IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NYXOAH, INC., and
NYXOAH SA,
Petitioners,

v.

INSPIRE MEDICAL SYSTEMS, INC.,
Patent Owner.

U.S. Patent No. 11,806,526

Issue Date: November 7, 2023

Title: STIMULATION FOR TREATING SLEEP DISORDERED BREATHING

Inter Partes Review No.: IPR2026-00091

DECLARATION OF DR. GERALD LOEB IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,806,526

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Petitioners' Exhibit List

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1001	U.S. Patent No. 11,806,526 (the "'526 Patent")
1002	Select portions of the prosecution history of the '526 Patent ("File History")
1003	[Reserved]
1004	Declaration of Petitioner's Expert Dr. Ingrid Hsieh-Yee
1005	International Patent Application Publication No. WO 2016/149344
1006	U.S. Patent Application Publication No. 2006/0224211 ("Durand")
1007	U.S. Patent Application Publication No. 2015/0094962 ("Hoegh")
1008	International Patent Application Publication No. WO 2010/006218 ("Headley")
1009	Tran et al., "Development of Asynchronous, Intralingual Electrical Stimulation to Treat Obstructive Sleep Apnea," Proceedings of the 25th Annual International Conference of the IEEE EMBS, Cancun, Mexico (September 17-21, 2003) ("Tran-I")
1010	Tran et al., "First Subject Evaluated with Simulated BION^{TM} Treatment in Posterior Genioglossus to Prevent Obstructive Sleep Apnea," Proceedings of the 26th Annual International Conference of the IEEE EMBS, San Francisco, CA (September 1-5, 2004) ("Tran-II")
1011	U.S. Patent No. 5,944,680 ("Christopherson")
1012	U.S. Patent Application Publication No. 2014/0228905 ("Bolea")
1013	Mortimer, "Electrical Excitation of Nerve," Neural Prostheses – Fundamental Studies, Chapter 3 (1990) ("Mortimer")
1014	Anagnostopoulos, et al., "Electronic Pacemakers of the Heart, Gastrointestinal Tract, Phrenic Nerve, Bladder, and Carotid Sinus: Current Status," Surgery 60:2, 480-494 (August 1966) ("Anagnostopoulos")
1015	Glenn et al., "Electrical Stimulation of Excitable Tissue by Radio-Frequency Transmission," Annals of Surgery 160:3, 338-350 (1964) ("Glenn")

Exhibit #	***Description***
1016	Judson et al., "Radio-Frequency Electrophrenic Respiration – Long-Term Application to a Patient with Primary Hypoventilation," JAMA 203:12, 1033-1037 (March 18, 1968) ("Judson")
1017	Singh, et al., "Recruitment Properties of Intramuscular and Nerve-Trunk Stimulating Electrodes," IEEE Transactions on Rehabilitation Engineering, 8:3, 276-285 (September 2000) ("Singh")
1018	Richmond et al., "Tactical Application of Sensorimotor Prosthetic Technology," Proceedings of the 25th Annual International Conference of the IEEE EMBS, Cancun, Mexico (September 17-21, 2003) ("Richmond")
1019	Edmonds, et al., "The Effects of Transcutaneous Electrical Stimulation During Wakefulness and Sleep in Patients with Obstructive Sleep Apnea," Am Rev Respir Dis, 146:1030-1036 (1992) ("Edmonds")
1020	Miki et al., "Effects of Submental Electrical Stimulation During Sleep on Upper Airway Patency in Patients with Obstructive Sleep Apnea," Am Rev Respir Dis 140:1285-1289 (1989) ("Miki")
1021	Decker et al., "Functional Electrical Stimulation and Respiration During Sleep," Journal of Applied Physiology, 75(3): 1053-1061 (1993) ("Decker")
1022	Eisele et al., "Direct Hypoglossal Nerve Stimulation," Arch. Otolaryngol Head Neck Surg., 123:57-61 (1997) ("Eisele1997")
1023	Fuller et al., "Effect of Co-Activation of Tongue Protrudor and Retractor Muscles on Tongue Movements and Pharyngeal Airflow Mechanics in the Rat," Journal of Physiology 519, 2, 601-613 (1999) ("Fuller")
1024	U.S. Patent No. 6,572,543 ("Christopherson '543")
1025	Schwartz et al., "Electrical Stimulation of the Lingual Musculature in Obstructive Sleep Apnea," J Appl Physiol. (81(2):643-652 (1996) ("Schwartz1996")
1026	Goding et al., "Relief of Upper Airway Obstruction With Hypoglossal Nerve Stimulation in the Canine," Laryngoscope, 108:162-169 (1998) ("Goding")
1027	U.S. Patent No. 4,830,008 ("Meer")

Exhibit #	***Description***
1028	Yoo et al., “Selective Stimulation of the Hypoglossal Nerve: A FINE Approach to Treating Obstructive Sleep Apnea,” Proceedings of the Second Joint EMBS/BMES Conference, 2049-2050 (October 23-26, 2002) (“Yoo”)
1029	Fairbanks et al., “Neurostimulation for Obstructive Sleep Apnea,” ENT Journal (January 1993) (“Fairbanks”)
1030	Schwartz et al., “Therapeutic Electrical Stimulation of the Hypoglossal Nerve in Obstructive Sleep Apnea,” Arch Otolaryngol Head Neck Surg., Vol. 127 (Oct. 2001) (“Schwartz2001”)
1031	Oliven, “Treating Obstructive Sleep Apnea with Hypoglossal Nerve Stimulation,” Current Opinion in Pulmonary Medicine 17:419-424 (2011) (“Oliven”)
1032	Mwenge et al., “Targeted Hypoglossal Neurostimulation for Obstructive Sleep Apnoea: a 1-Year Pilot Study,” Eur Respir J. 41:360-367 (2013) (“Mwenge”)
1033	Zaidi et al., “Tongue Anatomy and Physiology, the Scientific Basis for a Novel Targeted Neurostimulation System Designed for the Treatment of Obstructive Sleep Apnea,” Neuromodulation; 16:376-386 (2013) (“Zaidi”)
1034	Steier et al., “Continuous Transcutaneous Submental Electrical Stimulation in Obstructive Sleep Apnea,” Chest 140:998-1007 (2011) (“Steier”)
1035	Agnew et al., “Considerations for Safety with Chronically Implanted Nerve Electrodes,” Epilepsia, 31 (Suppl. 2): S27-32 (1990) (“Agnew”)
1036	U.S. Patent No. 7,277,749 (“Gordon”)
1037	Meadows et al., “Effective of Targeted Activation of Tongue Muscles on Oropharyngeal Patency in the Rat,” Journal of the Neurological Sciences, 346:178-193 (August 2014) (“Meadows”)
1038	Eastwood et al., “Treating Obstructive Sleep Apnea with Hypoglossal Nerve Stimulation,” SLEEP, 34:11, 1479-1486C (2011) (“Eastwood”)
1039	Sinha et al., “Safety of Microstimulator During Radiation Therapy – A Preliminary Study on Head and Neck Cancer Patients,” J. Nucl. Med. Radiat. Ther. 5:4 (2014) (“Sinha”)

Exhibit #	*Description*
1040	Kaplan et al., "Preventing ischial pressure ulcers: III. Clinical pilot study of chronic neuromuscular electrical stimulation," Applied Bionics and Biomechanics 8, 345359 (2011) ("Kaplan")
1041	Bailey et al., "Anatomic consequences of intrinsic tongue muscle activation," J Appl Physiol 101:1377-1385 (2006) ("Bailey")
1042	Brennick et al., "MRI study of pharyngeal airway changes during stimulation of the hypoglossal nerve branches in rats," J Appl Physiol 90:1373-1384 (2001) ("Brennick")
1043	Oliven et al., "Upper airway response to electrical stimulation of the genioglossus in obstructive sleep apnea," J Appl Physiol 95:2023-2029 (2003) ("Oliven2003")
1044	Oliven et al., "Effect of coactivation of tongue protrusor and retractor muscles on pharyngeal lumen and airflow in sleep apnea patients," J Appl Physiol 103:1662-1668 (2007) ("Oliven2007")

I, Dr. Gerald Loeb, declare as follows:

I. INTRODUCTION

1. I have been retained by Duane Morris on behalf of Nyxoah, Inc. and Nyxoah SA (collectively, "Nyxoah" or "Petitioners") as an independent, technical expert consultant in this proceeding before the United States Patent and Trademark Office (USPTO).[1] I have been asked to consider whether certain references disclose or suggest the limitations found in the claims of U.S. Patent No. 11,806,526 ("'526 Patent'), which I may reference as the "Challenged Patent" in this Declaration as discussed in detail below. My opinions are set forth below.

2. I am being compensated at my rate of $600 per hour for my services. No part of my compensation depends on my opinions or the outcome of this proceeding. I have no financial interest in any of the parties to this petition.

3. Unless otherwise noted, all emphasis in quotations and/or annotations to figures have been added.

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[1] Where appropriate, I refer to exhibits that I understand are attached to the Petition for *Inter Partes Review* (IPR) of the Challenged Patent.

II. BACKGROUND AND QUALIFICATIONS

4. My complete qualifications and professional experience are described in my Curriculum Vitae, a copy of which is found in **Appendix A** to this Declaration.

5. The following is a brief summary of my relevant qualifications and professional experience.

6. I have a bachelor's and a medical degree from Johns Hopkins University. I am currently Professor of Biomedical Engineering at the Viterbi School of Engineering in the University of Southern California, a position I have held since 1999. I also have joint appointments as a Professor of Neurology and Pharmacy and I direct the Medical Device Development Facility at USC. From 1994 to 1999 I was Chief Scientist for Advanced Bionics Corp., where I was actively involved in the development of their BION® neuromuscular stimulator, their spinal cord epidural stimulator and their Clarion® cochlear implant system. From 2012 to 2020 I was Chief Scientist for General Stim Inc., where I led the development of their NuStim® neuromuscular stimulator. Most of my research and teaching has been on the development of implanted electronic medical devices and on the signal processing functions of the nervous system.

7. I have published over 400 journal articles and I am an inventor on over 75 issued US patents, of which about 40 are directly related to neuromuscular stimulation. A list of 31 journal articles that I have published on neuromuscular stimulation can be found at https://mddf.usc.edu/projects/bion-and-nustim-technology-application/. I have published two papers and been awarded one US patent specifically on neuromuscular stimulation to relieve obstructive sleep apnea and one US patent for neuromuscular stimulation to relieve snoring.

8. I teach courses on the development and regulation of medical devices and specifically on implantable devices and instrumentation whereby bioelectric signals can be used to diagnose and treat neurological and neuromuscular disorders.

III. LEGAL STANDARDS

9. I am not an attorney and offer no legal opinions. My analysis and opinions are based on my expertise in this technical field and on the instructions that counsel has given me for the legal standards relating to patentability as outlined in the rest of this section. I have applied these principles in reaching the opinions set forth herein, but I do not provide any legal opinions in this Declaration. I have been informed and understand that certain legal standards

are to be applied by technical experts in forming opinions regarding the meaning and validity of patent claims.

10. I understand and the standard that I have used throughout my Declaration is that, in this proceeding, a patent claim may be deemed unpatentable as "anticipated" if it is shown by a preponderance of the evidence that each-and-every feature of the claim is found in a single prior art reference or rendered "obvious" if, in view of a prior art reference or a combination of prior art references, it would have been obvious to a person of ordinary skill in the art (POSITA) at the time of the invention, taking into account the following four issues: (1) the scope and intent of the prior art, (2) the differences between the prior art and the claim under consideration, (3) the level of ordinary skill in the art, and (4) any secondary evidence bearing on obviousness.

11. Counsel has informed me that legal principles regarding unpatentability of a claim due to obviousness have been addressed by the U.S. Supreme Court and that, while not absolute, the principles relating to a "motivation," "suggestion," or "teaching" in the prior art to combine references are useful in analyzing whether an invention is obvious. Counsel has also informed me that the suggestion or motivation may be either explicit or implicit and may come from knowledge generally available to a POSITA, from the nature of

the problem to be solved, or from a combination of these factors. The test for an implicit motivation, suggestion, or teaching is what the combined teachings, knowledge of a POSITA, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art. The analysis is not focused on the specific problem solved by the invention, but the general problem that confronted the inventor prior to the invention.

12. Counsel has further informed me that the U.S. Supreme Court has clarified that additional principles may also be applied in such an analysis. Some of those principles are set forth below.

13. I have been informed by counsel that it is no longer always required to present evidence of an explicit teaching, suggestion, or motivation to combine prior art references for purposes of determining whether an invention is obvious. Prior art can be combined based on several factors including: an express teaching, suggestion, or motivation from the prior art itself, or from a reasoned explanation of an expert or other witness.

14. I have been informed that a patent claim composed of several elements is not proved obvious merely by demonstrating that each of its elements was independently known in the prior art. In evaluating whether such a claim would have been obvious, I may consider whether there is a reason that would

have prompted a person of ordinary skill in the field to combine the elements or concepts from the prior art in the same way as in the claimed invention.

15. To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple pieces of prior art, to the effects of demands known to the design community or present in the marketplace, and to the background knowledge possessed by a POSITA. Also, in determining obviousness, one must be aware of the distortion caused by hindsight bias and be cautious of arguments relying upon hindsight reasoning. An obviousness argument cannot be sustained by mere conclusory statements. Instead, it must be some articulated reasoning with some rational underpinnings to support the legal conclusion of obviousness.

16. In an obviousness analysis, it is my understanding that there are "secondary considerations" that should be analyzed if they apply. I am told that these considerations include (a) whether the prior art teaches away from the claimed invention, (b) whether there was a long felt but unresolved need for the claimed invention, (c) whether others tried but failed to make the claimed invention, (d) skepticism of experts, (e) whether the claimed invention was

commercially successful, (f) whether the claimed invention was praised by others, and (g) whether the claimed invention was copied by others.

17. I have also been informed that for evidence of secondary considerations to be significant, there must be a sufficient relationship between the claimed invention and the evidence of secondary considerations. I understand that this relationship serves to provide a link between the merits of the claimed invention and the evidence of secondary considerations provided.

18. I have been informed by counsel that the Board construes claims according to the so-called "Phillips" standard. Under the Phillips standard, terms in a claim are given their ordinary and customary meaning, consistent with the patent's specification, as understood by a POSITA. I have been informed by counsel that what is to be considered includes the claims, the patent specifications and drawings, and the prosecution history, including any art listed by the examiner or the Applicant. I have been informed by counsel that information external to the patent, including expert and inventor testimony and unlisted prior art, are to be considered if ambiguities remain. However, expert testimony may be useful in helping to explain the technology.

19. I have been informed and understand that a patent claim is not patentable as obvious if the differences between the patent claim and the prior art are such

that the claimed subject matter, as a whole, would have been obvious at the time the claimed invention was made to a person having ordinary skill in the relevant art.

20. In analyzing the relevance of the differences between the claimed invention and the prior art, I have been informed that I must consider the impact of such differences on the obviousness or non-obviousness of the invention as a whole, not merely some portion of it. A POSITA faced with a problem can apply their experience and ability to solve the problem and also look to any available prior art to help solve the problem.

21. I have been informed and understand that there are recognized, exemplary rationales for combining or modifying references to show the obviousness of claimed subject matter. Some of the rationales include the following: combining prior art elements according to known methods to yield predictable results; simple substitution of one known element for another to yield predictable results; use of a known technique to improve a similar device (method or product) in the same way; applying a known technique to a known device (method or product) ready for improvement to yield predictable results; choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; known work in one field of endeavor

may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; and some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art teachings to arrive at the claimed invention.

IV. LEVEL OF ORDINARY SKILL IN THE ART

22. It is my understanding that a person of ordinary skill in the art (POSITA) is a hypothetical person who is used to analyze the prior art without the benefit of hindsight. I have been instructed that the level of ordinary skill may be reflected by the prior art of record, and that a person of ordinary skill in the art to which the claimed subject matter pertains would have the capability of understanding the scientific and engineering principles applicable to the pertinent art. I have been instructed that there are multiple factors that may be considered in determining the level of ordinary skill in the art may include: (1) type of problems encountered in the prior art; (2) prior art solutions to those problems; (3) rapidity with which innovations are made; (4) sophistication of the technology; and (5) educational level of active workers in the field. I also understand that a POSITA is also a person of

ordinary creativity, not an automaton. They would be able to fit the teachings of multiple patents together like a puzzle and have the capability of understanding the scientific and engineering principles applicable to the pertinent art.

23. I have been asked to provide a definition for the level of ordinary skill in the art in the field of the Challenged Patent at the time priority application (i.e., U.S. Provisional Patent Application No. 62/135,305) was filed, i.e., March 19, 2015. As stated in the Challenged Patent, the disclosure is directed to methods of treating obstructive sleep apnea via applying nerve stimulation. EX-1001 3:28-30.

24. In my opinion, a POSITA at the time of the ’526 Patent (i.e., March 2015) would have at least a bachelor’s degree in Electrical Engineering, Biomedical Engineering, or a related field and at least five years of training or additional work experience in neurostimulators or a related field. Through this formal education and/or training, a POSITA understood neuromuscular anatomy and physiology. Additional hands-on and design experience could compensate for less formal education and vice versa at the time of the priority date.

25. When forming my opinions herein, I analyzed and applied the prior art and claim constructions from a POSITA’s perspective at the time of the invention.

26. I understand that a POSITA is presumed to have knowledge of all references that are sufficiently related to one another to the pertinent art and to have knowledge of all arts reasonably pertinent to the particular problem that the claimed invention addresses.

27. All of my opinions in this Declaration are from the perspective of a POSITA, as I have defined it above and during the relevant time frame, i.e., on or around date of the priority application. During this time frame, I possessed at least the qualifications of a person of ordinary skill in the art, as defined above, and I am capable of addressing the issues from the perspective of such a person. My opinions in this declaration reflect how a POSITA would have understood the claims and the specification of the challenged patent, the prior art to the patent, and the state of the art on or around the priority date.

V. TECHNICAL BACKGROUND AND STATE OF THE ART

28. The following section describes the state of the art for neurostimulation devices, including neurostimulation devices for treating obstructive sleep apnea (OSA). The prior art references and the knowledge of a POSITA provide the factual support for the general description of the state of the art at the time of the invention and provide additional motivation to modify and/or

combine reference(s). Accordingly, these references should be considered by the Board.

A. <u>Neuromuscular Stimulators</u>

29. Nerves in the human body can be excited by an applied electrical impulse that induces movement of ions in saltwater that surrounds the elongated axon of neurons, changing the ionic concentration differences of potassium ions (K+) predominantly inside of the axon and sodium ions (Na+) predominantly outside of the axon. EX-1013 (Mortimer), p. 68. This electrical excitability phenomenon has been understood for decades and is the fundamental principle behind clinical neuromuscular stimulators, which are medical devices that deliver electrical impulses to the nervous system for the purpose of providing a therapeutic benefit. EX-1013 (Mortimer), p. 82; EX-1014 (Anagnostopoulos), p. 480.

30. Cardiac pacemakers were one of the earliest stimulators used clinically and by the 1960s were available in transcutaneous or implantable form factors using asynchronous (fixed) or synchronous stimulation protocols to pace a human heart. EX-1014 (Anagnostopoulos), pp. 480-82. By the 1960s, pacemaker technology was being used to treat other neuromuscular disorders,

including respiratory issues. EX-1014 (Anagnostopoulos), p. 488 (phrenic nerve); EX-1015 (Glenn), pp. 339-346; EX-1016 (Judson), p. 1033.

31. Application of neuromuscular stimulation to create desired movements and prevent or reverse atrophy of muscles as a result of chronic muscle inactivity was known. EX-1017 (Singh), p. 276; EX-1018 (Richmond), p. 2018; EX-1015 (Glenn), pp. 338, 343-348. Skeletal muscles themselves require the application of very large and prolonged electrical impulses to become active and generate contractions, which are impractical to generate and potentially painful or toxic. EX-1017 (Singh), p. 276. Muscle fibers, however, are innervated by large diameter motor axons that originate in the central nervous system (typically brainstem or spinal cord). EX-1017 (Singh), p. 276. These motor axons are more sensitive to electrical stimulation, which may be applied anywhere along their length. EX-1017 (Singh), pp. 276-277. Typical stimulation electrodes include (i) nerve cuff electrodes wrapped around peripheral nerve trunks or branches to individual muscles or neuromuscular compartments; (ii) patch electrodes sutured onto the connective tissue of a nerve or muscles or fascia adjacent to the nerve; and (iii) intramuscular wire electrodes implanted near the terminal branches of the motor axons as they approach the muscle fibers that they innervate. EX-1014 (Anagnostopoulos),

pp. 481-482; EX-1019 (Edmonds), p. 1031; EX-1017 (Singh), pp. 276-277; EX-1020 (Miki), pp. 1285-1286. Because electrical excitation of any axon spreads throughout the branches of that axon regardless of where excitation was initiated, the effects on the muscle are the same for these different electrode locations and types.

32. Pulse generators for stimulating muscles, such as those available from Grass Instruments and Medtronic (e.g., the Itrel, Dynex, and Respond lines of stimulators), were known and frequently used in laboratory and clinical settings. EX-1021 (Decker), p. 1055; EX-1019 (Edmonds), p. 1031; EX-1022 (Eisele1997), p. 58; EX-1023 (Fuller), p. 603; EX-1024 (Christopherson '543) 16:13-23. These stimulators, which could be external or implanted, allowed adjustments of the voltage or current amplitude, pulse width, and/or frequency at which stimulation was to be applied, as well as the length of the burst durations and the intervals between bursts, by simply turning dials on the devices and/or through other straight-forward programmable means. EX-1021 (Decker), p. 1055; EX-1019 (Edmonds), p. 1031; EX-1022 (Eisele1997), p. 58; EX-1023 (Fuller), p. 603. These stimulators typically included a processor and memory storing instructions for execution by the processor (i.e., software/firmware) and were configured to provide pulse

trains of different amplitudes (e.g., current and voltage), pulse width, and frequency. EX-1006 (Durand) ¶ 15 ("The control system 22 also typically includes a processor for setting up stimulation parameters to achieve the desired outcome for the individual patient or otherwise controlling the stimulation."); EX-1024 (Christopherson '543) 16:13-35; EX-1012 (Bolea) ¶ 462.

B. <u>Obstructive Sleep Apnea Treatment</u>

33. OSA is caused by obstruction of the upper airway during sleep. EX-1020 (Miki), p. 1285. More particularly, during sleep, the tongue prolapses due to diminished neuromuscular activity of the muscle controlling tongue protrusion (i.e., the genioglossus) causing pharyngeal occlusion. EX-1025 (Schwartz1996), p. 643; EX-1020 (Miki), p. 1285; EX-1026 (Goding), pp. 162-163. While continuous positive airway pressure (CPAP) devices were the gold standard for treating OSA, these devices were known to be limited in their effectiveness due to low patient compliance. EX-1027 (Meer), 1:47-52; EX-1012 (Bolea) ¶ 6; EX-1028 (Yoo), p. 2049.

34. By the 1990s, neuromuscular stimulation of the hypoglossal nerve/genioglossus muscle, in addition to other nerves responsible for

stimulating the upper airway muscles, was being investigated as an OSA treatment. EX-1020 (Miki), p. 1285; EX-1027 (Meer), 2:67-3:5, 4:16-25; EX-1019 (Edmonds), p. 1031; EX-1025 (Schwartz1996), pp. 643-644; EX-1029 (Fairbanks), pp. 52-53; EX-1021 (Decker), p. 1053; EX-1022 (Eisele1997), p. 58; EX-1026 (Goding), pp. 166-167; EX-1023 (Fuller), p. 601.

35. The development of neurostimulation therapies for OSA progressed from these early proof-of-concept studies to sophisticated clinical systems by the early 2000s. EX-1030 (Schwartz2001), p. 1217; EX-1031 (Oliven), pp. 337-339. These clinical systems included both closed-loop systems that stimulated synchronously with the patient's respiratory cycle and open-loop systems that stimulated asynchronously. EX-1031 (Oliven), p. 339; EX-1030 (Schwartz2001), p. 1217; EX-1038 (Eastwood), p. 1480.

36. Regardless of the type of therapy system (e.g., open loop or closed loop), titration was a typical step in providing the treatment and was done after implantation of the device. EX-1012 (Bolea) ¶¶ 536-537, 556-592; EX-1031 (Oliven), p. 422; EX-1032 (Mwenge), pp. 361-362. Titration typically involved applying stimulation to a patient under observation and varying one or more stimulation characteristics or parameters (e.g., pulse width,

amplitude, frequency, and duty cycle). EX-1012 (Bolea) ¶¶ 556-592. The goal of titration was to identify the optimal stimulation settings that would provide an effective, desired response (e.g., increased airway patency) in a manner that was safe and comfortable to the patient to ensure compliance with the treatment. EX-1012 (Bolea) ¶¶ 527, 556-558. Titration and the adjustment of one or more stimulation characteristics or parameters, including increasing/decreasing the stimulation duty cycle, involved nothing more than the exercise of routine skill in the art.

1. Closed-Loop Systems

37. Clinical closed-loop systems included an electrode(s), a pulse generator, and at least one sensor for actively sensing a patient's respiration cycle. EX-1030 (Schwartz2001), p. 1217; EX-1038 (Eastwood), p. 1480. In some systems, an intrathoracic pressure sensor was used to monitor the patient's respiratory cycle to synchronize a burst of electrical impulses (e.g., pulse train) from a pulse generator to a cuff electrode wrapped around the hypoglossal nerve, timing the stimulation to the onset of the patient's inspiration. EX-1030 (Schwartz2001), p. 1217; EX-1038 (Eastwood), p. 1480. The stimulation parameters (e.g., voltage or current amplitude, pulse width, and pulse frequency) provided by the pulse generator were configured specifically for

each person, as was the duration during which the stimulation was provided upon the sensing of the onset of the patient's inspiration. EX-1030 (Schwartz2001), p. 1217; EX-1038 (Eastwood), pp. 1480-81.

2. <u>Open-Loop Systems</u>

38. Clinical open-loop systems similarly included a pulse generator and an electrode, but differed in that they did not require the use of a sensor. EX-1032 (Mwenge), pp. 361-362; EX-1033 (Zaidi), p. 384. Instead, these systems relied on either continuous (e.g., constantly pulsed) or intermittent (e.g., periodically pulsed) stimulation protocols to reduce sleep disordered breathing. EX-1034 (Steier), p. 999; EX-1033 (Zaidi), p. 384.

C. <u>Duty Cycles</u>

39. Duty cycles (e.g., the proportion of time stimulation is applied to a nerve during a given period) have long been used in neurostimulation to provide the nerve being stimulated time to recover and avoid neural damage and muscle fatigue. EX-1035 (Agnew), pp. S27, S29; EX-1026 (Goding), p. 167; EX-1033 (Zaidi), pp. 382, 384; EX-1037 (Meadows), p. 191; EX-1036 (Gordon), 10:1-29. The muscle fibers in the tongue generally are less susceptible to fatigue compared to other muscles. EX-1033 (Zaidi), p. 376. However, even

within the tongue, the posterior muscles were known to be more susceptible to fatigue than the anterior tongue muscles due to their physical properties. EX-1033 (Zaidi), pp. 377-379. The tongue is a muscular hydrostat (e.g., muscles surrounding a fluid mass) in which the hydrostatic pressure associated with contracting muscles may cut off its blood supply. EX-1036 (Gordon), 10:6-13. Recovery periods allow blood flow to resume, avoiding muscle fatigue. EX-1036 (Gordon), 10:6-13.

40. Both open-loop and closed-loop systems for treating OSA utilized duty cycles. EX-1033 (Zaidi), p. 384; EX-1026 (Goding), p. 163; EX-1030 (Schwartz2001), p. 1217. While the duty cycle in closed-loop systems could vary based on the actively sensed respiratory cycle of a patient, the duty cycle of an open-loop system typically was fixed based on a patient's historical average of sleeping respiratory rate. EX-1012 (Bolea) ¶ 266 ("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.)"); EX-1030 (Schwartz2001), p. 1217; EX-1033 (Zaidi), p. 384; EX-1026 (Goding), p. 163.

41. Activation of the genioglossus muscle by stimulating the hypoglossal nerve causes the tongue to protrude, which increases the aperture size of the upper airway and resists collapse of the airway during inspiration, allowing unobstructed inspiration. EX-1012 (Bolea) ¶ 162; EX-1018 (Richmond), pp. 2017-2018; EX-1036 (Gordon), 7:20-28, 8:61-9:15. Stimulation of the hypoglossal nerve (and thus activation of the genioglossus) was targeted to the inspiratory phase of a patient's respiratory cycle. EX-1026 (Goding), p. 168 ("Nerve stimulation would need to coincide with inspiration."); EX-1030 (Schwartz2001), p. 1221 ("Nevertheless, when the stimulation was well synchronized with inspiration, improvement in apnea was consistently observed."); EX-1038 (Eastwood), p. 1480 ("Respiration is monitored via implanted thoracic leads that sense changes in bioimpedance with chest wall motion, delivering stimulation immediately prior to and during the inspiratory phase of respiration, when upper airway is most vulnerable to sleep related narrowing and collapse."). To ensure that an open-loop system would apply stimulation during the inspiratory phase, duty cycles of greater than 50% were used. EX-1012 (Bolea) ¶ 473 ("Thus, in some instances, the stimulation duty cycle may run above normal (e.g., above 50% to 60%) to achieve a better likelihood of covering the inspiratory phase."). If the inspiratory phase

initiates when stimulation is off and the airway is occluded, the inspiratory effort tends to be prolonged, so the eventual onset of asynchronous stimulation will open the airway and allow inspiratory airflow, effectively resynchronizing the patient's breathing to the applied stimulation. EX-1018 (Richmond), p. 2019; EX-1009 (Tran-I), p. 377; EX-1010 (Tran-II), p. 4288.

VI. OVERVIEW OF THE '526 PATENT

A. Priority Date

42. I have been instructed, for the purpose of this IPR, to assume the priority date for the '526 Patent is the filing date of U.S. Provisional Patent Application No. 62/135,305, which is March 19, 2015. To the extent the Challenged Claims are entitled to a different priority date, such as the March 16, 2016 filing date of International Patent Application No. PCT/US2016/022611, my analysis herein would not change.

B. Overview of the Disclosure of the '526 Patent

43. U.S. Patent No. 11,806,526 ("'526 Patent") issued on November 7, 2023 from U.S. Patent Application No. 17/012,481 ("'481 Application"), which is a continuation of U.S. Patent Application No. 15/562,714, which is a national phase entry of International Patent Application No. PCT/US2016/022611,

filed March 16, 2016 claiming priority to U.S. Provisional Patent Application No. 62/135,305, which was filed March 19, 2015.

44. The ’526 Patent is directed to a device for treating disordered breathing that includes a stimulation element to stimulate an upper-airway-patency-related nerve. EX-1001 Abstract. FIG. 1A is a block diagram of a stimulation element 12 that includes an independent stimulation function 14 that applies electrical stimulation to an airway-patency-related nerve, such as the protrusor branches of the hypoglossal nerve. More particularly, the independent stimulation function 14 provides stimulation according to a first stimulation protocol not synchronized to sensed respiratory information (also referred to as asynchronous stimulation) and in which each simulation cycle includes a stimulation period and a non-stimulation period. EX-1001 7:48-8:7.

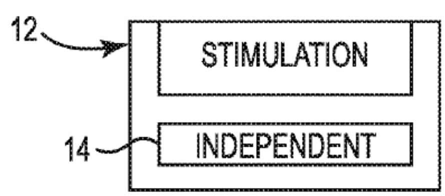


Fig. 1A

EX-1001 FIG. 1A.

45. FIG. 2A illustrates a system 20 includes an implantable pulse generator (IPG) 35 and a stimulation lead 32 electrical coupled with the IPG 35 via a

connector. The lead 32 includes a stimulation electrode portion 45, which may be a cuff electrode as disclosed in U.S. Patent No. 8,340,785 that may be positioned in contact with a desired nerve, enables simulation of the nerve via a lead 32 as disclosed in U.S. Patent Application Publication No. 2011/0160827 and an implantable stimulation system as disclosed in U.S. Patent No. 6,572,463 (EX-1024, Christopherson '543). The electrode portion 45 includes at least one operative contact group of at least two electrodes 52, although the stimulation electrode portion 45 may include multiple separate cuff electrodes. EX-1001 9:68-10:31.

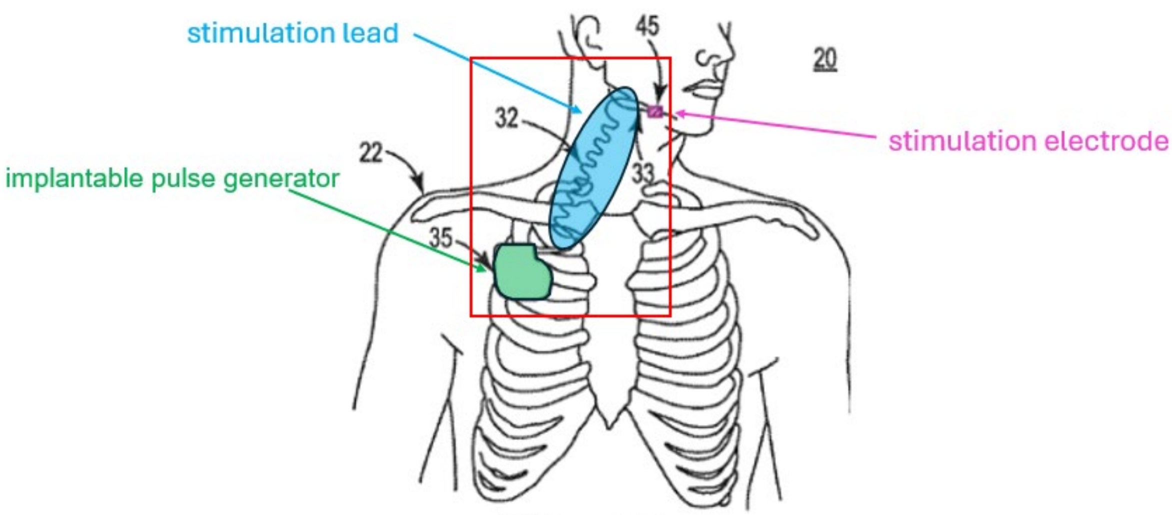


Fig. 2A

EX-1001 FIG. 2A (annotated).

46. FIG. 2D illustrates an exemplary system 80 that includes a nerve-coupling electrode portion 82 and a pulse generator 84. The nerve-coupling electrode portion 82 may be a mechanically and electrically coupled relative to a nerve 72 or the electrode portion 82 may not be mechanically coupled to the nerve 72, but instead mechanically coupled or secured in close proximity to the nerve 72 to enable electrical coupling of the electrode portion 82 to the nerve 72. The pulse generator may be solely an internal component or it may include a combination of internal components 90 and external components 92. EX-1001 11:60-12:22.

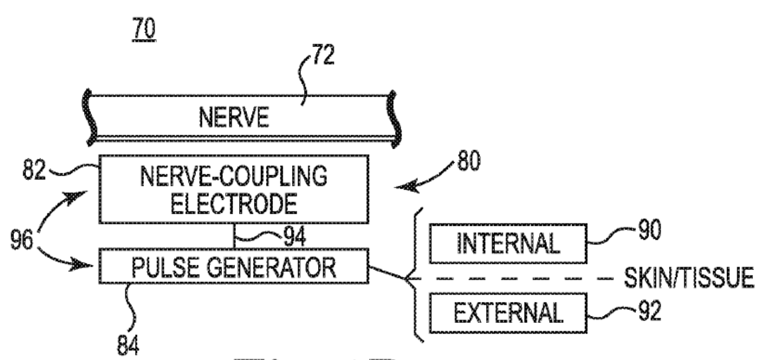


Fig. 2D

EX-1001 FIG. 2D.

47. FIG. 3A illustrates a normal breathing pattern 150 in which a respiratory cycle 160 includes an inspiratory phase 162 and an expiratory phase 170. The inspiratory phase 162 includes an initial portion 164, an intermediate portion

165, and an end portion 166. The expiratory phase 170 includes an initial portion 174, an intermediate portion 175, an end portion 176, and an expiratory peak 177. EX-1001 12:43-56.

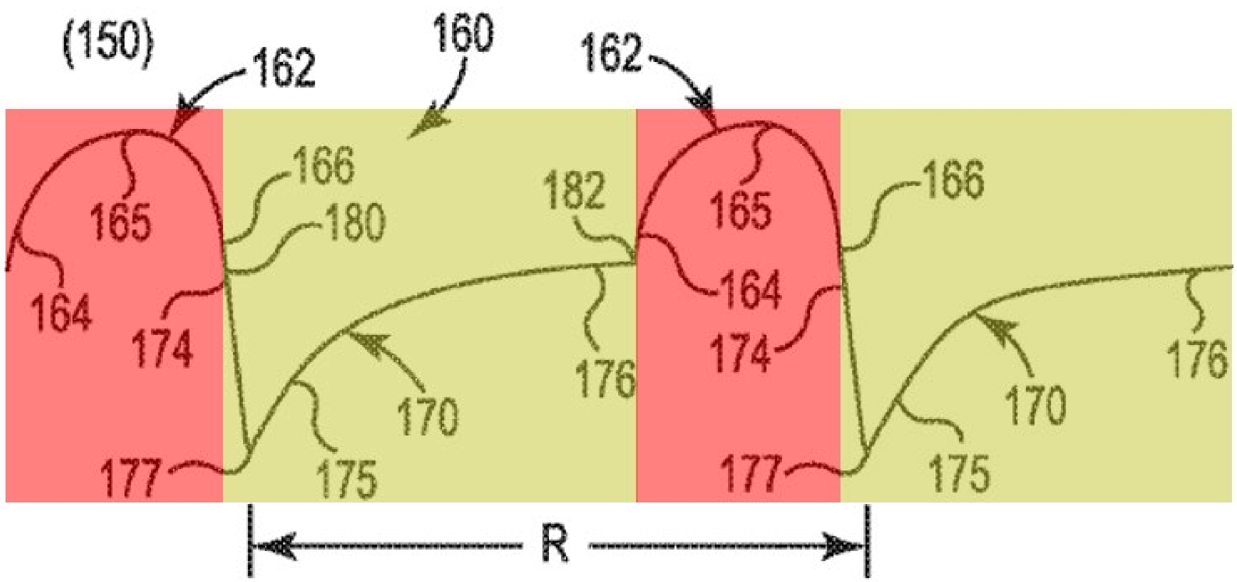
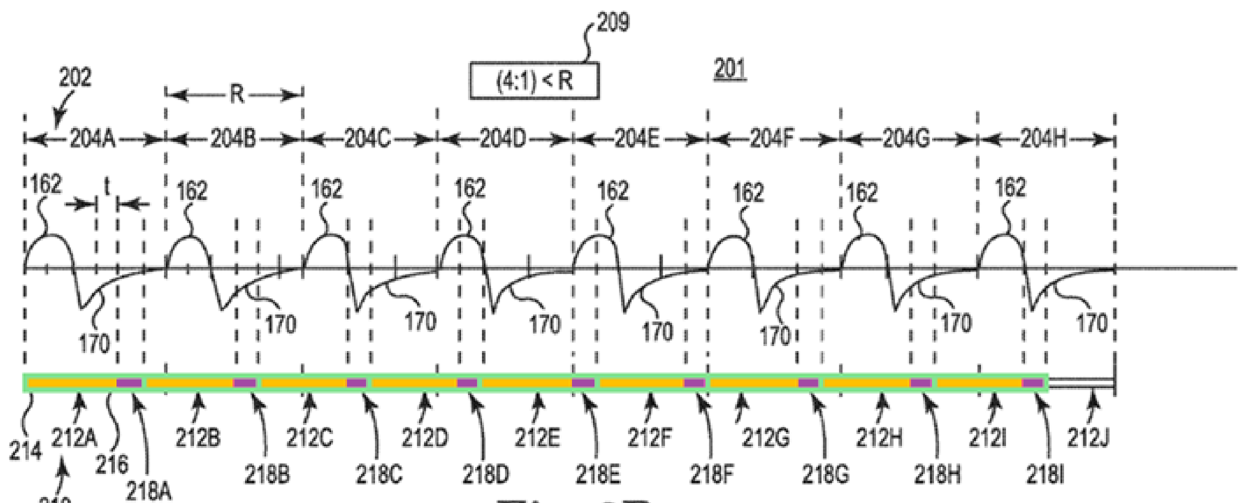


Fig. 3A

EX-1001 FIG. 3A (annotated).

48. FIG. 3B is a diagram schematically illustrating a stimulation protocol 210 implemented via the independent stimulation function 14. A respiratory pattern 202 includes a series of reference respiratory cycles 204A-204H each having a duration R. The respiratory pattern 202 represents a stable respiratory pattern, such as one that occurs during normal daytime breathing and/or from the application of stimulation protocol, and has a duration R based

on at least one of a historical patient-specific average respiratory cycle or a multi-patient average respiratory cycle. EX-1001 12:57-13:20, 13:37-45.



EX-1001 FIG. 3B (annotated).

49. The stimulation protocol 210 includes a series of separate stimulation periods (pulses) 212A-212J spaced apart by non-stimulation periods 218A-218I such that the respiratory cycle has a duration R divided into six time units t. For at least some of the patient population, the duration of the entire respiratory period is about 3-6 seconds, which corresponds to a respiratory rate of 10-18 breaths/minute. In FIG. 3B, the stimulation protocol 210 operates according to a stimulation cycle having a duration that is less than the duration R of the reference respiratory cycle, and the duration of the stimulation period exceeds

the duration of the non-stimulation period by a factor of 3. EX-1001 13:21-27, 13:46-14:2.

50. According to the ’526 Patent, because the overall duration of the stimulation cycle (i.e., stimulation period and non-stimulation period) does not match the duration R of the reference respiratory cycle, the stimulation protocol 210 ensures that each successive stimulation period within the series of stimulation cycles will fall along a different portion of the successive respiratory cycles and overlap with at least a portion of the inspiratory phase. EX-1001 14:56-15:2.

51. FIG. 3C illustrates another stimulation protocol 220 that operates according to a stimulation cycle having a duration that is greater than the duration R of the reference respiratory cycle. The stimulation period is 4½ time units in length and the non-stimulation period is 2½ units in length, such that the overall stimulation cycle is 7 time units in length and is greater than the 6 time unit duration of the reference respiratory cycle. EX-1001 16:39-51.

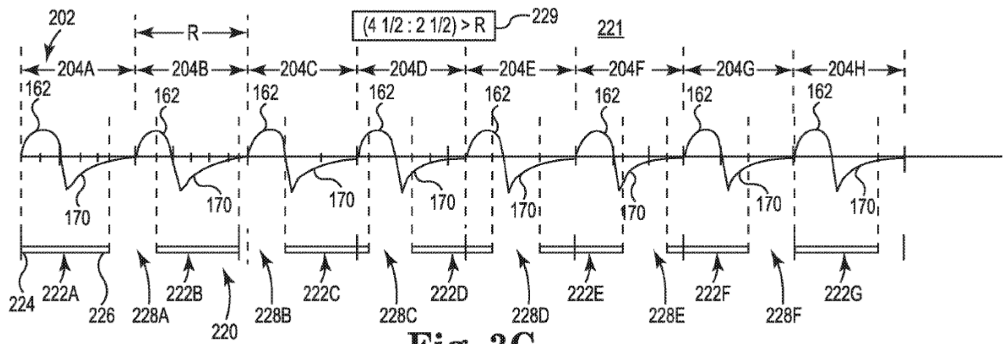


Fig. 3C

EX-1001 FIG. 3C.

52. The ’526 Patent also discloses that a duty cycle of the repeating stimulation cycle may vary on a respiratory cycle-by-respiratory cycle basis as illustrated in FIG. 3D. For example, during respiratory cycle 204A, the duty cycle is six time units of continuous stimulation, which equals 100%, but during respiratory cycles 204B and 204E the stimulation duty cycle is 3½ time units of continuous stimulation and 2½ time units of non-stimulation for a duty cycle of 58%. EX-1001 18:8-16.

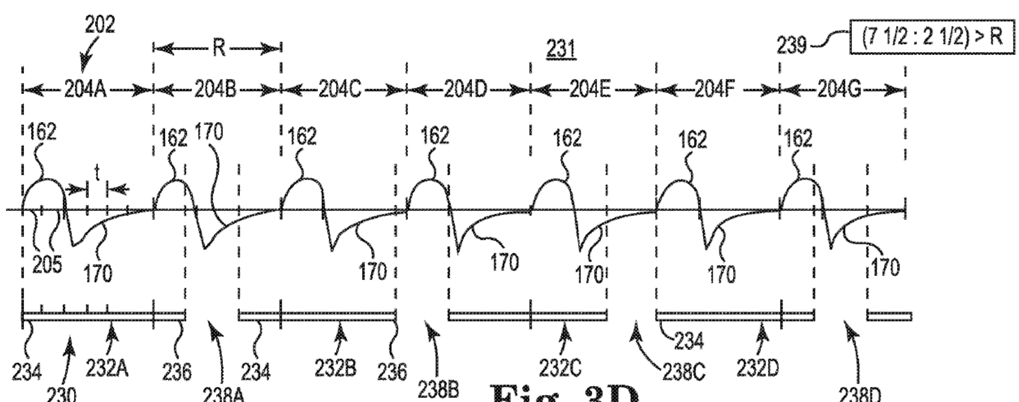


Fig. 3D

EX-1001 FIG. 3D.

53. The ’526 Patent further discloses that the stimulation system may operate in cooperation with a sensing function, which includes a sensing element 330 shown in FIG. 7A that may be incorporated into the IPG 50 illustrated in FIG. 2B. The sensing element 330 receives and tracks signals from at least one physiologic sensor to gather information regarding sleep disordered breathing, such as a respiratory state, whether the patient is sleeping, or other respiratory-associated indicators. EX-1001 24:4-25:3.

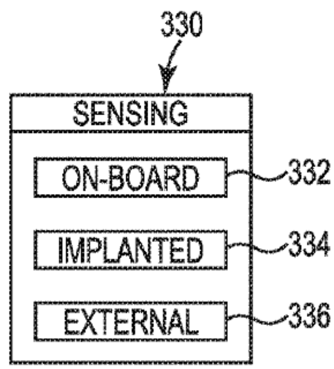


Fig. 7A

EX-1001 FIG. 7A.

C. <u>Prosecution History</u>

54. The ’481 Application, which issued as the ’526 Patent, was filed with 24 claims of which claims 1, 17, and 23 were in independent form. EX-1002 01561-1564. As originally presented, claims 1, 17, and 23 recited:

> 1. A device for treating obstructive sleep apnea, comprising:
>
> a non-cardiac stimulation element to stimulate an upper airway patency-related nerve, according to a first stimulation protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and wherein the duration of each respective stimulation period is based on a reference respiratory-related parameter.

EX-1002 01561.

> 17. A device for treating obstructive sleep apnea, comprising:
>
> a non-cardiac stimulation element to stimulate an upper airway patency-related nerve, according to a first stimulation protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, wherein the first stimulation protocol is to deliver multiple stimulation periods within a duration of a reference respiratory cycle.

EX-1002 01563.

> 23. A device for treating obstructive sleep apnea, comprising:
>
> a non-cardiac stimulation element to stimulate an upper airway patency-related nerve, according to a first stimulation protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and wherein a combined duration of a respective one of the stimulation periods and a respective one of the non-stimulation periods is greater than a duration of a reference respiratory cycle.

EX-1002 01564.

55. A non-final office action issued on November 2, 2022, in which all pending claims were rejected for being obvious from U.S. Patent Application Publication No. 2014/00228905 (EX-1012, "Bolea"), either alone or in combination with another reference (e.g., U.S. Patent Application Publication No. 2014/0194793, Nakata). EX-1002 00155-163.

56. In a response to the non-final office action filed on March 2, 2023, Applicant amended each of the independent claims to recite "a first stimulation <u>therapy</u> protocol," canceled claim 10, and added a new claim 25 depending from claim 1. EX-1002 00129-133. Specifically, the independent claims were amended to recite:

> 1. (Currently Amended) A device for treating obstructive sleep apnea, comprising:
>
> a non-cardiac stimulation element to stimulate an upper airway patency-related nerve, according to a first stimulation ~~therapy~~ protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and wherein the duration of each respective stimulation period is based on a reference respiratory-related parameter.

EX-1002 00129.

> 17. (Currently Amended) A device for treating obstructive sleep apnea, comprising:
>
> a non-cardiac stimulation element to stimulate an upper airway patency-related nerve, according to a first stimulation ~~therapy~~ protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, ~~wherein each stimulation period comprises continuous pulsed stimulation,~~ wherein the first stimulation protocol is to deliver multiple stimulation periods within a duration of a reference respiratory cycle.

EX-1002 00131.

> 23. (Currently Amended) A device for treating obstructive sleep apnea, comprising:
>
> a non-cardiac stimulation element to stimulate an upper airway patency-related nerve, according to a first stimulation ~~therapy~~ protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and wherein a combined duration of a respective one of the stimulation periods and a respective one of the non-stimulation periods is greater than a duration of a reference respiratory cycle.

EX-1002 00132.

57. In addition to amending the claims, Applicant argued that Bolea only discloses using an asynchronous or fixed mode during daytime familiarization and not as a therapy for sleep apnea. Specifically, Applicant argued:

> **Claim Rejections under 35 U.S.C. § 103**
>
> **Claims 1-18 and 20-24 stand rejected under 35 U.S.C. § 103 as being unpatentable over Bolea (US 2014/0228905).**
>
> Independent Claim 1
>
> Applicants respectfully traverse the rejection regarding independent claim 1. Applicants submit that the cited portion of Bolea (US 2014/0228905) in Paragraphs 460, 473-474, 514 taken in context with the full passage of Paragraphs 466-474 regarding FIGS. 64A-64D, conflicts with at least the recitation "a non-cardiac stimulation element to engage and to stimulate an upper-airway-patency-related nerve, according to a **first stimulation therapy protocol (including alternating stimulation periods and non-stimulation periods) in which a timing of the stimulation periods is asynchronous relative to patient breathing**" in Applicants' independent claim 1. (Bolea Paragraphs 514-516 are discussed below)
>
> Paragraphs 472-474 of Bolea (cited in the rejection of Applicants' independent claim 1) describe aspects of various stimulation duty cycles. In doing so, it would be apparent to one skilled in the art that such stimulation duty cycles relate to the embodiments of preceding Paragraphs 466-471 of Bolea, which depend on stimulation timing synchronized relative to a detected peak of the respiration signal "Z."
>
> In particular, Paragraphs 466-467 relate to a bio-impedance respiration signal and triggering stimulation based on a fiducial (e.g. begin-expiration) within this respiration signal,

among other details. As noted in Paragraph 468 of Bolea, "an algorithm is used to predict respiratory period and determine stimulation trigger time. The predictive algorithm is contained in software and executed by a microprocessor resident in the INS circuitry 1130, thus enabling the INS 1100 to generate stimulation synchronous with inspiration." Example predictive algorithms are described in Paragraphs 469, 470 in association with FIGS. 64B, 64C. As further noted in Paragraph 471:

> A feature common to the predictive algorithms is illustrated in FIG. 64D. This feature provides a sequence of predicted respiratory periods in case the respiration impedance signal ("Z") is temporarily lost (e.g. due to change in respiratory effort). Until a subsequent respiratory peak is detected, stimulation parameters which are based on the measured respiratory period (e.g. stimulation period) are unchanged. **Thus, stimulation timing remains synchronous to the last detected peak.** (emphasis added)

With this in mind, as the following Paragraphs 472-474 of Bolea (cited in the Office Action) describe aspects of various stimulation duty cycles, it would be apparent to one skilled in the art that such stimulation duty cycles relate to the embodiments of Paragraphs 466-471, which depend on stimulation timing <u>synchronized</u> relative to a detected peak of the respiration signal "Z."

Accordingly, at least this cited portion of Bolea conflicts with at least the recitation "a stimulation element to stimulate an upper-airway-patency-related nerve, according to a **first stimulation therapy protocol (including alternating stimulation periods and non-stimulation periods) in which a timing of the stimulation periods is asynchronous relative to patient breathing**" in Applicants' independent claim 1.

Applicants note that FIGS. 80A-80 and Paragraphs 489-499 of Bolea, also conflict with Applicants' independent claim 1 at least because such passages (particularly Paragraph 496) provide substantially similar information to Paragraphs 466-471 at least with respect to being conflicting relative to Applicants' independent claim 1.

Accordingly, for at least these reasons, Bolea fails to meet each and every recitation of Applicants' independent claim 1 and/or otherwise significantly conflicts with independent claim

> 1. Therefore, Bolea fails to reasonably make obvious Applicants' independent claim 1. Claims 2-9 and 11-16 are patentable at least based on their dependency from independent claim 1.
>
> Applicants further submit that Paragraphs 514-516 (cited in the Office Action), and particularly Paragraph 515, of Bolea fails to meet the recitations of Applicants' independent claim 1. In particular, while Paragraph 514-515 does refer to asynchronous stimulation, this Paragraph 515 explains that "the asynchronous mode (fixed mode) may be used during daytime familiarization", which is not a **therapy** for sleep apnea when a patient would be sleeping. Bolea further explains:
>
>> This mode may be used to **test** the benefits of asynchronous stimulation compared to inspiratory synchronous stimulation. Asynchronous stimulation may be initiated by programming the device to fixed mode and starting a therapy session. Fixed mode stimulation may be in any available pulse train configuration.
>
> In view of the particular context in which asynchronous stimulation is described (e.g. daytime familiarization, testing), and given that other portions of Bolea do not appear to directly address such asynchronous stimulation, it would appear to one skilled in the art that Bolea does not address asynchronous stimulation as a "**first stimulation therapy protocol**" in the manner recited in Applicants' independent claim 1. Rather, during a treatment period in which the patient would be sleeping, Bolea relies on inspiratory synchronous stimulation.
>
> Accordingly, for at least these reasons, Bolea fails to meet each and every recitation of Applicants' independent claim 1 and/or otherwise significantly conflicts with independent claim 1. Therefore, Bolea fails to reasonably make obvious Applicants' independent claim 1. Claims 2-9 and 11-16 are patentable at least based on their dependency from independent claim 1.

EX-1002 00134-136.

58. I disagree with the foregoing attorney argument as to what a POSITA understood from Bolea. For example, Bolea expressly discloses that the

asynchronous (fixed) mode may be used during a therapy session, including as when the signal received from the sensing lead is lost.

> Stimulation may also be delivered in two modes which are not inspiratory synchronous: manual stimulation and asynchronous (fixed) stimulation.

EX-1012 (Bolea) ¶ 514.

> Asynchronous mode (fixed mode) is when stimulation is delivered at regular programmable intervals (e.g., 2.5 seconds of stimulation, followed by 2.5 seconds off). The intervals may be set to a rate similar to a respiratory cycle, (e.g., 5 seconds)…In addition, ***this mode may be used to test the benefits of asynchronous stimulation compared to inspiratory synchronous. Asynchronous stimulation may be initiated by programming the device to fixed mode and starting a therapy session***. Fixed mode stimulations may be in any available pulse train configuration.

EX-1012 (Bolea) ¶ 515.[2]

> The stimulation duty cycle may be fixed or adaptive. In the fixed mode, the stimulation duty cycle is set using to programmer

[2] All ***bold-italics*** emphasis added unless otherwise stated.

> system 2100 to a fixed value. ***This fixed value may be increased when the respiratory signal is lost, increasing the likelihood of aligning with actual inspiration***.

EX-1012 (Bolea) ¶ 498.

59. Thus, while Bolea discloses that the asynchronous (fixed) mode may be used during the daytime for testing, Bolea expressly discloses that the asynchronous stimulation is applied during a "therapy session," may be used in testing whether asynchronous stimulation is more beneficial than synchronous stimulation, and may be used when a respiratory signal is lost.

60. If a respiratory signal is lost, a POSITA understood that there is no active sensing of the patient's respiratory cycle. Once there is no actively-sensed respiration information, then there cannot be any synchronization to actively-sensed respiratory information. Indeed, if the respiratory signal is lost, then the device would either not provide stimulation or provide stimulation asynchronously because there is no respiratory signal with which the system may use to perform the synchronization. However, Bolea does not disclose that the stimulation ceases when the respiratory signal is lost, but instead expressly discloses providing stimulation with an increased duty cycle to ensure overlap with the inspiratory period of the patient.

61. Further, Bolea expressly discloses that a patent's respiratory rate may vary, which a POSITA understood means that the older actively-sensed respiratory information would not provide synchronicity or be considered actively-sensed. *See* EX-1012 (Bolea) ¶ 493 ("In people without OSA, inspiration is typically 25%-50% of the respiratory cycle, with variations in respiration rate being common. Variations may cause inspiration to differ from predicted inspiration.").

62. Moreover, Bolea expressly discloses that a therapy controller may allow a patient (or other individual) to control select therapy settings, including the stimulation mode.

> The therapy controller may have additional functionality (e.g., more buttons) which can be set to give the patient limited ***control over select therapy settings***. These settings include, but are not limited to, stimulation intensity (e.g., amplitude), ***stimulation mode***, pulse train configuration, core hours stimulation settings, ramp, programmable schedule clock, and motion inhibit programmable values.

EX-1012 (Bolea) ¶ 528.

63. As noted above, Bolea expressly discloses that asynchronous stimulation is a non-synchronous mode of stimulation. EX-1012 (Bolea) ¶ 514 ("Stimulation

may also be delivered in ***two modes which are not inspiratory synchronous***: manual stimulation and ***asynchronous (fixed) stimulation***."). As such, a POSITA understood that asynchronous stimulation could be selected by a patient to be used in a therapy session. In sum, Bolea expressly contemplates using asynchronous stimulation during a therapy session, including in the complete absence of a sensor signal for actively sensing the respiration of the patient. EX-1012 (Bolea) ¶¶ 498-501, 515-516, 528).

64. The Examiner, having apparently been persuaded by Applicant's arguments regarding Bolea (and overlooking several of the above-identified disclosures in Bolea), issued a first Notice of Allowance on July 6, 2023. EX-1002 00088. The first Notice of Allowance included an examiner's amendment in which each independent claim was amended to require the non-cardiac stimulation means to include an implantable electrode and/or an implantable pulse generator, as shown below.

EXAMINER'S AMENDMENT

3. Authorization for this examiner's amendment was given in an interview with Paul Grunzweig on 6/26/2023.

4. Para. 1 of the Specification is amended as follows:

5. [0001] This application is a continuation of utility application Serial Number 15/562,714, filed September 28, 2017, now US Patent 10,898,709, which is a 371 National Phase Application of PCT Patent Application No. PCT/US20 16/022611, filed March 16, 2016, entitled STIMULATION FOR TREATING SLEEP DISORDERED BREATHING, which claims benefit from U.S. Provisional Patent Application 62/135,305, filed March 19, 2015, all of which are herein incorporated by reference.

6. Claim 1 is amended as follows: A device for treating obstructive sleep apnea, comprising: a non-cardiac stimulation ~~element to stimulate~~ means for stimulating an upper airway patency-related nerve, wherein, the non-cardiac stimulation element comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode according to a first stimulation therapy protocol including alternating stimulation periods and non- stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-

stimulation period, and wherein the duration of each respective stimulation period is based on a reference respiratory-related parameter.

7. Claim 17 is amended as follows: A device for treating obstructive sleep apnea, comprising: a non-cardiac ~~stimulation element to stimulate~~ <u>means for stimulating</u> an upper airway patency-related nerve<u> wherein, the non-cardiac stimulation element comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode</u>, according to a first stimulation therapy protocol including alternating stimulation periods and non- stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, wherein each stimulation period comprises continuous pulsed stimulation, wherein the first stimulation protocol is to deliver multiple stimulation periods within a duration of a reference respiratory cycle.

8. Claim 23 is amended as follows: A device for treating obstructive sleep apnea, comprising: a non-cardiac ~~stimulation element to stimulate~~ <u>means for stimulating</u> an upper airway patency-related nerve<u>, wherein, the non-cardiac stimulation element comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode</u>, according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and wherein a combined duration of a respective one of the stimulation periods and a respective one of the non-stimulation periods is greater than a duration of a reference respiratory cycle.

9. Claim 15 is cancelled.

EX-1002 00093-94.

65. After the Applicant contacted the Examiner on July 14, 2023 (EX-1002 00083), a second Notice of Allowance was mailed on July 21, 2023, which included another Examiner's amendment in which the manner in which the independent claims was amended was changed to appear at the end of the claims, as shown below.

EXAMINER'S AMENDMENT

3. Authorization for this examiner's amendment was given in an interview with Paul Grunzweig on 7/14/2023.

4. Para. 1 of the Specification is amended as follows:

5. [0001] This application is a continuation of utility application Serial Number 15/562,714, filed September 28, 2017, <u>now US Patent 10,898,709,</u> which is a 371 National Phase Application of PCT Patent Application No. PCT/US20 16/022611, filed March 16, 2016, entitled STIMULATION FOR TREATING SLEEP DISORDERED BREATHING, which claims benefit from U.S. Provisional Patent Application 62/135,305, filed March 19, 2015, all of which are herein incorporated by reference.

6. Claim 1 is amended as follows: A device for treating obstructive sleep apnea, comprising: a non-cardiac stimulation ~~element to stimulate~~ <u>means for stimulating</u> an upper airway patency-related nerve, according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and wherein the duration of each respective stimulation period is based on a reference respiratory-related parameter<u>, wherein, the non-cardiac stimulation means for</u>

stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.

7. Claim 17 is amended as follows: A device for treating obstructive sleep apnea, comprising: a non-cardiac ~~stimulation element to stimulate~~ means for stimulating an upper airway patency-related nerve, according to a first stimulation therapy protocol including alternating stimulation periods and non- stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, wherein each stimulation period comprises continuous pulsed stimulation, wherein the first stimulation protocol is to deliver multiple stimulation periods within a duration of a reference respiratory cycle, wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.

8. Claim 23 is amended as follows: A device for treating obstructive sleep apnea, comprising: a non-cardiac ~~stimulation element to stimulate~~ means for stimulating an upper airway patency-related nerve, according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing, wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and wherein a combined duration of a respective one of the stimulation periods and a respective one of the non-stimulation periods is greater than a duration of a reference respiratory cycle, wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.

9. Claim 15 is cancelled.

10. Claim 16 is amended as follows: The device of claim 1, comprising: a processor; and a non-volatile computer readable medium storing instructions, executable on the processor, to implement the first stimulation therapy protocol via the non-cardiac stimulation means for stimulating.

Allowable Subject Matter

11. Claims 1-9,11-14 and 16-25 are allowed.

Reasons for Allowance

12. The following is an examiner's statement of reasons for allowance: Claims 1-9,11-14 and 16-25 are allowed over the prior art because the Examiner found that none of the cited prior art discloses a first stimulation therapy protocol with alternating stimulation periods and non-stimulation periods in which a timing of stimulation periods is asynchronous relative to patient breathing.

13. Examiner found closest prior art would be Bolea, cited previously, that the asynchronous is used for familiarization (eg. Para. 514-515), but does not use it as a therapy for sleep apnea.

14. Another close prior art found was US 2011/0093032 A1 that discloses asynchronous stimulation with pulse trains (eg. Para. 39, 42, 162, and 171) but does not disclose the duration of each respective stimulation period is based on a reference respiratory-related parameter.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

EX-1002 00079-81.

66. The '526 Patent issued on November 7, 2023 (EX-1002 00067-68); however, the text of the Examiner's amendment in the second Notice of Allowance was not included. The Patent Owner filed a Request for Certificate of Correction on February 24, 2025, requesting the language of second Notice of Allowance

be used to correct the ’526 Patent. EX-1002 00007-8. A Certificate of Correction issued on February 24, 2025 correcting the claim language as follows.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 11,806,526 B2 Page 1 of 1
APPLICATION NO. : 17/012481
DATED : November 7, 2023
INVENTOR(S) : Darrell Wagner et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

At Claim 1 in Column 42, Line 12, cancel the text beginning with "wherein, the non-car-" and ending with "the implantable electrode" in Column 42, Line 15

At Claim 1 in Column 42, Line 23, after the term "parameter", insert the following text:
--, wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode--

At Claim 14 in Column 43, Line 11, between the text "stimulation" and "protocol", insert the following text:
--therapy--

At Claim 14 in Column 43, Line 11, after the text "protocol", insert the following text:
--via the non-cardiac stimulation means for stimulating--

At Claim 16 in Column 43, Line 17, cancel the text beginning with "wherein, the non-cardiac stimulation" and ending with "the implantable electrode" in Column 43, Line 20

At Claim 16 in Column 43, Line 29, after the term "cycle", insert the following text:
--, wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode--

At Claim 22 in Column 44, Line 19, cancel the text beginning with "wherein, the non-cardiac stimulation" and ending with "the implantable electrode," in Column 44, Line 22

At Claim 22 in Column 44, Line 31, after the term "cycle", insert the following text:
--, wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode--

Signed and Sealed this
Twenty-fifth Day of March, 2025

Coke Morgan Stewart

Coke Morgan Stewart
Acting Director of the United States Patent and Trademark Office

EX-1002 00002.

VII. OVERVIEW OF THE PRIOR ART

A. Durand (EX-1006)

1. Prior Art Status

67. U.S. Patent Application Publication No. 2006/0224211 in the name of Durand et al. (EX-1006, "Durand") published on October 5, 2006. I understand that Durand qualifies as prior art to the '526 Patent. The patent corresponding to Durand (i.e., U.S. Patent No. 7,680,538) was cited in one of two information disclosure statements filed on October 29, 2020 (EX-1002 01538), along with over 350 other references (EX-1002 01506-1517, 01521-1551), but was not applied by the Office during the prosecution of the Challenged Claims.

2. Summary of Durand's Disclosure

68. Durand, titled "Method of treating obstructive sleep apnea using electrical nerve stimulation," is directed to a method of treating obstructive sleep apnea using electrical nerve stimulation. EX-1006 (Durand), Title, Abstract. Specifically, Durand describes a method for treating obstructive sleep apnea by electrically stimulating the hypoglossal nerve, which uses at least one of the following techniques: (a) continuous low-level electrical stimulation; (b) electrical stimulation synchronized with a physical process, such as inspiration, without feedback from the nerve being stimulated; and

(c) intermittent electrical stimulation at controlled intervals based on the patient's metabolism. EX-1006 (Durand), Abstract, ¶ 1. Durand explains that "electrical stimulation of the hypoglossal nerve…can maintain the patency of the upper airway by activating the upper airway dilator muscles, thereby minimizing or eliminating airway collapse during sleep." EX-1006 (Durand) ¶ 12.

69. FIG. 1 of Durand shows apparatus 20 for stimulating a nerve, including control system 22 for generating the desired electrical stimulus and electrode 24 in the form of a nerve cuff connected to the nerve to transmit the electrical stimulus to the nerve:

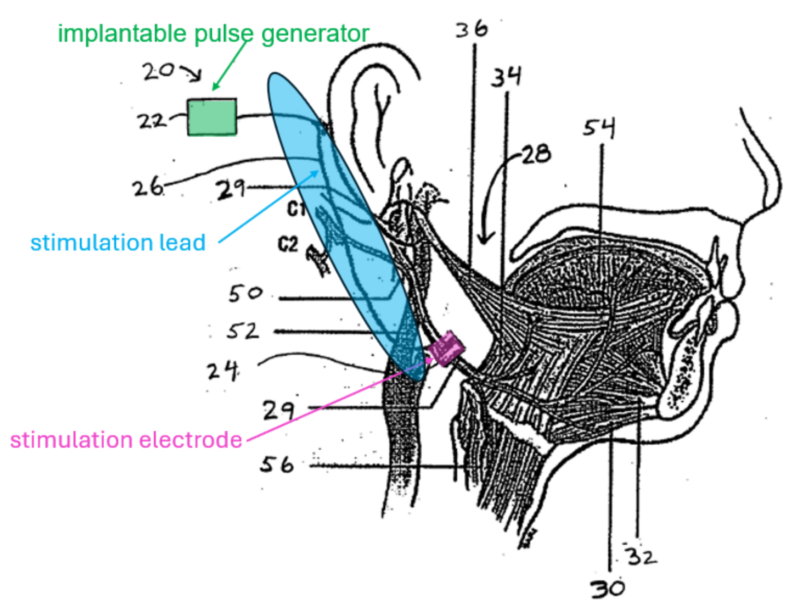


FIG. 1

EX-1006 (Durand) FIG. 1 (annotated), ¶ 14 ("The electrode 24 preferably is a cuff electrode that provides an intimate connection to the nerve.").

70. Durand describes that "control system 22 controls the application of the electrical stimulation" and that "[p]ortions of the control system 22, in addition to the electrode 24, can be implanted in the patient's body." EX-1006 (Durand) ¶ 16. Durand explains that "the muscles that control the upper airway 28 and are innervated by the hypoglossal nerve 29 include the geniohyoid muscle 30, the genioglossus muscle 32, the hyoglossus muscle 34 and the styloglossus muscle 36." EX-1006 (Durand) ¶ 19. Durand further explains that "genioglossus 32 is the main tongue protruder (the muscle that pushes the tongue out) and plays an important role in maintaining the patency of the upper airway." EX-1006 (Durand) ¶ 19.

71. Durand discloses both synchronous and asynchronous techniques for treating OSA. With respect to asynchronous stimulation, Durand discloses that "initiation of the electrical stimulation can be synchronized with a physical process, such as inspiration sensed by a remote sensor, without feedback from the nerve being stimulated." EX-1006 (Durand) ¶ 23. In one embodiment, Durand discloses that "the controller can be programmed to provide stimulation at a predetermined interval without either detecting a physical

process or requiring feedback from the nerve being stimulated." EX-1006 (Durand) ¶ 25. "In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle." EX-1006 (Durand) ¶ 25. Durand describes that "a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains." EX-1006 (Durand) ¶ 25.

72. A POSITA understood that a typical respiratory rate for an adult was around 12-20 breaths per minute (BPM), which corresponds to a respiratory cycle duration of around three seconds (20 BPM) to five seconds (12 BPM). Durand's disclosure of four (i.e., two seconds of stimulation; two seconds off) to six (i.e., three seconds of stimulation; three seconds off) second stimulation cycle durations overlaps with, and generally corresponds to, these typical adult respiratory rates.

B. Hoegh (EX-1007)

1. Prior Art Status

73. U.S. Patent Application Publication No. 2015/0094962 in the name of Hoegh et al. ("EX-1007, "Hoegh") is the pre-grant publication of U.S. Patent Application No. 14/505,151, which was filed on October 2, 2014, claiming priority to U.S. Provisional Application Nos. 61/885,991, filed October 2, 2013, and 62/058,914, filed October 2, 2014. I understand that Hoegh qualifies as prior art to the '526 Patent. Hoegh was not cited or applied by the Office during the prosecution of the Challenged Claims.

2. Summary of Hoegh's Disclosure

74. Hoegh, titled "Obstructive sleep apnea treatment screening methods," relates to methods for treatment of obstructive sleep apnea. EX-1007 (Hoegh) Title, Abstract ¶ 2 ("[T]he embodiments described herein relate to devices, systems and methods for treating obstructive sleep apnea."). Hoegh discloses "a screening method for evaluating patient suitability for an implanted hypoglossal nerve stimulation (HGNS) device." EX-1007 (Hoegh) Abstract.

75. FIG. 1 of Hoegh shows hypoglossal nerve stimulation (HGNS) system 100 comprising internal components 1000 and external components 2000:

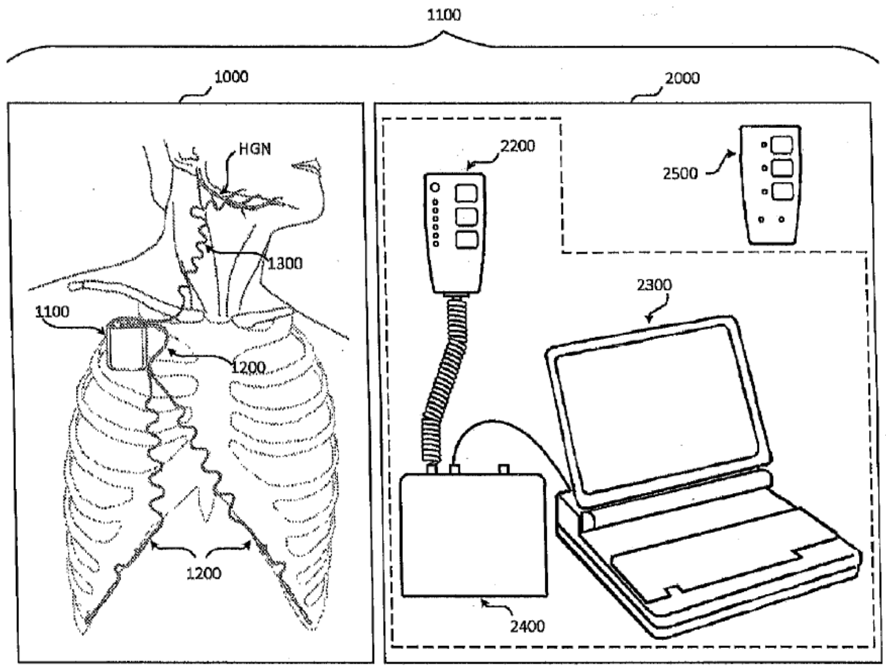


FIG. 1

EX-1007 (Hoegh), FIG. 1.

76. Hoegh describes that "HGNS system 100 may treat obstructive sleep apnea (OSA) by increasing neuromuscular activity to the genioglossus muscle via stimulation of the hypoglossal nerve (HGN), such as synchronous with inspiration, to mitigate upper airway collapse during sleep." EX-1007 (Hoegh) ¶ 50. Hoegh further describes that "[s]timulation may be generated by an implantable neurostimulator (INS) 1100, for example synchronized with inspiration as measured by the respiration sensing lead (RSL) 1200 using bio-impedance, and delivered to the hypoglossal nerve by a stimulation lead (STL) 1300." EX-1007 (Hoegh) ¶ 50.

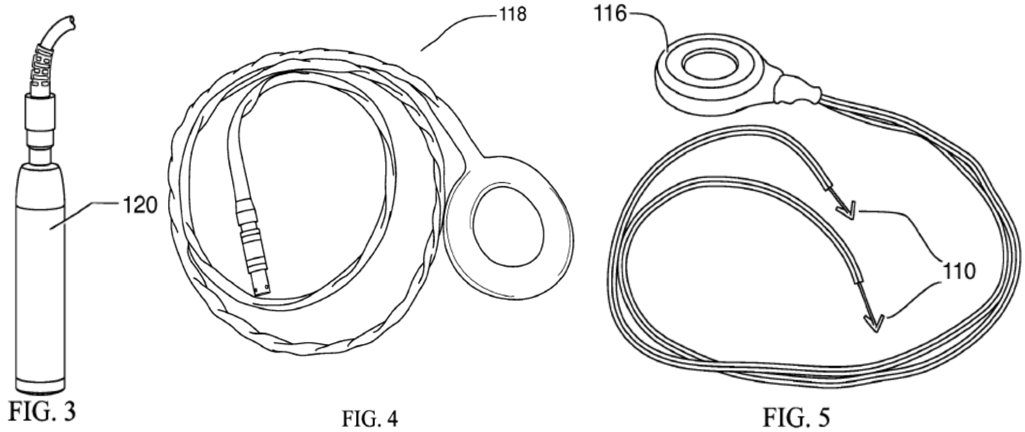
C. Headley (EX-1008)

1. Prior Art Status

77. International Patent Application Publication No. WO 2010/006218 in the name of Headley (EX-1008, "Headley") published on January 14, 2010, which I understand qualifies the reference as prior art to the '526 Patent. Headley was not cited or applied by the Office during prosecution of the Challenged Claims.

2. Summary of Headley's Disclosure

78. Headley is titled "Sleep Apnea Device and Method" and "involves the implantation of a muscle stimulation electrode directly into the muscle of the genioglossus that advances the posterior aspect of the tongue anteriorly thus relieving the obstruction of the tongue in sleep apnea." EX-1008 (Headley) Abstract. More particularly, the device includes a power source 120 (FIG. 3), an antenna 118 (FIG. 4), a receiver 116, and a stimulating electrode 110 (FIG. 5). EX-1008 (Headley) ¶ 29.



EX-1008 (Headley) FIGS. 3-5.

79. In use, the device provides for alternating on/off "intermittent" treatment where tissue is stimulated for a given period, then allowed to rest for a given period. EX-1008 (Headley) ¶ 48. Headley discloses on/off duty cycles ranging from 12/1 (e.g., 60 seconds on; 5 seconds off) to 1/1 (e.g., 5 seconds on; 5 seconds off), with on/off periods as short as 1 second each. EX-1008 (Headley) ¶ 48.

D. <u>Tran (EX-1009, EX-1010)</u>

1. <u>Prior Art Status</u>

80. Tran are the collective works of Tran et al. and includes two papers, i.e., Tran et al., "Development of Asynchronous, Intralingual Electrical Stimulation to Treat Obstructive Sleep Apnea," which was presented as the Proceedings of the 25th Annual International Conference of the IEEE EMBS in Cancun,

Mexico, September 17-21, 2003 (EX-1009, "Tran-I"), and Tran et al., "First Subject Evaluated with Simulated BION^{TM} Treatment in Posterior Genioglossus to Prevent Obstructive Sleep Apnea," which was presented at the Proceedings of the 26th Annual International Conference of the IEEE EMBS in San Francisco, CA, September 1-5, 2004 (EX-1010, "Tran-II") and cites and builds on Tran-I.

81. Tran-I was publicly accessible no later than February 2004, EX-1004 (Hsieh-Yee Decl.) ¶¶ 48-50, and I understand qualifies as prior art to the '526 Patent. Tran-II was publicly accessible no later than November 2004, EX-1004 (Hsieh-Yee Decl.) ¶¶ 86-90, and I understand qualifies as prior art to the '526 Patent. Neither Tran-I nor Tran-II was cited or applied by the Office during prosecution of the Challenged Claims.

2. **Summary of Tran's Disclosure**

82. Tran-I discloses using asynchronous electrical stimulation via an implantable stimulator electrode to treat obstructive sleep apnea. EX-1009 (Tran-I) Title, Abstract, p. 375 ("using a single intralingual BION™ microstimulator to prevent airway obstruction in patients with obstructive sleep apnea (OSA)"). Tran-I describes that "[n]euromuscular and hypoglossal nerve stimulation of the genioglossus" was known "to expand the oropharyngeal airway and

reduce[] the severity of sleep disordered breathing." EX-1009 (Tran-I), Abstract, p. 375. Tran-I further describes that "OSA occurs when the soft tissues of the upper airway collapse and occlude airflow during inspiration" and "[c]ollapse of the tongue is the most common cause of OSA." EX-1009 (Tran-I), p. 375.

83. Tran-I describes that the implantable electrode can be injected in or near muscles and nerves and receives power and digital command data via an RF transmission coil to produce stimulation pulses. EX-1009 (Tran-I), p. 375. Figure 3 of Tran-I shows that the device can be implanted into the patient from under the chin along the midline, where it would stimulate the intramuscular branches of the same motor axons as may be stimulated in the hypoglossal nerve:

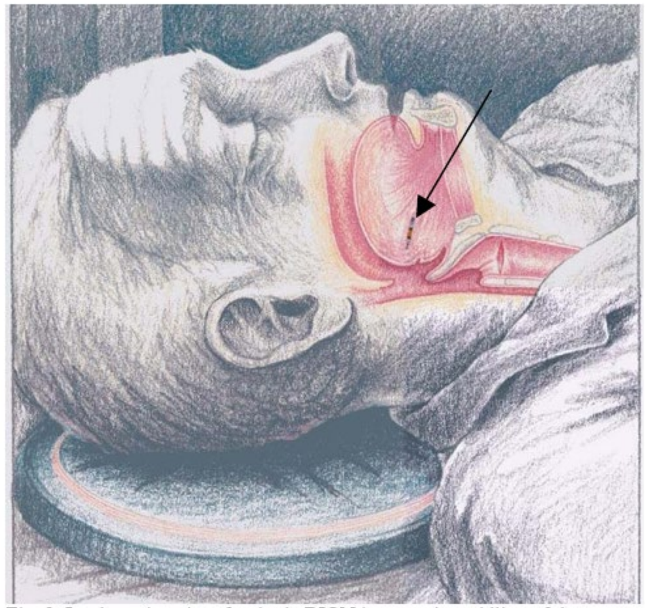


Fig. 3. Implantation site of a single BION in posterior midline of the genioglossus muscle with tantalum electrode (effective cathode) near the endplates (toward the tongue base).

EX-1009 (Tran-I), FIG. 3, p. 376.

84. Regarding asynchronous electrical stimulation, Tran-I discloses that "intermittent opening of airway at the same rate but not synchronized to the respiratory cycle may be effective" to treat OSA. EX-1009 (Tran-I), p. 375. Tran-I explains that "if brief trains of stimulation pulses were applied to the [genioglossus] at intervals close to the respiratory cycle of the patient, the patient would tend to synchronize spontaneously with the resulting intermittent periods of patency in the airway." EX-1009 (Tran-I), p. 377. Tran-I explains that this occurs "because an inspiratory phase that happens not to coincide with [genioglossus] stimulation will tend to be prolonged until

the next train of [genioglossus] stimulation opens the airway." EX-1009 (Tran-I), p. 377.

85. Tran-II, titled "First Subject Evaluated with simulated BION™ Treatment in Posterior Genioglossus to Prevent Obstructive Sleep Apnea," describes "using percutaneous electrical stimulation to simulate BION™ activation of posterior genioglossus during sleep to prevent occurrences of obstructive sleep apnea (OSA)." EX-1010 (Tran-II), Title, Abstract, p. 4287. Tran-II explains that OSA is a "common breathing disorder caused by repetitive upper airway obstruction that stops breathing during sleep" and "the primary mechanism causing the obstruction is the pronounced decrease in muscle tone during sleep…permitting the tongue to prolapse, closing the airway during the negative pressure of inspiration." EX-1010 (Tran-II), p. 4287. Tran-II further explains that "[p]reventing obstructive sleep apnea will reduce the patient's susceptibility to cardiovascular and cerebrovascular diseases and will improve their quality of life." EX-1010 (Tran-II), p. 4287.

86. Like Tran-I, Tran-II describes using an implantable stimulation electrode to prevent airway obstruction in patients with OSA. EX-1010 (Tran-II), p. 4287 (disclosing "a single channel, wireless microelectronic stimulator…that can be injected into a muscle such as the tongue" and "receives power and digital

command data from a nearby RF transmission coil to produce stimulation pulses"). Tran-II discloses that the device is "used to stimulate the tongue muscle to move it out of the airway of the sleeping patient and help prevent OSA." EX-1010 (Tran-II), p. 4287.

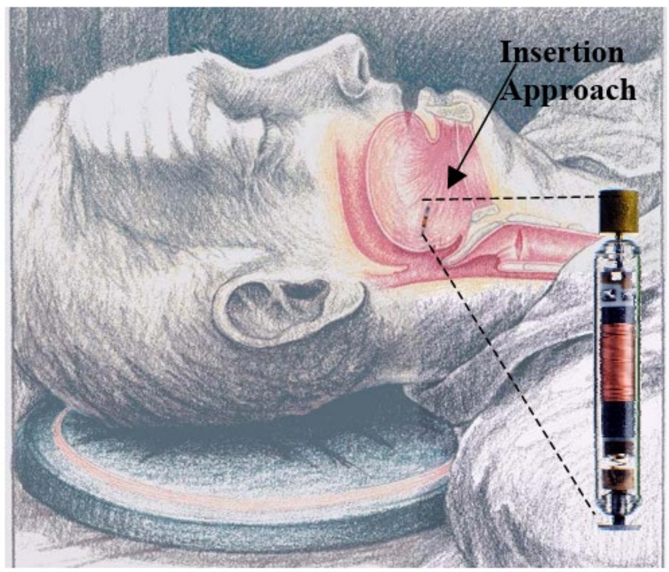


Fig. 1. Closure of the airway during sleep can be prevented by stimulating the tongue protrusor motor units, whose endplates are located near the midline at the posterior genioglossus. A single BION inserted into the posterior genioglossus can be powered and controlled by a transmitting coil located in the pillow.

EX-1010 (Tran-II), FIG. 1.

87. Regarding asynchronous electrical stimulation, Tran-II discloses that "electrical stimulation does not have to synchronize with inspiration to prevent OSA." EX-1010 (Tran-II), p. 4287. Tran-II discloses that "repetitive intermittent electrical stimulation could be used to recover or maintain airway

patency." EX-1010 (Tran-II), p. 4287. In one example, Tran-II describes applying "a brief train of electrical pulses during an ON period followed by no stimulation during an OFF period" and explains that "[t]his method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sensor to synchronize stimulation with breathing." EX-1010 (Tran-II), p. 4287.

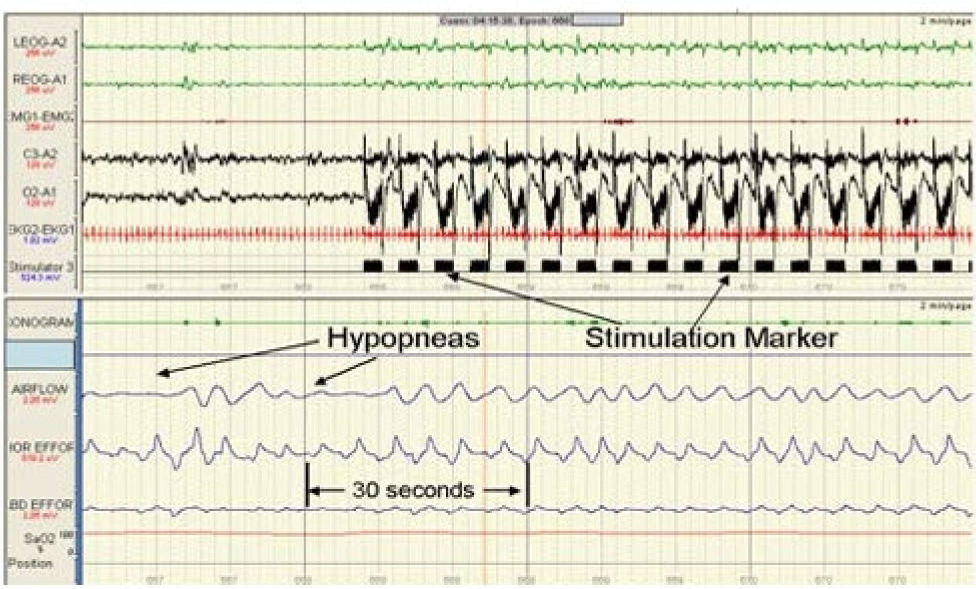


Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010 (Tran-II), FIG. 4.

88. Tran-II discloses that "[s]timulation in midline posterior genioglossus produce[s] selective tongue base protrusion" and "does not disrupt sleep" and that "using neuromuscular stimulation without synchronizing with breathing

(repetitive intermittent electrical stimulation) in [the] posterior genioglossus… may be useful to prevent development of hypopnea and OSA." EX-1010 (Tran-II), p. 4288.

VIII. SUMMARY OF INVALIDITY GROUNDS

89. The Challenges are set forth in detail below and summarized as follows:

Ground	Claims	Basis	Reference
1	1-8, 10-18, and 21-23	§ 103	Durand, either alone or in view of Hoegh
2	1-23	§ 103	Headley in view of Tran

IX. GROUND 1: CHALLENGED CLAIMS 1-8, 10-18, AND 21-23 ARE OBVIOUS FROM DURAND, EITHER ALONE OR IN VIEW OF HOEGH

A. Reasons to Combine Durand and Hoegh

90. As discussed above in VII.A.2 (Summary of Durand's Disclosure), Durand discloses a device including a cuff electrode and a control system for treating OSA by stimulating the HGN that uses trains of stimulus pulses at stimulation intervals that are "determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate" such that "[t]he resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle," which avoids "the added

complexity of closed-loop feedback." EX-1006 (Durand) ¶ 25. Durand further discloses that the duration of the stimulation period (2-3 seconds) may be equal to or longer than the non-stimulation period (2-3 seconds). EX-1006 (Durand) ¶ 25 ("For example, a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between pulse trains.").

91. Durand recognizes that the stimulation interval can be based on the patient normal nighttime interval, but does not provide further details including any example numbers for a typical respiration cycle and its relative duration compared to the stimulus interval. However, this is not surprising because as discussed in V (Technical Background and State of the Art), it was well-known how to determine and an effective stimulus interval based on a patient's typical respiration cycle. EX-1012 (Bolea) ¶¶266, 527, 556-558. Further, as noted above, a POSITA understood that a typical respiratory rate for an adult was around 12-20 breaths per minute (BPM), which corresponds to a respiratory cycle duration of around 3 seconds (20 BPM) to 5 seconds (12 BPM). Durand's disclosure of four (i.e., two seconds of stimulation; two seconds off) to six (i.e., three seconds of stimulation; three seconds off)

second stimulation cycle durations overlaps with, and generally corresponds to, these typical adult respiratory rates.

92. While Durand does not expressly disclose the duration of the stimulation period relative to a reference respiratory-related parameter (e.g., a patient's breathing cycle) or provide much detail regarding a patient's nighttime basal metabolism and how the stimulation cycle may be optimized for a given patient to improve the efficacy of the OSA treatment, Hoegh does and a POSITA would have been motivated to look for other references that provide a more detailed discussion of OSA and treatment protocols.

93. For example, Hoegh, which is in the same field of endeavor as Durand, provides a detailed description of a suitable implantable neurostimulator ("INS") (EX-1007 (Hoegh) ¶¶ 74-119), stimulation lead ("STL") (EX-1007 (Hoegh) ¶¶ 53-59), programmer system (EX-1007 (Hoegh) ¶¶ 120-125), and therapy controller (EX-1007 (Hoegh) ¶¶ 126-130) that may be used to treat OSA. In addition to providing a more robust description of the relevant hardware, Hoegh provides a detailed description of the surgical technique for implanting the device and an exemplary titration process. EX-1007 (Hoegh) ¶¶ 134-158, 190-213.

94. Hoegh further discloses a detailed analysis of the patient's natural physiology and its relationship to treating OSA, including that "[t]he hypoglossal nerve usually activates approximately 300 ms before inspiration and remains active for the entire respiratory phase" and "[t]o mimic this natural physiology, stimulation may be delivered during to the hypoglossal nerve during the inspiratory phase plus a brief pre-inspiratory period of about 300 ms." EX-1007 (Hoegh) ¶ 92. Hoegh further discloses various duty cycles (i.e., the ratios of stimulation periods to non-stimulation periods) that may be used to treat OSA, including that "the maximum stimulation duty cycle may be set from 41% to 69% in 3% increments" and that the duration of the stimulation cycle may be increased to "decrease the probability of missing two consecutive inspirations, and increase the probability of providing the patient with stimulation during the entire respiratory cycle." EX-1007 (Hoegh) ¶¶ 98, 114. A duty cycle of 40% means that the duration a stimulus is applied is 40% of the duration of the stimulation cycle duration, which is based on the patient's respiratory cycle. As such, the 40% duration cycle corresponds to stimulus being applied for 40% of the patient's respiratory cycle.

95. A POSITA would have been motivated to combine the teachings of Hoegh and Durand and would have expected that the teachings could be combined

with a reasonable expectation of success at least because both references are directed to methods for treating OSA using implanted devices for electrical stimulation of the hypoglossal nerve and because Hoegh's disclosure is consistent with Durand's disclosure. EX-1006 (Durand), Title, Abstract, ¶¶ 13, 14, 21, 25; EX-1007 (Hoegh), Abstract, ¶ 92.

96. A POSITA would have had a reasonable expectation of success combining Durand's and Hoegh's teachings for several reasons. *First*, both references disclose treatment methods for OSA using implantable devices, including a nerve cuff and control system/pulse generator, to electrically stimulate the hypoglossal nerve asynchronously. EX-1006 (Durand) ¶¶ 13-16, 21, 25; EX-1007 (Hoegh) ¶¶ 50-51, 92-93.

97. *Second*, both references disclose similar device types and implantation locations:

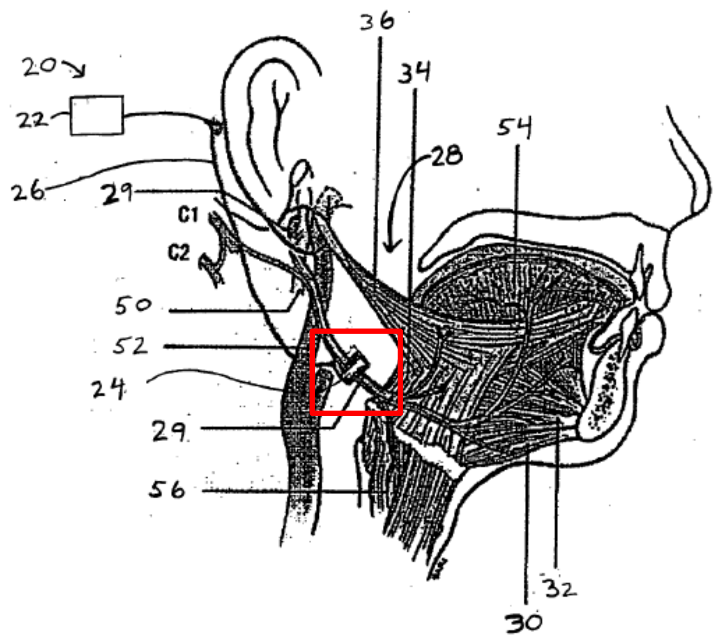
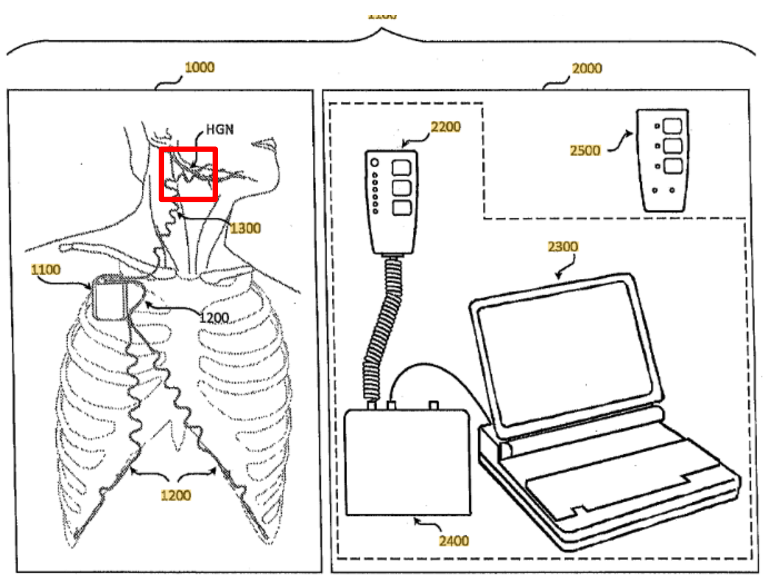


FIG. 1

EX-1006 (Durand), FIG. 1 (annotated).



EX-1007 (Hoegh), FIG. 1 (annotated).

98. *Third*, both references disclose a duty cycle that is determined based on a typical respiration cycle duration for a patient, with the only difference being that Hoegh provides more details of a typical respiration cycle and its relative duration compared to the stimulus interval. EX-1006 (Durand) ¶ 25; EX-1007 (Hoegh) ¶¶ 98, 114. A POSITA would have recognized that such modifications disclosed by Hoegh, such as varying the duty cycle and/or duration of the overall stimulation cycle, were well within the routine in the art. Specifically, these modifications simply required changes to the software to increase the stimulation period and/or overall duration of the stimulation cycle of Durand's intermittent on/off electrical stimulation. Such modifications could be done at the time of manufacture, such as in the firmware or other program code, or could be made by a practitioner during a titration procedure after the device was implanted, as expressly disclosed by Hoegh. As discussed above in V.B (Technical Background, OSA Treatment), titration involved the adjustment of one or more stimulation parameters (e.g., duty cycle, cycle duration, pulse width, amplitude, etc.) and was routinely performed after the patient healed from the implantation procedure and was about to use the device therapeutically. *See also* EX-1007 (Hoegh) ¶¶ 190-213.

99. A POSITA would have had a reasonable expectation of success in combining Durand's and Hoegh's teachings because both references disclose applying methods (asynchronous stimulation) using devices (implantable pulse generator and cuff electrodes) to achieve results (treatment of OSA) that were known in the art before the priority date of the '526 Patent, such that their teachings would have been readily applied to the other using only routine skill.

B. Application of Durand and Hoegh to Challenged Claims 1-8, 10-18, and 21-23

1. Claim 1

a. [1.pre] *A device for treating obstructive sleep apnea, comprising:*

100. To the extent the preamble is limiting, Durand discloses an apparatus [*device*] for treating OSA.

> FIG. 1 is a schematic illustration of an ***apparatus*** and the nerves and muscles ***used in treating obstructive sleep apnea***.

EX-1006 (Durand) ¶ 11.

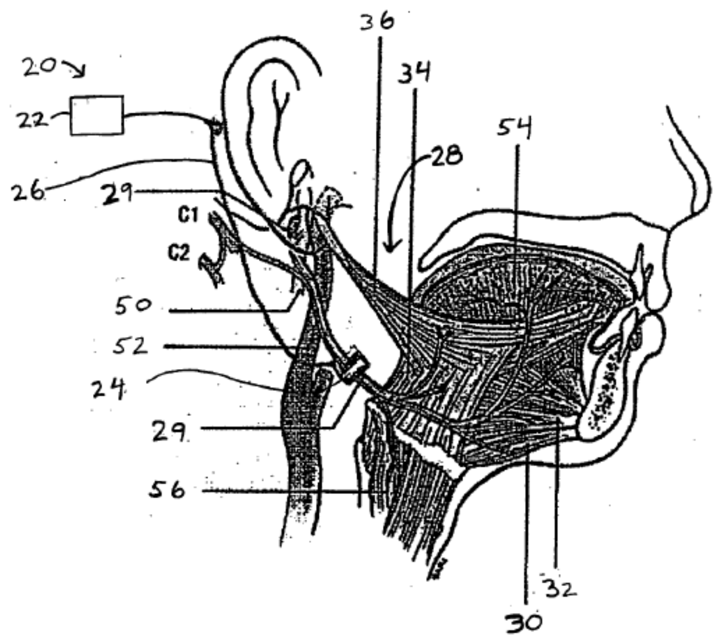


FIG. 1

EX-1006 (Durand), FIG. 1.

101. Accordingly, Durand discloses a device for treating OSA.

b. [1.a1] ***a non-cardiac stimulation means for stimulating an upper airway patency-related nerve;***

102. Durand discloses the apparatus [*device*] includes a control system 22 and a cuff electrode 24 [*non-cardiac stimulation means for stimulating*] that is intimately connected to the hypoglossal nerve [*upper airway patency-related nerve*] and which provides electrical stimulation.

> ***In the case of obstructive sleep apnea, electrical stimulation of the hypoglossal nerve, for example, can***

> ***maintain the patency of the upper airway*** by activating the upper airway dilator muscles, thereby minimizing or eliminating airway collapse during sleep.

EX-1006 (Durand) ¶ 12.

> An exemplary ***apparatus 20 for stimulating a nerve*** in accordance with the present invention is shown schematically in FIG. 1. ***The apparatus 20 includes a control system 22 (shown schematically) for generating the desired electrical stimulus, and an electrode 24 connected to the nerve to transmit the electrical stimulus to the nerve. The electrode 24 preferably is a cuff electrode that provides an intimate connection to the nerve***. The cuff electrode 24 can have a variety of geometries or configurations, but preferably provides an intimate connection around the nerve. A lead wire 26 connects the electrode 24 to the control system 22 in the illustrated embodiment.

EX-1006 (Durand) ¶ 14.

103. Accordingly, Durand discloses claim element [1.a1].

c. [1.a2] ***according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing,***

104. Durand discloses that the control system generates intermittent electrical stimulation at controlled intervals [*alternating periods of stimulation and non-stimulation*] based on the patient's previously observed respiratory rate [*first stimulation therapy protocol*].

> More particularly, a method provided in accordance with the invention includes ***controlling the patency of a patient's airway by stimulating a nerve using at least one of the following techniques***: (a) continuously electrically stimulating at least one fascicle of the hypoglossal nerve at a predetermined a low level amplitude throughout the respiratory cycle; (b) electrically stimulating a nerve and initiating the stimulation in response to a physical process, such as inspiration, using a remote sensor, without feedback from the nerve being stimulated; and (c) ***intermittently electrically stimulating a nerve at controlled intervals, predetermined based on the patient's resting nighttime metabolism, which can be determined from the patient's observed respiratory rate***, for example.

EX-1006 (Durand) ¶ 13.

105. Durand further discloses that the controller does not detect a physical process or require feedback from the nerve being stimulated because the rate is predetermined [*a timing of the stimulation periods is asynchronous relative to patient breathing*].

> In a third embodiment of the method, the controller can be programmed to provide stimulation at a predetermined interval ***without either detecting a physical process or requiring feedback from the nerve being stimulated***. In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. For example, a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains. The pulse trains can each have an amplitude that is at or greater than the patient's activation threshold, up to about 20% above the patient's activation threshold, for example. In this embodiment, ***the stimulation is provided at predetermined rate or pace without the added complexity of closed-loop feedback***.

EX-1006 (Durand) ¶ 25.

106. As noted above, Durand identifies the benefits of providing asynchronous stimulation (i.e., providing stimulation that is not based on actively-sensed information) is that the added complexity of closed-loop feedback can be avoided. EX-1006 (Durand) ¶ 25. Further, a POSITA understood that providing such feedback typically included the use of a sensor, which was known in the art to add complexity in programming and, sometimes, additional surgical intervention to implant a sensing lead. EX-1032 (Mwenge), p. 366 ("The THN method appears, in this regard, to be simpler, in that it obviates the need for sensors and extra hardware, thereby decreasing the surgical procedure time and associated risks."); EX-1033 (Zaidi), p. 384 ("This stimulator design is able to avoid fatigue, without the need for additional implanted feedback sensors…."); EX-1010 (Tran-II), p. 4288 ("This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sensor to synchronize stimulation with breathing."). Thus, providing asynchronous stimulation reduced the complexity of the system while at the same time reduced the time and complexity of the surgical intervention required to implant the device.

107. Accordingly, Durand discloses claim element [1.a2].

d. [1.b] ***wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period,***

108. Durand discloses this claim element, either alone or in combination with Hoegh. For example, Durand discloses providing a train of stimulation pulses for 2-3 seconds (preferably 2.5 seconds) [*a duration of each respective stimulation period*] and a wait period of at least 2-3 seconds between pulse trains [*a duration of each respective non-stimulation period*].

> In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. For example, ***a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains***.

EX-1006 (Durand) ¶ 25.

109. Thus, Durand discloses a 2 second wait period [*duration of a respective non-stimulation period*], which has a duration that is less than a 2½-3 second train of stimulation pulses [*duration of a respective stimulation period*] that closely

simulates the patient's normal nighttime respiratory cycle to ensure that the tongue is protruding during inspiration. *See*, *e.g.*, EX-1006 (Durand) ¶ 20 (describing stimulating the HGN to maintain upper-airway patency). As such, Durand discloses claim element [1.b].

110. However, to the extent Patent Owner argues that Durand does not disclose this claim element, Hoegh does and provides motivation for increasing the duration of the stimulation period. For example, Hoegh discloses stimulating the hypoglossal nerve for at least 300 ms longer than the inspiratory phase of the patient to mimic the natural physiology of the patient [*a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period*].

> To mimic this natural physiology, stimulation may be delivered to the hypoglossal nerve during the inspiratory phase plus a brief pre-inspiratory period of about 300 ms.

EX-1007 (Hoegh) ¶ 92.

111. Thus, while Durand discloses that a duration of a stimulation period may be longer than a duration of a non-stimulation period, Hoegh provides further teachings and motivation as to why it would be beneficial to increase the duration of the stimulation period, i.e., to mimic the patient's physiology by

increasing the duration of the stimulation by at least 300 ms relative to the natural inspiratory phase duration of the patient and to increase the probability of overlapping the inspiratory phase with stimulation.

112. Hoegh further discloses that the length of stimulation [*a duration of each respective stimulation period*] may be increased when operating asynchronously (i.e., when the respiratory signal is lost) to increase the likelihood overlapping the stimulation with the patient's inspiratory period.

> The stimulation duty cycle may be fixed or adaptive. In the fixed mode, the stimulation duty cycle may be set using the programmer system 2100 to designate a fixed percentage value. ***This fixed value may be increased when the respiratory period signal is lost, increasing the likelihood of aligning with actual inspiration***. In adaptive mode, the duty cycle may be allowed to vary as a function of a characteristic of respiration. For example, the adaptive duty cycle may increase when prediction is less accurate (higher variability in respiration rate) or when the respiratory signal is lost. Thus, in some instances, ***the stimulation duty cycle may run above normal (e.g., above 50% to 60%) to achieve a better likelihood of covering the inspiratory phase***.

EX-1007 (Hoegh) ¶ 97.

113. Thus, the teachings of Durand and Hoegh disclose that a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period. Further, a POSITA would have been motivated to provide a stimulation period with a duration that exceeds the duration of the non-stimulation period to mimic the patient's natural physiology and to increase the likelihood of the stimulation period overlapping the patient's inspiratory phase. *See* V.C (Duty Cycles) (referencing Goding, Bolea, Schwartz2001, Eastwood, and others).

114. Accordingly, claim element [1.b] is obvious from Durand, either alone or in view of Hoegh.

e. [1.c] ***wherein the duration of each respective stimulation period is based on a reference respiratory-related parameter,***

115. Durand discloses this claim element, either alone or in combination with Hoegh. Durand expressly discloses that the stimulation is provided [*duration of each respective stimulation period*] to closely simulate the patient's previously observed normal nighttime respiration cycle [*based on a reference respiratory-related parameter*].

> In a third embodiment of the method, the controller can be programmed to provide stimulation at a predetermined interval

> without either detecting a physical process or requiring feedback from the nerve being stimulated. In this method, ***the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle***.

EX-1006 (Durand) ¶ 25.

116. To the extent Patent Owner argues that Durand does not expressly disclose this limitation, Hoegh does, and a POSITA would have combined the references for the reasons discussed above in IX.A (Reasons to Combine Durand and Hoegh).

117. Hoegh discloses mimicking the patient's natural physiology using the patient's previous breaths to predict subsequent breaths [*based on a reference respiratory-related parameter*].

> ***To mimic this natural physiology***, stimulation may be delivered to the hypoglossal nerve during the inspiratory phase plus a brief pre-inspiratory period of about 300 ms.

EX-1007 (Hoegh) ¶ 92.

> Accordingly, an algorithm may be used to predict respiratory period and determine the start of the stimulation burst. The predictive algorithm may be contained in software and executed by a microprocessor resident in the INS circuitry 1130, thus enabling the INS 1100 to generate stimulation synchronous with inspiration. ***One example of a prediction algorithm uses the respiratory period of previous breaths to predict the respiratory period of each subsequent breath***.

EX-1007 (Hoegh) ¶ 93.

118. While Hoegh references synchronization to the patient's respiratory cycle and, potentially, the use of a sensor, Hoegh also expressly discloses that fixed mode stimulation is to be applied at the same or an increased rate when the respiratory signal is lost (i.e., when it is impossible to perform synchronization with the patient's respiratory rate).

> The stimulation duty cycle may be fixed or adaptive. In the fixed mode, the stimulation duty cycle may be set using the programmer system 2100 to designate a fixed percentage value. ***This fixed value may be increased when the respiratory signal is lost, increasing the likelihood of aligning with actual inspiration***.

EX-1007 (Hoegh) ¶ 97.

119. Hoegh further discloses that the asynchronous (fixed) mode stimulation may be applied asynchronously, i.e., without being synchronized to the patient's breathing based on actively sensed respiratory information, during an OSA therapy session.

> Asynchronous mode (fixed mode) is when stimulation is delivered at regular programmable intervals (e.g., 2.5 seconds of stimulation), followed by 2.5 seconds off). ***The intervals may be set to a rate similar to a respiratory cycle (e.g., 5 seconds)***…***Asynchronous stimulation may be initiated by*** programming the device to fixed mode and ***starting a therapy session***.

EX-1007 (Hoegh) ¶ 114.

> The therapy controller may have additional functionality (e.g., more buttons) which can be set to give the patient limited control over ***select therapy settings. These settings include***, but are not limited to, stimulation intensity (e.g., amplitude), ***stimulation mode***, pulse train configuration, core hours stimulation settings, ramp, programmable schedule, clock, and motion inhibit programmable values.

EX-1007 (Hoegh) ¶ 127.

120. Thus, given the express teachings of both Durand and Hoegh, a POSITA would have been motivated to base a duration of each respective stimulation period on a reference respiratory-related parameter to simulate the patient's normal nighttime respiration cycle and mimic the patient's natural physiology. EX-1006 (Durand) ¶ 25; EX-1007 (Hoegh) ¶ 92; *see also* IX.A (Reasons to Combine Durand and Hoegh).

121. Accordingly, this claim element is disclosed by Durand, either alone or in combination with Hoegh.

f. [1.d] *wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.*

122. Durand discloses a cuff electrode 24 that provides intimate connection to the hypoglossal nerve [*implantable electrode*] and a control system 22 for generating the desired electrical stimulus [*implantable pulse generator*] that is connected to the cuff electrode 24 via a lead wire 26 [*electrically connectable*].

> An exemplary apparatus 20 for stimulating a nerve in accordance with the present invention is shown schematically in FIG. 1. The apparatus 20 includes ***a control system 22 (shown schematically) for generating the desired electrical stimulus,***

> ***and an electrode 24 connected to the nerve to transmit the electrical stimulus to the nerve***. The electrode 24 preferably is a cuff electrode that provides an intimate connection to the nerve. The cuff electrode 24 can have a variety of geometries or configurations, but preferably provides an intimate connection around the nerve. ***A lead wire 26 connects the electrode 24 to the control system 22 in the illustrated embodiment***.

EX-1006 (Durand) ¶ 14.

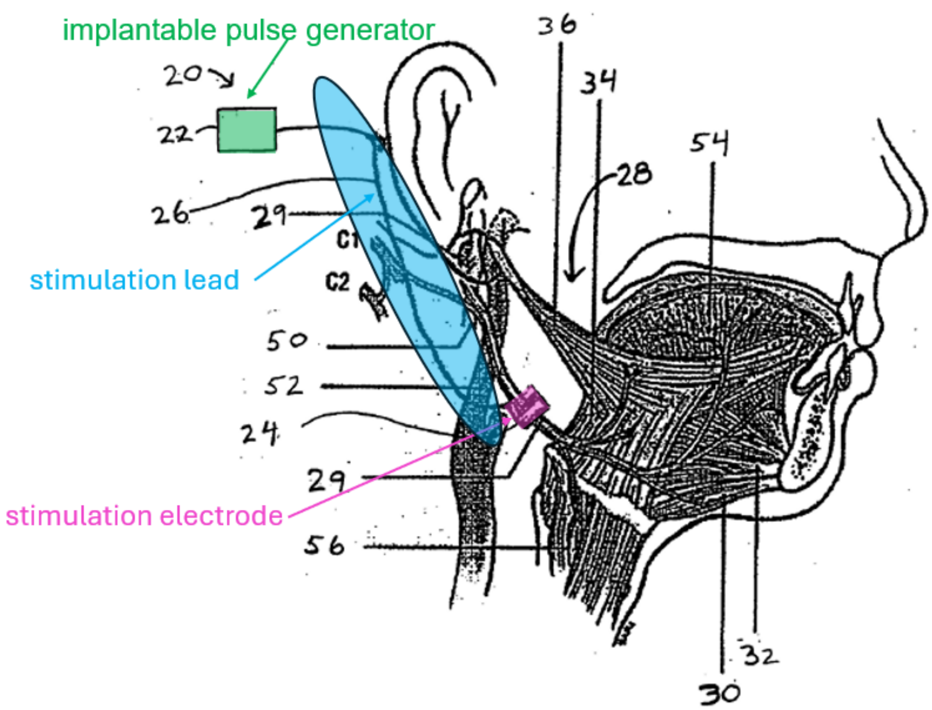


FIG. 1

EX-1006 (Durand), FIG. 1 (annotated).

123. A POSITA understood that a cuff electrode, as disclosed by Durand, would be considered an "implantable electrode" given that the cuff is wrapped around the hypoglossal nerve and is thus implanted within a patient, shown in FIG. 1 of Durand. Indeed, Durand expressly discloses that the electrode 24 and at least portions of the control system 22 may be implanted. EX-1006 (Durand) ¶ 16 ("Portions of the control system 22, in addition to the electrode 24, can be implanted in the patient's body."). A POSITA further understood that the lead wire 26 connecting the electrode 24 and the control system 22 provided an electrical connection between the two components.

124. Accordingly, Durand discloses claim element [1.d]. As such, claim 1 is obvious from Durand, either alone or in view of Hoegh.

2. <u>Claim 2</u>

a. [2] *The device of claim 1, wherein the asynchronous timing of the stimulation relative to patient breathing comprises the timing being not based on actively-sensed respiration during application of the first stimulation therapy protocol.*

125. Durand, either alone or in view of Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Durand discloses that the timing of the pulse trains [*stimulation periods*] is implemented without detecting a physical process or requiring feedback from the hypoglossal nerve

[*not based on actively-sensed respiration during application of the first stimulation therapy protocol*].

> In a third embodiment of the method, the controller can be programmed to provide stimulation at a predetermined interval ***without either detecting a physical process or requiring feedback from the nerve being stimulated***. In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. For example, a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains. The pulse trains can each have an amplitude that is at or greater than the patient's activation threshold, up to about 20% above the patient's activation threshold, for example. In this embodiment, ***the stimulation is provided at predetermined rate or pace without the added complexity of closed-loop feedback***.

EX-1006 (Durand) ¶ 25.

126. Thus, Durand expressly discloses the limitations of this claim and the benefits for not using a sensing element for timing stimulation for synchronization

relative to sensed respiratory information, i.e., simplifying the device by omitting a sensor for actively sensing the respiration.

127. Accordingly, claim 2 is obvious from Durand, either alone or in view of Hoegh.

3. Claim 3

a. [3] *The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory pattern.*

128. Durand, either alone or in view of Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Durand further discloses that the stimulation is provided at predetermined intervals based on the patient's observed nighttime resting respiratory rate [*reference respiratory pattern*].

> In a third embodiment of the method, the controller can be programmed to provide stimulation at a predetermined interval without either detecting a physical process or requiring feedback from the nerve being stimulated. In this method, ***the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate***. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. For example, a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2

> seconds to about 3 seconds between the pulse trains. The pulse trains can each have an amplitude that is at or greater than the patient's activation threshold, up to about 20% above the patient's activation threshold, for example. In this embodiment, the stimulation is provided at predetermined rate or pace without the added complexity of closed-loop feedback.

EX-1006 (Durand) ¶ 25.

129. Thus, Durand expressly discloses the limitations of claim 3.

130. Similarly, Hoegh discloses providing stimulation based on a patient's natural physiology (e.g., the patient's respiratory cycle) [*reference respiratory pattern*].

> In people without OSA, ***inspiration is typically 25-50% of the respiratory cycle***, with variations in respiration rate being common. Variations may cause actual inspiration to differ from predicted inspiration. ***The hypoglossal nerve usually activates approximately 300 ms before inspiration and remains active for the entire inspiratory phase. To mimic this natural physiology, stimulation may be delivered to the hypoglossal nerve during the inspiratory phase plus a brief pre-inspiratory period of about 300 ms***.

EX-1007 (Hoegh) ¶ 92.

131. Accordingly, claim 3 is obvious from Durand, either alone or in view of Hoegh.

4. Claim 4

a. [4.a] *The device of claim 3, wherein the reference respiratory pattern comprises a reference respiratory cycle, and*

132. Durand, either alone or in view of Hoegh, renders obvious claim 3, as discussed above in IX.B.3 (Ground 1, claim 3). Durand further discloses providing stimulation based on the patient's observed nighttime resting respiratory rate [*reference respiratory cycle*].

> In a third embodiment of the method, the controller can be programmed to provide stimulation at a predetermined interval without either detecting a physical process or requiring feedback from the nerve being stimulated. In this method, ***the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle***. For example, a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains. The pulse trains can each have an amplitude that is at or greater than the

> patient's activation threshold, up to about 20% above the patient's activation threshold, for example. In this embodiment, the stimulation is provided at predetermined rate or pace without the added complexity of closed-loop feedback.

EX-1006 (Durand) ¶ 25.

133. Thus, Durand expressly discloses the limitations of claim 4.

134. Although not needed to demonstrate that this claim element is disclosed by the prior art, Hoegh also discloses the limitations of claim 4. For example, as also noted above, Hoegh discloses applying stimulation based on a patient's respiratory cycle [*reference respiratory cycle*].

> In people without OSA, ***inspiration is typically 25-50% of the respiratory cycle***, with variations in respiration rate being common. Variations may cause actual inspiration to differ from predicted inspiration. ***The hypoglossal nerve usually activates approximately 300 ms before inspiration and remains active for the entire inspiratory phase. To mimic this natural physiology, stimulation may be delivered to the hypoglossal nerve during the inspiratory phase plus a brief pre-inspiratory period of about 300 ms***.

EX-1007 (Hoegh) ¶ 92.

135. Accordingly, Durand discloses this claim element, either alone or in combination with Hoegh.

b. [4.b] *wherein a duration of each respective stimulation period is greater than a duration of an inspiratory phase of the reference respiratory cycle.*

136. Durand and Hoegh disclose this claim element. Specifically, Durand discloses providing a train of stimulation pulses for 2-3 seconds (preferably 2.5 seconds) [*duration of each respective stimulation period*].

> In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. For example, ***a train of stimulus pulses can be applied for about 2 secs to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains***.

EX-1006 (Durand) ¶ 25.

137. Hoegh discloses stimulating the hypoglossal nerve for at least 300 ms longer than the inspiratory phase of the patient to mimic the natural physiology of

the patient [*each respective stimulation period is greater than a duration of an inspiratory phase of the reference respiratory cycle*].

> To mimic this natural physiology, ***stimulation may be delivered to the hypoglossal nerve during the inspiratory phase plus a brief pre-inspiratory period of about 300 ms***.

EX-1007 (Hoegh) ¶ 92.

138. Hoegh further discloses that the length of stimulation [*duration of stimulation period*] may be increased when operating asynchronously (i.e., when the respiratory signal is lost) to increase the likelihood of overlapping the stimulation with the patient's inspiratory period.

> The stimulation duty cycle may be fixed or adaptive. In the fixed mode, the stimulation duty cycle may be set using the programmer system 2100 to designate a fixed percentage value. ***This fixed value may be increased when the respiratory period signal is lost, increasing the likelihood of aligning with actual inspiration***. In adaptive mode, the duty cycle may be allowed to vary as a function of a characteristic of respiration. For example, the adaptive duty cycle may increase when prediction is less accurate (higher variability in respiration rate) or ***when the respiratory signal is lost***. Thus, in some instances, ***the stimulation duty cycle may run above normal (e.g., above 50%***

> ***to 60%) to achieve a better likelihood of covering the inspiratory phase***.

EX-1007 (Hoegh) ¶ 97.

139. Thus, the teachings of Durand and Hoegh disclose that a duration of each respective stimulation period is greater than a duration of an inspiratory phase of the reference respiratory cycle. A POSITA understood providing a stimulation period that is greater than the inspiratory phase of the reference respiratory cycle would increase the likelihood of the stimulation overlapping the inspiratory phase, which was known to be beneficial. *See* V.C (Technical Background, Duty Cycles) (referencing Goding, Bolea, Schwartz2001, Eastwood, and others).

140. Accordingly, claim 4 is obvious from Durand and Hoegh.

5. <u>Claim 5</u>

a. [5] *The device of claim 1, wherein the reference respiratory-related parameter is based on stable respiration.*

141. Durand, either alone or in view of Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Durand and Hoegh further disclose the limitations of claim 5. Specifically, Durand discloses that a

reference respiratory-related parameter is based on a patient's observed nighttime resting respiratory rate [*stable respiration*].

> In this method, the stimulation interval can be determined from the ***patient's nighttime basal metabolism***, e.g., ***based on the patient's observed nighttime resting respiratory rate***. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. For example, a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains.

EX-1006 (Durand) ¶ 25.

142. A POSITA understood a patient's basal metabolism to be the patient's minimum metabolic rate to function at a basic level. Given the foregoing disclosures from Durand, a POSITA understood that Durand's goal was to identify a stable respiratory rate for the patient while the patient is sleeping in order to apply stimulus at this rate to maintain the patient's natural (unobstructive) sleeping rhythm. Accordingly, Durand discloses the limitations of claim 5.

143. Although not necessary to demonstrate that this claim is disclosed by the prior art, Hoegh also discloses the desire to identify a stable respiratory rate when treating a patient so that the stimulation duty cycle may be maintained and/or reduced. EX-1007 (Hoegh) ¶ 97 ("Thus, when the prediction is highly accurate (stable respiration rate), the stimulation duty cycle may be reduced.").

144. Accordingly, claim 5 is obvious from Durand, either alone or in view of Hoegh.

6. <u>Claim 6</u>

a. [6.a] *The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory cycle and*

145. Durand, either alone or in view of Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Durand, either alone or in combination with Hoegh, further discloses the limitations of this claim element for the same reasons discussed in IX.B.4.a (Ground 1, claim element [4.a]), as this claim element is identical to claim element [4.a].

b. [6.b] *wherein a combined duration of each respective stimulation period and of each respective non-stimulation period is less than the reference respiration-related parameter, which comprises a duration of a reference breath.*

146. Durand discloses stimulation cycles as short as four seconds (two seconds of stimulation pulses; two seconds waiting).

> For example, a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains.

EX-1006 (Durand) ¶ 25.

147. Hoegh discloses that a patient's respiratory cycle is about five seconds. EX-1007 (Hoegh) ¶ 114 ("The intervals may be set to a rate similar to a respiratory cycle (e.g., 5 seconds)."). A POSITA understood a four (or 4½) second stimulation cycle, as disclosed by Durand, has a duration less than a duration of a patient's five second respiratory rate, which a POSITA understood to be a reference breath (i.e., inspiratory period and expiratory period).

148. As discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and stimulation cycle duration, was routine in the art and was a typical part of the titration process

performed by a physician after implantation of an OSA treatment device. I further note that the ’526 Patent does not identify any unexpected results resulting from providing a combined duration of each respective stimulation period and of each respective non-stimulation period that is less than a duration of a reference breath. At most, the ’526 Patent discloses that this is useful to ensure overlap with the inspiratory period, but such a goal was known in the art. EX-1007 (Hoegh) ¶ 92 (“To maximize stimulation coverage of actual inspiration….”), ¶ 97 (“Thus, in some instances, the stimulation duty cycle may run above normal (e.g., above 50% to 60%) to achieve a better likelihood of covering the inspiratory phase.”), ¶ 114 (“Alternatively, longer intervals (e.g. 8 seconds) may decrease the probability of missing two consecutive inspirations, and increase the probability of providing the patient with stimulation during an entire respiratory cycle.”); *see also* V.C (Technical Background, Duty Cycles). As such, not only do Durand and Hoegh disclose the limitations of claim element [6.b], but the claim element itself recites nothing more than routine optimization (i.e., a duty cycle and stimulation cycle duration that provide the desired outcome of increasing airway patency while sleeping).

149. Accordingly, providing a combined duration of each respective stimulation period and of each respective non-stimulation period that is less than a duration of a reference breath required nothing more than the exercise of routine skill, i.e., optimizing a duty cycle and/or stimulation/wait periods, which a POSITA would have been motivated to provide to increase the efficacy while maintaining the safety. EX-1007 (Hoegh) ¶ 96.

150. Accordingly, Durand and Hoegh disclose claim element [6.b] and render obvious claim 6.

7. __Claim 7__

a. [7.a] ***The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory cycle and***

151. Durand, either alone or in view of Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Durand further discloses this claim element for the same reasons as discussed above in IX.B.4.a (claim element [4.a]), as this claim element is identical to claim element [4.a].

b. [7.b] *wherein the combined duration of a respective one of the stimulation periods and a respective one of the stimulation periods is no greater than a duration of a reference respiratory cycle.*

152. Durand and Hoegh disclose claim element [7.b] for the same reasons as those discussed above in IX.B.6.b (Ground 1, claim element [6.b]) given that there is no significant difference between a duration that is "less than the reference respiration-related parameter" (claim element [6.b]) and a duration that is "no greater than a duration of a reference respiratory cycle" (claim element [7.b]).

153. Accordingly, claim 7 is obvious from Durand and Hoegh.

8. <u>Claim 8</u>

a. [8] *The device of claim 1, wherein the duration of the respective stimulation periods remain uniform.*

154. Durand, either alone or in view of Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Durand discloses providing intermittent stimulation at controlled intervals at a predetermined rate.

> More particularly, a method provided in accordance with the invention includes controlling the patency of a patient's airway by stimulating a nerve using at least one of the following techniques: … (c) ***intermittently electrically stimulating a nerve a controlled intervals***, predetermined based on the patient's resting nighttime metabolism, determined by observing the nighttime respiratory rate, for example.

EX-1006 (Durand) ¶ 4.

> In a third embodiment of the method, the controller can be programmed to provide stimulation at a ***predetermined interval*** without either detecting a physical process or requiring feedback from the nerve being stimulated…The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. For example, ***a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains***.

EX-1006 (Durand) ¶ 25.

155. Accordingly, Durand discloses the limitations of claim 8.

156. Although not believed to be needed to demonstrate that the prior art of Ground 1 discloses the limitations of claim 8, Hoegh also demonstrates the limitations of this claim element are disclosed and reinforces a POSITA's understanding regarding Durand. For example, Hoegh discloses using a fixed duty cycle [*the respective stimulation periods remain uniform*].

> The stimulation duty cycle may be fixed or adaptive. In the fixed mode, the stimulation duty cycle may be set using the programmer system 2100 to designate a fixed percentage value.

EX-1007 (Hoegh) ¶ 97.

> ***Asynchronous mode (fixed mode) is when stimulation is delivered at regular programmable intervals*** (e.g., 2.5 seconds of stimulation, followed by 2.5 seconds off). The intervals may be set to a rate similar to a respiratory cycle, (e.g., 5 seconds). Alternatively longer intervals (e.g. 8 seconds) may decrease the probability of missing two consecutive inspirations, and increase the probability of providing the patient with stimulation during an entire respiratory cycle…***Fixed mode stimulations may be in any available pulse train configuration***.

EX-1007 (Hoegh) ¶ 114.

157. A POSITA understood the predetermined, controlled intervals disclosed by Durand and the programmed, regular pulse train intervals disclosed by Hoegh as providing uniform stimulation periods. This understanding is reinforced by Hoegh expressly contemplating the use of variable periods in the adaptive mode, and thus expressly distinguishes between fixed (e.g., uniform periods) and variable (e.g., adaptive periods). EX-1007 (Hoegh) ¶ 97 ("In adaptive mode, the duty cycle may be allowed to vary as a function of a characteristic of respiration.").

158. Accordingly, Durand discloses the limitations of claim 8, either alone or in combination with Hoegh.

9. <u>Claim 10</u>

a. [10] ***The device of claim 1, wherein a respective one of the stimulation periods and a respective one of the non-stimulation periods are in a proportion of at least 1.5 to 1.***

159. Durand, either alone or in view of Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Durand discloses providing a train of stimulation pulses [*a respective one of the stimulation periods*] for three seconds and a wait period [*a respective one of the non-stimulation periods*] of two seconds.

> In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. For example, ***a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains***.

EX-1006 (Durand) ¶ 25.

160. A three-second train of stimulation pulses and two-second wait period corresponds to a proportion of 1.5 to 1, as 3/2 = 1.5.

161. Thus, Durand discloses stimulation periods [*a respective one of the stimulation periods*] and a wait period [*a respective one of the non-stimulation periods*] are in a proportion of at least 1.5 to 1, as recited in claim 10.

162. Although not believed to be needed to demonstrate invalidity, I note that Hoegh discloses exemplary, non-limiting duty cycles of up to 69%, which equates to the stimulation pulses [*a respective stimulation period*] being applied by over a proportion of 2 (69% stimulation / 31% non-stimulation= 2.23 stimulation/non-stimulation).

> The following stimulation duty cycle parameters are given by way of example, not limitation. In fixed mode, ***the maximum stimulation duty cycle may be set from 41% to 69%*** in 3% increments, and the default setting may be 50%.

EX-1007 (Hoegh) ¶ 96.

163. Thus, Hoegh discloses stimulation periods [*a respective stimulation period*] and a wait period [*a respective non-stimulation period*] are in a proportion of at least 1.5 to 1, as recited in claim 10.

164. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. I further note that the ’526 Patent does not identify any unexpected results from providing a stimulation period and a non-stimulation period in a proportion of at least 1.5 to 1. As such, not only do Durand and Hoegh disclose the limitations of claim 10, but the claim itself recites nothing more than routine optimization (i.e., a duty cycle that provides the desired outcome of increasing airway patency while sleeping).

165. Accordingly, claim 10 is obvious from Durand, either alone or in combination with Hoegh.

10. <u>Claim 11</u>

a. [11] *The device of claim 1, wherein a duration of a respective one of the stimulation periods exceeds the duration of a respective one of the non-stimulation periods by a factor of 3.*

166. Durand, either alone or in view of Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Hoegh discloses using exemplary duty cycles ranging between 41% to 69%.

> The following stimulation duty cycle parameters are given by way of example, ***not limitation***. In fixed mode, the maximum

> stimulation duty cycle may be set from 41% to 69% in 3% increments, and the default setting may be 50%.

EX-1007 (Hoegh) ¶ 98.

167. A POSITA understood that a 69% duty cycle would provide stimulation pulses [*stimulation period*] for a duration that exceeds the wait period [*non-stimulation period*] by over a factor of 2 (i.e., 69% / 31% = 2.23). However, Hoegh expressly discloses that the disclosed duty cycles are not limiting (*see* ¶ 98, *supra*) and that "[t]he stimulation duty cycle may vary to meet efficacy and safety requirements." EX-1007 (Hoegh) ¶ 96.

168. Given these express teachings, one of ordinary skill in the art would have understood that the duty cycle could be increased beyond 69%, such as to 75% to provide a duration of the stimulation period that exceeds a duration of the non-stimulation period by a factor of three (75% / 25% = 3), to meet the desired efficacy. Indeed, the prior art includes examples of duty cycles in which the stimulation period exceeds the non-stimulation period by a factor 4 and 12 (e.g., an on/off period in the proportion of 20/5 and 60/5). EX-1008 (Headley) ¶ 48 ("On/off intermittent periods include from 5/5, ***20/5***, 10/10, 5/60, ***60/5***, 20/20, 30/30, 40/40, 50/50, 60/60, and so forth."). Further, Durand discloses providing constant stimulation to improve upper-airway patency.

Durand ¶ 22 ("In a first embodiment of the method, electrical stimulation can be provided to the hypoglossal nerve continuously throughout the respiration cycle, during both inspiration (breathing in) and expiration (breathing out) phases, to maintain the desired muscle tone for patency of the upper airway.").

169. As discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. I further note that the '526 Patent does not identify any unexpected results resulting from providing each respective stimulation cycle with a duration that is less than a duration of a reference respiratory cycle and in which a duration of the stimulation period exceeds a duration of the non-stimulation period by a factor of at least three. As such, not only do Durand and Hoegh disclose the limitations of claim 11, but the claim itself recites nothing more than routine optimization (i.e., a duty cycle that provides the desired outcome of increasing airway patency while sleeping).

170. Accordingly, providing stimulation cycles in which a duration of the stimulation period exceeds the duration of the non-stimulation period by a factor of at least three required nothing more than the exercise of routine skill,

i.e., optimizing a duty cycle, which a POSITA would have been motivated to provide to increase the efficacy while maintaining the safety. EX-1007 (Hoegh) ¶ 96.

171. Accordingly, Durand and Hoegh render obvious claim 11.

11. <u>Claim 12</u>

a. [12.a] *The device of claim 1, wherein a combination of a respective one of the stimulation periods and a respective one of the non-stimulation periods comprises a stimulation cycle, and*

172. Durand, either alone or in view of Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Durand further discloses intermittent electrical stimulation [*stimulation cycle*] that includes stimulating a nerve at controlled intervals using a train of stimulus pulses [*stimulation period*] after waiting a predetermined amount of time [*non-stimulation period*].

> More particularly, a method provided in accordance with the invention includes controlling the patency of a patient's airway by stimulating a nerve using at least one of the following techniques:…***(c) intermittently electrically stimulating a nerve at controlled intervals, predetermined based on the patient's resting nighttime metabolism, which can be determined from the patient's observed respiratory rate, for example***.

EX-1006 (Durand) ¶ 13.

> The resulting timing of the stimulation pulse trains will closely stimulate the patient's normal nighttime respiration cycle. For example, ***a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains***.

EX-1006 (Durand) ¶ 25.

173. Accordingly, Durand discloses claim element [12.a].

b. [12.b] ***wherein a duration of the respective one of the stimulation periods comprises at least 80 percent of a duration of the stimulation cycle.***

174. As noted above in IX.B.11.a (Ground 1, claim element [12.a]), Durand discloses providing a train of stimulus pulses for two to three seconds, waiting two to three seconds, and then applying the train of stimulus pulses. EX-1006 (Durand) ¶ 25. A POSITA thus understood Durand as disclosing stimulation periods of up to 60% of a stimulation cycle when providing a train of stimulus for three seconds and a wait time of two seconds for a stimulation cycle duration of five seconds.

3 seconds ON; 2 seconds OFF

$$\frac{3}{5} \times 100\% = 60\%$$

175. As discussed above with respect to claim 11, Hoegh discloses exemplary duty cycles ranging between 41% to 69%.

> The following stimulation duty cycle parameters are given by way of example, ***not limitation***. In fixed mode, the maximum stimulation duty cycle may be set from 41% to 69% in 3% increments, and the default setting may be 50%.

EX-1007 (Hoegh) ¶ 98.

176. Hoegh further discloses that the disclosed duty cycles are not limiting (*see* ¶ 98, *supra*) and that "[t]he stimulation duty cycle may vary to meet efficacy and safety requirements." EX-1007 (Hoegh) ¶ 96.

177. Given these express teachings, one of ordinary skill in the art would have understood that the duty cycle could be increased beyond 69%, such as to 80% to obtain the desired efficacy. Indeed, the prior art includes examples of duty cycles of up to 92% (e.g., an on/off period of 60/5). EX-1008 (Headley) ¶ 48 ("On/off intermittent periods include from 5/5, 20/5, 10/10, 5/60, ***60/5***, 20/20, 30/30, 40/40, 50/50, 60/60, and so forth."). Notably, Durand discloses providing constant stimulation to improve upper-airway patency. EX-1006

(Durand) ¶ 22 ("In a first embodiment of the method, electrical stimulation can be provided to the hypoglossal nerve continuously throughout the respiration cycle, during both inspiration (breathing in) and expiration (breathing out) phases, to maintain the desired muscle tone for patency of the upper airway.").

178. As discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. I further note that the '526 Patent does not identify any unexpected results resulting from providing stimulation periods that are at least 80% of a duration of a stimulation cycle. As such, not only do Durand and Hoegh disclose the limitations of claim element [12.b], but the claim element itself recites nothing more than routine optimization (i.e., a duty cycle that provides the desired outcome of increasing airway patency while sleeping).

179. Accordingly, providing stimulation cycles in which a duration of the stimulation period is at least 80% of a duration of the stimulation cycle required nothing more than the exercise of routine skill, i.e., optimizing a duty

cycle, which a POSITA would have been motivated to provide to increase the efficacy while maintaining the safety. EX-1007 (Hoegh) ¶ 96.

180. Accordingly, Durand, either alone or in combination with Hoegh, discloses claim element [12.b], and claim 12 is obvious from Durand and Hoegh.

12. <u>Claim 13</u>

a. [13] *The device of claim 1, wherein each respective stimulation period comprises continuous pulsed stimulation.*

181. Durand, either alone or in view of Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Durand further discloses the limitations of this claim. As noted above, the '526 Patent describes continuous stimulation as "a train of stimulation pulses which occur in a relatively short time frame," such as "a finite number (e.g. 5, 10, etc.) of stimulation pulses per second":

> In some examples, each stimulation period within a stimulation cycle includes continuous stimulation. In some examples, continuous stimulation refers to a train of stimulation pulses which occur in a relatively short time frame. For instance, in some examples, continuous stimulation corresponds to at least a finite (e.g. 5, 10, etc.) of stimulation pulses per second.

EX-1001 4:37-43.

182. Similarly, Durand discloses that the train of stimulation pulses, having pulses provided at a frequency of about 10-30 Hertz (i.e., 10-30 pulses per second) [*continuous pulsed stimulation*].

> Other suitable combinations of stimulation amplitude and frequency can be provided on a patient-dependent basis. For example, the electrical stimulation can be provided by pulse trains of an intermittent duration or continuously, at a frequency of about 10 Hertz (Hz) to about 30 Hertz (Hz), with a pulse width of about 50 microseconds (μs).

EX-1006 (Durand) ¶ 21.

> In a third embodiment of the method, the controller can be programmed to provide stimulation at a predetermined interval without either detecting a physical process or requiring feedback from the nerve being stimulated. In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. ***For example, a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains***. The pulse trains can each have an amplitude that is at or greater than the

> patient's activation threshold, up to about 20% above the patient's activation threshold, for example. In this embodiment, ***the stimulation is provided at predetermined rate or pace without the added complexity of closed-loop feedback***.

EX-1006 (Durand) ¶ 25.

183. Accordingly, Durand discloses the limitations of claim 13.

13. <u>Claim 14</u>

a. [14.a] *The device of claim 1, comprising: a processor; and*

184. Durand, either alone or in combination with Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Durand further discloses that the control system includes a processor for setting up stimulation parameter and controlling the stimulation [*first stimulation therapy protocol*].

> ***The control system 22 also typically includes a processor*** for setting up stimulation parameters to achieve the desired outcome for the individual patient or otherwise controlling the stimulation.

EX-1006 (Durand) ¶ 15.

185. Accordingly, Durand discloses the limitations of claim element [14.a].

b. [14.b] *a non-volatile computer readable medium storing instructions, executable on the processor, to implement the first stimulation therapy protocol via the non-cardiac stimulation means for stimulating.*

186. As noted above, Durand discloses that the control system includes a processor for setting up stimulation parameters to achieve the desired outcome or otherwise control the stimulation [*implement the first stimulation therapy protocol via the non-cardiac stimulation means for stimulating*]. IX.B.13.a (Ground 1, claim element [14.a]). A POSITA understood that a processor functions by executing instructions that are stored in a non-volatile computer-readable medium. V.A (Technical Background, Neuromuscular Stimulators).

187. Consistent with this understanding Hoegh expressly discloses that processors include such non-volatile storage elements and control the stimulation provided to a patient.

> The microprocessor may contain built-in support circuits (***RAM, flash memory***), analog to digital (A/D) converter, timers, serial ports and digital IO) used to interface with the rest of the [implantable neurostimulator] circuit 1130, including accelerometer 1150.

EX-1007 (Hoegh) ¶ 82.

> The stimulation output circuits may deliver bursts of biphasic stimulation pulses to the STL 1300…***The microprocessor may select the amplitude*** (e.g., 0.4 mA to 5 mA) of the output current from the current source circuit which may be applied through the switching network.

EX-1007 (Hoegh) ¶ 85.

> ***The INS 1100 may deliver stimulation*** as a train of pulses with constant pulse width and amplitude at a set frequency for a duration limited by duty cycle. This train of pulses may be described as a pulse train envelope and is illustrated in FIG. 6D. The envelope describes a series of biphasic pulses delivered consecutively during a stimulation burst. When the stimulation level of the positive phase of each biphasic pulse is uniform, this level is the level of the stimulation burst. The INS 1100 may also deliver stimulation in pulse train envelopes wherein the pulses are non-uniform (e.g., pulses may have different amplitudes).

EX-1007 (Hoegh) ¶ 100.

188. Given the foregoing, to the extent Patent Owner argues that Durand does not expressly disclose this limitation, Hoegh does, and a POSITA understood Durand and Hoegh disclosing a processor and non-volatile computer readable medium that together implement the non-cardiac stimulation element as

claimed in claim 14. Accordingly, claim 14 is obvious from Durand, either alone or in combination with Hoegh.

14. <u>Claim 15</u>

a. [15] *The device of claim 1, wherein the first stimulation therapy protocol is to be applied during a treatment period in which the patient is to engage in sleeping behavior.*

189. Durand, either alone or in combination Hoegh, renders obvious claim 1, as discussed above in IX.B.1 (Ground 1, claim 1). Durand further discloses the limitations of claim 15, as Durand expressly discloses that the electrical stimulation is applied to the hypoglossal nerve [*first stimulation therapy protocol*] to treat OSA that occurs during sleep.

> ***Sleep apnea is characterized by temporary cessation of breathing during sleep***, which can lead to or aggravate many health problems. ***Obstructive sleep apnea*** (often abbreviated OSA) is primarily caused by the collapse of the upper airway.

EX-1006 (Durand) ¶ 2.

> The present invention provides a method for ***treating*** a medical condition, such as ***obstructive sleep apnea, by directly electrically stimulating a nerve*** to control one or more muscles to achieve a desired effect for a patient.

EX-1006 (Durand) ¶ 12.

190. Accordingly, Durand discloses the limitations of claim 15.

15. <u>Claim 16</u>

a. [16.pre] *A device for treating obstructive sleep apnea, comprising:*

191. To the extent the preamble is limiting, Durand discloses a device for treating OSA for the same reasons discussed above in IX.B.1.a (Ground 1, claim element [1.pre]), as the two limitations are identical. Accordingly, Durand discloses claim element [16.pre] to the extent it is limiting.

b. [16.a1] *a non-cardiac means for stimulating an upper airway patency-related nerve,*

192. Durand discloses this claim element for the same reasons discussed above in IX.B.1.b (Ground 1, claim element [1.a1]), as the two limitations are identical. Accordingly, Durand discloses claim element [16.a1].

c. [16.a2] *according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing,*

193. Durand discloses this claim element for the same reasons discussed above in IX.B.1.c (Ground 1, claim element [1.a2]), as the two limitations are identical. Accordingly, Durand discloses claim element [16.a2].

d. [16.b] *wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period,*

194. Durand discloses this claim element, either alone or in combination with Hoegh, for the same reasons discussed above in IX.B.1.d (Ground 1, claim element [1.b]), as the two limitations are identical. Accordingly, Durand discloses claim element [16.b], either alone or in combination with Hoegh.

e. [16.c] *wherein each stimulation period comprises continuous pulsed stimulation, and*

195. Durand discloses this claim element for the same reasons discussed above in IX.B.12 (Ground 1, claim 13), as this limitation is identical to the limitations of claim 13. Accordingly, Durand discloses claim element [16.c].

f. [16.d] *wherein the first stimulation therapy protocol is to deliver multiple stimulation periods within a duration of a reference breath of a reference respiratory cycle, and*

196. Durand and Hoegh disclose this claim element. For example, Durand and Hoegh both disclose providing electrical stimulus a rate [*first stimulation therapy protocol*] based on the patient's nighttime respiratory rate [*reference respiratory cycle*].

> The resultant timing of the stimulation pulse trains will closely simulate the ***patient's normal nighttime respiration cycle***. For

> example, a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between pulse trains.

EX-1006 (Durand) ¶ 25.

> Asynchronous mode (fixed mode) is when stimulation is delivered at regular programmable intervals (e.g., 2.5 seconds of stimulation, followed by 2.5 seconds off). ***The intervals may be set to a rate similar to a respiratory cycle, (e.g. 5 seconds)***. Alternatively, longer intervals (e.g. 8 seconds) may decrease the probability of missing two consecutive inspirations, and increase the probability of providing the patient with stimulation during an entire respiratory cycle.

EX-1007 (Hoegh) ¶ 114.

197. Hoegh further discloses that inspiration is typically about 25-50% of a respiratory cycle and that the duty cycle may be varied to meet efficacy and safety requirements.

> In people without OSA, ***inspiration is typically 25-50% of the respiratory cycle***, with variations in respiration being common.

EX-1007 (Hoegh) ¶ 92.

> The stimulation duty cycle may vary to meet efficacy and safety requirements. Generally, the stimulation duty cycle may be used to determine the stimulation period of the predicted respiratory period (stimulation period=duty cycle x predicted respiratory period).

EX-1007 (Hoegh) ¶ 96.

198. Given the foregoing teachings, one of ordinary skill in the art would have understood the combination of Durand and Hoegh as disclosing that multiple stimulation periods could be provided within a duration of a reference breath of a reference respiratory cycle. Specifically, 25 percent of a five-second reference respiratory cycle corresponds to a stimulation period of 1.25 seconds. A POSITA understood that the goal was to stimulate the hypoglossal nerve at least during the inspiratory phase of a patient's respiratory cycle and thus would provide stimulus for at least 1.55 seconds (i.e., 1.25 seconds corresponding to the inspiratory phase plus the 300 ms to mimic the patient's natural physiology). EX-1007 (Hoegh) ¶ 92 ("The hypoglossal nerve usually activates approximately 300 ms before inspiration and remains active for the entire inspiratory phase.").

199. To avoid fatigue, a wait period would be provided; however, a POSITA understood that the tongue is a hydrostat and is less susceptible to fatigue than other muscles such that shorter wait periods may be provided. *See* V.C (Technical Background, Duty Cycles). As such, a wait period [*non-stimulation period*] that was 31% of the duration of the stimulation cycle would yield a wait period of approximately 0.7 seconds to achieve a 69% duty cycle as expressly taught by Hoegh. EX-1007 (Hoegh) ¶ 98 ("In fixed mode, the maximum ***stimulation duty cycle may be set*** from 41% to ***69%*** in 3% increments, and the default setting may be 50%."). Indeed, the prior art expressly discloses stimulation periods and non-stimulation periods as short as one second. EX-1008 (Headley) ¶ 48 ("On periods may range, without limitations from 1 to 120 seconds, and off periods similarly.").

200. A stimulation period of 1.55 seconds and a 0.7 second wait period [*non-stimulation period*] would correspond to stimulation cycle having 2.25 seconds in duration such that multiple (i.e., two) stimulation periods would be provided within a duration of a reference breath of a reference respiratory cycle of five seconds.

201. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and stimulation cycle

duration, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. I further note that the '526 Patent does not identify any unexpected results resulting from delivering multiple stimulation periods within a duration of a reference breath of a reference respiratory cycle. As such, not only do Durand and Hoegh disclose the limitations of claim element [16.d], but the claim element recites nothing more than routine optimization (i.e., a stimulation period and stimulation cycle duration that provides the desired outcome of increasing airway patency while sleeping).

202. Accordingly, delivering multiple stimulation periods within a duration of a reference breath of a reference respiratory cycle required nothing more than the exercise of routine skill, i.e., optimizing a stimulation period and stimulation cycle duration, which a POSITA would have been motivated to provide to increase the efficacy while maintaining the safety. EX-1007 (Hoegh) ¶ 96.

203. Thus, claim element [16.d] is obvious from Durand and Hoegh.

g. [16.e] ***wherein, the non-cardiac stimulation means for stimulating comprises an implantable pulse electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.***

204. Durand discloses this claim element for the same reasons discussed above in IX.B.1.f (Ground 1, claim element [1.d]), as the two limitations are identical. Accordingly, Durand discloses claim element [16.e].

205. In view of the foregoing, claim 16 is obvious from Durand and Hoegh.

16. <u>Claim 17</u>

a. [17] ***The device of claim 16, wherein the duration of each respective non-stimulation period is at least less than half of the duration of each respective stimulation period.***

206. Durand and Hoegh render obvious claim 16, as discussed above in IX.B.15 (Ground 1, claim 16). Hoegh further discloses the limitations of claim 17. For example, Hoegh discloses exemplary, non-limiting duty cycles of up to 69%, which equates to the stimulation pulses [*respective stimulation period*] being applied by over a proportion of two relative to the non-stimulation periods (69% / 31% =2.23).

> The following stimulation duty cycle parameters are given by way of example, not limitation. In fixed mode, ***the maximum stimulation duty cycle may be set from 41% to 69%*** in 3% increments, and the default setting may be 50%.

EX-1007 (Hoegh) ¶ 96.

207. Thus, Hoegh discloses that the stimulation period [*respective stimulation period*] and wait period [*respective non-stimulation period*] are in a proportion of up to 2.23:1, which corresponds to a duration of each wait period [*respective non-stimulation period*] being at least less than half of the duration of each respective stimulation period.

208. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. I further note that the '526 Patent does not identify any unexpected results from providing stimulation cycle in which the duration of each respective non-stimulation period is at least less than half of the duration of each respective stimulation period. As such, not only do Durand and Hoegh disclose the limitations of claim 17, but the claim itself recites nothing more than routine optimization (i.e., a duty cycle that provides the desired outcome of increasing airway patency while sleeping).

209. Accordingly, claim 17 is obvious from Durand and Hoegh.

17. Claim 18

a. [18] *The device of claim 16, wherein the reference respiratory cycle comprises at least one of: a historical patient-specific reference respiratory cycle; and a multiple patient reference respiratory cycle.*

210. Durand in view of Hoegh renders obvious claim 16, as discussed above in IX.B.15 (Ground 1, claim 16). Durand further discloses this claim element, either alone or in combination with Hoegh. For example, Durand expressly discloses that the stimulation is provided to closely simulate the patient's normal nighttime respiration cycle [*historical patient-specific reference respiratory cycle*].

> In a third embodiment of the method, the controller can be programmed to provide stimulation at a predetermined interval without either detecting a physical process or requiring feedback from the nerve being stimulated. In this method, ***the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle.***

EX-1006 (Durand) ¶ 25.

211. Thus, Durand discloses the limitations of claim 18. To the extent Patent Owner argues Durand does not disclose these limitations, a POSITA would have modified Durand's teachings to include those of Hoegh. Specifically, Hoegh discloses mimicking the patient's natural physiology using the patient's previous breaths to predict subsequent breaths [*historical patient-specific average respiratory cycle*].

> ***To mimic this natural physiology***, stimulation may be delivered to the hypoglossal nerve during the inspiratory phase plus a brief pre-inspiratory period of about 300 ms.

EX-1007 (Hoegh) ¶ 92.

> Accordingly, an algorithm may be used to predict respiratory period and determine the start of the stimulation burst. The predictive algorithm may be contained in software and executed by a microprocessor resident in the INS circuitry 1130, thus enabling the INS 1100 to generate stimulation synchronous with inspiration. ***One example of a prediction algorithm uses the respiratory period of previous breaths to predict the respiratory period of each subsequent breath***.

EX-1007 (Hoegh) ¶ 93.

212. Thus, both Durand and Hoegh disclose using a patient's observed respiratory cycle [*historical patient-specific reference respiratory cycle*] as the basis for the reference respiratory cycle. As such, claim 18 is obvious from Durand and Hoegh.

18. <u>Claim 21</u>

a. [21.a] *The device of claim 16, wherein a combination of a respective one of the stimulation periods and a respective one of the non-stimulation periods comprises a stimulation cycle.*

213. Durand and Hoegh render obvious claim 16, as discussed above in IX.B.15 (Ground 1, claim 16). Durand further discloses the limitations of this claim element, as Durand discloses intermittent electrical stimulation [*stimulation cycle*] in which electrical stimulation is repeatedly applied [*stimulation period*] after wait periods [*non-stimulation period*] according to a duty cycle.

> More particularly, a method provided in accordance with the invention includes controlling the patency of a patient's airway by stimulating a nerve using at least one of the following techniques:… (c) ***intermittently electrically stimulating a nerve at controlled intervals, predetermined based on the patient's resting nighttime metabolism, which can be determined from the patient's observed respiratory rate***, for example.

EX-1006 (Durand) ¶ 13.

> In a third embodiment of the method, the controller can be programmed to provide stimulation at a predetermined interval without either detecting a physical process or requiring feedback from the nerve being stimulated…For example, ***a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains***.

EX-1006 (Durand) ¶ 25.

214. A POSITA understood the foregoing disclosures from Durand as disclosing a stimulation cycle that includes a stimulation period and a non-stimulation period as claimed. Accordingly, Durand discloses claim element [21.a].

b. [21.b] *wherein the first stimulation therapy protocol is to deliver more than one stimulation cycle within a duration of the reference respiratory cycle.*

215. Durand and Hoegh disclose this claim element for reasons similar to those discussed above in IX.B.15.f (Ground 1, claim element [16.d]). For example, both Durand and Hoegh disclose a reference respiratory cycle as having a duration of five seconds.

> The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. For

> example, ***a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between pulse trains***.

EX-1006 (Durand) ¶ 25.

> ***Asynchronous mode (fixed mode) is when stimulation is delivered at regular programmable intervals (e.g., 2.5 seconds of stimulation, followed by 2.5 seconds off)***. The intervals may be set to a rate similar to a respiratory cycle, (e.g. 5 seconds).

EX-1007 (Hoegh) ¶ 114.

216. Hoegh further discloses that inspiration is typically about 25-50% of a respiratory cycle and that the duty cycle may be varied to meet efficacy and safety requirements.

> In people without OSA, inspiration is typically 25-50% of the respiratory cycle, with variations in respiration being common.

EX-1007 (Hoegh) ¶ 92.

> The stimulation duty cycle may vary to meet efficacy and safety requirements.

EX-1007 (Hoegh) ¶ 96.

217. Given the foregoing teachings, one of ordinary skill in the art would have understood the combination of Durand and Hoegh as disclosing that multiple stimulation periods could be provided within a duration of a reference respiratory cycle. Specifically, 25 percent of a five second reference respiratory cycle corresponds to a stimulation period of 1.25 seconds. A POSITA understood that the goal was to stimulate the hypoglossal nerve at least during the inspiratory phase of a patient's respiratory cycle and thus would provide stimulus for at least 1.55 seconds (i.e., 1.25 seconds corresponding to the inspiratory phase plus the 300 ms to mimic the patient's natural physiology). EX-1007 (Hoegh) ¶ 92 ("The hypoglossal nerve usually activates approximately 300 ms before inspiration and remains active for the entire inspiratory phase.").

218. To avoid fatigue, a wait period would be provided; however, a POSITA understood that the tongue is a hydrostat and is less susceptible to fatigue than other muscles such that shorter wait periods may be provided. *See* V.C (Technical Background, Duty Cycles). As such, a wait period [*non-stimulation period*] that was 31% of the duration of the stimulation cycle would yield a wait period of approximately 0.7 seconds to achieve a 69% duty cycle as expressly taught by Hoegh. EX-1007 (Hoegh) ¶ 98 ("In fixed mode,

the maximum ***stimulation duty cycle may be set*** from 41% to ***69%*** in 3% increments, and the default setting may be 50%."). Indeed, the prior art expressly discloses stimulation periods and non-stimulation periods as short as one second. EX-1008 (Headley) ¶ 48 ("On periods may range, without limitations from 1 to 120 seconds, and off periods similarly.").

219. A stimulation period of 1.55 seconds and a 0.7 second wait period [*non-stimulation period*] would correspond to stimulation cycle having 2.25 seconds in duration such that multiple (i.e., two) stimulation periods would be provided within a duration of a five-second reference respiratory cycle.

220. Moreover, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and stimulation cycle duration, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. The '526 Patent does not identify any unexpected results resulting from delivering multiple stimulation periods within a duration of a reference respiratory cycle. As such, not only do Durand and Hoegh disclose the limitations of claim element [21.b], but the claim element itself recites nothing more than routine optimization (i.e., a stimulation period and

stimulation cycle duration that provides the desired outcome of increasing airway patency while sleeping).

221. Accordingly, delivering multiple (i.e., more than one) stimulation cycles within a duration of a reference respiratory cycle required nothing more than the exercise of routine skill, i.e., optimizing a stimulation period and stimulation cycle duration, which a POSITA would have been motivated to provide to increase the efficacy while maintaining the safety. EX-1007 (Hoegh) ¶ 96.

222. Thus, claim element [21.b] is obvious from Durand and Hoegh. Consequently, claim 21 is obvious from Durand and Hoegh.

19. Claim 22

a. [22.pre] *A device for treating obstructive sleep apnea, comprising:*

223. To the extent the preamble is limiting, Durand discloses a device for treating OSA for the same reasons discussed above in IX.B.1.a (Ground 1, claim element [1.pre]), as the two limitations are identical. Accordingly, Durand discloses claim element [22.pre] to the extent it is limiting.

b. [22.a1] ***a non-cardiac means for stimulating an upper airway patency-related nerve,***

224. Durand discloses this claim element for the same reasons discussed above in IX.B.1.b (Ground 1, claim element [1.a1]), as the two limitations are identical. Accordingly, Durand discloses claim element [22.a1].

c. [22.a2] ***according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to a patient breathing,***

225. Durand discloses this claim element for the same reasons discussed above in IX.B.1.c (Ground 1, claim element [1.a2]), as the two limitations are identical. Accordingly, Durand discloses claim element [22.a2].

d. [22.b] ***wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and***

226. Durand discloses this claim element, either alone or in combination with Hoegh, for the same reasons discussed above in IX.B.1.d (Ground 1, claim element [1.b]), as the two limitations are identical. Accordingly, Durand discloses claim element [22.b], either alone or in combination with Hoegh.

e. [22.c] ***wherein the combined duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods is greater than a duration of a reference respiratory cycle,***

227. Hoegh expressly discloses that the regular programmable intervals of stimulation [*respective one of the stimulation periods*]/no stimulation [*respective one of the stimulation periods*] can be provided in durations longer than a respiratory cycle [*reference respiratory cycle*], such as in a duration of eight seconds.

> Asynchronous mode (fixed mode) is when stimulation is delivered at regular programmable intervals (e.g., 2.5 seconds of stimulation, followed by 2.5 seconds off). The intervals may be set to a rate similar to a respiratory cycle, (e.g. 5 seconds). Alternatively, ***longer intervals (e.g. 8 seconds)*** may decrease the probability of missing two consecutive inspirations, and increase the probability of providing the patient with stimulation during an entire respiratory cycle.

EX-1007 (Hoegh) ¶ 114.

228. Thus, Hoegh expressly discloses a combined duration (i.e., eight seconds) of a respective one of the stimulation periods and of a respective one of the non-stimulation periods that is greater than a five-second reference respiratory cycle. Accordingly, Hoegh discloses the limitations of claim element [22.c].

f. **[22.d]** ***wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.***

229. Durand discloses this claim element for the same reasons discussed above in IX.B.1.f (Ground 1, claim element [1.d]), as the two limitations are identical. Accordingly, Durand discloses claim element [22.d].

230. In view of the foregoing, claim 22 is obvious from Durand and Hoegh.

20. <u>Claim 23</u>

a. **[23]** ***The device of claim 22, wherein the duration of a respective one of the stimulation periods is greater than the duration of the reference respiratory cycle.***

231. Durand and Hoegh render obvious claim 22, as discussed above in IX.B.19 (Ground 1, claim 22). Hoegh further discloses the limitations of claim 23. For example, as discussed above in IX.B.19.e (Ground 1, claim element [22.c], Hoegh discloses a stimulation cycle having a duration (referred to below as an "interval") of five seconds, when based on a patient's respiratory rate, and up to eight seconds to decrease the probability of missing two consecutive inspirations.

> The intervals may be set to a rate similar to ***a respiratory cycle (e.g. 5 seconds)***. Alternatively, ***longer intervals (e.g. 8 seconds)*** may decrease the probability of missing two consecutive

> inspirations, and increase the probability of providing the patient with stimulation during an entire respiratory cycle.

EX-1007 (Hoegh) ¶ 114.

232. Hoegh further discloses duty cycles of up to 69 percent.

> The following stimulation duty cycle parameters are given by way of example, not limitation. In fixed mode, the maximum stimulation duty cycle may be set from 41% to 69% in 3% increments, and the default setting may be 50%.

EX-1007 (Hoegh) ¶ 98.

233. A 69 percent duty cycle of an eight second stimulation cycle corresponds to a duration of a stimulation period of more than five seconds, which is more than a five-second respiratory rate as also disclosed by Hoegh.

8 Second Stimulation Cycle Duration; 69% Duty Cycle

$$8 \times .69 = 5.52$$

234. Moreover, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and stimulation cycle duration, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA

treatment device. The ’526 Patent does not identify any unexpected results resulting from a duration of the respective one of the stimulation periods being greater than the duration of the reference respiratory cycle. As such, not only do Durand and Hoegh disclose the limitations of claim [23], but the claim itself recites nothing more than routine optimization (i.e., a stimulation period and stimulation cycle duration that provides the desired outcome of increasing airway patency while sleeping).

235. Accordingly, Durand and Hoegh disclose the limitations of claim 23.

X. GROUND 2: CHALLENGED CLAIMS ARE OBVIOUS FROM HEADLEY IN VIEW OF TRAN

A. Reasons to Combine Headley and Tran

236. As detailed above in VII.C.2 (Summary of Headley’s Disclosure), Headley discloses an implantable device that is used to asynchronously stimulate the genioglossus (GG), which is in close proximity to the HGN, to treat OSA. Specifically, Headley discloses providing the stimulation in the form of alternating on/off treatment in which the tissue is stimulated for a given period then allowed to rest for a given period before being stimulated again. EX-1008 (Headley) ¶ 48 (“In use, the device as described herein and/or the method as described herein provides for alternating on/off ‘intermittent’

treatment wherein the tissue is stimulated for a given period, and then the tissue is allowed to rest for a given period."). Headley states that the intermittent treatment periods and parameters may be adjusted based on patient-specific characteristics, such as, the "patient's physical condition" or "quality of sleep," but does not elaborate on these characteristics and parameters. EX-1008 (Headley) ¶¶ 10, 13.

237. Headley concludes by citing and incorporating by reference a number of references that "relate to teaching the level of ordinary skill in this art and for any disclosure necessary for the commoner understanding of the subject matter of the claimed invention." EX-1008 (Headley) ¶¶ 50-62. Thus, a POSITA would have been motivated to look at these and other references (e.g., Tran) to obtain a greater understanding of Headley's disclosure and the relevant state of the art given Headley's express instructions to do so.

238. Tran discloses a device that had been actually reduced to practice, i.e., a BIONTM, for treating OSA that operates like the device disclosed by Headley in that the device may be implanted in the tongue in close proximity to where the hypoglossal nerve branches to the GG enter the tongue. EX-1009 (Tran-I) p. 376 ("The hypoglossal nerve branches to the GG muscle enter the tongue inferolaterally to innervate muscles that are oriented transversely,

longitudinally and radially in parasagittal fans.”). The device recruits the motor units stimulated by the hypoglossal nerve to produce symmetrical protrusion of the tongue thereby opening the airway. EX-1009 (Tran-I) p. 376 (“This suggests that a single site of stimulation located in the midline (near these endplates as illustrated in Fig. 3) would recruit selectively those motor units that will produce symmetrical protrusion of the tongue, thereby opening the airway.”). Brief trains of stimulation pulses are applied “at intervals close to the respiratory cycle of the patient” to synchronize the patient “spontaneously with the resulting intermittent periods of patency in the airway.” EX-1009 (Tran-I) p. 377.

239. While Headley provides a high-level disclosure of the stimulation device and parameters, Tran discloses an actual device that operates similar to the one disclosed by Headley along with clinical results, including stimulation parameters. For example, Tran discloses the duration of stimulation relative to the patient’s respiratory rate, including the duration of the stimulation relative to the duration of the inspiratory phase. EX-1009 (Tran-I), p. 377; EX-1010 (Tran-II), p. 4288. Further, Tran teaches the use of historical patient-specific averages to estimate the patient’s respiratory rate. EX-1009 (Tran-I), p. 377. A POSITA would have been motivated to combine the

teachings of Headley to provide a stimulation device that could be programmed with the stimulation parameters disclosed by Tran for treating OSA that provides stimulation based on the patient's respiratory rate to have the patient spontaneously synchronize with the intermittent periods of patency in the airway. Advantageously, the combination of the references would provide a device that obviates the need for a sensor to synchronize stimulation with breathing while effectively improving airway patency. EX-1010 (Tran-II), p. 4288 ("This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sensor to synchronize stimulation with breathing."). The construct of the BION™ disclosed by Tran was "low-risk, reliable and cost-effective" (EX-1009 (Tran-I), p. 375) and had been implanted adjacent to various nerves, including the HGN.

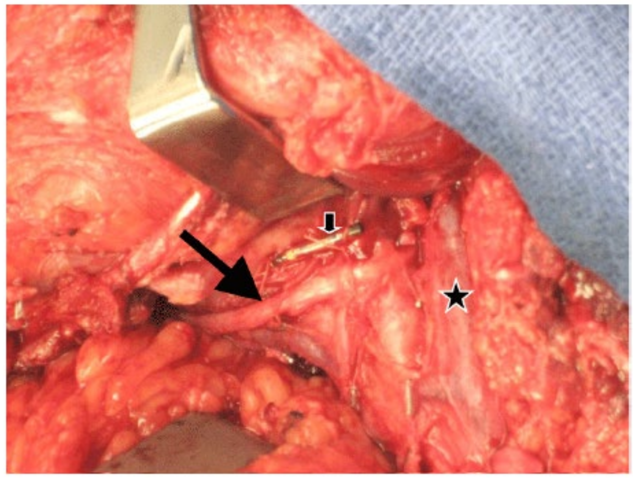


Figure 3: MS (small arrow) is placed above the left hypoglossal nerve (large arrow) during left modified radical neck dissection. Star indicates the origin of ansa cervicalis nerve.

EX-1039 (Sinha), p. 3.

240. A POSITA would have been motivated to combine the teachings of Headley and Tran to provide an improved method to prevent development of OSA, and would have had a reasonable expectation of success in doing so for several reasons.

241. *First*, both references disclose treatment methods for OSA using implantable electrodes that are externally powered to stimulate the tongue, which is in close proximity to the HGN, asynchronously (i.e., without actively sensing the patient's respiration in order to synchronize the stimulation to the patient's respiration).

> This present invention is generally directed toward the implantation of a medical device for treating patients with a specific physiologic dysfunction and in particular, treating patients with obstructive sleep apnea.

EX-1008 (Headley) ¶ 1.

> In use, the device as described herein and/or the method as described herein provides for alternating on/off "intermittent" treatment wherein the tissue is stimulated for a given period, and then the tissue is allowed to rest for a given period.

EX-1008 (Headley) ¶ 48.

242. Like Headley, Tran discloses treatment methods involving "intermittent electrical stimulation" applied to the tongue in "a brief train of electrical pulses during an ON period followed by no stimulation during an OFF period." EX-1010 (Tran-II), p. 4287.

> Each BION receives power and digital command data via an RF transmission coil to produce stimulation pulses with controlled current (0-30mA) and duration 4-512 μs).

EX-1009 (Tran-I), p. 375.

> We hypothesized that if brief trains of stimulation pulses were applied to the GG at intervals close to the respiratory cycle of the

> patient, the patient would tend to synchronize spontaneously with the resulting intermittent periods of patency in the airway.

EX-1009 (Tran-I), p. 377.

243. *Second*, both references disclose similar implantation locations (i.e., within the tongue near the hypoglossal nerve to stimulate the hypoglossal nerve and genioglossus):

FIG. 1

EX-1008 (Headley), FIG. 1 (annotated).

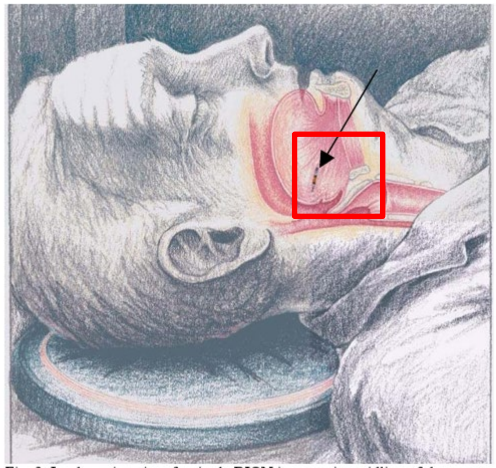


Fig. 3. Implantation site of a single BION in posterior midline of the genioglossus muscle with tantalum electrode (effective cathode) near the endplates (toward the tongue base).

EX-1009 (Tran-I), FIG. 3 (annotated).

244. *Third*, the modifications to Headley based on the teachings of Tran were well within the routine skill in the art. Specifically, because both references disclose using implantable electrodes to stimulate the tongue asynchronously in substantially the same way, a POSITA would have recognized that modifying Headley's asynchronous stimulation cycle to approximate the patient's respiratory cycle, as taught by Tran, would require only simple software modifications and routine modifications to Headley's intermittent on/off electrical stimulation periods and parameters. As discussed above in V.B (Technical Background, OSA Treatment), titration involved the adjustment of one or more stimulation parameters (e.g., duty cycle, cycle duration, pulse width, amplitude, etc.) and was routinely performed after the

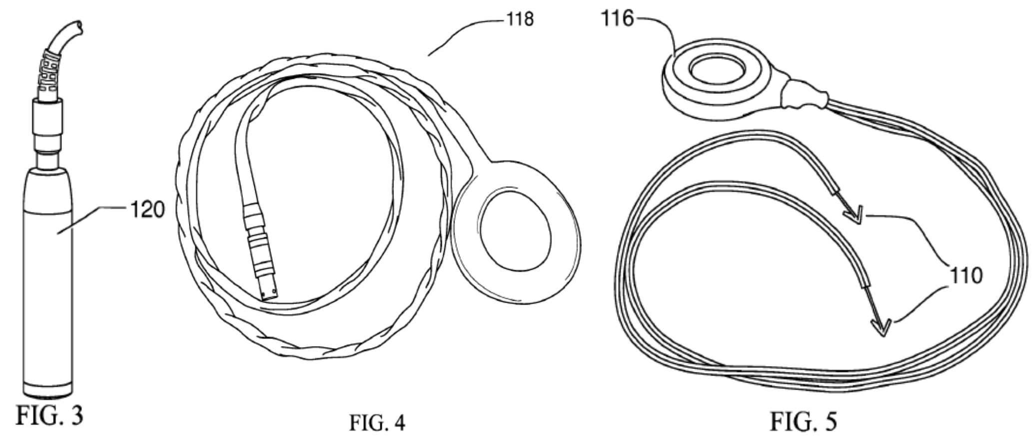
patient healed from the implantation procedure and was about to use the device therapeutically. A POSITA would have had a reasonable expectation of success in combining Headley's and Tran's teachings, such as basing the stimulation cycle duration on the patient's respiratory rate, because both references disclose applying methods (asynchronous stimulation) using devices (implantable electrodes) to achieve results (preventing development of OSA) that were known in the art before the priority date of the '526 Patent, such that their teachings would have been readily applied to the other using only routine skill.

B. Application of Headley and Tran to the Challenged Claims

1. Claim 1

a. [1.pre] *A device for treating obstructive sleep apnea, comprising:*

245. To the extent the preamble is limiting, Headley discloses a device for treating obstructive sleep apnea. For example, Headley expressly discloses "***[a] device*** and method is described ***for the treatment of obstructive sleep apnea***." EX-1008 (Headley), Abstract. The device includes a power source 120 (FIG. 3), an antenna 118 (FIG. 4), a receiver 116, and a stimulating electrode 110 (FIG. 5). EX-1008 (Headley) ¶ 29.



EX-1008 (Headley), FIGS. 3-5.

246. Thus, Headley discloses the limitations of claim element [1.pre].

247. Although not believed necessary to demonstrate that prior art of Ground 2 discloses the limitations of [1.pre] given the foregoing disclosures of Headley, I note that Tran also discloses a device as claimed. Specifically, as discussed above, Tran discloses a device, i.e., a BION™, that had been actually reduced to practice and implanted adjacent to the HGN. VII.D.2 (Summary of Tran's Disclosure); EX-1039 (Sinha); EX-1040 (Kaplan). Thus, to the extent Patent Owner were to argue Headley does not disclose the limitations of the preamble, Tran does and a POSITA would have combined the references for the reasons disclosed in X.A (Reasons to Combine Headley and Tran).

248. Accordingly, Tran also discloses a device for treating OSA to the extent the preamble is limiting.

b. [1.a1] *a non-cardiac stimulation means for stimulating an upper-airway-patency-related nerve;*

249. Headley, either alone or in combination with Tran, discloses claim element [1.a1]. Headley discloses a receiver 116 and a stimulating electrode 110 that are inserted into the genioglossal muscle of the tongue to apply electrical stimulation [*non-cardiac stimulation means*] to stimulate the genioglossus muscle.

> In one embodiment, there is provided a method of treating obstructive sleep apnea in a patient comprising the steps of: ***applying direct intramuscular electrical stimulation to a specific set of muscle fibers in a muscle of the patient's airway***, wherein the electrical stimulation is provided by ***an implanted electrode assembly, wherein the electrode assembly comprises one or more electrodes connected to an implanted receiver***….

EX-1008 (Headley) ¶ 8.

> Referring now to the figures, FIG. 1 shows a cross section of the upper airway in particular the tongue (genioglossus muscle) 20. FIG. 1 also shows the locations, L1 and L2, of the specific placements for the electrodes 110.

EX-1008 (Headley) ¶ 28.

FIG. 1

EX-1008 (Headley), FIG. 1.

250. A POSITA understood that by inserting the electrodes into the genioglossus, the electrodes would not be providing cardiac stimulation given that the applied stimulation to the tongue would not stimulate the heart. *See*, *e.g.*, EX-1014 (Anagnostopoulos) (distinguishing between cardiac pacemakers (pp. -480-486) and other types of neurostimulators (pp. 486-490), i.e., non-cardiac neurostimulators); EX-1015 (Glenn) (same); EX-1016 (Judson) (same). As such, a POSITA understood the receiver 116 and electrodes 110 implanted within the tongue/genioglossus as providing non-cardiac stimulation. EX-

1008 (Headley) ¶ 28, FIG. 1; EX-1014 (Anagnostopoulos); EX-1015 (Glenn); EX-1016 (Judson).

251. Further, a POSITA understood that the genioglossus is innervated by (i.e., supplied by) the hypoglossal nerve (also known as cranial nerve XII or CN-XII) thus forming a neuromuscular system. EX-1023 (Fuller), pp. 601-603; EX-1033 (Zaidi) p. 379; V.A-V.B. The motor axons control the muscle activity of the genioglossus muscle. EX-1023 (Fuller), pp. 601-603; EX-1033 (Zaidi) p. 379; V.A-V.B. A POSITA further understood that electrical stimulation applied by the electrode implanted into the genioglossus muscle would conduct to and be applied to the same motor axons passing through the hypoglossal nerve and result in movement of the genioglossus muscle. EX-1033 (Zaidi) pp. 379 ("The human HGN, or XII cranial nerve, is the primary motor nerve that innervates seven of the eight muscles of the hemi-tongue."), 382; V.A-V.B.

252. The foregoing understanding is consistent with the disclosure of the '526 Patent, which discloses that a nerve-coupling electrode simply may be electrically coupled to (i.e., placed in "close proximity to") the hypoglossal nerve:

> In some examples, the electrode portion 82 comprises a cuff, such as one of the stimulation electrode portions 45 described in association with FIG. 2A in which the electrode portion is both mechanically and electrically coupled relative to the nerve 72. However, in some examples, the nerve-coupling electrode portion 82 comprises a cuff-less structure that is both mechanically and electrically coupled relative to the nerve 72.
>
> In some examples, ***the nerve-coupling electrode portion 82 is not mechanically coupled to the nerve 72, but is mechanically coupled or secured in a location in close proximity to the nerve 72 and that enables electrically coupling of the electrode portion 82 relative to the nerve 72. In one instance, such examples include the electrode portion 82 being delivered to the target nerve 72 via a percutaneous access delivery***. In one instance, such examples include the electrode portion 82 being delivered to the target nerve 72 via a transvenous delivery method in which the electrode portion 82 is delivered on a lead maneuvered within and through the vasculature of the patient.

EX-1001 11:60-12:12.

253. A POSITA understood from the foregoing disclosure that the intramuscular stimulation disclosed by Headley would activate motor axons. EX-1033 (Zaidi) pp. 379, 382; V.A-V.B. The activation of the motor axons would then

synaptically activate muscle fibers – the muscle fibers themselves would not be directly excited by the electrical stimulus. EX-1033 (Zaidi) pp. 379, 382; V.A-V.B.

254. Moreover, Headley expressly incorporates by reference several papers, including papers by Brennick (EX-1042) and Yoo (EX-1028) that expressly reference hypoglossal nerve stimulation in their titles and several others (e.g., Bailey (EX-1041)) that describe the neuromuscular relationship between the genioglossus muscle and hypoglossal nerve. EX-1008 (Headley) ¶¶ 50-62 (citing EX-1014 (Anagnostopoulos), EX-1041 (Bailey), EX-1042 (Brennick), EX-1021 (Decker), EX-1019 (Edmonds), EX-1023 (Fuller), EX-1016 (Judson), EX-1020 (Miki), EX-1043 (Oliven2003), EX-1044 (Oliven2007), EX-1025 (Schwartz1996), EX-1028 (Yoo)). As such, a POSITA understood that implanting the electrodes 110 into the genioglossus the electrodes would be placed in close proximity to the hypoglossal nerve, as disclosed in the ’526 Patent. A POSITA further understood that applying electrical stimulation at the site identified in FIG. 1 and as described in paragraphs 8 and 28-30 of Headley results in stimulation of the hypoglossal nerve to achieve the desired result of maintaining upper airway patency to treat OSA.

> In one embodiment, there is provided a method for treating obstructive sleep apnea in a patient comprising the steps of: applying direct intramuscular electrical stimulation to a specific set of muscle fibers in a muscle of the patient's airway, wherein the electrical stimulation is provided by an implanted electrode assembly, wherein the electrode assembly, wherein the electrode assembly comprises one or more electrodes connected to an implanted receiver, and wherein the implanted electrode assembly is in operative associated with an external electromagnetic frequency transmitting antenna located on or near a patient's body, such that said electrical stimulation is provided when the antenna transmits an electromagnetic frequency to the implanted electrode, wherein upon receiving the frequency the implanted electrode assembly generates an electrical current in the one or more electrodes, and wherein the electrical current is delivered directly by wire to specific set of muscle fibers.

EX-1008 (Headley) ¶ 8.

> The receiver includes an electrical pulse source, or pulse generator. The electrodes impart electrical pulses, generated by the pulse generator, directly by wire to the genioglossus muscle to stimulate the specific fibers to a point where the patient's tongue is moved anteriorly to maintain upper airway patency.

EX-1008 (Headley) ¶ 30.

255. The foregoing is reinforced when Headley is combined with Tran, which expressly discloses neuromuscular stimulation of the genioglossus muscle and hypoglossal nerve:

> Bipolar hooked wires are inserted percutaneously into the tongue muscle, from under the chin at midline, and ***used for neuromuscular stimulation***.

EX-1010 (Tran-II), p. 4287.

> Bipolar wire electrodes were strategically placed ***at the optimal stimulation site in the genioglossus [citing Tran-I]***.

EX-1010 (Tran-II), p. 4288.

> ***The hypoglossal nerve branches to the [genioglossus] muscle enter the tongue inferolaterally to innervate muscle fibers that are oriented transversely, longitudinally and radially in parasagittal fans***. The posteriorally directed portion of the parasagittal fan originates from the mandible and produces protrusion. Endplate bands innervate the midpoints of these fibers and extend to the midline [12]. Sanders et al using Sihler's stain have shown ***motor endplates near the tongue base are innervated by a separate hypoglossal nerve branch (human***

genioglossus illustrated in Fig. 2). This suggests that a single site of stimulation located in the midline (near these endplates as illustrated in Fig. 3) would recruit selectively these motor units that will produce symmetrical protrusion of the tongue, thereby opening the airway.

EX-1009 (Tran-I), p. 376.

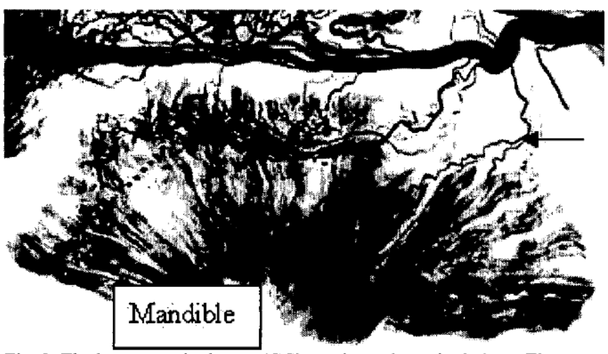


Fig. 2. The human genioglossus (GG), as shown in sagittal view. The single motor endplate band (red dotted line). A separate nerve branch innervates the motor endplates near the tongue base (arrow). Photo courtesy of Dr. Ira Sanders.

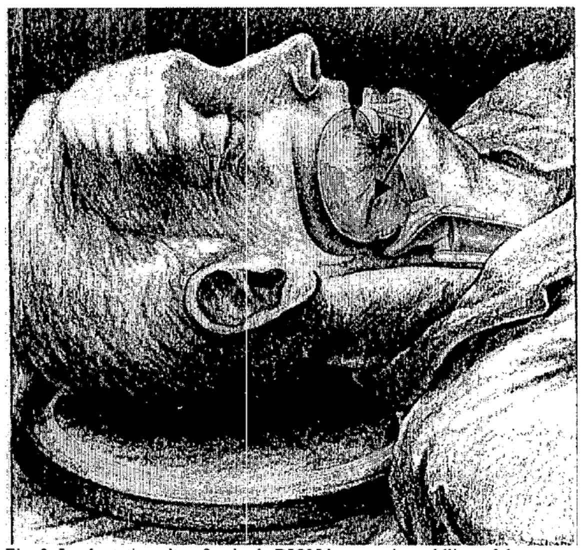


Fig. 3. Implantation site of a single BION in posterior midline of the genioglossus muscle with tantalum electrode (effective cathode) near the endplates (toward the tongue base).

EX-1009 (Tran-I), FIGS. 2-3.

256. Further, a POSITA understood that the BION™ device disclosed by Tran could be implanted within a patient at a variety of locations, including adjacent or directly attached to nerves. In fact, the BION had been implanted in a clinical setting adjacent to the HGN and other nerves prior to March 19, 2015, as shown below.

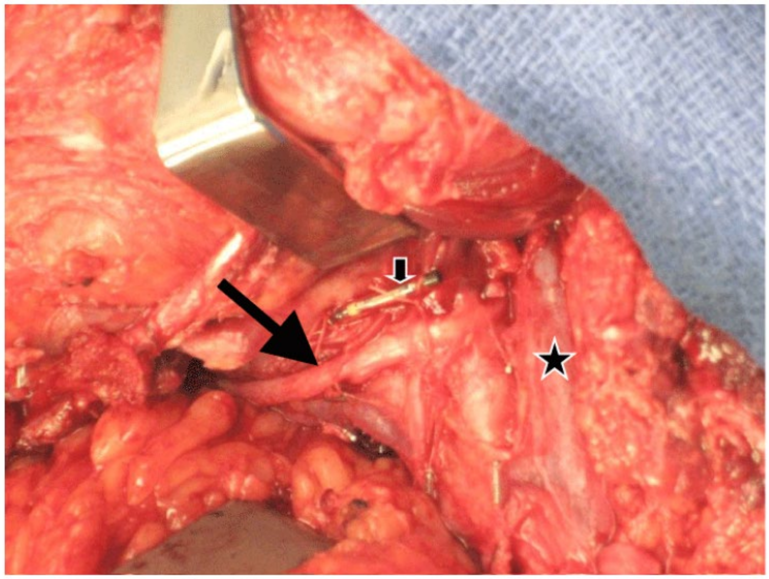


Figure 3: MS (small arrow) is placed above the left hypoglossal nerve (large arrow) during left modified radical neck dissection. Star indicates the origin of ansa cervicalis nerve.

EX-1039 (Sinha), p. 3.

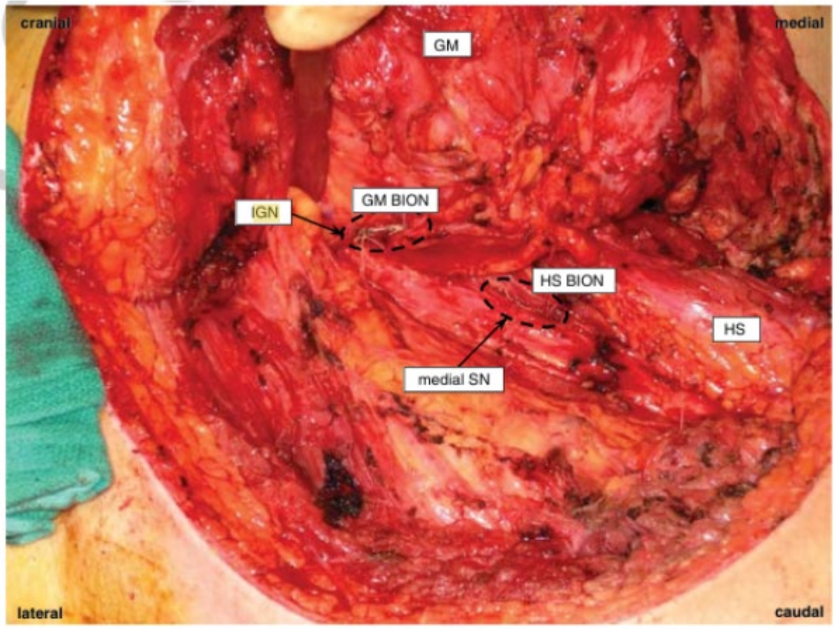


Fig. 2. Intraoperative BION placement.

EX-1040 (Kaplan), p. 348 (describing the implantation of the BIONs adjacent to the inferior gluteal nerve ("IGN") and sciatic nerve ("SN") for stimulating these nerves).

257. Thus, to the extent Headley does not expressly disclose stimulating an upper-airway-patency-related nerve, such as the hypoglossal nerve, Tran does. Further, moving the BION^{TM} to another location, such as adjacent or attached to the HGN, would have been obvious to a POSITA, as it was known to implant the BION^{TM} in such locations to achieve the desired result of stimulating one or more muscles by stimulating one or more nerves. EX-1039 (Sinha), p. 3; EX-1040 (Kaplan), p. 348.

258. Accordingly, Headley discloses element [1.a1], either alone or in combination with Tran.

c. [1.a2] *according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulating periods in which a timing of the stimulation periods is asynchronous relative to patient breathing,*

259. Headley discloses that the receiver 116 and a stimulating electrode 110 [*non-cardiac stimulation means*] provides stimulation using an alternating on/off "intermittent" treatment [*first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods*].

> In use, the device as described herein and/or the method as described herein provides for alternating on/off "intermittent" ***treatment wherein the tissue is stimulated for a given period, and then the tissue is allowed to rest for a given period***.

EX-1008 (Headley) ¶¶ 10, 48.

260. Although Headley discloses the use of ***optional*** sensors, such as sound-activation means and/or oxygen-sensing means, these sensors are not actively sensing respiration for purposes of synchronizing the stimulation to the patient's respiration [*a timing of the stimulation periods is asynchronous*

relative to patient breathing]. EX-1008 (Headley) ¶ 14. Instead, these sensors are detecting when a patient snores or the patient's oxygen level.

> In another preferred embodiment, the medical device further comprises alternatively sound-activation-means for allowing the power unit to turn on when the sound of snoring is received from the patient thus allowing the device to be utilized only during times when the patient may actually experience the apneic episodes, and/or oxygen-sensing means and auto-start means for having the device turn on when the patient's oxygen concentration as measured by a transcutaneous receiver placed on the antenna over the patient's skin would detect an oxygen concentration of less than 96%.

EX-1008 (Headley) ¶ 14.

261. Further, these ***optional*** sensors are not used for purposes of synchronizing the first stimulation therapy protocol to the patient's respiratory cycle, but instead are used to initiate the first stimulation therapy protocol after sensing that the patient is first experiencing an apneic episode. EX-1008 (Headley) ¶ 14. Put another way, the at least one sensor disclosed by Headley is used to trigger therapy – not for synchronizing the therapy to the patient's respiratory cycle.

262. Accordingly, Headley discloses the limitations of claim element [1.a2].

263. Although not needed to demonstrate that the prior art references of Ground 2 disclose the limitations of claim element [1.a2], I note that Tran also discloses these limitations in a manner that is consistent with the Teachings of Headley. Specifically, Tran discloses the use of "repetitive intermittent electrical stimulation" in which the "stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant" to "recover and prevent or maintain airway patency" [*timing of the stimulation periods is asynchronous relative to patient breathing*]. EX-1010 (Tran-II), p. 4288. Tran expressly states that the repetitive intermittent electrical stimulation [*first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods*] is applied "without synchronizing with breathing." EX-1010 (Tran-II), p. 4289. Thus, the teachings of Headley could be combined with those of Tran, if needed, and the resultant device would provide the stimulation according to a first stimulation therapy protocol asynchronously relative to patient breathing.

d. [1.b] ***wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period,***

264. Headley discloses this claim element. Specifically, Headley discloses an alternating on/off "intermittent" treatment [*first stimulation therapy protocol*]

that includes a period of stimulation [*stimulation period*] and a rest period in which the stimulation is turned off [*non-stimulation period*].

> In use, the device as described herein and/or the method as described herein provides for alternating on/off "intermittent" ***treatment wherein the tissue is stimulated for a given period, and then the tissue is allowed to rest for a given period***.

EX-1008 (Headley ¶ 48).

265. Headley further discloses that the periods of stimulation [*duration of each respective stimulation period*] is greater than a duration of the rest periods [*duration of each respective non-stimulation period*].

> In one preferred embodiment, the device or method ***applies stimulation*** for 5 seconds, and then stimulation is turned off for 5 seconds. In another preferred embodiment, the ***period of stimulation*** ranges from 1 to 20 seconds, with ***varying rest periods***. In another preferred embodiment, the ***period of stimulation is 20 seconds and the rest period is 5 seconds***. In yet another preferred embodiment, the period is 60 seconds on with 60 seconds off. On periods may range, without limitations from 1 to 120 seconds, and off periods similarly. On/off intermittent periods include from 5/5, ***20/5***, 10/10, 5/60, ***60/5***, 20/20, 30/30, 40/40, 50/50, 60/60, and so forth.

EX-1008 (Headley) ¶ 48.

266. As discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. I further note that the '526 Patent does not identify any unexpected results resulting from providing each respective stimulation period with a duration that is greater than a duration of each respective non-stimulation period. As such, not only do Headley and Tran disclose the limitations of claim element [1.b], but the claim itself recites nothing more than routine optimization (i.e., a duty cycle that provides the desired outcome of increasing airway patency while sleeping).

267. Accordingly, a POSITA understood Headley as disclosing the limitations of claim element [1.b].

268. Although not needed to demonstrate that the prior art references of Ground 2 disclose the limitations of claim element [1.b], I note that Tran also discloses these limitations in a manner that is consistent with the teachings of Headley. Specifically, Tran discloses repetitive intermittent electrical stimulation that

includes an ON period [*stimulation period*] and an OFF period [*non-stimulation period*].

> We hypothesized that electrical stimulation does not have to synchronize with inspiration to prevent OSA [4,5]. Instead, repetitive intermittent electrical stimulation could be used to recover or maintain airway patency. In this method, we applied a brief train of electrical pulses during an ***ON period*** followed by ***no stimulation during an OFF period***. ***This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant***, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010 (Tran-II), p. 4288.

e. [1.c] *wherein the duration of each respective stimulation period is based on a reference respiratory-related parameter,*

269. Headley in view of Tran discloses this claim element. Specifically, Tran expressly discloses a respiratory rate of 5 seconds [*reference respiration-related parameter*] for a sleeping patient based on studying a patient while sleeping.

> Two patients with documented severe OSA (>40 episodes/hr) were studied overnight. ***Baseline information such as***

> ***respiratory rate*** and level of oxygen saturation ***was acquired during the first hour of sleep***. Various duty cycles of gating of CPAP (30-50%) were studied at random during the night. For example, a 40% duty cycle ***in a 5 second respiration period*** means CPAP is applied for 3 sec and gated off for 2 sec.

EX-1009 (Tran-I), p. 377.

270. Tran further discloses providing the electrical stimulation [*respective stimulation period*] based on the observed respiratory rate [*reference respiration-related parameter*] of the patient.

> In this method, we applied a brief train of electrical pulses during an ON period followed by no stimulation during an OFF period. This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010 (Tran-II), p. 4288.

271. FIG. 4 of Tran-II is a screen capture of a polysomnogram of a patient, which shows the patient's inspiratory phase to be approximately 2 seconds and the stimulation markers indicating an ON period [*stimulation period*] of approximately 2.5 seconds.

Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010 (Tran-II), FIG. 4.

272. Thus, Tran discloses that the ON period [*stimulation period*] has a duration based on the inspiratory phase of the patient's respiratory cycle [*reference respiratory-related parameter*].

273. A POSITA would have been motivated to modify the teachings of Headley to provide the reference respiratory cycle using *a reference respiration-related parameter* as taught by Tran at least for the reasons discussed above in X.A (Reasons to Combine Headley and Tran).

274. Accordingly, Headley in view of Tran discloses claim element [1.c].

f. [1.d] *wherein the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.*

275. Headley discloses this claim element. Specifically, Headley discloses a stimulating electrode 110 [*implantable electrode*] emanating from [*electrically connectable to*] a receiver 116 [*implantable pulse generator*].

> The device itself consists of 4 parts. First is a power source 120 (Fig. 3). Second is an antenna 118 (Fig. 4). ***Third is a receiver 116 and fourth is the stimulating electrode 110 (Fig. 5)***. The power source provides the power for the device and is of small size so that it can be clipped to the upper nightwear of the patient being treated. This is connected to the antennae which deliver the radio frequency to the ***receiver which has been implanted in the neck of the patient with the stimulating electrodes emanating from the receiver*** and entering into specific muscle sites in the tongue of the patient.

EX-1008 (Headley) ¶ 29.

> The receiver includes an ***electrical pulse source, or pulse generator***. ***The electrodes impart electrical pulses, generated by the pulse generator***, directly by wire to the genioglossus muscle to simulate the specific muscle fibers to a point where the patient's tongue is moved anteriorly to maintain upper airway

> patency. ***The pulse generator has an output that provides electrical pulses*** having selectable properties of mode, polarity, amplitude, current, pulse width, and frequency.

EX-1008 (Headley) ¶ 30.

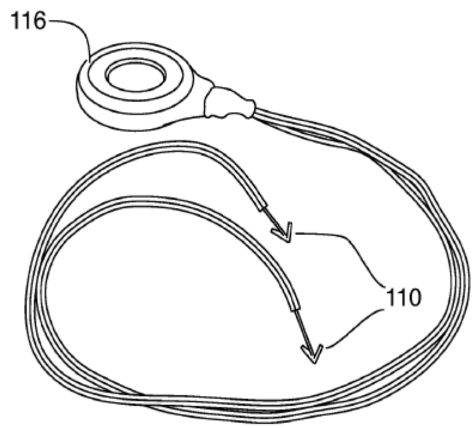


FIG. 5

EX-1008 (Headley), FIG. 5.

276. Thus, Headley expressly discloses claim limitation [1.d].

277. Although not needed to demonstrate that the prior art references of Ground 2 disclose the limitations of claim element [1.d], I note that Tran also discloses these limitations in a manner that is consistent with the teachings of Headley. Specifically, as discussed above in X.A (Reasons to Combine Headley and Tran), a POSITA understood that the BION™ had been actually reduced to practice and could be used to treat OSA. X.A (Reasons to Combine Headley and Tran); *see also* EX-1039 (Sinha); EX-1040 (Kaplan). The BION™ [*non-*

cardiac stimulation means] included an anodized sintered Ta electrode and an iridium electrode [*implantable electrode*] and circuitry (e.g., copper coil, Schottky diode, ASIC) [*implantable pulse generator*] electrically connected to the electrodes.

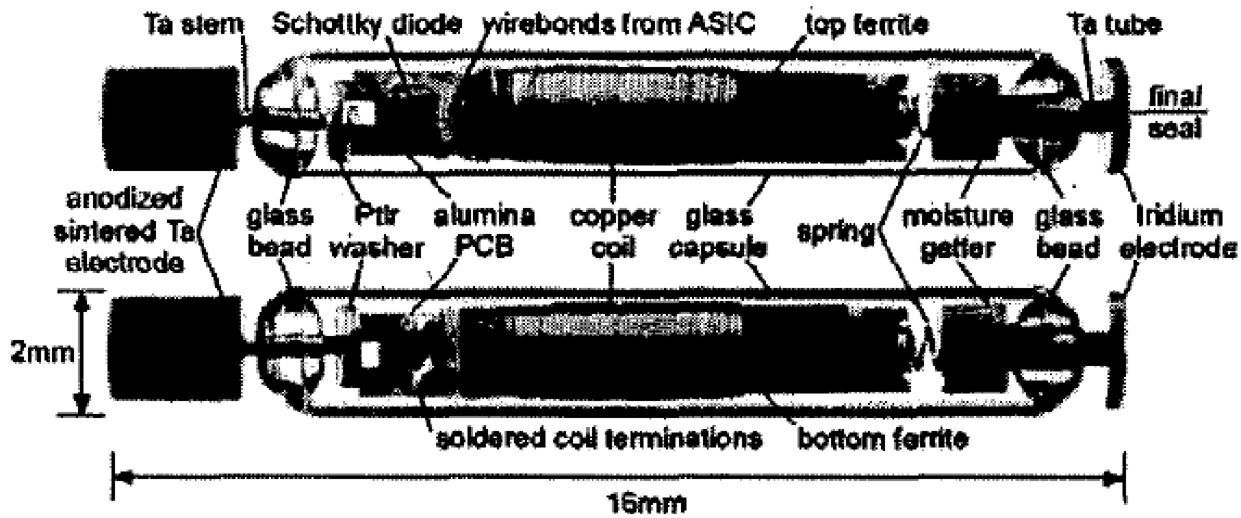


Fig. 1. The main components of BION implant.

EX-1009 (Tran-I), p. 375.

278. Accordingly, claim 1 is obvious from Headley in view of Tran.

2. Claim 2

a. [2] ***The device of claim 1, wherein the asynchronous timing of the stimulation relative to patient breathing comprises the timing being not based on actively-sensed respiration during application of the first stimulation therapy protocol.***

279. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley and Tran further disclose the limitations of claim 2. As discussed above in X.B.1.c (Ground 2, claim element [1.a2], Headley discloses the use of optional sensors, such as sound-activation means and/or oxygen-sensing means, but these sensors are not actively sensing respiration for purposes of synchronizing the electrical stimulation to the patient's breathing [*asynchronous timing of the stimulation relative to patient breathing comprising timing being not based on actively-sensed respiration during application of the first stimulation therapy protocol*]. Instead, these sensors are detecting when a patient snores or the patient's oxygen level.

> In another preferred embodiment, the medical device further comprises alternatively sound-activation-means for allowing the power unit to turn on when the sound of snoring is received from the patient thus allowing the device to be utilized only during times when the patient may actually experience the apneic episodes, and/or oxygen-sensing means and auto-start means for having the device turn on when the patient's oxygen

> concentration as measured by a transcutaneous receiver placed on the antenna over the patient's skin would detect an oxygen concentration of less than 96%.

EX-1008 (Headley) ¶ 14.

280. Accordingly, these ***optional*** sensors are not used for purposes of synchronizing the first stimulation therapy protocol to the patient's respiratory cycle, but instead are used to initiate the first stimulation therapy protocol after sensing that the patient is first experiencing an apneic episode. EX-1008 (Headley) ¶ 14. Put another way, the at least one sensor disclosed by Headley is used to trigger therapy – not for synchronizing the therapy to the patient's respiratory cycle.

281. Moreover, Tran discloses the use of "repetitive intermittent electrical stimulation" in which the "stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant" to "recover and prevent or maintain airway patency" [*asynchronous timing of the stimulation periods*]. EX-1010 (Tran-II), p. 4288. Notably, Tran expressly states that the repetitive intermittent electrical stimulation [*first stimulation therapy protocol*] is applied "without synchronizing with breathing." EX-1010 (Tran-II), p. 4289. Thus, when the teachings of Headley

are combined with those of Tran, the resultant device would provide the stimulation according to a first stimulation therapy protocol asynchronously relative to patient breathing, i.e., not based on actively-sensed respiration during application of the first stimulation therapy protocol.

282. Accordingly, claim 2 is obvious from Headley in view of Tran.

3. <u>Claim 3</u>

a. [3] ***The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory pattern.***

283. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley and Tran further disclose this claim element, as Tran discloses providing repetitive intermittent electrical stimulation based on the natural respiratory rhythm of the patient [*reference respiratory pattern*].

> Continuous stimulation of the GG to maintain airway patency might be expected to result in muscle fatigue. Stimulation could be administered only when the patient is in the inspiratory phase of respiration, but this would require the addition of a sensor. We hypothesized that if brief trains of stimulation pulses were applied to the GG at intervals close to the ***respiratory cycle of the patient***, the patient would tend to synchronize spontaneously with the resulting intermittent periods of patency in the airway.

EX-1009 (Tran-I), p. 377.

> We hypothesized that electrical stimulation does not have to synchronize with inspiration to prevent OSA [4, 5]. Instead, repetitive intermittent electrical stimulation could be used to recover or maintain airway patency. In this method, we applied a brief train of electrical pulses during an ON period followed by no stimulation during an OFF period. This method of stimulation is repeated in ***continuous cycles at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sensor to synchronize stimulation with breathing***.

EX-1010 (Tran-II), p. 4288.

284. Accordingly, claim 3 is obvious from Headley and Tran.

4. <u>Claim 4</u>

a. [4.a] ***The device of claim 3, wherein the reference respiratory pattern comprises a reference respiratory cycle, and***

285. Headley in view of Tran renders obvious claim 3, as discussed above in X.B.3 (Ground 2, claim 3). Headley and Tran further disclose the limitations of this claim element for the same reasons as those discussed above with respect to claim 3, as the only difference between the claim language is that claim 3 recites a "reference respiratory pattern" and claim 4 recites "reference respiratory cycle. As detailed above, Tran expressly discloses providing

"trains of stimulation pulses…at intervals close to the respiratory cycle of the patient." EX-1009 (Tran-I), p. 377.

286. Accordingly, Headley and Tran disclose claim element [4.a].

b. [4.b] ***wherein a duration of each respective stimulation period is greater than a duration of an inspiratory phase of the reference respiratory cycle.***

287. Headley in view of Tran discloses that the period of stimulation/ON period [*duration of each respective stimulation period*] is greater than the inspiratory phase of the patient's respiratory cycle [*duration of an inspiratory phase of the reference respiratory cycle*]. For example, Tran discloses a five-second respiratory rate and shows the patient's inspiratory phase to be approximately two seconds in duration while the stimulation markers show that stimulation is applied for approximately 2.5 seconds in duration.

> Various duty cycles of gating of CPAP (30-50%) were studied at random during the night. For example, a 40% duty cycle in ***a 5 second respiration period*** means CPAP is applied for 3 sec and gated off for 2 sec.

EX-1009 (Tran-I), p. 377.

Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010 (Tran-II), FIG. 4.

288. Thus, Tran discloses that each ON period [*each respective stimulation period*] has a duration that is greater than the inspiratory phase of the patient's natural respiratory rhythm [*reference respiratory cycle*]. Headley further discloses that the ON periods [*respective stimulation periods*] may be applied for up to 120 seconds.

> In use, the device as described herein and/or the method as described herein provides for alternating on/off "intermittent" treatment wherein ***the tissue is stimulated for a given period, and then the tissue is allowed to rest for a given period***. In one

> preferred embodiment, the device or method applies stimulation for 5 seconds, and then stimulation is turned off for 5 seconds. In another preferred embodiment, the period of stimulation ranges from 1 to 20 seconds, with varying rest periods. In another preferred embodiment, ***the period of stimulation is 20 seconds and the rest period is 5 seconds***. In yet another preferred embodiment, the period is 60 seconds on with 60 seconds off. On periods may range without limitations from 1 to 120 seconds, and off periods similarly. ***On/off intermittent periods include*** from 5/5, ***20/5***, ***10/10***, 5/60, ***60/5***, ***20/20***, ***30/30***, ***40/40***, ***50/50***, ***60/60***, and so forth.

EX-1008 (Headley) ¶ 48.

289. A POSITA understood that the duration of the ON periods [*respective stimulation periods*] disclosed by Headley to be greater than a patient's inspiratory phase – especially the five-second respiratory phase disclosed by Tran. EX-1009 (Tran-I), p. 377. As such, Headley and Tran disclose this claim element.

290. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and stimulation cycle duration, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. I

further note that the '526 Patent does not identify any unexpected results resulting from providing a duration of stimulation via the first stimulation protocol during a treatment period that is greater than an inspiratory phase of a patient's respiratory cycle beyond the desired goal to provide stimulation during the inspiratory phase. As such, not only do Headley and Tran disclose the limitations of claim 4, but the claim itself recites nothing more than routine optimization (i.e., a duty cycle and stimulation cycle duration that provides the desired outcome of increasing airway patency while sleeping).

291. Accordingly, claim 4 is obvious from Headley in view of Tran.

5. <u>Claim 5</u>

a. [5] *The device of claim 1, wherein the reference respiratory-related parameter is based on stable respiration.*

292. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley and Tran further disclose the limitations of claim 5. For example, Tran discloses observing the patient while sleeping to identify the patient's natural respiratory rhythm [*reference respiratory-related parameter*] while sleeping [*stable respiration*].

> In this method, we applied a brief train of electrical pulses during an ON period followed by no stimulation during an OFF period. This method of stimulation is repeated in continuous cycles at

> approximately the ***natural respiratory rhythm of the sleeping participant***, obviating the need for a sensor to synchronize stimulation without breathing.

EX-1010 (Tran-II), p. 4288.

293. A POSITA understood that the goal of observing the patient while sleeping to identify the patient's natural respiratory rhythm was to identify the patient's stable respiratory rate while sleeping so that stimulus would be applied at this rate to avoid OSA incidents while not disturbing the patient's sleep. EX-1010 (Tran-II), p. 4287 ("The primary objects of this study are to evaluate:…3. Stimulation parameters that prevent prolapse without disturbing sleep."), p. 4289 ("However, stimulation with parameters of 3.0 mA, 200 µsec pulse width, 20 PPS, and duty cycle of 30% or more were well tolerated and seemed to be effective in preventing the development of hypopnea…No sleep was interrupted by neuromuscular stimulation.")

294. Accordingly, claim 5 is obvious from Headley in view of Tran.

6. <u>Claim 6</u>

a. [6.a] ***The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory cycle and***

295. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley and Tran further disclose the limitations of this claim element for the same reasons discussed above in X.B.4.a (claim element [4.a]), as claim element [6.a] is identical to claim element [4.a].

b. [6.b] ***wherein a combined duration of a respective one of the stimulation periods and a respective one of the non-stimulation periods is less than a duration of the reference respiratory cycle.***

296. Headley and Tran disclose this claim element. Headley discloses applying stimulation for periods [*respective one of the stimulation periods*] as short as one second and off periods [*respective one of the non-stimulation periods*] as short as one second.

> On periods may range, without limitations from 1 to 120 seconds, and off periods similarly.

EX-1008 (Headley) ¶ 48.

297. As previously noted, Tran discloses a patient's observed natural respiratory rhythm is five seconds [*duration of the reference respiratory cycle*]. EX-1009

(Tran-I), p. 377 ("For example, a 40% duty cycle in a 5 second respiration period…."); EX-1010 (Tran-II), p. 4288 ("This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sense to synchronize stimulation with breathing.").

298. A combined duration of a one second ON period [*each respective stimulation period*] and a one second OFF period [*each respective non-stimulation period*], i.e., two seconds as disclosed by Headley, is less than the five second respiration period [*duration of the reference respiratory cycle*], as disclosed by Tran. Accordingly, Headley and Tran disclose the limitations of claim element [6.b].

299. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and duration of the stimulation cycle, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. I further note that the '526 Patent does not identify any unexpected results resulting from providing a combined duration of a stimulation period and non-stimulation period that is less than a duration of the reference respiratory cycle. As such, not only do Headley and Tran disclose the

limitations of claim element [6.b], but the claim element itself recites nothing more than routine optimization (i.e., a duty cycle that provides the desired outcome of increasing airway patency while sleeping).

300. Accordingly, claim 6 is obvious from Headley in view of Tran.

7. <u>Claim 7</u>

a. [7.a] *The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory cycle and*

301. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley and Tran further disclose the limitations of this claim for the same reasons discussed above in X.B.4.a (Ground 2, claim element [4.a]), as claim element [7.a] is identical to claim element [4.a].

b. [7.b] *wherein the combined duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods is no greater than a duration of a reference respiratory cycle.*

302. Headley in view of Tran disclose this claim element for the same reasons as discussed above in X.B.6.b (Ground 2, claim element [6.b]) given that there is no significant different between " a combined duration of a respective one of the stimulation periods and a respective one of the non-stimulation periods is less than a duration of the reference respiratory cycle" and a "combined

duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods is no greater than a duration of a reference respiratory cycle."

303. Accordingly, claim 7 is obvious from Headley and Tran.

8. Claim 8

a. [8] *The device of claim 1, wherein the duration of the respective stimulation periods remain uniform.*

304. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley and Tran further disclose the limitations of claim 8. As discussed previously, Headley discloses providing "alternating on/off 'intermittent' treatment wherein the tissue is stimulated for a given period, and then the tissue is allowed to rest for a given period." EX-1008 (Headley) ¶ 48. A POSITA understood that these given periods to remain uniform during the treatment because it was routine and well-known for stimulation periods to remain uniform for such treatments. *See*, *e.g*., EX-1010 (Tran-II), FIG. 4 (showing uniform stimulation markers).

305. The same is true with respect to Tran, which discloses that "stimulation is repeated in ***continuous cycles*** at approximately the natural respiratory rhythm of the sleeping participant." EX-1010 (Tran-II), p. 4288. These "continuous

cycles" would be understood by a POSITA to be of uniform during treatment, unless otherwise programmed.

306. Accordingly, Headley and Tran render obvious claim 8.

9. Claim 9

a. [9.a] *The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory cycle, and*

307. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley and Tran further disclose the limitations of this claim element for the same reasons discussed above in X.B.4.a (Ground 2, claim element [4.a]), as claim element [9.a] is identical to claim element [4.a].

b. [9.b] *wherein the combined duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods is less than 30 percent of a duration of a reference breathing pattern.*

308. Headley and Tran render obvious this claim element. Headley discloses applying stimulation for periods [*respective one of the stimulation periods*] as short as one second and off periods [*respective one of the non-stimulation periods*] as short as one second, although expressly discloses that these times are not limiting.

> On periods may range, ***without limitations*** from 1 to 120 seconds, and off periods similarly.

EX-1008 (Headley) ¶ 48.

309. Tran discloses a patient's observed natural respiratory rhythm is five seconds [*duration of the reference respiratory cycle*]. EX-1009 (Tran-I), p. 377 ("For example, a 40% duty cycle in a 5 second respiration period…."); EX-1010 (Tran-II), p. 4288 ("This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sense to synchronize stimulation with breathing.").

310. A combined duration of a one second ON period [*each respective stimulation period*] and a one second OFF period [*each respective non-stimulation period*], i.e., two seconds as taught by Headley, is 40 percent of a five second respiration period [*duration of the reference respiratory cycle*], as taught by Tran. While 40 percent is greater than 30 percent, a POSITA understood that different patients have different respiratory rates and each patient may themselves have different respiratory rates depending on their activity level and/or position. EX-1010 (Tran-II), p. 4288 ("We screen prospective participants for significant level of positional obstructive apnea (i.e. at least 50% more frequent on their back than on their side) because our current study

aims to treat OSA due to tongue prolapse."); EX-1012 (Bolea) ¶ 473 ("For example, the adaptive duty cycle may increase with an increase in ***respiratory period variability***…."), ¶ 492 ("The stimulation level may be recorded alongside therapy session data, for example cycling rate…***variations in respiratory rate***…."). Thus, while Tran references a five-second respiratory rate, a POSITA understood that such a respiratory rate may increase in duration and a two-second duration of a stimulation cycle may correspond to less than 30 percent of a patient's respiratory cycle [*reference breathing pattern*].

311. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and duration of a stimulation cycle, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. The '526 Patent does not identify any unexpected results from providing a respective one of the stimulation periods and of a respective one of the non-stimulation periods with a combined duration that is less than 30 percent of a duration of a reference breathing pattern. As such, the claim itself recites nothing more than routine optimization (i.e., a stimulation cycle

duration and duty cycle that provides the desired outcome of increasing airway patency while sleeping).

312. Accordingly, claim 9 is obvious from Headley and Tran.

10. <u>Claim 10</u>

a. [10] *The device of claim 1, wherein a respective one of the stimulation periods and a respective one of the non-stimulation periods are in a proportion of at least 1.5 to 1.*

313. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley further discloses claim 10. Specifically, Headley discloses duty cycles in which the ON period [*respective one of the stimulation periods*] and the rest/off periods [*respective one of the non-stimulation periods*] are in a proportion of at least 1.5:1, as Headley expressly discloses proportions of 20:5 (i.e., 4:1) and 60:5 (i.e., 12:1). EX-1008 (Headley) ¶ 48 ("On/off intermittent periods include from 5/5, ***20/5***, 10/10, 5/60, ***60/5***, 20/20, 30/30, 40/40, 50/50, 60/60, and so forth.").

314. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. I further note that the '526 Patent does not identify any unexpected results from providing a stimulation cycle

in which a respective one of the stimulation periods and a respective one of the non-stimulation periods are in a proportion of at least 1.5 to 1. As such, not only does Headley disclose the limitations of claim 10, but the claim itself recites nothing more than routine optimization (i.e., a duty cycle that provides the desired outcome of increasing airway patency while sleeping).

315. Accordingly, Headley and Tran render obvious claim 10.

11. <u>Claim 11</u>

a. [11] *The device of claim 10, wherein a duration of a respective one of the stimulation periods exceeds the duration of a respective one of the non-stimulation periods by a factor of 3.*

316. Headley in view of Tran renders obvious claim 10, as discussed above in X.B.10 (Ground 2, claim 10). Headley further discloses the limitations of claim 11. Headley expressly discloses duty cycles in which the ON period [*respective one of the stimulation periods*] has a duration that exceeds a duration of the rest/off periods [*respective one of the non-stimulation periods*] by factors of 4 (20/5) and 12 (60/5), both of which are greater than 3. EX-1008 (Headley) ¶ 48 ("On/off intermittent periods include from 5/5, ***20/5***, 10/10, 5/60, ***60/5***, 20/20, 30/30, 40/40, 50/50, 60/60, and so forth.").

317. As discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle, was routine in the art

and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. I further note that the ’526 Patent does not identify any unexpected results from providing a stimulation cycle in which a duration of a respective one of the stimulation periods exceeds a duration of a respective one of the non-stimulation periods by a factor of 3. As such, not only does Headley disclose the limitations of claim 11, but the claim itself recites nothing more than routine optimization (i.e., a duty cycle that provides the desired outcome of increasing airway patency while sleeping).

318. Accordingly, Headley and Tran render obvious claim 11.

12. Claim 12

a. [12.a] *The device of claim 1, wherein a respective one of the stimulation periods and a respective one of the non-stimulation periods comprises a stimulation cycle, and*

319. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley and Tran further disclose this claim element. For example, both Headley and Tran disclose alternating on/off [*a respective one of the stimulation periods and a respective one of the non-stimulation periods*] “intermittent” treatment cycles [*stimulation cycle*].

> In use, the device as described herein and/or the method as described herein provides for alternating on/off "intermittent" treatment wherein the tissue is stimulated for a given period, and then the tissue is allowed to rest for a given period.

EX-1008 (Headley) ¶ 48.

> In this method, we applied a brief train of electrical pulses during an ON period followed by no stimulation during an OFF period. This method of stimulation is repeated in ***continuous cycles*** at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010 (Tran-II), p. 4288.

320. Accordingly, Headley discloses the limitations of claim element [12.a].

b. [12.b] *wherein a duration of the respective one of the stimulation periods comprises at least 80 percent of a duration of the stimulation cycle.*

321. Headley discloses this claim element, as Headley expressly discloses providing stimulation and non-stimulation periods in ratio of 60 ON / 5 OFF. Specifically, Headley discloses:

> On periods may range, without limitations from 1 to 120 seconds, and off periods similarly. On/off intermittent periods include

> from 5/5, 20/5, 10/10, 5/60, ***60/5***, 20/20, 30/30, 40/40, 50/50, 60/60, and so forth.

EX-1008 (Headley) ¶ 48.

322. A POSITA understood that a ratio of 60/5 means that stimulation is provided for 92 percent of a given stimulation cycle.

On/off period of 60/5; total cycle length 65:

$$\frac{60}{65} \times 100\% = 92.3\%$$

Thus, Headley expressly discloses providing a stimulation cycle in which the duration of the respective one of the stimulation periods comprises at least 80 percent (i.e., 92 percent) of the duration of the stimulation cycle.

323. Accordingly, Headley discloses the limitations of claim element [12.b], and claim 12 is obvious from Headley and Tran.

13. <u>Claim 13</u>

a. [13] *The device of claim 1, wherein each respective stimulation period comprises continuous pulsed stimulation.*

324. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley and Tran further disclose this claim element. As a preliminary matter, the ’526 Patent describes continuous stimulation as

"a train of stimulation pulses which occur in a relatively short time frame," such as "a finite number (e.g. 5, 10, etc.) of stimulation pulses per second":

> In some examples, each stimulation period within a stimulation cycle includes continuous stimulation. In some examples, continuous stimulation refers to a train of stimulation pulses which occur in a relatively short time frame. For instance, in some examples, continuous stimulation corresponds to at least a finite (e.g. 5, 10, etc.) of stimulation pulses per second.

EX-1001 4:37-43.

325. Headley discloses that the pulse generator is configured to vary the properties of the electrical pulses applied during the therapy.

> The receiver includes an electrical pulse source, or pulse generator. ***The electrodes impart electrical pulses, generated by the pulse generator***, directly by wire to the genioglossus muscle to stimulate the specific muscle fibers to a point where the patient's tongue is moved anteriorly to maintain upper airway patency. ***The pulse generator has an output that provides pulses having selectable properties of*** mode, polarity, amplitude, current, pulse width, and ***frequency***...The stimulator may be variably set to provide ***direct current pulses*** having an amplitude, a ***frequency***, and a duration to provide a non-

> awakening stimulation directly by wire to the specific muscle fibers.

EX-1008 (Headley) ¶ 30.

326. Similarly, Tran discloses that the electrical stimulation may be applied at 20 pulses per second (PPS):

> However, stimulation with parameters of 3.0 mA, 200 µsec pulse width, ***20 PPS***, and duty cycle of 30% or more were well tolerated and seemed to be effective in preventing the development of hypopnea.

EX-1010 (Tran-II), p. 4289.

327. A POSITA understood from at least the foregoing disclosures of Headley and Tran as providing continuous pulsed stimulation – at least as is disclosed by the ’526 Patent.

328. Accordingly, Headley and Tran disclose claim 13.

14. Claim 14

a. [14.a] *The device of claim 1, comprising a processor; and*

329. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley further discloses that the pulse generator of the receiver includes a microprocessor [*processor*].

> Commercially available ***pulse generators provide pulses having many of the previously mentioned variables and may include microprocessors*** and electronics for signal processing and cooperation with apnea detection device. The stimulator may be variably set to provide direct current pulses having an amplitude, a frequency, and a duration to provide non-awakening stimulation ***directly by wire*** to the specific muscle fibers.

EX-1008 (Headley) ¶30.

330. Accordingly, Headley discloses claim element [14.a].

b. [14.b] *a non-volatile computer readable medium storing instructions, executable on the processor, to implement the first stimulation therapy protocol via the non-cardiac stimulation means for stimulating.*

331. A POSITA understood that a commercially available pulse generator included a non-volatile computer readable medium storing instructions, executable by the microprocessor [*processor*], to perform the alternating on/off "intermittent" treatment [*first stimulation therapy protocol*] disclosed by Headley via the stimulating electrode [*non-cardiac stimulation means for stimulating*]. EX-1008 (Headley) ¶ 29; *see also* V.A (Technical Background, Neuromuscular Stimulators) (citing Christopherson, Bolea, and others).

332. Accordingly, Headley discloses claim element [14.b], and Headley and Tran render obvious claim 14.

15. Claim 15

a. [15] *The device of claim 1, wherein the first stimulation therapy protocol is to be applied during a treatment period in which the patient is to engage in sleeping behavior.*

333. Headley in view of Tran renders obvious claim 1, as discussed above in X.B.1 (Ground 2, claim 1). Headley further discloses the limitations of claim 15, as Headley discloses that the stimulator provides "non-awakening stimulation," which a POSITA understood as providing treatment while the patient is asleep. EX-1008 (Headley) ¶ 30 ("The stimulator may be variably set to provide direct current pulses having an amplitude, a frequency, and a duration to provide a non-awakening stimulation directly be wire to the specific muscle fibers.").

334. Accordingly, Headley and Tran render obvious claim 15.

16. Claim 16

a. [16.pre] *A device for treating obstructive sleep apnea, comprising:*

335. To the extent the preamble is limiting, Headley (and Tran) disclose a device for treating OSA for the same reasons as discussed above in X.B.1.a (Ground

2, claim element [1.pre]), as the two limitations are identical. Accordingly, Headley (and Tran) disclose claim element [16.pre] to the extent it is limiting.

b. [16.a1] ***a non-cardiac means for stimulating an upper airway patency-related nerve,***

336. Headley, either alone or in combination with Tran, discloses this claim element for the same reasons discussed above in X.B.1.b (Ground 2, claim element [1.a1]), as the two limitations are identical.

337. Accordingly, Headley, either alone or in combination with Tran, discloses claim element [16.a1].

c. [16.a2] ***according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing,***

338. Headley and Tran disclose this claim element for the same reasons discussed above in X.B.1.c (Ground 2, claim element [1.a2]), as the two limitations are identical. Accordingly, Headley and Tran disclose claim element [16.a2].

d. [16.b] *wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period,*

339. Headley discloses this claim element for the same reasons discussed above in X.B.1.d (Ground 2, claim element [1.b]), as the two limitations are identical. Accordingly, Headley discloses claim element [16.b]).

e. [16.c] *wherein each stimulation period comprises continuous pulsed stimulation, and*

340. Headley and Tran disclose this claim element for the same reasons discussed above in IX.B.12 (Ground 2, claim 13), as the two limitations are identical. Accordingly, Headley and Tran disclose claim element [16.c].

f. [16.d] *wherein the first stimulation therapy protocol is to deliver multiple stimulation periods within a duration of a reference breath of a reference respiratory cycle, and*

341. Headley and Tran disclose this claim element. For example, Headley discloses repeatedly applying stimulation [*multiple stimulation periods*] to a patient and also discloses that the duration of the applied stimulation may be provided for periods of 1 to 120 seconds.

> In use, the device as described herein and/or the method as described herein provides for alternating on/off "intermittent" treatment wherein the tissue is stimulated for a given period, and

> then the tissue is allowed to rest for a given period.…On periods may range, without limitations from 1 to 120 seconds, and off periods similarly.

EX-1008 (Headley) ¶ 48.

342. Tran discloses a patient's natural respiratory rhythm [*reference breath of a reference respiratory cycle*] having a duration of approximately five seconds.

> This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010 (Tran-II), p. 4288.

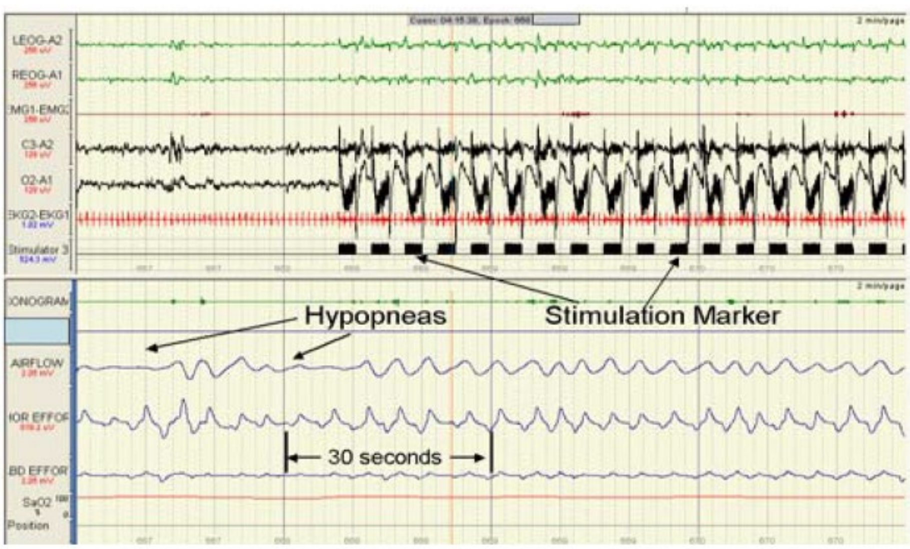


Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010 (Tran-II), p. 4289.

> For example, a 40% duty cycle in a ***5 second respiration period*** means CPAP is applied for 3 sec and gated off for 2 sec.

EX-1009 (Tran-I), p. 377.

343. Thus, Headley discloses that multiple (e.g., at least two) stimulation periods (e.g., one second ON periods) may be provided in the five-second duration of a reference breaths of a reference respiratory cycle taught by Tran.

344. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and stimulation cycle duration, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. I further note that the ’526 Patent does not identify any unexpected results resulting from delivering multiple stimulation periods within a duration of a reference breath of a reference respiratory cycle. As such, not only do Headley and Tran disclose the limitations of claim element [16.d], but the claim element itself recites nothing more than routine optimization (i.e., a stimulation period and stimulation cycle duration that provides the desired outcome of increasing airway patency while sleeping).

345. Accordingly, Headley and Tran disclose claim element [16.d].

g. [16.e] ***wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.***

346. Headley (and Tran) disclose this claim element for the same reasons discussed above in X.B.1.f (Ground 2, claim element [1.d]), as the two limitations are identical.

347. Accordingly, Headley (and Tran) disclose claim element [16.e] In view of the foregoing, claim 16 is obvious from Headley and Tran.

17. <u>Claim 17</u>

a. [17] ***The device of claim 16, wherein the duration of each respective non-stimulation period as at least less than half of the duration of each respective stimulation period.***

348. Headley and Tran render obvious claim 16, as discussed above in X.B.16 (Ground 2, claim 16). Headley further discloses the limitations of claim 17. For example, Headley discloses ON periods [*duration of each respective stimulation period*[and OFF periods [*duration of each respective non-stimulation period*] in proportions of 20/5 (i.e., 4:1) and 60/5 (i.e., 12:1).

> On periods may range, without limitations from 1 to 120 seconds, and off periods similarly. On/off intermittent periods include from 5/5, ***20/5***, 10/10, 5/60, ***60/5***, 20/20, 30/30, 40/40, 50/50, 60/60, and so forth.

EX-1008 (Headley) ¶ 48.

349. When stimulation is applied in proportions of 20/5 and 60/5, the duration of each respective OFF period [*non-stimulation period*] is at least less than half of the duration of each respective ON period [*stimulation period*].

350. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. Moreover, the '526 Patent does not identify any unexpected results resulting from a duration of each respective non-stimulation period being at least less than half of the duration of each respective stimulation period. As such, not only does Headley disclose the limitations of claim 17, but the claim itself recites nothing more than routine optimization (i.e., a stimulation period and stimulation cycle duration that provides the desired outcome of increasing airway patency while sleeping).

351. Accordingly, Headley discloses the limitations of claim 17.

18. <u>Claim 18</u>

a. [18] *The device of claim 16, wherein the reference respiratory cycle comprises at least one of: a historical patient-specific respiratory cycle; and a multiple patient reference respiratory cycle.*

352. Headley and Tran render obvious claim 16, as discussed above in X.B.16 (Ground 2, claim 16). Tran further discloses the limitations of this claim. Specifically, Tran discloses observing a sleeping patient to determine the patient's respiratory rate [*historical patient-specific reference respiratory cycle*].

> ***Two patients with documented severe OSA (>40 episodes/hr) were studied overnight***. Baseline information such as respiratory rate and level of oxygen saturation was ***acquired during the first hour of sleep***. Various duty cycles of gating of CPAP (30-50%) were studied at random during the night. For example, a 40% duty cycle in a 5 second respiration period means CPAP is applied for 3 sec and gated off for 2 sec.

EX-1009 (Tran-I), p. 377.

> In this method, we applied a brief train of electrical pulses during an ON period followed by no stimulation during an OFF period. ***This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping***

> ***participant***, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010 (Tran-II), p. 4288.

353. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. Moreover, the '526 Patent does not identify any unexpected results resulting from the reference respiratory cycle being a historical patient-specific respiratory cycle. As such, not only does Headley disclose the limitations of claim 18, but the claim itself recites nothing more than routine optimization (i.e., use of known reference respiratory cycles).

354. Accordingly, claim 18 is obvious from Headley and Tran.

19. <u>Claim 19</u>

a. [19] *The device of claim 16, wherein the first stimulation therapy protocol is to deliver at least some of the multiple stimulation periods within a duration of an inspiratory phase of the reference respiratory cycle.*

355. Headley and Tran render obvious claim 16, as discussed above in X.B.16 (Ground 2, claim 16). Headley and Tran also disclose the limitations of claim

19. For example, Headley discloses that a stimulation cycle may be two seconds, i.e., one second ON and one second OFF. EX-1008 (Headley) ¶ 48 ("On periods may range, without limitations from 1 to 120 seconds, and off periods similarly.").

356. From FIG. 4 of Tran-II, which is reproduced below, it can be seen that the patient's inspiratory phase is approximately two seconds.

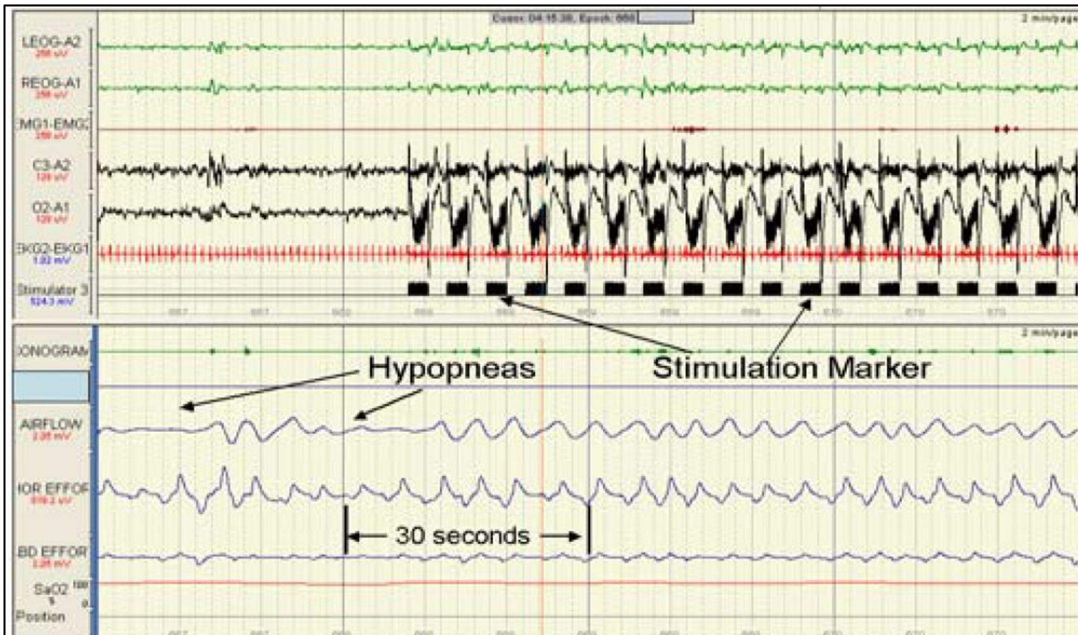


Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010 (Tran-II), FIG. 4.

357. At least one [*at least some*] of the one-second ON periods [*stimulation periods*] disclosed by Headley may be delivered within the two-second

inspiratory phase illustrated in FIG. 4 of Tran-II. As such, Headley and Tran disclose the limitations of claim 19.

20. <u>Claim 20</u>

a. [20] ***The device of claim 16, wherein the duration of each respective stimulation period is at least less than 30 percent of a duration of the reference respiratory cycle.***

358. Headley and Tran render obvious claim 16, as discussed above in X.B.16 (Ground 2, claim 16). Headley and Tran also disclose the limitations of this claim. As noted previously, Tran discloses a patient's natural respiratory rhythm [*reference respiratory cycle*] having a duration of approximately five seconds.

> This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010 (Tran-II), p. 4288.

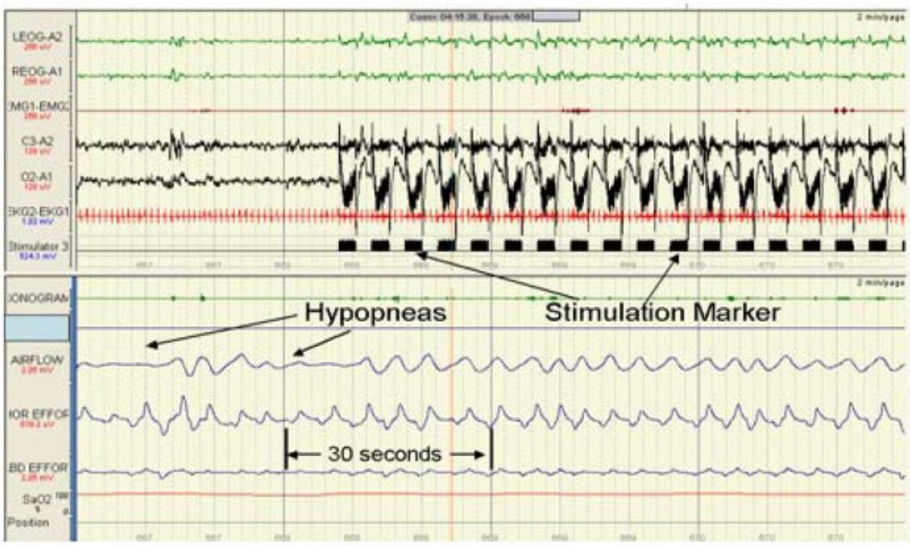


Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010 (Tran-II), p. 4289.

> For example, a 40% duty cycle in a ***5 second respiration period*** means CPAP is applied for 3 sec and gated off for 2 sec.

EX-1009 (Tran-I), p. 377.

359. Headley discloses stimulation ON periods [*respective stimulation period*] of one second [*duration*]. EX-1008 (Headley) ¶ 48 ("On periods may range, without limitations from 1 to 120 seconds, and off periods similarly."). A one second ON period is 20 percent, i.e., less than 30 percent, of a five second respiratory cycle.

On period of 1 second; stimulation cycle length 5 seconds:

$$\frac{1}{5} \times 100\% = 20\%$$

360. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and stimulation cycle duration, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. Moreover, the ’526 Patent does not identify any unexpected results resulting from a duration of each respective stimulation period being at least less than 30 percent of a duration of the reference respiratory cycle. As such, not only do Headley and Tran disclose the limitations of claim 20, but the claim itself recites nothing more than routine optimization (i.e., a stimulation period and stimulation cycle duration that provides the desired outcome of increasing airway patency while sleeping).

361. Accordingly, claim 20 is obvious from Headley and Tran.

21. <u>Claim 21</u>

a. [21.a] *The device of claim 16, wherein a combination of a respective one of the stimulation periods and a respective one of the non-stimulation periods comprises a stimulation cycle, and*

362. Headley and Tran render obvious claim 16, as discussed above in X.B.16 (Ground 2, claim 16). Headley and Tran further disclose the limitations of

this claim element for the reasons set forth above in X.B.4.a (Ground 2, claim element [4.a]), as this claim element substantively is the same as claim element [4.a].

b. [21.b] ***wherein the first stimulation therapy protocol is to deliver more than one stimulation cycle within a duration of the reference respiratory cycle.***

363. Headley and Tran also disclose this claim element. As discussed previously, Tran discloses a five second respiratory cycle [*reference respiratory cycle*] and Headley discloses ON/OFF periods [collectively, *stimulation cycle*] as short as one two seconds (i.e., one second ON / one second OFF).

> This method of stimulation is repeated in continuous cycles at approximately the ***natural respiratory rhythm of the sleeping participant***, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010 (Tran-II), p. 4288.

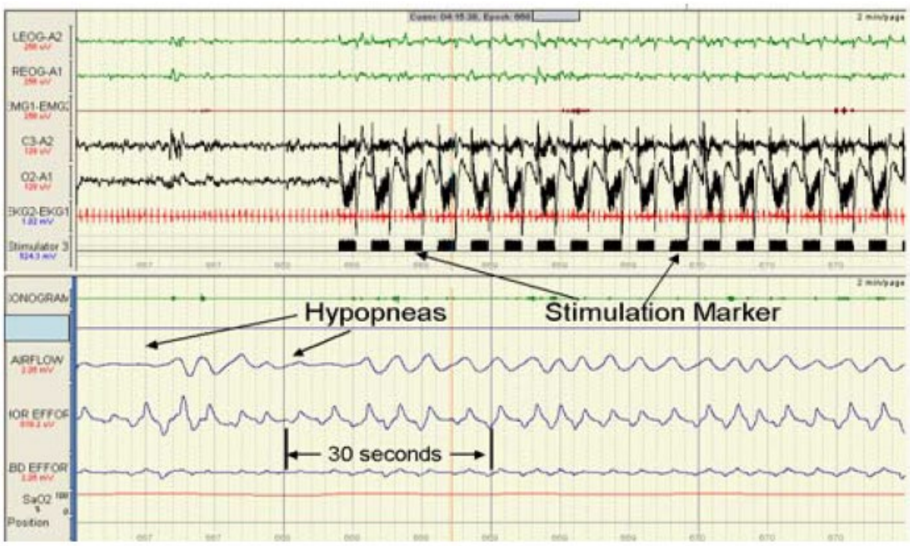


Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010 (Tran-II), p. 4289.

> For example, a 40% duty cycle in a ***5 second respiration period*** means CPAP is applied for 3 sec and gated off for 2 sec.

EX-1009 (Tran-I), p. 377.

> On periods may range, without limitations from 1 to 120 seconds, and off periods similarly.

EX-1008 (Headley) ¶ 48.

364. A two-second ON/OFF period [*stimulation cycle*] can be delivered at least twice [*more than one*] in a five-second respiratory cycle [*reference respiratory cycle*].

365. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and stimulation cycle duration, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. Moreover, the '526 Patent does not identify any unexpected results resulting from delivering more than one stimulation cycle within a duration of the reference respiratory cycle. As such, not only do Headley and Tran disclose the limitations of claim element [21.b], but the claim element itself recites nothing more than routine optimization (i.e., a stimulation period and stimulation cycle duration that provides the desired outcome of increasing airway patency while sleeping).

366. Accordingly, Headley and Tran disclose claim element [21.b] and render obvious claim 21.

22. <u>Claim 22</u>

a. [22.pre] *A device for treating obstructive sleep apnea, comprising:*

367. To the extent the preamble is limiting, Headley (and Tran) disclose a device for treating OSA for the same reasons as discussed above in X.B.1.a (Ground 2, claim element [1.pre]), as the two limitations are identical.

Accordingly, Headley (and Tran) disclose claim element [22.pre] to the extent it is limiting.

b. [22.a1] *a non-cardiac means for stimulating an upper airway patency-related nerve,*

368. Headley, either alone or in combination with Tran, discloses this claim element for the same reasons discussed above in X.B.1.b (Ground 2, claim element [1.a1]), as the two limitations are identical.

369. Accordingly, Headley discloses claim element [22.a1], either alone or in combination with Tran.

c. [22.a2] *according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing,*

370. Headley and Tran disclose this claim element for the same reasons discussed above in X.B.1.c (Ground 2, claim element [1.a2]), as the two limitations are identical. Accordingly, Headley and Tran disclose claim element [22.a2].

d. [22.b] ***wherein a duration of each respective stimulation is greater than a duration of each respective non-stimulation period, and***

371. Headley discloses this claim element for the same reasons discussed above in X.B.1.d (Ground 2, claim element [1.b]), as the two limitations are identical. Accordingly, Headley discloses claim element [22.b].

e. [22.c] ***wherein the combined duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods is greater than a duration of a reference respiratory cycle,***

372. Headley and Tran disclose this claim element. Headley discloses the combined duration of an ON period [*stimulation period*] and an OFF period [*non-stimulation period*] as short as two seconds and as long as 240 seconds (i.e., 120 seconds ON / 120 seconds OFF).

> In use, the device as described herein and/or the method as described herein provides for alternating on/off "intermittent" treatment wherein the tissue is stimulated for a given period, and then the tissue is allowed to rest for a given period.…On periods may range, without limitations from 1 to ***120 seconds***, and off periods similarly.

EX-1008 (Headley) ¶ 48.

373. Tran discloses a patient's natural respiratory rhythm [*reference respiratory cycle*] having a duration of approximately five seconds.

> This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010 (Tran-II), p. 4288.

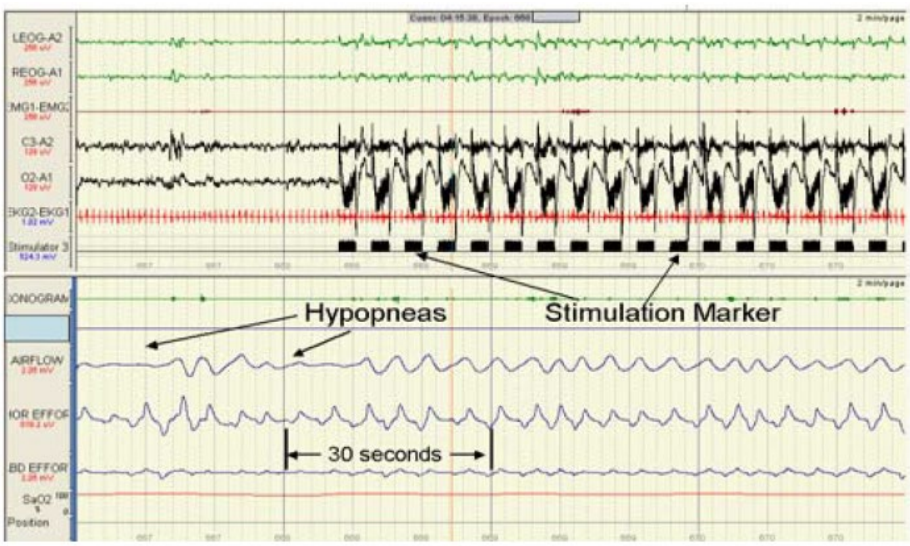


Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010 (Tran-II), p. 4289.

> For example, a 40% duty cycle in a ***5 second respiration period*** means CPAP is applied for 3 sec and gated off for 2 sec.

EX-1009 (Tran-I), p. 377.

374. A 240-second stimulation cycle duration disclosed by Headley is greater than the five-second reference respiratory period disclosed by Tran.

375. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and stimulation cycle duration, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. Moreover, the '526 Patent does not identify any unexpected results resulting from the combined duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods being greater than a duration of a reference respiratory cycle.. As such, not only do Headley and Tran disclose the limitations of claim element [22.c], but the claim element itself recites nothing more than routine optimization (i.e., a stimulation period and stimulation cycle duration that provides the desired outcome of increasing airway patency while sleeping).

376. Accordingly, Headley and Tran disclose claim element [22.c].

f. [22.d] ***wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.***

377. Headley and Tran disclose this claim element for the same reasons discussed above in X.B.1.f (Ground 2, claim element [1.d]), as the two limitations are identical.

378. Accordingly, Headley and Tran disclose claim element [22.d] In view of the foregoing, claim 22 is obvious from Headley and Tran.

23. <u>Claim 23</u>

a. [23] ***The device of claim 22, wherein the duration of a respective one of the stimulation periods is greater than the duration of the reference respiratory cycle.***

379. Headley and Tran render obvious claim 22, as discussed above in X.B.22 (Ground 2, claim 22). Headley and Tran further disclose the limitations of claim 23. As discussed above with respect to claim element [22.d], Headley discloses that the ON periods [*respective one of the stimulation periods*] may have a length [*duration*] of up to 120 seconds.

> In use, the device as described herein and/or the method as described herein provides for alternating on/off "intermittent" treatment wherein the tissue is stimulated for a given period, and then the tissue is allowed to rest for a given period.…On periods

may range, without limitations from 1 to ***120 seconds***, and off periods similarly.

EX-1008 (Headley) ¶ 48.

380. Tran discloses a patient's natural respiratory rhythm [*reference respiratory cycle*] having a duration of approximately five seconds.

> This method of stimulation is repeated in continuous cycles at approximately the ***natural respiratory rhythm of the sleeping participant***, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010 (Tran-II), p. 4288.

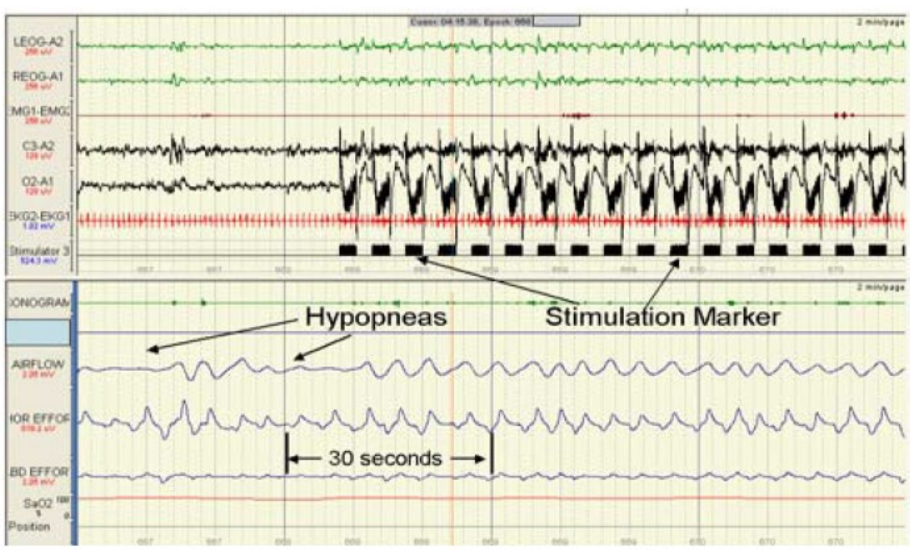


Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010 (Tran-II), p. 4289.

> For example, a 40% duty cycle in a ***5 second respiration period*** means CPAP is applied for 3 sec and gated off for 2 sec.

EX-1009 (Tran-I), p. 377.

381. A 120-second stimulation ON period [*respective one of the stimulation periods*] disclosed by Headley is greater than the five-second reference respiratory period [*reference respiratory cycle*] disclosed by Tran.

382. Further, as discussed above in V.B (Technical Background, OSA Treatment), adjusting stimulation parameters, including duty cycle and stimulation cycle duration, was routine in the art and was a typical part of the titration process performed by a physician after implantation of an OSA treatment device. Moreover, the '526 Patent does not identify any unexpected results resulting from the combined duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods being greater than a duration of a reference respiratory cycle. As such, not only do Headley and Tran disclose the limitations of claim 23, but the claim itself recites nothing more than routine optimization (i.e., a stimulation period and stimulation cycle duration that provides the desired outcome of increasing airway patency while sleeping).

383. Accordingly, Headley and Tran disclose the limitations of claim 23.

XI. SECONDARY CONSIDERATIONS DO NOT REBUT THE PRIMA FACIE CASE OF OBVIOUSNESS

384. In my opinion, secondary considerations do not rebut the prima facie case of obviousness for at least two reasons.

385. *First*, I have not seen any evidence of any secondary considerations to date. As such, I do not believe any such secondary considerations exist. To the extent Patent Owner seeks to proffer evidence of any secondary considerations in this proceeding, I reserve the right to comment on such evidence.

386. *Second*, I do not believe that Patent Owner will be able to establish a nexus between any secondary considerations and the Challenged Claims. I have been advised that a nexus does not exist where the alleged secondary considerations result from something other than what is both claimed and novel in the claims.

387. As I have explained above, there is nothing novel in the claims. Indeed, all claim elements are disclosed in the prior art. Thus, I do not see any basis for Patent Owner to assert that there is a nexus between any secondary considerations and the claims.

XII. CONCLUSION

388. My findings and opinions set forth in this Declaration are based on my work and examination to date. I may continue my examinations in view of additional documents or other factual evidence over the course of this proceeding that may necessitate supplementing and/or refining my opinions. I reserve the right to add to, alter, or delete any of my opinions and my Declaration upon discovery of additional information. I reserve the right to make any changes as necessary.

389. In signing this Declaration, I understand that this Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allowed for cross-examination. I declare that all statements made herein of my knowledge, all statements made on information and belief are believed to be true, and these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code.

Dated: Dec. 17, 2025

Dr. Gerald Loeb

APPENDIX A

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Gerald E. Loeb, M.D.

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https://en.wikipedia.org/wiki/Gerald_E._Loeb

Education:

1965-1969 - B.A. The Johns Hopkins U. (Human Biology Major)
1968-1972 - M.D. The Johns Hopkins U. School of Medicine

Professional History:

2023- present Director of the Biomedical Engineering Innovation Space, University of Southern California
2008-present Professor of Pharmacy, University of Southern California (secondary appointment)
2007-present President, Biomed Concepts Inc. (consulting and prototyping in biomedical engineering)
2006-present Professor of Neurology, University of Southern California (secondary appointment)
1999-present Professor of Biomedical Engineering (primary appointment) and Director of the Medical Device Development Facility, University of Southern California
2021-2022 Founder and Chief Scientist (consulting), Chironics Ltd., UK (healthcare decision software)
2013-2015 Distinguished Scientist of the Strategic Advisory Committee, Chongqing Institute for Green and Intelligent Technology, Chinese Academy of Science (robotics)
2012-2020 Chief Scientist (consulting), General Stim Inc. (injectable neuromuscular stimulators)
2008-2024 Founding CEO and Director, SynTouch Inc. (biomimetic tactile sensors and haptics)
2003-2009 Deputy Director, NSF Engineering Research Center on Biomimetic MicroElectronic Systems
1999-2008 Director of Medical Device Development, Alfred E. Mann Institute for Biomedical Engineering at the University of Southern California

1994-1999 Chief Scientist (consulting), Advanced Bionics Corp., Sylmar, California
1991-1999 Director of Bio-Medical Engineering Unit and Professor of Physiology, Queen's University
1990-1999 Member, Medical Research Council Group in Sensory-Motor Neuroscience, Queen's University
1988-1991 Director of Special Projects, Biomedical Engineering Unit, and Professor of Physiology, Queen's University, Kingston, Ontario
1987-1988 Special Expert, Lab. of Neural Control, IRP, NINCDS, NIH
1986-1987 Chief, Neurokinesiology Section, Lab. of Neural Control, IRP, NINCDS, NIH (Sr. Surgeon, U.S. Public Health Service)
1985-1987 Adjunct Associate Professor of Bioengineering, U. Utah
1981-1990 President, Biomed Concepts, Inc. (consulting and prototyping in biomedical engineering)
1980-1981 Partner in Bak Electronics, Inc.(electrophysiological research instrumentation)
1979-1986 Permanent Sr. Investigator, Lab. of Neural Control, IRP, NINCDS, NIH
1979-1981 Guest Researcher, Depts. Otolaryngology and Physiology, UCSF School of Medicine
1974-1979 Medical Officer, Lab. of Neural Control, IRP, NINCDS, NIH
1973-1974 Research Associate, Lab. of Neural Control, IRP, NINCDS, NIH
1972-1973 Internship, Department of Surgery, Univ. of Arizona
1971-1972 Independent R&D of real-time scientific programming language for minicomputers
1971 Guest Research Associate, Univ. of Utah Artificial Eye Project
1967-1972 Research Assistant to Dr. William B. Marks, Dept of Biophysics, Johns Hopkins Univ.
1966-1967 Training in thin film microelectronics, Johns Hopkins Univ. Applied Physics Lab.

Awards and Honors:

Manville High School Hall of Fame, 2025
Top 200 Best Scientists in Engineering and Technology, 2022, Research.com
Tribute Award, 2022, Division of Biokinesiology & Physical Therapy, Univ. Southern California
Fellow of the National Academy of Inventors (NAI)
Technology Pioneer 2014 – World Economic Forum
Breakthrough Innovator Award 2013 – Popular Mechanics
Medical Device & Diagnostic Industry Magazine's 100 Notable People in the Medical Device Industry
Fellow of the American Institute for Medical and Biological Engineering (AIMBE)
Queen's National Scholar - Queen's University
International Exchange Fellowship to Bulgaria - National Academy of Sciences
Commendation Medal - U.S. Public Health Service
Seeing Eye, Inc. Fellowship, 1969-72

Research Interests:

Neuroprosthetics and neural control techniques
Sensorimotor control in mammals
Implantable medical devices
Haptics for robots

Research & Scholarly Activities:

Publications: 439 (excluding abstracts) **Google H-index: 111**

Electronic reprints available through http://bme.usc.edu/gloeb and
https://www.ncbi.nlm.nih.gov/myncbi/gerald.loeb.1/bibliography/public/

Books: 1

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Full-Length Original Research Reports in Refereed Journals: 188

Biomedical Engineering, Modeling and Methodology: 124

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Sunwoo, J., Goodner, J.R. and Loeb, G.E. “Dimensionality reduction of the spinal-like regulator model improves motor learning,” Society for Neuroscience, Nov. 11, 2013, San Diego, CA.

Li, Y., Loeb, G.E., Sunwoo, J. and Cerne, T. “Are high dimensional spinal neural circuits configured to facilitate rapid learning?” SIAM, July 9, 2013, San Diego, CA.

Tsianos, G.A., Loeb, G.E. and Goodner, J. “A realistic model of spinal circuitry facilitates control of center-out reaching movements”. Abst. 275.03, Society for Neuroscience, Oct. 14, 2012, New Orleans.

Goodner, J., Tsianos, G.E., Lie, Y. and Loeb, G.E. “BioSearch: A physiologically plausible learning model for the sensorimotor system”. Abst. 275.22, Society for Neuroscience, Oct. 14, 2012, New Orleans.

Guest Lectures (previous 25 years only):

International Conference on Medical Device Safety, Amsterdam, Netherlands, “From Concept to Design: Managing Safety Risks in Breakthrough Devices,” April 24-25, 2025.

Neurorehabilitation Seminar, University of Southern California, “The Stuff between Cortex and Muscles,” Feb. 29, 2025.

International Regulatory Science Forum 2024, Mahidol University, Bangkok, Thailand, “Design Considerations for Digital Health Devices,” Mar. 13, 2024.

Queen’s University, Kingston, Canada, “Learning to Use Muscles,” Oct. 19, 2023.

Asia Pacific Economic Cooperation, “Essential Principles of Medical Device Safety and Performance,” Oct. 12, 2023.

Göteborg University, Sweden, “The Stuff between Cortex and Muscles,” June 5, 2023.

Caltech Medical Engineering Program, Pasadena, CA, “From Haptic Robots to Bayesian Exploration to Differential Diagnosis,” Oct. 3, 2023.

SysInt 2022, Genoa, Italy, “Self-Organizing Middleware for Haptically Enabled Robots,” Sept. 8, 2022.

Lund University, Sweden, “Self-Organizing Middleware for Haptically Enabled Robots,” Sept. 5, 2022.

National Center for Adaptive Neurotechnologies, Stratton VA Medical Center, Albany, NY, “Animals and Machines that Learn,” May 25, 2021.

INTUITIVE EU Innovative Training Network, Lund, Sweden, “Intelligent Machines that Grasp Affordance,” May 4, 2021.

Horizons Lecture, Kimberly-Clark Corporation, “Intelligent Machines that Grasp Affordance,” April 14, 2021.

Asia-Pacific Economic Coooperation, Medical Devices 2021, “Case Studies in Classification, Safety, Performance and Risk,” April 6-8, 2021.

Taiwan-U.S. Joint Medical Device Forum, Tainan, "Developing an Invasive Device," Feb. 4, 2021.
Caltech Medical Engineering Program, Pasadena, CA, "Bayesian Exploration for Intelligent Haptics and Medical Diagnosis," Oct. 8, 2020.
EuroHaptics THUMB Workshop, Leiden, Netherlands, "Haptic Intelligence," Sept. 6, 2020.
Salk Institute for Biological Studies, La Jolla, CA, "Learning to Use Muscles," Mar. 24, 2020.
USC Division of Biokinesiology and Physical Therapy, Los Angeles, CA, "Learning to Use Muscles," Feb. 28, 2020.
Caltech Medical Engineering Program, Pasadena, CA, "From Haptic Robots to Bayesian Exploration to Differential Diagnosis," Oct. 31, 2019.
Tsinghua University, Beijing, China, "Medical Device Development," Oct. 25, 2019.
6th International Autumn School on Movement Science, Humboldt-Universität zu Berlin, "Learning to Use Muscles," Oct. 7, 2019.
AI for Good, Geneva, Switzerland, "Decision support for cost-effective diagnosis and treatment by inverting Bayesian probability," May 29, 2019.
Caltech Medical Engineering Program, Pasadena, CA, "From Haptic Robots to Bayesian Exploration to Differential Diagnosis," Oct. 11, 2018.
China Pharmaceutical University, Nanjing, China, "Intellectual Property Rights," July 18, 2018.
Frequently Unasked Questions in Neuroscience, Alicante, Spain, "How do all the parts fit together?" May 21-23, 2018.
Dexterous Anthropomorphic Robot Effectors, Pittsburgh, PA, "Bio-Inspired Robotic Design," April 29-30, 2018.
Regulatory Science, University of Addis Ababa, Ethiopia, "Design Controls and Risk Analysis for Medical Devices," April 23-26, 2018.
USC Jimmy Iovine and Andre Young Academy, Los Angeles, CA, "Neural Prosthetic Technology," Mar. 26, 2018.
Winter Conference on Brain Research, Whistler, Canada, "Understanding Human Haptics by Building Robotic Systems," Jan. 17, 2018.
Shanghai FDA, China, "Challenges for Development and Clinical Trials of Electroceuticals," October 27 & 30, 2017.
Progress in Motor Control XI 2017, Miami, FL, "Optimal Isn't Good Enough," July 19-22, 2017.
IIT-Madras, India, "Neural Prosthetics – Case Studies in Regulation," April 5, 2017.
Bearg Lecture in Brain Science, Carnegie Mellon University, "Understanding Human Haptics by Building Robotic Systems," March 8, 2017
China Pharmaceutical University, Nanjing, "Using Electrons as a Locally Delivered Excitatory Neuromodulator," Nov. 24, 2016.
IEEE Humanoids 2016 Workshop on Tactile Sensing for Manipulation, Cancun, "Machine Touch for Dexterous Robotic and Prosthetic Hands," Nov. 15, 2016.
Barrels XXIX, Los Angeles, CA, "Understanding human haptics by building robotic systems," Nov. 10, 2016.
Motor Control 2016 – Bridging Motor Control and Biomechanics, Wisla, Poland, "Useful properties of spinal circuits for learning and performing sensorimotor tasks," Sept. 14, 2016.

ISEK XXI Pre-Congress Workshop, Chicago, IL, "Insight into neural mechanisms of afferent pathways learned from neural recordings, mathematical modeling and real-time neuromorphic simulations," July 5, 2016.
Biomechanics & Neural Control of Movement, Engineering Foundation Conference, Deer Creek, Ohio, "20 Years from Now," June 17, 2016.
Automotive Interiors Expo, Stuttgart, Germany, "Quantifying human touch and feel – without humans," June 1, 2016.
University of Lund, Sweden, "Representing the World in the Brain: Reverse Biomimetic Design from Haptic Robots," Sept. 7, 2015.
Rehabilitation Institute of Chicago, "Machine Touch for Dexterous Robotic and Prosthetic Hands," May 8, 2015.
Google DeepMind, London, U.K., "Representing the World in the Brain: Reverse Biomimetic Design from Haptic Robots," April 13, 2015.
National Science Foundation Workshop on Robotic Locomotion and Manipulation, Arlington, VA, "Machine Touch for Dexterous Robotic and Prosthetic Hands," April 2, 2015.
McGill University, Montreal, Canada, "Representing the World in the Brain: Reverse Biomimetic Design from Haptic Robots," Mar. 18, 2015.
Annual Sensorimotor Control Conference, University of Queensland, Brisbane, Australia, Keynote Address, "Representing the World in the Brain: Reverse Biomimetic Design from Haptic Robots," Feb. 21, 2015.
University of California at Riverside Distinguished Speaker, "Machine Touch for Dexterous Robotic and Prosthetic Hands," Oct. 29, 2014.
RoboBusiness Conference, Boston, MA, "The Future of Machine Touch," Oct. 16, 2014.
American Society of Mechanical Engineers, Los Angeles Chapter, "Machine Touch for Dexterous Robotic and Prosthetic Hands," April 17, 2014.
Aquitaine Institute for Cognitive and Integrative Neuroscience, Bordeaux, France, "Understanding Haptics by Building Computational and Physical Models," April 1, 2014.
CNRS-AIST Joint Robotics Laboratory, Montpellier, France, "Machine Touch for Dexterous Robotic and Prosthetic Hands," March 31, 2014.
University of Paris Marie Curie, "Biomimetic Strategies for Machine Touch," March 27, 2014.
L'Oreal, Paris, "Biomimetic Strategies for Machine Touch," March 26, 2014.
DARPA Sensorimotor Prosthetics Workshop, Scottsdale, AZ, "Biomimetic Strategies for Dexterity," February 13, 2014.
Chongqing Institute for Green and Intelligent Technology (CIGIT), Chongqing, China, "Biomimetic Design for Robotic Systems," Sept. 26, 2013.
Peking University, Beijing, China, "Innovative Device Development in China: An American's Perspectives," Sept. 21, 2013.
Korean Advanced Institute for Science and Technology (KAIST), Seoul, "Biomimetic Technology for Haptically Enabled Robots," Dec. 3, 2012.
Medtronic Korea, Seoul, "New Opportunities in Neural Prosthetic Technologies," Dec. 4, 2012.
Medical Scientist Training Program, University of California at Irvine, keynote speaker, "Feeding the Medical-Industrial Complex," Oct. 6, 2012.
ITRI, Taiwan, "Understanding Haptics by Evolving Mechatronic Systems," Feb. 14, 2012.

International Workshop on Bio-Inspired Systems and Prosthetic Devices (BioPro 2012), Taichung, Taiwan, “Biomimetic Tactile Sensors for Prosthetic Hands and Personal Assistive Robots,” Feb. 13, 2012.

Drexel University, Philadelphia, “Understanding Haptics by Evolving Mechatronic Systems,” June 22, 2012.

Chongqing Institute of Green and Intelligent Technology (CIGIT), Chinese Academy of Sciences, Chungqing, China, “Biomimetic Technology for Haptically Enabled Robots,” June 19, 2012.

Adept Technology, Pleasanton, CA, “Understanding Haptics by Evolving Mechatronic Systems,” Feb. 8, 2012.

3rd Military Medical School, Chongqing, China, “Clinical Applications of BION Injectable Neuromuscular Stimulators,” June 18, 2012.

West China Hospital, Chengdu, China, “Challenges and Opportunities in Neural Prosthetic Interfaces,” Nov. 30, 2011.

Suzhou Institute of Biomedical Engineering (SIBET), Chinese Academy of Sciences, Suzhou, China, “Challenges and Opportunities in Neural Prosthetic Interfaces,” Sept. 22, 2011.

Summer School on Impedance, STIFF EC Project, Frauenchiemsee, Germany, “What Roboticists Need to Know About NeuroMusculoSkeletal Systems,” July 25, 2011.

Shanghai Medical College of Fudan University, Shanghai, China, “Challenges and Opportunities in Neural Prosthetic Interfaces,” Dec. 1, 2011.

Shaanxi Qinming, Xian, China, “BION Injectable Neuromuscular Stimulators: Technology and Clinical Applications,” Sept. 23, 2011.

Multimodal & Sensorimotor Bionics Workshop, Munich, Germany, “Biomimetic Strategies for Dexterous Robots and Prosthetic Limbs,” July 27, 2011.

Life Science Park, Shanghai, China, “Regulation and Management of Medical Device Design,” Sept. 19, 2011.

IEEE-EMBS Distinguished Lecturer Event, San Fernando Valley, CA, “Biomimetic Strategies for Dexterous Robots and Prosthetic Limbs,” May 17, 2011.

HRL Laboratories, Malibu, CA, “Practical, Multi-modal Tactile Sensing,” Nov. 10, 2011.

Computational Motor Control Workshop, Beer Sheva, Israel, “Understanding Haptics by Evolving Mechatronic Systems,” June 15, 2011.

Chongqing Institute of Green and Intelligent Technology (CIGIT), Chinese Academy of Sciences, Chongqing, China, “Tactile Sensing for Dexterous Robots and Prosthetic Limbs,” Dec. 6, 2011.

Chinese Pharmaceutical University, Nanjing, China, “Regulation and Management of Medical Device Design,” Dec. 4, 2011.

Ben Gurion University, President’s Distinguished Guest, Beer Sheva, Israel, “Spinal Circuitry Makes Motor Control Easy to Do but Hard to Understand,” June 13, 2011.

University of Southern California, Los Angeles, CA, “Biomimetic Tactile Sensing for Prosthetic and Robotic Hands”,”Nov. 8, 2010.

Transformational Technologies Conference, Rancho Los Amigos National Rehabilitation Center, Downey, CA, “Multimodal Biomimetic Tactile Sensors for Prosthetic Limbs”, Sept. 2, 2010.

Telluride Neuromorphic Cognition Engineering Workshop, Telluride, CO, "Brain Machine Interfaces", June 28-30, 2010.
Neural Control of Movement Annual Conference, Naples, FL, "Biomimetic Tactile Sensors" and "Spinal-Like Regulators", April 20-25, 2010.
ISSCC 2010, San Francisco, evening session on Bionic Systems, "System design challenges in a very complex system indeed," Feb. 9, 2010.
IEEE-EMBS, Thousand Oaks, CA, "Biomimetic Strategies for Dexterous Robots and Prosthetic Limbs", Sept. 29, 2010.
EPFL, Lausanne, Switzerland, ""Biomimetic Haptics for Robots", Aug. 30, 2010.
Computational Motor Control Workshop, Beer Sheva, Israel, "Spinal-like regulator simplifies control of multiple degree-of-freedom limbs," June 16, 2010.
Caltech, Pasadena, CA, "What Does the Brain Control", Oct. 18, 2010.
Brain Machine Interfaces, Ystad Saltsjobad, Sweden, "What Does the Brain Control?", Aug. 28, 2010.
17th Joint Symposium on Neural Computation, Los Angeles, CA, "What Does the Brain Control?", May 22, 2010.
XXXIX Neurohike Meeting, Jasper, Canada, "Taking care of business," Sept. 26, 2009.
Workshop on Multi-Scale Muscle Mechanics, Woods Hole, MA, "Things that bother a mammalian neurophysiologist about muscle," Sept. 19, 2009.
Robotics Science and Systems, Workshop on Understanding the Human Hand for Advancing Robotic Manipulation, Seattle, "Robust Biomimetic Tactile Sensing and Grip Control," June 28, 2009.
NSF-CMMI Workshop on Neuromechanical Engineering, Arlington, VA, "Exploiting Neural and Muscular Trophisms for Rehabilitation," Sept. 14, 2009.
Neurosurgery Grand Rounds, USC, "Opportunities & Challenges for Prosthetic Sensorimotor Interfaces," May 4, 2009.
International Workshop on Neuromorphic Systems and Neural Prostheses, Taiwan, "Bio-Inspired Strategies for Dexterous Robots and Prosthetic Limbs," May 21, 2009.
Human Nature and Self Design, Tuebingen, Germany, "Neuroimplants and Beyond," Aug. 1, 2009.
First International Academic Conference of Acupuncture and Moxibustion Instrumentation, Shanghai, China, "The Art and Science of Neural Stimulation," Dec. 11, 2009.
University of Utah, Salt Lake City, UT, "Making the Deaf Hear and the Blind See – Some Challenges Along the Way," Nov. 10, 2008.
Korean Institute for Science and Technology, Seoul, Korea, "Prosthetic Interfaces with the Nervous System," April 25, 2008.
International Symposium on Functional Electrical Stimulation, Taipei, Taiwan, "Opportunities and Chalenges for the Use of Neuromuscular Electrical Stimulation in Rehabilitation Medicine" (keynote), "BIONic Interfaces to Reanimate Paralyzed Limbs," April 26-27, 2008.
Fourth China International Life Science Summit, Hangzhou, China, "Trends and Opportunities in Medical Devices," Sept. 22, 2008.
Erasmus University, Rotterdam, Netherlands, "Making the Deaf Hear, the Blind See and the Lame Walk," May 5, 2008.

Engineering Neuroscience & Health, USC, "The Spinal Cord Makes Sensorimotor Control Easy to Do but Difficult to Understand," Sept. 29, 2008.

DLR Inst. Robotics and Mechatronics, Wessling, Germany, "Biomimetic Interfaces for Mechatronic Limbs," May 7, 2008.

Advanced Neural Microsystems, ISCAS-2008, Seattle, WA, "General Purpose Technology for a General Purpose Nervous System," May 19, 2008.

Neurorehabilitation Grand Rounds, Rancho Los Amigos National Rehabilitation Center, Downey, CA, "BIONic Interfaces for Neuromuscular rehabilitation," Oct. 25, 2007.

IEEE International Solid-State Circuits Conference, San Francisco, CA, "BIONic Neuromuscular Interfaces," Feb. 13, 2007.

4th World Congress of the International Society of Physical and Rehabilitation Medicine, Seoul, Korea, "The Many Interfaces Required for Functional Reanimation of Limbs," June 12, 2007.

35th Annual Conference of Indian Association for Physical Medicine and Rehabilitation, Patna, India, "BION Injectable Neuromuscular Stimulators: Technology and Clinical Applications," Jan. 20, 2007.

US-China Workshop on Neural Interface Technologies, Kunming, China, "Injectable Muscle Stimulators and Sensors for Motor Function," July 9-11, 2006.

University of California at Irvine Engineering Symposium on Prosperity thru Technology, May 15, 2006.

Simon Fraser University, Vancouver, Canada, "Reanimating Limb = Technology + Neurophysiology," Sept. 25, 2006.

Second Computational Motor Control Workshop, Ben-Gurion University of the Negev, Beer-Sheva, Israel, "Biomimetic Integration of Sensorimotor Neural Prostheses", June 7, 2006.

Sate of the Science Workshop on Functional Restoration for the Stroke Survivor, "Practice", keynote speaker, La Jolla, CA, March 7, 2006.

Neural Interfaces Workshop, National Institutes of Health, Bethesda, MD, "BIONic Neuromuscular Interfaces," Aug. 21-23, 2006.

Johns Hopkins University Center for Hearing and Balance, Baltimore, MD, "Reanimating Limbs = Technology + Neurophysiology," Aug. 23, 2006.

International Symposium on Biomedical Engineering, Taipei, Taiwan, "BION Injectable Neuromuscular Interfaces to Reanimate Paralyzed Limbs" (keynote), Dec. 15, 2006

Global Digital Healthcare, Cambridge Healthtech Institute, Baltimore, MD, "Neural Prostheses: Crossing the Last Meter in Personal Telecommunications," Oct. 10-11, 2006.

Alberta Motor Control, Kananaskis, Canada, "Mathematical Models of Proprioceptors," "Prosthetic Proprioception," Sept. 23-24, 2006

University of Southern California, Los Angeles, CA, "Design and Fabrication of Disposable, Percutaneous Chemical Sensors", Jan. 31, 2005

SoCalBio Investor Conference, Los Angeles, CA, "The Sencil™: Indwelling Percutaneous Optical Fibers with Nanoengineered Chemical Sensors", Mar. 23, 2005.

Rutgers University, New Brunswick, NJ, "Biomimetic Reanimation of Paralyzed Limbs", Nov. 21, 2005.

First International Conference on Neural Interface and Control, Wuhan, China, "FES and BION™ Development", May 27, 2005.

Biotechnology Club, University of Southern California, “The Development of Medical Devices: Research, Construction and Distribution”, Mar. 30, 2005.
Design of Medical Devices Conference, University of Minnesota, Minneapolis, “Modular Injectable Interfaces with the Body”, April 13, 2005.
University of California at Santa Cruz, "Making the Deaf Hear, the Blind See and the Lame Walk", June 8, 2004.
Univ. of Indonesia, Jakarta, “Treatment of Hearing Loss: Technology Meets Economics”, Dec. 15, 2004
SoCalBio Medical Technology Showcase, Los Angeles, “Implantable Glucose Sensor”, June 16, 2004.
Rehabilitation Institute of Chicago, IL, “Making the Deaf Hear, the Blind See and the Lame Walk”, Mar. 10, 2004.
Nano and Microtechnology Symposium, California Institute for Quantitative Biomedical Research, “BIONic Reanimation of Paralyzed Limbs”, April 17, 2004
Multidisciplinary Research Colloquium in Gerontology, USC, “Making the Deaf Hear, the Blind See and the Lame Walk”, Jan. 22, 2004.
Humanoids 2004, Santa Monica, CA, “Biomimetic Sensorimotor Control for Paralyzed Patients and Robots”, Nov. 12, 2004.
Dept. Aerospace & Mechanical Engineering, University of Southern California, “Neural Prosthetic Reanimation of Paralyzed Limbs,” Sept. 29, 2004.
Cornell University, Ithaca, NY, “Neural Prosthetic Reanimation of Paralyzed Limbs”, Nov. 23, 2004.
Canadian Physiological Society, British Columbia, Canada, “Biomimetic Prosthetic Proprioception”, Jan. 28-Feb. 1, 2004.
Brandeis University, Boston, MA, “Neural Prosthetic Reanimation of Paralyzed Limbs”, Nov. 22, 2004.
Bionics and Prosthetics - 2003 Whitney Symposium, GE Global Research, Schenectady, NY, “BIONics”, Mar. 8-9, 2004.
BioNEMS Symposium, Los Angeles, CA, “Survival Strategies for Millimeter Scale Injectable Stimulators”, May 22, 2004.
Spinal Cord Conference, Keynote Speaker for Ernest Bors Symposium, Long Beach, CA, “BIONic Therapy for Paralyzed Legs”, June 5, 2004.
Strategic Partnering Opportunities Conference, Southern California Biomedical Council, “The BION Project”, March 12, 2003.
Neurology/Neurosurgery Grand Rounds, University of Southern California, “Strategies for Neuromuscular Stimulation”, Feb. 25, 2003.
Biomedical Engineering Seminar, USC, Los Angeles, CA, “Modular Injectable Interfaces with the Body – A New Direction for Medical Devices & Diagnostics?”, Sept. 16, 2003.
AARP Workshop, Los Angeles, CA, “The Emerging Reality of Neural Prosthetics”, June 16, 2003.
Spinal Cord Conference and Training, Long Beach, CA, “BIONs – History and Potential”, June 5, 2003.
Science & Technology Series, Johns Hopkins U. Center for Talented Youth, “Neural Prosthetics – Making the Deaf Hear, the Blind See, and the Lame Walk”, Nov. 16, 2003.

USC School of Pharmacy Winter Retreat, Ojai, CA, "Embedded Electronics in our Bodies, our Homes and our Lives", Jan. 19, 2002.

USC School of Engineering, 2002 Technology Equity Conference, San Diego, CA, "Alfred Mann Institute for Biomedical Engineering – An Experiment in Technology Transfer" and "BION Implants to Reanimate Paralyzed Muscles", Sept. 24, 2002.

University of Chicago, IL, "Reanimating Paralyzed Limbs – Coping with Spatially Distributed, Multimodal Systems", Oct. 23, 2002.

UCLA Biomedical Engineering Student Association, Los Angeles, CA, "BIONic Reanimation of Paralyzed Muscles and Limbs", Mar. 8, 2002

Society for Neuroscience Symposium on Computational Motor Control, Orlando, FL, "Model-Based Analysis of Sensorimotor Control Strategies", Nov. 2, 2002.

Llewellyn-Thomas Lecture, Institute of Biomaterials & Biomedical Engineering, Toronto, Canada, "Prosthetic Interfaces with the Nervous System", June 6, 2002.

Christopher Reeve Paralysis Foundation, Research Consortium Associates Meeting, Irvine, CA, "Learning From the Spinal Cord," May 18, 2002.

Catholic University of America, Washington, DC, "We Made the Deaf Hear….Now What?", October 8, 2002.

Association of Pacific Rim Universities, Los Angeles, CA, "AMI-USC: An Experiment in Biomedical Technology Transfer", May 30, 2002.

VA/NIH Prosthetics Roundtable, Bethesda, MD, "BIONic Interfaces for Rehabilitation and Repair," June 25, 2001.

University of Minnesota, Minneapolis, MN, "Neural Prosthetic Interfaces Between Electronics and Neurons: Making the Deaf Hear, the Blind See and the Lame Walk", Nov. 26, 2001.

Neurosurgical Grand Rounds, Massachusetts General Hospital, Boston, MA, "Making the Deaf Hear, the Blind See and the Lame Walk", June 21, 2001.

Neural Prosthesis Workshop, NIH, Bethesda, MD, "Clinical Experience with Microstimulators," Oct. 19, 2001.

Neural Information and Coding Workshop 2001, Big Sky, Montana, "Useful Effects from Lousy Signals: How to Build a Clinically Successful Neural Prosthesis", March 20, 2001.

MIT Leg Lab, Cambridge, MA, "BIONic Implants for Distributed Neural Prosthetic Interfaces", June 20, 2001.

Long Beach VA Medical Center and UC Irvine, CA, "BION Injectable Muscle Stimulators: Current Clinical Trials and Potential Application to Sleep Apnea", Sept. 26, 2001.

Jet Propulsion Lab, Pasadena, CA, "BIONic Implants for Distributed Neural Prosthetic Interfaces", June 28, 2001.

International Symposium on Movement and Sensation, Cairns, Australia, principal speaker, "The Importance of Biomechanics," Sept. 6, 2001.

Industrial Technology Research Institute (ITRI), Taipei, Taiwan, "The Field of Neural Prosthetics" and "BION Technology and Biomimetic Control Strategies to Reanimate Paralyzed Limbs", Dec. 17, 2001.

Hospital for Special Care, New Haven, CT, "BIONs – Injectable Electrical Stimulators for Paralyzed Muscles", June 13, 2001.
CI2001, Los Angeles, CA, "Managing Extreme Versatility – CLARION II Implant Architecture", March 3, 2001.
Cal Tech, Visual Research Lab Seminar, "Command and Control: Does our reach exceed our grasp?", Nov. 5, 2001.
Cal Tech, Pasadena, CA, Sloan Seminar, "Making the Deaf Hear, the Blind See and the Lame Walk", Nov. 5, 2001.
5th SIAM Conference on Control and its Applications, San Diego, CA, "Get Real: Biological and Neural Prosthetic Control of Muscles and Limbs", July 12, 2001.
Symposium on Spinal Cord Function and Rehabilitation, sponsored by J. Physiol. In honor of Prof. Jankowska, New Orleans, LA, "Learning *From* the Spinal Cord", 11/2000.
Rehabilitation Medicine Rounds, Veterans Administration Hospital, Los Angeles, "BIONic Implants for Therapeutic Electrical Stimulation," 3/00.
NIPS*2000 Workshop on Algorithms, Technologies and Neural Representations for Neuroprosthetics and Neurorobotics, Breckenridge, CO, "Primitives or Primitive: Forgetting Knowledge about the Spinal Cord", 12/2000.
Marquette University, Milwaukee, WI, "Bionic Man: Myth, Reality and Progress," 3/2000.
IEEE USC Student Chapter, Los Angeles, CA, "Electronic Interfaces with the Brain", 10/2000.
Engineering the Future of Medicine Symposium, A.E. Mann Institute for Biomedical Engineering, University of Southern California, "A Brief History of Neural Prosthetics," 2/2000.
7th Joint Symposium on Neural Computation, Los Angeles, CA, Keynote speaker: "Dialogs with the Nervous System," 5/2000.
1st Annual International IEEE EMBS Special Topic Conference on Microtechnology in Medicine and Biology, Lyon, France, "Design and Fabrication of Hermetic Microelectronic Implants", 10/2000.
National Institute of Mental Health, Neural Prosthetics Conference, Washington, DC, "We Made the Deaf Hear. Now What?" 8/99.
IVth International Symposium on the Head/Neck System, Tokyo, "Is the Neck a Leg?", 8/99.
Institute of Movement Science, University College London, England, "How Might the Brain Represent Muscles, Limbs and Spinal Circuits?" 3/99.
Institute of Electronic Systems, Aalborg University, Aalborg, Denmark, "Bionic Neurons for Electrical Stimulation of Paralyzed Muscles: Technology and Biology," 3/99.

Administrative

Professional Memberships:

American Institute for Medical and Biological Engineering (AIMBE)
Institute of Electrical and Electronics Engineers (IEEE, senior member)
Society for Neuroscience
Biomedical Engineering Society (BMES)
Phi Beta Kappa

Advisory Posts (previous 20 years only):

Editorial Boards: Associate Editor, *IEEE Trans. Neural Systems and Rehabilitation Engineering* (2002-4); *J. Neurophysiol.* (1987-90); *Exercise & Sports Science Reviews* (1985-1995); *Exp. Brain. Res.* (1992-2008); Honorary Editorial Board of *Applied Bionics and Biomechanics*, (2003-present), Editorial Advisory Panel, *Expert Review of Medical Devices* (2004-present); Advisory Board, *IEEE Transactions on Neural Systems & Rehabilitation Engineering* (2005-present); Editorial Board, *Open Biomedical Engineering Journal* (2007-present); Editorial Board, *Tech Briefs* (2017-present), Advisory Council, *Research Directions: Bioelectronics* (2022-present),

Frequent Referee: *Nature, J. Neuroscience, J. Neurophysiology, Exp. Brain Res., J. Physiol., IEEE-BME, IEEE-TNRE, J. Neurosci. Methods, Med. & Biol. Engng. & Comput., J. Biomech., Ann. Biomed.Engng., Muscle & Nerve, J. Neural Engng., PLoS Computational Biology, Frontiers (various)*

Ad hoc Study Section member: US NIH, US NSF, MRC Canada, NSERC Canada

Steering Committee, Consortium for Technology & Innovation in Pediatrics (CTIP)

Advisory Board, STEM Academy of Hollywood

Advisory Board, Chongqing Institute for Green and Intelligent Technology, Chinese Academy of Science

Faculty Advisor, MEDesign Club, University of Southern California

Lead Mentor, Career Advancement and Development in Rehabilitation Research (CADDRE) Program, USC Division of Biokinesiology and Physical Therapy

Academic Committees (USC only)

2022-: Health Innovation Advisory Committee, Iovine & Young Academy

2022: Joint APT/EFC Merit Review Subcommittee

2021-23; 2010-12: Appointments, Promotions & Tenure Committee, Viterbi School of Engineering

2020-24: Strategic Vision Committee, Biomedical Engineering Dept.

2020-2021: RTPC Faculty Review Committee, Biomedical Engineering Dept.

2019-2021: Engineering Faculty Council, Chairman Research Committee, Senate Alternate

2016-18, 2020: Faculty Merit Review Committee, Biomedical Engineering Dept.

2016-17: Senate Task Force on Innovation

2015-: Faculty Advisor, USC MEDesign Club and teams

2014-2021: Viterbi Research Committee

2014-2020: Neural Engineering Faculty Recruitment Committee

2014-16: Advisory Board for Body Engineering Los Angeles GK-12

2012-15: Ph.D. Admissions Committee, Biomedical Engineering; chair 2014-15

2012-13: Curriculum Committee, Neuroscience Graduate Program

2012-13: Ph.D. Admissions Committee, Neuroscience Graduate Program

2011-17: Space Utilization Committee, Biomedical Engineering Dept.

2011-12: Advisory Committee for Global Initiatives, Viterbi School of Engineering

2005-7: University Research Committee for the Academic Senate

2005-: Board of Advisors, Regulatory Science Program

2004-5: Committee on Nanotechnology, Viterbi School of Engineering

2004-10: Faculty Advisory Committee to the Distance Education Network

2004: Task Force on Restructuring of the Independent Health Professions

2004-10: USC Health Faculty Collaborative

2003-4: Provost's Strategic Planning Committee

2002-7: University Committee on Academic Review

2002-3: MS Program Review Committee, School of Engineering

2002: Internal Review Committee, Dept. of Electrical Engineering

2001-3: Board of Advisors, National Network for Technology Education and Commercialization (NSF funded)

2001-2: Research Committee for the School of Engineering

2001-2: Board of Advisors, Technology Commercialization Alliance

2000-3: Research Committee of the Academic Senate; chair 2001-3

2000-2: Appointments, Promotion and Tenure Committee for the School of Engineering

1999-2008: Steering Committee, Institute for Health in an Aging Population

Scientific Meeting Organization:

Organizing Committee, Computational Motor Control Workshop, Beer Sheva, Israel, 6/2010, 6/2011.

Workshop Organizer, Winter Conference on Brain Research, 1/1985, 1/2007.

Track Chairman, Neural Engineering Committee, Biomedical Engineering Society, 1/2007.

Track Chair, Neural Engineering, BioMedical Engineering Society Annual Meeting, 9/2007.

Track Chair, Neural Prosthetics and Rehabilitation, IEEE-EMBS, Shanghai, 9/2005.

Organizer, Symposium Series “Engineering the Future of Medicine”, A.E. Mann Institute:

- “Can we make the blind see?” Feb., 19, 2000
- “Putting the brain in command” July 8, 2000
- “Breaching barriers to drug entry” Mar. 31, 2001
- “Electric power in vivo” Feb. 28, 2004

Program Committee, 1st Annual International IEEE EMBS Special Topic Conference on Microtechnology in Medicine and Biology, Lyon, France, 10/2000.

Meeting Organizer, “Musculoskeletal Modeling Workshop”, sponsored by A.E. Mann Institute for Biomedical Engineering, Morro Bay, CA, 8/2000

Session Organizer, NCM2000 Satellite on Computational Models, Key West, FL, 4/2000.

Organizing Committee, Conference for Research in Action and Perception, Kingston, ON, 6/98.

Program Committee, Neural Prostheses - Motor Systems V Conference, Burnaby, BC, 8/97.

Focus Group Leader, 1997 Conference on Implantable Auditory Prostheses, Pacific Grove, Ca, 8/97.

Scientific Panel Organizer, Neural Control of Movement Meeting, Cancun, Mexico, 4/97.

Program Committee, Engineering Foundation Conference on Biomechanics & Neural Control of Movement IX, Deer Creek, Ohio, 6/96.

Panel Organizer, "Linking Neural Control to Movement: Insights from Biomechanics," Neural Control of Movement, Marco Island, Florida, 4/93.

Scientific Committee, North Sea Conference - Biomedical Engineering 90, Antwerp, Belgium.

Cochairman, Engineering Foundation Conference on Biomechanics & Control, Henniker, NH, 7/87.

Panel Organizer, "Neural Prosthetic Electrode Arrays: The Perennial Promise of Microelectronics," Materials Research Society, 12/85.

Panel Organizer, 16th Annual Neural Prosthesis Workshop, NINCDS, 11/85.

Steering Committee, Engineering Foundation Conference on Neural Prostheses, Henniker, NH, 8/85.

Steering Committee, Engineering Foundation Conference on Biomechanics & Neural Control of Movement, Henniker, NH, 7/85.

Teaching

Program Development:

Founding Director, USC Master of Science in Medical Device and Diagnostic Engineering (2000-2010, 2023-present)

Founding Director, USC BME Innovation Space (2023-present)

Post-doctoral Fellowship Supervision and Funding Source:

K.E. Aktogan (2011- 2012), Government of Turkey
Yao Li (2010- 2013), DARPA
V.J. Santos (2007- 2008), AMI-USC
N. Rodriguez (2005-2007), AMI-USC
A. Inmann (2002-2003), AMI-USC
R. Davoodi (1999-2001), AMI-USC
Wan Jiang (1997-98), MRC Canada Grant
H. Ruddy (1991-1993), Network of Centres of Excellence/NIH Program-Project Grant
R.P. Young (1990-1992), NIH Grant
J. Weytjens (1986-1988), Fulbright Scholar
C.J. Heckman (1986-1988), PHS NRSA
J. Blaszczyk (1985-1987), Fogarty International Fellowship
S.J. Duenas (1984-86), Fogarty International Fellowship
S. Spector (1984-86), PHS NRSA
C.A. Pratt (1979-80), PHS NRSA
J. Duysens (1977-78), Fogarty International Fellowship

Ph.D. Thesis Adviser:

X. Huang (2017), Dept. of Biomedical Engineering, USC
L. Zhou (2016), Dept. of Biomedical Engineering, USC
A. Nicholson-Vest (2015), Dept. of Biomedical Engineering, USC
G. A. Tsianos (2012), Dept. of Biomedical Engineering, USC
J. A. Fishel (2012), Dept. of Biomedical Engineering, USC
N.A. Wettels (2011), Dept. of Biomedical Engineering, USC
M. Hauschild (2010), Dept. of Biomedical Engineering, USC
R. Kaliki (2009), Dept. of Biomedical Engineering, USC
G. Raphael (2009), Dept. of Biomedical Engineering, USC
Dan Song (2008) Dept. of Biomedical Engineering, USC
H. M. Kaplan (2008), Dept. of Biomedical Engineering, USC
K.C. Liao (2006) Dept. of Biomedical Engineering, USC

W. Tan (2006), Dept. of Biomedical Engineering, USC
M. P. Mileusnic (2005), Dept. of Biomedical Engineering, USC
A.C. Dupont (2001), Dept. Physiology, Queen's Univ.
I.E. Brown (1998), Dept. Physiology, Queen's Univ.
T. Cameron (1996), Dept. Physiology, Queen's Univ.
S.H. Scott (1993), Dept. Physiology, Queen's Univ.
A.J. Rindos (1988), Dept. Elect. Engineering, Univ. Maryland
C.M. Chanaud (1988), Dept. Zoology, Univ. Maryland

M.Sc. Thesis Adviser:

J.E. Arguelles-Morales (2013), Dept. of Biomedical Engineering, USC
M. Lai-Chuck-Choo (2012), Dept. of Biomedical Engineering, USC
Zhe Su (2012), Dept. of Biomedical Engineering, USC
C.S. Lin (2011), Dept. of Biomedical Engineering, USC
J. Goodner (2011), Dept. of Biomedical Engineering, USC
N. Sachs (2006), Dept. of Biomedical Engineering, USC
H.C. Fornwalt (2005), Dept. of Biomedical Engineering, USC
M. Rodriguez (2005), Dept. of Biomedical Engineering, USC
D. M. Kleiman (2003), Dept. of Biomedical Engineering, USC
J. Singh (2002), Dept. of Biomedical Engineering, USC
E. Cheng (1999), Dept. Physiology, Queen's Univ.
I.E. Brown (1995), Dept. Physiology, Queen's Univ.
C. Engstrom (1990), Dept. of Anatomy, Queen's Univ.
A.J. Rindos (1982), Dept. Zoology, Univ. Maryland

Doctoral Thesis Committees:

Nikolas Barrera (in progress) Alfred Mann Dept. of Biomedical Engineering, USC
Brianna Thielen (in progress) Alfred Mann Dept. of Biomedical Engineering, USC
Colleen Watson (2024) Doctoral Program in Regulatory Science, USC
Romina Mir (in progress) Alfred Mann Dept. of Biomedical Engineering, USC
Jaehoon Lee (in progress) Ming Hsieh Dept. of Electrical Engineering, USC
Ravinder Singh (in progress) Neuroscience Graduate Program
Yannick Darmon (2023) Dept. of Biokinesiology, USC
Suraj Chakravarthi Raja (in progress) Dept. of Electrical Engineering - Systems, USC
Rechu Divakar (external assessor, 2024) Human Movement & Nutrition Sci., U. Queensland, Australia
Samuele Contemori (external assessor, 2023) Human Movement & Nutrition Sci., U. Queensland, Australia
Andres Camarena (chair; 2023) Neuroscience Graduate Program, USC
Andrew Petersen (in progress) Dept. of Biomedical Engineering, USC
Amanda Rios (2023) Neuroscience Graduate Program, USC

Susan Bissmeyer (2022), Dept. of Biomedical Engineering, USC
Ali Marjaninejad (2020) Dept. of Biomedical Engineering, USC
Akira Nagamori (2020) Dept. of Biomedical Engineering, USC
Daniel Hagen (2020), Dept. of Biomedical Engineering, USC
Ahuva Weltman (2019), Dept. of Biomedical Engineering, USC
John Hartigan (2017), Doctoral Program in Regulatory Science, USC
Darin Oppenheimer (2017), Doctoral Program in Regulatory Science, USC
Anton Spanne (external reviewer, 2015), University of Lund, Sweden
Shanie Liyanagamage (2016), Dept. of Biomedical Engineering, USC
Zhe Su (2019), Dept. of Biomedical Engineering, USC
Emily Lawrence (2017), Dept. of Biomedical Engineering, USC
Joseph Crew (2016), Dept. of Biomedical Engineering, USC
Alexander Reyes (2015), Dept. of Biomedical Engineering, USC
Cesar Medina (2015), Doctoral Program in Regulatory Science, USC
Kobby Dankwah (2015), Doctoral Program in Regulatory Science, USC
Taranjit Singh (2012), Doctoral Program in Regulatory Science, USC
Tony Chan (2012), Doctoral Program in Regulatory Science, USC
Susan Bains (2012), Doctoral Program in Regulatory Science, USC
Duane Mauzey (2012), Doctoral Program in Regulatory Science, USC
Bardia Fallah Behabadi (2012), Dept. of Biomedical Engineering, USC
Arthi Srinivasan (2012), Dept. of Biomedical Engineering, USC
Navya Davuluri (2011), Dept. of Biomedical Engineering, USC
Michael Jamieson (2011), Doctoral Program in Regulatory Science, USC
Monika Jadi (2010), Dept. of Biomedical Engineering, USC
Alan Horsager (2009), Dept. of Biomedical Engineering, USC
N. Sachs (2007), Dept. of Biomedical Engineering, USC
Joe Fu-Jiou Lo, Ph.D. (2007), Dept. of Biomedical Engineering, USC
J Henry Lin (2007), Dept. of Pathology, USC
J. Y. Hwang (2006), Dept. of Biomedical Engineering, USC
Eric Ortega, Ph.D. (2006), Dept. of Biomedical Engineering, USC
Chunhong Zhou, Ph.D. (2005), Dept. of Biomedical Engineering, USC
Juji Harimoto, Ph.D. (2003), Dept. of Biomedical Engineering, USC
Javier Jo, Ph.D.(2003), Dept. of Biomedical Engineering, USC
Deniz Baskent, Ph.D. (2003), Dept. of Biomedical Engineering, USC

Course Development:

Physiological Instrumentation, PHGY 484/884, Queen's Univ.
Applied Electrophysiology, seminar and laboratory, BME 620L, USC
Development and Regulation of Medical Products, BME 415/416L, USC
Advanced Overview of Neuroscience (core course, organizer for Sensorimotor System) NEUR 525, USC

Guest Lecturer, USC courses:

BME 201 Biomedical Engineering Practice
BME 414 Rehabilitation Engineering
BME 501 Advanced Topics in Biomedical Systems
BME 504 Neuromuscular Systems
BAEP 551 Introduction to New Ventures
RSCI 601 Biomedical Commerce
RSCI 604 Regulation in Asia
RSCI 605 Management of Human Resources
RSCI 608 Regulation in Europe and the Americas
RXRS 416 Medical Products: From Idea to Market
MPTX 511 Introduction to Medical Product Regulation
MPTX 515 Quality Systems and Standards
NEUR 532 Systems and Behavioral Neurobiology
NEUR 524 Advanced Overview of Neuroscience

Special Course Faculty:

Quality Systems for Medical Products, Addis Ababa University, Ethiopia, 2017

National Center for Adaptive Neurotechnologies, Summer Course, Albany, NY, 2016, 2017, 2019

Workshop on Neuromorphic Engineering, Telluride, CO, 2010.

UCLA Dept. of Biomedical Engineering, BME260 Neuroengineering, guest lecturer 2000-2002

USC School of Pharmacy Short Course, Clearing Roadblocks in the New-Product Path, 2000.

Queen's University, PHGY 801 - Beyond Academia: Using Biomedical Science in Business and Government, 1996 - 1999.

Advanced Bionics Corp., Continuing Education in Medical Devices, 1994 - 1999.

Cold Spring Harbor Course on Computational Neurobiology, 1985, 1986, and 1988.

<u>Research Support</u>
Current External Grants and Contracts (academic only):
5P50FD004896-03 Espinoza (Director), Loeb (Steering Committee) 09/16/2018-09/15/2023
US Food & Drug Administration
Southern California Center for Technology and Innovation in Pediatrics (CTIP)
The goal is to facilitate the development, production and distribution of pediatric medical devices by identifying companies working in the space and providing advice, networking, and direct and indirect financial support on the road to commercialization.

Minimally Invasive Micropacemakers Bar-Cohen (PI), Loeb (coPI) 09/01/2020-12/31/2023
Children's Hospital of Los Angeles
Development and preclinical animal testing of a cardiac pacemaker suitable for small pediatric patients and others for whom a conventional endovascular pacemaker is contra-indicated.

Subcortical Control of Human Reaching Carroll (PI), Loeb (coPI) 01/01/2024-12/31/2028
DP240101968, Discovery Project, Australian Research Council
Experiments in human subjects to identify circuits and mechanisms for control of rapid arm movements.

<u>Recently Completed Grants and Contracts (academic only):</u>
Tectal Circuits Involved in Rapid Reaching Behavior Carroll (PI), Loeb (coPI) 01/01/2017-12/31/2021
DP170101500, Australian Research Council
Experiments in normal human subjects to identify circuits and mechanisms for control of rapid arm movements
Predictive Haptic Coding Devices in Next Generation Interfaces Jorntell (PI), Loeb (coPI)
#829186, EU H2020 FETOpen project 1/1/2019-12/31/2021
Experiments on and models of somatosensory neural signal processing
DP170101500 Carroll (PI), Loeb (co-PI) 01/01/2017-12/31/2019
Australian Research Council Discovery Projects
A Common Sub-Cortical System for Human Eye and Limb Control
Multi-investigator project to test hypotheses regarding the role of the midbrain tectum in control of rapid reaching and gaze shifts to targets in extrapersonal space.
R01 AR-052345 Valero-Cuevas (PI), Loeb (Co-PI) 2014-2018
Structure and Function of the Fingers' Tendinous Apparatus
Creates neuromorphic circuitry to replicate the function of the spinal cord controlling afferented muscles that produce finger function.
5P50FD004896-02 Bar-Cohen (PI), Loeb (co-PI) 09/16/2013-08/31/2018
US Food & Drug Administration
Pediatric Medical Device Consortium

The goal is the creation of a multi-disciplinary network at USC, CHLA and other academic medical centers and businesses to foster development of promising new medical devices specifically for pediatric applications.

Development of an Epicardial Micropacemaker Bar-Cohen (PI), Loeb (co-PI) 09/01/2016-06/30/2018
L.K. Whittier Foundation
Translational Research Project
Supports development and preclinical testing of a novel cardiac pacemaker and minimally invasive implantation system suitable for infants and others who are not candidates for conventional endovascular pacemaker leads.

1 R01 HD075135-01 Bar-Cohen (PI), Loeb (co-PI) 12/01/2012 – 11/30/2017
National Institutes of Health
Preclinical Development of a Fetal Micropacemaker

Funds the design, fabrication and chronic animal studies of a minimally invasive cardiac pacemaker that can be injected into the chest of a fetus in utero to treat complete heart block with hydrops fetalis.
Development of a Common Platform for Unifying Humanoids Research
This grant fund the development of anthropomorphic robots and their controllers for a consortium of US labs; my group is development the tactile sensors and reflex control loops.

Contract Administration:
Project Officer, #N01-NS-7-2366, Stanford Univ., Development of a Multichannel Electrode for an Auditory Prosthesis, 1976-79.

Project Officer, #N01-NS-7-2364, University of California at San Francisco, Development of a Multichannel Electrode for an Auditory Prosthesis, 1976-79

Project Officer, #N01-NS-3-2348, Univ. of Maryland, Kinesiological Modeling of the Cat Hindlimb, 1982-1986 and #N01-NS-6-Z300, 1986-89.

Principal Investigator, NIH Contracts #N01-NS-9-2327, #N01-NS-2-2322, #N01-NS-5-2325 to A.E. Mann Foundation, Micro-stimulator for Functional Neuromuscular Stimulation, 1989-98.

Consulting (partial listing)
Fish & Richardson P.C. (2025-present)
IntuiCell AB, Lund, Sweden, Advisory Board, (2022-present)
Nalu Medical Inc., Carlsbad, CA (2021-2022)
Urovant Sciences Inc., Irvine, CA (2020)
Neuromuscular Dynamics, LLC, Glendale, CA, Advisory Board (2019-present)
ANA Avatar XPRIZE, Advisory Board (2018-2023)
General Stim Inc., Los Angeles and Hangzhou, China (2014-2022)
MicroNuronix, Los Angeles and Hangzhou, China (2012-2014)
Sheppard Mullin Richter & Hampton LLP (2012-2016)
Nurotron, Hangzhou, China (2011-2013)
Purdue University (2011-2013)
Rehabilitation Institute of Chicago (2010-2013)
Setpoint Medical, Boston, MA (2009-2012)
Kardium Corp., Vancouver, Canada (2006-2008)
Connolly Bove Lodge & Hutz LLP, Los Angeles (2008-2012)
Shanghai Medical Cochlear Corp., Shanghai, China (2007- 2010)
Victhom Human Bionics, Saint-Augustin-de-Desmaures, Canada (2008-2010)
Bioness Inc., Valencia, CA (2006-2008)
Advanced Neuromodulation Systems, Plano, Texas (2001)
Advanced Bionics Corp., Sylmar, California (1993-1999)
A.E. Mann Foundation, Sylmar, California (1987-1999)
PI Medical, Portland, Oregon (1992-1996)
Advanced Surface Technology, Billerica, Massachusetts (1991-1993)
Trovan Ltd., Luxembourg (1988-1992)
Jet Process Corp., New Haven, Connecticut (1991-1992)
Biophor Corp., Billerica, Massachusetts (1991-1992)
Mentor Technologies, Inc., Rockville, Maryland (1987-1990)
Ionic Atlanta, Atlanta, Georgia (1988-1990)
Abiomed Inc., Danvers, Massachusetts (1989-1990)
Taymar Inc., Westminster, Colorado (1987-1988)

Travenol Laboratories, Deerfield, Illinois (1986-1987)
Microprobes for Life Science, Clarksburg, Maryland (1984-1987)
University of California, Dept. of Urology, San Francisco, California (1984-1986)
Intermedics, Freeport, Texas (1985-1986)
Identification Devices, Inc., Boulder, Colorado (1985-1986)
Gentronix, Inc., Rockville, Maryland (1984-1986)
Collier's Encyclopedia, Macmillan Publishers, New York (1986)
BTS, Inc., Greenbelt, Maryland (1985-1986)
Storz Instrument Company, St. Louis, Missouri (1983-1985)
Biostim, Inc., Princeton, New Jersey (1983-1985)
Bak Electronics, Inc., Rockville, Maryland (1979-1984)
Parco Scientific Company, Vienna, Ohio (1981-1983)

AUTOBIOGRAPHICAL SKETCH

I received both my bachelors and medical degrees from The Johns Hopkins University through their accelerated/combined program 1965-1972. While an undergraduate and medical student, I worked on several projects involving microelectronic fabrication of electrode arrays for neurophysiological research and neural prosthetics, including service as principal investigator on a biomaterials development contract from NIH to Johns Hopkins and as a guest researcher at the University of Utah Artificial Eye Project. I trained for one year as a resident in the Department of Surgery, University of Arizona, and I am a licensed physician in the State of California.

From 1973 to 1987, I was a medical officer and Section Chief in the USPHS in the Laboratory of Neural Control, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland. In 1983, I received the Commendation Medal of the U.S. Public Health Service. I was responsible for planning and conducting a wide range of studies concerning the sensorimotor control of locomotion, electrophysiological studies of peripheral nerve conduction, and development of novel research techniques for neurokinesiological studies. In particular, my research group developed a variety of implantable electrodes and transducers that permit detailed study of single neuron and whole muscle activity during natural behavior in intact animals. I directed a collaborative project with the University of Maryland to develop a comprehensive musculoskeletal model of the cat hindlimb.

In addition to pursuing basic research, I have been involved in a variety of biomedical engineering projects in various capacities, including a guest appointment at University of California at San Francisco, adjunct associate professor at University of Utah, and president of Biomed Concepts, Inc., a consulting and prototype development business with several current projects (www.BiomedConceptsGroup.com). During the period 1979-1981, I commuted regularly to UCSF, where I was responsible for recruiting and leading the engineering team that developed the forerunner of the CLARION® cochlear implant, which now provides functional speech perception for hundreds of thousands of profoundly deaf patients. From 1988-1998 I led an inter-institutional team (Queen's University, Mann Foundation, and Illinois Institute of Technology) that developed a new class of implantable electronic devices (BION®) for a wide range of applications involving therapeutic and functional electrical stimulation of weak and paralyzed muscles. I led a joint venture with a Chinese company to commercialize a new version of this technology to treat urinary stress incontinence. From 1994-1999 I was Chief Scientist for Advanced Bionics Corp. (Sylmar, California), working on commercialization and further development of the CLARION and BION systems. In 2008, my students and I formed SynTouch Inc., which developed and sold BioTac® biomimetic tactile sensors and haptic instrumentation (www.SynTouchInc.com) and was designated a Technology Pioneer by the World Economic Forum.

I have authored or coauthored over 400 publications (excluding abstracts), including a book on electromyography (in press since 1986), 65 full-length physiological research reports in refereed journals and 123 full-length biomedical engineering papers in refereed journals. I have served on the editorial boards of 8 journals and regularly referee for several others. I hold 79 issued US patents (others pending) and I am a Fellow of the National Academy of Inventors.

My research strategy is to understand how the nervous system solves problems in sensorimotor control and perception so that we can apply biomimetic strategies to the design of robotic and prosthetic systems. My students and I strive to combine the basic research, clinical medicine, applied engineering and industrial relations that are required for such "high-tech" endeavors to succeed.