the patient. The sensors **916**/**918** generally include one or more inductive transducers and an electronics module **942**. The inductive transducers may comprise one or more shaped (e.g., zig-zag or sinusoidal) stranded wires to accommodate stretching and may be carried by (e.g., sewn into) the garment **945** to extend around the patient's abdomen and chest, for example. As the patient breathes, the patient's chest and/or abdomen expands and contracts, thus changing the cross-sectional area of the shape (i.e., hoop) formed by the wire resulting in changes in inductance. The electronics module may include an oscillator (LC) circuit with the inductive transducer (L) comprising a part of the circuit. Changes in frequency of the oscillator correspond to changes in inductance of the shaped wires which correlate to respiratory effort. The electronics module may be integrated with an ENS (not shown) or connected to an ENS via a wired or wireless link for triggering stimulus as described previously.

[0203] The garment **945** may include features to minimize movement artifact and accommodate various body shapes. For example, the garment **945** may be form-fitting and may be sleeveless (e.g., vest) to reduce sensor artifacts due to arm movement. Further, the garment **945** may be tailored to fit over the patient's hips with a bottom elastic band which helps pull the garment down and keep the sensors **9161'918** in the proper location.

[0204] Description of a Specific External (Partially Implanted) Embodiment

[0205] With reference to FIGS. **52**A-**52**G a specific embodiment utilizing an external neurostimulator system inductively coupled to an internal/implanted receiver is schematically shown. With initial reference to FIG. **52**A, the illustrated hypoglossal nerve stimulator includes several major components, namely; an implantable electronics unit that derives power from an external power source; a stimulation delivery lead that is anchored to the nerve or adjacent to the nerve and provides electrical connection between the electronics unit and the nerve, an external (non-implanted) power transmitting device that is inductively coupled with the implant to convey a powering signal and control signals; a power source for the external device that is either small and integrated into the body-worn coil and transmitter or is wired to the transmitter and transmit induction coil and can be powered by primary or secondary batteries or can be line powered; and a respiratory sensor such as those described previously.

[0206] These components may be configured to provide immediate or delayed activation of respiration controlled stimulation. Initiation of the stimulation regimen may be by means of activation of an input switch. Visual confirmation can be by an LED that shows adequate signal coupling and that the system is operating and is or will be applying stimulation. As a means of controlling gentleness of stimulation onset and removal, either pulse width ramping of a constant amplitude stimulation signal can be commanded or amplitude of a constant pulse width stimulation signal or a combination thereof can be performed.

[0207] The electrical stimulation signal is delivered by the stimulation lead that is connected to the implanted nerve stimulator and attached to or in proximity of a nerve. The implanted electronics unit receives power through a magnetically coupled inductive link. The operating carrier frequency may be high enough to ensure that several cycles (at least 10) of the carrier comprise the output pulse. The operating frequency may be in a band of frequencies approved by governmental agencies for use with medical instruments operating at high transmitted radio frequency (RF) power (at least 100 milliwatts). For example, the operating frequency may be 1.8 MHz, but 13.56 MHz is also a good candidate since it is in the ISM (Industrial/Scientific/Medical) band. The non-implanted (external) transmitter device integrates respiration

interface, waveform generation logic and transmit power driver to drive an induction coil. The power driver generates an oscillating signal that drives the transmitter induction coil and is designed to directly drive a coil of coil reactance that is high enough or can be resonated in combination with a capacitor. Power can come from a high internal voltage that is used to directly drive the transmit induction coil or power can come from a low voltage source applied to a tap point on the induction coil.

[0208] With reference to FIGS. **52**B-**52**E, the waveform generation logic may be used to modulate the carrier in such a way that narrow gaps in the carrier correspond to narrow stimulation pulses. When stimulator pulses are not needed, interruptions to the carrier are stopped but the carrier is maintained to ensure that power is immediately available within the stimulator upon demand. Presence or absence of electrical nerve stimulation is based on respiration or surrogates thereof. The transmitted signal may comprise a carrier of about 1.8 MHz. To control the implanted electronics unit to generate individual nerve stimulation pulses, the carrier signal is interrupted. The duration of the interruption is about equal to the duration of the output stimulation pulse. The stimulation pulses may be about 110 microseconds in duration and are repeated at a rate of approximately 33 per second. In addition, multiple pulses can be transmitted to logic within the implant to control stimulation pulse amplitude, pulse width, polarity, frequency and structure if needed. Further, onset and removal of stimulation can be graded to manage patient discomfort from abruptness. Grading may comprise pulse width control, signal amplitude control or a combination thereof.

[0209] An indicator (not shown) may be used to show when the transmitter is properly positioned over the implant. The indicator may be a part of the transmitter or by way of communication with the transmitter, or a part of related patient viewable equipment. Determination of proper position may be accomplished by monitoring the transmitter power output loading relative to the unloaded power level. Alternatively, the implant receive signal level transmitted back by a transmitter within the implant may be monitored to determine proper positioning. Or, the implant receive signal level that is communicated back to the transmitter by momentarily changing the loading properties presented to the transmitter, such a shorting out the receive coil may be monitored to determine proper positioning. Such communication may be by means of modulation such as pulse presence, pulse width, pulse-to-pulse interval, multi-pulse coding.

[0210] The transmitter may be powered by an internal primary power source that is used until it is exhausted, a rechargeable power source or a power source wired to a base unit. In the case of the wired base unit, power can be supplied by any combination of battery or line power.

[0211] The respiration interface may transduce sensed respiratory activity to an on-off control signal for the transmitter. Onset of stimulation may be approximately correlated slightly in advance of inspiration and lasts through the end of inspiration, or onset may be based on anticipation of the next respiration cycle from the prior respiration cycle or cycles. The respiration sensor may comprise any one or combination of devices capable of detecting inspiration. The following are examples: one or more chest straps; an impedance sensor; an electromiographical measurement of the muscles involved with respiration; a microphone that is worn or is in proximity to the patients' face; a flow sensor; a pressure sensor in combination with a mask to measure flow; and a temperature sensor to detect the difference between cool inspired air versus warmed expired air.

[0212] The circuit illustrated in FIG. **52**F may be used for the implanted electronics unit. There are five main subsystems within the design: a receive coil, a power rectifier, a signal rectifier, an output switch and an output regulator. The signal from the inductive link is received by L**1** which is resonated in combination with C**1** and is delivered to both the power and signal rectifiers. Good coupling consistent with low transmitter coil drive occurs when the transmit coil diameter is equal to the receive coil diameter. When coil sizes are matched, coupling degrades quickly when the coil separation is about one coil diameter. A large transmit coil diameter will reduce the criticality of small coil spacing and coil-to-coil coaxial alignment for maximum signal transfer at the cost of requiring more input drive power.

[0213] The power rectifier may comprise a voltage doubler design to take maximum advantage of lower signal levels when the transmit to receive coil spacing is large. The voltage doubler operates with an input AC voltage that swing negative (below ground potential) causes D**1** to conduct and forces C**2** to the maximum negative peak potential (minus a diode drop). As the input AC voltage swings away from maximum negative, the node of C**2**, D**1**, D**2** moves from a diode drop below ground to a diode drop above ground, forward biasing diode D**2**. Further upswing of the input AC voltage causes charge accumulated on C**2** to be transferred through D**2** to C**3** and to "pump up" the voltage on C**3** on successive AC voltage cycles. To limit the voltage developed across C**3** so that an over-voltage condition will not cause damage, and Zener diode, D**3** shunts C**3**. Voltage limiting imposed by D**3** also limits the output of the signal rectifier section. The power rectifier has a long time constant, compared to the signal rectifier section, of about 10 milliseconds.

[0214] The signal rectifier section may be similar in topology to the power rectifier except that time constants are much shorter—on the order of 10 microseconds—to respond with good fidelity to drop-outs in the transmitted signal. There is an output load of 100K (R**1**) that imposes a controlled discharge time constant. Output of the signal rectifier is used to switch Q**1**, in the output switching section, on and off.

[0215] The output switching section compares the potential of C**3** to that across CS by means of the Q**1**, Q**2** combination. When there is a gap in the transmitted signal, the voltage across CS falls very rapidly in comparison with C**3**. When the voltage difference between CS and C**3** is about 1.4 volts, Q**1** and Q**2** turn on. Q**1** and Q**2** in combination form a high gain amplifier stage that provides for rapid output switching time. R**3** is intended to limit the drive current supplied to Q**2**, and R**2** aids in discharging the base of Q**2** to improve the turn-off time.

[0216] In the output regulator section, the available power rectifier voltage is usually limited by Zener diode D**3**. When the coil separation becomes suboptimal or too large the power rectifier output voltage will be come variable as will the switched voltage available at the collector of Q**2**. For proper nerve stimulation, it may be necessary to regulate the (either) high or variable available voltage to an appropriate level. An acceptable level is about 3 volts peak. A switched voltage is applied to Zener diode D**6** through emitter follower Q**3** and bias resistor R**5**. When the switched voltage rises to a level where D**6** conducts and develops about 0.6 volts across R**4** and the base-emitter junction of Q**4**, Q**4** conducts. Increased

conduction of Q4 is used to remove bias from Q3 through negative feedback. Since the level of conduction of Q4 is a very sensitive function of base to emitter voltage, Q4 provides substantial amplification of small variations in D6 current flow and therefore bias voltage level. The overall result is to regulate the bias voltage applied to Zener diode D6. Output is taken from the junction of the emitter of Q3 and D6 since that point is well regulated by the combination of Zener diode breakdown voltage combined with the amplification provided by Q4. In addition to good voltage regulation a the junction of the emitter of Q3 and D6, the output is very tolerant of load current demand since the conductivity of Q3 will be changed by shifts in the operating point of Q4. Due to amplification by Q3 and Q4, the circuit can drive a range of load resistances. Tolerable load resistances above 1000 ohms and less than 200 ohms. The regulator has the advantage of delivering only the current needed to operate the load while consuming only moderate bias current. Further, bias current is only drawn during delivery of the stimulation pulse which drops to zero when no stimulation is delivered. As a comparison, a simple series resistance biased Zener diode requires enough excess current to deliver a stimulation pulse and still maintain adequate Zener bias. As a further comparison, conventional integrated circuit regulators, such as three terminal regulators are not designed to well regulate and respond quickly to short input pulses. Experiment shows that three-terminal regulators exhibit significant output overshoot and ramp-up time upon application of an input pulse. This can be addressed by applying a constant bias to a regulator circuit or even moving the regulator before the output switching stage but this will be at the cost of constant current drain and subsequently reduced range.

[0217] The implanted electronics unit may be used to manage the loss of control and power signals. With this design, more than enough stimulation power is stored in C3 to supply multiple delivered stimulation pulses. This design is intended to ensure that the voltage drop is minimal on any individual pulse. One of the consequences is that when signal is lost, the circuit treats the condition as a commanded delivery of stimulation and will apply a single, extended duration, energy pulse until the full stored capacity of C3 is empty. An alternative method may be to use an indirect control modulation to command delivery of a nerve stimulation pulse through logic and provide for a time-out that limits pulse duration.

[0218] To stimulate tissue, a modified output stage may be used to mitigate electrode corrosion and establish balanced charging. The output stage is illustrated in FIG. **52**G and includes a capacitive coupling between the ground side of the stimulator and tissue interface in addition to a shunt from the active electrode to circuit ground for re-zeroing the output coupling capacitor when an output pulse is not being actively delivered.

[0219] Description of Alternative Screening Methods

[0220] Screening generally refers to selecting patients that will be responsive to the therapy, namely neurostimulation of the upper airway dilator nerves and/or muscles such as the hypoglossal nerve that innervates the genioglossus. Screening may be based on a number of different factors including level of obstruction and critical collapse pressure (Pcrit) of the upper airway, for example. Because stimulation of the hypoglossal nerve affects the genioglossus (base of tongue) as well as other muscles, OSA patients with obstruction at the level of the tongue base and OSA patients with obstruction at the level of the palate and tongue base (collectively patients with tongue base involvement) may be selected. Because stimulation of the hypoglossal nerve affects upper airway collapsibility, OSA patients with airways that have a low critical collapse pressure (e.g., Pcrit of less than about 5 cm water) may be selected. Pcrit may be measured using pressure transducers in the upper airway and measuring the pressure just prior to an apnea event (airway collapse). Alternatively, a surrogate for Pcrit such as CPAP pressure may be used. In this alternative, the lowest CPAP pressure at which apnea events are mitigated may correlate to Pcrit.

[0221] The critical collapse pressure (Pcrit) may be defined as the pressure at which the upper airway collapses and limits flow to a maximal level. Thus, Pcrit is a measure of airway collapsibility and depends on the stability of the walls defining the upper airway as well as the surrounding pressure. Pcrit may be more accurately defined as the pressure inside the upper airway at the onset of flow limitation when the upper airway collapses. Pcrit may be expressed as:

$$Pcrit = Pin - Pout$$

[0222] where

[0223] Pin=pressure inside the upper airway at the moment of airway collapse; and

[0224] Pout=pressure outside the upper airway (e.g., atmospheric pressure).

[0225] Other screening methods and tools may be employed as well. For example, screening may be accomplished through acute testing of tongue protruder muscle contraction using percutaneous fine wire electrodes inserted into the genioglossus muscle, delivering stimulus and measuring one or more of several variables including the amount of change in critical opening pressure, the amount of change in airway caliber, the displacement of the tongue base, and/or the retraction force of the tongue (as measured with a displacement and/or force gauge). For example, a device similar to a CPAP machine can be used to seal against the face (mask) and control inlet pressure down to where the tongue and upper airway collapse and occlude during inspiration. This measurement can be repeated while the patient is receiving stimulation of the geneoglossus muscle (or other muscles involved with the patency of the upper airway). Patients may be indicated for the stimulation therapy if the difference in critical pressure (stimulated vs. non-stimulated) is above a threshold level.

[0226] Similarly, a flexible optical scope may be used to observe the upper airway, having been inserted through the mask and nasal passage. The difference in upper airway caliber between stimulation and non-stimulation may be used as an inclusion criterion for the therapy. The measurement may be taken with the inlet air pressure to the patient established at a pre-determined level below atmospheric pressure to better assess the effectiveness of the stimulation therapy.

[0227] Another screening technique involves assessing the protrusion force of the tongue upon anterior displacement or movement of the tongue with and without stimulation while the patient is supine and (possibly) sedated or asleep. A minimum increase in protrusion force while under stimulation may be a basis for patient selection.

[0228] For example, with reference to FIG. **53**, a non-invasive oral appliance **530** may be worn by the patient during a sleep study that can directly measure the protrusion force of the tongue as a basis for patient selection. The oral appliance **530** may include a displacement probe **532** for measuring tongue movement protrusion force by deflection (D). The oral

appliance **530** may also include a force sensor **534** for measuring the force (F) applied by protrusion of the tongue. The sensors in the displacement probe **532** and the force sensor **534** may be connected to measurement apparatus by wires **536**.

[0229] FIG. **54** illustrates another example of a non-invasive oral appliance **540** that may be worn by the patient during a sleep study to directly measure the protrusion force of the tongue as a basis for patient selection. The oral appliance **540** includes a displacement sensor **542** for measuring tongue movement and a force sensor for measuring tongue protrusion force. The displacement sensor and the force sensor may be connected to measurement apparatus by wires **546**.

[0230] Oral appliances **530** and **540** could be worn during a sleep study and would measure the tongue protrusion force during (and just prior to) an apnea event when the protruder muscle tone is presumed to be inadequate to maintain upper airway patency. The protrusion force measured as the apnea is resolved by the patient will increase as the patient changes sleep state and the airway again becomes patent. The force difference may be used as a basis for patient selection.

[0231] Another screening technique involves the use of an oral appliance with sub-lingual surface electrodes contacting the base of the tongue or fine wire electrodes inserted into the genioglossus muscle to stimulate the tongue protrudes muscle(s) synchronous with respiration during a sleep study. The oral appliance may be fitted with a drug delivery system (e.g., drug eluting coating, elastomeric pump, electronically controlled pump) for topical anesthesia to relieve the discomfort of the electrodes.

[0232] For example, with reference to FIG. **55**, an oral appliance **550** includes a pair of small needle intramuscular electrodes **552** that extend into the genioglossus. The electrodes **552** are carried by flexible wires **554** and may be coupled to an external pulse generator (not shown) by wires **556**. The electrodes **552** may be supported by a drug (e.g., anesthetic) eluting polymeric member **558**.

[0233] Alternatively, with reference to FIG. **56**, an oral appliance **560** includes a cathode electrode **562** guarded by two anode electrodes **564** carried by a soft extension **565** that extends under the tongue. The surface electrodes **562** and **564** contact the floor of the mouth under the tongue to indirectly stimulate the genioglossus. The electrodes **562** and **564** may be coupled to an external pulse generator (not shown) by wires **566**. The extension **565** may incorporate holes **568** through which a drug (e.g., anesthetic) may be eluted.

[0234] Oral appliances **550** and **560** may be used during a sleep study and stimulation of the target tissue can be performed synchronous with respiration and while inlet airflow pressure can be modulated. The ability to prevent apneas/hypopneas can be directly determined. Also the critical opening pressure with and without stimulation can be determined. Alternatively or in addition, the intramuscular or surface electrodes may be used to measure genioglossus EMG activity, either with or without stimulation. On any of theses bases, patient selection may be made.

[0235] Patient selection may also be applied to the respiratory sensors to determine if the respiratory sensors will adequately detect respiration for triggering stimulation. For example, in the embodiment wherein bio-Z is used to detect respiration using an implanted lead **70**, skin surface or shallow needle electrodes may be used prior to implantation to determine if the signal will be adequate. This method may also be sued to determine the preferred position of the electrodes (i.e., optimal bio-Z vector). This may be done while the patient is sleeping (i.e., during a sleep study) or while the patient is awake.

[0236] Description of Alternative Intra-Operative Tools

[0237] Intra-operatively, it may be desirable to determine the correct portion of the nerve to stimulate in order to activate the correct muscle(s) and implant the nerve cuff electrode accordingly. Determining the correct position may involve stimulating at different locations along the length or circumference of the nerve and observing the effect (e.g., tongue protrusion). In addition or in the alternative, and particularly in the case of field steering where multiple combinations of electrode contacts are possible, it may be desirable to determine optimal electrode or filed shape combinations.

[0238] An example of an intra-operative stimulating tool **570** is shown in FIGS. **57**A and **57**B. In this embodiment, the tool **570** includes a first shaft **571** with a distal half-cuff **573**. Tool **570** further includes a second shaft **575** with a proximal movable collar **574** and a distal half-cuff **575**. Stimulating tool **570** includes multiple electrodes **572** on half-cuff **573** and/or half-cuff **575** that may be arranged in an array or matrix as shown in FIG. **57**C, which is a view taken along line A-A in FIG. **57**B. The half-cuffs **573** and **575** may be longitudinally separated for placement about a nerve and subsequently closed such that the half-cuffs **573** and **575** gently grasp the nerve. The electrodes **575** may be sequenced through a series of electrode/field shape combinations to optimize (lower) the critical opening pressure, airway caliber, tongue protrusion force or other acute indicia of therapeutic efficacy.

[0239] The tool **570** may be part of an intra-operative system including: (1) tool **570** or other tool with one or more stimulating electrodes that are designed to be easily handled by the surgeon during implant surgery; (2) an external pulse generator which triggers off of a respiration signal; (3) a feedback diagnostic device that can measure critical closing pressure intra-operatively; and (4) an algorithm (e.g., firmware or software in the programmer) that is design to automatically or manually sequence through a series of electrode configurations that will identify the best placement of electrode cuffs on the nerves and configuration of electrode polarity and amplitude settings. Information from the intra-operative system may greatly speed the process of identifying where to place the electrode cuff(s) on the hypoglossal nerve and what field steering may be optimal or necessary to provide efficacy.

[0240] Description of Miscellaneous Alternatives

[0241] The implanted neurostimulation system may be configured so that stimulation of the nerve is set at a relatively low level (i.e., low voltage amplitude, narrow pulse width, lower frequency) so as to maximize battery life of the INS and to minimize the chances that the electrical stimulation will cause arousal from sleep. If apneas/hypopneas are detected, then the electrical stimulation can be increased progressively until the apneas/hypopneas are no longer detected, up to a maximum pre-set stimulation level. This auto titration may automatically be reset to the low level after the patient is awakened and sits up (position detector) or manually reset using the patient controller. The stimulation level may be automatically reduced after a period of time has elapsed with no (or few) apneas/hypopneas detected.

[0242] The stimulation level (i.e., voltage amplitude, pulse width, frequency) may be adjusted based on changes in respiration rate. Respiration rate or patterns of rate change may be indicative of sleep state. A different power level based on sleep state may be used for minimal power consumption, minimal unwanted stimulation (sensory response), etc., while providing adequate efficacy.

[0243] The electrical field shape used to stimulate the target nerve can be changed while the system is proving therapy

based on feedback indicating the presence (or lack) of apneas/hypopneas. The electrical field shape for an implanted system can be changed by adjusting the polarity, amplitude and other stimulation intensity parameters for each of the electrodes within the nerve stimulating cuff. An algorithm within the INS may change the currently operating electrical field shape if the presence of apneas/hypopneas is detected, and then wait a set period of time to determine if the new configuration was successful in mitigating the apneas/hypopneas before adjusting the field shape again. Additionally, the system may be designed to keep a log of the most successful stimulation patterns and when they were most likely to be effective. This may allow the system to "learn" which settings to be used during what part of the night, for example, or with specific breathing patterns or cardiac signal patterns or combinations thereof.

[0244] The proportion of stimulation intensity of two electrode cuffs used to stimulate a nerve can be modulated while the system is providing therapy based on feedback indicating the presence (or lack) of apneas/hypopneas. For example, one nerve stimulating electrode cuff may be place on the more proximal section of the hypoglossal nerve, while a second is placed more distally. The proximal cuff will be more likely to stimulate branches of the hypoglossal nerve going to muscles in the upper airway involved with tongue or hyoid retrusion while the more distal electrode cuff will more likely stimulate only the muscles involved with tongue/hyoid protrusion. Research suggests that to best maintain upper airway patency, stimulating both protrudes and retruders (in the right proportion) may be more effective that stimulating protruders alone. Software within the INS may change the currently operating proportion of electrical stimulation going to the distal electrode cuff in proportion to that going to the proximal cuff based on the presence of apneas/hypopneas detected. The system may then wait a set period of time to determine if the new configuration was successful in mitigating the apneas/hypopneas before adjusting the system again. Additionally, the system software may be designed to keep a log of the most successful stimulation proportion and when they were most likely to be effective. This may allow the system to "learn" which settings to be used during what part of the night, for example, or with specific breathing patterns or cardiac signal patterns or combinations thereof.

[0245] The system described above may modulate electrical stimulation intensity proportion based on electromyogram (EMG) feedback from the muscles in the upper airway being stimulated or others in the area. This feedback may be used to determine the correct proportion of stimulation between protruders and retruders. The correct ratio of EMG activity between retruders and protruders may be determined during a sleep study for an individual, may be determined to be a constant for a class of patients or may be "learned" my the implanted system by using the detection of apneas/hypopneas as feedback.

[0246] A library of electrical stimulation parameter settings can be programmed into the INS. These settings listed in the library may be selected by the patient manually using the patient programmer based on, for example: (1) direct patient perception of comfort during stimulation; (2) a log of the most successful settings compiled by the software in the INS (assumes apnea/hypopnea detection capability); (3) a sleep physician's or technician's assessment of the most effective stimulation as determined during a sleep study; and/or (4) a list of the most effective parameters produced for a particular class of patient or other.

[0247] The electrical stimulation parameters described above may be adjusted based on patient position as detected by a position sensor within the INS. The best setting for a given position may be determined by, for example: (1) a log of the most successful settings compiled or learned by the software in the INS (assumes apnea/hypopnea detection capability); (2) a sleep physician's or technician's assessment of the most effective stimulation as determined during a sleep study; and/or (3) a list of the most effective parameters produced for a particular class of patient or other.

[0248] To avoid fatigue using a normal duty cycle or to extend the time that the upper airway is opened through neurostimulation, different parts of the genioglossus muscle and/or different muscles involved with establishing patency of the upper airway can be alternately stimulated. For example, using two or more nerve or muscle electrode cuffs, the left and right side genioglossus muscles can be alternately stimulated, cutting the effective duty cycle on each muscle in half. In addition, different protruder muscles on the ipsilateral side such as the geniohyoid and the genioglossus muscle can be alternately stimulated to the same effect. This may also be accomplished through one electrode cuff using field steering methods that selectively stimulated the fascicles of the hypoglossal nerve going to one group of protruders alternating with stimulating the fascicles leading to a different protruder muscle group. This method may also be used to alternately stimulate one group of muscle fibers within the genioglossus muscle with the compliment of muscle fibers in the same muscle group.

[0249] To increase the ability of the upper airway to open during a (sensed) apnea/hypopnea through neurostimulation, different parts of the genioglossus muscle and/or different muscles involved with establishing patency of the upper airway can be simultaneously stimulated. For example, using two or more nerve or muscle electrode cuffs, the left and right side genioglossus muscles can be simultaneously stimulated, greatly increasing the protrusion forces. In addition, different protruder muscles on the ipsilateral side such as the geneohyoid and the genioglossus muscle can be simultaneously stimulated to the same effect. This may also be accomplished through one electrode cuff using field steering methods that selectively stimulated the fascicles of the hypoglossal nerve going to one group of protruders simultaneously with stimulating the fascicles leading to a different protruder muscle group. This may be achieved with one electrode cuff using field steering on a more proximal location on the hypoglossal nerve or two or more electrode cuffs, one on each branch going to a muscle involved with maintaining muscle patency.

[0250] A sensor inside the INS (or elsewhere in system implanted) may detect body position and automatically shut off stimulation when patient sits up or stands up. This will prevent unwanted stimulation when patient is no longer sleeping. The device may automatically restart the stimulation after the sensor indicates the patient is again horizontal, with or without a delay. The system may also be configured so that the stimulation can only be restarted using the patient controller, with, or without a delay.

[0251] The respiration signal using impedance and/or EMG/ENG are easily capable of determining heart rate. The stimulation may be interrupted or turned off when the heart rate falls outside out a pre-determined acceptable range. This may be an effective safety measure that will decrease the chance that hypoglossal nerve stimulation will interfere with mitigating physiological processes or interventional emergent medical procedures.

[0252] Respiration waveforms indicating apneas/hypopneas or of other clinical interest may be recorded and automatically telemetered to a bed-side receiver unit or patient programmer. Respiration waveforms indicating frequent

apneas/hypopneas, abnormal breathing patterns, irregular heart rate/rhythm may be recorded and automatically telemetered to a bed-side deceiver unit or patient programmer causing an alarm to be issued (audible/visible). The INS status such as low battery or system malfunction may also trigger an alarm.

[0253] Electrical stimulation intensity could be ramped up for each respiration cycle by increasing amplitude or pulse width from 0 to a set point to prevent sudden tongue protrusion or sudden airway opening causing the patient to wake up. During inspiration, the system may deliver approximately 30 pulses per second for a length of time of one to one and one half seconds, totaling between about 30 and 45 pulses per respiration cycle. Prior to delivery of these 30 to 45 pulses, amplitude of each individual therapy pulse (in an added group of pulses) could be ramped up from 0 to a set point at a rate of <10% of the amplitude intended for the active duty cycle or 200 mS, whichever is less. The pulse width of each individual therapy pulse could be ramped up from 0 to a set point at a rate of <10% of the active duty cycle or 200 mS, whichever is less. Each of these ramp methods would require a predictive algorithm that would stimulate based on the previous inspiration cycle.

[0254] Nerves innervating muscles that are involved with inspiration, such as the hypoglossal nerve, have been shown to have greater electrical activity during apnea or hypopnea. This signal cannot be easily measured while simultaneously stimulating the same nerve. One method of stimulating and sensing using the same lead is to interleave a sensing period within the stimulation pulse bursts during the duty cycle. In other words, the sensing period may occur between pulses within the stimulation pulse train. This approach may be used with electrodes/leads that directly stimulate and alternately sense on a nerve involved with inspiration or on a muscle involved with inspiration or a combination of the two. The approach may allow sensing of apnea/hypopnea, as well as therapeutic stimulation.

[0255] From the foregoing, it will be apparent to those skilled in the art that the present invention provides, in exemplary non-limiting embodiments, devices and methods for nerve stimulation for OSA therapy. Further, those skilled in the art will recognize that the present invention may be manifested in a variety of forms other than the specific embodiments described and contemplated herein. Accordingly, departures in form and detail may be made without departing from the scope and spirit of the present invention as described in the appended claims.

1-74. (canceled)

75. A method of stimulating a hypoglossal nerve, comprising:
- chronically implanting a nerve cuff electrode on a portion of the hypoglossal nerve;
- sensing a signal corresponding to respiration;
- predicting inspiratory onset from the sensed signal; and
- delivering a stimulus to the portion of the hypoglossal nerve via the nerve cuff electrode, wherein the stimulus is delivered as a function of the predicted inspiratory onset.

76. A method as in claim **75**, wherein the sensed signal is a bio-impedance signal.

77. A method as in claim **75**, wherein inspiratory onset is predicted based on historical respiratory data.

78. A method as in claim **75**, wherein inspiratory onset is predicted for a future respiratory cycle using respiratory data from a previous respiratory cycle and a current respiratory cycle.

79. A method as in claim **75**, wherein the method further comprises processing the sensed signal to remove one of cardiac and motion artifacts.

80. A method as in claim **78**, wherein respiratory data from the previous and the current respiratory cycles are weighted differently.

81. A method as in claim **78**, wherein respiratory data from the current respiratory cycle is weighted negatively relative to data from the previous respiratory cycle.

82. A method as in claim **75**, wherein inspiratory onset is predicted based on expiratory onset.

83. A method as in claim **75**, wherein the portion of the hypoglossal nerve corresponds to a portion innervating a genioglossus muscle of the patient.

84. A method as in claim **75**, wherein the nerve cuff electrode includes an electrode contact arrangement configured for selectively activating only one of the superior, inferior, lateral, and medial fascicles of the hypoglossal nerve.

85. A method as in claim **75**, wherein the stimulus is delivered approximately 300 ms before the predicted inspiratory onset.

86. A device for stimulating a hypoglossal nerve, comprising:
- a neurostimulator for generating an electrical stimulus signal;
- a lead connected to the neurostimulator, the lead having a nerve cuff electrode for delivering the electrical stimulus to a portion of the hypoglossal nerve; and
- an algorithm contained in the neurostimulator that triggers stimulation delivery as a function of predicted inspiratory onset, wherein the prediction of inspiratory onset is based on a sensed respiratory signal.

87. A device as in claim **86**, wherein the sensed respiratory signal is bio-impedance.

88. A device as in claim **87**, further comprising a sensor for sensing bio-impedance.

89. A device as in claim **86**, wherein the algorithm predicts inspiratory onset based on historical respiratory data.

90. A device as in claim **86**, wherein the algorithm predicts inspiratory onset for a future respiratory cycle using respiratory data from previous and current respiratory cycles.

91. A device as in claim **86**, wherein the algorithm is configured to process the sensed respiratory signal to remove one of cardiac and motion artifacts.

92. A device as in claim **90**, wherein the algorithm applies differing weights to the data from the previous and current respiratory cycles.

93. A device as in claim **90**, wherein the algorithm applies a negative weight to data from the current respiratory cycle relative to data from the previous respiratory cycle.

94. A device as in claim **86**, wherein the algorithm predicts inspiratory onset based on expiratory onset.

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