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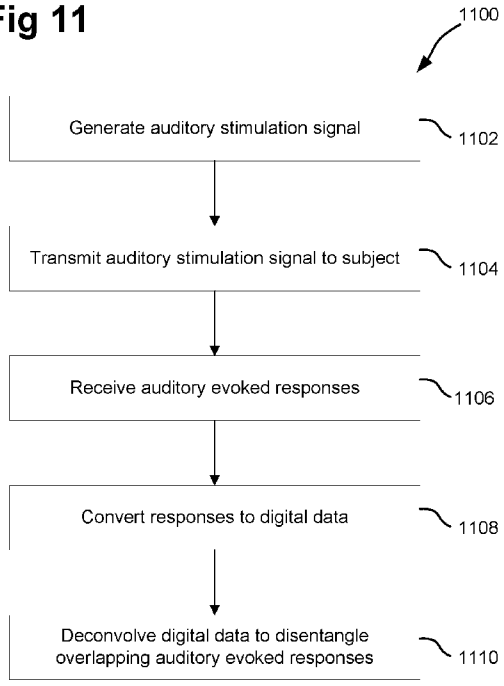
Fig 11



(57) Abstract: System and method for for obtaining auditory evoked potentials from apical portions of the cochlea are described. The system comprises: a computing device configured to: generate an auditory stimulation signal having a characteristic frequency (cf) in the frequency range of the apical region, the auditory stimulation signal comprising a one-period sinusoidal signal having a duration in the region of 1/cf seconds, transmit the generated auditory stimulation signal at an average rate of cf to an audio output device in communication with a subject; receive overlapping auditory evoked responses from one or more electrodes connected to the subject, the auditory evoked responses generated by the subject in response to the auditory stimulation signal; deconvolve the received overlapping auditory evoked responses to create a disentangled record of the responses.

[Continued on next page]

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SYSTEMS AND METHODS FOR OBTAINING AUDITORY EVOKED POTENTIALS

TECHNICAL FIELD

[0001] Aspects of the present disclosure are directed to techniques for obtaining auditory evoked potentials and more particularly to systems and methods for obtaining auditory evoked potentials from apical portions of the cochlea.

BACKGROUND

[0002] The developments described in this section are known to the inventors. However, unless otherwise indicated, it should not be assumed that any of the developments described in this section qualify as prior art merely by virtue of their inclusion in this section, or that those developments are known to a person of ordinary skill in the art.

[0003] A human ear has three parts: the outer ear, the middle ear, and the inner ear – each with a dedicated function. The outer ear consists of the ear shell (pinna) and the auditory canal. Its function is to guide air pressure waves to the middle ear – with the ear shell increasing the sensitivity of the ear to the front side of the head, supporting front/rear localisation of audio signals. The middle ear consists of the eardrum (tympanic membrane), attached to the inner ear through a delicate bone structure (malleus, incus and stapes). The middle ear acts as an impedance-matching device that improves sound transmission, reduces the amount of reflected sound and protects the inner ear from excessive sound pressure levels. The inner ear consists of the cochlea - a rolled-up tube having a base and an apex. The middle ear's stapes connect to the base of the cochlea.

[0004] When the cochlea is unrolled and stretched, it resembles a thin tube with three cavities – scala vestibuli and scala timpani (filled with perilymph fluid), and scala media (filled with endolymph fluid). The cavities are separated by two membranes – the Reissner's membrane and the basilar membrane.

[0005] The basilar membrane is populated with thousands of hair cells and is dedicated to hearing. The membrane is typically thin and stiff at the base of the cochlea, and wide and sloppy at the apex and performs a crucial auditory function. Incoming pressure waves - delivered to the cochlear fluid by the stapes - cause displacement of the basilar membrane leading to a traveling wave, which presents a maximum deflection at the base of the cochlea (for high-frequency sounds, tuned up to 20 kHz) or at the apex (for low-frequency sounds,

tuned up to 20 Hz). The basilar membrane deflection activates the hair cells, thus acting as a filterbank.

[0006] The hair cells are divided in rows of inner hair cells and outer hair cells. The inner hair cells pick up any vibrations on the membrane (like a microphone) and the outer hair cells feed mechanical energy back to the membrane in order to improve the frequency specificity of the cochlear filters, actively increasing the system's sensitivity by up to 60dB(*4C).

[0007] The hair cells in turn are connected to the brainstem with a nerve string containing sensory neurons (auditory nerve fibers) that transport information from the hair cells to the brainstem and motor neurons that transport information from the brainstem back to the hair cells.

[0008] Fig. 1 illustrates a typical human auditory system 100. This figure highlights an unrolled cochlea 102, auditory nerve fibers 104, and the brainstem 101. The main neural stations of the brainstem 101 are cochlear nucleus 106, superior olivary complex 108, lateral lemniscus 110, and inferior colliculus 112.

[0009] The cochlear nucleus 106 is the first site of neuronal processing of the signals received from the inner ear. The superior olivary complex 108 receives projections predominantly from the cochlear nucleus and detects interaural level differences and interaural time differences. The lateral lemniscus 110 is a tract of axons in the brainstem that carries information about sound from the cochlear nucleus 106 to various brainstem nuclei and ultimately to the midbrain. The inferior colliculi 112 are located just below the visual processing centers and act to integrate information (specifically regarding sound source localization from the superior olivary complex and cochlear nucleus before sending it to the cortex).

[0010] When auditory stimuli are applied, the response of the neurons of the human auditory system 100 can be recorded with surface electrodes placed on the subject's scalp. Since the amplitude of the neural response is very small at the electrodes and this signal is highly contaminated by many sources of noise (electromagnetic, electric, and myogenic), it is a common practice to present the same stimulus (usually a click) several times and average the neural response obtained at the electrodes, thus obtaining a response commonly referred to as auditory evoked potentials (AEPs).

[0011] AEPs are a number of voltage peaks that represent the synchronous activation of the neurons in specific stages of the auditory pathway. AEPs elicited in the cochlea and the

brainstem are known as auditory brainstem responses (ABRs).

[0012] ABRs typically show up to seven peaks within the first 10 ms from stimulus onset. Fig. 2 illustrates a typical ABR 200 including multiple peaks. The most robust components of the ABR are waves I (generated by the cochlea), III (generated by the superior olivary complex) and V (generated in the upper midbrain), as well as the trough following wave V shown in Fig. 2.

[0013] In order to avoid overlapping of ABRs, conventional methods of stimulation apply stimuli periodically at a slow fixed rate (typically lower than 100 stimulations/sec).

[0014] In addition to clicks (which are not frequency-specific), ABRs can also be recorded with some frequency specificity using tone-bursts. Tone-bursts consist of a number of cycles of a sinusoidal signal of a certain characteristic frequency (cf), usually windowed within a specific window.

[0015] Because of the non-invasive nature of the recording process, ABRs are often used as a clinical tool to assess hearing thresholds at different frequencies.

[0016] The inventors have recognized that although tone-bursts are efficient to evoke ABRs at high characteristic frequencies. The recording of ABRs from portions of the cochlea close to the apex 114 (sensitive to low frequency sounds) is a challenge with current electrophysiological approaches. This is because the slowing travel time of the basilar membrane at apical regions (i.e., regions close to the apex of the cochlea), and the long 'ring' time of low-frequency auditory filters leads to reduced neural synchronization and, consequently, smaller evoked brainstem potentials than at more basal regions (i.e., regions sensitive to higher frequency sounds).

SUMMARY

[0017] According to an aspect of the present invention, there is provided method for obtaining auditory evoked potentials from an apical region of the cochlea, the method comprising: generating a stimulus comprising a one-period sinusoidal signal having a characteristic frequency (c_f) in the frequency range of the apical region, and a duration of $1/c_f$ seconds, presenting a plurality of the stimuli as a stimulation signal at an average rate of c_f, stimuli per second; transmitting the auditory stimulation signal to an audio output device in communication with a subject; receiving overlapping auditory evoked responses from one or more electrodes connected to the subject, the auditory evoked responses generated by the subject in response to the auditory stimulation signal; and deconvolving the received

overlapping auditory evoked responses to create a disentangled record of the response.

[0018] According to a second aspect of the present invention, a series of stimuli for inducing resonance in a specific portion of the basilar membrane that is sensitive to a particular characteristic frequency c_f is provided. Each stimulus comprises a one-period sinusoidal signal with frequency equal to the particular characteristic frequency c_f in the frequency range of apical region, windowed using a window of the same duration. These stimuli are presented with an average rate equal to c_f using randomized inter-stimulus intervals (ISI) with an ISI dispersion between 20% to 80% of the stimulus duration.

[0019] According to a third aspect of the present invention, a system for obtaining auditory evoked potentials from apical portions of the cochlea is provided. The system comprising: a computing device configured to: generate an auditory stimulation signal having a characteristic frequency (c_f) in the frequency range of the apical region, the auditory stimulation signal comprising a plurality of one-period sinusoidal signals, each having a duration in the region of $1/c_f$ seconds, transmit the generated auditory stimulation signal to an audio output device in communication with a subject; receive overlapping auditory evoked responses from one or more electrodes connected to the subject, the auditory evoked responses generated by the subject in response to the auditory stimulation signal from the auditory output device; deconvolve the received overlapping auditory evoked responses to create a disentangled record of the responses.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] In the drawings:

[0021] Fig. 1 illustrates a typical human auditory system, highlighting the unrolled cochlea, auditory nerve fibers and main neural stations of the brainstem.

[0022] Fig. 2 illustrates a typical auditory brainstem response (ABR) signal.

[0023] Fig. 3 is a plot of basilar membrane displacement to a conventional auditory stimulus (a click) presented at a conventional low stimulus rate.

[0024] Fig. 4 shows an example of a stimulus and a windowing function for a characteristic frequency of 500 Hz.

[0025] Fig. 5 is a plot illustrating a stimulus according to the present disclosure and the corresponding basilar membrane response.

[0026] Fig. 6 is a plot illustrating an auditory stimulation signal according to aspects of

the present disclosure and the corresponding basilar membrane response.

[0027] Fig. 7 is a plot illustrating overlapping ABRs to multiple stimuli presented with a fixed stimulus rate, leading to a steady-state response at the electrodes, from which it is not possible to deconvolve and obtain the transient ABR.

[0028] Fig. 8 illustrates an example of ISI dispersion of a randomized stimulation sequence in which the ISI is varied randomly according to a uniform distribution between 1.8 and 2.2 ms, thus with a jitter of 0.4 ms.

[0029] Fig. 9 is a plot illustrating overlapping ABRs to multiple stimuli presented with a randomized stimulus rate, leading to a quasi-steady state signal at electrodes, from which it is possible to deconvolve and obtain the transient ABR.

[0030] Fig. 10 is an exemplary system for recording ABRs generated by the apical region of a subject's cochlea.

[0031] Fig. 11 is a flowchart illustrating an exemplary method for recording auditory evoked responses generated by the apical region of a subject's cochlea.

[0032] While the invention is amenable to various modifications and alternative forms, specific embodiments are shown by way of example in the drawings and are described in detail. It should be understood, however, that the drawings and detailed description are not intended to limit the invention to the particular form disclosed. The intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the present invention as defined by the appended claims.

DETAILED DESCRIPTION

[0033] In the following description, for the purposes of explanation, numerous specific details are set forth in order to provide a thorough understanding of the present invention. It will be apparent, however, that the present invention may be practiced without these specific details. In some instances, well-known structures and devices are shown in block diagram form in order to avoid unnecessary obscuring.

[0034] As described previously, it is difficult to evoke large enough ABRs from the apical portion of the cochlea. Fig. 3 illustrates a plot of the basilar membrane displacement 302 from the apical portion when conventional stimulation 304 (i.e., clicks) having a rate of less than 100 stimulations/sec is applied. As seen in Fig. 3, the stimulus 304 evokes the portions of the cochlea sensitive to low frequencies, but the deflection magnitude of the response 302 is small and the frequency specificity is low as a broad range of frequencies are

activated by this stimulus.

[0035] To address one or more of these issues, aspects of the present disclosure provide novel systems and methods for recording auditory evoked potentials elicited by neurons located at apical portions of the cochlea. In particular, the disclosed systems and methods evoke brainstem responses from the apical portion by generating resonance in the basilar membrane using short duration stimuli presented at faster rates than conventionally used. To some extent, this takes advantage of the resonant property of cochlear filters to maximize the brainstem neural response to low-frequency sounds.

[0036] The disclosed systems and methods can be used to objectively estimate hearing threshold to low-frequency sounds, which is of interest when evaluating subjects unable to provide a reliable behavioral feedback, e.g., newborns, young children or adults with dementia.

[0037] Further, as compared to conventional techniques that utilize tone bursts or clicks, the disclosed systems and methods are able to provide a more synchronized neural response from apical portions of the cochlea, thus evoking a larger-magnitude ABR which facilitates detection of neural response activation at different stages of the auditory pathway in response to low-frequency sounds.

Method overview

[0038] One issue with using conventional short duration stimuli, or clicks, that present most of their energy in high frequency bands, is that the contribution from apical portions of the cochlea (which are sensitive to low frequency sounds) is minimal. Another issue is that the traveling wave is faster in the basal portions and slows down in the apical portion, which causes any response from the apical portions to be out of synchronization with the stimulus.

[0039] To address these issues, the presently disclosed systems and methods evoke enhanced brainstem responses to low-frequency sound of a specific characteristic frequency by inducing basilar membrane resonance in the cochlea region sensitive to this characteristic frequency. To do this, the disclosed systems and methods utilize an optimized stimulus and stimulation strategy.

[0040] The stimulus consist of one period of a sinusoidal signal having a characteristic frequency in the frequency range of the apical portion of the cochlea (i.e., 10–1000Hz), windowed with a specific window function of the same duration. A non-limiting example of the windowing filter can be a Blackman window. The duration of the stimuli is inversely

proportional to the characteristic frequency – e.g., for a characteristic frequency of 500 Hz, the stimulus duration is $1/c_f$, i.e., 2 ms.

[0041] Fig. 4 shows an example of the stimulus (in solid lines) 402 and the Blackman window (in broken lines) 404 for a c_f equal to 500 Hz.

[0042] When such a stimulus is used (instead of clicks) using conventional presentation rates, the contribution from high frequency portions (basal portions) is minimal, but a large range of frequencies in the apical portion of the cochlea are activated.

[0043] Fig. 5 is a plot 500 illustrating the stimulus 502 and the corresponding basilar membrane response 504. As seen in this figure, although there are no deflections in the high frequency range, the response 504 evoked in the lower frequency range is spread over a large range of frequencies and the deflections of the response are minimal. This is because the stimulation paradigm is not yet optimized.

[0044] To increase the frequency specificity of the response and its magnitude, inventors of the presently disclosed systems and methods have discovered that presenting the defined stimulus in phase with the inherent fluctuations of the basilar membrane, induces resonance, which in turn can aid in increasing the frequency specificity and magnitude of the response. It is found that by presenting the stimulus at an average rate of c_f stimulations/sec basilar membrane resonance can be induced at a portion of the cochlea sensitive to the c_f. For example, a rate of 500 stimulations/sec may be used to induce a basilar membrane resonance at a portion of the cochlea sensitive to 500 Hz. Accordingly, for a stimulus signal having a characteristic frequency of 500 Hz, a stimulus presented every 2 ms generates a resonance in the basilar membrane portion sensitive to 500 Hz sounds.

[0045] Fig. 6 illustrates a plot 600 of this stimulus 602 and the corresponding basilar membrane response 604. As seen in Fig. 6, this stimulus 602 evokes a response around 500 Hz and the magnitude/deflection of the response 604 is increased as compared to the response 404 illustrated in Fig. 5.

[0046] However, presenting stimuli at the rate of c_f stimuli/second poses another challenge – overlapping responses. Fig. 7 is a plot 700 of basilar membrane responses 702 to a series of stimuli at the fixed rate of 500 stimuli/second (i.e., stimuli are presented periodically every 2 ms). The vertical bars 704 depict the instances in which the stimuli are presented, i.e., every 2 ms. This figure illustrates that presenting stimuli with a fixed inter stimulus interval (ISI) of $1/c_f$ leads to overlapping of responses and contamination of the

responses by adjacent responses if the ISI is shorter than the duration of the brainstem response, thereby creating a steady state response at the electrodes (see electrode response 710) from which it is difficult if not impossible to estimate the transient ABR 200.

[0047] To address this further problem, a jitter is introduced in the stimulus rate and deconvolution is used to disentangle the overlapping responses. The jitter is defined as the amount of ISI dispersion compared to a fixed presentation rate (which would have jitter equal to 0 ms). In particular, the ISI is not fixed, but varied randomly according to a uniform distribution between two defined values from one stimulus to the next.

[0048] Fig. 8 illustrates an example of the ISI dispersion of a randomized stimulation sequence in which the ISI is varied randomly according to a uniform distribution between 1.8 and 2.2 ms, thus leading to a jitter of 0.4 ms.

[0049] This variation in ISI leads to a quasi-steady state signal in the electrodes, from which it is possible to estimate the transient ABR using deconvolution techniques. In some embodiments, an iterative randomized stimulation and averaging deconvolution technique is employed.

[0050] Fig. 9 shows an example of the quasi-steady state signal at the electrodes when an asynchronous stimulation rate is used. The non-periodicity of the presentation of the stimuli allows the transient ABR to be obtained using a deconvolution algorithm.

[0051] Determining the optimal amount of jitter includes a trade-off. On one hand, narrow jitters (i.e., small differences in the ISI) is optimal for achieving basilar membrane resonance, but increases the complexity of deconvolving overlapping responses. On the other hand, wide jitters (i.e., large differences in the ISI) facilitate deconvolution, but fail to induce basilar membrane resonance.

[0052] Through a number of experiments, the inventors of the presently disclosed systems and methods have eventually determined that a jitter of 0.4 ms for a 500Hz stimulation signal leads to basilar resonance and the jitter is sufficient enough to deconvolve the overlapping responses evoked by such a stimulation signal. In essence, the optimal jitter should be set as the minimum jitter that allows deconvolution without distorting the signal, and it will likely depend on each characteristic frequency and may be different for different characteristic frequencies and stimulus presentation level.

System Overview

[0053] Figs. 10 and 11 illustrate an exemplary system 1000 and an exemplary method

1100 for recording brainstem responses evoked from the apical portion of the cochlea. Specifically, Fig. 10 illustrates the systems involved in generating stimulus, recording brainstem responses and processing the responses to generate ABR recordings and Fig. 11 described the process steps for doing so. For generating the stimuli, the system 1000 includes a computing device 1002, audio generator with sound card 1004 and audio output devices 1006 (e.g., headphones, earphones, loudspeakers, etc). For recording brainstem responses, the system 1000 includes electrical response detectors 1008 (e.g., scalp electrodes), an electroencephalography recorder 1010, and the computer 1002. The stimulus generating elements may be connected to each other via wires, wirelessly, or a combination of the two. Similarly, the signal recording elements may be connected to each other via wires, wirelessly, or a combination of the two. In Fig. 10, the computing device 1002 and audio generator 1004 are depicted as separate units, but in some emobidments, the computing device and audio generator may be combined into a single computing device with a sound card.

[0054] At step 1102, an auditory stimulation signal is generated. In certain embodiments, the computing device 1002 in conjunction with the sound card 1004 is configured to generate the auditory stimulation signal. In certain embodiments, the auditory stimulation signal is centered around a characteristic frequency (c_f) in the range of 10Hz – 2 kHz. In some preferred embodiments, the auditory signal is centered around a characteristic frequency in the range of 125Hz to 1 kHz. And in more preferred embodiments, the auditory signal can have a characteristic frequency of 500Hz. Further, the auditory signal includes stimuli every $1/c_f$ seconds (i.e., at a rate of c_f stimuli/second) having a duration of about $1/c_f$ each.

[0055] Further still, the auditory stimulation signal generated by the computing device 1002 may have a jitter, i.e., an irregular ISI. In certain embodiments, the jitter may be between 1% and 100% of the duration of each stimulus.

[0056] At step 1104, the auditory stimulation signal is transmitted to the subject. For stimulus transmission, the computer 1002 is connected to the audio generator with sound card 1004, which delivers the generated auditory stimulation signal to a subject through the audio output device 1006 (e.g., a pair of insert earphones). At this stage, for example, at the beginning of each stimulus transmission, the soundcard 704 may also be configured to send a trigger pulse to the EEG recorder 1010 via a trigger box 1012 to indicate the time instant at which a stimulus was transmitted to the subject.

[0057] At step 1106, basilar membrane responses are recorded. For this purpose, electrical signal detectors (e.g., electrodes) are placed on the skin at different predetermined

positions on the subject's scalp. These electrical signal detectors 1008 detect changes in voltage on the scalp evoked by the auditory stimuli and transmit signals associated with the detected changes to the EEG recorder 1010. The EEG recorder 1010 in turn converts the signals received from the electrodes into digital data and forwards the recorded digital data back to the computing device 1002, for further processing.

[0058] It will be appreciated that the EEG records the signals received from the electrodes in a conventional manner, e.g., as used in any clinical or research protocol. Because of this, the proposed stimulation and analysis method can be implemented in any EEG recording system, and it does not require any special hardware element.

[0059] At step 1108, the basilar membrane responses are processed. Since the duration of the auditory evoked response is at least as long as or longer than the duration of the ISI, presentation of the auditory stimulation signal at the aforementioned stimulation rates leads to overlapping auditory evoked responses, which leads to a distorted version of the signal at the electrodes 1008.

[0060] Accordingly, at step 1108, the computing device 1002 is configured to disentangle the overlapping responses using a process called deconvolution. In certain embodiments, an 'iterative randomized stimulation and averaging (IRSA)' algorithm may be used. This algorithm is described in detail in Valderrama, de la Torre et al. (2014) – *Auditory brainstem and middle latency responses recorded at fast rates with randomized stimulation* – Journal of the Acoustical Society of America 136, 3233-3248, which is incorporated herein in its entirety.

[0061] The approach in this algorithm is based on iterations that include estimation of the interference associated with overlapping responses, subtraction of the estimation from the recorded EEG, and re-estimation of the auditory evoked response. The improved auditory evoked response estimate on each iteration leads to a better estimate of the interference associated with overlapping responses, and a better auditory evoked response estimate can therefore be obtained recursively. The accuracy of the auditory evoked response estimate increases with the number of iterations.

[0062] The mathematical formulation of this algorithm is described below. Using randomized stimulation and averaging notation, the estimate of the transient evoked response $\hat{x}(j)(j = 1, \ldots, J)$ is obtained by an iterative process in the time domain. Each iteration *(i)* results in an estimate of the transient evoked response, represented by $\widehat{h_i}(j)$. The auditory evoked response estimate in each iteration by this method is obtained as the average of the K

sweeps, in which the contribution of the adjacent responses to each current response is suppressed –

$$\widehat{h_i}(j) = \frac{1}{K}\sum_{k=1}^{K} y_k\left(j + m(k)\right), \qquad (1)$$

where $y_k(n)(n = 1, \ldots, N)$ represents the EEG in which the *kth* response is kept, but all the other responses (i.e., the overlapping responses) are subtracted. The $y_k(n)$ signals can be obtained for each stimulus as the original electroencephalogram $y(n)$ minus the auditory evoked response estimates on the preceding iteration $\hat{h}_{i-1}$ corresponding to all stimuli excluding the stimulus k,

$$y_k(n) = y(n) - \left(s(n) - s_k(n)\right) * h_{i-1}, \qquad (2)$$

where $s_k(n)$ represents the stimulation signal for the stimulus k, and the symbol * is the convolution operator. Considering the signal $z(n)$ as the original EEG with all auditory evoked responses suppressed:

$$z(n) = y(n) - s(n) * h_{i-1}, \text{ then}$$

$$y_k(n) = y(n) - s(n) * h_{i-1} + s_k(n) * h_{i-1}$$

$$= z(n) + s_k(n) * h_{i-1} \qquad (3)$$

[0063] The sections of y_k corresponding to the averaging window of the stimulus k can thus be obtained as:

$$y_k\left(j + m(k)\right) = z\left(j + m(k)\right) + s_k\left(j + m(k)\right) * h_{i-1} \qquad (4)$$

[0064] The $s_k(n)$ signal can be represented as $\delta(n - m(k))$, where $\delta(n)$ represents the Dirac delta function, with the value 1 for $n = 0$, and 0 otherwise. Hence

$$y_k\left(j + m(k)\right) = z\left(j + m(k)\right) + \delta\left(j + m(k) - m(k)\right) * h_{i-1}$$

$$= z\left(j + m(k)\right) + h_{i-1}, \qquad (5)$$

since $\delta(j) * f = f$ for whatever function f. Therefore, Eq. 1 can be rewritten as

$$\widehat{h_i}(j) = \frac{1}{K}\sum_{k=1}^{K}\left[z\left(j + m(k)\right) + h_{i-1}\right]$$

$$= h_{i-1} + \frac{1}{K}\sum_{k=1}^{K}\left[z\left(j + m(k)\right)\right] \qquad (6)$$

[0065] In this equation, the term $(1/K)\sum_{k=1}^{K} z(j + m(k))$ represents the correction made to the auditory evoked response estimate on the preceding iteration h_{i-1}. Under certain jitter

distributions and stimulation rates, this correction parameter may cause instability problems, leading to worse auditory evoked response estimates in successive iterations. The inventors have verified (with simulations and real ABR and MLR signals) that problems of instability usually arise with narrow distributions of the jitter and stimulation rates in which the averaged ISI is close to a maximum value of the auditory evoked response autocorrelation function. The instability issue can be solved by inserting a correction factor α, which may constrain (α-values lower than 1) or enhance (α-values greater than 1) the correction made to h_{i-1}. Thus, the auditory evoked response estimate in iteration i is obtained as

$$\widehat{h_i}(j) = h_{i-1} + \alpha . \frac{1}{K} \sum_{k=1}^{K} [z(j + m(k))] \qquad (7)$$

[0066] The value of the α parameter can be defined either as a fixed value in all iterations or adaptive in each iteration. Theoretically, the optimal α -value is the greatest value of α that avoids instability. Greater α–values would provide increasing oscillations in successive iterations, leading to an unstable solution. Lower α–values slow down the speed of convergence toward the auditory evoked response estimate, even though convergence would be guaranteed.

[0067] The estimated auditory evoked response on each iteration $\widehat{h_i}(j)$ is used in the following iteration as $\widehat{h_{i-1}}(j)$. The I-RSA method is initialized with $\widehat{h_0}(j) = 0 \ \forall j$. Finally, the estimate of the transient auditory evoked response by I-RSA $\hat{x}(j)$can be obtained either as the estimated auditory evoked response after a predefined number of iterations I ($\hat{x}(j) = \widehat{h_i}(j)$), or when the differences between the auditory evoked response estimates in successive iterations are negligible ($\hat{x}(j) = \widehat{h_i}(j)$ if $\widehat{h_i}(j) \approx\_ \widehat{h_{i-1}}(j)$).

[0068] In short, according to equation 7, i.e. $\widehat{h_i}(j) = h_{i-1} + \alpha * \frac{1}{K} \sum_{k=1}^{K} [z(j + m(k))]$, the estimate of the brainstem response in the iteration i [$\widehat{h_i}$] is the estimate of the brainstem response in the previous iteration [h_{i-1}] plus an averaged residual $\frac{1}{K} \sum_{k=1}^{K} [z(j + m(k))]$ weighted by a factor α. This α factor is necessary to avoid instability problems, in which successive iterations lead to a worse estimate of the response. Lower α-values slow down the speed of convergence toward the auditory evoked response estimate [i.e., more iterations are needed to reach convergence], even though convergence would be guaranteed.

[0069] In the foregoing specification, embodiments of the invention have been described with reference to numerous specific details that may vary from implementation to implementation. Thus, the sole and exclusive indicator of what is the invention, and is

intended by the applicants to be the invention, is the set of claims that issue from this application, in the specific form in which such claims issue, including any subsequent correction. Any definitions expressly set forth herein for terms contained in such claims shall govern the meaning of such terms as used in the claims. Hence, no limitation, element, property, feature, advantage or attribute that is not expressly recited in a claim should limit the scope of such claim in any way. The specification and drawings are, accordingly, to be regarded in an illustrative rather than a restrictive sense.

[0070] As used herein the terms “include” and "comprise" (and variations of those terms, such as “including”, “includes”, "comprising", "comprises", "comprised" and the like) are intended to be inclusive and are not intended to exclude further features, components, integers or steps. Further, the terms “process” and “method” are interchangeably used.

[0071] Various features of the disclosure have been described using flowcharts. The functionality/processing of a given flowchart step could potentially be performed in various different ways and by various different systems or system modules. Furthermore, a given flowchart step could be divided into multiple steps and/or multiple flowchart steps could be combined into a single step. Furthermore, the order of the steps can be changed without departing from the scope of the present disclosure.

[0072] It will be understood that the embodiments disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the embodiments.

CLAIMS

What is claimed is:

1. A method for obtaining auditory evoked potentials from an apical region of the cochlea, the method comprising:

generating a stimulus comprising a one-period sinusoidal signal having a characteristic frequency (c_f) in the frequency range of the apical region, and a duration of $1/c_f$ seconds,

presenting a plurality of the stimuli as an auditory stimulation signal at an average rate of c_f, stimuli per second;

transmitting the auditory stimulation signal to an audio output device in communication with a subject;

receiving overlapping auditory evoked responses from one or more electrodes connected to the subject, the auditory evoked responses generated by the subject in response to the auditory stimulation signal;

deconvolving the received overlapping auditory evoked responses to create a disentangled record of the response.

2. The method of claim 1, wherein presenting the auditory stimulation signal includes using randomized inter-stimulus intervals (ISI) with the minimum amount of ISI dispersion that avoids distortion of the auditory evoked responses during deconvolving.

3. The method of claim 2, wherein the auditory stimulation signal has an ISI dispersion of about 20% to 80% of the duration of a stimulus in the stimulation signal.

4. The method of claim 1, wherein the characteristic frequency (c_f) is in the range of 10Hz-2 kHz.

5. The method of claim 4, wherein the characteristic frequency (c_f) is in the range of 125Hz to 1 kHz.

6. The method of claim 5, wherein the characteristic frequency (c_f) is in the region of 500Hz.

7. The method of claim 6, wherein the ISI dispersion is about 0.4ms.

8. The method of claim 1, wherein deconvolving the received overlapping auditory evoked reponses includes applying an iterative randomized stimulation and averaging (IRSA) algorithm.

9. The method of claim 1, wherein the auditory stimulation signal induces a resonance in a specific portion of the basilar membrane that is sensitive to the characteristic frequency c_f.

10. A series of stimuli for inducing resonance in a specific portion of the basilar membrane that is sensitive to a particular characteristic frequency c_f, each stimulus in the series comprising a one-period sinusoidal signal with frequency equal to the particular characteristic frequency c_f, windowed using a window of the same duration, the stimuli having an average rate equal to c_f using randomized inter-stimulus intervals (ISI) with an ISI dispersion between 20% to 80% of the stimulus duration.

11. A system for obtaining auditory evoked potentials from apical portions of the cochlea, the system comprising:

a computing device configured to:

generate an auditory stimulation signal having a characteristic frequency (c_f) in the frequency range of the apical region, the auditory stimulation signal comprising a plurality of one-period sinusoidal signals, each having a duration in the region of $1/c_f$ seconds,

transmit the generated auditory stimulation signal to an audio output device in communication with a subject;

receive overlapping auditory evoked responses from one or more electrodes connected to the subject, the auditory evoked responses generated by the subject in response to the auditory stimulation signal from the auditory output device;

deconvolve the received overlapping auditory evoked responses to create a disentangled record of the responses.

12. The system of claim 11, wherein transmitting the generated auditory stimulation signal includes using randomized inter-stimulus intervals (ISI) with the minimum amount of ISI dispersion that avoids distortion of the auditory evoked responses during devonvolving.

13. The system of claim 12, wherein the auditory stimulation signals have an ISI dispersion of about 20% to 80% of the stimulus duration.

14. The system of claim 11, wherein the characteristic frequency (c_f) is in the range of 10Hz-2 kHz.

15. The system of claim 1, wherein the characteristic frequency (c_f) is in the range of 125Hz to 1 kHz.

16. The system of claim 15, wherein the characteristic frequency (c_f) is in the region of 500Hz.

17. The system of claim 16, wherein the ISI dispersion is about 0.4ms.

18. The system of claim 11, wherein deconvolving the received overlapping auditory evoked response includes applying an iterative randomized stimulation and averaging (IRSA) algorithm.

19. The system of claim 11, wherein the auditory stimulation signal induces a resonance in a specific portion of the basilar membrane that is sensitive to the characteristic frequency c_f.

20. The system of claim 11, wherein the overlapping auditory evoked responses are

received via an electroencephalography (EEG) recorder.

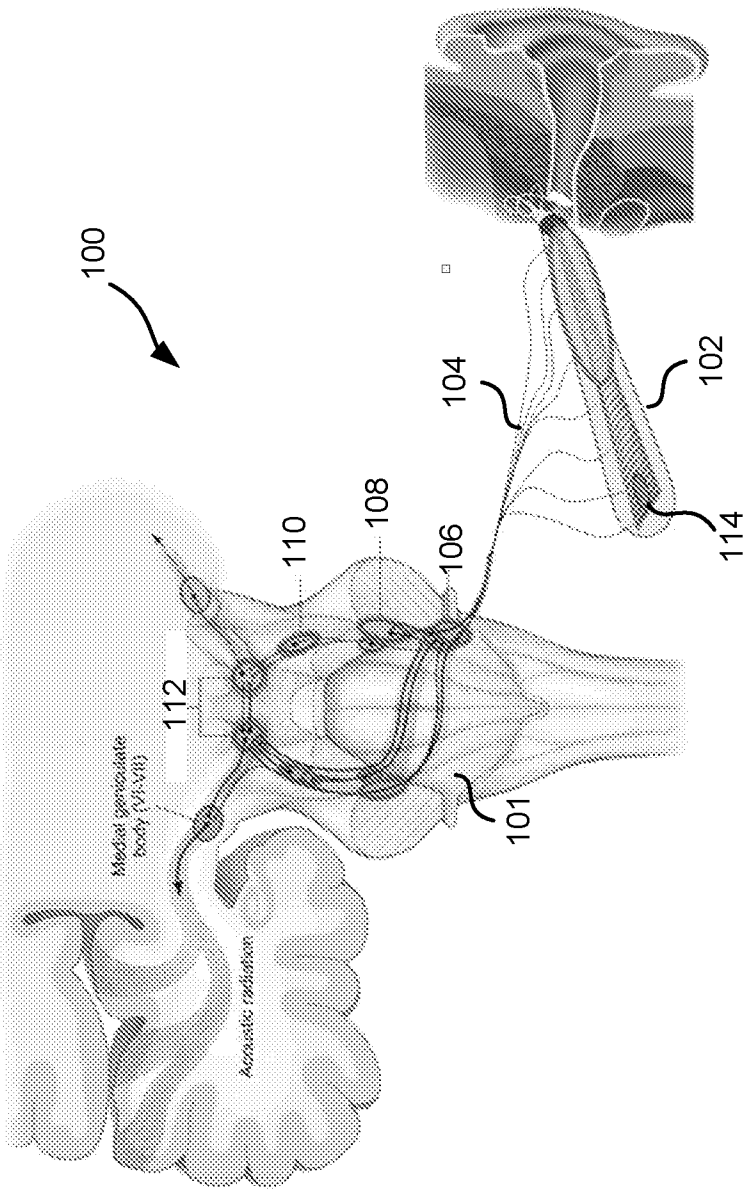
100
102
104
106
108
110
112
114
101
Medial geniculate body (VI-VII)
Acoustic radiation

Fig 1

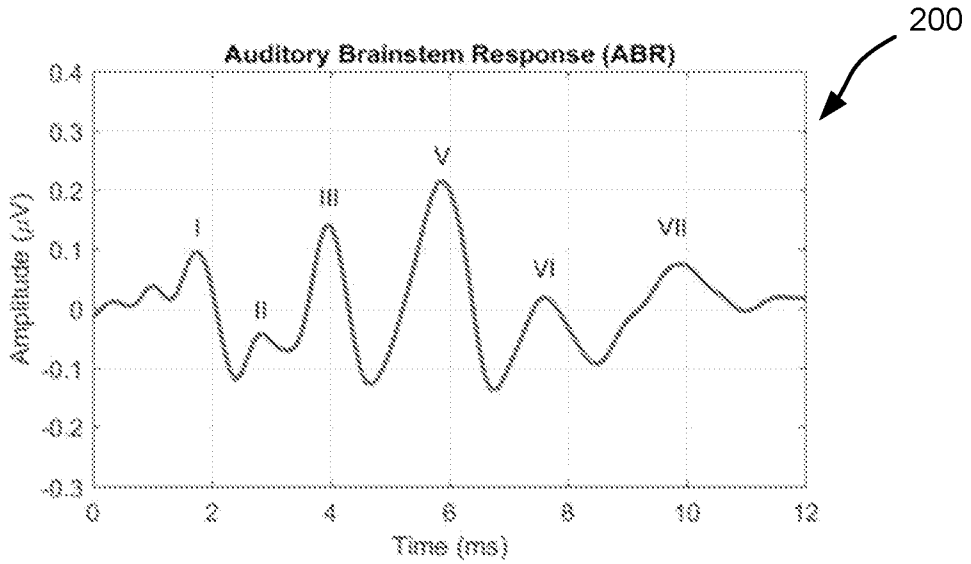
200
Auditory Brainstem Response (ABR)
Amplitude (μV)
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
I
II
III
V
VI
VII
0
2
4
6
8
10
12
Time (ms)

Fig 2

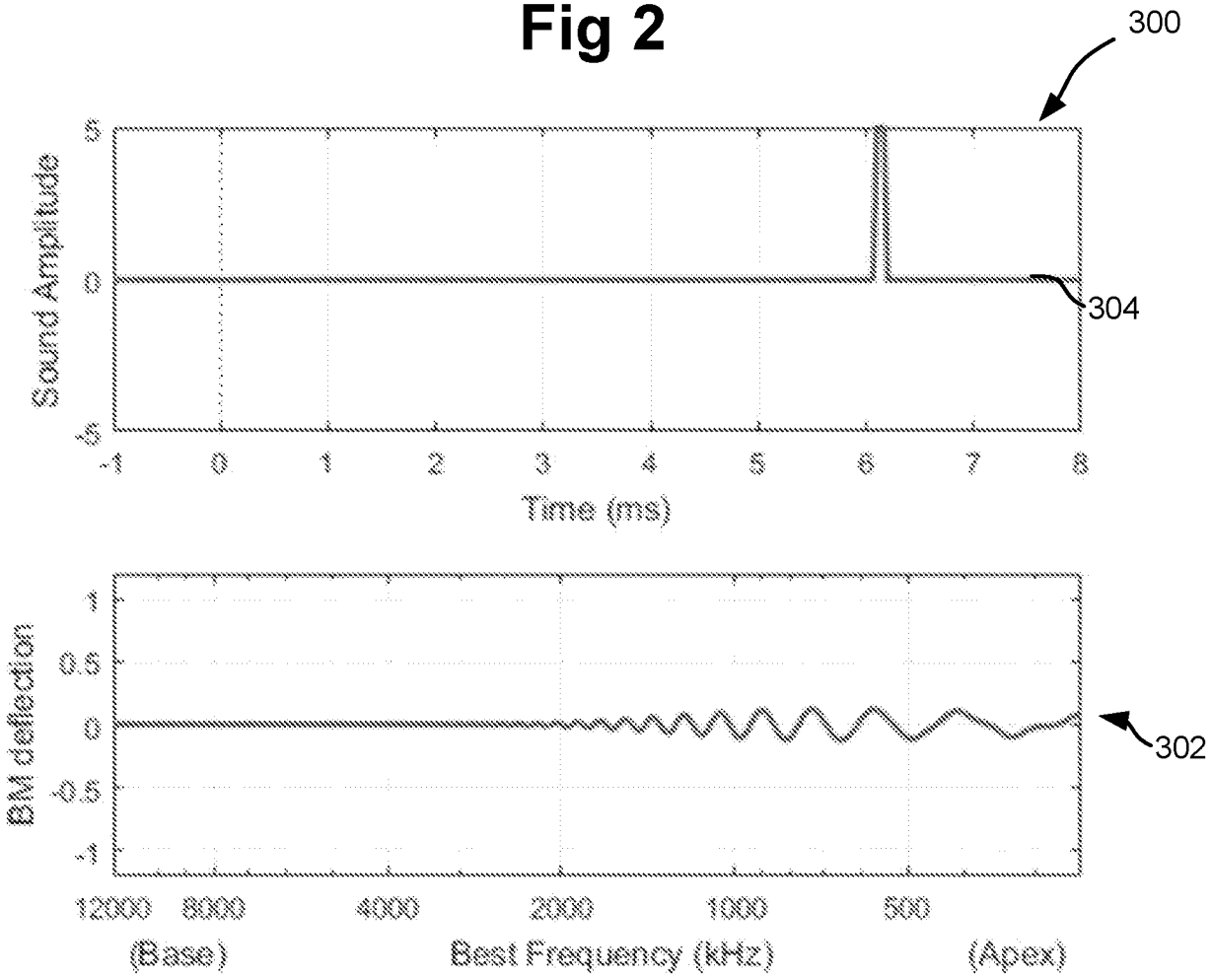
300
Sound Amplitude
5
0
-5
304
-1
0
1
2
3
4
5
6
7
8
Time (ms)
BM deflection
1
0.5
0
-0.5
-1
302
12000
8000
4000
2000
1000
500
(Base)
Best Frequency (kHz)
(Apex)

Fig 3

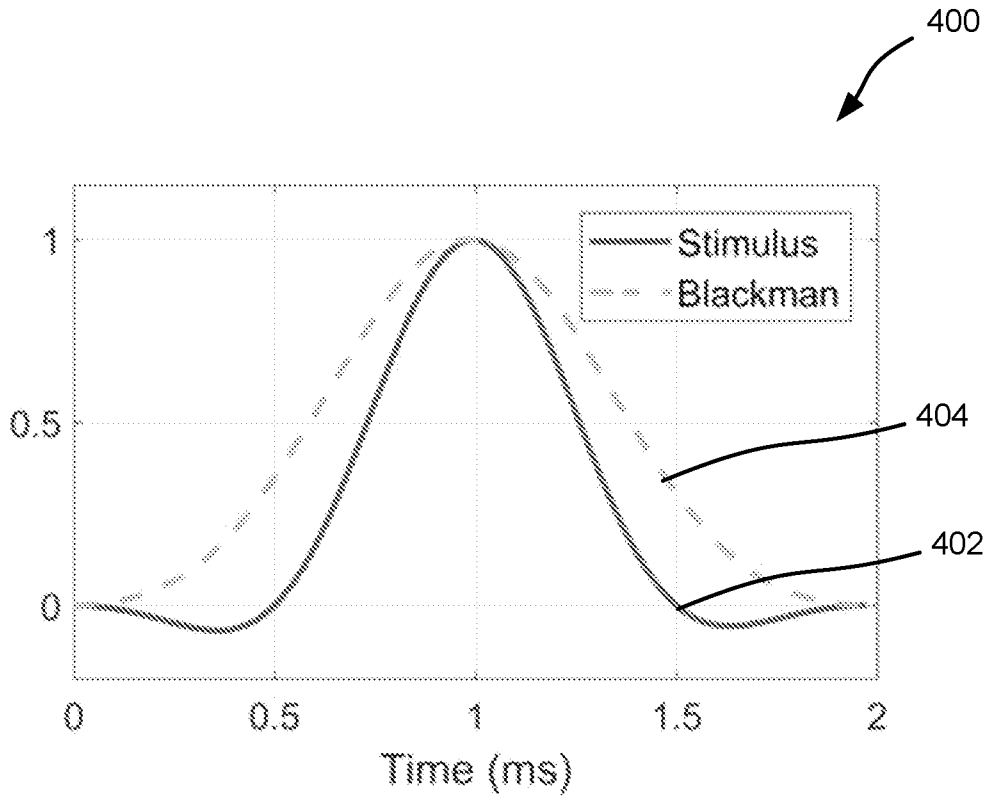

Fig 4

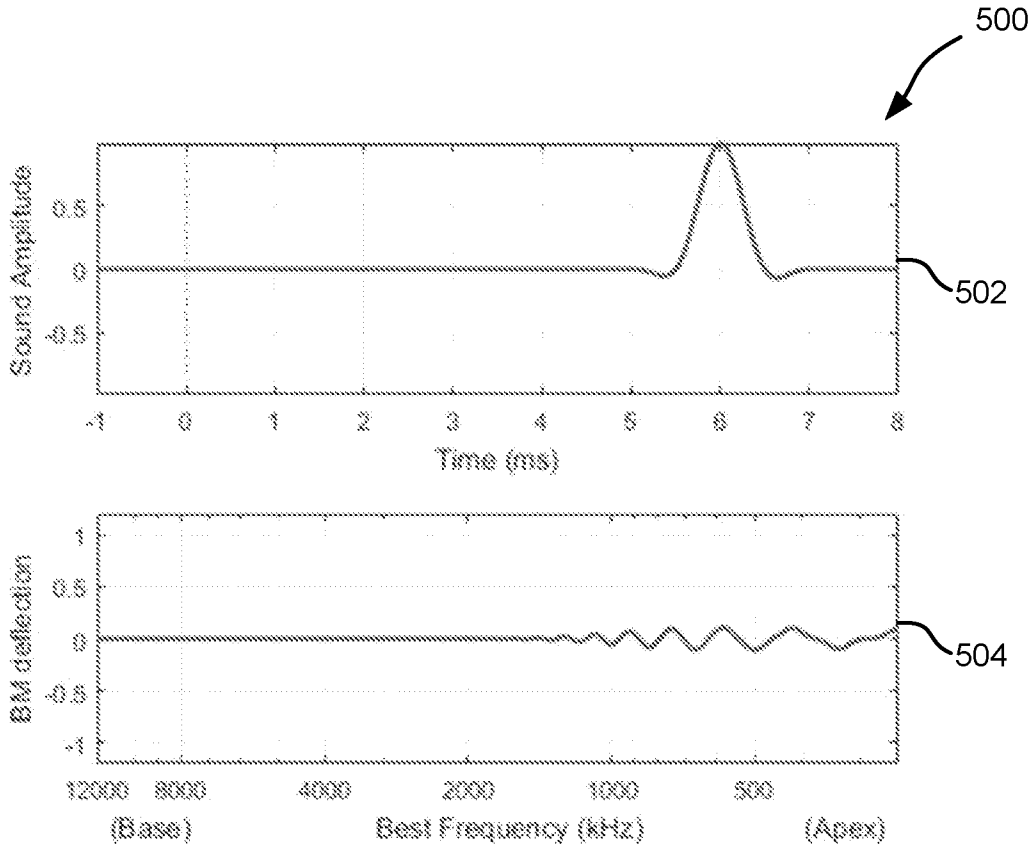
500
Sound Amplitude
0.5
0
-0.5
-1
0
1
2
3
4
5
6
7
8
Time (ms)
502
BM deflection
1
0.5
0
-0.5
-1
12000
8000
4000
2000
1000
500
(Base)
Best Frequency (kHz)
(Apex)
504

Fig 5

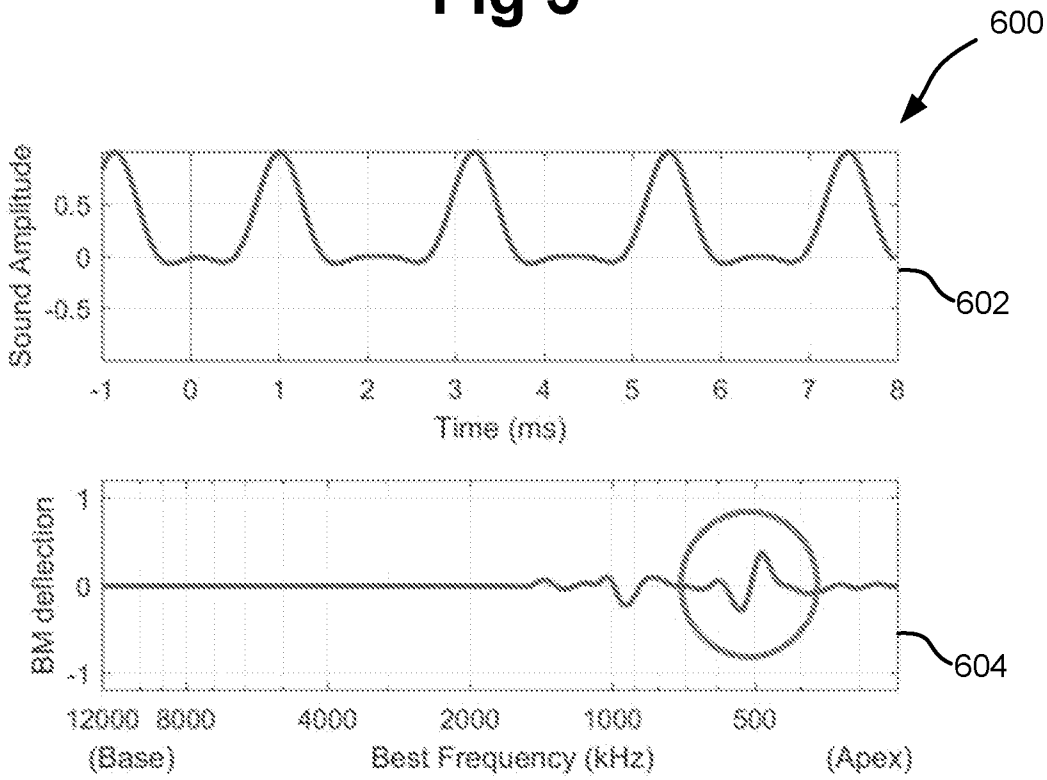
600
Sound Amplitude
0.5
0
-0.5
-1
0
1
2
3
4
5
6
7
8
Time (ms)
602
BM deflection
1
0
-1
12000
8000
4000
2000
1000
500
(Base)
Best Frequency (kHz)
(Apex)
604

Fig 6

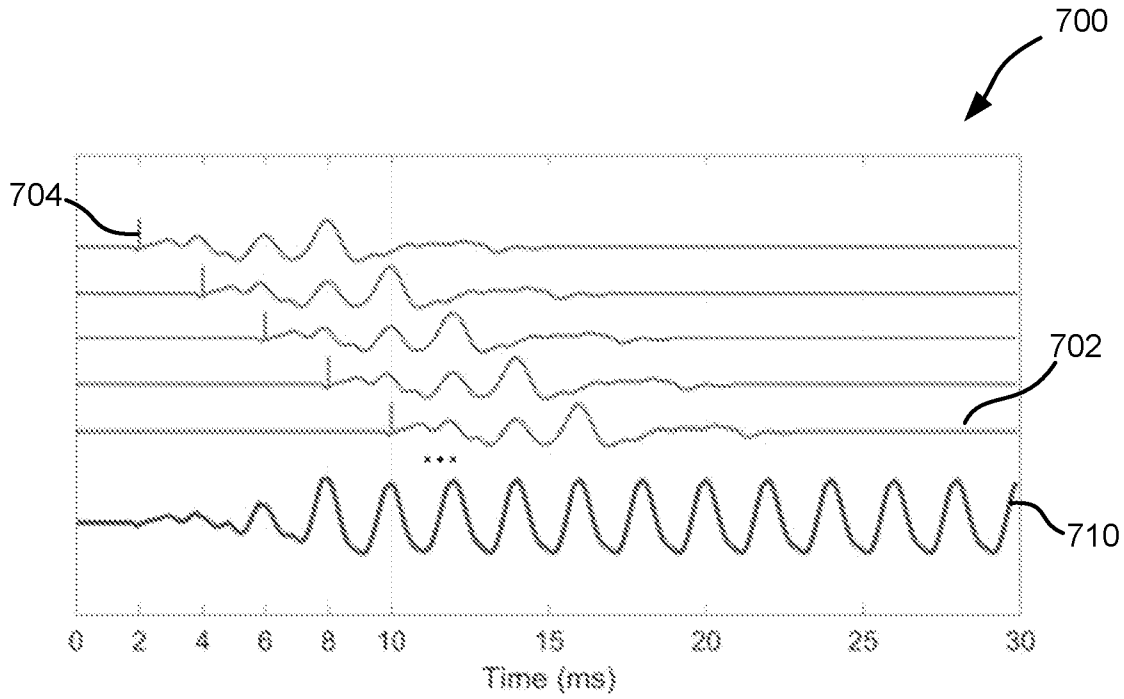
700
704
702
710
0
2
4
6
8
10
15
20
25
30
Time (ms)

Fig 7

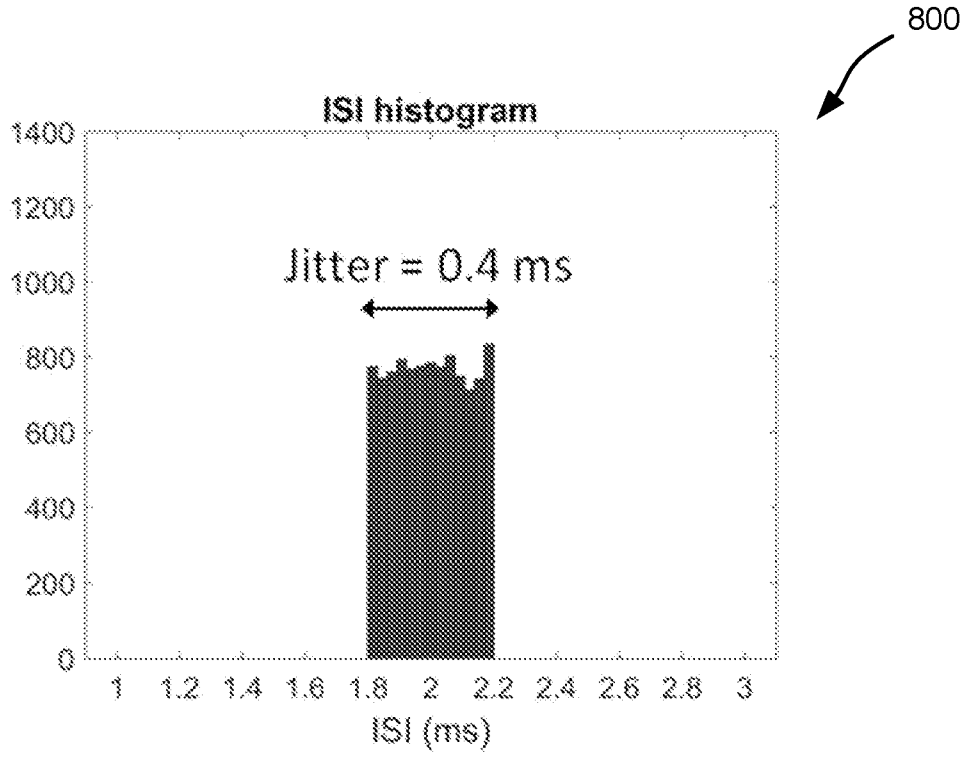
800
ISI histogram
Jitter = 0.4 ms
1400
1200
1000
800
600
400
200
0
1
1.2
1.4
1.6
1.8
2
2.2
2.4
2.6
2.8
3
ISI (ms)

Fig 8

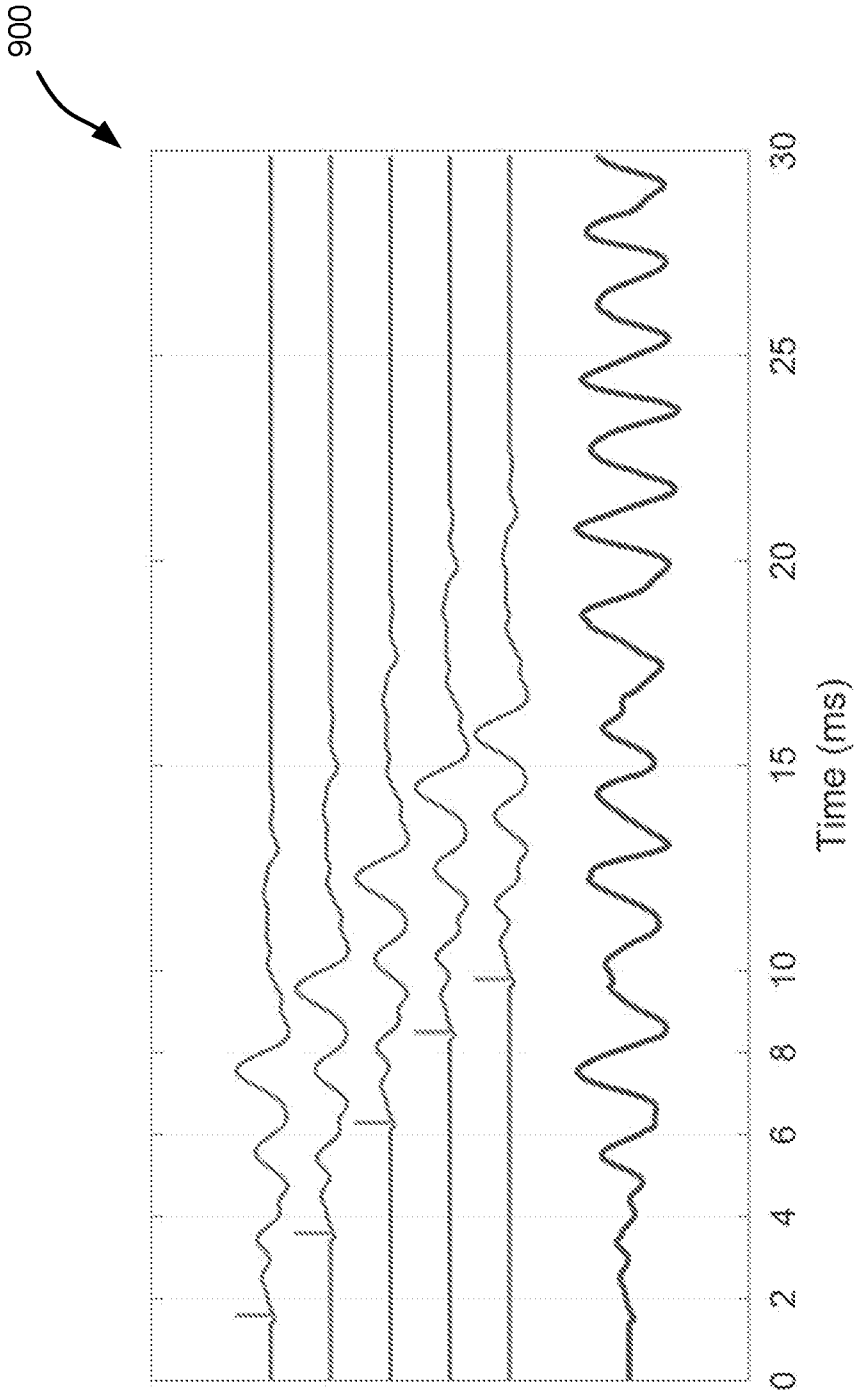

Fig 9

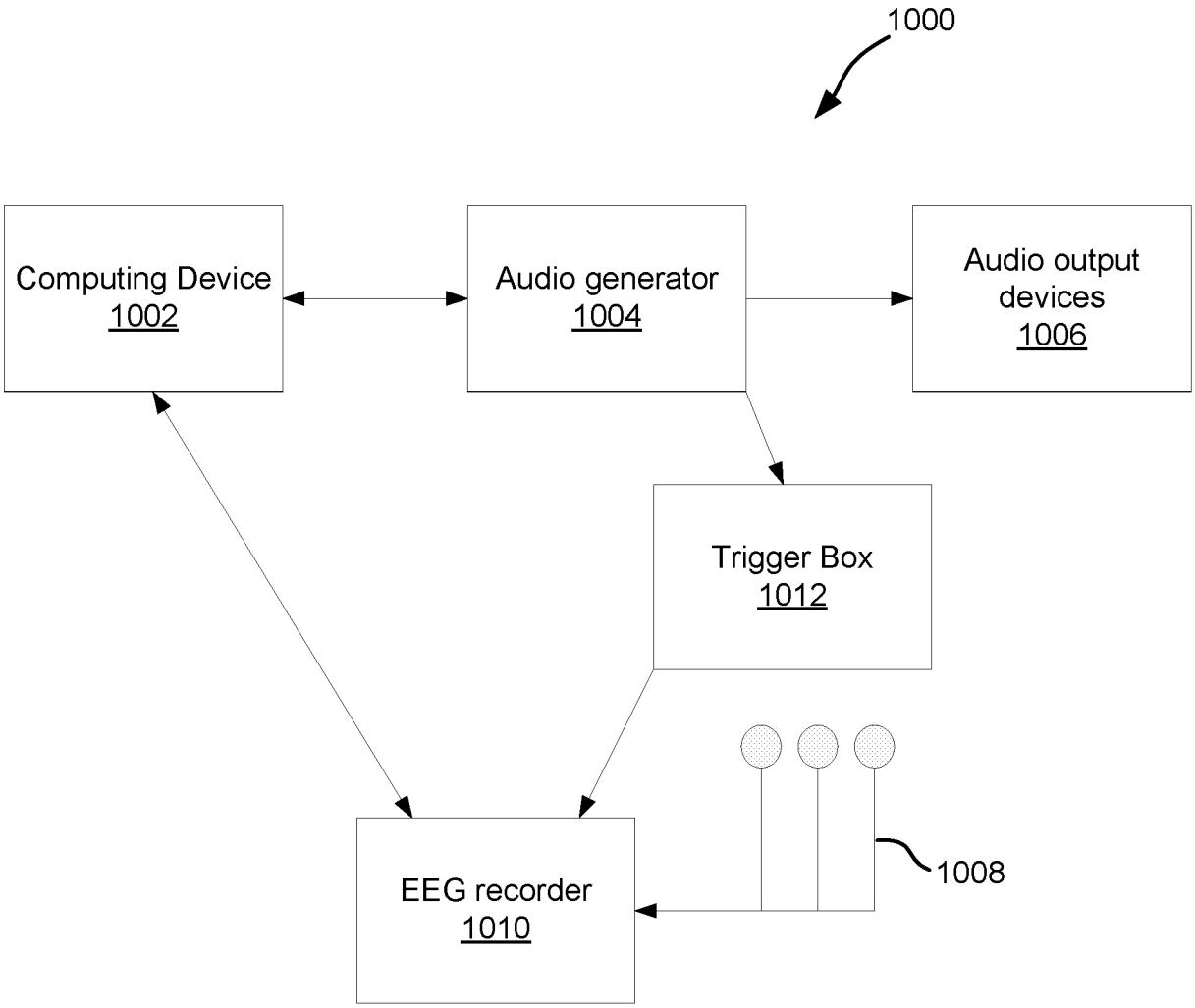
1000
Computing Device
1002
Audio generator
1004
Audio output
devices
1006
Trigger Box
1012
EEG recorder
1010
1008

Fig 10

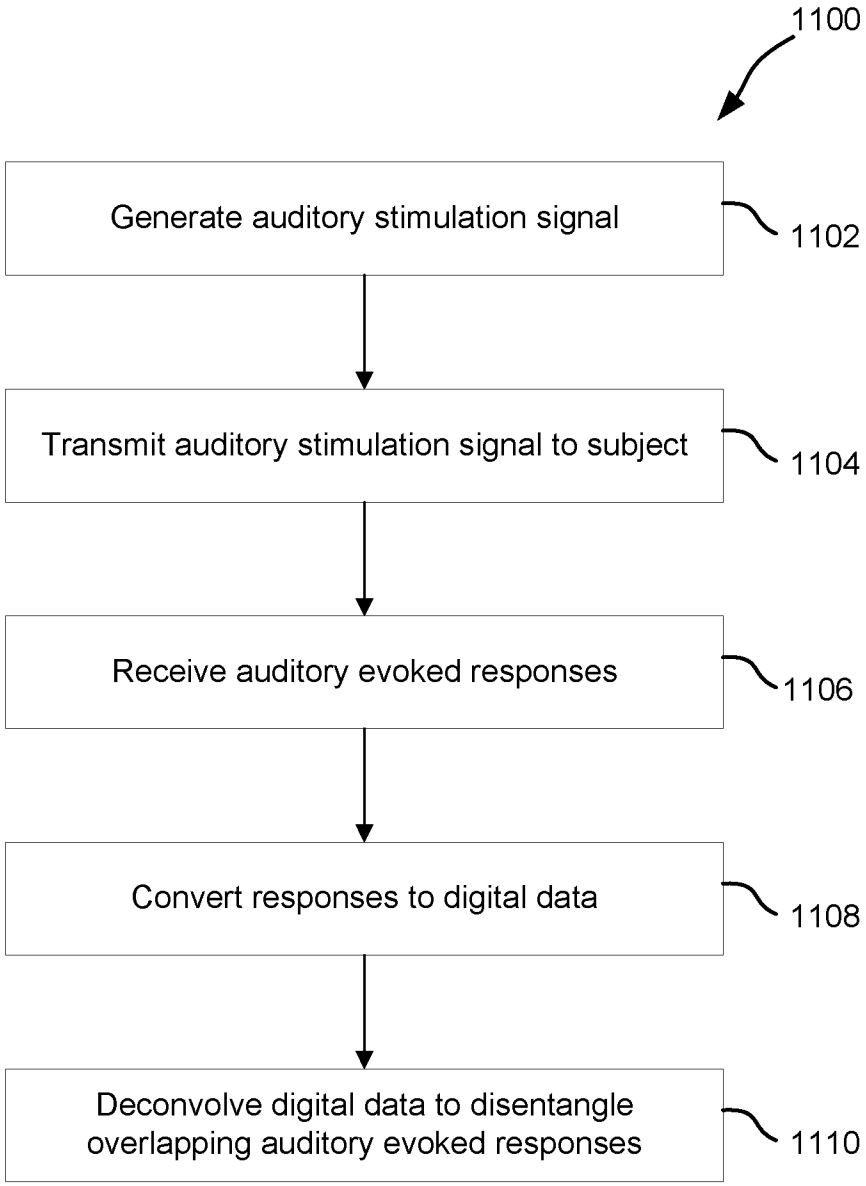
1100
Generate auditory stimulation signal
1102
Transmit auditory stimulation signal to subject
1104
Receive auditory evoked responses
1106
Convert responses to digital data
1108
Deconvolve digital data to disentangle overlapping auditory evoked responses
1110

Fig 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2019/050648

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/0484 (2006.01) A61B 5/12 (2006.01) A61B 5/0478 (2006.01) A61B 5/04 (2006.01) G06F 17/16 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases PATENW (EPOQUE-defined) IPC/CPCs and OR A61B5/0476, A61B5/0484, A61B5/0478, A61B5/0482 and lower sub-classes in IPCs; A61B5/04845, A61B5/0484, A61B5/0482, A61B5/0478, A61B5/72, A61B5/121, A61B5/126, G06F17/16, G06K9/0053, A61B5/04012, A61B5/743 and lower sub-classes in CPCs and the like; databases MEDLINE and NPL (EPOQUE) and keywords such as: Auditory Brainstem Response (ABR); sine wave, pure tone, cosine wave, sinusoid wave, random stimulus, interval, evoke brainstem, basilar membrane; resonance, stimuli, randomized stimulus sequence, low frequency deconvolution inverse problem and the like; inventors' names/ and or applicants' names and the logical Boolean Operators on combination of the listed keywords and/or IPCs and CPCs with appropriate search limitations and the like. Google Patents and Google Scholar searches with keywords such as jitter, sinusoidal wave, stimuli, ABR Loop Average deconvolution and the like in Boolean combination with some of the listed CPCs marks above. ESPACENET and CPCs A61B5/04845 or A61B5 or G06F17/16 and the phrase brainstem response (in the title and abstract) and the like and the keyword "auditory" in the title or abstract and CPC G06F17/16 and the like. Applicant(s)/Inventor(s) name searched in internal databases.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 2019	14 August 2019

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Telephone No. +61262832676

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2019/050648**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LACHOWSKA, M. et al. "Simultaneous Acquisition of 80 Hz ASSRs and ABRs From Quasi ASSRs for Threshold Estimation." Ear & Hearing, 2012, VOL. 33, NO. 5, pages 660-671. "Objectives"; pages 660-664, part "Background" 3rd – 6th paragraph, sub-part "Stimulus and Sequence Characteristics" Figs. 1, 2 "Continuous Loop Averaged Deconvolution" (CLAD) – see part "Background" 5th paragraph and part "Stimulus and Sequence Characteristics" see part "ABR Extraction" & "Objective FMP Analysis of ABRs and QASSR's "RESULTS" "DISCUSSION" see also Figs. 2-4 and Tables 1 and 2 page 667, text on pages 663-671	1, 4-6, 9, 11, 14-16, 19, 20
Y	Entire document	2, 3, 7, 8, 10, 12, 13, 17, 18
Y	VALDERRAMA, J. T. et al. "Recording of auditory brainstem response at high stimulation rates using randomized stimulation and averaging." The Journal of the Acoustical Society of America, 2012, Vol. 132 (6) pages 3856-3865. Entire document, Fig. 1A and 2A having Randomised Stimulation and Averaging (RSA) – part "II. RSA" Fig 1A-1C and 2A	2, 3, 7, 8, 10, 12, 13, 17, 18
X	WANG, T. et al. "Wiener filter deconvolution of overlapping evoked potentials." Journal of Neuroscience Methods, 2006, Vol. 158(2), pages 260-270. Abstract, part "I. Introduction," "2.3 Stimulus Sequence" page 263, Fig. 1E, part "2. Methods," and sub-para 2.3-2.7, "3. Results," Figs. 4, 5 and 7	1, 4-6, 9, 11, 14-16, 19, 20
Y	Entire document	2, 3, 7, 8, 10, 12, 13, 17, 18
Y	VALDERRAMA, J. T. et al. "Selective processing of auditory evoked responses with iterative-randomized stimulation and averaging: A strategy for evaluating the time-invariant assumption," Hearing Research, 2016, Vol. 333, pages 66-76. Entire document, esp. Abstract, part "1. Introduction," paragraphs 4-6; part "2. Methods," esp. sub-parts 2.1, Fig. 1, 2.3.3, 2.3.4, 2.3.5 part "3. Results" Figs. 2 and 4 and text related to these figures, part "4. Discussion."	2, 3, 7, 8, 10, 12, 13, 17, 18
A	US 2015/0005660 A1 (NORTHWESTERN UNIVERSITY) 01 January 2015 Entire document	1-20
A	ROBLES, L. et al. "Mechanics of the Mammalian Cochlea," Physiological Review, 2001, Vol. 81(3), pages 1305-1352 Entire document	1-20

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2019/050648**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 2015/0005660 A1	01 January 2015	US 2015005660 A1	01 Jan 2015
		EP 1893083 A1	05 Mar 2008
		JP 2008539977 A	20 Nov 2008
		US 2006282004 A1	14 Dec 2006
		US 8014853 B2	06 Sep 2011
		US 2011313309 A1	22 Dec 2011
		US 8712514 B2	29 Apr 2014
		US 2012197153 A1	02 Aug 2012
		US 8825149 B2	02 Sep 2014
		WO 2006122304 A1	16 Nov 2006

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.