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Ni et al.

(54) **METHOD AND SYSTEM FOR APPLYING STIMULATION IN TREATING SLEEP DISORDERED BREATHING**

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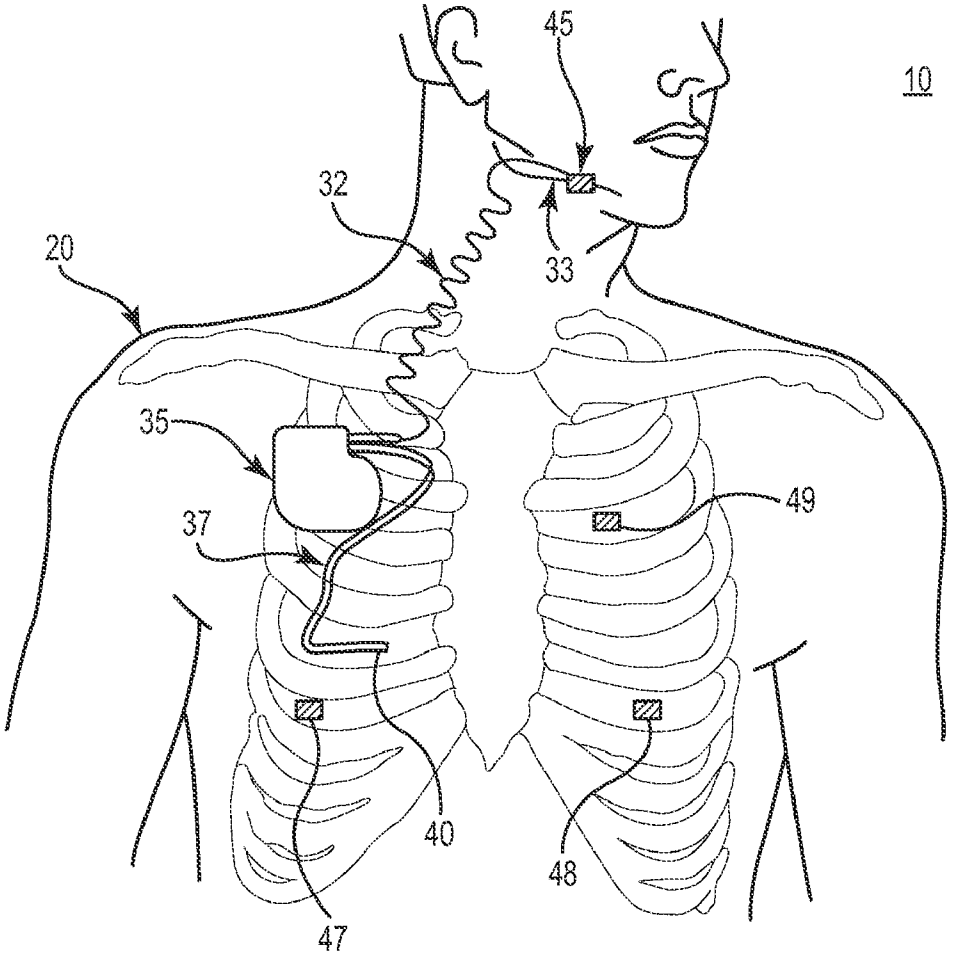
USPC **607/42**

(57) **ABSTRACT**

A stimulation protocol determination system includes an input module and a selector module. The input module is provided to receive an indication of an upper airway flow limitation via sensed respiratory effort information. The selection module is provided to automatically select, based on the indicated upper airway flow limitation, a stimulation protocol.



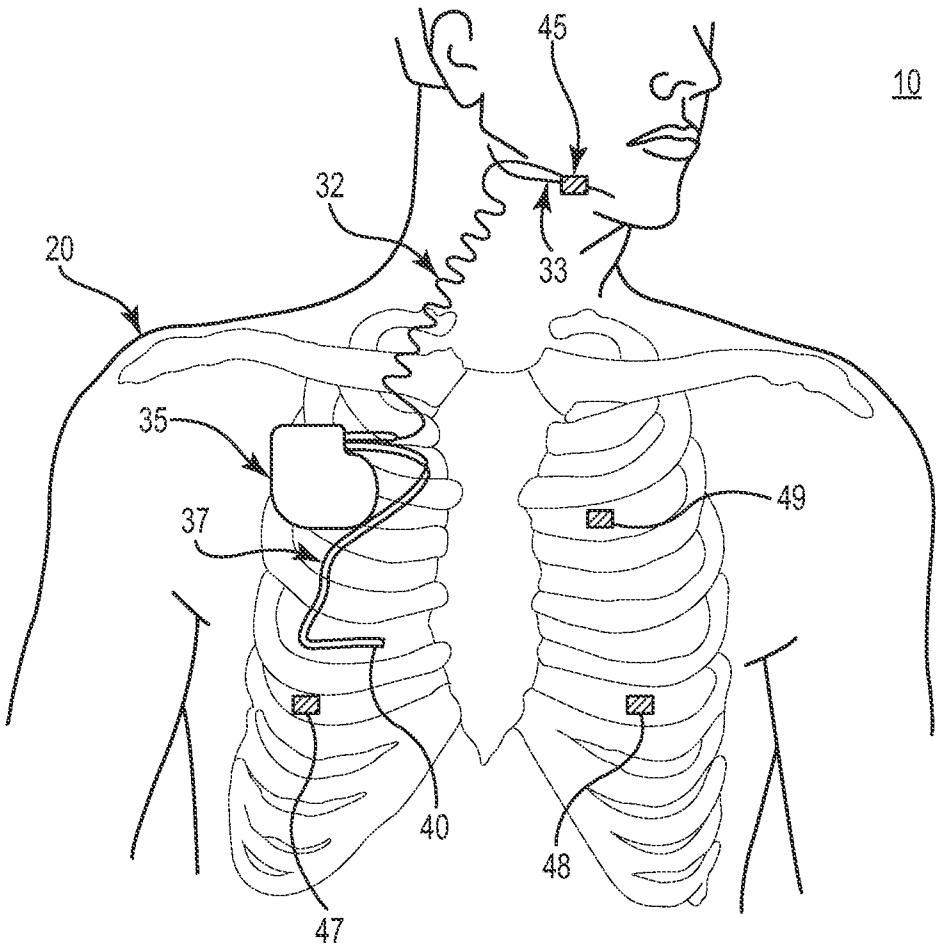


Fig. 1A

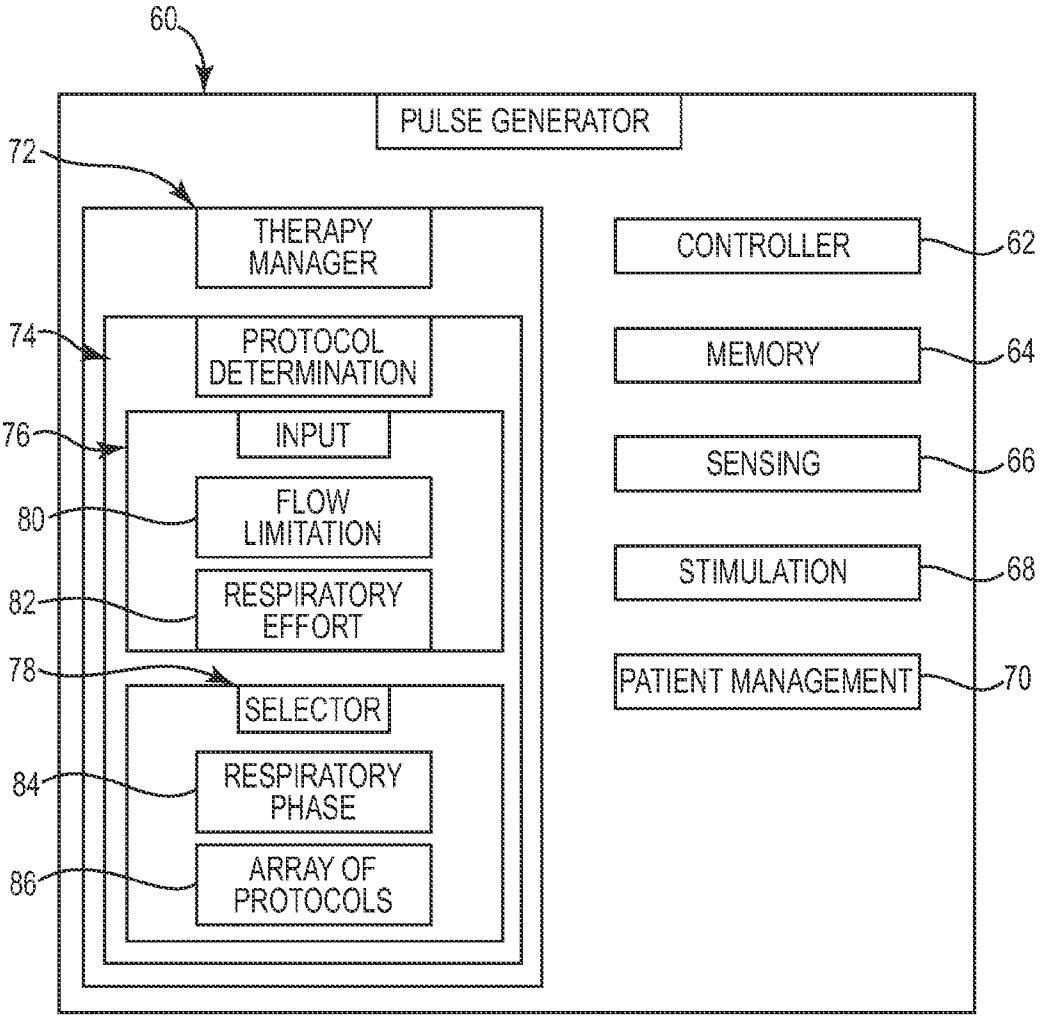
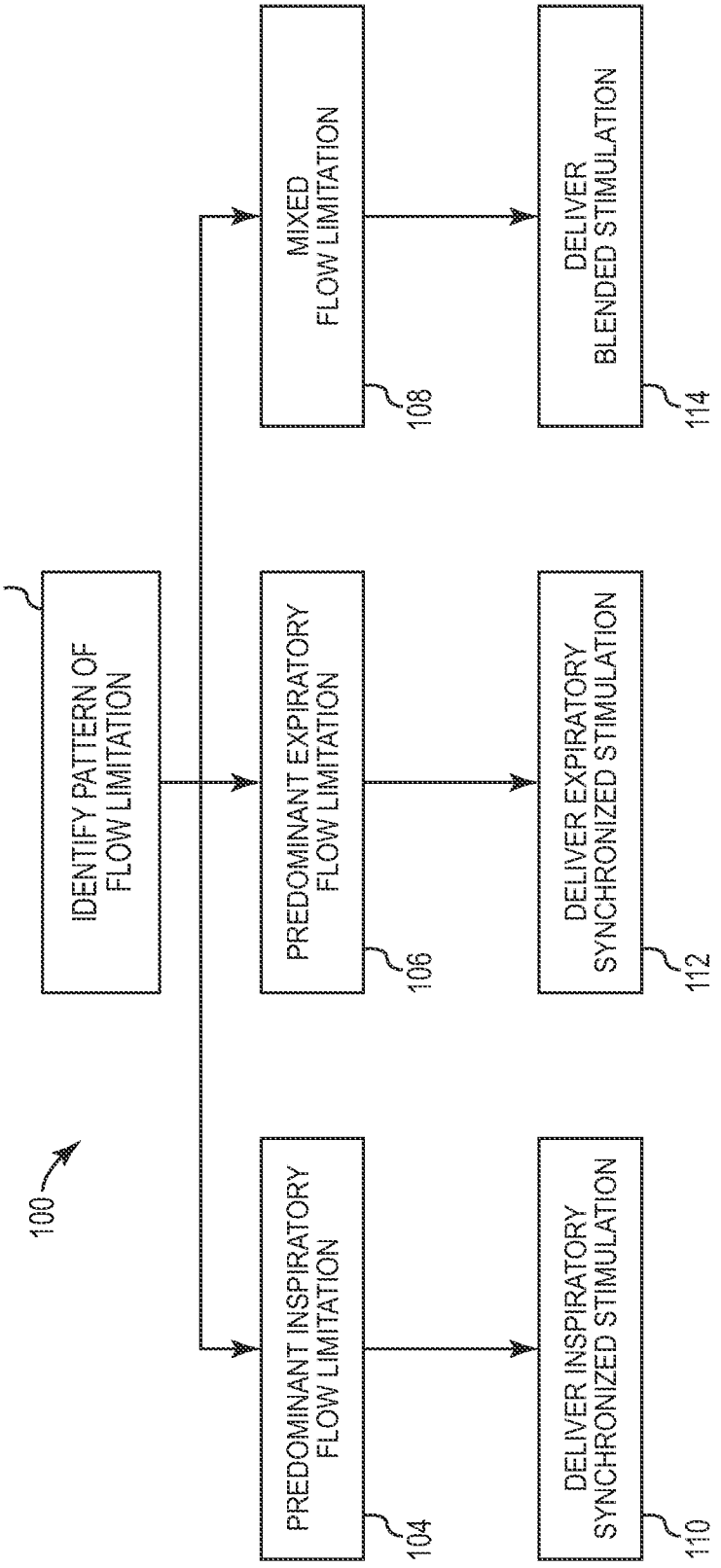

60
PULSE GENERATOR
72
THERAPY MANAGER
74
PROTOCOL DETERMINATION
76
INPUT
80
FLOW LIMITATION
82
RESPIRATORY EFFORT
78
SELECTOR
84
RESPIRATORY PHASE
86
ARRAY OF PROTOCOLS
CONTROLLER
62
MEMORY
64
SENSING
66
STIMULATION
68
PATIENT MANAGEMENT
70

Fig. 1B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IDENTIFY PATTERN OF FLOW LIMITATION
PREDOMINANT INSPIRATORY FLOW LIMITATION
104
PREDOMINANT EXPIRATORY FLOW LIMITATION
106
MIXED FLOW LIMITATION
108
DELIVER INSPIRATORY SYNCHRONIZED STIMULATION
110
DELIVER EXPIRATORY SYNCHRONIZED STIMULATION
112
DELIVER BLENDED STIMULATION
114

Fig. 1C

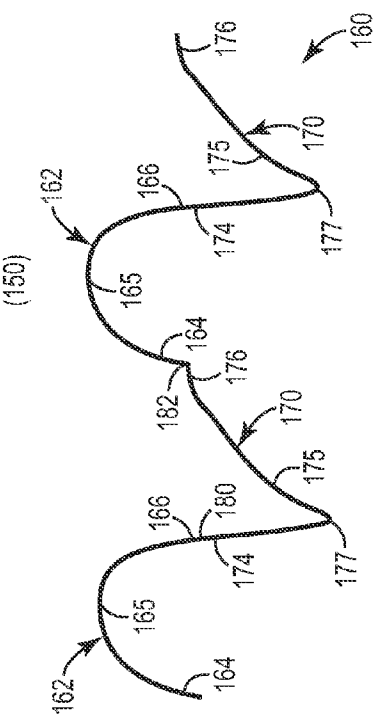

Fig. 2

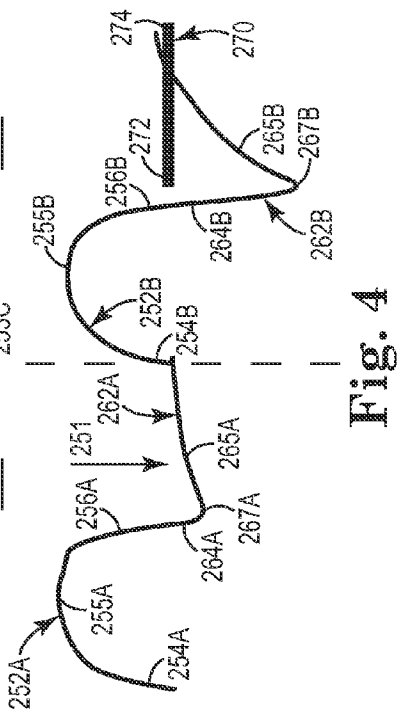

Fig. 4

Fig. 3

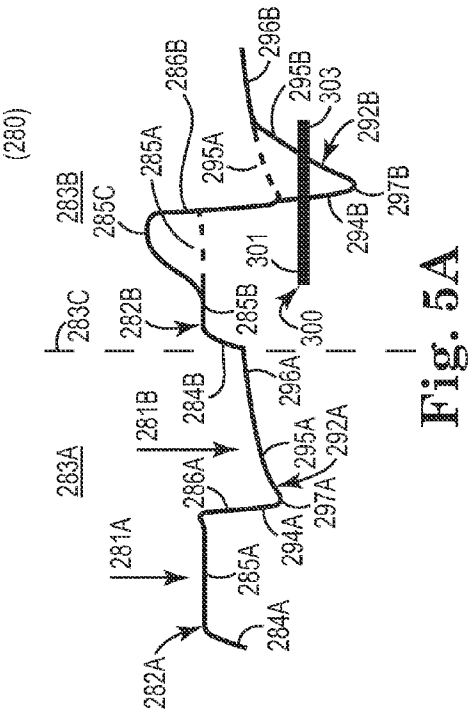

Fig. 5A

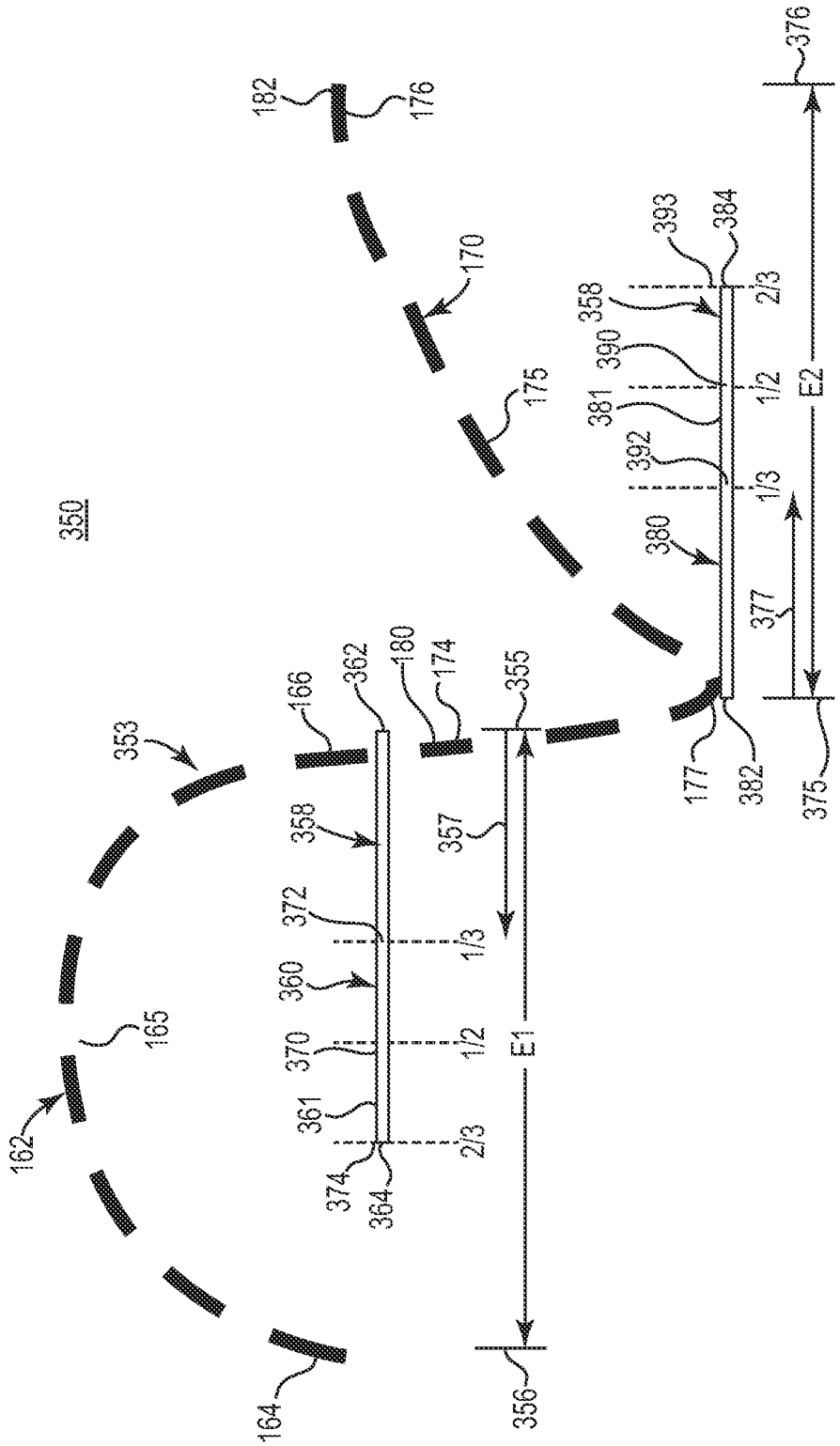
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Fig. 5B

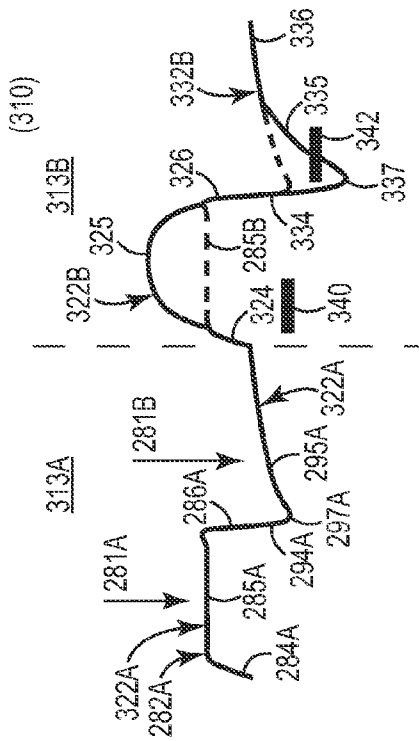
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Fig. 6

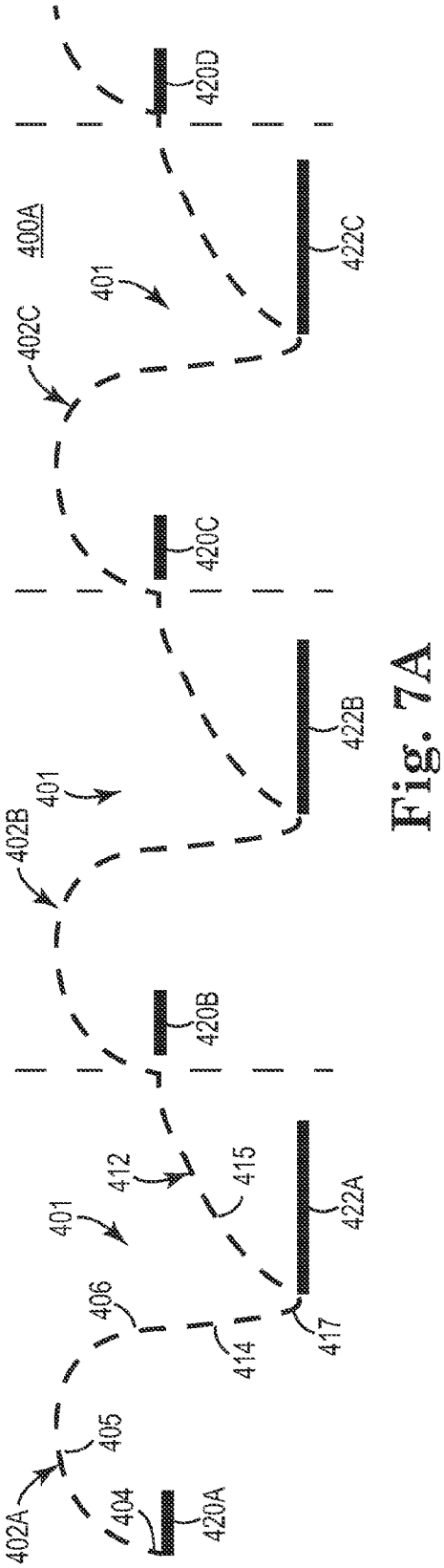
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Fig. 7A

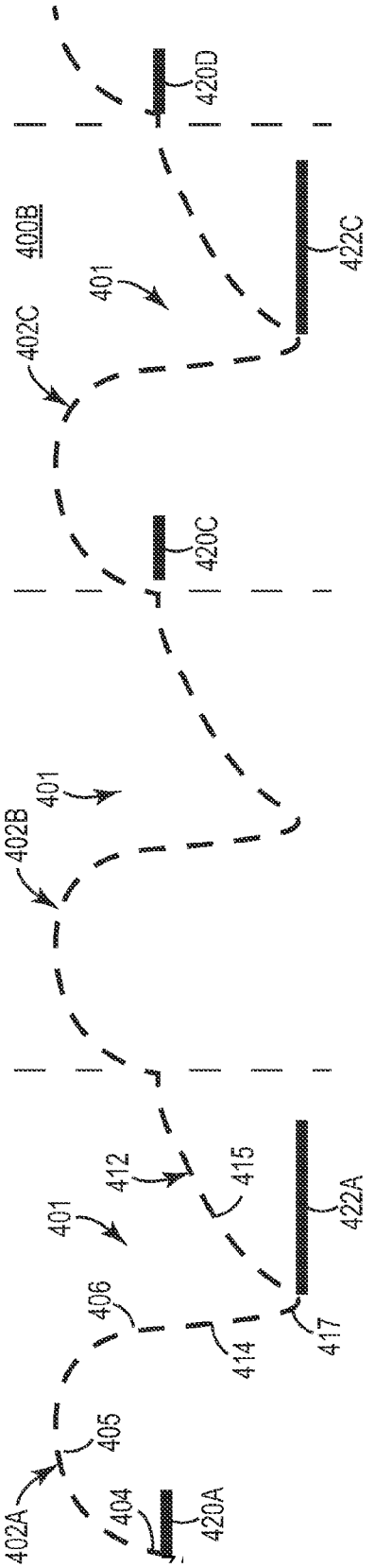
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Fig. 7B

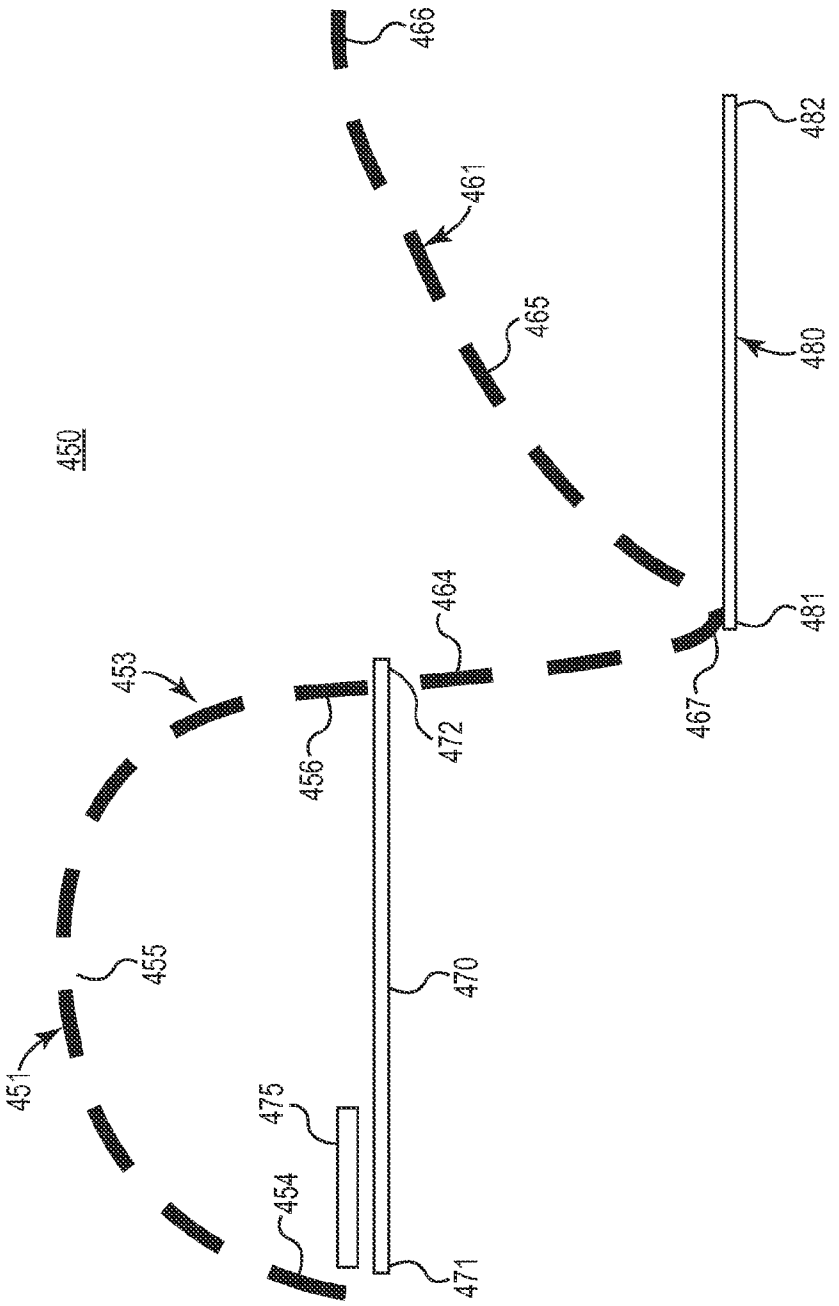
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Fig. 8

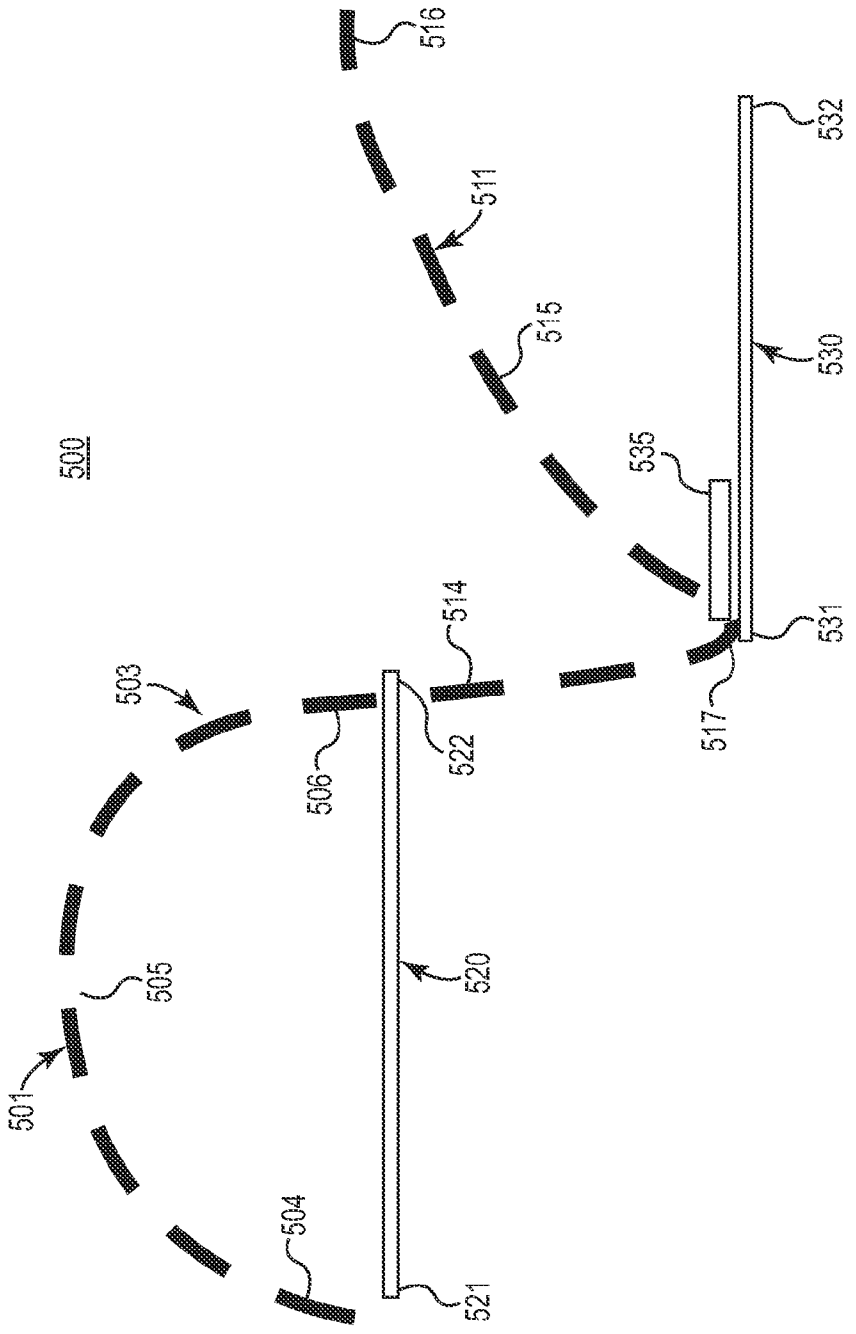
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Fig. 9

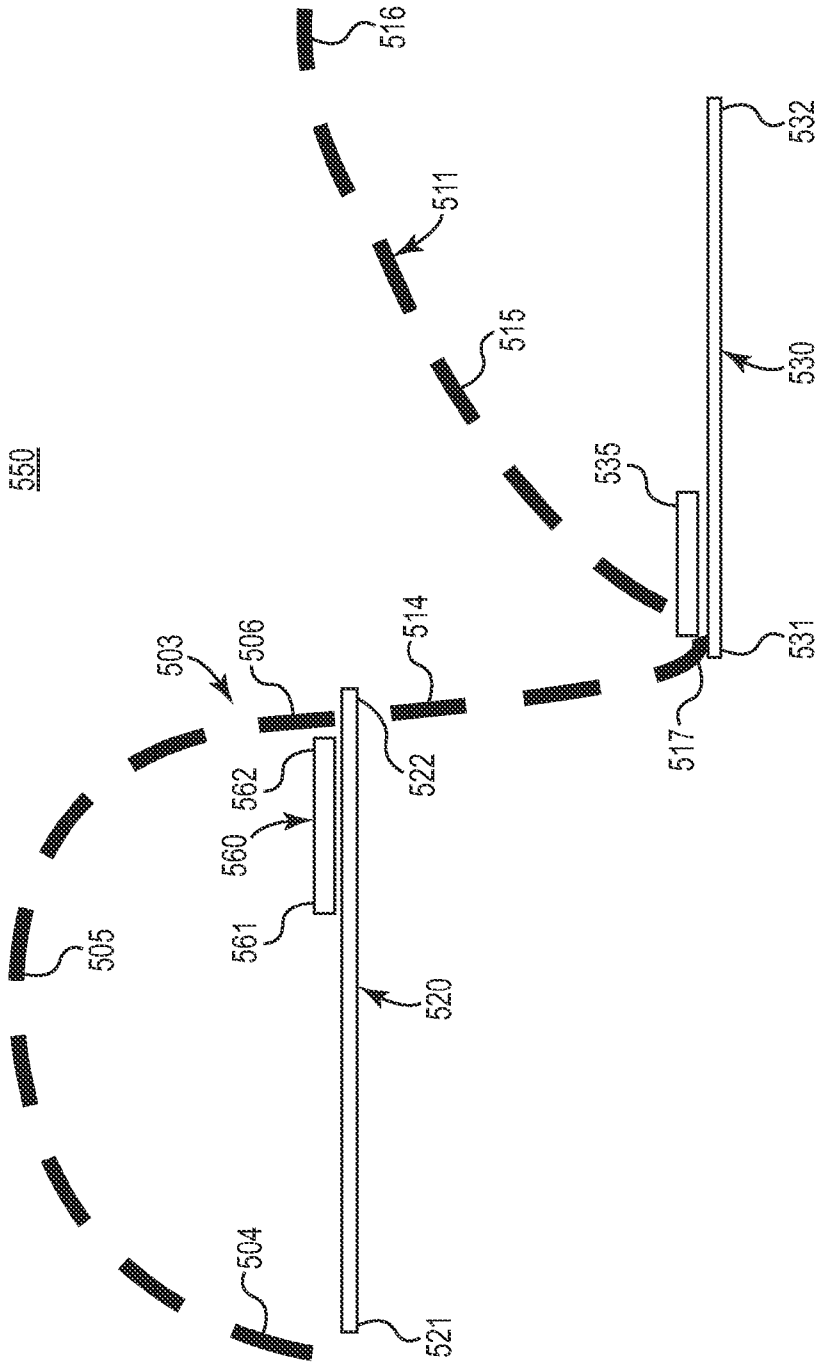
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Fig. 10

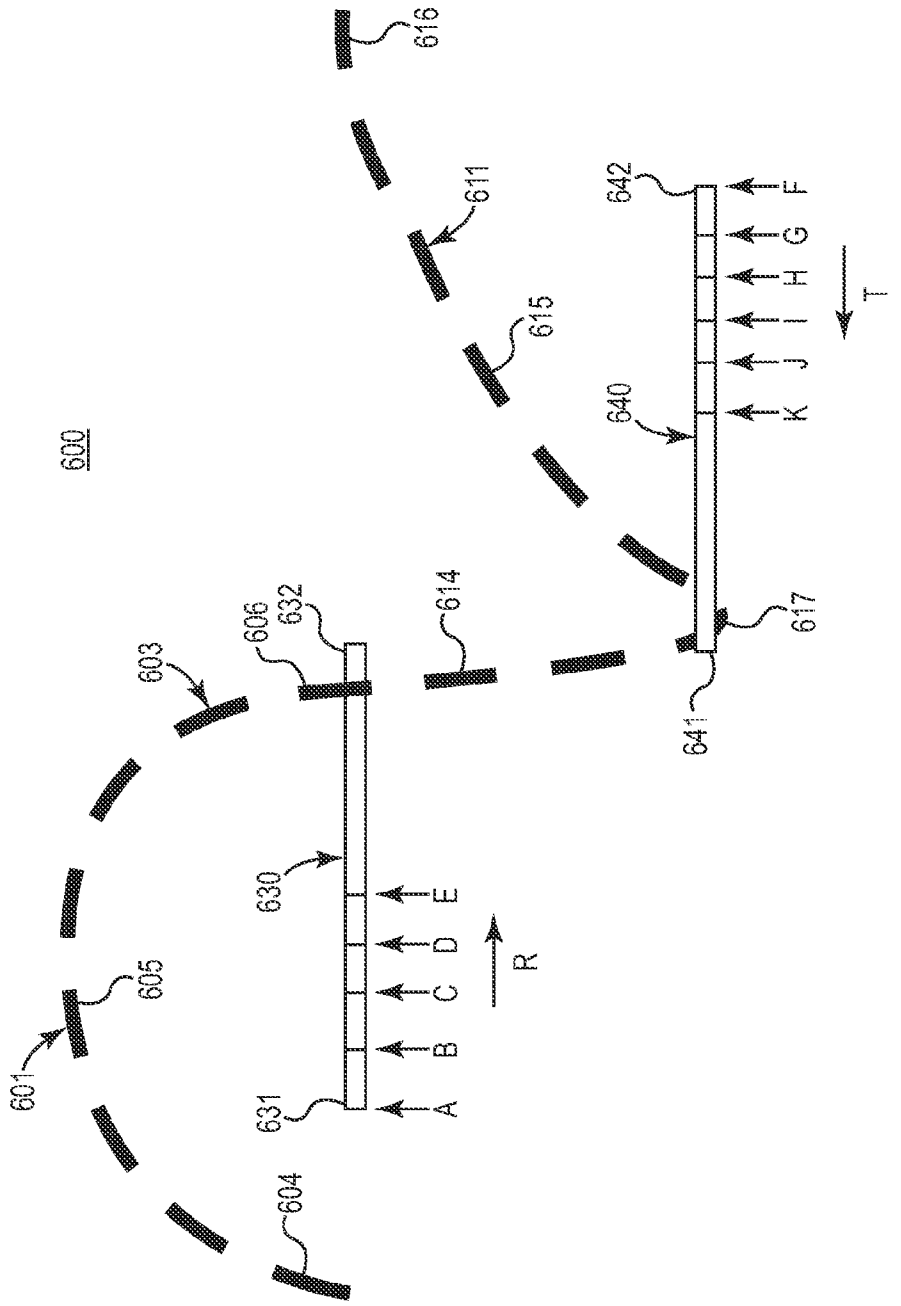
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Fig. 11

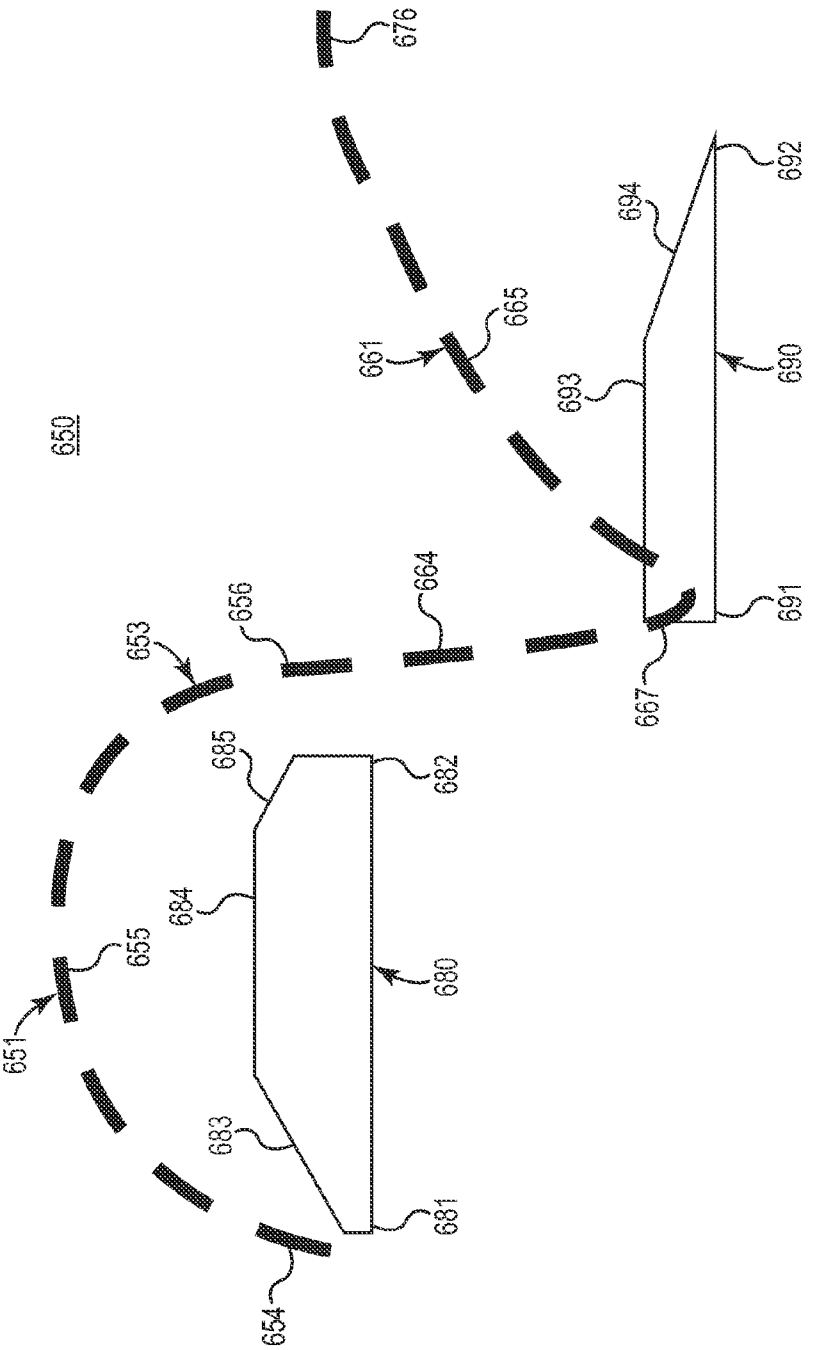
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Fig. 12

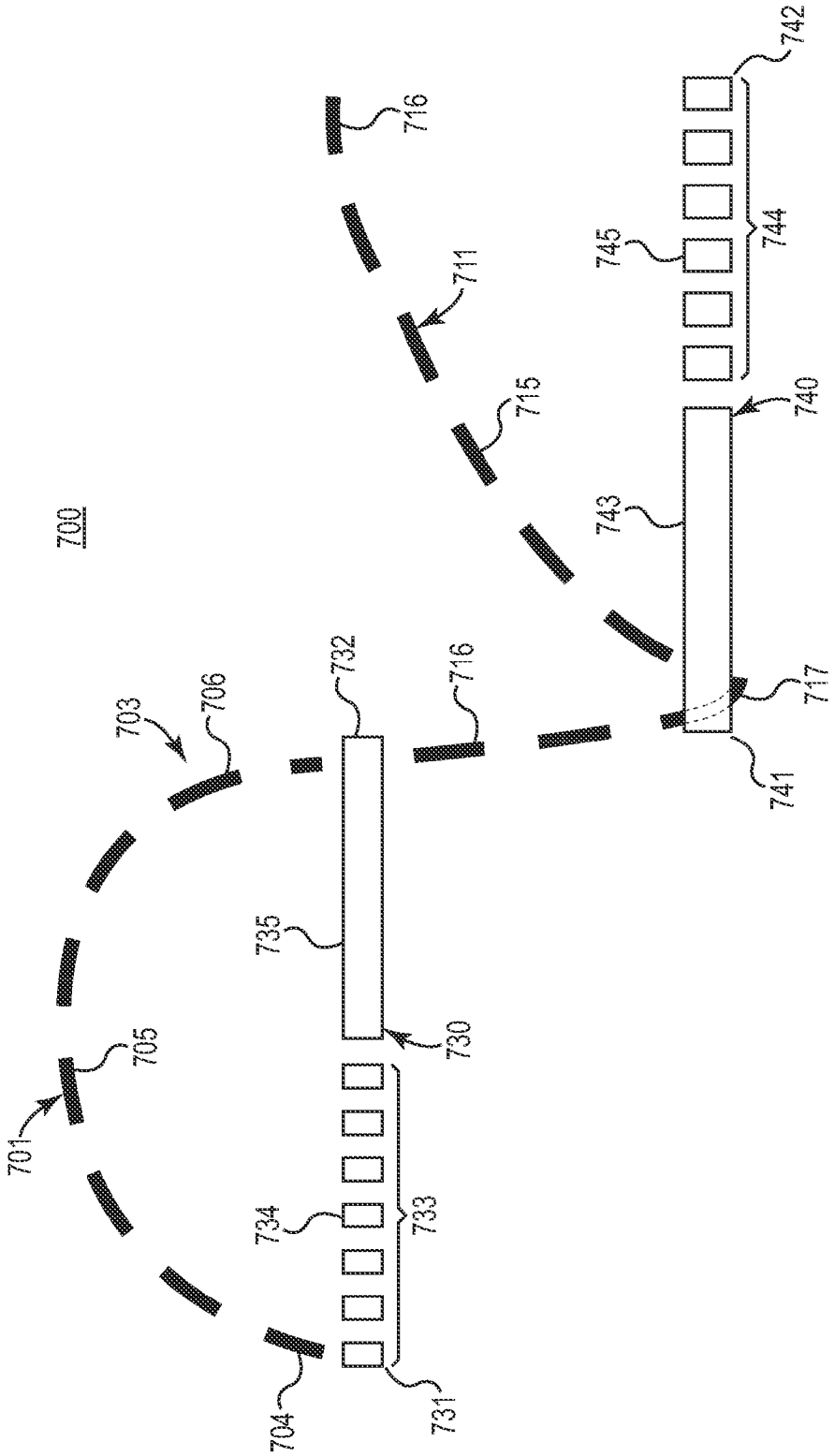
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Fig. 13

METHOD AND SYSTEM FOR APPLYING STIMULATION IN TREATING SLEEP DISORDERED BREATHING

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a Non-Provisional application of Provisional U.S. Patent Application Ser. No. 61/522,426, entitled "Method and System for Applying Stimulation in Treating Sleep Disordered Breathing," filed Aug. 11, 2011, incorporated herein by reference.

BACKGROUND

[0002] In cases in which sleep disordered breathing is caused by upper airway obstructions, one form of treatment includes stimulating one or more nerves that affect upper airway dilation. In a conventional technique, the stimulation is applied continuously or synchronized to the respiratory cycle. However, in some instances, continuous stimulation may not desirable because of any potential long-term effects of over-stimulating the nerve.

BRIEF DESCRIPTION OF THE DRAWINGS

[0003] The accompanying drawings are included to provide a further understanding of embodiments and are incorporated in and constitute a part of this specification. The drawings illustrate embodiments and together with the description serve to explain principles of embodiments. Other embodiments and many of the intended advantages of embodiments will be readily appreciated as they become better understood by reference to the following detailed description. The elements of the drawings are not necessarily to scale relative to each other. Like reference numerals designate corresponding similar parts.

[0004] FIG. **1**A is a schematic diagram of an at least partially implantable stimulation system relative to a patient, according to an example of the present disclosure.

[0005] FIG. **1**B is a block diagram schematically illustrating a pulse generator, according to one example of the present disclosure.

[0006] FIG. **1**C is flow diagram schematically illustrating a method of treating an upper airway flow limitation, according to one example of the present disclosure.

[0007] FIG. **2** is a diagram schematically illustrating respiratory cycles in one example breathing pattern, according to one example of the present disclosure.

[0008] FIG. **3** is a diagram schematically illustrating a first respiratory cycle exhibiting a flow limitation that occurs predominantly during an inspiratory phase and schematically illustrating a second respiratory cycle exhibiting mitigation of the flow limitation in response to a nerve stimulation protocol, according to one example of the present disclosure.

[0009] FIG. **4** is a diagram schematically illustrating a first respiratory cycle exhibiting a flow limitation that occurs predominantly during an expiratory phase and schematically illustrating a second respiratory cycle exhibiting mitigation of the flow limitation in response to a nerve stimulation protocol, according to one example of the present disclosure.

[0010] FIG. **5**A is a diagram schematically illustrating a first respiratory cycle exhibiting a mixed flow limitation that overlaps a portion of an inspiratory phase and a portion of an expiratory phase and schematically illustrating a second respiratory cycle exhibiting mitigation of the flow limitation in response to one example nerve stimulation protocol, according to one example of the present disclosure.

[0011] FIG. **5**B is a diagram schematically illustrating portions of a generally continuous stimulation period relative to portions of the respective inspiratory and expiratory phases of a respiratory cycle, according to one example of the present disclosure.

[0012] FIG. **6** is a diagram schematically illustrating a first respiratory cycle exhibiting a mixed flow limitation that overlaps a portion of an inspiratory phase and a portion of an expiratory phase and schematically illustrating a second respiratory cycle exhibiting mitigation of the flow limitation in response to one example nerve stimulation protocol, according to one example of the present disclosure.

[0013] FIGS. **7**A-**7**B are a pair of diagrams with each diagram schematically illustrating a series of respiratory cycles during which one example nerve stimulation protocol is applied, according to one example of the present disclosure.

[0014] FIGS. **8**-**13** are a series of diagrams with each diagram schematically illustrating a respiratory cycle during which one example nerve stimulation protocols is applied, according to one example of the present disclosure.

DETAILED DESCRIPTION

[0015] In the following Detailed Description, reference is made to the accompanying drawings which form a part hereof, and in which is shown specific examples of the present disclosure which may be practiced. In this regard, directional terminology, such as "top," "bottom," "front," "back," "leading," "trailing," etc., is used with reference to the orientation of the Figure(s) being described. Because components of examples of the present disclosure can be positioned in a number of different orientations, the directional terminology is used for purposes of illustration and is in no way limiting. It is to be understood that other examples may be utilized and structural or logical changes may be made without departing from the scope of the present disclosure. The following detailed description, therefore, is not to be taken in a limiting sense.

[0016] At least some examples of the present disclosure are directed to methods of treating obstructive sleep apnea via applying stimulation in intervals or periods during targeted portions of the respiratory cycle. By doing so, upper airway patency is maintained and/or increased while preventing collapse of the upper airway. At the same time, by using targeted stimulation, one can limit the overall volume of stimulation applied to a given nerve or set of nerves.

[0017] FIG. **1**A is a schematic diagram of an at least partially implantable stimulation system, according to an example of the present disclosure. As illustrated in FIG. **1**A, in one example system **10** an implantable pulse generator (IPG) **35**, capable of being surgically positioned within a pectoral region of a patient **20**, and a stimulation lead **32** electrically coupled with the IPG **35** via a connector (not shown) positioned within a connection port of the IPG **35**. The lead **32** includes a stimulation electrode portion **45** and extends from the IPG **35** so that the stimulation electrode portion **45** is positioned in contact with a desired nerve, such as the hypoglossal nerve **33** of the patient **10**, to enable stimulation of the nerve **33**, as described below in detail. An exemplary implantable stimulation system in which lead **32** may be utilized, for example, is described in U.S. Pat. No. 6,572,543 to Christopherson et al., and which is incorporated herein by reference in its entirety. In one embodiment, the lead **32**

further includes at least one sensor portion **40** (electrically coupled to the IPG **35** and extending from the IPG **35**) positioned in the patient **10** for sensing respiratory effort, such as respiratory pressure.

[0018] In some embodiments, the sensor portion **40** detects respiratory effort including respiratory patterns (e.g., inspiration, expiration, respiratory pause, etc.) in order to trigger activation of an electrode portion to stimulate a target nerve. Accordingly, with this arrangement, the IPG **35** (FIG. **1**) receives sensor waveforms from the respiratory sensor portion **40**, thereby enabling the IPG **35** to deliver electrical stimulation synchronously with inspiration (or synchronized relative to another aspect of the respiratory cycle) according to a therapeutic treatment regimen in accordance with examples of the present disclosure. It is also understood that the respiratory sensor portion **40** is powered by the IPG **35** and the IPG **35** also contains internal circuitry to accept and process the impedance signal from the stimulation lead **32**.

[0019] In some embodiments, the sensor portion **60** is a pressure sensor. In one example, the pressure sensor in this embodiment detects pressure in the thorax of the patient. In other examples, the sensed pressure could be a combination of thoracic pressure and cardiac pressure (e.g., blood flow). With this configuration, the controller is configured to analyze this pressure sensing information to detect the respiratory patterns of the patient.

[0020] In some other embodiments, the respiratory sensor portion **40** comprises a bio-impedance sensor or pair of bio-impedance sensors and can be located in regions other than the pectoral region. In one aspect, such an impedance sensor is configured to sense a bio-impedance signal or pattern whereby the control unit evaluates respiratory patterns within the bio-impedance signal. For bio-impedance sensing, in one embodiment, electric current will be injected through an electrode portion within the body and an electrically conductive portion of a case of the IPG **35** (FIG. **3**A) with the voltage being sensed between two spaced apart stimulation electrode portions (or also between one of the stimulation electrode portions and the electrically conductive portion of the case of IPG **35**) to compute the impedance.

[0021] In some embodiments, system **10** also comprises additional sensors to further obtain physiologic data associated with respiratory functions. For example, system **10** may include various sensors (e.g., sensors **47**, **48**, **49** in FIG. **1**) distributed about the chest area for measuring a trans-thoracic bio-impedance signal, an electrocardiogram (ECG) signal, or other respiratory-associated signals.

[0022] In some embodiments, the sensing and stimulation system for treating obstructive sleep apnea is a totally implantable system which provides therapeutic solutions for patients diagnosed with obstructive sleep apnea. In other embodiments, one or more components of the system are not implanted in a body of the patient. A few non-limiting examples of such non-implanted components include external sensors (respiration, impedance, etc.), an external processing unit, or an external power source. Of course, it is further understood that the implanted portion(s) of the system provides a communication pathway to enable transmission of data and/or controls signals both to and from the implanted portions of the system relative to the external portions of the system. The communication pathway includes a radiofrequency (RF) telemetry link or other wireless communication protocols.

[0023] Whether partially implantable or totally implantable, the system is designed to stimulate the hypoglossal nerve during some portion of the repeating respiratory cycle to thereby prevent obstructions or occlusions in the upper airway during sleep. In one embodiment, the implantable system comprises an implantable pulse generator (IPG), a peripheral nerve cuff stimulation lead, and a pressure sensing lead.

[0024] FIG. **1**B is a block diagram schematically illustrating an implantable pulse generator (IPG) **60**, according to one example of the present disclosure. In one embodiment, IPG **60** generally includes at least substantially the same features and attributes as IPG **35** of FIG. **1**A. As illustrated in FIG. **1**B, in one example, implantable pulse generator **60** includes controller **62**, memory **64**, sensing module **66**, stimulation module **68**, patient management module **70**, and a therapy manager **72**.

[0025] Via an array of parameters, the sensing module **66** receives and tracks signals from various physiologic sensors (such as a pressure sensor, blood oxygenation sensor, acoustic sensor, electrocardiogram (ECG) sensor, or impedance sensor) in order to determine a respiratory state of a patient, whether or not the patient is asleep or awake, and other respiratory-associated indicators, etc. Such respiratory detection may be received from either a single sensor or any multiple of sensors, or combination of various physiologic sensors which may provide a more reliable and accurate signal. In one example, sensing module **90** receives signals from sensor portion **40** and/or sensors **47**, **48**, **49** in FIG. **1**A.

[0026] In one example, a controller **62** of IPG **60** comprises one or more processing units and associated memories configured to generate control signals directing the operation of IPG **60** and system **10** (FIG. **1**A). In particular, in response to or based upon commands received via an input and/or machine readable instructions (including software) contained in the memory **64** associated with the controller **62** in response to physiologic data gathered via the sensors, controller **62** generates control signals directing operation of pulse generator **60** to selectively control stimulation of a target nerve, such as the hypoglossal nerve, to restore airway patency and thereby reduce or eliminate apnea events. In one example, controller **62** is embodied in a general purpose computer.

[0027] For purposes of this application, in reference to the controller **62**, the term "processor" shall mean a presently developed or future developed processor (or processing resources) that executes sequences of machine readable instructions (such as but not limited to software) contained in a memory. Execution of the sequences of machine readable instructions causes the processor to perform actions, such as operating IPG **60** to provide apply stimulation to a nerve in the manner described in the examples of the present disclosure. The machine readable instructions may be loaded in a random access memory (RAM) for execution by the processor from their stored location in a read only memory (ROM), a mass storage device, or some other persistent storage or non-volatile form of memory, as represented by memory **64**. In one example, memory **64** comprises a computer readable medium providing non-transitory or non-volatile storage of the machine readable instructions executable by a process of controller **62**. In other examples, hard wired circuitry may be used in place of or in combination with machine readable instructions (including software) to implement the functions described. For example, controller **62** may be embodied as

part of at least one application-specific integrated circuit (ASIC). In at least some examples, the controller **62** is not limited to any specific combination of hardware circuitry and machine readable instructions (including software), nor limited to any particular source for the machine readable instructions executed by the controller **62**.

[0028] With this in mind, in general terms the therapy manager **72** acts to synthesize respiratory information, to determine suitable stimulation parameters based on that respiratory information, and to direct electrical stimulation to the target nerve.

[0029] In one example, among other components, therapy manager **72** includes a stimulation protocol determination module **74**.

[0030] In one example, the stimulation protocol determination module **74** includes an input function **76** and a selector function **78**. In general terms, the input function receives an indication of an upper airway flow limitation that is sensed via respiratory effort information. In one example, input function **76** includes a flow limitation parameter **80** and a respiratory effort parameter **82**.

[0031] In one example, the flow limitation parameter **80** detects and tracks when a flow limitation is present in the upper airway of a patient. In one aspect, the flow limitation parameter **80** tracks the degree and/or duration of flow limitation. Various examples of recognizing a flow limitation are further described below in association with at least FIGS. **3-13**.

[0032] In one example, the respiratory effort parameter **82** detects and tracks respiratory effort information obtained via sensing respiratory information such as, but not limited to, the respiratory sensing methods previously described above in association with FIGS. **1A-1B**. This respiratory effort information corresponds to air flow and enables constructing or determining a degree and/or duration of a flow limitation in the upper airway of a patient.

[0033] As noted above, the therapy manager **72** also includes a selector function **78**, which in general terms, enables the IPG **60** to select an appropriate stimulation protocol that is responsive to a particular type of upper airway flow limitation. In one example, the selector function **78** includes a respiratory phase parameter **84** and a protocol array parameter **86**. The respiratory phase parameter **84** determines which respiratory phase or phases, or portions of the respective phases, in which stimulation should be applied. In one aspect, these determinations are made based on the ongoing sensing of respiratory effort, with the sensed information being received by input function **76**.

[0034] The protocol array parameter **86** provides an array of stimulation protocols suitable for delivering to a nerve of a patient, depending upon the type, degree, and/or duration of a flow limitation. The protocol array parameter **86** does so in cooperation with respiratory phase parameter **84** and input function **76**.

[0035] Specific examples of treating disordered breathing via the therapy manager **72**, and in particular, treating upper airway flow limitations (i.e. obstructions) via the functions, components, parameters, and/or features of protocol determination module **74** of therapy manager **72** are further described and illustrated below in association with FIGS. **3-13**.

[0036] In general terms, the stimulation module **68** of IPG **60** is configured to generate and apply a neuro-stimulation signal via electrode(s) (such as stimulation electrode(s) **45** in FIG. **1A**) according to a treatment regimen programmed by a physician and/or in cooperation with therapy manager **72**, such as via protocol determination module **74**.

[0037] In general terms, the patient management module **70** is configured to facilitate communication to and from the IPG **60** in a manner familiar to those skilled in the art. Accordingly, the patient management module **70** is configured to report activities of the IPG **70** (including sensed physiologic data, stimulation history, number of apneas detected, etc.) and is configured to receive initial or further programming of the IPG **60** from an external source, such as a patient programmer, clinician programmer, etc.

[0038] In one example, as shown in FIG. **1C**, prior to applying stimulation to maintain and/or restore patency in the upper airway, at **102** the method **100** includes identifying a pattern of flow limitation during the respiratory cycle. In one aspect, method **100** identifies the circumstances in which a flow limitation primarily occurs. In particular, with further reference to FIG. **1**, method **100** distinguishes between a flow limitation occurring: (1) predominantly during inspiration (at **104**); (2) predominantly during expiration (at **106**); or (3) during both a portion of inspiration and a portion of expiration which acts as a mixed flow limitation (at **108**). In one aspect, in the context of the present disclosure, a flow limitation corresponds to a narrowing of the upper airway of the type typically associated with obstructive sleep apnea or other disordered breathing patterns, as familiar to those skilled in the art.

[0039] As shown in FIG. **1C**, in one example, in the event that the flow limitation occurs predominantly during inspiration (at **104**), then stimulation is applied during and/or synchronized with inspiration (at **110**). On the other hand, in another example, in the event that the flow limitation occurs predominantly during (i.e. coincides with) expiration (at **106**), and then stimulation is applied during and/or synchronized with expiration (at **112**).

[0040] However, in some examples, when the flow limitation occurs predominantly during (i.e. coincides with) a portion of inspiration and a portion of expiration (at **108**), the stimulation is applied during some portion of inspiration and some portion of expiration (at **114**).

[0041] In one example, when the flow limitation overlaps the transition between the end of inspiration and the beginning of expiration, the stimulation will be applied to overlap the transition between the end of inspiration and the beginning of expiration.

[0042] In another example, when the flow limitation occurs during a portion of inspiration and a portion of expiration (at **108**), the stimulation is applied to cover an entire respiratory cycle, including an entire inspiratory phase and an entire expiratory phase.

[0043] In order to recognize a flow limitation, the method **100** uses as a reference point a normal breathing pattern **150**, as shown in FIG. **2**. Of course, variances may exist from patient-to-patient so it will be understood that the normal breathing pattern **150** is a representative example provided for illustrative purposes and is not intended to strictly define a breathing pattern that is universally normal for all patients. With this in mind, in some embodiments, the method **100** uses the particular breathing pattern of a specific patient (to which the method is applied) as the reference point to evaluate the presence or absence of a flow limitation in breathing.

[0044] In the example of normal breathing pattern **150** shown in FIG. **2**, a respiratory cycle **160** includes an inspiratory phase **162** and an expiratory phase **170**. The inspiratory

phase **162** includes an initial portion **164**, intermediate portion **165**, and end portion **166** while expiratory phase **170** includes an initial portion **174**, intermediate portion **175**, end portion **176**, and an expiratory peak **177**. A first transition **180** occurs at a junction between the end inspiratory portion **166** and the initial expiratory portion **174** while a second transition **182** occurs at a junction between the end expiratory portion **176** and the initial inspiratory portion **164**.

[0045] In one example, the various stimulation protocols described and illustrated in association with FIGS. **3-13** are implemented via system **10** (FIG. **1**A) and/or IPG **60** (FIG. **1**B) including at least therapy manager **72** and/or protocol determination module **74**. However, in another example, the various stimulation protocols described and illustrated in association with FIGS. **3-13** are implemented via other component, modules, and systems.

[0046] FIG. **3** is a diagram **200** illustrating a disordered breathing pattern **203**A and treated breathing pattern **203**B (separated by dashed line **203**C), according to one embodiment of the present disclosure. As shown in FIG. **3**, disordered breathing pattern **203**A reflects the presence of a flow limitation in the upper airway that occurs predominantly during the inspiratory phase of a respiratory cycle. The inspiratory phase **202**A includes an initial portion **204**A, an intermediate portion **205**A, and an end portion **206**A while the expiratory phase **210**A includes an initial portion **214**A, intermediate portion **215**A, peak **217**A, and end portion **216**A. In one aspect, intermediate portion **205**A of inspiratory phase **202**A forms a generally flat or horizontal shape corresponding to a substantially truncated amplitude (as compared to a normal breathing pattern, such as FIG. **2**) and that reflects the occurrence of a flow limitation (symbolically represented by arrow **201**) in the upper airway during inspiration. However, via application of stimulation (symbolically represented by bar **221**), breathing is restored as represented by treated breathing pattern **202**B in which intermediate portion **205**B of inspiratory phase **202**B resumes a generally parabolic shape corresponding to a generally normal amplitude and that represents amelioration of the flow limitation. In one embodiment, the stimulation is represented by bar **221**, which extends from a first end **222** to a second end **224**, with the stimulation substantially coinciding with the entire duration of the inspiratory phase **202**B. As shown in FIG. **3**, the stimulation **221** terminates prior to the expiratory phase **210**B. However, as will be explained in more detail below, in other embodiments, the applied stimulation does not extend the entire duration of inspiratory phase **202**B but is applied to select portions of the inspiratory phase **202**B.

[0047] It will be understood that, in one example, the detection of flow limitations and/or associated apneas), as well as the detection of the beginning and end of the respective inspiratory and expiratory phases of the respiratory cycle to enable determining when to stop or start stimulation, is performed according to, or in cooperation with, known methods and devices for doing so. Some non-limiting examples of such devices and methods to recognize and detect the various features and patterns associated with respiratory effort and flow limitations include, but are not limited to: PCT Publication WO/2010/059839, titled A METHOD OF TREATING SLEEP APNEA, published on May 27, 2010; Christopherson U.S. Pat. No. 5,944,680, titled RESPIRATORY EFFORT DETECTION METHOD AND APPARATUS; and Testerman U.S. Pat. No. 5,522,862, titled METHOD AND APPARATUS FOR TREATING OBSTRUCTIVE SLEEP APNEA.

[0048] FIG. **4** is a diagram **250** illustrating a disordered breathing pattern **253**A and treated breathing pattern **253**B, according to one embodiment of the present disclosure. As shown in FIG. **4**, disordered breathing pattern **253**A reflects the presence of a flow limitation in the upper airway that occurs predominantly during the expiratory phase of a respiratory cycle. In the disordered breathing pattern **253**A, the inspiratory phase **252**A includes an initial portion **254**A, an intermediate portion **255**A, and an end portion **256**A, with the inspiratory phase **252**A exhibiting a generally normal breathing pattern **150** (FIG. **2**). Referring again to FIG. **4**, the expiratory phase **262**A includes an initial portion **264**A, intermediate portion **265**A, peak **267**A, and end portion **266**A. In one aspect, expiratory phase **262**A has a relatively shallow peak **267**A corresponding to an amplitude or peak pressure that is substantially smaller than a peak **177** of an expiratory phase **170** in a normal breathing pattern **150** (FIG. **2**). The pattern of expiratory phase **262**A, which corresponds to a generally shallow expiration, reflects the occurrence of a flow limitation (symbolically represented by arrow **251**) in the upper airway during expiration. Moreover, because the peak **267**A is so shallow, the intermediate portion **265**A in the expiratory phase **262**A has a relatively gradual upward slope instead of the generally steep upward slope present in the intermediate portion **175** in the normal expiratory phase **170** (of a normal breathing pattern **150** in FIG. **2**).

[0049] However, as shown in FIG. **4**, via application of stimulation (symbolically represented by bar **270**), the expiratory phase **262**B becomes corrected such that peak **267**B resumes its full amplitude and intermediate portion **265**B of expiratory phase **262**B is restored to a generally steep upward slope, both of which represents amelioration of the flow limitation. In one embodiment, the stimulation (**270**) is represented by bar **271** (which extends from a first end **272** to a second end **274**) and substantially coincides with the entire duration of the expiratory phase **262**B. However, as will be explained in more detail below, in other embodiments, the applied stimulation extends only part of the duration of expiratory phase **262**B.

[0050] In one embodiment, application of the stimulus occurs at an inspiratory phase (FIG. **3**) or at an expiratory phase (FIG. **4**), respectively, of every respiratory cycle. However, in other embodiments, application of the stimulus is applied selectively to just some respiratory cycles, as needed, in association with an auto-titration method. One example of such auto-titration methods include A METHOD OF TREATING SLEEP APNEA as described and illustrated in PCT Publication WO/2010/059839, published on May 27, 2010.

[0051] FIG. **5**A is a diagram **280** illustrating a disordered breathing pattern **283**A and treated breathing pattern **283**B, according to one embodiment of the present disclosure. As shown in FIG. **5**A, disordered breathing pattern **283**A represents a flow limitation in the upper airway that occurs during both a portion of an inspiratory phase **282** and a portion of the expiratory phase **292** of a respiratory cycle. As shown in FIG. **5**A, the inspiratory phase **282**A includes an initial portion **284**A, an intermediate portion **285**A, and an end portion **286**A while the expiratory phase **292**A includes an initial portion **294**A, intermediate portion **295**A, peak **297**A, and end portion **296**A.

[0052] In one aspect, FIG. **5**A illustrates that in disordered breathing pattern **283**A, intermediate portion **285**A of inspiratory phase **282**A forms a generally flat or horizontal shape corresponding to a substantially truncated amplitude (as compared to the inspiratory phase **162** of a normal breathing pattern **150**, such as FIG. **2**), with this generally flat shape reflecting the occurrence of a flow limitation (symbolically represented by arrow **281**A) in the upper airway during inspiration.

[0053] In another aspect, disordered breathing pattern **283**A also includes an expiratory phase **292**A having a peak **297**A corresponding to an amplitude or peak pressure that is substantially smaller than a peak **177** of an expiratory phase **170** in a normal breathing pattern **150** (FIG. **2**). This pattern **283**A, which corresponds to generally shallow expiration, results from a flow limitation (symbolically represented by arrow **281**B) in the upper airway during expiration. Moreover, because the peak **297**A is so shallow, the intermediate portion **295**A has a relatively gradual upward slope instead of the generally steep upward slope present in the intermediate portion **175** in the normal expiratory phase **170** (of a normal breathing pattern **150** in FIG. **2**).

[0054] In one example, the indicated upper airway flow limitation predominantly coincides with both of a first portion of the inspiratory phase and a first portion of the expiratory phase. In another aspect, this indicated flow limitation does not predominantly coincide with a second portion of inspiratory phase and with a second portion of the expiratory phase.

[0055] However, via application of blended stimulation (symbolically represented by bar **300**) directed to at least a portion of the inspiratory phase and a portion of the expiratory phase, the flow limitations are mitigated. As shown in treated breathing pattern **283**B, a latter segment **285**C of intermediate portion **285**B (and end portion **286**B) resumes a more parabolic shape better resembling a baseline inspiratory phase prior to the flow limitation and that corresponds to amelioration of the "inspiratory" flow limitation.

[0056] Likewise, because this stimulation overlaps from the inspiratory phase **282**B into the expiratory phase **292**B, the treated breathing pattern **283**B exhibits a peak **297**B approaching a baseline amplitude prior to the flow limitation (like amplitude **177** in the expiratory phase **170** of normal breathing pattern **150** of FIG. **2**). This treated breathing pattern **283**B also exhibits an intermediate portion **295**B that is restored to steeper upward slope amplitude, both of which represents amelioration of the "expiratory" flow limitation.

[0057] In one embodiment, the stimulation is represented by bar **300**, which extends from a first end **301** (in the inspiratory phase **282**B) to a second end **303** (in the expiratory phase **292**B). The stimulation is applied as a generally continuous stimulation period that is initiated (at a start point located away from a beginning portion **284**B of the inspiratory phase **252**B) from partway through the intermediate portion **285**B and through the end portion **285**C of the inspiratory phase **282**B, through the transition from inspiration to expiration, through the initial portion **294**B and peak **297**A of the expiratory phase **292**B, and at least partway through the intermediate portion **295**B of the expiratory phase **292**B (to a termination point prior to end portion **296**B of expiratory phase **292**B).

[0058] In one example, the embodiment of FIG. **5**A addresses the situation for some patients in which the greatest risk for airway collapse appears to occur near the end of inspiration and the beginning of expiration. In these instances, besides harmfully limiting a duration and volume of inspiration, a partially restricted upper airway throughout the inspiratory phase predisposes the upper airway to be more susceptible to further collapse at the end of the inspiratory phase and/or to the beginning of the expiratory phase. Accordingly, in the embodiment of FIG. **5**A, the blended stimulation (represented by bar **300**) begins at start point approximately midway through the inspiratory phase **282**B and extends substantially continuously through a transition between the end of inspiration and the beginning of expiration until reaching a termination point approximately midway through the expiratory phase **292**B. In one aspect, this blended stimulation is terminated after a bulk of the expiration would have been expected to occur. In this way, continuous stimulation of the hypoglossal nerve through complete respiratory cycles is avoided, which in turn, minimizes unnecessary stimulation of the hypoglossal nerve. Instead, in these embodiments, stimulation is applied strategically in targeted portions of one or more respiratory cycles to prevent upper airway collapse so that stimulation is applied more judiciously while still achieving efficacious results.

[0059] Further, it will be understood that diagram **280** in FIG. **5**A provides just one example schematically illustrating the application of a blended stimulation that overlaps the end of the inspiratory phase and the beginning of the expiratory phase.

[0060] Accordingly, applying this blended stimulation overcomes expiratory narrowing, which otherwise might render the upper airway vulnerable to complete collapse during a subsequent inspiratory effort.

[0061] Without being bound to any particular theory, it is believed that the blended stimulation that overlaps the end of inspiratory phase and the expiratory phase acts to maintain a minimum level of pressurization within the lungs, which in turn helps maintain airway patency because the minimum level of pressurization helps to prevent a high intensity vacuum from the lungs on the airway, which would otherwise potentially cause collapse of the upper airway.

[0062] In this way, for some patients, the stimulation is applied during a period having a higher risk for collapse without having to continuously apply stimulation through the entire respiratory cycle, which in turn, saves energy and minimizes potentially unnecessary stimulation of the nerves.

[0063] In one example of a stimulation protocol, such as the one described and illustrated in association with FIG. **5**A, the generally continuous stimulation period (as represented by bar **300** in FIG. **5**A and spanning over a portion of the inspiratory phase and a portion of the expiratory phase) is applied to a set of consecutive respiratory cycles over a first time period. Moreover, an input module (such as input module **76** of protocol determination module **74** of therapy manager **72** in FIG. **1**B) is configured to evaluate whether flow limitations are persisting despite the stimulation protocol or whether the stimulation protocol has mitigated or eliminated the previously occurring flow limitations. Accordingly, in one aspect, the input module of the therapy manager determines if at least some indications of upper airway flow limitations are received within the first time period. In another aspect, the input module of the therapy manager increases a duration of the generally continuous stimulation period if the input module receives the at least some indications during the first time period when such indications exceed a threshold. In another aspect, the input module of the therapy manager reduces the duration of the generally continuous stimulation period if the

input module receives no indications of upper airway flow limitations (or a number of indications less than a threshold) during the first time period.

[0064] In one example, the first time period (over which the set of respiratory cycles take place) is a duration, based on an apnea-hypopnea index of a patient, in which an apnea would be expected to occur in the absence of stimulation.

[0065] FIG. **5**B is a diagram schematically illustrating portions of a generally continuous stimulation period relative to portions of an inspiratory phase and an expiratory phase, according to one example of the present disclosure.

[0066] As a reference point for illustrating the generally continuous stimulation period, FIG. **5**B provides substantially the same depiction of a respiratory cycle **160** that was previously shown in FIG. **1**. Accordingly, the illustrated respiratory cycle **160** includes an inspiratory phase **162** and an expiratory phase **170**. The inspiratory phase **162** includes an initial portion **164**, intermediate portion **165**, and end portion **166** while expiratory phase **170** includes an initial portion **174**, intermediate portion **175**, end portion **176**, and an expiratory peak **177**. A first transition **180** occurs at a junction between the end inspiratory portion **166** and the initial expiratory portion **174** while a second transition **182** occurs at a junction between the end expiratory portion **176** and the initial inspiratory portion **164**.

[0067] According to one example of the present disclosure, FIG. **5**B further illustrates a first bar **361** that represents a first portion **360** of a generally continuous stimulation period **358** and a bar **381** that represents a second portion **380** of a generally continuous stimulation period **358**. As shown in FIG. **5**B, the bar **361** includes first end **362** that generally coincides with junction **180** (the end of inspiratory phase **162** and beginning of expiratory phase **170**) and a second end **364** located in an intermediate portion of the inspiratory phase **162**. As shown in FIG. **5**B, bar **381** includes first end **382** that generally coincides with junction **180** (the end of inspiratory phase **162** and beginning of expiratory phase **170**) and a second end **384** located in an intermediate portion of the expiratory phase **170**.

[0068] As further demonstrated by FIG. **5**B, while the generally continuous stimulation period overlaps the inspiratory and expiratory phases **162**, **170**, the duration of each of the first and second portions of the generally continuous stimulation period can vary among different nerve stimulation protocols as determined by the protocol determination module **74** of therapy manager **72** (FIG. **1**B).

[0069] In one example, the first portion **360** of the generally continuous stimulation period **358** has a duration of at least one-third (identified by marker **372**) of an entirety (E1) of the inspiratory phase **162**. In one aspect, the relative proportion of one-third is measured starting at end **362** of bar **361**, per directional reference arrow **357**. In another example, the first portion **360** of the generally continuous stimulation period **358** has a duration of at least one-half (identified by marker **370**) of the entirety (E1) of the inspiratory phase **162**. In another example, the first portion **360** of the generally continuous stimulation period **358** has a duration of at least two-thirds (identified by marker **374**) of the entirety (E1) of the inspiratory phase **162**

[0070] In another example, the second portion **380** of the generally continuous stimulation period **358** has a duration of at least one-third (identified by marker **392**) of an entirety (E2) of the expiratory phase **170**. In one aspect, the relative proportion of one-third is measured starting at end **382** of bar **381**, per directional reference arrow **377**. In another example, the first portion **380** of the generally continuous stimulation period **358** has a duration of at least one-half (identified by marker **390**) of the entirety (E2) of the expiratory phase **170**. In another example, the first portion **380** of the generally continuous stimulation period **358** has a duration of at least two-thirds (identified by marker **393**) of the entirety (E2) of the expiratory phase **170**.

[0071] In one example, the first portion (during which stimulation is applied) of the inspiratory phase **162** corresponds to at least a majority of an entirety (E1) of the inspiratory phase **162** and the first portion (during which stimulation is applied) of the expiratory phase **170** corresponds to at least a majority of an entirety (E2) of the expiratory phase **170**. In one example, a majority is defined as at least fifty-one percent (i.e. 51%). In another example, the majority of the inspiratory phase **162** is defined as an at least two-thirds majority of the entirety (E1) of the inspiratory phase **162** and the majority of the expiratory phase is defined as an at least two-thirds majority of the entirety (E2) of the expiratory phase **170**.

[0072] In one example, variations on the stimulation protocol associated with FIGS. **5**A and **5**B are further described later in association with at least FIGS. **6** and **11**.

[0073] In another embodiment, as shown in FIG. **6**, diagram **310** schematically illustrates a disordered breathing pattern **333**A resulting from a mixed flow limitation that is substantially similar to the mixed flow limitation in FIG. **5**A. However, unlike the substantially continuous segment of stimulation **300** applied in FIG. **5**A, in the embodiment shown in FIG. **6**, stimulation is applied in two separate relatively short bursts **340**, **342**. One burst **340** is applied at the beginning of the inspiratory phase **322**B while the other burst **342** is applied at the beginning of the expiratory phase **332**B. In this embodiment, the stimulation is targeted to anticipate an obstruction, and in turn, apply stimulation at the beginning of one or both of the respective inspiratory and expiratory phases. By stimulating (for a short duration) at the beginning of a respective inspiratory and expiratory phases, the upper airway is held open prior to the maximum flow of air in that phase so that once the flow of air commences, with the upper airway already open to a generally full degree, the inspired or expelled air (respectively) completes the job of maintaining the upper airway in the open state during the remainder of the respective inspiratory or expiratory phase. In another aspect, one potential benefit from applying a stimulation burst at the beginning of an inspiratory phase is the resulting counteraction of the negative pressure (generated by the inspiratory effort) applied to the upper airway.

[0074] Without being bound to any particular theory, it is believed that by applying a stimulation burst (e.g., an additional stimulation burst on top of a baseline level of stimulation or an isolated burst of stimulation without a baseline level of stimulation) at the beginning of the inspiratory phase, the stimulation causes or ensures radial expansion of the airway at the very time that a high intensity vacuum would be applied (via the lungs) to the upper airway such that the radial expansion of the upper airway (caused by the stimulation burst) directs action or response of tissues in a direction opposite the action of tissue that would might otherwise occur when the vacuum from lungs acts on the upper airway tissues. Accordingly, the stimulation is timed to produce momentum in the tissues of the upper airway toward radial expansion prior to the high intensity vacuum pull (which might otherwise contribute to collapse of the upper airway) from the lungs during

the onset of inspiration. Because there is a delay associated with, or caused by, a time constant in the response of the upper airway tissues, by first stimulating the tissue in advance of the vacuum pull from the lungs, enough momentum is established toward radial expansion of the upper airway via the stimulation burst that this momentum counteracts or prophylactically negates the otherwise potentially collapsing effects of the vacuum pull on the upper airway tissues.

[0075] In one aspect, by applying stimulation in this manner, it is believed that airway patency is maintained with less overall stimulation being applied because stimulation is applied strategically within one or more respiratory cycles rather than indiscriminately through entire respiratory cycles. With this in mind, in one embodiment the total combined duration of burst **340** and burst **342** (shown in FIG. **6**) is substantially less than the duration of the stimulation pulse **300** in FIG. **5**A. Accordingly, adequate airway patency is achieved while significantly reducing the total volume of stimulation applied to the nerve.

[0076] In some embodiments in which separate bursts of stimulation are applied to the inspiratory and expiratory phases, respectively, the duration of the bursts in the inspiratory phase differ from the duration of the burst applied in the expiratory phase. For example, as shown in the diagram **400** of FIG. **7**A, a representative or normal breathing pattern **401** is maintained by applied stimulation. A stimulation burst (represented by bar **420**A) of a first duration is applied at the beginning of the inspiratory phase **402**A while a second stimulation burst (represented by bar **422**A) is applied during substantially the entire expiratory phase **412**A. This pattern of stimulation bursts is repeated throughout successive respiratory cycles **402**B, **402**C, etc.

[0077] In one aspect, the determination regarding the duration of each "inspiratory phase" burst (**420**A, **420**B, **420**C) and the duration of each "expiratory phase" burst (**422**A, **422**B, **422**C) can vary from patient-to-patient depending upon whether the particular patient tends to exhibit a greater flow limitation in the inspiratory phase **403**A or in the expiratory phase **413**A. In the example, shown in FIG. **7**A, the "expiratory phase" bursts (**422**A, **422**B, **422**C) have a longer duration than the "inspiratory phase" bursts (**420**A, **420**B, **420**C) to treat a patient that generally exhibits a mixed flow limitation (both inspiratory and expiratory) but having greater flow limitations during the expiratory phase.

[0078] In one embodiment, anyone of or all of an amplitude, a pulse width, a frequency of applied stimulation during the inspiratory phase is different than anyone of (or all of) an amplitude, a pulse width, a frequency of applied stimulation during the expiratory phase. In addition, a ramped stimulation pattern in which stimulation ramps upward (increases) at the beginning of a stimulation period or ramps downward at the end of a stimulation period, can be applied in one or both of the inspiratory and expiratory phases.

[0079] In some embodiments, as shown in FIG. **7**B, instead of applying a stimulation burst with each respiratory cycle, the stimulation bursts (e.g. **420**A, **420**C, **422**A, **422**C) are applied every other respiratory cycle, such that an intermediate "inspiratory phase" burst **422**A and an intermediate "expiratory phase" burst **422**B are omitted. In this embodiment, the patient need not receive a stimulation burst each respiratory cycle because with this stimulation pattern the patient receives enough oxygen to keep the respiratory drive in equilibrium. In another embodiment, the pattern of stimulation bursts in the inspiratory phase (applied every respiratory cycle, such as **420**A, **420**B, **420**C) need not be matched by the pattern of stimulation bursts in the expiratory phase (applied every other respiratory cycle, such as **422**A and **422**C), or vice versa. In this way, the upper airway remains patent and the patient receives sufficient oxygen without receiving stimulation in each inspiratory phase or in each expiratory phase.

[0080] In yet other embodiments, other forms of alternating stimulation bursts are applied. For example, in one pattern of stimulation, a low amplitude continuous pulsed stimulation is applied and one or more relatively shorter duration stimulation bursts are applied in a targeted and additive manner to the low amplitude continuous stimulation. FIG. **8** is a diagram **450** schematically illustrating a method of treating sleep disordered breathing via a stimulation pattern, according to one embodiment of the present disclosure. As shown in FIG. **8**, a respiratory cycle **453** includes an inspiratory phase **451** and an expiratory phase **461**. The inspiratory phase **451** includes an initial portion **454**, an intermediate portion **455**, and an end portion **456** while the expiratory phase **461** includes an initial portion **464**, intermediate portion **465**, peak **467**, and end portion **466**.

[0081] As further shown in the diagram **450** of FIG. **8**, a low amplitude continuous pulsed stimulation (represented by bar **470**) is applied in the inspiratory phase **451** and a low amplitude pulsed continuous stimulation (represented by bar **480**) in the expiratory phase **461**. While bars **470**, **480** are shown as separate elements for illustrative purposes, it will be understood that the generally continuous stimulation is substantially uninterrupted through the transition from the inspiratory phase **451** to the expiratory phase **461**. In addition, as shown in FIG. **8**, a shorter duration stimulation burst **475** is applied only in the inspiratory phase **451** (for patients having predominantly inspiratory-based flow limitations) in addition to the generally continuous pulsed lower amplitude tone stimulation **470**. While the additional stimulation burst **475** could be applied anywhere within the inspiratory phase **451**, in the example shown in FIG. **8**, the burst is applied at the initial portion **454** of the inspiratory phase **451**. In one aspect, applying the burst at the initial portion **454** helps to ensure full patency of the upper airway as inspiration begins because the stimulation causes a response like the action of a virtual stent in the upper airway to pre-establish patency prior to the vacuum pull from the lungs. As previously noted, the initial portion of stimulation (during a peak pressure period) effectively establishes momentum of the upper airway to be moving in direction of expansion (radially outward) such that upon a vacuum applied via the lungs during inspiration, the upper airway tends to stay expanded because response of tissue is slow enough such that the vacuum (generated by the lungs) cannot fully overcome the already established momentum of radial expansion of the upper airway and therefore the initial portion of stimulation prevents collapse of the upper airway.

[0082] Without being bound by any particular theory, it is believed that using a burst of stimulation (for example, burst **475** in FIG. **8**) helps to keep blood oxygenation levels and carbon dioxide levels within an acceptable range, which in turn moderates the respiratory drive, which in turn minimizes peak respiratory pressures. Together, these factors minimizes the risk of an upper airway collapse because the lungs are not forced (via the respiratory drive) to exert extra vacuum pressure on an upper airway in an attempt to acquire more oxygen.

[0083] In one embodiment, the stimulation pattern in FIG. **8** is modified, such that the modified pattern omits the base

level of generally continuous stimulation **470** in the inspiratory phase **451**, leaving just one or more stimulation bursts **475** in the inspiratory phase **451**. Meanwhile, the modified pattern retains the base level stimulation **480** during the expiratory phase **461**, which effectively acts to maintain tone and patency of the upper airway during the expiratory phase **461**.

[0084] FIG. **9** is a diagram **500** schematically illustrating a method of treating sleep disordered breathing via a stimulation pattern that is modified relative to the stimulation pattern of FIG. **8**, according to one embodiment of the present disclosure. As shown in FIG. **9**, a respiratory cycle **503** includes an inspiratory phase **501** and an expiratory phase **511**. The inspiratory phase **501** includes an initial portion **504**, an intermediate portion **505**, and an end portion **506** while the expiratory phase **511** includes an initial portion **514**, intermediate portion **515**, peak **517**, and end portion **516**. As further shown in diagram **450** of FIG. **9**, a shorter duration stimulation burst **535** is applied only in the expiratory phase **511** (for patients having predominantly expiratory-based flow limitations) in addition to the generally continuous pulsed lower amplitude tone stimulation **530**. In particular, as shown in FIG. **8**, a low amplitude pulsed continuous stimulation (represented by bar **520**) is applied in the inspiratory phase **501** and a low amplitude continuous stimulation (represented by bar **530**) in the expiratory phase **511**. While the additional stimulation burst **535** could be applied anywhere within the expiratory phase **511**, in the example shown in FIG. **9**, the burst is applied at the initial portion **514** and peak portion **517** of the expiratory phase **511** to ensure full patency during peak expiration. In another aspect, in this arrangement the low level generally continuous stimulation **530** and burst **535** are applied at the point at which the patient has exhibited the most significant flow limitations in the upper airway.

[0085] FIG. **10** is a diagram **550** schematically illustrating a method of treating sleep disordered breathing via a stimulation pattern that is modified relative to the stimulation pattern of FIG. **8**, according to one embodiment of the present disclosure. As shown in FIG. **10**, a respiratory cycle **503** includes an inspiratory phase **501** and an expiratory phase **511**. The inspiratory phase **501** includes an initial portion **504**, an intermediate portion **505**, and an end portion **506** while the expiratory phase **511** includes an initial portion **514**, intermediate portion **515**, peak **517**, and end portion **516**.

[0086] As further shown in FIG. **10**, the stimulation pattern of FIG. **8** is modified so that one additional stimulation burst **560** (in addition to the lower amplitude continuous stimulation **520**) is applied at the latter portion of the inspiratory phase **501** and one additional stimulation burst **535** is applied at the initial portion **514** and peak portion **517** of the expiratory phase **511** (in substantially the same manner as in diagram **500** of FIG. **8**). In this embodiment, the two bursts **560**, **535** of stimulation mimic the stimulation pattern in FIG. **5** with the overall stimulation pattern also including the low level generally continuous stimulation **520**, **530** throughout both the inspiratory and expiratory phases **501**, **511**.

[0087] In some embodiments, the moment at which stimulation burst is initiated (within a given inspiratory phase or give expiratory phase) is optimized so that no surplus stimulation is applied. For example, in an example in which a patient has a mixed flow limitation, and a single longer stimulation burst is applied that overlaps both the inspiratory phase and the expiratory phase (such as shown in FIG. **5**), an autotitrating method is applied in which a start point is selected for initiating stimulation during the inspiratory phase and a termination point is selected for terminating stimulation during the expiratory phase.

[0088] With further reference to FIGS. **8-10** and **13**, it will be understood that adjusting the stimulation amplitude is just one way of modulating the intensity of stimulation, and that in other embodiments, the stimulation intensity is modulated via adjusting the frequency, pulse width, duration, polarity, etc. of pulsed stimulation. For example, instead of applying a stimulation burst of increase amplitude (such as burst **475** in FIG. **8** or burst **535** in FIG. **9**), the stimulation burst can include an increased pulse width, increased frequency, or change in polarity.

[0089] FIG. **11** shows a diagram **600** schematically illustrating a method of treating disordered breathing, according to one embodiment of the present disclosure. As shown in FIG. **11**, a respiratory cycle **603** includes an inspiratory phase **601** and an expiratory phase **611**. The inspiratory phase **601** includes an initial portion **604**, an intermediate portion **605**, and an end portion **606** while the expiratory phase **611** includes an initial portion **614**, intermediate portion **615**, peak **617**, and end portion **616**. As shown in diagram **600** of FIG. **11**, an initial start point for stimulation **630** is identified (point A) and an initial termination point of stimulation **640** is identified (point F). It will be understood that in at least one example, stimulation segments **630**,**640** are shown as separate elements for illustrative clarity, and that in fact segments **630**, **640** represent a single substantially continuous period of stimulation.

[0090] Using these parameters, therapy is applied through a period of time to observe whether the applied stimulation is efficacious. In the event that the stimulation period (segments **630** and **640**) within the respiratory cycle is sufficient to ameliorate the sleep disordered breathing, the method begins to scale back the total duration of the stimulation period (segments **630**, **640**). Accordingly, the start point of stimulation segment **630** is moved to point B, corresponding to a shorter period of stimulation (in the inspiratory phase **601**), and therapy is applied for a period of many respiratory cycles while observing whether the shortened duration of stimulation is efficacious. This adjustment process is continued in which the duration of stimulation segment **630** in the inspiratory phase **601** is reduced one step at a time (as represented by directional arrow R), until a start point (e.g. A, B, C, D, E, etc.) is identified at which the inspiratory-phase stimulation segment **630** becomes too short as evidenced by the stimulation starting to lose its effectiveness in maintaining and/or restoring airway patency. In other words, the start point is moved in decrements closer to the end portion of the inspiratory phase until a loss of efficacious stimulation therapy is identified.

[0091] In one example, once the start point has been adjusted by a decrement (one step), the new duration is maintained for a set of consecutive respiratory cycles to provide a sufficient period of time over which to evaluate the new settings.

[0092] With this information, one can identify the last initiation point at which the desired effectiveness was achieved, and this point is adopted as the optimal start point for stimulation segment **630** in the inspiratory phase **610** for this patient. For example, if the start point D resulted in a stimulation segment **630** that proved ineffective in maintaining or restoring airway patency, while start point C was the last successful start point, then the optimal stimulation segment **630** would have a start point C. Once the optimal start point is

adopted, each stimulation segment **630** within a give respiratory cycle **603** would begin at start point C.

[0093] In one example, the size of the decrements or steps between the respective start points (A, B, C, etc.) correspond to a fraction (such as 1/10, 1/5, or 1/8, etc. of the entire duration of the first portion **360** of the stimulation period **358**.

[0094] In another example, the initial starting point (e.g. A) is selected to correspond to one of the example durations (two-thirds, one-half, or one-third) of the first portion **360** of the generally continuous stimulation period **358** shown in FIG. **5**B.

[0095] A similar method is applied to the expiratory phase **611** such that the optimal termination point of the stimulation period (segments **630** and **640**) is determined for a given respiratory cycle. In doing so, an initial termination point (e.g. point F) for stimulation segment **640** is identified, and therapy is applied. Provided that efficacy was achieved, the method continues by adopting an earlier termination point (e.g. point G), corresponding to a shorter period of stimulation (in the expiratory phase **611**), and therapy is applied for a period of time covering many respiratory cycles. The response of the patient is observed to determine if any loss of efficacy has occurred due to shortening the stimulation segment **640**. This process is continued in which the duration of stimulation **640** in the expiratory phase **611** is reduced one step at a time (as represented by directional arrow T), until a termination point (anyone of points F, G, H, I, J, K, etc.) is identified at which the expiratory-phase stimulation **640** becomes too short as evidenced by the stimulation starting to lose its effectiveness in maintaining and/or restoring airway patency. In other words, the termination point is moved in decrements closer to the beginning portion of the expiratory phase until a loss of efficacious stimulation therapy is identified.

[0096] With this information, one can identify the last termination point at which the desired effectiveness was achieved, and this point is adopted as the optimal termination point of stimulation segment **640** for this patient to overcome the mixed flow limitation (i.e. a flow limitation that overlaps both the inspiratory and the expiratory phases **601**, **611**).

[0097] In one example, once the termination point has been adjusted by a decrement (one step), the new duration is maintained for a set of consecutive respiratory cycles to provide a sufficient period of time over which to evaluate the new settings.

[0098] In one example, the size of the decrements or steps between the respective termination points (F, G, H, etc.) corresponds to a fraction (such as 1/10, 1/5, or 1/8, etc. of the entire duration of the second portion **380** of the stimulation period **358**.

[0099] In another example, the initial starting point (e.g. F) is selected to correspond to one of the example durations (two-thirds, one-half, or one-third) of the second portion **380** of the generally continuous stimulation period **358** shown in FIG. **5**B.

[0100] It will be understood, that in addition to optimizing the duration of the stimulation segments **630**, **640** shown in association with FIG. **11**, one also can optimize for other parameters of the stimulation, such as amplitude, polarity, frequency, pulse width, etc., where an increase or decrease in amplitude, frequency, pulse width, duration, etc. (or change in polarity) can allow a concomitant decrease or increase in the duration of the stimulation.

[0101] In some embodiments, an implantable stimulator also can be operated in a first mode which attempts to maintain airway patency (and is therefore prophylactic) or a second mode, which recovers airway patency that has been lost. In the first mode, a stimulation pattern is applied that uses the minimum amount of stimulation required to maintain airway patency, and may include (but is not limited to) one of the stimulation patterns previously described and illustrated in association with FIGS. **1**-**11**. However, in the event that an apnea occurred despite the attempt by the first mode to prevent conditions leading to apnea, the implantable stimulator would switch to a second, "acute" mode of operation, in which the stimulation pattern would become more aggressive in amplitude, frequency, pulse width, and duration of each stimulation burst. The selected duration, amplitude, and frequency would be based on a pre-obstruction respiratory rate. In one embodiment, managing the switch between the first mode and the second mode, as well as managing the stimulation parameters in the second mode, is performed using substantially the same systems and methods, as described in as described and illustrated in PCT Publication WO/2010/059839, entitled A METHOD OF TREATING SLEEP APNEA, published on May 27, 2010, and which is hereby incorporated by reference.

[0102] In some embodiments, a flow limitation in the upper airway is detected via respiratory sensors and/or pressure sensors to determine a relative degree of obstruction. These sensors also can be used to determine whether the obstruction is occurring during inspiration, during expiration, or during both. Moreover, because each type of obstruction yields a pressure/impedance pattern that is characteristic of the particular type of obstruction, one can use this sensing information to determine an efficacious stimulation pattern.

[0103] In some embodiments, a stimulation pattern mimics the pattern of the particular breathing phase. As shown in FIG. **12**, a respiratory cycle **653** includes an inspiratory phase **651** and an expiratory phase **661**. The inspiratory phase **651** includes an initial portion **654**, an intermediate portion **655**, and an end portion **656** while the expiratory phase **661** includes an initial portion **664**, intermediate portion **665**, peak **667**, and end portion **676**. As further shown in the diagram **650** of FIG. **12**, stimulation patterns **680** and **690** are applied, in which the greatest volume of stimulation corresponds to ensuring airway patency during the greatest volume of air flow during inspiration and expiration. Accordingly, in one stimulation pattern **680** applied during the inspiratory phase **651**, the amplitude of stimulation ramps up through the progression of the inspiratory phase **651**. In particular, stimulation pattern **680** includes a start point **681**, ramp portion **683**, plateau portion **684**, descent **685**, and end portion **682**. In general terms, this ramped stimulation pattern increases the stimulation amplitude (via ramp portion **683**) as inspiration commences and then maintains heightened stimulation amplitude (via plateau portion **684**) throughout most of the second half of the inspiratory phase **651**. While the plateau portion **684** ends prior to completion of the inspiratory phase **651** in the example shown in FIG. **12**, it will be understood that the plateau portion **684** could be extended to last through the completion of the inspiratory phase **651**.

[0104] Meanwhile, in some embodiments, a ramped stimulation pattern **690** is applied to the expiratory phase **661** as further shown in FIG. **12**. The stimulation pattern **690** includes a start point **691**, plateau portion **693**, ramp portion **694**, and end portion **692**. In general terms, this ramped stimulation pattern begins with a heightened stimulation amplitude (via plateau portion **693**) as inspiration com-

mences and then decreases the stimulation amplitude (via ramp portion **694**) throughout most of the second half of the expiratory phase **651**. In this stimulation pattern **690**, a greater stimulation is applied and maintained via plateau portion **693** at (and immediately following) peak expiration **667** in order to ensure airway patency at the beginning of the expiratory phase **661**, thereby proactively preventing airway collapse. Once expiration has commenced, then the stimulation is decreased via ramp portion **694**, as the volume of air from expiration acts to help maintain airway patency, with the stimulation pattern **690** terminating before the end portion **676** of the expiratory phase **661**.

[0105] FIG. **13** includes a diagram **700** schematically illustrating a stimulation pattern **730**, **740**, according to one embodiment of the present disclosure. As shown in FIG. **13**, a respiratory cycle **703** includes an inspiratory phase **701** and an expiratory phase **711**. The inspiratory phase **701** includes an initial portion **704**, an intermediate portion **705**, and an end portion **706** while the expiratory phase **711** includes an initial portion **716**, intermediate portion **715**, peak **717**, and end portion **716**. As further shown in FIG. **13**, the stimulation pattern **730** in the inspiratory phase **701** includes a first portion **733** of bursts **734** of stimulation in the first half of the inspiratory phase **701** and then a generally continuous stimulation segment **735** throughout the second half of the inspiratory phase **701**. Meanwhile, the stimulation pattern **740** in the expiratory phase **711** includes a first generally continuous stimulation segment **743** through the first half of the expiratory phase **711** and then a second portion **744** of bursts **745** of stimulation in the second half of the expiratory phase **711**. It will be understood that in some embodiments, the stimulation segment **735** and the stimulation segment **743** form a substantially continuous single stimulation segment, but are shown separately in FIG. **13** for illustrative purposes.

[0106] In this embodiment, stimulation is applied in bursts **734** in the early portion of the inspiratory phase **701** to maintain tone of the upper airway and then continuous stimulation **735** is applied during the latter half of the inspiratory phase **701** when maximum air flow would occur and just prior to expiration when the airway could be at greater risk for collapse. On the other hand, in the expiratory phase **711**, continuous stimulation **743** is applied during the first half of the expiratory phase when there is a greater risk of airway collapse (and maximum air flow needs to take place) while bursts **745** of stimulation are applied during the second half of the expiratory phase **711** to maintain tone and nominal airway patency.

[0107] Although specific embodiments have been illustrated and described herein, it will be appreciated by those of ordinary skill in the art that a variety of alternate and/or equivalent implementations may be substituted for the specific embodiments shown and described without departing from the scope of the present disclosure. This application is intended to cover any adaptations or variations of the specific embodiments discussed herein. Therefore, it is intended that this present disclosure be limited only by the claims and the equivalents thereof.

1. A stimulation protocol determination system comprising:

an input module to receive an indication of an upper airway flow limitation via sensed respiratory effort information, wherein the indicated upper airway flow limitation corresponds to at least a partial obstruction of the upper airway associated with sleep apneas; and

a selection module to automatically select, based on the indicated upper airway flow limitation, a nerve stimulation protocol including at least one of:

a first protocol to apply nerve stimulation generally synchronous with an expiratory phase of a respiratory cycle; and

a second protocol to apply nerve stimulation during both of a portion of an inspiratory phase of the respiratory cycle and a portion of the expiratory phase.

2. (canceled)

3. The system of claim **1**, wherein the first protocol is automatically selected when the indicated upper airway flow limitation predominantly coincides with the expiratory phase.

4. The system of claim **1**, wherein the second protocol is automatically selected when the indicated upper airway flow limitation predominantly coincides with both of a first portion of the inspiratory phase and a first portion of the expiratory phase but does not predominantly coincide with a second portion of inspiratory phase and with a second portion of the expiratory phase.

5. The system of claim **4**, wherein the first portion of the inspiratory phase includes at least an end portion of the inspiratory phase and excludes a beginning portion of the inspiratory phase, and wherein the first portion of the expiratory phase includes at least a beginning portion of the expiratory phase and excludes an end portion of the expiratory phase.

6-7. (canceled)

8. The system of claim **5**, wherein the second protocol includes a generally continuous stimulation period applied during at least a portion of at least some respiratory cycles, wherein the generally continuous stimulation period predominantly coincides with the first portion of the inspiratory phase and with the first portion of the expiratory phase, and

wherein the generally continuous stimulation period includes an initial start point located after a beginning of the inspiratory phase and an initial termination point located prior to an end of the expiratory phase.

9. The system of claim **8**, wherein the second protocol includes the application of the generally continuous stimulation period for a set of consecutive respiratory cycles over a first time period and wherein the input module is configured to:

determine if at least some indications of upper airway flow limitations exceeding a dysfunction threshold are received within the first time period;

maintain or increase a duration of the generally continuous stimulation period if the input module receives the at least some indications during the first time period;

reduce the duration of the generally continuous stimulation period if the input module receives no indications during the first time period.

10. The system of claim **9**, wherein the first time period, based on an apnea-hypopnea index, for which an apnea would likely occur in the absence of stimulation.

11. The system of claim **9**, wherein reducing the duration includes at least one of:

decrementally moving the initial start point closer to the end portion of the inspiratory phase for the next set of consecutive respiratory cycles;

decrementally moving the initial termination point closer to the beginning portion of the expiratory phase for the next set of consecutive respiratory cycles.

12. The system of claim **8**, wherein a first portion of the generally continuous stimulation period coincides with the first portion of the inspiratory phase and has a duration of at least one of:

at least one-third of an entirety of the inspiratory phase;

at least one-half of the entirety of the inspiratory phase; and

at least two-thirds of the entirety of the inspiratory phase.

13. The system of claim **8**, wherein a second portion of the generally continuous stimulation period coincides with the first portion of the expiratory phase and has a duration of at least one of:

at least one-third of the entirety of the expiratory phase;

at least one-half of the entirety of the expiratory phase; and

at least two-thirds of the entirety of the expiratory phase.

14. The system of claim **5**, wherein the first portion of the inspiratory phase corresponds to at least a majority of the inspiratory phase and the first portion of the expiratory phase corresponds to at least a majority of the expiratory phase.

15. The system of claim **14**, wherein the majority of the inspiratory phase comprises at least two-thirds of the inspiratory phase and the majority of the expiratory phase comprises at least two-thirds of the expiratory phase.

16. The system of claim **1**, wherein the selection module is configured to automatically select a third protocol to apply stimulation generally synchronous with the inspiratory phase when the flow limitation generally coincides with the inspiratory phase, and wherein the system comprises a respiration sensor to provide the sensed respiratory effort information.

17. The system of claim **1**, comprising

an implantable pulse generator; and

a nerve cuff electrode electrical couplable to the pulse generator to apply a respective one of the first and second stimulation protocols.

18. The system of claim **1**, wherein the nerve stimulation protocol is applied to at least the hypoglossal nerve.

19. (canceled)

20. A non-transitory computer readable medium for storing machine readable instructions to provide a stimulation protocol determination module comprising:

an input function to receive an indication of an upper airway flow limitation via sensed respiratory effort information; and

a selection function to automatically select, based on the indicated upper airway flow limitation, a stimulation protocol including at least one of:

a first protocol to apply stimulation generally synchronous with an expiratory phase of a respiratory cycle; and

a second protocol to apply stimulation during a portion of both of an inspiratory phase of the respiratory cycle and the expiratory phase.

21. The system of claim **1**, comprising:

a non-volatile memory for storing, and a processor for executing, machine readable instructions to provide the input module and the selection module.

22. A method of nerve stimulation comprising:

sensing respiratory effort information to identify an upper airway flow limitation associated with obstructive sleep apneas; and

automatically applying stimulation from an implantable pulse generator through a cuff electrode to an airway-patentcy-related nerve, based on the identified upper airway flow limitation, according to least one of:

a first protocol to apply stimulation to the nerve generally synchronous with an expiratory phase of a respiratory cycle; and

a second protocol to apply stimulation to the nerve during both of a portion of an inspiratory phase of the respiratory cycle and a portion of the expiratory phase.

23. The system of claim **22**, wherein the automatically applying comprises:

automatically selecting the first protocol when the indicated upper airway flow limitation predominantly coincides with the expiratory phase; and

automatically selecting the second protocol when the indicated upper airway flow limitation predominantly coincides with both of a first portion of the inspiratory phase and a first portion of the expiratory phase but does not predominantly coincide with a second portion of inspiratory phase and with a second portion of the expiratory phase.

24. The system of claim **23**, wherein the first portion of the inspiratory phase includes at least an end portion of the inspiratory phase and excludes a beginning portion of the inspiratory phase, and wherein the first portion of the expiratory phase includes at least a beginning portion of the expiratory phase and excludes an end portion of the expiratory phase.

25. The system of claim **24**, wherein automatically applying stimulation via the second protocol includes:

applying a generally continuous stimulation period during at least a portion of at least some respiratory cycles, wherein the generally continuous stimulation period predominantly coincides with the first portion of the inspiratory phase and with the first portion of the expiratory phase, and

wherein the generally continuous stimulation period includes an initial start point located after a beginning of the inspiratory phase and an initial termination point located prior to an end of the expiratory phase.

26. The system of claim **25**, comprising:

applying the generally continuous stimulation period for a set of consecutive respiratory cycles over a first time period, including:

determining if at least some indications of upper airway flow limitations exceeding a dysfunction threshold are received within the first time period;

maintaining or increasing a duration of the generally continuous stimulation period if the at least some indications are received during the first time period; and

reducing the duration of the generally continuous stimulation period if no indications are received during the first time period.

27. The system of claim **26**, wherein reducing the duration includes at least one of:

decrementally moving the initial start point closer to the end portion of the inspiratory phase for the next set of consecutive respiratory cycles;

decrementally moving the initial termination point closer to the beginning portion of the expiratory phase for the next set of consecutive respiratory cycles.

28. The system of claim **25**, wherein a first portion of the generally continuous stimulation period coincides with the first portion of the inspiratory phase and has a duration of at least one of:

at least one-third of an entirety of the inspiratory phase;

at least one-half of the entirety of the inspiratory phase; and

at least two-thirds of the entirety of the inspiratory phase.

29. The system of claim **25**, wherein a second portion of the generally continuous stimulation period coincides with the first portion of the expiratory phase and has a duration of at least one of:

at least one-third of the entirety of the expiratory phase;

at least one-half of the entirety of the expiratory phase; and

at least two-thirds of the entirety of the expiratory phase.

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